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Obesity and the hypothalamic-pituitary-adrenal axis in adolescent girls

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ABSTRACT

Stress and stress-related concomitants, including hypothalamic-pituitary-adrenal (HPA) axis activation, are implicated in obesity and its attendant comorbidities. Little is known about this relationship in adolescents. To begin to address this important knowledge gap, we studied HPA axis activity in 262 healthy adolescent girls aged 11, 13, 15, and 17 years. We hypothesized that obesity would be correlated with increased HPA axis activity and reactivity. Measures of HPA axis activity included 3 blood samples obtained midday (between 1:00 and 2:00 PM) over the course of 40 minutes; overnight urine free cortisol; and cortisol levels 0, 20, and 40 minutes after venipuncture (cortisol reactivity). Measures of adiposity included body mass index (BMI), BMI z score (BMI-Z), percentage body fat, and fat distribution (central adiposity) assessed by dual-energy x-ray absorptiometry. Daytime levels of serum cortisol were inversely associated with BMI-Z and central adiposity ($P < .05$). The urine free cortisol excretion rate was positively correlated with BMI, BMI-Z, and central adiposity. There was blunting of cortisol response to venipuncture with increasing adiposity. Our results suggest that there may be reduced cortisol levels during the day and increased levels at night with increasing degree of adiposity. This study provides preliminary findings indicating an alteration of the circadian rhythm of cortisol with obesity. We conclude that obesity is associated with altered HPA activity in adolescent girls. The clinical implications of our findings require further investigation.

1. Introduction

Obesity is widespread in the United States and other industrialized nations [1,2], leading to significant health problems that impact nearly every organ system. Multiple endocrine disturbances, such as type 2 diabetes mellitus and polycystic ovary syndrome, often coexist with obesity. In addition, changes in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis have been implicated as both a cause and a consequence of obesity [3,4]. Furthermore, obesity constitutes a chronic stressor with central and peripheral consequences. It has been proposed that a prolonged period of HPA axis stimulation secondary to the chronic stress of obesity is followed by a breakdown in the regulatory

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mechanisms of the HPA axis [5]. For example, individuals with increased abdominal obesity have greater endogenous glucocorticoid responses to a meal [6] or adrenocorticotropic hormone challenge [7]. It is also known that exogenous glucocorticoids increase food intake [8] and promote deposition of abdominal fat that is predictive of cardiovascular disease, particularly in women [5,6]. These observations support the notion that changes in the HPA axis in the setting of obesity may confer greater risk to develop obesity-related comorbidities including anxiety and depression, hypertension, hyperlipidemia, and diabetes.

Determining causality and directionality of the interactions between the HPA axis activity and obesity is hampered by difficulty in characterizing a dynamic axis with a pronounced diurnal pattern. Not only is the cortisol rhythm diurnal, cortisol levels rise following meals or in response to illness, psychosocial challenge, and exercise. In the circulation, the greatest amount of cortisol is bound to plasma proteins (>90%), particularly corticosteroid binding globulin (CBG) and sex hormone binding globulin (SHBG), whereas tissues "see" only the free (unbound) fraction. Because the secretion of cortisol is diurnal and pulsatile, a single time point for cortisol is inherently unreliable in estimating the total cortisol secretion. Thus, it is not surprising that there are conflicting results concerning the association between cortisol and obesity using single cortisol measures [9,10]. More consistent findings were reported in studies using serial measures of the HPA axis [11-14]. Strain and colleagues revealed an increased metabolic clearance rate of cortisol among obese compared with nonobese women [13] and a positive association between absolute cortisol production and relative body weight in men and women [14]. Stimulated measures of the HPA axis reflect the reactivity (ie, hypoactivity vs hyperactivity) of the stress system. Only one study examined the association between cortisol reactivity and obesity in children [15], demonstrating a positive association between cortisol reactivity to a stressful situation and body mass index (BMI).

An individual's reaction to acute and chronic stress has been hypothesized to be related to the development of obesity. Bjorntorp [16] postulated that a heightened vulnerability to psychosocial stress increases exposure to stress-induced cortisol, which in turn promotes central fat deposition. Other studies supported this theory, particularly among women with central body fat distribution (increased waist-to-hip ratio) [12,17,18]. In addition, research has evaluated whether increased stress contributed to the obesity epidemic in children [19]. In Swedish infants (N = 7443) followed through age 5 years, children in families reporting stress in at least 2 of the 4 domains assessed had significantly higher odds (odds ratio, 2.6) of being obese [19].

The pediatric literature contains few studies involving the HPA axis and obesity. Chelew and colleagues [20] evaluated serial serum cortisol concentrations over 20 to 24 hours in 16 obese male and female subjects aged 5 to 16 years. Compared with lean children, the obese children had significantly lower mean cortisol concentrations. Another study reported no significant associations between the HPA axis and percentage body fat in prepubertal obese children [21]. However, when central adiposity was examined, a significant inverse association with salivary cortisol response to a meal was found among females but not males; and a positive association between urinary glucocorticoid metabolites and central adiposity was also found among females [21]. Although studies have begun to explore associations between the HPA axis and obesity in childhood, much remains unknown; thus, investigations in younger, nonadult cohorts may provide insight into the roots of metabolic disease that are expressed in adulthood.

In examining the association between measures of the HPA axis and degree of adiposity in adolescent girls, we hypothesized that measures of adiposity would be correlated with increased HPA axis activity and reactivity. As a secondary aim, we evaluated whether measures of the HPA axis are independently associated with central adiposity when controlling for percentage body fat. This study is unique in capturing multiple measures of both the HPA axis and adiposity in a large cohort of adolescent girls.

2. Methods and procedures

Two-hundred sixty-two healthy girls aged 11, 13, 15, and 17 years were enrolled in a cross-sequential longitudinal study evaluating the impact of psychological symptoms and smoking on reproductive and bone health [22]. The cross-sequential design allows for a cost-effective and more efficient way to capture change across development. Participants are enrolled at different ages and followed for fewer years compared with a traditional longitudinal design that enrolls all participants at the same age and follows the girls for many years. The current study is a secondary data analysis and includes only baseline data that are only available for girls (ie, no boys were enrolled in the original study).

Participants were recruited from an academic medical center and the surrounding community of a Midwestern city. Exclusion criteria included pregnancy or breastfeeding within 6 months, primary (≥16 years) or secondary (<6 menstrual cycles per year and >2 years postmenarche) amenorrhea, BMI less than or equal to the first percentile or weight greater than 300 lb (limitation of dual- energy x-ray absorptiometry [DXA] table), medication or medical disorder influencing bone health, or severe psychological disabilities impairing comprehension or compliance with the protocol.

Institutional review board approval was obtained. Parents provided consent and adolescents assent for participation. Visits were conducted at the General Clinical Research Center of a children's hospital. Eligible participants received a container in which to collect overnight urine on the night before their study visit. Instructions indicated to void before sleep and to save their urine from sleep onset through the first morning void. Times of sleep onset and awakening were recorded to determine the duration of the collection.

The study visit began between 11:00 AM and 12:30 PM; postmenarcheal girls were scheduled during days 5 through 9 of their menstrual cycle. Participants had a physical examination for pubertal maturation. Menstrual interview and medication history, including use of hormonal

contraceptives, were conducted by the medical professional. Height and weight were measured. Following a 2-hour fast, blood samples were obtained. Subsequently, a DXA scan was performed.

2.1. Measures

2.1.1. Anthropometric measures

Body mass index was determined by the mean of 3 measures of height and weight using a wall-mounted stadiometer (Holtan, Crymych, Dyfed, UK) and digital scale (Scaletronix, Carol Stream, IL), respectively. Body mass index was computed as weight (kilograms)/height (square meters).

Body mass index z score (BMI-Z) is a standard calculation to account for relative adiposity in growing children and adolescents [23]. The z score accounts for age and sex by generating a standard deviation score from reference data from Centers for Disease Control and Prevention growth curves [24,25].

Percentage body fat was determined from DXA Hologic QDR4500A scans (Hologic, Bedford, MA) analyzed using software version 12.4. Percentage body fat was derived from total body fat (kilograms) divided by total body mass (kilograms).

Fat distribution, as a measure of central adiposity, was determined from DXA subregion analyses, with 4 regions described by anatomical landmarks: android subscapular, android waist, gynoid hip, and gynoid thigh. *Fat distribution* is defined as the ratio of fat mass in the upper (android) vs lower (gynoid) body regions [26]. This method has been used in prior pediatric studies to evaluate central adiposity [27,28]. Fat distribution is analogous to waist-to-hip ratio and provides an objective assessment of the pattern of fat deposition, with higher values corresponding to greater central adiposity.

2.1.2. HPA axis measures

Serum cortisol was determined from 3 samples obtained via an indwelling catheter every 20 minutes beginning at 1:00 to 2:00 PM. Girls fasted for 2 hours before the venipuncture. Radioimmunoassay (Coat-A-Count; Diagnostic Products, Los Angeles, CA) was used for cortisol measurement, with a detection limit of 0.3 μg/dL and standard curve range of 0.5 to 60 μg/dL. Inter- and intraassay coefficients of variation were 6.6% and 6.0%, respectively. Cortisol areas under the curve with respect to ground (AUC_g) and increase (AUC_i) were computed [29] to represent integrated measures. Computation of the AUC is a method used to comprise repeated measurements over time and, in this instance, to estimate overall hormone secretion over a specific time (ie, 40 minutes). AUC_g is a method that incorporates baseline hormone levels; AUC_i is an alternative method that does not incorporate baseline hormone levels and therefore represents the change (ie, increase or decrease) in overall hormone secretion.

Urine free cortisol (UFC) excretion rate was obtained from an overnight urine collection, which is highly correlated with a 24-hour collection [30]. Subjects were instructed to void before going to bed, collect any urine eliminated overnight, and collect the first morning void.

Urine free cortisol was measured using a modified radioimmunoassay (Coat-A-Count). Urine free cortisol concentration, sleep duration, and volume of urine collected were the components used to determine the UFC excretion rate (nanomoles per hour).

Cortisol reactivity cluster groupings were created using the K-means method [29,31] based on participants' serial serum cortisol measures in response to venipuncture [32,33]. Cluster centers are chosen in a first pass of the data. Subsequent iterations grouped an observation based on the distance to the mean, minimizing within-cluster variance and maximizing variability between clusters [29,31]. The K-means method does not depend on the order of the observations as do hierarchical cluster analyses methods. We anticipated 3 reactivity groupings based on previous literature [32]. Participants were grouped into the following 3 clusters based on their serial serum cortisol concentrations: (1) low concentration, stable; (2) moderate concentration, slightly increasing; and (3) high concentration, increasing.

2.2. Covariates

Tanner stage breast [34] was assessed by a trained medical professional using inspection and palpation; 2 clinician researchers demonstrated 100% agreement on the Tanner stage in a nonrandom sample (n = 23). Socioeconomic status (SES) was determined using the Hollingshead Four-Factor Index of Social Status, with a higher score corresponding to higher SES [35]. Physical activity was assessed with the Physical Activity Questionnaire for Older Children. Participants recalled amount of moderate to vigorous activity over the preceding 7 days. An average was used to create a score ranging from 1 (low) to 5 (high) activity [36]. Use of hormone contraceptives in the previous 2 weeks was ascertained by interview.

2.3. Statistical analyses

Distributions were assessed for all primary variables and covariates. Adiposity and HPA axis measures were all normally distributed with the exception of UFC excretion rate. Thus, the $\log_{10}$ of the UFC excretion rate was used in subsequent analyses. Multiple linear regression was used to evaluate associations between adiposity and (*a*) integrated serum cortisol (AUC_g, AUC_i) and (*b*) $\log_{10}$ UFC excretion rate. Along with age, potential covariates were considered based on the literature. Only significant covariates ($P < .10$) were retained in the models. Analysis of variance was used to evaluate group differences in adiposity (BMI-Z) among the 3 cortisol reactivity clusters.

3. Results

3.1. Participants

Two-hundred sixty-two girls were enrolled. Demographic characteristics are summarized in Table 1. Table 2 reports descriptive statistics for adiposity and HPA axis measures.

Table 1 – Sample characteristics of the participants (N = 262)

Characteristic	Value
Race/ethnicity, n (%)	
White	162 (61.8)
Black	86 (32.8)
Other	14 (5.3)
Age, mean (SD), y	14.9 (2.2)
SES, mean (SD) [a]	37.3 (13.7)
Tanner breast stage, n (%)	
1	4 (1.5)
2	5 (1.9)
3	27 (10.3)
4	39 (14.9)
5	187 (71.4)
Postmenarcheal, n (%)	
Yes	209 (79.8)
No	53 (20.2)
Weight category [b]	
Normal weight	155 (59.4)
Overweight	49 (18.7)
Obese	58 (22.1)
Currently using hormonal contraceptive (any type)	
Yes	67 (25.6)
No	195 (74.4)

[a] Hollingshead et al [35].
[b] Normal weight = BMI <85th percentile; overweight = BMI ≥85th to <95th percentile; obese = BMI ≥95th percentile.

3.2. Measures of the HPA axis and adiposity

Results of multiple regression for associations between cortisol AUC_g and AUC_i with all measures of adiposity are shown in Table 3. Serum cortisol AUC_g was inversely associated with BMI-Z ($B = -.014$, $P = .004$) and fat distribution ($B = -.003$, $P = .02$). Specifically, a 10-unit decrease in cortisol AUC_g was associated with a 0.14-unit increase in BMI-Z and a 0.03 increase in the ratio of fat mass in upper vs lower body regions. Cortisol AUC_i was inversely associated with BMI-Z ($B = -.019$, $P = .02$), and there was a trend toward an inverse association with fat distribution ($B = -.004$, $P = .07$).

Associations between the UFC excretion rate and measures of adiposity are displayed in Table 3. After controlling for the stated covariates, overnight UFC ($\log_{10}$) excretion rate was positively associated with BMI, BMI-Z, and fat distribution. Higher UFC excretion rates were associated with higher BMI, BMI-Z, and ratio of fat mass in upper vs lower body regions.

3.3. Cortisol reactivity and adiposity

Fig. 1 displays the mean cortisol concentrations by computed cortisol reactivity clusters. Results of analysis of variance, controlling for covariates, revealed significant differences ($P = .04$) in mean BMI-Z scores between cluster 1 ("low, stable") and cluster 3 ("high, increasing"). Specifically, the "high, increasing" reactivity cluster had a lower BMI-Z compared with the "low, stable" cluster. There was a trend toward a significant difference ($P = .09$) in the mean BMI-Z between cluster 2 ("moderate, slightly increasing") and cluster 3.

3.4. HPA axis and central adiposity

To determine whether measures of the HPA axis were independently associated with central adiposity, percentage body fat was included in the models with fat distribution. Serum cortisol AUC_g was independently and inversely associated with fat distribution ($\beta = -.111$, $B = -.002$, $P = .007$). That is, higher AUC_g was associated with decreased fat distribution or less fat mass in the upper (central) body. There also was a trend toward an inverse association of serum cortisol AUC_i with fat distribution ($P = .06$) and a positive association with overnight UFC excretion rate ($P = .09$).

4. Discussion

To our knowledge, this is the first study to evaluate associations between various measures of the HPA axis and adiposity in a community sample of adolescent girls. We found that serum cortisol measures (AUC_g, AUC_i) were inversely associated with adiposity (BMI-Z, fat distribution) and that the UFC excretion rate was positively associated with adiposity. Surprisingly, greater cortisol reactivity (ie, hyperactivity of the HPA axis) was associated with decreased adiposity, highlighting that individuals respond differently to stress and suggesting that this response may be weight related and/or associated with weight-related consequences. Our study contributes to the literature by demonstrating that adiposity is associated with altered HPA activity in early and mid adolescence. The causality and directionality of our findings require further investigation to put into clinical perspective.

Table 2 – Anthropometric and hormonal characteristics of participants (N = 262)

	Mean (SD)
Obesity measure	
BMI [a]	24.0 (6.2)
BMI-Z [b]	0.7 (1.0)
Percentage body fat (DXA)	29.2 (7.7)
Fat distribution [c]	0.6 (0.2)
Measures of the HPA axis	
Daytime serum cortisol (n = 255)	
Cortisol, μg/dL (mean 3 samples)	9.7 (4.9)
Cortisol AUC (AUC_g) [d]	19.5 (10.0)
Cortisol net response (AUC_i) [d]	1.2 (7.5)
Overnight urine free cortisol (n = 218)	
Urine cortisol excretion, nmol/h	3.0 (2.5)
Cortisol reactivity	
Cortisol reactivity cluster, mean cortisol, μg/dL	
Cluster 1: low, stable (n = 168)	6.9 (2.0)
Cluster 2: moderate, slightly increasing (n = 69)	14.4 (2.8)
Cluster 3: high, increasing (n = 18)	27.4 (5.5)

[a] Calculated as weight (kilograms)/height (square meters).
[b] Calculated from the 2000 Centers for Disease Control and Prevention growth curve data [24,25].
[c] Calculated as fat mass in upper/lower body regions (DXA).
[d] Calculated as described by Pruessner et al [29].

Table 3 – Associations between HPA axis and obesity measures using multiple regression

	Serum cortisol				Serum cortisol				Urine free cortisol			
	Area under the curve (AUC_g)				Net response (AUC_i)				Log_{10} excretion rate (nmol/h)			
	β	B	SE (B)	P-value	β	B	SE (B)	P-value	β	B	SE (B)	P-value
Dependent variable												
BMI [a]	−.103	−.049	.028	.09	−.076	−.062	.048	.20	.181	3.544	1.237	.005
BMI-Z [b]	−.174	−.014	.005	.004	−.144	−.019	.008	.02	.178	.560	.205	.007
Percentage body fat [c]	−.046	−.027	.038	.48	−.045	−.045	.065	.49	.109	2.597	1.658	.12
Fat distribution [d,e]	−.146	−.003	.001	.02	−.114	−.004	.002	.07	.146	.110	.050	.03

[a] Model adjusted for age, race, Tanner stage, and SES.
[b] Model adjusted for race, Tanner stage, and SES.
[c] Model adjusted for age, race, and SES.
[d] Model adjusted for Tanner stage and SES.
[e] Fat distribution = fat mass in upper/lower body regions (DXA).

4.1. *Measures of the HPA axis and adiposity*

In the literature, an inverse association between daytime serum cortisol and adiposity has been shown in adult women [12,13] and in a small sample of obese preadolescent boys and girls [20]. In the current study, serum cortisol measures (AUC_g, AUC_i) were also inversely associated with BMI-Z and fat distribution, extending this finding to adolescent girls.

Several existing theories support an inverse association between serum cortisol measures and adiposity. First, it is well documented that obesity is associated with insulin resistance, even during childhood [37]. Cortisol and other hormones (eg, growth hormone) antagonize insulin action to raise blood glucose levels. Thus, lower serum cortisol concentrations in the context of adolescent obesity may be an early adaptive mechanism to assist in the maintenance of glucose and metabolic homeostasis when one is insulin resistant. Second, inverse associations of HPA axis measures and adiposity may be related to the properties of cortisol and its binding mechanisms. Serum cortisol reflects the total concentration of cortisol in circulation, including that bound to proteins. Most cortisol circulates while bound to CBG or other serum proteins (SHBG, albumin); only about 10% is unbound or "free." Corticosteroid binding globulin and SHBG levels have been shown to be inversely correlated with BMI and waist-to-hip ratio among adult men and women [38,39]. Because serum cortisol includes that bound to CBG and other serum proteins, it is not surprising that total cortisol levels would be lower in obese women. Finally, there is evidence that androgens (ie, testosterone) attenuate HPA axis activity [40]. Obesity contributes to increased circulating androgen levels through decreased SHBG, stimulation of ovarian stroma production of testosterone via insulin, or increased peripheral conversion of estradiol to testosterone by aromatase in fat tissues. Thus, interaction between obesity and androgen levels may occur during the HPA axis reactivity to stress. Whether these mechanisms explain the inverse association between serial serum cortisol measures and obesity remains an empirical question. Because of the secondary nature of these analyses, we were not able to explore these mechanisms in this study.

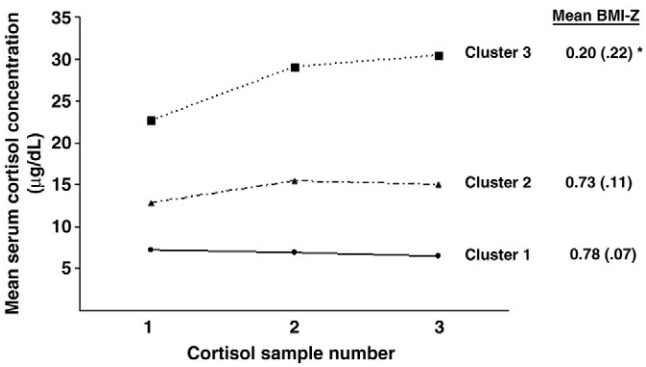

Fig. 1 – Mean daytime serum cortisol concentrations for cortisol reactivity cluster groupings in response to venipuncture. *Denotes significant difference in mean BMI-Z between clusters 1 and 3 (P = .04). Cortisol clusters: 1 = "low, stable" (n = 168); 2 = "moderate, slightly increasing" (n = 69); 3 = "high, increasing" (n = 18). Clusters were created using the K-means method [31] based on 3 serial serum cortisol samples (every 20 minutes) from participants in response to venipuncture.

The UFC excretion rate was positively associated with measures of adiposity in our study, corroborating earlier findings in adults [11,41]. Furthermore, our finding of increased UFC excretion with greater fat mass in upper vs lower body regions is in agreement with previous adult studies that demonstrated increased nighttime UFC excretion in the setting of central compared with peripheral fat distribution using waist-to-hip ratio to discriminate body fat distribution [11]. The physiologic impact of greater overnight excretion of cortisol with increased adiposity remains unclear. The current study also corroborates the findings of Barat and colleagues [21] of increased 24-hour total glucocorticoid metabolites in the urine of pre- and postadolescent girls with a greater distribution of body fat in upper body regions. Our findings should be interpreted with caution in that increased UFC excretion or clearance rate does not necessarily translate to overall increased cortisol production. This study used an overnight urine collection vs a 24-hour collection. Although the 2 are highly correlated, they are not identical [30]. In addition, other factors may impact cortisol excretion in

the urine including consumption of caffeine or alcohol, medications, and hydration status.

4.2. *Cortisol reactivity and adiposity*

The HPA axis is involved in the stress response, and cortisol reactivity has not been widely studied in the setting of obesity. To our knowledge, the only study that evaluated the association between cortisol reactivity and obesity using a laboratory stressor was conducted by Dockray and colleagues [15], who reported heightened salivary cortisol response (hyperactivity of the HPA axis) to the Trier Social Stress Test with greater adiposity (BMI). Our findings stand in opposition to the study of Dockray et al, although such differences may be evident because the study of Dockray et al measured salivary cortisol (free). In the current study, serum cortisol (total; free + bound) was measured; and girls in the "high, increasing" cortisol cluster had a lower mean BMI-Z score compared with those in the "low, stable" cortisol cluster. Mean BMI-Z for the "high, increasing" cluster was 0.20, representing a normal and healthy weight. This outcome suggests that the HPA axis in these girls may be responding in a more "normative" manner to a potentially stressful situation, whereas other patterns of cortisol reactivity may be abnormally attenuated; girls with obesity may demonstrate hypoactivity of the HPA axis in response to a stressor.

There may be other differences about the girls in the "high, increasing" cortisol cluster that resulted in activation of their stress axis. For example, Loucks and colleagues [42] described differential responses to a submaximal exercise challenge among women with functional hypothalamic amenorrhea (FHA) compared with eumenorrheic ovulatory women. Women with FHA had a significantly greater increase in cortisol in response to the exercise challenge compared with eumenorrheic ovulatory women. Therefore, it is possible that the girls in our study who showed "high, increasing" cortisol in response to venipuncture may exhibit some other factor resembling FHA that is influencing their HPA axis. Another possible explanation of our findings may be related to the differential perception of venipuncture as a stressor. For example, obese girls may have more experience with venipuncture in a clinical setting compared with normal-weight girls, thereby minimizing activation of the stress response differentially among obese girls in this study. However, using venipuncture as a stressor has been successful among adolescent girls; and group differences have been shown [32,33]. There are likely behavioral and genetic influences that further influence the stress response that were not evaluated in this study.

Despite the strengths of the study, additional limitations should be noted. First, these analyses were cross-sectional; and thus, causality cannot be determined. Second, use of waist circumference is the standard for measuring central adiposity. However, we did not have measures of waist circumference and therefore used fat distribution from DXA regions, which has been used in other pediatric samples. Third, there was a wide range in urine volume and duration involving the overnight urine collection. Adolescent sleep patterns are more varied than adult patterns in terms of time to bed and awakening, and this study purposely did not impose a set bedtime and wake-up time. To account for some of this variability in duration of collection, we calculated cortisol excretion as a rate in nanomoles per hour. Finally, this is a secondary data analysis; and we did not have many of the other hormonal variables of interest that could differentially impact cortisol levels and the cortisol response to stress.

This study offers initial insight into the complex and interrelated associations of the HPA axis and obesity during adolescence. Although we did not perform dynamic testing of the HPA axis, the cortisol reactivity analysis suggests that, among obese adolescent girls, a relative hypoactivity of the HPA axis may exist in response to a stressor (venipuncture). We demonstrated reduced cortisol levels during the day and increased levels at night with increasing degree of adiposity, possibly indicating alteration of the circadian rhythm of cortisol with adiposity as described by Nader et al [43]. Furthermore, our finding of an inverse association of cortisol AUC_g with fat distribution, after controlling for percentage body fat, has not previously been shown among adolescent girls. This is an important association because it suggests that, as early as adolescence, changes in the HPA axis in the setting of obesity may have occurred and that the pattern of fat distribution is relevant to this association. In support of this, a recent study demonstrated that cortisol excess (UFC excretion) and central adiposity were associated with greater concentrations of markers of cardiovascular disease among adolescent girls [44]. Future research is critical to confirm and replicate our findings and to extend this observation toward establishing a link between the HPA axis and obesity-related comorbidities in this age group.

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Conflict of Interest

The authors have no conflicts of interest or financial disclosures.

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