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Experiences of racial discrimination and adverse gene expression among black individuals in a level 1 trauma center sample

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ABSTRACT

Up to 40 % of individuals who sustain traumatic injuries are at risk for posttraumatic stress disorder (PTSD) and the conditional risk for developing PTSD is even higher for Black individuals. Exposure to racial discrimination, including at both interpersonal and structural levels, helps explain this health inequity. Yet, the relationship between racial discrimination and biological processes in the context of traumatic injury has yet to be fully explored. The current study examined whether racial discrimination is associated with a cumulative measure of biological stress, the gene expression profile conserved transcriptional response to adversity (CTRA), in Black trauma survivors. Two-weeks (T1) and six-months (T2) post-injury, Black participants ($N = 94$) provided a blood specimen and completed assessments of lifetime racial discrimination and PTSD symptoms. Mixed effect linear models evaluated the relationship between change in CTRA gene expression and racial discrimination while adjusting for age, gender, body mass index (BMI), smoking history, heavy alcohol use history, and trauma-related variables (mechanism of injury, lifetime trauma). Results revealed that for individuals exposed to higher levels of lifetime racial discrimination, CTRA significantly increased between T1 and T2. Conversely, CTRA did not increase significantly over time in individuals exposed to lower levels of lifetime racial discrimination. Thus, racial discrimination appeared to lead to a more sensitized biological profile which was further amplified by the effects of a recent traumatic injury. These findings replicate and extend previous research elucidating the processes by which racial discrimination targets biological systems.

1. Introduction

Each year in the United States over 37 million individuals present at an Emergency Department for a traumatic injury (Cairns et al., 2021). Traumatic injury is defined as an injury to the body as a result of violence or accidental event, for example, motor vehicle collisions, gunshot or stab wounds, among others (Dumovich & Singh, 2022). How an individual physically and psychologically recovers after an injury is influenced by structural and social determinants of health (Centers for Disease Control and Prevention, 2022). There are significant health inequities in trauma outcomes, such that more severe and chronic health trajectories are observed among members of marginalized groups, including those from racially minoritized backgrounds (Loberg et al., 2018; Vella et al., 2020). For example, Black injury survivors are more likely to experience poorer mental health outcomes and quality of life following injury compared to White injury survivors (Bernard et al., 2022; Bird et al., 2021; Geier et al., 2023). Racial health inequities in trauma outcomes are created and maintained by economic, racial, and

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social inequity. One specific driver is the insidious experience of racial discrimination, defined as disadvantage and prejudice based on one's race, which may be interpersonal, structural, or institutional in nature (Kirkinis et al., 2021). Racial discrimination is particularly prevalent among Black individuals, with rates of racial discrimination ranging from 50 to 70 % among national polling data (Bleich et al., 2019; Kaiser Family Foundation, 2020) and has been linked to various negative consequences physically and psychologically (Bird et al., 2021; Williams et al., 2020). Addressing post-injury outcomes in Black individuals requires this contextualization and a thorough understanding into how experiences of racial discrimination become biologically embedded and exacerbated by traumatic injuries.

Although racial discrimination does not currently qualify as a Criterion A traumatic event (defined in the Diagnostic Statistical Manual of Mental Disorders – Fifth Edition [DSM-5]), theoretical and empirical work suggests racial discrimination is a form of trauma, evoking posttraumatic stress symptoms that mirror the hallmarks of PTSD (e.g., avoidance, hyperarousal; Carter, 2007). However, unlike the traumatic events defined in the DSM-5, exposure to racial discrimination is pervasive and chronic (Carter, 2007). Data from our team (Bird et al., 2021; Harb et al., 2023) and others (e.g., Mekawi et al., 2021; Sibrava et al., 2019) highlight that racial discrimination is independently associated with posttraumatic stress symptoms and related to increased risk for PTSD after a DSM-5 Criterion A qualifying event among Black individuals. One explanation as to why racial discrimination increases risk for future PTSD, is that experiences of racism over the lifetime position Black individuals to activate biological stress responses more readily (Carter, 2007; Carter et al., 2021; Goosby et al., 2018), which may be exacerbated following a new trauma. Examining interactions between racial discrimination and measures of biological stress may meaningfully progress our understanding of the cumulative impact of racialized stress and how future trauma amplifies the effects of racial discrimination.

The physical health consequences of racism are well documented, illustrating that racial discrimination has been associated with early mortality, cardiovascular disease, chronic pain, diabetes management, and increased medical comorbidities (Brown et al., 2018; Loberg et al., 2018; Panza et al., 2019;). Racial discrimination, including at both interpersonal and structural levels, helps explain the racial health inequities in these physical outcomes (Bailey et al., 2017; Carter et al., 2017; Priest and Williams, 2017). The weathering hypothesis, put forth by Geronimus (1992), posits that chronic exposure to a structurally racist society and hostile environment throughout one's life has a deleterious impact on the health and wellbeing of Black individuals (Geronimus, 1992; Carter et al., 2021). Repeated experiences of racial discrimination chronically activate physiological processes attempting to deploy and regulate the biological stress response. Over time, chronic activation of the systems responsible for maintaining homeostasis (e.g., immune, cardiovascular) can lead to physiological 'wear and tear' and ultimately significant impairments to mental and physical health (Forde et al., 2019; Geronimus,1992; Goosby et al., 2018).

One consistent example of the link between racism, physiological wear and tear, and stress disorder pathophysiology is the association between racial discrimination and immune function. Stress-induced alterations to the immune system, as evidenced by higher levels of systemic inflammation (e.g., higher C-reactive protein, inflammatory cytokines), are associated with greater exposure to racial discrimination (Brody et al., 2015; Giurgescu et al., 2016; Simons et al., 2021). Recent work suggests racism-related immune dysfunction (indexed by C-reactive protein levels) moderates how the brain processes threat (Albasheir et al., 2023), suggesting a mechanism by which racial discrimination influences how individuals biologically respond to acute trauma/stress and emphasizing the interrelated nature of physiological responses. In acute trauma survivors, higher levels of inflammation are also predictive of PTSD following a traumatic event (reviewed in Michopoulos et al., 2017). However, the majority of previous work has investigated the effects of trauma or racial discrimination on levels of specific immune markers rather than examining the "upstream" control pathways responsible for generating the immune responses (i.e., gene expression).

In line with the weathering framework, the field of human social genomics has begun to identify how socio-ecological environments impact patterns of gene expression through biological embedding of chronic stress (Cole, 2014; Lee et al., 2021). There is now mounting evidence that functioning of inherited genes are influenced by one's social milieu and that the social environment and individual experience of that environment affects gene expression. Not only are specific genes individually regulated by social stress and adverse social conditions, but entire groups or functional families of genes can be influenced by the social environment (Cole, 2013). The conserved transcriptional response to adversity (CTRA) gene expression profile characterizes a molecular mechanism (alterations to pro-inflammatory and antiviral transcription control pathways) by which stressors impacts physical and mental health (Cole, 2019).

Exposure to conditions of chronic stress results in a systematic shift in basal gene expression profiles, characterized by increased expression of genes involved in inflammation and decreased expression of genes involved in type I interferon (IFN) antiviral responses and IgG antibody synthesis (Cole, 2014; Knight et al., 2016). Across preclinical models and humans, various forms of adversity (e.g., poverty, deprivation) have evoked this pattern of activity (Cole, 2019). Exposure to stress, threat, or uncertainty is the main precipitant of increased CTRA expression. This provoked increased expression can be remediated behaviorally (Antoni et al., 2012; Antoni et al., 2016) or pharmacologically (Hiller et al., 2020; Knight et al., 2020), with an observable shift in expression occurring over a period of days to weeks. However, environmental and social stressors vary extensively, and limited research has been conducted to understand the impact of individual-level stressors, such as racial discrimination, on the dysregulation of CTRA gene expression.

As an example of environmental conditions contributing to CTRA gene expression, one study showed that the acute stress of caregiving for a family member with brain cancer resulted in increased CTRA expression (Kim et al., 2021). Chronic stressors associated with social isolation or loneliness (Cole et al., 2007), as well as lower socioeconomic status (SES) in childhood (Chen et al., 2011; Miller et al., 2009), have also been implicated in shifting CTRA expression. SES-related differences in CTRA expression have subsequently been linked to adverse health outcomes, as shown in a study of cancer patients (Knight et al., 2016), where low SES was associated with elevated CTRA expression, which in turn was associated with poor clinical outcomes following hematopoietic cell transplantation. To date, only one study has examined how racial discrimination is related to CTRA gene expression, such that past experiences with racial discrimination could potentially explain 50 % of the difference in CTRA gene expression when comparing Black individuals to White individuals (Thames et al., 2019). However, Thames and colleagues demonstrated these findings in a cross-sectional design and were focused on understanding HIV outcomes. While not focusing on the CTRA per se, two other analyses from the Multi-Ethnic Study of Atherosclerosis have also linked experiences of racial discrimination to elevated expression of inflammatory genes (Brown et al., 2020). However, no research has examined the impact of racial discrimination and CTRA gene expression (1) in a prospective design or (2) among traumatically injured individuals.

The current study examined how experiences of racial discrimination contributes to alterations to biological systems among Black trauma survivors in hopes to better understand a potential root cause of widely documented post-trauma health inequities. The study utilized a longitudinal, prospective design to elucidate the connection between racial discrimination and CTRA gene expression at two-weeks and six-months following an acute traumatic injury, while adjusting for demographic characteristics (age, gender), health-related behavior (smoking, heavy alcohol use, body mass index [BMI]), lifetime trauma, and mechanism of injury (MOI; assaultive versus non-assaultive). The examination of these

pre-morbid stress factors in the context of traumatic injury is particularly important due to the heightened risk for negative health outcomes within traditionally marginalized populations. Given previous literature, we hypothesized that lifetime racial discrimination would be associated with greater increases over time in CTRA gene expression following an acute traumatic injury.

2. Materials and methods

2.1. Participants

Traumatic injury survivors were recruited to participate in a prospective longitudinal cohort study at a Midwestern Level 1 trauma center. The sample and data are a part of a larger study (Imaging Study on Trauma and Resilience, iSTAR; see Bird et al., 2021, Webb et al., 2021, Weis et al., 2022) which investigated potential biological predictors of PTSD development in trauma survivors. Participants were recruited between March 2016 and October 2019 using a daily trauma census, a real time list of all trauma patients seen in the emergency department for injury. Eligibility criteria included the ability to read and write in English and to schedule a study visit within two-weeks of the injury. In an attempt to oversample those at heightened risk for PTSD, individuals completed the Predicting PTSD Questionnaire (Rothbaum et al., 2014). Individuals who indicated the injury was a severe/near-death experience or scored at risk for PTSD (as indexed by a score of >3 on the Predicting PTSD Questionnaire) were eligible. Exclusion criteria included the use of illegal drugs, a blood alcohol content of higher than 0.08 during the time of the trauma, or a self-inflicted injury. Individuals who had a spinal injury with neurological deficits, a moderate-to-severe cognitive impairment due to a head injury, or a history of manic, PTSD, or psychotic symptoms, were also considered ineligible. Individuals (N = 966) between the ages of 18 and 65 years old were approached by the recruitment team. Of these individuals, 524 met study inclusion/exclusion criteria. Of the 524 eligible individuals, 60 % were Black and 19 % were White. The majority of eligible individuals experienced a motor vehicle collision (70 %). A total of 245 individuals (63 % Black, 24 % White, 9 % Hispanic) were enrolled in the broader study. Only data from Black participants were included in the current analyses.

Consent and enrollment in the study were carried out by trained research associates. Study procedures were approved by the Medical College of Wisconsin Institutional Review Board and participants were monetarily compensated for their time.

2.2. Procedures

Approximately two-weeks post-injury (T1), participants completed their first study visit which involved completing a battery of self-report assessments, biospecimen collection (i.e., blood draw), and neuroimaging. At six-months post-injury (T2), participants returned for follow-up assessments, completing similar procedures to the T1 visit. In line with previous work (Bird et al., 2021; Webb et al., 2021) examining racial discrimination, only participants who identified as Black or African American were included in the analytic sample. Of the 155 Black participants, 108 (70 %) provided a biospecimen and 94 of these participants had a usable CTRA profile ($n = 7$ excluded after quality checks) and baseline self-report assessments ($n = 7$ missing data).

2.3. T1 and T2 self-report measures

Racial Discrimination. The Perceived Ethnic Discrimination Questionnaire (Brondolo, et al., 2005) was used to evaluate lifetime exposure to racial discrimination and was administered at T1. Items represented potential discriminatory experiences falling into four domains: social exclusion, stigmatization, workplace, and threat/harassment. An additional item asked about police maltreatment. Participants endorsed how often each of the 17-items had happened to them on a scale of 1 (*never)* to 5 (*very often)*. In this sample, the Cronbach's alpha for the PEDQ was 0.94. The total score was created by averaging the responses to each item, where higher scores were indicative of greater exposure to racial discrimination.

PTSD Symptoms. The 20-item Post-Traumatic Checklist for DSM-5 (PCL-5; Blevins et al., 2015) was administered at T1 and T2 to evaluate the presence and severity of PTSD symptoms. Participants indicated how much each symptom bothered them on a 5-point Likert scale from 1 *(not at all)* to 5 *(extremely)*. Total symptom scores were created by summing all responses such that higher scores reflected more severe symptoms (sample Cronbach's alpha = 0.95).

Health-Related Measures. BMI was calculated using body weight and height. At T1, participants were asked if they smoked and this response was dummy coded (0 = not a smoker, 1 = smoker). Alcohol use was assessed using 10-item Alcohol Use Disorders Identification Test (AUDIT; World Health Organization, 2001). Participants responded to questions about their heaviest year of alcohol use, including the amount and frequency of alcohol consumption and presence of problems caused by drinking.

Lifetime Trauma. To evaluate lifetime trauma exposure (not including racial discrimination), the Life Events Checklist for DSM-5 (LEC-5; Gray et al., 2004) was administered at T1. The LEC-5 is a 17-item list of potentially traumatic events such as natural disasters or kidnapping. Participants indicated whether they had a) learned about the event, b) witnessed the event, or c) the event had happened to them. A newly developed (Weis et al., 2021) weighted scoring method was applied in which proximity of the event was considered (Cronbach's alpha = 0.87). Directly experienced events were weighted by a 3, witnessed events were weighted with a 2, and events that were learned of were weighted with a 1.

2.4. T1 and T2 CTRA gene expression measurements

CTRA gene expression was quantified using an established mRNA contrast score involving a pre-specified set of pro-inflammatory gene transcripts and transcripts involved in Type I interferon innate antiviral responses, as previously described (Cole, 2019; Cole et al., 2020). Briefly, venipuncture whole blood samples were collected into PAXgene RNA tubes and stored at −20 °C for batch analysis by RNA sequencing in the UCLA Social Genomics Core Laboratory, with total RNA extracted (Qiagen RNeasy; Cole, 2019; Cole et al., 2020), tested for suitable mass (PicoGreen RNA) and integrity (Agilent TapeStation), reverse-transcribed to cDNA (Lexogen QuantSeq 3′ FWD), and sequenced on an Illumina NovaSeq instrument following the manufacturers' standard protocols. Assays targeted 4 million reads per sample (achieved average = 4.5 million), each of which was mapped to the GRCh38 reference human transcriptome using the STAR aligner (achieved average 98 % mapped). mRNA abundance was quantified as transcripts per million total mapped reads and $\log_2$ transformed for analysis.

2.5. Statistical analyses

Pearson's correlations were conducted to evaluate the relationships between all continuous variables. In addition, independent *t*-tests (two-sided) examined whether there were significant differences in study measures between men and women or MOI. As the majority of Black participants (76 %) experienced a motor vehicle collision, MOI was considered a dichotomous variable (i.e., assaultive versus non-assaultive). In addition, we conducted independent *t*-tests examining if there were significant differences between those who completed T2 assessments and individuals who only completed T1.

The primary outcome analyzed in this study was the average expression of a pre-specified set of 53 CTRA indicator genes used in previous research (Cole, 2019; Cole et al., 2020), including 19 pro-inflammatory genes (*IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS,*

FOSB, FOSL1, FOSL2, JUN, JUNB, JUND, NFKB1, NFKB2, REL, RELA, RELB) that serve as positive indicators of the CTRA profile, and 34 genes involved in Type I interferon responses (*GBP1, IFI16, IFI27, IFI27L1-2, IFI30, IFI35, IFI44, IFI44L, IFI6, IFIH1, IFIT1-3, IFIT5, IFIT1L, IFITM1-3, IFITM4P, IFITM5, IFNB1, IRF2, IRF7-8, MX1-2, OAS1-3, OASL*) and antibody synthesis (*JCHAIN, IGLL1, IGLL3P*), with the latter two gene sets reverse-scored to reflect their role as inverse indicators of the CTRA profile (Cole, 2019; Cole et al., 2020). Among this set of 53 indicator genes, 7 transcripts showed minimal levels of expression (predominately 0 values; *FOSB, FOSL1, IFNB1, IGLL1, IGLL3P, IL1A, IL6)* and minimal variability (SD < 0.5 log2 units) and were thus excluded from analysis to facilitate convergence of maximum likelihood statistical model estimation.

Statistical analyses used mixed effect linear model analyses relating average expression of 46 z-score transformed CTRA indicator gene transcripts (with antiviral genes sign-inverted to reflect their inverse contribution to the CTRA profile, all treated as repeated measures) to racial discrimination while controlling for study time point (T1 or T2, repeated measure), age, gender, BMI, smoking history, heavy alcohol use history, and trauma-related variables (mechanism of injury, lifetime trauma). Analyses were conducted using SAS PROC MIXED as previously described (Cole et al., 2020), with maximum likelihood estimation of fixed effects for indicator gene (repeated measure within subjects), time-invariant covariates (age, gender, lifetime trauma, etc.), racial discrimination, study time-point, and a racial discrimination x time-point interaction term (to test whether CTRA association with racial discrimination increased in the aftermath of trauma), accompanied by a random effect of study participant (parameterized as a compound symmetry covariance matrix) to accommodate correlation of residuals across genes and time points. Following SAS's default coding, the Time x Racial Discrimination effects were computed as the Time 1 - Time 2 difference.

3. Results

3.1. Descriptive statistics

The complete demographics for the 94 participants in the analytic sample are reported in Table 1. Bivariate relationships between study variables are displayed in Table 2. There was no significant difference between men and women on T1 or T2 PTSD symptoms (men $n = 38$, T1 M = 24.58, SD = 17.81; women $n = 56$, T1 M = 26.84, SD = 19.13, $t(92) = -0.58$, $p = .565$; men $n = 30$, T2 M = 14.17, SD = 14.83; women $n = 50$, T2 M = 21.78, SD = 20.74, $t(78) = -1.76$, $p = .083$) or racial discrimination (men $n = 38$, M = 1.89, SD = 0.72; women $n = 56$, M = 1.86, SD = 0.83, $t(92) = 0.48$, $p = .631$). In addition, mechanism of injury (MOI) did not significant impact T1 (assaultive $n = 13$, T1 M = 21.77, SD = 14.96; non-assaultive $n = 81$, T1 M = 26.59, SD = 19.05, $t(92) = 0.87$, $p = .387$) or T2 PTSD symptoms (assaultive $n = 12$, T2 M = 21.42, SD = 17.85; non-assaultive $n = 68$, T2 M = 18.49, $t(78) = 0.31$, $p = .625$). Fourteen participants (14.9 %) did not complete T2 assessments; however, there were no differences between individuals who dropped out and those who completed the follow-up visit on racial discrimination ($t(92) = 0.07$, $p = .662$), T1 PTSD symptoms ($t(92) = 0.78$, $p = .662$), age ($t(92) = 0.26$, $p = .697$), BMI ($t(92) = 2.78$, $p = .822$), heavy alcohol use ($t(92) = 0.19$, $p = .291$), or lifetime trauma ($t(92) = 1.16$, $p = .950$). The difference between these groups on income approached significance ($t(92) = 2.56$, $p = .067$).

3.2. Associations between CTRA gene expression and study measures

Preliminary models examined the association between CTRA gene expression and study measures. After controlling for demographic characteristics (age, gender), health-related behavior (smoking, heavy alcohol use, BMI), and trauma-related variables (mechanism of injury, lifetime trauma), there was no association between change in PCL-5 total scores and CTRA gene expression, F(1, 7495) = 1.19, $p = .275$; b = -0.001, standard error (SE) = 0.001). In addition, income was not associated with CTRA gene expression, F(1, 87) = 0.09, $p = .759$; b = 0.004, SE = 0.013).

Table 1
Sample Characteristics ($N = 94$).

Variable	*Mean (Standard Deviation) or % (n)*	*Range*
Gender	59.6 % Women ($n = 56$)	
Age (years old)	35.41 (10.97)	19.30–60.30
Mechanism of Injury	86.2 % ($n = 81$) *n*on-assaultive 13.8 % ($n = 13$) assaultive	
Income		
$0–9,999	26.6 % (25)	
$10,000–19,999	18.1 % (17)	
$20,000–29,999	16.0 % (15)	
$30,000–39,999	7.4 % (7)	
$40,000–49,999	11.7 % (11)	
$50,000–59,999	5.3 % (5)	
$60,000–69,999	6.4 % (6)	
$70,000–79,999	<5%	
$80,000–89,999	<5%	
$90,000–99,999	<5%	
$100,000+	<5%	
missing	<5%	
Smoking	36.2 % Smoker ($n = 34$)	
Alcohol Use	2.72 (3.52)	0.00–19.00
Body Mass Index (BMI)	32.10 (8.03)	15.10–52.56
Racial Discrimination (PEDQ)	1.87 (0.78)	1.00–4.76
2-Week PTSD Symptoms (PCL-5)	25.93 (18.54)	0.00–80.0
6-Month PTSD Symptoms (PCL-5) [+]	18.93 (19.00)	0.00–76.00
Lifetime Trauma (LEC-5)	29.10 (17.34)	0.00–85.00

Note: [+] 14 participants were missing 6-month assessments. *Abbreviations:* **PEDQ:** Perceived Ethnic Discrimination Questionnaire; **PCL-5:** PTSD Checklist for DSM-5; **LEC-5:** Life Events Checklist for DSM-5 (weighted score).

3.3. Racial discrimination and CTRA gene expression

Primary analyses quantified the association between lifetime racial discrimination and average expression of 45 CTRA indicator gene transcripts at T1 and T2 while controlling for demographic characteristics (age, gender), health-related behavior (smoking, heavy alcohol use, BMI), and trauma-related variables (mechanism of injury, lifetime trauma). Mixed effect linear models (Table 3**)** identified a significant interaction between racial discrimination and time point (F(1, 7541) = 12.99, $p < .001$), with a regression coefficient indicating greater increase in CTRA gene expression from 2 weeks to 6 months post-injury in those with higher levels of experienced discrimination (b = -0.081 log2 CTRA RNA abundance per SD discrimination, SE = 0.023, p <.001; Fig. 1). Similar effects emerged in sensitivity analyses (see supplemental analyses) that additionally controlled for income and change in PTSD symptoms (racial discrimination x time interaction: F(1, 7039) = 11.44, $p = .001$; b = -0.08, SE = 0.02) or for the relative abundance of major leukocyte subsets (as indicated by mRNA abundances for genes encoding leukocyte subset markers CD3, CD4, CD8, CD19, CD16, CD56, and CD14; racial discrimination x time interaction: F(1, 7534) = 7.78, $p = .005$; b = -0.06, SE = 0.02).

4. Discussion

The current study demonstrates a significant, prospective relationship between CTRA gene expression and racial discrimination among a sample of Black trauma survivors. Specifically, greater lifetime exposure to racial discrimination was associated with increasing CTRA gene expression from two-weeks to six-months post-injury after accounting for demographic factors, health behaviors, and MOI. These findings

Table 2
Correlations between study measures.

Variables	T1 PCL-5	T2 PCL-5^{+}	PEDQ	Age	AUDIT-10	BMI	LEC-5	Income
T1 PCL-5	–							
T2 PCL-5	**0.55*****	–						
PEDQ	**0.47*****	0.12	–					
Age	-0.01	0.01	0.05	–				
AUDIT-10	0.02	-0.17	0.06	-0.13	–			
BMI	-0.01	-0.20	0.02	**0.27****	-0.06	–		
LEC-5	**0.37*****	0.08	**0.37*****	**0.24***	<0.01	**0.27****	–	
Income	−0.8	-0.19	-0.13	0.06	-0.14	-0.06	0.03	–

Abbreviations: **PCL-5**: PTSD Symptom Checklist for DSM-5; **PEDQ:** Perceived ethnic discrimination questionnaire; **AUDIT-10:** Alcohol Use Disorders Identification Test; **BMI:** Body Mass Index; **LEC-5:** Lifetime Trauma Checklist for DSM-5 (weighted score); *Note:* Pearson's correlation coefficients are provided. $^{+}$ T1 PTSD $N = 94$ and correlations with T2 PTSD $n = 80$; *** $p < .001$; ** $p < .01$; * $p < .05$.

Table 3
Mixed effect linear model results examining interaction between time and racial discrimination.

Variable	Coefficient	Standard Error	Degrees of Freedom	*t*-statistic	*p*-value
Age	0.00	0.00	85	−0.17	0.864
Gender	**−0.20**	**0.06**	**85**	**−3.27**	**0.002****
LEC-5	0.00	0.00	85	1.45	0.150
Smoking Status	0.06	0.07	85	0.86	0.394
AUDIT-10	0.01	0.01	85	0.68	0.500
BMI	0.00	0.00	85	−0.05	0.961
Mechanism of Injury	−0.07	0.09	85	−0.86	0.390
Racial Discrimination	0.04	0.03	85	1.17	0.246
Time	−0.01	0.02	72	−0.34	0.735
Racial Discrimination*Time^{+}	**−0.08**	**0.02**	**7541**	**−3.60**	**<0.001*****

Note: $^{+}$ Interaction term reflects Time 1 - Time 2; *Abbreviations:* **AUDIT-10:** Alcohol Use Disorders Identification Test; **BMI:** Body Mass Index; **LEC-5:** Lifetime Trauma Checklist for DSM-5 (weighted score); *Note:* intercept variables for each gene are not reported because the mean expression level of each gene is constrained to 0 by standardization; *** $p < .001$; ** $p < .05$.

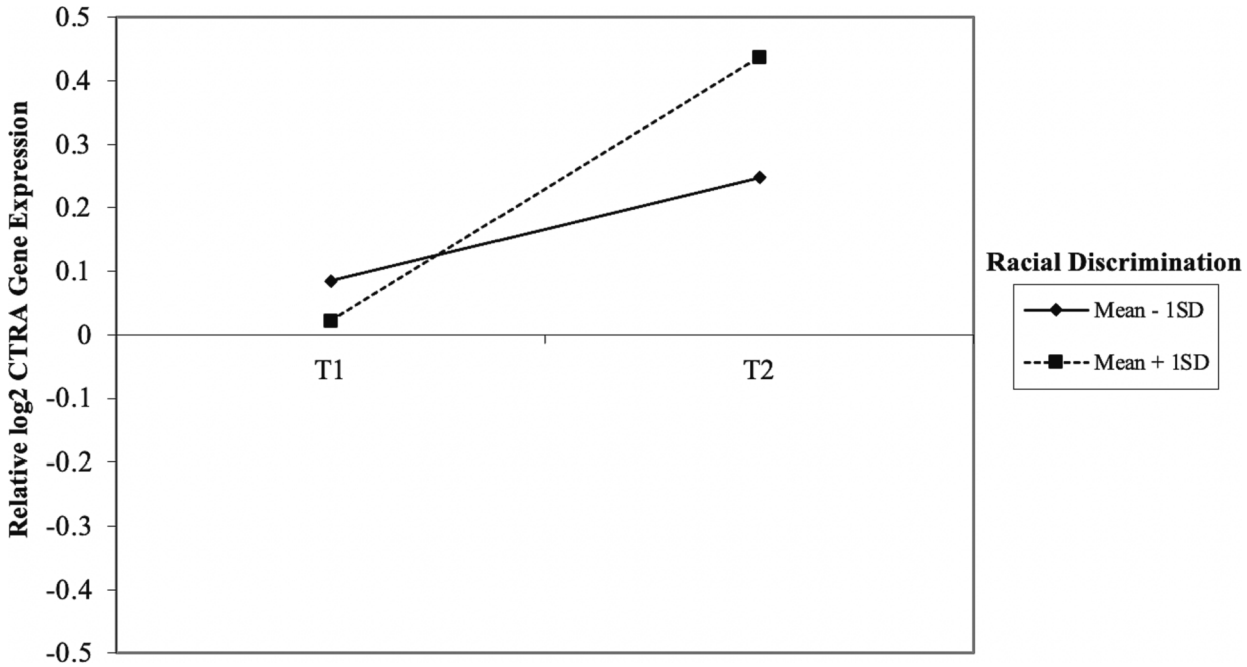

Fig. 1. The moderating effect of racial discrimination on the association between time post-injury and CTRA gene expression. For illustrative purposes, lower experiences of racial discrimination (-1 standard deviation below the mean) and higher experiences of racial discrimination (+1 standard deviation above the mean) are depicted.

highlight and reinforce previous research demonstrating the inimical effects of racial discrimination on biological systems. In the context of a traumatic injury, those who experienced higher levels of previous racial discrimination showed increasing CTRA gene expression over time, whereas CTRA gene expression, while trending upward, did not show significant increase in the aftermath of injury for those who experienced lower levels of racial discrimination. These findings extend the limited previous research connecting racial discrimination to CTRA gene expression and greater inflammatory signaling (Brown et al., 2019; Brown et al., 2020; Thames et al., 2019), being the first to demonstrate

this association among a sample of recently trauma exposed Black adults.

Notably, the current study is also the first to establish a relationship between racial discrimination and CTRA gene expression in a prospective, longitudinal design. Very limited research has demonstrated the association between inflammation and racial discrimination; however, these studies have all been cross-sectional in nature (Brown et al., 2019; Brown et al., 2020; Thames et al., 2019). Current findings highlight the deleterious effects of racial discrimination in the context of acute injury, such that only those who reported a history of high racial discrimination were found to have higher CTRA expression six months post-injury, while this pattern did not hold for those reporting lower racial discrimination. This prospective design also allows the separation of increased inflammation due to the body responding to traumatic injury, which may be expected in the aftermath of physical trauma. Instead, racial discrimination perpetuates the upregulation of CTRA six-months later in a way that does not occur for those who have not experienced high levels of racial discrimination. These differential findings highlight the greater risk for health inequity among Black individuals, who report one of the highest rates of racial discrimination in the United States (Lee et al., 2019). This also advances understanding of the impact of racial discrimination on not only psychological consequences, which are well documented throughout the literature (Carter et al., 2017; Priest and Williams, 2017), but on how racial discrimination impacts biological functioning on a cellular level.

Black Americans are at risk for poorer outcomes following traumatic injury (Meneses et al., 2021; Russo et al., 2013; Suneja et al., 2022). The current study highlights a pathway through which this risk may be conferred. The weathering hypothesis is supported by study results such that racial discrimination appears to serve as a chronic stressor that, over time, breaks down the stress response system, contributing to the wear and tear of biological processes and results in greater inflammation (Forde et al., 2019; Geronimus, 1992). Current findings provide unique support for this due to the examination of CTRA expression over six-months and highlight the impact of chronic stress over time. These results are in line with previous research linking environmental stressors to increased CTRA expression (Cole, 2014; Lee et al., 2021) and further our understanding of the impact of individual level stressors on this gene profile. Current study findings are also in line with previous work demonstrating the link between racial discrimination and sustained biological burden, including epigenetic aging and HPA-axis functioning (Goosby et al., 2018; Lim et al., 2022). While more research is needed, these findings are foundational in understanding biologically embedded vulnerability perpetuating health inequity.

Due to the inflammatory nature of CTRA gene, upregulated expression of this gene profile increases risk of disease and dysregulation within the body (Cole, 2019). Previous research has offered evidence of this linking increased pro-inflammatory genes and decreased antiviral cell activity to multiple chronic diseases, including, diabetes, kidney disease, cancer and cancer reoccurrence, emphysema, bronchitis, and heart disease, among others (Knight et al., 2016; Knight et al., 2019; Simons et al., 2017). Given the results of the current study linking lifetime racial discrimination with increased CTRA gene expression, it is plausible that these shifts in CTRA expression could link racial discrimination and negative health outcomes, furthering our understanding of the pervasive health disparities among racially minoritized groups.

These findings demonstrate the potential depth of damage and consequence of racial discrimination on the body and health, yet it is imperative to recognize the impact and caution against the possibly harmful narrative these findings may perpetuate for marginalized communities. Therefore, it is critical to note that previous research has also shown the malleability of CTRA gene expression in the context of trauma and chronic stress, such that, individuals who employ methods of resilience (Kohrt et al., 2016), use of propranolol (Knight et al., 2020), identify meaning in life (Lee et al., 2020), engage in pro-social behavior (Nelson-Coffey et al., 2017; Regan et al., 2022; Seeman et al., 2020), and practice mindfulness meditation (West et al., 2022) showed reduced inflammatory markers. While the ultimate goal is to eradicate racial discrimination and the detrimental effects it has on health, these studies suggest a potential role for clinical intervention in reducing the gene regulatory impact of racial discrimination, particularly in the aftermath of traumatic injuries that may additionally sensitize immune system gene regulation.

There are several limitations to the current study that should be noted. The current sample was also somewhat homogenous, with a majority of the participants experiencing a motor vehicle crash. Traumatic injury survivors are an understudied population, making the current sample important in many ways, it may also represent a specific type of experience which could be less generalizable to different traumatic injury populations. In addition to the homogenous trauma type, the majority of participants reported lower income (42 % under $19,999 annual household income) and had low reported levels of exposure to DSM-5 Criterion A stressors. Surprisingly, there were no significant associations between CTRA gene expression and income or lifetime trauma. However, the previous work identifying an association with socioeconomic status had greater variability in income (Knight et al., 2015). Therefore, future work in larger samples of Black trauma survivors should examine the differential impact of income and racial discrimination on CTRA gene expression and PTSD symptoms. Overall, participants reported relatively lower levels of exposure to racial discrimination. As with all retrospective self-report measures, this method is prone to respondent biases (Lalande and Bonanno, 2011). Race concordance between participants and research staff may have also impacted the reporting of racial discrimination. The majority of the study team were female, and all identified as White (Bird et al., 2021). Prior work has indicated that racial and ethnic concordance is an important predictor of study attrition (Mindlis et al., 2020) as well as trust, satisfaction, and rapport with providers (Nazione, Perrault, & Keating, 2019). It is important to also note the strength of the current study's prospective design which revealed the impact of chronic racial discrimination over time following an acute injury, which would be missed in a cross-sectional design.

The current findings are the first to demonstrate the relationship between racial discrimination and CTRA gene expression following a traumatic injury in Black Americans. Further inquiry is needed to better understand the role of chronic stress, such as racial discrimination, on dysregulation of biological systems and gene expressions and how this may impede recovery after injury. As it is conceivable that racial discrimination may be a mechanism through which increased inflammation (e.g., increased CTRA gene expression) contributes to chronic disease among racially marginalized groups, future empirical study is needed to explore this. While continuing to advocate for the eradication of racial discrimination in our society, it is also important to promote effective coping strategies and other interventions through which the detrimental effects of racism may be buffered in order to improve the lives and health of racially marginalized individuals.

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Declaration

Submission declaration and verification: This work has not been published previously and is not under consideration for publication elsewhere.

Ethics approval: All study procedures were approved by the Medical College of Wisconsin Institutional Review Board.

Consent to participate: Informed consent was acquired from all

participants prior to initiation of study procedures, and it was emphasized that participants could withdraw at any time without penalty.

Consent for publication: All authors have provided consent for publication of the manuscript in its current form.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.12.009.

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