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ORIGINAL ARTICLE

Rheumatoid arthritis is a protective factor against Alzheimer's disease: a bidirectional two-sample Mendelian randomization study

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Abstract

Background Epidemiological evidence suggests that there is an association between rheumatoid arthritis (RA) and Alzheimer's disease (AD). However, the causal relationship between RA and AD remains unclear. Therefore, this study aimed to investigate the causal relationship between RA and AD.

Methods Using publicly available genome-wide association study datasets, bidirectional two-sample Mendelian randomization (TSMR) was performed using the inverse-variance weighted (IVW), weighted median, MR−Egger regression, simple mode, and weighted mode methods.

Results The results of MR for the causal effect of RA on AD (IVW, odds ratio [OR] = 0.959, 95% confidence interval [CI]: 0.941–0.978, $P = 2.752E-05$; weighted median, OR = 0.960, 95% CI: 0.937–0.984, $P = 0.001$) revealed a causal association between genetic susceptibility to RA and an increased risk of AD. The results of MR for the causal effect of AD on RA (IVW, OR = 0.978, 95% CI: 0.906–1.056, $P = 0.576$; weighted median, OR = 0.966, 95% CI: 0.894–1.043, $P = 0.382$) indicated that there was no causal association between genetic susceptibility to AD and an increased risk of RA.

Conclusions The results of this two-way two-sample Mendelian randomization analysis revealed a causal association between genetic susceptibility to RA and a reduced risk of AD but did not reveal a causal association between genetic susceptibility to AD and an increased or reduced risk of RA.

Keywords Rheumatoid arthritis · Alzheimer's disease · Bidirectional · Mendelian randomisation study · Causality

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with a prevalence of 0.5–1% (Smolen et al. 2016). RA affects multiple tissues and organs and causes chronic synovitis, which ultimately leads to joint destruction, chronic disability and shortened life expectancy (Song and Lin 2017). RA occurs due to an interaction between genetic susceptibility, environmental factors and immunological factors, with genetic factors accounting for 50–60% of the risk of RA (Van Der Woude and Van Der Helm-Van Mil 2018; Venetsanopoulou et al. 2022). The disease is characterized by a systemic inflammatory response affecting articular cartilage and bone (Smolen et al. 2016). Alzheimer's disease is a neurological disorder and neurodegenerative disease (Long and Holtzman 2019). It is the leading cause of cognitive impairment and dementia in people over 65 years of age worldwide (Atri 2019). AD is characterized by a long-term, progressive disease process that begins with pathophysiological changes in the brain years before any clinical manifestations are observed in affected individuals (Jack et al. 2013). It is estimated that by 2050, the global prevalence of AD will exceed 152 million people, and as the population ages, the annual cost of Alzheimer's disease could exceed $600 billion (Lane et al. 2018; Trzeciak et al. 2021). Its pathophysiological manifestations include accumulation of

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the toxic substance β-amyloid (amyloid-β, Aβ), formation of neuroprotective fibre tangles by overphosphorylated tau proteins, and neurodegeneration due to secretion of neurotoxins and inflammatory factors (Scheltens et al. 2016; Li et al. 2022; Xu et al. 2022).

Although the relationship between RA and AD is not fully understood, the pathogenesis of both diseases exhibits a chronic inflammatory response and an overreaction of the immune system (Xu et al. 2022). The dysregulation of multiple genetic and environmental factors involved in the inflammatory cascade is a common feature of both RA and AD (Ferraccioli et al. 2012). Existing studies have shown a positive correlation between AD and RA, and observational studies have demonstrated that the incidence of AD is much higher in the population of patients with RA than in healthy individuals (Lin et al. 2018). In another study, people with arthritic diseases, especially RA, had cognitive decline later in life (Wallin et al. 2012). However, some studies have also indicated that there is a negative correlation between RA and AD, that RA may be a protective factor against AD and that the incidence of AD is lower in people with RA (Breitner et al. 1994). These studies have used a variety of methods. However, most of them used small samples of patients with AD and RA; there is a lack of large-sample studies. While researchers have suggested that RA protects against AD, this may be due to the role of nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate, which are used to treat RA and may have influenced the observed results (McGeer et al. 1990; Zandi and Breitner 2001). However, in a 7-year randomized controlled trial (RCT), namely, the Alzheimer's Disease Anti-Inflammatory Prophylaxis Trial (AADPT), the results showed that treatment with naproxen and celecoxib did not reduce the incidence of AD. The results showed that naproxen and celecoxib treatment did not reduce the incidence of AD (Alzheimer's Disease Anti-inflammatory Prevention Trial Research Group 2013). In addition, the use of etanercept, a TNF-α inhibitor, did not cause significant changes in cognition, behaviour or overall functioning among AD patients (Butchart et al. 2015). These findings suggest that the role of anti-inflammatory drugs in the prevention of AD in patients with RA may have been exaggerated (Price 2003).

Elucidating the causal relationship between rheumatoid arthritis and Alzheimer's disease is, therefore, crucial for prevention and treatment, but it is unclear whether such a causal relationship exists. Due to various confounding factors in observational clinical studies, observations often do not provide convincing answers regarding the causal relationship between rheumatoid arthritis and Alzheimer's disease. Causal inferences from observational studies are susceptible to bias due to reverse causation and potential confounders (Evans and Smith 2015), which weakens our understanding of the causal relationship between rheumatoid arthritis and Alzheimer's disease. Randomized controlled trials (RCTs) are the gold standard for causal inference in epidemiological studies. Some randomized controlled trials are difficult to perform for reasons of medical ethics, subject selection and extrapolation of results. Mendelian randomization (MR) is a technique that uses genetic variation as an instrumental variable (IV) to assess whether observed associations between exposure factors and outcomes are consistent with causal effects (Bae and Lee 2018a). Genetic variation is not influenced by external environmental, social behaviour or other factors and is a stable exposure factor over time. MR can minimize bias by avoiding the influence of confounders and reverse causality on the effects of interest in observational studies. In this study, previously published data were collected and analysed using a bidirectional two-sample Mendelian randomization (TSMR) study to determine whether there was a bidirectional causal relationship between RA and AD.

Methods and materials

Ethics/consent statement

No ethical approval or informed consent was needed, as this study was based on previously published articles and public databases.

Data sources

Relevant genome-wide association study (GWAS) datasets were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk). The GWAS dataset for RA was derived from a GWAS that included 3636 cases and 15,554 controls of European ancestry (Okada et al. 2014). The GWAS dataset for AD was derived from another GWAS that included 75,024 cases and 987,844 controls of European ancestry (Schwartzentruber et al. 2021) (Supplementary Table 1).

Screening of IVs

Single-nucleotide polymorphisms (SNPs) were used as IVs, and a P value $< 5.0 \times 10–8$ was set as a threshold. To avoid linkage disequilibrium (LD) bias, LD with significant *SNPs* associated with exposure factors must meet the following conditions: $r^2 < 0.001$ and a genetic distance of 10,000 kb. SNPs that are significantly associated with exposure factors were extracted from the GWAS dataset of outcome variables, and the resulting IVs were examined to extract the following information: the effect allele, allele effect sizes (beta), standard error, and p value. The F-statistic was used to test the strength of each IV and was calculated using the following formula: $F = \mathrm{R2(N-2)/(1-R2)}$, where R^2 is the

proportion of the exposure factor variation explained by each IV (Chen et al. 2022), and N is the sample size of the exposure dataset. When $F > 10$, there is no weak IV bias (Burgess and Thompson 2011).

Research design

To better estimate the causal effect, three key assumptions should be met when SNPs are used as IVs in the TSMR analysis (Burgess et al. 2013): (1) IVs must be closely related to exposure factors; (2) IVs are independent of confounding factors; and (3) IVs can only influence the outcome through exposure and not through other pathways.

Statistical analysis

Summary statistics for the exposure and outcome datasets were harmonized such that the effect of SNPs on exposure and the effect of SNPs on outcome corresponded to the same alleles. TSMR analyses using inverse-variance weighted (IVW), weighted median, MR−Egger regression, simple mode, and weighted mode methods were performed to infer causal associations, and weighted mode methods were performed to infer causal associations. We used IVW as the primary method for MR. When each genetic variation met the IVW hypothesis, the IVW method combined with the IVW method was used. hypothesis, the IVW method combined the Wald ratio estimates of the causal effects of different SNPs and provided a consistent estimate of the causal effect of exposure on the outcome effect of exposure on the outcome (Bae and Lee 2018b). The results of the IVW method were most reliable when there was no horizontal pleiotropy of the IVs (Huang et al. 2021). When at least half of the SNPs are effective IVs, the weighted median can provide a consistent estimate of the causal effect (Bowden et al. 2016). MR−Egger regression is used to confirm whether horizontal pleiotropy of IVs exists, and its intercept represents the effect estimate of horizontal pleiotropy (Burgess and Thompson 2017). When the IVs have horizontal pleiotropy, MR−Egger regression can still obtain an unbiased estimation of causal association. The weighted median method improves the accuracy of the results compared to the IV method and improves the accuracy of the results compared to the MR−Egger method (Xiang et al. 2021). Simple mode and weighted mode were used for complementary analyses (Hua et al. 2022). The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test was used to detect and correct horizontal pleiotropy by removing the outliers (Lin et al. 2022). Statistical analysis was performed using *R* (version 4.3.1) and R packages (TwoSampleMR and MR-PRESSO). The test level α was 0.05 ($P < 0.05$), and the difference was statistically significant.

Results

Causal effects of RA on AD

SNPs

Basic information RA was the exposure factor, and AD was the outcome variable. In total, 56 SNPs were screened and identified as IVs, with F values greater than 10. (Supplementary Table 2). The intercept of the MR−Egger regression can be used as an indicator to test whether horizontal pleiotropy of the IVs influences the results of TSMR analysis. The intercept was close to 0 (Egger intercept = 0.004, $P = 0.074$) (Table 1), indicating that there was no horizontal pleiotropy of the *IVs*, and it was unlikely to influence the results of the TSMR analysis (Fig. 1b).

Two-sample Mendelian randomization analysis

The results of MR supported a causal association between genetic susceptibility to RA and reduced risk of AD, i.e., RA may be a protective factor against AD. In the absence of multivariate validity at the level of IVs, IVW was used as the primary method for estimating the causal association between genetic susceptibility to RA and reduced risk of AD (IVW results: OR = 0.959, 95% CI: 0.941–0.978, $P = 2.752E-05$). The results of other methods were as follows: MR−Egger, OR = 0.940, 95% CI: 0.914–0.967, $P = 0.0001$; weighted median, OR = 0.960, 95% CI: 0.937–0.984, P = 0.001; simple mode, OR = 0.964, 95% CI: 0.913–1.017, $P = 0.191$; weighted mode, OR = 0.951, 95% CI: 0.932–0.971, $P = 1.338E-05$ (Table 2 and Fig. 1a and b).

Table 1 Heterogeneity test and horizontal pleiotropy test

Exposure	Outcome	Heterogeneity test (MR−Egger)			Heterogeneity test (IVW)			Horizontal pleiotropy test (MR−Egger)	
		Cochran's Q	Q_df	*P*	Cochran's Q	Q_df	*P*	Intercept	*P*
RA	AD	83.52	54	0.006	88.64	55	0.002	0.004	0.074
AD	RA	63.76	30	0.0003	64.02	31	0.0004	− 0.003	0.729

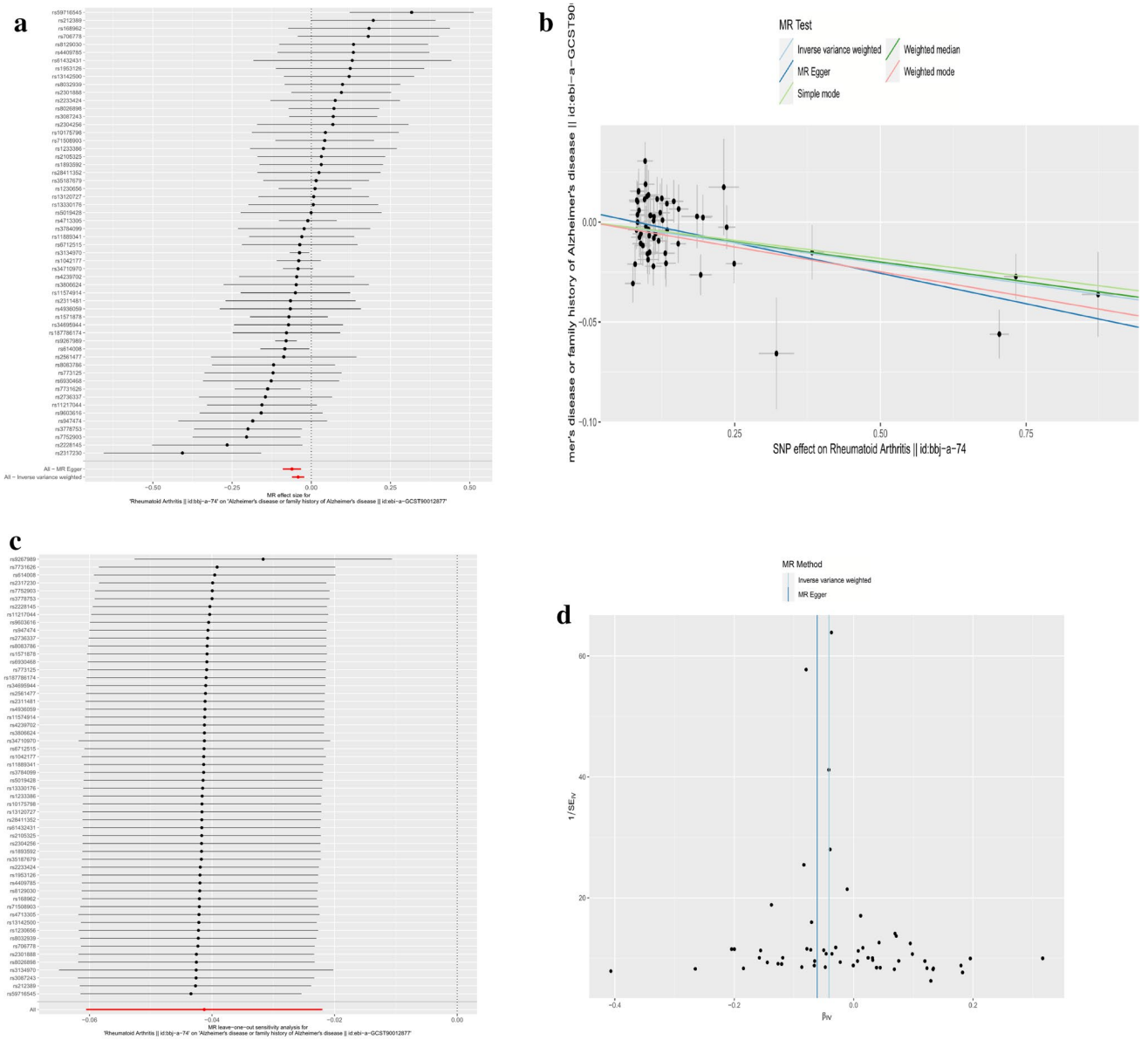

Fig. 1 Forest plot (**a**), scatter plot (**b**), sensitivity analysis (**c**), and funnel plot (**d**) of the effect of RA on AD

Table 2 Mendelian randomization analysis of causal association between RA and the risk of AD

Methods	SNPs	Beta	SE	OR (95% CI)	*P*
MR−Egger	56	− 0.061	0.014	0.940 (0.914, 0.967)	0.0001
Weighted median	56	− 0.039	0.012	0.960 (0.937, 0.984)	0.001
IVW	56	− 0.041	0.009	0.959 (0.941, 0.978)	2.752E-05
Simple mode	56	− 0.036	0.027	0.964 (0.913, 1.017)	0.191
Weighted mode	56	− 0.049	0.010	0.951 (0.932, 0.971)	1.338E-05

Heterogeneity test and sensitivity analysis

Heterogeneity between IVs was detected using IVW and MR−Egger regression analysis. Heterogeneity was quantified using Cochran's Q test, and $P < 0.05$ indicated significant heterogeneity. If heterogeneity existed between IVs, causal effects were estimated using a random effects IVW model. MR−Egger regression (Cochran's $Q = 83.52$,

$P = 0.006$) and IVW (Cochran's $Q = 88.64$, $P = 0.002$) (Table 1 and Fig. 1d) showed heterogeneity among IVs, and therefore, causality was estimated using a random effects IVW model ($P = 2.752644e\text{-}05$). The causal effect of TSMR was estimated using the MR-PRESSO test to remove outlier SNPs (rs5019428) and correct for outliers ($P = 0.00003$) (Supplementary Table 3).

Sensitivity analysis was performed by removing SNPs one at a time, and the causal effects of the remaining SNPs were compared with the results of the TSMR analysis of all SNPs to determine whether the causal associations were due to a single IV. The sensitivity analysis indicated that the results of the TSMR analysis were robust (Fig. 1c).

Reverse TSMR analysis

In reverse TSMR, MI was the exposure factor, and RA was the outcome variable. In total, 32 SNPs were screened and identified as IVs, with F values greater than 10. The proportion of variance explained by these IVs was 2.6% for MI (Supplementary Table 4). The horizontal pleiotropy test (Egger intercept = − 0.003, $P = 0.729$) (Table 1) indicated that there was no horizontal pleiotropy for the IVs. The MR results did not support a causal association between the IVs and genetic susceptibility to AD or an increased risk of RA (IVW, OR = 0.978, 95% CI: 0.906–1.056, $P = 0.576$). The results of other methods were as follows: MR−Egger, OR = 0.980, 95% CI: 0.870–1.144, $P = 0.980$; weighted median, OR = 0.966, 95% CI: 0.894–1.043, $P = 0.094$. − 1.043, $P = 0.382$; simple mode, OR = 0.892, 95% CI: 0.739–1.077, $P = 0.245$; and weighted mode, OR = 962, 95% CI: 0.889–1.040, $P = 0.340$ (Table 3 and Fig. 2a and b). Among the heterogeneity test results, MR−Egger regression showed relatively small heterogeneity (Cochran's Q = 63.76, $P = 0.0003$), IVW regression (Cochran's $Q = 15.18$, $P = 0.056$) showed heterogeneity between IVs (Table 1 and Fig. 2d), and the random effects IVW model was used to estimate the causal relationship ($P = 2.752644e\text{-}05$). The MR-PRESSO test was used to remove the abnormal SNP (rs1859788 rs1878036), and the causal effect of TSMR was estimated after the outliers were corrected ($P = 0.448$) (Supplementary Table 3). Sensitivity analysis was performed using the leave-one-out method, and the results of TSMR analysis were found to be reliable (Fig. 2c).

Table 3 Mendelian randomization analysis of the causal association between AD and the risk of RA

Methods	SNPs	Beta	SE	OR (95% CI)	*P*
MR−Egger	32	− 0.001	0.007	0.998 (0.870, 1.144)	0.980
Weighted median	32	− 0.034	0.039	0.966 (0.894, 1.043)	0.382
IVW	32	− 0.021	0.039	0.978 (0.906, 1.056)	0.576
Simple mode	32	− 0.113	0.095	0.892 (0.739, 1.077)	0.096
Weighted mode	32	− 0.038	0.340	0.962 (0.889, 1.040)	0.040

Discussion

This study analyzed previously published GWAS datasets using a bidirectional TSMR approach to determine whether there is a bidirectional causal association between RA and AD in a European population. Our results indicate that there is a causal association between genetic susceptibility to RA and a reduced risk of AD (IVW, OR = 0.959, 95% CI: 0.941–0.978, $P = 2.752E\text{-}05$). However, our results did not support a causal association between genetic susceptibility to AD and an increased or decreased risk of RA (IVW, OR = 0.978, 95% CI: 0.906–1.056, $P = 0.576$). Sensitivity analyses indicated that the results of MR were robust and reliable.

Paradoxically, previous observational studies have suggested that RA, an inflammatory disease in its own right, is also associated with risk factors for AD and is often considered a negative risk factor for the development of AD. Recently, a large-sample observational study based on Clinical Practice Research Datalink (CPRD) and a two-sample Mendelian study were performed to investigate the relationship between inflammatory diseases and AD (Huang et al. 2023). The results indicated that the relationship between inflammatory diseases and AD was not as strong as in previous studies (Chou et al. 2016; Yasuoka et al. 2023). The results showed that, consistent with previous observational studies, inflammatory diseases are associated with a higher risk of AD. However, these associations were not supported by MR analyses, and there was no causal relationship, suggesting that the association between inflammatory diseases and AD in observational studies is affected by confounding factors. However, the results of our two-way two-sample Mendelian randomization study suggest that RA may be a protective factor against AD, while the results of the reverse Mendelian randomization showed that AD does not increase the risk of developing RA and that there is no causal relationship. Our results are in agreement with the MR results of Huang et al. (2023) and Policicchio et al. (2017), probably because a different GWAS AD dataset was selected. However, the results of this study are consistent with the previous results of a simple two-sample Mendelian randomization by Bae and Lee (2019). In contrast, we conducted a more comprehensive two-way two-sample Mendelian randomization analysis while applying a newer and larger GWAS database for the study, thus making our results more convincing.

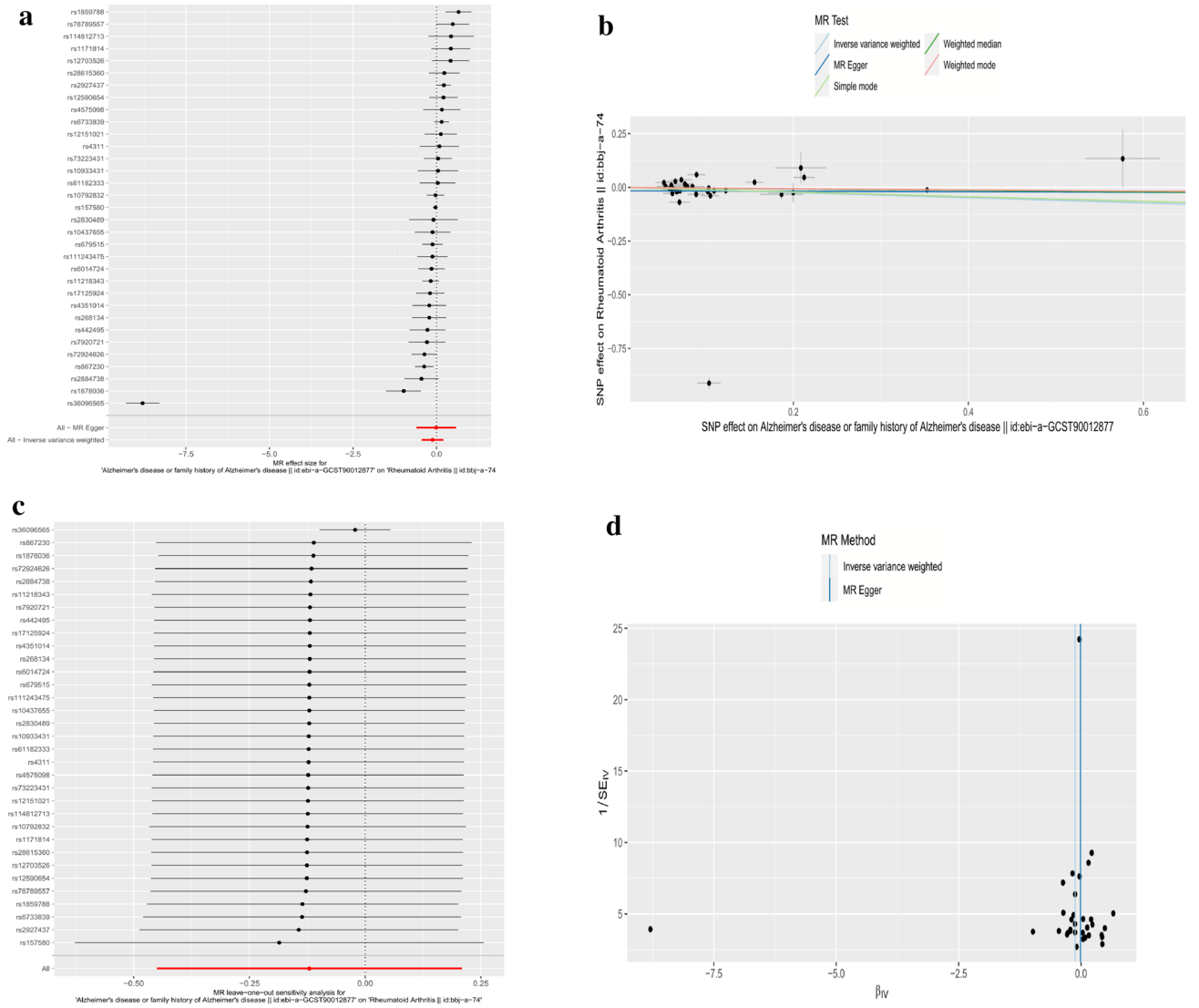

Fig. 2 Forest plot (**a**), scatter plot (**b**), sensitivity analysis (**c**), and funnel plot (**d**) of the effect of AD on RA

There may be two mechanisms underlying the role of RA as a protective factor against AD. First, this causal effect may be due to the deregulation of cellular and molecular regulatory mechanisms intrinsic to the inflammatory cascade response (Ferraccioli et al. 2012). In an animal study, researchers investigated the effect of RA on *β*-amyloid (Aβ) disposition in collagen-induced arthritis (CIA) rats and found that microglial hyperplasia and astrocyte hyperplasia were both significantly increased in the brains of CIA rats compared to controls and that these glial cells have a significant effect on neuronal responses (Lai et al. 2021). These glial cells are essential for neuronal and brain health (Castellani and Schwartz 2020; Linnerbauer et al. 2020; Vainchtein and Molofsky 2020). Although the effects of glial cells on Aβ and tau accumulation and clearance are unknown, researchers realize that these are important interactions with potential for therapeutic intervention (Fakhoury 2018; Long and Holtzman 2019). McAlpine et al. (2021) found in mice and humans that astrocyte-derived interleukin-3 (*IL-3*) reprogrammed microglia to ameliorate Alzheimer's disease pathology. Upon recognition of *Aβ* deposition, microglia increase *IL-3R* (the specific receptor for *IL-3*), making them responsive to *IL-3*. Astrocytes constitutively produce *IL-3*, which triggers transcriptional, morphological and functional reprogramming of microglia, endowing them with an acute immune response program, enhanced motility and the ability to aggregate and clear Aβ and tau aggregates (McAlpine et al. 2021), and astrocytes themselves can take up and degrade Aβ. These changes limit the pathology and cognitive decline in Alzheimer's disease (McAlpine et al. 2021). In addition, some ADs indicate the potential role of microglia in synaptic remodelling (Wake et al. 2009). Microglia perceive neuronal activity, thereby

regulating synaptic plasticity and learning and memory mechanisms. Therefore, they are the main components that determine cognitive function (Morris et al. 2013; Sipe et al. 2016). It has also been found that changes in the expression of microglia-related genes may promote late-onset AD (LOAD) (Hansen et al. 2018).

Second, it has been shown that granulocyte macrophage colony stimulating factor (GM-CSF) is produced in large quantities in RA synovitis and that GM-CSF signalling plays an important role in structural plasticity associated with learning and memory and protects neurons in traumatic brain injury (TBI) mice (Schäbitz et al. 2008; Krieger et al. 2012; Shultz et al. 2014). Additionally, GM-CSF appears to have trophic effects on neuronal cells, such as enhancing brain functions, including short-term memory skills (Boyd et al. 2010; Kiyota et al. 2018). On one hand, GM-CSF induces the differentiation of myeloid cells into specialized cells such as microglia, which transform them into appropriate amyloid scavenging factories that remove amyloid deposits. Amyloid accumulation plays a special role in the pathogenesis of Alzheimer's disease (AD) (Boyd et al. 2010). On the other hand, GM-CSF promotes the recruitment of mononuclear macrophages from the peripheral blood into the brain and affects the clearance of Aβ plaques (Boyd et al. 2010; Darlington et al. 2015; Fu et al. 2016). In addition, GM-CSF attenuates the proinflammatory microglial phenotype in AD (Zuroff et al. 2017).

MR uses genetic variants to estimate the health effects of phenotypes affected by those genetic variants (Riaz et al. 2018). This is a relatively novel epidemiological approach that uses genetic variation to infer causal relationships between exposure factors and outcome variables. MR provides a method of investigating associations that is free of the typical biases inherent in observational epidemiological studies (e.g., reverse causation and potential confounders). Our results differ from the MR results of Cai et al. (2018), possibly because a different GWAS dataset was selected. Therefore, future studies with newer, larger GWAS datasets are needed.

This study has some limitations. First, the MR results are based on a European population, and extrapolation of the results is limited. Further studies are needed to confirm whether causality exists in other populations. Second, the SNPs used for analysis may be correlated with other traits due to genetic polymorphisms, thus leading to confounding bias that could affect causal inference. Third, the strength of IV depends on the sample size of the GWAS, and a larger GWAS is needed to identify more genetic variation in MR.

Conclusions

In conclusion, bidirectional TSMR analyses support a causal association of genetic susceptibility to RA as a protective factor for AD but do not support a causal association between genetic susceptibility to AD and increased or decreased risk of RA. However, due to the limitations of the study, further research is necessary.

Author contributions GSL, YZY, GRM and PFL: conceptualization, investigation, data curation, writing—original draft. ZZZ, FKZ, QHC and ARZ: conceptualization, investigation, writing—original draft. HF, XY: investigation, writing—review and editing. HZG: conceptualization, writing—review and editing. All authors contributed to the article and approved the submitted version.

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Data availability The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Code availability The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval No ethical approval or informed consent was needed, as this study was based on previously published articles and public databases.

Consent to participate Not applicable to this article.

Consent to publish Not applicable to this article.

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