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ORIGINAL RESEARCH

CSF TNF-α Levels Were Associated with Longitudinal Change in Brain Glucose Metabolism Among Non-Demented Older People

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Purpose: Emerging studies have suggested that tumor necrosis factor-alpha (TNF-α) is implicated in the pathogenesis of Alzheimer's disease (AD), and that cerebral glucose hypometabolism is a key feature of AD. However, the association of CSF TNF-α levels with changes in cerebral glucose metabolism has not been studied among non-demented older people.

Patients and Methods: At baseline, there were a total of 214 non-demented older people from Alzheimer's Disease Neuroimaging Initiative (ADNI) study. We examined the cross-sectional and longitudinal associations of CSF TNF-α with global cognition (as assessed by mini-mental state examination), verbal memory (as assessed by Rey Auditory Verbal Learning Test-total learning score), and cerebral glucose metabolism (as measured by FDF-PET). Linear mixed-effects models were used to examine the longitudinal association of CSF TNF- α with change in each outcome over time with adjustment of age, educational level, gender, and APOE4 status.

Results: In the cross-sectional study, CSF TNF-α was negatively associated with MMSE scores, but not verbal memory or FDG-PET. In the longitudinal study, higher CSF TNF- α at baseline was associated with a faster decline in cerebral glucose metabolism, but not MMSE scores or RAVLT total learning scores.

Conclusion: Higher CSF TNF-α levels were associated with a steeper decline in cerebral glucose metabolism among non-demented older people.

Keywords: mild cognitive impairment, Alzheimer's disease, TNF-α, cerebral glucose metabolism, FDG-PET

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairment and the formation of two core pathological markers (β-amyloid plaques and neurofibrillary tangles).[1] Emerging evidence has suggested that neuroinflammation plays an important role in the pathogenesis of AD.[2] Observational studies have shown that the use of anti-inflammatory drugs is associated with a decreased risk of developing AD dementia.[3] Tumor necrosis factor-alpha (TNF- α) is one of the most important inflammatory cytokines expressed by activated microglia and astrocytes, and is elevated in several brain regions of patients with AD dementia.[4] In addition, a previous study found that higher levels of TNF- α were associated with incident AD among cognitively normal community-dwelling older people.[5]

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Reduced cerebral glucose metabolism, assessed by FDG-PET, is a core feature of AD dementia.[6,7] However, to the best of our knowledge, the association of CSF TNF-α levels with longitudinal changes in brain glucose metabolism (reflecting neuronal and synaptic function) over time has not been investigated among non-demented older people. If this association does exist, it may provide some insights into the effect of TNF- α on neuronal and synaptic function. Therefore, we aimed to examine the cross-sectional and longitudinal associations of CSF TNF- α with global cognition, verbal memory, and brain glucose metabolism (as assessed by FDG-PET) among non-demented older people from Alzheimer's Disease Neuroimaging Initiative (ADNI) study.

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI) Study

Cross-sectional and longitudinal data used in the preparation of this work were extracted from the ADNI database (adni.loni.usc.edu). The ADNI study was initiated in 2003 with the primary goal of examining whether positron emission tomography (PET), serial magnetic resonance imaging (MRI), biological markers, and neuropsychological assessments could be integrated to measure the progression of mild cognitive impairment (MCI) and early AD.

Participants

At baseline, there were a total of 214 non-demented older people, including 85 subjects with normal cognition (NC) and 129 subjects with MCI. These participants had baseline CSF TNF-α samples and follow-up examinations of global cognition, verbal memory, and brain glucose metabolism. At ADNI centers, participants provided written informed consents, and local institutional review board approved the ADNI study. The official or affiliated names of the approving local ethics committee could be found at the website: http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/policy/ADNI_Acknowledgement_List%205-29-18.pdf.

Diagnostic Criteria

Individuals with NC had a Clinical Dementia Rating (CDR)[8] score of 0 and a Mini-mental State Examination (MMSE)[9] score of 24 or higher. Individuals with MCI had a CDR score of 0.5, an MMSE score of 24 or higher, essentially preserved activities of daily living, verbal memory impairment as evidenced by delayed recall scores of the Wechsler Memory Scale Logical Memory II, and an absence of dementia.

Neuropsychological Assessments

The ADNI participants underwent a comprehensive neuropsychological assessment. In this study, we selected two primary cognitive outcomes: MMSE scores and Rey auditory verbal learning test (RAVLT)[10] total learning scores. MMSE scores and RAVLT total learning scores were utilized to examine global cognition and verbal memory, respectively.

FDG Standardized Uptake Value Ratio (SUVR) Measurement

Levels of brain glucose metabolism were examined by FDG PET, details of which have been described previously[11] and can also be found at the ADNI website (http://adni.loni.usc.edu/methods/pet-analysis/). The mean of FDG uptake was determined within middle/inferior temporal gyrus, bilateral angular gyri, and bilateral posterior cingulate gyrus due to the fact that low levels of glucose metabolism within these regions have been found to be associated with cognitive deficits in patients with MCI and AD dementia.[12,13] SUVRs were determined by averaging uptakes of these regions and dividing by cerebellum.

Measurement of CSF TNF-α Levels

Levels of CSF TNF-α were determined using commercially available multiplex immunoassays (Millipore Sigma, Burlington, MA) by the Hu lab (Dr. William Hu), Department of Neurology, Emory University. Initially, a total of 15 analytes were examined, whereas only levels of TNF-α in CSF were reported because it is our variable of interest in the present study. Samples were randomized across twelve 96-well plates for each of the five assays (60 plates total) encompassing 15 analytes. All CSF samples were run in duplicate along with six CSF standards on each plate. Samples were normalized across plates using CSF standard values. The inter-plate CV (%) of the measurement of TNF-α was 9.38. The median sample concentration of TNF-α was 1.7 pg/mL. The LLOD (MFI) was 49.2. The median MFI was 53.53. Values were given as pg/mL.

Statistical Analysis

Descriptive statistics were utilized to summarize the variables of our study sample, including demographics and

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clinical variables. The distribution of MMSE was negatively skewed, whereas the distribution of other variables (TNF- α, RAVLT total learning score and FDG) was largely normal based on the histograms of these variables. Therefore, Pearson's correlation tests were used to examine the cross-sectional associations of baseline CSF TNF- α levels with RAVLT total learning score and FDG SUVR. However, Spearman correlation test was used to examine the relationship between TNF-α and MMSE. In the longitudinal analysis, several linear mixed models were utilized to examine the associations of baseline CSF TNF- α levels (categorized into the High and Low groups based on the median) with changes in each outcome (MMSE sores, RAVLT total learning scores, and FDG SUVR) over time among non-demented older people. Each model included the main effects of baseline CSF TNF-α, age, gender, educational level, APOE4 genotype and their interactions with time, along with a random intercept and a random slope for each subject. All statistical work was performed with R software (version 3.6.0).[14] The "lme4" package[15] was used to conduct linear mixed models.

Results

Demographics and Clinical Variables

In the present study, a total of 214 non-demented older people were included. Socio-demographic and clinical variables are summarized in Table 1. The mean age (mean ± SD) for the whole study sample was 74.9 ± 7 years. Eighty-seven (40.7%) participants were females. Ninety-one (42.5%) participants were APOE4 carriers and 129 (60.3%) were MCI patients.

Table 1 Demographic and Clinical Characteristics of 214 Non-Demented Older People

Variables	Non-Demented Older People
Numbers of participants	214
Age, years	74.9 ± 7
Education, years	15.8 ± 2.9
Female gender, n (%)	87 (40.7)
APOE4 carriers, n (%)	91 (42.5)
MCI diagnosis, n (%)	129 (60.3)
MMSE	27.8 ± 1.8
RAVLT total learning scores	35.3 ± 10.8
FDG SUVR [a]	1.23 ± 0.14
CSF TNF- α levels, pg/mL	1.7 ± 0.5

Notes: [a]There were a total of 107 participants having FDG SUVR data.
Abbreviations: MCI, mild cognitive impairment; MMSE, mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratio; TNF, tumor necrosis factor.

Cross-Sectional Associations of CSF TNF-α with Global Cognition, Memory, and FDG SUVR Among Non-Demented Older People

To examine the cross-sectional associations of baseline CSF TNF-α with MMSE scores, RAVLT total learning scores, and FDG SUVR among non-demented older people, Pearson's correlation tests were used. As shown in Table 2, CSF TNF-α levels were negatively associated with MMSE scores (rho = −0.17, p = 0.011), but not RAVLT total learning scores (r = −0.13, p = 0.053) or FDG SUVR (r = −0.12, p = 0.22). Further, CSF TNF-α was associated with age (r = 0.39, p < 0.001).

Longitudinal Associations of Baseline CSF TNF-α with Global Cognition, Memory, and FDG SUVR Among Non-Demented Older People

To examine the associations of baseline CSF TNF-α levels with changes in MMSE scores (Table 3), RAVLT total learning scores (Table 4), and FDG SUVR (Table 5) over time among non-demented older people, several linear mixed models were fitted for each outcome. As shown in Tables 3–5 and Figure 1, we found that among non-demented older people, higher CSF TNF-α levels were associated with a faster decline in FDG SUVR (estimate = −0.0089, se= 0.0043, p value = 0.0385), but not MMSE scores (estimate = −0.1246, se= 0.1592, p value = 0.4341) or RAVLT total learning scores (estimate = 0.0105, se= 0.2333, p value = 0.9641).

Supplementary Analyses

We further examined whether amyloid status (positive vs negative) can modify the association of CSF TNF- α with change in MMSE score, RAVLT total learning score and

Table 2 Cross-Sectional Relationships Between CSF TNF- α and AD-Related Makers

	CSF TNG- α Levels	
	r/rho	P values
MMSE	−0.17	0.011
RAVLT total learning scores	−0.13	0.053
FDG SUVR	−0.12	0.22

Notes: The relationship between CSF TNG- α levels and MMSE was examined using Spearman' correlation test.
Abbreviations: MMSE, mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratio; TNF, tumor necrosis factor.

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Table 3 Longitudinal Association of Baseline CSF TNF-α with MMSE Scores

Terms	Estimate	Se	P values
Higher CSF TNF- α × years	−0.1246	0.1592	0.4341
Age × years	0.0006	0.0115	0.9586
Education × years	−0.0316	0.0260	0.2240
Female gender × years	−0.2111	0.1568	−0.1782
APOE4 × years	−0.8398	0.1523	< 0.0001

Notes: Main effects of independent variables (CSF TNF-α, age, education, gender, and APOE4 genotype) are included in models (estimates not displayed).
Abbreviations: MMSE, mini-mental state examination; TNF, tumor necrosis factor.

Table 4 Longitudinal Association of Baseline CSF TNF-α with RAVLT Total Learning Scores

Terms	Estimate	Se	P values
Higher CSF TNF- α × years	0.0105	0.2333	0.9641
Age × years	−0.0277	0.0179	0.1213
Education × years	−0.0463	0.0389	0.2337
Female gender × years	−0.4366	0.2389	0.0676
APOE4 × years	−1.4830	0.2359	< 0.0001

Notes: Main effects of independent variables (CSF TNF- α, age, education, gender, and APOE4 genotype) are included in models (estimates not displayed).
Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; TNF, tumor necrosis factor.

Table 5 Longitudinal Association of Baseline CSF TNF-α with FDG SUVR

Terms	Estimate	Se	P values
Higher CSF TNF- α × years	−0.0089	0.0043	0.0385
Age × years	0.0010	0.0003	0.0026
Education × years	−0.0001	0.0007	0.9257
Female gender × years	−0.0004	0.0047	0.9367
APOE4 × years	−0.0144	0.0045	0.0016

Notes: Main effects of independent variables (CSF TNF- α, age, education, gender, and APOE4 genotype) are included in models (estimates not displayed).
Abbreviations: FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratio; TNF, tumor necrosis factor.

FDG SUVR over time among MCI subjects. At baseline, patients with MCI were further classified into two groups according to their amyloid status (amyloid-positive: CSF Aβ42 < 192 pg/mL; amyloid-negative: CSF Aβ42 ≥ 192 pg/mL): 40 amyloid-negative MCI subjects and 89 amyloid-positive MCI subjects. Several linear mixed models were utilized to examine the associations of this interaction term (amyloid status*CSF TNF-α) with change in each outcome (MMSE sores, RAVLT total learning scores, and FDG SUVR) over time among older people with MCI. Each model included the amyloid status*CSF TNF- α interaction term, age, gender, educational level, APOE4 genotype and their interactions with time, along with a random intercept and a random slope for each subject. We found that this interaction term was significant for FDG, but not for MMSE or RAVLT total learning score (Data not shown), indicating that amyloid status may modify the association of CSF TNF- α with change in FDG over time among MCI subjects. Therefore, an amyloid-stratified analysis was further performed. In the amyloid-positive group, CSF TNF-α was not associated with change in FDG over time in MCI ($p > 0.05$, Table 6, Figure 2A). However, higher CSF TNF-α levels were associated with a steeper decline in FDG SUVR in the amyloid-negative group ($p < 0.05$, Table 6, Figure 2B).

In addition, we examined whether the clinical diagnosis (MCI vs normal cognition) can modify the association of CSF TNF- α with change in MMSE score, RAVLT total learning score and FDG SUVR over time among non-demented older people. Several linear mixed models were utilized to investigate the association of the clinical diagnosis*CSF TNF-α interaction term with change in each outcome (MMSE sores, RAVLT total learning scores, and FDG SUVR) over time among non-demented older people. Each model included the clinical diagnosis*CSF TNF- α interaction term, age, gender, educational level, APOE4 genotype and their interactions with time, along with a random intercept and a random slope for each subject. However, this interaction term was not significant for any outcomes (all $p > 0.05$, data not shown), suggesting that there was no significant difference in the association of CSF TNF-α with change in MMSE score, RAVLT total learning score or FDG SUVR over time between normal cognition and MCI.

Discussion

To the best of our knowledge, this is the first study to examine the association of baseline CSF TNF-α levels with longitudinal changes in MMSE scores, RAVLT total learning scores, and brain glucose metabolism (as assessed by FDG-SUVR) among non-demented older people. We found that higher CSF TNF-α levels were linked to a steeper decline in FDG-SUVR, but not MMSE or RAVLT total learning scores among non-demented older people.

In terms of the biology of TNF-α, it and its receptors participate in a variety of biological functions in the body, such as immune responses to fight microbial infections, immune surveillance, and apoptosis.[16–18] One previous study showed that levels of CSF TNF-α in AD

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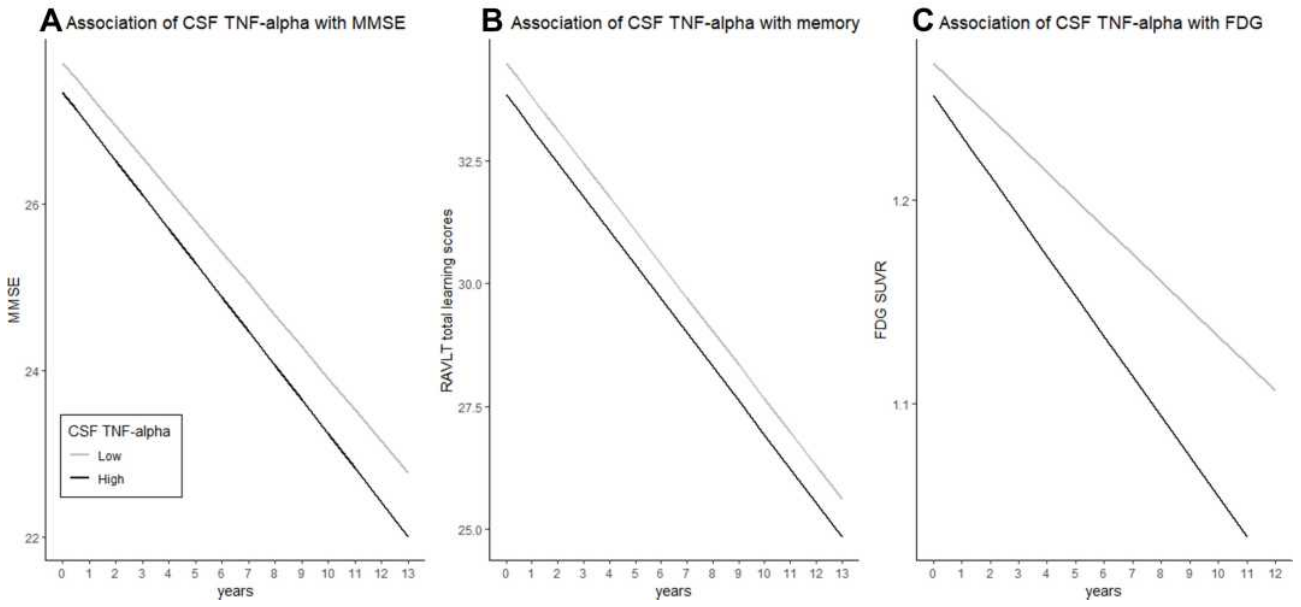

Figure 1 Associations of CSF TNF- α with change in AD-related markers over time. Higher CSF TNF-α levels were associated with a faster decline in FDG SUVR (estimate = −0.0089, se= 0.0043, p value = 0.0385, (**C**) but not MMSE scores (estimate = −0.1246, se= 0.1592, p value = 0.4341, (**A**) or RAVLT total learning scores (estimate = 0.0105, se= 0.2333, p value = 0.9641, (**B**).

Abbreviations: MMSE, mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratio; TNF, tumor necrosis factor.

patients are higher than those of normal controls.[19] This was further supported by elevated levels of TNF-α observed in the blood of patients with AD compared to normal controls.[20] Furthermore, in previous cross-sectional studies, higher levels of blood TNF-α were found to be associated with worse cognitive performance among AD patients.[21,22] In addition, preclinical studies have also been suggested that TNF-α could activate the astroglial response, contributing to the neuroinflammatory process.[23,24] TNF-α could stimulate the NF-kB pathway that leads to the elevation of Aβ accumulation.[25] Taken together, both preclinical and clinical studies support the notion that TNF-α is an important cytokine that plays a critical role in the pathogenesis of AD.

Table 6 Longitudinal Association of CSF TNF- α with Change in FDG SUVR in the Amyloid Negative MCI Subjects and Amyloid Positive MCI Subjects

	Amyloid Negative		
Terms	**Estimate**	**Se**	**P values**
Higher CSF TNF-α × years	−0.0211	0.0085	0.0129
Age × years	0.0009	0.0005	0.0574
Education × years	0.0014	0.0016	0.3889
Female gender × years	−0.0055	0.0076	0.4675
APOE4 × years	0.0052	0.0163	0.7489
	Amyloid Positive		
Terms	Estimate	Se	P values
Higher CSF TNF-α × years	0.0049	0.0077	0.5253
Age × years	0.0015	0.0005	0.0043
Education × years	0.0009	0.0013	0.4788
Female gender × years	−0.0003	0.0080	0.9670
APOE4 × years	−0.0047	0.0092	0.6079

Notes: Main effects of independent variables (CSF TNF- α, age, education, gender, and APOE4 genotype) are included in models (estimates not shown).

Abbreviations: FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratio; TNF, tumor necrosis factor.

Reduced cerebral glucose metabolism is a core feature of AD dementia.[6,7] In the present study, we found that higher CSF TNF-α levels were associated with a steeper decline in FDG-SUVR among non-demented older people, indicating that TNF-α may play an important role in neuronal and synaptic dysfunction in AD. There are several possible explanations for this finding. First, the adverse effect of TNF-α on FDG-PET may be Aβ-mediated. For example, it has been reported that TNF-α increases apoptosis of neurons administrated with Aβ and impacts Aβ production in cell culture studies.[26–28] Further, microglia are unable to efficiently phagocytose Aβ in the presence of increased TNF levels.[29] Given that the close relationship between Aβ accumulation in the brain and cerebral glucose hypometabolism,[30] it is possible that the detrimental effect of TNF-α on cerebral glucose metabolism may be Aβ-mediated.

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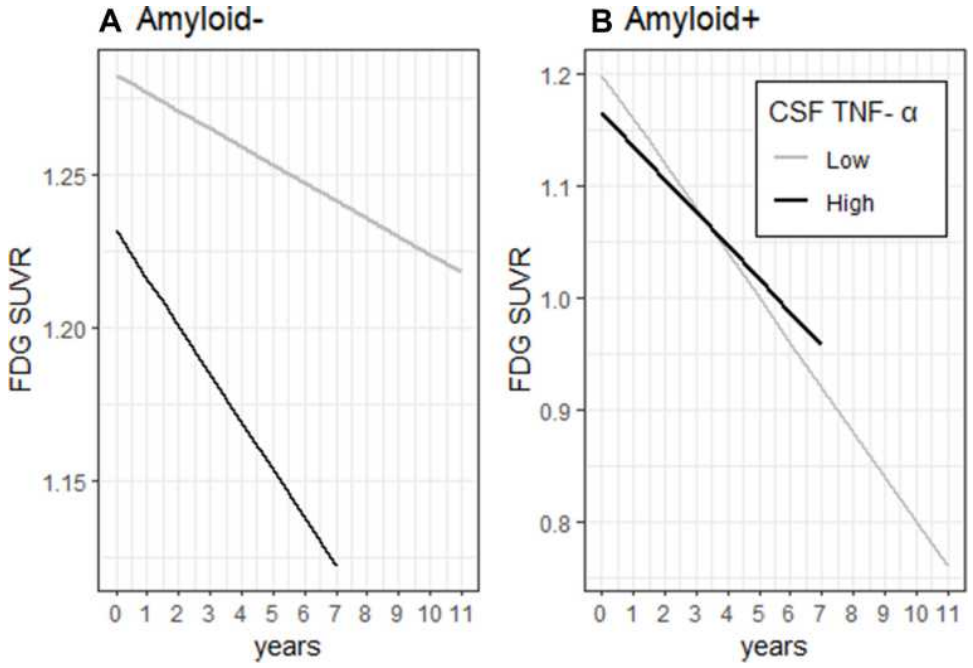

Figure 2 Associations of CSF TNF- α with change in FDG SUVR over time in the amyloid negative MCI subjects and amyloid positive MCI subjects. In the amyloid-positive group, CSF TNF-α was not associated with change in FDG over time in MCI ($p > 0.05$, **A**). However, higher CSF TNF-α levels were associated with a steeper decline in FDG SUVR in the amyloid-negative group ($p < 0.05$, **B**).

Second, TNF-α may directly affect synaptic and neuronal functions and contribute to neurodegeneration. For instance, numerous studies have suggested that TNF-α could mediate activation of oxidative stress cascades, neuronal and synaptic dysfunction, and exacerbation of neurodegeneration.[31,32]

Third, it is also possible that TNF-α-related neuroinflammation may contribute to hyperphosphorylation and accumulation of tau, thus leading to axonal malfunction and neurodegeneration.[33]

Interestingly, we found that among non-demented older people, higher CSF TNF-α levels were associated with a steeper decline in FDG SUVR, but not cognitive assessments. Based on the amyloid cascade hypothesis, amyloid accumulation precedes cerebral glucose hypometabolism, which is followed by cognitive impairment.[11,34] It is possible that among non-demented older people, dysregulation of neuroinflammation may be a contributing factor for cerebral glucose hypometabolism (synaptic and neuronal dysfunction), but not for cognitive impairment. However, evidence on the effect of neuroinflammation on cognitive impairment and clinical progression has been inconsistent.[2] For example, a recent study examining the association of the levels of 27 cytokines in CSF with cognitive impairment and clinical progression in AD patients found that some of cytokines may be "protective".[35] It has been reported that neuroinflammation is not exclusively beneficial or detrimental in the pathogenesis of AD.[36] Further studies should be conducted to further clarify the relationship between CSF TNF-α and AD-related markers at different stages of the disease.

There are several limitations in this study. First, the observational nature of this study does not allow us to address the causal relationship between CSF TNF-α and cerebral glucose metabolism among non-demented older people. Second, because most of the ADNI participants were white and well educated, sample selection bias may affect the interpretation of our findings. Third, in the present study, only one cytokine (CSF TNF-α) was used to examine its relation with AD-related markers. Further studies should utilize a group of cytokines to investigate the association of the pattern of various cytokines with cognitive impairment and clinical progression. Additionally, this approach should also be applied at different stages of the disease.

In conclusion, higher CSF TNF- α levels were associated with a steeper decline in cerebral glucose metabolism among non-demented older people.

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Disclosure

The authors declare that they have no conflicts of interest.

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