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ORIGINAL ARTICLE

Amyloid pathology mediates the associations between plasma fibrinogen and cognition in non-demented adults

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Abstract

Though previous studies revealed the potential associations of elevated levels of plasma fibrinogen with dementia, there is still limited understanding regarding the influence of Alzheimer's disease (AD) biomarkers on these associations. We sought to investigate the interrelationships among fibrinogen, cerebrospinal fluid (CSF) AD biomarkers, and cognition in non-demented adults. We included 1996 non-demented adults from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) study and 337 from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The associations of fibrinogen with AD biomarkers and cognition were explored using multiple linear regression models. The mediation analyses with 10000 bootstrapped iterations were conducted to explore the mediating effects of AD biomarkers on cognition. In addition, interaction analyses and subgroup analyses were conducted to assess the influence of covariates on the relationships between fibrinogen and AD biomarkers. Participants exhibiting low Aβ42 were designated as A+, while those demonstrating high phosphorylated tau (P-tau) and total tau (Tau) were labeled as T+ and N+, respectively. Individuals with normal measures of Aβ42 and P-tau were categorized as the A−T− group, and those with abnormal levels of both Aβ42 and P-tau were grouped under A+T+. Fibrinogen was higher in the A+ subgroup compared to that in the A− subgroup ($p = 0.026$). Fibrinogen was higher in the A+T+ subgroup compared to that in the A−T− subgroup ($p = 0.011$). Higher fibrinogen was associated with worse cognition and Aβ pathology (all $p < 0.05$). Additionally, the associations between fibrinogen and cognition were partially mediated by Aβ pathology (mediation proportion range 8%–28%). Interaction analyses and subgroup analyses showed that age and *ApoE* ε4 affect the relationships between fibrinogen and Aβ pathology. Fibrinogen was associated with

Abbreviations: AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment Scale; ADNI database, Alzheimer's Disease Neuroimaging Initiative database; *ApoE* ε4, apolipoprotein E4; Aβ, amyloid-β; BBB, blood–brain barrier; CABLE study, Chinese Alzheimer's Biomarker and LifestylE study; CI, confidence interval; CN, cognitively normal; CSF, cerebrospinal fluid; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; EXF, executive functions; FIB, fibrinogen; MCI, mild cognitive impairment; MEM, memory functions; MLR, multiple linear regression; MMSE, Minimum Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NIA-AA, the National Institute on Aging-Alzheimer's Association; P-tau, phosphorylated tau; ROS, reactive oxygen species; SCD, subjective cognitive decline; SD, standard deviations; Tau, total tau.

Li-Yun Ma and Jing-Hui Song contributed equally to the present work.

[#]Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

both cognition and Aβ pathology. Aβ pathology may be a critical mediator for impacts of fibrinogen on cognition.

KEYWORDS
Alzheimer's disease, cerebrospinal fluid biomarkers, cognitive impairment, plasma fibrinogen

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive deterioration (Ahn et al., 2010). Its incidence has been increasing in the global aging society. Since its pathological mechanism is still unclear, it is a great challenge to develop effective treatments for AD. The histopathological hallmarks of AD are extracellular Aβ plaques and intraneuronal neurofibrillary tangles of tau (Bloom, 2014). Moreover, many AD patients also exhibited abnormal hemostasis (Mari et al., 1996).

Fibrinogen, a glycoprotein involved in blood clotting, has been implicated in various inflammatory and thrombotic processes that may also affect the brain (McLarnon, 2021; Weisel, 2005). Under health conditions, fibrinogen circulates through the brain and the spinal cord vasculature without entering the brain parenchyma because of the presence of the blood–brain barrier (BBB), but there were evidences of fibrinogen deposition in the brain parenchyma of AD patients (Fiala et al., 2002; Lipinski & Sajdel-Sulkowska, 2006; Paul et al., 2007; Ryu & McLarnon, 2009). Additionally, coagulation abnormalities have previously been detected in AD patients. There is growing evidence that elevated plasma fibrinogen can cause a series of pathological changes, including oxidative stress and neuronal damage, thereby accelerating the pathological processes of dementia. Hyperfibrinogenemia is associated with risk of vascular diseases such as cerebral thrombosis (Machlus et al., 2011), which can predispose people to dementia. The relationships between fibrinogen and cognitive impairment or dementia have been extensively studied. Evidence from a TgCRND8 mouse model of AD has shown that fibrinogen crosses the damaged BBB and binds to relevant receptors on the surface of neuronal cells, leading to neuronal cell death and cognitive decline (Cortes-Canteli et al., 2010). A meta-analysis and systematic review have shown that fibrinogen is associated with cognitive decline and dementia (Quinn et al., 2011). Prospective population-based cohort studies have demonstrated a significant association between elevated plasma fibrinogen and the risk of AD or cognitive impairment (Gallacher et al., 2010; Gillett et al., 2018; Marioni et al., 2009; Rafnsson et al., 2007, 2010; van Oijen et al., 2005; Xu et al., 2008). Although a few animal studies have suggested the potential impact of fibrinogen on AD pathology (Paul et al., 2007; Ryu & McLarnon, 2009), there is still a lack of population-based clinical studies to comprehensively explore the interconnections between AD pathology, cognition, and fibrinogen.

Therefore, our study included 1996 non-demented individuals from the CABLE study to (1) explore the relationships between plasma fibrinogen and cognitive function, (2) examine the associations between plasma fibrinogen and CSF AD biomarkers, and (3) determine if the influences of plasma fibrinogen on cognition are mediated by AD biomarkers. In addition, we replicated the findings obtained from the CABLE study in the 337 participants from another independent cohort, the ADNI database.

2 | METHODS

2.1 | Study participants

2.1.1 | The CABLE study

The CABLE study was conducted at Qingdao Municipal Hospital in Shandong Province, China since its establishment in 2017 (Ou et al., 2020). The CABLE study was designed to identify the genetic and environmental risk factors of AD for prevention and early diagnosis of this disease. For all the participants, we performed clinical and neuropsychological assessments, conducted biochemical tests, as well as collected biological samples. Comprehensive questionnaires and an electronic medical record system were used to collect demographic data, AD risk factor profiles, and medical history. Participants with a prior diagnosis of any of the following conditions would be excluded: (1) serious neurological disorders (e.g., epilepsy, central nervous system infection, head trauma, and multiple sclerosis); (2) family history of hereditary diseases; (3) serious systemic diseases (e.g., malignant tumors); and (4) major psychological disorders (Text S1). To avoid the potential impact of anticoagulant drugs on fibrinogen levels, individuals receiving warfarin therapy were excluded from the study (Gillett et al., 2018). After excluding individuals with warfarin medication records ($N = 6$), a total of 1996 non-demented adults, aged between 40 and 90 years, were recruited from the CABLE study.

Based on the neuropsychological assessment results, brain magnetic resonance imaging (MRI) scans, and CSF biomarker measurements, we made a cognitive diagnosis for each individual in compliance with the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup diagnostic criteria (McKhann et al., 2011). Individuals were classified into three groups: cognitively normal (CN), subjective cognitive decline (SCD), and mild cognitive impairment (MCI). The diagnostic criteria for MCI (Winblad et al., 2004) are as follows: (1) memory impairment is the primary complaint; (2) the Montreal Cognitive Assessment (MoCA) score is below 24 (<24 for >12 years of education, <22 for 7–12 years of education, <19 for ≤6 years of education) (Hu et al., 2022); (3) preservation of daily

living abilities; (4) absence of dementia. Among participants with a MoCA score of 24 or above, those who reported subjective memory complaints were classified into the SCD group, while those who did not were classified into the CN group (Ou et al., 2019).

The CABLE study was carried out according to the principles of the Declaration of Helsinki. It received approval from the Institutional Ethics Committee at Qingdao Municipal Hospital. The ethics approval reference number for the CABLE study is 2020 Clinical Examination Character Y No. 010 (Fast). All enrolled subjects provided written informed consent for participation.

2.1.2 | ADNI database

Our findings in the non-demented participants from the CABLE study were further validated using another independent cohort from the ADNI database. Initiated in 2003, the ADNI project is a multi-centered cohort study. Its objective is to combine genetic, clinical, imaging, and biochemical biomarkers to develop predictors of late-onset AD. The inclusion criteria of ADNI were detailed on the website www.adni-info.org. We excluded the participants with the use of anticoagulant drugs based on medical history and medication records. After excluding 24 individuals with the use of warfarin and 44 individuals with the use of heparin at baseline, 337 participants remained for further analyses. Written informed consent was obtained from all ADNI participants, and ADNI received approval from the institutional review boards at all participating institutions.

2.2 | Cognitive measures

Considering that the MoCA score demonstrated higher sensitivity than the Minimum Mental State Examination (MMSE) score, particularly in preclinical AD (Hemmy et al., 2020), the CABLE study used the Chinese Version of MoCA score as an indicator of cognitive function. The MoCA scale covers nine cognitive domains, including executive function, fluency, orientation, calculation, abstraction, delayed recall, visual perception, naming, and attention. However, since the majority of the participants had no available MoCA score, the ADNI database assessed global cognition using the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS), and assessed memory functions (MEM) and executive functions (EXF) using neuropsychological batteries (Gibbons et al., 2012).

2.3 | Measurements of CSF AD biomarkers

In the CABLE study, CSF samples were collected by lumbar puncture from subjects after an overnight fast at Qingdao Municipal Hospital. The samples were centrifuged at 2000*g* for 10 min, and stored in EP tubes (100 EPPENDORF TUBES® PCR clean, catalog number: 0030108302) at −80°C for subsequent steps. The thawing–freezing cycle should not exceed two. CSF AD biomarkers (Yu et al., 2020), including amyloid-β (Aβ42), phosphorylated tau protein (P-tau), and total tau protein (Tau), were analyzed at room temperature using the enzyme-linked immunosorbent assay (ELISA) kit [Innotest β-AMYLOID (1–42), catalog number: 81583; PHOSPHO-TAU (181p), catalog number: 81581, and hTAU-Ag, catalog number: 81579; Fujirebio Europe N.V. Technologiepark 6, 9052 Ghent, Belgium]. All assays were performed in duplicate by experienced laboratory technicians, who were blinded to the clinical data and the subjects' cognitive status, and the average of the two duplicates was used for subsequent data analyses. For CSF AD biomarkers, the within-batch coefficient of variation (CV) was <5%; and the inter-batch CV was <15%. In ADNI, CSF AD biomarkers were assessed using the electrochemiluminescence immunoassays Elecsys on a cobas 601 instrument (Wang et al., 2022).

The 2011 NIA-AA diagnostic criteria for preclinical AD included normal cognition but with aberrant AD biomarkers (Soldan et al., 2016; Sperling et al., 2011). Around one-third of CN old people had AD pathology (Rowe et al., 2010; Schneider et al., 2009; Soldan et al., 2016). Therefore, it is of great importance to determine cutoff values of CSF AD biomarkers to categorize participants into normal or abnormal. In the CABLE study, abnormal levels of CSF Aβ42 were defined as those below 116.74 pg/mL (A+), and abnormal levels of P-tau and Tau were defined as those above 39.00 pg/mL (T+) and 180.26 pg/mL (N+), respectively (Zhang et al., 2022). Similarly, in the ADNI database, the cutoff values for CSF Aβ42, P-tau, and Tau were 977, 24, and 300 pg/mL, respectively (Blennow et al., 2019).

2.4 | Measurements of plasma fibrinogen

In the CABLE study, the hematological measurements were carried out on blood taken from the antecubital vein using vacuum tubes after an overnight fast of 8 hours. Plasma fibrinogen levels were determined using the Clauss method (STA®-Fibrinogen ⑤, catalog number: 00674, Diagnostica Stago, France). In the ADNI database, the data of plasma fibrinogen were from the "Use of Targeted Multiplex Proteomic Strategies to Identify Plasma-Based Biomarkers in Alzheimer's Disease" project, and the plasma fibrinogen levels were measured using Luminex xMAP technology by Rules-Based Medicine (RBM). For more comprehensive information, please refer to the document titled 'Biomarkers Consortium Plasma Proteomics Data Primer.pdf' available on the ADNI website (https://adni.loni.usc.edu/).

2.5 | *ApoE* ε4 genotyping

In the CABLE study, DNA was extracted from blood samples with the QIAamp® DNA Blood Mini Kit (250) (catalog number: 51106), and the extracted DNA was stored in an enzyme-free EP tube (PCR® TUBES, catalog number: PCR-02-C) at −80°C until the *ApoE* genotyping was performed. Restriction Fragment Length Polymorphism technology was utilized for genotyping, which included two specific

loci rs7412 and rs429358. According to the *ApoE* ε4 status, participants were categorized into *ApoE* ε4 non-carriers and carriers with at least one ε4 allele in both the ADNI database and the CABLE study.

2.6 | Statistical analyses

We tested the normality distribution for data using the Kolmogorov–Smirnov test, and the variables with skewed distributions were normalized by Box-Cox transformations (Chen & Pounds, 1998). The baseline characteristics of participants were presented as numbers and percentages for categorical variables, as well as means and standard deviations (SD) for continuous variables. The extreme values beyond 3SDs of the mean were eliminated prior to subsequent analyses. To facilitate model comparison, continuous variables were standardized to *z* scores. The intergroup comparisons of plasma fibrinogen based on the classification of AD biomarkers were carried out using *T*-test. To compare three or more groups, ANOVA and Tukey Honest significant post hoc analyses were carried out. Next, multiple linear regression (MLR) models were used to explore the associations of plasma fibrinogen with cognitive function and CSF AD biomarkers. Interaction analyses and subgroup analyses were conducted to evaluate the influence of covariates (age, gender, years of education, and *ApoE* ε4 carrier status) on the relationship between plasma fibrinogen and AD biomarkers. The above analyses were adjusted for age, gender, years of education, and *ApoE* ε4 status. Sensitivity analysis was presented by correcting for more variables, including body mass index (BMI), cigarette use, alcohol use, stroke, diabetes mellitus (DM), and hypertension (Table S1).

A two-tailed *p*-value <0.05 was considered statistically significant. All the statistical analyses and figure preparation were performed using R Studio software (version 4.2.3).

3 | RESULTS

3.1 | Basic characteristics of participants

In the CABLE study, subjects were recruited from January 2017 to July 2023. A total of 2128 participants were assessed; however, 132 individuals were excluded after population screening (Figure S1). Similarly, in the ADNI database, 566 participants had available data on fibrinogen levels, cognition, and AD biomarkers. However, 229 individuals were excluded after screening (Figure S2). The demographic information, plasma fibrinogen levels, CSF AD biomarkers, and cognitive scores of our participants from the CABLE study (*N* = 1996) and ADNI database (*N* = 337) were summarized in Table 1. The cohort (*N* = 1996) we included from the CABLE study had a mean plasma fibrinogen level of 3.19 g/L (SD = 0.85), a mean age of 62.28 years (SD = 10.18), average education years of 9.32 (SD = 4.33), a female proportion of around 56.72%, and an *ApoE* ε4 carrier proportion of 13.23%. We included a cohort of 337 individuals from the ADNI database for replication. They had a mean plasma fibrinogen level of 6.20 g/L (SD = 1.27), a mean age of 74.35 years (SD = 7.07), and an average of 15.82 years (SD = 2.97) of education.

TABLE 1 Characteristics of study participants.

Variable	The CABLE study	ADNI database
N	1996	337
Fibrinogen mean (SD)[a]	3.19 (0.85)	6.20 (1.27)
Age (years) mean (SD)	62.28 (10.18)	74.35 (7.07)
Gender (Female) *N* (%)	1132 (56.72)	116 (34.42)
ApoE ε4 carrier status *N* (%)	264 (13.23)	136 (40.36)
Education (years) mean (SD)	9.32 (4.33)	15.82 (2.97)
MoCA	22.67 (4.87)	—
ADAS	—	15.93 (7.07)
MEM	—	0.12 (0.54)
EXF	—	0.35 (0.55)
CSF AD biomarkers and their ratios (mean ± SD)		
CSF Aβ 42 (pg/mL)	12.59 (2.78)	6.65 (0.46)
CSF P-tau (pg/mL)	7.41 (1.10)	3.17 (0.45)
CSF Tau (pg/mL)	6.72 (0.74)	5.54 (0.39)
CSF P-tau/Aβ 42 ratio	−2.26 (0.86)	−2.04 (0.25)
CSF Tau/Aβ 42 ratio	−0.47 (0.69)	−0.79 (0.42)

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; ADNI database, Alzheimer's Disease Neuroimaging Initiative database; *ApoE* ε4, apolipoprotein epsilon 4; Aβ, amyloid-β; CABLE study, Chinese Alzheimer's Biomarker and LifestylE study; CSF, cerebrospinal fluid; EF, executive function; MEM, memory function; MoCA, Montreal Cognitive Assessment; *N*, number; P-tau, phosphorylated tau; SD, standardized deviation; Tau, total tau.

[a]In the CABLE study, plasma fibrinogen is measured in g/L, but in the ADNI database, it is measured in mg/dL.

As for cognitive assessments, different cognitive scales were adopted for the two cohorts, with details described in the method section. In our cohort from the CABLE study, the mean global cognitive score was 22.67 (SD = 4.87) and the mean score of abstraction was 2.29 (SD = 1.03) (detailed information on the nine cognitive domains based on the MoCA can be found in Table S2). In our study from the ADNI database, the mean global cognitive score was 15.93 (SD = 7.07) and the two cognitive domains' average scores were 0.12 (SD = 0.54) (MEM), 0.35 (SD = 0.55) (EXF), respectively.

3.2 | The relationships of fibrinogen with cognition and CSF AD biomarkers in the CABLE study

We conducted multiple intergroup comparisons of plasma fibrinogen to examine the difference in fibrinogen levels between people with different cognitive states. Differences in fibrinogen levels were observed across different cognitive states, with higher levels in MCI participants compared to those with CN ($p = 0.013$), and also higher

levels in those with MCI compared to SCD ($p=0.025$) (Figure S3, Table S3). Furthermore, to evaluate the associations between plasma fibrinogen and CSF AD biomarkers, we conducted intergroup comparisons of plasma fibrinogen based on the classification of AD biomarkers. We found that plasma fibrinogen concentration was significantly higher in the A+ subgroup compared to that in the A− subgroup ($p=0.026$) (Figure 1a; Table S4). However, no substantial difference ($p=0.233$) in fibrinogen level was found between the T+ and T− subgroups (Figure 1b; Table S4). Plasma fibrinogen level in the N+ subgroup was significantly higher than the N− subgroup ($p<0.001$) (Figure 1c; Table S4). Additionally, plasma fibrinogen was significantly higher in the A+T+ subgroup compared to that in the A−T− subgroup ($p=0.011$) (Figure S4, Table S5).

Plasma fibrinogen was not associated with global cognition on the MoCA scale ($\beta=-0.022$, $p=0.317$), but it was associated with a specific cognitive domain function (abstraction) based on the MoCA test ($\beta=-0.064$, $p=0.011$) using the MLR model (Table S6). Next, we also used the MLR models to examine the relationships between plasma fibrinogen and CSF AD biomarkers. Elevated fibrinogen levels showed a significant correlation with decreased CSF Aβ42 ($\beta=-0.103$, $p<0.001$) (Figure 1d), while no significant associations were found with P-tau ($\beta=-0.037$, $p=0.160$) (Figure 1e) or Tau ($\beta=0.005$, $p=0.835$) (Figure 1f). Further, we calculated the ratios of CSF amyloid and tau biomarkers and subsequently analyzed the associations of plasma fibrinogen with these ratios. Our analyses indicated that plasma fibrinogen was positively associated with both P-tau/Aβ42 ($\beta=0.084$, $p=0.004$) (Figure 1g) and Tau/Aβ42 ($\beta=0.108$, $p<0.001$) ratios (Figure 1h).

Finally, we performed mediation analyses to determine if the relationships between plasma fibrinogen and cognitive function were mediated by CSF AD biomarkers. Our result showed that the association of fibrinogen with lower cognitive function was partially mediated by the Tau/Aβ42 ratio, with a mediating proportion of 8.33% (Figure 1i).

3.3 | The relationships of fibrinogen with cognition and CSF AD biomarkers in the ADNI database

Consistent with the results in the CABLE study, increased fibrinogen was found to be associated with worse cognitive function (ADAS $\beta=0.173$, $p=0.001$; MEM $\beta=-0.166$, $p=0.002$; and EXF $\beta=-0.212$, $p<0.001$) (Table S7) using MLR analyses in the ADNI database. In the ADNI database, we also found that plasma fibrinogen showed a significant association with CSF Aβ42 ($\beta=-0.109$, $p=0.034$) (Figure 2a) rather than other CSF AD biomarkers and ratios, such as P-tau, Tau, P-tau/Aβ42 ratio, and Tau/Aβ42 ratio ($p>0.05$) (Figure 2b–e). Similarly, we also observed that Aβ42 mediated the relationships between plasma fibrinogen and cognitive functions, with the mediating proportions varying from 12% to 28% ($p<0.05$) (Figure 2f–h).

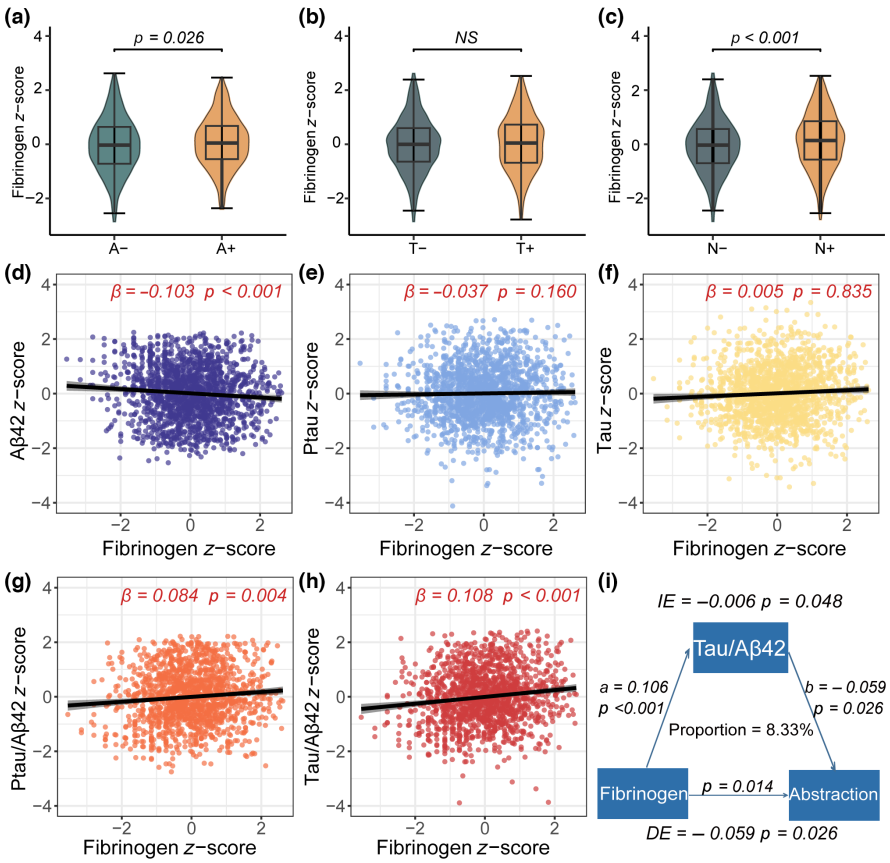

FIGURE 1 Associations of fibrinogen with cognition and CSF AD biomarkers in the CABLE study. Differences of fibrinogen in the CSF biomarker classifications were examined by *T*-test (a–c). MLR models were used to examine associations of fibrinogen with CSF AD biomarkers (d–h). Mediation analysis with 10 000 bootstrapped iterations was used to examine the mediation effect of Aβ pathology on cognition (i). The number of participants (*n*) who underwent the above analyses was 1996. Adjusted: each path of the model was adjusted for age, sex, years of education, and *ApoE* ε4 status. The cutoff values to define abnormal CSF biomarkers were <116.46 pg/mL for Aβ42 (A+), >38.47 pg/mL for P-tau (T+), and >176.46 pg/mL for Tau (N+). A+, amyloidosis; *ApoE* ε4, apolipoprotein E4; Aβ, amyloid-β; CSF, cerebrospinal fluid; MLR, Multiple linear regression; N+, neurodegeneration; P-tau, phosphorylated tau; T+, pathologic tau; Tau, total tau.

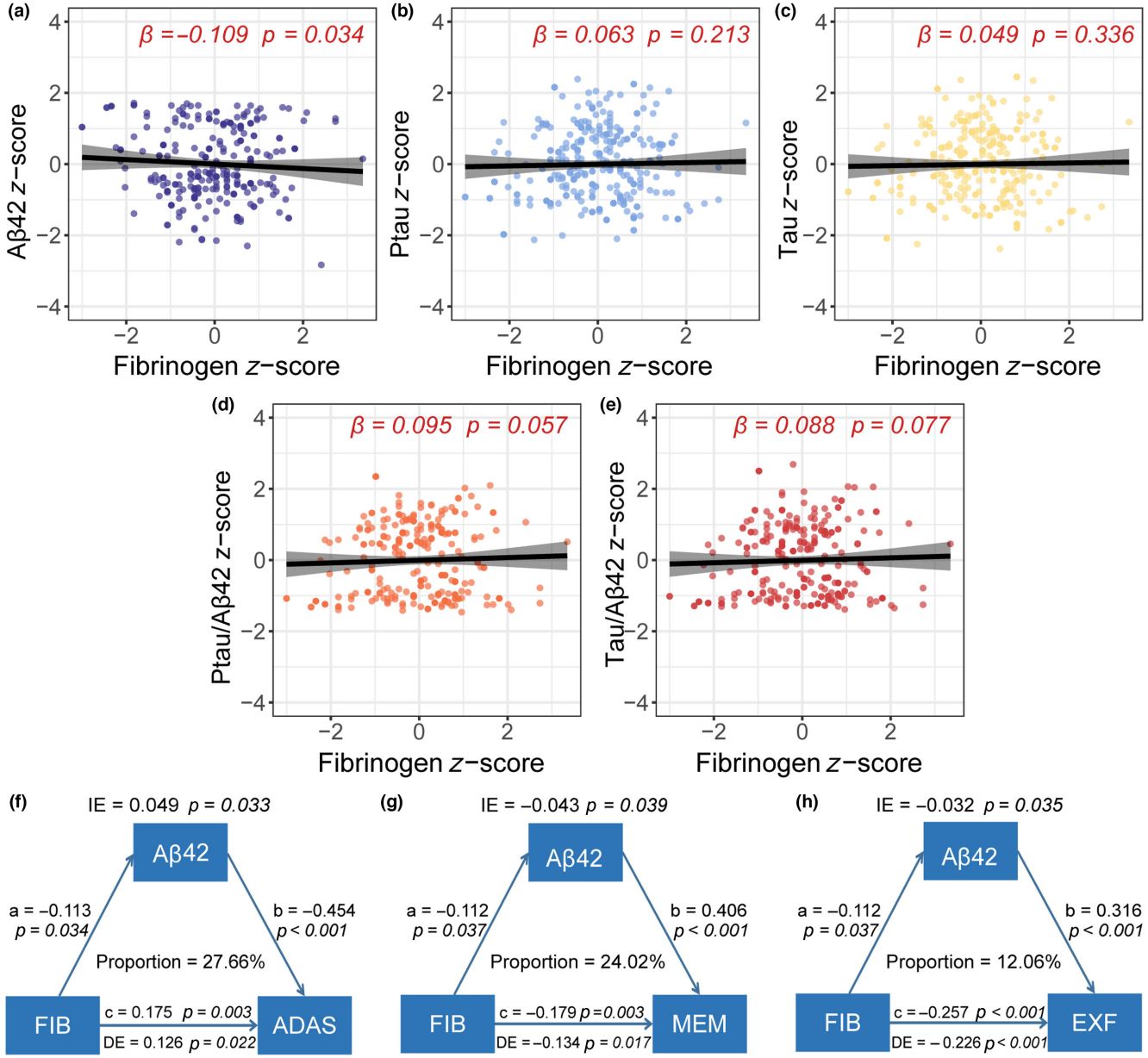

FIGURE 2 Associations of fibrinogen with cognition and CSF AD biomarkers in the ADNI database. MLR models were used to examine associations of fibrinogen with CSF AD biomarkers (a–e). Mediation analyses with 10000 bootstrapped iterations were used to examine the mediation effects of Aβ pathology on cognition (f–h). The number of participants (*n*) who underwent the above analyses was 337. Adjusted: each path of the model was adjusted for age, sex, years of education, and *ApoE* ε4 status. ADAS, Alzheimer's Disease Assessment Scale; *ApoE* ε4, apolipoprotein E4; Aβ, amyloid-β; CSF, cerebrospinal fluid; EXF, executive function; FIB, fibrinogen; MEM, memory function; MLR, Multiple linear regression.

3.4 | Influence of covariates on the relationships between fibrinogen and CSF AD biomarkers

Our interaction analyses showed that the interactions of fibrinogen with *ApoE* ε4 status and age had significant effects on CSF AD biomarkers only in the CABLE study ($p < 0.05$), but not in the ADNI database (Table S8). As for the influence of age, the associations observed in the total population remained significant across the age subgroups in the CABLE study, while the association between plasma fibrinogen and CSF Aβ42 was only significant in the late-life group in the ADNI database (Figure 3; Table S9). As for the influence of *ApoE* ε4, the subgroup analyses stratified by *ApoE* ε4 status yielded inconsistent results in the two databases. Specifically, the associations observed in total participants were still significant only in *ApoE* ε4 non-carriers in the CABLE study (Figure 3a; Table S9), while the association between fibrinogen and CSF Aβ42 remained significant only in *ApoE* ε4 carriers in the ADNI database (Figure 3b; Table S9).

To avoid the influence of other covariates on the results, we added covariates, including BMI, cigarette use, alcohol use, stroke,

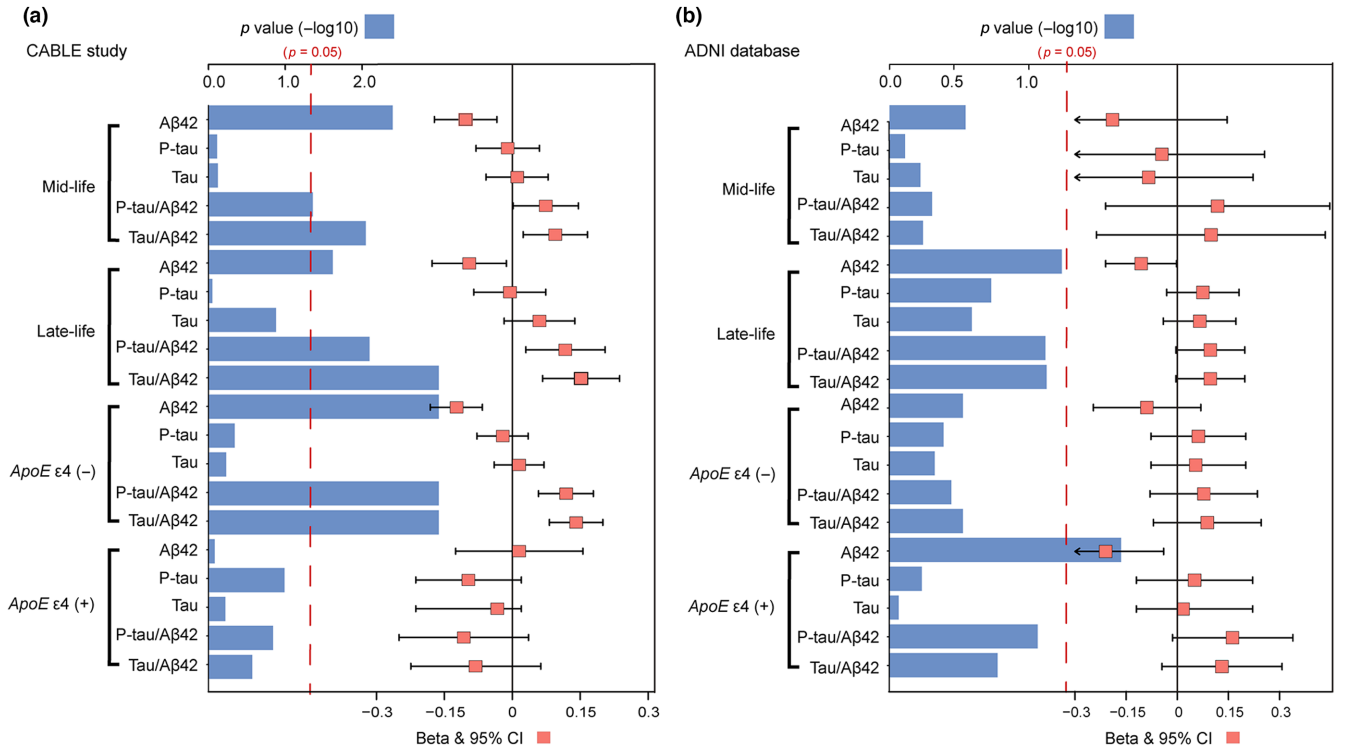

FIGURE 3 The associations of fibrinogen with AD biomarkers stratified by age and *ApoE* ε4 status. The number of participants (*n*) who underwent the analyses in the CABLE study was 1996, and the corresponding figure for the ADNI database was 337. Adjusted: Each path of the model was adjusted for age, sex, years of education, and *ApoE* ε4 status. *ApoE* ε4, apolipoprotein E4; Aβ, amyloid-β; CI, confidence interval; P-tau, phosphorylated tau; Tau, total tau.

DM, and hypertension, to multiple linear regression models. We found that the relationships between fibrinogen and CSF AD biomarkers still existed in the CABLE study (Table S10).

4 | DISCUSSION

The current study aimed to comprehensively examine the interrelationships of fibrinogen, cognitive decline, and CSF AD biomarkers in non-demented individuals. Our findings were as follows. (a) Individuals with amyloid pathology exhibited higher fibrinogen levels than those without amyloid pathology. (b) Increased fibrinogen levels were associated with both cognitive decline and Aβ pathology. (c) The impact of fibrinogen on cognition could be mediated by Aβ pathology. The study explored how plasma fibrinogen was involved in cognitive decline, and suggested a potential role of fibrinogen in AD pathogenesis.

Previous literature provides support for our finding that increased fibrinogen levels are associated with cognitive decline. Prospective longitudinal studies demonstrated that a high level of fibrinogen has detrimental effects on global cognition (Gillett et al., 2018; Marioni et al., 2009) and various neurocognitive domains, such as verbal declarative memory, nonverbal reasoning, verbal fluency, and processing speed (Marioni et al., 2009; Rafnsson et al., 2007). Two population-based cohort studies have shown that fibrinogen was associated with an elevated risk of dementia (Gallacher et al., 2010; van Oijen et al., 2005). An autopsy study has revealed that the zones of fibrinogen leakage surrounding the microvessels in AD tissues were significantly larger compared to those in the normal control group (Fiala et al., 2002). In vitro, the introduction of fibrinogen through intravenous administration led to the stimulation of microglia, synaptic deficits, and a reduction in dendritic spine density, all of which contributed to a cognitive decline (Merlini et al., 2019). Evidence from interventional experiments showed beneficial cognitive effects of anticoagulant therapy, in which lowered fibrinogen levels either halted cognitive disease progression or improved cognition in both AD mouse models and patients with dementia (Barber et al., 2004; Ratner et al., 1972; Walsh, 1983, 1993; Walsh et al., 1978), supporting that elevated fibrinogen was associated with cognition.

People with Aβ pathology reflected by CSF indicators (including Aβ42, P-tau/Aβ42, Tau/Aβ42) had increased levels of fibrinogen in our study. We also found that fibrinogen was associated with Aβ pathology, and Aβ pathology might partially mediate the effects of fibrinogen on cognition (the mediating proportion range 8%–28%). However, fibrinogen had no connection to tau pathology, defined as high CSF P-tau, or neurodegeneration, defined as high CSF Tau. Our findings seem to support the theory that fibrinogen potentially has detrimental effects on amyloid metabolism in adults without dementia. Although the clinical research is limited, animal studies and in vitro studies provided evidence for the association between fibrinogen and Aβ pathology. Anthony Cerami et al. reported that the interaction between Aβ42 and fibrinogen induced oligomerization

and abnormal structures of fibrinogen, which played a key role in AD (Ahn et al., 2010). The fibrinogen-Aβ interaction was found to be linked to cognitive impairment in both humans (Ramos-Cejudo et al., 2018) and mice (Muradashvili et al., 2015).

Our study found that age influenced the associations between fibrinogen and Aβ pathology. In the ADNI database, we observed a significant association among those older than 65 years, whereas it was not significant among those younger than 65 years. It is worth noting that the ADNI study included participants who had an average age of 74.35 years, with the majority being old people. Notably, only 36 participants were younger than 65 years. Given the small sample size of this younger subgroup, the observed inconsistency in results can be attributed to limited statistical power. Our interaction analyses and subgroup analyses suggested that *ApoE* ε4 status influenced the associations between fibrinogen and Aβ pathology in both the CABLE study and ADNI databases. An animal experiment has demonstrated that knocking out *ApoE* ε4 in mice results in a reduction in the peripheral Aβ42 clearance (Sharman et al., 2010), suggesting *ApoE* ε4 potentially influences the association between fibrinogen and Aβ pathology. There is currently a lack of direct clinical evidence for the association between *ApoE* ε4 and fibrinogen. Therefore, how *ApoE* ε4 influences the association between fibrinogen and Aβ pathology still remains to be elucidated in the future. Besides, the associations between fibrinogen and Aβ pathology yielded robust results even after adjusting for more covariates, including BMI, cigarette use, alcohol use, stroke, DM, and hypertension, indicating that these associations were barely impacted by complicated confounders.

Although the precise mechanisms underlying the role of plasma fibrinogen in AD pathology remained obscure, there are several possible pathways (Figure 4). Firstly, the interaction between fibrinogen and Aβ might trigger abnormal fibrinogen structures (Ahn et al., 2010; Zamolodchikov & Strickland, 2012). These abnormal structures showed greater resistance to degradation by fibrinolytic enzymes (Cortes-Canteli et al., 2010). They could result in reduced blood flow, vascular deficiencies, and neuroinflammation, all of which play a role in AD pathogenesis (Figure 4a) (Wen et al., 2004). Secondly, fibrinogen causes neuronal death by binding to fibrinogen receptors on the neuronal cell surface, contributing to the development of AD (Figure 4b) (Sulimai et al., 2021a). Thirdly, increased levels of fibrinogen lead to alteration in vascular reactivity and disruption of endothelial cell layer integrity through its binding with receptors on the endothelial cell membrane (Ernst & Resch, 1993; Guo et al., 2009; Lominadze et al., 2010). Previous studies have shown that elevated fibrinogen levels were associated with pro-inflammatory outcomes, including the activation of microglia (Clark et al., 2018; Davalos & Akassoglou, 2012; Lominadze et al., 2005). Specifically, fibrinogen deposition in the brain parenchyma, induced by vascular damage or BBB dysfunction, activates microglia and leads to the generation of reactive oxygen species (ROS), which in turn inhibits neurite outgrowth (Figure 4c) (Davalos et al., 2012;

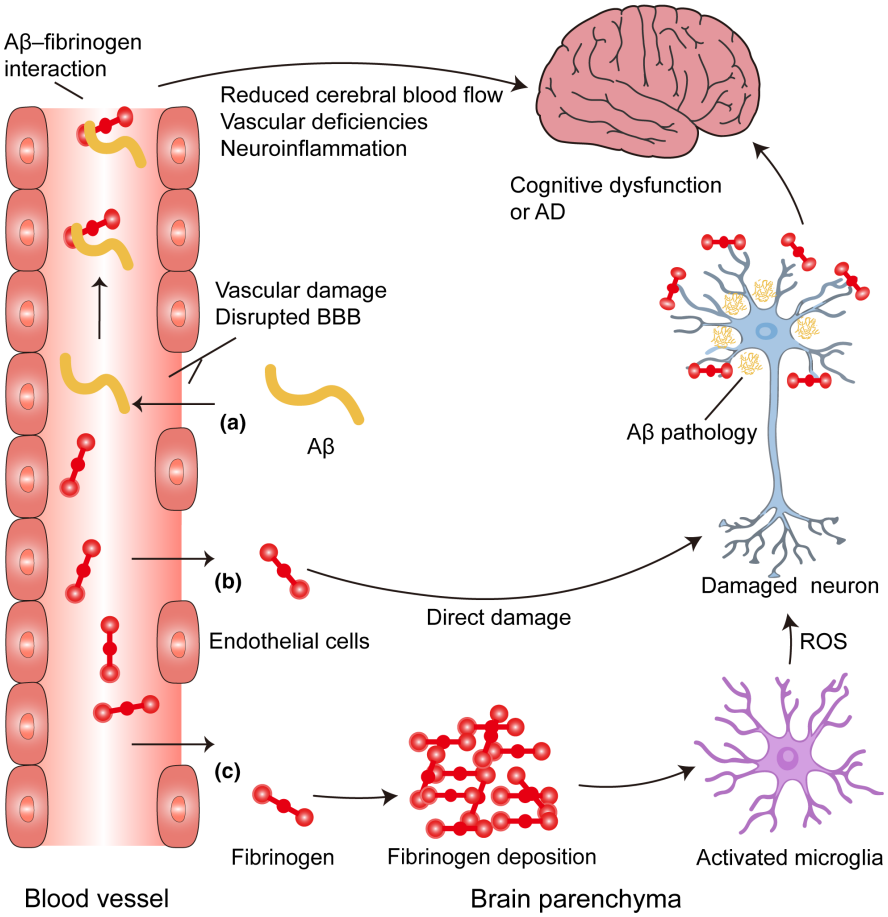

FIGURE 4 A schematic graph depicting associations among fibrinogen, AD pathologies, and cognition was shown. Combining our study with previous studies, there are several plausible explanations. (a) The interaction between fibrinogen and Aβ might trigger abnormal fibrinogen structures. These abnormal structures could result in reduced blood flow, vascular deficiencies, and neuroinflammation, all of which play a role in AD pathogenesis. (b) Fibrinogen causes neuronal death by binding to fibrinogen receptors on the neuronal cell surface, contributing to the development of AD. (c) Fibrinogen deposition in the brain parenchyma, induced by vascular damage or BBB dysfunction, activates microglia and leads to the generation of reactive oxygen species (ROS), which in turn inhibits neurite outgrowth. Aβ, amyloid-β; BBB, blood–brain barrier; ROS, reactive oxygen species.

Merlini et al., 2019; Sulimai et al., 2021b). Our findings provided new insights into the relationship between fibrinogen and Aβ pathology and had important implications for developing new measures to ameliorate Aβ pathology.

Several strengths of our study enhanced the reliability of our results. Firstly, we excluded participants with severe mental conditions (such as anxiety and depression) and poor ability to perform activities of daily living. Additionally, we conducted blinded quality control on the CSF data. Thereby, our study avoided confounding bias. Secondly, our study was the first to explore the associations between fibrinogen and CSF AD biomarkers in population-based cohorts. However, two limitations should be noted when interpreting our findings. One limitation is the cross-sectional design, which limits our ability to establish causal relationships. Hence, we need to replicate our findings in longitudinal studies in the future. A lack of imaging data is another limitation in our study. Given that brain imaging data (such as Tau-PET) more accurately reflect the link between AD pathology and fibrinogen, future prospective cohorts with available neuroimaging data can help validate or supplement evidence regarding the role of fibrinogen. In spite of these limitations, the findings revealed in this study offered novel insights into the pathogenesis of AD.

5 | CONCLUSION

The study demonstrated that plasma fibrinogen was associated with both cognitive impairment and Aβ pathology, and Aβ pathology might be a critical mediator for impacts of fibrinogen on cognitive decline. Aβ pathology may provide an important complement to elucidating the pathological mechanisms of fibrinogen involved in AD. This study enhanced our understanding of fibrinogen's pathogenic role in AD and revealed the potential of fibrinogen as a promising biomarker for preclinical AD.

AUTHOR CONTRIBUTIONS

LYM, JHS, and PYG organized data. LYM and PYG carried out the statistical analysis. LYM and JHS participated in the first draft of the manuscript. LYM, YNO, and PYG designed and drew the figures. LYM, JHS, and YNO participated in the revision of the manuscript. YF, DDZ, LYH, ZTW, CRP, YCM, and LT participated in the reviewing and editing of the manuscript. YNO and LT designed the study. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no financial disclosures or competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jnc.16105.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this publication and/or are available from the corresponding author on reasonable request.

CONSENT TO PARTICIPATE

Written informed consent was obtained from all ADNI participants, and ADNI received approval from the institutional review boards at all participating institutions.

CONSENT FOR PUBLICATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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