The Relationships Among Stress, Loss of Control Eating, and Physical Health in Youth

by

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ABSTRACT

Title of Dissertation: The Relationships Among Stress, Loss of Control Eating, and Physical Health in Youth

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The subjective experience of loss of control (LOC) over eating, regardless of the amount of food consumed, is commonly reported by youth, particularly among those prone to excess weight. Youth with LOC eating are at increased risk for weight and fat gain. Preliminary research suggests that youth with LOC eating are at increased risk of adverse metabolic outcomes, even after adjusting for adiposity. Affect regulation theories, such as interpersonal theory, propose that LOC eating occurs in response to psychological stressors; however, no study has examined the relationship between temporally sensitive reports of stress, negative affect, and food intake in youth with LOC eating. Three studies were conducted to further our understanding of the relationships between stress, LOC eating, and physical health. The first study examined whether youth with LOC eating have elevated high-sensitivity C-reactive protein (hsCRP), a marker of chronic inflammation, compared to youth without LOC eating. Chronic inflammation has been implicated in the development of deleterious health outcomes, including metabolic syndrome and cardiovascular disease. In a sample of 194 youth, youth with LOC eating had significantly

greater hsCRP than youth without LOC eating (p = .02). This finding suggests that youth with LOC eating may be an important subgroup at risk for adverse inflammation-related outcomes. The second study was a secondary analysis of a trial that enrolled adolescent girls with excess weight and LOC eating, and examined whether LOC remission (vs. persistence) at end-of-treatment was associated with changes in metabolic syndrome components at 6-month follow-up. In a sample of 103 adolescent girls, youth with LOC eating remission at end-of-treatment had lower glucose (p = .02), higher high-density lipoprotein cholesterol (p = .01), and lower triglycerides (p = .02) at follow-up compared to youth with persistent LOC eating. No other component differed by LOC eating status (ps > .05). These findings lend support to a causal relationship between LOC eating and cardiometabolic health, and suggest that reducing or eliminating LOC eating in adolescent girls may have a beneficial impact on some components of the metabolic syndrome. The third study examined the role of interpersonal stress in the relationships between LOC eating, mood, and eating behavior by examining the interpersonal model of loss of control eating in the laboratory. In a sample of 117 adolescent girls with excess weight and LOC eating, only pre-meal state anxiety was a significant mediator for recent social stress and palatable food intake (p < .05). These findings suggest that interventions that focus on improving both social functioning and anxiety may prove most effective at preventing and/or ameliorating disordered eating in these adolescents. Taken together, the findings from these three studies provided a foundation for the development of a novel conceptual model that proposes integrative relationships among acute stress, LOC eating, dietary intake, mood symptoms, fat mass, chronic inflammation, and adverse physical health outcomes such as metabolic syndrome. Future research should focus on elucidating the prospective relationships among these variables, with a particular focus on the potential role of stress reactivity in these relationships. The

integration of psychological stress, disordered eating, and physical health may elucidate the mechanisms through which adverse health outcomes occur, potentially providing a pathway for novel pediatric prevention and intervention programs.

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CHAPTER 1: Introduction

OVERVIEW

The subjective feeling of loss of control (LOC) over eating, or the perceived inability to control what or how much one is eating, is commonly reported by youth. LOC eating is predictive of excess weight and fat gain (157; 457; 473), and preliminary research suggests that youth with LOC eating are at increased risk of adverse physical health outcomes, such as metabolic syndrome, above and beyond the contribution of adiposity (369; 465). It is theorized that LOC eating is a learned behavior that is developed and/or maintained as a coping response to psychological stressors and/or negative affect (28; 189; 237), which may at least partially explain the relationship between LOC eating and adverse health outcomes (145; 229). To elucidate this possibility, this dissertation involves a series of three studies directed at understanding the relationships among stress, LOC eating, and physical health in youth. Two of the three studies examine the relationships between LOC eating and physical health (studies 1 and 2), while the third study examines the impact of recent social stress on eating in youth with LOC eating. This dissertation will provide a background on these topics, present the studies, summarize and integrate the findings across the three investigations, and discuss ongoing and future directions based on this foundational program of research.

OVERWEIGHT AND OBESITY IN THE UNITED STATES

In the United States, overweight and obesity have become endemic conditions. Adult body weight categories such as overweight and obesity are classified using body mass index (BMI), which is calculated by dividing weight in kg by height in meters squared (362). Using BMI, overweight for adults is classified as having a BMI between 25.0 and 29.9, while obesity for adults is classified as having a BMI of 30 or greater (362). The epidemic of

overweight/obesity in the United States has significant costs to society, both direct through healthcare costs, as well as indirect through pathways such as lost productivity (90). Direct medical costs are estimated to be 42% higher among adults with obesity compared to healthy weight adults (132), and it is estimated that in 2008, the medical costs attributable to obesity was $147 billion in the United States alone (133).

Prevalence of Overweight and Obesity

The prevalence of adults with overweight/obesity has increased markedly over the past several decades in the United States (135) as well as worldwide (336). For 2009-2010, the age-adjusted prevalence of overweight and obesity was 68.8% in the United States, with 73.9% of men and 63.7% of women meeting criteria for overweight/obesity (134). For 2015-2016, the prevalence of adults with obesity in the United States is estimated to 39.8% (179). For children and adolescents, overweight is defined as at or above the 85th percentile and obesity is defined as at or above the 95th percentile, adjusted for age and sex (255; 258; 341). It is estimated that 18.5% of children in the United States aged 2-19 years have obesity (179) and 1 in 3 children in the United States have overweight or obesity (258). Approximately 55% of children with obesity and 80% of adolescents with obesity continue to have obesity in adulthood (418).

Etiology of Obesity

Obesity arises from an imbalance of energy intake and energy expenditure (258; 362). However, the etiology of obesity is complex (362; 391), involving genetic, behavioral, psychosocial, and environmental contributions (56; 181; 208; 213; 258; 287; 308; 433). The heritability of obesity is estimated to be 50-70% (258; 308; 497), with polygenetic obesity most commonly observed, in which a large number of genes appearing to have partial and additive contributions to the risk of obesity (213; 258; 308). Obesity in both children and adults is

associated with a number of adverse health conditions such as type 2 diabetes, nonalcoholic fatty liver disease, hypertension, heart disease, obstructive sleep apnea, musculoskeletal problems, and dyslipidemia (208; 258; 287). Obesity has also been associated with certain types of cancer, such as breast, colon, kidney, and esophageal cancer (208; 287). It is also associated with psychosocial problems, such as depression, anxiety, and poor self-esteem (117; 258).

The complex etiology of obesity (56) is likely reflected in the limited success of behavioral and lifestyle interventions with regard to weight loss and weight loss maintenance (117). Within a few years after behavioral intervention, most individuals regain all lost weight (117; 397). The refractory nature of obesity has led researchers to propose subtyping individuals with obesity so that specific, targeted interventions may be designed and implemented (56; 126). For example, two subtypes of obesity may be individuals with a low responsiveness to internal satiety signals and individuals who report binge eating. If these were established to be two distinct subtypes, then these subtypes would likely benefit from two different interventions (126). The focus of this proposal will involve one potential subtype of obesity, specifically individuals with who report behaviors related to binge eating.

BINGE EATING DISORDER

Binge eating disorder (BED) is characterized by recurrent episodes of consuming objectively large amounts of food while experiencing a subjective sense of lack of control (22). For an individual to meet criteria for BED, these episodes must occur an average of once a week for the past three months, must cause significant distress, and involve at least three of the following factors: eating rapidly, eating until uncomfortably full, eating large amounts when not physically hungry, eating alone out of embarrassment, or feeling disgusted, depressed or guilty (22). BED cannot be diagnosed if recurrent inappropriate compensatory behaviors, such as

purging or excessive exercise, are endorsed and cannot occur exclusively within the context of bulimia nervosa or anorexia nervosa (22).

The average age of onset of full-syndrome BED is 23.3 years (240), and the point prevalence of BED in adults is estimated to range from less than 1% to 5% in community samples (84; 98; 210; 240; 288; 328; 425; 446). Elevated rates of BED are found in individuals with excess weight, and the estimated prevalence in adults seeking weight-loss treatment is 16-30% (84; 98; 210; 240). Women also have elevated rates of BED compared to men (85; 240; 425). The lifetime and 12-month prevalence of BED for women is estimated to be 3.5% and 1.6%, respectively, while the lifetime and 12-month prevalence of BED for men is estimated to be 2.0% and 0.8%, respectively (22; 210).

Comorbidities of BED

BED is associated with a number of adverse psychological and physical comorbidities. It is estimated that 74-79% of individuals with BED have a lifetime diagnosis of another psychological disorder (169; 210; 387). The presence of BED is associated with increased depressive symptoms and rates of major depressive disorder (33; 85; 257; 314; 477; 515), increased rates of anxiety disorders (169; 172; 387), increased eating-related psychopathology (85; 257; 448; 477), decreased self-esteem (86; 448), and increased rates of personality disorders (85; 477; 515). BED is also associated with impairments in health-related quality of life and increased healthcare utilization and costs (8; 9). This may be due, in part, to findings that BED in adults is associated with elevated chronic inflammation (450) and an increased risk of adverse health conditions such as pain conditions (240; 342), diabetes (211; 240; 342; 370), impaired glucose (313), dyslipidemia (211; 313; 342), hypertension (211; 240; 313; 342), metabolic syndrome (211), and gastrointestinal disorders (342). Therefore, targeting BED is important in

order to avoid or minimize these significant adverse psychological and physical comorbidities.

Pediatric Loss of Control Eating

Full criteria for BED are rarely met in youth (461). In growing children and adolescents, it can be difficult to determine the appropriate amount of food that would qualify as objectively large, given varying nutritional needs (204; 214; 254; 415; 461). Youth may also have difficulties reporting their eating behavior (416; 456), and the type of assessment methodology can impact the determination of objectively large LOC eating episodes (44; 64; 456). Therefore, LOC eating (as opposed to classic objectively large binge episodes) is frequently examined in youth, encompassing both objectively and subjectively large LOC eating episodes (461). LOC eating is defined as the subjective experience of being unable to stop eating, regardless of the amount reportedly consumed (461).

For children and adolescents, a growing body of literature suggests that the experience of LOC eating, rather than the amount of food consumed, is the most salient indicator of aberrant eating (64; 416; 475). For example, one study showed that children who consumed objectively large or subjectively large episode sizes in the past month did not differ significantly on important variables such as disordered eating attitudes, symptoms of depression and anxiety, or adiposity. Additionally, both groups had significantly worse levels of these variables compared to children without LOC eating regardless of the amount of food reported consumed (415). A second study in adolescents with overweight found that youth with either objectively large LOC eating episodes or youth with subjectively large LOC eating episodes reported more weight/shape concern and depressive symptoms than youth without overeating or LOC eating episodes (156). Moreover, the two LOC eating groups did not differ with regards to weight/shape concern or depressive symptoms (156). A third study had similar findings, with youth reporting

different LOC eating episode sizes not differing on emotional eating, eating in the absence of hunger, eating-related psychopathology, depressive symptoms, trait anxiety, or parent-reported behavior problems (491). However, both groups had higher psychopathology across these variables than youth who did not report any disordered eating (491). With regard to weight, youth reporting different episode sizes do not appear to differ on BMI-*z*, and both groups are heavier than youth who did not report any overeating or LOC eating episodes (460; 491). Children who report objectively large LOC eating episodes may nevertheless be more likely to pursue weight-loss treatment (460).

Some studies have had mixed findings with regard to the importance of episode size. For example, youth with full-syndrome BED have been shown to have more eating-related psychopathology, negative mood, and anxiety than youth with subclinical binge eating (146). Additionally, while one study in youth with obesity found that youth with LOC eating showed more concern about eating, weight, and shape than youth without LOC eating, as well as higher rates of emotional eating, external eating, and depressive symptoms, many of these relationships appeared to be primarily driven by youth who reported objectively large episodes (163). A third study in a sample of treatment-seeking youth with overweight found that youth who reported objectively large episodes had greater shape concern, weight concern, overall eating-related psychopathology, depressive symptoms, and anxiety symptoms than youth who only reported subjectively large episodes (105). However, given these studies examined youth with full-syndrome BED, youth with overweight/obesity, and treatment-seeking youth with obesity, these differences may have been observed due to the increased severity of LOC eating in these samples. Given the conflicting findings, additional research examining the importance of LOC eating episode size in different samples of youth is warranted.

Prevalence estimates for recent LOC eating in youth range from approximately 6-60%, with increased prevalence associated with elevated weight, adolescence, being female, and seeking weight-loss treatment (64; 130; 164; 316; 400; 416; 429; 430; 461; 475; 486). In children and adolescents with overweight and obesity, a recent meta-analysis estimated the prevalence of recent binge eating at 22.2% and recent loss of control eating at 31.2% (190). Of youth who report LOC eating episodes (i.e., presence of at least one episode in the past one or three months) at one time point, approximately 40-50% report persistent LOC eating over time (198; 199; 464). The presence of recent LOC eating is associated with adverse psychological correlates, different eating behaviors, and adverse physical correlates. Of note, previous research has typically defined recent LOC eating as at least one episode occurring in the past one to three months. While findings are generally consistent regardless of the time frame used, this paper will note the time frame when discussing particular studies.

Psychological Correlates of Loss of Control Eating in Youth

LOC eating is associated with a number of adverse psychological correlates. For example, studies have found that youth with LOC eating have reduced quality of life (371; 479; 486), poorer social functioning (110), lower self-esteem (4; 89; 146; 217; 459), more externalizing (355; 459) and internalizing (146) problems, as well as higher emotional distress (320; 400; 444) compared to youth without LOC eating. LOC eating has also been found to predict the development of threshold or subthreshold BED (198; 199; 464). However, the majority of studies have focused on the relationship between LOC eating, disordered eating attitudes, and mood symptoms.

Compared to youth who do not report LOC, those with recent LOC eating are consistently found to have significantly higher disordered eating attitudes, such as eating, shape,

and weight concerns (89; 105; 146; 156; 162; 163; 199; 212; 217; 334; 400; 415; 459; 474; 479; 491; 504). Prospectively, persistent LOC eating predicts increases in disordered eating attitudes and eating-related psychopathology over time (199; 464). There are mixed findings as to whether eating-related psychopathology predicts the onset of LOC eating over time; one study found that eating-related psychopathology did not predict the onset of LOC eating (165); while several other studies found that eating-related psychopathology did predict future onset of LOC eating (160; 440; 445).

With respect to mood symptoms, most studies have found that the presence of recent LOC eating is associated with increased symptoms of depression and anxiety (4; 17; 42; 105; 146; 156; 163; 164; 217; 355; 415; 453; 479; 486; 491). Using structural equation modeling, one study found a direct pathway from depressive symptoms to the presence of LOC eating in youth with overweight (162). However, some studies have found no cross-sectional relationship between LOC eating status and depressive symptoms (89; 164). Prospectively, LOC eating may predict increases in depressive symptoms over time (130; 430; 443; 464). This relationship may be bidirectional, as other studies have found that depressive symptoms (160; 165; 419; 445) and negative affect (357; 440) predict later onset of LOC eating. However, not all studies have support these findings, with some studies finding LOC eating does not prospectively predict depressive symptoms (199; 419).

LOC eating has been proposed to be associated with these adverse psychological outcomes through a variety of pathways, such as chronic stress (523), less emotional awareness (41; 464), emotion dysregulation (78; 236), and reduced dispositional mindfulness (364), or differences in reward responsivity (83; 464) and impulsivity (155; 187; 329; 376; 523). Taken together, youth with LOC eating appear to be at high-risk for increased psychopathology cross-

sectionally, as well as prospectively over time. However, future research is needed to further elucidate the mechanisms underlying the relationships between LOC eating and psychopathology.

Loss of Control Eating and Eating Behavior in Youth

Youth with LOC eating also appear to have different eating behaviors, food preferences, and diet quality than youth without LOC eating. One study found that children who reported at least one LOC eating episode in the past three months ate faster at a family mealtime at home as measured by bite speed, with the highest eating speed in children with recurrent LOC eating (77). Children and adolescents reporting LOC in the month prior to assessment are less likely to consume lunch and dinner, but more likely to consume morning, afternoon, and nocturnal snacks compared to youth without LOC eating (298).

Recent LOC eating is also associated with reports of other disinhibited eating behaviors. Youth with LOC eating report more emotional eating, or eating in response to emotional cues (105; 163; 164; 415; 460; 469; 499). In a sample of adolescent girls, the presence of emotional eating was associated with an increased risk of binge eating onset at 2-year follow-up (445), although additional prospective studies are needed to determine the directionality of this relationship. Youth with LOC eating also report more external eating, or eating in response to environmental cues, as well as eating in the absence of hunger (163; 415; 460; 463).

When examining eating behavior in the laboratory, most but not all (202) studies have found that youth with LOC eating do not consume more overall calories than youth without LOC eating at "typical" meals (158; 223; 462). In laboratory meals, youth with recent LOC eating also appear to consume a greater percentage of calories from carbohydrates and a smaller percentage of calories from protein, as well as more snack- and dessert-type foods, than youth without LOC

eating (202; 462). While one study found that youth with LOC eating consumed more fat and protein at a laboratory test meal, this study did not adjust for total intake to determine if the percentage of these macronutrients varies across groups (202). It is possible that the test meal composition and instruction, as well as participant factors such as weight status, may explain these mixed findings. For example, while one study found no differences between groups in total intake during a typical test meal, when instructed to "binge" before the test meal, girls with both overweight and LOC eating consumed more calories than girls with overweight but without LOC eating (462).

During LOC episodes, youth with LOC eating in the past month report consuming more calories from carbohydrates and fewer calories from protein, as well as of more snack- and dessert-type foods than eating episodes without LOC (480). An ecological momentary assessment data found that reported LOC episodes were associated with both increased total caloric intake and a greater percentage of calories from carbohydrates, compared to non-LOC eating episodes (200). Overall, youth with LOC eating appear to have different eating behaviors and patterns compared to youth without LOC eating.

Loss of Control Eating and Physical Health in Youth

The presence of recent LOC eating is cross-sectionally associated with excess body weight in community samples of children and adolescents (5; 127; 128; 265; 332; 333; 400), as well as in samples of non-treatment seeking youth with overweight (320) and youth with type 2 diabetes (479). LOC eating has also been cross-sectionally associated with elevated adiposity in non-treatment seeking youth (415; 474). Prospectively, recent LOC eating predicts excess weight (125; 155; 441; 445; 473) and fat (457) gain in youth and the incidence of overweight/obesity in adolescence and young adulthood (130; 430). However, not all studies have supported the

association between LOC eating and excess weight/fat. For example, one study found no cross-sectional association between BMI-*z* score and LOC eating status in a sample of treatment-seeking adolescents with overweight (146), while another study found no association between BMI-*z* and LOC eating status in a sample of non-treatment-seeking of children with overweight aged 6-12 (312). Prospectively, one study found that LOC eating status in children aged 8-13 years did not predict change in BMI over 5.5 years (198), while another found that LOC eating status did not predict BMI trajectory in children aged 8-13 years over 2 years (199). Another study found no difference based on LOC eating status in a sample of treatment-seeking adolescents with obesity (146). Inconsistent findings may potentially be due to differences in the measurement of LOC eating, as well as sample differences in weight status, age or pubertal status, or weight loss treatment-seeking status. Additional research needs to be conducted to better elucidate the relationship between LOC eating and weight across the lifespan.

Regardless of the relationship with weight, even when adjusting for weight/adiposity, youth who report LOC eating appear to be at increased risk for associated co-morbidities. For example, youth who reported at least one LOC eating episode in the past month had higher systolic blood pressure, higher low-density lipoprotein cholesterol, and lower high-density lipoprotein cholesterol compared to youth without LOC eating (369). However, the study found no difference in waist circumference, triglycerides, diastolic blood pressure, glucose, or total cholesterol between the two groups (369). Another cross-sectional study found that youth with LOC eating had higher serum leptin than youth without LOC eating, even after adjusting for fat mass, suggesting these youth may have increased leptin resistance (311). Prospectively, in a sample of children aged 5-12 years at high risk of adult obesity, the presence of LOC eating in the past six months at baseline was associated with worsening triglycerides, increased waist

circumference, and a 5.33 greater odds of meeting criteria for metabolic syndrome at 5-year follow-up (465). This association was only partially explained by differences in weight gain between youth with and without LOC eating (465). LOC eating may be related to worsened metabolic health through a variety of pathways, such as poor diet quality (13; 52; 144; 351), alternations in satiety signaling (6; 311), frequent episodes of perceived stress (330), or increased eating speed during LOC eating episodes (22). However, additional research is needed to fully understand the relationship between LOC eating in youth and physical health.

AFFECT THEORY OF LOSS OF CONTROL EATING

One promising theoretical framework that can be used to understand the development and maintenance of LOC eating is the affect theory of LOC eating (505). Affect theory posits that LOC eating occurs because it provides relief from negative affective states that arise from stressful situations (28; 189; 237). It can provide relief either through escape or by "trading" a less aversive emotion due to the LOC eating episode (e.g., guilt) with the more aversive emotion that precipitated the LOC eating episode (237). This process is reinforcing, as LOC eating provides relief from the more aversive emotion (437). However, this relief is often temporary (437), and LOC eating becomes a maladaptive strategy for managing episodes of negative affect (374).

A limited but growing body of research supports the affect theory of LOC eating in both children and adults. In general, negative affect appears to be linked with LOC eating (40; 74; 153; 437) as well as palatable food intake (374; 393; 411). However, the majority of research testing the affect theory of LOC eating has occurred in adults. Ecological momentary assessment studies have supported the premise that negative affect is a common precipitant of LOC eating episodes in the natural environment in both adults with BED (168; 437) as well as adults with

subthreshold binge/LOC eating (87; 501). Laboratory research is more limited, but also supports the affect theory of LOC eating. For example, adults with BED who underwent a social-evaluative stressor— the Trier Social Stress Test— had higher self-reported desire to binge and sweet craving post-stressor compared to adults without BED, and the desire to binge and sweet craving were correlated with self-reported stress and anxiety (389). Similarly, a laboratory experiment found that while there was no effect of a negative mood induction, negative affect across negative mood and neutral conditions was associated with LOC eating during a buffet meal (476).

In youth, the presence of recent LOC eating has been associated with difficulties in regulating negative emotions (78) and youth report LOC eating episodes frequently occur after negative emotions and/or a triggering event (460). However, an ecological momentary assessment study found that interpersonal problems, but not self-reported negative affect, predicted subsequent LOC eating episodes in overweight adolescent girls (372). In contrast, another study found that negative affect mediated the relationship between parent-reported child social problems and the presence of LOC eating episodes in the past month (110).

In the laboratory, pre-meal negative affect in adolescent girls with at least one LOC eating episode in the past month was associated with increased palatable food intake during a laboratory test meal (374). Similarly, one study found that after a sad mood induction, while there was no difference in total caloric intake, girls with overweight and reported LOC eating in the past three months consumed more energy from fat compared to a neutral condition (158). Additionally, increased negative affect— particularly at baseline, before the negative mood induction— predicted an increased likelihood of experiencing a LOC eating episode after the induction (158). However, in another mood induction study, adolescents with LOC eating

reported more negative mood across both conditions (neutral and sad) than adolescents without LOC eating; yet, LOC eating status did not influence cortisol response in either condition (368). Similarly, youth who reported LOC eating had more eating in the absence of hunger post-induction, but this relationship was not moderated by induction condition (368). While there have been some mixed findings, preliminary research suggests that affect theory may be a useful framework to understand the development and maintenance of LOC eating in both adults and children. However, future research should continue to examine components of the affect theory of LOC eating both in the natural environment as well as in well-controlled laboratory environments with paradigms that manipulate exposure to stressors and/or affect.

PSYCHOLOGICAL STRESS

There are a number of distinct, but overlapping, definitions of psychological stress. One frequently-used definition proposes that stress is a relationship between the individual and an environment appraised as taxing or exceeding available resources, thus endangering the individual's well-being (267). Stressors— or events in the environment that potentially tax available resources— can consist of a variety of stimuli, such as physical, environmental, psychological, social, or cognitive stimuli (267; 407). Whether or not these variables lead to stress is influenced by a variety of factors, such as the individual's coping capacity and appraisal of the stressor (267; 407).

One integrative model posits that stress can be defined as "a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease" (70, p. 3). When individuals experience these environmental demands (i.e., the stressor), appraisal occurs, during which the individual determines if they are able to cope with the demands (70). If they find

environmental demands particularly taxing and also view their coping resources as inadequate, then they will perceive themselves as experiencing stress, resulting in negative affect (70). If the perception of stress and resulting negative affect is extreme, the stressor can lead to behavioral and/or physiological responses that place persons at increased risk for both mental and physical disease (70). However, when examining the impact of stress on mental and physical health, it is important to differentiate between types of psychological stress.

Acute Stress Versus Chronic Stress

Stress can be generally divided into two categories. Acute stress represents a temporary state with a pattern of specific onset and conclusion, and generally promotes adaptation (304). Chronic stress represents a prolonged state without a pattern of specific onset and conclusion, and is theorized to lead to "wear-and-tear" on the body over time due to prolonged arousal (304). Of note, the presence of chronic stress can also impact the response to acute stress, given that past research has shown that individuals who are experiencing chronic stress also display increased and prolonged psychological and physiological reactivity to acute stressors (273). In order to better understand the scope of potential impacts of acute and chronic stress, it is important to examine the physiological response to acute stress as well as stress over time.

The Physiological Response to Stress

In response to the detection of an acute stressor, several physiological responses occur. The activation of the sympathetic nervous system leads to the production of epinephrine and norepinephrine by the adrenal medulla through the sympathetic-adrenal-medullary (SAM) axis (69; 145). Additionally, corticotropin-releasing hormone (CRH) is released by the hypothalamus, activating the hypothalamic-pituitary-adrenal (HPA) axis (145; 426). As part of the HPA axis, in response to the release of CRH, the pituitary gland releases adrenocorticotropic hormone

(ACTH) into circulation (426). In turn, the release of ACTH results in the production of glucocorticoid hormones such as cortisol, as well as the precursor to endorphins, by the adrenal cortex (69; 145). Glucocorticoids significantly contribute to the regulation of HPA axis activation; for example, there is a negative feedback loop such that elevated levels of glucocorticoids inhibit HPA activity in the hypothalamus and pituitary (426). Lastly, a variety of other hormones, such as prolactin and growth hormone, are also released during these processes (145). Altogether, the physiological response to stress involves systems throughout the body and can have far-reaching impacts.

Sex and Development as Potential Moderators of Stress Reactivity

Research suggests that there are sex differences in stress reactivity that vary across developmental stage. In childhood, there do not appear to be sex differences; however, differences begin to emerge during adolescence and persist into adulthood (344). During and after adolescence, in response to acute stressors, females tend to report more negative affect and display more reactivity in the corticolimbic system compared to males (344). Conversely, males tend to have higher reactivity to acute stressors when measured by HPA axis and/or autonomic nervous system reactivity (344). For example, males show greater increases in salivary cortisol in response to social stressors, despite no differences in baseline cortisol (256). However, sex differences may also vary by menstrual cycle phase. In one study, women in the luteal phase had similar increases in salivary cortisol to men in response to acute stressor, while women in the follicular stage had blunted stress reactivity as measured by salivary cortisol (244). These differences may be explained by sex-specific hormones; for example, differences in corticosteroid-binding protein levels induced by estradiol (244). Of note, it does not appear that sex differences vary according to the type of acute stressor utilized (344).

Allostasis and Allostatic Load

The body constantly responds to events in order to maintain homeostasis, or a stable equilibrium (305). Allostasis refers to the active process by which the body maintains that stability through change (305), and it reflects the dynamic ability of the body's systems to adapt to environmental demands, including acute and chronic stressors (229). However, chronically increased allostasis can lead to allostatic load (229). Allostatic load can arise from several scenarios, such as chronic stress, a lack of an ability of systems to adapt to a repeated stressor, an inadequate response to a stressor, or from the failure of a system to stop the stress response when no longer needed (305). Over time, allostatic load causes "wear-and-tear" of the body that contributes to pathophysiology over time by increasing susceptibility to stress-related diseases (229; 305). Chronic over-activation of the SAM and HPA axes leads to prolonged secretion of stress hormones such as epinephrine, norepinephrine, and cortisol (229). Related systems compensate for this prolonged secretion through allostasis to maintain function, potentially leading to outcomes such as elevated blood pressure, increased visceral adipose tissue, and chronic inflammation (229). As the allostatic load progresses, full syndrome pathophysiology can occur (229). Thus, while the physiological response to stress is typically beneficial and adaptive, either under- or over-activation of the stress systems in order to maintain homeostasis may contribute to the development or maintenance of pathology in vulnerable individuals (229; 305; 426).

Acute Psychological Stressors in the Laboratory

In order to examine the response to acute psychological stressors, many studies have attempted to develop and/or use controlled paradigms in the laboratory. As a result, paradigms in the literature have been heterogeneous- varying in the type as well as the duration and

characteristics of the task (96). To ensure that laboratory stressors are having the intended effect, it is important to examine both subjective (i.e., self-report) and objective (i.e., physiological) measures of the stress response to laboratory paradigms (510). The use of physiological measures of the stress response allow for the examination of potential physiological causal pathways (302). Additionally, physiological measures are not susceptible to the same biases that threaten self-report measures, such as social desirability bias or recall bias (302).

In a review of 208 studies using acute psychological stressors in healthy adults and using cortisol as a marker for the physiological stress response, five primary types of tasks were identified: cognitive tasks, public speaking tasks, tasks that utilize a combination of public speaking and cognitive tasks, emotion induction tasks, and noise exposure tasks (96). However, only the first three categories were found to produce significant cortisol responses, with tasks that combined public speaking and cognitive tasks producing the largest average effect size (96). This review found no effect for duration of stressor (96). Lastly, when examining characteristics of the tasks, the authors found that stressors with components of social-evaluative threat (defined as an evaluative audience or negative social comparison) and uncontrollability (in which tasks were designed such that individuals could not succeed) were associated with a greater cortisol stress response than other types of stressors (96).

Supporting this finding, one study (422) involved twenty healthy men undergoing either a control condition or one of four common laboratory stressors, specifically the Stroop test (449), a cold pressor test (e.g., 354), the Trier Social Stress Test (245), and a physical exercise stress test (e.g., 18). While undergoing each procedure, perceived stress, salivary cortisol, salivary alpha-amylase, and heart rate were recorded (422). The Trier Social Stress Test was found to evoke the highest perceived stress and HPA axis response, with the Stroop and cold pressor tests evoking

the lowest perceived stress, HPA, and autonomic stress responses (422). The Trier Social Stress Test involves a public speaking task in front of a neutral and non-reactive panel of judges and a video recorder as well as a challenging mental arithmetic task (197; 245). It is theorized that the Trier Social Stress Test has been shown to evoke the strongest stress response because of its elements of social-evaluative stress, or that the task performance is judged by others, and uncontrollability, in which an individual's behavior does not impact the outcome (96; 197; 422). Therefore, it is important to consider how different components of a laboratory stressor, such as the presence or absence of social-evaluative stress, can influence the stress response.

Measuring Stress Reactivity and Recovery in the Laboratory

Previous research has taken a variety of approaches to conceptualizing and measuring stress reactivity and recovery in the laboratory. Stress reactivity is typically defined by the change from a baseline period to a stressor period, while recovery is typically defined by a period of rest post-stressor to examine the return to baseline (271; 279). Traditionally, researchers have separated out analyses for stress reactivity and recovery (271; 279). Approaches to examine stress reactivity have often included change scores or the use of repeated measures analyses (279). The use of change scores typically entails calculating the difference between pre- and post-stressor values of the outcome of interest (e.g., 99; 422; 512), while repeated measures analyzes differences across time of the outcome of interest (e.g., 131; 422; 488; 489; 511). However, several concerns have been raised about using change scores or repeated measures analyses to examine stress reactivity. Change scores have typically been shown to be unreliable unless calculated multiple times, and responsivity is often correlated with baseline values (271; 279). One method to examine stress reactivity that addresses several of these concerns is a

repeated measures analysis that uses residualized change scores as the dependent variable, with the impact of baseline on recovery adjusted on an individual (not group) level (279).

There is also a lack of consensus on the best way to measure stress recovery (271; 279). Traditional approaches to examine stress recovery have included the time to recovery, area under the curve, post-stress values at specific time intervals, and post-stress change scores at multiple specific time intervals (256; 271; 279). However, these traditional approaches typically also have limitations. For time to recovery, two potential limitations are that individuals may not return to baseline within the time frame measured, and that it ignores the slope of recovery (279). The area under the curve approach overcomes these limitations by taking into account the slope of recovery and not requiring individuals to return to baseline levels. While area under the curve analyses are likely influenced by the degree of stress reactivity, this concern can be alleviated by calculating a single area under the curve calculation from baseline to the last measurement (279). Area under the curve with respect to ground (AUC_G) and area under the curve with respect to increase (AUG_I) are two common area under the curve approaches (122). AUC_G calculates the total area under the curve, while AUG_I only takes into account the area above the baseline measurement, ignoring the distance from zero for all measurements. AUC_G is more commonly used, and represents total hormonal output (122). While AUG_I is more focused on changes over time, there is limited guidance for when measurements fall below baseline measurements (122). Other recommended approaches for measuring stress reactivity include curve-fitting estimates (279) and multilevel modeling (271), as these approaches can provide estimates on baseline, stressor, and reactivity parameters simultaneously (271; 279).

PSYCHOLOGICAL STRESS, PHYSIOLOGICAL STRESS RESPONSE, AND EATING BEHAVIOR

Stress has been shown to impact eating behavior in both the animal and human literature

(6), and is theorized to promote the development and maintenance of obesity (510). In human beings, while some individuals decrease their food intake in response to stress, the majority of individuals increase their food intake in response to stress (79). In response to an acute stressor, CRH is immediately released, inhibiting appetite (192; 428). However, after this phase, concentrations of both the orexigenic hormone ghrelin (359; 428) and glucocorticoids become elevated (428). Glucocorticoids increase fat storage in visceral fat by enhancing lipoprotein lipase activity in adipose tissue (113; 290; 390; 428). Glucocorticoids, such as cortisol, also stimulate appetite through a variety of signaling pathways (428). For example, glucocorticoids decrease the brain's sensitivity to leptin, a satiety-signaling hormone, and contribute to leptin resistance (224; 428). Similarly, glucocorticoids contribute to insulin resistance by impacting insulin's ability to inhibit certain neurons in the hypothalamus, decreasing appetite suppression (23; 29; 428). While stress has been shown to impact appetite and overall food consumption, it has also been shown to impact the type of food consumed.

Stress and Palatable Food Intake

Glucocorticoids appear to influence food choice, potentially by suppressing reward pathways (428). If rats do not have access to palatable food (e.g., lard or sugar), stress has been associated with decreased food intake (6; 275; 321). However, if rats have access to palatable food, stress has been associated with increased food intake (6; 79), and animals that are chronically stressed prefer high-calorie foods (137; 358). Interestingly, high-calorie foods appear to suppress the HPA axis through a reward-mediated negative feedback loop, suggesting high-calorie "comfort" foods alleviate stress symptoms (79; 137; 428). In one study, rats that underwent a chronic stress procedure were given either normal chow or free access to high palatable foods (358). Rats that had free access to palatable foods had suppressed levels of

plasma ACTH and glucocorticoids, and became heavier, than the rats that were given only normal chow (358).

Laboratory studies in human beings provide additional support for these relationships. Healthy participants who underwent an acute laboratory stressor (unsolvable anagrams) reported higher levels of stress and consumed more palatable food (M&Ms) and less healthy food (grapes) than the control group (521). Past research has also demonstrated that individual differences in stress reactivity, as measured by cortisol, influences food intake in healthy participants (6). For example, adults who had high cortisol after the Trier Social Stress Test consumed more calories post-stressor (particularly of palatable food) than participants who had low cortisol after the stressor (112). However, there was no difference in food consumption between the groups on a separate control day, suggesting that cortisol reactivity to stress may play a role in the overconsumption of palatable food (112).

Physiological Adaptations to Chronic Stress and Eating Behavior

It has been proposed that stress not only changes eating patterns, but can impact allostatic load and physiological adaptations that may promote "addictive-like" behavior (516). This process has been theorized to be mediated by various factors such as changes in the HPA axis, appetite-related hormones, and/or neuropeptides in the hypothalamus (322; 516). Chronic stress appears to impact brain circuits related to stress and motivation, such as the mesolimbic dopaminergic system, potentially impacting reward sensitivity, food preference, and desire to consume palatable foods (322; 516). For example, past research suggests that stress increases "wanting," or cue-triggered motivation to obtain a reward, potentially leading to addictive-like behaviors over time (365). However, additional research is needed to understand these relationships over time.

Individual Differences in Stress and Eating Behavior

While chronic stress appears to lead to energy conservation and appetite stimulation, and in turn, places an individual at risk of excess weight gain and visceral fat accumulation, not all individuals experience an increase in appetite and weight gain in response to chronic stress (428). Therefore, it is important to consider how individual differences impact the relationship between stress and eating behavior, and the presence of disinhibited eating may be particularly relevant. One study found that compared to a control condition, men and women consumed more food, and specifically more sweet foods after a stressor (394). However, differences in energy intake were predicted by the change in state anxiety during the stressor, with a stronger relationship in subjects with high state anxiety and subjects with higher disinhibition scores on the Three Factor Eating Questionnaire (394). Similarly, one study found no differences in cortisol stress reactivity between females with high and low levels of emotional eating after a Trier Social Stress Test (489). However, emotional eating moderated the relationship between reactivity and an increase in food consumption at the post-stressor test meal compared to a control meal (489). Individuals with high levels of emotional eating and a blunted cortisol response ate more food post-stressor compared to individuals with high levels of emotional eating but without a blunted cortisol response. Yet, there was no such relationship in the group with low levels of emotional eating (489). Taken together, previous research suggests that the presence of disordered eating is an important variable when considering the relationship between acute stress, stress reactivity, and eating behaviors.

Stress and Loss of Control Eating

Chronic stress has been associated with an increased risk of the development and/or maintenance of BED (186). In adolescents, greater life event stress (523) and weight-based

teasing from parents (343) have been associated with more severe LOC eating. In adults, recent LOC eating has been associated with self-reported stress (388), adverse life experiences (349), self-reported interpersonal trauma (315) as well as experiences of interpersonal weight discrimination (103) and weight stigma (19), two proposed chronic stressors (367). Overall, it has been proposed that stressful and aversive life events may increase vulnerability to disordered eating (14; 60; 349). Additionally, stress may play a role in the onset or maintenance of LOC eating episodes, as well as altered eating behavior in individuals with LOC eating.

Stress and Loss of Control Eating Episodes

Past research suggests that adults often report the presence of stress (147; 361) and negative affect (201) prior to binge or loss of control eating episodes. However, other factors such as coping and appraisal may impact whether an individual engages in binge eating in response to stress. For example, in one study in female college studies, emotion-focused coping style partially mediated the relationship between self-reported stress and binge eating behaviors, as measured by the Binge Eating Scale (452). Similarly, a study in lesbian and bisexual women— a population at risk for minority stress— found that proximal stressors were associated with negative affect and binge eating. This relationship was mediated by social isolation and emotion-focused coping (295). A previous study also showed that females who engaged in more binge eating behaviors, as measured by the Binge Eating Scale, appraised laboratory-based stressors as more stressful than a control group (183). Additionally, with respect to coping, the females who engage in binge eating were more likely to report catastrophizing and positive coping strategies during the stressor compared to the control group (183). Taken together, stress and factors influencing the stress response (e.g., negative affect, coping, and appraisal) appear to impact binge/LOC eating.

Laboratory Stressors and Eating Behavior in Individuals with LOC Eating

Laboratory-induced stress has been shown to impact eating behavior in adults with BED. After the Trier Social Stress Test, adults with obesity and BED had an increase in their initial eating rate, and a diminished deceleration of eating towards the end of the meal, compared to a laboratory test meal without a laboratory stressor (401). However, no differences between the stress-induced test meal and the control test meal were observed in adults with obesity but without BED (401). Similarly, women with obesity and BED had a greater increase in average eating rate and spoonful frequency of a palatable food (chocolate pudding) after completing the Trier Social Stress Test compared to women with obesity but without the disorder (264). However, another study found no group-level differences in food consumption at a laboratory test meal after a mental arithmetic stressor between individuals with and without recent binge eating (393). Taken together, while it appears that there may be a relationship between stress and eating behavior in adults with BED, not all studies are in agreement.

Physiological Response to Stress in Individuals with LOC Eating

Studies are mixed when examining differences in the physiological response to stress between individuals with and without BED. In response to a mental stress task, women with obesity and the disorder had a significant reduction in high-frequency heart rate variability (HF-HRV; representing parasympathetic regulation of heart rate variability) compared to women with obesity but without BED (140). Additionally, binge eating frequency was negatively associated with HF-HRV during the stressor. Taken together, these findings suggest women with BED may have elevated stress vulnerability compared to weight-matched peers without BED (140). However, another study examining heart rate variability in women with BED compared to women with obesity but without the disorder found that HF-HRV did not change in the BED

group, but decreased in the control group with obesity (309). Additionally, both the BED and control group did not show full recovery to baseline, suggesting persistent sympathetic activation in both groups (309). Lastly, in women with obesity and BED, an increase in hunger in response to a mental arithmetic stressor was associated with greater increases in systolic and diastolic blood pressure; however, this association was not found in women with obesity but without the disorder or in healthy weight controls (246). Additionally, there was no group by time interaction for change in blood pressure in response to the laboratory stressor (246).

Three studies have examined physiological stress reactivity to a cold pressor test in women with obesity and BED compared to women with obesity but without the disorder (148-150). Two studies focused on cortisol, with one finding that the BED group had greater area under the curve cortisol after the stressor (149) and one finding that the difference was non-significant, but trending towards significance (148). One of the studies examined waist circumference and found that it was positively associated with area under the curve cortisol and peak cortisol stress responsivity in the group with BED (149). The other study examined self-report measures, and found that the women with BED reported greater hunger and desire to binge after the stressor compared to women without BED (148). One study focused on ghrelin, and found that while ghrelin increased in response to a cold pressor test across participants in one study, there were no differences in ghrelin concentrations between adults with obesity who did or did not have BED (150). Moreover, ghrelin concentration was not related to self-reported stress, hunger, or desire to eat after the cold pressor test (150). Another study examined cortisol response to the Trier Social Stress Test in individuals with obesity and with or without BED (389). The study found that individuals with BED had a blunted cortisol response to the stressor compared to a healthy weight control group as well as a control group with obesity but without

the disorder (389). Additionally, in the BED group only, there was a positive association between area under the curve cortisol during the stressor and change in desire to binge (389). Therefore, while it appears that there may be differences in the physiological response to stress between individuals with and without BED, future research is needed to continue to elucidate the nuances of this relationship.

Stress and LOC Eating in Youth

Few studies have examined the relationship between stress and LOC eating in youth. Using ecological momentary assessment in adolescent females with overweight or obesity, interpersonal problems predicted momentary LOC eating, but self-reported stress was not directly examined (372). Similarly, one study examined cortisol response to a negative mood induction among adolescents with and without a LOC eating episode in the past month (368). While adolescents with LOC eating reported more negative mood across both the experimental and control conditions, LOC eating status was not related to cortisol response to the negative mood induction (368). Given the small number of studies that have examined this topic, future research needs to continue exploring the physiological response to stress among youth with LOC eating.

THE IMMUNE SYSTEM

The immune system is composed of cells, tissues, and organs that work together to protect an individual by identifying and eliminating invading pathogens (67; 331). Lymphoid organs, such as the spleen and bone marrow, produce or maintain white blood cells known as lymphocytes (331). The lymphatic system is a network of vessels that carry lymph (a fluid mixture of substances from epithelia and tissues) throughout the body (1). Lymph nodes are aggregates of lymphoid tissues within the lymphatic system, and lymph moves from the tissues

to the lymph nodes then back into circulation (1). As the lymph moves through the lymph nodes, antigens of microbes become concentrated in draining lymph nodes (1). Together, the coordinated action of the immune system— or the cells, molecules, organs, and systems in the body that respond to pathogens— represents the immune response (1).

Functions of the Immune System

The immune system has several important functions. It uses structural features of the pathogen to discriminate the pathogen from the host's cells in a process called "self-nonself discrimination" (67; 331). Once a foreign pathogen is identified, the immune system responds through two sets of responses: innate and adaptive (67). While the two systems work together, the innate system response is engaged broadly and rapidly, while the adaptive symptom response is targeted to specific pathogens and typically takes longer to engage than the innate system (67). Innate immunity begins with the skin and mucous membranes, which are designed to block pathogen entry (1). If pathogens enter the tissues or circulation, there are several innate immunity cells that recognize and react, such as phagocytes, natural killer cells, and plasma proteins (1). Of note, the innate system primarily responds to microbes by two methods: antiviral mechanisms and inflammation (1). The antiviral mechanisms aim to make viral infection and reproduction impossible in host cells while inflammation aims to destroy the microbes and repair damaged tissue (1). The adaptive immune system primarily consists of lymphocytes and related cells, including those that produce antibodies (1). Additionally, the adaptive immune system can be broken down into two additional components: humoral and cell-mediated immunity. Humoral immunity is mediated by antibodies produced by B lymphocytes, which enter circulation and eliminate microbes and related toxins that are outside of host cells (1). Cell-mediated immunity is mediated by T lymphocytes, which target intracellular microbes by methods such as activating

phagocytes or killing infected host cells (1). In summary, the immune system involves a coordinated set of expansive mechanisms that work together as part of the immune response to remove pathogens and protect the host.

Acute Inflammation

Inflammation is one component of the immune response of the organism to harmful physical, chemical, and biological stimuli (317; 409). The inflammatory response involves the coordinated action of cellular and humoral processes in order to reestablish homeostasis by restoring the damaged tissue to its pre-injury state (317; 409). The acute inflammatory response is the initial response to harmful stimuli — it typically occurs within the first few hours or days (409). Endothelial cells are activated, causing the expression of adhesion molecules for leukocytes on the cell surfaces, as well as the production of chemokines and proinflammatory cytokines to attract neutrophils (409). Additionally, there is a reversible opening of endothelial cells tight junctions to increase vascular permeability and allow proteins and fluids to move from the vascular compartment into the extravascular compartment to the injured tissue (409). Outside the blood vessel, granulocytes navigate to the injured site through a process called chemotaxis, in which a chemical gradient is created by chemotactic factors such as the release of chemokines (409). While the acute inflammatory response is specific to the location of injured tissue, systemic symptoms such as fever, increased heart rate, and increased circulating neutrophils often occur (409). Therefore, the acute inflammatory response can have impacts across multiple systems in the body.

Acute Inflammation and Tissue Repair

The acute inflammatory response is closely regulated to minimize extensive injury to healthy tissue (317). As the harmful stimuli are eliminated, anti-inflammatory mediators such as

anti-inflammatory cytokines and protease inhibitors are activated, resolving the acute inflammatory response (317; 409). Tissue leucocytes undergo apoptosis (programmed cell death) then phagocytosis by macrophages (317). Macrophages then depart the site of injury by lymphatic drainage (317). If the immune system is not able to neutralize the harmful stimuli or if the resolution of inflammation does not occur properly, acute inflammation will continue, resulting in more extensive tissue injury (409). If the tissue injury is mild, necrotic cells can be replaced by new cells (regeneration), but if the tissue injury is severe, the tissue will have to undergo more extensive repair (409). Ideally, the acute inflammatory response concludes successfully by eliminating the harmful stimuli, resolving the inflammatory response, removing cell debris, and allowing successful tissue repair to occur (317; 409).

Communication Between the Immune, Endocrine, and Nervous Systems

There are complex multi-directional relationships between the immune, endocrine, and nervous systems (145). Two particular pathways for immune system dysregulation are through the SAM system and HPA axis (145). As discussed previously, through these processes, hormones such as epinephrine, norepinephrine, ACTH, cortisol, prolactin, and growth hormone are released in response to a stressor (145). These hormones, as well as other "stress hormones," can directly or indirectly impact immune function (145). Most immune cells have receptors for one or more stress hormones; therefore, immune function can be directly altered by one of these stress hormones binding to an immune cell (145). Indirectly, stress hormones can impact immune function through a variety of mechanisms, such as through the dysregulation of cytokine production (145). Through these mechanisms, it is also possible for secondary effects to occur; for example, cytokines often serve many different functions throughout the body (145). It is also important to note that the immune system can bidirectionally impact the central nervous system

through a variety of pathways. Cytokines such as IL-1 can modulate the production of CRH by the hypothalamus (145). Lymphocytes can synthesize related hormones such as ACTH and prolactin (145). Lastly, nerve fibers in the lymphoid organs serve as direct connections to the sympathetic nervous system (145). While these pathways are becoming better understood, psychoneuroimmunology research continues to work to elucidate the connections between the nervous, endocrine, and immune systems (145).

CHRONIC INFLAMMATION AND HEALTH

Chronic inflammation is caused by the persistent activation of the innate and/or adaptive immune responses and often has a duration of long periods, such as several months or years (409). Morphologically, chronic inflammation is defined by the ongoing presence of lymphocyte, macrophages, and plasma cells in tissues (409). It is believed that chronic inflammation is caused by the persistent activation of the innate and acquired immune response, and the chronic inflammatory response can persist from days to years (409). In areas of chronic inflammation, proinflammatory mediators are produced by macrophages. In response to the proinflammatory mediators, fibroblasts lay down collagen and in turn, activate macrophages and lymphocytes to release mediators (409). This process creates a feedback loop that can perpetuate the inflammatory response, leading to chronic inflammation.

Chronic Inflammation and Mental Health

Chronic inflammation appears to play a role in the pathophysiology of several mental health conditions. There is a significant association between depression and elevated markers of inflammation, such as serum IL-6 and CRP (80; 216), and it has been suggested that depression can impact the immune system through a variety of physiological and behavioral pathways (216). However, this relationship appears to be bidirectional, with cytokine abnormalities

contributing to depression (216). Medically ill patients with immune-related conditions experience high rates of depression, and cytokine-based therapies have been shown to cause behavioral alterations similar to depression (216). Cytokines play a role in neuroendocrine function, neurotransmitter function, and information processing, suggesting several potential pathways to influence the pathophysiology of depression (216). In addition to depression, chronic inflammation has also been proposed to play a role in other psychological disorders such as anxiety (363; 496) and bipolar disorder (180; 207). However, the relationship between chronic inflammation and psychopathology is still being elucidated.

Chronic Inflammation and Physical Health

Chronic inflammation also appears to play a role in the pathophysiology of several physical diseases. For example, inflammation plays a significant causal role in atherosclerosis, the primary pathological process in cardiovascular disease (109). Fatty streaks, a precursor to atherosclerosis, are accumulations of cells beneath the endothelium, including macrophages and T cells (184). Over time, a fatty streak can develop into atherosclerotic lesions, in which the artery wall is thickened, and into a fibrous plaque (75; 184; 278; 409). Local inflammation appears to play a significant role in the location of plaque formation, as well as plaque composition and rupture (409). When inflammatory cells infiltrate the cap covering these plaques, the cap becomes thin and more vulnerable to ruptures, leading to acute cardiovascular events (409).

In type 2 diabetes, chronic inflammation induces insulin resistance and β-cell dysfunction (241). It is theorized that adipose tissue macrophages produce local and systemic pro-inflammatory mediators. In turn, these mediators suppress other cells such as cytokine signaling proteins and certain kinases, impairing insulin signaling in insulin target tissues (241). This

process leads to insulin resistance, as peripheral target tissues cannot effectively respond to circulating insulin (241). A similar process is theorized to occur in the pancreas, leading to the death of pancreatic β-cells and β-cell dysfunction, in which β cells can no longer produce enough insulin (241). This represents one pathway through which chronic inflammation can directly impact physical health.

Obesity, Chronic Inflammation, and Physical Health

Obesity is robustly associated with chronic subclinical inflammation (88; 317; 337), and the relationship appears to be at least partially due to the persistent activation of the innate immune system in individuals with obesity (317; 337). In individuals with obesity, several components of the immune system are increased: acute-phase proteins such as C-reactive protein (487), endothelial cell activation markers (493), complement factors (185), cytokines produced by activated macrophages tumor necrosis factor-α (249; 487), and neutrophil activation (337). In individuals with obesity, adiponectin (a protein with anti-inflammatory actions) concentration is decreased, while concentrations of pro-inflammatory cytokines such as IL-6, free fatty acids, estrogen, and leptin are increased (93). Moreover, inflammatory markers in individuals with obesity are reduced with weight loss, suggesting that adiposity directly contributes to chronic inflammation (12; 375; 395). Adipose tissue is the largest endocrine organ in the body, and can secrete over 50 different adipokines, cytokines, and chemokines into circulation (93; 285; 494). In obesity, over-nutrition leads to adipose tissue and adipocyte expansion, altering adipose tissue histology and function (93). It is hypothesized that through this process, lipid secretion, adipocyte lipolysis, and the production of proinflammatory factors are enhanced (93), and obesity-related inflammation is characterized by increased concentrations of macrophages and increased production of pro-inflammatory cytokines in adipose tissue (241).

Due to the effects of these increased pro-inflammatory factors on peripheral target tissue in individuals with obesity, adverse health outcomes such as insulin resistance, hyperlipidemia, and hyperglycemia can occur (93). Importantly, obesity-associated inflammation has been found to be a stronger predictor of adverse health outcomes than obesity alone, and it is believed that many obesity-related comorbidities are mediated by chronic inflammation (93). For example, metabolic dysfunction in individuals with obesity appears to be regulated by chronic inflammation, and individuals with obesity but without metabolic dysfunction have less inflammation and decreased risks of adverse health outcome such as cardiovascular disease and certain obesity-related cancers compared to individuals with obesity and metabolic dysfunction (93; 319). Similarly, in women with overweight/obesity undergoing a weight loss program, both a reduction in visceral adipose tissue and concentrations of the pro-inflammatory cytokine IL-6 independently contributed to improvements in insulin sensitivity (395). This suggests that while obesity and inflammation are closely related, both factors may contribute to physical health independently as well (395).

METABOLIC SYNDROME

Metabolic syndrome (MetS) is a constellation of related risk factors for adverse health outcomes such as type 2 diabetes, cardiovascular disease, and all-cause mortality (91; 233; 424). The components of MetS include glucose intolerance, elevated triglycerides, decreased high-density lipoprotein cholesterol, visceral adiposity, and hypertension (10; 317). It is estimated that about 25% of the global population meets criteria for MetS (215; 340). The prevalence of MetS in adults in the United States was estimated to be 34.2% in 2007-2012, an increase of more than 35% from 1988-1994 (318). MetS is closely associated with overweight/obesity (317). While one study showed that approximately 17.27% of healthy weight adults met criteria for MetS, risk

increased with increasing BMI, even in the healthy weight range. When individuals in the healthy weight range were split into tertiles, compared to females and males in the lowest weight tertile, the odds ratios of MetS were females and males in the upper tertile was 3.97 and 2.16, respectively (451). However, a variety of additional factors appear to impact the risk for MetS, such as genetics, diet, physical activity, smoking, lack of education, and increasing age (61; 233; 318).

Metabolic Syndrome in Youth

Although MetS has historically been considered an adult disorder, the processes underlying MetS appears to begin as early as childhood (10). Given the large increase in childhood obesity over the past several decades, MetS has become a significant public health problem (10; 57; 341). Therefore, current guidelines recommend that children as well as adults are screened for cardiovascular risk factors and MetS (317). However, given the controversy over specific MetS criteria for youth (15; 30; 482), the MetS components are typically examined continuously in youth. Given the significant systemic effects of MetS, a focus on prevention, early identification, and early intervention is needed (10; 233). Autopsy studies have shown that the presence of MetS factors, such as high blood pressure and dyslipidemia, are associated with the degree of atherosclerosis in children (10; 39; 306; 335). Prevention and primary intervention strategies focus on lifestyle changes such as weight loss, physical activity, and healthy diet, but pharmacological interventions may be appropriate if lifestyle changes do not improve MetS components (233). If pharmacological interventions are used, each MetS component is typically targeted separately (233).

Metabolic Syndrome and Chronic Inflammation

It is believed that inflammation plays a significant role in the pathology of MetS (114;

233), and MetS is considered to be a state of chronic, low-grade inflammation (233). Individuals with MetS have increased concentrations of circulatory cytokines, which regulate a variety of tissues through local, central, and peripheral mechanisms (59). While some mechanisms have been identified, all pathways through which inflammatory factors can impact the pathology of MetS are still not yet fully understood. CRP, an acute-phase protein, can impact cardiovascular-related systems by binding to low-density lipoprotein cholesterol, initiating coagulation processes and increasing the risk for thrombosis and myocardial infarction (59; 121). Tumor necrosis factor (TNF)-α and IL-6, pro-inflammatory cytokines, can modulate insulin sensitivity through a variety of mechanisms such as decreasing glucose transporter-4 in adipocytes and decreasing insulin receptor signaling pathways (59). Adiponectin, an anti-inflammatory plasma protein that is reduced in individuals with excess weight, protects against insulin resistance and the associated endothelial dysfunction (59; 243). These mechanisms explain at least some of the observed relationship between inflammation and MetS pathology.

Inflammation may also explain the close link between obesity and MetS-related disorders (2; 59; 88; 399). For example, the prevalence of MetS is higher in populations with inflammatory diseases such as rheumatoid arthritis and lupus (2), and obesity— a pro-inflammatory condition— is closely linked to MetS (399). However, individuals of healthy weight can still meet criteria with MetS, with one study estimating 0.9-3.0% of individuals with a BMI of 18.5-20.9 kg/m^2 met criteria for MetS (434). Therefore, in addition to excess weight, it is important to elucidate other factors conferring increased risk for chronic inflammation and the associated adverse health outcomes. One theory proposes that sympathetic nervous system activity, chronic stress, and repeated activation of the HPA axis leads to immune system dysfunction and inflammation, in turn contributing to MetS components, such as obesity, insulin resistance, and

hypertension, through immune system dysfunction (48; 206).

STRESS AND THE IMMUNE SYSTEM

The central nervous system, endocrine system, and the immune system interact with each other bi-directionally in complex ways (82; 145). In response to stress, immune cells can be activated through several pathways. Activation of the SAM system and HPA axis each impact the immune system, as almost all immune cells have a variety of receptors that can bind stress-related hormones such as epinephrine, norepinephrine, and glucocorticoid hormones (69; 145; 405). Additionally, the lymphoid organs can be directly innervated by the sympathetic nervous system through nerve fibers in the spleen and thymus (145; 405).

Catecholamines released by the SAM system impact the immune system in a variety of ways, including an increase in systemic inflammatory activity through up-regulating transcription of proinflammatory immune response genes such as *TNF* and *IL6* (423). Glucocorticoids released by the HPA axis, such as cortisol, are typically considered to have anti-inflammatory effects; however, it is theorized that some individuals develop glucocorticoid resistance during certain conditions such as chronic stress (423). One study examined both cortisol and serum pro-inflammatory cytokines (IL-6 and IL-1ra), and divided participants into two groups: cortisol responders (the 40% of participants with the highest cortisol response to stress), and cortisol non-responders (the 40% of participants with the lowest cortisol response to stress). The study found that cortisol stress responsivity was inversely associated with cytokine levels and changes, with cortisol non-responders showing greatest change as measured by IL-6 and IL-1ra (259). This study suggests that the SAM system and HPA axis each play an important role in the stress-related immune response. In addition to the SAM system and HPA axis, immune cells also have receptors that can bind to other hormones impacted by stress, such as

prolactin and growth hormone (145). Through these various pathways, immune cells (e.g., NK cells and T cells) can be directly impacted by stress, as well as the cytokines produced by these cells (145).

Moreover, the relationship between these systems is bidirectional, and the immune system can impact the nervous and endocrine systems through a variety of pathways. Cytokines produced by immune cells can modulate hypothalamic activity (82). For example, the cytokine interleukin-1 can impact the production of adrenocorticotropic hormone, activating the HPA axis and increasing stress hormone levels (145). Lymphocytes can also synthesize relevant hormones such as adrenocorticotropic hormone, prolactin, and growth hormone (145). Therefore, there are important and complex bi-directional pathways among the central nervous system, endocrine system, and the immune system.

Stress and Dysregulation of the Immune Response

Over time, stressors can affect how these systems interact with each other, leading to the dysregulation of the immune response (82; 145). Although it was originally believed that stress was broadly immunosuppressive, more recent models suggest that repeated stress shifts the balance of the immune system, producing simultaneous enhancement and suppression of the immune response through altered cytokine secretion patterns (291; 405). While the stress response may be adaptive in the short-term, chronic stress can contribute to cumulative changes (304). For example, chronic stress can lead to prolonged HPA axis activation and cortisol secretion, leading to the down-regulation of glucocorticoid receptors. In turn, this down-regulation decreases the cells' ability to respond to anti-inflammatory signals (405). This pathway represents one potential mechanism through which stress could contribute to or exacerbate the disease processes involving elevated nonspecific chronic inflammation in

vulnerable individuals (404; 405).

CURRENT RESEARCH GAPS

There are several important research gaps in the current literature. Although one study found worsened metabolic and inflammatory markers in adults with obesity and binge eating disorder compared to their peers without binge eating disorder (450), it is unknown if chronic inflammation is elevated in youth with LOC eating. If youth with LOC eating have elevated markers of chronic inflammation, this may at least partially explain the observed relationship between LOC eating and adverse physical health outcomes (369; 465). Additionally, although preliminary data from cross-sectional and observational prospective studies suggest that LOC eating may place youth at risk for metabolic dysfunction, it is not known whether LOC eating remission improves metabolic health. Lastly, while affect theory has been proposed to explain the development and/or maintenance of LOC eating, further research is needed to better understand the temporal relationship between stress, negative affect, and LOC eating.

PROPOSED SERIES OF STUDIES

Accordingly, three studies were proposed to address these research gaps and further our understanding of the relationship among LOC eating, physical health, and stress. Given previous research in the area of LOC eating, a conceptual model was developed (Dissertation—Figure 1) outlining the known relationships between LOC eating, food intake, mood symptoms, adiposity, and physical health. Two of the three studies built upon this knowledge by examining the relationship between LOC eating and physical health (studies 1 and 2), while the third study examined the impact of recent social stress on eating using the interpersonal model of LOC eating (471).

The first two studies furthered our understanding of the relationship between LOC eating and physical health. The first study proposed a role of chronic inflammation in this relationship (Dissertation—Figure 2) and examined the relationship between LOC eating and high-sensitivity C-reactive protein, a marker of chronic inflammation, in a convenience sample of boys and girls. If youth with LOC eating have increased chronic inflammation, this may at least partially explain the observed adverse health outcomes in youth with LOC eating. The second study tested the relationship between LOC eating and physical health (Dissertation—Figure 3) by examining the relationship between LOC eating remission (vs. persistence) at end-of-treatment and components of metabolic health at 6-month follow-up by conducting a secondary analysis of a trial that enrolled adolescent girls with LOC eating. If metabolic health improves with the remission of LOC eating, this finding would lend support to the causal relationship between LOC eating and adverse health outcomes. The third study explored the role of stress in the relationships between LOC eating, mood symptoms, and food intake (Dissertation—Figure 4) by examining whether different components of negative affect (anger, confusion, depression, fatigue, and anxiety) mediated the relationship between recent social stress and palatable food intake in adolescent girls with LOC eating. This study used temporally sensitive measures to potentially show the importance of recent stress in LOC eating. Taken together, these three studies further our understanding of the relationship between LOC eating, physical health, and stress, and provide a foundation for a programmatic line of research focused on elucidating these relationships.

STUDY INVOLVEMENT AND STATUS

Study 1 has already been completed and published in *Childhood Obesity* (Shank and colleagues; 412). Ms. Shank conceived the idea, and under the guidance of Dr. Yanovski and Dr. Tanofsky-Kraff, she compiled, cleaned, and analyzed the data, interpreted the findings, and

generated the manuscript. Study 2 has also already been completed and published in the *International Journal of Eating Disorders* (Shank et al.; 413). Ms. Shank and Dr. Tanofsky-Kraff conceived the idea, and under the guidance of Dr. Tanofsky-Kraff and Dr. Yanovski, Ms. Shank compiled, cleaned, and analyzed the data, interpreted the findings, and generated the manuscript. Lastly, study 3 has already been completed and is published in *Comprehensive Psychiatry* (Shank and colleagues; 411). Dr. Tanofsky-Kraff and Ms. Shank conceived the idea, and under the guidance of Dr. Tanofsky-Kraff and Dr. Yanovski, Ms. Shank compiled, cleaned, and analyzed the data, interpreted the findings, and generated the manuscript. Additional documentation of involvement for all studies, including emails, is available upon request.

CHAPTER 2: Study One—Pediatric Loss of Control Eating and High-Sensitivity C-Reactive Protein Concentrations

INTRODUCTION

Obesity is associated with persistent low-grade chronic inflammation (88). In individuals with obesity, secretion of inflammatory cytokines is increased and secretion of adiponectin is decreased, promoting a low-grade chronic proinflammatory state (88). This proinflammatory state is associated with several obesity-related diseases, such as type 2 diabetes (T2D) and cardiovascular disease (47; 88). C-reactive protein (CRP) is a protein secreted in the liver in response to increases in pro-inflammatory cytokines, particularly interleukin (IL)-6 (92; 101). Although CRP is an acute phase reactant that rises dramatically in response to acute inflammation (101), among those who are not acutely ill, variation in CRP concentration as measured by high-sensitivity CRP (hsCRP) has also been shown to be a clinically useful marker of subclinical, low-grade chronic inflammation (27; 88). CRP concentration has been positively associated with obesity, metabolic syndrome, and T2D in adults (124), as well as elevated systolic and diastolic blood pressure in youth (408). Prospectively, and independent of body mass index (BMI), CRP concentration has been shown to predict several negative health outcomes, such as the development of hypertension (410) and T2D (139) in adults. Such data suggest that chronic inflammation may play a *causal* role in the development of obesity-related comorbidities, including aspects of the metabolic syndrome and cardiovascular disease (115; 218; 278; 381). Addressing chronic inflammation may reduce cardiometabolic risk and prevent the development of negative health outcomes (115; 382).

Binge eating disorder is also highly associated with obesity and its negative physiological consequences, such as insulin resistance and dyslipidemia (3; 211; 246). Although the association between binge eating and obesity-related comorbid conditions may be in large part

explained by the increased weight of those with binge eating (3; 98; 514), some preliminary data suggest that even independent of adiposity, adults with obesity and binge eating disorder have worse metabolic and inflammatory profiles than adults with obesity but without the disorder (450).

Although youth typically do not meet full criteria for binge eating disorder, loss of control eating (LOC), the subjective experience of being unable to stop eating regardless of the amount of food consumed, is commonly reported by children and adolescents (461). For youth who report a recent LOC eating episode, it appears that the subjective experience of LOC is a more salient indicator of aberrant eating than episode size (156; 415). The presence of a recent LOC eating episode is associated with excess body weight and adiposity (474), and reports of recent LOC eating increases the risk of excess adiposity gain during childhood (457), as well as incidence of overweight and obesity in adolescents and young adults (430). After adjusting for fat mass, youth who report a recent LOC eating episode have higher blood pressure and higher low-density lipoprotein cholesterol compared to their peers who do not report LOC eating (369). Moreover, those who report at least one recent LOC eating episode are five times more likely to develop metabolic syndrome at 5-year follow-up, with changes in BMI only partially explaining this association (465). However, it is unknown if youth with LOC eating have elevated inflammatory factors, which may contribute to the worsening metabolic components and increased cardiometabolic risk observed.

We therefore examined the relationship between LOC eating and hsCRP concentration in a sample of children and adolescents. Based on findings that adults with obesity and binge eating disorder have worse metabolic and inflammatory profiles compared to their counterparts with obesity but without the disorder (450), and that youth with reported LOC eating have worse

metabolic characteristics than those without LOC eating (369), we hypothesized that children and adolescents who reported LOC eating would have higher serum concentrations of hsCRP than youth without LOC, after adjusting for adiposity. Additionally, given that past research has shown a bidirectional link between psychopathology and inflammation (24; 34; 100), and that youth with LOC eating report more psychopathology than youth without LOC eating (108; 320; 474), we examined whether depressive symptoms or eating-related psychopathology mediated the relationship between LOC eating and hsCRP concentration.

METHODS

Participants

A cross-sectional secondary data analysis was carried out using a convenience sample of 194 children and adolescents assembled from prior studies approved by the Institutional Review Board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The studies adhered to the ethical standards of the Helsinki Declaration. Participants who completed the Eating Disorder Examination and had serum hsCRP concentrations measured within a 4-month window were included. All studies were enriched by design for subjects having overweight (BMI $\geq 85^{th}$ - $<95^{th}$) percentile for age and sex) or obesity (BMI $\geq 95^{th}$ percentile) according to the Center for Disease Control and Prevention growth standards (255). Exclusion criteria were pregnancy, major medical or psychiatric illnesses, and use of medication known to affect weight or eating behavior. Subjects had participated in either a non-intervention protocol (ClinicalTrials.gov ID: NCT00631644, $n = 7$; NCT00320177, $n = 31$; NCT00001522, $n = 11$; NCT00001195, $n = 20$) or an intervention protocol (NCT00263536, $n = 51$, a pilot trial to prevent weight gain in children and adolescents with overweight or obesity; NCT00001723, $n = 74$, a treatment trial for non-Hispanic Black and White adolescents with

obesity and at least one weight-related comorbidity). Only baseline data were used from the two intervention protocols, while either baseline or follow-up data were used from the four non-intervention protocols. If a participant had data available at multiple time points, then the earliest available time point was used for analysis**.** Written consent and assent were provided by parents and children, respectively.

Procedure

For all studies, participants and a parent or guardian were seen at the NIH Hatfield Clinical Research Center. Anthropometric measurements and a blood draw were collected after an overnight fast and before breakfast was consumed. Participants completed the following assessments:

Body Mass Index (BMI)

Triplicate measures of height were collected by stadiometer and weight was measured by calibrated scale to the nearest 0.1kg. BMI (kg/m^2) was calculated using weight and average height. BMI-*z* score was calculated adjusting for age and sex according to the Center for Disease Control and Prevention growth standards (255).

Body Composition

Body fat mass (kg) was measured using dual-energy x-ray absorptiometry (DXA) or air displacement plethysmography (Bod Pod; Life Measurement Inc., Concord, CA). DXA measurements were taken using a calibrated Hologic QDR Discovery instrument (Hologic, Bedford, MA). Both DXA (111; 392) and air displacement plethysmography (417) have been validated as measures of body composition. Data were adjusted to account for known differences between the Bod Pod and DXA (386).

Pubertal Status

Pubertal status was categorized using Tanner staging (454) based on physical examination by an endocrinologist or nurse practitioner. Breast development in girls was assessed by inspection and palpation and assigned according to the five stages of Tanner (292). If stage was discordant between right and left testes/breasts, the higher Tanner stage was assigned. For boys, testicular volume (mL) was measured by using a set of orchidometer beads as standards according to Prader (455) and assigned to one of five stages: Tanner Stage 1 (testes ≤ 3 mL), Tanner Stage 2 (testes 4 mL—9 mL), Tanner Stage 3 (testes 10 mL—15 mL), Tanner Stage 4 (testes 16—24 mL), or Tanner Stage 5 (testes ≥ 25 mL).

Loss of Control (LOC) Eating and Eating-Related Psychopathology

Participants completed the Eating Disorder Examination (EDE) version 12.0(118) or the child version of the EDE (58). The two versions have been effectively combined in prior studies (146). The number of LOC eating episodes was recorded and LOC eating was deemed present if participants endorsed at least one episode of LOC in the past 28 days. The EDE global score, which represents the average of four subscales assessing restraint, and eating, shape and weight concerns, was used as a measure of eating-related psychopathology (118). The EDE has shown excellent inter-rater reliability and discriminant validity in pediatric samples (146; 474).

Children's Depression Inventory (CDI)

The CDI (251) is a 21-item self-report measure assessing depressive symptoms in the past two weeks, with greater scores indicating higher pathology. The CDI is a reliable and valid measurement of depressive symptoms in youth,(379) including acceptable internal consistency and test-retest reliability in both clinical (141) and community samples (427).

Serum HsCRP

Fasting serum hsCRP (mg/L) was measured by enzyme-linked immunosorbent assay (ELISA) at the NIH Clinical Research Center Department of Laboratory Medicine, using a Cobas 6000 Analyzer (Roche Diagnostics, Indianapolis, IN).

Statistical Analysis

All statistical analyses were conducted using IBM SPSS 23.0 Statistics 23 (Armonk, NY). All data were screened for outliers and normality. For hsCRP concentration, one outlier was re-coded to the next highest value. Group differences were assessed using *t*-tests and Chi-square analyses as appropriate. HsCRP concentration, number of LOC episodes in the past 28 days, and CDI scores were log transformed to achieve normality.

The following covariates were considered: age (years), study (coded as treatment vs. non-treatment), sex (coded as male or female), race (coded as non-Hispanic White or other), fat mass (kg), height (cm), and Tanner stage. As only sex and fat mass significantly contributed to any model, all models included sex and fat mass as covariates. Additionally, height was included as a covariate to adjust body fat mass measurements for height (akin to calculating weight for height as done for the body mass index). All tests were two-tailed, and differences were considered significant when p values were $\leq .05$.

One-way analysis of covariance (ANCOVA) was used to compare the hsCRP concentration of participants with and without LOC in the past 28 days. For hsCRP concentrations, unadjusted mean and standard deviation values are provided, as well as adjusted mean and standard error values, which have been adjusted for sex, fat mass, and height. A multiple linear regression model was conducted to examine if LOC eating frequency was associated with hsCRP concentration, adjusting for sex, fat mass, and height.

To examine whether psychopathology explained the relationship between LOC eating and hsCRP concentrations, ANCOVAs were repeated with depressive symptoms and eating-related psychopathology as additional covariates. In addition, four mediation models were conducted using Preacher and Hayes Indirect Mediation macro for SPSS (406). Mediation models examined whether: 1) depressive symptoms mediated the relationship between the presence of LOC eating and hsCRP concentrations, 2) depressive symptoms mediated the relationship between the frequency of LOC eating and hsCRP concentrations, 3) eating-related psychopathology mediated the relationship between the presence of LOC eating and hsCRP concentrations, and 4) eating-related psychopathology mediated the relationship between the frequency of LOC eating and hsCRP concentrations. Bootstrapping with 1000 resamples was used to estimate the 95% confidence interval (CI) for indirect effects in each mediation model.

RESULTS

Participants were 194 children and adolescents between the ages of 8 and 18 years (M = 14.28, SD = 2.10). The majority of participants had overweight (14.4%) or obesity (57.2%). Seventy-five (38.7%) participants reported at least one episode of LOC eating in the past 28 days. Among those with LOC eating, 36 (48.0%) reported subjectively large LOC episodes only, 17 participants (8.8%) reported both subjectively and objectively large LOC episodes, and 22 participants (11.3%) reported only objectively large LOC episodes in the past 28 days. Based on the number of objectively large LOC episodes in the past 28 days, 10 participants met criteria for binge eating disorder. Among all youth who reported LOC eating, the number of reported episodes in the past 28 days ranged from 1 to 58 (M = 4.87, SD = 8.12). On average, the time between the EDE interview and the hsCRP blood draw was 13.33 days (SD = 24.96). Participant characteristics based on LOC eating status are shown in Table 1. Youth reporting LOC eating

were slightly younger, were more likely to be female, had significantly greater BMI-*z* score, CDI and EDE Global Scores, and greater hsCRP (not adjusted for covariates) than those who did not report LOC.

HsCRP and LOC Eating

Adjusting for covariates, LOC eating presence was significantly associated with hsCRP concentration [$F(1,168) = 5.51$, $p = .02$, $\eta^2_p = .03$; Figure 1; Table 2], such that youth who reported LOC had higher hsCRP concentration (unadjusted: $M = 4.34$, $SD = 5.57$; adjusted $M \pm SE$ interval: [1.44±1.83]) than youth who did not report LOC eating (unadjusted: $M = 3.68$, $SD = 6.86$; adjusted $M \pm SE$ interval: [1.03±1.24]). The number of LOC eating episodes was significantly associated with hsCRP concentration, such that an increase in the frequency of LOC eating episodes was associated with an increase in hsCRP [$b = .25$, $t(168) = 2.49$, $p = .01$].

HsCRP, LOC Eating, and Psychopathology

Including depressive symptoms and eating-related psychopathology in the model (Table 3), LOC eating status remained significantly related to hsCRP concentration [$F(1,144) = 4.92$, $p = .03$]. Neither depressive symptoms [$F(1,144) = 0.10$, $p = .75$] nor eating-related psychopathology [$F(1, 144) = 0.04$, $p = .84$] was significantly related to hsCRP concentration. Furthermore, depressive symptoms did not significantly mediate the relationship between the presence of LOC eating and hsCRP concentration (95% CI: [-.11, .08]) or the relationship between the frequency of LOC eating and hsCRP (95% CI: [-.05, .08]). Similarly, eating-related psychopathology did not significantly mediate the relationship between the presence of LOC eating and hsCRP concentration (95% CI: [-.14, .22]) or the relationship between the frequency of LOC eating and hsCRP (95% CI: [-.14, .14].

DISCUSSION

Consistent with previous findings in adults with binge eating disorder (450), we found that youth with LOC eating had significantly higher inflammation, as measured by hsCRP, than those without LOC, even after adjusting for differences in fat mass. Notably, these findings were independent of other factors that might contribute to elevated hsCRP. In past research, psychopathology (such as depression, stress, and anxiety) has been robustly associated with elevated inflammation (24; 34; 100). Consistent with prior studies (164; 166; 474), youth with LOC eating in the current sample reported higher depressive symptoms and eating-related psychopathology than youth without LOC eating; however, depressive symptoms and eating-related psychopathology were sub-clinical across all participants. Therefore, the lack of association between psychopathology and LOC eating may have been due to the limited range of psychopathology in the sample. It is possible that a mediation effect would have been observed in a sample with clinically significant depressive symptoms or eating-related psychopathology. Alternatively, the relationship between LOC eating and hsCRP values may be mediated by other factors, such as diet quality.

Youth with reported LOC eating tend to consume meals comprised of more calories from carbohydrates and fewer calories from protein, as well as more high-calorie dessert-type foods (462). Youth with LOC eating also appear to eat in response to negative mood. Indeed, state negative affect immediately before a laboratory test meal was associated with greater carbohydrate, snack, and dessert intake and less protein, fruit, and dairy intake in a sample of adolescents with LOC eating (374). Poor diet quality, in turn, has been associated with chronic inflammation (13; 52; 144; 351). Therefore, diet quality and mood-induced eating may be potential mediators of the relationship between LOC eating and elevated hsCRP concentration.

Additional characteristics inherent to LOC eating episodes may also mediate the relationship between LOC eating and increased hsCRP. This is supported by our finding of a significant and positive association between LOC eating frequency and hsCRP, even after adjusting for sex, fat mass, and height. For example, individuals often report eating rapidly during binge eating episodes (289). Increased eating speed is associated with increased cardiometabolic risk (269; 522); therefore, it could be hypothesized that the rapid consumption of food during frequent LOC eating episodes may impact chronic inflammation. However, little is known about the association between such characteristics and chronic inflammation, thus future research is warranted.

Notably, the average unadjusted serum hsCRP in both groups was greater than 3 mg/L, which is the cut-off value for high cardiovascular risk (380). This is likely due to our sample, which was greatly enriched for overweight and obesity. In the current study, the average sex-age-specific BMI was at the 95th percentile. Excess adiposity has been robustly associated with elevated hsCRP concentrations in both children and adults (503; 513). Indeed, fat mass was strongly associated with elevated hsCRP concentration in all of the current study's analyses. Recruitment of a cohort expected to have high hsCRP concentration may have allowed us to observe associations between LOC eating and hsCRP that might not be detectable among primarily non-overweight cohorts that would be expected to have little elevation in inflammatory markers. However, given the strong association between fat mass and inflammatory markers, it is particularly notable that differences in youth with and without LOC eating were observed in a sample enriched for overweight and obesity.

Our findings suggest that chronic inflammation may be present in youth with disinhibited eating. This is important as it may be particularly vital to identify, and ultimately intervene with,

youth to reduce cardiometabolic risk associated with chronic inflammation. Approximately 80% of adolescents with obesity will remain obese in adulthood (418). Youth who remain obese into adulthood are at increased risk for adulthood hypertension, T2D, elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, elevated triglycerides, and increased intima-media thickness of the carotid artery (228). However, these disease processes may begin in childhood. For example, one study found that intima-media thickness – a marker for early atherosclerotic changes – is higher in children with obesity compared to healthy weight children (377). However, not all youth who are overweight develop negative health outcomes as adults; therefore, screening youth for chronic inflammation may help to identify high-risk youth for targeted interventions (49; 88).

Strengths of this study include the relatively large sample size, assessment of LOC eating using a structured clinical interview, and objective assessment of fat mass. Limitations include the convenience nature of the sample, which may limit generalizability. As our analyses were cross-sectional, the directionality of findings is unknown, and causality cannot be determined. It is possible that inflammatory and/or metabolic markers increase the likelihood of LOC eating in vulnerable individuals. Additionally, LOC eating was assessed at one time point only. Approximately 30-50% of youth report persistent LOC eating over time (199; 464), thus it is unknown if the significant effects were driven by youth with persistent LOC eating. Moreover, although hsCRP has been shown to be a clinically useful marker of low-grade chronic inflammation (88), other markers of inflammation, such as proinflammatory and anti-inflammatory cytokines, were not examined. Additionally, we did not confirm that hsCRP was correlated with metabolic markers in our sample, or adjust for components of metabolic health such as cholesterol or blood pressure. While CRP has been shown to predict cardiometabolic

health above and beyond the contribution of traditional metabolic markers such as total and high-density lipoprotein cholesterol (383), there may be a bi-directional link between these markers and inflammation (48). However, it is unknown if the interaction between LOC eating and inflammation would differentially impact metabolic health. Future research should examine temporal relationships between LOC eating, inflammation, and metabolic health.

In conclusion, elevated inflammation may begin to manifest in childhood and adolescence among individuals with disinhibited eating. Thus, youth with LOC eating may be a particularly important subgroup at high-risk for negative health outcomes associated with both chronic inflammation and obesity. Interventions that successfully target disinhibited eating, or its underlying causes, in youth may reduce inflammation and improve health outcomes. Future research should replicate these findings and examine alternative potential mechanisms of the relationship between LOC eating and inflammatory markers, such as diet quality or eating speed. Most importantly, research should prospectively examine the relationship between LOC eating, inflammatory markers, and cardiometabolic health.

CHAPTER 3: Study Two— Remission of Loss of Control Eating and Changes in Components of the Metabolic Syndrome

OVERVIEW

The previous study showed that youth who report LOC eating have elevated hsCRP, a marker of chronic inflammation, compared to youth who do not report LOC eating. This effect remained significant even after adjusting for adiposity, depressive symptoms, and eating-related psychopathology. Based on this finding, Dissertation—Figure 2 shows the proposed relationship among these variables. It is possible that LOC eating is associated with chronic inflammation directly, but also through three potential causal pathways involving food intake, fat mass, and mood symptoms. While Study 1 study did not find that depressive symptoms mediated the relationship between LOC eating and chronic inflammation, given that youth with LOC eating report more depressive symptoms (e.g., 156), as well as the strong link between depression and inflammation (e.g., 242), this relationship may be observed in samples with elevated depressive symptoms. Chronic inflammation has been linked with adverse health outcomes such as metabolic syndrome (e.g., 317), yet few studies have prospectively examined the relationship between LOC eating and metabolic syndrome. One study that found baseline LOC eating predicted worsening of triglycerides and central adiposity over a 5-year follow-up, and it was also associated with a 5.33 greater odds of meeting criteria for metabolic syndrome 5-years later (465). Given these findings, additional research examining whether LOC eating is causally associated with adverse health outcomes is warranted. Therefore, Study 2 utilizes data from a clinical trial to examine whether the remission of LOC eating at end-of-treatment is associated with improvements in cardiometabolic health at 6-month follow-up.

Introduction

In concert with the high rates of pediatric obesity, in recent decades there has been a substantial increase during childhood and adolescence in the prevalence of type 2 diabetes (299) and other aspects of the metabolic syndrome including dyslipidemia and hypertension (102; 326). Moreover, pediatric obesity that persists into adulthood is a risk factor for the development of hypertension, hypercholesterolemia, and type 2 diabetes in adulthood—even if youth do not have metabolic syndrome in childhood (228). Identifying and reducing modifiable factors that promote obesity and its metabolic complications may help prevent the development of full or partial metabolic syndrome (43).

One potentially modifiable risk factor for obesity and metabolic dysfunction is binge eating (22; 211). Compared to adults who do not endorse binge eating, adults with binge eating may differ in endocrine and autonomic functioning (140; 282; 309). Furthermore, the evidence for distinct cardiovascular and psychological phenotypes, even independent of weight status, suggests that binge eating and obesity may be specific phenotypes with respect to psychophysiological outcomes (246). Indeed, adults who endorse binge eating episodes are more likely to have hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL-C), insulin resistance, elevated inflammation, and metabolic syndrome than adults without binge eating (3; 450). Moreover, binge eating disorder in adults predicts the development of significant health problems, particularly of the cardiovascular and endocrine systems (209), even after accounting for the contributions of weight status.

Loss of control (LOC) eating is a prevalent disordered eating pattern among youth. LOC eating is the subjective experience of an inability to stop eating, and includes eating episodes with an objectively large amount of food (i.e., binge eating) as well as episodes with an ambiguously large amount of food (461). For children and adolescents, it appears that the

experience of LOC eating, rather than the amount of food consumed, is the most salient indicator of aberrant eating (415). Approximately 3-5% of youth of healthy weight (16; 474) and 20-35% of weight loss treatment-seeking youth (46; 146) report recent LOC eating. Compared with adolescents who do not report LOC eating, those with LOC are more likely to be overweight and to have greater adiposity (320; 400; 474). Further, even infrequent LOC eating is predictive of excess weight gain in prospective studies (125; 473).

Independent of adiposity, LOC eating also appears to put youth at risk for metabolic dysfunction. A cross-sectional analysis found that presence of LOC eating was associated with higher systolic blood pressure and higher low-density lipoprotein cholesterol (LDL-C) compared to youth without LOC eating, even after adjusting for the association of LOC eating with adiposity (369). Prospectively, one study that found pediatric binge eating predicted worsening of components of the metabolic syndrome, namely, triglycerides and central adiposity, over a 5-year follow-up (465). In the same study, baseline LOC overeating was associated with a 5.33 greater odds of meeting criteria for metabolic syndrome 5-years later (465) Taken together, preliminary data suggests that LOC eating may place youth at risk for metabolic dysfunction.

If the prospective link between LOC eating and worsening metabolic function reflects a causative pathway, then reducing or eliminating this behavior would be expected to promote improvements in metabolic dysfunction. Therefore, we carried out a secondary analysis of a trial that studied adolescent girls with LOC eating prior to and following interventions aimed at reducing excess weight gain. In the primary outcome analyses for this trial, there were no significant differences in how LOC eating or body mass index (BMI) indices changed between a 12-week interpersonal group psychotherapy experimental program and a standard-of-care group health education program (467). Therefore, we hypothesized that adolescent girls whose LOC

eating remitted, regardless of intervention assignment, would evidence greater improvements in metabolic function compared to girls whose LOC eating persisted.

METHODS

Participants

This study is a secondary analysis of healthy adolescent girls, 12-17-years-old, recruited for participation in a randomized controlled clinical trial at the Uniformed Services University of the Health Sciences (USUHS) and the National Institutes of Health (NIH) Hatfield Clinical Research Center in Bethesda, Maryland (ClinicalTrials.Gov ID: NCT00680979). Findings from the primary aims, describing group condition differences on mood, LOC eating, and weight, are reported elsewhere (467). This manuscript is the first presentation of the study's metabolic data that were collected as secondary outcomes.

As previously described (467), all participants were deemed at risk for excess weight gain due to a BMI (kg/m^2) between the 75^{th} and 97^{th} percentiles (129) and the report of at least one episode of LOC eating in the previous month (473). Girls were excluded from the trial if they had a major medical or psychiatric condition other than binge eating disorder, if they were in behavioral weight loss or psychotherapy, or were taking medications known to affect body weight or appetite, including oral contraceptives. Girls were excluded from this secondary analysis if they did not complete their 6-month follow-up visit ($n = 10$). Adolescents were recruited through the NIH clinical trials website, local area community flyer postings, and direct mailings to homes within a 50-mile radius of Bethesda, Maryland. Recruitment materials were directed to parents who were concerned about their daughter's body weight and eating behavior. The study was approved by the USUHS and *Eunice Kennedy Shriver* National Institute of Child

Health and Human Development institutional review boards. Parents and daughters provided written consent and assent, respectively.

Procedure

At a baseline visit, following an overnight fast, girls completed physiological and psychological assessments. Participants were then randomized to a 12-week interpersonal group psychotherapy or group health education control program, as previously described (467). The interpersonal psychotherapy group was modified from existing programs focused on the prevention of depression in adolescents (518) and the treatment of binge eating disorder (506). The health education program was adapted from the HEY-Durham manual (54). Follow-up assessment of LOC eating took place at the end of the 12-week intervention and metabolic function was re-assessed six months following the initiation of the programs.

Measures

LOC Eating

The Eating Disorder Examination Version 14 OD/C.2 (119) was administered to assess the presence and frequency of LOC eating at baseline and the presence of LOC eating at end-of-treatment. The presence of LOC eating was defined by at least one objective or subjective binge episode in the previous 28 days. The Eating Disorder Examination has shown good inter-rater reliability and discriminant validity in child and adolescent samples (146; 474), and in the current sample (467). As all participants reported LOC eating at baseline, girls were categorized as those with LOC eating persistence (i.e., reported at least one LOC eating episode in the past 28 days at end-of-treatment) or LOC eating remission (i.e., did not report LOC eating in the past 28 days at end-of-treatment).

Depressive Symptoms

Depressive symptoms were measured using the Beck Depression Inventory II (36), a self-report questionnaire containing twenty-one items that query about depressive symptoms such as sadness, anhedonia, and irritability. A total score is calculated by summing all items, each scored from 0 to 3, with higher scores representing increased severity of depressive symptoms. Based on the total score, the severity of depressive symptoms is considered minimal (0-13), mild (14-19), moderate (20-28), or severe (29-63). The Beck Depression Inventory has been shown to be valid and reliable in adolescent samples (20; 37). In this sample, the Beck Depression Inventory had good internal consistency (Cronbach's $\alpha = 0.82$), and depressive symptoms were included as a covariate in all models.

Anthropometric Measurements

Height (cm) was measured in triplicate by calibrated stadiometer. Weight (kg) was obtained in a fasted state with a calibrated digital scale. BMI (kg/m^2) was calculated using average height and weight, and then BMI-*z* score was generated by adjusting for age and sex according to CDC growth standards (255). Body fat mass (kg) was estimated with dual-energy X-ray absorptiometry (DXA), a validated measure of body composition (111; 392), using a calibrated Hologic Discovery instrument (Hologic, Inc., Marlborough, MA). Waist circumference (cm) was measured at the iliac crest with a non-elastic tape measure.

Metabolic Function

Fasting triglycerides, plasma glucose, and total cholesterol were measured from blood samples using a Hitachi 917 analyzer using reagents from Roche Diagnostics (Indianapolis, IN). A Cobas FARA analyzer was used to directly measure high-density lipoprotein cholesterol (HDL-C) using reagents from Sigma chemical (St. Louis, MO). LDL-C was then calculated

using the following formula: total cholesterol – HDL-C – (triglycerides/5). Blood pressure was measured using an automated blood pressure monitor (Dynamap, GE Healthcare) at the right brachial artery while participants were seated. Metabolic functioning was examined continuously due to the lack of consensus for clinical cut-offs for metabolic health components in youth (11; 366; 438; 524).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 24 (Armonk, NY). All data were screened for outliers and normality. Across all variables at baseline and 6-month follow-up, nineteen values were identified as extreme outliers (defined as more than three standard deviations from the mean) and were recoded to the next lowest or highest value for that variable. LOC eating frequency at baseline was log-transformed to achieve normality. For all participants, baseline differences between youth with LOC eating persistence versus LOC eating remission at end-of-treatment were assessed using independent samples *t*-tests and chi-square analyses, as appropriate. For participants with valid measures at both baseline and 6-month follow-up, metabolic and anthropometric variables within each group were examined over time using paired samples *t*-tests.

Given that the randomized controlled trial found no intervention effect of interpersonal psychotherapy versus health education for LOC eating at any follow-up visit (467), participants were collapsed across intervention assignment for the primary analyses. Missing data varied across metabolic outcomes due to protocol deviations including an inability to draw blood following two sticks, or issues with the samples (e.g., hemolysis) or with laboratory analysis. In order to maximize sample size for each analysis, a series of seven analyses of covariance (ANCOVAs) were conducted to examine the impact of LOC eating remission at end-of-

treatment on metabolic syndrome components (waist circumference, triglycerides, LDL-C, HDL-C, plasma glucose, systolic blood pressure, and diastolic blood pressure), with LOC eating status (persistence vs. remission at end-of-treatment) as the independent variable. Participants may have been excluded from each ANCOVA if they were missing the respective outcome data from the 6-month follow-up or if they were missing data for a covariate. The following covariates were included in each ANCOVA: race (coded as non-Hispanic White vs. other), baseline age (y), baseline depressive symptoms, baseline LOC eating frequency, baseline fat mass (kg), baseline height (cm) change in height from baseline to 6-months (cm), change in fat mass from baseline to 6-months (kg), and the baseline value of each respective metabolic syndrome component. If LOC eating status at end-of-treatment was found to be significant in any ANCOVA, follow-up ANCOVAs were conducted including all covariates, LOC eating status at end-of-treatment, intervention assignment, and the interaction between LOC eating status and intervention assignment to confirm there were no main or interactional effects of intervention condition. All tests were two tailed, and differences were considered significant when p-values were $< .05$.

RESULTS

Participants were 103 adolescent girls between the ages of 12 and 17 years ($M = 14.5$ years, $SD = 1.7$). At baseline, the average BMI-z was 1.5 ($SD = 0.3$) and 56.3% of participants classified themselves as non-Hispanic White. Participants reported an average of 4.5 ($SD = 6.02$) LOC eating episodes in the past 28 days at baseline. Two participants met criteria for binge eating disorder (22). At end-of-treatment, 58 (56.3%) reported LOC eating persistence, and 45 (43.7%) remitted from LOC eating. At baseline, adolescents with LOC eating persistence at end-of-treatment did not differ from adolescents with LOC eating remission at end-of-treatment with regard to race/ethnicity, age, BMI-z score, fat mass, height, waist circumference, triglycerides,

LDL-C, HDL-C, systolic blood pressure, or diastolic blood pressure. However, youth with LOC eating persistence at end-of-treatment had significantly more LOC eating episodes in the past 28 days at baseline (M = 5.6, SD = 5.7) than youth with LOC eating remission at end-of-treatment (M = 2.5, SD = 3.2; $p < .001$). Youth with LOC eating persistence also had significantly higher depressive symptoms at baseline (M = 12.1, SD = 7.2) than youth with with LOC eating remission (M = 8.6, SD = 5.8, $p = .01$). Baseline participant characteristics based on LOC eating status at end-of-treatment follow-up are shown in Table 1.

For girls with LOC eating remission, baseline and 6-month follow-up values did not differ significantly for BMI-*z* score, fat mass, triglycerides, LDL-C, HDL-C, systolic blood pressure, or diastolic blood pressure. However, girls with LOC eating remission were taller at 6-month follow-up than at baseline (162.6±7.1 vs. 163.6±6.7 cm; $p = .001$), had a larger waist circumference at 6-month follow-up than at baseline (84.1±9.2 vs. 87.7±10.7 cm; $p = .001$), and had lower plasma glucose at 6-month follow-up than at baseline (86.8±6.3 vs. 83.8±6.3 mg/dL; $p = .02$). Girls with LOC eating persistence did not differ significantly between baseline and 6-month follow-up for BMI-*z* score, waist circumference, triglycerides, LDL-C, plasma glucose, or systolic blood pressure. However, girls with LOC eating persistence had higher fat mass at 6-month follow-up than at baseline (26.0±5.3 vs. 26.8±6.1 kg; $p = .04$), were taller at 6-month follow-up than at baseline (161.7±7.3 vs. 162.9±7.0 cm; $p < .001$), had lower HDL-C at 6-month follow-up than at baseline (46.8±10.0 vs. 44.8±11.9 mg/dL; $p = .02$), and had higher diastolic blood pressure at 6-month follow-up than at baseline (65.8±5.9 vs. 68.2±7.1 mmHg; $p = .02$).. Anthropometric and metabolic components at baseline and 6-month follow-up within each LOC eating group is shown in Table 2.

When conducting between-groups analyses, after adjusting for covariates, waist circumference at 6-month follow-up did not significantly differ between youth with LOC eating persistence (M = 88.8 cm, SD = 8.8) versus LOC eating remission at end-of-treatment [M = 87.6 cm, SD = 10.8; $F(1, 82) = 0.32$, $\eta^2_p = 0.004$; $p = .57$; Supplemental Table S1]. LDL-C at 6-month follow-up did not significantly differ between youth with LOC eating persistence (M = 86.9 mg/dL, SD = 21.6) versus LOC eating remission at end-of-treatment [M = 77.0 mg/dL, SD = 23.8; $F(1, 60) = 1.74$, $\eta^2_p = 0.03$; $p = .19$; Supplemental Table S1]. Systolic blood pressure at 6-month follow-up did not significantly differ between youth with LOC eating persistence (M = 118.4 mmHg, SD = 10.3) versus LOC eating remission at end-of-treatment [M = 118.0 mmHg, SD = 9.6; $F(1, 88) = 1.61$, $\eta^2_p = 0.02$; $p = .21$; Supplemental Table S1]. Likewise, diastolic blood pressure at 6-month follow-up did not significantly differ between youth with LOC eating persistence (M = 68.2 mmHg, SD = 7.1) versus LOC eating remission at end-of-treatment [M = 67.1 mmHg, SD = 7.4; $F(1, 88) = 2.78$, $\eta^2_p = 0.03$; $p = .10$; Supplemental Table S1].

By contrast, after adjusting for covariates, girls with LOC eating persistence had significantly lower HDL-C (M = 44.8 mg/dL, SD = 11.9) than those with LOC eating remission at end-of-treatment [M = 50.3 mg/dL, SD = 11.8; $F(1, 79) = 7.26$, $\eta^2_p = 0.08$; $p = .01$; Supplemental Table S1; Figure 1B]. Follow-up analyses confirmed that there were no main (p = .73) effects of intervention condition (interpersonal psychotherapy versus health education) or interaction effects of intervention condition and LOC eating status at 6-month follow-up (p = .95) for HDL-C. Moreover, girls with LOC eating persistence had significantly higher fasting plasma glucose at 6-month follow-up (M = 86.5 mg/dL, SD = 5.8) than those with LOC eating remission [M = 83.9 mg/dL, SD = 6.4; $F(1, 78) = 5.76$, $\eta^2_p = 0.07$; $p = .02$; Supplemental Table S1; Figure 1A]. There were no main (p = .54) or interaction effects (p = .87) of intervention

condition for plasma glucose. Girls with LOC eating persistence also had significantly higher triglycerides (M = 96.9 mg/dL, SD = 53.7) than those with LOC eating remission at end-of-treatment [M = 84.4 mg/dL, SD = 46.2; $F(1, 68) = 5.53$, $\eta^2_p = 0.08$; $p = .02$; Supplemental Table S1; Figure 1C]. No main ($p = .44$) or interaction effects ($p = .82$) of intervention condition for triglycerides were identified.

DISCUSSION

Among adolescent girls at risk for excess weight gain, we observed greater improvements in some metabolic syndrome components at a 6-month follow-up when LOC eating remitted at end-of-treatment. Specifically, adolescents whose LOC eating remitted had lower fasting plasma glucose, higher HDL-C, and lower triglycerides at a 6-month follow-up than adolescents whose LOC eating persisted, despite no baseline differences in these components. These findings complement previous research showing a prospective relationship between LOC eating and the development of metabolic syndrome in youth (465), and provide preliminary support for the notion that ceasing to engage in LOC eating may improve some metabolic components.

One potential mechanism by which remission of LOC eating could promote improvements in metabolic health is through alteration of macronutrient selection and eating patterns. Despite mixed data on whether youth with LOC eating consume more total energy at meals than their peers without LOC eating, data more consistently demonstrate that intake of youth with LOC eating is distinguished by the consumption of a greater proportion of energy from carbohydrates, including snacks and desserts, and less from protein (202; 462; 480). Dietary patterns that involve a high intake of snacks and desserts have been associated with increased risk of metabolic syndrome in both adults and children (94; 234). However, in the current sample, we previously found that compared to the health education control group, snack-

type food intake was reduced more in the interpersonal psychotherapy intervention group (458). While not tested directly, given that we found no main effect of group or interactional effects of group by LOC eating remission on HDL-C, glucose, or triglycerides, it is likely that the reduction of snack-type food intake does not fully explain the relationship between LOC eating remission and improvements in these metabolic components. Likewise, although our main outcome paper found that interpersonal psychotherapy was more effective at reducing objective binge eating than health education (467), we found no main effects of group or interaction effects of group by LOC eating remission on these components. Thus, it is also unlikely that a change in objective binge eating episodes would fully explain the relationship between LOC eating remission and improvements in metabolic health. Other features that characterize LOC eating across both subjectively and objectively large episodes may explain the relationship between LOC eating remission and change in metabolic health warrant exploration. For example, increased eating speed has been associated with worsened cardiometabolic health (268; 522), and individuals often report eating rapidly during LOC eating episodes (289). Future research should continue to elucidate the relationship between LOC eating, diet quality, and metabolic health as well as examine other potential mechanisms (e.g., depressive symptoms, diet quality, episode size, and other characteristics of LOC eating episodes), between LOC eating and cardiometabolic health.

While previous studies have found that binge eating (LOC with overeating) in adults and LOC eating in youth are associated with increased risk of metabolic syndrome (3; 211; 465), not all studies have reported this association (35). When examining associations of specific components of metabolic health, findings have been further mixed. LOC eating in adults has been associated with decreased HDL-C, increased glucose, increased triglycerides, and

hypertension (3), while LOC eating in youth has been associated with increased LDL-C and systolic blood pressure (369). Prospectively, LOC eating has been linked to dyslipidemia in adults (211) and increased triglycerides in youth (465). The findings from the present study align with previous studies that have found that LOC eating is associated with dyslipidemia (3; 211; 465) and increased glucose (3); however, no association with blood pressure or LDL-C was found in the current study. The lack of consistency in the literature may be due to differences across samples (e.g., severity or duration of LOC/binge eating, age, weight, or sex distribution) or study methodology (e.g., how LOC eating was assessed, covariates included in analyses, or whether outcomes were examined continuously or categorically). It is also possible that LOC eating impacts cardiometabolic health through non-specific pathways, such as inflammation. Cross-sectional analyses have shown that adults (450) and youth (411) who report LOC eating have increased markers of inflammation relative to their peers. It is important for future research to examine how LOC eating impacts specific components of metabolic health.

Strengths of the current study include the use of a well-validated, interview measure of LOC eating. The direct estimation of fat mass and metabolic dysfunction using criterion methods are strengths, as opposed to relying on BMI and self-reported metabolic function as in previous studies **(211)**. Yet, longer-term prospective data using larger samples are vital to more fully explore potential mediators and moderators of the relationship between LOC eating and metabolic syndrome. For example, variables that were not measured in this study, such as menstrual cycle phase or duration of LOC eating, may be potential mediators or moderators of the relationship between LOC eating remission and changes in metabolic health. The analysis was also quasi-experimental, as participants were not randomized to LOC eating remission or persistence; therefore, there are several alternative explanations for the observed findings and

this analysis should be considered hypothesis generating. Additionally, inflammatory markers were not collected as part of this study; future research should examine if changes in inflammation at least partially explain improvements in metabolic health. Our sample may also lack generalizability, as we recruited only weight gain prevention-seeking, adolescent girls with above average BMI. It is also important to note that this sample was primarily healthy and the changes in metabolic health within each group were not large. However, metabolic components were examined only at 6-month follow-up. It is possible that the effects of LOC eating are cumulative, leading to more clinically significant differences over time. For example, a previous study found that youth with objectively large LOC eating episodes had a 5.33 greater odds of developing metabolic syndrome over the course of five years (465). Although there is no consensus for clinical cut-offs for components of metabolic health in youth (e.g., 11; 366; 438; 524), previous research in young adults suggests that even relatively small increases within the clinically healthy range in metabolic components such as fasting plasma glucose confers increased risk for the development of type 2 diabetes (481).

In conclusion, while previous research has found cross-sectional and prospective associations between the presence of LOC eating and metabolic syndrome components, this study has extended this line of research to show that the remission of LOC eating is associated with an improvement in some metabolic syndrome components. Future research should continue to elucidate the relationship between LOC eating and physical health to determine whether remission from LOC eating may improve metabolic health in the long-term. If the remission of LOC eating improves long-term metabolic health, then it may represent a modifiable lifestyle factor that can be targeted to help prevent the development of full or partial metabolic syndrome.

CHAPTER 4: Study Three—Examination of the Interpersonal Model of Loss of Control Eating in the Laboratory

OVERVIEW

Study 2 showed that after an intervention, youth with LOC eating remittance at end-of-treatment had improvements in some metabolic components at 6-month follow-up compared to youth with LOC eating persistence. Based on the findings in Study 1 and Study 2, Dissertation—Figure 3 shows an updated conceptual model linking these variables. It proposes that LOC eating is associated with adverse physical health outcomes such as metabolic syndrome through the pathways of increased adiposity and chronic inflammation. The adiposity pathway is hypothesized because previous research has shown that youth with LOC eating have higher adiposity (474), and there is a strong link between adiposity and metabolic dysfunction (e.g., 138; 239; 345). The chronic inflammation pathway is proposed given that youth with LOC eating have elevated chronic inflammation (412) and chronic inflammation is robustly associated with metabolic dysfunction (e.g., 317).

Further research should examine additional pathways between LOC eating and physical health, as identifying potentially modifiable risk factors can inform intervention and prevention programs. Affect theory proposes that LOC eating occurs as a coping mechanism for negative affect (191; 201), which may be brought on by stressors such as interpersonal conflict (384; 470). Stress may be particularly relevant for the relationship between LOC eating and physical health, given the known relationships between stress and adverse health outcomes (e.g., 66; 68; 229; 305; 356; 426). While some papers have supported components of the affect theory of LOC eating (110; 158; 372; 460), future research is needed to better elucidate the relationships among stress, negative mood, and LOC eating. Therefore, Study 3 examines whether negative affect

mediates the relationship between recent social stress and palatable food intake, used as a proxy for LOC eating.

INTRODUCTION

Loss of control (LOC) eating, or the subjective experience of being unable to stop eating, regardless of the amount of food consumed, is commonly reported by youth (461). The endorsement of recent LOC eating is associated with greater depressive and anxiety symptoms (156; 163; 164), lower self-esteem (157; 459), higher likelihood of overweight and obesity (430), more physiological markers of stress (373; 412), and a greater odds of presenting with components of the metabolic syndrome (369). Of particular concern are data demonstrating that LOC eating places youth at undue risk for excess weight and fat gain (125; 473) and exacerbation of metabolic syndrome components (465). This may be partially be due to the consistent finding that youth with LOC eating tend to consume meals comprised of highly palatable dessert and snack-type foods compared to their peers without LOC eating (152; 462; 480). Moreover, reports of LOC eating in adolescence and emerging adulthood appear to increase risk for future psychosocial impairment, depression (294; 430), the development of partial- and full-syndrome binge eating disorder (465), and the worsening of mood symptoms (464).

One theoretical framework for understanding LOC eating is interpersonal theory (505). Originally stemming from the adult depression literature (247), the interpersonal model of LOC eating highlights the importance of negative affect for both the development and maintenance of aberrant eating (505). Specifically, the interpersonal model proposes that difficulties characterized by high or poorly resolved conflict and/or inadequate support in relationships lead to negative emotions. In turn, negative emotions contribute to the onset and/or persistence of

LOC eating as a mechanism to cope with interpersonal distress (191; 384; 471). Thus, interpersonal theory is an extension of affect theory, which proposes that out of control eating provides relief from negative affective states either through escape or by means of a "trade off" between an aversive emotion that precipitates the LOC eating episode (e.g., anger, frustration, anxiety) and a less aversive emotion following the episode (e.g., guilt; 237). While eating provides initial relief from the negative affective state and thus is reinforcing, relief is often temporary (437). As a result, in some individuals, eating develops into a maladaptive strategy for managing negative affect, as repeated LOC eating episodes become needed to sustain relief (374).

A number of studies have supported components of the affect theory of LOC eating (21; 110; 219; 372; 374). For example, in a cohort of adolescent girls who reported LOC eating, we found that a composite score of several negative affective states (anger, confusion, depression, fatigue, and anxiety) was positively linked to highly palatable snack food intake as measured by meal intake at a laboratory test meal. Examining palatable food intake as a proxy for LOC eating (462; 480) provided a more objective measure of out of control eating than self-report (374). Yet, we did not evaluate the individual components of negative affect or the role of interpersonal factors in this report. Elucidating specific facets of negative affect and interpersonal factors would allow for more targeted, and thus potentially more effective, interventions in these youth. Extending these data to test the full interpersonal model may be particularly important for understanding LOC eating in adolescence. During this developmental stage, relationships are closely tied to self-evaluation and are often a primary source of social stress (325). In part because of the association with having excess weight, youth with LOC eating are particularly vulnerable to forms of social stress such as weight-related teasing and social isolation (294). Not

surprisingly, these factors have been suggested to influence the onset and course of LOC eating (159; 161; 198; 421; 445). Indeed, results from longitudinal studies indicate that family weight-based teasing (178; 334) and impaired interpersonal functioning (442) predicts increases in and the onset of future disordered eating behaviors. Similarly, among females, greater psychosocial problems in late adolescence increase the odds of having binge eating in early adulthood, thus highlighting interpersonal problems as a putative risk factor for binge eating later on in life (161).

While the interpersonal model has been widely used to explain binge eating in adults (e.g., 21; 25; 219; 220; 281; 436), and interpersonal psychotherapy has been adapted as an efficacious treatment for adult binge eating disorder (505; 509), only two studies have simultaneously evaluated all components of the interpersonal model of LOC eating in youth (110; 372). The first study used structural equation modeling in a large sample of children and adolescents and found that parent-reported social problems were positively associated with children's reported presence of LOC eating. This relationship was mediated by children's reports of trait-like negative affect (110). However, this study had several limitations. There was no objective measurement of food intake, and by having all measures collected at one time point, the temporal sequence of constructs remains unclear (203). The second study used ecological momentary assessment in adolescent girls with overweight and found that although interpersonal problems predicted LOC eating episodes, and between-subjects interpersonal problems predicted increased negative affect, negative affect did not predict LOC eating episodes (372). However, this study was not adequately powered for mediation and also did not examine specific components of interpersonal problems or negative affect (372).

Therefore, to extend on our prior work (110; 374), the objective of this study was to examine the validity of the interpersonal model of LOC eating using temporally sensitive reports of interpersonal stress, distinct negative mood states, and snack food intake as a proxy for LOC eating (462; 480). Using the conceptual model shown in Figure 1, we hypothesized that among adolescent girls with reported LOC eating, recent social stress would be associated with highly palatable dessert and snack food intake in the laboratory (374). Moreover, we explored several negative affective states to determine the specific moods that mediate the relationship between social stress and intake.

METHODS

Participants and Recruitment

Participants were adolescent girls (12-17 y) recruited for a prevention trial aimed at reducing excess weight gain in adolescent girls at high-risk for adult obesity (ClinicalTrials.gov ID: NCT00263536). Some of these data have been previously published (374; 458; 490), and this paper is an extension of previously published research (374).

To be eligible for the study, girls were deemed at risk for excess weight gain due to a body mass index (BMI, kg/m^2) between the 75^{th} and 97^{th} percentiles and the report of at least one episode of LOC eating in the month prior to assessment. Participants were recruited through advertisements in local newspapers, referrals from physicians' offices, mailings to local area parents, flyers distributed through local middle and high school parent listservs, postings at the National Institutes of Health (NIH) and the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Maryland, and local public facilities, with permission. Girls were excluded if they had a major medical or psychiatric condition (other than binge eating disorder), were currently taking medication known to impact eating behavior and/or weight, or

had a recent significant weight loss for any reason (exceeding 3% of body weight). The protocol was reviewed and approved by the Institutional Review Boards at USUHS and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Procedure and Measures

Informed parental/guardian consent and child assent were obtained for all participants. At baseline, prior to participation in the prevention program, girls completed two screening visits. At the first visit, participants completed body measurements, psychological interviews, and self-report questionnaires about recent social stress. At a second visit (within 1-2 weeks of the first screening appointment), girls completed a questionnaire assessing state negative affect and then immediately following consumed lunch from a laboratory test meal designed to model a LOC eating episode (312; 462).

Body Measurements

Height (cm) was measured in triplicate by stadiometer and fasting weight (kg) was measured by calibrated scale to the nearest 0.1 kg. BMI (kg/m^2) was calculated using height, averaged across the three measurements, and weight. We then calculated age- and sex-adjusted BMI-*z*, based on the Centers for Disease Control and Prevention growth standards (255). Body lean mass (kg) and body fat mass (%) were measured using dual-energy x-ray absorptiometry (DXA). DXA measurements were taken using a calibrated Hologic QDR-4500A instrument (Bedford, MA). Pubertal staging (454) was based on physical examination by an endocrinologist or nurse practitioner. Breast development was assessed by inspection and palpation and assigned according to the five stages of Tanner (292). If stage was discordant between right and left breasts, the higher Tanner stage was assigned. Tanner stage categories were then combined into

pre-puberty (Tanner Stage 1), early/mid-puberty (Tanner Stages 2 and 3), and late puberty (Tanner Stages 4 and 5).

LOC Eating

Participants were administered the Eating Disorder Examination version 12.0 (118) to determine the presence of at least one episode of LOC eating in the past 28 days. The Eating Disorder Examination has demonstrated good inter-rater reliability and discriminant validity in pediatric samples (146; 474) and excellent reliability in the present sample (467).

Social Adjustment

The Social Adjustment Scale (502) is a questionnaire assessing social functioning in four domains: school, friends, family, and dating. The Social Adjustment Scale has shown excellent reliability and validity (143) and has been successfully adapted for adolescents (323; 324). Consistent with prior studies (466; 467), only the friends, family, and school subscales of the Social Adjustment Scale were included. The Social Adjustment Scale demonstrated good reliability in the present sample (Cronbach's $\alpha = .86$).

Loneliness and Social Dissatisfaction

The Loneliness and Social Dissatisfaction Scale (31), a self-report questionnaire, was used to assess the participant's loneliness and social dissatisfaction with social relationships. The Loneliness and Social Dissatisfaction Scale asks participants to rate 24 items (e.g., "I don't get along with other children," "I can find a friend when I need one") on a 5-point Likert scale ranging from "always true" to "not at all true," with higher scores on the total score indicating greater loneliness and social dissatisfaction. The Loneliness and Social Dissatisfaction Scale has shown acceptable internal consistency and reliability (31; 142). The Loneliness and Social

Dissatisfaction Scale also demonstrated excellent reliability in the present sample (Cronbach's α = .90).

Pre-Meal State Negative Affect

Immediately before the test meal, participants completed the Brunel Mood Scale (478). The Brunel Mood Scale assesses present mood by asking participants to rate how they currently feel for 24 mood descriptors on a 5-point Likert scale, with 0 representing "not at all" and 4 representing "extremely". The Brunel Mood Scale generates six subscales: anger, confusion, depression, fatigue, anxiety/tension, and vigor (53; 462; 478). All scales, other than vigor, capture negative affective states (478; 492).

Observed Intake During Laboratory Test Meal Modeled to Capture a LOC Eating Episode

Following an overnight fast beginning at 10:00pm the night before, at approximately 11:00am, participants were presented with a buffet test meal (9,835 kcal; 12% protein, 51% carbohydrate, 37% fat) containing a broad array of foods that varied in macronutrient composition (312; 374; 462). Girls were played a tape-recorded instruction to "let yourself go and eat as much as you want," and then were left alone in a private room to consume the meal. The energy content and macronutrient composition for each item were determined using data from nutrient information supplied by food manufacturers as well as the U.S. Department of Agriculture Nutrient Database for Standard Reference (485). Individual foods were weighed on electronic balance scales (in grams) before and after the meal, and both total intake and snack-type food intake were calculated for each participant. As described in previous studies (374; 462), snack-type food intake included both sweet snacks (e.g., jellybeans, chocolate candy) and salty snacks (e.g., pretzels, tortilla chips). Previous research has shown that LOC eating status moderates the relationship between test meal instruction and total food intake in girls with

overweight, such that the combination of a "binge meal" instruction (versus an instruction to eat normally) and the presence of LOC eating leads to the greatest overall intake (462). As reported previously (374), the majority (54.5%) of participants reported that the laboratory eating episode was slightly, moderately, very much or extremely similar to a typical LOC eating episode.

Data Analysis

All analyses were conducted using SPSS Version 23.0. Data were screened for outliers and normality. Four extreme outliers were identified: one for snack-type calories consumed and three for total pre-meal Brunel Mood Scale score. Outliers were recoded to the respective next highest value for each variable (500). Pre-meal Brunel Mood Scale anger, confusion, and depression subscales were log-transformed to achieve normality. Given the significant overlap in the constructs measured by the Loneliness and Social Dissatisfaction Scale and Social Adjustment Scale, a composite score for recent social stress was created by averaging these two standardized scores (Cronbach's $\alpha = .88$).

To identify which individual pre-meal negative affective states mediated the relationship between social stress and palatable food intake in the laboratory, five mediation models were conducted using the Preacher and Hayes Indirect Mediation macro for SPSS (406). The five models were: 1) composite social stress score as the independent variable, snack-type food intake as the dependent variable, and pre-meal anger as the mediator, 2) composite social stress score as the independent variable, snack-type food intake as the dependent variable, and pre-meal confusion as the mediator, 3) composite social stress score as the independent variable, snack-type food intake as the dependent variable, and pre-meal depression as the mediator, 4) composite social stress score as the independent variable, snack-type food intake as the dependent variable, and pre-meal fatigue as the mediator, and 5) composite social stress score as

the independent variable, snack-type food intake as the dependent variable, and pre-meal anxiety as the mediator. In exploratory analyses, the same mediation models were repeated, using total caloric intake as the dependent variable instead of snack-type food intake.

To understand if the model was relevant for all facets of interpersonal stress, for significant negative affect subscales, four follow-up exploratory mediation analyses were conducted to examine separately the components of the composite score as independent variables: Social Adjustment Scale friends, family and school subscales and the Loneliness and Social Dissatisfaction Scale. For all mediation models, bootstrapping with 10,000 resamples was used to estimate the 95% bias-corrected confidence interval (CI) for indirect effects. All mediation analyses adjusted for age, race (coded as non-Hispanic White or other), pubertal stage, height (cm), fat mass (%), and lean mass (kg). No statistical test assumptions were violated. All tests were two-tailed. Differences and similarities were considered significant when *p*-values were $\leq .05$.

RESULTS

Participant Characteristics

Data from 117 adolescent girls aged 12-17 years ($M = 14.47$, $SD = 1.65$ years) were analyzed. Participants had an average BMI-*z* of 1.54 ($SD = 0.34$). Sixty-three (53.8%) participants identified as Non-Hispanic White, 31 (26.5%) as Non-Hispanic Black, 10 (8.5%) as Hispanic, and 13 (11.1%) as multiple races or another racial/ethnic group. On average, participants reported 4.65 ($SD = 6.04$) LOC eating episodes in the past 28 days. Based on the number of LOC eating episodes that were objective binge episodes in the past 3 months, one participant met DSM-5 criteria for binge eating disorder (22). The pattern of findings did not

differ with and without this participant; therefore, her data were included. Participant demographics, questionnaire data, and food intake data are shown in Table A.

Mediation Model

The Brunel Mood Scale anxiety subscale was a significant mediator of the relationship between the composite recent social stress score and snack-type food intake ($R^2 = 0.14$; ab = 18.06, 95% bootstrap CI: [2.14, 50.63]; Figure 2). Recent social stress was significantly associated with Brunel Mood Scale anxiety ($a = 0.69$, $SE = .20$, $p < .001$) and, in turn, Brunel Mood Scale anxiety was significantly associated with intake of snack-type food ($b = 27.04$, SE = 10.31, $p = .01$). The direct effect of recent social stress on intake of snack-type food ($c = 37.23$, $SE = 22.06$, $p = .09$) was decreased with the addition of Brunel Mood Scale anxiety ($c' = 18.48$, $SE = 22.64$, $p = .42$).

By contrast, the anger ($R^2 = 0.11$; 95% bootstrap CI: [-2.39, 29.46]), confusion (R^2 = 0.11; 95% bootstrap CI: [-0.32, 32.33]), depression ($R^2 = 0.09$; 95% bootstrap CI: [-3.62, 21.47]), and fatigue ($R^2 = 0.10$; 95% bootstrap CI: [-1.61, 22.07]) subscales did not significantly mediate the association between the composite recent social stress score and intake of snack-type food. In exploratory analyses, no mood state subscale significantly mediated the relationship between the composite recent social stress score and total caloric intake (ps > .05).

Follow-Up Exploratory Analyses for Anxiety and Palatable Food Intake

Social adjustment: Family subscale

The Brunel Mood Scale anxiety subscale was a significant mediator of the relationship between Social Adjustment Scale family and snack-type food intake ($R^2 = 0.14$; 95% bootstrap CI: [1.61, 69.34]). The family subscale was associated with Brunel Mood Scale anxiety (a = 1.16, $SE = .25$, $p < .001$), and state anxiety, in turn, was associated with intake of snack-type

food (b = 24.65, SE = 10.70, p = .02). The significant effect of the family subscale on intake of snack-type food (c = 63.10, SE = 28.01, p = .03) became non-significant with the addition of Brunel Mood Scale anxiety (c' = 34.45, SE = 30.16, p = .26).

Social adjustment: Friends subscale

The Brunel Mood Scale anxiety subscale was a significant mediator of the relationship between Social Adjustment Scale friends subscale and snack-type food intake (R^2 = 0.15; 95% bootstrap CI: [0.82, 80.69]). The friends subscale was positively associated with Brunel Mood Scale anxiety (a = 1.13, SE = 0.32, p = .001), and state anxiety was associated with greater snack-type food intake (b = 24.97, SE = 10.25, p = .02). The significant effect of the friends subscale on intake of snack-type food (c = 80.73, SE = 35.20, p = .02) became non-significant with the addition of Brunel Mood Scale anxiety (c' = 52.60, SE = 36.31, p = .15).

Social adjustment: School subscale

The Brunel Mood Scale anxiety subscale did not significantly mediate the relationship between Social Adjustment Scale school problems and snack-type food intake (R^2 = 0.15; 95% bootstrap CI: [-.06, 9.10].

Loneliness and social dissatisfaction

The Brunel Mood Scale anxiety subscale was a partial mediator of the relationship between the Loneliness and Social Dissatisfaction Scale score and snack-type food intake (R^2 = 0.16; 95% bootstrap CI: [0.06, 4.13]). The Loneliness and Social Dissatisfaction score was associated with greater state anxiety (a = 0.05, SE = 0.02, p = .009), and state anxiety was associated with more intake of snack-type food (b = 24.75, SE = 9.94, p = .01). The significant effect of Loneliness and Social Dissatisfaction score on intake of snack-type food (c = 5.27, SE =

1.99, $p = .01$) was attenuated by the addition of state anxiety, but remained significant ($c' = 4.04$, $SE = 2.00$, $p = .046$).

DISCUSSION

In this test of the interpersonal model of LOC eating using in-laboratory food intake, we found pre-meal anxiety significantly mediated the relationship between recent social stress and the consumption of palatable (i.e., snack-type) food intake. Other aspects of pre-meal negative affect (anger, confusion, depression, and fatigue) did not significantly mediate the relationship between recent social stress and intake.

Prior studies have shown that state negative affect is linked with subsequent LOC eating (40; 74; 153; 196; 437) and palatable food intake (374; 393). However, we found only pre-meal state anxiety, but not state, anger, confusion, depression or fatigue, explained the relationship between recent social stress and palatable food intake. Anxiety may be particularly important for the onset and maintenance of LOC eating. Not only are anxiety disorders commonly comorbid with binge eating disorder in adults (169), but LOC eating is associated with (164; 415), and predictive of anxiety symptoms in youth (464). Moreover, neural data suggest that similar to youth with anxiety problems (300; 301), those with LOC eating are highly responsive to experimentally-induced exposure to social anxiety, both in terms of brain region activation and subsequent eating behavior (223). In the results from the trial from which data for the current analysis was collected, we found that found that anxiety moderated outcome. Specifically, compared to a standard-of-care control group, girls with high anxiety who received interpersonal psychotherapy had the greatest improvements in BMI-*z* and adiposity (466). Notably, these findings are consistent with other trials testing interpersonal psychotherapy in adolescents (175; 517; 519) and may speak to the relevance of anxiety in the interpersonal model. Taken together,

these findings suggest that anxiety may be a particularly important facet of negative affect in adolescent girls who are above-average weight and who experience LOC eating.

In follow-up analyses, we found that all components of recent social stress, other than social problems pertaining to school, supported the interpersonal model. This finding is not entirely surprising. Unlike the Social Adjustment Scale friends and family subscales and the Loneliness and Social Dissatisfaction Scale that all assess the quality of interpersonal relationships, the Social Adjustment Scale school subscale primarily captures academic functioning (31; 502), which may not be as directly relevant to interpersonal theory. The current data lend support to the interpersonal model, suggesting that interpersonal stressors uniquely contribute to the development and/or maintenance of LOC eating and excessive palatable food intake (505). However, it is possible that other types of stressors (e.g., academic stress), impact the development and/or maintenance of LOC eating and excessive palatable food intake through mechanisms other than anxiety.

In concert with some (158; 462; 480), but not all (200; 312) data, we found no relationship between negative affect and *total* intake in a laboratory test meal. Indeed, prior studies show that snack intake better distinguishes youth with LOC eating from youth without LOC eating than total intake (462; 480), and may account for the associations between LOC eating and metabolic syndrome components (369) and C-reactive protein, a measure of chronic inflammation (412). Thus, impacting dessert and snack food intake, specifically, may be an important target of excess weight gain prevention. In other findings from this trial, dessert and snack food intake was reduced following interpersonal psychotherapy relative to health education among girls with LOC eating (458). Taken together, the interpersonal model may be particularly applicable for the excessive consumption of palatable foods. Further data are needed

to examine the various components of social functioning and negative affective states to better elucidate and refine the interpersonal model of LOC eating in youth.

Study strengths include the use of a relatively diverse sample of adolescents, an objective assessment of body composition, and a well-controlled laboratory test meal. While not allowing for the determination of causality, the sequenced assessments of recent social stress, negative affect, and laboratory test meal allowed us to examine the construct validity of the interpersonal model of LOC eating using temporally sensitive measures over time. Limitations of the study include potentially reduced ecological validity, due to the use of a laboratory test meal. Ecological momentary assessment studies may be especially sensitive in assessing the temporal relationships between social stress, anxiety, and food intake in the natural environment. It is also possible that the failure to find certain effects was due to sample characteristics, given that girls with significant psychopathology were excluded. Additionally, this study only examined the interpersonal model of LOC eating in adolescent girls; therefore, these findings may not be generalizable to males or to other age groups. Moreover, although there are no clinical cutoffs for the questionnaires used in the current study, girls were generally healthy. The study also did not adjust for multiple comparisons, potentially increasing the risk of a type I error. Future replication studies in mixed-sex samples, younger children, as well as clinical populations are required. Future research should also involve examining anxiety and palatable food intake by experimentally manipulating exposure to social stress to elucidate the causality of these constructs. Finally, alternative biological and psychological mediators of the relationship between social stress and highly palatable food intake may identify novel intervention targets.

In conclusion, the interpersonal model appears to be salient among adolescent girls with LOC eating. The presence of state anxiety in response to recent social stress may place

adolescents with LOC eating at high risk for exacerbated disordered eating, mood disturbances, and obesity. Interventions that focus on improving both social functioning and anxiety may be most effective for ameliorating eating and weight problems in adolescents with LOC eating.

CHAPTER 5: General Discussion

OVERVIEW AND SUMMARY OF STUDY FINDINGS

Based on the findings of Studies 1, 2, and 3, Dissertation—Figure 4 shows an updated conceptual model, with the addition of acute stress impacting LOC eating, dietary intake, and mood symptoms. This series of studies provides the foundation for a programmatic line of future research focused on the relationships among stress, disordered eating, and physical health. Study 1 used a convenience sample to examine the relationship between LOC eating and chronic inflammation, and found that youth who reported recent LOC eating had increased hsCRP compared to youth who did not report LOC eating, even after adjusting for adiposity. Study 2 examined whether LOC eating remission at end-of-treatment predicted improvements in metabolic health at 6-month follow-up, compared to youth with LOC eating persistence. This study found that youth with LOC remission at end-of-treatment had lower glucose, higher high-density lipoprotein cholesterol, and lower triglycerides at follow-up compared to youth with persistent LOC, despite no baseline group differences in these components. Study 3 examined if stress and negative affect contributed to palatable food intake in youth with LOC eating. This study found that state anxiety mediated the relationship between recent social stress and palatable food intake, highlighting the importance of considering the role of stress and mood in LOC eating. Taken together, the findings from these studies led to the development of a novel conceptual model (Dissertation—Figure 4), proposing integrative relationships among acute stress, LOC eating, dietary intake, mood symptoms, fat mass, chronic inflammation, and adverse physical health outcomes such as metabolic syndrome.

Interpreting the Conceptual Model in an Allostasis Framework

As described in Chapter 1, the human body constantly attempts to adapt to environmental

demands such as chronic stress by maintaining a stable equilibrium through a process known as allostasis (229; 305). During allostasis, an individual may undergo behavioral, psychological, and physiological responses to attempt to achieve stability (229; 304; 305). Chronically increased allostasis, which can result from frequent or prolonged psychological stressors, can result in allostatic load, or "wear-and-tear" of the body (229; 305). The proposed conceptual model (Dissertation—Figure 4) can potentially be viewed through the framework of allostasis and allostatic load.

In response to the perception of an acute stressor, the body responds by activating the HPA axis, releasing glucocorticoids such as cortisol, and the SAM system, releasing catecholamines (229). Glucocorticoids appear to influence the reward pathways to increase the preference for highly palatable foods, particularly in the presence of stress (137; 358; 428). This drive to consume palatable foods may reflect a reward-mediated negative feedback loop, as previous research suggests high-calorie foods alleviate stress symptoms (79; 137; 428). Glucocorticoids also promote central obesity, a component of MetS, particularly in the presence of insulin (79). This pathway may also be a negative feedback loop in an attempt to maintain homeostasis, as intra-abdominal adiposity is associated with decreased HPA responsivity and CRF expression in the hypothalamus in animals with chronic stress (79). In addition to an increased preference for palatable food, it has been proposed that stress can promote "addictive-like" behavior, potentially through the mesolimbic dopaminergic system, which has been closely associated with reward (352; 516). In response to stress, prefrontal cortex activity is diminished, while limbic circuits have increased activity (304; 305; 516). This combination likely promotes more "automatic" behaviors, including a stronger drive to eat and a decreased ability to inhibit palatable food intake (516). This drive to consume food may potentially underlie the experience

of LOC eating for some individuals. These physiological changes may also increase the risk for the development of depression, anxiety, and related psychiatric disorders (304). For vulnerable individuals, these feedback loops may serve as negative reinforcement conditioning for palatable food intake and LOC eating, allowing them to ameliorate the aversive physiological effects of stress (352).

The repeated activation of the HPA axis and SAM system in response to stress can also impact other physiological systems throughout the body, increasing the risk for adverse physical health outcomes such as metabolic syndrome (229). For example, elevated blood pressure in response to chronic stress promotes atherosclerotic changes, while the presence of elevated glucocorticoids and catecholamines promotes insulin resistance and type 2 diabetes (303; 304). The immune system is also impacted through allostasis. With the prolonged HPA axis activation of chronic stress, glucocorticoid receptors are down-regulated, decreasing the cells' ability to respond to anti-inflammatory signals (405). This pathway can increase nonspecific chronic inflammation in vulnerable individuals, further conferring risk for adverse metabolic outcomes (405). This process may be exacerbated in individuals with excess weight, given that excess adipose tissue— particularly excess visceral adipose tissue— is strongly associated with immune dysregulation an increase in pro-inflammatory cytokines (182; 307). Together, these pathways represent multiple mechanisms through which stress contributes to the disease processes involving chronic inflammation in vulnerable individuals.

In summary, while the physiological response to stress is typically beneficial, with frequent or prolonged psychological stressors, chronic under- or over-activation of these systems can lead to allostatic load and full-syndrome pathophysiology (229; 305; 426). In an attempt to return to homeostasis, in response to chronic stress, vulnerable individuals may experience a

drive to consume palatable food, LOC eating, increased central adiposity, and worsened metabolic and inflammatory markers. Taken together, the process of allostasis and allostatic load may explain much of the relationships between stress, food intake, LOC eating, inflammation, and physical health. Future research should continue to examine these variables using an allostasis framework across the lifespan.

STRENGTHS AND LIMITATIONS

As with all research, each study has relevant strengths and limitations. Study 1 utilized a large sample size (n = 194), and all three studies had relatively diverse samples. Moreover, for all studies body composition was directly assessed using reliable and valid methods (111; 392; 417). Given the overlap between adiposity and physical health (e.g., 120), adjusting for adiposity allowed us to examine the relationships between stress, LOC eating, and physical health above and beyond the contribution of adiposity. Similarly, the direct objective estimation of metabolic dysfunction in Study 2, as well as the use of temporally sensitive measures and a well-controlled laboratory test meal in Study 3, increases internal validity for these studies. Each study also experimentally controlled for time of day in the procedure, to ensure that fasting blood draws and food intake were measured at similar times for all participants, increasing the internal validity for the studies. Across all three studies, LOC eating was assessed using a semi-structured clinical interview, which is considered a valid and reliable method to assess LOC eating (58; 119; 146; 467; 472); however, it is unknown if we would see similar effects if LOC eating was assessed by self-report questionnaires. Given that self-report questionnaires are commonly used to assess LOC eating (e.g., 272; 316; 429; 447; 465; 486), future research should examine these relationships across LOC eating measurements. Additionally, each study assessed LOC eating only once at baseline; however, only approximately 30-50% of youth report persistent LOC

eating over time (199; 464). Therefore, it is unknown if the significant effects were driven by youth with persistent LOC eating, and future research should consider LOC eating history.

Taken together, this series of studies has several important considerations. The first study consisted of a convenience sample across multiple studies, potentially inducing bias and limiting generalizability (116). Studies 2 and 3 were drawn from the same sample, which consisted of weight gain prevention-seeking, adolescent girls with above average BMI. Future research should continue to examine the relationships among stress, LOC eating, and physical health in community samples of boys and girls. It is also important to examine these relationships prospectively across the lifespan to better determine the directionality and causality of these relationships. Of note, youth with major medical or psychiatric conditions were excluded from these studies. The relationships among stress, LOC eating, and physical health may be stronger or different in youth with medical comorbidities compared to healthy individuals; therefore, future research should examine these relationships in clinical populations. These studies also did not consider the role of menstrual cycle phase in these relationships, which may influence LOC eating (248), negative mood (71), and inflammatory markers (176). Future research should consider how these relationships change across menstrual cycle phases in post-pubertal girls. Lastly, studies that integrate acute stress, disordered eating, and physical health through innovative research paradigms and technologies are needed to better elucidate the short- and long-term relationships between these variables.

CURRENT RESEARCH GAPS

Future research should focus on addressing the above limitations as well as a number of important research gaps. Most importantly, there is a lack of an integrative understanding of the relationships among these variables with physical health. Prospective studies should utilize novel

paradigms in order to elucidate the relationship among stress, disordered eating, and physical health in both community samples and high-risk youth, with a strong focus on examining potential moderators and mediators of these relationships. Importantly, little is known about one potential mediator between stress and physical health, the physiological reactivity to stress, in youth with and without LOC eating. Based on the findings from these three studies, an ongoing research study, "The Inflammatory Response to Stress and Loss of Control Eating," was designed to address several of these research gaps and provide a more integrative understanding of these variables by examining stress reactivity, as measured by salivary markers of inflammation, in youth with and without LOC eating.

THE INFLAMMATORY RESPONSE TO STRESS AND LOSS OF CONTROL EATING STUDY

Salivary Markers of Inflammation as a Marker of Acute Stress

Salivary markers of inflammation are a novel and innovative method for measuring the physiological response to acute stress (424). Traditionally, inflammatory responses to acute stress have been measured by examining serum collected by venous puncture (302; 508), which is invasive and involves potential risks to participants, such as discomfort and bruising (508). More recently, dried blood spot samples, which are drops of whole blood collected on a paper via finger prick, have been used in research as a less invasive method than venous puncture for measuring biomarkers (302). However, this method still has several disadvantages: finger pricks are still relatively invasive, assay protocols must be developed specifically for dried blood spots, and only a small quantity of sample is collected (302).

Salivary diagnostics is an important emerging field that offers several advantages: salivary collection is less invasive and has a smaller risk of side effects compared to blood collection, saliva contains most of the same molecules found in systemic circulation, and some

markers (such as IL-1β and IL-6) are more measurable as they appear at higher concentrations in saliva than serum (310; 424; 508). The majority of saliva is formed by the parotid, submandibular, and sublingual glands (26; 72), and is primarily composed of water (26). Salivary constituents, such as hormones and immunological molecules, can enter saliva by two methods: 1) via plasma and serum by passive diffusion or an active transport mechanism, or 2) by being produced locally by the saliva glands (51). Salivary markers of inflammation, such as IL-6 and CRP, appear to have diurnal patterns, with highest concentrations upon awakening (221). Additionally, over the course of two days, concentrations of salivary IL-6 and CRP were have been found to have moderate to high stability (221). Of note, many salivary markers of inflammation are poorly correlated with serum markers of inflammation at a given time point, potentially due to the lack of significant infiltration of proteins in blood into saliva, as well as individual differences in oral health (424). Salivary CRP may be more closely correlated with serum CRP as it is primarily secreted by the liver, and not directly into saliva (346); however, not all studies have shown a significant association between salivary and serum CRP concentrations (97; 424). Therefore, while salivary markers of inflammation are novel and offer several advantages over serum markers of inflammation, not all facets of these markers are fully understood.

Salivary markers of inflammation have been associated with negative physical and mental health. For example, salivary CRP is associated with increased BMI, serum IL-6 concentrations, and smoking status (346). Increased salivary CRP has also been observed in acute myocardial infarction patients (136). Salivary CRP is also associated with smoking status in healthy youth, with higher concentrations in active smokers than non-smokers (32). With respect to mental health, salivary IL-6 concentrations after awakening were found to be

positively correlated with hopelessness, depression, and exhaustion in a sample of middle-aged adults (420). In children, salivary IL-6 was associated with depressive and anxiety symptoms, as well as parent-reported impulsivity in girls; but not in boys (235). However, the research examining salivary markers of inflammation and physical/mental health is currently limited.

Salivary Markers of Inflammation in Response to Acute Psychological Stress

There is a growing literature suggesting that pro-inflammatory cytokines such as IL-1β, TNF-α, IL-8, and IL-6, as well as anti-inflammatory cytokines such as IL-4, increase in response to acute psychological stress (424). Salivary IL-1β in policemen was higher at the beginning of the work shift than at the end of the work shift (520). Salivary TNF-α, IL-2, and IL-4 concentrations were found to be higher in professors 120 minutes after a 2-hour lecture compared to baseline concentrations, with no changes observed on a non-lecture control day (131). However, this study found no change in IL-10 concentrations on lecture days (131). One study found salivary IL-1β in healthy students was higher during the mid-year exam period than during the period before and after the mid-year exam period (286). However, another study found increased salivary IL-6 and IL-2 concentrations in healthy students on only one of three exam days compared to baseline, but did find increases in IL-12 concentrations on two of the three exam days compared to baseline (274).

Some studies have used laboratory-based stressors to examine the inflammatory response to acute stress. In one study, adults with and without psoriasis underwent a 5-minute mental arithmetic stressor. Salivary IL-1β was elevated at baseline in adults with psoriasis versus the healthy controls, and the two groups reported similar levels of subjective stress. However, 10 minutes post-stressor, the healthy controls had an increase in salivary IL-1β, while the participants with psoriasis showed a blunted response to stress, with no change in salivary IL-1β

concentrations (296). Yet, another study found no differences in salivary IL-6 concentrations from baseline to 10 minutes post-stressor in police officers undergoing virtual reality scenarios of a motorcycle chase or gun confrontation scenario (170). One study used the Trier Social Stress Test to examine salivary IL-6 concentrations in healthy young adults. IL-6 concentrations were significantly higher immediately post-stressor, 10 minutes post-stressor, and 20 minutes post-stressor, with IL-6 concentrations returning to baseline levels at 60 minutes post-stressor (222). In another study, CRP, an acute phase protein secreted by the liver, did not differ across baseline, immediately post-stressor, and 30 minutes post-stressor in healthy undergraduate students completing the Trier Social Stress Test. In a recent study, healthy young adult women were randomized to either an emotional stress or control condition (414). Salivary IL-1β, IL-6, and IL-8 were measured pre- and post-manipulation. The study found that in the emotional stress condition, concentrations of IL-1β, IL-6, and IL-8 significantly increased, with similar effect sizes found for all three cytokines (414).

Sex differences in the response to acute psychological stress, as measured by salivary markers of inflammation, are not well-understood (424). However, research using serum measures of inflammation suggest that sex differences in salivary measures would be expected. One study has examined sex differences in serum IL-6 concentrations in response to a stressful mental arithmetic task (106). In this study, men displayed peak serum IL-6 concentrations earlier than women, with highest levels 30-minutes post-stressor, while women had peak serum IL-6 60-minutes post-stressor (106). In another study, women displayed greater serum IL-6 and IL-1ra responses but smaller serum TNF-α responses compared to men (439). These differences may be due to sex-steroid hormones, which can have heterogeneous effects on the immune system— for example, testosterone has been shown to suppress macrophage immune functioning, while

estrogen has been shown to stimulate macrophage cytokine production (81). While these studies suggest that sex may be an important consideration, future research should continue to elucidate sex differences in stress reactivity as measured by both salivary and serum markers of inflammation.

Taken together, salivary markers of inflammation are a novel and innovative method for measuring the physiological response to acute stress, and offers several advantages over serum markers. Salivary markers of inflammation appear to be associated with negative physical and mental health, similar to serum markers of inflammation. Additionally, preliminary research suggests that these markers of inflammation increase in response to acute psychological stress. However, few studies have examined salivary markers of inflammation in response to acute psychological stress, there is limited research in youth, and no known studies have been conducted in individuals with disordered eating.

The Present Study

The proposed Stress-Inflammation Model of LOC Eating (Dissertation—Figure 5A) is an integrative model that combines research in acute stress, LOC eating, inflammation, and physical health and proposes a potential role of the inflammatory response to stress within and among these relationships. Youth who report LOC eating are at increased risk for excess weight (125; 430; 473) and fat (457) gain and the development of adverse health outcomes such as components of the metabolic syndrome (465). Independent of adiposity, youth with LOC eating have elevated chronic inflammation (412). Psychological stress may play a significant role in the development and maintenance of LOC eating (28; 147; 154; 177; 464). Acute psychological stressors may also activate the immune response, leading to changes in inflammatory processes (291; 405), and these inflammatory responses may at least partially mediate the relationship

between acute psychological stressors and adverse health outcomes in vulnerable individuals (304; 404). However, it is unknown if youth with LOC eating demonstrate a dysregulated stress response. Additionally, only one study has examined inflammation in youth with LOC eating (412) and no study has examined salivary markers of inflammation in response to acute stress in individuals with disordered eating. Salivary markers of inflammation have been used in a limited number of studies examining the physiological reactivity to stress, and few investigations have examined stress recovery using salivary markers of inflammation. The proposed study will test components of the Stress-Inflammation Model of LOC Eating (Dissertation—Figure 5B) and fill major research gaps by using an integrative framework to examine stress reactivity and recovery using salivary markers of inflammation in youth with disinhibited eating.

Aims and Hypotheses

Aim 1

Examine the relationship between LOC eating and systemic inflammation.

Hypothesis 1: Youth with LOC eating will have higher baseline inflammatory markers (salivary IL-1β, IL-6, IL-8, TNF-α; serum IL-1β, IL-6, IL-8, TNF-α; hsCRP) than youth without LOC eating, after adjusting for relevant covariates such as adiposity.

Exploratory Hypothesis 1: If youth with LOC eating have elevated systemic inflammation, the relationship will be at least partially mediated by psychopathology (depression, state anxiety, and anxiety sensitivity).

Aim 2

Examine stress reactivity and recovery, as indicated by changes in salivary measures of inflammation.

Hypothesis 2: Youth with LOC eating will demonstrate an exacerbated inflammatory

response to stress, indicated by higher salivary inflammatory markers (IL-1β, IL-6, IL-8, TNF-α) at all time points post-stressor than youth without LOC eating, after adjusting for relevant covariates.

Exploratory Aim

Examine if stress reactivity and recovery, as indicated by changes in salivary measures of inflammation, mediates the relationship between LOC eating and metabolic syndrome.

Exploratory hypothesis a: The magnitude of the inflammatory response to stress, indicated by change in pre- to post-stressor levels of salivary inflammatory markers (IL-1β, IL-6, IL-8, TNF-α), will mediate the relationship between LOC eating and components of the metabolic syndrome, after adjusting for relevant covariates.

Exploratory hypothesis b: Stress recovery, indicated by post-stressor area under the curve (AUC) salivary inflammatory markers IL-1β, IL-6, IL-8, TNF-α), will mediate the relationship between LOC eating and components of the metabolic syndrome, after adjusting for relevant covariates.

Methods

Research Design

This study proposal is one component of the Children's Growth and Behavior Study (ClinicalTrials.gov ID: NCT02390765). Only the procedures and measures relevant to this proposal are presented in the Methods section. The proposed study will use a cross-sectional design to examine differences in the inflammatory response to a laboratory stressor experimental paradigm among adolescents with and without LOC eating. Additionally, a bootstrapping approach will be employed to examine whether the inflammatory response to stress mediates the relationship between LOC eating status and components of the metabolic syndrome.

Participants and Recruitment

One hundred and fifty adolescent boys and girls across the weight spectrum [75 (50%) who report LOC eating in the past 28 days and 75 (50%) who do not report LOC eating in the past 28 days] will be recruited for the proposed study. Participants will be recruited from Washington, D.C. and the surrounding areas through multiple methods: referrals from local physicians and clinics, advertisements in local newspapers, flyers posted in local public facilities as well as National Institutes of Health (NIH) and Uniformed Services University of the Health Sciences (USU), mailing to local families, and advertisements distributed through local middle and high school parent listservs.

Youth will be eligible if they are 12-17 years, are cognitively capable of completing study procedures, and have body mass index (BMI, kg/m^2) ≥ 5th percentile for age and sex according to Centers for Disease Control and Prevention 2000 U.S. standards (255). Individuals will be excluded if they have a major medical or psychiatric illness, current pregnancy or history of pregnancy, a diagnosis of periodontal disease, are "highly active" (i.e., vigorous-intensity activity on at least three days and accumulating at least 1500 metabolic equivalent-minutes per week or seven days of any combination of walking, moderate-intensity or vigorous intensity activities achieving at least 3000 metabolic equivalent-minutes per week) as defined by the International Physical Activity Questionnaire Short Form (50), current and regular use of tobacco products and/or alcohol, significant reduction in weight during the past three months (>5% body weight), or regular use of medications known to impact eating behavior, weight, autonomic functioning, or endocrine functioning, including oral contraceptives.

Participants are asked not to consume or use any potentially confounding medications or supplements (e.g., hydrocortisone cream), in the 24 hours before the laboratory visit. Additionally, in the three hours before the laboratory visit, adolescents are asked not to consume

any food or drink aside from water, consume caffeine in any form, or engage in excessive physical exercise, defined as exercise during which the participant is sweating and/or breathing heavily. Lastly, participants cannot be in extreme physical pain during the visit. If an adolescent meets any of these visit-specific exclusion criteria upon arrival to the laboratory visit, the visit will be rescheduled.

Study Procedure

A telephone screen will be conducted to determine preliminary eligibility for the Children's Growth and Behavior Study. Potentially eligible families will be seen at NIH Hatfield Clinical Research Center (CRC) in Bethesda, Maryland for three visits. Participants will undergo the following procedure at each visit.

Screening Visits

Participants will have two screening visits. At the beginning of the first visit, participants will undergo consent/assent. The study's purposes, testing procedures, and possible study risks will be described in detail. Interested parents and youth will sign NIH-approved consent and assent forms, respectively. Participants will complete a physical examination, 24-hour dietary recall, psychodiagnostic interviews, and questionnaires. For the second screening visit, participants will complete an overnight fast beginning at 10:00 P.M. the night before the visit. Vital signs, including blood pressure, will be assessed by a trained practitioner. Fasting anthropometric measurements, a fasting blood draw will be collected, and body composition will be measured using dual-energy x-ray absorptiometry. The second screening visit will be completed approximately 14 days, and no more than three months, after the first screening visit.

Experimental Visit

The Experimental Visit must be completed within three months of the second screening visit. The procedure for the Experimental Visit is depicted in Dissertation—Figure 6. All study visits will occur on a weekday or weekend afternoon, beginning at approximately 3:30 PM to control for time of day. Participants will be instructed to not consume any food or drinks except for water within three hours of the Experimental Visit. They will also be instructed not to use any over-the-counter medications within 24 hours of to the laboratory visit. Upon arrival to the laboratory, participants will be asked reminder questions to ensure that the adolescent is still eligible to participate in the study. If so, then they will undergo the following procedure, which includes a baseline period, the laboratory stressor, and a post-stressor period. Saliva samples will be collected throughout these periods.

After determining eligibility, the procedure will begin by having participants undergo a 45-minute baseline period. In the first 25 minutes, adolescents will be instructed to relax and will be provided educational magazines and/or drawing materials. Participants will then be asked to close their eyes for 10 minutes, and then will have another 10-minute relaxation period during which they can utilize educational magazines and/or drawing materials. The first saliva collection to examine inflammatory markers will be collected 35 minutes into the baseline period, 10 minutes pre-stressor. Youth will also complete a questionnaire about their subjective measure of stress twice during baseline.

Laboratory Stressor

The Children's Paced Auditory Serial Addition Test (CHPASAT; Appendix A) is a 20-minute cognitive task that was modified from the Paced Auditory Serial Addition Test (PASAT) for adults (171). Participants will listen to instructions and complete training trials (5 minutes). After they understand the task, youth will begin the actual arithmetic task (15 minutes). For the

task, participants will be instructed to add 2 sequentially presented single digit numbers from 1 to 9 while retaining the later of the 2 in memory for subsequent addition to the next number presented. Adolescents will be instructed to add the number they've just heard to the immediate previous number and to report the result verbally. Numbers are presented in 5 blocks (61 numbers each) of differing speeds: one digit every 2.8, 2.4, 2.0, 1.6, and 1.2 seconds. The CHIPASAT is modified from the PASAT to account for lower mathematical ability such that the sum of any two numbers will never exceed 10; the presentation rates of the task are identical (104). The CHIPASAT has been shown to have excellent test-retest reliability in healthy children (104; 225). The CHIPASAT has also been found to have high internal consistency, with a split half correlation of .92 (225; 483).

Given that laboratory stressors involving a social-evaluative threat have been shown to increase proinflammatory cytokine activity (95) and to consistently increase cortisol (96), youth will be told that their performance will be evaluated afterward by judges for speed and accuracy and compared with their peers. The participant's verbal production during the task will be recorded by both an audio-recorder, as well as by the administrator using a scoring form. Numbers will be presented by a CD recording, and participants will not be given accuracy feedback. The PASAT has been used as a laboratory stressor in several previous studies (205; 283; 284; 435) and has been shown to increase self-reported anxiety (283; 435) and to induce moderate-to-large effects on endocrine and cardiovascular responses among healthy adults (96; 205; 283; 435; 507). For example, in healthy adults, the PASAT increased heart rate by 18% from baseline, with an effect size of $d = 0.86$ (205). However, while the CHIPASAT has shown acceptable reliability in youth (104; 225) the PASAT has been validated as a stressor in adults (205; 283; 284; 435), and the CHIPASAT has been used as a stressor in youth in conjunction

with the Trier Social Stress Test (347), no known study has used the CHIPASAT as the primary laboratory stressor in youth.

Post-Stressor Period

Post-stressor recovery will occur over 90 minutes, during which six saliva samples will be collected and several questionnaires will be completed. Immediately post-stressor, participants will be instructed to close their eyes for 10 minutes and relax. After completing a questionnaire, participants will then be verbally coached, using a pre-recorded audio file, to slow their breathing for 15 minutes to increase parasympathetic activity (227; 348). After the paced breathing, adolescents will be instructed to relax and engage in restful activities (e.g., reading magazines, drawing, watching a non-stimulating movie) for about 65 minutes in order to capture stress recovery. Participants will also complete five questionnaires during the final rest period.

Debriefing

After the post-stressor period, participants will be debriefed (script shown in Appendix B). During the debriefing, adolescents will be informed that their performance on the CHIPASAT is not the focus of the current protocol. Rather, their stress response is the variable of interest. Participants will be asked not to share this information with anyone else who may participate in the study, and adolescents will be given the opportunity to let the researcher know if they have any questions or concerns about the deception.

Measures

Pubertal Development

A brief medical history and physical exam will be conducted by a doctor or trained nurse practitioner. Pubertal development will be assessed in the physical examination according to the stages of Tanner (292; 293). For girls, the Tanner stage will be assigned based on breast

development, which will be assessed by inspection and palpation (292). If Tanner stage is discordant between the right and left breasts, the higher Tanner stage will be assigned. For boys, testicular volume (mL) will be measured using a set of orchidometer beads as standards according to Prader (455), and Tanner stages will be assigned as follows: Tanner Stage 1 (testes ≤ 3 mL), Tanner Stage 2 (testes 4 mL—9 mL), Tanner Stage 3 (testes 10 mL—15 mL), Tanner Stage 4 (testes 16—24 mL), or Tanner Stage 5 (testes ≥ 25 mL). If Tanner stage is discordant between the right and left testes, the higher Tanner stage will be assigned.

Psychopathology

Adolescents will be screened for threshold psychiatric disorders (22) using the K-SADS (231; Appendix C) by trained clinicians or advanced graduate students. The K-SADS is a semi-structured interview (231) that takes between 35 and 75 minutes to administer (232). The K-SADS has been shown to have excellent concurrent validity (231), convergent validity (266), divergent validity (45), inter-rater agreement in scoring and diagnosis (231), and test-retest diagnostic reliability (231) in youth.

Anthropometric Measurements

Fasting body weight will be measured in triplicate to the nearest 0.1 kg using a calibrated scale. Body height (cm) will be measured in triplicate by stadiometer. A BMI-*z* score will be calculated to adjust for age and sex based on the Centers for Disease Control and Prevention growth standards (65). Dual-energy x-ray absorptiometry (DXA) will be used to determine total body fat mass, lean mass, and bone mass in the Metabolic Suites at NIH using the Lunar iDXA (GE Healthcare, Madison, WI). For the DXA scan, participants will lie still on a cushioned table for 5-10 minutes. Postmenarcheal girls will provide a urine sample for pregnancy test prior to DXA. DXA has been validated as a measure of body composition (111), including in obese

subjects (392) and adolescents (431). In children and adolescents, DXA measurements of adiposity have been shown to be significantly correlated with clinical indicators such as insulin, C-reactive protein, triglycerides, total cholesterol, systolic blood pressure, and glucose (76).

Physical Activity

The International Physical Activity Questionnaire (IPAQ) Short Form (50; Appendix D) will be used to determine study eligibility. The IPAQ Short Form asks about physical activities, broken into the categories of walking, moderate activity, and vigorous activity, over the past seven days. Based on the responses, participants are then categorized into three levels of physical activity: low, moderate, or high (50). The IPAQ Short Form has shown very good test-retest reliability (55; 73). While over-reporting physical activity is a potential issue with the IPAQ Short Form (107; 396), studies have typically shown a fair-to-moderate agreement with accelerometers (73; 107). Participants who are designated as "high" on the IPAQ Short Form (i.e., vigorous-intensity activity on at least three days and accumulating at least 1500 metabolic equivalent-minutes per week or seven days of any combination of walking, moderate-intensity or vigorous intensity activities achieving at least 3000 metabolic equivalent-minutes per week) will be excluded from the study, given that high levels of physical activity may impact physiological reactivity to acute stressors (385). Excluding adolescents with high levels of physical activity as reported by the IPAQ Short Form is conservative, given that most studies find the IPAQ short form overestimates physical activity level (270).

Loss of Control Eating

The Eating Disorder Examination (EDE) version 14 OD/C.2 (119; Appendix E) will be administered by a trained interviewer to assess the presence and frequency of LOC eating episodes over the past three months. The EDE contains 21 items that assess disordered attitudes

and behaviors related to eating, body-shape and weight, and 13 items designed and adapted to diagnose specific DSM-5 eating disorders. Participants who meet criteria for a DSM-5 eating disorder will be excluded from the study, except for BED. The EDE has demonstrated sound psychometric properties in adolescents, including good internal consistency and inter-rater reliability in both clinical and non-clinical samples (146; 338; 474; 498). The EDE will be used to assess the presence and frequency of LOC eating episodes over the past three months. For children and adolescents, it appears that the experience of LOC eating, rather than the amount of food consumed, is the most salient indicator of aberrant eating (415). Therefore, similar to the three studies presented above (411-413), both objectively large and subjectively large episodes will be considered LOC eating episodes, and youth will be considered to have LOC eating if they endorse at least one episode in the past three months. The presence of LOC eating, as assessed by the EDE, has been shown to prospectively predict increases in disordered eating attitudes (464), the development of BED (464), and excess weight gain (473).

Psychological Questionnaires

Depressive symptoms will be assessed using the Children's Depression Inventory (CDI; Appendix F), a 27-item self-report measure (250). The CDI assesses symptoms of depression over the past two weeks such as worthlessness, negative mood, and fatigue (63; 251). Items are scored from 0 to 2 (possible range: 0 to 54), with greater scores indicating greater depressive symptoms (250). A clinical cut-off score of 19 is generally accepted on the CDI (250). The CDI has been shown to have high internal consistency (62; 163; 250) and can discriminate between clinical and healthy youth (62; 398).

Trait anxiety will be assessed using the State-Trait Anxiety Inventory for Children (STAIC; 432; Appendix G). The STAIC is a 40-item self-report measure that has two

components: 20 items that assess state anxiety and 20 items that assess trait anxiety (432). The trait anxiety scale asks respondents how frequently (hardly-ever, sometimes, or often) they feel like the various statements (e.g., "I worry about making mistakes"), with higher scores indicating higher levels of anxiety (432). The STAIC-Trait has been shown to have acceptable internal consistency (327; 350; 432) and have high correlation with other measures of anxiety in children (432).

Social anxiety will be assessed using the Social Anxiety Scale for Children-Revised (SASC-R; 263; Appendix H) for participants who are less than twelve years old or the Social Anxiety Scale for Adolescents (SAS-A; 262; Appendix I) for participants who are at least twelve years old. Both versions ask participants to rate how true 22 statements (18 social anxiety items and 4 filler items) are for them on a 5-point Likert scale. The social anxiety items assess the subjective experiences and behavioral consequences of obesity. The scale produces a total social anxiety score and three subscales: fear of negative evaluation from peers; social avoidance and distress specific to new situations/unfamiliar peers; and social avoidance and distress generally experienced in company of peers. Both the SASC-R and the SAS-A have demonstrated acceptable internal consistency, test-retest reliability, and validity (260-263; 495).

Dietary Intake and Diet Quality

With the assistance of their parent/guardian, adolescents will provide information on food intake during the 24 hours before their visit, using a multi-pass approach to limit the extent of under-reporting. This method has been validated against the doubly labeled water method in children (226) and takes approximately 20 minutes to administer. After collecting information on dietary intake, the Healthy Eating Index-2010 (Appendix J; 226) will be used to assess diet quality based on the 24-hour recall data. The Healthy Eating Index-2010 is a measure of diet

quality based on the 2010 Dietary Guidelines for Americans (484). Healthy Eating Index-2010 has 12 components: 1) total fruit, 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; 9) fatty acids; 10) refined grains; 11) sodium; and 12) added sugars. The twelve components are summed to produce a total score, with higher scores on all scales reflecting better diet quality (173; 174; 238). Healthy Eating Index-2010 scores have been found to inversely associated with the risk of hypertension (277) and is positively associated with self-rated diet quality (7). Improvement in Healthy Eating Index scores has also been associated with lower risk of type 2 diabetes (276; 402).

State Perceived Stress

As a manipulation check, the Short Stress State Questionnaire (SSSQ; 193; Appendix K) will be completed at six time points during the visit (30 minutes pre-stressor, 5 minutes pre-stressor, 10 minutes post-stressor, 25 minutes post-stressor, 40 minutes post-stressor, and 60 minutes post-stressor) in order to assess subjective stress responses throughout the laboratory visit. The SSSQ is a 24-item scale that measures 3 aspects of subjective stress: task engagement, distress, and worry. This scale shows adequate reliability and validity (194). Version A of the SSSQ asks participants about thoughts and feelings now as well as during the past ten minutes. Version B asks participants about thoughts and feelings during the CHIPASAT. Participants will complete Version B after the CHIPASAT, and will complete Version A at all other time points.

Perception of Stressor

As a manipulation check, participants will be asked to rate their perception of the laboratory stressor (Appendix L) during the recovery period to confirm that the laboratory stressor was perceived as stressful. The questionnaire was developed by the study team and asks

participants to rate how stressed, sad, anxious, and angry they felt during the stressor using a 7-point Likert scale rating. The questionnaire also asks if they have completed a similar task before.

Oral Health

As oral health can impact salivary measures of inflammation (414; 424), participants will complete the Oral Health Questionnaire, an investigator-developed questionnaire (Appendix M) about symptoms of gum disease, the use of orthodontic equipment such as dental braces, and the frequency of oral health-related behaviors. The questionnaire should take less than five minutes to complete.

Serum Measures of Inflammation

At the second screening visit, participants will complete a fasting blood draw. Serum hsCRP concentrations will be measured by enzyme-linked immunosorbent assay (ELISA), using a Cobas 6000 Analyzer (Roche Diagnostics, Indianapolis, IN) at the NIH Clinical Research Center Department of Laboratory Medicine. Serum concentrations of IL-1β, IL-6, IL-8 and TNF-α will be examined using cytokine ELISA kits (R&D Systems, Minneapolis, Minnesota). The sensitivity for the IL-1β, IL-6, IL-8 and TNF-α is 0.063 pg/mL, 0.09 pg/mL, 0.4 pg/mL, and 0.049 pg/mL, respectively.

Salivary Measures of Inflammation

To collect saliva, a synthetic oral swab (Sarstedt, Newton, NC) will be placed under the tongue for 5 minutes. After collection, samples will be placed on ice then stored in a -20°C freezer immediately after the study visit. Saliva will be collected at the following time points: 1) 10 minutes pre-stressor, 2) immediately post-stressor, 3) 30 minutes post-stressor, 4) 45 minutes

post-stressor, 5) 55 minutes post-stressor, 6) 65 minutes post-stressor, and 7) 85 minutes post-stressor. As the timing of change in salivary markers of inflammation in response to acute stress is not well-defined (424), these time points were chosen to capture stress recovery as comprehensively as possible over the 90 minutes recovery. Salivary concentrations of IL-1β, IL-6, IL-8 and TNF-α will be determined using a salivary cytokine multiplex panel (Salimetrics, Carlsbad, CA). Preliminary research has shown that salivary concentrations of IL-1β, IL-6, TNF-α, and IL-8 may increase in response to acute psychological stress; however, it is unknown if there are similar time courses across these cytokines (424). For the panel, the required test volume is 25 μL and the recommended collection is 100 μL. The sensitivity for IL-1β, IL-6, IL-8 and TNF-α is 1.2 pg/mL, 0.18 pg/mL, 64 pg/mL, and 0.15 pg/mL, respectively.

Metabolic Syndrome (MetS) Components

While various criteria have been used for MetS, recent guidelines suggest that to meet criteria, adults should meet at least three out of the five following criteria: 1) elevated triglycerides, defined as at least 150 mg/dL; 2) reduced high-density lipoprotein cholesterol, defined as less than 40 mg/dL in males and less than 50 mg/dL in females; 3) high blood pressure, defined as systolic blood pressure greater than or equal to 130 mmHg and/or diastolic blood pressure greater than or equal to 85 mmHg; 4) elevated fasting glucose, defined as greater than or equal to 100 mg/dL; and 5) elevated waist circumference, based on population- and country-specific definitions (10). However, the specific cut-off criteria for a diagnosis of MetS in youth is more controversial, with inconsistent criteria frequently used (15) and low diagnostic stability (482).

For this study, MetS components will be measured through a variety of methods. At the second screening visit, blood will be drawn by a phlebotomist or registered nurse and fasting

blood glucose, triglycerides, and high-density lipoprotein will be assessed. Waist circumference (cm) at the iliac crest will be obtained with a non-elastic tape measure as a measure of visceral adiposity and age- and sex-adjusted waist circumference scores will be calculated (123). Blood pressure (diastolic and systolic) will be assessed by a trained practitioner using the appropriate pediatric or adult cuffs for the participant's arm size. Given the potential limitations of specific cut-off values for youth and the potentially low prevalence of full MetS diagnosis in a sample of generally healthy youth (438), MetS components (glucose, triglycerides, high-density lipoprotein cholesterol, waist circumference, systolic blood pressure, and diastolic blood pressure) will be examined continuously for all analyses.

Participant Compensation

All adolescents will receive $75 for completing Screening Visit 1, $120 for completing Screening Visit 2, and $75 for completing Study Visit 1, for a maximum of $270.

Data Analytic Approach

All analyses will be conducted using SPSS Version 24.0. Data will be examined for outliers ad screened for normality. Extreme outliers, defined as less than three standard deviations below or greater than three standard deviations above the mean, will be recoded to the next lowest or highest value, respectively, to minimize its influence on the data analyses. Variables with a non-normal distribution will be transformed using log, inverse, square root, or arcsine transformations as appropriate. The assumptions of all analyses will be checked. Differences in demographics between adolescents with and without LOC eating will be examined using independent samples *t*-tests, chi-square tests, and Fisher's exact tests where appropriate.

Given the anticipation that valid values of inflammatory markers will not be available for

all participants for all time points, analyses will be repeated with and without imputed inflammatory markers. Multiple imputation will be conducted for missing inflammatory markers using the fully conditional specification method and linear regression model type. Five imputations with 100 iterations between imputations will be conducted, and the range of *p* values across the five imputations will be assessed.

Unless otherwise stated, the following covariates will be considered in all analyses: depressive symptoms (CDI score), trait anxiety (STAIC trait score), pubertal status (Tanner stage), race (Non-Hispanic White versus other), sex, body fat (%), lean mass (kg), height (cm), age (years), and diet quality (Healthy Eating Index-2010). Variables that are not significantly different between adolescents with and without LOC eating and do not contribute significantly to any analysis will be removed from the final set of analyses. Differences for all tests will be considered significant when *p* values are ≤ .05, and all tests will be two-tailed.

Aim 1

Examine the relationship between LOC eating and systemic inflammation.

Hypothesis 1: Nine one-way analysis of covariances (ANCOVAs) will be conducted with LOC eating (presence; absence) as the between-subjects independent variable (IV) and baseline inflammatory markers (salivary IL-1β, IL-6, IL-8, TNF-α; serum IL-1β, IL-6, IL-8, TNF-α; hsCRP) as the dependent variables (DVs).

Exploratory Hypothesis 1: If the relationship with LOC eating is significant for any specific inflammatory marker, follow-up mediation analyses will be conducted using Preacher and Hayes Indirect Mediation macro for SPSS (438). Mediation models will use psychopathology variables (depressive symptoms, anxiety symptoms, anxiety sensitivity) as mediators, LOC eating as the IV, and the baseline inflammatory marker as the DV. All

covariates except for the respective psychopathology variables will be included. Bootstrapping with 10,000 resamples will be used to estimate the 95% confidence interval for indirect effects in each mediation model. All mediation models will also be conducted in the opposite direction, with each respective metabolic syndrome component as the IV and LOC eating as the DV.

Aim 2

Examine stress reactivity and recovery, as indicated by changes in salivary measures of inflammation.

Hypothesis 2: Four linear mixed models will be conducted with LOC eating (presence; absence) as the between-subjects IV, time (samples 2-6) as the within-subjects IV, the interaction of LOC eating and time as an additional IV, and salivary IL-1β, IL-6, IL-8, and TNF-α as DVs. Several possible structures will be considered for the within-subjects covariance, including unstructured, compound symmetric, and first-order autoregressive. The best-fitting structure will be selected based on two fit indices: the Akaike Information Criterion (AIC) and the Bayesian information criterion (BIC). For each model, the respective pre-stressor baseline saliva score will be included as an additional covariate.

Exploratory Aim

Examine if stress reactivity and recovery, as indicated by changes in salivary measures of inflammation, mediates the relationship between LOC eating and metabolic syndrome.

Exploratory hypothesis a: Several mediation analyses will be conducted using Preacher and Hayes Indirect Mediation macro for SPSS (38). Mediation models will use the change in pre- to post-stressor salivary inflammatory markers (IL-1β, IL-6, IL-8, TNF-α) as mediators, LOC eating as the IV, metabolic syndrome components as the DVs, and the respective pre-stressor salivary inflammatory markers (IL-1β, IL-6, IL-8, TNF-α) as covariates. Bootstrapping

with 10,000 resamples will be used to estimate the 95% confidence interval for indirect effects in each mediation model. All mediation models will also be conducted in the opposite direction, with each respective metabolic syndrome component as the IV and LOC eating as the DV.

Exploratory hypothesis b: Several mediation analyses will be conducted using Preacher and Hayes Indirect Mediation macro for SPSS (406). Mediation analyses will use AUC salivary inflammatory markers (IL-1β, IL-6, IL-8, TNF-α) as mediators, LOC eating as the IV, metabolic syndrome components as the DVs, and respective pre-stressor salivary inflammatory markers (IL-1β, IL-6, IL-8, TNF-α) as covariates. AUC with respect to ground will be calculated for each salivary inflammatory marker using all post-stressor time points (samples 2-6), and will be normalized with respect to 1 at sample 2 (i.e., samples 2-6 will be divided by the value at sample 2) to account for differences in stress reactivity. Bootstrapping with 10,000 resamples will be used to estimate the 95% confidence interval for indirect effects in each mediation model. All mediation models will also be conducted in the opposite direction, with each respective metabolic syndrome component as the IV and LOC eating as the DV.

Preliminary Analyses and Results

Participant Characteristics

Forty-six adolescents have completed the full experimental procedure. Just over a majority of participants were female (54.3%). The racial/ethnic breakdown was 39.1% non-Hispanic White, 26.1% non-Hispanic Asian, 23.9% non-Hispanic Black, 4.3% Hispanic, and 6.5% other or unknown. The age ranged from 12.0 to 17.8, with an average of 14.8 (*SD* = 1.7). BMI-*z* ranged from -1.5 to 2.2, with an average of 0.5 (*SD* = 0.9). Three participants (6.5%) reported LOC eating in the past three months.

Self-Reported Stress

Near the end of the experimental visit, participants reported how much stress (M = 3.2, SD = 1.7; range: 0-7), sadness (M = 0.7, SD = 1.2, range: 0-4), anxiety (M = 2.4, SD = 1.7, range: 0-6), and anger (M = 1.0, SD = 1.6; range: 0-6) they felt during the task. Six times throughout the visit, participants also reported distress, engagement, and worry on the SSSQ. SSSQ ratings are shown in Dissertation—Table 1. The two baseline SSSQ ratings (-30 and -5 minutes pre-stressor) we averaged together to create a baseline SSSQ rating. Paired samples t-tests showed that distress 10 minutes post-stressor (M = 1.5, SD = 0.4) was significantly higher than baseline distress (M = 1.2, SD = 0.2; $p < .001$). All other time points were not significantly different from baseline (ps = .10-.72). Worry 10 minutes post-stressor (M = 1.7, SD = 0.6) was significantly higher than worry at baseline (M = 1.6, SD = 0.5; p = .004). While worry 25 minutes post-stressor was not significantly different from baseline (p = .94), worry 40 minutes (M = 1.4, SD = 0.5; p = .01) and 60 minutes post-stressor (M = 1.4, SD = 0.5; p = .02) were significantly lower than baseline. Task engagement 10 minutes post-stressor (M = 3.2, SD = 0.7) did not different from baseline engagement (M = 3.2, SD = 0.6, p = .33). However, engagement 25 minutes post-stressor (M = 2.8, SD = 0.7, $p < .001$), 40 minutes post-stressor (M = 2.9, SD = 0.7, p = .001), and 60 minutes post-stressor (M = 2.9, SD = 0.7, p = .01) were significantly lower than baseline.

Salivary Markers of Inflammation

Salivary data from 29 (63.0%) participants have been analyzed for all time points. One participant had values that were extreme outliers (defined as more than three standard deviations from the mean) on all four cytokines at baseline; therefore, that participant was not included in preliminary data. Differences of the log scores were calculated between each following time point and the baseline value, representing the log of the ratio of each time point to baseline, and data was descriptively examined. For the log of the ratio of each time point to baseline, zero

would represent equivalent values, a negative value would represent that the baseline value was greater than the time point value, and a positive value would represent that the time point value was greater than the baseline value. Means and standard errors of the log of the ratio are shown in Dissertation—Figure 7 for each cytokine. As the difference of the log scores were negative for all time points, on average, participant salivary cytokines did not increase at any time point relative to baseline.

Discussion

Summary of Preliminary Results

Forty-six adolescents have completed the study protocol. Participants retrospectively rated that they felt moderate levels of stress and low-to-moderate levels of anxiety during the laboratory stressor. Compared to baseline, participants had small but statistically significant increases in distress and worry 10 minutes post-stressor (ps < .05). When descriptively examining saliva data from a subset of 28 participants, participant salivary cytokines did not increase at any time point relative to baseline. It may be possible that the stressor is not potent enough to produce a cytokine effect across all participants. However, it may be possible that only a subset of participants are displaying stress reactivity as measured by salivary markers of inflammation, and the study is not yet sufficiently powered to examine predictors of between-subjects variability.

Strengths and Limitations

This study has several strengths. First, fat mass is directly assessed using DXA. This is particularly important given the relationship between adiposity and inflammation (182; 307). Second, this study uses a standardized and validated laboratory stressor. Many previous studies examining salivary markers of inflammation used non-standardized stressors (424), which can be

problematic for interpretation and replication. Additionally, social-evaluative components were integrated into the stressor. Given that social-evaluative stressors have been shown in previous studies to induce a consistent cortisol response (96), as well as an inflammatory stress response (424), this is a study strength. Lastly, measurements collected represent both stress reactivity and recovery. Previous research examining salivary markers of inflammation have has focused primarily on stress reactivity; therefore, less is known about stress recovery over time (424). In this study, salivary markers of inflammation will be examined up to 90 minutes post-stressor.

However, this study also has several limitations. Other markers of stress reactivity, such as cortisol, are not being examined in addition to salivary markers of inflammation. Other markers are not being examined in this study due to limited funds and to reduce participant burden. In addition, only four markers of inflammation (IL-1β, IL-6, IL-8, TNF-α) are being examined. Therefore, a broader understanding of how other markers of inflammation change in response to acute stress, including markers traditionally classified as anti-inflammatory, will not be uncovered. Moreover, serum markers of IL-1β, IL-6, IL-8, and TNF-α are not being assessed, which would allow for comparison of concentrations in saliva and serum. Lastly, despite previous research showing potential differences in the physiological reactivity to acute stress based on sex and, for females, phase of menstrual cycle (81; 424), the study will likely not be adequately powered to examine such differences. However, given that there are no data in adolescents with LOC eating, this study is a critical first step, and all primary analyses will include sex as a covariate. Additionally, the potential impact of menstrual cycle phase can be examined in a subset of participants who are female and report regular menses. Future research should address these limitations by measuring multiple markers of inflammation in both serum and saliva and enrolling a larger sample size to ensure that sex differences can be adequately

examined.

Study Summary

In summary, this ongoing research study is testing components of the Stress-Inflammation Model of LOC Eating by examining the relationship between LOC eating, acute psychological stress, salivary markers of inflammation, and MetS components in adolescents. The integration of these constructs in one study will build upon previous research in order to better elucidate the relationship among these variables.

Future Clinical Research Directions

In addition to examining the role of stress reactivity in these relationships, several important future clinical directions remain. While the presence of LOC eating has been associated with several psychological and physiological outcomes as listed above, it is unknown if interventions should target all youth who report LOC eating, or if these findings are being driven by a subset of youth with LOC eating. Of youth who report a recent LOC eating episode, only about 40-50% will report persistent LOC eating over time (198; 199; 464). In a study of boys and girls aged 8-13 years, children who reported LOC eating at baseline were assessed four additional times over two years: 3.6% had persistent LOC eating at all five time points, 41.8% had recurring LOC eating at multiple time points, and 54.5% fully remitted from LOC eating after baseline (199). Youth with recurring or persistent LOC eating may be the most important group to target with interventions. In a sample of youth who reported LOC eating at baseline, youth who still reported LOC eating at 5-year follow-up had greater increases in mood symptoms and disordered eating attitudes than youth who did not report persistent LOC eating (464). Future studies should examine how the duration and/or stability of LOC eating influence psychological and physiological outcomes.

In addition to the duration and stability of LOC eating, future research should consider whether additional criteria are needed to identify which youth with LOC eating are at risk of adverse outcomes. Given that few youth with LOC eating meet criteria for BED (461), different criteria have been proposed for youth. For example, provisional criteria for loss of control eating disorder (LOC-ED) in children less than 13 years old has been proposed (461). The proposed criteria for LOC-ED are: 1) recurrent episodes of LOC eating, 2) LOC eating episodes are associated with at least three of the following five features- negative affect before the episode, secrecy, a feeling of numbness, eating more than others, or negative affect after the episode, 3) LOC eating episodes occur at least six times over three months, 4) the absence of inappropriate compensatory behaviors, and 5) criteria is not met for anorexia nervosa, bulimia nervosa, or binge eating disorder (461). Compared with children who reported LOC eating but did not meet criteria for LOC-ED, children with LOC-ED had higher BMI-*z* and adiposity, and reported greater disordered eating attitudes and concerns (297). However, youth who reported LOC eating but did not meet criteria for LOC-ED also reported greater disordered eating attitudes and concerns and had higher BMI-*z* than youth who did not report LOC eating (297). Future research should prospectively examine whether psychological and physiological outcomes differ in youth who meet criteria for LOC-ED compared to youth who report LOC eating but do not meet criteria for LOC-ED.

In addition to determining how to identify high-risk subgroups of youth who report LOC eating, potential interventions should be examined in youth who report LOC eating. One promising intervention for reducing binge eating and preventing excess weight gain is interpersonal psychotherapy, which targets interpersonal stressors (468; 471; 505; 509). A recent trial examined whether an interpersonal psychotherapy group intervention (vs. a health education

control group) improved outcomes for youth with excess weight and LOC eating. The trial found that no group differences in BMI-*z* or adiposity at 1-year or 3-year follow-up (466; 467). However, participants in the interpersonal psychotherapy intervention (vs. the control group) had a greater reduction in objective binge eating episodes (467) and consumed less palatable snack-type food in a laboratory test meal (458) at 1-year follow-up. Additionally, for youth with high levels of social adjustment problems or trait anxiety, interpersonal psychotherapy was more effective than the control group for reducing excess weight gain (466). This suggests that interpersonal psychotherapy may be particularly effective in a subset of youth who report LOC eating and experience interpersonal problems and/or trait anxiety.

Another promising category of interventions for targeting LOC and binge eating is mindfulness-based approaches. Mindfulness targets the processing of internal and external stimuli by focusing attention in the present with an accepting, non-judgmental approach (378). General mindfulness-based interventions, such as meditation and mindfulness-based stress reduction (MBSR), have been shown to improve autonomic, inflammatory, and neurobiological markers of stress (353; 378). It is theorized that mindfulness-based interventions reduced sympathetic nervous system activity, decreasing stress reactivity (353; 378). Following MBSR, neuroimaging studies have demonstrated decreased activity in the amygdala, lending support to the theory that stress reactivity is an important mediator of the relationship between mindfulness-based interventions and improved physiological health (167; 188; 378). Given the proposed links between LOC eating, stress, and stress reactivity, mindfulness-based approaches may be effective in youth with LOC eating.

Several interventions for individuals with eating disorders have been developed using mindfulness-based approaches (252). Examples of adapted interventions for BED include

dialectical behavior therapy (280), mindfulness-based cognitive therapy (403), and mindfulness-based awareness training (253). A systematic review and meta-analysis examined the impact of mindfulness-based interventions in treating binge eating disorder, and estimated the effect size between medium-large and large (151), while other reviews have found that these interventions also reduce binge and emotional eating in non-clinical populations (230; 339). However, few mindfulness-based interventions for disinhibited eating have been conducted in non-clinical youth. In one study, healthy adolescents who underwent a brief mindful eating training showed less impulsive food-related choices, as measured by a food-based delay-discounting task, than adolescents in a control condition (195). Although mindfulness-based interventions have been successfully adapted for children and adolescents (360), no known studies have examined the impact of these types of interventions on youth with LOC eating.

Conclusion

In conclusion, the findings from the series of three studies led to the development of a novel conceptual model, proposing integrative relationships among acute stress, LOC eating, dietary intake, mood symptoms, fat mass, chronic inflammation, and adverse physical health outcomes such as metabolic syndrome. Future research should focus on elucidating the prospective relationships among these variables, as well as examine other potentially important mediators and moderators of these relationships. The ongoing research study, "The Inflammatory Response to Stress and Loss of Control Eating," provides an important first step examining the potential role of stress reactivity in these relationships. Future research should also focus on determining which subgroups of youth who report LOC eating are at high-risk for adverse outcomes, and examine whether interventions targeting stress, such as mindfulness-based approaches, improve these outcomes. Ultimately, the integration of psychological stress,

disordered eating, and physical health may lead to identifying mechanisms through which adverse health outcomes occur, potentially providing a pathway for novel pediatric prevention and intervention programs.

Study 1—Table 1. Participant Characteristics

	LOC eating (n = 75)	No LOC eating (n = 119)	p
Age in years, *M (SD)*	13.55 (2.27)	14.73 (1.85)	<.001
Sex, *n* (%)			.03
Male	20 (26.7%)	50 (42.0%)	
Female	55 (73.3%)	69 (58.0%)	
Race, *n* (%)			.76
Non-Hispanic White	28 (37.3%)	47 (39.5%)	
Non-Hispanic Black	32 (42.7%)	58 (48.7%)	
Hispanic	6 (8.0%)	3 (2.5%)	
Other/Unknown	9 (12.0%)	11 (9.2%)	
BMI-*z* score, *M (SD)*	1.91 (0.80)	1.46 (1.17)	.002
Fat Mass (kg), *M (SD)*	35.61 (19.03)	31.00 (21.01)	.14
Pubertal Status*, *n* (%)			.26
Pre-Puberty	4 (5.3%)	6 (5.0%)	
Early/Mid Puberty	24 (32.0%)	27 (22.7%)	
Late Puberty	37 (49.3%)	73 (61.3%)	
Not Available	10 (13.3%)	13 (10.9%)	
Height (cm), *M* (*SD*)	159.98 (9.50)	164.69 (10.60)	.003
HsCRP (mg/L), *M* (*SD*)	4.34 (5.57)	3.68 (6.86)	.004
CDI, *M* (*SD*)	7.61 (5.32)	4.78 (4.46)	<.001
EDE Global Score, *M* (*SD*)	1.28 (0.80)	0.56 (0.60)	<.001

Note: LOC, loss of control; hsCRP, high-sensitivity C-reactive protein; CDI, Children's Depression Inventory; EDE, Eating Disorder Examination**.** *Defined as prepuberty (Tanner Stage 1), early/midpuberty (Tanner Stage 2-3) and late puberty (Tanner Stage 4-5).

Study 1—Table 2. ANCOVA for HsCRP by LOC Presence

	df	*F*	η^2_p	*p*
Sex	1	10.21	.06	.002
Total Fat Mass	1	254.29	.59	<.001
Height	1	9.64	.05	.002
LOC Presence	1	5.51	.03	.02
Error	168			

Note: hsCRP, high-sensitivity C-reactive protein; LOC, loss of control.

Study 1—Table 3. ANCOVA for HsCRP by LOC Presence with Psychopathology

	df	*F*	η^2_p	*P*
Sex	1	11.24	.07	.001
Total Fat Mass	1	141.35	.50	<.001
Height	1	9.18	.06	.003
CDI	1	0.10	.001	.75
EDE Global Score	1	0.04	<.001	.84
LOC Presence	1	4.92	.03	.03
Error	144			

Note: hsCRP, high-sensitivity C-reactive protein; LOC, loss of control; CDI, Children's Depression Inventory; EDE, Eating Disorder Examination.

Study 2—Table 1. Participant Characteristics at Baseline Based on LOC Eating Status at End-of-Treatment

	LOC Remission (n = 45)	LOC Persistence (n = 58)	p
Age in years, *M (SD)*	14.3 (1.6)	14.6 (1.8)	.37
Race, *n* (%)			.35
Non-Hispanic White	23 (51.1)	35 (60.3)	
Non-Hispanic Black	14 (31.1)	11 (19.0)	
Hispanic	4 (8.9)	5 (8.6)	
Other/Unknown	4 (8.9)	7 (12.1)	
BMI-*z* score, *M (SD)*	1.6 (0.3)	1.5 (0.3)	.33
Fat Mass (kg), *M (SD)*	26.6 (6.5)	26.0 (5.3)	.61
Height (cm), *M* (*SD*)	162.5 (7.0)	162.0 (7.4)	.74
Waist circumference (cm), *M* (*SD*)	84.1 (9.2)	86.2 (8.1)	.25
Triglycerides (mg/dL), *M* (*SD*)	87.4 (44.1)	93.7 (49.6)	.53
LDL-C (mg/dL), *M* (*SD*)	82.1 (32.5)	88.9 (23.1)	.29
HDL-C (mg/dL), *M* (*SD*)	48.8 (10.3)	46.6 (9.8)	.29
Plasma glucose (mg/dL), *M* (*SD*)	87.2 (6.3)	86.6 (7.2)	.69
Systolic blood pressure (mmHg), *M* (*SD*)	117.5 (8.0)	116.9 (9.4)	.77
Diastolic blood pressure (mmHg), *M* (*SD*)	67.0 (6.0)	65.8 (5.8)	.32
LOC eating episodes, past 28 days, *M* (*SD*)	2.5 (3.2)	5.6 (5.7)	<.001*
Depressive symptoms, *M* (*SD*)	8.6 (5.8)	12.1 (7.2)	.01*

Note. Baseline data presented from all participants (n = 103). *Abbreviations:* LOC, loss of control; BMI-z, body mass index adjusted for age and sex; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. *Significant at $p < .05$.

Study 2—Table 2. Anthropometric and Metabolic Components at Baseline and 6-Month Follow-Up Within Each LOC Eating Group

	Baseline	6-Month Follow-Up	*p*
BMI-*z* score, *M (SD)*			
LOC Remission (*n* = 45)	1.6 (0.3)	1.5 (0.3)	.47
LOC Persistence (*n* = 58)	1.5 (0.3)	1.5 (0.4)	.32
Fat mass (kg), *M (SD)*			
LOC Remission (*n* = 44)	26.4 (6.5)	27.7 (7.1)	.08
LOC Persistence (*n* = 58)	26.0 (5.3)	26.8 (6.1)	.04*
Height (cm), *M* (*SD*)			
LOC Remission (*n* = 44)	162.6 (7.1)	163.6 (6.7)	.001*
LOC Persistence (*n* = 58)	161.7 (7.3)	162.9 (7.0)	<.001*
Waist circumference (cm), *M* (*SD*)			
LOC Remission (*n* = 44)	84.1 (9.2)	87.7 (10.7)	.001*
LOC Persistence (*n* = 50)	86.3 (8.3)	88.8 (8.8)	.05
Triglycerides (mg/dL), *M* (*SD*)			
LOC Remission (*n* = 36)	87.8 (45.5)	86.9 (47.9)	.89
LOC Persistence (*n* = 44)	93.0 (51.7)	96.9 (53.7)	.55
LDL-C (mg/dL), *M* (*SD*)			
LOC Remission (*n* = 32)	82.6 (32.9)	77.0 (23.4)	.10
LOC Persistence (*n* = 40)	89.6 (23.6)	86.9 (21.6)	.42
HDL-C (mg/dL), *M* (*SD*)			

LOC Remission (n = 41)	49.3 (10.0)	50.0 (11.8)	.58
LOC Persistence (n = 50)	46.8 (10.0)	44.8 (11.9)	.02*
Plasma glucose (mg/dL), *M* (*SD*)			
LOC Remission (n = 41)	86.8 (6.3)	83.8 (6.3)	.02*
LOC Persistence (n = 49)	86.8 (7.4)	86.5 (5.8)	.75
Systolic blood pressure (mmHg), *M* (*SD*)			
LOC Remission (n = 44)	117.5 (8.0)	117.9 (9.5)	.76
LOC Persistence (n = 56)	116.8 (9.5)	118.4 (10.3)	.31
Diastolic blood pressure (mmHg), *M* (*SD*)			
LOC Remission (n = 44)	67.0 (6.0)	66.8 (7.7)	.87
LOC Persistence (n = 56)	65.8 (5.9)	68.2 (7.1)	.02*

Note. For each variable, data is presented only for participants who had a valid measure at both baseline and 6-month follow-up. *Abbreviations:* LOC, loss of control; BMI-*z*, body mass index adjusted for age and sex; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. *Significant at $p < .05$.

Study 2—Supplemental Table S1. Analysis of Covariances for Metabolic Syndrome Components at 6-Month Follow-Up by LOC Eating Persistence

A. Waist Circumference	*df*	*F*	η^2_p	*p*
Baseline Waist Circumference	1	11.78	0.13	.001*
Baseline Depressive Symptoms	1	0.06	0.001	.81
Race	1	0.41	0.01	.52
Baseline Age	1	0.001	<0.001	.97
Baseline Height	1	1.40	0.02	.24
Baseline Fat Mass	1	20.73	0.20	<.001*
Change in Height	1	0.002	<0.001	.97
Change in Fat Mass	1	17.54	0.18	<.001*
LOC Eating Frequency	1	0.19	0.002	.67
LOC Eating Persistence	**1**	**0.32**	**0.004**	**.57**
Error	82			
B. Triglycerides	*df*	*F*	η^2_p	*p*
Baseline Triglycerides	1	55.72	0.45	<.001*
Baseline Depressive Symptoms	1	2.42	0.03	.13
Race	1	0.99	0.01	.32
Baseline Age	1	0.46	0.01	.50
Baseline Height	1	0.56	0.01	.46
Baseline Fat Mass	1	0.19	0.003	.66
Change in Height	1	10.62	0.14	.002*
Change in Fat Mass	1	0.002	<0.001	.96

LOC Eating Frequency	1	1.71	0.03	.20
LOC Eating Persistence	**1**	**5.53**	**0.08**	**.02***
Error	68			

C. LDL-C	*df*	*F*	η^2_p	*p*
Baseline LDL-C	1	74.65	0.55	<.001*
Baseline Depressive Symptoms	1	3.79	0.06	.06
Race	1	0.01	<0.001	.91
Baseline Age	1	0.06	0.001	.81
Baseline Height	1	2.10	0.03	.15
Baseline Fat Mass	1	0.20	0.003	.66
Change in Height	1	0.96	0.02	.33
Change in Fat Mass	1	5.01	0.08	.03*
LOC Eating Frequency	1	0.06	0.001	.81
LOC Eating Persistence	**1**	**1.74**	**0.03**	**.19**
Error	60			

D. HDL-C	*df*	*F*	η^2_p	*p*
Baseline HDL-C	1	152.62	0.66	<.001*
Baseline Depressive Symptoms	1	1.31	0.02	.26
Race	1	0.14	0.002	.71
Baseline Age	1	11.11	0.12	.001*
Baseline Height	1	0.03	<0.001	.87
Baseline Fat Mass	1	1.79	0.02	.19
Change in Height	1	1.19	0.02	.28

Change in Fat Mass	1	1.26	0.02	.27
LOC Eating Frequency	1	0.25	0.003	.62
LOC Eating Persistence	**1**	**7.26**	**0.08**	**.01***
Error	79			

E. Plasma Glucose	*df*	*F*	η^2_p	*p*
Baseline Plasma Glucose	1	5.55	0.07	.02*
Baseline Depressive Symptoms	1	0.97	0.01	.33
Race	1	0.02	<0.001	.90
Baseline Age	1	1.50	0.02	.22
Baseline Height	1	3.78	0.05	.06
Baseline Fat Mass	1	0.10	0.001	.75
Change in Height	1	1.41	0.02	.24
Change in Fat Mass	1	<0.001	<0.001	>.99
LOC Eating Frequency	1	0.14	0.002	.71
LOC Eating Persistence	**1**	**5.76**	**0.07**	**.02***
Error	78			

F. Systolic Blood Pressure	*df*	*F*	η^2_p	*p*
Baseline Systolic Blood Pressure	1	7.94	0.08	.01*
Baseline Depressive Symptoms	1	0.23	0.003	.64
Race	1	0.004	<0.001	.95
Baseline Age	1	1.24	0.01	.27
Baseline Height	1	1.16	0.01	.29
Baseline Fat Mass	1	1.38	0.02	.24

Change in Height	1	0.07	0.001	.80
Change in Fat Mass	1	0.10	0.001	.75
LOC Eating Frequency	1	3.90	0.04	.05
LOC Eating Persistence	**1**	**1.61**	**0.02**	**.21**
Error	88			

G. Diastolic Blood Pressure	*df*	*F*	η^2_p	*p*
Baseline Diastolic Blood Pressure	1	7.63	0.08	.01*
Baseline Depressive Symptoms	1	2.09	0.02	.15
Race	1	1.98	0.02	.16
Baseline Age	1	0.26	0.003	.61
Baseline Height	1	0.02	<0.001	.88
Baseline Fat Mass	1	1.08	0.01	.30
Change in Height	1	0.25	0.003	.62
Change in Fat Mass	1	0.28	0.003	.61
LOC Eating Frequency	1	0.22	0.003	.64
LOC Eating Persistence	**1**	**2.78**	**0.03**	**.10**
Error	88			

Abbreviations: LOC, loss of control; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. *Notes*: Participants missing outcome or covariate data were excluded from each respective analysis: waist circumference (n = 10), triglycerides (n = 24), LDL-C (n = 32), HDL-C (n = 13), plasma glucose (n = 14), systolic blood pressure (n = 4), and diastolic blood pressure (n = 4). *Significant at $p < .05$.

Study 3—Table 1. Participant Characteristics

Age in years, *M (SD)*	14.47 (1.65), range: 12.01-17.76
Race, *n* (%)	
Non-Hispanic White	63 (53.8)
Non-Hispanic Black	31 (26.5)
Hispanic	10 (8.5)
Other/Unknown	13 (11.1)
BMI-*z* score, *M (SD)*	1.54 (0.34), range: 0.68-2.06
Lean Mass (kg), *M (SD)*	44.09 (5.76), range: 29.95-57.65
Fat Mass (%), *M (SD)*	36.37 (5.24), range: 22.40-47.70
Height (cm), *M* (*SD*)	162.92 (8.00), range: 142.83-182.87
Pubertal Stage*, *n* (%)	
Pre-Puberty	3 (2.6)
Early/Mid-Puberty	18 (15.4)
Late Puberty	96 (82.1)
LOC Eating Episodes in past 28 days, *M (SD)*	4.65 (6.04), range: 1-39
Social Adjustment Scale	
Family, *M (SD)*	1.89 (0.64), range: 1.00-4.00
Friends, *M (SD)*	1.96 (0.51), range: 1.10-3.40
School, *M (SD)*	3.45 (2.78), range: 1.00-8.00
Loneliness and Social Dissatisfaction Scale, *M (SD)*	29.16 (9.10), range: 16-58
Brunel Mood Scale	
Anger, *M (SD)*	0.53 (1.44), range: 0-9

Confusion, *M (SD)*	0.97 (1.63), range: 0-7
Depression, *M (SD)*	0.50 (1.16), range: 0-7
Fatigue, *M (SD)*	5.83 (4.03), range: 0-16
Anxiety, *M (SD)*	1.30 (1.81), range: 0-9
Snack-type food intake (kcal), *M (SD)*	295.15 (196.67), range: 0.00-873.02
Total food intake (kcal), *M (SD)*	1172.75 (437.95), range: 199.57-1172.75

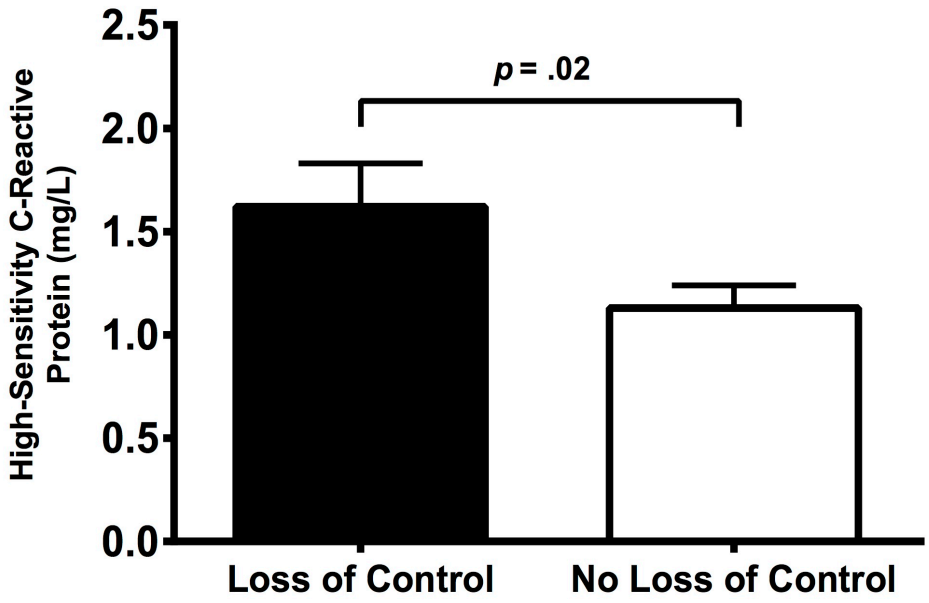
Note: N = 117; LOC, loss of control; *Pubertal stage defined as: pre-puberty (Tanner Stage 1), early/mid puberty (Tanner Stages 2 and 3), and late puberty (Tanner Stages 4 and 5).

Dissertation—Table 1. Short Stress State Questionnaire (SSSQ) Ratings

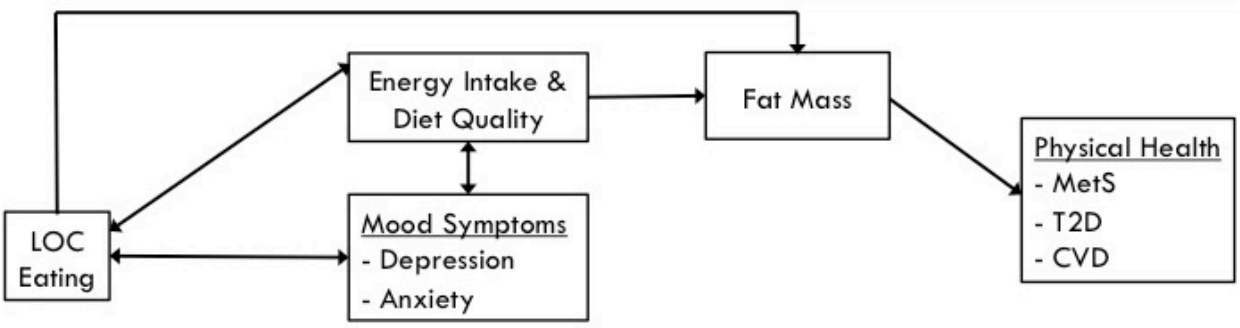
	M (*SD*), range	*p*
Distress		
-30 minutes	1.1 (0.2), 1.0-2.0	-
-5 minutes	1.2 (0.3), 1.0-2.0	-
Average baseline	1.2 (0.2), 1.0-1.9	-
10 minutes	1.5 (0.4), 1.0-2.8	<.001*
25 minutes	1.2 (0.3), 1.0-2.9	.72
40 minutes	1.1 (0.2), 1.0-1.8	.10
60 minutes	1.1 (0.2), 1.0-2.1	.33
Worry		
-30 minutes	1.6 (0.5), 1.0-2.8	-
-5 minutes	1.6 (0.5), 1.0-2.6	-
Average baseline	1.6 (0.5), 1.0-2.6	-
10 minutes	1.7 (0.6), 1.0-2.8	.004*
25 minutes	1.6 (0.5), 1.0-3.0	.93
40 minutes	1.4 (0.5), 1.0-2.8	.01*
60 minutes	1.4 (0.5), 1.0-2.9	.02*
Engagement		
-30 minutes	3.2 (0.6), 1.8-4.3	-
-5 minutes	3.1 (0.6), 1.8-4.3	-
Average baseline	3.2 (0.6), 1.8-4.1	-
10 minutes	3.2 (0.7), 1.3-5.0	.33

25 minutes	2.8 (0.7), 1.0-4.1	<.001*
40 minutes	2.9 (0.7), 1.0-4.4	.001*
60 minutes	2.9 (0.7), 1.0-4.3	.01*

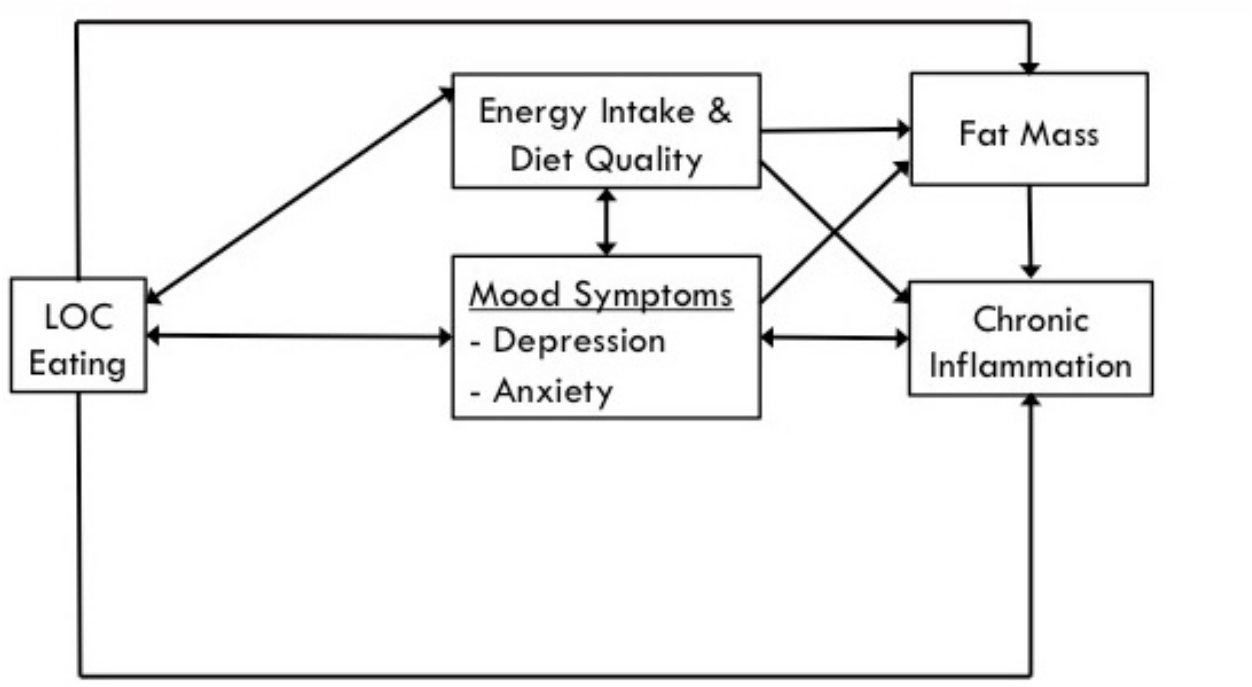
Note. Time points are relative to end of stressor. Average baseline is a summary of -30 and -5 minute time points. *P*-values are from paired samples *t*-tests comparing each time point to the average baseline. *Significant at $p < .05$.



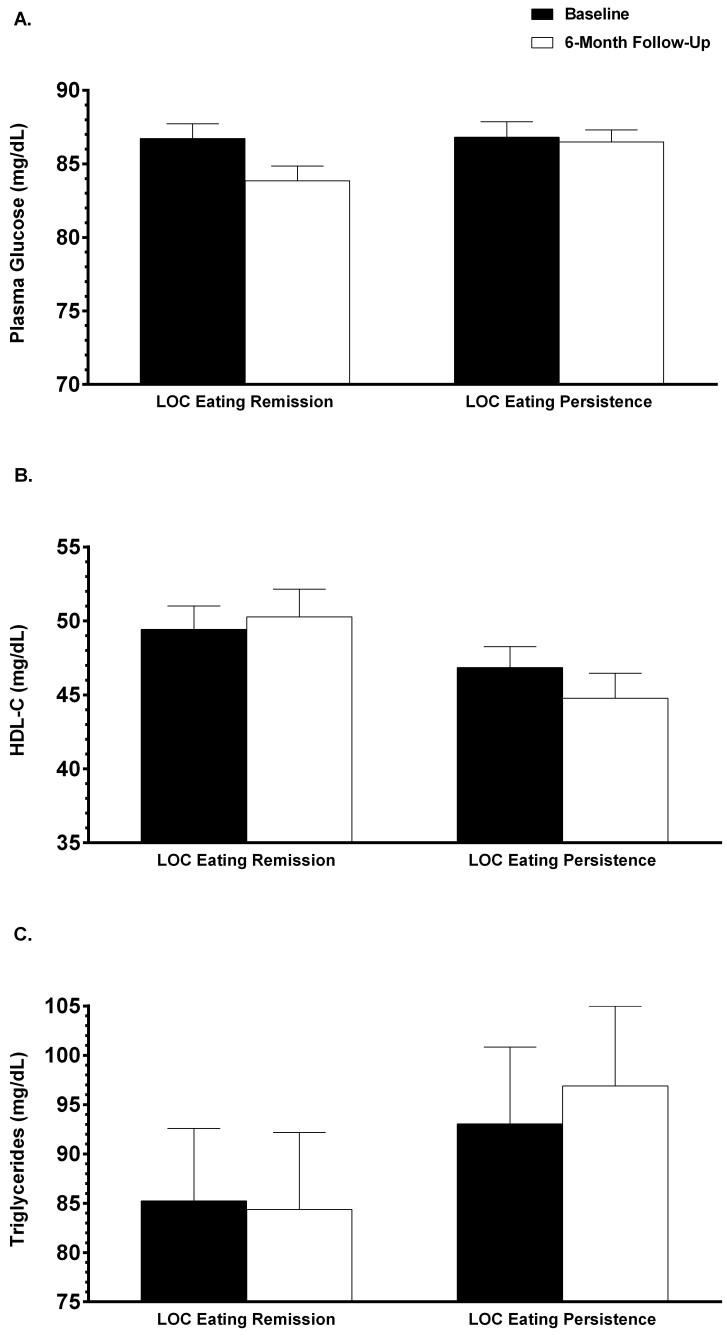
Study 1—Figure 1. High-sensitivity C-reactive protein (hsCRP) concentrations by LOC eating status. HsCRP concentrations in youth with loss of control eating were significantly greater than hsCRP concentrations in youth without loss of control eating; $p = .02$. Data from ANCOVA, adjusted for sex, fat mass (kg), and height (cm). Bars represent adjusted mean ± standard error of the mean for youth who reported loss of control eating and youth who did not report loss of control eating.



Dissertation—Figure 1. Proposed conceptual model based on the known relationships between LOC eating, food intake, mood symptoms, adiposity, and physical health.

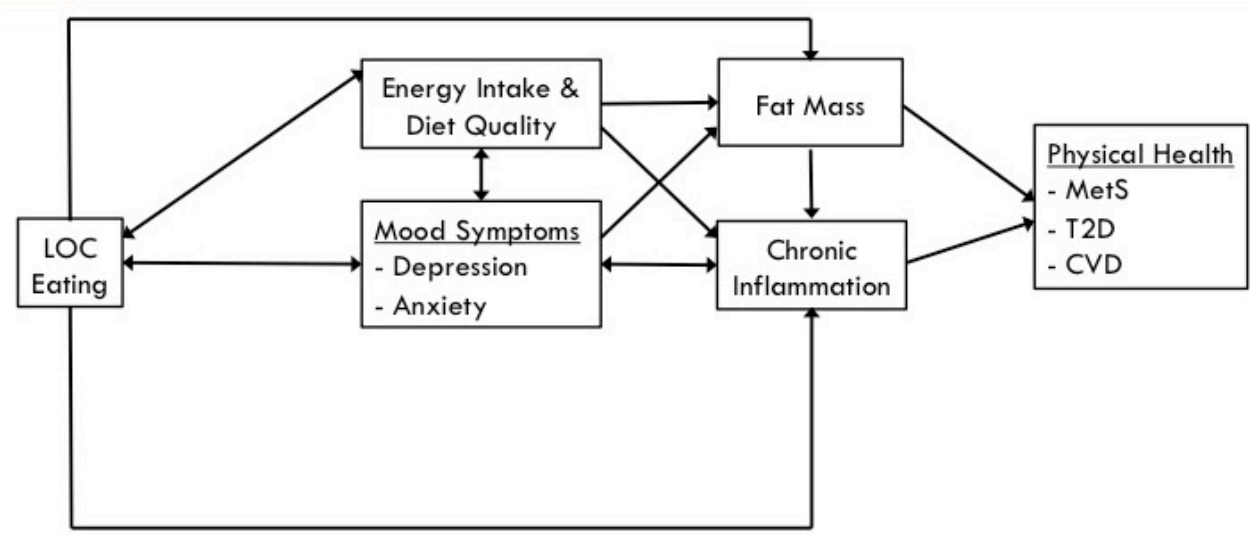


Dissertation—Figure 2. Proposed relationships based on Study 1. It is proposed that LOC eating is associated with chronic inflammation. In addition to a direct pathway, three potential causal pathways involve food intake, fat mass, and mood symptoms.

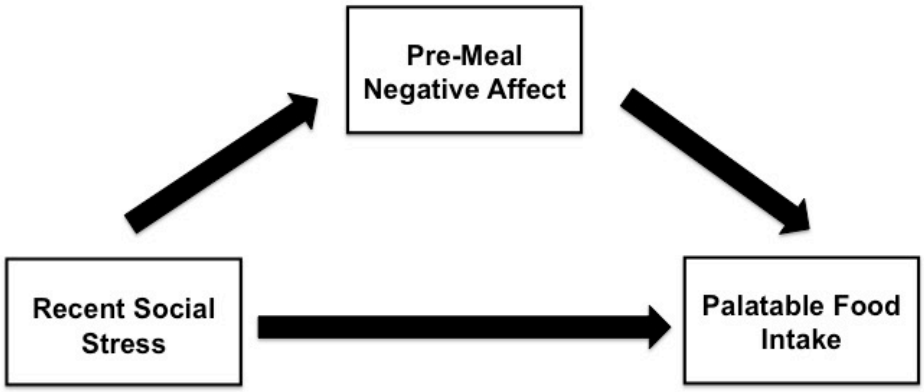


Study 2—Figure 1. Unadjusted means and standard errors for metabolic components at baseline and 6-month follow-up are shown by loss of control (LOC) eating status at end-of-treatment. A. Unadjusted means and standard errors for plasma glucose at baseline and 6-month follow-up are shown by LOC eating remission versus persistence at end-of-treatment for participants with data at both time points. After adjusting for covariates including baseline plasma glucose, youth with persistent LOC eating had significantly higher fasting plasma glucose than girls whose LOC eating whose LOC eating had remitted at 6-month follow-up (p = .02). B. Unadjusted means and standard errors for high-density lipoprotein cholesterol (HDL-C) at baseline and 6-month follow-up are

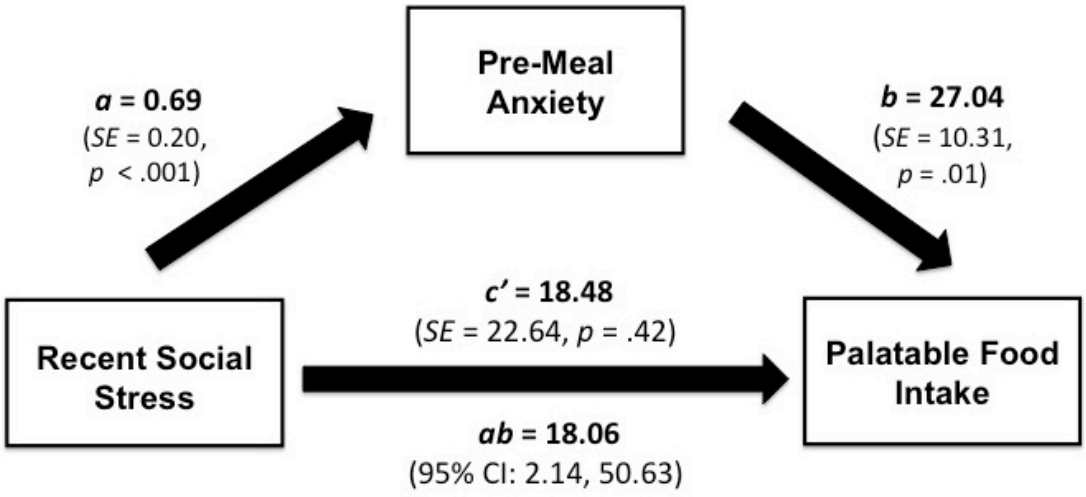
shown by LOC eating remission versus persistence at end-of-treatment for participants with data at both time points. After adjusting for covariates including baseline HDL-C, youth with persistent LOC eating had significantly lower HDL-C than girls whose LOC eating whose LOC eating had remitted at 6-month follow-up (p = .01). C. Unadjusted means and standard errors for triglycerides at baseline and 6-month follow-up are shown by LOC eating remission versus persistence at end-of-treatment for participants with data at both time points. After adjusting for covariates including baseline triglycerides, youth with persistent LOC eating had significantly lower triglycerides than girls whose LOC eating had remitted at 6-month follow-up (p = .02).



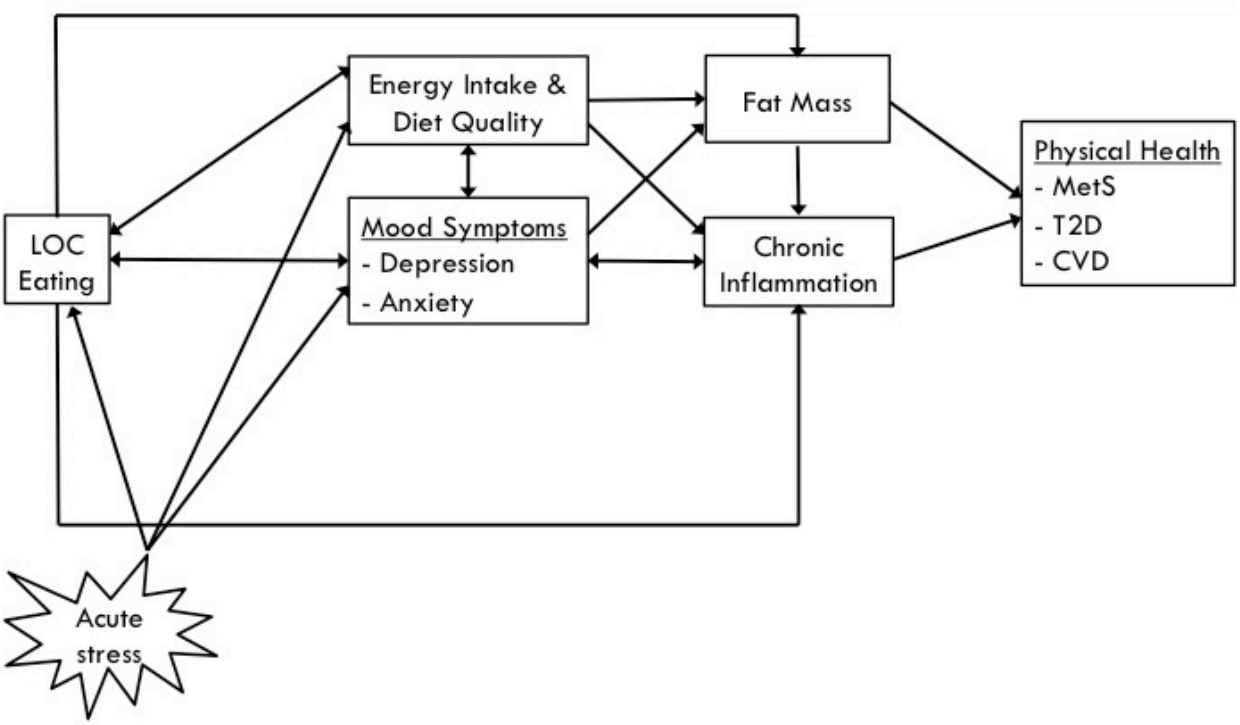
Dissertation—Figure 3. Proposed relationships based on Study 1 and Study 2. It is proposed that LOC eating is associated with adverse physical health outcomes such as MetS through the pathways of increased adiposity and chronic inflammation.



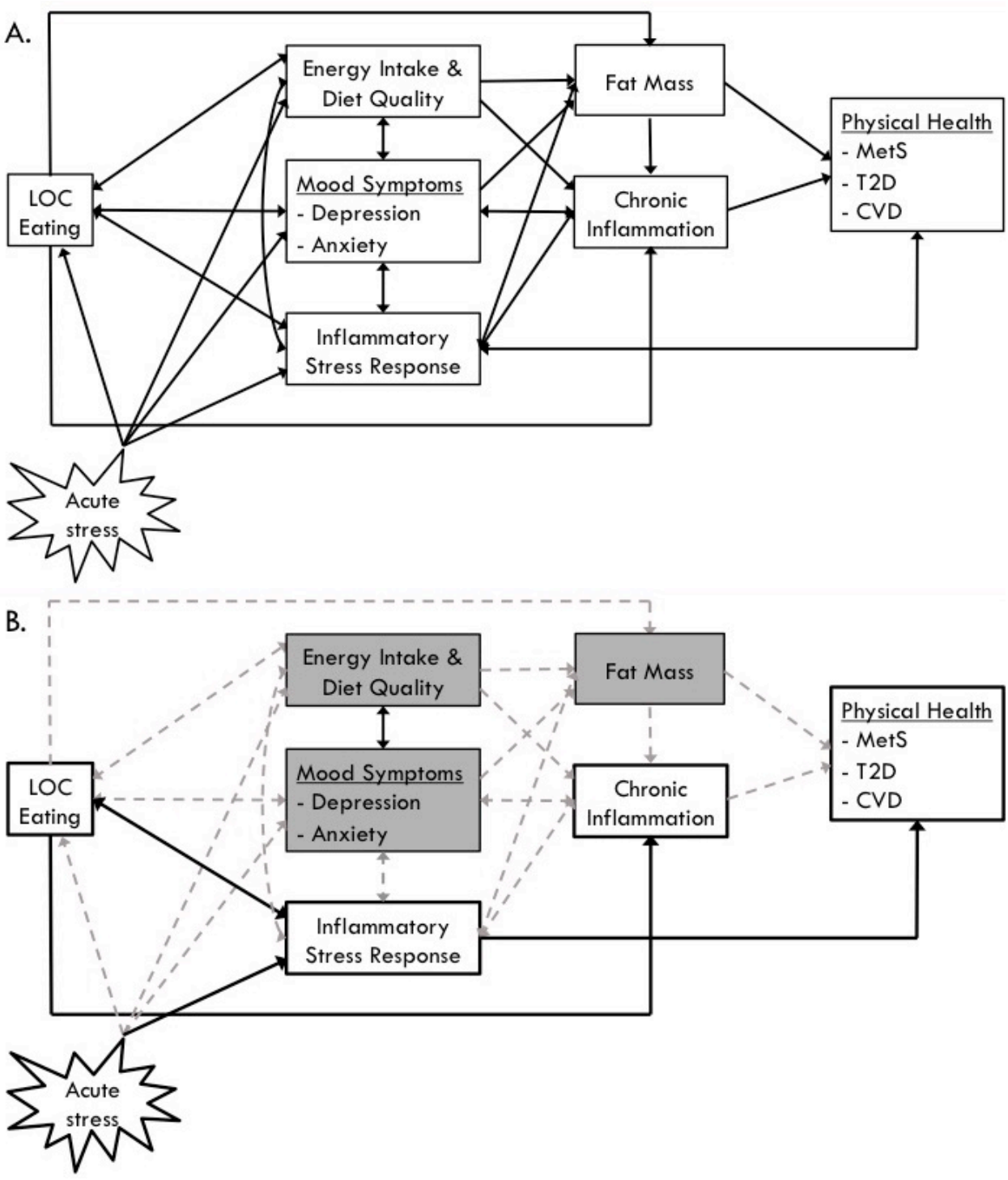
Study 3—Figure 1. The conceptual model of mediation is displayed. Each model examined one of the Brunel Mood Scale negative affect subscales (i.e., anger, confusion, depression, fatigue, and anxiety) as the mediator, the composite social stress score as the independent variable, and snack-type food intake as the dependent variable.



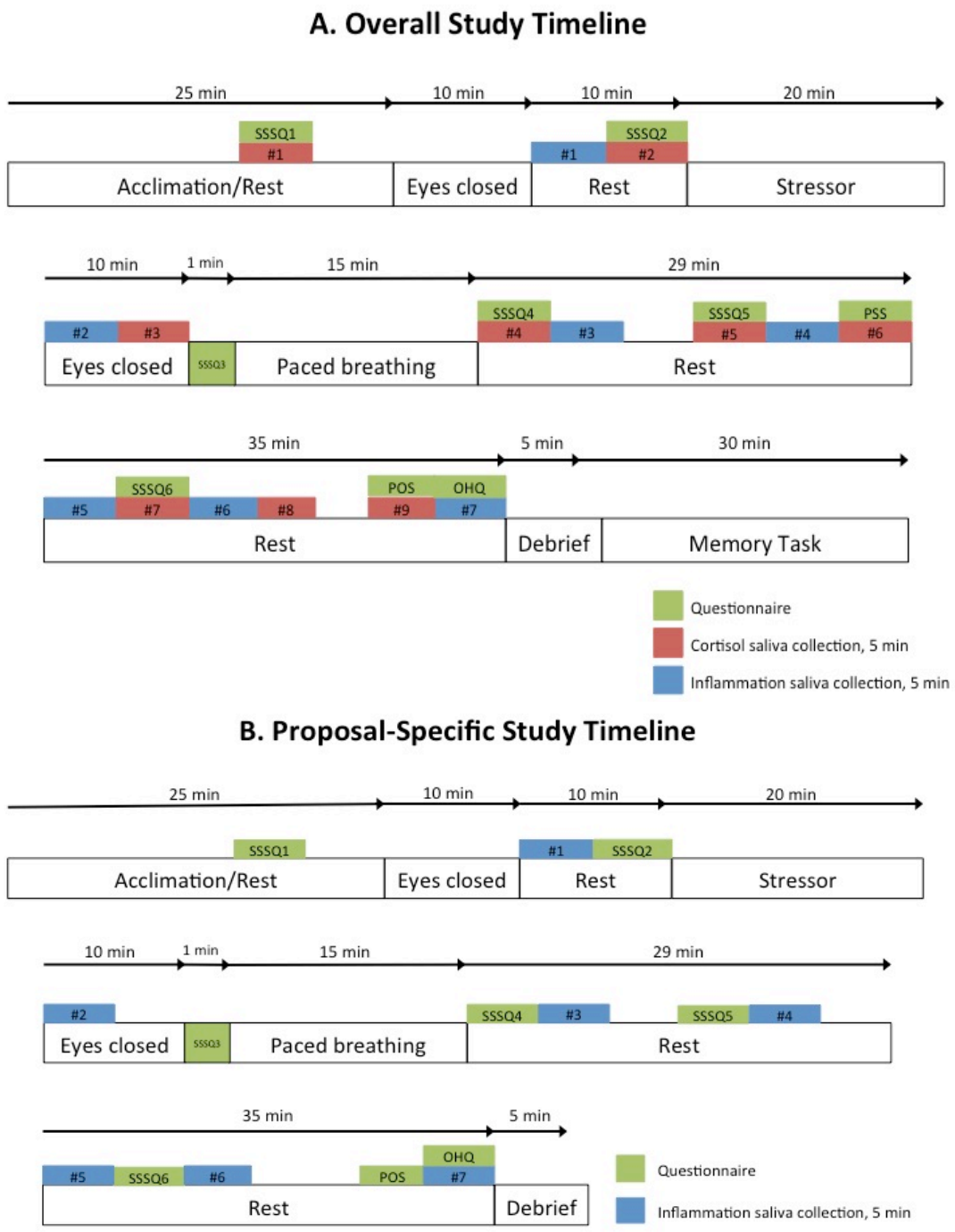
Study 3—Figure 2. Mediation model examining the relationship between recent social stress, pre-meal anxiety, and palatable food intake. The Brunel Mood Scale anxiety subscale was a significant mediator of the relationship between the composite recent social stress score and snack-type food intake (R^2 = 0.14; *ab* =18.06, 95% bootstrap CI: [2.14, 50.63]). Recent social stress was significantly associated with Brunel Mood Scale anxiety (*a* = 0.69, *SE* = .20, *p* < .001), and Brunel Mood Scale anxiety was significantly associated with intake of snack-type food (*b* = 27.04, *SE* = 10.31, *p* = .01). The effect of recent social stress on intake of snack-type food (*c* = 37.23, *SE* = 22.06, *p* = .09) was decreased with the addition of Brunel Mood Scale anxiety (*c'* = 18.48, *SE* = 22.64, *p* = .42). Mediation analyses adjusted for age, race (coded as non-Hispanic White or other), pubertal stage, height (cm), fat mass (%), and lean mass (kg).



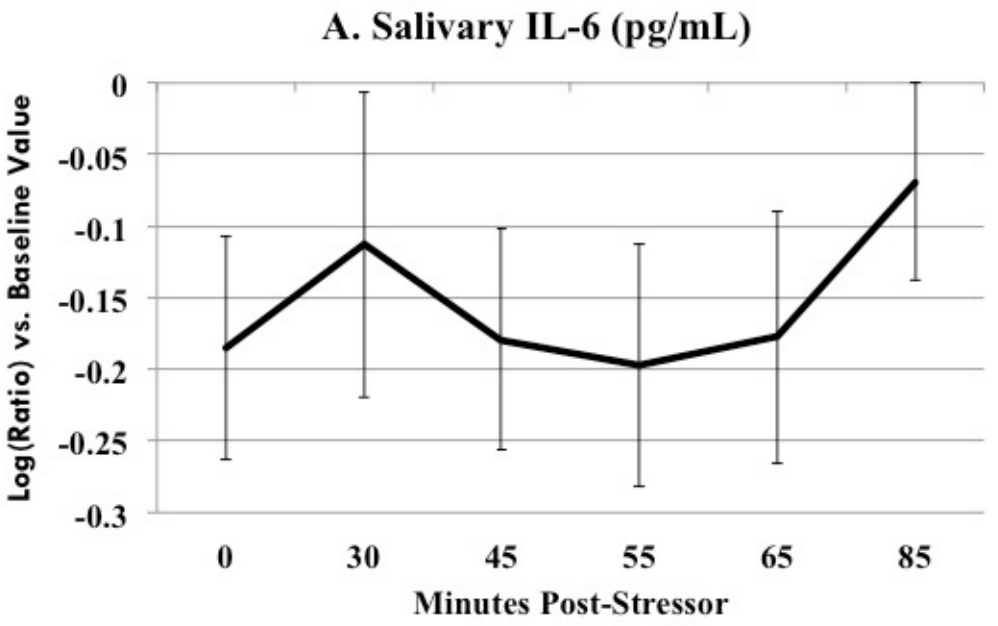
Dissertation—Figure 4. Proposed relationships based on Studies 1, 2, and 3. The updated conceptual model proposes that acute stress can impact LOC eating, diet intake, and mood symptoms.

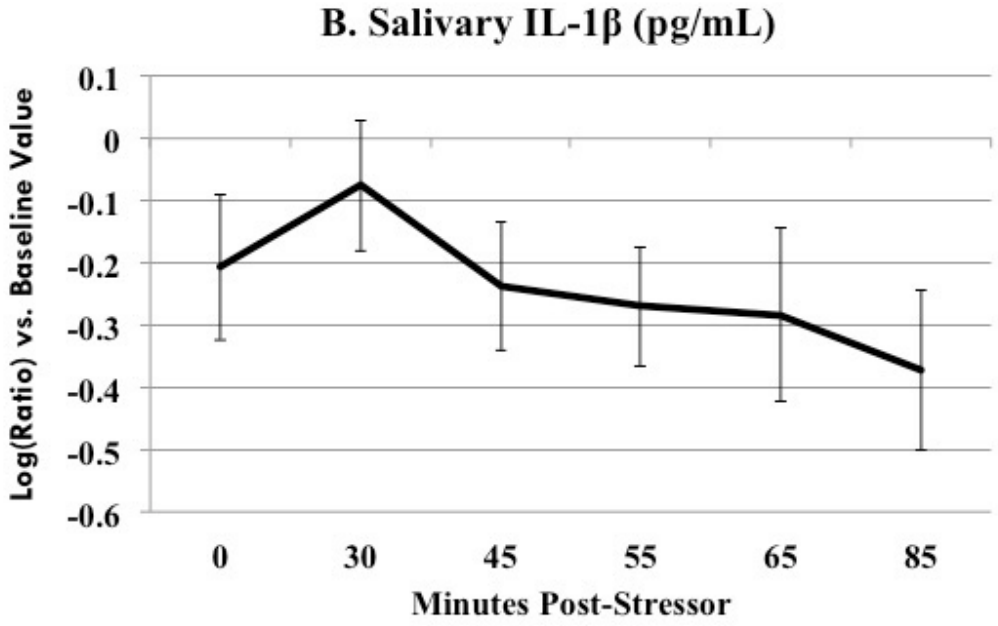


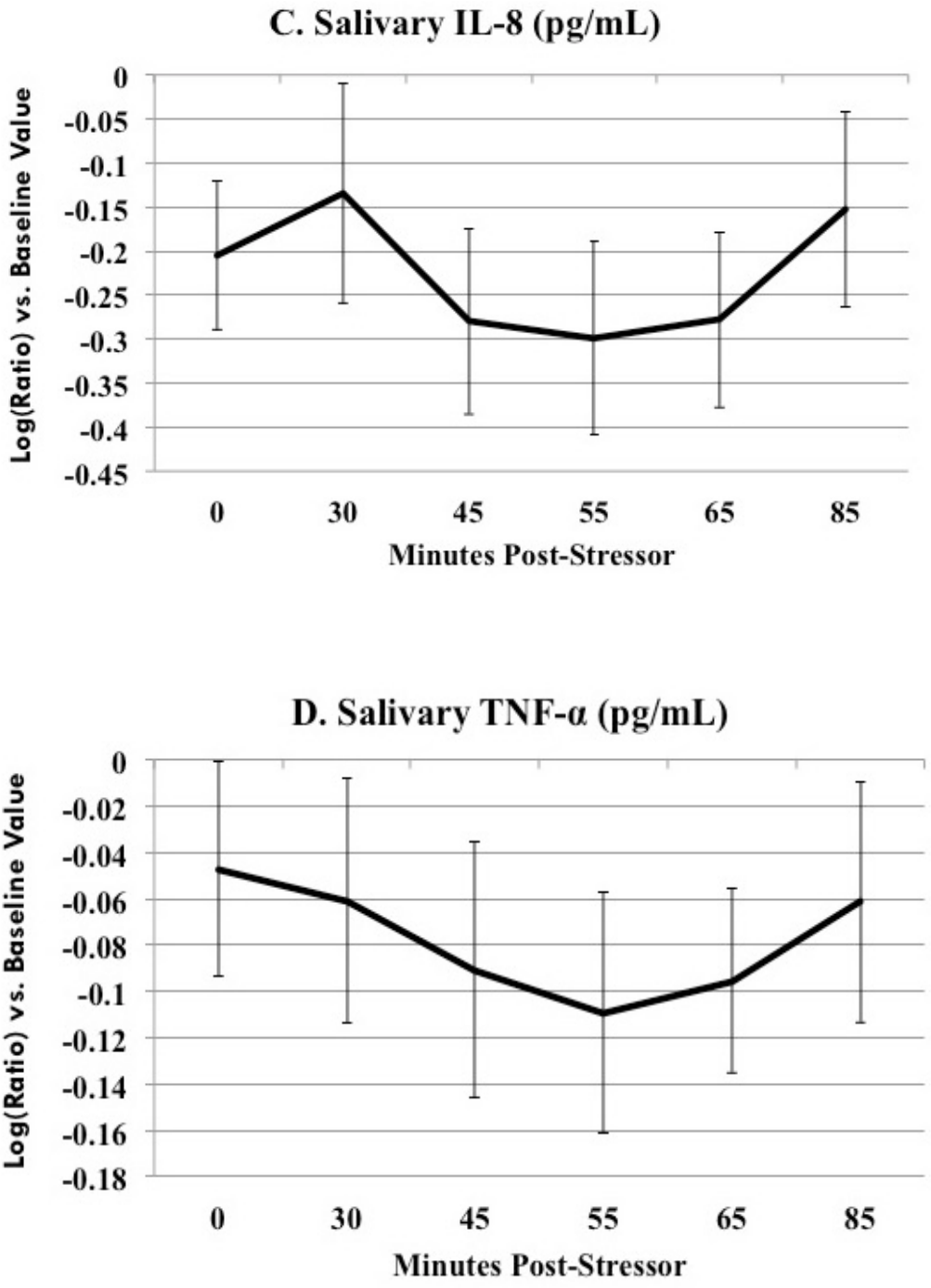
Dissertation—Figure 5. The Stress-Inflammation Model of LOC Eating. Figure 4A displays the full conceptual model. Figure 4B depicts the specific pathways being tested in the proposed study, represented by white boxes and black lines. The grey boxes represent variables that will be measured and adjusted for in the proposed study, and the grey lines represent potential relationships that will not be directly tested in this study.



Dissertation—Figure 6. Visual depiction of the procedure for Experimental Visit. Figure 5A depicts the overall study visit, while Figure 5B depicts the components of the study visit relevant to this proposal. Abbreviations: SSSQ, Short Stress State Questionnaire; PSS, Perceived Stress Scale; POS, Perception of Stressor; OHQ, Oral Health Questionnaire.


A. Salivary IL-6 (pg/mL)
Log(Ratio) vs. Baseline Value
0
-0.05
-0.1
-0.15
-0.2
-0.25
-0.3
0
30
45
55
65
85
Minutes Post-Stressor


B. Salivary IL-1β (pg/mL)
Log(Ratio) vs. Baseline Value
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
0
30
45
55
65
85
Minutes Post-Stressor



Dissertation—Figure 7. Means and standard errors for the logs of the ratio of each time point relative to baseline.

Appendix A: Children's Paced Auditory Serial Addition Task

MATERIALS NEEDED
An audiocassette tape or CD player, audiocassette tape or CD with CHIPASAT stimuli, clipboard, CHIPASAT Record Forms to administer the test.

Completing the CHIPASAT Record Form
Place a check next to all correct answers. Write in any incorrect responses in the space provided. Place a dash when no response was given. If the patient corrects him/herself after giving a response, count the amended answer as the response. The amended response is the one that will be used in determining total correct, regardless of whether it was the correct or incorrect response. Slash through the old response and write in 'SC' with a circle around it to indicate that the patient self-corrected.

Each section of the CHIPASAT has a maximum of 60 correct answers (i.e. 61 digits are presented for each part). Count the total number correct (number of circled answers) and record on the Record Form.

Finally, record any circumstances that you believe may have affected the patient's performance. These are factors that may have affected the trial, but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to, the following:
- Subtle noises outside of the testing room, Patient reports frustration or mild distress, Patient talked during test (other than to give answers)

If a trial must be repeated, indicate this and specify the reason why it had to be repeated. Examples of reasons to repeat a trial include, but are not limited to the following:
- Test interrupted (e.g. someone walked into the room or other major disturbance)
- Examiner error, such as starting the tape in the wrong place or using the wrong form. Record only totals for the successfully completed CHIPASAT. If the patient is unable to perform the CHIPASAT (i.e., cannot get at least two correct on any 3" practice and at least one correct on the test portion), the examiner should indicate "Unable to complete due to cognitive limitations" and record any specific observations. If the patient did not complete a trial for any other reason, record the reasons for this as well (e.g., patient refused to complete test, examiner forgot to administer, etc.).

CHIPASAT INSTRUCTIONS

Hi. This is an adding game. To play this game you must add two numbers together at a time, and then say your answer aloud so that it can be written down for you. You will hear me read a list of numbers to you one after the other. You will always add the first number to the second, the second number to the third, and so on. I won't say 1 + 2 , I'll just say 1, 2. You hear 1, 2, and then you think,
1 + 2 = 3. Then you say "3" aloud.

You will need to listen carefully because I will say each number only once. For example, if I say 1, 2, 3, 4: you add 1 + 2, and say "3"; Remember the number 2, and add 2 + 3 and say "5"; remember the number 3, and add 3 + 4 and say "7". I want you to add each number to the one that came just before it, not to your answer. If your answer starts to become too big, you are probably adding the number to your answer, rather than to the number that came just before it. When you play this game correctly, your answer will never be larger than 10.

If you have trouble keeping up, don't worry. Just jump back in again as soon as you can. It is better to jump back in than to get behind trying to add numbers that have past.

Okay, let's have a practice. Listen carefully to the numbers I am going to read to you. Remember to add the number to the one just before it, not to your answer. You add them together in your mind and then say your answer aloud.

READY. Listen carefully.
2 , 3 , 1 , 4

That's very good. Let's go over that. You were asked to add the 2 and the 3 together giving the answer 5; then the 3 and the 1 together giving the answer 4; the 1 and the 4 together giving the answer 5.

Let's try another practice. This time the list will be longer.
READY. Listen carefully.

1,3,4,2,5,3,2,4 (changed from 11 to 8 #'s)

That's very good. Let's go over that. You were asked to add the 1 and the 3 together giving the answer 4; then

3	and the 4	together giving	7;
4	2		6;
2	5		7 ;
5	3		8;
3	2		5;
2	4		6

Now that you understand what you have to do, we shall try the first trial. This first one is just as fast as the practice you have just done, but it is much longer. Don't worry if you make a mistake or leave some numbers out. I want to see how long you can keep going without stopping, but also how quickly you can pick up again when you do stop.

READY. Listen carefully (Proceed with Trial 2.8)

That's very good. Let's try another trial. The numbers will come slightly faster than before.

READY. Listen carefully (Proceed with Trial 2.4).

That's very good. Let's try another trial. The numbers will come slightly faster than before.

READY. Listen carefully (Proceed with Trial 2.0).

That's very good. Let's try another trial. The numbers will come slightly faster than before.

READY. Listen carefully (Proceed with Trial 1.6).

That's very good. Let's try another trial. The numbers will come slightly faster than before.

READY. Listen carefully (Proceed with Trial 1.2).

That's the end of the test. Well done.

CHIPASAT Name_____ NP #

DOE_____ BD _____ Age_____ Examiner_____

Demons.	Practice	Practice	Repeat	Repeat
2	1	2 (5)	1	2 (5)
3 (5)	3 (4)	4 (6)	3 (4)	4 (6)
1 (4)	4 (7)	1 (5)	4 (7)	1 (5)
4 (5)	2 (6)	1 (2)	2 (6)	1 (2)
	5 (7)	3 (4)	5 (7)	3 (4)
	3 (8)		**3 (8)**	

2.8 sec.		2.4 sec.		2.0 sec.		1.6 sec.		1.2 sec.	
Trial 1	Trial 1	Trial 2	Trial 2	Trial 3	**Trial 3**	Trial 4	Trial 4	Trial 5	Trial 5
1	2 (7)	1	1 (2)	2	3 (4)	1	3 (5)	1	2 (3)
2 (3)	4 (6)	2 (3)	3 (4)	1 (3)	2 (5)	4 (5)	4 (7)	4 (5)	1 (3)
5 (7)	1 (5)	**4 (6)**	**5 (8)**	**4 (5)**	4 (6)	5 (9)	1 (5)	5 (9)	4 (5)
1 (6)	2 (3)	1 (5)	**3 (8)**	2 (6)	3 (7)	2 (7)	2 (3)	1 (6)	2 (6)
4 (5)	1 (3)	**3 (4)**	**3 (6)**	2 (4)	1 (4)	3 (5)	**5 (7)**	5 (6)	2 (4)
5 (9)	4 (5)	5 (8)	1 (4)	3 (5)	5 (6)	2 (5)	1 (6)	3 (8)	3 (5)
1 (6)	2 (6)	**5 (10)**	5 (6)	5 (8)	1 (6)	3 (5)	4 (5)	5 (8)	5 (8)
5 (6)	2 (4)	2 (7)	4 (9)	5 (10)	2 (3)	5 (8)	5 (9)	2 (7)	5 (10)
3 (8)	3 (5)	3 (5)	4 (8)	2 (7)	4 (6)	4 (9)	1 (6)	2 (4)	2 (7)
5 (8)	5 (8)	4 (7)	5 (9)	1 (3)	1 (5)	4 (8)	5 (6)	4 (6)	1 (3)
2 (7)	5 (10)	1 (5)	2 (7)	4 (5)	3 (4)	1 (5)	3 (8)	5 (9)	4 (5)
2 (4)	2 (7)	2 (3)	**4 (6)**	**3 (7)**	**5 (8)**	**3 (4)**	**5 (8)**	**2 (7)**	**3 (7)**
4 (6)	1 (3)	**5 (7)**	1 (5)	4 (7)	5 (10)	**3 (6)**	2 (7)	3 (5)	4 (7)
5 (9)	4 (5)	1 (6)	2 (3)	5 (9)	2 (7)	2 (5)	2 (4)	2 (5)	5 (9)
2 (7)	3 (7)	4 (5)	1 (3)	1 (6)	3 (5)	**4 (6)**	**4 (6)**	3 (5)	1 (6)
3 (5)	4 (7)	5 (9)	4 (5)	4 (5)	4 (7)	1 (5)	**5 (9)**	2 (5)	4 (5)
2 (5)	5 (9)	1 (6)	2 (6)	5 (9)	1 (5)	1 (2)	2 (7)	4 (6)	5 (9)
3 (5)	1 (6)	5 (6)	2 (4)	2 (7)	2 (3)	3 (4)	**3 (5)**	1 (5)	2 (7)
2 (5)	4 (5)	3 (8)	3 (5)	**3 (5)**	5 (7)	2 (5)	2 (5)	1 (2)	3 (5)
4 (6)	5 (9)	5 (8)	5 (8)	2 (5)	1 (6)	**4 (6)**	3 (5)	3 (4)	2 (5)
1 (5)	2 (7)	2 (7)	5 (10)	**3 (5)**	**4 (5)**	3 (7)	**2 (5)**	5 (8)	**3 (5)**
1 (2)	3 (5)	2 (4)	2 (7)	**5 (8)**	5 (9)	1 (4)	4 (6)	3 (8)	5 (8)
3 (4)	2 (5)	4 (6)	1 (3)	4 (9)	1 (6)	5 (6)	1 (5)	3 (6)	4 (9)
5 (8)	3 (5)	5 (9)	4 (5)	**4 (8)**	5 (6)	1 (6)	1 (2)	1 (4)	**4 (8)**
3 (8)	5 (8)	2 (7)	3 (7)	1 (5)	3 (8)	2 (3)	**3 (4)**	5 (6)	1 (5)
3 (6)	4 (9)	3 (5)	4 (7)	3 (4)	5 (8)	4 (6)	5 (8)	4 (9)	3 (4)
1 (4)	4 (8)	2 (5)	5 (9)	3 (6)	2 (7)	1 (5)	3 (8)	4 (8)	3 (6)
5 (6)	1 (5)	3 (5)	1 (6)	2 (5)	2 (4)	**3 (4)**	3 (6)	5 (9)	**2 (5)**
4 (9)	3 (4)	2 (5)	4 (5)	4 (6)	4 (6)	**5 (8)**	1 (4)	2 (7)	**4 (6)**
4 (8)	3 (6)	**4 (6)**	5 (9)	1 (5)	**5 (9)**	5 (10)	**5 (6)**	**4 (6)**	1 (5)
5 (9)		1 (5)		1 (2)		**2 (7)**		1 (5)	

	# correct	Mean for Age	Std. Dev.	Z Score	Errors	Omissions	Sequence
(1) 2.8							
(2) 2.4							
(3) 2.0							
(4) 1.6							
(5) 1.2							

Pres. Rate	8-9 yrs	9-10 yrs	10-11 yrs	11-12 yrs	12-13 yrs	13-14 yrs	14-15 yrs
2.4	M 22.5 SD 5.5	M 27.1 SD 7.1	M 30.5 SD 8.3	M 33.8 SD 8.5	M 32.3 SD 9.1	M 37.4 SD 9.4	M 41.1 SD 9.9
2.0	M 19.4 SD 6.5	M 23.0 SD 6.6	M 26.2 SD 7.1	M 28.3 SD 7.2	M 29.6 SD 7.9	M 33.4 SD 10.1	M 38.3 SD 8.0
1.6	M 16.4 SD 6.4	M 19.8 SD 6.5	M 20.8 SD 6.3	M 23.1 SD 6.2	M 24.4 SD 7.4	M 27.7 SD 9.1	M 31.5 SD 6.8
1.2	M 9.9 SD 5.2	M 13.1 SD 5.9	M 14.9 SD 5.9	M 16.6 SD 5.4	M 16.1 SD 6.8	M 19.3 SD 7.4	M 20.6 SD 5.7
overall	M 17.1 SD 5.5	M 20.7 SD 5.8	M 23.1 SD 6.2	M 25.5 SD 6.2	M 25.6 SD 7.0	M 29.4 SD 8.4	M 32.9 SD 6.9

Appendix B: Debriefing Script

"Thank you for so much for your participation in this study. What I am about to tell you is important. You were told in the beginning that your performance on the math challenge (how well and how fast you did) would be compared with other kids/teens your age who are also in this study. However, the truth is that your scores will not actually be a focus of this study and we won't be comparing how well you did to other people in the study. We were really interested in how you reacted to a stressful situation (the math test). We told you that you were being compared to other kids/teens, because people act differently if they think they are being evaluated by someone else. We have designed these tasks so that they will be the most helpful to others in the future, and in order for us to do this, we needed you to believe that you were competing against other people. The only thing that we ask is that you do not share this information with anyone because it is very important that everyone in our study believes they are being evaluated by judges on the math challenge. If some people know that they are not actually being evaluated and compared with their peers, then our study would not tell us anything. Do you have any questions or concerns?"

Appendix C: Kiddie Schedule for Affective Disorders and Schizophrenia

K-SADS-PL 2009

Working Draft

Includes:

A. Screen Interview

B. Supplements

- **I. Affective Disorders Supplement**
- **II. Psychotic Disorders Supplement**
- **III. Anxiety Disorders Supplement**
- **IV. Behavioral Disorders Supplement**
- **V. Substance Use Disorders Supplement**
- **VI. Eating Disorders Supplement**
- **VII. Tic Disorders Supplement**
- **VIII. Autism Spectrum Disorders**

Advanced Center for Intervention and Services Research (ACISR)
for Early Onset Mood and Anxiety Disorders

Western Psychiatric Institute and Clinic

Subject

Date / / 2 0 0

Interviewer

Draft

Appendix D: International Physical Activity Questionnaire

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Appendix E: Eating Disorder Examination

EATING DISORDER EXAMINATION

(12th edition with text edits from 14 and 15)

Version 12

Christopher G Fairburn and Zafra Cooper

University of Oxford

Appendix F: Children's Depression Inventory

Remember, pick out the sentences that describes your feelings and ideas in the past two weeks.

1. _____ I am sad once in awhile
   _____ I am sad many times
   _____ I am sad all the time

2. _____ Nothing will ever work out for me
   _____ I am not sure if things will work out for me
   _____ Things will work out for me ok

3. _____ I do most things ok
   _____ I do many things ok
   _____ I do everything wrong

4. _____ I have fun in many things
   _____ I have fun in some things
   _____ Nothing is fun at all

5. _____ I am bad all the time
   _____ I am bad many times
   _____ I am bad once in awhile

6. _____ I think about bad things happening to me once in awhile
   _____ I worry that bad things will happen to me
   _____ I am sure that terrible things will happen to me

7. _____ I hate myself
   _____ I do not like myself
   _____ I like myself

8. _____ All bad things are my fault
   _____ Many bad things are my fault
   _____ Bad things are usually not my fault

9. _____ I do not think about killing myself
   _____ I think about killing myself, but would not do it
   _____ I want to kill myself

10. _____ I feel like crying everyday
_____ I feel like crying many days
_____ I feel like crying once in awhile
11. _____ Things bother me all the time
_____ Things bother me many of the times
_____ Things bother me once in awhile

12. _____ I like being with people
_____ I like being with people many times
_____ I do not want to be with people at all

13. _____ I can not make up my mind about things
_____ It is hard to make up my mind about things
_____ I make up my mind about things easily

14. _____ I look ok
_____ There are some bad things about my looks
_____ I look ugly

15. _____ I have to push myself all the time to do my schoolwork
_____ I have to push myself many times to do my schoolwork
_____ Doing schoolwork is not a big problem

16. _____ I have trouble sleeping every night
_____ I have trouble sleeping many nights
_____ I sleep pretty well

17. _____ I am tired once in awhile
_____ I am tired many times
_____ I am tired all the time

18. _____ Most days I do not feel like eating
_____ Many days I do not feel like eating
_____ I eat pretty well

19. _____ I do not worry about aches and pains
_____ I worry about aches and pains many times
_____ I worry about aches and pains all the time

20. _____ I do not feel alone
_____ I feel alone many times
_____ I feel alone all the time

21. _____ I never have fun at school
_____ I have fun at school only once in awhile
_____ I have fun in school many times

22. _____ I have plenty of friends
_____ I have some friends but I wish I had more
_____ I do not have any friends

23. _____ My schoolwork is alright
_____ My schoolwork is not as good as before
_____ I do very badly in subjects I used to be good in

24. _____ I can never be as good as other kids
_____ I can be as good as other kids if I want to
_____ I am just as good as other kids

25. _____ Nobody really loves me
_____ I am not sure if anybody loves me
_____ I am sure that somebody loves me

26. _____ I usually do what I am told
_____ I do not do what I am told most times
_____ I never do what I am told

27. _____ I get along with people
_____ I get into fights many times
_____ I get into fights all the time

Appendix G: State-Trait Anxiety Inventory for Children- Trait

HOW-I-FEEL QUESTIONNAIRE

STAIC Form C-2

Name: _____ Age: _____ Date: _____

DIRECTIONS: A number of statements which boys and girls use to describe themselves are given below. Read each statement carefully and decide if it is *hardly-ever*, or *sometimes*, or *often* true for you. Then for each statement, put an X in the box in front of the word that seems to describe you best. There are no right or wrong answers. Don't spend too much time on any one statement. Remember, choose the word which seems to describe how you usually feel.

1. I worry about making mistakes	☐ hardly-ever	☐ sometimes	☐ often
2. I feel like crying	☐ hardly-ever	☐ sometimes	☐ often
3. I feel unhappy	☐ hardly-ever	☐ sometimes	☐ often
4. I have trouble making up my mind	☐ hardly-ever	☐ sometimes	☐ often
5. It is difficult for me to face my problems	☐ hardly-ever	☐ sometimes	☐ often
6. I worry too much	☐ hardly-ever	☐ sometimes	☐ often
7. I get upset at home	☐ hardly-ever	☐ sometimes	☐ often
8. I am shy	☐ hardly-ever	☐ sometimes	☐ often
9. I feel troubled	☐ hardly-ever	☐ sometimes	☐ often
10. Unimportant thoughts run through my mind and bother me	☐ hardly-ever	☐ sometimes	☐ often
11. I worry about school	☐ hardly-ever	☐ sometimes	☐ often
12. I have trouble deciding what to do	☐ hardly-ever	☐ sometimes	☐ often
13. I notice my heart beats fast	☐ hardly-ever	☐ sometimes	☐ often
14. I am secretly afraid	☐ hardly-ever	☐ sometimes	☐ often
15. I worry about my parents	☐ hardly-ever	☐ sometimes	☐ often
16. My hands get sweaty	☐ hardly-ever	☐ sometimes	☐ often
17. I worry about things that may happen	☐ hardly-ever	☐ sometimes	☐ often
18. It is hard for me to fall asleep at night	☐ hardly-ever	☐ sometimes	☐ often
19. I get a funny feeling in my stomach	☐ hardly-ever	☐ sometimes	☐ often
20. I worry about what others think of me	☐ hardly-ever	☐ sometimes	☐ often

Appendix H: Social Anxiety Scale for Children-Revised

Instructions:

On the following page are some questions about your thoughts and feelings. We would like you to first read the instructions, and then answer each question as honestly as possible.
Answer every question even if some are hard to decide. Do not circle two answers for the same sentence.
There are no right or wrong answers. Only you can tell us how you think and feel about yourself.
Use these numbers to show HOW MUCH YOU FEEL something is true for you:
1= Not at all
2 = Hardly ever
3 = Sometimes
4 = Most of the time
5 = All the time

Questions:

1. I worry about doing something new in front of other kids.	○1 ○2 ○3 ○4 ○5
2. I like to play with other kids.	○1 ○2 ○3 ○4 ○5
3. I worry about being teased.	○1 ○2 ○3 ○4 ○5
4. I feel shy around kids I don't know.	○1 ○2 ○3 ○4 ○5
5. I only talk to kids that I know really well.	○1 ○2 ○3 ○4 ○5
6. I feel that other kids talk about me behind my back.	○1 ○2 ○3 ○4 ○5
7. I like to read.	○1 ○2 ○3 ○4 ○5
8. I worry about what other kids think of me.	○1 ○2 ○3 ○4 ○5
9. I'm afraid that others will not like me.	○1 ○2 ○3 ○4 ○5
10. I get nervous when I talk to kids I don't know very well.	○1 ○2 ○3 ○4 ○5
11. I like to play sports.	○1 ○2 ○3 ○4 ○5
12. I worry about what others say about me.	○1 ○2 ○3 ○4 ○5
13. I get nervous when I meet new kids.	○1 ○2 ○3 ○4 ○5
14. I worry that other kids won't like me.	○1 ○2 ○3 ○4 ○5
15. I'm quiet when I'm with a group of kids.	○1 ○2 ○3 ○4 ○5
16. I like to do things by myself.	○1 ○2 ○3 ○4 ○5
17. I feel that other kids make fun of me.	○1 ○2 ○3 ○4 ○5
18. If I get into an argument with another kid, I worry that he or she will not like me.	○1 ○2 ○3 ○4 ○5

19. I'm afraid to invite other kids to do things with me because they might say no.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
20. I feel nervous when I'm around certain kids.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
21. I feel shy even with kids I know well.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
22. It's hard for me to ask other kids to do things with me.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5

Appendix I: Social Anxiety Scale for Adolescents

Instructions:

On the following page are some questions about your thoughts and feelings. We would like you to first read the instructions, and then answer each question as honestly as possible.

Answer every question even if some are hard to decide. Do not circle two answers for the same sentence. There are no right or wrong answers. Only you can tell us how you think and feel about yourself.

Use these numbers to show HOW MUCH YOU FEEL something is true for you:
1 = Not at all
2 = Hardly ever
3 = Sometimes
4 = Most of the time
5 = All the time

Questions:

1. I worry about doing something new in front of others.	○ 1	○ 2	○ 3	○ 4	○ 5
2. I like to do things with my friends.	○ 1	○ 2	○ 3	○ 4	○ 5
3. I worry about being teased.	○ 1	○ 2	○ 3	○ 4	○ 5
4. I feel shy around people I don't know.	○ 1	○ 2	○ 3	○ 4	○ 5
5. I only talk to people that I know really well.	○ 1	○ 2	○ 3	○ 4	○ 5
6. I feel that peers talk about me behind my back.	○ 1	○ 2	○ 3	○ 4	○ 5
7. I like to read.	○ 1	○ 2	○ 3	○ 4	○ 5
8. I worry about what others think of me.	○ 1	○ 2	○ 3	○ 4	○ 5
9. I'm afraid that others will not like me.	○ 1	○ 2	○ 3	○ 4	○ 5
10. I get nervous when I talk to peers I don't know very well.	○ 1	○ 2	○ 3	○ 4	○ 5
11. I like to play sports.	○ 1	○ 2	○ 3	○ 4	○ 5
12. I worry about what others say about me.	○ 1	○ 2	○ 3	○ 4	○ 5
13. I get nervous when I meet new people.	○ 1	○ 2	○ 3	○ 4	○ 5
14. I worry that others don't like me.	○ 1	○ 2	○ 3	○ 4	○ 5

15. I'm quiet when I'm with a group of people.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
16. I like to do things by myself.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
17. I feel that others make fun of me.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
18. If I get into an argument, I worry that the other person will not like me.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
19. I'm afraid to invite others to do things with me because they might say no.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
20. I feel nervous when I'm around certain people.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
21. I feel shy even with kids I know well.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
22. It's hard for me to ask others to do things with me.	○ 1 ○ 2 ○ 3 ○ 4 ○ 5

Appendix J: Healthy Eating Index- 2010

Instructions and tools for calculating and using the Healthy Eating Index-2010 can be found at: https://epi.grants.cancer.gov/hei/tools.html. Relevant overview information is included below.

Step 1: Identify the set of foods under consideration.

The total foods and beverages consumed by individuals is the subject of interest at this level. Most often, researchers are interested in the usual (or long-run average) diets of groups of individuals. Information on foods consumed by individuals on a day or over a longer period of time can be collected using various methods. These include 24-hour recall, food record, or food frequency questionnaire. For example, HEI scores can be calculated for recall data collected in the What We Eat in America component of the National Health and Nutrition Examination Survey (NHANES) or using the Automated Self-Administered 24-hour Recall (ASA24) system. Other types of 24-hour recall, food record, and food frequency questionnaire data can also be used to calculate HEI scores if linkages to appropriate databases can be made (see step 2). Calculating HEI scores requires information on the total diet and thus data from brief instruments, such as screeners, focused on particular aspects of the diet cannot be used for this purpose.

Step 2: Determine the amount of each relevant dietary constituent in the set of foods.

Determining the amounts of each dietary constituent contained in the total quantity of foods under consideration requires linking to relevant databases. Values for energy and the relevant nutrients can be obtained from a nutrient composition database. Obtaining values for the other relevant dietary constituents requires a database that translates the foods into amounts of fruits, vegetables, lean meat, and so on. One publicly available database designed for this purpose is the Food Patterns Equivalents Database (FPED), formerly the MyPyramid Equivalents Database (MPED). The FPED links to the USDA's Food and Nutrient Database for Dietary Studies (FNDDS) and has been used to evaluate the US diet in relation to dietary guidance such as the USDA food patterns, which are part of the Dietary Guidelines for Americans. It translates the amounts of foods, as eaten, into cup and ounce equivalents that are consistent with the units of measure used for the HEI scoring standards. Depending on the databases used, additional steps may be required to determine the amount of each constituent required to calculate HEI scores. Regardless of the data source and databases used, attention should be paid to the degree to which it is possible to estimate amounts of the dietary constituents required to calculate HEI scores.

Step 3: Derive pertinent ratios and score each HEI component using the relevant standard.

In the case of individual diets, multiple approaches to creating ratios are possible. The most appropriate approach depends on the specific research question. Two SAS macros for implementing step 3 are available.

Mean HEI scores for a population, subpopulation, or group can be estimated using 24-hour recall data and the population ratio method. This approach has been shown to be the preferred method

of estimating a population's mean usual HEI–2005 component and total scores on the basis of a single day of recall data. To apply the population ratio method, the mean intake of the relevant food groups, nutrients and energy among the population of interest is calculated first; then ratios of the means are calculated and compared with the applicable standards for scoring. See Freedman et al. 2008 for a description and application of the population ratio method using the HEI–2005. SAS code for calculating HEI scores using the population ratio method is available for use with 24-hour recall data collected in NHANES and through the ASA24 system, below. The sample code can be adapted for other data sources. For the calculation of HEI-2010 scores using NHANES data, two examples are available. The output includes mean component and total HEI–2010 scores for the population, along with their standard errors and confidence intervals. Further details are available in the documentation that accompanies the code. SAS code for calculating HEI-2010 or HEI-2005 scores using the population ratio method from the Automated Self-Administered 24-hour (ASA24) dietary recall system is also available. The output includes mean component and total HEI–2010 scores for the population, along with their standard errors confidence intervals. This code can be modified to use with other datasets that do not involve complex sampling designs. With individual-level data, it also is possible to calculate mean scores or scores of the mean ratio. This approach is not recommended for the purposes of describing mean HEI scores.

Appendix K: Short Stress State Questionnaire

VERSION A

General Instructions. This questionnaire is concerned with your feelings and thoughts while you were performing the task. Please answer **every** question, even if you find it difficult. Answer, as honestly as you can, what is true of **you**. Please do not choose a reply just because it seems like the 'right thing to say'. Your answers will be kept entirely confidential. Also, be sure to answer according to how you felt **DURING THE CHALLENGE.** You should try and work quite quickly: The first answer you think of is usually the best.

Please indicate how well each word describes how you feel **AT THE MOMENT**.

Not at all = 1 A little bit = 2 Somewhat = 3 Very much = 4 Extremely = 5

1. Dissatisfied	1	2	3	4	5
2. Alert	1	2	3	4	5
3. Depressed	1	2	3	4	5
4. Sad	1	2	3	4	5
5. Active	1	2	3	4	5
6. Impatient	1	2	3	4	5
7. Annoyed	1	2	3	4	5
8. Angry	1	2	3	4	5
9. Irritated	1	2	3	4	5
10. Grouchy	1	2	3	4	5

Please indicate how true each statement is of your thoughts **DURING THE PAST TEN MINUTES**.

Not at all = 1 A little bit = 2 Somewhat = 3 Very much = 4 Extremely = 5

11.	I am committed to attaining my performance goals	1 2 3 4 5
12.	I want to succeed on the task	1 2 3 4 5
13.	I am motivated to do the task	1 2 3 4 5
14.	I'm trying to figure myself out.	1 2 3 4 5
15.	I'm reflecting about myself.	1 2 3 4 5
16.	I'm daydreaming about myself.	1 2 3 4 5
17.	I feel confident about my abilities.	1 2 3 4 5
18.	I feel self-conscious.	1 2 3 4 5
19.	I am worried about what other people think of me.	1 2 3 4 5
20.	I feel concerned about the impression I am making.	1 2 3 4 5
21.	I expect to perform proficiently on this task.	1 2 3 4 5
22.	Generally, I feel in control of things.	1 2 3 4 5
23.	I thought about how others have done on this task.	1 2 3 4 5
24.	I thought about how I would feel if I were told how I performed.	1 2 3 4 5

VERSION B

General Instructions. This questionnaire is concerned with your feelings and thoughts while you were performing the task. Please answer **every** question, even if you find it difficult. Answer, as honestly as you can, what is true of **you**. Please do not choose a reply just because it seems like the 'right thing to say'. Your answers will be kept entirely confidential. Also, be sure to answer according to how you felt **DURING THE MATH CHALLENGE TASK.** You should try and work quite quickly: The first answer you think of is usually the best.

Please indicate how well each word describes how you felt DURING THE MATH CHALLENGE TASK.

Not at all = 1 A little bit = 2 Somewhat = 3 Very much = 4 Extremely = 5

1. Dissatisfied	1	2	3	4	5
2. Alert	1	2	3	4	5
3. Depressed	1	2	3	4	5
4. Sad	1	2	3	4	5
5. Active	1	2	3	4	5
6. Impatient (Restless)	1	2	3	4	5
7. Annoyed	1	2	3	4	5
8. Angry	1	2	3	4	5
9. Irritated	1	2	3	4	5
10. Grouchy	1	2	3	4	5

Please indicate how true each statement was of your thoughts **WHILE PERFORMING THE MATH CHALLENGE TASK**.

Not at all = 1 A little bit = 2 Somewhat = 3 Very much = 4 Extremely = 5

11.	I was committed to attaining my performance goals	1 2 3 4 5
12.	I wanted to succeed on the task	1 2 3 4 5
13.	I was motivated to do the task	1 2 3 4 5
14.	I tried to figure myself out.	1 2 3 4 5
15.	I reflected about myself.	1 2 3 4 5
16.	I daydreamed about myself.	1 2 3 4 5
17.	I felt confident about my abilities.	1 2 3 4 5
18.	I felt self-conscious.	1 2 3 4 5
19.	I was worried about what other people think of me.	1 2 3 4 5
20.	I felt concerned about the impression I was making.	1 2 3 4 5
21.	I performed proficiently on this task.	1 2 3 4 5
22.	Generally, I felt in control of things.	1 2 3 4 5
23.	I thought about how others have done on this task.	1 2 3 4 5
24.	I thought about how I would feel if I were told how I performed.	1 2 3 4 5

Appendix L: Perception of Stressor

Please SELECT one choice for each question

1) How stressed out did you feel while participating in the math challenge task?

0 1 2 3 4 5 6 7

(not at all) (extremely)

2) How sad did you feel while participating in the math challenge task?

0 1 2 3 4 5 6 7

(not at all) (extremely)

3) How much anxiety did you feel while participating in the math challenge task?

0 1 2 3 4 5 6 7

(not at all) (extremely)

4) How angry did you feel while participating in the math challenge task?

0 1 2 3 4 5 6 7

(not at all) (extremely)

5) Had you ever participated in the math challenge task before?

Yes No

Appendix M: Oral Health Questionnaire

For each question, please circle the most correct response.

1) Have you ever been told that you have periodontal disease or gum disease?

Yes No Not Sure

If you answered "yes" or "not sure" to #1, please explain:

2) Do you currently have dental braces?

Yes No

3) Besides dental braces, do you currently use any other type of orthodontic equipment, such as a retainer or "night guard"?

Yes No Not Sure

If you answered "yes" or "not sure" to #3, please list the type of equipment and how you use it (for example, what time of day you use it and how frequently you use it):

Type of Equipment	How Used
Example: retainer	*Example: wear on bottom teeth at night only*

For questions #4-7, please answer as the average level over the past month.

4) On average over the past month, how often did you brush your teeth?

Less than once per week Once per week Every other day Once per day Twice per day More than twice per day

5) On average over the past month, how often did you floss?

Never Less than once per week Once per week Every other day Once per day At least twice per day

6) On average over the past month, how often did your gums feel swollen or sore?

Never Rarely Sometimes Often Always

7) On average over the past month, how often did your gums bleed when you brushed your teeth?

Never Rarely Sometimes Often Always

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