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Running Head: BINGE EATING AND METABOLIC DYSFUNCTION IN YOUTH

Binge Eating, Urine-Free Cortisol, and Metabolic Characteristics in Children and Adolescents

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Abstract

Overweight youth are likely to exhibit disordered eating pathology, specifically binge eating behaviors. Preliminary research indicates that binge eating and associated psychopathology in youth are associated with components of the metabolic syndrome. While metabolic dysfunction is inherently tied to obesity, some preliminary studies have found that binge eating and psychological stress are independently associated with metabolic dysfunction. This study explored the relationship between binge eating and metabolic dysfunction, and the potential mediating role of cortisol among children and adolescents. Participants were 396 overweight and non-overweight youth between the ages of 5 and 18 years. Children with binge eating had significantly greater total cholesterol, LDL cholesterol, waist circumference, insulin resistance and insulin levels than children without binge eating (ps $\leq$.05). However, BMI-z (standard deviations of BMI based on CDC growth charts) accounted for most of the results. There were no significant differences in HDL, blood pressure, and triglyceride levels among individuals with out without binge eating (ps >.05). Among adolescents, relationships existed between urine free cortisol and LDL cholesterol, even after adjusting for BMI-z, age, sex, and race (ps $\leq$ .05). Binge eating was unrelated to cortisol. We conclude that binge eating in youth may be related to metabolic dysfunction, but these associations are primarily accounted for by the links that binge eating has with body weight. Given the prevalence of binge eating among children, longitudinal research is warranted to examine whether children's binge eating exerts a unique effect on metabolic characteristics beyond its effects on weight gain.

Background and Significance

The Problem: Obesity in Youth. Obesity is a growing national concern. Rates have risen dramatically among children and adolescents over the past 30 years (Ogden, Carroll, Curtin, Lamb, & Flegal, 2010). According to recent estimates, between 2007 and 2008, approximately 13% of children and adolescents, aged 6 to 19 years old, are overweight (body mass index, BMI, kg/m^2, $\geq 97^{th}$ percentile for age and sex) (Ogden et al., 2010). Overweight in childhood and adolescence (BMI between the 85^{th} and 95^{th} percentile) is a risk factor for obesity in adulthood (Field, Cook, & Gillman, 2005). Furthermore, individuals who are obese (BMI > 95^{th} percentile) are at greater risk than their non-obese counterparts for a variety of negative health consequences including heart disease, respiratory problems, hormonal dysfunction, osteoarthritis, certain cancers, and liver disease (Bray, 2003). Childhood obesity is associated with health problems in adulthood (Dietz, 1998). Additionally, obesity during childhood or adolescence places an individual at risk for developing health problems during youth (e.g., hypertension, hyperlipidemia, and insulin resistance) (Dietz, 1998).

Physiological Outcomes of Obesity in Children: Metabolic Syndrome. One particularly severe, and well established association with obesity in adulthood is metabolic syndrome (Zimmet et al., 2007). The metabolic syndrome (also known as syndrome X) is characterized by the following cluster of markerss: insulin resistance, central obesity, higher than normal triglyceride levels, lower than normal levels of HDL cholesterol, dyslipidemia and hypertension. In combination, these physiological markers dramatically increase an individual's risk for developing heart disease and risk for type 2 diabetes (up to 30 times more than the rest of the population). The more physiological markers present, the greater the risk for heart disease and diabetes. Central, abdominal obesity (as opposed to peripheral obesity, or excess fat in the

hips, thighs, and buttocks) has a strong relationship with cardiovascular disease. This type of obesity is perhaps the greatest risk factor for metabolic syndrome, and is characterized by increased production of cortisol (Bjorntorp & Rosmond, 2000a).

Currently, there exist three widely used definitions of metabolic syndrome in adults, from the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), the World Health Organization (WHO) and the International Diabetes Federation (IDF). The common features of these three definitions are that all use the same five criterion components and require a minimum of three symptoms to meet diagnostic criteria. However, the specific cut-offs to qualify as "symptomatic" vary (Huang, Ball, & Franks, 2007). Additionally, the WHO definition requires a diagnosis of either diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance for a metabolic syndrome diagnosis. The IDF definition requires the presence of central obesity. A major problem with the WHO definition is that it does not identify those merely at risk for diabetes, but rather those with a full disorder, which may be problematic in studies of younger populations (Huang et al., 2007).

Researchers and clinicians have not yet reached a consensus on a universal definition for metabolic syndrome in children. In particular, there are discrepancies in terms of which components of metabolic syndrome should be considered risk factors for heart disease and diabetes (e.g., abdominal obesity, triglycerides). Additionally, there is variation in the cut-offs used for each component of the metabolic syndrome to be considered "at risk" for heart disease or diabetes (Huang et al., 2007). As a result, many studies have adapted adult definitions of metabolic syndrome to apply to pediatric populations, which translates into a great deal of variability in cut-offs for certain risk factors among younger populations. Despite a lack of a clear definition, the estimated prevalence of metabolic syndrome in children seems to mirror

rates of obesity and overweight in youth worldwide, indicating a strong relationship between these two variables ((Invitti et al., 2006). Rates vary widely, from 0-26% of metabolic syndrome present in preadolescent girls, depending on the definitions and cut-offs used (Chi, Wang, Wilson, & Robinson, 2006). Among adolescent boys and girls (between 12 and 19 years of age) from NHANES III data collected between 1988 and 1994 (de Ferranti et al., 2004), full metabolic syndrome was prevalent among 9.2% of the sample (9.5% of boys vs. 8.9% of girls). However, among this sample, 63.4% had at least one metabolic abnormality in one of the above five components (de Ferranti et al., 2004). Metabolic syndrome is most prevalent among overweight youth (28.7% of overweight adolescents aged 12-19 in the U.S.) compared to a prevalence of 0-1% among normal weight youth (Chi et al., 2006). Additionally, Weiss et al. (2004) estimated that as many as 50% of severely obese children had a metabolic syndrome. Youth particularly at risk for metabolic dysfunctions include African-American, Hispanic, South Asian, Native American, Pacific Islander, and First Nation Canadian (Huang et al., 2007).

Screening for Metabolic Syndrome. Components of the metabolic syndrome tend to cluster, and in combination, exponentially increase risk for cardiovascular disease and type II diabetes. The Bogalusa Heart Study (Chen, Srinivasan, Elkasabany, & Berenson, 1999) identified two specific clusters of syndromes in youth, the first combining fasting insulin, HDL, and triglycerides. The second cluster was composed of fasting insulin and blood pressure. These two clusters were found to be highly heritable, and symptoms tended to manifest early on in childhood and remain stable into adulthood (Eisenmann, Welk, Wickel, & Blair, 2004).

While there is a lack of consensus in terms of what constitutes metabolic syndrome in youth, Huang et al. (2007) highlight the importance of screening for any of the five symptoms of the disorder, as each individually can be a risk for severe outcomes in child and adulthood. The

presence of one or more symptoms (rather than the standard three in adults) may be vital for identifying youth who are at greatest risk for disease and who can benefit from early intervention. Additionally, while no pre-determined, meaningful cut-offs currently exist for each component, many researchers continue to use adult criteria, which may be problematic, as the levels of metabolic dysfunction may present differently in children and adolescents.

Risk Factors of Metabolic Syndrome in Youth. Obesity is considered a primary cause of insulin resistance and metabolic syndrome in youth, and it, in turn, may be caused by a variety of factors including genetic, endocrine, psychiatric and socioeconomic. It is thought that the prevention or treatment of obesity in youth can offset the negative trajectory of metabolic syndrome (Biltoft & Muir, 2009). There is relatively weak support for a link between physical inactivity and metabolic syndrome in youth, with only one study indicating a positive association between physical inactivity and increased insulin levels, triglycerides and adiposity, indicating that other factors may be operating in the development of metabolic syndrome (Craig, Bandini, Lichtenstein, Schaefer, & Dietz, 1996). Overall quality of diet does seem to predict metabolic dysfunction; however, this relationship is poorly understood. In general, increases in carbohydrate and decreases in fat consumption are positively associated with insulin sensitivity, and increases in fat intake are associated with lower insulin sensitivity, and fruit and vegetable intake may protect against several components of the metabolic syndrome (Huang et al., 2007).

Components of the Metabolic Syndrome.

Among adults and children, it is thought that central obesity and insulin resistance are the best predictors of metabolic syndrome, and drive all other components of the syndrome, including dyslipidemia and glucose intolerance, through changes in hormone and cell signaling (Biltoft & Muir, 2009).

Insulin Resistance. Insulin resistance refers to the improper functioning of the hormone insulin despite normal levels present in the blood (Biltoft & Muir, 2009). Insulin turns glucose (from food) into usable energy, thus providing energy homeostasis. When cells become resistant to the metabolic effects of insulin, hyperglycemia results because glucose cannot be transported from blood into the cells. This process can also result in abnormal synthesis of low-density lipoprotein and triglycerides, which in combination cause dyslipidemia (or higher than normal levels of cholesterol or fat in the blood). Insulin sensitivity (used to determine insulin resistance) is measured in a variety of ways, including using a euglycemic-insulin clamp that infuses insulin and glucose. It can also be measured using fasting glucose levels, with levels > 110 mg/dL indicating insulin resistance. However, the gold standard for measuring insulin resistance is an intravenous glucose tolerance test (IVGTT). Research is beginning to indicate that among children, insulin resistance predicts type II diabetes, hypertension, and cardiovascular disease, independent of body weight (Biltoft & Muir, 2009). However, the mechanisms by which obesity causes insulin resistance are poorly understood in children and adults.

Hypertension. High blood pressure, or hypertension, is the result of pressure in the arteries that remains too high over time, forcing the heart to work harder to pump blood throughout the body. Among adults, it is defined by a systolic and/or diastolic blood pressure at >95th percentile for height, age and gender (August & Oparil, 1999). "Pre-hypertensive" in children is indicated by a blood pressure reading of at least 120/80 mm Hg, but only after an average of three consecutive readings has been taken (Biltoft & Muir, 2009). Hypertension contributes to the hardening of the arteries, as well as heart failure. It can be influenced by the condition and size of the arteries, the volume of fluid in the body, the amount of blood the heart pumps, the amount of salt in the body, the condition of the kidneys and nervous system, as well

as hormone levels (Guyton & Hall, 2006). Specific risk factors for the development of hypertension include being obese or overweight, eating a diet high in salt, heavy alcohol consumption, sedentary lifestyle, smoking, older age, having a parent or sibling with high blood pressure, or being of African or Caribbean heritage (Biltoft & Muir, 2009). A blood pressure of 120/80 mmHg is considered normal. Typically hypertension is diagnosed if the top number (systolic blood pressure, i.e., the pressure in arteries when heart pumps blood out) is 140 mmHg or greater, and the lower number (diastolic blood pressure, or pressure in arteries when heart relaxes and fills with blood) is 90 mmHg or greater (August & Oparil, 1999).

Dyslipidemia. High levels of triglycerides and low HDL levels define dyslipidemia. These levels are the result of insulin resistance. The NHANES III study used an elevated fasting triglyceride level > 90th percentile and a low HDL level, < 10th percentile in their definition of dyslipidemia in youth (Biltoft & Muir, 2009; Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003).

Central Obesity. Central obesity refers to an abnormally high distribution of fat around the abdomen, and is considered a strong risk factor for cardiovascular disease. Waist circumference is often used in adults as a measure of central obesity, however in children BMI is often used because of a lack of normative values for circumference in youth. Additionally, development during puberty may confound measures of waist circumference (Biltoft & Muir, 2009).

Risk Factor	**Defining level according to National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High**	**Defining level according to Third National Health and Nutrition Examination Survey**	**Defining level according to Weiss et al. (2004)**

	Blood Cholesterol in Adults		
Central Obesity	Males: > 102 cm Females: > 88cm	>90th percentile for age and gender from sample population	BMI ≥ 97th percentile for age and gender
Triglycerides	≥ 150 mg/dL	≥ 110 mg/dL	≥95th percentile for age and gender
HDL cholesterol	Males: < 40 mg/dL Females: < 50 mg/dL	≤ 40 mg/dL	≤5th percentile for age and gender
Blood pressure	≥ 130/≥85 mmHg	≥90 percentile for age, gender and height	≥95th percentile for age, gender and height
Fasting glucose	≥ 110 mg/dL	≥ 110 mg/dL	Impaired glucose tolerance

Table 1. Overview of metabolic syndrome components and diagnostic criteria for children and adolescents according to three different sources. Adapted from Biltoft & Muir (2009)

Obesity, Metabolic Components, and Stress

Stress, Cortisol and HPA Axis Dysregulation. In addition to obesity, chronic stress has been identified as a risk factor for developing a number of the component symptoms of metabolic syndrome. Prolonged exposure to environmental stress may play a role in the development of metabolic syndrome through hyper-activation of the hypothalamic-pituitary-adrenal (HPA) axis.

Normal functioning of the HPA Axis. The HPA axis, often referred to as governing the "fight or flight" response, is critical to the body's response to acute stress. Under acute stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the bloodstream. ACTH reaches the adrenal glands and triggers the release of cortisol (the "stress hormone") from the adrenal cortex. Cortisol is critical for mobilizing the release of glucose for quick energy. Cortisol is a lipid soluble glucocorticoid hormone, which must be bound to proteins when circulating in the blood, and generally acts slower than protein hormones, yet has a longer duration of effect. It suppresses the immune system, increases blood pressure and cardiovascular

tone, and causes euphoria in the central nervous system. During activation of the HPA axis, the adrenal medulla releases the catecholamine epinephrine and the nerve terminals of the sympathetic nervous system release norepinephrine. These hormones prepare the body to react to stress by increasing cardiac output, mobilizing fuel and increasing metabolism, and increasing physiological arousal. Measurable effects of this sympathetic activation include pupil dilation, sweating, bronchial dilation, tachycardia, and inhibition of smooth muscle in gastrointestinal tract as well as constriction of the sphincter. Essentially, many other processes of the body are inhibited to conserve energy for the "fight or flight" response. Normally, when a stressor is removed, hormone secretion of CRH, ACTH, cortisol and catecholamines returns to baseline. Also at this point, the parasympathetic nervous system kicks in to return heart rate and blood pressure to normal (Guyton & Hall, 2006).

During chronic stress, the negative feedback loop between the brain and adrenal gland is overridden, resulting in chronically high levels of cortisol in the blood. Individuals with abnormally high levels of cortisol often develop abdominal obesity (fat stores move from the limbs to the abdomen) and high blood pressure (Guyton & Hall, 2006).

Substantial evidence from clinical and physiological studies demonstrates that elevated cortisol, combined with secondary, consequential inhibition of sex steroids and growth hormone secretions, results in the accumulation of fat in visceral adipose tissues as well as metabolic abnormalities, as seen in the metabolic syndrome. Exposure to high levels of cortisol tends to be followed by increased food intake (Guyton & Hall, 2006). Some factors, which may affect the stress system include psychosocial and socioeconomic impairments, depressive and anxiety traits, alcohol and smoking. There are also several genes associated with the physiological stress reactions seen among obese women. Overall, the research suggests that a combination of

environmental, perinatal and genetic factors induce neuroendocrine dysregulation followed by abdominal obesity with its associated co-morbidities (Bjorntorp, 2001; Hu, 2003).

Individuals with metabolic syndrome have been shown to have a dysregulated HPA axis, in addition to higher cortisol levels and increased activity in the sympathetic nervous system. Essentially, the HPA axis becomes "burned out" when individuals are exposed to environmental stress, and the sympathetic nervous system as well as the neuroendocrine system have trouble responding appropriately (Bjorntorp & Rosmond, 2000a). A prospective study in Britain (Chandola, Brunner, & Marmot, 2006) sought to identify the role of chronic stress and work in the development of metabolic syndrome among adults. Over 10,000 men and women between the ages of 35 and 55 years were followed for an average of 14 years, and they were asked to report levels of work stress at each time point (e.g., job demands, job decision latitude, and job control) and at the last time point, physiological measures were collected to assess for metabolic syndrome. The results of the study showed that both men and women from lower employment grades were more likely to develop metabolic syndrome, independent of other risk factors such as age, employment grade, and health behaviors. Additionally, a dose-response was observed wherein the greater the levels of job stress reported over time, the more participants were likely to develop metabolic syndrome. In particular, women with high levels of work stress were more than 5 times more likely to have metabolic syndrome than women who reported no job stress.

Another prospective study (Raikkonen, Matthews, & Kuller, 2002) supports the notion that psychological stress – symptoms of anxiety and depression – have a detrimental impact on an individual's health and specifically increase the likelihood of developing metabolic syndrome. Participants (n= 425 adult women) who exhibited high levels of depression, tension, and anger at baseline, and those who reported increases in anger between baseline and approximately 7

years later, had an elevated risk for developing the metabolic syndrome at follow-up. Additionally, individuals with metabolic syndrome at baseline displayed increases in anger and anxiety approximately 7 years later. Thus, the association between anger and the metabolic syndrome was found to be reciprocal. It is possible that chronic stress exposure has direct effects on the autonomic nervous system and neuroendocrine activity, which in turn promote more psychological stress. Chronic stress may reduce the body's resilience and ability to maintain homeostasis. Cortisol levels are clearly disrupted, which may have an effect on components of the metabolic syndrome.

In addition to examinations of stress and metabolic syndrome as a whole, stress also has been linked to individual components of the metabolic syndrome, especially insulin resistance. Rosmond and Bjorntorp (2000) propose that psychological stress, especially of a defeatist or helpless nature (e.g., "learned helplessness") activates the HPA axis, which provokes abnormalities in the endocrine system, including high levels of cortisol and low levels of sex steroids. These abnormalities interfere with insulin's ability to turn glucose into usable energy for the body. The effect of stress on the HPA axis also promotes the development of visceral fat, and the development of insulin resistance as well as hyperglycemia, and impaired insulin secretion. In support of the biological mechanisms by which stress impacts an individual's susceptibility to insulin resistance and type 2 diabetes, several longitudinal studies have documented strong links between chronic stress and the development of the disease. Swedish researchers (Agardh et al., 2003) surveyed 4,281 healthy, middle-aged women about their work stress, specifically work demands and decision-making latitude at work (e.g., "do you have the freedom to decide how your work should be performed?") and discovered that women who reported low decision latitude (low skill and ability to master work activities) were more likely

to have a diagnosis of type 2 diabetes than women who reported a sense of mastery in their work environment.

Another study (E. S. Epel et al., 2000) examined healthy, lean and overweight pre-menopausal women with high and low levels of abdominal obesity, across a range of BMI's (including lean and overweight women). All participants were exposed to laboratory stress tests over the course of four days, and measures of cortisol and psychological measures were collected following each session. The authors hypothesized that psychological stress would be linked to abdominal obesity, because increases in vulnerability to stress are linked to increases in cortisol exposure which in turn is linked to central fat deposition. While the study was cross-sectional in nature, the findings revealed a significant relationship between high waist-to-hip ratio and the tendency to perceive laboratory stressors as more challenging and threatening. Participants with high waist-to-hip ratio also reported greater overall levels of chronic stress. Additionally, these women secreted significantly more cortisol during the first stress session. Perhaps the most interesting finding of this study was that this relationship persisted even when controlling for BMI. In other words, lean women with higher levels of abdominal obesity displayed significant increases in cortisol following a stressor, compared to lean women with low waist-to-hip ratio. Additional cross-sectional studies (Taylor, Hubbard, & Anderson, 1999) have found support for a relationship between the ingestion of a single, large meal ("binge") and metabolic changes in glucose, insulin, and leptin, among healthy, lean individuals.

Psychological Correlates of Obesity in Children: Binge Eating,

Stress, Negative Affect and Binge Eating in Adults. As the above research indicates, stress may play a role in the development of metabolic dysregulation and obesity. In addition to

physiological factors (metabolic dysfunction) being strongly linked with obesity in youth, psychological factors are highly co-morbid with obesity. Binge eating disorder (BED) disproportionately affects individuals who are overweight or obese (Spitzer et al., 1993). Up to 30% of individuals who seek treatment for obesity meet diagnostic criteria for BED, which is a disorder characterized by disorganized patterns of eating and overeating during non-binge periods (Yanovski, 2003). Symptoms of BED include episodes of overeating in a short period of time, at least 2 days a week over past 6 months, accompanied by perceived loss of control and followed by marked guilt, disgust with oneself, or depressed mood (APA, 2000). It is commonly believed that binge eating is a means of coping with stress and negative emotion (Arnow, Kenardy, & Agras, 1992). Individuals with BED who are obese tend to have a greater body mass index (BMI) and greater levels of depression compared to non-BED obese individuals, and they tend to have negative body image, lower self-esteem, and lower self-efficacy for eating compared to individuals without the diagnosis of BED (Latner & Wilson, 2000). BED is associated with many other psychological factors, including depression, personality disorders, and cognitive distortions (Latner & Wilson, 2000). Morbidly obese binge eating disorder individuals have significantly higher rates of lifetime prevalence for major depressive disorder compared to the general population (29-51% vs. 17%, respectively) (Hsu et al., 1998). Individuals with binge eating are also more likely to drop out of weight loss programs and tend to regain weight faster following weight loss interventions, than non-bingers who are obese (Marcus, Wing, & Hopkins, 1988).

The affect-regulation model of binge eating (Figure 1) describes the importance of negative emotional experiences in triggering a binge (Heatherton & Baumeister, 1991; Stice, Akutagawa, Gaggar, & Agras, 2000; Telch & Agras, 1996). This model views individuals with

binge eating problems as being deficient in skills to adaptively cope with negative emotions. Binge eating becomes the primary means of coping to numb emotional pain (Arnow et al., 1992). Once an individual has initiated a binge episode, a cognitive narrowing occurs. The individual is no longer focused on the adverse emotional state or the attributions associated with the experience. Binge eating helps individuals escape emotional distress, enabling them to "numb" their distress (Wiser & Telch, 1999). Research in support of this model indicates that a stressful situation produced negative affect, which triggers binge eating behaviors. In fact, negative affect is one of the most frequently cited vulnerabilities to episodes of binge eating reported (Whiteside, et al., 2007; Telch & Agras, 1996).

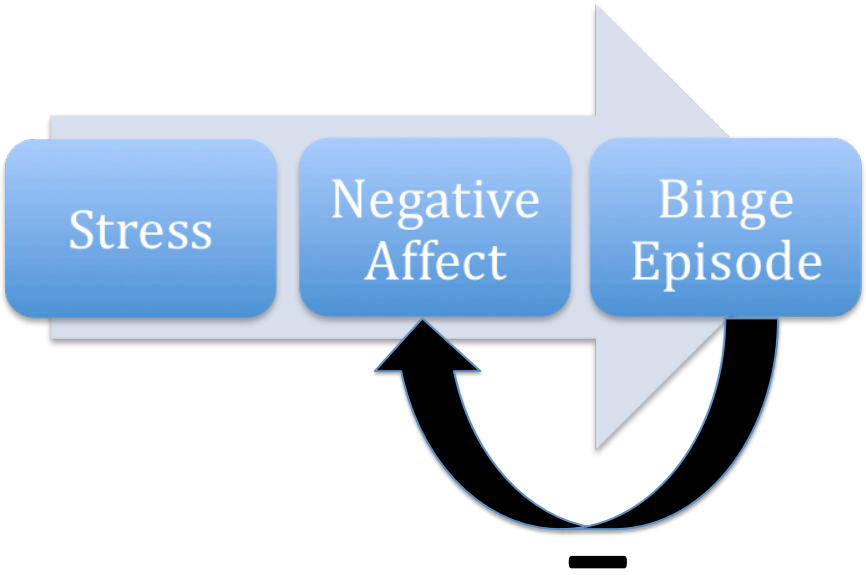

Figure 1. Affect-regulation model of binge eating

Apart from obesity and metabolic syndrome, stress also plays a role in the initiation of binge episodes and their maintenance (Lingswiler, Crowther, & Stephens, 1987). Women with BED may have a greater physiological response to stress, with one study demonstrating women

with BED having a hyperactive HPA-axis and higher basal cortisol levels following a cold pressor test (Gluck, Geliebter, Hung, & Yahav, 2004). High cortisol reactivity in response to stress often leads to consumption of greater calories and consumption of more sweet foods. Additionally, negative mood following stress is significantly related to greater food consumption (E. Epel, Lapidus, McEwen, & Brownell, 2001). Increased heart rate and attention to food following a stress induction in lab has also been observed among adolescents with bulimia nervosa (Laberg, Wilson, Eldredge, & Nordby, 1991).

Stress, Negative Affect and Binge Eating in Youth. While full-syndrome BED is rarely diagnosed among children and adolescents, episodes of loss of control (LOC) eating are often reported by youth (Tanofsky-Kraff et al., 2004). LOC is characterized by eating episodes wherein individuals report an experience of lack of control, irrespective of the amount of food consumed. When compared with overweight children who do not report LOC eating behaviors, overweight children who report LOC eating are more likely to have greater adiposity, to report increased symptoms of depression and anxiety, disturbed cognitions around eating, and lower self-esteem (Tanofsky-Kraff, Faden, Yanovski, Wilfley, & Yanovski, 2005). Their parents are also more likely to report that they struggle with internalizing and externalizing behavioral problems. LOC is the most prevalent disordered eating pattern among overweight adolescents, accounting for 6 to 40% of community samples of adolescents (Croll, Neumark-Sztainer, Story, & Ireland, 2002). Children (8-13y) who endorse infrequent LOC eating are at risk for gaining excess weight (Tanofsky-Kraff, Yanovski, et al., 2009), and partial or full-syndrome BED (Tanofsky-Kraff et al., 2006) in prospective studies.

Among overweight, treatment-seeking youth with binge eating and other eating pathology, depressive and anxious symptoms are rather prevalent (Eddy et al., 2007). In fact,

youth with binge eating behaviors tend to be characterized by greater levels of emotional and external eating styles, and disinhibition (Goossens, Braet, & Decaluwe, 2007; Tanofsky-Kraff et al., 2007). Eating in response to negative affect was endorsed by 63% of youth seeking treatment for weight loss, including those (30%) with LOC eating (Shapiro et al., 2007). Children and adolescents with binge eating behaviors may lack coping skills, including the ability to regulate negative emotions such that binge eating serves as a coping mechanism to temporarily relieve negative emotional states and to regulate stress. As a result, binge eating becomes negatively reinforced. In fact, children with LOC eating exhibit more dysfunctional emotion regulation strategies under conditions of negative affect (Czaja, Rief, & Hilbert, 2009). Using self-report questionnaires among children in grades 3-7, Czaja, Rief, & Hilbert (2009) found that youth with LOC reported more maladaptive coping strategies for regulating anxiety.

Preliminary Research Examining the Relationships among Binge Eating, Stress and Metabolic Syndrome

Although binge eating appears to be associated with stress and obesity, limited data have investigated whether binge eating is related to components of metabolic syndrome. An especially pertinent question is whether binge eating is associated with metabolic syndrome features above and beyond the effects of BMI. A recent study (Adam & Epel, 2007) highlights the relationship between psychological factors and metabolic dysfunction. The authors posit that chronic psychological stress can result in chronic over-activation of the HPA axis, producing excess cortisol, which in turn contributes to visceral and abdominal obesity. Psychological stress can trigger increases in energy intake, appetite, and occurrence of binge episodes (or "stress-induced food intake"). The authors propose a model of reward based stress eating, wherein binge eating

behaviors are maintained by stimulating the release of opioids which may counter the body's response to chronic stress, increasing the reward value of food, particularly sweets, and contributing to a feedback loop of stress, cortisol, eating and pleasure.

Existing data have reported mixed results in the relationship between binge eating and components of the metabolic syndrome. Epel et al., (2004) for example, examined the relationship between "stress eating" - defined as eating more during stressful periods, a phenomenon similar to binge eating - and metabolic functioning among medical students (21-36 years of age). Individuals who self-identified as "stress eaters" gained more weight over time than those who self-identified as "stress-less eaters" (reportedly eating less during stress). Compared to stress-less eaters, stress eaters also exhibited higher levels of insulin, cortisol and total/HDL cholesterol ratios, suggesting that those who tend to eat more during stress are more physiologically stressed and may be at risk for metabolic syndrome components such as insulin resistance, abdominal obesity, and poor cholesterol. Interestingly, there were no significant differences in BMI, dietary intake, cortisol, insulin and lipids at baseline between the stress eaters and non-stress eaters, which may imply a function of stress-related eating beyond weight. Despite several confounds of this study (including self-reports of stress-eating type and dietary intake), the findings suggest that binge eating behaviors can place individuals at increased risk for metabolic syndrome during periods of stress, at least transiently.

Children, Stress and Metabolic Syndrome. A study of psychological factors in children (Raikkonen, Matthews, & Salomon, 2003) examined the role of hostility in the prediction of metabolic syndrome and its components. In a longitudinal design, the authors measured baseline hostility among 134 African American and European American children (ages 8-17y) using the Cook-Medley Hostility Scale. The authors defined metabolic syndrome as the

presence of two or more risk factors that were above the 75th percentile for age, race and sex. Findings revealed that baseline hostility scores predicted the development of metabolic syndrome at 3-year follow-up. These results highlight a potential link between psychological and metabolic variables in children (confirming previous adult study findings) above and beyond an increase in BMI. Specifically central obesity (measured via BMI) and insulin resistance were driving the relationship between hostility and metabolic syndrome. The authors speculate that hostility may lead an individual to perceive the environment as being more stressful, which can in turn contribute to stress-related behaviors such as binge eating.

A recent study (Lourenco et al., 2008) highlights yet another potential pathway between psychological factors and metabolic dysregulation. This study compared 128 treatment-seeking obese children and adolescents (8-13) with and without binge eating, cross-sectionally, on the following metabolic measures: insulin resistance, blood pressure, lipid profile, and dietary intake. While the presence of binge eating was not significantly related to metabolic syndrome compared to non-binge eaters, this group displayed much greater levels of carbohydrate intake. These results echo previous studies of obese adults with and without binge eating, who do not display significant differences in insulin, triglycerides, and HDL and LDL cholesterol (Adami et al., 1995) (Wadden, Foster, Letizia, & Wilk, 1993). However, the observed increased carbohydrate consumption among children and adolescents with LOC eating (Tanofsky-Kraff, McDuffie, et al., 2009) may highlight yet another potential pathway by which binge eating results in insulin resistance and increased triglyceride levels, and may provide an additional point of intervention.

The above studies highlight the poorly understood relationship between eating pathology and other psychological factors and metabolic dysfunction in children and adolescents. Results

from a recent study, however, provide more clear-cut support for a link between depressive symptoms at baseline and insulin resistance among adolescents after accounting for the contribution of body weight (Shomaker et al., 2009). Only one study to date (Hudson et al., 2010) has found, prospectively, a relationship between binge eating disorder in adults and components of the metabolic syndrome at 5-year follow-up. When adjusting for BMI, age, sex, and race, baseline binge eating disorder was associated with dyslipidemia, hypertension, and type 2 diabetes**,** as among adults.

What the research findings so far seem to indicate is that (even among lean individuals), binge eating and other psychopathology can have a very negative trajectory for individuals (E. S. Epel et al., 2000). Provided psychological factors such as binge eating and depression may predict the onset of metabolic syndrome (or components of it) in youth, it is vital to understand more fully the nature of this relationship. Given the high levels of cortisol secreted among individuals with both binge eating and depression, it is highly plausible that cortisol may mediate the relationship between these psychological variables (binge eating and depression) and the metabolic syndrome.

Current Study

The proposed study seeks to explore the complex relationship between binge eating, urine free cortisol and metabolic dysregulation. It is important to understand the potential risk factors for metabolic syndrome (given its severity) and the mechanisms underlying its development in youth, beyond weight gain. Identifying the appropriate risk factors, such as eating pathology, early may prove to be vital to offset the negative metabolic outcomes of obesity in youth.

Specific Aims and Hypotheses

We hypothesize that the presence of binge eating in youth will be associated with metabolic dysfunction. In particular, binge eating is expected to be associated with greater levels of insulin resistance and abdominal obesity. We also predict that cortisol (obtained via 24 hour urine samples, and serving as a physiological measure of stress) will mediate the relationship between psychological factors (binge eating and depression) and metabolic dysfunction, via the stress pathway. Figure 2, shown below, provides a graphic representation of the model we propose to test.

Specific Aim 1: To determine if there is a relationship between binge eating in children and adolescents and metabolic dysfunction in children and adolescents.

Hypothesis 1.1*:* The presence of binge eating in children and adolescents will be associated with metabolic syndrome.

Hypothesis 1.2: In particular, binge eating will be associated with an increase in insulin resistance and abdominal obesity.

Specific Aim 2: To determine if there is a relationship between binge eating in children and adolescents and metabolic dysfunction, after accounting for body mass index (BMI).

Hypothesis 2.1*:* The presence of binge eating in children and adolescents will be associated with metabolic dysfunction, after adjusting for BMI.

Specific Aim Three: To evaluate whether the relationship between binge eating and metabolic dysfunction in children and adolescents is mediated by urine free cortisol.

Hypothesis 3.1: There will be a relationship between the presence of binge eating and urine free cortisol.

Hypothesis 3.2: There will be a relationship between urine free cortisol and metabolic dysfunction.

Hypothesis 3.3: Urine free cortisol will mediate the relationship between binge eating and metabolic dysfunction.

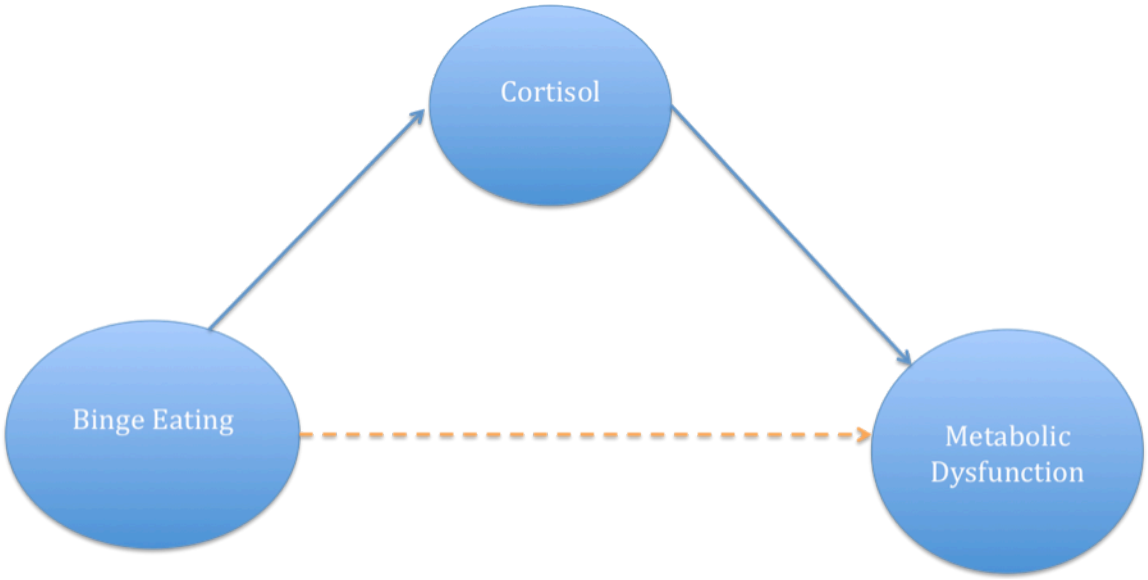

Figure 2. Proposed relationship between binge eating, metabolic syndrome, and urine free cortisol in youth. The proposed model in this study predicts that urine free cortisol mediates the relationship between binge eating symptoms and metabolic dysfunction, via the stress pathway (measured by urine free cortisol).

Method

Design

The present study sought to examine two archival databases of overweight and non-overweight participants. Data was obtained from two de-identified databases from the Unit on Growth and Obesity at the Eunice Kennedy Shriver National Institute of Child Health and Human

Development (NICHD). The sample consisted of overweight and non-overweight, male and female, Caucasian and African American children and adolescents (5-18y, n= 396). Data consisted of anthropometric measures, including height and weight, as well as metabolic assessments of blood pressure, waist circumference, fasting insulin and glucose used to calculate the homeostatic model of insulin resistance (HOMA-IR), triglycerides and total cholesterol. HPA axis activation was assessed by 24-hour urine free cortisol. Additionally, participants completed questionnaire measures of binge eating and depressive symptoms. Data were collected and analyzed to understand, cross-sectionally, the relationship between eating pathology (binge presence) and metabolic dysfunction.

Parent Studies

Data for the present study was drawn from two archived databases from the National Institutes of Health (NIH) representing a range of BMI-z. One study consisted of 179 overweight and non- overweight male and female children at high-risk for adult obesity by virtue of their own overweight or their parents' overweight. This protocol was a longitudinal study of body composition and a variety of metabolic factors (herein referred to as the Child Longitudinal Study). The second database consisted of 217 overweight male and female adolescents who participated in a combined medication and behavioral weight loss trial (herein referred to as the Adolescent Weight Loss Study). Baseline data from both protocols was examined, and all data was de- identified (no personal identifiers, such as names, medical record numbers, or addresses, were included). Data included demographic, anthropometric, and psychological variables, including: age, sex, race, height, weight, metabolic dysfunction, binge eating and depressive symptoms. Both parent studies were approved by the National Institutes of Child Health and Human Development Institutional Review Board. Likewise, the use of archival data for the current study was approved by the Uniformed Services University of the Health Sciences

Institutional Review Board.

Study participants

For both studies, children and adolescents (n= 396) were recruited through letters sent to appropriate-aged children in the Montgomery County, Fairfax County, and Washington DC school systems, by advertisements in local newspapers, and by referral from physicians who see children in the Washington area. Each child and parent received a written explanation of the purposes, procedures, and potential hazards of the study. The subject's assent as well as the consent of the parent or guardian was documented in the medical record. The study protocol was explained in detail to all participants and a parent/guardian.

Children in the Longitudinal Study. Participants (n= 179) were required to sign and assent/consent every 5 years, with each iteration of the protocol's procedures. All subjects were informed of their right to withdraw from the study. For this study, participants were compensated according to established Healthy Volunteer guidelines. They received $270.00 for each iteration of the extended outpatient and inpatient protocol procedures (every 5 years). Subjects were also compensated with $70.00 for yearly follow-up visits. If requested, a $20 reimbursement for travel expenses was also offered for each visit. While treatment was not provided for any condition noted during the evaluations, abnormal results were communicated to the participants and their parents, and made available to the participant's primary care physician. A list of obesity treatment programs for children and adults available in the greater Washington area were also made available to study participants.

Inclusion criteria for participants included good general health (absence of renal, hepatic, and most endocrinologic or pulmonary disorders) and absence of psychiatric illness (axis I and

II disorders). Participants in this study were normal weight, overweight, or obese. Overweight and obese participants were included if they had a BMI for age above the 85th percentile, as determined by NHANES I data, (Ogden et al., 2010). Additionally, normal weight participants with a BMI between the 5th and 85th percentiles were included if they had obese parents (with parental BMI above 25 kg/m^2 or with a history of a BMI above 25 kg/m^2). Participants were included if they had a tanner stage of pubertal development at initial visit, of I (pre-pubertal) or II (early pubertal) pubic hair and breast stage of development for girls, and Tanner I or II pubic hair and testes size (6mL) for boys. Participants were 6 to 12 years at intake and girls who were menstruating had a negative pregnancy test. Additionally, for this parent study, the race of all four grandparents was self-identified either as all Caucasian or all African American.

Adolescent Weight Loss Study. In this study, all participants (n= 217) were obese, with a BMI for age above the 95th percentile, as determined by NHANES I data for age, sex and race (Ogden et al., 2010). Participants also had evidence for a quantifiable obesity-related comorbidity, including hypertension, type 2 diabetes, impaired glucose tolerance, hyperinsulinemia and hyperlipidemia. Obese participants were not excluded if they were taking medications for obesity-related comorbid conditions. Participants were 12 to 17 years at the start of the study and girls with childbearing potential had a negative pregnancy test before enrolling in the weight loss program. Most participants had a tanner stage of at least III at the start of the study. Adolescent girls who were pregnant or nursing an infant, or were having unprotected intercourse were excluded from the study. Additionally, for this parent study, the race of all four grandparents was self-identified either as all Caucasian or all African American.

Participants were excluded, and referred to non-experimental treatment programs, if they had a parent or guardian with current substance abuse or a psychiatric disorder which could have

impeded competence or compliance, thus hindering completion of the study. Additionally, participants who were regularly using prescription medications unrelated to the complications of obesity, or who had recently used (within six months) anorexiant medications for the purpose of weight reduction were excluded.

Measures

While measures for both parent studies were collected at several time points, the current analysis examined data at baseline only (one time point), prior to the initiation of any form of weight loss treatment. Psychological questionnaires, fasting blood tests, and physical exam were conducted in the pediatric outpatient clinic. Measures of insulin resistance (via the hyperglycemic clamp), resting metabolic rate, and blood samples to assess triglyceride and cholesterol levels were collected during an inpatient visit.

Physiological Measures

Anthropometrical data. Three repeated measures of body weight (kg), measured using a calibrated digital scale to the nearest 0.1 kg (Scale- Tronix, Wheaton, IL) and height (m) using a calibrated electronic stadiometer (Holtain, Crymych, & Wales) were collected at baseline. BMI was calculated as (weight in kg)/(height in m)^2. Percentiles for age and sex were used to distinguish between overweight ($\geq 85^{th}$ percentile) and non-overweight ($< 85^{th}$ percentile) (Kuczmarski et al., 2000).

Pubertal development. Physical examination by a pediatric endocrinologist or pediatric nurse practitioner was conducted to determine puberty according to the stages of Tanner. Among girls breast development was used (Marshall & Tanner, 1969). Among boys, pubertal development was determined by testicular volumes (Tanner, 1981).

Measures of metabolic dysfunction

Insulin Resistance. Insulin sensitivity was measured by a two hour oral glucose tolerance test. Participants were asked to drink 1.75 gm/kg glucose mixed with water and decaffeinated cola syrup (e.g., Glucola). Serum glucose, insulin, c-peptide and free fatty acids were collected two hours later. Insulin resistance (or impaired fasting glucose) was indicated by a fasting glucose value of ≥110 mg/dL (Biltoft & Muir, 2009)

Blood pressure (Hypertension). Systolic and diastolic blood pressure were measured at the right brachial artery via a heart rate monitor while subjects are seated. Hypertension was defined as > the 95th percentile for height, age and sex (Biltoft & Muir, 2009). Adolescents are considered pre-hypertensive if they have blood pressure > 120/90 mm Hg. While it is not anticipated that children in this sample will be hypertensive, blood pressure was examined along a continuum to assess for risk for hypertension in adulthood (Biltoft & Muir, 2009).

Waist circumference (Abdominal Obesity). Waist circumference measurements were taken twice, with a flexible, non-elastic tape measure at the midpoint between the bottom of the rib cage and above the tope of the iliac crest. Abnormal waist circumferences as defined by NHANES III is above the 90th percentile for age and sex (Biltoft & Muir, 2009).

Triglycerides. Fasting triglyceride levels were measured from blood samples, using a Hitachi 917 analyzer using reagents from Roche Diagnostics (Indianapolis, IN). Elevated levels were defined as ≥90th percentile for age and sex (Biltoft & Muir, 2009).

HDL cholesterol. Cholesterol levels were also obtained from blood samples, using a Hitachi 917 analyzer using reagents from Roche Diagnostics (Indianapolis, IN). A Cobas FARA analyzer was used to directly measure HDL-cholesterol levels using reagents from Sigma

chemical (St. Louis, MO). Low HDL levels are defined as ≤10th percentile for age and sex (< 40 mg/dL) (Biltoft & Muir, 2009).

Assessment of Cortisol Levels

Urine samples were collected from participants to measure 24-hour urine free cortisol. Participants were asked to collect all urine excreted within the 24-hour time period they were present in the clinic center. This measurement provides an average level of cortisol throughout the day. Data were log-transformed and adjusted for body surface area (Haycock, Schwartz, & Wisotsky, 1978)

Psychological Measures

Binge eating. To assess for the presence of binge eating, participants completed the Questionnaire on Eating and Weight Patterns, Adolescent version (QEWP-A), a self-report measure used to screen for BED and bulimia nervosa (BN). The QEWP-A is based upon the Questionnaire on Eating and Weight Patterns - Revised (QEWP) for adults. The main difference between the two measures is that the QEWP-A uses simpler synonyms so that it is more appropriate for younger populations. This measure was used to assess the presence vs. absence of one or more binge episodes in the previous 6 months, and has excellent internal validity, when measuring binge eating in a laboratory (Mirch et al., 2006).

Depressive Symptoms. The Child Depression Inventory (CDI) was administered to examine depressive symptoms. The CDI is a widely used measure of depression among children with very good reliability and validity, and internal consistency ranges from .70-.86 for the total score (Kovacs, 1985). The CDI is a 27-item measurement adapted from the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and consists of five subscales:

negative mood, interpersonal problems, ineffectiveness, anhedonia, negative self-esteem, in addition to an overall score. The total score is determined by adding all subscale scores, and can range from 0 to 54. A score of 12 has been proposed to be a cut-off for youth at-risk for clinical depression is 12 (90th percentile among youth) (Kazdin, Colbus, & Rodgers, 1986). Total CDI score was used, and examined along a continuum for the purposes of this study.

Socioeconomic Status

The Hollingshead Two-Factor Scale was completed by parents to assess socioeconomic status (SES) based upon parental occupation and education level. The scores range from 1-5 (1= highest SES bracket, 5= lowest SES bracket) (Hollingshead, 1975).

Procedures

Outpatient Evaluation

For the first assessment, participants were seen in the pediatric outpatient clinic where a medical history was conducted. During this visit, fasting blood tests for normal metabolic function were performed (including HDL and LDL cholesterol, triglycerides, free fatty acids, and insulin). Vital signs, including blood pressure, height and weight, were collected, as well as an examination to determine pubertal stage. During this visit, psychological questionnaires, including the CDI were administered by a trained examiner, and examination of socioeconomic status was collected using the Hollingshead scale. Finally, a screening 2hr oral glucose tolerance test was conducted to assess insulin resistance.

Inpatient Admission

During a separate visit, participants were admitted overnight to the inpatient pediatric ward of NIH for 24-hour urine collection in order to measure urine free cortisol (in addition to 17-hydroxycorticosteroids and creatinine for the an evaluation of hypercortisolism). A hyperglycemic clamp was conducted during this visit, in addition to the QEWP-A.

Power analysis

A priori power analyses were conducted using nQuery. For a multiple linear regression model (that includes five covariates) with a squared multiple correlation R^2 of 0.15, a sample size of 400 will have 80% power to detect at an alpha of 0.05 an increase in R^2 of 0.012 due to including one additional covariate.

Data Analytic Strategy

Preliminary Data Analysis

Data were examined for outliers and problems of skew or kurtosis. All variables approximated a normal distribution (skew < 3 and kurtosis < |10|). Outliers (.86% of all data points) were recoded to approximately ± 3 standard deviations of the mean.

This study has three specific aims. The first aim will be to determine if there is a relationship between binge eating in children and adolescents and metabolic dysfunction. The second specific aim will be to investigate if there is a relationship between binge eating in children and adolescents and metabolic dysfunction, after accounting for body mass index (BMI). Finally, we will investigate whether the relationship between binge eating and metabolic dysfunction in children and adolescents is mediated by urine free, log-transformed cortisol.

Aim One: To determine if there is a relationship between binge eating in children and adolescents and metabolic dysfunction.

Based on previous research, it is hypothesized that the presence of binge eating in children and adolescents will be associated with metabolic dysfunction. In particular, binge eating will be associated with an increase in insulin resistance and abdominal obesity. This hypothesis is based on previous cross-sectional (E. Epel et al., 2004) and longitudinal research in adults (Hudson et al., 2010), and children and adolescents (Lourenco et al., 2008; Taylor et al., 1999). In the present study, binge presence will be operationalized as a dichotomous variable according to endorsement of ≥ 1 binge episode on the Questionnaire on Eating and Weight Patterns- Adolescent Version (QEWP-A) in the past 6 months. Metabolic dysfunction will be examined continuously using the following components: waist circumference (cm), serum insulin (UU/mL), serum glucose (mg/dL), insulin resistance (using the homeostatic model of insulin resistance, or HOMA-IR), serum triglycerides (mg/dL), serum cholesterol (total cholesterol, HDL cholesterol and LDL cholesterol in mg/dL), and systolic and diastolic blood pressure (mmHg). Additionally, metabolic dysfunction will be examined categorically as a dichotomous variable of metabolic syndrome. Metabolic syndrome will be defined by the presence of 3 or more of the following factors: waist circumference ≥ 90^{th} percentile for age and sex; triglycerides ≥ 90^{th} percentile for age and sex; HDL cholesterol ≤ 10^{th} percentile for age and sex; blood pressure ≥ 95^{h} percentile for height, age and sex and fasting glucose ≥ 110 mg/dL.

Data analytic strategy for Aim One

Independent sample t-tests will be used to examine the relationship between binge eating and metabolic dysfunction. The grouping variable will be binge presence (yes/no) and the test variable will be each metabolic dysfunction variable mentioned above. Additionally, a chi-square test will be used to examine the relationship between binge eating and metabolic

syndrome, as a dichotomized variable. Given that multiple comparisons will be made, a Bonferroni adjusted alpha level of .008 (.05/6) will be used.

Aim Two. : Relationship between binge eating and metabolic dysfunction in children and adolescents, after accounting for BMI-z.

It is hypothesized that the presence of binge eating in children and adolescents will be associated with metabolic dysfunction after accounting for BMI-z, which is a standardized measure of BMI based on Center for Disease Control growth charts for children and adolescents. Again, endorsement of ≥ 1 binge episode on the Questionnaire on Eating and Weight Patterns-Adolescent Version (QEWP-A) in the past 6 months will be used to operationalize binge presence. Similarly, metabolic dysfunction will be examined continuously using the following components: waist circumference (cm), serum insulin (UU/mL), serum glucose (mg/dL), insulin resistance (using the homeostatic model of insulin resistance, or HOMA-IR), serum triglycerides (mg/dL), serum cholesterol (total cholesterol, HDL cholesterol and LDL cholesterol in mg/dL), and systolic and diastolic blood pressure (mmHg). BMI-z will be examined as a continuous variable.

Data analytic strategy for Aim Two

A series of ANCOVAs will be used to examine the influence of BMI-z on the relationship between binge presence and metabolic dysfunction. Binge presence will represent the fixed factor variable, BMI-z will be examined as a covariate, and each metabolic dysfunction component will be examined as a dependent variable. Given that multiple comparisons will be made, a Bonferroni adjusted alpha level of .008 (.05/6) will be used.

Aim Three. : To evaluate whether the relationship between binge eating and metabolic dysfunction in children and adolescents is mediated by cortisol.

It is hypothesized that there will be a relationship between the presence of binge eating and cortisol, there will be a relationship between cortisol and metabolic dysfunction, and that urine free cortisol will mediate the relationship between binge eating and metabolic dysfunction. The relationship between binge eating and cortisol is supported in a number of adult studies ((E. Epel et al., 2001; Gluck et al., 2004; Lingswiler et al., 1987) as well as some child and adolescent studies (Czaja et al., 2009; Eddy et al., 2007; Goossens et al., 2007; Shapiro et al., 2007). Additionally, relationships between cortisol and metabolic dysfunction have been observed in a number of recent studies in adults (Agardh et al., 2003; Bjorntorp & Rosmond, 2000a; Chandola et al., 2006; E. S. Epel et al., 2000) and pediatric samples (Raikkonen et al., 2003; Shomaker et al., 2010).

Again, endorsement of ≥ 1 binge episode on the Questionnaire on Eating and Weight Patterns- Adolescent Version (QEWP-A) in the past 6 months will be used to operationalize binge presence. Similarly, metabolic dysfunction will be examined continuously using the following components: waist circumference (cm), serum insulin (UU/mL), serum glucose (mg/dL), insulin resistance (using the homeostatic model of insulin resistance, or HOMA-IR), serum triglycerides (mg/dL), serum cholesterol (total cholesterol, HDL cholesterol and LDL cholesterol in mg/dL), and systolic and diastolic blood pressure (mmHg). Urine free cortisol will also be examined continuously. We will examine 24-hour urine free cortisol collected during an inpatient stay (ug/24/m^2), that is log-transformed and adjusted for body surface area (Haycock et al., 1978)

Data Analytic strategy for Aim Three

The Sobel Test (MacKinnon & Dwyer, 1993) will be used to test for mediation. Cortisol may be considered a mediator to the extent to which it carries the influence of binge presence (the independent variable) to metabolic dysfunction (the dependent variable). Generally speaking, mediation can be said to occur when (1) the IV (binge presence) significantly affects the mediator (cortisol), (2) the IV (binge presence) significantly affects the DV (metabolic dysfunction) in the absence of the mediator (cortisol), (3) the mediator (cortisol) has a significant unique effect on the DV (metabolic dysfunction), and (4) the effect of the IV (binge presence) on the DV (metabolic dysfunction) shrinks upon the addition of the mediator (cortisol) to the model.

Results

Participant characteristics. A total of 396 youth participated: 179 children participating in the longitudinal study and 217 adolescents in the weight loss study prior to treatment. A majority (86%) of these children were overweight (BMI > 85th percentile, Ogden et al., 2010; BMI mean ± SD = 33.06 ± 11.66 kg/m^2, range = 13.20 - 62.85), and slightly more were female (57%). The entire sample consisted of similar percentages of African American (51%) and Caucasian (49%) participants. Participant demographic and anthropometric characteristics are displayed separately for each study in Table 1. Compared to children in the longitudinal study, youth in the adolescent weight loss study were significantly older and heavier (both by design), and were more likely to be female and African American (*p*s < .01; Table 1).

As expected due to the nature of the study designs, there were significant differences in metabolic characteristics among children at-risk for adult obesity and youth in the adolescent obesity study. Compared to the child sample, the adolescent sample had significantly higher systolic blood pressure (108.22 ± 12.56 vs. 122.96 ± 13.47 mmHg), diastolic blood pressure (62.89 ± 7.03 vs. 67.18 ± 8.06 mmHg), waist circumference (71.56 ± 14.32 vs. 108.98 ± 14.58

cm), insulin resistance (2.22 ± 1.56 vs. 6.36 ± 3.58 mg/dL), and triglycerides (71.91 ± 34.10 vs. 114.75 ± 56.53 mg/dL, children at-risk for adult obesity study vs. adolescent obesity study, respectively, all *p*s < .001). Also, a significantly greater percentage of the adolescent sample met criteria for metabolic syndrome (16.2%, n = 34) compared to the child sample (6.8%, n = 11, χ^2 = 7.49, p = .006). Given the significant demographic and metabolic differences between the two groups, primary analyses were performed separately for each study sample, and secondary analyses examined the combined sample as a whole.

Results for Longitudinal Study Sample

Relationships between youths' binge eating and metabolic characteristics. Table 2 displays the unadjusted comparisons of metabolic characteristics in youth with and without binge eating for each study sample. Given that multiple comparisons were made, a Bonferroni adjusted alpha level of .008 (.05/6) was used. Children in the longitudinal study with binge eating had significantly higher total cholesterol (p = .024), LDL cholesterol (p = .03), waist circumference (p = .001), insulin (p = .035), and insulin resistance (p = .03) than children without binge eating (Table 2). However, these relationships were no longer significant when accounting for age, sex, race, and BMI-z (*p*s = .11 to .97). When metabolic syndrome was considered categorically, there was no statistically significant relationship between binge eating status and metabolic syndrome (χ^2 = 2.11, p = .16).

Binge eating, urine free cortisol, and metabolic characteristics. Among children in the longitudinal study, analyses examining the relationship between binge eating status and urine free cortisol indicated no significant difference between children with and without binge eating (p = .44). With respect to the relationship between urine free cortisol and metabolic

characteristics (using a a Bonferroni adjusted alpha level of .008 (.05/6)), there was a significant association between urine free cortisol and HDL cholesterol (F= 5.30, p = .023) as well as between urine free cortisol and triglycerides (F= 5.00, p = .028). However, when adjusting for BMI-z, neither of these relationships remained significant (ps > .05). The relationship between urine free cortisol and metabolic syndrome classification was significant, such that children with metabolic syndrome had higher levels of log-transformed urinary free cortisol (3.66 ± .36 ug/24) compared with children who did not have metabolic syndrome (3.07 ± 56 ug/24, t = 3.05, p = .003). This relationship remained significant when adjusting for BMI-z (p = .027).

Examination of frequent binge eating. We also explored the relationship between frequent binge eating (defined as reported binge episodes occurring at least two days a week for the past six months) and metabolic characteristics. Within the children in the longitudinal study, four (2.2%) children endorsed frequent binge eating. Compared to those without frequent binge eating, children with frequent binge eating had significantly higher levels insulin resistance (4.23 vs. 2.19, p = .02). This difference was no longer significant after adjusting for BMI-z, age, sex, and race, (p = .67).

Results for Adolescents Weight Loss Study Sample

Relationships between youths' binge eating and metabolic characteristics. In the adolescent weight loss study sample (using a a Bonferroni adjusted alpha level of .008 (.05/6)),, those with binge eating tended to have higher LDL cholesterol compared to adolescents who did not report binge eating, but not significantly (p = .09; Table 2). No significant differences were observed in other metabolic characteristics. When metabolic syndrome was considered categorically, there was no statistically significant relationship between binge eating status and metabolic syndrome (χ^2 = .029, p = .74).

Binge eating, urine free cortisol, and metabolic characteristics. Adolescents in the weight loss study with binge eating did not exhibit significantly different levels of urinary free cortisol compared to those who did not report binge eating (p = .67). However (using a a Bonferroni adjusted alpha level of .008 (.05/6)), there was a significant positive correlation between urine free cortisol and LDL cholesterol (r = .23, p = .002). After accounting for BMI-z, age, sex, and race, the relationship of urine free cortisol with LDL cholesterol (p = .002) remained significant.. There was no relationship between urine free cortisol and metabolic syndrome classification in this sample (p = .74).

Examination of frequent binge eating. Within the adolescent weight loss study, eight (3.2%) adolescents reported frequent binge eating. There was a significant relationship between frequent binge eating status and LDL cholesterol such that those with frequent binge eating had higher LDL cholesterol than those with infrequent or no binge eating (142.83 vs. 111.65 mg/dL, p = .02).

Results for the Combined Study Samples

Relationships between youths' binge eating and metabolic characteristics. As a secondary analysis, we examined the relationship between binge eating status and metabolic characteristics across the entire sample (i.e., both studies combined). Binge eating was significantly associated with LDL cholesterol in unadjusted analyses (p = .01) and analyses adjusted only for BMI-z (p = .04) using a a Bonferroni adjusted alpha level of .008 (.05/6). However, adjusting for age, sex, and race in addition to BMI-z, the relationship between binge eating and LDL cholesterol did not reach statistical significance (p = .09). Additionally, binge eating was significantly associated with total cholesterol in unadjusted analyses (p = .02) but not in analyses adjusted for BMI-z (p = .24). When metabolic syndrome was considered

categorically, there was no statistically significant relationship between binge eating status and metabolic syndrome ($\chi^2 = .53$, $p = .44$).

Binge eating, urine free cortisol, and metabolic characteristics. In secondary analyses, we also examined the relationship between binge eating status and urine free cortisol in the entire sample. Consistent with the primary analyses, binge eating was not significantly associated with urine free cortisol in either unadjusted analyses or analyses adjusted for BMI-z, age, sex, and race (*ps* = .32 & .35, respectively). However, (using a a Bonferroni adjusted alpha level of .008 (.05/6)), urine free cortisol was significantly related to LDL cholesterol (r = .16, p = .001), waist circumference (r = -.26, $p < .001$), and triglycerides (r = .19, p = .001). When adjusting for BMI-z, age, sex, and race, the relationship between urine free cortisol and LDL cholesterol remained significant (p = .001). The relationship between urine free cortisol and triglycerides remained significant when adjusting for BMI-z (p = .009), however when adjusting for BMI-z, age, sex, and race, this relationship only trended toward significance (p = .07). There was no significant relationship between urine free cortisol and metabolic syndrome diagnosis (p = .09).

Discussion

In this study, we examined the relationship between binge eating, urine-free, cortisol and metabolic dysfunction in two separate samples; one among children at high-risk for adult obesity and the second in a sample of obese adolescents prior to participating in a weight-loss trial. The two samples were combined to explore these relationships among a diverse range of BMI-z, and analyzed separately as well. Because there were significant demographic and metabolic differences between the two groups, primary analyses were performed separately for each study sample, and secondary analyses examined the combined sample as a whole.

Children at-risk for Adult Obesity

Relationships between youths' binge eating and metabolic characteristics. Among children who were at risk for adult obesity (by virtue of their own overweight, or having overweight parents), binge eating was associated with total cholesterol, LDL cholesterol, waist circumference, insulin, and insulin resistance. Consistent with adult research (E. Epel et al., 2004; Hudson et al., 2010; Taylor et al., 1999), binge eating may be associated with metabolic dysfunction in children at-risk for adult obesity. This finding has clinical implications, in that binge eating in youth may serve as a potential marker for metabolic dysfunction among non-overweight and overweight children. However, in youth, these associations are primarily accounted for by body weight. These results echo other studies that have failed to find a cross-sectional link between binge eating and metabolic dysfunction after accounting for BMI-z (Adami et al., 1995; Lourenco et al., 2008; Wadden et al., 1993).

Binge eating was studied as a dichotomized variable, using self-report measures. It may be more beneficial to examine binge eating in terms of severity, using an interview measure of eating pathology. Indeed, it has been suggested that interview methods are superior to self-reports of aberrant eating behaviors (DecaluwÈ & Braet, 2004). Additionally, there is a lack of a clear definition of metabolic syndrome in youth, and very little is understood about how metabolic dysfunction manifests in children. Furthermore, our sample of 5 to 12 year olds may be too young to observe metabolic dysfunction and/or binge eating, as both pathologies often manifest later in adulthood.

Despite these limitations, the findings lend support for some relationship between binge eating and the presence of metabolic dysfunction in children. As little is understood about the relationship between binge eating and metabolic dysfunction in youth, the results of the current

study help to fill the gaps in this burgeoning field of health research. This study used highly valid physiological measures of metabolic dysfunction among a group of children across a broad range of weights, rather than self-reported metabolic dysfunction as in previous studies.

Relationships between youths' binge eating, urine-free cortisol and metabolic characteristics. Binge eating was not related to urine-free cortisol. Interestingly, and in concert with the adult literature (Chandola et al., 2006; E. S. Epel et al., 2000; Raikkonen et al., 2002), there did appear to be a relationship between cortisol and metabolic dysfunction in children at-risk for adult obesity. Cortisol was associated with metabolic syndrome, such that children with metabolic syndrome had higher levels of cortisol compared to children who did not have metabolic syndrome, even when adjusting for BMI-z.

It is plausible that in this sample, the adverse consequences of chronic stress have resulted in disturbed metabolic functioning, above the contributions of weight alone, suggesting a distinct stress-mediated pathway towards metabolic dysfunction. Given the cross-sectional nature of the current study, however, causation between cortisol and metabolic dysfunction cannot be inferred. Longitudinal research is necessary to examine if cortisol, in addition to binge eating, exerts a unique effect on metabolic characteristics beyond the effects of weight gain. Given that only one prospective study to date has found a relationship between baseline binge eating disorder in adults and components of the metabolic syndrome at 5-year follow-up (Hudson et al., 2010), more longitudinal data are needed. Specifically, such data in pediatric samples are vital.

In summary, among children at-risk for adult obesity by virtue of their own overweight, or having overweight parents, the relationship between binge eating and metabolic dysfunction is primarily accounted for by children's body weight. However cortisol is uniquely related to full

metabolic syndrome in youth, suggesting that metabolic dysfunction may manifest through the stress pathway.

Adolescent Weight Loss Study Sample

Relationships between youths' binge eating and metabolic characteristics. No relationship between binge eating and any component of metabolic dysfunction was identified in either unadjusted or adjusted analyses among obese adolescents. This finding is likely due to the high prevalence of metabolic dysfunction among this weight-loss treatment-seeking sample of obese adolescents, regardless of the presence of binge eating (e.g., 16.2% met full criteria for metabolic syndrome and 20% had at least one symptom of metabolic dysfunction) making it difficult to detect the relationship between binge eating and metabolic dysfunction. However, among those participants who reported frequent binge eating (n = 8, 3.2%), there was a significant relationship between binge eating and LDL cholesterol, even after adjusting for BMI-z, suggesting that the severity of eating pathology among obese adolescents may be more important in terms of elucidating a relationship with metabolic dysfunction.

Relationships between youths' binge eating, urine-free cortisol and metabolic characteristics. As in the child sample, among this sample urine-free cortisol was not associated with binge eating. However, cortisol was associated with metabolic dysfunction. Even after adjusting for BMI-z, cortisol was related to higher levels of LDL cholesterol. Again, as with the child sample, there is the possibility that among older, obese weight-loss treatment-seeking youth the adverse consequences of chronic stress have resulted in disturbed metabolic functioning, above the contributions of weight alone, suggesting a distinct stress-mediated pathway towards metabolic dysfunction.

The finding that binge eating was not associated with cortisol in either children or adolescents was surprising. While the relationship between cortisol and binge eating has been largely unexplored in youth, in adults this is a rather consistent finding (Gluck et al., 2004; Lingswiler et al., 1987). One potential explanation for this lack of a relationship between binge eating and cortisol in youth is that abnormalities in the HPA-axis have not yet manifested youth with binge eating behaviors. In fact, the current study also failed to find a relationship between BMI-z and cortisol, a highly established relationship in adult studies (Bjorntorp & Rosmond, 2000b; Vicennati, Pasqui, Cavazza, Pagotto, & Pasquali, 2009). Therefore, childhood and adolescence may be an important point of preventive intervention for youth with binge eating, given the strong links between eating pathology, psychosocial stress, and HPA-axis dysregulation in adulthood (E. Epel et al., 2001; Gluck et al., 2004; Lingswiler et al., 1987).

In summary, among obese, treatment-seeking adolescents, the presence binge eating did not appear to be associated with metabolic dysfunction, however more severe binge eating was associated with metabolic dysfunction. Furthermore, among obese adolescents, cortisol was associated with metabolic dysfunction, similar to children at-risk for adult obesity, conferring the possibility of a unique relationship between stress pathways and metabolic dysfunction, independent of weight gain.

Strengths

Strengths of this study include use of well-validated psychological and physiological measures among children and adolescents to explore the relationships among the relatively unstudied area of binge eating and metabolic dysfunction in youth. This study used highly valid measures of metabolic dysfunction among a group of children across a broad range of weights, rather than self-reported metabolic dysfunction as in previous adult studies. Additionally, this

study is novel in its use of direct physiological measures of stress via 24-hour urine-free cortisol rather than less reliable self-report measures as in previous studies (Hudson et al., 2010).

Limitations

A significant limitation of the study involves controversy with regard to urine-free cortisol as an effective measure of chronic stress. For instance, collection of urine samples over a period of 24-hours may in and of itself be stressful, above and beyond a child's normal level of stress throughout the day. In fact, with respect to cortisol, controversy surrounds its ability to capture reactivity to stress, including chronic stress (Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008). Indeed, high cortisol levels do not necessarily indicate greater levels of chronic stress. Cortisol has a number of different effects on the HPA axis, and studies of cortisol levels among adults with binge eating have produced mixed findings (Lo Sauro et al., 2008). A recent review of stress measures among individuals with eating disorders (Lo Sauro et al., 2008) highlights the potential for using other measures such as CRH (corticotrophin-releasing hormone), AVP (arginine vasopressin), ACTH (adrenocorticotropic hormone) and norepinephrine as biological markers of stress that may be more reliable. Additional biomarkers of stress should be examined, including epinephrine, norepinephrine, salivary cortisol, serum dihydroepiandrosterone sulphate (DHEA-S), insulin-like growth factor 1 (IGF1), and interleukin 6 (IL6), in addition to self-reported measures of stress (both trait and state measures of stress). Reactivity to stress among youth with binge eating should ideally be measured following a lab-induced stress (Gluck et al., 2004) or via ecological momentary assessments of stress (Smyth et al., 1998).

Conclusion

The results of the current study elucidate the relationships between binge eating and metabolic dysfunction in two high-risk samples. As little is understood about the relationship between binge eating in youth, cortisol and metabolic dysfunction, this study has used well-validated psychological and physiological measures among children and adolescents. Additionally, this study is novel in its use of direct physiological measures of stress via 24-hour urine-free cortisol, and metabolic dysfunction, rather than less reliable self-report measures as in previous studies (Hudson et al., 2010). Childhood and adolescence may be an important point for preventive interventions in youth with binge eating, given the links between eating pathology, psychosocial stress, metabolic dysfunction and HPA-axis dysregulation in adulthood. Longitudinal research in addition to different biomarkers of stress (e.g., epinephrine, norepinephrine, salivary cortisol, serum dihydroepiandrosterone sulphate and interleukin 6) may be vital to understand the nature of the relationship between binge eating and metabolic dysfunction more fully. Additionally, lab-induced stressors (Gluck et al., 2004) as well as ecological momentary assessments of stress (Smyth et al., 1998) may provide more valid assessments of psychosocial and physiological distress in youth.

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Table 1

Demographic and anthropometric characteristics of participants in each sample

Variable	Children At-Risk for Adult Obesity (BMI > 85th %ile or obese parent) (n = 179)	Obese Adolescents (BMI >95th %ile) (n = 217)	Combined Sample (n = 396)	T or χ^2
Age (y)[a]	8.6 ± 1.7 (5- 16)	14.5 ± 1.5 (11- 18)	11.5 ± 3.3 7 (5- 18)	-38.11***
Sex (%)	49.5% Female	64.3 % Female	57% Female	6.55**
Race (%)	61.3% Caucasian 38.7% AA[b]	39% Caucasian 61% AA[b]	50% Caucasian 50% AA[b]	18.78***
BMI (kg/m^2)[a]	23.05 ± 6.2 (13.2 - 41.4)	41.11 ± 8.3 (27.00 - 62.85)	33.06 ± 11.66 (13.20 - 62.85)	-24.71***
BMI-z[a]	1.56 ± 1.0 (-1.28 - 3.40)	2.53 ± .35 (1.54 - 3.52)	2.10 ± .88 (-1.28 - 3.52)	-11.90***
BMI percentile[a]	85.51 ± 21.59 (2.86 - 99.97)	99.14 ± .93 (93.97 - 99.97)	93.07 ± 15.92 (2.86 - 99.97)	-8.34***
Height (cm)[a]	136.77 ± 12.5 (107.3 - 167.3)	164.36 ± 8.76 (142.95 - 191.50)	151.96 ± 17.34 (107.30 - 191.50)	-24.98***
Weight (kg)[a]	44.18 ± 17.48 (17.40 - 90.95)	114.38 ± 25.98 (69.90 - 185.95)	82.81 ± 41.60 (17.40 - 185.95)	-32.07***
SES (median)	3	3	3	7.93

[a]M ± SD (Range).

[b]AA = African American.

*p < .05, **p < .01, ***p < .001.

Table 2

Metabolic characteristics of youth with binge eating (BE) compared to youth without binge eating

	Children At-Risk for Adult Obesity (BMI > 85th %ile or obese parent) (n=179)			**Obese Adolescents (BMI >95th %ile) (n= 217)**		
Variable[a]	**BE (n=24)**	**No BE (n=155)**	**t or χ^2**	**BE (n=17)**	**No BE (n=203)**	**t or χ^2**
Total Cholesterol (mg/dL)	183 ± 26.3 (139 - 249)	167.3 ± 29.8 (95 – 249)_	-2.28*	*Data not available*		
HDL (mg/dL)[b]	45.4 ± 10.7 (25 - 62.5)	46.7 ± 9.6 (22 - 62.5)	.60	40 ± 6.8 (27 - 51)	41.1 ± 8.2 (25 - 62.5)	.51
LDL (mg/dL)[c]	120.4 ± 25.5 (71.2 - 171.6)	107.6 ± 25.6 (41.2 - 180)	-2.14*	126.2 ± 33.6 (64 - 191)	111.5 ± 31.8 (16 -192.5)	1.72†
Waist (cm)	80.3 ± 14.8 (51.2 - 112)	70.2 ± 13.8 (50.6 - 112)	-3.32***	110.2 ± 16.4 (87.9 - 150)	108.9 ± 14.5 (83.3 - 150.6)	.36
HOMA-IR[d]	2.90 ± 1.8 (.59 - 6)	2.1 ± 1.5 (.4 - 6)	-2.17*	5.9 ± 2.5 (2.6 - 10)	6.4 ± 3.7 (-3.7 - 15.4)	-.50
Insulin (UU/mL)	12.9 ± 7.8 (3 - 26.4)	9.6 ± 6.6 (2 - 26.4)	-2.12*	24.9 ± 10.3 (13 - 43.5)	29.2 ± 15 (4.2 - 65.9)	-1.15
Glucose (mg/dL)	89.8 ± 5.9 (80 - 101)	88.4 ± 6.2 (74 - 103)	-.96	92.2 ± 10.3 (75 - 109.5)	86.9 ± 12.1 (-9 - 109.5)	1.69†
Trig (mg/dL)[e]	78 ± 37.4 (41 - 145.3)	71 ± 33.6 (5 - 145.3)	-.88	107.7 ± 53.6 (56 - 254.5)	115.3 ± 56.9 (0 - 254.5)	-.53

SBP (mmHg)[f]	110.3 ± 13.5 (74 - 134.4)	107.9 ± 12.4 (60 - 134.5)	-.86	125.4 ± 12.4 (103 - 151)	122.8 ± 13.6 (90 - 158)	.76
DBP (mmHg)[g]	62.2 ± 9 (44 - 80.5)	63 ± 6.7 (47 - 80.5)	.54	66.9 ± 8 (52 - 81)	67.2 ± 8.1 (45 - 88.5)	-.16
MetS (%)[h]	14.3% (n=3)	5.7% (n=8)	2.11	17.6% (n=3)	16.1% (n=31)	.029

[a]M ± SD (Range)

[b]HDL= High-density Lipoprotein; [c]LDL= Low-density Lipoprotein; [d]HOMA-IR=Homeostatic Model of Insulin Resistance; [e]Trig=Triglycerides; [f]SBP= Systolic Blood Pressure; [g]DBP= Diastolic Blood Pressure; [h]MetS=Metabolic Syndrome, defined as 3 or more components of waist circumference ($\geq 90^{th}$ percentile), HDL cholesterol ($<10^{th}$ percentile), glucose ($\geq$100 mg/dL), blood pressure ($\geq 90^{th}$ percentile), and triglycerides ($\geq 90^{th}$ percentile).

[†]p <.10, *p < .05, **p < .01, ***p ≤ .001