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Inflammatory Mechanisms Underlying the Effects of Everyday Discrimination on Age-Related Memory Decline

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Abstract

BACKGROUND/OBJECTIVES: Previous research suggests that everyday discrimination is associated with worse episodic memory and partially mediates Black-White disparities in memory aging. The biological mechanisms underlying the link between everyday discrimination and memory are unclear but may involve inflammatory processes. This study aimed to determine whether systemic inflammation, indexed by blood levels of C-Reactive Protein (CRP), mediates associations between everyday discrimination and episodic memory over six years. DESIGN: A longitudinal mediation model quantified associations between baseline everyday discrimination, four-year change in CRP, and six-year change in episodic memory.

SETTING: The Health and Retirement Study (HRS).

PARTICIPANTS: 12,624 HRS participants aged 51 and older.

MEASUREMENTS: Everyday Discrimination Scale, high-sensitivity CRP assays of dried blood spots, composite scores of immediate and delayed recall of a word list.

RESULTS: Black participants reported greater everyday discrimination. Greater discrimination was associated with lower baseline memory and faster memory decline. Higher CRP at baseline partially mediated the negative association between discrimination and baseline memory, but CRP change did not mediate the association between discrimination and memory decline.

CONCLUSION: This U.S.-representative longitudinal study provides evidence for deleterious effects of discrimination on subsequent episodic memory. The fact that elevated CRP only partially explained the concurrent association between discrimination and memory highlights the need for more comprehensive investigations of biological mechanisms underlying the link between

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social stress and age-related memory decline in order to better characterize potential intervention targets to reduce racial inequalities in memory aging.

Keywords

Race; C-reactive protein; episodic memory; social stress

Introduction

Social stressors have been linked to worse episodic memory functioning. For example, self-reported everyday experiences of discrimination are associated with lower episodic memory level[1] and faster episodic memory decline.[2] Discrimination may be particularly relevant for memory because identity-relevant stressors can be more psychologically damaging than stressors that threaten less valued role involvements.[3] Indeed, elevated levels of discrimination independently mediate racial inequalities in memory aging, such that Black older adults report more discrimination than non-Hispanic Whites, and greater discrimination predicts faster subsequent memory decline.[2] While the effects of discrimination on mental and physical health outcomes are increasingly being recognized, the biological mechanisms linking everyday discrimination to worse memory functioning are unclear. A better understanding of these mechanisms can facilitate the development and evaluation of interventions to reduce inequalities in late-life memory decline.

According to the biopsychosocial model described by Clark and colleagues (1999), discrimination triggers psychological and physiological stress responses that can lead to negative health outcomes.[4] A growing body of work implicates inflammatory processes in the harmful physiological effects of everyday discrimination. Social stressors such as interpersonal discrimination likely trigger the same, highly conserved biological response as physical threat or injury.[5] Chronic stress-related activation of the sympathetic nervous system (i.e., norepinephrine release), and the hypothalamic-pituitary-adrenal axis (i.e., glucocorticoid resistance) both up-regulate the transcription of pro-inflammatory cytokines,[6] including interleukin-6 (IL-6). Epidemiological studies have documented positive associations between self-reported discrimination and levels of IL-6,[7] as well as C-reactive protein (CRP),[8,9] an acute-phase protein secreted in response to elevated levels of pro-inflammatory cytokines. Inflammation induces immune cells to migrate into vascular lesions, leading to adiposity, plaque instability, and thrombi formation, which occludes arteries and triggers clinical and subclinical coronary events.[10–12] Thus, inflammatory mechanisms likely underlie associations between everyday discrimination and many important health outcomes, including incident cardiovascular disease[13] and mortality.[14]

In addition to these important health outcomes, inflammation may also underlie associations between everyday discrimination and age-related memory decline. Indeed, elevated levels of CRP have been associated with worse performance on episodic memory tasks,[15,16] and an experimental animal study demonstrated that administering CRP to rats led to impaired long-term memory.[17] Peripheral inflammation can modulate central inflammatory processes, resulting in neurodegeneration.[18] Indeed, correlational evidence suggests that brain volumes, particularly within the temporal lobe, mediate associations between peripheral inflammation

and episodic memory performance.[15,16] Episodic memory may be particularly susceptible to the negative effects of inflammation due to relatively high concentrations of pro-inflammatory cytokines and their receptors in brain regions important for memory, including the hippocampus.[19] Together, the studies reviewed provide rationale for the hypothesis that inflammatory processes mediate the effects of everyday discrimination on episodic memory.

Embedded within the biopsychosocial framework,[4] the overall goal of the current study was to provide empirical evidence for a social-biological pathway leading from everyday discrimination to worse episodic memory. Specifically, we aimed to determine whether systemic inflammation, indexed by blood levels of CRP, mediates associations between everyday discrimination and episodic memory over six years, using longitudinal cognitive and biomarker data from a nationally-representative sample of participants aged 51 and older in the Health and Retirement Study.

Methods

Participants

Data were drawn from the Health and Retirement Study (HRS), a nationally representative sample of Americans aged 51 and older followed since 1992.[20] Details of the HRS longitudinal panel design, sampling, and all assessment instruments are available on the HRS website (http://hrsonline.isr.umich.edu). Participants in HRS are interviewed every two years. In 2006, the HRS initiated an enhanced face-to-face interview, which included collecting biomarker and psychosocial data. A random one half of the sample was selected to participate in these procedures in 2006, and the other half was selected to participate in 2008. These individuals then participated in a follow-up face-to-face interview four years later (i.e., 2010 for participants originally interviewed in 2006, 2012 for participants originally interviews in 2008). In the current study, data obtained in 2006 and 2008 were combined to form a baseline time point, and data obtained in 2010 and 2012 were combined to form a second time point. Finally, data from 2012 and 2014 were combined to form a third time point, at which only episodic memory was assessed. Characteristics of the 12,624 individuals included in the current study are provided in Table 1. All participants provided written informed consent, and all study procedures were approved by the University of Michigan institutional review board.

Measures

Memory.—Episodic memory functioning was assessed during the core HRS interview at all three time points. Participants heard a list of 10 words and were asked to recall the words immediately and following a 5-minute delay. To ensure standardized presentation, interviewers were trained to read the items at a slow and steady rate as they appeared on a computer screen, approximately one word every two seconds. To improve reliability of the memory outcome in the current study, raw scores on immediate and delayed recall trials were combined into a z-score composite using the means and standard deviations (SD) from the entire biomarkers subsample at baseline (i.e., either 2006 or 2008).

CRP.—A detailed description of biomarker collection in the HRS is available.[21] In brief, high-sensitivity assays conducted primarily at the University of Vermont measured CRP levels from blood spots. In line with HRS recommendations, the current study used NHANES-equivalent values of CRP, which are based on serum blood, available in 2006/2008 and 2010/2012. In line with American Heart Association and Centers for Disease Control and Prevention guidelines, CRP levels were categorized in terms of cardiovascular disease risk: low (<1 mg/L), moderate (1–3 mg/L), and high (>3 mg/L).[22] Sensitivity analyses indicated that modeling CRP as a continuous variable did not change the pattern of results.

Discrimination.—Everyday discrimination was assessed at baseline with the five-item Everyday Discrimination Scale, administered as part of a leave-behind questionnaire.[23] Items included, "You are treated with less courtesy or respect than other people," "You receive poorer service than other people at restaurants or stores," "People act as if they think you are not smart," "People act as if they are afraid of you," and "You are threatened or harassed." Items are rated for frequency on a 6-point Likert-type scale (1=Almost every day to 6=Never). In the current study, mean scores on the scale were reversed prior to analysis so that higher scores correspond to greater everyday discrimination. Internal consistency for everyday discrimination was adequate ($\alpha = .80$).

Race and ethnicity.—Self-reported race/ethnicity was dummy-coded into four categories: non-Hispanic White, non-Hispanic Black, Hispanic (of any race), and non-Hispanic other. The largest category, non-Hispanic White, was treated as the reference group.

Covariates.—Age (in years) corresponded to age at the time of the 2006 or 2008 assessment wave, depending on the biomarker subsample. Gender was quantified as a dichotomous variable, and male was the reference category. Education was self-reported years of education (0–17). Physical health was assessed during the core HRS interview with self-reported chronic diseases. Chronic disease burden was quantified as the sum of the self-reported presence of the following six chronic conditions: hypertension, diabetes, cancer, lung disease, heart problems, and arthritis. Current smoking was operationalized as self-reported smoking status, with current non-smokers as the reference group. Body mass index (BMI) was computed with the following formula: (weight in pounds) / (height in inches)^2) * 703.

Analytic Strategy

Descriptive statistics were computed in SPSS. Effects of race, ethnicity, and everyday discrimination on CRP and memory trajectories were examined using longitudinal mediation models[24] in Mplus Version 8.[25] All models were weighted using HRS biomarker sample weights and were estimated using maximum likelihood estimation with robust standard errors. Missing data were managed with Full Information Maximum Likelihood. Model fit was evaluated with the following commonly-used indices: comparative fit index (CFI), root-mean-square error of approximation (RMSEA), and standardized root-mean square residual (SRMR). CFI > 0.95, RMSEA < 0.06, and SRMR < 0.05 were used as criteria for adequate model fit.[26]

All models controlled for age, gender, and years of education. Longitudinal associations among discrimination, CRP, and memory were modeled by regressing 2012/2014 memory onto 2010/2012 CRP, which was regressed onto 2006/2008 (baseline) discrimination. All autoregressive paths were also included. Within the same model, cross-sectional associations among discrimination, CRP, and memory were examined by regressing baseline memory onto baseline CRP and discrimination, and by regressing baseline CRP onto baseline discrimination. In addition, all variables were regressed onto race and ethnicity. Indirect effects were defined as the product of regression coefficients within a given path.

Because intersectionality between social identities may be relevant for the variables of interest, a subsequent model controlled for all possible interactions among sociodemographic variables (i.e., gender, race, ethnicity, and education), in addition to the main effects of these variables. Finally, separate models additionally controlled for potential health-related mediators of associations among discrimination, CRP, and memory: smoking status, BMI, and chronic disease burden. These variables were added one at a time in order to pinpoint which might be influencing the pattern of results.

Results

Table 2 displays differences in the primary study variables across the different sociodemographic groups represented in this heterogeneous sample. Non-Hispanic White and Hispanic participants reported less discrimination than non-Hispanic Blacks and non-Hispanic participants who self-identified as a member of any other racial group. Non-Hispanic Blacks were most likely to have high CRP, followed by Hispanics, non-Hispanic Whites, and others. Non-Hispanic Whites obtained higher episodic memory scores than the other three groups. Men reported more discrimination than women, women were more likely to have high CRP than men, and women obtained higher episodic memory scores than men. Years of education was not significantly related to discrimination, but more education was associated with a lower likelihood of having high CRP and better episodic memory scores.

The longitudinal mediation model fit well: CFI = 0.998; RMSEA=0.023 (95% confidence interval: 0.16 – 0.031); SRMR = 0.005. Results from this model are summarized in Figure 1. Independent of CRP trajectories and all covariates, there were significant, independent direct effects of discrimination on both baseline memory and memory six years later. Specifically, greater discrimination was associated with lower memory at baseline ($p < 0.001$) and six years later ($p = 0.031$). In addition, there was a significant indirect effect of discrimination on baseline memory through baseline CRP ($p = 0.029$). As shown in Figure 1, greater discrimination was associated with higher baseline CRP ($p = 0.001$), and higher baseline CRP was associated with lower baseline memory ($p = 0.004$). Baseline discrimination was not associated with CRP four years later ($\beta = 0.02$; SE = 0.01; $p = 0.111$), independent of baseline CRP. Baseline CRP was not associated with memory four years later ($\beta = -0.01$; SE = 0.01; $p = 0.215$), and CRP at the second time point was not associated with memory two years later ($\beta = 0.00$; SE = 0.01; $p = 0.707$). In a subsequent model that additionally controlled for interactions among the sociodemographic variables, the pattern of results was unchanged.

With regard to race and ethnicity, there were significant indirect effects of Black race on baseline episodic memory through baseline discrimination ($p = 0.001$), baseline CRP ($p = 0.011$), and the multiple-mediator pathway involving baseline discrimination and baseline CRP ($p = 0.041$). Specifically, non-Hispanic Black participants reported greater discrimination ($\beta = 0.07$; SE = 0.01; $p < 0.001$). In turn, greater discrimination was associated with higher baseline CRP and lower baseline memory, and higher baseline CRP was associated with lower baseline memory, as summarized above and in Figure 1. Black race was also associated with lower baseline memory independent of discrimination and CRP ($\beta = -0.13$; SE = 0.01; $p < 0.001$). There was also a significant indirect effect of reporting a race/ethnicity other than Hispanic, non-Hispanic Black, or non-Hispanic White on baseline memory through discrimination ($p = 0.007$). Specifically, these participants also reported greater discrimination ($\beta = 0.05$; SE = 0.02; $p = 0.001$), and greater discrimination was associated with lower baseline memory as indicated in Figure 1. This heterogeneous group also obtained lower baseline memory scores independent of discrimination and CRP ($\beta = -0.07$; SE = 0.01; $p < 0.001$).

Next, potential health-related mediators of associations among discrimination, CRP trajectories, and memory trajectories (i.e., smoking status, BMI, and chronic disease burden) were added to the model one at a time. When smoking and chronic disease burden were added to the model, results were similar but slightly attenuated. When BMI was added to the model, results were similar with one exception. Specifically, there was no longer a significant association between discrimination and baseline CRP ($\beta = 0.01$; SE = 0.01; $p = 0.264$) independent of BMI.

Discussion

This nationally representative, longitudinal study provides preliminary evidence that inflammation partially mediates the deleterious effects of everyday discrimination on episodic memory performance among older adults. While CRP significantly mediated the negative association between discrimination and episodic memory at baseline, discrimination also predicted worse memory over the six-year study period independent of CRP and health covariates (i.e., smoking status, BMI, and chronic disease burden). CRP did not significantly mediate the longitudinal effect of discrimination on memory. Therefore, heightened inflammation does not appear to fully explain the harmful effects of discrimination on episodic memory.

The finding of negative associations between everyday discrimination and episodic memory trajectories is in line with previous work in other datasets.[1,27] The current study extends these findings by demonstrating that the concurrent association between discrimination and episodic memory is partially mediated by inflammation, operationalized as blood levels of CRP. Everyday discrimination triggers a biological stress response that can up-regulate inflammatory processes.[6,28] The fact that the concurrent association between discrimination and CRP was eliminated when BMI was added to the model indicates that behavioral and physiological processes that influence weight may represent another potential pathway by which discrimination could lead to inflammation, in line with previous work.[9] Chronic inflammation can then lead to worse episodic memory by directly influencing

neurodegenerative processes[18,29] and/or indirectly via adverse effects on vascular processes[28–30] Indeed, both neurodegenerative and vascular pathologies can underlie episodic memory decline and dementia risk in older adults. In the current study, blood levels of CRP were only associated with baseline episodic memory performance, not subsequent episodic memory change. This sample of adults aged 51 and older exhibited very little memory decline over six years. Modeling episodic memory trajectories over a longer period of time is likely to yield greater decline, more precise estimates of decline, as well as greater variability in decline, which together could reveal associations between CRP and memory trajectories. Experimental evidence that administration of CRP worsens memory lends support to our interpretation that CRP is causally related to episodic memory.[17] However, future studies should examine other markers of inflammation (e.g., IL-6), as well as other biomarkers that may underlie both concurrent and longitudinal associations between discrimination and memory change.

It is notable that everyday discrimination was independently associated with both baseline and follow-up memory despite the relatively short follow-up period, which lends important longitudinal support to the hypothesis that discrimination leads to worse episodic memory. Importantly, reports of everyday discrimination in this sample varied as a function of race, and pathways involving discrimination and CRP partially mediated the association between race and lower episodic memory functioning at baseline. These results provide additional support that both discrimination and inflammation shape racial inequalities in cognitive aging, in line with a biopsychosocial model.[4]

Given the residual effects of everyday discrimination on both baseline memory and longitudinal memory change above and beyond the health and inflammatory markers examined in this study, additional investigations of mechanisms underlying the link between discrimination and episodic memory are needed. For example, observational and experimental studies indicate that experiences of discrimination may induce a broader range of adverse physiological effects involving blood pressure, heart rate, and cortisol,[31] as well as poorer mental health.[23] Future studies should endeavor to integrate vascular, inflammatory, hormonal, and health behavior variables into a more comprehensive model of the longitudinal physiological and cognitive effects of everyday discrimination on episodic memory.

Limitations of this study include the availability of only two time-points of biomarker data, which precluded the use of growth curve modeling to more precisely estimate rates of change. However, the availability of longitudinal biomarker data over four years allowed for a preliminary investigation of longitudinal relationships among everyday discrimination, CRP, and episodic memory that extends the cross-sectional literature. In addition, the list-learning task used in this largescale study is a relatively coarse measure of episodic memory in that it includes only a single learning trial and a relatively brief delay (i.e., five minutes). However, this measure has been shown to be sensitive to age-related decline[2] and dementia.[32] It should also be noted that cognitive performance among diverse adults can be affected by stereotype threat,[33] which can contribute to group differences and cannot be fully evaluated with the available data. This study was also limited by the use of self-reports of doctor-diagnosed health conditions to control for chronic disease burden. Future studies are

needed to more objectively evaluate the role of specific health conditions in the pathway between everyday discrimination and episodic memory. Given that CRP was the only available inflammatory biomarker, future studies should also include a more comprehensive set of biomarkers to better characterize the influence of everyday discrimination on inflammatory processes. Indeed, the HRS recently collected venous blood, which can be subjected to additional assays of inflammatory and other biomarkers.

Another limitation is the availability of only an abbreviated (five-item) version of the Everyday Discrimination Scale. While this measure exhibited adequate internal consistency in this sample (α=0.80), it may have reduced sensitivity and/or specificity, which could have decreased our ability to precisely estimate associations between discrimination and outcomes. In line with previous work,[2,13,27,34,35] this study operationalized everyday discrimination as self-reported frequency of discrimination experiences without reference to individuals' attributions (e.g., age, gender, race, ethnicity). Future studies could explore whether pathways linking discrimination and health differ across attributions, but it is important to note that significant discrimination-health associations have been found across sociodemographic groups and regardless of attributions.

In addition to race, levels of discrimination differed across gender in the current study. Research on the equivalence of the Everyday Discrimination Scale across race and ethnicity has been conflicting,[36,37] and scale equivalence has not been systematically evaluated across other sociodemographic groups. Such work is complicated by intersectionality between social identities such as race, gender, and social class. The current study attempted to account for such intersectionality by controlling for interacting effects of these variables on both CRP and memory. It should also be noted that the self-report discrimination measure used in this and many other studies quantifies subjective perceptions of events without objective verification. Given that stress responses are believed to be a primary pathway linking discrimination and health,[38] the perception of discrimination is most relevant to health since subjective interpretations drive physiological stress response.[39]

Strengths of this study include its large, nationally-representative sample of older adults. The use of sampling weights allows the current findings to be generalized to the larger U.S. population of adults over age 50. The mediation framework also allowed for an empirical demonstration that inflammation may represent a mechanism underlying discrimination-memory pathways, but mediation was limited to concurrent, baseline measures. Thus, more comprehensive biopsychosocial models are needed to more fully understand mechanisms underlying the longitudinal association between discrimination and episodic memory observed in this and other studies. Results from this study underscore the cognitive health relevance of everyday discrimination and extend our understanding of social-biological pathways to successful versus unsuccessful cognitive aging, as well as cognitive inequalities. Findings can be used to guide future prevention and intervention efforts at the social and biological levels to promote healthy memory functioning with age.

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- Perceived discrimination predicts greater age-related memory decline prospectively
- Perceived discrimination is associated with higher levels of C-reactive protein
- Higher C-reactive protein is associated with worse memory in older adults
- C-reactive protein partially mediates negative effects of discrimination on memory
- Inflammation is a mechanism of the negative cognitive impact of discrimination

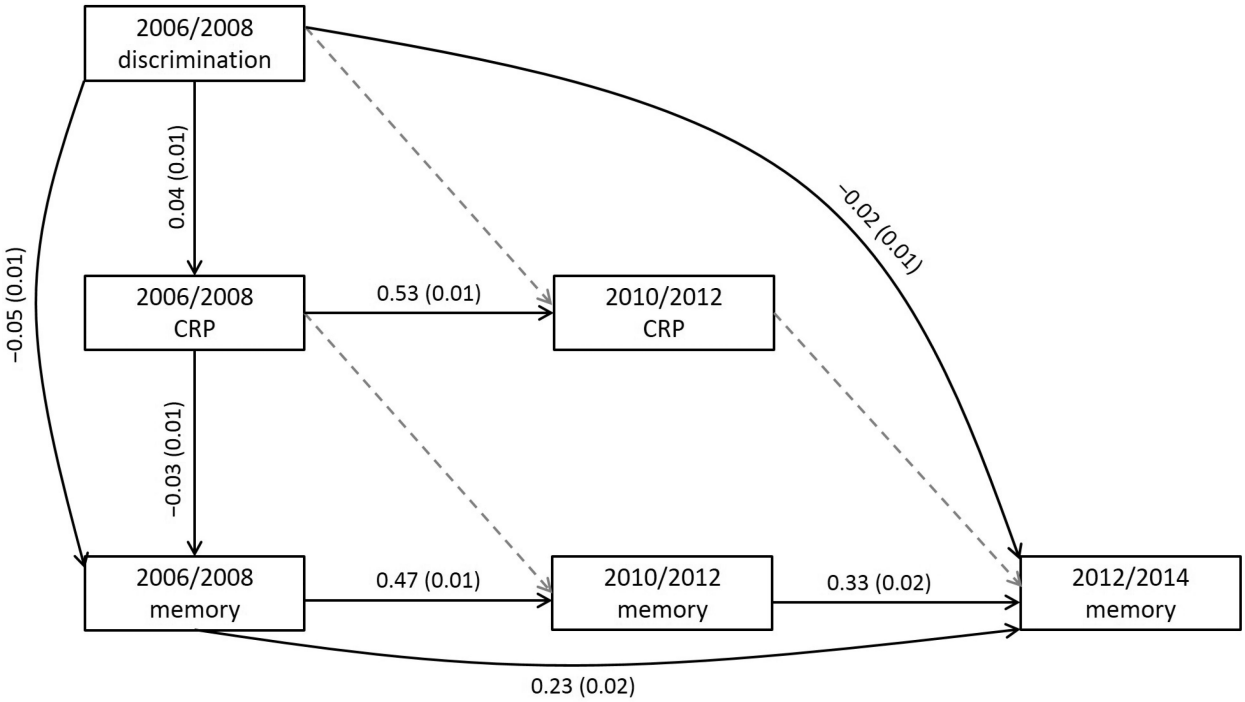

Figure 1.

Schematic of the longitudinal mediation model. Solid lines indicate significant (p<0.05) paths, and dotted lines indicate nonsignificant paths. Values shown are standardized estimates (standard errors). For simplicity, race, ethnicity, and covariates (i.e., age, gender, education) are not shown. *Note.* CRP = C-Reactive protein.

Table 1.

Sample characteristics at baseline

	Mean (SD) or %
Age (51–101)	68.8 (9.9)
Gender (% women)	58.9
Race/ethnicity (%)	
Non-Hispanic White	76.2
Non-Hispanic Black	12.9
Hispanic (any race)	8.8
Other	2.1
Education (0–17)	12.5 (3.2)
Smoking (% yes)	13.1
Body mass index	28.2
Chronic disease burden (0–6)	1.9 (1.3)
Everyday discrimination (1–6)	1.6 (0.7)
CRP	
% Low (<1 ug/mL)	29.0
% Moderate (1–3 ug/mL)	34.0
% High (>3 ug/mL)	37.0
Immediate recall (0–10)	5.4 (1.6)
Delayed recall (0–10)	4.3 (2.0)

Note. CRP = C-Reactive Protein.

Table 2.

Sociodemogra phic differences in primary variables of interest at baseline (2006/2008)

	Discrimination	CRP (% High)	Episodic memory
Race and ethnicity			
Non-Hispanic White	1.6 (0.7)	35.1	0.9 (0.9)
Non-Hispanic Black	1.8 (0.9)	48.1	−0.4 (0.9)
Hispanic (any race)	1.6 (0.8)	39.8	−0.3 (0.9)
Non-Hispanic Other	1.9 (0.9)	27.3	0.2 (0.9)
Group differences	W=H<B=O [a]	O<W<H<B [b]	B=H=O<W [a]
Gender			
Male	1.7 (0.8)	31.8	−0.2 (0.9)
Female	1.6 (0.7)	40.7	0.9 (0.9)
Group differences	F<M [c]	M<F [b]	M<F [c]
Education (years)	Fewer = More [d]	More < Fewer [c]	Fewer < More [d]

Note. CRP = C-reactive protein (High = >3ug/mL); GED = General Equivalency Diploma; B = Non-Hispanic Black; H = Hispanic (any race); W = Non-Hispanic White; O = Other race/ethnicity

[a]Based on one-way analysis of variance with Bonferroni-corrected post hoc tests

[b]Based on Bonferroni-corrected chi square test(s)

[c]Based on independent samples t-test

[d]Based on Pearson correlation