

# Systemic inflammation during midlife and cognitive change over 20 years

## The ARIC Study

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*Neurology*® 2019;92:1-12. doi:10.1212/WNL.0000000000007094

## Abstract

### Objective

To examine the association between systemic inflammation measured during midlife and 20-year cognitive decline.

### Methods

Within the Atherosclerosis Risk in Communities cohort study, inflammatory biomarkers were measured during middle adulthood. We created an inflammation composite score using 4 blood biomarkers measured at visit 1 (fibrinogen, white blood cell count, von Willebrand factor, and factor VIII); we measured C-reactive protein (CRP) at visit 2. Cognition was assessed over 3 visits spanning 20 years using measures of memory, executive function, and language.

### Results

A total of 12,336 participants (baseline age 56.8 [5.7], 21% black, 56% women) were included. After adjusting for demographic variables, vascular risk factors, and comorbidities, each standard deviation (SD) increase in midlife inflammation composite score was associated with an additional 20-year decline of  $-0.035$  SD (95% confidence interval:  $-0.062$  to  $-0.007$ ) on the cognitive composite score. We found a similar association between each SD increase in midlife CRP level and additional 20-year cognitive decline ( $-0.038$  SD, 95% confidence interval:  $-0.057$  to  $-0.019$ ). Participants with a midlife inflammation composite score in the top quartile had a 7.8% steeper cognitive decline, compared to participants in the lowest quartile; CRP in the top quartile was associated with an 11.6% steeper cognitive decline. In cognitive domain-specific analyses, elevated midlife inflammatory markers were most consistently associated with declines in memory. Results were similar after adjusting for attrition using inverse probability weighting.

### Conclusions

Our findings highlight what may be an early pathogenic role for systemic inflammation as a driver of cognitive decline in the decades leading up to older adulthood.

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## Glossary

**ARIC** = Atherosclerosis Risk in Communities; **CRP** = C-reactive protein; **HDL** = high-density lipoprotein; **IPAW** = inverse probability of attrition weighting.

In light of the growing body of evidence implicating aberrant immune functioning in the pathophysiology of Alzheimer disease and related dementia,<sup>1</sup> understanding the relationship between inflammation and neurocognitive functioning has become a priority in recent years. The majority of studies linking systemic inflammation to cognitive impairment have been cross-sectional, and have therefore been unable to clarify the temporal relationship between systemic inflammation and cognitive outcomes. While several prospective studies have found greater rates of cognitive decline among individuals with higher levels of circulating inflammatory markers,<sup>2,3</sup> the majority of these studies measure inflammatory markers only during older adulthood and have brief follow-up periods ( $\leq 10$  years). Although age-related cognitive decline begins to accelerate during midlife,<sup>4,5</sup> it is currently unclear to what degree systemic inflammation may contribute to such declines. Similarly, it is unknown which aspects of cognition may be most vulnerable to the effects of systemic inflammation.

It is essential to examine the long-term effects of midlife systemic inflammation because it is during the midlife period when many of the pathologic processes underlying age-related cognitive impairment and dementia are thought to begin and to perhaps be most responsive to intervention. Using a large, biracial, community-based sample, we tested the hypothesis that elevated systemic inflammation during midlife is associated with greater cognitive decline over a 20-year period spanning from mid- to late-life. Given previous findings that suggest sex,<sup>6</sup> race,<sup>7,8</sup> and *APOE*  $\epsilon 4$  status<sup>9</sup> modify the association between systemic inflammation and neurologic

outcomes, we examined the moderating effects of each of these demographic factors.

## Methods

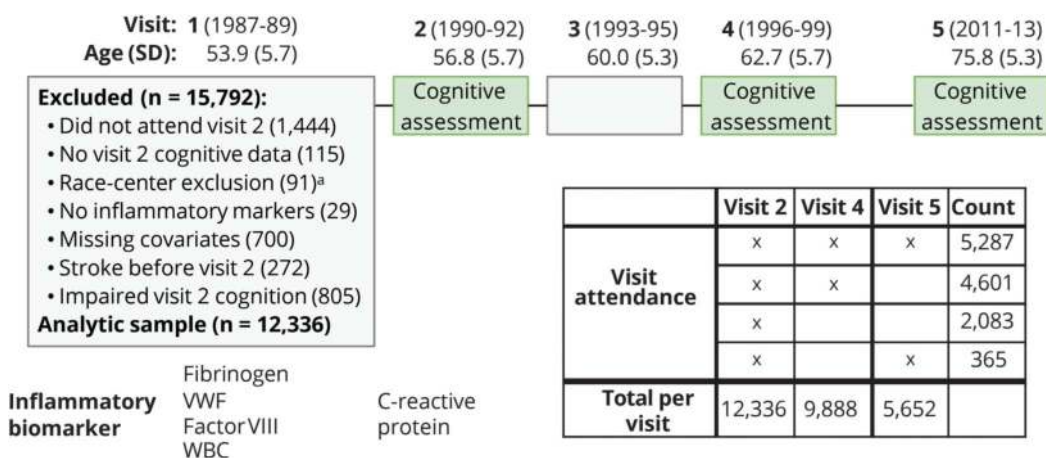
### Study population

The Atherosclerosis Risk in Communities (ARIC) Study, an ongoing population-based, prospective cohort study, enrolled 15,792 adults between the ages of 45 and 65 years from communities within the United States: Washington County, MD; Forsyth County, NC; northwestern suburbs of Minneapolis, MN; and Jackson, MS, from 1987 to 1989.<sup>10</sup> As shown in figure 1, participants were evaluated in person over 5 visits until 2011–2013 and contacted annually via telephone. Participants received a serial cognitive assessment at visits 2, 4, and 5. Of the 14,348 participants who attended visit 2 (1990–1992), we excluded participants on the basis of missing baseline cognitive data ( $n = 115$ ), nonwhite or nonblack race ( $n = 42$ ), black race living in Minneapolis or Washington County ( $n = 49$ ), unavailable inflammatory biomarkers ( $n = 29$ ), missing covariates ( $n = 700$ ), clinical stroke before visit 2 ( $n = 272$ ), or a score below the 5th percentile on any cognitive test at visit 2 ( $n = 805$ ). The ARIC Study protocols were approved by the institutional review boards at each participating center. All participants gave written informed consent at each study visit.

### Inflammatory biomarkers

Inflammatory biomarkers were measured in blood samples collected at visits 1 and 2. Four biomarkers were measured at visit 1: fibrinogen (mg/dL), von Willebrand factor (% of

**Figure 1** Study flow diagram



Study visits, assessments, and participant numbers are tabulated. <sup>a</sup>We excluded 42 participants for nonwhite or nonblack race, and 49 black participants living in Minneapolis or Washington County. VWF = von Willebrand factor; WBC = white blood cell count.

standard), factor VIII activity (% of standard), and white blood cell count, from blood stored at  $-70^{\circ}\text{C}$  using standardized protocols that have been described previously.<sup>11</sup> A visit 1 inflammation composite score<sup>12</sup> was created by converting each of the 4 inflammatory markers to a standardized  $z$  score (based on the visit 1 population) and calculating the mean of the 4  $z$  scores for each participant. We measured high-sensitivity C-reactive protein (CRP) levels in 2011–2013 from blood collected at visit 2 and stored at  $-70^{\circ}\text{C}$ . CRP was measured on the Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN) using an immunoturbidimetric assay. Interassay coefficients of variation were below 8% for fibrinogen, factor VIII, white blood cell count, and CRP, and 17%–19% for von Willebrand factor based on repeated testing.<sup>11,13</sup>

## Cognitive change

Cognition was measured at visits 2, 4, and 5 using 3 standardized neuropsychological measures: the Delayed Word Recall Test, the Digit Symbol Substitution Test, and the Word Fluency Test, each of which has been described in detail previously.<sup>14</sup> The Delayed Word Recall Test is a measure of verbal memory for which participants are asked to learn 10 common nouns by reading each noun and using it in a sentence. After a 5-minute distractor-filled delay period, participants were asked to recall each of the 10 nouns. Participant scores ranged from 0 to 10 based on the number of correctly recalled words. The Digit Symbol Substitution Test is a measure of executive function and processing speed for which participants are asked to translate a series of numbers based on their corresponding nonsense symbols using a key that uniquely associates a number with a different symbol. The total score was calculated based on the total number of correctly completed symbols in 90 seconds. The Word Fluency Test is a measure of verbal fluency for which participants are asked to list as many words as possible that begin with the letter “F,” “A,” and “S” (excluding proper nouns) within three 1-minute word-naming trials. The total score was based on the number of words generated. We converted test scores from each visit to  $z$  scores based on the visit 2 population mean (SD). A composite  $z$  score was created as the sum of the 3 test-specific  $z$  scores and standardized to the visit 2 composite  $z$  score mean and SD for all participants.

## Assessment of covariates

Participants reported race, education, and sex at visit 1. *APOE* was genotyped using the TaqMan assay (Applied Biosystems, Foster City, CA). Past long-term anti-inflammatory medication use (e.g., nonsteroidal anti-inflammatory drug, arthritis medication) was assessed at visit 5 by self-report. All other covariates were assessed at visits 1 and 2, concurrent with the inflammatory biomarker assessment. History of alcohol and cigarette use was assessed by self-report. Body mass index was calculated using measured height and weight ( $\text{kg}/\text{m}^2$ ). The enzymatic method was used to measure total cholesterol.<sup>15</sup> High-density lipoprotein (HDL) cholesterol was measured following the precipitation of non-HDL lipoprotein.<sup>16</sup> Hypertension was defined as systolic blood pressure  $>140$  mm

Hg, diastolic blood pressure  $>90$  mm Hg, or use of hypertensive medication. Coronary heart disease was defined based on participant self-report at visit 1 and was adjudicated based on medical record evidence of previous myocardial infarction, coronary artery bypass graft or angioplasty, or ECG evidence of myocardial infarction for events occurring between visits 1 and 2. Heart failure was identified based on medical record evidence of heart failure–related hospitalization or self-reported heart failure medication use. Diabetes was defined as a fasting glucose  $\geq 126$  mg/dL or nonfasting glucose of  $\geq 200$  mg/dL, current use of diabetes medication, or self-report of physician-diagnosed diabetes. Cancer diagnoses were ascertained using information from state cancer registries; this was supplemented by abstraction of medical records and hospital discharge codes as part of ongoing hospital surveillance.<sup>17</sup>

## Statistical analysis

We used generalized estimating equations with an unstructured correlation matrix and robust variance to estimate the difference in population-averaged cognitive change over time according to midlife inflammatory biomarker level. We modeled midlife inflammatory biomarker levels as categorical (quartiles) and continuous parameters. For use as a continuous variable, CRP was log-transformed to correct for skewness. We additionally created a categorical variable based on the number of visit 1 inflammatory markers (0, 1–2, 3–4) in the top quartile. Time on study was modeled with a 2-piece linear spline with a knot at year 6 (the approximate time of visit 4). Given evidence for steeper rates of cognitive decline after midlife,<sup>18</sup> this spline term allowed us to model a nonlinear association between time and cognitive decline in a manner that fits our study design, while also allowing the effect of midlife inflammation to vary across time.<sup>19,20</sup> An interaction term between inflammatory biomarker exposure and each of the 2 time spline terms was included in all models to examine whether rates of cognitive change differ by inflammatory biomarker level. All participants with cognitive data available at baseline (visit 2) were included in the analyses.

We examined 3 models. The first model adjusted for a set of potential confounders: baseline age and age squared, sex, race/center (white-MD/white-MN/white-NC/black-NC/black-MS), education (less than high school; high school/GED/vocational school; any college), *APOE*  $\epsilon 4$  status (0/1/2  $\epsilon 4$  alleles), body mass index, total cholesterol, HDL, cigarette and alcohol use (current/former/never), cholesterol-lowering medication use (yes/no), and anti-inflammatory medication use (yes/no/missing). A second fully adjusted model additionally adjusted for variables that may lie in the causal pathway between inflammation and cognitive decline: hypertension, diabetes, coronary heart disease, heart failure, and cancer. We examined a third model that used inverse probability of attrition weighting (IPAW) to account for the effects of differential study dropout (informative missingness). IPAW is a weighting procedure used to correct for sampling bias by applying larger weights to participants with characteristics associated with study dropout. This application of IPAW<sup>19</sup> incorporated demographic, physiologic, and clinical variables listed in table 1 to derive attrition weights;

**Table 1** Baseline (visit 2) participant characteristics stratified by visit 1 inflammation composite score

| Characteristic                               | Visit 1 inflammation composite score     |   |  |   |
|--|--|---|--|---|
|  | 1st quartile (n = 3,012),<br>≤ -0.47 (z) | 2nd quartile (n = 3,001),<br>-0.46 to -0.07 (z) | 3rd quartile (n = 2,995),<br>-0.08 to 0.36 (z) | 4th quartile (n = 2,966),<br>≥ 0.37 (z) |
| <b>Demographic variables</b>                 |  |   |  |   |
| Age, mean (SD), y                            | 55.5 (5.4)                               | 56.7 (5.6) <sup>a</sup>                         | 57.3 (5.7) <sup>a</sup>                        | 57.8 (5.7) <sup>a</sup>                 |
| Female, n (%)                                | 1,630 (54.1)                             | 1,665 (55.5)                                    | 1,709 (57.1) <sup>a</sup>                      | 1,741 (58.7) <sup>a</sup>               |
| Black race                                   | 486 (16.1)                               | 519 (17.3)                                      | 599 (20.0) <sup>a</sup>                        | 829 (28.0) <sup>a</sup>                 |
| <b>Education</b>                             |  |   |  |   |
| Less than high school                        | 367 (12.2)                               | 461 (15.4) <sup>a</sup>                         | 582 (19.4) <sup>a</sup>                        | 737 (24.9) <sup>a</sup>                 |
| High school/GED/vocational                   | 1,291 (42.9)                             | 1,294 (43.1)                                    | 1,300 (43.4)                                   | 1,269 (42.8)                            |
| College/graduate/professional                | 1,354 (45.0)                             | 1,246 (41.5)                                    | 1,113 (37.2)                                   | 960 (32.4)                              |
| <b>APOE ε4 alleles</b>                       |  |   |  |   |
| 0  | 2,108 (70.0)                             | 2,078 (69.2)                                    | 2,057 (68.7)                                   | 2,091 (70.5)                            |
| 1  | 817 (27.1)                               | 857 (28.6)                                      | 868 (29.0)                                     | 791 (26.7)                              |
| 2  | 87 (2.9)                                 | 66 (2.2)  | 70 (2.3)                                       | 84 (2.8)                                |
| <b>Mean cognitive z score</b>                |  |   |  |   |
| Composite cognitive score                    | 0.30 (0.86)                              | 0.22 (0.86) <sup>a</sup>                        | 0.10 (0.87) <sup>a</sup>                       | -0.06 (0.88) <sup>a</sup>               |
| Delayed Word Recall Test                     | 0.19 (0.89)                              | 0.15 (0.89) <sup>a</sup>                        | 0.08 (0.90) <sup>a</sup>                       | 0.02 (0.88) <sup>a</sup>                |
| Digit Symbol Substitution Test               | 0.31 (0.87)                              | 0.23 (0.87) <sup>a</sup>                        | 0.09 (0.88) <sup>a</sup>                       | -0.12 (0.91) <sup>a</sup>               |
| Word Fluency Test                            | 0.20 (0.95)                              | 0.13 (0.94) <sup>a</sup>                        | 0.07 (0.94) <sup>a</sup>                       | -0.03 (0.94) <sup>a</sup>               |
| <b>Physiologic and lab variables</b>         |  |   |  |   |
| Body mass index, kg/m <sup>2</sup>           | 26.5 (4.4)                               | 27.3 (4.7) <sup>a</sup>                         | 28.3 (5.4) <sup>a</sup>                        | 29.3 (6.2) <sup>a</sup>                 |
| Systolic blood pressure, mm Hg               | 117.0 (16.2)                             | 119.4 (17.9) <sup>a</sup>                       | 120.4 (17.5) <sup>a</sup>                      | 122.6 (18.4) <sup>a</sup>               |
| Diastolic blood pressure, mm Hg              | 72.7 (10.5)                              | 72.9 (10.7)                                     | 73.1 (10.6)                                    | 73.5 (11.0) <sup>a</sup>                |
| Total cholesterol, mg/dL                     | 205.6 (38.2)                             | 209.4 (38.2) <sup>a</sup>                       | 211.7 (38.5) <sup>a</sup>                      | 212.4 (41.5) <sup>a</sup>               |
| HDL, mg/dL                                   | 52.3 (17.4)                              | 50.1 (16.4) <sup>a</sup>                        | 48.5 (16.4)                                    | 46.8 (16.0) <sup>a</sup>                |
| LDL, mg/dL                                   | 128.6 (36.0)                             | 133.1 (35.8) <sup>a</sup>                       | 135.3 (35.7) <sup>a</sup>                      | 136.4 (37.7) <sup>a</sup>               |
| <b>Medical comorbidity</b>                   |  |   |  |   |
| Hypertension                                 | 781 (26.0)                               | 945 (31.6) <sup>a</sup>                         | 1,036 (34.7) <sup>a</sup>                      | 1,249 (42.3) <sup>a</sup>               |
| Diabetes mellitus                            | 130 (4.3)                                | 192 (6.4) <sup>a</sup>                          | 312 (10.5) <sup>a</sup>                        | 597 (20.2) <sup>a</sup>                 |
| Coronary heart disease                       | 114 (3.8)                                | 161 (5.5) <sup>a</sup>                          | 201 (6.8) <sup>a</sup>                         | 303 (10.4) <sup>a</sup>                 |
| Heart failure                                | 8 (0.3)                                  | 6 (0.2)   | 16 (0.6)                                       | 40 (1.5) <sup>a</sup>                   |
| Cancer                                       | 181 (6.0)                                | 198 (6.6)                                       | 204 (6.9)                                      | 229 (7.7) <sup>a</sup>                  |
| <b>Medication</b>                            |  |   |  |   |
| Anti-inflammatory (regular use) <sup>b</sup> | 273 (9.1)                                | 258 (8.6) <sup>a</sup>                          | 197 (6.6) <sup>a</sup>                         | 144 (4.9) <sup>a</sup>                  |
| Cholesterol-lowering (last 2 wk)             | 151 (5.0)                                | 187 (6.2) <sup>a</sup>                          | 190 (6.4) <sup>a</sup>                         | 252 (8.5) <sup>a</sup>                  |
| <b>Cigarette smoking status</b>              |  |   |  |   |
| Current                                      | 357 (11.9)                               | 571 (19.0) <sup>a</sup>                         | 707 (23.6) <sup>a</sup>                        | 955 (32.2) <sup>a</sup>                 |
| Former                                       | 1,241 (41.2)                             | 1,169 (39.0)                                    | 1,127 (37.6)                                   | 1,029 (34.7)                            |
| Never  | 1,414 (47.0)                             | 1,261 (42.0)                                    | 1,161 (38.8)                                   | 982 (33.1)                              |

Continued

**Table 1** Baseline (visit 2) participant characteristics stratified by visit 1 inflammation composite score (continued)

| Characteristic             | Visit 1 inflammation composite score     |   |  |   |
|----------------------------|--|---|--|---|
|                            | 1st quartile (n = 3,012),<br>≤ -0.47 (z) | 2nd quartile (n = 3,001),<br>-0.46 to -0.07 (z) | 3rd quartile (n = 2,995),<br>-0.08 to 0.36 (z) | 4th quartile (n = 2,966),<br>≥ 0.37 (z) |
| <b>Alcohol consumption</b> |  |   |  |   |
| <b>Current</b>             | 1,938 (64.3)                             | 1,833 (61.1) <sup>a</sup>                       | 1,698 (56.7) <sup>a</sup>                      | 1,499 (50.5) <sup>a</sup>               |
| <b>Former</b>              | 468 (15.5)                               | 534 (17.8)                                      | 592 (19.8)                                     | 766 (25.8)                              |
| <b>Never</b>               | 606 (20.1)                               | 634 (21.1)                                      | 705 (23.5)                                     | 701 (23.6)                              |

Abbreviations: GED = general education development; HDL = high-density lipoprotein; LDL = low-density lipoprotein. Values are displayed as means (SD) for continuous variables, and frequencies (column percentages) for categorical variables, unless otherwise specified. Table includes only participants with available baseline cognitive data.

<sup>a</sup> Difference between group and the 1st quartile (reference) group statistically significant ( $p < 0.05$ ).

<sup>b</sup> Assessed at visit 5 (2011–2013).

methods are described in detail in data available from Dryad (appendix e-1): doi.org/10.5061/dryad.vn806pd. All models were also adjusted for the interaction between time spline terms and the demographic and clinical variable covariates. Covariates that varied with time (e.g., age, comorbid disease) were updated to be concurrent with inflammatory marker assessment. To evaluate whether the association between midlife inflammatory biomarkers and cognitive decline was subject to effect modification by race (white/black), sex (male/female), and *APOE*  $\epsilon 4$  genotype (positive/negative), we used 3-way multiplicative interaction terms. Estimates of additional total cognitive change over a 20-year period are presented for all analyses.

We conducted several sensitivity analyses. We repeated analyses using only participants who were assessed at all 3 visits to ensure our inferences regarding 20-year cognitive change were reflected among participants with complete 20-year follow-up. To determine whether our results occurred independent of stroke, we repeated analyses after censoring participants following clinical stroke up to the time of visit 5. To isolate the effect of low-grade systemic inflammation, we repeated analyses after removing cases with abnormally elevated inflammatory marker levels, suggestive of an acute inflammatory response (i.e., visit 1 inflammation composite score  $> 2$  SD or visit 2 CRP  $> 10$  mg/L). A 2-sided  $p$  value  $< 0.05$  was used as the cutoff for statistical significance. All analyses were conducted using Stata version 14 (StataCorp, College Station, TX).

### Data availability

On inquiry, the ARIC Study data used here can be made available. For information on how to access available data and study protocols, see [www2.csc.unc.edu/aric/](http://www2.csc.unc.edu/aric/).

## Results

A total of 12,336 participants were included in the current study (21% black, 56% women). Participants were 56.8 years of age (5.7 SD) at the time of baseline cognitive assessment

(visit 2: 1990–1992) and 75.8 years of age (5.3 SD) at the time of the final cognitive assessment (visit 5: 2011–2013). Participants' characteristics are presented stratified according to visit 1 inflammation composite score (table 1) and visit 2 CRP level (data available from Dryad [table e-1]: doi.org/10.5061/dryad.vn806pd). Participants with higher levels of midlife inflammatory markers were older, more likely to be female and black, have greater rates of cardiovascular risk factors, and have lower baseline cognition. Of the participants who were assessed at visit 2, 83% had at least 1 follow-up visit and 46% of participants were assessed at the final visit, visit 5 (figure 1). Thirty-seven percent of participants contributed data to only visits 2 and 4 (6 years of follow-up), whereas 17% of participants had only visit 2 data available and thus only contributed to the estimate of baseline differences in cognition. The mean and median time between baseline and final cognitive assessment was 14.2 years (7.4 SD) and 19.4 years (Q1 to Q3: 6.0–21.0 years), respectively.

After adjusting for demographic and cardiovascular risk factors, participants with a higher visit 1 inflammation composite score had a steeper 20-year decline on the composite cognitive score (table 2). Having an inflammation composite score in the 2nd, 3rd, and 4th quartile was associated with cognitive declines that were 7.5%, 7.7%, and 8.9% steeper, respectively, than that of the 1st quartile. These findings were similar after additionally adjusting for potentially mediating disease variables, and after additionally incorporating IPAW weights to account for attrition (table 2). In domain-specific analyses, a higher inflammation composite score was associated with steeper declines in memory, but not executive function or language (table 3). There was an interaction between the inflammation composite score (specified as a continuous variable) and race; however, this interaction was not reflected in our results, which examined inflammation composite score quartiles (table 4). We found no evidence for effect modification by sex or *APOE*  $\epsilon 4$  status ( $p$ -interactions  $> 0.108$ ). Findings were similar in sensitivity analyses that examined only participants with 20 years of complete cognitive data

**Table 2** Adjusted difference in 20-year cognitive change according to visit 1 inflammation composite score and visit 2 C-reactive protein

|  | Model 1                        |                                   | Model 2                        |                                   | Model 2 with IPAW              |                                   |
|--|--------------------------------|-----------------------------------|--------------------------------|-----------------------------------|--------------------------------|-----------------------------------|
|  | Estimate (95% CI) <sup>a</sup> | % Additional decline <sup>b</sup> | Estimate (95% CI) <sup>a</sup> | % Additional decline <sup>b</sup> | Estimate (95% CI) <sup>a</sup> | % Additional decline <sup>b</sup> |
| <b>Visit 1 inflammation composite score (n = 11,974)</b> |                                |                                   |                                |                                   |                                |                                   |
| <b>Q1, -1.97 to -0.47 (z)</b>                            | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 |
| <b>Q2, -0.46 to -0.07 (z)</b>                            | -0.061 (-0.104 to -0.018)      | 7.5 (2.2, 12.7)                   | -0.061 (-0.104 to -0.018)      | 7.5 (2.2, 12.7)                   | -0.073 (-0.129 to -0.018)      | 8.9 (15.8, 2.2)                   |
| <b>Q3, -0.08 to 0.36 (z)</b>                             | -0.063 (-0.108 to -0.018)      | 7.7 (2.2, 13.2)                   | -0.058 (-0.102 to -0.013)      | 7.1 (1.6, 12.5)                   | -0.072 (-0.131 to -0.014)      | 8.8 (16.0, 1.7)                   |
| <b>Q4, 0.37 to 6.12 (z)</b>                              | -0.073 (-0.123 to -0.024)      | 8.9 (2.9, 15.0)                   | -0.064 (-0.114 to -0.014)      | 7.8 (1.7, 13.9)                   | -0.076 (-0.149 to -0.004)      | 9.3 (18.2, 0.4)                   |
| <b>Per 1 SD (continuous)</b>                             | -0.042 (-0.069 to -0.014)      | —                                 | -0.035 (-0.062 to -0.007)      | —                                 | -0.044 (-0.083 to -0.005)      | —                                 |
| <b>Visit 2 C-reactive protein (n = 9,976)</b>            |                                |                                   |                                |                                   |                                |                                   |
| <b>Q1, ≤1.04, mg/L</b>                                   | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 |
| <b>Q2, 1.05 to 2.19, mg/L</b>                            | -0.081 (-0.130 to -0.033)      | 9.7 (15.6, 4.0)                   | -0.080 (-0.128 to -0.032)      | 9.6 (3.8, 15.4)                   | -0.070 (-0.133 to -0.006)      | 8.4 (16.0, 0.7)                   |
| <b>Q3, 2.20 to 4.68, mg/L</b>                            | -0.071 (-0.121 to -0.021)      | 8.5 (14.5, 2.5)                   | -0.067 (-0.117 to -0.017)      | 8.1 (2.1, 14.1)                   | -0.079 (-0.145 to -0.013)      | 9.4 (17.4, 1.6)                   |
| <b>Q4, 4.69+, mg/L</b>                                   | -0.103 (-0.155 to -0.051)      | 12.3 (18.6, 6.1)                  | -0.096 (-0.149 to -0.044)      | 11.6 (5.2, 17.8)                  | -0.128 (-0.200 to -0.054)      | 15.3 (24.0, 0.6)                  |
| <b>Per 1 SD (continuous)</b>                             | -0.040 (-0.059 to -0.022)      | —                                 | -0.038 (-0.057 to -0.019)      | —                                 | -0.044 (-0.071 to -0.018)      | —                                 |

Abbreviations: CI = confidence interval; IPAW = inverse probability of attrition weighting; Q = quartile; ref = reference.

Model 1 is adjusted for baseline age and age squared, sex, race-center, education, *APOE* ε4 status, body mass index, total cholesterol, high-density lipoprotein, cigarette and alcohol use status, cholesterol-lowering medication use, and anti-inflammatory medication use and interactions of demographic variables and medical comorbidity with time spline terms. Model 2 is additionally adjusted for hypertension, diabetes, coronary heart disease, heart failure, and cancer.

<sup>a</sup> Values represent estimated additional cognitive change over a 20-year period.

<sup>b</sup> Percentage of additional cognitive decline (i.e., [decline of participants in the nth quartile - decline in participants in the 1st quartile]/[decline of participants in the 1st quartile]).

**Table 3** Test-specific adjusted difference in 20-year cognitive change according to visit 1 inflammation composite score and visit 2 C-reactive protein

|  | DWRT z score                   |                                   | DSST z score                   |                                   | WFT z score                    |                                   |
|--|--------------------------------|-----------------------------------|--------------------------------|-----------------------------------|--------------------------------|-----------------------------------|
|  | Estimate (95% CI) <sup>a</sup> | % Additional decline <sup>b</sup> | Estimate (95% CI) <sup>a</sup> | % Additional decline <sup>b</sup> | Estimate (95% CI) <sup>a</sup> | % Additional decline <sup>b</sup> |
| <b>Visit 1 inflammation composite score (n = 11,974)</b> |                                |                                   |                                |                                   |                                |                                   |
| <b>Q1, -1.97 to -0.47 (z)</b>                            | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 |
| <b>Q2, -0.46 to -0.07 (z)</b>                            | -0.108 (-0.177 to -0.040)      | 10.5 (17.3, 0.9)                  | -0.035 (-0.071 to 0.001)       | 4.7 (9.5 to -0.1)                 | -0.020 (-0.063 to 0.024)       | 11.7 (36.9 to -14.1)              |
| <b>Q3, -0.08 to 0.36 (z)</b>                             | -0.082 (-0.153 to -0.011)      | 8.0 (14.9, 1.0)                   | -0.037 (-0.075 to 0.005)       | 5.0 (10.1 to -0.7)                | -0.033 (-0.078 to 0.013)       | 19.3 (45.7 to -7.7)               |
| <b>Q4, 0.37 to 6.12 (z)</b>                              | -0.085 (-0.164 to -0.007)      | 8.3 (16.0, 0.7)                   | -0.021 (-0.063 to 0.021)       | 2.8 (8.5 to -2.8)                 | -0.047 (-0.097 to 0.002)       | 27.5 (56.8 to -1.1)               |
| <b>Per 1 SD (continuous)</b>                             | -0.042 (-0.085 to 0.001)       | —                                 | -0.012 (-0.035 to 0.011)       | —                                 | -0.027 (-0.054 to 0.001)       | —                                 |
| <b>Visit 2 C-reactive protein (n = 9,976)</b>            |                                |                                   |                                |                                   |                                |                                   |
| <b>Q1, ≤1.04, mg/L</b>                                   | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 | 0 (ref)                        | —                                 |
| <b>Q2, 1.05 to 2.19, mg/L</b>                            | -0.150 (-0.227 to -0.073)      | 14.2 (21.5, 6.9)                  | -0.007 (-0.048 to 0.033)       | 0.9 (6.2 to -4.3)                 | -0.016 (-0.065 to 0.032)       | 9.7 (39.4 to -19.5)               |
| <b>Q3, 2.20 to 4.68, mg/L</b>                            | -0.089 (-0.168 to -0.009)      | 8.4 (15.9, 0.9)                   | -0.007 (-0.050 to 0.034)       | 0.9 (6.5 to -4.4)                 | -0.060 (-0.111 to -0.010)      | 36.4 (67.4 to 6.1)                |
| <b>Q4, 4.69+, mg/L</b>                                   | -0.123 (-0.207 to -0.040)      | 11.6 (19.6, 3.8)                  | -0.021 (-0.065 to 0.024)       | 2.7 (8.4 to -3.2)                 | -0.056 (-0.109 to -0.003)      | 34.0 (66.2 to -1.9)               |
| <b>Per 1 SD (continuous)</b>                             | -0.047 (-0.078 to -0.017)      | —                                 | -0.007 (-0.023 to 0.009)       | —                                 | -0.027 (-0.046 to -0.008)      | —                                 |

Abbreviations: CI = confidence interval; DSST = Digit Symbol Substitution Test; DWRT = Delayed Word Recall Test; Q = quartile; ref = reference; WFT = Word Fluency Test.

Models are adjusted for baseline age and age squared, sex, race-center, education, *APOE* ε4 status, body mass index, total cholesterol, high-density lipoprotein, cigarette and alcohol use status, hypertension, diabetes, coronary heart disease, heart failure, cancer, cholesterol-lowering medication use, and anti-inflammatory medication use, and interactions of demographic variables and medical comorbidity with time spline terms (model 2).

<sup>a</sup> Values represent estimated additional cognitive change over a 20-year period.

<sup>b</sup> Percentage of additional cognitive decline (i.e., [decline of participants in the nth quartile - decline in participants in the 1st quartile]/[decline of participants in the 1st quartile]).

**Table 4** Adjusted difference in 20-year cognitive change according to visit 1 inflammation composite score and visit 2 C-reactive protein stratified by race

| Visit 1 inflammation composite score | White, composite z score                      |                                   | Black, composite z score                      |                                   | p-Interaction |
|--------------------------------------|---|-----------------------------------|---|-----------------------------------|---------------|
|                                      | Estimate (95% CI) <sup>a</sup><br>(n = 9,541) | % Additional decline <sup>b</sup> | Estimate (95% CI) <sup>a</sup><br>(n = 2,433) | % Additional decline <sup>b</sup> |               |
| <b>Q1, -1.97 to -0.47 (z)</b>        | 0 (ref)                                       | —                                 | 0 (ref)                                       | —                                 | —             |
| <b>Q2, -0.46 to -0.07 (z)</b>        | -0.062 (-0.108 to -0.017)                     | 7.4 (1.5, 12.8)                   | -0.081 (-0.194 to 0.032)                      | 11.7 (-5.6 to 28.1)               | —             |
| <b>Q3, -0.08 to 0.36 (z)</b>         | -0.061 (-0.110 to -0.013)                     | 7.2 (1.5, 12.9)                   | -0.058 (-0.169 to 0.052)                      | 8.4 (-7.5 to 24.4)                | —             |
| <b>Q4, 0.37 to 6.12 (z)</b>          | -0.103 (-0.157 to -0.048)                     | 12.2 (5.7, 18.7)                  | -0.025 (-0.135 to 0.086)                      | 3.6 (-12.4 to 19.6)               | —             |
| <b>Per 1 SD (continuous)</b>         | -0.066 (-0.097 to -0.034)                     | —                                 | 0.003 (-0.051 to 0.057)                       | —                                 | 0.020         |

| Visit 2 C-reactive protein    | White, composite z score                      |                                   | Black, composite z score                      |                                   | p-Interaction |
|-------------------------------|---|-----------------------------------|---|-----------------------------------|---------------|
|                               | Estimate (95% CI) <sup>a</sup><br>(n = 7,935) | % Additional decline <sup>b</sup> | Estimate (95% CI) <sup>a</sup><br>(n = 2,041) | % Additional decline <sup>b</sup> |               |
| <b>Q1, ≤1.04, mg/L</b>        | 0 (ref)                                       | —                                 | 0 (ref)                                       | —                                 | —             |
| <b>Q2, 1.05 to 2.19, mg/L</b> | -0.046 (-0.096 to 0.005)                      | 5.3 (-0.4 to 11.1)                | -0.310 (-0.444 to -0.176)                     | 46.5 (26.4 to 66.5)               | —             |
| <b>Q3, 2.20 to 4.68, mg/L</b> | -0.072 (-0.125 to -0.020)                     | 8.4 (2.3 to 14.5)                 | -0.118 (-0.248 to 0.012)                      | 17.7 (-1.8 to 37.2)               | —             |
| <b>Q4, 4.69+, mg/L</b>        | -0.115 (-0.172 to -0.058)                     | 13.4 (6.8 to 20.0)                | -0.176 (-0.301 to -0.050)                     | 26.3 (7.5 to 45.2)                | —             |
| <b>Per 1 SD (continuous)</b>  | -0.045 (-0.065 to -0.024)                     | —                                 | -0.050 (-0.095 to -0.005)                     | —                                 | 0.954         |

Abbreviations: CI = confidence interval; Q = quartile; ref = reference.

Models are adjusted for baseline age and age squared, sex, race-center, education, *APOE* ε4 status, body mass index, total cholesterol, high-density lipoprotein, cigarette and alcohol use status, hypertension, diabetes, coronary heart disease, heart failure, cancer, cholesterol-lowering medication use, and anti-inflammatory medication use, and interactions of demographic variables and medical comorbidity with time spline terms (model 2).

<sup>a</sup> Values represent estimated additional cognitive change over a 20-year period.

<sup>b</sup> Percentage of additional cognitive decline (i.e., [decline of participants in the nth quartile - decline of participants in the 1st quartile]/[decline of participants in the 1st quartile]).



**Table 5** Adjusted difference in 20-year cognitive change according to visit 1 inflammation composite score and visit 2 C-reactive protein among participants with complete 20-year follow-up

|   | Composite z score, estimate <sup>a</sup><br>(95% CI) | DWRT z score, estimate <sup>a</sup><br>(95% CI) | DSST z score, estimate <sup>a</sup><br>(95% CI) | WFT z score, estimate <sup>a</sup><br>(95% CI) |
|---|--|---|---|--|
| <b>Visit 1 inflammation composite score (n = 4,969)</b> |  |   |   |  |
| <b>Q1, -1.97 to -0.47 (z)</b>                           | 0 (ref)  | 0 (ref)   | 0 (ref)   | 0 (ref)  |
| <b>Q2, -0.46 to -0.07 (z)</b>                           | -0.064 (-0.112 to -0.016)                            | -0.112 (-0.193 to -0.030)                       | -0.031 (-0.067 to 0.005)                        | -0.007 (-0.056 to 0.042)                       |
| <b>Q3, -0.08 to 0.36 (z)</b>                            | -0.073 (-0.124 to -0.022)                            | -0.098 (-0.184 to -0.013)                       | -0.043 (-0.081 to -0.005)                       | -0.032 (-0.084 to 0.019)                       |
| <b>Q4, 0.37 to 6.12 (z)</b>                             | -0.059 (-0.116 to -0.002)                            | -0.078 (-0.175 to 0.018)                        | -0.029 (-0.072 to 0.013)                        | -0.037 (-0.095 to 0.021)                       |
| <b>Per 1 SD (continuous)</b>                            | -0.032 (-0.063 to 0.000)                             | -0.041 (-0.094 to 0.013)                        | -0.018 (-0.041 to 0.006)                        | -0.020 (-0.052 to 0.012)                       |
| <b>Visit 2 C-reactive protein (n = 4,171)</b>           |  |   |   |  |
| <b>Q1, &lt;1.04, mg/L</b>                               | 0 (ref)  | 0 (ref)   | 0 (ref)   | 0 (ref)  |
| <b>Q2, 1.05 to 2.19, mg/L</b>                           | -0.109 (-0.164 to -0.054)                            | -0.198 (-0.290 to -0.106)                       | -0.013 (-0.054 to 0.029)                        | -0.045 (-0.100 to 0.011)                       |
| <b>Q3, 2.20 to 4.68, mg/L</b>                           | -0.073 (-0.130 to -0.015)                            | -0.118 (-0.215 to -0.021)                       | -0.001 (-0.044 to 0.042)                        | -0.055 (-0.114 to 0.003)                       |
| <b>Q4, 4.69+, mg/L</b>                                  | -0.098 (-0.159 to -0.038)                            | -0.154 (-0.256 to -0.053)                       | -0.028 (-0.074 to 0.017)                        | -0.054 (-0.116 to 0.007)                       |
| <b>Per 1 SD (continuous)</b>                            | -0.039 (-0.061 to -0.017)                            | -0.060 (-0.096 to -0.023)                       | -0.010 (-0.026 to 0.006)                        | -0.024 (-0.047 to -0.002)                      |

Abbreviations: CI = confidence interval; DSST = Digit Symbol Substitution Test; DWRT = Delayed Word Recall Test; Q = quartile; ref = reference; WFT = Word Fluency Test.

Models are adjusted for baseline age and age squared, sex, race-center, education, *APOE* ε4 status, body mass index, total cholesterol, high-density lipoprotein, cigarette and alcohol use status, hypertension, diabetes, coronary heart disease, heart failure, cancer, cholesterol-lowering medication use, and anti-inflammatory medication use, and interactions between demographic variables and medical comorbidity and time spline terms (model 2).

<sup>a</sup> Values represent estimated additional cognitive change over a 20-year period.

(table 5), censored cases after incident stroke, and excluded participants with abnormally elevated inflammatory markers (data available from Dryad [tables e-2 and e-3]: doi.org/10.5061/dryad.vn806pd).

Relatedly, we found that participants with a higher number of elevated (top quartile) visit 1 inflammatory markers had a steeper decline on the composite cognitive score in a dose-dependent manner. Similar findings were observed for measures of memory and language in domain-specific analyses (figure 2).

Elevated visit 2 CRP was also associated with a steeper 20-year cognitive decline after adjusting for demographic and cardiovascular risk factors (table 2). A CRP level in the top 2nd, 3rd, and 4th quartile was associated with 9.7%, 8.5%, and 12.3% steeper decline on the cognitive composite score, respectively, compared to participants with CRP in the 1st quartile. Results were similar after additionally adjusting for disease variables, and after incorporating IPAW weights to account for attrition (table 2). We found no evidence for effect modification by race (table 4), sex, or *APOE* ε4 status (*p*-interactions >0.094). In domain-specific analyses, a higher CRP level was associated with steeper declines on a measure of memory, and to a lesser extent, a measure of language (table 3). Findings were not substantively changed in sensitivity analyses that included only participants with 20 years of

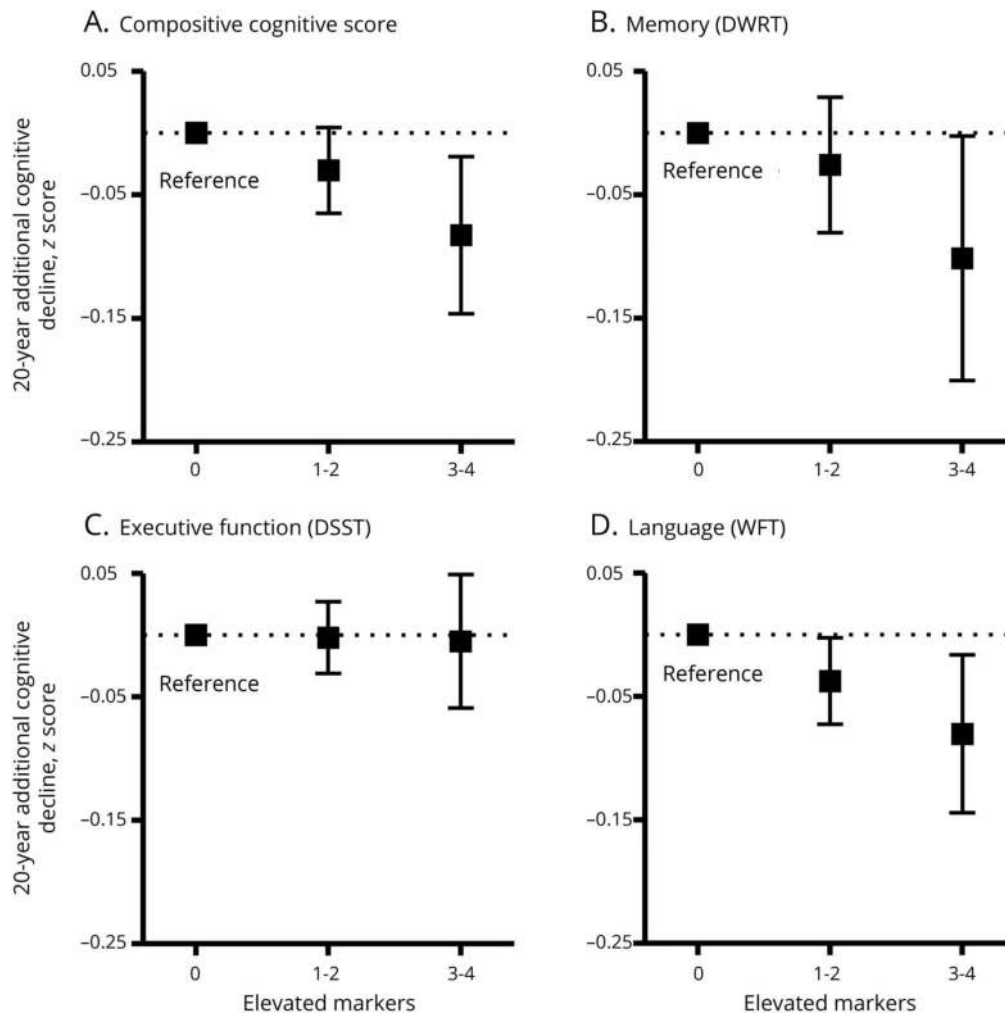
complete cognitive data (table 5), censored cases after incident stroke, and omitted cases with atypically high CRP levels (data available from Dryad [tables e-2 and e-3]: doi.org/10.5061/dryad.vn806pd).

Based on our findings that suggest CRP levels in the top 3 quartiles are associated with similar levels of additional cognitive decline, we performed a secondary analysis to determine whether a CRP threshold could be determined. Our results, which examined 10 candidate CRP cutpoints (CRP deciles), indicate a CRP threshold near 1.05 mg/L, above which is most strongly associated with subsequent cognitive decline (data available from Dryad [table e-4 and figure e-1]: doi.org/10.5061/dryad.vn806pd).

## Discussion

Using a large community sample, we have demonstrated that a midlife elevation of circulating inflammatory markers is associated with greater cognitive decline over the decades leading up to older adulthood. Specifically, participants with an elevated inflammation composite score, an elevated CRP level, or a greater number of elevated inflammatory markers during midlife experienced steeper cognitive decline over a 20-year period. Each of these associations occurred independent of potentially confounding variables and incident

**Figure 2** Number of elevated inflammatory markers and additional 20-year cognitive decline



Estimates and 95% confidence intervals of additional 20-year cognitive decline from generalized linear models fit using covariate-adjusted generalized estimating equations for composite and domain-specific cognitive decline among participants with 0, 1–2, and 3–4 elevated inflammatory markers. Findings were observed for the composite cognitive score (A), memory (B), executive function (C), and language (D) in domain-specific analyses. Inflammatory marker levels were classified as elevated if they were in the top quartile ( $\geq 75$ th %tile). Models are adjusted for baseline age and age squared, sex, race-center, education, *APOE*  $\epsilon 4$  status, body mass index, total cholesterol, high-density lipoprotein, cigarette and alcohol use status, hypertension, diabetes, coronary heart disease, heart failure, cancer, cholesterol-lowering medication use, and anti-inflammatory medication use, and interactions of demographic variables and medical comorbidity with time spline terms (model 2). DSST = Digit Symbol Substitution Test; DWRT = Delayed Word Recall Test; WFT = Word Fluency Test.

stroke and did not differ according to sex or *APOE*  $\epsilon 4$  genotype. A comparison of our results to previously published findings from the ARIC Study suggests that the effect on 20-year cognitive decline of midlife inflammation in the upper 3 quartiles is greater than that of midlife hypertension.<sup>21</sup>

Although systemic inflammation has been associated with cognitive decline among older adults,<sup>3,22,23</sup> few studies have investigated the effects of systemic inflammation during middle adulthood on later cognitive outcomes.<sup>24,25</sup> Accordingly, the degree to which midlife systemic inflammation contributes to declines in cognition over the decades spanning from mid- to late-life, when cognitive change is thought to accelerate,<sup>4,5</sup> has remained unknown. Here, we demonstrate that midlife systemic inflammation may constitute a risk factor for accelerated cognitive decline in the decades leading

up to older adulthood. Our findings are supported by those from the Honolulu-Asia Aging Study, which demonstrated that individuals with higher levels of CRP during midlife are at greater risk of dementia 25 years later.<sup>25</sup> Given that neuro-pathologic processes associated with dementia, such as  $\beta$ -amyloid deposition, are believed to begin during midlife, decades before the onset of clinical symptoms,<sup>26</sup> the current findings provide support for the idea that systemic inflammation may have an early pathologic role in driving or accelerating some of the pathologic processes underlying late-life cognitive decline.<sup>1</sup> However, there are several alternative explanations that should be considered in the context of the current findings. For example, it is possible that systemic inflammation during midlife is a marker, not a cause, of neurodegenerative disease or neuronal or glial injury.<sup>27</sup> In addition, inflammation may serve as a compensatory response

to the emergence of neural proteopathies, such as  $\beta$ -amyloid, which have been shown in previous studies to generate a local inflammatory response.<sup>28,29</sup>

Because most studies have used cognitive screening tests to explore inflammation-related cognitive decline,<sup>2,22,24</sup> the degree to which systemic inflammation is associated with decline in discrete cognitive domains is unclear. Our results indicate that episodic memory is more vulnerable to the effects of systemic inflammation, relative to language, executive function, and processing speed. These findings stand in contrast to the results from studies of midlife vascular risk factors, such as hypertension<sup>21</sup> and elevated lipid levels,<sup>20</sup> which are more strongly associated with declines in executive function and processing speed. Thus, inflammation- and vascular-related cognitive decline may result from pathologically or neuroanatomically distinct processes. Consistent with the current findings, systemic inflammation in rodent models has been found to lead to changes in hippocampal structure and function.<sup>30,31</sup> Through multiple routes (e.g., vagal nerve signaling, circumventricular organs), activation of the peripheral inflammatory response can generate a neuroinflammatory response, which can, in turn, disrupt neural and glial functioning.<sup>32</sup>

The additional absolute level of cognitive change associated with systemic inflammation was modest overall, but comparable to that which has been associated with vascular risk factors such as hypertension and diabetes.<sup>19–21</sup> Our analysis of the total sample did not reveal a linear dose-response increase in rate of cognitive decline with higher levels of midlife inflammation. Rather, groups in the top 3 quartiles displayed similar rates of cognitive change. However, in race-stratified analyses, we observed the expected dose-response increase in cognitive decline among white, but not black, participants. A potential explanation for the absence of a dose-response increase among black participants is a heightened rate of attrition due to death and dropout among participants with high levels of systemic inflammation during midlife (data available from Dryad [table e-5]: doi.org/10.5061/dryad.vn806pd), as black participants were overrepresented in the groups with higher levels of midlife inflammation (table 1 and data available from Dryad [table e-1]: doi.org/10.5061/dryad.vn806pd). Although we found evidence for an interaction between race and the linear specification of midlife inflammation composite score on cognitive change, this finding was neither reflected in our analysis of inflammation composite score quartiles nor observed in our analyses that examined CRP. Taken together, our results did not show strong support for a modifying effect of race on the association between midlife systemic inflammation and cognitive decline. However, additional studies using alternative markers of systemic inflammation will be needed to confirm this finding.

The current study has several strengths, including the use of a large, biracial, population-based sample, the long follow-up period, and the careful ascertainment of and adjustment for potentially confounding variables. However, there are several

limitations. First, potential bias related to selective attrition represents a major limitation of the current study. Fifty-four percent of the sample dropped out or died before the final cognitive assessment and 17% of participants had only a baseline cognitive assessment. Accordingly, only data from a subset of participants who attended visit 5 contributed to inferences about cognitive decline during late-life. Given that participants with higher levels of systemic inflammation at baseline were more likely to drop out or die before the final follow-up visit (data available from Dryad [table e-5]: doi.org/10.5061/dryad.vn806pd), it is possible that a survivorship effect may have biased our results, especially for participants with higher levels of systemic inflammation during midlife. However, our findings, which incorporated IPAW to mitigate the effect of differential attrition, suggest that our results are robust to selection bias. We should also note that the absence of more than 2 time points for the majority of the sample limits the study's ability to characterize the dynamic trajectory of cognitive decline related to midlife systemic inflammation. Future studies with more frequent cognitive assessments will be informative in this regard. Second, because our serial cognitive battery was limited to 3 measures, we were unable to provide a precise assessment of specific domains or a comprehensive assessment of all relevant cognitive domains. Third, although our analyses were adjusted for demographic confounders, vascular risk factors, and medical comorbidity, we are unable to fully rule out the possibility of bias related to residual confounding from unmeasured covariates, such as subclinical disease. Lastly, the current study used a panel of acute-phase proteins, which are upregulated following an inflammatory event, to assess systemic inflammation. The use of a broader assay of inflammatory markers, including inflammatory cytokines and chemokines, in future studies may facilitate a more nuanced understanding of pro- and anti-inflammatory signaling as it relates to cognitive decline. Despite these limitations, the current study provides support for an association between midlife systemic inflammation and subsequent cognitive decline, and in doing so, provides additional evidence for an early pathogenic role of systemic inflammation in late-life neurocognitive impairment.

### Author contributions

Drafting or revising the manuscript for content: K.A.W., R.F.G., A.W., D.S.K., A.L.G., T.H.M., E.S., and B.G.W. Study concept or design: K.A.W., R.F.G., and B.G.W. Interpretation of the data: K.A.W., R.F.G., A.W., D.S.K., A.L.G., T.H.M., E.S., and B.G.W. Statistical analysis: K.A.W. and A.L.G. Study supervision or coordination: R.F.G., D.S.K., and T.H.M. Obtaining funding: R.F.G., T.H.M., and E.S.

### Acknowledgment

The authors thank the staff and participants of the ARIC Study for their important contributions.

### Study funding

The Atherosclerosis Risk in Communities Study is conducted as a collaborative study supported by National Heart, Lung,

and Blood Institute contracts (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). Neurocognitive data are collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the NIH (NHLBI, NINDS, NIA, and NIDCD), and with previous brain MRI examinations funded by R01-HL70825 from the NHLBI. This study was also supported by contracts T32 AG027668 (Dr. Walker), K24 AG052573 (Dr. Gottesman), and K01 AG050699 (Dr. Gross) from the National Institute on Aging; and K24 DK106414 and R01 DK089174 (Dr. Selvin) from the National Institute of Diabetes and Digestive and Kidney Diseases. The reagents for the C-reactive protein assays were donated by Roche Diagnostics. The sponsors had no role in the design and conduct of the study; collection management, analysis, and interpretation of the data; or preparation review or approval of the manuscript.

## Disclosure

K. Walker reports no disclosures relevant to the manuscript. R. Gottesman is associate editor for *Neurology*<sup>®</sup> and receives research support from NIH. A. Wu reports no disclosures relevant to the manuscript. D. Knopman serves on a data safety monitoring board for the DIAN Study; is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the Alzheimer's Disease Cooperative Study; and receives research support from NIH. A. Gross receives research support from NIH. T. Mosley receives research support from NIH. E. Selvin receives research support from NIH. B. Windham is an investigator/dementia expert on a CMS Coverage with Evidence Development (CED) study and has been an investigator in a clinical trial sponsored by ACADIA Pharmaceuticals; receives research support from NIH. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

## Publication history

Received by *Neurology* June 29, 2018. Accepted in final form November 1, 2018.

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## Systemic inflammation during midlife and cognitive change over 20 years: The ARIC Study

Keenan A. Walker, Rebecca F. Gottesman, Aozhou Wu, et al.  
*Neurology* published online February 13, 2019  
DOI 10.1212/WNL.00000000000007094

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