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Research Article

Interleukin-6 and C-Reactive Protein Levels and 9-Year Cognitive Decline in Community-Dwelling Older Women: The Women's Health and Aging Study II

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Abstract

Background. Elevated inflammation is a proposed mechanism relating chronic diseases to cognitive dysfunction. The objective of this study was to test the hypothesis that greater levels of inflammation, as measured by the proinflammatory cytokine interleukin-6 (IL-6) and C-reactive protein, are associated with faster rates of cognitive decline among cognitively intact community-dwelling older women.

Methods. We analyzed 336 women from the Women's Health and Aging Study II. Cognitive assessments were performed at baseline and every 18–36 months, and included the following domains: immediate and delayed memory (Hopkins Verbal Learning Test), psychomotor speed (Trail Making Test, Part A), and executive function (Trail Making Test, Part B). Aggregate measures of IL-6 and C-reactive protein, based on the average from visits one and two, were analyzed categorically. Random effects models were employed to test the relationship between tertiles of each inflammatory marker and changes in cognitive domain scores over 9 years.

Results. Moderate and high levels of IL-6 predicted early declines in psychomotor speed by 1.0 connection/min per year. There were no differences in baseline scores or rates of change across tertiles of IL-6 in memory or executive function. No differences were observed across tertiles of C-reactive protein for all cognitive domains.

Conclusions. Higher levels of serum IL-6 were associated with greater declines in psychomotor speed over 9 years. This finding could suggest that elevated IL-6 may result in microvascular changes that may lead to damage of myelin sheaths that line neuronal axons, leading to decreased neuron propagation and impaired processing speed; however, mechanistic studies are needed to evaluate these hypotheses.

Key Words: Interleukin-6—C-reactive protein—Psychomotor speed—Cognitive decline.

Inflammation has been linked to both cardiovascular disease (CVD) and diseases of the brain, including vascular dementia and Alzheimer's dementia (AD). With the aging of the U.S. population and greater incidence of chronic diseases compared to infectious diseases, recent literature has focused on exploring cardiovascular risk factors for cognitive decline and dementia. Elevated inflammation has been suggested as one possible mechanism relating such chronic diseases to cognitive dysfunction. Inflammatory markers have also been implicated in the development of amyloid beta peptides, a primary component of amyloid plaques that are the hallmark characteristic of AD.

An increasing number of studies have explored the associations between inflammation and dementia outcomes; however, far fewer have characterized inflammation in relation to preclinical domain-specific cognitive declines. In a cohort of Japanese Americans, participants in the highest quartile of C-reactive protein (CRP) had a three times greater risk for all-cause and cause-specific dementias (1). Similar results were observed in a population-based sample from the Netherlands (2), the Framingham Study and Uppsala Longitudinal study of Adult Men (3). Other studies have found that inflammatory markers, such as CRP and proinflammatory cytokine interleukin-6 (IL-6), did not independently predict a greater risk for dementia, but that in combination with other elevated inflammatory markers, a greater risk for dementia was observed (4).

Fewer studies have examined the association between inflammation and domain-specific cognitive declines. In a longitudinal study of older adults, inflammation was associated with global cognitive decline, but not declines in memory, intelligence, or processing speed (5). Another longitudinal study of aging examined the impact of inflammation on delayed memory recall, but did not include a test of immediate memory (6). Prior analyses have not studied inflammation-related cognitive decline in the domains of executive function and psychomotor speed, both of which are important to functional independence (7).

Inflammation may be a precipitating factor linking vascular diseases and dementia and age-related cognitive decline. The objective of this study was to test the hypothesis that higher levels of inflammation, as measured by serum IL-6 and CRP, are associated with faster rates of decline over 9 years in three major cognitive domains among cognitively intact community-dwelling older women: verbal memory (immediate and delayed), psychomotor speed, and executive function.

Methods

Study Population

The Women's Health and Aging Study (WHAS) II is a prospective cohort study that followed community-dwelling older adult women in Baltimore, Maryland. The primary aim of the study was to identify the causes and courses of disability. The participants in WHAS II were identified and selected randomly from the Health Care Financing Administration's Medicare eligibility list for 12 zip codes of Eastern Baltimore City and County. Participants in WHAS II were sampled to be representative of the two-thirds least disabled women. Inclusion was limited to women aged 70–79 years who had difficulty in no or only one area of physical functioning (ie, upper extremity function or basic self-care) and had intact cognitive function at baseline, as measured by a Mini-Mental State Examination (8) score ≥24. Specifics regarding this study have been described elsewhere (7,9). Written informed consent was obtained from all participants. The Johns Hopkins IRB approved all protocols.

Baseline data for WHAS II were collected between 1994 and 1996. Among the 880 women screened and eligible for WHAS II, 49.5% agreed to participate. Compared with those participants who were enrolled, those who declined to participate had less education and fewer diseases but did not significantly differ in race (7). Follow-up questionnaires were administered every 18–36 months. Data are currently available from six rounds of data collection with approximately 9 years of follow-up. Each round was separated by 1.5 years, except between rounds 3 and 4, which was separated by a 3-year interval. Of the 436 women enrolled in WHAS II, 387 had complete cognitive data at baseline and 363 had complete cognitive test data for baseline and at least one follow-up visit. Of these, 25 and 19 were missing baseline IL-6 and CRP values, respectively. Those with missing data were less educated, more likely to have CVD and more often nonwhite; however, they were no more depressed, overweight, or likely to smoke or drink than the nonmissing. The final analytic sample included 336 participants with available baseline IL-6 and CRP data.

Exposure: IL-6 and CRP

Nonfasting blood specimens were collected. A commercial immunosorbent assay was used to measure IL-6 in frozen specimens (High Sensitivity Quantikine Kit, R&D Systems, Minneapolis, MN). CRP was analyzed at Quest Diagnostics Laboratories (Teteroboro, NJ).

Outcome: Cognitive Test Scores

The cognitive domains assessed include verbal memory (immediate and delayed recall), psychomotor speed, and executive function. All cognitive tests were administered at baseline and all five follow-up visits.

The memory domain was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R) (10). Components include a test of both immediate and delayed recall. For immediate recall, participants were orally presented with a 12-word list to recall in a series of three trials. Following a 20-minute delay, participants were asked to recall the list. Scoring for the HVLT-R is based on the total number of correctly recalled words over three trials for immediate recall (maximum = 36) and for one trial of delayed recall (maximum = 12).

The psychomotor speed domain was assessed using the Trail Making Test, Part A, (TMT, Part A) (11). In a timed test, participants were presented with circled numbers 1–25 positioned randomly on one side of a paper. Participants were asked to connect the numbers in ascending order as fast as they could without taking their pencil off the paper. A maximum of 4 minutes was allocated to complete the task. Scoring for the TMT, Part A, was based on time (in seconds) to completion, with a possible range in scores from 0 to 240 seconds (a lower time indicates better performance).

Executive functioning governs goal-directed behavior, including initiation and inhibition of a task. The executive function domain was assessed using the Trail Making Test, Part B (TMT, Part B) (11). Following presentation of the TMT, Part A, participants were presented with numbers and letters positioned randomly on one side of a paper. Participants were asked to connect the numbers and letters in numeric-alpha ascending order (1-A-2-B-3-C) as fast as they could without taking their pencil off the paper. A maximum of 6 minutes was allocated to complete the task. Scoring for the TMT, Part B, is based on time (in seconds) to completion of task, with a possible range in scores from 0 to 360 seconds (a lower time indicates better performance). In keeping with previous literature and to account for non-normality of the TMT, Part A, and TMT, Part B, test times were

converted to number of connections per minute to capture speed to task completion ([7](#)).

Covariates

Covariates were selected based on a priori theory, prior literature, and univariate analyses suggesting that they were associated with both inflammation and cognitive test outcomes. Age (years), education (years), and body mass index were modeled as continuous variables. Race was dichotomized as Caucasian or African American. Smoking status was categorized as never, former, or current smoker. Alcohol use was dichotomized as yes/no based on the question, "Do you usually drink alcoholic beverages, including beer, wine, sherry, or liquor, at least once every week?" ([9](#)).

Cardiovascular diseases included heart attack or myocardial infarction, angina, congestive heart failure, stroke, and peripheral artery disease. All diseases and conditions in the WHAS studies were adjudicated by two physicians based on examination, medication list, radiographs, blood tests, and medical records ([9](#)). A standardized algorithm was also used to adjudicate diabetes at baseline ([9](#)). Hypertension was based on a self-report of a physician diagnosis. Depressive symptoms were measured using the Geriatric Depression Scale and analyzed continuously ([12](#)).

Analyses involving the TMT, Part B (and executive function domain [which included the TMT, Part B]) were further adjusted for continuous values of the TMT, Part A, to partition out the psychomotor speed component and better isolate the executive functioning task.

Statistical Analysis

IL-6 and CRP were analyzed categorically. Values were classified based on tertile cut points from the analytic sample and defined as low, moderate, or high. An aggregate measure, defined as the average of IL-6 and CRP values from rounds 1 and 2, was used to determine the tertile cut points. The cut points for IL-6 were: low (<2.34 pg/mL), moderate (2.34–3.42 pg/mL), and high (>3.42 pg/mL). The cut points for CRP were: low (≤2.0 mg/L), moderate (2.1–4.90 mg/L), and high (>4.90 mg/L). These cut points are consistent with previous studies of older adults ([6,13](#)).

A longitudinal analysis incorporating random effects for baseline cognitive function (ie, intercepts) and random effects for change (ie, slopes) was conducted. Separate models were run for each of the four cognitive tests. An interaction between the inflammatory marker and time in the random effects model was used to estimate the effect of the inflammatory marker on changes in domain-specific cognitive function over 9 years of follow-up. Because of a nonlinear trend in rates of cognitive decline, a two-piece spline term was incorporated at Year 3 to allow for the rate of cognitive decline to differ between Years 1–3 and 3–9 ([14](#)). All analyses were performed using STATA 13.0 (Stata Corp, College Station, TX).

Results

[Table 1](#) displays the baseline characteristics of the analytic sample (*n* = 336). The mean age (standard deviation, *SD*) was 74.0 (2.8) years. Most of the sample achieved at least a high-school education with the mean education (*SD*) of the sample being 12.8 (3.2) years. Fifteen percentage of the sample was nonwhite. The cohort had a relatively high prevalence of hypertension (46.7%) and CVD (80.0%), but a low prevalence of diabetes (7.7%). Sixty-six percentage of participants were using anti-inflammatory medications at

Table 1. Baseline Demographic and Cognitive Characteristics of WHAS II Participants (*N* = 336)

Characteristic	Analytic Sample (*N* = 336)
Age, years, mean ± *SD*	74.0 ± 2.8
Education, years, mean ± *SD*	12.8 ± 3.2
Nonwhite, *n* (%)	51 (15.2)
Clinical CVD, *n* (%)	269 (80.0)
Diabetes mellitus, *n* (%)	26 (7.7)
Hypertension, *n* (%)	157 (46.7)
Arthritis, *n* (%)	84 (25.0)
Difficulty with activities of daily living	22 (6.5)
BMI, kg/m², mean ± *SD*	26.5 ± 4.8
Current smoker, *n* (%)	34 (10.1)
Drinking status, *n* (%)	112 (33.3)
Anti-inflammatory medication use, *n* (%)	224 (66.7)
Interleukin-6, pg/mL, mean (IQR)	4.0 (2.2–4.1)
C-reactive protein, mg/L, mean (IQR)	5.1 (2–6)
HVLT—Immediate, words recalled, mean ± *SD*	23.0 ± 5.0
HVLT—Delayed, words recalled, mean ± *SD*	8.3 ± 2.6
TMT—Part A, seconds, mean ± *SD*	45.2 ± 18.5
TMT—Part A, number of connections/min, mean ± *SD*	36.3 ± 12.5
TMT—Part B, seconds, mean ± *SD*	125.9 ± 68.5
TMT—Part B, number of connections/min, mean ± *SD*	14.1 ± 5.8

Notes: BMI = body mass index; CVD = cardiovascular disease; HVLT = Hopkins Verbal Learning Test; IQR = Interquartile range; TMT = Trail Making Test; WHAS = Women's Health and Aging Study.

baseline. Means (*SD*) and ranges for baseline cognitive test scores in the sample, by tertiles of IL-6, are provided in [Table 2](#) (by tertiles of CRP: [Supplementary Table S1](#)). Baseline cognitive test performance did not differ significantly across tertiles of IL-6 or CRP for any of the cognitive tests. The distribution of cognitive test scores by tertiles of IL-6 and CRP are shown in [Supplementary Figures S1](#) and [S2](#), respectively, in the [Supplementary Material](#). Scatter plots of cognitive test scores across continuous IL-6 and CRP values are provided in [Supplementary Figures S3](#) and [S4](#), respectively, in the [Supplementary Material](#).

Annual rates of change between Years 1–3 and Years 3–9 in cognitive test scores are depicted for each tertile of IL-6 in [Table 3](#). No differences were observed at baseline or in rates of change across tertiles of IL-6 in the domains of memory and executive function. On the TMT, Part A, a measure of psychomotor speed, there were no significant differences in adjusted baseline cognitive test scores across tertiles of IL-6. Individuals with either moderate or high levels of IL-6 experienced a significant annual decline on psychomotor speed in Years 1–3, but not during Years 3–9, compared with individuals with a low IL-6. In Years 1–3, individuals with a moderate IL-6 level showed declines in psychomotor speed at an average rate of roughly 1.0 connection per minute per year (95% CI: –1.7, –0.4) compared with those with low IL-6. Individuals with high baseline IL-6 levels showed declines in psychomotor speed at an average rate of approximately 1.1 connections per minute per year (95% CI: –1.8, –0.5) compared with those with low baseline IL-6 levels during Years 1–3.

No differences in baseline measures or rates of change were observed across tertiles of CRP for all cognitive domains assessed ([Supplementary Table S2](#)). A sensitivity analysis, incorporating baseline anti-inflammatory medication use as a covariate, was performed

Table 2. Baseline Distribution of Cognitive Test Scores Across Tertiles of IL-6

Cognitive Test	Low IL-6 (<2.34 pg/mL), N = 96	Moderate IL-6 (2.34–3.42 pg/mL), N = 103	High IL-6 (>3.42 pg/mL), N = 137	p Value
Memory: HVLT—Immediate, mean ± SD (range)	23.6 ± 5.1 (11–35)	23.1 ± 5.1 (8–33)	22.5 ± 4.9 (7–32)	.27
Memory: HVLT—Delayed, mean ± SD (range)	8.5 ± 2.5 (0–12)	8.3 ± 2.9 (0–12)	8.1 ± 2.5 (0–12)	.25
Psychomotor speed: TMT—Part A*, mean ± SD (range)	35.0 ± 11.1 (12.7–65.5)	37.4 ± 12.8 (12.3–72.7)	36.3 ± 13.2 (9.4–84.7)	.55
Executive function: TMT—Part B*, mean ± SD (range)	14.6 ± 5.6 (3.4–30.6)	14.4 ± 6.1 (3.4–32.7)	13.5 ± 5.7 (4.6–30.6)	.34

Notes: HVLT = Hopkins Verbal Learning Test; IL-6 = interleukin-6; TMT = Trail Making Test.
*Speed to task completion = number of connections/min (higher scores are better).

and the results were unchanged. The coefficients and inferences were unchanged between the demographically adjusted and fully adjusted models (Supplementary Tables S3 and S4).

Discussion

In WHAS II, we observed that moderate and high levels of IL-6 predicted early declines in psychomotor speed by about 1.0 connection per minute per year. These findings both contradict and support the limited data reported previously on inflammation and age-related cognitive decline. Contrary to a study with similarly functioning older adult men and women, we found no association between inflammation and declines in memory (6). However, our study participants may have been healthier by virtue of higher education and with fewer comorbid conditions at baseline, which have been found to be protective against future cognitive decline and dementia risk (15). In a sample of older adults from Amsterdam, researchers found declines in processing speed over a 3-year follow-up, but only for high levels of α_1-antichymotrypsin, not for high levels of CRP or IL-6 (5). The literature is inconsistent and indicates the need for more research examining this association, particularly for specific cognitive domains, to elucidate the mechanistic pathway by which inflammation may influence the risk for and stages of accelerated cognitive decline and dementia.

An examination of the impact of inflammatory processes on age-related risk for cognitive decline, mild cognitive impairment, and subsequent dementia is important for identifying how inflammation contributes to causal pathways, as well as providing areas for targeted interventions. Cerebral white matter lesions and age-related myelin sheath degeneration have been associated with slowed processing speed as well as slowed gait speed in older adults (16–18). Recent data in animal models have supported these findings (19). Given the poorer psychomotor speed we observed among individuals with high levels of IL-6, we hypothesize that elevated IL-6 may result in microvascular changes in white matter integrity and myelination of axons. Myelin sheaths are a protective layer of lipid or fat that coats the axon to speed the transmission of signals from one neuron to another. Damage to the myelin sheaths results in poor propagation of signals between neurons and may possibly lead to reductions in reaction times and speed of mental processing. Related research in WHAS II guided this hypothesis by showing a benefit of high cholesterol on psychomotor speed (20). We suggested that high cholesterol levels, in older adults, might counteract the negative effects of the natural aging process, such as increased inflammation, by preventing myelin deterioration (20). Further neuroimaging

studies are needed to confirm these hypothesized mechanisms among those with cognitive impairment.

In an effort to further characterize this mechanistic pathway, others have examined the modifying effect of inflammation on metabolic syndrome and cognitive decline, and they found that the association was greatest among individuals with high levels of inflammation (21). Additional studies are needed to explore the effects of inflammation on cognition, and other potential modifying factors, such as cholesterol.

In this study, we found an association with IL-6, but not CRP. Dissimilar findings are expected. CRP, although sensitive, is a non-specific marker of inflammation (22). In a comprehensive analysis of inflammatory markers, researchers found that compared with CRP, higher IL-6 levels were more strongly associated with declines in physical and cognitive functions and incident CVD events (23). These seemingly stronger associations with IL-6, compared with CRP, have been replicated in studies of ischemic heart disease (24), diabetes (25), and non-AD (3). Furthermore, there are data to suggest that cytokines, including IL-6, are readily able to cross the blood–brain barrier. Activation of the peripheral immune system, as in the case of a bacterial infection, may induce a rapid release of cytokines and, if severe enough or amongst immune-comprised individuals, such as older adults, a prolonged neuroinflammatory response can occur peripherally and in the brain (26). Such a prolonged neuroinflammatory response in the brain has been linked to memory impairment (26).

These results are not without some limitations. First, the study population is community-dwelling older adult women who had intact baseline cognitive function, minimal functional limitations and were highly educated. Thus, the results may be less generalizable to more cognitively and functionally vulnerable populations. In addition, because this is a study of women, these results may not be extrapolated to men. However, this information is valuable considering the greater longevity among women compared with men and their greater susceptibility to living with disabling chronic conditions. Second, there are no defined clinical cut points for IL-6 and CRP in older adults. IL-6 and CRP were classified in this study according to the statistical distribution in our cohort and defined as low, medium, and high. This may result in misclassification of risk; however, a cut point of 2.5 pg/mL is evidenced as a point above which there is a much higher risk of developing adverse outcomes (27,28). A time-varying analysis of IL-6 or CRP was not conducted due to the missing data in later rounds of follow-up. Considering the acute fluctuations of inflammatory markers, future analyses should incorporate time-varying effects of IL-6 and CRP to improve

Table 3. Random Effects Models: Annual Rate of Change in Cognitive Test Scores, by Tertiles of IL-6 ($N = 336$)

Cognitive Test	Annual Rate of Change, Years 1–3				Annual Rate of Change, Years 3–9			
	Log (IL-6), N = 336	Low IL-6 (<2.34 pg/mL), N = 96	Moderate IL-6 (2.34–3.42 pg/mL), N = 103	High IL-6 (>3.42 pg/mL), N = 137	Log (IL-6), N = 336	Low IL-6 (<2.34 pg/mL), N = 96	Moderate IL-6 (2.34–3.42 pg/mL), N = 103	High IL-6 (>3.42 pg/mL), N = 137
Memory: HVLT—Immediate	0.3* (0.1, 0.4)	0.18 (−0.15, 0.50)	0.05 (−0.27, 0.36)	0.03 (−0.24, 0.31)	−0.2* (−0.4, −0.04)	−0.51 (−0.71, −0.31)	−0.35 (−0.56, −0.15)	−0.68 (−0.88, −0.49)
Memory: HVLT—Delayed	0.1* (0.03, 0.2)	−0.07 (−0.23, 0.08)	−0.05 (−0.20, 0.10)	−0.08 (−0.21, 0.05)	−0.1 (−0.1, 0.04)	−0.26 (−0.36, −0.16)	−0.27 (−0.38, −0.17)	−0.31 (−0.41, −0.21)
Psychomotor speed: TMT—Part A	−0.4* (−0.8, −0.05)	0.24 (−0.47, 0.94)	−1.04* (−1.73, −0.35)	−1.14** (−1.75, −0.54)	−0.3 (−0.7, 0.06)	−0.69 (−1.12, −0.26)	−0.86 (−1.30, −0.41)	−0.77 (−1.19, −0.34)
Executive function: TMT—Part B	−0.1 (−0.3, 0.1)	−0.54 (−0.84, −0.24)	−0.64 (−0.93, −0.34)	−0.62 (−0.88, −0.36)	0.001 (−0.1, 0.1)	−0.42 (−0.59, −0.25)	−0.45 (−0.63, −0.27)	−0.47 (−0.64, −0.31)

Notes: CVD = cardiovascular disease; HVLT = Hopkins Verbal Learning Test; IL-6 = interleukin-6; TMT = Trail Making Test. Models are adjusted for age, education, race, smoking, alcohol use, CVD, diabetes, hypertension, body mass index, depressive symptoms, and TMT—Part A (executive function only).

*$p < .05$.

**$p < .05$ for a significantly different slope compared with reference group (low IL-6).

accuracy with tested outcomes. A better understanding of the biological mechanism for the effects of inflammation on cognitive outcomes may warrant the use of a lag analysis when incorporating inflammation as time-varying. Third, the sample size for this analysis, specifically when categorizing the biomarkers, is small and we may have insufficient power to detect significant differences in cognitive function between tertiles of the inflammatory biomarkers. Declines in psychomotor speed may be due to new CVD events (eg, stroke) in this initially high-functioning group of women. Adjudicated incident events are not available in this cohort and are a limitation of this study. Self-reported incidence of events is available for a few diseases (Supplementary Table S5); however, the data have not been considered reliable and were, therefore, not included in this analysis. In addition, imaging and postmortem data from other observational studies suggest that the form of CVD we are hypothesizing as deleterious is subclinical and largely undetected when measured by incident events (16,29,30). Nonetheless, the number of participants reporting incident stroke was small ($n = 77$) and would likely not significantly alter the results. Lastly, 25% of participants reported arthritis; however, <1% had difficulty completing the task due to arthritis or hand tremors that could plausibly affect coordination or fine motor movements.

Much of the literature examining the associations between vascular disease and cognitive outcomes has found decrements in processing speed. Our finding that high levels of inflammation, particularly IL-6, results in decline in processing speed could indicate a mechanistic pathway between vascular disease and preclinical cognitive declines through chronic inflammatory processes. To further elucidate this hypothesis, future studies should explore the modifying and mediating effects of inflammation on vascular and nonvascular diseases and cognitive outcomes.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology. oxfordjournals.org/

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