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Experienced homophobia and gene expression alterations in Black and Latino men who have sex with men in Los Angeles County

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Abstract

Men who have sex with men (MSM) experience high rates of homophobic victimization, which is linked to myriad chronic physical and mental health disparities. Social adversity such as rejection, isolation, and racial discrimination can induce a conserved transcriptional response to adversity (CTRA) involving upregulation of proinflammatory genes and downregulation of type I interferon and antibody synthesis genes. This study specifically examines whether homophobic victimization is associated with expression of CTRA profiles in Black and Latino MSM living in Los Angeles. Analyses linked behavioral survey data with quantified RNA from leukocytes from blood samples of 70 participants over 12 months. CTRA gene expression was increased by 3.1-fold in MSM who experienced homophobic victimization while adjusting for major leukocyte subsets and sociodemographics. Accounting for all these factors, CTRA gene expression was significantly enhanced in MSM who identified as Black compared to Latino. Our findings identify experiences of homophobic victimization as drivers of inflammatory and type I interferon gene expression profiles, which can contribute to physical and mental health challenges in Black and Latino MSM.

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Keywords

transcriptome; gene expression; inflammation; immune system; homophobia; men who have sex with men; victimization

1. Introduction

Men who have sex with men (MSM) experience high rates of verbal and physical victimization due to biases against their sexuality (Kosciw et al., 2018). In the U.S., MSM also have higher rates of chronic physical and mental health conditions compared to similar heterosexual adults (Hoy-Ellis and Fredriksen-Goldsen, 2016; Kim and Fredriksen-Goldsen, 2017; Mays et al., 2018; Wallace et al., 2011). These two processes may be linked. According to Minority Stress Theory, social environment such as bias-motivated violence, harassment, and other experiences of discrimination lead to chronic physical and mental health problems (Meyer, 2003; Mustanski et al., 2016). Experiences of homophobic victimization is associated with elevated levels of allostatic load, depression, anxiety, suicidality, and substance use disorders in MSM (Bouris et al., 2016; Flynn et al., 2016; Hatzenbuehler, 2014; Hatzenbuehler et al., 2008; Hoy-Ellis and Fredriksen-Goldsen, 2016; Kosciw et al., 2018; Li et al., 2014; Li et al., 2018; Mays et al., 2018; Meyer, 2003). However, the biological mechanisms in which experiences of discrimination drive chronic physical and mental health conditions are only in the nascent stages of research.

The field of social genomics has demonstrated that experiences of social rejection, threat, and adversity (e.g., poverty, racial discrimination, isolation) evoke a common pattern of conserved transcriptional response to adversity (CTRA) among leukocytes (Brown et al., 2019; Cole, 2019; Levine et al., 2017; Thames et al., 2019). The CTRA involves increased expression of proinflammatory genes through the activation of transcription factors such as nuclear factor kappa B (NF-κB) and the β-adrenergic-responsive transcription factor cAMP response element-binding protein (CREB). The CTRA also involves decreases in expression of genes involved in innate antiviral responses and antibody synthesis through the inhibition of transcription factors such as interferon regulatory factors (IRFs) (Fredrickson et al., 2013). Chronic expression of the CTRA profile has been implicated in increased risk of inflammation-related chronic diseases such as Type II diabetes, atherosclerosis, neurodegeneration, and metastatic cancer (Cole, 2019; Flentje et al., 2018; Fredrickson et al., 2013; Powell et al., 2013), viral infections (Sloan et al., 2007), and psychiatric illnesses such as anxiety and depressive disorders (Dantzer et al., 2008; Sloan et al., 2007).

Previous research has assessed the relationship between CTRA and social adversity that affect the broader population such as interpersonal problems and poverty (Levine et al., 2017; Murphy et al., 2013; Powell et al., 2013). However, there has been limited investigation into the unique social stressors experienced by minority communities (e.g., discrimination and structural stigma) from the social genomic perspective (Brown et al., 2019; Thames et al., 2019). Furthermore, growing attention has been given to the impact of minority stress on health disparities in MSM of color such as Black and Latino MSM, as the added stigma and stressors on dual minorities may further increase risk of mental health

problems (Bogart et al., 2017; Cyrus, 2017; Ramirez and Paz Galupo, 2019). For these reasons, the present study aims to determine whether experiences of homophobic victimization are associated with greater CTRA gene expression among Black and Latino MSM.

2. Methods

2.1. Study Design

We used data from the MSM and Substances Cohort at UCLA Linking Infections Noting Effects (mSTUDY), a longitudinal cohort study of HIV-negative and HIV-positive MSM sponsored by the National Institute on Drug Abuse (NIDA). Additional details of the mSTUDY are published elsewhere (Aralis et al., 2018; Li et al., 2018; Okafor et al., 2017). Briefly, the mSTUDY focuses enrollment of diverse race/ethnicity (primarily Black/African American and Latino/Hispanic) MSM between 18 and 45 years of age who were assigned male at birth. The primary aim of the mSTUDY is to study the effects of substance use on immune functioning, behavior, and HIV transmission and disease progression. Recruitment of participants began in July 2014. Participants in the mSTUDY return every 6 months for physical examinations, laboratory testing, specimen collection, and completion of a computer-assisted self-interview (CASI) survey collecting sociodemographic, psychosocial, psychological and behavioral data. To minimize confounding by race/ethnicity and HIV status, we restricted our analysis to participants who identified as Black/African American or Latino/Hispanic and who were enrolled as HIV-negative. Moreover, focusing our analysis on racial minority MSM aligns with current research priorities to study stress-related health disparities among people of multiple minority statuses (Bogart et al., 2017; Cyrus, 2017; Ramirez and Paz Galupo, 2019). Our analysis excluded participants with inflammatory conditions such as current infections including sexually transmitted infections (chlamydia, gonorrhea, and syphilis) and hepatitis A, B, and C, as well as allergic reactions or other clinically significant event. In mSTUDY, half the sample were enrolled as HIV-negative high-risk men and eligible if they reported unprotected anal intercourse with a man in the past 6 months. For this analysis, we used data from 70 HIV-negative Black and Latino MSM, of whom 52 participants had CTRA transcriptome data from two visits 12-months apart, while 18 had CTRA data from one visit. The sample was compiled on July 10, 2018 and included all available cases at that time.

2.2. Behavioral and Clinical Measures

Responses to questions from the self-administered questionnaires and clinical assessment assessed demographics and recent behaviors and experiences from the same visits where the blood specimens were drawn that analyzed for socio-genomics. These included homophobic victimization, age, race, employment status, smoking status, housing instability, and BMI. Homophobic victimization was the primary variable hypothesized to capture stressors specific to MSM, which was assessed using 5 questions adapted from the National Health, Aging, and Sexuality/Gender Study (NHAS) ($\alpha = .85$) (Fredriksen-Goldsen and Kim, 2017). The measure asked, “Which of the following have happened to you in the past 12 months…because you are, or were thought to be, gay or bisexual?” Items followed included being (1) verbally insulted (yelled at, criticized); (2) being threatened with physical

violence; (3) had an object thrown; (4) punched, kicked or beaten; and (5) threatened with a weapon. Possible responses were “No” and “Yes.” A composite score was computed by summing the number of “Yes” responses, for a possible range from 0 to 5, with greater scores representing more variety and greater severity of homophobic victimization experiences.

We collected other social, behavioral, and biological information that may influence CTRA gene expression from CASI and other clinical assessments. Age (years) and race (Black or Latino), as well as past 6 months report of employment status (working, not working), weekly alcohol use (3 or less times per week, 4 or more times per week), current smoking status (yes, no), and housing instability (housed, any housing instability) were obtained from CASI. Based on physical assessment at study visit, we computed body mass index (BMI), which is a known risk factor for inflammatory gene expression and a standard biological covariate in social genomics analysis (Fredrickson et al., 2013; Freedman et al., 2010; Lumeng and Saltiel, 2011; Powell et al., 2013).

Past 6-month substance use status was determined using self-report and urine toxicology test at each visit. The *in vitro* screen Fastect II 4-panel drug test by CLIAwaived, Inc. was used for rapid detection of drug and drug metabolites in urine. Substance use behaviors in the past 6 months were classified into 3 categories: none, cannabis use only, and other substance use. We classified participants as having not used any substances in the past 6 months if they both reported no substance use in the past 6 months and tested negative on all urine toxicology tests. We classified participants as having used only cannabis in the past 6 months if they self-reported only using cannabis use in the past 6 months in the CASI, if they had a positive urine toxicology result for only cannabis at their visit, or if they met both criteria. Participants were classified as having used other substances (including polysubstance use with cannabis) in the past 6 months if they self-reported using any substance besides cannabis (e.g., methamphetamine, cocaine, opioids) within the past 6 months, if they had a positive urine toxicology test for any substance besides cannabis, or if they met both criteria.

2.3. Dependent variable: CTRA transcriptome profiling

Briefly, we conducted genome-wide transcriptional profiling of peripheral blood mononuclear cells (PBMCs) using methods previously established and validated procedures of CTRA profiling (Fredrickson et al., 2013). Per the parent mSTUDY, every 6 months, PBMCs were obtained from 125 mL of blood taken from venipuncture and stored at −70° C in the mSTUDY biorepository. We used PMBCs from 70 participants, of whom 52 participants had PBMCs with sufficient RNA from two visits 12-months apart, while 18 had PBMCs with sufficient RNA from one visit. Originally, 124 frozen PBMC samples were retrieved from the biorepository and transferred to the UCLA Social Genomics Core Laboratory. From the PBMCs, total RNA was extracted using standard methods (Qiagen RNeasy) and tested for suitable mass (RiboGreen) and integrity (Agilent TapeStation). High quality samples were converted to cDNA (Lexogen QuantSeq 3’ FWD) and sequenced on an Illumina HiSeq 4000 instrument in the UCLA Neuroscience Genomics Core Laboratory, all following the manufacturers’ standard protocols. Assays targeted >12 million reads per

sample (average 15.1 million), which were mapped to the consensus human transcriptome sequence and quantified at the gene level using the STAR aligner. Read counts were normalized to transcripts per million mapped reads (TPM) and $\log_2$ transformed for analysis of differential gene expression as described below.

2.4. Statistical analysis

Statistical analyses were conducted using a standard generalized estimating equation (GEE) linear statistical model relating the abundance of 15 pre-specified CTRA indicator genes to measures of homophobic victimization while controlling for covariates (listed below) and accounting for intra-individual correlation among genes (i.e., treating them as a repeated measure). To account for correlations between multiple observations of participants across time and across genes, we used GEE analyses with the identity link function to test the association between homophobic victimization and the response variable, CTRA indicator gene expression. Analytic models were estimated using SAS PROC GENMOD, treating genes as a repeated measure with a fully saturated (unstructured) covariance matrix. The 15 analyzed genes derived from a set of 53 CTRA indicator genes used in previous research (Fredrickson et al., 2013), less 2 unavailable from the current RNA sequencing assay pipeline and removing 36 genes that showed limited variability in this data set (SD <1), leaving 7 pro-inflammatory genes (*CXCL8, FOS, FOSB, IL1A, IL1B, PTGS2, TNF*; each positively weighted to reflect inflammation's positive contribution to the CTRA profile), and 8 genes related to Type I interferon activity and antibody synthesis (*IFI27, IFI30, IFI44L, IFIT1, IFIT3, IFITM1, IFITM3, JCHAIN*; each negatively weighted to reflect the inverse contribution of interferon and antibody activity to the CTRA profile). Removal of genes with SD<1 was required to facilitate convergence of maximum likelihood estimation in SAS PROC GENMOD. Two participants' samples yielded insufficient RNA for quantification and sequencing, leaving a total of 122 samples in the analytic sample.

In Model 1, we estimated the association of homophobic victimization with CTRA gene expression while adjusting for time (every 12 months). In Model 2 we additionally adjusted for age, identifying as Black (rather than Latino), BMI, current smoking status, weekly alcohol use, housing instability, being employed, use of only cannabis in the past 6 months, and other substance use in the past 6 months (Fredrickson et al., 2013). In order to show that associations did not stem from any confounding by individual differences in leukocyte subset distributions, we further expanded this analysis in Model 3 by controlling for the relative abundance of 7 gene transcripts encoding markers of major leukocyte subsets (*CD3D, CD19, CD4, CD8A, FCGR3A, NCAM1,* and *CD14*) (Fredrickson et al., 2013).

3. Results

Table 1 presents participant characteristics in the overall sample and stratified by race. The mean age for participants was 30 years (SD = 6.65). Sixty percent of participants (n=42) identified as Black, while the remaining 40% (n=28) identified as Latino. At baseline, less than half of participants were employed (39%), 40% reported any unstable housing in the past 6 months, 29% used only cannabis in the past 6 months, 43% used other drugs in the

past 6 months, 43% currently smoked cigarettes, and 12% reported having 4 or more drinks per week during the past 6 months. The mean BMI of the sample was 27.6 (SD = 6.11).

Table 2 reports the results for the three GEE models relating homophobic victimization to CTRA gene expression. Model 1 indicates that, without adjusting for sociodemographic or behavioral covariates, participants who reported experiencing high homophobic victimization had an 8.7-fold greater level of CTRA gene expression than those who did not report experiencing homophobic victimization in the past 12 months (B=3.11, 95% CI [1.09, 5.14], p=.003). Model 2 indicates that, after adjusting for race, age, BMI, smoking, alcohol use, housing instability, employment, and substance use, homophobic victimization was still associated with greater CTRA gene expression (B=1.92, 95% CI [0.49, 3.36], p=.009). In Model 3, homophobic victimization also remained significantly associated with a greater CTRA scores—by 3.1 fold (B=1.63, 95% CI [0.26, 3.00], p=.020) after additionally adjusting for 7 mRNA markers of major leukocyte subset abundance. Net of other effects (including homophobic victimization), those who identified as Black had greater CTRA scores than Latino participants in both Model 2 (B=1.27, 95% CI [0.39, 2.15], p=.005) and Model 3 (B=1.09, 95% CI [0.27, 1.91], p=.009). Figure 1 is derived from Model 3's estimates, and graphs the fold-difference in CTRA gene expression levels (with 95% confidence intervals) as a function of homophobic victimization, and as a function of identifying as Black.

4. Discussion

The present study elaborates on Minority Stress Theory by elucidating a link between minority stress experiences and the social genome in Black and Latino MSM. Among HIV-negative Black and Latino MSM, those who experienced homophobic victimization in the past 12 months showed significantly greater CTRA gene expression compared to those who did not report victimization. Experiences of homophobic victimization were associated with CTRA upregulation even after controlling for sociodemographic, behavioral, and biological variables previously shown to be associated with CTRA expression (e.g., race, BMI), and even after controlling for other potential confounders such as housing instability, employment status, and drug use (including tobacco smoking, heavy alcohol consumption, cannabis, and other substances). These findings advance our understanding of the biological responses to discrimination and violence in the life contexts of diverse young MSM who experience homophobic victimization.

The demonstrated association between homophobic victimization and CTRA gene expression is consistent with prior research examining social stressors such as social isolation and chronic interpersonal conflict (Murphy et al., 2013; Powell et al., 2013; Thames et al., 2019) and expands upon this literature by demonstrating that the unique social challenges experienced by racial minority MSM may also impact immune cell gene regulation. As such, CTRA gene regulation may represent one mechanistic pathway connecting social stressors to poor health as posited in the Minority Stress Theory and may contribute to disparities in chronic mental and physical health among LGBT populations. Surprisingly, employment status and housing instability were not significantly associated with CTRA while accounting for homophobic victimization, though markers of

socioeconomic status (SES) have shown be to be associated with CTRA expression in prior social genomics research (Levine et al., 2017; Powell et al., 2013). One explanation is that the socioeconomic variation in this sample may be too low to explain any differences in gene expression. Another possibility is that CTRA genes may more readily activate gene expression in the presence of direct violence and harassment in minority MSM than to structural challenges, particularly among Black MSM. Other research has shown that many sexual minorities with housing instability attribute their lack of housing to homophobia and fear of homophobia, so it is possible that participants perceive that homophobic victimization underlies much of their life stress (Choi et al., 2015; Durso and Gates, 2012). It is also important to note that homophobia is complex, encompassing passive (e.g., microaggressions) and structural stigma (e.g., discriminatory policy, negative media representation) in addition to the specific victimization experiences measured in this study (Hatzenbuehler, 2014; Herek, 2016; Li et al., 2017; Nadal et al., 2011). These additional indirect forms of homophobia may also impact health in sexual minorities via reductions in social capital, access to healthcare, psychosocial well-being, or economic/educational opportunity (Hatzenbuehler and Pachankis, 2016; Herek, 2016; Pachankis et al., 2015). Future investigation into structural stigma and CTRA is needed for a more comprehensive understanding of the complex impact of homophobia on pathogenesis in MSM and other sexual minorities.

Being of Black (rather than Latino) racial identity and experiencing homophobic victimization were simultaneously, significantly associated with greater CTRA levels in Models 2 and 3, suggesting that different life circumstances associated with race further contribute to CTRA gene expression (i.e., beyond the effects of homophobic victimization). This would be consistent with prior minority stress research indicating that among sexual minorities, being of racial minority status may have an additive impact on minority stress beyond that related to homophobia alone (Balsam et al., 2011; Bogart et al., 2017; Cyrus, 2017; Hightow-Weidman et al., 2011; Ramirez and Paz Galupo, 2019). Because the sample did not include a non-race/ethnicity-minority reference group (e.g., White MSM), we were not able to determine whether Latino MSM have higher CTRA expression compared to White MSM.

Findings from this study should be considered within the scope of its limitations. Due to the cross-sectional nature of this study, limited inferences about the temporal relationship between homophobic victimization and CTRA can be made. It is possible that participants with higher levels of CTRA expression are more susceptible to homophobic victimization, but this seems unlikely given that the self-reported victimization would have taken place prior to blood draws at each observation. These data were collected in one temporal, regional, and racial/ethnic setting, and so it is unclear how the observed relationships might pertain outside of Black and Latino MSM recently local to Los Angeles County. This study did not have available any measures of the upstream neuroendocrine mediators that might potentially drive CTRA gene expression (e.g., catecholamines, glucocorticoids, etc.) and assessment of those upstream mediators is another important topic for future research. It is important to note that the gene transcripts analyzed here were specified a priori as two functionally-defined sets, based on previous studies using them as representative examples of pro-inflammatory and Type I interferon-related genes (Cole, 2019). This study was not

designed or powered to discover statistically significant associations between individual gene transcripts and homophobic victimization, and so the present results should not be interpreted in terms of specific individual genes' function, but only in terms of the overall functional themes these gene sets share (i.e., involvement in inflammation or Type I interferon responses). Using additional biological assessment methods in future research in MSM may provide deeper insight into the relationship between homophobia and chronic disease pathogenesis.

Together, these findings suggest that CTRA transcriptome profiles may function as genomic markers of minority-related stress. Prior research has shown that homophobic victimization is linked to myriad psychiatric and psychosocial health problems including depression, substance use disorders, and suicidality (Bouris et al., 2016; Hatzenbuehler, 2014; Hatzenbuehler et al., 2008; Kosciw et al., 2018; Li et al., 2014; Li et al., 2018; Meyer, 2003). In turn, increased CTRA expression has been shown to be associated with depressive and anxiety-related symptoms and social-behavioral withdrawal (Miller et al., 2009; Pike and Irwin, 2006; Slavich and Irwin, 2014; Sloan et al., 2007). Behavioral scientists have long-debated whether the health consequences of hostile social environments are predominantly due to barriers to resources, restricted networks and social support, and limited economic opportunities, or due to the psychosocial experience of threat and stress (8). Social genomics research suggests that both access to social resources and subjective wellbeing contribute to health, and some data suggest these distinct psychosocial mechanisms involve distinct gene regulatory pathways (8). Based on our study's findings, it appears that increased CTRA gene expression may offer one biological explanation for the relationship between homophobic victimization and psychiatric and other chronic conditions experienced by MSM and MSM of color (Bouris et al., 2016; Hatzenbuehler, 2014; Hatzenbuehler et al., 2008; Kosciw et al., 2018; Li et al., 2014; Li et al., 2018; Meyer, 2003). Conversely, these social experiences could potentially influence individual social perception and sickness behavior via effects of CTRA on brain function (Dantzer et al., 2008; Eisenberger et al., 2010; Eisenberger et al., 2016). Further investigation is needed to longitudinally ascertain the degree to which CTRA mediates the association between minority stressors and health disparities in MSM. Evidence of CTRA's role in these processes would further support the need for translational, multilevel efforts to address minority stress, such as reducing stigma at the institutional level or attenuating CTRA through behavioral or pharmacologic intervention.

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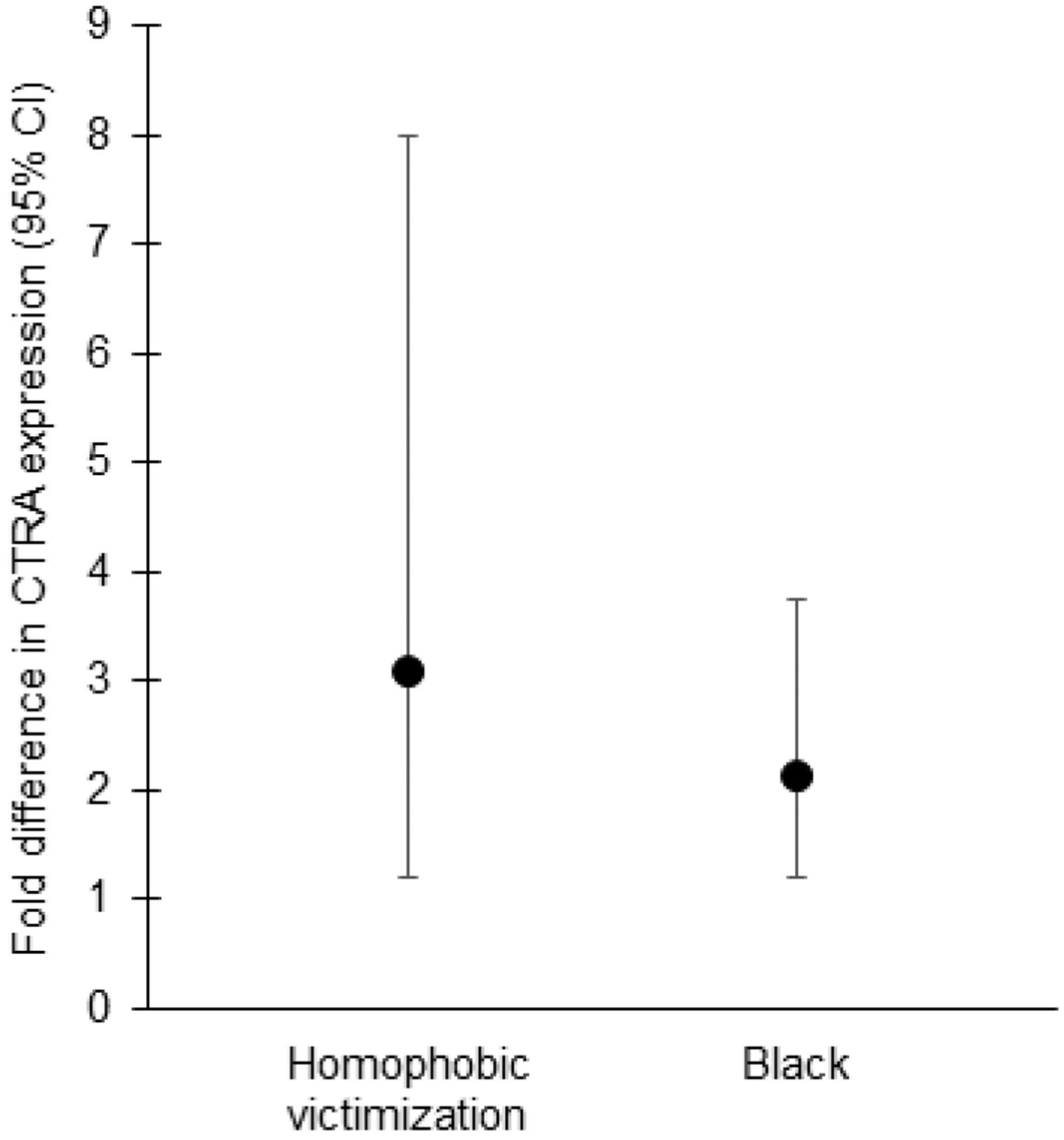

Figure 1.

Fold difference in CTRA gene expression among those who experienced homophobic victimization compared to those who did not, and among Black MSM compared to Latino MSM.

Note: Estimates were based on Model 3, which accounts for both homophobic victimization and race simultaneously. Error bars represent 95% confidence intervals.

Table 1.

Baseline demographics, homophobic victimization, substance use, and CTRA contrast scores (n=70)

	All participants (n = 70)		Black (n = 42)		Latino (n = 28)		p
	M	**SD**	**M**	**SD**	**M**	**SD**	
Age	29.84	6.65	30.43	6.45	28.96	6.95	.370
BMI	27.59	6.11	27.57	6.09	27.62	6.25	.971
	n	%	n	%	n	%	p
Homophobic victimization							.344
No	33	47.14	21	50.00	12	42.86	
Yes	37	52.86	21	50.00	16	57.14	
Current smoker							.324
No	40	57.14	22	52.38	18	64.29	
Yes	30	42.86	20	47.62	10	35.71	
Alcohol (past 6 months)							.328
≤ 3 drinks per week	59	84.29	37	88.10	22	78.57	
≥ 4 drinks per week	11	11.90	5	21.43	6	21.43	
Housing instability (past 6 months)							.921
No	42	60.00	25	59.52	17	60.71	
Yes	28	40.00	17	40.48	11	39.29	
Employed							.367
No	43	61.43	24	57.14	19	67.86	
Yes	27	38.57	18	42.86	9	32.14	
Substance use (past 6 months)							.841
None	20	28.57	13	30.95	7	25.00	
Cannabis use only	20	28.57	12	28.57	8	28.57	
Other substance use (past 6 months)	30	42.86	17	40.48	13	46.43	

Table 2.

Results of generalized estimating equation of homophobic victimization on CTRA contrast score (N_{obs}=122, $n_{persons}$=70)

	Model 1			Model 2			Model 3		
	B	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Intercept	0.05	−1.29, 1.38	.946	1.79	−1.34, 4.92	0.262	1.63	−3.87, 7.13	.561
Homophobic victimization	3.11	1.09, 5.14	.003	1.92	0.49, 3.36	0.009	1.63	0.26, 3.00	.020
Time (6 months)	1.98	0.20, 3.76	.030	1.04	0.02, −2.10	0.054	0.99	0.04, 1.94	.040
Age	-			−0.05	−0.13, 0.04	0.294	−0.02	−0.10, 0.06	.620
Black	-			1.27	0.39, 2.15	0.005	1.09	0.27, 1.91	.009
BMI	-			−0.06	−0.13 0.02	0.126	−0.02	−0.09, 0.05	.548
Smoking (current)	-			−0.19	−1.37, 0.99	0.753	−0.12	−1.27, 1.04	.843
Alcohol (≥ 4 drinks per week in past 6 months)	-			0.21	−1.09, 1.51	0.753	−0.01	−1.18, 1.15	.981
Housing instability (past 6 months)	-			−0.23	−1.42, 0.96	0.706	−0.24	−1.40, 0.91	.682
Employed (full or part time)	-			0.05	−1.17, 1.28	0.933	0.19	−0.98, 1.37	.747
Substance use									
Cannabis use only	-			0.02	−1.57, 1.62	0.976	−0.02	−1.51, 1.47	.974
Other substance use	-			0.71	−0.66, 2.08	0.312	0.58	−0.64, 1.81	.352
Genes for major leukocyte subset									
CD3D	-			-			0.20	−1.21, 1.61	.782
CD19	-			-			−1.01	−1.89, −0.13	.025
CD4	-			-			−0.24	−1.66, 1.18	.743
CD8A	-			-			0.03	−1.06, 1.11	.960
FCGR3A	-			-			0.31	−0.44, 1.06	.416
NCAM1	-			-			0.38	−0.52, 1.28	.407
CD14	-			-			0.01	−0.88, 0.90	.987

Note: The dependent variable, CTRA expression, is on a $\log_2$ scale.