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Intersectional vulnerability in the relationship between discrimination and inflammatory gene expression

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ABSTRACT

Addressing social disparities in health and well-being requires understanding how the effects of discrimination become biologically embedded, and how embedding processes might vary across different demographic contexts. Emerging research suggests that a threat-related gene expression response may contribute to social disparities in health. We tested a contextual vulnerability model of discrimination embedding using an empirical intersectionality (interaction discovery) analysis of pro-inflammatory gene expression in a national sample of non-institutionalized, English-speaking adults with RNA biomarker data (n = 543). At the time of data collection, the average age of participants was 55 years (SD = 13.26) and approximately half identified as female (50.46%). Most participants identified as White (~73%) and had some college experience (~60%). Results showed significant variation in the strength of association between daily discrimination and inflammatory gene expression by race and sex ($b = -0.022$; 95% CI:-0.038,-0.005, $p = .009$) with the estimated marginal association larger for racially-minoritized males ($b = 0.007$; 95% CI:-0.003,0.017, $p = .163$), compared to White males ($b = -0.006$; 95% CI:-0.013,0.001, $p = .076$). This study indicates that the link between daily discrimination and inflammatory gene expression may vary by sociodemographic characteristics. To improve initiatives and policies aimed at ameliorating disparities within populations, greater attention is needed to understand how interlocking systems of inequalities contribute to physiological health.

1. Introduction

Over the last few decades, studies have documented discrimination exposure as a social determinant of a wide range of chronic conditions, including major depression, hypertension, cardiovascular disease, diabetes, and kidney disease (Lewis et al., 2015; Paradies et al., 2015; Williams et al., 2019). Growing research has begun to elucidate the relevant biological processes to better understand how discrimination "gets under the skin". Studies suggest that, regardless of racial/ethnic background of the victim, discrimination can increase the risk of disease through multiple biological pathways, including increased inflammatory responses, higher blood pressure reactivity, and reduced endothelial response (Cuevas et al., 2020; Lewis et al., 2015; Wagner et al., 2013, 2015).

Recent advances in social genomics may help further clarify the biological processes by which discrimination increases the risk of disease (Cole, 2013, 2014, 2019). Psychosocial adversities can activate the central nervous system (CNS) circuits responsible for processing safety and threat. CNS threat signaling, in turn, can activate the sympathetic nervous system (SNS), which can modulate gene expression in immune cells via transcription factors, such as the β-adrenergic-responsive transcription factor cAMP response element-binding protein (CREB), the pro-inflammatory transcription factor nuclear factor for kappa light gene rearrangement in B cells (NF-kB), and inhibition of interferon regulatory factors (IRF). These dynamics lead to increased expression of proinflammatory genes and decreased expression of antiviral genes, and, subsequent induction of inflammation and other immunological responses (Finch, 2007; Simons et al., 2017). This pattern—known as conserved transcriptional response to adversity (CTRA)—is associated with increased risk of disease, including viral infection, cardiovascular

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and metabolic disease, and breast cancer (Cole, 2019). Discrimination exposure can operate like any other psychosocial stressor (Lewis et al., 2015; Williams et al., 2019), and, therefore, induce CTRA molecular profile, that is, upregulation of proinflammatory genes and down-regulation of type I interferon and antibody synthesis genes (Brown et al., 2019; K. M. Brown et al., 2020; Li et al., 2020; Thames et al., 2019). Studies have found up-regulated expression of inflammatory genes in those exposed to higher levels of discrimination (Brown et al., 2019; K. M. Brown et al., 2020; Li et al., 2020; Thames et al., 2019). However, these studies have not tested whether different demographic subgroups vary in vulnerability to the biological impact of discrimination.

One major limitation of many studies on discrimination and health is the absence of an intersectionality lens (Beatty Moody et al., 2021; Lewis et al., 2015; Lewis and Van Dyke, 2018). Intersectionality posits that interconnecting systems of different -isms (e.g., racism, sexism, heterosexism, classism) give rise to differing levels and distinct forms of discrimination and social exclusion of marginalized individuals and groups (Crenshaw, 1990). As such, holding intersecting identities contributes to variations in experiences and levels of discrimination. For example, studies find that Black men tend to report more discrimination than Black women (Beatty Moody et al., 2021; Beydoun et al., 2017; Halanych et al., 2011). Other studies find that higher-SES and younger racially-minoritized groups report more discrimination than do their lower-SES and older counterparts, respectively (Cardarelli et al., 2007; Findling et al., 2019; Halanych et al., 2011; National Public Radio (NPR) 2018). Yet, it remains unclear whether certain intersectionally-defined subgroups are more vulnerable to the negative effects discrimination relative to others (Lewis and Van Dyke, 2018) or whether the biological processes that undergird the deleterious health outcomes show intersectional variation. The few studies that have tested the vulnerability hypothesis find that the effects of discrimination on health are more pronounced for women and higher educated racially-minoritized adults compared to men and less educated racially-minoritized counterparts, respectively (Lewis and Van Dyke, 2018; Williams et al., 2019). It has long been theorized that differential vulnerability to discrimination contributes to existing disparities and further research is warranted to better characterize the pathogenic potential of discrimination exposure (Ali et al., 2017; L. L. Brown et al., 2020; Sternthal et al., 2011; Turner and Avison, 2003). Thus, coalescing the intersectionality framework with social genomic analyses has the potential to allow us to better identify those most at-risk from the harmful effects of discrimination.

Elucidating the association between discrimination and gene expression in larger and more representative samples is an important step toward early life prevention and clinical interventions that address pre-disease physiological disparities. However, analyzing the effects of intersectionality is complicated by the curse of dimensionality, or the vast expansion of demographic "interaction cells" that emerge from combinations of even a few basic demographic dimensions. To address the analytic challenges that arise from such massive combinatorial search spaces, we applied multiple stepwise model building approaches to high-dimensional intersection (interaction) sets to empirically define those combinatorial sub-groups that showed most pronounced modification of basal associations between discrimination and pro-inflammatory gene expression. Statistical interaction terms were used as opposed to other methodologies, such as latent class analysis, given the identities in the study are observable and the number of groups are known. The primary analyses focused on the pro-inflammatory subcomponent of the CTRA composite because inflammation is the CTRA component most prominently involved in the cardiovascular disease outcomes that have most often been linked to discrimination in social epidemiological studies (Cole, 2019; Lewis et al., 2015). Using a national sample of mid-life adults, the current study examined the effects of multiple social identities, operationalized using self-reports of demographic factors (gender, race/ethnicity, and education) in modulating the strength of association between perceived discrimination and pro-inflammatory gene expression. We hypothesize that the association between discrimination and pro-inflammatory gene expression differs by demographic characteristics.

2. Method

2.1. Sample

Cross-sectional data were analyzed from the biomarker subsample of the Refresher Cohort in the study of Midlife in the United States (MIDUS; $n = 863$). All data derive from participants living in the United States (US). MIDUS I (1995–1996) is a nationally representative Random Digit Dial sample of noninstitutionalized, English-speaking adults in the US, originally designed to be an interdisciplinary examination of the role of sociodemographic, psychosocial, and behavioral factors for mental and physical health (Brim et al., 2004; Ryff and Krueger, 2018). Respondents were selected from working telephone banks in the US (Brim et al., 2004; Ryff and Krueger, 2018). In 2011–2014, MIDUS investigators recruited a national probability sample of 3577 adults (known as MIDUS Refresher), designed to replenish the original MIDUS 1 cohort and obtain the same assessments as MIDUS 1 (Ryff and Krueger, 2018). A subsample of MIDUS Refresher respondents participated in a comprehensive assessment of biomarkers, which involved 2-day visits to biomedical clinicals (for additional details, see Dienberg Love et al., 2010). Further information regarding participant recruitment, study design, and data collection is reported elsewhere (Ryff and Krueger, 2018). Gene expression composite scores are available for a portion of the biomarker sample ($n = 543$). Sample characteristics are reported in Supplemental Table S1. Participants' ages spanned 25–76 years (mean = 52.00) and approximately half identified as female (50.46%). See Supplemental Table S2 for mean age, standard deviation, and age range of subgroups within sex, race, and education. Most of the sample identified their main racial origins as White (~73%), while ~16% identified as Black, and ~11% identified with another race/ethnicity. The most common levels of educational attainment among participants were a bachelor's degree (~25%), a master's degree (~20%), 1–2 years of college with no degree (~15%), and a high school diploma (~12%). The inclusion criteria for the analysis were complete data of demographic factors, relevant behavioral and physical health indicators, discrimination measures, and gene expression.

2.2. Measures

2.2.1. Demographic, behavioral & physical health factors

Participants reported their age at the time of data collection, as well as biological sex, level of education, and race/ethnicity. Health-risk behavior was measured with self-reports of smoking behavior and alcohol consumption. Participants responded to "Have you ever smoked cigarettes regularly – that is, at least a few cigarettes every day?" (Yes = ~38%, No = ~62%) and "During the past month, how often did you drink any alcoholic beverages, on the average?" (~31% = Never, ~26% = less than one day a week, ~18% = 1–2 days a week). Physical health indicators were body mass index (mean BMI = 27.69, SD = 7.12) and self-reported chronic conditions that participants had been diagnosed with or treated for in the past 12 months. The MIDUS administrative staff created a composite score of the total number of chronic conditions reported by participants (~21% reported no conditions, median = 2). Further details on descriptive statistics for the continuous variables are reported in Supplemental Table S3.

2.2.2. Daily discrimination

The daily perceived discrimination scale is based on nine questions that capture how often participants experience unfair treatment interpersonally (Williams et al., 1997). Participants reported their perception of how often they were 1) treated with less courtesy than other people; 2) treated with less respect than other people; 3) received poorer service

than other people; people acted as if they were 4) not smart, 5) afraid of them, 6) dishonest, 7) not as good as they were; 8) they were called names or insulted; and 9) they were threatened or harassed. Each item was answered on a 4-point scale ("never", "rarely", "sometimes", "often"). The scale was constructed by calculating the sum of the values of each item such that higher scores reflect greater frequency of perceived discrimination. The scale displayed high internal consistency by both classical (Cronbach's $\alpha = 0.94$) and modern ($\omega_t = 0.96$, $\omega_h = 0.87$) psychometric approaches, and has been well-validated in the specific context of MIDUS research (Cuevas and Williams, 2018). Additional descriptive statistics for daily discrimination by subsample groups are reported in Supplemental Table S4.

2.2.3. Gene expression

The data collection and subsequent calculation of gene expression composite scores is explained by Mann et al. (2020) and restated in supplemental materials. *A priori* gene composite scores were calculated because CTRA gene expression involves the increased expression of inflammatory genes and decreased expression of genes involved in interferon responses and antibody production. As a result, composite scores were calculated reflecting the average expression of 19 inflammatory genes (IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS, FOSB, FOSL1, FOSL2, JUN, JUNB, JUND, NFKB1, NFKB2, REL, RELA, & RELB), the average expression of 32 antiviral genes (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, IGJ, IGLL1, & IGLL3), and the difference between the two (i.e., a CTRA composite). The variance and average of RNA expression are heterogenous across different genes. Therefore, to prevent arithmetic means from being predominantly weighted by a small number of genes, expression values were log2 transformed and standardized before calculating mean composite scores. Main analyses focused on average expression of inflammatory genes. Nevertheless, descriptive statistics for composite scores of antiviral genes and CTRA composite are reported in Supplemental Table S3.

2.3. Data analytic procedures

Data were analyzed using R Studio version 1.4.1717–3. After calculating descriptive statistics, a set of ordinary least squares (OLS) regressions were computed to estimate associations between daily discrimination and the inflammatory gene expression composite score, controlling for demographic factors (age, sex, race/ethnicity, and level of education), dummy-coded assay batch plates, and RNA transcripts indicting the relative prevalence of T lymphocytes, B lymphocytes, NK cells, and monocytes. In addition, behavioral and physical health factors (alcohol use, history of smoking, BMI, and number of chronic conditions) were included as covariates. Of the 543 participants with gene expression scores, only 27 (5%) had missing data on the discrimination measure or one of the covariates. Therefore, we conducted complete case analyses.

In these models (reported in Supplemental Table S6), age was mean-centered, and level of education was standardized (M = 0, SD = 1). History of smoking (No = 1, Yes = 1), sex (male = −0.5, female = 0.5), and race (White = 0, racially-minoritized = 1) were included as categorical predictors. Finally, a product term between mean-centered age and effects-coded sex was included to account for the previous finding that age-related differences in gene expression vary as a function of sex (Mann et al., 2020).

Next, OLS regressions were expanded to include product terms between focal study variables to test whether demographic factors moderated the association between daily discrimination and the three scores (i.e., pro-inflammatory gene score, antiviral gene score, and the CTRA composite score). First, a fully saturated model was estimated wherein all possible subsets of the interactions between each of the five variables of interest (discrimination, age, sex, race/ethnicity, and education) were included (i.e., an interaction between all 5 variables, the 5 possible interactions between sets of 4 variables, the 10 possible interactions between sets of 3 variables, and the 10 possible interactions between sets of 2 variables). The same technical and health covariates were included as previously noted, and this model is reported in Supplemental Table S5.

The results of the fully saturated model revealed a number of statistically significant interactions (see Results section). However, to increase model parsimony and avoid numerical complications resulting from high predictor: case ratios, we implemented stepwise regression procedures to minimize the number of predictors of inflammatory gene expression. At each step, variables were chosen based on their change in Akaike information criterion (AIC). Results were compared for three separate stepwise model selection procedures: First, product terms were trimmed using backward elimination of predictors from the fully saturated model; Second, product terms were selected by forward stepwise selection from a null model that included no predictors, with the fully saturated model as the reference; Finally, a bidirectional procedure was utilized, beginning with a "middle" model that included only 2-way interaction terms (but none of the 3, 4, or 5-variable interactions), where variables were sequentially checked for inclusion or elimination based on change in AIC. Forward stepwise model building is known to yield biased results due to power limitations and omitted variable bias (Brown, 2018). However, to exercise multiple selection procedures, we included forward stepwise selection in the analyses.

The distributions of gene expression composite scores approximated normality. To evaluate robustness, sensitivity analyses estimated multiple linear regressions using maximum likelihood with robust standard errors (MLR) using the "lmtest" (Zeileis and Hothorn, 2002) and "sandwich" (Zeileis et al., 2020) packages in R. Across models estimated using OLS and MLR, hypothesis tests remained unchanged, as did the approximate size and precision of estimated associations. The programming syntax in R can be found at Open Science Framework: [link redacted for blind review].

3. Results

Table 1 reports results from three alternative analytic approaches for identifying possible intersectional modifiers of associations between discrimination and inflammatory gene expression: namely model selection by backward elimination, bidirectional elimination, and forward stepwise selection. Supplemental Tables S7 and S8 estimate associations with *antiviral* gene expression and *CTRA* composite scores respectively, but otherwise are specified in the same manner.

Results of moderation analyses indicate that the association between inflammatory gene expression and daily discrimination varied significantly by combinations of race and sex, when using both the bidirectional ($b = -0.022$; 95% CI: −0.038,-0.005, $p = .009$) and backward elimination ($b = -0.022$; 95% CI: -0.040,-0.003, $p = .022$). Controlling for all other variables, the estimated marginal association of inflammatory gene expression with daily discrimination was larger for racially-minoritized males ($b = 0.007$; 95% CI:-0.003, 0.017, $p = .163$), compared to White males ($b = -0.006$; 95% CI: −0.013, 0.001, $p = .076$), displayed in Fig. 1. While this interaction was not included as a predictor in the most conservative forward stepwise selection model, the interaction remained statistically significant and unchanged in terms of effect size in the sensitivity analyses estimated using MLR ($b = -0.022$; 95% CI:-0.040, −0.004, $ps = 0.011$, 0.019). Thus, this interaction effect was observed across ¾ of the models that were tested.

The association between inflammatory gene expression and daily discrimination was also moderated by age and sex in the bidirectional elimination model ($b = -0.0007$; 95% CI: -0.0013, −0.0001, $p = .019$). Controlling for all other variables, the estimated marginal association of inflammatory gene expression with daily discrimination was larger for younger (−1 SD in age) ($b = 0.004$; 95% CI: -0.004, 0.011, $p = .318$), compared to older (+1 SD) females ($b = -0.015$; 95% CI: -0.025,

Table 1
Multiple linear regressions of inflammatory gene composite score on daily discrimination, technical covariates, demographic factors (including interactions), and indicators of behavioral and physical health estimated using ordinary least squares and 3 stepwise selection approaches.

	Inflammatory Composite (Backward Elimination)			Inflammatory Composite (Bidirectional Elimination)			Inflammatory Composite (Forward Selection)		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
Technical Covariates									
Batch Plate 2	**−0.195**	**0.076**	**0.010**	**−0.200**	**0.075**	**0.008**	**−0.198**	**0.076**	**0.009**
Batch Plate 3	**−0.144**	**0.040**	**< 0.001**	**−0.147**	**0.039**	**< 0.001**	**−0.144**	**0.040**	**< 0.001**
Batch Plate 4	**−0.148**	**0.039**	**< 0.001**	**−0.141**	**0.038**	**< 0.001**	**−0.127**	**0.039**	**0.001**
Batch Plate 5	0.034	0.040	0.398	0.035	0.040	0.375	0.034	0.040	0.398
Batch Plate 6	**−0.085**	**0.043**	**0.048***	−0.081	0.042	0.054	−0.062	0.041	0.134
Batch Plate 7	−0.074	0.043	0.083	−0.074	0.042	0.079	−0.062	0.040	0.122
Batch Plate 8	**0.242**	**0.042**	**< 0.001**	**0.244**	**0.041**	**< 0.001**	**0.252**	**0.039**	**< 0.001**
CD3D	0.023	0.015	0.127	0.024	0.015	0.101	0.027	0.015	0.078
CD4	**0.061**	**0.020**	**0.002**	**0.055**	**0.020**	**0.005**	**0.056**	**0.020**	**0.005**
CD8A	**0.029**	**0.012**	**0.013**	**0.028**	**0.011**	**0.015**	0.020	0.011	0.074
CD14	**0.167**	**0.014**	**<0.001**	**0.167**	**0.013**	**< 0.001**	**0.169**	**0.013**	**< 0.001**
CD19	–	–	–	–	–	–	0.016	0.009	0.080
FCGR3A	**0.021**	**0.010**	**0.038***	**0.023**	**0.010**	**0.020**	**0.030**	**0.010**	**0.003**
Demographic Variables									
Age	0.006	0.003	0.061	**0.006**	**0.002**	**0.006**	–	–	–
Sex (Female)	−0.048	0.073	0.514	−0.048	0.069	0.487	–	–	–
Race (Racially-minoritized)	0.048	0.072	0.508	−0.010	0.063	0.871	–	–	–
Level of Education	−0.009	0.038	0.805	−0.002	0.010	0.867	–	–	–
Daily Discrimination	−0.004	0.003	0.144	−0.005	0.003	0.062	−0.003	0.002	0.131
Age x Sex	**0.012**	**0.006**	**0.047**	**0.013**	**0.004**	**0.002**	–	–	–
Age x Racially-minoritized	0.001	0.005	0.830	–	–	–	–	–	–
Age x Education	0.000	0.003	0.915	**0.0018**	**0.0008**	**0.018**	–	–	–
Age x Discrimination	−0.0003	0.0002	0.153	**−0.0004**	**0.0002**	**0.023**	–	–	–
Sex x Racially-minoritized	**0.317**	**0.144**	**0.029**	**0.311**	**0.126**	**0.014**	–	–	–
Sex x Education	0.058	0.077	0.449	–	–	–	–	–	–
Sex x Discrimination	0.003	0.005	0.639	0.003	0.005	0.576	–	–	–
Racially-minoritized x Education	−0.014	0.096	0.882	–	–	–	–	–	–
Racially-minoritized x Discrimination	−0.001	0.005	0.779	0.003	0.004	0.534	–	–	–
Education x Discrimination	0.001	0.003	0.722	–	–	–	–	–	–
Age x Sex x Racially-minoritized	0.008	0.011	0.425	–	–	–	–	–	–
Age x Sex x Education	−0.005	0.007	0.406	–	–	–	–	–	–
Age x Sex x Discrimination	−0.0007	0.0005	0.158	**−.0007**	**.0003**	**0.019**	–	–	–
Age x Racially-minoritized x Education	−0.004	0.006	0.480	–	–	–	–	–	–
Age x Racially-minoritized x Discrimination	−0.0000	0.0003	0.987	–	–	–	–	–	–
Age x Education x Discrimination	0.0000	0.0002	0.787	–	–	–	–	–	–
Sex x Racially-minoritized x Education	0.020	0.192	0.917	–	–	–	–	–	–
Sex x Racially-minoritized x Discrimination	**−0.022**	**0.009**	**0.022**	**−0.022**	**0.008**	**0.009**	–	–	–
Sex x Education x Discrimination	−0.004	0.006	0.496	–	–	–	–	–	–
Racially-minoritized x Education x Discrimination	0.002	0.007	0.821	–	–	–	–	–	–
Age x Sex x Racially-minoritized x Education	0.014	0.013	0.261	–	–	–	–	–	–
Age x Sex x Racially-minoritized x Discrimination	−0.001	0.001	0.407	–	–	–	–	–	–
Age x Sex x Education x Discrimination	0.0003	0.0005	0.513	–	–	–	–	–	–
Age x Racially-minoritized x Education x Discrimination	0.0005	0.0004	0.237	–	–	–	–	–	–
Sex x Racially-minoritized x Education x Discrimination	−0.005	0.014	0.734	–	–	–	–	–	–
Age x Sex x Racially-minoritized x Education x Discrimination	−0.002	0.001	0.081	–	–	–	–	–	–
Health Indicators									
Alcohol Consumption	−0.013	0.007	0.063	−0.013	0.007	0.056	–	–	–

Notes. *b* = unstandardized multiple regression coefficient. *SE* = standard error. *p* = *p*-value for multiple regression coefficient. Statistically significant ($p < .05$) effects are printed in bold font. Predictors are chosen by backward elimination (left), bidirectional elimination (middle), and forward selection (right).
– indicates that predictor was not selected for model. Some predictors (e.g. history of smoking) are absent from all 3 models and, thus, not reported.
*Effect was significant ($p < .05$) in this OLS model, but not MLR robust standard error model.

−0.006, $p = .002$), but did not vary across older ($b = -0.003$; 95% CI: -0.01, 0.006, $p = .440$) and younger ($b = -0.003$; 95% CI: -0.010, 0.004, $p = .543$) males. This predictor fell short of traditional significance thresholds in the more saturated backward elimination model ($b = -0.0007$; 95% CI: -0.0016, 0.0003, $p = .158$), and was not included in the most conservative forward stepwise selection model, but remained statistically significant in sensitivity analyses estimated using MLR ($b = -0.0007$; 95% CI: -0.0014, −0.00004, $p = .038$).

Several additional interaction terms were retained in the backward and bidirectional elimination models. However, no other three- or four-way interactions were statistically significant (*p*s > .05), and only one additional two-way interaction term was significant that was not subsumed under one of the previously analyzed three-way interactions (e.g., we did not interpret the *sex by racially-minoritized* interaction because *sex by racially-minoritized by discrimination* was already analyzed). That *age by education* interaction emerged only from the bidirectional elimination model predicting inflammatory gene expression ($b = 0.0018$; 95% CI:0.0003, 0.0033, $p = .018$), such that the estimated marginal association of expression with age was greater for more highly educated (+1 SD) ($b = 0.0032$; 95% CI:0.0008, 0.0057, $p = .009$), compared to less highly educated (−1 SD) individuals ($b = -0.0004$; 95% CI:0-0.0027, 0.0019, $p = .747$). However, this predictor was not statistically significant in the more saturated backward elimination model ($b = 0.0004$, $p = .915$), was not included in the most conservative forward stepwise selection models, but remained significant in sensitivity analyses estimated using MLR ($b = 0.0018$; 95% CI: 0.0002, 0.0035, $p = .031$).

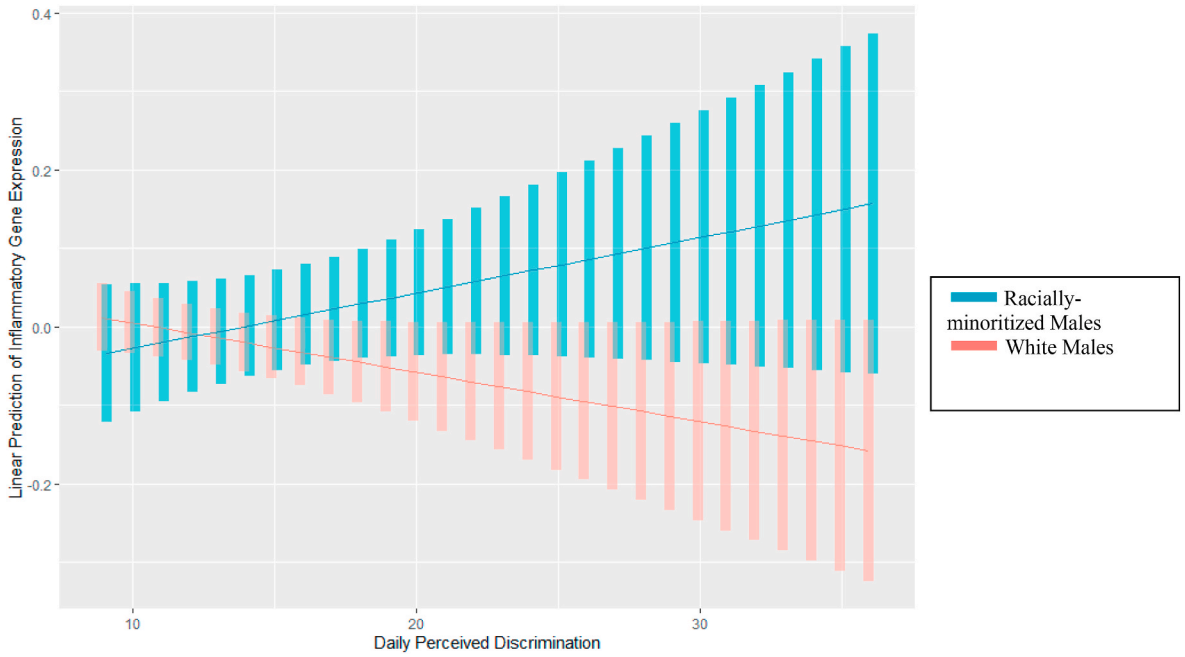

Fig. 1. Prediction of Inflammatory Gene Expression by Discrimination x Racially-minoritized x Sex.
Note. The slopes derive from the ordinary least squares regression predicting the inflammatory gene expression composite score, choosing predictors using bidirectional elimination. Error bars derive from 95% confidence intervals.

4. Discussion

The present study used a large sample of adults to test whether the association between discrimination and activities of key pro-inflammatory and antiviral genes varied across multiple intersecting social identities (i.e., race, sex, education, and age). Results indicate that the association between daily discrimination and elevated inflammatory signaling activity was stronger for racially-minoritized men compared to White men. There was no evidence that daily discrimination was associated with pro-inflammatory gene expression in other subgroups. There was also no evidence that daily discrimination was associated with antiviral gene expression in general, nor did that association differ significantly across subgroups.

Previous studies have found associations between different psychosocial stressors (e.g., social isolation, bereavement childhood adversity) and CTRA gene expression (Cole et al., 2015a; Levine et al., 2015; Miller et al., 2014). These patterns of pro-inflammatory/antiviral transcriptome activation have also been observed in animals who have been experimentally exposed to a variety of social adversities, such as social defeat and lower social status (Powell et al., 2013; Snyder-Mackler et al., 2016). These experiences of threat and uncertainty (whether real or imagined) induce a pro-inflammatory/anti-antiviral gene expression response to immune challenge. Discrimination may operate like these stressors, in that it can induce negative emotional reactions and activate physiological systems associated with stress regulation to activate inflammatory genes. Two recent studies support this hypothesis, finding that higher levels of discrimination are associated with up-regulated expression of inflammatory genes (Li et al., 2020; Thames et al., 2019). Building from these studies and using an intersectional vulnerability approach, we find that the relationship between discrimination and pro-inflammatory gene expression is contingent on social identities. The effects of discrimination may be stronger for racially-minoritized men compared to White men, racially-minoritized women, and White women. Activation of the SNS due to the perceptions of social threat contributes to elevated inflammatory signaling activity (Cole, 2013). However, psychosocial resources (e.g., social support, coping strategies) can help mitigate the impact of social threats, and, thus, lower the expression of pro-inflammatory genes (Cole et al., 2015b; Jutagir et al., 2017). Racially-minoritized males, particularly Black and Latino males, are less likely to receive social support and more likely to engage in coping strategies (e.g., avoidance, smoking) that may exacerbate the effects of discrimination on health (Brittian et al., 2013; Horton and Loukas, 2013; Hudson et al., 2016; Mincey et al., 2015). Results of the current study suggest that the unpredictable nature of discrimination and the lack of health-promoting resources may place racially-minoritized men at risk for early inflammatory dysfunction. Further research is warranted to identify the psychosocial resources that moderate the relationship between discrimination and gene expression for racially-minoritized men.

The limitations of this study should be considered when interpreting these findings. Due to the cross-sectional design of the study, the causal direction of the associations between discrimination and gene expression cannot be determined. The Everyday Discrimination scale tries to capture the chronicity of minor forms of mistreatment (Williams et al., 1997). Discrimination is multidimensional and can function as neighborhood level discrimination, encompassing factors such as restricted educational and economic opportunities, poor access to health promoting resources (e.g., healthcare, parks and open spaces, nutritious healthy food options), disproportionate exposure to crime, police, and criminal injustice, and poor air and water quality (Bailey et al., 2017, 2021; Krieger, 2020; Williams et al., 2019; Williams and Mohammed, 2009). Given its ubiquitous nature and potential to affect individuals at sensitive periods in the life course, neighborhood-level discrimination may contribute to CTRA gene expression, above and beyond interpersonal forms of discrimination.

Our study focused on four major identities—race, sex, age, and education. However, other identities (e.g., sexual orientation) may interact with race, sex, age, and education that, in turn, play a role in the level and susceptibility to discrimination exposure and inflammatory gene expression. Future research should leverage datasets with larger samples to examine the role that other intersecting identities play in discrimination experiences and CTRA gene expression. Last, the inclusion criteria for our study were participants with complete data. Complete-case analyses can lead to biased results as participants with complete

data may not be representative of the whole study sample or population. There may be differences in discrimination exposure, gene expression levels, and demographic characteristics between those included and those excluded due to missing data. Further, complete-case analyses can lead to loss of power (due to the reduced sample size) and decreased precision of estimated effects (Karahalios et al., 2012). In leveraging samples with larger datasets, investigators should consider different methods for handling missing data (e.g., multiple imputation, full information maximum likelihood).

As noted by elsewhere (Smith, 2018), the use of forward selection, backward elimination, and stepwise regression procedures may be considered a limitation of the current study, as variables with true causal effects will not necessarily or always decrease information criteria in a given sample, while "nuisance" variables may lower information criteria coincidentally by capitalizing on sampling variability. However, the current study utilized these automated regression procedures as a form of sensitivity analysis to determine whether interaction effects remained robust in more parsimonious models that considered the impact of moderation effects on information criteria, in addition to a sensitivity analysis that estimated standard errors that are robust to deviations from normality. Importantly, if the interaction of discrimination x racially-minoritized in males had not decreased information criteria, then this would have dampened our confidence in the interaction reported in Fig. 1. However, the prediction of inflammatory gene expression in males by the interaction of discrimination x racially-minoritized remained unchanged in terms of the size, precision, and statistical significance of the effect in both the fully saturated model with and without robust standard errors, and was included in 2/3 automated regression procedures, which increases our confidence in the reported results.

Studying how multiple identities interact does not imply the need to use a multiplicative statistical interaction approach (Bauer, 2014; Hancock, 2007). Intersectionality theory suggests that interlocking systems of oppression will produce distinct experiences of marginalization, exclusion, and discrimination for individuals and groups of certain identities. For instance, the discriminatory experiences of Black women with a secondary education are distinct from the discriminatory experiences of Black men with lower educational attainment. The manner in which multiple social identities experience a limited set of discriminatory events does not capture how different forms of inequalities shape population health outcomes (Agénor, 2020). Moreover, a single measure of discrimination does not capture the full experience nor the totality of the actual drivers of inequalities that are unique to members of different social identities. Future research should consider alternative methods and measures to identify and understand the root causes and mediating mechanisms of health inequities for specific group members. Such efforts will help refine initiatives and policies aimed at addressing disparities within populations.

The present findings highlight one potential biological pathway through which discrimination "gets under the skin", particularly for racially-minoritized men. Pro-inflammatory genes contribute to multiple chronic diseases including cardiovascular, neurodegenerative, and neoplastic diseases that show well established social disparities, underscoring the need to develop lifestyle behavioral or pharmacologic interventions to reduce CTRA (Li et al., 2020). It is important to note, however, CTRA is just one pathway through which discrimination affects health. For other groups, particularly historically marginalized group members, discrimination may increase the risk of disease through other biobehavioral pathways. Therefore, alleviating the impact of discrimination at the policy and institutional level has broad potential to improve health at the population-level.

As the impact of public policy or institutional change was not assessed in the present study, results have no clear implications for policy recommendations or intervention strategies. In other words, findings are descriptive, not prescriptive. Nevertheless, community redevelopment that provides high quality early childhood care, and education programs, facilities, and services that buttress health and increase goods and resources (e.g., employment opportunities) not only has the potential to improve health across generations, but also dismantle a system that reinforces discriminatory beliefs and values (Bailey et al., 2017). These approaches can also help shift the burden of responsibility away from victims of discrimination and more on systems and actors that perpetuate systems of inequality. Therefore, in addition to focusing on experiences of daily discrimination, future work should also draw attention to the social structures and policies that have bolstered interpersonal discrimination and implement policy changes to redress their effects on health.

Declaration of competing interest

The authors have no conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100580.

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