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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Sex Differences and Gender Diversity in Stress Responses and Allostatic Load Among Workers and LGBT People

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Abstract

Measuring biological sex differences and socio-cultural gender diversity provides insights into individual variation in stress physiology and the development of "sex-specific" diseases.

Purpose of Review

In this selective review, we summarize recent findings that assess sex and gender in relation to the stress hormone cortisol and multi-systemic physiological dysregulation called allostatic load. The focus of this research centers on workers as well as sexual and gender minorities as these populations provide unique insights into sex and gender at various levels of analysis from the micro-level to the macro-level.

Recent Findings

Male/female sex, sex hormones, gender identity, gender roles, and sexual orientation are all variables that are distinctly correlated with stress physiology. Beyond identifying patterns of vulnerability to stress-related diseases, pathways towards resilience are of high priority in emerging literature.

Summary

Stress scientists must account for both sex and gender in biobehavioral research. Future directions should assess macro-level constructs like institutionalized gender, occupational sex composition, and structural stigma to better understand the social determinants of health.

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Introduction

The sexes differ in the risk of developing distinct diseases. In general, men are more prone to substance abuse, schizophrenia, autism, antisocial personality disorder, attention deficit hyperactivity disorder, Tourette's syndrome, Parkinson's disease, and premature mortality. By contrast, women are more prone to mood disorders, post-traumatic stress disorder, bipolar II hypomania, somatic complaints, sleep problems, borderline personality disorder, and autoimmune diseases. In terms of psychiatric conditions, males suffer more from disorders with developmental origins, while females suffer more from disorders with adult onset [1•].

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The gender gap of diseases can change over time. For example, cardiovascular disease now kills more women than men in Canada and Germany [2, 3]. Yet, this was not the case just 50 years ago. To better understand these historical changes in "sex-specific" health outcomes, researchers must adopt conceptual models that account for both biological sex-based and socio-cultural gender-based factors. The current selective review will summarize research that applies sex- and gender-based analyses to study stress-disease processes. Focus will be given to stress biomarker research conducted among workers as well as sexual and gender minorities as these populations provide unique insights into sex and gender variation in stress physiology.

Biological Sex and Socio-cultural Gender

Biological *sex* is a categorical construct comprised of genes, anatomy, gonads, and hormones that make up male/female differences [4]. Beyond one's birth-assigned sex, socio-cultural *gender* refers to diverse roles, orientations, and identities that influence health across lifespan development. As an example of gender, *gender roles* represent our appropriation of stereotypically masculine (e.g., competitive) and feminine (e.g., cooperative) behaviors [5]. In addition, *gender identity* and *sexual orientation* are constructs that crystallize at different stages. Taken together, sex and gender must be considered together to better understand biobehavioral responses to stress that ultimately contribute to "sex-specific" health outcomes.

Stress Physiology

Studying stress allows us to better understand how environmental and individual factors shape risk and resilience to sex-specific diseases. As concisely defined by McEwen, *stress* is any real or perceived threat to our physiological and psychological integrity that triggers adaptive responses [6]. When the brain detects a threat, our stress response systems are activated via the *sympathetic-adrenal-medullary* (SAM) axis which releases *adrenalin* within seconds followed by the *hypothalamic-pituitary-adrenal* (HPA) axis that produces the stress hormone *cortisol* within minutes. Stress hormones mobilize energy via *catabolic* ("upward") processes that break down *anabolic* ("downward") fat stores. Homeostasis is thus recalibrated to potentiate biobehavioral stress responses. Taylor and colleagues have proposed that evolution has preserved a male-typic "fight-or-flight" pattern, whereas the female-typic "tend-and-befriend" favors nurturing and socializing behaviors to cope with stress [7].

Until as recently as the year 1995, females represented only 17% of subjects/participants in stress studies that otherwise systematically excluded them due to their cyclic hormone variations [7]. This implicated the *hypothalamic-pituitary-gonadal* (HPG) axis production of sex hormones such as testosterone, estrogens, and progesterone [7] that were viewed as a confounding nuisance. HPG axis variability does not justify the exclusion of females [8]. Despite increasing inclusion of women in stress studies today, we still know little about the impact that within-sex differences in sex hormones have on human SAM and HPA axes functioning. Earlier studies showed that men mount a twofold higher cortisol reactivity than women [9] to laboratory-based psychosocial stressors like the Trier Social Stress Test that includes public speaking and mental arithmetic tasks [10]. By contrast, women appear to be more stress reactive to social rejection components of the Yale Interpersonal Stressor [11, 12]; however, this latter result needs to be replicated or expanded upon with stress reactivity paradigms that consistently elicit amplified stress reactivity among women compared with men.

Stress responses differ by sex and gender due respectively to sex hormones and gendered socialization [13]. Despite the fact that men show higher HPA axis reactivity, women subjectively report more psychosocial distress on questionnaires. Moreover, HPA axis reactivity differs markedly as a function of the menstrual cycle, contraceptive use, and pregnancy [13]. Yet, stress studies do not systematically measure sex hormone fluctuations. To address this, focus must turn to actual measurement of sex hormones and their role in modulating stress physiology [14•, 15•] rather than simply inferring hormonal status. Notably, there are wide inter-individual differences in sex hormone concentrations. We have shown that statistically controlling for salivary sex hormones (testosterone, estradiol, and progesterone in both sexes) provides insights into elevated cortisol profiles among women not otherwise detected in studies that omit sex hormone variation [14•]. By contrast, sex differences in cortisol reactivity disappear when accounting for these sex hormones [14•]. In addition to methodologically accounting for sex hormones in studies of HPA axis functioning, more research is needed to identify how gender socialization sensitizes men, women, and gender diverse people to react similarly or differently to specific stressors.

Allostasis, Allostatic States, and Allostatic Load

Stress response mediators and sex hormone functions are dynamic biological processes that facilitate adaptation to environmental demands. The process whereby organisms adapt their homeostatic functions to meet environmental demands is referred to as allostasis. By definition, *allostasis* is the process of achieving "stability through change" by recalibrating physiological and behavioral processes [16]. The stress response is an allostatic mechanism because it mobilizes energy when acutely activated and appropriately attenuated. To use

an analogy, allostasis can be thought of as the "see-sawing" of interconnected biomarkers that promote adaptation [17]. Over time, *allostatic states* [18] may ensue if physiological responses become dysregulated due to repeated activations, a lack of adaptation, prolonged responses, or inadequate responses. Dysregulation of stress mediators induces a "domino effect" that strains inter-connected physiological systems and contributes to pathophysiology (Fig. 1).

Allostatic load (AL) represents the multi-systemic "wear and tear" of chronic stress in conjunction with unhealthy behaviors [19]. To return to the analogy of "see-sawing," imagine the minimal strain on the "see-saw" if only two light children are engaged. This can be thought of as allostasis. Now imagine the strain exerted on the "see-saw" if two heavy sumo wrestlers are engaged [17]. This analogy aptly represents the "wear and tear" of AL as allostatic mechanisms become overloaded.

Allostatic Load Index

AL is quantified with a battery of stress-related biomarkers. AL indices generally contain between 10 and 20 biomarkers representing neuroendocrine (e.g., cortisol), immune (e.g., cytokines), metabolic (e.g., insulin), and cardiovascular (e.g., blood pressure) systems. For the last 25 years, AL has been indexed using algorithms that essentially sum the number of dysregulated biomarkers for a given individual based on subclinical and clinical thresholds [19, 20]. This approach is a better predictor of stress-related diseases than traditional biomedical approaches that only assess individual biomarkers that pass a clinical threshold (e.g., total cholesterol + 5.2 nmol/L; [21]) or systemic clusters (e.g., metabolic syndrome; [22]).

High AL is linked to numerous deleterious factors such as higher adversity, including low socio-economic status (SES),

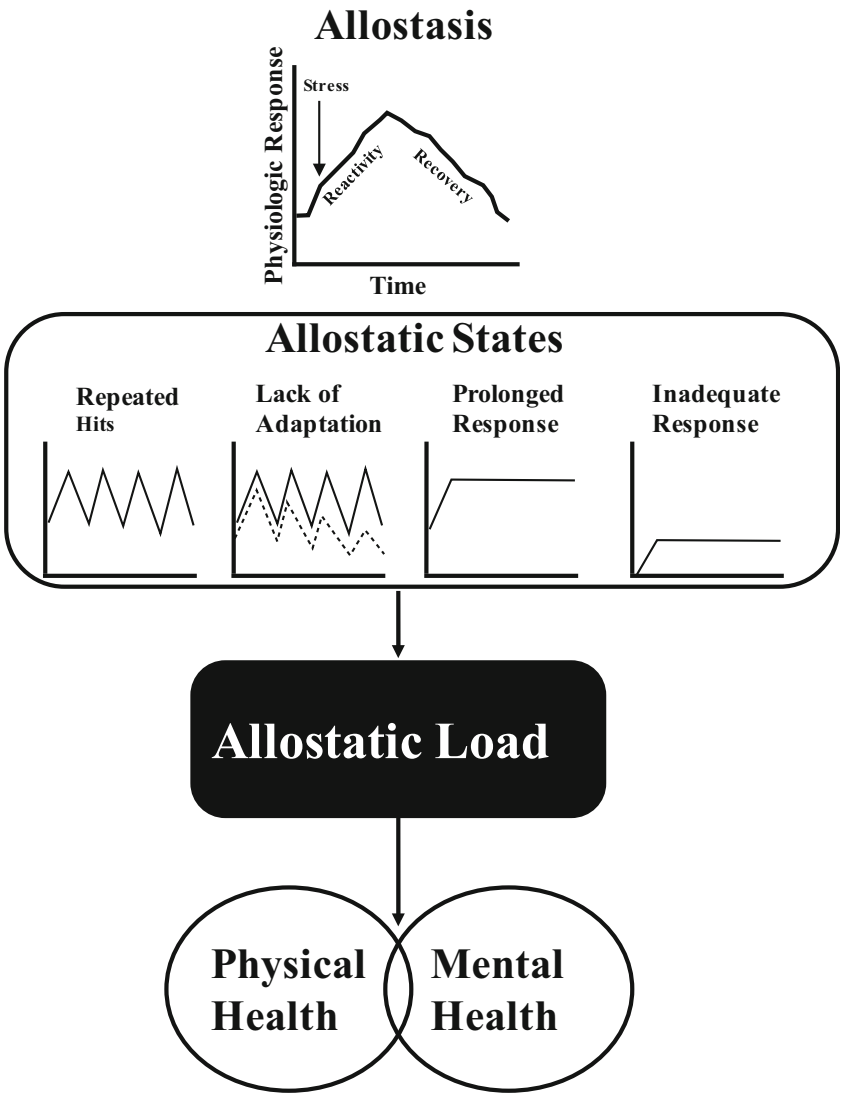

Fig. 1 Allostasis, allostatic states, and allostatic load. Source: Juster, R. P., Russell, J. J., Almeida, D., and Picard, M. (2016). Allostatic load and comorbidities: a mitochondrial, epigenetic, and evolutionary perspective. *Development and Psychopathology*, 28(4pt1), 1117–1146. https://doi.org/10.1017/S0954579416000730

social isolation, and non-White race/ethnic minority status to name but a few [23]. AL indices, in turn, predict accelerated aging, as well as numerous physical and mental health outcomes [24]. The advantages of applying a multi-systemic, sub-clinical approach when calculating AL lie in the fact that they collectively represent: (1) *early warning signals* since cutoffs are anchored at sub-clinical thresholds, (2) *multi-finality* in that similar AL algorithms predict different health outcomes, (3) *flexibility* since calculations are based on different biomarker combinations, (4) *synergism* capturing the cumulative interaction of numerous biomarkers, and finally (5) *antecedents* documented in the stress literature are powerfully predictive of individual variation in AL [25]. In sum, AL reflects the functioning of multiple biological systems that are intricately interconnected with genetic, neurological, developmental, behavioral, cognitive, and social factors [26•].

Sex*Gender and Allostatic Load

Sex differences and gender diversity in AL are the major focus of our groups' research program. Many AL biomarkers show sex differences and also interact with sex hormones to modulate physiological processes. For example, estrogen functioning is linked to cognitive protection, insulin sensitivity, cardiovascular disease, stroke risk, bone metabolism, Alzheimer's and Parkinson's diseases, and autoimmune diseases [27]. Simultaneously, testosterone functioning is linked to neuronal development, cytokines, diabetes, insulin resistance, obesity, atherosclerosis, metabolic syndrome, and cardiovascular disease. Our group has identified that testosterone in women and estrogen in men modulate stress physiology [14•, 15•]. To date, however, very little is known about sex and gender factors more broadly as they relate to the SAM axis, HPA axis, HPG axis, and multi-systemic AL more broadly.

In addition to sex differences, socio-cultural variation must be considered in AL research [28]. To use a cross-cultural example, a pilot study of Japanese elders measuring AL based on 33 biomarkers revealed that they were leaner with slightly more elevated blood pressure and cholesterol than Europeans and Americans [29]. Despite a lack of age differences, sex differences were also found for specific biomarkers like dopamine, uric acid, glutamic pyruvic transaminase (liver enzyme), and white blood cells. Although preliminary and requiring continued cross-cultural comparisons, we propose that delineation of sex- and age-specific differences will require gender-based perspectives that appreciate differential socialization patterns such as social networks, diet and alcohol consumption, and leisure activities that are gendered. Indeed, men and women around the world differ in their health behaviors.

Our understanding of sex differences can be complemented by incorporating gender perspectives when interpreting the AL literature [30]. It has been argued that socio-cultural factors may be more important than biological factors in explaining sex differences in stress physiology [31]. In addition, the sexes benefit from different protective factors in ways that may be gendered. For instance, AL levels were lower for elderly men with a spouse, while both sexes benefit from ties with close friends and neighbors in a Taiwanese analysis [32]. Interestingly, the perceived quality of these social relationships is not consistently linked to AL, suggesting that cross-cultural differences to Western societies may be influenced by socio-cultural factors (e.g., virtues of collectivism/interdependence, social obligation). These socio-cultural differences are inherently influenced by gender-based constructs related to broader societal structures (e.g., patriarchy, matriarchy). In summary, many of the antecedents of AL such as social support, personality traits, occupational characteristics, and health behaviors are influenced by socio-cultural factors for which gender perspectives can be applied [27].

Sex X gender interactions might also divergently influence biopsychosocial stress. In particular, extremely traditional or hegemonic masculine gender roles (e.g., hostile, dictatorial, impatient) are strongly linked to coronary-prone behaviors (e.g., inhibited emotional expression, lack of empathy, homophobia) that overlap considerably with hostile personality traits. Hostility has been shown to mediate the association between low SES with increased AL [33, 34]. As women increasingly occupy non-traditional professions (e.g., managers, engineers) around the world [35], changing gender roles might incur both health-promoting and health-damaging consequences [36]. We propose that these changes in gender role appropriations might help explain changes in sex-specific diseases (e.g., cardiovascular disease). It follows that individual differences in unique configurations of AL psychosocial antecedents might differ according to gendered behaviors [27, 37]. As the following will demonstrate, gendered constructs applied to occupational health provides a unique lens to study stress physiology.

Sex*Gender Perspectives in Occupational Stress Research

Applying a *sex- and gender-based analysis* [38] can illuminate how variations in biological sex and psychosocial gender relate to AL among working populations. Nuancing sex and gender factors that influence occupational stress has been of major interest since the 1980s. For example, pioneering work among Scandinavian women in non-traditional or "masculine" occupations (e.g., managerial versus clerical) showed that they reported more distress, hostility, inability to recover after work, physical complaints when older, and manifested pathophysiological functioning [36, 39]. Even today, the appropriation of multiple gender roles regarding work and home responsibilities among women has not been matched by

appropriate social equity. In general, women still retain more "feminine" roles and responsibilities than men in both work and home life [35, 40•, 41•, 42]. This is often the case even though women may also have to simultaneously appropriate more "masculine" gender roles at work when engaged in professions traditionally dominated by men.

Gender Roles

Our group has demonstrated that gender roles are related to AL. We conducted a pilot study that assessed whether age, sex, and gender roles were associated with AL levels and physical complaints among Montreal workers from diverse occupations [43]. Results showed that (1) increased masculinity (e.g., independent, assertive) and age predicted high AL levels, while sex did not; (2) increased masculinity and being female together predicted increased physical complaints; and finally (3) high AL corresponded to increased physical complaints. That higher masculinity being related to increased objective physiological dysregulation and subjective physical complaints (e.g., nausea, dizziness, pain) suggests an overall increased vulnerability to hyper-arousal pathologies such as cardiovascular disease among masculine-typed individuals. These triangulated findings are clinically important. In particular, atypical prodromal symptoms of acute coronary syndrome for women include physical complaints [44]. This provides preliminary support for the inclusion of gender roles in studies investigating AL with differences otherwise attributable solely to sex or age.

Androgyny

In evolving our gender schema throughout lifespan development, we encode and process gender-based information and systematically appropriate sex-specific behaviors consistent with our *gender identity* representing the sex we see ourselves as [45]. Bem argued that "gender-typed" individuals are those that rigidly conform exclusively to their masculine or feminine schemas at the detriment of their psychological well-being. For example, self-identification as a hyper-masculine heterosexual man might lead to distress when enacting cross-gender behaviors associated with femininity (e.g., nurturing, sensitive). The paragons of mental health according to Bem were "androgynous" individuals who can effectively navigate both masculine and feminine behaviors in different contexts. By contrast, "undifferentiated" individuals would show below average propensities of either masculinity or femininity that she proposed was the most maladaptive profile [5]. While immensely influential in the psychosocial literature, Bem's *gender schema theory* [45] and proposal of androgyny versus undifferentiation have until only recently been substantially using biological approaches to measure stress.

Recently, our group provided the first biological support for Bem's theory. In a study of 204 workers from a large psychiatric hospital in Montreal, we showed a sex X gender role interaction effect for AL [46•]. Specifically, androgynous men showed the lowest AL compared with undifferentiated men. It is worth noting that men overall had higher AL than women when using an AL algorithm that did not account for sex differences in biomarker cutoffs. By contrast, using a sex-specific AL index was what allowed us to detect a sex by gender role interaction (Fig. 2). This is of importance for future research because most studies use AL indexes that do not account for sex differences in biomarkers. In clinical practice, considerations of sex and gender should likewise inform clinical decision-making related to diagnostic tests, medications, and other treatment options [47•]. Lastly, no differences by gender role were found among women in our study. This may be explained by macro-level gendered factors that we did not account for but that we will address next.

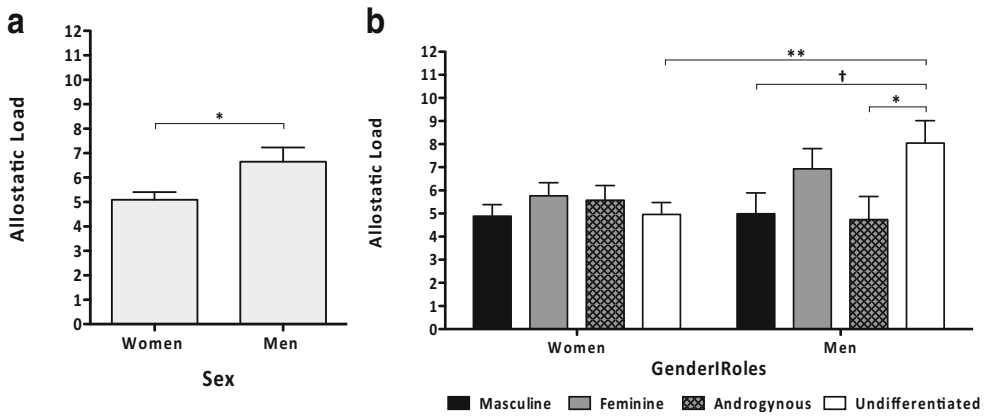

Fig. 2 "All-inclusive" allostatic load as a function of sex (**a**) and "sex-specific" allostatic load as a function of sex and gender roles (**b**) while adjusting for age, sex hormones (testosterone, estradiol, progesterone), sexual orientation, chronic stress, and mental health condition. Source: Juster, R. P., Pruessner, J. C., Desrochers, A. B., Bourdon, O., Durand, N., Wan, N., et al. (2016). Sex and Gender Roles in Relation to Mental Health and Allostatic Load. ***Psychosomatic Medicine***, 78(7), 788–804. https://doi.org/10.1097/PSY.0000000000000351

Institutionalized Gender

In pursuing research on occupational stress and AL, we propose that investigators attempt to apply macro-level perspectives related to *institutionalized gender*. This refers to the socio-cultural systems that preserve gendered expectations and responsibilities. Institutionalized gender reflects the distribution of power between men and women in political, educational, and social institutions within society [4]. The institutionalized aspect of gender also shapes social norms that define, reproduce, and often justify different expectations and opportunities for men and women [4]. For example, women are often paid less than men for similar work and different professions are often dominated by one sex.

Occupational status represents the prestige, education, and income associated with one's occupational position. Occupational status (indexed based on individuals' profession) is also associated with AL differently among working men and women [48]. In a study of 199 Montreal workers [48], we found that men showed a positive association and women showed a negative association between occupational status and AL. As occupational status is considered beneficial to health, these sex differences are rather perplexing if we do not consider gender. By further nuancing institutionalized gender among workers from diverse professions and departments, we expect that workers with gender profiles that mismatch or "gender bend" from that typical for their profession will evidence elevated AL. For example, a hyper-masculine male nurse might experience distress in a nursing profession where feminine traits (e.g., caring) are highly valued.

Occupational Sex Composition

Occupational sex composition represents the concentration of men and women in a specific occupation. In general, men and women work in different occupations (horizontal segregation) and in different positions within the same occupation (vertical segregation) [49]. Occupations are therefore often stereotyped: some occupations are seen as more appropriate for men than for women, or vice versa [50]. The concept of *horizontal sex segregation* describes the unequal concentration of men and women in different occupations [49, 51]. Because of this segregation, the minority group (e.g., women in male-dominated occupations or men in female-dominated occupations) is often exposed to more stressors than the majority group (e.g., men in male-dominated occupations or women in female-dominated occupations) [50].

Men and women are also challenged by different stressors in the workplace [52] due to the differential distribution of psychosocial and socio-economic factors. For example, women often report stressors embedded within society at large (e.g., work-family interface, social support, discrimination), from organizations (e.g., coworker social pressures, sexual harassment, sex discrimination, "old boys network"), and from women themselves (e.g., behavior, self-esteem, personal control) [52]. By contrast, men are more vulnerable to financial stressors [52] and social stress related to masculinity [53]. For example, nurses [54, 55], domestic workers, or teachers [49] are female-dominated occupations. Compared with men working in male-dominated occupations, men working in these female-dominated occupations are more likely to be bullied [55], to have higher odds of mild to severe depression [56•], and to have higher social stress and psychological strain [53]. However, men working in female-dominated occupations have lower suicide rates than men in male-dominated occupations [57•]. They also perceive higher workplace support than women working in the same female-dominated occupation [50].

Many occupations are male-dominated, such as metal workers [54], managers, or engineers [50]. Compared with women in female-dominated occupations, women working in these male-dominated occupations have higher rates of sick-leave [54], poorer well-being and sense of meaning at work [58•], and higher incidence of musculoskeletal disorders [59]. Women are also vulnerable to sexual harassment in the workplace, which can lead to lower job satisfaction and organizational commitment, poor physical and mental health, symptoms of post-traumatic disorder, and higher distress for other female coworkers [52]. Moreover, they perceive less workplace support than men working in the same male-dominated occupation [50]. Still, women working in male-dominated occupations have slightly lower suicide rates than women in female-dominated occupations [57•]. Taken together, we propose that measuring occupational sex composition can allow researchers to tease apart potential social determinants of health embedded within the broader construct of institutionalized gender.

Institutionalized discrimination transcends sex and gender. Sub-groups embodying multiple stigmatized identities (e.g., racial/ethnic, sexual, and gender minority identities) experience added stigma that can further strain their health [60, 61]. As the following section will demonstrate, sexual and gender minorities have distinct HPA axis and AL profiles that have only recently begun to be assessed with stress biomarkers.

Allostatic Load Among Lesbian, Gay, Bisexual, and Transgender People

Lesbian, *gay*, *bisexual*, *and transgender* (LGBT) people are vulnerable to stress-related health outcomes. As a whole, adolescent and adult LGBT people are anywhere from 1.5 to 4 times more likely to self-report depression, anxiety, suicidal ideation/attempts, substance abuse, eating disorders, risky sexual behaviors, homelessness, and victimization than

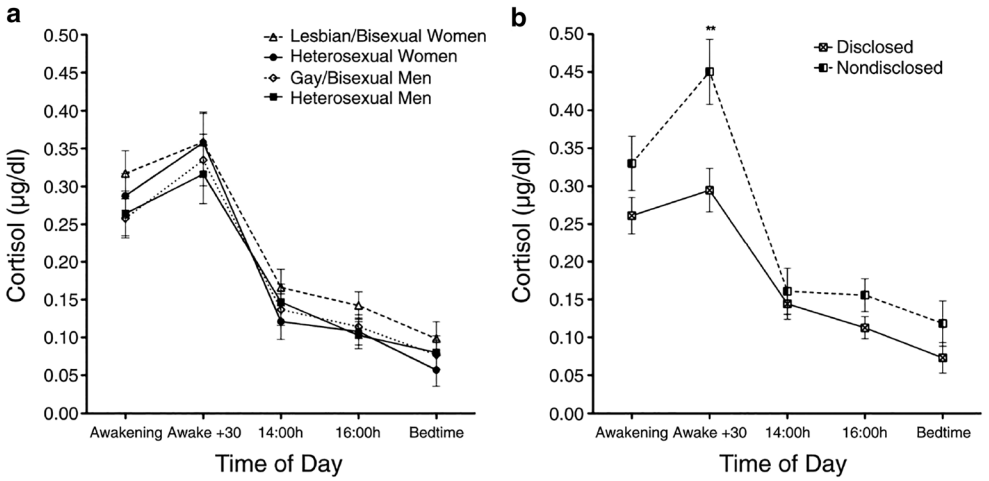

Fig. 3 Salivary diurnal cortisol concentrations for two averaged days as a function of sexual orientation and sex while controlling for chronic stress and awakening time (**a**) and for disclosed and nondisclosed sexual minorities while controlling for conscientiousness and awakening time (**b**). Source: Juster, R. P., Smith, N. G., Ouellet, E., Sindi, S., & Lupien, S. J. (2013). Sexual orientation and disclosure in relation to psychiatric symptoms, diurnal cortisol, and allostatic load. ***Psychosomatic Medicine***, 75(2), 103–116. https://doi.org/10.1097/PSY.0b013e3182826881

heterosexuals [62–65]. Given these staggering statistics, the Institute of Medicine mandated in 2011 that the health of LGBT people become a research priority [62].

Sexual and Gender Minority Stress

A key social determinant of LGBT health is stigma experienced at the individual, interpersonal, and structural levels. *Sexual minority stress* models [66–69] propose that the stress of living in environments that stigmatize minority sexual orientations contribute to later health disparities according to two stress processes. First, *proximal minority stress processes* refer to individual-level experiences like internalized homophobia and concealment of one's minority identity [70]. Second, *distal minority stress processes* refer to objective stressors like discrimination and violence experienced at the interpersonal level. At the macro-level, *structural stigma* represents the social conditions, cultural norms, and institutional policies that constrain the opportunities, resources, and well-being of the stigmatized [71]. This construct is akin to institutionalized gender described previously. Sexual minority stress also applies to the understudied experiences of gender minorities like transgender and gender fluid people who face unique challenges in societies that often denigrate gender non-conformity [72]. *Gender minority stress* therefore represents the proximal (e.g., internalized transphobia) and distal (e.g., violence against transgender people, discriminatory laws) stress processes experienced among transgender and gender diverse people.

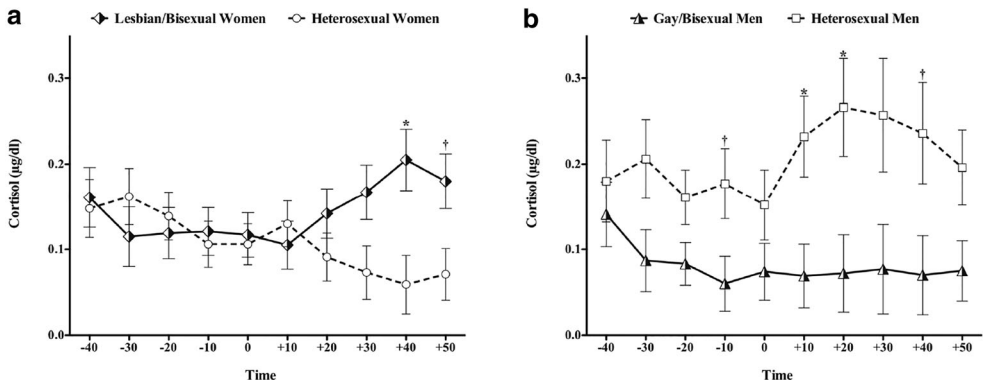

Fig. 4 Salivary free cortisol concentrations in response to the Trier Social Stress Test among women ($n = 40$) (**a**) and men ($n = 46$) (**b**) as a function of sexual orientation. Values are adjusted for sex hormones (estradiol-to-progesterone ratio for women and testosterone for men), age, self-esteem, and disclosure status. Source: Juster, R. P., Hatzenbuehler, M. L., Mendrek, A., Pfaus, J., Smith, N. G., Johnson, P. J., Lefebvre-Louis, J.-P., Raymond, C., Marin, M.-F., Sindi, S., Lupien, S. J., & Pruessner, J. C. (2015). Sexual orientation modulates endocrine stress reactivity. ***Biological Psychiatry***, 77, 668–676. https://doi.org/10.1016/j.biopsych.2014.08.013

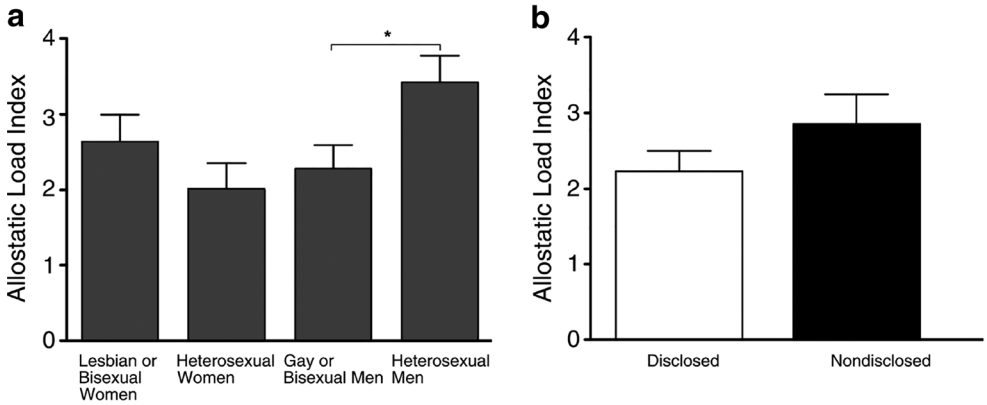

Fig. 5 Allostatic load indices based on 21 biomarkers as a function of sexual orientation and sex while controlling for chronic stress and age (**a**) and for disclosed and nondisclosed sexual minorities while controlling for conscientiousness and age (**b**). Montreal sample ($N = 87$). Source: Juster, R. P., Smith, N. G., Ouellet, E., Sindi, S., & Lupien, S. J. (2013). Sexual orientation and disclosure in relation to psychiatric symptoms, diurnal cortisol, and allostatic load. ***Psychosomatic Medicine***, 75(2), 103–116. https://doi.org/10.1097/PSY.0b013e3182826881

Diurnal Cortisol Among Sexual and Gender Minorities

Stress pathophysiology and AL may be exacerbated among LGBT individuals due to stigma [28, 61]. With a focus on diurnal cortisol, emerging research assessing LGBT-related dysregulation has fallen into two camps: (1) *between-groups* analyses whereby LGBT profiles are assumed to differ from heterosexuals because of sexual and gender minority stress that is not actually measured or (2) *within-groups* analyses only among sexual minorities who differ in their self-reports of sexual/gender minority stress. Between-groups analyses of young adults from Canada [73] and the USA [74] have found no disparities in diurnal cortisol profiles when contrasting sexual minorities to heterosexual individuals. By contrast, within-groups analyses of internalized stigma have consistently been associated with hypersecretion of diurnal cortisol among LGBT individuals [73, 75, 76•] with one exception [77]. Measuring LGBT-specific stigma (e.g., "coming out") may be a prerequisite to detecting variability in diurnal cortisol profiles (Fig. 3).

Allostatic Load and Resilience Among Sexual and Gender Minorities

Our research group has pioneered the comprehensive assessment of HPA axis functioning and AL to the study of LGBT health. For decades, stress reactivity paradigms have been used to assess disease susceptibilities that differ by sex. As described earlier, greater cortisol stress reactivity is seen in men when facing social-evaluative threat. Employing the Trier Social Stress Test, we found that sexual orientation [78•] and sex hormones [15•] further modulate cortisol reactivity in a self-selected sample of 87 Montrealers. Specifically, gay/bisexual men showed low cortisol reactivity while lesbian/bisexual women showed high cortisol reactivity and

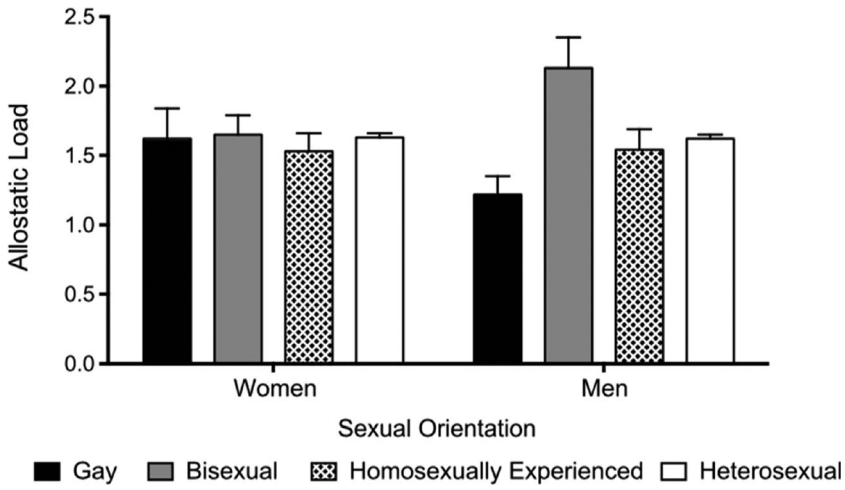

Fig. 6 Allostatic load as a function of sexual orientation stratified by sex in the *National Health and Nutrition Examination Survey* from 2001 to 2010 ($N = 13,911$). Source: Mays, V. M., Juster, R. P., Williamson, T. J., Seeman, T. E., & Cochran, S. D. (2018). Chronic physiologic effects of stress among lesbian, gay, and bisexual adults: Results from the National Health and Nutrition Examination Survey. ***Psychosomatic Medicine***, 80, 551–563. https://doi.org/10.1097/PSY.0000000000000600

androgen levels relative to sex-matched heterosexual individuals (Fig. 4). Surprisingly, gay/bisexual men also showed lower depressive symptoms and AL than heterosexual men [73]. This resilient profile was driven by a hardy subset of sexual minorities who were fully "out" to family and friends and experienced less psychiatric symptoms and lower cortisol than those who had not fully disclosed (Fig. 5). Moreover, those who engaged in more social support seeking and less avoidance coping evidenced lower AL [79].

These findings were recently expanded upon in an analysis of the National Health and Nutrition Examination Survey ($N > 13{,}000$). Mays and colleagues [80•] showed that gay men have the lowest AL while bisexual men have the highest AL compared with heterosexual men (Fig. 6). In other studies with American collaborators, we found that diurnal cortisol was also elevated among young race/ethnic minority gay/bisexual men [81•] and transgender men experiencing transition-related stigma [76•]. It is worth noting that much more health research is needed among transgender and gender diverse people who experience more stigma than other LGBT sub-groups. As a result of this continued research, our ultimate goal is to identify modifiable individual factors associated with resilient functioning. This is complementary to perspectives focused solely on vulnerabilities, which remain somewhat limited in addressing the remarkable resilience many marginalized populations can demonstrate.

Conclusions

Sex and gender drive variability in biobehavioral responsivity to chronic stress and AL. Because sex and gender can modulate numerous physiological functions [3], they have applications to medical specialities like cardiology, pulmonology, immunology, gastroenterology, hepatology, nephrology, endocrinology, hematology, neurology, pharmacology, and especially psychiatry. It has been suggested that sex differences can be classified according to four dimensions: (1) persistent vs transient across the lifespan. (2) context independent vs dependent, (3) dimorphic vs continuous, and (4) direct vs indirect consequences of sex [1•]. Clearly, measuring sex as a binary "male/female" classification is not sufficient if scientists and practitioners are attempting to understand and treat "sex-specific" conditions such as depression and cardiovascular disease.

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Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent The human studies that are part of the corresponding authors' research program all involve ethically sound research and informed consent following international standards.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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