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ORIGINAL ARTICLE

Structural Determinants of Health and Markers of Immune Activation and Systemic Inflammation in Sexual Minority Men With and Without HIV

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Abstract Among sexual minority men (SMM), HIV and use of stimulants such as methamphetamine are linked with immune activation and systemic inflammation. Throughout the COVID-19 pandemic, SMM encountered financial challenges and structural obstacles that might have uniquely contributed to immune dysregulation and systemic inflammation, beyond the impacts of HIV and stimulant use. Between August 2020 and February 2022, 72 SMM with and without HIV residing in South Florida enrolled in a COVID-19 prospective cohort study. Multiple linear regression analyses examined unemployment, homelessness, and history of arrest as structural correlates of soluble markers of immune activation (i.e., sCD14 and sCD163) and inflammation (i.e., sTNF-α receptors I and II) at baseline after adjusting for HIV status, stimulant use, and recent SARS-CoV-2 infection. Enrolled participants were predominantly Latino (59%), gay-identified (85%), and with a mean age of 38 (SD, 12) years with approximately one-third (38%) of participants living with HIV. After adjusting for HIV status, SARS-CoV-2 infection, and recent stimulant use, unemployment independently predicted higher levels of sCD163 ($\beta = 0.24$, $p = 0.04$) and sTNF-α receptor I ($\beta = 0.26$, $p = 0.02$). Homelessness ($\beta = 0.25$, $p = 0.02$) and history of arrest ($\beta = 0.24$, $p = 0.04$) independently predicted higher levels of sCD14 after adjusting for HIV status, SARS-CoV-2 infection, and recent stimulant use. Independent associations exist between structural barriers and immune activation and systemic inflammation in SMM with and without HIV. Future longitudinal research should

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further elucidate complex bio-behavioral mechanisms linking structural factors with immune activation and inflammation.

Keywords COVID-19 · HIV · Homelessness · Inflammation · Stimulant and unemployment

Introduction

In people living with HIV, immune activation and systemic inflammation play crucial roles in the pathogenesis and progression of the HIV disease [1]. HIV triggers a cascade of immune responses, resulting in chronic immune activation and inflammation marked by heightened activity of innate and adaptive immune cells [2]. As the virus replicates and spreads within the cells, it triggers the secretion of pro-inflammatory mediators such as interleukine-6 (IL-6) as well as a variety of soluble markers associated with systemic inflammation and immune dysregulation which will eventually lead to a chronic inflammatory status [2].

Strong evidence suggests that levels of soluble markers of innate immunity released from monocytes and macrophages upon activation, soluble CD14 (sCD14) and soluble CD163 (sCD163) may predict HIV disease progression and severity of immune dysregulation as well as the morbidity and mortality among treated people with HIV (PWH) [3]. Similarly, tumor necrosis factor alpha (TNF-α), a pro-inflammatory mediator involved in immunologic responses to infection, cell proliferation, and apoptosis (programmed cell death), along with TNF-α receptors I and II, play significant roles in regulating immune responses by contributing to immune activation and sustained inflammation. [4]. Markedly, TNF-α and its receptors, TNF-α receptors I and II, are extensively recognized for their involvement in regulating HIV disease progression and subsequent HIV-associated comorbidities by modulating various intricate signaling pathways. These pathways can contribute to endothelial dysfunction, dysregulated lipid metabolism, and subsequent atherosclerosis [5], all of which are recognized risk factors for chronic disorders such as cardiovascular disease [6].

Although antiretroviral therapy (ART) improves immune function and when used consistently, eliminates the risk of AIDS-related morbidity and mortality, HIV persists in lymphoid tissues while perpetually replicating even after long-term suppressive use of ART [7]. Among treated PWH, even despite a suppressed level of viral load, markers of systemic inflammation and immune dysfunction remain elevated [8]. Activation of several cascading immune processes related to a low-level yet persistent HIV replication even when a treated person is virologically suppressed is found to be the main factor responsible for the subsequent higher rates of chronic inflammation and immune dysregulation as well as poorer health outcomes among people living with HIV [9].

In addition to HIV, the use of stimulants such as methamphetamine (meth) is further associated with immune activation and systemic inflammation. Among sexual minority men (SMM), research indicates that use of meth and other stimulants can be up to 20 times more prevalent than their heterosexual peers [10]. Meth use is associated with increased rates of sexual risk behavior, HIV transmission, delayed diagnosis and initiation of therapy, inadequate adherence to ART, and higher levels of HIV viral load [11]. Recent stimulant use such as meth has been further associated with elevated levels of inflammatory and pro-inflammatory cytokines such as IL-6 and TNF-α in plasma, intestine, and rectal mucosa [12]. Among SMM with untreated HIV, meth use is additionally linked to CD4 + T-cell depletion, immune activation, systemic inflammation, and the promotion of HIV entry to cells further contributing to HIV disease progression [13].

Ultimately, the effects of stimulant use such as meth have been extensively studied in treated SMM living with HIV. Among SMM with HIV, studies have found that stimulant use such as meth could further intensify immune activation, immune exhaustion, and chronic systemic inflammation [14]. One cross-sectional study in treated SMM with undetectable viral load observed significant associations between meth use and increased spontaneous CD4 + and CD8 + T-cell proliferation as well as T-cell exhaustion compared to non-users [14]. A more recent study has further highlighted the associations between recent biologically confirmed stimulant use with higher levels of sCD14 among treated virally suppressed meth using SMM with HIV [15]. Altogether, findings suggest that among SMM with HIV, stimulant use leads to increased chronic inflammation and immune dysfunction, exceeding the impact of HIV alone.

Alongside the concurrent effects of HIV and stimulant use, immune responses associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection may additionally influence markers of immune activation and systemic inflammation. A recent study found that SARS-CoV-2 infection may activate circulating monocytes and macrophages while increasing levels of sCD14 and sCD163 in plasma in patients with severe disease compared to those with mild or moderate disease [16]. Another study demonstrated that TNF-α + CD4 + T cells may be the predominant population of leukocytes detected between 5 days to 4 months post SARS-CoV-2 infection [17]. TNF-α + CD4 + T cells will eventually bind to TNF-α RI and TNF-α RII which may then be released into blood circulation as soluble forms of TNF-α receptors [18]. Higher levels of soluble TNF-α RI and TNF-α RII are found to be associated with higher rates of mortality in COVID-19 patients indicating significantly higher rates of systemic inflammation and immune dysregulation [18].

Despite a wealth of research surrounding interactions of HIV, stimulant use, and SARS CoV-2, previous studies have not adequately investigated the impacts of macro-level structural determinants that could either directly or indirectly fuel systemic inflammation and immune dysregulation in SMM. In general population, unemployment and financial hardship are commonly associated with altered immune responses such as increased levels of IL-6 and higher rates of chronic disorders including cardiovascular disease such as heart attack and heart failure [19]. Similarly, people experiencing homelessness are additionally found to be at increased risk for new health problems such as diabetes and exacerbating existing ones such as several chronic diseases including hypertension [20]. Housing instability and homelessness may be further associated with overcrowding and frequent moves which are found to be correlated with negative mental and physical health outcomes as well as reduced access to quality health care [20]. Finally, indices of criminal justice involvement including a history of arrest are associated with negative mental and psychophysiological health [21], lower self-reported health [22], and accelerated biological aging [23] marked by disruptions in DNA methylation patterns and shorter telomere length.

This cross-sectional study examined whether structural factors such as financial hardship and homelessness are independently associated with immune activation and systemic inflammation in SMM with and without HIV in the era of COVID-19. As shown in Fig. 1, we investigated the associations of unemployment, homelessness, and history of arrest with markers of monocyte activation (i.e., sCD14 and sCD163) and inflammation (i.e., TNF-α receptors I and II) in SMM. Because stimulant use, HIV, and SARS-CoV-2 infection have important implications for immune activation and dysfunction, these were included as covariates to accurately estimate the independent influence of structural factors on markers of immune activation and inflammation.

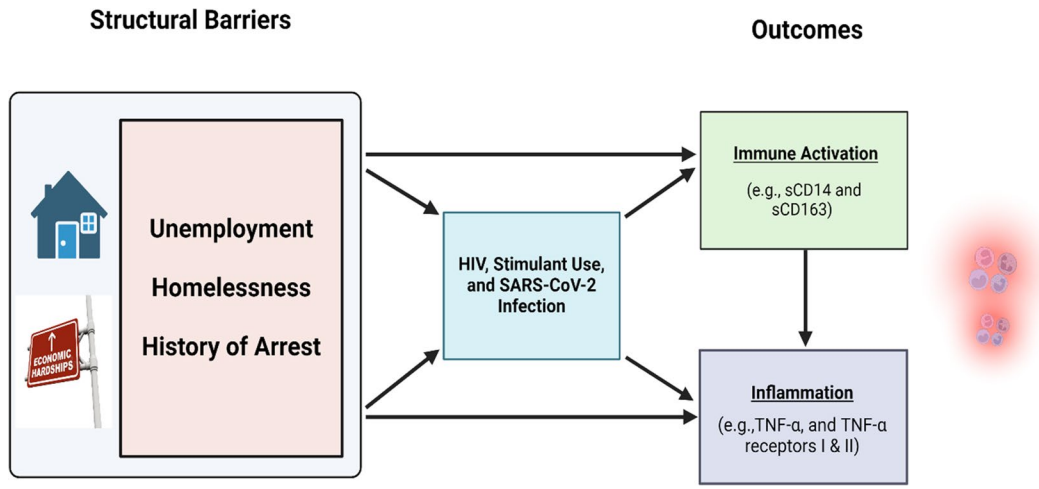

Fig. 1 Conceptual model of the impacts of structural barriers and immune activation and inflammation

Methods

From August 2020 to February 2022, SMM in South Florida were enrolled in a 6-month prospective cohort study. Participants were recruited mainly via advertisements on social media applications such as Grindr and Scruff. Eligibility criteria included (1) being a cisgender male, (2) being 18 years old and older, (3) reporting anal sex with at least one cisgender male within the prior year, and (4) demonstrating English language proficiency. The present study includes baseline data using self-reported questionnaires and plasma biospecimens analyses results. Participants received $25 upon completion of the baseline survey and an additional $50 upon providing biospecimens during their in-person visit to the on-site laboratory. Participants who did not provide a blood draw at baseline were excluded from the study. All study activities were approved by the University of Miami Institutional Review Board. Each participant provided an in-person written informed consent prior to completing the online questionnaire and the laboratory visit. During the laboratory visit, participants provided a nasal swab and peripheral venous blood samples to screen for SARS-CoV-2 infection and measure soluble markers of immune activation and systemic inflammation.

Measures

Sociodemographic factors – sociodemographic factors were obtained using items on age, sexual identity, race and ethnicity, level of education, and income.

Structural factors – structural factors were measured using surveys that included questions on participants' unemployment status, being homeless (identified as residing in a homeless shelter within the previous 12 months), and a lifetime history of arrest at baseline.

HIV status – HIV status was primarily self-reported in baseline survey. If a participant reported an HIV negative status, HIV status was confirmed via Oraquick ADVANCE® Rapid HIV test (Roche) during the in-person visit. Blood samples were additionally used to measure HIV viral load (VL) if a participant reported being HIV positive. VL was classified as "detectable" if exceeding 40 copies per milliliter.

Stimulant use – recent stimulant use within the past three months was defined as either self-reported use of stimulants or a reactive iCup ABBOTT® urine test (Redwood Biotech, Inc.; Santa Rosa, CA). The iCup ABBOTT® on-site screening device was used during the in-person visit to detect metabolites that reflect use of stimulants within the past 72 h of the visit.

SARS-CoV-2 infection – nasal swabs were used to conduct polymerase chain reaction (PCR) for SARS-CoV-2 RNA. An enzyme-linked immunoassay tested for the presence of nucleocapsid immunoglobulin G (IgG) antibodies. Testing for SARS-CoV-2 nucleocapsid IgG is particularly beneficial because it does not cross-react with antibodies similarly produced by COVID-19 vaccination. Participants who tested positive for SARS-CoV-2 RNA or nucleocapsid IgG antibody were categorized as having been infected with SARS-CoV-2.

Soluble markers of immune activation and inflammation – soluble markers of immune activation including sCD14 and sCD163 were measured in plasma using Luminex bead–based multiplex analysis, with a limit of detection between 3.2 and 3122 ng/ml. Beads (carboxylated microspheres) were procured from Luminex Corporation, USA. Markers of systemic inflammation including TNF-α RI and TNF-α RII were measured in plasma using ELISA immunoassays, with a limit of detection between 1.4 and 1128 ng/ml using a plate-based assay technique designed for detecting and quantifying soluble markers in plasma.

Statistical Analysis

Analyses were conducted with R software version 4.2.1 (R Core Team, 2020). We primarily conducted zero-order correlations to examine bivariate associations among soluble markers of immune activation and inflammation with structural factors (i.e., unemployment, homelessness, and history of arrest), stimulant use, and HIV status. Zero-order Pearson correlation analysis was used for continuous variables and zero-order Spearman correlation analysis was used for categorical and dichotomous variables. All measures were normally distributed except for sCD163 which was $\log_{10}$ transformed. Guided by bivariate analyses, we conducted 12 multiple linear regression analyses examining the associations of structural factors with plasma markers of immune activation and systemic inflammation while controlling for stimulant use, HIV status, and SARS-CoV-2 infection. To avoid the issue of multiple testing and decreasing the likelihood of finding statistically significant results by chance alone, all significant p values were additionally adjusted for false discovery rate using the Benjamini–Hochberg

procedure [24]. Specifically, we ranked the p values of all models from smallest to largest, adjusted each p value based on its rank and the total number of tests, and subsequently compared the adjusted p values to the chosen significance threshold ($\alpha = 0.05$) to control type I errors and maintain the validity of study findings.

Results

As shown in Table 1, enrolled participants ($n = 72$) were predominantly Latino (59%), gay-identified (85%), with a mean age of 38 (SD, 12) years. Approximately 39% of participants were living with HIV and 46% were classified as using stimulants. Regarding structural factors, a significant proportion of respondents (approximately 43%) reported being unemployed, 7% reported being in a homeless shelter within the previous year, and almost one-third (32%) reported a history of arrest.

As shown in Table 2, we primarily examined bivariate correlations among structural factors and soluble markers of inflammation and immune dysregulation. Unemployment was directly correlated with significantly higher levels of TNFα-RI ($r = 0.31$, $p < 0.01$) and TNFα-RII ($r = 0.14$, $p < 0.05$). Greater rates of homelessness ($r = 0.27$, $p < 0.05$) and a history of arrest ($r = 0.33$, $p < 0.01$) were directly correlated with significantly higher sCD14 levels.

Table 1 Stimulant use by HIV group differences and sociodemographic, structural, and other characteristics, $n = 72$

	STIM-HIV − ($n = 23$)	STIM + HIV − ($n = 20$)	STIM-HIV + ($n = 14$)	STIM + HIV + ($n = 15$)	Overall ($n = 72$)	P*
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
Race/ethnicity	6 (27)	4 (20)	3 (20)	5 (33)	18 (25)	0.16
Non-Hispanic White	2 (8)	1 (5)	4 (32)	3 (20)	10 (15)	
Non-Hispanic Black	15 (64)	15 (75)	7 (47)	6 (40)	43 (59)	
Hispanic/Latino	0 (0)	0 (0)	0 (0)	1 (7)	1 (1)	
Other						
Level of education	2 (8)	2 (10)	1 (7)	0 (0)	5 (7)	0.90
High school or less	8 (35)	4 (20)	4 (27)	5 (33)	22 (29)	
Some college	10 (43)	11 (55)	6 (40)	7 (53)	36 (48)	
College degree	3 (12)	3 (15)	4 (27)	2 (13)	12 (16)	
Graduate degree						
Employment status						
Employed	27 (38)	15 (27)	16 (22)	11 (14)	69 (57)	**0.03**
Unemployed	4 (13)	11 (31)	7 (13)	9 (44)	31 (43)	
Annual income < $25 K	8 (35)	4 (20)	5 (33)	4 (32)	21 (31)	
$25–$49 K	6 (24)	10 (54)	5 (33)	6 (40)	27 (37)	0.53
> $50 K	9 (36)	4 (19)	5 (33)	4 (27)	22 (29)	
Homeless shelter						
Yes	1 (1)	2 (50)	1 (25)	1 (25)	5 (7)	**0.04**
No	23 (34)	18 (27)	13 (19)	13 (21)	67 (93)	
History of arrest						
Yes	3 (13)	5 (22)	7 (31)	8 (35)	23 (32)	0.06
No	20 (41)	15 (31)	7 (14)	7 (14)	49 (68)	
SARS-CoV-2 infection						
Yes	5 (24)	7 (35)	5 (40)	2 (13)	19 (28)	0.19
No	15 (64)	11 (55)	6 (40)	13 (87)	45 (61)	
Missing	3 (12)	2 (10)	3 (20)	0 (0)	8 (11)	
	***M* (SD)**	***M* (SD)**	***M* (SD)**	***M* (SD)**	***M* (SD)**	
Age	**35 (13)**	**34(10)**	**38 (12)**	**46 (11)**	**38 (12)**	**0.03**

*p-values for categorical variables were calculated using Fisher's exact tests. p-values for continuous variables were calculated using one-way analysis of variance (ANOVA) F-tests

Table 2 Bivariate correlations of structural factors and soluble markers of immune activation and inflammation ($n=72$)

	1	2	3	4	5	6	7	8	9
1. sCD14	–								
2. sCD163	0.19	–							
3. TNFα-RI	0.21	0.34**	–						
4. TNFα-RII	0.48***	0.46***	0.79***	–					
5. Unemployment	0.09	0.19	0.31**	0.14*	–				
6. Homelessness	0.27*	−0.05	0.13	0.21	−0.00	–			
7. History of arrest	0.33**	−0.01	0.13	0.22	0.05	0.14	–		
8. HIV +	0.30*	0.00	0.19	0.11	0.12	0.12	0.32***	–	
9. Stimulant use	0.27*	0.05	0.04	0.08	0.11	0.13	0.11	0.05	–
N (%)	–	–	–	–	60 (57)	7 (7)	34 (32)	41 (39)	35 (49)
Mean	978.87	5.80	1225.30	1594.18	–	–	–	–	–
SD	249.70	0.26	366.55	721.30	–	–	–	–	–
Skewness	0.56	−0.19	2.12	1.96	–	–	–	–	–
Kurtosis	1.12	0.42	5.40	4.78	–	–	–	–	–

sCD14 soluble CD14, *sCD163* soluble CD163, *TNFα*-RI tumor necrosis factor alpha receptor I, *TNFα-RII* tumor necrosis factor alpha receptor II, *SD* standard deviation. sCD163 was log10 transformed. Analyses were zero-order Pearson correlations for continuous variables and zero-order Spearman correlations for continuous and dichotomous variables. *$p<.05$, **$p<.01$, ***$p<.001$

Additionally, multiple linear regression analyses examined the direct associations of structural factors with soluble markers of immune activation and inflammation (Table 3). After adjusting for stimulant use, HIV status, and SARS-CoV-2 infection, greater unemployment was independently associated with higher levels of sCD163 ($\beta=0.24$; $p=0.04$) and TNFα-RI ($\beta=0.27$; $p=0.02$). Homelessness ($\beta=0.27$; $p=0.02$) and history of arrest ($\beta=0.24$; $p=0.04$) were independently associated with higher values of sCD14. Boxplots of the associations of structural barriers with these outcomes are provided in Fig. 2. It is worth noting that the first model captured 4% of the variance ($R^2=0.04$) in sCD163 and 8% of the variance ($R^2=0.08$) in TNFα-RI. The second model explained 10% of the variance ($R^2=0.10$) in sCD14 and the third model accounted for 12% of the variance ($R^2=0.12$) in sCD14.

Table 3 Associations of structural factors with soluble markers of immune activation and inflammation ($n=72$)

Predictors	Outcomes	R^2	β	SE	95% CI	p
Unemployment	sCD14	0.09	0.07	0.11	(−0.15, 0.30)	0.53
	sCD163	0.04	0.24	0.12	(0.00, 0.48)	0.04*
	TNFα-RI	0.08	0.27	0.12	(0.03, 0.50)	0.02*
	TNFα-RII	0.02	0.22	0.12	(−0.02, 0.45)	0.07
Homelessness	sCD14	0.10	0.27	0.12	(0.03, 0.50)	0.02*
	sCD163	0.01	−0.18	0.13	(−0.45, 0.07)	0.16
	TNFα-RI	0.09	0.04	0.13	(−0.22, 0.30)	0.75
	TNFα-RII	0.08	0.13	0.13	(−0.13, 0.39)	0.31
History of arrest	sCD14	0.12	0.24	0.12	(0.00, 0.47)	0.04*
	sCD163	0.01	−0.04	0.13	(−0.30, 0.22)	0.77
	TNFα-RI	0.02	0.06	0.13	(−0.20, 0.32)	0.67
	TNFα-RII	0.04	0.16	0.13	(−0.09, 0.42)	0.20

All significant *p*-values were additionally adjusted for false discovery rate using the Benjamini–Hochberg procedure. *sCD14* soluble CD14, *sCD163* soluble CD163, *TNFα-RI* tumor necrosis factor-alpha receptor 1, *TNFα-RII* tumor necrosis factor-alpha receptor 2. sCD163 was log10 transformed. All models were adjusted for HIV status, stimulant use, and SARS-CoV-2 infection. *$p<.05$

Discussion

This study examined the independent associations of structural factors including unemployment, homelessness, and history of arrest with markers of immune activation and systemic inflammation in SMM with and without HIV. Findings demonstrated that structural determinants were independently associated with clinically relevant measures of monocyte activation and systemic inflammation after adjusting for stimulant use, HIV status, and SARS-CoV-2 infection. Although results are aligned with the extant knowledge regarding associations between structural factors such as economic

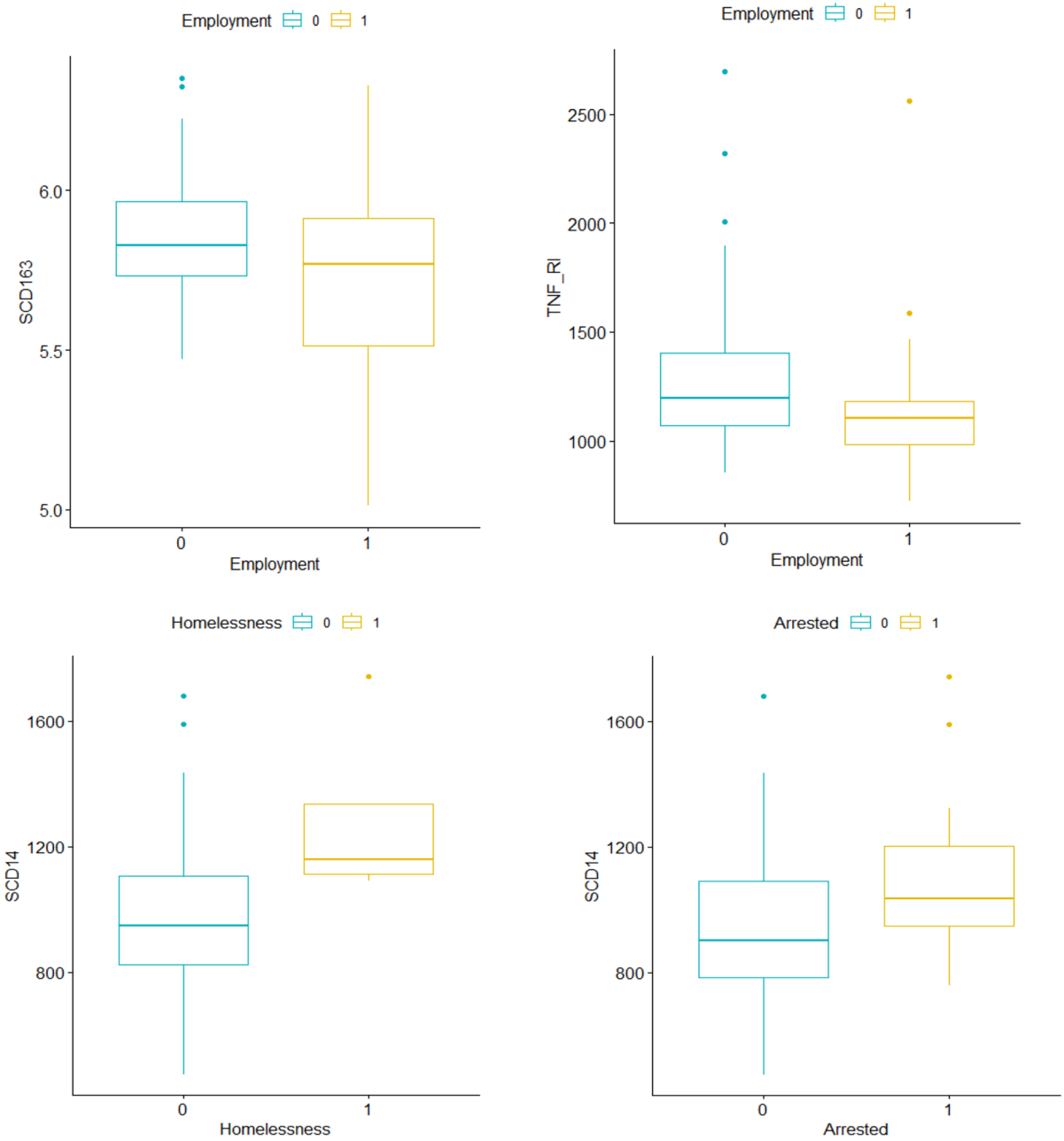

Fig. 2 Box plots of associations between structural factors and markers of immune activation and systemic inflammation

hardship and housing instability with markers of immune dysregulation and dysfunction, there has been limited research investigating immunologic consequences of exposure to structural adversities among SMM. Existing research indicate that sexual minority individuals encounter a multitude of systemic and structural factors that lead them to work in industries with high rates of labor market discrimination and employment instability [25]. Particularly during the COVID-19 pandemic where employment insecurity and financial hardship were widespread, this may have amplified the influence of other structural vulnerabilities such as decreased social status and housing instability which have been previously associated with sexual risk behavior, substance use, and involvement with the law enforcement system in SMM [26]. Despite higher rates of unemployment and housing instability, however, current literature lacks specific studies that link SMM with substance use, exposure to structural adversities, immune activation and dysfunction, and negative mental and physical health outcomes.

Among general population, an expanding body of literature has provided compelling evidence that social and structural adversities have the potential to induce a state of low-grade inflammation along with a compromised immune system in individuals facing macro-level adversities such as employment-based discrimination and unstable economic conditions. Interestingly, researchers have demonstrated the deleterious effects of unequal social status as well as harassment during social interactions on T cells, natural killer cells, and gene expression pathways associated with negative health outcome in macaques [27]. Among humans, structural factors such as unemployment and lack of stable housing present multitude of ways to continuously disrupt bodily homeostasis which may further activate hypothalamus–pituitary–adrenal axis (HPA) and autonomous nervous system (ANS) while inducing a chronic hyperactivated inflammatory status [28, 29]. Studies further show that unemployment and housing instabilities are commonly associated with lower rates of having healthcare insurance and preventive care as well as delays in necessary care with higher rates of chronic disorders including atherosclerosis and cardiovascular disease such as hypertension and heart attack. Substance use, including stimulant use such as meth, is additionally associated with higher rates of arrest and incarceration [30]. Despite our efforts to locate studies investigating the association between any types of interactions with the law enforcement system and markers of immune activation and inflammation, we were unable to find relevant research in this area. A point that further underscores the need for future mechanistic studies that aim to explore pathways between structural vulnerabilities and altered immune responses related to negative mental and physical health outcomes.

Our findings also build upon prior research documenting that a specific type of stress—sexual minority stress—may further fuel inflammation, immune dysregulation, and cellular aging in SMM. The minority stress model [31] proposes that sexual minority individuals experience unique forms of social stigma such as discrimination, prejudice, and isolation that may have physical health consequences [32]. Recent studies with SMM have documented that indices of greater sexual minority stress are associated with leukocyte mRNA gene expression patterns relevant to greater inflammation and altered DNA methylation patterns indicative of accelerated cellular aging [33, 34]. It may also be plausible that experiences of stigma and discrimination influence determinants such as unemployment and homelessness examined in the present study. Moreover, structural determinants such as unemployment may profoundly influence stimulant use by fostering environments conducive to substance use. Unemployment fosters stress as well as economic insecurity, and social isolation, prompting individuals to seek solace in substance use such as stimulants as a coping mechanism. Limited job prospects exacerbate feelings of hopelessness and may push individuals towards substance use to alleviate distress. Additionally, unemployment disrupts social networks, increasing exposure to peer influences that normalize substance use. Financial constraints resulting from unemployment further impede access to healthcare and support services, compounding vulnerability to stimulant use disorders. These structural determinants intersect with poverty, housing instability, and systemic inequalities, forming a

complex nexus of risk factors. Further longitudinal research is needed to examine the complex interplay of structural determinants, sexual minority stress, and stimulant use with inflammation and immune dysregulation among SMM.

Finally, addressing these issues necessitates comprehensive interventions that tackle social, economic, and environmental factors to effectively mitigate the burden of stimulant use within communities. Study findings underscore the importance of adapting existing methods and evidence-based interventions that target structural factors and integrating them with evidence-based individual-level interventions. By combining efforts at both the structural and individual levels, we can maximize the effectiveness of interventions and create a more inclusive and sustainable solution to the challenges posed by structural and behavioral factors. While establishing labor market policies that promote job security, fair wages, and worker protection is critical, offering employment skill development programs to provide relevant and updated training to help individuals adapt to changing job market demands can be a beneficial added section to an individual-level behavioral intervention for HIV and stimulant use. Finally, it may be beneficial to integrate individual-level interventions with assistance programs specifically designed to support individuals who have been involved with the law enforcement system to facilitate their successful reintegration into employment. By combining targeted support services and employment assistance, we may assist individuals overcome the barriers they may face due to their past involvement with the law enforcement system and support their transition into stable and meaningful employment opportunities. In addition, individual-level interventions can be used as a platform to provide emergency supportive housing. Emergency supportive housing refers to temporary housing options designed to provide shelter and support for individuals experiencing housing instability or homelessness. It combines elements of emergency shelter and supportive services to offer a more comprehensive approach to addressing homelessness.

It is important to additionally underscore the limitations of this cross-sectional study. Although this study is among the first to investigate the associations of some structural factors with markers of immune activation and inflammation, we are unable to establish causality since data was captured at a single time point, making it challenging to determine the temporal sequence of events. Additionally, the challenges posed by the COVID-19 pandemic, including safety concerns, public health restrictions, reduced access to in site laboratory facilities, and competing demands on participants' time collectively contributed to our inability to recruit more than 72 participants during the study period which may have impacted the study's validity, generalizability, and statistical power. Moreover, while our results were obtained after adjusting for stimulant use, it is plausible that many of these structural factors may be serving as proxies for a severe stimulant use disorder. Stimulant use disorder—marked by a pattern of behaviors indicating impaired control over stimulant use, continued use despite negative consequences, and physiological dependence on the stimulants—can significantly impact various aspects of an individual's life, including employment, housing stability, and involvement with the criminal justice system by leading to difficulties in maintaining stable employment and straining relationships with family and friends that may have led to social isolation, lack of support, engaging in illegal activities to obtain drugs or support drug habits, increasing the likelihood of arrest and other legal consequences [35]. Future research should prioritize longitudinal studies to replicate and expand our understanding of current findings. In addition, exploring a more comprehensive panel of systemic and structural determinants may further investigate the interplay between different levels of structural factors while elucidating the complex web of influences on immune and biological responses related to health among SMM with and without HIV.

Taken together, these findings suggest that structural factors are important indicators of higher level disadvantage that may exacerbate immune responses in SMM, regardless of HIV status and stimulant use. By recognizing the influence of structural factors such as economic and housing hardship as well as systemic barriers such as involvement in law enforcement services we can develop more comprehensive approaches and multi-level interventions to improve health outcomes and reduce disparities among SMM with and without HIV.

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