Early Life Adversity and Inflammation in African Americans and Whites in the Midlife in the United States Survey

Natalie Slopen, MA, ScD, Tené T. Lewis, PhD, Tara L. Gruenewald, PhD, Mahasin S. Mujahid, PhD, Carol D. Ryff, PhD, Michelle A. Albert, MD, MPH, and David R. Williams, PhD, MPH

Objectives: To determine whether early life adversity (ELA) was predictive of inflammatory markers and to determine the consistency of these associations across racial groups. **Methods:** We analyzed data from 177 African Americans and 822 whites aged 35 to 86 years from two preliminary subsamples of the Midlife in the United States biomarker study. ELA was measured via retrospective self-report. We used multivariate linear regression models to examine the associations between ELA and C-reactive protein, interleukin-6, fibrinogen, endothelial leukocyte adhesion molecule-1, and soluble intercellular adhesion molecule-1, independent of age, gender, and medications. We extended race-stratified models to test three potential mechanisms for the observed associations. **Results:** Significant interactions between ELA and race were observed for all five biomarkers. Models stratified by race revealed that ELA predicted higher levels of log interleukin-6, fibrinogen, endothelial leukocyte adhesion molecule-1, and soluble intercellular adhesion molecule-1 among African Americans ($p < .05$), but not among whites. Some, but not all, of these associations were attenuated after adjustment for health behaviors and body mass index, adult stressors, and depressive symptoms. **Conclusions:** ELA was predictive of high concentrations of inflammatory markers at midlife for African Americans, but not whites. This pattern may be explained by an accelerated course of age-related disease development for African Americans. **Key words:** childhood, early life adversity, inflammation, life course epidemiology, race/ethnicity, chronic disease risk.

BMI = body mass index; **CRP** = C-reactive protein; **CVD** = cardiovascular diseases; **E-selectin** = endothelial leukocyte adhesion molecule-1; **ELA** = early life adversity; **GCRC** = general clinical research center; **IL** = interleukin; **MIDUS** = Midlife in the U.S. survey; **SEP** = socioeconomic position; **sICAM-1** = soluble intercellular adhesion molecule-1.

INTRODUCTION

A life course approach to chronic disease directs us to consider childhood origins of adult diseases (1). Research indicates that early life adversity (ELA) is associated with an increased risk for a broad range of diseases, including cardiovascular diseases (CVD), diabetes, cancers, and psychiatric disorders (2–4). Recently, researchers (5–7) have begun to investigate physiologic mechanisms linking early life experiences to health later in life. One physiological pathway that is gaining interest as a potential link between ELA and increased risk of morbidity later in life is inflammation, as inflammatory processes are involved in a number of health conditions that might vary by level of life adversity. Large-scale epidemiologic studies (8–11) provided support for an association between several blood markers of inflammation and age-related diseases, including CVD and cancer. A growing body of research (12–15) has demonstrated associations between social conditions in adulthood and inflammatory outcomes, and evidence (5,6,16–18) is mounting that early life social conditions are also linked to levels of inflammatory burden later in life. To date, little is known about the extent to which the relationship of ELA with the health of African Americans (or blacks, we use the terms interchangeably) in midlife differs from that of whites.

Among previous investigations of the association between ELA and inflammation, researchers have documented increased risk of inflammation associated with low socioeconomic position (SEP) in childhood (16–18), harsh family environment (6), and maltreatment (5). A limitation of this series of work is that most studies consider the influence of an isolated stressor; however, multiple stressors in childhood often co-occur (19). It is important to study multiple adversities simultaneously, because individuals exposed to a variety of stressors are at great risk of exhausting psychological and physiological resources to effectively cope with stress (20).

Childhood adversity experiences may vary by sociodemographic variables, including race/ethnicity. In the United States, as a result of severe residential segregation, it is common for black and white children to inhabit distinct environments (21). As a consequence, blacks and whites may be exposed to dramatically different types of stressors and stress-buffering resources throughout the life course. Researchers have hypothesized that African Americans may experience more rapid deterioration in health, relative to whites, due to cumulative exposure to multiple sources of social and economic adversity. Accelerated aging theories, such as the Weathering Hypothesis (22,23), direct us to consider multiple sources of stressors over time, and draw attention to the role of differential exposure to stress in producing racial inequities in health. On this basis, application of a life course perspective to understanding racial health disparities is important.

In the present study, our first objective was to examine the association between a composite measure of ELA and concentration of five markers of inflammation known to be associated

From the Harvard School of Public Health (NS, DRW), Boston, MA; Yale School of Public Health (TTL), New Haven, CT; David Geffen School of Medicine at UCLA (TLG), Los Angeles, CA; School of Public Health (MSM), University of California, Berkeley, Berkeley, CA; Institute of Aging (CDR), University of Wisconsin, Madison, Madison, WI; and Brigham and Women's Hospital (MAA), Harvard Medical School, Boston, MA.

Address correspondence and reprint requests to Natalie Slopen, MA, ScD, Department of Society, Human Development, and Health, 677 Huntington Avenue, Boston, MA 02115.

Received for publication September 23, 2009; revision received April 29, 2010.

This research was supported, in part, by Grant P01-AG020166 from the National Institute on Aging to conduct a longitudinal follow-up of the MIDUS (Midlife in the United States) investigation. The original study was supported by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development. Support was also provided by Grant 1UL1RR025011 (University of Wisconsin) from the Clinical and Translational Science Award program of the National Center for Research Resources, National Institutes of Health. This research was also supported, in part, by a Doctoral Research Award from the Canadian Institutes of Health Research awarded to the first author. T. Lewis was supported by Grant HL092591 from the National Heart, Lung and Blood Institute.

DOI: 10.1097/PSY.0b013e3181e9c16f

0033-3174/10/7207-0694

with CVD: C-reactive protein (CRP) (24), interleukin-6 (IL-6) (25), fibrinogen (26), endothelial leukocyte adhesion molecule-1 (E-selectin) (10), and soluble intercellular adhesion molecule-1 (sICAM-1) (27). These inflammatory markers were selected based on prior evidence of patterning by social exposures (5,17,28,29). We hypothesized that greater exposure to ELA would be associated with higher concentrations of each inflammatory marker. The second objective was to determine whether these associations were similar for black and white respondents. On the basis of evidence for an accelerated course of disease progression among individuals exposed to a high burden of stressors (23,30), we hypothesized that the association between ELA and inflammation at midlife would be more pronounced for African Americans in our sample. In secondary analyses, we evaluated health, behavioral, and psychosocial risk factors that may serve as potential mechanisms by which ELA leads to higher levels of inflammation in midlife.

Sample

The sample for our analysis was comprised of two preliminary subsamples from the Midlife in the United States (MIDUS) biomarker study: one from participants who were enrolled in the original MIDUS longitudinal sample, and the other from a city-specific sample of African Americans from Milwaukee, Wisconsin. The original MIDUS participants (n = 7108, aged 25–74 years at baseline) were recruited between January 1995 and September 1996 from a national random-digit-dial sample of noninstitutionalized adults living in the 48 contiguous states (31). This sample included siblings for some respondents, and some pairs of twins. Between January 2004 and August 2005, a follow-up of 4,963 MIDUS I respondents took place (70% response rate; referred to as MIDUS II). At this time, a supplement sample of 592 African Americans from Milwaukee, Wisconsin was recruited to participate. This supplement sample increased the participation of African Americans in MIDUS and facilitated analyses of biopsychosocial influences on health in a highly segregated American city that was in geographic proximity to one of the clinic sites. The research team also had prior experience in bringing African Americans from Milwaukee to Madison, Wisconsin, for biological data collection.

Respondents from the MIDUS II and Milwaukee samples were eligible to participate in the biomarker study if they participated in the telephone interview (or home interview for Milwaukee) and mail surveys, and lived in the continental United States; this required an overnight at one of three General Clinical Research Centers (GCRC). As of July 2008, a total of 1,038 individuals participated in biological assessments, 999 of whom comprised the sample for these analyses. There were 39 non-black minority participants from the MIDUS II cohort excluded from this analysis because this group was not large enough to create independent samples by racial category. The sample of 999 individuals included 822 whites and 26 blacks from MIDUS II, and 151 blacks from the Milwaukee sample.

Data collection for the MIDUS, Milwaukee, and biomarker studies were approved by Institutional Review Boards at the University of Wisconsin, Madison, as well as UCLA and Georgetown University, which served as additional sites of data collection for the biomarker substudy. All participants provided their informed consent.

For both the MIDUS II and Milwaukee samples, individuals who participated in the GCRC assessment were significantly more likely to have a college degree relative to nonparticipants; no significant differences were observed for age, gender, marital status, or employment status. For the African American respondents only, the mean ELA score was modestly but significantly higher for individuals who participated in the biomarker study relative to those who did not (by approximately one quarter of a standard deviation [SD]).

Measures

Inflammatory Markers

Fasting serum samples were assayed for CRP, IL-6, fibrinogen, E-selectin, and sICAM-1, according to the manufacturer's guidelines (Dade Behring Inc., Deerfield, IL, for CRP and fibrinogen; R&D Systems, Minneapolis, MN, for IL-6, E-selectin, and sICAM-1). Citrated plasma CRP and fibrinogen were assayed, using immunonephelometric assay; IL-6 was assayed, using enzyme-linked immunosorben assay; and E-selectin and sICAM-1 were assayed, using high-sensitivity enzyme-linked immunosorbent assay. For all biomarkers, the laboratory coefficients of variance were $<$11%. In regression models, CRP and IL-6 were log-transformed to improve normality of the distributions, and all inflammatory markers were modeled as continuous variables. In addition, we created a summary score to capture overall inflammatory burden. We assigned 1 point for each inflammatory marker above the sample median (range, 0–5), following an approach used in previous publications (16). A score was only created for individuals with valid observations for all five outcomes (n = 978).

ELA

ELA was measured using retrospective report of events or conditions experienced in childhood and adolescence, collected in surveys that were completed before recruitment for biological assessment. It is a composite score reflecting three domains of stress. First, stressful events during childhood/adolescence were measured, using a nine-item inventory; events included school failure, being sent away from home for doing something wrong, parental unemployment when wanting to work, parental alcohol problems, parental drug problems, dropped out of school, expelled/suspended from school, receipt of welfare, moved to new neighborhood/town two or more times. Second, self-report rating of relationship with parents during childhood was evaluated, using two items (1 item for mother, 1 item for father), using a 5-point scale. Third, frequency of verbal and physical assault by parents was evaluated, using six items from the Conflict Tactics Inventory (32); three items referred to interactions with mother, three items referred to interactions with father. The items captured frequency of verbal and emotional abuse, and moderate and extreme acts of physical violence on a 4-point scale ("never"

to "often"). Because the three domains of ELA were each measured on a different scale (i.e., had different ranges of values), we standardized the domain scores into Z scores, and then created a Z-scored composite of the three domains. The composite score was standardized for the full sample of all MIDUS and Milwaukee participants.

Demographic Covariates

Demographic covariates were selected based on the prior literature (33). Self-reported race and gender were coded using indicator variables, and a linear covariate for age was used. Educational attainment was measured using a three-category variable: high school degree or less, some college (no degree), and Associate's/Bachelor's degree. We adjusted for use of four classes of medications (as inventoried by staff at the GCRC): use of antihypertensive, lipid-lowering, corticosteroid, and antidepressant medications was indicated with dummy variables. We adjusted for use of these medications based on research showing that these medications affect circulating markers of inflammation (34–37).

Covariates in Extended Models

Secondary analyses were conducted to determine if any observed associations between ELA and elevated inflammation were independent of body mass index (BMI), health behaviors (smoking, exercise), stressful life events in adulthood, and depressive symptoms. These factors were selected based on research (2,3,38,39) suggesting that individuals exposed to ELA have increased risk of these experiences and conditions, and other research (5,6,16,40) showing that these factors may act as pathways through which ELA is associated with elevated inflammation. In addition, in the extended models, we adjusted for self-reported physician-diagnosed history of CVD (stroke or heart attack), diabetes mellitus, and cancer, because it is possible that the onset of these conditions may have temporally preceded elevations in inflammation.

BMI and Health Behaviors

BMI (kg/m^2) was measure by GCRC staff and modeled continuously. Vigorous exercise, reflective of cardiorespiratory fitness, was defined as self-report of vigorous activity at least three times per week, and was modeled using a dichotomous variable. Smoking status was a three-category variable (current, previous, or never).

Adult Stress Events

A measure of adult stress events was created, using responses from the MIDUS stressful life event inventory, created for the purpose of the MIDUS study. The inventory includes acute stressors similar to those included in standard stressful life event measures (e.g., child died, parent died, sexual assault, bankruptcy, combat experience) (41). The inventory asked participants to identify the age at which each event occurred. Separate scores were created for: 1) stressful events in the past 5 years ($n = 20$ events); and 2) stressful events >5 years ago ($n = 23$ events). If the respondent endorsed an event but no age was specified, the event was categorized as occurring >5 years ago. Similar to the procedure used to create the ELA composite score, the two inventory scores were standardized into Z scores, and the two standardized scores were summed. The summated value was then standardized into a Z score.

Depressive Symptoms

A continuous measure of depressive symptoms in the past week was created, using the 20-item Center for Epidemiological Studies Depression Inventory (42).

Statistical Analyses

Analyses were performed, using SAS 9.2. Descriptive statistics were generated for all variables (means and SDs for continuous variables; proportions for discrete variables). Linear regression models were used to estimate the effect of ELA on inflammation, using separate models for each outcome. All models were adjusted for age, gender, and medication use. First, we ran a series of baseline models to examine the effect of ELA on each inflammatory marker. We tested for effect modification by race, using an interaction term, and then we constructed race-stratified models when appropriate.

To test hypotheses about possible mechanisms that may underlie the association between ELA and inflammation, we extended race-stratified models. The stratified models were adjusted for educational attainment to control for SEP, in addition to age, gender, medication use, and prior history of CVD, diabetes, and cancer. We assessed the potential role of BMI and health behaviors, adult stress events, and depressive symptoms by considering the percent change in the size of the ELA coefficient when these covariates were included.

The sample included 103 pairs of twins, and no sibling pairs: 101 pairs of twins were white and 2 were black. For models that included white participants, we ran models using 1) ordinary regression, and 2) generalized estimating equations (GEE) to account for clustering. We observed that the findings were nearly identical. Given that there were only two sets of twins in the African American sample, generalized estimating equations were not appropriate for models that included only African American participants. Therefore, to test the potential effect of the two twin pairs in the African American sample within race-stratified models, we compared models using the full sample to models that excluded the two sets of twins: we observed that the results were unchanged. Informed by these sensitivity analyses documenting that our findings are not affected by the presence of twins, we report the findings from the single-level models in order to present a consistent modeling strategy for all analyses.

Missing Data

Information from the mail survey was used in the measures of ELA and adult stress events, and some surveys were returned with incomplete information. We used multiple imputation to estimate missing values for the measures within the composite scores of ELA and adult stress events. Multiple

TABLE 1. Characteristics of White and Black Study Participants (n = 999); Study of Midlife in the United States (MIDUS)

	White Respondents (n = 822) Mean (SD) or %	African American Respondents (n = 177) Mean (SD) or %	p
Age	58.66 (11.65)	54.15 (10.71)	<.001
Gender			
Male	47.20	32.77	.001
Female	52.80	67.23	
Inflammatory markers			
CRP (μg/mL)	2.75 (4.52)	4.93 (6.97)	<.001
IL-6 (pg/mL)	2.73 (2.81)	4.11 (3.45)	<.001
Fibrinogen (mg/dL)	336.00 (84.82)	386.80 (100.70)	<.001
E-selectin (ng/mL)	38.44 (18.38)	43.75 (22.98)	.001
sICAM-1 (ng/mL)	305.70 (98.74)	305.10 (177.80)	.96
Summary score[a]	2.35 (1.51)	3.13 (1.39)	<.001
Early life adversity (Z score)	0.01 (1.00)	0.17 (1.06)	.08
Stress events (Z score)	−0.13 (0.86)	0.39 (1.18)	<.001
Relationship with parents (Z score)	0.13 (1.00)	−0.20 (0.98)	<.001
Verbal/physical abuse (Z score)	0.01 (1.01)	0.16 (1.10)	.09
Education			
<High school degree	24.09	46.89	<.001
Some college	22.38	26.55	
Associate's/Bachelor's Degree	53.53	26.55	
Adult stress events (Z score)	−0.03 (0.96)	0.82 (1.29)	<.001
Past 5 yrs (Z score)	−0.06 (0.92)	0.58 (1.50)	<.001
6+ years ago (or unidentified; Z score)	0.01 (0.99)	0.61 (1.16)	<.001
Health behaviors			
Current smoker	11.21	29.94	<.001
Ex-smoker	33.86	33.33	
Never Smoker	54.93	36.72	
Vigorous exercise >3 times/wk	25.87	14.11	<.001
BMI	29.14 (5.95)	33.35 (8.89)	<.001
CVD diagnosis (% yes)	14.23	13.56	.82
Diabetes diagnosis (% yes)	10.34	24.29	<.001
Prior cancer diagnosis (% yes)	14.96	10.17	.10
CES-D symptoms	7.99 (7.78)	12.46 (10.02)	<.001
Current medications (% yes)			
Blood pressure medication	34.55	47.46	.001
Cholesterol medication	29.93	18.64	.002
Corticosteroid medication[b]	12.17	9.60	.34
Antidepressant medication	15.45	7.91	.009

[a] The summary score ranges from 0 to 5; 1 point is given for each maker above the sample median.
[b] Corticosteroid medication includes adrenals, estrogens, anti-estrogens, and estrogen agonists-antagonists.
SD = standard deviation; CRP = C-reactive protein; IL = interleukin; E-selectin = endothelial leukocyte adhesion molecule-1; sICAM-1 = soluble intercellular adhesion molecule-1; BMI = body mass index; CVD = cardiovascular disease; CES-D = Center for Epidemiological Studies Depression Inventory.

imputation is a strategy that can reduce bias and is preferred to complete case analysis because it does not assume that data are missing completely at random and makes full use of available data (43). IVEware (44) was used to create ten imputed data sets, and PROC MIANALYZE was used for the regression models to analyze the imputed data.

RESULTS

Table 1 presents characteristics of the white and African American participants. The mean age of the sample was 57.86 years (range, 35–86 years). African American participants were younger, less educated, and more likely to be female than white participants. On average, the African American respondents had a higher ELA score, but this difference was not statistically significant (p = .08). The mean inflammation values for the black respondents were significantly higher for CRP, IL-6, fibrinogen, and E-selectin relative to the white respondents (all $p < .01$); there was not a significant difference by race for sICAM-1 (p = .96).

Table 2 presents multiple regression models adjusted for age, gender, and medication use. In the first set of models, we tested our hypothesis that individuals exposed to high levels of ELA have increased risk for elevated markers of inflammation in adulthood. ELA was significantly associated with elevated concentration of sICAM-1 (b = 9.17, $p < .05$), but not with any of the other outcomes. In a second set of models, which included an interaction term to examine effect modification by race, all five inflammatory outcomes and the summary score showed a significant interaction between ELA and race. These models indicated that higher inflammation level was associ-

TABLE 2. Unstandardized Ordinary Least Square Regression Coefficients (and Standard Errors) for Inflammatory Outcomes; Study of Midlife in the United States (MIDUS)

	Log CRP (μg/mL) b(SE)	Log IL-6 (pg/mL) b(SE)	Fibrinogen (mg/dL) b(SE)	E-selectin (ng/mL) b(SE)	sICAM-1 (ng/mL) b(SE)	Summary[a] b(SE)
Model 1. Baseline Models[b]						
Early life adversity (Z score)	0.01 (0.04)	0.01 (0.02)	2.48 (2.77)	0.84 (0.63)	9.17 (3.74)*	0.04 (0.05)
Race						
African American	0.46 (0.10)***	0.47 (0.06)***	51.00 (7.39)***	4.73 (1.65)**	−1.42 (10.02)	0.75 (0.13)***
White (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Model 2. Including Interaction Term[b]						
Early life adversity (Z score)	−0.03 (0.04)	−0.02 (0.03)	−1.07 (3.09)	0.21 (0.70)	2.93 (4.16)	−0.03 (0.05)
Race						
African American	0.43 (0.09)***	0.45 (0.06)***	48.71 (7.43)***	4.30 (1.67)**	−5.74 (10.05)	0.70 (0.13)***
White (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Early Adversity × Race						
African American	0.22 (0.09)*	0.16 (0.06)**	17.52 (6.76)**	3.13 (1.53)*	31.23 (9.16)**	0.34 (0.12)**
White (reference)	1.00	1.00	1.00	1.00	1.00	1.00

[a] The summary score ranges from 0 to 5; 1 point is given for each maker above the sample median.
[b] Models 1 and Model 2 include the presented covariates, in addition to age, gender, and medication use (blood pressure, cholesterol, steroid, and antidepressant medications). Unstandardized coefficients and standard errors are from separate linear regression models.
* $p < .05$; ** $p < .01$; *** $p < .001$.
CRP = C-reactive protein; IL = interleukin; E-selectin = endothelial leukocyte adhesion molecule-1; sICAM-1 = soluble intercellular adhesion molecule-1; SE = standard error.

TABLE 3. Unstandardized Ordinary Least Square Regression Coefficients (and Standard Errors) for Inflammatory Outcomes in Race-Stratified Models; Study of Midlife in the United States (MIDUS)

	Log CRP (μg/mL) b(SE)	Log IL-6 (pg/mL) b(SE)	Fibrinogen (mg/dL) b(SE)	E-selectin (ng/mL) b(SE)	sICAM-1 (ng/mL) b(SE)	Summary[a] b(SE)
White Sample[b]						
Early life adversity (Z score)	−0.04 (0.04)	−0.02 (0.03)	−1.96 (3.01)	0.17 (0.67)	2.86 (3.56)	−0.04 (0.05)
African American Sample[b]						
Early life adversity (Z score)	0.14 (0.09)	0.11 (0.05)*	15.66 (7.03)*	3.54 (1.70)*	29.49 (12.90)*	0.25 (0.10)*

[a] The summary score ranges from 0 to 5; 1 point is given for each maker above the sample median.
[b] Models adjusted for age, gender, education, and medication use (blood pressure, cholesterol, steroid, and antidepressant medications). Unstandardized coefficients and standard errors are from separate linear regression models.
* $p < .05$.
CRP = C-reactive protein; IL = interleukin; E-selectin = endothelial leukocyte adhesion molecule-1; sICAM-1 = soluble intercellular adhesion molecule-1; SE = standard error.

ated with ELA for the African American respondents, relative to the white respondents, for each outcome. Therefore, we used race-stratified models for the remainder of our analysis.

Table 3 presents race-stratified models, adjusted for age, gender, medications, and educational attainment. For the white sample, the models did not indicate a main effect of ELA for any of the inflammatory markers or the summary score. However, for the black sample, models indicated that ELA had a significant positive association with log IL-6 (b = 0.11, SE = 0.05; $p < .05$), fibrinogen (b = 15.66, SE = 7.03; $p < .05$), E-selectin (b = 3.54, SE = 1.70; $p < .05$), sICAM-1 (b = 29.49, SE = 12.90; $p < .05$), and the summary score (b = 0.25, SE = 0.10; $p < .05$). The association for log CRP was marginally significant in the expected direction (b = 0.14, SE = 0.09; $p = .12$); therefore, it was retained for consideration in the extended models.

In Table 4, we present extended models to examine whether the observed associations between ELA and the inflammatory outcomes in the black sample were independent of potentially relevant variables. The models were organized to consider the impact of adjustment for 1) BMI, smoking, and vigorous exercise; 2) adult stressful life events; and 3) depressive symptoms. The baseline (comparison) model (Model 1) in this analysis is adjusted for age, gender, medications, educational attainment, and prior history of CVD, diabetes, or cancer. The effect estimates in Model 1 show statistically significant associations between ELA and IL-6, fibrinogen, E-selectin, sICAM-1, and the summary score, adjusting for the

TABLE 4. African American Sample, Models Extended to Include Health Behaviors, Adult Stress Events, and Depressive Symptoms; Study of Midlife in the United States (MIDUS)

	Log CRP (μg/mL) b(SE)	Log IL-6 (pg/mL) b(SE)	Fibrinogen (mg/dL) b(SE)	E-selectin (ng/mL) b(SE)	sICAM-1 (ng/mL) b(SE)	Summary[a] b(SE)
Model 1. Baseline (Comparison) Model[b]						
Early life adversity (Z score)	0.13 (0.09)	0.10 (0.05)*	15.69 (7.10)*	3.69 (1.72)*	28.32 (13.02)*	0.24 (0.10)*
Model 2. Health Behaviors[b]						
Early life adversity (Z score)	0.10 (0.08)	0.09 (0.05)	13.19 (6.56)*	3.80 (1.72)*	29.11 (13.01)*	0.22 (0.09)*
Current smoker	0.10 (0.22)	0.29 (0.14)*	20.26 (18.55)	4.03 (4.72)	46.92 (36.01)	0.37 (0.25)
Ex-smoker	0.10 (0.21)	0.08 (0.13)	−4.99 (17.00)	−5.75 (4.40)	−14.67 (33.57)	−0.22 (0.23)
Never smoked (ref)	1.00	1.00	1.00	1.00	1.00	1.00
Vigorous exercise	−0.38 (0.25)	−0.01 (0.16)	−19.76 (20.56)	−4.79 (5.34)	−58.90 (40.75)	−0.76 (0.28)*
BMI	0.06 (0.01)***	0.03 (0.01)***	4.84 (0.84)***	0.04 (0.22)	−0.11 (1.65)	0.06 (0.01)***
Model 3. Stressful Events in Adulthood[b]						
Early life adversity (Z score)	0.10 (0.10)	0.09 (0.06)	12.98 (7.75)	2.77 (1.86)	29.33 (14.16)*	0.21 (0.10)*
Adult stress events (Z score)	0.07 (0.08)	0.03 (0.05)	5.97 (6.83)	2.08 (1.60)	−2.30 (12.30)	0.07 (0.09)
Model 4. Depressive Symptoms[b]						
Early life adversity (Z score)	0.13 (0.09)	0.11 (0.06)	16.21 (7.40)*	2.66 (1.80)	27.01 (13.87)	0.22 (0.10)*
CES-D Symptoms	0.00 (0.01)	0.00 (0.01)	−0.08 (0.85)	0.42 (0.20)*	0.56 (1.58)	0.01 (0.01)

[a] The summary score ranges from 0 to 5; 1 point is given for each maker above the sample median.

[b] Models 1, 2, 3, and 4 include the covariates presented, in addition to age, gender, education, medication use (blood pressure, cholesterol, steroid, and antidepressant medications), and indicator variables for prior history of cardiovascular disease, diabetes, and cancer. Unstandardized coefficients and standard errors are from separate linear regression models.

* $p < .05$; ** $p < .01$; *** $p < .001$.

CRP = C-reactive protein; IL = interleukin; E-selectin = endothelial leukocyte adhesion molecule-1; sICAM-1 = soluble intercellular adhesion molecule-1; SE = standard error; BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Inventory.

covariates noted above. Model 2, which includes covariates for vigorous exercise, smoking status, and BMI, shows that significant positive associations between ELA and fibrinogen, E-selectin, sICAM-1 and the summary score were maintained; however, the association between ELA and log IL-6 was no longer statistically significant. The percent change in the size of the ELA parameter estimates was largest for log IL-6, fibrinogen, and the summary score when exercise, smoking status, and BMI were included in the models (8% to 16%), whereas the estimated coefficients for E-selectin and sICAM-1 were relatively similar to Model 1.

Model 3 included a covariate for adult stress events; in this series of models, only sICAM-1 and the summary score maintained significant associations with ELA; the significance of the associations between ELA with IL-6, fibrinogen, and E-selectin dropped below $p = .05$. Relative to the baseline model, the parameter estimates were reduced by 10%, 17%, 25%, and 13%, respectively, for IL-6, fibrinogen, E-selectin, and summary score. The coefficient for sICAM-1 did not change. In Model 4, we included a covariate for depressive symptoms: the parameter estimates for the association between ELA with fibrinogen and the summary score remained significant at $p < .05$, whereas the other associations were no longer statistically significant. For this model, including depressive symptoms, the coefficient estimate for the association between ELA and E-selectin was substantially attenuated in comparison to Model 1 (reduced by 28%).

This series of extended models suggests that the association between ELA and inflammation may partially operate through the influence of ELA on health behaviors and particularly, BMI. In general, the coefficients for adult stress events and depressive symptoms were not significant in these adjusted models, yet inclusion of these covariates causes the effect of ELA to drop from significance for several of the inflammatory markers. This may suggest that these variables have a small role for some of the observed associations that cannot be detected in our small sample.

Of note, for the majority of the inflammatory markers that have significant associations with ELA, standard cut-points for clinically meaningful risk are not yet established. However, the extended models can provide insight on biological significance by allowing for a comparison between the estimated coefficients for ELA and the estimated coefficients for BMI, a known risk factor for a wide range of chronic diseases (45). For each of the outcomes considered, each 1-unit increase in ELA (i.e., equivalent to the SD) is associated with an increase in inflammatory score that is larger than the increase associated with each 1-unit increase in BMI (Table 4, Model 2).

Supplemental Analyses

To rule out concern that the associations between ELA and inflammation were caused by the dominant influence of one component of our ELA measure, we performed post hoc analyses to determine if there was a single necessary component for the patterns observed. We replicated our models, using ELA measures that included only two of the three scales that comprised our measure (data not shown). In these analyses, the statistical interaction effects were largely unchanged for all three variations,

demonstrating that there is not a dominant component causing the effect modification by race. In the race-stratified models with the African American sample, the coefficient estimates for the partial ELA scores were generally smaller than the estimates obtained with the original measure, which demonstrates the value of integrating multiple forms of adversity. In addition, we examined a complete-case analysis and found comparable results to those obtained using multiple imputed data sets.

DISCUSSION

The data from the MIDUS provide a unique opportunity to examine the association between ELA and inflammation, and to compare the impact of ELA on these markers for African Americans and whites in the sample. In comparison to prior investigations of the association between adversity in childhood and later inflammation, the pattern of our results is generally consistent with previous findings for the African Americans in our sample but not for the white participants (5,6,16–18).

Previous research (6,16) related to the association between ELA and inflammation that has utilized racially heterogeneous samples showed inconsistent findings with regard to uniformity of effects across racial groups. In some studies (6), results are consistent for African Americans and whites, whereas in other studies (16) this is not the case. For example, Pollitt and colleagues (16) found significant associations between cumulative exposure to low SEP and elevated fibrinogen and white blood cells for white participants; however, results were weaker and less consistent for African American participants. We were only able to identify one study with a similar pattern to our findings (although the exposure was in adulthood rather than childhood): in a study of chronic stress burden, Troxel and colleagues (46) found that a composite stress index and unfair treatment were associated with higher carotid intima-media thickness among blacks, but not whites.

Theories of accelerated biological aging (23), which posit that differential exposure to adversities engender racial health disparities, may offer a possible explanation for this pattern. An implication of this notion is that physiological aging is accelerated in contexts of high exposure to adversity (47), and therefore statistical adjustment for chronological age cannot account for accelerated physiologic aging. Of note, the associations between ELA and some of the markers of inflammation were maintained for the African American sample in the race-stratified models even after adjustment for CVD, diabetes, and cancer (Table 4, Model 1); it is possible that, because the sample is still in midlife, an accelerated course of aging may not have yet resulted in disease outcomes. Longer follow-up is needed to determine the potential role of accelerated aging in the associations observed here: a theory of accelerated aging will only be applicable if the association between ELA and inflammation is eventually observed for white participants as well. Research (23) has indicated that patterns consistent with accelerated aging are most pronounced in urban areas with high poverty concentration; this is important to note, given that a large majority of blacks in our sample originate from Milwaukee, Wisconsin, a highly segregated city. Future studies should seek to identify the specific aspects of the social environment related to institutionalized discrimination that may have produced additional risk for the African American participants (e.g., neighborhood environment, work conditions).

There are several limitations to the present study. First, our measure of ELA was self-report and retrospective, which may lead to measurement inaccuracies. The questions used to generate the ELA assessments were only assessed at a single time point, and therefore repeated measurement reliability of these retrospective measures cannot be assessed.

Second, there are limitations associated with the sampling design. The majority of the African American respondents (85%) were recruited as part of the Milwaukee supplement sample; therefore, our analyses are largely describing white respondents originally recruited as part of a national sample, and African American respondents from Milwaukee, Wisconsin. In addition, for the African American participants only, the sample who participated in biological assessments had a slightly higher mean ELA summary score relative to African American respondents who did not participate in the biological assessment. Thus, the generalizability of our findings is unknown. An important next step is to repeat this analysis in more representative samples.

Third, although we hypothesize that depression may be on the pathway between ELA and inflammation, because depression and inflammation were measured concurrently, we do not have information about temporal ordering between these variables.

Finally, due to the limited sample size in the stratified models, we could not adjust for all covariates one might include in an ideal context (e.g., blood pressure, lipids); therefore, it is important to repeat this study in a larger sample that can accommodate additional covariates.

Two strengths of this study include the broad set of inflammatory markers considered, and the application of a life course perspective to research on racial disparities in health in midlife. This study contributes to a growing body of research from MIDUS linking ELA to health (48,49); it expands on previous work by examining early experiences in relationship to biomarkers of risk, and comparing the magnitude of these associations by race.

In conclusion, the present study found that ELA predicted markers of inflammation for the African Americans respondents, but not for the white respondents. A potential explanation for this pattern is that the African Americans in our sample, who were chronologically younger, are on an accelerated course of disease progression relative to whites. Future research should investigate how social trajectories post ELA may differ for African Americans and whites, and work to identify exposures and behaviors throughout the life course that may exacerbate or attenuate the negative effect of ELA on later health.

REFERENCES

1. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health 2005;26:1–35.
2. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14:245–58.

3. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, Anda RF. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation 2004;110:1761–6.
4. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA 2009;301:2252–9.
5. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A 2007;104:1319–24.
6. Taylor SE, Lehman BJ, Kiefe CI, Seeman TE. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biol Psychiatry 2006;60:819–24.
7. Surtees P, Wainwright N, Day N, Brayne C, Luben R, Khaw KT. Adverse experience in childhood as a developmental risk factor for altered immune status in adulthood. Int J Behav Med 2003;10:251–68.
8. Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 2006;83:456S–60S.
9. Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH, Jr, Heimovitz H, Cohen HJ, Wallace R. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506–12.
10. Malik I, Danesh J, Whincup P, Bhatia V, Papacosta O, Walker M, Lennon L, Thomson A, Haskard D. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis. Lancet 2001;358:971–6.
11. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA 2004;291:1978–86.
12. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A 2003;100:9090–5.
13. Loucks EB, Berkman LF, Gruenewald TL, Seeman TE. Relation of social integration to inflammatory marker concentrations in men and women 70 to 79 years. Am J Cardiol 2006;97:1010–6.
14. Steptoe A, Marmot M. Burden of psychosocial adversity and vulnerability in middle age: associations with biobehavioral risk factors and quality of life. Psychosom Med 2003;65:1029–37.
15. Friedman EM, Williams DR, Singer BH, Ryff CD. Chronic discrimination predicts higher circulating levels of E-selectin in a national sample: the MIDUS study. Brain Behav Immun 2009;23:684–92.
16. Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur J Epidemiol 2007;22:55–66.
17. Brunner E, Davey Smith G, Marmot M, Canner R, Beksinska M, O'Brien J. Childhood social circumstances and psychosocial and behavioural factors as determinants of plasma fibrinogen. Lancet 1996;347:1008–13.
18. Wilson TW, Kaplan GA, Kauhanen J, Cohen RD, Wu M, Salonen R, Salonen JT. Association between plasma fibrinogen concentration and five socioeconomic indices in the Kuopio Ischemic Heart Disease Risk Factor Study. Am J Epidemiol 1993;137:292–300.
19. Dong M, Anda RF, Felitti VJ, Dube SR, Williamson DF, Thompson TJ, Loo CM, Giles WH. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. Child Abuse Negl 2004;28:771–84.
20. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.
21. Acevedo-Garcia D, Osypuk TL, McArdle N, Williams DR. Toward a policy-relevant analysis of geographic and racial/ethnic disparities in child health. Health Aff (Millwood) 2008;27:321–33.
22. Geronimus AT, Hicken M, Keene D, Bound J. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. Am J Public Health 2006;96:826–33.
23. Geronimus AT. Understanding and eliminating racial inequalities in women's health in the United States: the role of the weathering conceptual framework. J Am Med Womens Assoc 2001;56:133–6, 49–50.
24. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387–97.
25. Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Angleman SB, Wensley F, Higgins JP, Lennon L, Eiriksdottir G, Rumley A, Whincup PH, Lowe GD, Gudnason V. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. PLoS Med 2008;5:e78.
26. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
27. Hwang SJ, Ballantyne CM, Sharrett AR, Smith LC, Davis CE, Gotto AM, Jr., Boerwinkle E. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation 1997;96:4219–25.
28. Loucks EB, Sullivan LM, D'Agostino RB, Sr., Larson MG, Berkman LF, Benjamin EJ. Social networks and inflammatory markers in the Framingham Heart Study. J Biosoc Sci 2006;38:835–42.
29. Loucks EB, Sullivan LM, Hayes LJ, D'Agostino RB, Sr, Larson MG, Vasan RS, Benjamin EJ, Berkman LF. Association of educational level with inflammatory markers in the Framingham Offspring Study. Am J Epidemiol 2006;163:622–8.
30. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 2004;101:17312–5.
31. Keyes CLM, Ryff CD. Generativity in adult lives: Social structural contours and quality of life consequences. In: McAdams DP, de St. Aubin E, editors. Generativity and Adult Development: How and Why We Care for the Next Generation. Washington, DC: American Psychological Association; 1998.
32. Straus MA. Measuring intrafamily conflict and violence: the Conflict Tactics (CT) scales. Journal of Marriage and Family 1979;41:75–88.
33. O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. Brain Behav Immun 2009;23:887–97.
34. Doggrell SA. Relating statin therapy to C-reactive protein levels. Expert Opin Pharmacother 2005;6:1597–600.
35. Guzic-Salobir B, Keber I, Seljeflot I, Arnesen H, Vrabic L. Combined hormone replacement therapy improves endothelial function in healthy postmenopausal women. J Intern Med 2001;250:508–15.
36. Serebruany VL, Glassman AH, Malinin AI, Nemeroff CB, Musselman DL, van Zyl LT, Finkel MS, Krishnan KRR, Gaffney M, Harrison W, Califf RM, O'Connor CM. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events—The Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) platelet substudy. Circulation 2003;108:939–44.
37. Isma N, Barani J, Mattiasson I, Lindblad B, Gottsater A. Lipid-lowering therapy is related to inflammatory markers and 3-year mortality in patients with critical limb ischemia. Angiology 2008;59:542–8.
38. Lissau I, Sorensen TI. Parental neglect during childhood and increased risk of obesity in young adulthood. Lancet 1994;343:324–7.
39. Korkeila K, Korkeila J, Vahtera J, Kivimaki M, Kivela SL, Sillanmaki L, Koskenvuo M. Childhood adversities, adult risk factors and depressiveness: a population study. Soc Psychiatry Psychiatr Epidemiol 2005;40:700–6.
40. Lesperance F, Frasure-Smith N, Theroux P, Irwin M. The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. Am J Psychiatry 2004;161:271–7.
41. Turner RJ, Wheaton B. Checklist measures of stressful life events. In: Gordon L, Cohen S, Kessler RC, editors. Measuring Stress: A Guide for Health and Social Scientists. New York: Oxford University Press; 1995.
42. Devins GM, Orme CM. Center for Epidemiologic Studies Depression Scale. Test Critiques 1985;21:267–83.
43. Allison PD. Missing Data. Thousand Oaks, CA Sage; 2001.
44. Raghunathan TE, Van Hoewyk J, Solenberger P. IVEware: Imputation and Variance Estimation Software User Guide. Ann Arbor, MI: University of Michigan; 2002.
45. Malnick SD, Knobler H. The medical complications of obesity. QJM 2006;99:565–79.
46. Troxel WM, Matthews KA, Bromberger JT, Sutton-Tyrrell K. Chronic stress burden, discrimination, and subclinical carotid artery disease in African American and Caucasian women. Health Psychol 2003;22:300–9.
47. Rowland Hogue CJ. Toward a systematic approach to understanding—and ultimately eliminating—African American women's health disparities. Women's Health Issues 2002;12:222–37.
48. Shaw BA. Lack of emotional support from parents early in life and alcohol abuse later in life. Int J Aging Hum Dev 2006;63:49–72.
49. Greenfield EA, Marks NF. Violence from parents in childhood and obesity in adulthood: using food in response to stress as a mediator of risk. Soc Sci Med 2009;68:791–8.