PRENATAL PATHWAYS TO EARLY PUBERTY: TESTING THE THRIFTY PHENOTYPE AND FETAL OVERNUTRITION HYPOTHESES

by

Olivia C. Robertson

A Thesis

Submitted to the Faculty of Purdue University

In Partial Fulfillment of the Requirements for the degree of

Master of Science

Department of Human Development and Family Studies

West Lafayette, Indiana

December 2021

THE PURDUE UNIVERSITY GRADUATE SCHOOL
STATEMENT OF COMMITTEE APPROVAL

Dr. Kristine Marceau, Chair

Department of Human Development and Family Studies

Dr. Valerie Knopik

Department of Human Development and Family Studies

Dr. Kameron Moding

Department of Human Development and Family Studies

Approved by:

Dr. David J. Purpura

ACKNOWLEDGEMENTS

The data for this thesis came from The Fragile Families and Child Wellbeing Study. This thesis acknowledges the generous support of the Fragile Families study funders—NICHD and HHS along with a consortium of funders—without which the Fragile Families study would not be possible.

National Institute of Child Health & Development (NICHD)
California HealthCare Foundation
Commonwealth Fund Ford Foundation
Foundation for Child Development
Fund for New Jersey
William T. Grant Foundation
Healthcare Foundation of New Jersey
William and Flora Hewlett Foundation
Hogg Foundation
Christina A. Johnson Endeavor Foundation
Kronkosky Charitable Foundation
Leon Lowenstein Foundation
John D. and Catherine T. MacArthur Foundation
A.L. Mailman Family Foundation
Charles S. Mott Foundation
National Science Foundation
David and Lucile Packard Foundation
Public Policy Institute of California
Robert Wood Johnson Foundation
St. David's Hospital Foundation
St. Vincent Hospital and Health Services
US Department of Health and Human Services (ASPE and ACF)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

This thesis outlined a novel operationalization and extension of the thrifty phenotype and fetal overnutrition hypotheses, two evolutionary developmental hypotheses stemming from the developmental origins of health and disease perspective, for developmental pathways from prenatal risk through child growth to early puberty. Support has accumulated for both, but previous studies have not clearly determined which hypothesis better predicts early puberty. Using the Fragile Families and Child Wellbeing Study (*n*=4898), the thrifty phenotype and fetal overnutrition pathways were tested against each other, separately by sex, and race/ethnicity for adrenal, and gonadal pubertal markers. Results indicated that in general, both hypotheses were supported. Contrary to hypotheses, the thrifty phenotype pathway did not predict perceived pubertal timing better in boys and the fetal overnutrition pathway did not predict perceived pubertal timing best in girls. Instead, both pathways predicted puberty equally well between girls and boys and the fetal overnutrition pathway stemming from maternal gestational weight gain was stronger than the pre-pregnancy BMI pathway. Individual paths of the hypothesized pathways were generally supported when analyzed by race/ethnicity group separately, but support for the entire pathways were sparse. Implications of this work are that pubertal timing may be similarly programmed by restrictive and overnutrition prenatal risks, both should be prioritized, and that interventions for maternal gestational weight should be prioritized over interventions for pre-pregnancy BMI for reducing rates of early puberty.

INTRODUCTION

Puberty is a set of interrelated biological processes involved in physical and reproductive maturation that spans the very beginnings of sexual maturation to the attainment of full sexual reproductive capacity and beyond. Puberty is embedded within the developmental period of adolescence, but puberty and adolescence are not interchangeable. Broadly, adolescence is the transition from childhood to adulthood and concerns the psychological, social and cognitive changes associated with adolescence while puberty primarily concerns the significant biological and physical changes that teens experience (Dorn et al., 2006; Dorn et al., 2019). The timing of puberty is a major evolutionary milestone in the lifespan, and it is characterized by the reawakening of the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-gonadal axis, and the appearance of secondary sex characteristics. Off timing of puberty, that is, developing earlier or later than same sex and aged peers seems to be problematic across an array of domains (e.g., achievement, psychosocial, risk behaviors, and health; Copeland et al., 2010; Day et al., 2015; Dubas et al., 1991; Negriff & Susman, 2011; Patton et al., 2004).

Furthering the study of puberty may be key to better understanding health trajectories throughout the life course (Dorn et al., 2019). Early timing of puberty has been associated with poor markers of health in adolescence and non-communicable diseases in adulthood, such as type II diabetes, obesity, cardiovascular disease, and reproductive cancers in men and women (Day et al., 2015; Jacobsen et al., 2009; Ong et al., 2012; Remsberg et al., 2005). The rise in prevalence of type II diabetes, obesity and cardiovascular disease in industrialized populations are burdensome and costly public health crises due to their chronicity and difficulty to treat (Kim & Basu, 2016). This is in part because type II diabetes, obesity and cardiovascular disease are all complex chronic diseases with genetic and environmental determinants across the lifespan, and

may also be particularly influenced by intrauterine development (Barker & Bagby, 2005; Hales & Barker, 1992; Hruby & Hu, 2015; Tabish, 2007). Given the association between earlier timing of puberty and poor adolescent and adult health, studying antecedents of pubertal timing could be useful in better predicting and understanding post pubertal health trajectories.

Sexual maturation and growth are closely related, which suggests that metabolic pathways may be in some way shared between somatic and pubertal development (Bulik-Sullivan et al., 2015; Roth & DiVall, 2016). Although concerning in its own right, the associations between earlier pubertal timing and poor health outcomes may be especially alarming given that a declining secular trend in the age at pubertal maturation has been reported in boys and girls (Euling et al., 2008; Ohlsson et al., 2019). Further, the declining secular trend in pubertal timing has been speculated to be coinciding with another costly public health crisis, rising rates of childhood obesity (Reinehr & Roth, 2019). A wealth of literature suggests higher childhood body mass index (BMI), a proxy for adiposity or fat tissue, is associated with earlier timing of puberty and some studies suggest this relationship is causal (Busch et al., 2019; Y. C. Chen et al., 2019; Li et al., 2017). Childhood obesity has been similarly associated with type II diabetes, coronary heart disease and some cancers (Llewellyn et al., 2016). Importantly, effects of pubertal timing on health outcomes generally persist after controlling for BMI or body composition (Ohlsson et al., 2020; Remsberg et al., 2005), although taking into account the role of pubertal maturation in studies of adolescent health is lacking (Dorn et al., 2006; Dorn et al., 2019). Nonetheless, considering both pubertal timing and adiposity is important as they may contribute independently or jointly to poor health outcomes.

Pubertal timing and childhood obesity share common genetic, prenatal, birth, and infancy risk factors (Bulik-Sullivan et al., 2015; Castillo-Laura et al., 2015; Juul et al., 2017; Lawn et al.,

2018; Ong et al., 2009; Qiao et al., 2015; Silva et al., 2002; Won Kyoung & Byung-Kyu, 2016). Collectively, this indicates that childhood obesity and pubertal timing may operate through common developmental pathways from the beginning of the life course. According to the developmental origin of health and disease (DOHaD) perspective, pathways stemming from prenatal insults may be particularly important for somatic growth and the reproductive axis since prenatal insults experienced in utero may permanently program metabolic functioning (Roth & DiVall, 2016). Although heritable factors are relevant to the study of pubertal timing (Ge et al., 2007), in this thesis, I focused only on the prenatal environment and the cascade of postnatal changes that follow as these influences are arguably more malleable than heritable factors.

Previous studies have identified risk factors from the prenatal environment through childhood for early puberty, though many studies either investigate prenatal and birth risk factors with childhood adiposity *or* infancy risk factors and childhood BMI in the study of pubertal timing (Brix, Ernst, Lauridsen, Arah, et al., 2019; Deardorff et al., 2013; Lawn et al., 2018; Ong et al., 2009). Rarely are all these risks investigated in the same study (e.g.; Karaolis-Danckert et al., 2009). This is a key limitation of the field, as tracing common developmental pathways is important for better understanding and quantifying the relative contributions of each risk factor for early pubertal timing. Additionally, no prior investigations have tested the pathway longitudinally from the prenatal environment through birth, infancy, and childhood to pubertal timing. This is also a key limitation of the pubertal timing literature since lifespan perspectives suggest that prenatal risk factors may put into motion a series of downstream consequences that cascade across the early life course and culminate in influencing the timing of puberty (Jazwiec & Sloboda, 2019). Thus, the current thesis sought to contribute to the literature by examining prenatal pathways to earlier puberty including birth, infancy and childhood risk factors using a

analytic framework congruent with a lifespan perspective. This work purposed to better understand the developmental sequelae of early puberty by contributing a more precise model of predicting pubertal timing, and more distally, to better inform the prediction and the prevention of the costly public health concerns that are associated with pubertal timing.

Theoretical Framework: The Developmental Origins of Health and Disease

Initially arising from the Barker hypothesis, the DOHaD perspective is supported by a large body of work that centers on the premise that exposures experienced during intrauterine development are consequential for later life health outcomes. The DOHaD is guided by the principle that the nutritional, hormonal and metabolic environment provided by the mother may permanently program the structure and physiology of the offspring (Barker, 1995; Kwon & Kim, 2017). Barker first brought attention to this phenomenon by observing and proposing a direct link between poor prenatal nutrition and late onset of coronary heart disease in England and Wales (Barker & Osmond, 1986). This landmark study showed that prenatal experiences could potentially have far reaching effects on adult health and contributed greatly to conceptualizing the idea of prenatal programming for adult health.

Next, I introduce two key hypotheses from the DOHaD perspective that have been previously applied to explain trajectories from prenatal insults to obesity and pubertal timing (Deardorff et al., 2013; Oken & Gillman, 2003). First, I explain the metabolic mechanism of each hypothesis as they were originally posited. Second, I detail their application to pubertal maturation. Finally, empirical evidence that supports each hypothesis is explained in further detail in the literature review section.

The Thrifty Phenotype Hypothesis

Barker (1990, 1995, 2007) suggested that the fetus uses the prenatal environment as a forecast of what postnatal life will be like and then adapts to intrauterine conditions as a means to prepare for life outside the womb thereby maximizing chances of survival. Guided by principles of developmental plasticity, which suggests early life environments may influence later life traits, this mechanism is adaptive when the conditions the fetus experiences in utero accurately reflect the postnatal environment. However, the prenatal and postnatal environment are not always consistent with each other. Hales and Barker (1992) later put forward the thrifty phenotype hypothesis which explains the deleterious health consequences for when prenatal and postnatal life conditions do not align. The thrifty phenotype hypothesis originally posited that poor fetal and infant growth leads to greater risk of developing insulin resistance and type II diabetes in adulthood (Hales & Barker, 1992), and specifically when those children experience a postnatal environment that is not marked by similar deprivation. Notably, this hypothesis centers on metabolic programming and somatic growth, and has since been expanded to explain the role of the prenatal environment for other physiological and behavioral development (e.g., Biro & Deardorff, 2013; Deardorff et al., 2013).

The primary driver of poor fetal growth is poor nutrition, and the major cause of early life malnutrition often stems from *maternal* malnutrition (Barker, 2001). The supply of nutrients from the mother is the primary regulator of growth which depends on the mother's body composition and size, nutrient stores, pregnancy diet and transport of nutrients to and across the placenta (Bauer et al., 1998). When nutrient demand is greater than the placental supply from the mother (i.e., undernutrition), the fetus first becomes catabolic, meaning that it metabolizes its own substrates in order to utilize its own energy (Harding & Johnston, 1995). If low availability of resources persists, growth rate slows and the fetus begins to lessen its rate of consumption of

nutrients in an attempt to increase chances of survival by lowering its metabolic rate (Barker, 2001). This may then lead to permanent alterations in the structure and function of visceral organs (e.g., liver, pancreas) involved in metabolic activity (Hales & Barker, 1992). More specifically, these survival mechanisms are associated with metabolic changes like decreased glucose oxidation, increased amino acid and lactase oxidation, hypoxemia (low blood oxygen levels) and redistribution of blood away from internal organs to the brain ("brain sparing"; Cohen et al., 2015; Rudolph, 1984), and changes in the production of fetal and placental hormones involved in growth (e.g., increased levels of cortisol and decreased levels of insulin and insulin growth factor; Fowden, 1989; Fowden, 1995). Collectively, these changes program the fetus for nutritional thrift and put it at higher risk of insulin resistance (Gluckman & Pinal, 2001; Ravelli et al., 1998). Following these adaptations, the fetus would be adept at surviving in postnatal environments that are similarly nutritionally scarce, and an insensitivity to insulin would not be so problematic.

Adaptations programmed in utero may produce unintended consequences when prenatal and postnatal conditions are incongruent with each other. A malnourished gestation paired with chronic, positive energy balance in postnatal life may trigger glucose intolerance which increases the risk of obesity and type II diabetes (Berends et al., 2018; Gluckman & Pinal, 2001; Ravelli et al., 1998). This pattern is especially common in non-industrialised populations that are transitioning from chronic malnutrition to conditions of nutritonal adequacy or excess, urbanization and reduced physical acitvity (Fall, 2001). However, other prenatal insults that serve to restrict fetal growth can set off similar metabolic programming and thus result in a thrify phenotype even without maternal malnutrition as the originating cause. Smoking during pregnancy (SDP) is one such prenatal insult that is associated with growth restriction in the fetus

which could potentially contribute to an incongruency between the prenatal and postnatal environment in a developed country like the United States (Swanson et al., 2009).

The Thrifty Phenotype in Relation to Puberty

Although the thrifty phenotype was initially developed as an explanation for ischemic heart disease and later type II diabetes, it has also been usefully applied to the study of pubertal timing (Biro & Deardorff, 2013; Deardorff et al., 2013). From an evolutionary perspective, an intrauterine environment that impairs growth will prompt the fetus to make adaptations that reduce or slow growth in utero and will contribute to programming postnatal physiology by biologically instilling the expectation that the postnatal environment will also be impoverished (Gluckman & Hanson, 2004). These adaptations prepare the developing organism to (implicitly) expect a shorter lifespan and adopt a faster life history strategy, or in other words, to go through puberty earlier, reach sexual maturation faster, and to be able to sexually reproduce at a younger age (Gluckman & Hanson, 2006a). Those that are prompted to mature early gain the vital evolutionary benefit of increasing the probability of passing on genes to the next generation through a higher likelihood of producing more offspring, but crucially, this comes at the cost of later adult health (Belsky & Shalev, 2016). The adaptations that enable an organism to become sexually mature earlier may be the same or similar adaptations that contribute to poor health. This cost benefit principle has been referred to as evolutionary "tradeoffs" due to "predictive adaptive responses" the organism makes based on its early environment (Gluckman & Hanson, 2006a, 2006b). In summary, the thrifty phenotype hypothesis suggests that nutritional deprivation during pregnancy, as indicated by maternal malnutrition or other prenatal insults restricting fetal growth, are further linked to poor adult health via metabolic programming that is

exacerbated by a mismatch between the prenatal and postnatal nutritional environment and that pubertal timing may be programmed via similar mechanisms.

The Fetal Overnutrition Hypothesis

The United States and much of the western world is currently facing an unprecedented problem of over nutrition and excess energy in our evolutionary history. Current Center for Disease Control (CDC) estimates are now indicating that 42.4% of adults within the USA are obese (Hales et al., 2020). The increased prevalence of obesity in adults means that more mothers are likely to provide an intrauterine environment characterized by nutritional excess than one that is nutritionally scarce. Thus, a rising number of developing children are likely to have experienced an intrauterine environment that is congruent with a nutritionally abundant postnatal environment common in industrialized countries. DOHaD perspectives also suggest that prenatal environments that are metabolically abundant may lead to poor health in adulthood as well (Oken & Gillman, 2003). The fetal overnutrition hypothesis posits that fetuses that experience overnutrition prenatally are at increased risk of obesity from birth through the rest of the lifespan (e.g., Lawlor et al., 2006; Sauder et al., 2017). Two key prenatal indicators of fetal overnutrition that are frequently used in the literature are pre-pregnancy BMI and maternal gestational weight gain (GWG).

Maternal GWG and pre-pregnancy BMI have largely been considered as similar prenatal risks and generally show similar effects on childhood overweight and obesity outcomes (Voerman et al., 2019). Nevertheless, they are distinct, and it is important to consider their differences. For instance, they differ with regard to timing of risk to the offspring. Maternal GWG occurs during pregnancy only, while pre-pregnancy BMI may reflect a combination of risk before and during pregnancy. Pre-pregnancy BMI may also reflect shared environmental and

genetic influences between mother and offspring more broadly, with about half the variance in pre-pregnancy BMI being estimated to be explained by genetic factors (Hong et al., 2017; Perng et al., 2019). Maternal GWG has generally been conceptualized as a marker of environmental risk that may be, in particular, driven by diet and activity levels during pregnancy but it is also a product of changes in biology to the mother (e.g. vascular fat deposition, vascular expansion), the placenta and fetal growth (Rasmussen & Yaktine, 2009). Relatedly, maternal GWG has also been shown to be under genetic influence with at least 20% of the phenotypic variance reported to be explained by heritable maternal genetic variants in a genome wide association study (Warrington et al., 2018). Collectively, maternal GWG and pre-pregnancy BMI present similar but distinct risks to the fetus and may account for some amount of common genetic variance between mother and child, although likely more so for pre-pregnancy BMI.

Mechanisms by which pre-pregnancy BMI and maternal GWG influence fetal programming for later disease are still in need of clarification (Heerwagen et al., 2010), however, it is clear that an over-nutritious intrauterine environment is associated with insulin resistance in the fetus (Boerschmann et al., 2010; Maftei et al., 2015; Sauder et al., 2017). Obesity in the absence of pregnancy is associated with insulin resistance, excess fat cells, dyslipidemia (elevated unhealthy fat cells and decreased healthy fat cells) and increased inflammation. Pregnancy itself is associated with weight gain, insulin resistance and inflammatory changes (Catalano et al., 1998; Denison et al., 2010). Given that obesity and pregnancy are independently linked with insulin resistance and inflammatory changes, they may exacerbate each other and transmit increased risk for metabolic dysregulation to the fetus (Heerwagen et al., 2010). For example, hormones that promote insulin resistance in pregnancy, (e.g., leptin and placental growth hormone; McIntyre et al., 2010) may exacerbate the pre-existing inflammation and

insulin resistance of obesity. Together, this could lead to greater mobilization of maternal fuel stores and transfer of lipids to the fetus. Consequently, this increase in fetal lipid exposure may program the liver, skeletal muscle, adipose tissue, brain and pancreas and increase the risk of higher adiposity in childhood in the offspring (Heerwagen et al., 2010).

The Fetal Overnutrition Hypothesis in Relation to Puberty

The fetal overnutrition hypothesis may be linked to earlier pubertal timing through higher childhood adiposity by the same mechanisms described above. Mechanistically, the association of childhood adiposity and pubertal timing mentioned earlier may be underpinned by adipose tissue, leptin activity and their interaction with the kisspeptin system (Uenoyama et al., 2019). Leptin is a key hormone secreted by adipocytes that helps regulate appetite and metabolism, and it signals through its hypothalamic receptor to report on levels of fat stores. Animal and later human studies suggest there may be a "permissive" fat mass where the feedback from fat stores influences the initiation of pubertal onset by stimulating central pulsatile gonadotrophin secretion (Ahima et al., 1997). Longitudinal studies in developing children suggest that leptin steadily increases during the pre-pubertal period, though a range of leptin levels were reported at pubertal onset (Ahmed et al., 1999). Additionally, higher levels of adipose tissue lead to increased aromatase activity, and increased conversion of androgens to estrogen may promote earlier breast development (Dunger et al., 2005). Thus, there is good evidence that elevated adiposity in childhood precedes earlier pubertal timing, and that metabolic processes are key to this association. In summary, the fetal overnutrition hypothesis suggests that relative overnutrition during pregnancy, as operationalized by high pre-pregnancy BMI and maternal GWG, are linked to childhood adiposity via metabolic programming for insulin resistance, and that childhood

adiposity subsequently increases the likelihood of early puberty via leptin and kisspeptin permissive factors.

Developmental Trajectories

Adaptations prompted by prenatal stimuli may put into motion a series of downstream consequences that affect birth weight, infancy weight gain, and adiposity throughout childhood which have all been found to be associated with the timing of puberty (Ong et al., 2009; Reeves & Bernstein, 2008; Won Kyoung & Byung-Kyu, 2016). Thus, studying risks for early puberty from the prenatal environment to late childhood may be key to gaining a better understanding of which adolescents might mature earlier and ultimately identify those who may be on trajectories likely to lead to poor health in adolescence and adulthood.

Low birth weight and high birth weight may be associated with a trajectory toward earlier pubertal timing. A review by Oken and Gillman (2003) identified a sort of paradox of birthweight wherein infants born at both ends of the birth weight spectrum are at risk for higher adiposity. This paradox is supported by the thrifty phenotype and overnutrition hypotheses. Infants born at a higher than average birth weight are at greatest risk to become overweight or obese in childhood and adulthood (in line with the overnutrition hypothesis; Sørensen et al., 1997; Yu et al., 2011). On the other hand, infants born low birth weight are at the greatest risk of developing later central obesity, insulin resistance and metabolic syndrome (consistent with the thrifty phenotype hypothesis; Biosca et al., 2011; McKeigue et al., 1998; Rich-Edwards et al., 1997). This may be due in part to accelerated weight gain in infancy (i.e., rapid catch-up weight gain), one prominent manifestation of the incongurency between prenatal and postnatal life early in the lifespan relevant to the thrify phenotype.

Accelerated weight gain occurs within the first couple years of life and is the acceleretion of growth beyond a normal rate that typically happens in order to compensate for prior impaired intrauterine growth. It is an adaptive mechanism that in the short term increases the infant's chances of survival, although it may have long term consequences (Victora et al., 2001). Importantly, accelerated weight gain is predomiantely chracterized by a disproportionate gain of fat tissue compared to lean tissue, which possibly may have helped insure future survival amidst previous times of intermitent famines (Dulloo et al., 2006; Won Kyoung & Byung-Kyu, 2016), but in present times may be problematic and exacerbated when postnatal food supply is more regular. The predominant gain of fat tissue is likely promoted by a period of insulin sensitivity during infancy that is present in some infants who are born low birthweight (Sole, 2006). Three biological regulatory control systems have been suggested as possible explanations for accelerated weight gain: 1) An overcompensatory hyperphagic drive (i.e., drive to overeat to make up for lost nutrients), 2) a shift in control of the body's partitioning of energy from lean to fat tissue, (i.e., storing more fat tissue for long term storage than for building muscle), 3) An increase in efficiency of the body's metabolic processes through suprressing thermogenesis (i.e., less heat or energy production from metabolizing food that would have otherwise burnt more calories) which is characteristic of a "thrifty metabolism" (Dulloo et al., 2006). Collectively, these systems increase food intake, increase fat storage and reduce the metabolic energy required to process food. A combination of these systems likely mediate the rapid accumulation of weight that is charactersitic of accelerated weight gain. Thus, accelerated weight gain is one of the key, early postnatal manifestations supporting the thrifty phenotype pathway. The manifestation of accelerated weight gain illustrates how adaptations prompted by the prenatal environment for

short term survival may put into motion a series of downstream consequences that may later come at a cost to the organism later in development.

In summary, there is conceptual reasoning and empirical evidence indicating there may be two distinct pathways to obesity and associated health conditions with perhaps more evidence to suggest the pathway operating through low birth weight and greater accelerated weight gain is particularly risky for adult health outcomes (Oken & Gillman, 2003) and possibly for pubertal timing as well. Figure 1 illustrates the conceptual thrifty phenotype pathway (red) and overnutrition pathway (blue) linking prenatal insults to childhood adiposity and pubertal timing that will be tested in the current thesis. Previous studies have not clearly determined which pathway better predicts early puberty. Specifically, it is unknown whether those who are on a thrifty phenotype trajectory (i.e., were born low birth weight and experienced accelerated weight gain leading to higher childhood adiposity or to earlier puberty directly) or who are on a purely overnutrition trajectory (i.e., were born high birth weight and maintained higher weight into childhood) are at higher risk for early puberty. Further, the prenatal and early postnatal growth risk factors for early puberty mentioned above have been well studied in insolation but have seldom been studied in the context of the same model (e.g., Karaolis-Danckert et al., 2009).

Figure 1 Conceptual model of the thrifty phenotype and fetal overnutrition hypotheses applied to pubertal timing.
Note: The path between child adiposity and pubertal timing is illustrated as purple to show that both pathways may operate through child adiposity.

Testing the relevant risks for pubertal timing in the context of one model will help elucidate the relative contribution of each risk factor as well clarify conflicting findings due to a failure to account for omitted factors. Given that prenatal exposures may start a developmental cascade of

risk for earlier puberty, it is worthwhile to test these pathways from an analytic framework consistent with a lifespan perspective. Finally, boys and children of both sexes from racial and ethnic minority groups have been historically understudied in the study of puberty and more studies with their inclusion are needed (Deardorff et al., 2019; Mendle et al., 2019). This is particularly needed given that there may be sex and race/ethnicity differences in prenatal programming (summarized below).

Sex Differences in Prenatal Programming

Sex differences in intrauterine growth may lead male and female fetuses to weather prenatal exposures differently. Sex differences in intrauterine growth may emerge very early on in gestation, possibly as early as within the first trimester of pregnancy (Broere-Brown et al., 2016). Male fetuses grow more rapidly than do female fetuses which means that they undergo more cell cycles for the same length of gestation. Given this, they may have greater exposure to prenatal insults than females who undergo less cell cycles on average (Aiken & Ozanne, 2013). This may lead male fetuses to be particularly vulnerable to prenatal insults associated with intrauterine growth restriction (IUGR; e.g. SDP). Further, male fetuses have been considered by some to be more vulnerable to prenatal insults generally (DiPietro & Voegtline, 2017; Kraemer, 2000). On the other hand, female fetuses may be more vulnerable to risks of overnutrition with respect to pubertal timing. Several studies generally find more consistent evidence of maternal overnutrition predicting earlier timing of puberty in girls (Brix, Ernst, Lauridsen, Arah, et al., 2019) although other evidence suggests female fetuses are more protected from overnutrition risk than are males (Chang et al., 2019). For these reasons, the thrifty phenotype hypothesis may better predict how prenatal insults associated with growth restriction may lead to earlier timing

of puberty in boys. And the fetal overnutrition hypothesis may better predict the pathway to earlier puberty through overnutrition prenatal risks in girls.

Race/ethnicity Differences in Prenatal Programming

Race/ethnicity differences in these pathways are far more exploratory. Fetal growth may differ by race/ethnicity, although it was not until recently that appropriate standards of fetal growth were created for U.S. racial/ethnic minority groups (Buck Louis et al., 2015). Buck Louis and colleagues studied 2,334 healthy women with low risk, singleton pregnancies using ultrasonography for precise fetal measurement, and found that estimated fetal weight (among other fetal anthropometric measures) was significantly different across race/ethnicity by 20 weeks of gestation after adjusting for maternal age, pre-pregnancy height and weight, employment status, marital status, health insurance, income, education and fetal sex. White fetuses had the highest estimated weight at the 50th percentile followed by Hispanic, Asian and Black fetuses, respectively. Low risk pregnancies were specifically selected in order to remove influences that affect fetal growth to yield as unbiased estimates as possible, although these estimates may be subject to limitations of sample selection and retention, measurement, and possible residual confounding. Notwithstanding these limitations, this evidence suggests that race/ethnicity differences may exist in normal fetal growth. While it is not immediately clear what may be creating the observed differences, their existence may lead to race/ethnicity differences in prenatal programming and may contribute to previously identified race/ethnicity phenotypic differences later on in the lifespan (e.g., accelerated weight gain, child BMI, pubertal timing).

Current Thesis

The current thesis sought to address the gap in understanding whether the thrifty phenotype or fetal overnutrition pathway better predicts early puberty. Both pathways were tested in an analytic framework consistent with a lifespan perspective by studying risk factors from the prenatal environment to late childhood using longitudinal structural equation modeling (SEM) and also considered sex and race/ethnicity differences in these pathways. To those ends, the current thesis used The Fragile Family and Child Wellbeing Study (FFCWS), a longitudinal, birth cohort study of approximately 5,000 children followed from birth to age 15 to achieve the study's primary aims. The FFCWS has many qualities that made it an optimal sample for studying developmental pathways for pubertal timing. Namely, it is a large, racially diverse birth cohort containing measures of puberty in both sexes. Families were followed prospectively through their child's life from around the time of birth through infancy, childhood and into adolescence. These are key strengths as more longitudinal studies that begin before puberty are needed in order to help uncover the origins of disease and conditions associated with puberty (Dorn et al., 2019) and more studies of pubertal timing in boys and non-White samples are needed (Deardorff et al., 2019; Mendle et al., 2019).

The remainder of this thesis provides an overview of pubertal development (Chapter 2), a detailed literature review for the hypothesized pathways in Figure 1 (Chapter 3), the methods (Chapter 4), the results (Chapter 5) and a discussion of the study's findings and conclusion (Chapter 6).

PUBERTAL DEVELOPMENT

Processes of Puberty

Pubertal development is a complex series of cascading processes driven by the release of gonadotropins, gonadal steroids, physical growth hormone and the reactivation of the hypothalamic-pituitary-gonadal axis after a period of relative quiescence in the early postnatal period (Styne & Grumbach, 2016). There are two major overlapping but distinct biological processes that primarily characterize the pubertal transition. The first of which is adrenarche, or the awakening of the adrenal glands. This process is characterized by rises in adrenal androgens like androstenedione (delta-4A), dehydroepiandrosterone (DHEA), and its sulfate (DHEAS). Adrenarche happens in youth around the ages of six to nine and occurs earlier in girls than boys (Byrne et al., 2017). Adrenarche drives pubertal changes like oily skin, acne, skeletal maturation, and pubic hair growth which is also referred to as pubarche (Dorn et al., 2006).

The second major cluster of biological activity is gonadarche, or the maturational process of the gonads. Gonadarche happens approximately one to two years after adrenarche and is responsible for the development of secondary sex characteristics via increased production of sex steroids from the gonads. In developing female youth, increased levels of estrogens facilitate the development of breast tissue, hip growth and menstruation. In male youth, higher circulating levels of testosterone drive testicular development, facial hair growth and voice changes. Gonadarche is a more gradual and relatively slow developing process that takes approximately four to five years to complete. Gonadarche is similar to adrenarche in that girls start this process one year to a year and half earlier than boys do. The first sign of gonadarche in girls is the onset of breast development, which is also referred to as thelarche. In boys, the first gonadal event typically reported is testicular growth.

Measuring Puberty

When deciding how to measure pubertal development, the most important concept to consider is that the chosen measure is appropriate for the research question by ensuring that the specific aspect(s) of puberty measured is/are the most relevant to the study (Dorn et al., 2006). There is no single best measure of puberty and even physical examination by a health professional, regarded as the gold standard, may be inappropriate for certain study foci (Dorn et al., 2006; Mendle et al., 2019). Dorn et al. (2006) recommended that studies examining adolescent health use measures of puberty by physical examination when feasible and perceived self-report measures when studying social constructs. Next, I review strengths and limitations of common measures of puberty in order to contextualize findings summarized in the literature review and provide a context for how pubertal timing findings from this thesis could be interpreted.

Physical Exam using Tanner Criteria

Historically, physicians began using Tanner staging to classify pubertal status of developing youth based on breast and pubic hair development in girls and testicular and pubic hair development in boys (Marshall & Tanner, 1969, 1970). Tanner staging describes pubertal development using a categorization system from 1-5. Tanner Stage 1 indicates no visible signs of development and Tanner Stage 5 indicates full physical maturation. Tanner staging can be completed by nurses or other medical personnel with training in physical examination methods. Despite the gold standard status of the Tanner staging, there are key limitations to this method. The original photographs from which the timing norms were based were in black and white. They were of 192 White girls and 228 White boys from England in approximately the 1970s who were not representative of the British population because they were from very low

socioeconomic background and lived in children's homes, although they were within normal limits of growth in stature (Marshall & Tanner, 1969, 1970). Tanner staging can also be assessed by administering photographs or other visual depictions of the pubertal stages to youth or parents of youth. Separately, or sometimes together, youth and parents of youth report on their own maturation or maturation of their child, respectively.

Physical Examination of Puberty Limitations

When assessing breast development during a physical exam, visual inspection may be inadequate on its own. Due to the propensity for adipose tissue to accumulate around the breasts, developing girls who have overweight or obese BMIs may be misclassified into a more advanced Tanner stage (Dorn et al., 2006). One study reported that overweight girls who were only assessed visually may be categorized into Tanner stage 2 or 3 when in actuality they should have been classified as Tanner stage 1 when compared to areolar staging (Biro et al., 1992). Areolar staging involves assessing the contour, pigmentation and diameter of the areola, which is more objective and unaffected by excess adipose tissue. However, areolar staging has been conducted in very few studies and information about norms are lacking. Dorn and colleagues (2006) recommend palpation of breast tissue during physical examinations as it is impossible to discern between adipose tissue and breast tissue by visual inspection only, and this distinction is difficult even for experienced examiners. The tendency for more advanced breast development to be confounded with overweight and obese status in girls due to inaccurate measurement upwardly biases associations between elevated adiposity in childhood status with more advanced pubertal development or earlier timing. This is an important limitation of the childhood obesity and pubertal timing literature (reviewed in Chapter 3). Assessment of testicular development through visual inspection during physical exams in boys may also not be sufficient compared to use of

palpation. Palpation of testes is recommended over determining male genital stage by visual inspection of length and width of the penis and scrotum given previous reports of disagreement with objective methods (Dorn et al., 2006).

Age at Menarche

Age at menarche (AAM), or the age at first appearance of the menstrual cycle is a relatively late gonadal event in girls. AAM is usually measured through self-reported age of when menarche began by youth themselves, but it may also be reported by a parent. Despite its ease of measurement, AAM has been considered a poor measure of pubertal *timing* by some since it is a late gonadal event and does not truly reflect onset of puberty (Dorn et al., 2006). Nonetheless, it is the most widely used measure of pubertal timing in girls and especially in studies of large sample sizes (Li et al., 2017). Additionally, AAM has also shown high recall reliability, making it a good measure for retrospective assessment (Lundblad & Jacobsen, 2017). Notably, there is no corresponding measure in boys, although sometimes age at voice break or spermarche is used (Dorn et al., 2006).

Pubertal Development Scale

In addition to Tanner staging, researchers have also commonly used the Pubertal Development Scale (PDS; Petersen et al., 1988) most often when physical assessment is not feasible or when studying psychosocial phenomena. The PDS is made up of five items for male and female youth that assess perceived changes in height, body hair and skin. For female youth only, the PDS also assesses breast development and age at the onset of menstruation. Male youth are uniquely asked about facial hair and voice deepening. Questions are asked on a 4-point Likert Scale from 1-not yet started, 2-has barely started, 3-is definitely underway, and 4-Seems

completed for all developmental milestones except menses. Since the PDS is self-reported by youth or parents of youth, PDS scores reflect *perceived pubertal timing*.

Self-Report of Puberty Limitations

Girls who meet criteria for overweight or obese status are also more likely to report more advanced breast development. Approximately 38% of girls with obesity compared to 25% of girls without, overestimated Tanner breast stage (Bonat et al., 2002). Overestimation of breast development by female youth or parents similarly biases the association between puberty and adiposity just as in physical examination (Biro et al., 1992). Girls self-report of pubic hair seems to be generally consistent with physical examination at all levels of BMI although boys may overestimate pubic hair growth regardless of BMI (Bonat et al., 2002). Youth and parents are also likely to over report gonadal development in boys (Dorn et al., 2006).

Hormone concentrations

Puberty has also been often studied using hormone concentrations from saliva and more recently from hair (Grotzinger et al., 2018; Shirtcliff, Dahl, & Pollak, 2009). In particular, dehydroepiandrosterone (DHEA), testosterone and estradiol have often been used in the study of puberty. Shirtcliff and colleagues (2009) studied agreement across pubertal hormones and reports of puberty including the PDS and physical exam. They found that PDS, physical exam and hormone measures were generally in agreement with each other which suggests that self-reported measures of puberty are adequate when high precision of measurement is not necessary (Shirtcliff et al., 2009). Self-reported measures may also be adequate when physical exam is not feasible or unavailable.

Measuring the Timing of Puberty

The measures of puberty summarized up until this point are indices of pubertal *status* at a given point in time. These same measures and others can be used to quantify the *timing* of pubertal development. Generally, measures of puberty have been operationalized categorically or continuously with respect to an "anchor" (Dorn et al., 2006). For example, some studies dichotomize timing into an early and late group or trichotomize timing into an early, an on time and a late group based on published norms (Euling et al., 2008; Herman-Giddens et al., 2012) for pubertal status measures (e.g., breast development stage, genital stage) or by defining cut off values (e.g., ± 1 SD) within samples (Copeland et al., 2010; Ge et al., 2001). Other studies regress out age and sex to create a continuous timing variable where higher values represent more advanced pubertal development with respect to same age and sex peers (Dorn et al., 2003; Ge et al., 2007). In a review of the measurement of puberty in a recent puberty-focused special issue of the *Journal of Research on Adolescence*, Mendle and colleagues (2019) recommended creating pubertal timing variables through residuals or standardizing within age bands as opposed to creating categories of timing based on norms since published norms are not often up to date, do not often have adequate representation of non-white populations and reduce statistical power. Thus, this thesis operationalized pubertal timing continuously with respect to age and sex.

Sex Differences in Puberty

Pubertal processes are different in male and female youth as shown by adrenarche and gonadarche reported to begin earlier in girls and phenotypic difference in secondary sex characteristics (Byrne et al., 2017; Dorn et al., 2006; Mendle et al., 2019). Additionally, adrenarche seems to be entirely responsible for the development of pubic hair in girls while pubic hair in boys seems to be associated with both increase of testosterone and DHEA which

suggests that both gonadarche and adrenarche contribute to the development of pubic hair in boys (Dorn et al., 2006). In light of known biological differences in puberty between sexes, considering sex differences in the study of puberty is necessary. Thus, the current study proposes to analyze developmental trajectories predicting pubertal timing separately by sex.

Race/ethnicity Differences in Puberty

Historically, the puberty field has primarily focused on studied girls of European descent and because of this, the field's understanding of certain populations is lacking and basic studies describing normative variation in some groups are still needed (Deardorff et al., 2019; Marceau et al., 2019; Ramnitz & Lodish, 2013). Most racial ethnic minority groups in the U.S. are generally found to mature earlier than White youth, with Black youth starting puberty earliest, followed by Hispanic, non-white Hispanic and Asian youth (Braithwaite et al., 2009; Deardorff et al., 2014; Euling et al., 2008). Additionally, there is some evidence that race differences in puberty are likely products of social inequalities or at least greatly exacerbated by them. A study by Deardorff and colleagues (2014) using a sample of girls from the National Longitudinal Study of Youth (NLYS) found that Black and Hispanic girls had earlier menarche than White girls, but the effects were substantially reduced after controlling for socioeconomic status which indicates that these differences are likely driven at least in part by social inequalities. Of particular importance to the current thesis, race/ethnicity differences in pubertal timing seem to mirror the prevalence of childhood obesity rates by race; Black and Hispanic youth also have higher body mass index than their White counterparts (Guerrero et al., 2016; Ramnitz & Lodish, 2013). Given that childhood obesity disparities are also likely due in large part to socioeconomic inequalities (Rogers et al., 2015) and if the rise of childhood obesity is contributing to early timing of puberty (Reinehr & Roth, 2019) then socioeconomic inequalities more broadly may be

driving race differences in puberty and more distally could be contributing to adult health disparities in the United States.

Puberty and Health

In terms of early puberty predicting health risk factors, findings from predominantly cross-sectional studies in adolescence (e.g., body fat percentage, abdominal circumference, unfavorable blood pressure) generally hold when adjusting for concurrent BMI or body composition (Remsberg et al., 2005). This suggests that early puberty may independently contribute to health outcomes beyond what is explained by adiposity. Further, independent effects of puberty after adjusting for BMI have been shown in samples of Black and White youth using a variety of measures of pubertal timing (e.g. menarche, PDS, tanner staging; (Canoy et al., 2015; Chen & Wang, 2009).

Puberty has also been shown to independently predict health outcomes in adulthood, although whether the effect persists after controlling for adiposity at or around the time of puberty tends to depend on the specific health outcome. For example, early menarche has been associated with obesity and type II diabetes, but after controlling for childhood adiposity the association for type II diabetes weakened slightly and the association with adult obesity was greatly attenuated (Cheng et al., 2020; Freedman et al., 2003). In White European men, one study showed that earlier age at peak height velocity predicted type II diabetes in adulthood, and that the association was similar after adjusting for childhood BMI (Ohlsson et al., 2020), whereas a similar study found the association to be largely attenuated after controlling for childhood BMI when examining adiposity at 18 years of age and cardiometabolic traits (Bell et al., 2018). Overall, there is good evidence that early puberty independently predicts worse health in adulthood for some outcomes although more studies are needed to confirm that these

associations are not the product of confounding between puberty and adiposity and more resolution on how they may vary by sex, pubertal marker and race/ethnicity is needed.

Pubertal Timing in the Current Thesis

The current thesis used parent perceived PDS and took into account youth sex and age and disaggregated adrenal and gonadal items following guidance from Dorn et al. (2006) and Shirtcliff et al. (2009) given that adrenarche and gonadarche function differently across sex. This measure of pubertal timing therefore represented perceived pubertal timing relative to other same sex youth in the sample (e.g., with relative socioeconomic disadvantage and a diverse racial/ethnic makeup). Perceived pubertal timing is different than physical examination of puberty and this measure is not ideal for use in studies related to adolescent health (Dorn et al., 2006). Specifically, perceived pubertal maturation encompasses both physiological changes and the social manifestations and meanings of those changes, which may be more likely to tap into both physiological and social mechanisms of influence (Beltz et al., 2014; Marceau et al., 2015; Shirtcliff et al., 2009). Self- or parent-reported puberty is far more feasible than nurse/practitioner reported Tanner Staging which allows for larger, more diverse and longitudinal samples to be collected, and this measure has been successfully employed in other nationally representative samples (e.g., The National Longitudinal Study of Adolescent to Adult Health). The strategy used in the FFCWS is parent-report of the PDS, which assesses parents' perceptions of their youths' pubertal timing and taps a different aspect of social mechanisms than youth self-report would. Parent-reported puberty avoids some of the error associated with reporting on one's own puberty before a child has any understanding of what pubertal changes are. For example, there is evidence that younger children and children in earlier stages of puberty tend to over-report their pubertal status (Shirtcliff et al., 2009). Overall, the strength of the

FFCWS in terms of its measures comprising the developmental pathways of interest here and its large racially and ethnically diverse sample outweighs the limitations of this measure of puberty. Further, disaggregating this measure into adrenal and gonadal development scores, and using age- and sex- specific measures of timing are considered to be the best way to use data such as these to create meaningful, informative measures of pubertal timing (Mendle et al., 2019).

LITERATURE REVIEW

The conceptual model in this thesis includes one pathway from key prenatal insults linked to restricted fetal growth (e.g. SDP) to test the thrifty phenotype hypothesis and one pathway from prenatal insults linked to overnutrition (pre-pregnancy BMI and maternal GWG) to test the fetal overnutrition hypothesis. Figure 2 depicts a simplified analytic model for both hypotheses as well main effects for key study variables. The pathway for the thrifty phenotype is hypothesized to operate from SDP to low birth weight (path 1), low birth weight to accelerated weight gain (path 2), and accelerated weight gain to earlier pubertal timing (path 3) *or* paths 1, 2, accelerated weight gain to child BMI (path 4) and child BMI to earlier pubertal timing (path 5) *or* both of these pathways independently. Paths for the fetal overnutrition hypothesis are hypothesized to operate from pre-pregnancy BMI or maternal GWG to high birth weight (path 6), high birth weight to child BMI (path 7) and child BMI to earlier pubertal timing (path 5). I will review the evidence for the previously named paths for each hypothesis, beginning with the main effects for each key study variable (paths 8-13), and review the evidence of mediating pathways for both hypothesized pathways.

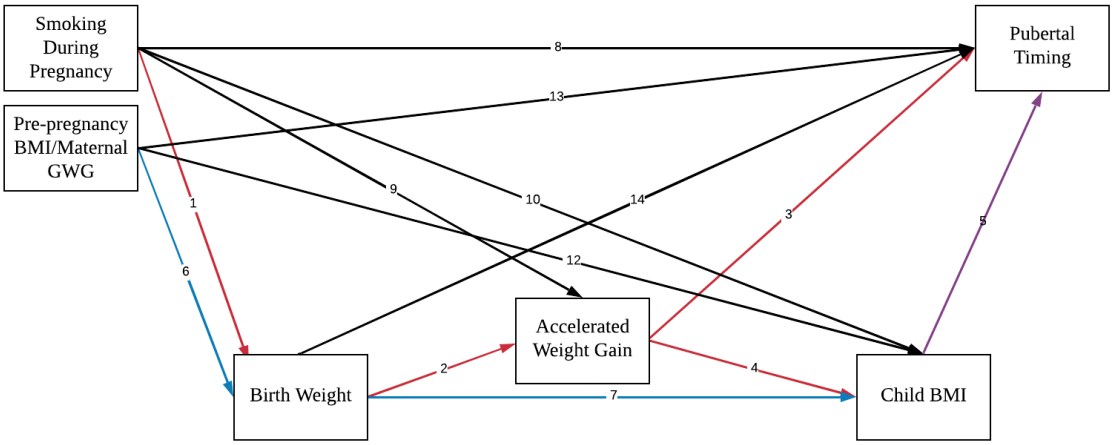

Figure 2 Simplified analytic model

Note: Path 5 is illustrated as purple to show that both pathways may operate through the child BMI to pubertal timing path.

Thrifty Phenotype

Smoking during Pregnancy as a Predictor of Pubertal timing

In the pubertal timing literature, SDP has been associated with earlier onset of menarche (path 8) in many studies (Behie & O'Donnell, 2015; D'Aloisio et al., 2013; Ernst et al., 2012; Maisonet et al., 2010; Shrestha et al., 2011; Windham et al., 2008) and later AAM in others (Ferris et al., 2010; Windham et al., 2008). A recent meta-analysis concluded that SDP is possibly associated with earlier age at menarche in girls and that the risk of early voice break in boys slightly increased with smoke exposure, but more cohort studies with boys are needed (Chen et al., 2018). One recent study following Chen et. al (2018) found exposure to smoking was associated with earlier genital development, pubic hair and voice break in boys and early breast development, pubic hair and menarche in girls in a large Danish cohort study (Brix, Ernst, Lauridsen, Parner, et al., 2019). Collectively, these studies suggest that SDP *may* lead to earlier timing of puberty and also exemplifies the preponderance of studies on girls with menarche as a

pubertal marker and a lacking number of studies in boys, although the latter is improving. Additionally, many of the samples are predominantly comprised of individuals of White European descent (Behie & O'Donnell, 2015; Brix, Ernst, Lauridsen, Parner, et al., 2019)

Alcohol use during Pregnancy

Alcohol use during pregnancy (ADP) is another prevalent form of substance use during pregnancy that has been linked to birthweight (Patra et al., 2011). Compared to SDP, the relation between ADP and pubertal timing is much less clear in both sexes. Many studies find null results of association between ADP and pubertal timing (Brix, Lauridsen, et al., 2019; Shrestha et al., 2011; Windham et al., 2004). Other studies have found evidence that puberty is delayed but only at the high end of the ADP spectrum (e.g., binge drinking; Hakonsen et al., 2014; Robe et al., 1979). A systematic review concluded that ADP has a delaying effect on age at menarche in girls and that reproductive development in boys is affected as evidenced by perturbations in testosterone levels, although more work is needed to clarify the direction of effect in terms of pubertal timing (Akison et al., 2019). Additionally, inconsistencies including reporting and timing of exposure, as well as a narrow range of outcomes studied prevents drawing firmer and more generalized conclusions. A recent study following this review, examined an array of pubertal markers and found that a combination of several pubertal markers (e.g., axillary hair and breast development) was associated with ADP in the first trimester in early puberty in girls (Brix, Lauridsen, et al., 2019). However, combining adrenal and gonadal pubertal markers is generally not recommended by experts in the puberty field as it conflates the processes of adrenarche and gonadarche (Dorn et al., 2006), and it is unclear what an association with a combined measure of pubertal timing means especially in the absence of association of individual markers.

Some of the mixed findings in the ADP literature may be due to weaker association between ADP and intrauterine growth compared to SDP. A meta-analysis and systematic review found a dose response relationship between ADP and low birth weight but only when upwards of 10 grams of pure alcohol/day (i.e. ~ 1 drink/per day); below this point there was no increased risk of low birth weight (Patra et al., 2011). Therefore, since the relationship between ADP and IUGR may not be as potent as SDP (Reeves & Bernstein, 2008), and seems to only be present at higher levels, ADP may not be an ideal prenatal insult for the current conceptualization of the thrifty phenotype pathway to earlier puberty. Further, there is mixed evidence of association of ADP with childhood adiposity which may also depend on the severity of use (Fuglestad et al., 2014; Hill et al., 2005). One study reported that growth restriction persists from birth through age 9, delays of postnatal growth at 12 months and lower body fat percentage at age 9 in offspring exposed to heavy ADP when compared to lower use or offspring in a control group (Carter et al., 2012). Collectively this evidence may suggest that after exposure to ADP postnatal patterns of growth may be altered in such a way that is not characteristic of patterns more consistently found with undernutrition or SDP. For these reasons, ADP was not considered as a key prenatal insult since it may not operate in line with the thrifty phenotype hypothesis but was adjusted for in all analytic models. Further sections reviewed associations of SDP and key study variables only.

Smoking during Pregnancy and Key Features of the Thrifty Phenotype Pathway

Smoking during Pregnancy as a Predictor of Birth Weight.

SDP is a salient prenatal insult that may operate in line with the thrify phenotype hypothesis to predict low birth weight (path 1). A large literature supports this effect; several systematic reviews and meta analyses report a reduction in fetal size and birth weight after SDP

with many studies identifying a dose response relationship between cigarettes smoked and birth weight (Abraham et al., 2017; Pereira et al., 2017; Quelhas et al., 2018). Further, the effect of SDP has been shown to persist after controlling for genetic and familial confounds using various measures of SDP and study designs (D'Onofrio et al., 2003; Knopik et al., 2016; Kuja-Halkola et al., 2014). Important for the current thesis, effects of SDP also seem to persist after controlling for maternal pre-pregnancy BMI (Laml et al., 2000). This suggests that the effect of SDP on low birth weight persists when prenatal risks for higher birth weight may also be present (e.g. high pre-pregnancy BMI).

The mechanism through which SDP may lead to low birth weight is not completely understood although there are plausible explanations. For example, tobacco smoke is a toxic and reactive substance that contains over 5000 chemicals, including nicotine and carbon monoxide (Talhout et al., 2011). Nicotine is a highly pharmacologically active compound in smoke and together with carbon monoxide may exert a large vasoconstricting effect, meaning that it leads to reduced blood flow through the placenta and oxygen supply to the fetus (Banderali et al., 2015; Lambers & Clark, 1996). Fetal hypoxia may then cause IUGR (Ream et al., 2008) which is one example of an environmental exposure that may operate in line with the thrifty phenotype hypothesis (Swanson et al., 2009). Taken together, evidence of specific mechanistic effects of SDP coupled with evidence of non-overlapping effects of pre-pregnancy BMI supports the hypothesis that SDP is expected to be operate via the thrify phenotype hypothesis to predict low birth weight in the current thesis.

Smoking during Pregnancy as a Predictor of Accelerated Weight Gain.

Following IUGR, infants born low birth weight have a strong propensity to gain weight rapidly in the first couple years of life (path 9). Various studies have shown effects of accelerated

weight gain in infants following SDP exposure (Conter et al., 1995; Nafstad et al., 1997; Suzuki et al., 2011; Suzuki et al., 2012; Vik et al., 1996) and at least one study found there is a dose dependent relationship between the number of cigarettes smoked and infancy growth even after controlling for maternal GWG, birth weight, and type of feeding during infancy (Mine et al., 2017). Another study found potential evidence of sex differences using a mixed method that showed SDP in boys was more strongly associated with BMI z-score across time (Suzuki et al., 2012). This is consistent with other work that suggests male fetuses are more sensitive to certain prenatal insults, including SDP (Gariepy et al., 2000; Kraemer, 2000). The association between SDP and accelerated weight gain has been studied in certain European, Asian and American samples (Mine et al., 2017; Nafstad et al., 1997; Suzuki et al., 2012) although study of this effect in non-white Americans beyond 5-10% subsamples is lacking (Sowan & Stember, 2000). This is important because Black and Hispanic populations may be especially susceptible to negative health effects from accelerated weight gain (Andrea et al., 2017).

Smoking during Pregnancy as a Predictor of Childhood Adiposity.

A large literature also supports the association between SDP and childhood adiposity (path 10). A systematic review and meta-analysis published in 2008 found evidence that exposure to SDP increases the risk for having an overweight BMI in childhood by about 50% from 14 studies (Oken et al., 2008). Since then a study using data from the Nurses' Health Study with a sample of 35,370 found SDP to be associated with increased body size in childhood between age 5 and 10 even after controlling for pre-pregnancy maternal BMI, paternal BMI, maternal GWG, family history of diabetes, paternal smoking, parental education, birth weight, gestational age and breastfeeding history (Harris et al., 2013). A more recent systematic review and meta-analysis included 64 studies who either evaluated risk of overweight and obesity,

higher BMI or both, found that SDP was associated with higher odds of overweight or obesity and higher mean BMI in childhood, and that these effects persisted into adulthood when those data were available (Magalhães et al., 2019). Additionally, SDP has been associated with childhood *adiposity* as measured by various skin fold thickness measurements and waist circumference (Li et al., 2016) which has been less often studied in large samples likely due to the feasibility and cost of obtaining body composition data. Overall, this literature shows strong support that SDP may be implicated in programming obesity risk in childhood and possibly beyond.

The Thrifty Phenotype Developmental Pathway

In summary, SDP is presumed to have an effect on earlier timing of puberty via prenatal growth patterns and birth weight through an IUGR mechanism possibly due to exposure to chemicals contained in tobacco smoke (path 1; da Silva Magalhães et al., 2019; Montgomery & Ekbom, 2002). SDP is also associated with growth in infancy (path 9), childhood adiposity, (path 10) pubertal timing (path 8) and type II diabetes in adulthood in the offpspring which collectively suggests that SDP may have a developmental cascade effect across the lifespan (Brix, Ernst, Lauridsen, Parner, et al., 2019; Jaddoe et al., 2014; Li et al., 2016; Mine et al., 2017). I will next detail the relationships of the postnatal features of thrifty phenotype pathway in relation to each other and to pubertal timing as the outcome.

Birth Weight

Low birth weight has been found to predict earlier pubertal timing (path 14), although it also has been shown to predict later pubertal timing (Juul et al., 2017). A recent systematic review (Juul et al., 2017) of longitudinal studies found that lower birth weight was associated

with earlier menarche in nine out of thirteen studies (Adair, 2001; Behie & O'Donnell, 2015; D'Aloisio et al., 2013; Dossus et al., 2012; Karaolis-Danckert et al., 2009; Kelly et al., 2017; Romundstad et al., 2003; Sloboda et al., 2007; Sorensen et al., 2013). Three studies showed a null association of birth weight (dos Santos Silva et al., 2002; Maisonet et al., 2010; Terry et al., 2009) and one study showed that higher birth weight was associated with an ealier timing of menarche (Wang et al., 2012). Importantly, one of the studies that found a null association between low birth weight and menarche initially found that low birth weight was associated with early onset of menarche, but when growth in infancy between zero and two years of age was included the effect became reversed (higher birth weight predicted earlier menarche) before eventually becoming null when growth between two and seven years was included (dos Santos Silva et al., 2002). This shows that growth in infancy *may* mediate the association between low birth weight and earlier age of menarche (reviewed in more detail below) and including childhood growth variables are important in the study of pubertal timing. Notably, most of the studies in the literature summarized above are comprised of white samples of european ancestry (Juul et al., 2017).

In terms of studies examining the association between birth weight and pubertal markers besides menarche, results are generally consistent although somewhat lacking in number for boys. A recent meta-analysis of eight studies of fetuses born low birth weight using various markers of puberty found that there is some evidence that low birth weight may be associated with earlier puberty in girls (Deng et al., 2017), although for boys, a subgroup analysis did not indicate earlier pubertal onset. Another study found an association between low birth weight and timing of growth spurt when girls and boys were analyzed together while controlling for accelerated weight gain between zero and two years of age, but not for age at peak height

velocity (Karaolis-Danckert et al., 2009). However, given sex differences in puberty, girls and boys should be analyzed seperately and the findings of the Karaolis-Danckert and colleagues study could possibly differ by sex.

Accelerated Weigth Gain

Despite mixed associations of low birth weight with pubertal timing, the association between low birth weight and accelerated weight gain (path 2) in infants born small for gestational age is robust and has been referred to as ubiquitous by some (Hack et al., 1984; Hack et al., 2003; Jain & Singhal, 2012). In additon to sex differences in interuterine growth mentioned previously, there is also evidence of that these differences persist into infancy (Broere-Brown et al., 2016). Some work also suggests growth in infancy may differ by race/ethicity with one study showing that Black infants had lower birth weight, faster infant weight increase and higher odds of being on a rising BMI trajectory (Bichteler & Gershoff, 2018).

In turn, accelerated weight gain has been a key focus of studies on earlier pubertal timing (path 3). A meta-analysis found that nine out of nine studies found an effect of greater weight or greater change in BMI with earlier AAM (Juul et al., 2017). Researchers have most often considered change in weight between birth and two or less than two years of age (Dunger et al., 2006). For example, one study found that only early weight gain (0-2 months and 2-9 months) to be predictive of later adiposity and earlier menarche but relatively later weight gain (9-19 months) to not be predictive either adiposity or AAM (Ong et al., 2009). Other studies have found change in weight between zero and two months and from zero and four months (Houghton et al., 2018; Ong et al., 2012) and between 1 and 2 years and between 2 and 5 years of age (Wang et al., 2012) to be predictive of earlier menarche. In a recent study that sought to explain

discrepancies between mixed directions between SDP and AAM, Houghton and colleagues (2018) found that when analyses were stratified by postnatal growth patterns, findings across cohorts converged and were related to a seven-month acceleration of menarche in the rapid growth group. This study's findings suggest that the association between exposure to SDP on AAM depends on postnatal growth patterns, which may explain heterogeneity in the association between birth weight and onset of menarche when accelerated weight is not considered. Similar to other areas of puberty research, studies in this area have historically been conducted in girls using AAM as an outcome, although more recently, corroborating evidence has been accumulating in boys (Aydin et al., 2017; Ong et al., 2012).

Accelerated weight gain has also been shown to predict higher childhood adiposity (path 4). Evidence of association between accelerated weight gain and puberty (path 3, reviewed above) and the association between child adiposity and early puberty (path 5, reviewed below) suggest that accelerated weight gain and childhood adiposity may independently contribute to earlier timing of puberty. A recent systematic review synthesized literature on patterns of early life growth and later obesity and found that accelerated weight gain was associated with later obesity or higher BMI in nine out of ten studies (Andrea et al., 2017). They also concluded that this relationship is strongest in studies with higher concentration of racial and ethnic minority groups or lower SES samples.

Childhood Adiposity

As previously mentioned, higher childhood adiposity has been shown to predict earlier timing of puberty (path 5). The puberty literature has primarily relied on child BMI as a proxy measure for adiposity in childhood. A greater number of studies have examined the relationship between BMI and pubertal timing and fewer with more direct measures of adiposity itself.

Nonetheless, results have generally been consistent. For example, body fat percentage at age 5 and BMI and waist circumference at age 7 all predicted earlier timing of puberty using the PDS at age 9 (Davison et al., 2003). In terms of sex differences, obesity during childhood has consistently been found to be a risk factor for early pubertal timing in girls (Lee et al., 2007) with mixed evidence and possibly curvilinear effects in boys (Lee et al., 2016; Wang, 2002). Further, a meta-analysis provided evidence that obesity may contribute to earlier menarche in girls but concluded there was insufficient evidence to make a parallel claim in boys (Li et al., 2017). Since then, several studies have found associations with pubertal markers other than AAM, and in boys. For instance, one study found evidence of association between higher pre-pubertal BMI and earlier age at thelarche, and pubarche in girls (Lawn et al., 2018) and another study in boys found evidence that higher pre-pubertal BMI at age 7 predicted more advanced pubertal markers including gonadal development, pubic hair, axillary air and earlier peak height velocity (Busch et al., 2019).

Despite fairly strong longitudinal evidence of higher childhood adiposity being associated with earlier puberty these findings are correlational in nature, and the causal nature of the developmental mechanisms supporting this association remain to be determined (Reinehr & Roth, 2019). Recent studies using Mendelian randomization techniques have begun to accumulate evidence in favor of a causal direction of the association between adiposity and puberty and may be causal in both sexes (Busch et al., 2019; Y. C. Chen et al., 2019). Chen and colleagues used a large sample of youth from Taiwan with follow up at age 18 to test the causal association between adiposity at 7-10 years of age and puberty at 11-12 years of age. Using self-reported Tanner stages, AAM in girls and age at voice break in boys they found that the instrumental variable for child BMI predicted earlier timing of puberty. Findings from a large

Danish birth cohort indicated that higher BMI was causally related to earlier age of voice break (Busch et al., 2019). Collectively, these studies indicate that there is good preliminary evidence that greater adiposity may cause earlier puberty in certain populations, is particularly strong in girls, and may vary by race/ethnicity group.

Despite strong evidence for the association between adiposity and pubertal timing it should be noted that sex differences in childhood adiposity may upwardly bias associations between breast development and BMI. As previously mentioned, the accumulation of adipose surrounding breast tissue creates the appearance of more advanced development (Biro et al., 1992; Dorn et al., 2006) although this issue of measurement validity is mostly mitigated by palpation in physical exam (Aghaee et al., 2019) and is not a factor when the pubertal marker outcome is AAM or another pubertal marker (e.g. pubic hair development)

Correspondence between childhood BMI and measures of adiposity have generally been found to be moderate to high, although BMI is not a perfect measure of adiposity and is subject to some limitations (Javed et al., 2015; Katzmarzyk et al., 2015). For example, the same BMI percentile does not correspond to the same level of adiposity at different ages, or across sex and race (Flegal & Ogden, 2011). These discrepancies may over or underestimate associations with pubertal timing depending on the accuracy of the correspondence to actual adiposity.

Fetal Overnutrition

Overnutrition Prenatal Risk as a Predictor of Pubertal Timing

Pre-pregnancy BMI is typically obtained from self-reported height and weight during pregnancy or perinatally from mothers' weight prior to becoming pregnant or during early pregnancy. Maternal GWG is most typically based on whether the mother gained inadequate,

adequate or excessive weight according to IOM guidelines which are recommended based on pregnancy BMI (IOM, 2009). Both prenatal risks have been shown to consistently predict earlier pubertal timing, and are key indicators implicated in the fetal overnutrition hypothesis. Associations between prenatal risks of overnutrition and AAM is well supported in girls (Boynton-Jarrett et al., 2011; Deardorff et al., 2013; Keim et al., 2009), and more recent evidence is corroborating menarche findings with other markers of puberty (Lawn et al., 2018). Lawn and colleagues (2018) found associations between pre-pregnancy BMI and maternal GWG with early pubarche and with thelarche and Aghaee and colleagues (2019) also reported associations between excessive maternal GWG with early pubarche and with thelarche.

Boys have been studied less overall, but studies have generally found similar associations across sex, although mainly at the high end of the overnutrition risk spectrum (Brix, Ernst, Lauridsen, Arah, et al., 2019; Hounsgaard et al., 2014). For example, Hounsgaard et al. (2014) found an association of earlier timing of beginning shaving with having a mother with a pre-pregnancy BMI classified as obese. Earlier age of voice break, acne and first nocturnal emission showed a consistent pattern with maternal overweight and obesity, although only at a trend level. Brix and colleagues (2019) examined several pubertal markers in a large sample of Danish 11-year-old girls and boys. In girls, mothers' overweight and obese pre-pregnancy BMI were associated with daughters' earlier timing of all pubertal markers but one. In contrast, associations were mostly only found with mothers' obese pre-pregnancy BMI (and not overweight) with son's earlier timing, and generally for later stages of adrenal development. In summary, associations of overnutrition with puberty in girls is highly consistent and is also fairly consistent in boys although associations are more modest and tend to be present only at obese levels of pre-pregnancy BMI. In terms of race/ethnicity differences for the association between pre-pregnancy

BMI and maternal GWG and pubertal timing, Deardorff and colleagues (2013) used the 1979 National Longitudinal Survey of Youth which comprised a sample of 48% Black, 44% Hispanic and 36% White mother daughter pairs and did not find evidence that these exposures differed by race/ethnicity. No studies have tested for race/ethnicity differences for this association in boys.

Overnutrition Prenatal Risks and Features of the Fetal Overnutrition pathway

Overnutrition Prenatal Risk as a Predictor of Birth weight

An overwhelming amount of literature suggests that the relationship between pre-pregnancy BMI is associated with higher infant birth weight ((path 6); Liu et al., 2016; Luke et al., 1981; Tyrrell et al., 2016; Yu et al., 2013). One systematic review and meta-analysis concluded that in comparison to mothers with a BMI classified in the normal range, pre-pregnancy overweight or obese status increased the risk of being born high birth weight and large for gestational age (Yu et al., 2013). A more recent meta-analysis done in 2016 reported similar findings; mothers who had a BMI classified as overweight or obese were at the greatest risk of having heavier infants, birthing an infant large for gestational age and at low risk of having an infant born small for gestational age (Liu et al., 2016). Additionally, evidence for a dose dependent relationship between increasing BMI and infants born large for gestational age was found. In terms of maternal GWG, another systematic review and meta-analysis found that weight gain in excess of IOM guidelines was associated with a 3% decreased risk of infants born small for gestational age and 4% increased risk of infants born large for gestational age (Goldstein et al., 2017). Further, a recent study of 33 randomized trials across 16 countries using individual participant data found that weight gain above IOM recommendations was associated

with twice the odds of having an infant born large for gestational age (Rogozińska et al., 2019). Overall, this body of work strongly supports the fetal overnutrition hypothesis at birth.

Overnutrition Prenatal Risk as a Predictor of Childhood Adiposity

Pre-pregnancy BMI and maternal GWG have also been found to be strong predictors of childhood adiposity (path 12; Yu et al., 2013). The fetal overnutrition hypothesis posits that greater maternal adiposity results in increased risk of obesity throughout life. If this is true, then maternal associations with offspring adiposity should be stronger than paternal associations. Explicit empirical tests of prenatal metabolic programming effects for the fetal overnutrition hypothesis are somewhat mixed although more recent evidence is accumulating in its favor (Mei et al., 2018; Sørensen et al., 2016). Some evidence suggests that maternal pre-pregnancy BMI is more strongly associated with offspring BMI than is the paternal-offspring association (Lawlor et al., 2007; Linabery et al., 2013), whereas others conclude no difference (Lawlor et al., 2008; Veena et al., 2013). A systematic published in early 2013 concluded that "limited" evidence existed supporting the fetal overnutrition hypothesis, although it was limited to 7 studies (Patro et al., 2013). However, later in 2013, Linabery et al. (2013) reported evidence of a stronger maternal influence on offspring BMI using longitudinal growth curve modeling to compare parental BMI and offspring growth across infancy, which addressed some methodological shortcomings of previous studies (Patro et al., 2013). Newer evidence from the Danish National Birth Cohort also finds stronger association between maternal pre-pregnancy BMI and child BMI from birth through age 7 compared to paternal associations (Sørensen et al., 2016) and so does a large sample study from China, although with more modest associations and only until age 2 (Mei et al., 2018). Overall, there is sufficient evidence to suggest that there may be a programming effect of maternal pre-pregnancy BMI on offspring BMI.

The Fetal Overnutrition Developmental Pathway

Birth weight

The literature from birth weight to pubertal timing (path 14) has already been covered in the Thrifty Phenotype literature section. Briefly, less evidence exists that finds associations between high birth weight with earlier timing of puberty than with low birth weight; only one study found that higher birth weight was associated with earlier menarche (Juul et al., 2017).

In contrast, a large literature supports the association between infants born at a high birthweight and higher childhood and adolescent BMI, in line with the fetal overnutrition hypothesis (Qiao et al., 2015; Schellong et al., 2012; Yu et al., 2011). Two systematic reviews and meta-analyses find evidence of a positive linear relationship between birth weight and increased risk of overweight for high birth weight defined as > 3000g and > 4000g infants (Schellong et al., 2012; Yu et al., 2011). Additionally, to corroborate evidence from large scale studies that have mostly relied on BMI as a measure of adiposity, at least one study has found that higher birthweight was related to greater central obesity as measured by waist to hip ratio in a sample of Chinese children between the ages of 7 and 17 (Yuan et al., 2015). Most relevant to the current thesis, recent work that has specifically examined the effect of high birth weight on BMI at around kindergarten age through the second grade found that infants who were born heavy had higher BMI at each grade level (Kapral et al., 2018). Importantly, this study had a large, nationally representative U.S. sample and adjusted for child sex, race/ethnicity, parental education and household income. Additionally, another study examined sex differences for the association between birth weight and childhood obesity and found a positive relationship for girls and a U-shaped relationship for boys. Overall, this literature shows strong support for the

fetal overnutrition hypothesis and suggests that sex differences must be considered (Qiao et al., 2015).

Childhood adiposity

The literature on childhood adiposity and earlier puberty (path 5) has been reviewed in the Thrifty Phenotype literature section as this path is identical in the current thesis' conceptualization of both hypotheses. In this literature review thus far, I have summarized evidence supporting main effects for the thrifty phenotype and fetal overnutrition hypotheses and two pathways for how they might be operationalized across the early lifespan with pubertal timing as the outcome. However, it is currently unknown which hypothesis better predicts how prenatal insults may lead to earlier timing of puberty. Finding that one pathway better predicts how prenatal risk may transmit across the early part of the lifespan could be informative in understanding poor later life health trajectories associated with earlier timing of puberty (Dorn et al., 2019). I will next review literature that has tested mediation through any part of the two pathways as they have been operationalized here.

Mediation Support for the Thrifty Phenotype and Fetal Overnutrition Hypotheses

Many studies in this literature conceptualize SDP, pre-pregnancy BMI and maternal GWG as prenatal insults that influence offspring to mature early according to DOHaD and evolutionary developmental perspectives (Behie & O'Donnell, 2015; Deardorff et al., 2013). Some studies have further tested for mediating effects of childhood adiposity and birth weight (Deardorff et al., 2013; Lawn et al., 2018), although none have tested the mediating role of accelerated weight gain. By far the most commonly tested indirect effect is whether childhood adiposity mediates the relationship between prenatal overnutrition risks and pubertal timing (Aghaee et al., 2019;

Deardorff et al., 2013; Kubo et al., 2018; Lawn et al., 2018). Deardorff et al. (2013) found no evidence for girls pre-pubertal BMI (age 7) mediating the relationship between pre-pregnancy BMI and AAM in 2497 mother daughter pairs from the 1979 NLSY. However, Lawn and colleagues (2018) found that girls pre-pubertal BMI (age 7.5) fully mediated the relationship for both pre-pregnancy BMI and maternal GWG, and AAM in the Avon Longitudinal Study of Parents and Children. They also found that pre-pubertal BMI partially mediated the relationship between prenatal risk and thelarche, and fully and partially mediated the relationship of pre-pregnancy BMI and maternal GWG, respectively, for pubarche. In a large sample of Scandinavian girls and boys, Brix colleagues (2019) found that prepubertal BMI (age 7) fully mediated most pubertal milestones in boys and partially mediated all pubertal milestones in girls at overweight or obese levels of maternal pre-pregnancy BMI. Aghaee and colleagues (2019) used data from a racially and ethnically diverse Kaiser Permanente Northern California cohort and found that maternal GWG that exceeded IOM guidelines was associated with early thelarche and pubarche as assessed by physical examination of Tanner stages (with breast palpation), and that prepubertal BMI at approximately age 6 attenuated the associations, although they remained significant for both puberty outcomes. Overall, this suggests that prepubertal BMI is important to the relationship between pre-pregnancy BMI and maternal GWG with pubertal timing but that there are likely other factors through which these prenatal risks contribute to programming the timing of puberty (Aghaee et al., 2019), and more studies testing this association in boys are needed.

In comparison, less work has tested the mediating effect of childhood BMI for SDP on pubertal timing. Brix and colleagues (2019) found that childhood BMI at age 7 slightly attenuated the associations between SDP and pubertal markers in girls and boys in a large sample

of Danish children. In contrast, Windham and colleagues (2017) found no evidence that child BMI between 6-8 years of age mediated the relationship between SDP and pubarche using a large ethnically diverse U.S. sample. This initial evidence suggests that prepubertal BMI may be important to the pathway from SDP to pubertal timing, but other pathways likely contribute, and more research is needed to clarify this.

In terms of whether birth weight may mediate the relationship between SDP and pubertal timing, most studies do not find evidence of mediation despite tests across multiple pubertal markers. Deardorff and colleagues (2013) did not find evidence that birth weight mediated the relationship between pre-pregnancy BMI and AAM. Attenuation of effects by birth weight was also not found for thelarche or pubarche in two studies using Kaiser Permanente Northern California data (Aghaee et al., 2019; Windham et al., 2017). Lawn and colleagues (2018) found evidence of a small positive indirect effect that birth weight mediated the relationship between pre-pregnancy BMI and maternal GWG with AAM, although the direct effect estimates remained virtually unchanged. Based on the literature above, there is weak evidence that birth weight alone substantially mediates the relationship between pre-pregnancy BMI and maternal GWG. No previous studies have tested whether birth weight mediates the relationship between SDP and pubertal timing, although Brix and colleagues (2019) explicitly did not test this indirect effect because of concerns of collider stratification bias.

In addition to the mediation effects summarized above, it is important to note the absence of studies testing the potential mediating effect of accelerated weight gain between prenatal risks associated with growth restriction and pubertal timing. This is a critical gap given the strong relations between SDP and accelerated weight gain and accelerated weight gain and pubertal timing (Mine et al., 2017; Ong et al., 2009). Further, many studies normally control for key

variables like birth weight and child pre-pubertal BMI (Behie & O'Donnell, 2015; Brix, Ernst, Lauridsen, Parner, et al., 2019) when testing associations between prenatal risks and puberty but fail to adjust for accelerated weight gain which is likely important to quantify since accelerated weight gain has been shown independently predict earlier timing of puberty (path 3) in addition to childhood BMI (paths 4 & 5; Ong et al., 2009; Reeves & Bernstein, 2008). Only one previous study has included birth weight, accelerated weight gain, prepubertal BMI and prenatal risk in the same model (Karaolis-Danckert et al., 2009). Karaolis-Danckert and colleagues (2009) found independent contributions for birth weight, accelerated weight gain and prepubertal BMI for two pubertal outcomes, although maternal overweight status did not predict age at peak height velocity and was only present at $p < .10$ level when prepubertal BMI was added to the AAM model. Therefore, there is a shortage of studies that take into account key postnatal risk factors in studies examining prenatal influences on pubertal timing, and no studies that have tested multiple mediation through more than one postnatal risk factor despite their connection across the early part of the lifespan.

Environmental Influences for Earlier Pubertal Timing

Many complimentary theoretical perspectives suggest that pubertal processes may be altered by environmental risk. Draper and Harpending (1982) proposed that early experiences in the family such as father absence shapes the child's future reproductive strategy to maximize reproductive fitness later in life. Central to Draper and Harpending's application of modern evolutionary theory is the position that children are evolved to be sensitive to the context of their early rearing environment and consequently develop particular patterns of behavior and psychological orientations that influence their future reproductive strategy. Belsky, Steinberg, and Draper (1991) later proposed a more general, evolutionary-developmental, theoretical

framework of socialization that explains how distal and proximal psychosocial factors may influence a child's reproductive strategy. Drawing on life history theory, and consistent with Draper and Harpending, the theory posits that children may respond to psychosocial cues by developing earlier to reach sexual maturity. For example, ecological stressors to the family (e.g. scarcity or instability of resources) may indirectly lower parental involvement by increasing marital conflict or reducing support and warmth in parent child relationships. According to the theory, children may be implicitly prompted by these cues to respond with adopting a faster life history which biases toward earlier pubertal timing. Central to these ideas is the hypothesis that if an organism is able to reach sexual maturity earlier, they are increasing the likelihood of passing on their genes. Accordingly, in contexts characterized by stability and adequate levels of support, children should have relatively later pubertal timing (Belsky et al., 1991). Note that a change in reproductive strategy and pubertal timing is theorized to be a process that takes place at an unconscious level not a conscious decision made by the child. Generally speaking, it follows that environmental influences that reflect decreased parental involvement and increased risk of dying should bias individuals towards earlier maturation.

Influences such as father absence, maltreatment, harsh parenting and family contextual factors have been presumed to bias children toward earlier maturation, but they have mostly only been empirically tested and observed in girls (Deardorff et al., 2011; Ellis & Essex, 2007; Lu et al., 2019; Mendle et al., 2011). For example, Mendle and colleagues found that sexual abuse was associated with earlier timing of puberty, and physical abuse was related to faster pubertal tempo using the PDS in a sample of girls living in foster care. One study using the National Growth and Health Study (NGHS) with a sample of approximately 2000 found that white girls in the highest quartile of income were least at risk for early menarche but Black girls in the highest quartile

were at the most risk of early menarche (Braithwaite et al., 2009). Deardorff and colleagues found that father absence assessed at 6-8 years of age predicted earlier breast development as measured by visual inspection and palpation when family income status was high (>$50,000) and that this effect was strongest in Black girls. A recent meta-analysis of the effect of adverse child events (ACEs) on pubertal timing in girls found that there was no overall effect of total ACEs, but father absence, sexual abuse and family dysfunction was related to earlier timing of puberty in girls (Zhang et al., 2019). Overall, this suggests that the type of environment threat matters, father absence and sexual abuse are particularly salient risk for girls, and more research is needed in boys and these associations may vary by race/ethnicity group. However, most studies investigating prenatal associations with pubertal timing do not control for environmental threat (e.g., Deardorff et al., 2013; Lawn et al., 2018). Thus, it is important to consider key postnatal environmental influences in the study of prenatal programming of pubertal timing to more precisely clarify the lasting effect of the prenatal environment. The current thesis will control for these key postnatal influences such as father absence, family socioeconomic status and child maltreatment in order to gain clearer and more precise estimation of the thrifty phenotype and overnutrition hypotheses.

THE CURRENT STUDY

The current thesis investigated prenatal pathways to early puberty by testing the thrifty phenotype and fetal overnutrition hypotheses. First and foremost, it addressed the gap in understanding which pathway better predicts early pubertal timing. Furthermore, the current study addressed a number of smaller gaps within the extant puberty literature. The current study used the FFCWS dataset, which is a large, racially and ethnically diverse, birth cohort that has adrenal and gonadal indicators of pubertal development. The current thesis therefore adds to the literature a longitudinal investigation of early pubertal timing from prenatal insults through key postnatal risk factors within a sample of racially/ethnically diverse, male and female youth using parent perceived puberty.

Research Question 1.

Do the thrifty phenotype and fetal overnutrition pathways predict earlier puberty equally well in boys and girls?

Hypothesis 1a.

Each of the paths for the thrifty phenotype pathway will be present (path 1-5) for boys and girls. There will be an indirect effect from SDP to pubertal timing through birth weight (path 1), and accelerated weight gain (path 2) to pubertal timing directly (path 3) as well as an indirect effect from SDP to pubertal timing through birth weight (path 1), accelerated weight gain (path 2), and child BMI (path 4) to early timing of puberty (path 5) for boys and girls. The thrifty phenotype pathway will better predict puberty in boys compared to girls.

Hypothesis 1b.

Each of the paths for the fetal overnutrition pathway will be present (paths 6, 7, 5) for boys and girls. There will be an indirect effect from pre-pregnancy BMI and maternal GWG to pubertal timing through birth weight (path 6) and child BMI (path 7) to pubertal timing (path 5) for boys and girls. The fetal overnutrition pathway will better predict puberty in girls compared to boys.

Hypothesis 1c.

The thrifty phenotype pathway will better predict the pathway to earlier pubertal timing within boys and the fetal overnutrition pathway will better predict the prenatal pathway to earlier pubertal timing within girls.

Research Question 2.

Do the prenatal pathways predict earlier puberty equally well across race/ethnicity?

Given the relative lack of studies that investigate race/ethnicity differences in many paths of the proposed models, this was an exploratory research question with no specific hypotheses for each group.

METHODS

Sample Study Description

Data for the current thesis came from the FFCWS. The FFCWS is a population-based birth cohort study comprising six waves of data collection across time. The primary goal of the FFCWS was to learn more about the nature of the relationships within "fragile families" in the United States. The term "fragile families" refers to unmarried parents and their children to emphasize that they are indeed families, that they are at higher risk of union dissolution and that they are more likely to live in poverty than more traditional families. To the end of better understanding fragile families and the challenges they face, the FFCWS employed a simple stratified random sampling technique and oversampled 3 to 1 non-marital births to marital births in order to gather a large U.S. representative sample of unwed parents and their children. The FFCWS started with 4,898 children born between 1998 and 2000 in 20 large U.S. cities with births from 75 hospitals (Reichman, Teitler, Garfinkle, & Mclanahan, 2001). The study design resulted in successfully recruiting approximately 3,600 unwed couples and 1,100 married couples. The sample of children was 47.80% female. In terms of race/ethnicity, the sample was 18.07% White, 49.04% Black, 24.90% Hispanic/Latino, 2.63% other, non-Hispanic, and 5.36% multiracial based on mother's race/ethnicity.

Interview Assessments

Baseline interviews were conducted primarily in the hospital shortly after the focal child's birth with follow-ups after 1, 3, 5, 9, and 15 years; the 15-year follow-up took place from 2014 to 2017. Follow-up interviews were conducted over the phone with a variety of in-home assessments. The present thesis uses data from baseline, and age 1, 3, 5, and age 9 assessments.

Median age at the age 9 assessment, which was when puberty was measured, was 9.33 (M = 9.39, SD 0.38, range=8.67-11 years of age). Crude attrition rate using mother's relationship with father from the baseline to the year 1 assessment was 11%, attrition from the year 1 to year 3 was 15%, attrition from the year 3 to year 5 assessment was 18%, and attrition from the year 5 to year 9 assessment was 35%. Overall attrition from the baseline to age 9 assessment was 30%.

Medical Birth Record Data

For the current thesis, I obtained restricted use medical birth record data from the FFCWS in order to use accurate information from the birth hospitalization records for mothers and focal children. These data are available for 75% of the sample or 3,684 births (mothers and focal children). Medical birth record data were obtained by a member of the FFCWS research team who went to each participating hospital and filled in the FFCWS abstraction form from hospital records for each FFCWS birth. When there are no medical record data for a given case it was for 1 of 3 reasons: (1) The hospital did not permit the FFCWS team to abstract records or there were too few cases for it to be financially feasible to collect data at that hospital (38%; 10% of the total sample), (2) the mother refused consent (33%; 8% of the total sample), or (3) the records could not be located in the hospital (29%; 7% of the total sample). Key variables drawn from the medical birth record data for the current study are mother's pre-pregnancy BMI, maternal GWG and infant birth weight and gestational age.

Measures

Pubertal Development

Puberty was reported by the primary caregiver using the PDS (Petersen et al., 1988) at age 9. The PDS reports on growth spurt, presence of body hair, and skin changes. Sex specific

questions for boys include facial hair growth and voice deepening. In girls, questions about breast development and whether or not menstruation had begun were asked. Questions were asked on a 4-point Likert Scale from 1-not yet started, 2-has barely started, 3-is definitely underway, and 4-Seems completed for all developmental milestones except menstruation which was recoded to 1 if menstruation had not yet begun and 4 if menstruation had begun. Adrenal and gonadal items were separated into an adrenal PDS score and gonadal PDS score in order to capture these key features of pubertal maturation (Shirtcliff et al., 2009). Growth spurt, breast development and menarche indexed gonadal development for girls. For boys, growth spurt, voice deepening, and facial hair growth indexed gonadal development. In both sexes, pubic/body hair and skin changes indexed adrenal development.

Means and distributions of the adrenal and gonadal PDS items (i.e., indicating pubertal status at the time of the age 9 assessment) were examined together and separately by sex. As expected, girls overall PDS scores (M_{boys} = 1.37, SD_{boys} = .29; M_{girls} = 1.58, SD_{girls} =.58) and adrenal and gonadal sub scores were higher than boys. Unexpectedly, boys and girls gonadal scores, (M_{boys} = 1.50, SD_{boys} = .37; M_{girls} = 1.70, SD_{girls} =.46) were on average higher than adrenal scores, (M_{boys} = 1.18, SD_{boys} = .35; M_{girls} = 1.40, SD_{girls} =.53), suggesting that some of the items were likely reported as more advanced than in reality. Examination of the pubertal markers suggested that adrenal PDS scores and gonadal PDS were correlated, r = .35, p <.001, suggesting that they represent related yet distinct markers of puberty in this sample. Bivariate correlations were also examined between all study variables separately by sex and by adrenal and gonadal PDS scores in order to further explore the practicality and value of analyzing the hypothesized models separately by pubertal processes (described in more detail below). The descriptive

analysis suggested this was worthwhile. Based on this evidence, all models were thus analyzed separately by adrenal and gonadal PDS score for both research questions.

Perceived pubertal timing was operationalized by regressing each score on age (within sex), and the residuals were saved in separate adrenal and gonadal pubertal timing (relative to same age- and sex- youth) variables for boys and girls (Ge et al., 2007). This measure therefore reflects perceived pubertal timing as indexed by primary caregiver's report of child pubertal status relative to other children in the sample where higher values indicate earlier timing for adrenal and gonadal pubertal markers separately. See Table 1 for more descriptive statistic information for girls and boys and by race/ethnicity group for pubertal markers and all key study variables described below.

Self-reported Prenatal Substance Use

Mothers were asked to self-report use of cigarettes, alcohol and drug use during their pregnancy at the baseline interview, usually shortly after birth before leaving the hospital. For SDP, mothers were given the following response options to report how many cigarettes they used per week during their pregnancy: (1) 2 or more packs of cigarettes per day, (2) between 1 and 2 packs per day, (3) less than 1 pack per day, and (4) none. SDP scores were recoded in order for higher values to indicate more cigarette use during the pregnancy, with 0 indicating none and 3 indicating 2 or more packs per day. For ADP, mothers were asked to self-report how frequently they drank alcohol and were given the following response options to indicate their use: (1) every day, (2) several times a week, (3) several times a month, (4) less than once a month, and (5) never. ADP scores were recoded in order for higher values to indicate more alcohol use during the pregnancy, with 0 indicating none and 4 indicating every day. Other drug use during pregnancy (ODP), which included marijuana, cocaine or heroin, followed the same

response options as ADP. ODP scores were also recoded in order for higher values to indicate more ODP use during the pregnancy. Overall, 19% endorsed smoking during their pregnancies with 17% endorsing smoking less than a pack a day. For ADP, 11% of the sample endorsed some kind of ADP with 8% endorsing drinking less than once a month. Approximately 6% of the sample endorsed ODP with 3% endorsing using another substance less than once a month.

Medical Record Pre-Pregnancy BMI

Height and pre-pregnancy weight information was abstracted from medical records, and pre-pregnancy BMI was then constructed from these variables as the weight in kilograms divided by the square of height in meters (kg/m^2) by the FFCWS team. The sample average for pre-pregnancy BMI was a BMI of 26, which is classified in the overweight category.

Medical Record Maternal Gestational Weight Gain

Maternal GWG was constructed from the difference of pre-pregnancy weight and weight at hospital admission for delivery in kilograms and recoded into categories of exceeded, met, and below based on IOM guidelines according to the pre-pregnancy BMI by the FFCWS team. According to IOM guidelines, mothers with a pre pregnancy BMI of <18.5, 18.5-24.9, 25-29.9 and ≥ 30 are expected to gain 28-40, 25-35 pounds, 15-25 pounds and 11-20 pounds, respectively (IOM, 2009). Overall, 29% of the sample did not gain enough weight to meet IOM guidelines, 20% of the sample met the guidelines and 52% exceeded them.

Medical Record Birth Weight

Infant birth weight in grams was abstracted from the birth medical record. Birth weight in grams was rescaled into pounds to ensure reasonable variance values relative to other variables in model estimation. The mean birth weight for the sample was 7.09 (1.37) pounds.

Accelerated Weight Gain

Accelerated weight gain was calculated as the change between weight-for-age z-score at birth to weight-for-age z-score at age 1 using the 2000 World Health Organization growth charts (WHO, 2006). Birth weight was abstracted from the medical record and weight at age 1 in pounds was reported by the mother. Using these weights and the growth charts, a SAS program provided by the Center for Disease Control (CDC) was used to calculate weight-for-age z-scores at birth and age 1. Accelerated weight gain was then computed as the change in weight-for-age z-score between birth and age 1. The mean change in z-score for the sample was 0.44 (1.76).

Child Body Mass Index

Child BMI was calculated as the weight in kilograms divided by the square of height in meters (kg/m^2) from primary caregiver reported height and weight of the focal child at the age 5 assessment. BMI z-score was constructed by the FFCWS team using the CDC's SAS programs *gc-setup.sas and gc-calculate.sas* which corrects for age and sex of the focal child based on the 2000 CDC growth charts (Kuczmarski et al., 2002). Mean BMI z-score at the age five assessment was 0.60 (1.15). Approximately 15% and 8% of the sample had BMIs that would be classified as overweight and obese, respectively, per CDC guidance.

Covariates

Medical Record Gestational Age

Gestational age at birth was abstracted from the birth medical record and constructed by the FFCWS team. Gestational age was a covariate on all key study variables. The average gestational age at birth was 38.54 (2.45) weeks.

Maternal Age

Mean maternal age was 25.28 (6.04) at the time of the baseline survey. Maternal age was a constructed variable from the baseline survey which typically took place before mothers left the hospital after delivery.

Socioeconomic Status

Socioeconomic status was measured by a combination of total household income, highest level of education, material hardship and food insecurity as self-reported by the primary caregiver in the core survey at the birth of the focal child, age 1, 3, 5 and 9 assessments. Association of socioeconomic variables and data aggregation are described below.

Household Income

Total household income is a constructed variable created by the FFCWS team in each wave of the study from primary caregivers self-reported household income in exact dollar amount or self-reported income range. When household income was missing, primary caregiver household income was supplemented with father report if the couple was married or cohabitating or from imputed household income for those who were unable or unwilling to provide an estimate of household income. For those that reported a range of household income, the mean

value of the income bracket was imputed. If a report of income was otherwise missing household income was imputed using Stata's regression-based impute command based on the following covariates: city, age, years of education, race/ethnicity, earnings, immigrant status, employment in the last year, hours worked, total adults in the household, reception of welfare and marital status.

Household income was coded into 9 income brackets of: less than $10,000, $10,000-$14,999, $15,000-$24,999, $25,000-$34,999, $35,000-$49,999, $50,000-$74,999, $75,000-$99,999, $100,000-$149,999 and above $150,000. Correlation of household income bracket from birth of the target through age 9 ranged from r = .43-.68 and had a Cronbach's alpha of .86. Income measures were averaged into a single household income variable. At baseline, 25% of the sample was coded into the less than $10,000 income bracket, 11% were in the $10,000-$14,999 bracket, 19% were in the $15,000-$24,999 bracket, 14% were in the $25,000-$34,999 bracket, 13% were in the $35,000-$49,999 bracket, 11% were in $50,000-$74,999 bracket, less than 1% were in the $75,000-$99,999 bracket, 7% were in the $100,000-$149,999 bracket and 0% in the above $150,000 bracket.

Education

Highest level of education attained was self-reported by the primary caregiver at the time of the focal child's birth with response options of less than high school degree, high school degree or equivalent, some college or technical school and college degree or graduate degree. Highest level of education at all other study time points assessed past baseline (age 1, 3, 5, 9) was constructed from previous waves when primary caregivers did not report any new education, training or schooling. Highest educational attainment by the primary caregiver was correlated very highly across time, ranging from r = .79-.95. Given the high level of stability, this measure

was also averaged across time into a single education attainment variable. At baseline, 35% endorsed having less education than a high school degree, 30% endorsed having a high school degree or equivalent, 24% endorsed having some college education or technical school, and 11% had a college degree or graduate degree.

Material Hardship

Four questions derived from the "Basic Needs – Ability to Meet Expenses" section of the Survey on Income and Program Participation (SIPP) 1996 Panel Wave 8 Adult Well-Being Topical Module Questionnaire (Nord & Nord, 2012) were used to assess degree of material hardship at each assessment from the age 1 through the age 9 assessment. These items asked primary caregivers about whether they were able to pay their rent or mortgage, were evicted from a home or an apartment, were unable to pay any utility bills, and if they themselves or a household member needed to see a doctor or go to the hospital but were unable to due to financial reasons. The four items assessing material hardship from the age 1 through age 9 assessment were first summed together within waves and then averaged across time. The Cronbach's alphas ranged from .45 - .50 and correlated with each other r = .25-.43 across waves.

Food Security

The 18 item Household Food Security Module was completed by primary caregivers to assess the degree of food security the family had at the age 3 and age 5 assessment (Andrews et al., 1999). Items asked questions about whether the primary caregiver worried food would run out, if they couldn't afford to eat balanced meals, whether adults in the household reduced portion sizes, skipped meals, did not eat the whole day, children's meal sizes were cut, and whether children had to skip meals or children did not eat the whole day. Higher scores indicate

poorer food security status. The 18 food security items were summed at the age 3 and age 5 assessment, respectively, and then averaged together. Sum scales from the age 3 and 5 assessment had Cronbach's alphas of .86 and .88 and correlated with each other r = .46. Average food security for the overall sample was 1.15 (2.23).

Maltreatment

Child maltreatment was measured by self-report using Parent-Child Conflict Tactics Scales (CTSPC) by the primary caregiver at age 5 (Straus, 2007). Specifically, the physical assault and psychological aggression subscales was averaged and included as a covariate on pubertal timing to index threat in the child's environment that may act as a fast life history cue (Belsky et al., 1991; Mendle et al., 2011). Child maltreatment items were averaged together within a wave and averaged over year 3 and 5 assessment. Cronbach's alphas for the age 3 and 5 assessment were .58 and .61, respectively and correlated with each other r = .51. Average child maltreatment for the overall sample was 1.65 (.94).

Breastfeeding

Duration of breastfeeding status was assessed at the year 1 assessment where mothers reported how long the focal child was breast fed for. Breastfeeding duration was included as a covariate on accelerated weight gain, child BMI and perceived pubertal timing given evidence that short duration of breastfeeding may exacerbate accelerated weigh gain and be associated with childhood obesity (Carling et al., 2015). Mothers first indicated whether they breastfed their child or not at the age 1 assessment, if breastfeeding was indicated they further indicated for how long in weeks or months. Duration of breastfeeding was recoded into weeks. If mothers indicated that they were still breastfeeding their child, then the length of breastfeeding was equal to the

child's age in weeks at the time of assessment. Average breastfeeding duration for the overall sample was 10.61 (15.53) weeks.

Father Absence

Father absence was quantified by using constructed relationship status variables from the time of birth of the child, and the age 1, 3, and 5 assessment. If the mother and father were not cohabitating at any of these assessments, then the home was considered to be "father absent". Father absence was included as a covariate on perceived pubertal timing only (Belsky et al., 1991; Deardorff et al., 2011). From baseline to the age 5 assessment, 40%, 43%, 49% and 56% of fathers were not cohabitating with the mother and child, respectively. Overall, 63% of fathers were considered "absent" because of not cohabitating with the mother at some point in the first five years of the child's life.

Missing data

Percentages of missing data from the initial sample of 4,898 for key study variables were 29% for pubertal timing, 56% for child BMI, 40% for accelerated weight gain, 25% for birth weight, 39% for pre-pregnancy BMI, 42% for maternal GWG and <1% for SDP. We tested whether key study variables as well as average household income and race/ethnicity group were significantly associated with missingness on pubertal timing, child BMI, accelerated weight gain, birth weight, pre-pregnancy BMI, maternal GWG, and SDP using a series of Kruskal-Wallace tests for continuous variables and chi-square tests for categorical variables.

Of 48 tests, 15 (31%) reached significance at $p < 0.05$ (un-adjusted for multiple testing in order to conservatively understand potential biases in the data). Children who were missing on pubertal timing were more likely to have mothers who smoked during their pregnancies, more

likely to have mothers with lower pre-pregnancy BMIs, more likely to have lower household incomes and have mothers who identified as Hispanic or as other race/ethnicity. Children who were missing on child BMI z-score were more likely to have mothers with lower pre-pregnancy BMIs, more likely to have mothers who gained more weight during their pregnancies, have lower household incomes and more likely to have mothers who identified as other race/ethnicity. Children who were missing on accelerated weight gain were more likely to have mothers who gained more weight during their pregnancies, were more likely to have lower birth weights, and lower family household income. Children who were missing on birth weight were more likely to have mothers who gained more weight during their pregnancies, have higher household incomes and more likely to have mothers who identified as Hispanic and as other race/ethnicity. Children who were missing on mother's pre-pregnancy BMI were more likely to have mothers who gained more weight during their pregnancies, were more likely to have lower birth weights, to have higher accelerated weight gain, have lower household incomes and were more likely to have mothers who identified as Black or as other race/ethnicity. Children who were missing on maternal GWG were more likely to have mothers who identified as Black or as other race/ethnicity. Missingness on SDP was not associated with any key study or demographic variables.

Table 1 Sample descriptive statistics for study variables

	Total (n= 4897)	Boys (n=2556)	Girls (n=2341)	Black (n= 2326)	White (n= 1030)	Hispanic (n= 1336)	Other (n= 194)
Age at age 9 assessment	9.39 (.38)	9.38 (.38)	9.40 (.38)	9.37 (.38)	9.3 (.33)	9.47 (.39)	9.45 (.46)
Overall PDS	1.47 (.36)	1.37 (.29)	1.58 (.40)	1.54 (.38)	1.36 (.30)	1.42 (.33)	1.41 (.35)
Adrenal markers	1.28 (.46)	1.18 (.35)	1.40 (.53)	1.37 (.51)	1.17 (.34)	1.21 (.38)	1.25 (.50)
Gonadal markers	1.6 (.43)	1.50 (.37)	1.70 (.46)	1.66 (.44)	1.49 (.40)	1.57 (.42)	1.51 (.38)
Pre-pregnancy BMI	26.23 (6.58)	26.13 (6.39)	26.35 (6.79)	26.97 (7.04)	25.00 (6.30)	26.25 (5.89)	24.38 (6.26)
Maternal gestational weight gain							
Inadequate	29%	28%	29%	32%	22%	27%	27%
Adequate	20%	20%	20%	17%	24%	19%	28%
Excessive	52%	52%	51%	51%	53%	52%	44%
Smoking during pregnancy							
None	81%	82%	79%	79%	71%	90%	88%
<1 pack a day	17%	16%	18%	20%	23%	9%	11%
2 packs a day	2%	2%	2%	2%	5%	<1%	<1%
2 or more packs a day	<1%	<1%	<1%	<1%	<1%	<1%	0%
Alcohol use during pregnancy							
Never	89%	90%	89%	89%	84%	93%	94%
< Once a month	8%	8%	9%	8%	14%	5%	5%
Several times a month	2%	1%	2%	2%	2%	<1%	<1%
Several times a week	<1%	<1%	<1%	<1%	<1%	<1%	0%
Everyday	<1%	<1%	<1%	<1%	<1%	<1%	0%
Other drug use during pregnancy							
Never	94%	95%	94%	92%	96%	97%	96%
< Once a month	3%	3%	3%	4%	2%	2%	2%
Several times a month	1%	1%	2%	2%	<1%	<1%	2%

Table 1 continued

Several times a week	<1%	<1%	<1%	1%	<1%	<1%	0%
Everyday	<1%	<1%	<1%	<1%	<1%	0%	0%
Maternal age at delivery	25.28 (6.04)	25.17 (6.02)	25.39 (6.06)	24.56 (5.77)	27.10 (6.48)	24.81 (5.77)	27.18 (6.19)
Birth weight	7.09 (1.37)	7.19 (1.41)	6.98 (1.31)	6.85 (1.39)	7.31 (1.42)	7.33 (1.26)	7.15 (1.20)
Gestational age	38.54 (2.45)	38.56 (2.48)	38.52 (2.40)	38.34 (2.65)	38.68 (2.41)	38.79 (2.12)	38.40 (2.06)
Accelerated weight gain	7.13 (1.53)	7.37 (1.55)	6.87 (1.45)	7.30 (1.63)	6.89 (1.33)	7.06 (1.46)	7.10 (1.46)
BMI_z	0.60 (1.15)	0.59 (1.17)	0.61 (1.14)	0.53 (1.16)	.50 (1.21)	0.85 (1.14)	0.39 (1.14)
Income (median at baseline)	$15,000-$24,000	$15,000-$24,999	$15,000-$24,999	$15,000-$24,999	$35,000-$49,999	$15,000-$24,999	$25,000-$34,999
Education (median at baseline)	High school or equivalent	High school or equivalent	High school or equivalent	High school or equivalent	Some college or technical school	Less than high school	Some college or technical school
Material needs	0.47 (.58)	0.46 (.58)	0.47 (.57)	0.52 (.56)	0.45 (0.63)	0.41 (.55)	0.40 (.62)
Food security	1.15 (2.23)	1.21 (2.30)	1.08 (2.14)	1.23 (2.27)	0.81 (1.97)	1.28 (2.30)	0.93 (2.20)
Maltreatment	1.65 (.94)	1.70 (.95)	1.58 (.92)	1.81 (.94)	1.58 (.88)	1.43 (.93)	1.61 (1.13)
Breastfeeding	10.61 (15.53)	10.58 (15.65)	10.64 (15.40)	7.97 (13.96)	13.69 (17.01)	12.48 (16.14)	16.96 (16.77)
Father absence	63%	63%	64%	80%	42%	55%	44%

Analytic Strategy

The current thesis used observed variable path analysis in a structural equation model (SEM) framework in order to test study hypotheses. All models were analyzed using M*plus* software V.8 (Muthén & Muthén, 1998-2017) using the Full Information Maximum Likelihood estimator (MLR), which robustly accounts for data missingness and can account for non-normality of data. Overall model fit of a priori models testing the thrifty phenotype and fetal overnutrition hypotheses (described below) was evaluated with RMSEA, CFI, SRMR, and chi-square values. Per convention, CFI values above 0.95, RMSEA below 0.05, SRMR below 0.05 and a non-significant chi-square value indicate a well-fitting model and values of RMSEA and SRMR between 0.5-.08 indicate fair model (Hu & Bentler, 1998, 1999; MacCallum et al., 1996). Wald tests were used to test the relative strength of indirect effects. Additionally, modification indices were examined to consider adding parameters to improve model fit and standardized residuals were examined for areas of model strain (absolute values above 1.96) if significant misfit was indicated.

Bivariate correlations were examined between all continuous study variables and covariates separately for boys and girls for research question 1 and were examined by sex and race ethnicity group for research question 2. Bivariate associations at the $p < .10$ level were specified as covariate paths in the hypothesized models.

Model Specification

There were two main multi-group SEM models for research question 1: one each for adrenal and gonadal PDS scores, with boys and girls modeled as separate groups. There were four main multi-group SEM models for research question 2: one each for boys' and girls' adrenal and gonadal PDS scores, with each race/ethnicity modeled as separate groups. All models were

specified as depicted in Figure 2 along with additional direct effects as follows: ADP, ODP, maternal age at delivery, household income, maternal education and race/ethnicity group were allowed to predict birth weight, accelerated weight gain, child BMI z-score and perceived pubertal timing. Additionally, material needs, food security and breastfeeding were allowed to predict accelerated weight gain, child BMI z-score and perceived pubertal timing. Finally, child maltreatment and father absence were allowed to predict perceived pubertal timing only, for a total 65 direct effects in each model. Bivariate associations at the $p < .10$ level were specified as covariate paths in the hypothesized models by child sex for the analysis of research question 1 and by child sex and race/ethnicity for research question 2 models. See appendices A-H for specific model correlations.

Hypotheses 1a and 1b were tested first on whether the hypothesized direct and indirect paths for the thrifty phenotype and overnutrition pathways were absent or present at $p < 0.05$ and in the expected direction. Next, parameter constraints were used to constrain the indirect effects to equality for each hypothesized pathway across sex in order to statistically test for sex differences in the indirect effects. Specifically, Wald tests were used to determine whether specific paths could be constrained to equality with or without a decrement in model fit. In the models used to test hypotheses 1a and 1b, there were two hypothesized thrifty phenotype pathways and two indicators for the prenatal overnutrition hypothesis pathway. Before testing for sex differences, the strongest thrifty phenotype (through accelerated weight gain vs. through child BMI) and fetal overnutrition (beginning with pre-pregnancy BMI vs. with GWG) indirect effects among boys and girls were determined in order to reduce the number of model comparisons. Thus, sex differences between the thrifty phenotype and overnutrition pathways

were tested between only the strongest of each pathway (separately for adrenal and gonadal markers).

In the test of hypothesis 1c, constraints were used to identify which pathway was stronger within sex (separately for adrenal and gonadal PDS scores) for the thrifty phenotype and overnutrition pathway identified as the strongest for hypothesis 1a and 1b.

The same strategy of first examining the absence/presence of direct and indirect effects and then constraining indirect effects to equality was used to examine research question 2, but with race/ethnicity as the grouping variable in multi-group SEM models (modeled separately by sex).

In total, there were 65 unique direct effects in each model for research question 1 and 2. There were 85 unique direct effects across all the analyses due to overlap in many of the earlier pathways (e.g., maternal GWG to birth weight) and some unique paths (e.g., BMI to adrenal PDS scores vs. gonadal PDS scores). Given the large number of direct effects, a Bonferroni adjusted p-value of 0.00058 was used (0.05/85=0.00058). M*plus* only provides p-values to three decimal places, however, since most p-values that would be under the adjusted p-value would likely round to 0.000, the M*plus* cut off of 0.000 was used. Findings that survive this adjustment are noted in bold in the corresponding figure for each model. The M*plus* cut off may be slightly more conservative but findings were interpreted holistically by weighing information based the $p < .05$ significance level cut off, effects sizes, consistency of findings with zero-order correlations and internal replication of effects across models within the study.

RESULTS

Preliminary analyses

Main hypothesized bivariate associations by sex.

All bivariate associations of key study variables for the hypothesized pathways were present and in the expected directions. SDP correlated negatively with birth weight in boys and girls, r_{boys} = -.16, p < .001, r_{girls} = -.16, p < .001; birth weight correlated negatively with accelerated weight gain r_{boys} = -.54, p < .001, r_{girls} = -.57, p < .001; accelerated weight gain correlated positively with child BMI, r_{boys} = .16, p < .001, r_{girls} = .10, p = .006; accelerated weight gain correlated positively with both adrenal, r_{boys} = .15, p < .001, r_{girls} = .14, p < .001, and gonadal PDS scores, r_{boys} = .11, p < .001, r_{girls} = .12, p < .001 and child BMI correlated positively with adrenal PDS scores, r_{boys} = .13, p < .001, r_{girls} = .08, p = .012 and gonadal PDS scores, r_{boys} = .19, p < .001, r_{girls} = .12, p < .001.

Pre-pregnancy BMI correlated positively with birth weight in boys and girls, r_{boys} = .14, p < .001, r_{girls} = .12, p < .001; birth weight correlated positively with child BMI, r_{boys} = .15, p < .001, r_{girls} = .27, p < .001. Maternal GWG correlated positively with birth weight in boys and girls, r_{boys} = .27, p < .001, r_{girls} = .23, p < .001.

Additionally, pre-pregnancy BMI and maternal GWG were positively correlated although only modestly, r_{boys} = .17, p < .001, r_{girls} = .16, p < .001, thereby permitting them to be included in the same model without threat of multicollinearity. See Tables 2 and 3 for correlations among study variables in boys and girls.

Table 2 Boys' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.25**																
3. ADP	-.00	-.01															
4. ODP	.03	.02	.28**														
5. SDP	.04	.05*	.21**	.28**													
6. Maternal GWG	-.00	.00	-.06*	-.02	-.08**												
7. Pre-pregnancy BMI	.04	.04	-.02	.00	-.05*	.16**											
8. Maternal age	-.05*	-.03	.12**	-.01	.02	.02	.14**										
9. Birth weight	-.08**	-.03	-.07**	-.08**	-.16**	.23**	.12**	.07**									
10. Gestational age	-.07**	-.01	-.03	-.06**	-.08**	.13**	.04	-.03	.71**								
11. ACC weight gain	.14**	.12**	.08**	.05*	.11**	-.12**	-.01	-.06*	-.54**	-.45**							
12. BMI5z	.08*	.12**	.00	.01	-.02	.20**	.24**	.01	.27**	.16**	.10**						
13. Income	-.06*	-.13**	-.02	-.12**	-.13**	.07**	-.07**	.32**	.10**	.03	-.10**	-.06*					
14. Education	-.02	-.08**	-.02	-.11**	-.13**	.06*	-.02	.35**	.05*	.01	-.05*	-.07*	.58**				
15. Material Needs	.10**	.01	.07**	.09**	.20**	-.03	.08**	-.06**	-.03	-.01	.07**	-.01	-.18**	-.05*			
16. Food Security	.04	.03	.04	.08**	.09**	-.01	.06*	-.04	-.02	.02	.04	-.01	-.26**	-.15**	.36**		
17. Maltreatment	.06*	.03	.05*	.09**	.08**	-.05	.03	-.13**	-.05	.01	.04	.03	-.04	-.01	.21**	.15**	
18. Breastfeeding	-.05*	-.10**	-.03	-.09**	-.16**	.05	-.02	.19**	.10**	.05	-.10**	.01	.26**	.23**	-.04	-.05*	-.10**

Note * indicates $p < .05$. ** indicates $p < .01$.

Table 3 Girls' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.35**																
3. ADP	-.01	-.04															
4. ODP	.01	.01	.33**														
5. SDP	.00	.01	.25**	.36**													
6. Maternal GWG	.03	.09**	-.02	-.08**	-.04												
7. Pre-pregnancy BMI	.12**	.11**	-.01	-.04	-.01	.17**											
8. Maternal age	-.00	-.06*	.14**	.07**	.01	.00	.17**										
9. Birth weight	-.09**	.00	-.10**	-.17**	-.16**	.27**	.14**	.00									
10. Gestational age	-.07*	-.00	-.11**	-.16**	-.09**	.19**	.05	-.08**	.68**								
11. ACC weight gain	.15**	.11**	.03	.08**	.08**	-.09**	-.03	-.04	-.57**	-.46**							
12. BMI5z	.13**	.19**	-.00	.04	-.02	.16**	.26**	.03	.15**	.00	.16**						
13. Income	-.03	-.10**	-.07**	-.15**	-.19**	.07**	-.06*	.26**	.13**	.06*	-.05*	.03					
14. Education	.03	-.08**	-.04*	-.10**	-.18**	.05	.00	.31**	.07**	.04	-.04	.00	.57**				
15. Material Needs	.10**	.04	.04	.02	.15**	.02	.09**	-.06**	.03	.06*	-.03	.06	-.18**	-.06**			
16. Food Security	.01	.04	.06**	.09**	.10**	-.01	.05	-.02	-.03	-.00	.01	.02	-.26**	-.17**	.33**		
17. Maltreatment	.07**	.02	.12**	.12**	.17**	.06	.05	-.12**	-.01	.01	-.00	.02	-.06*	-.03	.20**	.11**	
18. Breastfeeding	-.04	-.08**	-.03	-.10**	-.17**	.01	-.09**	.16**	.08**	.06*	-.11**	-.02	.25**	.20**	-.02	-.05	-.13**

Note. * indicates $p < .05$. ** indicates $p < .01$.

Main hypothesized bivariate associations by sex and race/ethnicity group

Black.

Most bivariate associations were present for key study variables in the hypothesized pathways and those that were present were in the expected direction. The exceptions were that there was no correlation between child BMI and adrenal PDS scores in boys, r_{boys} = .06, p = .151 and there was no correlation between accelerated weight gain and gonadal PDS scores in girls, r_{girls} = .05, p = .225. See Tables 4 and 5 for correlations among study variables in Black boys and girls.

White.

Most bivariate associations of key study variables in the hypothesized pathways were present and were in the expected directions. The exceptions were that accelerated weight gain was not correlated with child BMI in boys, r_{boys} = -.01, p = .95. Accelerated weight gain was not correlated with gonadal PDS scores in boys or girls, r_{boys} = .05, p = .409, r_{girls} = .07, p = .285, respectively. Child BMI was not correlated with adrenal PDS scores in boys, r_{boys} = .13, p = .068. Child BMI was not correlated with gonadal PDS scores in boys or girls, r_{boys} = .10, p = .134, r_{girls} = .12, p = .087, respectively. See Tables 6 and 7 for correlations among study variables in White boys and girls.

Hispanic

Most bivariate associations of key study variables in the hypothesized pathways were present for the Hispanic group and were in the expected directions except for that accelerated weight gain did not correlate with gonadal PDS scores in boys, r_{boys} = .09, p = .099, and pre-

pregnancy BMI did not correlate with birth weight in boys, r_{boys} = .05, p = .261. See Tables 8 and 9 for correlations among study variables in Hispanic boys and girls.

Other

There were very few bivariate associations for key study variable among the other race/ethnicity group. The sparseness of associations was likely due to a comparatively much smaller sample size of youth with mother's who identified as another race/ethnicity with analytic samples sizes for the bivariate associations ranging from 35 to 103.

Table 4 Black boys' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.25**																
3. ADP	.01	.02															
4. ODP	.03	.00	.37**														
5. SDP	.05	.03	.25**	.40**													
6. Maternal GWG	.01	-.04	-.06	-.05	-.10*												
7. Pre-pregnancy BMI	.04	.01	-.01	-.02	-.02	.16**											
8. Maternal age	.00	.05	.13**	.03	.12**	.02	.26**										
9. Birth weight	-.06	-.01	-.07*	-.07*	-.13**	.26**	.15**	.07*									
10. Gestational age	-.06	-.02	-.05	-.06	-.05	.11**	.04	-.02	.73**								
11. ACC weight gain	.10*	.10*	.10**	.05	.05	-.15**	-.04	-.02	-.54**	-.47**							
12. BMI5z	.06	.09*	.03	.04	-.01	.23**	.21**	.06	.23**	.12**	.09						
13. Income	.03	-.06	-.14**	-.15**	-.20**	.07	.03	.20**	.10**	.04	-.06	.02					
14. Education	.04	-.04	-.11**	-.18**	-.17**	.04	.06	.25**	.09**	.05	-.04	-.01	.53**				
15. Material Needs	.10**	-.00	.10**	.06	.14**	.00	.13**	.06*	.03	.05	.01	-.02	-.04	.06*			
16. Food Security	.07	.03	.05	.05	.10**	-.02	.03	.02	.00	.05	.02	.03	-.20**	-.12**	.28**		
17. Maltreatment	.06	.00	.05	.04	.06	-.03	-.02	-.11**	-.05	.00	.03	.06	.03	.00	.17**	.14**	
18. Breastfeeding	-.03	-.11**	-.06	-.08*	-.13**	.04	.10*	.12**	.08*	.00	-.08	.02	.24**	.22**	.08*	-.03	-.04

Note. * indicates $p < .05$. ** indicates $p < .01$.

Table 5 Black girls' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.33**																
3. ADP	-.01	-.04															
4. ODP	-.00	-.02	.42**														
5. SDP	-.02	-.04	.33**	.43**													
6. Maternal GWG	-.01	.08	-.06	-.12**	-.09*												
7. Pre-pregnancy BMI	.05	.07	.01	-.06	-.03	.17**											
8. Maternal age	.11**	.00	.20**	.14**	.14**	-.01	.19**										
9. Birth weight	-.03	.05	-.16**	-.18**	-.20**	.27**	.14**	-.11**									
10. Gestational age	-.03	.02	-.15**	-.17**	-.13**	.21**	.05	-.16**	.72**								
11. ACC weight gain	.10*	.05	.06	.09*	.11**	-.11*	-.07	.03	-.55**	-.47**							
12. BMI5z	.14**	.20**	.04	.10*	.00	.21**	.25**	.01	.19**	.04	.11*						
13. Income	.09**	-.04	-.15**	-.18**	-.25**	.11**	-.00	.17**	.13**	.06	-.04	.08					
14. Education	.07*	.00	-.12**	-.14**	-.23**	.06	.01	.23**	.10**	.05	-.02	.07	.54**				
15. Material Needs	.02	-.01	.01	-.01	.06	.01	.11**	-.02	.07*	.07*	-.05	.11*	-.03	.04			
16. Food Security	-.00	-.01	.04	.11**	.05	-.06	.03	-.00	-.04	.03	-.03	.03	-.20**	-.15**	.27**		
17. Maltreatment	.03	-.02	.10**	.11**	.10**	.06	.02	-.08*	.05	.04	-.01	.04	-.01	-.04	.19**	.10**	
18. Breastfeeding	.01	-.05	-.05	-.11**	-.12**	.10*	-.02	.08*	.06	.06	-.06	.01	.27**	.23**	.07	.03	-.02
1. Adrenal markers																	

Note. * indicates $p < .05$. ** indicates $p < .01$.

Table 6 White boys' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.26**																
3. ADP	-.04	-.05															
4. ODP	-.01	.06	.12**														
5. SDP	.07	.14**	.12**	.13**													
6. Maternal GWG	.02	.02	-.09	.03	-.12*												
7. Pre-pregnancy BMI	.01	-.04	.02	.01	-.14**	.13*											
8. Maternal age	-.09	-.12*	.16**	-.09*	-.20**	.07	.15**										
9. Birth weight	-.07	.02	-.02	-.07	-.27**	.25**	.18**	.01									
10. Gestational age	-.03	.01	.02	-.08	-.16**	.15**	.08	-.08	.71**								
11. ACC weight gain	.20**	.05	.10	.05	.27**	-.07	-.09	-.04	-.58**	-.49**							
12. BMI5z	.13	.10	-.07	-.01	-.02	.25**	.27**	.00	.35**	.27**	-.01						
13. Income	-.10*	-.20**	.10*	-.09*	-.32**	.07	-.03	.48**	.07	.05	-.11	-.10					
14. Education	-.09	-.23**	.05	-.09*	-.37**	.08	.03	.53**	.15**	.07	-.10	-.00	.62**				
15. Material Needs	.03	.05	.04	.12**	.31**	-.07	-.03	-.25**	-.07	-.03	.16**	-.02	-.40**	-.29**			
16. Food Security	.01	.00	.09	.10*	.20**	-.03	-.10	-.13**	-.01	.01	.03	-.06	-.32**	-.19**	.58**		
17. Maltreatment	-.02	.10	.10	.14**	.10*	-.07	.00	-.12*	-.04	-.03	.06	-.01	-.14**	-.15**	.19**	.20**	
18. Breastfeeding	.01	-.08	-.04	-.10	-.27**	.08	-.09	.22**	.10	.09	-.18**	.05	.34**	.38**	-.16**	-.11	-.17**

Note. * indicates $p < .05$. ** indicates $p < .01$.

Table 7 White girls' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.24**																
3. ADP	-.09	-.03															
4. ODP	-.09	.02	.10*														
5. SDP	.07	.13*	.11*	.25**													
6. Maternal GWG	.07	.06	.00	.01	.01												
7. Pre-pregnancy BMI	.23**	.01	-.05	-.04	.03	.05											
8. Maternal age	-.04	-.18**	.08	-.03	-.22**	.04	.24**										
9. Birth weight	-.15*	-.04	-.07	-.03	-.15**	.25**	.18**	.14**									
10. Gestational age	-.14*	.02	.00	-.04	-.05	.15**	.04	.08	.64**								
11. ACC weight gain	.24**	.07	-.01	-.05	.13*	-.13*	-.00	-.16**	-.64**	-.43**							
12. BMI5z	.19**	.12	.03	-.07	-.00	.11	.24**	.00	.06	-.08	.26**						
13. Income	-.08	-.15**	.03	-.14**	-.37**	.02	-.03	.42**	.17**	.12*	-.09	.01					
14. Education	-.09	-.20**	.05	-.10*	-.40**	.08	.07	.50**	.14**	.11*	-.15*	-.03	.58**				
15. Material Needs	.12*	.08	.08	.08	.36**	.02	.07	-.22**	-.04	.03	.00	-.02	-.43**	-.32**			
16. Food Security	.03	.05	.13*	.03	.26**	-.04	-.03	-.09	-.11	-.05	.08	.03	-.39**	-.21**	.48**		
17. Maltreatment	-.02	-.00	.18**	.25**	.25**	.10	-.01	-.11*	.08	.09	-.09	-.00	-.15**	-.17**	.27**	.22**	
18. Breastfeeding	-.05	-.15*	.14*	-.01	-.26**	.02	-.11	.32**	.05	.10	-.10	-.06	.35**	.39**	-.18**	-.16**	-.15*

Note. * indicates $p < .05$. ** indicates $p < .01$.

Table 8 Hispanic boys' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.20**																
3. ADP	.03	-.06															
4. ODP	-.01	-.01	.12**														
5. SDP	.04	-.01	.20**	.16**													
6. Maternal GWG	.00	.15*	-.04	-.03	-.04												
7. Pre-pregnancy BMI	-.00	.09	-.06	.01	.00	.19**											
8. Maternal age	-.06	.01	.07	-.00	.04	-.03	.08										
9. Birth weight	-.05	.02	-.12**	-.10*	-.12**	.13**	.05	.03									
10. Gestational age	-.10	.03	-.03	-.02	-.05	.15**	-.01	-.05	.66**								
11. ACC weight gain	.17**	.09	.05	.08	.08	-.05	.03	-.07	-.51**	-.37**							
12. BMI5z	.15*	.25**	-.01	-.04	.04	.11	.24**	-.05	.20**	.13	.19**						
13. Income	-.02	.04	.03	-.08*	-.04	.01	-.09	.13**	.04	-.02	-.01	-.09					
14. Education	-.05	.04	-.01	-.05	-.01	.04	-.02	.20**	-.07	-.11**	.01	-.04	.45**				
15. Material Needs	.09	-.07	.04	.11**	.15**	-.06	.07	-.04	-.04	-.08	.05	.02	-.13**	.04			
16. Food Security	-.05	-.03	-.00	.10*	-.00	-.00	.16**	.02	-.04	-.03	.04	-.05	-.27**	-.15**	.33**		
17. Maltreatment	.04	-.03	-.00	.08	.10*	-.04	.08	-.10*	.03	.07	-.01	.11	.04	.04	.23**	.09*	
18. Breastfeeding	-.03	.03	.01	-.07	-.12*	.03	-.10	.16**	.07	.10	-.03	-.07	-.01	-.00	-.10*	-.01	-.08

Note. * indicates $p < .05$. ** indicates $p < .01$.

Table 9 Hispanic girls' study variable correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Adrenal markers																	
2. Gonadal markers	.24**																
3. ADP	-.09	-.03															
4. ODP	-.09	.02	.10*														
5. SDP	.07	.13*	.11*	.25**													
6. Maternal GWG	.07	.06	.00	.01	.01												
7. Pre-pregnancy BMI	.23**	.01	-.05	-.04	.03	.05											
8. Maternal age	-.04	-.18**	.08	-.03	-.22**	.04	.24**										
9. Birth weight	-.15*	-.04	-.07	-.03	-.15**	.25**	.18**	.14**									
10. Gestational age	-.14*	.02	.00	-.04	-.05	.15**	.04	.08	.64**								
11. ACC weight gain	.24**	.07	-.01	-.05	.13*	-.13*	-.00	-.16**	-.64**	-.43**							
12. BMI5z	.19**	.12	.03	-.07	-.00	.11	.24**	.00	.06	-.08	.26**						
13. Income	-.08	-.15**	.03	-.14**	-.37**	.02	-.03	.42**	.17**	.12*	-.09	.01					
14. Education	-.09	-.20**	.05	-.10*	-.40**	.08	.07	.50**	.14**	.11*	-.15*	-.03	.58**				
15. Material Needs	.12*	.08	.08	.08	.36**	.02	.07	-.22**	-.04	.03	.00	-.02	-.43**	-.32**			
16. Food Security	.03	.05	.13*	.03	.26**	-.04	-.03	-.09	-.11	-.05	.08	.03	-.39**	-.21**	.48**		
17. Maltreatment	-.02	-.00	.18**	.25**	.25**	.10	-.01	-.11*	.08	.09	-.09	-.00	-.15**	-.17**	.27**	.22**	
18. Breastfeeding	-.05	-.15*	.14*	-.01	-.26**	.02	-.11	.32**	.05	.10	-.10	-.06	.35**	.39**	-.18**	-.16**	-.15*

Note. * indicates $p < .05$. ** indicates $p < .01$.

Research Question 1

In order to test the whether the thrifty phenotype or fetal overnutrition hypotheses were present and which predicted perceived pubertal timing better (Research Question 1), two multigroup SEM models with sex as the grouping variable were specified for adrenal and gonadal pubertal PDS scores as outcomes.

Main Hypothesized paths by sex

Adrenal results

The model for boys' and girls' adrenal PDS scores had 65 direct effects, 17 exogenous variances and 4 endogenous residuals for boys and girls each, and 102 exogenous covariances for girls and 97 exogenous covariances for boys. The model converged normally within the default number of iterations, with no Heywood cases present, and was overidentified with 70 degrees of freedom. The model evinced excellent fit, Chi Square (df) = 68.59 (70), p= .522; CFI=.1; RMSEA=.000; SRMR=.011, suggesting that the model fit the data well.

Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.28, *SE* = .05, *p* = .000. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.54, *SE* = .04, *p* = .000. Greater accelerated weight gain predicted higher adrenal PDS scores (earlier pubertal timing; path 3), *b* = .02, *SE* = .01, *p* = .045, and greater child BMI, *b* = .21, *SE* = .02, *p* = .000. Greater child BMI did not predict pubertal timing (path 5), *b* = .02, *SE* = .01, *p* = .091. Therefore, hypothesis 1a was partially supported for boys' adrenal results. Also as hypothesized, greater pre-pregnancy BMI and greater maternal GWG predicted higher birth weight (path 6), *b* = .02, *SE* = .004, *p* = .000, *b* = .18, *SE* = .03, *p* = .000, respectively. Higher birth weight predicted

greater BMI (path 7), *b* = .32, *SE* = .04, *p* = .000. See full boys' adrenal results in Figure 3, panel A.

Boys' adrenal indirect effects

There was no thrifty phenotype indirect effect from SDP to pubertal timing through birth weight and accelerated weight gain directly (Figure 2 paths 1→2→3; herein referred to as the thrifty phenotype through accelerated weight gain pathway), *β* = .003, *SE* = .002, *p* = .058, and no indirect effect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2 paths 1→2→4→5; herein referred to as the thrifty phenotype through BMI pathway), *β* = .001, *SE* = .001, *p* = .109. Indirect effects from both pre-pregnancy BMI and maternal GWG hypothesized to operate through birth weight, child BMI, to pubertal timing (Figure 2 paths 6→7→5, herein referred to as the fetal overnutrition pathways) were also not present, *β* = .002, *SE* = .001, *p* = .121, *β* = .003, *SE* = .002, *p* = .110, respectively.

Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.22, *SE* = .03, *p* = .000. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.65, *SE* = .04, *p* = .000. Greater accelerated weight gain predicted higher child BMI, *b* = .25, *SE* = .03, *p* = .000. Greater accelerated weight gain predicted higher adrenal PDS scores (earlier puberty; path 3), *b* = .03, *SE* = .01, *p* = .026 and so did greater child BMI (path 5), *b* = .05, *SE* = .02, *p* = .006. Also as hypothesized, greater pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), *b* = .02, *SE* = .004, *p* = .000, *b* = .20, *SE* = .03, *p* = .000, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .36, *SE* = .04, *p* = .000. See full girls' adrenal results in Figure 3, panel B.

Girls' adrenal indirect effects

There was an indirect effect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2 paths 1→2→4→5), β = .002, *SE* = .001, *p* = .024, but not for the indirect effect from SDP to pubertal timing through birth weight and accelerated weight gain directly (Figure 2 paths 1→2→3), β = .004 *SE* = .002, *p* = .051. There were indirect effects from both pre-pregnancy BMI and maternal GWG hypothesized to operate through birth weight, child BMI, to pubertal timing (Figure 2 paths 6→7→5), β = .004, *SE* = .002, *p* = .022, β = .005, *SE* = .002, *p* = .015, respectively.

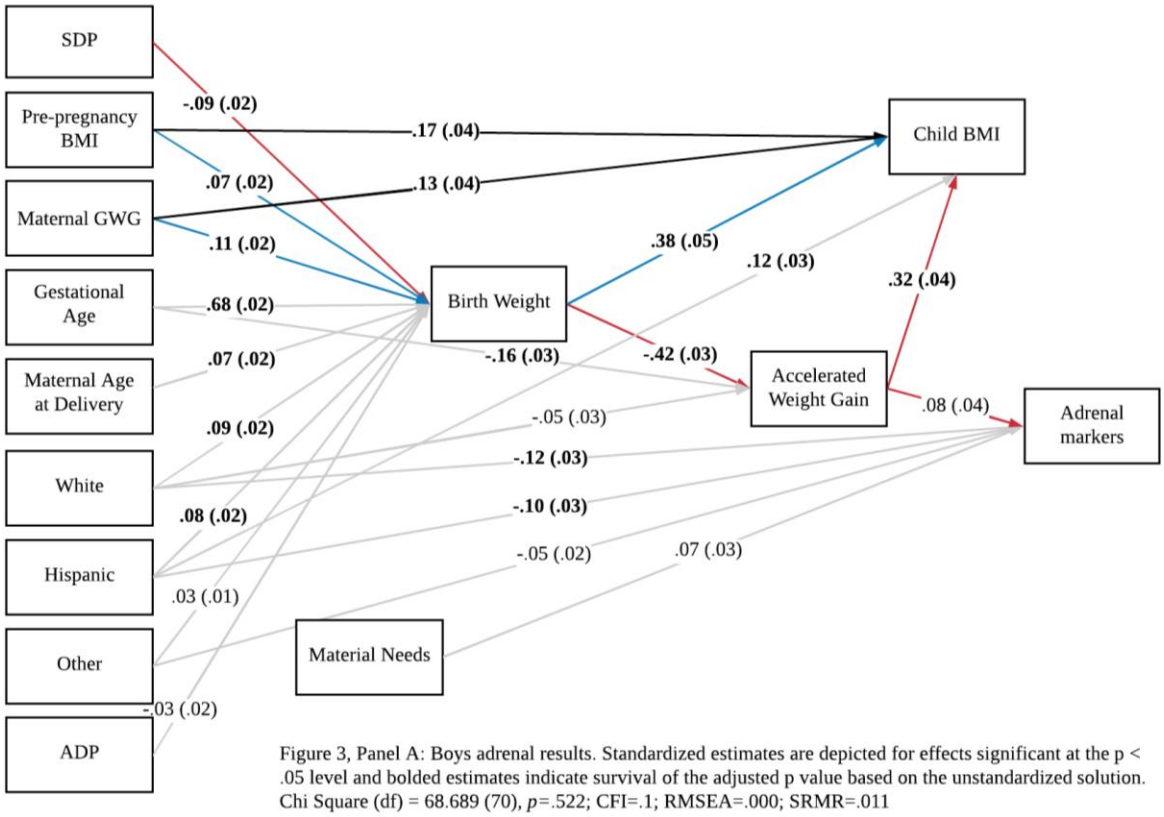

Figure 3, Panel A: Boys adrenal results. Standardized estimates are depicted for effects significant at the p < .05 level and bolded estimates indicate survival of the adjusted p value based on the unstandardized solution. Chi Square (df) = 68.689 (70), *p*=.522; CFI=.1; RMSEA=.000; SRMR=.011

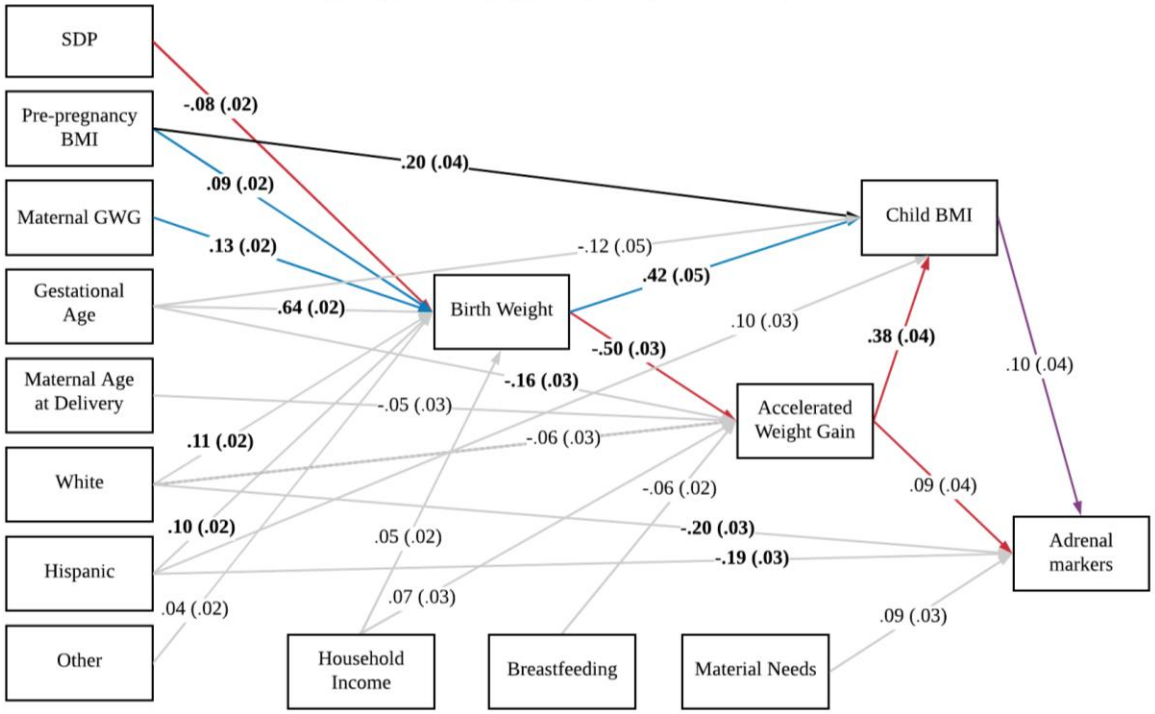

Figure 3, Panel B: Girls adrenal results.

Figure 3 Boys' and girls' adrenal results

Gonadal results

The model for boys' and girls' gonadal pubertal PDS scores had 65 direct effects, 17 exogenous variances and 4 endogenous residuals for boys and girls each, and 102 exogenous covariances for girls and 97 exogenous covariances for boys. The model converged normally within the default number of iterations with no Heywood cases present and was overidentified with 70 degrees of freedom. The model evinced excellent model fit, Chi Square (df) = 68.466 (70), p =.530; CFI=.1; RMSEA=.000; SRMR=.011, suggesting that the model fit the data well.

Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), b = .28, SE = .05, p = .000. Lower birth weight predicted greater accelerated weight gain (path 2), b = -.54, SE = .04, p = .000. Greater accelerated weight gain predicted higher gonadal PDS scores (earlier pubertal timing; path 3), b = .02, SE = .01, p = .003 and greater child BMI (path 4), b = .21, SE = .02, p = .000. Greater child BMI also predicted higher gonadal PDS scores (earlier pubertal timing; path 5), b = .04, SE = .01, p = .002. Also as hypothesized, greater pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), b = .02, SE = .004, p = .000, b = .18, SE = .03, p = .000, respectively. Higher birth weight predicted greater BMI (path 7), b = .33, SE = .04, p = .000. See full boys' gonadal results in Figure 4, panel A.

Boys' gonadal indirect effects

There was an indirect effect from SDP to pubertal timing through birth weight and accelerated weight gain directly (Figure 2 paths 1→2→3), β = .004, SE = .002, p = .013, and also from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2 paths 1→2→4→5), β = .001, SE = .001, p = .007. There were also indirect effects from

both pre-pregnancy BMI and maternal GWG hypothesized to operate through birth weight, child BMI, to pubertal timing (Figure 2 paths 6→7→5), β = .003, *SE* = .001, *p* = .014, β = .005, *SE* = .002, *p* = .007, respectively.

Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.22, *SE* = .05, *p* = .000. Lower birth weight then predicted greater accelerated weight gain (path 2), *b* = -.66, *SE* = .04, *p* = .000. Greater accelerated weight gain predicted higher gonadal PDS scores (earlier pubertal timing; path 3), *b* = .02, *SE* = .01, *p* = .047 and also greater child BMI (path 4), *b* = .26, *SE* = .03, *p* = .000. Greater child BMI predicted higher gonadal PDS scores (earlier pubertal timing; path 5), *b* = .06, *SE* = .01, *p* = .000. Also as hypothesized, greater pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), *b* = .02, *SE* = .004, *p* = .000, *b* = .20, *SE* = .03, *p* = .000, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .36, *SE* = .04, *p* = .000. See full girls' gonadal results in Figure 3, panel D.

Girls' gonadal indirect effects

There was an indirect effect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2 paths 1→2→4→5, β = .003, *SE* = .00, *p* = .001, but no indirect effect from SDP to pubertal timing through birth weight and accelerated weight gain directly (Figure 2 paths 1→2→3), β = .004, *SE* = .002, *p* = .070. There were also indirect effects from both pre-pregnancy BMI and maternal GWG hypothesized to operate through birth weight, child BMI, to pubertal timing (Figure 2 paths 6→7→5), β = .006, *SE* = .002, *p* = .002, β = .009, *SE* = .002, *p* = .000, respectively.

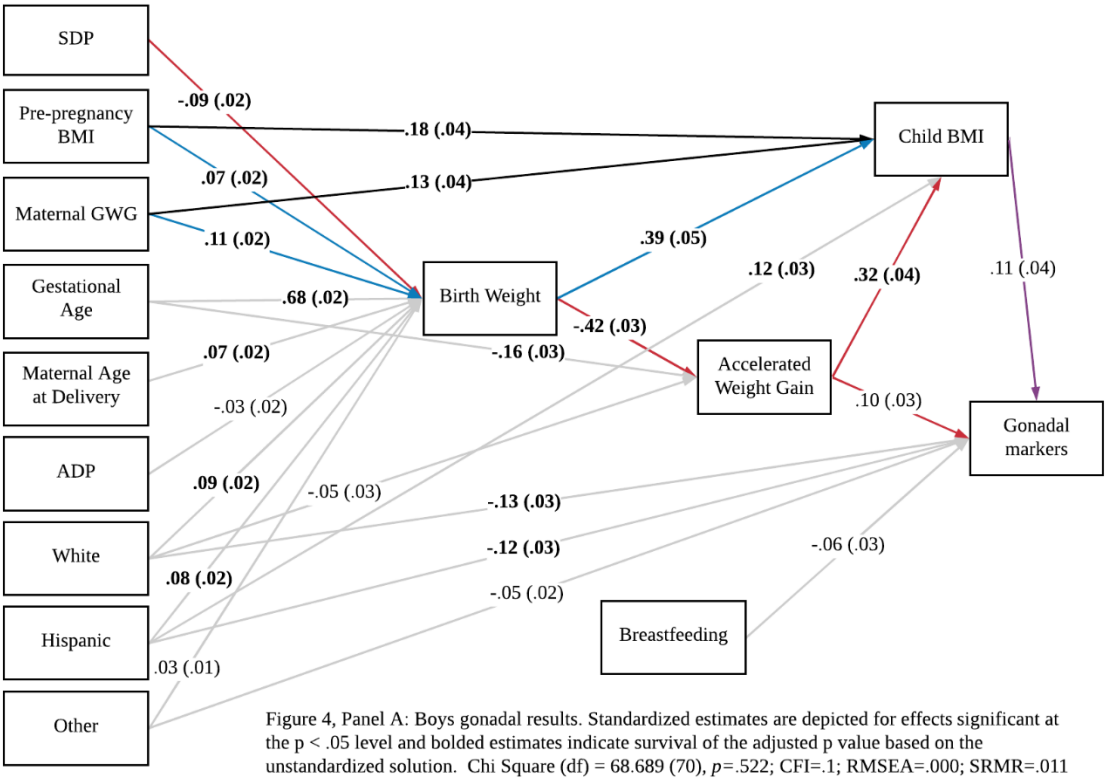

Figure 4, Panel A: Boys gonadal results. Standardized estimates are depicted for effects significant at the p < .05 level and bolded estimates indicate survival of the adjusted p value based on the unstandardized solution. Chi Square (df) = 68.689 (70), *p*=.522; CFI=.1; RMSEA=.000; SRMR=.011

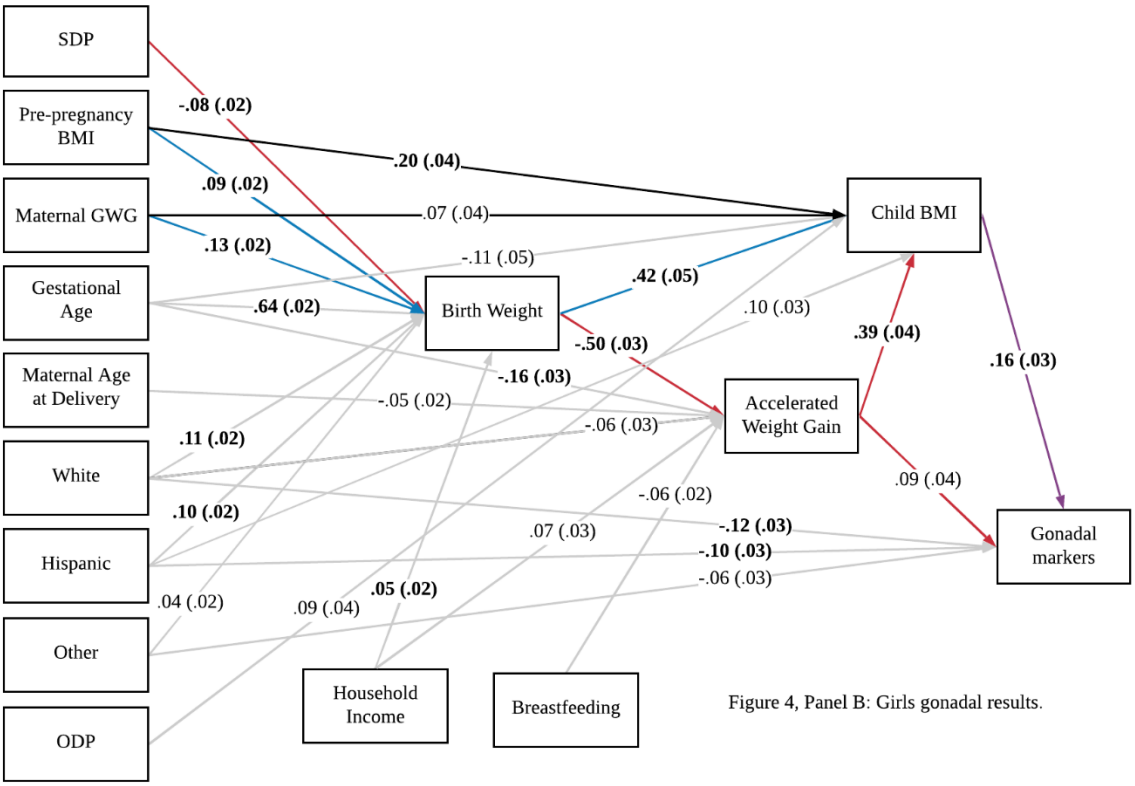

Figure 4, Panel B: Girls gonadal results.

Figure 4 Boys' and girls' gonadal results

Determining the strongest pathways

The formal tests of sex differences (hypotheses 1a and 1b) and the thrifty phenotype vs. fetal overnutrition hypotheses within sex (hypothesis 1c) were conducted after determining the strongest thrifty phenotype (through accelerated weight gain vs. through child BMI) and fetal overnutrition (beginning with pre-pregnancy BMI vs. with GWG) indirect effects among boys and girls, in order to reduce the number of model comparisons. This was accomplished using model constraints and Wald tests; Wald tests that yield a significant chi-square value when two indirect effects are constrained to equality indicates a reduction in model fit and in this case that the indirect effects are non-equivalent. The stronger indirect effect was then determined by examining and comparing the standardized estimates of the indirect effects.

Boys' adrenal

These comparisons were not made because none of the indirect effects were different from zero at the $p < .05$ significance level.

Girls' adrenal

The Wald test for the thrifty phenotype pathways comparing the size of the indirect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2, paths 1→2→4→5) and from SDP to pubertal timing through birth weight and accelerated weight gain directly (Figure 2, paths 1→2→3) yielded a χ^2 value of 1.05 (1), $p = .306$, indicating that the indirect effects could be constrained to equality without a decrement in model fit. The thrifty phenotype pathway operating from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing was carried forward for future tests since it passed the $p < .05$ threshold, whereas the thrifty phenotype pathway from SDP to pubertal timing through birth weight and

accelerated weight gain directly did not. The Wald test for the indirect effects from both pre-pregnancy BMI and maternal GWG through birth weight, child BMI, to pubertal timing (Figure 2, paths 6→7→5) yielded a χ^2 value of 5.74 (1), p = .017, indicating that the indirect effects were non-equivalent and the fetal overnutrition pathway beginning with maternal GWG was interpreted as the stronger indirect effect.

Boys' gonadal

The Wald test for the thrifty phenotype pathways comparing the size of the indirect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2, paths 1→2→4→5) and from SDP to pubertal timing through birth weight and accelerated weight gain directly (Figure 2, paths 1→2→3) yielded a χ^2 value of 2.60 (1), p = .107, indicating that the indirect effects could be constrained to equality without a decrement in model fit. The thrifty phenotype indirect effect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2, paths 1→2→4→5) was carried forward in future tests for better comparison with the same indirect effect in girls. The Wald test for the indirect effects from both pre-pregnancy BMI and maternal GWG through birth weight, child BMI, to pubertal timing (Figure 2, paths 6→7→5) yielded a χ^2 value of 6.69 (1), p = .010, indicating that the indirect effects were non-equivalent. Thus, the fetal overnutrition pathway beginning from maternal GWG was interpreted as the stronger indirect effect.

Girls' gonadal

The Wald test for the thrifty phenotype pathways comparing the size of the indirect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2, paths 1→2→4→5) and from SDP to pubertal timing through birth weight and accelerated weight

gain directly (Figure 2, paths 1→2→3) yielded a χ^2 value of 0.268 (1), p = .605, indicating that the indirect effects could be constrained to equality without a decrement in model fit. The thrifty phenotype pathway indirect effect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing was carried forward for future tests as it was statistically different from 0 at the $p < .05$ level. The Wald test for the indirect effects from both pre-pregnancy BMI and maternal GWG hypothesized to operate through birth weight, child BMI, to pubertal timing (Figure 2, paths 6→7→5) yielded a χ^2 value of 12.08 (1), p = .001, indicating that the indirect effects were non-equivalent. Thus, the fetal overnutrition pathway beginning from maternal GWG was interpreted as the stronger indirect effect.

In summary, the strongest thrifty phenotype pathway was the indirect effect from SDP through birth weight, accelerated weight gain, and child BMI to pubertal timing (Figure 2, paths 1→2→4→5) for girls' adrenal PDS scores, and boys' and girls' gonadal PDS scores. The strongest fetal overnutrition pathway was the indirect effect from maternal GWG through birth weight, and child BMI to pubertal timing for girls' adrenal PDS scores, and boys' and girls' gonadal PDS scores.

Between sex differences in the hypothesized pathways.

The formal test of hypothesis 1a compared the magnitude of the thrifty phenotype pathway through child BMI across boys and girls. In the adrenal model, the Wald test for the thrifty phenotype pathway through child BMI (Figure 2, paths 1→2→4→5) for girls and boys yielded a χ^2 value of 1.47 (1), p = .226, indicating that the indirect effects could be constrained to equality across sex without a decrement in model fit. In the gonadal model, the Wald test for the thrifty phenotype pathway through child BMI between girls and boys yielded a non-significant χ^2

value, 1.97 (1), p = .160, indicating that the indirect effects could be constrained to equality across sex without a decrement in model fit.

The formal test of hypothesis 1b compared the magnitude of the overnutrition pathway beginning with maternal GWG across boys and girls. In the adrenal model, when the indirect effects for boys' and girls' fetal overnutrition pathways from maternal GWG (Figure 2, paths 6→7→5) were constrained to equality, the Wald test yielded a χ^2 value, of 1.80 (1), p = .180, indicating that the indirect effects could be constrained to equality without a decrement in model fit. Finally, in the gonadal model, when the indirect effects for boys' and girls' fetal overnutrition pathways from maternal GWG (Figure 2, paths 6→7→5) were constrained to equality, the Wald test yielded a χ^2 value, of 2.53 (1), p = .112, indicating that the indirect effects could be constrained to equality without a decrement in model fit.

Within sex differences in the hypothesized pathways

Finally, the indirect effects for the optimal thrifty phenotype and fetal overnutrition pathways were compared within sex (Hypothesis 1c).

Adrenal

The indirect effects for the girls' thrifty phenotype pathway operating through BMI (Figure 2, paths 1→2→4→5) and girls' maternal GWG (Figure 2, paths 6→7→5) pathways were constrained to equality. The Wald test yielded a χ^2 value of 3.13 (1), p = .077, indicating that the indirect effects could be constrained to equality without a decrement in model fit. These comparisons were not made for boys because none of the indirect effects were different from zero at the p <.05 significance level.

Gonadal

The indirect effects for the girls' thrifty phenotype through child (Figure 2, paths 1→2→4→5) BMI and girls' maternal GWG pathways (Figure 2, paths 6→7→5) were constrained to equality, the Wald test yielded a χ^2 value of 4.04 (1), $p = .045$, indicating that the indirect effects were non-equivalent and the maternal GWG indirect effect was interpreted as the stronger effect. The same comparison was made in boys and the Wald test yielded a χ^2 value of 2.85 (1), $p = .092$, indicating that the indirect effects could be constrained to equality without a decrement in model fit.

Research Question 1 Summary

Support for hypothesis 1a was mixed. All hypothesized paths of the thrifty phenotype pathways were supported in girls for the adrenal markers and boys' and girls' gonadal models but not in the adrenal model for boys. There were also no indirect effects for the thrifty phenotype pathways in the boys' adrenal model and only the thrifty phenotype pathway through child BMI was present in the girls' adrenal model. Contrary to what was hypothesized, the thrifty phenotype pathway did not more strongly predict pubertal timing in either the adrenal or gonadal models for boys.

Support for hypothesis 1b was also mixed. All paths were present for girls in the adrenal model and boys' and girls' gonadal models but not in the in the boys' adrenal model. All of the hypothesized fetal overnutrition pathways for pre-pregnancy BMI and maternal GWG were present in the girls' adrenal model, boys' and girls' gonadal model but not the boys' adrenal model. Contrary to hypotheses, the fetal overnutrition pathway predicted puberty equally well in boys and girls in both the adrenal and gonadal models.

Hypothesis 1c was mixed. Contrary to hypotheses, the thrifty phenotype pathway was equivalent to the maternal GWG fetal overnutrition pathway within boys in both the adrenal and gonadal models. The same was true for the girls' adrenal model. However, as hypothesized, the maternal GWG fetal overnutrition pathway did predict puberty better within girls in the gonadal model. Please see Table 2 for a summary of boys' and girls' results.

Table 10 Summary of key findings for research question 1: Boys and girls by pubertal marker

	Boys		Girls	
	Adrenal	**Gonadal**	**Adrenal**	**Gonadal**
Thrifty Phenotype	**Partial Support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater accelerated weight → earlier pubertal timing **Confirmed indirect effects:** None	**Full support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater accelerated weight and greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** 1→2→4→5 1→2→3	**Partial Support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater BMI z-score and greater accelerated weight gain → earlier pubertal timing **Confirmed indirect effects:** 1→2→4→5	**Full Support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater BMI z-score and greater accelerated weight gain → earlier pubertal timing **Confirmed indirect effects:** 1→2→4→5
Fetal Overnutrition	**Partial Support** Higher pre-pregnancy BMI/excessive GWG → higher birth weight Higher birth weight → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Full Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** 6→7→5 for both pre-pregnancy BMI/greater GWG	**Full Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** 6→7→5 for both pre-pregnancy BMI/excessive GWG	**Full Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** 6→7→5 for both pre-pregnancy BMI/excessive GWG

Research Question 2

Models for research question 2 were run separately by sex for each race/ethnicity group. Therefore, six multi-group SEM models were estimated to examine race/ethnicity differences in Black, White and Hispanic youth within each sex for both adrenal and gonadal PDS scores.

Adrenal results by race/ethnicity group

Boys

The model for boys by race/ethnicity for adrenal PDS scores had 53 direct effects, 17 exogenous variances and 4 endogenous residuals for each race/ethnicity group (Black, White Hispanic), and 51, 57, and 39 exogenous covariances for each group, respectively. The model converged normally within the default number of iterations with no Heywood cases present and was overidentified with 108 degrees of freedom. The model evinced excellent model fit, Chi Square(df) = 112.331 (108), p =.368; CFI=.1; RMSEA=.007; SRMR=.023, suggesting that the model fit the data well. No modification indices were indicated. See Figure 5, Panels A, B, C for Black, White and Hispanic boys' estimates, respectively.

Black Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), b = -27., SE = .08, p = .000. Lower birth weight predicted greater accelerated weight gain (path 2), b = -.55, SE = .07, p = .000. Greater accelerated weight gain predicted greater child BMI (path 4), b = .18, SE = .03, p = .000, but not pubertal timing (path 3), b = .01, SE = .01, p = .351. Greater child BMI also did not predict pubertal timing (path 5), b = .02, SE = .02, p = .459. As hypothesized, greater pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), b = .01, SE

= .01, *p* = .014, *b* = .24, *SE* = .04, *p* = .000, respectively. Higher birth weight predicted greater child BMI (path 7), *b* = .31, *SE* = .07, *p* = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

White Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.29, *SE* = .10, *p* = .003. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.49, *SE* = .06, *p* = .000. Greater accelerated weight gain predicted higher adrenal PDS scores (earlier pubertal timing; path 3), *b* = .03, *SE* = .02, *p* = .045 and also greater child BMI (path 4), *b* = .18, *SE* = .07, *p* = .008. Greater child BMI did not predict pubertal timing (path 5), *b* = .04, *SE* = .02, *p* = .120. Also as hypothesized, greater pre-pregnancy BMI and greater maternal GWG predicted higher birth weight (path 6), *b* = .22, *SE* = .07, *p* = .049, *b* = .22, *SE* = .07, *p* = .001, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .33, *SE* = .09, *p* = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

Hispanic Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = 27., *SE* = .10, *p* = .009. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.56, *SE* = .07, *p* = .000. Greater accelerated weight gain predicted greater child BMI (path 4), *b* = .25, *SE* = .05, *p* = .000 but not pubertal timing (path 3), *b* = .03, *SE* = .02, *p* = .055. Greater child BMI did not predict pubertal timing (path 5), *b* = .02, *SE* = .02, *p* = .250. Contrary to hypotheses, high pre-pregnancy BMI and excessive maternal GWG did not predict higher birth weight (path 6), *b* = .01, *SE* = .01, *p* = .217, *b* = .04, *SE* = .06, *p* = .490, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .32, *SE* = .08, *p* = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

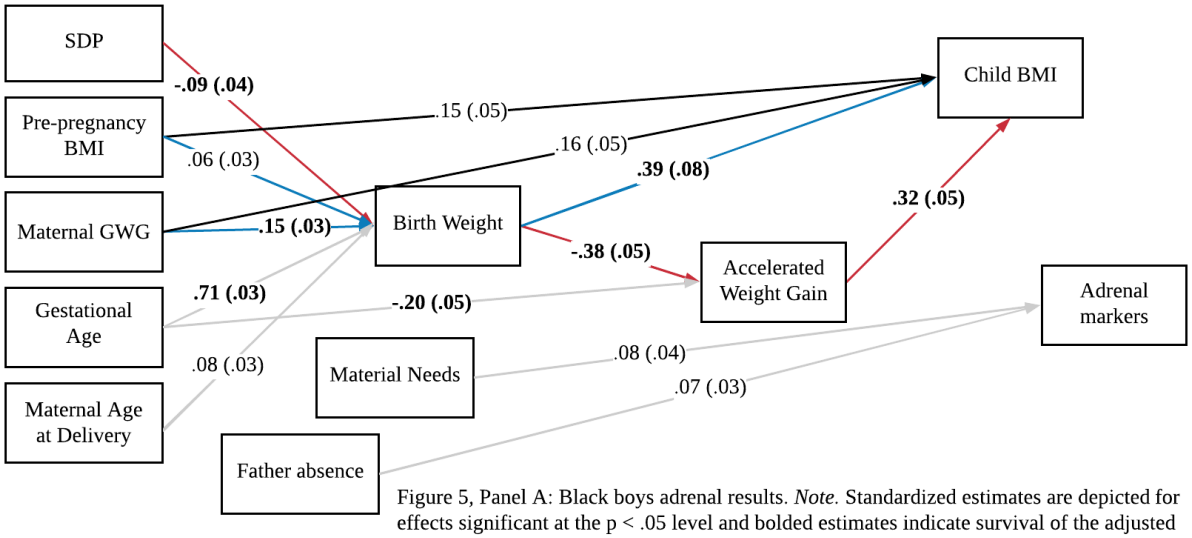

Figure 5, Panel A: Black boys adrenal results. *Note.* Standardized estimates are depicted for effects significant at the p < .05 level and bolded estimates indicate survival of the adjusted p value based on the unstandardized solution. Chi Square(df) = 112.331 (108), p =.368; CFI=.998; RMSEA=.007; SRMR=.023

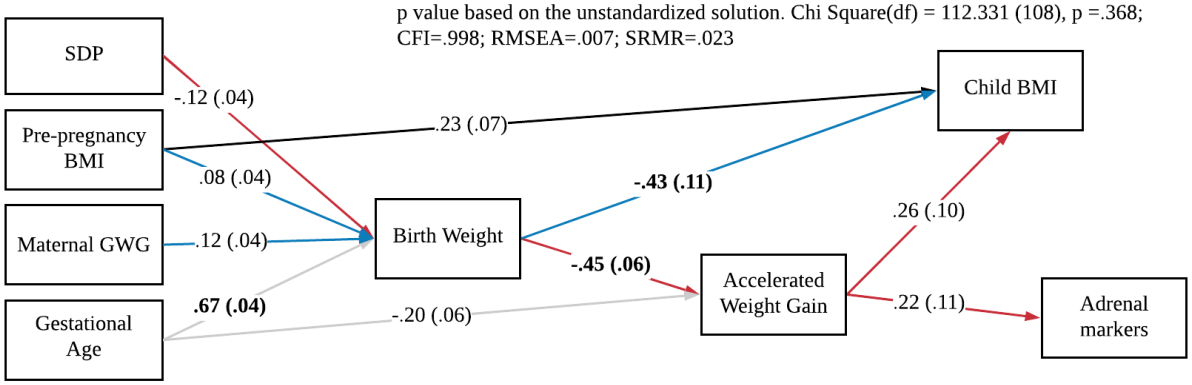

Figure 5, Panel B: White boys adrenal results.

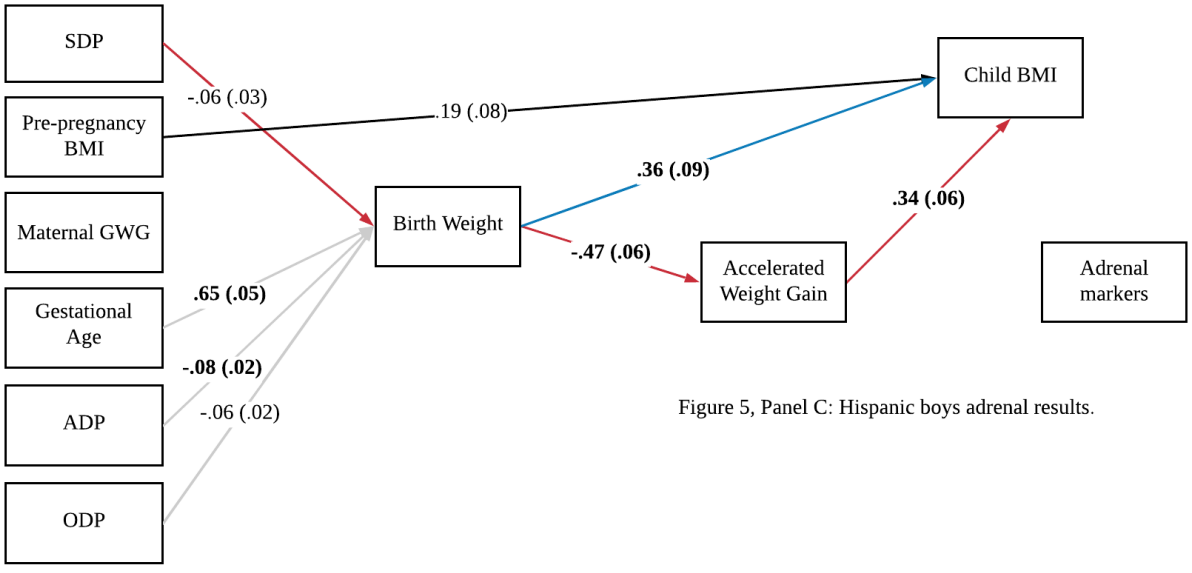

Figure 5, Panel C: Hispanic boys adrenal results.

Figure 5 Boys adrenal results by race/ethnicity

Girls

The model for girls by race/ethnicity for adrenal PDS scores 53 direct effects, 17 exogenous variances and 4 endogenous residuals for each race/ethnicity group (Black, White Hispanic), and 54, 51, and 43 exogenous covariances for each group, respectively. The model converged normally within the default number of iterations with no Heywood cases present and was overidentified with 106 degrees of freedom. The model evinced excellent model fit, Chi Square(df) = 108.508 (106), p =.414; CFI=.1; RMSEA=.006; SRMR=.025, suggesting that the model fit the data well. No modification indices were indicated. See Figure 6, Panels A, B, C for Black, White and Hispanic girls' estimates, respectively.

Black Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), b = -.20, SE = .07, p = .005. Lower birth weight then predicted greater accelerated weight gain (path 2), b = -.59, SE = .07, p = .000. Greater accelerated weight gain predicted greater child BMI (path 3), b = .22, SE = .04, p = .000 but not pubertal timing (path 4), b = .03, SE = .02, p = .156. Greater child BMI predicted higher adrenal PDS scores (earlier pubertal timing; path 5), b = .07, SE = .03, p = .015. As hypothesized, greater pre-pregnancy BMI and maternal GWG predicted higher birth weight (path 6), b = .02, SE = .01, p = .003, b = .15, SE = .04, p = .000, respectively. Higher birth weight predicted greater child BMI (path 7), b = .39, SE = .06, p = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

White Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), b = -.24, SE = .09, p = .005. Lower birth weight predicted greater accelerated weight gain (path 2), b = -.77, SE = .07,

p = .000. Greater accelerated weight gain predicted greater child BMI (path 4), *b* = .29, *SE* = .08, *p* = .000, but not pubertal timing (path 3), *b* = .04, *SE* = .02, *p* = .074. Greater child BMI also did not predict pubertal timing (path 5), *b* = .05, *SE* = .03, *p* = .077. Also as hypothesized, greater pre-pregnancy BMI greater maternal GWG predicted higher birth weight (path 6), *b* = .03, *SE* = .01, *p* = .002, *b* = .26, *SE* = .07, *p* = .000, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .33, *SE* = .11, *p* = .003.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

Hispanic Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.20, *SE* = .09, *p* = .029. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.65, *SE* = .08, *p* = .000. Greater accelerated weight gain predicted greater child BMI, *b* = .27, *SE* = .04, *p* = .000 but not pubertal timing, *b* = .04, *SE* = .02, *p* = .051. Greater child BMI did not predict pubertal timing, *b* = .02, *SE* = .03, *p* = .546. Also as hypothesized, high pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), *b* = .02, *SE* = .01, *p* = .041, *b* = .22, *SE* = .05, *p* = .000, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .35, *SE* = .08, *p* = .001.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

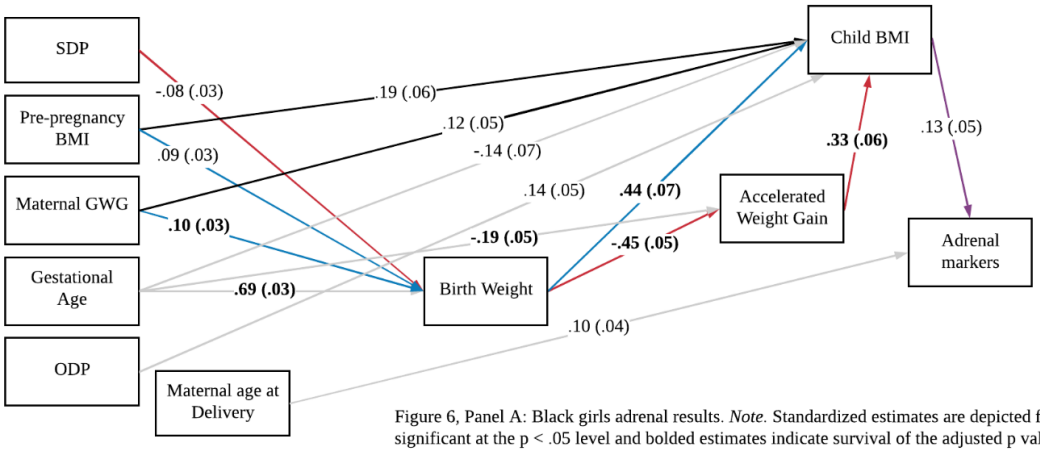

Figure 6, Panel A: Black girls adrenal results. *Note*. Standardized estimates are depicted for effects significant at the p < .05 level and bolded estimates indicate survival of the adjusted p value based on the unstandardized solution. Chi Square(df) = 108.508 (106), p =.414; CFI=.998; RMSEA=.006; SRMR=.025

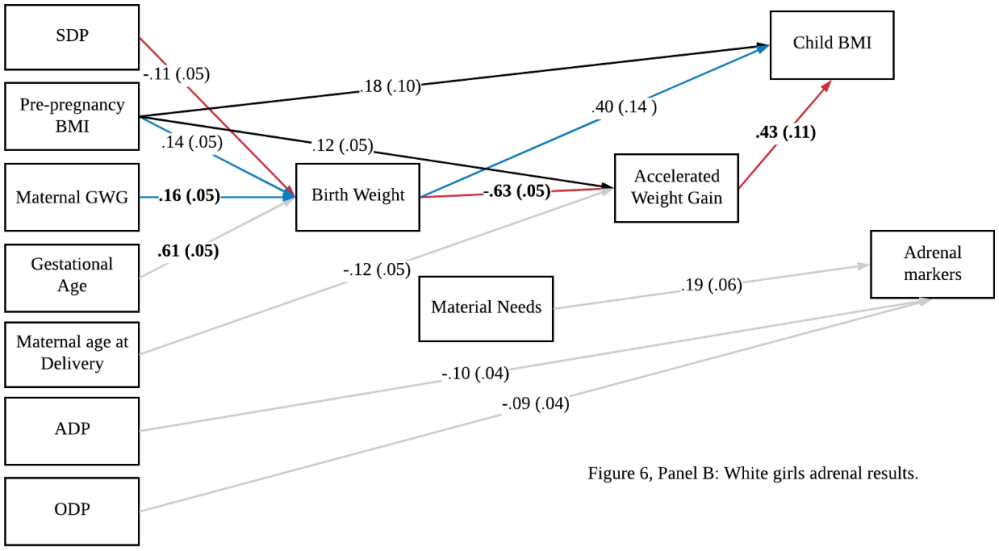

Figure 6, Panel B: White girls adrenal results.

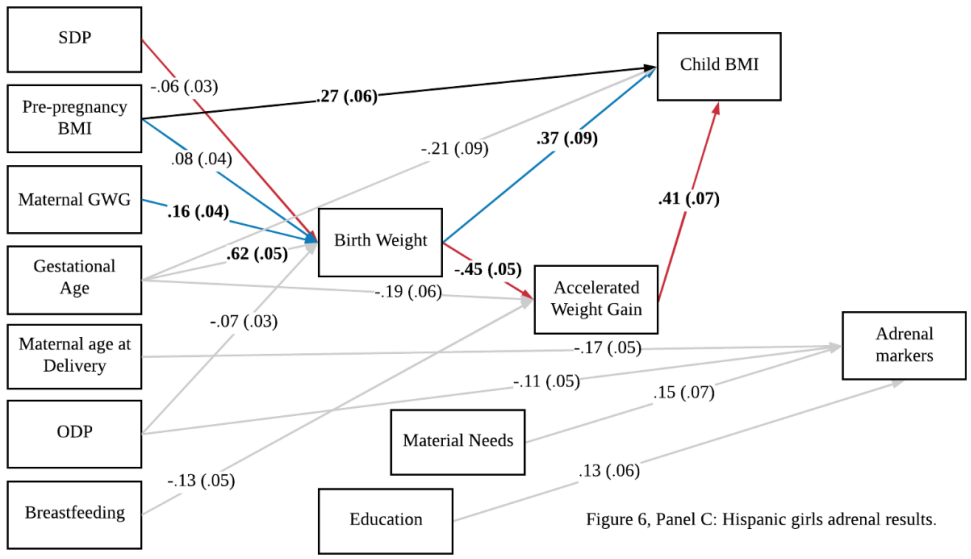

Figure 6, Panel C: Hispanic girls adrenal results.

Figure 6 Girls adrenal results by race/ethnicity

Gonadal results by race/ethnicity group

Boys

The model for boys by race/ethnicity for gonadal PDS scores had 53 direct effects, 17 exogenous variances and 4 endogenous residuals for each race/ethnicity group (Black, White Hispanic), and 51, 57, and 39 exogenous covariances for each group, respectively. The model converged normally within the default number of iterations with no Heywood cases present and was overidentified with 108 degrees of freedom. The model evinced excellent model fit, Chi Square(df) = 112.235 (108), p =.371; CFI=.998; RMSEA=.007; SRMR=.023, suggesting that the model fit the data well. No modification indices were indicated. See Figure 7, Panels A, B, C for Black, White and Hispanic boys' estimates, respectively.

Black Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), b = -.28, SE = .07, p = .000. Lower birth weight predicted greater accelerated weight gain (path 2), b = -.55, SE = .07, p = .000. Greater accelerated weight gain predicted greater child BMI (path 4), b = .18, SE = .03, p = .000 but not pubertal timing (path 3), b = .02, SE = .01, p = .065. Greater child BMI predicted higher gonadal score (earlier pubertal timing; path 5), b = .04, SE = .02, p = .041. As hypothesized, higher pre-pregnancy BMI and greater maternal GWG predicted higher birth weight (path 6), b = .01, SE = .01, p = .531, b = .24, SE = .04, p = .000, respectively. Higher birth weight predicted greater child BMI (path 7), b = .32, SE = .06, p = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

White Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.29, *SE* = .10, *p* = .004. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.49, *SE* = .06, *p* = .000. Greater accelerated weight gain predicted greater child BMI (path 4) *b* = .20, *SE* = .07, *p* = .007, but not pubertal timing (path 3), *b* = .02, *SE* = .02, *p* = .401. Greater child BMI did not predict pubertal timing, *b* = .03, *SE* = .02, *p* = .270. Greater maternal GWG predicted higher birth weight (path 6), *b* = .22, *SE* = .07, *p* = .001, but pre-pregnancy BMI did not, *b* = .02, *SE* = .01, *p* = .053, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .33, *SE* = .09, *p* = .001.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

Hispanic Boys

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.27, *SE* = .10, *p* = .008. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.57, *SE* = .07, *p* = .000. Greater accelerated weight gain predicted greater child BMI (path 4), *b* = .25, *SE* = .05, *p* = .000 but not pubertal timing (path 3), *b* = .03, *SE* = .02, *p* = .190. Greater child BMI predicted higher gonadal PDS score (earlier pubertal timing; path 5), *b* = .07, *SE* = .02, *p* = .002. Contrary to hypotheses, pre-pregnancy BMI and maternal GWG did not predict birth weight (path 6), *b* = .01, *SE* = .01, *p* = .204, *b* = .03, *SE* = .06, *p* = .582, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .36, *SE* = .008, *p* = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

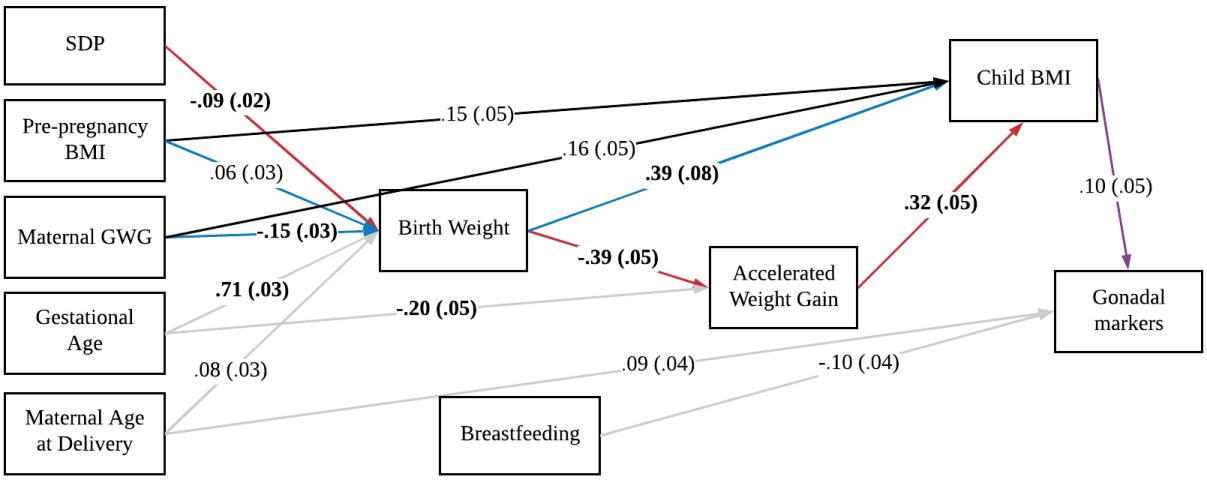

Figure 7, Panel A: Black boys gonadal results. Standardized estimates are depicted for effects significant at the p < .05 level and bolded estimates indicate survival of the adjusted p value based on the unstandardized solution. Chi Square(df) = 112.235 (108), p =.371; CFI=.998; RMSEA=.007; SRMR=.023

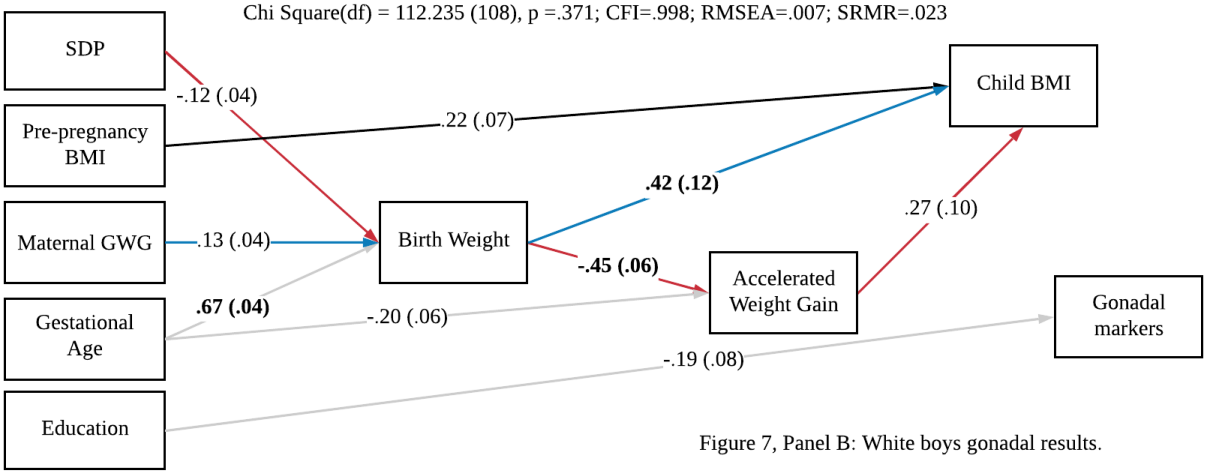

Figure 7, Panel B: White boys gonadal results.

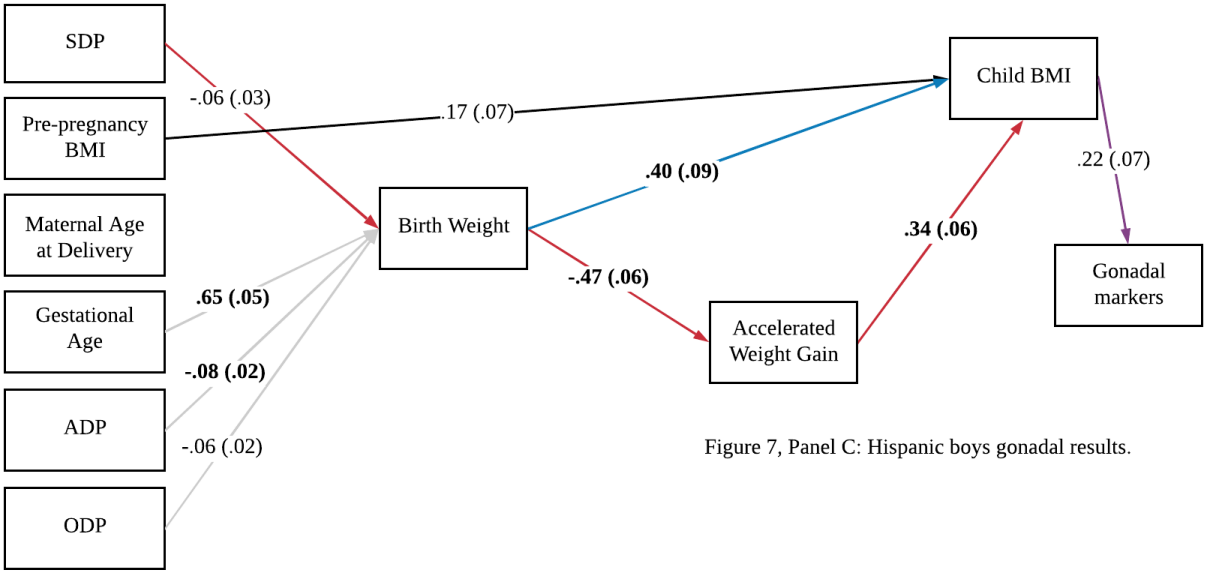

Figure 7, Panel C: Hispanic boys gonadal results.

Figure 7 Boys gonadal results by race/ethnicity

Girls

The model for girls by race/ethnicity for gonadal PDS scores had 53 direct effects, 17 exogenous variances and 4 endogenous residuals for each race/ethnicity group (Black, White Hispanic), and 54, 51, and 43 exogenous covariances for each group, respectively. The model converged normally within the default number of iterations with no Heywood cases present and was overidentified with 106 degrees of freedom. The model evinced excellent fit, Chi Square(df) = 109.051 (106), p =.400; CFI=.998; RMSEA=.006; SRMR=.026, suggesting that the model fit the data well. No modification indices were indicated. See Figure 8, Panels A, B, C for Black, White and Hispanic girls' estimates, respectively.

Black Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), b = -.20, SE = .07, p = .005. Lower birth weight then predicted greater accelerated weight gain (path 2), b = -.59, SE = .07, p = .000. Greater accelerated weight gain predicted greater child BMI (path 4), b = .23, SE = .04, p = .000 but not pubertal timing (path 3), b = .02, SE = .02, p = .200. Greater child BMI predicted higher gonadal PDS scores (earlier pubertal timing; path 5), b = .07, SE = .02, p = .000. As hypothesized, greater pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), b = .02, SE = .01, p = .003, b = .15, SE = .04, p = .000, respectively. Higher birth weight predicted greater child BMI (path 7), b = .39, SE = .06, p = .000.

Indirect effects. There were only indirect effects for the fetal overnutrition pathways operating from maternal GWG and pre-pregnancy BMI, β = .007, SE = .003, p = .023, β = .008, SE = .003, p = .012, respectively.

White Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.25, *SE* = .09, *p* = .006. Lower birth weight then predicted greater accelerated weight gain (path 2), *b* = -.77, *SE* = .07, *p* = .000. Greater accelerated weight gain predicted greater child BMI (path 4), *b* = .30, *SE* = .08, *p* = .000, but not pubertal timing (path 3), *b* = -.03, *SE* = .03, *p* = .336. Greater child BMI predicted higher gonadal PDS scores (earlier pubertal timing; path 5), *b* = .07, *SE* = .03, *p* = .018. As hypothesized, greater pre-pregnancy BMI and greater maternal GWG predicted higher birth weight (path 6), *b* = .03, *SE* = .01, *p* = .002, *b* = .26, *SE* = .07, *p* = .000, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .32, *SE* = .11, *p* = .005.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

Hispanic Girls

As hypothesized, greater SDP predicted lower birth weight (path 1), *b* = -.20, *SE* = .09, *p* = .030. Lower birth weight predicted greater accelerated weight gain (path 2), *b* = -.66, *SE* = .08, *p* = .000. Greater accelerated weight gain predicted greater child BMI (path 4), *b* = .27, *SE* = .04, *p* = .000 but not pubertal timing (path 3), *b* = .04, *SE* = .03, *p* = .100. Greater child BMI predicted higher gonadal PDS scores (earlier pubertal timing; path 5), *b* = .06, *SE* = .03, *p* = .039. High pre-pregnancy BMI and excessive maternal GWG predicted higher birth weight (path 6), *b* = .02, *SE* = .01, *p* = .039, *b* = .22, *SE* = .05, *p* = .000, respectively. Higher birth weight predicted greater BMI (path 7), *b* = .35, *SE* = .08, *p* = .000.

Indirect effects. There was no evidence for any of the hypothesized indirect effects.

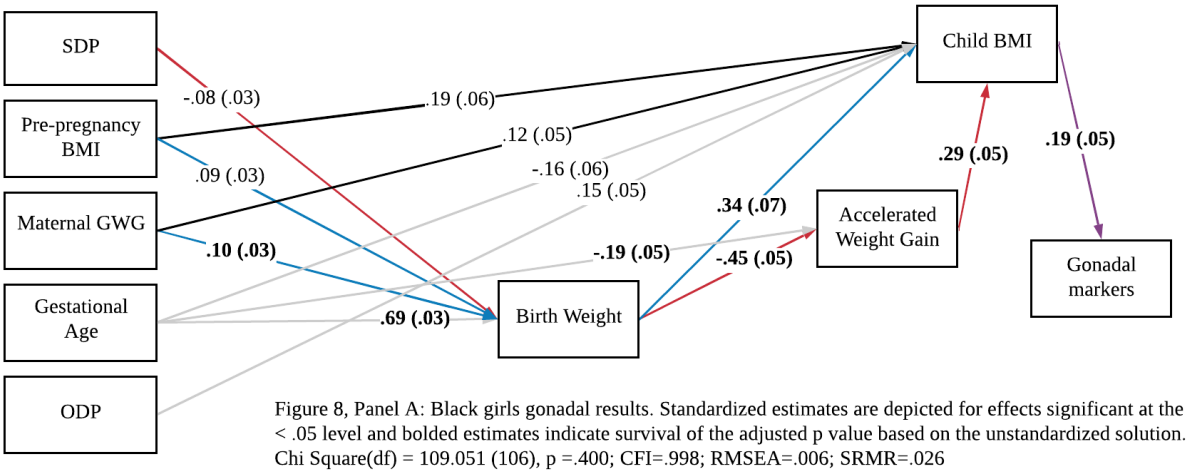

Figure 8, Panel A: Black girls gonadal results. Standardized estimates are depicted for effects significant at the p < .05 level and bolded estimates indicate survival of the adjusted p value based on the unstandardized solution. Chi Square(df) = 109.051 (106), p =.400; CFI=.998; RMSEA=.006; SRMR=.026

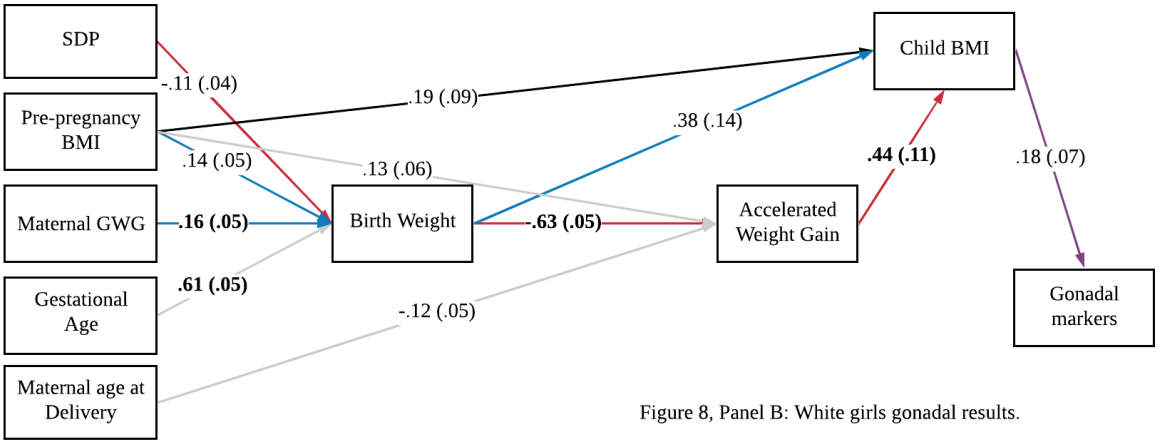

Figure 8, Panel B: White girls gonadal results.

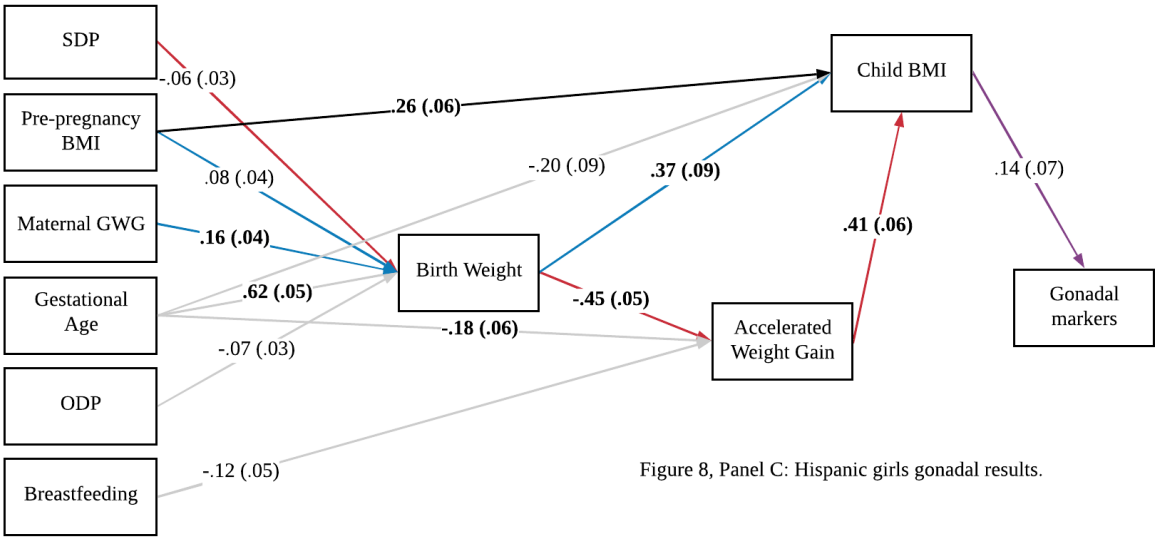

Figure 8, Panel C: Hispanic girls gonadal results.

Figure 8 Girls gonadal results by race/ethnicity

Research Question 2 Summary

Overall, most paths for both the thrifty phenotype and fetal overnutrition pathways were supported, although the relations between accelerated weight gain and childhood BMI with perceived pubertal timing (paths 3 & 5) were sparse. No indirect effects were supported for boys and girls in any race/ethnicity group except for the fetal overnutrition pathways from maternal GWG and pre-pregnancy BMI in the Black girls' gonadal model. See tables 11, 12 and 13 for a summary of research question 2.

Table 11 Summary of key findings for research question 2: Black boys and girls by pubertal marker

	Boys		Girls	
	Adrenal	**Gonadal**	**Adrenal**	**Gonadal**
Thrifty Phenotype	**Partial Support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight gain → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight →greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None	**Partial Support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight gain → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** SDP → lower birth weight Lower birth weight → greater accelerated weight gain Greater accelerated weight →greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None
Fetal Overnutrition	**Partial Support** Higher pre-pregnancy BMI/excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Full Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** 6→7→5 for both pre-pregnancy BMI/excessive GWG

Table 12 Summary of key findings for research question 2: White boys and girls by pubertal marker

	Boys		Girls	
	Adrenal	**Gonadal**	**Adrenal**	**Gonadal**
Thrifty Phenotype	**Partial Support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater accelerated weight gain → earlier pubertal timing **Confirmed indirect effects:** None	**Partial support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None
Fetal Overnutrition	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None

Table 13 Summary of key findings for research question 2: Hispanic boys and girls by pubertal marker

	Boys		Girls	
	Adrenal	**Gonadal**	**Adrenal**	**Gonadal**
Thrifty Phenotype	**Partial Support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None.	**Partial support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None	**Partial Support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Full Support** SDP → lower birth weight Lower birth weight → accelerated weight gain Greater accelerated weight gain → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None
Fetal Overnutrition	**Low Support** No associations with birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Low Support** No associations with birth weight Higher birth weight → Greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None	**Partial Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → Greater BMI z-score No associations with puberty **Confirmed indirect effects:** None	**Full Support** Higher pre-pregnancy BMI and excessive GWG → higher birth weight Higher birth weight → greater BMI z-score Greater BMI z-score → earlier pubertal timing **Confirmed indirect effects:** None

DISCUSSION

This thesis is the first to trace developmental pathways from the prenatal period to the beginning of puberty according to the thrifty phenotype and fetal overnutrition hypotheses. I used a large, racially and ethnically diverse sample of boys and girls to answer two main research questions. My first research question investigated whether the thrifty phenotype or the fetal overnutrition pathway better predicted perceived pubertal timing in girls or boys. I hypothesized that both pathways would be present, but the thrifty phenotype pathway would better predict perceived pubertal timing in boys and the fetal overnutrition pathway would better predict perceived pubertal timing in girls. In general, both hypothesized pathways were supported, but contrary to hypotheses, the thrifty phenotype did not predict perceived pubertal timing best in boys, compared to girls, and the fetal overnutrition pathway did not predict perceived pubertal timing better in girls, compared to boys. Instead, the thrifty phenotype and fetal overnutrition pathways were equivalent across boys and girls for both adrenal and gonadal puberty markers. And finally, the fetal overnutrition pathway, when compared to the thrifty phenotype pathway, was only stronger in girls for gonadal markers of perceived pubertal timing.

My second research question further examined the hypothesized pathways by stratifying the sample by race/ethnicity group to try to better understand known race/ethnicity differences in pubertal timing. I had no specific hypotheses for the pattern of findings for the different race/ethnicity groups for the two hypothesized pathways. In general, most paths of both pathways were present, but support for the entire hypothesized pathways were sparse. This seemed to be largely to due to the lack of support for the relation between child BMI and perceived pubertal timing (path 5) and between accelerated weight gain and perceived pubertal timing (path 4) when race/ethnicity groups were analyzed separately. There were also only

indirect effects for the fetal overnutrition pathways for pre-pregnancy BMI and maternal GWG in the black girls' gonadal analysis.

Perceived Pubertal Timing Construct

It is important to keep in mind that the current thesis used a parent perceived PDS measure. As mentioned previously, measures of perceived pubertal timing are not ideal for studies of adolescent health since perceived measures of puberty capture not only physiological development but also psychosocial elements to puberty (Beltz et al., 2014; Marceau et al., 2015; Shirtcliff et al., 2009) which are extraneous to classifying youth accurately based solely on their physical maturity. Parent perceived puberty may circumvent some issues associated with child self-report as children in earlier stages of puberty tend to over report their development (Shirtcliff et al., 2009), but parent report may offer an incomplete view of their child's development. Parents may not have a good reference of normative development from which to accurately judge how far along their own child is or be able to continuously monitor every aspect of puberty. For instance, some items of the PDS may be more or less noticeable to parents. PDS items like growth spurt, skin changes, onset of menstruation, voice changes and facial hair growth may be more obvious to parents but changes in markers like breast development, pubic and underarm hair may still be noticeable to parents but not to the same degree that youth may be aware of the changes happening to their body or to the eye of a trained professional.

While there are some drawbacks to using parent perceived pubertal timing, a number of steps were taken in order to optimize its efficacy. Namely, adrenal and gonadal items were disaggregated separately by child sex, following guidance from Dorn and colleagues (2006) and Shirtcliff and colleagues (2009) given that adrenarche and gonadarche are separate underlying processes and have sex specific indicators. Age was also regressed out of the adrenal and

gonadal markers PDS scores separately by sex (Ge et al., 2007) in order to create a measure of perceived pubertal timing relative to other same sex youth in the sample which is the recommended protocol (Mendle et al., 2019). This was important for the current study as associations between gonadal pubertal markers were likely biased for girls (e.g., inflation of association between breast development and BMI) and so the adrenal pubertal markers should be less biased. The most ideal measure of pubertal timing for this thesis' research questions would be a physical examination by a trained professional with palpation of breast tissue. Although the parent perceived pubertal timing measure was not the most ideal measure of puberty, important information on the developmental pathways to early pubertal timing can still be gleaned in light of the known limitations.

The Thrifty Phenotype Hypothesis

Under the umbrella of the DOHaD perspective, the thrifty phenotype hypothesis posits that nutritional deprivation during pregnancy is linked to poor adult health via metabolic programming that is exacerbated by a mismatch between the prenatal and postnatal nutritional environment and that pubertal timing may be implicated in this pathway and be programmed via similar mechanisms (Biro & Deardorff, 2013; Hales & Barker, 2001). A wealth of independent bodies of literature supports each individual path of the thrifty phenotype pathway conceptualized and operationalized here. This thesis extended existing work by confirming these specific paths in large sample of racially and ethnically diverse youth for perceived pubertal timing. By and large, each hypothesized path of the thrifty phenotype pathway was supported in boys and girls. As hypothesized and informed by the extant literature, greater SDP predicted lower birth weight (path 1; Abraham et al., 2017), lower birth weight predicted greater accelerated weight gain in infancy (path 2; Jain & Singhal, 2012) and greater accelerated weigh

gain in infancy often times independently predicted greater childhood BMI (path 4) and earlier perceived pubertal timing (path 3; Ong et al., 2009), and greater childhood BMI predicted earlier perceived pubertal timing (path 5; Y.-C. Chen et al., 2019).

This thesis combined the extant theoretical and empirical literature, empirically tested and provided evidence of a specific developmental pathway for the thrifty phenotype hypothesis. Doing so extended the DOHaD theoretical perspective and thrifty phenotype hypothesis by way of finding support for a specific developmental pathway for pubertal timing that emanates from SDP as a primary prenatal insult that puts the pathway into motion (Swanson et al., 2009). This indicates that SDP may serve as a restrictive prenatal insult that contributes to producing the "mismatch" between nutritionally scarce intrauterine conditions and nutritionally plentiful postnatal conditions in line with the theory behind the thrifty phenotype hypothesis for the study of pubertal timing (Biro & Deardorff, 2013; Hales & Barker, 2001). Further, support of the pathway through birth weight, accelerated weight gain in infancy and childhood BMI suggests that SDP contributes to the programming through a specific developmental pathway of child growth risk factors that were previously known to be associated with early puberty. To this point, it is notable that there were no main effects of SDP on perceived pubertal timing across all models despite the presence of association between SDP and perceived pubertal timing for some subgroups at the bivariate association level. Similarly sized prior studies and meta-analytic evidence that find a reduction in the age of puberty after exposure to SDP typically have only adjusted for child BMI (Brix, Ernst, Lauridsen, Parner, et al., 2019; Chen et al., 2018). The novel findings generated in this thesis may indicate that the mediating pathway variables (birth weight, accelerated weight gain and child BMI z-score) fully explain the pathway between SDP and pubertal timing. And notably, almost all the previous studies do not adjust for birth weight,

accelerated weight gain in infancy and childhood BMI together (Karaolis-Danckert et al., 2009). This thesis extends the literature by adjusting for all these factors and provides stronger evidence for a developmental pathway from SDP to perceived early pubertal timing.

Of the two thrifty phenotype pathways conceptualized here, the pathway operating through childhood BMI was superior to the pathway operating through accelerated weight gain to perceived pubertal timing directly. This likely reflects the relative importance and mechanistic role of adipose tissue in the suspected to be causal relationship between childhood obesity and early pubertal timing (Ahmed et al., 2009; Y.-C. Chen et al., 2019; Reinehr & Roth, 2019). However, that both were supported indicates that accelerated weight gain and childhood BMI independently contribute to influencing pubertal timing, which the extant literature supports (Li et al., 2017; Ong et al., 2009). Ideally, more studies should include both, especially in racially and ethnically diverse samples due to disparities in BMI trajectories across early childhood (Guerrero et al., 2016). This thesis also contributes an investigation including accelerated weight gain as a predictor of adrenal and gonadal markers of puberty in a large sample of boys and girls to a body of literature in which the vast majority of prior studies predict age at menarche as pubertal outcome (Juul et al., 2017).

There were, however, some features of the thrifty phenotype pathway that were unsupported. The relation between childhood BMI and perceived pubertal timing (path 5) was unsupported in the analysis of boys' adrenal markers but was supported in the girls' adrenal marker analysis and the boys' and girls' gonadal marker analyses. The relation between child BMI and adrenal markers was also not supported in any of the race/ethnicity sub analyses. It could be that elevated child BMI may be less relevant in boys for adrenal processes of puberty than for gonadal development. That the relation between accelerated weight gain and more advanced adrenal

development (path 3) was supported is a relatively novel finding as previous investigations have so far mostly only found associations of accelerated weight gain with gonadal markers of puberty in boys (Karaolis-Danckert et al., 2009; Ong et al., 2012). This finding needs replication, however, as it had a relatively small effect size and did not survive the adjusted p-value. That being said, this effect was stronger in the White boys' analyses of adrenal markers but unsupported in both the Black and Hispanic boys' models indicating that the effect might have been driven by the White boys' subsample in the overall boys' analysis. This is surprising as accelerated weight gain has been shown to be particularly salient in non-White populations generally, but studies with accelerated weight gain as a predictor of pubertal timing using non-White samples are sorely lacking (Karaolis-Danckert et al., 2009; Ong et al., 2012).

In the overall analysis of gonadal markers in boys, the relation between accelerated weight gain and childhood BMI with perceived pubertal timing were both supported (path 3 & 5). The relation between childhood BMI and perceived pubertal timing (path 5) was supported in the Black boys and Hispanic boys' analyses which corroborates trends and disparities of elevated child BMI and earlier pubertal development in non-white populations (Fryar et al., 2018; Ogden et al., 2014; Ramnitz & Lodish, 2013). Surprisingly, the relation between accelerated weight gain and perceived pubertal timing (path 3) was unsupported across all race/ethnicity subgroups. This is may have been due to the smaller sample sizes of the race/ethnicity groups since the effect was relatively small (.09) and the smaller sample size may have limited the power to detect the findings. This may have also been true for girls as the relation between accelerated weight gain and perceived pubertal timing (path 3) was supported in the overall girls' adrenal and gonadal analyses but not at all in the analyses by race/ethnicity group for either adrenal or gonadal markers. Previous literature has mostly only studied the association between accelerated weight

gain and age at menarche in predominantly White samples using a variety of accelerated weight gain variables between different ages (Juul et al., 2017). Collectively, this may indicate that accelerated weight gain may be more salient for late gonadal pubertal events like onset of menstruation and has a very modest contribution to relatively early adrenal and gonadal markers, at least as measured by parent perceived puberty, and that the race/ethnicity sub groups may have been inadequately powered to detect this effect.

The association between childhood BMI and perceived pubertal timing (path 5) was supported in the overall girls' analysis for adrenal and gonadal markers and in every group in the girls' gonadal marker by race/ethnicity analyses. This could be due to role that excessive adiposity plays in promoting aromatase activity (conversion of androgen to estrogen) which may promote breast development (Dunger et al., 2005). However, it could also be explained by a known inflation in the association between breast development (contributes to the gonadal PDS score) and higher childhood BMI. Since the measure of pubertal timing was based on parents' perception and not palpation of breast tissue, parents of daughters with overweight or obese BMIs may systematically report higher breast development due to the visual confounding of adipose and breast tissue (Biro et al., 1992; Dorn et al., 2006; Mendle et al., 2019). Thus, those associations were likely upwardly biased. On the other hand, in the girls' adrenal analysis by race/ethnicity, the relation between childhood BMI and perceived pubertal timing (path 5) was not biased by the same measurement confounding as in the gonadal analyses but was only supported in Black girls. This may be because Black girls are at disproportionate risk for childhood obesity and had some of the highest prevalence rates for girls of any race/ethnicity for the past 20 years (Fryar et al., 2018) and thus the association was stronger and able to be detected. However, it is surprising that this effect was not also found in Hispanic girls as this

group is at similar risk for childhood obesity and has had similarly high prevalence rates over time (Fryar et al., 2018) and is generally counter to previous literature (Deardorff et al., 2021). Future studies, ideally using a physical examination measure of puberty with palpation of breast tissue should attempt to replicate these findings and may hypothesize particularly strong effects for Black girls based on these findings.

The Fetal Overnutrition Hypothesis

At the other end of the nutritional spectrum, the fetal overnutrition hypothesis posits that exposure to metabolic excessive prenatal insults engenders increased risk of obesity throughout life through metabolic programming and early pubertal timing may also be programmed via similar mechanisms (Dunger et al., 2005; Roth & DiVall, 2016). A large amount of evidence supports the association from prenatal risks of greater pre-pregnancy BMI and greater maternal GWG for higher birth weights, greater childhood BMI and earlier timing of puberty (Goldstein et al., 2017; Lawn et al., 2018; Liu et al., 2016; Yu et al., 2013). Overall, both of the hypothesized pathways for pre-pregnancy BMI and maternal GWG conceptualized in this investigation were generally supported. This thesis extends the DOHaD perspective by putting forward a more specific developmental pathway for overnutrition exposure to pubertal timing in line with the fetal overnutrition hypothesis. A number of previous studies have tested the mediating role of childhood BMI or birth weight between prenatal overnutrition risks and early pubertal timing but have not tested both as serial mediators (Aghaee et al., 2019; Brix, Ernst, Lauridsen, Arah, et al., 2019; Deardorff et al., 2013; Lawn et al., 2018). This thesis extended existing work in this literature by testing a specific developmental pathway from overnutrition prenatal risks of high pre-pregnancy BMI and maternal GWG to higher birth weight (path 6), to greater childhood BMI (path 7) to earlier perceived puberty in a large sample of racially and ethnically diverse

boys and girls. This thesis also fills a gap for a lack of investigations of overnutrition prenatal risk factors and adrenal and gonadal markers of puberty in boys (Aghaee et al., 2019).

Between the two overnutrition pathways tested here, both the pre-pregnancy and maternal GWG pathways showed roughly equivalent support for the hypothesized paths, but it was the maternal GWG pathway that proved to the superior pathway in both boys and girls. Effect sizes were similar across models, but the maternal GWG effects were larger and when the pathways were compared statistically, maternal GWG consistently came out on top. This may be because maternal GWG and pre-pregnancy BMI reflect similar but different timing of overnutrition risk but maternal GWG may more accurately reflect overnutrition conditions *during* gestation whereas pre-pregnancy BMI may more so reflect fuel stores and shared genetic as well as environmental factors between mother and offspring (Perng et al., 2019). That maternal GWG may more so reflect in utero overnutrition risk to the fetus may also be why it was the more salient prenatal insult. Similar prior investigations also find evidence of larger effects of maternal GWG than pre-pregnancy BMI when examining them separately (Lawn et al., 2018), while others found the opposite (Deardorff et al., 2013). Future studies should include both, if possible, or use composite measure to account for both influences in the same model (Aghaee et al., 2019).

Similar to SDP, there were no main effects of either prenatal overnutrition risk on pubertal timing in any of the analyses although both maternal GWG and pre-pregnancy BMI were associated with perceived early pubertal timing in girls at the bivariate level. Just as for the thrifty phenotype pathways, this may indicate that the mediating variables in the pathway (birth weight and childhood BMI) fully explained the relation between prenatal overnutrition risks and perceived early pubertal timing. Previous studies have found either full mediation by childhood

BMI (Brix, Ernst, Lauridsen, Arah, et al., 2019), partial mediation (Aghaee et al., 2019), or null results (Deardorff et al., 2013). The results here may indicate that additionally including birth weight in the pathway may be important for fully accounting for the relation between prenatal risk and puberty.

Although the fetal overnutrition pathway was generally well supported across this study there were some exceptions. In addition to the lack of findings for the childhood BMI to perceived pubertal timing path (path 5), which is common between the two hypothesized pathways, there was a notable absence of association between overnutrition risk and birth weight in the model for Hispanic boys. In both the adrenal and gonadal models for Hispanic boys there were no associations between either pre-pregnancy BMI or maternal GWG with birth weight despite there being a positive bivariate correlation between maternal GWG and birth weight and despite strong associations that survived the adjusted p-value in the corresponding models for Hispanic girls and for all other race/ethnicity models. This is surprising given the extant literature and in particular, prior studies that find evidence that excessive maternal GWG predicts higher birth weight specifically in Hispanic samples (Elwan et al., 2021) and higher risk of obesity from higher pre-pregnancy BMI until age 9 (Kjaer et al., 2019).

Thrifty Phenotype vs. the Fetal Overnutrition Hypothesis

Early experiences such as prenatal risks associated with growth restriction and excessive growth may both lead to the same developmental outcome of early puberty (e.g., equifinality). This thesis showed evidence for pathways of both the thrifty phenotype and fetal overnutrition leading to earlier perceived pubertal timing. Given the negative health and psychosocial outcomes associated with early puberty both in adolescence and later on in life, identifying potential intervening or preventative factors is important. Further, understanding which pathway

transmits the most risk is important knowledge to gain in order to prioritize which is the most problematic. This thesis extends the study of pubertal timing by showing that puberty may be similarly subject to a "paradox" wherein birth weight at both ends of the spectrum (and corresponding prenatal risks) lead to poorer outcomes in much the same way as for BMI and increased adiposity (Oken & Gillman, 2003).

In the investigation of testing which of the two developmental pathways better predicted perceived pubertal timing, the thrifty phenotype pathway through child BMI and the fetal overnutrition pathway from maternal GWG predicted perceived pubertal timing equally well between boys and girls for adrenal markers and gonadal markers. This was contrary to my hypotheses as I had hypothesized that the thrifty phenotype would better predict perceived pubertal timing in boys because they may be potentially more susceptible to restrictive prenatal risks (Gariepy et al., 2000; Kraemer, 2000) and since male fetuses are on average larger at birth and have to grow more rapidly during gestation and so any perturbation in growth would be more detrimental than for female fetuses that tend to be smaller in comparison (Aiken & Ozanne, 2013). Additionally, I hypothesized that the fetal overnutrition pathway would be strongest in girls as prior investigations have generally shown more consistent and stronger association of overnutrition prenatal risks with pubertal timing in girls compared to boys (Brix, Ernst, Lauridsen, Arah, et al., 2019). In line with my hypothesis, the maternal GWG fetal overnutrition pathway predicted perceived puberty best within girls but only for gonadal pubertal markers. Given these findings, future studies testing these pathways may hypothesize equivalent effects across boys and girls and possibly stronger effects for the fetal overnutrition pathway within girls for gonadal pubertal markers, but it will be important to use a measure of pubertal timing that is

not upwardly biased by elevated BMI (e.g., physical exam with palpation of breast tissue, age at menarche).

The relative importance of the fetal overnutrition pathway for both boys and girls is an important finding in the context of rising levels of overnutrition globally (Wong et al., 2020). In particular, the maternal GWG pathway was stronger than the pre-pregnancy BMI pathway. Given this, prevention efforts may do better to prioritize maternal GWG interventions over those devised for pre-pregnancy BMI for several reasons. A large proportion of pregnancies are unplanned and individuals who become pregnant may not become aware that they are until well into their pregnancy. This makes it unfeasible for a significant number to be reached by a potential pre-pregnancy intervention. Further, those planning to get pregnant may already be aware of appropriate weight gain guidelines and conscientious of other health behaviors to support healthy pregnancies and so may not benefit as much or be in need of the intervention to the same degree as those who are not planning to get pregnant. Targeting maternal GWG on the other hand, may prove to be more fruitful since pregnancy is a time when expecting mothers may be more willing and motivated to make changes to their lifestyles for their own health benefit and for the health of their future child. Further, prenatal care visits provide a convenient opportunity for clinicians and researchers to deliver interventions or education for appropriate weight gain during pregnancy. Intervening on maternal GWG could potentially reduce early puberty trends by reducing childhood BMI. Finally, Aghaee and colleagues (2019) provide epidemiological evidence that women who have BMIs in the overweight or obese category who stay within IOM guidelines for GWG have a reduced risk for earlier pubertal timing in daughters. This suggests that intervening on maternal GWG even in those with overweight or obese BMIs may be effective at reducing risk.

The thrifty phenotype pathway proved to be just as salient as the fetal overnutrition pathway between boys and girls. This is in spite of SDP being much less prevalent in this sample than overnutrition risks (19% vs. 52% excessive GWG), but the pathways still bore out and the effect sizes for the pathways were similar. Thus, even though SDP may affect fewer people compared to those affected by overnutrition, the negative effects should not be ignored. Further, while prevalence rates of SDP are generally decreasing, they still remain relatively high in some areas of the U.S., in some European countries, and are increasing in low- and middle-income countries as they make the first demographic transition (Collaborators, 2017; Lange et al., 2018). Additionally, there have been past cohorts exposed to higher levels of SDP that are currently in adulthood or about to enter older adulthood that may be on risky health trajectories possibly through thirty phenotype type mechanisms and extending these pathways to the study of adult health conditions may help better understand trajectories of health across the lifespan and disparities in disease burden.

A future extension of the hypothesized pathways tested here could be to predict extended outcomes of adult health conditions since child obesity and early puberty may differentially predict certain health conditions. For instance, variance in cardiometabolic traits seem to be largely explained by obesity over and above the effect of early age at menarche and some have argued that the emphasis of prevention should be put on child BMI (Bell et al., 2018). On the other hand, a recent systematic review confirmed that early age at menarche is associated with type II diabetes above and beyond the effect of adiposity (Cheng et al., 2020). Another study, in White European men, showed that earlier age at peak height velocity predicted type II diabetes in adulthood and that the association was similar after adjusting for childhood BMI (Ohlsson et al., 2020), indicating that childhood BMI and pubertal timing independently contribute to the

development of type II diabetes. Towards the ultimate aim of better understanding health trajectories throughout the lifespan and reducing disease burden, especially for non-white populations in which these conditions are disproportionately present, testing whether the fetal overnutrition or thirty phenotype pathways better predicts various health conditions may prove insightful. While both pathways were generally equivalent at predicting earlier perceived pubertal timing based on the current investigation, it's unclear which would be the more potent pathway for certain adult health conditions. Some literature suggests that higher obesity through restriction may be more problematic because of stronger associations with central obesity (Oken & Gillman, 2003), but as overnutrition rises, purely obesogenic pathways may become even more important and the most burdensome for disease.

Sex Differences

Puberty is a sexually dimorphic trait with common and unique adrenal and gonadal indicators for boys and girls. Despite these inherent underlying sex differences and some literature suggesting that fetuses of different sexes may weather prenatal insults differently (DiPietro & Voegtline, 2017; Kraemer, 2000), effect size estimates from prenatal risk variables to birth weight were remarkably similar. Most of the effect sizes for other paths of the hypothesized pathways were also relatively similar with exception to the birth weight and accelerated weight gain path (path 2), where it was stronger in girls. As discussed above, this may be consistent with previous literature that found that male fetuses were larger at birth and were heavier until 12 months of age when female infants surpassed males in weight (Broere-Brown et al., 2016). Thus, a larger effect between birth weight and of accelerated weight gain (change in z-score between birth and age 1) age may account for this observed pattern. Other differences, including the lack of findings between accelerated weight gain and child BMI with

pubertal timing (path 3 & 5) and relatively stronger effects for the child BMI and perceived pubertal timing (path 5) in girls were likely induced (at least in part) by measurement bias and limitations.

Race/ethnicity Differences

Race/ethnicity differences have been consistently observed in the study of pubertal timing with non-white populations generally having earlier ages of puberty (Deardorff et al., 2019; Ramnitz & Lodish, 2013). The current thesis sought to explore race/ethnicity differences in the developmental pathways for the thrifty phenotype and fetal overnutrition hypotheses separately by sex and race/ethnicity group in order to better understand race/ethnicity differences in pubertal timing. Most components of each pathway were supported, but it is difficult to interpret whether any observed differences in the patterns of findings by race/ethnicity group are real or a product of a combination reduced sub-group sample size and measurement issues with the perceived pubertal timing variable, as discussed above. Overall, there were more sparse findings in the race/ethnicity analyses, especially for the boys' adrenal analyses and for the relations between accelerated weight gain and child BMI with perceived pubertal timing (paths 3 & 5) more generally. Further, the only supported indirect effects for the developmental pathways were for the maternal GWG and pre-pregnancy BMI fetal overnutrition pathways in Black girls with gonadal markers as outcome, which are upwardly biased by the confounding between elevated BMI and breast tissue. Future studies may attempt to replicate these effects using less biased measures of pubertal maturation (e.g., physical exam of pubertal status, specifically with palpation of breast tissue), and based on these findings, hypothesize stronger effects for Black girls.

Previous literature investigating race/ethnicity differences in many of the hypothesized paths have shown that differences in infancy weight gain, childhood BMI and pubertal timing as being in large part attenuated by socioeconomic disparities (Andrea et al., 2017; Deardorff et al., 2014). To this end, the current thesis adjusted for several socioeconomic indicators (household income, parent education, material needs, and food security) and several other covariates highly intercorrelated with race/ethnicity group and socioeconomic status (breastfeeding duration, child maltreatment, father absence). Despite this effort, there were still some differential findings by race/ethnicity that were unable to be explained. While it is unclear what exactly drove these differences in the current investigation due to the limitations previously discussed, there could additionally be residual confounders such as dietary quality (e.g., sugar sweetened beverages, fast food), physical activity and neighborhood level indicators of socioeconomic status, physical activity, dietary quality and exposures that also disproportionately vary by race/ethnicity (Biro et al., 2009; Deardorff et al., 2012; Goran et al., 1998; Guerrero et al., 2016; Timperio et al., 2008). In particular for the current thesis, accounting for diet quality and consumption of sugar sweetened beverages may play a role in modifying the hypothesized pathways and explain some of the differential findings by race/ethnicity for the relation between child BMI and perceived pubertal timing. Prior work by Guerroro and colleagues (2016) showed that Black and Hispanic children had the highest average BMI trajectories compared to White children and consumption of soda and fast food was strongly associated with higher BMI trajectories. They suggested targeting reducing the consumption of and sugar sweetened beverages as a potential for intervention BMI trajectories in childhood and that this may benefit Black and Hispanic children the most.

Limitations and Strengths

The current thesis tested both the thrifty phenotype and overnutrition hypotheses applied to the study of pubertal timing, using a novel operationalization of associated pathways in a large, racially and ethnically diverse birth cohort. Several limitations must be considered when weighing the impact and implications of the present findings. As previously discussed, the measure of pubertal timing in the current thesis is not ideal, although not prohibitively so to not warrant this investigation. In brief, the limited ability of parent report of child puberty to capture true physiological pubertal development does not outweigh the potential benefit of learning about understudied populations in the study of pubertal timing in the models proposed here. Relatedly, the young age of the sample is a potential limitation that may have driven lack of findings, especially in the boys' adrenal analysis, as age 9 is relatively young to capture pubertal timing and may lead to bias in the associations reported here. Namely, this bias may have strengthened the association between accelerated weight gain and childhood BMI with earlier perceived pubertal timing (path 3 & 5) by not providing a strong counterfactual (i.e., children with greater accelerated weight gain rates or elevated BMI with normal or even late timing of puberty). However, this sample is considered relatively high risk and so while this investigation may be biased toward early developers, these are the populations that may be at the most risk for the associated negative effects of early puberty and in most need of being identified and studied.

The operationalization of the thrifty phenotype and fetal overnutrition hypotheses were limited to gross markers of growth. Birth weight is only a rough proxy for intrauterine growth and the use of BMI is limited as a measure of adiposity and may vary more so for non-white children. In order to limit the lack of precision of these two measures I obtained medical record birth weights and used BMI z-scores derived from standardized growth charts which corrects for child sex and age. While these markers of growth are widely used and were optimized as much

as possible within the parameters of the FFCWS, they are nevertheless lacking in precision and so both are limitations to the current study.

The measure of self-reported SDP in the FFCWS was also a limitation to the current thesis because it did not ask mothers to report the *timing* of the exposure; it only asked for mothers to report on their average use throughout the entire pregnancy. Timing of SDP may be important for precision in testing the thrifty phenotype pathway since the majority of fetal growth takes place in the third trimester and may have a more salient effect on intrauterine growth at that time. Additionally, self-reported SDP is known to be underreported compared to more objective methods (Klebanoff et al., 1998). However, since effects of SDP were found, it is possible their effect size were underestimated and are stronger in reality.

Despite these limitations, this thesis has a number of strengths, and adds to the puberty literature in several critical ways. First, this thesis determined that the thrifty phenotype and fetal overnutrition pathway generally equally predict perceived pubertal timing using measures of the developmental pathways that are often unavailable or unused in a single study. Relatedly, it also controlled for key environmental influences (a variety of sociodemographic indicators throughout childhood, breastfeeding duration, maltreatment and father absence) often unadjusted for in prenatal studies of pubertal timing. Together, this resulted in a comprehensive test of the hypothesized pathways and more precise estimates of perceived pubertal timing as an outcome. Second, the use of medical record data for obtaining prenatal indicators of the fetal overnutrition hypothesis and birth weight is a strength. Third, this thesis was the first to test multiple mediation in a longitudinal analytic framework that is consistent with both hypothesized pathways. This is particularly important in light of calls for longitudinal studies that begin before puberty in order to elucidate the origins of disease and conditions associated with early puberty (Dorn et al.,

2019). Finally, this study contributed an investigation of perceived pubertal timing in a large sample of racially and ethnically diverse youth, who are understudied in the puberty literature (Deardorff et al., 2019; Mendle et al., 2019).

Conclusions

This thesis tested developmental pathways for the thrifty phenotype and fetal overnutrition hypotheses applied to pubertal timing. This thesis found evidence that the thrifty phenotype and fetal overnutrition developmental pathways predicted perceived pubertal timing equally well in boys and girls. The maternal GWG fetal overnutrition pathways predicted puberty better in girls compared to the thrifty phenotype pathway but only for gonadal pubertal markers. Both pathways were generally supported when the sample was analyzed by race/ethnicity but the paths between accelerated weight gain and child BMI with perceived pubertal timing and indirect effect for the pathways were sparse. Future studies should use more objective measure of pubertal timing, such as, physical examination by a trained professional to limit bias in the developmental pathways.

APPENDIX A. BOYS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with GAcon;
SDP with Incomecat;
SDP with Education;
SDP with MatNeeds;
SDP with Maltreat;
SDP with Food;
SDP with bfed;
SDP with fabs;
SDP with White;
SDP with Hispanic;
SDP with other;
SDP with PrepregBMI;
SDP with catwtgain;
ADP with ODP;
ADP with mage;
ADP with MatNeeds;
ADP with Maltreat;
ADP with fabs;
ADP with White;
ADP with Hispanic;
ADP with Other;
ADP with catwtgain;
ODP with GAcon;
ODP with incomecat;
ODP with MatNeeds;
ODP with Education;
ODP with Food;
ODP with Maltreat;
ODP with bfed;
ODP with fabs;
ODP with Hispanic;
PrepregBMI with mage;
PrepregBMI with catwtgain;
PrepregBMI with Incomecat;
PrepregBMI with MatNeeds;
PrepregBMI with Food;
PrepregBMI with White;
PrepregBMI with Other;
PrepregBMI with fabs;
catwtgain with GAcon;
catwtgain with Incomecat;
catwtgain with Education;
catwtgain with White;
mage with Incomecat;
mage with Education;
mage with MatNeeds;
mage with Food;
mage with Maltreat;
Mage with bfed;
mage with fabs;
mage with White;
mage with Hispanic;
mage with other;
GAcon with bfed;
GAcon with Hispanic;
Incomecat with Education;
Incomecat with MatNeeds;
Incomecat with Food;
Incomecat with maltreat;
Incomecat with bfed;
Incomecat with fabs;
Incomecat with White;
Incomecat with Hispanic;
Incomecat with Other;
Education with MatNeeds;
Education with Food;
Education with bfed;
Education with fabs;
Education with White;
Education with Hispanic;
Education with Other;
MatNeeds with Food;
MatNeeds with bfed;
MatNeeds with Maltreat;
MatNeeds with fabs;
MatNeeds with Hispanic;
MatNeeds with Other;
Food with maltreat;
Food with bfed;
Food with fabs;
Food with White;
Maltreat with bfed;
Maltreat with fabs;
Maltreat with White;
Maltreat with Hispanic;
bfed with fabs;
bfed with White;
bfed with Hispanic;
bfed with Other;
fabs with WHite;
fabs with Hispanic;
fabs with other;
Hispanic with White;
Other with White;
Other with Hispanic;

APPENDIX B. GIRLS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with GAcon;
SDP with Incomecat;
SDP with Education;
SDP with MatNeeds;
SDP with Maltreat;
SDP with Food;
SDP with bfed;
SDP with fabs;
SDP with White;
SDP with Hispanic;
SDP with Other;
ADP with ODP;
ADP with mage;
ADP with GAcon;
ADP with Incomecat;
ADP with Education;
ADP with MatNeeds;
ADP with Maltreat;
ADp with Food;
ADP with fabs;
ADP with Hispanic;
ADP with Other;
ODP with catwtgain;
ODP with mage;
ODP with GAcon;
ODP with incomecat;
ODP with Education;
ODP with Food;
ODP with Maltreat;
ODP with bfed;
ODP with fabs;
ODP with White;
ODP with Hispanic;
PrepregBMI with mage;
PrepregBMI with GAcon;
PrepregBMI with catwtgain;
PrepregBMI with Incomecat;
PrepregBMI with MatNeeds;
PrepregBMI with Food;
PrepregBMI with bfed;
PrepregBMI with White;
catwtgain with GAcon;
catwtgain with Incomecat;
catwtgain with Education;
catwtgain with maltreat;
mage with GAcon;
mage with Incomecat;
mage with Education;
mage with MatNeeds;
mage with Maltreat;
Mage with bfed;
mage with fabs;
mage with White;
mage with Hispanic;
mage with other;
GAcon with Incomecat;
GAcon with MatNeeds;
GAcon with bfed;
GAcon with fabs;
GAcon with White;
GAcon with Hispanic;
Incomecat with Education;
Incomecat with MatNeeds;
Incomecat with Food;
Incomecat with maltreat;
Incomecat with bfed;
Incomecat with fabs;
Incomecat with White;
Incomecat with Hispanic;
Education with MatNeeds;
Education with Food;
Education with bfed;
Education with fabs;
Education with White;
Education with Hispanic;
Education with Other;
MatNeeds with Food;
MatNeeds with Maltreat;
MatNeeds with fabs;
MatNeeds with Hispanic;
Food with maltreat;
Food with bfed;
Food with fabs;
Food with Hispanic;
Food with Other;
Maltreat with bfed;
Maltreat with fabs;
Maltreat with White;
Maltreat with Hispanic;
Maltreat with Other;
bfed with fabs;
bfed with White;
bfed with Hispanic;
bfed with Other;
fabs with WHite;
fabs with Hispanic;
fabs with other;
Hispanic with White;
Other with White;
Other with Hispanic;

APPENDIX C. BLACK BOYS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with catwtgain;
SDP with mage;
SDP with Incomecat;
SDP with Education;
SDP with MatNeeds;
SDP with Food;
SDP with Maltreat;
SDP with bfed;
SDP with fabs;
ADP with ODP;
ADP with mage;
ADP with Incomecat;
ADP with Education;
ADP with MatNeeds;
ADP with Maltreat;
ADP with fabs;
ODP with GAcon;
ODP with incomecat;
ODP with Education;
ODP with MatNeeds;
ODP with Food;
ODP with Maltreat;
ODP with bfed;
PrepregBMI with mage;
PrepregBMI with catwtgain;
PrepregBMI with bfed;
catwtgain with GAcon;
catwtgain with Incomecat;
mage with Incomecat;
mage with Education;
mage with MatNeeds;
mage with Maltreat;
Mage with bfed;
mage with fabs;
Incomecat with Education;
Incomecat with food;
Incomecat with bfed;
Incomecat with fabs;
Education with MatNeeds;
Education with bfed;
Education with fabs;
MatNeeds with Maltreat;
MatNeeds with bfed;
MatNeeds with food;
MatNeeds with fabs;
Food with maltreat;
Food with fabs;
bfed with fabs;

APPENDIX D. WHITE BOYS' CORRELATIONS

SDP with bfed;
SDP with food;
SDP with fabs;
SDP with maltreat;
ADP with ODP;
ADP with mage;
ADP with food;
ADP with maltreat;
ADP with Incomecat;
ODP with mage;
ODP with incomecat;
ODP with Education;
ODP with MatNeeds;
ODP with Maltreat;
ODP with bfed;
ODP with food;
ODP with fabs;
PrepregBMI with mage;
PrepregBMI with catwtgain;
catwtgain with GAcon;
mage with Incomecat;
mage with Education;
mage with MatNeeds;
Mage with bfed;
mage with fabs;
mage with food;
mage with Maltreat;
Incomecat with Education;
Incomecat with MatNeeds;
Incomecat with Food;
Incomecat with maltreat;
Incomecat with bfed;
Incomecat with fabs;
Education with MatNeeds;
Education with Food;
Education with Maltreat;
Education with bfed;
Education with fabs;
MatNeeds with Maltreat;
MatNeeds with fabs;
MatNeeds with bfed;
MatNeeds with food;
Food with maltreat;
Food with bfed;
Food with fabs;
Maltreat with bfed;
Maltreat with fabs;
bfed with fabs;

APPENDIX E. HISPANIC BOYS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with MatNeeds;
SDP with Maltreat;
SDP with bfed;
SDP with fabs;
ADP with ODP;
ADP with mage;
ODP with incomecat;
ODP with MatNeeds;
ODP with fabs;
ODP with bfed;
ODP with food;
ODP with Maltreat;
PrepregBMI with catwtgain;
PrepregBMI with Incomecat;
PrepregBMI with bfed;
PrepregBMI with food;
catwtgain with GAcon;
mage with Incomecat;
mage with Education;
mage with Maltreat;
Mage with bfed;
mage with fabs;
GAcon with Education;
GAcon with MatNeeds;
GAcon with bfed;
Incomecat with Education;
Incomecat with MatNeeds;
Incomecat with Food;
Incomecat with fabs;
Education with Food;
MatNeeds with Maltreat;
Matneeds with food;
MatNeeds with bfed;
MatNeeds with fabs;
Food with maltreat;
Food with fabs;
bfed with fabs;

APPENDIX F. BLACK GIRLS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with catwtgain;
SDP with mage;
SDP with GAcon;
SDP with Incomecat;
SDP with Education;
SDP with MatNeeds;
SDP with Maltreat;
SDP with bfed;
SDP with fabs;
ADP with ODP;
ADP with mage;
ADP with GAcon;
ADP with Incomecat;
ADP with Education;
ADP with Maltreat;
ADP with fabs;
ODP with catwtgain;
ODP with GAcon;
ODP with mage;
ODP with incomecat;
ODP with Education;
ODP with Food;
ODP with Maltreat;
ODP with bfed;
ODP with fabs;
PrepregBMI with mage;
PrepregBMI with catwtgain;
PrepregBMI with MatNeeds;
PrepregBMI with fabs;
catwtgain with GAcon;
catwtgain with Incomecat;
catwtgain with bfed;
mage with GAcon;
mage with Incomecat;
mage with Education;
mage with Maltreat;
Mage with bfed;
mage with fabs;
Incomecat with Education;
Incomecat with food;
Incomecat with bfed;
Incomecat with fabs;
Education with food;
Education with bfed;
Education with fabs;
MatNeeds with Maltreat;
MatNeeds with bfed;
MatNeeds with food;
MatNeeds with fabs;
Food with maltreat;
Food with fabs;
bfed with fabs;

APPENDIX G. WHITE GIRLS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with mage;
SDP with Incomecat;
SDP with Education;
SDP with MatNeeds;
SDP with bfed;
SDP with food;
SDP with fabs;
SDP with maltreat;
ADP with ODP;
ADP with mage;
ADP with MatNeeds;
ADP with food;
ADP with maltreat;
ADP with bfed;
ODP with incomecat;
ODP with Education;
ODP with MatNeeds;
ODP with Maltreat;
ODP with fabs;
PrepregBMI with mage;
catwtgain with GAcon;
mage with Incomecat;
mage with Education;
mage with MatNeeds;
Mage with bfed;
mage with fabs;
mage with food;
mage with Maltreat;
Incomecat with Education;
Incomecat with MatNeeds;
Incomecat with Food;
Incomecat with maltreat;
Incomecat with bfed;
Incomecat with fabs;
Education with MatNeeds;
Education with Food;
Education with Maltreat;
Education with bfed;
Education with fabs;
MatNeeds with Maltreat;
MatNeeds with fabs;
MatNeeds with bfed;
MatNeeds with food;
Food with maltreat;
Food with bfed;
Food with fabs;
Maltreat with bfed;
Maltreat with fabs;
bfed with fabs;

APPENDIX H. HISPANIC GIRLS' CORRELATIONS

SDP with ADP;
SDP with ODP;
SDP with Incomecat;
SDP with Education;
SDP with MatNeeds;
SDP with Maltreat;
SDP with bfed;
SDP with fabs;
ADP with ODP;
ADP with mage;
ADP with GAcon;
ADP with Food;
ODP with GAcon;
ODP with education;
ODP with fabs;
ODP with food;
PrepregBMI with catwtgain;
PrepregBMI with mage;
PrepregBMI with bfed;
catwtgain with GAcon;
catwtgain with incomecat;
catwtgain with bfed;
catwtgain with fabs;
mage with GAcon;
mage with Incomecat;
mage with Education;
mage with Maltreat;
Mage with bfed;
mage with fabs;
GAcon with Education;
GAcon with MatNeeds;
Incomecat with Education;
Incomecat with MatNeeds;
Incomecat with Food;
Incomecat with fabs;
Education with Food;
Education with Maltreat;
Education with Fabs;
MatNeeds with Maltreat;
Matneeds with food;
MatNeeds with fabs;
Food with fabs;
bfed with fabs;

REFERENCES

Abraham, M., Alramadhan, S., Iniguez, C., Duijts, L., Jaddoe, V. W., Den Dekker, H. T., Crozier, S., Godfrey, K. M., Hindmarsh, P., Vik, T., Jacobsen, G. W., Hanke, W., Sobala, W., Devereux, G., & Turner, S. (2017). A systematic review of maternal smoking during pregnancy and fetal measurements with meta-analysis. *PLoS One*, *12*(2), e0170946. https://doi.org/10.1371/journal.pone.0170946

Adair, L. S. (2001). Size at birth predicts age at menarche. *Pediatrics*, *107*(4), E59. https://doi.org/10.1542/peds.107.4.e59

Aghaee, S., Laurent, C. A., Deardorff, J., Ferrara, A., Greenspan, L. C., Quesenberry, C. P., Kushi, L. H., & Kubo, A. (2019). Associations of maternal gestational weight gain and obesity with the timing of pubertal onset in daughters. *American Journal of Epidemiology*, *188*(7), 1262-1269. https://doi.org/10.1093/aje/kwz068

Ahima, R. S., Dushay, J., Flier, S. N., Prabakaran, D., & Flier, J. S. (1997). Leptin accelerates the onset of puberty in normal female mice. *The Journal of Clinical Investigation*, *99*(3), 391.

Ahmed, M., Ong, K., Morrell, D., Cox, L., Drayer, N., Perry, L., Preece, M. A., & Dunger, D. B. (1999). Longitudinal study of leptin concentrations during puberty: Sex differences and relationship to changes in body composition. *Journal of Clinical Endocrinology and Metabolism*, *84*(3), 899-905.

Ahmed, M. L., Ong, K. K., & Dunger, D. B. (2009). Childhood obesity and the timing of puberty. *Trends in Endocrinology & Metabolism*, *20*(5), 237-242. https://doi.org/10.1016/j.tem.2009.02.004

Aiken, C. E., & Ozanne, S. E. (2013). Sex differences in developmental programming models. *Reproduction*, *145*(1), R1-R13. https://doi.org/10.1530/REP-11-0489

Akison, L. K., Moritz, K. M., & Reid, N. (2019). Adverse reproductive outcomes associated with fetal alcohol exposure: A systematic review. *Reproduction*, *157*(4), 329-343. https://doi.org/10.1530/REP-18-0607

Andrea, S. B., Hooker, E. R., Messer, L. C., Tandy, T., & Boone-Heinonen, J. (2017). Does the association between early life growth and later obesity differ by race/ethnicity or socioeconomic status? A systematic review. *Annals of Epidemiology*, *27*(9), 583-592.e585. https://doi.org/10.1016/j.annepidem.2017.08.019

Andrews, M., Nord, M., Bickel, G., & Carlson, S. (1999). Household food security in the United States. *Food Assistance and Nutrition Research Report*, *8*.

Aydin, B. K., Devecioglu, E., Kadioglu, A., Cakmak, A. E., Kisabacak, S., Gokcay, G., Bas, F., Poyrazoglu, S., Bundak, R., & Darendeliler, F. (2017). The relationship between infancy growth rate and the onset of puberty in both genders. *Pediatric Research*, *82*(6), 940-946. https://doi.org/10.1038/pr.2017.194

Banderali, G., Martelli, A., Landi, M., Moretti, F., Betti, F., Radaelli, G., Lassandro, C., & Verduci, E. (2015). Short and long term health effects of parental tobacco smoking during pregnancy and lactation: A descriptive review. *Journal of Translational Medicine*, *13*(1), 327. https://doi.org/10.1186/s12967-015-0690-y

Barker, D. J. (1990). The fetal and infant origins of adult disease. *BMJ*, *301*(6761), 1111-1111. https://doi.org/10.1136/bmj.301.6761.1111

Barker, D. J. (1995). Fetal origins of coronary heart disease. *BMJ*, *311*(6998), 171-174. https://doi.org/10.1136/bmj.311.6998.171

Barker, D. J. (2001). The malnourished baby and infant. *British Medical Bulletin*, *60*(1), 69-88. https://doi.org/10.1093/bmb/60.1.69

Barker, D. J. (2007). The origins of the developmental origins theory. *Journal of Internal Medicine*, *261*(5), 412-417. https://doi.org/10.1111/j.1365-2796.2007.01809.x

Barker, D. J., & Bagby, S. P. (2005). Developmental antecedents of cardiovascular disease: A historical perspective. *Journal of the American Society of Nephrology*, *16*(9), 2537. https://doi.org/10.1681/ASN.2005020160

Barker, D. J., & Osmond, C. (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*, *1*(8489), 1077-1081. https://doi.org/10.1016/s0140-6736(86)91340-1

Bauer, M. K., Harding, J. E., Bassett, N. S., Breier, B. H., Oliver, M. H., Gallaher, B. H., Evans, P. C., Woodall, S. M., & Gluckman, P. D. (1998). Fetal growth and placental function. *Molecular and Cellular Endocrinology*, *140*(1-2), 115-120. https://doi.org/10.1016/S0303-7207(98)00039-2

Behie, A. M., & O'Donnell, M. H. (2015). Prenatal smoking and age at menarche: Influence of the prenatal environment on the timing of puberty. *Human Reproduction*, *30*(4), 957-962. https://doi.org/10.1093/humrep/dev033

Bell, J. A., Carslake, D., Wade, K. H., Richmond, R. C., Langdon, R. J., Vincent, E. E., Holmes, M. V., Timpson, N. J., & Davey Smith, G. (2018). Influence of puberty timing on adiposity and cardiometabolic traits: A Mendelian randomisation study. *PLoS Med*, *15*(8), e1002641. https://doi.org/10.1371/journal.pmed.1002641

Belsky, J., & Shalev, I. (2016). Contextual adversity, telomere erosion, pubertal development, and health: Two models of accelerated aging, or one? *Development and Psychopathology*, *28*(4), 1367-1383. https://doi.org/10.1017/S0954579416000900

Belsky, J., Steinberg, L., & Draper, P. (1991). Childhood experience, interpersonal development, and reproductive strategy: An evolutionary theory of socialization. *Child Development*, *62*(4), 647-670. https://doi.org/DOI 10.1111/j.1467-8624.1991.tb01558.x

Beltz, A. M., Corley, R. P., Bricker, J. B., Wadsworth, S. J., & Berenbaum, S. A. (2014). Modeling pubertal timing and tempo and examining links to behavior problems. *Developmental Psychology*, *50*(12), 2715-2726. https://doi.org/10.1037/a0038096

Berends, L., Dearden, L., Tung, Y., Voshol, P., Fernandez-Twinn, D., & Ozanne, S. (2018). Programming of central and peripheral insulin resistance by low birthweight and postnatal catch-up growth in male mice. *Clinical, Translational and Experimental Diabetes and Metabolism*, *61*(10), 2225-2234. https://doi.org/10.1007/s00125-018-4694-z

Bichteler, A., & Gershoff, E. T. (2018). Identification of children's BMI trajectories and prediction from weight gain in infancy. *Obesity*, *26*(6), 1050-1056. https://doi.org/10.1002/oby.22177

Biosca, M., Rodríguez, G., Ventura, P., Samper, M. P., Labayen, I., Collado, M. P., Valle, S., Bueno, O., Santabárbara, J., & Moreno, L. A. (2011). Central adiposity in children born small and large for gestational age. *Nutrición Hospitalaria*, *26*(5), 971-976. https://doi.org/10.1590/s0212-16112011000500008

Biro, F. M., & Deardorff, J. (2013). Identifying opportunities for cancer prevention during preadolescence and adolescence: puberty as a window of susceptibility. *The Journal of Adolescent Health*, *52*(5 Suppl), S15-S20. https://doi.org/10.1016/j.jadohealth.2012.09.019

Biro, F. M., Falkner, F., Khoury, P., Morrison, J. A., & Lucky, A. W. (1992). Areolar and breast staging in adolescent girls. *Adolescent and Pediatric Gynecology*, *5*(4), 271-272.

Biro, F. M., Wolff, M. S., & Kushi, L. H. (2009). Impact of yesterday's genes and today's diet and chemicals on tomorrow's women. *Journal of Pediatric Adolescence Gynecology*, *22*(1), 3-6. https://doi.org/10.1016/j.jpag.2008.12.003

Boerschmann, H., Pflüger, M., Henneberger, L., Ziegler, A.-G., & Hummel, S. (2010). Prevalence and predictors of overweight and insulin resistance in offspring of mothers with gestational diabetes mellitus. *Diabetes Care*, *33*(8), 1845-1849. https://doi.org/10.2337/dc10-0139

Bonat, S., Pathomvanich, A., Keil, M. F., Field, A. E., & Yanovski, J. A. (2002). Self-assessment of pubertal stage in overweight children. *Pediatrics*, *110*(4), 743. https://doi.org/10.1542/peds.110.4.743

Boynton-Jarrett, R., Rich-Edwards, J., Fredman, L., Hibert, E. L., Michels, K. B., Forman, M. R., & Wright, R. J. (2011). Gestational weight gain and daughter's age at menarche. *Journal of Women's Health*, *20*(8), 1193-1200. https://doi.org/10.1089/jwh.2010.2517

Braithwaite, D., Moore, D. H., Lustig, R. H., Epel, E. S., Ong, K. K., Rehkopf, D. H., Wang, M. C., Miller, S. M., & Hiatt, R. A. (2009). Socioeconomic status in relation to early menarche among black and white girls. *Cancer Causes & Control*, *20*(5), 713-720. https://doi.org/10.1007/s10552-008-9284-9

Brix, N., Ernst, A., Lauridsen, L. L. B., Arah, O. A., Nohr, E. A., Olsen, J., Henriksen, T. B., & Ramlau-Hansen, C. H. (2019). Maternal pre-pregnancy obesity and timing of puberty in sons and daughters: A population-based cohort study. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyz125

Brix, N., Ernst, A., Lauridsen, L. L. B., Parner, E. T., Olsen, J., Henriksen, T. B., & Ramlau-Hansen, C. H. (2019). Maternal smoking during pregnancy and timing of puberty in sons and daughters: A population-based cohort study. *American Journal of Epidemiology, 188*(1), 47-56. https://doi.org/10.1093/aje/kwy206

Brix, N., Lauridsen, L. L. B., Ernst, A., Olsen, J., Henriksen, T. B., & Ramlau-Hansen, C. H. (2019). Alcohol intake during pregnancy and timing of puberty in sons and daughters: A nationwide cohort study. *Reproductive Toxicology, 91*, 35-42. https://doi.org/10.1016/j.reprotox.2019.11.003

Broere-Brown, Z. A., Baan, E., Schalekamp-Timmermans, S., Verburg, B. O., Jaddoe, V. W., & Steegers, E. A. (2016). Sex-specific differences in fetal and infant growth patterns: A prospective population-based cohort study. *Biology of Sex Differences, 7*, 65. https://doi.org/10.1186/s13293-016-0119-1

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P.-R., ReproGen, C., Psychiatric Genomics, C., Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control, C., Duncan, L., Perry, J. R. B., Patterson, N., Robinson, E. B., Daly, M. J., Price, A. L., & Neale, B. M. (2015). An atlas of genetic correlations across human diseases and traits. *Nature Genetics, 47*(11), 1236-1241. https://doi.org/10.1038/ng.3406

Busch, A. S., Hollis, B., Day, F. R., Sorensen, K., Aksglaede, L., Perry, J. R. B., Ong, K. K., Juul, A., & Hagen, C. P. (2019). Voice break in boys-temporal relations with other pubertal milestones and likely causal effects of BMI. *Human Reproduction*. https://doi.org/10.1093/humrep/dez118

Byrne, M. L., Whittle, S., Vijayakumar, N., Dennison, M., Simmons, J. G., & Allen, N. B. (2017). A systematic review of adrenarche as a sensitive period in neurobiological development and mental health. *Developmental Cognitive Neuroscience*, *25*, 12-28. https://doi.org/10.1016/j.dcn.2016.12.004

Canoy, D., Beral, V., Balkwill, A., Wright, F. L., Kroll, M. E., Reeves, G. K., Green, J., & Cairns, B. J. (2015). Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation*, *131*(3), 237-244. https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.114.010070?download=true

Carling, S. J., Demment, M. M., Kjolhede, C. L., & Olson, C. M. (2015). Breastfeeding duration and weight gain trajectory in infancy. *Pediatrics*, *135*(1), 111-119. https://doi.org/10.1542/peds.2014-1392

Carter, R. C., Jacobson, J. L., Molteno, C. D., Jiang, H., Meintjes, E. M., Jacobson, S. W., & Duggan, C. (2012). Effects of heavy prenatal alcohol exposure and iron deficiency anemia on child growth and body composition through age 9 years. *Alcoholism, Clinical and Experimental Research*, *36*(11), 1973-1982. https://doi.org/10.1111/j.1530-0277.2012.01810.x

Castillo-Laura, H., Santos, I. S., Quadros, L. C., & Matijasevich, A. (2015). Maternal obesity and offspring body composition by indirect methods: A systematic review and meta-analysis. *Cad Saude Publica*, *31*(10), 2073-2092. https://doi.org/10.1590/0102-311X00159914

Catalano, P. M., Roman-Drago, N. M., Amini, S. B., & Sims, E. A. H. (1998). Longitudinal changes in body composition and energy balance in lean women with normal and abnormal glucose tolerance during pregnancy. *American Journal of Obstetrics and Gynecology*, *179*(1), 156-165. https://doi.org/10.1016/S0002-9378(98)70267-4

Chang, E., Hafner, H., Varghese, M., Griffin, C., Clemente, J., Islam, M., Carlson, Z., Zhu, A., Hak, L., Abrishami, S., Gregg, B., & Singer, K. (2019). Programming effects of maternal and gestational obesity on offspring metabolism and metabolic inflammation. *Scientific Reports*, *9*(1), 16027. https://doi.org/10.1038/s41598-019-52583-x

Chen, X., & Wang, Y. (2009). The influence of sexual maturation on blood pressure and body fatness in African-American adolescent girls and boys. *American Journal of Human Biology*, *21*(1), 105-112. https://doi.org/10.1002/ajhb.20832

Chen, Y.-C., Fan, H.-Y., Yang, C., Hsieh, R.-H., Pan, W.-H., & Lee, Y. L. (2019). Assessing causality between childhood adiposity and early puberty: A bidirectional Mendelian randomization and longitudinal study. *Metabolism: Clinical and Experimental*, *100*, 153961. https://doi.org/10.1016/j.metabol.2019.153961

Chen, Y., Liu, Q., Li, W., Deng, X., Yang, B., & Huang, X. (2018). Association of prenatal and childhood environment smoking exposure with puberty timing: A systematic review and meta-analysis. *Environmental Health and Preventive Medicine*, *23*(1), 33. https://doi.org/10.1186/s12199-018-0722-3

Chen, Y. C., Fan, H. Y., Yang, C., Hsieh, R. H., Pan, W. H., & Lee, Y. L. (2019). Assessing causality between childhood adiposity and early puberty: A bidirectional Mendelian randomization and longitudinal study. *Metabolism*, *100*, 153961. https://doi.org/10.1016/j.metabol.2019.153961

Cheng, T. S., Day, F. R., Lakshman, R., & Ong, K. K. (2020). Association of puberty timing with type 2 diabetes: A systematic review and meta-analysis. *PLoS medicine*, *17*(1), e1003017-e1003017. https://doi.org/10.1371/journal.pmed.1003017

Cohen, E., Baerts, W., & van Bel, F. (2015). Brain-sparing in intrauterine growth restriction: Considerations for the neonatologist. *Neonatology*, *108*(4), 269-276. https://doi.org/10.1159/000438451

Collaborators, G. B. D. T. (2017). Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: A systematic analysis from the Global Burden of Disease Study 2015. *Lancet*, *389*(10082), 1885-1906. https://doi.org/10.1016/S0140-6736(17)30819-X

Conter, V., Cortinovis, I., Rogari, P., & Riva, L. (1995). Weight growth in infants born to mothers who smoked during pregnancy. *BMJ*, *310*(6982), 768-771. https://doi.org/10.1136/bmj.310.6982.768

Copeland, W., Shanahan, L., Miller, S., Costello, E. J., Angold, A., & Maughan, B. (2010). Outcomes of Early Pubertal Timing in Young Women: A Prospective Population-Based Study. *American Journal of Psychiatry*, *167*(10), 1218-1225. https://doi.org/10.1176/appi.ajp.2010.09081190

D'Aloisio, A. A., DeRoo, L. A., Baird, D. D., Weinberg, C. R., & Sandler, D. P. (2013). Prenatal and infant exposures and age at menarche. *Epidemiology*, *24*(2), 277-284. https://doi.org/10.1097/EDE.0b013e31828062b7

D'Onofrio, B. M., Turkheimer, E. N., Eaves, L. J., Corey, L. A., Berg, K., Solaas, M. H., & Emery, R. E. (2003). The role of the children of twins design in elucidating causal relations between parent characteristics and child outcomes. *Journal of Child Psychology and Psychiatry*, *44*(8), 1130-1144. https://doi.org/10.1111/1469-7610.00196

da Silva Magalhães, E. I., Peixoto Lima, N., Baptista Menezes, A. M., Gonçalves, H., Wehrmeister, F. C., Formoso Assunção, M., & Lessa Horta, B. (2019). Maternal smoking during pregnancy and offspring body composition in adulthood: Results from two birth cohort studies. *BMJ*, *9*(6), e023852-e023852. https://doi.org/10.1136/bmjopen-2018-023852

Davison, K. K., Susman, E. J., & Birch, L. L. (2003). Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. *Pediatrics*, *111*(4), 815-821. https://doi.org/DOI 10.1542/peds.111.4.815

Day, F. R., Elks, C. E., Murray, A., Ong, K. K., & Perry, J. R. B. (2015). Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: The UK Biobank Study. *Scientific Reports*, *5*. https://doi.org/ARTN1120810.1038/srep11208

Deardorff, J., Abrams, B., Ekwaru, J. P., & Rehkopf, D. H. (2014). Socioeconomic status and age at menarche: an examination of multiple indicators in an ethnically diverse cohort. *Annals of Epidemiology*, *24*(10), 727-733. https://doi.org/10.1016/j.annepidem.2014.07.002

Deardorff, J., Berry-Millett, R., Rehkopf, D., Luecke, E., Lahiff, M., & Abrams, B. (2013). Maternal pre-pregnancy BMI, gestational weight Gain, and age at menarche in daughters. *Maternal and Child Health Journal*, *17*(8), 1391-1398. https://doi.org/10.1007/s10995-012-1139-z

Deardorff, J., Ekwaru, J. P., Kushi, L. H., Ellis, B. J., Greenspan, L. C., Mirabedi, A., Landaverde, E. G., & Hiatt, R. A. (2011). Father absence, body mass index, and pubertal timing in girls: Differential effects by family income and ethnicity. *The Journal of Adolescent Health*, *48*(5), 441-447. https://doi.org/10.1016/j.jadohealth.2010.07.032

Deardorff, J., Fyfe, M., Ekwaru, J. P., Kushi, L. H., Greenspan, L. C., & Yen, I. H. (2012). Does neighborhood environment influence girls' pubertal onset? findings from a cohort study. *BMC Pediatrics*, *12*, 27. https://doi.org/10.1186/1471-2431-12-27

Deardorff, J., Hoyt, L. T., Carter, R., & Shirtcliff, E. A. (2019). Next steps in puberty research: Broadening the lens toward understudied populations. *Journal of Research on Adolescence*, *29*(1), 133-154. https://doi.org/10.1111/jora.12402

Deardorff, J., Reeves, J. W., Hyland, C., Tilles, S., Rauch, S., Kogut, K., Greenspan, L. C., Shirtcliff, E., Lustig, R. H., Eskenazi, B., & Harley, K. (2021). Childhood Overweight and Obesity and Pubertal Onset Among Mexican American Boys and Girls in the CHAMACOS Longitudinal Study. *American Journal of Epidemiology*. https://doi.org/10.1093/aje/kwab100

Deng, X., Li, W., Luo, Y., Liu, S., Wen, Y., & Liu, Q. (2017). Association between small fetuses and puberty timing: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, *14*(11). https://doi.org/10.3390/ijerph14111377

Denison, F. C., Roberts, K. A., Barr, S. M., & Norman, J. E. (2010). Obesity, pregnancy, inflammation, and vascular function. *Reproduction, 140*(3), 373-385. https://doi.org/10.1530/REP-10-0074

DiPietro, J. A., & Voegtline, K. M. (2017). The gestational foundation of sex differences in development and vulnerability. *Neuroscience, 342*, 4-20. https://doi.org/10.1016/j.neuroscience.2015.07.068

Dorn, L. D., Dahl, R. E., Woodward, H. R., & Biro, F. (2006). Defining the boundaries of early adolescence: A user's guide to assessing pubertal status and pubertal timing in research with adolescents. *Applied Developmental Science*, *10*(1), 30-56. https://doi.org/10.1207/s1532480xads1001_3

Dorn, L. D., Hostinar, C. E., Susman, E. J., & Pervanidou, P. (2019). Conceptualizing Puberty as a Window of Opportunity for Impacting Health and Well-Being Across the Life Span. *Journal of Research on Adolescence*, *29*(1), 155-176. https://doi.org/10.1111/jora.12431

Dorn, L. D., Susman, E. J., & Ponirakis, A. (2003). Pubertal Timing and Adolescent Adjustment and Behavior: Conclusions Vary by Rater. *Journal of Youth and Adolescence*, *32*(3), 157-167. https://doi.org/10.1023/A:1022590818839

dos Santos Silva, I., De Stavola, B. L., Mann, V., Kuh, D., Hardy, R., & Wadsworth, M. E. (2002). Prenatal factors, childhood growth trajectories and age at menarche. *International Journal of Epidemiology*, *31*(2), 405-412. https://doi.org/10.1093/ije/31.2.405

Dossus, L., Kvaskoff, M., Bijon, A., Fervers, B., Boutron-Ruault, M. C., Mesrine, S., & Clavel-Chapelon, F. (2012). Determinants of age at menarche and time to menstrual cycle regularity in the French E3N cohort. *Annals of Epidemiology, 22*(10), 723-730. https://doi.org/10.1016/j.annepidem.2012.07.007

Dubas, J. S., Graber, J. A., & Petersen, A. C. (1991). The Effects of Pubertal Development on Achievement during Adolescence. *American Journal of Education*, *99*(4), 444-460. https://doi.org/10.1086/443993

Dulloo, A. G., Jacquet, J., Seydoux, J., & Montani, J. P. (2006). The thrifty 'catch-up fat' phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. *International Journal of Obesity*, *30 Suppl 4*, S23. https://www.nature.com/articles/0803516.pdf

Dunger, D. B., Ahmed, M. L., & Ong, K. K. (2006). Early and late weight gain and the timing of puberty. *Molecular and Cellular Endocrinology*, *254-255*, 140-145. https://doi.org/10.1016/j.mce.2006.04.003

Dunger, D. B., Lynn Ahmed, M., & Ong, K. K. (2005). Effects of obesity on growth and puberty. *Best Practice & Research Clinical Endocrinology & Metabolism*, *19*(3), 375-390. https://doi.org/10.1016/j.beem.2005.04.005

Ellis, B. J., & Essex, M. J. (2007). Family environments, adrenarche, and sexual maturation: A longitudinal test of a life history model. *Child Development*, *78*(6), 1799-1817. https://doi.org/10.1111/j.1467-8624.2007.01092.x

Elwan, D., Olveda, R., Medrano, R., & Wojcicki, J. M. (2021). Excess pregnancy weight gain in latinas: Impact on infant's adiposity and growth hormones at birth. *Preventive Medicine Reports*, *22*, 101341. https://doi.org/https://doi.org/10.1016/j.pmedr.2021.101341

Ernst, A., Kristensen, S. L., Toft, G., Thulstrup, A. M., Hakonsen, L. B., Olsen, S. F., & Ramlau-Hansen, C. H. (2012). Maternal smoking during pregnancy and reproductive health of daughters: A follow-up study spanning two decades. *Human Reproduction*, *27*(12), 3593-3600. https://doi.org/10.1093/humrep/des337

Euling, S. Y., Herman-Giddens, M. E., Lee, P. A., Selevan, S. G., Juul, A., Sorensen, T. I., Dunkel, L., Himes, J. H., Teilmann, G., & Swan, S. H. (2008). Examination of US puberty-timing data from 1940 to 1994 for secular trends: Panel findings. *Pediatrics, 121 Suppl 3*, S172-191. https://doi.org/10.1542/peds.2007-1813D

Fall, C. H. D. (2001). Non-industrialised countries and affluence: Relationship with type 2 diabetes. *British Medical Bulletin, 60*(1), 33-50. https://doi.org/10.1093/bmb/60.1.33

Ferris, J. S., Flom, J. D., Tehranifar, P., Mayne, S. T., & Terry, M. B. (2010). Prenatal and childhood environmental tobacco smoke exposure and age at menarche. *Paediatric and Perinatal Epidemiology, 24*(6), 515-523. https://doi.org/10.1111/j.1365-3016.2010.01154.x

Flegal, K. M., & Ogden, C. L. (2011). Childhood obesity: Are we all speaking the same language? *Advances in Nutrition, 2*(2), 159S-166S. https://doi.org/10.3945/an.111.000307

Fowden, A. L. (1989). The role of insulin in prenatal growth. *Journal of Developmental Physiology, 12*(4), 173-182.

Fowden, A. L. (1995). Endocrine regulation of fetal growth. *Reproduction, Fertility and Development, 7*(3), 351-363. https://doi.org/10.1071/RD9950351

Freedman, D. S., Khan, L. K., Serdula, M. K., Dietz, W. H., Srinivasan, S. R., Berenson, G. S., & Bogalusa heart, s. (2003). The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. *BMC Pediatrics, 3*, 3-3. https://doi.org/10.1186/1471-2431-3-3

Fryar, C. D., Carroll, M. D., & Ogden, C. L. (2018). Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2015–2016.

Fuglestad, A. J., Boys, C. J., Chang, P.-N., Miller, B. S., Eckerle, J. K., Deling, L., Fink, B. A., Hoecker, H. L., Hickey, M. K., Jimenez-Vega, J. M., & Wozniak, J. R. (2014). Overweight and obesity among children and adolescents with fetal alcohol spectrum disorders. *Alcoholism, Clinical and Experimental Research*, *38*(9), 2502-2508. https://doi.org/10.1111/acer.12516

Gariepy, J., Denarie, N., Chironi, G., Salomon, J., Levenson, J., & Simon, A. (2000). Gender difference in the influence of smoking on arterial wall thickness. *Atherosclerosis*, *153*(1), 139-145. https://doi.org/10.1016/s0021-9150(00)00382-8

Ge, X., Conger, R. D., & Elder, G. H., Jr. (2001). Pubertal transition, stressful life events, and the emergence of gender differences in adolescent depressive symptoms. *Developmental Psychology*, *37*(3), 404-417. https://doi.org/10.1037//0012-1649.37.3.404

Ge, X., Natsuaki, M. N., Neiderhiser, J. M., & Reiss, D. (2007). Genetic and Environmental Influences on Pubertal Timing: Results From Two National Sibling Studies. *Journal of Research on Adolescence*, *17*(4), 767-788. https://doi.org/10.1111/j.1532-7795.2007.00546.x

Gluckman, P. D., & Hanson, M. A. (2004). The developmental origins of the metabolic syndrome. *Trends in Endocrinology & Metabolism*, *15*(4), 183-187. https://doi.org/10.1016/j.tem.2004.03.002

Gluckman, P. D., & Hanson, M. A. (2006a). Changing times: The evolution of puberty. *Molecular and Cellular Endocrinology, 254-255*, 26-31. https://doi.org/10.1016/j.mce.2006.04.005

Gluckman, P. D., & Hanson, M. A. (2006b). Evolution, development and timing of puberty. *Trends in Endocrinology & Metabolism, 17*(1), 7-12. https://doi.org/10.1016/j.tem.2005.11.006

Gluckman, P. D., & Pinal, C. (2001). Glucose tolerance in adults after prenatal exposure to famine. *Lancet, 357*(9270), 1798-1798. https://doi.org/10.1016/S0140-6736(00)04909-6

Goldstein, R. F., Abell, S. K., Ranasinha, S., Misso, M., Boyle, J. A., Black, M. H., Li, N., Hu, G., Corrado, F., Rode, L., Kim, Y. J., Haugen, M., Song, W. O., Kim, M. H., Bogaerts, A., Devlieger, R., Chung, J. H., & Teede, H. J. (2017). Association of gestational weight gain with maternal and infant outcomes: A systematic review and meta-analysis. *Journal of the American Medical Association, 317*(21), 2207-2225. https://doi.org/10.1001/jama.2017.3635

Goran, M. I., Gower, B. A., Nagy, T. R., & Johnson, R. K. (1998). Developmental changes in energy expenditure and physical activity in children: evidence for a decline in physical activity in girls before puberty. *Pediatrics, 101*(5), 887-891. https://doi.org/10.1542/peds.101.5.887

Guerrero, A. D., Mao, C., Fuller, B., Bridges, M., Franke, T., & Kuo, A. A. (2016). Racial and ethnic disparities in early childhood obesity: Growth trajectories in body mass index. *Journal of Racial and Ethnic Health Disparities, 3*(1), 129-137. https://doi.org/10.1007/s40615-015-0122-y

Hack, M., Merkatz, I. R., McGrath, S. K., Jones, P. K., & Fanaroff, A. A. (1984). Catch-up growth in very-low-birth-weight infants: Clinical correlates. *The American Journal of Diseases of Children*, *138*(4), 370-375. https://doi.org/10.1001/archpedi.1984.02140420036013

Hack, M., Schluchter, M., Cartar, L., Rahman, M., Cuttler, L., & Borawski, E. (2003). Growth of very low birth weight infants to age 20 years. *Pediatrics*, *112*(1), E30-E38. https://doi.org/DOI 10.1542/peds.112.1.e30

Hakonsen, L. B., Brath-Lund, M. L., Hounsgaard, M. L., Olsen, J., Ernst, A., Thulstrup, A. M., Bech, B. H., & Ramlau-Hansen, C. H. (2014). In utero exposure to alcohol and puberty in boys: a pregnancy cohort study. *BMJ*, *4*(6), e004467. https://doi.org/10.1136/bmjopen-2013-004467

Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2020). Prevalence of obesity and severe obesity among adults: United States, 2017–2018.

Hales, C. N., & Barker, D. J. (1992). Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. *Diabetologia*, *35*(7), 595-601. https://doi.org/10.1007/bf00400248

Hales, C. N., & Barker, D. J. (2001). The thrifty phenotype hypothesis: Type 2 diabetes. *British Medical Bulletin*, *60*(1), 5-20. https://doi.org/10.1093/bmb/60.1.5

Harding, J. E., & Johnston, B. M. (1995). Nutrition and fetal growth. *Reproduction, Fertility and Development*, *7*(3), 539-547. https://doi.org/10.1071/RD9950539

Harris, H. R., Willett, W. C., & Michels, K. B. (2013). Parental smoking during pregnancy and risk of overweight and obesity in the daughter. *International Journal of Obesity*, *37*(10), 1356-1363. https://doi.org/10.1038/ijo.2013.101

Heerwagen, M. J. R., Miller, M. R., Barbour, L. A., & Friedman, J. E. (2010). Maternal obesity and fetal metabolic programming: A fertile epigenetic soil. *American Journal of Physiology*, *299*(3), R711. https://doi.org/10.1152/ajpregu.00310.2010

Herman-Giddens, M. E., Steffes, J., Harris, D., Slora, E., Hussey, M., Dowshen, S. A., Wasserman, R., Serwint, J. R., Smitherman, L., & Reiter, E. O. (2012). Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. *Pediatrics*, *130*(5), e1058-1068. https://doi.org/10.1542/peds.2011-3291

Hill, S. Y., Shen, S., Locke Wellman, J., Rickin, E., & Lowers, L. (2005). Offspring from families at high risk for alcohol dependence: Increased body mass index in association with prenatal exposure to cigarettes but not alcohol. *Psychiatry research*, *135*(3), 203-216. https://doi.org/10.1016/j.psychres.2005.04.003

Hong, X., Hao, K., Ji, H., Peng, S., Sherwood, B., Di Narzo, A., Tsai, H. J., Liu, X., Burd, I., Wang, G., Ji, Y., Caruso, D., Mao, G., Bartell, T. R., Zhang, Z., Pearson, C., Heffner, L., Cerda, S., Beaty, T. H., Fallin, M. D., Lee-Parritz, A., Zuckerman, B., Weeks, D. E., & Wang, X. (2017). Genome-wide approach identifies a novel gene-maternal pre-pregnancy BMI interaction on preterm birth. *Nature Communications*, *8*, 15608. https://doi.org/10.1038/ncomms15608

Houghton, L. C., Goldberg, M., Wei, Y., Cirillo, P. M., Cohn, B. A., Michels, K. B., & Terry, M. B. (2018). Why do studies show different associations between intrauterine exposure to maternal smoking and age at menarche? *Annals of Epidemiology*, *28*(3), 197-203. https://doi.org/10.1016/j.annepidem.2018.01.004

Hounsgaard, M. L., Hakonsen, L. B., Vested, A., Thulstrup, A. M., Olsen, J., Bonde, J. P., Nohr, E. A., & Ramlau-Hansen, C. H. (2014). Maternal pre-pregnancy body mass index and pubertal development among sons. *Andrology*, *2*(2), 198-204. https://doi.org/10.1111/j.2047-2927.2013.00171.x

Hruby, A., & Hu, F. B. (2015). The epidemiology of obesity: A big picture. *PharmacoEconomics*, *33*(7), 673-689. https://doi.org/10.1007/s40273-014-0243-x

Hu, L.-t., & Bentler, P. M. (1998). Fit Indices in Covariance Structure Modeling: Sensitivity to Underparameterized Model Misspecification. *Psychological Methods*, *3*(4), 424-453. https://doi.org/10.1037/1082-989X.3.4.424

Hu, L.-T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, *6*(1), 1-55. https://doi.org/10.1080/10705519909540118

IOM. (2009). In K. M. Rasmussen & A. L. Yaktine (Eds.), *Weight Gain During Pregnancy: Reexamining the Guidelines*. https://doi.org/10.17226/12584

Jacobsen, B. K., Oda, K., Knutsen, S. F., & Fraser, G. E. (2009). Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: The Adventist Health Study, 1976-88. *International Journal of Epidemiology*, *38*(1), 245-252. https://doi.org/10.1093/ije/dyn251

Jaddoe, V. W. V., de Jonge, L. L., van Dam, R. M., Willett, W. C., Harris, H., Stampfer, M. J., Hu, F. B., & Michels, K. B. (2014). Fetal exposure to parental smoking and the risk of type 2 diabetes in adult women. *Diabetes Care*, *37*(11), 2966. https://doi.org/10.2337/dc13-1679

Jain, V., & Singhal, A. (2012). Catch up growth in low birth weight infants: Striking a healthy balance. *Reviews in Endocrine and Metabolic Disorders*, *13*(2), 141-147. https://doi.org/10.1007/s11154-012-9216-6

Javed, A., Jumean, M., Murad, M. H., Okorodudu, D., Kumar, S., Somers, V. K., Sochor, O., & Lopez-Jimenez, F. (2015). Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: A systematic review and meta-analysis. *Pediatric Obesity*, *10*(3), 234-244. https://doi.org/10.1111/ijpo.242

Jazwiec, P. A., & Sloboda, D. M. (2019). Nutritional adversity, sex and reproduction: 30 years of DOHaD and what have we learned? *Journal of Endocrinology*, *242*(1), T51-t68. https://doi.org/10.1530/joe-19-0048

Juul, F., Chang, V. W., Brar, P., & Parekh, N. (2017). Birth weight, early life weight gain and age at menarche: A systematic review of longitudinal studies. *Obesity Reviews*, *18*(11), 1272-1288. https://doi.org/10.1111/obr.12587

Kapral, N., Miller, S. E., Scharf, R. J., Gurka, M. J., & DeBoer, M. D. (2018). Associations between birthweight and overweight and obesity in school-age children. *Pediatric Obesity*, *13*(6), 333-341. https://doi.org/10.1111/ijpo.12227

Karaolis-Danckert, N., Buyken, A. E., Sonntag, A., & Kroke, A. (2009). Birth and early life influences on the timing of puberty onset: Results from the DONALD (DOrtmund Nutritional and Anthropometric Longitudinally Designed) Study. *American Journal of Clinical Nutrition*, *90*(6), 1559-1565. https://doi.org/10.3945/ajcn.2009.28259

Katzmarzyk, P. T., Barreira, T. V., Broyles, S. T., Chaput, J. P., Fogelholm, M., Hu, G., Kuriyan, R., Kurpad, A., Lambert, E. V., Maher, C., Maia, J., Matsudo, V., Olds, T., Onywera, V., Sarmiento, O. L., Standage, M., Tremblay, M. S., Tudor-Locke, C., Zhao, P., & Church, T. S. (2015). Association between body mass index and body fat in 9-11-year-old children from countries spanning a range of human development. *International Journal of Obesity Supplements*, *5*(Suppl 2), S43-46. https://doi.org/10.1038/ijosup.2015.18

Keim, S. A., Branum, A. M., Klebanoff, M. A., & Zemel, B. S. (2009). Maternal body mass index and daughters' age at menarche. *Epidemiology*, *20*(5), 677-681. https://doi.org/10.1097/EDE.0b013e3181b093ce

Kelly, Y., Zilanawala, A., Sacker, A., Hiatt, R., & Viner, R. (2017). Early puberty in 11-year-old girls: Millennium Cohort Study findings. *Archives of Disease in Childhood*, *102*(3), 232. https://doi.org/10.1136/archdischild-2016-310475

Kim, D. D., & Basu, A. (2016). Estimating the medical care costs of obesity in the United States: Systematic review, meta-analysis, and empirical analysis. *Value in Health*, *19*(5), 602-613. https://doi.org/10.1016/j.jval.2016.02.008

Kjaer, T. W., Faurholt-Jepsen, D., Medrano, R., Elwan, D., Mehta, K., Christensen, V. B., & Wojcicki, J. M. (2019). Higher Birthweight and Maternal Pre-pregnancy BMI Persist with Obesity Association at Age 9 in High Risk Latino Children. *Journal of Immigrant and Minority Health*, *21*(1), 89-97. https://doi.org/10.1007/s10903-018-0702-0

Klebanoff, M. A., Levine, R. J., Clemens, J. D., DerSimonian, R., & Wilkins, D. G. (1998). Serum cotinine concentration and self-reported smoking during pregnancy. *American Journal of Epidemiology*, *148*(3), 259-262. https://doi.org/10.1093/oxfordjournals.aje.a009633

Knopik, V. S., Marceau, K., Palmer, R. H. C., Smith, T. F., & Heath, A. C. (2016). Maternal smoking during pregnancy and offspring birth weight: A genetically-informed approach comparing multiple raters. *Behavior Genetics*, *46*(3), 353-364. https://doi.org/10.1007/s10519-015-9750-6

Kraemer, S. (2000). The fragile male. *BMJ*, *321*(7276), 1609-1612. https://doi.org/10.1136/bmj.321.7276.1609

Kubo, A., Deardorff, J., Laurent, C. A., Ferrara, A., Greenspan, L. C., Quesenberry, C. P., & Kushi, L. H. (2018). Associations between maternal obesity and pregnancy hyperglycemia and timing of puberty onset in adolescent girls: A population-based study. *American Journal of Epidemiology*, *187*(7), 1362-1369. https://doi.org/10.1093/aje/kwy040

Kuczmarski, R. J., Ogden, C. L., Guo, S. S., Grummer-Strawn, L. M., Flegal, K. M., Mei, Z., Wei, R., Curtin, L. R., Roche, A. F., & Johnson, C. L. (2002). 2000 CDC Growth Charts for the United States: methods and development. *Vital and Health Statistics Series*(246), 1-190.

Kuja-Halkola, R., D'Onofrio, B. M., Larsson, H., & Lichtenstein, P. (2014). Maternal smoking during pregnancy and adverse outcomes in offspring: Genetic and environmental sources of covariance. *Behavior Genetics*, *44*(5), 456-467. https://doi.org/10.1007/s10519-014-9668-4

Kwon, E. J., & Kim, Y. J. (2017). What is fetal programming?: A lifetime health is under the control of in utero health. *Obstetrics & Gynecology Science*, *60*(6), 506-519. https://doi.org/10.5468/ogs.2017.60.6.506

Lambers, D. S., & Clark, K. E. (1996). The maternal and fetal physiologic effects of nicotine. *Seminars in Perinatology*, *20*(2), 115-126. https://doi.org/10.1016/s0146-0005(96)80079-6

Laml, T., Hartmann, B. W., Kirchengast, S., Preyer, O., Albrecht, A. E., & Husslein, P. W. (2000). Impact of maternal athropometry and smoking on neonatal birth weight. *Gynecologic and Obstetric Investigation*, *50*(4), 231-236. https://doi.org/10.1159/000010322

Lange, S., Probst, C., Rehm, J., & Popova, S. (2018). National, regional, and global prevalence of smoking during pregnancy in the general population: A systematic review and meta-analysis. *The Lancet Global Health*, *6*(7), e769-e776. https://doi.org/https://doi.org/10.1016/S2214-109X(18)30223-7

Lawlor, D. A., Smith, G. D., O'Callaghan, M., Alati, R., Mamun, A. A., Williams, G. M., & Najman, J. M. (2006). Epidemiologic evidence for the fetal overnutrition hypothesis: Findings from the Mater-University Study of Pregnancy and Its Outcomes. *American Journal of Epidemiology*, *165*(4), 418-424. https://doi.org/10.1093/aje/kwk030

Lawlor, D. A., Smith, G. D., O'Callaghan, M., Alati, R., Mamun, A. A., Williams, G. M., & Najman, J. M. (2007). Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the Mater-University Study of Pregnancy and Its Outcomes. *American Journal of Epidemiology*, *165*(4), 418. https://doi.org/10.1093/aje/kwk030

Lawlor, D. A., Timpson, N. J., Harbord, R. M., Leary, S., Ness, A., McCarthy, M. I., Frayling, T. M., Hattersley, A. T., & Smith, G. D. (2008). Exploring the developmental overnutrition hypothesis using parental-offspring associations and FTO as an instrumental variable. *PLoS medicine*, *5*(3), e33-e33. https://doi.org/10.1371/journal.pmed.0050033

Lawn, R. B., Lawlor, D. A., & Fraser, A. (2018). Associations between maternal prepregnancy body mass index and gestational geight gain and daughter's age at menarche: The Avon Longitudinal Study of Parents and Children. *American Journal of Epidemiology*, *187*(4), 677-686. https://doi.org/10.1093/aje/kwx308

Lee, J. M., Appugliese, D., Kaciroti, N., & Corwyn, R. (2007). Weight status in young girls and the onset of puberty. *Pediatrics*, *119*(3), 624-630. https://doi.org/doi:10.1542/peds.2006-2188

Lee, J. M., Wasserman, R., Kaciroti, N., Gebremariam, A., Steffes, J., Dowshen, S., Harris, D., Serwint, J., Abney, D., Smitherman, L., Reiter, E., & Herman-Giddens, M. E. (2016). Timing of puberty in overweight versus obese boys. *Pediatrics*, *137*(2). https://doi.org/10.1542/peds.2015-0164

Li, L., Peters, H., Gama, A., Carvalhal, M. I., Nogueira, H. G., Rosado-Marques, V., & Padez, C. (2016). Maternal smoking in pregnancy association with childhood adiposity and blood pressure. *Pediatric Obesity*, *11*(3), 202-209. https://doi.org/10.1111/ijpo.12046

Li, W. Y., Liu, Q., Deng, X., Chen, Y. W., Liu, S. D., & Story, M. (2017). Association between obesity and puberty timing: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, *14*(10). https://doi.org/ARTN 1266 10.3390/ijerph14101266

Linabery, A. M., Nahhas, R. W., Johnson, W., Choh, A. C., Towne, B., Odegaard, A. O., Czerwinski, S. A., & Demerath, E. W. (2013). Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatric Obesity*, *8*(3), 159. https://doi.org/10.1111/j.2047-6310.2012.00100.x

Liu, P., Xu, L., Wang, Y., Zhang, Y., Du, Y., Sun, Y., & Wang, Z. (2016). Association between perinatal outcomes and maternal pre-pregnancy body mass index. *Obesity Reviews, 17*(11), 1091-1102. https://doi.org/10.1111/obr.12455

Llewellyn, A., Simmonds, M., Owen, C. G., & Woolacott, N. (2016). Childhood obesity as a predictor of morbidity in adulthood: A systematic review and meta-analysis. *Obesity Reviews*, *17*, 56-67. https://doi.org/10.1111/obr.12316

Lu, W., Zhang, X., Wu, J., Mao, X., Shen, X., Chen, Q., Zhang, J., Huang, L., & Tang, Q. (2019). Association between trimester-specific gestational weight gain and childhood obesity at 5 years of age: results from Shanghai obesity cohort. *BMC Pediatrics*, *19*(1), 139. https://doi.org/10.1186/s12887-019-1517-4

Luke, B., Dickinson, C., & Petrie, R. H. (1981). Intrauterine growth: Correlations of maternal nutritional status and rate of gestational weight gain. *European Journal of Obstetrics and Gynecology*, *12*(2), 113-121. https://doi.org/10.1016/0028-2243(81)90024-1

Lundblad, M. W., & Jacobsen, B. K. (2017). The reproducibility of self-reported age at menarche: The Tromsø Study. *BMC Women's Health*, *17*(1), 62-62. https://doi.org/10.1186/s12905-017-0420-0

MacCallum, R. C., Browne, M. W., & Sugawara, H. M. (1996). Power Analysis and Determination of Sample Size for Covariance Structure Modeling. *Psychological Methods*, *1*(2), 130-149. https://doi.org/10.1037/1082-989X.1.2.130

Maftei, O., Whitrow, M. J., Davies, M. J., Giles, L. C., Owens, J. A., & Moore, V. M. (2015). Maternal body size prior to pregnancy, gestational diabetes and weight gain: Associations with insulin resistance in children at 9-10 years. *Diabetic Medicine*, *32*(2), 174-180. https://doi.org/10.1111/dme.12637

Magalhães, E., Sousa, B. A., Lima, N. P., & Horta, B. L. (2019). Maternal smoking during pregnancy and offspring body mass index and overweight: A systematic review and meta-analysis. *Cad Saude Publica*, *35*(12), e00176118. https://doi.org/10.1590/0102-311x00176118

Maisonet, M., Christensen, K. Y., Rubin, C., Holmes, A., Flanders, W. D., Heron, J., Ong, K. K., Golding, J., McGeehin, M. A., & Marcus, M. (2010). Role of prenatal characteristics and early growth on pubertal attainment of British girls. *Pediatrics*, *126*(3), e591-600. https://doi.org/10.1542/peds.2009-2636

Marceau, K., Abar, C. C., & Jackson, K. M. (2015). Parental Knowledge is a Contextual Amplifier of Associations of Pubertal Maturation and Substance Use. *Journal of Youth and Adolescence*, *44*(9), 1720-1734. https://doi.org/10.1007/s10964-015-0335-8

Marceau, K., Hottle, S., & Yatcilla, J. K. (2019). Puberty in the last 25 years: A retrospective bibliometric analysis. *Journal of Research on Adolescence*, *29*(1), 96-114. https://doi.org/10.1111/jora.12396

Marshall, W. A., & Tanner, J. M. (1969). Variations in Pattern of Pubertal Changes in Girls. *Archives of Disease in Childhood*, *44*(235), 291-&. https://doi.org/DOI 10.1136/adc.44.235.291

Marshall, W. A., & Tanner, J. M. (1970). Variations in Pattern of Pubertal Changes in Boys. *Archives of Disease in Childhood*, *45*(239), 13-&. https://doi.org/DOI 10.1136/adc.45.239.13

McIntyre, H. D., Chang, A. M., Callaway, L. K., Cowley, D. M., Dyer, A. R., Radaelli, T., Farrell, K. A., Huston-Presley, L., Amini, S. B., Kirwan, J. P., Catalano, P. M., Hyperglycemia, & Adverse Pregnancy Outcome Study Cooperative Research, G. (2010). Hormonal and metabolic factors associated with variations in insulin sensitivity in human pregnancy. *Diabetes Care*, *33*(2), 356-360. https://doi.org/10.2337/dc09-1196

McKeigue, P. M., Lithell, H. O., & Leon, D. A. (1998). Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth. *Diabetologia*, *41*(10), 1133-1138. https://doi.org/10.1007/s001250051042

Mei, H., Guo, S., Lu, H., Pan, Y., Mei, W., Zhang, B., & Zhang, J. (2018). Impact of parental weight status on children's body mass index in early life: Evidence from a Chinese cohort. *BMJ*, *8*(6), e018755-e018755. https://doi.org/10.1136/bmjopen-2017-018755

Mendle, J., Beltz, A. M., Carter, R., & Dorn, L. D. (2019). Understanding puberty and its measurement: Ideas for research in a new generation. *Journal of Research on Adolescence*, *29*(1), 82-95. https://doi.org/10.1111/jora.12371

Mendle, J., Leve, L. D., Van Ryzin, M., Natsuaki, M. N., & Ge, X. (2011). Associations between early life stress, child maltreatment, and pubertal development among girls in foster care. *Journal of Research on Adolescence*, *21*(4), 871-880. https://doi.org/10.1111/j.1532-7795.2011.00746.x

Mine, T., Tanaka, T., Nakasone, T., Itokazu, T., Yamagata, Z., & Nishiwaki, Y. (2017). Maternal smoking during pregnancy and rapid weight gain from birth to early infancy. *Journal of epidemiology*, *27*(3), 112-116. https://doi.org/10.1016/j.je.2016.10.005

Montgomery, S. M., & Ekbom, A. (2002). Smoking during pregnancy and diabetes mellitus in a British longitudinal birth cohort. *BMJ*, *324*(7328), 26-27. https://doi.org/10.1136/bmj.324.7328.26

Nafstad, P., Jaakkola, J. J., Hagen, J. A., Pedersen, B. S., Qvigstad, E., Botten, G., & Kongerud, J. (1997). Weight gain during the first year of life in relation to maternal smoking and breast feeding in Norway. *Journal of Epidemiology and Community Health*, *51*(3), 261-265. https://doi.org/10.1136/jech.51.3.261

Negriff, S., & Susman, E. J. (2011). Pubertal Timing, Depression, and Externalizing Problems: A Framework, Review, and Examination of Gender Differences. *Journal of Research on Adolescence*, *21*(3), 717-746. https://doi.org/10.1111/j.1532-7795.2010.00708.x

Nord, M., & Nord, C. M. (2012). Survey of income and program participation 1996 wave 8 food security data file technical documentation and user notes.

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2014). Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. *JAMA*, *311*(8), 806-814. https://doi.org/10.1001/jama.2014.732

Ohlsson, C., Bygdell, M., Celind, J., Sonden, A., Tidblad, A., Savendahl, L., & Kindblom, J. M. (2019). Secular trends in pubertal growth acceleration in Swedish Boys born From 1947 to 1996. *Journal of the American Medical Association Pediatrics*. https://doi.org/10.1001/jamapediatrics.2019.2315

Ohlsson, C., Bygdell, M., Nethander, M., & Kindblom, J. M. (2020). Early puberty and risk for type 2 diabetes in men. *Diabetologia*, *63*(6), 1141. https://doi.org/10.1007/s00125-020-05121-8

Oken, E., & Gillman, M. W. (2003). Fetal origins of obesity. *Obesity Research*, *11*(4), 496-506. https://doi.org/10.1038/oby.2003.69

Oken, E., Levitan, E. B., & Gillman, M. W. (2008). Maternal smoking during pregnancy and child overweight: Systematic review and meta-analysis. *International Journal of Obesity*, *32*(2), 201-210. https://doi.org/10.1038/sj.ijo.0803760

Ong, K. K., Bann, D., Wills, A. K., Ward, K., Adams, J. E., Hardy, R., Kuh, D., National Survey of, H., Development, S., & Data Collection, T. (2012). Timing of voice breaking in males associated with growth and weight gain across the life course. *The Journal of Clinical Endocrinology & Metabolism*, *97*(8), 2844-2852. https://doi.org/10.1210/jc.2011-3445

Ong, K. K., Emmett, P., Northstone, K., Golding, J., Rogers, I., Ness, A. R., Wells, J. C., & Dunger, D. B. (2009). Infancy weight gain predicts childhood body fat and age at menarche in girls. *The Journal of Clinical Endocrinology & Metabolism*, *94*(5), 1527-1532. https://doi.org/10.1210/jc.2008-2489

Patra, J., Bakker, R., Irving, H., Jaddoe, V. W. V., Malini, S., & Rehm, J. (2011). Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA): A systematic review and meta-analyses. *BJOG: An International Journal of Obstetrics & Gynaecology*, *118*(12), 1411-1421. https://doi.org/10.1111/j.1471-0528.2011.03050.x

Patro, B., Liber, A., Zalewski, B., Poston, L., Szajewska, H., & Koletzko, B. (2013). Maternal and paternal body mass index and offspring obesity: A systematic review. *Annals of Nutrition and Metabolism*, *63*(1-2), 32-41. https://doi.org/10.1159/000350313

Patton, G. C., McMorris, B. J., Toumbourou, J. W., Hemphill, S. A., Donath, S., & Catalano, R. F. (2004). Puberty and the onset of substance use and abuse. *Pediatrics*, *114*(3), e300-e306. https://doi.org/10.1542/peds.2003-0626-F

Pereira, P. P., Da Mata, F. A., Figueiredo, A. C., de Andrade, K. R., & Pereira, M. G. (2017). Maternal active smoking during pregnancy and low birth weight in the Americas: A systematic review and meta-analysis. *Nicotine & Tobacco Research*, *19*(5), 497-505. https://doi.org/10.1093/ntr/ntw228

Perng, W., Oken, E., & Dabelea, D. (2019). Developmental overnutrition and obesity and type 2 diabetes in offspring. *Diabetologia*. https://doi.org/10.1007/s00125-019-4914-1

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A Self-Report Measure of Pubertal Status - Reliability, Validity, and Initial Norms. *Journal of Youth and Adolescence*, *17*(2), 117-133. https://doi.org/Doi 10.1007/Bf01537962

Qiao, Y., Ma, J., Wang, Y., Li, W., Katzmarzyk, P. T., Chaput, J. P., Fogelholm, M., Johnson, W. D., Kuriyan, R., Kurpad, A., Lambert, E. V., Maher, C., Maia, J., Matsudo, V., Olds, T., Onywera, V., Sarmiento, O. L., Standage, M., Tremblay, M. S., Tudor-Locke, C., Church, T. S., Zhao, P., Hu, G., & Group, I. R. (2015). Birth weight and childhood obesity: A 12-country study. *International Journal of Obesity Supplements*, *5*, 74-79. https://doi.org/10.1038/ijosup.2015.23

Quelhas, D., Kompala, C., Wittenbrink, B., Han, Z., Parker, M., Shapiro, M., Downs, S., Kraemer, K., Fanzo, J., Morris, S., & Kreis, K. (2018). The association between active tobacco use during pregnancy and growth outcomes of children under five years of age: A systematic review and meta-analysis. *BMC Public Health*, *18*(1), 1372-1372. https://doi.org/10.1186/s12889-018-6137-7

Ramnitz, M. S., & Lodish, M. B. (2013). Racial disparities in Pubertal Development. *Seminars in Reproductive Medicine*, *31*(5), 333-339. https://doi.org/10.1055/s-0033-1348891

Rasmussen, K. M., & Yaktine, A. L. (2009). Composition and components of gestational weight gain: Physiology and metabolism. In *Weight Gain During Pregnancy: Reexamining the Guidelines*. National Academies Press (US).

Ravelli, A., van Der Meulen, J., Michels, R., Osmond, C., Barker, D., Hales, C., & Bleker, O. (1998). Glucose tolerance in adults after prenatal exposure to famine. *The Lancet*, *351*(9097), 173-177. https://doi.org/10.1016/S0140-6736(97)07244-9

Ream, M., Ray, A. M., Chandra, R., & Chikaraishi, D. M. (2008). Early fetal hypoxia leads to growth restriction and myocardial thinning. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *295*(2), R583-R595. https://doi.org/10.1152/ajpregu.00771.2007

Reeves, S., & Bernstein, I. (2008). Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. *Expert Review of Obstetrics & Gynecology*, *3*(6), 719-730. https://doi.org/10.1586/17474108.3.6.719

Reinehr, T., & Roth, C. L. (2019). Is there a causal relationship between obesity and puberty? *Lancet Child & Adolescent Health*, *3*(1), 44-54. https://doi.org/10.1016/S2352-4642(18)30306-7

Remsberg, E. K., Demerath, W. E., Schubert, M. C., Chumlea, C. W., Sun, S. S., & Siervogel, M. R. (2005). Early menarche and the development of cardiovascular disease risk factors in adolescent girls: The Fels Longitudinal Study. *The Journal of Clinical Endocrinology & Metabolism*, *90*(5), 2718-2724. https://doi.org/10.1210/jc.2004-1991

Rich-Edwards, J. W., Stampfer, M. J., Manson, J. E., Rosner, B., Hankinson, S. E., Colditz, G. A., Willett, W. C., & Hennekens, C. H. (1997). Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ*, *315*(7105), 396-400. https://doi.org/10.1136/bmj.315.7105.396

Robe, L. B., Robe, R. S., & Wilson, P. A. (1979). Maternal heavy drinking related to delayed onset of daughters menstruation. *Currents in Alcoholism*, *7*, 515-520. https://www.ncbi.nlm.nih.gov/pubmed/552346

Rogers, R., Eagle, T. F., Sheetz, A., Woodward, A., Leibowitz, R., Song, M., Sylvester, R., Corriveau, N., Kline-Rogers, E., Jiang, Q., Jackson, E. A., & Eagle, K. A. (2015). The relationship between childhood obesity, low socioeconomic status, and race/ethnicity: Lessons from Massachusetts. *Childhood Obesity*, *11*(6), 691-695. https://doi.org/10.1089/chi.2015.0029

Rogozińska, E., Zamora, J., Marlin, N., Betrán, A. P., Astrup, A., Bogaerts, A., Cecatti, J. G., Dodd, J. M., Facchinetti, F., Geiker, N. R. W., Haakstad, L. A. H., Hauner, H., Jensen, D. M., Kinnunen, T. I., Mol, B. W. J., Owens, J., Phelan, S., Renault, K. M., Salvesen, K. Å., Shub, A., Surita, F. G., Stafne, S. N., Teede, H., van Poppel, M. N. M., Vinter, C. A., Khan, K. S., Thangaratinam, S., & International Weight Management in Pregnancy Collaborative, G. (2019). Gestational weight gain outside the Institute of Medicine recommendations and adverse pregnancy outcomes: Analysis using individual participant data from randomised trials. *BMC Pregnancy and Childbirth*, *19*(1), 322-322. https://doi.org/10.1186/s12884-019-2472-7

Romundstad, P. R., Vatten, L. J., Nilsen, T. I., Holmen, T. L., Hsieh, C. C., Trichopoulos, D., & Stuver, S. O. (2003). Birth size in relation to age at menarche and adolescent body size: Implications for breast cancer risk. *International Journal of Cancer*, *105*(3), 400-403. https://doi.org/10.1002/ijc.11103

Roth, C. L., & DiVall, S. (2016). Consequences of early life programing by genetic and environmental influences: A synthesis regarding pubertal timing. *Puberty from Bench to Clinic: Lessons for Clinical Management of Pubertal Disorders*, *29*, 134-152. https://doi.org/10.1159/000438883

Rudolph, A. M. (1984). The fetal circulation and its response to stress. *Journal of Developmental Physiology*, *6*(1), 11.

Sauder, K. A., Hockett, C. W., Ringham, B. M., Glueck, D. H., & Dabelea, D. (2017). Fetal overnutrition and offspring insulin resistance and β-cell function: The Exploring Perinatal Outcomes among Children (EPOCH) study. *Diabetic medicine : A journal of the British Diabetic Association*, *34*(10), 1392-1399. https://doi.org/10.1111/dme.13417

Schellong, K., Schulz, S., Harder, T., & Plagemann, A. (2012). Birth weight and long-term overweight risk: Systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. *PLoS One*, *7*(10), e47776-e47776. https://doi.org/10.1371/journal.pone.0047776

Shirtcliff, E. A., Dahl, R. E., & Pollak, S. D. (2009). Pubertal development: correspondence between hormonal and physical development. *Child Development*, *80*(2), 327-337. https://doi.org/10.1111/j.1467-8624.2009.01263.x

Shrestha, A., Nohr, E. A., Bech, B. H., Ramlau-Hansen, C. H., & Olsen, J. (2011). Smoking and alcohol use during pregnancy and age of menarche in daughters. *Human Reproduction*, *26*(1), 259-265. https://doi.org/10.1093/humrep/deq316

Silva, I. d. S., De Stavola, B. L., Mann, V., Kuh, D., Hardy, R., & Wadsworth, M. E. J. (2002). Prenatal factors, childhood growth trajectories and age at menarche. *International Journal of Epidemiology*, *31*(2), 405-412. https://doi.org/10.1093/ije/31.2.405

Sloboda, D. M., Hart, R., Doherty, D. A., Pennell, C. E., & Hickey, M. (2007). Age at menarche: Influences of prenatal and postnatal growth. *Journal of Clinical Endocrinology & Metabolism*, *92*(1), 46-50. https://doi.org/10.1210/jc.2006-1378

Sole, K. (2006). Infant postnatal weight gain predicts insulin resistance. *Nature Clinical Practice Endocrinology & Metabolism*, *2*(3), 125-125. https://doi.org/10.1038/ncpendmet0109

Sørensen, H. T., Sabroe, S., Rothman, K. J., Gillman, M., Fischer, P., & Sørensen, T. I. (1997). Relation between weight and length at birth and body mass index in young adulthood: cohort study. *BMJ*, *315*(7116), 1137-1137. https://doi.org/10.1136/bmj.315.7116.1137

Sorensen, K., Juul, A., Christensen, K., Skytthe, A., Scheike, T., & Kold Jensen, T. (2013). Birth size and age at menarche: A twin perspective. *Human Reproduction*, *28*(10), 2865-2871. https://doi.org/10.1093/humrep/det283

Sørensen, T., Ajslev, T. A., Ängquist, L., Morgen, C. S., Ciuchi, I. G., & Davey Smith, G. (2016). Comparison of associations of maternal peri-pregnancy and paternal anthropometrics with child anthropometrics from birth through age 7 y assessed in the Danish National Birth Cohort. *American Journal of Clinical Nutrition*, *104*(2), 389-396. https://doi.org/10.3945/ajcn.115.129171

Sowan, N. A., & Stember, M. L. (2000). Effect of maternal prenatal smoking on infant growth and development of obesity. *The Journal of Perinatal Education*, *9*(3), 22-29. https://doi.org/10.1624/105812400X87734

Straus, M. A. (2007). Conflict tactics scales. *Encyclopedia of Domestic Violence, 190*, 197.

Suzuki, K., Kondo, N., Sato, M., Tanaka, T., Ando, D., & Yamagata, Z. (2011). Gender differences in the association between maternal smoking during pregnancy and childhood growth trajectories: Multilevel analysis. *International Journal of Obesity*, *35*(1), 53-59. https://doi.org/10.1038/ijo.2010.198

Suzuki, K., Kondo, N., Sato, M., Tanaka, T., Ando, D., & Yamagata, Z. (2012). Maternal smoking during pregnancy and childhood growth trajectory: A random effects regression analysis. *Journal of Epidemiology*, *22*(2), 175-178. https://doi.org/10.2188/jea.je20110033

Swanson, J. M., Entringer, S., Buss, C., & Wadhwa, P. D. (2009). Developmental origins of health and disease: Environmental exposures. *Seminars in Reproductive Medicine, 27*(5), 391-402. https://doi.org/10.1055/s-0029-1237427

Tabish, S. A. (2007). Is diabetes becoming the biggest epidemic of the twenty-first century? *International Journal of Health Sciences*, *1*(2), V-VIII. https://pubmed.ncbi.nlm.nih.gov/21475425

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068646/

Talhout, R., Schulz, T., Florek, E., van Benthem, J., Wester, P., & Opperhuizen, A. (2011). Hazardous compounds in tobacco smoke. *International Journal of Environmental Research and Public Health*, *8*(2), 613-628. https://doi.org/10.3390/ijerph8020613

Terry, M. B., Ferris, J. S., Tehranifar, P., Wei, Y., & Flom, J. D. (2009). Birth weight, postnatal growth, and age at menarche. *American Journal of Epidemiology*, *170*(1), 72-79. https://doi.org/10.1093/aje/kwp095

Timperio, A., Ball, K., Roberts, R., Campbell, K., Andrianopoulos, N., & Crawford, D. (2008). Children's fruit and vegetable intake: associations with the neighbourhood food environment. *Preventative Medecine*, *46*(4), 331-335. https://doi.org/10.1016/j.ypmed.2007.11.011

Tyrrell, J., Richmond, R. C., Palmer, T. M., Feenstra, B., Rangarajan, J., Metrustry, S., Cavadino, A., Paternoster, L., Armstrong, L. L., De Silva, N. M. G., Wood, A. R., Horikoshi, M., Geller, F., Myhre, R., Bradfield, J. P., Kreiner-Møller, E., Huikari, V., Painter, J. N., Hottenga, J.-J., Allard, C., Berry, D. J., Bouchard, L., Das, S., Evans, D. M., Hakonarson, H., Hayes, M. G., Heikkinen, J., Hofman, A., Knight, B., Lind, P. A., McCarthy, M. I., McMahon, G., Medland, S. E., Melbye, M., Morris, A. P., Nodzenski, M., Reichetzeder, C., Ring, S. M., Sebert, S., Sengpiel, V., Sørensen, T. I. A., Willemsen, G., de Geus, E. J. C., Martin, N. G., Spector, T. D., Power, C., Järvelin, M.-R., Bisgaard, H., Grant, S. F. A., Nohr, E. A., Jaddoe, V. W., Jacobsson, B., Murray, J. C., Hocher, B., Hattersley, A. T., Scholtens, D. M., Davey Smith, G., Hivert, M.-F., Felix, J. F., Hyppönen, E., Lowe, W. L., Jr, Frayling, T. M., Lawlor, D. A., Freathy, R. M., & Consortium, f. t. E. G. G. (2016). Genetic evidence for causal relationships between maternal obesity-related traits and birth weight. *Journal of the American Medical Association*, *315*(11), 1129-1140. https://doi.org/10.1001/jama.2016.1975

Uenoyama, Y., Inoue, N., Nakamura, S., & Tsukamura, H. (2019). Central mechanism controlling pubertal onset in mammals: A triggering role of kisspeptin. *Frontiers in Endocrinology*, *10*. https://doi.org/ARTN 31210.3389/fendo.2019.00312

Veena, S. R., Krishnaveni, G. V., Karat, S. C., Osmond, C., & Fall, C. H. D. (2013). Testing the fetal overnutrition hypothesis; the relationship of maternal and paternal adiposity to adiposity, insulin resistance and cardiovascular risk factors in Indian children. *Public Health Nutrition*, *16*(9), 1656. https://doi.org/10.1017/S1368980012003795

Victora, C. G., Barros, F. C., Horta, B. L., & Martorell, R. (2001). Short-term benefits of catch-up growth for small-for-gestational-age infants. *International Journal of Epidemiology*, *30*(6), 1325-1330. https://doi.org/10.1093/ije/30.6.1325

Vik, T., Jacobsen, G., Vatten, L., & Bakketeig, L. S. (1996). Pre- and post-natal growth in children of women who smoked in pregnancy. *Early Human Development*, *45*(3), 245-255. https://doi.org/10.1016/0378-3782(96)01735-5

Voerman, E., Santos, S., Patro Golab, B., Amiano, P., Ballester, F., Barros, H., Bergström, A., Charles, M.-A., Chatzi, L., & Chevrier, C. (2019). Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: An individual participant data meta-analysis. *PLoS medicine*, *16*(2), e1002744.

Wang, Y. (2002). Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. *Pediatrics*, *110*(5), 903. https://doi.org/10.1542/peds.110.5.903

Wang, Y., Dinse, G. E., & Rogan, W. J. (2012). Birth weight, early weight gain and pubertal maturation: A longitudinal study. *Pediatric Obesity*, *7*(2), 101-109. https://doi.org/10.1111/j.2047-6310.2011.00022.x

Warrington, N. M., Richmond, R., Fenstra, B., Myhre, R., Gaillard, R., Paternoster, L., Wang, C. A., Beaumont, R. N., Das, S., Murcia, M., Barton, S. J., Espinosa, A., Thiering, E., Atalay, M., Pitkänen, N., Ntalla, I., Jonsson, A. E., Freathy, R., Karhunen, V., Tiesler, C. M. T., Allard, C., Crawford, A., Ring, S. M., Melbye, M., Magnus, P., Rivadeneira, F., Skotte, L., Hansen, T., Marsh, J., Guxens, M., Holloway, J. W., Grallert, H., Jaddoe, V. W. V., Lowe, W. L., Jr., Roumeliotaki, T., Hattersley, A. T., Lindi, V., Pahkala, K., Panoutsopoulou, K., Standl, M., Flexeder, C., Bouchard, L., Aagaard Nohr, E., Marina, L. S., Kogevinas, M., Niinikoski, H., Dedoussis, G., Heinrich, J., Reynolds, R. M., Lakka, T., Zeggini, E., Raitakari, O. T., Chatzi, L., Inskip, H. M., Bustamante, M., Hivert, M. F., Jarvelin, M. R., Sørensen, T. I. A., Pennell, C., Felix, J. F., Jacobsson, B., Geller, F., Evans, D. M., & Lawlor, D. A. (2018). Maternal and fetal genetic contribution to gestational weight gain. *International Journal of Obesity*, *42*(4), 775-784. https://doi.org/10.1038/ijo.2017.248

WHO. (2006). *WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development*. World Health Organization.

Windham, G. C., Bottomley, C., Birner, C., & Fenster, L. (2004). Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea during pregnancy. *American Journal of Epidemiology*, *159*(9), 862-871. https://doi.org/10.1093/aje/kwh117

Windham, G. C., Lum, R., Voss, R., Wolff, M., Pinney, S. M., Teteilbaum, S. L., Sosnoff, C. S., Dobraca, D., Biro, F., Hiatt, R. A., Greenspan, L. C., Galvez, M., & Kushi, L. H. (2017). Age at pubertal onset in girls and tobacco smoke exposure during pre- and postnatal susceptibility windows. *Epidemiology*, *28*(5), 719-727. https://doi.org/10.1097/EDE.0000000000000704

Windham, G. C., Zhang, L., Longnecker, M. P., & Klebanoff, M. (2008). Maternal smoking, demographic and lifestyle factors in relation to daughter's age at menarche. *Paediatric Perinatology Epidemiology*, *22*(6), 551-561. https://doi.org/10.1111/j.1365-3016.2008.00948.x

Won Kyoung, C., & Byung-Kyu, S. (2016). Catch-up growth and catch-up fat in children born small for gestational age. *Korean Journal of Pediatrics*, *59*(1), 1-7. https://doi.org/10.3345/kjp.2016.59.1.1

Wong, M. C., Huang, J., Wang, J., Chan, P. S., Lok, V., Chen, X., Leung, C., Wang, H. H., Lao, X. Q., & Zheng, Z.-J. (2020). Global, regional and time-trend prevalence of central obesity: A systematic review and meta-analysis of 13.2 million subjects. *European Journal of Epidemiology*, *35*, 673-683.

Yu, Z. B., Han, S., Zhu, J., Sun, X., Ji, C., & Guo, X. (2013). Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: A systematic review and meta-analysis. *PLoS One*, *8*(4), e61627-e61627. https://doi.org/10.1371/journal.pone.0061627

Yu, Z. B., Han, S. P., Zhu, G. Z., Zhu, C., Wang, X. J., Cao, X. G., & Guo, X. R. (2011). Birth weight and subsequent risk of obesity: A systematic review and meta-analysis. *Obesity Reviews*, *12*(7), 525-542. https://doi.org/10.1111/j.1467-789X.2011.00867.x

Yuan, Z. P., Yang, M., Liang, L., Fu, J. F., Xiong, F., Liu, G. L., Gong, C. X., Luo, F. H., Chen, S. K., Zhang, D. D., Zhang, S., & Zhu, Y. M. (2015). Possible role of birth weight on general and central obesity in Chinese children and adolescents: A cross-sectional study. *Annals of Epidemiology*, *25*(10), 748-752. https://doi.org/10.1016/j.annepidem.2015.05.011

Zhang, L., Zhang, D. D., & Sun, Y. (2019). Adverse childhood experiences and early pubertal timing among girls: A meta-analysis. *International Journal of Environmental Research and Public Health*, *16*(16). https://doi.org/ARTN 288710.3390/ijerph16162887