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Abstract

Background: The prevalence of obesity in adolescents with Down syndrome (DS) far exceeds that in the general population. Cortisol, an adrenal hormone, can be obesogenic when dysregulated. However, the diurnal patterns of this hormone have not been examined among individuals with DS. Variations in adiposity may also mediate cortisol regulation. This study sought to examine diurnal cortisol patterns in adolescents with DS as well as associations between cortisol function and obesity.

Method: A total of 32 adolescents, including 16 with DS and 16 controls with typical development (TD) of similar sex, age, and Tanner pubertal stage (p >.05) participated in this preliminary study. Participants completed a dual-energy x-ray absorptiometry (DXA) scan to measure body composition and collected saliva samples for cortisol measurements in the morning, afternoon, and night. Linear mixed models with random intercepts and repeated measures were used to examine the daily trajectory of log-transformed cortisol concentrations between adolescents with and without DS. A second model examined the interaction between DS and presence of elevated body fatness.

Results: Adolescents with DS had higher morning cortisol concentrations (intercept = 0.37 µg/dL), but this was not significantly different than in TD (0.35 µg/dL, p = .16). Cortisol significantly declined across hours (b = -0.026 µg/dL/hr, p < .001), but this decline also did not differ from that observed in TD (b = -0.024 µg/dL/hr, p = .43). While cortisol levels were slightly higher among adolescents with elevated body fatness, this difference was not statistically significant (p > .05; d = .30).

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Conclusions: This study is the first to examine diurnal cortisol in DS, but is limited in sample size. These preliminary findings suggest that diurnal cortisol patterns are not significantly different between adolescents with DS and TD and that cortisol levels are not associated with adiposity in this population. Despite these non-significant differences, youth with DS continue to be an 'at-risk' population for paediatric obesity in need of clinical intervention.

Keywords: Down syndrome, cortisol, adiposity, obesity, puberty, endocrine

Introduction

Down syndrome is the most common genetic form of intellectual disability, with a prevalence estimated at 14.47 per 10,000 live births (Parker et al., 2010). While the life expectancy of persons with Down syndrome has increased substantially due to advancements in health care, morbidity and early mortality remain significantly higher than in the general population (Glasson et al., 2014, Torr et al., 2010). Addressing secondary health conditions is critical to improving long-term health outcomes in this population. Obesity is highly prevalent among persons with Down syndrome. Approximately 55% of youth with Down syndrome are overweight or obese (Rimmer et al., 2010) compared to 31% of youth in the general population (Ogden et al., 2014). Adolescents with Down syndrome have also been shown to exhibit greater body fat percentages, more total fat mass, less total lean mass, and greater abdominal obesity than the general population (Bandini et al., 2012, Gonzalez-Aguero et al., 2011, Loveday et al., 2012, Pitchford et al., 2018).

The foundation for obesity is energy imbalance between caloric intake and energy expenditure, but many factors contribute to the development of excess fat mass. A recent

systematic review from Bertapelli et al. (2016) provided a thorough overview of potential determinants of obesity in children and adolescents with Down syndrome, including physical activity levels, dietary intake and feeding behaviours, resting energy expenditure, and thyroid function. Additional physiological functions, such as leptin (Magge et al., 2008), may also play mechanistic roles in obesity for this population, but are in need of further investigation.

The hypothalamic-pituitary-adrenal (HPA) axis regulates a variety of endocrine processes, including energy storage and energy expenditure (De Vriendt et al., 2009, Rodriguez et al., 2015, Adam and Epel, 2007, Bjorntorp, 2001). Activation of the HPA axis increases cortisol secretion from the adrenal glands (Bjorntorp, 2001, Adam and Epel, 2007, De Vriendt et al., 2009, Bjorntorp, 1996). Cortisol can affect circulating energy substrate levels in the blood by increasing gluconeogenesis and lipolysis (Adam and Epel, 2007, Bjorntorp, 2001, Bjorntorp and Rosmond, 2000). Visceral adipose tissue is especially sensitive to cortisol due to an increased density of glucocorticoid receptors and regulating enzymes. Glucocorticoids, including cortisol, enhance the size and number of fat cells and may play a role in the redistribution of adiposity into the visceral depot (Bjorntorp, 2001, Adam and Epel, 2007, Bjorntorp, 1996, De Vriendt et al., 2009, Rodriguez et al., 2015).

HPA axis hormones, including cortisol, are characterised by a circadian diurnal pattern with high levels in the morning and decay of output throughout the day (Pasquali et al., 2006). Multiple types of cortisol dysregulation can influence the development of obesity. First, higher cortisol levels upon waking are commonly associated with greater BMI (Bjorntorp, 2001,

Bjorntorp, 1996, De Vriendt et al., 2009). Second, blunted cortisol reactivity and circadian rhythms throughout the day are associated with greater abdominal obesity (Bjorntorp, 2001, Adam and Epel, 2007, De Vriendt et al., 2009, Bjorntorp, 1996); as these likely result in greater total cortisol output across the day. Third, cortisol is also associated with greater insulin and leptin resistance, increased neuropeptide Y release, and multiple markers of metabolic syndrome, thus promoting metabolic dysregulation and increased food intake (Bjorntorp, 2001, Adam and Epel, 2007, Nieuwenhuizen and Rutters, 2008, Pasquali et al., 2006).

Although most research has been conducted in adults, multiple studies have identified associations suggesting that cortisol levels are higher in youth with greater adiposity (Reinehr et al., 2014, Misra et al., 2008, Guzzetti et al., 2014, Weigensberg et al., 2008, Barat et al., 2007, Veldhorst et al., 2014, Hill et al., 2011, Rosmalen et al., 2005). It should be noted that these associations are highly variable and many significant findings are limited to specific sub-groups within studies (e.g., obese girls) (Hill et al., 2011, Rosmalen et al., 2005). However, multiple large studies report the opposite direction of association with lower cortisol levels significantly associated with higher adiposity (Ruttle et al., 2013, Ondrak et al., 2011, Shirtcliff et al., 2012, Kjölhede et al., 2014). Independent of BMI or adiposity, cortisol has strong positive associations with insulin resistance and other markers of metabolic syndrome (Rubin et al., 2005, Adam et al., 2010, Prodam et al., 2013, Reinehr et al., 2014, Misra et al., 2008, Guzzetti et al., 2014, Weigensberg et al., 2008, Barat et al., 2007), indicating further relevance of this hormone to overall physical health.

There is limited research on cortisol function in persons with Down syndrome (Murdoch et al., 1979, Arnell et al., 1996, Hestnes et al., 1991, Anneren et al., 1986, Bricout et al., 2008), but the most recent evidence suggests that persons with Down syndrome may exhibit characteristics of cortisol dysfunction that could promote obesity (Bricout et al., 2008). Significantly lower cortisol levels during rest and a blunted cortisol response to exercise were observed in young adult men with Down syndrome compared to controls (Bricout et al., 2008). However, other studies have reported normal cortisol values or differences that did not reach statistical significance (Anneren et al., 1986, Hestnes et al., 1991, Arnell et al., 1996, Murdoch et al., 1979). To our knowledge, no studies have tracked changes in cortisol across the day in this population, despite the known diurnal fluctuation of cortisol (Pasquali et al., 2006). Describing this diurnal pattern among individuals with Down syndrome is a first step in examining the association between this hormone and health outcomes. Furthermore, cortisol function has not been examined within the scope of obesity in Down syndrome. Given the influence of cortisol on body fat (Bjorntorp and Rosmond, 2000), the high rates of obesity and greater fat mass observed in adolescents with Down syndrome (Gonzalez-Aguero et al., 2011, Rimmer et al., 2010) may be associated with dysregulation of cortisol.

The purpose of this study was to provide a preliminary investigation of the clinical differences in diurnal cortisol patterns in adolescents with Down syndrome and with typical development. Furthermore, this study sought to examine the independent and interactive associations between Down syndrome and elevated body fatness on diurnal cortisol function.

These associations may be clinically relevant to understanding the potential contributions of cortisol dysregulation to the high rates of obesity in this at-risk population.

Methods

Participants

Participants were adolescents with Down syndrome or typical development between 12 and 18 years old and Tanner stages III to V (Marshall and Tanner, 1969, Marshall and Tanner, 1970). Exclusion criteria to participation included **a)** documented history of hormonal insufficiency (e.g., hypothyroid); **b)** use of medication that could alter metabolic functions (e.g., prednisone, central nervous system stimulants, growth hormone, thyroid hormone); **c)** comorbid disease (e.g., diabetes); and/or **d)** dual disability diagnosis (e.g., autism). Adolescents with and without Down syndrome had similar group averages for sex ratio, age, and Tanner pubertal stage ($p > .05$). Matching groups on cognitive function or other developmental indices was considered, but would have resulted in a pre-pubertal control group with different hormone profiles. Participants were recruited through Down syndrome parent support groups in Michigan and northern Ohio, family referrals, and from previous study engagement with the Center on Physical Activity and Health in Pediatric Disabilities. The study was approved by the Institutional Review Board of the University of Michigan Medical School.

Procedures

Puberty. Tanner's stages of pubertal development were used to describe the maturational state of participants (Marshall and Tanner, 1969, Marshall and Tanner, 1970).

Pubertal stage was estimated via parental report using schematic line drawings (Morris and Udry, 1980). Strong correlations have been shown in Tanner assessment between line drawings and physical exams (Morris and Udry, 1980). Parental reports can provide an acceptable estimate of pubertal stage (Coleman and Coleman, 2002) and are less invasive and stressful than traditional physical assessment. Minimising stress, which directly influences cortisol levels (Bjorntorp, 2001, De Vriendt et al., 2009), was critical to not skew study outcomes. Tanner stage was calculated as the average of reported stages for each participant (i.e., females: breast and pubic hair development; males: genital and pubic hair development). All participants were adolescents in Tanner stages III to V.

Anthropometry. All anthropometric measurements were conducted according to established guidelines (Lohman et al., 1988). Height was measured to the nearest 0.1 cm and weight was measured to nearest 0.01 kg to calculate BMI (kg/m^2) and BMI percentile from the U.S. Centers for Disease Control growth reference (Kuczmarski et al., 2000).

Dual-Energy X-Ray Absorptiometry. Each participant completed one DXA scan (Lunar Prodigy Advance [DPX-IQ 240] densitometer; GE Healthcare, Madison, WI). DXA scans provided a three-component (fat mass, lean body mass, and bone mass) analysis of body composition. Participants wore light clothing and were positioned in a supine position with hands by the sides in a neutral position. A warm blanket was used to assist the participant with maintaining position during the scan, if needed. Paediatric software (enCore 14.0; GE

Healthcare, Madison, WI) estimated body fat percentage. Obesity was classified based on age- and sex-specific cut-points for elevated total body fat percentage (Freedman et al., 2009).

Saliva Sampling. To measure diurnal patterns in cortisol, each participant provided three saliva samples per day for three consecutive days (nine samples total). Salivary cortisol is highly correlated with free serum cortisol (Dorn et al., 2007) and is the most common approach to naturalistic cortisol measurement. The three daily samples were scheduled respective to the participant's waking times on that day. Sampling times included: **1)** immediately after waking; **2)** an afternoon measurement occuring when the participant returned home from school or daily activity (approximately 3:00 to 5:00pm); and **3)** immediately prior to bedtime. These timepoints were consistent with methodology for diurnal salivary cortisol measurement (Hoyt et al., 2014, Keiver et al., 2015, Ruttle et al., 2013, Shirtcliff et al., 2012). Participants were instructed not to eat, drink, or brush their teeth in the 30 minutes before each sample. The participant's wake time, bedtime, and saliva sample collection times were reported on a brief questionnaire.

Saliva was collected with an oral swab (Salimetrics, State College, PA). Participants placed the swab underneath the tongue to absorb saliva for 3 to 5 minutes while seated. The saturated swab was then stored in an individually-numbered polypropylene vial and frozen for storage. Cortisol concentration (µg/dL) was measured using enzyme-linked immunosorbent assay techniques with the Expanded High Range Sensitivity Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics, State College, PA). The assay had a lower limit of sensitivity of

0.007 μg/dL (Shirtcliff et al., 2001) and acceptable inter-assay (5.53%) and intra-assay (5.14%) coefficients of variation (Reed et al., 2002).

Statistical Analysis

All statistical analyses were conducted using SPSS 22.0 (IBM Corp., Armonk, NY) with an a priori α of 0.05. Characteristics of the sample were described using descriptive statistics, Pearson's Chi-square (X^2) tests for dichotomous data, and independent t-tests for continuous data with Cohen's *d* effect sizes.

To be included in analyses, a participant needed to have at least 5 valid cortisol measurements across 2 or more days. A total of 286 cortisol data points from the 32 participants were included in analyses, with 11 (3.7%) data points missing. The other measures (i.e., anthropometry, DXA, Tanner staging) did not have missing data. Cortisol data were not normally distributed; thus, all analyses were performed on logarithmically transformed cortisol values. However, figures were designed with raw cortisol values to aid in interpretation.

Linear Mixed Model (LMM) techniques were employed to examine associations between Down syndrome and adiposity on the diurnal pattern of cortisol. LMM allows for random parameters estimates, is not limited by non-independent observations (e.g., repeated measures), and does not require an equal number of data points, thus accommodating missing values. All models include random intercepts to estimate cortisol concentration at wakening and repeated time parameters to account for decreases in cortisol across the day. Hours since waking was included as a covariate in all models. Sex, age, and Tanner pubertal stage were all examined as

covariates, but were not statistically significant in any model and were removed in favour of parsimony and maximising statistical power. Each model examined specific associations with log-transformed diurnal cortisol pattern: **Model 1** examined the presence of Down syndrome on cortisol; **Model 2** examined the interaction between Down syndrome and adiposity on cortisol as well as the independent presence of elevated fat mass on cortisol in adolescents with Down syndrome (**Model 2b**) and typical development (**Model 2c**).

Results

The final sample included participants with valid cortisol data and all covariates (n = 32). Groups had similar compositions based on group averages of age, sex, and Tanner pubertal stage ($p > .05$; Table 1). Large differences were observed across all measures of body composition (Table 2), except for weight ($p = .99$, $d < .01$). Adolescents with Down syndrome had significantly greater BMI ($p = .001$, $d = 1.12$), BMI percentiles ($p < .001$, $d = 1.35$), and body fat percentage ($p = .04$, $d = .70$). The proportion of participants classified as overweight (Kuczmarski et al., 2000) and with an elevated body fat percentage (Freedman et al., 2009), were both significantly greater among adolescents with Down syndrome than with typical development ($p < .01$).

*****Insert Table 1*****

***** Insert Table 2*****

Cortisol followed the expected diurnal pattern with high levels in the morning and low levels at night. Model 1 (Table 3) showed a significant linear decrease in log-cortisol across hours of the day (b = -0.12, SE = 0.02, $p < .001$). This corresponds to an average decrease in

cortisol concentration of 0.026 μg/dL per hour. Adolescents with Down syndrome exhibited higher morning cortisol concentration (0.37 μg/dL) than did adolescents with typical development (0.35 μg/dL). However, there were no significant differences between groups in log-cortisol at the intercept (b = -0.23, SE = 0.16, p = .16) or in slope across time (b = 0.06, SE = 0.08, p = .43). The random intercept and within-subject variance of repeated measures were significant (p < .001), justifying the inclusion of random effects in the model. Diurnal cortisol trajectories across the day for adolescents with and without Down syndrome are shown in Figure 1.

*****Insert Table 3*****

*****Insert Figure 1*****

To further examine the association between cortisol and adiposity, Model 2 analysed the interaction between Down syndrome and elevated body fat groupings (Table 4). In total, 13 adolescents exhibited an elevated body fat percentage (40.62%), including ten with Down syndrome (62.50%) and three with typical development (18.75%). Once again, a significant effect of hours since waking on log-cortisol (b = -0.11, SE = 0.02, p < .001) was observed. The main effects between disability groups (b = -0.18, SE = 0.18, p = .34) and elevated fatness groups (b = 0.12, SE = 0.19, p = .50) were not statistically significant, nor were any of the disability by adiposity by time interactions. These relationships were confirmed to be consistent across both adolescents with Down syndrome and typical development in Models 2b and 2c. Diurnal cortisol patterns between groups by Down syndrome and body fatness are shown in

Figure 2. Planned post-hoc pairwise comparisons between disability and adiposity groups at each time-point were also not statistically significant ($p > .05$). Adolescents with elevated fatness had consistently higher cortisol levels, particularly in the morning, but of only a small magnitude ($d = 0.30$).

*****Insert Table 4*****

*****Insert Figure 2*****

Discussion

The current study examined whether diurnal cortisol pattern was associated with the presence of Down syndrome or degree of adiposity. To the best of our knowledge, this is the first study to track diurnal cortisol in adolescents with Down syndrome. Previous studies in persons with Down syndrome have examined cortisol in a single measure (Anneren et al., 1986, Arnell et al., 1996, Hestnes et al., 1991, Murdoch et al., 1979), during stress tests (Murdoch et al., 1979), and during short periods of rest and exercise (Bricout et al., 2008). Examining the diurnal cortisol patterns through multiple measurements across the day has provided more detailed information about HPA axis activity and potential associations with obesity.

A preliminary finding from this study is that adolescents with Down syndrome do not appear to have different diurnal cortisol trajectories than adolescents with typical development. A diurnal pattern with high morning cortisol levels and a log-linear decrease in concentration across the day was observed for both groups; consistent with the expected nature of this hormone

(Pasquali et al., 2006). Cortisol levels were higher in adolescents with Down syndrome at each time point compared to adolescents with typical development. However, neither the intercept (p = .16) nor slope (p = .43) were statistically different between groups. The lack of significant group differences is consistent with studies utilising single measurements of cortisol (Anneren et al., 1986, Hestnes et al., 1991, Arnell et al., 1996, Murdoch et al., 1979). The observed diurnal pattern, characterised by a significant negative slope across hours (p < .001), confirms that repeated measurements are required to properly describe cortisol function. While Bricout et al. (Bricout et al., 2008) found significantly lower cortisol levels during rest and a blunted response to exercise among young adult males with Down syndrome, it remains unclear how these short periods of time fit into the diurnal cortisol pattern. Absolute differences in cortisol concentration between adolescents with Down syndrome and typical development in the present study, regardless of statistical significance, were larger in the morning than at other time points. The significant differences observed by Bricout et al. (Bricout et al., 2008) all occurred in the morning, but the time from waking was not reported. Thus, the discrepancy in cortisol patterns between the two studies may be due to differences in the scope of measurement. Furthermore, the current study was conducted in adolescents while Bricout et al. (Bricout et al., 2008) examined young adult males. This suggests there may also be systematic differences due to sex, age, or pubertal status (De Vriendt et al., 2009, Tsai et al., 2013), despite the lack of a covariate effect within the current study.

A second preliminary finding was that within both adolescents with Down syndrome and typical development, the presence of elevated adiposity was not significantly associated with diurnal cortisol trajectory. Previous studies in typically developing children and adolescents have identified statistically significant positive associations between cortisol levels and BMI (Reinehr et al., 2014, Rosmalen et al., 2005, Veldhorst et al., 2014), visceral adipose tissue (Misra et al., 2008), truncal fat mass (Barat et al., 2007, Weigensberg et al., 2008), and waist circumference (Guzzetti et al., 2014, Reinehr et al., 2014). Conversely, statistically significant inverse relationships between cortisol and BMI indices have also been reported (Shirtcliff et al., 2012, Ruttle et al., 2013, Ondrak et al., 2011, Kjölhede et al., 2014). Additional researchers have published non-significant findings of weak positive (Hill et al., 2011, Syme et al., 2008), inverse (Adam et al., 2010, Hill et al., 2010), or non-directional associations (Rosmalen et al., 2005, Knutsson et al., 1997). Due to publication biases against non-significant findings, it is possible that additional examinations of cortisol and adiposity in children and adolescents are not reflected in the published literature.

A potential reason for this these inconsistent associations is the variety of research designs used to examine this relationship. Across the studies mentioned above, cortisol was measured through a variety of mediums (e.g., saliva, blood serum, blood plasma, urine, and hair), sampling frequencies (e.g., single measures, diurnal pattern), and time of day. Body composition and adiposity were also measured via BMI, total and segmental fat mass, and waist circumference. Finally, the age and pubertal status of the adolescents and children studied vary

widely across studies. Taken together, it is difficult to synthesise a clear correlation between cortisol function and body composition in youth as measurement, age, sex, and pubertal status may all influence this relationship. This point is best represented by studies that found significant associations in girls but not boys (Rosmalen et al., 2005) or in only overweight children but not normal weight or obese children (Hill et al., 2011).

The adolescents with Down syndrome in the present study reflect the common health issues of this population, with over 80% of the sample categorised as overweight or obese and over 60% categorised as exhibiting elevated adiposity. These findings are consistent with recent studies reporting BMI and DXA data in adolescents with Down syndrome (Bandini et al., 2012, Gonzalez-Aguero et al., 2011, Loveday et al., 2012, Rimmer et al., 2010, Pitchford et al., 2018), clearly demonstrating a health disparity experienced by many individuals with Down syndrome. Despite the high prevalence of excess adiposity, comorbid health conditions including metabolic syndrome, type II diabetes, and hypertension are surprisingly absent in Down syndrome (De Winter et al., 2012, Real de Asua et al., 2014, Draheim et al., 2002). The mechanism behind this phenomenon is unclear, but sympathetic hypoactivity and endocrine balances unique to Down syndrome have been proposed (Corsi et al., 2009, Adelekan et al., 2012, Agiovlasitis et al., 2010). Even with the lack of metabolic and atherosclerotic complications, obesity remains a serious health issue for persons with Down syndrome due to detrimental effects on mobility, independent living, community participation, and quality of life (Rimmer and Yamaki, 2006). Health promotion and direct intervention efforts are clearly needed for this at-risk population

(Pitetti et al., 2013, Shields et al., 2009, Rimmer et al., 2010). Study designs that allow researchers to examine relationships between health behaviours and health conditions at baseline before intervening to increase healthy behaviours may be particularly beneficial.

Limitations

The current study has a number of limitations that are important to consider when interpreting these results. First, the current sample size is small and limits both the statistical power and type of analyses that could be conducted. As such, findings from this study should be viewed as preliminary. The LMM procedures were able to converge and were appropriate for the data based on fit statistics. Interpretation of Model 2, however, is limited by the small number of participants in each subgroup and may not be generalisable. It is critical to re-examine these research questions with a sample capable of producing balanced subgroups. Furthermore, the general pattern within each group was that cortisol was lower among adolescents with normal body fat, but again, this was not significantly different. Given this trend, the high prevalence of overweight in adolescents with Down syndrome in the sample may be affecting the ability to identify differences between groups in Model 1. The lack of significant differences based on adiposity within adolescents with and without Down syndrome could be due to the small sample size of each group, the unbalanced proportions of obesity across groups, or are reflective of an inconsistent associative relationship between cortisol and adiposity. This potential confounder should be specifically addressed in future studies.

Second, the current sample had a greater proportion of overweight participants in the group with Down syndrome. Analyses with equal representation in BMI obesity status between groups may alter results. However, matching groups for obesity status, whether through BMI or body fat (Gonzalez-Aguero et al., 2011), is only possible with a leaner group of adolescents with Down syndrome and a more overweight group of adolescents with typical development. Such a sample would then have questionable generalisability to either population. If possible, future studies may attempt to recruit unique equally distributed samples of adolescents with and without Down syndrome as well as with and without obesity to examine the independent and joint effects of these factors.

Third, adolescents were excluded from the study if they exhibited hormonal insufficiency, such as hypothyroid, to remove any potential effect on the HPA axis (Walter et al., 2012). Hypothyroidism is a common condition among youth with Down syndrome (Bull and Committee on Genetics, 2011), thus the current sample and findings only represent adolescents with Down syndrome with normal thyroid function. Furthermore, through excluding potential participants with hypothyroidism we may have also excluded the adolescents most likely to exhibit elevated cortisol levels (Walter et al., 2012). Despite these limitations, the current results provide useful preliminary evidence to guide future research.

Conclusion

To our knowledge, this is the first study to describe the diurnal pattern of cortisol in adolescents with Down syndrome. An extensive body of evidence from the general population

supports the association between cortisol dysfunction and obesity in adults (Adam and Epel, 2007, Bjorntorp and Rosmond, 2000, Pasquali et al., 2006, Rodriguez et al., 2015, Bjorntorp, 2001, Bjorntorp, 1996, Nieuwenhuizen and Rutters, 2008); however, this relationship is highly variable in adolescents and children (Reinehr et al., 2014, Misra et al., 2008, Guzzetti et al., 2014, Weigensberg et al., 2008, Barat et al., 2007, Veldhorst et al., 2014, Hill et al., 2011, Rosmalen et al., 2005, Ruttle et al., 2013, Ondrak et al., 2011, Shirtcliff et al., 2012, Kjölhede et al., 2014). Our preliminary findings suggest that diurnal cortisol levels are not significantly different among adolescents with Down syndrome compared to typically developing peers; nor between adolescents with elevated compared to normal levels of adiposity. A larger study is warranted to better analyse these relationships. Understanding the unique factors that contribute to health disparities in obesity among individuals with Down syndrome is a critical step in efforts to design and implement health promotion interventions.

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Table 1. Characteristics of participants with and without Down syndrome

Demographics	**Total** (n = 32)	**Down syndrome** (n = 16)	**Typically developing** (n = 16)	***p***	***d***
Female, *n* (%)	15 (46.9%)	6 (37.5%)	9 (56.3%)	.29 [a]	
Age (years), *M* (*SD*)	14.8 (1.8)	14.7 (1.8)	14.9 (2.0)	.83 [b]	.08
Tanner (III/IV/V), *n*	10/15/7	5/9/2	5/6/5	.53 [a]	
Caucasian, *n* (%)	31 (96.9%)	15 (93.8%)	16 (100.0%)	.31 [a]	

Note: Values are Mean (Standard Deviation) or Frequency (Proportion) as noted.
Abbreviations: *n* = frequency, % = proportion of column sample, *d* = Cohen's *d* effect size.
[a] Pearson's chi-square test (X^2)
[b] Independent samples t-test (*t*)
* $p < .05$, **bolded**

Table 2. Differences in body composition between participants with and without Down syndrome

Body Composition	Total	Down syndrome	Typically developing	*p*	*d*
Weight (kg)	56.7 (13.5)	56.7 (10.3)	56.6 (16.4)	.99 [b]	.01
Height (cm)	155.2 (13.1)	146.6 (8.2)	163.7 (11.4)	**<.001** [b]*	1.31
BMI (kg/m^2)	23.6 (5.0)	26.3 (4.1)	20.8 (4.2)	**.001** [b]*	1.12
BMI %ile	70.3 (28.5)	89.6 (11.0)	51.0 (27.7)	**<.001** [b]*	1.35
Overweight/Obese, *n*(%)	16 (50.0%)	13 (81.2%)	3 (18.8%)	**<.001** [a]*	
Body Fat Percentage	29.5 (9.8)	32.9 (10.8)	26.0 (7.5)	**.04** [b]*	.70
Elevated BF, *n*(%)	13 (40.6%)	10 (62.5%)	3 (18.8%)	**.01** [a]*	

Note: Values are Mean (Standard Deviation) unless otherwise noted.
Abbreviations: *n* = frequency, % = proportion of column sample, *d* = Cohen's *d* effect size, BMI = body mass index, BMI %ile = BMI percentile based on Centers for Disease Control growth chart (Kuczmarski et al., 2000), Overweight/Obese = proportion of column sample $\geq 85^{th}$ %ile on CDC growth chart, Elevated BF = proportion of column sample with elevated body fatness based on criteria outlined by Freedman et al. (2009).
[a] Pearson's chi-square test (X^2)
[b] Independent samples t-test (*t*)
* $p < .05$, **bolded**

Table 3. Linear mixed model of diurnal cortisol between adolescents with and without Down syndrome (Model 1)

Ln Cortisol (μg/dL)	**Model 1** [a]		
Predictor	b	95% CI	*p*
Intercept	-0.80	(-1.18, -0.41)	**<.001***
Fixed effects			
Down syndrome (DS)	*REF*		
Typical development (TD)	-0.23	(-0.55, 0.09)	.16
Hours	-0.12	(-0.16, -0.07)	**<.001***
Time	-0.11	(-0.46, 0.25)	.56
TD * Time	0.06	(-0.10, 0.22)	.43
Random Effects			
var (morning)	0.16	(0.11, 0.26)	**<.001***
var (afternoon)	0.28	(0.19, 0.39)	**<.001***
var (night)	0.52	(0.37, 0.71)	**<.001***
Intercept	0.14	(0.08, 0.22)	**<.001***

Note: DS = Down syndrome; TD = typically developing; *REF* = reference group for categorical comparisons.
[a] Model 1: Schwarz's Bayesian Criterion (BIC) = 585.74
* $p < .05$, **bolded**

Table 4. Linear mixed model of diurnal cortisol by Down syndrome and elevated fat mass (Model 2)

Ln Cortisol (μg/dL)	**Model 2a**[a] Total			**Model 2b**[b] Down syndrome			**Model 2c**[c] Typical Development		
Predictor	b	95% CI	*p*	b	95% CI	*p*	b	95% CI	*p*
Intercept	-0.85	(-1.30, -0.40)	**<.001***	-0.74	(-1.23, -0.24)	**.004***	-1.16	(-1.71, -0.61)	**<.001***
Fixed effects									
Down syndrome (DS)	*REF*			--	--	--	--	--	--
Typical development (TD)	-0.18	(-0.54, 0.18)	.34	--	--	--	--	--	--
Elevated BF%	0.12	(-0.24, 0.49)	.50	0.05	(-0.35, 0.45)	.793	0.21	(-0.45, 0.88)	.53
Hours	-0.11	(-0.16, -0.06)	**<.001***	-0.10	(-0.16, -0.04)	**.002***	-0.13	(-0.21, -0.06)	**.001***
Time	-0.09	(-0.46, 0.27)	.61	-0.20	(-0.65, 0.25)	.382	0.06	(-0.46, 0.58)	.822
DS * Normal BF% * Time	*REF*			*REF*			--	--	--
DS * Elevated BF% * Time	-0.06	(-0.26, 0.14)	.58	-0.02	(-0.24, 0.19)	.845	--	--	--
TD * Normal BF% * Time	0.02	(-0.17, 0.22)	.80	--	--	--	*REF*		
TD * Elevated BF% * Time	0.04	(-0.26, 0.35)	.77	--	--	--	-0.02	(-0.33, 0.28)	.873
Random Effects									
var (morning)	0.17	(0.11, 0.26)	**<.001***	0.08	(0.03, 0.19)	**.026***	0.26	(0.15, 0.45)	**<.001***
var (afternoon)	0.28	(0.19, 0.40)	**<.001***	0.21	(0.13, 0.36)	**<.001***	0.35	(0.21, 0.57)	**<.001***
var (night)	0.52	(0.38, 0.72)	**<.001***	0.61	(0.39, 0.94)	**<.001***	0.42	(0.26, 0.68)	**<.001***
Intercept	0.14	(0.08, 0.22)	**<.001***	0.14	(0.07, 0.25)	**.001***	0.13	(0.06, 0.29)	**.014***

Note: DS = Down syndrome; TD = typical development; BF% = body fat percentage; Elevated BF = proportion of column sample with elevated body fatness based on criteria outlined by Freedman et al. (Freedman et al., 2009); *REF* = reference group for categorical comparisons.

[a] Model 2a: Schwarz's Bayesian Criterion (BIC) = 592.66

[b] Model 2b: BIC = 282.14

[c] Model 2c: BIC = 320.11

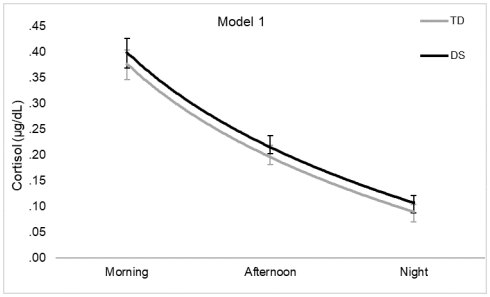
* $p < .05$, **bolded**

Figure 1. Diurnal cortisol pattern in adolescents with and without Down syndrome (Model 1)

Cortisol (μg/dL) across time points. Analyses are based on log-transformed cortisol. Post-hoc linear independent pairwise corrections with Bonferroni corrections based on estimated marginal means controlling for hours since waking. (*) Differences in cortisol between adolescents with Down syndrome and typical development, $p < .05$ (*no differences observed*)

Figure 2. Association between diurnal cortisol and adiposity in adolescents with and without Down syndrome (Model 2)

Cortisol (μg/dL) across time points. Analyses are based on log-transformed cortisol. Post-hoc linear independent pairwise corrections with Bonferroni corrections based on estimated marginal means controlling for hours since waking. (*) Differences in cortisol between adolescents with Down syndrome and typical development, $p < .05$ (*no differences observed*)



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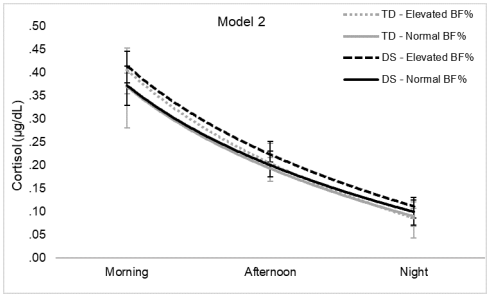

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