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Alzheimer Disease and Epilepsy

A Mendelian Randomization Study

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Abstract

Background and Objectives

Observational studies suggested a bidirectional relationship between Alzheimer disease (AD) and epilepsies. However, it remains debated whether and in which direction a causal association exists. This study aims to explore the relationship between genetic predisposition to AD, CSF biomarkers of AD (β-amyloid [Aβ] 42 and phosphorylated tau [pTau]), and epilepsies with 2-sample, bidirectional Mendelian randomization (MR) method.

Methods

Genetic instruments were obtained from large-scale genome-wide meta-analysis of AD ($N_{case/proxy}$ = 111,326, $N_{control}$ = 677,663), CSF biomarkers of AD (Aβ42 and pTau, N = 13,116), and epilepsy (N_{case} = 15,212, $N_{control}$ = 29,677) of European ancestry. Epilepsy phenotypes included all epilepsy, generalized epilepsy, focal epilepsy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, generalized epilepsy with tonic-clonic seizures, focal epilepsy with hippocampal sclerosis (focal HS), and lesion-negative focal epilepsy. Main analyses were performed using generalized summary data-based MR. Sensitivity analyses included inverse variance weighted, MR pleiotropy residual sum and outlier, MR-Egger, weighted mode, and weighted median.

Results

For forward analysis, genetic predisposition to AD was associated with an increased risk of generalized epilepsy (odds ratio [OR] 1.053, 95% CI 1.002–1.105, p = 0.038) and focal HS (OR 1.013, 95% CI 1.004–1.022, p = 0.004). These associations were consistent across sensitivity analyses and replicated using a separate set of genetic instruments from another AD genome-wide association study. For reverse analysis, there was a suggestive effect of focal HS on AD (OR 3.994, 95% CI 1.172–13.613, p = 0.027). In addition, genetically predicted lower CSF Aβ42 was associated with an increased risk of generalized epilepsy (β = 0.090, 95% CI 0.022–0.158, p = 0.010).

Discussion

This MR study supports a causal link between AD, amyloid pathology, and generalized epilepsy. This study also indicates a close association between AD and focal HS. More effort should be made to screen seizure in AD, unravel its clinical implications, and explore its role as a putative modifiable risk factor.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **CAE** = childhood absence epilepsy; **focal HS** = focal epilepsy with HS; **GSMR** = generalized summary data-based MR; **GTCS** = generalized epilepsy with tonic-clonic seizure; **GWAS** = genome-wide association study; **HS** = hippocampal sclerosis; **ILAE** = International League Against Epilepsy; **IVW** = inverse variance weighted; **JAE** = juvenile absence epilepsy; **JME** = juvenile myoclonic epilepsy; **MR** = Mendelian randomization; **MR-PRESSO** = MR pleiotropy residual sum and outlier; **MTL** = mesial temporal lobe; **OR** = odds ratio; **pTau** = phosphorylated tau; **SNP** = single nucleotide polymorphism; **TLE** = temporal lobe epilepsy.

Accumulating evidence indicates a close association between Alzheimer disease (AD) and epilepsies. Preclinical studies indicated a vicious cycle between AD and seizures. On one hand, β-amyloid (Aβ) demonstrated epileptogenic potential even in the early stages of the amyloid cascade.[1] Additional factors that contribute to the increased seizure susceptibility in AD might include excitatory/inhibitory imbalance, locus coeruleus degeneration, neuroinflammation, vascular dysregulation, and metabolic alteration.[2] On the other hand, epileptiform activity and chronic hyperexcitability promotes amyloid plaque deposition and tau hyperphosphorylation.[3]

In human, epidemiologic studies indicated a bidirectional association of epilepsy with AD.[4-8] A recent meta-analysis identified a 1.8-fold increased risk of AD in people with epilepsy, while patients with AD are at a 3.1-fold higher risk of epilepsy.[9] However, these retrospective studies are prone to confounding effects, such as cerebrovascular insults, education level, and use of different antiepileptic drugs with varying effect on cognition.

Several studies have depicted seizures in AD. In an earlier retrospective study that included 446 individuals with pathologically diagnosed AD, 17% had a new-onset seizure after clinical diagnosis of AD, with 89% presenting with generalized tonic-clonic seizures.[10] In recent years, with the aid of long-term EEG, focal seizures with impaired awareness was reported to be the most common type,[11] even presenting at prodromal stage.[12] Notably, temporal lobe epilepsy (TLE) and AD share several critical pathologic and neuroimaging features, including pathologic phosphorylation of amyloid and tau[13,14] and hippocampal sclerosis (HS).[15]

In addition, evidence indicated a putative link between childhood-onset epilepsies and AD. In an amyloidogenic mouse model, network hyperexcitability and increased seizure susceptibility was found at juvenile stage, long before the onset of cognitive decline and amyloid deposition.[16] In human, task-related hippocampal hyperactivity was also evident in asymptomatic young adults carrying autosomal dominant AD mutations,[17] asymptomatic young adults carrying *APOE* ε4 allele,[18,19] and asymptomatic adults at genetic risk of late-onset AD.[20] Furthermore, 5 decades after childhood-onset epilepsy, there was increased amyloid burden[21] and altered brain metabolism resembling possible preclinical AD.[22] However, these studies are limited by sample sizes and the possibility of confounding and reverse causality.

Given the close relationship between epilepsy and AD, it is essential to verify a true causal association because such an association would indicate a potentially modifiable cause or previously underrecognized consequence of AD. However, it remains debated whether epilepsy drives AD or vice versa.[23] In contrast to a causal association, it is also likely that there is a shared mechanism driving both conditions (e.g., neuroinflammation and neurovascular unit dysfunction). In addition, retrospective studies are potentially limited by confounding effect. For example, certain antiepileptic drugs, which might deteriorate cognition, are likely to contribute to the observed association between epilepsy and AD.

Mendelian randomization (MR) uses genetic variants that are robustly associated with exposure as instrumental variables to estimate the causal effect of a suspected exposure on outcome. When the underlying assumptions are satisfied, the MR approach minimizes several inherent limitations of conventional observational studies, including unobserved confounding and reverse causality.[24]

In this study, we investigated the bidirectional causal effect of AD and epilepsies by performing 2-sample MR analyses. We tested the hypotheses that (1) AD drives epilepsy and (2) epilepsy drives AD. We also studied the association between genetically predicted CSF biomarkers of AD (Aβ42 and phosphorylated tau [pTau]) and epilepsy.

Methods

Data Sources

Genome-wide association study (GWAS) summary statistics for epilepsy and subtypes were derived from the International League Against Epilepsy (ILAE) Consortium on Complex Epilepsies in 2018.[25] Seizures and epilepsy syndromes were diagnosed according to the ILAE classification. All cases were assessed and classified into subtypes according to EEG, imaging, and clinical histories by an epilepsy specialist at each participating site. Phenotype categories included genetic generalized epilepsy, focal epilepsy, and unclassified epilepsy. Approximately 95.5% of the participants were of European ancestry. *Z* scores were calculated for all epilepsy, focal epilepsy, and generalized epilepsy using fixed-effect transethnic meta-analyses. We transformed *z* scores into β and SE, as previously described.[26]

Genetic generalized epilepsy was further classified into (1) childhood absence epilepsy (CAE), (2) juvenile absence epilepsy (JAE), (3) juvenile myoclonic epilepsy (JME), (4) generalized epilepsy with tonic-clonic seizures (GTCS) alone, with spike and wave EEG, and (5) not otherwise specified. Subphenotypes of focal epilepsy included (1) focal epilepsy with HS (focal HS), (2) lesion other than HS, (3) lesion negative, and (4) not otherwise specified. For each subphenotype, a BOLT-LMM analysis that included only White individuals was performed. When analyzing the effect of AD on epilepsies, we used all epilepsy, generalized epilepsy, focal epilepsy, CAE, JAE, JME, GTCS, focal epilepsy with HS, and lesion-negative focal epilepsy as outcome.

For AD, we used the latest AD GWAS meta-analysis dataset initiated by the European Alzheimer & Dementia Biobank,[27] which included both patients with AD and proxy cases, that is, people with a family history of AD. To replicate the positive findings, we used an earlier GWAS dataset by the International Genomics of Alzheimer's project,[28] which enrolled only cases with late-onset AD and did not include any proxy cases.

Genetic predictors of CSF levels of Aβ42 and pTau were obtained from a recent study initiated by the European Alzheimer and Dementia Biobank including 13,116 European ancestry individuals from 31 study cohorts.[29] CSF levels were measured by each cohort separately. Participants spanned the full spectrum of AD, including subjective cognitive decline, mild cognitive impairment, and dementia. Details of laboratory procedures of CSF samples could be found from original studies. CSF levels were $\log_{10}$ transformed and normalized within cohorts and CSF assay type. Associations were adjusted for sex, age, assay type, and 10 ancestry principal components. There was no sample overlap between epilepsy and AD, CSF biomarkers, and AD datasets as we know of.

Instrument Selection and GSMR

For genetical instruments of AD and epilepsy, we used single-nucleotide polymorphisms (SNPs) that were strongly associated with each exposure ($p < 5 \times 10^{-8}$) as instruments. Linkage disequilibrium–based clumping and standard quality control (imputation info score, call rate, Hardy-Weinberg equilibrium test, and assessment of heterogeneity) has been performed by each original GWAS. When an exposure-associated variant was not found in the outcome GWAS, we attempted to find a SNP proxy in strong linkage disequilibrium ($R^2 > 0.8$) using Northern Europeans from Utah (CEU) reference samples from 1000 Genomes. We removed SNPs that were significantly associated with outcome ($p < 5 \times 10^{-5}$). Steiger filtering[30] was also performed to ensure variants demonstrated a stronger association with the outcome than with the exposure. SNPs were harmonized to ensure the effect alleles were identical in both exposure and outcome data. Nonbiallelic and palindromic SNPs (A/T, G/C) were excluded. SNPs with a minor allele frequency <0.01 were excluded because of potentially low confidence.

Generalized summary data–based MR (GSMR) was used as the primary analysis, which excludes potentially pleiotropic SNPs by the heterogeneity in dependent instruments (HEIDI) outlier removal test.[31] The GSMR method also accounts for weak linkage disequilibrium between instrumental SNPs. Five hundred three European samples from phase 3 of 1000 Genomes project were used as a reference.

Three SNPs for all epilepsy, 1 for focal epilepsy, 11 for generalized epilepsy, 1 for JME, 2 for CAE, and 2 for focal HS were GWAS-level significant and used as a proxy for each epilepsy phenotype. For JME, there was only 1 GWAS-level significant SNP (rs1046276), which was also strongly associated with AD ($p = 2.12 \times 10^{-4}$). Therefore, the effect of JME on AD was not analyzed.

MR Assumptions and Sensitivity Analyses

The MR method was based on 3 key assumptions, including that the instruments were strongly associated with exposure, were independent of confounders, and affect outcome through the exposure and not through alternative pathways. All the instrumental variables in these analyses demonstrated an *F*-statistic >10, indicating a low risk of weak instrument bias. For sensitivity analyses, we used SNPs retained after heterogeneity in dependent instruments (HEIDI) outlier removal test and performed inverse variance weighted (IVW), MR-Egger, weighted-median, weighted-mode, and MR pleiotropy residual sum and outlier (MR-PRESSO). These methods each rely on distinct assumptions. Horizontal pleiotropy was examined using MR-Egger regression. When the Egger intercept significantly deviated from zero, there was evidence of horizontal pleiotropy. Median-based and mode-based method is more robust to outliers and provides an estimate when up to 50% weights are from invalid instruments. Pleiotropy was also examined using the MR-PRESSO[32] Global test, and *p* values were calculated according to 1,000 simulations. If significant global heterogeneity was found, then a local outlier test was performed to detect outlying SNPs. When there was only 1 SNP available as the instrument, the Wald ratio was reported.

Leave-one-out analyses was performed to evaluate whether the MR result is relied on a particular variant. Cochran *Q* was also calculated to assess the evidence of heterogeneity. We depicted forest plots and funnel plots to visually inspect heterogeneity and horizontal pleiotropy.

When levels of CSF Aβ42 and pTau were exposure, we clumped SNPs at $r^2 < 0.1$ and used 5e-8 as significance level. As a sensitivity analysis, different clumping thresholds (0.001, 0.01, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8) and different GWAS significance levels (5e-8, 5e-6) were used. Because GSMR accounts for a weak correlation due to linkage disequilibrium, loosening clumping threshold might increase the number of genetic instruments and allow for an increased statistical power.

MR analyses were performed using R (version 4.1.0). Packages used included gsmr[31] (version 1.0.9), TwoSample MR[33] (version 0.5.6), MR-PRESSO[32] (version 1.0), and LdlinkR[34] (version 1.2.2). Results were reported following the strengthening

the reporting of observational studies in epidemiology using MR guideline.[35] All hypotheses testings were 2-sided. The threshold for significance was $p < 0.05$. Given the exploratory nature of our study, we did not perform correction of multiple comparisons. For statistically significant associations, we performed a series of sensitivity analyses and replication study using separate datasets.

Standard Protocol Approvals, Registrations, and Patient Consents

This study is based on publicly available data. The summary statistics for AD, CSF biomarkers, and epilepsy did not contain any personal information, and the GWAS have obtained ethical approval from relevant ethics review boards. Written consent to be enrolled in the databases was obtained from study participants or for those with substantial cognitive decline from a caregiver, legal guardian, or other proxy by each original GWAS. Patient consents for this analysis were waived because of the retrospective nature of the study.

Data Availability

Summary statistics of AD and CSF biomarkers by the European Alzheimer & Dementia Biobank were downloaded from the European Bioinformatics Institute GWAS Catalog (ebi.ac.uk/gwas/) under accession no. GCST90027158 (AD), GCST90129599 (CSF Aβ42), and GCST90129600 (CSF pTau). Summary statistics of AD by the International Genomics of Alzheimer's project were downloaded from the NIAGADS Data Storage Site (niagads.org/igap-summary-statistics-lambert-et-al-2013). Summary statistics of epilepsy and subtypes by the ILAE Consortium on Complex Epilepsies were downloaded from epigad.org/gwas_ilae2018_16loci.html.

Data used to generate the main result are summarized in eTable 1 (links.lww.com/WNL/C806). The bidirectional MR analysis results, heterogeneity test (Q statistics) results, Egger intercept results, and MR-PRESSO global test results are summarized in eTables 2–5, respectively. Codes are available on reasonable request.

Results

Basic information of the contributing GWAS is summarized in Table 1.

Effects of AD on Epilepsies

The effects of AD on epilepsies are shown in Figure 1. Notably, genetic predisposition to AD was associated with an elevated risk of focal HS (odds ratio [OR] 1.013, 95% CI 1.004–1.022, $p_{GSMR} = 0.004$) (Figure 1). Extensive sensitivity analyses yielded similar estimates in magnitude and direction

Table 1 GWAS Dataset Used in the Mendelian Randomization

Phenotype	Sample size		Population (%European)	Publication
	Cases, n	Controls, n		
All epilepsy	15,212	29,677	95.5	International League Against Epilepsy Consortium on Complex Epilepsies, 2018
Generalized epilepsy	3,769		98.3	
Focal epilepsy	9,671		94.0	
Childhood absence epilepsy	778	24,218	100[a]	
Juvenile absence epilepsy	415			
Juvenile myoclonic epilepsy	1,177			
GTCS alone, with spike and wave EEG	225			
Focal epilepsy with HS	709			
Focal epilepsy, lesion other than HS	2,751			
Focal epilepsy, lesion negative	2,660			
Alzheimer disease	39,106 diagnosed 46,828 proxy in stage I[b] 25,392 cases in stage 2	401,577 in stage 1[b] 276,086 in stage 2	100	Bellenguez et al., 2022[27]
	17,008 in stage 1[b] 8,572 in stage 2	37,154 in stage 1[b] 11,312 in stage 2	100	Lambert et al., 2013[28]
CSF Aβ42, and pTau	13,116 individuals with subjective cognitive decline, mild cognitive impairment, and dementia		100	Jansen et al., 2022[29]

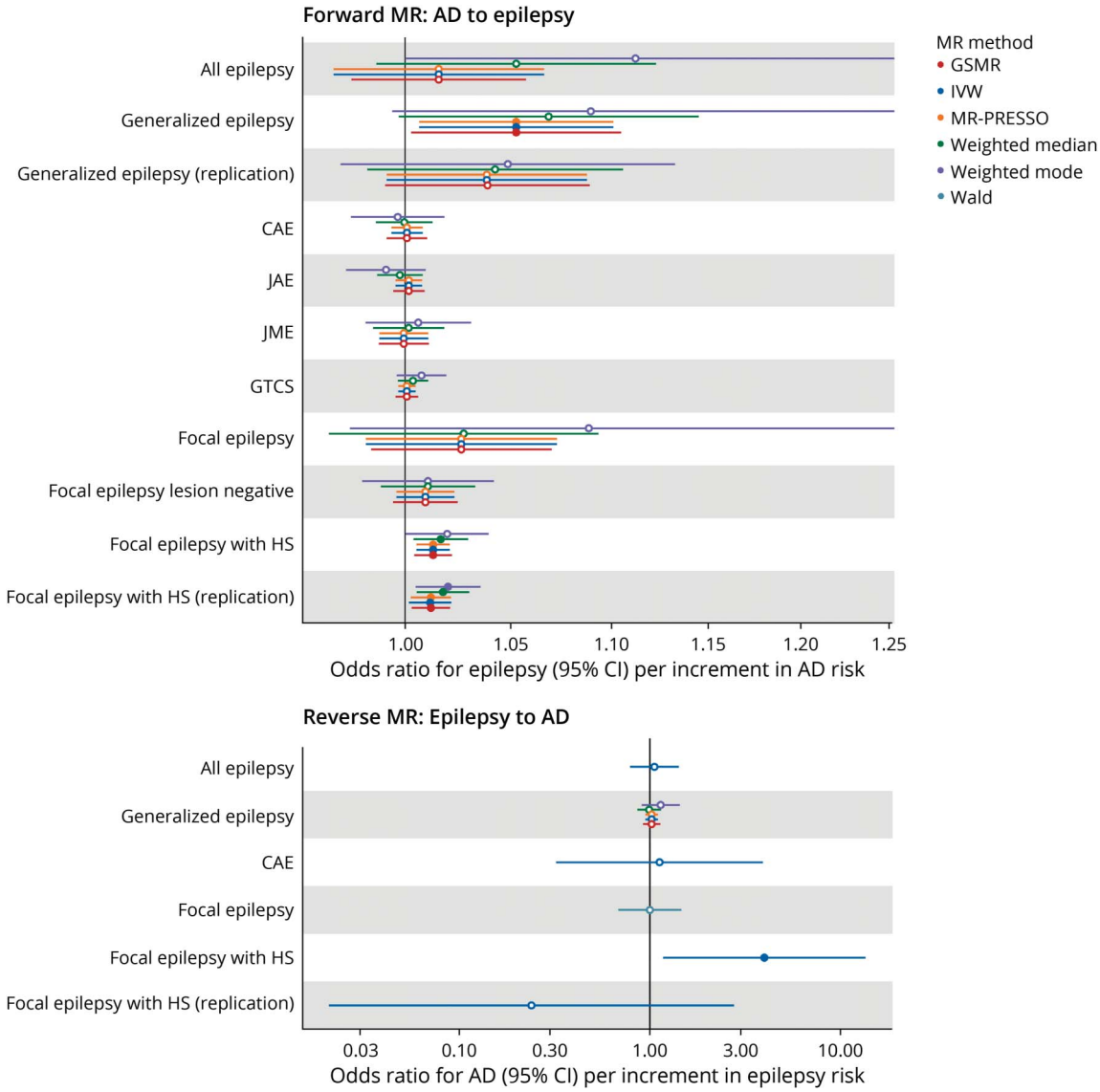
Abbreviations: Aβ = β-amyloid; GTCS = generalized epilepsy with tonic-clonic seizure; GWAS = genome-wide association study; HS = hippocampal sclerosis; pTau = phosphorylated tau; SNP = single-nucleotide polymorphism.
[a] GWAS of specific syndromes of genetic generalized epilepsy and phenotypes of focal epilepsy were limited to European ancestry.
[b] Stage 1 was used as outcome because these studies released publicly available stage 1 GWAS summary statistics. GWAS-level significant SNPs from meta-analysis of stages 1 and 2 were used as instrumental SNPs for exposure.

(p_{IVW} = 0.001, $p_{MR\text{-}PRESSO}$ = 0.003, $p_{Weighted\ median}$ = 0.011, $p_{Weighted\ mode}$ = 0.056) (Figure 2). Although estimates using the Egger method was not significant (p_{Egger} = 0.433), this method estimates horizontal pleiotropy at the cost of reduced power and precision.[36] No evidence of pleiotropy ($p_{Egger\ intercept}$ = 0.969; $p_{MR\text{-}PRESSO\ global\ test}$ = 0.777) or heterogeneity (p_{IVW_Q} = 0.786, p_{Egger_Q} = 0.743) was found. In addition, the leave-one-out analysis also suggested that the causal effect was not driven by a particular instrumental SNP (Figure 2C). Funnel plot demonstrated no evidence of asymmetry, indicating a low risk of directional pleiotropy (Figure 2D).

To further verify the association between AD and focal HS, we performed a replication analysis using instrumental SNPs from an earlier AD GWAS dataset,[28] which did not include proxy cases. The results indicated similar causal effect in magnitude and direction (p_{GSMR} = 0.009, p_{IVW} = 0.020, $p_{MR\text{-}PRESSO}$ = 0.033, $p_{Weighted\ median}$ = 0.005, $p_{Weighted\ median}$ = 0.029), further validating the causal association.

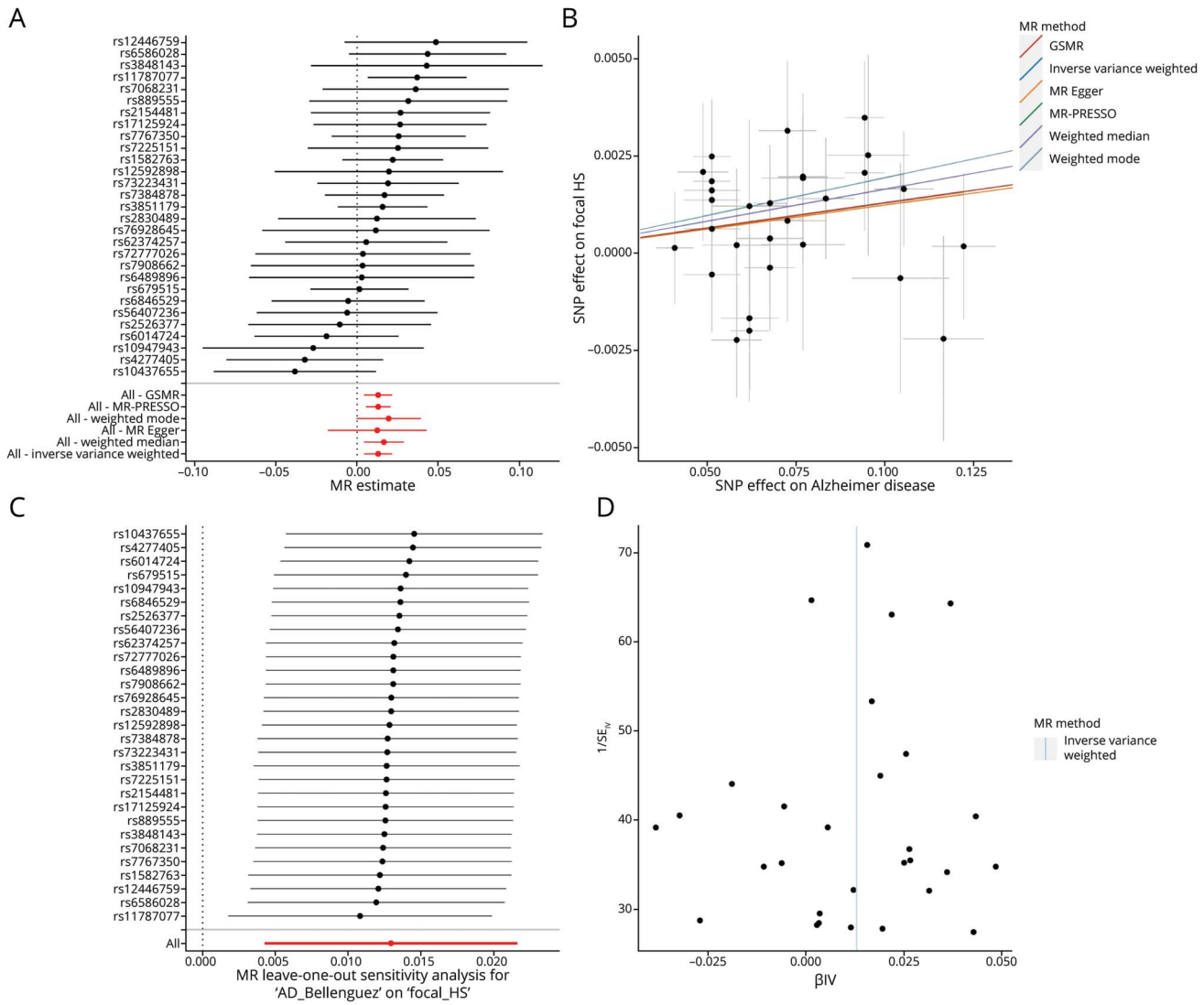
In addition, AD was associated with an increased risk of generalized epilepsy (OR 1.053, 95% CI 1.003–1.105, p_{GSMR} = 0.038). Sensitivity analyses yielded similar estimates in magnitude and direction (p_{IVW} = 0.025, $p_{MR\text{-}PRESSO}$ = 0.035, $p_{Weighted\ median}$ = 0.061, $p_{Weighted\ mode}$ = 0.079) (Figure 3). No evidence of pleiotropy ($p_{Egger\ intercept}$ = 0.480; $p_{MR\text{-}PRESSO\ global\ test}$ = 0.661) or heterogeneity (p_{IVW_Q} = 0.659, p_{Egger_Q} = 0.634) was found. The leave-one-out analysis and funnel plot were demonstrated in Figure 3, C and D. Using instrumental SNPs from the replication dataset,[28] the estimated effect of AD on generalized epilepsy was

Figure 1 Bidirectional Associations Between AD and Epilepsies Estimated by Mendelian Randomization



AD = Alzheimer disease; CAE = childhood absence epilepsy; focal HS = focal epilepsy with hippocampal sclerosis; GSMR = generalized summary data–based MR; GTCS = generalized epilepsy with tonic-clonic seizures; IVW = inverse variance weighted; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; MR = Mendelian randomization; MR-PRESSO = MR pleiotropy residual sum and outlier.

Figure 2 Association Between AD and Focal HS Estimated by the MR



(A) Forest plot of focal HS for each 1 SD increase of AD risk. (B) Scatter plot showing the effect of genetic instruments on AD risk against their effect on focal HS. (C) There was no substantial change of IVW causal estimate after removing any of the instrumental SNPs. (D) The funnel plot showed no asymmetry. AD = Alzheimer disease; focal HS = focal epilepsy with hippocampal sclerosis; GSMR = generalized summary data–based MR; IVW = inverse variance weighted; MR = Mendelian randomization; MR-PRESSO = MR pleiotropy residual sum and outlier; SNP = single-nucleotide polymorphism.

in similar direction (OR 1.039, 95% CI 0.991–1.089, p_{GSMR} = 0.114).

Effects of Epilepsies on AD

For reverse analysis, there was a significant effect of focal HS on AD (OR 3.994, 95% CI 1.172–13.613, p_{IVW} = 0.027) (Figure 1). We attempted to replicate this finding using the replication dataset; the estimated effect was not significant and in opposite direction (p_{IVW} = 0.252). Because there were only 2 instrumental SNPs for focal HS, no sensitivity analysis was performed.

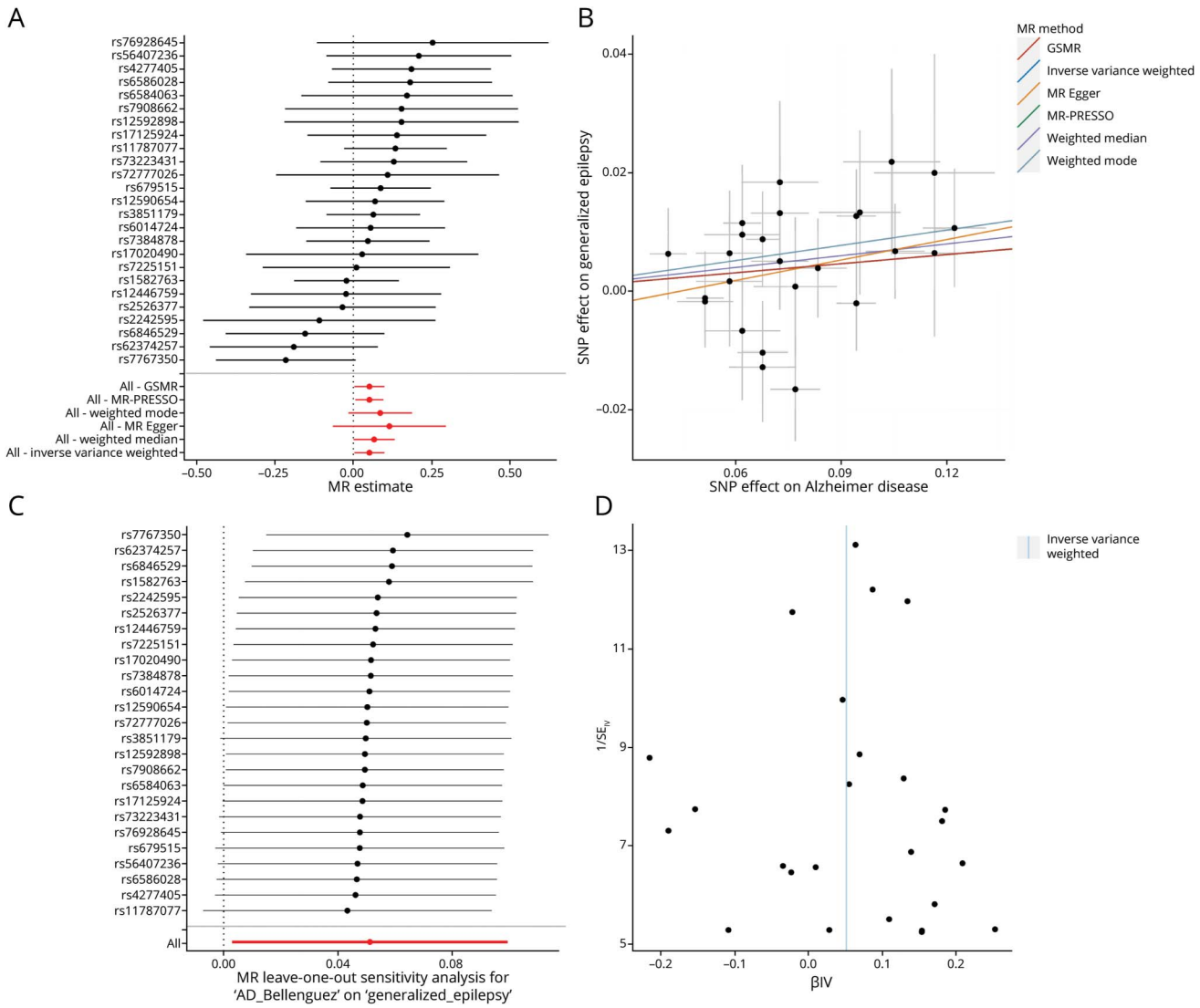
Effects of CSF Aβ42 and pTau on Epilepsies

The effects of CSF Aβ42 and pTau on epilepsies are displayed on Figure 4. A lower level of CSF Aβ42 was linked to an increased risk of generalized epilepsy (β = 0.090, 95% CI 0.022–0.158, p_{GSMR} = 0.010). Sensitivity analyses indicated similar estimates in magnitude and direction (p_{IVW} = 0.014, $p_{MR\text{-}PRESSO}$ = 3E-4, $p_{Weighted\ median}$ = 0.021, $p_{Weighted\ mode}$ = 0.139). No evidence of pleiotropy ($p_{Egger\ intercept}$ = 0.298; $p_{MR\text{-}PRESSO\ global\ test}$ = 0.996) or heterogeneity (p_{IVW_Q} = 0.975, p_{Egger_Q} = 0.993) was found. Furthermore, using different levels of GWAS significance threshold (5e-8, 5e-6) and clumping threshold, from rigorous to liberal, the estimated associations by GSMR were consistent in direction and magnitude (Figure 5, eTable 6, links.lww.com/WNL/C806). For reverse MR, no significant effect of epilepsy on CSF biomarkers was observed (eTable 2, links.lww.com/WNL/C806).

Discussion

In this study, we found a causal association between AD and generalized epilepsy, and this association was robust to

Figure 3 Association Between AD and Generalized Epilepsy Estimated by the MR



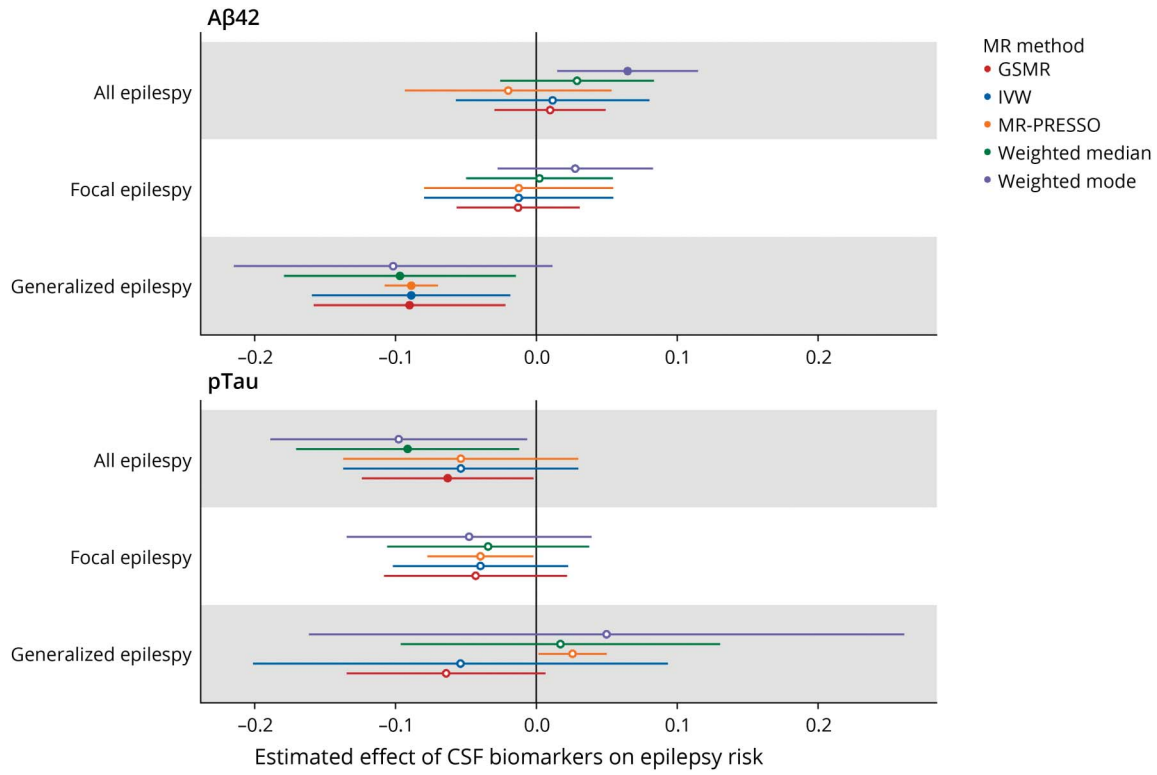
(A) Forest plot of generalized epilepsy for each 1 SD increase of AD risk. (B) Scatter plot showing the effect of genetic instruments on AD risk against their effect on generalized epilepsy. (C) There was no substantial change of IVW causal estimate after removing any of the instrumental SNPs. (D) The funnel plot showed no asymmetry. AD = Alzheimer disease; GSMR = generalized summary data–based MR; IVW = inverse variance weighted; MR = Mendelian randomization; MR-PRESSO = MR pleiotropy residual sum and outlier; SNP = single-nucleotide polymorphism.

sensitivity analyses and further validated by a significant association between lower CSF Aβ42 and an increased risk of generalized epilepsy. We also found that AD was causally linked to focal epilepsy with HS, which was robust to sensitivity analyses and replicated using a separate set of instrumental variables. There was also evidence of potential causal effect of focal epilepsy with HS on AD, although association in this direction was less compelling.

The causal association between AD and generalized epilepsy was consistent with previous observations. Generalized epilepsy have been observed in 15%–40% patients with AD at various disease stages.[23] The epileptogenic property of Aβ pathology has been demonstrated in various amyloidogenic mouse models and wild-type models with exogenous Aβ.[1] In human patients with late-onset epilepsy of unknown origin, there were lower levels of CSF Aβ42.[37,38] In patients with AD, Aβ-related alterations to large-scale network structure suggested propensity to generalized seizures according to a study using computational modeling with electrophysiologic data.[39] This study provides novel evidence that amyloid pathology is causally implicated in epileptogenesis in human.

Of interest, there was a significant effect of AD on generalized epilepsy but not on the subgroups CAE, JAE, JME, and GTCS. Approximately 34% cases with generalized epilepsy in the dataset belong to the "generalized epilepsy, not otherwise specified, with spike and wave EEG" subcategory, and this nonspecific subcategory might contribute most to the observed association. In addition, there was also limited sample size of each subgroup, which might limit the statistical power. Nevertheless, the potential association between

Figure 4 Association Between CSF Aβ42 Estimated by MR



For the association between Aβ42 and all epilepsy, between pTau and generalized epilepsy, the MR-PRESSO method found evidence of pleiotropy, and the results presented here are outlier-corrected. Aβ = β-amyloid; GSMR = generalized summary data–based MR; IVW = inverse variance weighted; MR = Mendelian randomization; MR-PRESSO = MR pleiotropy residual sum and outlier; pTau = phosphorylated tau.

early-life epilepsy and late-life neurodegeneration remains to be elucidated.

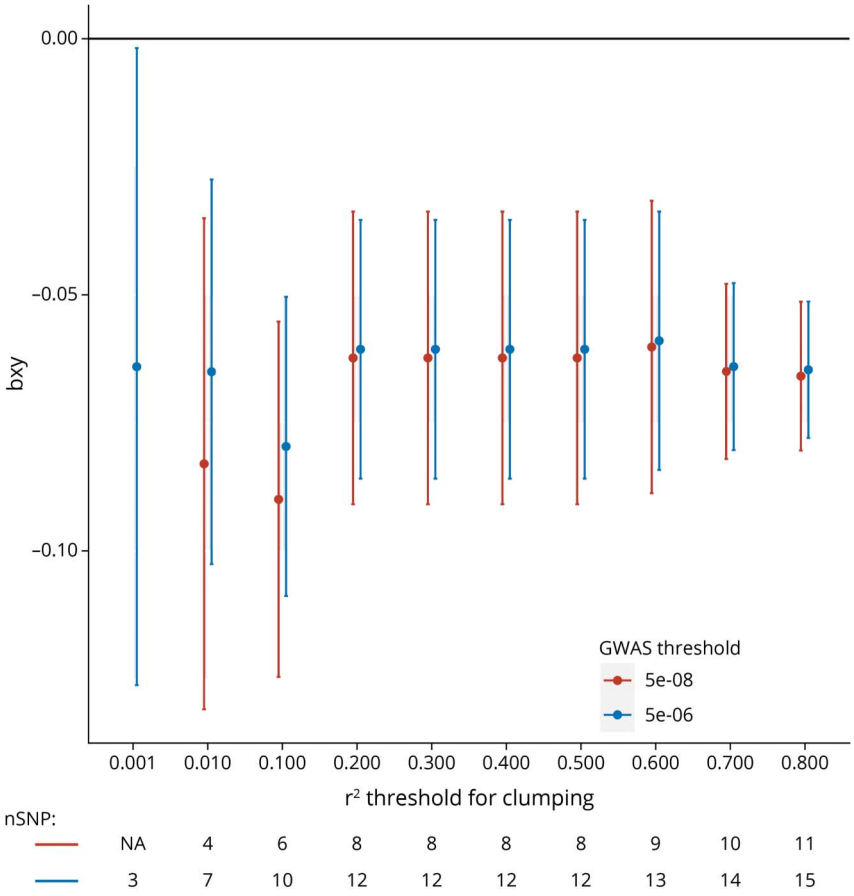
Our finding that AD was causally linked to focal epilepsy with HS adds to the previous body of literature that hippocampus and mesial temporal lobe (MTL) might account for network hyperexcitability and clinical seizures in AD. In an animal model of AD, spontaneous nonconvulsive seizure activity was detected in hippocampal network.[40] In patients with AD without a history of clinically overt seizures, most subclinical epileptiform discharges were detected in the temporal lobes.[41] In patients with early-stage AD and no clinical seizure, left temporal hyperexcitability was detected, while patients with AD with comorbid clinically overt seizures demonstrated temporal hyperexcitability in both hemispheres.[42]

The casual effect of AD on focal epilepsy with HS has several important implications. First, focal epilepsy with HS commonly presents as focal-onset seizures with or without impaired awareness presenting with déjà vu, amnestic spells, and fluctuation in cognition. Clinically, it is challenging to distinguish these nonconvulsive seizures from other transient events, including delirium, hallucinations, sundowning, syncope, transient ischemic attack, and metabolic disturbances, which are also commonly observed in older or demented patients. Therefore, a thorough and goal-directed history taking and long-term overnight EEG monitoring might facilitate the recognition of nonconvulsive seizures in patients with AD. Second, a large percent of MTL spikes and seizures are subclinical and are poorly transmitted to the scalp EEG electrodes.[43,44] The causal association between AD and focal epilepsy with HS indicates an urgent need to develop electrophysiologic biomarkers of MTL hyperexcitability.[42] Third, most of the studies in AD excluded patients with a personal history of seizure at enrollment. If seizure is an integral part of AD, future studies and trials may consider enrolling subjects with comorbid seizure.

Causal association is not necessarily exclusively unidirectional, and a potential bidirectional causal association has previously been reported.[45] In this study, we found that focal epilepsy with HS might be causally linked to AD. This finding is in accordance with previous observations that TLE gives rise to AD-like pathologic changes.[13,14] There was also an anecdotal report of a patient with drug-resistant HS diagnosed with AD 9 years after temporal lobe resection.[13] In this study, the suggestive causal effect of focal HS on AD implies that well-controlled focal HS would probably mitigate the risk of AD. Furthermore, targeting hyperexcitability is a feasible strategy to prevent or slow the progression of AD,[46] more bench and bedside studies are needed.

Confusion might arise when using the term "HS" in the context of AD and dementia. HS is a pathologic endpoint that

Figure 5 Estimates of Associations Between CSF Aβ42 and Generalized Epilepsy Estimated by GSMR Using Different Clumping Thresholds and GWAS Significance Levels



The estimated effect of CSF Aβ42 on generalized epilepsy remained in similar direction and magnitude and was consistently significant, except for clumping at 0.001. Vertical error bars represent standard error. When GWAS significance level was set at 5e-8 and clumping threshold was set at 0.001, only 1 SNP was left, and a GSMR analysis was not performed. Aβ = β-amyloid; GSMR = generalized summary data–based Mendelian randomization; GWAS = genome-wide association study; SNP = single-nucleotide polymorphism.

is associated with various underlying brain diseases, including TLE, HS of aging, tauopathy, nontauopathy FTD, and cerebrovascular disease.[47] Because overlap and discrepancies between HS aging and AD are gaining increasing attention, we would like to emphasize that the observed association between "focal HS" and AD does not represent such an association. The "focal HS" subgroup in this study was derived from the ILAE 2018 GWAS and represented a group of patients with focal epilepsy and evidence of HS on imaging.

There are several limitations in this study. First, clinical diagnosis of AD with different criteria at different centers was prone to inconsistency. Non-Alzheimer dementia, when incorrectly included, could drive a spurious association. Second, the MR method was unable to explore the time-specific effect. It remains unclear whether the epileptogenic process presents before, in parallel with, or after the onset of AD. As emerging evidence indicates that seizures could precede the onset of cognitive decline in AD,[38,48] more electrophysiologic studies in AD patients at various disease stages are needed. Third, although we used the largest available GWAS data, there is a relatively limited sample size for epilepsy subtypes and CSF biomarkers. Studies enrolling larger sample size are needed to replicate the current findings. In addition, this study constitutes participants of European ancestry. Future studies using GWAS data from other ethnicities (e.g., Biobank Japan, China Kadoorie Biobank) are needed to test the generalizability across different populations.

In conclusion, using MR, we provide novel evidence that AD was causally linked to generalized epilepsy and focal HS. Our finding highlights that AD and amyloid pathology give rise to epilepsies. More effort should be made to screen seizure in AD and understand its clinical implications.

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Disclosure

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