



## A biopsychosocial framework for understanding sexual and gender minority health: A call for action

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### ABSTRACT

The number of US adults identifying as lesbian, gay, bisexual, transgender, or a different sexual identity has doubled since 2008, and about 40 % of the sexual and gender minority population identify as people of color. Minority stress theory posits that sexual and gender minorities are at particular risk for stress via stigma and discrimination at the structural, interpersonal, and individual levels. This stress, in turn, elevates the risk of adverse health outcomes across several domains. However, there remains a conspicuously limited amount of research on the psychoneuroimmunology of stress among sexual and gender minorities. We developed the Biopsychosocial Minority Stress Framework which posits that sexual minority status leads to unique experiences of minority stress which results in adverse health behavioral factors, elevated psychological distress and sleep disturbance, and immune dysregulation. Moderators in the model include both individual differences and intersectional identities. There is a crucial need to understand the biological-psychological axis of stress among the increasingly visible sexual and gender minority population to increase their health, longevity, and quality of life.

### 1. Health disparities affecting sexual and gender minorities

The number of US adults identifying as lesbian, gay, bisexual, and transgender, among other emerging sexual and gender identities, on national population-based surveys has doubled since 2008 to 4.5 %, or more than 11 million adults (Newport, 2018). During this same time period, the number of US households headed by same-sex couples increased by 73 %, from 539,230–935,229 households (US Census Bureau, 2019), with continued increases expected in coming years. Sexual and gender minorities (SGM) have significantly greater risk for overweight/obesity, asthma, diabetes, cardiovascular disease, and some forms of cancer compared to cis-gender heterosexuals (Alzahrani et al.,

2019; Bostwick et al., 2010; Bradford et al., 2013; Caceres et al., 2017; Corte et al., 2013; Dilley et al., 2010; Institute of Medicine, 2011; Mayer et al., 2008; Morgan et al., 2019a; National Academies of Sciences, 2020; Patterson et al., 2020). Exposure to stressors including stigma and discrimination are implicated in these disparities, in part through behavioral factors including sleep, depression, and health behaviors (e. g., tobacco use, alcohol use, sedentary behavior; Blosnich et al., 2013; Boehmer et al., 2012; Frost et al., 2015; Gamarel et al., 2016; Garri-do-Hernansaiz et al., 2016; Jackson et al., 2016; LeBlanc et al., 2015; Lee et al., 2016; Lick et al., 2013; Liu et al., 2017; Patterson et al., 2018; Wight et al., 2012). However, data on biological functioning, and its association with stress and behavioral factors, in sexual and gender

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minority populations are remarkably limited.

An estimated 40 % of the sexual and gender minority population in the US are also racial/ethnic minorities, which is higher than the 33 % of cis-gender heterosexuals who are racial/ethnic minorities (Gates, 2017). It is critical to note that race is a social rather than biological construct and “racial groups are not genetically discrete, reliably measured, or scientifically meaningful” (Smedley and Smedley, 2005). In fact, Americans of African descent have greater genetic substructure than other groups, with 73.2–82.1 % West African, 16.7 %–24 % European, and 0.8–1.2 % Native American genetic ancestry on average (Bryc et al., 2010, 2015; Zakharia et al., 2009). Consistent with race as a social construct, Americans of African descent as well as members of other minoritized groups have unique stressor exposures as members of a mistreated racial minority group. These exposures, rather than genetic differences, impart vulnerability to health inequities (Boyd et al., 2020; Cooper, 2003).

In 2017, the percentage of US adults identifying as SGM was 4.0 % among White people, 5.0 % among Black people, 6.1 % among Hispanic people, 4.9 % among Asian people, and 6.3 % among those of other races/ethnicities (Newport, 2018), resulting in significantly higher identification as SGM among racial/ethnic minorities compared to Whites. Comparatively, the rate of US adults identifying as transgender was 0.5 % among White people, 0.8 % among Black people, 0.8 % among Hispanic people, and 0.6 % among those identifying as a different race or ethnicity (Flores et al., 2016). Despite this high frequency of co-occurring minoritized identities (Chae et al., 2010), the intersecting roles of sexual and racial/ethnic identities are rarely addressed in the biobehavioral health literature. Herein, we describe a

biopsychosocial framework for empirical studies (Fig. 1), as well as potential opportunities and obstacles for research in this area.

## 2. Stress and SGM health

Stigma refers to the co-occurrence of labeling, stereotyping, separation, status loss, and discrimination in a context in which unequal power exists (Hatzenbuehler et al., 2013b). Increasingly rigorous research locates stigma across structural, interpersonal, and individual levels as the primary source of the disproportionately poor health experienced by sexual and gender minorities (Hatzenbuehler and Pachankis, 2016; White Hughto et al., 2015). For instance, at the structural level, several natural experiments have shown that reductions in discriminatory laws and policies prospectively predict reductions in sexual minorities’ health care expenditures, health-risk behaviors, and mental health problems (e.g., Everett et al., 2016; Hatzenbuehler et al., 2012; Raifman et al., 2018). At the interpersonal level, discrimination and victimization are consistently associated with poor physical health among sexual minorities (e.g., Bränström et al., 2016; Frost et al., 2015). Among transgender people, discrimination and victimization are compounded, leading to poorer overall health through reduced access to a variety of services including mental health, and employment services (Bockting et al., 2013; White Hughto et al., 2015). Finally, cultural ideologies of anti-sexual and gender minority stigma can become internalized by the individual and directed toward the self. At the individual level, this type of self-stigma is consistently associated with poor mental health and health behaviors (e.g., Berg et al., 2013; Bockting et al., 2013; Newcomb and Mustanski, 2010).

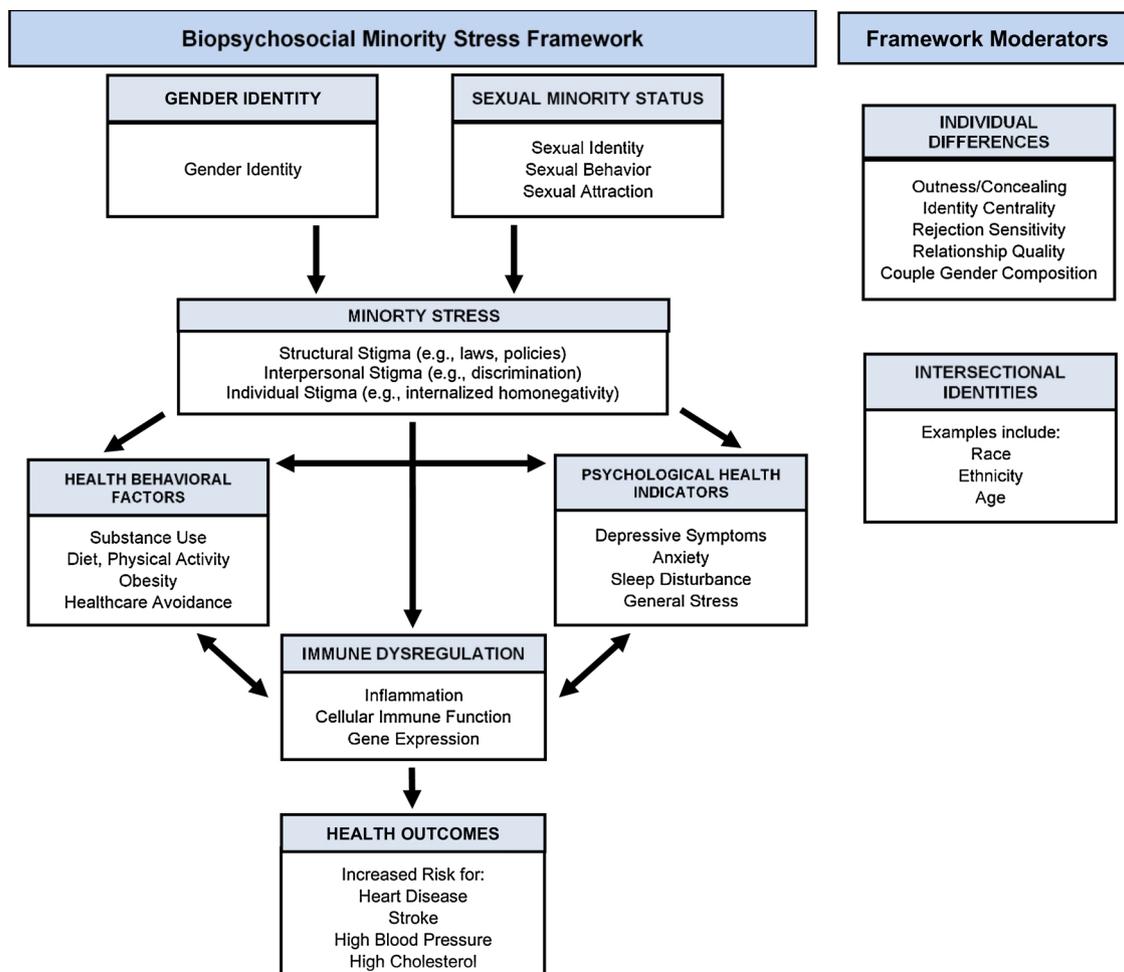


Fig. 1. Biopsychosocial Minority Stress Framework.

According to minority stress theory (Meyer, 2003), structural, interpersonal, and individual forms of stigma give rise to proximal stress experiences that in turn elevate health risk for sexual and gender minorities. These stigma-related stressors experienced by sexual and gender minorities across these levels compound general life stressors to additively confer risk for stress-related health outcomes (Bockting et al., 2019; Meyer et al., 2008; Puckett and Levitt, 2015). For instance, sexual minorities living in countries with higher degrees of structural stigma toward sexual minorities (e.g., more discriminatory laws and policies) report more internalized homonegativity, are more likely to conceal their sexual orientation, and experience greater social isolation than sexual minorities living in countries with lower degrees of structural stigma (Pachankis et al., 2020). Similarly, internalized transphobia can be described across four key domains: having pride in one's transgender identity, investment in passing as a cisgender person, alienation from other transgender people, and shame (Bockting et al., 2019). Interpersonal discrimination and victimization are closely associated with proximal minority stressors, including internalized homonegativity and sensitivity to status-based rejection, which are in turn associated with poor mental health and health-risk behaviors (Bockting et al., 2013; Feinstein et al., 2012; Frost et al., 2015; Frost and Meyer, 2009; Pachankis et al., 2015b). Anxious expectations of rejection might be particularly pronounced among gender minorities, with one study finding that two-thirds of transgender men report having experienced mistreatment in healthcare settings at some point in their lives and nearly half reported having avoided healthcare services in the past year (Hughto et al., 2018). Taken together, these data paint a picture of SGM populations at greater risk for a host of poor health outcomes.

Yet, not all sexual and gender minorities are similarly stressed by their exposure to structural and interpersonal forms of stigma, and even stigma processes at the individual level interact in complex ways to predict health outcomes. For example, the impact of structural stigma on substance use among sexual minority men is more pronounced for those who report greater tendencies to anxiously anticipate stigma-related rejection (Pachankis et al., 2014). And although rates of stigma-related substance use among transgender youth (aged 14–18) are partially mitigated by a feeling of family or school connectedness, overall levels remain much higher than among their cis-gendered peers (Watson et al., 2019). Similarly, the association between country-level structural stigma, discrimination, and mental health depends on the extent to which sexual and gender minority individuals conceal their identity (Mizock and Mueser, 2014; Pachankis and Bränström, 2018). Likewise, the association between concealment and mental health depends on social isolation – concealment is only associated with poor mental health for those with low social support (van der Star et al., 2019). Finally, minority stress theory proposes that the centrality of one's sexual minority identity moderates the impact of stigma-related stress on health, although this tenet currently has mixed empirical support (e.g., la Roi et al., 2019). Within the sexual and gender minority community, bisexual individuals are at unique risk for negative mental health outcomes (Ross et al., 2018; Salway et al., 2019; Schrimshaw et al., 2013) perhaps due to facing both heterosexism and monosexism which elevates intimate relationships and attractions between individuals who both identify as the same gender (Roberts et al., 2015). Further, individuals with non-LGB or multiple sexual identities may also experience the negative effects of both hetero and monosexism (Feinstein et al., 2020). Meta-analytic results suggest that bisexual individuals report the highest rates of suicide ideation and attempts (Salway et al., 2019), as well as depression and anxiety (Ross et al., 2018), compared to gay, lesbian, and heterosexual individuals. Bi-erasure can emerge from heterosexism and monosexism which is an internalized feeling of invisibility (Yoshino, 2017). As such, recent research identifies high levels of concealment in the bisexual and other non-monosexual

community, and this concealment was associated with elevated depression and anxiety (Feinstein et al., 2020). Importantly, the bulk of this research focuses on mental or behavioral health as operationalized by self-report measures without complementary data on biomarkers.

Health disparities among sexual and gender minorities also differ across race/ethnicity (Rodriguez-Seijas et al., 2019), sexual identity (e.g., bisexual vs. gay/lesbian; Dyar et al., 2019), gender identity (Bostwick et al., 2010; Reisner et al., 2014; White Hughto et al., 2015), partner gender (Dyar et al., 2019), and intersections thereof (Trinh et al., 2017). These disparities call for future research to determine whether these demographic factors might also moderate the impact of structural, interpersonal, and individual stigma exposure on sexual minority health (Lewis and Van Dyke, 2018). For instance, existing research shows that the mental health benefits of outness accrue more heavily to sexual minority women than men (Pachankis et al., 2015a) and that outness is associated with positive physical health for sexual minority men of higher socioeconomic status, but poorer physical health for sexual minority men of lower socioeconomic status (McGarrity and Huebner, 2014). Additional research suggests that transgender youth who have chosen a name aligning with their gender identity experience large reductions in poor health outcomes but limited gains in positive mental health outcomes (Pollitt et al., 2019). Future research is needed to investigate such associations across additional axes of identity-related stress, both sexuality- and gender-related.

### 3. Stress and the immune system: psychoneuroimmunology

Effects of chronic stress on the immune system are well documented. While early studies hypothesized that stress “impairs” immune function, it is now apparent that the body responds to chronic stress in a complex manner that is better described as immune dysregulation, with complementary up-regulation of inflammatory processes and down-regulation of viral monitoring. Inflammation increases risk for a variety of chronic diseases including cardiovascular and neurodegenerative diseases as well as some types of cancer, while reduced cellular immune function increases risk for acute illnesses via poorer responses to vaccines and reduced ability to fight viral infections.

Chronic stress affects the immune system directly via effects on the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. Stress also indirectly affects immune function by promoting poor sleep, depressed mood, and adverse health behaviors (e.g., poor diet/sedentary behavior) which act synergistically to impact health (Irwin et al., 2015; Kiecolt-Glaser et al., 2015, 2010; Lopresti et al., 2013; O'Neill et al., 2018; Shelton and Miller, 2010; Slavich and Irwin, 2014). Sexual and gender minority status increases risk for sleep disturbance, depression, and adverse health behaviors (Blosnich et al., 2013; Boehmer et al., 2012; Frost et al., 2015; Gamarel et al., 2016; Garrido-Hernansaiz et al., 2016; Harry-Hernandez et al., 2020; Jackson et al., 2016; LeBlanc et al., 2015; Lee et al., 2016; Lick et al., 2013; Liu et al., 2017; Patterson et al., 2018; White Hughto et al., 2015; Wight et al., 2012), with differential effects in SM women and men (e.g., compared to heterosexuals, lesbians have greater propensity toward sedentary behavior and obesity, while gay men show less; Conron et al., 2010). Links between sexual minority stress, behavioral factors, and biological health are poorly delineated. In addition, an extensive body of work documents effects of racial/ethnic minority status and discrimination on immune, neuroendocrine, and cardiovascular processes, with direct implication for disparities in health (Allen et al., 2019; Christian, 2020; Cunningham et al., 2012; Hall et al., 2009; Kershaw et al., 2016; Lewis et al., 2010; Moody et al., 2018; Slopen et al., 2010; Stepanikova et al., 2017; Williams, 1999). Critically, the intersectional effects of sexual, gender, and racial/ethnic minority status remain unexamined in the PNI literature.

### 3.1. Inflammation

As described, a central pathway by which stress exerts ill health effects is via enhancement of inflammatory processes. Inflammation is an essential immune response to infection or injury. Among multiple other functions, inflammation promotes destruction (phagocytosis) and clearance of pathogens and initiates wound healing. However, exaggerated or chronic inflammation is implicated in risk for a number of serious medical conditions including cardiovascular and neurodegenerative diseases, arthritis, diabetes, inflammatory bowel disease, periodontal disease, certain cancers, and age-related functional decline (Ben-Neriah and Karin, 2011; Cekici et al., 2014; Collaboration, 2012; Donath, 2014; Esser et al., 2014; Franceschi and Campisi, 2014; Michaud et al., 2013).

Studies have established that chronic stress enhances circulating levels of inflammatory markers – particularly interleukin-6 (IL-6) and C-reactive protein (CRP) – and increases inflammatory responses to behavioral and biological challenges (e.g., sleep deprivation, vaccination). Of particular relevance to minority health disparities, chronic stress associated with racial minority status and racial discrimination are linked with exaggerated inflammatory responses to acute laboratory stressors (Christian et al., 2013) and greater vulnerability to inflammatory dysregulation upon exposure to both poor diet and sleep disturbance (Blair et al., 2015; Christian et al., 2016, 2018). Data from Morgan and colleagues shows that CRP is broadly elevated among young sexual and gender minorities (50 % of sample  $\geq 3$  mg/L), independent of socioeconomic status, geographic location, or HIV status (Morgan et al., 2019a, b). Research is needed to examine the effects of sexual and gender minority status and the intersectional effects of racial minority status on inflammatory processes.

### 3.2. Cellular immune function

While inflammation is up-regulated in the context of chronic stress, cellular immune function is impaired, decreasing the body's ability to respond to vaccines and fight viral infections. Latent viruses provide an ideal opportunity for examining these effects (Christian et al., 2009). Normally viruses are eliminated from the host when infection is resolved. However, some viruses are maintained in the body in a latent (suppressed) state in asymptomatic individuals after primary infection. These include viruses from the herpesviruses family, such as varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). After primary infection, latent viruses are maintained within certain cells (e.g., B-lymphocytes for EBV). The immune system is typically quite effective in keeping these viruses suppressed (i.e., in a latent state). However, these viruses act opportunistically, reactivating when they detect that the cellular immune system is impaired. Thus, higher levels of EBV-specific antibodies indicate greater impairment of cellular immunity.

A methodological strength of studying EBV is that it is ubiquitous; >95 % of US adults are infected with EBV (Wolf and Morag, 1998). A meta-analysis of 20 immune outcomes found that EBV reactivation was among the strongest and most reliable correlates of stress (Van Rood et al., 1993). Greater EBV reactivation has been documented in the context of greater perceived stress, poorer sleep quality, caregiving for a spouse with dementia, stress of divorce/separation, and low social status and stress related to “Westernization” among Samoan youth (Kiecolt-Glaser et al., 1991, 1987, 1988; McDade, 2001, 2002). The chronic stress of racial minority status and exposure to racial discrimination has been associated with chronic elevations in EBV antibody titers across a 10 month assessment period (Christian et al., 2012). Data on stress and viral monitoring in relation to sexual minority status are lacking. These data, in conjunction with data on inflammatory status, would permit the

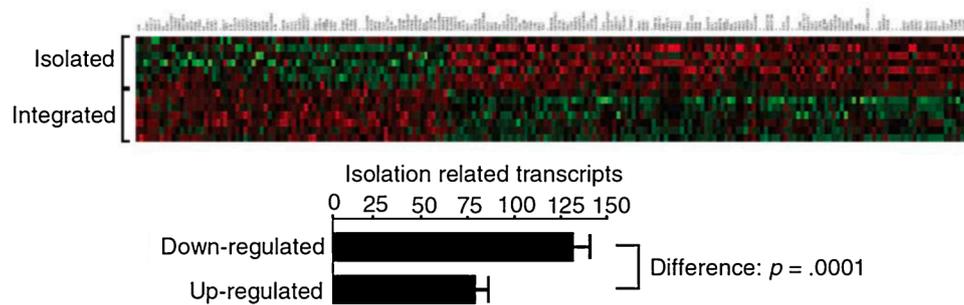
testing of the hypothesis that complementary up-regulation of inflammation and down-regulation of viral monitoring may typify chronic stress associated with sexual minority status.

### 3.3. Social genomics

As the AIDS epidemic emerged in the 1980s, PNI research began to map the biological pathways through which social and psychological processes impacted the speed of HIV disease progression and mortality. Issues of sexual identity played a central role in these analyses, with disease-related stigma compounding stigmatized sexual identities to emerge as some of the strongest psychosocial predictors of accelerated disease progression (e.g., immune decline, AIDS onset, and mortality in closeted gay men) (Cole et al., 1997, 1996b). A range of laboratory virological studies (Cole et al., 1999, 1998, 2001; Collado-Hidalgo et al., 2006), experimental animal models (Cole et al., 2015; Sloan et al., 2007, 2006), and human clinical studies (Cole et al., 2003, 2001) subsequently converged in mapping biological pathways through which threat-related psychosocial processes act through the sympathetic nervous system to accelerate HIV-1 replication via stimulation of viral gene expression, up-regulation of viral coreceptors on human host immune cells, and the inhibition of antiviral immune responses (particularly transcriptional down-regulation of the Type I interferon response to viral replication) (Cole, 2008; Collado-Hidalgo et al., 2006).

As the human genome sequence emerged, the gene regulatory principles, molecular analysis strategies, and bioinformatics tools originally developed to analyze social regulation of relatively simple viral genomes were soon directed toward the more complex human genome to understand how social epidemiological risk factors impacted the development of chronic non-infectious illnesses such as cancer, cardiovascular disease, and neurodegeneration. A seminal study analyzed gene expression profiles in peripheral blood leukocytes from chronically lonely older adults and found a striking pattern of up-regulated expression of pro-inflammatory genes and down-regulated expression of antiviral genes (including the Type I interferons previously implicated in HIV-1 infection; Fig. 2; Cole et al., 2007).

A similar pattern of pro-inflammatory / anti-antiviral transcriptome skewing has since been observed in leukocytes sampled from people exposed to a diverse array of adverse life circumstances such as imminent bereavement (Bourassa et al., 2020; Miller et al., 2008), traumatic stress (Yang and Jiang, 2020), social isolation (Cole et al., 2007; Frost et al., 2015; Smith, 2020), low SES (Chen et al., 2009; Muscatell et al., 2020), and cancer diagnosis (Lutgendorf et al., 2009; Peppas et al., 2020). Similar dynamics have also been observed in experimental animal models of social instability, low social rank, and repeated social defeat. Coined the “conserved transcriptional response to adversity” (CTRA) (Cole, 2013, 2014, 2019), this pattern of immune cell transcriptional alteration provided a molecular framework for understanding the previously puzzling epidemiological observation that chronic psychosocial adversities are often associated with diseases that involve both up-regulated immune function (inflammation-related diseases such as heart and neurodegenerative diseases, and some cancers) and down-regulated immune function (reduced responses to vaccines and viral infections in particular). The CTRA appears to be stimulated by “fight-or-flight” sympathetic nervous system activity whenever environmental conditions are experienced as threatening, stressful, or uncertain for an extended period of time (Cole, 2019). Of particular significance for sexual minorities, experiences of discrimination have also been linked to increased CTRA profiles (Brown et al., 2020; Thames et al., 2019), including discrimination based on sexual identity (Li et al., 2020). As such, the application of social genomics to understanding SM health disparities holds great promise.



**Fig. 2.** Leukocyte transcriptional fingerprint of social isolation. 209 human genes differentially expressed in leukocytes from chronically lonely and socially integrated older adults. Rows = individuals, Columns = genes, Cell color: red = up-regulated >30 %, green = down-regulated >30 %. (Reprinted from [Cole et al., 2007](#)).

#### 4. Available psychoneuroimmunology data among SGM

Within the PNI literature, robust effects of racial/ethnic discrimination are clear ([Allen et al., 2019](#); [Christian, 2012](#); [Cunningham et al., 2012](#); [Hall et al., 2009](#); [Kershaw et al., 2016](#); [Lewis et al., 2010](#); [Moody et al., 2018](#); [Slopen et al., 2010](#); [Stepanikova et al., 2017](#); [Williams, 1999](#)). Yet, studies of stress biology among SGM are sparse, with a few on cortisol ([Hatzenbuehler and McLaughlin, 2014](#); [Juster et al., 2015, 2013](#); [Manigault et al., 2018](#); [Parra et al., 2016](#)), CRP ([Everett et al., 2014](#); [Hatzenbuehler et al., 2013a](#); [Morgan et al., 2019a, b](#)), and/or immunity in HIV (e.g., [Burack et al., 1993](#); [Cole et al., 2003, 1996b](#)). Even fewer exist on immunity among the broader SGM population. These studies have had somewhat contradictory findings, and interpretation has been difficult due to insufficient assessment of key moderators/mediators (e.g., minority stress, outness). Data from National Health and Nutrition Examination Survey (NHANES) showed elevated allostatic load (a composite index of 9 indicators including CRP) in bisexual vs heterosexual men ([Mays et al., 2018](#)). The National Longitudinal Study for Adolescent to Adult Health (Add Health), which included 520 lesbian, gay, or bisexual individuals, found that gay/bisexual men had elevated CRP compared to heterosexual men, an effect not observed in lesbian/bisexual women (although these effects were significant only with specific variables added to the model, as the authors themselves note) ([Hatzenbuehler et al., 2013a](#)). Data from Add Health also showed complex interactions between gender and sexual minority status in relation to both CRP and EBV, effects that were not readily explainable ([Everett et al., 2014](#)). The authors called for more nuanced methodological approaches, including assessments of SGM stress. The little work available on other biomarkers (CRP, IL-6, IL-10, etc.) has been conducted primarily among young (aged 16–29) men who have sex with men and transgender women, noting broadly elevated levels of systemic inflammation ([Morgan et al., 2019a](#); [Morgan et al., 2019b](#)). Data on gene expression and SM health are particularly sparse. Among SM men with HIV, differential expression of genes related to inflammation/immune function as well as cancer and CVD risk was observed in those reporting high ( $n = 18$ ) vs low ( $n = 20$ ) SM stress ([Flentje et al., 2018](#)).

Sexual and gender minorities may choose to attempt to conceal their stigmatized status. “Outness” can differ by relational/social context (e.g., family, friends, work) ([Mohr and Fassinger, 2000](#)). Greater outness has paradoxically been associated with both better psychological resilience (positive identity) and stress-buffering effects (greater community acceptance), but also greater exposure to discrimination ([Doyle and Molix, 2016](#); [Juster et al., 2013](#)). For example, among 78 gay men, elevations in IL-6 were seen in those reporting greater discrimination, but only among those reporting greater outness ([Doyle and Molix, 2016](#)). Similar to sexual minorities, transgender adults in the U.S. typically conceal their identity to avoid stigma and victimization ([Rood et al., 2017](#)), however, findings within this population are much more limited. Outness has also been linked to greater physical health in gay men ([Cole et al., 1996a, b](#)) although this effect is complex, and modified by

individual sensitivity to social rejection (with closeting apparently providing some health-protective effects for those most vulnerable to homophobic rejection) ([Cole et al., 1997](#)). Similar to sexual minorities, a study conducted among 56 transgender and gender non-conforming youth (aged 9–20) found a significant association between inflammation (assessed via CRP and dried blood spots) and higher composite score on the Gender Minority Stress and Resilience scale, although individual components of the scale were not significantly associated with inflammation ([McQuillan et al., 2021](#)). Taken together, factors contributing to outness and mental/physical health effects are complex and multifactorial and must be examined in further detail ([Mohr and Fassinger, 2000](#)).

#### 5. Methodological hurdle: accessing a large, representative sample of SGM individuals

A central challenge of conducting biological research focused on SGM health is the difficulty in accessing a diverse, representative sample. In fact, it is difficult to even estimate how many Americans are sexual or gender minorities. Most federal surveys including the Census and the American Community Survey do not ask respondents their sexual and gender identity ([National Academies of Sciences, 2020](#)). Both the Census and the American Community Survey do now include questions for partnered individuals as to whether they are partnered with a person of the same or different-sex. About one million same-sex couples were reported in the US in 2019 according to the American Community Survey ([US Census Bureau, 2020](#)). But, same-sex married couples accounted for just 1 % of married-couple households and 5 % of cohabiting-couple households in the US in 2019. Just over 50 % of couples were same-sex couples headed by women. Of same-sex couples, about 15 % had a child under 18 in their household, about 58 % were married, and about 42 % were cohabiting ([Taylor, 2020](#)). And while reporting is limited among sexual minorities, no data exists regarding the number households headed by transgender individuals. Even more so, these counts miss the proportion of the population that identifies as a sexual or gender minority and are single, as well as those that identify as a sexual or gender minority and are partnered with someone of a different gender (e.g., a bisexual individual partnered with someone of a different-sex). As noted above, the percentage of US adults who identify as SGM has steadily increased since 2012 ([Gates, 2017](#)). Between 2012 and 2017, the percentage of US adults personally identifying as SGM grew from 3.5 % in 2012 to 4.5 % in 2017. The growth was most concentrated among Millennials who were born between 1980 and 1999; 5.8 % identified as SGM in 2012, and 8.2 % did in 2017. The growth occurred across the gender, race/ethnicity, and education spectrums. Yet even with this growth in the SGM population, their continued low incidence in the population make them a hard to reach population.

Collecting a large, diverse sample of sexual and gender minorities to understand their stress biology is important ([Comron et al., 2012](#)) because SGM who live in communities and states with adverse climates

(i.e. that lack sexual orientation or transgender employment discrimination bans) have elevated psychiatric disorders (Blosnich et al., 2016; Hatzenbuehler et al., 2009) and increased health care use and costs (Hatzenbuehler et al., 2012). As an indicator of how policy contexts shape health, sexual and gender minorities' wellbeing declined in the months before and after the 2016 presidential election (Gates, 2016). Further, intersectionality is “a theoretical framework that posits that multiple social categories (e.g., race, ethnicity, gender, sexual orientation, socioeconomic status) intersect at the micro level of individual experience to reflect multiple interlocking systems of privilege and oppression at the macro, social-structural level (e.g., racism, sexism, heterosexism)” (pp. 1267, Bowleg, 2012). Intersectionality plays out in the lives of sexual and gender minorities; sexual and gender minorities of color face greater stigma and hostility due to their sexual minority status (Groves et al., 2006; Lewis, 2003; Meyer et al., 2008; Schulte and Battle, 2004; Swank et al., 2013; Whitfield et al., 2014). For example, the self-rated health disadvantage of women in same-gender cohabiting unions as compared to women in different-gender marriages was higher in magnitude for women who were Black and Hispanic as compared to women who were White (Liu et al., 2017). Large, racially/ethnically and geographically diverse samples of sexual and gender minorities are critical to understand the contextual effects of stress in this population.

## 6. Methodological opportunities: biological data collection in the home

Historically, large community- and population-based studies investigating how social contexts and identities shape health have relied on vital records or participant self-reports of mental and physical functioning (McDade et al., 2007). An advantage of this approach is that it can be used to recruit large, representative, and diverse samples, as well as foreground a wide range of environments and experiences that have important effects on health. However, self-report measures are subjective and potentially biased, and cannot reveal the underlying biological mechanisms and pre-disease pathways that connect contexts and health outcomes. By contrast, biomedical approaches bring participants into controlled laboratory or clinical settings where it is feasible to collect direct measures of biological function and health status. But these studies rely on small, and often very select, samples of participants and rarely consider measures of social context and experience beyond standard measures of socioeconomic status or self-reported health behaviors.

Over the past 20 years, calls for more multi-level, integrative approaches to understanding health and health disparities, as well as the rapid expansion of methodological options for collecting biological samples in non-clinical settings, have helped bridge this gap (Lindau and McDade, 2007; Seeman and Crimmins, 2001). Some large population-based surveys (e.g., Add Health), as well as smaller community-based studies, are now including biological measures to facilitate investigations into the origins of health disparities in general, and disparities in SGM groups in particular.

The logistics and burdens associated with collecting blood—the clinical standard for many, if not most, measures of physiological function and health—pose barriers to implementation outside of the clinical setting. Now, however, several low cost, “field-friendly” alternatives to venipuncture exist, including dried blood spot (DBS) sampling, in-home collection of small vials of saliva or urine, or collection of small hair samples (Lindau and McDade, 2007). Dried blood spot sampling—drops of capillary whole blood collected on filter paper following a simple prick of the finger—has been integrated into several studies because it affords the following advantages (McDade et al., 2007): 1) Sample collection is relatively straightforward, and can be implemented in the home by non-medical interviewers, or by participants themselves (Roberts et al., 2016); 2) most biomarkers in DBS remain stable for days, if not weeks, at room temperature; 3) samples can be shipped through the regular mail; and 4) protocols for hundreds of biomarkers have been

validated, including indicators of endocrine, immune, reproductive, and metabolic function, as well as measures of gene sequence, expression, and DNA methylation (Freeman et al., 2018; McDade et al., 2016, 2007).

Saliva and hair contain a more circumscribed set of biomarkers, but may be particularly well-suited for research on stress physiology (Adam and Kumari, 2009; Russell et al., 2012). Saliva sampling is non-invasive and facilitates repeat sampling, which is particularly useful for modeling diurnal variation in cortisol production, and investigating responsiveness to acute stressors. Hair has the advantage of providing a retrospective, integrated measure of cortisol production over several weeks to generate insight into levels of chronic stress. However, in some cases this approach may be limited by participants' willingness to provide a hair sample, impacts of hair treatments on cortisol recovery, and inability to model diurnal cortisol rhythms or responses to acute stressors (Kirschbaum et al., 2009; Sauve et al., 2007).

The toolkit for the collection of biological samples in the home is rapidly expanding, and assay technologies increasingly allow the quantification of proteins, gene transcripts, epigenetic marks, and DNA sequences in smaller quantities of sample, at higher resolution, at lower per sample costs (McDade et al., 2016). In addition, wearable technologies and smart phone apps provide additional opportunities for objectively measuring sleep, physical activity, and aspects of cardiovascular function neural activity (George et al., 2017; Lindau and McDade, 2007; Marino et al., 2013). The ability to engage hard-to-reach and under-represented groups with methods that allow for biological data collection in the home has tremendous potential to advance our understanding of the determinants of health in SGM communities.

## 7. Call to action

As reviewed, existing studies of stress and health among SGM have marked limitations. First, there is a predominate focus on sexual minority men rather than sexual minority women, although 55 % of sexual minorities are women (Gates, 2017). Further, there is very little research distinguishing within sexual and gender identities. For example, given the elevated risk for psychological distress among bisexual individuals as compared to lesbian and gay identified individuals (Ross et al., 2018; Salway et al., 2019), it is critical that biological stress and health within-sexual and gender minority research is examined. Younger generations are less likely to identify as gay or lesbian (Gates, 2017), and thus understanding the experiences of non-monosexual identities which may be largely invisible (Yoshino, 2017) is critical. This begins with measurement that allows for individuals to identify their gender and sexual identity in multiple ways. Recent research indicated that during the COVID-19 pandemic, bisexual and individuals that identified as other non-monosexual or multiple sexual identities reported more stress than both gay and lesbian individuals, and sexual minorities reported more stress than heterosexual individuals (Manning and Kamp Dush, 2021). The long-term consequences of the unique stress of the pandemic (Goldberg et al., 2021; Moore et al., 2021), and the accompanying racial trauma stress sparked by the murder of George Floyd and others at the hands of police (Brodie et al., 2021; Liu and Modir, 2020) and elevated Asian American discrimination and violence (Hopwood, 2021; Jeung et al., 2021; OCA-Asian Pacific American Advocates, 2020; Ruiz et al., 2020), are unknown. Research and intervention efforts related to the stress of the pandemic and racial trauma must examine these intersectional issues and that begins with measurement. Studies that do not measure sexual identity and gender identity at (Moore et al., 2021) the minimum will have unmeasured, systematic, critical heterogeneity in their estimates. We call on scholars to include a question or series of questions on sexual and gender (Patterson et al., 2020), and we call on paper and grant reviewers to demand it, and if sexual and gender identity are not reported, it needs to be listed as a limitation.

It is remarkable how little research we have on the biological indicators of stress for sexual and gender minorities given how well documented their stress has been for over thirty years. As a key modifier

of effects, research examining biobehavioral health should routinely measure and report the sexual and gender identity of their samples. In addition, studies need to be designed and implemented that explicitly seek to understand the stress biology of sexual and gender minority individuals. Critically, the intersectional effects of sexual, gender, and racial minority status on biobehavioral health remain unexamined; 40% of sexual/gender minorities are also racial/ethnic minorities (Gates, 2017). Further, these studies need to include, in addition to the robust assessment of biological indicators of stress and health, sufficient assessment of minority stress, outness, and behavioral factors (sleep, depressive symptoms, and health behaviors) needed to delineate mechanistic pathways linking minority stress with biological health.

Data on stress biology among SGMs is critical for identifying modifiable mechanisms and highlighting structural factors linking stressor exposure with biological health. Specifically, stress biology indicators hold particular promise for identifying the mechanisms underlying sexual and gender minority health disparities. Without fully-powered stress biology studies of sexual and gender minorities, the underlying causes of biological stress will remain elusive, and mechanisms that can be identified as potential targets for change will remain hidden.

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