Published in final edited form as:

Front Neuroendocrinol. 2020 January ; 56: 100803. doi:10.1016/j.yfrne.2019.100803.

Individual differences in glucocorticoid regulation: Does it relate to disease risk and resilience?

Jasmine I. Caulfield, B.S.^{a,b,c}, Sonia A Cavigelli, Ph.D.^{a,b,c}

^aPennsylvania State University, Huck Institute for Life Sciences, 101 Life Sciences Building, University Park, PA 16802, USA

^bPennsylvania State University, Department of Biobehavioral Health, 219 Biobehavioral Health Building, University Park, PA 16802, USA

^cPennsylvania State University, Center for Brain, Behavior, and Cognition, University Park, PA 16802, USA

Abstract

Glucocorticoid (GC) signaling varies among individuals, and this variation may relate to individual differences in health outcomes. To determine if and which aspects of signaling (basal, circadian, integrative, or reactivity) are associated with specific health outcomes, we reviewed recent studies that relate GCs to health outcomes. We identified papers through PubMed and reviewed 100 original research articles related to mental health, cardiovascular health, cancer, diabetes, obesity, pulmonary health, sleep, and fitness. Many studies reported elevated GC secretion associated with worse health, but this was only particularly true for integrative GC measures. On the other hand, accentuated cortisol awakening response and a steeper circadian rhythm were both associated with positive health outcomes. Overall, relationships between GC secretion and health outcomes were relatively weak. This systematic review of relationships between GC metrics and health outcomes highlights the importance of careful consideration when selecting methods to measure GC regulation in health research.

Keywords

Disease risk; Disease resilience; Cortisol; Corticosterone; Mental health; Cardiovascular health; Cancer; Pulmonary health; Sleep; Fitness

Corresponding Author: Sonia Cavigelli, 219 Biobehavioral Health Building, Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA 16802, sac34@psu.edu, Phone: (814) 863-0210, Fax: (814) 863-7256.

Competing Interests Statement: The authors declare no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. INTRODUCTION

Glucocorticoid (GC) hormone signaling provides a global and general system for organisms to respond to environmental challenges. Unlike the other major physiological ‘stress system’ – i.e. activation of the sympathetic branch of the autonomic nervous system – GC signaling promotes a slower and more sustained response to challenges, which may therefore have a longer-lasting or more cumulative impact on physiology and health. GC hormones promote gluconeogenesis and thus affect metabolic activity globally. Further, GC hormones can directly affect the function of other physiological systems (e.g. immune, neurological) by binding to receptors on cells that mediate these processes, affecting their function and gene transcription (Kadmiel and Cidlowski, 2013). Increased GC signaling promotes sustained metabolic activity to support organismal responses to environmental challenges. However, sustained GC signaling has been associated with certain negative fitness and health consequences (e.g. obesity, cardiovascular function, reproductive success). In the current review, we examine this body of work to determine if and how individual GC production is related to health and fitness. We ask the question: “Do individual differences in GC signaling relate to health and fitness outcomes?” And if so, the goal is to determine what aspect of GC signaling is most closely associated with health outcomes. Because of the relative accessibility of GC metrics as a ‘biomarker’ of stress, there have been several decades of research dedicated to studying whether GCs are a mechanism by which stress affects health and fitness in humans and animals. Here, we review this literature to understand and reveal relationships between health outcomes and GC metrics.

GC signaling is regulated by complex feedforward and feedback mechanisms with dynamic receptor signaling (Cain and Cidlowski, 2015; Kadmiel and Cidlowski, 2013; Quax et al., 2013). This regulatory complexity allows for significant variability in GC signaling, both within and among individuals, in the amount of hormone secreted, the duration of elevated secretion periods, the temporal patterning of secretion, and the relative sensitivity of different cells to circulating hormones. Variability in GC signaling among individuals has long been proposed as a potential source for individual differences in health and fitness (McEwen, 1998; McEwen and Stellar, 1993), and the most widely-recognized individual differences in GC signaling have been in secretion (signal) and sensitivity (response). For example, individuals can differ widely in their secretion of GCs into the blood and also differ in their relative sensitivity to secreted GCs.

If individual differences in GC regulation could have long-term, cumulative influences on health outcomes, the assumption is that these individual differences are relatively consistent and stable within individuals over time. For example, an individual that has relatively high basal GC secretion will show this pattern over a significant portion of the life span. To address whether individual differences in GC regulation represent a trait-like characteristic, only a handful of studies have investigated the relative consistency in individual GC hormone circulation over time. These studies suggest that GC regulation is relatively consistent within an individual, with repeat measure correlation coefficients ranging from ~0.0 to 0.8, with an average of approximately 0.3 based on a recent meta-analysis using data from multiple animal taxa, primarily birds (Taff et al., 2018). These estimates vary depending on the time lag between repeat measures and the specific aspect of GC secretion

that is measured – i.e. basal secretion, secretion in response to a stressor, circadian rhythm/slope, total secretion over hours or months, etc. (Cavigelli et al., 2009; Cockrem, 2013; Cockrem et al., 2009; Cockrem and Silverin, 2002; Kralj-Fišer et al., 2007; Ross et al., 2014; Taff et al., 2018; Wada et al., 2008). Although the data are relatively limited because of the difficulty in measuring circulating GC hormones in a consistent manner within the same individual over time (e.g. always under basal conditions, or always in response to a standardized stressor, etc.), current results suggest that GC hormone secretion appears trait-like, particularly long-term measures, acute stress measures, overall daily output, and diurnal slope (Cockrem, 2013; Ross et al., 2014; Taff et al., 2018). As a suggestion of the relative predictive nature of these individual differences in GC regulation, a few studies have shown that elevated basal and integrated GC production predict a shortened lifespan in laboratory and free-ranging animals, however, results for basal GC prediction of overall fitness are quite mixed (Bonier et al., 2009; Cavigelli et al., 2009; Pride, 2005). In humans, an early study found an association between early morning circulating cortisol levels and suicide (Krieger, 1974).

Another important aspect to consider when thinking about whether GC hormones are related to health outcomes is that GC signaling is a dynamic process. GC signaling occurs throughout the day, even under ‘basal’ (i.e. ‘unstressed’) conditions. Low-grade GC pulses and changes in overall production occur across the day, and these dynamic patterns may have as much and/or different functional impacts as acute secretory elevations in response to environmental challenges (Romero, 2004; Sapolsky et al., 2000). Broadly speaking, GC measures usually involve a direct or indirect metric of secretion into circulation. These measures can be: (1) a snapshot of *basal* secretion at one point in time (e.g. basal salivary or blood measures), (2) an estimate of the acute elevation in secretion in *response* to a challenge (for example, a standardized psychological stressors like the Trier Social Stress Test, TSST, the cortisol awakening response usually measured at waking and 30 minutes later, CAR, or some other challenge), (3) multiple measures over the day used to calculate an index of *circadian* production (slope or change from morning to evening), and/or (4) an *integrated* measure of total production over hours to months (typically measured in urinary or hair samples). Each of these metrics provides a different estimate of GC regulation. A ‘basal’ GC measure provides an estimate of GC production during low-stress conditions and likely reflects the amount of GC secreted during a good portion of the day. These measures may be particularly ‘noisy’ because events prior to measurement can affect GC production and these events are not necessarily controlled or documented. Thus, these measures likely include estimates of basal production along with outliers from individuals that experienced a secretory surge after an undocumented stressor. Measures of GC ‘reactivity’ or ‘recovery’ (i.e. measured ~30 minutes or several hours after a natural or experimental stressor) are indicative of how GCs are released in response to a stressor, particularly with peak amplitude and rate of return to baseline after a challenge. Measures of the circadian rhythm provide an estimate of whether glucocorticoid production follows the normal circadian rhythm of high circulating levels at the beginning of the active period with lowest levels at the end of the active period and the first half of the inactive period (Dmitrieva et al., 2013; Krieger et al., 1971). This measure can involve the same kind of noise that is involved in basal measures; however, many researchers are moving toward measuring the GC circadian

rhythm over several days to provide more accurate estimates and a method to determine individual consistency (Karlamañgla et al., 2013; Kupper et al., 2005; Miller et al., 2016; Shirtcliff et al., 2012; Stawski et al., 2013). Urine and hair cortisol levels provide a more integrative estimate of GC secretion. Cortisol accumulates in these media over several hours (urine) or months (hair), so these metrics provide an integrated (average) estimate of overall secretion over time, which combines peaks in response to challenges and basal production during low-challenge periods. Importantly, different aspects of GC secretion (basal vs. reactivity) are not necessarily related; an individual that maintains high basal secretion does not necessarily have a high or low GC response to an acute stressor (Khoury et al., 2015). Prior studies have suggested that GC reactivity can be relatively consistent within an individual over time, whereas basal/integrative/circadian rhythm estimates of GC production may be more closely associated with health outcomes (Cavigelli et al., 2009).

Given the dynamics of GC secretion and the many different methods that have been used to quantify GC signaling, in the current review, we examined studies that have related different GC measures to health outcomes to determine which aspect(s) of GC signaling is/are most closely associated with health outcomes. Because of publication bias, we expect that many null results are missing in the literature. Thus, the goal of the current review was not to enumerate how often GCs have been related to health, but to determine which aspect of GC production (i.e. basal, reactive, circadian, or integrative) has been most often associated with specific health outcomes. This focus on comparing different GC metrics minimizes negative effects of publication bias and makes beneficial use of those studies that report a significant relationship between GCs and health outcomes. To further accommodate publication bias, we were careful to document all tested relationships between GC and health even when these led to non-significant (null) relationships, and if a study compared multiple GC metrics to health, we documented results for all metrics. *A priori*, we hypothesized that basal and longer-term integrated measures of elevated GC production (e.g. hair) would be more frequently related to negative health outcomes, whereas acute reactivity levels would be more often related to positive health outcomes. This hypothesis is based on prior literature that suggests that acute GC elevations may be beneficial for organismal function and that chronic GC elevations may have more negative impacts over the long-term (Cavigelli and Caruso, 2015; Schoenle et al., 2018)

2. METHODS

The methods for how searches were conducted are outlined in Figure 1. All searches were conducted between August 2018 and January 2019 using PubMed, and all health outcomes were researched using the following phrases: “cortisol and [outcome],” “corticosterone and [outcome],” and “glucocorticoids and [outcome].” Initial searches involved broad terms for outcome measures, including “health,” “disease,” “disease risk,” “disease resilience,” and “disease predictor.” Many of the studies that emerged distinguished cortisol awakening response as the cortisol measure related to the most health outcomes. A secondary broad search was conducted where we reviewed literature attained by searching for “cortisol awakening response” (CAR) paired with “health,” “predicting health,” and “disease.” Following these two broad searches, we determined that certain types of health and disease outcomes were most commonly reported in relation to glucocorticoids. In order to have a

more detailed review of these prominent health outcomes, the remainder of the searches were more targeted in outcome terminology to encompass the most common specific disease outcomes identified from the broad searches: “cancer,” “survival,” “fitness,” “cardiovascular health,” “diabetes,” “obesity,” “mental health,” and “airway disease.” In the review, sections are organized according to mental health, cardiovascular health, cancer, diabetes, obesity, pulmonary health, sleep, and fitness. In total, 100 original research articles have been reviewed in the body of the text, seven from 2000–2009, and ninety-three from 2010–2019.

For each article reviewed, we categorized the GC metric as: ‘basal’, ‘reactive’, ‘circadian’, ‘integrative’, or ‘exogenous administration’. For each metric within each paper, we documented whether authors identified a ‘positive’, ‘negative’, or ‘null’ relationship between their GC metric and the health outcome of interest. Specifically, if a study showed a statistically significant ($p < .05$) relationship between GC levels and health outcomes with elevated GC levels associated with better health, we categorized this as a ‘positive’ relationship. For studies that documented a statistically significant reverse relationship, where elevated GC levels were associated with poorer health, we categorized these results as a ‘negative’ relationship (Figure 2). For all studies that did not document a statistically significant relationship between a GC metric and health outcome, we categorized these results as ‘null’ relationships. In the case of the circadian GC rhythm, we defined a steeper diurnal slope as ‘elevated’ GC production, although recognize that a steeper slope can easily translate into lower overall production during the day. Referring back to our original hypotheses then, we expected elevated ‘basal’ and ‘integrative’ GC metrics to be associated with poor health (i.e. a ‘negative’ relationship), and elevated ‘reactive’ GC metrics to be associated with better health (i.e. a ‘positive’ relationship). Given our definition of the circadian GC rhythm, we expected that a steeper GC slope would predict better health outcomes (i.e. a ‘positive’ relationship). For studies that provided exogenous GCs to subjects, we expected a ‘negative’ relationship between GC and health because exogenous administration is often conducted in a chronic fashion (slow-release implants, daily corticosteroid dosing, etc.). We did not have *a priori* hypotheses about whether the above relationships would differ according to the specific health outcome categories.

3. RESULTS

A summary of all studies that related GC metrics to health outcomes are listed in Table 1, which is organized by health outcome then GC metric within each outcome. To further summarize the results, Table 2 provides overall number and direction of relationships between each GC metric and each health category. We provide a more detailed description of risk and resilience relationships between GC metrics and specific health outcomes in the text.

3.1 Mental Health

In studies that examined mental health outcomes, negative relationships with GC levels were most frequently reported and the most common GC metrics were basal, reactivity, and circadian estimates. In general, mental health issues were often associated with long-term alterations in GC secretion. In youth, a flattened circadian rhythm and an accentuated

cortisol response to challenge were often associated with risk for mental health issues. For example, young mental health patients had elevated hair cortisol concentrations compared to healthy controls (Heinze et al., 2016) and associated medication use (methylphenidate, antipsychotics or other antidepressants) predicted low salivary cortisol levels at wake compared to youth without these medications (Zandstra et al., 2015). Family-related precursors to mental health were also associated with altered GC regulation. Adolescents that felt responsible for their parents' conflict had a flatter cortisol slope (increased salivary cortisol concentration at bedtime) compared to adolescents that did not feel responsible for the parent conflict (Lucas-Thompson et al., 2017), and youth with parents with psychiatric histories were at increased risk for internalizing symptoms following chronic stress if they had lower salivary cortisol levels at wake (Zandstra et al., 2015). Children of depressed parents, and those with more negative cognitive style and cognitive vulnerability, and older youth with more depressive symptoms produced higher salivary levels of cortisol in response to the Trier Social Stress Test (TSST) (Hayden et al., 2014). In adults, similar trends of cortisol relationships with mental health are present. Lower CAR and lower basal cortisol levels were associated with increased mental health state in adults and elderly (Moraes et al., 2016; Zahn et al., 2015).

Cortisol secretion prior to a traumatic event did not predict PTSD susceptibility, but levels following a traumatic event were predictive. For example, a flatter cortisol rhythm (lower morning and higher afternoon salivary cortisol) two days after a traumatic event predicted greater PTSD symptoms at a six-month follow-up, but 24-hour urine cortisol levels were not predictive (McFarlane et al., 2011). In another study, lower cortisol and higher dehydroepiandrosterone sulfate levels in blood immediately after a traumatic event predicted PTSD symptoms six weeks later, and low cortisol at the time of the event also predicted PTSD symptoms six months later (Mouthaan et al., 2014). In policemen and firefighters who experienced a traumatic event, waking salivary cortisol levels before the event were not correlated with onset of PTSD symptoms but were positively associated with anxiety/mood symptom development after the event (Pineles et al., 2013). Military personnel and veterans with PTSD and service dogs experienced less anxiety, sleep disturbance, and aggression, and had elevated CAR and AUC from baseline compared to those without a service dog. However, PTSD symptoms were not specifically correlated with CAR or AUC from baseline (Rodriguez et al., 2018). Finally, interventions to minimize PTSD symptoms may reinvigorate CAR and cortisol production during the day, but these changes in cortisol secretion may not mediate PTSD symptoms.

Interestingly, other studies suggest that cortisol secretion may be associated with conditions that predict mental health in adults, although not necessarily specific mental health conditions *per se*. For example, hair cortisol was significantly and positively related to perceived chronic stress, drinking, smoking, and partner aggression, but not with anxiety symptoms measured by survey (Wells et al., 2014). In patients with type-1 diabetes, self-reported depression was associated with higher anxiety symptoms, greater prevalence of alexithymia, and high midnight salivary cortisol levels compared to non-depressed controls (Melin et al., 2017). In another study, long-term informal caregiving (often associated with poorer mental health) was dose-dependently associated with blunted salivary CAR in males but not females, with no differences in slope of cortisol rhythm for the rest of the day

between caregivers and non-caregivers (Mortensen et al., 2019). In pregnant women who had experienced domestic violence there was no association between CAR and the type or number of domestic violence forms experienced (Ziaei et al., 2016). Study participants at ultra-high risk for developing psychosis, without current medications, had blunted salivary CAR compared to healthy controls, without any other differences in cortisol levels measured during the rest of the day (Day et al., 2014). In another study, people who reported higher stress because of work also reported worse health status and significantly increased levels of cortisol in baseline plasma compared to those with better health (Yan et al., 2015). Individuals that took part in a yoga retreat showed improved scores on psychometrics related to anxiety and depression, and while overall daily cortisol AUC did not change, their CAR was significantly higher after the retreat compared to the start of the retreat (Cahn et al., 2017). Thus, there is suggestion that a blunted CAR and elevated basal or long-term integrated cortisol secretion are associated with conditions that predict poor mental health, but there is only weak indication that these metrics predict mental health risk or outcomes.

Exogenous prenatal GC exposure is associated with increased mental health issues in human and animal offspring. Children (8 year olds) that had been exposed to prenatal exogenous GCs had elevated inattention scores, although this was no longer the case by 16 years of age (Khalife et al., 2013). In mouse offspring of mothers treated with CORT during gestation had larger adrenal glands and male offspring had higher circulating CORT levels compared to same-sex controls at 6 months. This CORT increase disappeared by 12 months, but these males also had larger eosinophilic plaques in the adrenals compared to controls at this later age (Cuffe et al., 2017). In a rat model of postpartum depression, subcutaneous injections of CORT after first pregnancy caused higher serum CORT levels, smaller pups, and increased maternal depression-like behavior during a second pregnancy compared to control females (Wong et al., 2011). Offspring of wild largemouth bass mothers that received a cortisol treatment had lower wholebody cortisol levels in response to acute stress, less anxiety-like behavior, less exploratory behavior, and less tail-whipping behavior compared to control offspring (Redfern et al., 2017). These results indicate that experimentally-elevated maternal circulating CORT levels can have multiple mental health-related effects on offspring and mothers (e.g. attention, GC secretion, behavior), but that these effects may not persist into adolescence or adulthood.

Given the connection between psychiatric disorders, chronic stress, HPA axis activity, and brain-derived neurotrophic factor (BDNF), rat studies have shown that experimentally-induced BDNF overexpression in the hippocampus can reverse depression-related phenotypes in adult rats exposed to chronic stress. Further, adolescent rats that were resilient to depression-like behavior after chronic stress did not show a reduction in overall hippocampal BDNF expression that was observed in non-resilient and BDNF-knockdown rats, although they did have lower baseline and stress response CORT concentrations (Taliaz et al., 2011). These studies indicate that factors other than GC production likely confer mental health resilience to chronic stress.

In summary, a flattened cortisol circadian rhythm following a traumatic event predicted anxiety and PTSD symptoms, but cortisol levels prior to the event, and an integrated measure of cortisol after an event, were not predictive. In children, lower salivary cortisol,

flatter diurnal rhythm, and increased GC reactivity to standardized stressor tasks were associated with parental conflict and psychological history, suggesting an important influence on child mental health. A blunted CAR was observed in people at risk for psychosis, and CAR increased in individuals that underwent mental health-related intervention, although the mediating aspect of this restored CAR was not clear. Exposure to GCs can have detrimental effects on early development of offspring and on parent behavior, but detrimental effects of prenatal GC exposure may subside by adolescent years.

3.2 Cardiovascular Health

Studies that examined cardiovascular health most commonly reported negative relationships between GC measures and health outcomes, with basal and reactivity GC measures being the most frequently-used metrics.

Multiple cardiovascular health outcomes have been compared to GC levels, such as attack risk, survival, and different aspect of cardiovascular function. We would expect the various outcome measures to be differentially related to each GC metric used. For example, risk of an attack and attack intensity may be more closely associated with the intensity of a cortisol response to a stressor, whereas overall cardiovascular function may be more closely related to basal or circadian measures of GC secretion. This was generally the case. In neonates that underwent cardiopulmonary bypass surgery, higher baseline serum cortisol was correlated with increased severity of illness after operation, as indicated by the following proxy measures: higher lactate concentration peak, greater fluid requirements, and decreased urine output in the first 24 hours after surgery, but not steroid responsiveness to hydrocortisone therapy (Sasser et al., 2012). For patients with chronic heart failure scheduled for cardiac catheterization surgery, serum cortisol during the day prior to surgery predicted post-surgical cardiac events, where patients with high levels of both brain natriuretic peptide and cortisol were at a 15.5 fold higher risk for having a cardiac event compared to patients with low levels (Yamaji et al., 2009). In patients undergoing coronary artery bypass graft surgery, while overall AUC for the day had no predictive value, those with a flatter diurnal cortisol rhythm 30 days prior to surgery were at greater risk for having a major adverse cardiac event or death following surgery (Ronaldson et al., 2015). Also, high evening salivary cortisol (between 0.5–2.96 ng/mL) predicted higher mortality rates and more advanced heart failure in patients with systolic heart failure (Hammer et al., 2016). Serum cortisol levels immediately after resuscitation from cardiopulmonary arrest predicted a better chance of survival (Ito et al., 2004). Finally, male patients with acute myocardial infarction had higher cortisol in hair compared to control patients, and the occurrence of acute myocardial infarction increased with increasing levels of hair cortisol (Pereg et al., 2010). Thus, high acute cortisol responses tended to predict an increased risk of an attack but better survival, whereas elevated basal, integrated, and circadian production predicted poorer disease progression and prognosis. In individuals having surgery, high basal and flatter circadian rhythms predicted worse surgical outcomes.

In considering risk factors and symptom severity in cardiovascular health, a lower nocturnal rise and a lower CAR may be related to worse symptoms. In overweight African American and Latino youth with carotid artery intima-media thickness, elevated morning salivary

cortisol and an overnight rise in cortisol was associated with decreased cardiac thickness, whereas evening saliva, morning serum, and urinary cortisol were not associated with thickness (Toledo-Corral et al., 2013). In police officers, lower salivary cortisol AUC at waking during baseline evaluation predicted worsening brachial flow-mediated dilation at a follow-up time (Violanti et al., 2018). In peri- and postmenopausal women, self-reported hot flash bother was associated with a lower cardiac index, higher vascular resistance, and plasma IL-6 but not cortisol reactivity to TSST. Additionally, night sweats were associated with post-TSST IL-6 levels but not with higher cortisol responses to the stress test (Gordon et al., 2016). In adult rats exposed to acute, intermittent, or chronic stress, blood pressure was elevated compared to controls, but only in the chronic stress group was heart rate, blood pressure, basal plasma CORT, adrenaline, and noradrenaline elevated relative to all other experimental groups (Said and El-Gohary, 2016). These results suggest that chronic stress is required to elevate a suite of physiological processes that are all associated with cardiovascular disease risk, including elevated basal CORT secretion. In middle-aged adults, increased social isolation is associated with slower systolic blood pressure recovery after a stress test, increased cortisol 30 minutes after wake, and daily output of cortisol, but it is not associated with evening cortisol or daily decline slope (Grant et al., 2009). Thus, the literature is quite mixed on whether GC production is related to cardiovascular disease risk factors and/or symptoms. Lower CAR predicts some risk factors (e.g. brachial flow-mediated dilation), but a heightened awakening response has been associated with other risk factors (e.g. slower blood pressure recovery). Further, acute cortisol responses to a challenge other than waking was not closely related to symptoms.

Exogenous GC administration provides a method to test the causal role that GCs may play in cardiovascular disease risks, symptoms, and/or progression. In a Danish study glucocorticoid medication use increased risk for a venous thromboembolism (Johannesdottir et al., 2013). In rats, females exposed to dexamethasone (DEX) during pregnancy had adult male offspring that exhibited dysregulated heart function (decreased left ventricular ejection fraction, decreased fractional shortening, decreased max rate of increase in pressure, decreased max rate of decrease in pressure, larger myocardium infarct size, greater amount of apoptosis of cardiomyocytes, and differences in heart protein and DNA global methylation) compared to unexposed mother offspring (Peng et al., 2018). These results support numerous prior reports that early life events and maternal stress put males at greater risk for developmental disorders and other health problems (Bale and Epperson, 2015; Schwarz and Bilbo, 2012). Together, these studies indicate that experimentally-elevated GCs can cause a decline in cardiovascular function. However, removal of GCs by adrenalectomy in male mice led to worse left ventricle function, larger left ventricle wall thickness, and a larger heart six month after surgery compared to control mice; CORT administration to adrenalectomized mice returned normal heart function (Cruz-Topete et al., 2016). Thus, a basic level of circulating GCs is important for normal cardiac function and heart morphology.

In summary, the literature consistently suggests that a flatter diurnal cortisol rhythm is associated with negative cardiac outcomes. High basal circulating cortisol is associated with higher risk for cardiac events and mortality. Higher serum cortisol immediately after a cardiac event predicted better survival, suggesting a resilience mechanism, but high serum

cortisol is also associated with increased severity of illness for neonates after heart surgery. Finally, elevated cumulative cortisol measured in hair is associated with increased cardiac risk, indicating the effect of chronically-elevated GC exposure on cardiac risk.

3.3 Cancer, Disease Progression, and Mortality

In studies examining cancer, disease progression, and mortality, positive and negative relationships with GCs were almost evenly reported. Studies most frequently involved circadian GC production estimates and exogenous GC exposure.

Like cardiovascular disease, GC secretion has been related to multiple aspects of cancer outcomes, although most have to do with disease progression and survival. In patients with lung cancer, while CAR had no predictive value, a flattened salivary cortisol rhythm was predictive of significantly higher mortality rates within three years, with a flattened cortisol rhythm observed more in men than women and in individuals with more advanced stages of lung cancer (Sephton et al., 2013). In addition, lung cancer patients had higher salivary cortisol levels across the day compared to individuals without cancer, and a flatter cortisol slope was associated with more sleep disturbance (Chang and Lin, 2017). A flattened diurnal cortisol rhythm was also predictive of a shorter lifespan after sample collection in women with metastatic breast cancer, but diurnal AUC did not relate to survival (Sephton et al., 2000). In another study, no significant differences in survival time were observed based on sex or type of cancer for terminally ill cancer patients, but high random serum cortisol level collected at hospital admission was a significant predictor of survival time – patients with higher cortisol had a significantly shorter median survival time compared to low cortisol patients (Kim et al., 2016). In patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer, higher salivary cortisol levels at night prior to cancer-related surgery was associated with older age, later cancer stage, higher tumor grade, increased IL-6, and shorter survival time. A flattened circadian cortisol slope was also associated with higher tumor grade and increased IL-6 (Schrepf et al., 2015). In prostate cancer patients, while CAR was not predictive of depressive symptoms, a flatter circadian cortisol slope and less cortisol output overall was related to increased depressive symptoms (Hoyt et al., 2016). Higher cortisol concentration in the first urine of the morning was associated with lower melatonin-sulfate, a lower ratio of melatonin-sulfate/cortisol, and increased disease progression (Tai et al., 2016). Together, these studies indicate that a flatter diurnal cortisol rhythm has been frequently associated with more rapid cancer progression. Whether diurnal cortisol rhythms predict the risk of developing cancer in the first place is unknown.

Exogenous GC administration studies suggest both protective and risky aspects of GCs on survival and disease progression. In Danish patients who had undergone surgery for colorectal cancer, new users of GCs following surgery had increased 30-day mortality compared to nonusers (Ostenfeld et al., 2014). Importantly, the route of GC administration (systemic vs. inhaled vs. intestinal) did not influence these outcomes; breast cancer patients had no differences in recurrence rates based on the type of GC used (Lietzen et al., 2014). In a mouse model of epithelial ovarian cancer, in female mice injected with epithelial ovarian cancer cells and then given DEX injections starting 5 days after cell injection, DEX caused a decrease in the ovarian tumor size and abdominal metastasis and increased expression of

microRNA 708 (miR-708), which suppresses metastasis. DEX-treated mice also had increased expression of Rap1B, which is involved with regulating cell adhesion and motility, and it is a key factor in miR-708 suppression (K. T. Lin et al., 2017). In urothelial carcinoma cell lines, CORT and prednisone (PRED) did not cause an increase in cell proliferation, and when tested with cisplatin (chemotherapy drug), CORT and PRED did not cause cell growth increases but DEX did in a dose-dependent manner. In addition, CORT and PRED did not reduce cisplatin-induced apoptosis, but DEX did in GR-positive cells (Ishiguro et al., 2014). Clinical exogenous GC studies suggest that GC is a risk factor, whereas preclinical studies suggest it is protective, suggesting that an intermediate level is ideal.

Cortisol relations to disease state and survival have been reported in relation to other types of disease as well. Relapsing-remitting multiple sclerosis patients had a greater AUC at awakening compared to healthy controls, and there were no differences in rhythm between patients with different multiple sclerosis classifications. Secondary-progressive multiple sclerosis patients demonstrated significant associations between CAR AUC and neurological impairments (Kern et al., 2013). A study on patients with variceal bleeding and/or cirrhosis indicated that morning serum free cortisol, serum total cortisol, and salivary cortisol were higher in variceal bleeding patients compared to the cirrhosis group, with increased serum free cortisol and salivary cortisol as significant predictors of mortality within six weeks of admittance to the hospital (Triantos et al., 2014). In patients with rheumatoid arthritis, all-cause and cardiovascular-related deaths were associated with cumulative GC treatment dose, with a dose-dependent increase in all-cause deaths based on cumulative dose. GC exposure intensity per year was also significantly associated with mortality – minimum threshold daily dose of GCs (PRED) that was associated with increased risk for death was 8–15mg (del Rincón et al., 2014). The number of chronic organ damages in systemic lupus erythematosus patients was significantly higher in those that had a longer disease duration. A higher GC medication dose was associated with a larger damage index score, and a larger damage index score was associated with a shorter survival time (Tarr et al., 2017). Routine basal blood samples collected from patients with acute pancreatitis indicated that those with more severe pancreatitis had higher levels of cortisol compared to those with mild pancreatitis and those that could not be classified. Increased basal blood cortisol was the best predictor of the biomarkers measured for greater organ failure and death during this time (Nebiker et al., 2018).

In summary, higher baseline serum cortisol and flatter salivary diurnal cortisol were consistently associated with worse disease state and decreased survival time in patients with various diseases and cancers. Flatter salivary rhythm was also associated with worse mental health and worse sleep in cancer patients. Increased exogenous GC exposure was associated with increased mortality in cancer, rheumatoid arthritis, and lupus patients, but GC use does not appear to impact recurrence of breast cancer. Preclinical studies indicate that endogenous GC may help control cancer progression. Finally, there were relatively few studies on the potential impact of acute GC elevations on cancer progression.

3.4 Diabetes

Studies focusing on diabetes most frequently reported negative relationships with GC levels. In these studies, basal GC measures were the most common.

3.4.1 Type-1 Diabetes—When blood was sampled overnight every 10 minutes in type-1 diabetic patients and controls, diabetics had lower overnight free cortisol, lower ACTH efficacy and potency, and increased ACTH sensitivity, although total cortisol and ACTH concentrations did not differ between groups (Sharma et al., 2014). In a mouse model of type-1 diabetes (using a streptozotocin, STZ, injection on day 0), diabetic mice vs. controls had higher hair CORT concentrations (representing an integrated measure of CORT production over the 28 days after injection) and elevated serum CORT 28 days following injection (Erickson et al., 2017; Makimura et al., 2003). In addition, adrenalectomy along with STZ treatment caused a significant decrease in CORT compared to controls, and a combination of STZ, adrenalectomy, and fasting for 48 hours did not change CORT levels from controls. However, CORT implants increased serum insulin and leptin, suggesting the role for CORT in enhancing the diabetes profile (Makimura et al., 2003). In another STZ diabetes mouse model, mifepristone (MF, a GR blocker) injections led to elevated adrenal gland basal CORT concentrations after fifteen days of MF injections compared to shorter or no MF exposure (Kuznetsova et al., 2017). The type-1 diabetes hypoglycemic profile improved with a combination of glutamine dipeptide (administered through gavage) and intraperitoneal cortisol injection (Bataglini et al., 2017). Further, five weeks of chronic oral CORT administration led to increased glucose levels and decreased insulin sensitivity compared to controls. Both effects were reversed with the removal of CORT, and CORT also caused an increase in T lymphocytes, active macrophages, and GR activation in pancreatic tissue compared to controls (Burke et al., 2017).

In mice, an experimental model of Type-1 diabetes causes increased basal circulating CORT levels and chronic exogenous GCs increased the diabetic phenotype.

3.4.2 Type-2 Diabetes—Patients with type-2 diabetes demonstrated significantly higher salivary cortisol levels in the evening compared to those without diabetes. Diabetic females had higher salivary cortisol levels at night than non-diabetic females, and diabetic males had higher CAR than those without diabetes (Johar et al., 2016). However, in another study, while there were no differences between groups in wake or late-day decline of cortisol, diabetic women had a higher overall AUC compared to women without diabetes, and men with diabetes had lower CAR compared to those without diabetes (Champaneri et al., 2012). In patients with type-2 diabetes, morning and evening basal serum (but not salivary) cortisol levels were related to glycemic changes during a 7-day monitoring period (Bellastella et al., 2016). In a study of patients with major depression and/or type-2 diabetes, all groups (depression only, type-2 diabetes only, or both) had lower CAR compared to control participants, and no group differences were observed at any other time of day (Zahn et al., 2015). Higher basal cortisol levels in Type-2 diabetes patients (vs. Type-1 diabetes patients) were also associated with increased obesity and heart complications and lower presence of retinopathy and shorter diabetes duration (Melin et al., 2017).

In obese men, metformin (the most common drug prescribed with Type –2 diabetes) did not affect morning blood cortisol levels after an overnight fast in either diabetic or non-diabetic individuals, and having diabetes did not affect these post-fast morning cortisol levels. On the other hand, metformin along with a D4-cortisol infusion led to increased 11 β -hydroxysteroid dehydrogenase (11 β HSD), and this same result occurred after an oral dose of cortisone (Anderson et al., 2016). In another study, patients with and without diabetes that received a single local injection of GCs (40mg triamcinolone acetonide) in the epidural space (lumbar region) had lower morning basal cortisol levels on days one and seven after injection compared to baseline levels; twenty-one days after the injection, diabetic patients still had significantly lower morning basal cortisol levels, which was not the case for individuals without diabetes (Moon et al., 2014).

Rodent models of type-2 diabetes have been consistent in CORT-related findings. A study with genetically-diabetic mice (BKS.Cg-Dock7^m +/+ Lepr^{db}/J mice) showed that hair and basal serum CORT levels were higher in the diabetic vs. control mice on day 28 of the study (Erickson et al., 2017). In another study, Goto-Kakizaki rats, which are an inbred model for type-2 diabetes, had higher plasma CORT, urine CORT, and glucose compared to control rats, and Goto-Kakizaki rats administered ketoconazole (inhibitor of 11 β -hydroxylase) by gavage had lower plasma CORT, urine CORT, and glucose compared to Goto-Kakizaki rats that received water (Beddow and Samuel, 2012). Similarly, in a Sprague Dawley model for inducing type-2 diabetes, rats that received CORT pellet implants plus a high fat diet exhibited a more severe diabetes profile with higher fasting hyperglycemia, hyperinsulinemia, and insulin resistance (Shpilberg et al., 2012). In total, these results indicate that chronically-elevated CORT leads to worse diabetes symptoms.

In summary, inconsistent findings have been reported regarding baseline evening cortisol and CAR in diabetes patients. Morning cortisol is not affected in obese men by metformin, and cortisol in diabetics takes longer to return to baseline after a GC injection. In rodents, increased basal and integrated CORT is a feature of the diabetes model, and chronic exogenous CORT exaggerated diabetes symptoms.

3.5 Obesity

In studies examining obesity, positive and negative relationships with GCs were almost evenly reported. Integrated measures of GCs were most frequently used.

In overweight and obese children, salivary cortisol levels in the morning after a fast were significantly lower than in non-overweight children, regardless of hypertension state. In addition, cortisol/creatinine and cortisone/creatinine ratios in random urine samples were significantly higher for overweight/obese compared to non-overweight (Wirix et al., 2017). Overweight children in China had significantly higher morning salivary and urine cortisol and cortisone levels compared to normal-weight children of the same age (Chu et al., 2017). Hair cortisol and cortisone were associated with BMI and fat mass in a study with obese and overweight children. In this particular study, certain GR-gene polymorphisms were assessed but no significant associations were found with BMI or fat measures, thus specific genes to target for therapy still requires research (Noppe et al., 2016). Children that had experienced early adversity had a significantly flatter CAR in adolescence, and this flatter CAR predicted

a larger body mass index in adulthood. Thus, CAR may mediate the relationship between childhood adversity and adult weight (Miller et al., 2018).

Obese individuals reported increased weight discrimination experiences with increasing BMI. Hair cortisol was elevated in those that reported weight discrimination, and cortisol levels increased with more frequent discrimination (Jackson et al., 2016). Obese people who had undergone weight loss surgery demonstrated higher cortisol and higher cortisol/cortisone ratios in serum 14 months (on average) post-surgery after an overnight fast with DEX exposure and in response to oral cortisone acetate. However, there were no changes in 24-hour urine ratios from before and after surgery in these patients (Woods et al., 2015). In participants that were randomly assigned to a yoga intervention group, cortisol reactivity to stress and frequency of binge eating decreased by the end of the intervention, compared to people randomly assigned to the wait-list control group (Hopkins et al., 2016). In obese participants' blood that was exposed to endotoxin and cortisol, blood TNF levels were decreased on the morning after an overnight fast. TNF levels were related to depression scores, with a greater somatic depression score and a greater BMI predicting less cortisol-mediated inflammation, indicating impaired suppressive effects by cortisol in obese individuals (Cheng et al., 2016). A rat model for obesity, which involved administering a high fat diet to mothers during pregnancy and lactation, led to offspring with lower plasma CORT, triglycerides, cholesterol, and leptin at one day of age, increased CORT, leptin, and insulin at three weeks of age, and increased CORT at twenty-four weeks of age, compared to pups born to mothers on the control diet (Desai et al., 2014).

In summary, inconsistent results have been found regarding basal salivary morning cortisol and cortisone and body weight in humans, but cumulative measures of cortisol (in hair and urine) indicate that higher cortisol is associated with obesity and weight discrimination. Rodent studies also suggest that higher basal CORT is related to obesity. Human basal salivary cortisol and obesity-related behaviors decreased after participating in yoga, but there were no changes in urine cortisol after weight loss surgery suggesting a fundamental biological dysregulation.

3.6 Pulmonary Health

Pulmonary health studies most commonly reported negative relationships to health outcomes overall, with basal measures and exogenous GC manipulations most commonly described.

Anti-inflammatory properties of GCs suggest that they have important consequences for allergy-related pulmonary function. Infants of mothers with a history of asthma/allergic disease had a greater stress response in the clinic and a flatter saliva cortisol circadian rhythm (lower morning cortisol) compared to infants of mothers with no allergic history (Ball et al., 2006). In children with acute respiratory distress syndrome, patients who had relatively low baseline serum cortisol levels ($< 18\mu\text{g/dL}$) were overall less sick; however, these patients also were more likely to have continued hydrocortisone treatment (68% of those with $< 18\mu\text{g/dL}$ cortisol, vs. 44% of those with $> 18\mu\text{g/dL}$). Hydrocortisone treatment appeared to be less helpful for patients with relatively high basal cortisol levels ($> 18\mu\text{g/dL}$), as fewer days off a ventilator and higher mortality were reported (Yehya et al., 2016). In patients with chronic obstructive pulmonary disease (COPD), long-term treatment with

long-acting P2 agonist (LABA) plus inhaled corticosteroids led to increased bacteria in sputum, clinical disease improvements, and decreased disease exacerbation compared to treatment with LABA only (Contoli et al., 2017; Ferguson et al., 2017).

A study on adults with asthma and varying levels of life stress indicated that in response to the TSST, those with high life stress had a higher cortisol response in saliva compared to those with low life stress. For those with high life stress, it was evident that a greater salivary cortisol response was associated with an increased percentage of eosinophils in blood four hours after the stress test, and the reverse effect was evident in those with low life stress (Rosenkranz et al., 2016). This compares to what has been reported in children, where in response to the TSST, salivary cortisol reactivity is blunted in asthma children compared to controls (Buske-Kirschbaum et al., 2003).

Animal models commonly use ovalbumin sensitization to induce asthma; these models allow for experimental tests of the effect of GCs on allergic asthma. In a rat model of asthma, COPD, and asthma plus COPD, lower blood CORT and CRH mRNA in hypothalamus were observed in both groups with COPD compared to controls. Ones receiving just asthma had higher CORT and CRH mRNA expression compared to both COPD groups with no changes compared to controls (Cui et al., 2010). A similar downregulation in CORT concentration was observed in another asthma model, with this trend subsiding after asthma induction ends (Caulfield et al., 2018, 2017). In an allergic mouse model, treatment with OVA alone or with metyrapone-RU486 (GC inhibitor) led to an increase in eosinophils, nasal rubs, and sneezes, as well as a decrease in circulating CORT, IL-4 and IL-5 compared to control and/or allergic untreated mice (Zhang et al., 2009). The offspring of female mice that were exposed to restraint stress or DEX during gestation had higher circulating CORT four days later and higher eosinophil counts in response to ovalbumin injections. If the maternal CORT response to stress was inhibited (with metyrapone injection, a GC synthesis inhibitor) the offspring's increased eosinophil response was eliminated indicating that elevated GC exposure during gestation can lead to increased allergy susceptibility (Lim et al., 2014).

In summary, lower baseline cortisol is associated with less severe sickness in humans with acute respiratory distress. Flatter cortisol rhythms have been reported in infants from asthmatic mothers, and lower baseline CORT has also been observed in animal studies modeling airway diseases. Greater cortisol reactivity has been reported in infants from asthmatic parents and asthma patients with higher stress in life. GCs are common treatments for airway diseases, and numerous studies have shown that inhaled corticosteroids improve the treatment effects of long-acting beta-agonist alone.

3.7 Sleep and Health

Studies that measured sleep reported negative relationships with GCs, with circadian and reactivity measures equally reported.

There is some evidence that GC production is related to sleep quality; thus, sleep may serve as one mediating factor by which GCs may influence health outcomes. Patients with postural tachycardia syndrome have increased levels of salivary cortisol at all time points measured throughout the day and worse sleep quality compared to controls, and poor sleep quality was

significantly correlated with increased levels of cortisol at waking (J. Lin et al., 2017). In police officers that reported insufficient leisure time physical activity, poor quality sleepers had lower waking cortisol levels (AUC from ground, AUC from baseline, peak cortisol, total cortisol) compared to those with good sleep quality (Fekedulegn et al., 2018). In patients with obstructive sleep apnea, CPAP withdrawal caused an increase in free fatty acids, glucose, and cortisol in blood samples measured overnight, with lower cortisol levels during deeper sleep stages and higher cortisol levels during stages closer to wakefulness (Chopra et al., 2017). Cortisol was a significant predictor of sleep quality in patients with lung cancer, where a flatter cortisol slope due to higher evening cortisol was related to increased sleep disturbance (Chang and Lin, 2017). Military servicemen exposed to sleep deprivation had increased circulating cortisol concentrations that were positively correlated with mania, suggesting that sleep deprivation may cause worse mental health and that this effect is mediated by cortisol production (Song et al., 2015).

In summary, circadian cortisol measures are commonly reported in studies involving sleep as an outcome. Worse sleep quality is strongly associated with a flatter cortisol circadian rhythm in cardiac-related cases, sleep apnea, and cancer. In addition, lower cortisol awakening response was associated with worse sleep quality, and acute manipulations that lead to poor sleep also caused increased GC production. These results indicate that sleep quality can affect GC secretion, although it may also be the case that GC secretion affects sleep quality, and that the combination of these factors influence health outcomes.

3.8 Fitness

The following section includes references found using search terms related to fitness. This term captured different concepts across research areas, but provided a way to identify papers in which GCs have been related to health processes that are not disease-specific – e.g. wellness in the elderly, reproductive success in wild animal populations, and neurogenesis in experimental models. For this link, we kept these studies together under the broad umbrella of ‘fitness’ but include subsections focused on these different research areas to highlight this diversity. In studies measuring fitness, positive and negative relationships with GCs were evenly reported, with basal measures being the most frequent metric.

3.8.1 Elderly—Several studies have examined basal cortisol production in the elderly as it relates to their physical and mental wellness. Elevated afternoon salivary cortisol has been related to elderly frailty status, with patients in long-stay institutions that are considered frail having higher afternoon (between 4–5pm) levels than pre-frail participants, who had higher cortisol than nonfrail participants (Holanda et al., 2012). In elderly women living in health care support centers, a chair-based yoga program nullified the normal increase in basal salivary cortisol levels in control women, and baseline salivary cortisol levels were negatively correlated with lower-body flexibility, suggesting that yoga can improve elderly fitness by reducing cortisol secretion (Furtado et al., 2016). On the other hand, elderly adults with major depressive disorder had lower afternoon basal salivary cortisol levels than control adults, and the patients with major depressive disorder also had lower fitness and balance scores, and cortisol levels were associated with depression symptoms (Moraes et al., 2016). Elderly individuals with a slower walking speed had a smaller CAR magnitude, less physical

activity, and were older, whereas higher cortisol concentrations at wake were associated to younger age, later time at waking, and a larger mean time spent asleep (Pulopulos et al., 2016).

In summary, in the elderly, a higher afternoon basal cortisol level and a smaller CAR response were associated with frailty, less physical activity, and decreased flexibility. In addition, lower basal afternoon cortisol levels were reported in depressed elderly, which relates to other literature describing flatter diurnal rhythms in depression (Jarcho et al., 2013).

3.8.2 Reproductive Success and the Environment—In free-ranging animals (mostly birds), CORT/cortisol levels are often studied to determine if it related to environmental conditions and/or individual reproductive success (measured as offspring survival, offspring success, number of eggs or offspring, etc.). In barn swallows, parent birds that had higher stress-induced CORT secretion made fewer nest visits and took longer to return to the nest when a predator was near compared to those with lower stress-induced CORT responses. In addition, baseline and stress-induced CORT levels were higher in females that abandoned the nest during the nest building and incubation stages compared to those that did not abandon the nest, and higher parent stress-induced CORT levels were associated with fewer young fledging from the nest (Vitousek et al., 2014). Male Adeline penguins in Antarctica that were implanted with high-dose CORT pellets had elevated circulating serum CORT and abandoned the nest at a rate seven times higher than controls and those that received a low-dose CORT pellet treatment (Spée et al., 2011). In free-living adult blue tits (birds) with young chicks, basal CORT levels were higher in females compared to males, and baseline CORT was elevated in parents that had a larger brood, larger nesting mass, and in those living in areas with lower temperatures and increased rainfall (Henderson et al., 2017). The results suggest that in harsh environments elevated basal CORT production may increase performance and reproductive success. In breeding adult wild common loons that were fed different doses of mercury diet, mean blood and feather mercury levels were higher in males compared to females, but this was not reflected by sex differences in basal or isolation stress-induced CORT levels. Adult males showed a significant positive correlation between blood mercury and CORT, and offspring of mercury-exposed parents had blunted CORT reactivity compared to controls (Franceschini et al., 2017). In northern wheatears, baseline circulating CORT levels increased over the migratory season, and individuals with higher levels migrated earlier than those with lower levels (Eikenaar et al., 2017). In mouse lemurs during their annual active period, lower hair cortisol levels were associated with higher rates of survival (Rakotoniaina et al., 2017). In house wrens, nests with eggs that were injected with CORT weighed less than controls at hatching, but 11 days later the nests that received the highest CORT dose had the largest mass (Strange et al., 2016).

In free-ranging animals, there is evidence that higher basal CORT levels are associated with worse parenting behavior, worse reproductive success, worse environmental conditions, and faster migratory behavior (but also larger broods). Higher CORT reactivity is associated with worse parenting behavior and worse reproductive success, and chemical toxicity can lower this reactivity. Higher cumulative cortisol is associated with shorter survival, and prenatal

GC exposure has been shown to affect offspring growth rates. A review predating most of the above studies concluded that there are only weak relationships between GCs and reproduction/survival in free-ranging animals, and that these relationships may follow different and/or non-linear functions among species (Crespi et al., 2013).

3.8.3 Neurogenesis—Given how stress and CORT affect hippocampal neurogenesis, multiple studies have investigated how CORT affects cell composition to determine if it is implicated in mental illness development and progression. In adrenalectomized (ADX) male rats, apical dendrite length was shorter than sham controls, but dendrite length could be maintained at control levels with a CORT pellet implant. Although there was no significant correlation between CORT and hippocampal cell proliferation (quantified with bromodeoxyuridine staining), ADX+CORT-implanted rats did exhibit greater cell proliferation compared to controls. Together, these results demonstrate that CORT is important to maintain hippocampal plasticity (Martínez-Claros et al., 2013). In adult male rats exposed to ischemia, resveratrol (which regulates hippocampal neurogenesis) vs. saline treatment led to lower baseline CORT and increased spatial memory three days after ischemia and increased neuron survival 85 days after ischemia. Ischemic rats had a greater CORT response to acute restraint stress compared to controls and resveratrol treatment did not affect this. Ischemia caused an increase in neurogenesis, which was reduced by resveratrol treatment in a dose-dependent fashion, and this was evident 7 and 85 days after surgery (Girbovan et al., 2016). In female rats that had weaned pups one week prior, fluoxetine treatment led to increased basal CORT, CORT binding globulin, free CORT, and dorsal hippocampus neurogenesis compared to post-weaning females that only received vehicle. In addition, within vehicle-treated females, chronic pre-gestational stress caused lower CORT compared to controls, but because this effect was not observed between fluoxetine-treated animals, this suggests a reversal caused by the treatment (Gammel et al., 2018). In rats, exposure to one week of chronic restraint stress or chronic CORT injections led to increased oligodendrogenesis in hippocampus at 7 and 14 days after the start of these treatments compared to control rats. In neural stem cell culture, 75 hours of incubation with CORT induced oligodendrogenic potential as indicated by increased transcription of related markers in the cells (Chetty et al., 2014).

In summary, neurogenesis has been associated with high and low baseline blood CORT levels in different studies and with different drug treatments. CORT reactivity tends to increase after ischemia, and exogenous GC levels are associated with plasticity, neurogenesis, and oligodendrogenesis, suggesting the importance of GCs in brain plasticity.

4. DISCUSSION

In the 100 publications reviewed here, we found 169 comparisons between specific GC metrics and health. A greater number of relationships than publications is a result of multiple GC metrics within some papers. All four measures of GC signaling (basal, reactivity, circadian, and integrative) were represented, and we included additional experimental reports on the influence of exogenous GCs. The most frequent GC metric reported was basal secretion (32%), and the least frequently were integrated (13%) and circadian measures (13%). Fifty-four basal relationships were examined, and they were most often reported in

diabetes, mental health, and fitness studies (see Table 2). Twenty-two measures involved circadian GC production, and they were most commonly reported in relation to mental health and cancer/disease progression/mortality. Thirty-seven reports involved stress reactivity and/or CAR with the majority related to mental health and cardiovascular health. GC measures were reviewed, with the majority related to obesity, cardiovascular health, and diabetes. Additionally, thirty-four instances of exogenous GC exposure (as medication, implantation, injection, or other forms) were reported, with the majority of these related to cancer/disease progression/mortality, diabetes, mental health, and cardiovascular health. Across all metrics, more negative relationships to health outcomes (45%) were reported than positive (33%) or null relationships (22%).

Across all health outcomes, different GC metrics were differentially associated with health risk vs. resilience (summarized in Table 2). For example, in studies that included a basal GC measure, half of the associations indicated a negative relationship to health outcomes (50%), with the remaining studies showing both positive and null relationships (30 & 20%). Within the negative relationships, there were equal numbers of studies that associated poor health to elevated morning and to elevated evening GC levels. On the other hand, for the positive relationships, more studies indicated that elevated morning GC, rather than evening, was associated with positive health. Of the studies that used a circadian estimate of GC secretion, just over the majority indicated a positive relationship to health (55%), i.e. a steeper circadian slope was associated with better health. Very few showed a negative relationship (9%), and a good percent indicated no relationship to health (36%). Of the thirty-seven studies that reported GC reactivity, 19 involved a measure of the cortisol awakening response (CAR) while the remaining 16 involved responses to standardized or health-related challenges (e.g. after surgery or trauma). Reactivity metrics were evenly associated with both positive and negative health outcomes (41% for both). When these results were broken down according to CAR vs. non-CAR metrics, an elevated CAR was most frequently associated with positive health outcomes (11 of 20 studies), whereas an elevated GC response to other challenges was most frequently associated with negative health outcomes (12 of 17 studies). The strongest relationships with health came from integrated GC measures, with the majority of studies indicating a negative relationship with health outcomes (68%) and a good portion indicating no relationship (23%). For studies involving exogenous GC exposure, eleven positive (32%), seventeen negative (50%), and six null relationships (18%) were reported in relation to the health outcomes. Thus, based on the current review, elevated basal, integrated, reactivity to standardized stressors, and exogenous GCs were most often associated with negative health outcomes, whereas an elevated CAR and a steep circadian rhythm were most often associated with positive health. These overall results did not change if only mammalian or human studies were considered.

A summary of all outcomes and metric relationships are presented in Table 2. Briefly, across outcomes, basal production was associated with positive relationships for one health area ('fitness') and negative relationships in five health areas. This variance in the relationship between a one-time basal GC measure and health outcome might be expected because basal production measures can be relatively noisy. A one-time estimate of basal GC secretion level may not provide an accurate estimate of average basal production in an individual because GC production can be quite variable; secretion is highly responsive to changes in the

environment, which can affect secretion pulsatility, production across the day, and production in response to stressors that occur prior to sampling (Atkinson et al., 2006; Lightman et al., 2008; Romero and Reed, 2005; Young et al., 2004). Thus, like CAR, if basal GCs mediate health risk or resilience, it likely requires repeated measures to provide a reliable estimate of mean basal secretion in an individual. Circadian GC production was associated with positive relationships in three health areas and negative relationships in one health area. Again, this variability in results may reflect the relative noise involved in measuring circadian GC patterns, thus one day of measurement may not provide the best estimate of an individual's mean circadian rhythm. Stress reactivity was associated with positive relationships to health outcomes in three health areas and negative relationships in three health areas. This equal mix of results may reflect the fact that reactivity measures are collected in many different contexts (e.g. CAR vs. response to health-related stressor or standardized psychological stressors), and that elevated CAR was most often associated with better health outcomes whereas GC response to standardized stressors was more often associated with poor health outcomes. Integrative GC measures were associated with no overall positive relationships and negative relationships to five health areas. Exogenous GCs were associated with positive relationships in one health area and negative relationships to three health areas. Given these mixed outcomes, dose-response acute vs. chronic manipulations of exogenous GC exposure will provide a good experimental test of whether individual differences in naturally-occurring elevated acute or chronic GC responses are an important mechanism in disease risk and resilience.

Mechanistic studies have indicated multiple up- and downstream processes associated with GC secretion which may all contribute to a multitude of health-related outcomes. Some of the processes associated with GC secretion and stress include central neurobiological processes that can affect mental health outcomes. For example, corticotropin-releasing hormone, important for HPA stimulation and GC secretion, centrally affects amygdala processes that enhance anxiety-like responses (Gray et al., 2015), GC secretion modulates hippocampal glutamatergic processes involved in depression-like responses (Nasca et al., 2017, 2015), and GC secretion stimulates prefrontal dopaminergic efflux that affects cognitive function (Butts et al., 2011). Other GC-affected processes involve more systemic effects on metabolism and immune function which can influence health outcomes (Kadmiel and Cidlowski, 2013). Importantly, a handful of these mechanistic studies indicate that short-term elevations in GC secretion may have very different impacts on neurological, metabolic, endocrine, and immunological function as compared to more chronically-elevated GC levels (Cavigelli and Caruso, 2015; Dhabhar and McEwen, 1999; Joels et al., 2012; Kadmiel and Cidlowski, 2013; Karatsoreos et al., 2010; Skórzewska et al., 2006; Tan et al., 1998). This important temporal/functional distinction may explain why elevated integrated GC metrics, which provide an estimate of long-term GC overproduction, were most closely associated with negative health outcomes, while elevated acute GC responses to health-relevant processes (waking, surgery, trauma) was most often associated with positive health outcomes. Overall, up- and downstream physiological effects of GC secretion are multifaceted and complex; using GCs as a biomarker serves as a centralized and indirect method that taps into some of these processes. This central nature serves as an interesting biomarker, with the understood caveat that its indirect nature necessarily introduces a high

degree of noise. This is reflected in the current review which indicated relatively weak relationships between GC secretion and predictable health outcomes.

Overall, based on the current literature review, there is a relatively high degree of variance in whether and how GC secretion patterns are related to disease risk and resilience.

Interestingly, health researchers have tapped into many different aspects of the dynamic GC secretion process, with different studies using estimates of basal production, circadian rhythm, acute response to stressors, and mean GC production over hours or months. For the purpose of developing a ‘biomarker’ of cumulative stress, at present, the most likely best metrics are the integrative estimates of GC production, such as urine or hair cortisol measures. These metrics provide a cumulative measure of multiple different aspects of GC signaling: basal secretion, acute responses after a challenge, and natural changes in production over the day, including secretory fluctuations associated with pulsatility and circadian rhythm. Based on the current review, these integrated measures were most reliably associated with health outcomes, with elevated levels associated with negative health outcomes. However, these integrated measures have also been the least-used metrics of GC production. It should be noted that the magnitude of acute GC secretions were also found to be associated with health outcomes, with elevated GC responses to standardized psychological stressors (e.g. TSST) associated with poor health outcomes while elevated responses to waking (CAR) or to health-related experiences (e.g. surgery, trauma) were related to positive health outcomes. Thus, the ideal study should incorporate an integrative and acute reactivity estimate of GC secretion, with careful selection of when to measure GC reactivity (e.g., CAR or response to standardized psychological stressors or response to health-relevant stressors).

If individual differences in stress physiology are important for predicting individual health outcomes, and if this predictive ability is clinically-important, then it is likely that these more complex metrics of stress physiology are required. In the current review we focused on GC secretion dynamics and metrics because of well-recognized downstream effects of GCs (e.g. metabolic, immune, etc.) that can further influence individual stress resilience/susceptibility. If a simplified metric of GC secretion is to be targeted, the current literature suggests using a combination of an integrative and acute response metric.

ACKNOWLEDGEMENTS

We would like to acknowledge students in the Behavioral Neuroendocrinology Laboratory.

FUNDING

This work was supported, in part, by NIH Grant T32GM108563.

REFERENCES

- Anderson AJ, Andrew R, Homer NZ, Jones GC, Smith K, Livingstone DE, Walker BR, Stimson RH, 2016 Metformin increases cortisol regeneration by 11 β HSD1 in obese men with and without type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab* 101, 3787–3793. doi:10.1210/jc.2016-2069 [PubMed: 27459533]

- Atkinson HC, Wood SA, Kershaw YM, Bate E, Lightman SL, 2006 Diurnal variation in the responsiveness of the hypothalamic-pituitary-adrenal axis of the male rat to noise stress. *J. Neuroendocrinol* 18, 526–533. doi:10.1111/j.1365-2826.2006.01444.x [PubMed: 16774501]
- Bale TL, Epperson CN, 2015 Sex differences and stress across the lifespan. *Nat. Neurosci* 18, 1413–1420. doi:10.1038/nn.4112 [PubMed: 26404716]
- Ball TM, Anderson D, Minto J, Halonen M, 2006 Cortisol circadian rhythms and stress responses in infants at risk of allergic disease. *J. Allergy Clin. Immunol* 117, 306–311. doi:10.1159/000104857 [PubMed: 16461131]
- Bataglini C, Rezende DGL, Primo MA, Gomes CRG, Pedrosa MMD, Godoi VAF, 2017 Glutamine dipeptide and cortisol change the liver glucose metabolism and reduce the severity of insulin-induced hypoglycaemia in untreated T1DM Swiss mice. *Arch. Physiol. Biochem* 123, 134–144. doi:10.1080/13813455.2016.1273364 [PubMed: 28263096]
- Beddow SA, Samuel VT, 2012 Fasting hyperglycemia in the Goto-Kakizaki rat is dependent on corticosterone: a confounding variable in rodent models of type 2 diabetes. *Dis. Model. Mech* 5, 681–685. doi:10.1242/dmm.009035 [PubMed: 22864022]
- Bellastella G, Maiorino MI, De Bellis A, Vietri MT, Mosca C, Scappaticcio L, Pasquali D, Esposito K, Giugliano D, 2016 Serum but not salivary cortisol levels are influenced by daily glycemic oscillations in type 2 diabetes. *Endocrine* 53, 220–226. doi:10.1007/s12020-015-0777-5 [PubMed: 26511948]
- Bonier F, Martin PR, Moore IT, Wingfield JC, 2009 Do baseline glucocorticoids predict fitness? *Trends Ecol. Evol* 24, 634–642. doi:10.1016/j.tree.2009.04.013 [PubMed: 19679371]
- Burke SJ, Batdorf HM, Eder AE, Karlstad MD, Burk DH, Noland RC, Floyd ZE, Collier JJ, 2017 Oral Corticosterone Administration Reduces Insulinitis but Promotes Insulin Resistance and Hyperglycemia in Male Nonobese Diabetic Mice. *Am. J. Pathol* 187, 614–626. doi:10.1016/j.ajpath.2016.11.009 [PubMed: 28061324]
- Buske-Kirschbaum A, Von Auer K, Krieger S, Weis S, Rauh W, Hellhammer D, 2003 Blunted cortisol responses to psychosocial stress in asthmatic children: A general feature of atopic disease? *Psychosom. Med* 65, 806–810. doi:10.1097/01.PSY.0000095916.25975.4F [PubMed: 14508024]
- Butts KA, Weinberg J, Young AH, Phillips AG, 2011 Glucocorticoid receptors in the prefrontal cortex regulate stress-evoked dopamine efflux and aspects of executive function. *Proc. Natl. Acad. Sci. U. S. A* 108, 18459–64. doi:10.1073/pnas.1111746108 [PubMed: 22032926]
- Cahn BR, Goodman MS, Peterson CT, Maturi R, Mills PJ, 2017 Yoga, Meditation and Mind-Body Health: Increased BDNF, Cortisol Awakening Response, and Altered Inflammatory Marker Expression after a 3-Month Yoga and Meditation Retreat. *Front.Hum. Neurosci* 11, 315. doi:10.3389/fnhum.2017.00315 [PubMed: 28694775]
- Cain DW, Cidlowski JA, 2015 Specificity and sensitivity of glucocorticoid signaling in health and disease. *Best Pract. Res. Clin. Endocrinol. Metab* 29, 545–556. doi:10.1016/j.beem.2015.04.007 [PubMed: 26303082]
- Caulfield JI, Caruso MJ, Bourne RA, Chirichella NR, Klein LC, Craig T, Bonneau RH, August A, Cavigelli SA, 2018 Asthma Induction During Development and Adult Lung Function, Behavior and Brain Gene Expression. *Front. Behav. Neurosci* 12, 188. doi:10.3389/fnbeh.2018.00188 [PubMed: 30214402]
- Caulfield JI, Caruso MJ, Michael KC, Bourne RA, Chirichella NR, Klein LC, Craig T, Bonneau RH, August A, Cavigelli SA, 2017 Peri-adolescent asthma symptoms cause adult anxiety-related behavior and neurobiological processes in mice. *Behav. Brain Res* 326, 244–255. doi:10.1016/j.bbr.2017.02.046 [PubMed: 28284954]
- Cavigelli SA, Caruso MJ, 2015 Sex, social status and physiological stress in primates: The importance of social and glucocorticoid dynamics. *Philos. Trans. R. Soc. B* 370, 20140103. doi:10.1098/rstb.2014.0103
- Cavigelli SA, Ragan CM, Michael KC, Kovacsics CE, Bruscke AP, 2009 Stable behavioral inhibition and glucocorticoid production as predictors of longevity. *Physiol. Behav* 98, 205–214. doi:10.1016/j.physbeh.2009.05.012 [PubMed: 19477191]
- Champaneri S, Xu X, Carnethon MR, Bertoni AG, Seeman T, Roux AD, Golden SH, 2012 Diurnal salivary cortisol and urinary catecholamines are associated with diabetes mellitus: The Multi-

- Ethnic Study of Atherosclerosis. *Metabolism* 61, 986–995. doi:10.1016/j.metabol.2011.11.006 [PubMed: 22209664]
- Chang WP, Lin CC, 2017 Relationships of salivary cortisol and melatonin rhythms to sleep quality, emotion, and fatigue levels in patients with newly diagnosed lung cancer. *Eur. J. Oncol. Nurs* 29, 79–84. doi:10.1016/j.ejon.2017.05.008 [PubMed: 28720269]
- Cheng T, Dimitrov S, Pruitt C, Hong S, 2016 Glucocorticoid mediated regulation of inflammation in human monocytes is associated with depressive mood and obesity. *Psychoneuroendocrinology* 66, 195–204. doi:10.1016/j.psycheneu.2016.01.008 [PubMed: 26829709]
- Chetty S, Friedman AR, Taravosh-Lahn K, Kirby ED, Mirescu C, Guo F, Krupik D, Nicholas A, Geraghty AC, Krishnamurthy A, Tsai MK, Covarrubias D, Wong AT, Francis DD, Sapolsky RM, Palmer TD, Pleasure D, Kaufer D, 2014 Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Mol. Psychiatry* 19, 1275–1283. doi:10.1038/mp.2013.190 [PubMed: 24514565]
- Chopra S, Rathore A, Younas H, Pham LV, Gu C, Beselman A, Kim IY, Wolfe RR, Perin J, Polotsky VY, Jun JC, 2017 Obstructive sleep apnea dynamically increases nocturnal plasma free fatty acids, glucose, and cortisol during sleep. *J. Clin. Endocrinol. Metab* 102, 3172–3181. doi:10.1210/jc.2017-00619 [PubMed: 28595341]
- Chu L, Shen K, Liu P, Ye K, Wang Y, Li C, Kang X, Song Y, 2017 Increased Cortisol and Cortisone Levels in Overweight Children. *Med. Sci. Monit. Basic Res* 23, 25–30. doi:10.12659/MSMBR.902707 [PubMed: 28179618]
- Cockrem JF, 2013 Individual variation in glucocorticoid stress responses in animals. *Gen. Comp. Endocrinol* 181, 45–58. doi:10.1016/j.ygcen.2012.11.025 [PubMed: 23298571]
- Cockrem JF, Barrett DP, Candy EJ, Potter MA, 2009 Corticosterone responses in birds: Individual variation and repeatability in Adelie penguins (*Pygoscelis adeliae*) and other species, and the use of power analysis to determine sample sizes. *Gen. Comp. Endocrinol* 163, 158–168. doi:10.1016/j.ygcen.2009.03.029 [PubMed: 19351536]
- Cockrem JF, Silverin B, 2002 Variation within and between birds in corticosterone responses of great tits (*Parus major*). *Gen. Comp. Endocrinol* 125, 197–206. doi:10.1006/gcen.2001.7750 [PubMed: 11884065]
- Contoli M, Pauletti A, Rossi MR, Spanevello A, Casolari P, Marcellini A, Forini G, Gnesini G, Marku B, Barnes N, Rizzi A, Curradi G, Caramori G, Morelli P, Papi A, 2017 Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. *Eur. Respir. J* 50, 1700451. doi:10.1183/13993003.00451-2017 [PubMed: 28982774]
- Crespi EJ, Williams TD, Jessop TS, Delehanty B, 2013 Life history and the ecology of stress: how do glucocorticoid hormones influence life-history variation in animals? *Func. Ecol* 27, 93–106. doi:10.1111/1365-2435.12009
- Cruz-Topete D, Myers PH, Foley JF, Willis MS, Cidlowski JA, 2016 Corticosteroids are essential for maintaining cardiovascular function in male mice. *Endocrinology* 157, 2759–2771. doi:10.1210/en.2015-1604 [PubMed: 27219275]
- Cuffe JSM, Turton EL, Akison LK, Bielefeldt-Ohmann H, Moritz KM, 2017 Prenatal corticosterone exposure programs sex-specific adrenal adaptations in mouse offspring. *J. Endocrinol* 232, 37–48. doi:10.1530/JOE-16-0417 [PubMed: 27754933]
- Cui C, Hong-ying Z, Jing-jing L, Jing-cheng D, Yan C, Chang-qing X, Bao-jun L, Jinfeng W, Xiao-hong D, Yu-xue C, 2010 Inflammatory airway features and hypothalamic-pituitary-adrenal axis function in asthmatic rats combined with chronic obstructive pulmonary disease. *Chin. Med. J. (Engl)* 123, 1720–1726. doi:10.3760/cma.j.issn.0366-6999.2010.13.020 [PubMed: 20819636]
- Day FL, Valmaggia LR, Mondelli V, Papadopoulos A, Papadopoulos I, Pariante CM, McGuire P, 2014 Blunted Cortisol Awakening Response in People at Ultra High Risk of Developing Psychosis. *Schizophr. Res* 158, 25–31. doi:10.1016/j.schres.2014.06.041 [PubMed: 25048422]
- del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A, 2014 Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheumatol.* 66, 264–272. doi:10.1002/art.38210 [PubMed: 24504798]

- Desai M, Jellyman JK, Han G, Beall M, Lane RH, Ross MG, 2014 Maternal obesity and high-fat diet program offspring metabolic syndrome. *Am. J. Obstet. Gynecol* 211, 237.e1–237.e13. doi:10.1016/j.ajog.2014.03.025 [PubMed: 24631702]
- Dhabhar FS, McEwen BS, 1999 Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc. Natl. Acad. Sci* 96, 1059–1064. doi:10.1073/pnas.96.3.1059 [PubMed: 9927693]
- Dmitrieva NO, Almeida DM, Dmitrieva J, Loken E, Pieper CF, 2013 A day-centered approach to modeling cortisol: Diurnal cortisol profiles and their associations among U.S. adults. *Psychoneuroendocrinology* 38, 2354–2365. doi:10.1016/j.psyneuen.2013.05.003 [PubMed: 23770247]
- Eikenaar C, Müller F, Leutgeb C, Hessler S, Lebus K, Taylor PD, Schmaljohann H, 2017 Corticosterone and timing of migratory departure in a songbird. *Proc. R. Soc. B Biol. Sci* 284. doi:10.1098/rspb.2016.2300
- Erickson RL, Browne CA, Lucki I, 2017 Hair corticosterone measurement in mouse models of type 1 and type 2 diabetes mellitus. *Physiol. Behav* 178, 166–171. doi:10.1016/j.physbeh.2017.01.018 [PubMed: 28089708]
- Fekedulegn D, Innes K, Andrew ME, Tinney-Zara C, Charles LE, Allison P, Violanti JM, Knox SS, 2018 Sleep quality and the cortisol awakening response (CAR) among law enforcement officers: The moderating role of leisure time physical activity. *Psychoneuroendocrinology* 95, 158–169. doi:10.1016/j.psyneuen.2018.05.034 [PubMed: 29864672]
- Ferguson GT, Tashkin DP, Skärby T, Jorup C, Sandin K, Greenwood M, Pemberton K, Trudo F, 2017 Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: The 6-month, randomized RISE (Revealing the Impact of Symbicort in reducing Exacerbations in COPD) study. *Respir. Med* 132, 31–41. doi:10.1016/j.rmed.2017.09.002 [PubMed: 29229103]
- Franceschini MD, Evers DC, Kenow KP, Meyer MW, Pokras M, Romero LM, 2017 Mercury correlates with altered corticosterone but not testosterone or estradiol concentrations in common loons. *Ecotoxicol. Environ. Saf* 142, 348–354. doi:10.1016/j.ecoenv.2017.04.030 [PubMed: 28437726]
- Furtado GE, Uba-Chupel M, Carvalho HM, Souza NR, Ferreira JP, Teixeira AM, 2016 Effects of a chair-yoga exercises on stress hormone levels, daily life activities, falls and physical fitness in institutionalized older adults. *Complement. Ther. Clin. Pract* 24, 123–129. doi:10.1016/j.ctcp.2016.05.012 [PubMed: 27502812]
- Gemmel M, Harmeyer D, Bögi E, Fillet M, Hill LA, Hammond GL, Charlier TD, Pawluski JL, 2018 Perinatal fluoxetine increases hippocampal neurogenesis and reverses the lasting effects of pre-gestational stress on serum corticosterone, but not on maternal behavior, in the rat dam. *Behav. Brain Res* 339, 222–231. doi:10.1016/j.bbr.2017.11.038 [PubMed: 29203333]
- Girbovan C, Kent P, Merali Z, Plamondon H, 2016 Dose-related effects of chronic resveratrol administration on neurogenesis, angiogenesis, and corticosterone secretion are associated with improved spatial memory retention following global cerebral ischemia. *Nutr. Neurosci* 19, 352–368. doi:10.1179/1476830515Y.0000000020 [PubMed: 25866012]
- Gordon JL, Rubinow DR, Thurston RC, Paulson J, Schmidt PJ, Girdler SS, 2016 Cardiovascular, hemodynamic, neuroendocrine, and inflammatory markers in women with and without vasomotor symptoms. *Menopause* 23, 1189–1198. doi:10.1097/GME.0000000000000689 [PubMed: 27465715]
- Grant N, Hamer M, Steptoe A, 2009 Social isolation and stress-related cardiovascular, lipid, and cortisol responses. *Ann. Behav. Med* 37, 29–37. doi:10.1007/s12160-009-9081-z [PubMed: 19194770]
- Gray JM, Vecchiarelli HA, Morena M, Lee TTY, Hermanson DJ, Kim AB, McLaughlin RJ, Hassan KI, Kühne C, Wotjak CT, Deussing JM, Patel S, Hill MN, 2015 Corticotropin-releasing hormone drives anandamide hydrolysis in the amygdala to promote anxiety. *J. Neurosci* 35, 3879–3892. doi:10.1523/JNEUROSCI.2737-14.2015 [PubMed: 25740517]
- Hammer F, Deutschbein T, Marx A, Guder G, Michalski R, Ertl G, Allolio B, Angermann CE, Stork S, Fassnacht M, 2016 High evening salivary cortisol is an independent predictor of increased

mortality risk in patients with systolic heart failure. *Int.J. Cardiol.* 203, 69–73. doi:10.1016/j.ijcard.2015.10.084

- Hayden EP, Hankin BL, Mackrell SVM, Sheikh HI, Jordan PL, Dozois DJA, Singh SM, Olino TM, Badanes LS, 2014 Parental depression and child cognitive vulnerability predict children's cortisol reactivity. *Dev. Psychopathol* 26, 1445–1460. doi:10.1017/S0954579414001138 [PubMed: 25422972]
- Heinze K, Lin A, Reniers RLEP, Wood SJ, 2016 Longer-term increased cortisol levels in young people with mental health problems. *Psychiatry Res.* 236, 98–104. doi:10.1016/j.psychres.2015.12.025 [PubMed: 26749569]
- Hellhammer J, Fries E, Schweisthal OW, Schlotz W, Stone AA, Hagemann D, 2007 Several daily measurements are necessary to reliably assess the cortisol rise after awakening: State- and trait components. *Psychoneuroendocrinology* 32, 80–86. doi:10.1016/j.psyneuen.2006.10.005 [PubMed: 17127010]
- Henderson LJ, Evans NP, Heidinger BJ, Herborn KA, Arnold KE, 2017 Do glucocorticoids predict fitness? Linking environmental conditions, corticosterone and reproductive success in the blue tit, *Cyanistes caeruleus*. *R. Soc. Open Sci* 4, 170875. doi:10.1098/rsos.170875 [PubMed: 29134087]
- Holanda C.M. de A., Guerra RO, Nobrega P.V. de N., Costa HF, Piuvezam MR, Maciel ACC, 2012 Salivary cortisol and frailty syndrome in elderly residents of long-stay institutions: A cross-sectional study. *Arch. Gerontol. Geriatr* 54, e146–e151. doi:10.1016/j.archger.2011.11.006 [PubMed: 22153978]
- Hopkins LB, Medina JL, Baird SO, Rosenfeld D, Powers MB, Smits JAJ, 2016 Heated hatha yoga to target cortisol reactivity to stress and affective eating in women at risk for obesity-related illnesses: A randomized controlled trial. *J. Consult. Clin. Psychol* 84, 558–564. doi:10.1037/ccp0000091 [PubMed: 26963599]
- Hoyt MA, Bower JE, Irwin MR, Weierich MR, Stanton AL, 2016 Sleep quality and depressive symptoms after prostate cancer: the mechanistic role of cortisol. *Behav. Neurosci* 130, 351–356. doi:10.1037/bne0000107 [PubMed: 26820589]
- Ishiguro H, Kawahara T, Zheng Y, Kashiwagi E, Li Y, Miyamoto H, 2014 Differential regulation of bladder cancer growth by various glucocorticoids: corticosterone and prednisone inhibit cell invasion without promoting cell proliferation or reducing cisplatin cytotoxicity. *Cancer Chemother. Pharmacol* 74, 249–255. doi:10.1007/s00280-014-2496-7 [PubMed: 24880571]
- Ito T, Saitoh D, Takasu A, Kiyozumi T, Sakamoto T, Okada Y, 2004 Serum cortisol as a predictive marker of the outcome in patients resuscitated after cardiopulmonary arrest. *Resuscitation* 62, 55–60. doi:10.1016/j.resuscitation.2004.02.004 [PubMed: 15246584]
- Jackson SE, Kirschbaum C, Steptoe A, 2016 Perceived weight discrimination and chronic biochemical stress: A population-based study using cortisol in scalp hair. *Obesity* 24, 2515–2521. doi:10.1002/oby.21657 [PubMed: 27740706]
- Jarcho MR, Slavich GM, Tylova-Stein H, Wolkowitz OM, Burke HM, 2013 Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. *Biol. Psychol* 93, 150–158. doi:10.1016/j.biopsycho.2013.01.018 [PubMed: 23410758]
- Joels M, Sarabdjitsingh RA, Karst H, 2012 Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. *Pharmacol. Rev* 64, 901–938. doi:10.1124/pr.112.005892 [PubMed: 23023031]
- Johannesdottir SA, Horvath-Puho E, Dekkers OM, Cannegieter SC, Jørgensen JOL, Ehrenstein V, Vandenbroucke JP, Pedersen L, Sraensen HT, 2013 Use of glucocorticoids and risk of venous thromboembolism: A nationwide population-based case-control study. *JAMA Intern. Med* 173, 743–752. doi:10.1001/jamainternmed.2013.122 [PubMed: 23546607]
- Johar H, Emeny RT, Bidlingmaier M, Kruse J, Ladwig KH, 2016 Sex-related differences in the association of salivary cortisol levels and type 2 diabetes. Findings from the cross-sectional population based KORA-age study. *Psychoneuroendocrinology* 69, 133–141. doi:10.1016/j.psyneuen.2016.04.004 [PubMed: 27088372]
- Kadmiel M, Cidlowski JA, 2013 Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol. Sci* 34, 518–530. doi:10.1016/j.tips.2013.07.003 [PubMed: 23953592]

- Karatsoreos IN, Bhagat SM, Bowles NP, Weil ZM, Pfaff DW, McEwen BS, 2010 Endocrine and physiological changes in response to chronic corticosterone: A potential model of the metabolic syndrome in mouse. *Endocrinology* 151, 2117–2127. doi:10.1210/en.2009-1436 [PubMed: 20211972]
- Karlamangla AS, Friedman EM, Seeman TE, Stawski RS, Almeida DM, 2013 Daytime trajectories of cortisol: Demographic and socioeconomic differences-Findings from the national study of daily experiences. *Psychoneuroendocrinology* 38, 2585–2597. doi:10.1016/j.psyneuen.2013.06.010 [PubMed: 23831263]
- Kern S, Krause I, Horntrich A, Thomas K, Aderhold J, Ziemssen T, 2013 Cortisol Awakening Response Is Linked to Disease Course and Progression in Multiple Sclerosis. *PLoS One* 8, e60647. doi:10.1371/journal.pone.0060647 [PubMed: 23613736]
- Khalife N, Glover V, Taanila A, Ebeling H, Jarvelin MR, Rodriguez A, 2013 Prenatal glucocorticoid treatment and later mental health in children and adolescents. *PLoS One* 8, e81394. doi:10.1371/journal.pone.0081394 [PubMed: 24278432]
- Khoury JE, Gonzalez A, Levitan RD, Pruessner JC, Chopra K, Basile VS, Masellis M, Goodwill A, Atkinson L, 2015 Summary cortisol reactivity indicators: Interrelations and meaning. *Neurobiol. Stress* 2, 34–43. doi:10.1016/j.ynstr.2015.04.002 [PubMed: 26844238]
- Kim HM, Ha KS, Hwang IC, Ahn HY, Youn CH, 2016 Random Serum Cortisol as a Predictor for Survival of Terminally Ill Patients With Cancer: A Preliminary Study. *Am. J. Hosp. Palliat. Med* 33, 281–285. doi:10.1177/1049909114563065
- Kralj-Fiser S, Scheiber IBR, Blejec A, Moestl E, Kotrschal K, 2007 Individualities in a flock of free-roaming greylag geese: Behavioral and physiological consistency over time and across situations. *Horm. Behav* 51, 239–248. doi:10.1016/j.yhbeh.2006.10.006 [PubMed: 17196200]
- Krieger DT, Allen W, Rizzo F, Krieger HP, 1971 Characterization of the normal temporal pattern of plasma corticosteroid levels. *J. Clin. Endocrinol. Metab* 32, 266–284. doi: 10.1210/jcem-32-2-266 [PubMed: 4321505]
- Krieger G, 1974 The plasma level of cortisol as a predictor of suicide. *Dis. Nerv. Syst* 35, 237–240. [PubMed: 17894107]
- Kupper N, De Geus EJC, Van Den Berg M, Kirschbaum C, Boomsma DI, Willemsen G, 2005 Familial influences on basal salivary cortisol in an adult population. *Psychoneuroendocrinology* 30, 857–868. doi:10.1016/j.psyneuen.2005.04.003 [PubMed: 15949896]
- Kuznetsova NV, Palchikova NA, Selyatitskaya VG, Kuzminova OI, 2017 Effect of Mifepristone on Corticosteroid Production in Vitro by Adrenal Glands of Rats with Streptozotocin Diabetes. *Bull. Exp. Biol. Med* 162, 327–330. doi:10.1007/s10517-0173607-3 [PubMed: 28091906]
- Lietzen LW, Ahern T, Christiansen P, Jensen AB, Sorensen HT, Lash TL, Cronin-Fenton DP, 2014 Glucocorticoid prescriptions and breast cancer recurrence: a Danish nationwide prospective cohort study. *Ann. Oncol* 25, 2419–2425. doi:10.1093/annonc/mdu453 [PubMed: 25223486]
- Lightman SL, Wiles CC, Atkinson HC, Henley DE, Russell GM, Leendertz JA, McKenna MA, Spiga F, Wood SA, Conway-Campbell BL, 2008 The significance of glucocorticoid pulsatility. *Eur. J. Pharmacol* 583, 255–262. doi:10.1016/j.ejphar.2007.11.073 [PubMed: 18339373]
- Lim R, Fedulov AV, Kobzik L, 2014 Maternal stress during pregnancy increases neonatal allergy susceptibility: Role of glucocorticoids. *AJP Lung Cell. Mol. Physiol* 307, L141–L148. doi:10.1152/ajplung.00250.2013
- Lin J, Zhao H, Shen J, Jiao F, 2017 Salivary Cortisol Levels Predict Therapeutic Response to a Sleep-Promoting Method in Children with Postural Tachycardia Syndrome. *J. Pediatr* 191, 91–95. doi:10.1016/j.jpeds.2017.08.039 [PubMed: 29037796]
- Lin KT, Sun SP, Wu JI, Wang LH, 2017 Low-dose glucocorticoids suppresses ovarian tumor growth and metastasis in an immunocompetent syngeneic mouse model. *PLoS One* 12, e0178937. doi:10.1371/journal.pone.0178937 [PubMed: 28591224]
- Lucas-Thompson RG, Lunkenheimer ES, Dumitrache A, 2017 Associations Between Marital Conflict and Adolescent Conflict Appraisals, Stress Physiology, and Mental Health. *J. Clin. Child Adolesc. Psychol* 46, 379–393. doi:10.1080/15374416.2015.1046179 [PubMed: 26136117]
- Makimura H, Mizuno TM, Isoda F, Beasley J, Silverstein JH, Mobbs CV, 2003 Role of glucocorticoids in mediating effects of fasting and diabetes on hypothalamic gene expression. *BMC Physiol.* 3.

- Martinez-Claros M, Steinbusch HWM, van Selm A, van den Hove DLA, Prickaerts J, Pawluski JL, 2013 Adrenalectomy and corticosterone replacement differentially alter CA3 dendritic morphology and new cell survival in the adult rat hippocampus. *J. Chem. Neuroanat* 48–49, 23–28. doi:10.1016/j.jchemneu.2013.01.001
- McEwen BS, 1998 Protective and damaging effects of stress mediators. *N. Engl. J. Med* 338, 171–179. [PubMed: 9428819]
- McEwen BS, Stellar E, 1993 Stress and the individual: mechanisms leading to disease. *Arch Intern Med* 153, 2093–2101. [PubMed: 8379800]
- McFarlane AC, Barton CA, Yehuda R, Wittert G, 2011 Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology* 36, 720–727. doi:10.1016/j.psyneuen.2010.10.007 [PubMed: 21093988]
- Melin EO, Thunander M, Landin-Olsson M, Hillman M, Thulesius HO, 2017 Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison. *BMC Psychiatry* 17, 335. doi:10.1186/s12888-017-1495-8 [PubMed: 28931368]
- Mikolajczak M, Quoidbach J, Vanooteghem V, Lambert F, Lahaye M, Fillee C, de Timary P, 2010 Cortisol awakening response (CAR)'s flexibility leads to larger and more consistent associations with psychological factors than CAR magnitude. *Psychoneuroendocrinology* 35, 752–757. doi:10.1016/j.psyneuen.2009.11.003 [PubMed: 19959296]
- Miller KF, Arbel R, Shapiro LS, Han SC, Margolin G, 2018 Brief report: Does the cortisol awakening response link childhood adversity to adult BMI? *Heal. Psychol* 37, 526–529. doi:10.1037/hea0000601
- Miller R, Stalder T, Jarczok M, Almeida DM, Badrick E, Bartels M, Boomsma DI, Coe CL, Dekker MCJ, Donzella B, Fischer JE, Gunnar MR, Kumari M, Lederbogen F, Power C, Ryff CD, Subramanian SV, Tiemeier H, Watamura SE, Kirschbaum C, 2016 The CIRCORT database: Reference ranges and seasonal changes in diurnal salivary cortisol derived from a meta-dataset comprised of 15 field studies. *Psychoneuroendocrinology* 73, 16–23. doi:10.1016/j.psyneuen.2016.07.201 [PubMed: 27448524]
- Moon HJ, Choi KH, Lee S II, Lee OJ, Shin JW, Kim TW, 2014 Changes in blood glucose and cortisol levels after epidural or shoulder intra-articular glucocorticoid injections in diabetic or nondiabetic patients. *Am. J. Phys. Med. Rehabil* 93, 372–378. doi:10.1097/PHM.0000000000000001 [PubMed: 24508924]
- Moraes H, Deslandes A, Maciel-Pinheiro P. de T., Correa H, Laks J, 2016 Cortisol, DHEA, and depression in the elderly: the influence of physical capacity. *Arq. Neuropsiquiatr* 74, 456–461. doi:10.1590/0004-282X20160059 [PubMed: 27332070]
- Mortensen J, Dich N, Clark AJ, Ramlau-Hansen CH, Head J, Kivimäki M, Kumari M, Rod NH, 2019 Informal caregiving and diurnal patterns of salivary cortisol: Results from the Whitehall II cohort study. *Psychoneuroendocrinology* 100, 41–47. doi:10.1016/j.psyneuen.2018.09.030 [PubMed: 30290284]
- Mouthaan J, Sijbrandij M, Luitse JSK, Goslings JC, Gersons BPR, Olff M, 2014 The role of acute cortisol and DHEAS in predicting acute and chronic PTSD symptoms. *Psychoneuroendocrinology* 45, 179–186. doi:10.1016/j.psyneuen.2014.04.001 [PubMed: 24845188]
- Nasca C, Bigio B, Zelli D, de Angelis P, Lau T, Okamoto M, Soya H, Ni J, Brichta L, Greengard P, Neve RL, Lee FS, McEwen BS, 2017 Role of the Astroglial Glutamate Exchanger xCT in Ventral Hippocampus in Resilience to Stress. *Neuron* 96, 402–413. doi:10.1016/j.neuron.2017.09.020 [PubMed: 29024663]
- Nasca C, Bigio B, Zelli D, Nicoletti F, McEwen BS, 2015 Mind the gap: Glucocorticoids modulate hippocampal glutamate tone underlying individual differences in stress susceptibility. *Mol. Psychiatry* 20, 755–763. doi:10.1038/mp.2014.96 [PubMed: 25178162]
- Nebiker CA, Staubli S, Schäfer J, Bingisser R, Christ-Crain M, Dell-Kuster S, Mueller C, Scamardi K, Viehl CT, Kollet D, Von Holzen U, Oertli D, Rosenthal R, 2018 Cortisol outperforms novel cardiovascular, inflammatory, and neurohumoral biomarkers in the prediction of outcome in acute pancreatitis. *Pancreas* 47, 55–64. doi:10.1097/MPA.0000000000000962 [PubMed: 29215538]
- Noppe G, Van Den Akker ELT, De Rijke YB, Koper JW, Jaddoe VW, Van Rossum FC, 2016 Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body-fat distribution. *Int. J. Obes* 40, 1503–1509. doi:10.1038/ijo.2016.113

- Ostenfeld EB, Erichsen R, Thorlacius-Ussing O, Riis AH, Sorensen HT, 2014 Preadmission use of glucocorticoids and 30-day mortality following colorectal cancer surgery: a population-based Danish cohort study. *Aliment. Pharmacol. Ther* 39, 843–853. doi:10.1111/apt.12667 [PubMed: 24611938]
- Peng J, Zhou Y, Zhang Z, Wang Z, Gao L, Zhang X, Fang Z, Li G, Chen H, Yang H, Gao L, 2018 The detrimental effects of glucocorticoids exposure during pregnancy on offspring's cardiac functions mediated by hypermethylation of bone morphogenetic protein-4. *Cell Death Dis.* 9, 834. doi:10.1038/s41419-018-0841-1 [PubMed: 30082698]
- Pereg D, Gow R, Mosseri M, Lishner M, Rieder M, Van Uum S, Koren G, 2010 Hair cortisol and the risk for acute myocardial infarction in adult men. *Stress* 1–9. doi:10.3109/10253890.2010.511352 [PubMed: 20105052]
- Pineles SL, Rasmusson AM, Yehuda R, Lasko NB, Macklin ML, Pitman RK, Orr P, 2013 Predicting emotional responses to potentially traumatic events from preexposure waking cortisol levels: a longitudinal study of police and firefighters. *Anxiety, Stress Coping* 26, 241–253. doi:10.1080/10615806.2012.672976
- Pride RE, 2005 High faecal glucocorticoid levels predict mortality in ring-tailed lemurs (*Lemur catta*). *Biol. Lett* 1, 60–63. doi:10.1098/rsbl.2004.0245 [PubMed: 17148128]
- Pulopulos MM, Puig-Perez S, Hidalgo V, Villada C, Salvador A, 2016 Cortisol awakening response and walking speed in older people. *PLoS One* 11, e0152071. doi:10.1371/journal.pone.0152071 [PubMed: 27191847]
- Quax RA, Manenschijn L, Koper JW, Hazes JM, Lamberts SWJ, Van Rossum EFC, Feelders RA, 2013 Glucocorticoid sensitivity in health and disease. *Nat. Rev. Endocrinol* 9, 670–686. doi:10.1038/nrendo.2013.183 [PubMed: 24080732]
- Rakotoniaina JH, Kappeler PM, Kaesler E, Hämäläinen AM, Kirschbaum C, Kraus C, 2017 Hair cortisol concentrations correlate negatively with survival in a wild primate population. *BMC Ecol.* 17. doi:10.1186/s12898-017-0140-1
- Redfern JC, Cooke SJ, Lennox RJ, Nannini MA, Wahl DH, Gilmour KM, 2017 Effects of maternal cortisol treatment on offspring size, response to stress, and anxiety-related behavior in wild largemouth bass (*Micropterus salmoides*). *Physiol. Behav* 180, 15–24. doi:10.1016/j.physbeh.2017.08.001 [PubMed: 28782525]
- Rodriguez KE, Bryce CI, Granger DA, O'Haire ME, 2018 The effect of a service dog on salivary cortisol awakening response in a military population with posttraumatic stress disorder (PTSD). *Psychoneuroendocrinology* 98, 202–210. doi:10.1016/j.psyneuen.2018.04.026 [PubMed: 29907299]
- Romero LM, 2004 Physiological stress in ecology: Lessons from biomedical research. *Trends Ecol. Evol* 19, 249–255. doi:10.1016/j.tree.2004.03.008 [PubMed: 16701264]
- Romero LM, Reed JM, 2005 Collecting baseline corticosterone samples in the field: is under 3 min good enough? *Comp. Biochem. Physiol* 140, 73–79. doi:10.1016/j.cbpb.2004.11.004
- Ronaldson A, Kidd T, Poole L, Leigh E, Jahangiri M, Steptoe A, 2015 Diurnal Cortisol Rhythm Is Associated With Adverse Cardiac Events and Mortality in Coronary Artery Bypass Patients. *J. Clin. Endocrinol. Metab* 100, 3676–3682. doi:10.1210/jc.2015-2617 [PubMed: 26305622]
- Rosenkranz MA, Esnault S, Christian BT, Crisafi G, Gresham LK, Higgins AT, Moore MN, Moore SM, Weng HY, Salk RH, Busse WW, Davidson RJ, 2016 Mind-body interactions in the regulation of airway inflammation in asthma: A PET study of acute and chronic stress. *Brain. Behav. Immun* 58, 18–30. doi:10.1016/j.bbi.2016.03.024 [PubMed: 27039241]
- Ross KM, Murphy MLM, Adam EK, Chen E, Miller GE, 2014 How stable are diurnal cortisol activity indices in healthy individuals? Evidence from three multi-wave studies. *Psychoneuroendocrinology* 39, 184–193. doi:10.1016/j.psyneuen.2013.09.016 [PubMed: 24119668]
- Said MA, El-Gohary OA, 2016 Effect of noise stress on cardiovascular system in adult male albino rat: implications of stress hormones, endothelial dysfunction and oxidative stress. *Gen. Physiol. Biophys* 35, 371–377. [PubMed: 27174896]
- Sapolsky RM, Romero LM, Munck AU, 2000 How Do Glucocorticoids Influence Stress Responses? Preparative Actions. *Endocr. Rev* 21, 55–89. doi:10.1210/er.21.1.55 [PubMed: 10696570]

- Sasser WC, Robert SM, Carlo WF, Borasino S, Dabal RJ, Kirklin JK, Alten JA, 2012 Postoperative Serum Cortisol Concentration and Adrenal Insufficiency in Neonates Undergoing Open-Heart Surgery. *World J. Pediatr. Congenit. Hear. Surg* 3, 214–220. doi:10.1177/2150135111431268
- Schoenle LA, Zimmer C, Vitousek MN, 2018 Understanding Context Dependence in Glucocorticoid-Fitness Relationships: The Role of the Nature of the Challenge, the Intensity and Frequency of Stressors, and Life History. *Integr. Comp. Biol* 1–13. doi:10.1093/icb/icy046 [PubMed: 30053056]
- Schrepf A, Thaker PH, Goodheart MJ, Bender D, Slavich GM, Dahmouch L, Penedo F, DeGeest K, Mendez L, Lubaroff DM, Cole SW, Sood AK, Lutgendorf SK, 2015 Diurnal cortisol and survival in epithelial ovarian cancer. *Psychoneuroendocrinology* 53, 256–267. doi:10.1016/j.psyneuen.2015.01.010 [PubMed: 25647344]
- Schwarz JM, Bilbo SD, 2012 Sex, glia, and development: Interactions in health and disease. *Horm. Behav* 62, 243–253. doi:10.1016/j.yhbeh.2012.02.018 [PubMed: 22387107]
- Sephton SE, Lush E, Dedert EA, Floyd AR, Rebholz WN, Dhabhar FS, Spiegel D, Salmon P, 2013 Diurnal cortisol rhythm as a predictor of lung cancer survival. *Brain. Behav. Immun* 30, S163–S170. doi:10.1016/j.bbi.2012.07.019 [PubMed: 22884416]
- Sephton SE, Sapolsky RM, Kraemer H, Spiegel D, 2000 Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst* 92, 994–1000. doi:10.1016/S1359-6349(10)70535-8 [PubMed: 10861311]
- Sharma AN, Wigham J, Veldhuis JD, 2014 Corticotrophic axis drive of overnight cortisol secretion is suppressed in adolescents and young adults with type 1 diabetes mellitus. *Pediatr. Diabetes* 15, 444–452. doi:10.1111/pedi.12108 [PubMed: 24350820]
- Shirtcliff EA, Allison AL, Armstrong JM, Slattery MJ, Kalin NH, Essex MJ, 2012 Longitudinal stability and developmental properties of salivary cortisol levels and circadian rhythms from childhood to adolescence. *Dev. Psychobiol* 54, 493–502. doi:10.1002/dev.20607 [PubMed: 21953537]
- Shpilberg Y, Beaudry JL, D'Souza A, Campbell JE, Peckett A, Riddell MC, 2012 A rodent model of rapid-onset diabetes induced by glucocorticoids and high-fat feeding. *Dis. Model. Mech* 5, 671–680. doi:10.1242/dmm.008912 [PubMed: 22184636]
- Skorzevska A, Bidzinski A, Lehner M, Turzynska D, Wislowska-Stanek A, Sobolewska A, Szyndler J, Maciejak P, Taracha E, Plaznik A, 2006 The effects of acute and chronic administration of corticosterone on rat behavior in two models of fear responses, plasma corticosterone concentration, and c-Fos expression in the brain structures. *Pharmacol. Biochem. Behav* 85, 522–534. doi:10.1016/j.pbb.2006.10.001 [PubMed: 17107707]
- Song HT, Sun XY, Yang TS, Zhang LY, Yang JL, Bai J, 2015 Effects of sleep deprivation on serum cortisol level and mental health in servicemen. *Int. J. Psychophysiol* 96, 169–175. doi:10.1016/j.jpsycho.2015.04.008 [PubMed: 25913092]
- Spee M, Marchal L, Lazin D, Le Maho Y, Chastel O, Beaulieu M, Raclot T, 2011 Exogenous corticosterone and nest abandonment: A study in a long-lived bird, the Adelie penguin. *Horm. Behav* 60, 362–370. doi:10.1016/j.yhbeh.2011.07.003 [PubMed: 21763694]
- Stawski RS, Cichy KE, Piazza JR, Almeida DM, 2013 Associations among daily stressors and salivary cortisol: Findings from the National Study of Daily Experiences. *Psychoneuroendocrinology* 38, 2654–2665. doi:10.1016/j.psyneuen.2013.06.023 [PubMed: 23856186]
- Strange MS, Bowden RM, Thompson CF, Sakaluk SK, 2016 Pre- and Postnatal Effects of Corticosterone on Fitness-Related Traits and the Timing of Endogenous Corticosterone Production in a Songbird. *J. Exp. Zool* 325, 347–359. doi:10.1002/jez.2022
- Taff CC, Schoenle LA, Vitousek MN, 2018 The repeatability of glucocorticoids: A review and meta-analysis. *Gen. Comp. Endocrinol* 260, 136–145. doi:10.1016/j.ygcen.2018.01.011 [PubMed: 29355531]
- Tai S-Y, Huang S-P, Bao B-Y, Wu M-T, 2016 Urinary melatonin-sulfate/cortisol ratio and the presence of prostate cancer: a case-control study. *Sci. Rep* 6, 29606. doi:10.1038/srep29606 [PubMed: 27387675]

- Taliaz D, Loya A, Gersner R, Haramati S, Chen A, Zangen A, 2011 Resilience to Chronic Stress Is Mediated by Hippocampal Brain-Derived Neurotrophic Factor. *J. Neurosci* 31, 4475–4483. doi:10.1523/JNEUROSCI.5725-10.2011 [PubMed: 21430148]
- Tan JTT, Patel BK, Kaplan LM, Koenig JI, Hooi SC, 1998 Regulation of leptin expression and secretion by corticosteroids and insulin: Implications for body weight. *Endocrine* 8, 85–92. doi:10.1385/ENDO:8:1:85 [PubMed: 9666350]
- Tarr T, Papp G, Nagy N, Cserep E, Zeher M, 2017 Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens disease outcome in systemic lupus erythematosus. *Clin. Rheumatol* 36, 327–333. doi:10.1007/s10067-016-3492-6 [PubMed: 27889859]
- Toledo-Corral CM, Myers SJ, Li Y, Hodis HN, Goran MI, Weigensberg MJ, 2013 Blunted nocturnal cortisol rise is associated with higher carotid artery intima-media thickness (CIMT) in overweight african american and latino youth. *Psychoneuroendocrinology* 38, 1658–1667. doi:10.1016/j.psyneuen.2013.01.011 [PubMed: 23433749]
- Triantos CK, Kalafateli M, Samonakis D, Zisimopoulos K, Papiamoni N, Sapountzis A, Michalaki M, Theocharis G, Thomopoulos K, Labropoulou-Karatza C, Kyriazopoulou V, Jelastopulu E, Kouroumalis EA, Nikolopoulou V, Burroughs AK, 2014 Higher free serum cortisol is associated with worse survival in acute variceal bleeding because of cirrhosis: a prospective study. *Eur. J. Gastroenterol. Hepatol* 26, 1125–1132. doi:10.1097/MEG.000000000000158 [PubMed: 25089543]
- Violanti JM, Fekedulegn D, Andrew ME, Charles LE, Gu JK, Miller DB, 2018 Subclinical Markers of Cardiovascular Disease Among Police Officers. *J. Occup. Environ. Med* 60, 853–859. doi:10.1097/JOM.0000000000001358 [PubMed: 29787400]
- Vitousek MN, Jenkins BR, Safran RJ, 2014 Stress and success: Individual differences in the glucocorticoid stress response predict behavior and reproductive success under high predation risk. *Horm. Behav* 66, 812–819. doi:10.1016/j.yhbeh.2014.11.004 [PubMed: 25461975]
- Wada H, Salvante KG, Stables C, Wagner E, Williams TD, Breuner CW, 2008 Adrenocortical responses in zebra finches (*Taeniopygia guttata*): Individual variation, repeatability, and relationship to phenotypic quality. *Horm. Behav* 53, 472–480. doi:10.1016/j.yhbeh.2007.11.018 [PubMed: 18221739]
- Wells S, Tremblay PF, Flynn A, Russell E, Kennedy J, Rehm J, Van Uum S, Koren G, Graham K, 2014 Associations of hair cortisol concentration with self-reported measures of stress and mental health-related factors in a pooled database of diverse community samples. *Stress* 17, 334–342. doi: 10.3109/10253890.2014.930432 [PubMed: 24903269]
- Wirix AJG, Finken MJJ, von Rosenstiel-Jadoul IA, Heijboer AC, Nauta J, Groothoff JW, Chinapaw MJM, Kist-van Holthe JE, 2017 Is there an association between cortisol and hypertension in overweight or obese children? *J. Clin. Res. Pediatr. Endocrinol* 9, 344–349. doi:10.4274/jcrpe.4802 [PubMed: 28720554]
- Wong JHK, Brummelte S, Galea LAM, 2011 Elevated corticosterone levels during the first postpartum period influence subsequent pregnancy outcomes and behaviours of the dam. *J. Neuroendocrinol* 23, 1156–1165. doi:10.1111/j.1365-2826.2011.02169.x [PubMed: 21623960]
- Woods CP, Corrigan M, Gathercole L, Taylor A, Hughes B, Gaoatswe G, Manolopoulos K, Hogan AE, O'Connell J, Stewart PM, Tomlinson JW, O'Shea D, Sherlock M, 2015 Tissue specific regulation of glucocorticoids in severe obesity and the response to significant weight loss following bariatric surgery (BARICORT). *J. Clin. Endocrinol. Metab* 100, 1434–1444. doi:10.1210/jc.2014-4120 [PubMed: 25603461]
- Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, Horie M, 2009 Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure: The impact of oxidative stress. *Circ. Hear. Fail* 2, 608–615. doi:10.1161/CIRCHEARTFAILURE.109.868513
- Yan Y-X, Dong J, Liu Y-Q, Zhang J, Song M-S, He Y, Wang W, 2015 Association of suboptimal health status with psychosocial stress, plasma cortisol and mRNA expression of glucocorticoid receptor α / β in lymphocyte. *Stress* 18, 29–34. doi:10.3109/10253890.2014.999233 [PubMed: 25518867]
- Yehya N, Vogiatzi MG, Thomas NJ, Srinivasan V, 2016 Cortisol Correlates with Severity of Illness and Poorly Reflects Adrenal Function in Pediatric Acute Respiratory Distress Syndrome. *J. Pediatr* 177, 212–218. doi:10.1016/j.jpeds.2016.05.020 [PubMed: 27283464]

- Young EA, Abelson J, Lightman SL, 2004 Cortisol pulsatility and its role in stress regulation and health. *Front. Neuroendocrinol* 25, 69–76. doi:10.1016/j.yfrne.2004.07.001 [PubMed: 15571755]
- Zahn D, Petrak F, Franke L, Hagele AK, Juckel G, Lederbogen F, Neubauer H, Norra I, Herpertz S, 2015 Cortisol, platelet serotonin content, and platelet activity in patients with major depression and type 2 diabetes: An exploratory investigation. *Psychosom. Med* 77, 145–155. doi:10.1097/PSY.000000000000145 [PubMed: 25626989]
- Zandstra ARE, Hartman CA, Nederhof E, Van den Heuvel ER, Dietrich A, Hoekstra PJ, Ormel J, 2015 Chronic stress and adolescents' mental health: Modifying effects of basal cortisol and parental psychiatric history. The TRAILS study. *J. Abnorm. Child Psychol* 43, 1119–1130. doi:10.1007/s10802-014-9970-x [PubMed: 25617009]
- Zhang S, Shen Z, Hu G, Liu R, Zhang X, 2009 Effects of endogenous glucocorticoids on allergic inflammation and TH1/TH2 balance in airway allergic disease. *Ann. Allergy, Asthma Immunol* 103, 525–534. doi:10.1016/S1081-1206(10)60270-0 [PubMed: 20084847]
- Ziaei S, Frith AL, Ekstrom EC, Naved RT, 2016 Experiencing lifetime domestic violence: Associations with mental health and stress among pregnant women in Rural Bangladesh: The MINIMat randomized trial. *PLoS One* 11, e0168103. doi:10.1371/journal.pone.0168103 [PubMed: 27992478]

HIGHLIGHTS

- We reviewed 100 research articles that compared glucocorticoids to health.
- Specific GC metrics were considered: basal, reactivity, circadian, integrative.
- The most common measure, basal GC, was inconsistently related to health.
- Integrative and reactivity GC measures were most closely associated with health.
- Overall, relationships between GC and health were relatively weak.

Figure 1: PubMed search methods.

All search terms followed the same metric: "glucocorticoids and [outcome]," "cortisol and [outcome]," and "corticosterone and [outcome]". Broad searches included the following outcome terms: disease, disease risk, disease resilience, disease predictor, and health. Given the prevalence of studies incorporating cortisol awakening response, a secondary broad search was conducted and papers were reviewed if found through "cortisol awakening response" in combination with health, predicting health, or disease. Because common diseases emerged as outcomes from these searches, we incorporated more specific searches

to include terms targeting the common health outcomes: survival, fitness, cardiovascular health, cancer, mental health, airway disease, diabetes, and obesity.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 2: Defining relationships between glucocorticoids and health outcomes.

For consistency of interpretation and analysis of all relationships between glucocorticoids (GCs) and health outcomes that are reviewed in this manuscript, we established guidelines to define a positive or negative relationship. Briefly, a ‘positive’ relationship refers to a situation where increased GCs were associated with increased health (whether the GC metric be basal, circadian, reactivity, etc.). A ‘negative’ relationship refers to increased GC levels associated with decreased health. ‘Positive’ and ‘negative’ relationships reported in the review are based on only those relationships that reached statistical significance in the original published studies. For comparisons of GCs to health that did not reach statistical significance in published studies, we reported these results as ‘null’ – i.e. no documented relationship (either positive or negative) between GCs and health.

Table 1:
Summary of study results relating glucocorticoid metrics to health outcomes.

Studies are organized according to specific health outcomes (defined in Results section) and then by GC metric within each health category. A negative relationship indicates that higher GCs are associated with worse health, and a positive relationship indicates that higher GCs are associated with better health. Null relationships indicate no significant association between the GC metric and the health outcome.

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
Mental Health	Pineles et al., 2013	Policemen and firefighters	Basal	Saliva	Development of PTSD and other psychological symptoms after potentially traumatic event	Basal: Positive and Null
Mental Health	Yan et al., 2015	People with suboptimal health status (SHS)	Basal	Blood	Psychosocial stress in work setting	Basal: Negative
Mental Health	Ziaei et al., 2016	Pregnant women who experienced domestic violence	Basal	Saliva	Relationship to domestic violence experience	Basal: Null
Mental Health	Taliaz et al., 2011	Sprague Dawley rats (obtained at 21 days old)	Basal, Reactivity	Blood	CORT following chronic mild stress and hippocampal BDNF knockdown	Basal: Negative, Reactivity: Negative
Mental Health	Zandstra et al., 2015	Adolescents of parents with psychiatric history	Basal, Reactivity	Saliva	Adolescent externalizing and internalizing behavior	Basal: Positive and Null, Reactivity: Null
Mental Health	Wong et al., 2011	Sprague Dawley rats (3 months old)	Basal, GC Treatments	Blood, injection	Postpartum depression	Basal: Negative, GC Treatments: Negative
Mental Health	Lucas-Thompson et al., 2017	Parents with marital conflict and their children	Circadian	Saliva	Relationship with marital conflict and/or adolescent self-blame and internalizing behavior and adjustment problems	Circadian: Positive
Mental Health	Cahn et al., 2017	Yoga retreat participants	Circadian, Reactivity	Saliva	Psychometric and biological outcomes	Circadian: Null, Reactivity: Positive
Mental Health	Day et al., 2014	Ultra-high-risk patients for developing psychosis	Circadian, Reactivity	Saliva	Development of psychosis	Circadian: Null, Reactivity: Positive
Mental Health	Mortensen et al., 2019	Informal caregivers	Circadian, Reactivity	Saliva	Diurnal cortisol pattern	Circadian: Null, Reactivity: Positive
Mental Health	McFarlane et al., 2011	Patients admitted to the hospital following a traumatic event	Circadian, Integrated	Saliva, Urine	PTSD symptom development	Circadian: Positive, Integrated: Null
Mental Health	Hayden et al., 2014	Children of depressed parents	Reactivity	Saliva	Child depression risk and cognitive vulnerability to depression	Reactivity: Negative

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
Mental Health	Mouthaan et al., 2014	Patients hospitalized following a traumatic event	Reactivity	Blood	Development of PTSD symptoms	Reactivity: Positive
Mental Health	Rodriguez et al., 2018	Military persons or veterans with PTSD	Reactivity	Saliva	Effect of service dog on PTSD symptom severity, CAR	Reactivity: Positive and Null
Mental Health	Redfern et al., 2017	Wild largemouth bass	Reactivity, GC Treatments	Whole body, Prenatal	Offspring size, behavior, stress response	Reactivity: Negative, GC Treatments: Negative
Mental Health	Heinze et al., 2016	Young adults with mental health problems	Integrated	Hair	Characterization of mental health	Integrated: Negative
Mental Health	Wells et al., 2014	Patients recruited in Researching Health in Ontario Communities research program	Integrated	Hair	Self-reported measures of stress, anxiety	Integrated: Negative
Mental Health	Cuffe et al., 2017	Male and female C57BL/6 mice	GC Treatments	Prenatal, Adrenal gland	Adrenal size, morphology	GC Treatments: Negative
Mental Health	Khalife et al., 2013	Children and adolescents	GC Treatments	Prenatal	Mental health and behavior (ADHD)	GC Treatments: Negative and Null
Cardiac	Hammer et al., 2016	Systolic heart failure patients	Basal	Saliva	Mortality	Basal: Null and Negative
Cardiac	Said & El-Gohary, 2016	Adult male albino Wistar rats	Basal	Blood	Heart rate, blood pressure, hormone levels	Basal: Negative
Cardiac	Yamaji et al., 2009	Patients with chronic heart failure	Basal	Blood	Cardiac events (sudden death or hospitalization due to chronic heart failure)	Basal: Negative
Cardiac	Toledo-Corral et al., 2013	African American and Latino youth	Basal, Circadian, Reactivity, Integrated	Blood, Saliva, Urine	Carotid artery intima-media thickness	Basal: Positive and Null, Circadian: Positive, Reactivity: Null, Integrated: Negative
Cardiac	Grant et al., 2009	Middle-aged adults experiencing social isolation	Circadian, Reactivity, Integrated	Saliva	Physiological stress response	Circadian: Null, Reactivity: Negative, Integrated: Negative
Cardiac	Ronaldson et al., 2015	Coronary artery bypass graft surgery	Circadian, Integrated	Saliva	Heart-related outcomes	Circadian: Positive, Integrated: Null
Cardiac	Gordon et al., 2016	Peri- and postmenopausal women	Reactivity	Blood	Vasomotor symptoms	Reactivity: Negative and Null
Cardiac	Ito et al., 2004	Patients resuscitated after cardiopulmonary arrest	Reactivity	Blood	Mortality	Reactivity: Positive
Cardiac	Sasser et al., 2012	Neonates who underwent	Reactivity	Blood	Steroid responsiveness	Reactivity: Negative

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
		cardiopulmonary bypass surgery				
Cardiac	Violanti et al., 2018	Cardiovascular disease patients (police officers)	Reactivity	Saliva	CVD progression, as measured by brachial flow-mediated dilation (FMD)	Reactivity: Positive
Cardiac	Pereg et al., 2011	Males hospitalized for acute myocardial infarction	Integrated	Hair	Acute myocardial infarction risk	Integrated: Negative
Cardiac	Cruz-Topete et al., 2016	Male C57BL/6 mice	GC Treatments	Blood	Cardiovascular function	GC Treatments: Positive and Null
Cardiac	Johannesdottir et al., 2013	Patients first diagnosed with deep venous thrombosis or pulmonary embolism	GC Treatments	Medication	Venous thromboembolism	GC Treatments: Negative
Cardiac	Peng et al., 2018	Adult Sprague Dawley rats	GC Treatments	Prenatal	Offspring cardiac function at 12 or 24 weeks old after mothers were treated with DEX	GC Treatments: Negative and Null
Cancer, Disease Progression, and Mortality	Kim et al., 2016	Patients with terminal cancer	Basal	Blood	Mortality	Basal: Negative
Cancer, Disease Progression, and Mortality	Nebiker et al., 2018	Patients with acute pancreatitis	Basal	Blood	Disease severity, organ failure, death	Basal: Negative
Cancer, Disease Progression, and Mortality	Triantos et al., 2014	Patients with liver cirrhosis - with or w/o variceal bleeding	Basal	Blood, Saliva	Mortality	Basal: Negative
Cancer, Disease Progression, and Mortality and Sleep	Chang & Lin, 2017	Lung cancer patients	Circadian	Saliva	Sleep quality, emotion, fatigue	Cancer Circadian: Positive; Sleep Circadian: Positive
Cancer, Disease Progression, and Mortality	Schrepf et al., 2015	Patients with ovarian cancer	Circadian	Saliva	Survival	Circadian: Positive
Cancer, Disease Progression, and Mortality	Kern et al., 2013	Multiple sclerosis patients	Circadian, Reactivity	Saliva	Disease course/ progression (neurological symptoms) relation to cortisol	Circadian: Null, Reactivity: Negative
Cancer, Disease Progression, and Mortality	Sephton et al., 2013	Lung cancer patients	Circadian, Reactivity	Saliva	Mortality	Circadian: Positive, Reactivity: Null
Cancer, Disease Progression, and Mortality	Hoyt et al., 2016	Prostate cancer patients	Circadian, Reactivity, Integrated	Saliva	Sleep quality, depressive symptoms	Circadian: Positive, Reactivity: Null, Integrated: Positive

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
Cancer, Disease Progression, and Mortality	Sephton et al., 2000	Patients with metastatic breast cancer	Circadian, Integrated	Saliva	Mortality	Circadian: Positive, Integrated: Null
Cancer, Disease Progression, and Mortality	Tai et al., 2016	Prostate cancer patients	Integrated	Urine	Stage of cancer	Integrated: Negative
Cancer, Disease Progression, and Mortality	del Rincón et al., 2014	Patients with rheumatoid arthritis	GC Treatments	Medication	Mortality	GC Treatments: Negative
Cancer, Disease Progression, and Mortality	Ishiguro et al., 2014	Urothelial carcinoma cell lines	GC Treatments	Incubation	Bladder cancer growth	GC Treatments: Positive, Negative, and Null
Cancer, Disease Progression, and Mortality	K. T. Lin et al., 2017	Female C57BL/6 mice	GC Treatments	Injection	Ovarian cancer progression	GC Treatments: Positive
Cancer, Disease Progression, and Mortality	Lietzen et al., 2014	Patients diagnosed with breast cancer	GC Treatments	Medication	Breast cancer recurrence	GC Treatments: Null
Cancer, Disease Progression, and Mortality	Ostenfeld et al., 2014	Patients who had surgery for colorectal cancer	GC Treatments	Medication	30-day Mortality	GC Treatments: Negative
Cancer, Disease Progression, and Mortality	Tarr et al., 2017	Patients with systemic lupus erythematosus	GC Treatments	Medication	Chronic organ damage, mortality	GC Treatments: Negative
Diabetes	Anderson et al., 2016	Obese diabetic and nondiabetic men (type 2 diabetes)	Basal	Blood	11 β HSD enzyme function in response to metformin	Basal: Negative and Null
Diabetes	Bellastella et al., 2016	Type 2 diabetes patients	Basal	Blood, Saliva	Determine if cortisol is affected by glycemic oscillations	Basal: Negative and Null
Diabetes	Kuznetsova et al., 2017	Adult male Wistar rats	Basal	Adrenal gland	Compare normo- vs. hyperglycemic rats, mifepristone injections	Basal: Negative
Diabetes and Mental Health	Melin et al., 2017	Type 1 and Type 2 diabetes patients	Basal	Saliva	Relationship between diabetes, depression, anxiety, alexithymia, and cortisol	Mental Health Basal: Negative; Diabetes Basal: Positive and Negative
Diabetes	Sharma et al., 2014	Type 1 diabetes patients	Basal	Blood	ACTH and cortisol levels; ACTH-cortisol dose response behavior	Basal: Positive
Diabetes	Champaneri et al., 2012	Type 2 diabetes patients	Basal, Circadian, Reactivity, Integrated	Saliva	Diurnal cortisol pattern	Basal: Null, Circadian: Positive, Reactivity: Positive, Integrated: Negative

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
						(females) and Positive (males)
Diabetes	Johar et al., 2016	Type 2 diabetes patients	Basal, Reactivity	Saliva	Relationship between diabetes and cortisol	Basal: Negative, Reactivity: Null
Diabetes	Beddow & Samuel, 2012	Goto-Kakizakirat	Basal, Integrated	Blood, Urine	Glucose and cortisol changes, ketoconazole treatment	Basal: Negative, Integrated: Negative
Diabetes	Erickson et al., 2017	C57BL/6 mice, BKS.Cg-Dock7m +/- Leprdb/J mice	Basal, Integrated	Blood, Hair	Relationship of hair cortisol levels to diabetes in mice	Basal: Negative, Integrated: Negative
Diabetes	Makimura et al., 2003	Male C57BL/6 mice	Basal, GC Treatments	Blood, ADX and CORT implant	Impact from fasting, adrenalectomy	Basal: Negative, GC Treatments: Negative and Null
Diabetes	Moon et al., 2014	Type 2 diabetes patients	Basal, GC Treatments	Blood, injections	Glucose and cortisol changes after epidural or shoulder GC injection	Basal: Null, GC Treatments: Positive
Diabetes and Mental Health	Zahn et al., 2015	Type 2 diabetes patients, major depression patients	Circadian, Reactivity	Saliva	Relationship between diabetes, depression, and cortisol	Mental Health Circadian: Null, Reactivity: Positive; Diabetes Circadian: Null, Reactivity: Positive
Diabetes	Bataglini et al., 2016	Adult male albino Swiss mice with type-1 diabetes	GC Treatments	Injection	Impact on the diabetes profile	GC Treatments: Positive
Diabetes	Burke et al., 2017	Male nonobese diabetic mice	GC Treatments	Oral	Immunological and metabolic outcomes	GC Treatments: Negative
Diabetes	Shpilberg et al., 2012	Male Sprague Dawley rats	GC Treatments	Pellet implantation	Diabetes	GC Treatments: Negative
Obesity	Desai et al., 2014	Sprague Dawley rats	Basal	Blood	Offspring metabolic syndrome following maternal obesity	Basal: Positive and Negative
Obesity	Chu et al., 2017	Overweight children	Basal, Integrated	Saliva, Urine	Relationship between weight and cortisol, cortisone	Basal: Negative, Integrated: Negative
Obesity	Wirix et al., 2017	Overweight and obese children with or without hypertension	Basal, Integrated	Saliva, Urine	Determine association between cortisol and hypertension	Basal: Positive, Integrated: Negative
Obesity	Hopkins et al., 2016	Women age 25–45 years	Reactivity	Saliva	Obesity-related behavior (binge eating)	Reactivity: Negative
Obesity	Miller et al., 2018	Adults who had experienced childhood adversity	Reactivity	Saliva	BMI in adulthood	Reactivity: Positive
Obesity	Woods et al., 2015	Obese individuals	Reactivity, Integrated, GC Treatments	Blood, Urine	GC regulation after weight loss surgery	Reactivity: Positive, GC Treatments: Positive, Integrated: Null
Obesity	Jackson et al., 2016	Obese adults	Integrated	Hair	Perceived weight discrimination	Integrated: Negative

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
Obesity	Noppe et al., 2016	Overweight and obese children	Integrated	Hair	BMI, Gene polymorphisms related to obesity	Integrated: Negative and Null
Obesity	Cheng et al., 2016	Obese, overweight, normal humans	GC Treatments	Blood, Incubation	GC-mediated regulation of inflammation, depression	GC Treatments: Positive
Pulmonary	Cui et al., 2010	Brown Norway rats	Basal	Blood	Bronchial asthma, chronic obstructive pulmonary disease	Basal: Positive and Negative
Pulmonary	Yehya et al., 2016	Children with acute respiratory distress syndrome	Basal	Blood	Severity of illness	Basal: Negative
Pulmonary	Zhang et al., 2009	Adult male BALB/c mice	Basal	Blood	Allergic inflammation, metyrapone-RU486 injection	Basal: Positive and Negative
Pulmonary	Ball et al., 2006	Infants of allergic mothers	Circadian, Reactivity	Saliva	Stress response	Circadian: Positive, Reactivity: Negative
Pulmonary	Rosenkranz et al., 2016	Adults with asthma	Reactivity	Saliva	Response to stress	Reactivity: Negative
Pulmonary	Lim et al., 2014	BALB/c mice	Reactivity, GC Treatments	Blood, Prenatal	Allergic inflammation	Reactivity: Negative, GC Treatments: Negative
Pulmonary	Contoli et al., 2017	Patients with chronic obstructive pulmonary disease	GC Treatments	Inhaled corticosteroids plus long-acting beta-2 agonist	Sputum bacteria, clinical outcomes	GC Treatments: Positive and Negative
Pulmonary	Ferguson et al., 2017	Patients with chronic obstructive pulmonary disease	GC Treatments	Inhaled corticosteroids plus long-acting beta-2 agonist	Annual rate of COPD exacerbations	GC Treatments: Positive
Sleep	Chopra et al., 2017	Obstructive sleep apnea patients	Circadian	Blood	Metabolism, Sleep	Circadian: Negative
Sleep	J. Lin et al., 2017	Postural tachycardia syndrome patients - children	Circadian, Reactivity	Saliva	Sleep quality	Circadian: Negative, Reactivity: Negative
Sleep	Fekedulgen et al., 2018	Policemen	Reactivity	Saliva	Sleep quality, leisure time physical activity	Reactivity: Positive
Sleep	Song et al., 2015	Military servicemen	Reactivity	Blood	Mental health	Reactivity: Negative
Fitness	Eikenaar et al., 2017	Northern wheatear (bird)	Basal	Blood	Migration pattern	Basal: Positive
Fitness	Furtado et al., 2016	Elderly patients in long-stay institutions	Basal	Saliva	Falling, physical fitness	Basal: Positive
Fitness	Gammel et al., 2018	Adult female Sprague Dawley rats	Basal	Blood	Breeding success	Basal: Positive

Section	Article	Subjects	Cortisol/ CORT Metric	Sample Media	Health Measure	Relationship between Cortisol/CORT and Health Measure
Fitness	Henderson et al., 2017	Free-living blue tit (bird)	Basal	Blood	Reproductive success	Basal: Positive and Negative
Fitness and Mental Health	Moraes et al., 2016	Elderly	Basal	Saliva	Physical capacity and depression interaction	Mental health Basal: Positive; Fitness Basal: Positive
Fitness	Franceschini et al., 2017	Common loon (Gavia immer)	Basal, Reactivity	Blood	Adults, Offspring mercury toxicity	Basal: Null, Reactivity: Negative
Fitness	Girbovan et al., 2016	Adult male Wistar rats with ischemia surgery	Basal, Reactivity	Blood	Ischemia, Neurogenesis in hippocampus, Resveratrol treatment	Basal: Negative, Reactivity: Positive
Fitness	Pulopulos et al., 2016	Elderly	Basal, Reactivity	Saliva	Walking speed/ physical performance	Basal: Null, Reactivity: Positive
Fitness	Vitousek et al., 2014	Barn swallow (bird)	Basal, Reactivity	Blood	Reproductive success, nest care	Basal: Negative, Reactivity: Negative
Fitness	Martinez-Claros et al., 2013	Male Wistar rats	Basal, GC Treatments	Blood, CORT pellet implant	Apical dendrite length	Basal: Positive, GC Treatments: Positive
Fitness	Spée et al., 2011	Adelie penguins	Basal, GC Treatments	Blood, pellet implantation	Nest abandonment	Basal: Negative, GC Treatments: Negative
Fitness	Holanda et al., 2012	Elderly patients in long-stay institutions	Circadian, Integrated	Saliva	Frailty	Circadian: Null, Integrated: Negative
Fitness	Rakotonia in et al., 2017	Mouse lemur (Microcebus murinus)	Integrated	Hair	Survival	Integrated: Negative
Fitness	Chetty et al., 2014	Adult male Sprague Dawley rats	GC Treatments	Injection	Oligodendrocyte maturation in hippocampus	GC Treatments: Positive
Fitness	Strange et al., 2016	House wren (songbird)	GC Treatments	Prenatal	Offspring size	GC Treatments: Negative

Table 2:

Summary of GC metric and health outcome relationships.

The table summarizes relationships between specific GC metrics and health outcome. Within each metric, we note the number of positive, negative, and null relationships reported for each health outcome, and the total number of studies that used the metric. A positive relationship is one in which elevated GC levels were associated with increased health, and a negative relationship is one in which elevated GC levels were associated with decreased health. The last row of the table indicates the percentage of studies that showed positive, negative, and null results within each health categories. The final two sets of columns indicate the total numbers of positive, negative, and null relationships reported in each health outcome across all metrics (as numerical count and as percentages). In the “Relationship Totals by Health Area (Percentage)”, the “Total” column indicates the percentage of relationships reported within each health outcome as a function of total number of relationships analyzed.

Health Area	Basal Relationships				Circadian Relationships				Reactivity Relationships				Integrated Relationships				Exogenous GCs Relationships				Relationship Totals by Health Area			
	Positive	Negative	Null	Total	Positive	Negative	Null	Total	Positive	Negative	Null	Total	Positive	Negative	Null	Total	Positive	Negative	Null	Total	Positive	Negative	Null	Total
Mental Health	3	4	3	10	2	0	4	6	6	3	2	11	0	2	1	3	0	4	1	5	11	13	11	35
Cardiovascular Health	1	3	2	6	2	0	1	3	2	3	2	7	0	3	1	4	1	2	2	5	6	11	8	25
Cancer Disease Progression, and Mortality	0	3	0	3	5	0	1	6	0	1	2	3	1	1	1	3	2	4	2	8	8	9	6	23
Diabetes	2	8	4	14	1	0	1	2	2	0	1	3	1	3	0	4	2	3	1	6	8	14	7	29
Obesity	2	2	0	4	0	0	0	0	2	1	0	3	0	4	2	6	2	0	0	2	6	7	2	15
Pulmonary Health	2	3	0	5	1	0	0	1	0	3	0	3	0	0	0	0	2	2	0	4	5	8	0	13
Sleep and Health	0	0	0	0	1	2	0	3	1	2	0	3	0	0	0	0	0	0	0	0	2	4	0	6
Fitness	6	4	2	12	0	0	1	1	2	2	0	4	0	2	0	2	2	2	0	4	10	10	3	23
Overall Relationship Totals	16	27	11	54	12	2	8	22	15	15	7	37	2	15	5	22	11	17	6	34	56	76	37	169
	29.6%	50.0%	20.4%	32.0%	54.5%	9.1%	36.4%	13.0%	40.5%	40.5%	18.9%	21.9%	9.1%	68.2%	22.7%	13.0%	32.4%	50.0%	17.6%	20.1%	33.1%	45.0%	21.9%	100.0%