



Inflammatory Cytokines and Cognition in Alzheimer's Disease and Its Prodrome

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Objective The aim of this study was to investigate the association between blood levels of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) and cognitive impairments among elderly individuals.

Methods Peripheral concentration of TNF- α and IL-6 were measured in all subjects. To assess individual cognitive function, the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NP) was used, and standardized scores (z-scores) were calculated for each test. Cytokine levels were compared between the diagnostic groups, and correlations between blood inflammatory factor levels and z-scores were analyzed.

Results The 37 participants included 8 patients with Alzheimer's disease (AD), 15 subjects with mild cognitive impairment (MCI), and 14 cognitively healthy controls. TNF- α and IL-6 levels were higher in patients with AD than in healthy controls. TNF- α levels were higher in the AD group than in the MCI group. However, after adjusting for age, the associations between diagnosis and TNF- α and IL-6 were not significant. The higher the plasma IL-6 level, the lower the z-scores on the Boston Naming Test, Word List Learning, Word List Recognition, and Constructional Recall. The higher the serum TNF- α level, the lower the z-scores on the Word List Learning and Constructional Recall. Negative correlation between serum TNF- α level and the z-score on Word List Learning remained significant when age was adjusted.

Conclusion The difference in the blood levels of TNF- α and IL-6 between the diagnostic groups may be associated with aging. However, elevated TNF- α levels were associated with worse immediate memory performance, even after adjusting for age.

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Keywords Dementia; Cognitive impairment; Cytokine; Tumor necrosis factor-alpha; Interleukin-6.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly.¹ The characteristic pathological features of AD include amyloid- β (A β) plaques, neurofibrillary tangles, and inflammation. A β accumulation and plaque formation trigger inflammation including microglial activation and

excretion of pro-inflammatory cytokines, ultimately resulting in synaptic and neuronal loss.¹⁻⁴ Although it is well known that immune reactions occur during the development and progression of disease,⁴ the role of the immune system in the etio-pathophysiology of AD has not been fully elucidated. Accumulating evidence suggests that inflammation plays a critical role in the development and progression of AD pathology.^{5,6} In experimental studies on AD animal models, inflammatory process is concomitant with and associated with the pathologic deposition of A β .⁷⁻¹⁰ In humans, chronic inflammation, such as periodontitis, is associated with a higher risk of AD.¹¹ In genetic studies, polymorphisms in genes regulating the immune response have been associated with cognitive aging^{12,13} and the risk of AD.¹⁴ In vivo positron emission tomography studies have shown that microglial activation is increased in

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patients with AD.^{15,16} In postmortem studies, microglial activation and higher levels of pro-inflammatory cytokines have been observed in the brains of patients with AD.^{17,18}

Furthermore, extensive evidence has shown that neuroinflammation is not merely a consequence of plaques and tangles but rather an active contributor to the development of AD pathology.^{4,19–22} Research focusing on the pre-dementia stages, such as mild cognitive impairment (MCI), provides additional support for the early and significant role of inflammation in the development of dementia due to AD.⁵ Increased microglial activation parallels the accumulation of tau²³ and A β ²⁴ in patients with MCI. Pagoni et al.²⁵ suggested that neuron-specific inflammatory response may precede insoluble A β plaque and tau tangle formation. Various mechanisms, including prolonged activation or dysfunction of microglia, infiltration of peripheral immune cells, blood–brain barrier breakdown, interactions with peripheral immunity, and cytokine dysfunction, have been suggested to contribute to the pathology of AD.^{4,19,21,26}

Cytokines produced under normal and abnormal conditions are among the main factors involved in neuroinflammation. Cytokines modulate neural functions and affect cognition, including neurogenesis, synaptic plasticity, synaptic scaling, and long-term potentiation.^{27–29} Heneka et al.⁵ argued that cytokines affect nearly all neuroinflammatory mechanisms in AD pathology. Infection and tissue damage lead to interleukin (IL)-6 production, which triggers acute-phase responses and stimulates immune reactions.³⁰ A recent meta-analysis of 170 studies found that patients with AD and/or MCI have higher peripheral pro-inflammatory cytokine levels than healthy controls.³¹ However, the findings regarding individual cytokines remain inconsistent.

Furthermore, only a limited number of studies have explored the association between inflammatory markers and cognitive impairment.^{32–34} Specifically, there is insufficient research on the connection between pro-inflammatory cytokines and performance in distinct cognitive domains. Elevated levels of inflammatory cytokines in the brain can lead to an excessive immune response, triggering apoptosis, and potentially creating an environment that contributes to or exacerbates neurodegeneration.³⁵ Consequently, the production and distribution of inflammatory cytokines in specific brain regions can disrupt the normal brain function. Given that different regions and networks within the brain are linked to specific cognitive abilities,³⁵ inflammatory cytokines may affect specific cognitive functions, regardless of the presence of cognitive impairment.

Tumor necrosis factor (TNF)- α and IL-6 are representative pro-inflammatory cytokines that play a crucial role in immune responses in the brain. Increasing evidence revealed a

connection between the diagnosis of cognitive impairment and the levels of TNF- α and IL-6. However, studies examining the correlation between specific cognitive functions and TNF- α and IL-6 levels are lacking. Therefore, we aimed to investigate the association of blood TNF- α and IL-6 levels with different stages of cognitive disorders and domain-specific cognitive functions.

METHODS

Participants

Between January 2017 and February 2018, we conducted face-to-face surveys of community-dwelling individuals aged 60 years and older who agreed to participate in the study. Participants were asked about their medical history and sociodemographic factors, including age, sex, marital status, living arrangements, and employment status. Those who met any of the following criteria were excluded from the study: unconsciousness due to physical conditions, inability to be interviewed due to drug or alcohol addiction, acute infections, or inflammatory diseases, such as rheumatoid arthritis. The study participants were provided with modest financial compensation. Based on history taking, cognitive tests, laboratory tests, and brain imaging, geriatric psychiatrists diagnosed dementia due to AD according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria³⁶ and MCI due to the National Institute of Aging and Alzheimer's Association Working Group criteria.³⁷ They also determined the global severity of dementia using the Clinical Dementia Rating (CDR). Participants were diagnosed with MCI by the geriatric psychiatrists when they exhibited cognitive impairment (z-score less than -1.5) in any domain of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NP), but without experiencing any functional impairment in their daily lives. The control group comprised cognitively healthy individuals without cognitive impairment or difficulties in everyday life. This study was approved by the Institutional Review Board (IRB No. 2016-12-002-004) of Kangdong Sacred Heart Hospital. Prior to data collection, all participants were adequately informed of the purpose and methods of the study, and written consent was obtained.

Cognitive function assessment

Cognitive function was measured using the Korean version of the CERAD-NP.^{38–40} The CERAD-NP includes the Categorical Verbal Fluency Test, 15-item Boston Naming Test, Mini-Mental State Examination (MMSE), Word List Learning test, Constructional Praxis test, Word List Recall test, Word List

Recognition test, Constructional Recall test, and Trail Making Test. These tests were administered by a trained researcher following standardized protocols. As significant age and sex effects on cognitive function evaluated by the CERAD-NP have been reported,⁴¹ we calculated standardized scores (z-scores) for each test using the age-, sex-, and education-adjusted norms of healthy Korean older adults.⁴²

Biomarker evaluation

To measure TNF- α in the blood, 5 mL of blood was collected in a serum separator tube (Becton, Dickinson and Company, Seoul, South Korea). For IL-6 measurements, 3 mL of blood was collected in ethylenediaminetetraacetic acid tubes. The serum separator tube was allowed to clot for more than 30 min at room temperature, and an ethylenediaminetetraacetic acid tube (Becton, Dickinson and Company, Seoul, South Korea) was sufficiently mixed immediately after collection in the blood collection room. Both tubes were centrifuged at 3,000 rpm for 10 min and the separated upper layer was transferred to a microtube and frozen. TNF- α and IL-6 were measured using an enzyme-linked immunosorbent assay kit (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Inc., Minneapolis, MN, USA) (Quantikine HS Human TNF- α ; R&D Systems, Inc., Minneapolis, MN, USA), with a detection limit of 0.156–10.000 pg/mL.

Statistical analysis

Comparative analyses between diagnostic groups were conducted using non-parametric tests. Continuous variables, including blood cytokine levels, were compared using the Kruskal–Wallis test, and categorical variables were compared using Fisher's exact test. For post hoc analysis following the Kruskal–Wallis test, the Conover–Iman test was performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

We examined the association of blood cytokine levels with continuous sociodemographic and clinical variables and z-scores in cognitive tests using regression analysis. Statistical significance was set at $p < 0.05$ as statistically significant. All statistical analyses were performed using SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of the participants

The mean age of the 37 study participants was 72.38 years. The diagnoses of the participants were as follows: 14, 15, and 8 in the control, MCI, and AD groups, respectively (Table 1). Significant differences were observed among the groups in terms of mean age and the proportion of married and living-

alone individuals. The AD group had the highest mean age ($p < 0.001$) and lowest proportion of married individuals ($p = 0.006$). The number of individuals living alone was highest in the control group ($p = 0.030$). There were no significant differences between the groups in terms of sex, educational duration, or employment status.

Regarding the clinical characteristics of the subjects, we found significant differences in CDR scores among the groups. The most frequently observed CDR scores were 0 (64.3%), 0.5 (93.3%), and 1 (75.0%) for the control, MCI, and AD groups, respectively. The control group also had the highest average MMSE score ($p = 0.001$) and highest proportion of lipid panel abnormalities ($p = 0.001$). There were no significant differences in medical history, including diabetes, hypertension, hyperlipidemia, stroke, heart disease, and cancer.

Demographic and clinical factors and cytokines

When examining the impact of sociodemographic factors on cytokine serum levels, only age exhibited significant associations with both IL-6 and TNF- α concentrations. As age increased, TNF- α (Spearman's $\rho = 0.520$, $p = 0.001$) and IL-6 (Spearman's $\rho = 0.534$, $p = 0.001$) showed a corresponding increase (Table 2). In terms of clinical variables, neither the global nor the sum of the box scores of the CDR had a significant impact. There were no significant associations among cytokine levels, laboratory abnormalities, or past comorbidities.

Diagnosis and cytokines

The TNF- α concentration increased from a mean of 1.09 ng/mL in the control group to 1.23 ng/mL in the MCI group and 1.85 ng/mL in the AD group. The IL-6 concentration also increased from an average of 1.83 ng/mL in the control group to 2.09 ng/mL in the MCI group and 3.35 ng/mL in the AD group. While the Kruskal–Wallis test revealed that there were no significant differences in the peripheral IL-6 levels among the control, MCI, and AD groups ($p = 0.082$), TNF- α levels differed significantly among the three groups ($p = 0.048$) (Table 1). The results of the post hoc analysis using the Conover–Iman test indicated that the TNF- α levels were significantly elevated in the AD group compared with the control ($p = 0.0039$) and MCI ($p = 0.0027$) groups. No significant difference was found in TNF- α levels between the control and MCI groups (Figure 1).

Cognitive domains

Across all domains of the CERAD-NP test, the average z-scores varied significantly according to diagnosis. The average z-scores tended to decrease consistently from the control group to the MCI group and then to the AD group in all tests (Table 3).

Simple regression analysis revealed a significant negative

Table 1. Demographic and clinical variables

	Total (N=37)	CTL (N=14)	MCI (N=15)	AD (N=8)	p
Age (yr) [†]	72.38±7.61	66.86±4.93	72.87±6.66	81.13±3.91	<0.001*
Sex, male [‡]	13 (36.1)	3 (23.1)	8 (53.3)	2 (25.0)	0.226
Education (yr) [†]	6.70±4.87	8.36±5.53	6.00±4.74	5.13±3.31	0.239
Married [‡]	22 (59.5)	9 (64.3)	12 (80.0)	1 (12.5)	0.006*
Never been employed [‡]	3 (8.1)	1 (7.1)	2 (13.3)	0 (0.0)	0.784
Living alone [‡]	7 (18.9)	5 (35.7)	0 (0.0)	2 (25.0)	0.030*
CDR [‡]					<0.001*
0	10 (27.0)	9 (64.3)	1 (6.7)	0 (0.0)	
0.5	20 (54.1)	5 (35.7)	14 (93.3)	1 (12.5)	
1	6 (16.2)	0 (0.0)	0 (0.0)	6 (75.0)	
2	1 (2.7)	0 (0.0)	0 (0.0)	1 (12.5)	
MMSE total [†]	23.49±4.49	25.79±3.31	24.40±3.52	17.75±2.92	0.001*
CBC abnormality [‡]	12 (32.4)	3 (21.4)	4 (26.7)	5 (62.5)	0.150
Liver panel abnormality [‡]	10 (27.0)	1 (7.1)	7 (46.7)	2 (25.0)	0.067
Renal panel abnormality [‡]	8 (21.6)	3 (21.4)	3 (20.0)	2 (25.0)	>0.999
Lipid panel abnormality [‡]	13 (35.1)	10 (71.4)	1 (6.7)	2 (25.0)	0.001*
FBS abnormality [‡]	20 (54.1)	7 (50.0)	7 (46.7)	6 (75.0)	0.446
TFT abnormality [‡]	3 (8.1)	0 (0.0)	3 (20.0)	0 (0.0)	0.217
Vitamin B12 abnormality [‡]	3 (8.1)	2 (14.3)	1 (6.7)	0 (0.0)	0.595
Folate abnormality [‡]	2 (5.4)	0 (0.0)	1 (6.7)	1 (12.5)	0.685
Medical history [‡]					
Diabetes mellitus	16 (43.2)	6 (42.9)	6 (40.0)	4 (50.0)	0.916
Hypertension	22 (59.5)	10 (71.4)	8 (53.3)	4 (50.0)	0.520
Dyslipidemia	11 (29.7)	7 (50.0)	3 (20.0)	1 (12.5)	0.068
Stroke	2 (5.4)	0 (0.0)	1 (6.7)	1 (12.5)	0.685
Ischemic heart disease	4 (10.8)	1 (7.1)	2 (13.3)	1 (12.5)	>0.999
Cancer	2 (5.4)	0 (0.0)	2 (13.3)	0 (0.0)	0.336
IL-6 (ng/mL) [†]	2.24	1.83	2.09	3.35	0.082
TNF-α (ng/mL) [†]	1.31	1.09	1.23	1.85	0.048*

Values are presented as mean±standard deviation, number (%), or mean only. *p<0.05; †Kruskal–Wallis one-way analysis of variance; ‡Fisher's exact test. CTL, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; CBC, complete blood cell count; FBS, fasting blood sugar; TFT, thyroid function test; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α

Table 2. Spearman's rank correlation coefficient of blood cytokines and age

	Age	IL-6	TNF-α
Age	1		
IL-6	0.534**	1	
TNF-α	0.520**	0.382*	1

*p<0.05; **p<0.01. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α

correlation between IL-6 plasma concentration and z-scores on the Boston Naming Test (p=0.037), Word List Learning (p=0.009), Word List Recognition (p=0.038), and Construction-

al Recall (p=0.048) (Supplementary Table 1). An inverse relationship was also observed between the serum concentration of TNF-α and the z-scores on the Word List Learning (p=0.001) and Constructional Recall (p=0.039) (Supplementary Table 2). Overall, higher levels of IL-6 and TNF-α were associated with more severe cognitive impairment.

After adjusting for age, which showed a significant correlation with both cytokines, the multiple regression analysis revealed no significant associations between IL-6 levels and cognitive function. However, significant negative correlation was observed between TNF-α level and the z-score on the Word List Learning (Tables 4 and 5). Thus, even after adjusting for

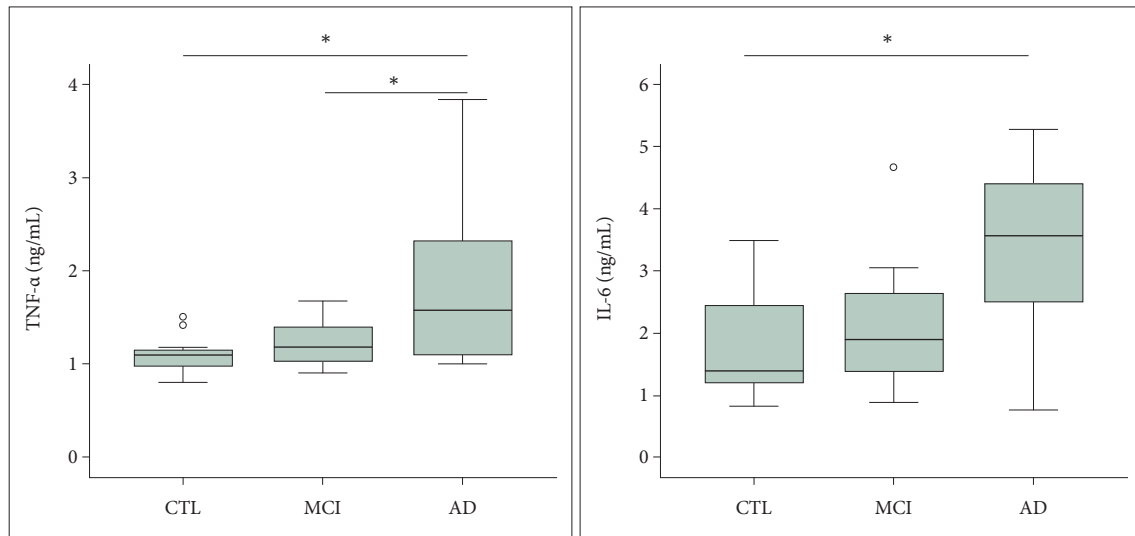


Figure 1. Comparison of cytokine levels by diagnosis. Cytokine levels were compared using the Kruskal–Wallis one-way analysis of variance. Post hoc analysis was conducted using the Conover–Iman test. No significant difference was found in IL-6 levels among the three groups. There were significant differences in the peripheral TNF- α levels among the control, MCI, and AD groups. Post hoc analysis showed that the TNF- α levels were significantly elevated in the AD group compared with the control ($p=0.0039$) and MCI ($p=0.0027$) groups. * $p<0.05$. TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; CTL, control; MCI, mild cognitive impairment; AD, Alzheimer's disease.

Table 3. Average z-scores of CERAD-NP test by diagnosis

	Total (N=37)	CTL (N=14)	MCI (N=15)	AD (N=8)	p
Categorical Verbal Fluency Test	-0.57	-0.06	-0.52	-1.56	0.001*
Boston Naming Test	-0.06	0.44	-0.03	-1.00	0.016*
MMSE	-0.81	-0.25	-0.41	-2.55	<0.001*
Word List Learning test	-0.84	-0.17	-0.64	-2.36	<0.001*
Constructional Praxis test	-0.76	-0.14	-0.92	-1.55	0.039*
Word List Delayed Recall test	-0.77	-0.18	-0.65	-2.04	<0.001*
Word List Recognition test	-0.98	0.08	-0.87	-3.03	<0.001*
Constructional Recall test	-0.49	0.20	-0.60	-1.62	<0.001*
Trail Making Test-A	-0.004	0.59	-0.39	-0.77	0.017*

* $p<0.05$. CERAD-NP, The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery; CTL, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination

age, higher levels of TNF- α were associated with worse immediate memory performance.

DISCUSSION

Although IL-6 is a representative pro-inflammatory cytokine, it plays an important role in maintaining brain function. At low concentrations, IL-6 affects neurogenesis, hippocampal long-term potentiation, and neural plasticity, all of which are associated with cognitive function.⁴³ Similarly, TNF- α has dual effects, depending on the circumstances. TNF- α typically plays a regulatory role in neuronal activity under normal condition, but in a deteriorated or diseased brain, TNF- α has cytotoxic effects⁴⁴ and can induce cell death, including apoptosis.

Accumulating evidence supports the association between

the diagnosis of cognitive impairment and TNF- α and IL-6 levels. A meta-analysis revealed that patients with AD and MCI showed elevated peripheral levels of IL-6 compared to cognitively normal subjects.^{31,45} Similarly, the concentrations of TNF- α ,⁴⁵ soluble TNF receptor 1,^{31,45} and soluble TNF receptor 2³¹ are higher in patients with AD compared with the control group. In addition, the levels of IL-6^{31,45} and TNF- α ⁴⁵ are elevated in the MCI group compared with the control group. Serum levels of soluble TNF receptors 1 and 2 were higher in patients with AD than in those with MCI.³¹ On the other hand, the results are mixed regarding the correlation between cognitive function and IL-6 and TNF- α . While several researchers have reported that individuals with poorer global cognition have higher blood concentrations of IL-6 and TNF- α among the community cohort,⁴⁵ longitudinal studies

Table 4. Association between plasma IL-6 level and z-scores of CERAD-NP tests (adjusted for age)

	Unstandardized coefficients		Standardized coefficients	t	p	F	R ²
	B	SE	β				
Categorical Verbal Fluency Test	0.047	0.162	0.059	0.292	0.772	1.509	0.086
Boston Naming Test	-0.036	0.142	-0.042	-0.251	0.804	9.050	0.361
MMSE	0.002	0.217	0.002	0.010	0.992	2.748	0.147
Word List Learning test	-0.261	0.164	-0.290	-1.585	0.123	5.131	0.243
Constructional Praxis test	0.199	0.212	0.192	0.941	0.354	0.974	0.057
Word List Delayed Recall test	-0.048	0.173	-0.053	-0.280	0.781	4.023	0.201
Word List Recognition test	-0.206	0.261	-0.146	-0.790	0.435	4.760	0.229
Constructional Recall test	-0.037	0.148	-0.042	-0.251	0.803	8.706	0.360
Trail Making Test-A	-0.047	0.196	-0.052	-0.239	0.813	3.650	0.226

IL-6, interleukin-6; CERAD-NP, The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery; SE, standard error; MMSE, Mini-Mental State Examination

Table 5. Association between serum TNF- α level and z-scores of CERAD-NP tests (adjusted for age)

	Unstandardized coefficients		Standardized coefficients	t	p	F	R ²
	B	SE	β				
Categorical Verbal Fluency Test	-0.056	0.319	-0.032	-0.175	0.862	1.787	0.095
Boston Naming Test	-0.030	0.321	-0.014	-0.092	0.927	9.278	0.353
MMSE	-0.463	0.430	-0.186	-1.078	0.289	3.781	0.182
Wordlist Learning test	-0.835	0.316	-0.406	-2.644	0.012*	9.265	0.353
Constructional Praxis test	0.034	0.439	0.014	0.077	0.939	0.714	0.040
Word List Delayed Recall test	-0.255	0.336	-0.130	-0.759	0.453	4.248	0.200
Word List Recognition test	-0.406	0.526	-0.133	-0.772	0.445	3.942	0.188
Constructional Recall test	-0.196	0.293	-0.101	-0.669	0.508	10.491	0.389
Trail Making Test-A	0.309	0.367	0.157	0.844	0.406	3.973	0.234

* $p < 0.05$. TNF- α , tumor necrosis factor- α ; CERAD-NP, The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery; SE, standard error; MMSE, Mini-Mental State Examination

have yielded contradictory results. For instance, higher IL-6 levels in cerebrospinal fluid were related to fewer p-tau changes in cerebrospinal fluid over time but not to cognitive function in cognitively unimpaired older adults.⁴⁶ A longitudinal study on 1,602 community-dwelling older adults reported no significant association between global cognition and IL-6 and TNF- α levels, both at baseline and follow-up. Only the risk of MCI is associated with higher IL-6 levels.⁴⁷ The effects of inflammatory cytokines on cognition have been repeatedly reported in other disease groups. Increased IL-6 levels are associated with cognitive impairment in patients with physical diseases, such as cardiovascular, rheumatic, and liver diseases,⁴⁸ as well as psychiatric disorders, including bipolar disorder⁴⁹ and schizophrenia.^{49,50} Cognitive deficits after stroke⁵¹ and severe acute respiratory syndrome coronavirus 2 infection⁵² are also associated with elevated pro-inflammatory biomarkers such as IL-6 and TNF- α .

In our study, contrary to the lack of significant differences observed in IL-6 concentrations among the groups, TNF- α levels were significantly higher in the AD group compared to the control and MCI groups. These results, which are partially inconsistent with those of previous meta-analyses, may be due to the underestimated significance derived from the small sample size of each group. Age, rather than diagnosis, may also affect blood cytokine levels. Both IL-6^{53,54} and TNF- α levels⁵³ are known to increase with age, and inflammation is reported to contribute to cognitive decline in elderly adults without neurodegenerative disorders.⁵⁵ In our study, the AD subjects were significantly older compared to the normal subjects, making it difficult to distinguish between the effects of age and diagnosis.

Concerning individual cognitive functions, the performance of domain-specific cognitive tasks can be affected by the regional distribution and production of cytokines in the brain.³⁵

Different areas and networks within the brain are linked to specific cognitive abilities.³⁵ Their functionality was assessed using cognitive tests. For example, the verbal fluency test can detect impairments in the frontal lobe function.⁵⁶ Excessive levels of inflammatory cytokines in the brain can trigger apoptosis and potentially foster an environment that contributes to or exacerbates neurodegeneration.³⁵ In fact, a study on cognitively normal elderly people with A β deposition reported that the pattern of cytokine increases differs according to brain regions: IL-1 β , IL-6, and eotaxin-3 in the temporal cortex, and monocyte chemoattractant protein-1 and IL-1 β in the parietal cortex.⁵⁷ Gray matter analysis revealed that IL-6 was negatively associated with gray matter thickness in the signature regions of AD (inferior temporal, middle temporal, inferior parietal, fusiform, precuneus, superior parietal, temporal pole, and entorhinal regions). In addition, gray matter thickness is associated with cognitive performance.⁵⁸ In patients with AD, plasma IL-6 levels are inversely correlated with cognitive performance and the volumes of the hypothalamus and hippocampus.¹⁸ Within the default mode network, IL-6 showed a negative correlation with the functional connectivity of the dorsal medial prefrontal cortex region⁵⁹ and left parietal region.⁶⁰

To date, few studies have investigated the relationship between individual cognitive function and cytokine levels across the spectrum of cognitive impairments, including dementia and MCI. Among healthy controls and MCI patients, higher IL-6 levels were associated with worse z-score in memory, language, and global cognition tests cross-sectionally, and baseline TNF- α levels were negatively correlated with language test scores, although the longitudinal analysis found no significant findings.⁴⁷ In a longitudinal study of 387 patients, including cognitively normal people and those with dementia, there was no association between IL-6 and cognition, although a higher baseline level of IL-8 was associated with worse cognition in attention, executive function, and visuospatial function over a 5-year follow-up.⁶¹

More evidence has accumulated on the relationship between cytokines and cognitive function in older adults without a diagnosis of cognitive impairment. Baune et al.⁶² found no significant association between IL-6 and TNF- α levels and cognitive function, as measured by standardized scores of memory, word fluency, perceptual/cognitive speed, attention and executive functioning, and motor speed tests, among elderly individuals residing in the community. However, a systematic review reported that elevated IL-6 levels were associated with worse cognition among healthy elderly adults.³⁵ Higher IL-6 levels were associated with poorer performance in executive function,⁶³⁻⁶⁵ processing speed,^{63,64} abstraction scores, language abilities, spatial abilities,⁶⁶ memory (imme-

diated, delayed, and spatial), verbal fluency, and orientation.⁶⁷ The combined inflammation z-score, which account for the levels of multiple biomarkers, including IL-6, exhibited a significant correlation with memory and psychomotor speed.⁶⁸ In other hand, TNF- α levels showed no significant association with cognitive performance on the Boston Naming Test, verbal fluency,⁶⁹ memory, and perceptual speed⁶² among healthy elderly adults. A longitudinal study was conducted among middle-aged individuals. Cross-sectionally, middle-aged participants with elevated IL-6 levels exhibited lower performance in terms of verbal fluency, wordlist learning,⁷⁰ auditory recognition memory, attention/working memory, and executive function.⁷¹ Longitudinally, in subjects with higher IL-6 and TNF- α , greater decline in verbal fluency and wordlist learning abilities were found after 10 years.⁷⁰

We found that higher blood levels of IL-6 and TNF- α were associated with worse performance in Word List Learning and Constructional Recall. Scores in the Naming and Word List Recognition domains were negatively correlated with IL-6 alone. However, only an inverse relationship of TNF- α and immediate memory learning remained significant after adjusting for age. When age was adjusted for, the absence of statistical significance suggested that the cognitive decline associated with IL-6 may be age-related rather than diagnosis-specific. There may be a potential association between TNF- α and immediate memory; however, due to limited existing research, further investigation is needed. While a previous cross-sectional analysis reported an association between inflammatory cytokines and cognitive impairment,⁴⁷ a longitudinal analysis indicated that elevated cytokine levels may not predict subsequent cognitive decline.^{47,61} These results suggest that high cytokine levels may be a consequence, rather than a precursor, of cognitive impairment.

These heterogeneous results may be due to the complexity of cytokine functions. First, there is a possibility that the impact on the brain may vary depending on the cytokine concentration. While high IL-6 levels significantly increased the risk of cognitive impairment, moderately elevated IL-6 levels did not.⁴⁵ Levels of pro-inflammatory cytokines were higher in subjects with AD than in those with MCI.³¹ Under normal conditions, low concentrations of IL-6 contribute to normal neuronal functions. However, high concentrations of IL-6 can hinder neurogenesis.⁴³ Therefore, detrimental effects may occur only when the cytokine levels are excessive. The degree of negative impact may not be directly proportional to cytokine levels. An inverse U-shaped relationship between brain inflammation and neuroplasticity has been suggested.²⁸

Second, cytokines may have different effects depending on the characteristics of the participants such as sex, age, and genetic vulnerability. A cross-sectional study reported that only

cognitive function in women was affected by elevated C-reactive protein.⁷² Increased levels of inflammatory cytokines in midlife have been reported to increase the risk of cognitive decline after 10 years⁷⁰; however, individuals in their 20s did not exhibit a significant association between IL-6 levels and cognitive function.⁷³ Apolipoprotein E (APOE)- ϵ 4 carriers exhibited a stronger association between higher IL-6 levels and the decline of global and memory function, compared to individuals without the allele.⁶⁵

Third, the role of these cytokines may vary depending on the stage of cognitive impairment. Although many studies reported a link between AD and the levels of IL-6 and TNF- α ,^{31,45} there was no association between elevated cytokine levels and faster progression in individuals with MCI or AD.⁷⁴ Furthermore, it has been suggested that cytokine elevation profiles vary across the different stages of the disease. Soluble triggering receptor expressed on myeloid cells 2 was increased in patients with AD, MCI, and subjective cognitive decline compared with healthy controls. However, increased monocyte chemoattractant protein 1 levels were observed in the MCI and AD groups. Chitinase-3-like protein 1 was elevated only in AD, compared to control and MCI groups.⁷⁵

Finally, the profile of cytokines affecting cognitive impairment could differ according to clinical subtypes and main pathology, even among patients with AD. A meta-analysis identified four biological subtypes of AD based on patterns of brain atrophy and tau-related pathology: typical, limbic-predominant, hippocampal-sparing, and minimal-atrophy AD.⁷⁶ Additionally, various clinical characteristics have been reported, including specific variants, such as posterior cortical atrophy, logopenic primary progressive aphasia, and the frontal variant of AD. This heterogeneity of neurodegeneration suggests variance in the patterns of neuroinflammation.

This study has several limitations. The small number of participants limited the analysis of potential confounding variables that may have influenced the relationship between cognitive function and cytokine levels. It is also possible that the small sample size led to underestimation of the significance of the association between cytokines and cognitive function. The power analysis (α value=0.05, effect size=0.5) revealed limitations in the statistical power of some analyses owing to the small sample size. These limitations raise the possibility that we may have missed other true associations not reported here. Additionally, possible confounding factors such as APOE ϵ 4 status were not included in the analysis. Finally, this study was cross-sectional, which poses challenges in establishing causality or determining temporal sequences.

Despite these limitations, our study has several strengths. First, we investigated the relationship between individual cognitive function and cytokines across a spectrum of cognitive

abilities ranging from normal cognition to MCI and AD. In previous studies, the relationship between cognitive function and cytokine levels has been investigated in individuals with AD or within a group of individuals with normal cognitive function. Studies across the spectrum of cognitive impairments have mainly focused on the association between cytokines and diagnosis.

Notably, we analyzed the relationship between individual cognitive function and cytokine levels using widely used standardized cognitive function test batteries instead of screening tests. Many studies have measured global cognition using total scores of screening tests or overall cognitive test scores. However, in our study, we analyzed cognitive function in various domains.

Furthermore, we used standardized z-scores, adjusted for age, education, and sex, in the neuropsychological battery to accurately estimate the degree of impairment in the respective cognitive domains. Cognitive function may decline as a result of normal aging and the normal range of cognitive test scores may differ depending on age, education, and sex. Consequently, it is difficult to accurately investigate the presence and severity of cognitive decline based solely on raw cognitive test scores. By employing standardized z-scores, we examined the relationship between the relative decline in cognitive function and cytokine levels, thereby enabling more accurate results.

Above all, to the best of our knowledge, this study is the first to find a significant relationship between TNF- α and individual cognitive functions. TNF- α has received relatively less attention even among the limited number of studies on cytokines and specific cognitive domains. Further studies would be required to determine the role of TNF- α on cognition, especially memory.

Supplementary Materials

The Supplement is available with this article at <https://doi.org/10.30773/pi.2024.0071>.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.

Conflicts of Interest

Ki Woong Kim, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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