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Inflammation, Executive Function, And Adiposity In Children With Or At Risk For Obesity

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INFLAMMATION, EXECUTIVE FUNCTION, AND ADIPOSITY IN CHILDREN WITH OR AT RISK FOR OBESITY

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MEDICAL CLINICAL PSYCHOLOGY

ABSTRACT

Obesity is associated with executive function (EF) deficits across the lifespan. Higher body mass index (BMI), greater severity of obesity, and poorer adherence and weight outcomes in obesity treatment have all been associated with EF deficits. Adult literature has begun to emphasize neuroinflammation in obesity as a possible pathway to later cognitive impairment. However, the pediatric obesity literature has yet to even establish associations between peripheral inflammation and EF. Thus, the present study aimed to examine associations and variability in inflammatory biomarkers, EF, and adiposity in children with or at risk for obesity. Additionally, inflammation was examined as a mechanism of the relationship between adiposity and EF. Results demonstrated mixed effects, with several significant associations found that suggest increased adiposity is associated with increased inflammation, which in turn is associated with poorer EF. Further, several analyses suggested that inflammation explains the relation between adiposity and EF, although results were mixed. With replication, these findings will inform future efforts to identify and target children at risk for obesity-related chronic illnesses by elucidating novel treatment targets. Further, results provide foundational evidence for future efforts to establish comprehensive psychoneuroimmunologic models of pediatric obesity.

Keywords: psychoneuroimmunology; pediatric psychology; pediatric obesity; chronic inflammation; executive function

DEDICATION

For my mother, Allison Prendergast, whose breast cancer survivorship journey revealed to me the power of inflammatory processes, and the equally powerful processes of strength, faith, and resiliency.

ACKNOWLEDGMENTS

My sincerest appreciation goes to my mentor, Dr. Marissa Gowey, for her excellent guidance on this project and commitment to my growth as a pediatric psychologist and young professional woman. Further, I extend my appreciation to my thesis committee, whose generous willingness to share their expertise was paramount to the success of this project. Finally, my deepest gratitude goes to my parents, Michael and Allison Prendergast, and fiancé, Connor King, for believing in me and for demonstrating their endless support of my education and career.

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Introduction

Obesity

Pediatric overweight/obesity affects 35.1% of children in the U.S. and is a significant predictor of adult overweight/obesity which affects 70.7% of Americans (Skinner et al., 2018). Even children with above average BMI within the 'normal range' have increased risk for overweight/obesity and hypertension as adults (Field, Cook, & Gillman, 2005). Both childhood and adult obesity are associated with increased incidence of cardiovascular disease, cancer, diabetes, and Alzheimer's disease. While disease associated cognitive impairments often receive attention in aging populations, increased risk for such conditions may begin quite early in individuals with overweight/obesity (herein referred to as obesity for simplicity) (Miller and Spencer, 2014). Indeed, the literature has generated robust support that children with obesity demonstrate EF deficits— or deficits in higher-level cognitive skills that allow a person to plan, organize, and complete complex tasks in an efficient manner. EF includes skills such as problem solving, reasoning, attention, planning, organization, and time management.

Obesity and Executive Function

Executive function deficits have been identified in individuals with obesity in particular domains, such as inhibitory control, cognitive flexibility, and delay discounting (Reinert et al., 2013; Hayes et al., 2017). In the context of behavioral weight management, this may translate to cognitive and behavioral processes that limit weight management

success. Greater difficulties may arise resisting palatable "unhealthy" foods readily available in the environment and problem-solving when barriers arise in carrying out pre-planned physical activity or meals. There may be greater likelihood to choose immediate, small-scale reinforcing behavior (e.g., watching TV and eating high calorie-low nutrient foods for immediate pleasure) over less immediate, large-scale reinforcing behavior (e.g., being physically active and eating low calorie-high nutrient foods for long-term health and disease prevention). Thus, EF deficits are predictive of lower adherence and poorer behavioral weight loss outcomes in treatment-seeking youth with obesity (Naar-King et al., 2016; Cortese et al., 2013).

The association between EF and obesity is likely bi-directional, such that executive dysfunction predicts obesity development (Graziano et al., 2013), and obesity may further compound EF deficits (Liang et al., 2014). Thus, untreated pediatric obesity is likely associated with EF impairments contributing to maintenance of the disease and increased risk for chronic diseases in adulthood. Furthermore, youth with obesity and EF deficits are at greater risk for dysregulated eating behavior, behavioral problems, parental distress, poorer health-related quality of life, and impairment in school performance (Gowey et al., 2017; Gowey et al., 2018; Kamijo et al., 2012). While pediatric obesity prevention efforts are underway, it is imperative that we simultaneously identify effective options for improving treatment outcomes in children with obesity.

Obesity and Inflammation

One mechanism by which obesity likely increases executive dysfunction is through chronic low-level inflammation (Miller and Spencer, 2014). Inflammation is the body's

natural defense mechanism, responsible for responding to harmful stimuli and beginning the healing process (Pahwa and Jialal, 2018). Acute inflammation occurs rapidly in response to tissue damage due to stimuli such as injury or infection lasting for a few days, while chronic, low-level inflammation occurs more slowly and lasts for months or years. In the case of overweight and obesity, chronic, low-level inflammation occurs due to an excess of adipocytes, or fat cells, which are endocrine organs releasing inflammatory agents, such as cytokines. This is because the types of cytokines secreted and subsequent effect of these agents on surrounding tissue and the body as a whole can change depending on the amount of adipocytes and location of adipose tissue (Ouchi et al., 2011). In obesity (where there is greater quantity of adipocytes across many locations of adipose tissue) there is an imbalance of pro- and anti-inflammatory cytokine release from adipocytes that leads to chronic, low-level inflammation (Ouchi et al., 2011). Recent literature has examined relations between obesity and inflammation in children, finding increased risk for inflammatory marker levels indicative of cardiovascular disease risk in children with obesity (Selvaraju et al., 2019) as young as 3 years old (Skinner et al., 2010). Another study found that greater adiposity is predictive of elevated inflammation (measured via serum C-Reactive Protein; CRP) even when excluding for children endorsing symptoms of illness or infection the week before and after (Parret et al., 2010). These inflammatory levels were below the threshold reflecting an acute inflammatory response (10 mg/L), thus indicating that higher percent body fat predicts the presence of chronic, low-level inflammation in prepubescent children (N=45) (Parret et al., 2010). Additionally, weight status and adiposity may have different relations with other markers of inflammation, as one study found that inflammation decreases with increases in adiposity in children without obesity,

while children with obesity showed increases in inflammation with increases in adiposity (Niemiro et al., 2016). The authors note this may be due to the measure of inflammation used, Circulating Progenitor Cells, which release agents having both pro- and anti-inflammatory effects, and thus may not be indicative of the imbalance between these agents that occurs in obesity. Another study found no association of salivary IL-6 and TNFa with BMI, potentially because the salivary cytokines may not be representative of adipokines secreted from adipose tissue, potential confounds of oral diseases influences salivary measure, and the sample being comprised of athletes (da Silva Peres et al., 2019). Adding to the already complex picture, other studies have found that children's fitness level, across levels of weight status or adiposity, can attenuate some inflammatory markers (Gil-Cosano et al., 2019; Hosick et al., 2013).

Inflammation and EF

Some literature has examined inflammation and EF in children but primarily in other disease populations (i.e., children with sickle cell, psychopathology, and preterm births; Andreotti et al., 2015; Cullen et al., 2017; Kuban et al., 2017). In children with and without indication of psychopathological symptoms, higher chronic inflammation was found to be associated with lower scores in EF domains of inhibition and switching (measured via the Delis–Kaplan Executive Function System [D-KEFS]), but not verbal working memory (measured via Wide Range Assessment of Memory and Learning 2nd Edition [WRAML2]; Cullen et al., 2017). Additionally, they found higher CRP to be predictive of poorer performance on a verbal fluency task of EF on the D-KEFS (Cullen et al., 2017). Of note, they did not find elevated CRP in children with obesity (N=5) versus

those without obesity (N = 99, N = 15 overweight and N = 84 with BMI in expected range) in their sample, which they indicated was contrary to previous findings and posited this was due to the underrepresentation of children with obesity as well as differential criteria used for determining overweight/obesity in London, where the study was conducted, versus the United States, where previous literature has indicated this. Taken together, this literature supports associations between adiposity and chronic inflammation as well as chronic inflammation and EF tasks, but highlights the need for additional research examining the potential for inflammation to serve as a mechanistic agent in obesity-associated executive dysfunction.

Obesity, Inflammation, and EF — Non-Mechanistic Findings

The literature examining inflammation *and* EF in relation to obesity—without a mechanistic approach (i.e., without a mediation design) —is focused primarily on adults and particularly bariatric surgery populations (Hawkins et al., 2015). One study in adults showed that subjects with obesity and chronic inflammation made more errors on a task measuring the EF domain of flexibility/shifting (intra/extra-dimensional set shifting test, extracted from the Cambridge Neuropsychological Test Automated Battery, CANTAB) compared to subjects without chronic inflammation both with and without obesity. A recent review of inflammation, cognitive impairment, and obesity points toward neuroinflammation as a predictive factor of executive deficits (Miller and Spencer, 2014). They note that neuroinflammation in the brain can lead to neurodegeneration and altered brain plasticity which impact cognitive functioning. In fact, a recent study in rats demonstrates similar responses to the western diet in both adipose tissue and the brain,

including increased TNFa in the hippocampus (Mazzoli et al., 2020). In the case of obesity, this neuroinflammation can result directly from enteric nervous system signaling (i.e. the gut-brain axis) and/or from peripheral chronic inflammation (typically measured in the bloodstream, as opposed to neuroinflammation which occurs in the brain) and both are ultimately related to excess caloric intake and type of diet (i.e. high fat, Western diets; Guillemot-Legris & Muccioli, 2017). Chronically taking in more calories than one burns alters homeostasis in several organs (including adipose tissue as mentioned before), ultimately leading to a shift in these organs such that a pro-inflammatory profile becomes dominant (Shu, Benoist, & Mathis, 2012). These shifts include increased secretion of pro-inflammatory cytokines TNFa and IL-6, which have been more commonly studied in relation to obesity and EF, and these cytokines trigger the liver to produce C-Reactive Protein (CRP), which has been perhaps the most studied pro-inflammatory biomarker in relation to obesity and EF deficits as well as their pathophysiology (Shu et al., 2012; Guillemot-Legris & Muccioli, 2017; Parret et al., 2010; Skinner et al., 2010). The recent review concluded that neuroinflammation represents a plausible pathway to cognitive impairment in obesity in adults but reflected that this is under-researched in children (Miller and Spencer, 2014). Current research in children has only utilized measures *related* to cognitive and inflammatory outcomes of interest with inconclusive results.

Non-mechanistic findings in children have been difficult to interpret due to utilization of measures such as cognitive fatigue rather than EF and more general inflammatory markers rather than pro-inflammatory markers documented to be elevated in obesity. For example, one study examining associations of weight status, EF, and inflammatory markers in children reported significantly different correlations between

Circulating Progenitor Cell quantity (CPC; a marker of the inflammatory response less commonly examined in the obesity literature) and executive processing (Woodcock Johnson III Tests of Executive Processing; also less commonly used for assessing EF) in male children aged 8-10 with overweight and obesity (n=11; positive association) and without obesity (n=16; negative association), such that increases in CPCs were related to decreases in EF in those without obesity and increases in EF in those with obesity (Niemiro et al., 2016). The different correlations of inflammatory markers with executive processing in children with versus without obesity disappeared when abdominal adiposity was controlled for, indicating adiposity may be an important contributor to the relationship between inflammation and EF across weight status groups (Niemiro et al., 2016). However, these findings are difficult to interpret with relevance to the present study as CPCs interface with many body systems and both measures are less commonly used, not to mention this finding has yet to be examined across genders, in groups larger than N = 16, or replicated. Another study examining all three variables of interest reported that higher hsCRP was predictive of more anhedonia on a measure of cognitive fatigue (Peds-QL, Fatigue Scales) in children with obesity (N=41), however this relationship was not maintained after controlling for adiposity (Barat et al., 2016). Anhedonia/motivation was a component of the Peds-QL, Fatigue Scale extracted via Principle Component Analysis, along with dimensions of concentration, energy, perceived cognitive efficiency, and sleep/rest which did not show significant associations with hsCRP. This may indicate that adiposity has an influence on both CRP and cognitive fatigue, although adiposity, in comparison to CRP, may be more robustly associated with cognitive fatigue. This is consistent with the idea that neuroinflammation at least partially mediates the relation of adiposity and cognitive

deficits. Granted, this finding may or may not generalize to the concept of EF, as the cognitive measure focused on motivation and anhedonia aspects of cognitive fatigue and was measured using a subscale that has not been investigated outside of this study. However, a recent review has noted that ample evidence supports executive dysfunction in children with versus without obesity but mixed findings have emerged for cognitive function more globally between these groups in children, suggesting we might suspect more robust associations when considering EF deficits rather than cognitive deficits more broadly (Miller and Spencer, 2014). Overall, literature examining adiposity, inflammation, and EF supports that neuroinflammation may mediate the relationship between adiposity and EF in adults warranting investigations using analyses capable of assessing this, and that findings in children are inconclusive but warrant similar further investigation.

Obesity, Inflammation, and EF — Mechanistic Findings

Shifting toward the few subsequent findings examining mechanistic models (i.e., studies examining these relations using a mediational design), one study of older adults did find inflammation partially explains the relationship between obesity and cognitive deficits (Gunathilake et al., 2016). The only mechanistic approach to date in children investigated CVD risk factors including CRP as a mechanism of the relationship between *weight status* and *cognitive* function in children with obesity, finding significant indirect effects of CRP (Tung et al., 2018), pointing to gaps in further knowledge. For instance, the measure of cognitive function used by Tung and colleagues (WISC-IV composite derived from selected subtests) did not isolate EF or examine results by cognitive domain, which—as noted above— has led to different patterns of results in the literature. Thus, additional work

is needed that utilizes EF measures to determine the associations between specific EF domains and CVD risk factors in children with obesity, particularly inflammatory markers, which will expand upon the current understanding of this mechanistic relationship.

Collectively, these findings demonstrate that inflammation may partially mediate weight status's effect on cognitive function. However, the status of inflammation as a mediator of adiposity's effect on EF (as opposed to weight status and more global cognitive functioning) has yet to be determined. The literature to date provides grounds from which to investigate— and highlights the clinical importance of examining— the proposed mechanistic model. The knowledge sought in this line of research has potential value in elucidating novel biomarkers of children at risk for EF deficits which could serve as targets to improve obesity treatment response and related chronic disease prevention.

Innovation

To our knowledge, this is the first study to explore associations between inflammatory cytokines including tumor necrosis factor alpha, interleukin 6, and c-reactive protein (TNF-a, IL-6, and CRP) and EF in pediatric obesity, at ages 8-12 in particular. This age group represents a critical period for behavioral intervention for obesity as these children generally do not yet have established health habits and their EF organization/regulatory skills are emerging and newly maturing, making them more amenable to change. If inflammatory biomarkers can be identified in this critical age range for treatment, it may have implications for optimizing treatment and thereby capitalizing on benefits of behavior change such as decreased long-term disease risk. Thus, this would represent the first evidence of potential signals of EF biomarkers in pediatric obesity that

could be incorporated into a precision medicine model for tailoring treatment approaches with further research. The evidence that does exist demonstrating the relationship between obesity, inflammation, and EF in adults and children has shown great heterogeneity in terms of the inflammatory and cognitive measures used, so the present study will use three *prominent* measures of inflammation and two prominent measures of EF to facilitate comparisons across the literature. Additionally, BMI has been the predominant measure of weight status to assess these relationships, although limitations of the measure BMI have been documented repeatedly, particularly for ethnic/racial minorities (who comprise at least 50% of our sample) (Gujral et al., 2017; Freedman et al., 2008). The current study expands on the literature by using adiposity measures (of the whole body, as opposed to abdominal adiposity only in Niemiro et al., 2016), which are considered more sensitive for diverse groups for weight status in addition to zBMI. The proposed study will also add to the literature by excluding children in the 'underweight' range (i.e. BMI < 5th percentile) due to identified health concerns at this BMI range which may account for increased inflammation. This distinguishes from a recent study which included children below the 5th percentile, which may have contributed to the study findings that higher inflammation was associated with lower BMI in children without obesity (i.e., BMIs < 85th percentile) (Niemiro et al., 2016). Further, we are also only including children at risk for or with obesity, adding to the literature by assessing children at risk for obesity – in addition to those with obesity – who are not typically considered in other studies as at-risk, although there is literature to support that they are at risk. The current study uses both self-report and performance-based measures of EF, to facilitate comparison to the literature and

rigorous neuropsychological measurement. Finally, the current study is the first to examine inflammation as a mechanism of the relationship between adiposity and EF in children.

Project Aims & Hypotheses

Aim 1

Aim 1 proposed to examine the associations between body composition and inflammation in children aged 8-12 with BMI ≥ 50th%. We hypothesized that higher percent body fat measured by DXA will show signals of association with higher inflammation, indicated by greater levels of TNF-a, IL-6, and CRP, in children with BMI ≥ 50th%.

Aim 2

Aim 2 explored the associations and levels of variability between inflammation and EF in children aged 8-12 with BMI ≥ 50th%. We hypothesized that signals of chronic inflammation, indicated by higher levels of TNF-a, IL-6, and CRP, would be identified in association with poorer EF, indicated by lower T-scores on the NIH Toolbox Cognitive Battery EF subtests and higher T-scores on the BRIEF 2 subscales in children with BMI ≥ 50th%, and we classified this hypothesis as Aim 2a. We further hypothesized that the strength of the relation between signals of chronic inflammation, indicated by higher levels of TNF-a, IL-6, and CRP, and EF would be dependent upon adiposity, such that chronic inflammation and EF would show a stronger relation in children with higher fat mass and higher levels of percent body fat in both total body less head and abdominal regions, and we classified this hypothesis as Aim 2b.

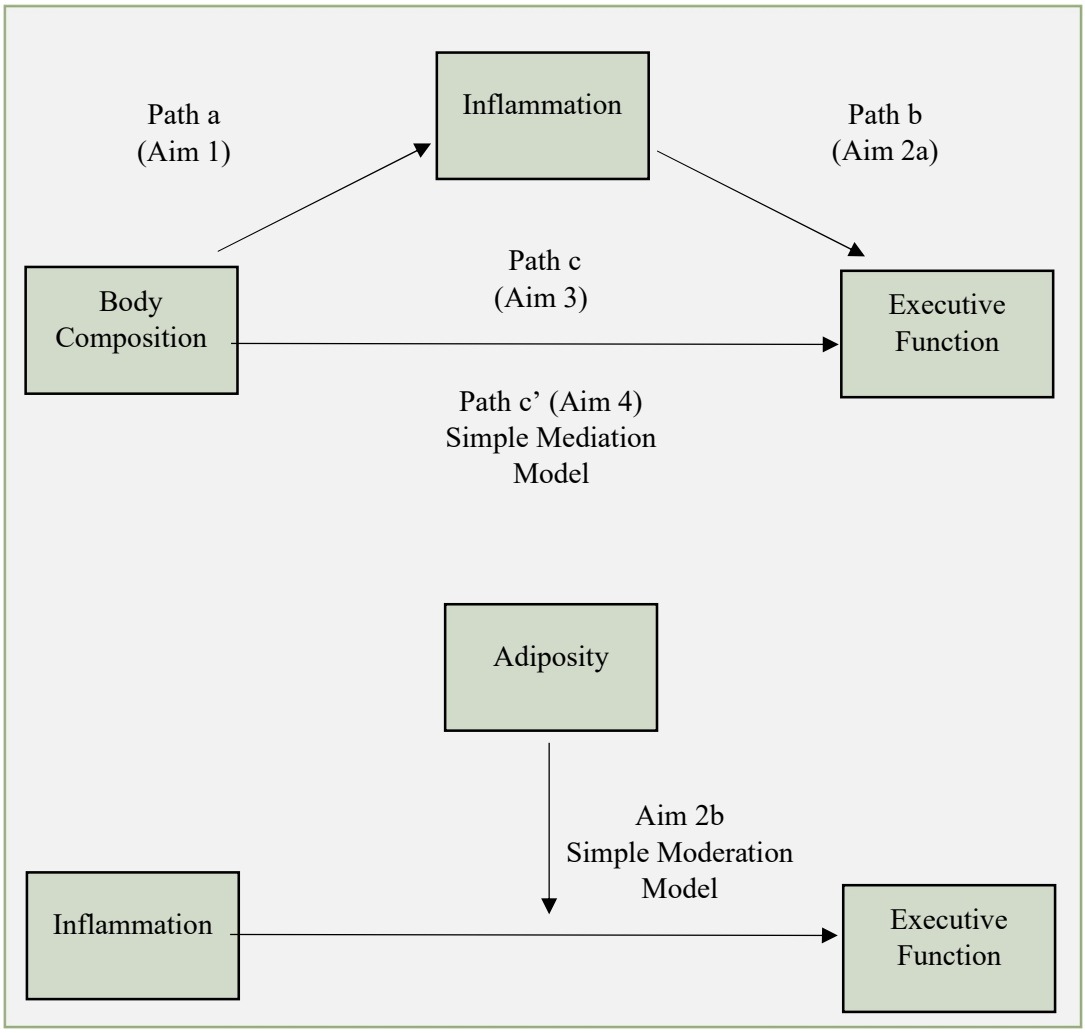
Aim 3

Aim 3 examined the associations between body composition and EF in children aged 8-12 with BMI ≥ 50th%. We hypothesized that higher percent body fat measured by DXA would show signals of association with poorer EF, indicated by lower T-scores on the NIH Toolbox Cognitive Battery EF subtests and higher T-scores on the BRIEF 2 subscales.

Aim 4

This aim explored whether inflammation mediates the association between body composition and EF in children aged 8-12 with BMI ≥ 50th%. We predicted that inflammation would mediate the association between body composition and EF, such that higher levels of CRP would explain a significant amount of variability in the association between higher DXA-measured % body fat and lower T-scores on the NIH Toolbox Cognitive Battery subtest Dimensional Change Card Sort Task, assessing cognitive flexibility and attention.

Figure 1
Aims and Corresponding Pathways



Note. Our final aim, aim 4, will investigate the mediation of the relation between body composition and executive function by inflammation, and each aim prior will investigate the independent pathways of the mediation. Aim 2b, however, will extend aim 2a by investigating the moderation of the relation between inflammation and EF by adiposity.

Methods

Participants

We set out to recruit 64 children aged 8-12 years with obesity: n=32 with overweight/obesity (i.e., ≥ 85th BMI percentile) and n=32 without obesity (i.e., 5^{th} ≤BMI percentile< 85^{th}). This study built onto the infrastructure of two ongoing studies by Dr. Gowey, where blood samples and cognitive and anthropometric data were collected from treatment-seeking children with overweight/obesity (n=32.) Inclusion criteria for the sample with obesity are (1) BMI ≥ 85^{th} percentile, (2) are ≥ 8 and ≤ 12 years old at the time of assessment, (3) can read, write, and speak English, along with their caregiver, (4) plan to stay living within the local area during the study period, (5) have a consenting caregiver who can commit to all study procedures and provide reliable travel. Exclusion criteria are (1) comorbid developmental/intellectual disability/traumatic brain injury/other identified condition known to substantially impact EF and/or weight management (i.e. conditions restricting ability to make dietary or physical activity changes, such as severe exercise-induced asthma); (2) taking medication that is known to affect weight or appetite, (3) recent infection that may cause confounds of acute inflammation, (4) have an uncorrected visual or hearing impairment that would prohibit completion of cognitive testing, and (5) are unable to use an iPad with appropriate training for cognitive testing. The children without obesity (n=32) have "normal-range" BMI scores (50^{th} ≤BMI percentile< 85^{th}) but have been shown to predict overweight/obesity in adulthood and otherwise follow the same inclusion/exclusion criteria. Inclusion/exclusion criteria are assessed via parent report and

EMR screening for children who are patients at CoA. The existing sample of children with overweight/obesity is diverse in terms of EF impairments, and we recruited children without obesity and variable levels of EF through a Primary Care Clinic at Children's of Alabama (CoA) Hospital in which children present for various reasons (i.e. well-child checks, behavioral concerns, ADHD, etc.). Additional recruitment occurred throughout the Birmingham area, through Children's of Alabama and UAB Health Systems as well as community hubs (i.e. public libraries, churches, etc.).

Procedures

This study utilized a cross-sectional design to explore signals of associations between inflammation, EF, and body composition in children with and without obesity. A portion of the sample with obesity (N=17) had already been recruited for ongoing projects and assessments conducted. Thus, children without obesity were recruited during regularly scheduled clinic appointments at CoA Primary Care Clinic or from other sources mentioned above. Participants were screened in clinic or via telephone for study eligibility, which included completion by parent/primary caregiver of the BRIEF 2 screener and collection of initial height/weight data for BMI. Once eligibility was confirmed, a study visit was scheduled. Participants were instructed to arrive fasted (overnight; minimum 9 hours) at the UAB Children's Health Research Unit (CHRU). At the study visit, the informed consent and assent process were conducted and appropriate consent/assent obtained. Following this, the participating child had basic anthropometry data collected (height, weight, %body fat, waist circumference) and was introduced to the CHRU phlebotomist for their blood draw. This process took approximately 45 minutes total. Pre-

labeled materials were brought by the research team for the blood draw. Following the blood draw, the phlebotomist provided the pre-labeled blood tubes back to the member of the research team for proper storage and processing, which occurred 30-60 minutes following collection of the blood. The child was then accompanied by their caregiver and the same member of the research team directly across the street to the UAB Webb Nutrition Sciences Building (5-minute walk) for the DXA scan. While the child's DXA scan was being completed, the blood was centrifuged and serum aliquots were created, and whole blood tubes along with sera aliquots were dropped off for storage in the NORC Metabolism Core space where the blood and sera is processed and analyzed. Sera was stored at -85 degrees Celsius until analyzed for TNF-a, IL-6, and CRP. The DXA scan took approximately 10 minutes to complete; thus, this portion of the visit took approximately 30 minutes total including travel and wait time. The child and caregiver were then accompanied back to CoA to the CHRU to eat a snack prior to EF testing. Following a 10-minute snack break, the child was administered the NIH Toolbox Cognitive Battery via iPad by a trained member of the research team in a private exam room which takes approximately 30 minutes. While the child was being tested, the caregiver completed a brief demographic and developmental history questionnaire via iPad which takes approximately 5 minutes. After completion of these measures, the visit was considered finished. At this time, the caregiver received a parking token (for free covered parking) and the child was provided a monetary incentive (initially $30, later increased to $60) for their participation. The entire battery of measurements took 3-4 hours to complete, depending on the child.

Measures

Inflammatory measures

Blood serum tumor necrosis factor alpha (TNF-a), Interleukin 6 (IL-6), and C-reactive protein (CRP) are pro-inflammatory cytokines indicative of chronic, low-level systemic inflammation when elevated. Children's fasting venous A.M. blood samples were drawn in the Children's Health Research Unit by experienced Clinical Research Support Program phlebotomists. Blood was processed and assayed in the UAB Webb Nutrition Sciences Building, which is across the street from the Children's Hospital where the blood samples were drawn, via UAB's Nutrition Obesity Research Center Metabolic Core. hsCRP was measured with Pointe Scientific (Canton, MI) turbidometric reagent on a Stanbio Sirrus (Boerne, TX) analyzer, while IL-6 and TNF-a were measured using a MesoScale Discovery (Rockville, MD) human Proinflammatory Panel I kit. CRP was considered the primary outcome for the mediation analysis.

Executive Function measures

EF was assessed using a multidimensional approach for increased internal and external validity.

NIH Toolbox Cognitive Battery (NIHTB-CB). The NIHTB-CB is an iPad application of adaptive, performance-based cognitive testing that was used to assess children's EF. It is a comprehensive measure of cognitive function that measures EF, attention, episodic memory, language, processing speed, and working memory. It produces fully-adjusted t-scores that were used in analyses, minimizing need for age, gender, and education covariates. It has good test-retest reliability (ICC=0.78-0.99), convergent

validity (r=0.48-0.93, all significant with p<0.001), and good discriminant validity (r=0.05-0.30 with differential constructs) (Weintraub et al., 2013). The primary outcome was the Dimensional Change Card Sort (DCCS) Task assessing cognitive flexibility and attention. This task first presents two pictures that vary in shape and color. Then, a third picture is presented preceded by a cue indicating along which of these domains participants must match an original stimulus with the new stimulus. This task assesses aspects of inhibition as well, which is the most studied domain of EF in obesity. However, cognitive flexibility may represent a more complex EF domain that requires both skills of inhibition and switching attention, thus the selection of this task as the primary outcome is aimed at advancing the literature by utilizing a more novel domain. Additionally, previous studies have found tasks similar to the DCCS, such as the Stroop task, to be more robustly impacted by greater inflammation than tasks measuring inhibition alone (Cullen et al., 2017). Secondary outcome measures examined via exploratory analyses included individual tasks and sum scores for specific EF domains. The remaining EF subtests included the Flanker Inhibitory Control and Attention Task and List Sorting Working Memory Task. The Flanker Task measures inhibitory control and attention, requiring that participants focus on a particular stimulus and simultaneously inhibit attention to stimuli on either side of it. In the List Sorting Task, which measures working memory, participants recall different visual and auditory stimuli in varying sequences.

Behavioral Rating Inventory of Executive Function 2 – Parent report (BRIEF 2; parent-report assessment). The BRIEF 2 Parent Report form was also administered via iPad and is a measure of child EF impairment completed by the child's caregiver that produces t-scores for 8 clinical subscales of EF in addition to a global score which was

used in analyses. It is an updated version of the BRIEF Parent-report form, which has been widely used in pediatric hospitals and has good psychometric properties in internal consistency reliability (Cronbach's α=0.47-0.93), convergent validity (r=0.61-0.64), and divergent validity (r=0.27-0.31) (LeJeune et al., 2010). This measure also served as a secondary outcome measure in exploratory analyses.

Demographics

A demographic and developmental history questionnaire developed for the study including child pubertal stages information was completed by the parent via iPad.

Weight-Related Measures

Weight Status. Height/weight measurements were converted to zBMI using CDC age and sex specific scales. Child height and weight were measured in light clothing and no shoes. Height was measured to the nearest 0.1 cm with a Seca 213 portable stadiometer. Weight was measured to the nearest 0.1 kg with a Tanita SC-240 bio-electrical impedance (BIA) analyzer and standard scale.

Body Composition/Adiposity. Body fat percent was assessed using GE Lunar iDXA total body scans (GE Healthcare, Madison, WI). Each child underwent a total body scan in the supine position with arms at their sides while wearing light clothing. iDXA scans were analyzed according to the manufacturer's guidelines using enCORE 2008 software version 12.3 by the same trained technician who administered the scan.

Analytical Plan

Statistical analyses were conducted via SPSS Version 26 and 27 and included simple linear regression modeling of inflammatory markers (IVs) and EF (DVs). Simple linear regressions were used for aims 1, 2a, and 3. In aim 1, the primary model examined adiposity as a predictor of hsCRP. Exploratory analyses for aim 1 regressed levels of IL-6 and TNF-a onto adiposity. In aim 2, the primary model examined CRP as a predictor of performance on the dimensional change card sort task, representing EF domains of switching, attention, and inhibition. Exploratory models for aim 2a included simple linear regression models examining CRP levels as a predictor of performance on secondary EF outcomes mentioned above (Flanker Inhibitory Control and Attention Task, List Sorting Working Memory Task, and the BRIEF 2 – Parent Report), as well as IL-6 and TNF-a as predictors of performance on these secondary EF outcomes along with the primary EF outcome. Thus, there were 11 exploratory regressions conducted for aim 2a. In aim 3, the primary model examined adiposity as a predictor of performance on the dimensional change card sort task. Exploratory analyses for aim 3 regressed the secondary EF outcomes onto adiposity.

For aim 4, the primary outcomes for each variable of interest were included in the exploratory mediation model which was tested using Andrew Hayes' PROCESS Model 4. For aim 2b, the primary and secondary outcomes for inflammation (predictor) and EF (dependent variable) were run through PROCESS Model 1, simple moderation, with adiposity serving as the moderating variable.

Due to the exploratory nature of the secondary analyses, analytic interpretation of these results did not rely solely on interpretation of statistical significance but also

considered other important indicators of association including the ability to identify signals, effect sizes, and variability of the data. Variability was considered particularly important to establish given the inclusion of children without obesity. The current literature is limited in its inclusion of children outside of disease populations of interest, and thus this study aims to amend this gap and identify levels of variability in EF and inflammatory markers in children without, but potentially at risk for, obesity. Relatedly, potential covariates were examined in relation to proposed models to evaluate their influence on this relationship, including fasting glucose, genetic predisposition to insulin resistance, gender, age, pubertal development, and SES. Given these potential covariates and the need for parsimony, priority was given to biological covariates of insulin, glucose, and Tanner Stage of pubertal development, because EF scores were automatically corrected for age, sex, education, and demographics factors. This approach will inform the feasibility of future longitudinal research to examine additional predictive and mechanistic models including these variables, as guided by the adult literature.

A Priori Power Analysis

Sobel's model for mediation power analysis was chosen as the most appropriate model given the novelty of this analytical approach and availability of published data. Sobel's model calculates mediational power as the multiplicative of the power of paths a and b. Power for path a was determined using statistics from Parret et al., (2010), while power for path b was determined using data from Cullen et al (2017). For path a, with an alpha = 0.05, slope B = 0.152, $\sigma_x = 8.6$, $\sigma_y = 2.2$, the required sample size for power = 0.99 was N = 36. For path b, with an alpha = 0.05, slope B = 0.07, $\sigma_x = 11.3$, $\sigma_y = 2.3$, the

required sample size for power = 0.81 was N = 63. Thus, the product of path a power (99%) and path b power (81%) yielded a power estimate for the mediation model of power = 0.8084, utilizing the path b required sample of at least 63. The planned sample for this study included 64 children, as the a priori estimate suggested the mediation analysis would be adequately powered. Due to COVID-19 research restrictions and recruitment problems, this sample size was not achieved.

Institutional Review Board Status

The University of Alabama at Birmingham Institutional Review Board approved all study protocols for the proposed study. The study was completely voluntary and involved low risk with a favorable risk/benefit ratio All children received prizes after the bloodwork was complete. Children without obesity initially received $30 for their participation, although this incentive was increased to $60 before the conclusion of the study due to difficulty with recruitment. Child/parent dyads enrolling in the adjacent treatment studies received monetary incentives of up to $90 for their participation in multiple visits.

Timeline

The present study's progression mirrored the progression of the studies it built upon. Recruitment occurred from 2018-2020. Baseline data collection occurred from 2018-2020. Processed blood data was received in June of 2020. Data analysis and manuscript preparation occurred in Summer-Fall 2020.

Results

Data Preparation

Data were entered in RedCap and exported to SPSS. Hotdeck Imputation was utilized to handle missing data in hsCRP, IL-6, TNFa (15.38% of cases (N = 6) missing each; Hotdeck is appropriate for variables with up to 20% of missing data), as well as DXA percent body fat and the BRIEF indices (2.56% of cases (N = 1) missing each; (Myers, 2011). The automatic data preparation function of SPSS was utilized to truncate outliers to the cutoff point of 3 standard deviations away from the mean for all variables, as well as for BoxCox transformation of non-normal variables (determined by Shapiro-Wilk test of normality and absolute values for skewness or kurtosis > 2) that were utilized as dependent variables in the proposed analyses (hsCRP, IL-6, TNFa, cognitive flexibility, and inhibition). Given the reduced sample size due to recruitment difficulties and COVID-19, candidate covariates were considered with parsimony to preserve power. Both performance-based and parent-rated EF scores are corrected for age, sex, and demographic variables such as race and education, so biomedical covariates (insulin, glucose, and Tanner Stage of Puberty Development) were prioritized in the analyses. Insulin and glucose each had 15.38% (N = 6) of cases missing which were also imputed via Hotdeck.

Table 1

Sociodemographic Characteristics of Participants at Baseline

Baseline characteristic	Full sample	
	N	% or Mean ± SD
Parental characteristics		
Age	39	38.6 ± 9.10
Sex, n (%)		
Female	30	76.9
Male	9	23.1
Race, n (%)		
Black	27	69.2
White	10	25.6
Other / No Response	2	5.2
Household Annual Income, n (%)		
Below $19,999	15	38.5
$20,000-$39,999	9	23.1
$40,000-$59,999	4	10.3
$60,000-$79,999	2	5.1
$80,000-$99,999	3	7.7
Above $100,000	6	15.4
Child characteristics		
Age	39	10.36 ± 1.48
Sex, n (%)		
Female	19	48.7
Male	20	51.3
Race, n (%)		
Black	27	69.2
White	9	23.1
Other / No Response	3	7.7
Ethnicity, n (%)		
Hispanic	4	10.3
Non-Hispanic	34	87.2
No Response	1	2.6

Note. Total N = 39.

Table 2

Descriptive statistics of adiposity, inflammation, executive function, and covariates.

Variable	Full sample
	Mean (SD)
Adiposity	
Percent Body Fat [DXA, Total Body Less Head (TBLH)]	46.37 ± 7.98
Inflammation	
hsCRP (mg/L)	4.82 ± 8.15
IL-6 (pg/ml)	2.08 ± 5.71
TNFa (pg/ml)	3.18 ± 0.86
Performance-Based Executive Function (NIH Toolbox Cognitive Battery)	
Cognitive Flexibility (Dimension Change Card Sort Test) [a]	41.54 ± 8.42
Inhibition (Flanker Inhibitory Control and Attention Test) [a]	41.90 ± 8.19
Working Memory (List Sorting Working Memory Test) [a]	44.59 ± 9.67
Processing Speed (Pattern Comparison Processing Speed Test) [a]	37.79 ± 12.89
Parent-Report Executive Function (BRIEF 2)	
Behavior Regulation Index (BRI) [a]	54.64 ± 10.91
Emotion Regulation Index (ERI) [a]	55.15 ± 10.41
Cognitive Regulation Index (CRI) [a]	54.71 ± 11.16
General Executive Composite (GEC) [a]	55.10 ± 10.23
Covariates	
Insulin	23.24 ± 23.91
Glucose	92.38 ± 8.34
Tanner Stage of Puberty Development	2.38 ± 1.07

Note. Total N = 39. For hsCRP, IL-6, TNFa, Percent Body Fat (DXA, TBLH), BRIEF 2 variables, Insulin, and Glucose, data are presented secondary to HotDeck Imputation. For CRP, IL-6, TNFa, cognitive flexibility, and inhibition data are presented prior to BoxCox transformations.

[a] Represents data for the fully-corrected T-score (Mean = 50, SD = 10) of the given measure. NIH Toolbox corrects for age, education, gender, and race/ethnicity. The BRIEF-2 corrects for gender and age.

Table 3

Correlations among variables included in analyses.

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. % Body Fat (DXA TBLH)	1.00													
2. hsCRP	.40*	1.00												
3. IL-6	.38*	.71**	1.00											
4. TNFa	.36*	.35*	.30	1.00										
5. Cognitive Flexibility (NIHTB)	.05	-.27	-.14	.04	1.00									
6. Inhibitory Control (NIHTB)	.02	.07	.24	.18	.24	1.00								
7. Working Memory (NIHTB)	.10	-.13	-.11	.16	.31	.27	1.00							
8. Processing Speed (NIHTB)	.26	-.10	-.03	.01	.28	.35*	.01	1.00						
9. GEC (BRIEF-2)[a]	.05	.33*	.28	.17	.02	-.25	-.10	-.26	1.00					
10. BRI (BRIEF-2)[a]	.01	.30	.11	.15	.18	-.19	.07	-.18	.79**	1.00				
11. ERI (BRIEF-2)[a]	.14	.38*	.28	.30	.16	-.02	.01	-.05	.79**	.87**	1.00			
12. CRI (BRIEF-2) [a]	.01	.37*	.36*	.01	-.10	-.28	-.24	-.32*	.81**	.60**	.61**	1.00		
13. Fasting Glucose	-.26	-.25	-.08	-.16	-.14	-.12	-.14	.00	-.06	-.06	-.12	-.01	1.00	
14. Insulin	.40*	.16	.27	.12	.01	-.16	-.02	-.01	.12	.09	.21	-.01	.20	1.00
15. Tanner Stage	-.17	-.29	-.26	-.16	.07	-.16	-.06	-.02	-.09	-.11	-.18	-.12	.15	.10

Note. Spearman's correlations are displayed for variables included in analyses.

*$p < 0.05$, **$p < 0.01$

[a]GEC = General Executive Composite, BRI = Behavior Regulation Index, ERI = Emotion Regulation Index, CRI = Cognitive Regulation Index

Preliminary Analyses

Sample Characteristics

Participants (N=39) were 51.30% male, 69.20% Black or African American, 87.20% non-Hispanic, and demonstrated a mean age of 10.36. See Table 1 for additional demographics. Central tendencies of primary and secondary variables are displayed in Table 2. Correlations among primary and secondary variables are displayed in Table 3. Further, for all analyses that follow, comprehensive tables detailing additional statistics can be referenced in Appendix B.

Effect of Adiposity on Inflammation (Aim 1)

Primary Analysis (hsCRP and % body fat DXA)

We first tested whether adiposity predicted inflammation utilizing primary variables of DXA percent body fat and high-sensitivity c-reactive protein (hsCRP). Adiposity predicted hsCRP such that those with higher percent body fat demonstrated higher levels of hsCRP ($\beta = .45$, $t(37) = 3.02$, $p < 0.01$, $R^2 = .20$).When glucose, insulin, and Tanner Stage of Pubertal development were included as covariates, the results were consistent. In this analysis, model 1 included the three covariates and was not significant ($R^2 = .15$, $F(3, 35) = 1.97$, $p = .14$), whereas model 2 added percent body fat as measured by DXA scan, and demonstrated a significant change in degree of hsCRP variance explained [$\beta = .39$, $t(34) = 2.35$; $\Delta R^2 = .12$, $\Delta F(1, 34) = 5.52$, $R^2 = 0.26$, $p < .05$].

Exploratory Analyses (TNFa, IL-6, and % body fat DXA)

Percent body fat as measured via DXA scan was examined in relation with both TNFa and IL-6 as well. DXA percent body fat significantly predicted both TNFa [$\beta = 0.38$, $R^2 = .15$, $F(1, 37) = 6.55$, $p < .05$] and IL-6 [$\beta = 0.44$, $R^2 = .19$, $F(1, 37) = 8.76$, $p < .01$]. When covariates were added, DXA percent body fat significantly predicted both TNFa [$\beta = 0.34$, $t(34) =$, $\Delta R^2 = .10$, $\Delta F(1, 34) = 4.15$, $R^2 = .17$ $p < .05$] and IL-6 [$\beta = 0.38$, $\Delta R^2 = .11$, $\Delta F(1, 34) = 5.08$, $R^2 = .24$, $p < .05$] over and above covariates (glucose, insulin, and Tanner Stage of Pubertal Development).

Post-Hoc Power Analyses

The following power analyses were conducted for the models including the primary variable (DXA percent body fat) only. For the model with no covariates (number of predictors = 1), with an alpha = 0.05, effect size $f^2 = .25$ (calculated from the squared multiple correlation or $R^2 = .20$), and sample size N = 39, the achieved power was determined to be 85.58%. For the model with covariates (total number of predictors = 4, and number of tested predictors = 1), with an alpha = 0.05, effect size $f^2 = .25$ (calculated from the partial $R^2 = .12$), and sample size N = 39, achieved power was computed as 60.65%.

Effect of Inflammation and Adiposity on Executive Function (Aim 2)

Primary Analyses (hsCRP, Cognitive Flexibility, and % body fat DXA)

Aim 2a. We then examined whether inflammation independently predicted EF utilizing primary variables of hsCRP and performance-based cognitive flexibility via

simple linear regression. hsCRP did not significantly and independently predict cognitive flexibility [β = -.23, $t(38) = -1.46$, $F(1, 37) = 2.14$, $R^2 = .06$, $p = 0.15$]. We further examined this relation with covariates glucose, insulin, and Tanner Stage of Pubertal development. Neither solely covariates [Model 1; $R^2 = .03$, $F(1, 35) = 0.39$, $p = .76$] nor the addition of hsCRP [Model 2; β = -0.30, $\Delta R^2 = .08$, $\Delta F(1, 34) = 2.85$, $p = .10$] significantly predicted cognitive flexibility. However, when covariates were added, hsCRP's relation with cognitive flexibility neared significance, such that higher levels of hsCRP were associated with poorer performance on the cognitive flexibility task. The effect demonstrated here may not have been detected as statistically significant due to insufficient statistical power (power analyses presented below), but nevertheless may be a meaningful effect.

Aim 2b. We next investigated the relation between both percent body fat and inflammation on cognitive flexibility, as well as the moderating role of percent body fat in the relation between inflammation and cognitive flexibility. Model 1 of the hierarchical regression model testing the effect of percent body fat and hsCRP on cognitive flexibility was not significant [$R^2 = 0.09$, $F(2, 36) = 1.76$, $p = .19$]. Within model 1, neither DXA percent body fat [β = .21, $t(38) = 1.17$, $p = .25$], nor hsCRP [β = -.33, $t(38) = -1.84$, $p = 0.075$] significantly predicted cognitive flexibility. However, hsCRP's effect demonstrated an inverse relation that neared statistical significance, such that those with higher hsCRP demonstrated poorer cognitive flexibility. Notably, this model was underpowered (power analyses presented below), and this result demonstrates signals of association that would likely demonstrate statistical significance with sufficient power. Model 2 of hierarchical regression model testing continuous variables of

adiposity, measured as percent body fat, as a moderator of the relation between hsCRP and cognitive flexibility was not significant [R^2 = 0.10, F(2, 35) = 1.24, p =.31]. In Model 2, the interaction between percent body fat and hsCRP did not significantly predict cognitive flexibility over and above Model 1 [β = 0.09, p =.62; ΔR^2 = .007, ΔF(1, 35) = .59, p =.62]. When this analysis was conducted with covariates, results were consistent. The interaction term did not significantly predict cognitive flexibility and demonstrated a very small effect [β = 0.04, p =.84; ΔR^2 = .001, ΔF(1, 32) = .04]. Again, post-hoc power analyses demonstrated that even without covariates, the moderation was significantly underpowered (power analysis presented below). However, the effect was so small that even if it were to achieve statistical significance within a larger sample, this effect is not likely to be meaningful.

Exploratory Analyses (cytokines and EF measures)

Aim 2a was tested using alternate measures for EF. The following results demonstrate the effect of hsCRP, IL-6, and TNFa on domains of both performance-based and parent-rated EF and both with and without covariates included (See Figure 1).

Performance-Based EF – Cognitive Flexibility. hsCRP's association with cognitive flexibility is presented in the primary analyses. IL-6 did not predict cognitive flexibility independently [R^2 = .00, F(1, 37) = .14 , β = -.06, p = .71], nor over and above biological covariates [ΔR^2 = .01, ΔF(1, 34) = .25, β = -.09, R^2 = .04, p = .62]. Likewise, TNFa was not a significant predictor of cognitive flexibility before [R^2 = .00, F(1, 37) = .02, β = -.02, p = .90] or after accounting for covariates [ΔR^2 = .00, ΔF(1, 34) = .06, R^2 = .03, β = -.04, p =.80].

Performance-Based EF – Inhibition. hsCRP did not significantly and independently predict performance-based inhibition [R^2 = .01, F(1, 37) = .17 , β = -.07, p=.63]. Results were consistent when biological covariates were included [ΔR^2 = .02, ΔF(1, 34) = .59 , R^2 = .05,; β = -.14, p = .45]. IL-6 results were consistent both without covariates [R^2 = .01, F(1, 37) = .18 , β = .07, p = .67], and with covariates [ΔR^2 = .01, ΔF(1, 34) = .36, β = .10, p = .55]. Similarly, TNFa did not predict inhibition before [R^2 = .00, F(1, 37) = .04, β = .03, p = .84] or after [ΔR^2 = .00, ΔF(1, 34) = .001, R^2 = .03, β = .01, p = .98] inclusion of covariates.

Performance-Based EF – Working Memory. Similarly**,** hsCRP did not singularly predict performance-based working memory [R^2 = .04, F(1, 37) = 1.35, β = -.19, p = .25]; the same was true when hsCRP was added to the model second to covariates [ΔR^2 = .07, ΔF(1, 34) = 2.49, R^2 = .09, p = .12; β = -.28, p = .12]. IL-6 results were consistent without covariates [R^2 = .05, F(1, 37) = 1.77 , β = -.21, p = .19]. With covariates added [ΔR^2 = .08, ΔF(1,34) = 2.90, R^2 = .10, β = -.30, p = .10], the effect of IL-6 nearly significantly predicted working memory, such that higher levels of IL-6 corresponded with lower performance in working memory. TNFa demonstrated non-significant results both without covariates [R^2 = .01, F(1, 37) = .39, β = .10, p = .54] and with covariates [ΔR^2 = .01, ΔF(1, 34) = .16, R^2 = .03, β = .07, p = .69].

Performance-Based EF – Processing Speed. hsCRP was not a significant predictor of processing speed [R^2 = .00, F(1, 37) = .07 , β = -.04, p =.79]. After accounting for covariates, results were unchanged [ΔR^2 = .00, ΔF(1, 34) = .11, R^2 = .01, p = .74; β = -.06, p = .74]. IL-6 results were consistent both without covariates [R^2 = .00, F(1, 37) = .08, β = .05, p = .79], and with covariates [ΔR^2 = .00, ΔF(1, 34) = .90, R^2 =

.01, β = .02, p = .90]. Further, TNFa showed consistent results both independently [R^2 = .00, F(1, 37) = .09, β = .05, p = .76] and after accounting for biological covariates [ΔR^2 = .00, ΔF(1, 34) = .07, R^2 = .01, β = .05 p = .79].

Parent-Reported EF – General Executive Composite. hsCRP was a significant predictor of the composite score of parent-reported child EF both without covariates included [R^2 = .15, F(1, 37) = 6.49, β = .39, p < .05], and over and above biomedical covariates [Model 2; ΔR^2 = .14, ΔF(1, 34) = 5.66, R^2 = .15, p < .05; β = .40, p < .05]. IL-6, however, did not significantly predict the BRIEF composite score either independently [R^2 = .06, F(1, 37) = 2.19, β = .23, p = .15], or after accounting for covariates [ΔR^2 = .05, ΔF(1, 34) = 1.89, R^2 = .07, β = .24, p = .18]. TNFa also did not demonstrate a significant relationship with the general executive composite pre-covariates [R^2 = .02, F(1, 37) = .74, β = .14, p = .40] or post-covariates [ΔR^2 = .01, ΔF(1, 34) = .50, R^2 = .03, β = .12, p = .48].

Parent-Reported EF – Behavior Regulation Index. hsCRP significantly and independently predicted the Behavior Regulation Index [R^2 = .11, F(1, 37) = 4.40, β = .33, p < .05]. However, when covariates were added, hsCRP neared statistical significance for a positive relationship with behavior regulation [ΔR^2 = .10, ΔF(1, 34) = 3.77, R^2 = .11, β = .34, p = .06]. In contrast, IL-6 did not demonstrate a significant relation with Behavior Regulation neither without covariates [R^2 = .01, F(1, 37) = .49, β = .11, p = .49] nor with covariates [ΔR^2 = .01, ΔF(1, 34) = .27, R^2 = .02, β = .10, p = .61] in the model. TNFa results indicated no relations with behavior regulation neither as an independent predictor [R^2 = .01, F(1, 37) = .48, β = .11, p = .49] nor over and above covariates [ΔR^2 = .01, ΔF(1, 34) = .30, R^2 = .02, β = .10, p = .59].

Parent-Reported EF – Emotion Regulation Index. Further, hsCRP significantly predicted emotion regulation both independently [R^2 = .15, F(1, 37) = 6.75, β = .40, p < .05], and after accounting for covariates [Model 2; ΔR^2 = .10, ΔF(1, 34) = 4.16, R^2 = .17, β = .34, p < .05]. As before, IL-6 showed no relations with Emotion Regulation without covariates included [R^2 = .07, F(1, 37) = 2.73, β = .26, p = .11] and with covariates included [ΔR^2 = .03, ΔF(1, 34) = 1.29, R^2 = .11, β = .20, p = .27]. Again, TNFa showed non-significant relations with emotion regulation without covariates included [R^2 = .04, F(1, 37) = 1.54, β = .20, p = .22] and after accounting for covariates [ΔR^2 = .02, ΔF(1, 34) = .70, R^2 = .09 β = .14, p = .40].

Parent-Reported EF – Cognitive Regulation Index. Finally, hsCRP significantly predicted cognitive regulation both singularly [R^2 = .11, F(1, 37) = 4.59, β = .33, p < .05], and once covariates were included [ΔR^2 = .12, ΔF(1, 34) = 4.29, R^2 = .14, β = .34, p < .05]. In this case, IL-6 also significantly predicted cognitive regulation [ΔR^2 = .11, ΔF(1, 34) = 4.16, R^2 = .14, p < .05; β = .34, p < .05] over and above covariates, but without covariates included, IL-6 only demonstrated a non-significant trend towards predicting cognitive regulation [R^2 = .10, F(1, 37) = 3.92, β = .31, p = .06]. Lastly, TNFa also did not demonstrate this relation both without covariates [R^2 = .00, F(1, 37) = .10, β = -.05, p = .75] and with covariates [ΔR^2 = .00, ΔF(1, 34) = .13, R^2 = .03, β = -.06, p = .73].

Aim 2b Exploratory Analyses. Given the weak effect size identified in Aim 2b primary analyses, only one exploratory analysis was conducted. A hierarchical regression was conducted to examine whether adiposity moderated the relation between hsCRP and the BRIEF 2 GEC. Model 1 of the hierarchical regression model testing the effect of

percent body fat and hsCRP on the GEC was significant [R^2 = 0.17, F(2, 36) = 3.562, p = .04]. Within model 1, DXA percent body fat did not predict the GEC [β = .21, t(38) = 1.17, p = .25], while hsCRP [β = -.33, t(38) = -1.84, p = 0.075] significantly predicted the GEC score. Model 2 of hierarchical regression model testing adiposity as a moderator of the relation between hsCRP and cognitive flexibility was not significant [R^2 = 0.19, F(2, 35) = 2.72, p =.06]. In Model 2, the interaction between percent body fat and hsCRP did not significantly predict cognitive flexibility over and above Model 1 [β = -0.17, p =.32; ΔR^2 = .02, ΔF(1, 35) = 1.03]. When this analysis was conducted with covariates, effect sizes were consistent. The interaction term did not significantly predict GEC and demonstrated a very small effect [β = -0.18, p =.33; ΔR^2 = .02, ΔF(1, 32) = .97].

Post-Hoc Power Analyses

Aim 2a. First, power analyses were conducted using primary variables (hsCRP and Cognitive Flexibility). For the model with no covariates (number of predictors = 1), with an alpha = 0.05, effect size f^2 = .06 (calculated from the squared multiple correlation or R^2 = .06), and sample size N = 39, the achieved power was determined to be 31.15%. For the model with covariates (total number of predictors = 4, number of tested predictors = 1), with an alpha = 0.05, effect size f^2 = .08 (calculated from the partial R^2 = .08), and sample size N = 39, achieved power was computed as 40.84%. An additional post-hoc power analysis revealed a total required sample of N=133, given these variables.

Second, power analyses were conducted using hsCRP and the parent-reported general executive composite score. For the model with no covariates (number of predictors = 1), with an alpha = 0.05, effect size f^2 = .18 (calculated from the squared

multiple correlation or R^2 = .15), and sample size N = 39, the achieved power was determined to be 72.07%. For the model with covariates (total number of predictors = 4, and number of tested predictors = 1), with an alpha = 0.05, effect size f^2 = .18 (calculated from the partial R^2 = .18), and sample size N = 39, achieved power was computed as 72.20%. A total sample of N = 46 would have resulted in adequate power for the covariate analysis given these inputs.

Aim 2b. Power analyses for aim 2b were conducted for primary variables (DXA, hsCRP, and Cognitive Flexibility). For model 1 (predictors = DXA & hsCRP, y = cognitive flexibility), with 2 predictors, N = 39, alpha = .05, and an effect size of f^2 = .10 (calculated from squared multiple correlation or R^2 = .09), achieved power was 36.95%. For model 2 (model 1 + interaction variable of DXAxCRP), with 3 total predictors, 1 tested predictor, N = 39, alpha = .05, and f2 = .01 (calculated from partial R2 = .01), power was determined to be 8.03%. A sample of N=787 would have been necessary for adequate power.

Effect of Adiposity on Executive Function (Aim 3)

Primary Analysis (% body fat DXA and Cognitive Flexibility)

We then examined whether adiposity independently predicted EF via primary variables of DXA percent body fat (DXA %BF) and cognitive flexibility. Adiposity did not independently and significantly predict cognitive flexibility (β = .06, $t(37) = .379$, $p = .71$, $R^2 = .00$). When covariates were included, neither solely covariates [Model 1; $R^2 = .03$, $F(3, 35) = 0.39$, $p = .76$] nor the addition of percent body fat as measured by DXA

scan [Model 2; $\Delta R^2 = .00$, $\Delta F(1, 34) = .00$, $R^2 = .03$, $p = .89$] significantly predicted cognitive flexibility.

Exploratory Analyses (% body fat DXA and EF measures)

Percent body fat as measured via DXA scan was also examined in relation to other domains of EF measured via performance-based tasks (inhibition, working memory, and processing speed) and parent report questionnaire (behavior regulation, emotion regulation, cognitive regulation, and general executive composite) with covariates included. Neither models with solely covariates nor the addition of DXA percent body fat significantly predicted any of these measures of EF (See Appendix B, Table 15).

Post-Hoc Power Analyses

The following power analyses were examined only for the models including the primary variables (DXA percent body fat and cognitive flexibility). For the model with no covariates (number of predictors = 1), with an alpha = 0.05, effect size $f^2 = .004$ (calculated from the squared multiple correlation or $R^2 = .004$), and sample size N = 39, the achieved power was determined to be 6.72%. Due to the limited power observed in this analysis, as well as the small effect size of DXA percent body fat on cognitive flexibility, a power analysis for the model that included covariates was not conducted. Of note, this effect sized differed from previous literature, which found a $\Delta R^2 = 0.04$ (Kamijo et al., 2012). Given our observed effect size, a sample of N = 1965 would have been necessary for adequate power to detect this effect.

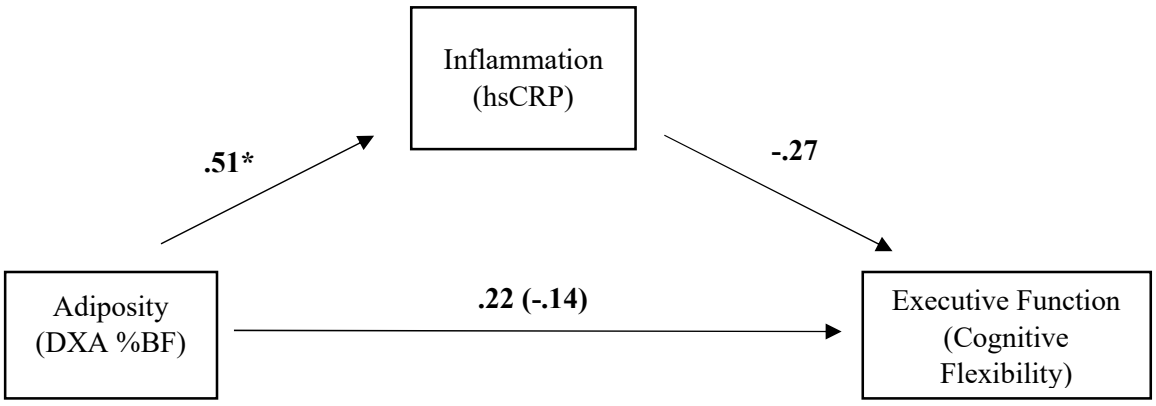
Mediating Role of Inflammation (Aim 4)

Primary Analysis (% body fat DXA, hsCRP, Cognitive Flexibility)

The relationship between adiposity and cognitive flexibility was not significantly mediated by hsCRP. Consistent with previous results, the standardized regression coefficient between adiposity and hsCRP was statistically significant, and the standardized regression coefficient between hsCRP and cognitive flexibility neared, but did not reach, statistical significance (See Figure 2). The standardized indirect effect was (.51)(-.27) = -.14. We tested the significance of this indirect effect using bootstrapping procedures. Unstandardized indirect effects were computed for each of 10,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. The bootstrapped unstandardized indirect effect was -.11, and the 95% confidence interval ranged from -.31, .02. Thus, the inverse indirect effect also neared, but did not reach, statistical significance.

Figure 2

Mediation of Adiposity and Cognitive Flexibility by hsCRP

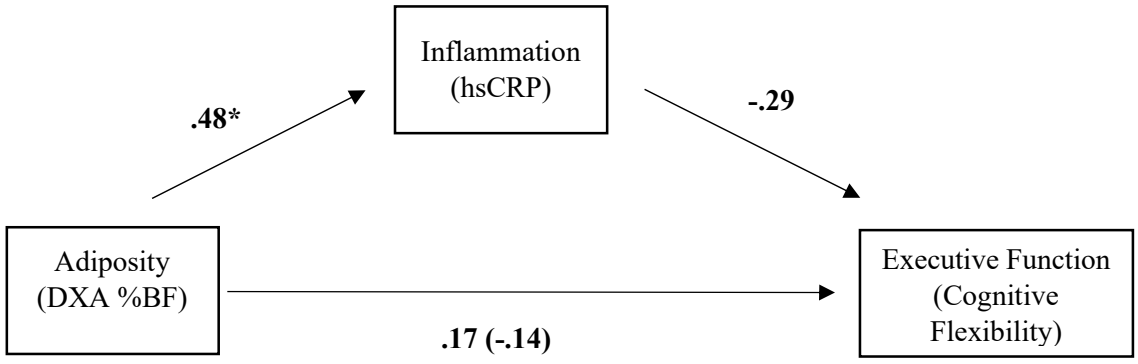


Note. Standardized regression coefficients for the relation between adiposity and cognitive flexibility, mediated by c-reactive protein. The standardized indirect effect of adiposity on cognitive flexibility, via c-reactive protein, is in parentheses. *$p < .05$

The primary analysis for Aim 4 was also conducted with covariates glucose, insulin, and Tanner Stage of Pubertal Development. Results were consistent with the model that did not include covariates. Adiposity significantly predicted hsCRP, and hsCRP neared, but did not reach statistical significance in predicting cognitive flexibility (see Figure 3). The standardized indirect effect was (.48)(-0.29) = -0.14. Using bootstrapping procedures to test the indirect effect's significance via 10,000 bootstrapped samples, the unstandardized indirect effect was -0.14, and the 95% confidence interval ranged from -0.34 to .03. Again, the inverse indirect effect neared, but did not reach, significance.

Figure 3

Mediation of Adiposity and Cognitive Flexibility by hsCRP with Covariates



Note. Standardized regression coefficients for the relation between adiposity and cognitive flexibility, mediated by c-reactive protein, including covariates of insulin, glucose, and Tanner Stage of pubertal development. The standardized indirect effect of adiposity on cognitive flexibility, via c-reactive protein, is in parentheses. *$p < .05$

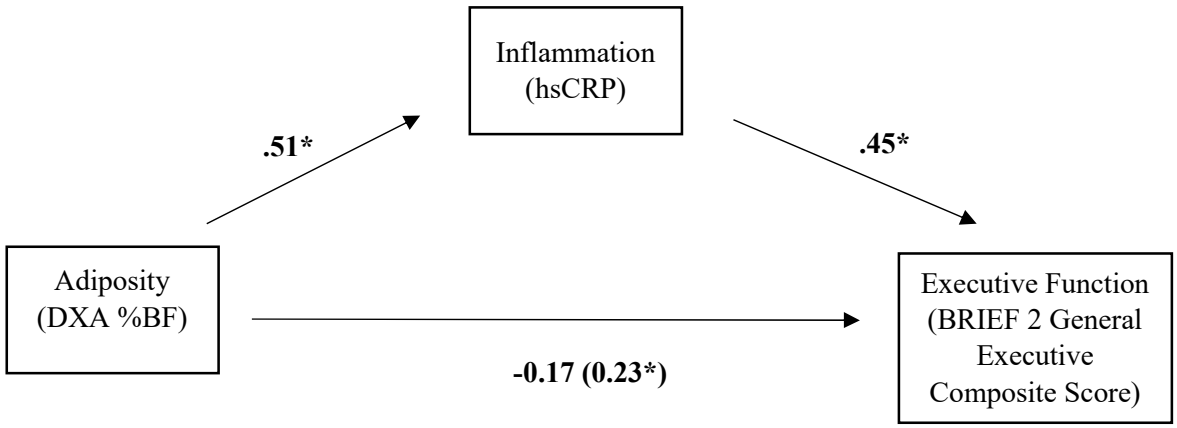
Exploratory Analyses (% body fat DXA, cytokines, EF measures)

The mediation analysis was conducted again for variable pairs demonstrating a significant 'b path.'

DXA Percent Body Fat on BRIEF 2 Composite via hsCRP. A significant, indirect effect of DXA percent body fat on the general executive composite score of the BRIEF 2 survey via hsCRP was observed (see Figure 4). The standardized indirect effect was .23. After testing the significance of the indirect effect via 10,000 bootstrapped samples, the unstandardized indirect effect was 1.99, and the 95% confidence interval ranged from .39, 4.06. The positive, significant effect suggests that as percent body fat increases, hsCRP increases, which in turn increases parent-reported EF scores. In the case of the parent-reported EF scores, higher scores signify greater levels of executive dysfunction, and therefore poorer EF. When the analysis was conducted with covariates included, effects were similar but significance was no longer maintained, likely due to aforementioned power constraints.

Figure 4

Mediation of Adiposity and GEC by hsCRP

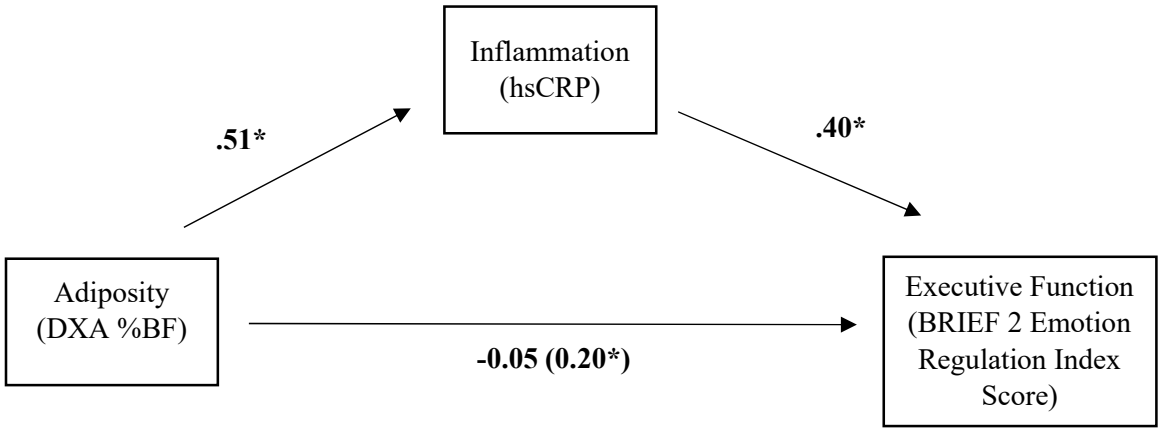


Note. Standardized regression coefficients for the relation between adiposity and the BRIEF 2 General Executive Composite (GEC) Score, mediated by c-reactive protein, excluding covariates of insulin, glucose, and Tanner Stage of pubertal development. The standardized indirect effect of adiposity on the GEC, via c-reactive protein, is in parentheses. *$p < .05$

DXA Percent Body Fat on BRIEF 2 Emotion Regulation via hsCRP. Again, a significant mediation was detected when examining the effect of DXA percent body fat on emotion regulation via CRP. The standardized indirect effect was .20, and when tested via bootstrapping as in prior analyses, the unstandardized indirect effect was 1.78, with the 95% confidence interval ranging from .21 to 4.00. The significant positive effect indicates that greater percent body fat is associated with higher levels of hsCRP which is associated with greater emotion regulation problems. When covariates were included, effects were similar but statistical significance was not achieved.

Figure 5

Mediation of Adiposity and Emotion Regulation by hsCRP

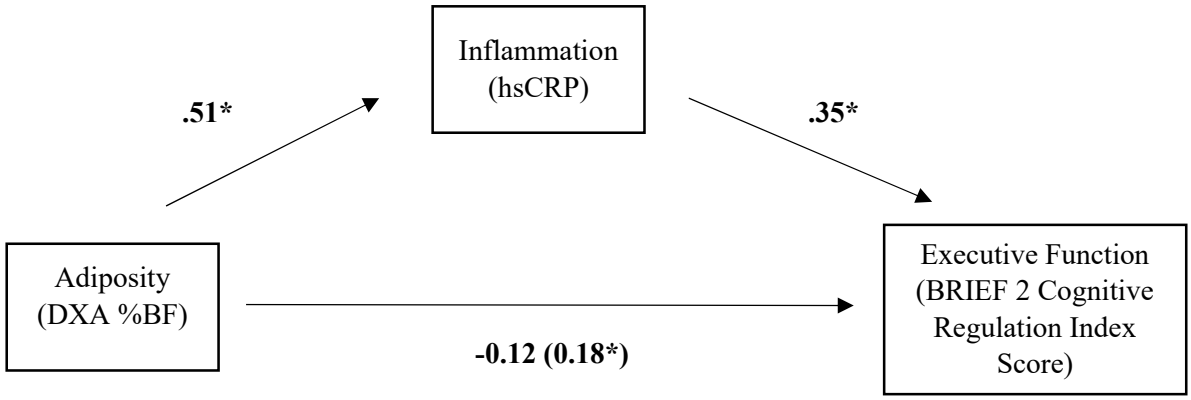


Note. Standardized regression coefficients for the relation between adiposity and the BRIEF 2 Emotion Regulation Index (ERI) Score, mediated by c-reactive protein, excluding covariates of insulin, glucose, and Tanner Stage of pubertal development. The standardized indirect effect of adiposity on the ERI, via c-reactive protein, is in parentheses. *$p < .05$

DXA Percent Body Fat on BRIEF 2 Cognitive Regulation via hsCRP. A third significant mediation was observed when predicting cognitive regulation from DXA percent body fat via hsCRP. A standardized indirect effect of .18 was detected, and bootstrapping procedures indicated an unstandardized effect of 1.71 with a 95% confidence interval of .05 to 3.80. As in prior analyses, significance was no longer detected once covariates were added, although effects were consistent.

Figure 6

Mediation of Adiposity and Cognitive Regulation by hsCRP

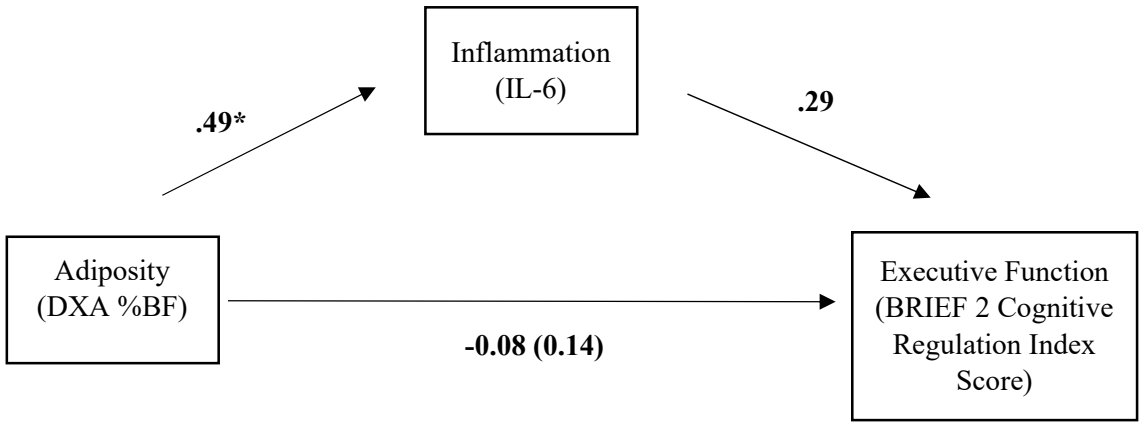


Note. Standardized regression coefficients for the relation between adiposity and the BRIEF 2 Cognitive Regulation Index (CRI) Score, mediated by c-reactive protein, excluding covariates of insulin, glucose, and Tanner Stage of pubertal development. The standardized indirect effect of adiposity on the CRI, via c-reactive protein, is in parentheses. *$p < .05$

DXA Percent Body Fat on BRIEF 2 Cognitive Regulation via IL-6. Finally, a mediation analysis of the effect of DXA percent body fat on cognitive regulation via IL-6 neared statistical significance for the mediation effect. The standardized indirect effect was .14, and bootstrapping procedures revealed an unstandardized effect of 1.38, with the 95% confidence interval spanning from -.36 to 3.64. When covariates were included, results were consistent.

Figure 7

Mediation of Adiposity and Cognitive Regulation by IL-6



Note. Standardized regression coefficients for the relation between adiposity and the BRIEF 2 Cognitive Regulation Index (CRI) Score, mediated by Interleukin-6, excluding covariates of insulin, glucose, and Tanner Stage of pubertal development. The standardized indirect effect of adiposity on the CRI, via IL-6, is in parentheses. *$p < .05$

Post-Hoc Power Analyses

For mediation analyses, post-hoc power analyses were conducted utilizing MedPower (Kenny, 2017). First, power analyses were conducted for the primary variables (DXA, hsCRP, and cognitive flexibility). For the model with no covariates,

with N = 39, alpha = .05, path a β = .45, path b β = -.33, and path c' (direct effect) β = .21, achieved power to detect a significant indirect effect was 37.10%. For the model with covariates, with N = 39, alpha = .05, path a β = .39, path b β = -.35, and path c' (direct effect) β = .14, achieved power to detect a significant indirect effect was 36.20%. A sample of N = 80 would have been sufficient to detect this effect with covariates included given our results, while N = 88 would have been sufficient for the model without covariates.

Second, power analyses were conducted for the mediation including DXA percent body fat (X), the parent-reported general executive composite (Y), and hsCRP (M). For the model with no covariates, with N = 39, alpha = .05, path a β = .45, path b β = .45, and path c' (direct effect) β = -.14, achieved power to detect a significant indirect effect was 61.70%. For the model with covariates, with N = 39, alpha = .05, path a β = .39, path b β = .45, and path c' (direct effect) β = -.13, achieved power to detect a significant indirect effect was 53.70%. A sample of N = 52 would have resulted in power of > 0.80 to detect the indirect effect without covariates, while a sample of N = 59 would have resulted in adequate power when covariates were included.

Discussion

The present study was the first to examine the relation between adiposity, chronic inflammation, and executive function in children with diverse weight statuses who were otherwise healthy. Greater adiposity significantly predicted higher levels of chronic inflammation as measured by pro-inflammatory cytokines TNFa, IL-6, and hsCRP. When both adiposity and inflammation were then used to predict executive function, small to medium effects were identified; these results were significant for particular measures of EF and inflammation but not others, likely due to limited power and differential relations among measure combinations. When mediation analyses were examined for the effect of adiposity on EF through chronic inflammation, significant results were identified for some, but not all examined measures, likely due to power restrictions and potentially due to disparate relations between certain variables. All analyses were limited by insufficient power, due to restricted sample because of coronavirus. Nevertheless, initial evidence was identified to support the hypothesis that greater adiposity leads to greater chronic inflammation which then leads to poorer executive functioning in children.

More specifically we saw that in Aim 2a, CRP independently demonstrated significant, small effects on parent-reported EF, such that increased CRP corresponded with higher levels of executive dysfunction. With the exception of the behavior regulation index, these results held even after accounting for covariates. However, the same results were not demonstrated for performance-based measures of EF. Effect sizes for CRP on performance-based EF measures did not reach the threshold of small effects

and were not significant. However, in Aim 2b, both CRP and adiposity were included as predictors of interest. In this model, CRP demonstrated a small, though still non-significant effect on cognitive flexibility. However, this analysis was limited by insufficient power. Taken together, we have detected evidence for CRP's association with EF among the parent-reported EF measures, and although we did not detect these relations among the performance-based measures, our evidence suggests that such a relationship may be detected with sufficient power and a larger sample.

IL-6 and TNFa, however, demonstrated limited effects on both performance-based and parent-reported EF. IL-6 significantly predicted parent-reported cognitive regulation and trended towards a small effect on performance-based working memory, although this result was not statistically significant. Despite power limitations, taken together with the parent-reported result, provides evidence that relations between IL-6 and domains of EF representing cognitive regulation may be detected with sufficient power and a larger sample. TNFa, however, demonstrated negligible relations with measures of EF. Considered along with the CRP results, these findings provide evidence to support our hypothesis that increased inflammation may correspond with poorer executive function, yet they leave much to be clarified about the discrepancies observed in the differential associations between specific inflammatory markers and EF measures.

In aim 2b, we observed that inflammation's effect on EF did not differ according to adiposity. This result may have been influenced by the range of BMI % included in the study. Previous studies have identified inflammation representative of CVD risk in kids with $\geq$ 50% BMI, so perhaps for a moderation relationship to be identified, children with < 50% BMI would need to be included in the analysis (Field et al., 2005). Further, this

result may have been observed because this relation is solely a mediation rather than a moderation as well. What we mean is that because we observed mediation effects such that inflammation partially explains the relation between adiposity and EF, it simply could be that adiposity would have no additional effect on the relation between inflammation and EF, given that it is already a significant contributor to the level of inflammation. Further evidence for this interpretation lies in that the effect size for this analysis was almost zero. Supporting this notion, power was very limited for the analysis, and combined with the extremely small effect size, this suggests that even if the effect were detected with a larger sample, it may not represent a meaningful influence.

In Aim 3, adiposity did not significantly predict any measure of EF. This was contrary to our hypotheses and previous research. This discrepancy may be due to the use of BMI, weight, or weight status as the primary anthropometric measures in previous research that found relations between obesity and EF in childhood (Reinert et al., 2013). Perhaps the use of adiposity rather than BMI, weight, or weight status unveils that the documented relations between BMI or weight and EF are not due to what BMI or weight is intended to approximate (body fat) but rather due to the corresponding increases in CVD risk factors, such as inflammation, that typically accompany increased body fat / BMIz. Interestingly, although still non-significant, a greater coefficient was observed for the relation between adiposity and EF when inflammation (CRP) was included as a predictor of interest. Together with previous research and Aims 1 and 2, these results provide support that adiposity may primarily indirectly influence executive function, which was examined in our final aim.

In Aim 4, the mediation analyses revealed interesting and promising results. Among primary variables (DXA percent body fat, CRP, and cognitive flexibility), as well as among secondary variables (DXA percent body fat (x), IL-6 (m), and BRIEF 2 Parent Reported Cognitive Regulation Index (y)), the mediation model neared but did not reach significance, suggesting that some inflammatory markers are explaining the relation between adiposity and some measures of EF. However, CRP did significantly mediate the relation between DXA and each of the following BRIEF 2 Parent-Report measures: General Executive Composite, Cognitive Regulation Index, Emotion Regulation Index. When biological covariates were added for each of these significant results, effects were similar, but statistical significance was no longer maintained. Further, results showed that both with and without covariates, these analyses were underpowered. Thus, the ability to detect indirect effects may withstand the addition of covariates given a larger sample. In sum, among multiple measures of inflammation and EF, evidence for an indirect effect of adiposity on EF through inflammation was discovered. Supporting our hypothesis, increased adiposity was found to affect EF through increased inflammation, which in turn was associated with poorer EF.

Interestingly, consistent discrepancies were demonstrated in results that utilized outcomes of performance-based EF versus parent-report EF. When performance-based EF measures were utilized as outcomes, effect sizes rarely met the criteria for ‘small’ effects and results were primarily non-significant. Analyses utilizing parent-reported EF, however, demonstrated many small effect sizes and significant relations. Further, correlations between the BRIEF 2 measures and NIH Toolbox measures were not observed as would intuitively be expected, but this finding is consistent with literature to

date (Ten Eycke & Dewey, 2016; Toplak, Bucciarelli, Jain, & Tannock, 2008). These differential relations and lack of correlations may be due to differences in the measures themselves (performance-based vs parent-report), rather than reflecting more broadly on the underlying construct. Performance-based testing is conducted in a quiet, focused one-on-one environment that is atypical to the real world; subjective reports are much more consistent with "real-world" everyday experiences. Thus, performance-based testing may be more indicative of true ability while subjective reports may be more indicative of actual behavior and observation in the more complex environment. Given our findings, this could potentially be interpreted as inflammation and adiposity aren't directly impacting EF capacity/ability (i.e., causing EF decline), but rather the behavioral expression of it (i.e., causing problems in the application of their EF abilities in their usual environment). Further, the NIH toolbox performance-based measure of EF represents a more acute snapshot of EF whereas the BRIEF 2 Parent-Report Survey represents the typical performance of the child and behaviors are rated accordingly to how often the parent has observed the child demonstrate them over the past 6 months. As such, the NIH toolbox, as opposed to the BRIEF 2 Parent Survey is more sensitive to temporary changes in the child such as wakefulness and cognitive energy secondary to post-prandial food response, which varies by biological sex and glucoregulation (Anderson et al., 2020). Thus, the results found here could also suggest that while there may be an effect of inflammation on EF ability as well as the behavioral expression of EF, this effect may be overshadowed by situational factors when true EF ability is observed in a single, acute snapshot.

Discrepancies were also identified among measures of inflammation in their relation to EF variables. While CRP demonstrated small effects in association with several measures of EF (including behavior and emotion regulation as well as the composite parent-report), IL-6 only demonstrated a small effect in association with parent-reported cognitive regulation and neared a small effect in association with performance-based working memory. TNFa, by contrast, showed no signals of association with EF measures. Because this study was among the first to examine all three of these variables in relation to EF in children, these findings are informative. CRP results are primarily consistent with previous studies in children with chronic illnesses. IL-6 results may indicate that cognitive regulation, and perhaps working memory, are associated with changes in IL-6, when other domains of EF are not. TNFa results may indicate that this marker of inflammation does not directly influence EF in children. However, much like the EF discrepancies, these results may be due in part to the measures themselves rather than the markers' influence themselves. These markers were measured systemically, that is, they were measured based on their levels in circulating plasma. To influence EF, these cytokines would have to enter the brain either through the nervous system itself or by permeating the blood brain barrier or choroid plexus. There is evidence that questions the representativeness of circulating cytokines to approximate cytokine levels in the brain, particularly in specific areas of the brain responsible for specialized cognitive function, given that some pathophysiological processes have differential effects on systemic and neuroinflammation (Huang, Irwin, Wong, & Chang, 2018; Wanrooy et al., 2018). Perhaps circulating CRP is more representative of brain-

based CRP, whereas circulating IL-6 and TNFa are not representative of levels of these cytokines in the brain.

Limitations

Several limitations must be considered when interpreting these results. As previously stated, there are inherent limitations in some of our measures. Cytokines were measured peripherally, rather than measured directly from the central nervous system. The present study may be limited in that we did not assess serum leptin levels, which has emerged as a link between metabolic responses and inflammation; however, given the novel state of this literature as well as lack of assay availability, it is infeasible for the present time. This will be an important step for future research to undertake. We also did not assess food records due to feasibility, which may be important in understanding inflammatory reactions to western and high fat diet and thus important to consider in future steps.

The NIH toolbox performance-based measures of EF represent a snapshot of EF performance, and may be more sensitive to variability due to situational factors, such as post-prandial cognition, fatigue, quality of sleep, timing of administration, etc. Further, the timing of glucose administration preceding EF measurements may also have limited EF testing results, in that children show varying cognitive reaction times to glucose. This timing was chosen because of feasibility issues and coordinating multiple measures at one visit. As such, due to the nature of our study's procedures' departure from the typical administration of the NIH toolbox, the scores obtained from our sample may not be comparable to those on whom the test was normed. In attempts to mitigate the influence

of post-prandial glucose levels' effect on cognition, we included fasting glucose as a covariate. It will be important for future studies to prioritize minimizing departures from the typical administration of the NIH toolbox to eliminate this potential influence on results.

The cross-sectional nature of this study further limits the interpretation of results. We cannot draw support for directionality of the examined relationships given that measures were obtained concurrently. Further, COVID-19 interrupted data collection and reduced the sample size for this study by approximately one-third of what we intended to collect. This had subsequent effects on statistical power, such that all but one of our aims was underpowered and many analyses were particularly underpowered with the addition of covariates. As such, we have relied more heavily on effect sizes, rather than statistical significance, in our interpretation of results. It is our hope to replicate this study in a larger sample with a longitudinal design to begin addressing some of these limitations.

Implications and Future Directions

Our findings extend upon adult psychoneuroimmunology research to demonstrate preliminary evidence that in children as young as 8 years of age, increased body fat is contributing to chronic inflammation across several markers of inflammation, which is a well-established risk factor for obesity-associated diseases in adulthood, including cancer, heart and lung diseases, and diabetes. In turn, this chronic inflammation is contributing to poorer EF, and EF is predictive not only of obesity treatment success, but also of educational success and overall quality of life (QOL; (Sanz et al., 2018; Watts, Duncan, & Quan, 2018). With replication, these results could unveil chronic

inflammation as a potential target for improving EF in children with obesity to improve EF-associated outcomes such as obesity treatment response. Further, the present study paves the way for longitudinal, contextual, and clinical extensions of the current study. In contextual extensions, it would be important to investigate the cyclical nature of the mediation (i.e. does executive function in turn influence adiposity through an influence on dysregulated eating behavior?) and how quality of life (QOL) may extend the mediation (i.e. does adiposity influence QOL through its indirect effect on EF?). Clinical extensions may identify and test mechanisms to ameliorate increased adiposity, inflammation, or executive dysfunction directly and/or mitigate their effect on one another. Further, clinical extension studies could examine resiliency factors among these relations (such as parent EF, global cognition, physical activity levels, etc.) to illuminate clinical targets for improving the deleterious effects of pediatric obesity on child health.

Conclusions

This study was the first to examine the immunopathology of obesity's effects on EF in school-aged children. Results primarily support our hypothesis that increased percent body fat is associated with increased inflammation, which is in turn associated with greater executive dysfunction. However, results were mixed, potentially due to study limitations, and leave much to be understood about the ubiquity of the observed findings. Nevertheless, this study represents an imperative step in documenting the psychoneuroimmunologic effects of overweight and obesity in children, such that clinical targets may be identified to improve pediatric obesity treatment outcomes and prevent the development of obesity-associated diseases in adulthood.

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APPENDIX A

IRB APPROVAL LETTER

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

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Birmingham, AL 35294-0104
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APPROVAL LETTER

TO: Gowey, Marissa

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 07-Aug-2018

RE: IRB-300001247
ACCEPT: Acceptance-Based Care for Child Eating and Physical Activity Treatment (Addressing Healthcare Disparities in Pediatric Obesity Treatment: Development of a Novel, Patient-Centered Intervention Targeting Executive Function)

The IRB reviewed and approved the Revision/Amendment submitted on 07-Aug-2018 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	4, 7
Determination:	Approved
Approval Date:	07-Aug-2018
Expiration Date:	12-Feb-2019

The following populations are approved for inclusion in this project:

- Children – CRL 1

Documents Included in Review:

- training.180807
- praf.180802
- training.180807

Project Revision/Amendment Form

Form version: June 26, 2012

In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck.

- **Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for Investigators for additional information.**
- **Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.). See Item 4 for more examples.**

1. Today's Date	8/2/18

2. Principal Investigator (PI)

Name (with degree)	Marissa Gowey, PhD	**Blazer ID**	mgowey
Department	Pediatrics	**Division (if applicable)**	Gastroenterology, Hepatology and Nutrition
Office Address	1600 7th Ave. S. 5th Floor Dearth Tower Suite 5604 McWane Birmingham, AL 35209	**Office Phone**	205-638-6418
E-mail	mgowey@peds.uab.edu	**Fax Number**	205-638-7455

Contact person who should receive copies of IRB correspondence (Optional)

Name	Caroline Keller, MPH	**E-Mail**	ckeller@peds.uab.edu
Phone	205-638-6543	**Fax Number**	205-638-7455
Office Address (if different from PI)			

3. UAB IRB Protocol Identification

3.a. Protocol Number	IRB-300001247
3.b. Protocol Title	ACCEPT: Acceptance-Based Care for Child Eating and Physical Activity Treatment (Addressing Healthcare Disparities in Pediatric Obesity Treatment: Development of a Novel, Patient-Centered Intervention Targeting Executive Function)

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☒ **Study has not yet begun** — **No participants, data, or specimens have been entered.**
- ☐ **In progress, open to accrual** — **Number of participants, data, or specimens entered:**
- ☐ **Enrollment temporarily suspended by sponsor**
- ☐ **Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)**
  - **Date closed:**
  - **Number of participants receiving interventions:**
  - **Number of participants in long-term follow-up only:**
- ☐ **Closed to accrual, and only data analysis continues**
  - **Date closed:**
  - **Total number of participants entered:**

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- ☐ **Protocol revision (change in the IRB-approved protocol)**
  In Item 5.c., if applicable, provide sponsor's protocol version number, amendment number, update number, etc.
- ☐ **Protocol amendment (addition to the IRB-approved protocol)**
  In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☐ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c., (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).

☐	**Change in source of funding; change or add funding** In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.
☐	**Add or remove performance sites** In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.
☐	**Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)** To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789.
☐	**Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)** In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.
☐	**Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)** In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.
☐	**Revise or amend consent, assent form(s)** Complete Item 5.d.
☐	**Addendum (new) consent form** Complete Item 5.d.
☐	**Add or revise recruitment materials** Complete Item 5.d.
☐	**Other (e.g., investigator brochure)** Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable. Include a copy of all affected documents, with revisions highlighted as applicable.

▶

5. Description and Rationale

In Item 5.a. and 5.b, check Yes **or** No **and see instructions for** Yes **responses.**
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

☐Yes ☒No	**5.a. Are any of the participants enrolled as normal, healthy controls?** If yes, describe in detail in Item 5.c. how this change will affect those participants.
☐Yes ☒No	**5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?** If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c. For more details on the UAB FAP, see www.uab.edu/cto.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

▶ Kathryn Prendergast is being added to protocol personnel. She is an incoming Medical Psychology PhD student who will assist with protocol implementation, screen potential participants, obtain consent, and assist with performing measures and intervention delivery. She will also assist with statistical analysis, interpretation of findings, and dissemination of research. She does not have any conflict of interest.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- **a copy of the currently approved document (showing the IRB approval stamp, if applicable)**
- **a revised copy highlighting all proposed changes with "tracked" changes**
- **a revised copy for the IRB approval stamp.**

▶

Signature of Principal Investigator_____ Date_8/2/18__

FOR IRB USE ONLY

☐ Received & Noted ☐ Approved Expedited* ☐ To Convened IRB

_____ _____

Signature (Chair, Vice-Chair, Designee) Date

DOLA _____

Change to Expedited Category **Y / N / NA**

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111

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APPROVAL LETTER

TO: Gowey, Marissa

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 02-Apr-2020

RE: IRB-300001247
ACCEPT: Acceptance-Based Care for Child Eating and Physical Activity Treatment (Addressing Healthcare Disparities in Pediatric Obesity Treatment: Development of a Novel, Patient-Centered Intervention Targeting Executive Function)

The IRB reviewed and approved the Revision/Amendment submitted on 01-Apr-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: b2
Determination: Approved
Approval Date: 02-Apr-2020
Expiration Date: 03-Dec-2020

The following populations are approved for inclusion in this project:

- Children – CRL 1

Documents Included in Review:

- recruitmentcomms.200401
- consent(ACBIO_clean).200401.doc
- recruitmentad.200401
- flyer.200401
- praf.200401.pdf

APPENDIX B

EXTENDED TABLES

Table 4

Aim 1: Regressing Inflammation onto Adiposity

Outcome: hsCRP				**Outcome: IL-6**				**Outcome: TNFa**			
Predictors	β	***t***	***p* -value**	**Predictors**	β	***t***	***p* -value**	**Predictors**	β	***t***	***p* -value**
Model 1 (R^2 = 0.198, p = 0.005)				***Model 1 (R^2 = 0.191, p = 0.005)***				***Model 1 (R^2 = 0.15, p = 0.015)***			
Percent Body Fat (DXA TBLH)	0.445*	3.022	0.005	Percent Body Fat (DXA TBLH)	0.438*	2.960	0.005	Percent Body Fat (DXA TBLH)	0.388*	2.559	0.015
Model 2 (R^2 = 0.145, p = 0.136)				***Model 2 (R^2 = 0.128, p = 0.181)***				***Model 2 (R^2 = 0.067, p = 0.484)***			
Insulin	0.127	0.809	0.424	Insulin	0.255	1.605	0.117	Insulin	0.124	0.757	0.454
Glucose	-0.226	-1.427	0.162	Glucose	-0.049	-0.305	0.762	Glucose	-0.159	-0.961	0.343
Tanner Stage of Pubertal Development	-0.268	-1.702	0.098	Tanner Stage of Pubertal Development	-0.252	-1.585	0.122	Tanner Stage of Pubertal Development	-0.160	-0.972	0.338
Model 3 (R^2 = 0.264, p = 0.030; ΔR^2 = 0.119)				***Model 3 (R^2 = 0.242, p = 0.046; ΔR^2 = 0.113)***				***Model 3 (R^2 = 0.168, p = 0.168; ΔR^2 = 0.102)***			
Insulin	-0.018	-0.109	0.914	Insulin	0.114	0.700	0.489	Insulin	-0.009	-0.053	0.958
Glucose	-0.126	-0.816	0.420	Glucose	0.048	0.306	0.761	Glucose	-0.067	-0.407	0.686
Tanner Stage of Pubertal Development	-0.215	-1.436	0.160	Tanner Stage of Pubertal Development	-0.200	-1.319	0.196	Tanner Stage of Pubertal Development	-0.111	-0.698	0.490
Percent Body Fat (DXA TBLH)	0.388*	2.348	0.025	Percent Body Fat (DXA TBLH)	0.378*	2.254	0.031	Percent Body Fat (DXA TBLH)	0.358*	2.037	0.049

Table 5

Aim 2a: Regressing Cognitive Flexibility onto Inflammation

Outcome: Dimensional Change Card Sort Test (Cognitive Flexibility)											
Predictors	β	***t***	***p*-value**	**Predictors**	β	***t***	***p* -value**	**Predictors**	β	***t***	***p* -value**
Model 1 (R^2 = 0.055, p = 0.152)				***Model 1 (R^2 = 0.004, p = 0.713)***				***Model 1 (R^2 = 0.000, p = 0.895)***			
hsCRP	-0.234	-1.463	.152	IL-6	-0.061	-0.371	0.713	TNFa	-0.022	-0.133	0.895
Model 2 (R^2 = 0.032, p = 0.760)				***Model 2 (R^2 = 0.032, p = 0.760)***				***Model 2 (R^2 = 0.032, p = 0.760)***			
Insulin	0.127	0.757	0.454	Insulin	0.127	0.757	0.454	Insulin	0.127	0.757	0.454
Glucose	-0.125	-0.740	0.464	Glucose	-0.125	-0.740	0.464	Glucose	-0.125	-0.740	0.464
Tanner Stage of Pubertal Development	0.080	0.477	0.636	Tanner Stage of Pubertal Development	0.080	0.477	0.636	Tanner Stage of Pubertal Development	0.080	0.477	0.636
Model 3 (R^2 = 0.264, p = 0.410; ΔR^2 = 0.101)				***Model 3 (R^2 = 0.039, p = 0.843; ΔR^2 = 0.007)***				***Model 3 (R^2 = 0.034, p = 0.875; ΔR^2 = 0.002)***			
Insulin	0.164	0.998	0.325	Insulin	0.149	0.852	0.400	Insulin	0.132	0.773	0.445
Glucose	-0.191	-1.134	0.265	Glucose	-0.129	-0.757	0.454	Glucose	-0.132	-0.761	0.452
Tanner Stage of Pubertal Development	0.001	0.004	0.997	Tanner Stage of Pubertal Development	0.057	0.328	0.745	Tanner Stage of Pubertal Development	0.073	0.423	0.675
hsCRP	-0.296	-1.688	0.101	IL-6	-0.089	-0.495	0.624	TNFa	-0.044	-0.253	0.802

Table 6

Aim 2a: Regressing Inhibitory Control onto Inflammation

Outcome: Flanker Inhibitory Control and Attention Test											
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**
Model 1 (R^2 = 0.005, p = 0.681)				***Model 1 (R^2 = 0.005, p = 0.673)***				***Model 1 (R^2 = 0001., p = 0.841)***			
hsCRP	-0.068	-0.415	0.681	IL-6	0.070	0.425	0.673	TNFa	0.033	0.202	0.841
Model 2 (R^2 = 0.034, p = 0.748)				***Model 2 (R^2 = 0.034, p = 0.748)***				***Model 2 (R^2 = 0.034, p = 0.748)***			
Insulin	-0.073	-0.438	0.664	Insulin	-0.073	-0.438	0.664	Insulin	-0.073	-0.438	0.664
Glucose	-0.062	-0.368	0.715	Glucose	-0.062	-0.368	0.715	Glucose	-0.062	-0.368	0.715
Tanner Stage of Pubertal Development	-0.145	-0.870	0.390	Tanner Stage of Pubertal Development	-0.145	-0.870	0.390	Tanner Stage of Pubertal Development	-0.145	-0.870	0.390
Model 3 (R^2 = 0.050, p = 0.772; ΔR^2 = 0.016)				***Model 3 (R^2 = 0.036, p = 0.861; ΔR^2 = 0.003)***				***Model 3 (R^2 = 0.034, p = 0.877; ΔR^2 = 0.000)***			
Insulin	-0.056	-0.328	0.745	Insulin	-0.087	-0.498	0.622	Insulin	-0.074	-0.433	0.668
Glucose	-0.093	-0.535	0.596	Glucose	-0.059	-0.347	0.731	Glucose	-0.061	-0.353	0.726
Tanner Stage of Pubertal Development	-0.182	-1.042	0.305	Tanner Stage of Pubertal Development	-0.132	-0.750	0.458	Tanner Stage of Pubertal Development	-0.145	-0.841	0.406
hsCRP	-0.138	-0.765	0.449	IL-6	0.055	0.306	0.762	TNFa	0.006	0.032	0.975

Table 7

Aim 2a: Regressing Working Memory onto Inflammation

Outcome: List Sorting Working Memory Test										
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	**P-value**
Model 1 (R^2 = 0.035, p= 0.253)				***Model 1 (R^2 = 0.046, p = 0.192)***				***Model 1 (R^2 = 0.010, p = 0.536)***		
hsCRP	-0.187	-1.161	0.253	IL-6	-0.214	-1.330	0.192	TNFa	0.102	0.625	0.536
Model 2 (R^2 = 0.020, p = 0.866)				***Model 2 (R^2 = 0.020, p = 0.866)***				***Model 2 (R^2 = 0.020, p = 0.866)***		
Insulin	0.089	0.527	0.602	Insulin	0.089	0.527	0.602	Insulin	0.089	0.527	0.602
Glucose	-0.083	-0.487	0.629	Glucose	-0.083	-0.487	0.629	Glucose	-0.083	-0.487	0.629
Tanner Stage of Pubertal Development	-0.079	-0.467	0.643	Tanner Stage of Pubertal Development	-0.079	-0.467	0.643	Tanner Stage of Pubertal Development	-0.079	-0.467	0.643
Model 3 (R^2 = 0.087, p = 0.527; ΔR^2 = 0.067)				***Model 3 (R^2 = 0.097, p = 0.465; ΔR^2 = 0.077)***				***Model 3 (R^2 = 0.025, p = 0.926; ΔR^2 = 0.005)***		
Insulin	0.124	0.746	0.461	Insulin	0.165	0.968	0.340	Insulin	0.080	0.465	0.645
Glucose	-0.146	-0.853	0.400	Glucose	-0.097	-0.587	0.561	Glucose	-0.071	-0.410	0.684
Tanner Stage of Pubertal Development	-0.153	-0.894	0.377	Tanner Stage of Pubertal Development	-0.154	-0.905	0.372	Tanner Stage of Pubertal Development	-0.067	-0.390	0.699
hsCRP	-0.279	-1.576	0.124	IL-6	-0.297	-1.704	0.098	TNFa	0.071	0.403	0.690

Table 8

AIM 2a: Regressing Processing Speed onto Inflammation

Outcome: Pattern Comparison Processing Speed Test											
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**
Model 1 (R^2 = 0.002, p = 0.793)				***Model 1 (R^2 = 0.002, p = 0.785)***				***Model 1 (R^2 = 0.003, p = 0.761)***			
hsCRP	-0.043	-0.264	0.793	IL-6	0.045	0.275	0.785	TNFa	0.050	0.307	0.761
Model 2 (R^2 = 0.010, p = 0.952)				***Model 2 (R^2 = 0.010, p = 0.952)***				***Model 2 (R^2 = 0.010, p = 0.952)***			
Insulin	0.060	0.353	0.727	Insulin	0.060	0.353	0.727	Insulin	0.060	0.353	0.727
Glucose	0.055	0.324	0.748	Glucose	0.055	0.324	0.748	Glucose	0.055	0.324	0.748
Tanner Stage of Pubertal Development	-0.055	-0.325	0.747	Tanner Stage of Pubertal Development	-0.055	-0.325	0.747	Tanner Stage of Pubertal Development	-0.055	-0.325	0.747
Model 3 (R^2 = 0.012, p = 0.978; ΔR^2 = 0.003)				***Model 3 (R^2 = 0.010, p = 0.986, ΔR^2 = 0.000)***				***Model 3 (R^2 = 0.012, p = 0.982, ΔR^2 = 0.002)***			
Insulin	0.067	0.389	0.699	Insulin	0.054	0.304	0.763	Insulin	0.054	0.312	0.757
Glucose	0.041	0.233	0.817	Glucose	0.056	0.325	0.747	Glucose	0.063	0.358	0.723
Tanner Stage of Pubertal Development	-0.071	-0.399	0.692	Tanner Stage of Pubertal Development	-0.049	-0.278	0.783	Tanner Stage of Pubertal Development	-0.048	-0.274	0.786
hsCRP	-0.061	-0.329	0.744	IL-6	0.022	0.121	0.904	TNFa	0.047	0.264	0.793

Table 9

AIM 2a: Regressing General Executive Composite onto Inflammation

Outcome: BRIEF-2 Parent Report General Executive Composite (GEC) Score											
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**
Model 1 (R^2 = 0.149, p = 0.015)				***Model 1 (R^2 = 0.056, p = 0.148)***				***Model 1 (R^2 = 0.020, p = 0.395)***			
hsCRP	0.386*	2.548	0.015	IL-6	0.236	1.479	0.148	TNFa	0.140	0.861	.395
Model 2 (R^2 = 0.013, p = 0.929)				***Model 2 (R^2 = 0.013, p = 0.929)***				***Model 2 (R^2 = 0.013, p = 0.929)***			
Insulin	-0.008	-0.047	0.963	Insulin	-0.008	-0.047	0.963	Insulin	-0.008	-0.047	0.963
Glucose	-0.059	-0.344	0.733	Glucose	-0.059	-0.344	0.733	Glucose	-0.059	-0.344	0.733
Tanner Stage of Pubertal Development	-0.089	-0.524	0.604	Tanner Stage of Pubertal Development	-0.089	-0.524	0.604	Tanner Stage of Pubertal Development	-0.089	-0.524	0.604
Model 3 (R^2 = 0.154, p = 0.0.212; ΔR^2 = 0.141)				***Model 3 (R^2 = 0.065, p = 0.673; ΔR^2 = 0.052)***				***Model 3 (R^2 = 0.027, p = 0.916, ΔR^2 = 0.014)***			
Insulin	-0.060	-0.372	0.712	Insulin	-0.070	-0.406	0.687	Insulin	-0.023	-0.136	0.893
Glucose	0.033	0.202	0.841	Glucose	-0.047	-0.277	0.783	Glucose	-0.039	-0.224	0.824
Tanner Stage of Pubertal Development	0.020	0.122	0.904	Tanner Stage of Pubertal Development	-0.027	-0.156	0.877	Tanner Stage of Pubertal Development	-0.069	-0.398	0.693
hsCRP	0.406*	2.380	0.023	IL-6	0.244	1.376	0.178	TNFa	0.124	0.709	0.483

Table 10

Aim 2a: Regressing Behavior Regulation onto Inflammation

Outcome: BRIEF 2 Parent-Report Behavior Regulation Index (BRI)											
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**
Model 1 (R^2 = 0.106, p = 0.043)				***Model 1 (R^2 = 0.013, p = 0.490)***				***Model 1 (R^2 = 0.013, p = 0.492)***			
hsCRP	0.326*	2.097	0.043	IL-6	0.114	0.697	0.490	TNFa	0.113	0.694	0.492
Model 2 (R^2 = 0.010, p = 0.949)				***Model 2 (R^2 = 0.010, p = 0.949)***				***Model 2 (R^2 = 0.010, p = 0.949)***			
Insulin	0.027	0.161	0.873	Insulin	0.027	0.161	0.873	Insulin	0.027	0.161	0.873
Glucose	-0.024	-0.143	0.887	Glucose	-0.024	-0.143	0.887	Glucose	-0.024	-0.143	0.887
Tanner Stage of Pubertal Development	-0.092	-0.543	0.591	Tanner Stage of Pubertal Development	-0.092	-0.543	0.591	Tanner Stage of Pubertal Development	-0.092	-0.543	0.591
Model 3 (R^2 = 0.109, p = 0.402; ΔR^2 = 0.099)				***Model 3 (R^2 = 0.018, p = 0.959; ΔR^2 = 0.008)***				***Model 3 (R^2 = 0.019, p = 0.949, ΔR^2 = 0.009)***			
Insulin	-0.016	-0.097	0.923	Insulin	0.003	0.017	0.986	Insulin	0.015	0.088	0.930
Glucose	0.052	0.310	0.758	Glucose	-0.020	-0.115	0.909	Glucose	-0.009	-0.052	0.959
Tanner Stage of Pubertal Development	-0.001	-0.005	0.996	Tanner Stage of Pubertal Development	-0.068	-0.384	0.704	Tanner Stage of Pubertal Development	-0.076	-0.441	0.662
hsCRP	0.340	1.941	0.061	IL-6	0.095	0.522	0.605	TNFa	0.097	0.551	0.585

Table 11

Aim 2a: Regressing Emotion Regulation onto Inflammation

Outcome: BRIEF 2 Parent-Report Emotion Regulation Index (ERI)											
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**
Model 1 (R^2 = 0.154, p = 0.013)				***Model 1 (R^2 = 0.069, p = 0.107)***				***Model 1 (R^2 = 0.040, p = 0.223)***			
hsCRP	0.393*	2.598	0.013	IL-6	0.262	1.653	0.107	TNFa	0.200	1.239	0.223
Model 2 (R^2 = 0.073, p = 0.441)				***Model 2 (R^2 = 0.073, p = 0.441)***				***Model 2 (R^2 = 0.073, p = 0.441)***			
Insulin	0.132	0.803	0.427	Insulin	0.132	0.803	0.427	Insulin	0.132	0.803	0.427
Glucose	-0.101	-0.610	0.546	Glucose	-0.101	-0.610	0.546	Glucose	-0.101	-0.610	0.546
Tanner Stage of Pubertal Development	-0.212	-1.295	0.204	Tanner Stage of Pubertal Development	-0.212	-1.295	0.204	Tanner Stage of Pubertal Development	-0.212	-1.295	0.204
Model 3 (R^2 = 0.174, p = 0.153; ΔR^2 = 0.101)				***Model 3 (R^2 = 0.107, p = 0.412; ΔR^2 = 0.034)***				***Model 3 (R^2 = 0.092, p = 0.497, ΔR^2 = 0.019)***			
Insulin	0.088	0.555	0.583	Insulin	0.081	0.481	0.633	Insulin	0.114	0.687	0.497
Glucose	-0.023	-0.141	0.889	Glucose	-0.091	-0.553	0.584	Glucose	-0.078	-0.465	0.645
Tanner Stage of Pubertal Development	-0.120	-0.736	0.467	Tanner Stage of Pubertal Development	-0.163	-0.963	0.342	Tanner Stage of Pubertal Development	-0.190	-1.137	0.264
hsCRP	0.344*	2.040	0.049	IL-6	0.197	1.134	0.265	TNFa	0.142	0.839	0.407

Table 12

Aim 2a: Regressing Cognitive Regulation onto Inflammation

Outcome: BRIEF 2 Parent-Report Cognitive Regulation Index (CRI)											
Predictors	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**	**Predictors**	**β**	***t***	**P-value**
Model 1 (R^2 = 0.11, p = 0.039)				***Model 1 (R^2 = 0.096, p = 0.055)***				***Model 1 (R^2 = 0.003, p = 0.750)***			
hsCRP	0.332*	2.143	0.039	IL-6	0.309	1.979	0.055	TNFa	-0.053	-0.322	0.750
Model 2 (R^2 = 0.027, p = 0.807)				***Model 2 (R^2 = 0.027, p = 0.807)***				***Model 2 (R^2 = 0.027, p = 0.807)***			
Insulin	-0.114	-0.678	0.502	Insulin	-0.114	-0.678	0.502	Insulin	-0.114	-0.678	0.502
Glucose	0.028	0.163	0.871	Glucose	0.028	0.163	0.871	Glucose	0.028	0.163	0.871
Tanner Stage of Pubertal Development	-0.120	-0.715	0.480	Tanner Stage of Pubertal Development	-0.120	-0.715	0.480	Tanner Stage of Pubertal Development	-0.120	-0.715	0.480
Model 3 (R^2 = 0.143, p = 0.248, ΔR^2 = 0.116)				***Model 3 (R^2 = 0.136, p = 0.275, ΔR^2 = 0.109)***				***Model 3 (R^2 = 0.031, p = 0.896, ΔR^2 = 0.004)***			
Insulin	-0.161	-0.996	0.326	Insulin	-0.204	-1.227	0.228	Insulin	-0.106	-0.619	0.540
Glucose	0.111	0.670	0.508	Glucose	0.045	0.277	0.783	Glucose	0.018	0.102	0.919
Tanner Stage of Pubertal Development	-0.021	-0.128	0.899	Tanner Stage of Pubertal Development	-0.031	-0.186	0.854	Tanner Stage of Pubertal Development	-0.130	-0.753	0.456
hsCRP	0.368*	2.146	0.039	IL-6	0.354*	2.071	0.046	TNFa	-0.062	-0.353	0.726

Table 13

AIM 2b: Moderation of Inflammation and Cognitive Flexibility by Adiposity

Outcome: Dimensional Change Card Sort Test (Cognitive Flexibility)			
Predictors	β	***t***	**P-value**
Model 1 (R^2 = 0.089, p = 0.186)			
hsCRP	-0.326	-1.836	0.075
Percent Body Fat (DXA TBLH)	0.207	1.167	0.251
Model 2 (R^2 = 0.096, p = 0.312, ΔR^2 = 0.007)			
hsCRP	-0.328	1.256	0.217
Percent Body Fat (DXA TBLH)	0.238	-1.826	0.076
CRP x DXA	0.086	0.503	0.618
Model 3 (R^2 = 0.120, p = 0.492)			
Insulin	0.119	0.669	0.508
Glucose	-0.167	-0.964	0.342
Tanner Stage of Pubertal Development	0.006	0.035	0.972
hsCRP	-0.345	-1.814	0.079
Percent Body Fat (DXA TBLH)	0.138	0.697	0.490
Model 4 (R^2 = 0.121, p = 0.624, ΔR^2 = 0.001)			
Insulin	0.113	0.617	0.542
Glucose	-0.158	-0.864	0.394
Tanner Stage of Pubertal Development	0.009	0.052	0.959
hsCRP	-0.344	-1.780	0.085
Percent Body Fat (DXA TBLH)	0.155	0.712	0.482
CRP x DXA	0.037	0.202	0.841

Table 14

AIM 2b: Moderation of Inflammation and GEC by Adiposity

Outcome: BRIEF 2 General Executive Composite Score			
Predictors	β	***t***	**P-value**
Model 1 (R^2 = 0.165, p = 0.039)			
hsCRP	0.449*	2.641	0.012
Percent Body Fat (DXA TBLH)	-0.141	-0.828	0.413
Model 2 (R^2 = 0.189, p = 0.059, ΔR^2 = 0.024)			
hsCRP	0.452*	2.661	0.012
Percent Body Fat (DXA TBLH)	-0.200	-1.113	0.273
CRP x DXA	-0.165	-1.015	0.317
Model 3 (R^2 = 0.284, p = 0.284)			
Insulin	-0.016	-0.093	0.927
Glucose	0.010	0.058	0.954
Tanner Stage of Pubertal Development	0.015	0.089	0.929
hsCRP	0.454*	2.448	0.020
Percent Body Fat (DXA TBLH)	-0.133	-0.690	0.495
Model 4 (R^2 = 0.190, p = 0.307, ΔR^2 = 0.024)			
Insulin	0.012	0.070	0.944
Glucose	-0.035	-0.200	0.843
Tanner Stage of Pubertal Development	0.001	0.005	0.996
hsCRP	0.448	2.412	0.022
Percent Body Fat (DXA TBLH)	-0.213	-1.019	0.316
CRP x DXA	-0.175	-0.983	0.333

Table 15

Aim 3: Regressing EF onto Adiposity

Outcome: Dimensional Change Card Sort Test (Cognitive Flexibility)				**Outcome: Flanker Inhibitory Control and Attention Test**				**Outcome: List Sorting Working Memory Test**			
Predictors	β	***t***	**P-value**	**Predictors**	β	***t***	**P-value**	**Predictors**	β	***t***	**P-value**
Model 1 (R^2 = 0.004, p = 0.707)				***Model 1 (R^2 = 0.000, p = 0.962)***				***Model 1 (R^2 = 0.003, p = 0.749)***			
Percent Body Fat (DXA TBLH)	0.062	0.039	0.707	Percent Body Fat (DXA TBLH)	-0.008	-0.048	0.962	Percent Body Fat (DXA TBLH)	0.053	0.322	0.749
Model 2 (R^2 = 0.032, p = 0.760)				***Model 2 (R^2 = 0.034, p = 0.748)***				***Model 2 (R^2 = 0.020, p = 0.866)***			
Insulin	0.127	0.757	0.454	Insulin	-0.073	-0.438	0.664	Insulin	0.089	0.527	0.602
Glucose	-0.125	-0.740	0.464	Glucose	-0.062	-0.368	0.715	Glucose	-0.083	-0.487	0.629
Tanner Stage of Pubertal Development	0.080	0.477	0.636	Tanner Stage of Pubertal Development	-0.145	-0.870	0.390	Tanner Stage of Pubertal Development	-0.079	-0.467	0.643
Model 3 (R^2 = 0.032, p = 0.886; ΔR^2 = 0.000)				***Model 3 (R^2 = 0.034, p = 0.874; ΔR^2 = 0.001)***				***Model 3 (R^2 = 0.020, p = 0.948, ΔR^2 = 0.000)***			
Insulin	0.125	0.681	0.501	Insulin	-0.064	-0.348	0.730	Insulin	0.093	0.501	0.619
Glucose	-0.124	-0.698	0.491	Glucose	-0.068	-0.385	0.702	Glucose	-0.085	-0.477	0.636
Tanner Stage of Pubertal Development	0.080	0.468	0.643	Tanner Stage of Pubertal Development	-0.149	-0.868	0.392	Tanner Stage of Pubertal Development	-0.080	-0.464	0.646
Percent Body Fat (DXA TBLH)	0.004	0.020	0.984	Percent Body Fat (DXA TBLH)	-0.025	-0.134	0.895	Percent Body Fat (DXA TBLH)	-0.011	-0.057	0.955

Outcome: Pattern Comparison Processing Speed				**Outcome: BRIEF-2 Parent Report General Executive Composite (GEC)**				**Outcome: BRIEF 2 Parent-Report Behavior Regulation Index (BRI)**			
Predictors	β	***t***	**P-value**	**Predictors**	β	***T***	**P-value**	**Predictors**	β	***t***	**P-value**
Model 1 (R^2 = 0.041, p = 0.218)				***Model 1 (R^2 = 0.003, p = 0.722)***				***Model 1 (R^2 = 0.000, p = 0.905)***			
Percent Body Fat (DXA TBLH)	0.202	1.252	0.218	Percent Body Fat (DXA TBLH)	0.059	0.359	0.722	Percent Body Fat (DXA TBLH)	0.020	0.120	0.905
Model 2 (R^2 = 0.010, p = 0.952)				***Model 2 (R^2 = 0.013, p = 0.929)***				***Model 2 (R^2 = 0.010, p = 0.949)***			
Insulin	0.060	0.353	0.727	Insulin	-0.008	-0.047	0.963	Insulin	0.027	0.161	0.873
Glucose	0.055	0.324	0.748	Glucose	-0.059	-0.344	0.733	Glucose	-0.024	-0.143	0.887
Tanner Stage of Pubertal Development	-0.055	-0.325	0.747	Tanner Stage of Pubertal Development	-0.089	-0.524	0.604	Tanner Stage of Pubertal Development	-0.092	-0.543	0.591
Model 3 (R^2 = 0.053, p = 0.754; ΔR^2 = 0.043)				***Model 3 (R^2 = 0.014, p = 0.979, ΔR^2 = 0.001)***				***Model 3 (R^2 = 0.010, p = 0.986, ΔR^2 = 0.000)***			
Insulin	-0.027	-0.151	0.881	Insulin	-0.024	-0.129	0.898	Insulin	0.032	0.171	0.865
Glucose	0.115	0.655	0.517	Glucose	-0.048	-0.265	0.793	Glucose	-0.028	-0.153	0.879
Tanner Stage of Pubertal Development	-0.023	-0.137	0.892	Tanner Stage of Pubertal Development	-0.083	-0.477	0.636	Tanner Stage of Pubertal Development	-0.093	-0.538	0.594
Percent Body Fat (DXA TBLH)	0.234	1.247	0.221	Percent Body Fat (DXA TBLH)	0.043	0.226	0.823	Percent Body Fat (DXA TBLH)	-0.012	-0.064	0.950

Outcome: BRIEF-2 Parent Report Emotion Regulation Index (ERI)				**Outcome: BRIEF 2 Parent-Report Cognitive Regulation Index (CRI)**			
Predictors	β	***T***	**P-value**	**Predictors**	β	***t***	**P-value**
Model 1 (R^2 = 0.016, p = 0.438)				***Model 1 (R^2 = 0.078, p = 0.636)***			
Percent Body Fat (DXA TBLH)	0.128	0.785	0.438	Percent Body Fat (DXA TBLH)	0.078	0.477	0.636
Model 2 (R^2 = 0.073, p = 0.441)				***Model 2 (R^2 = 0.027, p = 0.807)***			
Insulin	0.132	0.803	0.427	Insulin	-0.114	-0.678	0.502
Glucose	-0.101	-0.610	0.546	Glucose	0.028	0.163	0.871
Tanner Stage of Pubertal Development	-0.212	-1.295	0.204	Tanner Stage of Pubertal Development	-0.120	-0.715	0.480
Model 3 (R^2 = 0.074, p = 0.610, ΔR^2 = 0.001)				***Model 3 (R^2 = 0.041, p = 0.834, ΔR^2 = 0.014)***			
Insulin	0.119	0.662	0.513	Insulin	-0.163	-0.890	0.380
Glucose	-0.092	-0.529	0.600	Glucose	0.061	0.347	0.731
Tanner Stage of Pubertal Development	-0.208	-1.236	0.225	Tanner Stage of Pubertal Development	-0.102	-0.597	0.555
Percent Body Fat (DXA TBLH)	0.033	0.181	0.858	Percent Body Fat (DXA TBLH)	0.132	0.699	0.490