European Journal of Epidemiology
https://doi.org/10.1007/s10654-020-00683-8

NEURO-EPIDEMIOLOGY

Amyloid, tau and risk of Alzheimer's disease: a Mendelian randomization study

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Received: 27 April 2020 / Accepted: 26 August 2020

Abstract

This study was carried out to assess the effect of amyloid and tau on Alzheimer's disease using two-sample Mendelian randomization design. Genetic associations with plasma amyloid species (amyloid precursor protein, amyloid-like protein 2, serum amyloid P-component, amyloid beta peptide), cerebrospinal fluid (CSF) amyloid beta, total tau, and phosphorylated tau_{181} were extracted from the largest genome-wide association study (GWAS) available. Genetic associations with Alzheimer's disease were obtained from a GWAS of proxy-cases based on family history of Alzheimer's disease with 314,278 participants from the UK Biobank and a GWAS with clinically diagnosed Alzheimer's disease from the International Genomics of Alzheimer's Project (IGAP) with 21,982 cases and 41,944 controls. Estimates were obtained using inverse variance weighting with sensitivity analyses including MR-Egger, weighted median and MR-PRESSO. Presence of bias due to selective survival and competing risk was also considered. Plasma amyloid species, CSF total tau and phosphorylated tau_{181} were not associated with Alzheimer's disease. For CSF $A\beta_{42}$, no association was found using the proxy-cases but an inverse association was found after removing outliers with MR-PRESSO using IGAP. Higher genetically predicted ($p < 1 \times 10^{-5}$) plasma amyloid species, CSF total tau and phosphorylated tau_{181} (based on sample sizes ~ 3300) were not associated with Alzheimer's disease using family history or clinically diagnosed cases while effects of CSF $A\beta_{42}$ were inconsistent between the family history and IGAP GWAS.

Keywords Alzheimer's disease · Amyloid · Tau · Mendelian randomization

Introduction

The amyloid cascade hypothesis was proposed as a possible cause of Alzheimer's disease and has been the main focus of research for the past decades [1, 2]. However, randomized-controlled trials targeting amyloid have yet to show convincing results [3]. Circulating amyloid protein precursor and serum amyloid P-component as amyloid precursors have also been suggested as relevant to the development of Alzheimer's disease [4, 5]. In addition to amyloid beta protein, tau protein has also been suggested to be another possible cause through the formation of hyperphosphorylated tau and neurofibrillary tangles [6].

Given the long preclinical course of Alzheimer's disease, relatively few longitudinal studies have investigated the disease. Current evidence about possible causes of Alzheimer's disease, based on observational studies, may also be subjected to confounding. As such, Mendelian randomization provides a means to obtain unconfounded estimates of the association of amyloid and tau with Alzheimer's disease as demonstrated in previous studies investigating other modifiable pathways using the same methodology [7, 8].

To investigate the association of amyloid and tau with Alzheimer's disease, we conducted a two-sample Mendelian randomization study of the association of factors related to amyloid and tau, i.e., plasma amyloid precursor protein (APP), amyloid-like protein 2 (APLP2), serum amyloid P-component (SAP), plasma amyloid beta (Aβ) peptide as well as cerebrospinal fluid (CSF) amyloid beta ($A\beta_{42}$), total

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10654-020-00683-8) contains supplementary material, which is available to authorized users.

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Published online: 14 September 2020

tau, and phosphorylated tau ($ptau_{181}$) with Alzheimer's disease using a UK Biobank GWAS of family history of Alzheimer's disease and a GWAS of Alzheimer's disease from the International Genomics of Alzheimer's Project (IGAP).

Methods

Mendelian randomization is an instrumental variable analysis using genetic predictors [single-nucleotide polymorphisms (SNPs)] as instruments to predict the exposures of interest so as to obtain unconfounded estimates [9]. Genetic material is allocated randomly at conception, so Mendelian randomization is less likely to be affected by confounding [10]. Mendelian randomization relies on three assumptions, i.e., the genetic predictors are associated with the exposure, the genetic predictors are independent of factors that confound the exposure-outcome association, and the genetic predictors are only linked to the outcome through the exposure of interest (exclusion-restriction assumption) [11].

Study design

Genetic predictors of plasma APP, APLP2, SAP, $A\beta_{1-40}$, $A\beta_{1-42}$, CSF $A\beta_{42}$, total tau, and $ptau_{181}$

Genetic predictors of APP, APLP2 and SAP were obtained from a recent genome-wide association study (GWAS) of the human plasma proteome [12]. The study assessed more than 3600 proteins in 3301 individuals (mean age 43.7 years, 51.1% men) of European descent from the INTERVAL study [12]. Genetic associations were adjusted for age, sex, duration between blood draw and processing and the first three principal components of ancestry from multi-dimensional scaling [12].

Genetic predictors of plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides were obtained from a GWAS of the three-city (3C) study, Rotterdam study, Pittsburgh cardiovascular health study cognition study (CHS-CS) and the Alzheimer's disease neuroimaging initiative study (ADNI) consisting of 3528 healthy individuals of European descent (mean age 71.5 years, 59.8% men) [13]. Genetic associations were adjusted for age at blood collection, gender and principal components when population substructure was significantly associated with plasma amyloid beta [13].

Genetic predictors of CSF $A\beta_{42}$, total tau, and $ptau_{181}$ level were obtained from the most recent GWAS of 3146 participants (mean age 71.8 years, 50.4% men, 46.8% cases from 8 studies and 1 study without Alzheimer's disease status) from nine studies (Charles F and Joanne Knight Alzheimer's Disease Research Center, Alzheimer's Disease Neuroimaging Initiative, Predictors of Cognitive Decline Among Normal Individuals, Saarland University in Homburg/Saar, Germany, Mayo Clinic, Sahlgren's University Hospital, Sweden, Perelman School of Medicine at the University of Pennsylvania, University of Washington) [14]. Genetic associations were adjusted for age, gender and the first two principal components [14].

Genetic associations with Alzheimer's disease

Genetic associations with Alzheimer's disease were obtained from a GWAS using family history to obtain proxy-cases of Alzheimer's disease as well as the IGAP GWAS of clinically diagnosed late onset Alzheimer's disease (LOAD). The GWAS of family history has the advantage of capturing a population with a wider age range with less susceptibility to selection bias due to selective survival on exposure and competing risk of the outcome [15], but is based on a less precisely determined phenotype. IGAP has the advantage of precision from clinically diagnosed cases, but the GWAS is based on somewhat older people (mean age at onset: 72.9 years) so is more vulnerable to selection bias.

Genetic associations with proxy Alzheimer's disease cases were obtained from a GWAS of family history of Alzheimer's disease based on 314,278 participants from the UKBiobank [16]. After excluding participants with parents aged below 60 years, deceased before reaching 60 years or without age information, there were 27,696 maternal cases with 260,980 controls and 14,338 paternal cases with 245,941 controls [16]. Genetic associations with maternal or paternal Alzheimer's disease were obtained from a linear regression model and converted to odds ratios using observed sample prevalence [16]. The model was adjusted for age of parent at death or at time of the offspring's self-report, assessment center, genotype batch, array and 40 genetic principal components [16]. Results for paternal and maternal Alzheimer's disease were combined using meta-analysis [16].

Genetic associations with clinically diagnosed LOAD were obtained from a recent GWAS of the IGAP stage 1 discovery sample with 21,982 cases (mean age 72.9, 38.7% men) and 41 944 controls (mean age 72.4, 42.9% men) of European ancestry from four consortia (Alzheimer Disease Genetics Consortium, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium, The European Alzheimer's Disease Initiative, and Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium) [17]. Associations were adjusted for age (age-at-onset for cases and age-at-last exam for controls), sex and population substructure using principal components [17].

Selection of genetic predictors

We used all SNPs independently ($r^2 < 0.001$) and strongly (F-statistic > 10) predicting an exposure with $p < 1 \times 10^{-5}$. We did not use genome-wide significance because the sample sizes of the exposure GWAS were relatively small. Proxy SNPs ($R^2 > 0.8$) from LDLink (https://ldlink.nci.nih.gov/) were used if the original SNPs were not available for the outcome [18]. SNP-specific F-statistics were estimated as the square of the beta divided by the variance for the SNP-exposure association [19]. Since SNPs on the *APOE* region are highly associated with Alzheimer's disease which may lead to horizontal pleiotropy violating the "exclusion restriction" assumption, SNPs on the *APOE* region were removed a priori.

Statistical analysis

Estimates were obtained from meta-analysis of SNP-specific Wald estimates using inverse variance weighting with multiplicative random effects. This estimate assuming balanced pleiotropy was used as the main analysis. Results were presented in odds ratio (OR) of Alzheimer's disease per standard deviation (SD) increase in plasma amyloid species and OR per log-transformed SD increase in CSF $A\beta_{42}$, total tau, and $ptau_{181}$.

Sensitivity analyses with different assumption were also performed including Mendelian Randomisation (MR)-Egger, weighted median and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) [19–21]. MR-Egger provides valid estimates if the assumptions of MR as well as the InSIDE (INstrument Strength Independent of Direct Effect) assumption hold, even when all SNPs are invalid [20]. The MR-Egger intercept also provides evidence as to the presence of directional pleiotropy [20]. The weighted median provides valid estimates when at least 50% of the information comes from valid instruments [19]. MR-PRESSO tests and corrects for horizontal pleiotropy outliers assuming that at least 50% of the genetic variants are valid, have balanced pleiotropy and the InSIDE assumption holds [21].

Since selective survival on SNPs and competing risk of the outcome may also violate the "exclusion restriction" assumption by creating a pathway from SNPs to outcome not mediated through the exposure, we assessed whether the SNPs were associated with selective survival proxied by age at recruitment to UKBiobank [15, 22]. Genetic association with age at recruitment was obtained from the UKBiobank GWAS (http://www.nealelab.is/uk-biobank) with 361,194 participants from the UK [23]. The genetic associations were adjusted for the first 20 principal components and sex [23]. The main and sensitivity analyses were repeated after removing SNPs associated with age at recruitment.

All analyses were performed using R Version 3.4.2 with the R package "TwosampleMR", "MendelianRandomization" and "MRPRESSO" [21, 24, 25]. We used publicly available summary data so no ethical approval is required.

Results

Plasma APP, APLP2, SAP and amyloid beta peptide level with risk of Alzheimer's disease

The number of SNPs predicting APP, APLP2, SAP, $A\beta_{1-40}$ and $A\beta_{1-42}$ were 23, 26, 14, 10 and 8 respectively (Table e-1). 2 SNPs predicting APP and 3 SNPs predicting APLP2 (3 for GWAS of proxy-cases and 2 for IGAP GWAS) were not available in the outcome GWAS with no proxy SNPs available so they could not be included. All SNPs had F-statistics higher than 10. None of the plasma amyloid species were associated with the risk of Alzheimer's disease with consistent results using both proxy-cases and clinically diagnosed cases (Tables 1, 2). No pleiotropic effects were found using the MR-Egger intercept or MR-PRESSO with the exception of APP, APLP2 and $A\beta_{1-40}$. Estimates for APLP2 and $A\beta_{1-40}$ were consistent before and after removing outliers using MR-PRESSO while no significant outlier was identified for APP.

None of the SNPs were associated with age at recruitment using a p value corrected for multiple comparisons (0.05 divided by the number of SNPs used in the analysis; Table e-1).

CSF $A\beta_{42}$, total tau and $ptau_{181}$ level with risk of Alzheimer's disease

The number of SNPs predicting CSF $A\beta_{42}$, total tau and $ptau_{181}$ were 19, 19 and 21 respectively. 4 SNPs predicting CSF $A\beta_{42}$ (4 for GWAS of proxy-cases and 1 for IGAP GWAS), 1 SNPs predicting total tau and 1 SNP predicting $ptau_{181}$ for GWAS of proxy-cases were not available in the outcome GWAS without proxy SNPs so they were removed. The SNP rs769449 predicting CSF $A\beta_{42}$, total tau and $ptau_{181}$ was in the *APOE* region so it was also removed. All SNPs had F-statistics higher than 10 (Table e-1). After correcting for multiple comparison (0.05 divided by the number of SNPs used in the analysis), no SNP was associated with age at recruitment (Table e-1). CSF $A\beta_{42}$, total tau and $ptau_{181}$ were not associated with risk of Alzheimer's disease with consistent results in all sensitivity analyses using the GWAS of proxy-cases (Table 1). The MR-Egger intercept and MR-PRESSO did not show evidence of pleiotropy with the exception of CSF $A\beta_{42}$. The results were consistent before and after removing outliers using MR-PRESSO. Using IGAP, CSF total tau and $ptau_{181}$ were not

Table 1 Mendelian Randomization results for serum amyloid species, CSF amyloid and tau with risk of Alzheimer's disease using GWAS of family history

Exposure	SNPs	IVW				MR-Egger					WM			MR-PRESSO				
		OR	95% CI	*p*	I^2 (%)	OR	95% CI	*p*	intercept	intercept p	OR	95% CI	*p*	Global test p	SNPs	OR	95% CI	*p*
APP	21	0.97	0.92, 1.02	0.195	0	0.97	0.83, 1.12	0.639	< 0.001	0.999	0.99	0.92, 1.07	0.798	0.597				
ALPL2	23	0.97	0.91, 1.04	0.440	39	0.97	0.81, 1.16	0.727	0.001	0.945	0.99	0.92, 1.07	0.786	0.013	22	1.00	0.94, 1.06	0.923
SAP	14	1.01	0.95, 1.07	0.773	0	1.00	0.90, 1.12	0.972	0.002	0.897	1.00	0.92, 1.07	0.893	0.641				
$A\beta_{1–40}$	10	1.03	0.89, 1.18	0.732	48	0.96	0.59, 1.57	0.870	0.009	0.783	0.94	0.81, 1.09	0.425	0.011	9	0.98	0.84, 1.14	0.733
$A\beta_{1–42}$	8	0.92	0.77, 1.10	0.370	20	0.86	0.47, 1.56	0.616	0.007	0.804	0.90	0.74, 1.10	0.293	0.131				
CSF $A\beta_{42}$	14	0.69	0.38, 1.27	0.233	65	1.17	0.24, 5.73	0.846	−0.016	0.482	0.85	0.51, 1.43	0.548	< 0.001	12	0.85	0.53, 1.36	0.739
CSF total tau	17	1.08	0.81, 1.43	0.598	11	0.47	0.18, 1.21	0.116	0.029	0.071	1.12	0.78, 1.61	0.527	0.219				
CSF $ptau_{181}$	19	0.96	0.77, 1.20	0.738	0	0.80	0.38, 1.67	0.552	0.007	0.605	0.98	0.71, 1.34	0.885	0.613				

CI confidence interval, *IVW* inverse variance weighting, *OR* odds ratio, *p p*-value, *SNPs* single nucleotide polymorphisms, *WM* weighted median

OR represents change in odds ratio of Alzheimer's disease per standard deviation increase in APP, APLP2, SAP, $A\beta_{1–40}$, $A\beta_{1–42}$ and log-transformed SD increase in CSF Aβ42, total tau and $ptau_{181}$

Table 2 Mendelian Randomization results for serum amyloid species, CSF amyloid and tau with risk of Alzheimer's disease using IGAP GWAS

Exposure	SNPs	IVW				MR-Egger					WM			MR-PRESSO				
		OR	95% CI	*p*	I^2 (%)	OR	95% CI	*p*	intercept	intercept p	OR	95% CI	*p*	Global test p	SNPs	OR	95% CI	*p*
APP	21	1.02	0.94, 1.10	0.642	32	1.34	1.09, 1.64	0.005	−0.046	0.005	0.99	0.90, 1.09	0.809	0.036[a]				
APLP2	24	1.00	0.94, 1.07	0.925	21	1.08	0.90, 1.29	0.435	−0.015	0.425	1.01	0.93, 1.09	0.864	0.111				
SAP	14	1.02	0.97, 1.09	0.421	0	1.03	0.92, 1.16	0.577	−0.002	0.868	1.03	0.95, 1.13	0.445	0.736				
$A\beta_{1–40}$	10	1.01	0.91, 1.13	0.804	4	1.06	0.74, 1.51	0.755	−0.006	0.802	1.06	0.94, 1.20	0.360	0.262				
$A\beta_{1–42}$	7	0.97	0.83, 1.12	0.652	0	0.77	0.43, 1.40	0.395	0.020	0.447	0.89	0.73, 1.09	0.257	0.480				
CSF $A\beta_{42}$	17	0.46	0.17, 1.26	0.130	86	1.88	0.08, 43.42	0.694	−0.040	0.353	0.48	0.28, 0.83	0.009	$< 1 \times 10^{-5}$	14	0.54	0.35, 0.84	0.011
CSF total tau	17	1.20	0.92, 1.56	0.183	0	3.10	1.23, 7.82	0.016	−0.033	0.035	1.16	0.81, 1.66	0.429	0.366				
CSF $ptau_{181}$	20	1.25	0.92, 1.69	0.151	37	1.64	0.64, 4.25	0.306	−0.011	0.548	1.47	1.03, 2.09	0.032	0.023[a]				

OR represents change in odds ratio of Alzheimer's disease per standard deviation increase in APP, APLP2, SAP, $A\beta_{1–40}$, $A\beta_{1–42}$ and log-transformed SD increase in CSF Aβ42, total tau and $ptau_{181}$

CI confidence interval, *IVW* inverse variance weighting, *OR* odds ratio, *p p*-value, *SNPs* single nucleotide polymorphisms, *WM* weighted median

[a]No significant outliers found

associated with Alzheimer's disease (Table 2). There was also no association for CSF $A\beta_{42}$ before removing outliers but an inverse association was found after removing outliers using MR-PRESSO.

Discussion

This Mendelian Randomization study did not find evidence that plasma amyloid species (APP, APLP2, SAP, $A\beta_{1-40}$ and $A\beta_{1-42}$), CSF total tau or $ptau_{181}$ were associated with Alzheimer's disease, with consistent results using both proxy-cases and clinically diagnosed Alzheimer's disease. For CSF $A\beta_{42}$, no association was found using the GWAS with proxy-cases while an inverse association was found after removing outliers with MR-PRESSO using IGAP. These findings for amyloid are generally consistent with randomized-controlled trials targeting the amyloid cascade hypothesis showing no effect [3]. These findings are less consistent with observational studies showing tau, hyperphosphorylated tau and neurofibrillary tangles associated with Alzheimer's disease, and a recent Mendelian Randomization study showing an inverse association of $A\beta_{42}$ and a positive association of phosphorylated tau with Alzheimer's disease, but no association for total tau [26]. The inconsistency may be due to the use of an older age group where selection bias because of recruitment on surviving exposure and competing risk of Alzheimer's disease is likely to be more severe [15, 22].

In this study, we used both proxy-cases and clinically diagnosed Alzheimer's disease GWAS [27]. Given Alzheimer's disease mostly occurs in old age, a GWAS consisting only of clinically diagnosed Alzheimer's disease older participants may be more susceptible to bias due to selective survival (on exposure and competing risk) violating the "exclusion-restriction" assumption [15, 28]. Consistent results obtained for plasma amyloid species, CSF total tau and $ptau_{181}$ using both GWAS provides more confidence in the interpretation of the associations. The discrepant results for CSF $A\beta_{42}$ may be due to a different case definition in the IGAP GWAS of clinically diagnosed cases than in the family history GWAS with proxy-cases, or possible bias from selective survival and competing risk using the IGAP GWAS with relatively older participants.

The amyloid cascade hypothesis has been one of the main foci of Alzheimer's disease research [1]. Previous studies have proposed possible mechanisms for the association of amyloid beta with Alzheimer's disease [2]. However, concerns exist as to whether it is really the cause regardless of other evidence, because amyloid beta accumulation and deposition are only weakly correlated with cognitive decline [29]; cognitively normal people have significant amyloid plaque burden [30] and the relevance of evidence from transgenic mice translates to the etiology of Alzheimer's disease in humans is uncertain [1].

The tau hypothesis for Alzheimer's disease suggests that tau, hyperphosphorylated tau and neurofibrillary tangles could be responsible for the degeneration of neurons in Alzheimer's disease [3]. In this study, total tau was not associated with Alzheimer's disease which is inconsistent with observational studies showing CSF total tau associated with Alzheimer's disease [31]. Higher CSF total tau has also been associated with more rapid cognitive decline and hippocampal atrophy [32, 33]. Previous studies also showed CSF total tau increased after acute stroke and boxing reflecting neuronal or axonal damage [34, 35]. It is possible that increase in CSF total tau reflects but does not cause neuronal damage which may explain the inconsistency of positive associations in observational studies but not using mendelian randomization. We also found no association of $ptau_{181}$ with Alzheimer's disease, which is inconsistent with previous observational studies suggesting hyperphosphorylated tau is positively associated with Alzheimer's disease [31]. However, we only investigated the effect of $ptau_{181}$ but not the effect of the proportion of $ptau_{181}$ to total tau on Alzheimer's disease [36]. In addition, our study only assessed the association of $ptau_{181}$ in the CSF with Alzheimer's disease due to GWAS availability, while the association of tau with phosphorylation at other sites may be different [36]. Specifically, tau hyperphosphorylation at T111, T153, T205, S208 and T217 may be more relevant to Alzheimer's disease than that at T181 [36].

In this study, we did not find evidence that plasma amyloid species, CSF total tau or $ptau_{181}$ were associated with Alzheimer's disease with inconsistent results for CSF $A\beta_{42}$, suggesting these factors may not be causal but downstream factors affected by and reflective of the emergence of Alzheimer's disease. However, we proxied these exposures with lifelong genetic traits, which might not translate into rising levels specifically precipitating Alzheimer's disease, although higher lifelong levels might be expected to increase vulnerability to Alzheimer's disease. In addition, this study is based on genetic predictors of circulating amyloid species, CSF total tau, $ptau_{181}$ and CSF $A\beta_{42}$ whose correspondence with biological markers of Alzheimer's disease, such as amyloid plaques or tau tangle formation, in the brain is far from perfect. As such, a role of amyloid plaques and/or tau tangles in AD cannot be excluded. Further, mendelian randomization studies using genetic predictors of the specific brain pathology may clarify this point, but are currently infeasible because of a lack of available measurements and corresponding GWAS.

Limitations

Despite the strengths of the Mendelian Randomization design, it has important assumption. First, the SNPs should strongly predict the exposures. Here, we used a *p* value cut-off (1×10^{-5}) instead of genome-wide significant which may make it harder to detect an association. Nonetheless, F-statistics for all SNPs were larger than 10 indicating weak instrument bias may not be severe. However, we cannot entirely exclude the possibility that our null results are the result of weak instrument bias. Second, the SNPs were assumed to be independent from confounders of the exposure-outcome association, as shown in a previous study [37]. Third, the SNPs should be linked to the outcome through the exposure of interest only (i.e. exclusion restriction assumption). SNPs on the APOE region (rs769449) was removed a priori since it is highly associated with risk of Alzheimer's disease and possibly pleiotropic. Presence of other pleiotropic SNPs were also identified and corrected for using the MR-Egger intercept and MR-PRESSO. We also considered whether selective survival and competing risk may violate the exclusion-restriction assumption by assessing associations of the included SNPs with age at recruitment into the UK Biobank to proxy selective survival. We used GWAS of Alzheimer's disease with proxy-cases from the UK Biobank which has relatively younger participants, thus is less susceptible to selection bias, because fewer potential participants from the same underlying cohort are "already dead". We also repeated our analyses using the IGAP GWAS. Fourth, population stratification may affect the results. However, our results were based on people mainly of European ancestry with genomic control which should minimize that effect. Fifth, our results were obtained from mainly European populations so may not be generalizable to other populations. However, the underlying biological mechanisms should be consistent although they may be more or less relevant in different populations [38]. Sixth, we only assessed the possible causal association of amyloid and tau with risk of Alzheimer's disease but not the effect of Alzheimer's disease on amyloid and tau because of lack of suitable data. Seventh, we only assessed the effect of CSF $A\beta_{42}$, tau and $ptau_{181}$ on Alzheimer's disease while the effect of tau with phosphorylation on other phosphorylation site as well as $A\beta_{42}$ and tau in other region of the brain were not assessed. Eighth, family history of Alzheimer's disease may not perfectly capture Alzheimer's disease. We repeated our analyses using the IGAP GWAS giving clinically diagnosed Alzheimer's disease and similar results were obtained which gives more confidence in the results. However, we cannot eliminate the possibility that the null results are due to imprecision when using the GWAS of family history.

Higher genetically predicted ($p < 1 \times 10^{-5}$) plasma APP, APLP2, SAP, $A\beta_{1-40}$, $A\beta_{1-42}$, CSF total tau and $ptau_{181}$ (based on sample sizes ~ 3300) were not associated with Alzheimer's disease while effects of CSF $A\beta_{42}$ was inconsistent between the analyses using proxy-cases based on family history and clinically diagnosed Alzheimer's disease. Further investigation of the role of tau with phosphorylation at other sites as well as the role of amyloid plaques and tau tangles could be valuable for explicating the underlying association with Alzheimer's disease.

Acknowledgements We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i–Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD/PERADES was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) Grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES contract N01–AG–12100, the NHLBI Grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA Grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association Grant ADGC–10–196728. Data on family history Alzheimer's disease summary statistics have been contributed by Centre for Cognitive Ageing and Cognitive Epidemiology at the University of Edinburgh and have been downloaded from http://www.ccace.ed.ac.uk/about-us. Data on age at recruitment have been contributed by UK Biobank Ben Neale files and have been downloaded from http://www.nealelab.is/uk-biobank.

Authors' contributions All authors designed the study and interpreted the results. CHCY conducted the analyses and wrote the first draft of the article with critical feedback and revision from CMS, SLAY and KL. All authors gave approval for the final version of the article for publication.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and material All data are available in the submitted manuscript, supplementary files or related sources described in the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval We used publicly available summary data where no ethical approval is required.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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