

Associations of genetic predisposition to Alzheimer's disease with blood-based biomarkers: a community-based study

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Abstract

The blood-based biomarker (BBM) profiles associated with genetic susceptibility to Alzheimer's disease (AD) in general older populations remain poorly understood. We investigated the associations of apolipoprotein E (*APOE*) genotypes and polygenic risk score (PRS) with BBMs of Alzheimer's pathology, neurodegeneration, and inflammation in community-dwelling older adults in rural China. This population-based study included 3947 participants; of these, data on BBMs were available in 3837 participants for plasma phosphorylated tau (p-tau) variants and glial fibrillary acidic proteins; 1415 for plasma amyloid- β (A β), total tau, and neurofilament light chain; 1755 for plasma brain-derived tau; and 1815 for serum cytokines. *APOE* ϵ 4 allele (vs. ϵ 3/ ϵ 3) and a higher PRS were associated with elevated plasma p-tau217, a decreased A β 42/A β 40 ratio, and increased glial fibrillary acidic proteins and chronic low-grade inflammation, whereas *APOE* ϵ 2 allele was linked to reduced plasma p-tau217 (all Bonferroni-corrected $p < 0.05$). Neither *APOE* genotype nor PRS was significantly associated with plasma total tau, neurofilament light chain, or brain-derived tau after Bonferroni correction for multiple comparison ($p > 0.05$). These associations were stronger in participants aged ≥ 75 years and females ($p_{\text{interaction}} < 0.05$). The BBM profiles of genetic predisposition to AD are characterized by biomarkers reflecting Alzheimer's pathology, neuroinflammation, and systemic inflammation.

INTRODUCTION

Alzheimer's disease (AD) as the most common cause of dementia represents the major global public health challenge [1]. China has the largest number of people living with dementia (~ 17 million) in the world, accounting for up to 30% of global total dementia cases [2, 3]. The heterogeneity of AD etiopathogenesis, along with the long delayed manifestations of clinical symptoms relative to underlying neuropathology, complicates early detection and mechanistic elucidation [4]. Genetic predisposition plays a pivotal role in AD, with heritability of late-onset AD estimated to be up to 80% [5]. Genetic factors of AD affect not only disease susceptibility but also its clinical manifestations and underlying neuropathology [1]. Thus, genetic susceptibility to AD plays a crucial role in driving its diverse clinical phenotypes.

Apolipoprotein E (*APOE*) ϵ 4 allele is a well-established genetic risk factor for AD, whereas the *APOE* ϵ 2 allele appears to confer a protective effect, particularly in Caucasian and African populations [6]. While studies have frequently linked *APOE* ϵ 4 allele with increased AD risk in Asian populations, the protective effect of *APOE* ϵ 2 allele remains inconclusive [6, 7]. In addition, large-scale genome-wide association studies (GWAS) have identified multiple single nucleotide polymorphisms (SNPs) that contribute to AD risk [8]. These genetic variants can be aggregated into a polygenic risk score (PRS) that may confer substantial risk for AD [9]. Investigating the relationships of these genetic risk factors (e.g., *APOE* gene and PRS) with AD-specific biomarkers is crucial for understanding mechanisms underlying their clinical phenotypes associated with the genetic predisposition.

Numerous clinical studies have established robust associations of *APOE* genotype and PRS with central nervous system (CNS) biomarkers of AD pathologies. For instance, positron emission tomography (PET) imaging studies revealed that *APOE* ϵ 4 carriers exhibit earlier deposition, greater overall burden, and more extensive cortical distribution of amyloid- β (A β) and tau proteins in the brain [10–12], whereas *APOE* ϵ 2 carriers demonstrated delayed and reduced A β accumulation [13]. In addition, *APOE* ϵ 4 allele and a higher PRS were associated with cerebrospinal fluid (CSF) AD biomarkers such as reduced A β 42 and elevated total tau and phosphorylated tau (p-tau) proteins [14, 15]. Furthermore, inflammation and neurodegeneration are also involved in AD pathogenesis [16]. Notably, most of those studies in current literature have been conducted in the clinical settings of Caucasian patients with different cognitive disorders, and genetic characteristics of AD are known to vary across ethnic groups [7], which limits the generalizability of research findings from Caucasian populations into ethnically, geographically, and socioeconomically diverse populations. Advances in ultrasensitive immunoassays have revolutionized the detection of blood-based biomarkers (BBMs) for AD-related pathologies, enabling reliable quantification of plasma A β proteins, p-tau variants, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP). Collectively, these biomarkers capture the core neuropathological features of AD [17]. Importantly, BBMs detection is minimally invasive and cost-effective, making it particularly suitable for large-scale studies in general population settings.

Therefore, in this population-based study, we sought to characterize BBM profiles in older Chinese adults with a genetic predisposition to AD, defined by carrying the *APOE* ϵ 4 allele or having a high PRS, while taking into account potential variations in these profiles by age and sex.

METHODS AND MATERIALS

Study design and participants

This population-based study used data derived from the baseline assessments of the ongoing Multimodal Interventions to Delay Dementia and Disability in rural China (MIND-China) [18], which is one of the founding projects of the global network that was aimed at testing the Finnish FINGER multidomain lifestyle intervention models for dementia risk reduction and prevention across different cultures and settings, called the World-Wide FINGERS Network [19]. In short, the MIND-China project engaged individuals who were aged 60 years and older and residing in 52 villages of Yanlou Town, Yanggu County, located in western Shandong province, China. In March-September 2018, the baseline examination was performed during which a total number of 5,765 participants (74.9% of all eligible persons) were examined for MIND-China. Of these, 4006 participants were randomly selected for biomarkers measurement. Then, 59 participants were excluded due to major psychiatric disorders ($n = 8$), and missing data on genotypes ($n = 51$), leaving 3947 individuals for describing the characteristics of study participants. Of these participants, data on various plasma biomarkers were available in subsamples: plasma A β 42, A β 40, total tau, and NfL ($n = 1415$); plasma p-tau217, p-tau181, and GFAP ($n = 3837$); plasma BD-tau ($n = 1755$), and serum inflammatory biomarkers ($n = 1815$). These subsamples were randomly selected using a cluster (village)-based sampling method from all 52 villages, as previously reported [20], and were utilized to characterize the biological profiles in individuals with a genetic predisposition to AD (e.g., *APOE* genotype and PRS). Figure 1 shows the flowchart of the study participants.

The MIND-China project was approved by the Ethics Committee at Shandong Provincial Hospital Affiliated to Shandong First Medical University in Jinan, Shandong. Written informed consent was obtained from all the participants prior to their participation, or in the case of severely cognitively impaired persons, from a proxy (usually a family member). MIND-China as an interventional study was registered in the Chinese Clinical Trial Registry (Registration No.: ChiCTR1800017758).

Data collection and assessments

At baseline, all data were collected by trained medical professionals via face-to-face interviews, clinical and neuropsychological evaluations, and laboratory testing [18]. These data included demographic features (e.g., age, sex, and education), lifestyle and health behaviors (e.g., smoking, drinking alcohol, and physical activity), health conditions (e.g., diabetes, hyperlipidemia, hypertension, coronary heart disease [CHD], and stroke), and use of medication (e.g., antidiabetic and antihypertensive agents). Educational attainment was dichotomized into no schooling and primary school or above based on formal schooling attendance. Height and weight were measured in light clothes without shoes and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). After an overnight fast, peripheral blood samples were taken and fasting blood glucose, lipids, and serum creatinine were measured using a fully automated biochemical analyzer. Estimated glomerular filtration rate (eGFR) was calculated according to serum creatinine [21]. Diabetes, hyperlipidemia, hypertension, CHD, and stroke were defined according to clinical examinations, as described previously [22].

Genotyping and PRS

Genomic DNA was extracted from peripheral blood leukocytes using the TIANamp blood DNA kit (Tiangen, Beijing, China) in accordance with the manufacturer's protocol. Subsequently, DNA was determined using Qubit 3.0, and 100 ng of genomic DNA per sample served as template for library construction. Multiplex PCR primers were designed to capture all SNPs included in our study (<http://www.igenetech.com/design>). Sequencing libraries were prepared with the MultipSeqCustom Panel (iGeneTech, Beijing, China) according to the manufacturer's protocol, with unique index codes assigned to each sample. Finally, qualified libraries were processed by next-generation sequencing (NGS) on a NovaSeq platform (Illumina), and raw data were

cleaned to eliminate low-quality reads using FastQC. Genotyping was performed by an operator blinded to clinical information. The *APOE* genotypes determined by SNPs rs7412 and rs429358 were validated in a 5% subset by Sanger sequencing, demonstrating perfect agreement between methods [23].

The PRS for AD was generated following previously reported approaches [9]. In brief, of the initial 53 SNPs that were potentially associated with AD, SNPs were excluded if they had a minor allele frequency (MAF) < 0.01 or failed the Hardy-Weinberg equilibrium test ($p < 0.05$). We compared SNP allele frequencies between AD and non-AD participants in the baseline assessments of the 2018 MIND-China study. Then, we employed age- and sex-adjusted logistic regression models to estimate odds ratios (ORs) of AD associated with variant alleles and the common genotypes. We screened SNPs that showed associations with AD at $p < 0.30$ for the development of PRS, and 14 genetic variants plus the *APOE* gene were selected for generating the PRS (PRS_{*APOE*}), in which the PRS was computed as the sum of the products of SNP dosages for those selected genetic variants and their corresponding weights. In addition, we constructed a PRS without the *APOE* gene (PRS_{non*APOE*}) to assess the impact of *APOE* genotype on the biological profile of PRS for AD.

Blood-based biomarkers

After an overnight fast, peripheral blood samples were drawn into ethylenediaminetetraacetic acid (EDTA)-coated vacutainers, and then, centrifuged to isolate plasma. The plasma samples were stored at -80°C until further analysis. Plasma A β 40, A β 42, total tau, NfL, P-tau217, P-tau181, GFAP, and BD-tau were quantified using a single-molecule array (Simoa) on the HD-X platform (Quanterix Corp, MA, USA), as previously reported [20, 23]. In brief, we measured plasma A β 40, A β 42, and total tau with the Human Neurology 3-Plex A (N3PA) Kit, NfL with the NF-light Advantage Kit, P-tau217 with the ACC pTau217 Assay, P-tau181 with the pTau181 Advantage V2.1 Kit, GFAP with the GFAP Discovery Kit, and BD-tau with the sheep monoclonal antibody TauJ.5H3. Two quality control (QC) samples and one pooled sample were detected in duplicate on each plate for all analyses. The intra-assay and inter-assay coefficients of variability for both QC samples were controlled within 15% [24].

Serum cytokines (e.g., interleukin and interferon gamma) were measured using commercial kits from Meso Scale Discovery (MSD V-PLEX® Assays) following the manufacturer's protocols, as previously described [25]. Two QC samples were used to monitor the intra-assay and inter-assay coefficients of variation. The intra-assay and inter-assay coefficients of variation were all below 15%. We computed a composite score for chronic low-grade inflammation (CLGI) by integrating four serum cytokines (i.e., IL-6, IL-8, TNF α , and IFN γ), as previously reported [26]: (1) assigning values from -4 (1st-4th deciles) to $+4$ (7th-10th deciles), with the 5th-6th deciles as 0; and then, (2) summing values across four inflammatory markers. The composite CLGI score ranges from -16 to $+16$.

Statistical analysis

We reported frequencies (%) for categorical variables, means (standard deviation, SD) for normally distributed continuous variables, and medians (interquartile range, IQR) for continuous variables with skewed distributions. Characteristics of the study participants by sex were compared using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. The genetic predisposition to AD was assessed using the *APOE* gene and PRS. We categorized *APOE* genotype into $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 3$ (reference), $\epsilon 2/\epsilon 4$ or $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ in a similar way as used in a previous study [27].

In the subsamples, we used linear regression models to examine the associations of the *APOE* genotypes with plasma biomarkers. The restricted cubic spline (RCS) curves with three knots at the 10th, 50th, and 90th percentiles were fitted to flexibly model the patterns of association between PRS and BBMs. The likelihood-ratio test was used to test the potential non-linearity by comparing the model with only a linear term against the model with linear and cubic spline terms. If non-linearity was present (p for nonlinear < 0.05), we performed a stratified analysis by the inflection point (around median) of the PRS and presented stratum-specific β coefficients (95% confidence intervals, CIs); otherwise, we reported the β (95% CI) from the linear regression models for the total sample. Prior to the data analysis, plasma p-tau217, p-tau181, p-tau217/A β 42 ratio, NfL, BD-tau, and GFAP concentrations were log-transformed to reduce skewness. All analyses were adjusted for age, sex, education, BMI, diabetes, hyperlipidemia, hypertension, CHD, stroke, and eGFR because these factors are potentially associated with both the

genetic predisposition to AD and the examined BBMs [19, 23]. Statistical interactions of a genetic predisposition with age and sex on BBMs were assessed by simultaneously entering the independent variables and their cross-product term into the same model. Stratified analyses were performed when significant interactions were detected at *P* for interaction < 0.05.

We used Stata Statistical Software: Release 18.0 (Stata-Corp LLC, College Station, TX, USA) and R version 4.4.3 (The R Core Team, The R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>) for all analyses. Two-tailed *p* < 0.05 was considered statistically significant, and we used the Bonferroni test to adjust for multiple comparisons.

RESULTS

Characteristics of the study participants

The mean age of the 3947 participants was 70.67 years (SD, 5.80), 57.94% were female, and 40.74% had no formal school education. Compared to males, females were less educated and had lower eGFR, a higher BMI, and a higher prevalence of diabetes, hyperlipidemia, and CHD (*P* < 0.001) (Table 1). Among the 3947 participants, 521 (13.20%) carried the *APOE* ε2 allele, 587 (14.87%) carried one *APOE* ε4 allele, and only 23 (0.58%) exhibited *APOE* ε4 homozygosity. The mean PRS_{*APOE*} was 0.26 (SD, 0.56; range, -1.340-2.194) and the mean PRS_{non*APOE*} was 0.26 (SD, 0.54; range, -1.340-1.799) (Table 1).

Table 1
Characteristics of study participants in the total sample and by sex.

Characteristics ^a	Total sample (n = 3947)	Sex		
		Males (n = 1660)	Females (n = 2287)	<i>P</i> value
Age (years), mean (SD)	70.67 (5.80)	70.46 (5.62)	70.83 (5.92)	.105
Education (illiteracy), n (%)	1608 (40.74)	231 (13.92)	1377 (60.21)	< .001
BMI (kg/m ²), mean (SD)	24.85 (3.80)	24.39 (3.62)	25.18 (3.89)	< .001
Diabetes, n (%)	581 (14.72)	192 (11.57)	389 (17.01)	< .001
Hyperlipidemia, n (%)	967 (24.50)	286 (17.23)	681 (29.78)	< .001
Hypertension, n (%)	2661 (67.42)	1087 (65.48)	1574 (68.82)	.068
Coronary heart disease, n (%)	854 (21.64)	283 (17.05)	571 (24.97)	< .001
Stroke, n (%)	616 (15.61)	270 (16.27)	346 (15.13)	.332
eGFR, mL/min/1.73 m ² , median (IQR)	84.99 (19.25)	88.22 (15.29)	81.34 (20.49)	< .001
<i>APOE</i> genotypes, n (%)				.287
ε2/ε2 or ε2/ε3	521 (13.20)	231 (13.92)	290 (12.68)	
ε3/ε3	2816 (71.35)	1192 (71.81)	1624 (71.01)	
ε2/ε4 or ε3/ε4	587 (14.87)	228 (13.73)	359 (15.70)	
ε4/ε4	23 (0.58)	9 (0.54)	14 (0.61)	
PRS _{<i>APOE</i>} , median (IQR)	0.26 (0.56)	0.27 (0.58)	0.26 (0.58)	.373
PRS _{non<i>APOE</i>} , median (IQR)	0.26 (0.54)	0.26 (0.54)	0.26 (0.54)	.194

NOTE. ^aData were missing in 28 participants for BMI and in 47 for hypertension. In subsequent analyses, categorical variables with missing values were replaced with a dummy variable, and continuous variables with missing values were replaced with the mean value. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; *APOE*, apolipoprotein E gene; PRS_{*APOE*}, polygenic risk score with *APOE* gene; PRS_{non*APOE*}, polygenic risk score without *APOE* gene.

Associations of genetic predisposition with plasma biomarkers for AD

In the biomarker subsamples, compared with the *APOE* $\epsilon 3/\epsilon 3$ genotype, the *APOE* $\epsilon 2$ allele was significantly associated with lower plasma p-tau217 and p-tau217/A β 42 ratio ($P < 0.05$), whereas carrying one *APOE* $\epsilon 4$ allele was significantly associated with elevated p-tau217, p-tau181, and p-tau217/A β 42 ratio and a reduced A β 42/A β 40 ratio (all $P < 0.05$) and the *APOE* $\epsilon 4$ homozygotes showed much stronger associations with these plasma biomarkers than the $\epsilon 4$ heterozygotes (Table 2). After Bonferroni correction, the significant associations remained, except that the association between the *APOE* $\epsilon 2$ allele and p-tau217/A β 42 ratio became statically marginal (Bonferroni-corrected $P = 0.056$).

Table 2
Associations of *APOE* genotypes with core plasma biomarkers for Alzheimer's disease.

<i>APOE</i> genotypes	P-tau217 ^a (n = 3729)		P-tau181 ^a (n = 3763)		A β 42/A β 40 ratio ^b (n = 1415)		P-tau217/A β 42 ratio ^a (n = 1259)	
	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)
$\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$	487	-0.06 (-0.11-0.01)*	484	0.00 (-0.03-0.03)	188	0.07 (-0.18-0.32)	165	-0.11 (-0.20-0.02)*
$\epsilon 3/\epsilon 3$	2661	0.00 (reference)	2692	0.00 (reference)	1000	0.00 (reference)	890	0.00 (reference)
$\epsilon 2/\epsilon 4$ or $\epsilon 3/\epsilon 4$	561	0.13 (0.09–0.17)**	566	0.06 (0.02–0.09)**	216	-0.50 (-0.73-0.26)**	196	0.20 (0.12–0.29)**
$\epsilon 4/\epsilon 4$	20	0.47 (0.25–0.68)**	21	0.27 (0.12–0.42)**	11	-1.33 (-2.29-0.37)*	8	0.58 (0.19–0.96)*

NOTE. ^aThe original data were natural log-transformed to reduce skewness. ^bPlasma A β 42/A β 40 ratio was multiplied by 100. β coefficients (95% confidence intervals) were derived from the models that were adjusted for age, sex, education, body mass index, diabetes, hyperlipidemia, hypertension, coronary heart disease, estimated glomerular filtration rate, and stroke. Abbreviations: CI, confidence interval; *APOE*, apolipoprotein E gene; A β , amyloid-beta; P-tau, phosphorylated tau protein. * $p < 0.05$; ** $p < 0.001$.

The RCS analysis suggested a nonlinear association of PRS_{APOE} with plasma p-tau181 and A β 42/A β 40 ratio in the multivariable-adjusted models (p for nonlinear < 0.05), with the inflection point corresponding approximately to the median of PRS_{APOE} (i.e., 0.26). Further analyses stratified by the median of PRS_{APOE} suggested that among individuals with $PRS_{APOE} \geq 0.26$, a higher PRS_{APOE} was significantly associated with higher plasma p-tau181 ($\beta = 0.11$; 95% CI, 0.05 to 0.16) and a lower plasma A β 42/A β 40 ratio ($\beta = -0.54$; 95%CI, -0.93 to -0.15), whereas among persons with $PRS_{APOE} < 0.26$, PRS_{APOE} was not significantly associated with any of the examined plasma biomarkers (Fig. 2A2 and 2A3). In contrast, a higher PRS_{APOE} was linearly associated with higher plasma p-tau217 and p-tau217/A β 42 ratio in the total sample ($p < 0.01$) (Fig. 2A1 and 2A4). A higher $PRS_{nonAPOE}$ was significantly associated with increased plasma p-tau217 in the total sample and with increased plasma p-tau181 only in individuals with $PRS_{nonAPOE}$ above the median (i.e., 0.26) (Fig. 2B1 and 2B2).

Associations of genetic predisposition with plasma biomarkers for neurodegeneration

We explored the associations of the genetic predisposition to AD with plasma NfL, total tau, and BD-tau. *APOE* genotypes were not significantly associated with plasma NfL or total tau (Table 3). *APOE* $\epsilon 4$ homozygosity (vs. $\epsilon 3/\epsilon 3$), but not heterozygosity, was significantly associated with increased plasma BD-tau ($\beta = 0.23$; 95% CI, 0.03 to 0.43); however, the association became statistically non-significant after Bonferroni correction ($P = 0.082$). The PRS with or without *APOE* gene was not significantly associated with any of the examined plasma biomarkers for neurodegeneration (all $p > 0.05$, data not shown).

Table 3
Associations of *APOE* genotypes with plasma biomarkers for neurodegeneration and inflammation.

<i>APOE</i> genotypes	NfL ^a (n = 1414)		T-tau (n = 1415)		BD-tau ^a (n = 1755)		GFAP ^a (n = 3808)		CLGI ^b (n = 1811)	
	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)
ε2/ε2 or ε2/ε3	188	-0.06 (-0.14-0.01)	188	-0.00 (-0.15-0.15)	235	-0.01 (-0.06-0.03)	491	-0.06 (-0.10-0.03)**	251	0.39 (-0.54-1.32)
ε3/ε3	999	0.00 (reference)	1000	0.00 (reference)	1246	0.00 (reference)	2722	0.00 (reference)	1286	0.00 (reference)
ε2/ε4 or ε3/ε4	216	0.03 (-0.04-0.10)	216	-0.02 (-0.17-0.12)	265	0.04 (-0.01-0.08)	572	0.10 (0.07-0.14)**	262	0.36 (-0.56-1.28)
ε4/ε4	11	-0.02 (-0.32-0.27)	11	-0.10 (-0.68-0.49)	9	0.23 (0.03-0.43)*	23	0.15 (-0.01-0.32)	12	6.13 (2.21-10.06)*

NOTE. ^aThe original data were natural log-transformed to reduce skewness. ^bThe CLGI score was derived from serum IL-6, IL-8, TNFα, and IFNγ. β coefficients (95% confidence intervals) were derived from the models that were adjusted for age, sex, education, body mass index, diabetes, hyperlipidemia, hypertension, coronary heart disease, estimated glomerular filtration rate, and stroke. Abbreviations: CI, confidence interval; *APOE*, apolipoprotein E gene; NfL, neurofilament light chain; T-tau, total tau protein; BD-tau, brain-derived tau protein; GFAP, glial fibrillary acidic protein; CLGI, chronic low-grade inflammation; IL-6, interleukin-6; IL-8, interleukin-8; TNFα, tumor necrosis factor-alpha; IFNγ, interferon-gamma. *p < 0.05; **p < 0.001.

Associations of genetic predisposition with blood inflammatory biomarkers

We further investigated the relationships of genetic predisposition with blood biomarkers for systemic inflammation and neuroinflammation. Compared with the *APOE* ε3/ε3 genotype, the *APOE* ε2 allele was significantly associated with reduced plasma GFAP, while the *APOE* ε4 allele was associated with increased plasma GFAP (p < 0.001). For the composite systemic inflammatory biomarker, the *APOE* ε4 homozygosity was significantly associated with a substantially increased CLGI (β = 6.13; 95% CI, 2.21 to 10.06; p < 0.05) (Table 3).

The RCS analysis suggested a nonlinear relationship between PRS_{*APOE*} and plasma GFAP (p for nonlinear = 0.010). The stratified analyses by PRS median suggested that an increased PRS_{*APOE*} was significantly associated with an increased plasma GFAP on the right but not on the left of the median PRS (Fig. 3A1). A linear relationship was found between PRS_{non*APOE*} and plasma GFAP, such that a higher PRS_{non*APOE*} was significantly associated with higher plasma GFAP (p = 0.001) (Fig. 3B1). In addition, PRS_{*APOE*} and PRS_{non*APOE*} showed significantly linear relationships with CLGI (p < 0.05) (Fig. 3A2 and B2).

Interactions of genetic predisposition with age and sex on plasma biomarkers

We detected a statistically significant interaction of genetic predisposition to AD with age (60–74 vs. ≥75 years) on plasma p-tau217 (p for interaction < 0.05), but not on any other examined biomarkers. The stratified analyses by age groups suggested stronger associations of *APOE* genotype and PRS_{*APOE*} with plasma p-tau217 in individuals aged ≥ 75 years than in those younger than 75 years. Moreover, the association of the *APOE* ε2 allele with reduced plasma p-tau217 was statistically evident only in those aged ≥ 75 years (Fig. 4).

The *APOE* genotype showed a significant interaction with sex specifically on plasma Aβ42/Aβ40 ratio and GFAP (all p for interaction < 0.05). The stratified analyses by sex showed that the association of the *APOE* genotype with plasma Aβ42/Aβ40 ratio was more pronounced in females than in males (Fig. 4), while the association with plasma GFAP was more pronounced in

males than in females (Fig. 5). The PRS with or without *APOE* gene showed a statistical interaction with sex on plasma CLGI (all p for interaction < 0.05), with the association between PRS and CLGI being stronger in females than in males (Fig. 5).

Sensitivity analyses

To assess the robustness of the main results and the potential impact of clinically-diagnosed AD on the associations between genetic predisposition to AD and plasma biomarker profiles, we repeated the primary analyses among participants who were free of clinical dementia. Adjusting for all potential confounders, the direction and magnitude of the associations of *APOE* genotype and PRS with BBMs for AD, neurodegeneration, and inflammation were highly concordant with the findings in the full sample (Supplementary Information).

DISCUSSION

In this community-based study of rural-dwelling older adults in China, we systematically analyzed BBMs to characterize biological features associated with the genetic predisposition to AD. We found that *APOE* $\epsilon 4$ allele and a higher PRS are associated with plasma biomarkers indicative of AD pathology (e.g., increased p-tau217, p-tau181, and p-tau217/A β 42 ratio, and a reduced A β 42/A β 40 ratio), neuroinflammation (e.g., increased GFAP), and chronic systemic inflammation (e.g., increased CLGI); however, our study provided limited evidence supporting associations of AD genetic predisposition with plasma biomarkers of neurodegeneration. Together, these findings suggest that AD pathology, along with neural and systemic inflammation, represents key biological pathways underlying cognitive phenotypes linked to genetic predisposition to AD.

Previous studies have consistently linked the *APOE* $\epsilon 4$ allele with elevated CNS biomarkers of AD pathology (e.g., PET or CSF A β and tau proteins) [10,11,14]. Our large-scale population-based study extends these findings by revealing a clear dose-dependent relationship between the *APOE* $\epsilon 4$ allele and increased levels of core plasma AD biomarkers in a Chinese older population, which further supports the important role of the *APOE* $\epsilon 4$ allele in the pathogenesis of AD, potentially by modulating A β accumulation, tau hyperphosphorylation, and neuroinflammatory activation in the brain [28]. The protective effect of the *APOE* $\epsilon 2$ allele against clinical AD has been frequently reported among European and North American populations [29,30]. The *APOE* $\epsilon 2$ allele may confer protection mainly by reducing A β deposition [31,32], and evidence linking *APOE* $\epsilon 2$ with CNS biomarkers of tau pathology (p-tau181 and total tau) remains insufficient [33,34]. We found that *APOE* $\epsilon 2$ allele was associated with reduced plasma p-tau217 but not with p-tau181. Although both plasma p-tau217 and p-tau181 were markers of soluble abnormal tau hyperphosphorylation, p-tau217 is a dynamic biomarker that could capture the early neuronal response to A β plaques and the subsequent transition to tau aggregation, whereas p-tau181 reflects cumulative tau pathology and begins to plateau in advanced disease stages [35]. Additionally, p-tau217 is biologically less abundant and shows a stronger association with AD pathology than p-tau181 [36]. Our study suggested that PRS with and without *APOE* gene was linearly associated with increased plasma p-tau217 but showed a J-shaped relationship with plasma p-tau181, while only PRS with *APOE* gene exhibited an inverse J-shaped association with A β 42/A β 40 ratio. Together, these findings provide empirical evidence that polygenic architecture drives the core AD pathological cascade from early amyloid accumulation to subsequent tau-related neurodegeneration. However, data from ESTHER cohort failed to find any association between PRS and plasma p-tau181 in their linear regression analysis [37], in contrast to the "J-shape" relationship revealed by RCS analysis in our study. This discrepancy may partly reflect the potential that the violation of linearity assumption in general linear regression models may obscure their complex biological relationships. The nonlinear pattern of AD genetic predisposition with plasma p-tau181 may be biologically plausible, because tau aggregation is known to involve prion-like propagation and feedback amplification mechanisms that may be triggered once the amyloid burden reaches a critical level. Notably, PRS_{non*APOE*} showed no association with plasma A β 42/A β 40 ratio, further highlighting the dominant effect of the *APOE* $\epsilon 4$ allele in A β metabolism [38]. In line with the previous reports [33,39], our study showed that the associations between AD genetic predisposition and plasma AD-related biomarkers were more pronounced in old-old than young-old individuals and in females than males.

We found no clear evidence for an association between *APOE* genotype and plasma biomarkers of neurodegeneration (e.g., total tau and NfL), in line with previous reports from the population-based German ESTHER Study and the UK Biobank [40,41], although *APOE* $\epsilon 4$ allele has been linked to higher plasma NfL concentrations in clinical-based studies of selective patient

populations [42,43]. The observed association in clinical-based studies is likely because patients in clinical settings often have a higher proportion of *APOE* $\epsilon 4$ carriers and a heavier load of AD pathology in the brain than those in the general population settings. Similarly, an association of PRS with increased plasma NfL was reported in a clinical-based case-control study [44], but not in our study nor in the population-based ESTHER study [37]. Plasma BD-tau reflects the low molecular weight forms of tau predominantly expressed in the brain [45], and is considered a biomarker for A β -associated neurodegeneration [46]. Interestingly, we found that *APOE* $\epsilon 4$ homozygosity was associated with elevated plasma BD-tau, although this association did not survive the correction for multiple comparisons, which deserves further investigation in large samples. Biologically, *APOE* $\epsilon 4$ homozygotes could activate central tau pathology in a dose-dependent manner and promote the release of BD-tau, which may occur prior to structural axonal damage, as reflected by elevated plasma NfL [47].

The neuropathological hallmarks of AD are accompanied by profound neuroinflammation marked by persistent astrocytic and microglial activation as well as systemic inflammation characterized by increased circulating cytokines, chemokines, and immune cells [48]. Our study demonstrated that the *APOE* genotype showed differential associations with neuroinflammation (plasma GFAP) and peripheral inflammation (CLGI). The association between the *APOE* $\epsilon 4$ allele and elevated plasma GFAP was consistent with the report from the UK Biobank [41]. This association is supported by large-scale genetic studies identifying *APOE* $\epsilon 4$ variant rs429358 as the foremost locus that determines plasma GFAP levels [49]. However, the protective *APOE* $\epsilon 2$ allele showed no association with plasma GFAP in a subsample within the UK Biobank cohort [41], which was different from our findings. This discrepancy might be partly attributable to differences in demographic characteristics (e.g., age, sex, education, and ethnicity) between the study samples. Furthermore, we found a strong association between *APOE* $\epsilon 4$ homozygosity and CLGI, which is consistent with previous reports that *APOE* $\epsilon 4$ allele is strongly associated with a pro-inflammatory response in the peripheral system [50]. Consistent with previous studies of the general populations [37,51], we also found that PRS was associated with increased plasma GFAP. Our study further revealed, for the first time, a linear association between PRS and CLGI, regardless of whether the PRS included the *APOE* gene. Together, these results indicate that the overall polygenic risk burden for AD could influence neuroinflammatory and systemic immune phenotypes, underscoring the polygenic nature of AD-related inflammation. Furthermore, our study revealed sex-differential associations of genetic susceptibility to AD with neuroinflammation and systemic inflammation, such that AD genetic predisposition showed a more pronounced association with neuroinflammation (plasma GFAP) in males but a stronger association with peripheral inflammation (CLGI) in females. This divergence suggests that genetic predisposition to AD may engage distinct inflammatory pathways between sexes, potentially eliciting a more direct central glial response in males while preferentially modulating the peripheral immune interface in females.

Our study represents one of the first investigations to systematically characterize BBM profiles for AD genetic predisposition in the general population setting, specifically in a Chinese rural older population. The findings from our study could not only enhance the generalizability of existing evidence across diverse ancestries but also offer population-specific insights critical for advancing research on AD precision medicine. However, some limitations of this study should be discussed. First, the cross-sectional design of our study limits the ability to establish the chronological sequence of changes in various blood biomarkers. Second, although we used well-established BBMs for AD-related pathologies, caution is warranted when interpreting the neuropathological mechanisms underlying our findings, given the absence of CNS biomarkers. Third, although the overall sample size was relatively large, there was limited statistical power for the analysis of certain subgroups (e.g., *APOE* $\epsilon 4/\epsilon 4$ genotype). Finally, our study sample was derived only from one rural region in western Shandong province and included mainly Han majority, which should be kept in mind when generalizing our research findings to broader older populations.

In conclusion, this population-based study revealed that the BBM profiles of genetic predisposition to AD were characterized by blood biomarkers for AD pathology (A β and tau proteins), neuroinflammation (GFAP), and systemic inflammation (CLGI). These findings provide critical insight into the neuropathological and neurobiological pathways underlying cognitive phenotypes associated with AD genetic predisposition. Future prospective cohort studies are warranted to determine whether these BBM profiles can reliably predict the transition from preclinical pathological processes to overt cognitive outcomes, thereby informing early risk stratification and tailored preventive intervention strategies in genetically susceptible populations.

Abbreviations

MIND-China

Multimodal Interventions to Delay Dementia and Disability in Rural China

A β

amyloid-beta

NfL

neurofilament light chain

P-tau

phosphorylated tau protein

GFAP

glial fibrillary acidic protein

BD-tau

brain-derived tau protein.

Declarations

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QYW, TTH, YFD, and CQ developed the research concept and designed the study. LS, CCL, MZ, XYT, NT, HZ, and FG contributed to laboratory experiments. QYW and KKL performed data analysis. TTH, YFD, and CQ supervised this study. All authors contributed to the interpretation of the results and revision of the manuscript for important intellectual content and approved the final version of the manuscript.

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The data that support the findings of this study are available from the corresponding author upon reasonable request and approval by the steering committee of MIND-China at Shandong Provincial Hospital.

POTENTIAL CONFLICTS OF INTEREST

FG-O has served on scientific advisory boards and/or as a consultant for AIBL-Tecan. H. Zetterberg has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Celectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work). The other authors report no disclosures. All other authors declare that they have no conflicts of interest.

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Figures

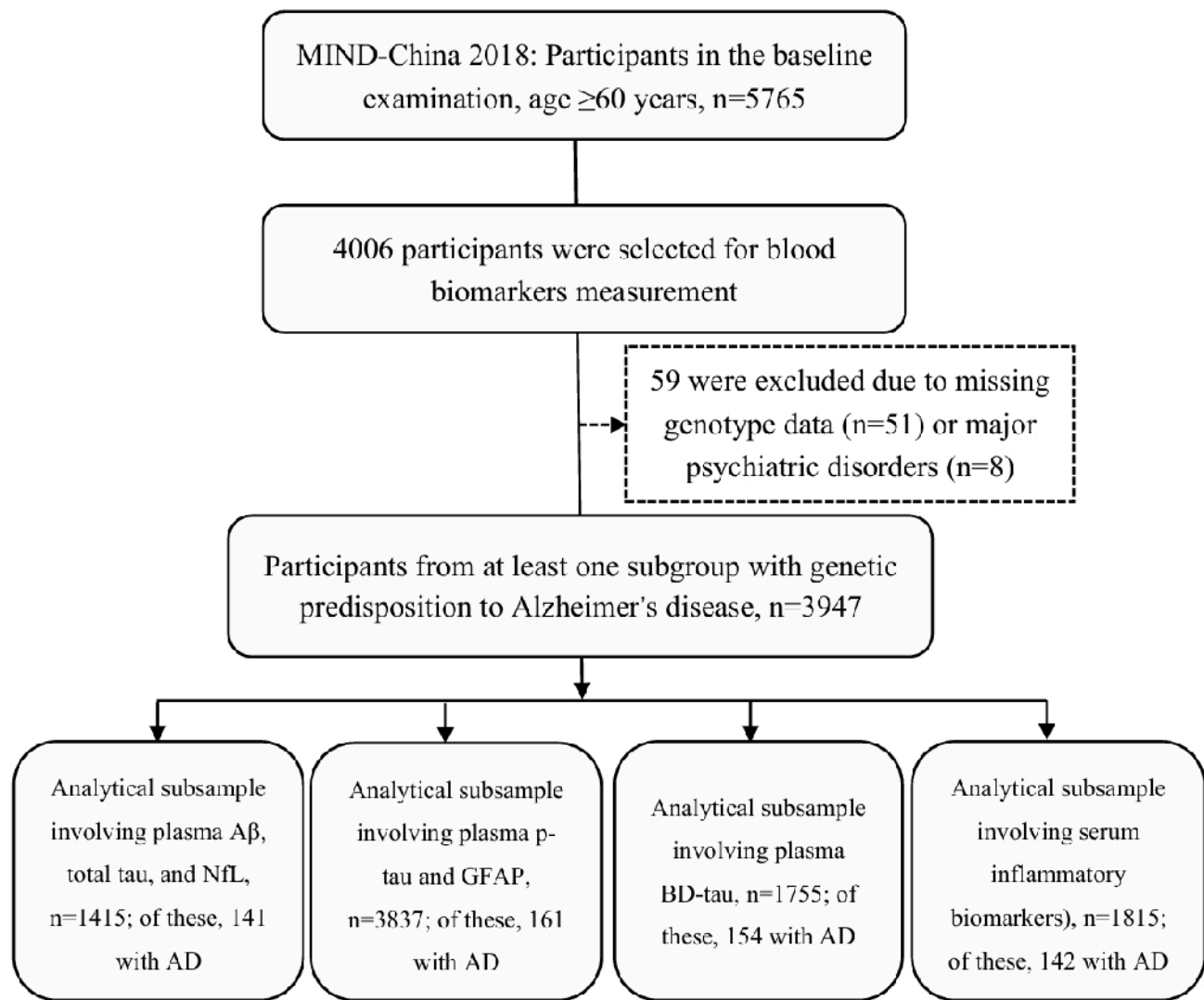


Figure 1

Flowchart of study participants.

Abbreviations: MIND-China, Multimodal Interventions to Delay Dementia and Disability in Rural China; Aβ, amyloid-beta; NfL, neurofilament light chain; P-tau, phosphorylated tau protein; GFAP, glial fibrillary acidic protein; BD-tau, brain-derived tau protein.

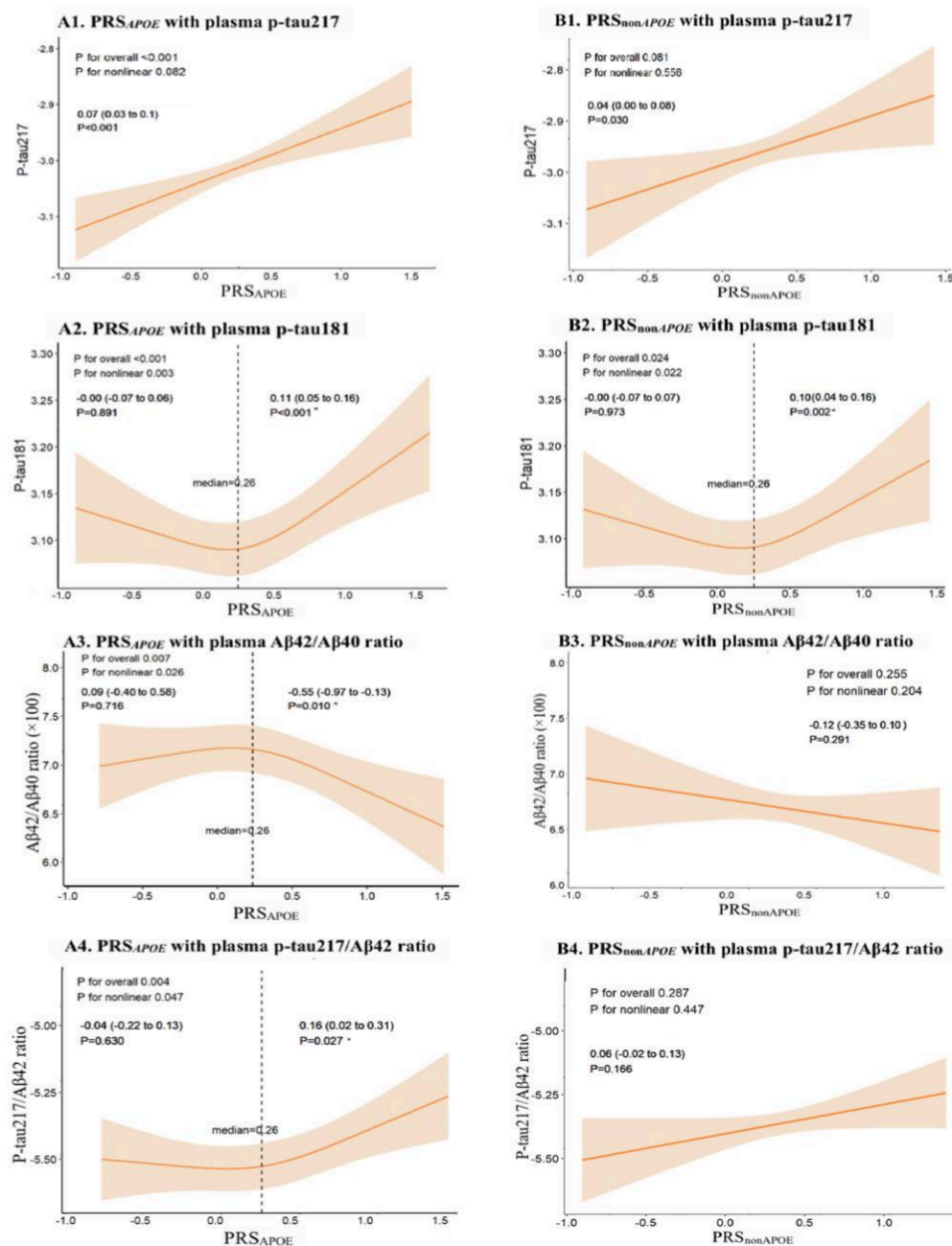


Figure 2

Associations of PRS with blood-based biomarkers for Alzheimer's disease from the restricted cubic spline models.

NOTE. A1-A4. Associations of PRS_{APOE} with plasma p-tau217 (A1), PRS_{APOE} with plasma p-tau181 (A2), PRS_{APOE} with plasma Aβ42/Aβ40 ratio (A3), and PRS_{APOE} with plasma p-tau217/Aβ42 ratio (A4). B1-B4. Associations of PRS_{nonAPOE} with plasma p-tau217 (B1), PRS_{nonAPOE} with plasma p-tau181 (B2), PRS_{nonAPOE} with plasma Aβ42/Aβ40 ratio (B3), and PRS_{nonAPOE} with plasma p-tau217/Aβ42 ratio (B4). Solid lines represent Alzheimer's disease core plasma biomarkers and shaded areas indicate 95% confidence intervals derived from restricted cubic spline regression models with three knots at the 10th, 50th, and 90th

percentiles. Data represent β coefficient (95% confidence intervals) of core plasma biomarkers of Alzheimer's disease associated with PRS_{APOE} and $PRS_{nonAPOE}$ derived from the models that were adjusted for age, sex, education, body mass index, diabetes, hyperlipidemia, hypertension, coronary heart disease, estimated glomerular filtration, and stroke. *The significant associations survived the Bonferroni corrections for multiple comparisons. Abbreviations: A β , amyloid-beta; P-tau, phosphorylated tau protein; PRS_{APOE} , polygenic risk score with *APOE* gene; $PRS_{nonAPOE}$, polygenic risk score without *APOE* gene.

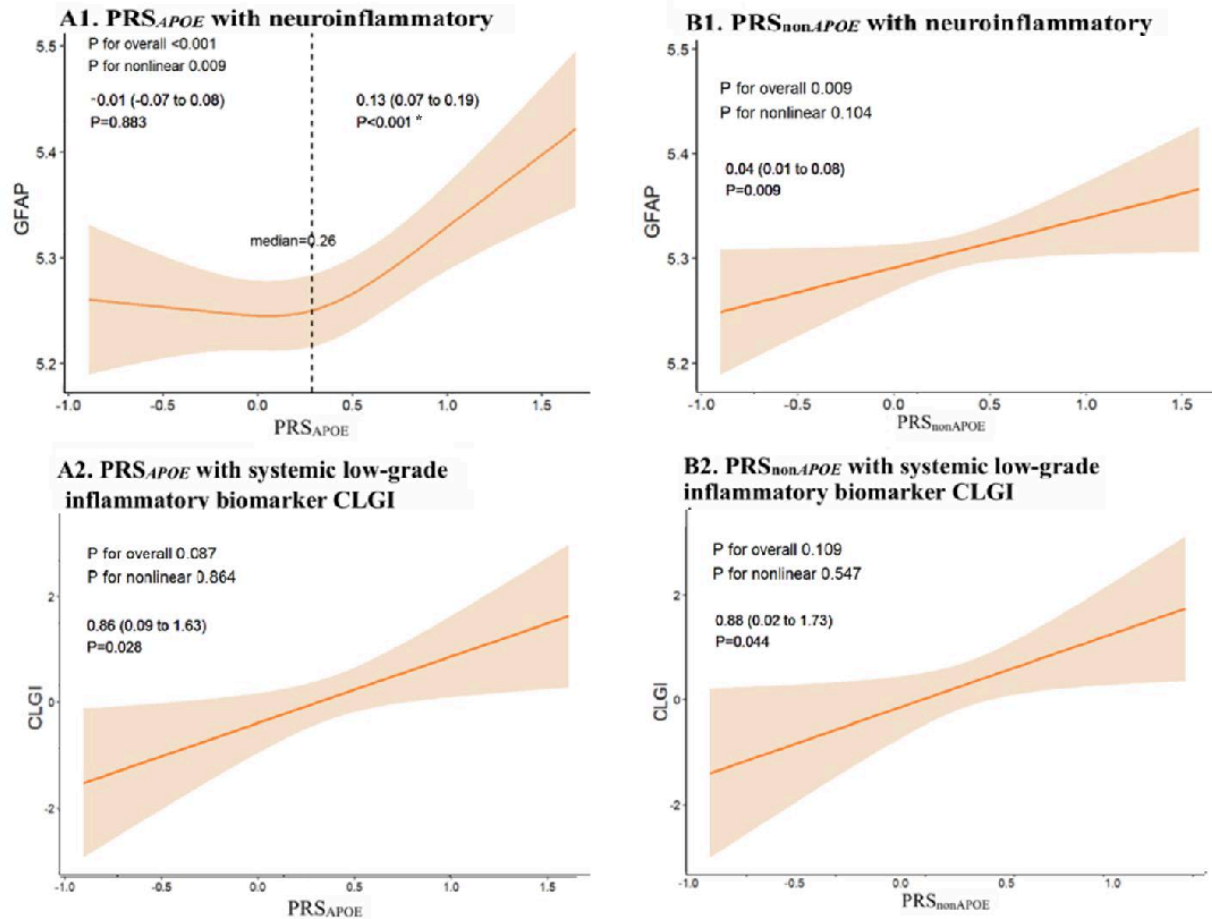


Figure 3

Associations of PRS with blood biomarkers for inflammation from the restricted cubic spline models.

NOTE. A1-A2. Association of PRS_{APOE} with neuroinflammatory biomarker GFAP (A1) and PRS_{APOE} with systemic low-grade inflammatory biomarker CLGI (A2). B1-B2. Associations of $PRS_{nonAPOE}$ with neuroinflammatory biomarker GFAP (B1) and $PRS_{nonAPOE}$ with systemic low-grade inflammatory biomarker CLGI (B2). Solid lines represent central and peripheral inflammation of Alzheimer's disease and shaded areas indicate 95% confidence intervals derived from restricted cubic spline regression models with three knots at the 10th, 50th, and 90th percentiles. Data represent β coefficient (95% confidence intervals) of GFAP and CLGI associated with PRS_{APOE} and $PRS_{nonAPOE}$ derived from the models that were adjusted for age, sex, education, body mass index, diabetes, hyperlipidemia, hypertension, coronary heart disease, estimated glomerular filtration, and stroke. *The significant associations survived the Bonferroni corrections for multiple comparisons. Abbreviations: GFAP, glial

fibrillary acidic protein; CLGI, chronic low-grade inflammation; PRS_{APOE}, polygenic risk score with *APOE* gene; PRS_{nonAPOE}, polygenic risk score without *APOE* gene.

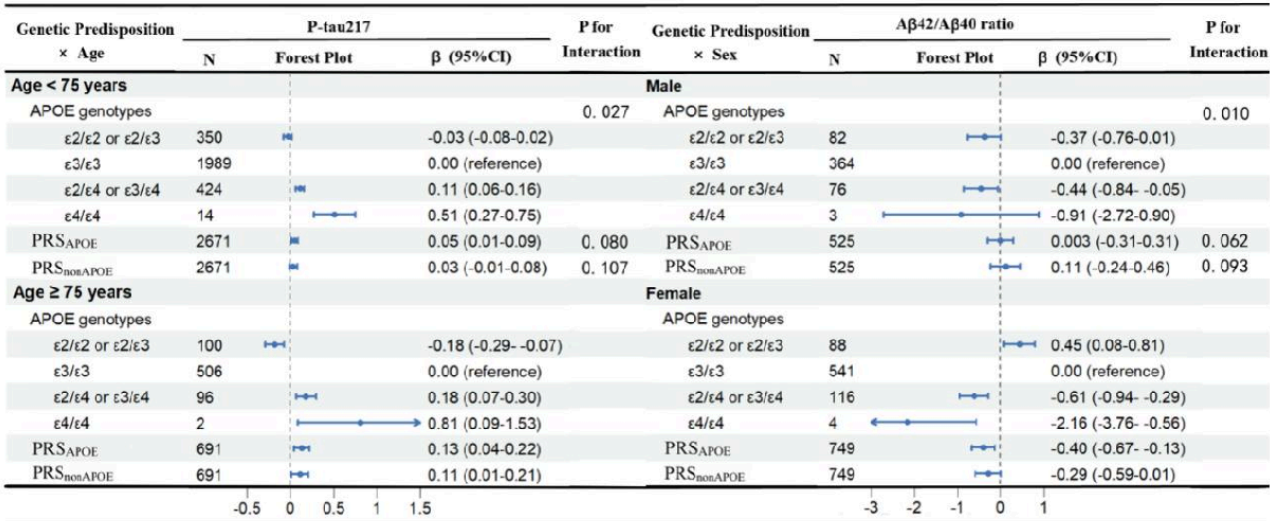


Figure 4

Associations of genetic predisposition with Alzheimer’s disease biomarkers by age and sex.

NOTE. β-coefficients (95% confidence intervals) were derived from the linear regression models that were adjusted for age, sex, education, body mass index, diabetes, hyperlipidemia, hypertension, coronary heart disease, estimated glomerular filtration, and stroke.

Abbreviations: *APOE*, apolipoprotein E gene; PRS_{APOE}, polygenic risk score with *APOE* gene; PRS_{nonAPOE}, polygenic risk score without *APOE* gene; P-tau, phosphorylated tau protein; Aβ, amyloid-beta.

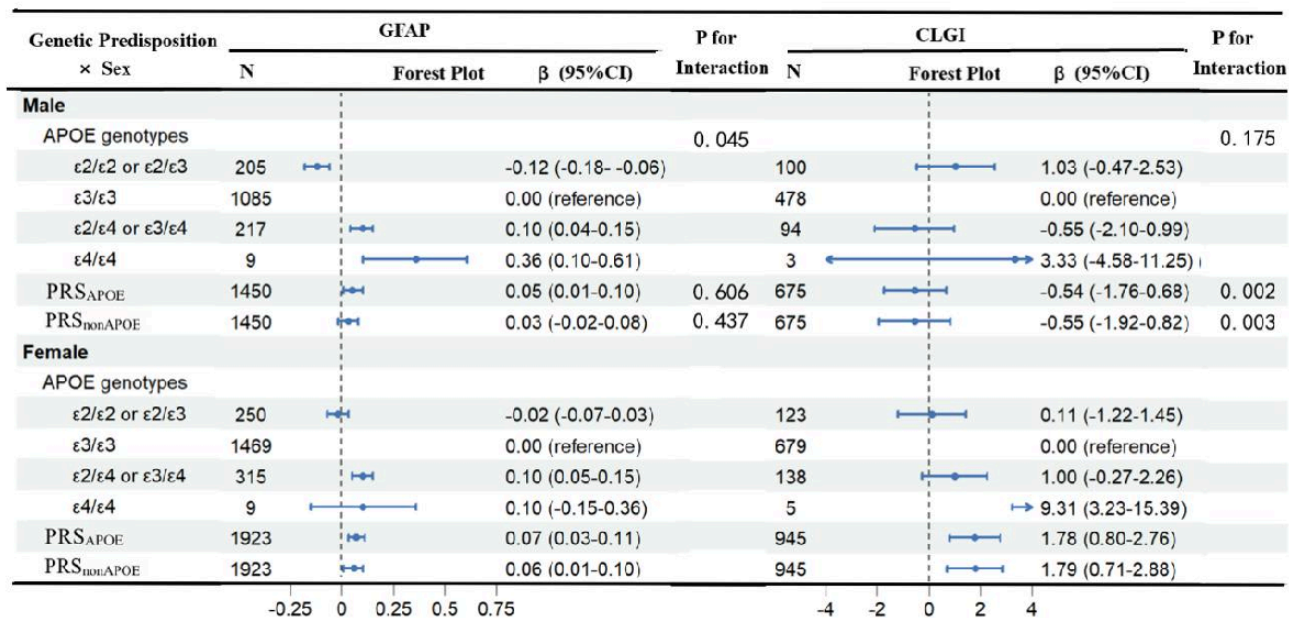


Figure 5

Associations of genetic predisposition to Alzheimer's disease with blood biomarkers for inflammation by sex.

NOTE. β-coefficients (95% confidence intervals) were derived from the linear regression models that were adjusted for age, sex, education, body mass index, diabetes, hyperlipidemia, hypertension, coronary heart disease, estimated glomerular filtration, and stroke.

Abbreviations: *APOE*, apolipoprotein E gene; PRS_{APOE}, polygenic risk score with *APOE* gene; PRS_{nonAPOE}, polygenic risk score without *APOE* gene; GFAP, glial fibrillary acidic protein; CLGI, chronic low-grade inflammation.

Supplementary Files

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