J Behav Med
https://doi.org/10.1007/s10865-019-00120-6

The relationship between minority stress and biological outcomes: A systematic review

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Received: 4 May 2019 / Accepted: 27 November 2019

Abstract Sexual minority (non-heterosexual) individuals experience higher rates of physical health problems. Minority stress has been the primary explanatory model to account for this disparity. The purpose of this study was to identify in published research empirically established relationships between minority stress processes and biological outcomes and identify avenues for future research. The PubMed database was queried with search terms relevant to minority stress and a comprehensive list of physical and biological outcomes. To be included in the analysis, studies had to examine the relationship between minority stress and a biological outcome among sexual minority individuals. Those meeting inclusion criteria were coded for key variables including methodology used, positive and null results, participant characteristics, and specific minority stress processes and biological outcomes considered. In total, 26 studies met inclusion criteria. Studies tested relationships between specific minority stress processes including prejudice, expectations of prejudice, concealment of sexual orientation, and internalized stigma and multiple biological outcomes, such as overall physical health, immune response, HIV specific outcomes, cardiovascular outcomes, metabolic outcomes, cancer related outcomes, and hormonal outcomes. Studies included both analyses that detected this relationship (42% of analyses) and analyses that did not detect this relationship (58%). There is substantial evidence to support the relationship between minority stress and biological outcomes, yet additional research is needed to identify the measurements and outcomes that have the most rigorous and replicable results.

Keywords Minority stress · Sexual minority · Lesbian · Gay · Bisexual · Biological outcomes

Introduction

Sexual minority (non-heterosexual) individuals experience higher prevalence of mental disorders (Cochran et al., 2003), substance use (Cochran et al., 2004; Stall et al., 2001), and poorer physical health (Cochran & Mays, 2007; Conron et al., 2010) when compared to heterosexual persons. Relative to mental health and substance use outcomes, far fewer studies address the physical health of sexual minority people. Yet, studies have shown that sexual minority people experience higher prevalence of some health problems such as asthma, activity limitation, and risk for or actual cardiovascular risk (Conron et al., 2010; Fredriksen-Goldsen et al., 2017; Lick et al., 2013). Sexual minority women are also at greater risk for obesity or being overweight (Boehmer et al., 2007).

The minority stress model has been the primary explanation for sexual minority health disparities (Herek &

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10865-019-00120-6) contains supplementary material, which is available to authorized users.

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Published online: 20 December 2019

Garnets, 2007; Institute of Medicine, 2011). The minority stress model describes stress processes related to stigma and prejudice, including experiences of prejudice and discrimination events and conditions, the expectations of prejudice and discrimination, concealment of sexual orientation, and internalization of societal stigma (Meyer, 2003). Minority stress is a unique source of stress in that it is related to societal conditions characterized by antigay stigma and prejudice, and, thus, exposes sexual minority people to excess stress above the stress experienced by their heterosexual peers. Minority stress has been conceptualized to include both distal stressors (i.e., objectively measurable events such as prejudice or discrimination events or conditions) and proximal, or internalized, stressors (i.e., expectations of prejudice and discrimination, concealment of sexual orientation, and internalization of societal stigma, Meyer, 2003). Research evidence has supported the relationship between minority stress and mental health outcomes, including substance use (Livingston et al., 2017; McCabe et al., 2010; Meyer, 2003). Evidence also suggests that minority stressors (e.g., concealment or community level stigma) are related to poorer physical health outcomes for sexual minority individuals (Lick et al., 2013), for example, with studies finding a relationship between minority stress and progression of HIV (Cole et al., 1996b) and poorer overall physical health (Frost et al., 2015).

Stress can cause biological changes that may impact the body at multiple levels ranging from systemic disease processes (Cohen et al., 2007) to the level of the expression of genes (Slavich & Cole, 2013). One can consider stress responses, which are necessary for everyday function, to be a process of allostasis, wherein multiple biological systems work together to maintain homeostasis of the body and stress response (McEwen, 2004). Chronic stressors, however, can result in overload of this system, termed allostatic load or overload, which involves multisystemic changes (e.g., immune, cardiovascular, metabolic) in response to stress (McEwen, 2004). One biological response to stress includes the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which may become less responsive in cases of chronic stress and can subsequently have impacts on immune function, such as increased risk of viral infection (Cohen et al., 2012). Chronic psychological stress can also lead to flatter cortisol slopes, which may be the result of lower waking cortisol, and reduced responsiveness to anti-inflammatory signals (Miller et al., 2002). Exposure to stress at critical times can also alter inflammatory function; for example, adverse childhood experiences can influence subsequent inflammation many years later (Miller & Cole, 2012). Chronic stress is also related to clinical outcomes, for example the development of metabolic syndrome, associated with risk for diabetes and heart disease, a syndrome defined by elements such as high blood pressure, collection of fat around the waist, and insulin resistance (Chandola et al., 2006).

The type of stressor is also related to the biological responses to stress. For example, stressful circumstances that involve social evaluation produce more robust increases in HPA-axis responses (Dickerson et al., 2009; Dickerson & Kemeny, 2004). Relatedly, sexual minority men have been shown to have greater fear of negative social evaluation than heterosexual men (Pachankis & Goldfried, 2006). Cognitive anticipation of stress, a process that is relevant to anticipating prejudice or discrimination, can also be related to cortisol response (Gaab et al., 2005).

The coping response to the stressor, understood here broadly to mean behaviors or cognitive processes in response to stress (Lazarus & Folkman, 1984), may also alter the subsequent biological response. Of note, a coping response is agnostic as to the effectiveness of the behavior or cognitive response in achieving a healthy outcome, the coping response is simply an attempt to respond to stress (Lazarus & Folkman, 1984). Under this definition, behaviors, such as substance use, which occur in response to minority stressors (e.g., Livingston et al., 2017), could be considered a coping response. Psychological mediators that have been proposed to impact the relationship between minority stress and mental health among sexual minority people include actions taken in response to a stressor such as emotion regulation, social isolation, or cognitive schemas (discussed in depth in Hatzenbuehler, 2009). These mediators may also alter biological responses to minority stress. Similarly, psychological mediators (e.g., schemas reflecting cynicism or hostile attributions to others) have been shown to partially or fully mediate the relationship between racial or ethnic discrimination and physical health among racial and ethnic minority individuals (Brondolo et al., 2011).

Chronic stressors have been implicated in changes in gene expression, which could be considered among the smallest units within the biological system, or inversely could be considered the great regulator of all other multisystemic effects. Epigenetic changes can occur with stress exposure (McEwen et al., 2012) and chronic interpersonal stress (Miller et al., 2009) and social isolation (Cole et al., 2007) are related to greater rates of expression of genes driving inflammatory processes. Inflammation, in turn, is related to earlier mortality (Kabagambe et al., 2011). Overall, and as depicted in Fig. 1, minority stress may alter biological function such as inflammation, immune function, cardiovascular function, metabolic function, and endocrine or hormonal function through dysregulation of the HPA-axis and changes in transcriptional regulation, either directly or through epigenetic mechanisms. These changes in biological function can, in turn, alter clinical outcomes (e.g., heart

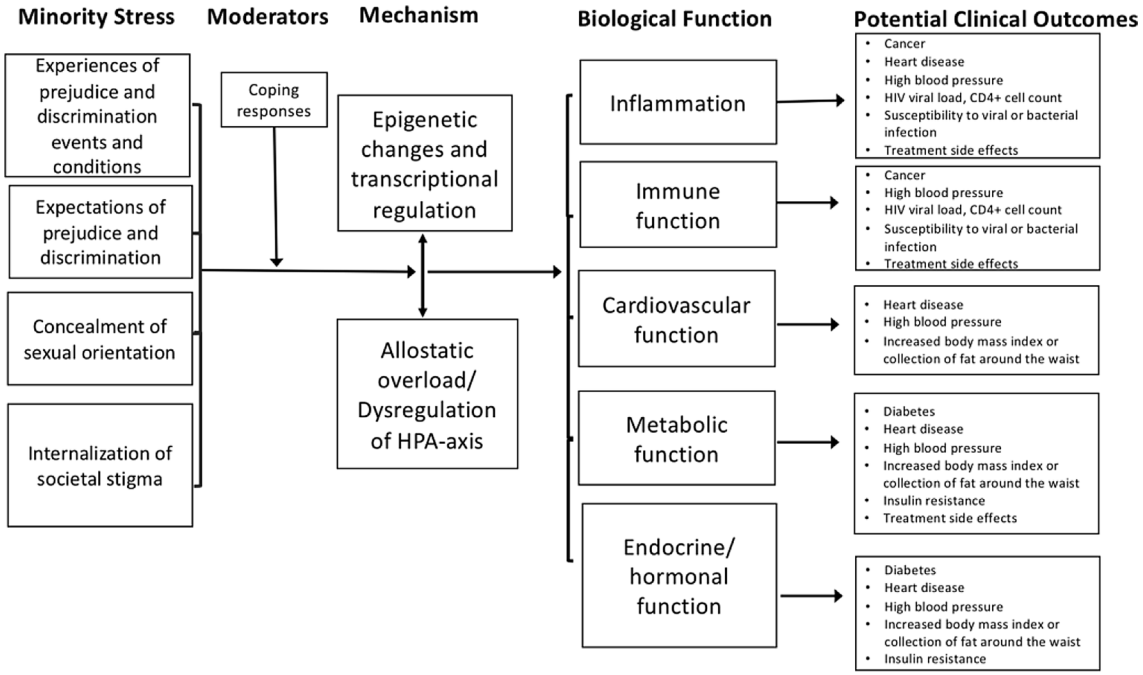

Fig. 1 Proposed conceptual model of how minority stress may impact health through biological mechanisms

disease, susceptibility to viral or bacterial infection) ultimately impacting the health of sexual minority individuals.

Despite the various biological pathways suggested, the mechanisms that play a role in the relationship between minority stress and health outcomes remain unclear. Furthermore, it is unknown which of the four broad minority stress components (i.e., prejudice events and conditions, expectations of rejection and discrimination, concealment of sexual identity, and internalized stigma) may impact biological processes and outcomes. The purpose of this systematic review is to identify existing research testing the relationship between minority stress processes and biological outcomes among sexual minority people. Due to heterogeneity in study methods and components of minority stress and biological outcomes tested, a meta-analytic review was determined to be inappropriate (Higgins & Green, 2011). The focus is minority stress related to sexual orientation, but not gender identity. Although the minority stress framework has been adapted for gender minority people (Hendricks & Testa, 2012), research on minority stress specific to gender identity and biological outcomes is limited.

Method

Data sources and search strategy

The PubMed database was queried between February and June of 2016 and again in November 2018 with minority stress related terms, and biological outcome terms (list of search terms can be found in Supplemental Material 1).

Inclusion criteria

To be included, studies had to meet the following criteria: (a) were empirical and published in peer-reviewed journals in English at any time through November of 2018; (b) included a measure of at least one minority stress process operationalized as prejudice events and conditions, expectations of rejection and discrimination, concealment of sexual orientation, or internalized stigma; (c) reported biological outcomes measured through assays and tests or self-report; (d) provided a statistical test of the relationship between at least one minority stress process and at least one biological outcome; and (e) included a report of results for sexual minority people.

Review of search results

Titles from the results of the PubMed searches were read by two research team members (a graduate student and a PhD-level researcher) and were determined to potentially

meet or not meet inclusion criteria. The Google Scholar database was also queried for the relevant search terms and results were reviewed by an undergraduate student and a post-baccalaureate research assistant until relevance declined considerably at the judgment of the reviewers. The purpose of the Google Scholar search was to identify articles that were not identified in the PubMed search. Abstracts of titles that were identified through searches were reviewed by two PhD-level researchers, and redundant results were identified and removed. When there was disagreement about whether or not a study met inclusion criteria, full manuscripts were reviewed and discussed, with inclusion disagreement resolved through consensus.

Coding

Articles meeting inclusion criteria were coded in a database to indicate the subject of the study; study methodology (cross-sectional versus multiple time measurement, and experimental versus observational); sexual orientation, gender, race/ethnicity, and HIV status of study participants; minority stress measures; biological outcomes measures; and whether the results showed a positive or null association between any minority stress measure and any biological outcome. The entries in this database were then checked for accuracy against the original articles by an additional researcher. When study results were unclear in terms of categorizing the variables described above, a member of the research team contacted the author of the relevant study to obtain additional information (this occurred for six studies, all but one of the authors provided the necessary information).

Because any study could provide more than one result, as when a study includes several independent or dependent variables, results are reported at both the study level (i.e. the study in which the results were published) and the analysis level (i.e., for each analysis across all studies). Analyses were interpreted as having detected a relationship if the reported p for the test statistic was less than 0.05; results were interpreted as not detecting a relationship if reported p for the test statistic was greater than 0.05, regardless of how authors had interpreted these associations. Thus, we did not include reported trends (e.g., $p < 0.10$) as significant.

Where authors reported both bivariate results and a multivariate test that included covariates intended to control for potentially confounding or other control variables in testing that relationship (e.g., demographic variables), we used the results of the multivariate relationship to represent the relationship detected by the study. However, we used the bivariate results when a multivariate model was included for a purpose other than improving the prediction of the relationship of the independent variable tested and the outcome (e.g., a model that examines a 3rd variable as a mediator). Interactions and simple slopes are included here when they were reported. Risk of bias was not assessed as there is no available tool to assess risk of bias across the multiple study designs (e.g., cross-sectional, longitudinal, randomized) examining the relationship between a minority stressor and a biological outcome (Page et al., 2018).

Characteristics of the studies

In total, 134 studies were identified as potentially meeting the inclusion criteria. Further review of these studies removed studies that did not meet inclusion criteria ($n = 108$, see Supplemental Material 2 for PRISMA Flow Diagram), for a total of 26 included studies. These studies, their outcomes, and relevant study results are summarized in Table 1. Studies that were generated from the same sample, but had different research questions and variables of interest are counted as separate studies within the following descriptive information (i.e., Cole et al., 1996b, 1997).

Sample characteristics

Twelve studies (46%) included only sexual minority men, six studies (23%) included sexual minority men and women, four studies (15%) included only sexual minority women, two studies (8%) included sexual minority people with nonbinary gender identities along with participants who identified as men and women, one study (4%) included heterosexual people along with sexual minority men and women, and one study (4%) included heterosexual and sexual minority women. Eight studies (31%) included only participants who were living with HIV, two (8%) studies included only participants who were HIV-negative, three (12%) studies included participants who were both living with HIV and were HIV-negative, and thirteen studies (50%) did not report participant HIV status. Four studies (15%) had samples of less than 50 sexual minority people, the remaining studies had more than 50 sexual minority people (range 62–6685). Across the studies, an average of 41% of the sexual minority respondents were also racial or ethnic minority (range 0–100%).

Study design

Most studies ($n = 17$, 65%) utilized cross-sectional data (one additional study was primarily longitudinal but also included a cross-sectional analysis; Cole et al., 1996b). There were nine longitudinal studies (35%), including three studies (12%) that collected data over 5 or more years, four studies (15%) that collected data over 1–7 days, and two experimental studies (8%), which over an hour collected data at

Table 1 Studies examining the relationship between minority stress and a biological or physiological outcome

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
1. Bauermeister et al. (2014)	Self-reported: health and days in the previous 30 when health was not good	397			n = 41 were living with HIV	Cross-sectional	More work discrimination was related to poorer self-rated health and more days when health was not good (including physical illness and injury).
2. Boehmer et al. (2013)	Arm morbidity related to cancer treatment gathered via self-report		181		Not stated	Cross-sectional	Discrimination was related to more arm symptoms among breast cancer survivors who were sexual minority women (tested through an interaction between sexual orientation and discrimination). Participants also included 257 heterosexual women.
3. Bogart et al. (2013)	Self-reported CD4 + cell count < or ≥ 200 and viral load (undetectable [< 50 copies per mL] versus detectable), number of AIDS-related symptoms such as diarrhea or fever experienced for more than 2 weeks of the past 3 months, side effect severity due to medications	348			Yes	Cross-sectional	Bivariate models tested the relationship between discrimination due to sexual orientation and biological outcomes, with separate models for Black and Latino sexual minority men. Among Black sexual minority men discrimination related to sexual orientation was related to AIDS-related symptoms but not medication side effects, CD4 + cell count ≥ 200, or undetectable viral load. Among Latino sexual minority men discrimination related to sexual orientation was related to more medication side effects, AIDS-related symptoms, and less likelihood of CD4 + cell count ≥ 200, but was not related to undetectable viral load.
4. Chae & Walters (2009)	Self-reported pain that was associated with impairment and self-appraised physical health	189	130	128	n = 96 were living with HIV	Cross-sectional	Discrimination related to race was not related to physical health. Discrimination related to race was predictive of greater pain/impairment.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
5. Cole et al. (1997)	CD4 + cell count, progression to low CD4 + cell count (≤ 15% of total lymphocytes measured by a laboratory), diagnosis of AIDS, or death	72			Yes	Longitudinal observational every 6 months for up to 9 years	Rejection sensitivity (operationalized as a measure of comfort/discomfort with social situations involving one's sexual orientation) related to situations with strangers or in public was related to faster progression to low CD4 count, faster progression to AIDS, and reduced life expectancy in models that accounted for CD4 level at baseline, age, and other variables associated with changes in CD4. The same relationships were not observed for rejection sensitivity related to family or friends. For men who partially concealed their sexual orientation (versus those who were "out of the closet most of the time" or "completely out of the closet") there was no relationship between rejection sensitivity and the HIV/AIDS related outcomes described above. In individuals with low levels of rejection sensitivity, concealment was associated with faster progression of HIV/AIDS related outcomes.
6. Cole et al. (1996a)	Self-reported incidence of cancer, pneumonia, bronchitis, sinusitis, and tuberculosis in the previous 6 months	222			No	Longitudinal observational every 6 months for up to 11 visits (5 years)	Greater concealment of sexual orientation was related to greater incidence of all disease outcomes (considered together as overall physical health) and also greater incidence of cancer (considered alone), all infectious diseases (considered together), and bronchitis and sinusitis (considered alone) in models including demographic, health behavior, and social desirability.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
7. Cole et al. (1996b)	CD4 + cell count, progression to low CD4 + cell count (≤ 15% of total lymphocytes measured by a laboratory), HIV-related symptoms, diagnosis of AIDS, or death	80			Yes	Observational every 6 months for up to 9 years, with cross-sectional analysis at baseline in addition to longitudinal analysis	Level of concealment of sexual orientation was not related to CD4 + cell count or HIV-related symptoms at baseline. More concealment of sexual orientation was related to faster progression to low CD4 + cell count, faster progression to AIDS, and reduced life expectancy in models that accounted for CD4 level at baseline, age, ARV use, and other variables associated with changes in CD4. This relationship was not accounted for by 17 potential mediators (e.g., anxiety, depression, coping).
8. Doyle & Molix (2016)	IL-6 from saliva	78	21		Not stated	Cross-sectional	Among men, discrimination and covering (downplaying one's minority identity as related to concealment) were not related to IL-6, but there was an interaction between discrimination and covering and IL-6 such that men who had high discrimination and low covering had higher IL-6 (confirmed through simple slopes analysis). Among women, high discrimination was related to lower IL-6 (contrary to expectation), but there was no relationship between covering and IL-6 nor was there an interaction between discrimination, covering, and IL-6.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
9. Flentje et al. (2018)	Gene expression from leukocyte RNA, plasma TNF-α and IL-6	38			Yes	Cross-sectional	Moderate or high versus low minority stress (covarying stimulant use) was related to differential expression of 90 genes and 138 pathways of genes evidencing 2-directional perturbation. Differentially expressed genes and pathways were related to inflammation, immune function, cardiovascular function, and cancer. There was no difference in plasma IL-6 or TNF-α by minority stress.
10. Friedman et al. (2018)	Viral load from self-report	1229			Yes	Cross-sectional	In a structural equation model, there was no relationship between violence/victimization and viral load ($p < .10$, but not $p < .05$).
11. Frost et al. (2015)	Self-appraised physical health and physical health problems (assessed by external ratings of physical health interviews)	198	198		Not stated	Cross-sectional study (longitudinal data were collected but not used in analyses of minority stress and biological outcomes).	In cross-sectional analyses covarying demographic covariates, prejudice events were related to physical health problems, but expectations of rejection based on identity, everyday discrimination, internalized homophobia, and outness were not, and none of these components of minority stress were related to self-appraised physical health.
12. Gamarel et al. (2015)	Detectable versus undetectable HIV viral load assessed through a laboratory test	371			Yes	Cross-sectional	Internalized heterosexism (of the participant or their partner) did not predict HIV viral load in models including HIV-related variables, alcohol, smoking, depression, and demographic variables.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
13. Hatzenbuehler & McLaughlin (2014)	Salivary cortisol collected at 3 time points (before a stressor, after a modified trier social stress task, and 20 min after the stressor ended)	34	40		Not stated	Experimental over 3 time points over an hour	The degree to which people perceive that others have stigma towards sexual minority people was not related to cortisol area under the curve in a model that included structural stigma, demographics, and covariates thought to impact cortisol. Structural stigma of the place of residence when the participant was an adolescent was not related to cortisol area under the curve when considered continuously, but was related when dichotomized (high versus low structural stigma environments).
14. Hengge et al. (2003)	Plasma based norepinephrine, epinephrine, and cortisol; blood pressure and heart rate; white blood cell count, neutrophilic granulocytes, CD8 cell count, and CD16/56 cell counts from while blood	25			n = 12, minority stress related to sexual orientation only tested in HIV-negative participants	Experimental: 15 min of relaxation, 30 min interview focusing on issues related to homosexual sexual orientation that were upsetting, 15 min of relaxation	Norephinephrine and epinephrine increased after exposure to discussion of stress related to homosexual sexual orientation that the participant had rated as upsetting (e.g., homosexual attitudes, occupational situations, sexuality), but was not at a level representative of statistical significance. Cortisol changes were not observed in response to the discussion of stress related to sexual orientation. Blood pressure and heart rate were higher during the exposure to the discussion of stress related to sexual orientation. White blood cell count and neutrophilic granulocytes increased after exposure to a discussion of stress related to sexual orientation, but there were no observed changes in CD8 cell counts or CD16/56 cell counts.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
15. Huebner & Davis (2005)	Salivary cortisol, collected at 11 am, 2 pm, and 5 pm on 2 days	73			No	Observational over 6 time points over 2 days	Being more out at work was related to more elevated cortisol levels and negative affect in models accounting for cortisol levels on days at home. A model testing whether negative affect mediates the relationship between outness and cortisol was not supported.
16. Johns et al. (2017)	BMI calculated from self-report		901		Not stated	Cross-sectional	BMI was not related to being bullied on school property, bullied electronically, or threatened or injured with a weapon on school property.
17. Juster et al. (2013)	Diurnal salivary cortisol collected 5 times per day over 2 days; allostatic load was calculated using 21 biomarkers representing immune/inflammatory, neuroendocrine, metabolic, and cardiovascular systems	26	20		Not stated	Longitudinal observational over 2 days	Disclosure of sexual orientation was associated with differences in diurnal cortisol in models that covaried conscientiousness and awakening time, and post hoc analyses identified that sexual minority people who disclosed their sexual orientation had lower cortisol 30 min after awakening. Disclosure status was not related to allostatic load in models covarying conscientiousness and age. Study included 41 heterosexual participants, but they were not included in analyses testing disclosure.
18. Li et al. (2017)	Sleep quality from self-report	2483	4202		Not stated	Cross-sectional	School bullying and victimization partially mediated the relationship between sexual minority status and poorer sleep quality.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
19. Manigault et al. (2018)	Salivary cortisol	13	15	17 did not specify, 4 identified gender as not man or woman	Not stated	Longitudinal, multiple time measurements over 1 week	Disclosure overall and disclosure to family was related to lower cortisol area under the curve. Neither disclosure to coworkers, disclosure to friends/coworkers/acquaintances, or disclosure to religious groups was related to cortisol area under the curve. Age of disclosure to siblings was related to lower cortisol area under the curve, but neither earliest age of disclosure nor age of disclosure to father, mother, family, or friends was related to cortisol area under the curve. Neither disclosure overall, nor to family, friends/coworkers/acquaintances, coworkers, nor religious groups was related to cubic cortisol trajectories. Disclosure overall and disclosure to family were related to lower cortisol upon awakening, 45 minutes after awakening, and 12 hours after awakening.
20. Martin-Storey et al. (2018)	Sleep restedness from self-report	53	66		Not stated	Cross-sectional: data was collected over 24 hours but restedness was measured at a single timepoint	Among women, there was an interaction between support for same-sex marriage in the state and sexual minority status in predicting restedness, there was no interaction among men. There was no interaction between sexual minority status and legality of same-sex marriage in the state among men or women.
21. Mason (2016)	BMI calculated from self-reported height and weight		377		Not stated	Cross-sectional	Outness was not related to being normal weight versus underweight. Outness was related to overweight status (versus normal weight), but was not related to obese status (versus normal weight).

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
22. Mason & Lewis (2015)	Overweight, obese, and normal weight derived from BMI based on self-reported height and weight		737		Not stated	Cross-sectional	Less public identification as lesbian (outness) was related to less likelihood of obesity compared to normal weight. Less public identification as lesbian was not related to differences in likelihood of obesity (compared to overweight) or overweight compared (compared to normal weight). Neither personal feelings about lesbian identity nor attitudes about other lesbians were related to BMI status.
23. Mereish (2014)	Overweight and obese derived from BMI based on self-reported height and weight		155		Not stated	Cross-sectional	More discrimination related to minority sexual orientation was related to being overweight and obese after accounting for demographic and weight related health behaviors.
24. Norcini Pala et al. (2015)	CD4 + cell count and HIV viral load measured via self-report	120			Yes	Cross-sectional	Within a structural equation model internalized homophobia was related to lower CD4 + cell counts and victimization/discrimination was related to higher viral load among sexual minority men living with HIV. Internalized homophobia was not related to viral load, and victimization/discrimination was not related to lower CD4 + counts. Expectation of family discrimination was not related to viral load nor to CD4 + cell count. In a mediation model, internalized homophobia mediated the relationship between expectations of family discrimination and CD4 + cell counts.

Table 1 (continued)

Source	Biological or physiological outcome	Sexual minority			Participants living with HIV	Method	Main findings
		Men	Women	Non-binary gender			
25. Parra et al. (2016)	Diurnal cortisol slopes measured through saliva assessed 6 times throughout a day	35	27		Not stated	Observational over 6 time points within a day	In bivariate models stressful life events (discrimination) related to LGB identity were not related to cortisol slopes ($p = .06$) and internalized homonegativity was not related to cortisol slope. In a mediation model, more stressful life events related to LGB status were related to greater depression and this was mediated by flatter diurnal cortisol slopes.
26. Ullrich et al. (2003)	CD4 + cell count assessed by laboratory	73			Yes	Cross-sectional	Concealment of sexual orientation was related to CD4 + cell count in models that covaried neuroticism and HIV progression. Depressive symptoms, degree to which they felt constrained when talking about HIV, and social support satisfaction did not mediate the relationship between concealment and CD4 + cell count. Social support satisfaction was a moderator of the relationship between concealment and CD4 + cell count such that among people with low social support satisfaction, there was a minimal relationship between concealment and CD4 + cell count, but among people with high social support satisfaction, greater concealment was associated with lower CD4 + cell count, and less concealment was associated with higher CD4 + cell count.

multiple time points. The latter two were the only studies that employed experimental methodology (8%); the remaining studies were all observational.

Measures

Twelve studies (46%) had objectively measured biological outcomes and 14 studies (54%) utilized self-reported outcomes.

Data presentation

We report results at the analysis level and study level. The 26 studies reported data from 125 different analyses. The count of analyses excludes analyses that examined minority stress in relation to expression of over 19,000 genes using a procedure to minimize the false discovery rate (Flentje et al., 2018). We describe proportions of analyses that detected a relationship between minority stress and a biological outcome overall, and then, separately, by biological outcome, minority stress process, and study methodology.

Results

Of the 125 analyses, 53 (42%) detected a statistically significant association between the component of minority stress and the biological outcome, and 72 (58%) analyses did not find evidence of a relationship. Twenty-one of the 26 studies (81%) included at least one analysis that documented an association between minority stress and a biological outcome and 20 of the 26 studies (77%) included at least one analysis that did *not* detect such a relationship. Outcomes and the specific components of minority stress measured across the studies are summarized in Table 2.

Results by minority stress processes

All of the components of minority stress were tested across the studies.

Prejudice events and conditions

Both acute and chronic exposure to prejudice events and conditions were tested in relationship to a biological outcome in 35 analyses (13 studies) with 15 (43%) of these analyses finding a relationship between prejudice and a biological outcome. Prejudice events and conditions were measured based on the frequency of prejudice related events in 24 analyses (7 studies) including 11 (46%) analyses that found a relationship between the frequency of prejudice related events and a biological outcome. A sample item of a prejudice event and condition is "How many times have you been treated unfairly by your coworkers, fellow students, or colleagues because you are a gay, lesbian, or bisexual person?" (adapted from Szymanski, 2006 and used by Mereish, 2014). Prejudice events and conditions were also operationalized as distress resulting from microaggressions (1 of 2 analyses detected, Chae & Walters, 2009); whether the participant had ever felt discriminated against (1 of 1 analysis detected, Boehmer et al., 2013); if the participant had ever been bullied, e-bullied, or threatened or injured with a weapon (none of the three analyses detected an effect, Johns et al., 2017); the experience of specific employment discrimination experiences (2 of 2 analyses detected, Bauermeister et al., 2014); the experience of physical assault or intimate partner violence (0 of 1 analysis detected, Friedman et al., 2018); or whether the participant lived in a place where same-sex marriage was not legal (0 of 2 analyses detected, Martin-Storey et al., 2018). Eighteen analyses (7 studies) set specific timeframes for the discrimination events (i.e., 3 months or 1 year), of which 9 (50%) analyses found a relationship between discrimination and a biological outcome.

Expectations of rejection and discrimination

Twenty-one analyses (5 studies) were run testing the relationship between expectations of rejection or discrimination and a biological outcome, with eight (38%) of these analyses detecting a relationship. Anticipation of rejection was measured in terms of the expectation that one's family would reject them (0 of 1 analyses detected, Norcini Pala et al., 2015). A sample item of anticipation of rejection was "As a homosexual/bisexual, I am afraid of being discriminated against by my family members" (Norcini Pala et al., 2015). Analyses also tested the relationship between rejection sensitivity, or the degree of discomfort in social situations when one's sexual orientation may be identified, and a biological outcome. Relationships between rejection sensitivity in regard to strangers (3 of 3 analyses detected) but not to family or friends (0 of 3 analyses detected) and biological outcomes were detected; further analyses showed that rejection sensitivity was only related to biological outcomes among those who were open about their sexual orientation (3 of 3 analyses detected) as opposed to those who were not (0 of 3 analyses detected, Cole et al., 1997). An additional analysis employed a measure rating perceived stigma towards gay and lesbian people and did not detect a relationship (Hatzenbuehler & McLaughlin, 2014). Two analyses tested the relationship between a composite of environmental stigma variables and a biological outcome and detected a relationship in one of two analyses (Hatzenbuehler & McLaughlin, 2014). Two analyses used a measure

that asked participants to assess how other people would accept or reject someone with similar individual characteristics (e.g., sexual orientation, race) and did not detect a relationship (Frost et al., 2015). Two analyses used the proportion of adults that supported same-sex marriage from the state of residence and detected a relationship between this construct and a biological outcome in one of two analyses (Martin-Storey et al., 2018).

Concealment of sexual orientation

Fifty analyses (10 studies) tested the relationship between concealment or outness and a biological outcome, 25 (50%) of these analyses detected a relationship. Sixteen analyses used a 5-point scale to assess the degree to which study participants were "in" or "out of the closet" relative to other sexual minority people (e.g. "relative to other lesbian/gay individuals, I am…" as in Mason, 2016), with 11 (69%) of these analyses detecting a relationship between minority stress and the biological outcome. Concealment was measured as disclosure to multiple categories of people (0 of 2 analyses detected, Frost et al., 2015); assessment of whether specific work colleagues know about one's sexual orientation (1 of 1 analysis detected, Huebner & Davis, 2005); a dichotomized variable representing disclosure of sexual orientation to family and friends (2 of 3 analyses detected, Juster et al., 2013); on a scale which measured comfort and fear related

Table 2 Number of studies and analyses that tested a relationship, by biological outcome and component of minority stress

	Total number		Proportion of analyses that detected a relationship
	Studies	Individual analyses	
Biological outcome			
Overall physical health			
Physical health	4	14	0.29
Pain	1	1	1.0
Sleep	2	5	0.4
Immune response			
Blood cell counts (non-HIV)	1	4	0.5
Respiratory infection	1	3	1.0
Circulating inflammatory markers (IL-6 or TNF-α)	2	10	0.2
HIV specific outcomes			
HIV-related laboratory outcome	7	22	0.41
HIV/AIDS related death	2	5	0.60
HIV/AIDS related symptoms or AIDS diagnosis	3	8	0.63
HIV treatment related side effects	1	2	0.5
Cardiovascular outcomes			
Change in blood pressure/heart rate	1	2	1.0
Metabolic outcomes			
BMI	3	13	0.31
Hormonal outcomes			
Cortisol	6	31	0.42
Norepinephrine/epinephrine	1	2	0.0
Cancer related outcomes			
Cancer incidence	1	1	1.0
Cancer treatment side effects	1	1	1.0
Allostatic load			
Allostatic load	1	1	0.0
Type of minority stress			
Prejudice related stress (chronic and acute)	13	35	0.43
Expectations of rejection and Discrimination	5	21	0.38
Concealment or component of concealment/outness	10	50	0.50
Internalized stigma	5	8	0.13
General stress related to sexual orientation	2	11	0.36

to concealment (1 of 3 analyses detected, Mason & Lewis, 2015); through a construct described as "covering"—that is, the degree to which sexual orientation is downplayed (0 of 2 analyses detected, Doyle & Molix, 2016); and using the Outness Inventory (Mohr & Fassinger, 2000) scale (9 of 22 analyses detected, Manigault et al., 2018).

Internalized stigma

Eight analyses (5 studies) tested the relationship between internalized stigma and a biological outcome, only one (13%) analysis detected this relationship. All of these studies employed different measures to assess internalized stigma, each of which consisted of multiple items assessing the construct (e.g., "felt that being gay is a personal shortcoming" from Frost & Meyer, 2009, as used by Frost et al., 2015).

General stress related to sexual orientation or multicomponent measure of minority stress

General stress related to sexual orientation, operationalized as a discussion of issues related to homosexuality that the participant found upsetting, was tested with four of nine (44%) analyses detecting a relationship (Hengge et al., 2003). A subscale of the Cultural Assessment for the Risk of Suicide (Chu et al., 2013), which assesses multiple components of minority stress, failed to detect a relationship between minority stress and biological outcomes (0 of 2 analyses); however, in analyses examining gene expression, multiple relationships were detected (90 individual genes and 138 gene set pathways, not included in counts; Flentje et al., 2018).

Results by biological outcome

The biological outcomes and components of minority stress included in each of the studies covered within this review and descriptions of relevant analyses are in Table 2. The outcomes are heterogenous and are included here to document which outcomes have been examined in relation to minority stress to inform future research in this area.

General physical health

In total, 20 analyses (7 studies) investigated the relationship between minority stress and overall physical health including pain and sleep, with seven detecting a relationship. Physical health outcomes included self-appraised physical health; number of days when health was not good; incidence of one or more disease outcomes or physical health problems; pain; and sleep quality, duration, and restedness.

Immune response

Seventeen analyses (4 studies) examined minority stress in relation to immune responses not attributable to HIV disease, with seven of these analyses detecting a relationship. Analyses that examined changes in blood cell counts in response to minority stress found that white blood cell count and neutrophilic granulocytes increased, while there were no changes in CD8 or CD16/56 cell counts (Hengge et al., 2003). Analyses found support for minority stress in relation to the incidence of respiratory infection, bronchitis, and sinusitis (Cole et al., 1996a). Analyses did not find a relationship between plasma levels of IL-6 or TNF-α and minority stress (circulating inflammatory markers), but found evidence of a relationship between minority stress and gene expression (both single genes and pathways) related to immune function and inflammation (gene expression results are not included in counts of analyses). Analyses examined the relationship between minority stress and salivary IL-6, finding no relationship for men and a relationship in the unanticipated direction for women as well as an interaction between two elements of minority stress for men, but not women.

HIV specific outcomes

In total, 37 analyses (7 studies) were run testing the relationship between minority stress and an HIV related outcome, including HIV laboratory outcomes (viral load or CD4 + cell count), HIV/AIDS related death, HIV/AIDS related symptoms or AIDS diagnosis, and HIV treatment related side effects. Of the 37 analyses, 18 (49%) detected a relationship between minority stress and an HIV-related outcome.

Cardiovascular outcomes

Two analyses (1 study) investigated a cardiovascular outcome and found that exposure to minority stress resulted in changes in both blood pressure and heart rate (Hengge et al., 2003). Analyses identified differential expression of genes and pathways of genes related to cardiovascular function (Flentje et al., 2018).

Metabolic outcomes

Thirteen analyses (4 studies) examined the relationship between minority stress and body mass index (BMI). Of these analyses, four (31%) detected a relationship between minority stress and BMI.

Hormonal outcomes

Thirty-three analyses (6 studies) examined the relationship between minority stress and a hormonal outcome, with 13 (39%) of these analyses detecting a relationship. Most (94%) of these analyses used cortisol as an outcome, all using repeated measurements. Analyses examined exposure to minority stress and did not detect changes in norepinephrine and epinephrine (Hengge et al., 2003).

Cancer

Of the two analyses (2 studies) testing a relationship between minority stress and an outcome related to cancer, both detected a relationship. One of these analyses examined minority stress in relationship to cancer incidence, and found a relationship with cancer incidence primarily occurring on the skin (Cole et al., 1996a). The other analysis examined the relationship between minority stress and cancer-related treatment side effects (i.e., arm morbidity), and supported this relationship (Boehmer et al., 2013). An additional study included analyses that detected a relationship between minority stress and expression of single genes and pathways related to cancer (Flentje et al., 2018, not included in count of analyses).

Allostatic load

One analysis (1 study) examined the relationship between minority stress and allostatic load, and this relationship was not detected (Juster et al., 2013). This study had an extremely small sample size ($n = 14$) of individuals considered high in minority stress.

Variability by methodology

In total, 63 cross-sectional analyses (18 studies) were run with 20 of these (32%) detecting relationships between minority stress and a biological outcome. In the longitudinal observational analyses that spanned 5 or more years, 14 out of 20 (70%) detected a relationship between minority stress and a biological outcome (Cole et al., 1996a, 1996b, 1997). In the 28 analyses that utilized data collected over multiple time points during a time period of 1–7 days, the relationship between minority stress and biological outcomes was detected in 12 analyses (43%; Huebner & Davis, 2005; Juster et al., 2013; Manigault et al., 2018; Parra et al., 2016). The analyses of an experimental paradigm (spanning up to 1 hour) found that minority stress and biological outcomes were related in five out of 12 analyses (42% Hatzenbuehler & McLaughlin, 2014; Hengge et al., 2003).

Of the 53 analyses (14 studies) that used self-report methods, 22 (42%) detected a relationship between minority stress and the self-reported biological outcome. Of the 73 analyses that used objectively measured outcomes (i.e. laboratory assays), 31 analyses (42%) detected a relationship between minority stress and the biological outcome tested.

Discussion

The purpose of this review was to identify the state of the current research literature on the relationship between minority stress and biological outcomes among sexual minority people. The results indicate that forty-two percent of the analyses detected relationships between minority stress and biological outcomes. Most of the studies used cross-sectional methods (65%) and self-report methods to capture biological outcomes (54%). Of note, few analyses detected relationships between minority stress and the biological outcome in unanticipated directions.

Minority stress was related to physical health; incidence of respiratory infection; immune response; HIV-related laboratory outcomes, symptoms, treatment side effects, and AIDS mortality; changes in cardiovascular function; BMI; cortisol; and cancer incidence and treatment side effects. Immune function, cancer, and cardiovascular function may show considerable promise for future investigation in relation to minority stress. Particularly compelling is that acute exposure to a minority stressor evidenced immediate changes in blood cell counts (Hengge et al., 2003), that minority stress was related to the development of subsequent respiratory infections (Cole et al., 1996a), and that minority stress was related to gene expression implicated in immune function (Flentje et al., 2018). Also concerning immune function, substantial work outlined here suggests that minority stress has impacts on HIV-related outcomes, presumably also impacted through immune pathways. Future research should identify the specific pathways by which minority stress may impact immune function. A single study showed that minority stress was related to subsequent development of cancer (Cole et al., 1996a), and a different study found that minority stress was associated with gene expression related to cancer (Flentje et al., 2018). This limited evidence suggests additional work in this area is warranted. Finally, acute exposure to a minority stressor resulted in changes in cardiovascular function (Hengge et al., 2003) and general minority stress exposure was related to gene expression implicated in cardiovascular function (Flentje et al., 2018). The limited studies in these areas suggest that replication will be important to identify if and how minority stress may impact immune function, cancer development, and cardiovascular function.

HIV-related outcomes appear to be the most frequently investigated biological outcomes in relation to minority

stress, comprising nearly one-third of the analyses reported in this review. This makes sense given the considerable resources dedicated to HIV research, the expense of studies that include biological outcomes, and the corresponding requisite financial support. Among people living with HIV, minority stress was related to earlier death, worse clinical laboratory values, more symptoms, and more treatment related side effects. Only recently were sexual and gender minority people recognized by the National Institutes of Health as a health disparity population (NIMHD, 2016), regardless of HIV status. While this move does not come with guaranteed funding, it legitimizes research funding on sexual and gender minority health. Moving forward, there is a need to investigate the biological underpinnings of minority stress among sexual and gender minority people living without HIV whose biological mechanisms may differ in the absence of both systemic effects of HIV and antiretroviral medications.

The components of minority stress that were studied included prejudice events and conditions, expectations of rejection and discrimination, concealment of sexual orientation, internalized stigma, and general stress related to sexual orientation. Of the components of minority stress, prejudice events and conditions and concealment of sexual orientation were most frequently investigated in relation to biological outcomes, collectively represented in over two-thirds of the analyses in this review. Conversely, expectations of rejection and discrimination (represented in less than one-quarter of analyses) and general stress related to sexual orientation (represented in less than one-tenth of the analyses) were the least investigated. Internalized stigma, of all of the elements of minority stress, appears to have the most null results among these studies (88% of analyses did not detect a relationship), suggesting that this may not be the best construct to investigate in relationship to biological outcomes in the future.

There was very little consensus on the measurement of different components of minority stress. For example, some studies measured the frequency of specific types of prejudice-related events, while another study queried distress related to microaggressions. Some studies focused on being treated with less respect or courtesy, other studies queried victimization, while other studies employed measures that incorporated both. Progress in sexual minority health research will benefit from consensus about and validation of the constructs and measures of minority stress. Valid measurement of constructs may result in more replicable and consistent results and would help to inform the overlapping nature of the different elements of minority stress. Most of the studies within this review relied upon self-report measures of minority stress. Future work should consider alternative methods for measuring minority stress that does not rely upon self-report. This is particularly important in light of work that indicates that a coping style of downplaying, omitting, or failing to recognize and process emotional distress is related to poorer immune function (e.g., Type C coping as in Temoshok et al., 2008 or depth processing as in O'Cleirigh et al., 2003) suggesting that using self-report measures of minority stress in studies with biological outcomes may systematically compromise the validity of the research. This suggests that a standardized paradigm for measuring minority stress that does not rely upon self-report would benefit the understanding of the biological mechanisms and clinical outcomes that are impacted by minority stress. It may also help to unpack the relationships between distal and proximal minority stressors.

Most of the studies investigated the individual components of minority stress alone, rather than trying to test the different minority stress processes together in a model or as latent variables. It is possible that some of the null results may have been impacted by the parsing out of the different elements of minority stress. There are potentially individual differences in vulnerability to the different components of minority stress, or interaction effects (Meyer, 1995), as were observed between concealment and discrimination (Doyle & Molix, 2016), and concealment and anticipation of discrimination (Cole et al., 1997) in the studies included in this review. Measures of minority stress tend to consider the separate processes, yet measures have been developed that incorporate multiple components of minority stress (Chu et al., 2013), though composite measures limit the ability to test likely meaningful interactions between components of minority stress. Future research in this area may also want to consider parallel findings among racial or ethnic minority people. For example, internalized stigma was not related to biological outcomes in most of the analyses we found within this review, yet internalized stigma may be critical to understanding the interrelationships of different elements of minority stress and biological outcomes. Previous research in the parallel area of racism has found that internalized racism among African American men moderates the effect between discrimination experiences and cardiovascular disease, such that individuals who have greater internalized racism and no experiences of discrimination have more cardiovascular disease (Chae et al., 2010). Incorporating multiple components of minority stress into the same study may ultimately help to understand these complex mechanisms.

While most of the studies documented here utilized cross-sectional methods, a substantial proportion (over one-third) used study designs that assessed participants at multiple time points. The nine studies that used multiple time points used innovative design approaches including: utilizing data collected as part of longitudinal cohort studies that spanned 5 or more years (Cole et al., 1996a, 1996b, 1997), collecting original data over a span of hours to days (Huebner & Davis, 2005; Juster et al., 2013; Manigault et al., 2018; Parra et al.,

2016), and using experimental paradigms that involved a stress exposure component (Hatzenbuehler & McLaughlin, 2014; Hengge et al., 2003). As advances are made in the understanding of how minority stress impacts biology, longitudinal studies of sexual and gender minority people that use naturalistic designs and studies that randomize to validated minority stressors can help to identify the relationship between minority stress and biological function more definitively than the cross-sectional work done to date. This will require the development of validated stress exposure paradigms. Furthermore, interventions that reduce the impacts of minority stress may allow us to track changes in or reversal of the biological effects of minority stress and would contribute significantly to our understanding of the biological impacts of minority stress.

While many analyses detected a relationship between minority stress and a biological outcome, most (58%) of the individual analyses did not detect a relationship. Within a given study, different components of minority stress or different biological outcomes did not evidence relationships. This suggests that while there are important relationships being captured here, the science is still exploratory and has not yet identified the measurement and outcomes that have the most rigorous and replicable results. As a comparison within a parallel research area, research on racism and health outcomes has only recently begun to amass enough research studies to identify specific biological outcomes that are or are not related to racism (e.g., blood pressure or hypertension, Paradies et al., 2015) suggesting that substantial additional work will have to be done before these relationships can be thoroughly unpacked among sexual minority individuals. Additional research can also help to understand the impact of intersectional minority stress due to multiple intersecting statuses (e.g., race, ethnicity, socioeconomic status, sexual orientation). Furthermore, there could be unaccounted for variables that are impacting the relationships described here such as coping style, sociodemographic variables, or geographical location that, once accounted for, may yield more consistent results in the future.

Limitations

This review gives a state of the current research in this area, but more research is needed before effect sizes between minority stress and biological outcomes can be identified. Heterogeneity in study methods including study design, components of minority stress as well as the measurement of these constructs, and biological outcomes measured, precluded meta-analysis. This review also did not capture unpublished results and used $p < 0.05$ as a cutoff, thus the results could be biased toward studies that found relationships between minority stress and biological outcomes at $p < 0.05$. We reported results at the analysis level rather than the study level allowing us to capture null results within published research studies which revealed that while 81% of studies included an analysis that supported the relationship between minority stress and a biological outcome, only 42% of analyses supported the relationship. Studies included here also used different methods of including covariates, thus the inconsistency of results could have been impacted by the covariates included in the analyses reported. Furthermore, we report the proportion of analyses that detected a relationship, and there could be additional analyses that were not reported due to null results.

Summary

The minority stress model has been the primary model explaining health disparities between sexual minority and heterosexual people. The study of the relationship between minority stressors and biological outcomes provides a strong test of this relationship. We found that research in this area is scarce—even though we included a broad definition of biological outcomes we identified only 26 studies that looked at this question. Understanding the relationship between minority stress and specific biological outcomes, thus, relies on very few studies. Our review demonstrates that there is substantial evidence to support the relationship between minority stress and biological outcomes, but findings do not consistently support the minority stress hypothesis. As Table 2 shows, the proportion of analyses that confirm the minority stress hypothesis ranges from 0 to 100% depending upon the biological outcome. This leaves many questions unanswered and considerable work remains to be done to understand the relationship of minority stress and biological outcomes. Specific methodological limitations in existing research in this area include a lack of consensus about measurement and limited use of validated measures, examination of only single components of minority stress rather than consideration of multiple components of minority stress together, and unaccounted for variables that may impact the relationships between minority stressors and biological outcomes. Our study suggests that future studies may want to consider immune function, cancer development, and cardiovascular function as biological outcomes that may be responsive to minority stress. Future studies should incorporate validated measures of minority stress and should consider experimental designs that manipulate minority stress exposure, account for the multiple components of minority stress, and directly measure biological outcomes. Furthermore, future research should examine reversal of biological effects of minority stress through intervention.

Acknowledgements Dr. Flentje's work on this paper was supported by the National Institute on Drug Abuse (K23DA039800). This paper does not reflect the views of the National Institutes of Health.

Compliance with ethical standards

Conflict of interest Annesa Flentje, Nicholas C. Heck, James Michael Brennan and Ilan H. Meyer declare that they have no conflict of interest.

Human and animal rights and Informed consent This study did not involve human subjects research.

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