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The interrelationships of CSF sTREM2, AD pathology, minimal depressive symptoms, and cognition in non-demented adults

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Abstract

Background Microglial activation has been suggested to be involved in the pathogenesis of depression and Alzheimer's disease (AD). Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) is a marker of microglial activation. The purpose of this study was to investigate the interrelationships of cerebrospinal fluid (CSF) sTREM2, AD pathology, as well as minimal depressive symptoms (MDSs), and cognition.

Methods A total of 545 non-demented individuals from the Alzheimer's Disease Neuroimaging Initiative cohort were included in our study. The average age of the total population was 72.6 years and the percentage of females was 42.6%. Linear regression models were conducted to investigate the linear relationships of MDSs with CSF sTREM2, AD pathology, cognition, and brain structure. Mediation models and structural equation models (SEM) were conducted to examine whether CSF sTREM2 mediated the relationships of MDSs with AD pathology and cognition.

Results Results revealed that individuals with MDSs had lower CSF sTREM2 levels than normal controls. Linear regression showed that MDSs were linearly associated with CSF sTREM2 ($P_{FDR} = 0.012$) and amyloid biomarkers ($P_{FDR} < 0.05$), as well as cognitive scores ($P_{FDR} < 0.05$) and hippocampal volume ($P_{FDR} = 0.003$). Mediation analyses revealed that CSF sTREM2 mediated the association between MDSs and amyloid pathology, with the mediating proportions ranging from 6.030 to 18.894%. However, SEM failed to reveal that MDS affected cognition through CSF amyloid pathology and CSF sTREM2.

Conclusions MDSs are associated with amyloid pathology and cognition. CSF sTREM2 may potentially be an intervenable target between depression and AD pathology.

Keywords sTREM2, Minimal depressive symptoms, Alzheimer's disease, Amyloid pathology, Cognition

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Background

The World Health Organization (WHO) has estimated that the global number of individuals affected by dementia will rise from 55 million in 2019 to 139 million in 2050 [1]. Alzheimer's disease (AD), the prevalent form of dementia, is characterized by cognitive and behavioral impairments [2]. The typical pathological features of AD include the deposition of amyloid-beta (Aβ) and the formation of neurofibrillary tangles (NFTs) [3]. Neuropsychiatric symptoms (NPSs) are core features of AD. As common NPSs in non-demented elderly, depressive symptoms have been proposed to be a prognostic marker for AD. However, the pathologic mechanisms underlying the association between depression and AD remain unclear. A recent study revealed an association between minimal depressive symptoms (MDSs), occurring before subclinical depressive symptoms [4], and both amyloid pathology and cognitive impairment [5].

Microglial activation, which is central to neuroinflammation, was considered to be a common causal factor for both AD and MDSs [6, 7]. In the absence of pathogenic stimuli, microglia play a neuroprotective role by producing cytokines and chemokines [8]. However, once activated, microglia produce neurotoxic substances, resulting in neuronal damage and accelerating the progression of depression and AD [9]. Triggering receptor expressed on myeloid cells 2 (TREM2) is a recently identified risk factor for AD [10]. What's more, cerebrospinal fluid (CSF) soluble TREM2 (sTREM2) has been identified as an important biomarker for microglia-mediated neuroinflammation [11]. Studies have demonstrated that higher levels of CSF sTREM2 are associated with lower amyloid burden [12], slower hippocampal atrophy, as well as smaller declines in episodic memory and overall cognition in the preclinical phase of AD [13]. Furthermore, in preclinical AD, individuals with MDSs had lower CSF sTREM2 levels, greater amyloid deposition, and cognitive decline [5, 7]. The above findings indicated that CSF sTREM2 might participate in the pathogenesis of MDS and AD. Therefore, microglia have the potential to be a promising target for preventing AD and MDS in the future. However, whether and how CSF sTREM2 affects the associations of MDSs with CSF AD pathology biomarkers (amyloid beta 42 [Aβ42], total tau [Tau], and phosphorylated tau [pTau]) and cognition function remains to be explored.

There is no effective treatment strategy for AD [14, 15] now. Identifying early biomarkers of the AD disease spectrum will enable earlier detection and intervention. Early-stage research can help develop effective prevention strategies and treatments that may be more effective than late-stage interventions. Therefore, utilizing data from non-demented participants in the large Alzheimer's Disease Neuroimaging Initiative (ADNI) database, we intended (1) to investigate the difference in CSF sTREM2 levels between MDS and normal control participants; (2) to examine the associations of MDSs with CSF sTREM2, CSF AD biomarkers, cognitive scores and brain structure; and (3) to explore whether CSF sTREM2 and CSF AD biomarkers mediated the association between MDSs and cognitive scores.

Materials and methods

Participants

Data for non-demented participants were downloaded from the ADNI database (http://adni.loni.usc.edu), which was initiated in 2003 under the leadership of Michael W. Weiner. The primary goal of the multicenter ADNI is to assess the feasibility of integrating magnetic resonance imaging (MRI), positron emission tomography (PET), biomarkers, and clinical and neuropsychological evaluations for tracking the progression of early AD. All the participants underwent a series of physical and neuropsychological assessments at the initial assessment and subsequent follow-ups. Also, participants were asked to provide samples of CSF, blood, and urine throughout the process. The age range of participants was between 55 and 92 years. All participants signed written informed consent. Detailed information can be found elsewhere [16–18]. According to predefined criteria, a total of 341 mild cognitive impairment (MCI, Clinical Dementia Rating [CDR] = 0.5, Mini-Mental State Examination [MMSE] = 24–30) participants and 204 cognitively normal (CN, CDR = 0, MMSE = 24–30) controls were included in this study. These participants had available Geriatric Depression Scale (GDS) score, CSF sTREM2, CSF AD biomarkers, cognitive score, and brain structure data.

Measurements of MDSs and cognition

The 15-item GDS (GDS-15) was utilized to assess the depressive symptoms of the participants. Individuals with a Geriatric Depression Scale score ≥ 1 and ≤ 7 were defined as having MDSs in ADNI [5]. Based on the definition, the participants were divided into the MDS group ($1 \leq GDS \leq 7$) and the normal group ($GDS = 0$).

Multiple cognitive assessment scales were used to assess the cognition of our participants, including the MMSE, CDR, and Alzheimer's Disease Assessment Scale 13 (ADAS13) for global cognition, as well as two composite scores of ADNI-Memory summary score (ADNI_MEM) and ANDI composite executive function score (ADNI_EF) for memory function and executive function [19, 20]. Higher ADAS13 scores, lower MMSE scores, as well as lower ADNI_MEM scores, and lower ADNI_EF scores indicate poorer cognition.

Measurements of sTREM2 and AD biomarkers

Initial CSF samples were obtained by lumbar puncture, sent to the ADNI Biomarker Core laboratory within 1 h, and stored in a -80 °C refrigerator. CSF procedural protocols have been described previously [21]. In brief, the concentrations of Aβ42, Tau, and pTau in CSF were measured using a sophisticated xMAP platform (Luminex Corporation) with research-use-only INNO-BIA AlzBio3 immunoassay kit reagents (Innogenetics, Ghent, Belgium) at the ADNI Biomarker Core Laboratory, University of Pennsylvania. The within-batch precision values were <10% (5.1–7.8% for Aβ42, 4.4–9.8% for Tau, and 5.1–8.8% for pTau). The relevant data was provided in the UPENNBIOMK9.csv file. Detailed information can be found elsewhere [21].

The measurement of CSF sTREM2 was used the ELISA method described in a previous study [22]. CSF sTREM2 was measured with the Meto Scale Discovery (MSD) platform (data can be obtained in a file named "MSD_sTREM2CORRECTED.csv" in the ADNI database). More details about CSF sTREM2 measurements can be found at https://ida.loni.usc.edu.

Measurements of Brain structure

All structural MRI data were downloaded from ADNI. The brain structure images were obtained by T1-weighted MRI scanning using 1.5 T and 3.0 T MRI systems with rapid acquisition of gradient echo sequences using sagittal volume magnetization preprocessing. Cortical thickness and subcortical volume were quantified by FreeSurfer (version 5.1 http://surfer.nmr.mgh.harvard.edu/).

Statistical analyses

Differences in baseline characteristics were tested, using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Categorical variables and continuous variables were expressed as numbers (percentages) and mean±standard deviation (SD), respectively. Outliers that were three SDs above or below the entire sample mean were excluded. Apart from Tau, pTau, and Aβ42, we also added CSF Tau/Aβ42 and pTau/Aβ42 ratios into our analyses, since they have been reported as more accurate predictors of preclinical AD [23].

Linear regression models were employed to investigate the relationships of MDSs (an independent variable) with CSF sTREM2, AD biomarkers (Aβ42, Tau, and pTau), cognition function (reflected in cognitive scores) and brain structure (continuous, dependent variables). Age, sex, years of education, and *ApolipoproteinE* (*ApoE*) ε4 status were considered as correction factors (covariates). Moreover, total intracranial volume serves as a corrective factor for brain structure. We corrected the *P*-values using a false discovery rate (FDR), and an FDR-corrected *P* value of <0.05 was considered statistically significant. We additionally used Pearson's correlation analysis to examine the association between CSF sTREM2 and all CSF AD biomarkers. To examine the differences in the observed associations across subpopulations, we performed several subgroup analyses stratified by age (<65 and ≥65 years), sex (male and female), *ApoE* ε4 carrier status (carriers and non-carriers), and clinical status (CN and MCI). Moreover, we additionally categorized participants into four groups based on amyloid pathology status as follows: A-MDS-, A+MDS-, A-MDS+, and A+MDS+. Amyloid pathological abnormal (A+) or normal (A-) status was defined by a cutoff value of 976.6 pg/mL for CSF Aβ42 [24].

We conducted mediation analyses to explore whether CSF sTREM2 and AD pathology mediated the association between MDSs and cognition. First, mediation models were used to investigate whether the relationships between MDS and AD pathology were mediated by CSF sTREM2. For each mediator model, the following requirements must be reached: (1) MDSs were significantly associated with CSF sTREM2; (2) MDSs were significantly associated with CSF AD biomarkers; (3) CSF sTREM2 was significantly associated with CSF AD biomarkers, and (4) the associations between MDSs and CSF AD biomarkers were attenuated when CSF sTREM2 was added in the regression model. Second, we further conducted multiple mediation models utilizing the structural equation model (SEM) to assess whether CSF sTREM2 and AD-related pathology contributed to the influence of MDS on subsequent cognition performance. All mediation analyses used 10,000 bootstrap replicates. These mediation models were adjusted for age, sex, education, and *ApoE* ε4 carrier status. All the mediation analyses were performed using "lavaan" and "mediation" in the R package (version 4.1.2) [25].

All the above statistical analyses and figure preparation were carried out using R version 4.1.0 software. Sample baseline characteristic tables were analyzed using SPSS Statistics 23.

Results

Participant characteristics

Table 1 and **Supplementary Table 1** summarize the baseline demographic characteristics of participants. A total of 545 non-demented individuals (204 CN vs 341 MCI; 361 MDS vs 184 controls) were included in our study. Briefly, the population had a mean age of 72.6 years, and 234 (42.9%) subjects were *ApoE* ε4 carriers. Compared to CN participants, those with cognitive impairment had higher pathologic burden (Aβ42: Z = -8.131, *P*<0.001; Tau: Z = -3.070, *P*=0.028; pTau: Z = -3.816, *P*=0.003; Tau/Aβ42: Z = -8.038, *P*<0.001 and pTau/Aβ42:

Table 1 Baseline characteristics of participants

Baseline characteristics	Total	CN	MCI	*P*-value
N(%)	545	204(37.43)	341(62.57)	
Age, year, mean ± SD	72.6 ± 6.9	73.6 ± 5.8	72.07 ± 7.41	0.136
Sex, Female (%)	232 (42.57)	100(49.02)	132(38.71)	0.165
Education years, mean ± SD	14.5 ± 3.1	14.61 ± 3.08	14.39 ± 3.09	0.290
ApoE ε4 carriers, n (%)	234 (42.9)	56(27.45)	178(52.20)	**< 0.001**
MDSs, n (%)	364(66.79)	110(53.92)	254(74.49)	**< 0.001**
ADAS13 score, mean ± SD	12.0 ± 5.5	9.09 ± 4.20	13.72 ± 5.44	**< 0.001**
MMSE score, mean ± SD	28.15 ± 1.81	29.04 ± 1.21	27.56 ± 1.90	**< 0.001**
ADNI_MEM score, mean ± SD	0.383 ± 0.829	0.91 ± 0.67	0.71 ± 0.76	**< 0.001**
ADNI_EF score, mean ± SD	0.309 ± 0.973	0.70 ± 0.90	0.74 ± 0.94	**< 0.001**
CDR score	(0,0.5)	0	0.5	**< 0.001**
CSF sTREM2 Mean ± SD	3554.9 ± 2121.2	3798.9 ± 2123.7	3408.83 ± 2109.36	0.115
CSF biomarkers and ratios, mean ± SD				
Aβ42 pg/mL	552.4 ± 297.3	685.02 ± 239.5	473.11 ± 270.42	**< 0.001**
A + T+	198(36.33)	55(26.96)	143(41.94)	**< 0.001**
Tau pg/mL	134.6 ± 59.2	122.6 ± 41.9	141.85 ± 66.45	**0.028**
pTau pg/mL	27.4 ± 16.4	22.98 ± 13.07	30.06 ± 17.58	**0.003**
Tau/Aβ42 ratio	0.367 ± 0.332	0.23 ± 0.19	0.45 ± 0.37	**< 0.001**
pTau /Aβ42 ratio	0.826 ± 0.927	0.05 ± 0.06	0.10 ± 0.10	**< 0.001**
Brain structure, mean ± SD				
HV (mm^3)	7034.62 ± 1132.665	7484.16 ± 889.7	6751.01 ± 1178.13	**< 0.001**
EC thickness (mm^3)	3448.68 ± 1005.687	3804.8 ± 773.5	3225.07 ± 1069.46	**< 0.001**
Ventricular volume (mm^3)	34910.99 ± 22676.354	29712.7 ± 19051.2	37947.30 ± 24059.88	**0.001**

Abbreviations: MDSs: minimal depressive symptoms, *ApoE*: *ApolipoproteinE*, MMSE: Mini-Mental State Examination, sTREM2: soluble triggering receptor expressed on myeloid cells 2, CSF: cerebrospinal fluid, Aβ 42: Amyloid β peptide 42, pTau: phosphorylated tau; ADAS, Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination; MEM, memory function; EF, executive function; HV hippocampal volume, EC entorhinal cortex

Z = -7.285, $P<0.001$), smaller hippocampal volumes (Z = -7.031, $P<0.001$), smaller entorhinal volumes (Z = -5.420, $P<0.001$), and larger ventricular volumes (Z = -3.974, $P=0.001$) (Table 1).

Compared to normal controls, MDS participants tended to be relatively younger and they were more likely to have poorer cognitive performance (ADAS13: Z = -1.986, $P=0.047$; ADNI_MEM: Z = -2.925, $P=0.005$; ADNI_EF: Z = -2.379, $P=0.008$), lower CSF sTREM2 levels (Z = -3.381, $P=0.001$), higher amyloid burden (Aβ42: Z = -3.251, $P=0.001$; Tau/Aβ42: Z = -2.394, $P=0.017$), and smaller hippocampal volume (Z = -2.243, $P=0.025$) (Supplementary Table 1).

Associations of MDSs with CSF sTREM2 and CSF AD biomarker

As shown in box Fig. 1A, CSF sTREM2 levels in MDS participants were significantly lower than in normal controls in the general population. Similar results were also obtained in the male, late-life, *ApoE* ε4carriers and *ApoE* ε4 non-carriers subgroups (Fig. 1B-G).

Linear regression model indicated that MDSs were significantly associated with sTREM2 (β = -0.074, 95%CI = [-0.268, -0.046], P_{FDR} = 0.012), Aβ42 (β = -1.749, 95%CI = [-5.755, -1.619], P_{FDR} = 0.005), and Tau/Aβ42 ratio ($\beta=0.006$, 95%CI = [5.012×10^{-8}, 2.195×10^{-7}], P_{FDR} = 0.007) in CSF (Fig. 2; Supplementary Tables 2–3). The Pearson correlations indicated that CSF sTREM2 was positively correlated with all CSF AD biomarkers. CSF sTREM2 was positively correlated with Aβ42 ($r=0.042$, 95%CI = [0.003, 0.125], $P=0.033$), pTau ($r=0.256$, 95%CI = [0.176, 0.333], $P<0.001$), Tau ($r=0.305$, 95%CI = [0.227, 0.379], $P<0.001$), Tau/Aβ42 ($r=0.115$, 95%CI = [0.031, 0.197], $P=0.007$), and pTau/Aβ42 ($r=0.121$, 95%CI = [0.037, 0.203], $P=0.005$) (Supplementary Table 4).

In male participants, MDSs were proved to be associated with CSF Aβ42 (β = -2.102, 95%CI = [-7.130, -1.703], P_{FDR} = 0.020) in linear regression model. MDSs were associated with CSF Tau/Aβ42 ($\beta=0.009$, 95%CI = [6.295×10^{-8}, 3.101×10^{-7}], P_{FDR} = 0.036) and pTau/Aβ42 ($\beta=0.004$, 95%CI = [0.001, 0.010], P_{FDR} = 0.035) in female participants. Similarly, we found that MDSs were associated with CSF sTREM2 (β = -1.043, 95%CI = [-3.823, -0.498], P_{FDR} = 0.024), Aβ42(β = -1.708, 95%CI = [-5.722, -1.330], P_{FDR} = 0.011), and Tau/Aβ42($\beta=0.007$, 95%CI = [7.586×10^{-8}, 3.927×10^{-7}], P_{FDR} = 0.013) in late-life participants. MDSs were associated with Aβ42 (β = -10.182, 95%CI = [-36.221, -6.131], P_{FDR} = 0.027) and Tau/Aβ42 ($\beta=1.340\times10^{-12}$, 95%CI = [$5.952\times10^{-13}$, 4.995×10^{-12}], P_{FDR} = 0.042) in *ApoE* ε4 non-carriers.

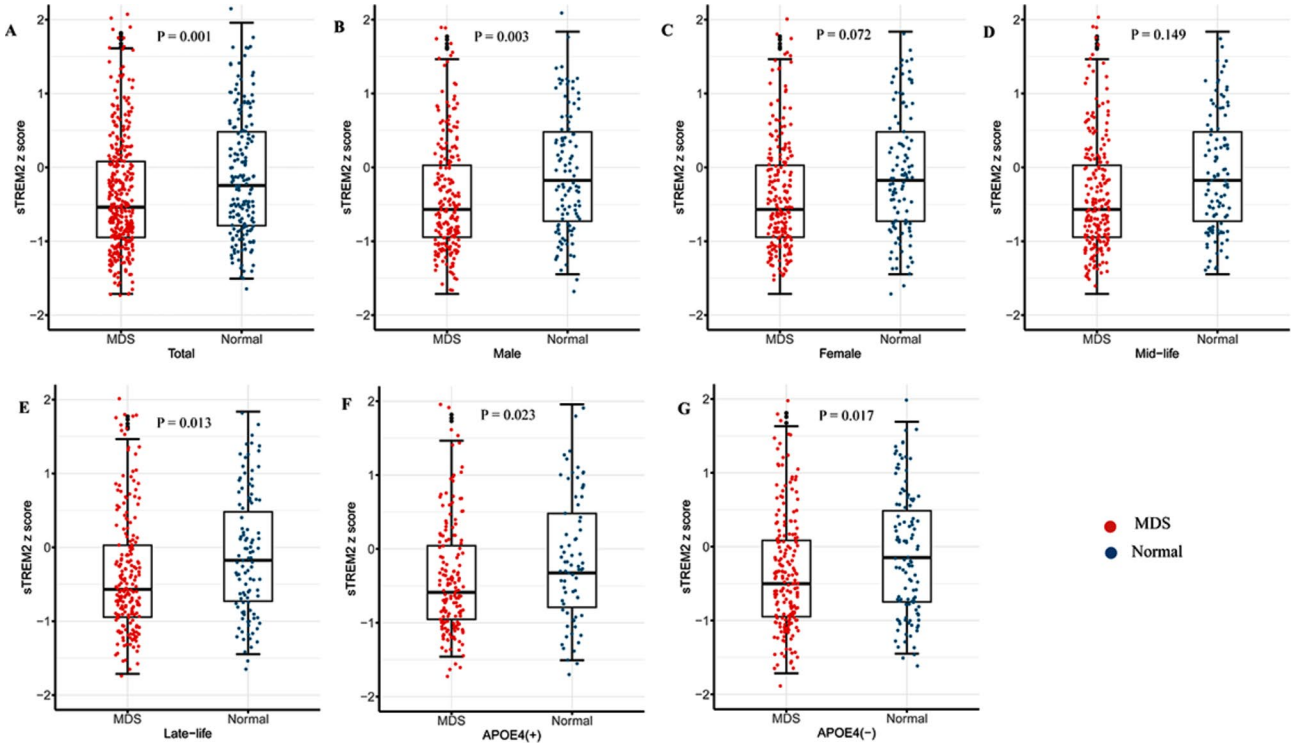

Fig. 1 Differences in CSF sTREM2 between MDS group and normal control group. CSF sTREM2 of MDSs is lower than normal in total subjects, and male, late-life, *ApoE* ε4 (+) as well as *ApoE* ε4 (-) subgroups. *Abbreviations*: MDS, minimal depressive symptom; *ApoE*, *apolipoproteinE*; sTREM2, soluble of trigging receptor expressed on myeloid cells 2

Associations of MDSs with cognition and brain structure

In the total participants, significant positive correlations of MDSs with ADAS13 (β=0.161, 95%CI = [0.070, 0.544], P_{FDR} = 0.018) scores were observed (Fig. 2; Supplementary Table 5). Significant negative associations were observed between MDS and ADNI_MEM (β = -0.105, 95%CI= [-0.367, -0.078], P_{FDR} = 0.007), ADNI_EF (β = -0.129, 95%CI = [-0.443, -0.103], P_{FDR} = 0.007), and hippocampal volumes (β = -2170000, 95%CI = [-3464061, -883217.1], P_{FDR} = 0.003) (Fig. 2; Supplementary Tables 5–6). Besides, subgroup analyses an association between MDSs and ADNI-MEM (female: β = -0.159, 95%CI = [-0.578, -0.097], P_{FDR} = 0.036; late-life: β = -0.107, 95%CI = [-0.373, -0.079], P_{FDR} = 0.012; *ApoE* ε4 non-carriers: β = -0.127, 95%CI = [-0.453, -0.075], P_{FDR} = 0.027) with ADNI_EF (female: β = -0.161, 95%CI = [-0.605, -0.079], P_{FDR} = 0.035; late-life: β = -0.123, 95%CI = [-0.431, -0.078], P_{FDR} = 0.013; *ApoE* ε4 non-carriers: β = -0.169, 95%CI = [-0.583, -0.122], P_{FDR} = 0.027) in female, late-life, and *ApoE* ε4 non-carriers. Besides, an association between MDSs and hippocampal volume was found in late-life (β = -2469000, 95%CI = [-3740704, -1196346], P_{FDR} = 0.010) and *ApoE* ε4 carriers (β = -487.300, 95%CI = [-784.743, -189.935], P_{FDR} = 0.015).

Additional analyses

Activation of microglia may be protective in the early stages, but harmful in the late stages. Therefore, we stratified the statistical model according to cognitive states (CN vs MCI). In the CN and MCI subgroups, MDS was not associated with CSF sTREM2, CSF AD biomarkers, cognitive scores, or brain structure (Fig. 2; Supplementary Tables 2–3, 5–6). To further verify whether amyloid affects CSF sTREM2 differences between MDS and normal controls, we performed subgroup analysis according to the status of amyloid pathology. Interestingly, we only found that CSF sTREM2 levels were lower in the A+MDS+group compared with the A+MDS- group (β = -0.247, 95%CI = [-0.448, -0.045], P_{FDR} = 0.009) (Fig. 3).

CSF sTREM2 mediated the relationship of MDSs with amyloid pathology

Based on the above-mentioned findings, we explored the influence of CSF sTREM2 on the effect of MDSs on AD pathology, we used the following mediation pathway: MDSs → CSF sTREM2 → AD pathology. Results of the mediation analyses showed that the association between MDS and Aβ42, Tau/Aβ42, with pTau/Aβ42 was mediated by CSF sTREM2 in all participants, with the proportion of mediation varying from 6.030 to 18.894% (Fig. 4A-C). We also found CSF sTREM2 mediated the association between MDS and the Tau/Aβ42 ratio in

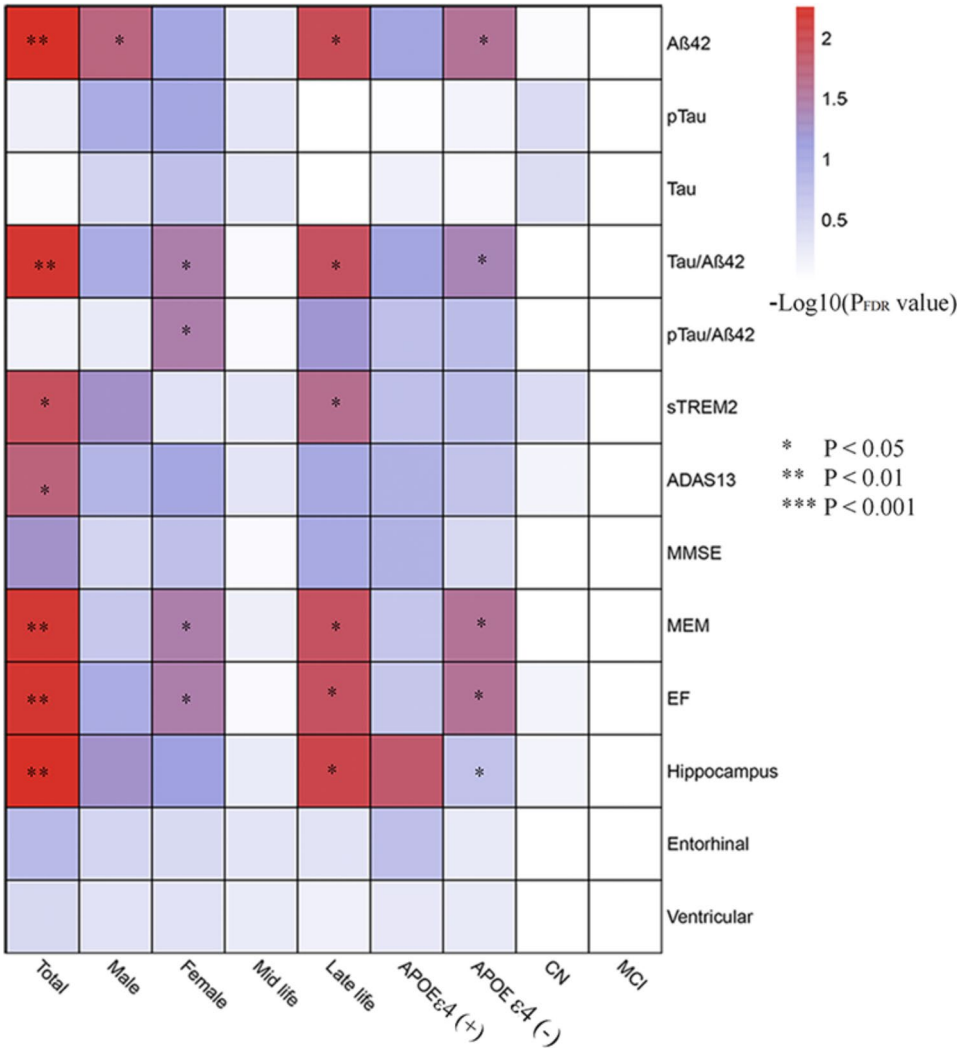

Fig. 2 Linear regression showed the associations of MDSs with CSF biomarkers, cognition and brain structure. MDSs were associated with CSF sTREM2, amyloid pathology, cognition, and brain structure in total and subgroups. The study was analyzed in subgroups by age, sex, and *ApoE* ε4 carrier status. *Abbreviations*: MDS, minimal depressive symptom; *ApoE*, *apolipoprotein E*; ADAS, Alzheimer's Disease Assessment Scale; MEM, memory function; MMSE, Mini-Mental State Examination; EF, executive function; CSF, cerebrospinal fluid; sTREM2, soluble of trigging receptor expressed on myeloid cells 2; Aβ 42, Amyloid beta 42; pTau, phosphorylated tau; HV hippocampal volume, EC entorhinal cortex

the late-life subgroup, with a mediating proportion of 12.330% (Fig. 4D). All the above findings suggest that CSF sTREM2 serves as a mediator in the association between MDSs and amyloid pathology.

Serial mediation between MDSs and cognition

CSF sTREM2 was activated in response to amyloid pathology [26]. The associations between amyloid pathology and cognition were significant (Supplementary Table 7). Therefore, we further analyzed whether sTREM2 and amyloid pathology influenced the effect of MDS on subsequent cognitive function. We used a chain multiple mediation model, including three mediation pathway analyses: (1) MDS → CSF amyloid pathology → CSF sTREM2 → ADNI_MEM; (2) MDS → CSF amyloid pathology → ADNI_MEM; and (3) MDS → CSF sTREM2 → ADNI_MEM.

CSF Aβ42 and the Tau/Aβ42 ratio rather than sTREM2 showed significant associations with ADNI_MEM. The third pathway results indicated that both Aβ42 and Tau/Aβ42 mediate the association between MDS and ADNI_MEM. The serial mediation model failed to find that the indirect effects of MDS on ADNI_MEM through CSF amyloid pathology and CSF sTREM2 were significant (Fig. 5A-C). In addition, we found that Aβ42, Tau/Aβ42, and pTau/Aβ42 mediated the association between MDS and ADNI_EF. Similarly, CSF sTREM2 is not an intermediate mediator in the association between MDS and ADNI_EF (Fig. 5D-F).

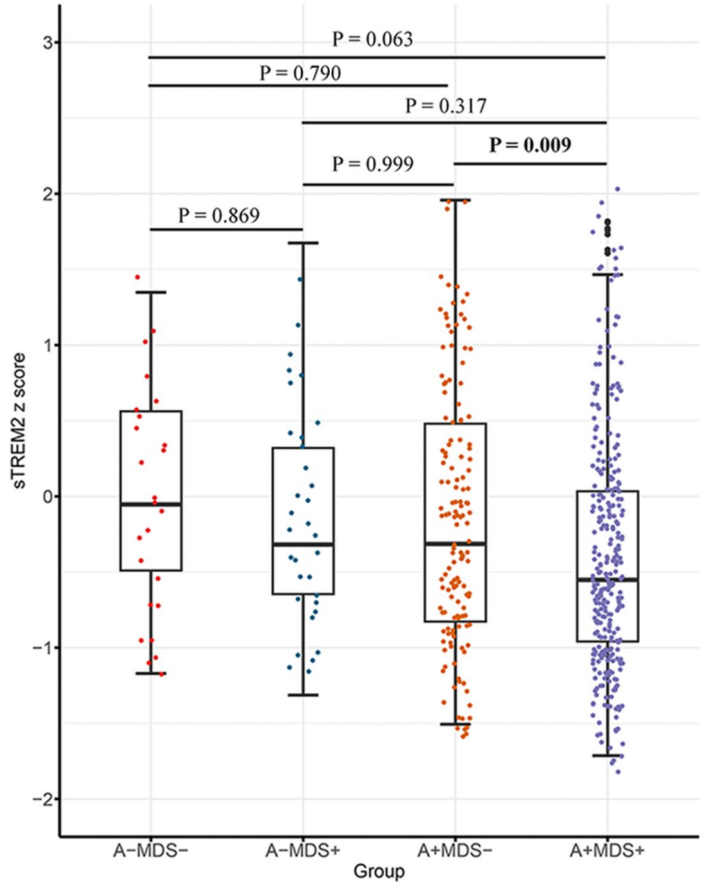

Fig. 3 CSF sTREM2 in the biomarker classification. The cutoff values to define abnormal CSF AD biomarkers were < 976.6 pg/mL for Aβ42 (A +). *Abbreviations*: sTREM2, soluble of trigging receptor expressed on myeloid cells 2; Aβ 42, Amyloid beta 42; MDS, minimal depressive symptoms

Discussion

Our study yielded four main findings: (1) individuals with MDSs had significantly lower CSF sTREM2 levels than normal controls; (2) the association between MDS and amyloid pathology was partially mediated by CSF sTREM2; (3) the association between MDS and cognitive scores (ADNI_MEM, ADNI_EF) was partially mediated by amyloid pathology; and (4) however, the correlation between MDS with cognition was not mediated by CSF amyloid pathology and sTREM2.

As reported in previous studies [27–29], major depression is a risk factor for developing AD. Our findings are consistent with a previous study which demonstrated that CSF sTREM2 levels were lower in the MDS group compared to normal controls [7]. Notably, both studies only included individuals diagnosed with minimal depressive symptoms. Similarly, in 2024, Reichert Plaska and colleagues found that CSF sTREM2 levels were also lower in individuals with late-life major depressive disorder compared to controls [30]. Moreover, they found a negative association between CSF sTREM2 and baseline scores of Hamilton Depression Rating Scale (HAMD). To summarize, lower sTREM2 was associated with greater depressive symptoms. To be clear, we only found this association in the late-life subgroup analyses. This suggests that age might also be an important factor, which is also supported by Stefan Teipel's article [31]. The sample sizes of these current studies are relatively small, and future multicenter large-sample studies are essential.

Neuroinflammation and microglial activation play important roles in the pathogenesis of depression and AD [6, 32]. A previous study [31] found that the level of CSF sTREM2 was significantly lower in participants with depression compared to healthy controls. Recently, HaiXia and her colleagues reported that microglial activation plays a role in the development of depression [33]. Animal models and PET imaging also provided evidence for the involvement of microglial activation in the pathogenesis of depression [34, 35]. A study demonstrated that higher levels of CSF sTREM2 were associated with slower rates of Aβ accumulation [12]. Several studies have demonstrated that elevated CSF levels of sTREM2 occur in the early preclinical AD stage [36, 37]; plateau in prodromal AD, and then increase again in mild to moderate AD where they correlate with pTau [36–38]. These changes of sTREM2 are highly associated with

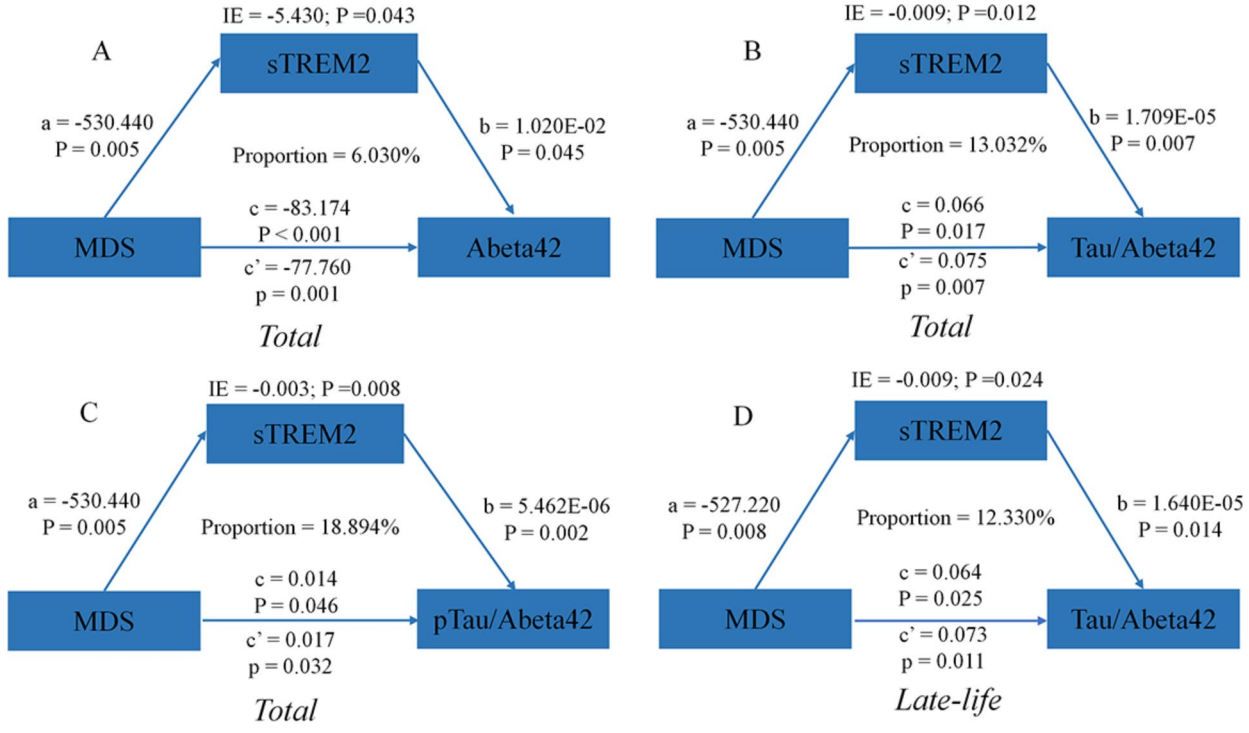

Fig. 4 CSF sTREM2 mediated the relationship between MDS and amyloid pathology. CSF sTREM2 mediated the association of MDS with Aβ42, Tau/Aβ42 and pTau/Aβ42. **P* < 0.05, ***P* < 0.01 and ****P* < 0.001. *Abbreviations*: MDS, minimal depressive symptom; CSF, cerebrospinal fluid; sTREM2, soluble of trigging receptor expressed on myeloid cells 2; Aβ 42, Amyloid beta 42; pTau, phosphorylated tau

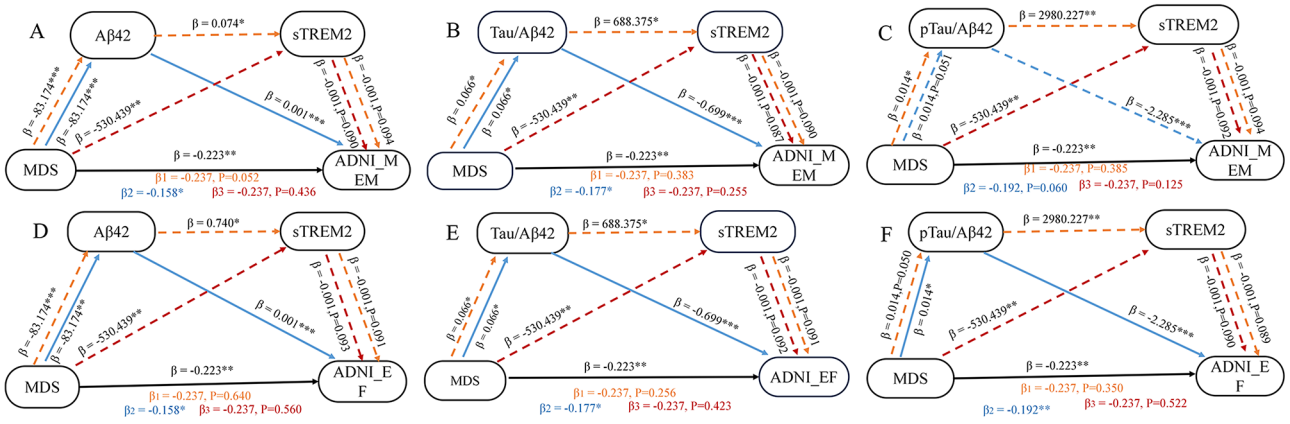

Fig. 5 Structural equation models. Three mediation pathways were conducted between MDS and MEM: (1) MDS → CSF amyloid pathology → CSF sTREM2 → ADNI_MEM; (2) MDS → CSF amyloid pathology → ADNI_MEM; (3) MDS → CSF sTREM2 → ADNI_MEM. All mediation paths were calculated by a bootstrap test with 10,000 resampling iterations and adjusted by age, sex, education, and *ApoE* ε4 status. The dotted line indicates that the indirect effect is not significant (*P* ≥ 0.05), and the solid line indicates that the indirect effect is significant (*P* < 0.05). **P* < 0.05, ***P* < 0.01 and ****P* < 0.001. *Abbreviations*: MDS, minimal depressive symptom; sTREM2, soluble of trigging receptor expressed on myeloid cells 2; Aβ, amyloid-β; MEM, memory function; *ApoE*, *ApolipoproteinE*

increased amyloid deposition and cognitive impairment [37]. Our study and that of Reichert Plaska et al [30] also confirmed lower CSF amyloid levels in those with minimal depressive symptoms and late-life major depression. Two studies from the same cohort confirmed this finding [39, 40]. However, our study failed to find a statistically significant difference in CSF sTREM2 between the MCI and CN subgroup. This inconsistency may be due to the differences in the included populations and longitudinal studies are needed to validate our findings.

Consistent with the previous study by Wei et al [5], our study also found that Aβ42 and Tau/Aβ42 ratio were mediators of the associations of MDS with ADNI_MEM and ADNI_EF scores. However, we did not find Aβ42 and Tau/Aβ42 as mediators of the association between MDS and ADAS 13 scores. This inconsistency across different

cognitive assessment scales might be due to selection bias. The Harvard Aging Brain Study (HABS) showed that higher amyloid load at baseline was associated with worsening depressive symptoms evaluated by the GDS scores over time in cognitively normal elderly [41]. In addition, studies have shown that depressive symptoms contribute to the progression of MCI [42, 43]. In our current study, we found that MDS not only could directly affect cognition but also could affect cognition through amyloid pathology. The mediation model revealed a negative association between MDS and CSF sTREM2. Furthermore, a positive association between CSF sTREM2 and CSF Aβ42 was observed, suggesting reduced brain amyloid pathology and indicating protective effects of higher CSF sTREM2 levels against brain amyloid deposition. A recent study suggested lower sTREM2 may be associated with decreased phagocytosis, which leads to decreased brain Aβ clearance, increased brain amyloid load, and decreased CSF Aβ42 [30]. This was confirmed in a 2023 article analyzing postmortem brains of major depressive disorder samples [44].

Limitations

The current study has certain limitations. First, our study was restricted to volunteers recruited from the ADNI who met the enrollment requirements. It's difficult to generalize our conclusions to other populations. Future large-scale studies are still needed to validate these findings. Second, our study was restricted to individuals with MDSs, which might contribute to an underestimation of the effect size of depression. Third, our research employs CSF AD biomarkers rather than PET imaging, potentially introducing biases such as the absence of pathological spatial distribution data, identification biases in early pathological changes, assessment biases in disease severity, and biases in the external validity of study findings. Fourth, this is a cross-sectional study, which means that causality cannot be established. Further high-quality longitudinal cohort studies are needed in the future.

Conclusions

Taken together, MDS was significantly associated with CSF sTREM2, amyloid pathology, cognitive scores, and hippocampal volume in a non-demented sample. Furthermore, the association between MDS and cognition may be partially explained by amyloid pathology.

Abbreviations

CSF	cerebrospinal fluid
sTREM2	soluble Triggering Receptor Expressed on Myeloid Cells 2
MDSs	minimal depressive symptoms
AD	Alzheimer's disease
Aβ	amyloid-β
NFTs	intracellular neurofibrillary tangles
NPSs	neuropsychiatric symptoms
pTau	phosphorylated tau
ADNI	Alzheimer's Disease Neuroimaging Initiative
MRI	magnetic resonance imaging
PET	positron emission tomography
MCI	mild cognitive impairment
CN	cognitively normal
GDS	Geriatric Depression Scale
MMSE	Mini-Mental State Examination
ADAS13	Alzheimer's Disease Assessment Scale 13
ADNI_MEM	ADNI-Memory summary score
ADNI_EF	ANDI composite executive function score
SD	standard deviations
ApoE	ApolipoproteinE
FDR	false discovery rate
SEM	structural equation model
HAMD	Hamilton Depression Rating Scale

Supplementary Information

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Supplementary Material 1

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Author contributions

XL: data processing, statistical analysis, interpretation of the results, and writing the manuscript; GXY: statistical analysis and interpretation of the results; MX, LYH, YF, and ZTW: interpretation of the results; YNO and LT: study concept and design, and critical revision of the manuscript. ADNI provided all data used for this study. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Partners Healthcare Institutional Review Board (IRB) approved the study, as did the IRB of each Alzheimer's Disease Neuroimaging Initiative (ADNI) site. Written informed consent was obtained from all participants prior to initiation of any study procedures in accordance with IRB guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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