Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Mendelian Randomization Analysis of the Relationship Between Immune-Related Diseases and Alzheimer's Disease

Dong-Hong Huang[1,*], Yue-ling Zhang[1,*], Sheng-Liang Shi[1], Tian-Jia Liang[2], Jun-jian Chen[3], Guo-Qiao Li[4], Zhao-De Chen[2]

[1]Department of Neurology, The Second Affiliated Hospital of Guangxi Medical University, Guangxi, 530000, People's Republic of China; [2]Department of Rehabilitation, The Second Affiliated Hospital of Guangxi Medical University, Guangxi, People's Republic of China; [3]Department of Respiratory, The Second Affiliated Hospital of Guangxi Medical University, Guangxi, People's Republic of China; [4]Department of Endocrinology, The Second Affiliated Hospital of Guangxi Medical University, Guangxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Sheng-Liang Shi, Department of Neurology, The Second Affiliated Hospital of Guangxi Medical University, No. 166, University East Road, Xixiangtang District, Nanning, Guangxi, 530000, People's Republic of China, Tel/Fax +86-07713278031, Email shishengliangssl@126.com; Tian-Jia Liang, Department of Rehabilitation, The Second Affiliated Hospital of Guangxi Medical University, No. 166, University East Road, Xixiangtang District, Guangxi, 530000, People's Republic of China, Email liangtianjia9kg@outlook.com

Objective: Emerging evidence suggests a genetic link between immune-related diseases and Alzheimer's disease (AD), though the underlying mechanisms remain unclear. This Mendelian randomization (MR) study investigates the genetic relationship between six immune-related diseases—type 1 diabetes (T1DM), systemic lupus erythematosus (SLE), asthma, myasthenia gravis (MG), endometriosis, and idiopathic thrombocytopenic purpura (ITP)—and AD.

Methods: Summary-level data were obtained from publicly available genome-wide association studies (GWAS) for the six immune-related diseases and AD. MR-estimation was conducted utilizing the inverse variance weighted (IVW), MR-Egger, and WM methods. Additionally, sensitivity analyses were performed, encompassing Cochran's Q test, MR-Egger intercept, MR-Pleiotropy residual sum and outlier (MR-PRESSO) method, leave-one-out analysis, and funnel plots.

Results: A statistically significant association was identified between asthma and a slightly lower risk of AD (odds ratio [OR] = 0.996, 95% CI: 0.994–0.997, P = 0.001); however, the effect size was negligible and likely lacks clinical significance. No significant genetic associations were found between T1DM, SLE, MG, endometriosis, or ITP and AD. Reverse MR analyses indicated no evidence of reverse causality from AD to these immune-related conditions.

Conclusion: Although a nominal association was observed, this MR analysis does not support a causal relationship between genetic liability to asthma and Alzheimer's disease. This relationship underscores the specificity of the association, as no causal connections were found between other studied immune-related diseases conditions—T1DM, SLE, MG, endometriosis, and ITP—and AD.

Keywords: immune-related diseases, Alzheimer's disease, causality, Mendelian, randomization

Introduction

Alzheimer's disease (AD), often denoted as AD, manifests primarily through symptoms encompassing memory decline, cognitive impairment, deficits in language, impaired judgment, and dysfunction in daily living activities. The exact etiology of AD remains elusive, yet discernible alterations in brain tissue, such as the presence of neurofibrillary tangles, deposition of β amyloid, brain atrophy, and glial damage, are commonly observed. The onset of AD arises from a multifaceted interaction involving genetic predisposition, aging, and immune-inflammatory responses.

Immune-related diseases are characterized by the immune system erroneously attacking the body's own tissues, yet the precise etiological mechanisms behind this phenomenon are not fully understood. Contributing factors are thought to include genetic predisposition, environmental factors, and immune system dysregulation. Moreover, advanced age,

Received: 10 April 2025
Accepted: 26 August 2025
Published: 24 September 2025

genetic predispositions, environmental influences, and metabolic irregularities contribute to the onset and progression of dementia.[1] The existing body of literature suggests a potential link between immune-related diseases and AD.[2,3] However, the genetic basis of this link remains unclear, partly due to residual confounding and reverse causation. While epidemiological studies have reported associations, these are likely confounded and not necessarily causal.

Recent advancements in Genome-Wide Association Studies (GWAS) databases have significantly enhanced the prominence of Mendelian Randomization (MR) studies. Positioned at the intersection of randomized controlled trials (RCTs) and observational research, MR studies offer a unique evidential framework. This methodological hybrid simulates RCTs by employing instrumental variables (IVs) for the identification of causal relationships between risk factors and diseases. Traditional observational inquiries often confront challenges associated with potential confounding variables and reverse causation. MR studies, conversely, leverage genetically correlated exposures to probe potential causal associations with outcomes, endeavoring to mitigate biases stemming from confounding or reverse causation.[4] Notably, this approach has been applied across 17 extensive GWAS summary datasets, elucidating causal networks encompassing 11 prevalent cardiovascular metabolic risk factors, four cardiovascular diseases (CAD, stroke, type 2 diabetes, AFib), AD, and asthma. This analytical avenue has unveiled compelling causal pathways.[5]

To date, few studies have systematically evaluated the potential causal relationships between specific immune-related diseases and AD using MR approaches. In this study, we selected six immune-related diseases—type 1 diabetes (T1DM), systemic lupus erythematosus (SLE), asthma, myasthenia gravis (MG), endometriosis, and idiopathic thrombocytopenic purpura (ITP)—based on three main criteria: (1) their established autoimmune or immune-mediated pathophysiology; (2) prior epidemiological or mechanistic links to neuroinflammation or neurodegeneration; and (3) the availability of large, high-quality GWAS datasets. These conditions represent diverse autoimmune phenotypes and collectively provide an opportunity to investigate potential shared genetic contributions to AD risk.

Methods

Study Design

We employed publicly accessible GWAS datasets for AD, T1DM, SLE, asthma, MG, endometriosis, and ITP to conduct MR analyses. The primary analysis utilized the inverse variance weighted (IVW) method, supplemented by secondary MR-Egger and weighted median approaches. Heterogeneity was assessed through Cochran's Q test, while pleiotropy was evaluated using MR-Egger intercept tests. Identification of potentially influential single nucleotide polymorphisms (SNPs) was carried out through leave-one-out analysis. Additionally, MR-PRESSO was employed to detect outliers for the evaluation of genetic causal associations between T1DM, SLE, asthma, MG, endometriosis, ITP, and AD risks, as well as for reverse validation. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University (Approval number: 2024-KYL-003). Vs were constructed using independent SNPs that were significantly associated with the exposure in GWASs. These SNPs were required to exhibit independence from the outcome and must uniquely influence the outcome solely through the exposure, while being unaffected by confounding factors. An F-statistic was employed to assess the strength of each genetic instrument, calculated using the formula $F = R^2 * (N-2)/1-R^2$, where R^2 is derived from the equation $R^2 = 2 * EAF * (1-EAF) \beta^2$. This statistic tests the robustness of each SNP as an instrumental variable, ensuring that it is a reliable predictor of the exposure and thus suitable for MR analysis.[2,6] In this equation, R^2 denotes the cumulative explained variance of the chosen IVs for T1DM, SLE, asthma, MG, endometriosis, and ITP. The term EAF refers to the effect allele frequency, while beta indicates the estimated effect of each SNP, and N denotes the sample size of the GWAS from which the data was derived. A threshold F-statistic exceeding 10 signifies robust predictive power of the IVs for AD. However, it is critical for the validity of the MR analysis that these IVs influence the outcome (AD) exclusively through the specified exposures, without affecting the outcome through any other pathways.[7] The detailed structure of the study design is illustrated in Figure 1.

Data Sources

In our study, the data were drawn from the EBI-a-GCST and iEU-b datasets of the GWAS database. These datasets primarily include populations of European descent. We examined six categories of immune-related diseases as potential exposure

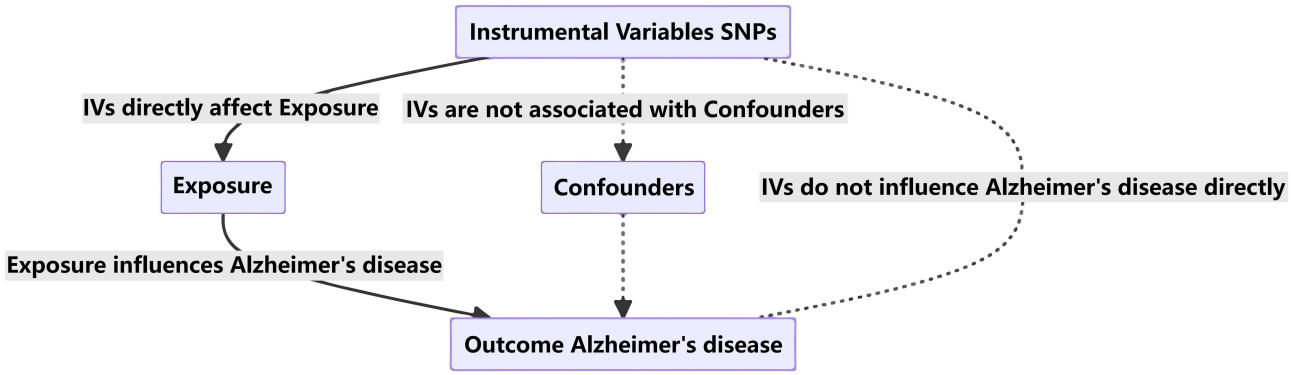

Figure 1 Flowchart illustrating the design of MR analysis for T1DM, SLE, asthma, MG, endometriosis, ITP and AD.
Abbreviations: AD, Alzheimer's disease; ITP, idiopathic thrombocytopenic purpura; MG, myasthenia gravis; MR, Mendelian Randomization; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes.

factors, encompassing T1DM (N =133, 251, SNP=12, 447, 116), SLE (N = 482, 911, SNP=24, 198, 877). The data were obtained from the comprehensive genome-wide association study conducted by Sakaue et al,[8] asthma (N = 484, 598, SNP=9, 587, 836), data derived from the GWAS performed by Dönertaş et al.[9] MG (N = 355, 142, SNP=19, 085, 239), endometriosis (N = 231, 771, SNP=24, 089, 752), and ITP (N = 489, 424, SNP=24, 199, 770), the data originate from the comprehensive GWAS study conducted by Sakaue et al.[8] We utilized summary statistics derived from previous large-scale sample GWAS databases for our analysis. The genetic associations related to AD were sourced from extensive GWAS datasets, encompassing AD (N = 488,285, SNP = 12,321,875). The data originates primarily from the UK Biobank. The origin data embodying this study is itemized in Table 1.

Genetic Instrumental Variables Selection

We utilized a genome-wide significance threshold of $P < 1\times10^{-5}$ for SNP selection in type 1 diabetes (T1DM), systemic lupus erythematosus (SLE), myasthenia gravis (MG), endometriosis, and idiopathic thrombocytopenic purpura (ITP). For asthma, a more stringent threshold of $P < 5\times10^{-8}$ was applied due to the larger number of genome-wide significant loci available. Linkage disequilibrium (LD) clumping was performed using data from the European 1000 Genomes Project, with an $r^2 < 0.001$ within a 10,000 kb window. SNPs correlated with potential confounders and those directly associated with Alzheimer's disease (AD) were excluded to obtain allele-corrected variants. Harmonization procedures were conducted to ensure effect allele alignment and account for LD structure.

Table 1 Details of the GWASs Included in the Mendelian Randomization

Consortium/Dataset	Phenotype	Sample Size	SNP (n)	Population
GWAS by Sakaue S et al (2021)[8]	Type 1 diabetes	133,251	12,447,116	East Asian
GWAS by Sakaue S et al (2021)[8]	SLE	482,911	24,198,877	European
GWAS by Dönertaş HM et al (2021)[9]	Asthma	484,598	9,587,836	European
GWAS by Sakaue S et al (2021)[8]	MG	355,142	19,085,239	European
GWAS by Sakaue S et al (2021)[8]	Endometriosis	231,771	24,089,752	European
GWAS by Sakaue S et al (2021)[8]	ITP	489,424	24,199,770	European
UK Biobank	AD	488,285	12,321,875	European

Abbreviations: AD, Alzheimer's disease; GWAS, genome-wide association studies; ITP, idiopathic thrombocytopenic purpura; MG, myasthenia gravis; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism.

https://doi.org/10.2147/JMDH.S533723

Statistical Method

IVW, weighted median (WM), and MR-Egger methods were used to evaluate the influence of six immune-related diseases (T1DM, SLE, asthma, MG, endometriosis, and ITP) on AD. IVW served as the primary MR method, aggregating Wald ratios of individual SNPs through a meta-analytic approach, while presuming a single route of exposure. Supplementary analyses employing the WM and MR-Egger methods scrutinized biases stemming from inappropriate IVs and horizontal pleiotropy.[10] The MR-Egger method's estimate may be affected by outlier genetic variances.[11] The WM approach exhibits minor bias, although it demonstrates reduced precision, particularly when the percentage of horizontal pleiotropy is < 50%.[12] Sensitivity analysis was used to assess non-homogeneity and address concerns related to horizontal pleiotropy. Cochran's Q test was used to evaluate the heterogeneity of the selected genetic instrumental variable effects. Moreover, MR-PRESSO analysis was employed to identify and mitigate the impact of outliers and horizontal pleiotropy.[12] Subsequently, MR-PRESSO was utilized to remove outliers and moderate horizontal pleiotropy.[13] The leave-one-out analysis scrutinizes the influence of excluding a single SNP on the overall results,[14] complemented by reverse validation (directionality test). We used the TwoSampleMR0.5.6 R software version 4.3.1. with statistical significance set at $P < 0.05$.

Results

Selection of Instrumental Variables

In exploring the potential causal relationships between immune-related diseases and AD, we identified SNPs as potential genetic regulators. Following meticulous screening procedures, we identified a total of 11,27,173,18,32, and 19 independent SNPs associated with T1DM, SLE, asthma, MG, endometriosis, and ITP, respectively.

Correlation Between Immune-Related Disease and AD

Utilizing the Mendelian Randomization (MR) methodology, we examined the genetic association between immune-related diseases and AD. Our investigation revealed diverse risk profiles across the six immune-related diseases and AD, as summarized in Table 2. Notably, the IVW analysis showed a statistically significant association for asthma (odds ratio [OR] = 0.994, 95% confidence interval [CI] 0.992–0.997, P = 4.332e-05). However, the effect size was very small and

Table 2 MR Analysis of Immune-Related Diseases and Alzheimer's Disease

Exposures	Methods	SNPs	Beta	Se	*P*	OR	95% CI
Type 1 diabetes	IVW	11	1.870e-05	8.705e-05	0.830	1.000	0.999–1.000
	MR-Egger	11	2.985e-06	1.456e-04	0.984	1.000	0.999–1.000
	Weighted median	11	−2.306e-05	9.935e-05	0.816	0.999	0.999–1.000
SLE	IVW	27	−2.137e-05	6.048e-05	0.724	1.000	0.999–1.000
	MR-Egger	27	5.852e-05	1.157e-05	0.618	1.000	0.999–1.000
	Weighted median	27	4.807e-05	9.145e-05	0.599	0.999	0.999–1.000
Asthma	IVW	173	−0.005	0.001	4.332e-05	0.994	0.992–0.997
	MR-Egger	173	−0.009	0.003	3.417e-03	0.991	0.985–0.997
	Weighted median	173	−0.007	0.002	1.225e-03	0.993	0.989–0.997
MG	IVW	18	3.959e-05	5.302e-05	0.455	1.000	0.999–1.000
	MR-Egger	18	−3.214e-05	1.008e-04	0.975	1.000	0.999–1.000
	Weighted median	18	2.589e-05	7.124e-05	0.702	1.000	0.999–1.000

(*Continued*)

Table 2 (Continued).

Exposures	Methods	SNPs	Beta	Se	*P*	OR	95% CI
Endometriosis	IVW	32	1.025e-04	1.788e-04	0.567	1.000	0.999–1.000
	MR-Egger	32	1.189e-05	4.518e-05	0.979	1.000	0.999–1.000
	Weighted median	32	7.573e-05	2.429e-04	0.754	1.000	0.999–1.000
ITP	IVW	19	−1.207e-04	8.352e-05	0.149	0.999	0.999–1.000
	MR-Egger	19	5.010e-05	1.176e-04	0.676	1.000	0.999–1.000
	Weighted median	19	−1.151e-04	1.104e-04	0.301	0.999	0.999–1.000

Abbreviations: CI, confidence interval; ITP, idiopathic thrombocytopenic purpura; IVW, inverse variance weighted; MG, myasthenia gravis; MR, Mendelian Randomization; OR, odds ratio; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism.

should be interpreted with caution, as it does not provide evidence for a causal or protective relationship between asthma and AD. Conversely, Table 2 illustrates that no statistically significant causal association was observed between T1DM, SLE, MG, endometriosis, ITP, and AD (T1DM: OR = 1.000, 95% CI 0.999–1.000, P = 0.830; SLE: OR = 1.000, 95% CI 0.999–1.000, P = 0.724; MG: OR = 1.000, 95% CI 0.999–1.000, P = 0.455; endometriosis: OR = 0.999, 95% CI 0.999–1.000, P = 0.567; ITP: OR = 1.000, 95% CI 0.999–1.000, P = 0.149). We conducted a comprehensive validation of our study findings through examinations for pleiotropy, heterogeneity, sensitivity analysis, and reverse validation. Our assessment of heterogeneity revealed notable distinctions (IVW Q = 162.056, P = 0.695) when examining the relationship between asthma and AD. Similarly, the MR-Egger intercept demonstrated no departure from zero (intercept = 2.690e-05, P = 0.192, Table 3), affirming the absence of pleiotropy. Reverse validation (P = 1e-10) corroborated the lack of a reverse causal association between AD and the Asthma disorders under investigation. Lastly, the leave-one-out analysis detected no causative SNPs, further reinforcing the robustness of our data (Table 3). The MR funnel plot exhibited consistent positioning of each SNP within the causal estimation. The forest plot generated from the MR analysis revealed the absence of influential SNPs. Alterations in individual SNPs had negligible effects on error bars, indicating that no single SNP significantly influenced the overall results. The scatter plots depict the effect sizes obtained through the MR method (Figures 2–7).

For T1DM, no discernible causal correlation was evident between T1DM and the risk of AD (OR=1.000, 95% CI: 0.999–1.000, P = 0.830). This finding aligns with the results obtained from MR-Egger (OR = 1.000, 95% CI: 0.999–1.000, P = 0.984) and WM analyses (OR = 0.999, 95% CI: 0.999–1.000, P = 0.816). Moreover, this MR analysis revealed no significant heterogeneity (Cochran's Q P = 0.229), horizontal pleiotropy (P for intercept = 0.893), or reverse

Table 3 Sensitivity Analysis of MR Analysis Results

Exposures	MR-Egger Intercept Test			Cochran's Q Heterogeneity Test			Directionality_Test
	Intercept	SE	*P* value	IVW Q	IVW Q df	IVW *P* value	*P* value
Type 1 diabetes	1.058e-05	7.620e-05	0.893	12.904	10	0.229	9.489e-41
SLE	−4.172e-05	5.153e-05	0.426	25.373	26	0.498	4.481e-55
Asthma	2.690e-05	2.052e-05	0.192	162.056	172	0.695	1e-10
MG	3.755e-05	7.455e-05	0.621	22.323	17	0.173	5.234e-32
Endometriosis	1.461e-05	6.670e-05	0.828	35.070	31	0.281	2.591e-92
ITP	−1.224e-04	6.325e-05	0.070	25.708	18	0.107	1.641e-28

Abbreviations: ITP, idiopathic thrombocytopenic purpura; IVW, inverse variance weighted; MG, myasthenia gravis; MR, Mendelian Randomization; SE, standard deviation; SLE, systemic lupus erythematosus.

https://doi.org/10.2147/JMDH.S533723

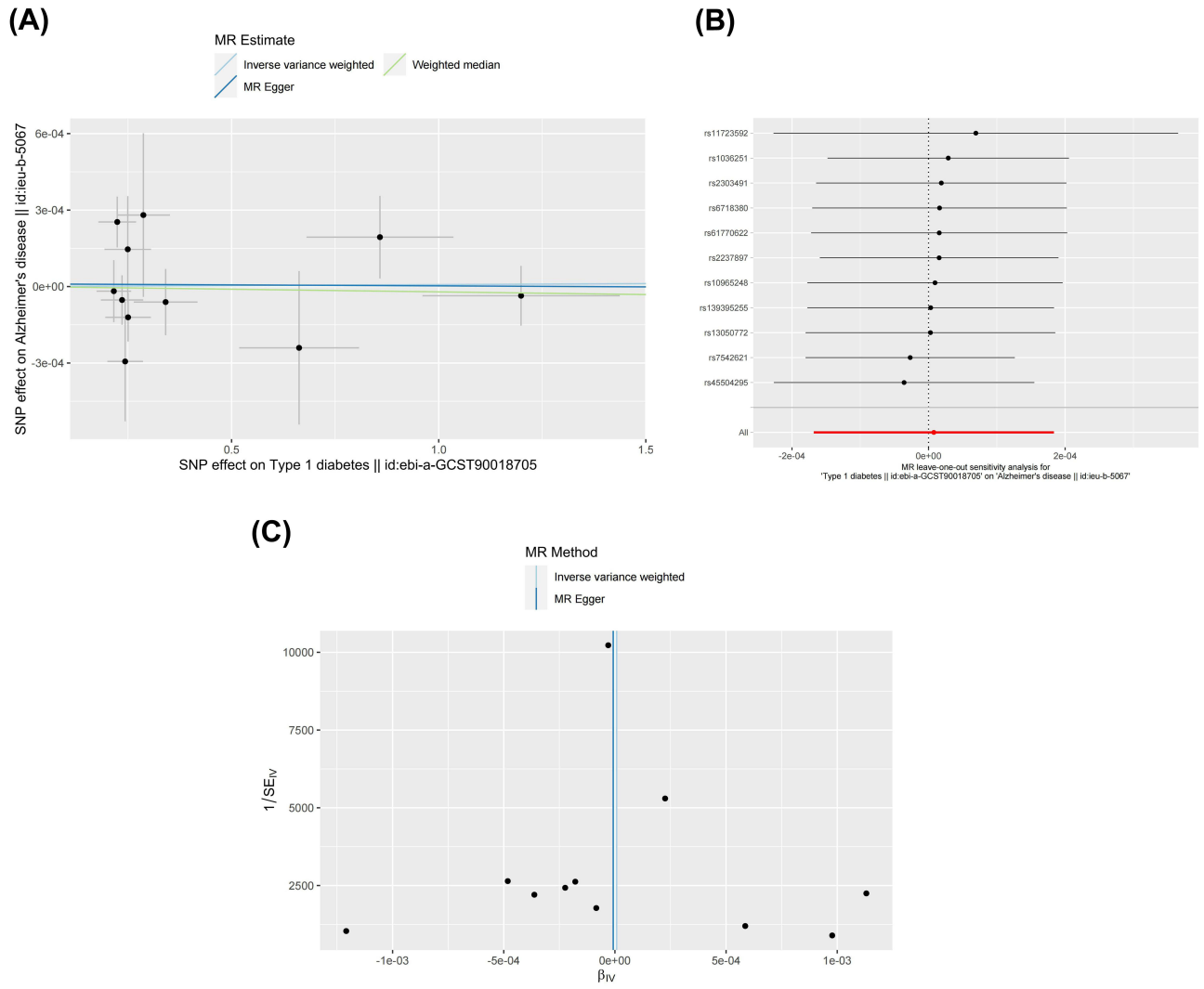

Figure 2 MR analysis of T1DM and AD. (**A**) SNP effect on T1DM; (**B**) MR leave-one-out sensitivity analysis. (**C**) MR-Egger.
Abbreviations: AD, Alzheimer's disease; MR, Mendelian Randomization; T1DM, type 1 diabetes.

causal relationship (directionality test P = 9.49e-41). The funnel plot showed a symmetrical SNP distribution, and the forest and leave-one-out plots suggested no influential SNPs. Scatter plots illustrated the estimated causal effects. In the SLE, our analysis did not reveal a statistically significant correlation between SLE and the risk of AD (OR = 1.000, 95% CI 0.999–1.000, P = 0.724). This finding mirrors the results obtained from both MR-Egger (OR = 1.000, 95% CI: 0.999–1.000, P = 0.618) and WM analyses (OR = 0.999, 95% CI: 0.999–1.000, P = 0.599) (Figure 3). Moreover, the MR analysis revealed no significant heterogeneity (Cochran's Q = 0.498), horizontal pleiotropy (P for intercept = 0.426), or reverse causality (directionality test P = 4.481e-55). The funnel plot illustrated an even distribution of each SNP in causal assessment, while the forest plot indicated the absence of influential SNPs influencing causal associations. Upon exclusion of individual SNPs, minor alterations in overall error bars were observed, indicating that no single SNP significantly impacted the results. Scatterplots visually depicted the effect sizes estimated through the MR method.

The genetic predisposition to asthma demonstrated a weak association with reduced risk of AD (OR = 0.994, 95% CI: 0.992–0.997, P = 4.332e-05), though the effect size was very small and its clinical relevance remains uncertain. This finding is consistent with results obtained from both MR-Egger (OR = 0.991, 95% CI: 0.985–0.997, P = 3.417e-03) and WM analyses (OR = 0.994, 95% CI: 0.991–0.998, P = 8.125e-04) (Figure 4). Heterogeneity (Cochran's Q P = 0.695), horizontal pleiotropy (P for intercept = 0.094), and reverse causal relationship (directionality test P = 1e-10) were not

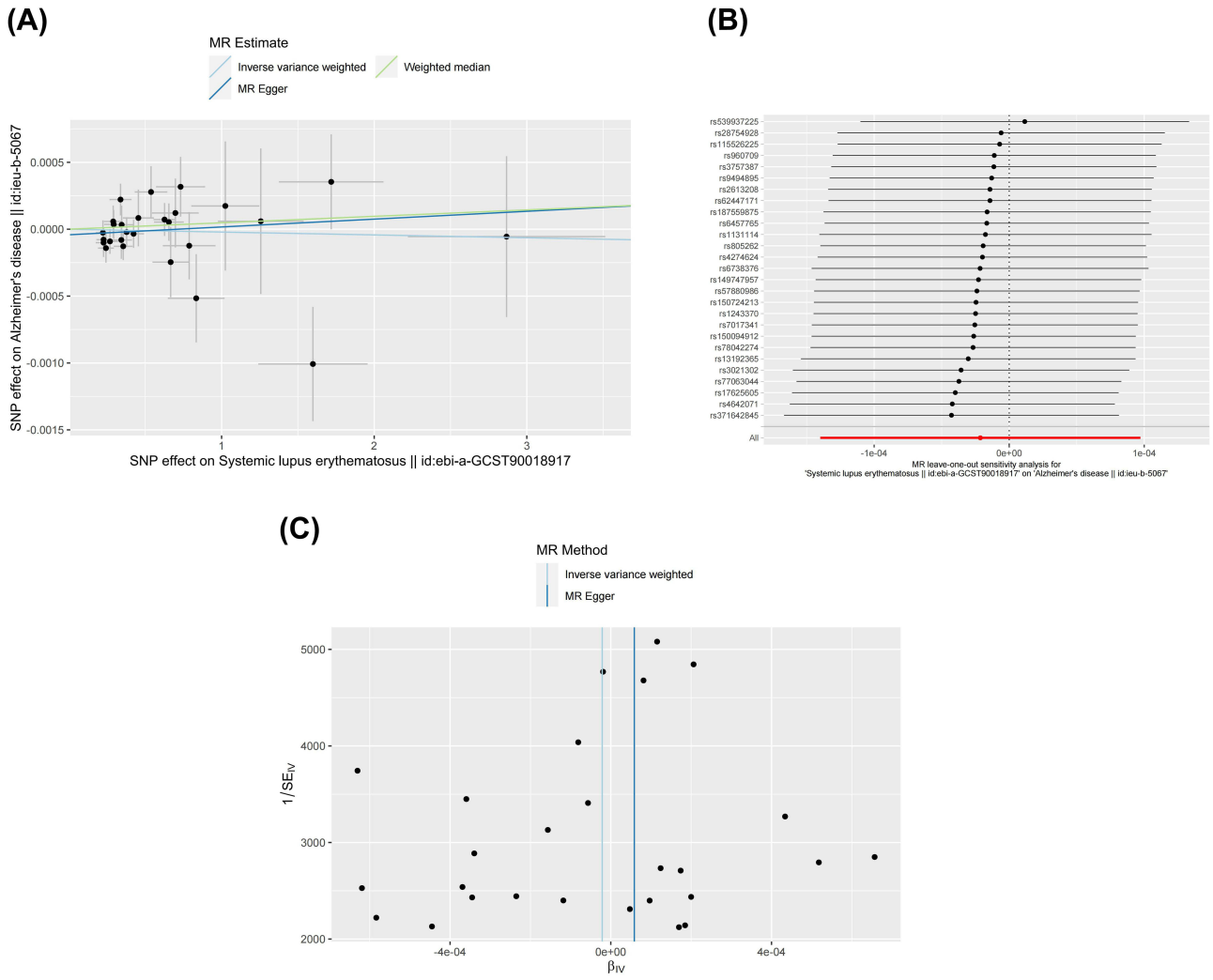

Figure 3 MR analysis of SLE and AD. (**A**) SNP effect on SLE; (**B**) MR leave-one-out sensitivity analysis; (**C**) MR-Egger.
Abbreviations: AD, Alzheimer's disease; MR, Mendelian Randomization; SLE, systemic lupus erythematosus.

observed in this MR analysis. The funnel plot showed a symmetrical SNP distribution, and the forest and leave-one-out plots suggested no influential SNPs. Scatter plots illustrated the estimated causal effects.

In the context of MG, there is no definitive evidence of a causal relationship between MG and the risk of AD (OR = 1.000, 95% CI 0.999–1.000, P = 0.455). This finding is consistent with the results obtained from both MR-Egger (OR = 1.000, 95% CI: 0.999–1.000, P = 0.975) and WM analyses (OR =1.000, 95% CI: 0.999–1.000, P = 0.702) (Figure 5). The MR analysis revealed no significant heterogeneity (Cochran's Q P = 0.173), no evidence of horizontal pleiotropy (P for intercept = 0.621), and no indication of reverse causality (directionality test P = 5.234e-32). The MR funnel plot showed a symmetrical distribution of SNP effects. The forest plot revealed no single SNP with a disproportionate influence on the causal estimate. After excluding individual SNPs, overall effect estimates remained stable The scatter plot displayed MR-estimated effect sizes using three different methods.

In the context of endometriosis, there is no definitive evidence of a causal relationship between endometriosis and the risk of AD (OR = 1.000, 95% CI 0.999–1.000, P = 0.567). This finding is consistent with the results obtained from both MR-Egger (OR = 1.000, 95% CI: 0.999–1.000, P = 0.979) and WM analyses (OR = 1.000, 95% CI: 0.999–1.000, P = 0.754) (Figure 6). The MR analysis revealed no significant heterogeneity (Cochran's Q P = 0.281), no evidence of horizontal pleiotropy (P for intercept = 0.828), and no indication of reverse causality (directionality test P = 2.591e-92). The MR funnel plot showed a symmetrical distribution of SNPs, indicating no directional bias. The forest plot revealed

https://doi.org/10.2147/JMDH.S533723

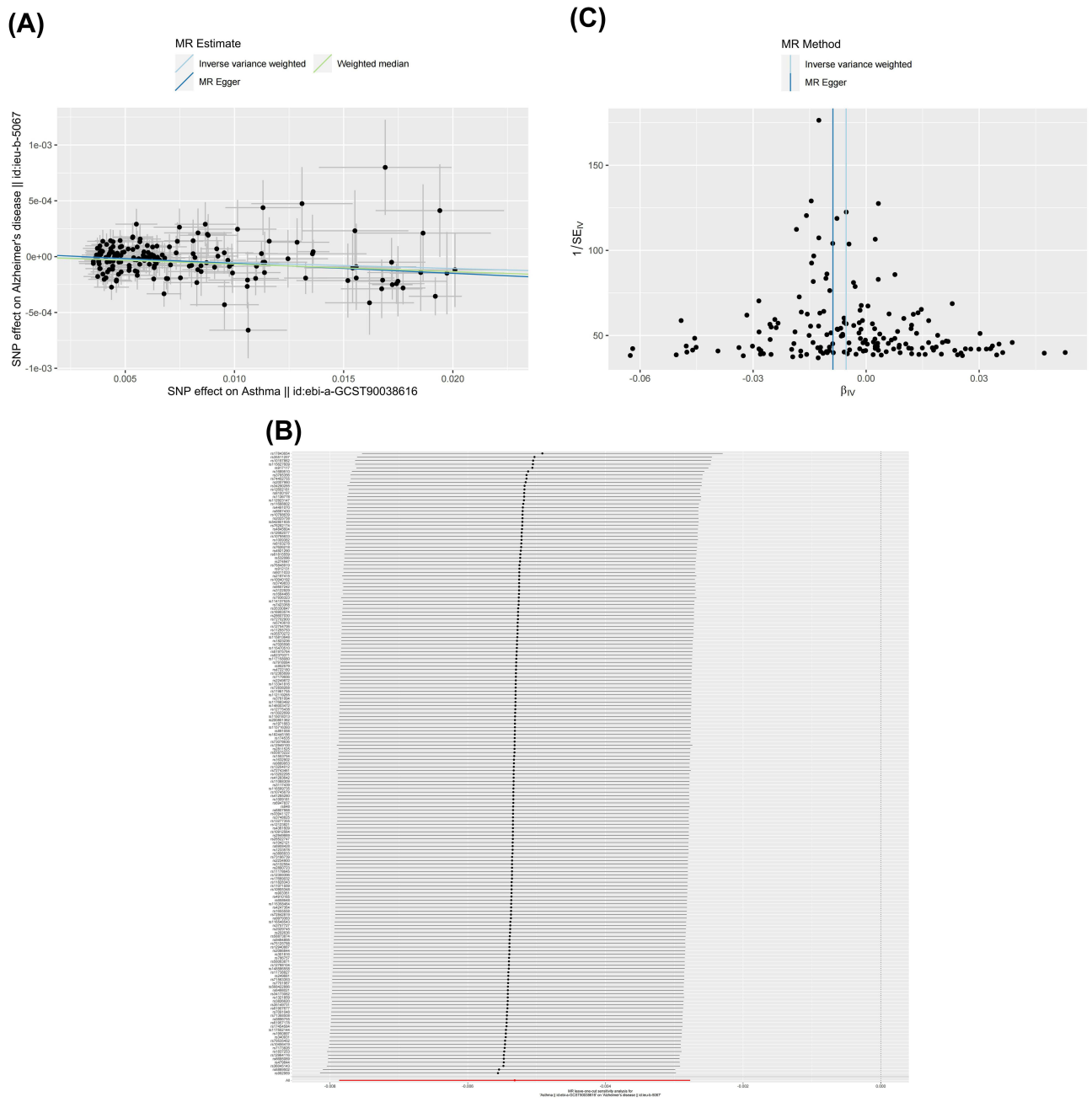

Figure 4 MR analysis of asthma and AD. (**A**) SNP effect on Asthma; (**B**) MR leave-one-out sensitivity analysis; (**C**) MR-Egger.
Abbreviations: AD, Alzheimer's disease; MR, Mendelian Randomization.

no single SNP had a strong influence on the causal estimate, as removing individual SNPs caused minimal changes in the overall error bars. The scatter plot displayed three lines representing effect size estimates from different MR methods.

In the context of ITP, a definitive causal relationship between ITP and the risk of AD is not evident (OR = 0.999, 95% CI 0.999–1.000, P = 0.149). This finding corresponds with the results obtained from both MR-Egger (OR = 1.000, 95% CI: 0.999–1.000, P = 0.676) and WM analyses (OR = 0.999, 95% CI: 0.999–1.000, P = 0.301) (Figure 7). The MR analysis demonstrated no significant heterogeneity (Cochran's Q P = 0.107), absence of horizontal pleiotropy (P for intercept = 0.070), or indication of reverse causality (directional test P = 1.641e-28). The funnel plot showed a symmetrical SNP distribution, and the forest and leave-one-out plots suggested no influential SNPs. Scatter plots illustrated the estimated causal effects.

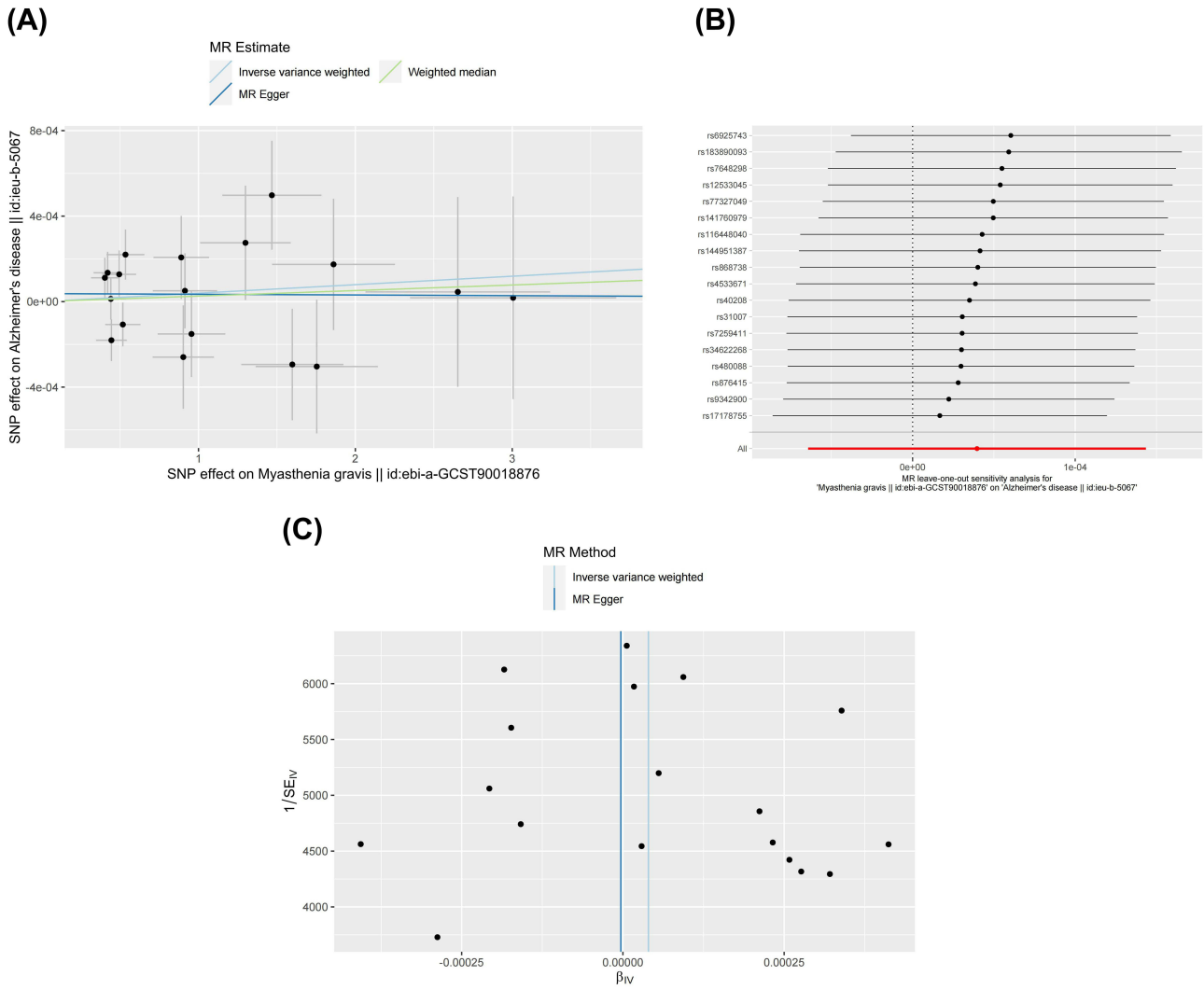

Figure 5 MR analysis of MG and AD. (**A**) SNP effect on MG; (**B**) MR leave-one-out sensitivity analysis; (**C**) MR-Egger.
Abbreviations: AD, Alzheimer's disease; MR, Mendelian Randomization; MG, myasthenia gravis.

Discussion

Although our two-sample MR study found a statistically significant association between asthma and AD, the effect size (OR = 0.996) was too small to imply meaningful clinical relevance. Simultaneously, we did not observe any causal relationships between T1DM, SLE, MG, endometriosis, ITP, and AD. Reverse validation analyses indicated that AD does not exhibit reverse causality with the aforementioned six immune-related diseases.

Recent prospective studies have demonstrated a notable association between asthma and heightened risks of all-cause dementia and AD.[15] Epidemiological studies underscore asthma as a potential risk factor for dementia and AD. Furthermore, to underscore the significance of asthma in cognitive impairment, imaging studies indicate alterations in cerebral white matter in individuals with asthma, akin to the neuroinflammatory changes observed in AD and other neurodegenerative conditions.[16]

Huang et al employed resting-state fMRI to investigate cerebral regions in individuals with asthma, identifying variations in uniformity values across the cerebellum, frontal lobe, temporal lobe, and occipital lobe.[17] Dynamic voxel-mirrored homotopic connectivity (dVMHC) analysis was employed to elucidate brain responses in individuals with asthma due to its precise assessment of neural activity magnitude, particularly relevant in mood-related disorders.[18] Their clinical study on asthma revealed heightened concentrations of dVMHC in the lingual gyrus and talus sulcus, alongside

https://doi.org/10.2147/JMDH.S533723

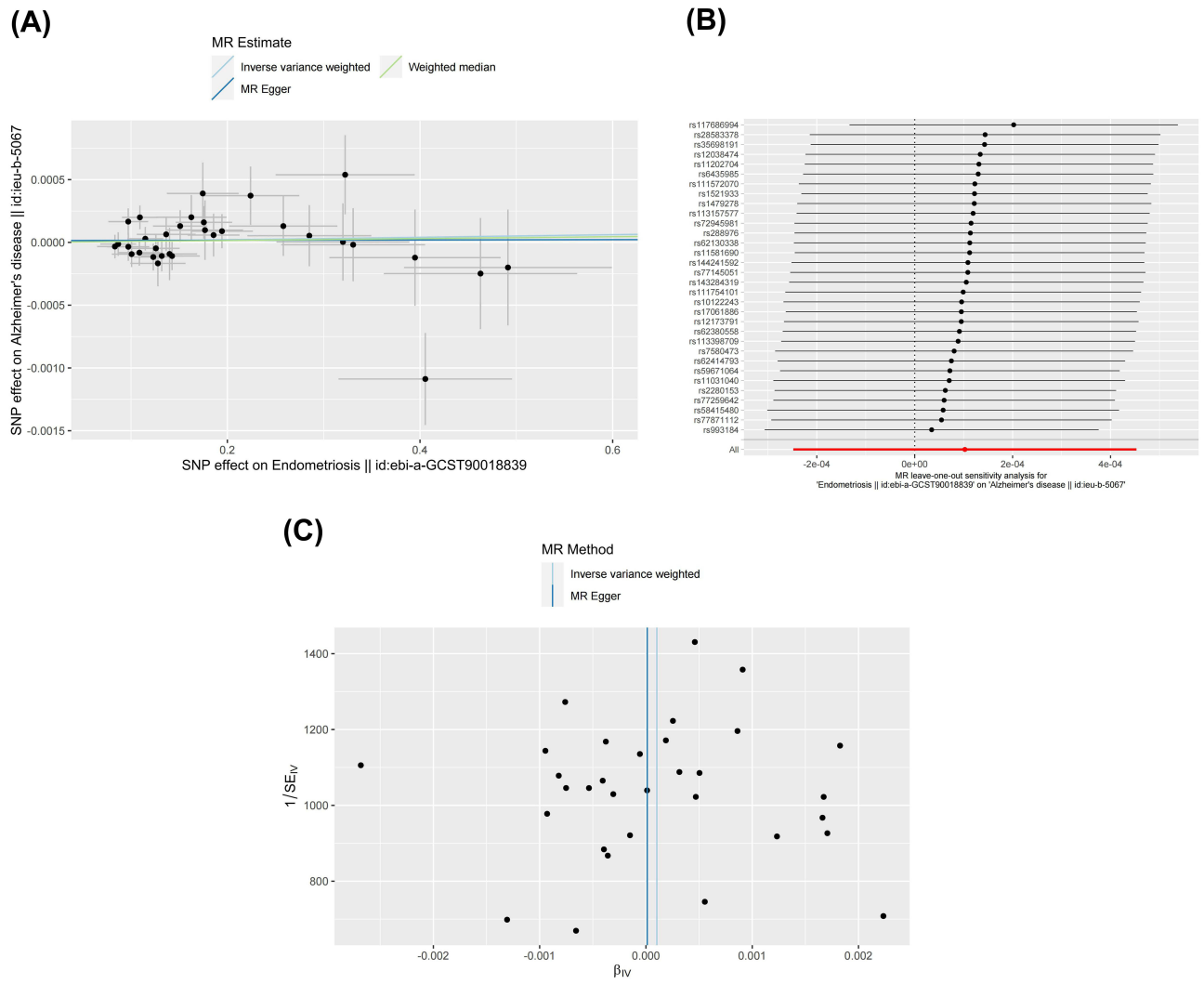

Figure 6 MR analysis of endometriosis and AD. (**A**) SNP effect on endometriosis; (**B**) MR leave-one-out sensitivity analysis; (**C**) MR-Egger.
Abbreviations: AD, Alzheimer's disease; MR, Mendelian Randomization.

distinctly reduced levels of dVMHC in the medial superior frontal gyrus, cingulate, and accessory motor regions. Within the context of asthma, a complex interplay between the lungs and brain ensues, mediated by neuroimmune mechanisms. Research indicates that asthma accelerates alterations in white matter and gray matter microstructure, akin to those observed with advanced aging and neuropathological changes, consequently hastening cognitive decline. The overall protective effect of asthma on AD incidence may be attributed to immune responses and inflammatory processes. Severe asthma, marked by chronic and intense inflammation, may result in prolonged exposure to elevated levels of inflammatory mediators. Chronic systemic inflammation is a recognized risk factor for various forms of dementia, including AD. Conversely, effective management of asthma may confer protective benefits and decelerate the advancement of cognitive symptoms.[19] There exists empirical evidence indicating that individuals with severe asthma exhibit a heightened risk of dementia compared to controls.[20] Although our study found a statistically significant association between asthma and AD ($P = 0.001$), the effect size was extremely small (OR = 0.996), indicating minimal clinical relevance. This highlights the distinction between statistical significance and clinical importance—especially in large-scale datasets where very small differences may reach significance without practical impact. Importantly, odds ratios do not directly reflect absolute risk, and an OR of 0.996 should not be interpreted as a 0.6% risk reduction. Given the limited effect size and inherent constraints of Mendelian randomization, these findings should be interpreted with caution. They are not sufficient to guide prevention or treatment decisions for asthma or AD. Instead, they serve as a basis for hypothesis generation. Future

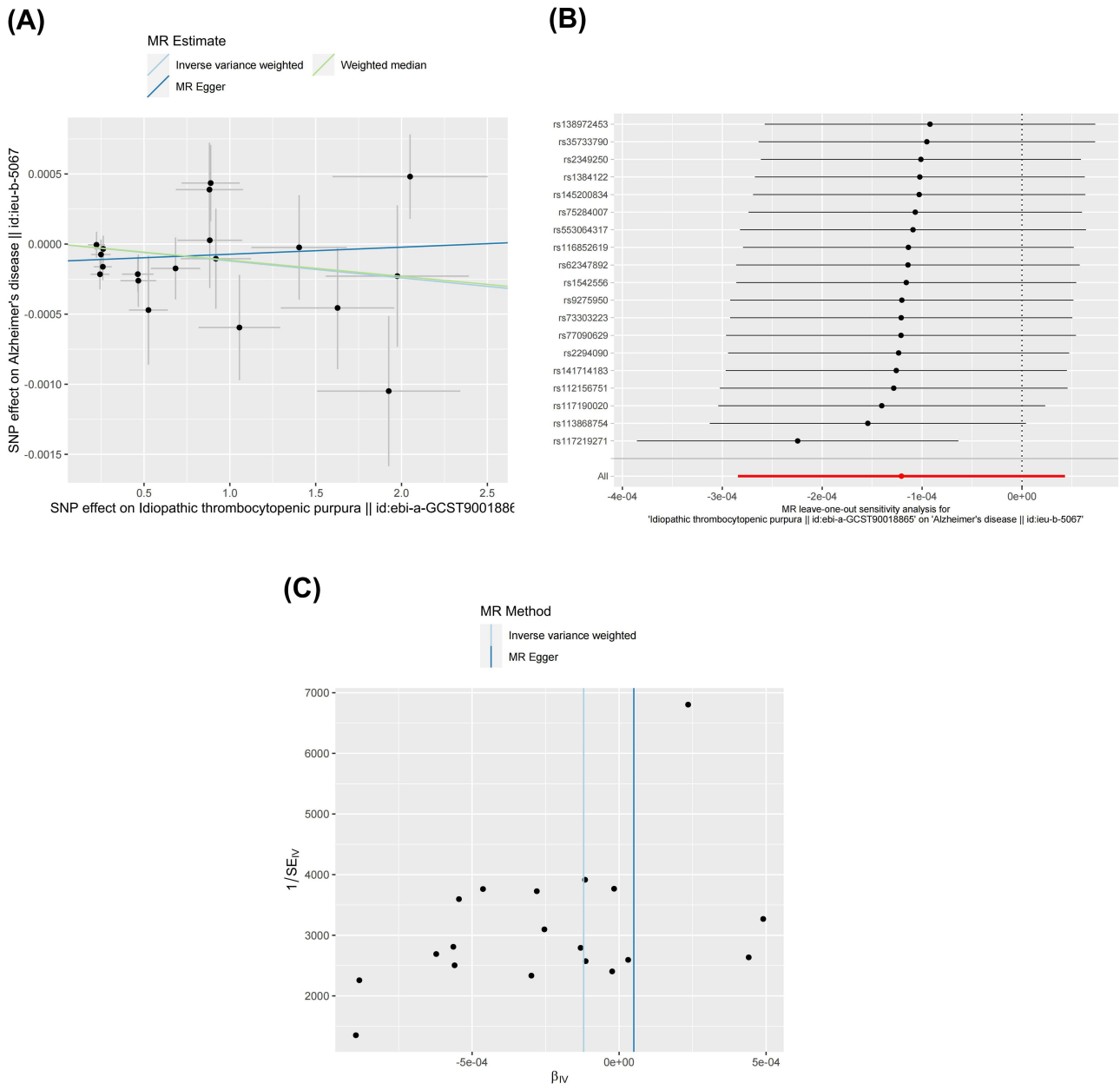

Figure 7 MR analysis of ITP and AD. (**A**) SNP effect on ITP; (**B**) MR leave-one-out sensitivity analysis; (**C**) MR-Egger.
Abbreviations: AD, Alzheimer's disease; ITP, idiopathic thrombocytopenic purpura; MR, Mendelian Randomization.

studies using individual-level data, with stratification by ancestry and asthma severity, may help clarify whether specific subgroups exhibit stronger associations and illuminate possible biological mechanisms underlying the asthma–AD link.

Insulin resistance has been proposed as a potential link between diabetes and Alzheimer's disease (AD).[21] Central-type insulin resistance is implicated as a component of the formal pathogenesis of AD.[22] Elevated blood glucose levels contribute to neuroinflammation and compromise the function of the blood-brain barrier (BBB).[23] In the present study, no association was observed between T1DM and genes related to AD, which aligns with findings from previous genetic investigations.[2,24,25] Despite the increased risk of AD and vascular dementia in individuals with diabetes, the burden of AD's characteristic pathologies, such as neurofibrillary tangles and amyloid plaques, remains consistent.[26] Following surgical procedures, patients with T1DM experience hyperglycemic episodes associated with reductions in cerebral gray matter density abnormalities.[27] The posterior cingulate cortex, hippocampi, and superior temporal gyrus play significant

https://doi.org/10.2147/JMDH.S533723

roles in memory and language processes.[28] Furthermore, growing evidence suggests that both the inflammatory response and BBB dysfunction in T1DM can lead to microvascular damage and cardiovascular pathology,[29] thereby contributing to the pathogenesis of AD.[28] Shared biomarkers between T1DM and AD indicate common pathological pathways and potential cognitive decline, independent of T1DM. Epigenetic changes driven by T1DM may regulate AD-related gene expression. Prospective studies on insulin resistance, glycemic control, and cognition in T1DM could elucidate their temporal relationship. Cohort studies have demonstrated a connection between SLE and an augmented risk of dementia.[30,31] A comprehensive analysis of extensive datasets corroborated an increased susceptibility to dementia among individuals with SLE.[32] Meta-analytical scrutiny further confirmed a heightened risk of dementia in patients with SLE.[33] The meta-analysis by Zhao, encompassing 11 analogous observational inquiries, underscored the adverse impact of SLE on cognitive function and the substantial elevation in dementia risk.[33] Our findings suggest the absence of a direct genetic correlation between SLE and dementia, in line with previous genetic investigations.[34] Observational inquiries imply a higher prevalence of mild cognitive impairment among individuals with SLE, potentially influenced by prolonged hormone usage and the administration of conventional synthetic anti-rheumatic medications.[35,36] Epidemiological studies have suggested a higher risk of dementia in systemic lupus erythematosus (SLE), but these associations remain difficult to interpret due to methodological heterogeneity and potential confounding. Although mild cognitive impairment has been observed in SLE patients, it may be influenced by medication effects or disease duration rather than direct genetic mechanisms.

Observational investigations have indicated a potential elevation in the prevalence of AD among patients with MG, highlighting a statistical correlation between the pathologies of these two diseases.[37] Additionally, empirical evidence suggests that individuals with MG experience more pronounced cognitive impairments compared to the general population.[38] Moreover, cognitive alterations may be linked to the prolonged use of glucocorticoids. Several studies support the notion that prolonged exposure to glucocorticoids induces cognitive deficits.[39,40] Animal model investigations have revealed that extended administration of glucocorticoid hormones may be adequate to incite or exacerbate the molecular features of AD thereby potentially hastening the progression of AD pathology.[35] However, our genetic analysis did not support a direct association between MG and AD. These results highlight the need for cautious interpretation of clinical observations, as confounding may play a role. Some shared pathophysiological mechanisms between endometriosis and AD may involve disruptions in germ cell homeostasis.[41] Endometriosis and AD have been linked to alterations in PGRMC1 (progesterone receptor membrane component protein) expression, epigenetic regulatory processes, or mechanisms involving gene silencing.[42] HP infection has been implicated in extragastric conditions such as ITP and AD. Notably, HP infection has been shown to increase the likelihood of developing both ITP and AD.[43] Endometriosis and idiopathic thrombocytopenic purpura (ITP) have been linked to systemic inflammation and immune dysregulation, which could theoretically influence neurodegenerative processes. Nonetheless, our MR analysis found no significant genetic association between endometriosis, ITP, and AD, suggesting that previously reported associations may reflect non-genetic factors or confounding.

Our study benefits from a large sample size and robust MR methodology, incorporating IVW, MR-Egger, and weighted median analyses, alongside comprehensive sensitivity tests to address potential pleiotropy and heterogeneity. However, several limitations should be acknowledged. First, the effect sizes observed were generally small. For example, while the association between asthma and AD reached statistical significance, the odds ratio (OR=0.996) indicates a negligible effect, unlikely to be of clinical relevance. This highlights a key distinction: statistical significance does not imply clinical significance, especially in large datasets.

Second, MR estimates rely on summary-level data from GWAS, which may not reflect individual-level variation or adequately adjust for environmental factors. Third, population stratification could bias results, particularly if ancestry is not well matched between exposure and outcome datasets. Fourth, rare variants and gene-gene interactions may be underrepresented in MR models, limiting their ability to capture the complexity of immune-related diseases.

Finally, while biological mechanisms linking immune activation and neurodegeneration are supported by prior studies, MR analysis cannot test these pathways directly. Future studies incorporating individual-level data and stratified analyses by ancestry, disease subtypes, or severity could provide deeper insight. Our findings suggest that immune-

related diseases studied here are not genetically linked to AD, though this does not exclude other types of associations. These results may inform future hypotheses exploring the neuroimmune interface in AD development.

Conclusion

The findings indicate a potential trend toward reduced AD risk among individuals with asthma; however, this association is modest and requires further validation. Simultaneously, no causal relationships were observed between T1DM, SLE, MG, endometriosis, and ITP and AD. Despite the weak evidence for a causal relationship, our findings suggest a potential inverse association between asthma and AD risk. While the observed effect size is modest and should be interpreted with caution, the possibility of underlying biological mechanisms warrants further investigation. These preliminary results may serve as a basis for future hypothesis-driven research, particularly to explore whether this association varies across specific subpopulations or is moderated by other factors. Clarifying the asthma–AD relationship could enhance our understanding of neuroinflammatory processes and contribute to the development of targeted preventive strategies. Future MR studies incorporating larger and more refined GWAS datasets, along with prospective multi-center cohorts evaluating cognitive function, biomarkers, and neuroimaging, are essential to validate and extend these findings in real-world settings.

Abbreviations

AD, Alzheimer's disease; MR, Mendelian randomization; T1DM, Type 1 diabetes; SLE, Systemic lupus erythematosus; MG, Myasthenia gravis; ITP, Idiopathic thrombocytopenic purpura; IVs, Instrumental Variables Selection; SNPs, Single nucleotide polymorphisms.

Data Sharing Statement

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author (Sheng-Liang Shi) on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University (Approval number:2024-KYL-003).

Funding

National Natural Science Foundation of China, Regional Science Foundation, research on the mechanism of PLA2G6 gene mutation in mediating mitophagy and chronic neuroinflammation in AD (32060189).

Disclosure

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.

References

1. Jia L, Du Y, Chu L, et al. COAST Group. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. *Lancet Public Health*. 2020;5(12):e661–e671. PMID: 33271079. doi:10.1016/S2468-2667(20)30185-7
2. Yeung CHC, Au Yeung SL, Schooling CM. Association of autoimmune diseases with Alzheimer's disease: a mendelian randomization study. *J Psychiatr Res*. 2022;155:550–558. PMID: 36198219. doi:10.1016/j.jpsychires.2022.09.052
3. Li X, Sundquist J, Zöller B, Sundquist K. Dementia and Alzheimer's disease risks in patients with autoimmune disorders. *Geriatr Gerontol Int*. 2018;18(9):1350–1355. PMID: 30044040. doi:10.1111/ggi.13488
4. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614–1621. PMID: 34698778. doi:10.1001/jama.2021.18236
5. Lin Z, Xue H, Pan W. Combining Mendelian randomization and network deconvolution for inference of causal networks with GWAS summary data. *PLoS Genet*. 2023;19(5):e1010762. PMID: 37200398; PMCID: PMC10231771. doi:10.1371/journal.pgen.1010762
6. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol*. 2011;40(3):740–752. PMID: 20813862; PMCID: PMC3147064. doi:10.1093/ije/dyq151

7. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525. PMID: 26050253; PMCID: PMC4469799. doi:10.1093/ije/dyv080
8. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. 2021;53 (10):1415–1424. PMID: 34594039. doi:10.1038/s41588-021-00931-x
9. Dönertaş HM, Fabian DK, Valenzuela MF, Partridge L, Thornton JM. Common genetic associations between age-related diseases. *Nat Aging*. 2021;1(4):400–412. PMID: 33959723; PMCID: PMC7610725. doi:10.1038/s43587-021-00051-5
10. Sanderson E. Multivariable Mendelian randomization and mediation. *Cold Spring Harb Perspect Med*. 2021;11(2):a038984. PMID: 32341063; PMCID: PMC7849347. doi:10.1101/cshperspect.a038984
11. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. PMID: 27061298; PMCID: PMC4849733. doi:10.1002/gepi.21965
12. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. Erratum in: Nat Genet. 2018;50(8):1196. PMID: 29686387; PMCID: PMC6083837. doi:10.1038/s41588-018-0099-7
13. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian Randomization analyses with multiple genetic variants. *Epidemiology*. 2017;28(1):30–42. PMID: 27749700; PMCID: PMC5133381. doi:10.1097/EDE.0000000000000559
14. Wu F, Huang Y, Hu J, Shao Z. Mendelian randomization study of inflammatory bowel disease and bone mineral density. *BMC Med*. 2020;18 (1):312. PMID: 33167994; PMCID: PMC7654011. doi:10.1186/s12916-020-01778-5
15. Joh HK, Kwon H, Son KY, et al. Allergic diseases and risk of incident dementia and Alzheimer's disease. *Ann Neurol*. 2023;93(2):384–397. PMID: 36093572. doi:10.1002/ana.26506
16. Busse W, Bartels C, Rosenkranz M. Brain-airway interactions in asthma. *Adv Exp Med Biol*. 2023;1426:185–214. PMID: 37464122. doi:10.1007/978-3-031-32259-4_9
17. Huang H, Li SY, Shi L, Huang X, Wang J. Altered spontaneous brain activity in patients with asthma: a resting-state functional MRI study using regional homogeneity analysis. *Neuroreport*. 2021;32(18):1403–1407. PMID: 34743166. doi:10.1097/WNR.0000000000001736
18. Liu F, Wang Y, Li M, et al. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Hum Brain Mapp*. 2017;38(2):957–973. PMID: 27726245; PMCID: PMC6866949. doi:10.1002/hbm.23430
19. Nair AK, Van Hulle CA, Bendlin BB, et al. Impact of asthma on the brain: evidence from diffusion MRI, CSF biomarkers and cognitive decline. *Brain Commun*. 2023;5(3):fcad180. PMID: 37377978; PMCID: PMC10292933. doi:10.1093/braincomms/fcad180
20. Nair AK, Van Hulle CA, Bendlin BB, et al. Asthma amplifies dementia risk: evidence from CSF biomarkers and cognitive decline. *Alzheimers Dement*. 2022;8(1):e12315. PMID: 35846157; PMCID: PMC9270636. doi:10.1002/trc2.12315
21. Jayaraj RL, Azimullah S, Beiram R. Diabetes as a risk factor for Alzheimer's disease in the Middle East and its shared pathological mediators. *Saudi J Biol Sci*. 2020;27(2):736–750. PMID: 32210695; PMCID: PMC6997863. doi:10.1016/j.sjbs.2019.12.028
22. Schubert M. The correlation between diabetes mellitus and neurodegenerative diseases. *Klin Monbl Augenheilkd*. 2023;240(2):130–135. English, German. PMID: 36626931. doi:10.1055/a-2009-9755
23. Lv YQ, Yuan L, Sun Y, et al. Long-term hyperglycemia aggravates α-synuclein aggregation and dopaminergic neuronal loss in a Parkinson's disease mouse model. *Transl Neurodegener*. 2022;11(1):14. PMID: 35255986; PMCID: PMC8900445. doi:10.1186/s40035-022-00288-z
24. Xue H, Zeng L, Liu S. Unraveling the link: exploring the causal relationship between diabetes, multiple sclerosis, migraine, and Alzheimer's disease through Mendelian randomization. *Front Neurosci*. 2023;17:1233601. PMID: 37694124; PMCID: PMC10488716. doi:10.3389/fnins.2023.1233601
25. Geng C, Meng K, Zhao B, Liu X, Tang Y. Causal relationships between type 1 diabetes mellitus and Alzheimer's disease and Parkinson's disease: a bidirectional two-sample Mendelian randomization study. *Eur J Med Res*. 2024;29(1):53. PMID: 38229119; PMCID: PMC10790511. doi:10.1186/s40001-023-01628-z
26. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol*. 2018;14 (10):591–604. PMID: 30022099; PMCID: PMC6397437. doi:10.1038/s41574-018-0048-7
27. Aye T, Mazaika PK, Mauras N, et al. Diabetes Research in Children Network (DirecNet) Study Group. Impact of early diabetic ketoacidosis on the developing brain. *Diabetes Care*. 2019;42(3):443–449. PMID: 30573652; PMCID: PMC6385695. doi:10.2337/dc18-1405
28. Shalimova A, Graff B, Gąsecki D, et al. Cognitive dysfunction in type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 2019;104(6):2239–2249. PMID: 30657922. doi:10.1210/jc.2018-01315
29. Zou X, Zhang L, Wang L, Wang S, Zeng Y. Exploring the causality of type 1 diabetes and stroke risk: a Mendelian randomization study and meta-analysis. *Mol Neurobiol*. 2023;60(12):6814–6825. PMID: 37493922. doi:10.1007/s12035-023-03517-2
30. Wotton CJ, Goldacre MJ. Associations between specific autoimmune diseases and subsequent dementia: retrospective record-linkage cohort study, UK. *J Epidemiol Community Health*. 2017;71(6):576–583. PMID: 28249989. doi:10.1136/jech-2016-207809
31. Lin YR, Chou LC, Chen HC, Liou TH, Huang SW, Lin HW. Increased risk of dementia in patients with systemic lupus erythematosus: a nationwide population-based cohort study. *Arthritis Care Res*. 2016;68(12):1774–1779. PMID: 27111329. doi:10.1002/acr.22914
32. Gendelman O, Tiosano S, Shoenfeld Y, et al. High proportions of dementia among SLE patients: a big data analysis. *Int J Geriatr Psychiatry*. 2018;33(3):531–536. PMID: 29114974. doi:10.1002/gps.4819
33. Zhao Z, Rocha NP, Salem H, Diniz BS, Teixeira AL. The association between systemic lupus erythematosus and dementia A meta-analysis. *Dement Neuropsychol*. 2018;12(2):143–151. PMID: 29988333; PMCID: PMC6022993. doi:10.1590/1980-57642018dn12-020006
34. Jin T, Huang W, Cao F, et al. Causal association between systemic lupus erythematosus and the risk of dementia: a Mendelian randomization study. *Front Immunol*. 2022;13:1063110. PMID: 36569847; PMCID: PMC9773372. doi:10.3389/fimmu.2022.1063110
35. Canet G, Zussy C, Hernandez C, et al. Chronic glucocorticoids consumption triggers and worsens experimental Alzheimer's disease-like pathology by detrimental immune modulations. *Neuroendocrinology*. 2022;112(10):982–997. PMID: 34923495. doi:10.1159/000521559
36. Chou MH, Wang JY, Lin CL, Chung WS. DMARD use is associated with a higher risk of dementia in patients with rheumatoid arthritis: a propensity score-matched case-control study. *Toxicol Appl Pharmacol*. 2017;334:217–222. PMID: 28927738. doi:10.1016/j.taap.2017.09.014
37. Morales-Casado MI, Diezma-Martín AM, Muñoz-Escudero F, et al. Association between myasthenia gravis and Alzheimer's disease. *Rev Neurol*. 2024;78(2):41–46. Spanish, English. PMID: 38223947. doi:10.33588/rn.7802.2023120

38. Ayres A, Winckler PB, Jacinto-Scudeiro LA, Rech RS, Jotz GP, Olchik MR. Cognitive performance in patients with Myasthenia Gravis: an association with glucocorticosteroid use and depression. *Dement Neuropsychol*. 2020;14(3):315–323. PMID: 32973985; PMCID: PMC7500821. doi:10.1590/1980-57642020dn14-030013
39. Brunner R, Schaefer D, Hess K, Parzer P, Resch F, Schwab S. Effect of corticosteroids on short-term and long-term memory. *Neurology*. 2005;64 (2):335–337. PMID: 15668434. doi:10.1212/01.WNL.0000149523.35039.4C
40. Coluccia D, Wolf OT, Kollias S, Roozendaal B, Forster A, de Quervain DJ. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. *J Neurosci*. 2008;28(13):3474–3478. PMID: 18367613; PMCID: PMC6670588. doi:10.1523/JNEUROSCI.4893-07.2008
41. Patel S. Disruption of aromatase homeostasis as the cause of a multiplicity of ailments: a comprehensive review. *J Steroid Biochem Mol Biol*. 2017;168:19–25. PMID: 28109841. doi:10.1016/j.jsbmb.2017.01.009
42. Pru JK. Pleiotropic actions of PGRMC proteins in cancer. *Endocrinology*. 2022;163(7):bqac078. PMID: 35595324; PMCID: PMC9186309. doi:10.1210/endocr/bqac078
43. Park AM, Tsunoda I. Helicobacter pylori infection in the stomach induces neuroinflammation: the potential roles of bacterial outer membrane vesicles in an animal model of Alzheimer's disease. *Inflamm Regen*. 2022;42(1):39. PMID: 36058998; PMCID: PMC9442937. doi:10.1186/s41232-022-00224-8