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Concurrent and Longitudinal Associations of Sex and Race with Inflammatory Biomarkers during Adolescence

Naoise Mac Giollabhui[1], **Lauren B. Alloy**[1], **Dominika Swistun**[2], **Christopher L. Coe**[2], **Lauren M. Ellman**[1], **Daniel P. Moriarity**[1], **Allison C. Stumper**[1], **Lyn Y. Abramson**[2]

[1] Department of Psychology, Temple University, Philadelphia, PA, USA

[2] Department of Psychology, University of Wisconsin-Madison, Madison, WI, USA

Abstract

Chronic, systemic inflammation is implicated in physical and mental health; little is known about whether sex and racial differences detected in adulthood are observed during adolescence or about normative changes occurring during adolescence. This longitudinal, United States-based study examined four biomarkers of systemic inflammation [C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and IL-8) in 315 adolescents (51% female; 58% black; baseline age = 16.49 years (*SD* = 1.56; range: 12.14–21.28)] at three timepoints. Notable results included: general decline in inflammatory biomarkers in older adolescents, lower levels of TNF-α/IL-8 in black adolescents, elevated CRP/IL-6 in females, and especially higher levels of IL-6 in black, female adolescents. Implications are discussed, particularly the potential health implications of elevated IL-6 in black females.

Keywords

Inflammation; Adolescence; Sex; Race; C reactive protein; Interleukin-6

✉ Naoise Mac Giollabhui naoise.macgiollabhui@temple.edu.

Authors' Contributions N.M.G. conceived of the manuscript hypotheses, wrote an initial draft of the manuscript and conducted data analysis; L.B.A. conceived of the overall study design and was awarded funding to collect data and provided substantive feedback at each stage of the conception, writing, and editing of the manuscript; D. S. played a central role in collecting data; C.L.C. assayed all biological specimens collected and provided substantive input in writing and revising this manuscript; L.M.E. provided critical input in the conception of these specific analyses and in revising this manuscript; both D.P.M. and A.C.S. contributed to data analysis and interpretation; L.Y. A. collaborated with L.B.A. in the conception of the overall study design and the funding application in addition to providing substantive feedback at each stage of the conception, writing, and editing of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Data Sharing and Declaration Datasets created and analyzed during the current study are not publically available, but may be made available by Dr. Lauren B. Alloy (lalloy@temple.edu) upon reasonable request.

Ethical Approval The Temple University Institutional Review Board approved the protocol (IRB protocol #6844) and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Written informed consent was collected from all study participants after explaining their role in the study and before starting data collection.

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Introduction

Inflammation is a process characterized by activation of both immune and non-immune cells that are designed to protect the host system from pathogens (e.g., bacteria, viruses) and to promote host tissue repair and recovery. The immune response typically persists for the duration of the threat to the host and is accompanied by a range of "sickness behaviors" (e.g., fatigue, somnolence, anhedonia) designed to conserve energy and increase the likelihood of host survival. Chronic inflammation, however, is characterized by activation of the immune system in the absence of threat (i.e., pathogens or injury) and is associated with a breakdown in immune tolerance, impaired immune system functioning, and increased risk for non-communicable diseases—in fact, 50% of all deaths are attributable to inflammation-related diseases (Roth et al. 2018). Inflammation also is implicated in the etiology of mental health conditions, such as depression (Mac Giollabhui et al. 2020b). Considerable evidence exists that an array of endogenous (e.g., DNA damage, oxidative stress) and exogenous (e.g., lifestyle-associated obesity, diet, stress) factors are associated with the emergence of chronic inflammation (Furman et al. 2019). Moreover, there is strong evidence that levels of inflammatory markers may vary systematically with demographic factors (O'Connor et al. 2009); however, considerably less is known about how the combination of demographic characteristics affect risk of chronic inflammation, particularly early in development. This study aims to examine whether the combination of sex and race is particularly associated with chronic inflammation; for instance, do black females exhibit higher levels of inflammation than white females as well as white and black men? An addition aim is to investigate this question during a critical period of development, adolescence, and to examine whether markers of chronic inflammation increase during adolescence more generally.

There is particularly strong evidence that sex can affect inflammatory physiology (Klein and Flanagan 2016). Females are more likely to be diagnosed with inflammatory diseases than males (e.g., rheumatoid arthritis, lupus, Sjoregen's) (Quintero et al. 2012) and epidemiological studies have found that inflammatory biomarkers are consistently higher in middle-aged and elderly adult females compared to males (Khera et al. 2005). In youth, inflammatory biomarkers typically are elevated in females (Ford et al. 2003), although contrary findings have been reported for Chinese (Wang et al. 2011) and Spanish (Warnberg et al. 2006) adolescent males. The mechanisms accounting for higher levels of inflammation in females are not fully understood. Both males and females exhibit comparable increases in inflammation following exposure to a laboratory-based psychological stressor, suggesting that sex differences in basal inflammation are not attributable to stress-reactivity (Steptoe et al. 2007). Instead, it may be that sex differences in levels of inflammation are due to greater exposure to risk factors (e.g., childhood adversity) that are themselves associated with persistent, low-grade inflammation (Derry et al. 2015). There also is research suggesting that increasing sex hormones during puberty (Carruba et al. 2003) or changes in the balance of sympathetic and parasympathetic activity (O'Connor et al. 2007) may lead to elevated inflammation in females. There is a burgeoning field of psychoneuroimmunology research examining the relationship between inflammatory biomarkers and psychopathology during adolescence, with many studies focusing on the possible roles played by low socioeconomic

status, higher body mass, dysregulated sleep, stress, early childhood adversity, and depression (Slavich 2020). Sex, however, is generally not a central construct of interest in studies, and typically only is included as a covariate or examined in sensitivity analyses. Further research is needed that considers how sex differences in inflammation may vary systematically based on other demographic factors, and there is strong evidence that race may, in fact, be one such factor.

Levels of inflammation also have been found to differ across racial and ethnic groups. Biomarkers of systemic inflammation [C reactive protein (CRP) and interleukin 6 (IL-6)] often have been reported as higher among black adults compared to white adults (Khera et al. 2005). Outside of the United States, differences between black and white adults also were found in South Africa and the United Kingdom (Evans and Goedecke 2011). The degree to which socioeconomic disparities or race-related environmental stressors contribute to racial/ethnic differences in inflammation is unclear and studies indicate that factors, such as smoking status (Gruenewald et al. 2009) and discrimination (Brody et al. 2015), may be implicated; however, race has been associated with inflammation independent of a wide range of biological and behavioral factors (Khera et al. 2005). In addition, there are a number of genetic factors, including both allelic variants and single nucleotide polymorphisms, that can affect cytokine synthesis and release, and it is known that their prevalence vary across populations (Ness et al. 2004). Importantly, it is still not known whether these effects of race are manifest similarly in females and males, and this question is an area of active investigation. In adult samples, black women tend to have higher levels of CRP than both black and white men as well as white women (Khera et al. 2005). Importantly, this pattern of results has been replicated over time (Farmer et al. 2020). Similarly, a separate study found that being female and belonging to a minority group (e.g., black or Hispanic) synergistically predicted higher levels of circulating CRP, both in young and middle aged adults (Richman 2017). Although there is some evidence that both female sex and minority race are associated with elevated inflammatory biomarkers, considerably less is known about when during development these differences emerge.

The majority of studies examining chronic inflammation and negative health outcomes have been conducted in middle-aged (Green et al. 2009) and elderly adult samples (Kabagambe et al. 2011), and there is a considerable, and rapidly growing, literature examining a wide range of factors driving changes in inflammation during adolescence (Brenhouse and Schwarz 2016). These factors include developmental [e.g., onset of puberty (Stumper et al. 2020)], psychological [e.g., depression (Moriarity et al. 2019), stress (Kautz et al. 2019)], behavioral [e.g., diet (Oddy et al. 2018), physical activity (Wärnberg et al. 2007)], and environmental factors [e.g., socioeconomic status (SES) (Muscatell et al. 2018)]. Considerably less is known about whether and when inflammation increases during adolescence. The existing literature typically is based on cross-sectional data (Ford et al. 2003) or longitudinal data examining transitions from childhood into adolescence and from adolescence into adulthood where change typically is examined following long (i.e., 5–7 year) intervals (Slopen et al. 2013). Given that inflammatory processes may disrupt neural development occurring during adolescence, such as myelination and the maturation of frontal cortical areas, a better understanding of whether chronic inflammation increases during adolescence is important.

Current Study

The goal of the current study is to examine whether and how inflammatory biomarkers change during adolescence and to test whether sex- and race-based differences observed in adulthood also are detectable during adolescence. Specifically, the study investigated whether inflammatory biomarkers changed over three annual assessments and whether sex- and race-based differences in four inflammatory biomarkers commonly used in studies of inflammatory physiology [CRP, IL-6, Tumor Necrosis Factor-alpha (TNF-α), and IL-8] could be observed after controlling for two important factors that vary according to sex and race in the US: body mass index (BMI) and SES. The study hypothesized that inflammatory biomarkers would increase over the three annual assessments (Hypothesis 1). The article also predicted that female sex would be associated with higher levels of inflammatory biomarkers (Hypothesis 2) and that black adolescents would exhibit higher levels of inflammatory biomarkers (Hypothesis 3). Finally, the article proposed that black female adolescents would have the highest levels of inflammatory biomarkers (Hypothesis 4).

Methods

Participants

Participants in the current study were drawn from a prospective, longitudinal study of adolescent-onset depression [Project Adolescent Cognition and Emotion (ACE)] in the United States. Project ACE recruited a diverse, urban community sample of 642 adolescents aged 12–13 years who self-identified as white, black, or biracial (investigating racial differences in depression was a goal of Project ACE) and their primary female caregivers. Participants were excluded if they had insufficient English reading/speaking skills to complete assessments or a psychotic, developmental, or learning disorder. Approximately four years after initial enrollment, participants were invited to enroll in a supplementary component of the study in which they would provide blood to assess peripheral inflammation; 315 participants at an average age of 16.49 years (SD = 1.56; range: 12.14–21.28) consented to one blood draw, with 231 participating in a second blood draw at an average age of 17.67 years (SD = 1.59; range: 12.93–22.36), and 148 in a third blood draw at mean age of 18.38 years (SD = 1.55; range: 13.74–21.89). In general, participants were included/excluded based on published guidelines (O'Connor et al. 2009). The 315 participants contributed 926 blood samples, which declined to 299 participants with a baseline assessment and 864 observations once participants with relevant medical conditions were removed (e.g., autoimmune disease, blood clotting disorder, etc.). The sample was reduced further to 284 participants with a baseline assessment and 780 observations once participants with CRP values >10 (potentially indicative of an acute infection) were removed. An additional eight observations were removed in which follow-up occurred less than six months following prior assessment in order to examine observations from approximately annual assessments. Thus, the final analytic sample at baseline included 284 participants with 772 observations provided across all assessments. Observations from the fourth or subsequent assessments were not included due to a relatively small number of observations (observations = 132) spread across four additional assessments; these

observations were excluded because the study focused on developmental trajectories and sought to estimate change occurring during a three-year window of development, rather than examining simultaneously in one analysis (i) a participant observed at two occasions when aged 15 and 16 years and (ii) a participant observed at five occasions when aged 17, 18, 19, 20, and 21. The final analytic sample included 640 observations. The analytic sample did not differ from the complete ACE sample by sex; however, the sample was more likely to include black individuals and persons who were of low SES at study baseline, as has been previously reported (Mac Giollabhui et al. 2020c).

Measures

Inflammation—Four inflammatory biomarkers were selected that are linked consistently with mental and physical health conditions and are known to play important roles in the innate immune response, although the biomarkers used in this study differ in their cellular and tissue origins, their functions, and unique associations with specific pathologies; interested readers can read more about the dynamic and nuanced functions played by CRP/IL-6 (Del Giudice and Gangestad 2018), TNF-α (Bradley 2008), and IL-8 (Remick 2005). For example, IL-6 is pleiotropic and produced by many other cell types beyond white blood cells, including hepatocytes, adipocytes and endothelial cells. In contrast, it is thought that the majority of IL-8 in the blood stream is derived from the monocyte/macrophage lineages and skin cells, with their primary action being to stimulate neutrophil recruitment and activation. A certified phlebotomist drew 10 mL of blood via antecubital venipuncture. Blood primarily was drawn in the late afternoon to control for diurnal variation and was centrifuged to separate the plasma fraction (BD Hemogard with K2 EDTA) before it was stored at −80 °C until the day of assay. Medication use, medical disorder status, time of last meal, time of day, and participant's BMI based on directly measured height and weight were recorded at each blood draw. Cytokines were quantified by multi-cytokine array (IL-6, IL-8 and TNF-α), and high-sensitivity CRP (CRP) was determined via singleplex assay using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for analyte detection (Meso Scale Discovery, Gaithersburg, MD). The analytes were run in duplicate, with intra-assay coefficients varying from 1.94–4.38%. Values were referenced to a standard curve generated from seven calibrators with known concentrations. The lower limit of detection for cytokines was 0.1 pg/mL, with a dynamic range up to 2000 pg/mL. However, CRP is present in sera at higher concentrations, and thus, plasma was diluted to correspond to the standard curve. Values were converted to mg/L units and were quantified down to 0.1 mg/L (Breen et al. 2011).

Body mass index—BMI was quantified as weight (kg), determined with an electronic scale, divided by height (cm).

Demographics—Age, sex, and race were assessed via participant self report. SES was assessed at baseline by either (i) maternal indication that the child received federally-subsidized school lunch (receipt of free lunch assumed to indicate low SES) or (ii) family income below $15,000. For sex, males were coded as zero and females as one. For SES, low socioeconomic status was coded as one and all other categories were coded as zero. Participants identifying as white were coded as zero and black as one.

Procedure

Participants in the ACE study completed two types of assessments. The first type was a comprehensive assessment scheduled to occur annually. During comprehensive assessments, participants and their mothers completed self-report questionnaires, behavioral assessments, and semi-structured interviews. Shorter six-month assessments also were scheduled in which participants completed measures of stressful life events in addition to self-report questionnaires. Participants were invited to contribute blood specimens at annual assessments and when assessments were missed, participants were invited to provide blood at six-month assessments.

Data Analysis

Analyses were conducted in R 3.6.0 (R Core Team 2019) and multilevel models with random intercepts and fixed slopes were estimated using packages lmer4 (Bates et al. 2015) and lmerTest (Kuznetsova et al. 2017). An advantage of multilevel models is that it does not assume an equal number of observations in longitudinal data and consequently can handle data generated by participants who attended different numbers of assessments (Hox 2000). All inflammatory biomarkers were log-transformed (CRP/IL-6/TNF-α/IL-8) to impose a normal distribution upon these outcome variables; estimates of skewness and kurtosis (respectively) improved for all transformed variables and transformed values now typically fell within an acceptable range [CRP (non-transformed: 2.32, 5.11; transformed: −0.17, −0.021); IL-6 (non-transformed: 8.73, 100.18; transformed: 0.9, 1.83); TNF-α (non-transformed: 6.09, 67.1; transformed: −0.11, 3.79); IL-8 (non-transformed: 6.6, 47.79; transformed: 1.59, 3.87)]. Bivariate correlations were examined initially. In order to produce accurate estimates for calculating statistical interactions, predictor variables were mean-centered across analyses. BMI was z-scored so that unit increases could be easily interpreted as an increase of a standard deviation. In both cross-sectional and longitudinal models, the association of age and inflammatory biomarkers was estimated in isolation first (Model 1), so that results may be compared with prior studies' reported unadjusted associations. The study examined the cross-sectional associations between inflammatory biomarkers and age, sex, race, BMI, and SES within a multivariate regression framework.

Prospective analyses used a mixed-model linear regression framework with random intercepts and fixed slopes. Random intercepts were selected because there was considerable variability in the age of participants at baseline (SD = 1.56; range: 12.14–21.28) and analyses sought to examine between-person change in inflammatory cytokines over a three-year period. Assumptions of linearity were corroborated through visual inspection of a random sample of 30 participants. For prospective analyses, age at baseline was mean-centered and the time variable indicated (number of years) since baseline assessment. Cross-sectional and prospective analyses examined whether levels of inflammatory biomarkers differed by age/time, sex, and race, while controlling for covariates. All regression coefficients reported were standardized. Additionally for cross-sectional analyses, identical models were tested following the introduction of an A*B interaction term testing whether levels of inflammatory biomarkers differed (i) for females versus males at different ages at baseline, (ii) for black versus white males and females, and (iii) for black and white adolescents at different baseline ages. For prospective analyses, interaction terms were

introduced to test whether trajectories of inflammatory biomarkers differed (i) by sex over time, (ii) for black versus white males and females, and (iii) for black and white participants over time. Although CRP values greater than 10 mg/L often are considered to be indicative of an acute immune challenge, there is strong evidence that CRP values >10 mg/L are not always indicative of acute infection/injury and, importantly, their removal may lead to biased samples and results. Consequently, the current manuscript follows guidelines suggesting publication of sensitivity analyses that replicate results where CRP values >10 mg/L are not automatically removed (Mac Giollabhui 2020a).

Results

Bivariate correlations and descriptive statistics for the main study variables are presented in Table 1 for 284 participants at the first blood draw. Raw CRP values may be of interest to readers and the means and standard deviations of raw CRP values are provided by sex and race at each time point in Table 2. At baseline, of the 284 individuals included in the analytic sample, 86.6% had CRP values less than 3 mg/L, 5.7% had values between 3 and 5 mg/L, and 7.7% had values between 5 and 10 mg/L. Based on the full sample of 315 individuals at baseline, 79.7% had CRP values less than 3 mg/L, 6.3% had values between 3 and 5 mg/L, 5.8% had values between 5 and 10 mg/L, and 7.6% had values greater than 10 mg/L.

At baseline, older participants had lower levels of IL-8. Females were more likely to have higher circulating levels of CRP and IL-6. Participants identifying as black were more likely to be of low SES and had lower levels of TNF-α and IL-8. Low SES was associated with lower TNF-α, and higher BMI was associated with higher levels of CRP and IL-6. Higher levels of IL-6 were associated with higher levels of CRP and TNF-α. The univariate associations between inflammatory biomarkers and baseline age are presented in Fig. 1.

Multivariate Cross-Sectional Models

Cross-sectional multivariate models predicting to inflammatory biomarkers are presented as Model 1 and Model 2 in Table 3. In Model 1 in Table 3, older age was not associated with higher CRP and IL-6 (although both associations were only slightly the above threshold for significance) and was significantly associated with lower IL-8 (see Fig. 1). In the multivariate model (Model 2), older age at baseline again was associated with lower levels of IL-8. Being female and having higher BMI were associated with higher levels of CRP and IL-6 in multivariate models. On the other hand, identifying as black was associated with lower levels of TNF-α and IL-8.

At baseline, black females experienced higher levels of IL-6 compared to white females (mean difference = 0.16, $p = 0.003$; see Fig. 2a) and both white (mean difference = 0.21, $p < 0.001$) and black males (mean difference = 0.23, $p < 0.001$). Similarly, females who were older had significantly higher levels of CRP (Female: −1 SD, $b = -0.02$, $p > 0.05$; Mean, $b = 0.17$, $p = 0.009$; +1 SD, $b = 0.35$, $p < 0.001$; not depicted in a figure). Finally, older age at baseline was associated with lower levels of IL-8 more strongly in white compared with black adolescents (see Fig. 2b).

Multivariate Prospective Models

Prospective multivariate models included observations from up to two subsequent blood draws. The associations of baseline age and time with inflammatory biomarkers are presented in Model 1, Table 4. Baseline age was associated with lower TNF-α and IL-8, and time after baseline was associated with higher CRP and lower IL-6 and TNF-α. In multivariate analyses (Model 2, Table 4), for every year participants aged after baseline, their levels of IL-6 and TNF-α declined. Being female continued to predict higher levels of IL-6 and CRP over time, but now also predicted lower levels of TNF-α. Identifying as black continued to predict lower levels of TNF-α and IL-8, and higher BMI was associated with higher levels of CRP and IL-6.

Over time, black females continued to have differentially higher levels of IL-6 compared to white females (mean difference = 0.12, $p < 0.001$), with both black females (mean difference = 0.21, $p < 0.001$) and white females (mean difference = 0.08, $p = 0.02$) experiencing higher levels of IL-6 than in their male counterparts (see Fig. 2c). Although an interaction between race and time was observed such that levels of IL-8 declined in whites more than blacks, neither slope differed significantly from zero (white: $b = -0.02$, $p = 0.14$; blacks: $b = 0.02$, $p = 0.14$ (see Fig. 2d)).

Sensitivity Analyses

Traditionally, CRP values greater than 10 mg/L were believed to index acute rather than chronic inflammation (i.e., the immune system is responding to illness or injury and is temporarily elevated). There is growing evidence that CRP values greater than 10 mg/L are commonly observed outside of acute inflammation and associated with health behaviors relevant to both physical and mental health (e.g., obesity, smoking). Consequently, recommendations to report sensitivity analyses testing whether results are dependent upon inclusion/exclusion of CRP values greater than 10 mg/L were followed (Mac Giollabhui 2020a). This broad pattern of results replicated when including participants with CRP values greater than 10 mg/L. The results of all sensitivity regression analyses are presented in Supplementary Tables 1 and 2.

Discussion

The immune system plays a crucial role in maintaining human health; however, dysregulation of the immune system that is characterized by chronic, low-grade, systemic inflammation is associated with negative physical and mental health outcomes. There is considerable evidence that female and black individuals are more likely to exhibit elevated inflammatory biomarkers indicative of chronic inflammation, but few studies have examined whether the combination of being female and black is differentially associated with higher inflammatory biomarker values. Moreover, no studies investigated this question during a critical window of development, adolescence, where comparatively less is known about precisely how inflammatory biomarkers change. This study investigated sex- and race-based differences as well as developmental trajectories of inflammation, as indexed by peripheral levels of four inflammatory biomarkers (CRP, IL-6, TNF-α, and IL-8), in a racially and socioeconomically diverse sample of adolescents who were followed over three years.

Three clear themes were evident in the results. First, consistent with findings in adults, female adolescents experienced higher levels of CRP and IL-6 than males, and lower levels of TNF-α and IL-8 were observable in black adolescents when compared to white adolescents. Second, this study also provides support for the double-jeopardy hypothesis of social disadvantage (that being black and female are two separate risk factors that compound when a person possesses both), given that black females experienced consistently higher levels of IL-6 compared to their white female peers as well as their black and white male counterparts. Finally, there was no clear pattern of results on how age related to circulating levels of inflammatory cytokines; however, the balance of evidence suggested a pattern of decline during later adolescence. Older adolescents exhibited lower levels of IL-8 and concentrations of two cytokines (IL-6 and TNF-α) that play a central role in activation of the innate immune system declined as adolescents aged.

This study found that female adolescents, aged 16.5 years, exhibited higher levels of both CRP and IL-6, but not TNF-α or IL-8, compared to male adolescents; a pattern observed at baseline and in subsequent assessments independent of both SES and BMI. These results are in line with sex-based differences previously observed in both experimental (Eisenberger et al. 2009) and observational studies (Lakoski et al. 2006) conducted in adults. These findings also are consistent with increased levels of CRP observed in female adolescents, aged approximately 16 years and older (Shanahan et al. 2013). Elevated levels of CRP/IL-6 also have been observed in girls aged 9 years (Khandaker et al. 2014). However, it should be noted that some studies have reported higher levels of CRP in Chinese (Wang et al. 2011) and Spanish adolescent males (Warnberg et al. 2006). Although these findings do not explain why females in a diverse urban sample of adolescents in the United States exhibit higher levels of CRP/IL-6, they do suggest that the difference cannot simply be attributed to socioeconomic status or body mass. It is unclear why increased levels of two pro-inflammatory biomarkers, such as CRP and IL-6, are observed in female teens, but not TNF-α or IL-8, but it may be due to the greater role that adipose tissue, which typically is present in higher levels in females, plays in stimulating IL-6 compared to TNF-α (Karastergiou et al. 2012). Adipose tissue is responsible for approximately 30% of circulating IL-6, which leads directly to stimulation of CRP, but does not significantly contribute to levels of circulating TNF-α (Mohamed-Ali et al. 1997). Other candidate mechanisms include: sex hormones (Laaksonen et al. 2003) or greater female exposure to risk factors (e.g., life stress) for elevated inflammation (Derry et al. 2015).

This study found that black females had significantly higher levels of IL-6 compared to their white female peers as well as to both black and white male adolescents, independent of the effects of SES, BMI, or age. This supports the double-jeopardy hypothesis that social disadvantage, in this case to be both black and female, may compound to increase health risks (Beal 2008). Elevated IL-6 among black females has been consistently observed in previous studies in black women (Farmer et al. 2020; Wee et al. 2008). Inasmuch as a similar vulnerability also has been observed in other groups of minority females (Richman 2017), this may indicate that specific environmental stressors, such as discrimination, may play an important role (Brody et al. 2015). Given the long-standing racial disparities in health outcomes in the United States and the association of inflammatory biomarkers

with health outcomes, a better understanding of the mechanisms by which black females experience higher levels of IL-6 is needed (Williams 2012).

Differences in circulating cytokines also were observed by race. Previously reported elevations in CRP and IL-6 seen in black individuals were not detected in the current study (Kelley-Hedgepeth et al. 2008). Failure to identify differences by race may indicate that these differences do not emerge until adulthood or, alternatively, that the association of race with IL-6/CRP largely is explained by "covariates", such as BMI or SES, that are associated with both race and inflammation in the United States. Indeed, BMI and/or SES may play a causal or mediating role in the association between race and inflammatory biomarkers. In fact, in prior studies, associations between race and inflammatory biomarkers are attenuated substantially or entirely absent in samples that control for factors like body mass (Albert et al. 2004). Alternatively, it may be that racial differences in CRP/IL-6 observed in prior population-based studies are being driven by the higher levels observable in black women (Khera et al. 2005).

This study found that black adolescents exhibited lower levels of both TNF-α and IL-8. Although fewer studies have examined the association of race with TNF-α and IL-8, particularly in community samples, prior research also has indicated that whites have higher levels of circulating TNF-α compared to blacks, with differences attributed to a range of unknown genetic and environmental factors (Olson et al. 2012). Although this study does not shed light on the underlying mechanism underpinning differences in TNF-α, it suggests that such differences also are observable early in life. The precise functional impact that lower levels of these biomarkers have on health is unclear, particularly given that both black and older adolescents more generally exhibited lower levels of IL-8 in this study. IL-8 is a chemokine involved in directing immune cells to the site of inflammation that has been implicated in structural brain changes (Ellman et al. 2010) as well as the onset of psychotic (Ellman et al. 2010) in addition to externalizing symptoms (Mac Giollabhui et al. 2019). Although a number of studies have examined the association of IL-8 with insulin resistance and adiposity in youth, no comparative data were found examining IL-8 in a healthy sample of adolescents (Tam et al. 2010). Additionally, given that there is substantial overlap and redundancy in the chemokine system, it is possible that lower levels of IL-8 may not be associated with any functional difference in immune functioning (Remick 2005).

Although older adolescents exhibited numerically higher levels of CRP and IL-6, they did not meet criteria for statistical significance and, moreover, these associations were not present once important factors, such as BMI, were included. Instead, in adjusted models, older adolescents had lower IL-8 concentrations and, significantly, longitudinal analyses indicated that there was a general decline in two acute-phase cytokines (IL-6 and TNF-α) as adolescents aged, although conversely CRP was observed to increase in univariate analyses. When considered as a whole, these results are at odds with prior findings that CRP and total leukocyte counts increase during adolescence, particularly late adolescence (Bartlett et al. 1998). Instead, the current study supports prior work that older adolescents have lower levels of several circulating cytokines (i.e., IL-2, IL-8, TNF-α) (Riis et al. 2014). It is unclear whether discrepant results stem from differences in sample characteristics or reflect the large number of variables influencing immune functioning (e.g., body mass, hormones,

increasing salience of social rewards/threats, stress and coping, levels of substance use and psychopathology) that are known to change during adolescence (Brenhouse and Schwarz 2016).

Although a central purpose of this study was to investigate sex- and race-based differences in inflammation, it is important to note that the results presented here likely underestimate such associations. For example, in the United States, there is considerable overlap between race and important 'confounds', such as SES and BMI, that are independently associated with elevated inflammation (Hero and Levy 2016). Consequently, when interpreting whether differences in inflammation exist, removing the contribution of low socioeconomic status to levels of inflammation in black adolescents or the contribution of body fat to levels of inflammation in female adolescents, in whom it is generally higher, may misrepresent true differences that can be observed in the population (Power and Schulkin 2008).

The current results should be considered in the context of the limitations of the study. First, whereas a number of patterns of results were predicted, unexpected associations also were observed. For example, although females experienced increased CRP and IL-6 in longitudinal analyses, decreased TNF-α also was associated with being female. Whereas it may be that increased levels of IL-6 inhibit release of TNF-α (Akira et al. 1990), there is increasing agreement that circulating cytokines and chemokines have much more complex and nuanced effects than simply exerting pro- or anti-inflammatory effects (including well-known "pro-inflammatory" biomarkers such as IL-6) (Del Giudice and Gangestad 2018). This inability to conclude that elevated inflammatory biomarkers index basal levels of innate immune activation alone substantially tempers the ability to interpret the concentration of a given inflammatory biomarker. Moreover, despite using a well-established panel of inflammatory biomarkers, it is unclear the degree to which variability across values of biomarkers is due to biological and behavioral factors or is due to the half-life and/or tissue origins of the inflammatory biomarkers, which may contribute to discrepant results frequently observed in psychoneuroimmunology (Marques-Vidal et al. 2011).

Future studies may benefit from utilizing new inflammatory biomarkers that may be more stable and interpretable markers of chronic, low-grade inflammation, such as soluble urokinase-type plasminogen activator receptor (suPAR) (Rasmussen et al. 2019). Second, assessment of inflammatory biomarkers in this study relied on non-fasting sera samples for which there was some diurnal variability in terms of the time at which blood was drawn; although significant confounds (e.g., medical conditions, indication of acute infection) were addressed, it is likely this 'noise' somewhat reduced the ability to reliably measure basal levels of circulating inflammatory biomarkers. To more fully understand how and whether inflammatory biomarkers change based on age, sex, and race, there is still need for a conclusive longitudinal study that recruits different age groups and follows them over time to map the developmental trajectory of immune functioning while concurrently minimizing variability due to sampling (e.g., fasting, diurnal variability). Third, although the study relied on multiple assessments in a socioeconomically and racially diverse sample, there was substantial attrition in the study and only 640 of a possible 852 sera samples were collected, and thus, the possibility that systematic biases affected the results reported here cannot be excluded. On the other hand, major strengths of this study included its longitudinal design,

its capacity to control for vital confounds such as BMI and SES, and the ability to carefully assess racial and sex interactions in a diverse adolescent sample.

Conclusion

Better understanding who is at risk for developing chronic inflammation is critically important to identifying and potentially preventing physical and mental health conditions. Despite a growing body of research investigating how inflammation is related to psychopathology and a range of risk factors for psychopathology, there are notably few studies of adolescents that examine normative changes in inflammatory biomarkers and differences based on sex and race. The present study addressed this gap by examining four inflammatory biomarkers in a socioeconomically and racially diverse sample of adolescent males and females repeatedly over three years. Previously reported and widely replicated sex differences in CRP and IL-6 in adults also were observed in the current study, although racially-based differences in CRP/IL-6 were not. It is notable that black female adolescents exhibited higher levels of an inflammatory biomarker (IL-6) that is consistently associated with negative health outcomes. Relative elevation of this indicator of inflammation early in life may contribute to the well-established disparities in health outcomes that differentially affect black women in the United States. At the very least, it calls for further research to investigate why black female youth are at greater risk for poorer health. The observation of demographic differences across a panel of commonly used inflammatory biomarkers highlights the importance of conceptualizing inflammatory processes within demographic contexts so that potentially important sex- and race-based differences are not overlooked.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

Naoise Mac Giollabhui is a doctoral candidate in Temple University's clinical psychology program. He works in Dr. Alloy's Mood and Cognition Lab at Temple University and is interested in how cognitive biases and neuropsychological functioning differ in those who have experienced depression. He also is interested in how immune functioning is implicated in the etiology of depression, specifically if immune dysfunction is related to weaknesses in neuropsychological functioning observed in depression.

Lauren B. Alloy is Laura H. Carnell Professor and Joseph Wolpe Distinguished Faculty in the Department of Psychology at Temple University. She received her doctorate in Experimental and Clinical Psychology from the University of Pennsylvania. Her major

research interests include cognitive, psychosocial, developmental, and neurobiological processes in the onset and course of depression and bipolar disorder.

Dominika Swistun is a research associate at the University of California, Los Angeles and Greater Los Angeles VA Healthcare, where she conducts research related to insomnia and sleep issues among women veterans. She also works as a clinician within the field of behavioral medicine. She received her doctorate degree at the University of Wisconsin-Madison with research interests centered around inflammatory processes and predisposition to depression among vulnerable populations.

Christopher L. Coe is the W.B. Cannon Professor of Biopsychology at the University of Wisconsin-Madison. He received his doctorate in the behavioral neurosciences at Downstate Medical Center, SUNY. His research interests include the relationship between biomarkers and health, with a focus on resilience and vulnerability at the beginning and end of the life course, specifically the prenatal period and old age.

Lauren M. Ellman is an Associate Professor of Psychology at Temple University. She received her doctorate in Clinical Psychology at the University of California-Los Angeles. Her major research interests include neurodevelopmental risk factors, including inflammation, for psychotic disorders (e.g., schizophrenia) and depression.

Daniel P. Moriarity is a doctoral student in Lauren B. Alloy's Mood and Cognition Lab at Temple University. His major research interests include how cognitive vulnerabilities and inflammation interact to confer risk for mood disorder comorbidities, symptom-level approaches to psychoneuroimmunology, and psychoneuroimmunology methodology.

Allison C. Stumper is a doctoral student in Lauren B. Alloy's Mood and Cognition Lab at Temple University. Her research interests include how biological and environmental factors interact to confer risk for adolescent depression, with an emphasis on the role of biological changes as a result of the pubertal transition.

Lyn Y. Abramson is the Sigmund Freud Professor of Psychology at the University of Wisconsin-Madison. She received her doctorate in Clinical Psychology from the University of Pennsylvania. Her major research interests include the developmental, cognitive, motivational, and cultural determinants of information processing about the self and the effects of early psychological, physical, and sexual maltreatment on the development of cognitive styles and vulnerability to depression in adulthood.

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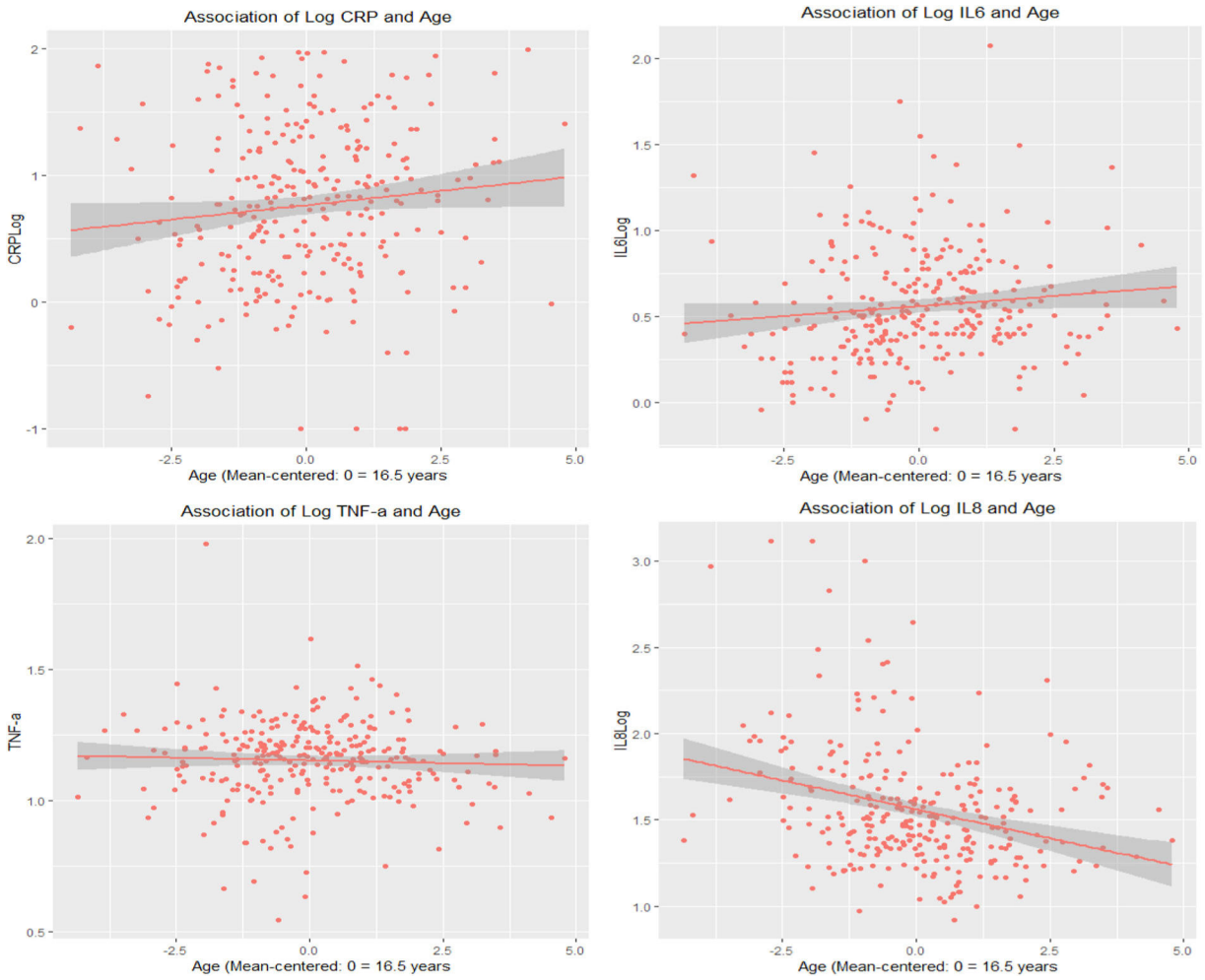

Fig. 1.

Cross-sectional associations of baseline age with log-transformed CRP, IL-6, TNF-α, and IL-8

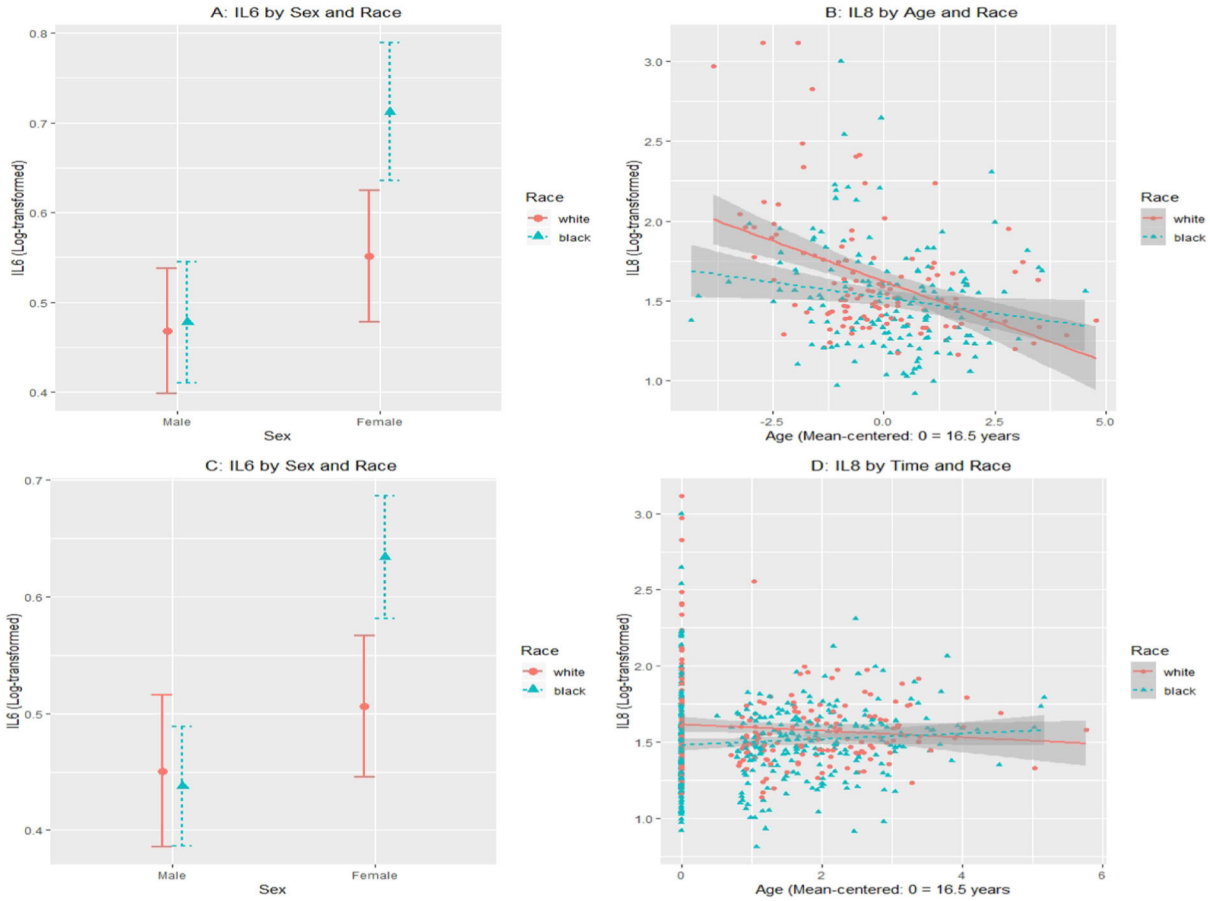

Fig. 2.

Cross-sectional (**a** + **b**) and prospective (**c** + **d**) interactions predicting to log-transformed IL-6 and IL-8

Table 1

Bivariate correlations and descriptive statistics of study variables for participants at baseline ($N = 284$)

	Age	Sex	Race	SES	BMI	CRP	IL-6	TNF-α	IL-8
Age	–								
Sex	0.01	–							
Race	0.08	−0.04	–						
SES	0.01	−0.02	0.38***	–					
BMI	0.09	0.10	0.05	0.03	–				
CRP	0.11	0.19***	0.02	−0.04	0.53***	–			
IL-6	0.10	0 27***	0.12	0.05	0.33***	0.48***	–		
TNF-α	−0.04	−0.08	−0.18**	−0.13*	−0.1	0.02	0.21***	–	
IL-8	−0.30	0.04	−0.16**	−0.01	−0.06	−0.03	−0.01	0.07	–
Mean	16.49	0.51	0.58	0.48	23.76	1.38	0.53	1.51	6.37
SD	1.56	0.50	0.49	0.50	5.85	1.98	0.88	0.68	14.43

For inflammatory cytokines, the correlations represent log-transformations of the raw data. Means and standard deviations for the inflammatory biomarkers represent untransformed values. Female sex is coded as one. Participants identifying as blacks were coded as one. Low socio-economic status was coded as one

SES Socioeconomic status, *BMI* Body Mass Index, *CRP C* reactive protein, *IL* Interleukin, *TNF* Tumor Necrosis Factor

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 2

Means and standard deviations of raw inflammatory biomarker values broken down by sex and race at three timepoints

			CRP		IL6		TNF-α		IL-8	
		Race	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Time 1	Age = 16.49 (1.56)	Black	0.97 (1.39)	1.79 (2.13)	0.43 (0.56)	0.81 (1.44)	1.48 (0.43)	1.36 (0.50)	4.53 (4.81)	5.40 (12.01)
		White	1.14 (1.72)	1.63 (2.49)	0.36 (0.25)	0.46 (0.44)	1.58 (0.42)	1.69 (1.13)	5.54 (9.37)	10.70 (24.87)
Time 2	Age = 17.77 (1.56)	Black	1.28 (2.01)	1.69 (1.89)	0.31 (0.29)	0.55 (0.84)	1.31 (0.38)	1.25 (0.34)	3.33 (1.63)	3.35 (1.52)
		White	1.32 (1.96)	1.86 (2.45)	0.37 (0.38)	0.34 (0.24)	1.75 (0.91)	1.34 (0.30)	4.57 (5.67)	3.26 (1.21)
Time 3	Age = 18.58 (1.48)	Black	1.21 (2.14)	1.99 (2.25)	0.29 (0.21)	0.49 (0.34)	1.36 (0.27)	1.41 (0.60)	4.30 (2.70)	3.49 (1.57)
		White	1.49 (1.63)	1.81 (1.90)	0.26 (0.20)	0.41 (0.32)	1.54 (0.38)	1.47 (0.47)	4.36 (1.98)	4.45 (2.10)

Standard deviation presented within parentheses

CRP C reactive protein, *IL* Interleukin, *TNF* Tumor Necrosis Factor

Table 3

Multivariate regression and interactive relationships at baseline (N = 284)

	CRP	IL-6	TNF-α	IL-8
Model 1				
Age (Mean-centered)	0.11[a]	0.10[b]	−0.04	−0.30***
Model 2				
Age (Mean-centered)	0.06	0.05	−0.02	−0.30***
Sex (Mean-centered)	0.14**	0.25***	−0.08	0.05
Race (Mean-centered)	0.03	0.11	−0.15*	−0.16*
SES (Mean-centered)	−0.06	0.01	−0.07	0.05
BMI (z-score)	0.50***	0.28***	−0.09	−0.04
Interactions				
Sex*Age	0.16***	n.s	n.s	n.s
Sex*Race	n.s	0.14**	n.s	n.s
Race*Age	n.s	n.s	n.s	0.13*

Interactions include variables specified in Model 1. Female sex is coded as one. Participants identifying as black were coded as one. Low socio-economic status was coded as one

SES Socioeconomic status, *BMI* Body Mass Index, *CRP* C reactive protein, *IL* Interleukin, *TNF* Tumor Necrosis Factor

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] 0.053

[b] $p = 0.065$

Table 4

Multivariate random intercept linear regression using longitudinal data (N = 284, obs. = 640)

	CRP	IL-6	TNF-α	IL-8
Model 1				
Baseline Age (Mean-centered)	0.06	0.03	−0.10*	−0.16***
Time	0.12***	−0.09**	−0.10**	−0.03
Model 2				
Baseline Age (Mean-centered)	0.02	0.00	−0.07	−0.15*
Time	0.05	−0.14***	−0.09***	−0.02
Sex (Mean-centered)	0.13**	0.22***	−0.09*	0.01
Race (Mean-centered)	−0.02	0.09	−0.18***	−0.16***
SES (Mean-centered)	−0.02	0.01	−0.01	0.06
BMI (z-score)	0.46***	0.32***	−0.02	−0.03
Interactions				
Sex*Time	n.s	n.s	n.s	n.s
Sex*Race	n.s	0.09*	n.s	n.s
Race*Time	n.s	n.s	n.s	0.04*

Interactions include variables specified in Model 1. Female sex is coded as one. Participants identifying as black were coded as one. Low socio-economic status was coded as one

SES Socioeconomic status, *BMI* Body Mass Index, *CRP* C reactive protein, *IL* Interleukin, *TNF* Tumor Necrosis Factor

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$