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DND Dementia and Neurocognitive Disorder

Original Article

Mendelian Randomization Reveals Unidirectional Links Between Amyloid-β and Tau in Alzheimer's Disease

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ABSTRACT

Background and Purpose: Prior research has indicated that changes in the amyloid-beta (Aβ) biomarker precede tau biomarker alterations in Alzheimer's disease (AD). However, establishing causality through temporal correlations remains contentious. This study aimed to explore the causal relationship between Aβ and tau using Mendelian randomization (MR) analysis.
Methods: We conducted two-sample MR analyses employing genome-wide association studies (GWASs) summary statistics for Aβ positron emission tomography (PET) and cerebrospinal fluid phosphorylated tau (CSF pTau). Additionally, to reinforce and validate the results of the two-sample MR, we performed two-sample MR using tau PET GWAS summary statistics and one-sample MR analysis using autopsy data. In the one-sample MR analysis, the exposure and outcome variables were neuritic plaque burden and neurofibrillary tangle burden, respectively, determined through neuropathological examination.
Results: The two-sample MR analysis unveiled a causal association between Aβ accumulation and CSF pTau level (BETA [standard error]=0.30 [0.10], p=0.004). The absence of heterogeneity and horizontal pleiotropy was confirmed. In contrast, there was no evidence causally relating CSF pTau level to Aβ accumulation (p=0.56). Our results were reinforced by consistently directional effects observed in the two-sample MR using tau PET GWAS and one-sample MR analysis, indicating a causal direction from Aβ burdens (measured by neuritic plaques) to tau burdens (measured by neurofibrillary tangles) (p=1.24×10^{-13}).
Conclusions: Our findings suggest a causal relationship between Aβ burdens and tau burdens in AD, reinforcing the notion of Aβ as a pivotal upstream factor in AD pathogenesis.

Keywords: Alzheimer's Disease; Amyloid Beta-Peptides; Tau Proteins; Positron-Emission Tomography; Cerebrospinal Fluid; Genome-Wide Association Study

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kim JP, Seo SW, Kim HN; Data curation: Kim JP, Nho K, Risacher SL, Saykin AJ; Formal analysis: Lee H, Kim BH; Funding acquisition: Seo SW, Kim HN; Investigation: Kim JP, Lee H, Kim BH; Methodology: Kim JP, Lee H, Kim HN; Project administration: Seo SW, Kim HN; Writing - original draft: Kim JP, Lee H, Kim HN; Writing - review & editing: Kim BH, Nho K, Risacher SL, Saykin AJ, Seo SW, Kim HN.

INTRODUCTION

The amyloid cascade hypothesis remains the dominant pathogenic theory, even though it does not offer a comprehensive explanation for Alzheimer's disease (AD).[1,2] According to this hypothesis, the accumulation of amyloid-beta (Aβ) is crucial in initiating a chain of subsequent events that includes tau aggregation, neuronal death, and cognitive impairment.[2] Given the compelling evidence that tau pathology is a major facilitator of neurodegeneration in AD, it is crucial to understand the intricate processes by which Aβ triggers this chain of events.[3] However, the causal relationship between Aβ and tau pathology has not been fully elucidated yet. There has been *in vitro* and *in vivo* animal model evidence suggesting Aβ-induced tau phosphorylation. Human studies have previously indicated a temporal relationship between Aβ and tau biomarkers, where a decline in cerebrospinal fluid (CSF) Aβ is followed by increased Aβ deposition on positron emission tomography (PET) scans, which is subsequently accompanied by increases in CSF tau levels or tau deposition on tau PET scans.[4] Opposing evidence suggests that tau pathology may manifest at younger ages than Aβ pathology.[5,6] Therefore, the assertion of causality relying solely on temporal relationships can be questioned.

In a recent study, mediation analysis was employed to explore the potential impact of an additional underlying factor affecting Aβ and tau levels across different time-points and the relationship between Aβ and tau.[7] The study concluded that the impacts of Aβ on neurodegeneration and cognitive decline were completely mediated by tau in genetically identical twins.[7] However, previous studies using mediation analysis[7,8] have been too limited in sample sizes to be definitive. Furthermore, the bidirectional associations between Aβ and tau have not been assessed. Diverse study designs in previous research, spanning observational studies to clinical trials and genetic analyses, has offered insights while underscoring the complexity and multifaceted nature of AD pathology. Significantly, existing literature highlights substantial gaps in our comprehension of the interplay between Aβ and tau proteins, particularly regarding causality.

This uncertainty emphasizes the need for innovative approaches such as Mendelian randomization (MR), which provides robustness against confounding factors and offers a clearer pathway to establishing causal relationships. In scenarios where assumptions such as having strong instruments and no horizontally pleiotropic pathways, are more plausible, MR could be utilized to enhance causal inference in mediation analysis.[9] MR holds specific advantages compared to non-instrument variable mediation methods where causal assumptions are required. Causal effect of the exposure on the outcome, the exposure on the mediator, and the mediator on the outcome can all be examined. Moreover, bi-directional MR can be employed to ascertain which of two variables serves as the causal exposure and causal mediator, particularly when this is unclear. Recent MR studies have primarily focused on evaluating the impact of various biomarkers, including amyloid and tau, on the clinical diagnosis of AD.[10,11] A previous MR study investigating the causal relationship between amyloid and tau has primarily relied on candidate gene approaches or small-scale genome-wide association studies (GWAS),[12] which may introduce selection bias and limit instrument strength. Large GWAS summary statistics provide an ideal framework for precisely examining bidirectional causal effect with improved statistical power and reliability. In this study, we conducted a two-sample MR analysis using the largest GWAS summary statistics available for PET Aβ and CSF tau, to the best of our knowledge, to investigate their causal relationship. To validate our findings and assess their relevance at the pathological level, we further performed a one-sample MR analysis using pathology-confirmed amyloid and tau data.

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METHODS

Study design

We aimed to explore the potential impact of Aβ accumulation on tau aggregation using MR. Two complementary MR approaches were employed: a two-sample MR approach using GWAS summary statistics and a one-sample MR study utilizing individual-level data from an independent cohort. The overall study design is illustrated in **Fig. 1**.

Data sources

The exposure dataset included GWAS summary statistics quantifying Aβ accumulation measured by PET imaging. Data were obtained from 13 cohorts,[13] comprising 11,816 non-Hispanic white (NHW) participants. The primary outcome dataset was derived from GWAS meta-analysis summary statistics for CSF pTau level. This dataset included a total of 13,116 participants from 31 European ancestry cohorts.[14] Additionally, a validation outcome dataset was obtained from a meta-analysis combining data from seven GWAS datasets, which include 1,446 individuals of NHW ancestry.[15] For further validation, GWAS summary statistics for tau accumulation measured by PET imaging were used. This dataset provided an independent means to confirm the robustness of the findings.

Selection of instrumental variables

Instrumental variables (IVs) were chosen based on three core MR assumptions: 1) IVs are strongly associated with the exposure, 2) IVs are not associated with confounders, and 3) IVs affect the outcomes only through the exposure. The clumping method (linkage disequilibrium

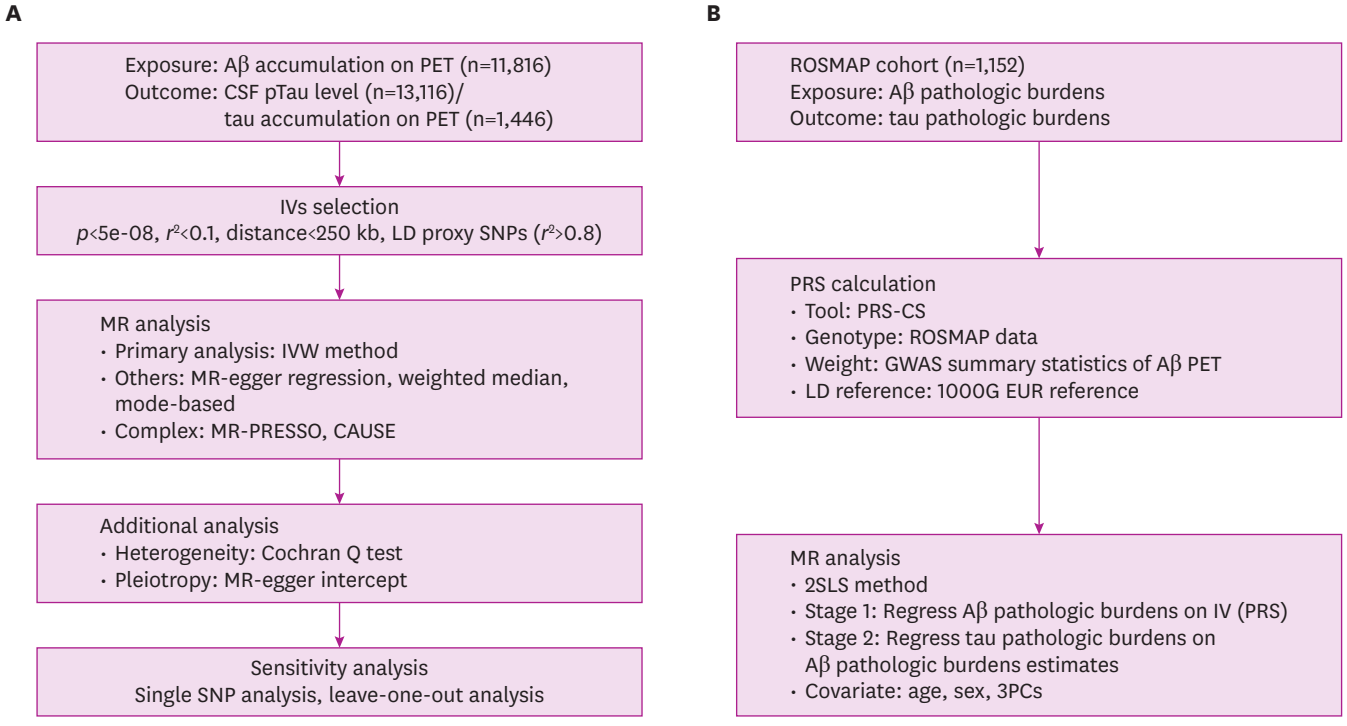

Fig. 1. Flow diagram of this study. (A) Flow diagram of two-sample MR analysis. (B) Flow diagram of one-sample MR analysis.
MR: Mendelian randomization, Aβ: amyloid beta, PET: positron emission tomography, CSF pTau: cerebrospinal fluid phosphorylated tau, IV: instrumental variable, LD: linkage disequilibrium, SNP: single nucleotide polymorphism, IVW: inverse-variance weighted, MR-PRESSO: MR Pleiotropy RESidual Sum and Outlier, CAUSE: Causal Analysis Using Summary Effect, ROSMAP: Religious Orders Study/Memory and Aging Project, PRS: polygenic risk score, PRS-CS: PRS continuous shrinkage, GWAS: genome-wide association study, 2SLS: two-stage least squares, PC: principal component.

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(LD) r^2 <0.1, clumping window <250 kb) was applied to ensure independence among IVs. Single nucleotide polymorphisms (SNPs) with the genome-wide significance threshold ($p<5\times10^{-8}$) were considered as potential IVs. IV strength was assessed using *F*-statistics, and SNPs with *F*-statistics exceeding 10 were included in the analysis.[16] SNPs associated with the outcome were excluded from the IVs to avoid pleiotropy. Multiple independent SNPs strongly associated with Aβ accumulation were selected as IVs for the MR analysis.

Statistical analysis

Two-sample MR

We utilized the inverse-variance weighted (IVW) method as the primary approach for MR analysis to assess the causal association between Aβ accumulation (exposure) and CSF pTau levels (outcome). A bidirectional MR analysis was conducted to determine whether genetic predisposition to tau (exposure) causally affects Aβ accumulation (outcome). The IVW method used a weighted linear regression model, assuming a zero intercept.[17]

Additional MR methods, including MR-Egger regression,[18] weighted median,[19] mode-based analysis,[20] and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO),[21] were applied to assess the robustness of the results. Heterogeneity between IVs in the MR was assessed using the Cochran Q test. MR-Egger intercept[18] was employed to evaluate for horizontal pleiotropy. Sensitivity analyses, such as single SNP analysis and leave-one-out analysis, were conducted to identify potential heterogeneous IVs. Identical analyses were conducted for the validation analysis using tau accumulation quantified by PET as the outcome. As effect sizes (betas) were not available in the summary data for the outcome, they were estimated from the z-statistic using the following equation:

$$\beta_{zy} = z_{zy} \times \sqrt{2p(1-p)(n + z_{zy}^2)}$$

where *y* is the trait (tau), *z* is a genetic variant, *p* is allele frequency, and *n* is the sample size. Allele frequencies were estimated from the Haplotype Reference Consortium reference panel.

To address biases due to sample overlap[22] between the two datasets used for validation, Causal Analysis Using Summary Effect (CAUSE)[23] was implemented as a Bayesian approach and established as one of the primary analyses. This method differentiates causal effects from correlated pleiotropy by modeling shared heritable factors and uses Bayesian model comparison to test whether observed correlations are consistent with causality rather than confounding.[23] Statistical analysis was performed using "TwosampleMR" (version 0.5.7)[24] package of R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).[25]

One-sample MR

To validate the findings from the two-sample MR analysis and further explore the causal relationship between Aβ and tau from postmortem brain, we performed a one-sample MR analysis using individual participant data from an independent cohort. This analysis not only confirmed the results of the two-sample MR analysis but also provided additional insights into the causal relationship. The one-sample MR analysis was conducted using data from the Religious Orders Study/Memory and Aging Project (ROSMAP) cohort, comprising 1,152 Caucasian participants. We excluded participants with 1) alternative primary causes of dementia, such as cerebrovascular stroke and Lewy bodies, and 2) those with the APOE ε2/ε4 genotype due to its established impact on AD risk, aiming to mitigate potential confounding effects.[26]

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In the ROSMAP cohort, Aβ and tau burdens were measured using composite scores derived from neuritic plaque burden and neurofibrillary tangle burden, as described previously.[27] Both burdens were assessed through microscopic examination of silver-stained slides from five regions (mid frontal cortex, mid temporal cortex, inferior parietal cortex, entorhinal cortex, and hippocampus). The count for each region was normalized by dividing it by the corresponding standard deviation (SD). The scaled regional measures were averaged to obtain summary composite measures for neuritic plaque burden and neurofibrillary tangle burden.

For the one-sample MR, a two-stage least squares (2SLS) method was performed to assess the causal association between exposure (Aβ pathologic burden) and outcome (tau pathologic burden) in ROSMAP cohort participants. In the stage 1 regression, polygenic risk scores (PRSs) of Aβ served as IVs. The PRSs were calculated using PRS-continuous shrinkage (CS)[28] with summary statistics from the Aβ PET dataset and individual genotypes from the ROSMAP cohort. PRS-CS was implemented using default parameters with the 1000G EUR reference panel as the LD reference. The SNP effect sizes derived from PRS-CS were then used to calculate PRS using Plink v1.9.[29] The normalized PRS served as an IV, with age, sex, and three principal components included as covariates in the regression model. A 2SLS method was used to estimate the causal association using "AER" (version 1.2-10) R package.[30]

Ethics statement

All GWAS summary statistics used in this study were obtained from the previously published studies, which had been approved by their respective Institutional Review Boards. No additional ethical approval and consent to participate declaration were required for this analysis.

RESULTS

The study cohort consisted of 11,816 NHW participants for the exposure dataset and 13,116 European ancestry individuals for the outcome dataset in the two-sample MR analysis. For the one-sample MR, demographic characteristics of the 1,152 samples from the ROSMAP cohort are summarized in **Table 1**.

Two-sample MR analysis

From the Aβ PET GWAS, seven significant SNPs (p <5×10^{-8}, LD r^2<0.1) were identified as IVs and used for the two-sample MR analysis. Detailed information on the selected SNPs is provided in **Supplementary Table 1**.

Table 1. Demographic information of genome-wide association study summary statistics used in this study

	Two-sample MR			One-sample MR
	Aβ	CSF pTau*	Tau PET†	ROSMAP
No.	11,816	13,116	1,444	1,152
Female (%)	50.1	53.1	47.4	66.3
Age (mean ± SD)	68.9±8.3	68.9±NA	73.3±7.3	80.9±6.9
APOE ε4+ (%)	31.0	47.2	39.5	24.3

MR: Mendelian randomization, Aβ: amyloid-beta, CSF pTau: cerebrospinal fluid phosphorylated tau, PET: positron emission tomography, ROSMAP: Religious Orders Study/Memory and Aging Project, SD: standard deviation, NA: not available.
*Due to the absence of individual-level data from each cohort, the overall SD for the CSF pTau cohort could not be calculated. APOE ε4+ rate was calculated after excluding two cohorts from the CSF pTau cohort that did not provide APOE information.
†Demographic data of two cases in the tau cohort are excluded to protect privacy.

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The two-sample MR analysis unveiled a statistically significant causal relationship between Aβ accumulation and CSF pTau levels in AD. The primary IVW method demonstrated a robust association between the exposure (Aβ accumulation) and outcome (CSF pTau levels) (BETA [standard error, SE]=0.30 [0.10], p=0.004) (**Figs. 2** and **3**). Supporting this, the weighted median method (BETA [SE]=0.31 [0.12], p=0.01) and MR-PRESSO method (BETA [SE]=0.3 [0.06], p=0.003) produced consistent results. However, MR-Egger, simple mode, and weighted mode methods showed similar coefficient trends but did not reach statistical significance The CAUSE method further validated the causal relationship between Aβ accumulation and CSF pTau levels (p=0.001).

Sensitivity analyses, including MR-Egger, weighted median, simple mode, weighted mode, and MR-PRESSO, provided additional support for the robustness of the IVW findings. The Cochran's Q statistic for the IVW method was 2.15 (p=0.91), indicating minimal heterogeneity and high reliability for the causal effect (**Table 2**). The MR-Egger regression intercept exhibited no evidence of directional horizontal pleiotropy (p=0.82, **Table 2**). A symmetric funnel plot indicated the absence of heterogeneity and horizontal pleiotropy (**Fig. 4**). Leave-one-out analysis affirmed the stability and reliability of MR analysis findings (**Fig. 5**), identifying no disproportionately influential single SNP. Additionally, MR-PRESSO global outlier test found no significant outliers (p=0.93).

For the reverse direction analysis, three SNPs associated with CSF pTau were included, as detailed in **Supplementary Table 2**. Using the IVW methods, no causal effect of tau on Aβ was observed ($BETA_{IVW}$=0.07, P_{IVW}=0.56). Similarly, CAUSE analysis also demonstrated consistent findings (p=0.73). The Cochran's Q test indicated no significant heterogeneity among IVs, as outlined in **Supplementary Table 2**. Analyses employing the MR-Egger regression intercept showed no significant evidence of horizontal pleiotropy (**Table 2**). MR-PRESSO was not conducted due to an insufficient number of IVs.

In the validation analysis using tau PET GWAS summary statistics, the causal relationship between Aβ accumulation and PET-measured tau accumulation was investigated. Twelve SNPs were utilized for MR analysis. Although the IVW and weighted median methods did

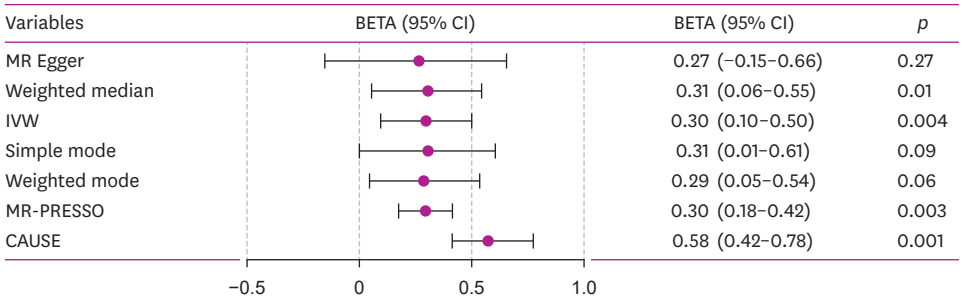

Fig. 2. Forest plots representing the causal associations estimated by two-sample MR analysis. The causal associations between exposure (Aβ accumulation on PET) and outcome (CSF pTau level) were significant in IVW, weighted median, MR-PRESSO, and CAUSE methods. Each horizontal line represents the BETA and 95% CI for the respective method.
MR: Mendelian randomization, Aβ: amyloid beta, PET: positron emission tomography, CSF pTau: cerebrospinal fluid phosphorylated tau, IVW: inverse-variance weighted, MR-PRESSO: Mendelian Randomization Pleiotropy RESidual Sum and Outlier, CAUSE: Causal Analysis Using Summary Effect, CI: confidence interval.

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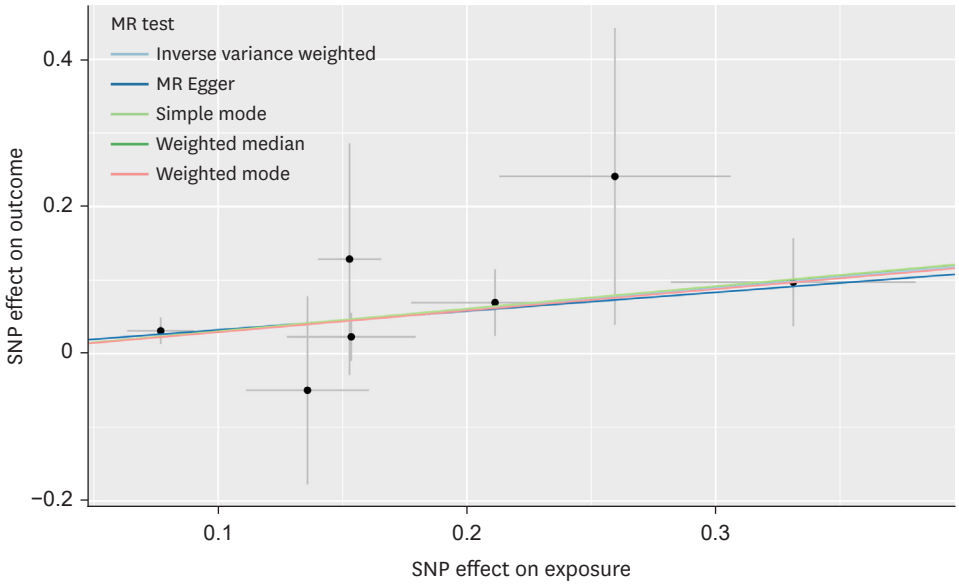

Fig. 3. Scatter plot illustrating the effect sizes of SNPs on Aβ and tau accumulation on PET. The slope of the straight line reflects the magnitude of the causal effect estimated by five different MR analysis methods. Each line corresponds to a different MR method: inverse variance weighted (green), MR Egger (blue), simple mode (light green), weighted median (dark green), and weighted mode (red). Error bars indicate 95% confidence intervals for each SNP effect size estimate.
SNP: single nucleotide polymorphism, Aβ: amyloid beta, PET: positron emission tomography, MR: Mendelian randomization.

Table 2. Results of sensitivity analysis

Exposure	Outcome	MR Egger regression		Heterogeneity analyses	
		Intercept	*p*-value	Method	Heterogeneity *p*-value
Aβ accumulation	CSF pTau level	0.007	0.82	IVW	0.91
				MR Egger	0.84
CSF pTau level	Aβ accumulation	0.08	0.46	IVW	0.13
				MR Egger	0.18

MR: Mendelian randomization, Aβ: amyloid beta, CSF pTau: cerebrospinal fluid phosphorylated tau, IVW: inverse-variance weighted.

not yield statistically significant results consistent with those obtained for CSF pTau, both MR-PRESSO (p=0.04) and CAUSE (p=0.001) analyses provided robust evidence supporting a causal association. The IVW Cochran's Q test revealed no significant heterogeneity, and the MR-Egger regression intercept indicated the absence of horizontal pleiotropy.

One-sample MR analysis

In the one-sample MR analysis, the 2SLS method unveiled a causal association between Aβ pathologic burdens (exposure) and tau pathologic burdens (outcome) (BETA [SE]=0.80 [0.11], p=1.24×10^{-13}). This finding was consistent with the two-sample MR analysis, further validating the causal relationship. Weak instrument bias was ruled out, as indicated by F statistics of 30, confirming the robustness of the IVs used in this analysis. In the ROSMAP cohort, Aβ and tau burdens were measured using composite scores derived from neuritic plaque and neurofibrillary tangle burdens. These measures further reinforced the directional relationship from Aβ accumulation to tau aggregation in AD.

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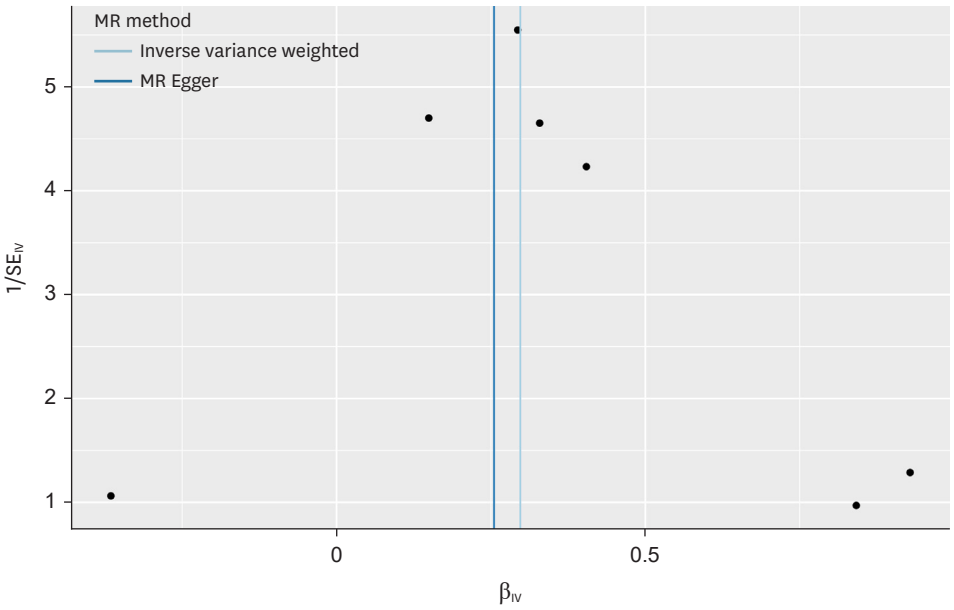

Fig. 4. Funnel plot to show no presence of horizontal pleiotropy. Each dot represents an individual instrumental variable used in the two-sample MR analysis.
MR: Mendelian randomization, SE: standard error.

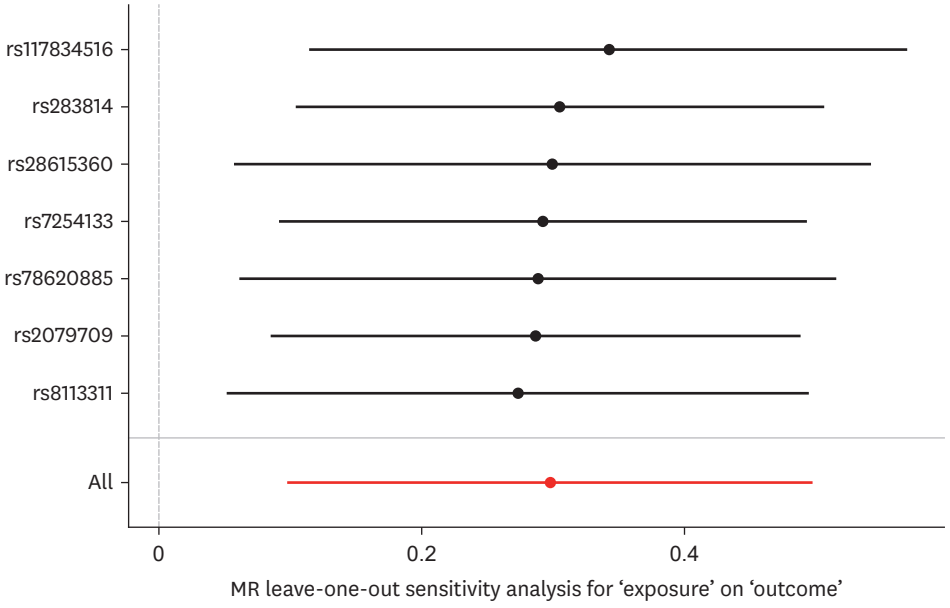

Fig. 5. Forest plot displaying the results of a two-sample MR leave-one-out sensitivity analysis. Each point represents the MR estimate for the effect of the exposure on the outcome when each SNP is individually excluded from the analysis. The horizontal lines represent the 95% confidence intervals for each estimate. The red line indicates the overall estimate across all SNPs, with the red point marking the estimate's mean and the horizontal span representing its 95% confidence interval. This analysis helps to determine if the overall MR estimate is unduly influenced by any single SNP.
MR: Mendelian randomization, SNP: single nucleotide polymorphism.

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DISCUSSION

In this study, we investigated the causal relationship between Aβ and tau using a comprehensive approach, which included bidirectional two-sample MR analysis based on molecular PET/CSF cohorts and one-sample MR analysis based on a pathologic cohort. We found that Aβ accumulation on PET causally impacts increased CSF pTau levels, whereas no evidence supports a causal effect of tau on Aβ deposition. Importantly, this causal relationship between Aβ and tau burdens was robustly replicated in the pathologic cohort, reinforcing the established temporal relationship between cortical Aβ and tau accumulation. These results are consistent with previous MR studies,[12] providing further evidence that Aβ pathology causally contributes to tau pathology in the brain. Our study, utilizing large-scale GWAS summary statistics to the best of our knowledge, strengthens this causal inference by reducing potential bias associated with small-scale or candidate-gene-based approaches. This human data evidence of causality lays a robust foundation for advancing therapeutic strategies targeting Aβ, considering its upstream position in the pathology cascade.

Our validation analysis using tau PET GWAS summary statistics further confirmed the robustness of the causal relationship between Aβ and tau accumulation. Although the IVW and weighted median methods did not replicate the results observed with CSF pTau, both MR-PRESSO and CAUSE analyses provided consistent evidence of causality. These findings highlight the consistency of results across alternative analytical approaches, even when using different modalities for detecting and quantifying tau pathology. Such consistency strengthens the evidence for a causal relationship between Aβ and tau burdens, emphasizing the robustness of the association across varying methodological frameworks.

Our major findings emphasize that cortical Aβ deposition, as assessed by amyloid PET, causally influenced CSF pTau levels. The MR estimate (β=0.30, SE=0.10) indicates the expected change in tau pathology per one SD increase in genetically predicted Aβ levels. While the effect size reflects genetic liability rather than direct exposure, a β of 0.30 indicates a moderate causal effect and is directionally consistent with previous observational studies. This aligns with earlier in vitro and in vivo model studies supporting Aβ-induced tau pathology. Specifically, multiple *in vitro* models have demonstrated Aβ-induced tau hyperphosphorylation.[31-38] Various forms of Aβ, including fibrillar,[31,33] oligomeric,[32,35,37] and dimeric[34] forms, have consistently elevated phosphorylated tau levels. While *in vitro* models primarily indicate Aβ-induced tau hyperphosphorylation, *in vivo* animal models have demonstrated the formation of neurofibrillary tangles induced by Aβ. These observations span a range of study designs, encompassing the injection of fibrillar Aβ peptides,[39] Aβ peptide-enriched brain extracts,[40-43] and Aβ-oligomers.[44] However, because of challenges in obtaining brain samples, the evidence at the patient level primarily hinges on the temporal correlation among pathologic markers.[4,45] Our real-world, large-sample data findings significantly enhance the evidence supporting a causal relationship between these core AD biomarkers.

In our investigation, we observed a lack of evidence supporting a causal effect of tau on Aβ deposition. Previous pathological studies have presented histopathological findings demonstrating the existence of tau pathology in the absence of amyloid pathology,[46,47] particularly in the locus coeruleus in the brainstem of very young cognitively normal individuals. However, *in vivo* studies have not substantiated the impact of tau pathology on amyloid pathology.[41,42,48,49] These seemingly discrepant findings can be reconciled by considering that subcortical and limbic tau pathology evolves slowly as part of the aging

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process, accelerating and spreading into the neocortex in the presence of Aβ.[50-52] Our results, indicating unidirectional causality, align with this explanatory framework.

Using different modalities for detecting and quantifying pathology, our study revealed a consistent causal association between Aβ and tau burdens. While PET imaging and CSF analysis serves as the standard method for quantifying AD pathology in clinical practice, the definitive diagnosis of AD relies on the microscopic examination of brain tissue.[53] PET imaging, though limited in sensitivity for detecting early pathological stages,[54,55] demonstrated consistent results with the golden standard of microscopic examination. The Aβ fibrils detected by amyloid PET and paired helical filaments detected by tau PET are the closest forms to the final Aβ and tau aggregates observed through microscopic examination. This close correspondence likely contributed to the consistency observed in both modalities.

Moreover, previous *in vitro* and *in vivo* studies have demonstrated Aβ-induced tau changes mediated by both soluble and insoluble Aβ species.[31-35,37] Our analyses utilizing CSF pTau and PET-measured tau yielded consistent findings, further suggesting a causal relationship that persists regardless of the protein's form.

Our study had several limitations that should be addressed. Firstly, the GWAS summary data used in the two-sample MR in this study were derived from individuals of European ancestry. While narrowing the sample to people of European ancestry helps reduce population structure bias, it may limit the generalizability of our findings to other populations. Further research involving diverse ethnic groups is necessary for a more comprehensive understanding of AD beyond Europeans. Secondly, overlapping samples in the exposure and outcome studies are likely, potentially leading to substantial bias and an inflated type 1 error rate.[22] While we utilized the CAUSE method to address overlapping samples, future analyses using non-overlapping samples may strengthen our findings. Third, some of the genetic variants categorized as amyloid- or tau-related were assigned based on proximity to GWAS-identified loci rather than confirmed biological function. While this locus-based classification is commonly used in large-scale genetic studies and does not affect the validity of the MR design, it may limit the mechanistic interpretation of the findings. Future studies incorporating functional annotation or expression data may help refine biological interpretation. Finally, the sample size in our one-sample MR analysis using the ROSMAP cohort might be insufficient to ensure significance. However, the one-sample MR results were enhanced by leveraging neuropathology data from postmortem brain analysis, providing a more precise investigation into the causal role of Aβ on tau in AD pathology. The results not only corroborate the findings from our two-sample MR analysis but also enhances the reliability and specificity of the causal inference between Aβ and tau. Despite the limitations, our findings are noteworthy as they contribute real-world, large sample-based evidence of a causal relationship between Aβ and tau pathology, employing a unique approach utilizing genetic data.

In conclusion, our extensive MR analysis establishes a causal relationship between Aβ deposition and tau pathology in AD. This reinforces the pivotal role of Aβ as an upstream factor in the pathogenesis of AD. These findings underscore the potential efficacy of anti-amyloid treatments and emphasize the necessity for further research to broaden our understanding of AD, ultimately leading to enhanced diagnostic and treatment approaches across diverse populations. Future studies should prioritize replication of these analyses in

diverse ethnic populations to validate the universality of the Aβ-tau causal relationship and ensure broader applicability of these findings.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Information on SNPs in MR analyses: harmonized data

Supplementary Table 2
Information on SNPs in reverse MR analyses: harmonized data

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