Research Paper

Associations of the *APOE* ε2 and ε4 alleles and polygenic profiles comprising *APOE-TOMM40-APOC1* variants with Alzheimer's disease biomarkers

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ABSTRACT

Capturing the genetic architecture of Alzheimer's disease (AD) is challenging because of the complex interplay of genetic and non-genetic factors in its etiology. It has been suggested that AD biomarkers may improve the characterization of AD pathology and its genetic architecture. Most studies have focused on connections of individual genetic variants with AD biomarkers, whereas the role of combinations of genetic variants is substantially underexplored. We examined the associations of the *APOE* ε2 and ε4 alleles and polygenic profiles comprising the ε4-encoding rs429358, *TOMM40* rs2075650, and *APOC1* rs12721046 polymorphisms with cerebrospinal fluid (CSF) and plasma amyloid β (Aβ40 and Aβ42) and tau biomarkers. Our findings support associations of the ε4 alleles with both plasma and CSF Aβ42 and CSF tau, and the ε2 alleles with baseline, but not longitudinal, CSF Aβ42 measurements. We found that the ε4-bearing polygenic profiles conferring higher and lower AD risks are differentially associated with tau but not Aβ42. Modulation of the effect of the ε4 alleles by *TOMM40* and *APOC1* variants indicates the potential genetic mechanism of differential roles of Aβ and tau in AD pathogenesis.

INTRODUCTION

Late-onset Alzheimer's disease (AD) has a multifactorial etiology, which is affected by a complex interplay of genetic and non-genetic factors [1]. The estimates of heritability of 45% for women and 58% for men in a study of Swedish twins [2] suggest that the genetic contribution to AD pathogenesis can be substantial. However, capturing the genetic architecture of AD is challenging because of the complex interplay of genetic and non-genetic factors in its etiology. Indeed, despite discoveries of AD loci in large-scale genome-wide association studies (GWAS) [3–6], these loci are considered risk rather than causal factors for AD. The challenging role of genes in AD is exemplified by the apolipoprotein E (*APOE*) ε4 allele, which is the strongest individual genetic risk factor for AD. Even though the *APOE*

gene has been studied for decades, its role in AD is not fully understood [7, 8].

The 2018 NIA-AA research framework [9–11] promoted the biological definition of AD pathology based on amyloid β (Aβ), tau, and neurodegeneration biomarkers. Positron emission tomography (PET) imaging studies identified Aβ and tau as valuable biomarkers to characterize AD development, with tau considered a more accurate AD biomarker than Aβ [12]. Cerebrospinal fluid (CSF) and plasma measurements of Aβ, particularly Aβ42 and tau, are used to facilitate AD diagnosis [13, 14]. Low levels of Aβ42 indicate accumulation of Aβ in plaques, whereas high tau levels are associated with neuronal injury [15]. The emergence of the biological definition of AD pathology opens a promising avenue in studies of the genetic architecture of AD.

Prior analyses showed that carriers of the *APOE* ε4 allele have lower levels of Aβ42 [16] and higher levels of tau [17] in CSF, although the latter might be controversial [18]. Given the multifactorial etiology of AD, the genetic architecture of AD and its biomarkers is likely heterogeneous. It is complicated by polygenicity, pleiotropy, and interactions with genetic and non-genetic factors. This complexity is in contrast to Mendelian traits; the traits, which may be caused by genetic mutations directly affecting protein function [19]. For example, the autosomal dominant form of early-onset AD can be caused by specific mutations in the *APP*, *PSEN1*, or *PSEN2* genes [20–23].

Studies also examined a role of an interplay between the *APOE* variants and other genetic factors in AD. For example, Franceschi's group identified a haplotype comprising the ε4 and rs405509_T promoter variants conferring the AD risk [24]. Haplotypes composed of non-coding variants in the *APOE* gene cluster were reported in [25, 26]. Roses's group showed a pivotal role of *TOMM40* poly-T rs10524523 and *APOE* ε2/ε3/ε4 haplotypes in AD pathogenesis [27]. Le Guen et al., [28] identified rare *APOE* functional variants co-inheriting with the ε4 allele and ameliorating its adverse effect. However, studies examining the relationships between combinations of genetic variants and AD biomarkers are in their infancy [29] and novel methods can be helpful for accelerating progress in the field.

A method examining differences in linkage disequilibrium (LD) structures in trait-affected and unaffected subjects was suggested to efficiently map promising associations [30]. Its advantage is that it helps identify connections between combinations of genetic variants and a complex trait. This method is well adapted to examine pairs of genetic variants, such as single nucleotide polymorphisms (SNPs). Recently, we generalized it from pairs of SNPs to triples of SNPs using the co-skewness metric [31]. Following these methods, we mapped compound genotypes—certain combinations of genetic variants—comprising rs429358 (*APOE*), rs2075650 (*TOMM40*), and rs12721046 (*APOC1*) SNPs to AD [31, 32]. We showed that a combination of the *APOE* ε4 allele (encoded by rs429358 minor allele) and minor alleles of rs2075650 and rs12721046 SNPs conferred a remarkably high risk of AD compared to the ε4-bearing compound genotypes which do not include minor alleles of rs2075650 and rs12721046 [32]. Here, we examine the associations of the *APOE* ε2 and ε4 alleles and the AD-risk-differentiating compound genotypes comprising rs429358, rs2075650, and rs12721046 SNPs with Aβ40, Aβ42, and tau AD biomarkers measured in CSF and plasma using data from three studies: the AD Neuroimaging Initiative (ADNI), the Atherosclerosis Risk in Communities (ARIC) study, and the Framingham Heart Study (FHS).

RESULTS

Study overview

We performed three types of analyses. First, we evaluated mean levels of Aβ40, Aβ42, and tau in CSF and plasma and the correlation between them. Second, we examined associations of the ε4 and ε2 alleles individually with AD biomarkers to establish benchmark effects in our samples. Third, as no significant associations of the ε2 allele with AD biomarkers were identified, we explored associations of the AD-risk-differentiating ε4-bearing compound genotypes comprising rs429358, rs2075650, and rs12721046 SNPs with the selected AD biomarkers. The goal was to identify whether the ε4 allele exerted effects on the selected biomarkers independently of the *TOMM40* rs2075650 and *APOC1* rs12721046 SNPs or whether its effect could be modulated by the latter two SNPs.

Plasma and CSF AD biomarkers: mean levels and correlation

Table 1 and Supplementary Table 1 show that the mean levels of both baseline- and longitudinally-measured AD biomarkers vary across the study cohorts (see Methods), and they are substantially larger in CSF than in plasma. Correlation analysis of the AD biomarkers shows that CSF total tau and p-tau are perfectly correlated with the Pearson correlation coefficient $r = 0.98$ in ADNI (Supplementary Table 2). Given that p-tau was not available in other studies, the results for p-tau were not included.

Table 1. Baseline characteristics of the genotyped participants of European ancestry in the selected studies.

Study	Source	*N*	Men (%)	Age (SD, SE), years	Aβ40 (SD, SE), pg/ml	Aβ42 (SD, SE), pg/ml	Tau (SD, SE), pg/ml	pTau (SD, SE), pg/ml
ARIC	Plasma	1560	723 (46.3)	77.4 (5.4, 0.1)	247.0 (84.5, 2.1)	39.1 (11.2, 0.3)	NA	NA
FHS_C1	Plasma	636	227 (35.7)	79.8 (4.2, 0.2)	168.3 (41.9, 1.7)	45.4 (11.5, 0.5)	5.0 (1.5, 0.1)	NA
FHS_C2	Plasma	3095	1443 (46.6)	61.0 (9.5, 0.2)	159.6 (40.5, 0.8)	43.7 (10.3, 0.7)	4.2 (2.7, 0.1)	NA
FHS_C3	Plasma	3029	1424 (47.0)	45.7 (8.0, 0.1)	242.5 (58.0, 1.1)	42.7 (10.0, 0.2)	4.1 (1.5, 0.02)	NA
ADNI-1	Plasma	612	374 (61.1)	75.4 (6.7, 0.3)	152.9 (50.5, 2.0)	37.2 (11.3, 0.5)	2.9 (1.6, 0.1)	NA
ADNI-1	CSF	350	212 (60.6)	74.9 (7.1, 0.4)	7737.3 (2352.3, 125.7)	769.0 (352.0, 18.9)	302.3 (118.4, 6.3)	29.7 (13.6, 0.7)
ADNI-2/GO	CSF	360	203 (56.4)	72.9 (7.4, 0.4)	8590.2 (2437.7, 130.1)	920.6 (368.2, 19.4)	271.6 (118.6, 6.3)	25.7 (13.1, 0.7)

N denotes the number of subjects; Abbreviations: CSF: cerebrospinal fluid; SD: standard deviation; SE: standard error; NA: not available. ARIC is the Atherosclerosis Risk in Communities Study; FHS_C1, FHS_C2, and FHS_C3 denote the Framingham Heart Study parental, offspring, and grandchildren cohorts, respectively; ADNI-1 and ADNI-2/GO denote the Alzheimer's disease Neuroimaging Initiative initial and extended cohorts, respectively. Age was defined at the time of the Alzheimer's disease biomarker measurement.

Table 2. Meta-analysis of the associations of the *APOE* ε4 allele with Alzheimer's disease (AD) biomarkers.

Biomarker	Source	$N_{reference}$	$N_{\varepsilon4}$	Beta	SE	*P* value	Direction
Aβ40	CSF*	334	304	−0.011	0.024	6.49E-01	−+????
Aβ40	Plasma**	5683	2109	−1.287	1.300	3.22E-01	−?−+−−
Aβ42	CSF*	259	292	−0.334	0.034	1.50E-22	−−????
Aβ42	Plasma**	5679	2106	−1.903	0.271	2.18E-12	−?−−−−
Tau	CSF*	341	302	0.261	0.031	6.58E-17	++????
Tau	Plasma*	3951	1484	0.006	0.011	5.67E-01	+?−+−?

$N_{reference}$ denotes the number of carriers of the ε33 genotype used as a reference. $N_{\varepsilon4}$ shows the number of the *APOE* ε4 carriers defined as having either ε34 or ε44 genotype. SE denotes standard error and CSF denotes cerebrospinal fluid. Asterisks denote a gamma general linear model with a log link function (*) and an ordinary linear model (**) used for the analysis. Column "Direction" shows sign of the effect beta in individual studies in the following order: ADNI-1, ADNI-2/GO, FHS_C1, FHS_C2, FHS_C3, and ARIC. Question mark indicates missing estimates. Note, CSF biomarkers were available only in ADNI cohorts; plasma biomarkers were not available in ADNI-2/GO, and tau was not reported in ARIC. Biomarkers were measured at baseline. More details with individual-study estimates are given Supplementary Table 3.

Associations of the *APOE* ε2 and ε4 alleles with AD biomarkers

The ε4 alleles were consistently associated (see Methods) with lower levels of both CSF and plasma Aβ42 in each cohort (Table 2 and Supplementary Table 3), despite the lack of significant correlation between them, $r = 0.074$ ($p = 0.219$) (Supplementary Table 2). Although CSF and plasma tau were weakly correlated ($r = 0.155$, $p = 4.5 \times 10^{-3}$), the *APOE* ε4 alleles were consistently associated with higher levels of CSF tau, but they were not significantly associated with plasma tau. The meta-analysis did not show significant associations with Aβ40 either in CSF or plasma, despite its modest-to-strong correlation with Aβ42, i.e., $r = 0.388$–0.703 in plasma and $r = 0.253$–0.304 in CSF. Qualitatively the same associations were observed using longitudinal measurements (Supplementary Table 3).

The ε2 alleles were associated only with CSF Aβ42 in the meta-analysis of the data available from baseline measurements in ADNI-1 and ADNI-2/GO ($\beta = 0.143$, $p = 0.032$) with a small number of subjects ($N = 37$), but not in longitudinal analysis of these data ($\beta = 0.112$, $p = 0.280$) with a larger number of observations ($N = 80$) (Supplementary Table 4).

Associations of compound genotypes with AD biomarkers

Given associations of the ε4 alleles with Aβ42 and tau, we examined associations of the AD-risk differentiating compound genotypes comprising the ε4-encoding rs429358, *TOMM40* rs2075650, and *APOC1* rs12721046 SNPs with Aβ42 and tau measured at baseline (see Table 3 and Supplementary Table 5 for notations and the results). The ε4-bearing compound genotypes were significantly associated with lower levels of CSF and plasma Aβ42 and higher levels of CSF tau regardless of minor alleles of the other two SNPs. However, the compound genotype with the ε4 alleles and no minor alleles of the other two SNPs was associated with smaller levels of plasma tau (Table 3, 100+200), whereas no significant associations were observed for

Table 3. Meta-analysis of the associations of compound genotypes with Alzheimer's disease (AD) Aβ42 and tau biomarkers.

Biomarker	Source	Genotype	*N*	Beta	SE	*P* value	Direction
Aβ42	CSF	0XY	59	0.026	0.055	6.37E-01	−+????
Aβ42	CSF	100+200	56	−0.272	0.057	2.13E-06	−−????
Aβ42	CSF	111+222	178	−0.341	0.039	2.46E-18	−−????
Aβ42	CSF	1XY+2XY	242	−0.373	0.037	2.18E-24	−−????
Aβ42	CSF	000	237		Reference		
Aβ42	Plasma	0XY	951	0.351	0.364	3.35E-01	−?−−++
Aβ42	Plasma	100+200	396	−2.305	0.551	2.82E-05	−?−−−−
Aβ42	Plasma	111+222	1462	−1.582	0.312	4.14E-07	−?−−−−
Aβ42	Plasma	1XY+2XY	1821	−1.656	0.287	7.98E-09	−?−−−−
Aβ42	Plasma	000	5549		Reference		
Tau	CSF	0XY	70	0.088	0.050	7.97E-02	++????
Tau	CSF	100+200	56	0.233	0.056	2.85E-05	++????
Tau	CSF	111+222	189	0.293	0.035	4.87E-17	++????
Tau	CSF	1XY+2XY	253	0.294	0.032	6.75E-20	++????
Tau	CSF	000	326		Reference		
Tau	Plasma	0XY	647	0.009	0.013	4.91E-01	−?−+−?
Tau	Plasma	100+200	289	−0.045	0.018	1.28E-02	+?−−−?
Tau	Plasma	111+222	1033	−0.010	0.011	3.66E-01	+?−−−?
Tau	Plasma	1XY+2XY	1280	−0.002	0.010	8.42E-01	+?−−−?
Tau	Plasma	000	3913		Reference		

Column "Genotype" shows compound genotypes encoded by triples of numbers and X and Y letters. Numbers show the counts of minor alleles (i.e., 0, 1, 2) in rs429358_T/c, rs2075650_A/g or rs12721046_G/a SNP, in that order. The upper/lower case denotes here major/minor allele. The most frequent 000 genotype denotes the major allele homozygote for all three SNPs, i.e., rs429358_TT, rs2075650_AA, rs12721046_GG. The 100+200 genotype indicates rs429358_Tc, rs2075650_AA, rs12721046_GG (100) and rs429358_cc, rs2075650_AA, rs12721046_GG (200). The 111+222 genotype denotes rs429358_Tc, rs2075650_Ag, rs12721046_Ga (111) and rs429358_cc, rs2075650_gg, rs12721046_aa (222). Letters X and Y indicate aggregation of minor alleles of rs2075650 and rs12721046, respectively. Then, 0XY aggregates all non-ε4 genotypes except 000. The 1XY+2XY genotype aggregates rs429358_Tc (1) and rs429358_cc (2) and all genotypes of rs2075650 (X) and rs12721046 (Y), except major allele homozygote of both SNPs, rs2075650_AA and rs12721046_GG (00), because it is included in the 100+200 genotype. Column "Direction" shows sign of the effect beta in individual studies in the following order: ADNI-1, ADNI-2/GO, FHS_C1, FHS_C2, FHS_C3, and ARIC. Question mark indicates missing estimates. Note, cerebrospinal fluid (CSF) biomarkers were available only in ADNI cohorts; plasma biomarkers were not available in ADNI-2/GO, and tau was not reported in ARIC. A gamma general linear model with a log link function was used for all biomarkers except Aβ42 measured in plasma. SE denotes standard error. More details with individual-study estimates are given Supplementary Table 5.

carriers of the compound genotypes aggregating minor alleles of those two SNPs (Table 3, 111+222 and 1XY+2XY). No significant associations were seen for non-carriers of the ε4 alleles who have minor alleles of rs2075650 and rs12721046 (Table 3, 0XY).

The ε4-bearing compound genotypes having (111+222 and 1XY+2XY) and not having (100+200) minor alleles of rs2075650 and rs12721046 represent polygenic profiles conferring higher and lower AD risk, respectively [32]. Then, we quantified potential differences in the associations of these compound genotypes with Aβ42 and tau (Table 4 and Supplementary Table 6). No significant differences in the associations of these ε4-bearing higher and lower AD risk compound genotypes with CSF and plasma Aβ42 were identified. Carrying the ε4 allele and minor alleles of rs2075650 and rs12721046 was associated with significantly higher levels of plasma tau compared to having the ε4 allele and no minor alleles of these two SNPs, $\beta = 0.047$, $p = 0.023$ (Table 4, 1XY+2XY), consistently across all cohorts (Supplementary Table 6). The same effect direction was also observed for CSF tau in the meta-analysis, $\beta = 0.060$, $p = 0.270$, and each cohort (Supplementary Table 6), although the estimates did not attain the significance due to a 5-fold smaller sample with CSF tau than plasma tau. Because plasma and CSF tau were measured in ADNI-1, we were able to examine the association of the aggregated compound genotype 1XY+2XY with CSF tau with adjustment for plasma tau. This analysis did not show the mediating effect of plasma tau because the difference in the

Table 4. Comparative meta-analysis of the associations of the selected compound genotypes with Alzheimer's disease (AD) Aβ42 and tau biomarkers.

Biomarker	Source	Genotype	*N*	Beta	SE	*P* value	Direction
Aβ42	CSF	111+222	178	-0.054	0.062	3.77E-01	––????
Aβ42	CSF	1XY+2XY	242	-0.091	0.060	1.32E-01	––????
Aβ42	CSF	100+200	56			Reference	
Aβ42	Plasma	111+222	1462	0.619	0.569	2.77E-01	–?++++
Aβ42	Plasma	1XY+2XY	1821	0.509	0.553	3.57E-01	–?++++
Aβ42	Plasma	100+200	396			Reference	
Tau	CSF	111+222	189	0.066	0.057	2.46E-01	++????
Tau	CSF	1XY+2XY	253	0.060	0.054	2.70E-01	++????
Tau	CSF	100+200	56			Reference	
Tau	Plasma	111+222	1033	0.033	0.021	1.25E-01	+?+++?
Tau	Plasma	1XY+2XY	1280	0.047	0.021	2.27E-02	+?+++?
Tau	Plasma	100+200	289			Reference	

Column "Genotype" shows compound genotypes encoded by triples of numbers and X and Y letters; these notations are detailed in Table 3 footnote. Column "Direction" shows sign of the effect beta in individual studies in the same order as in Table 3. A gamma general linear model with a log link function was used for all biomarkers except Aβ42 measured in plasma. SE denotes standard error. CSF denotes cerebrospinal fluid. More details with individual-study estimates are given Supplementary Table 6.

associations between the adjusted (β = 0.026, $p = 0.700$) and unadjusted (β = 0.030, $p = 0.650$) models by plasma tau in ADNI-1 was trivial.

We found that excluding carriers of the ε2 alleles did not make a difference (Supplementary Table 7).

DISCUSSION

We performed the analysis of the associations of the *APOE* ε2 and ε4 alleles and polygenic profiles represented by combinations of variants of the ε4 encoding rs429358, *TOMM40* rs2075650, and *APOC1* rs12721046 SNPs with CSF and plasma Aβ40, Aβ42, and tau AD biomarkers. Our primary finding is that the ε4-bearing polygenic profiles conferring higher and lower AD risks are differently associated with tau but not Aβ42. The other main results of our work are characterizations of the associations of the *APOE* ε2 and ε4 alleles with Aβ40, Aβ42, and tau biomarkers in ADNI-1, ADNI-2/GO, ARIC, and three FHS cohorts.

APOE ε2 and ε4 alleles and AD biomarkers

Our analysis confirmed robust associations of the ε4 alleles with both plasma and CSF Aβ42 levels [17] (Table 2). Unlike Aβ42, no significant associations of the ε4 allele with Aβ40 were identified despite a relatively high correlation between these biomarkers. By showing the robust and highly significant associations of the ε4 allele with CSF tau, our analysis supports previous findings on the connections between the ε4 allele and tau aggregation [17, 33, 34]. Meanwhile, we report no significant associations of the ε4 allele with plasma tau (Table 2).

We show that the ε2 allele is associated with CSF Aβ42 at nominal significance in the ADNI sample, which corroborates the results of previous analysis in this sample [35]. Nevertheless, longitudinal analysis using a larger number of CSF Aβ42 measurements from multiple visits did not confirm the significance of this association. However, ADNI sample includes relatively old subjects (Table 1), and longitudinal assessment was done at even older ages (Supplementary Table 1). Because studies showed that the ε2 allele might not be associated with CSF Aβ42 at older ages [36], the addition of Aβ42 measurements at older ages affected the significance of the estimate in our study. The ε2 allele was not significantly associated with plasma Aβ42 and CSF and plasma Aβ40 and tau (Supplementary Table 4).

Polygenic profiles and AD biomarkers

Our prior analysis identified that the ε4-bearing compound genotypes examined in the current study of AD biomarkers exerted 89% (OR [odds ratio] = 1.89, $p = 4.69 \times 10^{-13}$) higher odds of AD when the ε4 alleles clustered with minor alleles of *TOMM40* rs2075650 and *APOC1* rs12721046 SNPs than major alleles of these two SNPs, i.e., when the 1XY+2XY compound genotype (carriers of the ε4 alleles who also carry minor alleles of rs2075650 and rs12721046) was contrasted by 100+200 genotype (carriers of the ε4 alleles who do not carry minor alleles of rs2075650 and rs12721046) [32].

In this study, we show no significant difference in the associations of the 1XY+2XY and 100+200 compound genotypes with either plasma or CSF Aβ42. This result implies that the association of the ε4 allele with Aβ42 is likely due to this allele itself because its association is not significantly modulated by minor alleles of rs2075650 and rs12721046. In contrast, a significant difference in the associations of the 1XY+2XY and 100+200 compound genotypes with plasma tau (Table 4) (and, potentially, with CSF tau, Supplementary Table 6) suggests joint roles of the ε4 allele and minor alleles of rs2075650 and rs12721046 in tau aggregation. Because the 1XY+2XY compound genotype entails 89% higher odds of AD than the 100+200 genotype, the 1XY+2XY genotype is tighter linked to neurodegeneration than 100+200. Therefore, the identified difference in the associations of the ε4-bearing polygenic profiles conferring higher and lower AD risks is tied to tau but not Aβ.

Insights on potential *APOE*-related mechanism of AD

Our results align with prior findings based on the associations of the ε4 alleles with AD biomarkers. Differential associations of the ε4-bearing polygenic profiles with AD biomarkers help clarify connections of the ε4 allele with AD biomarkers and the role of Aβ and tau pathologies in AD pathogenesis. Indeed, studies showed that Aβ42 was tighter linked with the ε4 allele than clinically diagnosed cognitive impairment (AD or MCI), whereas tau and neurodegeneration were stronger associated with cognitive impairment than the ε4 alleles [15] (Figure 1). The CSF Aβ42 appears to be independently associated with AD and the ε4 alleles, as was shown in [16] and corroborated in [37]. PET imaging showed a tighter linkage of neurodegeneration to tau pathology than Aβ pathology [38]. These findings implicate the role of the ε4 alleles in AD via both Aβ and tau pathologies. They emphasize the primary role of the ε4 alleles in Aβ pathology, the reduced role of this allele in tau pathology, and the stronger link of tau with neurodegeneration. These findings support the mechanism that Aβ pathology is pronounced before the emergence of the AD clinical manifestation, whereas AD manifestation develops due to neurodegeneration [12, 15, 39]. Then, our results are aligned with these findings because: (i) the polygenic profile comprising the ε4 allele and minor alleles of rs2075650 and rs12721046 is a proxy for cognitive impairment because it is tied to higher AD risk (ε4-HRP-AD), (ii) this higher-AD-risk profile is differentiated from the lower-AD-risk profile (ε4-LRP-AD) based on the associations with tau, and (iii) this profile is not differentiated based on the associations with Aβ42. These insights indicate that the ε4 allele plays a role in Aβ pathology, whereas its role in tau pathology is modulated by minor alleles of *TOMM40* rs2075650 and *APOC1* rs12721046 SNPs when they are clustered in the higher-AD-risk profile. Therefore, our findings suggest that modulation of the effect of the ε4 allele by *TOMM40* and *APOC1* variants indicates a potential genetic mechanism of differential roles of Aβ and tau in AD pathogenesis.

Limitations

We acknowledge the limitations of this study. First, the samples used in this analysis were not optimal to examine the roles of compound genotypes comprising

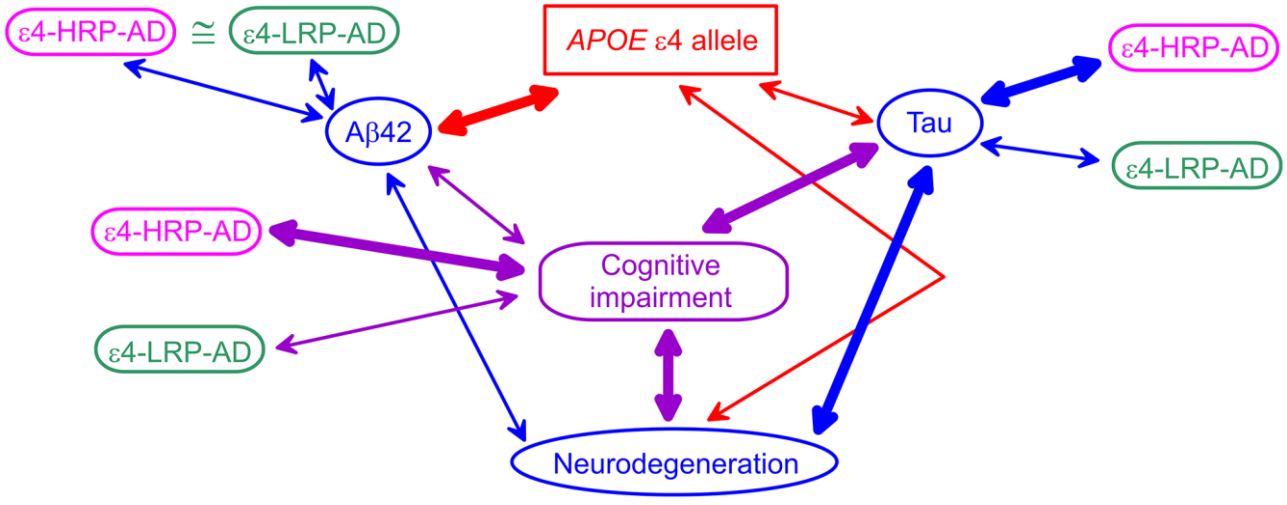

Figure 1. A schematic diagram of potential *APOE*-related mechanism of Alzheimer's disease (AD). Blue ovals indicate AD biomarkers. The red rectangle shows the *APOE* ε4 allele. The purple rounded rectangle indicates cognitive impairment (AD or mild cognitive impairment). Magenta and green rounded rectangles denote the ε4-bearing higher-AD-risk profile (ε4-HRP-AD) and lower-AD-risk profile (ε4-LRP-AD), respectively. The thickness of the arrows denotes tighter (thick lines) and weaker (thin lines) links between genetic variants, AD biomarkers, and cognitive impairment.

minor allele homozygotes of rs429358, rs2075650, and rs12721046 SNPs. Second, we did not explore the potential roles of haplotypes containing these SNPs due to the limited number of minor allele homozygotes. Third, further analyses using larger samples are needed to robustly examine associations of compound genotypes with CSF Aβ and tau. Fourth, we did not look at the potential roles of sex due to the limited sample size, particularly for CSF measurements.

MATERIALS AND METHODS

Study cohorts

The data for this paper were from the ADNI initial (ADNI-1) and extended (ADNI-2/GO) cohorts [40, 41], the ARIC study [42], and the FHS parental (FHS_C1), offspring (FHS_C2), and grandchildren (FHS_C3) cohorts [43]. The basic characteristics of the available samples are given in Table 1.

AD biomarkers

Alzheimer's disease neuroimaging initiative

Data used in the preparation of this article were obtained from the ADNI database (https://adni.loni.usc.edu/). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see https://adni.loni.usc.edu/.

Concentrations of Aβ42 and Aβ40 in plasma were measured using the Luminex xMAP platform and Innogenetics INNO-BIA AlzBio3 immunoassay reagents (Innogenetics NV, Ghent, Belgium). Plasma tau was measured in ADNI-1 and it was analyzed by the Single-Molecule array (Simoa) technique and the Human total tau assay. Concentrations of Aβ42, tau, and p-tau181 (p-tau) in CSF were assessed using an automated Elecsys cobas e 601 tool based on Roche Elecsys immunoassays [44]. CSF samples were collected in ADNI-1 and ADNI-2/GO between 2005 and 2016. In addition, immunoassay-independent measurements of CSF Aβ (Aβ40 and Aβ42) were done using a candidate reference 2D-UPLC/tandem mass spectrometry method.

Atherosclerosis risk in communities study

Plasma Aβ40 and Aβ42 concentrations were measured at the 5th examination. Amyloid was quantified by the Department of Molecular Pharmacology and Experimental Therapeutics at Mayo Clinic (Jacksonville, FL) from August to December 2014 using the INNO-BIA assay (Innogenetics NV, Ghent, Belgium). The Luminex 200 IS Total system was used for detecting fluorescence emitted by beads (xMAP microspheres; conjugate 1A) that were bound to Aβ40 and Aβ42 [45]. The minimal detectable levels for Aβ42 and Aβ40 were 12 pg/ml and 15 pg/ml, respectively [46, 47].

Framingham heart study

Plasma Aβ42 and Aβ40 concentrations were measured at the 23rd examination in FHS_C1, the 7th examination in FHS_C2, and the 2nd examination in FHS_C3 cohorts. Amyloid was quantified by the same Mayo Clinic facility as for ARIC from June to August 2012 and from January to June 2014 using the same Innogenetics NV assays. The minimal detectable levels were 12pg/ml for Aβ40 and 5pg/ml for Aβ42. Plasma tau was measured in blood samples obtained at the 28th examination in FHS_C1, the 8th examination in FHS_C2, and the 2nd examination in FHS_C3. Plasma samples were assayed from February to March 2017. Total tau was measured by Quanterix (Lexington, MA, USA) using a Simoa™ tau 2.0 Kit and a Simoa HD-1 analyzer. This is a molecule enzyme-linked immuno-sorbent assay (digital ELISA) with a minimum detectable level of 0.019 pg/ml [48].

Genotypes

We examined associations of the *APOE* ε4 and ε2 alleles encoded by minor alleles of rs429358 (T/c; upper/lower case denotes here major/minor allele) and rs7412 (C/t), respectively, and compound genotypes comprising rs429358, rs2075650 (*TOMM40*, A/g), and rs12721046 (*APOC1*, G/a) SNPs. To maximize the sample size, missing genotypes for some subjects in each study were imputed (Michigan Imputation Server, HRC panel). We retained genotypes with high imputation quality ($r^2 > 0.8$).

The ε4 allele was defined in the absence of the ε2 allele, i.e., by ε3/ε4 and ε4/ε4 genotypes. Likewise, the ε2 allele was defined in the absence of the ε4 allele, i.e., by ε2/ε3 and ε2/ε2 genotypes. The triple of rs429358, rs2075650, and rs12721046 SNPs, which are in about the same moderate pair-wise linkage disequilibrium $r^2 \approx 0.49$, was selected because its minor allele compound genotypes conferred an exceptionally high risk of AD [31, 32]. To streamline notations for triples, we used definitions based on the counts of minor alleles (i.e., 0, 1, 2) in an SNP, as detailed in Table 3 footnotes.

Statistical analysis

The associations of the ε4 or ε2 allele and compound genotypes of interest with AD biomarkers were

evaluated using their baseline (Table 1) and longitudinal (Supplementary Table 1) measurements. We used the ε3/ε3 genotype as a reference in the analyses of the ε4 or ε2 allele. References in the analyses of compound genotypes varied and are shown in the corresponding tables. AD biomarkers were used as outcomes. We employed the glm and lm functions from base R, as well as the glmer and lmer functions from the lme4 package [49]. Biomarkers CSF Aβ40, Aβ42, tau, and p-tau, and plasma tau showed gamma-like distributions; therefore, functions glm and glmer were used to run gamma general linear models with a log link function. The regression coefficients beta in these models can be interpreted as a fraction (or percentage) of change of a continuous outcome. All models were adjusted for sex, age, and age squared. If the model had convergence issues, age squared was removed. The analysis using longitudinal measurements was run in ADNI, and required the use of lmer and glmer to account for the correlation between repeated measurements on the individual. In FHS lmer and glmer were used to account for familial correlation. To examine the potential role of the ε2 alleles, we also performed the analysis excluding all subjects with ε2 alleles. No other adjustments were made. Meta-analysis was performed using a fixed-effects model with inverse-variance weighting. We used $p < 0.05$ as a significance level.

AUTHOR CONTRIBUTIONS

A.M.K. conceived and designed the experiment and wrote the paper, E.J.W. coded statistical tests and performed statistical analyses, Y.L., E.L., F.F., and I.C. prepared data for the analyses. All co-authors contributed to writing the paper.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

ETHICAL STATEMENT AND CONSENT

This study used existing data received from the data holders. Duke institutional review board approved the analysis of these data. As living subjects were not contacted in this study, informed consent was not required.

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SUPPLEMENTARY MATERIALS

This article was prepared using a data obtained through dbGaP (accession numbers phs000007.v31 [FHS] and phs000280, v.7 [ARIC]) and ADNI data obtained through the Image and Data Archive (IDA) run by the Laboratory of Neuro Imaging (LONI).

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Supplementary Tables

Supplementary Table 1. Basic characteristics of the genotyped participants of European ancestry in the selected studies over all available longitudinal measurements.

Study	Source	*N*	Men (%)	Age (SD, SE), years	Aβ40 (SD, SE), pg/ml	Aβ42 (SD, SE), pg/ml	Tau (SD, SE), pg/ml	pTau (SD, SE), pg/ml
ADNI-1	Plasma	2077	1269 (61.1)	76.6 (6.6, 0.1)	164.4 (46.7, 1.0)	39.9 (10.9, 0.2)	NA	NA
ADNI-1	CSF	948	571 (60.2)	76.7 (6.9, 0.2)	7844.7 (2326.7, 97.1)	768.6 (365.6, 11.9)	307.6 (122.3, 4.0)	29.7 (13.7, 0.4)
ADNI-2/GO	CSF	636	357 (56.1)	73.9 (7.4, 0.3)	8652.0 (2492.9, 105.0)	901.4 (369.0, 14.6)	279.6 (121.9, 4.8)	26.3 (13.3, 0.5)

Abbreviation: CSF: cerebrospinal fluid; SD: standard deviation; SE: standard error. *N* denotes the total number of observations of Alzheimer's disease (AD) biomarkers at four (plasma) and up to eight (CSF) examinations. ADNI-1 and ADNI-2/GO denote the AD Neuroimaging Initiative initial and extended cohorts, respectively. Age was defined at the time of the AD biomarker measurement.

Supplementary Table 2. Pearson pair-wise correlation estimates between Alzheimer's disease (AD) biomarkers in selected studies.

Study	Biomarker_1	Biomarker_2	*N*	Correlation, *r*	*P* value
ADNI-1	Aβ40_plasma	Aβ42_plasma	608	0.703	6.80E-92
ADNI-1	Aβ40_plasma	Tau_plasma	449	0.127	7.03E-03
ADNI-1	Aβ42_plasma	Tau_plasma	450	0.064	1.73E-01
ADNI-1	Aβ40_CSF	Aβ42_CSF	305	0.304	6.41E-08
ADNI-1	Aβ40_CSF	Tau_CSF	339	0.524	2.85E-25
ADNI-1	Aβ40_CSF	pTau_CSF	339	0.460	4.01E-19
ADNI-1	Aβ42_CSF	Tau_CSF	308	−0.275	9.27E-07
ADNI-1	Aβ42_CSF	pTau_CSF	308	−0.314	1.78E-08
ADNI-1	Tau_CSF	pTau_CSF	345	0.980	9.17E-244
ADNI-1	Aβ42_plasma	Aβ42_CSF	280	0.074	2.19E-01
ADNI-1	Aβ40_plasma	Aβ40_CSF	313	0.005	9.24E-01
ADNI-1	Tau_CSF	Tau_plasma	334	0.155	4.51E-03
ADNI-2/GO	Aβ40_CSF	Aβ42_CSF	274	0.253	2.22E-05
ADNI-2/GO	Aβ40_CSF	Tau_CSF	351	0.542	3.78E-28
ADNI-2/GO	Aβ40_CSF	pTau_CSF	351	0.464	4.13E-20
ADNI-2/GO	Aβ42_CSF	Tau_CSF	283	−0.269	4.39E-06
ADNI-2/GO	Aβ42_CSF	pTau_CSF	283	−0.326	2.04E-08
ADNI-2/GO	Tau_CSF	pTau_CSF	360	0.979	3.03E-250
FHS_C1	Aβ40_plasma	Aβ42_plasma	636	0.613	7.16E-67
FHS_C1	Aβ40_plasma	Tau_plasma	128	0.103	2.49E-01
FHS_C1	Aβ42_plasma	Tau_plasma	128	0.096	2.80E-01
FHS_C2	Aβ40_plasma	Aβ42_plasma	3095	0.500	9.43E-196
FHS_C2	Aβ40_plasma	Tau_plasma	2554	0.108	5.04E-08
FHS_C2	Aβ42_plasma	Tau_plasma	2554	0.068	5.77E-04
FHS_C3	Aβ40_plasma	Aβ42_plasma	3029	0.388	1.40E-109
FHS_C3	Aβ40_plasma	Tau_plasma	3026	0.021	2.45E-01
FHS_C3	Aβ42_plasma	Tau_plasma	3026	0.043	1.91E-02

N denotes the number of subjects. Abbreviation: CSF: cerebrospinal fluid. FHS_C1, FHS_C2, and FHS_C3 denote the Framingham Heart Study parental, offspring, and grandchildren cohorts, respectively; ADNI-1 and ADNI-2/GO denote the AD Neuroimaging Initiative initial and extended cohorts, respectively.

Supplementary Table 3. Associations of the APOE ε4 allele with Alzheimer's disease (AD) biomarkers.

Study	Type	Biomarker	Source	Genotype	*N* subjects	*N* observations	Beta	SE	*P* value
ADNI-1	Baseline	Aβ40	CSF	e4	171	171	−0.047	0.034	1.76E-01
ADNI-1	Baseline	Aβ40	CSF	e33	149	149	Reference		
ADNI-2/GO	Baseline	Aβ40	CSF	e4	133	133	0.022	0.033	5.06E-01
ADNI-2/GO	Baseline	Aβ40	CSF	e33	185	185	Reference		
Meta	Baseline	Aβ40	CSF	e4	304	304	−0.011	0.024	6.49E-01
Meta	Baseline	Aβ40	CSF	e33	334	334	Reference		
ADNI-1	Longitudinal	Aβ40	CSF	e4	173	271	−0.051	0.049	2.97E-01
ADNI-1	Longitudinal	Aβ40	CSF	e33	152	267	Reference		
ADNI-2/GO	Longitudinal	Aβ40	CSF	e4	134	216	0.034	0.045	4.58E-01
ADNI-2/GO	Longitudinal	Aβ40	CSF	e33	186	290	Reference		
Meta	Longitudinal	Aβ40	CSF	e4	307	487	−0.005	0.033	8.70E-01
Meta	Longitudinal	Aβ40	CSF	e33	338	557	Reference		
ADNI-1	Baseline	Aβ40	Plasma	e4	291	291	−0.795	4.345	8.55E-01
ADNI-1	Baseline	Aβ40	Plasma	e33	270	270	Reference		
FHS_C1	Baseline	Aβ40	Plasma	e4	114	114	−8.986	4.397	4.15E-02
FHS_C1	Baseline	Aβ40	Plasma	e33	432	432	Reference		
FHS_C2	Baseline	Aβ40	Plasma	e4	630	630	0.666	1.827	7.16E-01
FHS_C2	Baseline	Aβ40	Plasma	e33	1982	1982	Reference		
FHS_C3	Baseline	Aβ40	Plasma	e4	674	674	−2.299	2.609	3.78E-01
FHS_C3	Baseline	Aβ40	Plasma	e33	1916	1916	Reference		
ARIC	Baseline	Aβ40	Plasma	e4	400	400	−2.837	4.938	5.66E-01
ARIC	Baseline	Aβ40	Plasma	e33	1083	1083	Reference		
Meta	Baseline	Aβ40	Plasma	e4	2109	2109	−1.287	1.300	3.22E-01
Meta	Baseline	Aβ40	Plasma	e33	5683	5683	Reference		
ADNI-1	Longitudinal	Aβ40	Plasma	e4	296	961	−1.237	3.270	7.05E-01
ADNI-1	Longitudinal	Aβ40	Plasma	e33	277	942	Reference		
Meta	Longitudinal	Aβ40	Plasma	e4	296	961	−1.237	3.270	7.05E-01
Meta	Longitudinal	Aβ40	Plasma	e33	277	942	Reference		
ADNI-1	Baseline	Aβ42	CSF	e4	165	165	−0.407	0.048	7.15E-16
ADNI-1	Baseline	Aβ42	CSF	e33	125	125	Reference		
ADNI-2/GO	Baseline	Aβ42	CSF	e4	127	127	−0.256	0.049	3.94E-07
ADNI-2/GO	Baseline	Aβ42	CSF	e33	134	134	Reference		
Meta	Baseline	Aβ42	CSF	e4	292	292	−0.334	0.034	1.50E-22
Meta	Baseline	Aβ42	CSF	e33	259	259	Reference		
ADNI-1	Longitudinal	Aβ42	CSF	e4	178	433	−0.478	0.062	4.85E-14
ADNI-1	Longitudinal	Aβ42	CSF	e33	151	374	Reference		
ADNI-2/GO	Longitudinal	Aβ42	CSF	e4	132	223	−0.274	0.069	9.49E-05
ADNI-2/GO	Longitudinal	Aβ42	CSF	e33	142	231	Reference		
Meta	Longitudinal	Aβ42	CSF	e4	310	656	−0.387	0.046	7.32E-17
Meta	Longitudinal	Aβ42	CSF	e33	293	605	Reference		
ADNI-1	Baseline	Aβ42	Plasma	e4	291	291	−1.987	0.944	3.57E-02
ADNI-1	Baseline	Aβ42	Plasma	e33	273	273	Reference		
FHS_C1	Baseline	Aβ42	Plasma	e4	114	114	−3.912	1.194	1.12E-03

FHS_C1	Baseline	Aβ42	Plasma	e33	432	432	Reference		
FHS_C2	Baseline	Aβ42	Plasma	e4	630	630	−1.891	0.466	5.04E-05
FHS_C2	Baseline	Aβ42	Plasma	e33	1982	1982	Reference		
FHS_C3	Baseline	Aβ42	Plasma	e4	674	674	−1.019	0.454	2.50E-02
FHS_C3	Baseline	Aβ42	Plasma	e33	1916	1916	Reference		
ARIC	Baseline	Aβ42	Plasma	e4	397	397	−3.114	0.654	2.10E-06
ARIC	Baseline	Aβ42	Plasma	e33	1076	1076	Reference		
Meta	Baseline	Aβ42	Plasma	e4	2106	2106	−1.903	0.271	2.18E-12
Meta	Baseline	Aβ42	Plasma	e33	5679	5679	Reference		
ADNI-1	Longitudinal	Aβ42	Plasma	e4	296	962	−1.995	0.799	1.26E-02
ADNI-1	Longitudinal	Aβ42	Plasma	e33	277	950	Reference		
Meta	Longitudinal	Aβ42	Plasma	e4	296	962	−1.995	0.799	1.26E-02
Meta	Longitudinal	Aβ42	Plasma	e33	277	950	Reference		
ADNI-1	Baseline	Tau	CSF	e4	167	167	0.204	0.043	3.04E-06
ADNI-1	Baseline	Tau	CSF	e33	149	149	Reference		
ADNI-2/GO	Baseline	Tau	CSF	e4	135	135	0.323	0.045	6.80E-12
ADNI-2/GO	Baseline	Tau	CSF	e33	192	192	Reference		
Meta	Baseline	Tau	CSF	e4	302	302	0.261	0.031	6.58E-17
Meta	Baseline	Tau	CSF	e33	341	341	Reference		
ADNI-1	Longitudinal	Tau	CSF	e4	179	435	0.217	0.059	2.36E-04
ADNI-1	Longitudinal	Tau	CSF	e33	165	433	Reference		
ADNI-2/GO	Longitudinal	Tau	CSF	e4	138	237	0.304	0.059	3.13E-07
ADNI-2/GO	Longitudinal	Tau	CSF	e33	194	334	Reference		
Meta	Longitudinal	Tau	CSF	e4	317	672	0.260	0.042	3.59E-10
Meta	Longitudinal	Tau	CSF	e33	359	767	Reference		
ADNI-1	Baseline	Tau	Plasma	e4	235	235	0.102	0.053	5.75E-02
ADNI-1	Baseline	Tau	Plasma	e33	223	223	Reference		
FHS_C1	Baseline	Tau	Plasma	e4	20	20	−0.113	0.082	1.72E-01
FHS_C1	Baseline	Tau	Plasma	e33	93	93	Reference		
FHS_C2	Baseline	Tau	Plasma	e4	556	556	0.019	0.019	3.25E-01
FHS_C2	Baseline	Tau	Plasma	e33	1721	1721	Reference		
FHS_C3	Baseline	Tau	Plasma	e4	673	673	−0.003	0.013	8.31E-01
FHS_C3	Baseline	Tau	Plasma	e33	1914	1914	Reference		
Meta	Baseline	Tau	Plasma	e4	1484	1484	0.006	0.011	5.67E-01
Meta	Baseline	Tau	Plasma	e33	3951	3951	Reference		

ARIC is the Atherosclerosis Risk in Communities Study. FHS_C1, FHS_C2, and FHS_C3 denote the Framingham Heart Study parental, offspring, and grandchildren cohorts, respectively. ADNI-1 and ADNI-2/GO denote the Alzheimer's disease Neuroimaging Initiative initial and extended cohorts, respectively. Meta shows the results of meta-analysis. Meta-analysis field was shown for consistency for each biomarker even if the analysis was performed in one study only. Column "Type" indicates biomarker measurements at baseline or longitudinally. Abbreviations: CSF: cerebrospinal fluid; SE: standard error. The APOE ε4 allele was defined as e34 and e44 genotypes. A gamma general linear model with a log link function was used for all biomarkers except Aβ40 and Aβ42 measured in plasma.

Supplementary Table 4. Associations of the APOE ε2 allele with Alzheimer's disease (AD) biomarkers.

Study	Type	Biomarker	Source	Genotype	*N* subjects	*N* observations	Beta	SE	*P* value
ADNI-1	Baseline	Aβ40	CSF	e4	25	25	0.063	0.069	3.62E-01
ADNI-1	Baseline	Aβ40	CSF	e33	149	149	Reference		
ADNI-2/GO	Baseline	Aβ40	CSF	e4	31	31	−0.032	0.055	5.68E-01
ADNI-2/GO	Baseline	Aβ40	CSF	e33	185	185	Reference		
Meta	Baseline	Aβ40	CSF	e4	56	56	0.006	0.043	8.99E-01
Meta	Baseline	Aβ40	CSF	e33	334	334	Reference		
ADNI-1	Longitudinal	Aβ40	CSF	e4	25	27	0.075	0.093	4.21E-01
ADNI-1	Longitudinal	Aβ40	CSF	e33	152	267	Reference		
ADNI-2/GO	Longitudinal	Aβ40	CSF	e4	31	54	−0.058	0.080	4.67E-01
ADNI-2/GO	Longitudinal	Aβ40	CSF	e33	186	290	Reference		
Meta	Longitudinal	Aβ40	CSF	e4	56	81	−0.002	0.060	9.80E-01
Meta	Longitudinal	Aβ40	CSF	e33	338	557	Reference		
ADNI-1	Baseline	Aβ40	Plasma	e4	36	36	0.679	8.602	9.37E-01
ADNI-1	Baseline	Aβ40	Plasma	e33	270	270	Reference		
FHS_C1	Baseline	Aβ40	Plasma	e4	74	74	−1.922	5.561	7.30E-01
FHS_C1	Baseline	Aβ40	Plasma	e33	432	432	Reference		
FHS_C2	Baseline	Aβ40	Plasma	e4	402	402	1.457	2.213	5.10E-01
FHS_C2	Baseline	Aβ40	Plasma	e33	1982	1982	Reference		
FHS_C3	Baseline	Aβ40	Plasma	e4	370	370	−6.513	3.022	3.12E-02
FHS_C3	Baseline	Aβ40	Plasma	e33	1916	1916	Reference		
ARIC	Baseline	Aβ40	Plasma	e4	230	230	−12.561	6.078	3.90E-02
ARIC	Baseline	Aβ40	Plasma	e33	1083	1083	Reference		
Meta	Baseline	Aβ40	Plasma	e4	1112	1112	−2.091	1.608	1.93E-01
Meta	Baseline	Aβ40	Plasma	e33	5683	5683	Reference		
ADNI-1	Longitudinal	Aβ40	Plasma	e4	36	123	−3.345	6.555	6.10E-01
ADNI-1	Longitudinal	Aβ40	Plasma	e33	277	942	Reference		
Meta	Longitudinal	Aβ40	Plasma	e4	36	123	−3.345	6.555	6.10E-01
Meta	Longitudinal	Aβ40	Plasma	e33	277	942	Reference		
ADNI-1	Baseline	Aβ42	CSF	e4	17	17	0.162	0.106	1.27E-01
ADNI-1	Baseline	Aβ42	CSF	e33	125	125	Reference		
ADNI-2/GO	Baseline	Aβ42	CSF	e4	20	20	0.130	0.086	1.31E-01
ADNI-2/GO	Baseline	Aβ42	CSF	e33	134	134	Reference		
Meta	Baseline	Aβ42	CSF	e4	37	37	0.143	0.067	3.18E-02
Meta	Baseline	Aβ42	CSF	e33	259	259	Reference		
ADNI-1	Longitudinal	Aβ42	CSF	e4	19	42	0.142	0.150	3.42E-01
ADNI-1	Longitudinal	Aβ42	CSF	e33	151	374	Reference		
ADNI-2/GO	Longitudinal	Aβ42	CSF	e4	20	38	0.084	0.144	5.61E-01
ADNI-2/GO	Longitudinal	Aβ42	CSF	e33	142	231	Reference		
Meta	Longitudinal	Aβ42	CSF	e4	39	80	0.112	0.104	2.80E-01
Meta	Longitudinal	Aβ42	CSF	e33	293	605	Reference		
ADNI-1	Baseline	Aβ42	Plasma	e4	36	36	0.278	2.062	8.93E-01
ADNI-1	Baseline	Aβ42	Plasma	e33	273	273	Reference		
FHS_C1	Baseline	Aβ42	Plasma	e4	74	74	−1.185	1.499	4.30E-01

FHS_C1	Baseline	Aβ42	Plasma	e33	432	432	Reference		
FHS_C2	Baseline	Aβ42	Plasma	e4	402	402	0.228	0.567	6.88E-01
FHS_C2	Baseline	Aβ42	Plasma	e33	1982	1982	Reference		
FHS_C3	Baseline	Aβ42	Plasma	e4	370	370	−0.268	0.565	6.36E-01
FHS_C3	Baseline	Aβ42	Plasma	e33	1916	1916	Reference		
ARIC	Baseline	Aβ42	Plasma	e4	228	228	−0.198	0.830	8.12E-01
ARIC	Baseline	Aβ42	Plasma	e33	1076	1076	Reference		
Meta	Baseline	Aβ42	Plasma	e4	1110	1110	−0.105	0.346	7.61E-01
Meta	Baseline	Aβ42	Plasma	e33	5679	5679	Reference		
ADNI-1	Longitudinal	Aβ42	Plasma	e4	36	123	−0.982	1.751	5.75E-01
ADNI-1	Longitudinal	Aβ42	Plasma	e33	277	950	Reference		
Meta	Longitudinal	Aβ42	Plasma	e4	36	123	−0.982	1.751	5.75E-01
Meta	Longitudinal	Aβ42	Plasma	e33	277	950	Reference		
ADNI-1	Baseline	Tau	CSF	e4	24	24	−0.003	0.093	9.71E-01
ADNI-1	Baseline	Tau	CSF	e33	149	149	Reference		
ADNI-2/GO	Baseline	Tau	CSF	e4	31	31	−0.111	0.071	1.17E-01
ADNI-2/GO	Baseline	Tau	CSF	e33	192	192	Reference		
Meta	Baseline	Tau	CSF	e4	55	55	−0.072	0.056	2.02E-01
Meta	Baseline	Tau	CSF	e33	341	341	Reference		
ADNI-1	Longitudinal	Tau	CSF	e4	25	59	0.013	0.120	9.11E-01
ADNI-1	Longitudinal	Tau	CSF	e33	165	433	Reference		
ADNI-2/GO	Longitudinal	Tau	CSF	e4	31	61	−0.106	0.101	2.93E-01
ADNI-2/GO	Longitudinal	Tau	CSF	e33	194	334	Reference		
Meta	Longitudinal	Tau	CSF	e4	56	120	−0.057	0.077	4.64E-01
Meta	Longitudinal	Tau	CSF	e33	359	767	Reference		
ADNI-1	Baseline	Tau	Plasma	e4	32	32	−0.127	0.111	2.52E-01
ADNI-1	Baseline	Tau	Plasma	e33	223	223	Reference		
FHS_C1	Baseline	Tau	Plasma	e4	21	21	−0.127	0.055	2.12E-02
FHS_C1	Baseline	Tau	Plasma	e33	93	93	Reference		
FHS_C2	Baseline	Tau	Plasma	e4	350	350	0.011	0.020	5.77E-01
FHS_C2	Baseline	Tau	Plasma	e33	1721	1721	Reference		
FHS_C3	Baseline	Tau	Plasma	e4	370	370	0.037	0.019	4.80E-02
FHS_C3	Baseline	Tau	Plasma	e33	1914	1914	Reference		
Meta	Baseline	Tau	Plasma	e4	773	773	0.014	0.013	2.88E-01
Meta	Baseline	Tau	Plasma	e33	3951	3951	Reference		

ARIC is the Atherosclerosis Risk in Communities Study. FHS_C1, FHS_C2, and FHS_C3 denote the Framingham Heart Study parental, offspring, and grandchildren cohorts, respectively. ADNI-1 and ADNI-2/GO denote the Alzheimer's disease Neuroimaging Initiative initial and extended cohorts, respectively. Meta shows the results of meta-analysis. Meta-analysis field was shown for consistency for each biomarker even if the analysis was performed in one study only. Column "Type" indicates biomarker measurements at baseline or longitudinally. Abbreviations: CSF: cerebrospinal fluid; SE: standard error. The APOE ε2 allele was defined as e22 and e23 genotypes. A gamma general linear model with a log link function was used for all biomarkers except Aβ40 and Aβ42 measured in plasma.

Supplementary Table 5. Associations of compound genotypes with Alzheimer's disease (AD) Aβ42 and tau biomarkers measured at baseline.

Study	Biomarker	Source	Genotype	*N*	Beta	SE	*P* value
ADNI-1	Aβ42	CSF	0XY	30	−0.029	0.079	7.14E-01
ADNI-1	Aβ42	CSF	100+200	31	−0.347	0.084	6.82E-05
ADNI-1	Aβ42	CSF	111+222	101	−0.411	0.055	1.64E-12
ADNI-1	Aβ42	CSF	1XY+2XY	138	−0.450	0.050	1.08E-16
ADNI-1	Aβ42	CSF	000	112	Reference		
ADNI-2/GO	Aβ42	CSF	0XY	29	0.078	0.077	3.13E-01
ADNI-2/GO	Aβ42	CSF	100+200	25	−0.208	0.078	8.82E-03
ADNI-2/GO	Aβ42	CSF	111+222	77	−0.268	0.056	3.06E-06
ADNI-2/GO	Aβ42	CSF	1XY+2XY	104	−0.288	0.053	1.77E-07
ADNI-2/GO	Aβ42	CSF	000	125	Reference		
Meta	Aβ42	CSF	0XY	59	0.026	0.055	6.37E-01
Meta	Aβ42	CSF	100+200	56	−0.272	0.057	2.13E-06
Meta	Aβ42	CSF	111+222	178	−0.341	0.039	2.46E-18
Meta	Aβ42	CSF	1XY+2XY	242	−0.373	0.037	2.18E-24
Meta	Aβ42	CSF	000	237	Reference		
ADNI-1	Aβ42	Plasma	0XY	48	−2.137	1.752	2.23E-01
ADNI-1	Aβ42	Plasma	100+200	51	−1.342	1.769	4.49E-01
ADNI-1	Aβ42	Plasma	111+222	197	−2.598	1.067	1.53E-02
ADNI-1	Aβ42	Plasma	1XY+2XY	252	−2.418	1.012	1.73E-02
ADNI-1	Aβ42	Plasma	000	261	Reference		
FHS_C1	Aβ42	Plasma	0XY	60	−2.829	1.588	7.54E-02
FHS_C1	Aβ42	Plasma	100+200	22	−4.084	2.621	1.20E-01
FHS_C1	Aβ42	Plasma	111+222	50	−4.227	1.776	1.78E-02
FHS_C1	Aβ42	Plasma	1XY+2XY	77	−3.850	1.442	7.86E-03
FHS_C1	Aβ42	Plasma	000	344	Reference		
FHS_C2	Aβ42	Plasma	0XY	354	−0.582	0.585	3.20E-01
FHS_C2	Aβ42	Plasma	100+200	133	−2.231	0.931	1.66E-02
FHS_C2	Aβ42	Plasma	111+222	397	−1.670	0.573	3.59E-03
FHS_C2	Aβ42	Plasma	1XY+2XY	504	−2.093	0.516	5.12E-05
FHS_C2	Aβ42	Plasma	000	1843	Reference		
FHS_C3	Aβ42	Plasma	0XY	292	1.460	0.626	1.98E-02
FHS_C3	Aβ42	Plasma	100+200	128	−1.586	0.908	8.07E-02
FHS_C3	Aβ42	Plasma	111+222	512	−0.848	0.494	8.63E-02
FHS_C3	Aβ42	Plasma	1XY+2XY	615	−0.618	0.462	1.81E-01
FHS_C3	Aβ42	Plasma	000	1994	Reference		
ARIC	Aβ42	Plasma	0XY	197	1.809	0.860	3.56E-02
ARIC	Aβ42	Plasma	100+200	62	−4.463	1.463	2.34E-03
ARIC	Aβ42	Plasma	111+222	306	−2.109	0.724	3.65E-03
ARIC	Aβ42	Plasma	1XY+2XY	373	−2.304	0.671	6.15E-04
ARIC	Aβ42	Plasma	000	1107	Reference		
Meta	Aβ42	Plasma	0XY	951	0.351	0.364	3.35E-01
Meta	Aβ42	Plasma	100+200	396	−2.305	0.551	2.82E-05
Meta	Aβ42	Plasma	111+222	1462	−1.582	0.312	4.14E-07
Meta	Aβ42	Plasma	1XY+2XY	1821	−1.656	0.287	7.98E-09
Meta	Aβ42	Plasma	000	5549	Reference		
ADNI-1	Tau	CSF	0XY	31	0.158	0.075	3.61E-02
ADNI-1	Tau	CSF	100+200	30	0.234	0.080	3.99E-03
ADNI-1	Tau	CSF	111+222	105	0.247	0.049	8.28E-07
ADNI-1	Tau	CSF	1XY+2XY	142	0.244	0.043	4.96E-08
ADNI-1	Tau	CSF	000	142	Reference		
ADNI-2/GO	Tau	CSF	0XY	39	0.031	0.068	6.46E-01
ADNI-2/GO	Tau	CSF	100+200	26	0.232	0.077	3.05E-03
ADNI-2/GO	Tau	CSF	111+222	84	0.342	0.050	5.86E-11

ADNI-2/GO	Tau	CSF	1XY+2XY	111	0.355	0.048	1.38E-12
ADNI-2/GO	Tau	CSF	000	184	Reference		
Meta	Tau	CSF	0XY	70	0.088	0.050	7.97E-02
Meta	Tau	CSF	100+200	56	0.233	0.056	2.85E-05
Meta	Tau	CSF	111+222	189	0.293	0.035	4.87E-17
Meta	Tau	CSF	1XY+2XY	253	0.294	0.032	6.75E-20
Meta	Tau	CSF	000	326	Reference		
ADNI-1	Tau	Plasma	0XY	39	−0.059	0.099	5.49E-01
ADNI-1	Tau	Plasma	100+200	38	0.048	0.102	6.37E-01
ADNI-1	Tau	Plasma	111+222	156	0.085	0.059	1.53E-01
ADNI-1	Tau	Plasma	1XY+2XY	204	0.117	0.059	4.83E-02
ADNI-1	Tau	Plasma	000	216	Reference		
FHS_C1	Tau	Plasma	0XY	17	−0.024	0.092	7.93E-01
FHS_C1	Tau	Plasma	100+200	5	−0.040	0.052	4.43E-01
FHS_C1	Tau	Plasma	111+222	9	−0.099	0.133	4.58E-01
FHS_C1	Tau	Plasma	1XY+2XY	14	−0.172	0.103	9.89E-02
FHS_C1	Tau	Plasma	000	91	Reference		
FHS_C2	Tau	Plasma	0XY	300	0.030	0.020	1.27E-01
FHS_C2	Tau	Plasma	100+200	118	−0.054	0.030	7.47E-02
FHS_C2	Tau	Plasma	111+222	357	−0.022	0.019	2.34E-01
FHS_C2	Tau	Plasma	1XY+2XY	448	−0.008	0.017	6.55E-01
FHS_C2	Tau	Plasma	000	1615	Reference		
FHS_C3	Tau	Plasma	0XY	291	−0.005	0.018	7.86E-01
FHS_C3	Tau	Plasma	100+200	128	−0.047	0.026	7.72E-02
FHS_C3	Tau	Plasma	111+222	511	−0.007	0.015	6.07E-01
FHS_C3	Tau	Plasma	1XY+2XY	614	−0.002	0.013	8.88E-01
FHS_C3	Tau	Plasma	000	1991	Reference		
Meta	Tau	Plasma	0XY	647	0.009	0.013	4.91E-01
Meta	Tau	Plasma	100+200	289	−0.045	0.018	1.28E-02
Meta	Tau	Plasma	111+222	1033	−0.010	0.011	3.66E-01
Meta	Tau	Plasma	1XY+2XY	1280	−0.002	0.010	8.42E-01
Meta	Tau	Plasma	000	3913	Reference		

ARIC is the Atherosclerosis Risk in Communities Study. FHS_C1, FHS_C2, and FHS_C3 denote the Framingham Heart Study parental, offspring, and grandchildren cohorts, respectively. ADNI-1 and ADNI-2/GO denote the Alzheimer's disease Neuroimaging Initiative initial and extended cohorts, respectively. Meta shows the results of meta-analysis. Meta-analysis field was shown for consistency for each biomarker even if the analysis was performed in one study only. Column "Genotype" shows compound genotypes encoded by triples of numbers and X and Y letters. Numbers show the counts of minor alleles (i.e., 0, 1, 2) in rs429358_T/c, rs2075650_A/g or rs12721046_G/a SNP, in that order. The upper/lower case denotes here major/minor allele. The most frequent 000 genotype denotes the major allele homozygote for all three SNPs, i.e., rs429358_TT, rs2075650_AA, rs12721046_GG. The 100+200 genotype indicates rs429358_Tc, rs2075650_AA, rs12721046_GG (100) and rs429358_cc, rs2075650_AA, rs12721046_GG (200). The 111+222 genotype denotes rs429358_Tc, rs2075650_Ag, rs12721046_Ga (111) and rs429358_cc, rs2075650_gg, rs12721046_aa (222). Letters X and Y indicate aggregation of minor alleles of rs2075650 and rs12721046, respectively. Genotype 0XY aggregates all non-e4 genotypes except 000. The 1XY+2XY genotype aggregates rs429358_Tc (1) and rs429358_cc (2) and all genotypes of rs2075650 (X) and rs12721046 (Y), except major allele homozygote of both SNPs, rs2075650_AA and rs12721046_GG (00), because it is included in the 100+200 genotype. Column "SE" shows standard error. A gamma general linear model with a log link function was used for all biomarkers except Aβ42 measured in plasma.

Supplementary Table 6. Comparative analysis of the associations of the selected compound genotypes with Alzheimer's disease (AD) Aβ42 and tau biomarkers.

Study	Biomarker	Source	Genotype	*N*	Beta	SE	*P* value
ADNI-1	Aβ42	CSF	111+222	101	−0.047	0.081	5.62E-01
ADNI-1	Aβ42	CSF	1XY+2XY	138	−0.087	0.077	2.64E-01
ADNI-1	Aβ42	CSF	100+200	31	Reference		
ADNI-2/GO	Aβ42	CSF	111+222	77	−0.065	0.095	4.99E-01
ADNI-2/GO	Aβ42	CSF	1XY+2XY	104	−0.097	0.096	3.14E-01
ADNI-2/GO	Aβ42	CSF	100+200	25	Reference		
Meta	Aβ42	CSF	111+222	178	−0.054	0.062	3.77E-01
Meta	Aβ42	CSF	1XY+2XY	242	−0.091	0.060	1.32E-01
Meta	Aβ42	CSF	100+200	56	Reference		
ADNI-1	Aβ42	Plasma	111+222	197	−1.200	1.626	4.61E-01
ADNI-1	Aβ42	Plasma	1XY+2XY	252	−1.189	1.647	4.71E-01
ADNI-1	Aβ42	Plasma	100+200	51	Reference		
FHS_C1	Aβ42	Plasma	111+222	50	0.011	2.532	9.96E-01
FHS_C1	Aβ42	Plasma	1XY+2XY	77	0.004	2.163	9.98E-01
FHS_C1	Aβ42	Plasma	100+200	22	Reference		
FHS_C2	Aβ42	Plasma	111+222	397	0.442	0.962	6.46E-01
FHS_C2	Aβ42	Plasma	1XY+2XY	504	0.051	0.914	9.56E-01
FHS_C2	Aβ42	Plasma	100+200	133	Reference		
FHS_C3	Aβ42	Plasma	111+222	512	0.706	0.997	4.79E-01
FHS_C3	Aβ42	Plasma	1XY+2XY	615	0.939	0.992	3.44E-01
FHS_C3	Aβ42	Plasma	100+200	128	Reference		
ARIC	Aβ42	Plasma	111+222	306	2.508	1.460	8.66E-02
ARIC	Aβ42	Plasma	1XY+2XY	373	2.302	1.455	1.14E-01
ARIC	Aβ42	Plasma	100+200	62	Reference		
Meta	Aβ42	Plasma	111+222	1462	0.619	0.569	2.77E-01
Meta	Aβ42	Plasma	1XY+2XY	1821	0.509	0.553	3.57E-01
Meta	Aβ42	Plasma	100+200	396	Reference		
ADNI-1	Tau	CSF	111+222	105	0.041	0.072	5.70E-01
ADNI-1	Tau	CSF	1XY+2XY	142	0.030	0.066	6.50E-01
ADNI-1	Tau	CSF	100+200	30	Reference		
ADNI-2/GO	Tau	CSF	111+222	84	0.107	0.092	2.50E-01
ADNI-2/GO	Tau	CSF	1XY+2XY	111	0.121	0.095	2.04E-01
ADNI-2/GO	Tau	CSF	100+200	26	Reference		
Meta	Tau	CSF	111+222	189	0.066	0.057	2.46E-01
Meta	Tau	CSF	1XY+2XY	253	0.060	0.054	2.70E-01
Meta	Tau	CSF	100+200	56	Reference		
ADNI-1	Tau	Plasma	111+222	156	0.030	0.085	7.26E-01
ADNI-1	Tau	Plasma	1XY+2XY	204	0.063	0.098	5.18E-01
ADNI-1	Tau	Plasma	100+200	38	Reference		
FHS_C1	Tau	Plasma	111+222	9	0.075	0.288	8.02E-01
FHS_C1	Tau	Plasma	1XY+2XY	14	0.000	0.342	1.00E+00
FHS_C1	Tau	Plasma	100+200	5	Reference		

FHS_C2	Tau	Plasma	111+222	357	0.027	0.035	4.33E-01
FHS_C2	Tau	Plasma	1XY+2XY	448	0.053	0.032	1.01E-01
FHS_C2	Tau	Plasma	100+200	118	Reference		
FHS_C3	Tau	Plasma	111+222	511	0.037	0.029	2.03E-01
FHS_C3	Tau	Plasma	1XY+2XY	614	0.041	0.028	1.39E-01
FHS_C3	Tau	Plasma	100+200	128	Reference		
Meta	Tau	Plasma	111+222	1033	0.033	0.021	1.25E-01
Meta	Tau	Plasma	1XY+2XY	1280	0.047	0.021	2.27E-02
Meta	Tau	Plasma	100+200	289	Reference		

ARIC is the Atherosclerosis Risk in Communities Study. FHS_C1, FHS_C2, and FHS_C3 denote the Framingham Heart Study parental, offspring, and grandchildren cohorts, respectively. ADNI-1 and ADNI-2/GO denote the Alzheimer's disease Neuroimaging Initiative initial and extended cohorts, respectively. Meta shows the results of meta-analysis. Meta-analysis field was shown for consistency for each biomarker even if the analysis was performed in one study only. Column "Genotype" shows compound genotypes encoded by triples of numbers and X and Y letters. Numbers show the counts of minor alleles (i.e., 0, 1, 2) in rs429358_T/c, rs2075650_A/g or rs12721046_G/a SNP, in that order. The upper/lower case denotes here major/minor allele. The most frequent 000 genotype denotes the major allele homozygote for all three SNPs, i.e., rs429358_TT, rs2075650_AA, rs12721046_GG. The 100+200 genotype indicates rs429358_Tc, rs2075650_AA, rs12721046_GG (100) and rs429358_cc, rs2075650_AA, rs12721046_GG (200). The 111+222 genotype denotes rs429358_Tc, rs2075650_Ag, rs12721046_Ga (111) and rs429358_cc, rs2075650_gg, rs12721046_aa (222). Letters X and Y indicate aggregation of minor alleles of rs2075650 and rs12721046, respectively. The 1XY+2XY genotype aggregates rs429358_Tc (1) and rs429358_cc (2) and all genotypes of rs2075650 (X) and rs12721046 (Y), except major allele homozygote of both SNPs, rs2075650_AA and rs12721046_GG (00), because it is included in the 100+200 genotype. Column "SE" shows standard error. A gamma general linear model with a log link function was used for all biomarkers except Aβ42 measured in plasma.

Supplementary Table 7. Comparative analysis of the associations of the selected compound genotypes with Alzheimer's disease (AD) Aβ42 and tau biomarkers with carriers of the ε2 allele excluded.

Study	Biomarker	Source	Genotype	*N*	Beta	SE	*P* value
ADNI-1	Aβ42	CSF	111+222	97	−0.060	0.082	4.67E-01
ADNI-1	Aβ42	CSF	1XY+2XY	134	−0.099	0.078	2.06E-01
ADNI-1	Aβ42	CSF	100+200	31	Reference		
ADNI-2/GO	Aβ42	CSF	111+222	75	−0.054	0.094	5.67E-01
ADNI-2/GO	Aβ42	CSF	1XY+2XY	102	−0.091	0.096	3.46E-01
ADNI-2/GO	Aβ42	CSF	100+200	25	Reference		
Meta	Aβ42	CSF	111+222	172	−0.057	0.062	3.54E-01
Meta	Aβ42	CSF	1XY+2XY	236	−0.096	0.061	1.14E-01
Meta	Aβ42	CSF	100+200	56	Reference		
ADNI-1	Aβ42	Plasma	111+222	187	−1.291	1.661	4.38E-01
ADNI-1	Aβ42	Plasma	1XY+2XY	241	−1.261	1.685	4.55E-01
ADNI-1	Aβ42	Plasma	100+200	50	Reference		
FHS_C1	Aβ42	Plasma	111+222	43	0.658	2.716	8.09E-01
FHS_C1	Aβ42	Plasma	1XY+2XY	70	0.840	2.261	7.11E-01
FHS_C1	Aβ42	Plasma	100+200	21	Reference		
FHS_C2	Aβ42	Plasma	111+222	362	0.334	1.035	7.47E-01
FHS_C2	Aβ42	Plasma	1XY+2XY	465	−0.067	0.981	9.46E-01
FHS_C2	Aβ42	Plasma	100+200	116	Reference		
FHS_C3	Aβ42	Plasma	111+222	460	0.870	1.068	4.16E-01
FHS_C3	Aβ42	Plasma	1XY+2XY	561	1.088	1.063	3.06E-01
FHS_C3	Aβ42	Plasma	100+200	113	Reference		
ARIC	Aβ42	Plasma	111+222	273	2.587	1.474	8.02E-02
ARIC	Aβ42	Plasma	1XY+2XY	338	2.458	1.476	9.66E-02

ARIC	Aβ42	Plasma	100+200	59	Reference		
Meta	Aβ42	Plasma	111+222	1325	0.682	0.601	2.57E-01
Meta	Aβ42	Plasma	1XY+2XY	1675	0.594	0.584	3.09E-01
Meta	Aβ42	Plasma	100+200	359	Reference		
ADNI-1	Tau	CSF	111+222	100	0.036	0.071	6.16E-01
ADNI-1	Tau	CSF	1XY+2XY	137	0.023	0.065	7.22E-01
ADNI-1	Tau	CSF	100+200	30	Reference		
ADNI-2/GO	Tau	CSF	111+222	82	0.116	0.092	2.11E-01
ADNI-2/GO	Tau	CSF	1XY+2XY	109	0.128	0.094	1.79E-01
ADNI-2/GO	Tau	CSF	100+200	26	Reference		
Meta	Tau	CSF	111+222	182	0.066	0.056	2.43E-01
Meta	Tau	CSF	1XY+2XY	246	0.057	0.054	2.89E-01
Meta	Tau	CSF	100+200	56	Reference		
ADNI-1	Tau	Plasma	111+222	150	0.033	0.085	6.99E-01
ADNI-1	Tau	Plasma	1XY+2XY	197	0.067	0.099	4.97E-01
ADNI-1	Tau	Plasma	100+200	38	Reference		
FHS_C1	Tau	Plasma	111+222	8	0.079	0.299	7.98E-01
FHS_C1	Tau	Plasma	1XY+2XY	13	0.001	0.259	9.97E-01
FHS_C1	Tau	Plasma	100+200	5	Reference		
FHS_C2	Tau	Plasma	111+222	329	0.022	0.037	5.49E-01
FHS_C2	Tau	Plasma	1XY+2XY	417	0.050	0.034	1.46E-01
FHS_C2	Tau	Plasma	100+200	104	Reference		
FHS_C3	Tau	Plasma	111+222	459	0.031	0.029	2.93E-01
FHS_C3	Tau	Plasma	1XY+2XY	560	0.038	0.028	1.84E-01
FHS_C3	Tau	Plasma	100+200	113	Reference		
Meta	Tau	Plasma	111+222	946	0.028	0.022	2.03E-01
Meta	Tau	Plasma	1XY+2XY	1187	0.044	0.021	4.06E-02
Meta	Tau	Plasma	100+200	260	Reference		

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