Associations Between Inflammation and Cognitive Function in African Americans and European Americans

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OBJECTIVES: To examine associations between specific inflammatory biomarkers and cognitive function in African Americans (AAs) and European Americans (EAs) with prevalent vascular risk factors.

DESIGN: Cross-sectional analysis using generalized estimating equations to account for familial clustering; standardized β-coefficients, adjusted for age, sex, and education are reported.

SETTING: Community cohort study in Jackson, Mississippi, and Rochester, Minnesota.

PARTICIPANTS: Genetic Epidemiology Network of Arteriopathy (GENOA)–Genetics of Microangiopathic Brain Injury (GMBI) Study participants.

MEASUREMENTS: Associations between inflammation (high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, soluble tumor necrosis factor (TNF) receptor 1 and 2 (sTNFR1, sTNFR2)) and cognitive function (global, processing speed, language, memory, and executive function) were examined in AAs and EAs (N = 1,965; aged 26–95, 64% women, 52% AA, 75% with hypertension).

RESULTS: In AAs, higher sTNFR2 was associated with poorer cognition in all domains (global: −0.11, $P = .009$; processing speed: −0.11, $P < .001$; language: −0.08, $P = .002$; memory: −0.09, $P = .008$; executive function: −0.07, $P = .03$); sTNFR1 was associated with slower processing speed (−0.08, $P < .001$) and poorer executive function (−0.08, $P = .008$); higher CRP was associated with slower processing speed (−0.04, $P = .024$), and higher IL6 was associated with poorer executive function (−0.07, $P = .02$). In EA, only higher sTNFR1 was associated with slower processing speed (−0.05, $P = .007$). Associations were not found between cognition and sTNFR2, CRP, or IL6 in EA.

CONCLUSION: In a population with high vascular risk, adverse associations between inflammation and cognitive function were especially apparent in AAs, primarily involving markers of TNFα activity. **J Am Geriatr Soc 62:2303–2310, 2014.**

Key words: inflammation; cognition; ethnicity

Dementia affects approximately 5 million people in the United States, with Alzheimer's disease (AD) accounting for 60% to 80% of these cases and vascular cognitive impairment accounting for most of the remainder. Vascular disease causes cognitive impairment and amplifies the deleterious effects of AD pathology by lowering the threshold for cognitive impairment and augmenting the trajectory of cognitive decline.[1–3] Growing evidence suggests that inflammation may contribute to the pathophysiology of AD and vascular dementia (VaD).[4] Furthermore, studies demonstrating that adding inflammatory markers to the model improves predictive ability of lipid markers in cardiovascular disease outcomes[5] provide face validity for an inflammatory-mediated role in vascular disease of the brain, similar to that of other end organs.

Associations between cognitive function and interleukin-6 (IL6),[6–9] tumor necrosis factor (TNF)-α and soluble TNF receptors (sTNFRs),[10–12] and C-reactive protein (CRP)[8, 3–17] have been reported. Inflammation may be involved differently in VaD and AD and in different racial and ethnic groups. For example, TNFα,[18] CRP, and IL6[15] are higher in persons with VaD than in those with AD and may be important risk factors for cognitive impairment in persons with cardiovascular risk factors. Although African Americans (AAs) may be more likely to have dementia than European Americans (EAs),[19] few studies of inflammation and cognitive function have included AAs.[6,7,13] Inflammatory biomarker levels appear to differ between AAs and EAs[20–22]

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and AAs may have stronger responses to inflammatory stimuli than EAs.[23] In addition, some[20,21,24,25] but not all studies[26] suggest that levels and actions of inflammatory markers differ in EAs and AAs and may contribute differently to the pathophysiology of dementia. The purpose of this study was to examine associations between CRP, IL6, and TNFα activity and cognitive function in EAs and AAs with prevalent cardiovascular risk factors, all of whom had hypertension or two siblings with hypertension before age 60.

METHODS

Population

The Genetic Network of Arteriopathy (GENOA) study, begun in 1995, follows a well-characterized cohort of individuals with hypertension and their siblings recruited from Jackson, Mississippi (AA only) and Rochester, Minnesota (EA only) (N = 3,437; 66% female, 57% AA, aged 28–91, 52% obese at baseline). At least two members of each sibship had hypertension before age 60 at enrollment. Inflammatory markers were assayed at the second examination (GENOA Visit 2, 2000–04). Neurocognitive testing was conducted at or after Visit 2 (The Genetics of Microangiopathic Brain Injury [GMBI], 2001–06; hereafter included with Visit 2). Participants in Visit 2 and GMBI (n = 2,721) included 1,239 individual EAs (469 full-sibling pairs) and 1,482 individual AAs (626 full-sibling pairs). Of these, 162 (3 EA, 159 AA) were missing information on all inflammatory markers, and 10 self-reported a history of dementia and were excluded, leaving 2,549 participants. Cognitive data were available for 1,965 (960 EA, 1,005 AA), who constitute the analysis dataset, including those in the dataset for the sensitivity analyses, which addresses potential bias of missing data. Of these, 1,857 (95%) had inflammatory biomarker data and constitute the completers data set.

Inflammatory Markers

At Visit 2, fasting blood samples were centrifuged for 10 minutes at 4°C, aliquoted in 0.5- to 1-mL volumes of ethylenediaminetetraacetic acid plasma (serum for CRP), and stored at −80°C within 2 hours of venipuncture; frozen samples were shipped to the Mayo Clinic Immunochemical Core Laboratory (Rochester, MN) overnight on dry ice. CRP assays were performed using immunoturbidometric assays (Diasorin, Inc., Stillwater, MN; interassay imprecision 1.8–2.6%; intraassay imprecision 1.0–9.2%), and multiplex assays (SearchLight, Pierce, Boston, MA) were used for IL-6 and sTNFRs; sTNFR fractions show stability over time, with longer half-lives than TNFα levels, and have been validated as sensitive indicators of TNF-α system activation.[27,28] Precision of the assays performed using SearchLight was retrospectively determined based on data derived from a blinded internal plasma control sample. Algorithms were developed to reduce plate-to-plate variations in protein levels, and all analyses used these normalized data.[29]

Cognitive Testing

Neurocognitive tests were offered to all participants in the same sequence using standardized protocols to assess global mental status, memory, language, processing speed, and executive function. All scores were ordered so that higher values reflect better cognition, and standardized coefficients were used to allow comparisons across measures.

Global Cognitive Function

The Mini-Mental State Examination (MMSE, range 0 [worst] to 30 [best])[30] was administered according to protocol consistent with the Consortium for the Establishment of a Registry for Alzheimer's Disease battery.[31,32]

Processing Speed

The Wechsler Adult Intelligence Scale Revised Digit Symbol Substitution Task was used to test complex visual attention, sustained and focused concentration, response speed, and visuomotor coordination, and the Trail-Making Test Part A (TMT-A) was used to measure visual conceptual and visuomotor tracking, attention, sequencing, mental flexibility, visual search, and motor function (nearest 0.01 seconds, maximum 4 minutes).[32] Because slower times indicate poorer performance, times were multiplied by −1 for analyses so that higher numbers represented better performance.

Memory

The Rey Auditory Verbal Learning Test (range 0–15) assesses learning and memory using multiple learning trials and a 30-minute delayed recall of 15 items on a list.[32] The Wechsler Adult Intelligence Scale III Incidental Learning Task allows continuation of the Digit Symbol Substitution Task until the third row of the test has been completed.[33] After a 5-minute delay, the symbol pairs with free-recall[32] are presented again.

Language

The FAS was used to measure letter fluency; participants must spontaneously produce words beginning with a specific letter (F, A, S) within 60 seconds.[32] The Animal Naming Task was used to measure category (animals) fluency.[31]

Executive Function

The TMT-B was used to assess attention, sequencing, mental flexibility, visual search and motor function using time and error counts.[32] Times were multiplied by −1 so that higher scores represented better function.

Composite Cognitive Domain Measures

Composite measures for processing speed, memory, and language domains were constructed from two tests within each domain to reduce measurement error and floor and ceiling effects of individual tests.[34–36] A standardized *z*-score was created for each measure, and *z*-scores were averaged within a domain to create the composite.[34–36] A factor-analytical combination method for constructing the domain scores yielded similar associations between

inflammation and cognitive measures (results available on request).

Covariates

Blood pressure, measured three times in a seated, resting state with appropriately sized cuffs, was defined as the average of the second and third measurements. Hypertension was defined as measured blood pressure greater than 140/90, self-report of high blood pressure, or antihypertensive medication use. Diabetes mellitus was defined as fasting glucose of 126 mg/dL or greater, random glucose of 200 mg/dL or greater, self-report of diabetes mellitus, or hypoglycemic medication use. Antianxiety, antidepressant, hypnotic, and narcotic medications and sleep aids (over the counter or prescription) taken in the previous 2 weeks were classified as medications with potential to affect cognition. Never-smoker was defined as having never smoked more than 100 cigarettes. Height was measured using a stadiometer and weight using an electronic balance with participants wearing lightweight clothes. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2).

Statistical Analysis

Associations between inflammatory markers and each cognitive domain were estimated using linear models fit with generalized estimating equations (GEEs) to account for familial clustering and Huber-White robust standard error estimates. Because inflammatory markers and cognitive function scores all use different measurement units, standardized outcomes and predictors were modeled to facilitate comparison of models. Thus, a beta coefficient of −0.5 is interpreted as a 0.5–standard deviation (SD) decrease in the cognitive score outcome being associated with a 1-SD increase in the inflammatory marker. Diagnostic lowess smoothers revealed linear relationships on the natural scale, inflammatory markers were only mildly skewed, and estimates were resistant to any extreme value effects (Figure 1), hence associations are presented with standardized, non-log-transformed inflammatory markers. Primary adjusted models included age, education, and sex and accounted for familial clustering. Extended adjusted models also included diabetes mellitus, hypertension, BMI, smoking, stroke history, alcohol, lipid-lowering medications, and central nervous system medications. Differences according to race were examined using interaction terms, acknowledging that race and site are aliased by design (meaning that all AAs are from one site and all EAs from another). Results are presented stratified according to race as shorthand for AA (MS)/EA (MN) race (site) groups.

Characteristics of participants who had and who were missing cognitive data were evaluated according to race, and sensitivity analyses were conducted using weighted GEEs to examine the robustness of findings after accounting for missing cognitive data. Analyses were performed using STATA 12 (Stata Corp., College Station, TX).

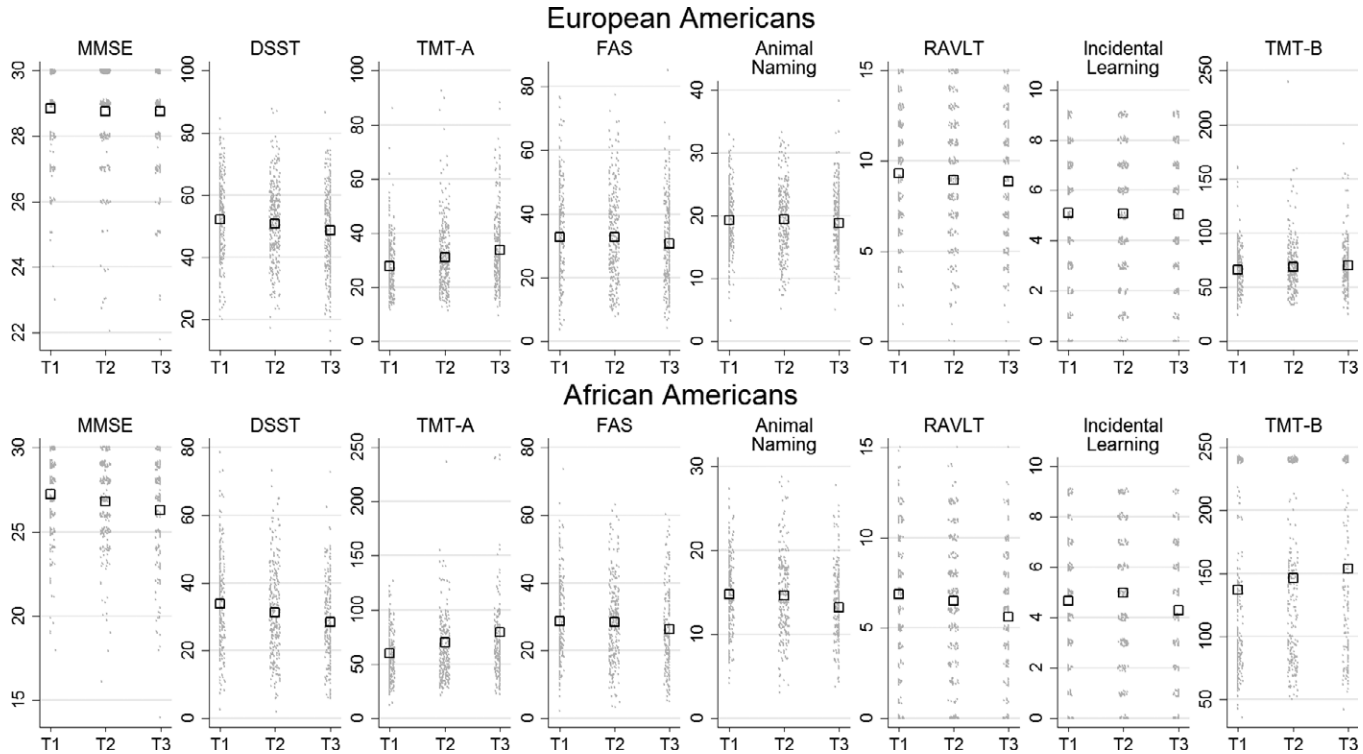

Figure 1. Raw cognitive score means according to race-stratified soluble tumor necrosis factor receptor 2 inflammatory tertile. Open squares indicate raw cognitive score means with individual raw cognitive scores displayed as points within each tertile. MMSE = Mini-Mental State Examination; DSST = Digit Symbol Substitution Task; TMT-A = Trail-Making Test Part A; RAVLT = Rey Auditory Verbal Learning Test; Incidental Learning—Wechsler Adult Intelligence Scale-III Incidental Learning Task; TMT-B—Trail-Making Test Part B; T1 = Tertile 1; T2 = Tertile 2; T3 = Tertile 3.

RESULTS

Characteristics are shown for participants with inflammatory marker data, stratified according to race and presence versus absence of cognitive data (Table 1). AAs were older and more likely to be female, to have diabetes mellitus, to have hypertension, to have ever smoked, to have a higher BMI, and to have higher CRP and IL6 and lower sTNFR1 levels; and sTNFR2 levels were similar in AAs and EAs. MMSE scores ranged from 14 to 30 (mean 27.9 ± 2.3). Fourteen AAs (2.0%) and eight EAs (1.1%) met race-specific criteria for cognitive impairment.[37]

All cognitive data were missing in 271 (22%) EAs and 421 (32%) AAs. In EAs, missing data were associated with being younger ($P = .02$) and male ($P = .008$) and having diabetes mellitus ($P = .04$). AAs who were missing cognitive data were more likely to have diabetes mellitus ($P = .003$) and to have a higher BMI ($P = .03$), a lower education level ($P < .001$), and higher levels of all inflammatory markers (sTNFR1, $P = .005$; sTNFR2, $P = .006$; CRP, $P = .01$; and IL6, $P = .006$) than AAs with cognitive data (Table 1).

Mean race-stratified cognitive scores according to inflammatory tertiles differed in AAs and EAs (Figure 1). For example, in AAs, all cognitive measures were worse with increasing tertile of sTNFR2. In EAs, only processing speed ($P < .001$) and executive function ($P = .03$) were associated with sTNFR2 (Table 2, Figure 1). In AAs, sTNFR1 was also associated with cognitive domains (all $P < .05$), except for memory, whereas in EAs, processing speed ($P < .001$), language ($P = .011$), executive function ($P < .001$), and marginally memory ($P = .097$) were associated with sTNFR1. CRP was associated with memory in EAs ($P = .04$), but no associations were observed between cognition and CRP or IL6 in AAs. IL6 was associated with processing speed ($P < .001$), language ($P < .002$), and executive function ($P = .03$) in EAs (Table 2, Figure 1).

In adjusted models, every 1-SD increase in sTNFR2 was associated with a 0.11-SD lower MMSE score in AA ($\beta = -0.11$, 95% confidence interval (CI) = −0.20 to −0.03, $P = .009$). The data did not support a similar association in EAs ($\beta = 0.03$, 95% CI = −0.01–0.07, $P = .14$); the interaction term supported a different relationship according to race ($\beta = -0.14$, 95% CI = −0.24 to −0.05, $P = .003$, Figure 2, Table 3). Similar to the MMSE outcome, the data supported inverse associations between sTNFR2 and all other cognitive domains for AAs but not EAs. (Table 3, Figure S1) Each SD increase in sTNFR2 in AAs was associated with poorer performance in processing speed ($\beta = -0.11$, 95% CI = –0.16 to −0.07, $P < .001$), language ($\beta = -0.08$, 95% CI = −0.13 to −0.03, $P = .002$), memory ($\beta = -0.0$, 95% CI = −0.16 to −0.02, $P = .008$), and executive function ($\beta = -0.07$, 95% CI = −0.13 to −0.01, $P = .03$). The inferences were the same in extended adjusted models (data available on request).

Higher sTNFR1 in AAs was associated with slower processing speed ($\beta = -0.08$, 95% CI = −0.12 to −0.04, $P < .001$) and executive function in adjusted models (Figure S1, Table 3: $\beta = -0.08$ 95% CI = −0.14 to −0.02, $P = .008$). The associations between sTNFR1 and MMSE or language in AAs were similar in magnitude but did not reach statistical significance (MMSE: $\beta = -0.07$, 95% CI = −0.16–0.0, $P = .09$; language: $\beta = -0.04$, 95% CI = −0.09–0.00, $P = .07$). In AAs, higher CRP was associated with slower processing speed ($\beta = -0.04$, 95%

Table 1. Participant Characteristics According to Race and Cognitive Data

Characteristic	European Americans		African Americans	
	With Cognitive Data, n = 960	Missing Cognitive Data, n = 272	With Cognitive Data, n = 1,005	Missing Cognitive Data, n = 474
Age, mean ± SD	59.2 ± 10.0	57.6 ± 10.9	62.9 ± 8.7	63.3 ± 10.9
Female, %	565 (59)	135 (50)	707 (70)	341 (72)
Body mass index, kg/m^2, mean ± SD	30.5 ± 6.0	31.6 ± 7.4	31.3 ± 6.3	32.4 ± 7.6
Hypertension, %	706 (74)	191 (70)	789 (79)	385 (81)
Diabetes mellitus, %	131 (14)	51 (19)	270 (27)	164 (35)
Never smoked, %	466 (49)	142 (52)	398 (40)	196 (41)
Education, %				
<12 years	51 ± 7	15 ± 7	301 ± 36	213 ± 52
12 years	402 ± 52	116 ± 53	279 ± 33	112 ± 28
Some college	139 ± 18	38 ± 17	18 ± 2	7 ± 2
≥College degree	182 ± 23	51 ± 23	246 ± 29	75 ± 18
sTNFR1, pg/mL, mean ± SD	1,362 ± 681	1,480 ± 947	1,171 ± 622	1,318 ± 754
sTNFR2, pg/mL, mean ± SD	1,953 ± 797	1,932 ± 884	1,878 ± 811	2,065 ± 976
C-reactive protein, SI, mean ± SD	40.4 ± 48.0	39.5 ± 48.4	53.9 ± 61.2	60.9 ± 63.6
Interleukin 6, SI, mean ± SD	1.11 ± 0.87	1.23 ± 0.97	1.23 ± 0.87	1.35 ± 0.91

SD = standard deviation; sTNFR = soluble tumor necrosis factor receptor.

Table 2. Cognitive Outcomes According to Race-Stratified Soluble Tumor Necrosis Factor Receptor Tertile

Cognitive Outcome	European Americans				African Americans			
	Tertile 1 (252–1,554)	Tertile 2 (1,544–2,084)	Tertile 3 (2,084–6,290)	*P*-Value for Trend	Tertile 1 (286–1,495)	Tertile 2 (1,495–1,995)	Tertile 3 (1,995–6,290)	*P*-Value for Trend
	Mean ± SD				Mean ± SD			
Mini-Mental State Examination (range 0–30)	28.9 ± 1.34	28.8 ± 1.58	28.8 ± 1.49	.85	27.3 ± 2.30	26.9 ± 2.49	26.3 ± 2.87	<.001
Digit Symbol Substitution Test (range 0–93)	52.5 ± 12.1	51.2 ± 13.0	49.1 ± 12.8	.006	34.2 ± 13.6	31.5 ± 13.4	28.8 ± 12.9	<.001
Trail-Making Test Part A, seconds	28.2 ± 10.8	31.5 ± 12.7	34.0 ± 14.2	<.001	61.0 ± 31.1	70.9 ± 43.2	80.3 ± 54.4	<.001
FAS, number of words	33.1 ± 14.2	33.1 ± 14.1	31.1 ± 13.2	.17	29.1 ± 11.5	28.7 ± 12.3	26.6 ± 11.7	.05
Animal Naming, number of animals	19.5 ± 4.82	19.5 ± 5.41	19.0 ± 4.78	.22	14.9 ± 4.30	14.8 ± 4.81	13.4 ± 4.23	<.001
Rey Auditory Verbal Learning Test (range 0–15)	9.37 ± 3.11	9.01 ± 3.43	8.94 ± 3.29	.25	6.95 ± 3.48	6.58 ± 3.58	5.68 ± 3.34	<.001
Wechsler Adult Intelligence Scale -III Incidental Learning Task (range 0–93)	5.15 ± 2.42	5.12 ± 2.48	5.09 ± 2.45	.95	4.72 ± 2.52	5.02 ± 2.63	4.33 ± 2.46	.02
Trail-Making Test Part B, seconds	67.2 ± 20.3	70.0 ± 24.6	71.2 ± 22.2	.12	138.1 ± 66.5	147.4 ± 65.3	154.7 ± 68.5	.04

SD = standard deviation.

Figure 2. Differential associations between soluble tumor necrosis factor receptor 2 (sTNFR2) and Mini-Mental State Examination (MMSE) score in African Americans (AAs: dark gray) and European Americans (EAs: light gray) from adjusted models. Solid lines are regression lines with shaded confidence bounds. Dashed lines are LOWESS nonlinear smoothers (diagnostic check). Race specific standard deviations (SDs) and standardized beta coefficients are shown with subscripted lower and upper 95% confidence limits (lower confidence limit "LCL" and upper confidence limit "UCL"), displayed as $_{LCL}\beta_{UCL}$.

CI = −0.070 to −0.010) $P = .02$), and higher IL6 was associated with poorer executive function ($\beta = -0.07$, 95% CI = −0.12 to −0.01, $P = .02$) (Table 3, Supplemental Figure).

In EAs, sTNFR1 was associated only with processing speed ($\beta = -0.05$, 95% CI = −0.08 to −0.01, $P = .007$); sTNFR2, IL6, and CRP were not statistically associated with any cognitive domain (Supplemental Figure, Table 3).

Sensitivity analyses using weighted GEEs suggested that the reported results comparably or more conservatively estimate associations between inflammatory markers and cognitive function (Supplementary Table).

DISCUSSION

In a cohort of EAs and AAs with hypertension and their siblings (with and without hypertension), substantial proportions of whom had other risk factors for cardiovascular disease, inflammatory markers were differently associated with cognitive function in AAs and EAs. In AAs, a biomarker of TNFα activity was associated with five domains of cognitive function, whereas IL6 and CRP were associated only with executive function and processing speed, respectively; in EAs, only markers of TNFα activity were associated with a single cognitive domain, processing speed. Although the cohort overall may be considered at high risk of cardiovascular disease, cardiovascular risk factors were also more prevalent in AAs than EAs. These findings suggest that, in these young to old AAs with hypertension or a strong family history of hypertension and prevalent cardiovascular risk factors, TNFα activity, and perhaps IL6 and CRP, may be important risk factors for cognitive dysfunction.

Table 3. Relationships Between Standardized Cognitive Domains and Standardized Inflammatory Markers in European Americans and African Americans

Cognitive Domain	sTNFR1		sTNFR2		High-Sensitivity C-Reactive Protein		Interleukin-6	
	European Americans	African Americans	European Americans	African Americans	European Americans	African Americans	European Americans	African Americans
	Standardized β (95% Confidence Interval) *P*-Value							
Global cognition	0.01 (−0.03–0.05) .68	−0.07 (−0.16–0.01) .09	0.03 (−0.01–0.07) .14	−0.11 (−0.20 to −0.03) .009	0.02 (−0.02–0.06) .33	0.01 (−0.05–0.08) .71	0.03 (−0.02–0.07) .22	−0.00 (−0.09–0.09) .95
Processing speed	−0.05 (−0.08 to −0.01) .007	−0.08 (−0.12 to −0.04) .001	−0.03 (−0.07–0.00) .08	−0.11 (−0.16 to −0.07) .001	−0.03 (−0.08–0.01) .11	−0.04 (−0.07 to −0.01) .024	−0.01 (−0.05–0.03) .46	−0.03 (−0.07–0.02) .20
Language	−0.03 (−0.08–0.03) .36	−0.04 (−0.09–0.00) .07	−0.02 (−0.07–0.04) .56	−0.08 (−0.13 to −0.03) .002	−0.03 (−0.08–0.03) .36	−0.03 (−0.06–0.01) .12	−0.03 (−0.09–0.02) .26	−0.02 (−0.07–0.02) .33
Memory	−0.02 (−0.09–0.05) .57	0.01 (−0.06–0.09) .78	0.02 (−0.04–0.08) .53	−0.09 (−0.16 to −0.02) .008	−0.01 (−0.06–0.04) .68	−0.02 (−0.07–0.03) .46	−0.02 (−0.08–0.03) .38	−0.02 (−0.08–0.05) .64
Executive function	−0.01 (−0.05–0.03) .63	−0.08 (−0.14 to 0.02) .008	−0.01 (−0.05–0.03) .55	−0.07 (−0.13 to −0.01) .03	−0.02 (−0.06–0.02) .24	−0.03 (−0.08–0.02) .23	0.02 (−0.02–0.06) .36	−0.07 (−0.12 to −0.01) .02

sTNFR = soluble tumor necrosis factor receptor.
Adjusted for age, sex, and education and accounting for familial clustering.

One explanation for these findings in this population could involve inflammatory-mediated cerebrovascular disease. Cardiovascular risk factors, inflammation,[5,7,13,38,39] brain structure abnormalities,[40] and poor cognitive function,[41,42] particularly executive function[41] and processing speed,[41] are interrelated. Mechanisms linking blood pressure to cognition are especially relevant for this study population and have been classified as functional (e.g., endothelial dysfunction or vascular dysregulation; altered blood flow, including nocturnal dipping patterns; reduced amyloid clearance), structural (e.g., white matter hyperintensities, atrophy), pharmacological (related to renin-angiotensin system), stroke related, and other (including hypertension with insulin resistance or impaired insulin signaling centrally).[43] AAs are disproportionately burdened by cardiovascular disease[44] and may exhibit heightened responses and greater endothelial dysfunction in response to inflammatory stimuli in vasculature, specifically TNFα pathways.[23] Furthermore, TNFα upregulation has been observed in individuals with hypertension,[45] and more than 70% of this cohort was hypertensive, whereas the remainder had at least two siblings with hypertension before age 60. Thus, inflammation may mediate cognitive decline through arteriosclerotic disease in the brain but may also adversely affect cognition through direct effects of inflammation on synaptic plasticity, neurogenesis, and neuromodulation that affect cognition.[46] High inflammatory biomarker levels can occur for a number of reasons, and mechanisms explaining the link between inflammation and cognition in this cross-sectional cohort study could not be elucidated, although these findings can be considered hypothesis generating in a sample of AAs most of whom had hypertension.

These findings further complement and expand upon those of other studies linking inflammation and cognition[4,6–10,13–18,47] by reporting findings from a relatively large AA cohort across a broad age range. Studies in older adults demonstrate associations between higher TNFα activity and poorer cognitive function,[10] higher TNFα activity in individuals with VaD than in those with AD,[18] and higher TNFα activity in individuals with VaD or AD than in controls.[18,48] In this cognitively unimpaired cohort aged 28 to 91, associations were found between inflammation and poor cognitive function in AAs. A longitudinal Swedish study that showed higher baseline sTNFR1 and sTNFR2 levels in persons with mild cognitive impairment who converted to dementia than in those with mild cognitive impairment who remained stable or in controls supported these findings.[12] A relationship between TNFα and executive function decline, but not other cognitive domains, was observed in the largely EA Framingham Offspring cohort.[10] Associations were observed with processing speed only in the GENOA EA. Differences in the cohorts' prevalent cardiovascular risk factors, with the GENOA cohort having a greater burden, might explain some of the inconsistency. In addition, the current analysis was cross-sectional, and the Framingham Offspring study was longitudinal.

The Framingham Offspring and GENOA cohorts were younger than many participants in studies of inflammation and cognition. Findings in these younger cohorts are of particular interest because interventions to halt or delay cognitive decline may be more effective in earlier stages. It would

also be of interest to see whether interventions that target the conditions that cause inflammation are more successful than interventions that target existing inflammation.

Although the individual estimates of associations between standardized inflammatory biomarkers and standardized cognitive measures may appear small, going from lowest to highest sTNFR2 values, there was an average 2-point difference in MMSE score, which is clinically meaningful. To put the sTNFR2 effect further into context, an increase in 1 SD of sTNFR2 ($\beta = -0.11$) would be similar to a 5-year difference in age (age $\beta = -0.02$ per year); across the range of sTNFR2 from 252 to 2,690 μg, this would be similar to 20 years of aging.

Some limitations warrant further discussion. The different results according to race could be due to regional differences in the AA and EA populations, because study sites were race specific. Regardless, the relationships are of interest. In addition to potential race and site effects, the higher risk profile in AAs (e.g., older age; more obesity, hypertension, diabetes mellitus) could contribute to differential findings. This explanation is of particular interest because it might identify mechanisms that are more relevant in populations with prevalent cardiovascular risk factors. In addition, this study was limited to four inflammatory markers (CRP, sTNFR1 and 2, and IL6), even though other proinflammatory markers have been found to be associated with cognition, including other ILs and serum amyloid A.[49,50] Nevertheless, the biomarkers in the current study are among those with biological plausibility and some evidence in other studies, although mostly in EAs, that they are important in vascular and nonvascular cognitive impairment. Numerous triggers can cause inflammatory biomarkers to be high, and the influence of other conditions that increase inflammation could not be excluded, although the results remained significant even after accounting for several comorbidities associated with inflammation, including cardiovascular disease and diabetes mellitus. In addition to adjusting for other potential confounders in parsimonious and extended adjusted models, standard approaches of stratification were included, and sensitivity analyses were conducted for potential informative missingness effects. Although the cognitive measures may not detect early decline, significant relationships were observed in this population. Additional limitations include the cross-sectional design, which limits inferences of causality. Volunteer bias may limit generalizability to dissimilar populations, but the findings reported are among a few reporting such relationships in AAs. Longitudinal studies could address some limitations by assessing temporal associations between inflammation and cognitive decline.

CONCLUSION

Inflammation is increasingly recognized as an important contributor to numerous health outcomes. Deleterious effects on cognitive function may be especially apparent in AAs with vascular risk factors. The associations between inflammation and cognitive function across a broad age spectrum in cognitively unimpaired AAs with vascular risk factors require further study to ascertain pathways through which inflammation, specifically TNFα activity, may erode cognitive function. In addition, studies targeting modifiable vascular risk factors and effects on inflammation and cognitive function in at-risk populations are needed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Associations Between standardized inflammatory markers and cognitive domains, adjusted for age, sex, and education and accounting for familial clustering. Regression coefficients with lower and upper confidence limits are shown. Black lines indicate statistically significant results. sTNFR, soluble tumor necrosis factor receptor; CRP, high sensitivity C-reactive protein; IL6, interleukin 6; MMSE, Mini-Mental State Examination; PS, Processing Speed; executive function, Executive Function.

Tables S1. Relationships Between Cognitive Domains and Inflammatory Markers in European and African Americans. Sensitivity to Missing Cognitive Outcomes Comparing Generalized Estimating Equations (GEE) and Weighted GEE (wGEE).

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