Shared genetic background between cerebrospinal fluid biomarkers and risk for Alzheimer's disease: A two-sample Mendelian randomisation study

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Research

Keywords: CSF biomarkers, Amyloid, Tau, Alzheimer's disease

Posted Date: March 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17511/v1

Version of Record: A version of this preprint was published at Journal of Alzheimer's Disease on April 6th, 2021. See the published version at https://doi.org/10.3233/JAD-200671.

Abstract

Background: Whether the epidemiological association of amyloid beta (Aβ) and tau pathology with Alzheimer's disease (AD) is causal remains unclear. Recent failures to demonstrate the efficacy of several Aβ-modifying drugs may indicate a possibility that the observed association is not causal, which led to efforts to develop tau-directed treatments whose efficacy remains tentative.

Methods: Herein, we conducted a two-sample Mendelian randomisation analysis to investigate shared genetic background between cerebrospinal fluid (CSF) biomarkers for amyloid and tau pathology and risk for AD, and to find genetic evidence for causal association between these CSF biomarkers and risk for AD. We used summary statistics of genome-wide association study (GWAS) for CSF biomarkers (Aβ 1-42 , phosphorylated tau 181 [p-tau], and total tau [t-tau]) in 3,146 individuals and for late-onset AD (LOAD) in 21,982 LOAD cases and 41,944 cognitively-normal controls. We tested association between changes in the genetically-predicted CSF biomarkers and LOAD risk.

Results: We found a decrease in the LOAD risk per one-standard deviation (SD) increase in the genetically-predicted CSF Aβ (odds ratio [OR], 2.87×10 -3 for AD; 95% confidence interval [CI], 1.54×10 -4 –0.05; p = 8.91×10 -5). Conversely, we observed an increase in the LOAD risk per one-SD increase in the genetically-predicted CSF p-tau (OR, 19.46; 95% CI, 1.50–2.52×10 2 ; p = 0.02) and t-tau (OR, 33.80; 95% CI, 1.57–7.29×10 2 ; p = 0.02).

Conclusions: Our findings suggest a shared genetic background between the CSF biomarkers and LOAD risk. Although it requires validation by future studies including more genetic variants identified in large-scale GWASs for CSF biomarkers, our results suggest a causal association between CSF biomarkers and risk for LOAD Keywords: CSF biomarkers, Amyloid, Tau, Alzheimer's disease

Background

Alzheimer's disease (AD), a leading cause of dementia, is the largest burden source of morbidity and mortality in older adults. One in every 85 individuals is expected to develop AD, which means that delaying the onset by 1 year can reduce the number of patients with AD worldwide by up to 9 million by 2020 [1]. Given that eightfold as many individuals have preclinical AD at risk of progression, the development of disease-modifying therapies is urgently required. Amyloid beta (Aβ) peptides are transmembrane amyloid precursor proteins and tau is a microtubule-associated protein. Decades of research have accumulated the evidence on the pathophysiology of Aβ and tau proteins that independently form plaques and tangles and lead normal functional neurons into a disabled state, AD. Understanding AD as the result of abnormal proteins, extracellular amyloid plaques, and intraneuronal neurofibrillary tau tangles, two-thirds of the novel treatment pipelines aim at disease-modifying therapies, 90% of which are anti-amyloid and anti-tau protein agents [2].

However, numerous trials aiming to develop disease-progression modification therapies, targeting the amyloid plaques, have recently failed. These failures could cast reasonable doubt regarding the role of Aβ

in the pathophysiology of AD with delicate elaboration. One possible explanation of the failure of clinical trials targeting the amyloid plaques is that the intervention is performed too late in the disease course to reverse the pathology in the trial participants [3]. However, the poor efficacy of the amyloid-targeting therapy may be due to the amyloid being a downstream result, rather than a cause of AD [4]. With these recent failures, tau protein has gained more attention as a target for disease-modifying therapies. Although previous animal studies have shown that the suppression of tau gene expression was protective to cognitive impairment, this impact required accompanying regulation of Aβ [5]. In addition, previous study related to the association between premortem cognitive function and AD neuropathology, including tau protein, has shown vague results [6]. These results also led to doubting tau pathology in AD. Thus, further research is required to determine whether Aβ or tau proteins are causal to AD or are surrogate markers for AD. This issue is crucial for the successful development of disease-modifying drugs.

One promising approach for investigating causality is Mendelian randomisation (MR) using genetic variants as the instrumental variables (IVs) [7]. The association between the genetic variants and the disease outcome can provide evidence of causation while, subject to certain assumptions, minimising confounding factors, including age, education, or other environmental exposures. This method may be useful to find shared genetic background between candidate drug target and AD [8], and to elucidate the causal relationship of Aβ or tau protein with AD without confounding factors and reverse causality.

Herein, we hypothesised that Aβ or tau protein in CSF have shared genetic background with late-onset AD (LOAD) and these biomarkers have a causal effect on the risk for LOAD. We tested the hypothesis using two-sample MR (TSMR) methods with summary statistics from large-scale genome-wide association studies (GWASs) of cerebrospinal fluid (CSF) biomarkers ($A\beta_{1\text{-}42}$ [Aβ], phosphorylated tau $_{181}$ [p-tau], and total tau [t-tau]) and late-onset AD [9, 10].

Methods

Exposure

In this study, we used three CSF biomarkers for AD, Aβ, p-tau, and t-tau, as exposures for investigating the causal relationship with the outcome of interest. Meta-analysed GWAS summary statistics of these biomarkers were obtained from 3,146 individuals of European ancestry in nine different studies (Knight ADRC, the Charles F. and Joanne Knight Alzheimer's Disease Research Center; ADNI1, Alzheimer's Disease Neuroimaging Initiative phase 1; ADNI2, Alzheimer's Disease Neuroimaging Initiative phase 2; BIOCARD, Predictors of Cognitive Decline Among Normal Individuals; HB, Saarland University in Homburg/Saar, Germany; MAYO, Mayo Clinic; SWEDEN, Skåne University Hospital; UPENN, Perelman School of Medicine at the University of Pennsylvania; UW, the University of Washington) [9]. The sample size of these GWASs is the largest at present with respect to Aβ, p-tau, and t-tau collected from CSF. The effect per single-

nucleotide polymorphism (SNP) in the GWAS summary statistics was defined as a standardised beta coefficient since each phenotype was converted using a log-transformation to follow the normal distribution.

Outcome

Our outcome of interest was LOAD, defined as AD with an onset at 65 years of age or older. We utilised the summary-level data from the stage 1 meta-analysis of the GWASs for LOAD in the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site [10]. The meta-analysis result was obtained from the four consortia (The Alzheimer Disease Genetics Consortium; The European Alzheimer's disease Initiative; The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; and The Genetic and Environmental Risk in AD Consortium Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium). It consisted of 46 case-control studies that included 63,926 individuals of European ancestry (21,982 LOAD cases and 41,944 cognitively normal controls).

Selection of instruments for MR

We performed the following procedures to select appropriate genetic variants that preferentially satisfy three IV assumptions of the MR analysis [11].

First, we selected top SNPs with a relaxed threshold ($p<1 \times 10^{-5}$), which was considered in recent MR analyses in the case when GWAS for exposure traits only yielded a small number of genome-wide significant SNPs [12]. The sample size of the data used in the present study is the largest on CSF biomarkers to date [9]. CSF biomarkers are expensive, acquired through an invasive procedure, and require skilled professionals, which results in difficulty to gather a sample size sufficient to identify many independent SNPs passing a genome-wide significance level ($p<5 \times 10^{-8}$). We relaxed the threshold ($p<1 \times 10^{-5}$) to compensate for the moderate sample size.

Second, we selected independent genetic variants among those that passed the relaxed threshold, using the cut-off of linkage disequilibrium (LD) value ($r^2<0{\cdot}001$) to ensure that the IVs for exposure were independent [13]. The LD between SNPs was calculated based on European individuals from the 1000 Genomes Project. If a certain SNP was not available in the summary statistics of the outcome, we substituted the SNP with its LD proxy SNP having a high correlation coefficient ($r^2 \geq 0{\cdot}8$) based on the European ancestry using the LDlink (https://ldlink.nci.nih.gov/). If such LD proxy SNP was not found, the SNP was excluded from the IV set.

Third, we eliminated SNPs with ambiguous alleles from the IV set when the alleles in the exposure and the outcome were not identical. For example, we excluded an SNP if the effect and non-effect alleles of the exposure and outcome were T/C and T/G, respectively [13].

Fourth, to ensure that there was no horizontal pleiotropy among the IVs, we conducted an MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) test that detects pleiotropic variants among the exposure-associated variants [14]. In our analysis, the MR-PRESSO removed more than 50% of the IVs, which means that MR-PRESSO might not detect true horizontal pleiotropy. Instead of removing the outliers detected by the MR-PRESSO, therefore, we considered excluding SNPs that have a known direct pleiotropic effect on LOAD, the outcome of interest. The Apolipoprotein E (*APOE*) region has been reported to have multiple pleiotropic effects in many previous studies. When the MR analysis is performed with the outliers detected by MR-PRESSO or variants in the *APOE* region, including the pleiotropic SNPs in the instruments, it may result in a positive bias or a negative bias due to horizontal pleiotropy and induce an inaccurate causal relationship [15]. Among the IVs of three CSF biomarkers, rs769449 is only one variant in the *APOE* region that is highly associated with LOAD [16]; therefore, we performed the MR analysis after excluding the *APOE* variant (rs769449) as a sensitivity test. Subsequently, to confirm the absence of horizontal pleiotropy, we performed a MR-Egger intercept test with the intercept unconstrained. The intercept of the MR-Egger regression represents a statistical estimate of the directional pleiotropic effect, which can be a confounding factor in MR. The selected genetic variants are listed in Additional file 1: Tables S1–S3.

Two-sample MR method(TSMR)

TSMR utilises GWAS summary statistics obtained from two large sample sets, allowing to use more robustly associated genetic instruments compared with one-sample MR [7]. TSMR in the present study was performed using the Two Sample MR R package (version 0·4·22) from the MR-Base platform [13]. To confirm that the findings of the estimation of the causal effect of the exposures on risk for LOAD are credible, we used diverse methods, including the inverse-variance weighted (IVW), MR-Egger regression, simple median, weighted median, and weighted mode. These multiple methods have been developed and differ from each other in terms of sensitivity to heterogeneity, bias, and power. We selected the IVW method as our primary MR method because it provides reliable results in the presence of heterogeneity in an MR analysis and is appropriate when using a large number of SNPs. The standard error (SE) of the IVW effect was estimated using a multiplicative random effects model. Because results of the IVW may be biased even though only one IV is invalid, we performed the MR-Egger regression that allows all IVs to be invalid under an InSIDE (instrument strength independent of direct effect) assumption [17]. The intercept term in the MR-Egger regression represents an estimate of overall pleiotropy. The null hypothesis for the MR-Egger intercept test is that the intercept term is equal to zero; therefore, we can trust the result of MR-Egger regression if the null hypothesis of the MR-Egger intercept test is rejected. We also tested two median-based estimators: simple median and weighted median which do not require the InSIDE

condition and assume that more than 50% of the IVs are valid. The weighted mode provides a single causal estimate based on the largest subset of IVs that have similar causal effects [18].

We used a forest plot to visualise the heterogeneity between the instruments due to horizontal pleiotropy and the contribution of each instrument to the overall estimate [13].

Power calculation

We calculated the statistical power of the MR using an online tool (https://sb452.shinyapps.io/power/) based on the proportion of variance in the exposure (R^2) explained by genetic instruments, true causal effect of the exposure on the outcome, sample size, and ratio of cases to controls of the outcome [19]. R^2 was obtained from the MR-Steiger directionality test. We estimated the true causal effect based on the observed odds ratios (ORs) between CSF biomarkers and risk for LOAD.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, or data interpretation. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Out of three CSF biomarkers, CSF Aβ and t-tau showed weak evidence of the causal effect on LOAD risk although all methods pointed in the same direction of effects. The IVW odds ratio [OR] for LOAD per one standard deviation (SD) increase in the genetically predicted CSF Aβ, 95% confidence interval [CI], and p value is 2.87×10^{-3}, 1.54×10^{-4}–0.05, and 8.91×10^{-5} (Table 1 and Fig. 1a). Those for CSF t-tau is 33.80, 1.57–7.29×10^{2}, and 0.02 (Table 1 and Fig. 1e). The MR tests after removing the *APOE* variant (rs769449) provided little evidence of causal effects of CSF Aβ and t-tau respectively, on risk for LOAD (CSF Aβ, IVW OR = 0.81, 95% CI = 0.46–1.41, p = 0.45; CSF t-tau, IVW OR = 1.22, 95% CI = 0.91–1.65, p = 0.19) (Table 1, Fig. 1b, and Fig. 1f).

We found a prominent association between CSF p-tau and risk for LOAD (IVW OR, 19.46 for LOAD per one SD increase in the genetically predicted CSF p-tau; 95% CI, 1.50–2.52×10^{2}; p = 0.02) (Table 1 and Fig. 1c). Unlike CSF Aβ and t-tau, the causal effects of p-tau on risk for LOAD were significant and consistent in the direction in multiple MR methods. Even in the MR test for CSF p-tau without the *APOE* variant, the casual effects of all methods except MR-Egger regression were marginally associated with risk for LOAD (IVW OR, 1.35 for LOAD per one SD increase in the genetically predicted CSF p-tau; 95% CI, 0.99–1.83; p = 0.0565) (Table 1 and Fig. 1d). MR-Egger was shown to yield minimally biased estimates regardless of the

pleiotropic SNPs in the instruments [20]. As we excluded the potential pleiotropic *APOE* variant in our MR test as *APOE* sensitivity analysis, the IVW has a greater power and derives a more precise estimate than the MR-Egger regression. The reason that the effect estimates of MR-Egger were not significant for all three CSF biomarkers is because MR-Egger is known to have reduced statistical power compared to IVW. We confirmed that there was no evidence for horizontal pleiotropy (intercept = -0.01, SE = 0.02, $p = 0.45$) and moderate heterogeneity between IVs (Q = 28, $p = 0.05$, I^2 [%] = 39) after removing the *APOE* variant for CSF p-tau (Table S4).

Given the observed ORs between measured CSF biomarkers and risk for LOAD, our MR analysis showed sufficient statistical power (>90%) to detect the causal effects of CSF biomarkers on risk for LOAD with a level of significance of 0·05. Table S5 presents the estimates of the statistical power for our MR analysis.

Discussion

Using TSMR with genetic instruments from large-scale GWASs, we investigated the shared genetic background between CSF biomarkers and risk for LOAD. In this MR study, we found the shared genetic background between CSF p-tau and the risk of LOAD, even after removing the *APOE* variant (rs769449). The CSF Aβ and t-tau instruments supported the shared genetic background between those biomarkers and the risk of LOAD at first but the association vanished after the exclusion of the *APOE* variant (rs769449). Our results are not only consistent with those of recent reports but also support the causal effect of these biomarkers, especially p-tau, in the risk of LOAD [21].

Although Aβ, p-tau, and t-tau in CSF have been reported to be useful as disease progression markers, randomised clinical trials (RCTs) have so far provided limited evidence on their causal relationship with LOAD [22, 23]. Recent RCTs on the elimination of accumulated Aβ or tau proteins could not provide solid evidence for improvement of the symptoms of LOAD [24, 25]. While clinical trials with small sample sizes have shown that eliminating Aβ elements led to symptomatic improvement, larger studies have failed to establish consistent results [24]. The agents reducing tau phosphorylation represented promising benefits in pilot clinical studies, but failed to show significant improvements in a cohort study [26]; tau aggregation inhibitors showed a similar pattern [27]. Although another approach for clarifying the causality for LOAD is the induced pathologic accumulation of Aβ and tau proteins in RCTs, such intervention in humans is not allowed due to ethical issues. Instead, the development of AD phenotypes has been attempted in numerous animal models with accumulating Aβ and tau proteins, and these still have various limitations [28, 29]. Transgenic animal models generally represent familiar AD rather than sporadic LOAD due to targeting a specific pathologic substance; therefore, they cannot provide a full explanation of LOAD. In addition, animal models could not represent the complex symptomatology of dementia that presents in humans.

In consideration of these perspectives, the principles of MR can be applied to clearly evaluate the shared genetic background between these biomarkers and risk for LOAD and to provide clues for the causality of these biomarkers in the aetiology of LOAD. This approach, which is conceptually similar to that of RCTs,

is based on Mendel's law of segregation that genetic variants are randomly allocated at meiosis and that these genetic variants are consequently independent of many confounding factors or reverse causation. Thus, an MR analysis could step forward the inference of the risk of LOAD driven through the genetically determined risk of amyloid accumulation and tau pathology. In our study, we found evidence supporting the potential causal relationships between Aβ, p-tau, and t-tau proteins in CSF and risk for LOAD. We also tried to clarify this association between p-tau and risk for LOAD after exclusion of impact of the *APOE* variant, using MR with genetic instruments selected from large-scale GWASs.

The causal estimates in our analysis were based on the largest GWAS to date, which may increase the precision of the estimates. We estimated a risk of LOAD 1.35-fold increase in the risk of LOAD per one SD increase in the CSF p-tau. These directions of association are consistent with those in previous reports [24]. Markedly increased levels of p-tau proteins and decreased levels of Aβ in CSF are represented as a specific finding in LOAD [21].

Aβ accumulation in the neuronal plaques and its binding to various receptors have been known as a hallmark of LOAD. Aβ binding to receptors has been understood as a process leading to neuronal toxicity, inducing mitochondrial dysfunction and oxidative stress [30]. The pathologic process of tau in LOAD consists of the development of phosphorylated pre-tangles and formation of the neuropil threads. After a process of hyperphosphorylation, acetylation, N-glycosylation, and truncation, tau forms the tangles in LOAD [31]. The observed shard genetic backgrounds of Aβ and p-tau observed in our MR analysis supports that Aβ and p-tau may play important roles in the pathophysiology of LOAD. In addition, further elaborated approach excluding the *APOE* variant, which led to maintained significant results, suggests independent implication of p-tau on risk for LOAD. Further studies investigating the biological mechanisms are needed.

T-tau in CSF and risk for LOAD was observed consistently with white matter hyperintensity change, which showed more emphasis on neurodegenerative change [32]. While tCSF p-tau levels are increased specifically in LOAD, CSF t-tau levels can be increased in various conditions of neurodegeneration, including LOAD and other brain disorders [33]. Our result may support a recent proposal emphasising tau hyperphosphorylation in AD versus excessive production of tau proteins [31].

The measured CSF biomarkers in AD reflect both the production and the clearance of these markers at a given time. In contrast, neuroimages represent the neuropathologic load or damage accumulated over time directly in the brain. Thus, imaging GWAS, such as amyloid or tau deposition in the brain measured by positron emission tomography (PET) as phenotypes [34], could provide additional information for the association between these biomarkers and risk for LOAD. However, the sample size of the current imaging genetic studies for these biomarkers is limited. Further studies with larger samples of genetic and imaging data could be helpful.

This study has several limitations. First, our causal estimates may be affected by several factors: horizontal pleiotropy, which was not detected by the applied MR sensitivity analysis methods, and the possibility of misclassified LOAD cases. Unlike the balanced or positive bias induced by horizontal

pleiotropy, the misclassified cases in the outcome may lead our results towards null. However, the estimates were statistically significant and consistent in various methods applied in our analysis. Second, our GWAS data included samples of Caucasian ancestry, which may limit the generalisation of our findings. Finally, even though we employed summary statistics from the largest GWASs on Aβ and tau proteins to date [9], we applied a relaxed threshold to include more IVs as performed in other psychiatric MR studies. Despite using instruments with a less stringent threshold, which may lead to null findings, our power analysis of the MR showed a statistical power greater than 90% and our analysis derived significant causal estimates.

Conclusions

In conclusion, we found shared genetic background between CSF biomarkers (Aβ, p-tau, and t-tau) and risk for LOAD in the TSMR analysis. The association between CSF p-tau and risk for LOAD was robust after excluding the *APOE* variant. Our results suggested the causal association between CSF biomarkers and risk for LOAD, and the aetiology of LOAD involves multiple biological processes, including amyloid and tau proteins in the AD pathophysiology. This complex nature of LOAD could partly explain recent multiple failures of clinical trials of anti-amyloid monotherapy. Further MR studies for multiple candidate biomarkers could be helpful to identify appropriate drug targets for LOAD and large-scale GWAS data with sufficient numbers of IVs are necessary to validate the causality of CSF Aβ and p-tau on risk for LOAD.

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Abbreviations

Aβ: Amyloid β; AD: Alzheimer’s disease; APOE: Apolipoprotein E; CSF: Cerebrospinal fluid; GWAS: Genome-wide association study; InSIDE: Instrument strength independent of direct effect; IV: Instrumental variable; IVW: Inverse-variance weighted; LD: Linkage disequilibrium; LOAD: Late-onset Alzheimer’s disease; MR: Mendelian randomization; MR-PRESSO: Mendelian randomization - Pleiotropy Residual Sum and Outlier; p-tau: Phosphorylated tau 181; SNP: Single-nucleotide polymorphism; t-tau: Total tau

Declarations

Acknowledgments

The authors thank the researchers at the Washington University School of Medicine for providing the summary statistics of GWAS for CSF biomarkers. This work was supported by a grant from the National Research Foundation (NRF) funded by the Ministry of Science and ICT (MSIT) [grant number NRF-2019R1A2C4070496 to HH Won; NRF-2018R1C1B6001708 to W Myung]. This work was also supported by grants from the National Institutes of Health [grant number R01LM012535, R03AG054936, and R03AG063250 to K Nho].

Authors' contributions

All authors contributed to the study concept and design. SK, KN, and HHW contributed

to the acquisition, analysis, or interpretation of the data. SK performed the statistical analysis.

KN, WM, and HHW obtained the funding. All authors wrote and revised the draft of the paper.

KN, WM, and HHW approved the final manuscript.

Funding

National Research Foundation of Ministry of Science and ICT, National Institutes of Health.

Availability of data and materials

These data do not belong to the authors, and the authors are not permitted to share them. The GWAS summary statistics for LOAD that supports the findings of this study is openly available in the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (https://www.niagads.org/). The GWAS summary statistics of Aβ, p-tau, and t-tau are available from the corresponding author (Dr. Deming, Y) of the CSF biomarker GWAS study upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB no. SMC 2016-12-064). Informed consent was waived by the board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Table 1

Table 1 Two-sample Mendelian randomisation for the causal relationship of amyloid beta, phosphorylated tau, and total tau with the risk for late-onset Alzheimer's disease

	Method	OR (95% CI)[a]	*p* value	p value of intercept	No. of SNPs[b]
	IVW	2.87×10^{-3} (1.54×10^{-4} to 0.05)	**8.91×10^{-5}**	-	15
	IVW[c]	0.81 (0.46 to 1.41)	0.45	-	14
	MR-Egger	7.03×10^{-6} (2.21×10^{-7} to 2.23×10^{-4})	**1.41×10^{-5}**	**1.10×10^{-3}**	15
	MR-Egger[c]	2.40 (0.56 to 10.34)	0.26	0.14	14
	Simple median	0.61 (0.34 to 1.09)	0.10	-	15
	Simple median[c]	0.75 (0.43 to 1.30)	0.30	-	14
	Weighted median	0.61 (0.34 to 1.08)	0.09	-	15
	Weighted median[c]	0.79 (0.44 to 1.39)	0.41	-	14
	Weighted mode	0.65 (0.28 to 1.53)	0.34	-	15
	Weighted mode[c]	0.72 (0.30 to 1.72)	0.47	-	14
ed tau	IVW	19.46 (1.50 to 2.52×10^{2})	**0.02**	-	19
	IVW[c]	1.35 (0.99 to 1.83)	0.0565	-	18
	MR-Egger	2.98×10^{4} (81 to 1.10×10^{7})	**3.29×10^{-3}**	**0.02**	19
	MR-Egger[c]	1.91 (0.75 to 4.89)	0.20	0.45	18
	Simple median	1.53 (1.07 to 2.20)	**0.02**	-	19
	Simple median[c]	1.47 (1.02 to 2.11)	**0.04**	-	18
	Weighted median	1.61 (1.13 to 2.31)	**9.09×10^{-3}**	-	19
	Weighted median[c]	1.59 (1.10 to 2.30)	**0.01**	-	18
	Weighted mode	1.88 (1.06 to 3.35)	**0.0451**	-	19
	Weighted mode[c]	1.93 (1.00 to 3.74)	0.0662	-	18
	IVW	33.80 (1.57 to 7.29×10^{2})	**0.02**	-	16
	IVW[c]	1.22 (0.91 to 1.65)	0.19	-	15
	MR-Egger	1.11×10^{6} (2.05×10^{3} to 6.03×10^{8})	**6.89×10^{-4}**	**3.70×10^{-3}**	16
	MR-Egger[c]	3.21 (1.24 to 8.30)	**0.03**	0.06	15
	Simple median	1.28 (0.86 to 1.89)	0.22	-	16
	Simple median[c]	1.21 (0.81 to 1.83)	0.35	-	15
	Weighted median	1.25 (0.83 to 1.87)	0.28	-	16
	Weighted median[c]	1.24 (0.83 to 1.84)	0.30	-	15
	Weighted mode	1.25 (0.60 to 2.57)	0.56	-	16
	Weighted mode[c]	1.29 (0.58 to 2.85)	0.54	-	15

IVW inverse variance-weighted, *MR* Mendelian randomisation, *OR* odds ratio, *CI* confidence interval, *SNP* single-nucleotide polymorphism. Significant values at the $p < 0.05$ level are highlighted in bold.

[a] Indicates odds ratio for AD per 1 standard deviation increase in genetically predicted amyloid beta, phosphorylated tau, or total tau.

[b] Top SNPs with $p < 1 \times 10^{-5}$ were included in the analysis.

[c] Indicates models excluding an *APOE* variant (rs769449).

Figures

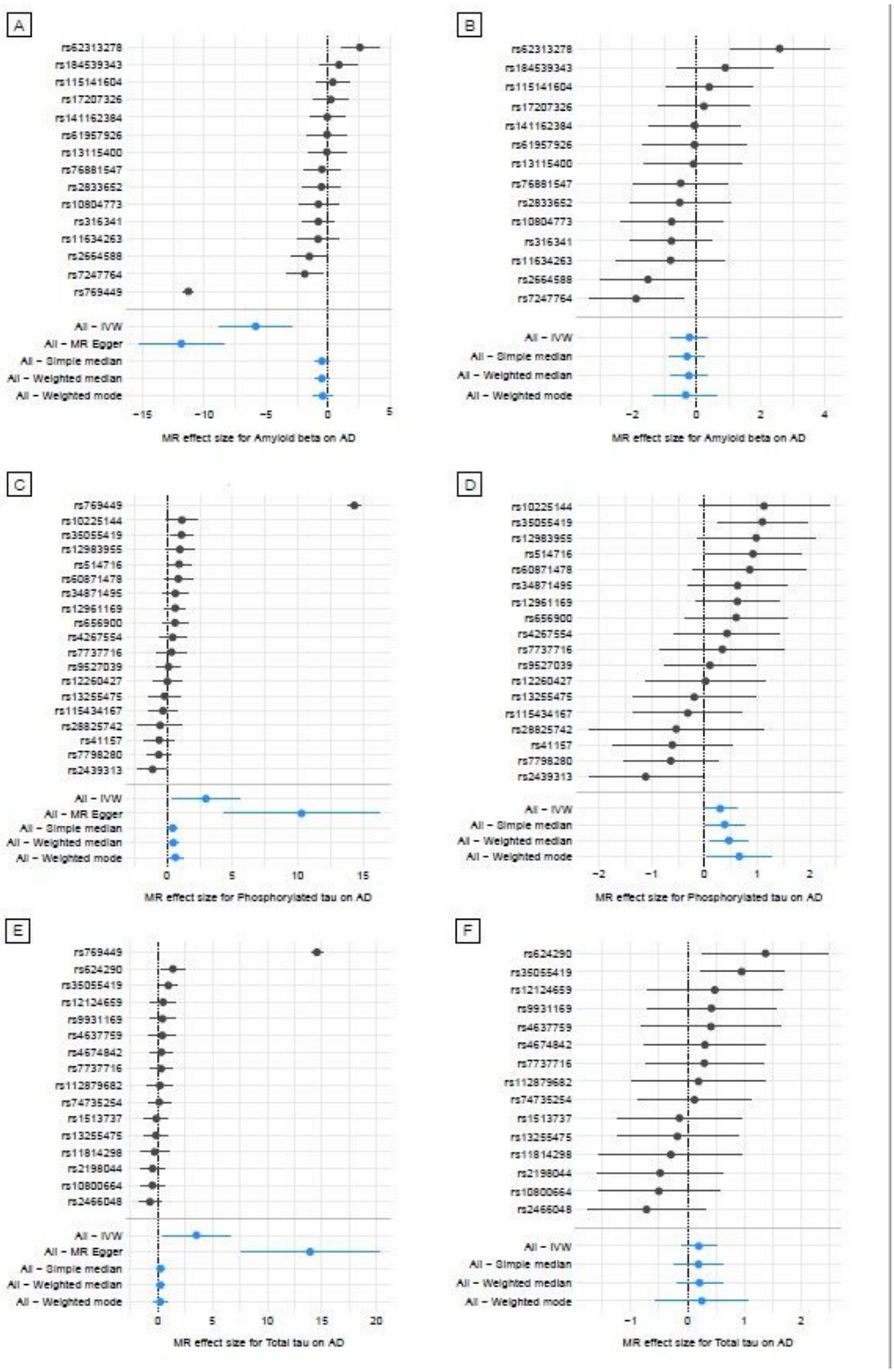

Figure 1

Estimated causal effects (logarithm of odds ratio)_of amyloid beta, phosphorylated tau, and total tau on the risk for late-onset Alzheimer's disease. (a) Forest plot of the estimate of amyloid beta on the risk for Alzheimer's disease for each or all variants. (b) Forest plot of the estimate of amyloid beta on the risk for Alzheimer's disease for each or all variants except the APOE variant (rs769449). (c) Forest plot of the estimate of phosphorylated tau on the risk for Alzheimer's disease for each or all variants. (d) Forest plot

of the estimate of phosphorylated tau on the risk for Alzheimer's disease for each or all variants except the APOE variant (rs769449). (e) Forest plot of the estimate of total tau on the risk for Alzheimer's disease for each or all variants. (f) Forest plot of the estimate of total tau on the risk for Alzheimer's disease for each or all variants except the APOE variant (rs769449).

Supplementary Files

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- SupportingDocumentation.docx