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Research Article

Inflammatory Biomarkers Predict Domain-Specific Cognitive Decline in Older Adults

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Abstract

Background: Vascular risk factors, including inflammation, may contribute to dementia development. We investigated the associations between peripheral inflammatory biomarkers and cognitive decline in five domains (memory, construction, language, psychomotor speed, and executive function).

Methods: Community-dwelling older adults from the Ginkgo Evaluation of Memory Study (n = 1,159, aged 75 or older) free of dementia at baseline were included and followed for up to 7 years. Ten biomarkers were measured at baseline representing different sources of inflammation: vascular inflammation (pentraxin 3 and serum amyloid P), endothelial function (endothelin-1), metabolic function (adiponectin, resistin, and plasminogen activating inhibitor-1), oxidative stress (receptor for advanced glycation end products), and general inflammation (interleukin-6, interleukin-2, and interleukin-10). A combined z-score was created from these biomarkers to represent total inflammation across these sources. We utilized generalized estimating equations that included an interaction term between z-scores and time to assess effect of inflammation on cognitive decline, adjusting for demographics (such as age, race/ethnicity, and sex), cardiovascular risk factors, and apolipoprotein E ε4 carrier status. A Bonferroni-adjusted significance level of .01 was used. We explored associations between individual biomarkers and cognitive decline without adjustment for multiplicity.

Results: The combined inflammation z-score was significantly associated with memory and psychomotor speed ($p < .01$). Pentraxin 3, serum amyloid P, endothelin-1, and interleukin-2 were associated with change in at least one cognitive domain ($p < .05$).

Conclusion: Our results suggest that total inflammation is associated with memory and psychomotor speed. In particular, systemic inflammation, vascular inflammation, and altered endothelial function may play roles in domain-specific cognitive decline of nondemented individuals.

Keywords: Inflammation—Cognitive decline—Vascular—Biomarkers—Longitudinal

Dementia, including Alzheimer's disease (AD), was estimated to affect 44 million people worldwide in 2014, and this prevalence estimate is expected to double by 2030 (1). Biomarkers that could track subclinical levels of disease to stabilize, delay onset, or prevent dementia could be crucial in devising therapies to curb the rising rates of dementia and its growing cost of care. Both vascular and neurodegenerative components contribute to the development and/or progression of dementia and its subtypes (2). Vascular risk factors which increase with age may damage brain capillaries; this may lead to stroke on its own, which may then initiate and sustain cognitive impairment (3). Various sources of inflammation contribute to vascular disease, including general and vascular inflammation, endothelial function, oxidative stress, and metabolic-related inflammation.

Systemic inflammation is a risk factor for cardiovascular disease (CVD) and atherosclerosis (4) and may cross the blood–brain barrier to provoke inflammatory responses that cause neurodegeneration and cognitive impairment (5). Interleukin (IL)-6, a marker of systemic inflammation, has been linked to cognitive decline and

alterations in brain morphology (5). Other interleukins that modulate inflammation include IL-2 and IL-10 (6). Vascular inflammation is also crucial in the pathogenesis of atherosclerosis and vascular disease (4). It may contribute to cerebral small-vessel disease and cerebral infarcts, which may lead to cognitive impairment and dementia (7). Pentraxin 3 (PTX3) and serum amyloid P (SAP) are both members of the pentraxin family and markers of vascular inflammation; they have been found in atherosclerotic lesions (8–10).

Endothelial dysfunction may result in vascular lesions, vasoconstriction, thrombosis, and plaque rupture—all contributors to CVD (11). It may also disrupt cerebral blood flow and lead to unwanted oscillations in perfusion pressure (7). During endothelial dysfunction, the potent proinflammatory vasoconstrictor endothelin-1 (ET-1) may be increased markedly (12). This dysfunction has led to considerable efforts to develop pharmacologic therapies that alter ET-1 function (13). In addition, endothelial damage may be caused by oxidative stress, which may also lead to inflammation and atherosclerosis (14). The receptor for advanced glycation end products (RAGE) is a receptor for products of nonenzymatic glycation and oxidation of proteins and lipids, modulates vascular disease (15), and mediates the influx of circulating Aβ into the brain (16).

Metabolic function is also important in vascular pathophysiology. Obesity is a strong risk factor for CVD and cognitive performance (17). Moreover, insulin resistance-associated impairment in cerebrovascular reactivity has been suggested to contribute to poor cognition in those with metabolic syndrome (17). Adiponectin and resistin are inflammatory markers elevated in metabolic disorders such as obesity (18,19). Plasminogen activator inhibitor-1 (PAI-1) is a serine protease which converts plasminogen to plasmin and is overexpressed during obesity (20).

These different sources of inflammation, although potentially inter-related, represent various facets of vascular disease and may exert disparate effects on cognition. We used data from the Ginkgo Evaluation of Memory Study (GEMS) to investigate the associations between inflammation and cognition in an elderly population. We investigated 10 biomarkers that represent different sources of inflammation: general inflammation (IL-6, IL-2, and IL-10), vascular inflammation (PTX3 and SAP), endothelial function (ET-1), oxidative stress (RAGE), and metabolic function (adiponectin, resistin, and PAI-1). Although we acknowledge that there are other biomarkers that may reflect these functions, we believe that those selected for this study provide a good representation of major sources of inflammation. As we were interested in the association between the combined inflammation from various sources and cognitive decline, we pooled data from the 10 biomarkers and created a *z*-score representing the combined inflammation from these different sources. A previous study using the GEMS study did not find strong evidence of associations between inflammatory biomarkers and the modified Mini-Mental State Examination (3MSE) (21). However, inflammation may be related to specific domains of cognition, which may be superficially examined in a global measure of cognition such as the 3MSE. We tested associations between this *z*-score and scores on tests of five cognitive domains: memory, construction, language, psychomotor speed, and executive function. We also explored the association between the individual biomarkers and cognition test scores.

Methods

Study Design and Population

GEMS was a double-blind, placebo-controlled randomized trial to determine the efficacy of *Ginkgo biloba* in the prevention of dementia in older adults (22). The study enrolled 3,069 adults free of prevalent dementia, aged 75 or older, and ended in 2008 after up to 8 years of follow-up for dementia and its subtypes. Participants were recruited using voter registries and purchased mailing lists from four sites: Hagerstown, Maryland (Johns Hopkins); Pittsburgh, Pennsylvania (University of Pittsburgh); Sacramento, California (University of California, Davis); and Winston-Salem and Greensboro, North Carolina (Wake Forest University) (22). Participants were evaluated every 6 months for cognitive decline and dementia onset during follow-up. Results from the clinical trial indicated no differences between *Ginkgo biloba* and placebo groups for the primary outcomes of dementia, AD, mild cognitive impairment, mortality, and CVD (22). Inflammatory biomarker levels were measured in 1,319 participants. The final analytical sample included 1,182 participants who had at least two non-missing scores on the five neuropsychological tests assessed.

Neuropsychological Tests

All participants underwent a full neuropsychological battery at baseline (22). Over the next 7 years, clinic visits to evaluate cognitive function were completed every 6 months as follows: From the second to sixth half-yearly visit, the neuropsychological battery was only administered if the follow-up score had declined from baseline beyond a predetermined threshold on two of three tests—the 3MSE, the Clinical Dementia Rating, or the cognitive subscale of the Alzheimer Disease Assessment Scale (22). From the seventh visit forward, the neuropsychological battery was administered yearly (every other visit).

The neuropsychological battery included a range of tests that measure performance in several cognitive domains. Here we focus on five tests: California Verbal Learning Test long delayed free recall for memory (23), 24-point modified Wechsler Adult Intelligence Scale-Revised block design for construction (24), 30-item Boston Naming Test for language (25), Trail Making Test A (in seconds) for psychomotor speed (26), and the Stroop color/word test (interference condition; number of colors named) for executive function (27). Higher scores represent higher cognition, except for the Trail Making Test A where lower scores reflect higher cognition.

Inflammatory Biomarkers and Covariates

Blood was drawn at baseline and stored as serum, plasma, and buffy coat for DNA. Biomarker levels were assayed from stored baseline blood samples at a central laboratory. PTX3, RAGE, and ET-1 were measured using ELISA (R&D Systems, Minneapolis, MN). SAP was measured using a single panel (Millipore, Billerica, MA). IL-10, IL-2, and IL-6 were measured using the Multiplex by Electrochemiluminescence (Meso Scale Discovery, Rockville, MD). Adiponectin, resistin, and PAI-1 were measured by immunoassay using Luminex technology (Millipore, Billerica, MA). A single composite inflammatory *z*-score was created using all 10 biomarkers by summing individual *z*-scores in the appropriate direction (all were positive except for SAP and IL-10, which were negative). A higher *z*-score represented more inflammation.

Other covariates used in regression analyses were age, race/ethnicity, sex, education, clinic location, treatment group, hypertension, diabetes, history of heart disease, body mass index (BMI), smoking status, alcohol intake, and presence or absence apolipoprotein E ε4 (ApoE ε4) genotype. Covariates were obtained by questionnaire, physical examination, or genotyping. ApoE ε4 carrier status was assayed from stored blood.

Data Analysis

Analytic models

Generalized estimating equations (GEEs) were used to evaluate the association between the combined inflammation biomarker *z*-score and cognitive decline with an autoregressive correlation structure. The same model was used in exploratory analyses of the associations between each biomarker and change in cognition scores. Our models included terms for baseline biomarker level, time, and an interaction between baseline biomarker and time. Coefficients for the interaction term between biomarkers and time represented the effect of baseline biomarker levels on change in cognition. The main effects term for baseline biomarkers reflected the baseline association between biomarkers and cognition (at $t = 0$). The coefficient for the interaction between baseline biomarker and time was of particular interest because it provided the association between baseline biomarker levels and cognitive decline, where biomarker levels were assessed prior to changes in cognition scores. We included main effects and interaction terms between the covariates and time for all covariates except age.

The distributions of all inflammatory biomarkers were right-skewed, except for SAP which was left-skewed. Each biomarker was logarithmically transformed (base 2) to assess relative changes and to satisfy model assumptions. Using log base 2, each unit higher log2(biomarker) can be interpreted as a twofold higher biomarker level. All adjustment covariates were assessed at baseline. The cognitive test scores were also standardized to allow for comparability of the effect sizes across different cognitive tests.

The analyses included three hierarchical models. The first model adjusted for age, race/ethnicity, sex, education, clinic site, and treatment groups. The second model additionally adjusted for BMI, smoking status, alcohol intake, hypertension, diabetes, and history of heart disease (history of heart disease was defined as ever having a heart attack, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, deep vein thrombosis, coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker implant, or defibrillator implant). Finally, the third model additionally adjusted for the presence of at least one copy of the ApoE ε4 allele. In secondary analyses, effect modification by ApoE ε4 carrier status, age, and sex were evaluated using multiplicative interaction terms.

A Bonferroni-adjusted significance level of $\alpha = .01$ was used to account for testing the associations between the cognition *z*-score and the five cognition tests within each of the three model stages. The baseline associations between biomarkers and cognition were also reported, but were not adjusted for multiple comparisons as they were not the primary focus of the analysis. The analyses for individual biomarkers and interactions were not adjusted for multiple comparisons because they were exploratory in nature.

Missing data

Missing data in the covariates were imputed five times using chained equations. All analyses were conducted using Stata version 12 (College Station, TX). There were missing data in four covariates: BMI (0.3% missing), smoking status (1.7% missing), alcohol intake (1.8% missing), and ApoE ε4 carrier status (20.1% missing). Some participants were also missing scores on neuropsychiatric tests. The missing data mechanism for outcomes was modeled using logistic regression, and propensity scores were generated for each participant at each time point based on baseline data, which included neuropsychological test scores, biomarker values, age, sex, smoking status, hypertension, 3MSE score, and BMI. Each complete observation was weighted by the inverse of the propensity score in GEE analyses. Sensitivity analyses were also conducted using participants with complete data to compare results from analyses with multiple imputation to those without.

Results

Sample Characteristics

Of the 1,182 participants included in the analysis (Table 1), 95% were White and 45% were women. Mean age of the entire study population was 78.9 (±3.4) years. Overall, 54.5% and 8.6% of participants were hypertensive and diabetic, respectively. Female participants were more likely to be hypertensive and never smokers and less likely to be diabetic or have a history of heart disease. Supplementary Table 1 summarizes baseline biomarker values and Supplementary Table 2 summarizes baseline scores on five neuropsychological tests representing different cognitive domains.

Association Between Baseline Inflammation and Cognitive Decline

Combined inflammation

Higher combined inflammation, as measured by the *z*-score, was associated with deficits in psychomotor speed (Table 2). In Model 1, every twofold higher inflammation *z*-score at baseline was associated with a 0.0044 *SD* decline in psychomotor speed per 6 months (95% confidence interval [CI]: 0.0022, 0.0067) and a –0.0029 *SD* decline in memory per 6 months (95% CI: –0.0046, –0.0011; Table 2). Additional adjustment for cardiovascular risk factors and ApoE ε4 in Models 2 and 3, respectively, did not change the results materially (Table 2). The combined inflammatory score tended to have stronger associations with cognitive decline than individual inflammatory biomarkers alone. Associations between language ($p = .013$) and executive function ($p = .036$) and inflammation were nominally significant; however, they did not reach statistical significance after correcting for multiple comparisons. Results of sensitivity analyses using participants with complete data were not materially different from those from the main analyses using multiple imputation (Supplementary Table 3). However, estimates were slightly attenuated in Model 3, where 21% of participants were removed mainly due to missing data in ApoE ε4 carrier status.

Individual markers of inflammation

Specific sources of inflammation were also associated individually with cognitive decline. Additional adjustment for cardiovascular risk factors and ApoE ε4 did not change the associations materially, although some associations were slightly attenuated. The associations between inflammatory biomarkers and each cognition test can be found in Supplementary Tables 4–8.

Both biomarkers of vascular inflammation (PTX3 and SAP) were associated with change in cognition. PTX3 was associated with decline in both psychomotor speed (β = 0.0165; 95% CI: 0.0058, 0.0273; Supplementary Table 7) and executive function (β = –0.0091; 95% CI: 0.0165, –0.0017; Supplementary Table 8). The association between PTX3 and psychomotor speed was the strongest observed among all the individual biomarkers. As opposed to PTX3, higher SAP was associated with a positive change in language (β = 0.0160; 95% CI: 0.0017, 0.0303; Supplementary Table 6) and executive function (β = 0.0141; 95% CI: 0.0014, 0.0268; Supplementary Table 8), where higher scores on these tests represent better cognition. General inflammation, as measured by IL-2, was associated with

Table 1. Demographics and Baseline Biomarker Values of Study Sample From the Ginkgo Evaluation of Memory Study by Sex (*n* = 1,182)

	Total (*n* = 1,182)	Female (*n* = 533)	Male (*n* = 649)
	n (%) or mean ± *SD*	*n* (%) or mean ± *SD*	*n* (%) or mean ± *SD*
Age (years, mean ± *SD*)	78.9 ± 3.4	79.1 ± 3.5	78.8 ± 3.2
Age group (%)			
80 and younger	733 (62.0)	326 (61.2)	407 (62.7)
80–84	362 (30.6)	160 (30.0)	202 (31.1)
85 and older	87 (7.4)	47 (8.8)	40 (6.2)
Race/ethnicity (%)			
White	1,124 (95.1)	503 (94.4)	621 (95.7)
Non-white	58 (4.9)	30 (5.6)	28 (4.3)
Education (years, mean ± *SD*)	14.3 ± 3.0	13.9 ± 2.9	14.6 ± 3.1
Body mass index (kg/m^2, mean ± *SD*)[a]	27.1 ± 4.3	26.9 ± 4.9	27.3 ± 3.7
Smoking status (%)[a]			
Never smoked	484 (41.7)	302 (57.5)	182 (28.6)
Former smoker	633 (54.5)	210 (40.0)	423 (66.4)
Current smoker	45 (3.9)	13 (2.5)	32 (5.0)
Alcohol (drinks per week, mean ± *SD*)[a]	3.6 ± 6.5	2.1 ± 4.8	4.8 ± 7.5
Hypertension (%)			
No	538 (45.5)	228 (42.8)	310 (47.8)
Yes	644 (54.5)	305 (57.2)	339 (52.2)
Diabetes (%)			
No	1,071 (91.4)	488 (92.2)	583 (90.7)
Yes	101 (8.6)	41 (7.8)	60 (9.3)
History of heart disease (%)[b]			
No	768 (65.0)	375 (70.4)	393 (60.6)
Yes	414 (35.0)	158 (29.6)	256 (39.4)
ApoE ε4 carrier (%)[a]			
No	693 (73.9)	299 (69.9)	394 (77.3)
Yes	245 (26.1)	129 (30.1)	116 (22.7)
Clinic			
WFU	298 (25.2)	142 (26.6)	156 (24.0)
UCD	359 (30.4)	146 (27.4)	213 (32.8)
JHU	191 (16.2)	88 (16.5)	103 (15.9)
Pittsburgh	334 (28.3)	157 (29.5)	177 (27.3)
Treatment group (%)			
Placebo	571 (48.3)	255 (47.8)	316 (48.7)
Gingko	611 (51.7)	278 (52.2)	333 (51.3)

Notes: ApoE ε4 = apolipoprotein E ε4; JHU = Johns Hopkins University; Pittsburgh, University of Pittsburgh; UCD = University of California, Davis; WFU = Wake Forest University.

[a]Covariate has missing data.

[b]Includes history of myocardial infarction, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, deep vein thrombosis, coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker implant, and defibrillator implant.

memory (β = −0.0040; 95% CI: −0.0074, −0.0006; Supplementary Table 4) and language (β = −0.0051; 95% CI: −0.0094, −0.0008; Supplementary Table 6). Finally, ET-1, a measure of endothelial dysfunction, was also associated with decline in language (β = −0.0126; 95% CI: −0.0240, −0.0013; Supplementary Table 6) and psychomotor speed (β = 0.0167; 95% CI: 0.0049, 0.0284; Supplementary Table 7). None of the biomarkers were associated with changes in construction test scores (Supplementary Table 5).

Baseline Association Between Inflammation and Cognition

The combined inflammation *z*-score was not associated with scores on any individual cognition tests at baseline (Table 3). However, higher PTX3 was found to be associated with lower construction score at baseline (β = −0.09; 95% CI: −0.17, −0.02). This association was attenuated only slightly with additional adjustment for cardiovascular risk factors and ApoE ε4 (data not shown). No other associations were found between individual inflammation biomarkers and cognitive test scores.

Discussion

The current study provides evidence linking inflammation to cognitive decline in persons without dementia. Our results suggest that psychomotor speed and memory are the two cognitive domains most strongly associated with higher combined inflammation from various sources. There is weaker evidence that combined inflammation was related to language and executive function, but associations did not reach Bonferroni-corrected significance. Individual inflammatory biomarkers including PTX3, ET-1, and IL-2 and lower levels of SAP were also associated with decline in cognitive function, providing supportive evidence that vascular inflammation, systemic inflammation, and endothelial dysfunction may be linked to cognitive decline.

Table 2. Association Between Twofold Higher Aggregated Inflammatory Biomarker *z*-Score and Rate of Change in Cognition Test Scores From the Gingko Evaluation of Memory Study

		Model 1[a]			Model 2[b]			Model 3[c]		
Test	*n*	Estimate	(95% CI)	*p*	Estimate	(95% CI)	*p*	Estimate	(95% CI)	*p*
Memory: California Verbal Learning Test Long Delayed Recall	1,144	−0.0029	(−0.0046, −0.0011)	.001	−0.0029	(−0.0046, −0.0011)	.001	−0.0028	(−0.0046, −0.0011)	.001
Construction: Block Design	1,146	−0.0013	(−0.0030, 0.0005)	.162	−0.0012	(−0.0029, 0.0006)	.190	−0.0012	(−0.0029, 0.0006)	.198
Language: Boston Naming Test	1,148	−0.0024	(−0.0042, −0.0005)	.013	−0.0023	(−0.0041, −0.0004)	.017	−0.0022	(−0.0041, −0.0004)	.018
Psychomotor speed: Trail Making Test A	1,145	0.0044	(0.0022, 0.0067)	<.001	0.0043	(0.0021, 0.0066)	<.001	0.0043	(0.0021, 0.0066)	<.001
Executive function: Stroop Task	1,023	−0.0017	(−0.0034, −0.0001)	.036	−0.0018	(−0.0034, −0.0002)	.029	−0.0018	(−0.0034, −0.0001)	.034

Notes: CI = confidence interval.

[a]Adjusted for the following demographic variables: age, race/ethnicity, sex, education, clinic, and treatment group.

[b]Adjusted for demographics, body mass index, smoking status, alcohol consumption, and the following cardiovascular disease risk factors: hypertension, diabetes, and history of heart disease (heart attack, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, deep vein thrombosis, coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker implant, and defibrillator implant).

[c]Adjusted for demographics, body mass index, smoking status, alcohol consumption, cardiovascular disease risk factors, and having at least one copy of the apolipoprotein E ε4 gene.

Table 3. Baseline Association Between Twofold Higher Aggregated Inflammatory Biomarker *z*-Score and Cognition Test Scores From the Gingko Evaluation of Memory Study

		Model 1[a]			Model 2[b]			Model 3[c]		
Test	*n*	Estimate	(95% CI)	*p*	Estimate	(95% CI)	*p*	Estimate	(95% CI)	*p*
Memory: California Verbal Learning Test Long Delayed Recall	1,144	−0.010	(−0.027, 0.007)	.231	−0.010	(−0.027, 0.007)	.244	−0.009	(−0.025, 0.008)	.321
Construction: Block Design	1,146	−0.015	(−0.032, 0.002)	.087	−0.014	(−0.031, 0.003)	.102	−0.013	(−0.030, 0.004)	.135
Language: Boston Naming Test	1,148	−0.012	(−0.029, 0.005)	.173	−0.012	(−0.029, 0.005)	.161	−0.011	(−0.027, 0.006)	.218
Psychomotor speed: Trail Making Test A	1,145	0.003	(−0.013, 0.019)	.713	0.005	(−0.012, 0.022)	.556	0.005	(−0.012, 0.022)	.566
Executive function: Stroop Task	1,023	−0.009	(−0.026, 0.008)	.284	−0.011	(−0.028, 0.006)	.205	−0.010	(−0.027, 0.007)	.250

Notes: CI = confidence interval.

[a]Adjusted for the following demographic variables: age, race/ethnicity, sex, education, clinic, and treatment group.

[b]Adjusted for demographics, body mass index, smoking status, alcohol consumption, and the following cardiovascular disease risk factors: hypertension, diabetes, and history of heart disease (heart attack, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, deep vein thrombosis, coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker implant, and defibrillator implant).

[c]Adjusted for demographics, body mass index, smoking status, alcohol consumption, cardiovascular disease risk factors, and having at least one copy of the apolipoprotein E ε4 gene.

Our observation of associations between inflammation and psychomotor speed and memory is consistent with research findings that relate directly to brain function. Inflammation induced by typhoid vaccination, which increased circulating cytokines, perturbed neural reactivity within the substantia nigra and was associated with slower reaction times (28). Moreover, inflammation has been linked with disruption in long-term potentiation (LTP) and reduced neurogenesis in the hippocampus, a requisite structure for memory and learning (29). Activated (proinflammatory) microglia can reduce new cell survival and proliferation and may also affect their integration into pre-existing neural networks. Although neuroinflammation has been linked strongly to cognitive deficits, there are still gaps in the understanding of the role of peripheral inflammation (29). However, peripheral cytokines can communicate with the central nervous system by stimulating vagal afferent nerves or brain vascular endothelial cells to produce proinflammatory cytokines that induce symptoms including poorer memory consolidation (30).

In our analyses, both PTX3 and SAP, markers of vascular inflammation, were associated with change in cognition over time, providing support for the involvement of a vascular component-related cognitive decline. Cross-sectional studies have found PTX3 to be associated with lower cognition (31) but not AD or mild cognitive impairment (32). In our study, SAP was associated positively with language and executive function, suggesting that SAP may have a protective effect. Contrary to our results, prior studies of the association between SAP and AD have found either no association in cerebrospinal fluid (33,34) or a positive association in brains (35,36) comparing those with AD to those without. SAP is present in all amyloid deposits and has been suggested to prevent the proteolysis of Aβ fibrils, thereby allowing amyloid plaques to persist (37). However, addition of purified SAP to a synthetic Aβ peptide in vitro inhibits initial fibril formation and dose dependently increases the solubility of the peptide (38).

Our finding that higher peripheral ET-1 was associated with worse psychomotor speed and language provides evidence that endothelial dysfunction may be important for cognitive impairment and/or its progression. Consistent with our results, previous cross-sectional studies have found higher levels of ET-1 in AD brains compared with control tissues (39,40). It has been suggested that endothelial dysfunction may lead to hypoxia and inadequate blood supply, contributing to amyloid plaques and neurofibrillary pathology (41).

IL-2, a marker of systemic inflammation, was associated with decline in memory and language in our study. The hippocampus and dentate gyrus of rodents express IL-2 receptors, suggesting that IL-2 may impact memory and learning (42). Consistent with this hypothesis, IL-2 was associated with decline in memory in our analysis. In mice, IL-2 was found to modify LTP and cognitive performance by interacting with septohippocampal cholinergic nerve terminals in the hippocampus (42). IL-2 knockdown in mice led to impaired learning and memory performance and sensorimotor gating. Consistent with these results, IL-2 was found to be upregulated in the postmortem hippocampi of AD patients (43).

The association between inflammatory biomarker levels and change in the 3MSE was recently investigated in the same sample of GEMS participants (21). In that study, combined inflammation (same pooled measure as the current study) was not associated with decline in 3MSE scores, a measure of global cognition. However, our study results provide evidence that inflammation may be associated with domain-specific cognition, as we found combined inflammation to be associated with memory and psychomotor speed. There remains much uncertainty regarding the etiologies and functions of the biomarkers and which cognitive domains they are likely to impact. In the previous study of 3MSE, the investigators found evidence that PTX3 was associated with a greater hazard of cognitive decline among participants with mild cognitive impairment. SAP also tended to be inversely related with decline in 3MSE scores. These results are consistent with our results showing a positive association between PTX3 and decline in both psychomotor speed and executive function and an inverse association between SAP and decline in language.

We recognize several limitations to this study. First, missing outcome data were assumed to be missing at random, but this assumption cannot be tested directly from the existing data. Given the nature of cognition as measured from neuropsychological tests, it is possible that the missingness may depend on the outcome itself. In other words, those with lower cognition are more likely to miss visits or be lost to follow-up. However, there are no methods to account for data that are not missing completely at random, and thus we used an inverse probability weighting method under a missing not at random mechanism to account for the missing data as best as possible. Importantly, analyzing only participants with complete data did not change the results materially (Supplementary Table 3). Model 3 estimates were slightly attenuated, where approximately one fifth of participants were excluded due to missing ApoE ε4 carrier status. This is most likely due to reduced power in that analysis. Secondly, the sample consisted of elderly individuals aged 75 or older without cognitive deficits at baseline. It is quite possible that these participants were cognitively healthier than the general population, thereby reducing the generalizability of our results. Moreover, our exploratory analyses of individual biomarkers did not account for multiple testing because they were not the primary focus of the analysis; results from the exploratory analyses are preliminary and should be re-examined more rigorously in future studies. Finally, our biomarkers were obtained from blood and may not represent more relevant levels such as those in the cerebral spinal fluid.

The strengths of the study include the large size of the cohort, rigorous assessment of cognition and dementia, and availability of a large number of inflammatory biomarkers. In addition, the longitudinal design of the study and availability of nondemented older adults at baseline allow for the identification of candidate biomarkers that may identify subclinical disease and predict progression into worsened cognition or dementia. In our study, baseline biomarkers were associated predominantly with decline, as opposed to baseline cognition. This observation points to the need for longitudinal studies of inflammation and cognition, as cross-sectional relationships may not shed light on how inflammation may affect the trajectory of cognitive decline, or may even be misleading.

In summary, our study used longitudinal measures of cognition to assess the association between inflammatory biomarkers and mean levels of cognition test scores across several domains over time. We observed evidence that combined inflammation and inflammatory biomarkers of vascular health, endothelial function, and systemic inflammation were associated with cognitive decline in nondemented individuals. The domains of cognition impacted included memory, psychomotor speed, language, and executive function. The effect of different sources of inflammation on cognition is likely to differ, and further research is needed to confirm whether peripheral inflammation markers associated with cognition can be used to track subclinical dementia for early onset detection, prevention, or amelioration of the progressive cognitive decline in aging. As a subsequent therapeutic step, interventions to suppress specific inflammatory markers in midlife may potentially aid in preservation of cognitive and psychomotor skills in late life.

Supplementary Material

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

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