



## Review

# Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: A systematic review



Angela C. Incollingo Rodriguez<sup>a</sup>, Elissa S. Epel<sup>b</sup>, Megan L. White<sup>a</sup>, Erin C. Standen<sup>a</sup>, Jonathan R. Seckl<sup>c</sup>, A. Janet Tomiyama<sup>a,\*</sup>

<sup>a</sup> University of California, Los Angeles, CA 90095, USA

<sup>b</sup> University of California, San Francisco, CA 94118, USA

<sup>c</sup> University of Edinburgh, Edinburgh EH1 1HT, Scotland, United Kingdom

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## ABSTRACT

**Background:** Although there is substantial evidence of differential hypothalamic-pituitary-adrenal (HPA) axis activity in both generalized and abdominal obesity, consistent trends in obesity-related HPA axis perturbations have yet to be identified.

**Objectives:** To systematically review the existing literature on HPA activity in obesity, identify possible explanations for inconsistencies in the literature, and suggest methodological improvements for future study.

**Data sources:** Included papers used Pubmed, Google Scholar, and the University of California Library search engines with search terms body mass index (BMI), waist-to-hip ratio (WHR), waist circumference, sagittal diameter, abdominal versus peripheral body fat distribution, body fat percentage, DEXA, abdominal obesity, and cortisol with terms awakening response, slope, total daily output, reactivity, feedback sensitivity, long-term output, and 11 $\beta$ -HSD expression.

**Study eligibility criteria:** Empirical research papers were eligible provided that they included at least one type of obesity (general or abdominal), measured at least one relevant cortisol parameter, and a priori tested for a relationship between obesity and cortisol.

**Results:** A general pattern of findings emerged where greater abdominal fat is associated with greater responsivity of the HPA axis, reflected in morning awakening and acute stress reactivity, but some studies did show underresponsiveness. When examined in adipocytes, there is a clear upregulation of cortisol output (due to greater expression of 11 $\beta$ -HSD1), but in hepatic tissue this cortisol is downregulated. Overall obesity (BMI) appears to also be related to a hyperresponsive HPA axis in many but not all studies, such as when acute reactivity is examined.

**Limitations:** The reviewed literature contains numerous inconsistencies and contradictions in research methodologies, sample characteristics, and results, which partially precluded the development of clear and reliable patterns of dysregulation in each investigated cortisol parameter.

**Conclusions and implications:** The literature to date is inconclusive, which may well arise from differential effects of generalized obesity vs. abdominal obesity or from modulators such as sex, sex hormones, and chronic stress. While the relationship between obesity and adipocyte cortisol seems to be clear, further research is warranted to understand how adipocyte cortisol metabolism influences circulating cortisol levels and to establish consistent patterns of perturbations in adrenal cortisol activity in both generalized and abdominal obesity.

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\* Corresponding author at: Department of Psychology, University of California, Los Angeles, 502 Portola Plaza, Los Angeles, CA 90095, USA.

E-mail address: [tomiyama@psych.ucla.edu](mailto:tomiyama@psych.ucla.edu) (A.J. Tomiyama).

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## 1. Introduction

### 1.1. Rationale

In an age where obesity has reached epidemic levels and is implicated in several of the leading causes of death in the United States (Ogden et al., 2014), it is essential to understand the physiological correlates, predictors, and consequences of obesity. This systematic review examines the relationship between obesity and perturbations of the hypothalamic-pituitary-adrenal (HPA) axis. Understanding these perturbations in obesity is particularly important given that dysregulation of the HPA axis is a risk factor for physical health conditions such as cardiovascular disease, insulin resistance and type 2 diabetes, stroke, and Cushing's syndrome (Pasquali et al., 2006; Rosmond and Bjorntorp, 2001), as well as mental health conditions such as depression and cognitive impairment (Hinkelmann et al., 2009; Reppermund et al., 2007). Additionally, in both human and animal models, cortisol has been causally demonstrated to promote the accumulation of fat cells and weight gain (Bjorntorp and Rosmond, 2000; Bjorntorp, 2001), implicating HPA axis functioning in the etiology of obesity. The literature, however, is inconsistent at best in terms of how the HPA axis is dysregulated in obesity. This gap precludes a comprehensive understanding of the pathophysiology of obesity. Furthermore, because it is unclear whether obesity contributes to HPA dysregulation or vice versa, it is difficult to identify appropriate intervention targets, thus hindering the development of effective treatments.

### 1.2. Cortisol background: measurement, stress-related weight gain, and adipocyte biology

To aid in the reading of this review, we first briefly summarize the broader relationships among stress, cortisol, adipocyte biology,

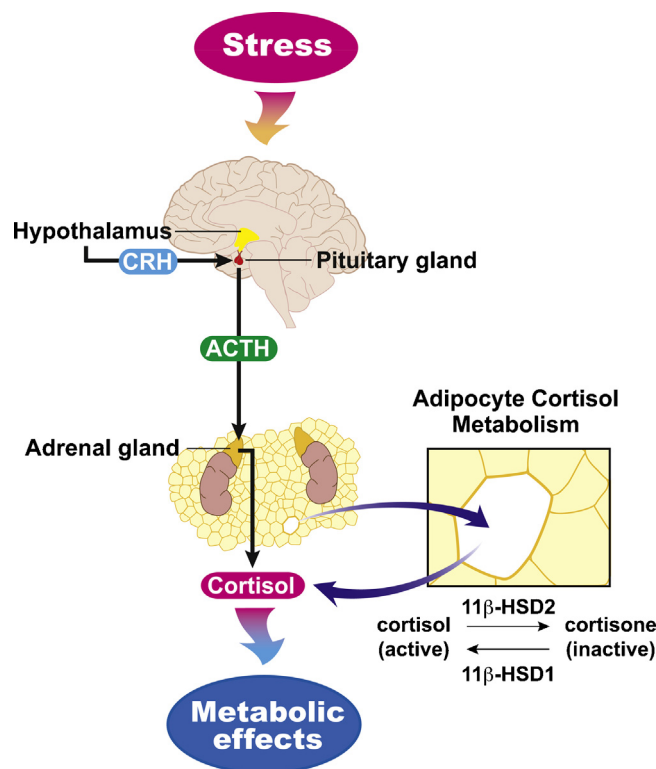


Fig. 1. Adipocyte cortisol metabolism in the context of HPA axis activity.

and weight gain (see Fig. 1). Fluctuations in cortisol concentrations occur according to a natural diurnal pattern as well as in response to both physiological and psychological stressors. Stress-related

HPA activation begins in the hypothalamus, with the release of corticotrophin-releasing hormone. This stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which in turn circulates through the bloodstream to the adrenal cortex, signaling the adrenal glands to secrete the hormone cortisol (Kyrou and Tsigos, 2009). Circulating cortisol can then be measured through saliva, blood (serum or plasma), or urine. Although plasma has been the “gold standard” for measuring cortisol in biological research, each of these three methods have been broadly and reliably used to measure cortisol concentrations (Kirschbaum and Hellhammer, 1994; Vining et al., 1983; Zumoff et al., 1974). When considering total cortisol output, salivary or urinary measurements may in fact be the better indices as they index free cortisol rather than bound cortisol (Yehuda et al., 2003). However, salivary and urinary cortisol are different measures and do not always correlate. This may be because urinary cortisol reflects total cortisol secreted whereas salivary cortisol reflects free cortisol already filtered from plasma, thus already accounting for clearance. Finally, while these methods index patterns of daily cortisol concentrations, hair can be used to measure long-term systemic cortisol output and has been shown to correlate with 24-h urinary free cortisol (UFC; Sauv e et al., 2007).

As psychological and physiological stressors can trigger cortisol secretion, both have implications for weight gain and obesity. Chronic psychological life stress, for example, has been linked to weight gain, especially in men (Torres and Nowson, 2007). In a meta-analysis of 13 studies including over 160,000 workers, job strain was found to be positively related to body mass index (BMI) both cross-sectionally and longitudinally (Nyberg et al., 2012). This is particularly relevant to obesity, as recent findings show that that obese individuals tended to report higher perceived stress (Abraham et al., 2013). Physiologically, increased cortisol concentrations have been causally linked to fat accumulation and weight gain, as glucocorticoids promote conversion of preadipocytes to mature adipocytes (for a review, see Peckett et al., 2011). In rodent models, male Sprague–Dawley rats that were stressed for 28 days showed significantly larger adipocytes than controls and had a tendency to display a heavier abdominal fat pad (Rebuff e-Scrive et al., 1992). This relationship is also echoed in human literature, as a large subset of findings have evidenced the relationship between stress and weight gain via elevated cortisol levels (e.g., Bj ornorp and Rosmond, 2000; Bj ornorp et al., 2000; Bj ornorp, 2001; Peeke and Chrousos, 1995; Wallerius et al., 2003). We do note, however, that cortisol’s role in fat physiology is very complex, and it does have other functions such as regulating lipolytic enzymes (Ottosson et al., 2000) and enhancing lipolysis and triglyceride uptake (Bj ornorp, 1996), thereby potentially causing weight loss in some instances. Cortisol also drives insulin resistance (Andrews and Walker, 1999) via proliferation of adipokines and the secretion of proinflammatory cytokines (Antuna-Puente et al., 2008). Effects may in fact be depot-specific. Cushing’s syndrome patients typically show truncal and visceral adipose depot gain, but peripheral (limb) adipose tissue depletion. Overall, though, it is clear that stress-related cortisol concentrations play a significant role in adipocyte biology and weight gain, potentially implicating it as a key component in the development of obesity. This review, therefore, endeavors to provide a more comprehensive understanding of cortisol activity and obesity in terms of perturbations in HPA axis activity.

### 1.3. Objectives

This review has three overarching aims: (1) To provide a systematic review of the existing literature regarding HPA dysregulation and obesity. (2) To identify explanations for inconsistencies in the existing literature. (3) To suggest potential methodological

improvements for future research directions to resolve discrepancies and achieve a definitive mechanistic understanding in this area.

### 1.4. Considerations

In systematically reviewing the existing research on obesity and HPA axis activity, we make two important distinctions in our categorization of the literature:

#### 1.4.1. General cortisol activity and adipocyte cortisol metabolism

We review cortisol activity and metabolism stemming both from the adrenal glands and from adipocyte metabolic sources, such as abdominal and subcutaneous adipose tissue and liver tissue (Fig. 1). Empirical evidence suggests that adipocyte cortisol metabolism may be a special case of cortisol dysregulation in obesity (Livingstone et al., 2000; Ljung et al., 2002, 1996), and we examine the possibility that dysregulated adipocyte cortisol metabolism may relate to HPA dysregulation. General cortisol activity measurements include salivary, blood, urinary, and hair cortisol. These are used to assess cortisol parameters including the cortisol awakening response (CAR), total daily output, diurnal slope, reactivity, feedback sensitivity, and long-term output. Adipocyte cortisol metabolism is best indexed through measures of 11- $\beta$ -hydroxysteroid dehydrogenases (11 $\beta$ -HSD1 and 2) from biopsied fat tissue.

#### 1.4.2. Anthropometric indices and sample considerations

The literature is highly varied regarding the anthropometric composition of study samples. For example, although obesity and adiposity are often linked, it is possible to concurrently have an obese body mass index (BMI; weight [kg]/height<sup>2</sup>[m]) and low abdominal obesity, or vice versa, a normal BMI and high abdominal obesity (Epel et al., 2001). Therefore, we consider two anthropometric types of obesity: generalized obesity, indexed crudely by BMI, and abdominal obesity and adiposity, indexed by measures such as waist-to-hip ratio (WHR; the ratio of the minimum circumference value between the iliac crest and the lateral costal margin or the circumference at the umbilicus to the maximum circumference value over the buttocks), waist circumference, and sagittal diameter (an index of visceral obesity measured as the distance from the small of the back to the front of the body). Larger WHR, waist circumference, and sagittal diameter measurements indicate more abdominal obesity; a WHR > 1 is usually indicative of abdominal obesity. Unfortunately, much of the literature includes only one type of obesity or includes both types but does not analyze them independently. Rather, these two types of obesity are often used interchangeably. Accordingly, we discuss which types of obesity were considered in the literature we review here and how they were measured and analyzed. Hereafter, when describing sample characteristics, we use the terms “obese” and “generalized obesity” to refer to BMI > 30, and we use measure-specific terminology to indicate abdominal obesity (i.e. WHR, waist circumference, etc.).

## 2. Methods

### 2.1. Search strategy, and inclusion/exclusion criteria

We conducted the present systematic review in accordance with the PRISMA guidelines (Moher, 2009) except where not applicable or not feasible. From January 2014 through May 2015, using Google Scholar, Pubmed, and the University of California Libraries catalog, we conducted a comprehensive search for studies meeting the following inclusion criteria: (1) at least one relevant measure of either generalized or abdominal obesity (BMI, WHR,

waist circumference, sagittal diameter, abdominal versus peripheral body fat distribution, body fat percentage, and abdominal obesity), and (2) at least one of the following cortisol parameters: cortisol awakening response, slope, total daily output, reactivity, feedback sensitivity, long-term output, 11 $\beta$ -HSD expression. Original research papers were considered eligible provided that they included one of the above-mentioned general or abdominal obesity measures, measured one or more of the above-mentioned cortisol parameters, and, importantly, that they a priori tested for a relationship between any type of obesity and at least one cortisol parameter. Papers were excluded if their focal purpose was to examine non obesity-related special populations (cancer patients, HIV+ individuals, etc.) or if they examined obesity and cortisol in a post-hoc manner.

## 2.2. Data extraction and evaluation procedure

To avoid the risk of selective reporting bias during the initial search process, trained research staff conducted blind literature reviews using the above search methods without any information as to the objectives of the present review (see sample search strings in [Appendix A](#)). They first examined paper titles, then abstracts, and then recorded citations. Two members of the study team then verified the eligibility of each recorded citation and extracted the following information from each article deemed eligible: study design, sample size, weight groups, sample sex, sample age, sample ethnicity, obesity type and measures, cortisol parameters, specimen(s) collected, sampling method, assay type, control variables, and results (see flow diagram in [Fig. 2](#)). In the case of discrepancies, the first and last author adjudicated the disagreement. Extraction of study characteristics and findings occurred prior to the authors writing this analysis, and more importantly, before attempting to determine patterns in the literature. After all information was extracted, we then described significant findings (or lack of significant findings) from each research article in the body of the review. We then adapted the GRADE guidelines (see [Guyatt et al., 2011](#)) to rate the overall strength of the evidence reviewed for each cortisol parameter. The original GRADE guidelines were developed in the context of evaluating research designs that include randomized, controlled trials. Given that it is difficult or impossible to randomly assign either obesity or HPA dysregulation, using traditional GRADE guidelines would have rendered most of the research reviewed here as “low” in quality. This would have limited any useful distinctions among the research reviewed. To maximize variability in GRADE ratings, therefore, we assign observational evidence an initial rating of “moderate” and use GRADE criteria to move ratings up or down from this initial rating ([Guyatt et al., 2011](#)).

## 3. Results

The following review of the existing literature’s findings comes from 34 empirical research papers (see [Table 1](#)). For each cortisol parameter, we begin with a brief overview. We then report our findings by first categorizing cortisol parameters of general cortisol activity, and then turning to a discussion of adipocyte cortisol metabolism. When appropriate, we cite animal studies as background for human studies. [Table 2](#) summarizes methodological features of each study.

### 3.1. General cortisol activity

Cortisol secretion and subsequent fluctuations in cortisol concentrations occur through activation of the HPA axis, which eventually leads to adrenal secretion of cortisol. Activity in the HPA axis is typically indicative of a stress response or diurnal rhythmicity, although we do note that factors such as light exposure and food

consumption can also lead to cortisol secretion ([Rosmond et al., 2000](#); [Scheer and Buijs, 1999](#)). There are several parameters used as indices of cortisol activity, which we review next: cortisol awakening response, diurnal cortisol slope, total daily output, reactivity, feedback sensitivity, and long-term output.

#### 3.1.1. Cortisol awakening response (CAR)

The cortisol awakening response (CAR) is the spike in salivary cortisol concentrations exhibited just after waking ([Pruessner et al., 2003](#)). Irregularities in this awakening response occur in the form of a blunted response or an exaggerated response. These two perturbations are perhaps the greatest indication of HPA axis dysregulation and are associated with various mental and physical health ailments ([Björntorp and Rosmond, 2000](#); [Fries et al., 2009](#)). CAR has also been shown to be related to life stress, where chronically stressed individuals demonstrate a greater CAR ([Schulz et al., 1998](#)). We review here 10 studies that have examined CAR and either type of obesity.

Of those, 5 studies have found a negative relationship between generalized obesity and/or abdominal obesity and CAR. For example, one study of middle-aged men found that morning cortisol concentrations were inversely related to WHR ([Ljung et al., 1996](#)). Another study in a large sample ( $n=1002$ ) of men and women found that BMI and waist circumference were negatively correlated with CAR ([Champaneri et al., 2013](#)). In a female sample, obese women showed a more blunted CAR than non-obese women ([Ranjit et al., 2005](#)). In a sample of insulin resistant adolescents, a similar relationship emerged wherein higher BMI was associated with a smaller CAR ([Ursache et al., 2012](#)). Finally, a slightly different result emerged in a sample of obese women, where those with an abdominal body fat distribution (WHR > 0.85) had a similar CAR as those with a peripheral body fat distribution (WHR < 0.85). However, the actual salivary cortisol values were significantly lower at each time point among those with an abdominal body fat distribution ([Duclos et al., 2005](#)).

Conversely, 3 studies found evidence in support of the opposite perturbation in CAR – an exaggerated response. One study, for example, found that CAR correlated positively with BMI, WHR, and sagittal diameter in men ([Wallerius et al., 2003](#)). In another study of men and women, WHR was again positively related to CAR in men, but not in women, and BMI was in fact unrelated to any cortisol parameters ([Steptoe et al., 2004](#)). Another study compared lean, obese, and formerly obese individuals, examining both generalized and abdominal obesity measures, and found that men with an elevated waist circumference and BMI demonstrated significantly higher cortisol concentrations after awakening both in absolute levels and relative to initial levels ([Therrien et al., 2007](#)). Among women in this sample, this relationship did not exist. Interestingly, women who had formerly been obese (BMI > 30) actually exhibited a significantly greater CAR than both lean and obese women, suggesting that weight loss itself may not be sufficient to affect excessive cortisol concentrations in response to awakening.

Finally, 2 studies found obesity and CAR to be unrelated. For instance, one study found that in a sample of obese men, no statistically significant relationships emerged between BMI and any trend in morning cortisol levels ([Filipovský et al., 1996](#)). Another study with a large sample of men and women however reported slightly different results, where both abdominal obesity (via waist circumference) and generalized obesity were associated with lower waking cortisol, but not with CAR ([Kumari et al., 2010](#)).

Given that the evidence here comes exclusively from cross-sectional studies and that there is considerable inconsistency in the findings, the GRADE rating of the quality of this evidence would be “low.” Whereas there is some evidence of a relationship between abdominal obesity and an exaggerated CAR, such a relationship has been observed only in men. When relationships emerge with

**Table 1**  
Included research studies and their characteristics.

Citation	Design	Sample size	Weight groups	Sex	Age (SD) [range]	Race/country of origin
Human studies						
Abraham et al. (2013)	Cross-sectional	429	Normal weight, overweight, obese	Overweight or obese (27.6% male); healthy (50% male)	Males: 50 [49–51]; females: 48 [36–60]	Overweight and obese sample: 82.7% White; healthy sample: 68% White
Champaneri et al. (2013)	Cross-Sectional	1002	Normal weight, overweight, obese (BMI 30.00–40.00), morbidly obese (BMI > 40.00)	47.44% Male	65 (9.8) [45–84]	White, Hispanic, Black
Desbriere et al. (2006)	Cross-sectional	22	Normal weight, obese	Female sample	36.19 [23–50]	Sample from Helsinki, Finland
Duclos et al. (2005)	Cross-sectional	53	Obese (BMI > 27.00) abdominal body fat distribution (WHR > 0.85); peripheral body fat distribution (WHR < 0.85)	Female sample	34.67 [18–51]	Not provided
Engeli et al. (2004)	Cross-sectional	70	3 BMI tertiles: 23.40 ± 2.00; 28.40 ± 2.60; 35.10 ± 4.60	Female sample	57	White
Epel et al. (2000)	Cross-sectional	59	Lean/high WHR (BMI < 24 and WHR ≥ 0.79); lean/low WHR (BMI < 24.00 and WHR ≤ 0.75); overweight/high WHR (BMI > 24.00, WHR ≥ 0.79), overweight/low WHR (BMI > 24.00, WHR ≤ 0.75)	Female sample	36 [30–46]	White
Filipovsky et al. (1996)	Cross-sectional	1528	3 BMI tertiles: 16.80–24.49; 24.50–27.09; 27.10–42.10	Male sample	47.1 (1.9) [40–53]	Sample from Paris, France
Jessop et al. (2001)	Cross-sectional	14	Normal weight, obese	Male sample	[20–50]	White
Kannisto et al. (2004)	Cross-sectional	34	Normal weight, obese	52.94% Male	[24–27]	Sample of monozygotic twins from Finland
Kumari et al. (2010)	Cross-sectional	3956	Underweight (BMI < 20.00), normal weight (BMI 20.00–24.99), overweight, obese	73.69% Male	[50–74]	Sample from London, England
Ljung et al. (1996)	Cross-sectional	22	Normal weight, obese; WHR < 1.0, WHR > 1.0	Male sample	[40–60]	Sample from Goteborg, Sweden
Ljung et al. (2002)	Cross-sectional	10	High WHR (> 1.0), low WHR (< 1.0)	Male sample	51.5 [46–60]	Sample from Goteborg, Sweden
Mårin et al. (1992)	Cross-sectional	87	Obese, 2 groups (WHR 0.93 ± 0.01 v. 0.77 ± 0.03; BMI 30.50 ± 1.20 v. 31.10 ± 1.10)	Female sample	<45	Sample from Goteborg, Sweden
Mariniello et al. (2006)	Cross-sectional	24	Normal weight, obese	29.17% Male	43.5	Not provided
Muñoz et al. (2009)	Cross-sectional	32	Morbidly obese (male: BMI 37.20 ± 3.20, WC 113 ± 8 cm; female: BMI 36.60 ± 3.60; WC 113 ± 14 cm)	34.4% Male	Male: 46 [30–62]; female: 44 [32–56]	Sample from Santiago, Chile
Pasquali et al. (2002)	Cross-sectional	121	Normal weight, obese	40.5% Male	36 [18–65]	Sample from Italy

Table 1 (Continued)

Citation	Design	Sample size	Weight groups	Sex	Age (SD) [range]	Race/country of origin
<a href="#">Paulmyer-Lacroix et al. (2002)</a>	Cross-sectional	30	Normal weight, obese	10% Male	41 [29–53]	Sample from Helsinki, Finland
<a href="#">Paulsen et al. (2007)</a>	Cross-sectional	37	Normal weight, obese	46% Male	Male 39 [30–48]; female 36 [29–43]	Not provided
<a href="#">Purnell et al. (2004)</a>	Cross-sectional	54	Mean BMI: 32.00 [19–64]	44% Male	[19–70]	Not provided
<a href="#">Ranjit et al. (2005)</a>	Cross-sectional	188	Non-obese, obese	Female sample	33.5 [18–54]	Black, White
<a href="#">Rask et al. (2001)</a>	Cross-sectional	34	Obese, lean	Male sample	49.43	Sample from Northern Sweden
<a href="#">Rask et al. (2002)</a>	Cross-sectional	40	Normal, overweight, obese	Female sample	54.44	Sample from Northern Sweden
<a href="#">Rosmond et al. (1998)</a>	Cross-sectional	284	3 WHR tertiles: low ( $\leq 0.89$ ), medium (0.94–0.96), high ( $\geq 1.01$ )	Male sample	51	Sample from Goteborg, Sweden
<a href="#">Sandeep et al. (2005)</a>	Cross-sectional	12	Normal weight, obese	Male sample	[20–50]	Sample from Edinburgh, UK
<a href="#">Stadler and Kirschbaum (2012)</a>	Cross-sectional	155	Mean BMI: 22.20 (3.40) [16.50–35.80] Mean BMI: 24.00 (4.90) [16.90–42.10]	26.45% Male 32.76% Male	24.1 (4.2) [18–46]; 30.5 (12.1) [20–70]	Sample from Dresden, Germany
<a href="#">Steptoe et al. (2004)</a>	Cross-sectional	172	Average WHR: male ( $0.91 \pm 0.07$ ) female ( $0.80 \pm 0.11$ ); average BMI: male ( $25.60 \pm 3.30$ ) female ( $25.40 \pm 4.00$ )	51.74% Male	52.2 [47–59]	Sample from London, England
<a href="#">Stewart et al. (1999)</a>	Cross-sectional	36	Normal weight, overweight, obese	50% Male	31.63 [23–44]	Sample from Birmingham, UK
<a href="#">Therrien et al. (2007)</a>	Cross-Sectional	82	Lean (BMI < 27.00, WC < 100 cm for men and < 90 cm for women), abdominally obese (BMI 30.00–35.00, WC > 100 cm for men and < 100 cm for women), reduced obese (BMI > 30.00, WC > 100 cm for men and < 100 cm for women before weight loss, minimal weight loss of 5 kg, still losing weight or just stabilized)	62.2% Male	[23–51]	Sample from Quebec, Canada
<a href="#">Travison et al. (2007)</a>	Cross-sectional, longitudinal	999	Non-obese, obese	Male sample	62.6 (8.3) [40–79]	Not provided
<a href="#">Ursache et al. (2012)</a>	Cross-sectional	53	Normal weight, obese	21% Male	17.81	Not provided
<a href="#">Vicennati and Pasquali (2000)</a>	Cross-sectional	46	Obese: abdominal fat distribution (BMI $42.10 \pm 6.30$ , WHR $0.92 \pm 0.07$ ), peripheral fat distribution (BMI $33.80 \pm 3.30$ , WHR $0.78 \pm 0.06$ ); normal: (BMI $21.60 \pm 2.00$ , WHR $0.72 \pm 0.04$ )	Female sample	Obese (abdominally: 30 [24–36], peripherally: 29 [22–36]), normal: 25 [21–30]	Sample from Bologna, Italy
<a href="#">Wake et al. (2003)</a>	Cross-sectional	32	Males: BMI $26.50 \pm 0.80$ , WHR $0.94 \pm 0.01$ ; females: BMI $25.30 \pm 0.90$ , WHR $0.87 \pm 0.02$	50% Male	55	White
<a href="#">Wallerius et al. (2003)</a>	Cross-sectional	28	Mean BMI: 26.40, mean WHR: 0.96, mean sagittal diameter: 22.10 cm	Male sample	53	Sample from Goteborg, Sweden
<a href="#">Wester et al. (2014)</a>	Cross-sectional	175	Normal weight, overweight, obese	43% Male	37 [18–68]	Sample from Helsinki, Netherlands

Note: BMI = body mass index ( $\text{kg}/\text{m}^2$ ); cm = centimeter; kg = kilogram; SD = standard deviation; UK = United Kingdom; WC = waist circumference; WHR = waist-to-hip ratio. Unless otherwise specified, normal weight = BMI 18.50–24.99; overweight = BMI 25.00–29.99; obese = BMI  $\geq 30.00$ .

**Table 2**  
Methodological characteristics of included studies.

Citation	Obesity type and measures	Cortisol parameters	Specimen type	Sampling method	Assay type	Control variables
Abraham et al. (2013)	BMI, WC	Total daily output, diurnal cortisol slope, cortisol feedback sensitivity	Urine, saliva, blood serum	24 h UFC, bedtime salivary cortisol, 1 mg dex suppression test	RIA, tandem mass spectrometry, LC-MS/MS	Age, SES, smoking status, alcohol consumption, waking time
Champaneri et al. (2013)	BMI, WC	CAR, total daily output	Saliva	Diurnal salivary cortisol sampling, 6 times/d for 3 d: awakening, +30 m, 1000 h, 1200 h (or before lunch), 1800 h (or before dinner, whichever was earlier), bedtime	CLIA (duplicated)	Age, ethnicity, sex, diabetes status, SES, $\beta$ -blockers, steroids, hormone replacement therapy, smoking status
Desbriere et al. (2006)	BMI, WC, sagittal diameter, SAT/VAT, body fat % (bioelectrical impedance)	ACM (11 $\beta$ -HSD)	Tissue biopsy	Abdominal superficial SAT biopsies taken 1 m after the beginning of a laparotomy (four controls and three obese patients) or a laparoscopy, between 0900 h and 1400 h; paired VAT biopsies obtained 5–10 m later	RT-PCR	Not provided
Duclos et al. (2005)	WHR, BMI, body fat% (DEXA)	CAR, total daily output, cortisol reactivity, cortisol feedback sensitivity	Saliva, urine, blood serum, blood plasma	CAR: Waking, +30 m, +1 h; total output: 24 h UFC; cortisol reactivity: saliva every 30 m from 1000 h to 1300 h; dex: 0.25 mg administered at 2300 h; blood: 0800 h morning after dex administration	Plasma cortisol: RIA; saliva: assayed in human dosteroidated serum (duplicated); urine: CORT-CT2 radioimmunoassay; dex: high-performance liquid chromatography	Not provided
Engeli et al. (2004)	WC, BMI, body fat% (bioelectrical impedance)	ACM (11 $\beta$ -HSD)	Abdominal SAT, blood plasma, urine	Periumbilical SAT obtained by needle biopsy – adipocytes stimulated for 0, 8, 16, 24, or 48 h with either 1 $\mu$ M 17- $\beta$ -estradiol, 1 $\mu$ M 3, 3', 5-triiodo-L-thyronine, 10 $\mu$ M angiotensin II, 10 $\mu$ M pioglitazone, or 100 $\mu$ M cortisol; blood samples obtained at 0900 h after overnight fast, 24 h UFC	Adipose tissue: RT-PCR; blood plasma: RIA (duplicated); urine: liquid chromatography (duplicated)	Not provided
Epel et al. (2000)	WHR, BMI, body fat% (Futrex-5000 body fat computer)	Cortisol reactivity	Saliva	Samples taken each session at 15, 30, 45, 60, 70, 90, 120, and 150 m	RIA (duplicated)	Rest-day cortisol AUC
Filipovsky et al. (1996)	BMI	CAR, diurnal cortisol slope	Blood plasma	Obtained during morning, fasting state	RIA	Age, smoking level, alcohol consumption
Jessop et al. (2001)	BMI	Cortisol feedback sensitivity (hydrocortisone)	Blood plasma	3 IV infusions of 7.5 mg or 15 mg hydrocortisone administered over 24 h on 3 separate days (at least 1 w apart) at 2100 h. After 11 h of hydrocortisone infusion, blood samples of 4 ml taken every 30 m over 12 h	RIA	Age, race, no cardiovascular disorders, history of epilepsy, anemia, or renal dysfunction
Kannisto et al. (2004)	BMI, body fat% (MRI and DEXA)	ACM (11 $\beta$ -HSD)	Adipose fat tissue	Needle aspiration biopsy after an overnight fast starting at 0800 h	Western blot analysis for 11 $\beta$ -HSD1 mRNA	Intrapair BMI and adipocyte differences
Kumari et al. (2010)	BMI, WC	CAR, diurnal cortisol slope	Saliva	Waking, +30 m, +2.5 h, +8 h, +12 h, and bedtime	CLIA	Age, sex, social position, waking time
Ljung et al. (1996)	BMI, WHR	Cortisol feedback sensitivity	Blood serum	Dex 0.05, 0.125, 0.25, and 0.5 mg administered at 2200 h in randomized order at 1-w intervals; blood serum taken following day at 0800 h in fasting state	RIA	Not provided
Ljung et al. (2002)	WHR	Cortisol feedback sensitivity	Blood serum	Dex 0.05, 0.125, 0.25, and 0.5 mg administered at 2200 h in randomized order at 1-w intervals; blood serum taken following day at 0800 h after fasting	RIA	Elevated LPL induction in absence of cortisol

Table 2 (Continued)

Citation	Obesity type and measures	Cortisol parameters	Specimen type	Sampling method	Assay type	Control variables
Mårin et al. (1992)	BMI, WHR	Total daily output, cortisol reactivity, cortisol feedback sensitivity	Urine, blood serum	24 h UFC; blood serum taken every hour for 6 h starting at 0600 h; 1.0 mg dex administered at 2300 h, sample taken at 0800 h day 1 and day 2, sample taken at 1500 h day 3	RIA	BMI
Mariniello et al. (2006)	BMI, WC	ACM (11 $\beta$ -HSD)	Omental adipose fat tissue	Adipose tissue biopsy, taken after surgery for gastric binding	RT-PCR and western blot analysis (duplicated)	Not provided
Muñoz et al. (2009)	BMI, WC	ACM (11 $\beta$ -HSD)	SAT, VAT	Paired sample biopsies of SAT and VAT were obtained at the moment of surgery	RT-PCR	Not provided
Pasquali et al. (2002)	BMI, WC, WHR	Cortisol feedback sensitivity	Blood plasma	Dex 1.00, 0.0035, 0.007, and 0.015 mg per kg body weight administered at 2300 h at 1-w intervals; blood serum taken following day at 0800 h in fasting state	EDTA (duplicated), RIA	Not provided
Paulmyer-Lacroix et al. (2002)	BMI	ACM (11 $\beta$ -HSD)	Abdominal adipose subcutaneous tissue, visceral subcutaneous adipose tissue	Tissue samples taken during abdominal lipectomy and gastroplasty, respectively	In situ hybridization	Not provided
Paulsen et al. (2007)	BMI	ACM (11 $\beta$ -HSD)	VAT (from omental region), SAT (from abdominal region)	Paired samples of adipose tissue were taken from the two adipose tissue depots at the beginning of the surgical procedure, after an overnight fast	RT-PCR (duplicated)	Not provided
Purnell et al. (2004)	BMI, body fat% (underwater weighing)	Total daily output	Blood plasma	30 m intervals over 24 h	CLIA (duplicated), RIA (duplicated)	Not provided
Ranjit et al. (2005)	BMI	CAR, diurnal cortisol slope	Diurnal cortisol	Samples taken at waking, +30 m, bedtime	Coat-a-Count tubes	Pregnancy status, smoking or eating prior to each measure
Rask et al. (2001)	BMI, WHR, body fat% (bioelectrical impedance)	Diurnal cortisol slope, total daily output, cortisol feedback sensitivity, ACM (11 $\beta$ -HSD)	Urine, blood plasma, SAT	24 h UFC; plasma cortisol taken at 0830 h and 1230 h, after overnight low-dose dex; subcutaneous fat biopsy	GCMS, RIA	Age, smoking, blood pressure, lean body mass, BMI
Rask et al. (2002)	BMI, WC, fat mass/lean mass	Total daily output, cortisol feedback sensitivity, ACM (11 $\beta$ -HSD)	Urine, blood serum, SAT	24 h UFC; dex dose (3.5 $\mu$ g/kg body weight from a 35 $\mu$ g/ml suspension) taken orally at 2300 h, blood serum taken at 0800 h in fasting state; umbilicus tissue biopsy	GCMS, RIA	Age, insulin sensitivity, lean body mass
Rosmond et al. (1998)	BMI, WHR, sagittal diameter	Cortisol reactivity	Saliva	Day 1: samples obtained in the morning (0800–0900 h), 1145 h, and +30, +45, and +60 m after a standardized lunch at 1200 h, 1700 h, before bedtime; Day 2: 0.5 mg dex tablet taken at 2200 h, salivary sampling repeated the following morning	RIA	Not provided
Sandeep et al. (2005)	BMI, WHR	ACM (11 $\beta$ -HSD)	Urine, paraumbilical subcutaneous abdominal adipose tissue	24 h UFC; tissue analyzed through in vivo microdialysis on following day, fasting state	GCMS, microdialysis	Not provided



Table 2 (Continued)

Citation	Obesity type and measures	Cortisol parameters	Specimen type	Sampling method	Assay type	Control variables
Stadler and Kirschbaum (2012)	BMI	Long-term cortisol output	Hair	Cortisol concentration – hair strands of a diameter of ~3 mm taken from scalp from posterior vertex region at the back of the head	CLIA (duplicated)	Age, sex, smoking status, oral contraceptive use, hair washing, hair treatment
Stephoe et al. (2004)	WHR, BMI	CAR, diurnal cortisol slope, long-term cortisol output	Saliva	Samples collected at waking, +30 m, and at 2 h intervals from 0800–0830 h to 2200–2230 h	Time resolved immunoassay (duplicated)	Age, SES, smoking status, alcohol consumption, waking time, cortisol level on waking, hormone replacement therapy
Stewart et al. (1999)	BMI, body fat% (DEXA)	Long-term cortisol output, cortisol feedback sensitivity, ACM (11 $\beta$ -HSD)	Urine, blood plasma	Day 1: 24 h UFC; Day 2: 1 mg dex dose administered at 2300 h, blood plasma obtained at 0900 h the following day (Day 3) in fasting state	UFC; RIA; blood plasma: CLIA	Not provided
Therrien et al. (2007)	BMI, WHR, WC, sagittal diameter, body fat% (hydrodensitometry)	CAR	Saliva	Samples taken at waking and +30 m; repeated on 3 occasions over a 2 month period	RIA	Not provided
Travison et al. (2007)	BMI, WHR, WC, body fat% (bioelectrical impedance)	Long-term cortisol output	Blood serum	2 Non-fasting samples within 4 h of waking; 32 samples drawn 30 m apart	RIA	Calorie intake, physical activity, depression, diabetes, smoking, daily alcohol intake, hours of sleep/day, age, employment, education, marital status, general health, life satisfaction, time of blood draw, hormone levels
Ursache et al. (2012)	BMI	CAR	Saliva	Samples collected at waking, +15, +30, and +60 m; then at 1100 h, 1500 h, and 2000h	CLIA	Age, sex, waking time
Vicennati and Pasquali (2000)	BMI, WHR	Total daily output, cortisol reactivity	Urine, blood serum	24 UFC; blood drawn in the morning (0800–0830 h) in fasting state and +5, +10, +15, +30 and +60 m after synthetic arginine vasopressin administration	Fluorescent method in polarized light (duplicated); RIA (duplicated)	BMI
Wake et al. (2003)	BMI, WHR, body fat% (bioelectrical impedance)	Cortisol feedback sensitivity, ACM (11 $\beta$ -HSD)	Urine, blood serum, SAT	24 h UFC; serum: measured in vivo after oral dex (0.0035 mg/kg body weight) at 2300 h, overnight fast, and IV cannulation at 0830 h; adipose tissue biopsy	GCMS, RIA, RT-PCR	Sex, insulin sensitivity
Wallerius et al. (2003)	BMI, WHR, sagittal diameter	CAR	Saliva	Saliva samples taken at waking, +15 m, and at 1145 h	RIA	BMI, WHR, sagittal diameter
Wester et al. (2014)	BMI	Long-term cortisol output	Hair	15 mg of ~3 cm of hair, weighed and cut	ELISA	Age, sex, hair treatment, hair products

Note: ACM=adipocyte cortisol metabolism; AUC=area under the curve; BMI=body mass index; CAR=cortisol awakening response; CLIA=chemi-luminescence assay; cm=centimeter; d= day; dex=dexamethasone; DEXA=dual-energy X-ray absorptiometry; EDTA=ethylene diamine tetra-acetic acid; ELISA=enzyme-linked immunosorbent assay; GCMS=gas chromatography-mass spectrometry; h=hour HSD=hydroxysteroid dehydrogenase IV=intravenous; kg=kilogram; LC-MS/MS=liquid chromatography-mass spectrometry/mass spectrometry; LPL=lipoprotein lipase; m=minute;  $\mu$ M=micrometer; mg=milligram; ml=milliliter; mm=millimeter; MRI=magnetic resonance imaging; RIA=radioimmunoassay; RT-PCR="real-time" reverse-transcription polymerase chain reaction; SAT=subcutaneous adipose tissue; SES=socioeconomic status; UFC=urinary free cortisol; VAT=visceral adipose tissue; w=week; WC=waist circumference; WHR=waist-to-hip ratio.

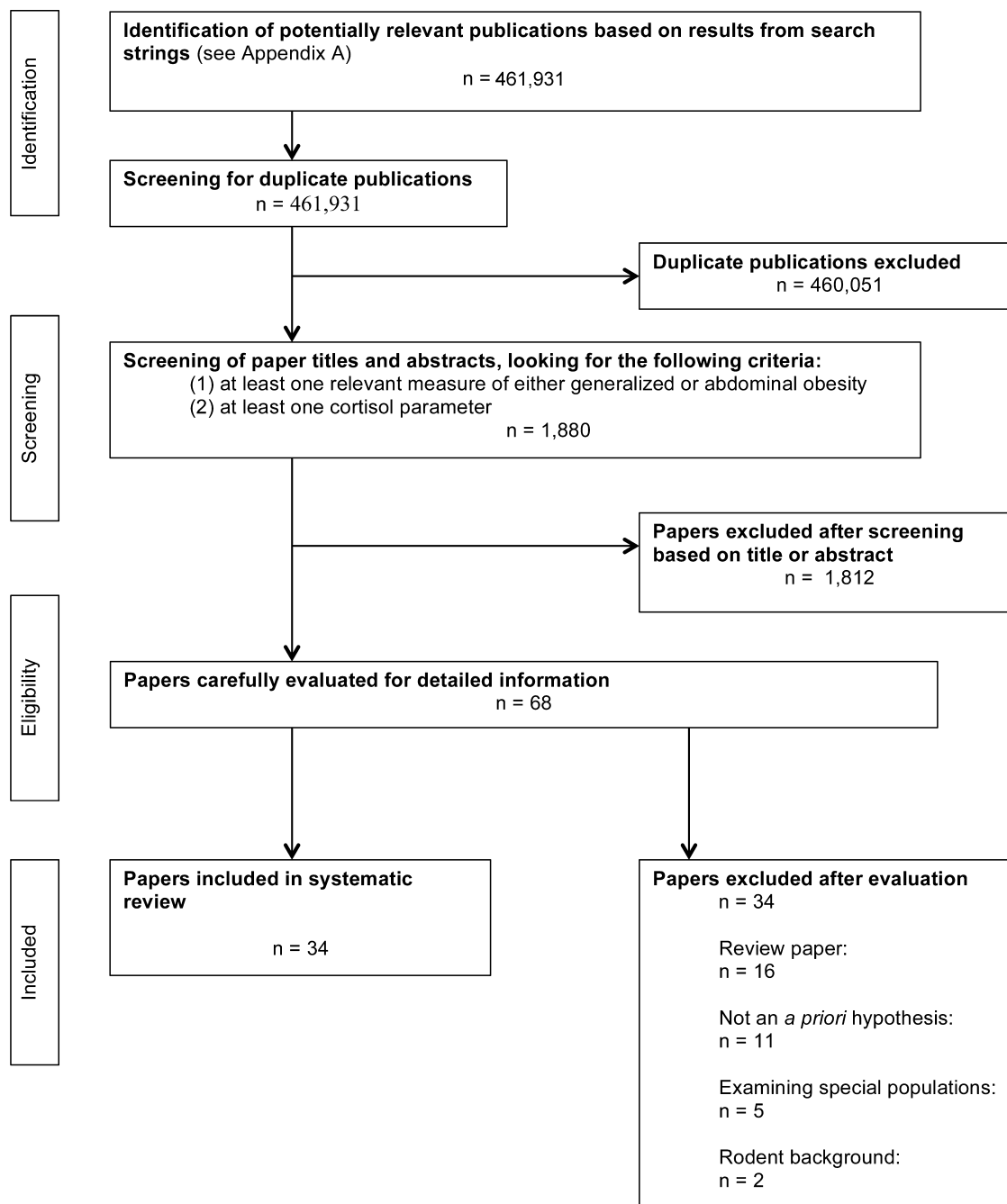


Fig. 2. Flow diagram.

BMI, CAR tends to be blunted. We suspect that this blunted CAR is the more reliable perturbation. For example, one of the strongest studies in terms of methodology (Champaneri et al., 2013), which conducted multi-point diurnal saliva sampling across three days in a large sample of men and women, evidences this negative relationship between obesity and CAR. Finally, considering that all but one reviewed study (Ursache et al., 2012), measured CAR as the difference between waking cortisol and thirty minutes post-waking, we recommend that future research incorporate smaller time intervals (e.g., 15 min), especially given that different trends at the 15-min interval level can have a marked impact on the resulting CAR calculation (Fekedulegn et al. 2007). This improvement in CAR measurement precision is an important step in clarifying the relationships between each type of obesity and CAR.

### 3.1.2. Diurnal cortisol slope

Diurnal cortisol slope measures the daily pattern of cortisol concentrations. The normative pattern of daily cortisol concentrations follows a negative slope (Stone et al., 2001), wherein cortisol concentrations increase sharply immediately upon waking (CAR) and then displays an attenuated decline throughout the day (Pruessner et al., 2003). However, flat slopes – those lacking a robust CAR or failing to reach sufficiently low levels by evening – are indicative of HPA dysregulation and are associated with negative physical and mental health outcomes (Fries et al., 2009). This is especially so in cases of abdominal obesity, and are associated with a higher risk of cardiovascular disease, type 2 diabetes, and stroke (Rosmond and Bjorntorp, 2001).

Assessing diurnal slope requires multiple cortisol measurements taken at various time points throughout the day – a

procedure that can be burdensome to participants. Therefore, some studies use single time points or examine portions of the slope (early decline, late decline) as proxies for the full slope. There are only 5 studies reviewed here that examined either whole slope or proxies of diurnal slope and general or abdominal obesity. One study of a large sample of men and women found that BMI was negatively correlated with the early decline (the decline in cortisol observed after the initial CAR, 30 min to 2 h post awakening) and thus positively correlated with the slope of the early decline (Champaneri et al., 2013). This indicates a failure to fully recover from the initial CAR, which suggests sustained increased cortisol concentrations throughout the day. Another sample of both men and women similarly found a positive relationship between WHR and slope, suggesting a shallower decline throughout the day (Stephoe et al., 2004). Using a single-time point proxy, a study of obese men found that plasma cortisol at 1230 h was inversely related to BMI (Rask et al., 2001), perhaps suggesting more marked flattening of the slope at higher BMIs. Another study found a strong relationship wherein salivary cortisol output at bedtime tended to increase with BMI, indicating that a negative diurnal rhythm was not allowing for cortisol to reach a sufficiently low point at the end of the day (Abraham et al., 2013). This measure correlated with waist circumference, but only in men, and in line with the majority of the existing literature, the study did not analyze obesity types individually. Conversely, in one study comparing obese women to non-obese women, no significant differences in slope emerged (Ranjit et al., 2005).

In light of the paucity of research, the imprecision in measuring slope (e.g., single time point proxies), and the inconsistency in the findings, the GRADE rating of the strength of this evidence would be “low.” As such, it is thus far unclear whether a consistent relationship exists between cortisol slope and either type of obesity. It does appear, however, that flatter, less sharply declining slopes are generally related to BMI and WHR, a finding supported by the strongest studies reviewed here (Champaneri et al., 2013; Steptoe et al., 2004). Both of these studies incorporate multiple sampling time points, which allows for a more precise slope measurement. Nonetheless, more research is warranted to verify this pattern and to further test the relationship between each type of obesity and slope. As an alternative to testing for linear relationships, there is some compelling evidence of a U-shaped relationship between BMI and waist circumference and diurnal cortisol slope. One recent study found that the shallowest salivary cortisol slopes – those believed to be most adverse (see Rosmond and Bjorntorp, 2001) – were significantly associated with BMI extremes (>31 and <21). The steepest, and therefore most healthy, slopes emerged among individuals with a BMI of 26, which falls at the lower end of the “overweight” BMI classification (Kumari et al., 2010). This study highlights the intriguing possibility that perhaps the healthiest HPA axis regulation might occur among those who are in fact “overweight” by BMI classification. This possibility parallels trends revealing that a BMI of 26 (“overweight”) is actually related to the lowest mortality rates, and that even some BMIs within the obese range have better mortality outcomes than normal or underweight BMIs (Flegal et al., 2005). However, we do note that those of underweight BMIs may also have other health conditions that might influence cortisol (e.g., cancer, anorexia). Therefore, studies of HPA axis dysregulation should consider the full spectrum of BMI, as both extremes may carry negative health implications. Additionally, a comprehensive understanding of abnormalities in daily slope would require measurement of the full daily rhythm including early and late decline.

### 3.1.3. Total daily output

Daily cortisol output is a cumulative measure of cortisol concentrations throughout the day, and is typically measured through

blood (serum or plasma), 24-h UFC, or multiple days of diurnal blood or salivary cortisol sampling. Diurnal salivary cortisol sampling requires collecting multiple saliva samples throughout the day from waking to bedtime to generate a curve of the daily cortisol concentrations. Area under the curve is then calculated according to the AUC with respect to ground formula (Pruessner et al., 2003).

There are 9 studies reviewed here examining total cortisol output with generalized and/or abdominal obesity. As with other parameters, the results are highly inconsistent, and some findings evidence hypercortisolism and others hypocortisolism in obesity.

Of the reviewed research, 5 studies found hypercortisolism. Of these studies, one found that both obese male and female individuals had higher daily output, as measured by UFC metabolites, but that this trend was only marginally significant (Stewart et al., 1999). Another study analyzing a sample of both sexes found that 24-h cortisol production was positively associated with both BMI and body fat percentage (Purnell et al., 2004). A similar study with a male sample found that BMI was associated with elevated cortisol metabolites measured by UFC (Rask et al., 2001). In an all-female sample, those with an elevated WHR showed greater cortisol output from UFC metabolites, in particular among those with visceral fat accumulation, as indexed by WHR (Mårin et al., 1992). Another female sample found that UFC metabolites were significantly positively associated with BMI, where participants in the upper tertile of BMIs demonstrated greater cortisol metabolite excretion (Rask et al., 2002).

Contrary to these findings, 4 studies found evidence of normal cortisol levels or even hypocortisolism. One study that compared different distributions of body fat (abdominal versus peripheral) found that females with an abdominal body fat distribution (WHR > 0.85) showed no differences in 24-h UFC compared to those with peripherally distributed body fat (WHR < 0.85), but that they had a higher urinary cortisone:cortisol ratio (cortisone is the inactive 11-keto metabolite of cortisol; Duclos et al., 2005). A similar study found that females with an abdominal body fat distribution (WHR > 0.85) showed significantly lower UFC excretion than those with peripheral body fat distributions (WHR < 0.80; Vicennati and Pasquali, 2000). In comparing obese males to non-obese males, the Massachusetts Male Aging Study found that obese males demonstrated somewhat lower serum cortisol concentrations, but because BMI was correlated with waist circumference and WHR, they did not test relationships with the latter two (Travison et al., 2007). However, seven years later, body fat percentage had no association with serum cortisol concentrations. Of note, this is the only study reviewed here that uses a longitudinal design which revealed that body size at baseline was positively associated with increases in cortisol concentrations seven years later without any increased BMI. Finally, one study found no relationship between BMI and total output, as measured by AUC (Champaneri et al., 2013).

Like other cortisol parameters, the findings with total output are contradictory, where inconsistency and imprecision again lead to a GRADE rating of the strength of the evidence of “low.” This parameter, in particular, appears to be one where findings from UFC, serum, and saliva are divergent. For example, Purnell et al. (2004) sampled blood at 30-min intervals over 24 h to estimate total daily output and found a positive relationship between obesity and total output. On the other hand, Champaneri et al. (2013) found no relationship between BMI and total output after taking six samples of saliva for three days. Given that these two methodologically strong studies find different results, future research should clarify the direction of these relationships in different specimens. If obese individuals do in fact show hypercortisolism, this condition could perhaps be perpetuating the accumulation of adipocytes and weight gain. We will also discuss in the review of adipocyte cortisol metabolism (see below) that hypocortisolism in general cortisol measurements

in abdominal obesity may result from simultaneous hyperactivity in the adipocyte metabolic system. Therefore, total output could potentially be used to identify dysregulation in adipocyte cortisol metabolism.

#### 3.1.4. Cortisol reactivity

Cortisol reactivity is a spike in cortisol concentrations observed after both physical and psychosocial acute stressors. This seems to be one parameter where results are consistent, with all 5 studies reviewed here finding increased cortisol reactivity in specifically abdominal obesity. For example, in a female sample exposed to physiological (cold-pressor) and psychological (arithmetic) stressors, higher abdominal obesity was associated with an elevated response of serum cortisol (Mårin et al., 1992). Similarly, in a male sample, stress-related increases in cortisol concentrations were associated with sagittal diameter, but not with BMI (Rosmond et al., 1998).

When pitting generalized obesity and abdominal obesity against one another, it appears that abdominal obesity is the better predictor of heightened cortisol reactivity. For instance, one study of females found that those with an abdominal body fat distribution (WHR > 0.85) showed greater cortisol responsivity to eating lunch than those with a peripheral body fat distribution (WHR < 0.85; Duclos et al., 2005). A similar study found that obese females with an abdominal body fat distribution (WHR > 0.85), compared to those with a peripheral body fat distribution (WHR < 0.80) and to normal weight females, demonstrated greater cortisol concentrations in response to acute stressors (Vicennati and Pasquali, 2000). Finally, in a study designed to isolate generalized from abdominal obesity, groups of females with either high-WHR ( $\geq 0.79$ ) or low-WHR ( $\leq 0.75$ ) were recruited, and groups were matched on BMI. Results showed that in response to a laboratory stressor, high-WHR females showed significantly higher cortisol concentrations than low-WHR females. Moreover, those with a low BMI but high WHR did not habituate to stress and, over subsequent days, continued to show significantly higher cortisol concentrations than women with a low BMI and low WHR (Epel et al., 2000). This study is unique in that it is one of the only to examine elevated abdominal adiposity paired with a normal BMI.

Overall, it appears that obese, or at least abdominally obese, individuals reliably demonstrate a greater acute stress-related cortisol response. Given the strong pattern of findings and the fact that some of the literature has attempted to examine generalized and abdominal obesity independently, the GRADE rating of the the strength of this evidence would be “moderate-to-high.” This consistent pattern of findings is of marked importance in this population as obese individuals tend to experience more repeated stressors (Abraham et al., 2013; Nyberg et al., 2012). In light of this evidence, high prevalence of life stressors paired with an overactive cortisol response may in fact perpetuate obesity and HPA-related diseases. Furthermore, as one study in this literature did successfully isolate the two types of obesity to identify abdominal obesity as the more likely cause of HPA perturbations, future directions in this literature should focus on abdominal obesity rather than just generalized obesity. Verifying the nuances of obesity type will help guide treatment efforts toward proper targets for intervention, for example so as to not low-BMI but high-adiposity individuals.

#### 3.1.5. Glucocorticoid feedback sensitivity – dexamethasone suppression test

The dexamethasone suppression test evaluates the functioning of the cortisol negative feedback system through administration of the potent synthetic glucocorticoid dexamethasone in the evening and measuring cortisol concentrations the following morning. Dexamethasone initiates a negative feedback response by binding to glucocorticoid receptors in the pituitary, thus suppressing the

release of ACTH and ultimately the secretion of cortisol. Empirical findings support the notion that the dexamethasone suppression test indexes the direct effects of increased glucocorticoid receptor activation in the pituitary on HPA axis-initiated cortisol secretion and subsequent blood concentrations (for example, see Cole et al., 2000). Essentially, during this test, a normally regulated HPA axis would attenuate the production of cortisol, as the dexamethasone would render the body’s natural endogenous cortisol production unnecessary. Lesser cortisol suppression (i.e., higher post-dexamethasone cortisol concentrations) is thus indicative of reduced feedback sensitivity (Carroll, 1985).

We review here 9 studies examining obesity and glucocorticoid feedback sensitivity through different administrations of the dexamethasone suppression test. Studies of dexamethasone suppression have again found mixed results with both general and abdominal obesity, but in general, point towards a negative relationship or no relationship between the two depending on the dose of dexamethasone. For example, one study found that among males with a WHR > 1.0, there was almost no inhibition of cortisol production, measured in serum, after the 0.05 mg and 0.125 mg doses of dexamethasone. At a 0.25 mg dose, these males showed no difference from those with a WHR < 1.0, but at the 0.5 mg dose, those with a WHR > 1.0 showed significantly less inhibition of cortisol production than the males with a WHR < 1.0. Moreover, at the 0.5 mg level, inhibition correlated negatively with WHR across the entire sample, where males with higher WHR tended to show less inhibition and therefore significant higher cortisol concentrations, and vice versa, suggesting a relationship between WHR and impaired feedback sensitivity. Interestingly however, these relationships were not observed with BMI (Ljung et al., 1996). This same group subsequently found that males with abdominal obesity (WHR > 1.0) demonstrated less serum cortisol inhibition after dexamethasone administration of 0.125 mg and 0.5 mg, as compared to controls (WHR < 1.0) who inhibited cortisol in a dose-response manner (Ljung et al., 2002). In a larger sample of obese males, BMI was negatively related to plasma cortisol at 1230 h after a 0.0035 mg per kilogram body weight dose of dexamethasone (Rask et al., 2001).

Despite these findings however, another study found that after 1.0 mg of dexamethasone, cortisol concentrations in serum were not associated with BMI (Abraham et al., 2013), and similarly, a sample of females found no relationship with any obesity measure and inhibition of cortisol secretion after 1.0 mg dexamethasone administration (Mårin et al., 1992). This study, however, did not measure or account for abdominal measures of obesity. Another study also found that dexamethasone suppression test results did not differ among normal, overweight, and obese groups of males and females after a 1.0 mg dose (Stewart et al., 1999). After a 0.0035 mg per kilogram body weight dose of dexamethasone, another sample of obese females did not differ from non-obese females in serum cortisol levels (Rask et al., 2002). Another sample of only females found that those with a WHR > 0.85 did not differ in feedback sensitivity, as indexed through plasma, from those with a WHR < 0.85 in response to a 0.25 mg dose of dexamethasone (Duclos et al., 2005). Finally, a study of both obese and normal BMI males and females found sex differences wherein obese females demonstrated significantly lower inhibition after dexamethasone doses of 0.0035 mg, 0.0070 mg, and 0.015 mg per kilogram of body weight, but that there were no differences in between obese and non-obese males (Pasquali et al., 2002). This study also found a negative relationship between BMI and waist circumference and cortisol suppression after dexamethasone administration.

Despite that there are inconsistencies in these findings, the fact that the results might indicate the presence of a dose-response relationship between obesity and feedback sensitivity would lead to a GRADE rating of “moderate.” The discrepancies in these findings

suggest that differences in feedback sensitivity tend to be subtle. Perhaps the perturbation in cortisol suppression occurs only at certain doses of dexamethasone, and dysregulation may be detectable only at certain thresholds (e.g., above 0.25 mg) and subject to ceiling effects (e.g., above 1.0 mg). Additionally, in general, null results tend to emerge when examining the relationship between feedback sensitivity and generalized obesity. However, abdominal obesity typically seems to be associated with poorer feedback sensitivity. This finding parallels (albeit not as reliably) the above findings for cortisol reactivity (Section 3.1.4), where abdominal obesity is the stronger correlate. Future research should endeavor to clarify this distinction. Lastly, it may be that feedback sensitivity is dependent on the time of day, as one study that used hydrocortisone, which is a less potent and shorter acting glucocorticoid than dexamethasone, found that obese males had impaired feedback sensitivity in the evening but not during the day (Jessop et al., 2001). It is also important to note that using hydrocortisone may have advantages over traditional dexamethasone, such as better access to the brain and better binding capabilities to both glucocorticoid receptors and the higher affinity mineralocorticoid receptors which are highly concentrated in the hippocampus and other CNS regions. Use of hydrocortisone thus tests the effects of feedback sensitivity on the brain as well as on the pituitary (De Kloet et al., 1998), suggesting that investigating feedback sensitivity using hydrocortisone may be a promising future direction. A notable caveat inherent in this, however, is that hydrocortisone makes estimation of subsequent blood cortisol levels complex, as excretion of the administered dose must be taken into account.

### 3.1.6. Long-term cortisol output in hair

Although a much smaller literature, cortisol measurements from hair offer a promising avenue for examining long-term integrated cortisol output, which could indicate sustained perturbations in cortisol activity (Stalder and Kirschbaum, 2012). As hair grows approximately one centimeter each month, hair cortisol measurements reflect cortisol concentrations over an extended period of time, rather than one day, and there is evidence that this measure is correlated with 24-h UFC (Sauvé et al., 2007).

Here we discuss 2 studies that point toward a positive relationship between obesity and hair cortisol. In a study examining groups of normal weight, overweight, and obese individuals, the obese group was found to have significantly higher hair cortisol than the normal weight and overweight groups (Wester et al., 2014). No significant differences emerged between the normal weight and overweight groups. Similarly, a study of two samples of both males and females found significant positive relationships between BMI and hair cortisol (Stalder et al., 2012). Although these two studies find consistent results, they did not record any measures of abdominal obesity.

Because research on this parameter is still quite limited, and the effects of environmental variables such as hair washing, hair dyeing, and sunlight exposure on hair cortisol levels are not yet fully clarified (Russell et al., 2012), it is difficult to draw concrete conclusions. Moreover, hair contains considerable amounts of cortisone, suggesting 11 $\beta$ -HSD1 and/or 11 $\beta$ -HSD2 activity or selective accumulation of cortisone from blood in hair, thus complicating interpretation. Therefore, the strength of this evidence would still be considered “low” by GRADE standards, although it holds promise for future directions. Nonetheless, the above studies agree with findings of hypercortisolism when examining total daily output (Section 3.1.3), wherein hypercortisolism may in fact promote the accumulation and maturation of adipocytes. This would in turn lead to weight gain. Because hair cortisol indexes cortisol concentrations over longer periods of time rather than over 1–3 days, it may be a particularly promising avenue for future study. Hair cortisol may capture greater frequencies of daily experiences of peak

stress reactivity, not just basal cortisol. Furthermore, hair cortisol collection requires very low subject burden compared to diurnal sampling protocols, and aggregates across day-to-day variations in HPA activity. Future research should expand upon these preliminary findings by further incorporating measures of abdominal obesity.

### 3.2. Adipocyte cortisol metabolism – 11- $\beta$ -hydroxysteroid-dehydrogenases

Thus far, we have reviewed general cortisol activity through various cortisol parameters measured using saliva, blood plasma or serum, UFC metabolites, and hair. Equally important to understanding HPA dysregulation in obesity, however, is adipocyte cortisol metabolism. Adipocyte cortisol metabolism activity affects intra-adipocyte cortisol concentrations that in turn affect tissue receptors and hence may have an effect on downstream physiology. The studies reviewed here point towards the possibility that adipocyte cortisol activity dysregulation may also be an indicator of adrenal HPA axis dysregulation and may in fact influence general cortisol activity.

In reviewing this literature, it may be helpful to first understand the physiological processes underlying adipocyte cortisol metabolism. Most important, the adipocyte metabolism functions through the 11 $\beta$ -hydroxysteroid-dehydrogenase (11 $\beta$ -HSD) enzymes types 1 and 2 (11 $\beta$ -HSD1 and 11 $\beta$ -HSD2). 11 $\beta$ -HSD1 catalyzes the intracellular regeneration of cortisol from inactive cortisone and has been shown to amplify the effects of cortisol in the liver and fat cells (Seckl, 2004). Conversely, 11 $\beta$ -HSD2 catalyzes rapid conversion of active cortisol to inactive cortisone. We therefore focus on studies examining the expression of these enzymes specifically in adipocytes versus hepatic tissue as these tissue types demonstrate a unique pattern of dysregulation with potential implications for general cortisol activity.

#### 3.2.1. Animal background

Because examining the 11 $\beta$ -HSD enzymes is typically conducted through tissue biopsies, adipocyte cortisol metabolism is easiest to examine in animal models. Accordingly, the current review is prefaced by a robust background of animal models. It is important to note that in rodents (mice and rats), the predominant physiological glucocorticoid is corticosterone rather than cortisol. One study of obese Zucker rats found that 11 $\beta$ -HSD1 messenger RNA levels were markedly decreased in the liver (Livingstone et al., 2000). This same study found that 11 $\beta$ -HSD1 was increased in fat cells, possibly increasing activation of local glucocorticoids and thus promoting obesity as a form of local “Cushing’s disease of adipose tissue.” Other studies in rodent models of obesity of various etiologies have mostly confirmed increased 11 $\beta$ -HSD1 activity and mRNA levels selectively in adipose tissue but not in the liver. In modeling this phenomenon, transgenic mice overexpressing 11 $\beta$ -HSD1 selectively in adipose tissue had visceral obesity and features indicative of metabolic syndrome (diabetes, dyslipidemia, hypertension). In contrast, mice lacking the enzyme resisted the negative ramifications of stress exposure (Seckl et al., 2004) and resisted metabolic disease with high fat feeding, suggesting that increased 11 $\beta$ -HSD1-driven elevation of intra-adipose tissue glucocorticoids in obesity may be one contributor in metabolic disease. Indeed, in transgenic mice overexpressing 11 $\beta$ -HSD1 only in adipose tissue, intra-adipose glucocorticoid levels are elevated, but blood levels, at least for a single interval sample, are unaffected. Since these mice demonstrated visceral obesity, the implication is that intra-adipose glucocorticoid levels are key drivers of obesity and metabolic disease over and above blood levels (Masuzaki et al., 2001), which of course contributes to, but is not the sole determinant of intra-adipose glucocorticoid concentrations. The authors of this work

suggest that increased adipose tissue 11 $\beta$ -HSD1 may be a factor in the etiology of abdominal obesity.

### 3.2.2. Findings from human literature

These findings from rodent models are reflected in human models studying male samples. For example, one study found enhanced 11 $\beta$ -HSD1 activity in subcutaneous adipose tissues in a sample of obese males (Rask et al., 2001). This study's authors suggest that this above-normal conversion of inactive cortisone to active cortisol in adipose tissue may actually exacerbate obesity, similar to rodent models. Another study found that while obese males showed no difference from non-obese males in their whole-body rate of cortisol regeneration, in subcutaneous abdominal adipose tissue in particular, cortisol regeneration was markedly greater (Sandeep et al., 2005).

Research findings in human female samples show similar patterns of results. For instance, one study of obese females found a positive relationship between BMI and 11 $\beta$ -HSD1 expression in adipose tissue (Rask et al., 2002). This relationship can in fact be quite extreme, as one study found a two-fold higher expression of 11 $\beta$ -HSD1 in human adipose tissue of abdominally obese females (WC = 106  $\pm$  7 cm) compared to non-abdominally obese females (WC = 74  $\pm$  4 cm). Moreover, they found a positive association between 11 $\beta$ -HSD1 adipose expression and waist circumference (Engeli et al., 2004). When examining expression of 11 $\beta$ -HSD2, this study found it was similarly lower by half in abdominally obese versus non-abdominally obese females, as indexed by waist circumference (Engeli et al., 2004). Another study examining obese females similarly found that 11 $\beta$ -HSD1 concentrations in visceral adipose tissue were significantly correlated with BMI, waist circumference, and sagittal diameter (Desbriere et al., 2006).

Consistent patterns of results have also emerged in samples of both males and females. One such sample found that among obese males and females, adipose 11 $\beta$ -HSD1 expression was positively correlated with BMI (Wake et al., 2003). Another sample of both sexes found a marked difference between obese and non-obese individuals, where 11 $\beta$ -HSD1 adipose expression was thirteen times greater in obese individuals (Mariniello et al., 2006). A similar sample of morbidly obese individuals compared subcutaneous adipose tissue to visceral adipose tissue. This study found that while 11 $\beta$ -HSD1 levels were higher in subcutaneous than visceral tissues, these two values were highly correlated (Muñoz et al., 2009). Additionally, subcutaneous expression increased accordingly with the BMI categories. A study in a smaller sample of both sexes found a slightly different result, where although subcutaneous adipose expression of 11 $\beta$ -HSD1 was slightly greater than visceral adipose expression, this difference was not significant (Paulmyer-Lacroix et al., 2002). Congruent with the above findings, however, this study found significantly higher 11 $\beta$ -HSD1 expression in both subcutaneous and visceral adipose tissues of obese versus non-obese individuals. Paralleling these findings, another study found that 11 $\beta$ -HSD1 expression was higher in both subcutaneous and visceral adipose tissue in male and female obese subjects compared to non-obese subjects (Paulsen et al., 2007). Finally, in a unique sample of monozygotic twin pairs with an average mean BMI difference of 3.8 kg/m<sup>2</sup>, intrapair differences in adipose 11 $\beta$ -HSD-1 expression correlated positively with differences in BMI and total cubic centimeters of subcutaneous fat (Kannisto et al., 2004). This general pattern of overexpression of 11 $\beta$ -HSD-1 in adipose tissue supports the notion that dysregulation in non-adrenal cortisol activity leads to subsequent HPA axis hyperactivity as a compensatory mechanism (Rask et al., 2002).

Some studies have reported levels of 11 $\beta$ -HSD2 mRNA in adipose tissue, and 11 $\beta$ -HSD2 activity found in adipose tissue may reflect the reversible nature of 11 $\beta$ -HSD1 under some circumstances. Recently, for example, Dube et al. (2015) have addressed

this more directly. Some 11 $\beta$ -HSD2-like activity was found in human adipose depots using a cold isotope technique and microdialysis in vivo. Unlike 11 $\beta$ -HSD1, this was not correlated with obesity in any depot examined. Thus, the bulk of the data suggest that adipose tissue 11 $\beta$ -HSD1 catalyzing 11 $\beta$ -reductase regeneration of active cortisol from inert cortisone is increased in obesity in humans and rodent models.

Regarding the human liver, findings are also consistent with rodent evidence of impaired 11 $\beta$ -HSD1 activity. In one study, obese males demonstrated greater glucocorticoid excretion as metabolites of cortisone rather than cortisol which suggests that 11 $\beta$ -HSD1 is impaired in central hepatic tissues (Rask et al., 2001). A study conducted with a female sample found similar results, wherein hepatic 11 $\beta$ -HSD1 activity was again impaired among obese females, as measured by urinary cortisone:cortisol ratio (Rask et al., 2002) in comparison to non-obese controls. Abnormal expression of 11 $\beta$ -HSD1 in hepatic tissue also has potential consequences for adrenal cortisol activity. For example, reduced regeneration of cortisol in the liver may drive a compensatory HPA axis response and promote a metabolic disease and obesity phenotype (Rask et al., 2002, 2001).

Overall, given the consistency of these findings and the tissue-specific confounds they address, the GRADE rating of the strength of the evidence would be "moderate-to-high". These findings together underscore the importance of considering the type of tissue when examining 11 $\beta$ -HSD1 (and 2) expression and endeavoring to identify targets for interventions. Interestingly, although dampening 11 $\beta$ -HSD1 has been suggested as a weight loss intervention tactic, there is evidence that weight reduction does not correct this abnormal expression of the 11 $\beta$ -HSD enzymes (Engeli et al., 2004). Other data are less clear, and given this, pharmacologically-induced 11 $\beta$ -HSD1 deficiency may be an efficacious therapeutic approach for obesity-related metabolic diseases, provided that the target is adipose tissue specifically (Seckl et al., 2004). Finally, as the literature on adipocyte cortisol metabolism in terms of 11 $\beta$ -HSD1 and 2 expression is the most consistent of those we have reviewed, it may be the most reliable place to begin targeting interventions, perhaps by targeting liposomes.

Nonetheless, the overall evidence we review here suggests that general cortisol activity and adipocyte cortisol metabolism do not operate independently, and indeed probably influence one another in a feedback loop. Therefore, future research should investigate how abnormal expressions of 11 $\beta$ -HSD1 and perhaps 2 in adipocytes and 11 $\beta$ -HSD1 and other steroid metabolic enzymes in the liver in turn influence parameters of cortisol activity where the existing literature is less consistent. We suspect that these systems are interrelated, with perturbations in any one of these entities (liver, adipocytes, HPA axis drive/adrenal cortisol secretion) having ramifications for the other two. Future research should also clarify the differences between visceral and subcutaneous adipose tissue, as findings from two studies reviewed here suggest that 11 $\beta$ -HSD1 expression may be different and have different effects in these two types of adipose tissue (Muñoz et al., 2009; Paulmyer-Lacroix et al., 2002).

## 4. Discussion and future directions

Over two decades ago, a review of obesity and adiposity concluded that generalized obesity versus abdominal distribution of adiposity constitute two separate entities and should therefore be treated as such when examining pathogenesis, clinical consequences, and treatment courses for physiological dysregulation (Björntorp, 1987). Considering the numerous inconsistencies in the existing literature, we reaffirm this sentiment and recommend that future research on cortisol and HPA axis dysregulation in obe-

sity also take into careful consideration generalized obesity versus abdominal adiposity. Furthermore, given the methodological divergences in the literature we have reviewed here, we strongly suggest that future research take into account the following methodological considerations and recommendations:

#### 4.1. Fat distribution vs. overall adiposity

We underscore here that BMI is an imprecise measure of obesity, with many known problems. For example, using BMI = 30+ as the definition of obesity means that very muscular individuals with low adipose tissue can be deemed “obese”. Furthermore, a one time point measure of BMI cannot capture differences between those who have been obese their entire lives, versus those who became obese only recently (see Section 4.5). Our findings, and the overall usefulness of the current literature, therefore, are hindered by the limitations of the current definition of obesity. An important implication of this, for this review in particular, is that an individual with a high BMI but very low abdominal obesity would likely express a cortisol profile very different from an individual with high BMI and high abdominal adiposity. Likewise, an individual with very low BMI but high abdominal adiposity may still exhibit HPA axis dysregulation, despite having a clinically “healthy” BMI. This is congruent with the above-reviewed findings that CAR (Section 3.1.1), cortisol reactivity (Section 3.1.4), and dexamethasone suppression (Section 3.1.5) results were often significantly related to WHR but not BMI. However, most studies treat BMI and abdominal adiposity similarly and do not control for one when analyzing the relationship between HPA axis activity and the other, and the two types are often highly correlated. The current literature is therefore insufficient to provide a definitive understanding of how generalized versus abdominal obesity relates to HPA axis dysregulation. While it may be more difficult to recruit high BMI-low abdominal adiposity and low BMI-high abdominal adiposity samples, at least one paper suggests it is feasible (Epel et al., 2000). If relationships between cortisol patterns and anthropometric measures could be analyzed in these uniquely characterized groups, the results could offer a transformative insight into directions of HPA axis dysregulation. At the very least, however, future studies should examine both generalized obesity and multiple measures of abdominal obesity, which will help to define consistent cortisol profiles.

#### 4.2. Specimens used in assessing general cortisol activity

The present review has included research using several different specimens of general cortisol activity, including plasma, serum, saliva, urine, and hair. While a broad literature now indicates that each of these can be employed to reliably measure cortisol concentrations, the relationships among these measurements are not fully understood (Kirschbaum and Hellhammer, 1994; Vining et al., 1983; Zumoff et al., 1974). Furthermore, even within the same specimen, there are marked variations in timing of sampling, number of samples, etc. (see Table 2). Therefore, some of the many inconsistencies we have identified likely arise from inconsistencies in cortisol measurement methodology, and in particular, from the discrepancies between bound and free cortisol, sampling protocol, and assay methodologies.

Moreover, recent data suggest that sequence variations in the gene encoding corticosteroid binding globulin, the major plasma binding protein for cortisol, are a major correlate of plasma cortisol concentrations and markers of glucocorticoid activity (Bolton et al., 2014; Gagliardi et al., 2010). Thus, both bound and free cortisol may be important in understanding tissue effects, as well as the complexity of intracellular levels determined by both blood levels and specific intracellular enzymes and the density of the two receptors. Therefore, future research should include not just one, but several of

these specimens, so as to achieve a comprehensive understanding of which specimens are the best indices of cortisol activity in particular target tissues. Additionally, future research should expand upon the currently limited, but generally consistent, findings when examining hair cortisol measurements.

#### 4.3. Role of sex and sex hormones

Sex is another factor that must be taken into account. There are inconsistent findings in the literature reviewed here based on sex that indicate that obesity plays a different role in HPA axis dysregulation for males and females. This highlights a necessity for future research to study sex differences in obesity and HPA axis dysregulation, as obesity-related dysregulation may have different health implications in one sex versus the other. For example, males have less gluteofemoral fat than females and tend to exhibit a normal or high waist-to-hip ratio, but are rarely “pear shaped” (Arner, 1997). This relationship may be driven by sex hormones as both subcutaneous and gluteofemoral fat, for instance, are shaped in part by estrogens (Karastergiou et al., 2012). Additionally, some research suggests that certain sex hormones might regulate the synthesis of corticosteroid binding globulin, which may affect cortisol reactivity when examining free cortisol measures (Misao et al., 1999), as is most commonly done in the studies reviewed on CAR, diurnal, and cortisol reactivity.

#### 4.4. General cortisol activity vs. adipocyte cortisol metabolism

The majority of the literature focuses on either one or more parameters of general cortisol activity or hone in on adipocyte cortisol metabolism, but very few studies examine both. However, intracellular adipocyte cortisol regeneration may in fact lead to lower general cortisol secretion, and as mentioned above, when less cortisol is regenerated in the liver, the HPA axis may respond with a compensatory activation to drive adrenal cortisol secretion (Rask et al., 2002, 2001). Therefore, we recommend that future research consider these inter-related processes, with adipocyte and liver cortisol metabolism being an interactive branch of overall cortisol activity, rather than separately functioning entities. Nonetheless, we acknowledge that obtaining tissue biopsies, particularly hepatic tissue biopsies, or invasive cold isotope infusion methods are difficult and carry a greater participant burden than measuring other peripheral cortisol parameters. Furthermore, initial phase 2 clinical trials suggest that inhibiting 11 $\beta$ -HSD1 in humans, although broadly having the same beneficial effects as in preclinical models, is not sufficiently efficacious to be a sole therapy for conditions associated cortisol irregularities, notably type 2 diabetes and obesity (Stomby et al., 2014). Whilst this may reflect a lesser importance of cortisol regeneration in human adipocytes, the inevitable “compensatory” HPA axis activation with 11 $\beta$ -HSD1 inhibition (to overcome loss of bulk regeneration of cortisol) could indicate alternative HPA-driven products that ameliorate the effects of local enzyme inhibition in vivo. Continuing to dissect adipocyte cortisol metabolism in the context of the entire HPA axis in humans is therefore exceedingly important.

#### 4.5. Which came first, obesity or HPA axis dysregulation? The need for longitudinal research

Despite the considerable literature on HPA axis functioning and dysregulation in obesity, the starting point for these relationships is still unclear. In the increasingly widespread calorie-dense environments that most humans inhabit, it is uncertain whether HPA dysregulation is driving obesity or whether obesity perturbs the HPA axis. This gap arises partially from the lack of longitudinal data. Given substantial evidence of hypercortisolism in obesity

and evidence that increased cortisol reactivity among those with abdominal obesity (not general obesity) may endure even for days (Epel et al., 2000), we suspect that it is possible that increased cortisol concentrations may at least perpetuate abdominal obesity, if not cause it. In this framework, obesity would lead to prolonged stress-induced increases in cortisol concentrations and overall output, thus promoting further accumulation of adipose tissue and weight gain. We therefore suggest that perhaps a dysregulated HPA axis is not a marker of obesity, but rather, a key player in the development and course of obesity, especially abdominal obesity.

However, we do not want to discount the possibility of a third variable driving the relationship. For example, in one study, when participants were selected based on chronic stress rather than obesity, they had more abdominal fat, and their HPA axis profiles suggested a dampened and hypoactive HPA axis (Tomiyama et al., 2011). Further, they reported more comfort food intake. Perhaps it is the case that under high levels of chronic stress, comfort food intake both increases abdominal fat and opioidergic inhibition on the HPA axis. Alternately, it may be that the observed hypoactivity of the HPA axis and consequent cortisol concentrations is in fact supplemented by irregularities in adipocyte cortisol metabolism, especially considering the strong link between abdominal obesity and the overexpression of 11 $\beta$ -HSD1 in adipose tissue and under-expression in hepatic tissue. Finally, there may be co-causation, for example, where both HPA axis abnormalities and metabolic disease are driven by genetic or early life programming (perhaps epigenetic) effects without the attractively plausible, but not proven, linear causation of one from the other.

Therefore, future research should test these relationships longitudinally to concretize the directionality or potential cyclical nature of the relationship between obesity and HPA axis dysregulation. Longitudinal research has the potential to identify whether non-obese individuals demonstrating HPA dysregulation (hyperactivity or hypoactivity; in general activity and adipocyte cortisol metabolism) might have greater odds of developing obesity over time. Furthermore, longitudinal study designs might test whether initial HPA axis hyperactivity leads to exacerbated excessive cortisol as obesity progresses. Alternatively, this prolonged hyperactivity could lead to HPA burnout, which would potentially promote an intensified prominence of cortisol regulation via adipocyte cortisol metabolism. These are processes that can be examined only through longitudinal research, yet all but one study reviewed here used cross-sectional designs. In this vein, therefore, longitudinal research can identify differences among those demonstrating lifelong obesity versus those who become obese later in life versus those demonstrating a consistent pattern of weight loss and gain. Ultimately, longitudinal research examining the progression of obesity in tandem with dysregulation of the HPA axis is sorely needed.

#### 4.6. Conclusion

As a final point, considering the limitations of the current research, the extant literature may be modeling the HPA axis incorrectly when examining obesity-related dysregulation. This possibility is exemplified by the previously discussed U-shaped relationship between BMI and daily slope (Kumari et al., 2010) – a relationship that we recommend should be tested with other cortisol parameters as well. A promising new modeling approach is dynamic systems modeling, which considers the functioning of a system as a whole rather than a series of linear relationships. Borrowing from the field of systems engineering, robustness theory describes how architectural features of a system (in this case, negative cortisol feedback loops, adrenal/non-adrenal interactions, and 11 $\beta$ -HSD and other enzymatic interactions) give rise to system functioning. Dynamic systems modeling has been used successfully

within the context of HPA function (Aschbacher et al., 2012; Sriram et al., 2012; Vinther et al., 2011), as well as in predicting metabolic health (Aschbacher et al., 2014). This approach to modeling HPA activity in obesity may be more appropriate and is a promising avenue for future research.

Overall, this systematic review found an overarching pattern of findings in which greater abdominal obesity is associated with greater responsiveness of the HPA axis and perturbations in adipocyte expression of 11 $\beta$ -HSD1. Generally speaking, it appears that obesity is often, but not always, related to a hyperresponsive HPA axis. Over two thirds of the United States population is currently overweight or obese and perturbations in HPA axis functioning often observed in obesity are related to several major diseases. Future research that carefully considers and corrects the current limitations in the existing literature is immediately warranted to advance the goal of developing a comprehensive understanding of the pathophysiology of obesity.

#### Conflict of interest

The authors declare no conflict of interest.

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#### Authors' contributions

ACIR, ESE, and AJT conceptualized the project. MLW and ECS conducted literature review and information extraction under the supervision of ACIR and AJT. ACIR drafted the manuscript, and all authors contributed to the manuscript authorship and revisions.

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#### Appendix A. Sample search strings

- *Sample search strings*
- Obesity AND Cortisol OR “Hypothalamic–Pituitary–Adrenal Axis”.
- Cortisol AND BMI OR Weight.
- “body fat” AND Cortisol OR 11 $\beta$ -HSD.
- “body fat” AND “cortisol reactivity”.
- “cortisol awakening response” AND BMI OR Obesity.

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