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Discrimination and the HPA axis: current evidence and future directions

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Abstract Numerous studies suggest that discrimination is associated with poor physical and mental health outcomes. Whereas the cardiovascular system has been extensively studied as a potential pathway linking discrimination with disease, the role of the hypothalamic–pituitary–adrenal (HPA) axis remains understudied. We conducted a systematic review of research on discrimination and related constructs as predictors and correlates of HPA axis activity. Twenty seven studies (10 experimental, 17 observational) met inclusion criteria. Studies suggest that discrimination is associated with alterations in HPA axis activity and that the direction of this association depends on the timing and chronicity of the discrimination experience. There is also evidence of important modulating variables (race, socioeconomic status) and contextual confounders (emotional, situational) that warrant further study. Accounting for the HPA axis in addition to the cardiovascular system will contribute to a more comprehensive understanding of the biobehavioral pathways contributing to physical and mental health inequities related to discrimination.

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Introduction

Discrimination, the unequal treatment of an individual or a group of individuals based on real or perceived differences, is a common experience, and is often based on a person's perceived or actual race, age, sex, nationality, religion, or disability. Discrimination is associated with increased mortality and a wide range of physical and, to a greater degree, mental health outcomes including depression and anxiety (Paradies et al., 2015; Williams & Mohammed, 2009). Moreover, there is growing evidence that discrimination may contribute to explaining health disparities that cannot be accounted for by sociodemographic differences (Williams, 1999; Williams & Collins, 1995).

One variable that may, at least in part, explain the health inequities experienced by groups that have long histories of being subjected to discrimination is the stress resulting from discrimination. In support of this hypothesis, numerous studies have found an association between perceptions of discrimination or racism and perceived stress (Landrine & Klonoff, 1996; Landrine et al., 2006; Utsey, 1999). Stress-related physiological pathways, in particular the sympathetic-adrenal-medullary system, have been implicated in the discrimination-health relationship as well. Results from a meta-analysis suggest increased cardiovascular reactivity, including changes in blood pressure, mean arterial pressure, and total peripheral resistance, to discrimination manipulations (Pascoe & Smart Richman, 2009). Overall, research implicates heightened cardiovascular activity resulting from the stress of discrimination as

one pathway to negative physical health outcomes, in particular cardiovascular disease.

It has been suggested that while cardiovascular dysregulations may be the primary contributor to cardiovascular disease, a physical health outcome, the influence of the stress-responsive hypothalamic–pituitary–adrenal (HPA) system may be more relevant in terms of mental health outcomes including, for example, depressive disorders (Berger & Sarnyai, 2015). However, few studies have tested this possibility empirically. Briefly, the hypothalamus releases corticotrophin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH), which then triggers cortisol release from the adrenal glands. The HPA axis regulates its own activity by a negative feedback system (Tsigos & Chrousos, 2002). Underlying the system's responsiveness to stressful stimuli is a pronounced circadian rhythm. Cortisol levels are highest in the morning, with a significant cortisol increase occurring within the first 30–45 min upon waking (Pruessner et al., 1997). This cortisol awakening response (CAR) is typically determined by sampling cortisol in saliva immediately after waking with one or more additional samples over the course of the next hour. Cortisol levels then decline steadily throughout the day, reaching their nadir around midnight (Weitzman et al., 1971). To obtain a diurnal profile and compute a diurnal slope, a minimum of two samples is required, one in the morning and one at night, with many studies sampling repeatedly over the course of the day. The HPA axis is also stress-responsive, and a number of procedures are available to experimentally stimulate the HPA axis by psychological, physical or pharmacological means. In the context of this discrimination literature, only psychological stress protocols have been used. In most studies, a baseline saliva sample is collected, the stress protocol is implemented, and a number of additional samples are collected after the stressor in order to obtain a response curve. For an overview of the benefits and challenges of assessing cortisol in saliva, we refer the interested reader to the literature reviews by Hellhammer et al. (2009), Clements (2013), and—with particular emphasis on the CAR—to Clow et al. (2010).

While the dynamic diurnal and stress-related processes characteristics of the HPA axis are generally adaptive, chronic dysregulations, including flatter than normal diurnal cortisol slopes, an exaggerated or attenuated cortisol awakening response, or an exaggerated or attenuated response to external stimuli, are maladaptive and have been associated with stress-related disease, including depression and anxiety (Chrousos & Gold, 1992; Tsigos & Chrousos, 2002).

We here review and evaluate studies directly testing the link between discrimination and HPA axis activity. Studying the effects of discrimination on biobehavioral pathways implicated in physical and mental health holds promise for improving our understanding of health disparities affecting ethnic minorities and other groups likely to be persistently exposed to discrimination. It is our hope this review will stimulate future work on this topic.

Method

Eligibility criteria

Studies needed to include a measure of discrimination as a predictor and an indicator of HPA axis activity as an outcome. Because social groups that experience discrimination are typically stigmatized, or devalued by society (Crocker & Major, 1989), studies conceptualizing stigma as a chronic stressor were also included. Experimental studies had to compare a manipulation that provoked a discrimination experience with a comparison condition, or use a stressful task combined with a measure of discrimination. Studies using group membership (e.g., race, sexual orientation) as a proxy for discrimination experiences were not included because the unique contribution of discrimination in those studies could not be isolated. For a similar reason, studies of discrimination experiences among individuals with chronic disease (e.g., diabetes) were excluded. Studies using allostatic load as an outcome variable were excluded unless associations with individual hormones were also reported. Studies focusing on related concepts such as *internalized racism* or *race-based rejection sensitivity* were deemed beyond the scope of this article. Only studies of human participants were included.

Literature search

PsycINFO and PubMed were searched for peer-reviewed studies published in English without setting restrictions on publication date. Keywords related to the HPA system included *cortisol, CRH, corticotropin releasing hormone, ACTH, adrenocorticotropin releasing hormone, beta-endorphin, Dehydroepiandrosterone,* and *DHEA*. These words were matched with the discrimination-related keywords: *discrimination [major headings: Pubmed: majr; PsycInfo: mjsub], prejudice [major headings], racis*, stigma, sexis*, unfair treatment, ageis*, homophob* and xenophob**. The final search was run in October of 2016.

Identification and selection of literature

The search located 138 entries through PubMed and 29 entries through PsycINFO, with 24 duplicate entries (Fig. 1). To locate additional articles the database search

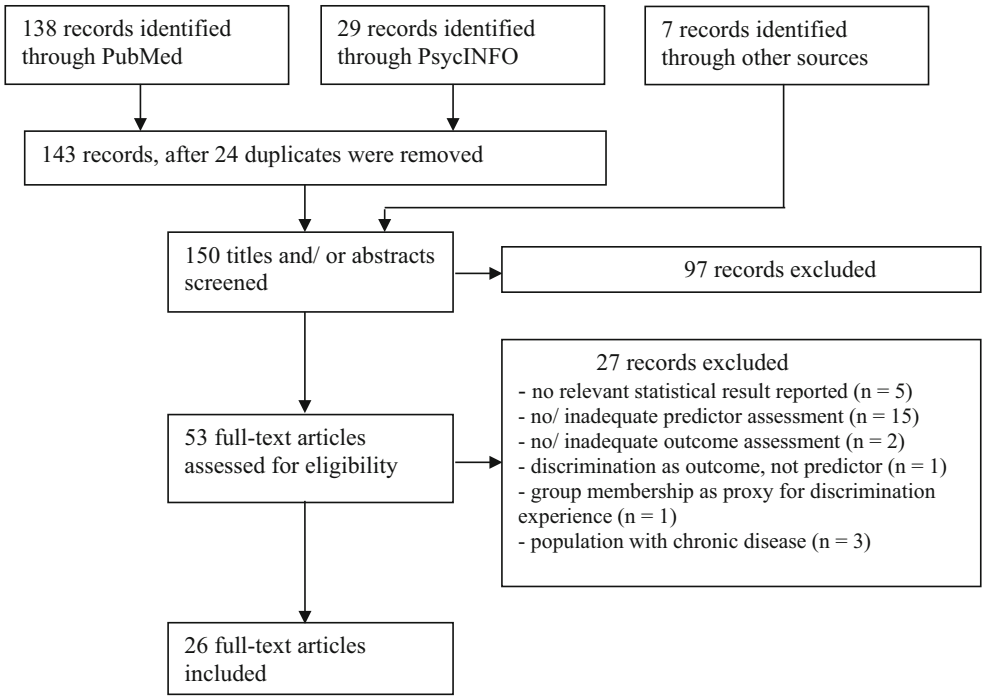

Fig. 1 Flow chart following guidelines in the PRISMA statement (Moher et al., 2009)

might have missed, review articles and relevant empirical articles were searched for additional references. Seven studies were found using this method. Thus, 150 manuscripts were further considered. A review of titles and abstracts resulted in the rejection of 97 articles that were either not empirical studies or clearly irrelevant. The remaining 53 full-text articles were further examined and 27 were excluded for various reasons (Fig. 1). The remaining 26 articles describing 27 studies met eligibility criteria and were included in this review.

These 27 studies reported on a total of 4328 participants, with sample sizes ranging from 33 participants in a unique study surrounding the 2006 Duke lacrosse scandal (Richman & Jonassaint, 2008) to 781 participants constituting a subsample of a large multisite study on race and socioeconomic status (Cohen et al., 2006). The mean study sample size was 160.3 (SD = 178.3). Ten studies included only female participants. In the 16 studies reporting gender breakdown, females comprised 58.4% of the combined study samples. In the 18 studies that reported age, participants' ages ranged from a low of 9 years (Martin et al., 2012) to a high of 98 years old (Hehman & Bugental, 2015), with a mean age of 27.0 (SD = 13.4) across studies. Twenty two studies collected their samples in the United States, and the remaining studies in Canada (n = 3), New Zealand (n = 1), and China (n = 1). Across all studies reporting race or ethnicity, most participants identified as White (31.2%), Black (27.0%) or Asian (23.9), and the remaining participants as Latino (14.5%) or other (3.4%).

Results

Ten studies used an experimental design, and 17 studies were observational with two longitudinal and 15 cross-sectional studies.

Experimental studies

The ten experimental studies varied in size between 33 and 110 participants (Table 1). All provided evidence of an association between discrimination or closely related concepts (e.g., structural stigma) and salivary cortisol reactivity, using a range of moderately stressful tasks, including experimentally induced discrimination experiences (Hehman & Bugental, 2015; Himmelstein et al., 2015; Jamieson et al., 2013; Matheson & Anisman, 2009; Matheson et al., 2008), speech tasks (Hatzenbuehler & McLaughlin, 2014; Richman & Jonassaint, 2008), and prejudiced work paradigms (Townsend et al., 2011, 2014). Discrimination experiences in these studies were based on participants' race (Jamieson et al., 2013; Richman & Jonassaint, 2008; Townsend et al., 2014), age (Hehman & Bugental, 2015), sex (Townsend et al., 2011, 2014), sexual orientation (Hatzenbuehler & McLaughlin, 2014), and body weight (Himmelstein et al., 2015). In all studies, at least two saliva samples were collected, one sample before the experimental manipulation and at least one sample after the task, reflecting reactivity and recovery.

Table 1 Studies of discrimination and the HPA axis

Study	Exclusion criteria[a]	Sample	Discrimination measure and/or experimental manipulation	HPA axis measure	Major findings and control variables (in italics)
Experimental studies					
Hatzenbuehler and McLaughlin (2014)		74 LGB adults, M_{age} = 24 years, 54% female, 60% non-White, 40% White, from colleges and community in large US metropolitan city	Stressor: TSST (5 min speech, 5 min math) Structural Stigma[b], perceived devaluation–discrimination scale	sCORT: Baseline, and 10 and 20 min after cessation of stressor	LGB youth w/prior structural stigma had blunted sCORT response *Age, sex, race, wake time, smoking, exercise, caffeine*
Hehman and Bugental (2015)		108 US adults, 47 younger adults: 49% female, 18—24 years, M_{age} = 19; 64% White, 15% Hispanic, 9% Asian, 6% Black, 6% other), 61 older adults: (72% female, 61—98 years, M_{age} = 75; 82% White, 12% Hispanic, 3% Black, 2% Asian, 2% other)	Delivering brief instructions for puzzle tasks (14 tasks of 60 or 120 s duration) using patronizing versus non-patronizing speech	sCORT: Baseline, and 20 min after completion of puzzle task	Marginal sCORT increase only in older adults in patronizing condition. Positive attitudes about aging and positive interactions with younger generation protective
Himmelstein et al. (2015)	Self-perception of being thin, smoking	110 US female undergraduate students, 17–57 years, M_{age} = 20 years, 28% Asian, 21% Hispanic, 15% White, 5% Black, 2% Middle Eastern, 1% Native American, 18% multi-racial, 10% other	Delivering brief instructions for a virtual shopping trip task w/or w/o induction of weight stigma	sCORT: Baseline, and 30 min after delivery of instructions	Women perceiving their weight as heavy in stigma condition w/higher sCORT after test than control group or women perceiving their weight as average. No effect of BMI *BMI, negative affect*
Jamieson et al. (2013)	Hypertension, pacemaker, cardiac meds, pregnant	91 US adults from student and community samples, M_{age} = 24 years, 55% female, 54% White, 46% Black, from Cambridge, MA	Stressor: Computerized social rejection task (20 min) including speech and discussion (chat) In-group versus outgroup rejection	sCORT: Baseline, immediately after and 20 min after task	Same-race rejection w/greater sCORT reactivity than cross-race rejection
Matheson and Anisman (2009)	Immune illness, meds affecting cortisol	91 first-year female university students, M_{age} = 20 years, 72% White, 14% Asian, 7% Black, 1% Hispanic, 6% other, from Canada	20-min writing task serving as mood prime (anger vs. shame vs. no mood prime control) followed by failure feedback (due to being female or due to merit)	sCORT: Baseline, immediately after mood prime, and 15 and 30 min following failure feedback	Anger prime plus problem-focused or avoidant coping w/decreasing sCORT. Shame prime plus avoidant coping w/reduced reactivity. No prime plus avoidant coping w/greater reactivity
Matheson et al. (2008)	Neuroleptics, drugs affecting cortisol	61 first-year female university students, M_{age} = 21 years, 80% White, 12% Asian, 7% Black, 1% other, from Canada	Short writing task serving as mood prime (anger vs. sadness) followed by sex discrimination protocol	sCORT: Baseline, and 15 and 30 min following discrimination event	Discrimination after anger prime w/elevated sCORT. Sad prime w/decreased sCORT *Time of day, med use*

Table 1 continued

Study	Exclusion criteria[a]	Sample	Discrimination measure and/or experimental manipulation	HPA axis measure	Major findings and control variables (in italics)
Richman and Jonassaint (2008)	Anti-depressant or anti-anxiety meds, anabolic steroids, nasal sprays, mouth lacerations, some medical conditions	33 Black university students, 52% female, from North Carolina (USA). 52% recruited pre-Duke Lacrosse scandal	Stressor: Speech task (5-min duration) Two conditions designed to increase either school or racial identity	sCORT: Baseline, and 20, 30, and 40 min after cessation of stressor	Post Duke Lacrosse w/elevated sCORT levels and blunted responses; stronger in women *Racial identity, OC use, time of day, major stress*
Townsend et al. (2014)		58 working and middle class US Latina women	Interview (5 min of answering questions +5 min math task) w/racist versus not racist interviewer	sCORT, DHEA: Baseline, and 20, 30 and 45 min after receiving negative feedback	Middle-class Latinas in prejudiced condition w/higher sCORT, lower anabolic balance
Townsend et al. (2011)		Study 1: 61 White female US college students Study 2: 52 White female US college students	Study 1: Job interview paradigm (5 min speech, 5 min math) w/merit or sexist rejection feedback Study 2: Interaction w/coworker following coworker's endorsement of prejudiced gender attitudes (vs. unknown gender attitudes)	sCORT: Study 1: Baseline, and 20, 30, and 40 min after cessation of the stressor Study 2: Baseline, and 15 and 35 min after being matched w/prejudiced vs. unprejudiced coworker	Study 1: Chronic perceived sexism and identity-threatening cues w/higher sCORT response than identity-safe cues Study 2: Chronic perceived sexism w/higher sCORT response regardless of condition *Baseline sCORT, wake time, menstrual cycle, age, anxiety, depression, perceived personal control*
Observational studies					
Adam et al. (2015)		112 US adults from the Maryland Adolescent Development in Context Study, assessed at ages 12 and 32, 61% female, 55% White, 45% Black	Perceived racial discrimination; modified daily life experiences scale of racism and life experiences scale	sCORT: 3 samples per day for 1 week (awakening, +30 min, bedtime)	Blacks w/lower waking sCORT than Whites. Waking sCORT decreased as cumulative perceived racial discrimination increased for Blacks *Depressive symptoms*
Brody et al. (2014)		331 US Black adults from rural Georgia, assessed repeatedly from 16 to 20 years, 66% female	Schedule of Racist Events at age 16–18	Allostatic load: BP, urinary cortisol, epinephrine, norepinephrine, C-reactive protein	High perceived discrimination w/high allostatic load. Trend for urinary cortisol. Emotional support buffered effects
Chi et al. (2015)	HIV infection (child)	645 children from villages in central China, 8–15 years (M_{age}: 10), 48% female, low SES, parent w/HIV infection	Stigma Against Children Affected by AIDS Scale	sCORT (awakening, +30 min, 1 h before dinner, bedtime)	High perceived stigma w/lower awakening sCORT and flatter diurnal slope. CAR n.s. *Age, sex, SES, wake time, sleep quality, stressful life events, parental death, perceived health, assessment time*

Table 1 continued

Study	Exclusion criteria[a]	Sample	Discrimination measure and/or experimental manipulation	HPA axis measure	Major findings and control variables (in italics)
Cohen et al. (2006)	Blind, deaf, mute, "mentally retarded", unable to walk on treadmill, pregnant	781 US White and Black adults, recruited at ages 18–24 and 25–30, from Chicago, Illinois and Oakland, CA	Self-reported frequency of discrimination	sCORT: 6 samples for 1 day (awakening, +45 min, +2.5, +8, +12 h, bedtime)	Blacks w/higher evening sCORT than Whites. sCORT and discrimination n.s. *Sex, age, BMI, wake time*
Doane and Zeiders (2014)		77 adolescents from southwestern US, M_{age} = 18 years, 77% female, 55% White, 23% Hispanic, 5% Asian, 5% Black, 12% multi-racial	10 item Everyday Discrimination Scale based	sCORT: 6 samples for 1 day (awakening, +45 min, +2.5, +8, +12 h, bedtime); EMA diary entries coordinated w/saliva samples	High discrimination w/increased sCORT responses to negative affect *Negative affect; wake time, sex, race, parent education, OC use*
Fuller-Rowell et al. (2012)		150 US adults, M_{age} = 57 years, 58% female, 67% White, 33% Black	The Prevalences of Lifetime and Day-To-Day Perceived Discrimination	sCORT: 4 samples/day for 4 days (awakening, +30 min, before lunch, bedtime)	Perceived discrimination w/steeper diurnal slope in Blacks. Low SES Blacks w/low discrimination had flattest slopes
Huynh et al. (2016)		292 US adolescents, M_{age} = 16 years, 58% female, 42% Latin American, 29% White, 23% Asian American, 6% other, from public high schools in Los Angeles, CA	10 item Everyday Discrimination Scale	sCORT: 5 samples/day for 3 days (awakening, +15 min, +30 min, before dinner, bedtime)	More discrimination w/greater total daily sCORT, lower waking sCORT, greater bedtime sCORT, and flatter daily decline *Wake time, ethnicity, gender, age, BMI*
Kaholokula et al. (2012)	Pregnant, <18 years	146 adult native Hawaiians (USA), M_{age} = 55 years, 71% female	10-item Oppression Questionnaire	sCORT: 2 samples, 1 a.m. and 1 p.m.	More attributed racism[c] w/lower diurnal sCORT *Perceived stress, cultural identity, BP, BMI, mainstream and ethnic identification, age, sex, education, marital status, Hawaiian ancestry*
Martin et al. (2012)	Steroids	179 preadolescents, 9–12 years, M_{age} = 11 years, 53% female, 50% Hispanic/Latino, 15% Black, 15% White, 4% Asian, 16% multiracial, from San Diego, CA	12-item perceived discrimination questionnaire	sCORT: 3 samples/day for 3 days (morning, afternoon, bedtime)	Discrimination w/sCORT n.s.
Parra et al. (2016)	Steroids	62 LGB young adults, 17–27 years (M_{age} = 21 years), 43% female, 79% White from Montreal, QC	12-item Revised Gay-Related Stressful Life Events Measure	sCORT: 6 samples for 1 day (awakening, +2, +4, +6, +8 and +12 h)	More LGB-related stress w/flatter diurnal slopes, which resulted in more depression
Ratner et al. (2013)	Pregnant, OC, breastfeeding, menopause	41 US women, M_{age} = 29 years, 66% Black, 27% Latina, 7% Black-Latina, from New York, NY	9-item Williams everyday discrimination scale	sCORT: 1 P.M. sample. Salivary DHEA	Discrimination w/cortisol, DHEA n.s.

Table 1 continued

Study	Exclusion criteria[a]	Sample	Discrimination measure and/or experimental manipulation	HPA axis measure	Major findings and control variables (in italics)
Skinner et al. (2011)		275 US adults, M_{age} = 20 years, about half female, 54% White; 46% Black from Seattle, WA	10 items from Harrell Discrimination Scale	sCORT: 4 samples/day for 3 days (awakening, +30 min, after lunch, bedtime)	Higher discrimination w/flatter diurnal slope. Blacks w/flatter slopes than Whites *Gender, family income in adolescence, sleep*
Thayer and Kuzawa (2015)		55 pregnant women, M_{age} = 31 years, 34–36 weeks' gestational age, 53% White, 27% Maori, 20% Asian, from New Zealand	Modified Williams Everyday Discrimination Scale	sCORT: 2 samples/day for 2 days. Infant saliva samples before and 25 min after vaccination	Ethnic discrimination w/higher pregnancy evening sCORT and greater response to vaccination in 6-week old infants *Time, age, BMI, ethnicity, meds*
Tomiyama et al., (2014)	BMI <25 or >40, menopausal, some disease states, pregnancy, relaxation techniques, substance use	47 US women from San Francisco, CA, M_{age} = 41 years, 62% White, 19% Asian/ Pacific Islander, 15% Hispanic/Latino, 4% Other	50-item stigmatizing situations inventory; 10-item stigma consciousness scale	sCORT: 3 samples/day for 4 days (awakening, +30 min, bedtime)	Weight stigma consciousness and frequency positively associated w/morning serum cortisol and CAR *Adiposity, oxidative stress, income, education, global perceived stress*
Tse et al. (2012)	Non-singleton pregnancy, steroid use, shift work	176 US pregnant women ≥18 years, 63% Hispanic, 26% Black, 11% White, from Boston, MA	Self-reported frequency of discrimination	pCRH, once between 20 and 37 weeks' gestational age (mean 28.1 weeks)	Discrimination w/higher pCRH in Blacks. *Parity, race, education, BMI, nativity*
Zeiders et al. (2012)	Corticosteroids	100 Mexican–American adolescents, M_{age} = 15 years, 51% female, 86% US-born	Brief perceived Ethnic Discrimination Questionnaire	sCORT: 3 samples/day for 3 days (awakening, +30 min, bedtime)	Perceived discrimination w/greater overall sCORT and steeper CAR
Zeiders et al. (2014)	Corticosteroids	140 young, upper-middle class US adults, 73% female, 54% white, 14% Latino, 8% black, 6% Asian, 11% multi-ethnic, 7% Other	Williams Everyday Discrimination Scale	sCORT: 6 samples/day for 3 consecutive weekdays	Diurnal sCORT and discrimination n.s. in Whites. In ethnic minority individuals, discrimination w/flatter slopes

BMI body mass index, *BP* blood pressure, *CAR* cortisol awakening response, *LGB* Lesbian, Gay, and Bisexual, *med* medication, *n.s.* not significant, *OC* oral contraceptives, *pCRH* placental corticotropin releasing hormone, *sCORT* salivary cortisol, *TSST* Trier Social Stress Test

[a] Exclusion criteria applicable to any study (e.g., insufficient saliva) or those related to participants not following study protocol are not listed

[b] Structural Stigma is an index consisting of (a) density of same-sex partner households, (b) proportion of Gay Straight Alliances per public high schools in the state, (c) state-level policies related to sexual orientation, (d) public opinion toward sexual minorities in each state (Hatzenbuehler & McLaughlin, 2014)

[c] Attributed oppression (or racism) is oppression attributed to an oppressive social group by the respondent (Kaholokula et al., 2012)

Heightened reactivity with discrimination

Four studies found more pronounced cortisol responses to an experimentally induced sex, age or race discrimination experience compared to a control condition. The most recent of these is a study of 108 younger and older adults who were given instructions for a task using either patronizing or non-patronizing speech. Older adults showed a marginal cortisol increase in response to the ageist treatment, whereas younger adults, and participants in the non-patronizing condition did not (Hehman & Bugental, 2015). An interactive effect was also observed in a sample of 58 working and middle class US Latinas who participated in a mock job interview with a racially prej-

udiced or unprejudiced interviewer (Townsend et al., 2014). Middle class Latinas in the prejudiced condition showed higher cortisol responses and lower anabolic balance than those in the unprejudiced condition. Working-class Latinas, however, did not show this pattern suggesting that SES may be an important moderator in the link between discrimination and cortisol reactivity.

The same group of authors, in a set of two studies, investigated how chronic perceptions of sexism can influence cortisol responses to situations in which sexist interactions occur or may occur (Townsend et al., 2011). In study 1, female participants acting as applicants in a mock job interview received either sexist or merit-based negative feedback about their performance. In the sexist but not in the merit condition, women who scored high on chronic perceptions of sexism had higher cortisol levels 20 and 30 min after cessation of the interview compared to low-scoring women. In study 2, female participants interacted with a male confederate with either sexist or unknown attitudes. Regardless of condition, the female participants with higher chronic perceptions of sexism had higher cortisol levels 15 and 35 min after learning about the confederate's attitudes, suggesting that chronic perceptions of sexism may predispose women to greater cortisol reactivity not only during sexist interactions but also during interactions where sexism is not overtly present, but also not precluded. In a fifth study, an overall cortisol increase to weight stigma exposure was not observed. However, in line with the pattern of increased responses in the four studies reported above, women who perceived their weight as heavy maintained higher cortisol levels 30 min after the weight stigma manipulation, whereas women who perceived their weight as normal showed cortisol decreases (Himmelstein et al., 2015).

Reduced reactivity with discrimination

In contrast, three studies reported blunted cortisol responses with discrimination (Hatzenbuehler & McLaughlin, 2014; Jamieson et al., 2013; Richman & Jonassaint, 2008). During data collection for a study on the role of racial identity in moderating social-evaluative threats, members of the Duke University lacrosse team were accused of sexual assault by an African American woman. This incident, which received extensive national publicity and exposed racial and class divides in the university community, created significant stress for African American students and African American women on campus in particular (Richman & Jonassaint, 2008). Participants in the study, all of whom were African American, who delivered a 5-min speech task before this naturally occurring stressor showed a typical stress response with peak cortisol levels at 20-min after cessation of the stressor. In contrast, participants who completed the stress task after the scandal had higher baseline cortisol levels and a flatter cortisol trajectory. This effect was particularly strong among women. In another study, Hatzenbuehler and McLaughlin (2014) found that Lesbian, Gay, and Bisexual (LGB) young adults who were raised in environments high in structural stigma showed blunted cortisol 10 and 20 min after cessation of a 10-min combined speech and math laboratory stressor compared to LGB youth raised in environments low in structural stigma. Finally, being rejected during a speech task by someone of a different race, which participants could interpret as an act of discrimination, resulted in lower cortisol levels immediately after and 20 min after the task compared to being rejected by someone of the same race (Jamieson et al., 2013).

Studies testing modulating variables

The final two studies used mood prime techniques to assess the role of emotions and coping on cortisol responses to an acute sex-discrimination protocol. In the first of these studies (Matheson et al., 2008), an overall cortisol response was not observed. However, among women who had been primed to feel sad, cortisol continued to decrease until 30 min after the discrimination protocol, while cortisol remained elevated in the anger-primed participants. In the second study, Matheson and Anisman (2009) found that among participants primed to feel anger, greater problem-focused coping was associated with cortisol decreases following a simulated discrimination experience. The combination of no mood prime and avoidant coping style was associated with higher levels of cortisol.

Observational studies

Among the 17 observational studies (Table 1), two used prospective designs whereas all others were cross-sectional. Most studies collected a baseline sample shortly after waking up and additional samples throughout the day for several days to obtain a diurnal cortisol profile. One study collected a single saliva sample in the afternoon, which was assessed for cortisol and DHEA (Ratner et al., 2013), one study assessed urinary cortisol (Brody et al., 2014) and one study collected a single blood sample for assessment of placental CRH in pregnant women (Tse et al., 2012).

Diurnal slope

The first and largest set of observational studies tested the link between the diurnal cortisol slope and discrimination,

hypothesizing that flatter cortisol slopes with lower morning and higher evening cortisol levels are maladaptive and associated with experiences of discrimination. Most studies reported results in support of this hypothesis. Adam et al. (2015) recruited 50 Black and 62 White individuals when they were 12 years old and followed them across a 20-year period. Perceived discrimination averaged over two decades predicted flatter diurnal cortisol in both Black and White adults, with a more pronounced effect among Blacks. Moreover, the effect was stronger when perceived discrimination was experienced in adolescence than when it was experienced in young adulthood, indicating that chronicity of the discrimination exposure may be of importance. Several cross sectional studies confirm this finding. Skinner et al. (2011), in a study of 275 young Black and White adults, found higher perceived lifetime experiences of discrimination with flatter cortisol slopes, regardless of race. Similarly, a study of LGB young adults linked stressful life events related to LGB identity occurring over the past three months with flatter cortisol slopes, which in turn predicted depressive symptoms (Parra et al., 2016). Moreover, a link between higher perceived stigma and flatter diurnal cortisol slopes as well as lower morning cortisol levels was found in a study of 645 children from rural China living in families with at least one HIV positive parent (Chi et al., 2015).

Two studies provide further evidence for flatter cortisol slopes with everyday experiences of discrimination and also report some indication of racial differences. Zeiders et al. (2014), in a study of 140 upper-middle class adolescents, found flatter diurnal cortisol slopes with perceived discrimination among ethnic minority adolescents, but not among European Americans. Similarly, Huynh et al. (2016), in a study of 293 high school students scoring low on everyday discrimination, found flatter cortisol slopes and lower morning cortisol levels in teenagers of European background but not among Latino adolescents. Two studies reported null findings for diurnal cortisol slopes, but found experiences of discrimination associated with higher evening cortisol in 179 preadolescents (Martin et al., 2012) and 55 women late in pregnancy (Thayer & Kuzawa, 2015), providing at least some support for diurnal changes in cortisol secretion in the hypothesized direction. Of interest, Thayer and Kuzawa (2015) further observed more pronounced cortisol responses in the six-week old offspring of women experiencing discrimination, suggesting a possible transgenerational pathway to health disparities.

Not all studies consistently link discrimination with flatter cortisol slopes, however. Another group of studies, some with large sample sizes, report null findings for the link between discrimination and the cortisol diurnal slope (Cohen et al., 2006; Doane & Zeiders, 2014) or individual cortisol samples in the morning or evening (Cohen et al., 2006; Doane & Zeiders, 2014; Ratner et al., 2013; Zeiders et al., 2012). A single study of 41 Black and Latina women found no association between afternoon DHEA and perceived racial discrimination (Ratner et al., 2013).

Two studies provide evidence for an association in the opposite direction. In older African American adults and a matched sample of European Americans, African Americans reporting higher levels of perceived, predominantly racial, discrimination showed a steeper cortisol decline over the course of the day compared to African Americans reporting lower levels of discrimination. Moreover, among low SES African Americans, those who reported low levels of discrimination had the flattest, or least healthy, diurnal cortisol slopes (Fuller-Rowell et al., 2012). Higher weight stigma experiences were also associated with higher morning serum cortisol among 47 women from the US, although no associations were found between weight stigma and the diurnal slope (Tomiyama et al., 2014).

Overall diurnal cortisol secretion

Two studies, both discussed above, found significantly more overall diurnal cortisol secretion in participants scoring high on perceived discrimination (Huynh et al., 2016; Zeiders et al., 2012). In contrast, a study of 146 adult Native Hawaiians found lower average cortisol levels among those with higher perceived racism (Kaholokula et al., 2012). Two studies point toward the absence of an association (Cohen et al., 2006; Tomiyama et al., 2014), a finding in line with the only longitudinal study testing this association; Brody et al. (2014) followed 331 Black 16-year olds for four years and found no associations between perceived discrimination and overnight 12-h urine cortisol.

The cortisol awakening response

Adam et al. (2015) found that averaged perceived discrimination over the past two decades predicted a lower cortisol awakening response in both Black and White adults, with a more pronounced effect among Blacks and when discrimination was experienced in adolescence. Three other studies found a link between discrimination experiences and a more pronounced cortisol awakening response. Zeiders et al. (2012) report a trend toward a steeper cortisol awakening response with higher perceived discrimination. In a separate sample of 77 adolescents, these authors replicate their previous finding, and provide further evidence of more pronounced cortisol responses to negative affects among those experiencing more discrimination (Doane & Zeiders, 2014). Similarly, weight stigma frequency was associated with a more pronounced cortisol

awakening response in one study (Tomiyama et al., 2014). Two large studies of 781 Black and White young adults (Cohen et al., 2006) and 645 Chinese youth from families affected by HIV reported no significant association between the morning cortisol increase and measures of discrimination and stigma, respectively.

CRH and discrimination

A single study tested the link between perceived racial discrimination and CRH levels in a predominantly Hispanic and Black sample of pregnant women (Tse et al., 2012). Although no associations were found in the full sample, analyses stratified by race showed a U-shaped association among Black women. Women reporting either no discrimination experiences or three or more types of discrimination had higher CRH levels than women with one or two types of discrimination experiences.

Discussion

We set out to review the literature on HPA axis activity and experiences of discrimination. Twenty-seven studies, ten experimental and 17 observational, were identified. For the most part, studies investigated the link between cortisol and discrimination. Two studies measured DHEA and one studied placental CRH. At first glance, findings appear inconsistent. Among the experimental studies, some provide evidence for more pronounced cortisol responses to acute laboratory stress while others point to blunted responses with discrimination. Similarly, among the observational studies, some associate discrimination with steeper diurnal slopes, higher morning and lower evening cortisol, lower overall diurnal output and a more pronounced cortisol awakening response, but at least as many studies yielded null findings or findings in the opposite direction. However, the majority of discrepant findings can be reconciled by considering the timing and chronicity of the discrimination experience, modulating variables such as race and SES, as well as emotional and situational contextual confounders.

In terms of the timing and chronicity of the discrimination experience, findings differed depending on whether studies conceptualized and measured discrimination as a chronic or life-time stressor versus an acute or fairly recent event. Looking at the experimental studies first, two types of studies could be identified. The first type of studies compared individuals' responses to laboratory stressors that either did or did not include an element of discrimination, thereby conceptualizing discrimination as an acute event. These studies showed more pronounced cortisol responses with discrimination experiences (Hehman & Bugental, 2015; Townsend et al., 2011, 2014), and in one case ongoing elevation of cortisol levels in the absence of a cortisol response (Himmelstein et al., 2015). These findings integrate well with a neurobiological model of racial discrimination and health, which posits that ongoing experiences of discrimination result in changes in HPA axis activity, which in turn lead to structural and functional changes in brain networks associated with heightened reactivity to acute stressors, and ultimately contribute to an increased risk of adverse mental health outcomes (Berger & Sarnyai, 2015). Conversely, the second set of studies compared how individuals with and without prior experiences of discrimination respond to a non-discriminatory laboratory stressor, thus conceptualizing discrimination as chronic. In those studies, a history of discrimination was associated with more blunted cortisol responses (Hatzenbuehler & McLaughlin, 2014; Jamieson et al., 2013; Richman & Jonassaint, 2008). Overall, it appears that individuals exposed to discrimination show blunted responses to stress, unless the stressor includes an element of discrimination, in which case heightened stress reactivity may occur.

In terms of the chronicity of experience, a similar pattern of findings emerged for the observational studies. The two studies assessing racial discrimination experiences over at least two decades provide evidence of flatter diurnal cortisol slopes (Adam et al., 2015; Skinner et al., 2011) and a lower cortisol awakening response (Adam et al., 2015). While conclusions based on two studies are necessarily preliminary, these findings align closely with those of an influential meta-analytic review of chronic stress and HPA axis function (Miller et al., 2007). Across 119 studies, individuals with high exposure to chronic stress exhibited a cortisol pattern characterized by a flatter diurnal cortisol slope, lower morning and higher evening cortisol levels, as well as higher cortisol output throughout the day. Differential health-related outcomes depending on the chronicity of the discrimination experience have also been documented in a nationally representative sample in which major depression in the past year was associated with everyday discrimination but not with past major events of discrimination (Hudson et al., 2012).

The remaining observational studies considered discrimination experiences that occurred over various periods of time but within a maximum of one year, and findings are more conflicting. Some studies are in line with a chronic stress pattern, linking discrimination with flatter diurnal slopes (Chi et al., 2015; Parra et al., 2016), flatter diurnal slopes in subgroups of individuals (Huynh et al., 2016; Zeiders et al., 2014), and higher evening cortisol levels in the absence of differences in diurnal slopes (Martin et al., 2012; Thayer & Kuzawa, 2015). Conversely, other studies

yielded patterns more consistent with changes in cortisol release expected with acute stress (Miller et al., 2007), and report on steeper cortisol diurnal slopes (Fuller-Rowell et al., 2012), higher morning cortisol levels in the absence of altered diurnal slopes (Tomiyama et al., 2014), and a more pronounced cortisol awakening response (Doane & Zeiders, 2014; Tomiyama et al., 2014; Zeiders et al., 2012) with discrimination. Yet another set of studies did not detect significant associations between discrimination experiences and the diurnal slope (Cohen et al., 2006; Doane & Zeiders, 2014), cortisol levels in the morning or evening (Cohen et al., 2006; Doane & Zeiders, 2014; Ratner et al., 2013; Zeiders et al., 2012), overall secretion throughout the day (Brody et al., 2014), or the cortisol awakening response (Chi et al., 2015; Cohen et al., 2006). Even though individuals in these studies were asked to consider only discrimination experiences in the past year, it may be that their discrimination experiences in the past year are reflective of a life-long pattern, and thus the observed changes in cortisol secretion map on to a chronic stress pattern. Other studies may have truly captured recent events, favoring the detection of cortisol changes indicative of acute stress. Of note, the only observational study measuring truly acute stress by assessing cortisol changes in response to negative affect using Ecological Momentary Assessment methods yielded findings in line with predictions for an acute stress model (Doane & Zeiders, 2014). It may, of course, also be the case that the somewhat inconsistent findings within the observational studies indicate that the neurobiological changes associated with ongoing discrimination may just be less apparent in the baseline functioning of the HPA system, and instead be more salient in the context of an acute discrimination stressor occurring (Berger & Sarnyai, 2015).

Our review further provides evidence that SES and race may modulate the association between discrimination and HPA axis activity. In terms of SES, one study observed the flattest diurnal cortisol slopes among African Americans who reported a low level of discrimination and were also low SES (Fuller-Rowell et al., 2012). Similarly, altered cortisol with discrimination was found among middle class but not working-class Latina American women (Townsend et al., 2014). Of note, higher SES in these studies was not protective, a finding aligned with reports of higher major depression rates in high SES compared to low SES African American men exposed to discrimination (Hudson et al., 2012). The authors of that study theorize that the salience of higher structural barriers and larger racial differences in financial compensation among highly educated African American men may explain these findings. Based on this limited evidence, SES appears to be a relevant moderator, although it should be pointed out that the link between discrimination and HPA axis regulation remained significant after controlling for income or education in a number of studies (Doane & Zeiders, 2014; Kaholokula et al., 2012; Skinner et al., 2011; Tomiyama et al., 2014; Tse et al., 2012).

In terms of race, study samples were typically racially diverse, and some tested the effects of race as a modulating variable in the link between discrimination and HPA axis function. From these studies, it appears that discrimination can be associated with alterations in HPA axis activity, regardless of race (e.g., Skinner et al., 2011) and that racial differences in HPA axis activity cannot be solely explained by discrimination experiences (e.g., Martin et al., 2012). Some studies provided evidence that discrimination and race interact to predict changes in cortisol secretion. For example, associations between self-reported discrimination and altered HPA axis activity were found in ethnic minority individuals but not in European Americans (Zeiders et al., 2014), in European Americans but not in Latinos (Huynh et al., 2016), and in African American but not in Latina pregnant women (Tse et al., 2012). There is ample evidence that strong family networks and social support may act as a buffer in the link between stress, stress-related biological processes and negative health outcomes (Cohen, 2004; Uchino, 2006; Uchino et al., 1996). Latinos tend to be higher in familism, a construct that describes a sense of interconnectedness, support, and obligation towards family (Sabogal et al., 1987). Thus, familism may be a more proximal predictor of HPA axis regulation than race, which could explain why some studies did not detect links between discrimination and cortisol alteration among Latinos. Alternatively, it is possible that discrimination itself is a mediator in the link between race and HPA axis activity. While we were unable to identify a study testing this hypothesis directly, there is certainly a need to address this question in future empirical work. Of course, another possibility is that low statistical power in some studies or the use of measures capturing discrimination adequately in one race but not the other, contributed to some of these negative findings.

Taking the above reflections another step further, it is also possible that race per se may neither prove to be a particularly useful predictor nor modulating variable in terms of furthering our understanding of the link between discrimination and negative health outcomes. In our view, it seems more likely that the study of socio-cultural and contextual variables related to race, such as the above-mentioned cultural construct of familism (Gallo et al., 2009) or variables related to social categorization and social hierarchy (Major et al., 2013), both individually and in their interaction, will deepen our understanding of this important issue.

Accordingly, a small set of studies has begun to directly test whether social contextual variables can influence how individuals respond to discrimination. One study points to

the importance of the race of the perpetrator of discrimination. Jamieson et al. (2013) found that cortisol responses to a laboratory stressor were blunted in individuals rejected by a member of a different race compared to individuals experiencing same-race rejection. Two other studies, published in a single manuscript, tested how interactions between dispositional attitudes and cues from an authority figure influence individuals' responses to potential discrimination. Findings suggest that chronic perceptions of sexism may predispose women to greater cortisol reactivity during sexist interactions and in interactions where sexism is not present but also not precluded (Townsend et al., 2011). Together, these studies suggest that detrimental effects of discrimination on HPA axis regulation do, in fact, depend on socio-contextual variables.

A final set of studies provide evidence for the importance of emotions and preferred coping strategies in the link between discrimination and HPA axis activity. One study showed that youth reporting high levels of discrimination showed more pronounced momentary cortisol increases to negative affect compared to youths experiencing lower levels of discrimination (Doane & Zeiders, 2014). Another study showed that an anger prime but not a sadness prime prolonged cortisol responses to an acute discrimination experience (Matheson et al., 2008). The same authors showed that among those primed with anger, problem-focused and avoidant coping styles were associated with decreasing cortisol following a simulated discrimination experience, whereas among those primed with shame an avoidant style was associated with reduced cortisol reactivity (Matheson & Anisman, 2009). A final study provided trend-level evidence pointing to emotional support as a buffer in the link between discrimination and cortisol activity (Brody et al., 2014). Together, these studies suggest that individuals' emotions and coping styles are relevant factors to consider in terms of HPA axis alterations following discrimination experiences.

In sum, our review of the literature suggests that experiences of discrimination are associated with alterations in HPA axis activity. Thus, accounting for the HPA axis in addition to the more frequently studied cardiovascular system is important in terms of developing a better understanding of the complex biobehavioral pathways that contribute to discrimination-related physical and mental health inequities. The literature reviewed here provides evidence that the timing and duration of discrimination experiences may be central to understanding how experiences of discrimination can lead to dysregulations in the HPA system, and ultimately result in stress-related disease. Finally, it appears that important modulators including race and SES as well as emotional and social contextual factors play an important role in this line of research.

Moving forward, we recommend that studies move away from simple correlational designs in favor of experimental designs and prospective approaches. We also suggest a more comprehensive assessment of multiple forms of discrimination because experiencing multiple forms of discrimination has been associated with worse mental and physical health than experiencing only one form of discrimination (Grollman, 2012). Similarly, studies should address the complexity of the physiological consequences of discrimination by carefully addressing interactive processes between stress-related systems, including for example the HPA axis and the cardiovascular system. Finally, there is a need for further research on relevant modulators in the link between discrimination and altered HPA axis activity, including socio-cultural and contextual variables that may be sources of vulnerability or resilience for groups chronically exposed to discrimination. This latter direction has the potential to shed light on inequities in minority health and may point toward promising approaches for achieving health equity. In sum, we recommend that future studies take a theory-driven, prospective approach to testing the biobehavioral mechanisms leading from discrimination experiences to negative physical and mental health outcomes.

Compliance with ethical standards

Conflict of interest David Busse, Ilona S. Yim, Belinda Campos and Christopher K. Marshburn declare that they have no conflict of interest.

Human and animal rights and Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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