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Research Article

The Cross-sectional and Longitudinal Associations Between IL-6, IL-10, and TNFα and Cognitive Outcomes in the Mayo Clinic Study of Aging

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Abstract

Background: Chronic inflammation has been linked with geriatric-related conditions, including dementia. Inflammatory cytokine levels, including interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF) α, in the blood have been associated with cognitive impairment and decline. However, evidence has been mixed.

Methods: We examined the cross-sectional and longitudinal associations between baseline-measured IL-6, IL-10, and TNFα levels and the ratio of IL-6/IL-10 with cognitive test performance and mild cognitive impairment (MCI) among 1,602 community-dwelling older adults (median age = 72.8) enrolled in the Mayo Clinic Study of Aging. Approximately half (46.5%) of participants were female and 98.6% were white. At baseline and follow-up visits (occurring at 15-month intervals), participants completed neuropsychological testing, blood draws, and had a clinical consensus diagnosis.

Results: In multivariable cross-sectional analyses, we did not observe an association between inflammatory cytokine levels and global or domain-specific cognitive *z* scores; however, higher IL-6 and IL-10 levels were associated with greater odds of a MCI diagnosis. Longitudinally, we did not observe any association between inflammatory cytokine levels and cognitive test performance or risk of MCI. Sex, age, cognitive status, *APOE* ε4 genotype, diabetes, depression, and cerebral amyloid-beta deposition were not effect modifiers.

Conclusions: These results suggest that plasma inflammatory markers may not be useful to ascertain risk for cognitive decline and MCI in the general population.

Keywords: Inflammation, Mild cognitive impairment, Epidemiology

Chronic inflammation is associated with several geriatric-related conditions, including dementia and cognitive decline (1,2), through multiple potential biological mechanisms such as disturbed sleep, neurotransmitter dysregulation, apoptosis, Alzheimer's disease (AD)-related pathology, and vascular insult (2,3). It remains unclear whether inflammatory processes have a causal role in the pathological changes leading to dementia, whether they modify the strength of association between a risk factor and dementia, or they the act as mediators. Regardless, measures of inflammatory markers, including IL-6, IL-10, and TNFα, in the blood may represent a means of determining who is at risk of poor cognitive outcomes.

Past cross-sectional studies have shown that higher inflammatory cytokine levels are associated with poorer cognition (4–6); however, this has not been shown consistently (7). Similarly, longitudinal studies have shown that higher inflammatory cytokine levels are associated with cognitive decline (4–6,8–11). Yet these findings are also mixed. Differences between studies, including demographics (eg, age, sex, race, *APOE* ε4 carrier status), comorbidities (eg, depression, diabetes), cognitive status, or follow-up time may have contributed to the mixed results (4–6,8,9). Additionally, because inflammatory cytokine levels are not static, fluctuating levels over time may be important in the association with cognition. Therefore,

these demographic and medical variables and follow-up time of studies may impact the observed associations.

We investigated the cross-sectional and longitudinal associations of serum levels of IL-6, IL-10, the ratio of IL-6 to IL-10, and TNFα with cognitive outcomes in the population-based Mayo Clinic Study on Aging (MCSA). To better understand the above-mentioned discrepant results, we utilized sensitive measures of inflammatory cytokines, a longitudinal study design including serial inflammatory markers, examined both continuous and categorical cognitive outcomes, and examined several potential effect modifiers (age, sex, *APOE*, diabetes, and depression). We also examined the ratio of IL-6 to IL-10. IL-6, IL-10, and TNFα are considered markers of inflammation, while the ratio of IL-6 to IL-10 is thought to be a marker of innate immune system function (12). Few studies have examined these ratios in relation to cognitive decline. We hypothesized that higher baseline levels and ratios of these markers would be associated with poorer cognitive outcomes.

Method

Participants

The MCSA is a prospective population-based study characterizing the incidence and prevalence of mild cognitive impairment (MCI) in Olmsted County, Minnesota (13). An age- and sex-stratified random sampling design was utilized to ensure that men and women were equally represented in each 10-year age strata. In 2004, Olmsted County residents between the ages of 70 and 89 were identified for recruitment using the Rochester Epidemiology Project medical records linkage system (14). The study was extended to include those aged 50 and older in 2012. The present study included 1,602 participants aged 50 years and older, who had measures of IL-6, IL-10, and TNFα and cognitive assessment. The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

Participant Assessment

MCSA visits included a physician examination, an interview by a study coordinator, and neuropsychological testing by a psychometrist (13). The physician examination included a medical history review, complete neurological examination, and administration of the Short Test of Mental Status (15). The study coordinator interview included demographic information, medical history, and questions about memory to both the participant and an informant using the Clinical Dementia Rating (CDR) scale (16).

The neuropsychological battery was administered by a psychometrist and included nine tests covering four domains: (a) memory (Auditory Verbal Learning Test Delayed Recall Trial (17); Wechsler Memory Scale-Revised Logical Memory II and Visual Reproduction II) (18); (b) language (Boston Naming Test (19) and Category Fluency (20); (c) attention (Trail Making Test B (21) and WAIS-R Digit Symbol subtest (22); and (d) visuospatial (WAIS-R Picture Completion and Block Design subtests) (22). We calculated sample-specific *z* scores for all cognitive tests, and created domain scores by averaging the *z* scores within each domain. We created a global cognitive score using the *z*-transformation of the average of the four domains.

Diagnostic Determination of Cognitive Status

For all participants, cognitive performance in each domain was compared with the age-adjusted scores of cognitively unimpaired (CU) individuals previously obtained using Mayo's Older American Normative Studies (23–25). This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Participants with scores approximately 1 standard deviation or more below the age-specific mean in the general population were considered for a diagnosis of possible MCI. A final decision to diagnose MCI was based on a consensus agreement between the study coordinator, examining physician, and neuropsychologist who evaluated the participant, after taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant clinical information (26). Individuals who performed in the normal range and did not meet criteria for MCI or dementia, which was diagnosed using DSM-IV criteria (27), were deemed CU.

Primary Exposure: Laboratory Analyses of IL-6, IL-10, and TNFα

Participants' blood was collected at the in-clinic exam, centrifuged, aliquoted, and stored at −80°C. Plasma IL-6, IL-10, and TNFα levels were measured on the Simoa HD-1 platform (Quanterix, Lexington, MA). Intra-assay coefficients of variation (CV) for IL-6, IL-10, and TNFα were 7.1%, 4.6%, and 4.0%, respectively. Inter-assay CVs were 5.6%, 6.2%, and 5.5%, respectively. The lower limits of detection were 0.0055, 0.0038, and 0.016 pg/mL, respectively. We calculated *z* scores for all inflammatory cytokine levels to create a more normal distribution. We calculated the ratio of IL-6 to IL-10, using the *z*-scored values of each, as a measure of immune response.

Assessment of Covariates

Demographic variables (eg, age, sex, and education) were collected by self-report during the in-clinic exam. Participants' height (cm) and weight (kg) were measured during the in-clinic exam, and used to calculate body mass index (BMI) (kg/m^2). Depressive symptoms were assessed using the Beck Depression Inventory (BDI) (28); participants with a score of ≥13 were considered to have depression. Medical conditions and the Charlson comorbidity index (29) were determined for each participant by medical record abstraction using the medical records-linkage system of the Rochester Epidemiology Project (14,30). Medications were collected via self-report and medical record abstraction. Participants' blood sample was used to determine *APOE* ε4 genotype.

Imaging

Amyloid (Aβ) PET images were formed using Pittsburgh Compound B (PiB) (31), and were obtained 40–60 minutes after injection. Imaging methods have been described in detail elsewhere (32). A PiB-PET SUVR ratio of >1.4 was used as the cut-point for elevated Aβ.

Statistical Analyses

Wilcoxon rank sum, Fisher's exact, Kruskal–Wallis, or chi-square tests were used to determine differences in participant characteristic and demographic variables by baseline cognitive status. We fit mixed effects models to investigate the cross-sectional and longitudinal associations between baseline inflammatory cytokine levels and cognitive test performance. The models included terms for baseline inflammatory cytokine level (indicating the cross-sectional association between inflammatory cytokines and cognition), time (indicating change in cognition over follow-up), and the interaction between inflammatory cytokines and time (indicating longitudinal association between baseline inflammatory cytokine level and change in

cognition). We specified a random intercept and random slope, and used an unstructured covariance matrix. We used logistic regression models to determine the cross-sectional association between inflammatory cytokine levels and MCI diagnosis. We fit Cox proportional hazard models to examine the association between baseline inflammatory cytokine levels and risk of incident MCI diagnosis. Participants who progressed directly from CU to dementia were excluded from analyses. We specified age as the time scale. Potential covariates and effect modifiers to be included in the models were based on those shown to be significantly different between the CU and MCI groups and evidence from the literature. We used a stepwise approach to determine which covariates should be included in the multivariable models. Multivariable models included age (mixed effects and logistic regression models only), sex, education, *APOE* ε4, the Charlson comorbidity index, and NSAID use. All analyses were completed using Stata Version 13.0 (StataCorp, College Station, TX).

Results

Of the 1,602 participants at baseline, the 1,416 CU participants were younger, had more years of education, fewer comorbidities, and lower levels of inflammatory cytokines compared with the 186 MCI participants (Table 1). MCI participants were more likely to be *APOE* ε4 carriers, have elevated PiB-PET SUVR, and use NSAIDS on a regular basis. We examined the Spearman rank correlation between IL-6, TNFα, and IL-10. IL-6 was strongly positively correlated with both TNFα (rho = .82, $p < .001$) and IL-10 (rho = .77, $p < .001$). Similarly, IL-10 and TNFα were positively correlated (rho = .68, $p = .015$).

Participants had a median of three visits, including the baseline visit (Table 1), corresponding to a median follow-up of 2.7 years. There were 503 participants who were lost to follow-up (died or dropped out). Compared to the participants who remained active, those lost to follow-up at baseline were older, and had more comorbidities, lower TNFα levels, and higher baseline IL-6 and IL-6/IL-10 levels (Supplementary Table 1).

In unadjusted models, higher baseline IL-6 levels were cross-sectionally associated with poorer memory ($B = -0.07$, 95% confidence interval [CI] = −0.12, −0.02), language ($B = -0.07$, 95% CI = −0.12, −0.02), and global ($B = -0.06$, 95% CI = −0.11, −0.01) cognitive test performance (Table 2). Longitudinally, the association between baseline IL-6 and cognitive test performance was no longer significant. In multivariable models, higher baseline TNFα levels were cross-sectionally associated with poorer performance on tests of language ($B = -0.04$, 95% CI = −0.08, −0.0005). We did not observe any longitudinal associations between TNFα and cognitive *z* scores. Baseline IL-10 levels and the ratio of IL-6/IL-10 were neither cross-sectionally nor longitudinally associated with any cognitive *z* score.

Cross-sectionally, higher baseline IL-6 levels were associated with higher odds of MCI diagnosis in unadjusted (odds ratio [OR] = 1.18, 95% CI = 1.04, 1.34) and multivariable adjusted (OR = 1.17, 95% CI = 1.01, 1.35) models (Table 3). Similarly, higher baseline IL-10 levels were associated with higher odds of MCI (OR = 1.18, 95% CI = 1.02, 1.36) in multivariable adjusted models. For longitudinal analyses examining the plasma inflammatory markers and risk of MCI, 1,586 baseline CU participants were followed a median of 2.7 years for a total of 6,037 person-years; 256 had a follow-up diagnosis of MCI. In Cox proportional hazard models, there were no associations between any of the inflammatory markers and risk of MCI (Table 4).

We performed several secondary analyses. First, to determine whether there was a dose–response or inverted U-shaped relationship between inflammatory cytokines and cognitive outcomes, we created tertiles and quartiles of each inflammatory cytokine measure. However, there was no evidence of an association for any analysis. Second, we investigated whether sex, age (<70 vs ≥70 years), or the presence of an *APOE* ε4 allele were effect modifiers and found they

Table 1. Participant Baseline Characteristics

Median (IQR) or *N* (%)	Total (*N* = 1,602)	CU (*N* = 1,416)	MCI (*N* = 186)	*p*
Age	72.8 (64.3, 79.6)	71.9 (63.6, 78.4)	79.7 (73.1, 84.7)	<.001
Female	745 (46.5)	669 (47.3)	76 (40.9)	.118
Education (years)	14.0 (12.0, 16.0)	14.0 (12.0, 16.0)	13.0 (12.0, 16.0)	<.001
≥1 *APOE* ε4 allele	454 (28.3)	384 (27.1)	70 (37.6)	.004
Charlson Comorbidity Index	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	7.0 (5.0, 9.0)	<.001
Elevated PiB (SUVR > 1.4)	424 (32.4)	335 (28.9)	89 (60.5)	<.001
Diabetes	261 (16.4%)	221 (15.7)	40 (22.0)	.043
Depression	120 (7.5%)	91 (6.4)	29 (15.6)	<.001
NSAID use ≥3/week	940 (58.7%)	811 (57.3)	129 (69.4)	.002
IL-6 (pg/mL)	2.6 (1.6, 4.9)	2.5 (1.6, 4.8)	3.1 (1.8, 5.7)	.009
IL-10 (pg/mL)	0.81 (0.56, 1.7)	0.80 (0.56, 1.6)	0.91 (0.60, 1.9)	.034
TNFα (pg/mL)	4.2 (3.5, 4.9)	4.3 (4.0, 5.2)	3.3 (2.1, 4.3)	.028
IL-6/IL-10	2.8 (1.8, 4.3)	3.8 (1.8, 4.3)	3.1 (1.9, 4.7)	.099
Memory (*z* score)	0.10 (−0.64, 0.75)	0.25 (−0.42, 0.82)	−1.4 (−1.9, −0.79)	<.001
Attention (*z* score)	0.15 (−0.54, 0.72)	0.26 (−0.37, 0.77)	−0.97 (−1.9, −0.32)	<.001
Language (*z* score)	0.13 (−0.51, 0.69)	0.22 (−0.33, 0.74)	−1.1 (−1.7, −0.35)	<.001
Visuospatial (*z* score)	0.13 (−0.54, 0.74)	0.19 (−0.42, 0.74)	−0.85 (−1.6, −0.17)	<.001
Global (*z* score)	0.13 (−0.57, 0.75)	0.25 (−0.35, 0.80)	−1.3 (−2.0, −0.85)	<.001
Follow-up (years)	2.7 (1.4, 4.1)	2.7 (1.4, 4.1)	2.7 (1.4, 4.1)	.697
Follow-up (no. of visits)	3 (1, 4)	3 (1, 4)	2 (1, 4)	.041

Note: CU = cognitively unimpaired; IQR = interquartile range; MCI = mild cognitive impairment; PiB = C^{11} Pittsburgh Compound B; SUVR = standardized uptake volume ratio.

Table 2. Longitudinal Association Between Baseline *Z*-Scored Inflammatory Cytokine Levels and Change in Cognitive Test Performance

Inflammatory Markers	*Z* Memory			*Z* Attention			*Z* Language			*Z* Visuospatial			*Z* Global	
	N	*B* (95% CI)	*p*	*N*	*B* (95% CI)	*p*	*N*	*B* (95% CI)	*P*	*N*	*B* (95% CI)	*p*	*N*	*B* (95% CI)	*p*
Model 1															
IL-6	1,583	−0.07 (−0.12, −0.02)	.007	1,552	−0.05 (−0.10, 0.003)	.065	1,562	−0.07 (−0.12, −0.02)	.004	1,554	−0.02 (−0.07, 0.03)	.439	1,537	−0.06 (−0.11, −0.01)	.015
Time		−0.01 (−0.02, −0.003)	.005		−0.07 (−0.08, −0.06)	<.001		−0.05 (−0.06, −0.04)	<.001		−0.01 (−0.02, −0.005)	.002		−0.04 (−0.05, −0.03)	<.001
IL-6 × Time		−0.002 (−0.01, 0.007)	.706		−0.007 (−0.02, 0.002)	.152		−0.004 (−0.01, 0.005)	.425		0.004 (−0.004, 0.01)	.322		−0.005 (−0.01, 0.003)	.187
IL-10	1,620	−0.04 (−0.08, 0.01)	.154	1,589	−0.009 (−0.06, 0.04)	.718	1,599	−0.03 (−0.08, 0.02)	.200	1,591	0.007 (−0.04, 0.06)	.763	1,574	−0.02 (−0.07, 0.03)	.380
Time		−0.01 (−0.02, −0.003)	.007		−0.07 (−0.08, −0.07)	<.001		−0.05 (−0.06, −0.04)	<.001		−0.01 (−0.02, −0.006)	.001		−0.04 (−0.05, −0.03)	<.001
IL-10 × Time		0.003 (−0.005, 0.01)	.484		−0.006 (−0.01, 0.002)	.150		−0.003 (−0.01, 0.006)	.543		0.004 (−0.003, 0.01)	.278		−0.003 (−0.01, 0.005)	.486
TNFα	1,591	−0.03 (−0.08, 0.02)	.277	1,560	−0.03 (−0.08, 0.02)	.214	1,570	−0.04 (−0.09, 0.008)	.099	1,562	0.0008 (−0.05, 0.05)	.974	1,545	−0.03 (−0.08, 0.02)	.194
Time		−0.01 (−0.02, −0.003)	.008		−0.07 (−0.08, −0.07)	<.001		−0.05 (−0.06, −0.04)	<.001		−0.01 (−0.02, −0.005)	.001		−0.04 (−0.05, −0.03)	<.001
TNFα × Time		0.002 (−0.005, 0.01)	.533		−0.007 (−0.02, 0.001)	.098		−0.0003 (−0.009, 0.008)	.940		0.005 (−0.004, 0.01)	.265		−0.002 (−0.009, 0.006)	.643
IL-6/IL-10	1,583	−0.001 (−0.003, 0.0005)	.194	1,552	−0.0004 (−0.002, 0.001)	.612	1,562	−0.001 (−0.003, 0.0006)	.227	1,554	−0.001 (−0.003, 0.0004)	.158	1,537	−0.001 (−0.003, 0.0005)	.172
Time		−0.01 (−0.02, −0.003)	.005		−0.07 (−0.08, −0.06)	<.001		−0.05 (−0.06, −0.04)	<.001		−0.01 (−0.02, −0.005)	.001		−0.04 (−0.05, −0.03)	<.001
IL-6/IL-10 × Time		−0.0001 (−0.0006, 0.0003)	.623		−0.00004 (−0.0005, 0.0004)	.873		0.0002 (−0.0003, 0.0007)	.379		0.0003 (−0.0002, 0.0008)	.280		0.00004 (−0.0003, 0.0004)	.842
Model 2															
IL-6	1,566	−0.02 (−0.06, 0.02)	.301	1,536	−0.001 (−0.04, 0.04)	.954	1,545	−0.04 (−0.08, 0.004)	.073	1,537	0.002 (−0.04, 0.05)	.920	1,521	−0.02 (−0.06, 0.02)	.359
Time		−0.009 (−0.02, −0.001)	.019		−0.07 (−0.08, −0.06)	<.001		−0.05 (−0.05, −0.04)	<.001		−0.01 (−0.02, −0.003)	.009		−0.04 (−0.04, −0.03)	<.001
IL-6 × Time		0.0003 (−0.008, 0.009)	.951		−0.005 (−0.01, 0.004)	.294		−0.002 (−0.01, 0.007)	.609		0.003 (−0.005, 0.01)	.441		−0.003 (−0.01, 0.005)	.495
IL–10	1,603	−0.03 (−0.07, 0.01)	.165	1,573	−0.004 (−0.04, 0.03)	.826	1,582	−0.03 (−0.07, 0.006)	.092	1,574	−0.01 (−0.05, 0.03)	.637	1,558	−0.02 (−0.06, 0.02)	.244
Time		−0.009 (−0.02, −0.001)	.025		−0.07 (−0.08, −0.06)	<.001		−0.05 (−0.06, −0.04)	<.001		−0.01 (−0.02, −0.003)	.004		−0.04 (−0.04, −0.03)	<.001
IL-10 × Time		0.004 (−0.004, 0.01)	.312		−0.005 (−0.01, 0.003)	.217		−0.002 (−0.01, 0.006)	.613		0.004 (−0.004, 0.01)	.365		−0.001 (−0.008, 0.006)	.709
TNFα	1,575	−0.02 (−0.06, 0.03)	.467	1,545	−0.02 (−0.06, 0.02)	.248	1,554	−0.04 (−0.08, −0.0005)	.047	1,546	−0.01 (−0.06, 0.03)	.520	1,530	−0.03 (−0.07, 0.007)	.115
Time		−0.008 (−0.02, −0.0009)	.029		−0.07 (−0.08, −0.06)	<.001		−0.05 (−0.06, −0.04)	<.001		−0.01 (−0.02, −0.003)	.007		−0.04 (−0.04, −0.03)	<.001

Table 2. *Continued*

Inflammatory Markers	N	Z Memory		Z Attention		Z Language		Z Visuospatial		Z Global	
		B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*P*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
TNFα × Time		0.003 (−0.004, 0.01)	.384	−0.006 (−0.01, 0.002)	.162	0.0002 (−0.008, 0.009)	.958	0.004 (−0.004, 0.01)	.322	−0.0006 (−0.008, 0.007)	.868
IL-6/IL-10	1,566	−0.0005 (−0.002, 0.0009)	.517	0.0005 (−0.0008, 0.002)	.465	−0.0003 (−0.002, 0.001)	.705	−0.0005 (−0.002, 0.0009)	.494	−0.0002 (−0.001, 0.001)	.706
Time		−0.009 (−0.02, −0.001)	.021	−0.07 (−0.08, −0.06)	<.001	−0.05 (−0.06, −0.04)	<.001	−0.01 (−0.02, −0.003)	.006	−0.04 (−0.04, −0.03)	<.001
IL-6/IL-10 × Time		−0.0001 (−0.0006, 0.0004)	.642	−0.00002 (−0.0005, 0.0005)	.939	0.0002 (−0.0003, 0.0007)	.370	0.0003 (−0.0002, 0.0008)	.248	0.00004 (−0.0003, 0.0004)	.833
	1,536				1,545		1,537		1,521		

Note: Model 1 unadjusted. Model 2 adjusted for age, sex, education, *APOE* ε4, Charlson comorbidity index, and NSAID use.

Table 3. Cross-sectional Association Between *Z*-Scored Inflammatory Cytokine Levels and MCI Diagnosis

Inflammatory Markers	Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*
IL-6	1.18 (1.04, 1.34)	.011	1.17 (1.01, 1.35)	.038
IL-10	1.14 (1.00, 1.30)	.058	1.18 (1.02, 1.36)	.025
TNFα	1.10 (0.96, 1.25)	.182	1.09 (0.94, 1.28)	.249
IL-6/IL-10	0.99 (0.98, 1.01)	.527	1.00 (0.98, 1.01)	.635

Note: Model 1 unadjusted. Model 2 adjusted for age, sex, education, *APOE* ε4, Charlson comorbidity index, and NSAID use. CI = confidence interval; MCI = mild cognitive impairment; OR: odds ratio.

Table 4. Longitudinal Association Between *Z*-Scored Inflammatory Cytokine Levels and Incident MCI Diagnosis

Inflammatory Markers	Model 1		Model 2	
	HR (95% CI)	*p*	HR (95% CI)	*p*
IL-6	1.03 (0.90, 1.18)	.700	0.93 (0.80, 1.07)	.292
IL-10	1.10 (0.97, 1.23)	.125	1.05 (0.94, 1.19)	.380
TNFα	1.01 (0.87, 1.16)	.934	0.94 (0.81, 1.09)	.410
IL-6/IL-10	1.00 (0.99, 1.01)	.620	1.00 (0.99, 1.00)	.578

Note: Model 1 unadjusted. Model 2 adjusted for age, sex, education, *APOE* ε4, Charlson comorbidity index, and NSAID use. CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment.

were not. We further investigated whether elevated Aβ deposition (SUVR > 1.4), depression, diabetes, or cognitive status (ie, CU vs MCI, mixed effects models only) were confounders or effect modifiers, but found they were not. Third, we investigated whether other anti-inflammatory medications (ie, analgesics, propionic acid derivatives, selective Cox-2 inhibitors, acetic acid derivatives, enolic acid derivatives, anthracitic acid derivatives, corticosteroids, inhaled steroids) were confounders and found they were not. Finally, because inflammatory markers vary within individuals over time, we conducted analyses examining the association between longitudinally collected inflammatory cytokine levels and change in cognition with mixed effects models. Using interclass correlation coefficients (ICC), we first examined trajectories of IL-6 (ICC = 0.81), IL-10 (ICC = 0.81), and TNFα (ICC = 0.81), and found levels were fairly stable over follow-up. In mixed effects models, we found no association between changes in inflammatory cytokine levels and change in cognitive *z* scores (results not shown).

Discussion

We investigated the cross-sectional and longitudinal relationships between levels of IL-6, IL-10, and TNFα, which are markers of inflammation, and the ratio of IL-6 to IL-10, a marker of innate immune response, and domain-specific and global cognitive test performance and MCI diagnosis. Higher levels of IL-6 and TNFα were cross-sectionally associated with poorer cognition and higher odds of MCI. However, baseline inflammatory cytokine levels were not associated with change in any cognitive domain or risk of incident MCI.

Our cross-sectional findings are somewhat consistent with past cross-sectional studies which showed that higher inflammatory cytokine levels were associated with poorer cognition (4–6). However, our lack of longitudinal findings is inconsistent with

studies reporting that higher levels of inflammatory cytokines were associated with cognitive decline (4–6,8–11). A meta-analysis also showed an overall association between higher IL-6 levels and an increased risk of incident all-cause dementia (33), but these findings were largely driven by one longitudinal study (34). Other longitudinal studies in community-based nondemented participants only found associations between specific inflammatory cytokines or in specific demographic characteristics (4,6) and decline in memory or global cognition. Similarly, prior studies showed differences in the association of inflammatory cytokines and cognitive outcomes based on sex (11,35), race (6,11,35), depression (35), cardiovascular and metabolic conditions (6,8,35), and cognition (4). Therefore, given our overall lack of association between inflammatory markers and cognitive outcomes, we conducted sensitivity analyses investigating whether sex, age, *APOE* ε4 genotype, depression, diabetes, elevated Aβ deposition (PiB PET SUVR > 1.4), or cognitive status modified the association between inflammatory cytokine levels and cognitive outcomes. However, we did not find any evidence for effect modification by these variables. Because the MCSA is predominately white, we were unable to assess whether race/ethnicity was an effect modifier in this study, despite evidence that inflammatory cytokine levels vary by race/ethnicity (36).

Another possible explanation for our observed lack of association between inflammatory cytokines and cognitive decline could be our short follow-up time, with a median of 2.7 years. Among studies with considerably longer follow-up time (ranging from 4–9 years) than the present study (4,5,9), inflammatory cytokines were associated with declines in global cognition, verbal memory or psychomotor speed and with incident cognitive impairment.

Because inflammatory cytokine levels change over time, we also investigated whether trajectories of inflammatory cytokines were associated with change in cognitive test performance or incident MCI using time-varying models. We again did not find longitudinal associations between the inflammatory markers and cognitive outcomes. Our results are similar to another study of older white women which examined inflammatory cytokine levels twice, approximately 6 years apart, and found no association between change in inflammatory cytokine levels and change in cognitive test performance in community-dwelling older adults (35). Because our study had serial measures of inflammatory markers, we were able to better assess trajectories of change associated with cognition. However, we still did not observe any longitudinal associations. It still remains possible that inflammatory cytokine levels are associated with cognitive decline over prolonged periods.

This study has multiple strengths, including the population-based sample, longitudinal design, and sensitive measures of plasma inflammatory cytokine levels. However, its limitations must also be considered. As mentioned, inflammatory cytokine levels vary by race/ethnicity (36). Because the MCSA cohort is predominately of Northern European descent, it may be that the present findings are not directly generalizable to different populations. Additionally, individuals who consent to participation in the MCSA tend to be healthier than individuals who are not, thus potentially introducing bias. However, because the MCSA uses a population-based sampling frame, this is less of a concern.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

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