

Discrimination and Inflammation in Adolescents of Color

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ABSTRACT

BACKGROUND: This study examined how experiences with discrimination relate to inflammation, a key biological pathway in mental and physical illnesses, and whether associations are moderated by gender across two samples of adolescents of color.

METHODS: Study 1 was a longitudinal study of 419 African American adolescents assessed on discrimination (ages 19–20), with trajectories of biomarkers of low-grade inflammation (C-reactive protein and soluble urokinase plasminogen activator receptor) measured from ages 25 to 29. Study 2 was a cross-sectional study of 201 eighth graders of color assessed on discrimination and mechanistic indicators of a proinflammatory phenotype: 1) *in vitro* studies of immune cells' inflammatory cytokine responses to stimuli; 2) *in vitro* studies of cells' sensitivity to anti-inflammatory agents; 3) circulating numbers of classical monocytes, key cellular drivers of low-grade inflammation; and 4) a composite of six biomarkers of low-grade inflammation.

RESULTS: Interactions of discrimination by gender were found across both studies. In study 1, African American males experiencing high discrimination showed increasing trajectories of soluble urokinase plasminogen activator receptor over time ($p < .001$). In study 2, adolescent boys of color experiencing greater discrimination evinced a more proinflammatory phenotype: larger cytokine responses to stimuli ($p = .003$), lower sensitivity to anti-inflammatory agents ($p = .003$), higher numbers of classical monocytes ($p = .008$), and more low-grade inflammation ($p = .003$). No such associations were found in females.

CONCLUSIONS: Discrimination is a pressing societal issue that will need to be addressed in efforts to promote health equity. This study suggests that adolescent males of color may be particularly vulnerable to its effects on mental health-relevant inflammatory processes.

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Discrimination—the treatment of a person or group of people in unfair or prejudiced ways because of background characteristics such as race/ethnicity—is a pressing social issue and commonly reported experience in U.S. society that has implications for the racial/ethnic health disparities observed in this country (1,2). Discrimination has been linked to a host of poor mental health outcomes, including depression, anxiety, substance use, and psychotic disorders (2–4), and various chronic physical conditions (1,5) in both adults and children (6–8).

One potential mechanistic pathway that could explain how discrimination is linked to mental and physical illnesses is excessive inflammation, a key contributor to psychiatric disorders such as depression, substance use, and schizophrenia (9–11), and physical conditions such as diabetes, coronary heart disease, and neurodegenerative diseases (12,13). Discrimination is viewed as a stressor that modulates neuroendocrine and autonomic outflow through the negative appraisals and affective reactions it elicits (14). Changes in the hormonal end products of these systems, in turn, alter patterns of immune cell trafficking and responsiveness in ways that boost inflammatory activity. Although this chain of events occurs following acute experiences of discrimination, over the long

term the accumulation of repeated discrimination experiences is theorized to contribute to more chronic alterations in steady-state low-grade inflammatory activity (15,16). Consistent with this scenario, discrimination has been linked to biomarkers of low-grade inflammation, such as C-reactive protein (CRP) (17–19), which forecast an increased likelihood of chronic illnesses later in life (20,21). However, an understanding of the ways in which discrimination relates to inflammation earlier in life to better understand the developmental origins and prevention of disease has been lacking. The vast majority of studies on discrimination and inflammation have been conducted in adults (14), with only two studies in children (22,23) and one investigating the transition to adulthood (24). In addition, very few studies have taken a developmental perspective in investigating changes in inflammation over time; most studies are cross-sectional, and only a small number of studies—all in adults—have assessed biomarkers of inflammation across time (25–28).

In addition, nearly all previous studies in this area focus on biomarkers of inflammation. However, these biomarkers do not provide mechanistic insights about underlying immunologic processes that might allow discrimination to trigger and/or

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maintain inflammatory activity. Past work highlights two such underlying processes that together are hypothesized to reflect a proinflammatory phenotype (29,30). One is the intensity of monocyte responses to triggering stimuli, and the other is these cells' sensitivity to inhibitory signals. Therefore, this article advances knowledge of discrimination and inflammation earlier in life by leveraging two samples of youth of color to ask: 1) how discrimination relates to 4-year trajectories of two inflammatory biomarkers, CRP and soluble urokinase plasminogen activator receptor (suPAR), during the transition to young adulthood; and 2) how discrimination during adolescence relates to multiple indicators of a proinflammatory phenotype. To bolster conclusions, these research questions were probed across two distinct study samples to determine whether consistent, replicable results would emerge.

In addition, given that males and females report different types of, frequency of, and ways of coping with discrimination (31,32), we tested whether associations between discrimination and inflammation might vary by gender. That is, we tested discrimination by gender interactions predicting trajectories of inflammation over time and proinflammatory phenotypes across two samples of youth of color.

METHODS AND MATERIALS: STUDY 1

In this article, we report findings across two distinct study samples and designs. Study 1 presents methods and results for the Strong African American Healthy Adults Project (SHAPE) sample. See the [Supplement](#) for additional details of the methods and [Table 1](#) for demographic information.

Participants

Data for the first study were drawn from the longitudinal SHAPE sample (33). SHAPE enrolled 667 African American children in fifth grade (mean age = 11.2 years, SD = 0.3) along with primary caregivers. The University of Georgia's Institutional Review Board approved the protocol, and written informed consent was obtained from participants and their caregivers at all assessments.

Procedures

When youth were 19 years old, 500 were randomly selected, due to funding constraints, to participate in a biological data collection. Psychosocial measures were assessed by youth report, and primary caregivers provided demographic information when youth were 19 and again at age 20. At age 19, participants' height and weight were assessed. When participants were 25, 27, and 29 years old, a phlebotomist visited participants' homes to draw fasting antecubital blood. A total of 419 participants provided blood during at least one time point, and analyses were conducted on this group.

Measures

See the [Supplement](#) for additional details.

Discrimination. Youth reported experiences with discrimination over the past year using the Schedule of Racist Events scale (34). Higher scores indicated greater discrimination, with scores averaged across ages 19 to 20. We used this time point of assessment to have a measure of discrimination that preceded our inflammation measures.

Table 1. Descriptives of the SHAPE and MWMH Samples

Descriptives	Percentage	Mean (SD) [Range]
SHAPE (<i>n</i> = 419)		
Female	59%	–
Intervention	58%	–
Family SES, ages 19–20	–	2.93 (1.59) [0 to 6]
BMI, age 19	–	28.08 (8.19) [15.36 to 55.03]
Discrimination, ages 19–20	–	3.18 (3.24) [0 to 18]
suPAR, age 25	–	3.33 (0.13) [2.96 to 4.22]
suPAR, age 27	–	3.37 (0.13) [3.02 to 4.47]
suPAR, age 29	–	3.36 (0.13) [2.77 to 4.10]
CRP, age 25	–	0.54 (0.43) [0 to 1.73]
CRP, age 27	–	0.54 (0.39) [0.08 to 1.86]
CRP, age 29	–	0.57 (0.41) [0.04 to 2.06]
MWMH (<i>n</i> = 201)		
Female	64%	–
Black	53%	–
Hispanic	44%	–
Age, years	–	13.50 (0.62) [12 to 15]
Pubertal category	–	3.74 (0.74) [1 to 5]
Family SES	–	–0.22 (0.34) [–0.51 to 1.95]
BMI	–	24.36 (6.65) [14.61 to 53.73]
Discrimination	–	18.14 (5.38) [10 to 34]
Stimulated cytokine production	–	0.03 (0.87) [–2.00 to 2.89]
Sensitivity to inhibitory signal	–	–0.08 (0.98) [–3.47 to 3.01]
Classical monocytes	–	134.39 (58.27) [20.08 to 332.44]
Low-grade inflammation	–	–0.01 (0.65) [–1.13 to 4.07]

Family SES, stimulated cytokine production, sensitivity to inhibitory signaling, and low-grade inflammation are all standardized and averaged composite variables.

BMI, body mass index; CRP, C-reactive protein; MWMH, My World My Heart; SES, socioeconomic status; SHAPE, Strong African American Healthy Adults Project; suPAR, soluble urokinase plasminogen activator receptor.

Low-Grade Inflammation. Two biomarkers of low-grade inflammation, CRP and suPAR, were assessed in fasting serum collected at ages 25, 27, and 29 by immunoassay (technical details in the [Supplement](#)). CRP is the most commonly assessed biomarker of inflammation (35) and has been prospectively associated with risk for diabetes, coronary heart disease, myocardial infarctions, and stroke (20,21,36). suPAR is a newer inflammatory biomarker that also has emerged as a predictor of cardiovascular disease, diabetes, cancer, and all-cause mortality independent of CRP (37,38) and has been speculated to reflect vascular inflammation (39). Distributions were normalized with log₁₀ transformations.

Gender. Gender was coded as male = 0.5 and female = –0.5.

Covariates

Statistical models included covariates of family socioeconomic disadvantage at ages 19 to 20 [measured using a composite of six different indicators (40–42)], body mass index (BMI) at age 19, and intervention status (the SHAPE cohort participated in

an unrelated randomized trial at age 11 to prevent child behavior problems and substance use). Supplemental analyses included youth depressive symptoms, anxiety, and perceived stress at ages 19 to 20 as additional covariates and tested BMI as a time-varying covariate. See the [Supplement](#) for details of these measures.

Statistical Analyses

We conducted latent growth curve models to characterize the overall trajectories of CRP and suPAR across ages 25, 27, and 29. Each marker was analyzed separately, given that we could not incorporate a composite score into growth curve models (see the [Supplement](#) for further details). Missing data at a certain wave were handled using full information maximum likelihood estimation (43). The model was tested across the three waves of data and included 1) an intercept parameter with time centered at age 25 and 2) a linear slope parameter representing the average linear change in CRP and suPAR (from ages 25–29). The growth parameters were predicted from 1) the covariates of socioeconomic disadvantage and intervention status, 2) the main effects of discrimination and gender, and 3) the interaction between discrimination and gender. Follow-up analyses included BMI at age 19 as a covariate, BMI at ages 25 to 29 as time-varying covariates, and depressive symptoms, anxiety, and perceived stress at ages 19 to 20 as covariates.

RESULTS: STUDY 1

Latent growth curve model analyses revealed that suPAR levels increased across ages 25 to 29 (slope mean = 0.027, SE = 0.003, $p < .001$). There was significant between-youth variation in both the intercept (variance = 0.019, SE = 0.002, $p < .001$) and the slope (variance = 0.003, SE = 0.001, $p < .001$). By contrast, CRP levels were stable across ages 25 to 29 (slope mean = 0.004, SE = 0.010, $p = .717$), although there was significant between-youth variation in the intercept (variance = 0.143, SE = 0.014, $p < .001$) and slope (variance =

0.014, SE = 0.006, $p = .017$). Discrimination scores did not differ by gender ($t = -0.041$, $p = .967$), and distributions of scores were equivalent across the two genders (Levene’s test for equality of variances: $F = 0.009$, $p = .923$).

Discrimination and Gender Effects

See [Table 2](#) for details of analyses.

Soluble Urokinase Plasminogen Activator Receptor. The latent growth curve model had borderline acceptable fit ($\chi^2 = 56.73$, comparative fit index = 0.92, Tucker Lewis index = 0.90, root mean squared error of approximation = 0.090) (44–46). After including covariates, there was a main effect of gender on the intercept, such that males ($p < .01$) had lower suPAR at age 25 than females. There was a significant gender \times discrimination interaction ($p = .02$) on the slope of suPAR. To decipher this interaction, we estimated gender-specific suPAR slopes at lower and higher levels of discrimination (-1 SD and $+1$ SD from the sample average). Males who experienced high discrimination at ages 19 to 20 had relatively steep suPAR increases from ages 25 to 29 (slope = 0.036, SE = 0.006, $p < .001$). By contrast, males who experienced low discrimination had smaller increases in suPAR levels over time (slope = 0.013, SE = 0.006, $p = .03$). These two slopes are significantly different from each other ($b = 0.012$, SE = 0.005, $p = .024$) ([Figure 1](#)). Among females, suPAR levels increased over time, but slopes were similar in those with high (slope = 0.024, SE = 0.005, $p < .001$) versus low (slope = 0.031, SE = 0.005, $p < .001$) discrimination.

C-Reactive Protein. The model fit the data well ($\chi^2 = 8.23$, comparative fit index = 1.00, Tucker Lewis index = 1.01, root mean squared error of approximation = 0). There was a main effect of gender on the intercept, such that males ($p < .01$) had lower CRP than females. There were no significant main effects of discrimination or gender \times discrimination interactions on the intercept or slope of CRP.

Table 2. Gender, Discrimination, and Trajectories of Inflammatory Markers: SHAPE Sample

Predictor	Intercept			Slope		
	<i>b</i>	SE	<i>p</i> Value	<i>b</i>	SE	<i>p</i> Value
Growth Parameters of suPAR						
SES disadvantage, ages 19–20	0.004	0.004	.30	–0.002	0.002	.40
Intervention status	–0.007	0.013	.61	0.005	0.006	.43
Gender	–0.057	0.013	<.01	–0.004	0.006	.56
Discrimination, ages 19–20	0.012	0.006	.06	0.002	0.003	.60
Gender \times discrimination	–0.005	0.013	.70	0.015	0.006	.02
Growth Parameters of CRP						
SES disadvantage, ages 19–20	0.012	0.013	.37	0.005	0.007	.47
Intervention status	0.016	0.042	.70	0.001	0.021	.95
Gender	–0.257	0.040	<.01	0.035	0.021	.10
Discrimination, ages 19–20	–0.020	0.020	.31	–0.006	0.010	.54
Gender \times discrimination	0.032	0.040	.42	0.018	0.021	.41

Family SES disadvantage score and intervention status entered on step 1; gender and discrimination entered on step 2; and the interaction term entered on step 3. Gender: female = -0.5 , male = 0.5 . Trajectories of inflammatory markers are from ages 25, 27, and 29.

CRP, C-reactive protein; SES, socioeconomic status; SHAPE, Strong African American Healthy Adults Project; suPAR, soluble urokinase plasminogen activator receptor.

Discrimination and Inflammation

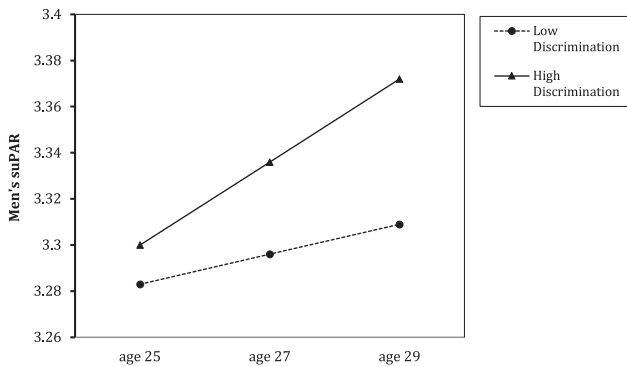


Figure 1. Soluble urokinase plasminogen activator receptor (suPAR) (log transformed) trajectories by levels of discrimination (ages 19–20) among males in the Strong African American Healthy Adults Project sample. Low and high values of discrimination represent ± 1 SD from the mean.

Controlling for BMI

Because adiposity contributes to inflammation, we tested whether adding BMI at age 19 to the models would alter the patterns reported above. It did not. The gender \times discrimination interaction for the suPAR slope remained significant ($b = 0.015$, $SE = 0.006$, $p = .02$). Males who experienced high discrimination continued to evince increases in suPAR over time (slope = 0.036, $SE = 0.006$, $p < .001$) relative to males with low discrimination (slope = 0.013, $SE = 0.006$, $p = .04$). Discrimination remained unrelated to suPAR in females. We further examined BMI from ages 25 to 29 as a time-varying covariate. The gender \times discrimination interaction for the suPAR slope remained significant (Table S1).

Controlling for Psychological Variables

In supplemental analyses, we tested whether adding the psychological covariates of depression, anxiety, or perceived stress would alter results. In all cases, the gender \times discrimination interaction for the suPAR slope remained significant (Table S1).

METHODS AND MATERIALS: STUDY 2

See the Supplement for additional details of methods and Table 1 for demographic information.

Participants

Eighth grade children from the Chicago area were recruited for the My World My Heart study. Each child gave written assent to participate, and parents gave written consent. Northwestern University's Institutional Review Board approved the protocol.

To parallel analyses in study 1, this study focused on 201 children of color enrolled (out of a total sample of 277). During a single study visit, children completed surveys (including the discrimination measure), gave fasting blood, and had height and weight assessed. Parents provided demographic information.

Measures

See the Supplement for details.

Discrimination. Children reported on the frequency of their day-to-day experiences with discrimination using the Everyday Discrimination Scale (47), with responses ranging from “never” to “often.” Higher scores indicated greater experiences with discrimination.

Child Gender. Gender was coded as male = 0.5 and female = -0.5 .

Proinflammatory Phenotype

As noted earlier, little is known about the immunologic processes that might be involved in triggering and maintaining the low-grade inflammation observed in study 1. Therefore, in study 2, we used fasting antecubital blood to conduct more in-depth assessments of inflammatory activity. These assessments included 1) in vitro studies of immune cells' inflammatory cytokine responses to multiple stimuli; 2) in vitro studies of these cells' sensitivity to anti-inflammatory agents; 3) circulating numbers of classical monocytes, key cellular drivers of low-grade inflammation; and 4) a composite of six circulating biomarkers of low-grade inflammation.

Cytokine Responsivity to Stimulation and Inhibition

With studies that rely solely on assessing biomarkers of inflammation in circulation, it can be difficult to ascertain the origins of these markers (i.e., whether they actually originate from immune cells vs. from adipose tissue or from other bodily systems) (48). Thus, a more direct approach is to challenge immune cells with stimuli in vitro and to quantify the production of cytokines. In these paradigms, a variety of stimuli can be used (e.g., bacterial, viral), and greater production of cytokines is interpreted as a sign of more aggressive inflammatory responding. In this study, whole blood was incubated with four distinct stimuli, representing both microbial and sterile triggers of inflammation. They were lipopolysaccharide, resiquimod, heat-shock protein 60, and advanced glycation end product from bovine serum albumin. In addition to assessing cytokine responsivity, another extension of this in vitro paradigm involves including an anti-inflammatory molecule (e.g., cortisol) to assess how sensitive immune cells are to inhibitory signals (the more sensitive they are to these signals, the more cytokine production will be curtailed). To quantify sensitivity to inhibitory signals, whole blood was co-incubated with lipopolysaccharide and compounds that provide local (interleukin [IL] 10) and systemic (glucocorticoid) anti-inflammatory feedback. In all conditions, four inflammatory cytokines were measured (IL-1 β , IL-6, tumor necrosis factor alpha, and IL-8) by multiplex immunoassay. Details of the protocol are provided in the Supplement. Assays were performed in duplicate. Intra-assay coefficients of variation ranged from 1.59% to 2.28%, and interassay coefficients of variation from 2.67% to 4.03%.

To alleviate concerns about false discovery, we decided a priori to conduct primary analyses on two composite end points. The first was a stimulated cytokine production composite, formed by averaging z-scored values across the four cytokines and across the four stimulating agents. Higher values represent larger cytokine responses to stimulating agents, which is consistent with a proinflammatory phenotype. The second was a sensitivity to anti-inflammatory signaling composite, formed

by estimating a child-specific sensitivity slope for each cytokine within each condition of lipopolysaccharide + an anti-inflammatory agent, and then averaging z-scored values of cytokine slopes across conditions. Here, lower values represent less sensitivity to the anti-inflammatory properties of inhibitory compounds, which suggests a more proinflammatory phenotype. See the [Supplement](#) for further details.

Classical Monocytes. Although multiple populations of immune cells participate in a typical inflammatory response, classical monocytes are one of the key cellular drivers of this process. Moreover, preclinical studies indicate that following exposure to stress, these cells migrate to the brain, where they induce anxiety-like behavior; to the walls of coronary arteries, where they worsen atherosclerosis; and to adipose tissue, where they promote insulin sensitivity and fat accumulation (49–51). Given these cells' roles in stress-related diseases, we enumerated them here using a standardized flow cytometry protocol (52). See the [Supplement](#) for protocol details.

Low-Grade Inflammation. Six circulating (basal) biomarkers of low-grade inflammation that are implicated in cardiovascular disease (53,54) were quantified by immunoassay, including CRP, suPAR, IL-6, IL-8, IL-10, and tumor necrosis factor alpha. CRP and suPAR were measured in duplicate, and cytokines were measured in triplicate. Intra-assay coefficients of variation ranged from 1.6% to 5.0%. See the [Supplement](#) for protocol details. Biomarkers were log transformed, standardized, and averaged into a composite. Higher values reflected more inflammation.

Covariates

Statistical models included covariates of child race (African American: yes/no), ethnicity (Hispanic: yes/no), pubertal status (55), family socioeconomic status measured as a composite of family income and savings, and child BMI. Child age was not included as a covariate because all children were in grade 8 (supplemental analyses that replaced pubertal status with child age found similar patterns of associations; see [Table S2](#)). Supplemental analyses included child anxiety, depression, and perceived stress as covariates. See the [Supplement](#) for details about these measures.

Statistical Analyses

We conducted hierarchical multiple regression analyses, in which inflammatory outcomes were predicted from 1) the covariates of race, ethnicity, pubertal status, and socioeconomic status; 2) the main effects of discrimination and gender; and 3) the interaction between discrimination and gender. Separate models were then fit for males versus females. Follow-up analyses added BMI as a covariate. Supplemental analyses added child age, anxiety, depression, and perceived stress as covariates.

RESULTS: STUDY 2

Overall, 53% of children were African American, 44% were Hispanic, and 13% identified as members of other racial/ethnic groups (multiple race/ethnicity categories were permitted). Discrimination scores did not differ by race, ethnicity, or

gender (all p values > .25). Distributions of discrimination scores were also equivalent across the two genders (Levene's test for equality of variances: $F < 0.001$, $p = .992$).

Discrimination and Gender Effects

See [Tables 3](#) and [4](#) for details of analyses.

Stimulated Cytokine Production Composite. There was a main effect such that higher discrimination was associated with larger cytokine responses to stimulating agents ($p = .023$). There was also a significant gender \times discrimination interaction ($p = .04$). Boys showed a positive association between discrimination experiences and cytokine production ($p = .003$), whereas no relationship was evident in girls ($p = .50$).

Table 3. Gender, Discrimination, and Proinflammatory Phenotype: MWMH Sample

Predictor	<i>b</i>	SE	<i>p</i> Value
Stimulated Cytokine Production			
Puberty status	−0.113	0.080	.16
African American	0.374	0.176	.04
Hispanic	−0.197	0.177	.26
SES	−0.244	0.179	.17
Gender	0.192	0.149	.20
Discrimination	0.026	0.011	.02
Gender \times discrimination	0.046	0.023	.04
Sensitivity to Anti-inflammatory Signaling			
Puberty status	0.289	0.087	<.01
African American	−0.450	0.191	.02
Hispanic	0.351	0.191	.07
SES	0.126	0.194	.52
Gender	−0.159	0.161	.32
Discrimination	−0.032	0.012	.01
Gender \times discrimination	−0.040	0.025	.10
Classical Monocytes			
Puberty status	3.145	5.571	.57
African American	24.385	12.397	.05
Hispanic	18.941	12.389	.13
SES	−12.872	12.456	.30
Gender	29.056	10.032	<.01
Discrimination	1.742	0.770	.02
Gender \times discrimination	3.408	1.554	.03
Low-Grade Inflammation			
Puberty status	−0.129	0.062	.04
African American	0.017	0.138	.90
Hispanic	0.020	0.138	.89
SES	−0.084	0.139	.55
Gender	0.187	0.114	.10
Discrimination	0.011	0.009	.22
Gender \times discrimination	0.044	0.018	.01

Puberty status, race, ethnicity, and family SES entered on step 1; gender and discrimination entered on step 2; and the interaction term entered on step 3. Gender: female = −0.5, male = 0.5.

MWMH, My World My Heart; SES, socioeconomic status.

Table 4. Associations of Discrimination With Proinflammatory Phenotype by Gender: MWMH Sample

Predictor	Boys			Girls		
	<i>b</i>	SE	<i>p</i> Value	<i>b</i>	SE	<i>p</i> Value
Stimulated Cytokine Production						
Puberty status	−0.083	0.137	.55	0.0004	0.144	.99
African American	0.241	0.314	.44	0.430	0.217	.05
Hispanic	−0.271	0.318	.40	−0.173	0.215	.42
SES	−0.415	0.269	.13	−0.095	0.245	.70
Discrimination	0.056	0.018	<.01	0.010	0.014	.50
Sensitivity to Anti-inflammatory Signaling						
Puberty status	0.396	0.145	<.01	0.073	0.158	.64
Hispanic	0.301	0.335	.37	0.376	0.235	.11
African American	−0.382	0.330	.25	−0.455	0.237	.06
SES	0.032	0.283	.91	0.154	0.268	.57
Discrimination	−0.060	0.019	<.01	−0.016	0.015	.29
Classical Monocytes						
Puberty status	7.167	10.090	.48	21.199	9.122	.02
Hispanic	28.546	24.252	.24	14.783	13.853	.29
African American	38.902	24.042	.11	15.308	13.982	.28
SES	−17.043	20.246	.40	−9.573	15.775	.54
Discrimination	3.853	1.399	<.01	0.617	0.909	.50
Low-Grade Inflammation						
Puberty status	−0.085	0.097	.39	−0.031	0.114	.78
Hispanic	−0.165	0.234	.48	0.100	0.173	.56
African American	−0.112	0.232	.63	0.060	0.174	.73
SES	−0.205	0.195	.30	−0.007	0.197	.97
Discrimination	0.041	0.013	<.01	−0.005	0.011	.65

Puberty status, race, ethnicity, and SES entered on step 1; discrimination entered on step 2.
MWMH, My World My Heart; SES, socioeconomic status.

Sensitivity to Anti-inflammatory Signaling Composite.

There was a main effect where higher discrimination was associated with lower sensitivity to anti-inflammatory compounds ($p = .009$). There was a marginal gender \times discrimination interaction ($p = .10$). Boys who experienced greater discrimination had lower sensitivity to anti-inflammatory agents ($p = .003$). By contrast, there was no relationship in girls ($p = .29$).

Classical Monocytes. There were main effects of both discrimination and gender, such that boys ($p = .004$) and those who experienced greater discrimination ($p = .025$) had higher numbers of proinflammatory classical monocytes. There was also a significant gender \times discrimination interaction ($p = .029$). Boys showed a positive association between greater discrimination and classical monocyte numbers ($p = .008$), whereas there was no relationship among girls ($p = .50$).

Low-Grade Inflammation. There were no main effects of either discrimination or gender, but the interaction was significant ($p = .014$). Boys showed a positive association between greater discrimination and more low-grade inflammation ($p = .003$), whereas girls showed no relationship ($p = .65$) (Figure 2).

Controlling for BMI

After controlling for BMI, boys who experienced greater discrimination continued to evince a more proinflammatory

phenotype, as indicated by larger cytokine responses to stimulating agents ($b = 0.053$, $SE = 0.018$, $p = .005$), lower sensitivity to anti-inflammatory agents ($b = -0.055$, $SE = 0.019$, $p = .004$), higher numbers of classical monocytes ($b = 3.513$, $SE = 1.377$, $p = .013$), and more low-grade inflammation ($b = 0.036$, $SE = 0.013$, $p = .006$). Girls showed no association of discrimination with any these measures (p values $> .25$).

Controlling for Psychological Variables

In supplemental analyses, we tested whether adding the psychological covariates of depression, anxiety, or perceived stress would alter results. In all cases, the patterns of significant gender \times discrimination interactions remained the same (Table S2).

DISCUSSION

The results of these two studies demonstrate that links between discrimination and a key disease-related biological process—inflammation—emerge during earlier periods of life. That is, across two studies, discrimination was associated with a proinflammatory phenotype in boys of color that worsened as they progressed into adulthood. Specifically, among adolescent boys of color, greater experiences with discrimination were associated with larger cytokine responses to multiple stimuli and lower sensitivity to local and systemic inhibitory signals that regulate inflammation. In addition, discrimination in boys of color was also associated with higher

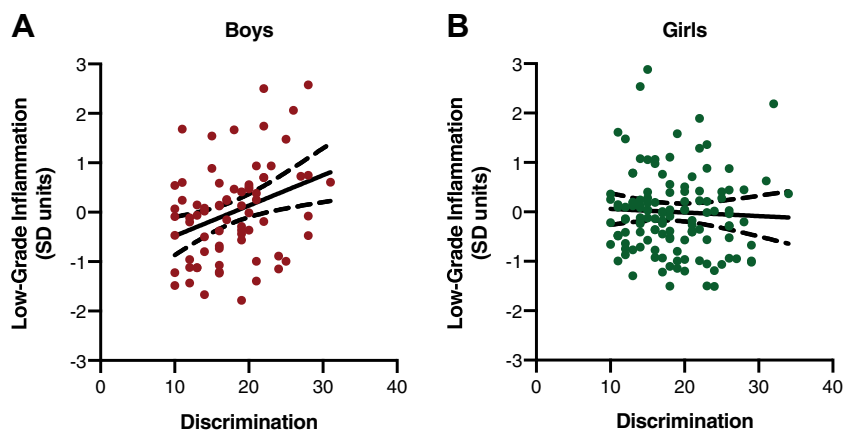


Figure 2. Low-grade inflammation as a function of discrimination scores for boys (A) vs. girls (B) in the My World My Heart sample (8th graders). The inflammation composite included C-reactive protein, interleukin (IL) 6, IL-8, IL-10, tumor necrosis factor alpha, and soluble urokinase plasminogen activator receptor (log transformed, standardized, then averaged). Interaction patterns for the other three proinflammatory phenotype measures (stimulated cytokine production composite, sensitivity to anti-inflammatory signaling composite, and classical monocytes) paralleled this figure.

concentrations of inflammatory biomarkers and with higher numbers of classical monocytes, key cellular drivers of inflammatory activity. In a second sample of African American youth, males who experienced more discrimination showed steeper increases in suPAR across their late 20s. Girls across both samples showed no associations of discrimination with inflammation. The consistency of findings across two distinct samples supports the reliability of these effects.

These findings provide a potential mechanistic explanation for associations documented in previous reviews between discrimination experienced during childhood and a variety of mental health, health behavior, and (to a lesser extent) physical health outcomes (2,6,7). Specifically, this article suggests the role of a biological mechanism— inflammation— that has been implicated in the development of many aging-related health conditions across the continuum of mental and physical illnesses (9,12,13,56,57).

In addition, this study extends prior longitudinal studies on discrimination and inflammation to an earlier period of life. Few studies of discrimination with multiple time points of inflammation have been conducted; among those that have, there are findings that discrimination predicts increases in inflammatory markers over time, although these studies have either focused on older adults or included a wide age range of adults (26,27). This study is the first to document that discrimination experienced during the extended adolescence period forecasts subsequent trajectories of inflammation (specifically among African American males).

Across both study 1 and study 2, discrimination findings emerged for males but not females. The gender pattern was replicated both across two distinct samples of youth of color and across multiple inflammatory measures. These patterns are consistent with the mental health literature in adolescence, which has documented that associations of discrimination with outcomes such as conduct problems and substance use are stronger in boys than girls (58–63), both cross-sectionally and longitudinally. We speculate that one reason for this pattern may be that the intersection of race and gender leads to different types of discrimination experiences. For example, African American males are more likely to report being profiled or having major life discrimination experiences, such as with police brutality (31,32,64). Consistent with this notion, African

American males are more likely to specifically report experiences of disrespect and being threatened than any other race/gender group, and both African American and Hispanic males are more likely than other race/gender groups to endorse that others seem afraid of them (65). It is possible that these particular types of discrimination experiences that revolve around physical threats are more strongly linked to physiological responses. In addition, males of color may also have been socialized to anticipate these types of threats and to prepare for bias (66), potentially resulting in greater physiological responses to certain stressors. Our pattern of findings are consistent with a study in African American youth that documented associations of race-related vigilance with poorer cardiovascular health (decreased arterial elasticity) in boys but not girls (67) and with a previous longitudinal study in women documenting no significant main effect of discrimination on CRP over time (25). Moreover, a few previous studies have tested gender by discrimination interactions on inflammatory outcomes, with some finding interaction patterns (27,68) but others not (17,24).

In this study, discrimination predicted trajectories of suPAR but not CRP. These findings are consistent with recent research indicating that adverse childhood experiences, such as violence and low socioeconomic status, are more strongly related to suPAR than CRP in adulthood (69,70). Some have speculated that biomarkers such as CRP can reflect both chronic and acute inflammatory states, whereas suPAR may be a more stable marker of chronic inflammation (69,70), but this premise is in need of further testing.

Strengths of this study include the two samples of youth of color (which demonstrates both the replicability of findings and the generalizability across two different types of cohorts), the multiple in-depth inflammatory measures, and the longitudinal findings in one of the cohorts. The fact that the pattern of gender interactions was replicated across the two samples lends credence to the reliability of these findings. Limitations include the lack of clinical health outcomes tracked into adulthood. In addition, the two studies used different measures of discrimination, although there are similarities in the questions posed. In addition, we note that these studies focus on interpersonal experiences of discrimination. However, it is important to acknowledge that racism exists at multiple levels, for example,

at the institutional or structural level, in addition to the interpersonal level. Future studies should investigate the effects of different types and levels of discrimination and discrimination across the life course. In addition, future studies should incorporate assessment strategies other than self-report questionnaires of discrimination (e.g., interviews) and should investigate the role of discrimination in comparison to other types of life stressors. Finally, both studies used observational designs, meaning that causality cannot be inferred; however, study 1's longitudinal design does allow us to draw some conclusions about directionality, in demonstrating that baseline discrimination predicted trajectories of suPAR over time.

By highlighting associations between discrimination and inflammation across two studies, this article begins to elucidate mechanistic possibilities for how discrimination may come to affect both mental and physical health outcomes over time. Among adolescent males of color, high levels of discrimination were associated with multiple indications of a proinflammatory phenotype and with low-grade inflammatory activity that worsened over time. Discrimination is a pressing societal issue that will need to be addressed as part of efforts to promote health equity, and this study contributes to a body of research establishing its relevance to adolescent and adult health.

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