THE INFLUENCE OF WEIGHT CYCLING AND CHRONIC OBESITY EXPOSURE ON SYSTEMIC INFLAMMATION: A LONGITUDINAL ANALYSIS

by

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ABSTRACT

ABIGAIL STROM HARDIN. The influence of weight cycling and chronic obesity exposure on systemic inflammation: A longitudinal analysis. (Under the direction of DR. JENNIFER WEBB)

Pediatric obesity is a growing public health concern while cardiovascular disease remains the number one cause of death among women. As a result, research is seeking to illuminate the links among obesity and chronic diseases in later life, and whether lifestyle modifications like diet and exercise interventions are effective. Yet, an excessive focus on diet may paradoxically contribute to morbidity risk through weight cycling and associated metabolic changes. The present study sought to investigate in what way weight cycling and chronic obesity may contribute to chronic disease trajectory in young girls and women. Results revealed that obesity exposure was a significant predictor of CRP above and beyond a girl's most recent weight; for each additional year of obesity exposure, girls could expect to increase their CRP in early adulthood by between .38 and .40 mg/L, depending on model. There was no evidence of impact of weight cycling factors on CRP early in adulthood. Results also suggested a mediated link between drive for thinness and CRP through numbers of attempts to lose weight and obesity exposure. Given these results, public health officials may consider alternative health behavior change interventions that discourage excessive focus on restrictive dieting. Conclusions, limitations and future directions are discussed.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Obesity [defined as having a body mass index (BMI) $\geq$ 30 kg/m^2], labeled in popular culture and by the CDC as a recent "epidemic," is a significant health concern and affects more than one third of adults in the United States, and about 17% of children and adolescents (CDC, 2012). Children in today's society are growing up in an "obesogenic" or obesity-inducing environment. In contrast with society about three decades ago, childhood obesity today is also considered an "epidemic" (Ogden et al., 2006). Between 1976 and 2006, the prevalence of overweight for young children aged two to five rose from only 5% to over 12% (CDC, 2009). Indeed, alarming increases in rates of obesity in children have been identified, even as young as two years old (Adair, 2008). The past three decades have witnessed a disturbing climb in obesity rates, leading researchers to call for population-based approaches to health promotion and public policy changes (Wang & Beydoun, 2007). Consequently, young adults in modern society are part of a new generation that has experienced a lifetime of obesity, as opposed to the development of obesity later in life. In fact, adolescents today experience obesity at a rate four times that of three decades ago (Ogden, Carroll, Kit & Flegal, 2014). The increase in both the prevalence and severity of obesity in recent decades is likely due to a complex interaction among genes, dietary intake, exercise, and environmental factors (Biro & Wien, 2010).

Due to these changes, children and adolescents having grown up in this obesogenic atmosphere may be the first to have the unique experience of encountering chronic, early-onset obesity, an experience rare for generations before them (Ogden et al., 2006). Thus, obesity today may be a life-course problem with earlier onset and potentially earlier health risks, including cardiovascular disease. Developmental models, including the Six-Cs (Harrison et al., 2011) model, have been invoked to understand the development and maintenance of obesity, yet these models are limited in their longitudinal applications and have been previously argued to be insufficient in fully understanding the potential health outcomes associated with chronic obesity or weight cycling (Hardin, Webb, Reeve, Bennett & Coffman, in progress). The Six-Cs model suggests that cell, child, clan, community, country and cultural factors may either promote or protect against overweight and obesity. The model includes factors such as school policy, eating, exercise, resources, media campaigns, genes, and a variety of other variables potentially relevant to the development and maintenance of obesity (Harrison et al., 2011). Importantly, the model proposes both biological and psychosocial factors as influences on the development of obesity.

For instance, the authors of the Six-Cs model propose both proximal mental health factors as well as proximal behavioral and biological factors, like food choices, exercise frequency and genetic predispositions, affect obesity development. The model also suggests interplay among factors of different levels such that distal factors, such as food availability, cultural values, state policies, and family variables, such as food shopping, likely affect more proximal factors like food consumption and body image.

The critical oversight, however, of the Six-Cs model is its treatment of a temporal factor. Though the Six-Cs model specifies that time may impact the relative weight of factors encountered at different points in the lifespan, this conceptualization of time may be missing a more crucial factor: cumulative effect. The inclusion of the cumulative nature of time within an updated Six-Cs model then would expand it to include not only time as impacting the types and amounts of factors encountered by the individual, but as a factor in and of itself.

A proposed updated model, the "Updated Harrison" model (Hardin, Webb, Reeve, Bennett & Coffman, in progress), maintains the Six-Cs factor structure, including the existing temporal element, but with several important additions. Most important among those, the proposed update includes a time "subfactor" of cumulative effect, conceptualized as a cumulative factor of influence in and of itself, with compounding influence over time. For instance, not only may obesity exposure over time impact physiological markers of systemic inflammation, like C-Reactive Protein (CRP), but as time passes, these influences of obesity may compound, such that duration of obesity exposure may be predictive itself of health outcomes. Thus, the "Updated Harrison" model may be useful in understanding the chronicity effects of obesity over time, particularly on inflammation and associated cardiovascular health outcomes like cardiovascular disease (CVD).

That inflammation may partially mediate the relationship between obesity and chronic diseases like CVD is demonstrated in the strong observed association between inflammation and CVD (Libby, 2007). Clear evidence has linked CVD to both obesity and some measures of weight fluctuation, yet mechanisms for this link continue to be

investigated (Anderson, Gutierrez, Kennedy & Hasty, 2013). Recent research also indirectly points to obesity over time as a risk factor for chronic disease. Indeed, research has indicated that obesity in childhood may have health consequences later in life, suggesting that the effect of obesity over time on the body may result in early predisposition to chronic disease. Results from Sabo, Lu, Daniels and Sun's (2012) recent analysis lend credence to this idea using blood pressure as an example. The authors found that blood pressure in early and mid-adulthood (ages 20-40) was at least partially accounted for by objectively measured childhood BMI. Evidence does support the supposition that inflammation and immune processes may link obesity broadly with cardiovascular disease (Anderson et al., 2013). Yet no known research to date has explored the relationship between chronicity of obesity and inflammation, completing the understanding of this three-way relationship with cardiovascular disease within the context of a lifetime of obesity. Furthermore, very little research has connected weight cycling with inflammation, leaving the obesity and weight cycling literatures problematically disparate, despite the reality that weight cycling and chronic obesity may frequently overlap, and indeed that weight cycling may impact subsequent body weight and composition changes and vice versa (Cereda et al., 2011; Kroke et al., 2002; Goyenechea et al., 2009). The present study sought to address these gaps by connecting objective measures of weight cycling and obesity chronicity with a marker of systemic inflammation longitudinally in a sample of girls to investigate the effects of chronic obesity and weight cycling on systemic inflammation early in development.

1.1 Obesity and Inflammation

Chronic obesity may have physiological health effects, particularly with respect to chronic disease via inflammation, that are different from adult-onset obesity or limited obesity exposure. To more carefully inspect this line of reasoning, a basic understanding of obesity's impact on inflammation is in order. The immune system is closely related to metabolic processes. Chronic inflammation markers like CRP have been associated reliably with cardiovascular risk factors and obesity, both in adults and children (Ford, 2003). Obesity in mice triggers both peripheral inflammation as well as CNS inflammation (Buckman et al., 2014). Moreover, weight loss treatments have likewise been shown to decrease CRP and other markers of inflammation in older adults (Nicklas et al., 2004). Though inflammation is an adaptive body response designed to repair damaged tissue due to injuries characterized by swelling, redness, pain and fever, prolonged inflammation is a different state altogether (Hotamisligil, 2006). In his watershed systematic review, Hotamisligil concluded that low-grade, chronic inflammation may be metabolically triggered principally by a chronic surplus of nutrients in the metabolic system (Hotamisligil, 2006). But at the cellular level, the pathways to chronic inflammation are much the same as in traditional inflammation in response to injury. Extant literature linking obesity to low-grade inflammation has proposed multiple mechanisms through which a chronic inflammatory state can be developed. One likely mechanism is through the proinflammatory effect of excess adipose tissue itself. This tissue holds adipocytes, or fat cells, which secrete pro-inflammatory cytokines. In this way, adipose tissue itself can be considered an endocrine organ, rather than a passive storage facility as was historically assumed (Calabro et al., 2009).

Indeed, adipose tissue has been consistently implicated in the development of systemic inflammation (Berg & Scherer, 2005). This inflammation in turn is strongly related to the progression of chronic disease, insulin resistance and diabetes (Calabro et al, 2009). Adipocyte-based inflammation may result particularly in obese individuals as the adipocytes become further removed from capillaries in the tissue, consequently developing hypoxia and resulting in an inflammatory safety response prior to new adipocytes being created to house the overabundance of energy (Calabro et al., 2009). Most is known about the pro-inflammatory cytokines released by adipocytes (known as adipocytokines) like CRP, IL-6, TNF-alpha, leptin, and resistin (Calabro et al., 2009). CRP may be released indirectly via IL-6, which is released by adipocytes and then upregulates liver generation of CRP (Mortenson, 2001), but some initial evidence also suggests that CRP may be directly released from fat tissue, further stimulating systemic inflammation (Ouchi et al., 2003). Adipocytes have been demonstrated to release CRP directly in response to the presence of certain cytokines (Calabro et al., 2005). Taken together, these results suggest that the development and maintenance of obesity indeed may result in physiological changes mediated by immunity that contribute to later disease risk. As stated previously, strong evidence links inflammation and CVD (Libby, 2007). It stands to reason that continual, as opposed to temporary, exposure to these proinflammatory substances as a result of high levels of adiposity would confer disease risk commensurate with exposure, including with respect to CVD. Yet presently research has not directly addressed this question of cumulative risk.

1.2 Cumulative Effects of Obesity

Generally, little research has directly assessed for cumulative or differential exposure to obesity and its relationship to disease risk. Yet consistent evidence shows a relationship between childhood overweight and cardiovascular outcomes and mortality in adulthood (Park, Falconer, Viner & Kinra, 2012). Indeed, when adult BMI is controlled for, adolescent BMI has been shown to be independently associated with coronary heart disease (Tirosh et al., 2011). But when controlling for BMI in adulthood, the association of diabetes with adolescent BMI was effectively nullified, indicating that some diseases, particularly coronary heart disease, may be more gradual than others like diabetes, and thus these cardiovascular diseases could be more sensitive to these ongoing effects of high BMI (Tirosh et al., 2011). Additionally, though inflammatory markers increase with age (Ferucci et al., 2005), it is unclear to what extent inflammation levels increase with age independent of weight gain or weight status history.

Importantly, there is preliminary evidence that even for adolescents and young adults, chronic disease risk may be heightened for those who are or have been obese. Ford and colleagues (2005) used NHANES data on adolescents aged 12-17 and observed that adolescents who had MetS, one of whose symptoms is obesity, had higher CRP concentrations than those who did not. Concerningly, the percentage of those showing a clinically significant level of CRP (>3.0mg/l) was 38.4% among those with MetS whereas among those without it, it was only 10.3%. Of all the MetS components, abdominal obesity as measured by waist circumference was the only component related to CRP concentrations, whereas the other MetS criteria were not (Ford et al., 2005). These findings suggest that abdominal obesity may increase CRP levels to clinically

meaningful cutoffs (>3.0mg/l) even in adolescence, far before screenings for heart health and other potential chronic diseases tend to take place routinely.

It appears few studies have examined effects of childhood BMI independently of or in conjunction with adulthood BMI (Park et al., 2012). In a systematic review of studies using objectively measured height and weight values for children aged 2-19, chronic disease outcomes later in life were consistently associated with adult BMI, but childhood obesity was very rarely assessed independently (Park et al, 2012). Therefore, there has been little consideration of the possibility of whether the effects of childhood and adolescent overweight/obesity may function and have effects of their own independent of later adult overweight status (Park et al., 2012). As stated above, some initial research on blood pressure does indeed suggest that adulthood disease risk may be attributable partially to childhood weight status, yet the question of whether these health outcomes respond differently depending on overall obesity exposure remains unanswered.

1.3 Dieting and Obesity

An additional factor of relevance in exposure to obesity over time includes diet and exercise. Common sense – and indeed the research literature – suggests that health behavior change interventions, particularly those that combine both diet and exercise, can produce long lasting and significant weight changes over time (Johns, Hartmann-Boyce, Jebb & Aveyard, 2014; Johansson, Neovius & Hemmingsson, 2013).

Yet simultaneously, an increasingly compelling body of evidence is beginning to suggest that in some cases, restriction of one's diet can also counter-intuitively contribute to obesity maintenance. For instance, previous research has shown that drive for thinness

is associated with overeating through negative affect (Strien, Engels, Leeuwe & Snoek, 2005). Additionally, research on dieting behaviors has suggested that drive for thinness may contribute to dieting behaviors that work to support obesity development and maintenance. In animal models, periods of dieting have been associated with greater fat deposition following re-feeding (Higginson & McNamara, 2016). Additionally, dieting behaviors in both girls and boys has been associated with long-term weight gain (Neumark-Sztainer, Wall, Guo, Story, Haines & Eisenberg, 2006). In part, the discrepancies between these two bodies of literature may highlight nuances in types of diets. For instance, modest weight loss accompanied by moderate exercise has been shown to sustain modest long-term (measured at 12 months) weight loss, generally associated with improved health and wellbeing (Johns, Hartmann-Boyce, Jebb & Aveyard, 2014). However, more extreme losses may be less effective long-term, or perhaps damaging. In a study of adults, those who engaged in a very low calorie diet, as opposed to a low calorie diet, lost more fat-free mass and experienced higher rates of weight re-gain (Vink, Roumans, Arkenbosch, Mariman & van Baak, 2016). Thus, while lifestyle changes may assist in producing beneficial body composition changes, some more extreme dieting behaviors, particularly when undertaken by young people, may produce unintended maladaptive consequences like weight re-gain and development of overweight and obesity.

In turn, a question of interest may be whether, or to what extent, caloric restriction may go on to influence inflammation. One proposed pathway could be through dieting itself, rather than through obesity development or maintenance. Yet, recent research finds no evidence that low calorie diets or very low calorie diets impact inflammation markers

(Strasser, Berger & Fuchs, 2015). Indeed caloric restriction per se may have a less direct relationship on inflammation than the type of foods consumed. In animal models, if in the course of a diet high fiber foods like resistant starch are reduced, there appears to be an up-regulation of pro-inflammatory processes (Vaziri et al., 2014). Indeed, a Mediterranean diet irrespective of caloric intake appears to reduce inflammatory cytokines like CRP and interleukin-6 (Schwingshackl & Hoffmann, 2014), while "Western" diets are robustly associated with increases in inflammatory biomarkers (Barbaresko, Koch, Schulze & Nothlings, 2013; Lopez-Garcia et al., 2004). Further evidence from the eating disorders literature supports this suggestion that caloric restriction is not anti-inflammatory; in a meta-analysis of Anorexia studies, despite participants having very low BMIs, Anorexia was again robustly associated with higher levels of pro-inflammatory biomarkers (Solmi et al., 2015). Thus, although obesity does appear to be associated with inflammation as discussed above, simple caloric restriction per se does not appear to reduce inflammation. Rather, the ensuing impact of dieting on inflammation may vary with the manner in which restriction takes place, the foods consumed, and the resulting body habitus..

1.4 Weight Cycling Effects On Inflammation

Though there is presently a dearth of evidence on the effects of weight cycling with respect to inflammation, some preliminary findings suggest weight cycling may exacerbate or lead to systemic inflammation. Yet the validity of this research has been frequently called into question due to methodological and analysis concerns. Here, weight cycling effects on inflammation are discussed, followed by a discussion of the limitations to this research.

Weight cycling has been linked to several measures of health like adiposity and weight distribution. Weight loss has been shown to improve metabolic syndrome symptoms, for example, but re-gain of that weight seems to return the risk (Thomas et al., 2010). Weight cycling has likewise been shown to be associated with weight accumulation and central body fat distribution (visceral fat) (Cereda et al., 2011). Yet the evidence tying inflammation to weight cycling is limited. Interestingly, the inflammation-weight cycling relationship may be bidirectional. Following one experimental 8-week, low-calorie diet, 6-month weight regain among adults aged 20-40 was significantly predicted by high concentrations of TNF-alpha at the end of the diet, along with baseline fat mass. This result may indicate that a pro-inflammatory state associated with high body fat may predict weight cycling, despite an overall drop in pro-inflammatory cytokine levels that accompanied the weight loss in that sample (Goyenechea et al., 2009). The authors speculated that the pro-inflammatory cytokines released by the adipose tissue could perhaps modulate food intake through work on the hypothalamus and HPA axis. A longitudinal study in Sweden of adult men supports the observation that inflammatory markers are associated with future weight gain (Engstrom et al., 2003), though fitness and diet were not controlled for. Evidence also suggests that weight cycling precedes inflammation, though this subset of the literature is likewise limited.

Despite the limited research on weight cycling and inflammation, animal models may provide some initial data to clarify the potential role of weight cycling on inflammation and chronic disease risk. Experimentally, rats exposed to weight cycling in succession with vacillations from high fat diet to standard chow diet were shown to have high levels of adipocytokines and other pro-inflammatory cytokines. They were also

shown to have a less pronounced body weight reduction during the standard chow diet after three consecutive exposures to the weight cycling. And following high fat re-feeding periods, the rats that had weight cycled were observed to have gained more body mass. The researchers pointed out that the reduction in body mass during the standard feeding period of a weight cycle was not sufficient to fully recover from the high levels of adipokines and pro-inflammatory cytokines increase that occurred during the high fat diet period, contributing to an overall rise in levels of these pro-inflammatory cytokines (Barbosa-da-Silva et al., 2012). If this rat model were to hold true for human weight cycling, it would then follow that humans might likewise experience an upward trajectory in inflammation accompanying repeated weight cycles.

Anderson-Baucum, Major and Hasty (2014) likewise found initial evidence to suggest that in animal models, weight-cycling appears to be related to T-cell accumulation in adipose tissue. The authors suggested that obesity may trigger a local secondary immune response to self-antigens generated by the adipose tissue itself (Anderson-Baucum et al., 2014). The research group showed that both CD4 and CD8 T-cells were more prevalent in the adipose tissue of rats that had weight cycled. Multiple cytokines also appeared elevated in response to weight cycling, apparently as a result of elevated Helper T-cell activation (Anderson, Gutierrez, Kennedy & Hasty, 2013).

Although these initial sources of evidence may imply a link between a pro-inflammatory state and weight cycling, to date no study has evaluated weight cycling as an independent contributor to systemic inflammation, and no study has used an objective measure of weight cycling. In fact, the weight cycling literature broadly appears to be rife with methodological challenges. For instance, one study defined weight cycling as five

self-reported cycles of weight gain and loss of 5 kg or more. The authors did find weight cycling to be associated with excess weight and abdominal fat, but their use of self-report, retrospective data suffers from the same methodological challenges as other weight cycling research (Cereda et al., 2011).

Previous studies, still relying on self-report data, have made an attempt to quantify the severity of weight cycling based on the amount of weight lost and regained. For instance, women who reported three or more instances of losing 20lbs or more were considered "severe" weight cyclers, whereas women who reported three or more instances of losing and then regaining 10lbs or more were considered "moderate" weight cyclers. Other women were considered "non-cyclers." (Mason et al., 2013). Yet this method, while in keeping with the current methodological standards in the weight cycling literature, confounds number of cycles with severity of cycles. Furthermore, this method uses continuous data to create categories, restricting the utility of the data. In a systematic review of weight cycling research, Mehta, Smith, Muhammad and Cazazza (2014) identified that the absence of a standard definition of weight cycling significantly impairs the validity of conclusions drawn from the literature. The authors found that few studies used cardio-metabolic biomarkers at all, and those that did were methodologically unsound. There was no mention of investigating inflammation in human weight cycling studies.

An additional concern with some weight cycling literature is that in some cases, obese and normal-weight weight status is determined without consideration of body weight distribution factors that may be relevant. Bosy-Westphal and Muller (2014) point out that results suggesting that an increase in body fat percentage tends to follow a weight

gain/loss cycle in normal weight individuals ignore the fact that a significant body weight decrease in a normal-weight individual typically comes with a decline in lean body mass, necessitating mathematically an increase in body fat percentage. Moreover, if that weight was lost subcutaneously, an accompanying increase in abdominal fat percentage would likewise be observed (Bosy-Westphal & Muller, 2014). The authors suggest that methodologies for examining weight cycling need to use valid and reliable measures of body composition in order to control for these issues, yet the authors do not address the need for more fully defined constructs.

Finally, the use of self-report data to create these groups calls into question the validity of the group distinctions on principle, as participants may not recall or incorrectly recall their number and severity of cycles. Importantly, the tendency to rely on self-report data on weight cycling is inadequate. A great deal of evidence suggests that individual self-report data on weight in general is invalid. Gorber, Tremblay, Moher and Gorber (2007) showed that there is wide variability in self-report accuracy, but that the trend is clearly in the direction of under-reporting past and current weights. The authors suggest using alternate methods or at least employing correction factors. In fact, this well-known downward bias in self-reporting weight has remained stable for the past decade (Hattori & Sturm, 2013). About one in six individuals are classified erroneously as non-obese due to improper self-reporting (Hattori & Sturm, 2013).

Perhaps as a result of the poor clarity in definitions as well as the questionable use of self-report data, the weight cycling literature has been accused of being inadequate methodologically (Cutter et al., 1996; Mehta et al., 2014). Even as early as the mid-nineties it was clear that this line of research was hampered by poor methodological

choices, ranging from weak construct definitions to inadequate statistical analyses for identifying cycles. Cutter and colleagues (1996) were the first to suggest that measures of cycles and measures of severity of those cycles, or amplitude, should be separately analyzed. The authors proposed that runs testing be used for measuring cycles, a technique that calculates whether a series of values (called a run) was randomly or non-randomly generated (Cutter et al., 1996). Yet runs testing fails to account for the severity or amplitude of cycles, making it an inadequate statistical approach for investigating weight cycling. At the time of writing, no studies using this runs test method were published, indicating that there has not been adoption of this technique within the weight cycling literature, and Cutters and colleagues' (1996) suggestion that measures of cycles should be separated from measures of severity has not been heeded.

1.5 Other Correlates of CRP

It is important to note that the inflammatory effects of obesity may be modified substantially by demographic variables, including ethnicity and sex, as well as psychosocial factors like depression. These factors are therefore important to control for when using CRP as an outcome variable.

Sex and CRP

Using a nationally representative NHANES samples, women were found to have generally higher upper limit CRP values than men across the age spectrum. Specifically, female children aged 4-11 and adolescents aged 12-19 had similar CRP ranges, though the 95th percentile score rose in women around the 20-39 age range (Wener, Daum & McQuillan, 2000). This suggests that women may generally exhibit higher CRP values than their male counterparts, and therefore may approach the clinically significant cutoff

values for CRP earlier in life. Female sex has been shown to predict elevated CRP levels in response to high objectively measured BMI in comparison to men (Laurson, McCann & Senchina, 2011). Although BMI was identified as the most salient predictor of CRP values accounting for the majority of the variance, the addition of demographic variables (race, sex and age) did modestly improve the variance accounted for, and among those demographic variables, sex was the most strongly predictive of CRP (Laurson, McCann & Senchina, 2011).

Ethnicity and CRP

Inflammation as measured by CRP has been previously associated with ethnicity, such that African Americans are at greater risk for both acutely high levels of CRP as well as chronic, low-grade inflammation (McDade, Lindau & Wroblewski, 2010). Much of the association, however, can be accounted for by behavioral and medical factors, leading researchers to suggest that lifestyle as a result of broad socio-structural conditions is more likely the cause of socioeconomic and by proxy, ethnic gradients in CRP. The upper limits of observed CRP values also appear to be higher among African American women. In fact, in a study using nationally representative NHANES data, African American women showed the highest 95th percentile CRP values among the entire study sample, including men and women of all ages and ethnicities (Wener, Daum & McQuillan, 2000). These demographic alterations to observed CRP suggest that women, and particularly African American women, may be at increased risk for high CRP levels in response to inflammatory conditions like obesity, and likewise may be at increased risk for poor health outcomes like CVD later in life. Additionally, among young girls aged about 9-10, overweight and obesity are more prevalent in African American girls,

potentially exposing them to obesity at an earlier age, and therefore to a greater total obesity exposure across the life course (Morrison, Sprecher, Barton, Waclawiw, & Daniels, 1999).

Depression and CRP

Likewise, depression has been associated with inflammation (Danese et al., 2009). Importantly, the relationship between depression and inflammation remains even after accounting for demographic, medical, and behavioral factors (Stewart, Rand, Muldoon & Kamarck, 2009). As such, it is likely that the biological effect of depression goes above and beyond the behavioral effects of having depression on eating and exercise variables. Indeed, depression is a risk factor in its own right for coronary heart disease (Suls & Bunde, 2005). Importantly, it has been shown that depression elevates inflammatory biomarkers like CRP (Stewart, Rand, Muldoon & Kamarck, 2009). Yet, there is also evidence that depression can appear as an apparent late result of existing chronic inflammation (Dantzer, O'Connor, Lawson & Kelley, 2011). Thus, it is possible that there is a bi-directional relationship between inflammation and depression such that depression augments inflammation and inflammation may boost depression to clinically detectable levels.

CHAPTER 2: METHODS

2.1 Participants

In the present study, participants were a sub-sample of 120 women from the NHLBI Growth and Health Study (NGHS). The procedures of this study are specified in detail elsewhere for interested readers (Kimm et al., 2001; NGHS Research Group, 1992). Briefly, however, the original NGHS participants were 2,379 girls between the ages of 9 and 11 enrolled between 1987 and 1988 who were followed for 9 years. The girls were assessed on a number of measures once per year, for a total of 10 time points including an initial baseline assessment. They were recruited from the Cincinnati, Ohio, Richmond, California and Washington D.C. areas, from school districts and a health maintenance organization. The recruitment locations were selected for use due to census data that showed roughly equal percentages of white and black students, and minimal income disparity. Within these locations, participants were randomly selected from the list of eligible students (Kimm, et al., 2002).

Participants for the present study were selected from the total original sample to ensure that all participants for the present study had as much data available as possible, including a final bio-specimen for time point 10. Participants in the original study were prompted to self-identify as Caucasian or African American. In this study, sixty Caucasian women and 60 African American women were chosen for the sub-sample to allow for adequate power for between-groups comparisons. Because more than 30 weight

cyclers of each ethnic group were available within the original sample, an overall list of potential sub-sample members was provided to BioLINCC, stratified by ethnicity, and a random sub-sample was selected by the BioLINCC staff while ensuring sufficient serum was available within the time point 10 biospecimen.

Within each ethnic group, half of the participants were chosen based on their available height and weight data as "weight cyclers", defined as having experienced at least two or more periods of losing and then regaining, or vice versa, more than 10 pounds (4.54 kg). This 10-pound cutoff was chosen as a criterion due to its status as the minimal cutoff for meaningful cardiometabolic improvements (including for CRP levels) as a result of weight loss (Dow et al., 2013).

Participants were excluded from the present study's subsample if they were ever smokers, or if they became pregnant at any point during original data collection, as ever smoking as well as having ever been pregnant are factors that have been shown to correlate to higher CRP values in adolescent girls and young women (Le-Ha et al., 2014; Kuzawa, Adair, Borja & McDade, 2013).

2.2 Measures

C-Reactive Protein (CRP). R&D Systems Human CRP ELISA Kits have been shown in R&D's own testing to be reliable between assays and within assays. The kit has also been shown to have adequate specificity for human CRP, indicating good test validity (EIA, R&D Systems, Minneapolis, MN). CRP values were calculated in mg/L, consistent with units of measurement used for clinical cutoff values.

Depression. Depression for each participant was measured using the CESD (Radloff, 1977) at time points 8 and 10. The measure was framed such that the participant

was asked, “During the past week” of taking the survey, 20 items such as “I felt sad” and “I felt hopeful about the future.” Responses were coded on a likert scale and scores combined into a total CESD score for each participant. The CESD has been shown to be a consistently valid and reliable measure of depression in adolescents (Radloff, 1991). The test has been shown to have good internal consistency (split-halves method coefficient alpha = .85), sufficient reliability among an adolescent sample (Chronbach’s alpha = 0.85) and moderate test-retest reliability (r= .45-.70) (Radloff, 1977; Chabrol et al., 2002). In the NGHS sample, Chronbach’s alpha values have been shown to be good, ranging from .85 to .91 (Franko et al., 2004).

Weight Percentile. Objective weight and height measures taken from each time point were converted into pediatric weight percentile, using the CDC weight percentile calculator available at https://nccd.cdc.gov/dnpabmi/calculator.aspx. This calculation integrates the individual child’s weight, height and age to calculate a percentile score that is sensitive to the developmental progress of the individual.

Weight Category. Objective weight category was determined using CDC cutoffs for pediatric weight percentiles (CDC, 2014).

Obesity exposure**.** Obesity exposure was measured by identifying the number of time points each participant evidenced a weight category at the “obese” level creating an exposure variable for each individual. This approach to quantifying exposure of assessing total time points for which a participant experiences a value over a pre-set cutoff for a given variable is not new; Evans and Kim (2007) used the approach successfully in a study of poverty exposure on children’s physiological markers of cumulative stress. Najman and colleagues (2009) employed a similar strategy in evaluating poverty

exposure and sensitive periods in childhood cognitive development. In fact the same research group has used this exposure analysis multiple times with success in evaluating childhood poverty, further supporting its general acceptance as an empirical method particularly in the developmental literature (Najman et al., 2009). The variable for obesity exposure was defined according to CDC percentile-for-age criteria, and measured as number of time points at which each participant met or exceeded the CDC threshold as being above the 95th percentile for age.

Weight cycling frequency. A weight cycle was defined as having gained and then subsequently lost, or lost and then subsequently gained in the next sequential data point, at least 10 pounds. Individual participant cycles were then counted to determine number of cycles experienced across all time points.

Weight cycling amplitude. Amplitude was measured as each participant's within person variance and calculated as an index of general amplitude of deviation. This was calculated as the standard error from each participant's average percentile for age. Thus, while each weight cycle was defined as being at least a deviance of 10 pounds or more from the starting weight, weight cycling amplitude was a quantification of the degree overall to which each participant varied from her own weight percentile. Because pediatric weight percentiles are inherently adjusted for age, this measure inherently accounts for the trend toward increasing weight with pubertal advancement.

Drive for Thinness. Drive for Thinness, a subscale within the Eating Disorders Inventory (Garner, Olmstead & Polivy, 1983), was administered to participants at time points 3, 5, 7, 9, and 10. The scale is a 7-question measure that uses a likert-type response scale ranging from "always" to "never". The scale includes questions such as "I am

preoccupied with a desire to be thinner." and "I think about dieting." The scale has been demonstrated to have good internal consistency (Chronbach's $\alpha = 0.85$) in a female university student control sample. The measure has likewise been shown to have good criterion validity and has been shown to correlate significantly with dietary restraint (Garner, Olmstead & Polivy, 1983). An average score for each participant was calculated to create the Drive for Thinness Average variable. Previous research using the NGHS sample has demonstrated that in black girls, the internal consistency for this scale is .80, and for white girls it is .88 (Franko et al., 2004).

Attempts to Lose Weight. At each time point during data collection, participants were asked a single question evaluating whether they had attempted to lose weight during the past year. Attempts to lose weight was calculated by summing the number of years each participant endorsed having attempted to lose weight during that time point. Thus, the variable reflects the total number of years each participant was actively attempting to lose weight across the 10-year study period.

Race. Self-identified race as indicated from the dataset was used, provided as African American or Caucasian.

2.3 Procedure

For the present study, the sub-sample included a 2x2 factorial design, with two ethnic groups crossed with the two cycling/non-cycling groups. Obesity exposure was measured in advance but not used for participant selection or assignment to group.

Serum samples delivered by BioLINCC were stored frozen at -80 C in Stress*WAVES* BRL until later assessment of CRP. CRP was measured by a commercially available enzyme-linked immunosorbent assay (EIA; R&D Systems; Minneapolis, MN).

For detailed description of the ELISA CRP procedure, interested readers are encouraged to look to the R&D Systems Human CRP Quantikine ELISA package insert (EIA; R&D Systems; Minneapolis, MN). All standards and samples were run in duplicate. Any sample with a coefficient of variance (CV) at 10% or greater was re-run to obtain a %CV lower than 10 to produce a reliable CRP value. Data analyses and summary of data reflect the mean CRP value of the two samples.

2.4 Hypotheses and Analytic Plan

Aim 1

This study sought to empirically evaluate the previously proposed "Updated Harrison" model of cumulative effect of high BMI on systemic inflammation. Likewise, this study aimed to answer a secondary question regarding the effect of weight cycling on systemic inflammation. Specifically, it was hypothesized that young women with greater obesity exposure, that is, those who spent more time classified in the "obese" category across time points would evidence significantly higher levels of CRP at time point 10 than those with obesity at fewer time points, exclusive of weight cycling. It was likewise expected that independent of obesity exposure, the number of weight cycles and their amplitude would predict significantly higher levels of CRP at time point 10 exclusive of weight cycling (both amplitude and number of cycles). Importantly, these hypotheses function such that the variables must be evaluated while controlling for one another. Therefore, two similar but distinct regression analyses provided the structure to evaluate both hypotheses. These hypotheses were analyzed using hierarchical linear regression with CRP as the dependent variable. In the first, self-identified race, weight percentile at time point ten, and CESD score at time point 10 were entered in step one. In step two,

average amplitude of cycles and number of cycles were entered, and obesity exposure was entered in step three. The variables were entered in blocks in this manner to determine whether obesity exposure significantly predicted CRP independent of variance due to the weight-cycling related variables. A meaningful change in R^2 associated with the entry of the obesity exposure would indicate that exposure is uniquely associated with CRP. The unstandardized regression coefficient can also be evaluated to examine the significance of the magnitude of impact (i.e., the degree of change in CRP due to a one unit change in exposure). In the second analysis, the same controls were again entered in step one. However, this time, obesity exposure was entered in step two, and average amplitude of cycles and number of cycles were entered in step 3. This analysis, while similar to the first, was structured such that variance in CRP would be preferentially attributed to obesity exposure to determine if the weight cycling variables significantly predict CRP above and beyond obesity exposure, again as measured by the unstandardized regression coefficient.

In all regressions, any missing data were handled using listwise deletion. Because missing data was present only in heights and weights that were not gathered for five participants, imputation was deemed to be an inappropriate data cleaning strategy.

Aim 2

Second, this study sought to investigate the specific role of weight cycling on systemic inflammation. It was hypothesized that the relationships between CRP and the independent variables obesity exposure, average amplitude and numbers of cycles may vary with respect to each other. Thus, it was hypothesized that number and amplitude of cycles would yield a unique interactive effect on CRP at time point 10. Specifically, it

was expected that there would be a synergistic effect such that the unique effect of number of cycles (i.e., its slope) would increase as the amplitude of cycles increase. In other words, it is expected that the effect of cycling would be worse the larger the amplitude of those cycles. Additionally, it was hypothesized that a three-way interaction may exist among these variables. Specifically, it was expected that the effect of the two-way interaction among the two weight cycling variables on CRP would vary as the level of obesity exposure changed.

These hypotheses were tested with two hierarchical moderated multiple regression analyses. CRP once again was the dependent variable in this analysis. In the first analysis, the standardized version of the total number of cycles and amplitude of cycles variables were entered in step one, and the product of these standardized variables (i.e., the interaction term) was entered in step two. In the second regression, the standardized variables were entered in step one, all three of the two-way interaction terms (i.e., number of cycles by amplitude; number of cycles by exposure; and amplitude by exposure) were entered in step two, and the three-way interaction term was entered in step three.

Aim 3

An exploratory secondary analysis was conducted to examine the potential effects of peak-end weight difference on inflammation. Specifically, the effect of peak-end weight percentile difference was analyzed via regression using the continuous CRP variable as the dependent variable. CESD score, weight percentile at time point 10 and race were entered in step one as controls. Obesity exposure was added in step two, and peak-end weight difference was entered in step three.

Aim 4

This aim sought to use exploratory analyses to determine potential predictors of weight cycling itself. To determine potential predictors of weight cycling behavior, race was entered in step one, attempts to lose weight and drive for thinness average score were entered in step two, obesity exposure was entered in step three, and peak-end percentile difference was entered in step four. It was hypothesized that the above predictor variables would predict greater frequency of cycling across the study.

Aim 5

Finally, an exploratory mediation model was tested to elucidate the possible relationships among these variables. Although this analysis was exploratory in nature, the following model was tentatively hypothesized in the context of previous research that has suggested that drive for thinness may contribute to dieting behaviors that work counterproductively to support obesity development and maintenance (Higginson & McNamara, 2016; Neumark-Sztainer, Wall, Guo, Story, Haines & Eisenberg, 2006). Thus, it was hypothesized that drive for thinness would affect CRP, but entirely through the behavioral and psychological effects resulting from attempts to lose weight and the ensuing development and maintenance of obesity exposure over time. For the Aim 4 mediation analyses, bias-corrected bootstrapping methods were used in conjunction with the PROCESS macro for SPSS (Hayes, 2013). Figure 1 depicts this proposed model.

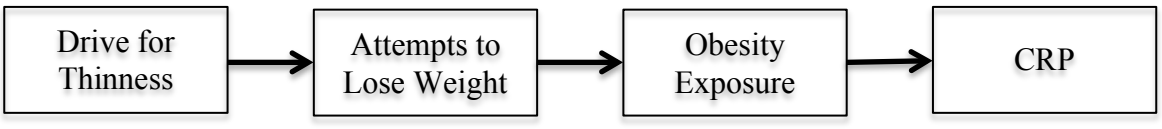

Figure 1. Proposed Serial Multiple Mediation Mode

CHAPTER 3 RESULTS

3.1 Demographics

The present sample included 120 girls, 60 of whom self-identified as Caucasian and 60 of whom self-identified as African American. Cases were included only if the girls had no history of ever smoking, and no history of pregnancy, and samples were selected intentionally to reduce the number of cases with substantial missing data. For cases that had unavoidable missing data, listwise deletion procedures were used for all analyses resulting in sample sizes of 115 or 120 for each of the following analyses. Five participants (4%) of the sample had one or more missing height or weight across the 10 time points. In this sample, ages ranged from 9 to 11 at time point one, and from 17.8 to 20.5 at time point ten. Weight status was determined by weight percentile as this sample was comprised of children. BMI below the 5^{th} percentile was considered underweight, BMI between the 5^{th} and 85^{th} percentiles was considered normal weight, BMI between the 85^{th} and 95^{th} percentiles were considered overweight, and BMI at or above the 95^{th} percentile was considered obese. Table 1 displays the distribution across weight category at each time point.

Table 1
Sample Distribution of Weight Category Across Time Points

Time Point	Percent Underweight	Percent Normal Weight	Percent Overweight	Percent Obese
1	2.5	50.8	20.8	25.8
2	1.7	50.8	19.2	28.3
3	1.7	53.4	17.8	27.1
4	0.8	48.3	25.0	25.8
5	0.0	50.8	22.9	26.3
6	0.0	52.5	21.7	25.8
7	0.8	55.1	18.6	25.4
8	0.8	52.1	22.7	24.4
9	0.0	57.1	15.1	27
10	0.0	57.5	17.5	25.0

3.2 Data Screening

Outlier analysis was conducted by comparing the 5% trimmed mean to sample mean for all variables entered into the regression and mediation analyses below, along with weight percentile scores at all ten time points. Additionally, extreme scores for these variables were identified and double-checked for accuracy. The results of this analysis identified no true outliers and therefore no data was screened from the study.

Multicollinearity diagnostics were also run to assess multicollinearity among average amplitude, obesity exposure, drive for thinness average, attempts to lose weight, total cycles and CRP value. Using a variance inflation factor cutoff of 3.0, the variables were systematically analyzed for multicollinearity using the multicollinearity diagnostic of a linear regression with those variables entered in step one, with each variable rotating as the dependent variable. The analysis found no VIF values over 3.0. Therefore, it is expected that the following coefficients are not significantly impacted by multicollinearity.

3.3 Descriptive Statistics

Descriptive statistics and zero-order correlations were computed to analyze associations among predictor and outcome variables. Table 2 shows descriptive statistics and correlations for these key variables. CRP level (mg/L) at time point 10 was not significantly associated with the total number of cycles. However CRP was significantly and positively associated with attempts to lose weight, race, obesity exposure, and with weight percentile at all time points (statistics displayed in Table 2). CRP was significantly yet negatively associated with peak-end weight percentile difference, and average amplitude of weight cycles. Total number of cycles was likewise negatively associated with peak-end percentile difference, as were attempts to lose weight, and drive for thinness average. Peak-end difference, as expected, was negatively associated as well with weight percentiles at all time points, as it was a measure of magnitude of weight lost. Total number of cycles was significantly and positively associated with obesity exposure and positively and significantly associated with weight percentile at all time points (see Table 2). Attempt to lose weight was strongly and positively associated with obesity exposure and positively associated with weight percentile at all time points. Finally, drive for thinness average was associated positively as expected with attempts to lose weight, obesity exposure, and weight percentile at all time points. For clarity, in Table 2 the weight-for-height percentiles at each time point are simply labeled Percentile 1 through Percentile 10.

Table 2
Descriptive Statistics and Zero-Order Correlations

	M	SD	1	2	3	4	5	6	7	8
1. CRP	3.39	5.15								
2. Total Cycles	0.66	0.74	0.60							
3. Obesity Exposure	2.6	3.62	0.42***	0.24**						
4. Drive for Thinness	6.03	4.84	0.12	0.14	0.42***					
5. Peak-End	28.16	19.87	-0.32***	-0.22*	-0.70***	-0.28**				
6. Attempts to Lose weight	2.18	1.87	0.28**	0.16	0.56***	0.60***	-0.47***			
7. Average Amplitude	2.98	2.18	-0.32***	-0.21*	-0.67***	-0.26**	0.98***	-0.47***		
8. Race	-	-	0.29**	0.10	0.42***	-0.05	-0.29**	0.13	-0.27**	
9. Percentile 1	68.21	30.88	0.32***	0.39***	0.60***	0.35***	-0.76***	0.58***	-0.72***	0.27**
10. Percentile 2	69.32	30.65	0.31**	0.34***	0.63***	0.38***	-0.75***	0.63***	-0.72***	0.29**
11. Percentile 3	70.42	29.27	0.27**	0.30**	0.63***	0.41***	-0.69***	0.63***	-0.66***	0.26**
12. Percentile 4	74.78	24.90	0.30**	0.32***	0.63***	0.40***	-0.68***	0.64***	-0.66***	0.31**
13. Percentile 5	73.98	25.07	0.27**	0.30**	0.65***	0.42***	-0.67***	0.61***	-0.65***	0.31**
14. Percentile 6	74.94	23.30	0.31**	0.31**	0.66***	0.46***	-0.61***	0.61***	-0.58***	0.27**
15. Percentile 7	74.43	23.95	0.28**	0.29**	0.64***	0.44***	-0.59***	0.53***	-0.56***	0.25**
16. Percentile 8	72.63	26.53	0.25**	0.29**	0.62***	0.40***	-0.60***	0.51***	-0.58***	0.27**
17. Percentile 9	72.32	26.60	0.28**	0.30**	0.63***	0.45***	-0.60***	0.59***	-0.60***	0.29**
18. Percentile 10	70.79	27.66	0.28**	0.24*	0.62***	0.43***	-0.59***	0.55***	-0.59***	0.30**

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

3.4 Analysis of Aims

Aim 1

This aim sought to test two hypotheses: 1) that obesity exposure would predict higher levels of CRP independent of amplitude and number of cycles, and 2) that the frequency of weight cycles and amplitude of cycles would predict CRP independent of obesity exposure. The results of these regressions are presented in Tables 3 and 4, respectively.

Regression 1. In the analysis addressing hypothesis one (Table 3), all three models were significant overall. The second model was not a significant improvement over the first, however the third model, including obesity exposure, was a significant improvement. In this third model the R^2 value of .19 indicated that the full model accounted for 19 percent of the variance in CRP. The change in R^2 for this step (.04) was significant, suggesting obesity exposure was a unique predictor of CRP at time point 10. While both race and T10 weight percentile were significant predictors of CRP in the first model, these fell below significance in later models. At no point were either average amplitude or total number of cycles significant in this analysis, nor did the inclusion of this functional set of variables lead to a significant improvement in model fit. Yet obesity exposure was a significant predictor of CRP, with its unstandardized regression coefficient ($b=0.38$) indicating that for every additional year of obesity exposure, CRP increased by 0.38 mg/L. The addition of obesity exposure to the model resulted in a significant increase in R^2 ($\Delta R^2 = 0.03$).

Table 3
Hierarchical Linear Regression Coefficients for Aim 1, Hypothesis 1

Model		*B*	*S.E.*	*β*	R^2	*F*
1					.14**	5.95**
	(Intercept)	-1.12	1.32			
	Race	2.4*	0.92	0.24		
	T10 Weight Percentile	0.04*	0.02	0.20		
	T10 CES-D	0.06	0.05	0.11		
2					.15	3.95**
	(Intercept)	1.28	2.19			
	Race	2.19*	0.93	0.22		
	T10 Weight Percentile	0.02	0.02	0.12		
	T10 CES-D	0.05	0.05	0.09		
	Average Amplitude	-0.36	0.26	-0.15		
	Total Cycles	-0.15	0.61	-0.02		
3					.19*	4.10**
	(Intercept)	1.02	2.16			
	Race	1.57	0.97	0.16		
	T10 Weight Percentile	0.02	0.02	0.04		
	T10 CES-D	0.04	0.05	0.08		
	Average Amplitude	-0.10	0.28	-0.05		
	Total Cycles	-0.25	0.60	-0.04		
	Obesity Exposure	0.38*	0.19	0.27		

Note. * $p < .05$; ** $p < .01$. $N = 115$.
Power for the above analysis was determined post-hoc using G-Power to be 0.88.

Regression 2. In the analysis addressing hypothesis two (presented in Table 4), the set of control variables again accounted for a significant portion of the criterion variance ($R^2 = .14$). The second model including obesity exposure yielded a significant increment in fit over the first model, uniquely accounting for an additional 4% percent of the variance in CRP. However the third model, including average amplitude and total number of cycles, was not a significant improvement on the second model ($\Delta R^2 = .01$). Yet obesity exposure remained a significant predictor of CRP even controlling for number of cycles and amplitude.

Table 4
Hierarchical Linear Regression Coefficients for Aim 1, Hypothesis 2

Model		*B*	*S.E.*	*β*	R^2	*F*
1					.14**	5.95**
	(Intercept)	-1.12	1.32			
	Race	2.4*	0.92	0.24		
	T10 Weight Percentile	0.04*	0.02	0.20		
	T10 CES-D	0.06	0.05	0.11		
2					.18**	6.17**
	(Intercept)	0.37	1.43			
	Race	1.57	0.96	0.16		
	T10 Weight Percentile	0.08	0.02	0.05		
	T10 CES-D	0.05	0.04	0.09		
	Obesity Exposure	0.40*	0.16	0.29		
3					.19	4.10**
	(Intercept)	1.02	2.16			
	Race	1.57	0.97	0.16		
	T10 Weight Percentile	0.01	0.02	0.04		
	T10 CES-D	0.04	0.05	0.08		
	Obesity Exposure	0.38*	0.19	0.27		
	Average Amplitude	-0.10	0.28	-0.05		
	Total Cycles	-0.25	0.60	-0.04		

Note. * $p < .05$; ** $p < .01$. $N = 115$.
Power for the above analysis was determined post-hoc using G-Power to be 0.88.

Aim 2

Aim two sought to test two hypotheses: 1) that the interaction between number of cycles and average amplitude would have a unique effect on CRP beyond their main effects, and 2) that a three-way interaction among number of cycles, amplitude, and exposure would be a significant predictor of CRP at time point 10. This aim was analyzed using two regressions, which are presented in Tables 5 and 6, respectively.

Regression 1. In the first analysis, the standardized version of the variables total number of cycles and amplitude of cycles were entered in step one, and the product of these standardized variables was entered in step two. In this model, the change in R^2 with

the addition of the interaction term in step two was not significant, adding nothing to the overall model ($\Delta R^2 = 0.0$). Thus, there was not a unique significant interaction effect of average amplitude and number of cycles on CRP.

Table 5
Hierarchical Linear Regression Coefficients for Aim 2, Regression 1

Model		*B*	*S.E.*	*β*	R^2	*F*
1					.10**	6.49**
	(Intercept)	3.39	0.45			
	Average Amplitude	-1.63**	0.46	-0.32		
	Total Cycles	-0.32	0.46	-0.01		
2					.10	4.30**
	(Intercept)	3.37	0.46			
	Average Amplitude	-1.63	0.46	-0.32		
	Total Cycles	-0.03	0.46	-0.01		
	Cycles X Amplitude	-0.09	0.46	-		

Note. * $p < .05$; ** $p < .01$. $N = 120$.
Power for the above regression was determined post-hoc using G-Power to be 0.95.

Regression 2. In this analysis, the standardized variables were entered in step one, all three of the two-way interaction terms were entered in step two, and the three-way interaction term was entered in step three. Results of this regression are shown in Table 6. As with the two-way interaction term, there was no significant change in R^2 in the third step, suggesting no significant three-way interaction effect on CRP.

Table 6
Hierarchical Linear Regression Coefficients for Aim 2, Regression 2

Model		*B*	*S.E.*	*β*	R^2	*F*
1					.18**	8.50**
	(Intercept)	3.39	0.43			
	Average Amplitude	-0.35	0.58	-0.07		
	Total Cycles	-0.24	0.45	-0.05		
	Obesity Exposure	1.99**	0.59	0.39		
2					.20	4.61**
	(Intercept)	2.65**	0.71			
	Average Amplitude	-1.02	0.80	-0.20		
	Total Cycles	-0.33	0.45	-0.06		
	Obesity Exposure	0.84	1.06	0.16		
	Amplitude X Exposure	-1.21	0.88	-		
	Amplitude X Cycles	0.29	0.62	-		
	Exposure X Cycles	-0.02	0.64	-		
3					.22	4.38**
	(Intercept)	2.14**	0.77			
	Average Amplitude	-1.54	0.86	-0.30		
	Total Cycles	-1.49	0.85	-0.29		
	Obesity Exposure	-0.15	1.22	-0.03		
	Amplitude X Exposure	-1.86	0.96	-		
	Amplitude X Cycles	-0.77	0.90	-		
	Exposure X Cycles	-1.88	1.31	-		
	Three-Way Interaction	-1.68	1.04	-		

Note. * $p < .05$; ** $p < .01$. $N = 120$.
Power for the above analysis was determined post-hoc using G-Power to be 0.87.

Aim 3

Aim 3 sought to test the hypothesis that peak-end percentile weight difference would predict CRP at time point 10. This aim was analyzed via regression using the continuous CRP variable as the dependent variable. The structural factors of CESD score, weight percentile at time 10 and race were entered in step one. Obesity exposure was added in step two, and peak-end difference was entered in step three. As in previous models, the addition of obesity exposure to the model resulted in a significant change in R^2, however the addition of peak-end difference did not significantly improve the model

($\Delta R^2 = 0.001$), suggesting that it was not a significant unique predictor of CRP at time point 10 above and beyond obesity exposure. The results of this regression are shown in Table 7.

Table 7
Hierarchical Linear Regression Coefficients for Aim 3

Model		*B*	*S.E.*	*β*	R^2	*F*
1					.14**	5.95**
	(Intercept)	-1.12	1.32			
	Race	2.4*	0.92	0.24		
	T10 Weight Percentile	0.04*	0.02	0.20		
	T10 CES-D	0.06	0.05	0.11		
2					.18*	6.17**
	(Intercept)	0.37	1.43			
	Race	1.57	0.97	0.16		
	T10 Weight Percentile	0.01	0.02	0.05		
	T10 CES-D	0.05	0.04	0.09		
	Obesity Exposure	0.40*	0.16	0.29		
3					.18	4.91**
	(Intercept)	0.81	2.20			
	Race	1.57	0.96	0.16		
	T10 Weight Percentile	0.01	0.02	0.04		
	T10 CES-D	0.04	0.05	0.09		
	Obesity Exposure	0.38*	0.19	0.27		
	Peak-End	-0.01	0.03	-0.03		

Note. * $p < .05$; ** $p < .01$. $N = 115$.
Power for the above analysis was determined post-hoc to be 0.90.

Aim 4

Aim four sought to use exploratory analysis to determine potential alternative predictors of weight cycling itself. To determine potential predictors of weight cycling behavior, race was entered in step one, attempts to lose weight and drive for thinness average score were entered in step two, obesity exposure was entered in step three, and peak-end percentile difference was entered in step four. It was hypothesized that the

above predictor variables would predict greater frequency of cycling across the study. However, no models were significant, and the full model accounted for only 7% of the variance in cycles. Results are presented in Table 8.

Table 8
Hierarchical Linear Regression Coefficients for Aim 4 Regression

Model		*B*	*S.E.*	*β*	R^2	*F*
1					0.01	1.24
	(Intercept)	0.58	0.09			
	Race	0.15	0.14	0.10		
2					0.04	1.48
	(Intercept)	0.42	0.13			
	Race	0.14	0.14	0.10		
	Attempts to Lose Weight	0.03	0.05	0.09		
	Drive for Thinness	0.02	0.02	0.10		
3					0.06	1.85
	(Intercept)	0.48	0.13			
	Race	0.02	0.15	0.02		
	Attempts to Lose Weight	0.00	0.05	0.01		
	Drive for Thinness	0.01	0.02	0.06		
	Obesity Exposure	0.05	0.03	0.21		
4					0.07	1.60
	(Intercept)	0.63	0.23			
	Race	0.03	0.15	0.02		
	Attempts to Lose Weight	-0.01	0.05	-0.01		
	Drive for Thinness	0.01	0.02	0.07		
	Obesity Exposure	0.03	0.03	0.14		
	Peak-End Difference	0.00	0.01	-0.10		

Note. * $p < .05$; ** $p < .01$. $N = 120$.
Power for the above analysis was determined to be 0.91 post-hoc.

Aim 5

In the serial mediation model (shown above in Figure 1) there was a significant direct effect from drive for thinness to weight loss attempts, $b = 0.23(0.029)$, 95% CI

[0.17, 0.29]. There was likewise a significant direct effect from weight loss attempts to obesity exposure, $b = 0.93(0.18)$, 95% CI [0.56, 1.29]. Accounting for weight loss attempts, the direct effect from drive for thinness average to obesity exposure dropped below significance, indicating full mediation through attempts to lose weight. As expected there was also a direct effect from obesity exposure to CRP, $b = 0.57(0.14)$, 95% CI [0.28, 0.85]. There was no significant direct effect of weight loss attempts on CRP when accounting for obesity exposure, likewise indicating full mediation through obesity exposure. In this model the direct effect from drive for thinness to CRP was not significant, again indicating full mediation through the serial mediators. While the two specific indirect effects from drive for thinness to CRP through attempts to lose weight and obesity exposure were nonsignificant, the indirect effect of drive for thinness on CRP through both attempts to lose weight and obesity exposure was significant, $b = 0.12$, 95% CI [0.044, 0.26]. Overall, the sum of indirect effects on CRP was also significant, $b = 0.26$, 95% CI [0.10, 0.48]. The model overall accounted for about 19% of the variance in CRP ($p < .0001$). Results are shown in Table 9 and summarized in Figure 2.

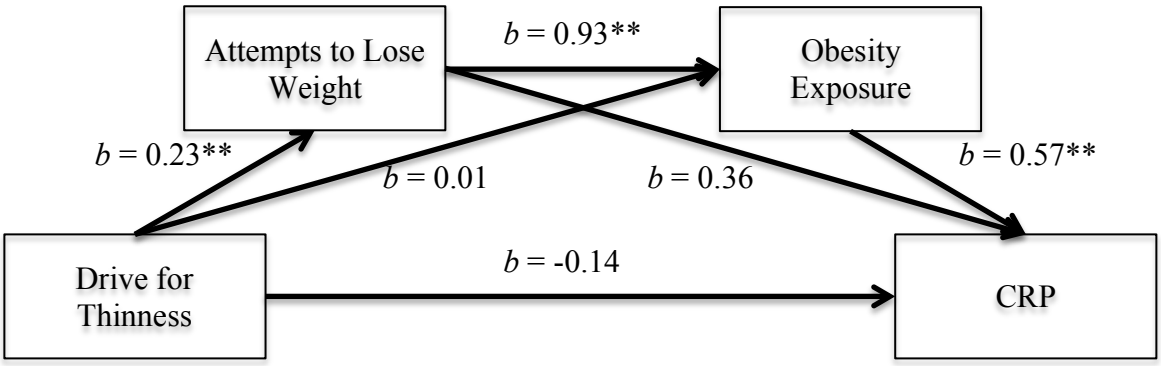

Figure 2. Unstandardized regression coefficients for the relationship between drive for thinness and CRP, as mediated by attempts to lose weight and obesity exposure. Hypothesized indirect effect $b = 0.12$. *$p < .05$, ** $p < .01$.

Table 9

Regression Coefficients, Standard Errors, and Model Summary Information for the Serial Multiple Mediator Model Depicted in Figure C.

	Consequent											
	M_1 (Weight Loss Attempts)				M_2 (Obesity Exposure)				Y (CRP)			
Antecedent		Coeff.	SE	*p*		Coeff.	SE	*p*		Coeff.	SE	*p*
X (Drive for Thinness)	a_1	0.23	0.029	<0.0000	a_2	0.097	0.071	0.18	c'	-0.14	0.11	0.23
M_1 (Weight Loss Attempts)		-	-	-	a_3	0.93	0.18	<0.0000	b_1	0.36	0.32	0.25
M_2 (Obesity Exposure)		-	-	-		-	-	-	b_2	0.57	0.14	<0.0001
Constant	i_{M1}	0.79	0.22	1.2	i_{M2}	0.79	0.22	0.0005	i_Y	1.94	0.72	0.0084
		R^2 =0.36				R^2 = 0.32				R^2 = 0.19		
		$F(1, 118) = 65.46$,				$F(2, 117) = 27.49$,				$F(3, 116) = 9.02$,		
		$p = 0.0000$				$p = 0.0000$				$p = 0.0000$		

Note. $N = 120$

CHAPTER 4: DISCUSSION

In the context of growing public health concerns regarding pediatric obesity development and maintenance, research is seeking to further elucidate the complexities of apparent links among obesity and chronic diseases in later life. Cardiovascular disease continues to be the leading cause of death for women (CDC, 2016). At the same time, an increasing focus on lifestyle modifications like diet and exercise interventions, particularly in children and young adults, has led to important questions regarding the efficacy of these interventions. It has been suggested that an excessive focus on diet and weight intervention may paradoxically contribute to morbidity risk through weight cycling behaviors and associated metabolic changes. The present study sought to investigate further two specific aims related to this topic: in what way weight cycling behaviors and chronic obesity may contribute to chronic disease trajectory in young girls and women.

4.1 Obesity Exposure and Systemic Inflammation

This study demonstrated that obesity exposure was a significant and meaningful predictor of CRP above and beyond a girl's most recent weight. This suggests that obesity, like other risk factors in chronic disease (smoking, sitting, etc.) may be more harmful in higher dosages. This dose effect is startling in its strength: in the present study models suggested that for each additional year of obesity exposure, girls could expect to increase their CRP in early adulthood by between .38 and .40 mg/L, depending on model.

Of note, widely accepted clinical cutoffs for CRP in adults suggest that levels between 1.0 and 3.0 mg/L are associated with increased cardiovascular disease risk (Yeh & Willerson, 2003). Moreover, this data supports the "Updated Harrison" model, in which exposure to obesity over time is conceptualized as it's own risk factor in the development of chronic diseases like CVD.

4.2 Weight Cycling and Systemic Inflammation

Importantly, the present study found no evidence of impact of weight cycling factors (number of cycles, amplitude of those cycles, or interaction of these factors) on CRP early in adulthood. In fact, in the present sample weight cycling was associated *negatively* with CRP in early adulthood. The present study likewise failed to find evidence of an effect of peak-end difference on CRP. The present study and current literature stands in contrast to initial investigations of weight variability. The Framingham Study found that in adults, variability in weight, as measured similarly to the present study, was related to cardiovascular mortality risk (Lissner et al., 1991). Similar findings were evidenced in the NHANES study, which benefitted from the use of a nationally representative sample (Diaz, Mainous & Everett, 2005).

Yet some important differences within the weight cycling literature may provide clues as to the source of these discrepancies: the present study was in a subsample of young girls, and it is possible that weight variability, like obesity exposure, may take time to manifest its actual effects. Additionally, while the present study used weight-for-height percentiles to calculate obesity exposure, weight cycling was defined on the basis of weight change, and therefore some amount of normative developmental change may have impacted measurement of that construct. Likewise, the present study was designed to

predict CRP, not cardiovascular mortality/morbidity directly. It is possible that weight cycling indeed does represent a risk for cardiovascular disease and mortality, but that CRP is not the correct biomarker that accounts for this physiological process.

Alternatively, some researchers have suggested that weight cycling behavior, rather than being metabolically risky, may be protective (Bosy-Westphal, Kahlofer, Lagerpusch, Skurk & Muller, 2015). Although grossly weight cycling may promote body weight gain overall, the authors suggest that weight cycling may result in more subtle metabolic changes, such as in insulin use and fat deposition changes that account for decreased metabolic risk overall. Thus, as of yet it is not clear what accounts for weight changes across cycles: lean body mass vs. fat, and what types of fat (visceral vs. subcutaneous). The question remains open, as the present state of the literature does not yet account for these discrepant findings. Indeed, it remains possible that two processes could simultaneously be at work: weight cycling may increase cardiovascular risk over long periods of time while simultaneously producing protective counter-effects in the short-term, like a reduction in visceral fat deposition and CRP. These short-term changes may be evidence of a systemic attempt to maintain homeostasis that, over time, yields to increasing disease risk. Future studies may find it beneficial rather than assessing weight cycling broadly, to assess fat deposition changes in response to diet and/or restraint behaviors across time, while attempting to predict both long-term cardiovascular disease and mortality, and also short and long-term biomarkers like insulin resistance, lipid profiles and CRP.

4.3 Predictors of Weight Cycling

The present study was unable to determine significant predictors of weight

cycling in this sample. Importantly, weight cycling is a largely understudied construct, and is a research area particularly prone to difficulties with data collection (e.g. response bias, inaccurate participant recall, etc.). Yet some preliminary evidence may suggest that predictors of weight cycling may be more subtle and behavioral in nature than the present study was able to detect. For instance a study by Tanaka and colleagues (2004) presented evidence that particular day-to-day weight variations may influence weight cycling longitudinally. That is, small weight variations detected by weighing oneself at night may predispose women to engage in weight cycling behaviors more than small day-to-day weight variations at other times of day. The present study did not have the temporal resolution necessary to detect these small variations and test them as predictors of weight cycling.

4.4 Relationship between Drive for Thinness and Systemic Inflammation

Notably, the present study also suggested a mediated link between drive for thinness and CRP through attempts to lose weight and obesity exposure. Two possible interpretations of this finding can be considered. First, it is possible that a drive for thinness results in behavioral modification attempts and psychological changes that in turn produce development and maintenance of obesity over time, thus impacting CRP. Recent evidence has examined dieting vs. restricted eating behaviors. In a systematic review of these studies, Lowe, Doshi, Katterman and Feig (2013) found robust evidence that dieting predicts weight gain, even in small samples with limited power. However, their analysis also identified that there may be an important difference between dieting as a construct and simple eating restraint.

Broadly, the difference may be with respect to individual predisposition to type of

restraint, and the quality of the restraint itself. In colloquial terminology, dieting may represent what the lay public may consider “crash dieting” whereas restraint may be conceptualized more as “watching one’s figure”. This perspective represents an extension of the original Restraint Theory of weight re-gain (Herman and Mack, 1975). Crash diets and resulting weight re-gain could also be a secondary outcome of high initial efficacy at weight-loss. Those who have experienced salient and “easy” weight loss initially may underestimate the challenges to more long-term weight loss, resulting in inconsistent eating habits (Abildso et al., 2014).

However, the directionality of the relationship between obesogenic environment and diet is also a consideration. It is also feasible that those in highly obesogenic environments perceive the likelihood and salience of future weight gain more acutely, resulting in more extreme dieting attempts (Lowe, Doshi, Katterman & Feig, 2013). Young girls in obesogenic environments, and/or with behaviors that may predispose them to obesity development and maintenance over time could be aware of their risk factors. Despite knowing this and developing intent and desire to lose weight (drive for thinness and attempts to lose weight), these individuals may either fail to lose weight, or be in an environment that makes altering this trajectory difficult. In this way diet behavior could be viewed as a mere proxy for obesogenic environment. Future research should investigate the directionality of the relationship between diet behavior and obesity, taking into account exposure to an obesogenic environment as one potential predictor of perceived need to diet. Moreover, within the present literature it is unclear how physical activity may play a role in weight trajectories for young women, including in the context of weight cycling. For instance, in addition to the physiological changes associated with

exercise, some evidence suggests that exercising may help develop self-efficacy that can generalize to successful health behavior changes more broadly (Annesi, 2012).

With either interpretation, the results of this study suggest that public health officials and providers consider two important and concerning factors: the more time a young girl spends obese, the more she may be at risk, and, simultaneously, her intent to be thin and certain attempts at behavioral modification may only serve to further increase risk.

4.5 Limitations and Future Directions

Several important limitations should be considered when contextualizing this work. First, the original data provided weight and height information in one-year intervals. This poor temporal resolution may therefore inadequately capture rapid changes in BMI. Conceivably, weight cycling may occur rapidly across the span of weeks to months; therefore this study may not have adequately captured the true rate of weight cycling for the current sample. Moreover, young girls, unlike adults, may actually have limited ability to control their food intake. In the current sample, the mean amplitude of weight variability (amplitude of cycles) was 2.98 kg, or about 6.6 pounds, well below the 10-pound cutoff for a defined weight cycle used in this study. As parents and schools enforce eating rules, girls may be inclined to lose weight, yet unable to alter their behaviors.

An additional limitation is that drive for thinness was averaged across the ten time points to reflect each participant's mean manifestation of this construct during the study period. Future studies could consider using multilevel modeling analysis to assess the effect of both drive for thinness and attempts to lose weight at various time points on

weight for height percentile, or other variables present in this data set.

Likewise, this study failed to take into account specific types of diet and exercise patterns. Some recent evidence has suggested that health behavior change in the context of body acceptance (Health at Every Size® Intervention) may produce more stable behavior changes that serve to decrease disease risk, and, secondarily, produce body weight reductions (Ulian et al., 2015). Further research examining whether obesity exposure is still risky, even when girls engage in non-dieting health behaviors (adhering to a Mediterranean diet, adhering to CDC exercise recommendations, etc.) may be warranted. Thus, even in the absence of weight changes, girls could be counseled to focus on the health-promoting effects of their behavior changes, and track more relevant markers of future disease risk than weight, like metabolic syndrome signs and symptoms.

As discussed above, future studies of weight cycling should focus on fat deposition changes, rather than BMI or weight changes overall. Likewise, diet and eating restraint should be investigated with respect to their effect both short term and long-term on metabolic biomarkers and cardiovascular morbidity and mortality. Future studies should also expand upon physiological processes underlying caloric restriction as an attempt to lose weight and its effect on weight gain and obesity maintenance. For instance recent research has suggested that Leptin may mediate the relationship between weight loss attempts and increased BMI, by altering neuropsychiatric processes like mood and craving. (Strasser, Berger & Fuchs, 2015).

4.6 Conclusions

Research is beginning to conceptually separate obesity and health, yet this research continues to collide both with growing evidence of obesity risk and with societal

thinness ideals and individual experiences of body dissatisfaction. A “goldilocks zone” of intake wherein individuals are cautious of developing and maintaining excessive adiposity, yet avoid developing disordered/overly restrictive eating patterns, has been elusive. The present study suggests that indeed exposure to excess adiposity may be very risky, and this risk may emerge early in life. Yet, striving for thinness and attempts to lose weight may not be indicated either, at least in their current forms (i.e. dieting).

Overall, the results of this study call for a change in perspective away from individual behavior change and focus on weight loss toward a compassionate approach that includes examination of obesogenic environments and societal factors that promote obesity, including, troublingly and counter-intuitively, thinness ideals. This study highlights how, for young women, a frustrating double bind may be present. Despite knowing the risks of excess body weight, girls may find themselves struggling to change their weight trajectories, and the very behaviors they attempt may simply fail them, or worse, increase risk.

Taken together, this picture suggests that public health officials search for creative ways to improve health, moving away from traditional, restrictive diet approaches, and away from encouraging girls to seek thinness. Alternative approaches with emerging evidence for their health promoting effects may be the Health at Every Size® approach, which may reduce disease risk through body acceptance and behavioral modifications *not* directly intended to reduce obesity exposure.

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