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NATURAL HISTORY OF CHILDHOOD OBESITY: CARDIOMETABOLIC AND SLEEP OUTCOMES AND THEIR UNDERLYING MECHANISMS

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ABSTRACT

The ever-increasing obesity epidemic has led to a corresponding increase in cardiometabolic co-morbidities. Although it is agreed upon that childhood obesity is detrimental for future health, little is known about the trajectories of such weight disorder and its corresponding impact on adverse health outcomes in adolescence. The aim of this study was to examine the natural history of childhood overweight into adolescence and to analyze its association with cardiovascular and metabolic health, sleep disorders, and immune biomarkers. We hypothesized that overweight children will remain overweight in adolescence, and will be associated with more severe forms of cardiometabolic and sleep dysfunction and inflammation, while those with new-onset, incident overweight in adolescence will have less severe adverse outcomes. In Aim 1, we studied the trajectories (natural history) of childhood weight in the transition to adolescence. In Aim 2, we studied the association between such natural history of childhood overweight with adverse cardiometabolic, sleep, and stress/immune-related outcomes in adolescence. In Aim 3, we studied sex differences in the natural history of childhood overweight and its association with adverse health outcomes. We used data from the Penn State Child Cohort, a random general population sample of 700 5-12 year old children, of whom 421 were followed-up as 12-23 year old adolescents. At both time points, subjects underwent a clinical history, physical examination, and in-lab polysomnography study. At follow-up, subjects underwent a dual-energy X-ray absorptiometry scan, to assess for adipose tissue distribution and composition, and a fasting blood draw, to assess for pro-inflammatory cytokines and adipokines. We found that 72% of children with a body mass index (BMI) percentile $\geq$ 85 persisted in their overweight category into adolescence, especially if they were female. These persistently overweight children were significantly associated with a blood pressure dysregulation, higher apnea/hypopnea index, visceral adipose tissue, cytokines and leptin, and lower adiponectin in adolescence. Interestingly, children with new-onset overweight in adolescence were associated with adverse health outcomes similar to persistently overweight children but only in specific cardiometabolic, sleep, and inflammatory outcomes. This study further supports that early prevention of comorbidities should focus on childhood-onset overweight. However, new-onset overweight in adolescence should not be regarded as a less severe form in terms of its adverse health risks. These data also support the clinical utility of a variety of measures of adiposity, other than BMI, to help identify a child's risk for future adverse health outcomes.

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ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADHD	Attention Deficit Hyperactivity Disorder
AHI	Apnea/Hypopnea Index
And/Gyn Ratio	Android to Gynoid Fat Mass Proportion
And/W Ratio	Android to Whole Body Fat Mass Proportion
ANOVA	Analysis of Variance
A/T	Adenotonsillectomy
AVP	Arginine Vasopressin
BMI	Body Mass Index
BMI%	Body Mass Index Percentile
BMR	Basal Metabolic Rate
CBVD	Cerebrovascular Disease
CDC	Center for Disease Control and Prevention
cMetS	Continuous Metabolic Syndrome Score
CNS	Central Nervous System
CRC	Clinical Research Center
CRF	Corticotropin-releasing Factor
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DXA	Dual-energy X-ray Absorptiometry
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
ELISA	Enzyme-linked Immunosorbent Assay
EMG	Electromylogram
ENT	Ear, Nose, and Throat
EOG	Electro-oculogram
Gyn/W Ratio	Gynoid to Whole Body fat Mass Proportion
HC	Hip Circumference
HDL	High-Density Lipoprotein

HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPA	Hypothalamic-pituitary-adrenal
IL-6	Interleukin-6
IOTF	International Obesity Task Force
IRB	Institutional Review Board
MAP	Mean Arterial Pressure
MetS	Metabolic Syndrome
NAFLD	Nonalcoholic Fatty Liver Disease
NC	Neck Circumference
OSA	Obstructive Sleep Apnea
PCOS	Polycystic Ovary Syndrome
PLMI	Periodic Limb Movement Index Score
PSCC	Penn State Child Cohort
PSCOM	Penn State College of Medicine
PSG	Polysomnography
REM	Rapid Eye Movement
SAM	Sympathetic-adrenal-medullary
SAT	Subcutaneous Adipose Tissue
SBP	Systolic Blood Pressure
SDB	Sleep Disordered Breathing
SOL	Sleep Onset Latency
SpO2	Hemoglobin Oxygen Saturation Level
T2D	Type II Diabetes
TG	Triglycerides
TNF-α	Tumor Necrosis Factor - Alpha
TSH	Thyroid Stimulating Hormone
TST	Total Sleep Time
VAT	Visceral Adipose Tissue
WASO	Wake After Sleep Onset
WC	Waist Circumference

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1. Background & Significance

1.1 Introduction: The Obesity Epidemic

The obesity epidemic in the United States is putting an increasing strain on the national healthcare system in regards to cost and resource allocation. Obesity is defined as an abnormal or excess accumulation of adipose tissue that impacts the patient's health (World Health Organization, 2016), and was not considered to be a chronic disease by the Centers for Medicare and Medicaid Services until 2004 (Possa *et al*., 2017; Wang *et al.*, 2015). Unlike many other chronic diseases, obesity intervention requires changes not only in metabolism but also lifestyle as it pertains to diet, sleep, and physical activity levels.

Obesity prevalence has been increasing since the mid-1990s, when at the time, only about 15% of the adult population were categorized as obese within the United States. As of 2013, the Center for Disease Control and Prevention (CDC) estimated that more than 70% of adults were overweight, with 30% of adults being obese, and 14% categorized as severely obese (CDC, 2017a; Wang *et al*., 2015). In 2016, 46 states had obesity rates 25% or higher, of which 25 states had obesity rates exceeding 30% of the state adult population and 5 states had rates higher than 35% (CDC, 2017b). This increase in obesity prevalence across the country has not only affected the health of the individual patients, but ultimately has impacted the healthcare system as a whole. The comorbidities of obesity have resulted in mass healthcare expenditure through Medicaid, Medicare, and private insurance companies. In 2014, it was estimated that the global economic impact of obesity is roughly $2 trillion, with estimate costs of $1 trillion in the United States alone (Kushner *et al*., 2018).

Unfortunately, childhood obesity has also shown a steady increase, paralleling that of adults. In 1963, childhood obesity was almost unheard of, with <5% of the United States

pediatric population suffering from the disorder, while the CDC estimated that in 2008 more than 20% of the pediatric population was obese (CDC, 2011). By 2014, more than 17% of 2-19 year olds were categorized as obese, with African-American and Hispanic youth showing increased prevalence rates of obesity at 19.5% and 21%, respectively (Ogden *et al*., 2015). It is projected that the lifetime medical costs of an obese child throughout adulthood results in additional expenses per child, with one estimation figuring an additional $14 billion in future healthcare costs for obese 10-year olds alone (Finkelstein *et al*., 2015). This estimate of course only accounts for medical expenses, and does not include non-medical associated costs, or the costs on quality of life.

The obesity epidemic is now not only affecting adults, as seen in previous generations, but also the pediatric population. In addition to a large increase in future healthcare expenditure, childhood-onset obesity affects the patient during a critical developmental period, resulting in longitudinal health concerns into adulthood. Therefore, studying the sequelae of obesity should not be limited to adult or adolescent populations, but rather, it should incorporate the health effects seen in obese children. With a growing population of obese patients in the United States, which more heavily affects lower income and minority populations, the national healthcare expenditure will only continue to rise unless something is done to combat this widespread chronic medical disorder.

1.2 Childhood Obesity vs. Lifespan Obesity

Childhood obesity cannot be conceptualized separately from adult obesity because many times they are an interconnected life-course phenomenon. For example, longitudinal studies have shown that 77% to 92% of obese adolescents remain obese in adulthood (Finkelstein *et al*., 2014). Overweight and obese children not only have co-occurring cardiometabolic disorders, but

they are also at an increased longitudinal risk of such disorders in adolescence and adulthood. In other words, cardiovascular morbidity related to obesity in adulthood may well have its origins in childhood (Reily *et al.,* 2003). Combating childhood overweight and obesity is imperative to prevent cardiometabolic disorders, such as hypertension and type 2 diabetes (T2D), cardiovascular disease (CVD), or cerebrovascular disease (CBVD) later in life. Implementing early prevention strategies into overall wellness checkups can help lessen the burden of childhood overweight and obesity before it can prospectively impact the health of the child.

Unlike in adults, where body mass index (BMI) alone is used to categorize weight imbalances, children's BMI is compared to the CDC's normative BMI data and percentiles to identify relative body weight (Styne *et al.,* 2017). The BMI percentile (BMI%) tracks the child's BMI in relation to the average BMI for the child's age and sex. Children are categorized as overweight if their BMI% is equal to or greater than the 85th percentile and as obese if their BMI% is equal to or greater than the 95th percentile (World Health Organization, 2007). As mentioned above, 17.4% of US children met the criteria for obesity, meaning they had a BMI% ≥ 95. In the same year, overweight but non-obese children (BMI% ≥ 85 and < 95) made up 33.4% of the US pediatric population (Skinner *et al.,* 2016). Thus, over 50% of the U.S. pediatric population was overweight or obese, further displaying the large prevalence of obesity.

Childhood obesity affects the patient during a critical developmental period, causing not only acute health problems but conditions that may become chronic. Although, the development of obesity in children and adults may differ in their cause, the weight imbalance should be analyzed from a longitudinal, lifespan standpoint. Due to the timing of weight gain during puberty, serious and lifelong adverse health outcomes may form, even if the individual loses weight later on in adulthood. This may be a result of residual damage to the metabolic and

hormonal health of the individual, as we review below. For this reason, childhood obesity should be studied and treated in relation to adult obesity because of the longitudinal adverse health outcomes that it may produce.

1.3 Etiology and Pathophysiology of Obesity

In order to understand the adverse health outcomes of obesity, we must first understand why and how obesity has become such a large epidemic due to unmodifiable and modifiable causes as well as how it develops into a chronic condition. The etiological and pathophysiological mechanisms of weight gain and obesity are summarized in **Figure 1** below.

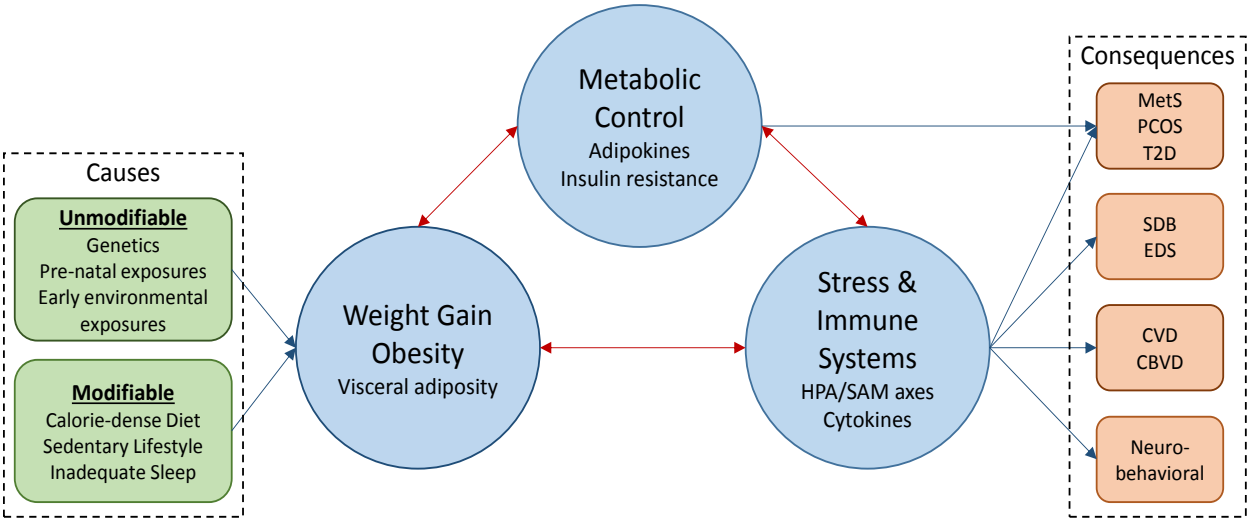

Figure 1. Etiology, pathophysiology, and consequences of obesity. Etiological factors contributing to weight gain and the development of obesity are depicted in green boxes, while pathophysiologic mechanisms are depicted in blue circles. The latter include adipokines dysregulation (leptin, ghrelin, and adiponectin), insulin resistance, low-grade inflammation (cytokines) and stress system activation (cortisol, norepinephrine). Bidirectional arrows represent the self-perpetuating vicious cycle of weight gain, metabolic changes, stress activation and low-grade inflammation. CBVD = cerebrovascular diseases. CVD = cardiovascular disease, including hypertension. EDS = excessive daytime sleepiness. HPA = hypothalamic-pituitary-adrenal. MetS = metabolic syndrome. PCOS = polycystic ovary syndrome. SAM = sympathetic-adrenal-medullary. SDB = sleep disordered breathing. T2D = type 2 diabetes. (Danisi *et al.*, 2019).

Modifiable causes imply that the individual has the ability to alter these factors, while unmodifiable causes are beyond their control. Obesity with an onset in childhood may be caused by a multitude of unmodifiable biological factors such as genetic heritability, pre-natal and early environmental exposures as well as early-onset endocrine disorders (Gurnani *et al.,* 2015). Environmental risk factors such as exposure to gestational diabetes in utero or a shorter breastfeeding duration, have been shown to increase a child's risk for obesity (Bass *et al.,* 2015).

The main source of childhood overweight and obesity, however, is an energy imbalance in regards to diet and physical activity. One of the primary modifiable causes feeding into the obesity epidemic is the change to a predominantly sedentary lifestyle. This is most likely the result of increasing computer usage in both the workplace and the home (Tremblay *et al.,* 2010). Children do not escape from this lifestyle change, with the popularity of video games and social media becoming the main form of communication between peers in this generation (Wright *et al.,* 2012). This decrease in physical activity generates a never ending spiral of obesity because it leads to health consequences that further limit physical behavior, and thus increases the patient's sedentary lifestyle, and consequently results in weight gain (Williams *et al*., 2015). Sedentary lifestyle alone is not the only cause of obesity, but is exacerbated by a change in the western diet. The western diet now encompasses a diet high in simple carbohydrates, saturated fat, and sugar, all of which have been linked to increased risk of obesity and heart disease (Wright *et al*., 2012; Serra-Majem *et al*., 2015). This decrease in physical activity, combined with an increase in caloric intake and decrease in micronutrients, has directly aided in the obesity epidemic via an imbalance in energy intake and energy expenditure (Simon *et al.,* 2006). In fact, the relative contribution of a sedentary lifestyle and increased caloric intake has been shown to affect the weight of children more dramatically than that in adults (Styne *et al*., 2017). Thus, early

childhood intervention strategies are important to help establish proper lifestyle choices, which will help prevent long term adverse health outcomes of weight gain.

Modifiable lifestyle factors creating an energy imbalance in addition to unmodifiable causes, such as genetic predisposition, raise the risk of a child to not only acquire excess adipose tissue, but as a result, increased low-grade inflammation. Overweight and obese individuals have been documented to have elevated levels of chronic inflammatory biomarkers, which ultimately contribute to systemic metabolic dysfunction. Chronic low-grade inflammation is defined by a 2-3-fold increase in cytokine concentration in the blood plasma that may lead to adverse health outcomes (Danesh *et al.*, 2000). Recently, there has been evidence that elevated inflammatory biomarkers in the vascular system can lead to increased risk of atherothrombosis, and other cardiovascular disorders (Ridker, 2016).

In order to understand why overweight and obese individuals exhibit systemic inflammation, the endocrine functionality of adipose tissue must first be addressed. Adipose tissue is recognized as a metabolically active endocrine organ and the main energy storage unit for the body (Nishimura *et al.*, 2009). Excess adiposity may lead to dysregulation of adipokines, adipose secretory factors that contribute to the development of systemic inflammation (Jung *et al.*, 2014). However, not all types of adipose tissue distribution have the same levels of cytokine secretion. Differences in adipose tissue distribution will be expanded upon later, but it is important to mention that one type of distribution in particular is involved in increased inflammation levels: visceral adipose tissue (VAT). This increased volume of inflammatory secretions seen by VAT impairs triglyceride storage and increases the release of free fatty acids by the liver, a major component of atherosclerotic plaque (Nishimura *et al.*, 2009). It is, however, not the adipose tissue itself that releases these inflammatory biomarkers, but rather

macrophages located within it. Macrophages in VAT secrete high levels of cytokines, leading to immune dysregulation. It is this immune dysregulation that has been linked to cardiometabolic abnormalities and comorbidities (Gaines *et al.,* 2016). Therefore, it is not the presence of the adipose tissue per se that causes metabolic abnormalities, but rather, the excess secretion of adipokines and cytokines via macrophages.

The five main inflammatory cytokines and adipokines released by adipose tissue are interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), adiponectin, leptin, and ghrelin. IL-6, a pro-inflammatory cytokine, stimulates an immune response in nearby tissue, and is thought to be the reason why obese individuals have increased C-Reactive protein (CRP) secretion by the liver, due to the proximity of VAT near the organ (Ridker, 2016). CRP is produced in response to high levels of inflammation, and aids in innate immunity. This system, however, can be flawed in that excess CRP will be produced in response to elevated levels of IL-6, even when no invading pathogen is present (King *et al.,* 2007). Beyond hepatic production, inflammatory cytokines have been shown to stimulate CRP production in human coronary artery myocytes and in human adipocytes, leading to increased risk of cardiovascular disease (Ridker, 2016). TNF-α is also a pro-inflammatory cytokine that works alongside IL-6 in the immune response, and is believed to be a factor in the development of insulin resistance (Nieto-Vazquez *et al.,* 2008). Therefore, IL-6, CRP, and TNF-α are used as inflammatory biomarkers due to their mechanistic release during periods of elevated inflammation.

Although these pro-inflammatory cytokines aid in local inflammation, they also play a large role in central nervous system (CNS) regulation. For example, IL-6 and TNF-α have been shown to stimulate the hypothalamic-pituitary-adrenal (HPA) axis, the predominate pathway for regulating chronic stress (Chrousos *et al.,* 2007). Specifically, IL-6 is thought to be a strong

activator of the parvocellular neurons within the paraventricular nucleus, which stimulates the release of corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) from the hypothalamus. These hormones target the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary (Chrousos *et al.*, 2007). ACTH acts on the adrenal gland in order to stimulate the release of glucocorticoids, specifically cortisol, a major factor in the stress response. An elevated production of cortisol in response to physiological stress has been shown to increase the presence of VAT, hypertension, insulin resistance, and dyslipidemia (Manenschijn *et al.*, 2013). Additionally, the sympathetic-adrenal-medullary (SAM) axis also regulates physiological stress via the acute stress response. Like that seen in the HPA axis, the hypothalamus stimulates the adrenal gland, however, epinephrine and norepinephrine are secreted as a result of sympathetic stimulation (Bitsika *et al.*, 2014). Thus, overproduction of cortisol and adrenal amines, such as epinephrine and norepinephrine, induces a recurring cycle of physiological stress and development of additional VAT, leading to further secretion of cytokines and adipokines.

There are other cytokines that are not involved in the stress/immune response, yet also play a large role in weight management and appetite. Other adipokines include adiponectin, leptin, and ghrelin. Adiponectin is a protein involved in glucose and lipid that decreases hepatic gluconeogenesis and increases fatty acid oxidation (Fiaschi *et al.*, 2014). Adiponectin has a protective effect by increasing insulin sensitivity; thus, low levels of adiponectin are usually found in obese individuals that exhibit symptoms of insulin resistance (Balsan *et al.*, 2015). In fact, the proportion of adiponectin to adipose tissue is actually an inverse relationship. This means that individuals with excess adipose tissue, such as those that are overweight or obese, would have low levels of adiponectin, leading to a lack of prevention of low-grade inflammation.

The adipokines ghrelin and leptin regulate body weight, energy balance, and hunger. Ghrelin is a hormone produced in the mucosa of the stomach, and is in charge of appetite control and energy balance (Solomou *et al.*, 2014). This hormone signals to the hypothalamus the state of fat storage, inhibiting food intake, and further adipose tissue accumulation (Wren *et al.*, 2001). Therefore, ghrelin is known as the "hunger" hormone and stimulates appetite when energy storage is low. Although in theory obese individuals should have low plasma levels of ghrelin, some studies show they are sensitive to the hormone, meaning they will feel hungry even when there is ample energy storage (Tamboli *et al.*, 2014). In addition to ghrelin, another hormone, leptin, stimulates the secretion of thyroid stimulating hormone (TSH) by the anterior pituitary gland, directly acting on the thyroid gland (Paz-Fiho *et al.*, 2015). In adults, the thyroid gland is responsible for maintaining a normal basal metabolic rate (BMR). Usually, metabolic rate will increase when an individual expends more energy, such as through exercise. Interference with BMR due to extreme weight gain, however, can cause damage to the gland, resulting in an imbalance of the BMR, and thus subsequent continued weight gain (Mullur *et al.*, 2013). Therefore, an obese individual may have accumulated damage to their BMR, preventing them from losing weight even after lifestyle modifications. Therefore, this continues the cycle of weight gain and increased low-grade inflammation.

Metabolic imbalances worsened by obesity not only affect the systemic health of the individual, but also their psychological health. Individuals who's BMI categorizes them as overweight or obese, may be at a greater risk for depression and anxiety (LaGrotte *et al.*, 2016). Social stigmas surrounding weight, particularly in women, may worsen depression, resulting in a never-ending cycle of emotional distress (Marmorstein *et al.*, 2014). States of depression may cause the individual to develop disorders that ultimately affect their weight, such as binge eating

disorders, that again can contribute to this endless cycle of weight gain and psychological malaise (Simon *et al.,* 2006). Additionally, shortened sleep, as a result of increased weight gain, may cause an individual to develop depression, in turn leading to less sleep and more subsequent weight gain (LaGrotte *et al.,* 2016). Therefore, although the cause of psychological disorders may not be directly generated by the comorbidities of obesity, they can play a significant role in the duration and severity of the excess adiposity.

Additionally, sleep plays a large role in the maintenance of a healthy body weight. Data has shown that disturbed, insufficient sleep has been associated with obesity (Vgontzas *et al*., 2014). Obese individuals may increase their caloric intake in order to compensate for their lack of energy during periods of poor sleep, leading over time to an imbalance between energy consumption and expenditure (Markwald *et al.,* 2013). Sleep disorders may also develop as a result of increased weight gain, or aid in continued weight gain. Sleep disordered breathing (SDB) is characterized as complete (apneas) or partial (hypopnea) breathing pauses and hypoxia (Seetho *et al.,* 2014). A common SDB disorder in the overweight or obese is obstructive sleep apnea (OSA), which is caused by an obstruction in any part of the upper airway of the respiratory system. Particularly in obese individuals, this is most commonly a result of excess fat and tissue compressing the pharynx, preventing breathing mechanisms to occur (Shrivastava, 2014; Vgontzas *et al.,* 2005).

Furthermore, shorter sleep duration, including disturbed sleep, has been linked to behavioral problems and decreased neurocognitive functioning, a factor that may impact psychological health, and thus indirectly cause less sleep and more weight gain (Frye *et al.,* 2018). Additionally, shorter sleep has been linked to higher levels of CRP and IL-6 production, leading to the development of low grade inflammation (Irwin *et al.,* 2016; Vgontzas *et al.,* 2008).

Therefore, individuals experiencing short or disturbed sleep, like that seen in OSA, may be at risk of developing comorbidities of obesity, such as T2D, hypertension, and dyslipidemia (Fernandez-Mendoza *et al.,* 2017). For example, one study demonstrated that 70% of obese diabetics had moderate or severe OSA (Trakada *et al.,* 2007). The association between disturbed sleep and metabolic impairments suggest an important role for sleep in the growing obesity epidemic.

1.4 Adipose Tissue Distribution in Relation to Cardiometabolic Disease

As previously stated, obesity is defined as the accumulation of adipose tissue that leads to adverse health conditions (World Health Organization, 2016). This accumulation of adipose tissue affects the hormonal and metabolic health of the individual in part through the development of low-grade inflammation. For example, obese females have higher rates of early-onset puberty, which entails an early development of menses (Marcovecchio *et al*., 2013). Obese males have shown the opposite effect; namely, a delayed development of mature testes (Solorzano *et al.,* 2010; Lee *et al.,* 2010). Earlier pubertal initiation in females may promote the development of adolescent polycystic ovary syndrome (PCOS), and neurobehavioral problems such as depression, anxiety, or risk-taking behaviors (Solorzano *et al.,* 2010). In addition to hormonal dysregulation, metabolic disorders can develop from the increased secretion of cytokines in excess adipose tissue. Specifically, this increased occurrence of obesity results in increased prevalence of T2D, hyperlipidemia, elevated blood pressure, CVD, and many other metabolic disorders (Agirbasali *et al.,* 2016). These cardiometabolic disorders, however, are more apparent in individuals with certain types of adipose tissue distribution.

There are four main types of adipose tissue patterning that is measured in regard to obesity. Android adiposity, which is commonly known as an “apple shape”, is found mainly around the trunk, particularly at the waist level, and the upper body, including the chest, shoulders, and neck (Merriam Webster, 2017). In contrast, gynoid adiposity is commonly known as a “pear shape” body. This adipose tissue distribution in the lower body is mostly centralized around the hips, buttocks, and thighs (Merriam Webster, 2017). Subcutaneous adipose tissue (SAT), also known as the hypodermis, is adipose tissue found directly under the skin. This type of adipose tissue is found throughout the body, and is not limited to the abdominal or thoracic cavity. As mentioned above, VAT accumulates around the internal organs located in the abdominal cavity and, thus, the android region.

Adiposity distribution throughout the body can have varying cardiometabolic effects on the individual depending upon the patterning of this distribution. These adipose distribution patterns are the result of metabolic effects, such as hormones, and can also be directly linked to the excess adiposity from obesity. For example, SAT increases as an individual gains weight, and has shown a stronger impact on insulin resistance when combined with high levels of VAT (He *et al.*, 2015). Prospective longitudinal studies, however, show that increased android adipose tissue distribution is independently associated with a higher risk of developing diabetes and cardiovascular disease (Pi-Sunyer, 2002). Therefore, it can be argued that central obesity is the most forbearing of all adiposity distributions. Central obesity is defined as the accumulation of adipose tissue in the android region, including SAT and VAT (He *et al.*, 2015). It is usually measured taking a waist circumference, via a tape measure, and compared to a waist-to-hip ratio. Unlike other forms of adipose distribution, central obesity is found not only in individuals that are categorized as obese by BMI standards, but also among overweight and even normal weight

individuals. For example, non-obese (BMI<30) men with central obesity (>102 cm waist circumference) have an 87% higher mortality risk than men with a similar BMI but no central obesity (Sahakyan *et al.*, 2015).

Central obesity poses risks to an individual's health partly due to the large accumulation of VAT. Unlike SAT, android, or gynoid adipose tissue distributions, VAT is deep within the abdomen surrounding the internal organs. The unique position of VAT in respect to the liver is thought to result in an increase secretion of fatty acids to the organ (Nishimura *et al.*, 2009). This excess fatty acid buildup in the liver leads to higher triglyceride and CRP production, and thus an increased risk of cardiac-related illnesses and systemic inflammation. Additionally, VAT's position around endocrine organs located in the abdomen, such as the pancreas, may lead to insulin resistance and other related metabolic abnormalities (Ridker, 2016). Thus, central obesity, independent from global obesity, is associated with a higher metabolic syndrome burden (He *et al*., 2015). These increased risks for cardiometabolic disease, therefore, place precedence on the distribution of adipose tissue, specifically central obesity, and not solely on the BMI of the patient like once thought.

Central obesity is associated with increased risk of insulin resistance-related syndrome and is a key component of the metabolic syndrome (MetS). MetS is a cluster of associated cardiovascular and metabolic traits consisting of central obesity, elevated blood pressure, insulin resistance, hypercholesterolemia, and hypertriglyceridemia (Martin *et al.*, 2015). Additionally, overweight and obese children are now suffering from cardiometabolic disorders that were once only present in adult patients, such as dyslipidemia or nonalcoholic fatty liver disease (NAFLD) (Singer *et al.*, 2017; Jung *et al*., 2014). Dyslipidemia and NAFLD are in part results of the accumulation of VAT on and around the liver, leading to dysregulation of hepatic metabolic

processes. These adverse cardiometabolic health outcomes are developing earlier in life because of an increase in childhood obesity, which causes more systemic damage due to the prolonged manifestation of these chronic disorders.

Additionally, these cardiometabolic disorders are not only a threat to present day health, but if left untreated, may develop into more serious chronic diseases and disorders. For example, long term dyslipidemia and high blood pressure increases an individual's risk of developing CVD or CBVD, such as coronary artery disease or ischemic stroke (DeMarco *et al.,* 2014). These cardiometabolic risk factors and BMI have been shown to have a linear relationship with CVD mortality (Martin *et al.,* 2015). Other uncontrolled chronic comorbidities of obesity also have the potential to affect the individual's quality of life. For example, uncontrolled T2D may develop into diabetic neuropathy, which entails patients losing sensation in the peripheral extremities, leading to increased risk of infection and potentially amputation (Clark *et al.,* 1995). In addition to the development of MetS, obesity may also have gynecological effects on an individual. Higher adiposity has been associated with increased free testosterone levels in the blood, one of the symptoms seen in PCOS. Females diagnosed with PCOS have increased levels of insulin resistance and severe forms can cause infertility due to scarring of the ovaries (Haffner, 2000). Obesity, therefore, not only affects the present-day metabolic health of the patient, but also may adversely impact future health and quality of life.

1.5 Sex Differences in Body Weight and Adipose Tissue Distribution

Individuals may vary in adipose tissue distribution, however, the different sexes have an even more distinct distribution. Males typically show higher central adipose tissue distribution, while females typically show a higher level of peripheral and gynoid adipose tissue distribution. These distributions are a result of differences in hormone ratios. Higher levels of testosterone

and lower levels of estrogen have been shown to cause women to switch from a gynoid distribution to an android distribution. This is seen during the first few years of menopause, a time where a female's risk for CVD sharply increases (Maas *et al.,* 2010). Additionally, women that had more android adipose tissue distribution had increased levels of free testosterone and decreased sex hormone binding, a phenomenon which is seen in PCOS patients (Haffner, 2000). The central distribution of adiposity in males also includes higher levels of VAT, which correlates to the higher rates of CVD seen in males (Maas *et al.,* 2010). For example, elevated CRP levels have been found to be the result of increased VAT and predict OSA in adolescent males but not females. (Gaines *et al.,* 2017).

This sexual dimorphism becomes already apparent during later stages of puberty as a result of increases in testosterone in males and estrogen in females. Sexual dimorphisms are found not only in peripheral adiposity deposits, but also in central adipose tissue distribution. Although it is thought that post puberty is when these differences become apparent, it has been observed that even young pre-pubertal girls store less adiposity in the waist region and more peripherally, specifically over the hips, than pre-pubertal boys (Taylor *et al.,* 2010). Adipose tissue distributions are important to understand because they correlate to different metabolic diseases. Thus, the study of the natural history of weight gain and childhood obesity in the transition to adolescence needs also to be approached from a gender perspective.

2. Specific Aims & Hypotheses

As previously stated, childhood obesity cannot be examined independently to adolescent and adult health. It needs to, rather, be looked at in a continuum because it greatly influences adult health status. The overarching goal of this proposal is to follow the weight status of young female and male children into adolescence, and observe the associated cardiometabolic outcomes that may persist or develop as a result of this corresponding weight change. We will address this overarching goal in the Penn State Child Cohort (PSCC), a random, general population sample of children 5-12 years old who were followed-up as adolescents or young adults 12-23 years old. The analysis of these findings can help understand childhood overweight, and eventually help develop an intervention suitable for this target population. In order to achieve this broader goal, we tested the following specific aims:

2.1 Specific Aim 1

To study the natural history of childhood overweight in the transition to adolescence. We conducted longitudinal analyses to describe the trajectories of childhood overweight, ascertained by BMI%, in adolescence.

- **Aim 1.1**: We hypothesized that childhood overweight is highly persistent in the transition to adolescence.
- **Aim 1.2**: We hypothesized that similar trajectories will be found for central obesity, ascertained by waist circumference (WC).

2.2 Specific Aim 2

To study the association between the natural history of childhood overweight with adverse cardiometabolic outcomes in adolescence and their underlying stress/immune-related mechanisms. We conducted longitudinal analyses to test the association between the trajectories

of childhood overweight, ascertained by BMI%, with cardiometabolic outcomes in adolescence. In addition, we conducted secondary analyses to examine the association of central obesity, ascertained by WC, with the same outcomes.

- **Aim 2.1**: We hypothesized that persistent overweight since childhood is associated with increased visceral adiposity, blood pressure, insulin resistance, dyslipidemia, and SDB in adolescence, while incident overweight in adolescence is less likely to show these cardiometabolic and sleep impairments.
- **Aim 2.2**: We hypothesized that persistent overweight since childhood is associated with increased pro-inflammatory cytokines, adipokines, and cortisol levels, while incident overweight in adolescence is less likely to show abnormal levels in these stress/immune-related biomarkers.

2.3 Specific Aim 3

To study sex differences in the natural history of childhood overweight and its association with adverse cardiometabolic outcomes and their underlying stress/immune-related mechanisms. We stratified our sample by males and females and conducted the longitudinal analysis mentioned above.

- **Aim 3.1**: In order to test our first hypothesis for this specific aim, we conducted longitudinal analyses to describe the trajectories of childhood overweight, ascertained by BMI%, in the transition to adolescence stratified by males and females. We hypothesized that childhood overweight is more persistent in males, while it is more likely to remit in females. We conducted similar analyses to describe the trajectory of central obesity, ascertained by WC.

- **Aim 3.2**: We hypothesized that persistent overweight since childhood is associated with increased visceral adiposity, blood pressure, insulin resistance, dyslipidemia, and SDB in males and females, while incident overweight in adolescence is associated with cardiometabolic or sleep impairments in males but not in females.
- **Aim 3.3**: We hypothesized that persistent overweight since childhood is associated with increased pro-inflammatory cytokines, adipokines, and cortisol levels in males and females, while incident overweight in adolescence is associated with abnormal levels in these stress/immune-related biomarkers in males but not in females.

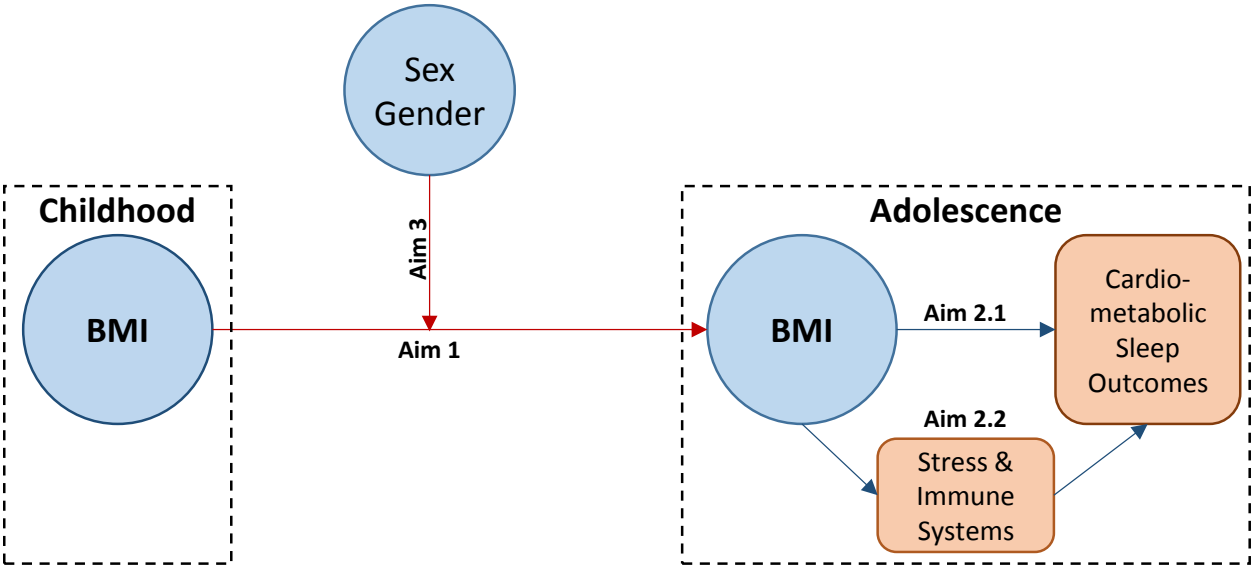

Figure 2. Conceptual framework of the specific aims in this study. Aim 1 examined the change in BMI and natural history of overweight and obesity from childhood to adolescence. Aim 2 analyzed the resulting cardiometabolic and stress/immune outcomes in adolescence in regards to the trajectory of BMI% from childhood to adolescence. Aim 3 examined sex / gender differences in the associations hypothesized in Aims 1 and 2. Cardiometabolic outcomes included visceral adiposity, blood pressure, insulin resistance and dyslipidemia, while sleep outcomes included SDB. Stress and immune systems biomarkers included, evening and morning cortisol, CRP, Il-6, TNF-α, leptin, and adiponectin levels.

3. Methods

3.1 The Penn State Child Cohort

The PSCC is a two-phase study that involved a random, general population sample of children. The PSCC sampled 18 public elementary schools within 3 school districts in Dauphin County (Bixler *et al.*, 2009). In phase 1, a questionnaire was sent home with 1500 elementary school students to be completed by the parents. This questionnaire collected information about sleep and behavioral patterns of the children in order to identify if a child was at a high risk for SDB. Overall, 7,312 questionnaires were sent home, and 5,740 were returned to the PSCOM, with a return rate of 78.5% (Bixler *et al.*, 2009). In the second phase of the experiment, 700 children aged 5-12 participated in a baseline examination of sleeping patterns and metabolic markers. First, the child completed a detailed evaluation and received a physical examination, before a filed polysomnography (PSG) was conducted. The physical examination included the following recordings: height, weight, waist and neck measurements, and blood pressure (Bixler *et al.*, 2009). An ENT specialist performed a visual evaluation, and the participant received respiratory function testing performed by a pediatric pulmonologist. The mean age at baseline was 8.7 ± 1.7 years, 52.2% were female, 93.7% non-Hispanic and 6.3% Hispanic, 82.6% were Caucasian, while 13.7% were Black/African American and 3.7% American Indian or Native Hawaiian/Asian.

Out of the 700 subjects, 421 completed the follow-up examination about 8.4 years later that yielded a response rate of 60%. This loss in follow-up participants was mainly due to the fact that participants had relocated from the area (Bixler *et al.*, 2016). The baseline demographic characteristics, however, were not significantly different between those who participated and those who did not participate in the follow-up study. The participants received a standardized

PSG recording and a repeat of the clinical history and physical examination performed at baseline. The mean age at follow-up was 16.5 ± 2.3 years old, 46.1% were female, 93.6% non-Hispanic and 6.4% Hispanic, 82.5% were Caucasian, while 12.6% were Black/African American and 2.9% American Indian or Native Hawaiian/Asian.

The Pennsylvania State University College of Medicine Institutional Review Board approved the present study protocol (IRB 98-228). Written informed consent was obtained from the parent or legal guardian of all study participants, and for those younger than 18 years of age, verbal consent was additionally obtained.

3.2 Measurements

Clinical history and physical examination

Clinical conditions along with current medication use were documented during a thorough clinical history at both baseline and follow-up. All participants also underwent neurocognitive and behavioral testing both at both time points (Frye *et al.*, 2018). Both at baseline and follow-up, all participants underwent a physical examination and included the following recordings: height (cm; stadiometer model 242, SECA; Hanover, MD), weight (kg; model 758C, Cardinal Manufacturing; Webb City, MO), waist and neck measurements in the standing position (cm, measuring tape and recorded in accordance to the CDC criteria). Seated position blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP), with the average of 3 blood pressure readings being recorded) (Bixler *et al*., 2009) and mean arterial pressure (MAP) was classified as diastolic pressures + ⅓ systolic pressure (He *et al.,* 2015). SBP and DBP levels were also measured in the supine and standing position and their reactivity

assessed. Additionally, pubertal development (Tanner staging) was determined via a self-administered rating scale at follow-up.

Overweight and obesity classification

The classification of body weight status was performed from the height and weight of the patient. The participants, while wearing light clothing, were weighed with a standard scale with an accuracy of 0.01 lb. Standing height without shoes was recorded using a standard height scale with an accuracy of 0.01 cm (Bixler *et al.*, 2009). The height and weight measurements were used to calculate BMI (kg/m^2) and converted to a percentile according to a formula based on the CDC's sex specific BMI-for-age growth charts. Body weight status was defined using the International Obesity Task Force (IOTF) age and sex specific percentile cut-off criteria of normal weight (BMI%<85), overweight (85≤BMI%<95) and obese (BMI%≥95) (Rodriguez-Colon *et al.,* 2011). This classification was also used to classify normal weight (BMI%<85) and overweight or obese (BMI%≥85). The WC was measured at the top of the iliac crest in the standing position (Rodriguez-Colon et al., 2011) and converted to a percentile according to a formula based on the NHANES's sex specific waist circumference-for-age growth charts (Sharma *et al*., 2015). For this study, we defined the presence of central obesity as a waist circumference percentile (WC%) ≥ 85.

Dual-energy X-ray absorptiometry (DXA) scan

A whole-body DXA scan was performed only at follow-up using a Hologic Discovery W scanner (Hologic Inc., Waltham, MA). The DXA scan uses two beams of low-energy x-rays that are collected by detectors after passing through body tissue (He *et al.,* 2015). The android region, gynoid region, SAT, and VAT were recorded from the scans. The height of the android region was defined as 20% of the distance between the iliac crest and the subject's chin. The height of

the gynoid region is 2 times the height of the android region, with the upper boundary 1.5 times the height of the android region below the iliac crest. The SAT and VAT were measured in an area that overlaps the android region, and SAT was directly measured on each side of the abdominal cavity. The amount of SAT over the visceral cavity can be estimated and subtracted from the total abdominal fat to get the VAT (He *et al.*, 2015). All regions of interest were identified by Hologic APEX 4.0 software (Hologic Inc., Bedford, MA) and verified by an experienced technician. The android/gynoid fat mass ratio (And/Gyn ratio), android/whole body fat mass proportion (And/W ratio), gynoid/whole body fat mass proportion (Gyn/W ratio), SAT, and VAT areas were specifically examined in this research experiment.

Continuous metabolic syndrome (cMetS) score

A cMetS score was only ascertained at follow-up. Glucose and insulin levels as well as lipid profiles, including total, HDL and LDL cholesterol levels, and triglycerides levels were obtained from fasting blood samples upon awakening from the PSG study. Five different MetS components were used to produce the score and quantify metabolic burden: WC, MAP, homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol (He *et al.,* 2015). HOMA-IR was calculated as [(fasting insulin level*fasting glucose level)/22.5]. HDL cholesterol levels are inversely related to metabolic risk, thus, it was multiplied by -1 (He *et al.,* 2015). When all cardiometabolic markers were combined, they produced a Z-score that was then summed into a cMetS; a higher score indicated a higher metabolic burden.

Inflammation

The fasting blood samples collected in the morning upon awakening from the PSG study were also used to assayed for pro-inflammatory cytokines and adipokines. Samples were

collected in an EDTA-containing tube, and then spun at 3,000 RPM for 10 minutes. The plasma was transferred into cryotubes and stored at -80°C until they were assayed. Plasma interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), high-sensitivity C-reactive protein (CRP), leptin, and adiponectin were measured via enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN). The intra- and inter-assay coefficients of variation were 4.7% and 5.1% respectively (IL-6), 4.6% and 4.9% (TNFα), 5.8% and 5.3% (CRP), 6.5% and 7.0% (leptin), and 5.6% and 5.6% (adiponectin). The lower detection limits were 0.039 pg/mL (IL-6), 0.106 pg/mL (TNFα), 0.010 ng/mL (CRP), 7.2 pg/mL (leptin), and 0.25 ng/mL (adiponectin). All samples and standards were run in duplicate (Gaines *et al.*, 2015).

Sleep laboratory

At both baseline and follow-up, the sleep evaluation consisted of the participant spending a night in a sound-attenuated, temperature, and light controlled room in the Clinical Research Center (CRC) at Penn State Hershey Medical Center. Sleep was continuously monitored for 9 hours, with the use of a digital PSG, including electroencephalogram (EEG), electro-oculogram (EOG), and submental and tibial electromyogram (EMG). Respiration was monitored throughout the night by a thermocouple at the nose and mouth, as well as nasal pressure, thoracic and abdominal strain gauges. Subjective snoring was obtained from parents and measured via a microphone positioned at the throat. Hemoglobin oxygen saturation levels (SpO_2) were obtained continuously throughout the night through the finger (Bixler *et al.*, 2009; Bixler *et al.*, 2016).

Apneas and hypopneas were defined based on age-specific criteria. An apnea was defined as a cessation of airflow with a minimum duration of 5 seconds for those aged <16 years and 10 seconds for those aged ≥16 years with an associated out-of-phase strain gauge movement. A hypopnea was defined as a reduction of airflow of approximately 50% with an associated

decrease in SpO_2 of ≥3% or an associated arousal (Bixler *et al.*, 2009; Bixler *et al.*, 2016; Frye *et al.*, 2019). Commensurate with previous studies (Bixler *et al.*, 2016; Frye *et al.*, 2018), the presence of SDB was categorized as AHI≥5 ("OSA"), 2≤AHI<5 ("mild SBD") and AHI<2 events per hour of sleep ("no SDB").

3.3 Statistical Analyses

The present study conducted univariate analyses using analysis of variance (ANOVA) for continuous variables, Chi-square test for binary variables, and multinomial logistic regression for categorical variables. In Aim 1, we examined the trajectory of body weight variables, including our primary independent variable (BMI%) and secondary independent variable (WC), as continuous measures of change from childhood into adolescence (Δ). Thereafter, we examined the trajectories of BMI% categories from childhood to adolescence. First, we examined the trajectory of childhood overweight (85≤ BMI%<95) and obesity (BMI%≥95) into adolescence. Second, we examined the trajectory of childhood overweight, including obesity (BMI%≥85), into adolescence. Based on these latter trajectories, the natural history of childhood overweight was defined as: normal weight (BMI%<85 at baseline and follow-up), incident overweight (BMI%<85 at baseline and BMI%≥85 follow-up), persistent overweight (BMI%≥85 at baseline and follow-up) and remitted overweight (BMI%≥85 at baseline and BMI%<85 follow-up). In Aim 2, we conducted longitudinal analyses with the natural history of childhood overweight as the independent variable and cardiometabolic, sleep, and stress/inflammatory variables as outcomes. These latter analyses were stratified by gender in Aim 3. The level of statistical significance was set at $p \leq 0.05$. Analyses were conducted using SPSS statistics version 24.0 (IBM corp. 2013).

4. Results

4.1 Specific Aim 1

Aim 1.1 Natural history of overweight and obesity

We first examined the change in anthropometric measures between childhood and adolescence, all as continuous variables. Thereafter, we explored the trajectories of body weight categories based on BMI% (i.e., normal weight, overweight, and obese) between childhood and adolescence. As shown in **Table 1**, the mean change in height was congruent to the development of the child into adolescence with the average child growing about 34 cm. Similarly, mean change in weight increased and is also congruent upon the fact that children naturally gain weight during their development into adolescence. Naturally, hip and waist circumference would also, on average, increase with development.

Table 1. Change in anthropometric measures from childhood to adolescence

	ΔHeight (cm)	ΔWeight (kg)	ΔHC (cm)	ΔWC (cm)	ΔNC (cm)	ΔBMI (z-score)	ΔBMI (%)
Mean (SD)	32.6 (11.2)	33.8 (12.8)	17.0 (13.5)	14.7 (9.9)	6.6 (5.5)	0.1 (0.9)	2.1 (22.9)
Minimum	0.0	2.3	-42.0	-12.0	-45.0	-2.3	-73.1
25th Percentile	25.5	25.4	9.0	8.5	4.5	-0.5	-9.4
Median	33.3	32.2	17.0	13.5	6.5	0.0	0.5
75th Percentile	40.6	40.5	24.5	20.0	8.5	0.5	13.5
Maximum	59.5	79.5	83.5	47.0	73.0	8.3	76.2

Δ = change from childhood to adolescence (i.e., follow-up value – baseline value). BMI = body mass index age and sex ascertained as a standardized z-score or percentile (%).SD = standard deviation. HC = hip circumference. WC = waist circumference. NC = neck circumference.

The change in BMI z-score and BMI%, however, showed that there were different trajectories of weight across subjects, with some losing weight, gaining weight, or persisting in their weight over time. The median BMI z-score and BMI% indicated that persisting in their relative body classification was the most common trajectory, regardless of whether this was a healthy or unhealthy body weight. The quartile BMI% distribution indicated that 25% of children experienced a weight gain of about half a standard deviation, or +13.5 percentiles, while another

25% experienced a weight loss of about half a standard deviation, or -9.4 percentiles, in the transition to adolescence.

As shown in **Table 2**, the prevalence of overweight in childhood was 12.6% while that of obesity was 18.8%. In adolescence, the prevalence of overweight increased to 18.8%, while that of obesity decreased to 15.2%. The data presented in **Table 2** below also depict the trajectories of these childhood body weight categories into adolescence. The majority of normal weight children remained normal weight in adolescence (83.7%), which is consistent with the median change for BMI z-score of 0.04 reported above. In normal weight children, the incidence rates of overweight and obesity during adolescence were 12.5% and 3.8%, respectively. Among overweight children, 41.5% experienced full remission to normal weight in adolescence, while 39.6% persisted in their overweight category and another 18.9% developed obesity in adolescence. Finally, the majority of obese children either persisted in their obesity category (54.4%) or partially remitted into overweight (27.8%), while only 17.7% experienced full remission to normal weight in adolescence.

Table 2. Trajectories of body weight categories from childhood to adolescence

	Adolescence (12-23y)			
Childhood (5-12y)	**Normal weight**	**Overweight**	**Obesity**	Prevalence
Normal weight	242 (83.7%)	36 (12.5%)	11 (3.8%)	289 (68.6%)
Overweight	22 (41.5%)	21 (39.6%)	10 (18.9%)	53 (12.6%)
Obesity	14 (17.7%)	22 (27.8%)	43 (54.4%)	79 (18.8%)
Prevalence	278 (66.0%)	79 (18.8%)	64 (15.2%)	421

Data are n (%). Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%.

Aim 1.2 Natural history of central obesity

We examined the trajectories of central obesity in the transition between childhood and adolescence. Using percentiles of waist circumference based on NHANES data (Sharma *et al.*, 2015), we defined the presence of central obesity as a waist circumference over the 85th percentile. As shown in **Table 3**, the vast majority of children that did not have central obesity at

baseline remained in the same category at follow-up (90.5%), while 9.5% developed central obesity in adolescence. The persistence and remission rates of central obesity were almost 50%, respectively.

Table 3. Trajectories of waist circumference categories from childhood to adolescence

	Adolescence (12-23y)		
Childhood (5-12y)	**Normal**	**Central Obesity**	Prevalence
Normal	258 (90.5%)	27 (9.5%)	285 (68.5%)
Central Obesity	67 (51.1%)	64 (48.9%)	131 (31.5%)
Prevalence	325 (78.1%)	91 (21.9%)	416

Data are n (%). Normal = waist circumference < 85th%, Central obesity = waist circumference ≥ 85th%.

4.2 Specific Aim 2

In aim 2, we studied the cardiometabolic and sleep outcomes and their stress/immune-related mechanisms of the natural history of overweight. As mentioned above in 4.1, we split the sample into four groups based on their BMI% trajectories: normal weight, incident overweight, persistent overweight, and remitted overweight. As a first step in addressing this aim, we examined for potential differences in demographic and clinical variables across these four groups. As shown in **Table 4**, male sex was significantly associated with incident and remitted overweight; however, female sex was not significantly associated with persistent overweight. Racial-ethnic minority was significantly associated with persistent overweight, but white-Caucasian race-ethnicity was not significantly associated with remitted overweight.

In regards to clinical factors, enlarged tonsils at baseline were significantly associated with persistent overweight, while tonsil inflammation at baseline was significantly associated with persistent and remitted overweight and, only marginally, with incident overweight. A higher Tanner stage score and heartburn at follow-up were significantly associated with persistent overweight, while less headaches were significantly associated with remitted overweight. Stimulant medication use was marginally associated with remitted overweight, while medications for other conditions were significantly associated with persistent overweight.

Table 4. Demographic and clinical characteristics of the sample stratified by the natural history of overweight

	0. Normal	1. Incident	2. Persistent	3. Remitted		Post- hoc			
	(n = 242)	(n = 47)	(n = 96)	(n = 36)	P	0 vs. 1	0 vs. 2	0 vs. 3	2 vs. 3
Female sex (%)	49.2	31.9	53.1	25.0	**0.004**	**0.032**	0.513	**0.009**	**0.005**
Minority (%)	18.2	19.1	32.2	22.2	**0.041**	0.875	**0.005**	0.563	0.262
A/T (%)	9.9	10.6	13.5	16.7	0.577	0.880	0.338	0.229	0.649
Baseline									
Age (years)	8.6 (1.7)	8.5 (1.8)	9.0 (1.6)	8.9 (1.9)	0.177	0.774	**0.048**	0.332	0.735
Cough, Exercise (%)	9.6	11.1	8.3	11.1	0.942	0.759	0.713	0.780	0.243
Chronic Cough (%)	5.8	15.6	6.3	2.8	***0.077***	**0.027**	0.860	0.464	0.611
Wheezing (%)	9.6	20.0	17.7	13.9	***0.099***	**0.048**	**0.042**	0.433	0.601
Headache (%)	17.3	6.7	15.6	11.1	0.240	***0.073***	0.627	0.321	0.513
Joint Pain (%)	6.6	6.7	6.3	8.3	0.980	0.995	0.896	0.708	0.673
Heartburn (%)	2.9	4.4	8.3	2.9	0.167	0.593	**0.038**	0.984	0.296
Regurgitation (%)	3.7	4.4	4.2	0.0	0.672	0.820	0.853		
Allergies (%)	61.8	57.8	56.8	69.4	0.566	0.609	0.401	0.379	0.191
Thyroid problems (%)	0.0	0.0	2.1	0.0	***0.081***				
Tonsils									
Enlarged (%)	31.4	42.6	44.8	38.9	***0.094***	0.113	**0.014**	0.473	0.375
Inflammation (%)	1.8	7.0	8.0	8.6	**0.036**	***0.070***	**0.014**	**0.037**	0.924
Psychiatric (%)	17.4	10.6	22.9	11.1	0.210	0.304	0.277	0.329	0.137
ADHD (%)	15.9	11.4	18.2	13.8	0.820	0.503	0.646	0.774	0.593
Learning Disorder (%)	11.2	11.4	16.2	6.9	0.557	0.973	0.277	0.486	0.229
Other Disorder (%)	7.0	8.6	9.3	3.4	0.756	0.741	0.521	0.482	0.333
Follow-up									
Age (years)	16.8 (2.2)	16.9 (2.7)	17.1 (2.2)	17.5 (1.9)	0.233	0.733	0.196	***0.067***	0.381
Tanner (stage)	4.1 (0.8)	4.1 (1.0)	4.4 (0.6)	4.2 (0.7)	**0.008**	0.758	**0.001**	0.341	0.216
Cough, Exercise (%)	8.3	12.8	12.5	5.7	0.458	0.759	0.713	0.780	0.622
Chronic Cough (%)	5.0	6.4	3.1	0.0	0.448	0.688	0.464		
Wheezing (%)	14.0	19.1	17.7	20.0	0.646	0.371	0.398	0.357	0.764
Asthma (%)	6.6	2.1	8.3	5.6	0.554	0.258	0.579	0.810	0.594
Headaches (%)	28.2	14.9	30.2	11.4	**0.038**	***0.062***	0.715	**0.043**	**0.036**
Joint pain (%)	17.8	10.6	16.8	11.4	0.541	0.231	0.828	0.350	0.451
Heartburn (%)	12.4	17.0	22.1	5.7	***0.053***	0.393	**0.027**	0.261	**0.045**
Abdominal Pain (%)	7.0	4.3	12.5	8.6	0.282	0.488	0.110	0.742	0.534
Regurgitation (%)	2.1	6.4	4.2	5.7	0.340	0.118	0.292	0.220	0.709
Allergies (%)	58.3	66.0	53.1	54.3	0.506	0.327	0.390	0.656	0.906
Thyroid problems (%)	1.2	0.0	3.1	0.0	0.360		0.253		
Psychiatric (%)	24.8	29.8	30.2	27.8	0.730	0.474	0.309	0.701	0.785
ADHD (%)	17.5	15.6	18.3	20.0	0.960	0.475	0.538	0.395	0.243
Learning Disorder (%)	8.7	0.0	6.6	11.4	0.190		0.290	0.633	0.248
Other Disorder (%)	7.7	9.3	11.5	0.0	0.223	0.728	0.297		
Medication use									
Stimulants (%)	9.1	2.1	11.5	19.4	***0.060***	0.140	0.509	***0.065***	0.239
Psychoactive (%)	7.9	12.8	11.5	0.0	0.131	0.278	0.296		
Sleep (%)	1.2	2.1	3.1	2.8	0.682	0.119	0.647	0.806	0.607
Allergy/asthma (%)	23.1	12.8	20.8	25.0	0.426	0.119	0.647	0.806	0.607
Steroids (%)	5.8	8.5	8.3	8.3	0.781	0.482	0.394	0.554	1.000
Other medical (%)	25.0	17.0	35.0	17.0	**0.041**	0.254	**0.050**	0.289	**0.042**
Oral contraceptive (%)	8.0	9.0	13.0	6.0	0.549	0.955	0.233	0.577	0.262

* Significant at $p \leq .05$ T Statistical trend at $p \leq .10$ Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. ADHD = attention deficit hyperactivity disorder. A/T = adenotonsillectomy.

Aim 2.1 Cardiometabolic and sleep consequences of persistent overweight

As shown in **Table 5**, the persistent overweight group was significantly taller than the normal weight and remitted overweight groups at baseline, but not at follow-up. Baseline weight, waist, hip, and neck circumference were found to be highest in the persistent overweight group.

As expected, all elevated body weight measurements at baseline were significantly associated with persistent and remitted overweight. Of the two overweight groups at baseline, lower childhood body weight measurements at baseline, including waist and hip circumferences, were significantly associated with remitted overweight as compared to persistent overweight. Interestingly, baseline weight and waist circumference were found to be significantly higher in incident overweight children than in persistently normal weight children. Follow-up weight and waist circumference mimicked that seen at baseline; the persistent overweight group were the heaviest and had the largest waist circumference. BMI% at baseline was not found to be significant between persistent overweight and remitted overweight groups, however follow-up BMI% was found to be significantly different between all groups (**Table 5**).

In regard to baseline BP, seated SBP, DBP, and MAP were significantly associated with persistent overweight. Follow-up seated SBP was found to be almost identical in the incident overweight and persistent overweight groups. Surprisingly, follow-up seated DBP and MAP were found to be highest in the incident overweight group. Supine and standing BP at follow-up were significantly associated with persistent overweight. The incident overweight and persistent overweight groups had the highest android distribution, while the normal weight and remitted overweight groups showed a much higher gynoid distribution. SAT and VAT composition were significantly higher in the persistent overweight group. HDL levels and cMetS score were similar between normal weight and remitted overweight (**Table 5**).

Table 5. Cardiometabolic characteristics of the sample stratified by the natural history of overweight

	0. Normal	1. Incident	2.Persistent	3. Remitted		Post- hoc			
	(n = 242)	(n = 47)	(n = 96)	(n = 36)	P	0 vs. 1	0 vs. 2	0 vs. 3	2 vs. 3
Baseline									
Height (cm)	134.0 (10.9)	135.4 (10.1)	142.6 (11.9)	137.1 (10.5)	**<0.001**	0.397	**<0.001**	0.107	**0.011**
Weight (kg)	29.4 (6.4)	32.5 (7.0)	50.3 (14.3)	41.1 (9.9)	**<0.001**	**0.038**	**<0.001**	**<0.001**	**<0.001**
Waist (cm)	59.9 (5.1)	63.8 (5.5)	79.1 (10.4)	72.3 (10.0)	**<0.001**	**0.001**	**<0.001**	**<0.001**	**<0.001**
Hip (cm)	68.7 (8.7)	71.5 (7.7)	86.2 (12.1)	78.6 (12.9)	**<0.001**	0.077	**<0.001**	**<0.001**	**<0.001**
Neck (cm)	27.9 (4.2)	28.3 (1.8)	31.6 (3.5)	29.8 (4.3)	**<0.001**	0.500	**<0.001**	**0.009**	**0.025**
BMI%	44.9 (22.5)	68.5 (13.9)	95.9 (3.5)	92.6 (4.5)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.345
SBP Seated	108.6 (11.3)	110.7 (11.2)	116.3 (12.1)	113.9 (12.5)	**<0.001**	0.265	**<0.001**	**0.010**	0.287
DBP Seated	64.6 (8.2)	63.0 (7.3)	66.7 (8.3)	66.3 (9.9)	**0.044**	0.238	**0.036**	0.242	0.817
MAP Seated	79.1 (8.1)	78.7 (7.6)	83.1 (8.2)	82.0 (9.2)	**<0.001**	0.780	**<0.001**	**0.046**	0.512
Follow-up									
Height (cm)	168.1 (9.8)	168.6 (11.0)	170.4 (8.9)	171.4 (8.6)	0.101	0.776	***0.054***	0.057	0.580
Weight (kg)	59.2 (10.0)	78.4 (12.2)	90.7 (20.1)	67.7 (10.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Waist (cm)	73.2 (7.1)	88.5 (9.1)	95.3 (14.6)	78.1 (7.2)	**<0.001**	**<0.001**	**<0.001**	**0.005**	**<0.001**
Hip (cm)	84.1 (9.3)	96.0 (10.0)	106.3 (14.1)	87.8 (8.5)	**<0.001**	**<0.001**	**<0.001**	***0.054***	**<0.001**
Neck (cm)	34.2 (5.1)	36.9 (3.4)	38.3 (4.3)	35.7 (3.2)	**<0.001**	**<0.001**	**<0.001**	0.084	**0.004**
BMI%	48.4 (24.2)	91.6 (4.3)	94.8 (4.1)	66.0 (17.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
SBP Seated	110.9 (11.0)	117.7 (13.1)	117.5 (12.0)	115.2 (14.2)	**<0.001**	**<0.001**	**<0.001**	**0.041**	0.318
DBP Seated	65.3 (8.7)	70.1 (10.0)	68.9 (8.4)	64.8 (9.7)	**<0.001**	**0.001**	**0.001**	0.780	**0.019**
MAP Seated	80.5 (8.6)	86.0 (10.3)	85.1 (8.6)	81.6 (10.3)	**<0.001**	**<0.001**	**<0.001**	0.475	**0.046**
SBP Supine	110.6 (9.7)	113.7 (11.9)	115.5 (11.2)	112.7 (9.9)	**0.001**	0.060	**<0.001**	0.260	0.157
DBP Supine	63.2 (7.6)	65.3 (8.1)	65.8 (8.2)	61.5 (8.6)	**0.006**	0.089	**0.006**	0.234	**0.005**
SBP Standing	116.4 (10.9)	121.5 (13.0)	123.6 (11.3)	119.0 (11.7)	**<0.001**	**0.004**	**<0.001**	0.193	**0.037**
DBP Standing	71.4 (8.4)	74.0 (9.4)	74.5 (8.6)	70.5 (7.8)	**0.007**	0.058	**0.003**	0.534	**0.016**
SBP Reactivity	5.7 (6.8)	7.8 (10.2)	7.9 (9.0)	6.3 (7.3)	***0.075***	0.096	**0.020**	0.692	0.277
DBP Reactivity	8.3 (5.7)	8.7 (6.9)	8.6 (6.9)	9.0 (5.8)	0.891	0.658	0.678	0.505	0.726
HDL cholesterol	51.3 (12.9)	45.8 (9.0)	47.9 (12.4)	51.3 (12.7)	**0.017**	**0.007**	**0.029**	0.921	0.206
Triglycerides	85.0 (36.3)	118.7 (76.4)	110.7 (49.1)	83.2 (24.2)	**<0.001**	**<0.001**	**<0.001**	0.832	**0.003**
Insulin	6.2 (26.5)	5.6 (3.3)	8.5 (12.1)	3.7 (6.6)	0.675	0.867	0.375	0.532	0.262
Glucose	87.3 (9.0)	88.8 (6.5)	90.4 (7.2)	93.6 (43.1)	***0.076***	0.512	***0.093***	**0.021**	0.281
HOMA-IR	1.4 (7.3)	1.2 (0.7)	2.0 (3.2)	0.9 (1.6)	0.771	0.822	0.463	0.592	0.345
cMetS score	-1.0 (2.5)	1.7 (2.8)	2.0 (3.1)	-1.2 (1.8)	**<0.001**	**<0.001**	**<0.001**	0.716	**<0.001**
Gyn/W ratio	18.6 (2.5)	17.3 (1.8)	17.1 (1.9)	18.1 (1.8)	**<0.001**	**<0.001**	**<0.001**	0.244	**0.019**
And/W ratio	5.5 (1.0)	7.4 (1.5)	7.6 (1.5)	6.3 (1.2)	**<0.001**	**<0.001**	**<0.001**	**0.001**	**<0.001**
SAT	139.7 (85.9)	298.9 (139.8)	387.8 (166.1)	160.3 (101.9)	**<0.001**	**<0.001**	**<0.001**	0.322	**<0.001**
VAT	38.4 (15.0)	86.8 (33.1)	103.1 (46.4)	50.8 (17.4)	**<0.001**	**<0.001**	**<0.001**	**0.014**	**<0.001**

*Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. SBP = systolic blood pressure. DBP = diastolic blood pressure. MAP = mean arterial pressure. HDL = high density lipoprotein. HOMA-IR = homeostatic model assessment of insulin resistance. cMetS = metabolic syndrome score. Gyn/W = gynoid-whole body ratio. And/W = android-whole body ratio. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue

Sleep characteristics were also studied and are reported in **Table 6**. Sleep onset latency, total sleep time, sleep efficiency, and all sleep stages did not significantly differ between groups at either time point. Additionally, the number of awakenings and wake after sleep onset time at both baseline and follow-up also did not significantly differ between groups.

A higher apnea/hypopnea index (AHI) at baseline was significantly associated with both persistent and remitted overweight. SDB at baseline was significantly associated with persistent and remitted overweight. AHI at follow-up did not display a significant difference between groups, with only a marginal association with persistent overweight. Interestingly, SDB at follow-up was significantly associated with incident overweight. An AHI≥5 at follow-up was significantly associated with incident and persistent overweight. SpO_2 at both baseline and follow-up was found to not be significantly different between groups. A higher baseline PLMI was significantly associated with remitted overweight, while a lower PLMI at follow-up was significantly associated with incident overweight, and marginally with persistent overweight (**Table 6**).

Aim 2.2 Stress- and immune-related biomarkers of persistent overweight

In regards to the neuroendocrine and cytokine levels presented in **Table 7**, elevated evening cortisol levels at baseline were significantly associated with remitted overweight. Interestingly, neither morning nor evening cortisol levels at follow-up were found to be significantly different between groups. As expected, CRP, IL-6, TNF-α, and leptin were all highest in the persistent overweight group, and adiponectin was highest in the remitted overweight group.

Table 6. Sleep characteristics of the sample stratified by the natural history of overweight

	0. Normal (n = 242)	**1. Incident** (n = 47)	**2. Persistent** (n = 96)	**3. Remitted** (n = 36)	**P**	**Post- hoc** 0 vs. 1	0 vs. 2	0 vs. 3	2 vs. 3
Baseline									
SOL (min)	26.5 (20.9)	33.1 (38.5)	25.8 (17.2)	32.0 (28.0)	0.181	0.080	0.808	0.190	0.178
Awakenings (#)	10.3 (5.7)	10.0 (6.2)	10.2 (5.9)	10.1 (5.5)	0.991	0.780	0.929	0.833	0.890
WASO (min)	42.9 (33.0)	39.9 (29.2)	42.0 (28.7)	44.2 (37.5)	0.924	0.558	0.814	0.817	0.721
TST (min)	461.1 (44.3)	450.7 (50.9)	461.6 (38.3)	453.3 (54.6)	0.386	0.145	0.924	0.328	0.341
% sleep efficiency	87.0 (7.7)	86.1 (8.1)	87.3 (6.5)	85.7 (9.6)	0.654	0.463	0.729	0.366	0.299
% stage 1	3.3 (2.7)	3.0 (2.3)	3.4 (2.4)	3.4 (2.7)	0.876	0.499	0.789	0.851	0.995
% stage 2	46.3 (10.8)	45.3 (12.2)	46.7 (11.1)	48.0 (8.5)	0.734	0.565	0.781	0.398	0.548
% stage 3	30.1 (10.2)	31.0 (11.5)	29.8 (10.1)	29.2 (9.2)	0.879	0.592	0.798	0.641	0.789
% stage R	20.4 (5.2)	20.7 (5.7)	20.2 (5.8)	19.4 (5.8)	0.724	0.792	0.713	0.299	0.470
Insomnia (%)	25.2	34.0	29.2	19.4	0.417	0.211	0.459	0.466	0.262
EDS (%)	13.2	19.1	16.7	13.9	0.688	0.296	0.422	0.917	0.689
AHI (#/hour)	0.7 (0.9)	0.6 (0.8)	1.0 (1.4)	1.3 (1.4)	**0.001**	0.439	**0.009**	**0.002**	0.241
AHI<2 (%)	92.6	91.5	80.2	72.2	**0.003**	---	---	---	---
2≤AHI<5 (%)	6.2	8.5	17.7	25.0		0.575	**0.002**	**<0.001**	0.339
AHI≥5 (%)	1.2	0.0	2.1	2.8			0.473	0.369	0.753
SpO_2	93.0 (4.5)	93.7 (2.9)	92.5 (3.4)	93.2 (2.9)	0.392	0.260	0.313	0.817	0.404
PLMI (events/hour)	0.8 (4.0)	0.3 (0.7)	0.4 (0.9)	2.07 (4.0)	**0.046**	0.323	0.246	**0.035**	**0.008**
Follow-up									
SOL (min)	26.9 (22.2)	27.7 (39.7)	24.9 (20.5)	22.9 (21.7)	0.731	0.840	0.499	0.361	0.676
Awakenings (#)	36.6 (11.3)	35.9 (15.4)	35.9 (11.5)	36.6 (13.9)	0.956	0.702	0.634	0.982	0.785
WASO (min)	67.9 (36.7)	67.5 (50.4)	76.2 (50.7)	64.9 (39.9)	0.374	0.953	0.113	0.704	0.185
TST (min)	447.8 (49.0)	447.5 (77.1)	441.0 (59.9)	454.4 (45.8)	0.611	0.973	0.309	0.504	0.216
% sleep efficiency	82.8 (8.9)	82.7 (14.3)	81.7 (11.0)	83.9 (8.6)	0.676	0.967	0.346	0.549	0.259
% stage 1	0.9 (1.0)	0.9 (3.1)	1.2 (1.4)	1.1 (1.6)	0.292	0.874	0.062	0.454	0.638
% stage 2	53.2 (10.2)	53.6 (10.8)	54.3 (9.1)	53.0 (8.7)	0.830	0.812	0.377	0.899	0.509
% stage 3	27.2 (9.6)	27.3 (10.1)	26.2 (8.5)	27.1 (8.4)	0.816	0.962	0.351	0.924	0.625
% stage R	18.6 (4.7)	18.2 (5.6)	18.3 (5.5)	18.8 (4.6)	0.889	0.554	0.635	0.809	0.608
Insomnia (%)	36.5	40.4	42.7	27.8	0.419	0.613	0.291	0.314	0.116
EDS (%)	67.9	60.9	69.5	62.9	0.312	0.714	0.394	0.973	0.579
AHI (# / hour)	2.3 (6.3)	3.4 (4.4)	3.5 (5.0)	2.0 (1.8)	0.224	0.231	***0.075***	0.794	0.180
AHI<2 (%)	70.2	38.3	55.2	58.3	**<0.001**	---	---	---	---
2≤AHI<5 (%)	23.6	46.8	24.0	36.1		**<0.001**	0.378	0.111	0.411
AHI≥5 (%)	6.2	14.9	20.8	5.6		**0.004**	**<0.001**	0.923	***0.080***
$Sp0_2$	91.6 (5.2)	91.1 (4.5)	90.9 (6.4)	92.7 (2.0)	0.323	0.567	0.290	0.222	0.077
PLMI (events/hour)	4.5 (6.8)	2.0 (2.6)	3.1 (5.1)	4.3 (5.7)	**0.032**	**0.009**	***0.060***	0.851	0.321

* Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI% = body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. SOL = sleep onset latency. WASO = wake after sleep onset. TST = total sleep time. EDS = excessive daytime sleepiness. AHI = apnea/hypopnea index. SpO2 = hemoglobin oxygen saturation level. PLMI = periodic limb movement index score.

Table 7 below presents the neuroendocrine and cytokine levels across normal weight, incident overweight, persistent overweight, and remitted overweight groups.

Table 7. Stress and inflammatory characteristics of the sample stratified by the natural history of overweight

	0. Normal (n = 242)	1. Incident (n = 47)	2.Persistent (n = 96)	3. Remitted (n = 36)	P	Post- hoc 0 vs. 1	0 vs. 2	0 vs. 3	2 vs. 3
Baseline									
Cortisol PM	0.4 (0.7)	0.3 (0.3)	0.3 (0.2)	0.9 (1.6)	**0.010**	0.615	0.377	**0.003**	**0.001**
Cortisol AM	1.2 (0.5)	1.1 (0.4)	1.2 (0.5)	1.2 (0.5)	0.651	0.243	0.819	0.947	0.942
Follow-up									
Cortisol PM	8.0 (6.8)	8.0 (6.0)	8.9 (9.8)	8.0 (5.2)	0.784	0.963	0.315	0.990	0.541
Cortisol AM	19.5 (8.6)	20.6 (10.8)	20.8 (9.0)	19.6 (9.2)	0.628	0.449	0.235	0.966	0.484
CRP	0.7 (0.6)	1.2 (1.6)	1.5 (1.5)	0.6 (0.4)	**<0.001**	**0.002**	**<0.001**	0.780	**<0.001**
IL-6	1.0 (0.9)	1.4 (0.8)	1.6 (1.2)	1.0 (0.6)	**<0.001**	**0.014**	**<0.001**	0.783	**0.001**
TNF-a	1.8 (1.2)	2.1 (1.4)	2.2 (1.5)	1.7 (0.6)	**0.034**	0.110	**0.012**	0.609	**0.044**
Adiponectin	8.4 (4.9)	5.9 (4.1)	6.7 (5.0)	9.2 (5.0)	**<0.001**	**0.001**	**0.005**	0.384	**0.011**
Leptin	8.4 (8.5)	15.0 (11.8)	22.9 (14.9)	7.2 (9.1)	**<0.001**	**<0.001**	**<0.001**	0.559	**<0.001**

* Significant at $p \leq .05$ T Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. CRP = C-Reactive protein. IL-6 = interleukin 6. TNF-α = tumor necrosis factor alpha.

4.3 Specific Aim 3

Aim 3.1 Sex differences in the natural history of overweight

Our third aim was to study the sex differences in the natural history of overweight. As a first step in addressing this aim, we examined the sex differences in the trajectory of weight from childhood to adolescence. We then examined for potential sex differences in demographic and clinical variables across the four groups.

Table 8. Trajectories of body weight categories in males from childhood to adolescence

	Adolescence (12-23y)			
Childhood (5-12y)	**Normal Weight**	**Overweight**	**Obesity**	Prevalence
Normal Weight	123 (79.4%)	25 (16.1%)	7 (4.5%)	155 (68.2%)
Overweight	15 (48.5%)	11 (35.5%)	5 (16.1%)	31 (13.6%)
Obesity	12 (29.3%)	6 (14.6%)	23 (56.1%)	41 (18.0%)
Prevalence	150 (66.0%)	42 (18.5%)	35 (15.4%)	227

Data are n (%). BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%.

As shown in **Table 8** above (males) and **Table 9** below (females), the majority of males and females who were normal weight at baseline remained normal weight at follow-up. A larger

proportion of males became overweight in adolescence, while also a larger proportion fully remitted from being overweight than compared to females. A larger proportion of females persisted in their overweight category into adolescence as compared to males. In fact, females had a significantly higher persistence rate (85.0% vs. 62.5%, p=0.006) of overweight as compared to males. However, females and males had almost identical obesity persistence rates (52.6% vs. 56.1%, p=0.825). Males, however, had a significantly higher incidence rate for overweight from childhood to adolescence (20.6% vs. 11.2%, p=0.037) as compared to females. Therefore, females are more likely to persist in their overweight category, but not obesity category, while males are more likely to show an incidence of overweight in adolescence.

Table 9. Trajectories of body weight categories in females from childhood to adolescence

	Adolescence (12-23y)			
Childhood (5-12y)	**Normal Weight**	**Overweight**	**Obesity**	Prevalence
Normal Weight	119 (88.8%)	11 (8.2%)	4 (3.0%)	134 (69.0%)
Overweight	7 (31.8%)	10 (45.5%)	5 (22.7%)	22 (11.3%)
Obesity	2 (5.3%)	16 (42.1%)	20 (52.6%)	38 (19.6%)
Prevalence	128 (65.9%)	37 (19.1%)	29 (14.9%)	194

Data are n (%). BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%.

There were no major sex differences in regards to demographic and clinical variables across groups (**Table 10** and **11** below). Females had a marginal association between baseline complaints of heartburn and persistent overweight. In males, complaints of headaches and heartburn at follow-up were highest among the persistently overweight group, while there was no significant difference seen in females.

In regards to medication use, males that remitted from overweight had a significantly higher stimulant use as compared to other groups. Female stimulant use was also found to be significantly different between the groups, however, the use was highest among the persistently overweight. Persistently overweight females were also documented to use a larger amount of

other medications (other than those listed above) as compared to other groups, however, this relationship was not seen in males where other medication use was found to be similar across groups (**Table 10** and **11** below).

Table 10. Demographic and clinical characteristics of male participants stratified by the natural history of overweight

	0. Normal (n = 123)	**1. Incident** (n = 32)	**2. Persistent** (n = 45)	**3. Remitted** (n = 27)	**P**	**Post- hoc** **0 vs. 1**	**0 vs. 2**	**0 vs. 3**	**2 vs. 3**
Minority (%)	15.4	25.0	28.9	22.2	0.226	0.209	***0.053***	0.395	0.535
A/T (%)	9.8	9.4	17.8	18.5	0.361	0.948	0.161	0.201	0.937
Baseline									
Age (years)	8.4 (1.6)	8.3 (1.7)	9.0 (1.6)	8.80 (1.8)	0.125	0.690	**0.039**	0.267	0.608
Cough, Exercise (%)	7.4	16.7	8.9	14.8	0.368	0.129	0.757	0.230	0.443
Chronic Cough (%)	6.6	16.7	6.8	3.7	0.230	0.087	0.952	0.579	0.586
Wheezing (%)	9.9	23.3	22.2	18.5	0.107	***0.054***	**0.043**	0.212	0.708
Headache (%)	16.4	3.3	17.8	14.8	0.295	0.097	0.832	0.840	0.744
Joint Pain (%)	8.2	6.7	6.7	7.4	0.984	0.781	0.744	0.892	0.905
Heartburn (%)	3.3	6.7	4.4	0.0	0.592	0.408	0.728		
Regurgitation (%)	3.3	6.7	4.4	0.0	0.580	0.403	0.721		
Allergies (%)	33.6	33.3	46.7	33.3	0.441	0.977	0.123	0.978	0.269
Thyroid Disease (%)	0.0	0.0	2.2	0.0	0.262				
Tonsils									
Enlarged (%)	33.1	44.8	48.7	42.3	0.278	0.376	0.233	0.717	0.219
Inflammation (%)	1.8	6.9	7.3	7.7	0.290	0.172	0.117	0.140	0.955
Psychiatric (%)	18.7	15.6	31.1	14.8	0.223	0.688	0.089	0.635	0.130
ADHD (%)	18.8	16.0	29.4	19.0	0.536	0.758	0.246	0.981	0.445
Learning Disorder (%)	16.0	12.0	18.2	9.5	0.802	0.658	0.843	0.482	0.445
Other Disorder (%)	6.4	12.0	12.1	4.8	0.590	0.341	0.337	0.794	0.417
Follow-up									
Age (years)	16.7 (2.3)	16.5 (2.7)	17.1 (1.9)	17.6 (2.0)	0.195	0.476	0.389	***0.081***	0.363
Tanner (stage)	3.8 (0.9)	3.8 (1.0)	4.2 (0.9)	4.1 (0.7)	***0.063***	0.993	**0.018**	0.117	0.733
Cough, Exercise (%)	7.3	12.5	6.7	3.7	0.622	0.352	0.885	0.504	0.600
Chronic Cough (%)	4.1	6.3	2.2	0.0	0.569	0.599	0.575		
Wheezing (%)	12.2	21.9	13.3	22.2	0.369	0.168	0.843	0.181	0.332
Asthma (%)	5.7	3.1	6.7	7.4	0.893	0.565	0.813	0.735	0.905
Headaches (%)	19.7	6.3	35.6	7.4	**0.004**	0.089	**0.035**	0.146	**0.016**
Joint pain (%)	16.3	9.4	17.8	14.8	0.762	0.336	0.815	0.853	0.744
Heartburn (%)	12.2	15.6	26.7	7.4	***0.078***	0.607	**0.027**	0.482	***0.061***
Abdominal Pain (%)	2.4	3.1	6.7	0.0	0.397	0.828	0.209		
Regurgitation (%)	0.8	6.3	2.2	3.7	0.286	0.093	0.478	0.282	0.714
Allergies (%)	56.9	68.8	55.6	55.6	0.625	0.227	0.875	0.898	
Thyroid Disease (%)	0.0	0.0	0.0	0.0	0.000				
Psychiatric (%)	26.8	28.1	31.1	33.3	0.890	0.869	0.654	0.486	0.786
ADHD (%)	32.5	26.7	22.2	40.7	0.362	0.463	0.234	0.369	0.098
Learning Disorder (%)	9.6	0.0	11.4	14.8	0.257		0.617	0.256	0.555
Other Disorder (%)	6.4	3.4	7.1	0.0	0.546	0.267	0.597	0.411	0.758
Medication use									
Stimulants (%)	13.0	3.1	6.7	25.9	**0.033**	0.144	0.259	0.098	**0.032**
Psychoactive (%)	6.5	12.5	4.4	0.0	0.236	0.267	0.619		
Sleep (%)	0.0	0.0	0.0	3.7	***0.059***				
Allergy/asthma (%)	25.2	15.6	22.2	22.2	0.718	0.258	0.691	0.745	1.000
Steroids (%)	4.1	12.5	11.1	11.1	0.203	0.084	0.100	0.157	1.000
Other medical (%)	22.0	18.8	24.4	14.8	0.777	0.694	0.732	0.410	0.335

***** Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$ Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. ADHD = attention deficit hyperactivity disorder. A/T = adenotonsillectomy.

Table 11. Demographic and clinical characteristics of female participants stratified by the natural history of overweight

	0. Normal (n = 119)	**1. Incident** (n = 15)	**2. Persistent** (n = 51)	**3. Remitted** (n = 9)	**P**	**Post- hoc 0 vs. 1**	**0 vs. 2**	**0 vs. 3**	**2 vs. 3**
Minority (%)	21.0	6.7	35.3	22.2	***0.083***	0.215	***0.052***	0.931	0.449
A/T (%)	10.1	13.3	9.8	11.1	0.981	0.699	0.956	0.922	0.904
Baseline									
Age (years)	8.7 (1.7)	8.9 (2.0)	8.9 (1.6)	9.0 (2.1)	0.859	0.648	0.460	0.625	0.901
Cough, Exercise (%)	11.9	0.0	7.8	0.0	0.321		0.440		
Chronic Cough (%)	5.0	13.3	5.9	0.0	0.516	0.220	0.823		
Wheezing (%)	9.3	13.3	13.7	0.0	0.585	0.624	0.397		
Headache (%)	19.3	13.3	13.7	0.0	0.413	0.577	0.382		
Joint Pain (%)	5.0	6.7	5.9	11.1	0.892	0.791	0.823	0.453	0.569
Heartburn (%)	2.5	0.0	11.8	11.1	***0.052***		**0.024**	0.193	0.955
Regurgitation (%)	4.2	0.0	3.9	0.0	0.793		0.933		
Allergies (%)	57.1	40.0	60.0	77.8	0.317	0.215	0.731	0.241	0.320
Thyroid Disease (%)	0.0	0.0	2.0	0.0	0.420				
Tonsils									
Enlarged (%)	34.5	50.0	48.9	33.3	0.706	0.770	0.312	0.616	0.303
Inflammation (%)	1.8	7.1	8.7	11.1	0.165	0.249	***0.060***	0.130	0.818
Psychiatric (%)	16.0	0.0	15.7	0.0	0.219		0.963		
ADHD (%)	12.9	0.0	9.3	0.0	0.428		0.647		
Learning Disorder (%)	6.5	10.0	14.6	0.0	0.356	0.791	0.127		
Other Disorder (%)	5.8	0.0	5.8	0.0	0.690		1.000		
Follow-up									
Age (years)	16.8 (2.1)	17.9 (2.6)	17.2 (2.4)	17.3 (1.8)	0.289	***0.074***	0.341	0.535	0.879
Tanner (stage)	4.4 (0.6)	4.7 (0.6)	4.6 (0.5)	4.6 (0.5)	**0.022**	**0.025**	**0.012**	0.359	0.762
Cough, Exercise (%)	9.2	13.3	17.6	12.5	0.487	0.616	0.125	0.762	0.720
Chronic Cough (%)	5.9	6.7	3.9	0.0	0.852	0.904	0.603		
Wheezing (%)	16.0	13.3	21.6	12.5	0.778	0.792	0.382	0.795	0.559
Asthma (%)	7.6	0.0	9.8	0.0	0.494		0.627		
Headaches (%)	37.0	33.3	25.5	25.0	0.498	0.783	0.148	0.500	0.976
Joint pain (%)	19.5	13.3	16.0	0.0	0.513	0.568	0.594		
Heartburn (%)	12.6	20.0	18.0	0.0	0.458	0.433	0.361		
Abdominal Pain (%)	11.8	6.7	17.6	37.5	0.145	0.561	0.307	***0.055***	0.208
Regurgitation (%)	3.4	6.7	5.9	12.5	0.601	0.533	0.454	0.233	0.499
Allergies (%)	59.7	60.0	51.0	50.0	0.726	0.980	0.295	0.592	0.959
Thyroid Disease (%)	2.5	0.0	5.9	0.0	0.537		0.290		
Psychiatric (%)	22.7	33.3	29.4	11.1	0.501	0.303	0262	0.556	0.336
ADHD (%)	16.7	6.7	20.8	0.0	0.344	0.358	0.564		
Learning Disorder (%)	7.8	0.0	2.1	0.0	0.315		***0.071***		
Other Disorder (%)	9.0	21.4	15.6	0.0	0.276	**0.010**	0.389		
Medication use									
Stimulants (%)	5.0	0.0	15.7	0.0	**0.043**		**0.028**		
Psychoactive (%)	9.2	13.3	17.6	0.0	0.290	0.616	0.125		
Sleep (%)	2.5	6.7	5.9	0.0	0.593	0.393	0.290		
Allergy/asthma (%)	21.0	6.7	19.6	33.3	0.434	0.215	0.836	0.395	0.364
Steroids (%)	7.6	0.0	5.9	0.0	0.577		0.696		
Other medical (%)	27.7	13.3	45.1	22.2	**0.049**	0.245	0.029	0.722	0.214
Oral Contraceptive (%)	16.8	26.7	23.5	22.2	0.658	0.353	0.306	0.679	0.932

***** Significant at $p \leq .05$ ^{T} Statistical trend at $p \leq .10$ Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. ADHD = attention deficit hyperactivity disorder. A/T = adenotonsillectomy.

Aim 3.2 Cardiometabolic and sleep consequences of persistent overweight by sex

We hypothesized that persistent overweight since childhood is associated with increased visceral adiposity, blood pressure, insulin resistance, dyslipidemia, and SDB in males and females, while incident overweight in adolescence is associated with cardiometabolic or sleep impairments in males but not in females. As expected, baseline and follow-up weight, waist, hip, and neck circumference were all significantly associated with persistent overweight in both males and females (**Table 12** and **13**).

In regards to blood pressure measurements, elevated baseline systolic, diastolic, and MAP were significantly associated with persistent overweight in males. In females, however, baseline DBP did not significantly differ between groups. At follow-up both males and females showed significant associations between elevated blood pressure and persistent overweight. In females, however, elevated diastolic blood pressure was significantly associated with incident overweight and not persistent overweight (**Tables 12** and **13**).

In both males and females, high cardiometabolic marker levels were significantly associated with persistent overweight (**Tables 12** and **13**). Females that remitted from overweight, however, had lower cardiometabolic marker levels as compared to persistently normal weight females. In regards to adipose tissue distribution, there was a significant association between elevated adipose tissue distribution and incident and persistent overweight in both males and females. Remitted overweight males and females displayed larger accumulations of VAT and SAT as compared to persistently normal weight individuals, even though they have similar BMI% at follow-up (**Tables 12** and **13**).

Table 12. Cardiometabolic characteristics of male participants stratified by the natural history of overweight

	0. Normal (n = 123)	1. Incident (n = 32)	2. Persistent (n = 45)	3. Remitted (n = 27)	P	Post-Hoc 0 vs. 1	Post-Hoc 0 vs 2	Post-Hoc 0 vs. 3	Post-Hoc 2 vs. 3
Baseline									
Height (cm)	133.0 (10.8)	135.0 (9.7)	142.2 (12.5)	136.0 (10.9)	**<0.001**	0.372	**<0.001**	0.200	**0.021**
Weight (kg)	28.8 (6.3)	31.8 (6.5)	49.7 (15.4)	40.5 (10.6)	**<0.001**	0.110	**<0.001**	**<0.001**	**<0.001**
Waist (cm)	60.0 (5.1)	63.1 (5.5)	79.1 (11.4)	72.2 (11.0)	**<0.001**	**0.044**	**<0.001**	**<0.001**	**<0.001**
Hip (cm)	67.9 (9.0)	70.8 (6.5)	85.7 (10.8)	77.1 (14.3)	**<0.001**	0.137	**<0.001**	**<0.001**	**0.001**
Neck (cm)	27.9 (2.6)	28.1 (1.6)	32.3 (3.5)	29.6 (5.0)	**<0.001**	0.695	**<0.001**	**0.012**	**0.001**
BMI%	44.4 (22.6)	68.4 (13.5)	95.8 (3.6)	93.2 (4.2)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.541
SBP Seated	109.0 (11.0)	112.7 (11.3)	115.9 (11.1)	112.8 (13.0)	**0.004**	0.101	**0.001**	0.111	0.266
DBP Seated	64.2 (8.0)	64.0 (7.1)	67.1 (7.5)	65.8 (9.5)	0.175	0.887	**0.041**	0.350	0.512
MAP Seated	79.0 (7.8)	80.1 (7.4)	83.2 (7.4)	81.3 (8.9)	**0.019**	0.490	**0.002**	0.160	0.326
Follow-up									
Height (cm)	172.9 (10.1)	172.5 (8.7)	176.3 (7.9)	174.5 (6.9)	0.147	0.827	**0.033**	0.399	0.424
Weight (kg)	62.1 (10.9)	79.8 (12.8)	97.1 (22.0)	70.3 (10.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Waist (cm)	74.9 (7.6)	89.5 (9.3)	98.9 (14.9)	79.7 (7.3)	**<0.001**	**<0.001**	**<0.001**	**0.019**	**<0.001**
Hip (cm)	83.4 (10.2)	95.9 (10.3)	105.9 (14.5)	88.9 (8.4)	**<0.001**	**<0.001**	**<0.001**	**0.019**	**<0.001**
Neck (cm)	36.0 (6.5)	38.1 (3.3)	41.0 (3.7)	37.0 (2.4)	**<0.001**	**0.044**	**<0.001**	0.366	**0.002**
BMI%	44.5 (24.9)	91.3 (4.4)	95.7 (3.6)	65.1 (18.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
SBP Seated	114.0 (11.0)	119.5 (13.3)	119.4 (9.3)	118.3 (12.9)	**0.008**	**0.015**	**0.006**	***0.076***	0.666
DBP Seated	64.3 (8.2)	70.1 (10.3)	68.4 (8.6)	64.7 (9.8)	**0.002**	**0.001**	**0.008**	0.811	***0.088***
MAP Seated	80.8 (8.2)	86.6 (10.5)	85.4 (7.6)	82.6 (10.0)	**0.001**	**0.001**	**0.003**	0.353	0.180
SBP Supine	113.2 (10.3)	114.9 (13.3)	119.0 (10.1)	115.2 (8.9)	**0.021**	0.414	**0.002**	0.376	0.141
DBP Supine	61.7 (7.8)	64.9 (8.3)	65.0 (8.5)	60.5 (9.0)	**0.021**	**0.047**	**0.018**	0.508	**0.023**
SBP Standing	118.4 (10.3)	123.0 (13.1)	126.1 (9.6)	121.0 (11.0)	**<0.001**	**0.032**	**<0.001**	0.247	***0.051***
DBP Standing	70.7 (7.7)	72.7 (10.0)	74.4 (9.5)	71.0 (7.9)	***0.071***	0.242	**0.011**	0.891	***0.089***
SBP Reactivity	5.2 (6.6)	8.1 (9.7)	7.3 (8.7)	5.8 (8.0)	0.179	***0.063***	0.113	0.693	0.428
DBP Reactivity	9.1 (5.6)	7.8 (6.9)	9.3 (7.1)	10.5 (5.5)	0.422	0.295	0.856	0.287	0.423
HDL cholesterol	47.3 (10.5)	44.9 (9.4)	42.6 (8.8)	47.4 (9.0)	**0.049**	0.237	**0.008**	0.971	***0.052***
Triglycerides	80.0 (29.3)	125.0 (86.9)	116.8 (47.7)	82.2 (20.6)	**<0.001**	**<0.001**	**<0.001**	0.826	**0.002**
Insulin	3.1 (2.2)	5.4 (3.4)	7.5 (9.0)	4.1 (7.6)	**<0.001**	**0.033**	**<0.001**	0.407	**0.011**
Glucose	88.8 (8.3)	90.3 (7.0)	92.8 (6.0)	96.8 (48.9)	0.211	0.703	0.235	**0.048**	0.378
HOMA-IR	0.7 (0.5)	1.2 (0.8)	1.7 (2.1)	1.0 (1.9)	**<0.001**	**0.038**	**<0.001**	0.293	**0.017**
cMetS score	-1.2 (1.6)	1.8 (3.3)	2.4 (2.7)	-0.8 (1.4)	**<0.001**	**<0.001**	**<0.001**	0.424	**<0.001**
And/W ratio	5.5 (0.9)	7.3 (1.6)	7.9 (1.6)	6.2 (1.2)	**<0.001**	**<0.001**	**<0.001**	**0.005**	**<0.001**
Gyn/W ratio	17.0 (1.9)	17.0 (2.0)	16.4 (1.6)	17.6 (1.7)	***0.057***	0.837	**0.060**	0.130	**0.007**
And/Gyn ratio	0.3 (0.1)	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	**<0.001**	**<0.001**	**<0.001**	0.105	**<0.001**
SAT	73.8 (41.5)	236.2 (110.0)	317.0 (159.3)	122.6 (81.5)	**<0.001**	**<0.001**	**<0.001**	**0.017**	**<0.001**
VAT	41.8 (12.1)	82.6 (32.6)	103.2 (44.5)	52.3 (16.1)	**<0.001**	**<0.001**	**<0.001**	***0.067***	**<0.001**

*Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. SBP = systolic blood pressure. DBP = diastolic blood pressure. MAP = mean arterial pressure. HDL = high density lipoprotein. HOMA-IR = homeostatic model assessment of insulin resistance. cMetS = metabolic syndrome score. Gyn/W = gynoid-whole body ratio. And/W = android-whole body ratio. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue.

Table 13. Cardiometabolic characteristics of female participants stratified by the natural history of overweight

	0. Normal Weight (n = 119)	1. Incident (n = 15)	2. Persistent (n = 51)	3. Remitted (n = 9)	P	0 vs. 1	Post-Hoc 0 vs 2	Post-Hoc 0 vs. 3	Post-Hoc 2 vs. 3
Baseline									
Height (cm)	134.9 (11.0)	136.5 (11.3)	143.0 (11.4)	140.5 (8.8)	**<0.001**	0.612	**<0.001**	0.147	0.538
Weight (kg)	30.1 (6.5)	34.0 (8.0)	50.7 (13.4)	42.8 (7.3)	**<0.001**	0.115	**<0.001**	**<0.001**	**0.016**
Waist (cm)	59.8 (5.0)	65.2 (5.4)	79.0 (9.5)	72.5 (7.3)	**<0.001**	**0.004**	**<0.001**	**<0.001**	**0.007**
Hip (cm)	69.6 (8.4)	73.0 (9.8)	86.6 (13.2)	82.7 (7.2)	**<0.001**	0.209	**<0.001**	**<0.001**	0.277
Neck (cm)	27.9 (5.4)	28.9 (2.0)	31.1 (3.6)	30.3 (1.9)	**0.002**	0.504	**<0.001**	0.141	0.642
BMI%	45.39 (22.39)	68.73 (15.22)	95.99 (3.44)	90.88 (4.96)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.439
SBP Seated	108.2 (11.7)	106.4 (10.1)	116.7 (13.1)	117.2 (11.0)	**<0.001**	0.592	**<0.001**	**0.029**	0.908
DBP Seated	65.0 (8.4)	61.0 (7.5)	66.4 (9.1)	67.9 (11.4)	0.150	0.096	0.341	0.335	0.630
MAP Seated	79.2 (8.4)	76.0 (7.1)	83.0 (9.0)	84.2 (10.6)	**0.007**	0.170	**0.010**	0.098	0.705
Follow-up									
Height (cm)	163.2 (6.7)	160.2 (10.4)	165.1 (6.1)	162.1 (6.1)	***0.079***	0.112	0.096	0.643	0.225
Weight (kg)	56.3 (8.0)	75.2 (10.5)	85.1 (16.5)	59.9 (4.6)	**<0.001**	**<0.001**	**<0.001**	0.346	**<0.001**
Waist (cm)	71.5 (6.1)	86.2 (8.6)	92.1 (13.7)	73.0 (3.9)	**<0.001**	**<0.001**	**<0.001**	0.625	**<0.001**
Hip (cm)	84.9 (8.3)	96.3 (9.7)	106.6 (13.9)	84.3 (8.4)	**<0.001**	**<0.001**	**<0.001**	0.886	**<0.001**
Neck (cm)	32.5 (1.9)	34.3 (1.5)	35.9 (3.1)	31.7 (1.1)	**<0.001**	**0.004**	**<0.001**	0.344	**<0.001**
BMI%	52.5 (22.8)	92.2 (4.2)	94.0 (4.3)	68.4 (14.1)	**<0.001**	**<0.001**	**<0.001**	**0.013**	**<0.001**
SBP Seated	107.7 (10.0)	113.9 (12.3)	115.8 (13.9)	106.0 (14.6)	**<0.001**	**0.051**	**<0.001**	0.677	**0.020**
DBP Seated	66.3 (9.0)	70.0 (9.6)	69.4 (8.4)	65.2 (9.7)	0.110	0.132	**0.041**	0.720	0.196
MAP Seated	80.1 (9.0)	84.6 (10.0)	84.9 (9.4)	78.8 (11.0)	**0.009**	***0.076***	**0.003**	0.687	***0.073***
SBP Supine	108.0 (8.4)	111.2 (7.8)	112.5 (11.3)	105.3 (9.2)	**0.014**	0.199	**0.004**	0.399	**0.032**
DBP Supine	64.7 (7.2)	66.2 (7.7)	66.5 (7.8)	64.4 (6.5)	0.504	0.468	0.160	0.904	0.441
SBP Standing	114.3 (11.1)	118.5 (12.8)	121.3 (12.4)	112.9 (12.1)	**0.003**	0.184	**<0.001**	0.734	**0.047**
DBP Standing	72.1 (9.0)	76.8 (7.5)	74.5 (8.2)	69.0 (7.6)	***0.059***	**0.050**	0.103	0.294	***0.078***
SBP Reactivity	6.3 (7.0)	7.3 (11.4)	8.5 (9.3)	7.6 (4.4)	0.423	0.651	0.100	0.629	0.755
DBP Reactivity	7.4 (5.6)	10.6 (6.7)	8.0 (6.7)	4.6 (4.3)	***0.098***	***0.052***	0.615	0.170	0.123
HDL cholesterol	55.3 (14.0)	47.7 (8.1)	52.6 (13.3)	62.9 (15.7)	***0.052***	**0.050**	0.255	0.126	**0.048**
Triglycerides	90.1 (41.7)	104.6 (45.1)	105.2 (50.1)	86.6 (35.0)	0.185	0.248	**0.049**	0.839	0.272
Insulin	9.2 (37.4)	5.9 (3.1)	9.5 (14.5)	2.5 (0.5)	0.916	0.698	0.964	0.548	0.551
Glucose	85.7 (9.4)	85.7 (3.8)	88.2 (7.5)	83.1 (6.3)	0.243	0.980	***0.084***	0.418	0.119
HOMA-IR	2.2 (10.4)	1.2 (0.7)	2.2 (3.9)	0.5 (0.1)	0.930	0.688	0.999	0.584	0.600
cMetS score	-0.8 (3.1)	1.4 (1.4)	1.7 (3.5)	-2.2 (2.4)	**<0.001**	**0.018**	**<0.001**	0.205	**0.001**
And/W ratio	5.6 (1.1)	7.6 (1.0)	7.4 (1.3)	6.4 (1.2)	**<0.001**	**<0.001**	**<0.001**	***0.056***	**0.023**
Gyn/W ratio	20.2 (2.1)	18.0 (1.1)	17.7 (1.9)	19.6 (1.2)	**<0.001**	**<0.001**	**<0.001**	0.368	**0.010**
And/Gyn ratio	0.3 (0.1)	0.4 (0.1)	0.0 (0.1)	0.3 (0.1)	**<0.001**	**<0.001**	**<0.001**	0.102	**0.001**
SAT	204.5 (66.9)	428.5 (101.1)	458.6 (142.2)	269.4 (73.2)	**<0.001**	**<0.001**	**<0.001**	**0.048**	**<0.001**
VAT	35.1 (16.8)	95.6 (33.4)	103.0 (48.7)	46.6 (21.2)	**<0.001**	**<0.001**	**<0.001**	0.261	**<0.001**

*Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. SBP = systolic blood pressure. DBP = diastolic blood pressure. MAP = mean arterial pressure. HDL = high density lipoprotein. HOMA-IR = homeostatic model assessment of insulin resistance. cMetS = metabolic syndrome score. Gyn/W = gynoid-whole body ratio. And/W = android-whole body ratio. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue.

Sleep characteristics were also stratified by sex in order to determine differences in sleep and the natural history of overweight (**Tables 14** and **15**). A longer sleep onset latency at baseline was significantly associated with incident overweight in males, while there was no association in females. Although there was no association between insomnia at baseline and the natural history of overweight in either males or females, at follow-up, there was a significant association between a lack of insomnia and remitted overweight in females.

Elevated baseline AHI was significantly associated with persistent and remitted overweight in females, but only marginally significant in males. Interestingly, in males and females an $2 \leq AHI > 5$ at baseline was significantly associated with both persistent and remitted overweight, while additionally in females, an $AHI \geq 5$ was significantly associated with remitted overweight. Follow-up AHI was significantly associated with incident and persistent overweight in males, while there was no significant association found in females. All these data stratified by sex are presented in **Table 14** (males) and **Table 15** (females) below.

Aim 3.3 Stress- and immune-related biomarkers of persistent overweight in males and females

We hypothesized that persistent overweight since childhood is associated with increased pro-inflammatory cytokines, adipokines, and cortisol levels in males and females, while incident overweight in adolescence is associated with abnormal levels in these stress/immune-related biomarkers in males but not in females. Data for baseline cortisol levels as well as data for cortisol and pro-inflammatory cytokines and adipokines at follow-up are presented in **Table 16** (males) and **Table 17** (females) in the following pages.

Table 14. Sleep characteristics of male participants stratified by the natural history of overweight

	0. Normal (n = 123)	1. Incident (n = 32)	2. Persistent (n = 45)	3. Remitted (n = 27)	P	Post-Hoc 0 vs. 1	0 vs 2	0 vs. 3	2 vs. 3
Baseline									
SOL (min)	23.6 (21.4)	37.2 (45.4)	22.9 (14.5)	32.4 (29.2)	**0.029**	**0.009**	0.871	0.113	0.134
Awakenings (#)	10.9 (5.7)	10.9 (6.7)	10.5 (5.5)	10.4 (5.7)	0.968	0.948	0.698	0.737	0.988
WASO (min)	41.2 (31.8)	45.5 (28.9)	42.8 (30.9)	41.9 (32.6)	0.923	0.496	0.779	0.917	0.913
TST (min)	456.2 (45.9)	442.5 (55.7)	465.1 (34.0)	454.4 (58.1)	***0.081***	**0.016**	0.992	0.283	0.352
% sleep efficiency	87.8 (7.6)	84.2 (8.7)	87.7 (6.2)	85.8 (9.6)	0.094	**0.020**	0.969	0.240	0.318
% stage 1	3.5 (2.7)	3.3 (2.6)	3.4 (2.2)	3.4 (2.9)	0.976	0.675	0.814	0.826	0.981
% stage 2	46.3 (10.7)	44.2 (11.8)	48.7 (11.0)	47.8 (8.5)	0.285	0.328	0.195	0.497	0.737
% stage 3	29.8 (10.6)	31.4 (11.5)	27.8 (9.7)	29.2 (8.9)	0.475	0.434	0.261	0.784	0.572
% stage R	20.4 (5.3)	21.1 (5.5)	20.1 (6.0)	19.6 (6.5)	0.783	0.521	0.824	0.525	0.691
Insomnia (%)	26.8	34.4	26.7	14.8	0.408	0.391	0.983	0.202	0.272
EDS (%)	12.2	21.9	20.0	14.8	0.439	0.179	0.217	0.734	0.557
AHI (#/hour)	0.7 (0.9)	0.4 (0.7)	0.8 (1.0)	1.0 (1.2)	***0.058***	0.126	0.302	***0.095***	0.471
AHI<2 (%)	93.5	93.7	84.4	77.8	***0.057***	---	---	---	---
2≤AHI<5 (%)	4.9	6.3	15.6	22.2		0.771	**0.032**	**0.006**	0.478
AHI≥5 (%)	1.6	0.0	0.0	0.0					
SpO_2	93.0 (5.0)	93.9 (2.8)	93.2 (3.2)	93.2 (3.1)	0.800	0.318	0.844	0.898	0.977
PLMI	1.2 (5.4)	0.4 (0.8)	0.2 (0.6)	2.4 (4.5)	0.157	0.366	0.211	0.167	**0.036**
Follow-up									
SOL (min)	23.9 (21.2)	26.7 (46.8)	23.4 (21.6)	22.6 (24.1)	0.934	0.598	0.915	0.814	0.898
Awakenings (#)	37.8 (10.5)	37.8 (17.2)	39.6 (11.4)	38.4 (14.6)	0.865	0.992	0.406	0.814	0.697
WASO (min)	74.2 (42.8)	75.5 (53.9)	87.6 (49.7)	65.0 (42.8)	0.206	0.879	0.095	0.348	**0.045**
TST (min)	445.2 (51.7)	439.3 (88.5)	430.5 (63.3)	454.9 (48.8)	0.356	0.623	0.164	0.449	0.098
% sleep efficiency	82.2 (9.5)	81.3 (16.4)	79.8 (11.5)	83.9 (9.1)	0.431	0.681	0.204	0.468	0.123
% stage 1	1.0 (1.1)	1.1 (3.7)	1.6 (1.6)	1.3 (1.7)	0.281	0.650	***0.057***	0.399	0.529
% stage 2	52.7 (11.1)	52.5 (12.4)	55.2 (10.4)	53.8 (8.7)	0.581	0.942	0.189	0.624	0.607
% stage 3	27.8 (10.4)	27.9 (11.5)	25.3 (10.2)	25.6 (8.1)	0.439	0.960	0.162	0.321	0.891
% stage R	18.5 (4.9)	18.4 (6.1)	18.0 (5.8)	19.3 (4.6)	0.806	0.907	0.560	0.519	0.327
Insomnia (%)	25.2	34.4	35.6	37.0	0.405	0.315	0.197	0.227	0.895
EDS (%)	55.0	61.3	68.2	53.8	0.252	0.285	***0.056***	0.662	0.324
AHI (# / hour)	2.2 (3.1)	4.1 (5.1)	5.3 (6.6)	2.4 (1.9)	**<0.001**	**0.028**	**<0.001**	0.854	**0.005**
AHI<2 (%)	64.2	31.3	37.8	48.1	**<0.001**	---	---	---	---
2≤AHI<5 (%)	29.3	46.9	31.1	44.4		**0.009**	0.152	0.115	0.832
AHI≥5 (%)	6.5	21.9	31.1	7.4		**0.002**	**<0.001**	0.621	**0.046**
$Sp0_2$	90.4 (6.4)	91.7 (2.0)	89.1 (8.8)	92.7 (1.9)	***0.078***	0.320	0.207	0.085	**0.017**
PLMI	5.8 (7.7)	2.0 (2.6)	3.1 (5.6)	4.7 (6.3)	**0.011**	**0.004**	**0.018**	0.435	0.311

***** Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI% = body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. SOL = sleep onset latency. WASO = wake after sleep onset. TST = total sleep time. EDS = excessive daytime sleepiness. AHI = apnea/hypopnea index. SpO2 = hemoglobin oxygen saturation level. PLMI = periodic limb movement index score

Table 15. Sleep characteristics of female participants stratified by the natural history of overweight

	0. Normal (n = 119)	**1. Incident** (n = 15)	**2. Persistent** (n = 51)	**3. Remitted** (n = 9)	**P**	**Post-Hoc 0 vs. 1**	**0 vs 2**	**0 vs. 3**	**2 vs. 3**
Baseline									
SOL (min)	29.54 (19.92)	24.23 (13.22)	28.46 (19.04)	30.83 (25.90)	0.779	0.323	0.742	0.849	0.739
Awakenings (#)	9.7 (5.7)	8.1 (4.6)	10.0 (6.3)	9.0 (4.7)	0.704	0.315	0.743	0.717	0.618
WASO (min)	44.6 (34.4)	27.9 (26.9)	41.3 (26.9)	51.0 (51.4)	0.259	***0.067***	0.549	0.572	0.413
TST (min)	456.91 (42.35)	468.17 (33.97)	458.57 (41.76)	449.83 (45.45)	0.724	0.327	0.813	0.625	0.564
% sleep efficiency	86.12 (7.78)	90.10 (5.02)	86.89 (6.74)	85.40 (9.66)	0.251	0.564	***0.052***	0.536	0.579
% stage 1	3.07 (2.76)	2.40 (1.55)	3.35 (2.57)	3.33 (1.87)	0.648	0.351	0.513	0.768	0.983
% stage 2	46.40 (10.82)	47.80 (13.23)	44.94 (10.99)	48.44 (9.28)	0.706	0.644	0.428	0.592	0.380
% stage 3	30.38 (9.90)	29.93 (11.79)	31.53 (10.28)	29.33 (10.74)	0.877	0.874	0.500	0.767	0.552
% stage R	20.51 (5.23)	19.80 (6.10)	20.24 (5.67)	18.89 (3.30)	0.813	0.627	0.757	0.381	0.487
Insomnia (%)	23.5	33.3	31.4	33.3	0.639	0.423	0.294	0.525	0.903
EDS (%)	14.3	13.3	13.7	11.1	0.994	0.921	0.924	0.793	0.836
AHI (#/hour)	0.72 (0.90)	0.95 (0.90)	1.20 (1.58)	2.09 (1.81)	**0.002**	0.478	**0.015**	**0.001**	**0.036**
AHI<2 (%)	91.6	86.7	76.5	55.6	**0.019**	---	---	---	---
2≤AHI<5 (%)	7.6	13.3	19.6	33.3		0.456	**0.022**	**0.014**	0.295
AHI≥5 (%)	0.8	0.0	3.9	11.1			0.165	**0.038**	0.300
SpO_2	92.97 (4.01)	93.40 (3.25)	91.92 (3.44)	93.22 (2.39)	0.329	0.674	0.099	0.844	0.339
PLMI	0.48 (1.27)	0.14 (0.39)	0.50(1.08)	0.96 (1.75)	0.459	0.310	0.930	0.252	0.291
Follow-up									
SOL (min)	29.92 (22.95)	29.67 (18.07)	26.18 (19.55)	23.78 (13.34)	0.660	0.965	0.297	0.408	0.757
Awakenings (#)	35.44 (11.95)	31.80 (9.92)	32.73 (10.77)	31.11 (10.25)	0.317	0.247	0.158	0.275	0.697
WASO (min)	61.38 (32.79)	50.23 (37.96)	66.08 (49.88)	64.83 (31.50)	0.559	0.290	0.465	0.795	0.929
TST (min)	450.49 (46.07)	464.97 (41.36)	450.27 (55.61)	452.89 (38.08)	0.738	0.978	0.886	0.274	0.881
% sleep efficiency	83.41 (8.33)	85.77 (7.93)	83.32 (10.37)	83.77 (6.92)	0.798	0.331	0.951	0.908	0.889
% stage 1	0.837 (0.89)	0.527 (0.48)	0.939 (1.04)	0.511 (0.30)	0.310	0.208	0.497	0.295	0.188
% stage 2	53.75 (9.22)	55.85 (6.00)	53.46 (7.86)	50.48 (8.44)	0.529	0.378	0.838	0.274	0.341
% stage 3	26.65 (8.56)	26.03 (6.01)	26.99 (6.56)	31.43 (7.88)	0.353	0.775	0.795	***0.081***	0.121
% stage R	18.71 (4.58)	17.59 (4.70)	18.63 (5.21)	17.59 (4.44)	0.768	0.389	0.918	0.495	0.546
Insomnia (%)	48.3	53.3	49.0	0.0	**0.038**	0.710	0.931	**0.005**	**0.007**
EDS	81.2	60.0	70.6	88.9	0.788	0.789	0.348	0.804	0.501
AHI (# / hour)	2.35 (8.50)	1.81 (1.12)	1.88 (2.10)	0.92 (0.88)	0.917	0.772	0.681	0.544	0.697
AHI<2 (%)	76.5	53.3	70.6	88.9	***0.080***	---	---	---	---
2≤AHI<5 (%)	17.6	46.7	17.6	11.1		**0.020**	0.857	0.573	0.538
AHI≥5 (%)	5.9	0.0	11.8	0.0		0.998	0.190		
$Sp0_2$	92.77 (3.11)	89.93 (7.35)	92.55 (2.01)	92.78 (2.44)	**0.025**	**0.002**	0.691	0.997	0.851
PLMI	3.12 (5.46)	1.86 (2.72)	3.17 (4.69)	3.00 (3.47)	0.831	0.364	0.956	0.943	0.925

***** Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI% = body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. SOL = sleep onset latency. WASO = wake after sleep onset. TST = total sleep time. EDS = excessive daytime sleepiness. AHI = apnea/hypopnea index. SpO2 = hemoglobin oxygen saturation level. PLMI = periodic limb movement index score

As shown in **Table 16** (males) and **Table 17** (females) below, males and females did not show a significant association between cortisol and weight at either time point. CRP and IL-6 were associated with both incident and persistent overweight in males. In females, CRP was only associated with persistent overweight, and IL-6 was not found to have a significant association with weight. TNF-α was found to be significantly associated with persistent overweight in males, while there was no association in females. In both males and females, leptin was significantly associated with both incident and persistent overweight. Interestingly, in males, adiponectin was significantly associated with both incident and persistent overweight, while in females, it was only significantly associated with remitted overweight.

Table 16. Stress and inflammatory characteristics of males stratified by the natural history of overweight

	0. Normal (n = 123)	**1. Incident** (n = 32)	**2. Persistent** (n = 45)	**3. Remitted** (n = 27)	**P**	**Post-Hoc** **0 vs. 1**	**0 vs 2**	**0 vs. 3**	**2 vs. 3**
Baseline									
Cortisol 7PM	0.3 (0.7)	0.3 (0.1)	0.2 (0.1)	0.8 (1.5)	0.123	0.683	0.564	**0.038**	**0.023**
Cortisol 7AM	1.2 (0.5)	1.1 (0.4)	1.1 (0.4)	1.2 (0.5)	0.739	0.308	0.567	0.954	0.659
Follow-up									
Cortisol 7PM	8.2 (5.6)	8.3 (5.6)	8.6 (5.0)	8.2 (5.2)	0.976	0.939	0.659	0.989	0.742
Cortisol 7AM	19.0 (7.9)	21.0 (10.4)	20.4 (9.1)	19.6 (8.9)	0.617	0.240	0.373	0.746	0.719
CRP	0.7 (0.5)	1.4 (1.9)	1.7 (1.9)	0.6 (0.4)	**<0.001**	**0.004**	**<0.001**	0.824	**<0.001**
IL-6	0.9 (0.8)	1.3 (0.8)	1.8 (1.3)	0.8 (0.5)	**<0.001**	***0.052***	**<0.001**	0.598	**<0.001**
TNF-a	1.7 (1.0)	2.1 (1.4)	2.3 (1.6)	1.6 (0.6)	**0.018**	0.127	**0.006**	0.588	0.108
Adiponectin	8.0 (5.0)	5.2 (2.2)	5.2 (3.3)	7.9 (4.4)	**<0.001**	**0.002**	**0.001**	0.938	**0.013**
Leptin	3.0 (4.2)	12.43 (8.7)	15.8 (11.0)	4.9 (7.8)	**<0.001**	**<0.001**	**<0.001**	0.244	**<0.001**

***** Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. CRP = C-Reactive protein. IL-6 = interleukin 6. TNF-α = tumor necrosis factor alpha.

Table 17. Stress and inflammatory characteristics of females stratified by the natural history of overweight

	0. Normal (n = 119)	**1. Incident** (n = 15)	**2. Persistent** (n = 51)	**3. Remitted** (n = 9)	**P**	**Post-Hoc** **0 vs. 1**	**0 vs 2**	**0 vs. 3**	**2 vs. 3**
Baseline									
Cortisol 7PM	0.4 (0.7)	0.4 (0.6)	0.3 (0.3)	1.1 (2.0)	0.097	0.913	0.518	**0.022**	**0.013**
Cortisol 7AM	1.2 (0.5)	1.1 (0.4)	1.3 (0.7)	1.2 (0.4)	0.763	0.412	0.958	0.584	0.736
Follow-up									
Cortisol 7PM	7.8 (7.9)	7.5 (7.0)	9.1 (12.7)	7.5 (5.5)	0.833	0.928	0.384	0.930	0.624
Cortisol 7AM	20.1 (9.2)	19.7 (11.9)	21.2 (8.9)	19.6 (10.6)	0.878	0.891	0.464	0.875	0.623
CRP	0.7 (0.6)	0.8 (0.6)	1.2 (1.0)	0.7 (0.6)	**0.002**	0.508	**<0.001**	0.920	0.114
IL-6	1.1 (0.9)	1.5 (0.8)	1.4 (1.0)	1.4 (0.8)	0.131	***0.082***	***0.068***	0.394	0.998
TNF-a	1.8 (1.4)	2.2 (1.4)	2.1 (1.5)	1.9 (0.4)	0.727	0.418	0.347	0.921	0.745
Adiponectin	8.9 (4.7)	7.4 (6.6)	8.0 (5.9)	13.4 (5.0)	**0.045**	0.309	0.358	**0.020**	**0.008**
Leptin	13.9 (8.4)	20.6 (15.8)	29.6 (14.9)	15.5 (9.2)	**<0.001**	**0.037**	**<0.001**	0.717	**0.002**

***** Significant at $p \leq .05$ [T] Statistical trend at $p \leq .10$. Data are means (SD) except otherwise stated. BMI%= body mass index percentile. Normal weight = BMI% < 85th%. Overweight = BMI% ≥ 85th% and < 95th%. Obesity = BMI% ≥ 95th%. CRP = C-Reactive protein. IL-6 = interleukin 6. TNF-α = tumor necrosis factor alpha.

5. Discussion

As obesity prevalence continues to rise, there is an eminent need to study the trajectory of obesity throughout a life course in order to determine the most effective preventative strategies and treatment plans. This study showed that the majority of young overweight children will persist in their overweight category into adolescence, especially if they are female. Additionally, persistently overweight children were found to have the highest visceral adiposity in adolescence among all the weight trajectory groups, further displaying the importance of controlling childhood global overweight early in order to prevent further visceral adiposity accumulation and central obesity. Persistently overweight children also had the highest levels of inflammatory biomarkers, most likely a result of their increased visceral adiposity. As hypothesized, males with persistent or incident overweight had high levels of cardiometabolic risk factors and inflammatory biomarkers, while females did not display the same degree of elevated levels as males. Therefore, these data stress the importance of prevention and early intervention protocols for childhood obesity in order to prevent long-term adverse impact on cardiometabolic health, and to ultimately improve the quality of life of the general public.

As reported in previous studies, the most common weight trajectory was persisting in the child's BMI% categorization, whether this was a healthy or unhealthy body weight (Moreno-Black *et al.*, 2016; Peneau *et al.*, 2017). This trajectory reiterates the importance of intervening early in childhood overweight and obesity, in order to prevent long-term weight gain and the development of comorbidities. Over 72% of children that were overweight or obese in childhood remained overweight or obese into adolescence, while only 28% experienced full remission. Therefore, childhood overweight should be considered a chronic medical condition, as it is unlikely that an overweight child will "grow out of it" like previously believed.

In addition to weight trajectory since childhood, we also studied the trajectory of central obesity into adolescence. Interestingly, the persistence and remission rates of central obesity from childhood were almost 50%, respectively. However, our remission rate contradicted that of central obesity trajectories previously studied (Araujo *et al.*, 2016; Kain *et al.*, 2016). Unlike BMI%, a child with central obesity may have a greater chance of reducing their central obesity through lifestyle modifications, and thus, potentially lowering their risk of developing cardiometabolic and inflammatory morbidities associated with android distribution and visceral adiposity. These data indicate that early intervention in reducing a child's central obesity would positively impact their future cardiometabolic health.

Normal weight children that became overweight or obese in adolescence were on average already heavier and had a larger waist circumference in childhood, despite having been categorized at the time as "normal weight" via BMI percentile standards. These data suggest that waist circumference measures should be used in addition to BMI percentile in clinical evaluations of children in order to detect all pre-morbid levels of risk for developing obesity and associated adverse health outcomes (Spolidoro *et al*., 2013; Alves *et al.*, 2017). Additionally, visceral adiposity was found to be significantly higher in adolescence who had been persistently overweight since childhood. We did hypothesize that adolescents with childhood-onset overweight should have had higher levels of visceral adiposity in adolescence as compared to adolescents with new-onset overweight because they had a longer exposure and more time to accumulate visceral adiposity. This hypothesis was important because our and other's data suggests that childhood central obesity may lead to further cardiometabolic dysfunction and inflammation (Andaki *et al.*, 2018; Suder *et al.*, 2017). This phenomenon is displayed in our data, with the persistent overweight adolescents having the highest levels of visceral adiposity

and all cytokines and adipokines tested (except for adiponectin that was lowest, as expected). Future analyses of these data will be performed with the help of an expert biostatistician in multi-level, longitudinal, mediation modelling to test whether stress/immune-related mechanisms (i.e., increased cytokines) mediate the relationship between persistent overweight since childhood and cardiometabolic and sleep outcomes in adolescence, as depicted in **Figure 2** above.

Surprisingly, visceral adiposity, but not subcutaneous adiposity, in adolescence was significantly elevated in those who had remitted from their childhood overweight. These data suggest that some overweight children who remit in the transition to adolescence may remain at risk of developing adverse health outcomes given the known association of visceral adiposity with inflammation (Jung *et al.*, 2014). Therefore, a child that loses weight during the transition to adolescence might not be out of harm's way like previously believed. It is, therefore, imperative to implement prevention and early intervention strategies into a child's clinical care in order to prevent residual effects of childhood obesity later in life. Also, it is necessary to develop fine-grained, feasible and reliable measures of visceral adiposity to be used in routine clinical practice.

There are clinical variables, however, that are not influenced by when the onset of overweight had occurred. Particularly, seated SBP in adolescence was found to be almost identically elevated in both persistent overweight children and incident overweight adolescents. Therefore, elevated SBP in childhood should be alleviated when the child loses weight and not create lasting effects (Son *et al.*, 2017; Schmidt *et al*., 2016). Additionally, SDB in adolescence was found to be raised in persistent overweight children and incident overweight adolescents. However, incident overweight adolescents were associated with an increased risk of mild SDB (i.e., $2 \leq AHI < 5$) and OSA (i.e., $AHI \geq 5$) in adolescence, while persistent overweight children

were associated with an increased risk of OSA, but not SDB. Therefore, SDB in adolescence is a result of recent weight gain and not necessarily the result of childhood-onset obesity (Kulkas *et al*., 2015; Frye *et al*., 2019; Young *et al*., 2005). These data, however, strongly suggest that children who exhibit excessive and continual weight gain should be clinically monitored for SDB before it can develop into OSA in a routine clinical manner.

This study also revealed that males and females have different weight trajectories in the transition from childhood to adolescence. Males were more likely to develop overweight or obesity in adolescence than females, but females were less likely to remit from their childhood overweight than males. These sex differences may be related to different developmental trajectories in males and females; for example, overweight young boys may experience a greater growth (height) with the onset of puberty that would re-classify them as normal weight in adolescence, while an overweight young girl may not experience such as a significant growth spurt, particularly in terms of height, which will keep her classified as overweight post-puberty. The use of fine-grained adiposity measures will also be essential in understanding whether the remission of childhood overweight or obesity in the transition to adolescence is associated with developmental processes or with actual reduction of critical adiposity deposits (e.g., visceral). Nevertheless, these data support the importance to intervene in childhood obesity, especially in females, in order to prevent long term weight gain and adverse outcomes, while it may be more important in males to prevent weight gain during the transition from childhood to adolescence instead of early childhood by watchful waiting (Smith *et al.,* 2015; Brown *et al.,* 2018).

In addition, remitted overweight males and females had larger accumulations of visceral and subcutaneous adiposity as compared to normal weight adolescents with similar BMI percentiles. This finding stresses the burden childhood obesity has on an individual; an

individual can lose weight and be deemed a healthy "normal weight" by BMI percentile standards yet have residual effects of their childhood obesity (i.e., visceral adiposity). As mentioned previously, increased levels of visceral adiposity may lead to increased risk of metabolic syndrome and cardiovascular disease (Maas *et al.*, 2010; He *et al*., 2015; Pi-Sunyer, 2002). Therefore, clinical intervention in central obesity is imperative in order to prevent lasting adverse effects even after substantial weight loss. Additionally, both incident and persistent overweight males showed higher levels of all inflammatory biomarkers, as compared to females that had similar associations only for CRP levels. Therefore, males have a higher risk of inflammation no matter the time period in which they become overweight, while females seem to have less significant pro-inflammatory effects. These data are consistent with the known greater resilience of women in terms of cardiovascular disease (Westerman *et al.*, 2016).

The results reported herein should be interpreted in light of some potential limitations. First, there was a lack of an evaluation between childhood and adolescence which allows for the hypothesis that some children may have become overweight or obese and lost weight before the adolescent follow-up. This hypothesis, however, is disproven with ours and other's data that indicate that childhood overweight and obesity is highly persistent in the transition to adolescence (Frye *et al.*, 2019; Vgontzas *et al*., 2014). Therefore, a course of normal weight → obese → normal weight, is highly unlikely to occur (Ward *et al*., 2017; Munthali *et al*., 2017). Second, the DXA scan and inflammatory biomarker collection were only assessed at follow-up. Thus, the change in body fat distribution and composition and inflammation could not be examined in a longitudinal manner. Further research should be completed in order to show the longitudinal effects of adolescent inflammation and body composition on adverse health outcomes in young adulthood, while future large, cohort studies should assay for pro-

inflammatory cytokines since childhood. Third, the relationship between sex hormones and childhood obesity and adolescent obesity could not be studied. Some preliminary studies have shown the presence of elevated estrogen and progesterone in male overweight children, and elevated testosterone in female overweight children (Anderson *et al*., 2014; Chang *et al*., 2018; Vandewalle *et al*., 2015). Future studies should be conducted to determine how these abnormal sex hormone levels play into the development of obesity and its comorbidities, particularly at the onset of puberty. Finally, the levels of "brown" and "white" adiposity (Saely *et al.*, 2012) in overweight and obese children and its trajectory into adolescence was not studied. Preliminary studies have shown that adult obese men have less activated brown adipose tissue than lean men (Leitner *et al*., 2017), and a similar association has been found in children (Deng *et al*., 2015; Rogers, 2015). Future studies should test whether overweight or obese children as per BMI percentile criteria have different levels of such brown or white adiposity as compared to normal weight children.

In conclusion, this work has shown the adverse effects of childhood-onset and adolescent-onset overweight, such as elevated cardiometabolic risk factors and increased levels of inflammation – all of which may lead to cardiovascular disease and other adverse health outcomes. By studying the trajectories of childhood overweight and obesity, we can solidify the impact that such weight gain has on future adolescent health. This study further supports that early prevention of comorbidities should focus on childhood-onset overweight. However, new-onset overweight in adolescence should not be regarded as a less severe form in terms of its increased risk of adverse health outcomes. These data also support the clinical utility of a variety of measures of adiposity, other than BMI percentile, to help predict a child's risk of future development of co-morbidities during their transition to adolescence.

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Publications

Danisi, J., Fernandez-Mendoza, J., Vgontzas, A.N., Calhoun, S.L., He, F., Sawyer, M.D., Liao, D., Bixler, E.O. (submitted). Visceral Fat and Inflammation in Normal Weight Adolescents with Sleep Apnea: A Longitudinal Study.

Danisi, J., Fernandez-Mendoza, J., Vgontzas, A.N., Bixler, E.O. (2019) *Obesity and Sleep Disturbances*. In: Murillo Rodríguez, E. (Ed.) Genetic, Biochemical, and Clinical Aspects of the Sleep-Wake Cycle. London, United Kingdom: Elsevier.

Abstracts and Presentations

Danisi, J., Fernandez-Mendoza, J., He, F., Sawyer, M.D., Calhoun, S.L., Liao, J., Liao, D., Vgontzas, A.N., Bixler, E.O. Visceral Obesity and Systemic Inflammation Predict Sleep Disordered Breathing in Normal Weight, Never Obese Adolescents: A Longitudinal, Population-Based Study. Graduate Student Research Forum. Hershey, Pennsylvania on February 28 – March 1, 2019. Penn State College of Medicine.

Danisi, J., Fernandez-Mendoza, J., He, F., Sawyer, M.D., Calhoun, S.L., Liao, J., Liao, D., Vgontzas, A.N., Bixler, E.O. Visceral Obesity and Systemic Inflammation Predict Sleep Disordered Breathing in Normal Weight, Never Obese Adolescents: A Longitudinal, Population-Based Study. EPI/Lifestyle 2019 Scientific Sessions. Houston, Texas on March 5 - 8, 2019. American Heart Association

Danisi, J., Fernandez-Mendoza, J., Calhoun, S.L., He, F., Puzino, K., Liao, D., Vgontzas, A.N., Bixler E.O. Longitudinal Association of the Natural Course of Childhood Overweight with Sleep Disordered Breathing in the Transition to Adolescence: The Penn State Child Cohort. Abstract submitted to the 33rd Annual Meeting of the Associated Professional Sleep Societies. San Antonio, Texas on June 8-12, 2019. Associated Professional Sleep Societies.

Fernandez-Mendoza, J., Calhoun, S.L., Puzino, K., Danisi, J., He, F., Liao, J., Liao, D., Vgontzas, A.N., Bixler, E.O. Natural History of Insomnia Symptoms from Childhood through Adolescence into Young Adulthood: The Penn State Child Cohort. Abstract submitted to the 33rd Annual Meeting of the Associated Professional Sleep Societies. San Antonio, Texas on June 8-12, 2019. Associated Professional Sleep Societies.