Maternal Pre-pregnancy BMI, Gestational Weight Gain, and Age at Menarche in Daughters

By

Rachel Leah Berry-Millett

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Committee in charge:

Professor Barbara Abrams, Chair
Professor Julianna Deardorff
Professor Douglas Jutte

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Table of Contents

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Part 1: Maternal factors & the determinants of menarche:
A review of the literature

Introduction:

Over the past several decades there has been a downward trend in the average age at menarche among girls in the United States and other developed nations.[1-3] Girls are going through puberty earlier and reaching menarche at younger ages.[1-3] Some recent research has focused on whether a correlation exists between low birth weight, early infant growth patterns, and the timing of menarche.[4-6] Other research has focused on the relationship between childhood overweight and obesity and menarcheal age.[7-10] Few studies, however, have examined whether a direct association exists between maternal factors, including maternal BMI and gestational weight gain, and the timing of menarche in offspring.

In a 2009 paper, Keim and colleagues used data from the Collaborative Perinatal Project (1959-66) to assess the association between maternal pre-pregnancy body mass index (BMI) and daughters' age at menarche. They found that daughters of obese mothers had an increased risk of experiencing early menarche (less than 12 years) compared to daughters of normal weight or underweight mothers, after adjusting for several potential mediating factors.[11] No other studies have confirmed this association. Furthermore, there is evidence that low birth weight and small size at birth are connected to the subsequent timing of menarche.[12-14] These findings provide support to the idea that intrauterine exposures and growth patterns may lead to fetal programming of future endocrine, metabolic, and reproductive pathways. However, until this year, there was no study that examined whether gestational weight gain – a potentially modifiable variable – may have its own independent relationship with daughters' age at menarche. In 2011, Boynton-Jarrett and colleagues published the first study questioning whether this correlation existed. They found a U-shaped association between gestational weight gain and early menarche: excessively high (>40lbs) and low (<10lbs) weight gain during pregnancy were both associated with a higher risk of early menarche in daughters.[15] Additional research is needed to confirm these findings, and to assess whether they differ by race/ethnicity.

The downstream significance of age at menarche has been studied extensively, with several studies linking early menarcheal age to poor health outcomes, including breast cancer, cardiovascular disease, glucose intolerance, and obesity.[16-20] Early menarche has also been associated with higher rates of depression and anxiety as well as engagement in risky behaviors during adolescence.[21-23] Given the current trends in declining age at menarche, and recent research shedding light on the important role of perinatal factors in the timing of menarche, further investigation into potentially mediating pathways is warranted.

The first part of this paper will review secular trends in the timing of menarche, racial disparities, and the importance of studying menarche as a health outcome, including some of the methodological challenges. The second part will examine the intricate,

sequential relationship between maternal weight, gestational weight gain, the perinatal environment, child birth weight, infant growth patterns, and childhood BMI as they relate to the timing of menarche in girls. More specifically, this paper will posit whether there may be an independent association between maternal BMI and gestational weight gain and daughters' age at menarche. I will also discuss why, in examining this hypothesized association, it is crucial to explore potentially strong mediators of this relationship, including birth weight and childhood weight.

Menarche & puberty physiology:

Menarche, defined as the first menstrual bleeding in girls, is a central event in female pubertal development.[24] Menarche is a relatively late marker of puberty. It occurs on average 2 to 3 years after the onset of puberty, with earlier events of puberty defined by the development secondary sexual characteristics, including breast tissue and alveolar development and pubic hair growth. The beginning of puberty is stimulated by a steady increase in gonadotropic hormone secretion from the pituitary, traditionally beginning around the 8th year of life, and menarche is an event triggered by continued positive feedback to the hypothalamic-pituitary-gonadal (HPG) axis.[25] Other endocrine hormones, including growth hormone and insulin, are also known to play a role in the activation of menarche, though the entirety of the physiologic pathways of menarche is not fully known. The onset of menarche is also associated with the degree of skeletal maturation in girls.[26] Since height is frequently used as a marker of bone growth in children, there is evidence that childhood height is inversely associated with age at menarche.[26, 27]

Since its discovery in 1994, the hormone leptin has also been studied for its role in the onset and progression of puberty. Leptin is produced primarily from adipocytes, and serum leptin concentrations are strongly associated with overall body fat.[24] Serum leptin concentrations have also been shown to increase with pubertal development in girls.[28, 29] It is believed that leptin plays a significant role in the maturation of the gonadotropin-releasing hormone pulsatile secretions that lead to the beginning of menses.[24]

Menarche sets a hormonal tone for a woman's life, and marks an important transition from childhood to early womanhood. Despite the fact that most women are not consistently ovulatory in the immediate period following menarche (and many women are not regularly ovulatory for 2-5 years after menarche),[30] it is nonetheless seen as a milestone marking the beginning of reproductive life, and thus represents a significant juncture in the female life course.

Early menarche & health outcomes:

Age at menarche has been shown to play a critical role not only during female adolescence, but also as a marker of health risks in adulthood. Girls who experience menarche at a younger age have a longer lifetime exposure to estrogens, and are thought to be at an elevated risk for estrogen-mediated cancers, such as breast and ovarian cancer.[16, 17, 31-35] In one study, women with an age at menarche of 11 years or younger had a significantly higher risk (OR=1.33, 95% CI 1.06-1.67) of developing breast cancer

compared to women with an age at menarche between 12 and 16 years (OR=1.0, 95% CI 0.87-1.15) and nearly twice the risk compared to women with an age at menarche at 17 years or older (OR=0.74, 95% CI 0.54-1.03).[33] Other studies have had similar findings.[31, 32, 34]

There also appears to be a connection between pre-menarcheal adiposity, menarcheal timing, and long-term cardiovascular health. Some studies have found a direct association between earlier menarche and adverse cardiovascular and metabolic outcomes,[19, 20, 36, 37] while others have found the relationship to be entirely mediated by either pre-menarcheal and/or adulthood body mass index.[18, 38] For example, in a population-based prospective study that included 15,807 women, Lakshman and colleagues found that women who had experienced early menarche (<12 years) had a higher risk of hypertension [OR=1.13, 95% CI 1.02-1.24], a higher incidence of cardiovascular disease [OR=1.17, 95% CI 1.07-1.27], coronary heart disease [OR=1.23, 95% CI 1.06-1.43], all-cause mortality [OR=1.22, 95% CI 1.07-1.39], cardiovascular disease mortality [OR=1.28, 95% CI 1.02-1.62], and cancer mortality [OR=1.25, 95% CI 1.03-1.51], all after adjusting for age, physical activity, smoking, alcohol, education, occupational social class, oral contraceptive use, hormone replacement therapy, parity, BMI, and waist circumference.[19] Similarly, Jacobsen et al examined the linear relationship between age at menarche and mortality outcomes. They found that a one-year delay in menarche was associated with 4.5% lower total mortality (95% CI 2.3-6.7), 6.0% lower ischemic heart disease mortality (95% CI 1.2-10.6), and 8.6% lower stroke mortality.[20]

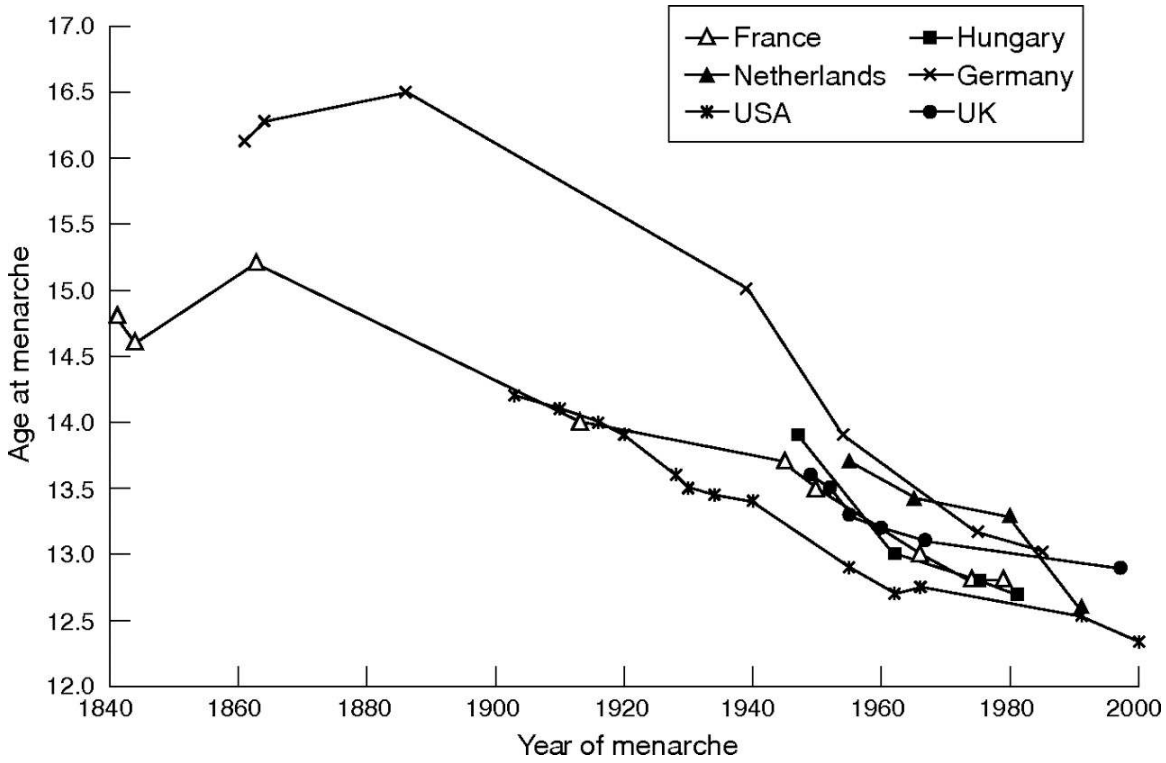
Additionally, research on the adolescent psychological and psychosocial impact of pubertal and menarcheal timing has revealed important relationships between early menarche and a higher prevalence of anxiety, depression, and engagement in risky behaviors.[21-23, 39, 40] Harlow and colleagues found an increasing rate of depression with decreasing age of menarche: girls with a menarcheal age ≤ 10 years were 2.4 times more likely to have depression that girls with an age at menarche between 12 and 13 years. The likelihood of depression continued to decline with increasing age at menarche.[40] Deardorff et al. examined the association between early puberty, alcohol use, and first pregnancy. They found that girls who attain menarche at an earlier age are more likely to initiate alcohol and cigarette use at an earlier age, and to have a younger age at first sexual intercourse. In turn, both alcohol use and age of sexual initiation played a role in predicting the timing of first pregnancy.[23]

The association between early menarche and diverse poor health outcomes highlights the importance of age at menarche as a marker of health and development and substantiates concern for the downward trend in age at menarche observed.

Secular trends & racial disparities in menarcheal timing:

The average age at menarche has been decreasing in girls throughout the world since the mid-1800s. Declines during the first half of the 20th century were largely attributed to improved nutritional status of the population. Between 1900 and 1945

Wyshak and Frisch documented a downward trend in age at menarche of about 3 months per decade in Western nations; a trend that correlated closely with a more rapid gain in body weight during the same time frame.[41] In the 1960s, the average age at menarche reached somewhat of a plateau. However, over the past few decades, studies have again documented a slow downward trend in age of menarche among girls in the United States and other developed nations.[1-3, 42]



Source: Bellis MA, Downing J, Ashton JR. Adults at 12? Trends in puberty and their public health consequences. J Epidemiol Community Health 2006;60:910-1.

Mean menarcheal age of girls as measured in the National Health Examination Survey (1963-1970) and the Third National Health and Nutrition Examination Survey (NHANES III) (1988-1994) dropped from 12.75 years to 12.54 years between the two surveys.[42] Between NHANES III and NHANES 1999-2002, the average age at menarche dropped an additional 2.3 months to 12.34 months.[3]

There are also well-documented racial differences in the onset of menarche in girls.[26, 42-45] Among white girls, the average age of menarche fell from an average of 12.80 years during the National Health Examination Survey (1963-1970) to 12.60 years during the NHANES III (1988-1994). For black girls between the same period, the average age of menarche dropped from 12.48 years to 12.14 years.[42] While a higher relative BMI z-score was associated with an earlier age of menarche in both racial groups, black girls still had a younger average menarcheal age compared to white girls after controlling for relative weight. Ten percent of non-Hispanic black girls, Mexican American and non-Hispanic white girls reached menarche at age 10.52, 10.81 and 11.32 years, respectively. The median age of menarche was 12.06 for non-Hispanic black girls, compared to 12.25 for Mexican

American girls and 12.55 for non-Hispanic white girls.[44] More recently, one study found that 46% of black girls had attained menarche before age 12, compared to 26% of white girls.[43]

Socioeconomic status, environmental exposures, genetic factors, and body composition have all been considered in explaining these racial disparities. These factors and their role in menarche will be discussed in the following section. There is also some evidence that there may be racial differences in leptin levels, which, as mentioned above, have been shown to play a role in the onset of menarche. In one study, Wong et al. found that a group of normal-weight African American girls had higher serum leptin compared to Caucasian girls (11.2ng/mL±6.4 versus 7.4±3.4ng/mL, $p<0.02$) after adjusting for sexual maturity and fat mass, among other covariates.[29]

The explanation for racial differences in menarche is likely multifactorial, and not fully known. Nonetheless, consideration of these differences is important when studying the trends and implications of age at menarche.

What influences age at menarche?

The age at which menarche occurs may be influenced by a complex interplay of genetic, biological, and environmental factors. Several of these factors have been considered as possible explanations for the downward trend in menarcheal age, including socioeconomic factors and changes in the general health of the population, endocrine system conditions or alterations, environmental exposures to toxins, pesticides, or exogenous hormones, and, perhaps most significantly, rising rates of overweight and obesity among all ages of the population. While this paper will focus on the role of maternal and child weight in menarcheal timing, a brief review of other proposed determinants is important to illustrate the complex, multifactorial nature of this topic.

Environmental exposures & menarche:

Some recent studies have found a positive association between organochlorine pollutants exposures during childhood and an earlier age at menarche. In a 2005 study of Chinese textile workers, aged 20-34 years, Ouyang and colleagues found that exposure to dichlorodiphenyl trichloroethane (DDT) – a known endocrine disruptor – was associated with a decreased age at menarche. Compared to women with the lowest quartile of serum DDT, women with the highest quartile of serum DDT had a mean age at menarche 1.11 years earlier.[46] In another study, Vasiliu et al. found that *in utero* exposure to dichlorophenyldichloroethylene (DDE), a metabolite of DDT with a much longer half-life, was associated with a reduced age at menarche. An increase in DDE exposure of 15μg was associated with a 1 year decease in age at menarche.[47] Polybrominated biphenyls (PBBs) have also been connected to earlier menarche.[48]

Other studies have not been conclusive or have yielded mixed findings.[49, 50] For example, in a 2006 study Axmon found no significant association between persistent

organochlorine pollutants (POPs), including DDE, and menarcheal timing.[51] Nonetheless, an expert panel that reviewed the existing literature on endocrine-disrupting chemicals and pubertal timing concluded that existing data does support a possible connection between the two, and recommended further etiologic research to isolate the chemicals, their physiologic mechanisms, and the most vulnerable times of exposure as they affect the timing of puberty.[49]

Genetic and hereditary components of menarche:

There is a relatively well-established role for genetic and hereditary determinants of menarcheal timing. Several studies provide evidence of a direct association between maternal age at menarche and daughters' age at menarche; a correlation frequently ranging between r=0.20-0.30[52, 53] Other studies have shown concordance of age at menarche between both monozygotic and dizygotic twins.[54, 55]

In one meta-analysis of 32 genome-wide association studies to identify loci for age at menarche, 32 common variants or single nucleotide polymorphisms associated with age at menarche were found.[56] Among these loci, four were also associated with body mass index, three were in or near genes associated with energy homeostasis, and three were in or near genes implicated in hormonal regulation. [56]

Father absence & other psychosocial factors

Belsky and colleagues developed an evolutionary theory of socialization based on a developmental pathway aimed at promoting "reproductive success."[57] Belsky's model argues that certain psychosocial stressors and influences – particularly the home and parental environment – can significantly affect the timing of pubertal onset. For example, the theory postulates that children lacking a stable home life – such as an absent father – may reach menarche earlier, thus establishing reproductive viability at a younger age in preparation for an unstable adult life not conducive to long-term partnering and mating.[57, 58] An opposing model to Belsky's argues that early menarche and its relationship to father absence is rooted in genetic, rather than psychosocial, variance. Comings et al. suggest that a variant X-linked androgen receptor, which may predispose fathers to behaviors including family abandonment, may also be found in their daughters, and may be a cause of early and precocious puberty.[59] Yet another viewpoint argues that menarche is pheromonally-driven. Matchock and Susman postulate that putative human pheromones can alter the timing of menarche as an anti-inbreeding strategy. They assert that preventing inbreeding is critical to the survival and reproduction of healthy genes, and thus reproductive physiology may be modulated by family composition and the presence or absence of certain figures.[60]

Regardless of the pathway by which it occurs, studies have linked early menarche to both father absence and to disordered paternal behavior in the home.[58, 61-64] One study, for example, found that younger sisters from disrupted families who were exposed to serious paternal dysfunction in early childhood reached menarche on average 11 months earlier than their older sisters or other comparison group younger sisters from disrupted families who were not exposed to paternal dysfunction.[61] While there are a few studies that failed

to find support for this relationship,[65, 66] the majority of research has confirmed the association between father absence and early menarche, and it remains an active area of continued research.

Methodological challenges of studying menarche:

Given its long-term clinical and health relevance, menarche has been studied widely, both as a predictor of various health outcomes, and an outcome of various health exposures. In puberty research, menarche is a commonly used outcome because it is a single event that can be assessed directly via recall with relatively good accuracy, as opposed to other markers of puberty, such as breast and pubic hair development or hormonal measures, which are best evaluated in a clinical setting by trained professionals. There are certain methodological challenges to the study of menarche, however, which warrant discussion.

Documenting menarcheal age typically consists of asking girls in different age groups and/or their parents whether or not they have had their first menses, and if so, at what age. Some studies use only year at menarche, while others use year and month at menarche. When possible, supplemental medical chart reviews or other collected data may help ensure accuracy of recall. Most studies utilize a retrospective measurement of age at menarche via recall by study participants. While recall has been shown to be a valid and relatively reliable method, a longer time between event and recall and various biases – including socioeconomic or cultural biases – may contribute to a loss of accuracy.[67-70] In one study, 66.1% of participants with a shorter recall interval (mean = 323 days) were able to recall the exact month and year of their first menses, compared to 44.8% of participants with a longer recall interval (mean=649 days).[67] Cooper et al. studied the validity of age at menarche recall later in adulthood using data from a prospective cohort study. 43.6% of women recalled exactly the same age at menarche at age 48 as they did at their medical examination at age 14-15. However, 20.6% of women recalled their age at menarche to be one year older, and 21.0% recalled it to be one year younger when asked at middle age.[70] While this indicates that there was no strong bias to younger or older reporting, it still challenges the validity of using age at menarche from self-reported data in middle aged women.

An established, standard definition of "early menarche" is lacking in the current literature. Some studies have used percentile distributions for defining menarcheal age categories, with early menarche characterized by the lowest 25% of girls within a given distribution. Other studies have defined a specific age, before which menarche is classified as early onset. Based on recent trends and national data, the majority of studies examining age at menarche as a categorical outcome define early menarche as occurring before age 12. Along these lines, it's important to consider that significant racial differences exist in the average age of onset, as discussed above.

The lack of a standard classification of early menarche may in part be due to the downward trend in the average age of onset over several decades. In 1969, Marshall and Tanner defined variations in the patterns of normal pubertal development in girls.[71] The

Tanner staging system remains the standard tool for measuring pubertal development in research and clinical practice today. While the average age of puberty onset may be decreasing, it's important to differentiate early puberty and early menarche from precocious puberty, as signs of precocious puberty indicate that a possible pathologic cause of puberty development should be explored. In most studies, the attainment of pubertal milestones is normally distributed within a standard deviation of approximately one year.[72] Abnormal or precocious puberty is defined as children who enter puberty more than 2.5 to 3 standard deviations earlier than the median or mean age.[72] Based on this definition, precocious puberty in girls is typically characterized as secondary sexual development before the age of 8; however, this remains a somewhat contentious topic of debate, as some recent research suggests that puberty onset before this age is becoming more normative. In one recent study, Biro et al found that breast maturation at age 7 was at Tanner stage ≥2 in 14.9% of Hispanic girls, 23.4% of black girls, and 10.4% of non-Hispanic white girls.[73] The percentage of white girls with Tanner stage ≥2 breast development at ages 7 and 8 had increased most significantly compared to data from girls who had been born 10-30 years earlier.[73] For menarche specifically, based on current research an age at menarche younger than 8 is likely to be considered abnormal or precocious puberty. Nonetheless, the results of recent studies such as Biro et al. support the need to continue re-examining current definitions of precocious versus early puberty.

Determinants of age at menarche: birth weight & early childhood growth

There has been extensive research looking at the factors that contribute to the timing of menarche in girls, and several of these factors have been discussed above. Recently, there have been a number of studies examining low birth weight, early childhood growth patterns, and increased childhood BMI as potentially significant predictors of early menarche. While there has been some inconsistency in the literature, the majority of studies have found positive associations between these variables and an earlier onset of menarche. Given that birth weight and early growth patterns are largely determined in utero, it's noteworthy to contextualize the evidence on birth weight and menarche with a discussion of the intrauterine environment and its associations with long-term health outcomes.

The intrauterine environment:

In the 1980s and 1990s David Barker and his colleagues examined the role of early life experiences and cardiovascular outcomes in adulthood. The results of their research led to the development of Barker's fetal origins hypothesis, which postulates that environmental insults – including undernutrition – during critical periods of intrauterine growth and development may have a long-term influence on the risk of adult disease, particularly cardiovascular health outcomes.[53, 74] According to Barker's theory – also known as the thrifty phenotype – in utero metabolic adaptations may occur that "program" the future structure and function of various organs, tissues, and body systems. The theory behind this idea was that in the setting of poor nutritional conditions, in utero adaptations would prepare the developing fetus to survive in a low-resource environment. However,

while protective to the fetus and often helpful in recovering weight in early infancy that was not obtained in the nutritionally restricted uterine environment, these same mechanisms lead to increased susceptibility to chronic disease later in life.[75]

Barker, Cooper and colleagues conducted one of the first studies that looked for an association between birth weight and menarcheal age among a cohort of British girls. In a study published in 1996, they found a positive relationship between birth weight and age at menarche: girls in the highest fifth of birth weight distribution were 2.2 months older at menarche than those in the lowest fifth.[10] While this association did not quite reach statistical significance ($p=0.07$), when examined as a trend along with child weight at age 7, the youngest age at menarche was observed among girls with low birth weight who became heavier at 7 years and the oldest age at menarche was among girls with a higher birth weight who were lighter at 7 years ($p<0.001$).[10] That is, a faster growth *trajectory* from weight at birth to weight at age 7 years was predictive of younger age at menarche.

Since Cooper et al.'s study, the correlation between low birth weight, increased early infant postnatal weight gain, and an earlier age at menarche has been confirmed by several studies.[4-6, 13, 14, 76] A low weight and/or length for a given gestational age are typically defined as below the third percentile or at least two standard deviations below an established standard. "Small for gestational age" infants (SGA) fall below the 10th percentile in birth weight, length, or head circumference for their gestational age. SGA status is often, but not exclusively, the result of intrauterine growth restriction (IUGR), which will be discussed further. Approximately 85-90% of newborns with a birth weight or length that classifies them as SGA will display significant "catch-up growth" within the first 12-18 months of life.[77] Periods of more rapid gain in the first year of life have subsequently been correlated with both increased body mass index during childhood, and an earlier age at menarche.[5, 14] For example, Ong and colleagues found that girls with earlier menarche had a slightly lower birth weight compared to girls with normal or late menarche, but that this relationship was mediated by a faster rate of growth between ages 0 and 2 months, and then again between 2 and 9 months.[5] Faster weight gain in infancy was also associated with increased body fat mass relative to lean mass at age 10 years.

Using data from a birth cohort in the Philippines, Adair examined the relationship between birth weight, birth length, and gestational age at birth to menarcheal timing. There was no direct relationship between birth weight and age at menarche, but a significant relationship did exist when birth length was considered. Girls who were long (>49cm) and light (<3kg) at birth experienced menarche earlier (mean age 12.8 years) than girls who were short and light (mean age 13.3 years).[78] The effect of thinness at birth was then explored within the context of early postnatal growth. Results showed that faster growth increments in the first year of life were associated with earlier menarche, and this effect was most exaggerated among girls who were light and lean at birth.[78] Tam and colleagues had similar findings in a 2006 study.[13]

The physiologic pathways that influence early childhood growth are not completely understood. It's known that early childhood growth is strongly influenced by insulin and insulin-like growth factor I (IGF-I), as well as by levels of growth hormone (GH). Rapid

early weight gain in infancy is associated with higher levels of insulin-like growth factor later in childhood. In one study comparing adiposity and insulin resistance in SGA infants who had experienced rapid postnatal growth, children born SGA had a similar body composition but were more insulin resistant at age 2 compared to children born with a normal birth weight.[79] They also had lower serum IGF-I levels and a lower total neutrophil count. Furthermore, between ages 2 and 4, the SGA children gained more abdominal fat and adiposity and less lean body mass compared to AGA children.[79] It's believed that the decreased neutrophil count – and overall decreased leukocyte count – occurs concomitantly with increasing insulin resistance as well as other markers of chronic inflammation.[79]

Early growth patterns are also strongly regulated by nutrition. Infants born at a low birth weight may have larger appetites, as some infant feeding studies have shown, and there are also differences in energy density and growth patterns based on formula (more energy dense) versus breast-fed babies.[4] Additionally, as previously discussed, there has been some attention to the role of leptin in patterns of early growth and pubertal progression.[80, 81] In one study, levels of leptin measured in cord blood were inversely related to early infant weight gain between 0 and 4 months, and accounted for 9.4% of the variance in infant weight gain.[80] It is believed that low levels of leptin reflect decreased adiposity at birth, and account for or contribute to the subsequent rapid weight gain.

In their 1996 paper, Cooper and colleagues speculate that the pattern of gonadotropin release, which, as discussed above, acts as a trigger for the onset of menarche, may be programmed in utero.[10] Since pulsatile discharges of gonadotropin releasing hormone occurs during infancy, then again at the time of puberty, the correlation between birth weight and menarcheal timing may be mediated by alterations in the patterns of GnRH secretion as a result of hormonal or nutritional influences on growth during certain critical periods of intrauterine life.[10]

Childhood weight & age at menarche

While the physiologic mechanisms of early growth patterns may not be fully elucidated, there is a clear linkage between growth patterns in early life and later adiposity in childhood. Similarly, several studies have shown a positive inverse relationship between increased childhood BMI and an earlier age at menarche.[7-10, 42] In 1970, Frisch and Revelle demonstrated that the age at which menarche occurs in normal girls was correlated with the attainment of a certain "critical weight" in girls. The Frisch-Revelle hypothesis postulated that menarche is associated with a decline in metabolic rate and the achievement of a characteristic body composition of 47.8 kilograms, or approximately 105 pounds. In their study, they found that while mean height at menarche increased with a later menarcheal age, mean weight at menarche remained stable, leading them to propose that there was a direct correlation between body weight and menarche.[82, 83]

While a number of studies have challenged the precise stipulations of the Frisch-Revelle hypothesis,[84, 85] several recent studies support the correlation of increased body mass index during childhood and an earlier onset of menarche.[9, 26, 86] Freedman and

colleagues found that the rate of early menarche (defined as <11.0 years) among girls in the 75th percentile for weight was 1.95 times (95% CI 1.6-2.3) that of girls in the 25th percentile of weight.[26] Wang et al. compared the prevalence of overweight and obesity among early maturers and non-early maturers. After adjusting for energy intake, physical activity, and SES markers, 34.4% and 15.6% of early maturing girls were overweight and obese, respectively, compared to 23.2% and 8.1% of non-early maturers.[9] While several studies have looked at child's weight near the onset of puberty (~ages 6-8), there is also evidence that earlier weight status can affect the timing of menarche. Lee et al. found a consistently positive association between higher BMI z-score at 36 months and higher rate of change of BMI between 36 months and grade 1 and earlier puberty, based on Tanner staging of breast development and onset of menarche.[87]

Given the alarmingly high and increasing rates of overweight and obesity among children in the United States, the positive relationship between child weight and menarcheal age creates an obvious cause for concern.

Maternal pre-pregnancy BMI & gestational weight gain:

While a body of research has focused on child growth factors and the timing of puberty, fewer studies have examined whether there may be intergenerational and in-utero influences on menarcheal age. There is a well-documented correlation between maternal age at menarche and daughters' age at menarche.[88-90] There is also evidence that some early childhood growth patterns may be predicted or influenced by maternal-uterine factors during pregnancy, including maternal smoking, alcohol use, and parity.[4, 91, 92] Correspondingly, these variables have also been shown to play a role in the timing of menarche in daughters.[92-94] Maternal weight – both pre-pregnancy BMI and weight gain during pregnancy – also play a role in child perinatal and postnatal growth, and have been shown to be predictors of child overweight and obesity.[95] Given what is known about these relationships, it is reasonable to theorize that they could affect the timing of menarche as well. What is not known with certainty is whether they have direct, independent relationships with the timing of menarche, or whether an observed effect is fully mediated by infant and/or child growth patterns and weight.

Maternal pre-pregnancy BMI:

Rates of overweight and obesity among women of child-bearing age have increased dramatically over the past 2-3 decades.[96] NHANES data from 2003-2004 showed that 59.7% of non-pregnant women between ages 20-39 were overweight, obese, or extremely obese.[97] Moreover, significant racial disparities exist. In 2003-2004, 52.0% of non-Hispanic white women between age 20-39 were overweight, obese, or extremely obese, compared to 89.4% of non-Hispanic black women and 77.9% of Mexican-American women.[97] Lower SES was also a risk factor for overweight and obesity.[96] In general, women are beginning pregnancy at higher BMIs, and some evidence shows that women with a higher pregravid weight are more likely to gain excessive weight during pregnancy.[96]

Both low (<19.8) and high (>26.1) pregravid BMI have been associated with poor birth outcomes. Low pre-pregnancy BMI is correlated with a risk of intrauterine growth retardation and pre-term birth.[98-101] As discussed above, intrauterine growth retardation (IUGR) is the primary cause of children born small-for-gestational-age (SGA), and the vast majority of these children will display rapid "catch-up growth" in the first 1-1.5 years of life.[77] Catch-up growth, subsequently, has been linked directly to early menarche. High pre-gravid BMI, on the other hand, has been associated with gestational diabetes and large-for-gestational-age (LGA) babies, among several other adverse pregnancy outcomes, including pre-eclampsia, birth defects, and cesarean sections.[96]

The 2009 study by Keim and colleagues was the first to explore whether a connection existed between maternal pre-pregnancy BMI and daughters' age at menarche. They found no significantly increased odds of earlier menarche (<12 years or 12-13 years) among daughters of overweight (BMI=25.0-29.9) mothers compared to daughters of normal or underweight mothers (BMI<25.0). However, daughters of obese mothers (BMI≥30.0) had an increased odds of early menarche (<12 years; OR=3.3) compared to daughters of normal or underweight mothers.[11] Obesity in motherhood was independently associated with early menarche; as the relationship was not attenuated after adjusting for childhood BMI or other potentially mediating covariates, including socioeconomic status, parity, and maternal age at menarche.[11]

Gestational weight gain:

Studies have clearly linked excess maternal weight gain during pregnancy with increased BMI or obesity in offspring,[95, 102-105] in some cases independent of maternal BMI.[106] There is evidence that women with a higher pre-pregnancy BMI are more likely to gain excess weight during pregnancy compared with women with a low or normal pre-pregnancy BMI.[107] Other studies, however, have found that women who were overweight or obese were more likely to lose weight during pregnancy compared to women with a normal BMI. While gestational weight loss among obese women is associated with a decreased risk of large-for-gestational-age infants, it has been shown to slightly increase the risk of small-for-gestational-age infants, which may partly explain the increased risk of childhood and adulthood obesity.[108, 109] Both low and high gestational weight gain have also been associated with an increased risk of low and high crude birth weights, respectively, as well as SGA and LGA.[110, 111] In examining weight outcomes in the offspring, Stuebe and colleagues found that, compared to the daughters of women with a gestational weight gain of 15-19 pounds, daughters of women with a low weight gain of <10lbs had a significantly increased risk of obesity both at age 18 (OR=1.54, 95% CI 1.02-2.34) and later in adulthood (OR=1.27, 95% CI 1.05-1.53).[105] At the same time, excess gestational weight gain >40lbs was associated with an even greater obesity risk at age 18 (OR=1.81, 95% CI 1.22-2.69) and later in adulthood (OR=1.74, 95% CI 1.48-2.04).[105] The results remained significant after adjusting for maternal pre-pregnancy BMI, child birth weight, and other covariates.

In the setting of the obesity epidemic, and specifically to address findings regarding the important role of gestational weight gain, in 2009 the Institute of Medicine established

new guidelines for recommended gestational weight gain, taking into account maternal pre-pregnancy BMI.

NEW RECOMMENDATIONS FOR TOTAL AND RATE OF WEIGHT GAIN DURING PREGNANCY, BY PREPREGNANCY BMI

Prepregnancy BMI	BMI† (kg/m²)	Total Weight Gain (lbs)	Rates of Weight Gain* 2nd and 3rd Trimester (lbs/week)
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5-24.9	25–35	1 (0.8–1)
Overweight	25.0-29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	≥30.0	11–20	0.5 (0.4–0.6)

Source: Institute of Medicine, Weight Gain During Pregnancy: Re-examining the Guidelines http://www.iom.edu/Reports/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines.aspx. Accessed June 17, 2011

To date, few if any observational studies have assessed the efficacy of these new guidelines, but compared to the 1990 guidelines, the new recommendations provide a more narrow range for weight gain for women who begin their pregnancy with a BMI that classifies them as obese. The guidelines are aimed at lowering both the short- and long-term risks to mother and baby that are associated with excessively high (as well as low) gestational weight gain.

Given the evidence linking gestational weight gain to both child and adult overweight and obesity, and the research linking childhood weight to age at menarche, its reasonable to hypothesize that excess gestational weight gain – and perhaps inadequate gestational weight gain as well – may be associated with the timing of menarche in daughters. However, its unclear whether this relationship would be fully mediated by child weight at various stages, or whether there may be other contributing mechanisms – such as in utero experiences and exposures – that could play a role in the timing of menarche in offspring. Boynton-Jarrett et al. published the first large-cohort study examining the relationship between gestational weight gain and daughters' age at menarche, using data from 32,218 women in the Nurses' Health Study II. As mentioned above, they found that

women whose mothers had gained less than 10 pounds or greater than 40 pounds during pregnancy were more likely to experience early menarche (<11 years), compared with women whose mothers had gained between 20-29lbs during pregnancy.[15] After adjusting for maternal pre-pregnancy weight, childhood body size at age 5, and other covariates, odds ratios were 1.31 (95% CI 1.05-1.62) and 1.27 (95% CI 1.06-1.56) for gestational weight gains of <10lbs and >40lbs, respectively.[15]

In contrast, a 2008 study by Terry et al. looking at birth weight, postnatal growth, and age at menarche reported that gestational weight gain did not alter an observed association between early childhood growth rates and age at menarche.[112] Therefore, there remains a need to confirm (or refute) the findings in Boynton-Jarrett et al.'s paper. Furthermore, no studies have examined racial differences in the relationship between gestational weight gain and daughters' age at menarche.

Proposed research:

The mechanisms by which gestational weight gain and the intrauterine environment may act to "program" the future development, structure, and physiology of various systems remain incompletely understood, but an active and important area of research. In this realm, menarche should be studied not as a single event, but rather as part of a life course perspective on women's health, and as a critical period that is intertwined with both early life exposures and later health outcomes.

The literature reviewed in this paper has looked at the well-documented association between child birth weight, rapid postnatal growth, childhood BMI, and the timing of menarche. Building off of the work by Keim et al. – who looked at the association between maternal pre-pregnancy BMI and daughters' age at menarche – and Boyton-Jarrett et al. – who examined the relationship between gestational weight gain and daughters' age at menarche – the proposed study will question whether maternal factors, specifically maternal pre-pregnancy BMI and gestational weight gain, are directly correlated with the timing of menarche in daughters. While Boynton-Jarrett et al. used raw gestational weight gain as their predictor, this study will categorize gestational weight gain into inadequate, recommended, and excessive, based on the 2009 IOM guidelines that consider maternal pre-pregnancy BMI. Any racial disparities in outcomes will also be discussed. I hypothesize that 1) maternal pre-pregnancy overweight and obesity will be associated with earlier menarche in daughters, and 2) excessive (and possibly inadequate) gestational weight gain will be associated with earlier menarche in daughters as well.

The objective of this research is to contribute to an understanding of factors associated with early menarcheal age and its existing racial disparity. As girls undergo puberty at younger ages, they experience hormonal and emotional changes that may surpass the level of their cognitive development. Along with becoming fertile at a younger age, they are also at a higher risk for poor health outcomes later in life, stressing the need to understand the causes of early menarche.

Ultimately, by helping to elucidate causal pathways that determine menarcheal age, the proposed project can contribute to a growing and pertinent field of research that has significant implications for women's health. Moreover, because maternal pre-pregnancy weight and gestational weight gain are potentially modifiable, an opportunity may exist to alter pathways that contribute to early menarche. Current and future findings may inform policy recommendations, and interventions may be designed – such as individualized counseling on gestational weight gain – that could have an effect on outcomes.

Sources:

1. Karlberg J. Secular trends in pubertal development. Horm Res 2002;57 Suppl 2:19-30.
2. Herman-Giddens ME. Recent data on pubertal milestones in United States children: the secular trend toward earlier development. Int J Androl 2006;29:241-6; discussion 86-90.
3. Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. J Pediatr 2005;147:753-60.
4. Dunger DB, Ahmed ML, Ong KK. Early and late weight gain and the timing of puberty. Mol Cell Endocrinol 2006;254-255:140-5.
5. Ong KK, Emmett P, Northstone K, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab 2009;94:1527-32.
6. dos Santos Silva I, De Stavola BL, Mann V, Kuh D, Hardy R, Wadsworth ME. Prenatal factors, childhood growth trajectories and age at menarche. Int J Epidemiol 2002;31:405-12.
7. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. BMC Pediatr 2003;3:3.
8. Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. Int J Androl 2006;29:272-7; discussion 86-90.
9. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002;110:903-10.
10. Cooper C, Kuh D, Egger P, Wadsworth M, Barker D. Childhood growth and age at menarche. Br J Obstet Gynaecol 1996;103:814-7.
11. Keim SA, Branum AM, Klebanoff MA, Zemel BS. Maternal body mass index and daughters' age at menarche. Epidemiology 2009;20:677-81.
12. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M. Age at menarche: Influences of prenatal and postnatal growth. J Clin Endocrinol Metab 2007;92:46-50.
13. Tam CS, de Zegher F, Garnett SP, Baur LA, Cowell CT. Opposing influences of prenatal and postnatal growth on the timing of menarche. J Clin Endocrinol Metab 2006;91:4369-73.
14. Persson I, Ahlsson F, Ewald U, et al. Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. Am J Epidemiol 1999;150:747-55.

15. Boynton-Jarrett R, Rich-Edwards J, Fredman L, et al. Gestational Weight Gain and Daughter's Age at Menarche. J Womens Health (Larchmt) 2011.
16. Kotsopoulos J, Lubinski J, Lynch HT, et al. Age at menarche and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Cancer Causes Control 2005;16:667-74.
17. Peeters PH, Verbeek AL, Krol A, Matthyssen MM, de Waard F. Age at menarche and breast cancer risk in nulliparous women. Breast Cancer Res Treat 1995;33:55-61.
18. Lakshman R, Forouhi N, Luben R, et al. Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. Diabetologia 2008;51:781-6.
19. Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009;94:4953-60.
20. Jacobsen BK, Oda K, Knutsen SF, Fraser GE. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976-88. Int J Epidemiol 2009;38:245-52.
21. Joinson C, Heron J, Lewis G, Croudace T, Araya R. Timing of menarche and depressive symptoms in adolescent girls from a UK cohort. Br J Psychiatry 2011;198:17-23, sup 1-2.
22. Kaltiala-Heino R, Kosunen E, Rimpela M. Pubertal timing, sexual behaviour and self-reported depression in middle adolescence. J Adolesc 2003;26:531-45.
23. Deardorff J, Gonzales NA, Christopher FS, Roosa MW, Millsap RE. Early puberty and adolescent pregnancy: the influence of alcohol use. Pediatrics 2005;116:1451-6.
24. Normal puberty. 2011. (Accessed July 19, 2011, at http://www.uptodate.com/contents/normal-puberty.)
25. Guyton A, Hall J. Medical Physiology. 11th ed: Elsevier Saunders; 2006.
26. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics 2002;110:e43.
27. St George IM, Williams S, Silva PA. Body size and the menarche: the Dunedin Study. J Adolesc Health 1994;15:573-6.
28. Blum WF, Englaro P, Hanitsch S, et al. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J Clin Endocrinol Metab 1997;82:2904-10.
29. Wong WW, Nicolson M, Stuff JE, et al. Serum leptin concentrations in Caucasian and African-American girls. J Clin Endocrinol Metab 1998;83:3574-7.
30. Metcalf MG, Skidmore DS, Lowry GF, Mackenzie JA. Incidence of ovulation in the years after the menarche. J Endocrinol 1983;97:213-9.
31. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer 1999;85:2400-9.
32. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36-47.
33. Magnusson CM, Persson IR, Baron JA, Ekbom A, Bergstrom R, Adami HO. The role of reproductive factors and use of oral contraceptives in the aetiology of breast cancer in women aged 50 to 74 years. Int J Cancer 1999;80:231-6.
34. Rockhill B, Moorman PG, Newman B. Age at menarche, time to regular cycling, and breast cancer (North Carolina, United States). Cancer Causes Control 1998;9:447-53.

35. La Vecchia C. Epidemiology of ovarian cancer: a summary review. Eur J Cancer Prev 2001;10:125-9.
36. Chen X, Wang Y. The influence of sexual maturation on blood pressure and body fatness in African-American adolescent girls and boys. Am J Hum Biol 2009;21:105-12.
37. Jacobsen BK, Heuch I, Kvale G. Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. Am J Epidemiol 2007;166:1431-7.
38. Kivimaki M, Lawlor DA, Smith GD, et al. Association of age at menarche with cardiovascular risk factors, vascular structure, and function in adulthood: the Cardiovascular Risk in Young Finns study. Am J Clin Nutr 2008;87:1876-82.
39. Stice E, Presnell K, Bearman SK. Relation of early menarche to depression, eating disorders, substance abuse, and comorbid psychopathology among adolescent girls. Dev Psychol 2001;37:608-19.
40. Harlow BL, Cohen LS, Otto MW, Spiegelman D, Cramer DW. Early life menstrual characteristics and pregnancy experiences among women with and without major depression: the Harvard study of moods and cycles. J Affect Disord 2004;79:167-76.
41. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med 1982;306:1033-5.
42. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. Pediatrics 2003;111:844-50.
43. Braithwaite D, Moore DH, Lustig RH, et al. Socioeconomic status in relation to early menarche among black and white girls. Cancer Causes Control 2009;20:713-20.
44. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. Pediatrics 2003;111:110-3.
45. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99:505-12.
46. Ouyang F, Perry MJ, Venners SA, et al. Serum DDT, age at menarche, and abnormal menstrual cycle length. Occup Environ Med 2005;62:878-84.
47. Vasiliu O, Muttineni J, Karmaus W. In utero exposure to organochlorines and age at menarche. Hum Reprod 2004;19:1506-12.
48. Blanck HM, Marcus M, Tolbert PE, et al. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. Epidemiology 2000;11:641-7.
49. Buck Louis GM, Gray LE, Jr., Marcus M, et al. Environmental factors and puberty timing: expert panel research needs. Pediatrics 2008;121 Suppl 3:S192-207.
50. Denham M, Schell LM, Deane G, Gallo MV, Ravenscroft J, DeCaprio AP. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. Pediatrics 2005;115:e127-34.
51. Axmon A. Menarche in women with high exposure to persistent organochlorine pollutants in utero and during childhood. Environ Res 2006;102:77-82.
52. Ersoy B, Balkan C, Gunay T, Egemen A. The factors affecting the relation between the menarcheal age of mother and daughter. Child Care Health Dev 2005;31:303-8.

53. Kuh D HR. A life course approach to women's health: does the past predict the present? In: Kuh D HR, ed. A Life Course Approach to Women's Health: Oxford University Press; 2002:3-20.
54. Treloar SA, Martin NG. Age at menarche as a fitness trait: nonadditive genetic variance detected in a large twin sample. Am J Hum Genet 1990;47:137-48.
55. Kaprio J, Rimpela A, Winter T, Viken RJ, Rimpela M, Rose RJ. Common genetic influences on BMI and age at menarche. Hum Biol 1995;67:739-53.
56. Elks CE, Perry JR, Sulem P, et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. Nat Genet 2010;42:1077-85.
57. Belsky J, Steinberg L, Draper P. Childhood experience, interpersonal development, and reproductive strategy: and evolutionary theory of socialization. Child Dev 1991;62:647-70.
58. Bogaert AF. Menarche and father absence in a national probability sample. J Biosoc Sci 2008;40:623-36.
59. Comings DE, Muhleman D, Johnson JP, MacMurray JP. Parent-daughter transmission of the androgen receptor gene as an explanation of the effect of father absence on age of menarche. Child Dev 2002;73:1046-51.
60. Matchock RL, Susman EJ. Family composition and menarcheal age: anti-inbreeding strategies. Am J Hum Biol 2006;18:481-91.
61. Tither JM, Ellis BJ. Impact of fathers on daughters' age at menarche: a genetically and environmentally controlled sibling study. Dev Psychol 2008;44:1409-20.
62. Deardorff J, Ekwaru JP, Kushi LH, et al. Father absence, body mass index, and pubertal timing in girls: differential effects by family income and ethnicity. J Adolesc Health 2011;48:441-7.
63. Moffitt TE, Caspi A, Belsky J, Silva PA. Childhood experience and the onset of menarche: a test of a sociobiological model. Child Dev 1992;63:47-58.
64. Romans SE, Martin JM, Gendall K, Herbison GP. Age of menarche: the role of some psychosocial factors. Psychol Med 2003;33:933-9.
65. Mendle J, Turkheimer E, D'Onofrio BM, et al. Family structure and age at menarche: a children-of-twins approach. Dev Psychol 2006;42:533-42.
66. Graber JA, Brooks-Gunn J, Warren MP. The antecedents of menarcheal age: heredity, family environment, and stressful life events. Child Dev 1995;66:346-59.
67. Koo MM, Rohan TE. Accuracy of short-term recall of age at menarche. Ann Hum Biol 1997;24:61-4.
68. Gilger JW, Geary DC, Eisele LM. Reliability and validity of retrospective self-reports of the age of pubertal onset using twin, sibling, and college student data. Adolescence 1991;26:41-53.
69. Artaria MD, Henneberg M. Why did they lie? Socio-economic bias in reporting menarcheal age. Ann Hum Biol 2000;27:561-9.
70. Cooper R, Blell M, Hardy R, et al. Validity of age at menarche self-reported in adulthood. J Epidemiol Community Health 2006;60:993-7.
71. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291-303.
72. Saenger. Overview of precocious puberty. In: UpToDate; 2010.
73. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics 2010;126:e583-90.

74. Barker DJ. Fetal origins of coronary heart disease. Br Heart J 1993;69:195-6.
75. Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health Nutr 2001;4:611-24.
76. Ong KK, Northstone K, Wells JC, et al. Earlier mother's age at menarche predicts rapid infancy growth and childhood obesity. PLoS Med 2007;4:e132.
77. de Zegher F, Francois I, van Helvoirt M, Van den Berghe G. Clinical review 89: Small as fetus and short as child: from endogenous to exogenous growth hormone. J Clin Endocrinol Metab 1997;82:2021-6.
78. Adair LS. Size at birth predicts age at menarche. Pediatrics 2001;107:E59.
79. Ibanez L, Ong K, Dunger DB, de Zegher F. Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. J Clin Endocrinol Metab 2006;91:2153-8.
80. Ong KK, Ahmed ML, Sherriff A, et al. Cord blood leptin is associated with size at birth and predicts infancy weight gain in humans. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Clin Endocrinol Metab 1999;84:1145-8.
81. Ong KK, Ahmed ML, Dunger DB. The role of leptin in human growth and puberty. Acta Paediatr Suppl 1999;88:95-8.
82. Crawford JD, Osler DC. Body composition at menarche: The Frisch-Revelle hypothesis revisited. Pediatrics 1975;56:449-58.
83. Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of menarche. Arch Dis Child 1971;46:695-701.
84. Scott E, Johnston F, Benso L, et al. Science, Nutrition, Fat, and Policy: Tests of the Critical-Fat Hypothesis [and Comments and Reply]. Current Anthropology 1985;40:463-73.
85. Johnston FE, Roche AF, Schell LM, Norman H, Wettenhall B. Critical weight at menarche. Critique of a hypothesis. Am J Dis Child 1975;129:19-23.
86. Bau AM, Ernert A, Schenk L, et al. Is there a further acceleration in the age at onset of menarche? A cross-sectional study in 1840 school children focusing on age and bodyweight at the onset of menarche. Eur J Endocrinol 2009;160:107-13.
87. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. Pediatrics 2007;119:e624-30.
88. Malina RM, Ryan RC, Bonci CM. Age at menarche in athletes and their mothers and sisters. Ann Hum Biol 1994;21:417-22.
89. Campbell BC, Udry JR. Stress and age at menarche of mothers and daughters. J Biosoc Sci 1995;27:127-34.
90. Ellis BJ, Essex MJ. Family environments, adrenarche, and sexual maturation: a longitudinal test of a life history model. Child Dev 2007;78:1799-817.
91. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. Pediatr Res 2002;52:863-7.
92. Windham GC, Bottomley C, Birner C, Fenster L. Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea during pregnancy. Am J Epidemiol 2004;159:862-71.
93. Shrestha A, Nohr EA, Bech BH, Ramlau-Hansen CH, Olsen J. Smoking and alcohol use during pregnancy and age of menarche in daughters. Hum Reprod 2011;26:259-65.
94. Maisonet M, Christensen KY, Rubin C, et al. Role of prenatal characteristics and early growth on pubertal attainment of British girls. Pediatrics 2010;126:e591-600.

95. Oken E, Rifas-Shiman SL, Field AE, Frazier AL, Gillman MW. Maternal gestational weight gain and offspring weight in adolescence. Obstet Gynecol 2008;112:999-1006.
96. Siega-Riz AM, Laraia B. The implications of maternal overweight and obesity on the course of pregnancy and birth outcomes. Matern Child Health J 2006;10:S153-6.
97. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549-55.
98. Kramer MS, Platt R, Yang H, McNamara H, Usher RH. Are all growth-restricted newborns created equal(ly)? Pediatrics 1999;103:599-602.
99. Abrams B, Newman V. Small-for-gestational-age birth: maternal predictors and comparison with risk factors of spontaneous preterm delivery in the same cohort. Am J Obstet Gynecol 1991;164:785-90.
100. Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Low maternal weight, failure to thrive in pregnancy, and adverse pregnancy outcomes. Am J Obstet Gynecol 2003;189:1726-30.
101. Schieve LA, Cogswell ME, Scanlon KS, et al. Prepregnancy body mass index and pregnancy weight gain: associations with preterm delivery. The NMIHS Collaborative Study Group. Obstet Gynecol 2000;96:194-200.
102. Moreira P, Padez C, Mourao-Carvalhal I, Rosado V. Maternal weight gain during pregnancy and overweight in Portuguese children. Int J Obes (Lond) 2007;31:608-14.
103. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. Am J Obstet Gynecol 2007;196:322 e1-8.
104. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. Circulation 2009;119:1720-7.
105. Stuebe AM, Forman MR, Michels KB. Maternal-recalled gestational weight gain, pre-pregnancy body mass index, and obesity in the daughter. Int J Obes (Lond) 2009;33:743-52.
106. Schack-Nielsen L ME, Michaelsen KF, TI S. . High maternal pregnancy weight gain is associated with an increased risk of obesity in childhood and adulthood independent of maternal BMI. *Pediatr Res* 2005;58:1020.
107. Brawarsky P, Stotland NE, Jackson RA, et al. Pre-pregnancy and pregnancy-related factors and the risk of excessive or inadequate gestational weight gain. Int J Gynaecol Obstet 2005;91:125-31.
108. Dodd JM, Robinson JS. Gestational weight loss in overweight and obese women is associated with an increased risk of small for gestational age infants. Evid Based Med 2011.
109. Bodnar LM, Siega-Riz AM, Simhan HN, Himes KP, Abrams B. Severe obesity, gestational weight gain, and adverse birth outcomes. Am J Clin Nutr 2010;91:1642-8.
110. Thorsdottir I, Birgisdottir BE. Different weight gain in women of normal weight before pregnancy: postpartum weight and birth weight. Obstet Gynecol 1998;92:377-83.
111. Abrams B, Altman SL, Pickett KE. Pregnancy weight gain: still controversial. Am J Clin Nutr 2000;71:1233S-41S.
112. Terry MB, Ferris JS, Tehranifar P, Wei Y, Flom JD. Birth weight, postnatal growth, and age at menarche. Am J Epidemiol 2009;170:72-9.

Part 2: Maternal Pre-pregnancy BMI, Gestational Weight Gain, and Age at Menarche in Daughters

Abstract:

Objectives: Low birth weight, rapid postnatal growth, and high childhood BMI are associated with earlier menarche in girls. Associations between maternal pregnancy experience and daughters' age at menarche are less understood. In this study, we examine whether maternal pre-pregnancy BMI and gestational weight gain are related to the timing of menarche in daughters.

Methods: The sample includes 2,181 mother-daughter pairs from the 1979 National Longitudinal Survey of Youth, a prospective cohort study. Survival analysis with Cox proportional hazards was used to estimate whether maternal pre-pregnancy overweight and obesity (BMI≥25.0 kg/m^2) and gestational weight gain adequacy (categorized as inadequate, recommended, and excessive based on 2009 Institute of Medicine guidelines) were associated with risk of earlier menarche among girls, controlling for important covariates.

Results: Maternal pre-pregnancy overweight and obesity were associated with daughters' earlier menarche (HR= 1.20, 95% CI 1.05, 1.38). Excess gestational weight gain was not associated with daughters' age at menarche (HR=1.10, 95% CI 0.97, 1.25) in the adjusted model, nor was inadequate gestational weight gain (HR=1.05, 95% CI 0.92, 1.19). Consistent with past literature, earlier maternal age at menarche, Hispanic and black race, and lower parental education were all associated with an increased risk of earlier menarche in daughters.

Conclusions: Maternal pre-pregnancy overweight and obesity is associated with an earlier menarcheal age in offspring. Further research is warranted to elucidate the pathways through which this relationship may operate. Gestational weight gain adequacy was not associated with menarcheal timing in this study after controlling for key covariates.

Introduction:

Over the past several decades there has been a downward trend in the average age at menarche among girls in the United States and other developed nations.[1-4] Girls enter puberty earlier and reach menarche at younger ages than in the past.[5] Moreover, significant racial disparities exist, with black girls tending to reach menarche significantly earlier than non-Hispanic white girls.[4, 6-9] Downstream health effects of early menarche have been studied extensively and show that early menarcheal age is associated with a risk for a number of deleterious outcomes across the life course, including breast cancer, cardiovascular disease, glucose intolerance and obesity in adulthood, as well as higher rates of depression and anxiety, and engagement in risky behaviors during adolescence.[10-19]

Studies of the determinants of menarcheal timing reveal that a number of hereditary and environmental factors likely influence the timing of puberty and first menstruation, and emerging evidence suggests that early life factors may be particularly important. Recent research has revealed a correlation between low birth weight, early infant growth patterns, and the timing of menarche, while other studies have established a relationship between childhood overweight and obesity and earlier menarcheal age.[20-25] Few studies, however, have examined whether a direct association exists between maternal factors, including maternal BMI and gestational weight gain, and the timing of menarche in offspring.

In a 2009 paper using data from the Collaborative Perinatal Project (1959-1965), Keim and colleagues found that daughters of obese mothers had an increased risk of experiencing early menarche (less than 12 years) compared to daughters of normal weight or underweight mothers.[26] In 2011, Boynton-Jarrett and colleagues published the first study examining the relationship between maternal gestational weight gain and daughters' age at menarche using data from the Nurses' Health Study.[27] Results suggested a U-shaped association between gestational weight gain (GWG) and early menarche, such that excessively high (>40lbs) and low (<10lbs) weight gain during pregnancy were each associated with a higher risk of early menarche in daughters.[27] One potential biological explanation for these findings is that intrauterine exposures and growth patterns may lead to fetal programming of future endocrine, metabolic, and reproductive pathways. Given the ethnic homogeneity in the Nurses' Health Study, it remains unknown whether this association differs across race/ethnicity. To address these gaps in the existent literature, we used data from the 1979 National Longitudinal Survey of Youth to examine whether maternal pre-pregnancy BMI and gestational weight gain are independently associated with an earlier age at menarche in daughters.

Methods:

Participants

The National Longitudinal Survey of Youth 1979 (NLSY79) is an ongoing prospective cohort study of a nationally representative sample of 12,686 men and women born between 1957 and 1964.[28] Participants were interviewed annually between 1979 and

1994, and biennially thereafter. Offspring born to women in the original cohort have also been surveyed biennially from 1986 to present as part of the NLSY Children and Young Adult survey. The NLSY79 includes a diverse array of topics, ranging from workforce and socioeconomic data to physical, mental, and reproductive health data. Since the data is de-identified and publicly accessible, the UC Berkeley Committee for Protection of Human Subjects waived the requirement for a formal review of this research.

We selected mother-daughter pairs and followed the daughters until 2008. We excluded girls with an age of menarche before the age of 9 (n=23) and after the age of 16 (n=12), as menarche before and after these ages are more likely to be the result of precocious puberty and delayed menarche due to an underlying pathology, respectively.[29] Race/ethnicity is categorized by the NLSY at baseline as black, Hispanic (includes all Hispanics, regardless of race), and white and others, including all non-Hispanic, non-black Asian, Pacific Islander, Native American, and other participants. White participants comprise close to 90% of this subgroup. This study did not have sufficient numbers of non-white individuals in this category to create separate categories of race/ethnicity beyond black and Hispanic. Children's race/ethnicity was based on mothers' racial/ethnic category at baseline.

Measures

The primary predictor variables in this study were maternal pre-pregnancy BMI and gestational weight gain (GWG) adequacy. Maternal pre-pregnancy BMI (weight [kg]/height [m^2]) was calculated based on self-reported pre-pregnancy weight for each gestation and height reported in 1985. Women were categorized as underweight (BMI <18.5), normal weight (BMI <18.5-24.9), and overweight and obese (BMI ≥ 25.0).[30] Descriptive analyses showed that there was not sufficient sample size to examine overweight and obesity separately, and sensitivity analyses (not shown) demonstrate that these two categories did not substantially differ. Gestational weight gain in kilograms was calculated as women's self-reported weight at delivery minus weight before delivery. We used an algorithm to convert raw GWG to "gestational weight gain adequacy," as described previously,[31] to reflect the 2009 Institute of Medicine (IOM) recommendations for maternal weight gain based on pre-pregnancy BMI and week of gestation at delivery for inadequate, recommended, and excessive GWG.[32]

The outcome of interest was daughter's age at menarche. Age at menarche in months was calculated using date of birth and reported year and month of first menstruation, reported by mothers for girls under age 14 and self-reported beginning in 1994 for girls age 14 and older. Because this was a prospective cohort study, less than two years of recall were required due to the study design of biennial surveys. Previous research indicates that retrospective report of age at menarche is reliable, particularly when the length of recall is short.[33, 34]

Based on the existing literature, we selected potential confounders to adjust for in our multivariate analysis, including socioeconomic status (SES), daughter's ethnicity,

parity, maternal smoking during pregnancy (yes/no to smoking during 12 months before birth of child), maternal age at menarche, and breastfeeding (yes/no). For SES, we included the log parental income (reported at child's birth) and maternal education level (at age 25).

Daughters' birth weight was calculated based on plausible values for gestational age between 22 and 44 weeks, as defined by Alexander et al.[35] Daughters' BMI at age 7 was used to provide a measure of pre-pubertal weight status, given national averages for girls' pubertal onset. BMI at age 6 or 8 was used if girls did not have weight and height measurements at age 7, and BMI was converted to BMI age- and sex-specific percentiles based on CDC definitions for children.[36] Birth weight and pre-pubertal BMI have well-documented associations with age at menarche [21-23] and might operate on the causal pathway (mediators) between our exposure of interest and age at menarche.

Analysis

All analyses were performed using Stata version 10.0. Survey weights were used to account for non-response bias and oversampling of black and Hispanic and low SES populations.[28, 37] We conducted preliminary bivariate analyses using the survey equivalent of ANOVA with Stata survey mean commands and Adjusted Wald F test for continuous variables to test for differences in maternal and daughter characteristics by age at menarche category.[37] We used survival analysis with Cox-proportional hazards to estimate the association of maternal pre-pregnancy BMI and GWG on daughters' age at menarche. The first model adjusted for race/ethnicity, SES, maternal age at menarche, maternal smoking during pregnancy, and whether the daughter was breastfeed. The second model included these variables plus birth weight and daughter's pre-pubertal BMI. Survival analysis allowed us to examine time to daughters' age at menarche, and to account for censored data for girls between ages 9 and 16 who had yet to achieve menarche at the time of their last interview. Hazard ratios can be interpreted similarly to a relative risk estimate.[37] For categorical exposures, the hazard ratio can be interpreted as the instantaneous probability of menarche for girls with and without each exposure, adjusting for covariates. The proportional hazards model assumes that this ratio of probabilities is the same for any age, given that menarche has not yet occurred. For our primary exposures – maternal pre-pregnancy BMI and GWG – "normal pre-pregnancy BMI" and "recommended GWG" served as reference baselines in the model, respectively. To assess for a different relationship between GWG and age at menarche by pre-pregnancy size or race/ethnicity, we created interaction terms for pre-pregnancy BMI category and continuous GWG, as well as for race categories and continuous GWG.

Results:

Our sample included 2,694 girls between the ages of 9 and 16 with menarche data between the years 1988 and 2008. Of these, 2,328 girls had a documented age at menarche and 366 girls had not yet attained menarche. Data were missing for one or more of the key covariates for 513 girls, yielding a final sample that included 2,181 girls (1,919 with menarche, 262 without menarche) with complete data for maternal pre-pregnancy BMI, gestational weight gain, and all covariates.

Table 1 displays mean characteristics of our analytic sample compared to the 513 girls who were excluded due to one or more missing covariates. There were statistically significant differences for our two categorical predictor variables. Those excluded had higher rates of pre-pregnancy underweight (16.6% vs. 7.4%) and lower rates of excess gestational weight gain (33.7% vs. 43.4%), though there was no statistical difference between the groups for average pre-pregnancy BMI and gestational weight gain in total pounds. The difference in parity was also statistically significant: 3.0 average children among those excluded compared to 2.9 for those in our sample.

Table 2 shows the distribution and bivariate tests of association of select variables by four categories of daughters' age at menarche (9-11, 12, 13, 14-17). Black and Hispanic girls were significantly more likely to experience earlier menarche (<12 years) compared to white girls: About 50% of black and Hispanic girls had at age of menarche between 9 and 11 years, compared to 38% of white girls. For all races, girls with earlier menarche were more likely to have had a lower birth weight, a mom with younger age at menarche, a mom with higher maternal pre-pregnancy BMI, and a higher childhood pre-puberty BMI. Almost half of women with an excessive GWG had a daughter with early menarche, compared to about one third of women who gained within the recommended range. Approximately 60% of women with a high pre-pregnancy BMI (>25) gained excess gestational weight, compared to less than 40% of woman with a pre-pregnancy BMI<25 (data not shown).

Table 3 shows the results of our multivariate survival analysis. After controlling for potential confounders, maternal pre-pregnancy overweight/obesity was associated with an earlier age at menarche (HR=1.20, 95% CI 1.05, 1.38) but underweight pre-pregnancy BMI was not associated (HR=0.94, 95% CI 0.80, 1.11). In unadjusted analyses (full model not shown), excess GWG was significantly associated with lower age at menarche (HR=1.19, 95% CI 1.01, 1.25), which remained significant after adding in maternal age at menarche; this association was no longer significant after including maternal pre-pregnancy BMI, and remained non-significant in the fully adjusted model (HR=1.10, 95% CI 0.97, 1.25). Inadequate gestational weight gain was not significant in the unadjusted model and remained so in the adjusted model (HR=1.05, 95% CI 0.92, 1.19).

Of the covariates in the model, earlier maternal age at menarche, Hispanic ethnicity and black race, and lower maternal education were all positively associated with an increased risk of earlier menarche in daughters. Cross products between maternal pre-pregnancy BMI and GWG and race and GWG did not detect any evidence of effect modification.

To compare our findings to Boynton-Jarrett et al, we also tested the association of continuous GWG, as well as 2 categories (GWG<10lb and GWG>40lb), but found no significant results. Finally, we added daughters' birth weight and pre-puberty BMI to our model, which we had hypothesized as potential mediators. Hazard ratios for maternal pre-pregnancy BMI (HR=1.20, 95% CI 1.04, 1.37) and excess gestational weight gain (HR=1.09, 95% CI 0.96, 1.23) were unchanged, suggesting no evidence that birth weight and pre-

puberty BMI operated in the causal pathway between maternal weight and daughters' age at menarche.

Discussion:

In this racially diverse, nationally representative sample of women and children, after adjusting for potential confounders, high maternal pre-pregnancy BMI was associated with earlier age at menarche in daughters. In contrast, while unadjusted analyses suggested that excessive GWG was associated with early menarche, the association was no longer significant after adjusting for pre-pregnancy BMI and other covariates. Consistent with prior work, we also found that earlier maternal age at menarche, black race and Hispanic ethnicity, and lower maternal education were associated with earlier menarche in daughters, but there was no evidence that associations between GWG and menarche were different by BMI nor were associations different by BMI and race/ethnicity.

Using normal weight women as a reference, Keim et al. reported an association between maternal pre-pregnancy obesity (BMI≥30) and a risk of early menarche (<12) (OR=3.3, 95% CI=1.1, 10.0) after adjusting for socioeconomic index, maternal parity, maternal age at menarche, and daughter's race; however, they did not find an increased odds of early menarche for daughters of overweight mothers (OR=1.10, 95% CI = 0.6, 2.1).[26] In our study, we combined overweight and obese mothers to increase power. We controlled for Keim et al.'s covariates, as well as smoking during pregnancy and breastfeeding status, both of which have been shown to potentially influence menarcheal timing and/or childhood growth patterns and pre-puberty weight status.[38-40] We also had a larger sample size (2,181 versus 597 for Keim). As in our study, Keim found that lower birth weight (characterized by small-for-gestational age (SGA) status at birth) and higher pre-puberty BMI (characterized by BMI-for-age z score at age 7) did not significantly mediate the association between maternal pre-pregnancy BMI and daughter's age at menarche.

Mechanisms to explain the relationship between high pre-pregnancy BMI and daughter's early age at menarche are not understood. One possibility is that the relationship operates through fetal size, whereby large-for-gestational age (LGA) infants are more likely to become overweight girls, who in turn have an increased risk of earlier menarche. Higher pre-pregnancy BMI has been associated with LGA babies;[41] however, the evidence from this study and Keim's suggests that fetal size did not alter the relationship between high pre-pregnancy and daughters' age at menarche. In-utero may be important, but are not yet understood. For example, since its discovery in 1994, the hormone leptin has also been studied for its role in the onset and progression of puberty. Leptin is produced primarily from adipocytes, and serum leptin concentrations are strongly associated with overall body fat. Serum leptin concentrations have also been shown to increase with pubertal development in girls, presumably through its role in the maturation of the gonadotropin-releasing hormone pulsatile secretions that lead to the beginning of menses.[42, 43] Higher exposures to leptin in-utero could play a role in determining these pathways, as well as exposure to other endocrine hormones, including insulin, insulin-like

growth factor I (IGF-I), and growth hormone, which have been shown to influence early childhood growth patterns.[20, 44]

Boynton-Jarrett et al, analyzed associations between maternal GWG and age at menarche in 32,218 mother-daughter pairs the Nurses' Health Study II, an ongoing prospective cohort study started in 1989, and the Nurses' Mothers' Cohort Study, a survey launched in 2001 of the study participants' mothers. In contrast to our finding that GWG was not associated with early menarche, they reported an increased odds of early menarche for daughters of women whose GWG was <10lb (OR=1.31, 95% CI 1.05, 1.62), and >40lb (1.27, 95% CI 1.06, 1.56).[27] Our results may differ for several reasons. Their sample was comprised of nurses and their mothers, who were primarily white, while our sample is much more heterogeneous in terms of race/ethnicity. With more than 30,000 participants, their study had the statistical power to detect significant differences at the extremes of GWG; while we attempted to examine those extremes, our sample size lacked power. Nonetheless, our point estimates are much lower than theirs, suggesting that the lack of association between GWG and age at menarche in our study is not simply due to low power. Future studies in diverse populations with large samples and well-measured data are needed to confirm the role of GWG and age of menarche. In this realm, menarche should be studied not as a single event, but rather as part of a life course perspective on women's health, and as a critical period that is intertwined with both early life exposures and later health outcomes.

Our study had several limitations. The NLSY79 depends on self-reported data: age at menarche for moms and daughters as well as all weight and height data were based on recall. Self-reported data are subject to error,[45] however, all girls or their mothers reported age at menarche within 2 years of its onset, and self-report of menarche has been found to be relatively good up to 30 years later.[34] Missing data were also a potential concern; there were few substantial differences in the characteristics of our sample compared to the girls who were excluded from the analysis however our results may be limited to a population with the characteristics to those analyzed. Our study also had notable strengths. The NLSY is a diverse, large, nationally representative prospective sample that allowed us to consider many relevant confounders, and our use of a 'time to event' model of survival analysis provided the most appropriate methodological approach given that there were censored observations in our sample, i.e. some girls had not yet undergone menarche. These methods allowed us to avoid substantial sample selection bias by including girls who had yet to reach menarche at the time of their last interview. Given the diversity of our sample, we were also able to investigate whether the relationship between BMI and age at menarche differed by race, and it did not.

In summary, high maternal BMI but not GWG was associated with earlier menarche in this US sample. The downstream effects of early menarche are substantial; by helping to elucidate pathways to menarcheal age, this study contributes findings with important implications for women's health. Moreover, high maternal pre-pregnancy weight and gestational weight gain, unlike genetics or maternal age at menarche, are potentially modifiable,[32] and thus opportunities may exist to alter pathways that contribute to early

menarche. Our data suggest that a focus on normalizing maternal weight prior to pregnancy may have an effect on the outcome of menarcheal timing in girls.

Table 1: Participant characteristics of included sample vs. excluded for missing data

	Sample (n=2,181)	Missing	P-value
Race/ethnicity	--	--	0.06
Black	8.3%	10.7%	
Hispanic	18.7%	20.6%	
White + other	72.9%	68.6%	
Average age at menarche (years)	12.3	12.5	0.08
Average maternal age at menarche	12.9	12.9	0.52
Average maternal pre-pregnancy BMI	23.2	22.7	0.21
Maternal pre-pregnancy BMI category			
Underweight (BMI<18.5)	7.4%	16.6%	0.00
Normal weight (BMI ≥18.5 & <25.0)	68.5%	60.1%	
Overweight & obese (BMI ≥25.0)	24.2%	23.3%	
Average birth weight (grams)	3288.6	3361.8	0.06
Average pre-puberty BMI among daughters	16.2	16.1	0.55
Gestational weight gain – Total pounds	31.3	30.2	0.30
Gestational weight gain category			
Inadequate GWG	25.9%	36.3%	0.01
Recommended GWG	30.6%	30.0%	
Excessive GWG	43.4%	33.7%	
Log parental income	10.6	10.6	0.75
Maternal education	12.6	12.4	0.20

(years)			
Maternal smoking during pregnancy[1]	34.0%	32.1%	0.55
Daughter breastfed[2]	52.2%	53.1%	0.76
Parity	2.9	3.0	0.02

Table 2: Participant characteristics by daughters' age at menarche

	9-11	**12**	**13**	**14-17**	**P-value**
Race/ethnicity	41.2%	32.2%	18.8%	7.8%	0.00
Black	49.8%	28.9%	14.0%	7.3%	
Hispanic	49.4%	31.9%	14.7%	4.0%	
White + other	38.1%	33.1%	20.5%	8.3%	
Average maternal age at menarche (months)	12.7	13.0	13.3	13.5	0.00
Average maternal pre-pregnancy BMI	23.9	23.2	22.1	22.0	0.00
Maternal pre-pregnancy BMI category					
Underweight (BMI<18.5)	35.6%	30.5%	25.6%	8.3%	
Normal weight (BMI ≥18.5 & <25.0)	38.5%	32.2%	20.3%	9.0%	
Overweight (BMI ≥25.0 & <30)	49.2%	32.4%	15.0%	3.4%	
Obese (BMI ≥30.0)	53.6%	33.5%	7.2%	5.7%	
Average birth weight (grams)	3238.8	3301.9	3383.1	3268.9	0.00
Average pre-puberty BMI among daughters	16.6	16.1	15.9	15.1	0.00
Gestational weight gain – Total pounds	31.3	31.0	31.5	32.1	0.85
Gestational weight gain category					
Inadequate GWG	40.7%	31.4%	20.6%	7.3%	0.01
Recommended GWG	34.6%	36.9%	19.5%	9.0%	
Excessive GWG	46.2%	29.4%	17.2%	7.2%	
Parity	2.8	2.9	2.9	2.8	0.73

[1] Number indicates percent of women who responded 'yes' to smoking within 12 months of delivering their child

[2] Number represents percent of women who indicated 'yes' when asked if their child was breastfed

Table 3: Hazard ratios for menarche from survival analysis with Cox proportional hazards

	Hazard ratio	p-value	95% confidence interval
Maternal pre-pregnancy BMI <18.5 (Underweight)	0.94	0.490	(0.80, 1.11)
Maternal pre-pregnancy BMI >25.0 (Overweight & obese)	1.20	0.008	(1.05, 1.38)
Excessive gestational weight gain	1.10	0.129	(0.97, 1.25)
Inadequate gestational weight gain	1.05	0.470	(0.92, 1.19)
Maternal age at menarche (months)	0.99	0.000	(0.98, 0.99)
Hispanic	1.36	0.000	(1.19, 1.56)
Black	1.23	0.002	(1.07, 1.40)
Log parental income	1.01	0.730	(0.94, 1.09)
Maternal education (years)	0.97	0.040	(0.94, 0.99)
Maternal smoking during pregnancy	1.12	0.057	(1.00, 1.25)
Daughter breastfed (yes/no)	0.93	0.157	(0.83, 1.03)
Parity	0.99	0.452	(0.95, 1.03)

Sources:

1. Karlberg J. Secular trends in pubertal development. Horm Res 2002;57 Suppl 2:19-30.
2. Herman-Giddens ME. Recent data on pubertal milestones in United States children: the secular trend toward earlier development. Int J Androl 2006;29:241-6; discussion 86-90.
3. Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. J Pediatr 2005;147:753-60.
4. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. Pediatrics 2003;111:844-50.
5. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics 2008;121 Suppl 3:S172-91.
6. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics 2002;110:e43.
7. Braithwaite D, Moore DH, Lustig RH, et al. Socioeconomic status in relation to early menarche among black and white girls. Cancer Causes Control 2009;20:713-20.
8. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. Pediatrics 2003;111:110-3.
9. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99:505-12.
10. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer 1999;85:2400-9.
11. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36-47.
12. Magnusson CM, Persson IR, Baron JA, Ekbom A, Bergstrom R, Adami HO. The role of reproductive factors and use of oral contraceptives in the aetiology of breast cancer in women aged 50 to 74 years. Int J Cancer 1999;80:231-6.
13. Rockhill B, Moorman PG, Newman B. Age at menarche, time to regular cycling, and breast cancer (North Carolina, United States). Cancer Causes Control 1998;9:447-53.
14. Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009;94:4953-60.
15. Jacobsen BK, Oda K, Knutsen SF, Fraser GE. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976-88. Int J Epidemiol 2009;38:245-52.
16. Chen X, Wang Y. The influence of sexual maturation on blood pressure and body fatness in African-American adolescent girls and boys. Am J Hum Biol 2009;21:105-12.
17. Jacobsen BK, Heuch I, Kvale G. Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. Am J Epidemiol 2007;166:1431-7.
18. Deardorff J, Gonzales NA, Christopher FS, Roosa MW, Millsap RE. Early puberty and adolescent pregnancy: the influence of alcohol use. Pediatrics 2005;116:1451-6.

19. Harlow BL, Cohen LS, Otto MW, Spiegelman D, Cramer DW. Early life menstrual characteristics and pregnancy experiences among women with and without major depression: the Harvard study of moods and cycles. J Affect Disord 2004;79:167-76.
20. Dunger DB, Ahmed ML, Ong KK. Early and late weight gain and the timing of puberty. Mol Cell Endocrinol 2006;254-255:140-5.
21. Ong KK, Emmett P, Northstone K, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab 2009;94:1527-32.
22. dos Santos Silva I, De Stavola BL, Mann V, Kuh D, Hardy R, Wadsworth ME. Prenatal factors, childhood growth trajectories and age at menarche. Int J Epidemiol 2002;31:405-12.
23. Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. Int J Androl 2006;29:272-7; discussion 86-90.
24. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002;110:903-10.
25. Cooper C, Kuh D, Egger P, Wadsworth M, Barker D. Childhood growth and age at menarche. Br J Obstet Gynaecol 1996;103:814-7.
26. Keim SA, Branum AM, Klebanoff MA, Zemel BS. Maternal body mass index and daughters' age at menarche. Epidemiology 2009;20:677-81.
27. Boynton-Jarrett R, Rich-Edwards J, Fredman L, et al. Gestational Weight Gain and Daughter's Age at Menarche. J Womens Health (Larchmt) 2011.
28. National Longitudinal Surveys. In: United States Department of Labor, Bureau of Labor Statistics.
29. Posner RB. Early Menarche: A Review of Research on Trends in Timing, Racial Differences, Etiology and Psychosocial Consequences. Sex Roles 2006;54:315-22.
30. Obesity: preventing and managing the global epidemic. Geneva, Switzerland: World Health Organization: World Health Organization; 2000.
31. Bodnar LM, Siega-Riz AM, Arab L, Chantala K, McDonald T. Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women. Public Health Nutr 2004;7:701-11.
32. Institute of Medicine FaNB. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: National Academy Press; 2009.
33. Cooper R, Blell M, Hardy R, et al. Validity of age at menarche self-reported in adulthood. J Epidemiol Community Health 2006;60:993-7.
34. Damon A, Bajema CJ. Age at menarche: Accuracy of recall after thirty-nine years. Human Biology 1974;46:381-4.
35. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163-8.
36. Defining childhood overweight and obesity. In: Centers for Disease Control.
37. Stata: Survey Data Reference Manual: Stata Press; 2009.
38. Dewey KG. Is Breastfeeding Protective Against Child Obesity? Journal of Human Lactation 2003;19:9-18.
39. Windham GC, Bottomley C, Birner C, Fenster L. Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea during pregnancy. Am J Epidemiol 2004;159:862-71.
40. Shrestha A, Nohr EA, Bech BH, Ramlau-Hansen CH, Olsen J. Smoking and alcohol use during pregnancy and age of menarche in daughters. Hum Reprod 2011;26:259-65.

41. Siega-Riz AM, Laraia B. The implications of maternal overweight and obesity on the course of pregnancy and birth outcomes. Matern Child Health J 2006;10:S153-6.
42. Blum WF, Englaro P, Hanitsch S, et al. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J Clin Endocrinol Metab 1997;82:2904-10.
43. Wong WW, Nicolson M, Stuff JE, et al. Serum leptin concentrations in Caucasian and African-American girls. J Clin Endocrinol Metab 1998;83:3574-7.
44. Ong KK, Ahmed ML, Sherriff A, et al. Cord blood leptin is associated with size at birth and predicts infancy weight gain in humans. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Clin Endocrinol Metab 1999;84:1145-8.
45. Bodnar LM, Siega-Riz AM, Simhan HN, Diesel JC, Abrams B. The Impact of Exposure Misclassification on Associations Between Prepregnancy BMI and Adverse Pregnancy Outcomes. Obesity 2010;18:2184-90.