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How Community Connection, Homophobia, and Racism Shape Gene Expression in Sexual Minority Men With and Without HIV

Jenna Alley[1], Jeffrey Gassen[1], Luis A. Parra[2], Michele D. Kipke[3, 4], Jeremy T. Goldbach[5], Steven W. Cole[1], and George M. Slavich[1]

[1] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles
[2] School of Nursing, University of Michigan
[3] Children's Hospital Los Angeles, Los Angeles, California, United States
[4] Keck School of Medicine, University of Southern California
[5] George Warren Brown School of Social Work, Washington University in Saint Louis

Objective: Although sexual minority men experience substantial discrimination, in addition to increased risk for several serious mental and somatic health problems, the biological mechanisms underlying these effects are unclear. To address this issue, we examined how experiences of social safety (i.e., community connection) and social threat (i.e., discrimination, in the forms of homophobia and racism) were related to conserved transcriptional response to adversity (CTRA) gene expression profiles across time, and whether these associations differed across HIV status, in a well-characterized, racially diverse sample of sexual minority men ($M_{age} = 22.61$, $SD = 1.90$). ***Method:*** Experiences of community connection, homophobia, and racism were assessed via self-report, and blood samples were obtained at three timepoints over approximately 2 years. We then used these blood samples to characterize participants' CTRA gene expression, which we quantified using an a priori 53-transcript composite score derived from RNA sequencing data from peripheral blood leukocytes. ***Results:*** As hypothesized, greater community connection was significantly related to decreased CTRA gene expression across time. These effects were similar regardless of HIV status and were robust to statistical adjustment for several potential confounding factors. In contrast, neither homophobia nor racism were related to CTRA gene expression. ***Conclusion:*** These results suggest that community connection may be a protective factor that reduces biological processes known to negatively impact health. Consequently, interventions and policies aimed at reducing health disparities in marginalized populations may benefit from increasing community connection and inclusion.

Public Significance Statement
This research identifies how experiences of social safety and threat impact health-relevant biological processes in a population known to have high health risks—namely, sexual minority men with and without HIV. We found that greater community connection was related to a gene expression pattern characterized by decreased expression of genes involved in inflammation and increased expression of genes involved in the antiviral response; in contrast, neither homophobia nor racism were related to this biological response. Interventions, policies, and programs aiming to promote health and well-being may thus benefit from enhancing individuals' sense of connection, inclusion, and belonging in the various communities to which they belong.

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George M. Slavich https://orcid.org/0000-0001-5710-3818

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Correspondence concerning this article should be addressed to Jenna Alley, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Room C8-176A, 760 Westwood Plaza, Los Angeles, CA 90095-7076, United States. Email: jalley@mednet.ucla.edu

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In the United States, sexual minority men (SMM) face significant mental and physical health disparities compared to their heterosexual counterparts. Indeed, there is a large body of research showing that compared to heterosexual men, SMM experience higher rates of psychological distress (Gonzales & Henning-Smith, 2017; Layland et al., 2020; Operario et al., 2015; Wallace et al., 2011) and several chronic disease conditions (Lick et al., 2013), such as diabetes and hypertension (Wallace et al., 2011). SMM also tend to engage in more risky behaviors, including substance use, which can have negative health and behavioral impacts over the long term (Operario et al., 2015).

One framework for understanding these effects is minority stress theory, which posits that minority stressors such as discrimination, victimization, isolation, and rejection negatively affect both mental and physical health over the life course (Hatzenbuehler & Pachankis, 2016; Meyer, 2003). Many studies have supported this model, showing, for example, that instances of minority stress in the form of interpersonal discrimination, disclosure of identity, homophobic victimization, social rejection, and loneliness are strongly related to mental and physical health in SMM (Burgess et al., 2007; DiGuiseppi et al., 2022; Hatzenbuehler et al., 2013; Hoy-Ellis & Fredriksen-Goldsen, 2016; S. E. Jackson et al., 2019; Lee et al., 2016; Lick et al., 2013; Operario et al., 2015; Saxby et al., 2022; Tsomokos & Slavich, 2024; Vargas et al., 2020). Conversely, research has also shown that certain protective factors, such as community connection and belonging, can have positive health effects (Slavich et al., 2022). More specifically, gay community connectedness and social support have been related to better mental health of SMM regardless of minority stress exposure (Boyd et al., 2021; Brennan-Ing et al., 2022; Lyons, 2016; Lyons et al., 2013). Research has also found that community connection may moderate the negative impact of minority stress on health and well-being (Salfas et al., 2019).

Biological Processes Linking Social Adversity and Health

Although the biological processes linking minority stress and health remain unclear (Flentje et al., 2020), theoretical work has posited that adverse social experiences increase disease risk in part by upregulating components of the immune system involved in inflammation (Slavich, 2020, 2022; Slavich, Roos, et al., 2023). In essence, the evolved purpose of the immune system is to keep the body safe from harm, and it accomplishes this task in part by upregulating inflammatory activity in response to bodily injury and infection (Slavich & Irwin, 2014). This inflammatory response is mediated by proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α). An acute inflammatory response is adaptive because it promotes healing (Slavich, 2015). However, systemic inflammation that is sustained over time can increase individuals' long-term susceptibility to both viral infections and inflammation-related diseases, reduce the effectiveness of vaccines, and directly damage tissues and organs throughout the body via oxidative stress (Furman et al., 2019). These processes have, in turn, been shown to promote risk for a variety of diseases, including Type 2 diabetes, cardiovascular diseases, asthma, arthritis, and certain cancers, as well as all-cause mortality (Couzin-Frankel, 2010; Furman et al., 2019).

Systemic inflammation is influenced by multiple biological and environmental factors, but one of its most notable triggers is social threats such as social devaluation, denigration, isolation, rejection, and exclusion (Chiang et al., 2019; Denson et al., 2009; Dickerson et al., 2009; Kiecolt-Glaser et al., 2010; Slavich & Irwin, 2014; Slavich et al., 2010). Studies have also found that experimentally eliciting states such as shame and threat (e.g., in the context of social evaluation and judgment) upregulates inflammatory activity (Carroll et al., 2011; Dickerson et al., 2009). Additionally, observational studies have found that experiencing interpersonal conflict, as well as the loss of a close social tie, is related to increases in inflammation over time (Chiang et al., 2019; Marin et al., 2009; Murphy et al., 2013).

Evidence that chronic social threat increases inflammatory activity has also been observed for racially marginalized populations, as well as for sexual and gender-diverse populations, such as SMM (Cuevas et al., 2020; Diamond et al., 2021). For example, Doyle and Molix (2015) showed that experiences of discrimination were associated with higher IL-6 in a sample of predominantly self-disclosed gay men. In a more recent study with a representative sample of over 2,000 adults, self-identified gay, lesbian, and bisexual participants had significantly higher CRP and IL-6 than self-identified heterosexuals, and this effect was partially mediated by self-reported daily and lifetime discrimination (Wardecker et al., 2021).

Human Social Genomics

Recently, scholars working in the growing field of human social genomics (Slavich & Cole, 2013; Slavich, Mengelkoch, & Cole, 2023) have suggested that alterations in gene expression may mediate increases in inflammation following adverse social experiences, such as social isolation (Cole et al., 2007). In brief, this research has found that experiences of social threat such as social isolation, rejection, and discrimination impact health by activating a conserved transcriptional response to adversity (CTRA) in circulating immune cells (Cole, 2019). The CTRA is characterized by increased expression of proinflammatory genes and reduced expression of antiviral genes—a transcriptional profile that is structured, in part, by nuclear factor kappa-B and the β-adrenergic-responsive transcription factor cAMP response element-binding protein. Although the CTRA is adaptive in the short run, chronic activation of the CTRA can increase the risk for both viral infections and inflammation-related disorders (Cole, 2019; Li et al., 2020).

Research on human social genomics over the past decade has provided several examples of how social threat relates to gene expression across a variety of populations. For example, Brown et al. (2019, 2020) found that greater lifetime discrimination was associated with more inflammation-related gene expression across two studies. Furthermore, research has found that the impact of discrimination on gene expression may be particularly high for socially marginalized groups, such as racial and ethnic minorities (Cuevas et al., 2020; Li et al., 2020; Thames et al., 2019). Studies have also revealed associations between daily discrimination and inflammatory gene expression, with marginally significant differences across race (Cuevas et al., 2020). At the same time, other studies have found significant differences across races. Specifically, in a sample of Black and White Americans with and without HIV, Thames et al. (2019) found that relative to White Americans, Black Americans exhibited higher levels of both inflammatory- and stress-related neuroendocrine signaling. Furthermore, these authors concluded that a significant amount of the variability in this elevated inflammatory signaling was due to having experienced racial discrimination. These patterns were robust across races and even while adjusting for HIV status.

Although most research on this topic has focused on racial differences in discrimination and gene expression, there is also a growing body of work examining these processes in sexual minority populations, thus providing the foundational basis for the present study. Specifically, Li et al. (2020) found that as compared to those reporting no victimization, Black and Latino SMM without HIV who experienced homophobic victimization during the past 12 months had significantly greater CTRA gene expression even while controlling for several potential confounding factors—namely, race, body mass index (BMI), and substance use. Consequently, social threat appears to be strongly related to health-relevant gene expression in historically marginalized groups.

In sum, existing research indicates that adverse social experiences such as discrimination may negatively impact health in part by altering inflammatory and antiviral gene expression. Studies have also found strong associations between positive social connection and health in SMM (Brennan-Ing et al., 2022; Lyons, 2016; Lyons et al., 2013). Although there is substantial theoretical support for the potentially positive biological impact of social safety such as inclusion, affirmation, support, and connection for all populations (Slavich, 2020; Slavich, Roos, et al., 2023)—but particularly sexual and gender-diverse individuals (Diamond & Alley, 2022)—research examining positive social connection with negative social experiences and gene expression in a sample of SMM is lacking. Indeed, we are aware of only one study that has examined how positive social interactions relate to gene expression. In this study, the authors found a marginal association between social support and inflammatory gene expression in a racially diverse sample (Brown et al., 2020). Given the distinct lack of research on biological mechanisms underlying the salutogenic effects of positive social experiences on health in SMM populations, additional work on this topic is warranted. Indeed, multiple scholars have called for longitudinal studies investigating how both positive and negative social experiences impact gene expression across time in vulnerable populations (Brown et al., 2019, 2020; Li et al., 2020).

Present Study

To address this critical gap in the literature, we investigated how experiences of social safety (i.e., community connection) and social threat (i.e., discrimination, as indexed by homophobia and racism) related to CTRA gene expression profiles that have been previously implicated in mental and physical health in a well-characterized sample of SMM with and without HIV who were studied longitudinally. More specifically, we examined the extent to which differences in self-reported experiences of community connection, homophobia, and racism predicted changes in gene expression over time, and whether these associations differed for individuals with and without HIV. Consistent with prior theoretical work on social safety theory (Slavich, 2020, 2022; Slavich, Roos, et al., 2023), we hypothesized that community connection, homophobia, and racism would each be related to changes in gene expression over time, with greater experiences of homophobia and racism predicting more CTRA gene expression (i.e., greater inflammatory gene expression, less antiviral gene expression), and greater experiences of community connection predicting less CTRA gene expression (i.e., less inflammatory gene expression, more antiviral gene expression).

Method

Participants

Participants were 250 young adults in the Healthy Young Men's (HYM) cohort study who provided blood samples for gene expression analysis. All participants lived in Los Angeles, California, or surrounding counties; were Black/African American, Hispanic/Latino, or multiracial/ethnic; were assigned male sex at birth; and self-identified as SMM ($M_{age} = 22.61$, $SD = 1.90$). Thirty-three participants (13.2%) in the study had HIV, and the sample characteristics stratified by HIV status are presented in Table 1.

Table 1
Sample Characteristics

Variable	*M* (*SD*) or frequency (%)	
	PWoH ($n = 217$)	PWH ($n = 33$)
Age (years)	22.62 (1.91)	22.55 (1.82)
Race/ethnicity		
Black	46 (21.2%)	8 (24.2%)
Hispanic	128 (59.0%)	17 (51.5%)
Multiracial/ethnic	39 (18.0%)	4 (12.1%)
Missing	4 (1.8%)	4 (12.1%)
Education		
Less than high school	6 (2.8%)	4 (12.1%)
High school/GED	41 (18.9%)	9 (27.3%)
Vocational school	5 (2.3%)	1 (3.0%)
Some college	92 (42.4%)	12 (36.4%)
Complete associate degree	19 (8.8%)	0 (0.0%)
Bachelor's degree	45 (20.7%)	3 (9.1%)
Some graduate school	3 (1.4%)	0 (0.0%)
Completed graduate school	2 (0.9%)	0 (0.0%)
Missing	4 (1.8%)	4 (12.1%)
BMI (kg/m^2)	25.04 (5.18)	23.83 (4.50)
Experiences of homophobia (0–18)	2.27 (2.41)	2.03 (2.76)
Experiences of racism (0–30)	6.32 (5.73)	4.55 (4.23)
Experiences of community connection (1–4)	2.62 (0.51)	2.53 (0.67)

Note. PWoH = people without HIV; PWH = people with HIV; GED = General Educational Development; BMI = body mass index.

Procedure

A complete description of the HYM study and its sampling methods can be found elsewhere (Kipke et al., 2019). In brief, we recruited participants using a venue-based strategy (e.g., lesbian, gay, bisexual, transgender, queer or questioning, or another diverse gender identity community centers, night clubs) and social media, as well as participant and health clinic referrals. Participants completed the survey measures (see below) at the beginning of the study and approximately every 6 months thereafter, starting in June 2016 and ending in July 2019 (for the data included in this article). During this time, a majority of participants also provided blood samples approximately once every 6 months (i.e., six blood samples total), and gene expression profiles were obtained from the samples taken at Study Visits 2, 4, and 6 (i.e., three blood samples/gene expression levels). The average time between the blood samples was thus approximately 1 year or, more precisely, 395.95 days ($SD = 73.87$) from Study Visit 2 (baseline timepoint for the present analysis) to Study Visit 4 (Time 2), and 367.13 days ($SD = 71.34$) from Study Visit 4 (Time 2) to Study Visit 6 (Time 3). The blood draws occurred between 10:56 a.m. and 14:52 p.m. to account for known diurnal patterns in inflammatory activity (Izawa et al., 2013). All participants provided informed consent at study enrollment, and all study procedures were preapproved by the Institutional Review Board at Children's Hospital Los Angeles.

Psychological Measures

Community Connection

At baseline, we assessed participants' experiences of community connection in adulthood using a 10-item scale developed by the HYM research team, in partnership with a community advisory board, to assess feelings of connection to the community at large, as well as to one's specific racial/ethnic group and to others with similar sexual identities (Kipke et al., 2019). Responses were provided on a 4-point scale (1 = *not at all*, 2 = *not very*, 3 = *somewhat*, 4 = *a lot*) to questions asking: "How much do you feel part of …" (a) the community you grew up in; (b) the community you live in now; (c) a gay community; (d) a racial/ethnic community; (e) a school community; (f) the online community; (g) the arts community; (h) a spiritual or religious community; (i) a work community; and (j) a club or party scene. We subsequently combined these responses to create a mean score for connection to community for each participant ($\alpha = .73$).

Homophobia

At baseline, we also assessed participants' experiences of interpersonal homophobia in adulthood using six items previously used for assessing this construct among minority SMM (Díaz et al., 2001). The items were: (a) "As an adult, how often have you been hit or beaten up for being gay or being perceived as effeminate (looking or acting like a woman)?"; (b) "Today, how often do you feel that your sexuality hurts and embarrasses your family?"; (c) "As an adult, how often have you had to pretend that you're straight in order to be accepted?"; (d) "How often have you lost a job or career opportunity for being gay?"; (e) "As an adult, how often have you had to move away from friends or family because of your sexuality?"; and (f) "As an adult, how often have you been harassed by the police for being gay?" Responses were provided on a 4-point scale (0 = *never*, 1 = *once or twice*, 2 = *a few times*, 3 = *many times*). The psychometric quality of this scale was reported as $\alpha = .75$ by both Díaz et al. (2001) and Sandfort et al. (2007). Participants' responses were summed, with higher scores indicating more experienced homophobia ($\alpha = .63$).

Racism

Finally, at baseline, we assessed participants' experiences of interpersonal racism in adulthood using 10 items taken from a prior study of minority SMM to assess exposure to both institutional and sexualized racism (Díaz et al., 2001). The specific items were: (a) "As an adult, how often have you been hit or beaten up because of your race or ethnicity?"; (b) "As an adult, how often have you been treated rudely or unfairly because of your race or ethnicity?"; (c) "As an adult, how often have you been harassed by police because of your race or ethnicity?"; (d) "How often have you been turned down for a job because of your race or ethnicity?"; (e) "How often have you been made to feel uncomfortable in a gay bar or club because of your race or ethnicity?"; (f) "How often have you had trouble finding loving relationships because of your race or ethnicity?"; (g) "In sexual relationships, how often do you find that people pay more attention to your race or ethnicity than to who you are as a person?"; (h) "How often have you been turned down for sex because of your race or ethnicity?"; (i) "How often did you hear sexual comments about your race or ethnicity?"; and (j) "How often have you been made to feel sexually objectified (like a piece of meat) because of your race or ethnicity?" Responses were provided on the same 4-point scale used for the homophobia assessment and, again, responses to the items were summed for each participant, with higher scores indicating more experienced racism. The internal consistency in the present sample ($\alpha = .84$) was similar to that previously reported by both Díaz et al. (2001) and Ibañez, et al. (2009; i.e., $\alpha = .82$).

Gene Expression

As described above, gene expression profiles were created using blood samples taken at Study Visits 2, 4, and 6. Consistent with prior research (e.g., Li et al., 2020; Thames et al., 2019), CTRA gene expression profiles were assessed in 0.5 ml peripheral blood buffy coat cell samples using a standard 53-gene composite score contrasting the relative abundance of 19 standard proinflammatory indicator gene transcripts (e.g., *IL1A*, *IL1B*, *IL6*, *IL8*, *TNF*) and 34 gene transcripts involved in Type I interferon response (e.g., *IFI*-, *OAS*-, and *MX*-family genes). The latter set was sign-reversed to reflect their inverse contribution to the CTRA profile.

Individual transcript abundance measures were derived from standard RNA sequencing, with total RNA extracted from blood samples (Qiagen RNeasy), converted to cDNA using a high-efficiency mRNA-targeted reverse transcription system (Lexogen QuantSeq 3′ FWD), and sequenced on an Illumina NextSeq instrument (Lexogen Services GmbH), all following the manufacturers' standard protocols. Sequencing targeted 5 million reads per sample (achieved median 5.82 million), each of which was mapped to the GRCh38 reference human transcriptome using the STAR aligner (average 98.3% mapped), and quantified as gene transcripts per million mapped reads. The resulting transcript abundance values were $\log_2$ transformed to stabilize variance, z score normalized to reduce heteroscedasticity, and averaged into a single composite score for use in the linear mixed-effects models described below.

Data Analysis

All statistical code and output files are available on the Open Science Framework website (see Gassen, 2024). Statistical differences in sample characteristics were analyzed using independent samples *t* tests (continuous variables) and χ^2 tests (categorical variables). Statistical analysis of the CTRA composite score was conducted using a linear mixed-effects model that quantified CTRA variation as a function of baseline levels of experienced community connection, homophobia, and racism (all *z* score standardized), while controlling for study visit number, HIV status, and, where indicated, additional covariates of age, race/ethnicity, BMI, and education level. Models were fit using SAS PROC MIXED, with a random intercept term to account for correlation among residuals from the same individual across timepoints. Data for each of the key predictors (i.e., community connection, homophobia, and racism) were collected at baseline only; therefore, the primary models estimated the effects that baseline levels of these variables had on overall CTRA gene expression levels across all of the timepoints (i.e., while adjusting for the nesting of timepoints within individuals). Follow-up models tested interactions between the focal predictors and study visit number to examine whether the strength or direction of the effects varied between visits. We also examined potential interactions between community connection and the two forms of discrimination (i.e., homophobia and racism). A final set of follow-up analyses tested the models again for each subcomponent of the CTRA gene expression composite (i.e., proinflammatory and antiviral).

To reduce the effects of measurement noise for transcripts with minimal expression levels (all- or mostly 0 transcript abundance), we excluded data from 12 gene transcripts that showed minimal levels and/or variance in expression ($SD < 0.5$ log2 transcript abundance: *CXCL8*, *FOSL1*, *IFI27L1*, *IFIT1B*, *IFITM5*, *IFITM4P*, *IFNB1*, *IGLL1*, *IGLL3P*, *IL1A*, *IL6*, *TNF*), leaving a total of 41 CTRA indicator gene transcripts contributing to the composite score. Among the total 568 samples analyzed, 72 (12.7%) failed one or more prespecified sequencing quality criteria and were excluded from further analysis (63 yielding <3 million sequencing reads due to insufficient input RNA, one additional sample showing transcript mapping rates <90%, and eight additional samples showing a median profile correlation with other samples $r < .30$). To control for minor residual variations in sequencing data quality among the 496 remaining samples, mixed models were estimated by weighting each sample by the cubed median profile correlation of each sample with all other samples (such that aberrant samples with low median correlations were weighted less than more consistent/reliable samples). Missing data on the above-described predictors reduced the final analytic data set to 479 observations collected from 209 individuals.

Results

Descriptive Statistics

Descriptive statistics for the key study variables, displayed separately for people with HIV (PWH) and people without HIV (PWoH), are shown in Table 1. The sample consisted of SMM, 33 PWH and 217 PWoH. These two groups were similar with respect to age (PWH: $M = 22.55$, $SD = 1.82$; PWoH: $M = 22.62$, $SD = 1.91$; $p = .863$), BMI (PWH: $M = 23.83$, $SD = 4.50$; PWoH men: $M = 25.04$, $SD = 5.18$; $p = .187$), and race/ethnicity (PWH: 24.2% Black, 51.5% Hispanic, and 12.1% multiracial; PWoH: 21.2% Black, 59.0% Hispanic, and 18.0% multiracial, $p = .700$). There were minor differences in highest level of education between the groups, attributable to more PWH having not completed high school than PWoH and fewer having progressed to an associate's degree or above (PWH: 12.1% less than high school, 27.3% high school/General Educational Development [GED], 3.0% vocational school, 36.4% some college, 0.0% associate degree, 9.1% bachelor's degree, 0.0% some graduate school, 0.0% completed graduate school, 12.1% missing data; PWoH: 2.8% less than high school, 18.9% high school/GED, 2.3% vocational school, 42.4% some college, 8.8% associate degree, 20.7% bachelor's degree, 1.4% some graduate school, 0.9% completed graduate school, 1.8% missing data; $p = .050$).

With respect to the main predictor variables, PWH and PWoH reported similar experiences of community connection (PWH: $M = 2.33$, $SD = 0.67$; PWoH: $M = 2.62$, $SD = 0.51$; $p = .489$) and homophobia (PWH: $M = 2.03$, $SD = 4.50$; PWoH: $M = 2.27$, $SD = 5.18$; $p = .668$). In terms of experienced racism, there was a modest group difference between the groups, with PWoH reporting slightly more racism than PWH (PWH: $M = 4.55$, $SD = 4.23$; PWoH: $M = 6.32$, $SD = 5.73$; $p = .050$). With respect to the interrelations between these variables, there was no significant correlation between community connection and homophobia ($r = .008$, $p = .874$); in contrast, the correlation between community connection and racism was small and marginally significant ($r = .099$, $p = .050$). Finally, as to be expected, the correlation between homophobia and racism was strong and statistically significant ($r = .387$, $p < .001$).

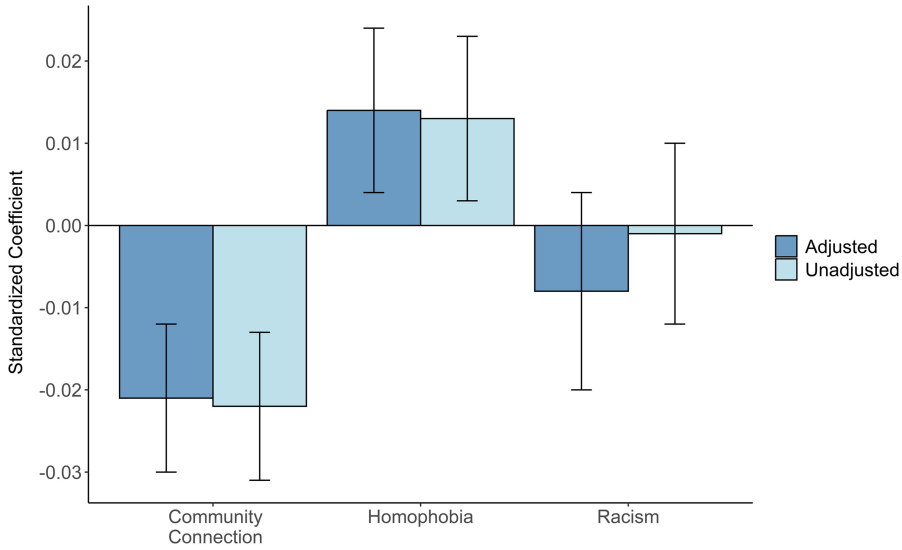
Primary Analyses

A graphical depiction of how community connection, homophobia, and racism related to participants' overall gene expression levels across the three study visits is shown in Figure 1. Our primary analyses aimed at assessing how these predictors were associated with overall CTRA gene expression profiles revealed that, while controlling for HIV status and study visit, CTRA gene expression showed a significant inverse association with community connection ($b = -0.022$ log2 mRNA abundance per *SD* of connection $\pm$ *SE* 0.009, $p = .021$) and no significant association with either homophobia (0.013 ± 0.01, $p = .190$) or racism (-0.001 ± 0.011, $p = .930$). The magnitude of these associations did not differ by HIV status (all interaction $ps > .290$), meaning that the effects of these psychological experiences on participants' gene expression levels were similar for PWH and PWoH. Moreover, similar results emerged in analyses that also controlled for age, race/ethnicity, BMI, and education level (community connection: -0.021 ± 0.009, $p = .021$; homophobia: 0.014 ± 0.010, $p = .178$; racism: -0.008 ± 0.012, $p = .513$), demonstrating the robustness of these findings.

We next examined whether the effects of community connection, homophobia, and racism on CTRA gene expression differed across visits by probing interactions between each predictor and study visit. Results revealed that there was a main effect of study visit, indicating that *z*-scored levels of CTRA expression did appear to decline across visits (see Figure 2), with estimated least squares means (i.e., from the primary model) decreasing from 0.04 ($SE = 0.02$) at Study Visit 2, to -0.05 ($SE = 0.02$) at Study Visit 4, and -0.05 ($SE = 0.02$) at Study Visit 6. However, there were no statistically significant interactions between study visit and community connection ($ps > .127$), homophobia ($ps > .739$), or racism ($ps > .435$), suggesting that associations between each predictor and CTRA gene

Figure 1

Standardized Regression Coefficients for Effects of the Focal Predictors on CTRA Gene Expression



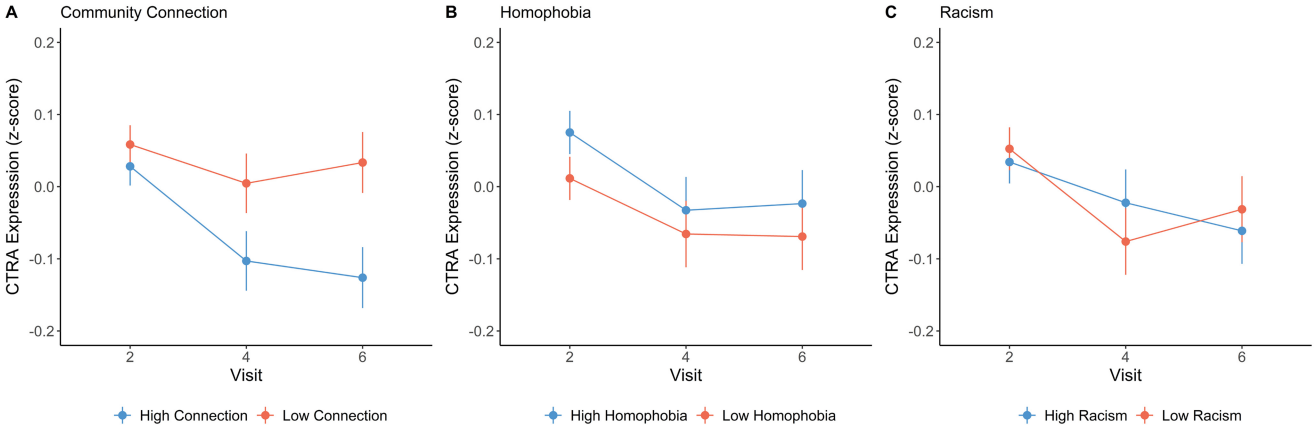
Note. Adjusted and unadjusted refer to analyses that did and did not include the full set of covariates (i.e., age, race/ethnicity, BMI, and education level). Both adjusted and unadjusted analyses controlled for study timepoint and HIV status. Error bars reflect standard errors for coefficients in each model. As shown, greater community connection was related to lower CTRA gene expression, whereas no statistically significant associations were found for experienced homophobia or racism. CTRA = conserved transcriptional response to adversity; BMI = body mass index. See the online article for the color version of this figure.

expression were relatively consistent across visits. Moreover, the plots of the interaction effects shown in Figure 2 appear to suggest that although the magnitude of association between community connection and CTRA expression was not significantly different across study visits, it was nonetheless greater at the latter two visits compared to Study Visit 2.

In addition to interactions between study visit and each predictor, we also assessed whether there were interactions between the predictors themselves. Analyses examining interactions between community connection, homophobia, and racism yielded null effects for all interaction terms (all interaction $ps > .632$). These results suggest that the effects of each predictor on CTRA gene expression do not

Figure 2

CTRA Gene Expression Across Visits



Note. Changes in CTRA gene expression across the three study visits, stratified by high versus low (A) community connection, (B) experienced homophobia, and (C) experienced racism. High and low levels reflect 2 *SD*s above and below the mean of each variable. No Study Visit × Predictor interactions reached statistical significance ($ps > .13$). CTRA = conserved transcriptional response to adversity. See the online article for the color version of this figure.

vary systematically across levels of the others. For community connection, specifically, this means that high levels of community connection were related to lower CTRA expression regardless of whether racism and homophobia were high versus low.

Follow-Up Analyses

We conducted several follow-up analyses to interrogate possible mechanisms underlying the main results described above. First, we tested whether the effect of community connection (and the other predictors) on CTRA expression was driven primarily by differences in either of the subcomponents that comprise the CTRA expression composite variable—namely, proinflammatory and antiviral gene expression. Results of separate models for each subcomponent revealed that none of the psychological predictors were associated with either proinflammatory or antiviral ($ps < .092$) transcripts individually ($ps < .459$), suggesting that the significant relation between community connection and CTRA gene expression was not due to particularly strong associations between community connection and either proinflammatory or antiviral gene expression specifically. Put another way, community connection was more strongly related to variation across both proinflammatory and antiviral transcripts together than to either CTRA subcomponent alone.

Finally, we investigated whether the effects of community connection on CTRA gene expression could be attributable to differences in leukocyte subset abundance. We tested this possibility by examining if community connection was related to the relative abundance of seven mRNA markers of major leukocyte subsets (CD3, CD4, CD8, CD19, CD56, CD16, and CD14), all while controlling for HIV status. However, no significant effects emerged ($ps > .140$), indicating that the association observed between community connection and diminished CTRA expression was likely driven by actual variation in transcriptional activity, rather than by differences in the abundance of particular leukocyte subsets.

Discussion

To the best of our knowledge, these data are among the first to characterize changes in gene expression across multiple timepoints in a racially diverse sample of SMM with and without HIV and to document how such changes in gene expression relate to individual differences in both social safety (i.e., community connection) and social threat (i.e., homophobia and racism). Contrary to hypotheses, experienced homophobia and racism were unrelated to CTRA gene expression and did not interact with HIV status to predict differences in gene expression. Consistent with hypotheses, however, we found that greater experiences of community connection—namely, being connected with and included by various communities that are important to one's identity (be it race or sexual orientation)—were related to lower CTRA gene expression across time. The magnitude of this effect corresponded to an approximate 10% reduction in CTRA indicator gene expression over the range of observed community connection scores. This effect was present regardless of HIV status and was robust to statistical adjustment for several potential confounding factors. Given that chronic activation of the CTRA can increase the risk of developing both inflammation-related diseases and viral infections (Cole, 2019; Li et al., 2020; Slavich & Cole, 2013), these results suggest that being connected with one's community may decrease CTRA activation and thus have potential salutary effects on mental and physical health for SMM, regardless of their HIV status.

Follow-up analyses tested two potential mechanisms underlying the associations observed between community connection and CTRA gene expression. The first set of follow-up analyses revealed that the association between community connection and CTRA gene expression was not driven by differences in either expression of proinflammatory or antiviral genes specifically, but rather by their combined patterns of expression. In addition to the mechanistic explanation for this finding, which is that combining these two CTRA subcomponents provides different—and arguably more useful—information than when proinflammatory and antiviral gene expression are considered separately, there are also potential statistical explanations for this result. For example, the significant association between community connection and the overall CTRA composite score may reflect its greater statistical precision (due to the greater total number of transcripts integrated into the composite) or greater control of sample heterogeneity (which can be accounted for by the bipolar nature of the CTRA composite: inflammatory—antiviral; but is not accounted for in the inflammatory or antiviral composite analyzed in isolation).

The second set of follow-up analyses assessed whether associations between community connection and CTRA gene expression might be explained by differences in the abundance of different leukocyte subsets. Arguing against this possibility, however, we found that community connection was not related to the abundance of major leukocyte subsets. The effects observed in our primary analyses were thus likely driven by differences in actual transcriptional activity, rather than by variation in the numbers of different leukocytes present.

Important to note about these findings is the fact that the measure of community connection we used was not specific to any part of an individual's identity, but rather encompassed how connected participants felt across multiple domains (e.g., racial/ethnic community, gay community, work community). These results thus provide important insights into how feeling connected to various communities, in aggregate, is related to health-related gene expression. At the same time, the broad nature of this measure does not indicate if and how connection to certain communities, specifically, differentially impacts CTRA gene expression. Furthermore, individuals may place greater weight on their relationships in some communities than others. For example, an individual with a rich social life may derive less benefit from connection to coworkers than someone who is relatively isolated outside of the workplace. Additionally, connection to one's racial community may be less impactful for a member of a racial majority as compared to someone who is a racial minority who routinely encounters race-based discrimination. Research supporting this possibility has found that in the context of discrimination, certain community connections that affirm and uplift aspects of one's identity (e.g., to racial and ethnic communities) may carry more weight than others (K. F. Jackson et al., 2012; Lindsey et al., 2020). Collectively, these possibilities highlight the need for additional well-powered studies that incorporate intersectionality and use more detailed surveys of connection to different communities.

Broadly speaking, these findings are both consistent with and contradict prior research on social patterning of gene expression in diverse populations. With regard to the contradictory findings, prior work has shown that lifelong discrimination (Brown et al., 2019, 2020), daily

discrimination (Cuevas et al., 2023), and discrimination experienced during the past year (Li et al., 2020) are related to differences in gene expression. One key difference between the present study and prior work is our focus on CTRA gene expression levels across multiple timepoints versus a single time point. Indeed, although the interaction between community connection and time was not statistically significant, we nonetheless found that the relation between connection and CTRA gene expression was stronger at the latter two study visits relative to the first. Accordingly, it is possible that variation in gene expression over time may influence the extent to which discrimination is related to CTRA expression. Environmental moderators, such as seasonality, may also affect if and how CTRA expression is associated with discrimination (Gassen et al., 2024). As is shown in Figure 2, however, we did not find links between discrimination and CTRA expression at any time point.

Another possible reason for the lack of significant findings pertaining to socially threatening experiences could be limited variability in our measures of discrimination. Although our sample had the full range of scores on these measures, with some participants scoring relatively high, average levels of homophobia and racism were quite low relative to the scale ranges (see Table 1). Therefore, these experiences may not have occurred frequently enough in the present sample to drive changes in CTRA gene expression. Moreover, given that the sample consists entirely of SMM, it is possible that different participants may have had relatively similar experiences of discrimination, which may also have limited our ability to detect differences in gene expression levels attributable to these variables. Additional research comparing associations between discrimination and CTRA gene expression levels in both SMM and nonsexual minority groups (i.e., who are less likely to experience discrimination) could lend important insights into the true magnitude of the effect that discrimination has on health-related biology.

It is also possible that discrimination could have been underreported in the present study (Van Dyke et al., 2022), and that associations between CTRA gene expression levels, racism, and homophobia would emerge if more objective indices of discrimination were used, or those that capture lifetime burden of discrimination. The few studies that have measured discrimination have employed different scales over different time courses, with some measuring lifetime discrimination, others measuring daily, and yet others measuring discrimination over the past year. Therefore, it could be that the measure of discrimination we employed here, although similar to those used in prior work, may not capture the aspect of discrimination that is most strongly related to health-related gene expression.

Yet another consideration is that many of the prior studies on this topic had larger sample sizes. Although Li et al. (2020) did have a smaller sample (i.e., only 70 participants), they nonetheless found significant associations between discrimination in the past 12 months and gene expression. However, their measure of discrimination differed from ours, with all instances of discrimination being focused on more physically threatening/aggressive events, such as being punched or threatened. Although our measures of discrimination did assess these experiences, we also measured more socially threatening experiences, such as feeling like your family is embarrassed or feeling the need to hide.

A very important, unique feature of the present study is that we simultaneously measured the influence of both social safety and social threat on health-relevant gene expression profiles. To our knowledge, only one other study has done such an analysis. Specifically, Brown et al. (2020) examined how both discrimination and social support were related to gene expression (in the same model), and found that whereas discrimination was a significant predictor, social support was only marginally significant. Contrary to their findings, we found that discrimination was not a significant predictor of gene expression, whereas community connection was. These differences could again be due to how social safety was measured across these studies. For example, whereas Brown et al. (2020) indexed social safety as the presence of social support, such as having friends that understand you and that you can rely on, we measured social safety as conceptualized by social safety theory—namely, as the presence of community connection, which we assessed by asking participants how much they felt they were a part of different communities that mattered to them (Slavich, 2020). Given that these scales are quite different, it is perhaps not surprising that the results differ across these studies, and the fact that they do may point to critical nuances or specificity in how human gene expression is socially patterned.

These differences aside, the present finding that community connection predicts CTRA profiles in a racially diverse sample of SMM with and without HIV provides novel insights into the social factors that impact health-related biology. These results are consistent with theoretical work articulating the importance of safety support and connection for reducing health disparities in marginalized populations (Diamond & Alley, 2022), and they also speak to the importance of increasing opportunities for social connection and inclusion not only for fostering psychological well-being but also for promoting long-term physical health. Indeed, prior research has shown that the CTRA is related to disparities in both mental and physical health outcomes across the life course (for reviews, see Slavich & Cole, 2013; Slavich, Mengelkoch, & Cole, 2023).

Lastly, and perhaps most importantly, consistent with prior research, we did not find that HIV status moderated any associations between social safety or social threat on gene expression. These results are similar to Thames et al. (2019), who found that racial discrimination was significantly related to racial differences in gene expression regardless of HIV status. This finding is vitally important given that many biopsychosocial studies—especially those focused on inflammatory biology—tend to exclude PWH individuals due to the impact their illness or medications can have on immune system function. Given the potential for human social genomics to advance our understanding of the social determinants of health disparities, understanding how associations between social factors, such as community connection, and gene expression do or do not differ by HIV status is critical. The present findings may thus guide future work contemplating the inclusion of PWH individuals in social genomics-focused research and help ensure that studies focused on health disparities do not unnecessarily exclude individuals who are PWH.

More broadly, these results provide support for social safety theory (Slavich, 2020, 2022; Slavich, Roos, et al., 2023) and for extensions of this theory that aim to explain health disparities in sexually diverse populations (Diamond & Alley, 2022). Specifically, we found that feeling connected to one's community—be it racial community, neighborhood, church, or sexually diverse community—was related to the expression of genes implicated in human health and behavior. The results thus have important implications for understanding how social experiences may lead to differences in risk for inflammation-related disorders, viral infections, and early mortality. These data also suggest that doctors and mental health professionals may be able to significantly benefit patients by

emphasizing the importance of forming strong social ties not only with friends and family but also with the community at large.

Strengths and Limitations

This study has several strengths, including a racially diverse, well-characterized sample of SMM with and without HIV; focus on risk and resilience factors in a vulnerable population known to experience substantial disease morbidity; assessment of key biological mediators that are known to link social experiences and health; and a theoretically informed examination of how community connection, homophobia, and racial discrimination affect disease-relevant biology. However, several limitations should also be noted. First, our key psychosocial predictors were based on self-report. We view this as a strength, given that psychological experiences drive gene expression, but these reports can nevertheless be influenced by a variety of social-cognitive factors and response biases. It is also possible that other social-environmental "signals" could be more strongly related to gene expression than the ones we chose to assess here. Furthermore, future research should consider examining how these psychosocial experiences impact gene expression across sexual identity (e.g., gay vs. bisexual vs. heteroflexible) given that bisexual men, in particular, face unique challenges with biphobia and erasure, which are sure to impact connection experiences within the gay community, especially for bisexuals of color (Gonzalez et al., 2021).

Second, although CTRA gene expression varied significantly as a function of community connection, the absolute magnitude of this association was small, and the health significance of these effects remains to be determined in future research. Third, this study focused on a specific a priori hypothesis involving CTRA-related genes, and it is possible that other genes, or aspects of inflammatory biology, may also vary significantly as a function of community connection, homophobia, or racism. Our use of RNA sequencing to assess CTRA indicator gene expression presents some limitations relative to previous research using microarray-based assessments. Although there was adequate transcript abundance to quantify the expression of most target genes, certain indicators of the CTRA were characterized by minimal expression levels and restricted variance (all/mostly 0 expression values) and were thus excluded from the composite variable. Future research is needed to replicate the present results using alternative assessment methods. Looking forward, the identification of additional transcriptional correlates will require larger sample sizes suitable for genome-wide exploratory/discovery analyses. Specifically, given recent findings (Carrico et al., 2024), it may be fruitful to consider how social affiliative experiences such as community connection impact oxytocin receptor methylation, which can have a substantial impact on inflammation and, thus, mental and physical health (Slavich & Auerbach, 2018).

Fourth, the study is correlational, and directionality and causality cannot be inferred. It is possible, for example, that unmeasured "third variables" could have influenced the results. Additionally, differences in immune system function could have influenced participants' social behavior (e.g., via immune system influences on central nervous system function) as opposed to the opposite, hypothesized effects of social experiences on cellular gene expression. The final limitation concerns the time course of our self-report and biological assessments. With regard to the self-report assessments, although we obtained blood samples at three timepoints, information on the psychosocial predictors was only collected at baseline, and it is possible that more frequent assessments of social safety and threat could have yielded different results. This is especially true if the assessments had been taken at the same time the blood samples were obtained (i.e., as opposed to over adulthood). The association we observed between community connection and participants' CTRA profiles appeared to be stronger (not weaker) at the later timepoints, but the underlying reason is unclear. Regardless, the lack of longitudinal measurement of the psychosocial predictors is a limitation, and future work should build upon the present study by surveying psychosocial experiences at the same time that each biological assessment is taken (Mengelkoch et al., 2023, 2024; Moriarity & Slavich, 2023).

Conclusion

Notwithstanding these limitations, the present results are the first that we know of to indicate that, in a racially diverse sample of SMM with and without HIV, community connection may have a positive effect on health-relevant gene expression, downregulating expression of genes that can exacerbate inflammation-related health problems and upregulating expression of those involved in the antiviral response. Moreover, these effects are present regardless of HIV status. These results thus suggest that efforts to increase social inclusion and connection in marginalized communities may have a significant positive effect on lifelong health and should therefore be a priority in programs aiming to reduce health disparities. Future research is needed to replicate these effects, to examine their generalizability to other populations, and to evaluate how best to harness the power of social connection and belonging to positively impact the health and longevity of SMM and, indeed, all populations.

Resumen

Objetivo: Aunque los hombres de minorías sexuales experimentan una discriminación sustancial, además de un mayor riesgo de varios problemas de salud mental y somáticos graves, los mecanismos biológicos subyacentes a estos efectos no están claros. Para abordar este tema, examinamos cómo las experiencias de seguridad social (es decir, conexión comunitaria) y amenaza social (es decir, discriminación, en forma de homofobia y racismo) se relacionaron con los perfiles de expresión genética de la Respuesta Transcripcional Conservada a la Adversidad (CTRA, por sus siglas en inglés) a lo largo del tiempo, y si estas asociaciones diferían según el estado del VIH, en una muestra racialmente diversa de hombres de minorías sexuales bien caracterizada (Medad = 22.61, SDedad = 1.90). ***Método:*** Las experiencias de conexión comunitaria, homofobia y racismo se evaluaron mediante autoinforme y se obtuvieron muestras de sangre en tres momentos durante dos años, aproximadamente. Luego utilizamos estas muestras de sangre para caracterizar la expresión del gen CTRA de los participantes, que cuantificamos utilizando una puntuación compuesta a priori de 53 transcripciones derivada de datos de secuenciación de ARN (RNA, por sus siglas en inglés) de leucocitos de sangre periférica. ***Resultados:*** Según la hipótesis, una mayor conexión comunitaria se relacionó significativamente con una disminución de la expresión del gen CTRA a lo largo del tiempo. Estos efectos fueron similares independientemente del estado del VIH y fueron sólidos ante el ajuste estadístico por varios posibles factores de confusión. Por el contrario, ni la homofobia ni el racismo estaban relacionados

con la expresión del gen CTRA. ***Conclusión:*** Estos resultados sugieren que la conexión comunitaria puede ser un factor protector que reduce los procesos biológicos conocidos que impactan negativamente la salud. En consecuencia, las intervenciones y políticas destinadas a reducir las disparidades de salud en poblaciones marginadas pueden beneficiarse de una mayor conexión e inclusión comunitaria.

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