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Perceived discrimination predicts elevated biological markers of inflammation among sexual minority adults

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Abstract Sexual minority (SM) adults (those who are lesbian, gay, or bisexual) consistently report more health problems compared to heterosexuals, and they tend to experience excess social stress. Although numerous studies have established links between social stress and clinical outcomes in SM adults, few studies have examined biological factors that may help explain how social stress leads to health disparities among SM adults. We used data from the Midlife in the United States Study (MIDUS) to examine whether two inflammatory markers that have been commonly associated with social stress—C-reactive protein (CRP) and interleukin-6 (IL-6)—differed by sexual orientation and whether any differences were explained by perceptions of discrimination. Participants self-identified as heterosexual ($n = 1956$) or lesbian, gay, or bisexual ($n = 81$). After controlling for age, gender, race, and education, SM individuals had higher CRP and IL-6 than heterosexuals on average and these differences were partially explained by perceptions of discrimination. Implications for inflammatory pathways as mechanisms related to SM health disparities and discrimination are discussed.

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Introduction

Sexual minority (SM) adults (those who identify as lesbian, gay, or bisexual) in the United States consistently report more mental and physical health problems compared to their heterosexual counterparts, including greater rates of depression, cardiovascular disease, and chronic pain (e.g., Fredriksen-Goldsen et al., 2013, 2017; Meyer, 1995, 2003). Minority stress theory proposes that the health disparities observed among SM adults are a direct result of their increased exposure to stigma and discrimination or social stress (Frost et al., 2015; Meyer, 1995, 2003). In a recent survey, a majority of SM adults in the United States say they have personally experienced slurs (60%) and offensive comments (51%) in their day-to-day lives specifically about their sexual orientation (Harvard School of Public Health, 2017). These negative experiences, especially when they occur repeatedly, can create social stress for SM individuals and can lead to the development of high blood pressure and depression, among other serious health conditions (Everett & Mollborn, 2013; Frost et al., 2015; Meyer, 2003). A wealth of studies have established links between social stress and specific clinical outcomes in SM adults (e.g., asthma, diabetes; for a review, see Lick et al., 2013); however, few studies have examined biological factors that may help explain how social stress leads to health disparities among SM adults. A better understanding of mechanisms related to SM health disparities would help identify potential causal pathways of risk and potentially illuminate novel intervention approaches.

Social stress, circulating markers of inflammation, and health

Broadly defined, social stress is stress that comes from an individual's social environment and can contribute to the development of adverse health outcomes and disease (Miller et al., 2009). Social stress can stem from a variety of situations, such as difficult interactions with family and friends (Kiecolt-Glaser et al., 2010), rejection from others (Dickerson & Kemeny, 2004), and perceptions of low status within a group or community (McEwen & Gianaros, 2010). SM individuals tend to experience excess social stress compared to heterosexuals as a result of their minority status. Minority stress can be thought of as a special type of social stress that tends to be chronic (Meyer, 1995, 2003). SM individuals often face stress from social environments that are unsupportive of them. Blatant forms of social stress can include exposure to antigay violence, physical and verbal assault, unfair treatment in the workplace, and family estrangement (Herek & McLemore, 2013). Importantly, even in situations when SM individuals are not directly mistreated, worry, rumination, and vigilance against perceived or anticipated social stress can maintain perceived stress and stress responses (Smyth et al., 2013). Expectations of rejection and negative reactions from others can cause SM individuals to be extra cautious and alert in social interactions, which uses a considerable amount of resources and energy (Crocker et al., 1998). In addition, more subtle forms of social stress for SM individuals relate to identity concealment and internalized homophobia. Some SM individuals may feel pressure to conceal their identity to avoid judgement and unsafe situations and others may experience internalized homophobia, or negative beliefs about themselves because of evaluations from society (Herek & McLemore, 2013). Thus, through both direct exposure and through indirect pathways, social stress can accrue over time. This may be particularly observable among older SM adults because of the accumulation of social stress over a lifetime (Fredriksen-Goldsen et al., 2015; Grossman et al., 2001).

A robust literature from the field of psychoneuroimmunology indicates that levels of peripheral inflammation help connect social stress and poor health (Marsland et al., 2017; Miller et al., 2009; Segerstrom & Miller, 2004; Steptoe et al., 2007). Social stress experienced repeatedly and over time can heighten signaling of inflammatory markers and induce chronically elevated inflammation in people's bodies (Bennett et al., 2013; Glaser & Kiecolt-Glaser, 2005; Miller et al., 2009). C-reactive protein (CRP) and interleukin-6 (IL-6) are markers of peripheral inflammation that have been most frequently linked with social stress and allostatic load, or the wear and tear on the body from overexposure to social stress (for reviews, see Marsland et al., 2017; Steptoe et al., 2007). Elevated concentrations of the inflammatory biomarkers CRP and IL-6 have been associated with the onset and progression of a wide range of diseases, such as cardiovascular disease (e.g., Stoner et al., 2013), diabetes mellitus (e.g., Pradhan et al., 2001), and certain types of cancers (e.g., Hodge et al., 2005). Thus, chronic social stress, including the minority stress experienced by SM individuals, may predispose an individual toward upregulation of inflammation, as indexed by CRP and IL-6, thereby increasing risk for adverse health outcomes and disease.

Perceived discrimination and circulating markers of inflammation

A few studies have examined associations of self-reported experiences of discrimination with markers of inflammation in racial minority individuals. A study by Doyle and Molix (2014) found that perceived day-to-day discrimination was directly related to elevated levels of serum IL-6 and CRP in African American men and women who participated in the Midlife in the United States Study (MIDUS). In another study, older African American adults who experienced more daily discrimination were more likely to show higher levels of CRP (Lewis et al., 2010), and these results held after accounting for other factors (e.g., age, gender, income) that often relate to inflammatory markers (O'Connor et al., 2009). Such findings add support to the minority stress perspective (Meyer, 2003) that people who experience greater prejudice and discrimination may show evidence of higher inflammation because of unique and frequent stress. Accordingly, not only may sexual minorities evidence higher levels of inflammatory markers compared to heterosexuals but also their reports of exposure to prejudice and discrimination may link specifically to their levels of peripheral inflammation (see Fig. 1 for a conceptual model underlying our hypotheses and approach and the pathways that may help to explain differences in health between heterosexual and SM adults).

Results from a study by Mays et al. (2018) found that bisexual men showed the highest allostatic load levels (a multi-systemic indicator of physiological 'wear and tear' from chronic stress and/or cumulative strain) and gay men showed the lowest allostatic load levels when compared to each other and to heterosexual men; women showed no differences in allostatic load by sexual orientation. However, this same study did not include and/or directly test associations between allostatic load and SM individuals' experiences of social stress or discrimination (Mays et al., 2018). Our study moves one step further by exploring individual biomarkers and their relationship to experiences of social stress. Only one published report to our knowledge has described the *direct* relationship between perceived discrimination and markers of inflammation in SM individuals, and it focused on the

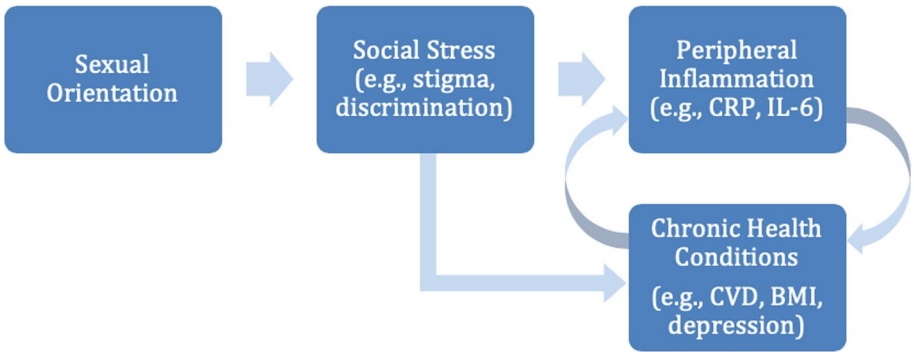


Fig. 1 Conceptual model underlying our hypotheses and approach and the pathways that may help to explain differences in health between heterosexual and SM adults

connection between daily discrimination and salivary IL-6 in lesbian and gay women and men (Doyle & Molix, 2016). Among gay men, perceived daily discrimination predicted higher levels of salivary IL-6 for those who were more open about their identity, presumably because they experienced more prejudice and discrimination. In this same study, the authors could not reliably interpret results for lesbian women because of convergence errors in their covariate-adjusted analyses due to a small sample of women ($n = 21$). Doyle and Molix (2016) provide a solid foundation for researchers to begin to understand the potential physiological consequences of discrimination in SM individuals and especially gay men; however, their study focused primarily on young adults ($M = 34.60$), did not include bisexuals or a heterosexual comparison group, measured one type of discrimination (daily), and included a single salivary inflammatory marker (IL-6).

We draw on data from individuals who participated in MIDUS to examine a wide age range of participants ($M = 52.86$). Our sample also includes bisexuals, who are a critical group of SM adults to include in health disparity research because they are the numeric majority of sexual minorities in the United States and tend to experience more discrimination and health problems compared to their gay and straight counterparts (e.g., Bostwick et al., 2015; Herbenick et al., 2010). In addition to IL-6, we examine CRP, a broad measure of systemic inflammation that is also linked with chronic stress (Chiang et al., 2019; Marsland et al., 2017; Steptoe et al., 2007) and implicated in the association between discrimination and health in racial minority individuals (Doyle & Molix, 2014). Finally, we include both daily and lifetime reports of discrimination because research with racial minorities finds a relationship between these two forms of discrimination and inflammation. For example, higher levels of daily and lifetime discrimination were separately associated with higher IL-6 among racial/ethnic minority women (Kershaw et al., 2016).

The present research

The first goal of this research was to examine whether measures of CRP and IL-6 differed by sexual orientation, accounting for core demographic factors that have sometimes been related to inflammation (i.e., age, gender, race, and education; O'Connor et al., 2009). Additional discussion of other covariates considered is provided below. Drawing on the minority stress hypothesis, we expected that SM adults would evidence higher levels of CRP and IL-6 compared to heterosexual counterparts. The second goal of this study was to test if discrimination mediated any associations between sexual orientation and these same inflammatory markers. We tested daily and lifetime discrimination as separate mediators to examine their unique roles in the sexual orientation-inflammation connection. Our prediction was that SM individuals would have elevated markers of CRP and IL-6, compared to heterosexual individuals, because they are exposed to more social stress, which we measured with perceptions of discrimination.

Method

Data and analytic sample

Data are from a sample of 2118 adults, ages 25–84, who participated in a biomarker assessment, as part of MIDUS (Brim et al., 2004; Love et al., 2010). MIDUS is a national probability sample of noninstitutionalized, English-speaking adults recruited through random digit dialing and was designed to investigate age-related changes in health across the adult lifespan. Participants were first interviewed in 1995–1996 (MIDUS-1), followed up a second time in 2004–2006 (MIDUS-2), and for a third time in 2013–2014 (MIDUS-3). In 2011–2014, MIDUS was augmented with a newly recruited national sample, known as the MIDUS Refresher (MIDUS-R). Biomarker assessments were

obtained from respondents in the MIDUS-2 ($n = 1255$) and MIDUS-R ($n = 863$) waves of data collection.

Biomarker data were collected during an overnight visit at one of three clinical research centers: University of California, Los Angeles; Georgetown University; and the University of Wisconsin-Madison. Participants provided a complete medical history, underwent a physical examination, and provided fasting blood samples at 7 am (before caffeine or nicotine consumption). Additional details about the biomarker procedure can be found elsewhere (Love et al., 2010). Data collection for the MIDUS studies were approved by Institutional Review Boards at each participating site, and all participants provided informed consent.

For the present work, we utilized the inflammatory biomarker IL-6, an inflammatory cytokine known to be stress responsive, and CRP, a broad marker of systemic inflammation produced in the liver in response to IL-6. Analysis was restricted to participants who reported their sexual orientation and from whom plasma/serum levels of at least one of these inflammatory markers was available. These criteria resulted in a final sample of 2037 participants (96.2% of the full biomarker sample). People who did not provide data on their sexual orientation ($n = 59$) or from whom at least one inflammatory marker was not obtained ($n = 22$), tended to be older, $t(2116) = 3.01$, $p = .003$, report more daily discrimination, $t(2097) = 2.58$, $p = .010$, and included a larger percentage of individuals who were non-White, $\chi^2(1, N = 2076) = 21.52$, $p < .001$, and without a college degree, $\chi^2(1, N = 2114) = 5.99$, $p = .020$, compared to those with complete data. Gender, perceived lifetime discrimination, and measures of CRP and IL-6 were not significantly different between those included and excluded from analysis.

Measures

Sexual orientation

Sexual orientation was measured with a self-administered questionnaire sent through the mail prior to individuals completing the biomarker assessment. A single item measured sexual orientation: "How would you describe your sexual orientation? Would you say you are heterosexual (sexually attracted only to the opposite sex), homosexual (sexually attracted only to your own sex), or bisexual (sexually attracted to both men and women)?" Participants identified themselves as heterosexual ($n = 1956$) or lesbian, gay, or bisexual ($n = 81$) and were coded as [0] heterosexual or [1] lesbian, gay, or bisexual.

Perceived lifetime discrimination

Lifetime discrimination was measured across 11 contexts: academics (discouraged from seeking higher education, denied a scholarship), employment (not hired or promoted, fired), financial (denied a bank loan, prevented from renting or buying a home, given inferior service), and experiences of social hostility (forced out of a neighborhood, hassled by the police, provided inferior medical care; Kessler et al., 1999). Participants reported the number of times they experienced each situation "because of race, ethnicity, gender, age, religion, physical appearance, sexual orientation, or other characteristics." Lifetime discrimination was calculated as a total of items for which respondents indicated experiencing the event at least once. Lifetime discrimination reports ranged from 0 to 11 events ($M = 1.21$). We treated lifetime discrimination as a continuous variable in our analyses.

Perceived daily discrimination

Day-to-day discrimination was evaluated with the question: "How often on a day-to-day basis do you experience each of the following types of discrimination?" with nine response items: "you are treated with less courtesy than other people," "you are treated with less respect than other people," "you receive poorer service than other people at restaurants or stores," "people act as if they are afraid of you," "people act as if they think you are dishonest," "people act as if they think you are not smart," "people act as if they think you are not as good as they are," "you are called names or insulted," and "you are threatened or harassed." Participants indicated how often they experienced these situations on a scale from 1 *(never)* to 4 *(often)*. Scores on the nine items were summed and higher values indicate higher levels of daily discrimination. Daily discrimination reports ranged from 9 to 36 ($M = 13.09$). Daily and lifetime discrimination were significantly correlated with each other at .50 in the current sample.

Inflammatory markers

Plasma CRP levels were measured using the BNII nephelometer (Dade Behring Inc., Deerfield, IL) with a particle enhanced immunonepholometric assay. Serum IL-6 levels were measured with the Quantikine high-sensitivity ELISA kit (R&D Systems, Minneapolis, MN). Inter-assay variability and intra-assay coefficient of variance were all at acceptable levels (see Love et al., 2010). Although CRP values exceeding 10.0 mg/L indicates the presence of current infection, injury, or chronic disease, results of prior studies suggest that discarding these cases may result in a loss of meaningful outcome variance (e.g., Graham-Engeland et al., 2018; O'Connor et al., 2009). Therefore, CRP values above 10.0 mg/L were retained (117 cases, with a mean of 20.08 and range of 10.01 to 79.30 mg/L) in primary analyses. Of these 117 participants with CRP values above 10.0 mg/L, 8 identified as a SM and 109 identified as heterosexual. A

Table 1 Descriptive statistics by sexual orientation for the sample: mean (standard deviation) or N (valid %)

	Heterosexual	Sexual minority	Total
ns	1956 (96.0%)	81 (4.0%)	2037 (100.0%)
Age (in years)	53.03 (12.49)[a]	48.63 (11.48)[b]	52.86 (12.48)
Gender			
Male	872 (44.6%)[a]	50 (61.7%)[b]	922 (45.3%)
Female	1084 (55.4%)[a]	31 (38.3%)[b]	1115 (54.7%)
Race/ethnicity			
White	1453 (75.8%)	61 (76.3%)	1514 (75.8%)
Non-White	465 (24.2%)	19 (23.5%)	484 (24.2%)
Education			
Some college or more	1499 (76.8%)	64 (79.0%)	1563 (76.8%)
High school or less	454 (23.2%)	17 (21.0%)	471 (23.2%)
Daily discrimination (9–36)	12.99 (4.88)[a]	15.45 (5.63)[b]	13.09 (4.93)
Lifetime discrimination (0–11)	1.19 (1.81)[a]	1.77 (2.01)[b]	1.21 (1.82)
CRP	3.22 (5.07)	4.33 (9.29)	3.26 (5.30)
IL-6	2.90 (2.74)	3.23 (2.73)	2.91 (2.74)
Body Mass Index (BMI)	29.97 (7.91)	31.05 (7.78)	30.01 (7.91)
Smoking			
No	1103 (56.4%)	43 (53.1%)	1146 (56.3%)
Yes	853 (43.6%)	38 (46.9%)	891 (43.7%)
Medications (use of statins)			
No	1413 (73.8%)	55 (69.6%)	1468 (73.6%)
Yes	502 (26.2%)	24 (30.4%)	526 (26.4%)
Chronic conditions (0–23)	3.29 (2.23)	3.42 (2.29)	3.29 (2.23)

Subscripts indicate instances in which *a* differs from *b* at $p < .05$ in independent-samples *t* tests. CRP = C-reactive protein; IL-6 = interleukin-6. Logged CRP and IL-6 were used in all analyses but raw values are shown here for ease of interpretation. Greater values indicate greater levels of daily discrimination, lifetime discrimination, CRP, IL-6, and chronic conditions

base-10 logarithm transformation was applied to CRP and IL-6 variables to reduce skew in the distributions. Inflammatory markers were modeled continuously to maximize power. CRP and IL-6 were correlated at .42 (.56 after log-transformation) in the analytic sample.

Covariates

Social and biodemographic covariates were selected based on their potential for confounding the associations between sexual orientation and inflammatory markers. Covariates were age (centered at 52.86 years), gender (coded as [0] male, [1] female), race (coded as [0] white, [1] non-white), and education (coded as [0] graduated high school or less, [1] attended some college or more). These variables have been dichotomized similarly in previous studies that have analyzed MIDUS data (e.g., Forbes et al., 2017; Riggle et al., 2009).

Given our small sample size and their lack of statistical association with SM status, we did not control for other factors that have sometimes been related to inflammation: body mass index (BMI), smoking, use of statin medication, and chronic conditions (using a sum of 23 chronic conditions; O'Connor et al., 2009).[1] The degree to which each of these factors was linked with SM status is provided in Table 1. In independent-samples *t* tests, there were no differences (at $p < .05$) by sexual orientation on these variables; for this reason and for our desire to not over-control for factors that theoretically might account for the association between SM status and peripheral levels of inflammation we do not

[1] Smoking was assessed with the question, "Have you ever smoked cigarettes regularly—that is, at least a few cigarettes every day?", coded as [0] no, [1] yes. Statin medication use was assessed with the question, "Are you taking cholesterol-lowering medication?", coded as [0] no, [1] yes. Number of chronic conditions was assessed with the question, "Have you ever had any of the following conditions?: heart disease, high blood pressure, circulation problems, blood clots, heart murmur, TIA or stroke, anemia or other blood disease, cholesterol problems, diabetes, asthma, emphysema/COPD, tuberculosis, positive TB skin test, thyroid disease, peptic ulcer disease, cancer, colon polyp, arthritis, glaucoma, cirrhosis or liver disease, alcoholism, depression, blood transfusion, coded as [0] no, [1] yes and summed.

Table 2 Unstandardized coefficients from regression analyses predicting CRP and IL-6

Predictor (reference category)	B [95% CI]	
	CRP	IL-6
Intercept	.171 [.113, .228]***	.337 [.302, .372]***
Sexual orientation (ref: heterosexual)	.127 [.011, .243]*	.088 [.018, .158]*
Age (mean centered at 52.86 years)	.004 [.002, .006]***	.008 [.007, .009]***
Gender (ref: male)	.153 [.107, .199]***	.023 [−.005, .050]
Race (ref: white)	.156 [.101, .210]***	.154 [.121, .187]***
Education (ref: graduated high school or less)	−.129 [−.183, −.074]***	−.076 [−.109, −.043]***
R^2	.062	.132

CRP [$F(5, 1978) = 26.03$, $p < .001$]; IL-6 [$F(5, 1988) = 60.38$, $p < .001$]. CI = confidence interval. Sexual orientation (0 = heterosexual, 1 = lesbian, gay, or bisexual); Gender (0 = male, 1 = female); Race (0 = white, 1 = non-white); Education (0 = graduated high school or less, 1 = attended some college or more). Logged CRP and IL-6 were used in these analyses. Higher values indicate higher levels of CRP and IL-6. *$p < .05$; **$p < .01$; ***$p < .001$

consider them any further in our analyses. However, it is important to note here that our measure of chronic conditions was a sum of 23 mental and physical illnesses, ranging from glaucoma to depression to heart disease. We examined each of these 23 conditions separately, and sexual minorities reported more alcoholism, $t(2027) = -1.98$, $p = .047$, and depression, $t(2009) = -4.80$, $p \leq .001$, compared to heterosexuals. Exploratory analyses controlling for alcoholism and depression are presented below.

Results

Preliminary analyses

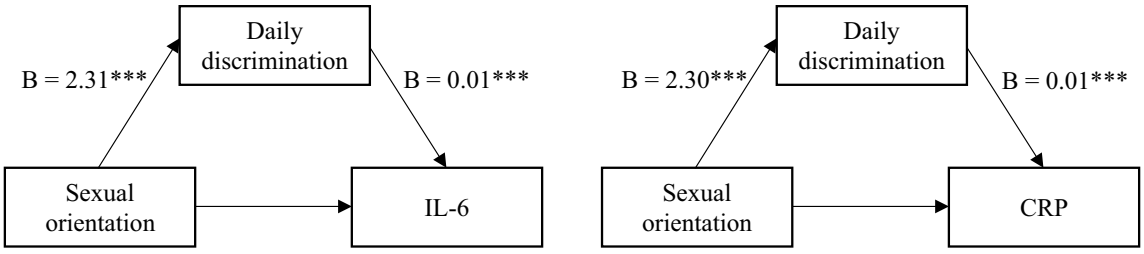
Descriptive statistics for the sample are presented by sexual orientation in Table 1. In independent-samples *t* tests and Chi square tests, compared with heterosexuals, SM individuals were slightly younger, $t(2035) = 3.12$, $p = .002$, more likely to be men, $\chi^2(1, N = 2037) = 9.23$, $p = .002$, and reported more daily discrimination, $t(2021) = -4.41$, $p < .001$, and lifetime discrimination, $t(1947) = -2.81$, $p = .005$. Neither race nor education differed (at $p < .05$) between heterosexual and SM adults. We account for these variables in the next series of analyses.

Sexual orientation and markers of inflammation

The first aim of this study was to examine whether sexual orientation predicted levels of CRP and IL-6. As shown in Table 1, levels of CRP and IL-6 did not differ between heterosexual and SM adults prior to controlling for sociodemographic factors; however, because these groups did vary on some sociodemographic factors, our subsequent analyses with CRP and IL-6 accounted for age, gender, race, and education. To test this research question, we conducted two separate linear regressions predicting each inflammatory marker (see Table 2). For each linear regression, predictors in the model were entered together and included sexual orientation, age, gender, race, and education. In Table 2, our results suggest that, on average, adults who are older (vs. younger), non-white (vs. white), and not college-educated (vs. college educated) have higher levels of CRP and IL-6 ($ps < .001$). IL-6 did not differ between women and men ($p = .110$); however, women were more likely to have higher CRP than men ($p < .001$). In support of our hypotheses, when accounting for age, gender, race, and education, sexual orientation was a significant predictor of both CRP and IL-6 ($ps \leq .032$), such that individuals who identified as lesbian, gay, or bisexual, had higher levels of CRP and IL-6 on average compared with heterosexuals. Notably, the effect sizes (unstandardized coefficients) of sexual orientation on CRP (B = .127) and IL-6 (B = .088) were similar to the effect sizes of identifying as non-White and not college educated on these same inflammatory markers.

Perceived discrimination, sexual orientation, and markers of inflammation

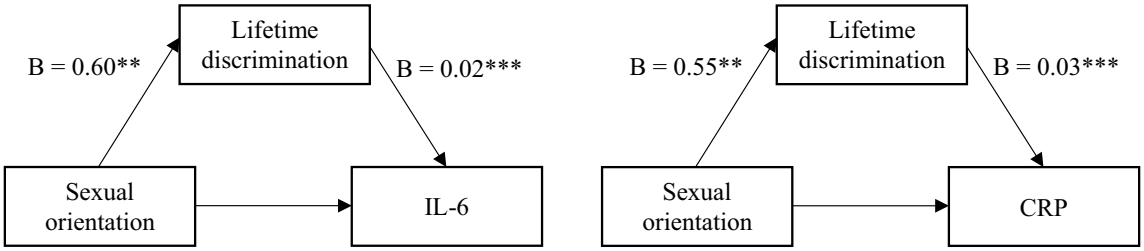
We proposed that perceived discrimination would explain (at least partially) the relationship between sexual orientation and markers of inflammation, and we explored whether one type of discrimination (daily) was a stronger mediator of this relationship than another type of discrimination (lifetime). We tested our proposed mediation model separately by daily and lifetime discrimination for ease of interpretation. We used bootstrapped mediation analysis with the PROCESS macro for SPSS (Hayes, 2013; Model 4) to test four models: (1) the indirect effect of sexual orientation on measures of IL-6, through daily discrimination, (2) the indirect effect of sexual orientation on measures of CRP, through daily discrimination, (3) the indirect effect of sexual orientation on



Direct effect, B = 0.08*
Indirect effect, B = 0.01, 95% CI [.004, .023]
Total effect, B = 0.09*
Total summary, $R^2 = .133$ [$F(5, 1974) = 60.32$, $p < .001$]

Direct effect, B = 0.10
Indirect effect, B = 0.03, 95% CI [.010, .048]
Total effect, B = 0.13*
Total summary, $R^2 = .062$ [$F(5, 1964) = 25.73$, $p < .001$]

Fig. 2 The mediating role of perceived daily discrimination on the association between sexual orientation and IL-6/CRP. *Note*. Unstandardized regression coefficients representing the relationship between sexual orientation, daily discrimination, and IL-6/CRP. Sexual orientation (0 = heterosexual, 1 = lesbian, gay, or bisexual). Age, gender, race, and education were entered as covariates. Logged CRP and IL-6 were used in these analyses. *$p < .05$; **$p < .01$; ***$p < .001$



Direct effect, B = 0.06
Indirect effect, B = 0.01, 95% CI [.002, .020]
Total effect, B = 0.07*
Total summary, $R^2 = .125$ [$F(5, 1900) = 54.17$, $p < .001$]

Direct effect, B = 0.10
Indirect effect, B = 0.02, 95% CI [.003, .036]
Total effect, B = 0.11
Total summary, $R^2 = .060$ [$F(5, 1892) = 24.30$, $p < .001$]

Fig. 3 The mediating role of perceived lifetime discrimination on the association between sexual orientation and IL-6/CRP. *Note*. Unstandardized regression coefficients representing the relationship between sexual orientation, lifetime discrimination, and IL-6/CRP. Sexual orientation (0 = heterosexual, 1 = lesbian, gay, or bisexual). Age, gender, race, and education were entered as covariates. Logged CRP and IL-6 were used in these analyses. *$p < .05$; **$p < .01$; ***$p < .001$

measures of IL-6, through lifetime discrimination and, (4) the indirect effect of sexual orientation on measures of CRP, through lifetime discrimination. We used bias-corrected bootstrapping techniques with 5000 samples in PROCESS software and this method is designed for and effective with rather small sample sizes so that the analyses are less susceptible to the influence of outliers. The distribution of the effects was used to obtain 95% confidence intervals for the size of the indirect effects of daily and lifetime discrimination. With the obtained confidence intervals, we interpreted whether the indirect effects were significant if the confidence intervals did not include zero. All analyses were conducted with age, gender, race, and education as covariates.

The results of our mediation models are presented in Figs. 2 and 3. In each of our mediation models, sexual orientation significantly predicted daily discrimination and lifetime discrimination (Bs > .55, *p*s < .05), such that SM individuals were more likely than heterosexuals to perceive both types of discrimination. Further, daily discrimination and lifetime discrimination significantly predicted IL-6 and CRP (Bs > .01, *p*s < .001), and these results suggest that, in general, as both types of discrimination are higher, IL-6 and CRP are also higher. In line with our hypothesis, lifetime and daily discrimination separately mediated the associations between sexual orientation and IL-6/CRP (Bs > .01; our confidence intervals did not include zero). These significant indirect effects support the notion that the sexual orientation-inflammation connection at least partially operates through an increase in perceived discrimination.

Lastly, we ran exploratory analyses to examine whether this connection was more strongly accounted for by daily or lifetime discrimination. When both daily and lifetime discrimination were entered together as mediators to predict IL-6, the total indirect effect (B = 0.02, 95% CI [.006, .028]) was accounted for more by daily discrimination (B = 0.009, 95% CI [.001, .019]) and less by lifetime discrimination

(B = 0.007, 95% CI [.0002, .016]). However, the difference between the strength of the mediators (daily discrimination minus lifetime discrimination) was not significant (B = 0.002, 95% CI [− .012, .016]). The pattern was the same for CRP, such that the total indirect effect (B = 0.03, 95% CI [.013, .054]) was accounted for more by daily discrimination (B = 0.02, 95% CI [.005, .039]) and less by lifetime discrimination (B = 0.01, 95% CI [.001, .027]), but the difference between the strength of the mediators was not significant (B = 0.01, 95% CI [− .014, .033]). Thus, perceived daily discrimination and lifetime discrimination should be considered as equal, unique, and important factors in the disparities we found in markers of inflammation between SM and heterosexual adults.

Discussion and conclusion

In the current research, we examined the connection between discrimination reported by sexual minorities, in the forms of everyday and lifetime, and two biological markers that mediate inflammatory responses, CRP and IL-6. Our results suggest that SM individuals may have higher CRP and IL-6 than heterosexuals on average and that these differences in inflammatory markers are driven to at least some extent by perceptions of stigma and discrimination. That discrimination may have a physiological cost for SM people is especially worrisome because there is evidence that heterosexual men and women ages 18–34 have become less tolerant of LGBTQ (lesbian, gay, bisexual, transgender, and queer) people between the years 2016 and 2018 (GLAAD, 2019). Another survey conducted in 2017 found that over half of SM adults in the United States encounter discrimination and harassment on a daily basis (Harvard School of Public Health, 2017). Even worse, data from the United States Federal Bureau of Investigation (FBI), indicates that anti-gay hate crimes have risen each year from 2014 to 2017 (FBI, 2017). These survey results together point to the potential and likelihood for LGBTQ people to experience substantial prejudice both now (in 2020) and in the future. The present research builds on existing findings and theory to suggest that such discrimination might contribute to inflammatory responses and thus, poor health.

Chronically elevated systemic inflammation has been implicated in the development of a host of illnesses and diseases and could help to explain the well-documented health disparities evident in the SM community, such as greater incidences of cardiovascular disease, cancer, and chronic pain (Fredriksen-Goldsen et al., 2013, 2017). For instance, plasma CRP levels predict future cardiovascular events over and above traditional risk indicators (Libby & Ridker, 2004; Ridker, 2003; Stoner et al., 2013). There is also evidence that IL-6 has a role in the development and progression of prostate, ovarian, and breast cancers, and serum IL-6 levels can even predict the clinical stage and patient prognosis of these cancers (Lukaszewicz et al., 2007; Nakashima et al., 2000). Excessive levels of CRP and IL-6 in SM adults may also precipitate health problems that are usually understood to increase (worsen) with age (Black, 2003). Osteoporosis, rheumatoid arthritis, and Alzheimer's Disease have been associated with high circulating levels of CRP and/or IL-6 (for reviews, see Maggio et al., 2006; Marsland et al., 2017; Steptoe et al., 2007). Thus, these biomarkers of inflammation could provide an objective window into those SM adults at elevated risk for poor health, perhaps before noticeable symptoms present.

Various approaches can be taken to counteract heightened inflammation in SM individuals. One way to maintain and/or lower inflammation is to target SM individuals' health behaviors. Previous studies have demonstrated that CRP and IL-6 are modifiable through lifestyle changes, such as modifications to diet, depression levels, medication, and physical activity (Kiecolt-Glaser et al., 2015). Physical fitness has been associated with smaller inflammatory cytokine responses to acute mental stress (Hamer & Steptoe, 2007), and sleep quality and latency (amount of time it takes to fall asleep) and diets higher in fruit and vegetable intake have been associated with lower levels of CRP and IL-6 (Irwin et al., 2006; Kiecolt-Glaser, 2010). Social support can also influence inflammation. In another study, daily positive events, such as "sharing a good laugh with someone" or "having a good conversation," were associated with lower levels of CRP and IL-6 among middle and older-aged adults (Sin et al., 2015). Social support and health behaviors should be investigated as targets for intervention for SM individuals. However, it should be noted that this approach unfairly places the burden on SM individuals to change their own behaviors to buffer themselves from the negative health effects of discrimination.

Another approach to improve SM health would be to create environments that are inclusive and that limit stress exposure for SM individuals. LGBTQ people are healthier, happier, and experience less internalized homophobia and more support when they live in geographic areas with more (vs. less) gay-friendly indicators, such as gay bars, pride flags, resource centers, and inclusive/nondiscriminatory policies (Duncan & Hatzenbuehler, 2014; Puckett et al., 2017; Raifman et al., 2017; Swank et al., 2012). These positive effects of gay-friendly indicators in communities have also been demonstrated to improve heterosexual people's perceptions and support for LGBTQ people (Tankard & Paluck, 2017). Research suggests that LGBTQ people often search for cues in their environment that signal acceptance because of valid concerns over threat and safety (Crocker et al., 1998) and therefore, it seems reasonable to expect that SM people would benefit from being in environments that

signal pride for LGBTQ lives. Taken together, communities that demonstrate respect towards LGBTQ individuals with subtle cues in the environment, could help to decrease social stress for SM individuals (e.g., lessen internalized homophobia and instances of discrimination) and in turn, potentially buffer the possible negative effects of discrimination on the immune system.

Limitations

Our study is not without limitations. One issue relates to the age of our sample, which was middle-aged on average ($M = 52.86$ years). Many of the adults in our sample were in young and middle adulthood through, for example, the Stonewall Riots in the 1960 s, the AIDS epidemic in the 1980 s, and when "homosexuality" was a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders until 1973 (Fredriksen-Goldsen et al., 2011). Accordingly, this generation of SM adults may have been exposed to more social stress, identity concealment, and internalized homophobia because they lived much of their adult life in a time when same-sex attractions and relationships were more heavily stigmatized (e.g., gay marriage was not federally legalized until 2015) and this could also explain why lifetime discrimination was equal in effect to daily discrimination. Future research is needed to determine whether the effects that we found of discrimination on inflammation are a function of cohort (e.g., changes that occur over time because of the unique experiences of a group of people of similar age), period (e.g., changes that occur over time because of an experience that affects all age groups) or age (e.g., changes that occur over time for everyone that are unrelated to cohort or period). Our sample was cross-sectional so we could not explore time effects; however, future research should draw from longitudinal samples of SM individuals to see how inflammation changes over time with exposure to discrimination. Although we could not determine the causal directionality of the associations between sexual orientation, discrimination, and markers of inflammation because of the cross-sectional nature of our data, it is unlikely that our mediation model functions in the opposite direction to what we predicted, such that elevated CRP and IL-6 "cause" discrimination and that discrimination "causes" sexual orientation.

Another limitation is that our discrimination measures were not specific to sexual minorities. MIDUS was not designed exclusively for SM participants; thus, the discrimination measures were designed to capture more broad experiences of social stress and mistreatment (e.g., "you are threatened or harassed") that could result from identities outside of sexual orientation such as race, ethnicity, gender, age, religion, and physical appearance. In the present study, sexual minorities perceived more discrimination than heterosexuals, and we suspect (but cannot know) that this difference in discrimination (or social stress and mistreatment) between sexual minorities and heterosexuals has at least some connection to sexual orientation, particularly because we controlled for other characteristics (i.e., race, gender, age, education) that could result in unfair treatment (Chrisler & Palatino, 2016; Jones, 2000). Future research in this area should examine the connection between inflammatory markers and unfair treatment that may better characterize sexual minorities' experiences (e.g., encounters with homophobia).

Further, 4.0% of the MIDUS sample identified as a SM and this percentage reflects the national prevalence in the United States (Gates, 2017). The MIDUS study did not include a gender identity question so we could not determine whether individuals identified as transgender, but transgender individuals may have been included in our study if they identified as lesbian, gay, bisexual, or heterosexual. Moreover, the small number of SM respondents in our sample precluded us from running analyses stratified by gender to examine whether SM men and women differed from heterosexual men and women, respectively. A few studies have examined CRP and sexual orientation in young adults (< 29 years old on average) and these studies found that SM men had elevated levels of CRP relative to heterosexual men but that SM women tended to show the opposite pattern, with lower levels of CRP relative to heterosexual women in models that adjusted for factors that are known to influence inflammation (Everett et al., 2014; Hatzenbuehler et al., 2013). It has been suggested that minority stress may play a role in producing these disparities, but discrimination was not included and/or directly tested in these studies. Though we controlled for gender, the pairwise comparisons between SM adults and their heterosexual counterparts by gender were not possible with this dataset. Similarly, we did not have the statistical power with our sample size to examine whether lesbian, gay, or bisexual individuals differed from each other in their levels of inflammation and/or whether other identities intersected with sexual orientation, such as race/ethnicity and socio-economic status, to predict both discrimination and inflammatory markers. There is increasing evidence that bisexuals experience significantly poorer health and more discrimination when compared not only to heterosexuals, but also to other sexual minorities (e.g., Bostwick et al., 2015; Herbenick et al., 2010). In relation to our results, bisexuals could be driving the higher levels of discrimination and consequently, the higher levels of CRP and IL-6, that we observed in sexual minorities compared to heterosexuals. Lastly, our sample was too small to include more covariates in our analyses because it is suggested that researchers have ~ 10 participants per parameter in regression models (Chen et al., 2016); however, as we describe below, it is possible that other factors and behaviors (e.g.,

chronic conditions, depression, BMI) accounted for the immune disparities we found between SM and heterosexual individuals. Future research could address this issue with datasets that include larger samples of SM individuals.

Notably, even with larger samples of SM individuals when it would be statistically appropriate to control for additional variables that are sometimes related to inflammatory markers, we encourage scientists to carefully consider covariates as well as cutoffs (with respect to inflammatory marker outliers). One consideration is that it can be important not to over-control for factors (or remove variance) that may help explain the connections between SM status and inflammation. It is important to consider such decisions in advance. Even if our sample size had not precluded us from controlling for many variables, we had decided a priori to control only for demographic variables (i.e., age, gender, race, education) that, for the most part, would not be expected to differ by sexual orientation (or be driven by excess social stress), at least from a minority stress perspective. Although we did not find significant differences in chronic conditions (e.g., arthritis, diabetes) by sexual orientation (see Table 1), it has been well-documented that sexual minorities experience more mental and physical health problems compared to heterosexuals, and is the reason the National Institutes of Health designated the LGBTQ community as a health disparate population (NIMHD, 2016).

This said, as an exploratory analysis, we reran our regression models with the addition of alcoholism and depression (the two items in our 23-item chronic condition measure that differed between heterosexuals and SMs) as covariates. The relationship between sexual orientation and logged IL-6 remained significant with the addition of these covariates. However, the coefficient for the relationship between sexual orientation and logged CRP changed from statistically significant to statistically non-significant, $B = .127$, $p = .03$ to $B = .118$, $p = .051$; this result supports our notion that controlling for chronic conditions (at least those that differ by sexual orientation) can essentially remove certain pathways (or variance) that may play a role in linking SM status with elevated markers of inflammation, especially in analyses with CRP. Likewise, clinical cutoffs of above 10 mg/L are sometimes used with CRP, because these values may suggest the presence of current infection or injury (Pearson et al., 2003). In the current sample, a higher percentage of SMs (10.0%) had CRP values above 10 mg/L, compared to 5.60% of heterosexuals. Because our prediction was theoretically-driven by the minority stress framework, it would have been counter-intuitive to remove high values of CRP (i.e., those above 10 mg/L) because we expected SMs to evidence higher levels of CRP as a result not only of the excess stress and negative behaviors (e.g., excessive drinking) that are over-represented in the SM community but also disparities in health problems that are presumably a result of such phenomena. That is, there may be reason to believe that the high values observed in this study among SMs may reflect the true extent of chronic stress and medical conditions in the SM population.

Conclusion

The current research links sexual orientation to higher levels of peripheral inflammation (both IL-6 and CRP) and specifically suggests that both perceived lifetime and perceived daily discrimination help account for this link. Elevated inflammation may be an important physiological mechanism that helps connect minority stress and disease. Although results will require replication and expansion, they indicate that further exploration of the role of inflammation and immune function may illuminate areas of intervention to reduce health disparities in SM individuals.

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Compliance with ethical standards

Conflict of interest Britney M. Wardecker, Jennifer E. Graham-Engeland and David M. Almeida declare that they have no conflict of interest. Each of the authors has contributed in a significant way to this manuscript and each has approved this version.

Human and animal rights and Informed consent All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individual participants included in the study.

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