



# White Matter and Alzheimer's Disease: A Bidirectional Mendelian Randomization Study

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## ABSTRACT

**Introduction:** Observational studies have indicated widespread comorbidity of white matter (WM) lesions and Alzheimer's disease (AD) in the elderly, but the causality and direction of their relationship remained unclear. Our study aims to examine the bidirectional causal relationship between WM change and AD using a genetically informed method.

**Methods:** We performed a bidirectional two-sample mendelian randomization (MR) study to investigate the correlation of three WM phenotypes—white matter hyperintensities (WMH,  $N = 18,381$ ), fractional anisotropy (FA,  $N = 17,673$ ), and mean diffusivity (MD,  $N = 17,467$ )—with AD ( $N = 63,926$ ) using summary statistics from genome-wide association studies (GWAS). The inverse variance weighted method (IVW) was used to evaluate the causal estimate and alternative methods to test the heterogeneity, horizontal pleiotropy, and outliers.

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**Results:** There was no significant causal evidence of WM MRI markers on AD across all MR methods. We identified significant evidence of causal effects of AD on the risk of WMH (OR 1.06, 95% CI 1.03–1.10,  $p < 0.01$ ). The same direction of effects was observed in MR-Egger, weighted median, and weighted mode analysis. Besides, we also observed a risk causal relationship between AD with MD in MR-Egger, weighted median, and weighted mode-based methods (MR-Egger OR 1.38, 95% CI 1.07–1.79,  $p = 0.02$ ; weighted median OR 1.21, 95% CI 1.02–1.45,  $p = 0.03$ ; weighted mode-based OR 1.32, 95% CI 1.14–1.53,  $p < 0.01$ ). However, the general significance of the causal effect of AD on WMH and MD disappeared when we removed the single nucleotide polymorphisms (SNPs) near the *APOE* regions, revealing that the ability of AD to increase the risk of white matter damage might be mediated by *APOE* to some extent. Unfortunately, we did not observe significant causal evidence of AD on FA across all MR analyses.

**Conclusions:** In this bidirectional MR study, we did not observe that WM injuries were associated with a higher risk of AD. Likewise, genetically predicted AD did not result in a causal effect on white matter damage. However, our research revealed that underlying mechanisms linking AD and white matter lesions might be related to the SNPs near *APOE* regions.

**Keywords:** Alzheimer's disease; White matter lesions; MRI markers; Mendelian randomization

### Key Summary Points

#### Why carry out this study?

Observational studies have indicated widespread comorbidity of white matter (WM) lesions and Alzheimer's disease (AD) in the elderly, but a direct clue of causation between WM lesions and AD remained unclear.

In this study, we examined the bidirectional causal relationship between WM change and AD using a genetically informed method.

#### What was learned from the study?

In this bidirectional mendelian randomization study, we did not observe that WM injuries were associated with a higher risk of AD. Likewise, genetically predicted AD did not result in a causal effect on WM damage.

Our research revealed that underlying mechanisms linking AD and WM lesions might be related to the single nucleotide polymorphisms (SNPs) near *APOE* regions.

This study suggested that SNPs near *APOE* regions might participate in the specific biological processes underlying the comorbid etiology of AD and WM damage.

## INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia, chiefly marked by amyloid plaques and neurofibrillary tangles [1, 2]. However, several large anti-amyloid trials for mild-to-moderate AD have yielded disappointing results [2, 3], which made researchers gradually move away from simple assumptions to more broad

causality. Substantial evidence showed that the vascular hypothesis might be an alternative theory for AD etiology [4]. Cerebral small vessel disease (CSVD) is a disorder of cerebral microvessels that always leads to white matter lesions and other abnormalities [5]. As an assessment, CSVD contributed to about 50% of dementia worldwide [5–7]. Recent meta-analyses have investigated and suggested that white matter hyperintensities (WMH) at baseline conferred a 25% elevated risk of AD, and periventricular WMH conferred a 1.51-fold excess risk for dementia [8]. Besides, diffusion tensor imaging (DTI) measures and assesses white matter microstructure integrity and white matter damage via estimation of fractional anisotropy (FA) and mean diffusivity (MD) [9]. Observational studies reported abnormalities in DTI, such as decreased fractional anisotropy (FA) and increased mean diffusivity (MD), in AD and mild cognitive impairment within a diversity of white matter regions [10–12]. Moreover, AD pathology was more likely to have a detrimental impact on WM lesions. Previous studies detected that A $\beta$  pathology developed early cerebral blood flow reductions [13] and brain amyloid could increase the posterior WMH loads [14]. Amyloid accumulation also had a worse effect on white matter integrity in the absence of cognitive impairment, particularly in amyloid stage I–II [15]. Current evidence about a possible relationship between AD and WM damage was mainly based on observational studies, but a direct clue of causation between white matter lesions and AD remained uncertain.

Mendelian randomization (MR) is an alternative means to obtain unconfounded causal inference for the association between white matter change and Alzheimer's disease as the MR approach takes advantage of genetic variants as instruments [16]. To this end, we extracted instruments from summary statistics of genome-wide association studies (GWAS) for white matter MRI markers and AD and applied a bidirectional two-sample MR design to assess the potential causal relationship of white matter lesions with the risk of AD, and vice versa.

## METHODS

### Data Source and Instruments

#### *MRI Markers of WM*

We drew all summary GWAS statistics of MRI markers of WM from UK Biobank, from patients aged between 40 and 69 years at recruitment [17]. This GWAS examined the following three MRI markers: white matter hyperintensities (WMH,  $N = 18,381$ ), fractional anisotropy (FA,  $N = 17,673$ ), and mean diffusivity (MD,  $N = 17,467$ ). In this GWAS, individuals diagnosed with major central nervous system (CNS) diseases that could be related to white matter changes (e.g., stroke, Parkinson's disease, multiple sclerosis, dementia, or any other CNS neurodegenerative condition) were excluded from the analysis. WMH trait was log-transformed and normalized for brain volume. Principal component analysis (PCA) was performed on the FA and MD measures of each of the 48 different brain tracts to obtain a single global white matter FA and MD measure. Summary level data for white matter markers that consisted of full sets of association results were available from Cerebrovascular Disease Knowledge Portal ([www.cerebrovascularportal.org](http://www.cerebrovascularportal.org)). In order to avoid bias introduced by overlapping cohorts between AD and WM traits, we did not apply the additional cohorts for WMH, such as Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE) and a study from patients with ischemic stroke, which were used in the published WMH GWAS. We selected the significant variants with a threshold of  $p < 5 \times 10^{-8}$ , and clumped single nucleotide polymorphisms (SNPs) for independence with SNPs correlated at  $r^2 < 0.001$  within 500 kb based on European ancestry reference data from the 1000 Genomes Projects.

#### *Alzheimer's Disease*

We drew on clinically diagnosed LOAD summary data from a recent GWAS of International Genomics of Alzheimer's Project (IGAP) stage 1 discovery study consisting of 21,982 cases and 41,944 controls [18]. All stage 1 samples are from four consortia: Alzheimer Disease Genetics

Consortium (ADGC; 14,428 cases and 14,562 controls), CHARGE Consortium (2137 cases and 13,474 controls), The European Alzheimer's Disease Initiative (EADI; 2240 cases and 6631 controls), and Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES; 3177 cases and 7277 controls). More detailed information about summary demographics was available in the original works. For MR analysis, independent SNPs were clumped meeting a threshold of  $p < 5 \times 10^{-8}$ .

#### **Standard Protocol Approvals, Registrations, and Patient Consent**

Studies contributing to WM MRI markers and AD were approved by an institutional review board in the original GWAS [17, 18]. In our study, we only applied summary data.

#### **Statistical Analysis**

Before MR analysis, we calculated the proportion of variance ( $R^2$ ) explained by the instrumental SNPs. The strength of instruments was judged by  $F$  statistics, with a strong instrument defined as an  $F$  statistic greater than 10 [19]. For each direction of potential influence, inverse-variance weighted (IVW) was performed for the primary MR estimates [20]. This method will return a biased result if SNPs present horizontal pleiotropy, which will be contrary to the MR assumption [21]. Therefore, we used other MR methods, (e.g., MR-Egger regression [21], weighted mode-based method [22], and weighted median approach [23]) as complementary analyses to decrease the bias of horizontal pleiotropy, which would result in loss of robust statistical power [24]. In addition to these four methods, we also applied Pleiotropy Residual Sum and Outlier (MR-PRESSO) to identify horizontal pleiotropic outliers [25] assuming that horizontal pleiotropy occurred in less than 50% of instruments. Finally, since SNPs on the apolipoprotein E (*APOE*) were highly associated with AD and some clues also indicated that *APOE* was a top hit in the white matter damage

[17, 26], MR analysis without SNPs near the *APOE* regions (Chr19:45,116,911–46,318,605) was considered as supplementary results to reduce the horizontal pleiotropy. Results are reported with odds ratios (ORs) per an approximate 1 standard deviation (SD) increment of each exposure. We estimated statistical power for our MR analyses using an online calculator (<https://sb452.shinyapps.io/power>). All analyses were performed using R version 4.0.3 with “TwosampleMR” and “MR-PRESSO” packages.

## RESULTS

### Statistical Power

The *F* statistic for each SNP was greater than 10, indicating less weak instrument bias (Table S1 in the supplementary material). When we considered all instruments, all statistical power for our MR estimates was more than 80%, except for the effect of AD on WMH (Table S2 in the supplementary material). However, the statistical power for the causal relationship of AD on WM sharply decreased if we removed the SNPs in the *APOE* regions (Table S2).

### Estimates of the Causal Effect of WM MRI Markers on AD

We did not find any statistically significant causal evidence of WM MRI markers on AD across all MR methods. MR estimates remained null even though we removed the outlier using MR-PRESSO methods (Fig. 1). The presence of heterogeneity and pleiotropic effect are shown in Table S2. In addition, we found that no single genetic variant influenced the results in leave-one-out analyses (Figs. S1–S3 in the supplementary material). Summary statistics for the genetic instruments used to assess the effect of WM on the risk of AD are shown in Table S3 in the supplementary material.

### Estimates of the Causal Effect of AD on WM MRI Markers

We identified significant evidence that genetically predicted AD was associated with a greater WMH load (IVW OR 1.06, 95% CI 1.03–1.10,  $p < 0.01$ ). The same direction of effects was observed in MR-Egger, weighted median, and weighted mode analysis (Fig. 2). There was significant heterogeneity in the IVW method and possible pleiotropy in the MR-Egger analysis of WMH ( $p < 0.05$ ) (Table S2). Besides, we also observed a risk causal relationship between AD with MD in MR-Egger, weighted median, and weighted mode-based methods (MR-Egger OR 1.38, 95% CI 1.07–1.79,  $p = 0.02$ ; weighted median OR 1.21, 95% CI 1.02–1.45,  $p = 0.03$ ; weighted mode-based OR 1.32, 95% CI 1.14–1.53,  $p < 0.01$ ) (Fig. 2). However, analyses leaving out each SNP revealed that rs679515 drove this association (Fig. S6 in the supplementary material). There was significant heterogeneity and possible pleiotropy in both analyses of WMH (IVW Cochran *Q*, 33.22,  $p = 0.03$ ; MR-Egger intercept,  $-0.01$ ,  $p < 0.01$ ; MR PRESSO Global test,  $p < 0.01$ ) and MD (IVW Cochran *Q*, 55.47,  $p < 0.01$ ; MR-Egger Cochran *Q*, 46.34,  $p < 0.01$ ; MR PRESSO Global test,  $p < 0.01$ ). There was no difference between estimates from MR-PRESSO before and after the outlier’s correction for WMH (MR PRESSO-Raw,  $p = 0.13$ ; MR PRESSO-Corrected,  $p = 0.07$ ) and MD (MR PRESSO-Raw,  $p = 0.39$ ; MR PRESSO-Corrected,  $p = 0.96$ ) (Fig. 2). Most importantly, when we removed the SNPs in the *APOE* regions, the general significance of the causal effect of AD on WMH and MD disappeared, revealing that the ability of AD to increase the risk of white matter damage might be mediated by *APOE* to some extent. Unfortunately, we did not observe significant causal evidence of AD on FA across all MR analyses (Fig. 2). The presence of heterogeneity and the pleiotropic effect is shown in Table S2. Summary statistics for the genetic instruments used to assess the effect of AD on the risk of WM are shown in Table S4 in the supplementary material. Leave-one-out analyses for AD on the WM lesions are shown in Figs. S4–S6 in the supplementary material.



◀**Fig. 1** Causal effect estimates of genetically predicted white matter change on Alzheimer's disease. For the causal effect of FA on Alzheimer's disease (AD), we detected two outliers (rs4150221 and rs76122535) using the MR-PRESSO (Pleiotropy Residual Sum and Outlier) method. For the causal effect of MD on AD, we detected one outlier (rs4150221) using the MR-PRESSO. *SNP* single nucleotide polymorphism, *N* number, *OR* odds ratios, *CI* confidence interval, *WM* white matter, *AD* Alzheimer's disease, *WMH* white matter hyperintensities, *FA* fractional anisotropy, *MD* mean diffusivity, *IVW* inverse variance weighted

## DISCUSSION

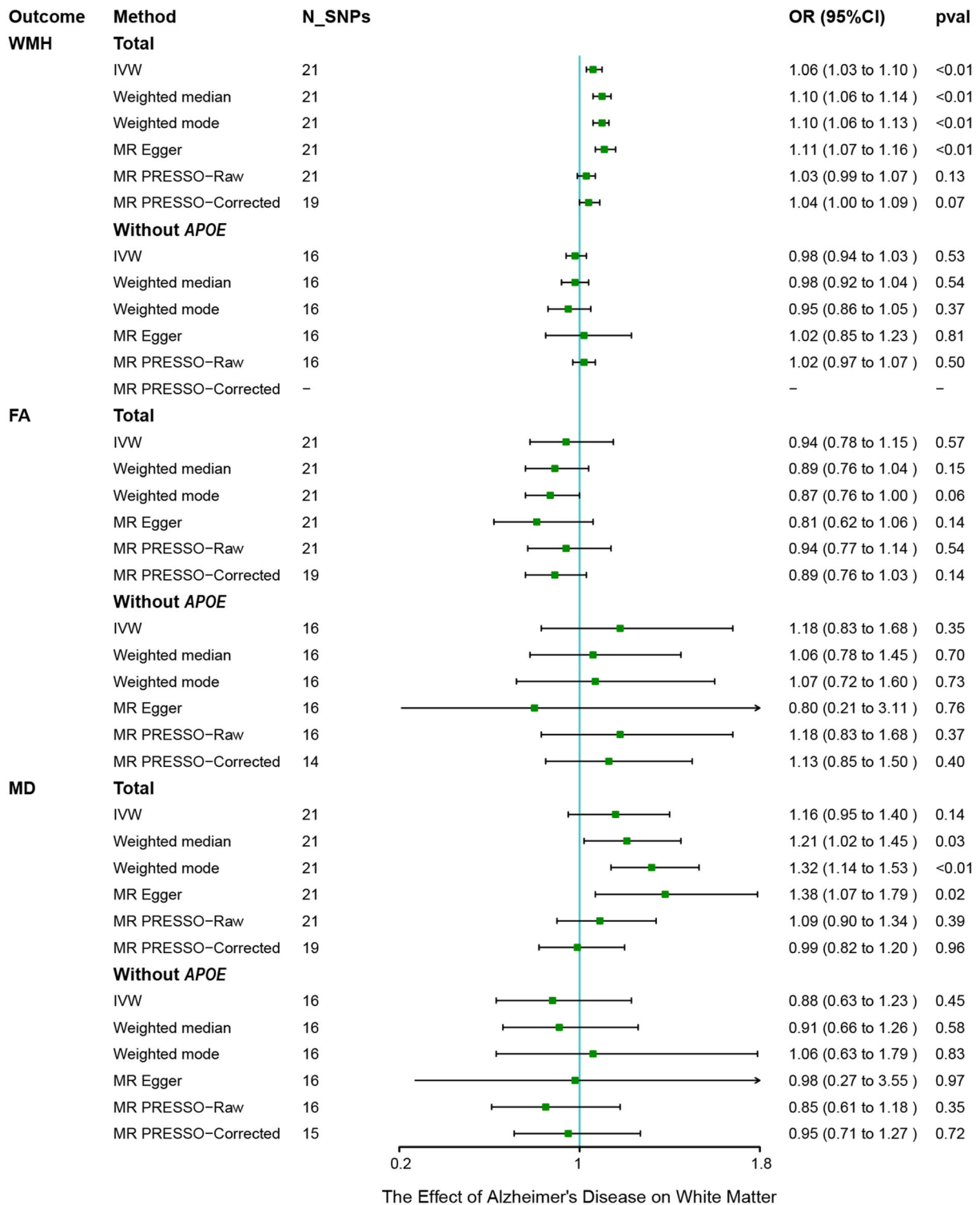
In this bidirectional MR study, a comprehensive MR analysis was performed to assess the association between AD and white matter lesions using a large sample size of GWAS pooled data involving more than 63,000 subjects in AD cohorts and over 17,000 individuals for WMH load and WM microstructural changes. Regrettably, we did not observe that WM injuries were associated with a higher risk of AD. Likewise, genetically predicted AD did not result in a causal effect on white matter damage. However, our research suggested that underlying mechanisms linking AD and white matter lesions might be related to the SNPs near *APOE*.

Some lines of evidence suggested the comorbidity of abnormalities in the brain microvascular system and AD [1, 13, 27, 28]. In the general population, the prevalence of white matter lesions increased exponentially with age, ranging from 11% to 21% at age 64 and 94% aged 82 [29]. Current findings indicated that WMH might predict AD a decade before the clinical stage [30]. In addition to the positive association between WMH and clinical AD [8], systematic reviews and meta-analysis studies also have shown a relationship between WMH and a higher risk of specific cognitive domains in patients with AD or MCI [31]. Moreover, a recent review has suggested colocalized widespread disrupted white matter integrity and AD predominant pathologies ( $A\beta_{42}$  or tau) in patients with subjective cognitive impairment (SCI), MCI, or AD [32]. Furthermore, oxidative stress and microglia-mediated inflammation

might be common possible pathogenesis of AD progression and white matter damage [33–41]. However, observational studies could not exactly distinguish consequences from causes because of the influence of confounding, as accumulating evidence suggested that cardiovascular disease and other lifestyle-related disorders, including diabetes, smoking, and obesity, might contribute to the progression of dementia and WM lesions [2, 34].

Using MR approaches, our results suggested that white matter damage containing WMH and white matter integrity could not elevate the risk of AD, which was consistent with a previous randomized controlled trial (RCT) showing that hypertension treatment with nilvadipine did not slow the decline in cognition or function in patients with mild- and moderate-stage AD [42], although a meta-analysis of RCT studies suggested blood pressure control prevented WMH progression [43, 44]. Moreover, intensive blood pressure control did not result in a significant reduction in the risk of probable dementia relative to standard blood pressure [45]. However, these findings were less consistent with a recent MR study showing a positive association of WMH volume with AD [46]. This inconsistency might be due to the selection bias because the population recruited in our study was limited to European ancestry and the age seemed to be more severe when at recruitment. Similarly, a recent MR analysis leveraging GWAS summary statistics for 110 DTI measurement revealed that the higher risk of AD was causally associated with genetically determined WM integrity in the corpus callosum [47], but not overall contribution of white matter connectivity. Therefore, white matter changes that increased the risk of AD from the observational study might be better explained by other factors rather than the direct effect. For example, underlying conditions with cardiovascular disease [48] could interfere with WM lesions and cause AD.

For the relationship between AD and white matter damage, the true causal relationship of AD to the risk of WM injuries was obscured by *APOE*. In our research, we observed a false positive result that AD could increase the WMH load and damage the WM microstructural integrity when we included all the instruments



◀**Fig. 2** Causal effect estimates of genetically predicted Alzheimer's disease on white matter lesions. For the causal effect of Alzheimer's disease (AD) on white matter lesions without *APOE*, we removed five SNPs near the *APOE* regions (Chr19:45,116,911–46,318,605), namely rs10416500, rs150685845, rs7412, rs1081105, and rs147711004. For the causal effect of AD on WMH in the total group, two outliers (rs1081105 and rs147711004) were detected by the MR-PRESSO (Pleiotropy Residual Sum and Outlier) method. For the causal effect of AD on FA in the total group, two outliers (rs11218343 and rs679515) were detected by the MR-PRESSO method. For the causal effect of AD on MD in the total group, two outliers (rs147711004 and rs679515) were detected by the MR-PRESSO method. *SNP* single nucleotide polymorphism, *N* number, *OR* odds ratios, *CI* confidence interval, *WM* white matter, *AD* Alzheimer's disease, *WMH* white matter hyperintensities, *FA* fractional anisotropy, *MD* mean diffusivity, *IVW* inverse variance weighted

of AD, whereas the positive result disappeared when we removed the SNPs in the *APOE* region. On the basis of this, we reasonably inferred that SNPs near *APOE* might explain the genetic correlation of AD with WM pathologies. As we all know, the presence of the  $\epsilon 4$  allele of *APOE* had the strongest association with sporadic AD [49]. Meanwhile, *APOE* has been reported to destroy blood–brain barrier integrity, affect cerebral blood flow, and cause neuronal-vascular coupling disorders [50, 51]. In line with our results, a recent study confirmed that a higher genetic risk score for AD, especially driven by *APOE*, was associated with WM lesion burden by examining the polygenic overlap between AD and vascular pathologies. Additionally, the effect of *APOE* on memory and global cognition might be partly mediated by WM damage in the mediation analysis [26]. Additionally, the *APOE*  $\epsilon 4$  allele could modulate brain WM structure before any impending cognitive or clinical manifestations of the disease [52] in an age-independent manner [53]. Besides, *APOE* genotype might influence the interaction of WM function with AD pathology. WMH was correlated with amyloid burden especially in the posterior brain regions in *APOE*  $\epsilon 4$  non-carriers but not in the *APOE*  $\epsilon 4$  carriers, suggesting that the influence of *APOE* might override the effect

of WMH on amyloid burden [54]. However, our MR analyses might not be powerful enough to detect the small effect of impact of AD on WMH after removing the SNPs near the *APOE* regions, which needs expanded future discovery GWAS. More evidence is needed to further investigate the mechanisms that underline the influence of AD on white matter.

### Limitations

A typical MR study should be designed following three core assumptions [55]: (1) instruments should be associated with exposure; (2) instruments should influence the outcome only through the exposure, rather than any other pathways; (3) instruments should not be associated with any confounders. To completely rule out all confounders was still a challenge for an MR study as it might not be possible to measure all confounders in the absence of an exact understanding of the complex biology of their relationship with the exposure [55]. In our study, in addition to the conventional IVW method, we applied four methods as sensitivity analysis, namely the MR-Egger method, weighted median, weighted mode-base method, and MR-PRESSO. A potential bias in our MR study was the presence of horizontal pleiotropy mainly caused by *APOE* when we assessed the causal effect of AD on the risk of white matter injuries. To solve this, we removed the instruments in the *APOE* regions. In addition, the causal relationship of genetically determined AD with white matter lesions was null after removing the SNPs near the *APOE* regions. However, the low power might be the reason for the null results. As population stratification might affect the genetic associations, we restricted the population to European ancestry.

### CONCLUSIONS

In the present study, we did not provide evidence to support a direct clue of causation between white matter lesions and AD risk using a bidirectional MR approach. However, we held that SNPs near the *APOE* region might explain the genetic correlation of AD with WM



pathologies. Further research is necessary to provide insight into specific biological processes underlying the comorbid etiology of AD and white matter damage.

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**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Author Contributions.** Yaqing Li was involved in study design, acquisition, statistical analysis, drafting and revising the manuscript. Tian Li and Jiaxin Zheng were involved in acquisition and statistical analysis. Junjian Zhang was involved in study design and obtaining funding. All authors contributed to manuscript revision, read and approved the submitted version.

**Disclosures.** Yaqing Li, Jiaxin Zheng, Tian Li and Junjian Zhang have nothing to disclose.

**Compliance with Ethics Guidelines.** All data sources used in the MR study received approval from an ethics standards committee on human experimentation and obtained informed consent from all participants, which could be obtained in the original GWAS.

**Data Availability.** The authors hereby declare that the generated datasets in this study will be presented upon request from the corresponding author.

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