Early-life Origins of Breast Development and the Implications for Breast Cancer Risk

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ABSTRACT

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Breast cancer incidence, particularly late-stage disease, is increasing in U.S. women under 40 years of age, pointing to the importance of exposures acting early in the life course to increase breast cancer risk. Earlier onset of breast development has recently been identified as an independent risk factor for breast cancer. Thus, identifying modifiable factors that can delay the onset of breast development may provide an opportunity for breast cancer primary prevention starting early in life. This dissertation examined the influence of the early-life environment on the age at onset of breast development through: 1) a systematic review of the literature relating maternal pre-pregnancy body size, gestational weight gain (GWG), birth size, and infant growth to the timing of breast development and menarche; 2) analyses assessing the associations between these factors and the onset of breast development in a pubertal cohort enriched for breast cancer family history (BCFH); and 3) a pilot study assessing whether these factors are associated with serum levels of insulin-like growth factor(IGF)-1 and insulin-like growth factor binding protein(IGFBP)-3 during puberty.

Our systematic review identified 96 studies, the majority of which examined the association between birthweight and age at menarche. Although low birthweight is often cited as a risk factor for early menarche, the majority of studies (40/73 total) that examined this association did not observe a statistically significant association. Differences in exposure assessment, inadequate control for confounders, and differences in postnatal growth across studies may drive inconsistencies in the birthweight literature. In contrast, higher maternal body mass index (BMI) prior to pregnancy, GWG in excess of recommended guidelines and faster rates of weight gain between birth and 2 years of age were consistently associated with earlier age at breast development and menarche.

We used data from the LEGACY Girls Study, a prospective cohort of girls primarily ages 6-13 years at baseline in which approximately 50% of girls had a family history of breast cancer, to examine the relations between maternal factors, birth size and infant growth and the onset of breast development,

defined as a maternal report of breast Tanner stage 2 or greater. Daughters of women with a pre-pregnancy BMI of 25 or greater and who gained 30lbs or more during pregnancy experienced breast development at an earlier age than daughters of women with a pre-pregnancy BMI less than 25 and who gained less than 30lbs. This association was similar in girls with and without a BCFH. Birthweight and birthlength were not associated with the timing of breast development.

In a subset of LEGACY girls with height and weight data during infancy available from medical records, we examined the associations between changes in weight-for-age and length-for-age Z-scores from birth to 1 year of age and the onset of breast development. We observed a modest association between faster rates of weight gain from 0-12 months and earlier age at breast development. When we examined smaller age intervals within infancy, faster weight gain from 2-4 months and 6-9 months were each associated with an earlier age at breast development. A similar pattern was observed for growth in length, and these associations did not vary by BCFH.

In our pilot study including 109 girls with available serum samples between 6-17 years of age at the LEGACY New York site, rapid weight gain from 0-12 months was associated with higher mean levels of IGF-1 relative to IGFBP-3. Although not statistically significant, girls with a maternal pre-pregnancy BMI≥25 and GWG≥30lbs also had higher mean levels of the IGF-1/IGFBP-3 ratio. Since serum IGF-1 and IGFBP-3 are objective measures that are known to increase rapidly during puberty, the results of our pilot study support that the maternal BMI, GWG and rapid infant weight gain are associated with biological changes in the girls. Our findings suggest that measurement error in outcome assessment or confounding did not drive the associations that we observed between these factors and earlier onset of breast development.

In conclusion, we identified higher maternal pre-pregnancy BMI, excess GWG and rapid growth during infancy as modifiable factors associated with earlier onset of breast development in girls across the spectrum of familial risk for breast cancer. While this suggests that modifying these factors may decrease breast cancer risk later in life, further research should consider additional and potentially opposing pathways, such as childhood body size, through which the early-life environment affects breast cancer risk.

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Chapter 1. Introduction

1.1 Background

Breast cancer is the most common cancer in women worldwide and one-third of global breast cancers are diagnosed in women under the age of 50,[1] indicating the importance of modifying exposures prior to mid-life to decrease risk. Exposures across the life course, including body size (weight, height, and weight for height, often assessed by body mass index (BMI)), have long been recognized as affecting breast cancer risk.[2–4] Weight, specifically, is of interest as it is often cited as a potentially modifiable risk factor for breast cancer.[4,5] The direction of the association between weight and breast cancer risk, however, changes over the life course. Weight in adulthood is positively associated with post-menopausal breast cancer risk, as is weight gain after age 18-25 years.[6–10] In contrast, adult weight is inversely associated with pre-menopausal breast cancer risk,[6,7]and most studies have not observed an association between long-term weight gain and risk of pre-menopausal breast cancer.[8,11–13] Weight during adolescence is inversely associated with both pre- and post-menopausal breast cancer risk.[14–17] Birthweight is positively associated with the risk of pre-menopausal breast cancer and may be modestly positively associated with post-menopausal cancer risk as well,[18] suggesting that breast cancer susceptibility may be altered by intrauterine factors that affect birthweight and early-life weight gain.[19] The associations in opposing directions between body weight at birth and in adolescence highlight the importance of examining associations between different trajectories of early-life growth, and factors that influence growth trajectories, and breast cancer risk. Maternal pre-pregnancy BMI and gestational weight gain influence fetal and postnatal growth,[20–22] but the few studies that have examined these factors and breast cancer risk have not consistently observed an association.[23,24] Birthweight also influences weight gain during infancy, a dynamic period of change when most infants triple their birthweight by 12 months of age.[25] However, no studies have assessed whether patterns of weight gain during multiple windows within infancy are associated with breast cancer risk.

Intrauterine factors that may explain the positive association between birthweight and breast cancer risk: Under the early-life etiologic model for breast cancer, intrauterine factors can affect offspring breast cancer risk both through an effect on the number of mammary tissue-specific stem cells and the replication rate of these cells in utero, which is affected by levels of growth-enhancing hormones.[19] While the

association between birthweight and breast cancer risk supports this hypothesis, birthweight is a measure of size, and only a crude indicator of fetal growth and the intrauterine environment in general.[26] The data connecting other characteristics that influence the intrauterine environment to breast cancer risk are limited. Maternal pre-pregnancy BMI and gestational weight gain are associated with birthweight[20] and maternal hormone levels during pregnancy,[27–29] but studies have not consistently supported an association with breast cancer risk.[23,24] Given the long induction time between the intrauterine environment and breast cancer diagnosis, most studies in the literature are from pregnancies over 50 years ago, when the prevalence of obesity and excess gestational weight gain was much lower than today.[30] Considering the increasing prevalence of these pregnancy conditions over time, it is important to examine the association between the intrauterine environment and breast cancer risk. Through this research, we can understand whether these factors drive the positive association between birthweight and breast cancer and identify modifiable factors, such as gestational weight gain and physical activity during pregnancy, to target during pregnancy for primary prevention.

Infancy is the missing link in the body size and breast cancer literature: Under the early-life etiologic model, postnatal growth could operate via the same mechanisms as intrauterine factors to affect breast cancer risk,[19] but few studies have examined the early postnatal period. In the 1946 British birth cohort, BMI velocity from 2-4 years was inversely associated with breast cancer risk, though there was no association with BMI at 2 years.[31] This study did not have measures of body size between birth and 2 years and could not examine growth rates within this window. In the Hertfordshire cohort born between 1911 and 1939, women in the lowest and highest third of the weight gain distribution from birth to one year both had increased risks of breast cancer mortality compared to those of average weight gain.[32] A Swedish study examining neonatal growth in 405 BC cases and 1081 controls found that neonates who gained ≥25 grams per day until hospital discharge after an initial weight loss of <200 grams after birth had a 50% increased risk of breast cancer later in life compared to those that gained <25 grams per day; the increased risk was twofold in women less than 50 years at diagnosis.[33] These studies suggest that infancy may be a key transition point when the positive association between birthweight and breast cancer risk changes direction to the inverse association observed between adolescent body size and breast cancer risk. Trajectories of weight and height growth may be more important than size at any given time point in relation to later breast

cancer risk. Evidence from pubertal cohorts suggest that rapid infant weight gain is a predictor of earlier pubertal onset, a breast cancer risk factor.[34,35] Recently, using prospective data from a 1960s U.S. birth cohort, we observed a two-fold increased risk of benign breast disease, a well-established breast cancer risk factor,[36] in women with rapid weight gain in infancy.[37] Previous studies have been unable to assess the association between size or growth during infancy and early childhood and breast cancer risk directly due to a lack of prospective anthropometric measures within the first year of life.[14] Since growth during these time periods cannot be assessed retrospectively, data on early-life growth has been largely limited to birth cohorts that collect these measures prospectively at specific time points, or data abstracted from medical records. With the recent widespread adoption of electronic medical records,[38] children born in the past 10-15 years will be the first generation where growth data will be available across the life course and can be linked to later health outcomes.

Puberty is a critical window for breast cancer risk: Although contemporary cohorts with prospective infant growth measures have yet to reach the age when incident breast cancer can be directly studied as an outcome, studies can examine associations between early-life growth and breast cancer risk factors that can be measured earlier in the life course. Early age at menarche is a well-established risk factor for breast cancer.[39,40] Recently, the Breakthrough Generations Study of 104,931 women found that earlier age at breast development and longer time period between breast development and menarche, also known as slower tempo, were both independently associated with a 20-30% increased risk of breast cancer.[41] While age at menarche has been fairly stable over the past 50 years, age at breast development has decreased rapidly over this same time period, suggesting that the pubertal tempo in girls today is likely slower than in the past.[42] Puberty is a period of rapid growth and development for the breast, when ductal branching occurs and the terminal ductal lobular units (TDLUs) form, though they do not fully differentiate until pregnancy.[43,44] TDLUs are the milk-producing structure of the breast and the structure within the breast where most breast cancers originate.[45,46] The breast is more susceptible to carcinogenic effects from environmental exposures during these periods of rapid growth and development, termed windows of susceptibility for breast cancer risk.[43] Factors that accelerate the onset of breast development and slow the tempo of breast growth may elongate this pubertal window of susceptibility and increase the risk of breast cancer later in life.

Drivers of normal breast development are unknown: Although puberty is recognized as a critical period for breast development, few studies have examined trajectories of normal breast development in childhood and adolescence. While mammography is assessed on a population level in adult women of screening age, there is no imaging method that is used clinically in adolescents. Mammography is not used in adolescents due to the radiation exposure. Some studies are currently using alternate methods to assess breast tissue composition in adolescents, including dual energy X-ray absorptiometry (DXA),[47,48] magnetic resonance imaging (MRI)[49] and optical spectroscopy (OS).[50] Longitudinal studies using these technologies will provide novel insights into the variability of normal breast development and factors that influence breast development. However, these methods are not yet available on a widespread basis. Age at onset of breast development, age at menarche and the tempo between these two events are markers of breast development that can be measured non-invasively through parent or self-reports. Studies that identify drivers of normal breast development are needed both to understand the secular trends in pubertal timing, but also to identify early-life factors that may affect how the breast develops during this critical window of susceptibility, increasing vulnerability to carcinogenesis in adulthood. In addition, investigating the associations between early-life factors and repeated measures of blood biomarkers, such as insulin-like growth factor (IGF)-1 and insulin-like growth factor-binding protein 3 (IGFBP-3), which are associated with stages of breast development,[51,52] can implicate specific pathways through which early-life factors affect normal breast development and breast cancer risk.

Gene-environment interactions matter for etiology and prevention: Examining whether associations between early-life environmental factors vary across the spectrum of underlying susceptibility for breast cancer is critical for breast cancer etiology and primary prevention efforts. Women with a family history of breast cancer are at an increased risk of being diagnosed themselves, and this risk increases with the number of relatives affected and the younger those relatives were diagnosed.[53] Recently, we observed that girls at an increased risk of breast cancer due to their family history experience earlier breast development than girls without a family history.[54] If there is no heterogeneity by susceptibility based on absolute risk estimated by family history, then risk factors will still have a greater effect on an absolute scale in those with greater underlying risk,[55,56] and *girls and women at high risk need to know that the environment*

matters and that their risk can be modified. If there is heterogeneity, then identifying the context in which the early-life environment affects risk will allow for targeted prevention to those groups that will benefit most.

1.2 Dissertation overview

In this dissertation, we examine the contribution of maternal factors, body size at birth and infant growth to the timing of breast development and consider the implications of these findings in light of breast cancer risk on an individual level and future trends in breast cancer incidence on a population level. We hypothesize that maternal factors, including higher maternal pre-pregnancy BMI, excess gestational weight gain and physical inactivity during pregnancy, and rapid weight gain during infancy are associated with earlier breast development, independent of birthweight, and that these associations may be modified by underlying susceptibility. We examine these hypotheses in the following chapters:

In **Chapter 2**, we systematically review and synthesize the epidemiologic literature on the associations between maternal body size, birth size, and infant growth and the timing of breast development and menarche. In this chapter, we examine sources of heterogeneity in the literature and identify gaps that future research should address. The findings from Chapter 2 inform the background and methodology of the analytic chapters that follow, which seek to address some of the identified gaps in the literature.

In the analytic chapters, we utilize data from the LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study, a prospective cohort of 1040 girls primarily ages 6-13 years at baseline that is enriched for breast cancer family history (BCFH),[57] in order to examine the associations between early-life factors and the onset of breast development overall and by BCFH. The LEGACY girls have been followed prospectively since 2011 with biospecimen, anthropometric and questionnaire data collected every 6 months and a 92% retention rate at the end of the first five years. Weight and height data prior to recruitment has been abstracted for 82% of the cohort from medical records.

In **Chapter 3**, we examine the association between maternal factors (including maternal pre-pregnancy BMI, gestational weight gain, and maternal physical activity during pregnancy), birth size

(weight and length at birth, adjusted for gestational age) and the onset of breast development in the LEGACY Girls Study. We also examine whether these associations are independent of childhood BMI and if they are modified by BCFH. The goal of this chapter is to identify modifiable factors during pregnancy that affect pubertal timing in order to inform primary prevention efforts.

In **Chapter 4**, we examine measures of infant size (weight and length prior to 12 months) and infant growth (rates of change in weight and length) and the onset of breast development in LEGACY girls. This chapter focusing on postnatal growth is a natural follow-up to Chapter 3**,** which focuses on factors that affect fetal growth. We also explore mediation by childhood body size and effect measure modification by BCFH. Few studies have examined the association between infant growth and breast cancer risk directly. By examining infant growth in relation to pubertal timing in girls with an increased risk of breast cancer due to their family history, the findings from this chapter may shed light on how infant growth may be associated with breast cancer risk.

In **Chapter 5,** we examine the association between the early-life exposures and serum levels of IGF-1 and IGFBP-3 during puberty in the New York site of LEGACY. The aim of this pilot study is to complement Chapters 3 and 4, which examined the maternal report of breast development as the outcome, by assessing whether maternal pregnancy factors, birth size and infant growth are associated with objectively measured biomarkers that are correlated with pubertal development.

In **Chapter 6**, we synthesize the findings of this dissertation and their contribution to our understanding of the pre- and postnatal periods as windows of susceptibility for breast development. We conclude with the implications of these findings for breast cancer risk, considering avenues for primary prevention. We also suggest areas for future research based on hypotheses generated from these findings.

Chapter 2. Size and growth during early life and pubertal timing in girls: a systematic review

ABSTRACT

Background: Earlier age at menarche is a well-established risk factor for breast cancer, and early age at breast development (thelarche) has recently been associated with breast cancer risk as well. Body size and growth in early life may be associated with pubertal timing, suggesting that these factors may also affect breast cancer risk. The majority of the literature examining early-life body size and pubertal timing focuses on birthweight and menarche, and findings have been inconsistent. Fewer studies have examined the associations between maternal body size and/or body size in infancy, in addition to birthweight, and age at menarche. More recently, this literature has expanded to include age at breast development and the time interval between breast development and menarche (pubertal tempo). The objective of this chapter is to systematically review studies that examine the association between at least one exposure of interest (maternal pre-pregnancy body mass index (BMI) or weight, gestational weight gain (GWG), birth weight or length and/or size or growth in weight or height during infancy) and at least one pubertal outcome (thelarche, menarche and/or tempo) in girls, and identify sources of heterogeneity in study-specific estimates that contribute to inconsistencies in the literature.

Methods: We conducted a systematic search of peer-reviewed studies in PubMed from 1970 through March 30, 2018 for original research articles published in English. We excluded studies if the study population included males and did not present sex-stratified results, the outcome was central or peripheral precocious puberty, the outcome was a pubertal event other than breast development, menarche or tempo between these two events, the exposure was body size or growth measured after 2 years of age, or the study population was comprised of children with conditions that would affect either pubertal development (such as endocrine disorders or precocious puberty) or early-life growth (such as pediatric cancers or autoimmune disorders). Multiple articles using data from the same study population were eligible for inclusion. Six studies of maternal pre-pregnancy weight or BMI, 1 study of GWG, 17 studies of birth size (weight or length), and 8 studies of size and/or growth during infancy were included in relation to age at breast development or pubertal tempo. For menarche, 14 studies of maternal size, 8 studies of GWG, 74 studies of birth size, and 18 studies of infant size and/or growth were included in the review.

Results: Higher maternal pre-pregnancy BMI was associated with earlier age at breast development in 4 of 5 studies, though 3 of these analyses were conducted within the same cohort, and higher pre-pregnancy weight was associated with earlier breast development in one study. Higher maternal pre-pregnancy BMI was associated with earlier age at menarche in 7 of 12 studies, as was higher maternal weight in 2 of 3 studies. Higher GWG was associated with earlier age at breast development in the one study that examined this association. Higher GWG was associated with earlier age at menarche in 3 studies that used multivariable-adjusted models, but not in 5 studies examining unadjusted associations. GWG in excess of the 2009 Institute of Medicine guidelines was also associated with age at menarche in two studies that used this categorization. The majority of studies examining birthweight or birthlength in relation to age at breast development were null, though 4 studies reported an association between lower birthweight and earlier breast development and 3 found the opposite. The results for birthweight and menarche were similar: 40 studies did not observe an association, 28 observed earlier menarche in girls with lower birthweight, and 5 observed earlier menarche in girls with higher birthweight. Most (11) studies of birthlength and menarche were also null, with 6 studies reporting contradictory results. Faster weight gain in infancy was associated with earlier age at breast development and menarche in 3 of 5 and 10 of 12 studies, respectively. Higher weight in infancy was also associated with earlier age at these pubertal events. Very few studies examined pubertal tempo as an outcome.

Conclusions: Studies suggest that higher maternal pre-pregnancy BMI, greater GWG and rapid postnatal weight gain are associated with earlier age at breast development and menarche with girls. There is insufficient data to determine if these exposures also affect pubertal tempo. The literature does not support an independent effect of birthweight on pubertal timing. Modifying weight gain prior to and throughout pregnancy in mothers and through infancy in their daughters may delay pubertal timing and potentially lower breast cancer risk in adulthood.

2.1 Background

Early age at menarche is a well-established risk factor for breast cancer.[39,40] Recently, the Breakthrough Generations Study of 104,931 women found that earlier age at breast development and a longer time period between breast development and menarche (slower tempo) were both independently

associated with a 20-30% increased risk of breast cancer.[41] Since women recalled age at breast development in adulthood and breast cancer was then assessed prospectively, non-differential misclassification likely biased the results towards the null, suggesting that the true association may be even larger. While age at menarche has been relatively stable over the past 50 years,[58,59] age at breast development has continued to decline rapidly.[60,61] The correlation between age at menarche and age at breast development has also decreased over time,[62] suggesting that girls with an earlier age at breast development progress through puberty at a slower rate.[42] These secular trends, when considered in light of the associations observed in the Breakthrough Generations Study,[41] suggest future increases in breast cancer incidence. The identification of modifiable factors that affect pubertal timing, defined as age at breast development and/or age at menarche, may have important implications for altering breast cancer risk.

The secular decrease in age at breast development parallels the increase in childhood obesity, and overweight girls have an earlier age at breast development and menarche than girls who are not overweight prior to puberty.[42] Larger body size starting at birth and rapid postnatal growth patterns both track to larger body size prior to puberty.[63–66] Earlier age at breast development has also been observed, however, in populations with a lower prevalence of childhood obesity, such as Hong Kong,[67] suggesting that early-life growth may affect breast development independent of childhood body size. In addition, there have been secular changes in the early-life environment, including maternal body size and infant growth patterns,[30,68] which parallel the decrease in the age at breast development. The pre- and postnatal periods may be an effective period for intervention on modifiable factors such as physical activity during pregnancy, gestational weight gain (GWG) and weight gain during infancy, as pregnant women and new parents are regularly engaged with clinicians who are already monitoring maternal body size and behaviors and infant growth.[69] However, although many studies have examined the association between birthweight, a proxy for fetal growth,[26] and age at menarche, the direction of the association is not clear. While some have observed that girls with lower birthweight have an earlier age at menarche,[70–72] many did not observe an association[73–75] and a few observed the opposite – earlier age at menarche in girls with high birthweight.[76,77] Studies of birthweight and the onset of breast development are similarly inconsistent.[73,75,78–80] Fewer studies have examined maternal body size and GWG or infant growth patterns in relation to pubertal timing, but these

studies suggest that higher maternal pre-pregnancy BMI,[73,81,82] increased GWG[82,83] and rapid postnatal weight gain[72,73,75,77] are associated with earlier age at breast development and menarche.

Since maternal body size and GWG are associated with size at birth,[20] which is correlated with infant growth,[84] it is extremely difficult to separate out the independent effects of these factors. Maternal body size may confound associations between birthweight and pubertal timing, while infant growth patterns could mediate or modify a birthweight effect. To illustrate the complexity of these relationships, **Figure 2.1** shows a directed acyclic graph (DAG) for a hypothesized causal structure between early-life body size and age at breast development. A comprehensive review that considers the evidence examining body size measures during early life (including pre-pregnancy weight or BMI, GWG and birth size, indicators of the intrauterine environment, and size and growth during infancy) and pubertal timing in girls, can explore whether patterns of early-life growth are consistently associated with pubertal timing and may identify methodological differences across studies that explain the heterogeneity in study findings.

Although previous reviews have been published regarding early-life factors and puberty,[85–89] most have not been systematic in nature.[86–88] These reviews focused predominantly on menarche as a measure of pubertal development, even though menarche occurs on average two years after the onset of pubertal development in girls.[90] More studies examined age at menarche since timing of menarche can be reliably recalled into adulthood.[91] Recently, as birth cohorts have aged into adolescence and pubertal cohorts have been established, studies have begun to examine prospective measures of breast and pubic hair development as markers of pubertal onset.[79,92,93] Previously, data on early-life growth has been largely limited to birth cohorts that collect these measures prospectively at specific time points, or data abstracted from medical records. With the recent widespread adoption of electronic medical records, there is an increasing number of studies with early-life growth data that can be examined in relation to later health outcomes, such as pubertal timing.

This review will address these limitations of previous reviews by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[94] to systematically identify studies that examine at least one of the exposures of interest (maternal pre-pregnancy weight or BMI, gestational weight gain (GWG), birth weight or length and/or size or growth in weight or height during infancy) and at

least one pubertal outcome (thelarche, menarche and/or tempo) in girls and examine sources of heterogeneity in study-specific estimates that contribute to inconsistencies in the literature. Given the importance of early puberty to the risk of breast cancer[41,95] and other chronic diseases,[96,97] in addition to the psychological and behavioral consequences of early puberty in girls,[98,99] identifying modifiable factors that can delay pubertal onset is crucial to women's health.

2.2 Methods

2.2.1. Search strategy

We conducted a systematic search following the PRISMA guidelines[94] to identify studies that examined the association(s) between maternal pre-pregnancy weight or BMI, GWG, birth size and/or size or growth during infancy (from birth to age 2 years) and the timing of puberty in girls. **Appendix A** details the protocol for this systematic review. We included normal breast development, age at menarche, and the tempo between these two events as our pubertal outcomes of interest. We identified studies by a systematic search of peer-reviewed studies in PubMed through March 30, 2018. We used both MeSH terms and key words identified from the literature as search terms. We combined terms related to the pubertal outcomes (i.e. 'breast development' OR 'thelarche' OR 'menarche') with terms related to body size and growth ('weight' OR 'height' OR 'length' OR 'ponderal index' or 'body mass index' OR 'BMI' OR 'obese' OR 'obesity' OR 'overweight' OR 'adiposity' OR 'growth' OR 'weight gain' OR 'height gain') and time period of exposure ('mother' OR 'birth' OR 'maternal' OR 'prenatal' OR 'pregnancy' OR "in utero" OR 'fetal' OR 'infant' OR 'infancy' OR 'postnatal' OR 'early life' OR 'early-life' OR 'childhood') using Boolean operators (see **Appendix A** for full list of search terms). We did not use any limits when conducting the search in PubMed to ensure that we would capture recent articles that had yet to be classified within PubMed.

2.2.2. Study selection

Original research articles published in English between January 1, 1970 and March 30, 2018 were eligible for inclusion. We chose 1970 as the lower limit for the review because the seminal paper by Marshall and Tanner describing the stages of pubertal development in girls was published in 1969.[100] I downloaded

the search results into a reference management software (Endnote X7) and removed duplicates. I screened titles and abstracts and identified articles that examined the association between at least one exposure of interest in relation to either normal breast development, menarche or tempo between these two events in girls for full-text review. We excluded studies published prior to 1970, reviews, editorials, letters or conference abstracts, animal studies, and case studies (defined as studies with a study population of 10 girls or less). We also excluded studies if: 1) the study population included males and did not present sex-stratified results; 2) the outcome was central or peripheral precocious puberty (puberty before age 8 years in females); 3) the outcome was a pubertal event other than breast development, menarche or tempo (i.e. adrenarche, pubarche, pubertal growth spurt); 4) the exposure was body size or growth measured after 2 years of age; or 5) the study population was comprised of children with conditions that would affect either pubertal development (such as endocrine disorders or precocious puberty) or early-life growth (such as pediatric cancers, autoimmune disorders). We excluded studies of size or growth after 2 years of age because childhood body size has been consistently associated with age at breast development and menarche, and has been the subject of multiple review articles.[89,101–104] A second reviewer screened 10% of identified articles using the same inclusion and exclusion criteria to assess the reliability of the single reviewer. The agreement between the two reviewers was 98.5% (18 discrepancies/1241 screened titles/abstracts), and all discrepancies were resolved after discussion. Given this high-level of agreement, I independently reviewed the full-text articles for inclusion in the review. I also reviewed the reference list of included articles and relevant review articles published in the last 10 years to identify additional articles for inclusion. We did not exclude studies based on design or the type of results presented (i.e. inclusion was not limited to studies that presented multivariable-adjusted effect estimates) in order to present a comprehensive review of the literature and avoid bias towards the inclusion of articles that present non-null findings.

2.2.3. Data extraction

I extracted the following information for each exposure and outcome of interest from all studies that met the inclusion criteria: author(s), publication year, study design, study setting and time frame, sample size, age range of participants, exposure assessment (definition and source), outcome assessment

(definition and source), covariate information, statistical methods, and results (differences in means or proportions or effect estimates and confidence intervals). I extracted results from multivariable-adjusted models with and without adjustment for childhood body size when available; if multivariable-adjusted results were not available, I extracted differences in means or proportions or crude associations. I assessed the quality of included studies by using the NIH Quality Assessment Tool for Observational and Cohort Studies[105] and the Newcastle-Ottawa Scale (NOS) for cohort or case control studies.[106] I assessed cross-sectional studies using a modified NOS for cohort studies, considering adequacy of response rate instead of follow-up rate. The quality scores did not affect the inclusion of the articles in the review, but we considered them when interpreting the results of the review. Given the heterogeneity in exposure and outcome assessment, as well as the statistical methods used, we present a qualitative synthesis of the included articles and did not quantitatively combine the study results in a meta-analysis.

2.3 Results

2.3.1. Search results

This systematic search resulted in 12,413 articles, with an additional 5 articles identified by a manual search of the reference lists of included articles and recent review articles (see **Figure 2.2** for flow chart of study selection). After removing 6 duplicates, I identified 12,412 articles for screening. I excluded 12,227 articles after title and abstract review, leaving 185 articles for full-text review. After full-text review, I excluded an additional 89 articles, leaving 96 articles that met the inclusion criteria to be included in the qualitative synthesis. **Figure 2.2** lists the reasons for exclusion of articles after full-text review. The most common reason for exclusion was the lack of at least one of the early-life body size exposures of interest (i.e. body size was measured after 2 years of age only) or the use of a pubertal outcome other than breast development, menarche or tempo (i.e. pubarche or peak height velocity). Many of the 96 included articles examined more than one exposure and/or outcome of interest. Some of the articles were also conducted within the same study population (i.e. three articles used the (Avon Longitudinal Study of Parent and Children (ALSPAC)) cohort to examine maternal pre-pregnancy BMI and the age at breast development[73,82,107]). We included multiple articles from the same cohort since the articles differed in the

analytic techniques used or in the subset of the population included, which is informative in considering how these differences contribute to heterogeneity in the literature. In addition, there was significant heterogeneity in terms of the results presented. Null results were sometimes presented in the text only (data not shown), and some studies provided descriptive statistics only, particularly older studies. **Table 2.1** details the number of included studies per exposure-outcome association and includes a breakdown of the type of results included for each exposure and outcome assessed (text only, descriptive statistics, crude models, and adjusted models). We did not include tempo as a separate outcome category in **Table 2.1** since few studies examined this outcome; tempo results are included in the tables for breast development when presented. I extracted data from all studies, regardless of the type of results presented, and present this information in the supplemental tables. However, we will focus more on the papers that present multivariable-adjusted models in the text. We have organized the summary of the results by exposure, with the results for breast development presented first, followed by the results for menarche.

2.3.2. Maternal pre-pregnancy body size, gestational weight gain and breast development

Maternal pre-pregnancy weight or BMI

Six articles from four unique studies examined the association between maternal pre-pregnancy body size and the timing of breast development in their daughters (**Supplemental Table 2.1**).[73,81,82,107–109] Higher maternal pre-pregnancy BMI was associated with earlier breast development in daughters in four of the five articles.[73,81,82,107] Three of these analyses were conducted within the ALSPAC birth cohort,[73,82,107] which contributes to the consistency in this literature. Four of the five studies examining maternal pre-pregnancy BMI assessed the exposure as a categorical variable, defining maternal overweight and obese using BMI cut-offs of 25 and 30, respectively,[73,81,107,109] while one analysis assessed BMI continuously.[82] One study examined maternal pre-pregnancy weight as a continuous variable and also observed an association between higher weight and earlier breast development.[108] All studies assessed breast development using Tanner staging,[100] which was assessed repeatedly via parent- and self-report in the ALSPAC study[73,82,107] and via trained research staff[109] or physician[81] in two U.S. studies.

A cross-sectional study of Belgian girls in secondary school found that higher maternal pre-pregnancy weight was associated with earlier age of onset of breast development in unadjusted models (RR=1.013, 95% CI=1.006, 1.021).[108] In the ALSPAC cohort, daughters of overweight and obese mothers, as assessed by a pre-pregnancy BMI ≥25, had an earlier age at transition to breast Tanner stage (TS) ≥2 or ≥3 after adjusting for other maternal characteristics (Difference in age at transition to TS≥2= -0.4, 95% CI= -0.62, -0.25 for maternal overweight and -0.7, 95% CI=-1.00, -0.40 for maternal obesity compared with maternal BMI in the normal range).[73] An additional study in ALSPAC that considered breast TS as an ordinal outcome also found an increased probability of being in a higher breast TS for daughters of overweight and obese mothers.[107] A more recent analysis of ALSPAC with follow-up extended through age 17 years also found an association between higher maternal pre-pregnancy BMI assessed continuously and earlier age at breast development in daughters in adjusted models. In addition, this study decomposed the total effect of pre-pregnancy BMI and found both a significant direct effect and an indirect effect through daughters' body size, while there was not an indirect effect via daughters' birthweight.[82] Using a retrospective cohort design using medical record data from Kaiser Permanente, Kubo et al also found that maternal overweight and obesity was associated with earlier age at breast TS≥2 in adjusted models, with partial mediation by daughters' pre-pubertal BMI (HR=1.39, 95% CI=1.30, 1.49 without daughters' BMI and HR=1.22, 95% CI 1.13, 1.31 with daughters' BMI in the model).[81] An earlier study by Kubo et al observed earlier breast development in daughters of mothers with a pregravid BMI ≥30 in unadjusted analyses, but the association was attenuated and no longer statistically significant after adjustment for race/ethnicity, household income and maternal age at menarche.[109] This study included only 386 girls and was likely underpowered in adjusted models.

Gestational weight gain

Only one study in the ALSPAC cohort examined the association between GWG and daughters' age at breast development.[82] After adjusting for maternal pre-pregnancy BMI and other maternal characteristics, this study found that higher GWG was associated with earlier age at breast development (β for 1 kilogram increase in GWG=-0.28, 95% CI= -0.42, -0.14).[82] Similar to the models examining pre-pregnancy BMI, the association was partially mediated by pre-pubertal BMI, but there was no evidence of

mediation by birthweight. Analyses that examined the period of GWG were consistent with an inverse association in both early (≤18 weeks) and late (≥28 weeks) of pregnancy, while no association was observed with weight gain in mid-pregnancy.

Summary

Overall, these studies consistently support an association between larger maternal pre-pregnancy body size and earlier breast development in their daughters. While daughters of underweight mothers did not have significantly different age at breast development compared with average-weight mothers in studies that examined this group separately,[73,81,107] the evidence suggests a linear trend overall between maternal pre-pregnancy body size and timing of breast development.[73,81,82] More studies are needed to replicate these findings, however, since five of the six articles are from the same two study populations. In addition, studies are needed that assess both maternal pre-pregnancy BMI and GWG separately and jointly in relation to age at breast development. For example, studies that examine GWG as inadequate, adequate or excessive based on pre-pregnancy BMI, such as using the classification of the 2009 Institute of Medicine (IOM) guidelines,[110] are directly relevant to clinicians and may inform the guidance that they give pregnant women regarding lifestyle modification and guideline adherence.

2.3.3. Maternal pre-pregnancy body size, gestational weight gain and menarche

Maternal pre-pregnancy weight or BMI

Fourteen articles examined the association between maternal pre-pregnancy body size and daughters' age at menarche, with 11 articles examining BMI,[71,73,82,111–118] two articles examining weight,[75,108] and one looking at both[77] (**Supplemental Table 2.2**). Three of these studies used data from the ALSPAC cohort,[73,82,114] four used data from various sites of the Collaborative Perinatal Project (CPP) cohort,[77,113,115,116] and two used data from the California Child Health and Development Studies (CHDS) cohort.[77,112] Age at menarche was reported during adolescence (age <18 years) in half of the included studies[71,73,75,82,108,112,114,118] and recalled in adulthood (age ≥18 years) in the other studies.[77,111,113,115–117] Most studies used pre-pregnancy weight measures reported by the mother during pregnancy. Higher maternal pre-pregnancy BMI or weight was associated with earlier age at menarche in daughters in nine of

the ten studies that used regression analyses.[73,75,77,82,108,111,114,115,117,118] Of the five studies that did not observe an association between maternal pre-pregnancy BMI and age at menarche, four were either based on descriptive statistics or stated the null results in the text only.[71,77,112,116] Windham et al observed a crude association between tertiles of maternal pre-pregnancy BMI and age at menarche, but the association was not statistically significant after adjustment for confounders including prenatal smoke exposure, maternal age at pregnancy, maternal age at menarche, maternal race, and other socioeconomic factors (β=-0.09, 95% CI=-0.34, 0.16 for BMI>26 compared with 20-26).[113]

Two studies observed a modest linear association between higher maternal pre-pregnancy weight and earlier age at menarche in unadjusted models.[75,108] Studies that assessed maternal BMI continuously also observed an inverse association with age at menarche. A follow-up of a Danish pregnancy cohort (recruited 1984-1987 in two Danish cities) observed a very modest association between age at menarche, reported to the nearest year only in approximately 50% of girls, and maternal pre-pregnancy BMI, equivalent to a decrease in age at menarche of 7.6 days for every one-unit increase in maternal pre-pregnancy BMI.[117] This association was attenuated after adjustment for daughters' BMI measured between 14-18 years of age (difference in days = 2.9, 95% CI=-4.3, 10.1), though BMI during this age range was likely measured after menarche for most girls. In the ALSPAC cohort of girls born 1991-1992, menarche occurred 3.4 months earlier for each one-unit increase in maternal pre-pregnancy BMI.[82] This study also found that the association was mediated by daughters' body size. Studies that examined maternal pre-pregnancy BMI as a categorical outcome were consistent with earlier menarche in daughters of overweight and obese mothers, though the categories used varied by study.[73,111,114,115,118] In contrast to the studies looking at continuous exposures, adjustment for daughters' pre-pubertal BMI did not attenuate the association between maternal overweight (BMI>25) or maternal obesity (BMI≥30) and earlier menarche in two U.S. populations.[115,118] Daughters of underweight mothers did not have significantly later menarche than daughters of average-weight mothers in analyses that examined this category separately.[73,82,111,119]

Gestational weight gain

Seven of the fourteen studies that examined maternal pre-pregnancy BMI also assessed the association between GWG and age at menarche (**Supplemental Table 2.2**).[71,75,77,82,113,116,118] One

additional study examined GWG and age at menarche in the Nurse's Health Study (NHS) II cohort, but did not present results for maternal pre-pregnancy weight.[83] Five of these studies reported no association between GWG and age at menarche, but none of these null studies used multivariable-adjusted models to estimate the association.[71,75,77,113,116] Three studies that did present multivariable-adjusted estimates, including adjustment for maternal pre-pregnancy weight or BMI, all observed an association between higher GWG and earlier age at menarche.[82,83,118] In NHSII women whose mothers participated in the Nurses' Mothers' Cohort and recalled their GWG, GWG≥40 lbs, compared with the referent group of 20-29lbs, was associated with early menarche (<11 years) but not late menarche (>15 years).[83] The association was U-shaped – daughters of mothers who gained <10lbs were also more likely to have early menarche. Adjustment for daughters' childhood body size did not attenuate the associations between low or high GWG and age at menarche. Similar findings were observed in the National Longitudinal Survey of Youth (HR for menarche=1.12, 95% CI 1.00, 1.25 for >40lbs and HR=1.19, 95% CI 0.96, 1.47 for <10lbs compared with 10-40lbs).[118] In the ALSPAC cohort, GWG assessed continuously had an inverse linear relationship with age at menarche, with partial mediation by daughters' pre-pubertal BMI.[82] There was not strong evidence of heterogeneity by period of gestation, though the inverse association was statistically significant only for GWG in late pregnancy in analyses that examined multiple time periods of gestation.

Two studies also examined GWG in relation to the 2009 IOM guidelines, which defines inadequate, adequate and excessive GWG differently based on pre-pregnancy BMI. For example, women with a pre-pregnant BMI≥30 are recommended to gain 11-20lbs, while women with a pre-pregnant BMI of 18.5-24.9 are recommended to gain 25-35lbs.[110] In the National Longitudinal Survey of Youth, GWG adequacy was calculated as the ratio of GWG divided by the expected amount based on pre-pregnancy BMI and gestational age at delivery and categorized as inadequate (<88%), adequate (88-123%) or excessive (>123%) based on the percent of the expected weight gain based on 2009 IOM guidelines. In models examining these categories with relation to age at menarche, excessive GWG was significantly associated with earlier menarche compared with adequate GWG. The point estimate for the inadequate GWG group also suggested earlier menarche in this group, but the association was not statistically significant.[118] In the ALSPAC cohort, GWG in excess of the 2009 IOM guidelines was associated with a 24% decrease in the odds of late menarche (defined as >1 SD above the sample mean, or age >13.8 years, compared to

menarche within 1 SD of the sample mean), but was not significantly associated with early menarche (defined as >1 SD below the sample mean, or age <11.5 years). Inadequate GWG was associated with a 22% decrease in the odds of early menarche compared with daughters of mothers with adequate weight gain, but was not significantly associated with late menarche.[82]

Summary

Although there is slightly more heterogeneity in the literature examining maternal pre-pregnancy BMI and menarche compared to the breast development literature, this is likely due to differences in adjustment for confounders. Most studies that controlled for maternal confounders in multivariable-adjusted models consistently observed an inverse association between maternal pre-pregnancy BMI and age at menarche. Studies of GWG consistently observed an association between high GWG, or GWG in excess of guidelines, and earlier age at menarche. While some studies observed earlier menarche in daughters of women with low GWG, this could be due to residual confounding by maternal pre-pregnancy BMI. Additional studies examining the interaction between maternal BMI and GWG and categorizations based on guidelines are needed to disentangle these two effects. In addition, since high maternal BMI and GWG are associated with both breast development and age at menarche, studies are warranted to examine if these factors have independent effects on pubertal tempo.

2.3.4. Birth size and breast development

Birthweight

Seventeen articles from sixteen unique studies assessed the association between birthweight and the timing of breast development (**Supplemental Table 2.3**).[73,75,78–80,107,120–130] Most studies used records of weight measured at birth, while three were based on parent recall of birthweight.[80,123,126] Breast development was assessed using TS, with 12 studies reporting breast TS as assessed by a clinician or trained research staff, 4 using parent or self-reports, and 1 study using the self-reported age at breast development as the outcome. Since studies differed in the assessment of breast development, I will consider studies of breast onset (TS≥2), later breast development (TS3-5) and pubertal tempo separately.

Onset of breast development

In the nine studies that examined the onset of breast development (TS≥2), six reported no association,[73,80,123,124,126,128] two observed earlier breast development in girls that were smaller at birth,[78,127] and one observed later breast development in girls that were smaller at birth.[75] In a study of 216 Indian girls born 1968-1971, Bhargava *et al* observed a median age at breast TS2 of 10.7 years in term girls with a birthweight <2000g who were small for date compared with 11.1 years in control girls with a birthweight ≥2500g.[127] Another study of 38 full-term girls in Italy also observed earlier age at breast development in girls with a birthweight below the third percentile for gestational age compared with girls with a birthweight between the 25th and 75th percentiles (9.9 vs 10.4 years, respectively).[78] However, neither study reported a test of statistical significance for this difference. A UK study of 69 girls with very low birthweight (defined as <1251g or <1501g and gestation<31 weeks) did not observe a difference in the number of girls with TS≥2 or median TS in adolescence compared with 81 normal birthweight controls, though the low birthweight girls in this study were all preterm.[128] In full-term girls in ALSPAC, neither birthweight measured continuously nor small for gestational age (SGA), defined as birthweight<10th percentile of gestational age, were significantly associated with age at breast development, though the point estimate for SGA was in the direction of earlier breast development (Diff= -0.23, 95% CI= -0.55, 0.09). Two studies in the U.S., a crude model in the BCERP pubertal cohort and a model adjusted for childhood body size in NHANES, did not observe an association between birthweight<2500g and age at breast development.[80,126] The only study that observed an inverse linear association between birthweight and breast development (earlier age in term girls of higher birthweight) presented results that were adjusted for weight gain in infancy and childhood.[75]

Later stages of breast development

In the eight studies that examined later stages of breast development, four were null,[79,107,120,130] two observed more advanced breast TS for age in smaller girls,[121,122] one observed more advanced breast TS at 14 years of age in higher birthweight girls,[129] and one observed a U-shape association between birthweight and breast TS.[80] Two studies of 35 and 29 girls, respectively, in the Netherlands observed a trend of lower chronological age adjusted for mean pubertal age in girls with lower birthweight, suggesting

a more advanced breast TS at a given age.[122,131] Given the small sample size in these studies, the associations observed could be due to chance. Two additional small studies of extremely low birthweight infants also did not observe a difference in the proportion of girls at higher TS compared with normal weight infants.[120,130] In a study of 130 Cuban adolescents that weighed at least 1500g at birth, a positive correlation was observed between birthweight and breast TS at 14 years of age, suggesting earlier maturation in higher birthweight girls.[129] A study of 956 girls age 8-11 years using NHANES, which did not observe an association with birthweight when comparing breast TS2 with TS1, observed a U-shape association between birthweight and being in TS3-5 compared with TS1. Compared with the referent group of 3000-3499g, girls with a birthweight of 2500-2999g were more likely to be in TS3-5 (OR=3.28, 95% CI=0.99, 7.32), as were girls with a birthweight ≥4000g (OR=3.18, 95% CI 1.39-8.25), in models adjusted for age, race/ethnicity, and childhood height and BMI. The U-shape suggests that postnatal growth patterns may modify the association between birthweight and breast development. In the ALSPAC cohort, the probability of being in a higher breast TS did not differ between girls with a birthweight <2500g, 2500-3999g or ≥4000g in models with and without adjustment for childhood BMI.[107] Birthweight, assessed continuously, was also not associated with breast TS in the Vulnerable Windows Cohort Study.[79]

Pubertal tempo

Two studies examined whether pubertal tempo differed in girls born SGA or with very low birthweight compared with appropriate for gestational age (AGA) or normal birthweight girls. There was no difference in the time interval between breast development and menarche in 116 girls born <2000g in New Delhi compared with 100 full-term girls with birthweight ≥2500g.[127] However, a study of 16 SGA and 25 AGA girls in Chile observed slightly faster progression through breast TS during two years of follow-up in the girls born SGA.[125]

Birthlength

Three studies examined the association between birthlength and the timing of breast development.[73,79,124] Birthlength was either measured at birth by study personnel or abstracted from medical records and assessed continuously in each study. Birthlength was not associated with timing of breast

development in any of the studies, with the outcome defined as breast TS at 11 years of age,[79] age at transition to breast TS 2 or 3,[73] or breast development between 8 and 9 years of age compared with greater than 9 years.[124]

Summary

Overall, there was no consistent pattern between birthweight and the timing of breast development. The studies that observed earlier breast development in low birthweight girls could be due to chance, given the small size of these studies (<150 girls).[78,127] However, these studies also compared girls that weighed either <2000g at birth or had a birthweight below the 3rd percentile for gestational age, representing the extreme low of the distribution, compared with normal birthweight or AGA girls. It may be that girls that are extremely low birthweight and/or preterm experience earlier breast development. However, studies with increased statistical power to study intrauterine growth restriction are needed to assess whether there is a threshold effect in the tail of the distribution. In general, studies that were not selected for low birthweight do not support an association between birthweight and age at breast development. The few studies that assessed birthlength in addition to birthweight also do not support an association with age at breast development.

2.3.5. Birth size and menarche

Birthweight

Seventy-three articles examined the association between birthweight and age at menarche, though several studies resulted in multiple included publications (i.e. three papers used the ALSPAC cohort, two papers used NHANES data, etc) (**Supplemental Table 2.4**). The majority of the studies assessing the association between birthweight and age at menarche were conducted in prospective cohorts (N=49), but we also identified 17 cross-sectional studies, 2 retrospective cohorts, 1 nested case-control study and 3 twin studies. Birthweight was measured prospectively or abstracted from records in 62% of studies, while the remainder relied predominately on parent recall. The majority of studies used self-reports of age at menarche from adolescent girls, while 14 studies used recalled age at menarche from adult participants. Overall, the results of these studies were not consistent. More than 50% of studies did not observe a

statistically significant association between birthweight and age at menarche. Of the studies that did observe an association, most observed earlier age at menarche in girls with lower birthweight, but a few observed an association in the opposite direction. Given the heterogeneity of this literature, particularly in terms of birthweight measures and analytical approaches used, I will briefly review studies presenting descriptive or crude analyses only and focus more on studies that presented multivariable-adjusted estimates of the effect of birthweight on age at menarche, particularly studies that reported results with and without adjustment for postnatal size or growth.

Descriptive statistics

In the twenty-five studies that presented descriptive statistics only (predominantly mean age at menarche by birthweight category), fifteen did not observe a significant association between birthweight and age at menarche.[112,115,128,132–143] Seven studies observed an earlier age at menarche in girls with lower birthweight,[35,78,118,120,144–146] though five of these studies did not present a test of statistical significance for the observed difference. The lowest mean birthweight was observed in girls with menarche before 12 years of age in a subset of women born in 1947 in the Thousand Families in Newcastle upon Tyne study.[144] Similar patterns were also observed in the ALSPAC cohort and the National Longitudinal Study of Youth Children and Young Adult survey of girls born in the late 1980s and 1990s.[35,118] Studies in Canada, the U.S. and Italy observed an earlier mean age at menarche in low birthweight or SGA girls compared with normal birthweight or AGA girls;[78,120,145] the observed differences were approximately 6 months or less. A study in monozygotic twins who suffered from twin-to-twin transfusion syndrome (TTTS) in utero, leading to large birthweight differences in co-twins, found that the twin with lower birthweight experienced menarche at an earlier age than her co-twin in 77% of pairs (10/13), with almost a year difference in median age between the lower and higher birthweight twin.[146] Although twin studies control for genetics and shared environment by design, twins exposed to TTTS are not representative of the general population. Three studies reported a later age at menarche in girls with lower birthweight. In a small Danish study, average age at menarche was 6 months later in 34 girls with birthweight <2000g compared with 31 girls born full-term with a birthweight between 3000-4000g.[147] In a follow-up study of 39 very low birthweight (<1000g), 42 low birthweight (1000-1499g) and 16 normal birthweight (≥2499g) infants in Australia at 14 years of age,

Ford *et al* observed that 15% of girls born<1000g were still pre-menarcheal at 14 years of age, compared with 6% of normal birthweight girls.[130] However, a p-value was not provided for this difference and all low birthweight girls were post-menarche, so the difference is likely due to chance.[130] A cross-sectional study of Greek adolescents reported a significant association between birthweight and age at menarche, with a later age at menarche in girls with a birthweight below 2500g;[148] however, this was limited to one of two regions, neither of which had a consistent pattern. Six studies reported no association between birthweight and age at menarche in the text only (data not shown).[123,149–153]

Unadjusted or age-adjusted models only

Nine studies presented crude or age-adjusted analyses only examining birthweight and menarche; of these, six were null,[79,114,154–158] two observed an earlier age at menarche in lower birthweight girls,[127,159] and one observed a later age at menarche in lower birthweight girls.[160] Bhargava *et al* found that the median age at menarche was earlier in Indian girls with a birthweight <2000g compared with girls with a birthweight ≥2500g; the difference was 6 months earlier in girls <2000g born pre-term and 12 months earlier in girls born full-term.[127] Median age at menarche was approximately 8 months earlier in girls in the lowest tertile of birthweight (<3200g) compared with the highest tertile (≥3700g) in a Norwegian cohort. In contrast, girls born at <2500g had later age at menarche than girls with a birthweight ≥2500g in a cross-sectional study in Poland.[160] In this same study, there was not a significant difference in age at menarche when size for gestational age (SGA, AGA and large for gestational age (LGA)) were examined instead of birthweight. Among the null studies, three did not observe a significant correlation between birthweight and age at menarche,[79,156,158] and two observed no difference in mean birthweight between pre-menarcheal and menarcheal girls, controlling for age.[155,157] There was also no association between continuous birthweight and odds of menarche by age 11 years in the ALSPAC cohort.[114]

Multivariable models without adjustment for postnatal size

Twelve studies examined the association between birthweight and age at menarche in study populations born in the 1950s through 2000s using multivariable models that did not adjust for postnatal body size. Six studies observed earlier age at menarche in girls with lower birthweight[70,71,161–164] and six did

not observe a significant association.[73,74,125,165–167] No studies observed a later age at menarche in low birthweight girls in confounder-adjusted models. Studies that did not observe an association between continuous measures of birthweight and menarche include analyses in larger cohorts such as ALSPAC in the U.K.[73] and the Young Lives cohort in India, Peru and Vietnam,[167] along with analyses of several hundred girls in NHANES[74] and Kaiser Permanente Hawaii[165] in the U.S. Small studies examining SGA girls in Chile[125] and very low birthweight girls in Finland[166] also did not find significant differences in age at menarche, adjusting for gestational age. In full-term, singleton girls in the Young-HUNT Study in Norway, girls in the highest quintile of birthweight had a later age at menarche than girls in the lowest quintile (p for trend=0.03).[70] This pattern was similar in models adjusting for gestational length, maternal age at menarche and parental height and weight. Birthweight below 2500g was associated with increased odds of menarche before age 11 years, controlling for early-life factors including prematurity, in women in the Sister Study, a cohort of women with a sister affected with breast cancer.[161] The Millennium Cohort Study in the U.K. also found, using a continuous measure of birthweight, that girls with lower birthweight had increased odds of menarche by age 11 years, controlling for income and ethnicity.[164] A small study of 58 South Asian women in central London also found lower birthweight to be associated with earlier age at menarche, adjusting for gestational age and first-generation migrant status.[163] In the Raine cohort in Western Australia, girls with an expected birthweight ratio (EBW), a measure of birthweight adjusted for maternal age, height, parity, sex and gestational age, below the median had a significantly earlier menarche than girls with an EBW above the median.[71] Sorensen *et al* examined the association between birthweight standardized for gestational age and age at menarche using both marginal models to measure population-level effects and paired analyses to measure within-family effects in Danish twins.[162] Interestingly, lower birthweight for gestational age was associated with earlier age at menarche in marginal models, but being the smaller twin was not associated with earlier age at menarche in within-twin comparisons. The within-pair associations were also null when limited to monozygotic twins and twins with a large birthweight difference (>1 or >2 SDS), which differs from the study of 13 twin sets with a large birthweight difference due to TTTS discussed above.[146] The authors suggest, given the differences between the marginal and paired analyses, that the association between low birthweight and early menarche is driven by factors shared by twins, which could be genetic or environmental, and is not by non-shared factors such as intrauterine nutritional factors.[162]

Multivariable models with adjustment for postnatal size

Twenty-four articles examined the association between birthweight and age at menarche while controlling for at least one measure of postnatal size or growth, which may mediate or moderate an association between birthweight and menarche. Fourteen articles observed a significant association between lower birthweight and earlier age at menarche while controlling for later growth,[34,71,72,164,167–176] four reported later age at menarche in girls with lower birthweight,[75–77,177] and six did not observe a significant birthweight association.[116,165,178–181] The studies that observed earlier age at menarche in girls with lower birthweight generally controlled for measures of body size in childhood or adolescence. In a cross-sectional study of Polish adolescents, girls born SGA were 2.5 times more likely to have reached menarche by age 14 years than AGA girls, adjusting for body size at 8 years.[173] The Millennium Cohort Study in the UK also observed increased odds of menarche by age 11 years in girls with lower birthweight, controlling for BMI at 7 years.[164] Birthweight was modestly associated with age at menarche in three studies, one in an Australian cohort,[171] one in the Philippines,[72] and one in a cohort of girls from Vietnam, Peru and India,[167] using Cox proportional hazard models, which controlled for BMI at age 8-9 years, BMI at 8 years and change in BMI and height Z-scores from 1-8 years, respectively.

In studies that used linear regression models to examine associations between continuous measures of birthweight and age at menarche, a one kilogram increase in birthweight was associated with a delay in age at menarche of 2-6 months, controlling for body size in childhood or adolescence.[168,170,174,176] The pattern was similar in studies that assessed birthweight in categories. In the DONALD study in Germany, girls with a birthweight between 2500-3000g experienced menarche 8 months earlier than girls with a birthweight >3000g after controlling for pre-pubertal BMI. In French women in the E3N cohort, girls with a birthweight >4000g had menarche 1.5 months later, on average, than girls with a birthweight <2500g, controlling for body silhouette at menarche, physical activity in adolescence and many early-life confounders.[169] Several studies also suggested that the earliest age at menarche occurred in girls who were light at birth, but heavier than their peers by childhood.[71,176] However, in the Newcastle Thousand Families study, girls who were youngest at menarche were born heavy for their gestational age and were

heavy at age 9 years, and the group with the latest age at menarche were also heavy for their gestational age and were light for their age at 9 years.[177]

However, six studies controlling for later growth did not observe a significant association between birthweight and menarche, though the point estimates were consistent with earlier menarche in lower birthweight girls in four of these studies.[165,178–180] In NHANES, point estimates suggested that both girls with birthweight <2500g and those with birthweight >4000g had earlier age at menarche than girls with normal birthweight (β=-0.24, 95% CI=-0.60, 0.12 and β=-0.32, 95% CI=-0.68, 0.03 for low and high birthweight, respectively) controlling for BMI-for-age percentile at age 8-15 years. Higher birthweight was also associated with earlier age at menarche in the New York site of the CPP controlling for changes in height and weight from birth to 7 years, though this association was limited to girls with a BMI below the median at age 7 years.[116] Higher birthweight was associated with earlier age at menarche in the North Carolina Infant Feeding Study as well, but only after controlling for changes in BMI Z-score from birth to 5 years of age.[75]

Studies that reported contradictory findings depending on the adjustment factors are particularly useful in understanding heterogeneity in the literature. For example, Cooper *et al* found a positive relationship between birthweight and age at menarche using adolescent follow-up data from the 1946 British Birth Cohort. Adjusting for height and weight at age 7 years, the girls with the lowest birthweight who became heavy by 7 years had the earliest age at menarche.[172] In another analysis of the same cohort, followed up to age 48 years, dos Santos Silva *et al* did not observe a significant crude association between birthweight and age at menarche, though the point estimate was consistent with earlier age in girls with lower birthweight (HR=0.96, 95% CI 0.87, 1.05).[76] After controlling for height growth in infancy, the association between birthweight and menarche reversed direction (HR=1.17, 95% CI=1.06, 1.36), leading the authors to conclude that menarche occurred earlier in girls with a higher birthweight for a given rate of postnatal growth. Similarly, birthweight was not associated with age at menarche in crude models in an adult follow-up of women born in the 1960s in the CHDS and CPP.[77] After controlling for postnatal changes in percentile rank change in weight from birth-4 years, birthweight was positively associated with age at menarche (HR=1.78, 95% CI 1.11, 2.85). However, when the authors controlled for conditional measures

of postnatal weight gain, which are not correlated with birthweight, the birthweight association was again null (see **Table 2.2** for an overview of different methods for modeling infant growth). Overall, the lack of consistency in the association between birthweight and menarche suggests that the association could actually be driven by postnatal growth patterns. Disentangling pre- and postnatal growth effects are challenging since they are naturally correlated, though the degree of statistical correlation depends on how these exposures are measured and modeled.

Birthlength

While more than 70 studies examined the association between birthweight and age at menarche, only 17 of these studies also assessed birthlength. Of these, 11 reported no association,[35,70,73,77,79,116,140,154,158,162,178] 3 observed earlier age at menarche in girls who were shorter at birth[108,159,170], and 3 observed later age at menarche in girls who were shorter at birth.[72,169,175] In birth cohorts from Switzerland,[158] New Zealand[140] and the U.K.,[35] mean birthlength did not differ by age at menarche. There was no correlation between birthlength and menarche in a Jamaican birth cohort[79] or in a Danish twin study.[162] Quintiles of birthlength were not associated with age at menarche in a Norwegian birth cohort.[70] Continuous measures of birthlength were also not associated with age at menarche in confounder-adjusted models in the ALSPAC cohort[73] or in models adjusted for birthweight and measures of postnatal growth in height and weight in analyses in adult follow-ups of two U.S. birth cohorts.[77,116] Age at menarche was not significantly different in girls born short or tall for gestational age, adjusted for maternal factors and postnatal growth in a Swedish study.[178] This was consistent with a study in Bangladesh which assessed relative size as an exposure and did not find a significant difference in babies classified as small compared with those born normal or tall.[154]

Birthlength was positively associated with age at menarche in a cross-sectional Belgian study when unadjusted for confounders.[108] A positive association was also observed in a Norwegian cohort of girls born in the 1980s, where the median age at menarche was 13.33 years for girls with a birthlength ≥51cm and 12.50 years for girls with a birthlength <49cm.[159] Although the medians were unadjusted, the authors noted that adjustment for potential confounders did not substantially affect the results. In European adolescents, birthlength was also positively associated with age at menarche, but only after controlling for BMI Z-score

in adolescence.[170] In contrast, three studies observed negative associations between birthlength and age at menarche in models that also controlled for birthweight. In the E3N cohort of more than 96,000 French women, girls with a birthlength >51cm experienced menarche 1.8 months earlier than girls with a birthlength <48cm, controlling for birthweight and other pre- and postnatal exposures.[169] Higher birthlength was also associated with earlier age at menarche, adjusting for birthweight, gestational age and maternal characteristics, in a birth cohort in the Philippines (HR per 1 cm increase=1.08, p<0.01).[72] However, there was an interaction between birthweight and birthlength, both dichotomized at the median. Compared to girls who were short and heavy at birth, the earliest age at menarche was observed in girls who were long and light (adjusted HR=1.54). A similar pattern was observed in an Australian cohort. Although neither weight nor length at birth were individually correlated with age at menarche, girls who were long and light experienced menarche one year earlier, on average, than girls who were short and heavy, adjusted for BMI Z-score in childhood.[175]

Summary

Overall, neither birthweight nor birthlength were consistently associated with age at menarche. Comparisons across studies is limited by differences in exposure assessment, including whether or not size at birth is adjusted for gestational age, and differences in adjustment factors and analytic techniques. Although there was heterogeneity in birthweight findings across each analytic group considered (descriptive statistics only, unadjusted associations, and multivariable associations with and without adjustment for postnatal growth), the majority of studies that controlled for measures of body size in childhood or adolescence observed associations between lower birthweight and earlier age at menarche. This suggests that growth patterns between these two time periods may contribute to the observed association, but studies that controlled for infant or early childhood growth patterns did not observe a consistent birthweight finding. Studies that examine the interaction between birthweight and postnatal growth patterns can determine whether different trajectories of growth in early life are associated with differences in age at menarche.

2.3.6. Size and growth during infancy and breast development

Eight prospective cohort studies examined the association between measures of either size or growth between birth and 2 years of age and the timing of breast development (**Supplemental Table 2.5**).[73,75,79,92,182–185] All studies assessed the exposure using prospectively collected anthropometric measures, either by trained study personnel or via a link to medical records. Four studies examined the age at breast development as the outcome,[73,75,92,184] while the other 4 studies examined breast TS at a specific age or study visit.[79,182,185,186] One study examined the tempo of breast development in addition to age at onset.[184] Breast TS was assessed by a physician or trained staff in most studies, while two used parent- and/or self-reports of breast TS.[73,75] Given the heterogeneity in exposure assessment, we will briefly summarize the results of each study.

Measures of size (weight, BMI or height) at specific time points

Four studies examined the association between measures of size (height, weight or BMI) at specific time points during infancy and timing of breast development. BMI at 1 year of age was positively correlated with breast TS (r=0.43) in high school students in Cuba, all of whom had a birthweight ≥2500g at birth and were TS 3, 4, or 5 at the study visit, suggesting that girls with a larger body size at 1 year reached advanced TS at an earlier age than girls who were smaller in infancy.[182] Using a mixed measures model of repeated measures of Z-scores in weight, height, or BMI from birth to 5 years of age in Turkish girls, Aydin *et al* observed that girls with breast development at age 6-9 years of age had a higher weight and BMI Z-score than girls without breast development starting at 9 months, but this difference was only statistically significant at 18 months of age and at the study visit. In contrast, height Z-score was only significantly different in girls with and without breast development at the study visit.[185] In a U.S. cohort, German *et al* observed inverse correlations between height and BMI Z-scores and age at breast development at 15 months of age, but the correlation for BMI Z-score did not reach statistical significance until 36 months of age.[184] This study also examined the progression of breast development, and did not observe an association with either height or BMI at any age. One study in Senegal compared breast TS in adolescence by stunting status in infancy, with stunting defined as at least one length measure <2 Z-scores based on World Health Organization (WHO) reference data between 6-18 months of age. This study did not observe a significant difference in the distribution of breast TS by stunting status,[183] though the growth patterns and

pubertal timing are likely different in this Sengalese population than in the other study populations examined, which were less likely to be malnourished.

Measures of growth (Change in weight, height or BMI)

Four studies examined the association between measures of growth (change in height, weight or BMI between two time points) in multiple time windows and the timing of breast development. In Jamaican girls, Boyne *et al* looked at the correlations between growth in height, weight and BMI from 0-6 months and 6 months-2 years and breast TS at 11 years of age. For each exposure, growth was defined as the amount that the size at the end of the time interval exceeded the size that would have been predicted by linear regression using the size at the beginning of the interval. The correlation coefficient was positive, suggesting earlier maturation, for weight, BMI and height gain and breast TS in each interval (range 0.02-0.15), but none of these correlations were statistically significant.[79] Maisonet *et al* examined the association between growth in weight and BMI, defined by changes in weight or BMI Z-scores, from 0-2 months, 2-9 months and 9-20 months in the ALSPAC cohort. Although the point estimates differed slightly depending on whether the analysis also controlled for birthweight and growth in other time periods or whether the outcome was breast TS $\geq$2 or TS $\geq$3, the inference was consistent with earlier age at breast development in girls with faster gain in weight or BMI in infancy.[73] These results were consistent with those in the North Carolina Infant Feeding Study, which found that faster weight gain from 0-6 months, 6-12 months and 1-2 years was also associated with earlier age at breast development,[75] and the Turkish cohort, which found that girls with breast development at ages 6-9 years of age were more likely to have experienced rapid weight gain from 6-15 months of age than girls without breast development.[185]

In the “Children of 1997” birth cohort in Hong Kong, the authors used latent class analyses to classify girls into 5 growth trajectories based on their birthweight and weight gain in the first year of life. Compared with girls with an average birthweight and stable weight gain in the first year, girls with below average birthweight and slow infant weight gain had later age at breast development (Time ratio (TR)=1.02, 95% CI=1.01, 1.03). The association was attenuated after adjusting for BMI in childhood and reversed direction with additional adjustment for height in childhood (TR=0.98, 95% CI=0.97, 0.99), which the authors attribute to the tendency of girls in this trajectory to be shorter and thinner throughout childhood.[92] While

this article supports an overall association between infant growth and breast development, the association from the mediator model is difficult to interpret. If there is interaction between infant growth and BMI or height in childhood, then the controlled direct effect differs depending on the level of the mediator.[187] In the case of infant growth and childhood BMI or height, the association between slow weight gain and age at breast development may differ for girls that catch up in height or BMI after infancy compared with those that remain shorter and thinner, and studies should examine this potential interaction.

Summary

Overall, these studies support that the rate of growth in weight or BMI during infancy is associated with the timing of breast development. Girls with rapid gain in weight or BMI at any point during the first two years of life experience earlier breast development than girls with stable or slow growth. These findings are also consistent with the studies of size, which suggest that girls with a higher BMI by late infancy mature earlier than girls with a lower BMI, and suggest a similar association with height in infancy. In comparison with the birthweight literature, rapid weight gain during infancy is a more consistent predictor of earlier breast development than small size at birth.

2.3.7. Size and growth during infancy and menarche

Eighteen studies examined the association between measures of size or growth during infancy and age at menarche (**Supplemental Table 2.6**);[34,35,71–73,75–77,79,116,158,167,183,184,188–191] two of these studies were both conducted within the ALSPAC cohort.[35,73] Fourteen of these studies collected age at menarche information in adolescence, while three used self-reports of age at menarche from adult participants and a one study used a mixture of reports in adolescence and in adulthood. The majority of studies looked at measures of both height and either weight or BMI in infancy. Six studies reported measures of size only, while 12 studies looked at measures of growth, sometimes in addition to size. Generally, most studies examined size measures using descriptive statistics, while growth measures were examined more often using multivariable-adjusted models.

Weight or BMI at specific time points

Twelve studies compared measures of weight or BMI during infancy in relation to age at menarche. BMI at 1-2 years of age and BMI Z-score at 15 months were not significantly correlated with age at menarche in two studies, respectively; however, the correlation coefficients were both inverse and similar to each other in magnitude.[184,188] In the Young Lives cohort, menarcheal girls had a significantly higher average BMI Z-score at 1 year of age than pre-menarcheal girls.[167] However, several other studies did not observe an association between BMI at 1 year[71,158] or 2 years[76,189] and age at menarche.

Studies that looked at multiple measures of weight in infancy tell a more consistent story. In the ALSPAC cohort, there was no difference in weight by age at menarche at 2 months of age, but by 9 months of age girls with menarche before age 12 had significantly higher weight, and this difference was even larger for weight at 19 months (similar results were also observed for BMI).[35] A similar pattern was observed in the North Carolina Feeding study and the Birth to Twenty cohort in South Africa, where differences in weight-for-age by age at menarche began to emerge by 1 year of age,[75,191] though in the South African cohort these trajectories converged again by 4 years of age.[191] Higher weight-for-age Z score (and weight-for-height Z-score) at 19.4 months was also associated with an increased risk of menarche before 12 years of age in the Pelotas birth cohort, adjusting for early-life confounders.[190] Finally, two studies examined the mean weight at 4 months and 12 months of age by menarche status at 12 years of age. In the New York site of CPP, there was no significant difference in weight at either age by age at menarche.[116] In an analysis of the New England CPP and the CHDS studies, girls with menarche before age 12 had a higher mean weight at both time points, but a test of statistical significance was not provided.[77] These studies are not consistent in identifying specific time points when higher weight is associated with age at menarche, but they suggest that girls with higher weight or BMI by late infancy may have an earlier age at menarche.

Growth (change in weight or BMI)

Twelve studies assessed the association between weight or BMI gain during infancy and age at menarche.[34,35,72,73,75–77,79,116,158,190,191] Ten of the twelve studies observed that faster growth in weight or BMI during at least one time period in infancy was associated with earlier age at menarche in girls. Fast growth from birth to 1 year, defined as a weight or length increment above the sample median, was associated with earlier age at menarche in the Cebu birth cohort in the Philippines in multivariable-adjusted models.[72]

Although the earliest age at menarche was observed in girls who were long and light at birth and experienced fast growth in infancy, girls with fast growth had an earlier age at menarche than girls with slow growth within each birth size category. The exception was girls who were short and heavy at birth - the group with the latest age at menarche overall. In the Birth to Twenty cohort, girls with rapid weight gain from birth to 1 year, defined as gain in weight Z-score >0.67, also had an earlier age at menarche compared with girls with slow growth, defined as a change in weight Z-score <-0.67 (12.5 vs. 13.1 years, respectively), which persisted after adjustment for early-life confounders.[191] Three studies that assessed growth from between birth and 2 years had similar inference. Girls in the highest tertile of BMI change from 0-2 years had an earlier age at menarche compared with girls in the lowest tertile in the 1946 British birth cohort, controlling for birthweight, infant and childhood growth in height and BMI rate in childhood; there was no evidence of effect modification by birthweight.[76] Rapid weight gain from 0-2 years, defined as >0.67 change in weight Z-score, was associated with earlier age at menarche compared with a change of ≤0.67 in girls from the DONALD cohort.[34] In this study, there was a significant interaction with birthweight, and girls with a birthweight between 2500-3000g who also experienced rapid infant weight gain experienced the earliest age at menarche. Rapid weight gain from 0-19.4 months was also associated with earlier age at menarche in the Pelotas Birth cohort; while the association was observed across birthweight tertiles, the risk of early menarche was highest in girls who were small at birth and experienced rapid weight gain in infancy.[190]

For studies that examined multiple windows of growth between birth and 2 years, associations were generally inverse, with some differences depending on the window of exposure. In an analysis of the ALSPAC cohort which examined age at menarche (<12, 12-13, and >13 years) as a continuous outcome, rate of weight gain from 0-2 months and 2-9 months were significantly associated with earlier menarche, controlling for maternal smoking during pregnancy, birth order and infant feeding, but not weight gain from 9-19 months.[35] In another analysis of a smaller subset of the ALSPAC cohort using survival methods, faster weight gain from 0-2 months, 2-9 months and 9-20 months, assessed using change in weight Z-score, were inversely associated with age at menarche, though the statistical significance of each time period differed slightly depending on the other growth measures in the model.[73] For example, the weight gain from 9-20 months was not a significant predictor of age at menarche until weight gain from 0-2 months and 2-9 months was also included in the model, which suggests that weight gain in late infancy was associated with

menarche only after conditioning for the weight gain trajectory up until that point. In contrast, the negative coefficient for weight gain from 0-2 months was not statically significant (p=0.15) after controlling for birthweight and birthlength though the precision of this estimate could be affected by the moderate correlation between weight gain from 0-2 months and birthweight (r=-0.41). The inference was similar, though the point estimates were lower in magnitude, in model examining the change in BMI Z-score instead of weight.

In the North Carolina Feeding Study, faster weight gain from 0-6 months, 6-12 months and 1-2 years were all associated with earlier age at menarche in models that included birth weight, weight gain in all three time periods, weight gain from 2-5 years, maternal pre-pregnancy weight and race.[75] This was consistent with the findings from two 1960s U.S. birth cohorts (CHDS and two sites of the CPP), which found that rapid weight gain, defined as the within-cohort percentile rank change, from 0-4 months and 4-12 months were associated with earlier age at menarche in the overall cohort and within sibling subsets,[77] which controls for many early-life confounders by design.[192] These results were consistent after adjusting for height gain in these same time periods. The results were also generally consistent when conditional growth methods were used instead of percentile rank change (see **Table 2.2** for a comparison of different methods for assessing infant growth, informed by [193–196]). Infants who grow rapidly in one time period are less likely to experience rapid growth in the adjacent time period, often referred to as the regression-to-the-mean effect.[193] The results from the conditional growth methods, which remove the correlation between the growth measures at different time points, were generally closer to the null than the effect estimates from the percentile rank change models. An analysis of the New York site of the CPP also found that girls with faster weight gain from 4-12 months had an earlier age at menarche, but not weight gain from 0-4 months.[116] The two studies that did not detect a significant infant weight gain association both had small sample sizes. In 96 Swiss girls, change in BMI Z-score from birth to 1 year of age was not associated with age at menarche in an unadjusted linear regression model.[158] There was also no association between gains in weight or BMI from 0-6 months and 6 months-2 years in 140 Jamaican girls – correlation coefficients were inverse, but not statistically significant.[79]

Measures of height

Thirteen studies provided some data on height between birth and 2 years and age at menarche, though many of the results shown were descriptive. Height at 1 year was not correlated with age at menarche in the Raine birth cohort.[71] Height at 1-2 years, however, was inversely correlated with age at menarche ($r=-0.35$, $p<0.05$) in data from women born in the 1930s and 1940s from the Harvard Longitudinal Studies of Child Health and Development.[188] The correlation coefficient between height at 15 months and age at menarche was also inverse in a study of U.S. girls born in 1990, but the correlation was not statistically significant until 54 months of age.[184] This was consistent with U.S. data from the Children of the National Longitudinal Study of Youth, which found statistically significant height differences by age at menarche starting at age 5 years, though the pattern was observed earlier.[189] In the Pelotas Birth cohort in Brazil, girls with menarche before 12 years had higher height-for-age Z-scores at 19.4 months than girls who experienced menarche at age 12 years or later, adjusting for maternal confounders (p for trend=0.01).[190] Higher height-for-age Z-scores at 1 year and 1-2 years were also observed in girls with earlier menarche in study populations in India, Peru and Vietnam[167] and South Africa,[191] respectively. In the ALSPAC cohort, height at 2 months did not differ by age at menarche. By 9 months, however, girls with menarche before 12 years were taller, on average, though the difference in height was not statistically significant until 19 months of age.[35] In the remaining studies that presented mean height by age at menarche, there was no association in two studies,[116,158] while an additional two studies suggested that girls with earlier menarche had taller mean height at 1 or 2 years of age without providing statistical tests of this difference.[76,77] Stunting was not associated with menarche status in a Sengalese cohort.[183] Overall, these studies suggest that girls who are taller by late infancy are more likely to experience menarche at an earlier age, though none of these studies controlled for weight.

Measures of height growth

Six studies examined the association between rate of height gain in infancy and age at menarche. In a Swiss cohort, mean height gain between birth and 1 year was similar in girls with early vs late menarche.[158] Using conditional measures to assess changes in height, neither height gain from 0-6 months nor 6 months-2 years were associated with menarche at age 11 years in the Vulnerable Windows Cohort Study in Jamaica.[79] In contrast, 3 studies did observe significant associations between height gain in infancy

and age at menarche. In the ALSPAC cohort, height gain from 2-9 months and 9-19 months, but not 0-2 months, was associated with earlier age at menarche; however, the associations were no longer statistically significant after adjustment for infancy weight gain.[35] A similar pattern was observed in an adult follow-up of the CHDS and CPP cohorts. Height gain from 0-4 months and 4-12 months were associated with earlier age at menarche in models that did not control for weight gain during those periods; however, when weight gain measures were also included, the effect estimates for height gain were attenuated.[77] Height gain during these same two periods was also not associated with age at menarche in the New York site of the CPP in models controlling for weight gain.[116] In the 1946 British Birth Cohort, girls in the highest tertile of height gain from 0-2 years had an earlier age at menarche compared with girls in the lowest tertile in models that did not adjust for changes in BMI.[76] This association was attenuated in models that adjusted for rate of height growth in childhood, and was null in models that additionally adjusted for gains in BMI in infancy and childhood. Together, these studies suggest that rates of weight gain may drive associations between rapid height gain and earlier age at menarche.

Summary

Similar to the studies of breast development, studies of infant growth and age at menarche consistently observed earlier age at menarche in girls with rapid gain in weight or BMI during the first two years of life. Studies of size found that higher weight or BMI by late infancy was also associated with earlier age at menarche, which again points to the importance of postnatal weight gain trajectories and their role in pubertal timing. Although fewer studies have examined infant weight gain compared with the birthweight literature, the consistency of these studies suggests that differences in postnatal growth could contribute to the heterogeneity in the birthweight literature. There is not clear evidence for a role of height gain during infancy and age at menarche, and more studies should consider weight, height and weight-for-height measures to determine whether these growth measures have independent effects on age at menarche.

2.3.8. Study quality

The quality assessment of the included studies is presented in **Supplemental Table 2.7** (NIH Quality Assessment Tool for Observational and Cohort Studies[105]) and **Supplemental Table 2.8** (NOS for

cohort or case control studies[106]). The NOS considers three domains of quality, Selection (4 possible points), Comparability (2 possible points) and either Outcome Assessment for cohort studies or Exposure Assessment for case-control studies (3 possible points), for a total possible quality score of 9. The scores ranged from 2-9, with a mean value of 5.1. Although the NOS does not provide a categorized assessment of bias based on the continuous scale, previous studies have used cut-offs of 0-3, 4-6 and 7-9 to indicate low, intermediate and high quality. Using this cut-off, the majority of studies (63.5%) were categorized as intermediate quality, and 19.8% and 16.7% of studies were categorized as low and high quality, respectively. Given the nature of the outcomes, particularly menarche, almost all studies relied on self-reports of age at menarche, or parent reports in some cases, which affected the quality scores. Self-reported outcomes may introduce some misclassification bias, which affects the quality score on the assessment scale. However, age at menarche has been shown to be reliably recalled into adulthood.[91] Many studies also lacked control for key early-life confounding variables or controlled inappropriately for variables that may be in the causal pathway as confounders. This is reflected in the comparability scores from the NOS, in that only 13 studies (13.5%) received two points for comparability, meaning that they adequately controlled for confounders and did not inappropriately control for potential mediators. In the birthweight literature, which had the most heterogeneity in terms of study findings, there were no obvious differences in quality scores between studies with conflicting results.

2.4 Discussion

Higher maternal pre-pregnancy BMI is associated with earlier breast development and earlier age at menarche. Although fewer studies examined GWG in relation to breast development and age at menarche, studies using multivariable-adjusted models suggest that breast development and menarche occur earlier in girls whose mothers gained more weight during pregnancy. Rapid weight gain in infancy is also consistently associated with earlier breast development and earlier age at menarche in girls. In contrast, birthweight is not consistently associated with timing of breast development or age at menarche. There were also no consistent patterns relating birthlength or height during infancy to age at breast development or menarche, particularly after controlling for weight. The associations observed between maternal and infant weight gain patterns and earlier age at breast development and menarche suggest that

these exposures may affect the timing of these milestones but not the time interval between them; however, more studies that examine this pubertal tempo directly as an outcome are needed to explore this hypothesis.

Heterogeneity in the birthweight literature may result from the lack of adjustment for confounders (such as maternal BMI and GWG) or adjustment for weight and/or weight gain measures later in the life course. After adjusting for at least one measure of size or growth later in the life course, 14 of 24 studies observed an earlier age at menarche in girls with low birthweight. Differences in the modeling strategies and time period of postnatal measurements across studies could also contribute to the heterogeneity of study findings. Studies that found an association between low birthweight and earlier pubertal development may be driven by infant weight gain patterns, as lower birthweight infants are more likely to experience rapid postnatal weight gain. As was noted in a recent review of prospective studies of birthweight and menarche,[89] differences in exposure assessment, particularly in the assessment of birthweight in relation to gestational age, across studies limits the comparability of study results and makes it difficult to disentangle prenatal size from growth.

In contrast to the birthweight literature, studies consistently observed earlier breast development and earlier age at menarche in daughters of overweight and obese mothers. Maternal pre-pregnancy body size may affect pubertal timing through an indirect pathway, where daughters of overweight or obese mothers are more likely to be overweight themselves, which could be due to shared genetic or lifestyle factors,[197] leading to earlier breast development and menarche. The lack of full mediation by daughters' body size suggests that there may also be a direct effect of maternal body size. A similar pattern was observed with GWG.[82] The developmental origins of health and disease (DOHAD) hypothesis posits that early-life exposures affect health throughout the life course, either through a direct effect on the developing organs during the critical period of fetal development or through a developmental programming mechanism.[198] The breast undergoes multiple periods of rapid development throughout the life course, including in utero, during puberty and pregnancy, post-partum and during menopause.[43,199] The rapidly developing breast is more susceptible to carcinogenic effects from the environment, leading these periods of rapid proliferation to be considered windows of susceptibility in terms of breast cancer risk.[43] The prenatal

period has been identified as a window of susceptibility since the ductal system of the breast develops rapidly in utero,[43,199,200] and exposures that affect this ductal development in utero could alter later breast development and cancer risk.[43,201,202]

Maternal overnutrition could also affect pubertal timing, and thus breast cancer risk indirectly, through a programming mechanism. Women who are overweight or obese during pregnancy have higher levels of hormones that are involved in energy regulation, such as leptin.[203] Exposure to high levels of these hormones in utero may program higher levels of these hormones in their daughters. Higher levels of leptin, an adipokine which plays a role in appetite regulation and may stimulate the hypothalamic-pituitary-gonadal (HPG) axis and allow for pubertal progression,[204] have been observed in girls with premature breast development[205] and has been associated with earlier age at menarche.[206] Maternal obesity is also associated with insulin resistance during pregnancy, which may predispose the offspring to the development of insulin resistance and compensatory hyperinsulemia.[207] Hyperinsulinemia is associated with decreased levels of sex hormone-binding globulin,[87] which in turn increases sex steroid bioavailability and may promote puberty.[208] Finally, maternal obesity may affect daughters' health later in life via an epigenetic mechanism, altering gene expression.[207,209] Patterns of DNA methylation are established in early life and persist into adulthood, and evidence from animal studies suggest that maternal overnutrition can induce epigenetic changes in the offspring.[210]

Studies also consistently observed associations between rapid weight gain during the first two years of life and earlier age at breast development and menarche, although the time period within infancy when rapid weight gain had the strongest association with pubertal timing varied by study. Some studies suggested that the earliest age at menarche occurred in girls who were small at birth and experienced rapid weight gain during infancy, though generally faster weight gain was associated with earlier puberty across the spectrum of birthweight. Although infancy has not been identified as a window of susceptibility for breast cancer,[43] the rapid growth that the breast undergoes in utero may continue in early postnatal life. Infancy is also associated with an activation of the HPG axis, termed "mini-puberty", when breast tissue is present along with increased levels of reproductive hormones.[211,212] In girls, follicle stimulating hormone (FSH) and luteinizing hormone (LH) both increase in early infancy and peak at 1-3 months. LH then decreases by 6-9

months, while elevated FSH levels are present until age 3-4 years. Estradiol levels in girls fluctuate during the first year of life, and then decrease until puberty.[213] While both male and female infants have breast tissue present at birth that regresses during infancy, breast tissue size is larger and persists for a longer time period in female infants.[211] Estradiol levels have been found to be positively associated with breast tissue size in 3-month old female infants, but not in males.[214] Together, this suggests that breast tissue in female infants is stimulated by endogenous hormones, which may affect breast development and later breast cancer risk.[214]

Rapid infant growth could also be associated with pubertal timing via a hormonal or epigenetic pathway, similar to maternal overnutrition in utero. Rapid infant growth is associated with hormonal changes such as increased levels of leptin, IGF-1 and insulin which affects growth throughout childhood and may lead to earlier initiation of puberty.[87] A recent study found that rapid weight gain in the first year of life was associated with increased *Alu* methylation, a measure of global DNA methylation, at age 20.[215] Changes in DNA methylation of imprinted genes are known to be associated with infant growth,[216] and are also associated with genomic instability and chronic disease in adulthood.[217] In addition, early-life environmental stimuli are associated with changes in promoter methylation of non-imprinted genes,[218] which could affect gene expression in insulin-signaling pathways[219] or changes in genes related to body size or pubertal timing.[220,221] Studies that incorporate biomarkers assessed prior to puberty are needed to examine whether these hormonal and epigenetic pathways mediate associations between early-life growth and early puberty. Earlier maternal age at menarche has also been associated with rapid growth in infancy,[222] suggesting that early-life growth and pubertal timing could have a shared genetic origin.

This review of the literature has informed the analytic approaches that we will use to examine the associations between maternal pre-pregnancy BMI, GWG and birth size (**Chapter 3)** and rates of change in weight and length during infancy (**Chapter 4**) of this dissertation. We will use a DAG (**Figure 2.1**) to inform our modeling strategy by considering common causes of the exposure and outcome as confounders and only controlling for mediators when interested in estimating direct, as opposed to total, effects. For example, we will control for maternal pre-pregnancy BMI as a confounder in models examining GWG as the exposure, but will not control for GWG in models examining the total effect of maternal BMI. We will

also use DAGs to prevent collider bias. Collider bias is a well-recognized problem in perinatal epidemiology, and can result when associations between intrauterine factors, such as intrauterine smoke exposure, and postnatal outcomes are adjusted for partial mediators like birthweight or gestational age,[223] as is often done in practice. However, since we will be examining multiple exposures of interest, we will indirectly be able to compare the point estimates from models that include potential mediators to my primary models. For example, since we will control for maternal pre-pregnancy BMI as a confounder in models examining birthweight as an exposure, we can assess how this adjustment influences the association between maternal pre-pregnancy BMI and pubertal timing and how our results compare with previous studies that have presented adjusted analyses.

Similarly, we will employ multiple analytic approaches to model birth size and infant growth, in order to examine how robust findings are to model specification and in order to compare the results from these chapters with previous studies. We will consider birthweight and birthlength with and without adjustment for gestational age as both continuous and categorical variables. We will also conduct sensitivity analyses excluding girls born preterm or low birthweight as the association with pubertal timing may differ in the extremes of the distribution. While our primary analyses will mutually adjust for weight and height measures, we will also examine these exposures independently, in addition to considering weight-for-height as an overall measure of body size as an exposure. Prior to modeling infant growth, we will examine the variability in height and weight at each time point, as well as the correlation between measures at different time points and the correlation with birthweight. Although we will employ progressive modeling techniques as a primary approach, which adjust only for measures earlier in the life course, we will also consider models mutually adjusted for growth in all time periods, as several prior studies have done.

We will also categorize exposures based on relevant guidelines so that the results from these analyses can inform clinical practice. For example, we will consider a joint categorization of maternal pre-pregnancy BMI and GWG based on the 2009 IOM guidelines in order to assess if the categories of inadequate, adequate and excessive GWG are associated with differences in pubertal timing in the daughters. We will also categorize infant weight gain based on crossing growth chart percentiles, a cut-off used clinically to assess catch-up or catch-down growth. Finally, we will examine interactions between

these measures, including maternal pre-pregnancy BMI and GWG, and birthweight and infant growth patterns.

In summary, a growing literature supports that higher maternal pre-pregnancy body size, excess GWG and rapid infant growth are risk factors for early puberty in girls. However, there are still gaps within this literature that future studies can address:

1. Most studies were conducted in developed countries and may not be generalizable to other settings. Studies conducted in low and middle income populations, where the prevalence of early-life growth patterns differs from high-income countries and the prevalence of childhood obesity is lower but increasing,[224,225] may help to clarify the direct role of early-life growth and pubertal timing by reducing the indirect pathway via childhood body size. Pubertal timing also differs by race/ethnicity,[60,62,226] but few studies have examined early-life exposures and pubertal timing in non-white populations.
2. From a methodological perspective, future analyses should be more explicit in how early-life factors are conceptualized in relation to the exposure and outcome of interest and modeled appropriately. For example, analyses of birthweight and infant weight gain should control for maternal confounders such as pre-pregnancy body size and GWG. However, analyses examining these maternal factors as exposures of interest should not control for postnatal factors as confounders in adjusted models. Instead, postnatal factors should be modeled as mediators or modifiers of the association, depending on the hypothesized causal structure (see **Figure 2.1**).
3. Additional studies of birthlength and height gain will help to clarify whether associations between rapid weight gain and pubertal timing are reflective of linear growth, particularly catch-up growth to expected body size based on genetic potential, or adiposity resulting from overnutrition.[227] Separating adiposity from linear growth may also clarify why some studies observed earlier puberty in girls who were small at birth, who are more likely to experience catch-up growth in infancy.[228]

4. Additional studies should examine pubertal tempo directly as an outcome. The recent secular decline in age at breast development suggests that the time period between onset of breast development and menarche is increasing.[42] Since puberty is a period of rapid growth for the breast, a slower pubertal tempo implies that the pubertal window, when the breast is more susceptible to environmental carcinogens, is widening.[43] In addition to examining associations between early-life growth and breast development and menarche independently, it's important to determine whether early-life growth has an effect on pubertal tempo, which also affects breast cancer risk.[41]
5. Studies that examine the full trajectory of early-life growth by modeling maternal body size, GWG, birth size and infant growth can explore whether pre- and postnatal growth have independent effects, or if particularly trajectories of early-life growth have synergistic effects. In addition, studies that examine multiple time points within infancy can help to clarify whether there are specific windows within the first two years of life that are a sensitive or critical period in influencing pubertal timing.[229] Although some studies have examined multiple windows within infancy,[73,75,77,79,116,222] time periods have differed by study, making comparisons difficult.
6. Twin and familial studies estimate that 50-80% of the variation in pubertal timing in girls is heritable (for review, see [42]). However, the rapid decline in age at puberty cannot be explained by genetics alone and supports the importance of environmental influences, which may act independently or interact with genetic susceptibility to influence pubertal timing. Since earlier ages at breast development and menarche are associated with increased breast cancer risk,[41] it is important to determine whether early-life factors that affect pubertal timing are modified by underlying susceptibility for breast cancer. Two studies have found that girls with a family history of breast cancer had an earlier age at breast development[54] and menarche,[165] respectively. If there is no heterogeneity in the associations between early-life growth and pubertal timing by underlying genetic susceptibility, then early-life growth will still have a greater effect on an absolute scale in those with greater underlying risk,[55,56] and girls and women at high risk need to know that the environment matters and that their risk can be modified. If there

is heterogeneity, then identifying the context in which the early-life environment affects risk will allow for targeted prevention to those groups that will benefit most.

2.5 Conclusions

A small but consistent literature suggests that higher maternal pre-pregnancy BMI, greater GWG and rapid postnatal weight gain are associated with earlier age at breast development and menarche in girls. The role of birthweight, however, is still not clear. The pre- and postnatal periods may be an effective period for intervention as pregnant women and new parents are regularly engaged with clinicians who are already monitoring maternal body size and behaviors and infant growth.[69] Empirical evidence from randomized trials show that interventions can successfully reduce gestational weight gain[230,231] and modify infant growth patterns.[232] Modifying weight gain prior to and throughout pregnancy in mothers and through infancy in their daughters may delay pubertal timing and potentially lower breast cancer risk in adulthood.

2.6 Tables and figures

Figure 2.1. Directed acyclic graph (DAG) of hypothesized causal structure linking maternal pre-pregnancy BMI, gestational weight gain, birthweight and infant weight gain to age at breast development

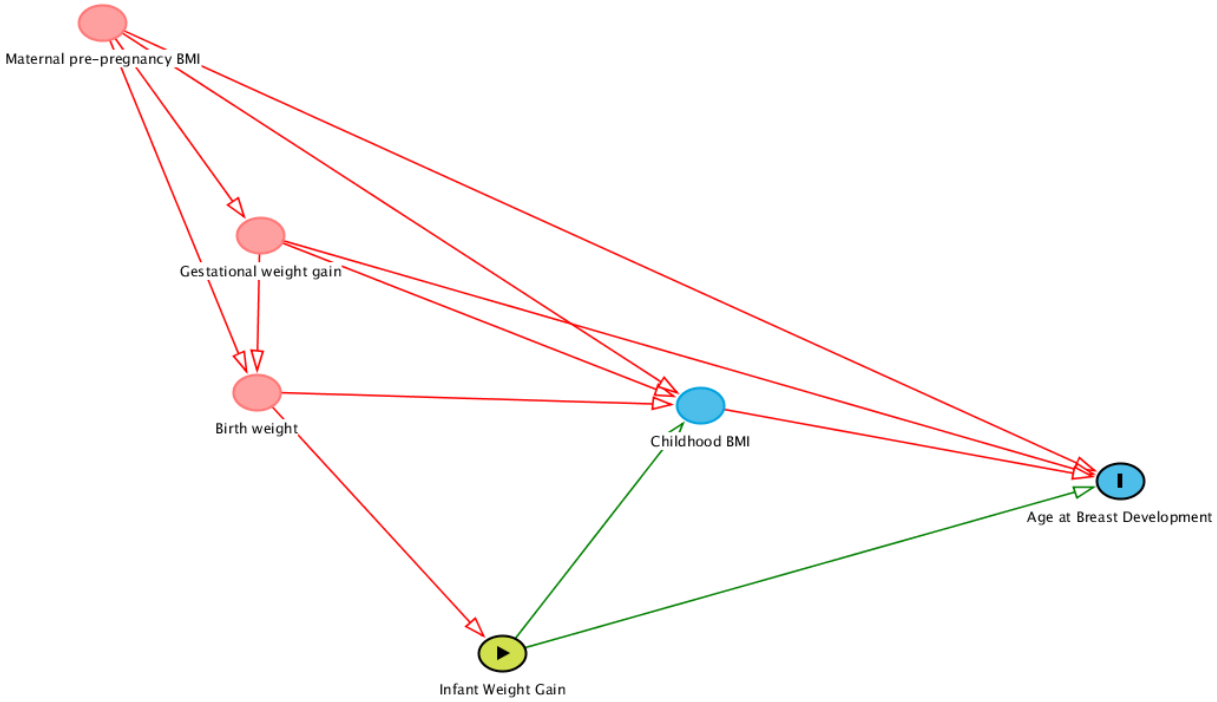
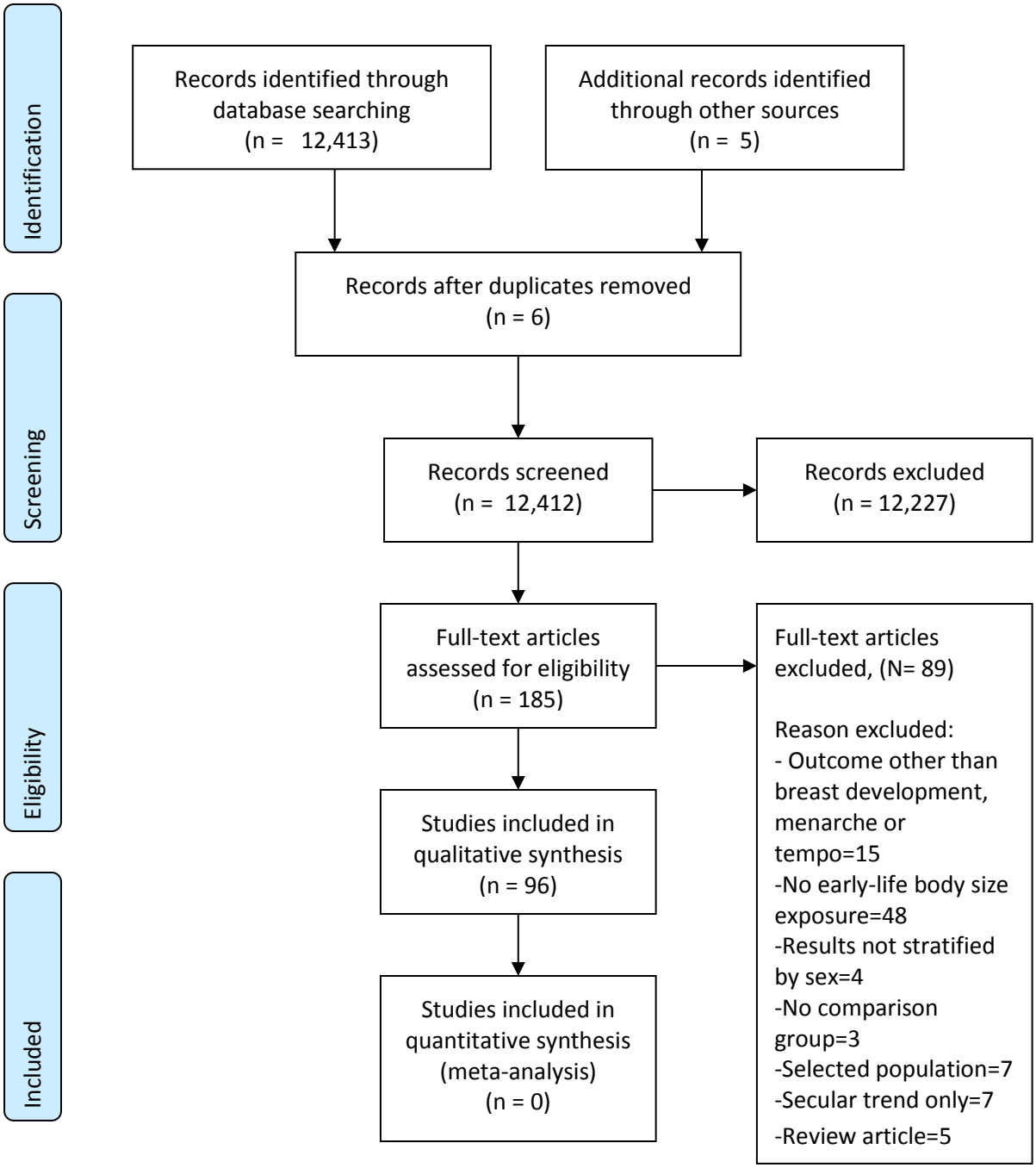


Figure 2.2. Flow diagram of study selection based on PRISMA 2009 guidelines



PRISMA flow diagram and additional information regarding the 2009 guidelines available from [94].

Table 2.1. Number of included studies for each exposure-outcome association (N=96 articles)

	Breast Development				**Menarche**			
	Maternal pre-pregnancy body size[1]	Gestational weight gain	Birth size[2]	Size or growth in infancy[3]	Maternal pre-pregnancy body size[1]	Gestational weight gain	Birth size[2]	Size or growth in infancy[3]
Text only	0	0	2	0	2	2	6	1
Descriptive statistics only	0	0	7*	1	2	2	25	2
Crude models	1	0	4	2	2	1	9	3
Adjusted models	5	1	4	5	8	3	34	12
Total	**6**	**1**	**17**	**8**	**14**	**8**	**74**	**18**

*Includes one study where outcome is tempo of breast development

[1]Body size refers to either maternal pre-pregnancy weight or BMI

[2]Includes studies of weight, length and/or BMI at birth

[3]Includes studies of size (weight, length and/or BMI between birth and 2 years) and/or growth (change in weight, length and/or BMI between birth and 2 years)

Table 2.2. Comparison of methods to assess infant growth

Method	Advantages	Disadvantages
Change in absolute value	Straightforward to implement and interpret	Absolute measures are more highly correlated than transformed values Differences in variability of measures at different time points makes comparisons difficult
Change in Z-score	Easy to interpret Change in Z-score is less correlated than absolute measures	Measures at different time points likely correlated, with stronger correlation the closer in time the measurements are taken
Change in percentile rank	Easy to interpret Clinically relevant (crossing of percentiles) Change in percentile rank is less correlated than absolute measures	Measures at different time points likely correlated, with stronger correlation the closer in time the measurements are taken
Conditional (difference between observed size and predicted based on size at beginning of interval)	Measures at different time points are statistically independent Not influenced by regression-to-the-mean effect – those that start at the extremes of size are more likely to experience larger rates of change	More difficult to interpret
Latent class analysis	Can identify non-linear trajectories Parsimonious way to examine patterns Compare absolute instead of conditional trajectories	Data driven and somewhat subjective in choosing the number of classes Cannot look at different windows within the trajectory

Chapter 3. Maternal pre-pregnancy BMI, gestational weight gain, and birth size in relation to age at breast development in the LEGACY Girls Study cohort

ABSTRACT

Background: Earlier onset of breast development (thelarche) is a known risk factor for breast cancer and may be influenced by maternal pre-pregnancy body mass index (BMI), maternal gestational weight gain (GWG) and infant body size. To date, the epidemiologic evidence is from cohorts of girls that were not enriched for breast cancer family history (BCFH). We investigated whether maternal BMI, GWG and size at birth were associated with age at breast development, and whether these associations varied by BCFH, using a prospective cohort of girls in which approximately half are at an increased risk of breast cancer due to their family history.

Methods: Using longitudinal Weibull models with left, right and interval censoring, we assessed whether maternal pre-pregnancy BMI, maternal physical activity during pregnancy, GWG, and daughters' weight and length at birth, reported by the mother at baseline, were associated with the age at breast development, defined as maternal report of Tanner stage≥2, in LEGACY girls participating with their biological mother (N=1031). We examined modification by BCFH and mediation by daughters' childhood BMI in adjusted models. LEGACY girls were primarily between 6-13 years of age when they entered the cohort, and 43% of girls experienced the onset of breast development prior to cohort entry (left censored). We conducted sensitivity analyses limited to girls age less than 8 years at baseline (n=259) to examine how sensitive results in the overall cohort were to the inclusion of older girls.

Results: Higher maternal pre-pregnancy BMI was associated with earlier breast development in daughters (Hazard ratio (HR)=1.03, 95% CI 1.01-1.05). This association was consistent in the subset of girls with clinical breast Tanner staging available and mediated by daughters' pre-pubertal body size. Higher gestational weight gain was also associated with earlier thelarche. Compared to daughters whose mothers had a pre-pregnancy BMI of <25 kg/m^2 and gained <30 lbs, girls whose mothers had a pre-pregnancy BMI ≥25 kg/m^2 and gained ≥30 lbs experienced the onset of breast development at a 60% faster rate (HR=1.57, 95% CI 1.17-2.12). This association was similar in girls with and without a BCFH, but was only statistically significant in the latter (HR in girls with a BCFH: 1.43, 95% CI 0.89, 2.29; HR in girls without a BCFH: 1.62,

95% CI 1.10, 2.39; RERI=0.13, 95% CI -0.95, 1.21). In the subset of girls <8 years at baseline, daughters were approximately two times more likely to experience earlier thelarche if their mothers had a pre-pregnancy BMI <25 kg/m^2 and gained ≥30 lbs or a pre-pregnancy BMI ≥25 kg/m^2, regardless of their GWG, compared with daughters of women with a BMI <25 kg/m^2 who gained <30 lbs. In younger girls, daughters of women who reported no recreational physical activity during pregnancy experienced earlier breast development than daughters of active women (HR=1.70, 95% CI 1.02, 2.83). This association was independent of maternal pre-pregnancy BMI and was not mediated by GWG or modified by BCFH. Daughters' weight and length at birth were not associated with the timing of thelarche.

Conclusions: Earlier thelarche was associated with three potentially modifiable risk factors – maternal pre-pregnancy BMI, maternal physical activity during pregnancy and GWG - in a cohort of girls enriched for BCFH. These associations were partially mediated by the daughters' pre-pubertal body size. Our results suggest that maintaining a healthy pre-pregnancy BMI, engaging in recreational physical activity during pregnancy, and moderate weight gain during pregnancy (<30lbs) may delay breast development in daughters.

3.1 Background

Breast cancer incidence, particularly advanced disease, is increasing in U.S. women under 40 years of age,[233] pointing to the importance of exposures acting early in the life course to increase breast cancer risk. Earlier age at menarche is a well-established risk factor for breast cancer.[95] Age at menarche has decreased over time, but this decline has stabilized over the last 50 years.[42] In contrast, age at breast development, or thelarche, has continued to decline rapidly.[42] In a recent prospective cohort study of over 100,000 women, earlier thelarche and longer time period between thelarche and menarche (tempo) were independently associated with a 20-30% increased risk of breast cancer.[41] Given the secular trends in pubertal timing, this suggests a future increase in breast cancer incidence.

Modifiable factors that are associated with pubertal timing could be a target for breast cancer primary prevention efforts starting early in life. Since breast cancer risk accumulates over the life course, modifying early-life exposures may have a greater impact in decreasing breast cancer risk later in life

compared with modifying exposures in adulthood.[4,5] Studies have found that higher birthweight is consistently associated with an increased risk of pre-menopausal breast cancer, and may be modestly associated with post-menopausal breast cancer risk as well (for review, see [18,234]), suggesting that factors that influence the intrauterine environment may affect breast cancer risk. Birthweight is a crude indicator of fetal growth and the intrauterine environment in general,[26] and is difficult to modify directly. However, the data connecting other prenatal characteristics to breast cancer risk is limited. Maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) are associated with birthweight[20] and maternal hormone levels during pregnancy,[27–29] but studies have not consistently supported an association with breast cancer risk.[23,24] However, most studies in the literature were from pregnancies over 50 years ago, when the prevalence of obesity and excess GWG was much lower than today.[30]

Maternal obesity and excessive GWG have increased in prevalence in parallel to the secular trends in pubertal timing. Higher maternal pre-pregnancy BMI and increased GWG are both associated with earlier age at menarche.[82,83,115,118] Increased maternal physical activity during pregnancy, which is associated with pre-pregnancy BMI and GWG,[235] was associated with later age at menarche in the Nurses' Health Study II cohort, independent of maternal BMI.[236] Few studies have examined these exposures in relation to age at thelarche, which occurs on average two years before menarche.[90] In the ALSPAC cohort, maternal pre-pregnancy BMI and GWG during pregnancy were both inversely associated with age at thelarche in daughters.[73,82] In studies conducted using electronic health record data from Kaiser Permanente Northern California (KPNC), maternal pre-pregnancy obesity[81] and GWG in excess of the 2009 Institute of Medicine (IOM) guidelines, in addition to inadequate GWG,[237] were all associated with earlier age at breast development in daughters. The associations with excess or inadequate GWG and breast development were stronger if mothers had a BMI≥30 before or at the beginning of pregnancy.[237] A prior study of 421 girls from the Cohort Study of Young Girls' Nutrition, Environment and Transitions (CYGNET), which also used KPNC data, found that girls whose mothers were overweight and had gestational diabetes experienced earlier pubic hair development, but there was no statistically significant association with thelarche in adjusted models.[109] Studies suggest that the association between maternal body size and earlier pubertal timing is partially mediated by daughters' BMI.[81,82,117]

To date, previous studies examining maternal body size, GWG and age at breast development were conducted in cohorts of girls at average-risk of breast cancer. We recently observed within the LEGACY Girls Study, a prospective pubertal cohort enriched for breast cancer family history (BCFH),[57] that non-overweight girls at an increased risk of breast cancer due to their BCFH experience earlier breast development than girls without a BCFH.[54] Since maternal pre-pregnancy BMI, physical activity during pregnancy and GWG are potentially modifiable, we investigated whether these exposures, in addition to size at birth, were associated with age at breast development in LEGACY. As secondary aims, we also examined whether associations were modified by BCFH and mediated by daughters' pre-pubertal body size.

3.2 Methods

3.2.1. Study population

The LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study is a prospective cohort study of 1040 girls recruited at five study sites in the U.S. (New York City, NY; Philadelphia, PA; Salt Lake City, Utah; San Francisco Bay Area, CA) and Canada (Toronto, ON) between 2011 and 2013 (for more details, see [57]). The girls were primarily between the ages of 6 and 13 years at recruitment, and half had a BCFH, defined as a report of breast cancer in a first- or second-degree relative by the participating mother/guardian at baseline. Younger siblings of cohort members can also join when they reach 6 years of age. The participating guardian at baseline was the biological mother for 97% of LEGACY girls.[57] We excluded girls whose participating guardian was not the biological mother from the analyses (N=37) because some exposures, such as maternal pre-pregnancy weight, were collected only from biological mothers, and other pregnancy exposures may be reported with error when completed by others. For this analysis, prospective follow-up data through August 2016 was included for 1031 girls participating with their biological mother, including 589 families with 1 participating daughter, 370 with 2 participating daughters and 24 with 3 participating daughters. Mothers provided written informed consent for themselves and for their daughters, and daughters provided written informed assent according to

institutional standards. The study was approved by the institutional review boards of the collaborating institutions.

3.2.2. Data collection

Maternal and pregnancy exposures. Mothers completed an early-life questionnaire at their daughters' baseline visit that included detailed information about their pregnancy, including pre-pregnancy weight (continuous), GWG (in categories) and physical activity. These questions were developed and used previously in the Nurses' Health Study cohort.[24] We calculated maternal pre-pregnancy BMI from mothers' self-reported height and pre-pregnancy weight. GWG was recorded as <10 lbs, 10-14 lbs, 15-19 lbs, 20-29 lbs, 30-39 lbs, 40-49 lbs, and 50 or more lbs (see **Appendix C.1** for more information about pregnancy exposures, including definitions of each category). Since guidelines for weight gain during pregnancy vary by BMI,[110] we created a categorical variable for GWG based on the 2009 IOM guidelines to categorize GWG as inadequate (below guidelines), adequate (within recommended range) and excessive (above guidelines). We modified the cutpoints used to define adequate GWG for LEGACY since GWG was collected in categories that did not directly correspond to the categories used in the 2009 IOM guidelines (see **Appendix C.2** for the 2009 IOM recommended ranges based on maternal pre-pregnancy BMI and type of gestation and the modified ranges used for this analysis).[110] We also considered maternal pre-pregnancy BMI and GWG jointly by creating a cross-classified variable with maternal pre-pregnancy BMI, using a cut-off of 25kg/m^2, and GWG, using a cut-off of either 30lbs or exceeding vs. not exceeding the guidelines.

Mothers reported their recreational physical activity level during pregnancy in five categories, from inactive (no walking or regular exercise) to highly active (equivalent to walking 3 miles or more per day). Mothers also reported their physical activity at home (mostly sitting, active housework most of the time, or heavy manual work) and at work (not working outside the home, mostly sitting and standing, mostly walking, or mostly heavy labor). We considered additional pregnancy characteristics as potential confounders in the analyses. Mothers reported whether they experienced diabetes or high blood sugar, toxemia or pre-eclampsia, and hypertension or high blood pressure during their pregnancy with the LEGACY daughter. Mothers provided information about all pregnancies lasting 6 months or longer, including the pregnancy

outcome and date that the pregnancy ended. We used this information to determine the birth order of the LEGACY daughter and the type of gestation (singleton or multiple). We calculated gestational age in weeks from the length that the pregnancy lasted, in weeks, months, or days before/after the due date, as reported by mothers. We considered a reported gestational age of less than 37 weeks as preterm. Mothers also reported if they smoked during their pregnancy with the LEGACY daughter; however, we did not include this variable in the analyses since only 1.2% of daughters were exposed to maternal smoke during pregnancy.

Mothers reported their daughters' weight (in grams or pounds/ounces) and length at birth (in centimeters or inches), and the source of this information (i.e. memory, medical records, baby book). We converted birthweight to kilograms and birthlength to centimeters for analysis. We created four body size groups based on the median birthweight and birthlength in the cohort (long/light, long/heavy, short/light and short/heavy) based on the schema by Adair, who observed differences in age at menarche by these categorizations.[72] We also calculated ponderal index at birth as weight in kilograms divided by height in meters cubed. We asked mothers to sign a medical release form at the baseline LEGACY visit to collect growth records prior to baseline from their daughters' pediatricians. We obtained growth charts and/or medical records for 82% of the cohort. For the subset of girls whose medical record data included measurements at birth, we examined the correlation between recalled birthweight and birthlength and the measures abstracted from the medical record.

Pubertal outcomes. We assessed pubertal development through the Growth and Development Questionnaire completed every 6 months by mothers. Mothers assessed their daughters' stage of breast development with the picture-based Sexual Maturation Scale (SMS)[238] showing the five Tanner stages.[100] Tanner stage (TS) 2 indicates the onset of breast development.[100] We previously found maternal reports of breast onset using TS to be highly reliable (kappa=0.73) and valid (sensitivity=77%, specificity=94%) in a subset of LEGACY girls that also had clinical TS data.[239] In addition, mothers reported whether their daughters' breast development had started using the non-picture-based Pubertal Development Scale (PDS),[240] in which a response of "breast development has barely started" was used to indicate the onset of breast development. Mothers that reported that breast development had started based on the PDS also

reported the age that they first noticed their daughters' breast development. Mothers reported their daughters' age at breast development in years and months at baseline, and in half-year intervals at subsequent visits. We used the first maternal report of TS≥2 as the primary outcome to be comparable with previous studies, including analyses in the ALSPAC cohort, of maternal body size and breast development.[73,82,108]

Covariates. In addition to the early-life variables described above, we also considered race/ethnicity, socioeconomic status (SES) and maternal age at menarche as potential confounders in adjusted models. Mothers reported the race/ethnicity of their daughters at baseline, which we categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, or other/mixed race/ethnicity for analyses. We assessed SES using maternal education, paternal education and family income; however, since 17.9% did not report family income and maternal and paternal education were correlated, we used maternal education to assess confounding by SES in the analyses. Mothers recalled their age at menarche to the nearest half-year at baseline, which we categorized as early (<12 years), average (12-13 years) and late (≥14 years). We considered BCFH as a modifier of the associations between early-life exposures and age at breast development.

At each study visit, trained research staff measured the height and weight of the girls at least twice using standardized instruments and we averaged these measures for the analysis. We also abstracted height and weight prior to baseline from medical records and growth charts obtained from girls' pediatricians. We calculated age-specific height, weight, and BMI percentiles based on the 2000 Centers for Disease Control and Prevention (CDC) growth charts.[241] Since we considered pre-pubertal body size as a potential mediator, we used body measurements at age 5-7 years when available from the medical record or measurements from the first clinic visit for girls age 5-7 years at baseline. We used <8 years as the cut-off to define pre-puberty since less than 5% of LEGACY girls had experienced the onset of breast development, defined as breast TS≥2, by 8 years of age. Of the 1031 girls included in the analysis, 619 (60.0%) had a BMI measure between 5-7 years and were included in this mediation analysis. We classified girls with a BMI-for-age percentile ≥85 as overweight and those less than the 85th percentile as average weight.

3.2.3. Statistical analysis

We examined the distribution of early-life exposures and baseline covariates in the overall cohort (N=1068) and in the three subsets used in these analyses: 1) girls participating with their biological mother (N=1031); 2) girls participating with their biological mother with BMI measured between 5-7 years (N=619); and 3) girls participating with their biological mother who were less than 8 years of age at baseline (N=259). We also examined whether the distributions of these variables differed by BCFH and by categories of maternal pre-pregnancy BMI based on the CDC classifications of underweight, normal or healthy weight, overweight and obesity.

We assessed associations between maternal pregnancy characteristics and the timing of breast development using longitudinal parametric Weibull models with age as the time scale to allow for left, interval and right censoring. In the primary analyses, girls whose mother reported that they had already experienced the onset of breast development, defined as TS≥2, at baseline were left-censored at their baseline age. Girls whose mothers reported breast TS≥2 at subsequent visits were interval-censored, with the daughters' age at the last visit where the mother reported TS1 as the beginning of the interval and the daughters' age at the first visit where the mother reported TS≥2 as the end of the interval. Girls who had yet to experience thelarche were right-censored at the age at the last study visit where mom reported TS1. Since some families had more than one participating daughter, we used cluster-robust standard errors to account for correlation within families.

We estimated time ratios (TR) and hazard ratios (HR), along with their respective 95% confidence intervals (CI)s for each exposure of interest in unadjusted models. We examined maternal pre-pregnancy BMI, birthweight and birthlength continuously and in categories. The TR is interpreted as the ratio of the median age or time at event for a given exposure level compared with the referent group, while the HR is interpreted as the ratio of the rate of transition to the pubertal event. A TR below 1 indicates that the exposure is associated with earlier onset of breast development, and a TR above 1 indicates that the exposure is associated with later breast development. For example, if the median age at breast development is 10 years in the referent group and the estimated TR for the exposure is 0.95, this

corresponds to a median age of 9.5 years for the exposed group, or a 6-month acceleration in the age at breast development.[242]

In multivariable models, we adjusted for confounders that were antecedent to the exposure. For example, we did not adjust for GWG, maternal physical activity during pregnancy and birth characteristics in models examining maternal pre-pregnancy BMI as the exposure of interest. In contrast, we adjusted models examining pregnancy physical activity or GWG as the exposure of interest for maternal pre-pregnancy BMI, and we adjusted models examining weight and length at birth for both maternal BMI and GWG. We mutually adjusted birth size models for weight and length, and also adjusted for gestational age in weeks.

We adjusted for race/ethnicity and maternal education in models for the full cohort since these variables were associated with maternal pregnancy characteristics and age at breast development. In the subset of girls <8 years at baseline, we present models adjusted for maternal education only due to small cell counts for several of the race/ethnicity groups. However, associations were similar in models additionally adjusted for race/ethnicity in this subset (data not shown). Associations were also similar, though slightly attenuated, when additionally adjusted for maternal age at menarche (data not shown). We did not adjust for other early-life characteristics such as birth order, multiple gestation, gestational diabetes, gestational hypertension and toxemia/pre-eclampsia since these factors were not associated with breast development. However, we ran sensitivity analyses restricting the analytic sample to singleton pregnancies since GWG and fetal growth patterns may differ in multiple gestation pregnancies.

In the subset of girls that had pre-pubertal body size measures, we examined the presence of mediation by daughters' pre-pubertal body size by adding BMI-for-age percentile and an interaction for BMI-for-age percentile and age at BMI measurement, centered at the mean, to parsimonious adjusted models. We also conducted sensitivity analyses excluding girls that were overweight prior to puberty (BMI-for-age percentile ≥85) as an alternate method to examine the influence of pre-pubertal body size.

We formally tested for effect measure modification by BCFH by adding a cross-product term between the exposure of interest and BCFH to adjusted models and assessed statistical significance using

the Wald test. If the cross-product term was statistically significant at $p<0.05$, we further examined effect modification through stratification by BCFH. We also calculated the relative excess risk due to interaction (RERI) to assess effect modification on the additive scale.[243]

We conducted several sets of additional analyses to examine how sensitive the results were to different modeling assumptions, the use of recalled data, and the method of assessing breast development (**Appendix C.3** and **C.4**). We imputed the recalled age at breast development from the PDS as though it were observed for left-censored girls (43% of girls experienced the onset of breast development prior to cohort entry based on mom's report of TS≥2 at first growth and development questionnaire). We also used the midpoint of the interval as the age at breast development for interval censored-girls. We then assessed associations using semi-parametric Cox proportional hazards models, in addition to parametric Weibull models, in analyses using these imputed values since these models included right-censored data only. We also used the PDS to define breast onset instead of TS. In the subset of girls at the New York and Utah LEGACY sites that had clinical TS data (N=311), we used clinical reports of breast TS≥2 to define the onset of breast development instead of maternal report. We limited the analyses to prospective data by excluding girls who were 8 years of age or older at baseline in order to examine how sensitive findings were to the inclusion of older girls and the use of recalled data using both SMS and PDS. We also ran sensitivity analyses excluding girls with inconsistent Tanner staging by maternal report (mothers reported a regression to TS1 at the visit after the first report of TS≥2; approximately 5% of girls in the full cohort and 10% of girls <8 years at baseline) to examine whether these inconsistent girls were driving the observed results. We conducted these analyses using SAS 9.4 and STATA 15.1.

3.3 Results

3.3.1. Participant characteristics

The distribution of baseline and early-life characteristics were similar across the three subsets used in this analysis compared with the full LEGACY cohort (**Table 3.1**). The average age at baseline was 10.0 years in all eligible girls participating their biological mother (N=1031), 9.2 years in girls with pre-pubertal BMI measures available (N=619) and 6.9 years in girls <8 years at baseline (N=259). The majority of the

cohort (63%) identified as non-Hispanic white, and 18% of girls had a BMI-for-age percentile ≥85th at baseline. Most mothers (71%) had a Bachelor's or graduate degree. The prevalence of pregnancy conditions including gestational diabetes and toxemia or pre-eclampsia were low at approximately 7%. Compared to the full cohort, fewer girls <8 years at baseline were overweight at baseline (14.5%) or were firstborn (37.5%).

The majority of mothers had a BMI in the normal range prior to pregnancy (18.5-24.9), while 4.7% were classified as underweight (<18.5), 17.9% as overweight (25-29.9) and 9.6% as obese (≥30). Approximately 30% of LEGACY mothers reported GWG in excess of the guidelines and 12% reported no recreational physical activity. Women that were obese prior to pregnancy were more likely to gain weight in excess of the guidelines, reported less recreational physical activity during pregnancy, and had a higher prevalence of pregnancy conditions (**Supplemental Table 3.1**). Daughters' birthweight was also higher in women with a higher pre-pregnancy BMI. The mean pre-pregnancy BMI was similar by BCFH, though women with a BCFH were slightly more likely to have inadequate GWG and report no recreational physical activity during pregnancy (**Supplemental Table 3.2**).

3.3.2. Association between maternal pre-pregnancy BMI, gestational weight gain and age at breast development

Maternal pre-pregnancy BMI was associated with earlier age at breast development in daughters (HR=1.03, 95% CI 1.01-1.05, adjusted for race/ethnicity and maternal education) (**Table 3.2**). Although point estimates from the categorical BMI model were not statistically significant, they supported a linear relationship between maternal BMI and age at breast development. Compared with daughters of women who gained 20-29lbs, daughters of women who gained 30lbs or more had an earlier age at breast development, though the association was only statistically significant in daughters of women who gained more than 50lbs during their pregnancy (HR=1.37, 95% CI 1.01-1.85, controlling for maternal pre-pregnancy BMI, maternal education and race/ethnicity). The TR corresponds to approximately 4.9 months earlier onset of breast development in girls whose mother gained 50 or more pounds compared with girls who mother gained 20-29 pounds, with all covariates at the reference level. The pattern for GWG was

slightly J-shaped, with daughters of women who gained less than 20lbs also experiencing slightly earlier development than the referent group (HR 1.15, 95% CI 0.86, 1.54). However, this pattern was not observed when GWG was categorized according to the modified 2009 IOM guidelines (**Supplemental Table 3.3**). These models supported earlier development in daughters of women who gained in excess of the guidelines, but no difference in age at breast development in girls whose mothers gained below the guidelines compared with girls whose mothers' GWG was within the recommended range.

When considering maternal pre-pregnancy BMI and GWG jointly, daughters of women with a pre-pregnancy BMI ≥25 and GWG ≥30lbs experienced breast development at a rate 1.6 times faster than daughters of women with a pre-pregnancy BMI <25 and GWG <30lbs (HR 1.57, 95% CI 1.17-2.12) (**Table 3.2**), a difference of approximately 7 months. In contrast, age at breast development was not earlier in daughters of women who gained ≥30lbs but had a pre-pregnancy BMI <25 or gained <30lbs, but were overweight prior to pregnancy. Results were similar when we considered GWG in excess of the guidelines jointly with maternal BMI instead of using a cut-off of 30lbs (**Supplemental Table 3.3**).

Associations between maternal pre-pregnancy BMI and GWG were in the same direction in the subset of girls <8 years at baseline. GWG of 30 lbs or more was associated with an 80-90% increased rate of breast development in girls <8 years of age (**Table 3.2**). In younger girls, the pattern of age at breast development by categories of maternal BMI and GWG was slightly different than the pattern observed in the full cohort. Daughters had approximately a two-fold increased rate of earlier thelarche if their mothers had a pre-pregnancy BMI <25 kg/m^2 and gained ≥30 lbs or a pre-pregnancy BMI ≥25 kg/m^2, regardless of their GWG, compared with daughters of women with a BMI <25 kg/m^2 who gained <30 lbs. The TRs correspond to approximately 12-12.5 months earlier onset of development in these girls.

3.3.3. Association between maternal physical activity during pregnancy and age at breast development

Daughters of women who reported no recreational physical activity during pregnancy experienced earlier onset of breast development than daughters of physically active women in unadjusted models, but the association was attenuated after adjustment for maternal pre-pregnancy BMI, race/ethnicity and maternal education in the full cohort (**Table 3.3**). There was no association between maternal physical

activity at home and age at breast development. In adjusted models, daughters of women who did not work outside the home experienced later onset of breast development than daughters of women who reported mostly sitting and standing at work during pregnancy (HR=0.77, 0.61-0.98).

In girls <8 years at baseline, daughters of women who reported no recreational physical activity experienced breast development at a rate 1.7 times faster than daughters of physical active women, a difference of approximately 8 months (HR 1.70, 95% CI 1.02, 2.83 adjusting for maternal pre-pregnancy BMI and maternal education). This association was independent of GWG (**Supplemental Table 3.4**). Age at breast development was not statistically different in daughters of women who reported mostly inactive or somewhat active physical activity levels during pregnancy compared with active women. Results for physical activity at home and at work were similar in younger girls compared with the full cohort.

3.3.4. Association between birth size and age at breast development

In girls with birthweight or birthlength available from both medical records/growth charts and maternal report (N=69 for birthweight and 44 for birthlength), the correlation between these measures was 0.91 for birthweight and 0.59 for birthlength. Neither birthweight, birthlength nor ponderal index were associated with age at breast development in the full cohort or the subset of girls <8 years at baseline (**Supplemental Table 3.5**). The inference was unchanged when models were restricted to singleton pregnancies only (data not shown). There were no statistically significant differences in the timing of breast development between girls classified as long/light, long/heavy, short/light or short/heavy at birth based on the median birthweight and birthlength (**Supplemental Table 3.6**).

3.3.5. Mediation by pre-pubertal body size

The inverse association between maternal pre-pregnancy BMI and age at thelarche was mediated by daughters' body size prior to puberty (HR 1.01, 95% CI 0.99-1.04 after adding daughters' BMI-for-age percentile and the interaction between BMI-for-age percentile and centered age at BMI measure to adjusted model in all girls with available BMI measures from 5-7 years of age) (**Table 3.4**). In contrast, effect estimates for GWG were only slightly attenuated after adjustment for daughters' body size and there was no evidence of mediation of the association between maternal physical inactivity during pregnancy and

earlier breast development. These patterns of mediation were the same in girls <8 years of age at baseline. The patterns of earlier breast development in daughters of women that reported no recreational physical activity during pregnancy, high pre-pregnancy BMI, and high GWG were also observed when we excluded girls that were overweight prior to puberty from adjusted models, suggesting that these associations hold across the range of daughters' pre-pubertal body size (**Supplemental Table 3.7**).

3.3.6. Modification by breast cancer family history

In the full cohort, the pattern of the associations between maternal pre-pregnancy BMI, GWG and timing of breast development differed by BCFH (**Table 3.5**). When considering maternal BMI and GWG as a composite variable, the overall interaction with BCFH was statistically significant (p from Wald test <0.01), which was driven by differences in the association for girls whose mothers had a pre-pregnancy BMI≥25 and gained <30lbs compared with the referent group. In girls without a BCFH, the daughters of women who were overweight or obese prior to pregnancy and gained <30 lbs were almost two times more likely to develop early (HR=1.98, 95% CI 1.29-3.05) compared with daughters of women with a pre-pregnancy BMI<25 who gained <30lbs. In girls with a BCFH, girls whose mothers had a pre-pregnancy BMI≥25 and gained <30lbs did not have an increased likelihood of early development compared with the referent group (HR=0.68, 95% CI 0.43-1.09). The negative multiplicative interaction between maternal BMI≥25, GWG <30lbs and BCFH was also statistically significant on the additive scale (RERI: -1.46, 95% CI -2.47, -0.44), suggesting that the joint effect of BCFH and maternal overweight and obesity with moderate GWG (<30lbs) is less than the sum of the effects of each of these exposures when considered individually. There was no interaction on the additive scale for the other two levels of the composite variable (RERI for maternal BMI<25, GWG≥30lbs and BCFH: -0.29, 95% CI -0.82, 0.25 and RERI for maternal BMI≥25, GWG≥30lbs and BCFH: 0.13, 95% CI -0.95, 1.21). This suggests that maintaining a healthy BMI prior to pregnancy and preventing excessive GWG (≥30lbs) could delay breast development in daughters with and without a BCFH. These patterns were similar in models stratified by BCFH in girls <8 years at baseline.

3.3.7. Sensitivity analyses for the association between maternal pre-pregnancy BMI, GWG and onset of breast development

Associations were similar when analyses were restricted to singleton pregnancies only and when girls with inconsistent maternal reports of the onset of breast development (TS≥2) were excluded from adjusted models (data not shown). In the full cohort, the inference was similar when the recalled age at breast development from the PDS was imputed as though it were observed in left-censored girls and/or the midpoint of the interval was imputed as the age of breast development for interval-censored girls (**Supplemental Table 3.8**). Hazard ratios from semi-parametric Cox proportional hazard models were also similar to the hazard ratios from the parametric Weibull models. The patterns of the associations were similar in models where we used PDS to define the onset of breast development instead of SMS, but effect estimates, particularly for maternal pre-pregnancy BMI, were slightly attenuated in both the overall cohort (**Supplemental Table 3.9**) and the subset of girls < 8 years at baseline (**Supplemental Table 3.10**). In the subset of girls with clinical breast TS, the association between maternal pre-pregnancy BMI and onset of breast development as assessed by trained personnel[239] was the same as the estimate using maternal reports of breast TS (HR 1.03, 95% CI 0.99-1.07, adjusted for maternal education and maternal pre-pregnancy BMI), while the estimate using maternal reports of PDS was closer to the null (**Supplemental Table 3.11**).

3.4 Discussion

In this prospective cohort enriched for BCFH, we found that three potentially modifiable risk factors – higher maternal pre-pregnancy BMI, lack of recreational physical activity during pregnancy and higher GWG, were associated with earlier breast development in daughters. The inverse linear relationship between maternal pre-pregnancy BMI and age at breast development was partially mediated by daughters' pre-pubertal body size. When we considered maternal BMI and GWG together, maternal overweight or obesity and high GWG (≥30lbs) was associated with earlier breast development compared with daughters of women with a pre-pregnancy BMI <25 who gained <30lbs during pregnancy, and this association was similar in girls with and without a BCFH. Thus, maintaining a healthy BMI prior to pregnancy and preventing excessive weight gain during pregnancy (≥30lbs) may delay breast development in girls across the spectrum of familial risk for breast cancer.

<u>Comparison with previous studies</u>

Our findings extend the previous literature conducted in study populations of girls predominantly at average-risk of breast cancer due to their family history. The inverse linear relationship between maternal pre-pregnancy BMI and age at breast development that we observed in girls without a BCFH is consistent with previous studies in the prospective ALSPAC birth cohort (β for age at menarche: -0.77, 95% CI -0.93, -0.60 per 1 BMI-unit increase) ,[73,82] and a retrospective pubertal cohort nested in KPNC (HR: 1.39, 95% CI 1.30, 1.49 for maternal BMI≥30 compared with 18.5-24.9, p for trend<0.0001).[81] Higher maternal pre-pregnancy BMI has also been consistently associated with earlier age at menarche.[73,82,111,115,117,118] Similar to our results, previous studies have also observed earlier age at breast development and menarche in daughters of women with greater absolute GWG or GWG in excess of guidelines.[82,83,118,237] However, the shape of this association at the extreme of low or inadequate GWG has not been consistent in the literature. In ALSPAC, GWG had an inverse linear relationship with age at thelarche and age at menarche, and inadequate GWG based on the 2009 IOM guidelines was associated with a decreased risk of early menarche compared with adequate GWG.[82] In contrast, inadequate GWG was associated with earlier age at breast development in KPNC.[237] A U-shaped association was also observed between GWG and early menarche in the Nurses' Health Study II cohort.[83] We did not observe a statistically significant difference in age at breast development in girls whose mothers gained <20lbs compared with 20-29lbs, but point estimates were in the direction of earlier breast development in this group. The inconsistent association between low GWG and pubertal timing could be due to heterogeneity within the group of women who do not gain much weight during pregnancy, particularly in terms of pre-pregnancy BMI. In girls <8 years at baseline, the HR for breast development for GWG<20lbs when adjusted for maternal pre-pregnancy BMI as a confounder was 1.64 (95% CI 0.91-2.94). However, when we considered GWG together with maternal pre-pregnancy BMI, we observed earlier breast development in girls with low GWG only if their mothers were overweight or obese prior to pregnancy. Although previous studies adjusted for pre-pregnancy BMI, the estimated association between low GWG and breast development without considering an interaction between GWG and maternal BMI would be an average effect over the distribution of maternal BMI. Differences in the distribution of maternal BMI in previous studies could explain inconsistencies in the associations between low GWG and pubertal timing in the literature. In the ALSPAC cohort, which did not observe earlier pubertal timing in daughters of inadequate GWG, only 21.7% of mothers had a BMI≥25

prior to pregnancy.[82] In KPNC, which did observe a statistically significant association between inadequate GWG and earlier breast development, more than 50% of mothers had a BMI≥25 at the beginning of pregnancy. The HR was elevated, but not statistically significant, comparing girls whose mother had a pre-pregnancy BMI<25 and inadequate GWG with girls whose mothers also had a pre-pregnancy BMI<25 and adequate GWG (HR=1.26, 95% CI 0.90-1.75). [237]

We observed earlier age at breast development in daughters of women that were physically inactive during pregnancy. The association between maternal physical activity and breast development was not linear and was limited to women that reported no walking or regular exercise, suggesting that even a small amount of physical activity during pregnancy may reduce the risk of early breast development in daughters. While we also observed later age at breast development in daughters of women who did not work outside the home, no difference was observed between daughters of women with more sedentary compared with more physically active jobs among women who worked outside the home. It seems unlikely that the observed association in daughters of women who do not work outside the home is due to physical activity, and may reflect an influence of socioeconomic status or other differences in the home environment in families where the mother does not work outside the home. Only one prior study has examined maternal physical activity levels during pregnancy in relation to pubertal timing. In the Nurses' Health Study II cohort, there was a modest linear relationship between maternal leisure-time physical activity and daughters' age at menarche, with a 1 month difference in age at menarche between daughters of highly active compared with inactive women.[236] The magnitude of this association is much smaller than what we observed for breast development, but age at menarche was recalled to the nearest year by participants in adulthood and measurement error on the outcome may have biased effect estimates towards the null.

While our results support that maternal factors that affect the intrauterine environment are associated with age at breast development, they do not support an independent role for birthweight or birthlength in regards to the onset of breast development. Mothers recalled birthweight and birthlength when girls were primarily 6-13 years of age and these measures are likely subject to some measurement error. We mailed the questionnaire for parents to complete at home, and 41% of mothers reported that the source of the birthweight information was a written record (birth certificate, baby book, birth announcement, etc.).

The correlation between maternal report of birthweight and birthweight abstracted from medical record data was also high (0.9) in our validation subset, and previous studies have found parental recall of birthweight to be reliable.[244,245] Birth cohorts using prospective measures of birthweight have also not observed an association between birthweight and onset of breast development,[73,79] which supports that our results are less likely to be driven by measurement error. Earlier age at breast development was observed in higher birthweight infants in the North Carolina Infant Feeding Study, but the association was adjusted for weight gain in infancy and early childhood and may reflect the influence of postnatal growth patterns.[75] The correlation for birthlength in our validation subset was modest at 0.6, and 13% of mothers did not report length at birth. However, assessments of length before standing height can be measured are more prone to measurement error and have been found to have poor reliability, even when measured by nurses.[246,247] Three previous studies using prospective measures of birthlength also did not observe an association with the timing of breast development.[73,79,124]

Potential mechanisms

Several potential mechanisms may link maternal pre-pregnancy BMI, GWG and maternal physical activity during pregnancy to the timing of breast development. Previous studies have found that the combination of excess GWG and higher maternal pre-pregnancy BMI is associated with rapid infant weight gain,[248,249] a risk factor for earlier age at breast development[73,75] and menarche.[34,72,76,77,190] The increased risk of early breast development that we observed in daughters of women that were overweight or obese prior to pregnancy and gained more than 30lbs may be mediated by rapid infant weight gain, a hypothesis that we will explore in **Chapter 4**. Overweight girls have earlier onset of breast development than girls of average weight,[54,60] and maternal pre-pregnancy BMI and GWG are both positively associated with daughters' BMI in childhood.[250] Our results suggest that the association between maternal pre-pregnancy BMI and earlier age at breast development is partially mediated by daughters' BMI, which could be due to shared genetic or lifestyle factors.[197] However, when we limited our analyses to girls with a pre-pubertal BMI <85th percentile, we still observed an inverse association between maternal BMI and age at breast development. Associations between higher GWG and maternal physical inactivity and earlier age at breast development were only slightly attenuated after adjusting for daughters' BMI.

Overall, the lack of full mediation by daughters' body size suggests that maternal pregnancy factors may have a direct effect on the developing breast. The developmental origins of health and disease (DOHAD) hypothesis posits that intrauterine exposures affect health throughout the life course, either through a direct effect on the developing organs during the critical period of fetal development or through a developmental programming mechanism.[198] The breast undergoes multiple periods of rapid development throughout the life course when it is more susceptible to carcinogenetic effects from the environment.[43,199] The prenatal period has been identified as a critical window of susceptibility since the ductal system of the breast develops rapidly in utero,[43,199,200] and exposures that affect this ductal development could alter later breast development and breast cancer risk.[43,201,202] In rats, maternal high fat diet during pregnancy has been associated with increased estrogen levels in mothers and earlier pubertal development and increased incidence of mammary tumors in offspring.[251] In humans, however, high-fat diet, maternal obesity and GWG have not been consistently associated with estrogen levels during pregnancy.[27,28,252,253]

Maternal overnutrition could also affect breast development via the programming of hormones related to glucose and insulin regulation. Women with higher pre-pregnancy BMI and greater GWG have higher levels of leptin.[203,254,255] Exposure to high leptin levels in utero may program higher levels of these hormones in their daughters. Higher levels of leptin, an adipokine which plays a role in appetite and energy regulation, may stimulate the hypothalamic-pituitary-gonadal (HPG) axis, leading to earlier onset of breast development.[204] Higher leptin levels have been observed in girls with premature breast development[205] and is associated with earlier age at menarche.[206] Maternal obesity is also associated with insulin resistance during pregnancy, which may predispose the offspring to the development of insulin resistance and compensatory hyperinsulemia.[207] Hyperinsulinemia is associated with decreased levels of sex hormone-binding globulin,[87] which in turn increases sex steroid bioavailability and may promote puberty.[208] Some studies have shown that physical activity during pregnancy is associated with reduced maternal leptin levels and increased insulin sensitivity (for review, see [256]), suggesting that physical activity during pregnancy could also affect pubertal timing through a hormonal mechanism. Maternal overnutrition may affect daughters' health later in life via an epigenetic mechanism.[207,209] Patterns of DNA methylation are established in early life and persist into adulthood, and evidence from animal studies suggest that maternal overnutrition can induce epigenetic changes in the offspring.[210]

Differences by breast cancer family history

We previously observed that girls with a BCFH experience earlier onset of breast development than girls without a BCFH.[54] Identifying risk factors for earlier puberty that are modifiable could therefore have a greater effect on an absolute scale in girls with a BCFH. We found that the association between maternal overweight or obesity, high GWG (≥30lbs) and earlier age at breast development did not differ by BCFH on the additive scale, as assessed by the RERI. This suggests that the absolute risk of early breast development can be modified, even in girls at increased risk due to their family history, by changing the early-life environment. Maintaining a healthy weight prior to pregnancy, preventing excessive GWG and engaging in physical activity during pregnancy has many additional health benefits for both the mother and the child. Raising awareness that these behaviors, which are in line with current clinical and public health recommendations, may delay the onset of breast development in daughters is an important public health message. This message may resonate in particular with mothers of girls with a BCFH, who have a greater level of breast-cancer specific distress.[257]

Methodological considerations in the assessment of breast development

One of the methodological challenges in studying pubertal timing is accurately capturing the onset of breast development. We ran multiple sensitivity analyses to examine how robust the association that we observed between maternal pre-pregnancy BMI, GWG and the onset of breast development was across different assessments of breast development and modeling strategies. In our sample, 43% of girls experienced the onset of breast development prior to study entry. Excluding girls based on their attainment of the outcome is recognized to bias studies of pubertal timing.[58] In particular, girls with earlier onset of breast development would be more likely to be excluded; if the exposure is associated with earlier development, this exclusion could lead to a bias towards the null in the observed measure of association. In our primary analysis, we included these girls in the model as left-censored without making additional assumptions about the timing of their breast development. We also ran sensitivity analyses imputing their age at breast development using recalled data. The imputation of an observed event time is more precise than left censored data, but is more prone to measurement error. Since we administered the growth and development questionnaire every 6 months, we had multiple reports of mothers' recalled age at onset of

breast development for a subset of the cohort. As daughters mature and mothers are recalling the age of onset further from the actual time of transition, the age at onset recalled by the mother became progressively later on average (data not shown). The estimated median age at breast development was later when we used recalled data for left-censored girls, but the estimated associations for our exposures of interest were largely unchanged. Our inference was also similar when we imputed the midpoint of the interval as though it were observed for interval-censored girls.

While we used maternal reports of breast TS as our main outcome since it was available for all LEGACY sites, we conducted sensitivity analyses in the subset of girls with clinical breast TS. While estimates in this subset lack precision, the patterns of association were similar to what we observed in the full cohort using maternal reports. We also ran sensitivity analyses assessing the onset of breast development using PDS. Compared with clinical TS as the gold standard, we've previously found that breast onset as measured by maternal report using PDS has higher sensitivity compared with maternal report of SMS, but slightly lower specificity (Sensitivity 86.6% vs 77.0% for PDS and SMS; Specificity 89.6% vs 94.3% for PDS and SMS).[239,258] Since mothers are more likely to report breast onset using PDS compared with SMS, a higher percentage of girls were left-censored when using PDS as the outcome, which could explain why the point estimates from the PDS models are slightly closer to the null than the SMS models. Girls with inconsistent development by either measure (a report of TS1 or PDS1 after a report of TS or PDS≥2, which may reflect inaccurate reporting by the mother of the initial onset) were more likely to be discordant across these two measures. Our results were similar when we excluded inconsistent girls based on TS from the analyses, which suggests that our findings are less likely to be driven by measurement error. Finally, the validity of breast TS when based on visual assessment is different in average-weight compared with overweight girls, even when assessed by clinicians, as fat tissue in overweight girls can be mistaken for breast tissue.[58] In LEGACY, we found that the sensitivity of maternal reports of breast onset, when assessed by SMS and PDS, is higher, but the specificity is lower, in overweight compared with average-weight girls.[239,258] Since maternal pre-pregnancy BMI and GWG are associated with daughters' body size, this differential outcome assessment could bias the results away from the null. We examined this potential bias by restricting our analyses to non-overweight girls, and the inference was the same in this subset. Overall, the associations between higher maternal pre-pregnancy

BMI, greater GWG and earlier breast development were robust to these different modeling strategies. The consistency across our sensitivity analyses reduces the likelihood that our findings are due to bias, but is also informative for the comparison of previous studies that use these different methodologies and the design of future studies of breast development. While biannual assessments of clinical TS with palpation has been recommended as a "wish list" for longitudinal studies,[58] our results suggest that, in the case of exposures with a strong signal, the bias from the use of maternal reports and recalled data is minimal and leads to similar inference.

Strengths and limitations

The utilization of the LEGACY cohort is a major strength of this research. LEGACY is the only pubertal cohort worldwide enriched for BCFH, which allowed us to examine whether the associations between these early-life factors and breast development varies by underlying breast cancer susceptibility. LEGACY girls have been followed for up to five years with visits at six-month intervals, and thus have breast development data collected at frequent intervals to assess breast onset. Previous studies have primarily assessed development on an annual basis,[82,109] decreasing precision. The collection of multiple measures of breast development is also a strength, and allowed us to compare findings across mother-reported breast TS, mother-reported PDS, and clinician-reported breast TS. The consistency of the finding that daughters of mothers who were overweight or obese prior to pregnancy and gained more than 30lbs during pregnancy across these measures support that this finding is less likely to be driven by measurement error in outcome assessment.

Limitations of this study include the use of self-reported exposure data and censoring of the breast development outcome. Maternal recall of prenatal exposures, including maternal body size and daughters' birth characteristics, could be subject to measurement error, though the use of categorical variables likely limited the amount of misclassification. GWG was not collected in a way to be able to create categories of inadequate, adequate, and excessive weight gain based on the exact recommendations of the 2009 IOM guidelines.[110] Since girls were predominantly between the ages of 6 and 13 years at baseline, some of the girls had already experienced breast development prior to cohort entry. We included these girls in the analyses by using both left censoring and recalled age at development in sensitivity analyses, but the lack

of prospective data on these girls could have biased our results towards the null. We also conducted analyses in the subset of girls <8 years at baseline, in which <5% of girls were left-censored for the outcome, limiting the potential for bias due to the use of retrospective data. However, the sample size of this subset affected precision and limited the number of confounders that we included in adjusted models. Overall, the consistency of the main study findings across the analytic subsets, which are susceptible to different sources of bias, support that bias is unlikely to explain the results that we observed.

3.5 Conclusions

Earlier thelarche was associated with three potentially modifiable risk factors – maternal pre-pregnancy BMI, maternal physical activity during pregnancy and gestational weight gain - in a cohort of girls enriched for BCFH. Health promotion campaigns should educate both women who are planning pregnancies and their clinicians that maintaining a healthy pre-pregnancy BMI, engaging in recreational physical activity during pregnancy, and moderate weight gain during pregnancy (<30lbs) may delay breast development in daughters, in addition to other health benefits to the mother and child.

3.6 Tables and figures

Table 3.1. Descriptive characteristics of the LEGACY Girls Study cohort overall and by analytic subset

	All of LEGACY (N=1068)	Participating guardian is biological mother (N=1031)	Subset with BMI measured at <8 years (N=619)	Subset age <8 years at baseline (N=259)
Early-life characteristics				
Maternal age at birth (Mean±SD)	32.3 ± 5.5	32.1 ± 5.4	32.5 ± 5.2	32.1 ± 5.5
Maternal height, m (Mean±SD)	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
Maternal pre-pregnancy weight, kg (Mean±SD)	64.0 ± 13.3	64.0 ± 13.3	64.0 ± 13.0	65.8 ± 14.5
Maternal pre-pregnancy BMI (Mean±SD)	23.8 ± 4.9	23.8 ± 4.9	23.7 ± 4.8	24.5 ± 5.6
Maternal pre-pregnancy BMI, categorized (N, %)				
<18.5	47 (4.4)	47 (4.6)	28 (4.5)	8 (3.1)
18.5 to <25	677 (63.4)	676 (65.6)	415 (67.0)	162 (62.6)
25 to <30	180 (16.9)	179 (17.4)	94 (15.2)	46 (17.8)
≥30	96 (9.0)	96 (9.3)	59 (9.5)	31 (12.0)
Missing	68 (6.4)	33 (3.2)	23 (3.7)	12 (4.6)
Gestational weight gain (n, %)				
<10 lbs	27 (2.5)	27 (2.6)	20 (3.2)	7 (2.7)
10-14 lbs	42 (3.9)	42 (4.1)	25 (4.0)	10 (3.9)
15-19 lbs	86 (8.1)	86 (8.3)	54 (8.7)	17 (6.6)
20-29 lbs	317 (29.7)	316 (30.7)	169 (27.3)	78 (30.1)
30-39 lbs	266 (24.9)	264 (25.6)	161 (26.0)	68 (26.3)
40-49 lbs	145 (13.6)	145 (14.1)	87 (14.1)	34 (13.1)
≥50 lbs	113 (10.6)	113 (11.0)	69 (11.2)	31 (12.0)
Missing	72 (6.7)	38 (3.7)	34 (5.5)	14 (5.4)
Gestational weight gain adequacy based on the 2009 IOM guidelines (n, %)				
Inadequate (below guidelines)	132 (12.4)	132 (12.8)	87 (14.1)	27 (10.4)
Adequate (within guidelines)	519 (48.6)	519 (50.3)	300 (48.5)	134 (51.7)
Excessive (above guidelines)	317 (29.7)	317 (30.8)	187 (30.2)	81 (31.3)
Missing	100 (9.4)	63 (6.1)	45 (7.3)	17 (6.6)
Maternal recreational physical activity during pregnancy (N, %)				
Inactive, no walking or other regular exercise	129 (12.1)	128 (12.4)	71 (11.5)	30 (11.6)
Mostly inactive, equivalent to walking about half a mile or less every day	241 (22.6)	235 (22.8)	156 (25.2)	71 (27.4)
Somewhat active, equivalent to walking about 1 mile every day	226 (21.2)	222 (21.5)	136 (22.0)	57 (22.0)
Active, equivalent to walking about 2 miles every day	384 (36.0)	379 (36.8)	215 (34.7)	85 (32.8)

Highly active, equivalent to walking about 3 or more miles every day	58 (5.4)	57 (5.5)	33 (5.3)	11 (4.3)
Missing	30 (2.8)	10 (1.0)	8 (1.3)	5 (1.9)
Maternal physical activity at home during pregnancy (N, %)				
Mostly sitting	212 (19.9)	209 (20.3)	123 (19.9)	51 (19.7)
Mostly walking and standing, with some sitting	412 (38.6)	403 (39.1)	246 (39.7)	108 (41.7)
Active housework most of the time with little sitting	405 (37.9)	400 (38.8)	236 (38.1)	90 (34.8)
Heavy manual work at home	5 (0.5)	5 (0.5)	2 (0.3)	2 (0.8)
Missing	34 (3.2)	14 (1.4)	12 (1.9)	8 (3.1)
Maternal physical activity at work during pregnancy (N, %)				
Not working	214 (20.0)	211 (20.5)	112 (18.1)	54 (20.9)
Mostly sitting and standing	422 (39.5)	413 (40.1)	258 (41.7)	103 (39.8)
Mostly walking with some sitting and standing	362 (33.9)	357 (34.6)	224 (36.2)	92 (35.5)
Mostly heavy labor with some walking and standing and little sitting	39 (3.7)	39 (3.8)	17 (2.8)	5 (1.9)
Missing	31 (2.9)	11 (3.8)	8 (1.3)	5 (1.9)
Maternal physical activity during pregnancy, 2nd trimester (N, %)				
Stayed the same	751 (70.3)	737 (71.5)	446 (72.1)	189 (73.0)
Substantially increased	54 (5.1)	54 (5.2)	29 (4.7)	8 (3.1)
Substantially decreased	233 (21.8)	231 (22.4)	136 (22.0)	57 (22.0)
Missing	30 (2.8)	9 (0.9)	8 (1.3)	5 (1.9)
Gestational diabetes during pregnancy with LEGACY daughter (N, %)				
Yes	80 (7.5)	78 (7.6)	50 (8.1)	24 (9.3)
No	944 (88.4)	930 (90.2)	555 (89.7)	225 (86.9)
Missing	44 (4.1)	23 (2.2)	14 (2.3)	10 (3.9)
Gestational hypertension, toxemia or pre-eclampsia during pregnancy with LEGACY daughter (N, %)				
Yes	76 (7.1)	74 (7.2)	42 (6.8)	20 (7.7)
No	947 (88.7)	932 (90.4)	557 (90.0)	227 (87.6)
Missing	45 (4.2)	25 (2.4)	20 (3.2)	12 (4.6)
Type of gestation (N, %)				
Multiple	45 (4.2)	45 (4.4)	34 (5.5)	13 (5.0)
Singleton	970 (90.8)	970 (94.1)	576 (93.1)	241 (93.1)
Missing	53 (5.0)	16 (1.6)	9 (1.5)	5 (1.9)
Birth order (Mean±SD)	1.8 ± 0.9	1.8 ± 0.9	1.7 ± 0.9	1.9 ± 0.9
Birth order, dichotomized (N, %)				
First-born	470 (44.0)	470 (45.6)	281 (45.4)	97 (37.5)
Not first-born	545 (51.0)	545 (52.9)	329 (53.2)	157 (60.6)
Missing	53 (5.0)	16 (1.6)	9 (1.5)	5 (1.9)
Gestational age in weeks (Mean±SD)	39.0 ± 2.1	39.0 ± 2.1	38.9 ± 2.2	38.8 ± 2.2

Gestational age, categorized (N, %)				
<37 weeks	121 (11.3)	120 (11.6)	80 (12.9)	32 (12.4)
≥37 weeks	909 (85.1)	893 (86.6)	525 (84.8)	218 (84.2)
Missing	38 (3.6)	18 (1.8)	14 (2.3)	9 (3.5)
Intrauterine smoke exposure (N, %)				
Yes	19 (1.8)	12 (1.2)	10 (1.6)	4 (1.5)
No	1017 (95.2)	1000 (97.0)	598 (96.6)	247 (95.4)
Missing	32 (3.0)	12 (1.2)	11 (1.6)	8 (3.1)
Birthweight, g (Mean±SD)	3293.7 ± 582.9	3298.3 ± 583.3	3297.8 ± 574.6	3287.2 ± 574.6
Birthweight, categorized (N, %)				
<2500g	81 (7.6)	78 (7.6)	43 (7.0)	19 (7.3)
2500-2999g	186 (17.4)	179 (17.4)	111 (17.9)	42 (16.2)
3000-3499g	397 (37.2)	388 (37.6)	233 (37.6)	104 (40.2)
3500-3999g	287 (26.9)	279 (27.1)	165 (26.7)	66 (25.5)
≥4000g	94 (8.8)	94 (9.1)	59 (9.5)	24 (9.3)
Missing	23 (2.2)	13 (1.3)	8 (1.3)	4 (1.5)
Birthlength, cm (Mean±SD)	50.5 ± 3.7	50.5 ± 3.6	50.4 ± 3.7	50.4 ± 3.8
Birthlength, categorized (N, %)				
<48.25	113 (10.6)	106 (10.3)	65 (10.5)	30 (11.6)
48.25-50.74	283 (26.5)	277 (26.9)	167 (27.0)	65 (25.1)
50.75-53.24	222 (20.8)	215 (20.9)	138 (22.3)	58 (22.4)
≥53.25	303 (28.4)	300 (29.1)	176 (28.4)	76 (29.3)
Missing	147 (13.8)	133 (12.9)	73 (11.8)	30 (11.6)
Ponderal index at birth, kg/m^3 (Mean±SD)	26.0 ± 6.3	25.8 ± 5.8	25.8 ± 5.2	25.7 ± 5.3
Ponderal index at birth, categorized (N, %)				
<22.98	241 (22.6)	238 (23.1)	146 (23.6)	59 (22.8)
22.98-25.21	222 (20.8)	217 (21.1)	122 (19.7)	57 (22.0)
25.22-28.11	230 (21.5)	225 (21.8)	152 (24.6)	64 (24.7)
≥28.12	228 (21.4)	218 (21.1)	126 (20.4)	49 (18.9)
Missing	147 (13.8)	133 (12.9)	73 (11.8)	30 (11.6)
Baseline characteristics				
Age at baseline, (Mean±SD)a	10.0 ± 2.4	10.0 ± 2.4	9.2 ± 2.3	6.9 ± 0.6
BMI-for-age percentile at baseline, (Mean±SD)[a]	50.5 ± 30.6	50.8 ± 30.5	50.2 ± 30.5	49.9 ± 30.6
BMI-for-age percentile at baseline, categorized (N, %)[a]				
≥85th BMI-for-age percentile	180 (16.9)	174 (16.9)	100 (16.2)	36 (13.9)
<85th BMI-for-age percentile	836 (78.3)	806 (78.2)	503 (81.3)	212 (81.9)
Missing	52 (4.9)	51 (5.0)	16 (2.6)	11 (4.3)
History of breast cancer in a first- or second-degree relative (N, %)				
BCFH+	543 (50.8)	530 (51.4)	310 (50.1)	134 (51.7)
BCFH-	525 (49.2)	501 (48.6)	309 (49.9)	125 (48.3)

BOADICEA lifetime risk score (Mean±SD)	14.6 ± 4.8	14.6 ± 4.8	14.4 ± 4.7	14.7 ± 5.0
Study site				
Philadelphia	159 (14.9)	153 (14.8)	112 (18.1)	24 (9.3)
New York	177 (16.6)	175 (17.0)	116 (18.7)	56 (21.6)
Utah	178 (16.7)	173 (16.8)	103 (16.6)	60 (23.2)
Ontario	192 (18.0)	179 (17.4)	106 (17.1)	46 (17.8)
Northern California	362 (33.9)	351 (34.0)	182 (29.4)	73 (28.2)
Race/ethnicity				
Non-Hispanic white	669 (62.6)	650 (63.1)	406 (65.6)	167 (64.5)
Non-Hispanic black	79 (7.4)	78 (7.6)	49 (7.9)	20 (7.7)
Hispanic	196 (18.4)	184 (17.9)	96 (15.5)	48 (18.5)
Asian/Pacific Islander	93 (8.7)	88 (8.5)	52 (8.4)	20 (7.7)
Other or mixed race/ethnicity	31 (2.9)	31 (3.0)	16 (2.6)	4 (1.5)
Maternal education				
Some college, vocational or technical school or less	296 (27.7)	287 (27.8)	147 (23.8)	75 (29.0)
Bachelor's degree	385 (36.1)	373 (36.2)	226 (36.5)	93 (35.9)
Graduate degree	361 (33.8)	346 (33.6)	232 (37.5)	85 (32.8)
Missing	26 (2.4)	25 (2.4)	14 (2.3)	6 (2.3)
Paternal education				
Some college, vocational or technical school or less	345 (32.3)	339 (32.9)	177 (28.6)	76 (29.3)
Bachelor's degree	306 (28.7)	298 (28.9)	189 (30.5)	83 (32.1)
Graduate degree	348 (32.6)	333 (32.3)	219 (35.4)	79 (30.5)
Missing	69 (6.5)	61 (5.9)	34 (5.5)	21 (8.1)
Maternal age at menarche (Mean±SD)	12.7 ± 1.5	12.7 ± 1.5	12.8 ± 1.6	12.8 ± 1.6
Maternal age at menarche, categorized				
<12 years	205 (19.2)	200 (19.4)	115 (18.6)	52 (20.1)
12-13 years	575 (53.8)	558 (54.1)	338 (54.6)	135 (52.1)
≥14 years	253 (23.7)	247 (24.0)	152 (24.6)	66 (25.5)
Missing	35 (3.3)	26 (2.5)	14 (2.3)	6 (2.3)

[a]Age at pilot baseline visit for girls with pilot data (N=21)

Table 3.2. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal pre-pregnancy BMI and GWG and the onset of breast development for the overall cohort and girls age <8 years at baseline

	Overall cohort					***Girls <8 years at baseline***				
		Unadjusted		Adjusted[a]			Unadjusted		Adjusted[b]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Maternal pre-pregnancy BMI										
<18.5	47	1.038 (0.999, 1.079)	0.75 (0.55, 1.01)	**1.055 (1.011, 1.101)**	**0.65 (0.46, 0.92)**		*Those with BMI<18.5 are in referent group due to small numbers			
18.5 to <25	667	Reference	Reference	Reference	Reference	165	Reference	Reference	Reference	Reference
25 to <30	178	0.979 (0.942, 1.017)	1.18 (0.87, 1.60)	0.993 (0.955, 1.031)	1.06 (0.78, 1.44)	46	0.959 (0.905, 1.016)	1.36 (0.89, 2.07)	0.977 (0.921, 1.037)	1.19 (0.76, 1.86)
≥30	96	**0.948 (0.912, 0.985)**	**1.51 (1.12, 2.04)**	0.967 (0.930, 1.006)	1.31 (0.95, 1.79)	31	**0.923 (0.858, 0.993)**	**1.80 (1.07, 3.01)**	0.927 (0.853, 1.008)	1.77 (0.96, 3.26)
Continuous (per kg/m^2)	988	**0.995 (0.993, 0.997)**	**1.04 (1.02, 1.06)**	**0.997 (0.994, 0.999)**	**1.03 (1.01, 1.05)**	242	**0.994 (0.991, 0.998)**	**1.04 (1.02, 1.07)**	**0.996 (0.992, 0.999)**	**1.04 (1.01, 1.07)**
Gestational weight gain										
<20lbs	155	0.975 (0.941, 1.010)	1.21 (0.92, 1.60)	0.983 (0.958, 1.019)	1.15 (0.86, 1.54)	34	**0.919 (0.846, 0.999)**	**1.85 (1.02, 3.37)**	0.938 (0.869, 1.013)	1.64 (0.91, 2.94)
20-29 lbs	315	Reference	Reference	Reference	Reference	77	Reference	Reference	Reference	Reference
30-39 lbs	261	0.988 (0.960, 1.020)	1.10 (0.88, 1.38)	0.975 (0.947, 1.004)	1.23 (0.97, 1.55)	67	0.952 (0.893, 1.015)	1.43 (0.91, 2.27)	**0.928 (0.872, 0.986)**	**1.78 (1.12, 2.86)**
40-49 lbs	143	0.979 (0.947, 1.013)	1.18 (0.91, 1.52)	0.974 (0.942, 1.007)	1.24 (0.95, 1.62)	33	0.929 (0.862, 1.001)	1.71 (0.99, 2.97)	**0.919 (0.854, 0.988)**	**1.92 (1.08, 3.40)**
≥50 lbs	109	0.969 (0.932, 1.010)	1.28 (0.95, 1.72)	**0.962 (0.926, 0.999)**	**1.37 (1.01, 1.85)**	29	0.917 (0.833, 1.009)	1.88 (0.94, 3.78)	0.923 (0.844, 1.009)	1.85 (0.93, 3.67)
Maternal pre-pregnancy BMI and GWG										
BMI<25 and <30 lbs	312	Reference	Reference	Reference	Reference	67	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	389	0.995 (0.971, 1.020)	1.04 (0.86, 1.25)	0.985 (0.960, 1.009)	1.13 (0.93, 1.38)	95	**0.915 (0.853, 0.982)**	**1.91 (1.15, 3.16)**	**0.907 (0.848, 0.970)**	**2.11 (1.28, 3.48)**
BMI≥25 and <30lbs	149	0.980 (0.937, 1.025)	1.17 (0.82, 1.66)	0.987 (0.944, 1.031)	1.11 (0.78, 1.59)	43	**0.887 (0.820, 0.960)**	**2.40 (1.39, 4.16)**	**0.910 (0.839, 0.987)**	**2.05 (1.13, 3.72)**
BMI≥25 and ≥30 lbs	118	**0.935 (0.901, 0.970)**	**1.69 (1.27, 2.26)**	**0.945 (0.911, 0.981)**	**1.57 (1.17, 2.12)**	32	**0.912 (0.831, 1.000)**	**1.97 (1.01, 3.84)**	**0.907 (0.826, 0.996)**	**2.11 (1.04, 4.28)**

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).

[b]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).

Table 3.3. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal physical activity during pregnancy and the onset of breast development for the overall cohort and girls age <8 years at baseline

	Overall cohort					***Girls <8 years at baseline***				
		Unadjusted		Adjusted[a]			Unadjusted		Adjusted[b]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Recreational physical activity										
Inactive, no walking or other regular exercise	127	**0.946 (0.909, 0.985)**	**1.54 (1.12, 2.11)**	0.977 (0.941, 1.015)	1.20 (0.89, 1.63)	30	**0.914 (0.853, 0.980)**	**1.95 (1.17, 3.25)**	**0.933 (0.873, 0.998)**	**1.70 (1.02, 2.83)**
Mostly inactive, equivalent to walking about half a mile or less every day	232	0.993 (0.958, 1.028)	1.06 (0.81, 1.39)	1.006 (0.976, 1.038)	0.95 (0.74, 1.22)	70	1.003 (0.947, 1.063)	0.98 (0.63, 1.51)	1.012 (0.951, 1.077)	0.91 (0.56, 1.47)
Somewhat active, equivalent to walking about 1 mile every day	220	0.990 (0.964, 1.017)	1.08 (0.88, 1.33)	1.010 (0.983, 1.038)	0.93 (0.75, 1.15)	56	1.022 (0.959, 1.088)	0.85 (0.54, 1.36)	1.008 (0.949, 1.071)	0.94 (0.59, 1.51)
Active or highly active, equivalent to walking 2 miles or more every day	433	Reference	Reference	Reference	Reference	93	Reference	Reference	Reference	Reference
Physical activity at home										
Mostly sitting	208	1.003 (0.972, 1.036)	0.97 (0.76, 1.25)	1.013 (0.981, 1.046)	0.90 (0.70, 1.17)	51	0.948 (0.889, 1.012)	1.48 (0.92, 2.37)	0.974 (0.912, 1.041)	1.22 (0.74, 2.02)
Mostly walking and standing, with some sitting	398	Reference	Reference	Reference	Reference	105	Reference	Reference	Reference	Reference
Active housework most of the time with little sitting or heavy manual labor	402	1.011 (0.986, 1.036)	0.92 (0.76, 1.12)	1.019 (0.995, 1.044)	0.86 (0.70, 1.04)	90	0.976 (0.925, 1.029)	1.20 (0.81, 1.76)	0.994 (0.942, 1.048)	1.05 (0.70, 1.57)
Physical activity at work										
Not working outside the home	208	1.013 (0.986, 1.042)	0.90 (0.73, 1.12)	**1.033 (1.003, 1.063)**	**0.77 (0.61, 0.98)**	53	1.050 (0.986, 1.118)	0.70 (0.45, 1.11)	**1.089 (1.021, 1.163)**	**0.52 (0.31, 0.86)**
Mostly sitting and standing	408	Reference	Reference	Reference	Reference	99	Reference	Reference	Reference	Reference
Mostly walking or heavy labor	395	0.996 (0.972, 1.020)	1.03 (0.86, 1.24)	1.004 (0.980, 1.028)	0.97 (0.80, 1.18)	97	1.000 (0.945, 1.058)	1.00 (0.67, 1.51)	1.016 (0.964, 1.070)	0.89 (0.59, 1.33)

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).
[b]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).

Table 3.4. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal pre-pregnancy BMI, recreational physical activity during pregnancy and GWG with adjustment for daughter's pre-pubertal body size

	Subset of cohort with pre-pubertal BMI measures					***Girls <8 years at baseline***				
		Multivariable-adjusted[a]		Additional adjustment for daughter's body size[b]			Multivariable-adjusted[c]		Additional adjustment for daughter's body size[d]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Maternal pre-pregnancy BMI										
<18.5	28	1.027 (0.977, 1.079)	0.81 (0.55, 1.20)	1.018 (0.969, 1.069)	0.87 (0.59, 1.29)		*Those with BMI<18.5 are in referent group due to small numbers			
18.5 to <25	402	Reference	Reference	Reference	Reference	157	Reference	Reference	Reference	Reference
25 to <30	92	0.960 (0.919, 1.004)	1.38 (0.97, 1.97)	0.970 (0.929, 1.013)	1.27 (0.90, 1.81)	42	0.970 (0.912, 1.031)	1.26 (0.80, 1.99)	1.009 (0.952, 1.069)	0.93 (0.59, 1.47)
≥30	55	0.967 (0.919, 1.018)	1.30 (0.87, 1.94)	1.006 (0.956, 1.061)	0.95 (0.63, 1.45)	27	**0.914 (0.838, 0.996)**	**1.95 (1.05, 3.63)**	0.983 (0.901, 1.071)	1.15 (0.58, 2.27)
Continuous (per kg/m^2)	577	**0.996 (0.992, 0.999)**	**1.04 (1.01, 1.06)**	0.999 (0.995, 1.002)	1.01 (0.99, 1.04)	226	**0.993 (0.989, 0.998)**	**1.05 (1.02, 1.09)**	0.998 (0.993, 1.004)	1.01 (0.97, 1.06)
Recreational physical activity[b]										
Inactive, no walking or other regular exercise	70	0.972 (0.923, 1.023)	1.25 (0.83, 1.89)	0.967 (0.921, 1.016)	1.31 (0.88, 1.95)	28	0.941 (0.879, 1.007)	1.59 (0.95, 2.67)	**0.924 (0.866, 0.985)**	**1.90 (1.13, 3.20)**
Mostly inactive, equivalent to walking about half a mile or less every day	138	0.984 (0.951, 1.018)	1.14 (0.87, 1.49)	0.978 (0.945, 1.012)	1.20 (0.91, 1.58)	59	0.996 (0.934, 1.062)	1.03 (0.63, 1.68)	0.991 (0.928, 1.058)	1.08 (0.64, 1.84)
Somewhat active, equivalent to walking about 1 mile every day	133	1.011 (0.978, 1.046)	0.91 (0.70, 1.19)	1.004 (0.969, 1.041)	0.97 (0.73, 1.29)	53	1.003 (0.942, 1.068)	0.98 (0.60, 1.58)	0.999 (0.939, 1.064)	1.01 (0.61, 1.67)
Active or highly active, equivalent to walking 2 miles or more every day	236	Reference	Reference	Reference	Reference	86	Reference	Reference	Reference	Reference
Gestational weight gain[b]										
<20lbs	95	0.975 (0.934, 1.017)	1.23 (0.87, 1.73)	0.979 (0.937, 1.023)	1.19 (0.83, 1.69)	32	0.940 (0.869, 1.018)	1.60 (0.88, 2.90)	0.941 (0.872, 1.016)	1.63 (0.88, 3.01)
20-29 lbs	160	Reference	Reference	Reference	Reference	72	Reference	Reference	Reference	Reference
30-39 lbs	153	0.980 (0.946, 1.015)	1.18 (0.89, 1.56)	0.980 (0.946, 1.016)	1.17 (0.88, 1.57)	58	**0.930 (0.871, 0.993)**	**1.74 (1.06, 2.86)**	0.939 (0.879, 1.004)	1.66 (0.97, 2.83)
40-49 lbs	85	0.963 (0.925, 1.001)	1.36 (0.99, 1.87)	0.968 (0.928, 1.009)	1.31 (0.93, 1.83)	31	**0.929 (0.863, 0.999)**	**1.76 (0.99, 3.11)**	0.930 (0.863, 1.002)	1.80 (0.97, 3.31)
≥50 lbs	67	**0.943 (0.901, 0.987)**	**1.61 (1.11, 2.32)**	**0.950 (0.906, 0.995)**	**1.52 (1.04, 2.22)**	28	**0.911 (0.832, 0.997)**	**2.04 (1.02, 4.08)**	0.921 (0.846, 1.002)	1.95 (0.98, 3.89)

Maternal pre-pregnancy BMI and GWG[a]										
BMI<25 and <30 lbs	180	Reference	Reference	Reference	Reference	65	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	240	0.977 (0.947, 1.007)	1.21 (0.95, 1.54)	0.979 (0.948, 1.011)	1.19 (0.92, 1.54)	89	**0.908 (0.847, 0.972)**	**2.07 (1.24, 3.45)**	**0.922 (0.861, 0.989)**	**1.91 (1.10, 3.31)**
BMI≥25 and <30lbs	75	0.954 (0.907, 1.004)	1.46 (0.97, 2.19)	0.975 (0.925, 1.029)	1.22 (0.79, 1.89)	39	**0.898 (0.826, 0.977)**	**2.24 (1.23, 4.07)**	0.949 (0.877, 1.028)	1.52 (0.81, 2.84)
BMI≥25 and ≥30 lbs	65	**0.935 (0.892, 0.980)**	**1.71 (1.17, 2.50)**	0.955 (0.912, 1.001)	1.45 (0.99, 2.12)	28	**0.904 (0.820, 0.998)**	**2.13 (1.02, 4.44)**	0.961 (0.871, 1.061)	1.37 (0.62, 3.01)

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).
[b]Adjusted for everything in [a] plus daughter's BMI-for-age percentile between age 5-7 years and interaction between BMI-for-age percentile and centered age at BMI measure.
[c]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).
[d]Adjusted for everything in [b] plus daughter's BMI-for-age percentile between age 5-7 years and interaction between BMI-for-age percentile and centered age at BMI measure

Table 3.5. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal pre-pregnancy BMI, recreational physical activity during pregnancy and GWG stratified by breast cancer family history

	Overall cohort						***Girls <8 years at baseline***					
	BCFH+			BCFH-			BCFH+			BCFH-		
	N	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)
Maternal pre-pregnancy BMI[a]												
<18.5	22	1.021 (0.950, 1.098)	0.85 (0.48, 1.51)	24	**1.076 (1.025,1.129)**	**0.54 (0.36, 0.82)**		*Those with BMI<18.5 are in referent group due to small numbers				
18.5 to <25	340	Reference	Reference	312	Reference	Reference	87	Reference	Reference	76	Reference	Reference
25 to <30	90	1.042 (0.987, 1.101)	0.72 (0.47, 1.10)	84	**0.946 (0.907, 0.986)**	**1.59 (1.12, 2.27)**	23	1.003 (0.938,1.072)	0.98 (0.54, 1.76)	21	0.953 (0.853, 1.065)	1.37 (0.66, 2.83)
≥30	41	0.977 (0.920, 1.037)	1.21 (0.75, 1.95)	50	0.960 (0.912, 1.011)	1.41 (0.92, 2.15)	13	0.957 (0.881,1.040)	1.47 (0.72, 3.02)	16	0.893 (0.764, 1.045)	2.08 (0.77, 5.59)
Continuous (per kg/m^2)	493	1.000 (0.996, 1.003)	1.00 (0.98, 1.03)	470	**0.994 (0.991, 0.998)**	**1.05 (1.02, 1.08)**	123	0.997 (0.994,1.001)	1.02 (0.99, 1.05)	113	0.991 (0.981, 1.001)	1.06 (1.00, 1.13)
Recreational physical activity[b]												
Inactive, no walking or other regular exercise	68	0.984 (0.936, 1.034)	1.14 (0.77, 1.69)	53	0.964 (0.911, 1.020)	1.37 (0.84, 2.21)	19	0.934 (0.866,1.006)	1.86 (0.96, 3.61)	11	0.896 (0.784, 1.025)	2.06 (0.85, 4.96)
Mostly inactive, equivalent to walking about half a mile or less every day	111	1.001 (0.955, 1.050)	0.99 (0.68, 1.44)	98	1.005 (0.970, 1.041)	0.96 (0.71, 1.30)	30	1.002 (0.936,1.073)	0.98 (0.53, 1.82)	33	1.023 (0.899, 1.163)	0.86 (0.37, 2.01)
Somewhat active, equivalent to walking about 1 mile every day	102	0.970 (0.937, 1.004)	1.27 (0.96, 1.68)	114	**1.040 (1.004, 1.077)**	**0.72 (0.53, 0.97)**	27	1.001 (0.938,1.067)	1.00 (0.55, 1.79)	27	1.001 (0.890, 1.125)	1.00 (0.46, 2.16)
Active or highly active, equivalent to walking ≥2 miles every day	212	Reference	Reference	205	Reference	Reference	47	Reference	Reference	42	Reference	Reference
Gestational weight gain[b]												
<20lbs	79	1.004 (0.957, 1.054)	0.97 (0.65, 1.43)	70	0.966 (0.920, 1.015)	1.34 (0.89, 2.01)	19	0.985 (0.908,1.070)	1.14 (0.54, 2.42)	15	0.872 (0.750, 1.013)	2.50 (0.93, 6.73)
20-29 lbs	163	Reference	Reference	140	Reference	Reference	38	Reference	Reference	36	Reference	Reference
30-39 lbs	123	0.980 (0.940, 1.021)	1.18 (0.85, 1.64)	124	0.974 (0.938, 1.011)	1.25 (0.92, 1.71)	30	0.969 (0.900,1.023)	1.46 (0.81, 2.65)	32	**0.884 (0.785, 0.996)**	**2.28 (1.03, 5.05)**
40-49 lbs	67	**0.938 (0.893, 0.985)**	**1.67 (1.13, 2.48)**	72	0.994 (0.955, 1.035)	1.05 (0.75, 1.48)	21	**0.909 (0.849,0.973)**	**2.39 (1.24, 4.63)**	11	1.040 (0.831, 1.302)	0.77 (0.17, 3.42)
≥50 lbs	50	0.988 (0.938, 1.040)	1.10 (0.73, 1.67)	57	**0.939 (0.891, 0.990)**	**1.69 (1.10, 2.61)**	12	0.998 (0.903,1.103)	1.02 (0.41, 2.55)	17	**0.823 (0.713, 0.950)**	**3.66 (1.36, 9.87)**

Maternal pre-pregnancy BMI and GWG[a]												
BMI<25 and <30 lbs	165	Reference	Reference	143	Reference	Reference	38	Reference	Reference	29	Reference	Reference
BMI<25 and ≥30 lbs	189	0.997 (0.966, 1.029)	1.02 (0.79, 1.32)	190	0.975 (0.941, 1.009)	1.24 (0.93, 1.65)	47	0.963 (0.898,1.031)	1.41 (0.76, 2.59)	46	**0.826 (0.722, 0.944)**	**3.74 (1.50, 9.33)**
BMI≥25 and <30lbs	77	1.049 (0.989, 1.113)	0.68 (0.43, 1.09)	67	**0.921 (0.873, 0.971)**	**1.98 (1.29, 3.05)**	19	0.996 (0.920,1.078)	1.04 (0.51, 2.10)	22	**0.792 (0.675, 0.928)**	**5.00 (1.75,14.30)**
BMI≥25 and ≥30 lbs	51	0.957 (0.903, 1.013)	1.43 (0.89, 2.29)	63	**0.944 (0.900, 0.989)**	**1.62 (1.10, 2.39)**	16	0.914 (0.838,1.008)	2.23 (0.93, 5.33)	14	0.908 (0.746, 1.105)	1.94 (0.51, 7.42)

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree) in full cohort. In girls <8 years, adjusted for maternal education only.

[b]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other), maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous) in full cohort. In girls <8 years, adjusted for maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).

Chapter 4. Infant growth and the onset of breast development in the LEGACY Girls Study cohort

ABSTRACT

Background: Rapid weight gain during infancy is associated with earlier onset of breast development. To date, the epidemiologic evidence has come from cohorts of girls that are not enriched for breast cancer family history (BCFH). Since earlier onset of puberty is associated with increased breast cancer risk, we examined the associations between size and growth during infancy and age at breast development, and whether these associations varied by BCFH, using a prospective cohort of girls in which approximately half are at increased risk of breast cancer due to their family history.

Methods: We abstracted weight and length data from medical records for 255 girls that had at least two anthropometric measures between 2 weeks and 16 months of age. Including birth size from either the medical record or maternal report, we then used individual constrained quadratic splines to interpolate weight and length at 2, 4, 6, 9 and 12 months of age for each girl, ages that correspond to recommended postnatal physician visits (mean number of measures for interpolation, including birth data=7.3, range = 3-22). We examined growth velocity, defined as the change in weight-for-age (WAZ) and length-for-age (LAZ) Z-scores between two time points, calculated in reference to the 2000 CDC growth charts, as exposures of interest. Using longitudinal Weibull models, we assessed the associations between rates of growth in weight and length during multiple windows from birth to one year and age at breast development, defined as maternal report of Tanner stage ≥2. We examined modification by BCFH and mediation by daughters' childhood BMI in adjusted models.

Results: Faster growth in weight and length between birth and one year were associated with earlier age at breast development in models adjusted for gestational age, race/ethnicity, maternal pre-pregnancy BMI and gestational weight gain (HR=1.20, 95% CI 1.02-1.41 for 1 SD increase in WAZ from 0-12 months and HR=1.15, 95% CI 1.00-1.33 for 1 SD increase in LAZ from 0-12 months). When we examined smaller age intervals within infancy, faster growth in weight and length between 2-4 months of age were associated with approximately a 50% increased rate of breast development, respectively (HR=1.54, 95% CI 1.13-2.12 for a 1 SD increase in WAZ from 2-4 months and HR=1.56, 95% CI 1.16-2.08 for 1 SD increase in LAZ from

2-4 months). Similar patterns of associations for growth in weight and length were observed from 6-9 months of age, but not in the other infancy time periods. Associations were similar when we excluded preterm, low birthweight and non-singleton infants, suggesting that the associations are not driven by catch-up growth in infants that are small at birth. Associations were similar after adjustment for pre-pubertal BMI in the subset of girls with available data and did not vary by BCFH.

Conclusions: We observed that faster rates of growth in both weight and length during infancy are associated with earlier onset of breast development in a prospective cohort of girls enriched for BCFH. Associations between rate of weight gain and rate of change in length were specific to two time periods within infancy, 2-4 months and 6-9 months, suggesting that these may be sensitive periods for exposures in the early-life environment to affect breast development. Our findings suggest that slow growth in weight and length during infancy may delay breast development, even in girls at an increased risk of breast cancer due to their family history.

4.1 Background

Modifiable factors that are associated with pubertal timing could be a target for breast cancer primary prevention efforts starting early in life, when maximum impact is possible.[4,5] Girls who are overweight in childhood have an earlier age at breast development and menarche.[60,76,140,175,259] High birthweight tracks to larger body size in childhood, as does rapid postnatal growth.[63–66] This may explain why both high[76,77] and low birthweight,[70–72] which is associated with rapid postnatal weight gain,[228] have both been associated with earlier age at menarche in previous studies. Some studies found that the association between birthweight and pubertal timing is modified by postnatal growth,[71,76,176] suggesting that growth trajectories across critical periods may be more important than body size at specific time points in programming pubertal timing. Studies that have examined weight gain between birth and two years have consistently observed earlier age at breast development[73,75] and menarche[34,72,76,77,190] in girls with rapid infant weight gain. However, studies vary in terms of the time period within this two-year window that is the most important to pubertal timing.[35,73,75,77,116]

Infancy is a dynamic period of growth. Most babies triple their birthweight by their first birthday.[25] Given the large degree of variability in growth patterns during this time period, the first 12 months after birth may be a vital time period for setting growth trajectories and programming pubertal timing. There have also been secular trends in infant weight and weight gain over time, which parallel the secular decrease in pubertal onset in girls. Infants from more recent birth cohorts experience a more rapid rate of weight gain and are larger throughout infancy than those in birth cohorts from earlier in the 20th century.[68] Infancy may also be a critical period of development for the breast. Infants experience an activation of the hypothalamic-pituitary-gonadal (HPG) axis that is termed mini-puberty.[213] Endogenous hormone levels peak in female infants the first 2-4 months after birth, some of which reach pubertal levels, and they remain elevated for much of the first year before decreasing until the next peak during puberty.[212,213] Both male and female infants are born with breast tissue, which later regresses. In females, breast tissue is present for longer than in males and is associated with estradiol levels,[214] suggesting that infancy may be a biologically important time period for the breast in females.

To date, previous studies examining infant growth and age at breast development were conducted in cohorts of girls at average-risk of breast cancer. We previously observed earlier breast development in girls with a breast cancer family history (BCFH).[54] Since earlier onset of breast development is associated with increased breast cancer risk,[41] it is important to determine whether early-life factors that affect timing of breast development are modified by underlying susceptibility for breast cancer. We investigated whether rates of weight and height gain during multiple time periods within infancy were associated with the timing of breast development in the LEGACY Girls Study, a prospective cohort of girls in which approximately half are at increased risk of breast cancer due to their family history,[57] and whether these associations varied by BCFH.

4.2 Methods

4.2.1. Study population

The LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study is a prospective cohort study of 1040 girls recruited at five study sites in the U.S. (New York City, NY;

Philadelphia, PA; Salt Lake City, Utah; San Francisco Bay Area, CA) and Canada (Toronto, ON) between 2011 and 2013 (for more details, see [57]). The girls were primarily between the ages of 6 and 13 years at recruitment, and half had a BCFH, defined as a report of breast cancer in a first- or second-degree relative by the participating mother/guardian at baseline. Younger siblings of cohort members can also join when they reach 6 years of age. The participating guardian at baseline was the biological mother for 97% of LEGACY girls,[57] so we will refer to participating guardians as mothers moving forward. Mothers provided written informed consent for themselves and for their daughters, and daughters provided written informed assent according to institutional standards. The study was approved by the institutional review boards of the collaborating institutions.

Willing LEGACY mothers signed an authorization form at baseline to allow the release of medical record information from the pediatrician's office of their child to the LEGACY Girls Study. We obtained medical record data for 82% of the cohort; however, the records included measurements prior to 16 months of age for 283 girls (33% of those with medical record data). For this analysis, we abstracted height and weight data from medical records between two weeks and 16 months of age and used measures of birthweight and birthlength from either the medical record or maternal report at baseline, since not all medical records include birth measurements. For girls with at least three measures of height or weight between birth and 16 months, we interpolated height and weight at specific time points. The final analytic sample included 255 girls with infancy data and prospective follow-up data through August 2016 from 216 families.

4.2.2. Data collection

Infant Growth Assessment. A LEGACY staff member at the New York site abstracted age at measurement, height and weight information from medical record data. We abstracted measurements directly from growth charts if the medical record was not available. We converted height and weight data from growth charts to centimeters and kilograms, respectively. Since girls had varying numbers of measurements assessed at different time points, we used individual quadratic constrained smoothing splines to interpolate measures for each girl at 2 months, 4 months, 6 months, 9 months and 1 year of age as these time points correspond with recommended postnatal clinician visits (see **Supplemental Figure**

4.1 for example smoothing splines for two individuals).[250] We included birthweight and birthlength, as reported by the mother at baseline or abstracted from the medical record, in the interpolation, along with all measures of length and/or weight available from the medical records between 2 weeks and 16 months of age. We used data measured within 100 days of the target time point in the interpolation. Weight and height data were interpolated separately, and girls with less than 3 measures between birth and 16 months were not included in the interpolation. A small subset of girls was missing data on birthlength (N=37) and birthweight (N=4), but had ≥3 infancy measures available from medical records. For these girls, we used the interpolated measures of weight and length at birth. For all other girls, we used the maternal report of birthweight and birthlength, and not the interpolated data.

We calculated Z-scores and percentiles for weight-for-age, length-for-age and weight-for-length measures based on both the 2000 Centers for Disease Control and Prevention (CDC) growth charts and the World Health Organization (WHO) growth charts for female infants from birth to 24 months using SAS macros available from the CDC.[260,261] The WHO growth charts, which reflect optimal infant growth and are based on longitudinal data from breastfed infants in six countries,[262] are recommended for use by U.S. pediatricians by the CDC.[260] The CDC growth charts are based on birth certificate and cross-sectional NHANES data from the 1980s and 1990s, and include both breastfed and formula-fed infants.[262] We used the 2000 CDC growth charts as the reference in the primary analyses, since this reference was used in a prior study of infant growth and pubertal timing in the North Carolina Infant Feeding Study[75] and our study population included both breastfed and formula-fed infants. We used the 2006 WHO growth charts in sensitivity analyses to examine how the choice of reference data affected the main study findings. Extreme values based on Z-scores are automatically flagged by the SAS programs that calculate the standardized measures as biologically implausible (see [260,261] for the cut-offs used to identify the extreme values by measure and reference). The interpolated weights were within the expected range, but 1.2% of the interpolated height values were flagged as extreme, including 11 of the interpolated birthlength values. We examined the individual interpolation splines for these observations, which had sparse data to contribute to the interpolation at the time points that yielded extreme values. We excluded these observations from the analyses, leading to a final sample size of 255 girls with infancy data. Of these girls, 5.9% had 3 measures

only, 5.1% had 4 measures, 7.5% had 5 measures, and the remaining 81.5% had 6 or more measures that were used in the interpolation (**Supplemental Figure 4.2**).

Pubertal outcomes. We assessed breast development through the Growth and Development Questionnaire completed every 6 months by mothers. Mothers assessed breast development using the picture-based Sexual Maturation Scale (SMS)[238] showing the five Tanner stages[100] in addition to the non-picture-based Pubertal Development Scale (PDS),[240] which also asked the mother to report the age that they first noticed their daughters' breast development for girls whose development had already started. Recalled age was reported as age in years and months at baseline, and in half-year intervals at subsequent visits. Tanner stage (TS) 2 indicates the onset of breast development.[100] We previously found maternal reports of breast onset using TS to be highly reliable (kappa=0.73) and valid (sensitivity=77%, specificity=94%) in a subset of LEGACY girls that also had clinical TS data.[239] We used the first maternal report of TS≥2 as the primary outcome and the first maternal report of development based on PDS in sensitivity analyses.

Covariates. Mothers completed an early-life questionnaire at their daughters' baseline visit that included detailed information about their pregnancy. These questions were developed and used previously in the Nurses' Health Study cohort.[24] We calculated maternal pre-pregnancy BMI from mothers' self-reported height and pre-pregnancy weight. Gestational weight gain (GWG) was recorded as <10 lbs, 10-14 lbs, 15-19 lbs, 20-29 lbs, 30-39 lbs, 40-49 lbs, and 50 or more lbs (**Appendix C.1** for more information on the early-life variables). Since we observed in **Chapter 3** that daughters of women with a pre-pregnancy BMI ≥25 and who gained ≥30 lbs during pregnancy had the highest risk of early breast development compared with daughters of women with a BMI<25 and GWG<30lbs, we controlled for this four-category composite variable of maternal pre-pregnancy BMI and GWG as a confounder in the adjusted analyses. Mothers provided information about all pregnancies lasting 6 months or longer, including the pregnancy outcome and date of that the pregnancy ended. We used this information to determine the birth order of the LEGACY daughter and the type of gestation (singleton or multiple). We calculated gestational age in weeks from the length that the pregnancy lasted, in weeks, months, or days before/after due date, as reported by mothers. Mothers reported whether they fed their daughter breastmilk and if so, for how long.

Mothers also reported whether they ever fed their daughter formula for one month or longer, and if so, for how long. We used this information to derive a variable for type of feeding (breastfed only, mixed feeding, formula fed only). If the participating guardian was not the biological mother, we collected pregnancy information from the participating relative when possible (i.e. from participating fathers). In the 255 girls in this analysis, only 4 girls participated with a guardian other than her biological mother; these girls were included in the analyses if they had available covariate data.

In addition to the early-life factors above, we considered race/ethnicity and maternal education as potential confounders. Mothers reported the race/ethnicity of the LEGACY daughter at baseline, and categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, or other (predominantly mixed race/ethnicity). For this analysis, we combined the non-Hispanic black and mixed race/ethnicity groups due to small cell counts and similar associations with the timing of breast development. Mothers reported their highest level of education achieved at baseline, which we categorized as some college, vocational or technical school or less, Bachelor's degree, and graduate degree. We considered BCFH (history of breast cancer in a first-or second-degree relative) as a modifier of the associations between early-life exposures and age at breast development.

At each study visit, trained research staff measured the height and weight of the girls at least twice using standardized instruments; we averaged these measures for the analysis. We also abstracted height and weight prior to baseline from the medical records and growth charts obtained from girls' pediatricians. We calculated age-specific height, weight, and BMI percentiles based on the 2000 CDC growth charts.[241] Since we considered pre-pubertal body size as a potential mediator, we used body measurements at age 5-7 years when available from the medical record or measurements from the first clinic visit for girls age 5-7 years at baseline. We used <8 years as the cut-off to define pre-puberty since less than 5% of LEGACY girls had experienced the onset of breast development, defined as breast TS≥2, by 8 years of age. Of the 255 girls included in the analysis, 185 (72.5%) had a BMI measure between 5-7 years and were included in this mediation analysis. We classified girls with a BMI-for-age percentile ≥85 as overweight and those less than the 85th percentile as average weight.

4.2.3. Statistical analysis

We examined the distribution of early-life characteristics and baseline covariates in girls with infant growth data and examined differences with the subset of the girls without infancy data. We then used histograms to examine the variability in size measures (weight-for-age, length-for-age, and weight-for-length Z-scores at birth, 2 months, 4 months, 6 months, 9 months and 12 months) and growth measures (change in Z-scores between subsequent time periods) calculated using both the CDC and WHO references. We plotted the mean weight-for-age, length-for-age and weight-for-length Z-scores using both references in order to visually examine the average growth patterns within the cohort. We also plotted the mean weight-for-age and length-for-age Z-scores by maternal pre-pregnancy BMI and GWG group in order to examine whether infant growth patterns differed by maternal weight patterns. We then examined the Pearson correlation matrices between weight-for-age Z-score at birth and changes in Z-score during each time interval, and did the same for length-for-age. We assessed the correlations between changes in weight-for-age Z-scores and changes in length-for-age Z-scores at each time period.

We first examined the associations between size at each time point, assessed by the weight-for-age and length-for-age Z-score, and the timing of breast development in order to identify whether the inverse association between pre-pubertal weight and height and age at breast development extends into infancy. We then examined rates of weight and length gain throughout the infancy period as the main exposures of interest. For these growth models, we defined the exposure of interest as the change in Z-score in the size measure of interest between two time periods (i.e. Weight-for-age Z-score at 4 months – weight-for-age Z-score at 2 months) as a continuous measure. In addition, we categorized the continuous change in Z-score measures into patterns of rapid, stable and slow growth. We defined rapid growth as an increase in Z-score of greater than 0.67, slow growth as a decrease in Z-score of greater than 0.67, and stable growth as a change of less than 0.67 (the referent group). A change of 0.67 standard deviations corresponds to an increase of a major percentile on standard growth charts (i.e. a change from the 25th to the 50th percentile), and this cut-off is commonly used in the infant growth literature.[191,263]

We assessed associations between infant growth and the age at breast development and menarche using longitudinal parametric Weibull models with age as the time scale to allow for left, interval

and right censoring. In the primary analyses, girls whose mother reported that they had already experienced the onset of breast development (TS≥2) at the first completed Growth and Development questionnaire were left-censored at age at questionnaire completion. Girls whose mothers reported TS≥2 at subsequent visits were interval-censored, with the daughters' age at the last visit where the mother reported TS1 as the beginning of the interval and the daughters' age at the first visit where the mother reported TS≥2 as the end of the interval. Girls who had yet to experience the onset of breast development during follow-up were right-censored at last study visit where mom reported TS1. Since some families had more than one participating daughter, we used cluster-robust standard errors to account for correlation within families.

We ran a series of unadjusted models regressing the age at breast development on rates of growth in weight and length during infancy, starting with wide intervals examined in previous studies and adding additional time points in subsequent models. First, we examined the full infancy period as the change in Z-score between birth and 12 months. Second, we considered growth from 0-6 months and 6-12 months. Third, we examined all available intervals (0-2 months, 2-4 months, 4-6 months, 6-9 months and 9-12 months). We adjusted all models for weight-for-age and length-for age Z-scores at birth and changes in prior intervals. For example, we adjusted models examining change in weight-for-age Z-scores from 2-4 months for weight-for-age Z-score at birth and change in Z-score from birth to 2 months. We examined weight-for-age and length-for-age models independently, and also ran models that included both weight and length measures. In multivariable models, we adjusted for gestational age in weeks, maternal pre-pregnancy BMI and GWG group, and race/ethnicity. We did not adjust for other early-life characteristics such as birth order, multiple gestation, gestational diabetes, gestational hypertension and toxemia/pre-eclampsia since these factors were not independently associated with breast development. For parsimony, we did not adjust for maternal education since it was not associated with age at breast development in this subset. Since growth rates differ in infants that are exclusively fed breastmilk compared with formula-fed infants,[68,264,265] we also considered adjustment for infant-feeding. While type of feeding could be a confounder of the association between growth and pubertal timing, it could also be a mediator if mothers change the type of feeding based on how their child is growing.[266] For this reason, we present models unadjusted for infant feeding; however, associations between rates of weight and length gain were similar

when adjusted for infant-feeding type, categorized as breastfed only compared with some formula (data not shown). We did not examine exclusively formula-fed separately due to small numbers in this group.

We examined the potential interaction between weight-for-age and length-for-age Z-scores at birth and growth measures through cross-product terms. Since infants that are growth-restricted in utero are more likely to experience rapid weight gain in infancy, we ran sensitivity analyses excluding low birth weight (<2.5 kilograms), preterm (<37 weeks) and non-singleton girls to examine the extent to which the infant growth results were driven by the extremes of the birthweight distribution, which may reflect a regression-to-the-mean effect.[227]

We examined the presence of mediation by daughters' pre-pubertal body size by adding the BMI-for-age percentile and an interaction for BMI-for-age percentile and age at BMI measurement, centered at the mean, to adjusted models in the subset of girls with pre-pubertal BMI measures (N=185). We also conducted sensitivity analyses excluding girls who were overweight at baseline (BMI-for-age percentile ≥85) to examine whether findings in the overall cohort were driven by earlier puberty in overweight girls (N=177). We used baseline anthropometric data instead of pre-pubertal data to define this subset in order to preserve sample size since studies have shown that BMI tracks during childhood.[267,268]

We formally tested for effect measure modification by BCFH by adding a cross-product term between the exposure of interest and BCFH to adjusted models and assessed statistical significance using the Wald test.

We conducted several sets of additional analyses to examine the potential impact of selection bias and information bias in the assessment of the exposure and outcome on the main study findings. We re-ran the primary analyses using inverse probability weighting to adjust for potential bias relating to the subset selection of the girls with infancy data.[269] In these analyses, we first regressed an indicator variable for being in the infancy subset (N=255) on early-life and baseline variables to predict the probability of having infant growth data. We then weighted the survival analyses by the inverse of the probability of being sampled and compared these results with the unweighted findings. In order to examine the influence of the choice of growth chart reference data to calculate the rates of weight and length change, we ran sensitivity

analyses using the 2006 WHO growth charts as the reference and compared these results with the primary analyses using the 2000 CDC growth charts as the reference. Similar to **Chapter 3**, we then ran several sensitivity analyses to examine how robust the results were to differences in outcome assessment. We imputed the recalled age at breast development from the PDS as though it were observed for left-censored girls (37% of girls in this subset experienced the onset of breast development prior to cohort entry based on mom's report of TS≥2 at first growth and development questionnaire). We also used the PDS to define breast onset instead of TS. Finally, we excluded girls with inconsistent Tanner staging by maternal report (mothers reported a regression to TS1 at the visit after the first report of TS≥2; approximately 8.6% of girls). We conducted the analyses using SAS 9.4 and STATA 15.1.

4.3 Results

4.3.1. Participant characteristics

Table 4.1 describes the baseline and early-life characteristics of the LEGACY cohort by the availability of infant growth measures. Compared with girls without infancy data (N=813), girls included in the infancy analyses (N=255) were younger at cohort entry (mean age 8.9 vs 9.7 years, respectively) and a smaller proportion were overweight at baseline. Girls from the New York and Ontario sites were over-represented in the infancy subset, while Hispanic girls were under-represented. The mean maternal pre-pregnancy BMI was also lower in girls with infancy data, with a smaller proportion of girls whose mothers were obese prior to pregnancy compared with girls without infancy data. The mean birthweight was slightly higher in girls with infancy data (3370g vs 3270g), and a smaller proportion of girls were born preterm.

4.3.2. Descriptive analyses of weight and height gain during infancy

The mean weight-for-age Z-score (WAZ) at birth was -0.01 when using the 2000 CDC growth charts as the reference population (**Table 4.2**). The mean WAZ increased until 4 months of age and then declined, with a mean WAZ of -0.10 at 12 months. While the overall change in WAZ from 0-12 month was negative with a mean of -0.06, there was substantial variation when weight gain was broken up into smaller age intervals. Compared with the reference population, the LEGACY girls had a faster rate of weight gain in

early infancy, particularly from 0-2 months, and then a slower rate of weight gain from 4 months onward. However, this pattern reversed when the 2006 WHO growth charts were used as the reference population (**Supplemental Figure 4.3**). LEGACY girls weighed more at birth (mean WAZ=0.24) but had a similar weight at 2 months (WAZ=-0.04) compared with the WHO reference, reflecting relatively slower weight gain in early infancy. The mean WAZ then increased from 2 months onward, so at 12 months the LEGACY girls weighed more on average than the WHO reference (mean WAZ=0.41) due to relatively faster rates of weight gain. Although the mean change in WAZ differed depending on the growth reference standard used, the variance of the change in WAZ for each interval was similar. The distribution of the change in WAZ in early infancy was shifted to the right when standardized to the 2000 CDC growth charts as opposed to the WHO growth charts (relatively faster weight gain), while distribution in later infancy using the CDC charts was shifted to the left (relatively slower weight gain) (**Supplemental Figure 4.4**). The shift in the distribution affected the percent of girls that were characterized as having "rapid" and "slow" weight gain patterns, using a cut-off of >0.67 or <-0.67 change in WAZ, based on each reference standard. For example, using the CDC growth charts, 38.4% of girls were categorized as having rapid weight gain, 53.3% as stable and 8.2% as slow weight gain from 0-2 months. Using the WHO growth charts, 12.9% were categorized as rapid, 53.7% as stable and 33.3% as slow weight gain. For this reason, we used continuous measures of change in Z-scores in the analyses unless there was evidence of non-linear associations based on sensitivity analyses using the categorical pattern variables.

The mean length-for-age Z-score (LAZ) at birth using the CDC reference was 0.45 and increased to 0.63 by 12 months of age (**Table 4.2**). Relative to the CDC reference, the LEGACY girls had a faster rate of length gain from 2-4 months of age, while the average rate of length gain in the other age intervals were similar to the reference population. Similar to the weight-for-age data, there were some differences in the pattern of mean LAZ depending on the reference standard used. Relative to the WHO growth charts, LEGACY girls were longer at birth (mean LAZ=0.9) and grew more slowly in length from 0-2 months (**Supplemental Figure 4.5**). From 2 months onward, the mean LAZ using the WHO reference increased. By 12 months, the LEGACY girls were taller on average compared with both the CDC and WHO reference populations.

The mean weight-for-length Z-scores (WFL) were similar using the CDC and WHO reference data from birth to 4 months and then diverged in late infancy (**Supplemental Figure 4.6**). Generally, the LEGACY girls had a lower weight-for-length in early infancy compared with both reference populations. From 4-12 months of age, the mean WFL was stable when compared with the CDC reference population, while the mean WFL continued to increase in comparison with the WHO reference population.

4.3.3. Correlations between change in WAZ and LAZ measures at different ages

WAZ at birth was negatively correlated with change in WAZ at each time interval, but the strength of the correlation decreased over time (**Table 4.3**). We observed the same pattern for LAZ at birth and change in subsequent intervals (**Table 4.4**). Change in WAZ between intervals were not highly correlated with each other, and there were no statistically significant correlations in change in LAZ between intervals. Change in WAZ was positively correlated with change in LAZ within the same interval (Pearson correlation coefficients of 0.24-0.27), with the exception of growth from 9-12 months (**Table 4.5**). Measures of size at each interval were more strongly correlated with each other than growth measures, with correlations for WAZ in subsequent intervals between 2-12 months ranging from 0.63-0.93 and correlations for LAZ ranging from 0.50-0.86 (data not shown).

4.3.4. Association between infant size and the onset of breast development

When we considered WAZ without adjustment for LAZ, higher WAZ at each time point was associated with earlier onset of breast development, adjusted for gestational age, maternal pre-pregnancy BMI, GWG and race/ethnicity (**Supplemental Table 4.1**). We observed similar associations between higher LAZ at each time point and earlier onset of breast development in models unadjusted for WAZ. When we mutually adjusted for WAZ and LAZ, associations were slightly attenuated but still supported earlier breast development in girls that were taller and heavier by late infancy.

4.3.5. Association between infant growth and the onset of breast development

Faster weight gain from 0-12 months was associated with earlier age at breast development (HR=1.32, 95% CI 1.05, 1.65 adjusted for WAZ at birth only; **Supplemental Table 4.2**). After adjusting for

gestational age at birth, race/ethnicity, maternal pre-pregnancy BMI and GWG, a one-unit increase in WAZ between birth and 1 year of age was associated with a 20% increased risk of earlier breast development (HR=1.20, 95% CI 1.02, 1.41; **Table 4.6**). When early and late infancy were considered separately, faster weight gain from 0-6 months (adjusted HR=1.15, 95% CI 0.99, 1.34) and 6-12 months (adjusted HR=1.25, 95% CI 0.98, 1.60) were both associated with earlier age at breast development. However, when we considered smaller age intervals, the association between rate of weight gain and onset of breast development was limited to change in WAZ between 2-4 months and 6-9 months (HR=1.54, 95% CI 1.13, 2.12 for one-unit increase in change in WAZ from 2-4 months and HR=1.63, 95% CI 1.09, 2.42 for one-unit increase in change in WAZ from 6-9 months, respectively). No associations were observed between rate of weight gain during the other time periods and timing of breast development.

Faster gain in length from 0-12 months was also associated with earlier age at breast development (adjusted HR=1.15, 95% CI 1.00, 1.33), and this association was driven by gain in length in the first 0-6 months (adjusted HR=1.21, 95% CI 1.03, 1.41) (**Table 4.6**). When we considered smaller age intervals, 2-4 months was the only time period when change in LAZ had a statistically significant association with age at breast development (adjusted HR=1.56, 95% CI 1.16, 2.08).

In models mutually adjusted for weight and length, effect estimates were attenuated but still suggested earlier development in girls with faster growth in weight and length from birth to 12 months (**Table 4.6**). Both rate of weight gain and rate of length gain from 2-4 months were associated with the timing of breast development in mutually adjusted models (HR=1.40, 95% CI 1.00, 1.96 for change in WAZ and HR=1.50, 95% CI 1.10, 2.04 for change in LAZ, respectively). The association between rate of weight gain from 6-9 months and timing of breast development was similar after adjustment for growth in length. The inference was the same when we used the 2006 WHO growth charts to calculate Z-scores instead of the 2000 CDC growth charts (**Supplemental Table 4.3**).

When we examined patterns of growth in weight and length from 2-4 months and 6-9 months, we observed similar associations in both time periods (**Figure 4.1**). Girls with slow weight gain had a decreased risk of early breast development compared to girls with stable weight gain (HR=0.53, 95% CI 0.32-0.90 for 2-4 months and HR=0.44, 95% CI 0.28-0.70 for 6-9 months), while girls with rapid gain in length had an

increased risk of early breast development compared to girls with stable length gain (HR=1.71, 95% CI 1.08-2.69 for 2-4 months and HR=1.96, 95% CI 1.08-3.56 for 6-9 months). Change in weight-for-length Z-scores were negative on average over the interval both for girls with slow weight gain and for girls with rapid length gain, which may explain why rates of change in weight-for-length Z-score in these intervals were not associated with age at breast development (**Supplemental Table 4.4**).

The inference regarding infant weight and length gain and onset of breast development were similar when we excluded preterm, low birthweight (<2500g) and non-singletons (**Supplemental Table 4.5**), suggesting that these associations hold in the majority of births and are not driven by the extremes of birth size. WAZ at birth did not modify the associations between rates of infant weight gain and timing of breast development ($p>0.05$ for all interaction terms). LAZ at birth did not modify the associations between growth in length after 2 months and onset of breast development. However, there was a statistically significant interaction between LAZ at birth and change in LAZ from 0-2 months ($p=0.04$), suggesting that faster rates of length gain from 0-2 months may be associated with earlier breast development in girls that were long at birth (data not shown).

4.3.6. Mediation by pre-pubertal body size

Similar patterns of association between weight and length gain during infancy and timing of breast development were observed when we restricted the analyses to girls with a BMI-for-age <85th percentile at baseline (**Supplemental Table 4.6**). In models mutually adjusted for weight and length, effect estimates for rate of length gain were similar to models without adjustment for weight gain, but rates of weight gain were slightly attenuated. In the subset of girls with pre-pubertal BMI data available, associations between rates of weight and length gain from 2-4 months and 6-9 months were attenuated and no longer statistically significant compared with all girls with infancy data (**Supplemental Table 4.7**). However, patterns were similar in this subset and adjustment for BMI-for-age percentile and the interaction between BMI-for-age percentile and age at BMI measurement had a negligible effect on the measures of association. Overall, these analyses suggest that the associations between infant growth and onset of breast development are not fully mediated by childhood body size.

4.3.7. Modification by breast cancer family history

BCFH did not modify the associations between rates of change in weight and length during infancy and timing of breast development (p for interaction>0.05 for all cross-product terms).

4.3.8. Maternal pre-pregnancy BMI, GWG and patterns of infant growth

Since we found that patterns of maternal pre-pregnancy BMI and GWG were associated with the timing of breast development in **Chapter 3**, we examined whether the mean weight-for-age and length-for-age Z-scores during infancy differed by maternal body size and GWG. Daughters of women who gained ≥30lbs during pregnancy weighed more at birth than daughters of women who gained <30lbs (**Supplemental Figure 4.7**). Daughters of women who were overweight prior to pregnancy and gained ≥30lbs weighed more throughout infancy than the other 3 groups, but their pattern of weight gain was similar to daughters of women who were not overweight prior to pregnancy. Daughters of women who were overweight prior to pregnancy but gained <30lbs had a slightly different weight gain trajectory. While all groups experienced an increase in WAZ from 0-2 months, daughters of women who were overweight prior to pregnancy but gained <30lbs were the only group that continued to experience an increase in average WAZ from 2-4 months as well. This group also had the smallest decline in average WAZ from 6-12 months, so that by 12 months of age their average WAZ was similar to daughters of women who were overweight prior to pregnancy and gained ≥30lbs, which may reflect catch-up growth after intrauterine growth restriction in this group. Patterns of LAZ were also different in this group, which had the highest LAZ at birth, compared with the other three groups (**Supplemental Figure 4.8**). Infant growth did not mediate the association between maternal pre-pregnancy BMI, GWG and the timing of breast development (data not shown). Daughters of women who were overweight prior to pregnancy and gained more than 30lbs experienced breast development at a faster rate than daughters of women with a BMI<25 who gained <30lbs after adjustment for rate of growth in weight and height from 0-12 months (HR=1.66, 95% CI 0.97, 2.85).

4.3.9. Sensitivity analyses for the association between infant growth and the onset of breast development

Although there were differences in the baseline and early-life characteristics between girls included in the infancy analyses and those that did not have infancy data (**Table 4.1**), the associations between rates of weight and length gain during infancy and timing of breast development were similar in models that accounted for these differences using inverse probability weighting (**Supplemental Table 4.8**). In addition, the association between faster gain in length from 6-9 months and earlier onset of breast development was statistically significant in the weighted analysis (adjusted HR=1.49, 95% CI 1.12, 1.98).

The associations between infant growth and timing of breast development were sensitive to differences in outcome assessment. The associations between rates of weight gain and onset of breast development were no longer statistically significant when girls with inconsistent Tanner staging were excluded from the models, but the point estimates were only slightly attenuated (**Supplemental Table 4.9**). When we imputed the recalled age at breast development for left-censored girls, rates of weight gain during infancy were not associated with the onset of breast development. In both of these sensitivity analyses, growth in length from 2-4 months still had a statistically significant association with age at breast development. When we used maternal report of breast onset based on the PDS instead of TS, there were no statistically significant associations between growth in weight or length during infancy and age at breast development. Although not statistically significant, the direction of the association between rates of growth in weight and length from 2-4 months were consistent with the primary models based on maternal report of TS (**Supplemental Table 4.9**).

4.4 Discussion

Rates of growth in both weight and length during infancy are associated with the timing of breast development in a prospective cohort of girls enriched for breast cancer family history. Our finding that faster weight gain between birth and one year is associated with earlier breast development is consistent with previous studies linking rapid weight gain between birth and two years with earlier onset of breast development[73,75,185] and earlier age at menarche.[34,35,72,73,75–77,116,190,191] Our study adds to the prior literature by examining changes in both weight and length during multiple time intervals within the first year and by formally testing the interaction between infant growth and BCFH. While we observed a modest association between rate of weight gain from 0-12 months and onset of breast development, stronger associations

between rate of weight gain from 2-4 months and 6-9 months were masked when looking only at the relatively wide one-year window. We observed a similar pattern for growth in length. Few studies have weight and length measures at multiple time points within infancy to examine smaller windows of growth.

Comparison with previous studies

Comparisons across studies is difficult since studies assess growth over different age intervals, which may be due more to data availability than by a priori hypotheses.[73] In the North Carolina Infant Feeding Study, increases in weight-for-age Z-scores from 0-6 months and 6-12 months were both associated with earlier age at breast TS>2 and earlier age at menarche, and point estimates were similar for each age interval.[75] However, weight gain during both time periods were included in the same model and were negatively correlated with each other, which may have resulted in a stronger parameter estimate for weight gain in early infancy due to the inclusion of weight gain in late infancy in the model. When we examined weight gain in these same intervals without adjustment for change in length, our inference for onset of breast development was similar, though the point estimate was slightly higher for 6-12 months than 0-6 months. In the ALSPAC cohort, increase in weight-for-age Z-scores from 0-2 months and 9-20 months was associated with earlier age at breast development; the point estimate for 2-9 months was also negative, but closer to the null and not statistically significant. For age at menarche, weight gain from 0-2 months was not associated with age at menarche in models adjusted for birth size, but weight gain from 2-9 and 9-20 months were both associated with earlier age at menarche.[73] When we considered change in WAZ over these same age intervals of 0-2 months and 2-9 months and the onset of breast development, there was no association with weight gain from 0-2 months, but rate of weight gain from 2-9 months was inversely associated with age at breast development (data not shown). However, the point estimate for weight gain from 2-9 months was closer to the null compared with the effect estimates for weight gain from 2-4 months and 6-9 months when these intervals were modeled separately. In two studies that examined rate of weight gain from 0-4 months and 4-12 months and age at menarche in U.S. birth cohorts, one found inverse associations between weight gain in both time periods and age at menarche,[77] while the other study only observed a statistically significant association with weight gain in late infancy.[116] When we considered these same intervals, we observed inverse associations between rate of weight gain in both time periods

and age at breast development in models unadjusted for growth in length (data not shown). While our results are therefore generally consistent with previous work, we were able to further refine the infancy window and identify two specific periods of time, 2-4 months and 6-9 months, during which patterns of growth had a particularly strong influence on age at breast development.

When we examined rate of growth in length during infancy, these same time periods of 2-4 months and 6-9 months were also identified as sensitive windows when rates of length gain were associated with the onset of breast development. In comparison with weight gain, fewer studies have examined change in length as an independent predictor of pubertal timing. Conditional measures of change in length from 0-6 months and 6-24 months were not correlated with breast TS at 11 years of age in the Vulnerable Windows Birth Cohort Study in Jamaica ($p>0.05$), though the correlation coefficient for 0-6 months was in the direction of faster gain in length being associated with earlier development.[79] Gains in weight and BMI during these time periods were also not associated with breast development in this study. Three studies did observe an association between faster growth in length during the first two years and earlier age at menarche.[35,76,77] In the 1946 British Birth Cohort, faster growth in length from 0-2 years was associated with increased risk of earlier menarche when examined independently, but the association was attenuated towards the null after adjustment for rate of growth in BMI from 0-2 years and childhood height growth.[76] Girls with menarche before 12 years of age also had faster rates of growth in length from 2-9 months and 9-19 months, but not 0-2 months, in the ALSPAC cohort, though the association was no longer statistically significant after controlling for weight gain during the same time periods.[35] A similar pattern was observed in two U.S. birth cohorts, where gain in length from 0-4 months and 4-12 months was associated with earlier age at menarche when examined independently, but these associations were attenuated after adjustment for weight gain.[77] While we also observed a modest attenuation of the effect estimates for weight and length when mutually adjusted, changes in weight and length from 2-4 months were both independently associated with the age at onset of breast development and we observed similar patterns of association from 6-9 months. Together, the associations between both rates of weight and length gain during the same two age intervals, when considered separately and when mutually adjusted, underscores the importance of growth during these specific windows to the timing of breast development.

Influence of maternal BMI, GWG and size at birth

The associations between rates of growth in weight and length and timing of breast development were observed across the spectrum of size at birth, suggesting that the associations observed were not driven by a regression-to-the-mean effect of catch-up growth in infants born small or catch-down growth in infants that were large at birth.[227] Birthweight and birthlength were not associated with the timing of breast development in confounder-adjusted models in the full cohort (see **Chapter 3**). After adjusting for rates of growth in weight and length during infancy, which were negatively correlated with birth size, the point estimates for both birthweight and birthlength were further from the null (data not shown). The statistical significance of the estimates differed depending on the infant growth measures included in the model. In the 1946 British Birth Cohort, an inverse association between birthweight and age at menarche was reversed after adjustment for growth in height and BMI from 0-2 years, suggesting that girls with a higher birthweight had an earlier age at menarche for a given rate of postnatal growth.[76] The dependence of the birthweight association on adjustment for postnatal growth supports the hypothesis that birthweight does not have an independent role in influencing pubertal timing. In contrast, the increased risk of early breast development in daughters of women who were overweight prior to pregnancy and gained more than 30lbs remained after controlling for infant growth, suggesting that these factors have independent effects on age at breast development.

Early-life nutrition and other potential mechanisms

Feeding practices are associated with patterns of weight and length gain during infancy and may be associated with the timing of breast development. Some studies have observed earlier onset of breast development[126] and earlier age at menarche[35,270] in formula-fed compared with breastfed infants, while others have not observed an association between infant feeding and pubertal timing.[34,271] On average, formula-fed infants have faster rates of weight gain than exclusively breastfed infants and are heavier by one year of age. However, breastfed infants gain weight faster than formula-fed infants in early infancy, then have slower rates of weight gain in later infancy.[272] While observational studies have observed lower risks of obesity in children that were breastfed,[273] the protective effect of breastfeeding on obesity is controversial since infant feeding is closely linked with socioeconomic status.[274] In addition, the clinical trial

of a breastfeeding promotion intervention in Belarus (PROBIT) succeeded in increasing breastfeeding rates, but did not observe any differences in childhood body size in children who received the intervention.[275] Associations between infant feeding and growth patterns are also difficult to disentangle – while form of feeding does influence rates of weight gain, parents may also modify their child's feeding practice in response to their growth trajectory.[266] Our results of earlier breast development in girls with faster rates of growth in weight and length in specific infant time periods were similar in models that also controlled for type of infant feeding, suggesting that infant feeding did not confound or mediate the effect of infant growth on onset of breast development. The introduction of solid foods could also influence growth patterns, though the evidence linking the timing of solid food introduction and childhood obesity is inconclusive.[276] The American Academy of Pediatrics and the WHO recommend introducing solid foods at 6 months of age.[277] It is possible that the associations that we observed between rates of weight and length gain, particularly from 6-9 months of age, and earlier breast development reflect changes in nutrient intake due to the addition of solid foods; however, we did not have data on the timing of solid food introduction to explore this hypothesis. Overall, more research is needed in study populations with detailed infant feeding data in order to examine the temporal associations between feeding and infant growth patterns and whether these factors interact to influence pubertal timing. Migrant and animal studies support that an energy-rich diet in early life affects mammary gland development and breast cancer risk.[251,278–280] Thus, early-life nutrition, which influences growth patterns in infancy, may also affect breast development.

Additional mechanisms that may link infant growth, onset of breast development and breast cancer risk include childhood body size, hormonal programming, genetic or epigenetic influences. Rates of growth in weight and length during infancy may set trajectories of height and weight gain in childhood. Infants who gain weight rapidly are at an increased risk of obesity starting in childhood,[64] and higher pre-pubertal weight is a well-recognized risk factor for earlier pubertal onset.[54,60] Our results from models adjusted for pre-pubertal BMI suggest that the association between rapid growth and earlier breast development is not fully mediated by childhood body size. Faster infant growth in length and weight is also associated with faster height growth and earlier age at peak height velocity,[34,35,87] an independent risk factor for breast cancer.[41] Rapid infant growth is associated with hormonal changes such as increased levels of leptin, insulin-like growth factor (IGF)-1 and insulin which affects growth throughout childhood and may lead to earlier initiation

of puberty.[87,204] Early-life growth and pubertal timing could also have a shared genetic origin. GWAS studies have identified multiple loci, including variants near *LIN28B*, that are associated with pubertal timing, linear growth and body size.[220,281,282] An epigenetic mechanism could also link infant growth, pubertal timing and chronic disease risk. Changes in DNA methylation of imprinted genes are known to be associated with infant growth,[216] and are also associated with genomic instability and chronic disease in adulthood.[217] Early-life environmental stimuli are associated with changes in promoter methylation of non-imprinted genes,[218] which could affect gene expression in insulin-signaling pathways[219] or changes in genes related to body size or pubertal timing.[220,221]

Potential importance of mini-puberty

Our identification of 2-4 months as a sensitive window when growth velocity is associated with timing of breast development coincides with mini-puberty, the transient activation of the HPG in infancy.[211,212] In girls, follicle stimulating hormone (FSH) and luteinizing hormone (LH) both increase in early infancy and peak at 1-3 months. LH then decreases by 6-9 months, while elevated FSH levels are present until age 3-4 years. Estradiol levels in girls fluctuate during the first year after birth, and then decrease until puberty.[213] While both male and female infants have breast tissue present at birth that regresses during infancy, breast tissue size is larger and persists for a longer time period in female infants.[211,283] Serum estradiol levels have been found to be positively associated with breast tissue size in 3-month old female infants, but not in males.[214] In girls who are born preterm and have a smaller amount of breast tissue at birth than full-term infants, breast tissue size was found to increase from 1-6 months of age and was associated with increased levels of urinary estradiol.[283] Together, this suggests that breast tissue in female infants is stimulated by endogenous hormones,[214,283] which may affect breast development and later breast cancer risk. Daughters exposed to pre-eclampsia *in utero,* which is associated with decreased maternal levels of estrogen and IGF-1 but higher levels of androgens and progesterone, have a decreased risk of breast cancer in adulthood.[284] A case-control study comparing the timing of pubertal development between 203 daughters of normotensive pregnancies and 120 daughters of pre-eclamptic pregnancies found that daughters exposed to moderate or severe pre-eclampsia in utero were more likely to experience the onset of pubic hair development as the first sign of puberty, implying later age at breast development in these

girls.[285] However, little is known about whether endogenous hormone levels in infancy are associated directly with the timing of breast development and breast cancer risk.

The long-term effects of mini-puberty are not well understood.[286] Increases in height and faster peak height velocity during adolescent puberty, a critical period for breast development when growth and reproductive hormone levels are rapidly increasing,[199] are associated with breast cancer risk.[14,287] Growth hormone (GH) and IGF-1 are two key hormones that regulate linear growth.[204,288] During puberty, rising estrogen levels in girls are thought to promote the pubertal growth spurt by stimulating the GH-IGF-1 axis.[204,289] Rising estrogen levels in girls during mini-puberty could have a similar stimulatory effect on infant growth,[288,290] in which case faster rate of gain in length from 2-4 months of age could reflect higher endogenous hormone levels. A recent study that examined the role of sex steroids during mini-puberty in regulating growth in length from birth to 6 months of age did not observe an association between urinary estradiol levels and growth velocity in females, though estradiol levels did peak between 1-4 months of age.[290] However, the authors noted that urinary estradiol levels likely did not reflect estradiol concentrations in the growth plate, which may explain why no association was observed between estradiol levels and linear growth velocity. Serum IGF-1 levels at 3 months were associated with faster linear growth in both male and female infants in the study, as were testosterone levels from 0-5 months of age, supporting the hypothesis overall that sex steroid levels during mini-puberty have a role in regulating linear growth.[288,290]

Strengths and limitations

The prospective assessment of weight and length across multiple time points in infancy due to the linkage to medical record data is a major strength of this study. We were able to replicate the results that others observed by examining the same age intervals.[73,75] In addition, we were able to examine smaller age intervals, which identified growth during two specific age intervals as driving the overall trends that we observed. Since LEGACY is enriched for breast cancer family history, we were also able to formally test whether the associations between infant growth and onset of breast development differed in girls at increased risk of breast cancer due to their family history. The lack of modification by BCFH suggests that the risk of earlier breast development, which is associated with increased breast cancer risk later in life,[41] can be modified by altering early-life growth patterns in girls across the spectrum of familial risk. However,

it is also possible that we did not have sufficient power to detect differences by BCFH since we lacked infant growth data for the majority of the cohort.

Although we had multiple measures of weight and length throughout infancy for the subset of girls with medical record data, our study was limited by the sample size of this subset. Small cell counts limited our ability to control for a large number of confounders in the analyses and also limited statistical power, particularly for interactions. For example, we lacked power to examine whether associations between infant growth and pubertal timing differed by infant feeding practices or in girls born preterm, questions that are worthwhile to consider in larger cohorts. Our results could also be affected by selection bias, as there were differences between the subset of girls with infancy data and those that were not included in the analysis. However, the inference was the same when we used IPW to adjust for these differences, supporting that selection bias did not drive the main results observed. We also relied on maternal reports of birthweight and birthlength, though the correlation with medical record data was high in our validation subset (see **Chapter 3**). There is also a potential for measurement error in the weight and length measurements from the medical record, since measures could vary between physician practices and were not assessed using a standardized protocol. Measures of length before standing height can be measured are more prone to measurement error and have been found to have poor reliability, even when measured by nurses.[246,247] While it is possible that measurement error may have influenced our findings regarding growth in length and onset of breast development, these errors would likely be random and we would expect a larger effect on the precision rather than the validity of study estimates.

4.5 Conclusions

We observed that faster rates of growth in both weight and length during infancy were associated with earlier onset of breast development in a prospective cohort of girls enriched for BCFH. Girls that were taller and heavier than their peers by late infancy experienced earlier onset of breast development. Associations between rate of weight gain and rate of change in length were specific to two time periods within infancy, 2-4 months and 6-9 months, suggesting that these may be sensitive periods for exposures in the early-life environment to affect breast development. These associations were not modified by BCFH,

suggesting that slow growth in weight and length during infancy may delay breast development, even in girls at an increased risk of breast cancer due to their family history.

4.6 Tables and figures

Table 4.1. Descriptive characteristics of the LEGACY Girls Study by availability of infant growth measures (N=1068)

	Girls with infancy data (N=255)	Girls without infancy data (N=813)
Early-life characteristics		
Maternal age at birth (Mean±SD)	33.3 ± 4.8	32.0 ± 5.7
Maternal height, m (Mean±SD)	1.6 ± 0.1	1.6 ± 0.1
Maternal pre-pregnancy weight, kg (Mean±SD)	63.0 ± 10.9	64.4 ± 14.0
Maternal pre-pregnancy BMI (Mean±SD)	23.4 ± 4.0	23.9 ± 5.1
Maternal pre-pregnancy BMI, categorized (N, %)		
<18.5	11 (4.3)	36 (4.4)
18.5 to <25	169 (66.3)	508 (62.5)
25 to <30	43 (16.9)	137 (16.9)
≥30	15 (5.9)	81 (10.0)
Missing	17 (6.7)	51 (6.3)
Gestational weight gain (n, %)		
<10 lbs	3 (1.2)	24 (3.0)
10-14 lbs	14 (5.5)	28 (3.4)
15-19 lbs	24 (9.4)	62 (7.6)
20-29 lbs	68 (26.7)	249 (30.6)
30-39 lbs	69 (27.1)	197 (24.2)
40-49 lbs	35 (13.7)	110 (13.5)
≥50 lbs	22 (8.6)	91 (11.2)
Missing	20 (7.8)	52 (6.4)
Maternal recreational physical activity during pregnancy (N, %)		
Inactive, no walking or other regular exercise	20 (7.8)	109 (13.4)
Mostly inactive, equivalent to walking about half a mile or less every day	64 (25.1)	177 (21.8)
Somewhat active, equivalent to walking about 1 mile every day	58 (22.8)	168 (20.7)
Active, equivalent to walking about 2 miles every day	98 (38.4)	286 (35.2)
Highly active, equivalent to walking about 3 or more miles every day	11 (4.3)	47 (5.8)
Missing	4 (1.6)	26 (3.2)
Type of gestation (N, %)		
Multiple	13 (5.1)	32 (3.9)
Singleton	235 (92.2)	735 (90.4)
Missing	7 (2.8)	46 (5.7)
Birth order (Mean±SD)	1.7 ± 0.8	1.8 ± 1.0

Birth order, dichotomized (N, %)		
First-born	118 (46.3)	352 (43.3)
Not first-born	130 (51.0)	415 (51.1)
Missing	7 (2.8)	46 (5.7)
Gestational age in weeks (Mean±SD)	39.3 ± 2.0	38.9 ± 2.2
Gestational age, categorized (N, %)		
<37 weeks	21 (8.2)	100 (12.3)
≥37 weeks	226 (88.6)	683 (84.0)
Missing	8 (3.1)	30 (3.7)
Birthweight, g (Mean±SD)	3370.2 ± 539.7	3270.2 ± 594.6
Birthlength, cm (Mean±SD)	50.8 ± 3.8	50.4 ± 3.7
Type of feeding during infancy (N, %)		
Exclusively breastfed	90 (35.3)	273 (33.6)
Mix of breastfeeding and formula	144 (56.5)	432 (53.1)
Exclusively formula-fed	14 (5.5)	77 (9.5)
Missing	7 (2.8)	31 (3.8)
Baseline characteristics		
Age at baseline (Mean±SD)[a]	8.9 ± 2.5	9.7 ± 2.3
BMI-for-age percentile at baseline, (Mean±SD)[a]	50.1 ± 28.9	50.6 ± 31.2
BMI-for-age percentile at baseline, categorized (N, %)[a]		
≥85th BMI-for-age percentile	32 (12.6)	148 (18.2)
<85th BMI-for-age percentile	208 (81.6)	628 (77.2)
Missing	15 (5.9)	37 (4.6)
Breast cancer family history in a first- or second-degree relative (N, %)		
BCFH+	138 (54.1)	405 (49.8)
BCFH-	117 (45.9)	408 (50.2)
BOADICEA lifetime risk score (Mean±SD)	14.6 ± 4.9	14.6 ± 4.7
Study site (N, %)		
Philadelphia	10 (3.9)	149 (18.3)
New York	59 (23.1)	118 (14.5)
Utah	23 (9.0)	155 (19.1)
Ontario	87 (34.1)	105 (12.9)
Northern California	76 (29.8)	286 (35.2)
Race/ethnicity (N, %)		
Non-Hispanic white	172 (67.5)	497 (61.1)
Non-Hispanic black	16 (6.3)	63 (7.8)
Hispanic	30 (11.8)	166 (20.4)
Asian/Pacific Islander	28 (11.0)	65 (8.0)
Other or mixed race/ethnicity	9 (3.5)	22 (2.7)
Maternal education (N, %)		

Some college, vocational or technical school or less	48 (18.8)	248 (30.5)
Bachelor's degree	111 (43.5)	274 (33.7)
Graduate degree	88 (34.5)	273 (33.6)
Missing	8 (3.1)	18 (2.2)
Maternal age at menarche (Mean±SD)	12.7 ± 1.4	12.7 ± 1.6

[a]Pilot baseline for girls with pilot data (N=21)

Table 4.2. Summary measures of height and weight by age and age interval (N=255)

	Birth		2 months		4 months		6 months		9 months		12 months	
Variable	Mean (SD)	IQR	Mean (SD)	IQR	Mean (SD)	IQR	Mean (SD)	IQR	Mean (SD)	IQR	Mean (SD)	IQR
Weight, kg	3.37 (0.54)	3.09, 3.71	5.15 (0.70)	4.71, 5.60	6.51 (0.81)	5.95, 7.03	7.48 (0.92)	6.89, 8.05	8.62 (1.03)	8.00, 9.25	9.49 (1.11)	8.80, 10.21
Weight-for-age Z-score	-0.01 (1.07)	-0.62, 0.67	0.42 (1.10)	-0.27, 1.13	0.45 (1.07)	-0.26, 1.15	0.28 (1.09)	-0.39, 0.97	0.06 (1.11)	-0.56, 0.76	-0.10 (1.14)	-0.73, 0.65
Length, cm	50.82 (3.80)	48.26, 53.34	57.97 (2.59)	56.13, 60.00	63.19 (2.70)	61.50, 65.00	67.13 (2.75)	65.55, 69.00	71.67 (3.03)	69.85, 73.72	75.56 (3.14)	73.66, 77.54
Length-for-age Z-score	0.45 (1.79)	-0.43, 1.50	0.50 (1.06)	-0.23, 1.34	0.68 (1.09)	0.00, 1.41	0.74 (1.07)	0.11, 1.46	0.67 (1.11)	-0.02, 1.41	0.63 (1.09)	-0.04, 1.31
	0-2 months		2-4 months		4-6 months		6-9 months		9-12 months		0-12 months	
Change in WAZ	0.43 (0.93)	-0.20, 1.03	0.03 (0.54)	-0.32, 0.31	-0.16 (0.52)	-0.43, 0.10	-0.21 (0.44)	-0.46. 0.01	-0.12 (0.42)	-0.41, 0.12	-0.06 (1.35)	-0.87, 0.68
Change in LAZ	0.02 (1.59)	-0.83, 0.63	0.19 (0.63)	-0.18, 0.52	0.06 (0.63)	-0.33, 0.40	-0.08 (0.77)	-0.44, 0.31	-0.03 (0.55)	-0.38, 0.30	0.19 (1.90)	-0.78, 0.89

*Z-scores calculated using the 2000 CDC growth charts

Table 4.3. Correlation matrix for birthweight Z-score and change in weight-for-age Z-score (WAZ) by age interval (N=255)

Parameter	Birthweight Z-score	Change in WAZ, 0-2 m	Change in WAZ, 2-4 m	Change in WAZ, 4-6 m	Change in WAZ, 6-9 m
Change in WAZ, 0-12 m	-0.58**				
Change in WAZ, 0-2 m	-0.40**				
Change in WAZ, 2-4 m	-0.32**	0.04			
Change in WAZ, 4-6 m	-0.21*	-0.03	0.10		
Change in WAZ, 6-9 m	-0.16*	-0.05	0.17*	0.25**	
Change in WAZ, 9-12 m	-0.08	-0.01	-0.00	-0.10	0.16*

*Pearson correlation coefficients: *p<.05, **p<.0001*

Table 4.4. Correlation matrix for birthlength Z-score and change in length-for-age Z-score (LAZ) by age interval (N=255)

Parameter	Birthlength Z-score	Change in LAZ, 0-2 m	Change in LAZ, 2-4 m	Change in LAZ, 4-6 m	Change in LAZ, 6-9 m
Change in LAZ, 0-12 m	-0.83**				
Change in LAZ, 0-2 m	-0.80**				
Change in LAZ, 2-4 m	-0.15*	-0.05			
Change in LAZ, 4-6 m	-0.17*	-0.06	0.04		
Change in LAZ, 6-9 m	-0.09	-0.03	-0.12	-0.10	
Change in LAZ, 9-12 m	-0.04	-0.01	-0.10	-0.09	0.09

*Pearson correlation coefficients: *p<.05, **p<.0001*

Table 4.5. Correlations between changes in weight-for-age and length-for-age Z-scores by age interval (N=255)

Parameter	Birthweight Z-score	Change in WAZ, 0-12 m	Change in WAZ, 0-2 m	Change in WAZ, 2-4 m	Change in WAZ, 4-6 m	Change in WAZ, 6-9m	Change in WAZ,9-12m
Birthlength Z-score	0.51**	-0.27**	-0.19*	-0.16*	-0.10	-0.01	-0.09
Change in LAZ, 0-12 m	-0.34**	0.38**	0.25*	0.28**	0.13	0.09	0.09
Change in LAZ, 0-2 m	-0.14*	0.19*	0.27**	0.04	0.03	-0.10	0.07
Change in LAZ, 2-4 m	-0.17*	0.24*	0.12	0.26**	-0.08	0.06	-0.01
Change in LAZ, 4-6 m	-0.25**	0.26**	0.09	0.21*	0.25*	0.05	0.03
Change in LAZ, 6-9 m	-0.17*	0.22*	0.03	0.09	0.13*	0.24*	0.02
Change in LAZ, 9-12 m	-0.03	-0.002	-0.14*	0.14*	0.03	0.06	0.03

*Pearson correlation coefficients: *p<.05, **p<.0001*

Table 4.6. Adjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between rates of weight and length gain during infancy and the onset of breast development in the LEGACY Girls Study

	Model 1[a] - Weight only		Model 2[a] - Length only		Model 3[a] - Weight and Length	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	**0.978 (0.960, 0.997)**	**1.20 (1.02, 1.41)**	–	–	0.986 (0.971, 1.001)	1.12 (0.99, 1.28)
Change in length Z-score, 0-12 months	–	–	0.983 (0.966, 1.000)	1.15 (1.00, 1.33)	0.988 (0.972, 1.005)	1.10 (0.96, 1.27)
Change in weight Z-score, 0-6 months	0.983 (0.966, 1.001)	1.15 (0.99, 1.34)	–	–	0.991 (0.971, 1.010)	1.08 (0.92, 1.28)
Change in weight Z-score, 6-12 months	0.973 (0.946, 1.001)	1.25 (0.98, 1.60)	–	–	0.982 (0.954, 1.010)	1.17 (0.92, 1.49)
Change in length Z-score, 0-6 months	–	–	**0.978 (0.960, 0.996)**	**1.21 (1.03, 1.41)**	0.981 (0.962, 1.001)	1.17 (0.99, 1.38)
Change in length Z-score, 6-12 months	–	–	0.994 (0.969, 1.020)	1.05 (0.85, 1.30)	0.995 (0.969, 1.020)	1.05 (0.84, 1.30)
Change in weight Z-score, 0-2 months	0.991 (0.971, 1.011)	1.08 (0.92, 1.27)	–	–	1.006 (0.986, 1.026)	0.96 (0.81, 1.12)
Change in weight Z-score, 2-4 months	**0.949 (0.915, 0.985)**	**1.54 (1.13, 2.12)**	–	–	**0.962 (0.926, 0.999)**	**1.40 (1.00, 1.96)**
Change in weight Z-score, 4-6 months	0.989 (0.940, 1.040)	1.10 (0.72, 1.69)	–	–	0.991 (0.940, 1.045)	1.08 (0.68, 1.72)
Change in weight Z-score, 6-9 months	**0.946 (0.904, 0.989)**	**1.63 (1.09, 2.42)**	–	–	**0.953 (0.910, 0.997)**	**1.55 (1.01, 2.36)**
Change in weight Z-score, 9-12 months	1.008 (0.968, 1.050)	0.93 (0.66, 1.32)	–	–	0.997 (0.955, 1.041)	1.03 (0.70, 1.51)
Change in length Z-score, 0-2 months	–	–	0.990 (0.968, 1.013)	1.09 (0.90, 1.31)	0.988 (0.966, 1.010)	1.11 (0.92, 1.33)
Change in length Z-score, 2-4 months	–	–	**0.949 (0.918, 0.982)**	**1.56 (1.16, 2.08)**	**0.955 (0.922, 0.989)**	**1.50 (1.10, 2.04)**
Change in length Z-score, 4-6 months	–	–	1.012 (0.974, 1.052)	0.90 (0.65, 1.25)	1.017 (0.979, 1.056)	0.87 (0.62, 1.21)
Change in length Z-score, 6-9 months	–	–	0.974 (0.944, 1.005)	1.25 (0.95, 1.65)	0.983 (0.953, 1.014)	1.17 (0.88, 1.54)
Change in length Z-score, 9-12 months	–	–	1.005 (0.969, 1.042)	0.96 (0.70, 1.31)	1.021 (0.982, 1.061)	0.83 (0.58, 1.18)

*Z-scores calculated using 2000 CDC growth charts as reference

[a]Estimates adjusted for weight and length Z-scores at birth, change in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

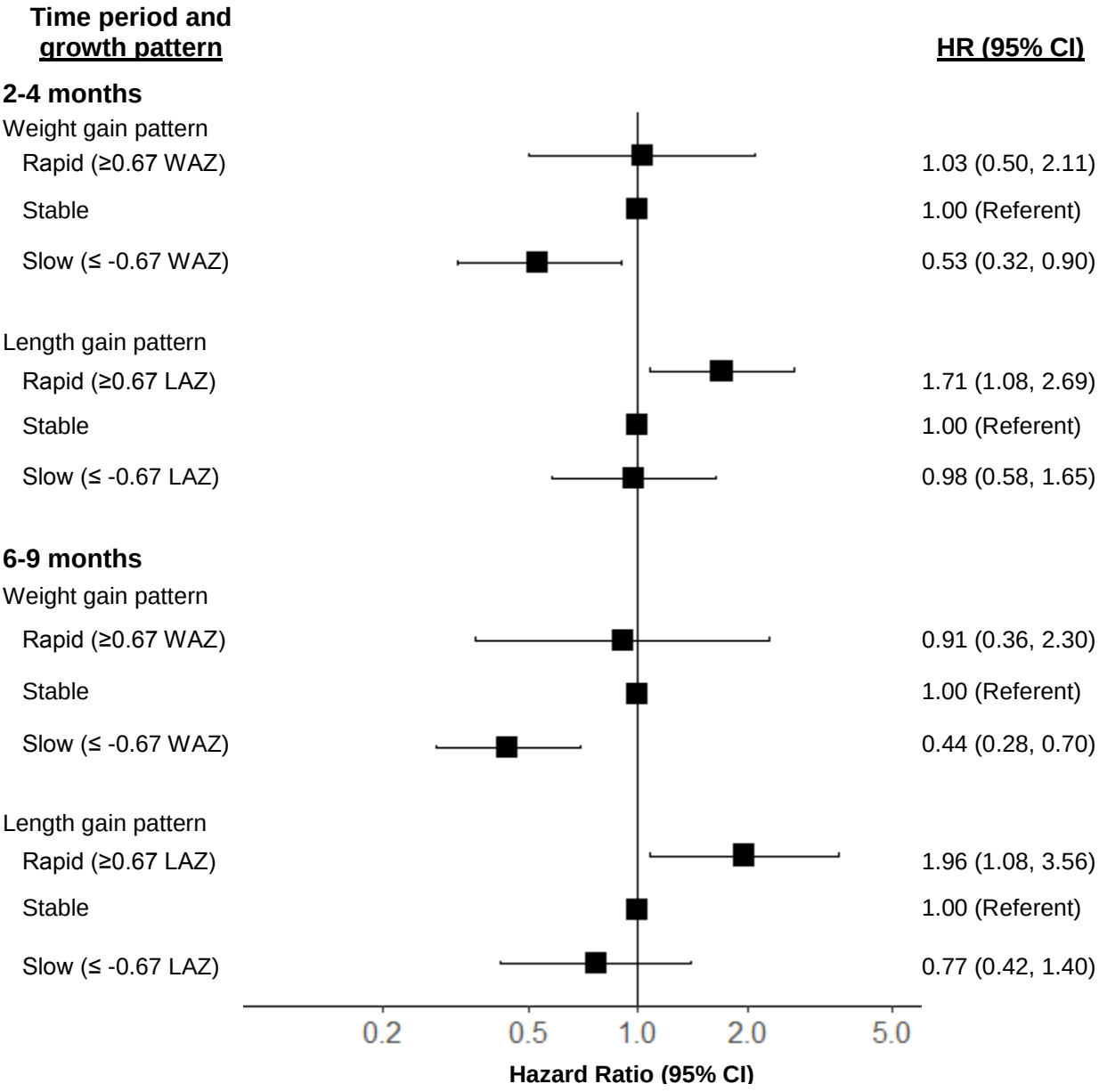


Figure 4.1. Associations between growth patterns from 2-4 months and 6-9 months and onset of breast development in the LEGACY Girls Study. Z-scores are calculated using the 2000 CDC growth charts. Estimates are adjusted for weight and length Z-score at birth, change in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI, gestational weight gain and race/ethnicity.

Chapter 5. Maternal pregnancy factors, birth size and infant growth in relation to IGF-1 and IGFBP-3 levels during puberty in the LEGACY Girls Study cohort

ABSTRACT

Background: Serum levels of insulin-like growth factor (IGF)-1 and insulin-like growth factor binding protein (IGFBP-3) increase rapidly during puberty. In this pilot study, we examined whether maternal pregnancy factors and rates of growth during infancy, which were associated with earlier onset of breast development in prior chapters, influenced serum levels of IGF-1 and IGFBP-3 in girls during puberty, and if so, whether these associations differ in girls with and without a breast cancer family history (BCFH).

Methods: We used linear mixed models to estimate the mean difference in serum levels of IGF-1(ng/ml), IGFBP-3(ng/ml) and the IGF-1/IGFBP-3 molar ratio by maternal pre-pregnancy body mass index (BMI), gestational weight gain (GWG), maternal physical activity during pregnancy and size at birth in 109 girls from the New York site of the LEGACY Girls Study, a pubertal cohort enriched for BCFH (ages 6-17 years at sample collection). We included all available serum samples for each girl (range 1-5, median 3) in the analyses, which were clustered on the individual and the family. In the subset of 33 girls with infant growth data available from medical records, we also examined differences in serum biomarker levels by growth patterns from birth to 12 months of age. We adjusted for age, breast Tanner stage and BMI-for-age percentile at sample collection and assessed effect modification by BCFH for each exposure of interest through cross-product terms.

Results: The mean age at the first available serum sample was 10.2 years. Forty percent of girls had a BCFH, and 46% were breast Tanner stage 1 at their first sample. Serum IGF-1 levels increased from Tanner stage 1-3, were at a peak in stages 3 and 4, and were lower in Tanner stage 5. A similar pattern was observed for the IGF-1/IGFBP-3 molar ratio. Faster rates of weight gain in infancy were associated with a higher molar ratio of IGF-1/IGFBP-3, which reflect higher levels of bioactive IGF-1 (β=0.03, 95% CI 0.01, 0.06 for one-unit increase in weight-for-age Z-score from birth to 12 months). Higher birthweight was associated with decreased levels of IGF-1, which was attenuated after adjustment for infant growth (β= -4.5 ng/ml, 95% CI -35.6, 26.6 per 500g increase in birthweight with adjustment for infant weight gain). These

patterns did not differ by BCFH, which was not associated with serum biomarker levels after adjustment for age and breast Tanner stage.

Conclusions: Rapid infant weight gain was associated with higher levels of the IGF-1/IGFBP-3 molar ratio, a serum biomarker that maps to pubertal development. This supports that the association that we observed between faster infant growth and earlier onset of breast development is less likely to be driven by error in outcome assessment or confounding.

5.1 Background

Serum IGF-1 levels increase slowly during early childhood with a more rapid rate of increase during puberty.[51] After a peak during puberty, IGF-1 levels decrease in adolescence and adulthood.[52] Insulin-like growth factor binding protein (IGFBP)-3, which binds 75-90% of circulating IGF-1 and regulates its bioactivity,[291] follows a similar pattern in childhood and adolescence.[52] While breast Tanner stage is a somewhat subjective assessment, even among trained professionals,[58] serum levels of IGF-1 and IGFBP-3 are objective measures that are correlated with pubertal stage.[51,52] In this pilot study, we examine whether maternal pregnancy factors and rates of growth during infancy, which were associated with earlier onset of breast development in prior chapters, influence serum levels of IGF-1 and IGFBP-3 in girls during puberty, and if so, whether these associations differ in girls with and without a breast cancer family history (BCFH). Associations between these factors and higher serum levels of IGF-1, IGFBP-3 or the IGF-1/IGFBP-3 molar ratio would indicate biological changes that map to pubertal development in the girls, and support that bias is less likely to drive the associations that we observed with pubertal timing.

5.2 Methods

5.2.1. Study population

The participants in this study were from the New York site of the LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study, a prospective pubertal cohort in which approximately 50% of girls have a breast cancer family history (BCFH) (for more information on the LEGACY cohort, see [57]). Girls were between the ages of 6 and 13 years when recruited into LEGACY

between 2011 and 2013 along with a participating guardian and have been prospectively followed every six months since baseline. Baseline data collected from mothers included family history of breast cancer in daughters' first- and second-degree relatives and detailed information about the pregnancy with the LEGACY daughter. At baseline and subsequent follow-up visits, mothers completed questionnaires assessing their daughters' pubertal development and trained staff members collected anthropometric measurements. Daughters were asked to provide a blood sample at baseline, the six-month follow-up visit, and annually thereafter. For this analysis, the study population was comprised of 109 girls from the New York LEGACY site who provided at least one blood sample over the course of the study. The participating guardian was the biological mother for 98% of these girls. The analysis included all available serum samples (N=289), along with prospective follow-up data on Tanner Stage, through August 2016. Mothers provided written informed consent for themselves and for their daughters, and daughters provided written informed assent according to institutional standards. The study was approved by the institutional review board at Columbia University Irving Medical Center.

5.2.2. Data collection

Maternal and infant exposures. Mothers completed an early-life questionnaire at their daughters' baseline visit that included detailed information about their pregnancy, including pre-pregnancy weight (continuous), gestational weight gain (GWG) (in categories) and physical activity. These questions were developed and used previously in the Nurses' Health Study cohort.[24] Mothers also reported the length of their pregnancy, which we used to calculated gestational age, along with their daughters' weight and length at birth. Weight and length through one year of age was available for a subset of the girls from medical records and growth charts obtained from pediatricians' offices. As described in **Chapter 4,** we interpolated weight and height at 2 months, 4 months, 6 months, 9 months and 12 months for each girl using individual quadratic smoothing splines as these time points correspond with recommended postnatal clinician visits.[250] We calculated weight-for-age (WAZ) and length-for-age (LAZ) Z-scores at each time point standardized to the 2000 Centers for Disease Control and Prevention (CDC) growth charts.[261] Rate of growth in weight and length was calculated as the change in WAZ and LAZ between two time points. We defined rapid growth as an increase in Z-score of greater than 0.67, slow growth as a decrease in Z-score of greater than 0.67,

and stable growth as a change of less than 0.67 between time points. A change of 0.67 standard deviations corresponds to an increase of a major percentile on standard growth charts (i.e. a change from the 25th to the 50th percentile), and is commonly used in the literature.[191,263]

Covariates. We considered history of breast cancer in a first or second-degree relative, as reported by the mother at baseline, as a potential modifier. At each study visit, trained research staff measured the height and weight of the girls at least twice using standardized instruments. We averaged these measures and calculated body mass index (BMI) at the visit. We also calculated BMI-for-age percentiles based on the 2000 CDC growth charts.[241] Mothers also reported their daughters' stage of breast development at the visit using was the picture-based Sexual Maturation Scale (SMS)[238] showing the five Tanner stages (TS).[100] Mothers reported their highest level of education attained at baseline, which was used as a measure of socioeconomic status (SES).

Biomarker assessment. We measured IGF-1 and IGFBP-3 concentrations in ng/ml in serum at the Irving Institute for Clinical and Translational Research Core Biomarkers Lab at Columbia University. IGF-1 was measured using a chemiluminescent immunoassay (CLIA) on the Immulite 1000 automated platform (Siemens Healthcare Diagnostics). Serum samples for the same girl were run on the same day, and the inter-day precision of the assay calculated from a pooled sample was 6.5%. IGFBP-3 was measured using a quantikine enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems), and all samples for the same girl were included on the same plate. The inter-assay precision calculated from a pooled sample was 11.4% and the intra-assay precision, calculated from samples run in duplicate, was 3.5%. All samples were above the limit of detection for IGF-1 and IGFBP-3. We calculated the molar ratio of IGF-1 to IGFBP-3 (IGF-1 in ng/ml times 0.1307 divided by IGFBP-3 in ng/ml times 0.03478, as in [292]) in order to examine the concentration of IGF-1 relative to its primary binding factor. The ratio is a reflection of the amount of bioactive IGF-1,[52,292] as opposed to total circulating IGF-1.

5.2.3. Statistical analysis

We examined the distribution of early-life characteristics and baseline covariates in girls with biomarker data and examined differences with the subset of the girls at the New York site without biomarker

data. We examined the distribution of IGF-1, IGFBP-3 and the molar ratio of IGF-1/IGFBP-3 by age and breast Tanner stage for all serum assessments (N=289 samples) and for the first serum assessment in each girl (N=109 samples). We then examined the distribution of the first IGF measures for each girl by SES and exposures of interest using boxplots. We also examined the correlation between continuous body size measures and the first available serum biomarker measures.

We used multivariable linear mixed models to assess associations between early-life exposures and the mean levels of IGF-1/IGFBP-3 and the IGF-1/IGFBP-3 molar ratio during puberty with a random intercept term for the individual and the family to allow for the clustering of repeated measures within girls and girls within families. The use of mixed models allows for a different number of measures per girl, so girls with only one biomarker measure and those with repeated measures can both contribute to the analysis. We adjusted all models for centered age at blood draw and the quadratic term for age to account for the decline in IGF-1 and IGFBP-3 after the peak during puberty.

Our exposures of interest for this analysis were maternal pre-pregnancy BMI, gestational weight gain, maternal recreational physical activity during pregnancy, birthweight and birthlength. We examined exposures as continuous variables if assumptions of linearity were not violated to avoid small cell counts. We adjusted models examining GWG and maternal physical activity for maternal pre-pregnancy BMI, and we adjusted birth size models for maternal pre-pregnancy BMI and prematurity (gestational age <37 weeks). Birth size models were run with and without mutual adjustment for weight and length. We additionally adjusted for breast TS and BMI-for-age percentile at visit. We tested for effect measure modification on the additive scale by adding a cross-product term between the exposure of interest and BCFH to adjusted models.

For the subset of girls with infancy data (N=33), we also examined rates of growth in weight and length between birth and one year. Due to the small sample size and few sets of siblings, infancy analyses were clustered on the individual only and adjusted for maternal pre-pregnancy BMI and size at birth. We ran models with and without mutual adjustment for growth in weight and length. We additionally adjusted for breast TS (TS≥2 vs TS1, due to small cell counts) and BMI-for-age percentile at visit and tested for interaction by BCFH.

We present our main models without transforming the outcome for interpretability, as the β estimates can be interpreted as the difference in the mean biomarker level between groups for a categorical exposure or for a one-unit increase in a continuous exposure. However, the distributions of IGF-1 and the IGF-1/IGFBP-3 molar ratio were slightly skewed, and normality was improved by using a square root transformation. We ran sensitivity analyses for our adjusted models using the square-root transformed IGF-1 and IGF-1/IGFBP-3 molar ratio measures. We also present the median and interquartile range using the first available biomarker measure across our exposures of interest (**Table 5.1**) and by age for all available measures (**Table 5.2**). Analyses were conducted using SAS 9.4.

5.3 Results

The analytic sample includes 109 girls with at least one serum sample available (median=3 samples per girl, range 1-5). The mean age at the first available serum sample was 10.2 years, and 46% of girls were breast Tanner stage 1 at their first sample (**Table 5.1**). Approximately 30% of mothers were overweight or obese prior to pregnancy, and 28% of girls were overweight at their first visit with serum available. Compared with girls from the New York site that did not provide a serum sample, girls that provided serum were slightly older at baseline and a greater percentage of girls were Hispanic (**Supplemental Table 5.1**). Forty percent of girls with serum had a first- or second-degree history of breast cancer, which was a lower percentage than in the overall cohort. Several families with a BCFH participated in LEGACY remotely and did not attend in-person clinic visits when serum samples were collected.

Girls were between the ages of 6-17 years at blood collection, and the range of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio overall and by age are shown in **Table 5.2**. The median levels of IGF-1 increased until 12 years of age and started to decline by late adolescence, though we had a relatively small number of samples collected at 16 and 17 years of age. The largest increases in median IGF-1 were between 9 and 11 years of age, which corresponds to the onset of puberty for many girls. IGFBP-3 levels also increased with age and appeared to plateau in adolescence. Similar patterns were observed when we considered the first serum sample available for each girl by breast Tanner stage at the visit (**Supplemental Figure 5.1**). IGF-1 levels increased from Tanner stage 1-3, were at a peak in stages 3 and 4, and were lower in Tanner stage 5. A similar pattern was observed for the IGF-1/IGFBP-3 molar ratio. Trends in

IGFBP-3 by Tanner stage were more subtle – the median increased as girls entered breast development and then remained elevated in the later Tanner stages. The distribution of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 ratio were similar by maternal education (**Supplemental Figure 5.2**), suggesting that these biomarkers are independent of SES.

There was significant tracking of IGF-1, IGFBP-3 and their molar ratio within girls during puberty, with intraclass correlation coefficients (ICCs) ranging from 0.60-0.70 when only within- and between-individual levels were considered. When we also considered familial clustering, 36.3% of the variance in IGF-1 was due to within-individual differences, 47.2% to between-individual differences and 16.5% to between-family differences. Similar patterns were observed for IGFBP-3 and the IGF-1/IGFBP-3 molar ratio, where the majority of the variance was due to between-individual and between-family differences.

BMI-for-age percentile at the visit had a modest positive correlation with serum levels of IGF-1 (r=0.20) and the IGF-1/IGFBP-3 molar ratio (r=0.23), while birthweight was inversely correlated with IGF-1 (r= -0.14) and the molar ratio (r= -0.17). The correlation between maternal pre-pregnancy BMI and serum IGF-1 was extremely weak (r=0.07). Infant weight gain had the strongest correlation with serum levels of IGF-1 and the IGF-1/IGFBP-3 ratio (r=0.36 for IGF-1 and r=0.41 for IGF-1/IGFBP-3 molar ratio) – double the magnitude compared with current BMI. None of the body size exposures were strongly correlated with IGFBP-3. In multivariable models controlling for age and breast Tanner stage, the association between current BMI and serum levels of IGF-1 and the molar ratio was attenuated and not statistically significant.

Although the associations were not statistically significant, serum IGF-1 and IGFBP-3 levels increased with increasing maternal pre-pregnancy BMI after controlling for age, current BMI and Tanner stage (**Table 5.3**). There was no association between maternal pre-pregnancy BMI and the IGF-1/IGFBP-3 molar ratio after controlling for daughters' BMI-for-age percentile and breast TS. There was a suggestion of a slight U-shape in the association between GWG and IGF-1, IGFBP-3 and their molar ratio. When maternal pre-pregnancy BMI and GWG were considered as a joint categorical variable, daughters of women who had a pre-pregnancy BMI≥25 and gained ≥30 lbs during pregnancy had higher serum IGF-1 levels than daughters of women who were not overweight prior to pregnancy and gained less than 30 lbs (β adjusted for age, breast TS and BMI-for-age percentile at visit=51.1 ng/ml, 95% CI 1.1, 101.1). Serum

IGF-1 levels in daughters of women with a pre-pregnancy BMI ≥25 and gained less than 30lbs or women with a BMI<25 and gained 30lbs or more were also elevated, but these differences were not statistically significant. There were no statistically significant differences in the IGF-1/IGFBP-3 molar ratio. However, the point estimates suggested that daughters of women who gained 30lbs or more during pregnancy had a greater ratio of IGF-1 to IGFBP-3 than daughters of women who gained less than 30 lbs in both average-weight and overweight women (β for BMI<25 and GWG≥30 lbs=0.02, 95% CI -0.01, 0.08; β for BMI≥25 and GWG≥30lbs=0.04, 95% CI=-0.01, 0.08, increases of 8% and 15%, respectively, in the mean molar ratio compared with the referent group of BMI<25 and GWG<30). There were no statistically significant differences in biomarker levels by maternal recreational physical activity during pregnancy. Point estimates were in the direction of lower levels of IGF-1, IGFBP-3 and their ratio in daughters of inactive women. Although levels of IGF-1, IGFBP-3 and their molar ratio were higher in girls with a BCFH in descriptive analyses (**Table 5.1**), there were no differences by BCFH after adjustment for breast Tanner stage and BMI-for-age percentile in addition to age (data not shown). The associations between maternal pregnancy factors, birth size and biomarker levels did not vary by BCFH (p>0.05 for all interaction terms).

Higher birthweight was associated with lower levels of serum IGF-1 and the IGF-1/IGFBP-3 molar ratio (β for IGF-1= -13.6 ng/ml, 95% CI -26.7, -0.5 per 500g increase in birthweight and β for IGF-1/IGFBP-3 molar ratio= -0.01, 95% CI -0.02, 0.00) (**Table 5.4**). BCFH did not modify the observed association. Birthlength was not associated with IGF levels. In the subset of girls with infancy data, boxplots suggested a dose-response relationship in levels of serum IGF-1 and the IGF-1/IGFBP-3 molar ratio by the pattern of weight gain in infancy, with the highest levels observed in girls with rapid weight gain (**Figure 5.1**). Effect estimates from multivariable-adjusted models examining the continuous change in weight-for-age Z-score from 0-12 months were consistent with this pattern (**Table 5.5**). A one-unit increase in weight-for-age Z-score between birth and 12 months of age was associated with approximately a 14% increase in the mean IGF-1/IGFBP-3 molar ratio after controlling for age, current BMI, Tanner stage, birthweight and maternal BMI. In this subset, we examined whether the negative association between birthweight and IGF-1 was mediated by infant weight gain. The estimated mean difference in IGF-1 per 500g increase in birthweight was similar, but not statistically significant in this subset (β= -12.6, 95% CI -38.4, 13.2), and was attenuated towards the null after adjustment for weight gain from 0-12 months (β= -4.5, 95% CI -35.6, 26.6)

(**Supplemental Table 5.2**). While we observed a similar pattern for change-in-length Z-score from 0-12 months in age-adjusted models, the difference was attenuated after adjustment for breast Tanner stage and BMI. When we considered growth from 0-6 months and 6-12 months separately, rate of weight gain in late infancy was associated with a larger increase in IGF-1 and the IGF1/IGFBP-3 molar ratio. Although infant growth measures were not associated with IGFBP-3 levels, there was a statistically significant interaction between change in weight Z-score from 0-12 months and 0-6 months and BCFH, which suggested lower levels of IGFBP-3 in girls with a BCFH that experienced faster weight gain. There was no evidence of interaction by BCFH for IGF-1 or the IGF-1/IGFBP-3 molar ratio ($p>0.05$). The interaction observed for IGFBP-3 could be due to chance, particularly given the small sample size for the infancy analyses.

The inference was the same for each exposure of interest when we modelled the square root of IGF-1 and the IGF-1/IGFBP-3 molar ratio as the outcome instead of the untransformed values (**Supplemental Table 5.3**).

5.4 Discussion

Similar to previous studies, we observed increases in serum levels of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio with age and breast Tanner stage with a peak in late puberty in a pubertal cohort enriched for BCFH. Although the associations were not statistically significant, serum levels of IGF-1 and the IGF-1/IGFBP-3 molar ratio were higher in girls whose mothers were overweight or obese prior to pregnancy and gained more than 30lbs. Higher birthweight was associated with lower serum IGF-1 levels. In the subset of girls with infant growth data, adjustment for weight gain from 0-12 months attenuated the negative association between birthweight and IGF-1, suggesting that the birthweight association is mediated by postnatal growth. We also observed an independent association between faster rates of weight gain during infancy and higher levels of the IGF-1/IGFBP-3 molar ratio in girls during puberty. The magnitude of the association for infant weight gain and the molar ratio was double that of current BMI, which was not associated with IGF levels after adjustment for Tanner stage. These findings support that rapid growth during infancy, and potentially maternal pre-pregnancy body size and GWG, are associated with biological differences in IGF levels that are consistent with pubertal development.

In **Chapters 3** and **4**, we found that higher maternal pre-pregnancy BMI, excess GWG, maternal physical inactivity during pregnancy and rapid growth during infancy were associated with earlier onset of breast development. Ruling out information bias and confounding as an explanation for these findings is a challenge, particularly since breast development was based on maternal report and maternal pregnancy factors, infant growth and pubertal timing are socially patterned.[242,293] This pilot study can help to assess the likelihood that the associations between these factors and the timing of breast development were driven by these potential biases. Lab personnel that conducted the serum assays were blinded to exposure and pubertal status, limiting the potential for systematic bias in biomarker assessment, and the reliability of the assays suggest a minimal amount of random error. Although our sample size was small, serum biomarkers of IGF-1 and IGFBP-3 increased with age and breast Tanner stage in our sample and can be considered a physiological indicator of pubertal onset. Therefore, the association between rapid infant weight gain and higher levels of IGF-1 relative to IGFBP-3 in this analysis reduces the likelihood that the association that we observed between infant growth and earlier onset of breast development is driven by error in maternal report of breast onset. Higher IGF-1 levels in girls with high maternal pre-pregnancy BMI and GWG are also consistent with our finding of earlier breast development in this group. In addition, IGF measures did not vary by maternal education, which supports that confounding by SES is also not a likely explanation for these associations. In contrast, maternal physical inactivity during pregnancy was associated with lower, albeit not statistically significant, levels of IGF-1, IGFBP-3 and their molar ratio, which is not consistent with our finding of earlier breast development in these girls.

BCFH did not modify the associations that we observed between maternal pregnancy and infant factors and serum measures of IGF-1 and the IGF-1/IGFBP-3 ratio. However, we would not rule out the possibility of interaction by BCFH based on these analyses as we may have lacked power to detect statistically significant differences by BCFH. We did not observe an association between BCFH and mean IGF-1 and IGFBP-3 levels after adjustment for age and breast Tanner stage. Studies of differences in IGF-1 by BCFH in adulthood have not consistently observed an association. A pooled study of over 9000 women (mean age varied from 35.5-71.8 by study included in the pooled analysis) did not find a difference in IGF-1 levels in adulthood in women with or without a first-degree family history of breast cancer.[294] However, a study of 400 women (mean age 56.6±7.1) did observe higher mean IGF-1 levels in women with a first-

degree family history of breast cancer.[295] Since BCFH may be associated with earlier age at menarche,[165] changes in IGF-1 and IGFBP-3 levels across puberty may differ in girls with a BCFH, a hypothesis that we will explore in future studies.

The relations between body size, growth and levels of IGF-1 across the life course is complex. Higher birthweight has generally been found to be associated with higher levels of IGF-1 in cord blood[296–298] and in blood samples measured shortly after birth.[299] However, previous studies have found negative correlations between birthweight and circulating IGF-1 levels as early as 3 months of age[300] and into childhood,[301–304] which is consistent with the negative association that we observed in girls during puberty. In childhood, the highest levels of IGF-1 have been observed in taller and heavier children that weighed less at birth.[302–304] Barker and colleagues have suggested that this negative association between birth weight and IGF levels is due to the re-programming of the IGF-1 axis in response to undernutrition *in utero*, either due to higher levels of postnatal nutrition than anticipated based on the intrauterine environment or to IGF-1 resistance developed in response to prenatal undernutrition.[303] An alternative hypothesis is that rapid postnatal weight gain, which is more common in low birthweight infants, programs higher IGF-1 levels into childhood. Our finding that faster infant weight gain is associated with higher levels of IGF-1 during puberty, and that infant weight gain may mediate the association between birthweight and lower levels of IGF-1, supports this alternative hypothesis. Rapid weight gain between birth and 2 years was also associated with higher levels of IGF-1 at 5 years of age in the ALSPAC cohort.[302] In a study of twins and their non-twin siblings, lower birthweight was associated with higher levels of IGF-1 at 18 years of age only in adolescents that experienced catch-up growth, defined as an increase of >0.67 SD from birth to 2 years of age.[305] These studies point to the importance of postnatal growth in setting IGF-1 trajectories in childhood and adolescence. Since higher IGF-1 levels during childhood have been associated with earlier age at menarche[306] and faster progression through the pubertal growth spurt,[307] rapid infant weight gain may affect pubertal tempo through programming pathways involving the IGF system. We will explore this hypothesis in future analyses.

Strengths of this study include the repeated assessment of IGF-1 and IGFBP-3 during puberty in girls with and without a BCFH and the prospective assessment of infant growth through medical record

data. Although our analysis was limited to 109 girls, the patterns of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio by age and breast Tanner stage in our sample were similar to the trends observed in large, cross-sectional studies.[51,52,289,292,308] The sample size did limit our power to detect significant differences in mean biomarker levels, particularly for categorical exposures, and limited the number of confounders that could be included in multivariable models. Since only a small subset of girls had both infancy and serum biomarker data, we could not examine smaller windows of growth during infancy in relation to IGF levels. Girls with a BCFH were relatively under-represented in the subset with IGF measurements, which could have reduced our power to detect a significant effect of BCFH on mean IGF measures or an interaction effect. Given our small sample size, replication of our results in larger studies is warranted.

5.5 Conclusions

Higher maternal pre-pregnancy BMI, increased GWG and rapid weight gain during infancy were associated with higher mean levels of serum IGF-1 and the IGF-1/IGFBP-3 molar ratio, a measure of bioactive IGF-1, in girls during puberty. These biological changes are consistent with pubertal development, which supports that the associations that we observed between these maternal pregnancy factors, infant growth and the timing of breast development are less likely to be driven by error in outcome assessment or confounding. Future analyses will examine whether early-life growth and BCFH are associated with trajectories of IGF-1 across puberty and the timing of later pubertal markers, including age at peak height velocity and age at menarche, which are associated with increased breast cancer risk.[41,287]

5.6 Tables and figures

Table 5.1. Biomarker concentrations from first available sample by early-life and adolescence characteristics (N=109 girls from the LEGACY Girls Study, New York site)

Early-life characteristics	Participants, N (%)	Biomarker concentrations, Median (Interquartile Range)		
		IGF-1 (ng/ml)	IGFBP-3 (ng/ml)	IGF-1/IGFBP-3 molar ratio*
Maternal pre-pregnancy BMI and gestational weight gain				
BMI <25 and GWG<30lbs	29 (27.6)	245 (131, 324)	3219.6 (2845.6, 3460.6)	0.28 (0.19, 0.35)
BMI <25 and GWG≥30lbs	44 (41.9)	189 (149, 290.5)	3060.9 (2711.2, 3393.6)	0.24 (0.20, 0.32)
BMI ≥25 and GWG<30 lbs	20 (19.1)	230 (146.5, 285.5)	3016.4 (2735.1, 3537.4)	0.31 (0.20, 0.35)
BMI≥25 and GWG≥30 lbs	12 (11.4)	277 (175, 323.5)	3590.9 (3062.9, 3765.6)	0.29 (0.18, 0.34)
Maternal recreational physical activity during pregnancy				
Inactive, no walking or other regular exercise	19 (17.8)	226 (134, 284)	3096.7 (2860.3, 3460.7)	0.26 (0.18, 0.33)
Mostly inactive, equivalent to walking about half a mile or less every day	26 (24.3)	209 (132, 315)	3112.6 (2657.7, 3562.8)	0.27 (0.19, 0.37)
Somewhat active, equivalent to walking about 1 mile every day	19 (17.8)	227 (146, 304)	3139.2 (2817.5, 3566.5)	0.26 (0.20, 0.30)
Active or highly active, equivalent to walking about ≥2 miles every day	36 (40.2)	217 (147, 332)	3259.3 (2742.5, 3688.7)	0.28 (0.19, 0.34)
Birthweight				
<2500g	13 (12.0)	226 (151, 340)	3155.1 (2701.2, 3374.6)	0.29 (0.20, 0.33)
2500-2999g	17 (15.7)	210 (167, 318)	3151.9 (2843.2, 3326.3)	0.26 (0.20, 0.35)
3000-3499g	35 (32.4)	245 (149, 315)	3308.9 (2858.3, 3713.7)	0.30 (0.19, 0.37)
3500-3999g	34 (31.5)	192.5 (137, 300)	3118.0 (2670.1. 3653.9)	0.24 (0.20, 0.32)
≥4000g	9 (8.3)	142 (102, 227)	2855.6 (2529.5, 2890.6)	0.20 (0.15, 0.29)
Birthlength				
<48.25	8 (9.8)	170.5 (112.6, 255)	3114.2 (2344.6, 3282.4)	0.21 (0.15, 0.32)
48.25-50.74	20 (24.4)	263 (167.5, 329)	3340.2 (2999.4, 3701.2)	0.31 (0.23, 0.34)
50.75-53.24	22 (26.8)	196 (159, 332)	3060.9 (3845.6, 3423.0)	0.25 (0.21, 0.34)
≥53.25	32 (39.0)	174 (141.5, 285)	2886.0 (2711.3, 3385.8)	0.24 (0.19, 0.32)

Weight gain pattern from 0-12 months				
Rapid	16 (44.4)	213.5 (146, 324.5)	3044.5 (3824.4, 3393.5)	0.24 (0.19, 0.38)
Stable	14 (38.9)	166.5 (142, 282)	3002.1 (2656.4, 3542.7)	0.23 (0.18, 0.33)
Slow	6 (16.7)	139 (112, 171)	3101.4 (2817.5, 3299.1)	0.20 (0.17, 0.20)
Height gain pattern from 0-12 months				
Rapid	9 (28.1)	282 (247, 325)	2939.3 (3845.6, 3262.4)	0.36 (0.29, 0.43)
Stable	15 (46.9)	146 (128, 210)	2864.9 (2642.7, 3212.0)	0.20 (0.18, 0.26)
Slow	8 (25.0)	172 (153, 238)	3261.4 (2978.4, 3657.2)	0.21 (0.19, 0.28)
Adolescent characteristics				
BMI-for-age percentile at first serum sample				
≥85th BMI-for-age percentile	30 (27.8)	226.5 (152, 299)	2917.6 (2775.9, 3446.7)	0.29 (0.21, 0.35)
<85th BMI-for-age percentile	78 (72.2)	205 (135, 313)	3215.8 (2742.5, 3584.5)	0.25 (0.18, 0.33)
Breast Tanner stage at first serum sample	,			
1	45 (46.4)	151 (126, 199)	2890.6 (2612.0, 3262.4)	0.20 (0.16, 0.25)
≥2	52 (53.6)	307 (248.5, 342.5)	3424.3 (2941.3, 3756.6)	0.33 (0.29, 0.37)
Breast cancer family history in a first- or second-degree relative				
BCFH+	44 (40.4)	263 (165, 314)	3257.6 (2850.6, 3663.9)	0.31 (0.21, 0.35)
BCFH-	65 (59.6)	186 (131, 292)	3073.2 (2680.0, 3401.8)	0.24 (0.17, 0.31)
Race/ethnicity				
Hispanic	43 (39.5)	227 (134, 304)	3219.6 (2775.9, 3713.7)	0.27 (0.18, 0.33)
Non-Hispanic black	14 (12.8)	249.5 (175, 343)	3103.1 (2803.1, 3271.8)	0.31 (0.24, 0.38)
Non-Hispanic white	43 (39.5)	171 (137, 282)	3096.7 (2656.4, 3423.0)	0.22 (0.19, 0.33)
Asian/Pacific Islander	4 (3.7)	298 (204.5, 318)	3232.8 (2909.6, 3648.8)	0.33 (0.22, 0.38)
Other or mixed race/ethnicity	5 (4.6)	299 (168, 383)	3210.3 (3017.6, 3729.8)	0.35 (0.23, 0.38)
Maternal education				
Some college, vocational or technical school or less	37 (33.9)	227 (139, 340)	3374.6 (2890.6, 3678.9)	0.28 (0.18, 0.34)
Bachelor's degree	30 (27.5)	226.5 (147, 299)	3072.4 (2803.1, 3401.8)	0.28 (0.20, 0.33)
Graduate degree	42 (38.5)	188 (131, 284)	3060.9 (2656.4, 3326.3)	0.23 (0.19, 0.32)

*Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

Table 5.2. Range of biomarker data by age (N=289 samples from 109 girls)

	N of samples	IGF-1 (ng/ml)					IGFBP-3 (ng/ml)					IGF-1/IGFBP-3 molar ratio[a]				
		Min	Q1	Med	Q3	Max	Min	Q1	Med	Q3	Max	Min	Q1	Med	Q3	Max
All	289	70.7	160	248	314	547	1549.5	2845.6	3210.3	3584.5	5203.4	0.121554	0.202596	0.288455	0.350003	0.570691
By age																
6	13	70.7	112	129	173	227	2018.5	2495.5	2881.3	3155.1	3614.1	0.127576	0.153264	0.172047	0.19694	0.29511
7	23	82.2	124	133	146	218	1960.3	2652.4	2855.6	3151.9	3826.3	0.12765	0.154843	0.175801	0.200882	0.281942
8	30	95.8	121	146	195	340	2010.9	2477.2	3183.8	3423	4066.2	0.121554	0.161206	0.190258	0.233524	0.428065
9	35	83.1	142	170	206	383	1549.5	2728.6	3050.3	3505	4173.7	0.128089	0.189028	0.21339	0.24702	0.476961
10	38	87.4	172	239	336	547	1709.2	2701.2	3057.2	3633.4	4768.4	0.122475	0.234879	0.306161	0.374165	0.570691
11	33	112	267	297	340	502	1981.5	3015.9	3401.8	3688.3	5203.4	0.127859	0.295235	0.337014	0.381115	0.491935
12	32	157	272	316	349	419	1918	3047.25	3236.1	3579.75	4487	0.165868	0.317843	0.351271	0.395075	0.52254
13	37	134	256	307	340	448	2108.7	3085.6	3271.8	3713.7	4281.6	0.176051	0.299655	0.326492	0.371517	0.50664
14	19	242	254	301	334	388	2303.9	3308.9	3518.3	3836.7	4680.9	0.270399	0.285803	0.334051	0.356746	0.450186
15	17	147	228	274	290	352	2438.8	2929.8	3408.1	3750	4285.3	0.196929	0.276324	0.296837	0.325793	0.46997
16	8	168	237	302	328	356	2301.3	3192.4	3561.9	3851.25	4526.8	0.183297	0.275556	0.304786	0.363522	0.387009
17	4	223	224	251	313	349	2854.7	2979.15	3655.9	4242.45	4276.8	0.247366	0.25869	0.283101	0.301423	0.306657

*Some age groups contain two samples from the same girl, as samples were sometimes taken 6 months apart.

[a]Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

Table 5.3. Difference in mean levels of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio by maternal factors

	IGF-1 (ng/ml)			***IGFBP-3 (ng/ml)***			***IGF-1/IGFBP-3 molar ratio****		
	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	p for intx with BCFH[c]	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	p for intx with BCFH[c]	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	p for intx with BCFH[c]
Maternal pre-pregnancy BMI (per 1 kg/m²)	3.18 (-0.06, 6.43)	1.77 (-1.72, 5.26)	0.39	17.76 (-5.97, 41.50)	22.72 (-3.35, 48.80)	0.12	0.002 (-0.001, 0.005)	0.000 (-0.003, 0.003)	0.07
Maternal recreational physical activity during pregnancy[d]			0.89			0.82			0.16
Inactive, no walking or other regular exercise	-29.24 (-68.40, 9.93)	-37.09 (-79.00, 4.82)		-139.37 (-426.05, 147.32)	-154.29 (-466.52, 157.94)		-0.02 (-0.06, 0.02)	-0.03 (-0.07, 0.01)	
Mostly inactive, equivalent to walking about half a mile or less every day	-10.07 (-41.83, 21.70)	-13.94 (-48.08, 20.19)		-125.64 (-377.45, 126.18)	-147.57 (-415.85, 120.70)		0.02 (-0.02, 0.05)	0.01 (-0.02, 0.04)	
Somewhat active, equivalent to walking about 1 mile every day	-8.05 (-41.48, 25.38)	-2.77 (-38.85, 33.30)		17.51 (-253.57, 288.59)	21.30 (-267.72, 310.32)		-0.01 (-0.05, 0.02)	0.00 (-0.03, 0.04)	
Active or highly active, equivalent to walking about ≥2 miles every day	Reference	Reference		Reference	Reference		Reference	Reference	
Gestational weight gain[d]			0.27			0.73			0.56
<20 lbs	17.21 (-23.30, 57.72)	1.22 (-42.15, 44.59)		99.10 (-260.64, 458.84)	94.26 (-239.84, 428.36)		0.02 (-0.02, 0.06)	0.01 (-0.03, 0.05)	
20-29 lbs	Reference	Reference		Reference	Reference		Reference	Reference	
30-39lbs	26.90 (-4.33, 58.13)	26.15 (-8.29, 60.59)		21.02 (-250.33, 292.37)	-9.94 (-293.75, 273.86)		**0.03 (0.00, 0.06)**	**0.04 (0.01, 0.07)**	
40-49lbs	6.72 (-29.44, 42.88)	11.54 (-29.07, 52.16)		-18.00 (-324.53, 288.52)	-25.57 (-352.18, 301.04)		0.01 (-0.03, 0.04)	0.02 (-0.02, 0.06)	
≥50 lbs	22.82 (-17.06, 62.70)	17.95 (-27.22, 63.11)		79.90 (-231.00, 390.80)	104.44 (-241.74, 449.96)		0.02 (-0.03, 0.05)	0.01 (-0.03, 0.06)	
Maternal pre-pregnancy BMI and GWG			0.10			0.10			0.16
BMI<25 and <30 lbs	Reference	Reference		Reference	Reference		Reference	Reference	
BMI<25 and ≥30 lbs	11.09 (-22.43, 44.60)	15.58 (-19.24, 50.40)		-37.01 (-286.87, 212.86)	-59.15 (-325.46, 207.16)		0.02 (-0.02, 0.05)	0.02 (-0.01, 0.08)	

BMI≥25 and <30lbs	20.08 (-20.28, 60.44)	15.70 (-26.25, 57.65)	73.46 (-226.27, 373.19)	85.78 (-234.76, 406.31)	0.01 (-0.03, 0.05)	0.00 (-0.04, 0.04)
BMI≥25 and ≥30 lbs	**48.46 (1.75, 95.18)**	**51.08 (1.10, 101.05)**	140.90 (-222.02, 503.82)	169.31 (-221.00, 559.63)	0.03 (-0.02, 0.07)	0.04 (-0.01, 0.08)

*Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

[a]Adjusted for age at blood draw (centered) and quadratic of age at blood draw (centered)

[b]Adjusted for age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit and BMI-for-age percentile at visit (centered)

[c]P for interaction from F test from Model 2

[d]Models also adjusted for maternal pre-pregnancy BMI (continuous)

Table 5.4. Difference in mean levels of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio by size at birth

	IGF-1 (ng/ml)				***IGFBP-3 (ng/ml)***				***IGF-1/IGFBP-3 molar ratio****			
	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)	p for intx with BCFH[d]	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)	p for intx with BCFH[d]	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)	p for intx with BCFH[d]
Birthweight (per 500g increase)	-12.53 (-25.27,0.20)	**-13.61 (-26.72,-0.50)**	-15.80 (-33.04,1.44)	0.09	-45.75 (-137.46,45.97)	-38.32 (-136.69,60.04)	-33.00 (-163.35,97.35)	0.26	-0.01 (-0.02,0.00)	-0.01 (-0.02,0.00)	-0.01 (-0.03,0.01)	0.41
Birthlength (per 1cm increase)	-1.02 (-6.00,3.97)	-0.17 (-5.11,4.78)	1.05 (-3.99,6.09)	0.18	4.49 (-31.09,40.06)	7.03 (-31.18,45.23)	9.68 (-30.13,49.50)	0.10	-0.001 (-0.006,0.004)	-0.001 (-0.006,0.004)	0.000 (-0.005,0.005)	0.53

*Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

[a]Adjusted for maternal pre-pregnancy BMI (continuous), preterm, age at blood draw (centered) and quadratic of age at blood draw (centered)

[b]Adjusted for maternal pre-pregnancy BMI (continuous), preterm, age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit and BMI-for-age percentile at visit (centered)

[c]Model 2 mutually adjusted for birthweight and birthlength

[d]P for interaction from F test from Model 2

Table 5.5. Difference in mean levels of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio by growth during infancy

	IGF-1 (ng/ml)				***IGFBP-3 (ng/ml)***				***IGF-1/IGFBP-3 molar ratio****			
	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)	p for intx with BCFH[d]	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)	p for intx with BCFH[d]	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)	p for intx with BCFH[d]
Growth from 0-12 months												
Change in weight-for-age Z-score	20.28 (-5.68,46.24)	14.49 (-13.29,42.27)	16.87 (-17.03,50.76)	0.40	-115.77 (-324.12,92.57)	-145.13 (-377.58,87.32)	-104.80 (-383.40,173.81)	0.02	**0.04 (0.01,0.06)**	**0.03 (0.01,0.06)**	0.03 (-0.00,0.06)	0.42
Change in length-for-age Z-score	20.03 (-8.33,48.40)	2.45 (-28.26,33.17)	-4.31 (-40.16,31.54)	0.78	-111.22 (-333.29,110.86)	-148.26 (-391.45,94.93)	-94.23 (-388.10,199.64)	0.18	**0.04 (0.01,0.06)**	0.02 (-0.01,0.05)	0.01 (-0.03,0.04)	0.18
Growth from 0-6 months												
Change in weight-for-age Z-score	12.07 (-17.29,41.43)	-1.50 (-34.50,31.50)	0.86 (-38.07,39.79)	0.43	-73.69 (-305.39,158.01)	-116.88 (-387.14,153.37)	-184.73 (-497.36,127.91)	0.01	0.02 (-0.01,0.05)	0.01 (-0.03 0.05)	0.02 (-0.02,0.06)	0.35
Change in length-for-age Z-score	11.03 (-14.03,36.09)	-4.71 (-30.93,21.51)	-1.31 (-32.70,30.08)	0.69	41.78 (-152.04,235.61)	26.27 (-184.32,236.86)	95.27 (-153.42,343.96)	0.60	0.01 (-0.02,0.03)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)	0.51
Growth from 6-12 months[e]												
Change in weight-for-age Z-score	37.52 (-9.96,84.99)	42.33 (-3.19,87.85)	58.04 (-4.91,120.99)	0.40	-198.56 (-587.84,190.72)	-179.62 (-77.83,218.58)	31.30 (-496.45,559.06)	0.50	**0.07 (0.02,0.11)**	**0.07 (0.03,0.12)**	**0.07 (0.01,0.13)**	0.59
Change in length-for-age Z-score	18.17 (-14.90,51.24)	6.31 (-28.75,41.36)	-18.29 (-62.04,30.18)	0.99	-178.30 (-434.40,77.80)	-210.41 (-488.83,68.00)	-211.40 (-577.00,154.19)	0.05	**0.04 (0.01,0.07)**	0.03 (-0.01,0.07)	-0.00 (-0.04,0.04)	0.07

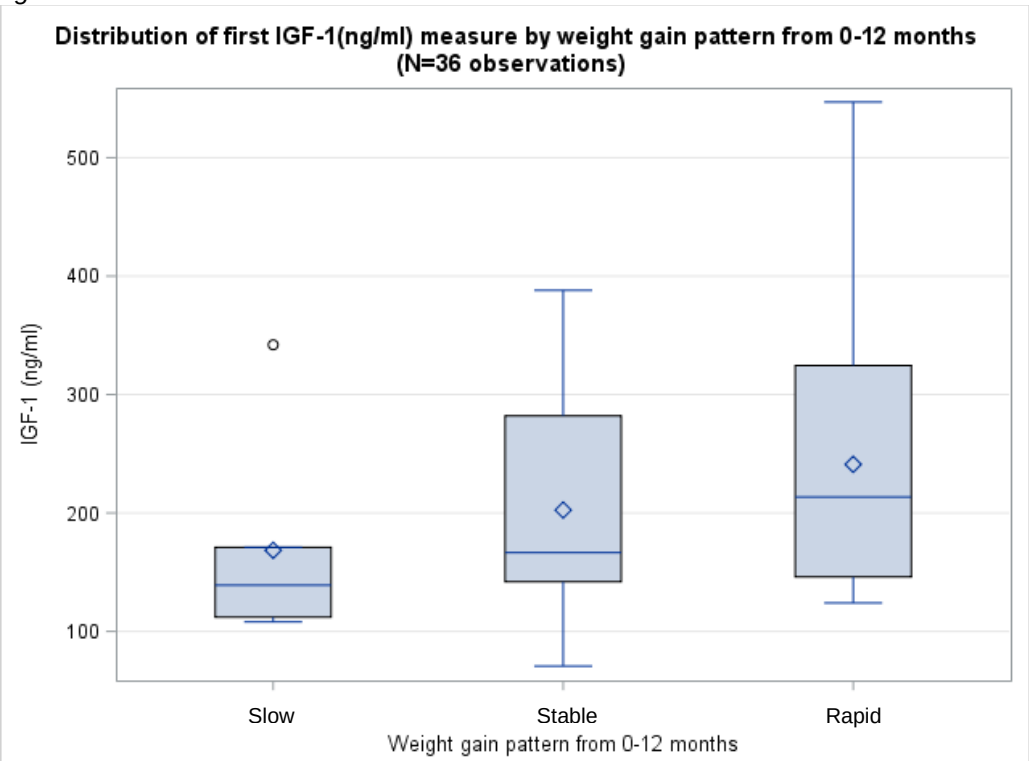
*Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

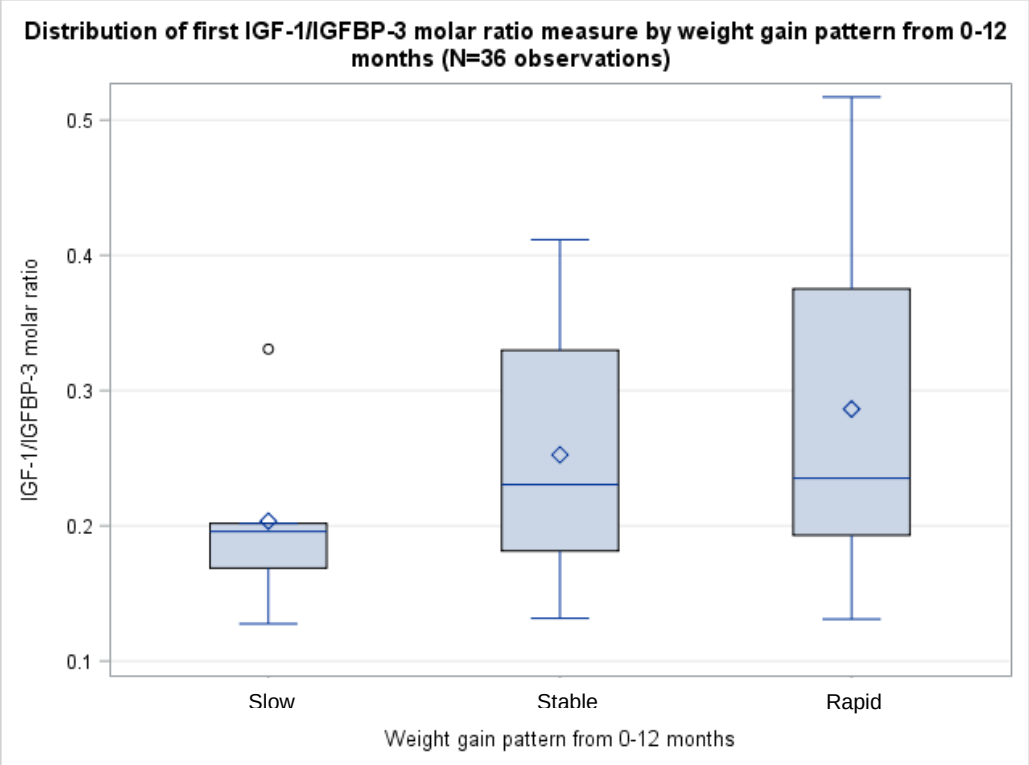
[a]Adjusted for maternal pre-pregnancy BMI (continuous), weight-for-age or length-for-age Z-score at birth, age at blood draw (centered) and quadratic of age at blood draw (centered)
[b]Adjusted for maternal pre-pregnancy BMI (continuous), weight-for-age or length-for-age Z-score at birth, age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit (TS1 vs. TS2+) and BMI-for-age percentile at visit (centered)
[c]Model 2 mutually adjusted for change in weight and length

[d]P for interaction from F test from Model 2

[e]Additionally adjusted for change in WAZ or LAZ from 0-6 months

Figure 5.1. Boxplots of first a) IGF-1 (ng/ml) and b)IGF-1/IGFBP-3 molar ratio measure by rapid, stable, and slow weight gain patterns from birth-12 months. *These plots include 36 girls, 6 with slow weight gain, defined as a change in weight-for-age Z-score from 0-12 months of less than -0.67, 14 girls with stable weight gain, defined as a change in weight-for-age Z-score from 0-12 months between -0.67 and 0.67, and 16 girls with rapid weight gain, defined as a change in weight-for-age Z-score from 0-12 months of greater than 0.67.*





Chapter 6. Conclusions

The age at onset of breast development has declined dramatically in the past 50 years.[42,60,61] The obesity epidemic contributes to earlier onset of breast development, but does not fully explain this secular trend.[61] Since earlier age at breast development is associated with higher breast cancer risk,[41] identifying modifiable factors that can delay the onset of breast development may provide an opportunity for breast cancer primary prevention starting early in life.[4,5] Thus, the overall goal of this dissertation was to identify modifiable factors that are associated with earlier age at breast development, and examine if these associations vary by underlying breast cancer susceptibility based on family history. First, we reviewed the literature connecting maternal body size, gestational weight gain (GWG), size at birth and growth during infancy and age at breast development and menarche to identify inconsistencies and gaps in the evidence base. Second, we examined associations between modifiable maternal factors, including pre-pregnancy BMI, GWG and physical activity during pregnancy, and birth size and the onset of breast development in girls with and without a breast cancer family history (BCFH). Third, we examined associations between rates of growth in weight and length during multiple age intervals from birth to one year and the onset of breast development and whether these associations varied by BCFH. Fourth, we conducted a pilot study assessing whether the modifiable maternal and infancy exposures associated with timing of breast development also influenced serum levels of IGF-1 and IGFBP-3, biomarkers that are known to increase during puberty. This chapter summarizes the results of this dissertation, the contribution of these findings for the design and interpretation of studies of breast development, and their public health implications.

6.1 Main findings

In **Chapter 2**, we identified 96 articles that examined at least one of our exposures of interest (maternal pre-pregnancy weight or BMI, GWG, size at birth, or measures of size and/or growth between birth and 2 years) in relation to the timing of breast development, menarche or the time period between these two events (pubertal tempo). There were three main findings of this systematic review. First, although low birthweight is often cited as a risk factor for early menarche, the majority of studies (40/73 total) that examined birthweight in relation to age at menarche did not observe a statistically significant association.

Differences in exposure assessment, such as whether or not gestational age was taken into consideration, and control for confounders contributed to this heterogeneity and made it difficult to compare results across studies. However, examining disparate findings within the same study population suggested that associations observed between birthweight and menarche may be driven by postnatal growth patterns, and that differences across studies may be related to differences in postnatal growth. The majority of studies examining birthweight and breast development also did not observe a statistically significant association. Second, although comparatively fewer studies examined maternal pre-pregnancy BMI, GWG and/or infant growth and pubertal timing compared with the birthweight literature, higher maternal BMI prior to pregnancy, GWG in excess of recommended guidelines and faster rates of weight gain between birth and 2 years were consistently associated with earlier age at breast development and menarche. A general limitation of this literature, which likely contributes to the consistency of associations, is that much of the evidence comes from the same cohorts. For example, three separate publications examined maternal obesity and pubertal timing in the ALSPAC cohort,[73,82,114] while two publications examined infant growth and menarche.[35,73] In addition, studies that examined growth during infancy considered different age intervals, which complicates comparisons across studies, and were not consistent in identifying smaller windows within infancy in which growth had a stronger influence on pubertal timing. Third, many studies inappropriately controlled for variables on the causal pathway between the early-life exposures and pubertal outcomes as confounders and did not interpret these associations as mediated effects. Studies should explicate their assumed causal framework and use a directed acyclic graph (DAG) to guide modeling decisions, as well as consider potential effect measure modifiers. In addition, few studies considered whether associations differed by factors associated with rapid weight gain, such as birthweight or infant feeding, and/or earlier pubertal timing, such as race/ethnicity, socioeconomic status or BCFH. Overall, this review of the literature highlights the methodological limitations that future studies can overcome in the analysis or design phase to strengthen the existing evidence and identifies gaps in the literature that future studies can address.

In **Chapter 3**, we addressed some of the limitations and gaps in the literature by examining associations between maternal pre-pregnancy BMI, GWG, and size at birth and the onset of breast development in the LEGACY Girls Study, a prospective pubertal cohort in which approximately 50% of girls had a BCFH. We used a DAG (**Figure 2.2**) to inform our strategy for modeling multiple exposures that have

an inherent temporal order and to avoid adjusting for variables on the causal pathway. We observed that while higher maternal pre-pregnancy BMI and higher GWG were each associated with earlier onset of breast development in daughters, daughters of women who were overweight or obese prior to pregnancy and gained more than 30lbs were at the highest risk of early breast development. Our findings were consistent with previous studies conducted in girls predominantly at average-risk for breast cancer, including the ALSPAC birth cohort[73,82] and a retrospective cohort nested in Kaiser Permanente Northern California (KPNC).[81,237] In addition, we found that girls experienced earlier breast development if their mothers did not engage in recreational physical activity during pregnancy. We extended the prior literature by formally testing whether these associations varied by BCFH. While we observed some differences by BCFH, our results suggested that among girls with a BCFH, girls still experienced earlier onset of breast development if their mothers were overweight or obese prior to pregnancy and gained more than 30lbs, or were not physically active during pregnancy. Consistent with the results of our systematic review, we did not observe associations between either birthweight or birthlength and the age at breast development. Altogether, our findings support that maternal body size prior to pregnancy, GWG and maternal physical activity during pregnancy, modifiable factors that are associated with the intrauterine environment, are associated with the timing of breast development in their daughters, but do not support an independent role for birth size.

It is possible that our findings could be due to chance given our modest sample size of just over 1,000 girls. However, the consistency of the observed association between earlier breast development in girls exposed to higher maternal pre-pregnancy BMI and higher GWG with studies conducted in cohorts like ALSPAC and KPNC, which included more than twice as many girls, suggest that our results are less likely to be spurious. In addition, the ALSPAC cohort also did not observe associations between birthweight or birthlength and timing of breast development.[73] LEGACY is the only pubertal cohort enriched for BCFH and therefore has greater statistical power to formally test interactions by BCFH than an average-risk cohort. That being said, it is possible that the interaction that we observed is due to chance, and our models stratified for BCFH are less precise than analyses using the full cohort.

In a similar vein, we can use a triangulation of evidence approach to consider the likelihood that our findings are due to selection bias, information bias or confounding by comparing our results to other studies that were susceptible to different types of biases. Selection bias can arise generally in a cohort study due to differential loss to follow-up. In addition, analyses that are limited to a subset of the overall cohort can also be vulnerable to bias resulting from subset selection. For our overall approach, we included all LEGACY girls participating with their biological mother (97% of the full cohort). The retention rate in LEGACY was 92% at the end of the first five years of follow-up, which limits the likelihood that bias related to loss to follow-up explains our study findings. However, since girls were primarily between the ages of 6-13 years at recruitment, approximately 40% of the cohort had already experienced the onset of breast development at cohort entry. We were concerned that we may induce selection bias if we excluded girls that had already experienced the onset of breast development prior to cohort entry. If the exposure was associated with earlier onset of breast development, excluding girls with early development would likely bias the results towards the null. We therefore included these girls by using left censoring in our primary analyses, and by using a recalled age at breast development in sensitivity analyses. We also limited our analyses to girls less than 8 years of age at baseline only, in which less than 5% experienced breast onset prior to cohort entry, and the inference was the same. Our findings were also consistent with the ALSPAC cohort, a birth cohort that collected pubertal development information starting at 8 years of age on all participants. Overall, this supports that selection bias is unlikely to explain the associations that we observed.

A limitation of the **Chapter 3** analyses is that the maternal and pregnancy exposures were recalled by mothers at the LEGACY baseline visit and may be reported with error. Validity studies of maternal recall of pregnancy exposures compared with either medical records or prospective maternal reports suggest that social desirability bias affects maternal recall of pregnancy-related events, particularly in the report of maternal behaviors, such as alcohol consumption during pregnancy.[309–311] In LEGACY, the prevalence of maternal smoking during pregnancy was less than 2%, which limited us from examining maternal smoke exposure on its own or as a confounder in the analyses due to small cell counts. Approximately 7% of women who gave birth in 2016 smoked during pregnancy based on data from the National Vital Statistics System,[312] suggesting that maternal smoking during pregnancy may be under-reported by LEGACY

mothers. While there likely is some under-reporting of smoking due to stigma, the prevalence of smoking in LEGACY may also be lower than the national average since the LEGACY cohort is skewed towards a higher socioeconomic status. Other pregnancy conditions such as pre-eclampsia and gestational diabetes may also be reported with error. While there is likely some misclassification of the maternal body size and birth size exposures as well, studies have observed fairly good agreement for factors such as birthweight, pre-pregnancy weight and duration of pregnancy.[309–311]

In cohort studies, it is commonly assumed that information bias related to the exposure is likely to be non-differential with respect to the outcome. If that were the case, maternal under-reporting of exposures including maternal pre-pregnancy BMI and GWG and over-reporting of recreational physical activity during pregnancy, which could result from social desirability bias, would likely bias our findings towards the null. However, since mothers recalled their pre-pregnancy weight, GWG and other pregnancy factors at the baseline interview when daughters were primarily 6-13 years old, this data could be susceptible to differential recall bias for the mothers whose daughters have already gone through breast development. While it seems unlikely that maternal recall of pregnancy characteristics would depend on her daughters' stage of breast development, it is possible that measurement error in maternal recall of pregnancy exposure data could differ by daughters' body size, which is associated with pubertal timing. For example, mothers of overweight daughters may be more or less likely to report that they were overweight prior to pregnancy, gained more weight during pregnancy, or exercised less. The bias in estimating associations between these factors and the onset of breast development, which is also reported by the mother, may be towards or away from the null. However, the similarity of our results with those of the ALSPAC and KPNC cohorts, which calculated GWG based on medical record data and, in the case of ALSPAC, validated self-reported pre-pregnancy BMI with medical records based in early pregnancy,[82] suggests that recall bias does not explain these associations.

In addition to exposure misclassification, error in assessing the onset of breast development may also bias study findings. As detailed in **Chapter 3**, we conducted multiple sensitivity analyses to consider how robust our findings were to different methods of assessing breast development, including the use of clinical breast Tanner staging in the subset of girls with clinical data, the use of the Pubertal Development

Scale to assess breast development, and the exclusion of girls with inconsistent Tanner staging. The inference was the same across these sensitivity analyses, which supports that errors in outcome assessment are less likely to explain our findings. When considering the literature as a whole, the consistency of the associations between maternal pre-pregnancy BMI and GWG and earlier onset of breast development across cohorts that used different sources of breast development information (i.e. medical records, parent assessments, and self-assessments) and assessed development at different age intervals (i.e. biannually, annually, or based on physician visits) supports that measurement error in assessing the onset of breast development is unlikely to drive the observed associations.

Finally, our findings could be due to confounding. Maternal body size, GWG and physical activity levels during pregnancy vary by race/ethnicity and socioeconomic status (SES), which are also associated with pubertal timing. While we controlled for race/ethnicity and maternal education in our primary analyses, there may be residual confounding by socioeconomic status. We were also concerned with sparse data due to small cell counts and violations of the positivity assumption, particularly in the subset of girls less than 8 years at baseline, which limited the amount of variables that we included in adjusted models. Again, the consistency of our findings with larger cohorts that were able to control for more confounding variables suggests that confounding is not completely driving the observed associations. As the cohort ages into adolescence and all girls experience the onset of breast development, future analyses within LEGACY will be able to take advantage of the many siblings sets within the cohort to conduct within-family analyses, which control for shared family characteristics such as SES by design.[313] In addition to confounding, future studies need to consider exposures that may modify the associations between maternal pregnancy factors and the onset of breast development, such as race/ethnicity, SES and birth order. Since interaction requires increased statistical power, these analyses will require either very large cohorts, such as a KPNC study of over 15,000 girls which found that race/ethnicity did not modify the association between maternal pre-pregnancy BMI and the onset of breast development,[81] or studies enriched for a modifier for interest, like LEGACY is enriched for BCFH. These studies will provide a valuable contribution to the literature and will also aid in the interpretation of smaller studies that are not powered to examine these interactions.

Although we cannot completely rule out bias as an explanation for our study findings, the consistency of our results with previous studies in which selection bias, information bias, and confounding would likely operate in different ways support that these types of biases are not driving our findings. Given the rich pubertal outcome data collected in LEGACY, we were also able to conduct multiple sensitivity analyses to examine how differences in the assessment of breast development affects the estimated age at onset of breast development and estimates of exposure-outcome associations. These analyses suggest that our findings are robust to differences in outcome assessment, and may be informative in the interpretation of future studies that use different methods to assess breast development.

Our primary goal in these analyses was to estimate the total effect of the maternal and pregnancy exposures on the age at breast development. As a secondary aim, we also considered whether these associations were mediated by daughters' body size prior to puberty. We considered a BMI measure between 5-7 years of age as pre-puberty, since less than 5% of girls had experienced the onset of breast development by 8 years of age. Since girls were mostly age 6-13 years at baseline, our mediation analyses were limited to the approximately 60% of the cohort that had a BMI measure available between 5-7 years of age, either from the baseline LEGACY visit for younger girls or from available medical record data. Within this subset, we used the Baron and Kenny approach[314] to examine the presence of mediation by comparing the results of models with and without adjustment for pre-pubertal BMI. Limitations of this approach is that the total effect does not decompose when using regression methods other than linear regression or in the presence of exposure-mediator interaction.[315] However, even when these assumptions are not met, this approach still provides a qualitative assessment of the presence or absence of mediation. Given these limitations, we do not interpret the results from models adjusting for pre-pubertal BMI as a quantitative estimate of the direct effect of the early-life exposure on the age at breast development. Instead, we interpret these models as supporting that a portion of the association between these early-life factors and the age at breast development works through the pathway of childhood body size. Since these models do not suggest full mediation by childhood body size, our findings also support that alternate pathways other than daughters' body size explain a portion of the association between early-life factors and breast development, and these additional pathways should be examined in future research. Since modifying these early-life factors would likely affect childhood body size in addition to these alternate pathways, the total

effect of these early-life exposures on the timing of breast development is of interest when considering primary prevention.

In **Chapter 4**, we used a subset of the LEGACY Girls Study with infant growth data available from medical record and growth chart data collected from pediatricians to address several gaps in the literature relating infant growth and the onset of breast development. We found that faster weight gain between birth and one year of age was related to earlier onset of breast development in girls, which was consistent with prior studies assessing infancy weight gain in relation to age at breast development and age at menarche. Since we had measures of height and weight across infancy from the linked medical records, we were able to replicate previous analyses by considering growth during the same age intervals. In addition, we identified stronger associations between rate of weight and length gain from 2-4 months and 6-9 months that were masked when looking only at wider age intervals. The specificity of these associations generated hypotheses that can be tested in future studies regarding the potential importance of mini-puberty, which corresponds approximately to the 2-4 months window, and nutrition during infancy and the timing of solid food introduction to breast development. We also formally tested the interaction between BCFH and infant growth and did not observe heterogeneity by BCFH in these associations.

As we did for **Chapter 3**, it is important to critically examine whether the associations that we observed between rates of change in weight and length and the timing of breast development arose from random or systematic error. While we obtained medical record data for 82% of LEGACY girls, multiple records of weight and length during infancy were only available for 24% of the full cohort, which limited the sample size for these analyses to 255 girls. If the infancy data were missing completely at random, random error could still lead to spurious findings in this subset. We also may not have had sufficient power in this subset to detect differences in the association by BCFH. A greater concern for the main effect of infant growth, however, is that the data is not missing completely at random and that selection bias affects the validity of our findings. We compared the distribution of baseline and early-life characteristics in girls by the availability of infancy data and observed differences by race/ethnicity and study site. Girls with infancy data also had a lower mean maternal pre-pregnancy BMI and a higher mean birthweight than girls without infancy data, suggesting that they may have had a lower prevalence of rapid weight gain during infancy.

We used inverse probability weighting (IPW) in sensitivity analyses to adjust for the differences between this subset and the full cohort under the assumption that the data were missing at random after conditioning on the variables included in the prediction model. IPW would not remove bias if data were not missing at random, but this missing data structure is less likely given the variables that were available to include in our prediction model. The inference was the same across the complete case and IPW analyses, suggesting that our findings are less likely to be caused by selection bias. In addition, our main findings were consistent with the analyses including more than 1,000 girls in the ALSPAC cohort, which are less likely to be driven by random error.

Information bias for the exposure is less of a concern for our infancy analyses since we used measures of weight and length from the medical record. While there may be some errors in measurement, errors are more likely to be random than systematic in nature. We did rely on parent recall of birthweight and birthlength, and also used imputed birthlength values for girls that were missing parent report. It is possible that parent recall of birth size could differ by daughters' body size. However, recalled birthweight was highly correlated with medical record data (r=0.9) in our validation subset, and birthlength had a moderate correlation (0.6). To minimize error due to the use of imputed birthlength data, we excluded girls whose imputed values were identified as outliers based on the Z-score values standardized to the CDC growth charts. While we imputed weight and length data at common time points, most girls had at least five different time points of measurements to include in the interpolation analysis. Therefore, we do not think that measurement error is a likely explanation for our study results. We assessed infant growth by using the change in weight-for-age and length-for-age Z-scores, standardized using the 2000 CDC growth charts. Our inference was similar when we used the 2006 WHO growth charts to calculate Z-scores, which supports that our choice of reference data did not drive our findings. Change in weight and length Z-scores across infancy were moderately correlated with birthweight and birthlength, respectively, and collinearity may have affected estimates from the mutually adjusted model. However, change in Z-scores between the smaller age intervals that we examined in our analyses were mostly uncorrelated with each other, which reduced concerns about collinearity.

Our infancy analyses were less robust to differences in outcome assessment than the associations that we observed between maternal factors and the onset of breast development. The sensitivity of these analyses to the use of recalled data for left censored girls or the use of the PDS to define breast onset may be due to the reduced sample size of this subset. It is also possible that higher sensitivity and lower specificity of maternal report of Tanner stage in overweight girls, who are more likely to have experienced faster infant weight gain, are driving the observed findings based on maternal report of Tanner stage. When we excluded overweight girls from the models, there was an attenuation of the effect estimates for weight gain, but only in models that also included growth in length. Analyses of infant weight gain in the ALSPAC and North Carolina Infant Feeding Study, which also used changes in Z-scores to assess growth, were based on parent and/or self-reports of breast Tanner stage and may have also been subject to information bias. Two studies of infant growth and breast development used clinical assessments of breast Tanner stage. In the 'Children of 1997' birth cohort, girls born light with slow growth during infancy, as assessed using latent class analysis, experienced later onset of breast development than girls with stable weight gain using biannual assessments of breast Tanner stage starting at 7 years of age from school health records.[92] In 140 girls from the Vulnerable Windows Cohort study in Jamaica, conditional measures of weight gain from 0-6 months and 6 month-2 years were not associated with breast Tanner stage assessed by research nurses at age 11 years.[79] However, this outcome likely did not capture onset of breast development, as the median breast Tanner stage of the girls was 2.8. Additional studies with repeated clinical assessments of breast Tanner stage will be helpful to rule out that associations between rapid weight gain and earlier breast development are the result of bias in outcome assessment.

The associations that we observed could be due to residual confounding by SES or maternal factors, as we controlled for a limited number of confounders in our infancy analyses due to the reduced sample size of this subset. We adjusted for the categorical maternal pre-pregnancy BMI and GWG variable that was associated with the timing of breast development in the full cohort and race/ethnicity, and our infant growth findings were independent of these effects. Our overall inference was also similar to the ALSPAC cohort, which adjusted for additional maternal characteristics including parity, smoking during pregnancy, maternal age at birth and at menarche, and maternal education.[73] In addition, the Children of 1997 cohort did not observe a significant confounding effect by variables including birth order, maternal

smoking during pregnancy, parent education and type of infant feeding in their analyses.[92] While these analyses reduce concerns about confounding, gaps in the literature that remain include the use of alternative design methods, such as sibling or twin studies, to control for confounding and the examination of modifiers, such as detailed infant feeding and nutrition data.

While we cannot eliminate the possibility that the associations that we observed are due to bias or chance, our study adds to a consistent literature that has identified rapid infant growth as a risk factor for earlier onset of breast development. Our study is the first to examine effect modification by BCFH, and we identified two narrow age intervals, 2-4 months and 6-9 months, where growth during infancy had a stronger influence on pubertal timing. While the specificity of these associations could be due to chance, the 2-4 month period corresponds with our hypothesis that growth during mini-puberty may be biologically relevant for breast development and suggests an avenue for future research.

In **Chapter 5**, we conducted a pilot study in 109 girls with available serum samples between 6-17 years of age at the LEGACY New York site to assess whether maternal pre-pregnancy BMI, GWG, maternal physical activity during pregnancy and growth during infancy were associated with levels of IGF-1 and IGFBP-3 during puberty. While breast Tanner stage is somewhat subjective even among trained professionals and may be reported with error by mothers,[58] serum IGF-1 and IGFBP-3 can be measured objectively and are known to increase rapidly during puberty.[51,52] Associations between the maternal and infant factors that were associated with earlier onset of breast development in **Chapters 3** and **4** and higher serum levels of IGF-1, IGFBP-3 or the IGF-1/IGFBP-3 molar ratio support that these factors are associated with biological changes that map to puberty in the girls.

Table 6.1 summarizes the direction of the association between each exposure of interest, age at breast development, and serum levels of IGF-1 and the IGF1/IGFBP-3 molar ratio. We observed higher mean levels of the IGF-1/IGFBP-3 molar ratio in girls with faster weight gain between birth and one year of age. We also observed higher ratio levels in girls with a maternal pre-pregnancy BMI≥25 and GWG≥30lbs compared with girls with a maternal pre-pregnancy BMI<25 and GWG<30lbs, though this difference was not statistically significant. While serum IGF-1 levels decreased with higher birthweight, this association was attenuated in models adjusting for weight gain in infancy. While recreational physical activity during

pregnancy was not significantly associated with IGF-1 levels at $p<0.05$, the point estimates suggested lower IGF-1 levels in girls whose mothers reported no recreational physical activity, which is in the opposite direction of our finding for breast development. The associations that we observed could be due to chance given our small sample size and should be replicated in larger samples. However, the patterns that we observed in IGF-1 and IGFBP-3 by age and Tanner stage are consistent with previous, larger studies,[51,52,289,292,308] which reduces concern about selection bias driving the results.

This pilot study therefore supports that our finding of earlier breast development in girls whose mothers had a pre-pregnancy BMI ≥25 and gained 30 or more lbs during pregnancy and in girls with rapid weight gain during infancy is not driven by measurement error in the assessment of breast development. IGF levels also did not vary by SES, as assessed by maternal education. Confounding by SES is therefore not a likely explanation for the associations between maternal BMI, GWG and infant growth and higher serum IGF levels, which supports that the associations between these factors and earlier onset of breast development is not driven by social patterning.

We summarized the major strengths and limitations overall and by analytic aim in **Table 6.2**. The main limitations of this dissertation relate to a lack of data prior to puberty for a subset of the cohort. Since girls were recruited from 6-13 years of age, some girls experienced the onset of breast development prior to cohort entry. Since we did not observe the outcome for these girls during the study period, we were limited to analytic methods that could incorporate left-censored data. We also did not have measures of pre-pubertal BMI on all girls, which limited the mediation analyses. However, there are a number of strengths of these dissertation analyses, including the utilization of multiple measures of breast development collected every 6 months using a standard protocol in LEGACY, the high retention rate in the cohort, and the enrichment of the LEGACY study population for BCFH. We had sufficient power to formally test the interactions between early-life exposures and BCFH in relation to the onset of breast development. Although we used maternal reports of breast Tanner stage as our primary outcome, we conducted sensitivity analyses using alternate reports of breast onset, including clinical breast Tanner staging data in at two LEGACY sites. We also took advantage of the multiple assessments of breast development available in LEGACY, including recalled age at development for left-censored girls, to examine the influence of

different analytic assumptions when modeling pubertal outcome data on the estimation of exposure-outcome associations.

6.2 Methodological considerations for studies of pubertal timing

One of the methodological challenges both in studying secular trends in the onset of breast development and in identifying risk factors for early puberty is accurately capturing the onset of breast development. While age at menarche is a well-defined event that can be reliably recalled into adulthood,[91] the transition from no breast development to breast budding is a gradual process as opposed to a single event and is less likely to be accurately recalled. The onset of breast development would ideally be studied by collecting repeated prospective assessments of breast Tanner stage by a trained rater starting at ages prior to the onset of puberty,[58] which requires large commitments of time and resources that many studies do not have available. Even if breast Tanner staging is assessed by clinicians at well-child visits and can be collected from medical records, as was done in KPNC,[81,237] most families do not visit a clinician every six months and would not have regular assessments of breast development. Due to these limitations, most studies that examine drivers of earlier development will need to rely on imperfect measures of breast development, leaving their results susceptible to information bias.

This dissertation contributes to this field by examining the influence of different assessments of breast development and modeling strategies on exposure-outcome associations. The associations between higher maternal pre-pregnancy BMI, greater GWG and earlier breast development were robust to different modeling strategies and different sources of assessment. These results suggest that, in the case of exposures with a strong signal, the bias from the use of maternal reports and recalled data is minimal and leads to similar inference. However, our infancy analyses, conducted in a smaller subset of the cohort that was more susceptible to random error, were more sensitive to differences in outcome assessment. In this case, the use of an objectively measured biomarker that is correlated with pubertal timing provided an additional method to minimize information bias in outcome assessment. These results can inform the design of future studies of breast development. While studies may not be able to collect repeated clinical Tanner assessments or biomarker measures on everyone in a large study populations, the collection of additional measures in a subset of the cohort can be used to conduct sensitivity analyses that aid in the interpretation

of the overall study findings.[239] Differences in the assessment of the onset of breast development will also affect the measurement of pubertal tempo,[258] which future studies examining drivers of pubertal tempo will need to take into account.

6.3 Implications and future directions

Earlier puberty in girls is associated with psychological and behavioral consequences, such as higher incidence of anxiety and depression, earlier sexual activity, earlier initiation of risk behaviors such as smoking and drinking (for review, see [316]), as well as increased risks of cardiovascular disease[96,97] and breast cancer.[41,95] Given this significant burden of earlier puberty on both the individual and population level, it is imperative to think about how we can apply what we know now about risk factors for early puberty to primary prevention. The importance of maintaining a healthy body weight in adult women, including prior to pregnancy, is an established public health recommendation. During pregnancy, clinicians are already advised based on the current Institute of Medicine guidelines to encourage women to avoid excessive weight gain during pregnancy and engage in physical activity during pregnancy.[110] In addition, pediatricians and parents monitor growth during infancy, and avoiding rapid weight gain during infancy is important for reducing the risk of childhood obesity.[64] Our findings support that maintaining a healthy pre-pregnancy weight, engaging in some degree of physical activity during pregnancy, and avoiding excess GWG and rapid growth during infancy may, in addition to other health benefits to the mother and child, delay the onset of breast development in daughters, even in girls with a BCFH. Raising awareness that these behaviors may delay the onset of breast development complements the existing recommendations by providing an additional benefit that can be gained by adhering to recommendations. This message may resonate with women that are worried about the timing of puberty and breast cancer risk, including women with a family history of breast cancer.

Our findings support that maternal pre-pregnancy BMI, GWG and infant growth patterns may be associated with increased breast cancer risk later in life through earlier onset of breast development. Since breast cancer risk accumulates early in the life course, modifying factors that act early in the life course to increase breast cancer risk may lead to a greater overall reduction in risk.[4,5] Colditz and Bohlke estimate up to a 22% decrease in breast cancer risk with behavior change starting in midlife. However, the potential

reduction in risk is up to 64% with prevention efforts starting in young adulthood.[5] We hypothesize that there can be an even greater reduction in risk when prevention starts even earlier in the life course. That being said, more research is needed to understand the total effect that modifying the early-life environment may have on breast cancer risk. For example, maternal obesity, higher GWG and rapid infant weight gain are also associated with increased adiposity in children.[317] Even though overweight girls go through puberty earlier, higher BMI in childhood and adolescence is associated with decreased risks of pre- and post-menopausal breast cancer.[14–17] It is also possible that associations between maternal BMI, GWG and breast cancer risk vary by childhood body size, a hypothesis that can be explored in future research. Future studies need to consider both of these pathways to understand how secular increases in obesity, GWG and rapid infant growth may affect future breast cancer incidence.

This dissertation has generated additional hypotheses that can be examined in future research. First, is the association that we observed between rapid growth in early infancy and earlier breast development related to the transient activation of the HPG axis in infancy, or mini-puberty? It is not clear whether the variations in hormone levels during this period have a long-term effect on either breast tissue or on hormone levels later in life, but this question has relevance to pubertal timing and breast cancer risk. Second, are maternal BMI, GWG and infant growth independently associated with pubertal tempo? Girls with earlier age at breast development have a longer pubertal tempo.[318] The elongation of this time period, when the breast is rapidly developing and vulnerable to environmental carcinogens,[43] is also associated with increased breast cancer risk.[41] Future research should examine whether maternal pre-pregnancy BMI, GWG and infant weight gain have independent effects on tempo, given their associations with both age at breast development and age at menarche. In addition, we observed a strong correlation between rapid weight gain during infancy and IGF-1 in our pilot study. In future studies, we will examine within-person patterns of IGF-1 and IGFBP-3 across puberty, and whether rapid infant growth, in addition to maternal pre-pregnancy BMI and GWG, are associated with these trajectories. While higher IGF-1 and IGFBP-3 levels in adulthood are associated with breast cancer risk,[294] more research is needed to understand whether higher levels of these biomarkers track across the life course and, if so, whether this can be modified.

In conclusion, we identified higher maternal pre-pregnancy BMI, excess GWG and rapid growth during infancy as modifiable risk factors associated with earlier onset of breast development in girls at average-risk for breast cancer and girls at increased risk due to their family history. This supports that breast cancer risk has origins in early life and that modifying these factors may reduce breast cancer risk. Future studies should also consider alternate pathways through which the early-life environment may affect risk. In addition, early puberty is associated with multiple adverse health outcomes in girls, and delaying the onset of breast development may benefit physical and mental health in adolescence and adulthood. We therefore recommend that clinicians consider incorporating into their conversations with expectant and new parents the message that adherence to existing recommendations regarding healthy maternal and infant weight gain, in addition to other health benefits for both the mother and child, may delay breast development in girls.

6.4 Tables and figures

Table 6.1. Summary of the direction of associations between maternal, birth and infant exposures with the timing of breast development and levels of serum biomarkers during puberty. *The green symbol indicates no association. Blue arrows indicate the direction of the association. Factors that are associated with earlier age at breast development and higher IGF-1 levels are consistent with earlier puberty.*

	Age at breast development[a]	Serum levels of IGF-1 and IGF-1/IGFBP-3 ratio[b]
Maternal BMI≥25 and GWG ≥30lbs		
Maternal physical inactivity during pregnancy		
Birthweight		
Birthlength		
Rate of weight gain during infancy		

[a]An arrow facing down indicates earlier age at breast development for an increase in the exposure

[b]An arrow facing up indicates higher levels of IGF-1 and/or IGF-1/IGFBP-3 molar ratio. Associations may not be statistically significant at $p<0.05$ for this exploratory analysis

Table 6.2. Summary of the strengths and limitations of this dissertation.

	Strengths	Limitations
Aim 1 (Systematic Review)	Comprehensive	Data too heterogeneous to combine
Aim 2 (Maternal and pregnancy analyses)	Examine differences by BCFH Sensitivity analyses using multiple reports of breast development, including clinical reports	Self-reported maternal and pregnancy exposures Maternal report of breast development
Aim 3 (Infancy analyses)	Exposure assessed through medical record data	Limited to subset of cohort with available infancy data Maternal report of breast development
Aim 4 (Biomarker analyses)	Objective biomarker measurement	Pilot study limited to girls at the NY site that provided a blood sample
Overall	Data collection every 6 months using standard protocol with high retention rate Enrichment for BCFH	Some girls experienced breast development prior to cohort entry Lack of pre-pubertal BMI measures on all girls

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Appendices

Appendix A Protocol for systematic review on early-life body size and pubertal timing in girls

Updated 11/27/2018

Title: Size and growth during early life and pubertal timing in girls: a systematic review

Review team: Mandy Goldberg (primary reviewer) and Sabine Oskar (secondary reviewer)

Objective: To systematically review the published literature in order to summarize the literature regarding size and growth during early life and pubertal timing and its implications for breast cancer risk.

a. Identify studies that have examined the association(s) between maternal body size characteristics, including maternal pre-pregnancy BMI and gestational weight gain, birth size and/or size or growth during infancy (from birth to age 2 years) and the timing of pubertal development in girls
b. Identify sources of heterogeneity in study-specific estimates

Search strategy:

Identify and review all published peer-reviewed studies that meet the criteria below:

Eligibility criteria

- Date: Article published between January 1, 1970 and present
- Language: English
- Main outcome is normal breast development, menarche or tempo between these two events

Exclusion criteria

- Non-humans
- Males only or both sexes without sex-stratified results
- Study population comprised of children with diseases that would affect pubertal development, such as endocrine disorders, or selected for precocious puberty
- Study population comprised of children with diseases that affect growth, such as pediatric cancers, CF, etc.
- Outcome is central or peripheral precocious puberty (puberty before age 8 years in females)
- Outcome is a pubertal event other than breast development or menarche: adrenarche, pubarche, pubertal growth spurt, etc.
- Body size and/or growth measured after age 2 years only
- Case study/series (N<10, descriptive)

I will also exclude studies if reviews, editorials, discussion papers, or conference abstracts.

Search databases

- PubMed

Search terms

I will conduct the database searches using search terms relating to the outcome, exposure and time period of interest:

PubMed:

"puberty"[MeSH Terms] OR "puberty"[All Fields] OR pubertal[All Fields] OR "pubertal onset"[All Fields] OR "pubertal development"[All Fields] OR "sexual maturation"[All Fields] OR "pubertal timing"[All Fields] OR “pubertal tempo” [All Fields] OR ("menarche"[MeSH Terms] OR "menarche"[All Fields]) OR ("menstruation"[MeSH Terms] OR "menstruation"[All Fields] OR "menses"[All Fields]) OR "menses onset"[All Fields] OR thelarche[All Fields] OR "Breast/growth and development"[Mesh] OR "breast development"[All Fields] OR "breast bud"[All Fields] OR “Tanner staging”

AND

Weight OR height OR length OR “ponderal index” or “body mass index” OR BMI OR obese OR obesity OR overweight OR adiposity OR growth OR “weight gain” OR “height gain”

AND

mother OR birth OR maternal OR prenatal OR pregnancy OR “in utero” OR fetal OR infant OR infancy OR postnatal OR “early life” OR early-life OR childhood

Title and abstract screening:

I will conduct the literature searches in PubMed and Google Scholar and download the results into Endnote in order to remove duplicates.

After duplicate removal, I will export the list of studies to Excel. I will screen the titles and abstracts of the identified articles and classify the articles into 3 categories:

- May be eligible; read full paper
- Unclear if eligible; read full paper
- Not eligible

Reasons for exclusion will be documented. A second reviewer (SO) will independently screen the titles and abstracts of a random 10% of the retrieved articles.

Full paper screening:

One reviewer (MG) will read the full papers for abstracts categorized as “may be eligible” or “unclear if eligible” to determine final eligibility for inclusion based on eligibility and exclusion criteria listed above. Reasons for exclusion will be documented.

Data Extraction:

One reviewer (MG) will extract the following information for exposures and outcomes of interest from all studies that meet the inclusion criteria: author(s), publication year, study design, sample size, study setting and time frame, age range of participants, exposure assessment, outcome assessment, covariate information, statistical methods, results (effect estimates and confidence intervals), conclusions and sources of bias.

One reviewer (MG) will also search reference lists of included articles and relevant systematic reviews for additional relevant articles.

Data Quality:

One reviewer (MG) will assess the quality of included studies by using the NIH Quality Assessment Tool for Observational and Cohort Studies and the Newcastle-Ottawa Quality Assessment Scales for Cohort and Case Control Studies.

Copies of these quality assessment tools are available at:

NIH NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies:
https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Newcastle-Ottawa Quality Assessment Scale:
http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Appendix B Supplemental tables for Chapter 2

Supplemental Table 2.1. Studies of maternal pre-pregnancy BMI, weight and gestational weight gain and the timing of breast development

Author, Location, Year	Study Design	Study Population (N, Age range, Name)	Exposure	Exposure source	Outcome	Outcome source	Statistical method	Results	Covariates
Vandeloo, 2007, Belgium	Cross-sectional	1146 girls Mean age=12.8 years Girls recruited in second year of secondary school from 10 centres of Medical School Supervision (MSS) in Belgian Limburg in 1999-2000 school year	Weight of the mother at the beginning of pregnancy, continuous (units not stated)	Not stated	Age at breast development (Tanner stage 2 or more)	Not stated	Cox regression model for age at onset of breast development (RR>1 indicates earlier breast development)	RR = 1.013, 95% CI=1.006, 1.021	None *Results for maternal pre-pregnancy weight were not shown for multivariable model
Maisonet, 2010, United Kingdom	Prospective cohort	2661 singleton girls with consistent pubertal staging and prenatal data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Maternal pre-pregnancy BMI, categorized: Underweight: <18.5 Normal: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	Self-reported pre-pregnancy BMI from mother during pregnancy	Age at transition to Breast Tanner stage ≥2 or ≥3	Breast Tanner stage reported by girls or mothers at repeated pubertal self-assessments between 8-14 years of age *Girls with inconsistent responses were excluded from analyses	Interval-censored parametric survival model for age at transition to breast Tanner stage ≥2 or ≥3 assuming a normal distribution (Diff <0 indicates earlier breast development)	Adjusted difference in median age at transition to breast Tanner stage ≥2: Underweight: Diff=0.14, 95% CI= -0.16, 0.43 Normal: referent Overweight: Diff= -0.4, 95% CI= -0.62, -0.25 Obese: Diff = -0.70, 95% CI= -1.00, -0.40 Breast Tanner stage ≥3: Underweight: Diff= -0.05, 95% CI -0.30, 0.20 Normal: referent Overweight: Diff= -0.41, 95% CI= -0.56, -0.25 Obese: Diff= -0.50, 95% CI= -0.75, -0.25	Maternal age at menarche, previous live births, smoking during pregnancy, maternal age at delivery, maternal education

Christensen, 2010, United Kingdom	Prospective cohort	3938 singleton girls with consistent pubertal staging and prenatal data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Maternal pre-pregnancy BMI, categorized: <18.5 18.5-24.9 25-29.9 ≥30	Self-reported pre-pregnancy BMI from mother during pregnancy	Breast Tanner stage	Breast Tanner stage reported by girls or mothers at repeated pubertal self-assessments between 8-14 years of age *Girls with inconsistent responses were excluded from analyses	Ordinal probit models for progression through Tanner stages of breast development, using repeated breast Tanner assessments (β>0 indicates increased probability of being in higher Tanner stage - earlier development)	Coefficients from ordinal probit model for progression through breast stages: <18.5: β= -0.03, SE=0.09, p=0.65 18.5-24.9: referent 25.0-29.9: β=0 .11, SE=0.06, p=0.05 ≥30: β= 0.26 SE=0.09, p=0.004 Without adjusting for girl's BMI, there was an interaction between girl's age and maternal BMI - "increasing age dampened the effect of overweight maternal BMI" (data not shown)	Age, daughter's BMI, mother's age at menarche, child ethnic background, birth order, interaction between age and daughter's BMI
Kubo, 2016, United States	Prospective cohort	386 girls with maternal BMI data Age 12-14 years at follow-up Cohort Study of Young Girls' Nutrition, Environment and Transitions (CYGNET), girls enrolled in 2005-2006 from Kaiser Permanente Northern California at ages 6-8 years	Maternal pregravid BMI, categorized: <25 25-<30 ≥30	Self-reported pre-pregnancy weight and height data from CYGNET baseline questionnaire	Onset of breast development, defined as Tanner stage 2 or above, vs. no onset (Tanner stage 1)	Assessed by trained research personnel at annual follow-up visit	Weibull parametric survival model for age at transition to breast Tanner stage ≥2, accommodating left, right and interval censoring (TR <1 and HR>1 indicates earlier breast development)	Time ratios and hazard ratios for transition to breast Tanner stage ≥2: <25: Referent 25-<30: TR=0.99, 95% CI= 0.96, 1.02; HR=1.15, 95% CI= 0.85, 1.56 ≥30: TR=1.00, 95% CI=0.97, 1.04; HR=0.96 (0.6, 1.39) P for trend = 0.57 for TR; 0.78 for HR	Race/ethnicity, household income and maternal age at menarche

Lawn, 2018, United Kingdom	Prospective cohort	2942 singleton girls with age at thelarche and data on either maternal prepregnancy BMI or GWG Age 17 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Maternal pre-pregnancy BMI, continuous Gestational weight gain in kg	Self-reported pre-pregnancy weight and height by mother on questionnaire in early pregnancy GWG calculated from last weight measured by midwives from obstetric measures and first measured weight for all women with at least 1 weight measure prior to 18 weeks gestation and 1 after 28 weeks gestation	Age at thelarche (Tanner stage ≥2), calculated as midpoint between last questionnaire with TS1 and first questionnaire where TS2+	Breast Tanner stage reported by parents and/or daughters in a series of annual questionnaires from 8-17 years or during clinic visits at 12.5 or 13.5 years.	Linear regression models for age at thelarche with multiple imputation for missing data (β<0 indicates earlier breast development - difference in months)	Pre-pregnancy BMI, continuous: Total effect from linear regression for age at thelarche: β=-0.77, 95% CI= -0.93, -0.60 Direct effect from linear regression for age at thelarche, controlling for pre-pubertal BMI as a mediator: β=-0.37, 95% CI= -0.54, -0.21 Gestational weight gain in kg, continuous: Total effect from linear regression for age at thelarche: β=-0.28, 95% CI= -0.42, -0.14 Direct effect from linear regression for age at thelarche, controlling for pre-pubertal BMI as a mediator: β=-0.16, 95% CI=-0.30, -0.02	Maternal age at delivery, daughter's ethnicity, parity, maternal smoking during pregnancy, socioeconomic status and maternal age at menarche. GWG models adjusted for covariates above, plus maternal prepregnancy BMI and gestational age.

Kubo, 2018, United States	Retrospective cohort	14,760 girls with at least one breast Tanner stage assessment at 6 years or more, at least 1 pre-pubertal BMI measure and information on maternal BMI during pregnancy 6-11 years at breast Tanner assessment Girls born in Kaiser Permanente Northern California in 2003-2006 with continuous KPNC membership through March 2017	Maternal BMI during pregnancy, categorized as: Underweight: <18.5 Normal weight: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	Maternal weight measured at time of the a-fetoprotein test (16-18 weeks gestation, 95%) from medical record. If not available, first weight measured after conception (range 0-16 weeks, 5%). BMI calculated using height recorded in medical record.	Thelarche, defined as transition from breast Tanner stage 1 to 2+. Age at thelarche defined as the interval between age at last clinic record with TS1 and age at first clinic record with TS2+	Medical record, assessed by physician using palpation and visual inspection as part of the routine pediatric appointments	Weibull parametric survival model for age at transition to breast Tanner stage ≥2, accommodating left, right and interval censoring (TR <1 and HR>1 indicates earlier breast development)	Time ratios and hazard ratios for transition to breast Tanner stage ≥2: Underweight: TR=1.03, 95% CI=1.00, 1.06; HR=0.75, 95% CI= 0.58, 0.97 Normal weight:Referent Overweight:TR=0.98, 95% CI=0.97, 0.99; HR=1.21 (1.13, 1.29) Obese:TR=0.97, 95% CI= 0.96, 0.97; HR=1.39, 95% CI= 1.30, 1.49 P for trend <0.0001 HR for maternal obesity, adjusting for pre-pubertal BMI = 1.22, 95% CI=1.13, 1.31 (other categories not shown)	Race/ethnicity, maternal age at delivery, education, parity and maternal smoking during pregnancy

Supplemental Table 2.2. Studies of maternal pre-pregnancy BMI, weight and gestational weight gain and the timing of menarche

Author, Location, Year	Study Design	Study Population (N, Age range, Name)	Exposure	Exposure source	Outcome	Outcome source	Statistical method	Results	Covariates
Windham, 2004, United States	Prospective cohort	994 girls with menarche data 15-17 years Follow-up of subset of California Child Health and Development Studies (pregnancies 1959-1966)	Maternal pre-pregnancy BMI	Pre-pregnancy weight and height obtained from interview during pregnancy	Age at menarche, examined continuously and in categories: Early: <12y Average: 12-13 years Late: >13 y	Recalled by girl at 15-17 years (years and months - though 45% of girls only gave year)	Mean age at menarche by category of independent variables using the F test and distribution of early and late menarche using chi-square test. Continuous data summarized using medians, IQ ranges and ranges	Stated in text that mother's prepregnancy body mass index was not related to age at menarche (data not shown)	None (data not shown)
Sloboda, 2007, Australia	Prospective cohort	776 girls with menarche data Age 12-14 years at follow-up Western Australian Pregnancy (Raine) Cohort, women enrolled during pregnancy in 1989-1990	Pre-pregnancy BMI and weight gain during pregnancy, unclear how assessed	Maternal clinic visits (women enrolled at 18 weeks of pregnancy)	Age at menarche	Self-report on puberty questionnaire or censored at age at last follow-up if no menarche reported	Kaplan-Meier survival probabilities to estimate probability of reaching menarche Multivariable Cox regression models to evaluate association between fetal and postnatal growth and age at menarche	Stated in text that maternal pre-pregnancy BMI and weight gain during pregnancy were not associated with age at menarche (data not shown)	Not stated

Vandeloo, 2007, Belgium	Cross-sectional	1146 girls Mean age=12.8 years Girls recruited in second year of secondary school from 10 centres of Medical School Supervision (MSS) in Belgian Limburg in 1999-2000 school year	Weight of the mother at the beginning of pregnancy, continuous (units not stated)	Questionnaire, partially completed by medical team with the remainder completed by girls and one parent	Age at menarche	Self-report with parent's help via questionnaire	Cox regression model for age at onset of breast development (RR>1 indicates earlier menarche)	RR = 1.015, 95% CI 1.006-1.025	None *Results for maternal pre-pregnancy weight were not shown for multivariable model

Windham, 2008, United States	Prospective cohort	1556 women with age at menarche data 22-33 years at follow-up Adult follow-up of 3 Collaborative Perinatal Project sites (pregnant women enrolled 1959-1966): Pathways to Adulthood Study (PAS), follow-up of Baltimore site when subjects were 27-33 years and Intergenerational Pregnancy Outcome Study (IPOS), follow-up of Philadelphia and Providence sites when subjects were 22-32 years	Maternal pre-pregnancy BMI, categorized: <20 20-26 >26 Maternal weight gain during pregnancy (data not shown)	Maternal report of pre-pregnancy weight during pregnancy and measured height	Age at menarche, continuous	Self-report (in whole years) by adult participants	Linear regression models for AAM examining prenatal factors childhood factors, and then prenatal + childhood combined (β<0 indicates earlier age at menarche	β (95% CI) from linear regression models with prenatal factors only for age at menarche: <20: β=0.13, 95% CI=-0.10, 0.36 20-26: Referent >26: β=-0.09, 95% CI=-0.34, 0.16 β (95% CI) from linear regression models with prenatal and childhood for age at menarche: <20: β=0.10, 95% CI=-0.14, 0.33 20-26: Referent >26: β= 0.03, 95% CI=-0.22, 0.29 *Maternal weight gain during pregnancy was not crudely associated with age at menarche (data not shown)	Prenatal only model adjusted for prenatal smoke exposure, maternal race, maternal age at baseline, maternal age at menarche, maternal marital status, maternal education, maternal parity, gestational age, family income, maternal employment and study site. Prenatal + childhood model adjusted for prenatal smoke exposure, maternal race, maternal age at baseline, maternal age at menarche, maternal marital status, maternal education, study site, total siblings at age 7, family income at age 7, rooms/person in home, BMI at age 7, height at age 7

Rubin, 2009, United Kingdom	Prospective cohort	4212 singleton girls with consistent menarche data Age 8-13 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Maternal pre-pregnancy BMI, categorized into tertiles: <21.1 21.1-23.4 >23.4	Self-reported by mother during pregnancy	Presence of menarche at 11 year old questionnaire	Reported at 11-year questionnaire by daughter, mother or both	Multivariable logistic regression for menarche by age 11 years (OR>1 indicates earlier menarche)	Adjusted ORs for menarche by age 11: <21.1 : Referent 21.1-23.4: OR=1.26, 95% CI=0.85, 1.87 >23.4: OR=1.77, 95% CI=1.22, 2.56 Adjusted ORs for menarche by age 11, mediation model adjusted for BMI at 8 years: <21.1 : Referent 21.1-23.4: OR=1.11 , 95% CI=0.75, 1.66 >23.4: OR=1.31, 95% CI=0.89, 1.93	Maternal age at menarche, previous livebirths , maternal smoking in third trimester, girls' race Mediation model additionally adjusts for BMI at 8 years (tertiles)
Keim, 2009, United States	Prospective cohort	597 women with complete menarche and maternal data available 22-32 years at follow-up Follow-up in 1987-1991 of subset of women from Providence and Philadelphia sites of the CPP cohort (pregnant women enrolled in 1959-1966)	Maternal pre-pregnancy BMI, categorized as: Underweight or normal weight (BMI<25) Overweight (BMI 25.0-29.9) Obese (BMI ≥30)	Pre-pregnancy weight self-reported by mother during pregnancy; height measured at first visit	Age at menarche, categorized as: ≤11 years 12 years 13 years 14+ years	Self-report during adult interview	Polytomous logistic regression to examine the relationship between daughter's age at menarche and maternal pre-pregnancy BMI	Adjusted ORs for daughter's age at menarche from polytomous logistic regression models with 14+ as reference group: ≤11 years: ≥30: OR = 3.3, 95% CI=1.1, 10.0 25-29.9: OR=1.1, 95% CI=0.6, 2.1 <25: Referent 12 years: ≥30: OR = 2.7, 95% CI=0.9, 8.3 25-29.9: OR=0.8, 95% CI=0.4, 1.5 <25: Referent 13 years: ≥30: OR = 1.8, 95% CI=0.5, 5.8 25-29.9: OR=0.9, 95% CI=0.5, 1.6 <25: Referent OR for ≤11 years adjusted for childhood BMI as a mediator= 3.2, 95% CI=1.0, 9.8 (data not shown for other categories)	Study site, SES, maternal parity, maternal age at menarche and daughter's race

Terry, 2009, United States	Prospective cohort	262 women 38-46 years at follow-up Follow-up in 2001-2006 of subset of women from New York site of the CPP birth cohort (born 1959-1963)	Maternal pre-pregnancy BMI Maternal weight gain (weight measured just prior to birth - reported weight prior to pregnancy)	Prepregnancy weight was self-reported during pregnancy, height and weight at the end of pregnancy were measured	Age at menarche, continuous and dichotomized as: ≤12 years >12 years	Self-reported by adult participant	Univariate associations using correlation coefficients for continuous variables, chi-square tests and analysis of variance to compare averages across subgroups.	Mean maternal pre-pregnancy BMI by menarche status (p=0.80): ≤12 years: 22.57, SE=3.68 >12 years: 22.44, SE=3.44 Mean gestational weight gain (kg) by menarche status (p=0.80): ≤12 years: 10.54, SE=4.99 >12 years: 10.71, SE=4.94	None (multivariable results not shown)
Maisonet, 2010, United Kingdom	Prospective cohort	2661 singleton girls with consistent pubertal data and prenatal data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Maternal pre-pregnancy BMI, categorized: Underweight: <18.5 Normal: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	Self-reported pre-pregnancy weight from mother during pregnancy	Age at menarche	Month and year of menarche, reported girls at pubertal self-assessments between 8-14 years of age. Girls with inconsistent responses were excluded from analyses	Interval-censored parametric survival model for age at menarche assuming a normal distribution (Diff <0 indicates earlier menarche)	Adjusted difference for median age at menarche: Underweight: Diff= 0.02, 95% CI=-0.19, 0.24 Normal: Referent Overweight: Diff=-0.25, 95% CI=-0.39, -0.12 Obese: Diff=-0.13, 95% CI=-0.34, 0.09	Maternal age at menarche, previous live births, smoking during pregnancy, maternal age at delivery, maternal education

Shrestha, 2011, Denmark	Prospective cohort	3169 girls (sample size varied by analysis) Age 17-21 years at follow-up 2005 follow-up of a subset of a pregnancy cohort in two Danish cities, Aalborg and Odense, recruited between April 1984-April 1987 as part of the "Health Habits for Two" campaign.	Maternal pre-pregnancy BMI, continuous	Mom reported pre-pregnancy height and weight to doctor at first routine antenatal visit	Age at menarche, continuous	Reported by girls in 2005 at 17-21 years. ~50% reported year and month and the other reported year only.	Multiple linear regression analyses were conducted to examine the association between maternal prepregnancy BMI and AOM, with results shown as the difference in age at menarche in days (d<0 indicates earlier menarche)	Results from linear regression models for sample with AOM in at least years: Maternal BMI: -7.6, 95% CI=-13.3, -1.8 Maternal BMI, adjusted for offspring BMI reported by mother at ages 14-18 years in mediation model: 2.9, 95% CI=-4.3, 10.1 Maternal BMI in subset of offspring with BMI<25 at 14-18 years: -8.2, 95% CI=-16.1, -0.2	Maternal education, marital status, maternal age at childbirth, maternal smoking during pregnancy.

Boynton-Jarrett, 2011, United States	Retrospective cohort	32,218 women from singleton births with information on GWG and age at menarche Average age at report of menarche=34 years Women in the NHSII cohort (started in 1989, women born between 1946-1965) whose mothers are in the Nurses' Mothers' Cohort (started in 2001)	Gestational weight gain: <10lbs 10-14 lbs 15-19 lbs 20-29 lbs 30-39 lbs ≥40 lbs	Reported by mother in categories on questionnaire	Age at menarche, categorized as: <11 years 11-15 years >15 years	Reported by daughter on baseline survey in 1989 in categories: ≤9, 10, 11, 12, 13, 14, 15, 16, 17+	Compared early menarche (<11 years) and late menarche (>15 years) to average (11-15 years) in separate logistic regression models. Covariates associated with age at menarche at p<0.10 were included in adjusted models. Tested nonlinear relations between maternal GWG and early and late menarche using cubic splines. For models with evidence of a nonlinear association, categorical indicator variables were used in regression models. Tested for interaction between maternal GWG and age at baseline.	Adjusted OR for early menarche (<11 years) vs. average (11-15 years): <10: OR=1.35, 95% CI=1.09, 1.67 10-14: OR=1.13, 95% CI=0.98, 1.30 15-19: OR=0.98, 95% CI=0.87, 1.11 20-29: Referent 30-39: OR=1.10, 95% CI=0.98, 1.25 ≥40: OR=1.30, 95% CI=1.08, 1.56 p=0.0015 Adjusted OR for late menarche (>15 years) vs. average (11-15 years): <10: OR=1.23, 95% CI=0.86, 1.68 10-14: OR=1.09, 95% CI=0.88, 1.33 15-19: OR=1.16, 95% CI=0.99, 1.36 20-29: Referent 30-39: OR=0.97, 95% CI=0.81, 1.17 ≥40: OR=0.96, 95% CI=0.71, 1.29 p for trend=0.04 Adjusted OR for early menarche (<11 years) vs. average (11-15 years), mediation model: <10: OR=1.31, 95% CI=1.05, 1.62 10-14: OR=1.08, 95% CI=0.94, 1.25 15-19: OR=0.97, 95% CI=0.86, 1.10 20-29: Referent 30-39: OR=1.10, 95% CI=0.97, 1.25 ≥40: OR=1.27, 95% CI=1.06, 1.54 p=0.0059	Age at baseline in 1989 (years), daughter's race/ethnicity, birth weight, gestational age, maternal prepregnancy weight, maternal height, paternal height, maternal age at daughter's birth, parental education Mediation model additionally includes maternal activity in pregnancy, child body size at age 5 years, childhood physical activity, childhood television viewing.

Adjusted OR for late menarche (>15 years) vs. average (11-15 years), mediation model:
<10: OR=1.21, 95% CI=0.86, 1.67
10-14: OR=1.08, 95% CI=0.88, 1.33
15-19: OR=1.16, 95% CI=0.98, 1.36
20-29: Referent
30-39: OR=0.98, 95% CI=0.81, 1.17
≥40: OR=0.98, 95% CI=0.72, 1.33
p for trend=0.07

Wang, 2012, United States	Prospective cohort	305 term girls Age 10-15 years at first report of pubertal status, followed annually until TS5 or max of 5 years Adolescent follow-up of subset of the North Carolina Infant Feeding Study, infants born 1978-1982	Maternal pre-pregnancy weight in kg, continuous Weight gain during pregnancy in kg, continuous	Self-report by mom during pregnancy and review of medical records	Age at menarche, continuous	Date of menarche reported by daughter on annual surveys (started in 1992 at age 10-15, followed for max of 5 years)	Univariable linear regression models to examine association between maternal factors and age at menarche (β<0 indicates earlier menarche)	Univariable linear regression for age at menarche: Pre-pregnancy weight, kg, β = -0.02, SE=0.01 (p<.05) Weight gain during pregnancy, kg, β = -0.00, SE=0.02 (p≥.05)	None *Maternal pre-pregnancy weight was included in multivariable model but results not shown

Deardorff, 2013, United States	Prospective cohort	2497 girls with complete data for maternal pre-pregnancy BMI, GWG, daughters' menarche and covariates. Excluded girls with menarche before 9 or after 16. Age 9-16 years at follow-up Daughters of women in 1979 National Longitudinal Survey of Youth, prospective study of nationally representative samples born 1957-1964. Offspring were surveyed biennially from 1986-2010 as part of the NLSBY Children and Young Adult Survey.	Maternal pre-pregnancy BMI, categorized as: Underweight (<18.5) Normal weight (18.5-24.9) Overweight/obese (≥25) Categorized mother's GWG as inadequate (<88%), adequate (88-123%) or excessive (>123%) based on her percent of the expected 2009 IOM weight gain recommendations for GA and BMI	Self-report by moms in 1985 of pre-pregnancy weight and height. Self-reported weight gain at delivery and pre-pregnancy weight was used to calculated gestational weight gain	Age at menarche, continuous	Year and months of menstruation, reported by mothers for girls <14 years and girls age 14 and over on biennial surveys	Cox proportional hazard models to estimate associations adjusting for covariates in order to include right censored girls (HR>1 indicates earlier menarche). All analyses weighted for complex sampling design	Adjusted hazard ratios for menarche: Maternal BMI: <18.5: HR=1.00, 95% CI=0.86-1.16 18.5-25: Referent >25: HR=1.20, 95% CI=1.06, 1.36 Gestational weight gain: Excessive: HR=1.13, 95% CI=1.01-1.27 Adequate: Referent Inadequate: HR=1.09, 95% CI=0.96, 1.22 Alternative categorization of GWG: >40 lbs: HR=1.12, 95% CI=1.00, 1.25 10-40 lbs: Referent <10 lbs: HR=1.19, 95% CI=0.96, 1.47 Including GWG, daughter's birthweight or pre-pubertal BMI did not change HR for maternal BMI (results not shown).	Maternal BMI models adjusted for maternal age at menarche, race, log parental income, maternal education, maternal smoking during pregnancy, daughter breastfed and parity GWG models adjusted for all confounders above + maternal pre-pregnancy BMI

Mariansdatter, 2016, Denmark	Prospective cohort	340 girls with menarche data Age 19-21 years at follow-up 2008 follow-up of daughters of Danish pregnancy cohort, which enrolled women at 30-week prenatal visit in Aarhus, Denmark in 1988-1989	Maternal pre-pregnancy BMI, categorized into tertiles: Low (15.8-20) Middle (20-21.9) High (22.0-37.0)	Pre-pregnancy weight and height self-reported by mother during 30th week of pregnancy	Age at menarche	Self-reported by daughters at age 19-21 years. 47% reported year and month; 53% reported year only. Month was imputed for girls that reported year only.	Multiple linear regression for age at menarche with maternal BMI tertile as main predictor (Diff<0 indicates earlier menarche)	Adjusted difference (95% CI) in age at menarche in months from linear regression: BMI ≤20: Diff= 1.6, 95% CI=-2.3, 5.5 BMI 20-21.9: Referent BMI≥22: Diff= -4.1, 95% CI=-8.0, -0.3 In sensitivity analysis, daughters of overweight mothers (BMI≥25) had menarche adjusted 5.1 (-0.8, 11.0) months earlier than daughter of normal-weight (18.5-24.99) mothers. No difference for underweight daughters.	Maternal smoking during pregnancy, maternal SES based on family annual income in 1988-1989, maternal age, maternal parity
Flom, 2017, United States	Prospective cohort	1126 women with age at menarche data Age 39-49 years at follow-up The Early Determinants of Mammographic Density Study, 2008 adult follow-up of female participants in the CHDS and Boston and Providence sites of NCPP birth cohorts (pregnancies 1959-1966)	Maternal pre-pregnancy weight and BMI, continuous Gestational weight gain (kg)	Maternal pre-pregnancy weight and height reported by mom at first antenatal visit. Gestational weight gain calculated from self-reported pre-pregnancy weight and measured weight at delivery	Age at menarche, categorized as: <12 years ≥12 years	Self-report by woman in adulthood	Mean maternal characteristics by menarche at 12 years	Maternal pre-pregnancy weight, kg (mean, SD) <12y: 61.39 (10.72) ≥12y: 61.17 (10.67) Maternal pre-pregnancy BMI (mean, SD) <12y: 23.62 (3.96) ≥12y: 23.10 (3.68) Gestational weight gain, kg (mean, SD) <12y: 9.41 (3.74) ≥12y: 9.37 (3.98)	None

Lawn, 2018, United Kingdom	Prospective cohort	3935 singleton girls with age at menarche and data on either maternal prepregnancy BMI or GWG Age 17 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Maternal pre-pregnancy BMI, continuous Gestational weight gain in kg, continuous	Self-reported pre-pregnancy weight and height by mother on questionnaire in early pregnancy GWG calculated from last weight measured by midwives from obstetric measures and first measured weight for all women with at least 1 weight measure prior to 18 weeks gestation and 1 after 28 weeks gestation	Age at menarche, continuous	First report of age at menarche, reported by parents and/or daughters in a series of annual questionnaires from 8-17 years or during clinic visits at 12.5 or 13.5 years. Used age reported by participant or, if age missing, midpoint between last questionnaire with pre-menarche report and first questionnaire where menarche reported	Linear regression models for age at menarche with multiple imputation for missing data (β<0 indicates earlier breast development - difference in months)	Pre-pregnancy BMI, continuous: Total effect from linear regression for age at menarche: β=-0.34, 95% CI= -0.45, -0.62 Direct effect from linear regression for age at menarche, controlling for pre-pubertal BMI as a mediator: β=-0.09, 95% CI= -0.20, 0.03 Gestational weight gain in kg, continuous: Total effect from linear regression for age at menarche: β=-0.17, 95% CI= -0.26, -0.07 Direct effect from linear regression for age at menarche, controlling for pre-pubertal BMI as a mediator: β=-0.09, 95% CI=-0.20, 0.03 Inference is similar in categorical models.	Maternal age at delivery, daughter's ethnicity, parity, maternal smoking during pregnancy, socioeconomic status and maternal age at menarche. GWG models adjusted for covariates above, plus maternal prepregnancy BMI and gestational age.

Supplemental Table 2.3. Studies of birth size and the timing of breast development

Author, Location, Year	Study Design	Study Population (N, Age range, Name)	Exposure	Exposure source	Outcome	Outcome source	Statistical method	Results	Covariates
Bhargava, 1995, India	Prospective cohort	116 girls with birthweight<2000g and 100 control girls with birthweight ≥2500g and 37-41 weeks gestation. Controls were matched by parental height, parental education and SES Age 14 years at follow-up Children born at Safdarjung Hospital, New Delhi, between 1968-1971	LBW: <2000g Controls: ≥2500g LBW group was further divided into: Preterm: weight appropriate for date SFD: term but small for date	Medical records	Breast Development (Breast Tanner stage 2)	Assessed by study staff at visits	Comparison of means using t-tests or ANOVA for more than two groups Sexual maturation data evaluated by probit analyses	"Almost half of LBW girls were B2 at 9.5 years compared to 28% amongst controls" Median age at B2: Controls: 11.1 years SFD girls: 10.7 years Puberty onset to menarche length similar among all groups (data not shown)	None
Powls, 1996, United Kingdom	Prospective cohort	69 VLBW and 81 control girls Age 11-13.5 years at follow-up Hospital-based cohort of VLBW children treated at Mersey regional neonatal unit, recruited while in primary school for two previous studies: 1. birthweight <1251g and born between Jan. 1980 and June	VLBW: <1251g or <1501g and <31 weeks Controls: normal birthweight	Hospital records for VLBW, not stated for controls	Breast Tanner stage at adolescent visit (Breast development > Stage 1)	Assessed by study staff at adolescent visit	Mann-Whitney U test for stages of puberty	Number of girls who reached breast Tanner >1: VLBW: 50/69 (72%) Control: 56/81 (68%) Median breast Tanner stage (IQR): VLBW: 2 (1-4) Control: 2 (1-4) (p=0.73)	None

		1981 2. birthweight <1501g and gestation <31 weeks and born between Jan. 1982 and Nov. 1983 Normal birthweight controls matched to age and sex, classmates of cases							
Bacallao, 1996, Cuba	Prospective cohort	130 girls (girls with missing length and those with birthweight <2500g were excluded) Age 13.6-14.5 years at follow-up Students in two high schools at the municipality of Boyeros in Havana in September 1986, subset of longitudinal study on height and weight that was initiated in Havana in 1972 when children aged 12 mo.	Birthweight in grams	Obstetric card	Breast Tanner stage at entry to high school	Assessed by study staff	Pearson correlation coefficients relating birthweight to stage of sexual development (Breast Tanner stage) Mean birthweight by breast Tanner stage Path analysis model relating birthweight, height at 14 years and breast Tanner stage	Mean and SD of birthweight in g in girls by their breast Tanner stage at 14 years TS3: Mean=2930g, SD=286 TS4: Mean= 3300g, SD=331 TS5: Mean= 3316g, SD=395 Actual and estimated correlations among birthweight and stage of sexual development in girls from path analysis model: Actual=0.18 Estimated=0.18	Path model included height at 14 years

Ford, 2000, Australia	Prospective cohort	39 VLBW, 42 LBW and 16 NBW girls with pubertal data Age 14 years at follow-up Infants born at Royal Women's Hospital in Melbourne and survived to age 14y: VLBW: Infants <1000g born between 1/1/1977 and 3/31/1982 LBW: Infants of 1000-1499g born in last 18 months of study NBW: infants >2499g randomly selected from births in last 18 months of study	VLBW:<1000 g LBW: 1000-1499g NBW: >2499g	Hospital records	Breast Tanner stage at visit, dichotomized as >3	Clinician rating at 14 year old visit	Comparison of N and % of girls with breast Tanner stage >3 at age 14y	N and % of girls with breast TS >3 at 14y: VLBW: 29/39 (74%) LBW: 29/42 (69%) NBW: 12/15 (75%)	None
Peralta-Carcelen, 2000, United States	Cross-sectional analysis of prospective cohort	31 ELBW and 31 NBW girls Age 12-17.9 years at visit ELBW infants (birthweight ≤1000g) born between 1978-1984 who had been monitored at least once through Newborn Follow-up Program at the University of Alabama at Birmingham and controls born between 1978	ELBW:≤1000 g NBW: ≥2500g	ELBW from medical records (Newborn Follow-Up Program Database), NBW from parent report in adolescence	Breast Tanner stage at visit, dichotomized as >3	Clinician rating at visit, blinded to birthweight status	Comparison of N and % of girls with breast Tanner stage >3 at visit	Number of girls with breast Tanner stage 4 or 5: ELBW: 27/31 (87%) NBW: 30/31 (97%)	None

		and 1984 at term (>37 weeks) and birthweight ≥2500g, matched to cases by age, race, sex and SES by Hollingshead scale							
Ghirri, 2001, Italy	Prospective cohort	19 full-term SGA girls and 19 normal weight controls girls matched by date of birth Age 17.5-18.5 years at follow-up Adolescent follow-up in Italy. Inclusion criteria: 1) GA between 37-41 weeks; 3) not multiple pregnancy; 4) no intrauterine infections, congenital anomalies, chromosomal alterations; no asphyxia at birth; age at evaluation of final height ≥14.5 years; no pubertal retardation; last 12 months growth velocity ≤0.5 cm; Italian origin.	SGA: birth weight below the third percentile for gestational age NBW: birthweight between 25th and 75th percentile	Medical records	Age at breast development	Self-reported by girl when 17.5-18.5 years	Comparison of means using t-tests	Age at breast development: SGA: 9.9 years NBW: 10.4 years	None

Delemarre-van de Waal, 2002, Netherlands	Cross-sectional analysis of prospective cohort	35 girls Age 12.3 +/- 1.5 years at first visit (both sexes) "Healthy" girls were seen twice in 1 year for longitudinal study of growth and development	Birthweight SDS, standardized on birthweight references for gestational age published by Campbell et al, and categorized into tertiles	Birthweight and birthlength obtained from obstetric records	Tanner breast stage at visit Chronological age adjusted for mean pubertal age, the age at which a certain breast stage is normally reached	Tanner breast stage assessed by study staff	Independent sample t tests for differences in sexual maturation of pubertal children with the tertiles with highest and lowest birth weight Pearson correlations between birth weight and breast stage adjusted for chronological age (lower CA/pubertal age indicates earlier breast development)	Correlation between birthweight and breast stage adjusted for CA: First measure: r=0.41, p=0.02 Second measure: r=0.31, p=0.10 Trend towards lower breast stage in girls with highest birthweight (p for highest vs lowest birthweight SDS tertile): First measure: p=0.15 Second measure: p=0.07 Trend towards higher CA/pubertal age X100 in girls with highest birthweight (p for highest vs lowest birthweight SDS tertile): First measure: p=0.08 Second measure: p=0.01	Age at visit when outcome is chronological age/pubertal age
Veening, 2004, Netherlands	Prospective cohort	12 AGA and 17 SGA term infants Mean age 9 years at first visit and 11.6 years at second visit Follow-up of SGA and AGA children traced from the database of all pregnancies, deliveries and perinatal events of children born in the VU University Medical Center (registered since 1980)	SGA: birthweight below the 10th percentile corrected for gestational age (GA), gender and parity using Dutch reference data AGA: birthweight >10th percentile using Dutch reference data	Birthweight and gestational age from register	Tanner breast stage at visit For girls in B2 or above, chronological age adjusted for mean pubertal age, the age at which a certain breast stage is normally reached according to reference data of the Dutch nationwide study	Tanner breast stage assessed by study staff	Chi-square test for qualitative variables and Student's t-test for quantitative variables for differences between SGA and AGA groups ((lower CA/pubertal age indicates earlier breast development)	Mean (SD) CA/PA*100% in pubertal girls only at second visit (13 girls still B1): SGA (N=13): Mean=94.4, SD=7.1 AGA (N=9): Mean=106.4, SD=10.4 p=0.004	Age at visit when outcome is chronological age/pubertal age

Semiz, 2009, Turkey	Cross-sectional	1562 girls (659 with breast Tanner stage) Age 6-16.5 years Cross-sectional school-based study of schoolchildren in grades 1-8 in primary schools in the Denizli province between March-May 2005	Birth weight	Reported by parents	Breast Tanner stage at visit, categorized into early, average or delayed based on age at B2: Early: Age at B2 <10th percentile (7.19 years) Delayed: Age at B2 > 90th percentile (11.10 years)	Assessed by pediatrician	Comparison of possible factors affecting pubertal onset to pubertal timing and birth weight using Chi-square test.	The relation between birth weight and onset of puberty in girls was not significant (p>.05, data not shown)	None
Boyne, 2010, Jamaica	Prospective cohort	140 girls who were seen at all scheduled visits between birth and 11 years Age 11 years at follow-up Vulnerable Windows Cohort Study, pregnant women were recruited in 1992-1993 at University Hospital of the West Indies, Kingston,Jamaica for birth cohort.	Birth weight, standardized BMI at birth, standardized Crown heel length at birth, standardized	Weight and crown heel length measured within 24 hours of delivery	Breast Tanner stage at 11 year visit	Breast Tanner stage assessed every 6 months starting at age 8 years by trained nurses (visual only, no palpation)	Multiple regression analyses to examine the relationships among child's growth and body composition and the stage of puberty with outcomes and predictors in standardized form, so that the regression coefficients were effectively correlation coefficients.	Correlations between the size at birth and growth of Afro-Caribbean girls and their stage of breast development at age 11 years: Birthweight: -0.07 BMI at birth: 0.02 Birthlength: -0.10 P≥.05 for all correlations	Age at clinic visit

Christensen, 2010, United Kingdom	Prospective cohort	3938 singleton girls with consistent pubertal staging and prenatal data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Birthweight, categorized as: <2500g 2500-3999g ≥4000g	Medical records	Breast Tanner stage	Breast Tanner stage reported by girls or mothers at repeated pubertal self-assessments between 8-14 years of age *Girls with inconsistent responses were excluded from analyses	Ordinal probit models for progression through Tanner stages of breast development, using repeated breast Tanner assessments (β>0 indicates increased probability of being in higher Tanner stage - earlier development)	Birthweight must not have been associated with breast development at P<.05 because it was not included in final model (data not shown) Without adjusting for girl's BMI, birthweight still was not a significant predictor of breast development (data not shown)	Age at assessment
Maisonet, 2010, United Kingdom	Prospective cohort	1316 singleton, term girls (37-42 weeks gestation) with consistent pubertal staging and birth size data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Birthweight, continuous Birthlength, continuous SGA: birth weight <10th percentile of weight for gestational age. Referent weight percentiles estimated by weight and gestational age data of singleton girls from the full ALSPAC cohort	Medical records	Age at transition to Breast Tanner stage ≥2 or ≥3	Breast Tanner stage reported by girls or mothers at repeated pubertal self-assessments between 8-14 years of age *Girls with inconsistent responses were excluded from analyses	Interval-censored parametric survival model for age at transition to breast Tanner stage ≥2 or ≥3 assuming a normal distribution (Diff <0 indicates earlier breast development)	Adjusted difference in median age at transition to breast Tanner stage ≥2: Birthweight: Diff=0.00, 95% CI=-0.00, 0.00 Birthlength: Diff= -0.02, 95% CI=-0.06, 0.03) SGA: Diff=-0.23, 95% CI=-0.55, 0.09 Adjusted difference in median age at transition to breast Tanner stage ≥3: Birthweight: Diff=0.00, 95% CI=-0.00, 0.00) Birthlength: Diff=-0.02, 95% CI=-0.06, 0.01 SGA: Diff=-0.17, 95% CI=-0.45, 0.10	Maternal age at menarche, previous live birth, maternal race or ethnicity, smoking during pregnancy, maternal prepregnancy BMI, maternal age at delivery, maternal education

Olivo-Marston, 2010, United States	Cross-sectional	956 girls with birthweight and Tanner stage data available Age 8-11 years Cross-sectional data from 1988-1994 NHANES III survey of girls age 8-11 years	Birthweight, treated as a continuous variable (per 100g) increase and categorized: <2500g 2500-2999g 3000-3499g 3500-3999g ≥4000	Reported by mother at home interview	Breast Tanner stage, categorized as B3-5, B2 and B1	Assessed by NHANES physician at clinic visit by observation (no palpation)	Multinomial logistic regression was used to estimate adjusted and unadjusted ORs of being Tanner Stage 2+ for asynchronous maturation vs. Stage 1 for the pubertal pathway. All analyses were weighted by the NHANES sample weights and the stratification and multistage cluster design used in the complex sampling was accounted for in the computation of standard errors, confidence interval (CI) and P-values.	Adjusted OR for asynchronous breast development, continuous birthweight (per 100g): OR for B2 vs. B1=1.01, 95% CI=0.96, 1.07 OR for B3-5 vs. B1=1.09, 95% CI=1.02-1.27 Adjusted OR for asynchronous breast development, categorized birthweight: OR for B2 vs. B1: <2500g: OR=0.87, 95% CI=0.27, 2.79 2500-2999g: OR=0.88, 95% CI=0.41, 1.89 3000-3499g: Referent 3500-3999g: OR=1.11, 95% CI=0.36, 3.40 ≥4000g: OR=1.25, 95% CI=0.62, 2.55 OR for B3-5 vs. B1: <2500g: OR=2.26, 95% CI=0.22, 13.13 2500-2999g: OR=3.28, 95% CI=0.99, 7.32 3000-3499g: Referent 3500-3999g: OR=1.53, 95% CI=0.49, 4.80 ≥4000g: OR=3.18, 95%CI=1.39, 8.25	Age, race/ethnicity, height and BMI

		61 girls with early puberty, defined as breast development before the age of 9 years but after the age of 8 years 100 control girls with onset of puberty after the age of 9 years 40 with IPP, defined as breast development before 8 years of age (not eligible for this review) Mean age (SD): Controls: 10.2 (1.6) Early puberty: 9.2 (0.8) IPP: 7.2 (1.1)			3 groups based on timing of breast development: Controls: healthy girls with onset of puberty after the age of 9 years Early puberty: girls with breast development before the age of 9 years but after the age of 8 years, as reported by parents IPP: girls with breast development before 8 years of age (not eligible for this review)			Mean (SD) birthweight in kg by group: IPP: Mean=3.11kg, SD=0.53 Early puberty: Mean=3.06kg, SD=0.41 Controls: Mean=3.11, SD=0.53 P ≥0.05 Mean (SD) of birthlength in cm by group: IPP: Mean=51.18cm, SD=2.29 Early puberty: Mean=49.94cm, SD=2.26 Controls: Mean=50.02cm, SD=2.42 P ≥0.05	
Papadimitriou, 2011, Greece	Case-control	Girls evaluated at the Pediatric Endocrinology unit of the Third Department of Pediatrics of the University of Athens, at "Attikon" University Hospital, Athens, Greece	Birth weight, kg Birthlength, cm	Abstracted from personal health book of the patient (usually made by private pediatrician)		Onset of breast development was reported by parents and verified by palpation by a physician	Comparison of birthweight and birthlength across 3 groups using ANOVA		None

Wang, 2012, United States	Prospective cohort	305 term girls Age 10-15 years at first report of pubertal status, followed annually until TS5 or max of 5 years Adolescent follow-up of subset of the North Carolina Infant Feeding Study, infants born 1978-1982	Birthweight in kg	Recorded at birth by nurse	Breast Tanner stage at first adolescent report, categorized for analysis as >2 or >3	Daughter self-report at first adolescent survey when available	Parametric survival analyses with log normal distribution for age at report of breast Tanner stage >2 or >3 (girls were either left or right censored at age of TS report) (β<0 indicates earlier age at attainment of breast stage)	Regression coefficient in adjusted log-normal survival analyses of time to Breast Stage >2 Birthweight: β=-0.06, 95% CI=-0.11, -0.01 Regression coefficients (95% CI) in adjusted log-normal survival analyses of time to Breast Stage >3 Birthweight: β=-0.05, 95%CI = -0.10, 0.01	Weight gain (change in Z-score) from 0-6 months, 6-12 months, 1-2 years, 2-5 years, maternal pre-pregnancy weight, maternal age at delivery and race (race for TS>3 model only due to small cell counts).

Hernandez, 2013, Chile	Prospective cohort	16 LBW and 25 AGA girls, TS2 at enrollment and BMI between 10th and 95th percentile and followed for 3 years 7-12 years at enrollment Age-matched LBW and AGA girls 7-12 years recruited from public schools in Santiago and Concepcion, Chile	AGA - birth weight between the 10th and 90th percentile for gestational age LBW - birth weight below the 10th percentile for gestational age	Birth weight, birth length and gestational age reported by parents and confirm in child's health control card	Breast Tanner stage progression	Breast Tanner stage assessed by researchers at biannual follow-up visits	Dichotomous variables were created for Tanner stage progression and for the Ferriman and Gallway scoring and evaluated by means of a logistic regression model using as a measurement of association the change in monthly odds ratios adjusted by the condition of AGA or LBW Differences in breast Tanner stage of the two groups assessed by Kaplan Meier survival analyses (log rank test)	LBW girls showed slightly faster breast development at first 2 years. - At 6 months of follow-up 55% of AGA and 23% of LBW were TS2. -After 1 year of follow-up ($p<0.05$) -59.3% of AGA and 34.6% of LBW girls were TS2 -40.7% and 57.7% were TS3 -7.7% of LBW and none of the AGA girls were in Tanner stage IV -At 2 years of follow-up ($p<0.05$) -48.3% of AGA and 35% of LBW girls were TS4 - 27.5% of AGA and 55 % of SGA were TS5	None

Kale, 2014, United States	Prospective cohort	1237 girls Age 6-8 years at enrollment, followed for 6 years BCERP Puberty Study, girls age 6-8 years at enrollment in 2004-2007 in 3 sites (New York, Cincinnati, Bay Area)	Birthweight, categorized as: <2500g ≥2500g	Reported by primary caregiver at baseline	Breast Tanner stage ≥2	Breast Tanner stage at study visit assessed by clinical staff (biannual visits for Cincinnati, annual visits for CA and NY sites)	Weibull survival models for age at onset of breast development, using interval and right censoring. 5 years was used as lower interval bound for girls with breast development at baseline (HR>1 indicates earlier breast onset)	HR for breast onset: <2500g: HR=0.9, 95% CI=0.7, 1.1 ≥2500g: referent	None (age as time scale)

Supplemental Table 2.4. Studies of birth size and the timing of menarche

Author, Location, Year	Study Design	Study Population (N, Age range, Name)	Exposure	Exposure source	Outcome	Outcome source	Statistical method	Results	Covariates
Miller, 1972, United Kingdom	Prospective cohort	230 women with menarche data Age 22 years at follow-up Subset of the Thousand Families in Newcastle upon Tyne study of babies born in May and June 1947 and seen regularly until 1962 (15 years of age).	Birthweight (kg)	Domiciliary midwifery service or maternity hospital records	Age at menarche	Recorded during adolescent visits	Mean birthweight by age at menarche	Mean birthweight (kg) by age at menarche: <12 years: 3.07 12 years: 3.25 13 years: 3.35 14: 3.27 15+: 3.33	None
Zacharias, 1976, United States	Prospective cohort	633 girls with menarche data Followed for 10 years Girls age 8-10 identified in September 1965 in Newton, MA via school records and followed for 10 years	"Girls born prematurely (birthweight< 2500g) and girls born at full term"	Source of birthweight data not stated	Age at menarche	Date of menarche recorded to the day	Mean age at menarche by birthweight category	Mean (SD) age at menarche by birthweight: <2500g: 12.7 years (SD=1.15) ≥2500g: 12.83 (SD=1.21) *Not statistically different from each other	None
Billewicz, 1981, United Kingdom	Prospective cohort	699 girls with menarche data Age 9-17 years Subset of White Newcastle-upon-Tyne subset of birth cohort, girls born in 1962 followed up every 6 months from 9-17 years	Birth weight, continuous	Birth cohort records	Age at menarche	Assume provided by girls at biannual follow-up visits	Correlation, comparison of means	Correlation between birthweight and age at menarche: r=0.007 Mean age at menarche in girls with birthweight ≤2.5kg: 13.46 years, SD 1.14 Mean age at menarche overall: 13.37 years	None

Fledelius, 1982, Denmark	Prospective cohort	34 LBW and 31 full-term girls Age 18 years at follow-up Follow-up of subset of 'University Hospital of Copenhagen Study 1959-1961 on the Significance of Gestation and Delivery for the Health and Development of the Child'	LBW: <2000g FT: 3-4000g	Hospital records	Age at menarche	Assumed reported by girls at 18 year follow-up	Comparison of mean	Mean age at menarche (years): LBW: 13.5 years FT: 13.0 years	None
Westwood, 1983, Canada	Prospective cohort	26 SGA infants and 26 controls. Controls must be singleton with GA between 38-42 weeks and birthweight between 25th and 75th percentiles, matched by sex, race, ethnic origin and SES to SGA infants. Age 13-19 years at follow-up SGA infants born at Royal Victoria Hospital, Montreal, between 1960-1966, and matched controls	SGA, defined as birthweight at least 30% less than expected weight by Streeter tables, which is more than 2 SD below the mean weight for the nursery of hospital where they were born. Control babies had birthweight between 25th and 75th percentiles	Hospital records	Age at menarche	Self-report	Comparison of means	Mean age at menarche: 12.4 years in SGA girls, 12.7 years in controls	None - matched for age (within 3 months), sex, race, ethnic origin and SES at birth (mother was a private or public patient and marital status)

Roberts, 1986, United Kingdom	Cross-sectional	1217 girls with birthweight and menarche data School age, range not provided 15 schools (junior, secondary grammar, Church of England, Catholic) in Cumbria region, visited in Oct-Nov 1976	1217 girls with birthweight and menarche data	School age, range not provided	Birth weight	Parent report in adolescence	Logistic regression, contribution of each variable was measured by the increase in deviance resulting from deleting that variable from the model. Significance assessed by chi-square test	No association between birthweight and age at menarche after controlling for family size and position (data not shown)	Age, family size, position
Stark, 1989, United Kingdom	Prospective cohort	3018 girls with data on birthweight, menarche and weight at age 7 (girls with gestational age <30 and >44 weeks were excluded) Age 16 years at follow-up Follow-up of subset of 1958 National Child Development Study (NCDS) (birth cohort of all children born in England, Scotland and Wales in one week in March 1958)	Birth weight	Medical records (assumed)	Age at menarche	Self-report by girl at 16 year old visit	Relative weight distribution by age at menarche	Birth weight and menarche were not related (data not shown)	None

Prapas, 1989, Greece	Cross-sectional	2336 Age 15-18 years Students from Crete and Thrace, March-May 1988	Birth weight, categorized (≤2500g, 2500-2900g, 3000-3400g, 3500-3900g, ≥4000g	Self-report in adolescence	Age at menarche	Self-report	Comparison of means by birthweight and residence (F test)	Mean menarcheal age by birthweight group: Crete: ≤2500g: 12.73 2500-2900g: 12.16 3000-3400g: 12.31 3500-3900g: 12.59 ≥4000g: 12.49 Thrace: ≤2500g: 12.53 2500-2900g: 12.48 3000-3400g: 12.34 3500-3900g: 12.42 ≥4000g: 12.38 Significant correlation (F4, 709=4.860, p<.0001 for Crete and F2, 49=4.183, p<.05) for Thrace	Region (stratified)
Moisan, 1990, Canada	Nested case-control	333 cases (girls whose mom reported menarche between 1986 baseline visit and 1987 follow-up contact) and 333 pre-menarcheal controls, matched to birthdate Girls age 9.5-12.5 years an enrollment Fifth-grade classes from 122 schools in Quebec City, Canada in 1986	Birth weight, categorized into quartiles for analysis	Parent report in adolescence	Early menarche	Parent report of menarche at follow-up questionnaire	Logistic regression for early menarche, with exposures in quartiles	No association between birthweight and menarche (data not shown)	Not shown

Frisancho, 1994,	Prospective cohort	756 girls Followed up to 17 years White participants in the Child Health and Development Studies, evaluated at birth and at 15, 16 and 17 years of age	SGA: birthweight<10th percentile of gestational age AGA: birthweight between 11th and 99th percentiles of gestational age	Gestational age (calculated from information on LMP) and birthweight measured at birth	Age at menarche	Not stated, assumed reported by adolescents at 15-17 years of age	Mean age at menarche in SGA vs. AGA (text only)	Mean (SD) of age at menarche: SGA: 12.68y (1.21) AGA: 12.78y (1.19)	None
St. George, 1994, New Zealand	Prospective cohort	415 girls with menarche data Followed up to 18 years of age Follow-up of Dunedin birth cohort, born April 1972-March 1973	Birth weight (kg), continuous BMI at birth, continuous Birthlength (cm), continuous	Study records	Age at menarche, categorized as: <12 years 12-13 years 13-14 years >14 years	Self-report when girls were 11, 13 and 15 years of age	Mean birthweight by age at menarche category	Mean birth weight in kg by age at menarche (p=0.91) <12 years: 3.35 12-13 years: 3.31 13-14 years:3.30 >14 years: 3.33 Mean BMI at birth by age at menarche(p=0.69) <12 years: 12.6 12-13 years: 12.4 13-14 years: 12.4 >14 years: 12.5 Birth length in cm (p=0.99) <12 years: 51.4 12-13 years: 51.4 13-14 years: 51.4 >14 years: 51.5	None

Bhargava, 1995, India	Prospective cohort	116 girls with birthweight<2000 g and 100 control girls with birthweight ≥2500g and 37-41 weeks gestation. Controls were matched by parental height, parental education and SES Age 14 years at follow-up Children born at Safdarjung Hospital, New Delhi, between 1968-1971	LBW: <2000g Controls: ≥2500g LBW group was further divided into: Preterm: weight appropriate for date SFD: term but small for date	Medical records	Age at menarche	Not specified, assume self-report of menarche at follow-up visits	Comparison of means using t-tests or ANOVA for more than two groups Sexual maturation data evaluated by probit analyses	Median age at menarche from probit analyses: Controls: 13.6 years 6 months earlier in preterms and 12 months earlier in SFD girls (estimates not given)	None stated
Cooper, 1996, United Kingdom	Prospective cohort	1471 girls with birthweight, body size at age 7 and menarche data Age 14-15 years at follow-up Follow-up of MRC National Survey of Health and Development studies, birth cohort born first week of March 1946	Birth weight, categorized into quintiles for analysis	Health visit and midwife records	Age at menarche	Month and year of menarche reported by mom when girls were 14-15 years	Mean age at menarche by birthweight quintile, tests for trend Weibull survival model for age at menarche with right censoring	Mean age at menarche by birthweight quintile (F-value for linear trend 3.27, p=0.07): Lowest: 12.85y 2: 12.81y 3:12.93y 4:12.84y Highest:13.03y Weibull model: birthweight significantly positively associated with menarche (Chi-sq=18.0, df=4, p<.00001), weight at seven years was inversely associated with age at menarche Earliest age at menarche in those with low birthweight who became heavy at 7 years	Weibull model included weight and height at 7 years Results similar after adjusting for birth order, birth interval, social class and general educational ability (not shown)

		69 VLBW and 81 control girls Age 11-13.5 years at follow-up Hospital-based cohort of VLBW children treated at Mersey regional neonatal unit, recruited while in primary school for two previous studies: 1. birthweight <1251g and born between Jan. 1980 and June 1981 2. birthweight <1501g and gestation <31 weeks and born between Jan. 1982 and Nov. 1983						Number of girls who reached menarche (p=0.7): VLBW: 15/69 (22%) Control: 20/81 (24%)	
Powls, 1996, United Kingdom	Prospective cohort	Normal birthweight controls matched to age and sex, classmates of cases	VLBW: <1251g or <1501g and <31 weeks Controls: normal birthweight	Hospital records for VLBW, not stated for controls	Age at menarche	Assume self-report of menarche by girl at adolescent visit	Chi-square for number of girls having reached menarche by group and median age at menarche by group	Median age at menarche: VLBW: 12.0 y (11.2-12.3) Control: 12.0 y (11.2-12.3)	None

Leger, 1997, France	Prospective cohort	133 SGA cases and 152 AGA controls, first person with normal birthweight for GA (25-75th percentile) born immediately after an SGA subject (not matched for sex or GA) Age 16.6-24.5 years at follow-up All singleton subjects born SGA and at term during 1971-8 were identified from the population-based registry in Haguenau, France	SGA: defined as having a birth weight or length (or both) below the third centile of the local standard values. Controls: birthweight for gestational age between 25th and 75th centile	Birth registry	Age at menarche	Assume self-report at follow-up	Difference between groups assessed by Chi-square test, Fisher's exact test and t test as appropriate	No significant difference in mean (SD) age at menarche between the two groups: SGA: 12.6 (1.6) AGA: 12.9 (1.7)	None

Persson, 1999, Sweden	Retrospecti ve cohort	263 "normal "girls with follow-up data and 229 "exposed" girls with menarche data. Record linkage through 18 years Cohorts selected from all singletons born alive at University Hospital of Uppsala from 1973-1977 whose parents had been born in Sweden and were residing in the city of Uppsala at that time using Medical Birth Registry	Groups defined using ICD-7 codes from Medical Birth Registry and Inpatient Registry and through Naegel's formula standardized for GA: Normal children: No registered abnormality in pregnancy or at delivery; Apgar score at 5 minutes; no postnatal abnormality SGA: Diagnosis of birth from Medical Birth Registry, or weight ≤2SD LGA: diagnosis of LGA from birth from Medical Birth Registry or weight ≥2 SD Short for GA: Diagnosis of short for GA birth or height ≤2SD Tall for GA: Diagnosis of tall for GA birth from Medical Birth Registry or height ≥2 SD	Medical records	Age at menarche	Medical records (routine visits to postnatal child health centers and regular medical check-ups during school from 7-18 years)	T-tests and analysis of covariance for age at menarche	Mean age at menarche (SD), p for difference, p for covariance comparing exposed to normal children: Normal: 13.1 y (1.0) SGA: 12.7y (1.1), pdiff=0.032, pcov = 0.33 LGA: 13.0y (1.1) pdiff=0.42, pcov=0.39 Short GA: 12.8y (1.0), pdiff=0.148, pcov = 0.71 Tall GA: 13.1y (1.5) pdiff=0.9, pcov=0.50	Analysis of covariance included maternal age, parity, and parameters from growth curve function from 0-6 years (using repeated-measure model with random coefficients for early childhood growth)

Tenhola, 2000, Finland	Prospective cohort	35 SGA girls and 35 AGA control girls matched for age and sex Mean age at follow-up: 12.2±0.2 years SGA cases and selected controls from all children born at Kuopio University Hospital between April 1, 1984 and March 31, 1986 (excluding July)	SGA: birth weight and/or length and/or ponderal index >2 SD score below the mean for gestational age. (N=20 defined by weight, 4 by length, 30 for both and 1 by PI) AGA: birthweight, birth length and ponderal index ≥-2 SD score and ≤2 SD score of the mean for gestational age.	Birthweight, birth length and gestational age from hospital records	Menarche status at 12 y visit	Assume reported by girl at clinic visit	Means compared by Wilcoxon matched-pair signed rank test	Prevalence of menarche at visit: 9/35 (25.7%) in both SGA and AGA girls	None
Ford, 2000, Australia	Prospective cohort	39 VLBW, 42 LBW and 16 NBW girls with pubertal data Age 14 years at follow-up Infants born at Royal Women's Hospital in Melbourne: VLBW: <1000g born between 1/1/1977 and 3/31/1982 LBW: 1000-1499g born in last 18 months of study -NBW: >2499g randomly selected from births in last 18 months of study	VLBW:<1000 g LBW: 1000-1499g NBW: >2499g	Hospital records	Menarche status at 14 year visit	Self-report by girl	Comparison of N and % of girls with no menarche at age 14y	N and % of girls without menarche at 14y: VLBW: 6/39 (15%) LBW: 0/42 NBW: 1/16 (6%)	None

Peralta-Carcelen, 2000, United States	Cross-sectional analysis of prospective cohort	31 ELBW and 31 NBW girls Age 12-17.9 years at visit ELBW infants (birthweight ≤1000g) born between 1978-1984 who had been monitored at least once through Newborn Follow-up Program at the University of Alabama at Birmingham and controls born between 1978 and 1984 at term (>37 weeks) and birthweight ≥2500g, matched to cases by age, race, sex and SES by Hollingshead scale	ELBW:≤1000 g NBW: ≥2500g	ELBW from medical records (Newborn Follow-Up Program Database), NBW from parent report in adolescence	Age at menarche	Assume self-report at visit	Comparison of means	Mean age at menarche by birthweight group: ELBW: 11.15 years NBW: 11.45 years	None
Saigal, 2001, Canada	Prospective cohort	53 ELBW girls and 55 control girls, matched for gender, age and SES to each individual child Age 12-16 years at follow-up Adolescent follow-up of ELBW (501-1000g) born between 1977-1982 to residence of a geographically defined region in	ELBW: 501-1000g at birth (22% were SGA) Controls: term infants	Medical records for ELBW, not stated for controls	Menarche status at adolescent visit and age at menarche	Recorded at adolescent visit, source not specified	ELBW and control participants compared using Student's t test to determine differences in means	No difference in proportion of girls who achieved menarche: ELBW: 90% Control: 91% No difference in mean age at onset of menarche: ELBW: 12 years (SD=1.1) Control: 12.2 years (SD=1.1)	None

central-west Ontario and term controls were recruited at 8 years of age from a random list through school boards (1977-1981 births)

								Adjusted HR, t-statistic and P-value from Weibull models for age at menarche with continuous exposure: Birthweight: HR=0.77, t=-2.48, p<0.05 Birth length: HR=1.08, t=3.54, p<0.01 Adjusted HR, t-statistic and P-value from Weibull mediation models for age at menarche with continuous exposure: Birthweight: HR=0.75, t=-2.71, p<0.01 Birth length: HR=1.06, t=3.02, p<0.01	Adjusted continuous model: Maternal age at menarche, maternal age at pregnancy, maternal height, maternal BMI after birth, maternal triceps skinfold thickness during pregnancy, maternal diet score, first pregnancy, SES, gestational age, birthweight and birth length Mediation model additionally includes BMI and sum of skinfolds at age 8 years
Adair, 2001, Philippines	Prospective cohort	966 girls with complete information on birth characteristics and anthropometry at 8 years Age 14-15 years at follow-up Cebu Longitudinal Health and Nutrition Survey, infants born in 1984-1984 from women in randomly selected urban and rural barangays in Metro Cebu, Philippines.	Birthweight, continuous Birth length, continuous 4 groups characterized by birth weight (cut at median, 3kg) and birth length (cut at median, 49cm): Long/light Long/heavy Short/light Short/heavy	Infant weight and length measured by project staff as soon as births were reported. Length measured using custom-made length boards.	Age at menarche, continuous	Girl's self-report of month and year of first menses from interview at 10-11 and 14-15 years	Parametric Weibull models to estimate associations between birth characteristics and age at menarche, with premenarcheal girls treated as right censored (~5%) (HR>1 indicates earlier menarche)	Adjusted HR, t-statistic and P-value from Weibull models for age at menarche with categorical exposure: Long/light: HR=1.61, t=3.91, p<0.01 Long/heavy: HR=1.37, t=2.77, p<0.01 Short/light: HR=1.17, t=1.42, p≥0.10 Short/heavy: Referent Adjusted HR, t-statistic and P-value from Weibull mediation models for age at menarche with categorical exposure: Long/light: HR=1.54, t=3.51, p<0.01 Long/heavy: HR=1.29, t=2.22, p<0.05 Short/light: HR=1.29, t=2.26, p>0.05 Short/heavy: Referent	Adjusted categorical model: Gestational age Mediation categorical model: Gestational age, BMI and skinfolds at 8 years, maternal height, maternal age at menarche, total energy intake, low fat, SES

Ghirri, 2001, Italy	Prospective cohort	19 full-term SGA girls and 19 normal weight controls girls matched to date of birth of SGA subject Age 17.5-18.5 years at follow-up Adolescent follow-up of 19 full-term SGA girls and 19 matched controls in Italy. Inclusion criteria: 1) GA between 37-41 weeks; 3) not multiple pregnancy; 4) no intrauterine infections, congenital anomalies, chromosomal alterations; no asphyxia at birth; age at evaluation of final height ≥14.5 years; no pubertal retardation; last 12 months growth velocity ≤0.5 cm; Italian origin.	SGA: birth weight below the third percentile for gestational age NBW: birthweight between 25th and 75th percentile	Medical records	Age at menarche	Self-reported by girl when 17.5-18.5 years	Comparison of means using t-tests	Age at menarche: SGA: 11.9 years NBW: 12.3 years	None

Koziel, 2002, Poland	Cross-sectional	1060 singleton girls Age 13.5-14.5 years Girls attending 7th grace of randomly selected primary schools in Wroclaw, Poland, examined medically during 1996-1997	SGA: birthweight below the 10th percentile for gestational age AGA: birthweight ≥10th percentile for gestational age	Birth weight recorded to nearest 10g and gestational age measured in weeks from last menstruation from booklet of Child Health, routinely filled out by neonatologist in maternity ward and provided by parents	Menarche status at visit (~14 years of age)	Self-report by girl at 13.5-14.5 years	Logistic regression with outcome pre- or post-menarche status (OR>1 indicates greater likelihood of menarche by 14 years)	Adjusted OR for menarche: SGA vs. AGA: OR=2.54, 95% CI=1.22, 5.28	Logistic regression adjusted for SES using PC score and BMI at 8 years (overweight, normal, lean)
dos Santos Silva, 2002, United Kingdom	Prospective cohort	2008 girls with menarche and early life data Followed up to 48 years MRC National Survey of Health and Development studies, birth cohort born first week of March 1946	Birthweight in kg, continuous	Hospital record	Age at menarche	Reported by mother when daughter was 15 or recalled by participant at 48 year-old follow-up visit if not available at 15 years (17%)	Mean difference in birthweight by menarche group (early: <11.75 years, average: 11.75-14.25, late: >14.25 years) Multivariable Weibull models for age at menarche	Mean birth weight in kg (SD) by menarche: Early: 3.3 (0.47) Average: 3.3 (0.48) Late: 3.4 (0.52) HR for age at menarche with birthweight in kg as continuous exposure from Weibull models: Univariate model for birthweight, kg: HR=0.96, 95%CI=0.87, 1.05 Adjusted for growth in infancy: HR=1.17, 95% CI=1.06, 1.36 Adjusted for growth in infancy and childhood and BMI profile: HR=1.09, 95% CI-0.87, 1.30	Growth in infancy model adjusted for rank changes in height from 0-2 years Growth in infancy and childhood and BMI profile adjusted for rank changes in height from 0-2 years, height rate from 2-4 and 4-7 years, rank changes in BMII from 0-2 years, BMI rate from 2-6 years *Note: random coefficients model for height includes mother's height, mother's age at

									birth, birth order, father's manual occupation and no. of younger siblings. Model for BMI includes father's manual occupation.
Hack, 2003, United States	Prospective cohort	92 VLBW females and 107 controls with non-missing growth measures and no neurosensory impairments Age 20 years at follow-up 20-year follow-up of VLBW (<1500g) infants admitted to Rainbow Babies and Children's Hospital in Cleveland, Ohio between 1977-1979, controls were NBW children born in 1977-1979, selected at age 8 years by a population sampling procedure	VLBW: <1500g NBW: born >37 weeks	Hospital records for VLBW, not stated for controls	Age at menarche	Assume reported by girl at 20 year visit	Difference in mean age at menarche using 2 sample t-tests	Mean age at menarche by group (p=0.55): VLBW: 12.4 years NBW: 12.3 years	None

								RR from Cox model for age at menarche with birthweight as exposure: Q1 (1840-3120g): Referent Q2 (3130-3390g): RR=0.98, 95% CI=0.87, 1.09 Q3 (3400-3620g): RR=0.93, 95% CI=0.83, 1.05 Q4 (3630-3980g): RR=0.91, 95% CI=0.81, 1.02 Q5 (3900-5330g): RR=0.88, 95% CI=0.79, 0.99 p for trend=0.03	
Romundstad, 2003, Norway	Retrospective cohort	3,343 girls with information on age at menarche. Girls born preterm or whose mothers were diagnosed with preeclampsia, gestational hypertension, or gestational diabetes, with insufficient perinatal information, congenital malformations and twins were excluded. Age 13-19 years at questionnaire Young-HUNT Study, girls 13-19 years who were residents in Nord Trondelag County in Norway and completed a questionnaire in 1996-1997	Birth weight in g, in quintiles Ponderal index (kg/m cubed), in quintiles Birth length in cm, in quintiles	Birthweight and birth length from Medical Birth Registry	Age at menarche, continuous	Self-reported in years and months at 13-19 years. If month not given, used year plus 6 months as estimate.	Cox proportional hazards model for age at menarche (RR>1 indicates earlier menarche). Exposures were in quintiles, p-values also presented for test for trend using continuous values.	RR from Cox model for age at menarche with ponderal index as exposure: Q1 (18.09-25.49): Referent Q2 (25.50-26.74): RR=0.90, 95% CI=0.81, 1.01 Q3 (26.76-27.92): RR=0.87, 95% CI=0.78, 0.97 Q4 (27.93-29.32): RR=0.90, 95% CI=0.81,1.01 Q5 (29.33-39.51): RR=0.93, 95% CI=0.83, 1.04 p for trend=0.28 1st quintile of PI vs. others, p=0.02 (data not shown) RR from Cox model for age at menarche with birth length as exposure: Q1 (43-48cm): Referent Q2 (49cm): RR=1.06,	None Stated that adjustment for length of gestation and age at attendance did not substantially influence association (data not shown) In subset with parental data, adjustment for maternal age at menarche and parental height and weight did not substantially alter results (data not shown)

								95% CI=0.93, 1.21 Q3 (50cm): RR=1.02, 95% CI=0.90, 1.14 Q4 (51cm): RR=0.96, 95% CI=0.85,1.09 Q5 (52-58cm): RR=0.96, 95% CI=0.86, 1.08 p for trend=0.03	
Windham, 2004, United States	Prospective cohort	994 girls with menarche data 15-17 years Follow-up of subset of California Child Health and Development Studies (pregnancies 1959-1966)	Birthweight, categorized: <2500g ≥2500g	Weight measured at birth	Age at menarche, examined continuously and in categories: - Early: <12y - Average: 12-13 years - Late: >13 y	Recalled by girl at 15-17 years (years and months - though 45% of girls only gave year)	Mean age at menarche by category of independent variables using the F test and distribution of early and late menarche using chi-square test.	Frequency of early and late menarche by birthweight: <2500g: Early menarche = 14.9% Late menarche = 27.7% ≥2500g: Early menarche = 15.6% Late menarche = 23.6% p=0.81 Mean age at menarche by birthweight:	None

								<2500g: Mean=13.08 years ≥2500g: Mean=12.95 years p=0.49	
Trentham-Dietz, 2005, United States	Cross-sectional	59 girls with menarche data Age 10-13 years Cross-sectional study of sixth-grade female students in Reedsburg, WI area school district in 1999	Birthweight in kg	Reported by parents	Menarche status at survey	Self-report by girl at 10-13 years	Analysis of variance models comparing least-squares means adjusted for age	Mean (SD) birthweight in kg by menstrual status (p=0.17): Menstruating: 3.4 (0.1) Not Menstruating: 3.6 (0.1)	Age at survey

								Mean (SD) of birthweight by menarche group (p=0.27 from ANOVA): Early: 3.3kg (0.37) Average: 3.42kg (0.54) Late: 3.31kg (0.46) Median (range) of PI (g/cm3) by menarche group (p=0.43 from Kruskal-Wallis): Early: 2.75 (2.07-3.29) Average: 2.79 (1.93-3.84) Late: 2.80 (2.36-3.39) Median (range) of birth length in cm by menarche group (p=0.047 from Kruskal-Wallis): Early: 49.0 (45.5-54.0) Average: 49.5 (44.0-57.5) Late: 48.0 (43.0-53.0)	
Tam, 2006, Australia	Prospective cohort	149 term girls with birth, anthropometry and menarche data Age 15 years at follow-up 2004 follow-up of subset of birth cohort (infants born at term (37-42 weeks) at Nepean Hospital, Penrith, in western Sydney between August 1989 and April 1990	Birthweight in kg Ponderal index (weight in g/height in cm cubed) Birthlength in cm Birth size groups defined by birth weight cut at median (3325g) and birth length cut at median (49.3cm): Long/light Long/heavy Short/Light Short/heavy	Weight and length at birth from hospital records	Age at menarche, categorized into 3 groups based on SD: Early: <11.5 years Average: 11.5-13.7 years Late: >13.7 years	Self-report by girls at 15 years (attained menarche, month and year of first period)	ANOVA and Kruskal Wallis to compare characteristics by menstrual group Pearson's correlation and Spearman's rho test to assess correlations between birth size and age at menarche Comparison of menarche in birth size group using analysis of covariance with BMI z score at 8 years as a covariate	No correlation between birth length or birthweight and age at menarche (data not shown) Average age at menarche by birth size group, adjusted for BMI Z-score at 8 years: Long/Light: 12.0 y, SD=0.3 Long/Heavy: 12.5 y, SD=0.1 Short/Light: 12.6y, SD=0.1 Short/Heavy: 13.0, SD=0.3 Girls who were long and light at birth and with a BMI z-score >0 at 8 years had earliest	BMI Z-score at 8 years

menarche. Among all birth size groups, higher BMI at age 8 was associated with earlier menarche.

van Weissenbruch et al, 2006, Netherlands	Prospective cohort	17 term SGA and 12 term AGA girls Latest visit: - SGA mean 14.6 +/-1.2 - AGA mean 14.7 +/-1.2 Follow-up of SGA and AGA children traced from the database of all pregnancies, deliveries and perinatal events of children born in the VU University Medical Center (registered since 1980)	SGA: birthweight below the 10th percentile corrected for gestational age (GA), gender and parity AGA: birthweight >10th percentile using Dutch reference data	Birthweight, gestational age abstracted from register	Age at menarche, continuous	Not stated, assumed reported by parents or adolescents at follow-up visits	Differences between SGA and AGA groups were tested by chi-square test for qualitative variables and Student's t-test for quantitative variables	By second follow-up, 8/9 girls born AGA reached menarche with mean age of 12.7 (1.5 years). 10/10 SGA girls reached menarche at mean age of 12.6 (1.5) years. Age at menarche was not statistically different between the two groups.	None
Sloboda, 2007, Australia	Prospective cohort	776 girls with menarche data Age 12-14 years at follow-up Western Australian Pregnancy (Raine) Cohort, women enrolled during pregnancy in 1989-1990	Expected birthweight ratio (EBW): ratio of observed birth weight appropriate for maternal height, sex, nulliparity, and gestational age IUGR defined as EBW<10th percentile	EBW calculated using data from study visit/medical record	Age at menarche	Self-report on puberty questionnaire or censored at age at last follow-up if no menarche reported	Continuous data summarized using medians, IQ ranges and ranges Multivariable Cox regression models to evaluate association between fetal and postnatal growth and age at menarche	EBW predicted age at menarche (p=.02) and girls with an EBW below the median had a significantly earlier menarche compared with girls with an EBW above the median (HR=1.29, 95% CI 1.04, 1.59) Age at menarche stratified by EBW and BMI at 8 years: EBW<1 & BMI≥16.3: Median age at menarche = 12.5yrs, IQ range 12.1-13.2, Range 9.4-14.4 EBW≥1 & BMI≥16.3: Median age at menarche = 12.8yrs, IQ range 12.2-13.6, Range 9.8-14.6 EBW<1 & BMI<16.3: Median age at	Cox model adjustment not stated. By using EBW as a measure, adjusted birthweight for maternal age, height, parity, infant sex and gestational age

								menarche = 13.0yrs, IQ range 12.6-14.2, Range 10.6-14.6 EBW≥1 & BMI<16.3: Median age at menarche = 13.2yrs, IQ range 12.8-14.4, Range 11.0-14.2	
Vandeloo, 2007, Belgium	Cross-sectional	1146 girls Mean age=12.8 years Girls recruited in second year of secondary school from 10 centres of Medical School Supervision (MSS) in Belgian Limburg in 1999-2000 school year	Length at birth	Questionnaire, partially completed by medical team with the remainder completed by girls and one parent	Age at menarche	Self-report with parent's help via questionnaire	Cox regression model for age at onset of breast development (RR>1 indicates earlier menarche)	RR = 0.974, 95% CI 0.945,1.004	None *Results for birth length were not shown for multivariable model
Bosch, 2008, Bangladesh	Prospective cohort	255 girls Age 12-16 years at follow-up 2001 follow-up of 320 girls in three villages in rural Bangladesh, originally enrolled in a study of infection disease at <5 years in 1988-1989	Baby's relative size at birth, dichotomized as: small normal or tall	Recalled by mother during adolescent visit (relatively small, normal or relatively tall)	Age at menarche, continuous	Reported by girl at adolescent visit	Univariate Cox proportional hazards models with age at menarche as outcome (β>0 indicates earlier menarche)	β from Cox model: Small: β = -0.323, SE = 0.240, p≥0.05 Normal or Tall: Referent	None

Blell, 2008, United Kingdom	Prospective cohort	276 women with menarche data Age 49-51 years at follow-up 1997 follow-up of subset of Newcastle Thousand Families birth cohort, prospective study of all 1142 children born in May and June 1947 to mothers resident in Newcastle-upon-Tyne, UK	Birthweight in kg Birthweight standardized for gestational age and sex	Midwife records	Age at menarche categorized into 3 groups based on SD: Early: <11.4 years Average: 11.41-14.49 years Late: >14.49 years	Age at menarche in years and months recalled by women at age 49-51 years	Multivariable ordinal logistic regression with a probit link was used to investigate relations between explanatory variables and categorical age at menarche (Oprobit coeff<0 indicates earlier menarche)	Mean (SD) birthweight in kg by menarche group: Early: 3.35 (0.57) Average: 3.39 (0.52) Late: 3.43 (0.43) Oprobit coeff = 0.094, 95% CI= -0.17, 0.36 Mean (SD) birth weight standardized for gestational age by menarche group: Early: 0.11 (1.27) Average: 0.02 (1.07) Late : 0.05 (1.00) Oprobit coeff = -0.02, 95% CI= -0.14, 0.10 p=0.03 for interaction between standardized weight at age 9 and standardized birth weight. Girls who were youngest at menarche were born heavy for their gestational age and were heavy at age 9. Those with latest menarche were also born heavy for their gestational age but were light for their age at 9.	None

Chaudhari, 2008, India	Prospective cohort	113 girls (34 PTSGA, 15 FTSGA, 29 PTAGA, 35 controls) Age 12 years a follow-up Prospective cohort of all infants weighing <2000g discharged from a neonatal special care unit from October 1987-April 1989 and followed up until age 12 years. Full-term neonates born in the same hospital during the same period with birthweight >2500 g were enrolled as controls	4 groups based on gestational age and birthweight (Singh criteria): PTSGA: Preterm small for gestational age FTSGA: Full term small for gestational age PTAGA: Preterm appropriate for gestational age FTAGA: Full term appropriate for gestational age	Birthweight and gestational age from hospital records	Age at menarche	Date of menarche reported by mothers when girls were 12 years old	Descriptive analysis only	Mean age at menarche (range) by group: PTSGA: 12.5 (10.4-13.8) FTSGA: 12.7 (8.8-14.3) PTAGA: 12.5 (10.4-14.0) FTAGA: 12.8 (10.8-14.5)	None

Opdahl, 2008, Norway	Prospective cohort	262 singleton, term girls Age 12.7-15.5 years at follow-up 2001-2002 follow-up of subset of Norwegian birth cohort (1985-1986). 10% of random sample of all women were followed along with another group of women at risk for giving birth to an SGA child (previous LBW child or perinatal death, cigarette smoking at conception, pre-pregnancy weight<50kg, chronic renal disorder or hypertension)	Birthweight in tertiles: <3200g 3200-3700g ≥3700g Ponderal index (g/cm cubed) in tertiles: <2.63 2.63-2.85 ≥2.85 Birth length in tertiles: <49cm 49-51cm ≥51 cm	Birthweight (g) and birthlength (crown to heel, to nearest half cm) measured at birth	Age at menarche	Reported by girl at adolescent visit (assumed)	Median age at menarche for each birth size group estimated by Kaplan-Meier analyses and multivariable analysis performed using Cox regression	Median (95% CI) age at menarche from Kaplan-Meier by tertile of exposure: Birth weight (p=0.001): <3200g: 12.58, 95% CI=12.32, 12.84 3200-3700g: 13.25, 95% CI=12.94, 13.56 ≥3700g: 13.33, 95% CI=12.97, 13.70 Ponderal index (p=0.099) <2.63: 12.83, 95% CI=12.53, 13.14 2.63-2.85: 13.08, 95% CI=12.82, 13.35 ≥2.85: 13.17, 95% CI=12.68, 13.65 Birth length(p<0.0001): <49cm: 12.50, 95% CI=12.26, 12.74 49-51cm: 13.08, 95% CI=12.94, 13.22 ≥51cm: 13.33, 95% CI=12.95, 13.72	None Stated in results that adjusted for potentially confounding factors (BMI, gestational age, age in adolescence, maternal age at menarche, residential area) did not alter results (data not shown)
Rubin, 2009, United Kingdom	Prospective cohort	4212 singleton girls with consistent menarche data Age 8-13 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Birth weight in kg	Medical records	Presence of menarche at 11 year old questionnaire	Reported at 11-year questionnaire by daughter, mother or both	Multivariable logistic regression for menarche by age 11 years (OR>1 indicates earlier menarche)	Birth weight in kg was not associated with menarche in univariate analyses at p≤0.20 (data not shown)	None

Labayen, 2009, Spain	Cross-sectional	788 girls with complete data Age 13-18.5 years 2002 survey of Spanish adolescents (AVENA study). Individuals from public and private secondary schools and technical colleges were included in the nationally representative sample (multi-staged, random, stratified by town of origin, SES, sex and age)	Birthweight Z-score, continuous, calculated with use of sex- and gestational age-specific percentiles for this population SGA: BW < 10th percentile for gestational age (6.7%) AGA: BW between 10th and 90th percentile (54.3%) LGA: BW > 90th percentile for gestational age (36.8%)	Birth weight and gestational age from health booklets (Issued at birth where pediatricians record infant's growth)	Age at menarche, continuous and categorized as: <12 years ≥12 years	Self-report by adolescent of age at menarche, calculated from year of first period	Linear regression analysis was used to assess associations between BW Z-score and age of menarche (β<0 indicates earlier menarche)	Multivariable models for association between BW Z-score and age at menarche: Unadjusted: β=0.228 , 95% CI=0.087, 0.368 Adjusted: β=0.45, 95% CI=0.287, 0.623 Low risk for early menarche (<12 years) in girls born LGA from logistic regression model (OR=0.63, 95% CI 0.45-0.89, p=.009, other results not shown)	Age, SES, physical activity, body fat percentage
Semiz, 2009, Turkey	Cross-sectional	1562 girls, 306 with menarche Age 6-16.5 years Cross-sectional school-based study of schoolchildren in grades 1-8 in primary schools in the Denizli province between March-May 2005	Birth weight	Reported by parents	Age at menarche, continuous	Reported by girl at visit	Comparison of menarcheal age to gestational age and birth weight using Chi-square test.	No statistically significant difference was found between gestational age, birth weight and menarcheal age (p>0.05, data not shown)	None

Keim, 2009, United States	Prospective cohort	597 women with complete menarche and maternal data available 22-32 years at follow-up Follow-up in 1987-1991 of subset of women from Providence and Philadelphia sites of the CPP cohort (pregnant women enrolled in 1959-1966)	SGA vs. not, unclear how defined	Birthweight and gestational age measured at birth	Age at menarche, categorized as: ≤11 years 12 years 13 years 14+ years	Self-report during adult interview	Polytomous logistic regression to examine the relationship between daughter's age at menarche and maternal pre-pregnancy BMI, SGA examined as a mediator	SGA status (N, %) by menarche group: ≤11 years: SGA=35 (29%); Not SGA=86 (71%) 12 years: SGA=42 (27%); Not SGA=116 (73%) 13 years: SGA=36 (24%); Not SGA=111 (76%) 14+ years: SGA 39 (23%); Not SGA=132 (77%) SGA did not mediate association between maternal obesity and age at menarche, although stated in text that SGA status was associated with daughter's age at menarche in models that included maternal BMI and other covariates (ORs ranged from 0.8-1.2)	None
Ong, 2009, United Kingdom	Prospective cohort	2715 singleton girls with age at menarche data Mean age at follow-up: 12.9 years (IQR 12.8-13.0) Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Birthweight in kg, continuous BMI at birth Birthlength in cm, continuous	Birth weight as recorded in delivery room, birth length measured by staff within 24 hours of birth	Age at menarche, categorized as: <12 12-13 >13	Reported by girl at adolescent visit (~13 years of age). Some missing data on age at first menstruation were imputed from similar data collected at 11 year visit.	Means (SD) of early-life measures by age at menarche group	Size at birth (Mean, SD) by girls' age at menarche: Birthweight (kg) (P for trend=0.04): <12: 3.38 (0.02) 12-13: 3.36 (0.02) >13: 3.42 (0.01) Birthlength (cm) (P for trend=0.2): <12: 50.4 (0.1) 12-13: 50.3(0.1) >13: 50.5 (0.1) BMI at birth (P for trend=0.2): <12: 13.3 (0.1) 12-13: 13.3(0.1) >13: 13.4 (0.1)	Age

Terry, 2009, United States	Prospective cohort	262 women 38-46 years at follow-up Follow-up in 2001-2006 of subset of women from New York site of the CPP birth cohort (born 1959-1963)	Birthweight in kg Birth length in cm	Measured by study staff	Age at menarche, continuous and dichotomized as: ≤12 years >12 years	Self-reported by adult participant	Univariate associations using correlation coefficients for continuous variables, chi-square tests and analysis of variance to compare averages across subgroups Multivariable linear regression models using age for age at menarche (β<0 indicates earlier menarche).	β for birthweight in kg from linear regression model: Univariable: β=-0.34, 95% CI= -0.80, 0.12 Adjusted β=-0.68, 95% CI=-1.59, 0.22 Average age at menarche was lower for higher-birthweight babies only among girls of lower weight at age 7 years β for birth length in cm from linear regression model: Adjusted β=0.02, 95% CI -0.18, 0.22	Fully adjusted parsimonious model includes birth weight, percentile change in weight from 0-4 months, 4-12 months, 1-7 years, birth length, percentile change in height from 0-4 months, 4-12 months and 1-7 years, family SES at age 7, maternal age at menarche
Karaolis-Danckert, 2009, Germany	Prospective cohort	87 term singleton girls with birthweight>2500 g, height at 6 and 13 years of age and at least 5 measures between these ages, anthropometrics at 24 months, complete data on maternal characteristics and age at menarche At least 13 years of age Subset of the DONALD (Dortmund National and Anthropometric Longitudinally Designed) Study started in 1985	Birthweight, categorized as: ≥2500-3000g >3000g	Standardized document given to all pregnant women in Germany	Age at menarche, continuous	Girls or their parents are asked if menarche occurred since previous visit, and if so, which month and year	Linear mixed-effects regression models (PROC MIXED) were used to construct longitudinal models of age at menarche (β<0 indicates earlier age at menarche).	Adjusted β from linear regression model: 2500-3000g: β=-0.49, SE=0.29, p=0.1 ≥3000g: Referent Adjusted β from pathway linear regression model: 2500-3000g: β=-0.68, SE=0.29, p=0.02 ≥3000g: Referent.	Rapid weight gain from 0-4 months, maternal overweight & BMI SDS score 1 year before ATO in pathway model Noted that adjustment for gestational age did not change results (data not shown)

Espetvedt Finstad, 2009, Norway	Cross-sectional	204 women Age 25-35 years Norwegian EBBA-I study, 2000-2002. Eligibility criteria included self-reported regular menstruation, not taking hormonal contraceptives, no pregnancy or lactation over previous 6 months and no history of endocrinological (eg diabetes, hypo/hyperthyroidism), gynecological or chronic disorders	Birthweight, categorized into tertiles: <3220g ≥3220 and <3530g ≥3530g	Personal health records	Age at menarche, continuous	Self-report by participant in adulthood	Mean age at menarche by birthweight tertile with p value from one-way ANOVA	Mean (SD) age at menarche by birthweight tertile (p=0.06): <3200g: 12.96y (1.3) ≥3200g to <3530g: 12.98 (1.3) ≥3530g: 13.40 (1.5)	None
Boyne, 2010, Jamaica	Prospective cohort	140 girls who were seen at all scheduled visits between birth and 11 years At least 11 years at follow-up Vulnerable Windows Cohort Study, pregnant women were recruited in 1992-1993 at University Hospital of the West Indies, Kingston,Jamaica for birth cohort.	Birthweight, g, continuous Birth length, cm, continuous BMI at birth	Weight and crown heel length measured within 24 hours of delivery	Age at menarche	Menstrual history was taken at each visit (biannual)	Multiple regression analyses to examine the relationships among child's growth and body composition and the stage of puberty with outcomes and predictors in standardized form, so that the regression coefficients were effectively correlation coefficients.	Correlations between the size at birth and growth of Afro-Caribbean girls and age at menarche at age 11 years: Birth weight: 0.05 BMI at birth: 0.02 Birth length: 0.05 p≥0.05 for all correlations	Age at clinic visit

Epplein, 2010, United States	Cross-sectional	348 girls with birthweight data whose race/ethnicity was White, Asian or Polynesian Age 9-18 years at visit First visit for the Female Adolescent Maturation (FAM) Study, cohort of girls age 9-14 in 2000-2001 enrolled from KP Hawaii followed up in 2002-2003 and 2004-2005 and new participants aged 12-18 in 2005-2007	Birthweight, continuous and in categories: Low: ≤2500g Normal: 2500-4000g High: ≥4000g	Hawaii State Department of Health birth record database on birth weight (75% of participants), parent recall for those without record data	Age at menarche	Self-reported by daughters through August 2008. If pre-menarche, censored at age at last contact	Cox proportional hazards model for age at menarche with age as the time scale (HR>1 indicates earlier menarche)	Adjusted HR for menarche: <2500g: HR=1.28, 95% CI=0.75, 2.18 2500-4000g: Referent ≥4000g): HR= 1.08, 95% CI=0.53, 2.20 Continuous: HR=1.00 (1.00, 1.00) Adjusted HR for menarche, mediation model: <2500g: HR=1.17, 95% CI=0.69, 2.00 2500-4000g: Referent ≥4000g: HR= 1.01, 95% CI=0.49, 2.07 Continuous: HR=1.00 (1.00, 1.00)	Age, race/ethnicity and gestational age Mediation model also includes waist circumference
Maisonet, 2010, United Kingdom	Prospective cohort	1316 singleton, term girls (37-42 weeks gestation) with consistent pubertal staging and birth size data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Birth weight (kg), Gestational age, birth length (cm) SGA = birth weight <10th percentile of weight for gestational age. Referent weight percentiles estimated by weight and gestational age data of singleton girls from the full ALSPAC cohort	Medical records	Age at menarche	Month and year of menarche, reported girls at pubertal self-assessments between 8-14 years of age. Girls with inconsistent responses were excluded from analyses	Interval-censored parametric survival model for age at menarche assuming a normal distribution (Diff <0 indicates earlier menarche)	Adjusted difference for menarche: Birthweight: Diff = 0.00, 95% CI= -0.00,0.00 Birth length: Diff = 0.00, 95% CI= -0.03, 0.04 SGA vs. non-SGA: Diff = -0.05, 95% CI= -0.29, 0.19	Maternal age at menarche, previous live birth, maternal race or ethnicity, smoking during pregnancy, maternal prepregnancy BMI, maternal age at delivery, maternal education

Morris, 2010, United Kingdom	Cross-sectional analysis of prospective cohort	81,606 women with age at menarche information (excluded those with history of BC, menarche >20 years, menarche at 3-4 years, and older siblings - only 1 woman per family included) 16-98 years at baseline (median 46) Breakthrough Generations Study Cohort (women >16 and above in the UK)	Birth weight, continuous	Birth weight in grams or lbs and oz self-reported on baseline questionnaire	Age at menarche	Self-report on baseline questionnaire, reported in whole years	Linear regression to assess differences in age at menarche in months (β<0 indicates earlier menarche.	β from linear regression for age at menarche in months for birthweight: Univariable (per 500g increase): β = 0.31, 95% CI=0.19, 0.43 Multivariable (per 500g increase): β = 1.24, 95% CI=1.10, 1.37 Mean age at menarche in years by childhood weight at 7 years: A little or much thinner than peers: <3099g: 13.01y 3100-3399g: 13.15y ≥3400g: 13.17y p for trend: <.0001 About the same as peers: <3099g: 12.52y 3100-3399g: 12.61y ≥3400g: 12.68y p for trend: <.0001 A little or much heavier than peers: <3099g: 11.99y 3100-3399g: 12.05y ≥3400g: 12.17y p for trend: <.0001 In subgroup analyses, birthweight had a positive association with menarcheal age in first- and second-born women (p for trend <.001) but not for women of a higher birth order	Stated that univariable results were similar after adjustment for SES and birth year (not shown) Also stated that effect of birthweight remained significant after adjustment for gestation length Multivariable model adjusted for maternal age at birth, ethnicity, weight at 7 years, height at 7 years, childhood exercise, number of siblings and birth order.

Ruder, 2010, United States	Prospective cohort	278 girls with birth and menarche data Age 25-29 years at follow-up Data from female participants in the original DISC study (1988-1997) with data supplemented by the DISC Follow-Up Study (conducted in 2006-2008, when women were 25-29 years of age)	Birth weight, birth length and gestational age as continuous variables and as quartiles	Self-report at adult follow-up of birthweight (pounds, oz), birthlength (nearest tenth of inch) and gestational age (in weeks, plus term or preterm) with birthweight data supplemented by maternal questionnaire report in 3rd year of original study (maternal report of birthweight used for 23 women who did not report birthweight at adult follow-up).	Age at menarche, continuous and categorized as: Early: ≤11.75 years Average: 11.76–13.74 years Late: ≥13.75 years	Age at menarche reported to nearest day (imputed to 15th if month only) and ascertained annually in original DISC study. Also self-reported in whole years at adult follow-up. In analysis, adolescent data was used for 250 girls and adult recalled data for 34 girls that were missing data from original data collection.	One-way ANOVA analyses were used to compare differences in mean birth weight, birth length, and gestational age, between menarche groups. Birth characteristics were treated as predictor variables (continuous and quartiles) with age at menarche in years as the dependent variable in linear regression models.	Mean birthweight in g (SD) by menarche group: Early: 3298.47 (496.89) Average: 3411.39 (479.61) Late: 3497.90 (545.38) Overall p-value 0.16 Mean birthlength in cm (SD) by menarche group: Early: 50.76 (3.0) Average: 51.06 (2.68) Late: 51.59 (3.01) Overall p-value 0.36 β from unadjusted linear regression results in subset with maternal age at menarche (N=161): Birth weight in quartiles: Q1: β=-0.52, 95% CI= -1.07, 0.03 Q2: β=-0.44, 95% CI=-0.97, 0.08 Q3: β=-0.59, 95% CI= -1.16, 0.02 Q4: Referent Trend test: p=0.12 Continuous (per 500g): β=0.20, 95% CI=-0.01, 0.40 β from adjusted linear regression results in subset with maternal age at menarche (N=161): Birth weight in quartiles: Q1: β=-0.38, 95% CI= -0.87, 0.11 Q2: β=-0.35, 95% CI= -0.82, 0.12 Q3: β=-0.55, 95% CI= -1.07, -0.04 Q4: Referent	Intervention group, race, BMI-for-age-percentile, mother's age at menarche

Trend test: p=0.24
Continuous (per 500g): β=0.14, 95% CI=-0.04, 0.32

Birthweight in quartiles and as continuous variable was positively associated with age at menarche (p<.01). With covariate adjustment, women in the lowest quartile of birthweight experienced menarche 0.51 years earlier compared to women in the highest quartile of birth weight (95% CI: -0.88, -0.14; p<0.01, p-trend<0.01). Modeling birthweight as a continuous variable with covariate adjustment also indicated that the adjusted birth weight effect was statistically significant (p<0.01) with each 500 g increase in birth weight associated with a 0.21 year delay in age at menarche.

Birthlength was not associated with age at menarche when modeled in quartiles or as a continuous variable (data not shown)

Cho, 2010, South Korea	Cross-sectional	620 girls with menarche data Age 10-19 years Girls born between 1986 and 1995 participating in the 2005 Korean National Health and Nutrition Survey (KHANES)	Birthweight in kg	Reported by mothers on self-administered questionnaire	Menarche status at visit	Self-report by girls	Exposures compared between premenarcheal and menarcheal girls using ANCOVA, controlling for age and chi-square test when variables were continuous and categorical	Mean birthweight by menarche status from ANCOVA (p = 0.328): Premenarcheal girls: 3.25kg (SD=0.39) Menarcheal girls: 3.20 kg (SD=0.24)	Age
Chevalley, 2011, Switzerland	Prospective cohort	115 women with body size data at birth (96 at 1 year) Mean age 20.4 at follow-up Follow-up of pre-pubertal girls participating in an RCT of calcium-enriched foods and bone mass growth (enrolled at mean 7.9 years, followed up to 20.4 years. Exclusion criteria at enrollment were ratio of weight/height <3rd or >97th percentile, physical signs of puberty, chronic disease, malabsorption, bone disease and regular use of medication)	Body weight, standing height and BMI at birth (converted to Z-scores)	Obtained retrospectively at baseline from questionnaires sent to parents and pediatricians	Age at menarche, continuous and dichotomized at the median (12.9 years)	Self-reported by daughter at interview at visits (8.9 years, 10 years, 12.4 years, 16.4 years)	Univariate linear regression analysis examining association between BMI Z-score at birth and 1 year or change in BMI Z-score from birth to 1 year and age at menarche Z-score. Differences in anthropometric characteristics between earlier and later menarche (dichotomized at the median) assessed by unpaired t-tests or by Wilcoxon signed rank test.	Mean (SD) of birth characteristics by median age at menarche: Weight (kg), p=0.995: Earlier: 3.2 (0.4) Later: 3.2 (0.4) Standing height (cm), p=0.680 Earlier: 49.4 (2.2) Later: 49.2 (1.9) BMI, p=0.706 Earlier: 13.0 (1.2) Later: 13.1 (1.3) β for age at menarche Z-score predicted by BMI at birth Z-score): β = -0.07, 95% CI= -0.259, 0.120), R-squared = 0.01	None

Orden, 2011, Argentina	Cross-sectional	1221 girls Age 9-15 years Cross-sectional study of 1221 school girls in Santa Rosa, Argentina, carried out in Sept-Nov 2009 (public and private schools selected from neighborhoods)	Birth weight	Parent report in adolescence	Menarche at study visit (status quo method). Girls were grouped at age at visit: 9-11, 12, 13 and 14-15 years	Self-report by girl (Girls reported age at menarche, but most specified age in years so status quo method was used)	Anthropometric differences between pre- and post-menarcheal girls were compared by the Mann-Whitney test. Logistic binary regression was used to model the association between menarche and independent variables.	Mean difference in birthweight between pre- and postmenarcheal girls according to age groups (prem-postm): 9-11: Birth weight diff = -17.8, p=0.858 12 : Birth weight diff = -38.3, p=0.624 13: Birth weight diff = 0.1, p=0.999 14-15: Birth weight diff = -4.6, p=0.963 Birth weight included in initial logistic regression model with anthropometric measures, p>.05 (results not shown, not included in final model)	None for differences, logistic regression adjusted for age, subscapular/tricipital index (STI) and anthropometric Z-scores at visit
Wehkalampi, 2011, Finland	Prospective cohort	21 VLBW SGA girls, 44 VLBW AGA girls and 92 control girls (matched to VLBW by age, sex and birth hospital) Mean age 22.5 years at follow-up Helsinki Study of Very Low Birthweight Adults, longitudinal follow-up of subjects born preterm at VLBW (<1500g) between 1978-1985 and treated in the Neonatal ICU of Children's Hospital of Helsinki	VLBW SGA: Infants weighing <1500g at birth and birthweight <-2SD based on Finnish standards VLBW AGA: Infants weighing <1500g at birth and birthweight ≥-2SD based on Finnish standards Controls: Term infants with birthweight ≥-2SD based on Finnish standards	Hospital records	Age at menarche	Self-reported by women	Age at menarche, corrected for gestational age at birth, were compared between VLBW and control subjects	Mean (SD) age at menarche by group: VLBW SGA (N=21): 12.6 (1.8) VLBW AGA (N=44): 12.2 (1.2) Controls (N=92): 12.5 (1.3) Not statistically different from each other	Gestational age at birth

		University Hospital and controls who were not SGA (birthweight>-2 SD)							
Szwed, 2012, Poland	Cross-sectional	273 girls with menarche data Age 17-21 years Outpatient clinic cards of "Vitamed" general outpatient clinic in the city of Poznan and cross-sectional research on girls from the province of Wielkopolska in Poland	Birthweight, continuous, and categorized as: Low:<2500g Appropriate: 2500-4000g High:>4000g Also birthweight for GA: SGA: birthweight <10th percentile for gestational age AGA: birthweight 10-90 percentile LGA birthweight >90th percentile for gestational age	Outpatient clinic cards	Age at menarche	Self-report by girl at visit. Only girls 17 and above included since latest age at menarche was 17 (excluded younger girls)	Kaplan–Meier method log-rank test for differences in age at menarche by exposure	Birthweight (categorized as low, appropriate, high) was associated with age at menarche (log rank test, p<.000001). Girls with low birthweight had latest age at menarche. No variation in age at menarche by SGA, AGA and LGA groups (log rank p value >.05)	None

Reagan, 2012, United States	Prospective cohort	2337 girls born between 1978-1998 with menarche data (pre-menarche girls excluded) Age 12-32 in 2010 Subset of U.S. National Longitudinal Surveys of Youth Child-Mother file (1979-2010 waves). 78% of eligible sample included	Birthweight in kg	Reported by mother during first interview after child's birth. Reported in lbs and oz and converted to kg.	Age at menarche	Reported by mothers when girls were 8-14 y or by girls at 14y and above. Reported year and month of menarche, used to calculate age	OLS regression with age at menarche as outcome and 2-stage IV analysis for age at menarche with maternal smoking during pregnancy, maternal pre-pregnancy BMI and GWG used as IVs	β for age at menarche for birthweight (kg): OLS model: β=1.80, 95% CI=0.63, 2.97 2-stage least squares model: β=3.00, 95% CI= 1.53, 4.48	Childhood BMI Z-score, percent poverty (0-5 years)*White, Percent poverty*African American, Maternal age at menarche, African-American. 2-stage results used pre-pregnancy BMI, high GWG and maternal smoking as IV
Wang, 2012, United States	Prospective cohort	305 term girls Age 10-15 years at first report of pubertal status, followed annually until TS5 or max of 5 years Adolescent follow-up of subset of the North Carolina Infant Feeding Study, infants born 1978-1982	Birthweight in kg	Recorded at birth by nurse	Age at menarche, continuous	Date of menarche reported by daughter on annual surveys (started in 1992 at age 10-15, followed for max of 5 years)	Univariate linear model for age at menarche. Multivariable-adjusted parametric survival analyses with log normal distribution for age at menarche (β<0 indicates earlier menarche)	Univariable linear regression model for birthweight, kg: β= -0.04, SE=0.15, p>.05 Regression coefficient in adjusted log-normal survival analyses of time to menarche Birthweight : β=-0.06, 95% CI= -0.10, -0.03 Early menarche group had highest weight Z-score starting at birth, but lines really start to diverge after age 1	Birthweight, weight gain (change in Z-score) from 0-6 months, 6-12 months, 1-2 years, 2-5 years, maternal pre-pregnancy weight and race.

								Mean (SD) for birthweight in kg and t-test by menarche group: Early: 3.1 (0.4) Avg/late: 3.2 (0.4) p=0.29	
Oh, 2012, South Korea	Cross-sectional	144 girls with menarche data Average age 12.8 years (SD 0.4) for early menarche group and 12.7 (SD 0.5) for late menarche group Survey conducted among grade 4 students from one middle school in Seoul in Nov-Dec 2008	Birthweight in kg and categorized into quartiles for analysis: Q1:<2.98 Q2:2.98-3.18 Q3:3.18-3.38 Q4: ≥3.38	Mother report on questionnaire when child in 7th grade	Age at menarche, dichotomized as: Early: ≤12 years Average or late: >12	Age at menarche reported by girl or mom	T-test to compare mean birthweight between early and average/late menarche group Multiple logistic regression for early menarche with Wald test for trend. Main exposure was BMI (or change in BMI) at ages 7, 8 , and 9 years. Birthweight was an adjustment factor.	OR for early menarche for birthweight (results from model with main exposure of BMI quartile at age 7): Q1: Referent Q2: OR=0.65, 95% CI=0.17, 2.60 Q3: OR=0.44, 95% CI=0.13, 1.47 Q4: OR=0.79, 95% CI=0.25, 2.55 P for trend: 0.55 *Results were similar when models adjusted for BMI or change in BMI in other childhood periods	BMI quartile at 7 years, ever breastfed, maternal age at menarche
Dossus, 2012, France	Prospective cohort (cross-sectional analysis)	96,493 women with data on age at menarche from 8-19 years (23.7% missing birthweight data and 29.3% missing birthlength data) 40-65 years at baseline E3N cohort, French women ages 40-65 years at baseline, insured with the Mutuelle Generale de l'Education Nationale, a national health insurance plan	Birthweight was categorized for full-term women: Low:<2500g Medium: 2500-4000g High: >4000g Birthlength was categorized: Low: <48cm Medium: 48-51cm High: >51cm	Birthweight self-reported by participant in adulthood, recorded in grams or using categories "low", "medium", "high" Birthlength self-reported by participant in adulthood, recorded in cm or using categories "low",	Age at menarche, continuous	Self-reported in first two questionnaires, with age from 8-19 in full years and additional categories for never menstruated or menstruated at ≤7 or ≥20 years (excluded)	Association between pre- and postnatal factors and age at menarche was assessed by multivariable-adjusted linear regression (β<0 indicates earlier menarche)	β (95% CI) for age at menarche in months from adjusted model: Birthweight (p for trend <.0001): Low: Referent Medium: β=0.61, 95% CI=0.09, 1.13 High: β=1.51, 95% CI=0.87, 2.16 Birthlength (p for trend <.0001): Low: Referent Medium:β= -1.05, 95% CI= -1.50, -0.59 High: β= -1.84, 95% CI= -2.45, -1.24	Birth cohort, Father's income index, Population of birth place, fetal number, number of siblings, maternal smoking during pregnancy, breastfeeding exposure, suffered from food deprivation during WWII, premature birth, birthweight, birth length, body silhouette at menarche, passive smoking during childhood, frequency of indoor exposure

		covering mostly teachers and recruited June 1990-Nov 1991		"medium", "high"					to passive smoking during childhood, extra-school physical activity at 8-15 years, walking activity at 8-15 years
D'Aloisio, 2013, United States	Cross-sectional	33,501 women with age at menarche, early-life and race information Age 35-59 years at baseline Sister Study participants, age 35-59 years at baseline (2003-2009)	Birthweight, categorized as: <2500 ≥2500g	Self-report by participant at baseline in lbs/ozs (age 35-59 years). Women were given a prepaid phone card and encouraged to call their mother/relatives for assistance.	Categorized as: ≤10 years 11 years 12-13 years 14 years ≥15 years	Age at menarche, recalled in years by participant during CATI interview at baseline. For women who did not know age, it was estimated from grade in school (n=77) or timing relatives to others (n=63)	Polytomous logistic regression to estimate relative risk ratios (RRRs) with 95% confidence intervals (cis) for each early-life exposure in association with very early (≤10 years), early (11 years), late (14 years), and very late (≥15 years) menarche relative to typical ages at menarche (12–13 years)	Polytomous logistic regression results for <2500g vs ≥2500g as referent, rRR (95% CI): ≤10y: OR=1.28, 95% CI=1.09, 1.50 11y: OR=1.09, 95% CI= 0.96, 1.24 12-13y: Referent 14y: OR=1.02, 95% CI=0.90, 1.16 ≥15y: OR=1.08, 95% CI= 0.94, 1.25 Additional adjusted model result for low birth weight and very early menarche, rRR=1.33, 95% CI=1.08-1.63	Race/ethnicity, participant's birth decade, childhood family income, and interaction between race and birth decade. Additional model (full results not shown) also adjusted for preterm birth, multiple birth, and maternal factors during pregnancy

Sorensen, 2013, Denmark	Twin study	2505 twin pairs were included (733 female MZ, 625 female dizygotic and 1147 opposite-sex dizygotic) Age 12-22 years at survey Subset of 1994 survey sent to all known twins born in Denmark from 1973-1982 (Danish Twin Register)	Sex-specific BW standard deviation scores (BW-SDS) adjusted for gestational age were calculated according to the twin BW reference by Glinianaia et al, 2000	Danish Medical Birth Registry (sex, birth order, birth length, birth weight, gestational age)	Age at menarche, continuous	Age at menarche in months and years, self-reported on 1994 survey	Marginal Cox proportional hazard survival models with cluster-corrected estimates of the SEs for estimates of effect on population level Random effects survival models for correlation within twins (timereg package, based on standard frailty modeling)	Adjusted HR from population Cox model in 3466 twin girls: BW-SDS: HR=0.962, 95% CI=0.928-0.998 Birthweight, birth length and GA were not individually associated with age at menarche (P≥0.15, data not shown) Paired analysis: Overall: BW-SDS HR=1.01, 95% CI=0.91, 1.12 MZ twins: BW-SDS HR=0.94, 95% CI=0.81, 1.10 DZ twins: BW-SDS HR=1.07, 95% CI=0.93, 1.24 Girls discordant by more than 1 BW-SDS: HR=1.05, 95% CI=0.93, 1.19 Girls discordant by more than 2 BW-SDS: HR=1.04, 95% CI= 0.87, 1.23	Population model Cox model adjusted for birth cohort and zygosity

Deardorff, 2013, United States	Prospective cohort	2497 girls with complete data for maternal pre-pregnancy BMI, GWG, daughters' menarche and covariates. Excluded girls with menarche before 9 or after 16. Age 9-16 years at follow-up Daughters of women in 1979 National Longitudinal Survey of Youth, prospective study of nationally representative samples born 1957-1964. Offspring were surveyed biennially from 1986-2010 as part of the NLSBY Children and Young Adult Survey.	Birthweight in kg	Reported by mother during first interview after child's birth. Reported in lbs and oz and converted to kg.	Age at menarche, continuous	Year and months of menstruation, reported by mothers for girls <14 years and girls age 14 and over on biennial surveys	Distribution of covariates by 4 menarche groups (9-11 years, 12 years, 13 years, 14-16 years, right censored as separate category) Cox proportional hazard models to estimate associations adjusting for covariates in order to include right censored girls.	Birthweight described only as difference in means by age at menarche; was included as a mediator for maternal BMI and GWG models. Mean birthweight in g by age at menarche: 9-11y: 3240.9g 12y: 3295.3 13y: 3378.9g 14-16y: 3273.2g P=0.04 Right censored girls: 3294.3g	None
Hernandez, 2013, Chile	Prospective cohort	16 LBW and 25 AGA girls, TS2 at enrollment and BMI between 10th and 95th percentile and followed for 3 years 7-12 years at enrollment Age-matched LBW and AGA	AGA - birth weight between the 10th and 90th percentile for gestational age LBW - birth weight below the 10th percentile for gestational age	Birth weight, birth length and gestational age reported by parents and confirm in child's health control card	Age at menarche	Assume reported by girls at biannual follow-up visits	Differences in menarche of the two groups assessed by Kaplan Meier survival analyses (log rank test)	"The mean age at menarche was 12.1 ± 0.8 years (AGA) vs. 12.4 ± 0.1.1 years (LBW). Log-rank test for equality of survivor functions (p = 0.2). AGA and LBW girls had similar age at menarche even after adjustment for maternal age at menarche (p = 0.067) and rate of progression from B2 to menarche."	Menarche results adjusted for maternal age at menarche and rate of progression from B2 to menarche.

		girls 7-12 years recruited from public schools in Santiago and Concepcion, Chile							
Jahanfar, 2013, Iran and Malaysia	Twin study	193 girls (54 MZ pairs, 34 DZ pairs, 17 females from opposite-sex twin pairs Age 16-63 years (mean 31.52) Twins born between 1945 and 1988 identified through the Iran Twin Registry in 2000 and twins born between 1951 and 1993 drawn from the Malaysian Twin Registry database	Birthweight	Not specified (assume self or parent report to zygosity questionnaire)	Age at menarche	Self-report in adulthood in years	Descriptive analysis and computation of variance and co-variance; genetic analysis using Falconer's formula for estimation of heritability and MLA analysis of twin data	Birthweight was not associated with age at menarche (p=0.830) (data not shown) Birthweight was not associated specifically with early or late menarche (p=0.925) (data not shown)	Not specified

Zhang, 2014, United States	Cross-sectional	652, nonpregnant girls age 8-15 years with complete data. Pre-menarcheal girls were excluded, as were races other than Mexican American, non-Hispanic black and non-Hispanic white Age 8-15 years NHANES 2003-2006	Birthweight, continuous and categorized as: Low: <2500g Normal: 2500-4000g High: >4000g	Birthweight reported to nearest ounce by parent/guardian in adolescence	Age at menarche, continuous	Self-report by girl in adolescence; pre-menarcheal girls excluded	Multiple linear regression models (PROC SURVEYREG) were used to evaluate the associations between age at menarche and birth weight as both continuous and categorical predictor variables (β<0 indicates earlier menarche)	Adjusted β for age at menarche in months: Per 500g increase in birthweight: β=-0.005, 95% CI= -0.061, 0.052 Low: β=-0.24, 95% CI= -0.60, 0.12 Normal: Referent High: β=-0.32, 95% CI=-0.68, 0.03	Survey cycle, race, maternal smoking status when pregnant and BMI-for-age percentile
Gavela-Perez, 2015, Spain	Prospective cohort	195 girls Age 13-16 years at follow-up Randomly selected 6-8 year-old Caucasian girls in the Four Provinces Study (random cluster sampling in schools). Girls with chronic diseases including precocious puberty were excluded.	Weight at birth z-score by gestational age	Birthweight and gestational age reported on questionnaire (assuming by parents)	Age at menarche	Self-report at ages 13-16 years	Spearman correlation analyses between weight at birth Z-score and age at menarche	Correlation between weight at birth Z-score and age at menarche = -0.010 (P≥0.05)	None

Meulenijzer, 2015, multiple countries in Europe	Cross-sectional	1069 girls with valid data on early-life factors and menarche Age 12.5-17.5 years HELENA-CSS (Healthy Lifestyle in Europe by Nutrition in Adolescence cross-sectional study)	Birthweight in kg, continuous Ponderal index (g/m3), continous and in quintiles Birthlength in cm, continuous	Birthweight, birth length, gestational age and duration of breastfeeding reported on parental questionnaire.	Age at menarche, dichotomized for analysis as below median (≤12) or above median (>12)	Menarche status and year of onset self-reported by girls	Multivariable linear regression for age at menarche (β<0 indicates earlier menarche)	β from adjusted linear model for age at menarche: Birthweight (kg), log-transformed: β=1.28, SE=0.44, p=0.01 Ponderal index (g/m3), log-transformed : β=0.17, SE=0.51, p=0.75 Ponderal index, quintiles: Q1: β=-0.15, SE=0.11, p=0.19 Q2: β=-0.08, SE=0.11, p=0.49 Q3: β=-0.10, SE=0.11, p=0.37 Q4: β=-0.11, SE=0.11, p=0.31 Q5: referent Birthlength (cm), log-transformed: β=3.09, SE=1.26, p=0.01	Center, BMI Z-score and age of adolescent
Behie & O'Donnell, 2015, Australia	Longitudinal	1493 girls with complete data Age 12-13 years at follow-up K-cohort from Growing Up in Australia, the Longitudinal Study of Australian Children (LSAC)	Birthweight in grams, continuous	Birthweight reported by parents at initial data collection point, when girls were 3-4 years old	Age at menarche	Reported by parents (year and month)	Cox proportional hazard models, with age at menarche or last follow-up for right censored girls as the outcome (HR>1 indicates earlier menarche)	HR (95% CI) for age at menarche: Birthweight: HR=0.86, 95% CI= 0.75-0.97	Maternal age at menarche, BMI at 8-9 years, maternal smoking

Wells, 2016, United Kingdom	Cross-sectional	58 women Age 18-30 years (mean=22.6) South Asian women in central London, UK, recruited near universities. Inclusion criteria = age 18-30 years, gestational age 37+ weeks, and four South Asian grandparents. Excluded twins, smokers, pregnant/lactating women, weight instability (>3kg change in 3 months), and medical conditions known to impact body composition or metabolism	Birthweight SDS, adjusted for gender and gestational age, using UK 1990 reference data	Birthweight and gestational age self-reported by participants (asked to contact their mothers)	Age at menarche, continuous	Self-report in adulthood	Linear regression model to investigate association between BW SDS and age at menarche (β<0 indicates earlier menarche)	Linear regression model of age at menarche, including birthweight SDS and gestational age: Birthweight SDS: β=0.49, 95% CI 0.14, 0.84	First-generation migrant status and gestational age
Krzyzanowska, 2016, United Kingtdom	Prospective	4483 girls with menarche data, excluded minorities Age 16 years at follow-up 16-year follow-up of girls in the 1958 British National Child Development Study (NCDS), birth cohort of all children born in England, Wales and Scotland the week of March 3-9, 1958	Birthweight in grams	Medical records	Age at menarche, continuous	Recalled in years by girls at age 16 years	Univariable and multivariable Interval censored Cox models, using Icens function in Epi package in R	Birthweight was not associated with age at menarche (p>0.10) in univariable analysis (data not shown)	None

Schulte, 2016, Germany	Twin study	13 female MZ twin pairs Age 13.2-15.8 years at follow-up Adolescent follow-up of 30 pairs (13 female) of MZ twins that underwent selective fetoscopic laser coagulation for TTTS (twin-to-twin transfusion syndrome) during pregnancy and had an intra-twin birthweight difference	Smaller vs. larger co-twin at birth, based on birthweight - Concordant birthweight pairs defined as birthweight difference <1SDS - Discordant birthweight pairs defined as birthweight difference > 1 SDS * In discordant pairs, the smaller twin met the criterion for SGA (birthweight <2 SD for GA)	Medical records	Age at menarche, continuous	Reported by parents and participants at follow-up	Intra-twin differences calculated as the data of the initially larger twin subtracted from the data of initially smaller co-twin Sign test used to compare intra-pair values for measurements on ordinal scale (i.e. Tanner stage Paired t-test or Wilcoxon test for ratio scales Intra-twin correlations using Pearson's r, Spearman's rho and Kendall's tau-b	In 77% of girls (10/13), the initially smaller twin experienced menarche before the co-twin (median age at menarche 12.1 vs 13.0) In 7/8 discordant female pairs, the initially smaller twin experienced menarche first (median 12.4 vs 13 years) Note: sign test showed that progression through tanner stages was different for initially smaller and larger twin (P=.021, 9 positive differences, 1 negative difference, 4 ties - not stratified by sex. The initially smaller twin also started pubertal maturation first in 63% (19/30 pairs) -- also not stratified by sex	None

Aurino, 2017, India, Peru, Vietnam	Prospective cohort	2001 girls with birthweight data 12 years at follow-up Young Lives cohort of Indian, Peruvian and Vietnamese girls born in 2001-2002, recruited at ~1 year and followed up to 12 years	Birthweight Z-score calculated using WHO international reference standards	Birthweight assessed from birth certificate if available. If not, information from other health records was used as long as it was recorded within 1 week of birth. If none, mother's report of birthweight was used. Birthweight from medical record (source 1 or 2) for 44% of sample (52% India, 66% Peru, 18% Vietnam)	Age at menarche, continuous	Self-reported in years by girls in 2013, when ~12 year of age	Weibull survival models estimated rate of menarche by ~12 years; pre-menarche girls were censored (HR>1 indicates earlier menarche)	HR (95% CI) for birthweight Z-score from Weibull models: Adjusted for country only: HR=1.05, 95% CI=0.97,1.13 Fully adjusted model: HR=0.88, 95% CI=0.81-0.95	Fully adjusted: Country, HAZ at 8 years, BMIZ at 8 years, First child, maternal height, maternal age at girl's birth, maternal education, urban location at 1 year, SES at 8 years, binary indicators of girls' previous day consumption of fruits and vegetables, meat and fish, eggs, legumes, and milk and dairy at 8 years, difference in BMIZ between 1 and 8 years, difference in HAZ between 1 and 8 years

								Birthweight not associated with menarche in univariable models (data not shown) Logistic regression, OR for early menarche (<12y): Adjusted for percentile rank change in weight and length: Birthweight (kg) OR=1.30, 95% CI=0.74, 2.31 Birthlength(cm): OR=1.07, 95% CI=0.95, 1.21) Adjusted for birthlength and conditional growth in weight and length: Birthweight (kg) OR=0.80, 95% CI=0.52, 1.24 Birthlength(cm): OR=1.00, 95% CI=0.92, 1.08)	
Flom, 2017, United States	Prospective cohort	1126 women with age at menarche data Age 39-49 years at follow-up The Early Determinants of Mammographic Density Study, 2008 adult follow-up of female participants in the CHDS and Boston and Providence sites of NCPP birth cohorts (pregnancies 1959-1966)	Birthweight in kilograms Birthlength in cm	Measured at birth	Age at menarche, continuous and categorized as: <12 years ≥12 years	Self-report by woman in adulthood	Multivariable logistic regression for early menarche (<12 y), GEE models and linear random effect models for age at menarche (continuous) using percentile rank change, conditional growth and pattern models (β<0 or OR>1 indicates earlier menarche).	Linear regression, β for menarche: Adjusted for percentile rank change in weight and length: Birthweight (kg) β=-0.23, 95% CI= -0.59, 0.12 Birthlength(cm): β=-0.06, 95% CI= -0.13, 0.01 Adjusted for birthlength and conditional growth in weight and length: Birthweight (kg) β=0.19, 95% CI= -0.13, 0.51 Birthlength(cm): β=-0.04 (-0.10, 0.02)	Adjusted for birthweight, birthlength, maternal age at menarche and either percentile rank change or conditional growth in height and weight from 0-4 months, 4-12 months, and 1-4 years

Workman & Kelly, 2017, United States	Cross-sectional	342 girls with complete data on height, birthweight and menarche Age 14-16 years Subset of NHANES 2007-2012 (born 1991-1998)	Birthweight in kilograms	Birth weight to near ounce reported by parent during home interview	Age at menarche, continuous	Self-report by girls in years during health history interview	Two-way correlation between age-adjusted height, birthweight, age at menarche and indicators of family SES. Linear regression model for age at menarche.	Linear regression for birthweight and menarche: Birthweight (kg): Coeff=-.03 year, β=-.01, p=0.838 No association within each birthweight quartile or when SES was included as a covariate (data not shown)	Family SES (not shown)
Kelly, 2017, United Kingdom	Prospective cohort	5839 singleton girls with menarche status at 11 years Age 11 years at follow-up Girls followed up to 11 years from the Millennium Cohort Study, UK nationally representative prospective cohort study of children born in 19,244 families between September 2000 and January 2002	Birthweight in kilograms	Reported by mother when daughter was 9 months old	Menarche at 11 year visit (Yes/No)	Mother reported using question adapted question from the Petersen Pubertal Developmen t Scale at 11 year visit: "Has she begun to menstruate (we mean started to have her period)?" (Yes/No/Don't know). Don't know (N=89) were excluded	Logistic regression was used to estimate associations between predictors and menarche status at 11 years with sample weights (OR>1 indicates earlier menarche)	OR for menarche at age 11 years (95% CI): Partially adjusted model: Birthweight(kg): OR=0.78, 95% CI=0.6, 0.9 Adjusted model (mediation): Birthweight(kg): OR=0.71, 95% CI=0.6-0.9	Partially adjusted: centered age, income, ethnicity Adjusted (mediation): centered age, income, ethnicity, birthweight, BMI at 7 years, mother's psychological distress, racism in area is fairly/very common, lone parent family, total difficulties score

Supplemental Table 2.5. Studies of infant size or growth and timing of breast development

Author, Location, Year	Study Design	Study Population (N, Age range, Name)	Exposure	Exposure source	Outcome	Outcome source	Statistical method	Results	Covariates
Amador, 1996, Cuba	Prospective cohort	173 girls with birthweight≥2500 g Age 13.6-14.5 years Students in two high schools at the municipality of Boyeros in Havana in September 1986, subset of longitudinal study on height and weight that was initiated in Havana in 1972 when children aged 12 mo.	BMI at 1 year	Calculated from weight and height measured at study enrollment at 1 year of age	Breast Tanner stage at entry to high school	Assessed by researchers	Pearson correlation coefficients relating birthweight to stage of sexual development (Breast Tanner stage) Mean birthweight by breast Tanner stage Path analysis model relating birthweight, height at 14 years and breast Tanner stage	Mean (SD) of BMI at 1 year in girls by their breast Tanner stage at 14 years TS3: 17.18 (1.72) TS4: 17.85 (2.13) TS5: 20.18 (2.62) p = 0.000 Actual and estimated correlations among BMI at 1 year and stage of sexual development in girls: Actual=0.43 Estimated = 0.39	Path model included BMI at 1, 4, 6, 12 and 14 years and height at 14 years

Benefice, 2001, Senegal	Prospective cohort	406 girls measured from 1995-1999 Mean age 11.4±0.5 years in 1995 and 15.4±0.5 years in 1999 Adolescent follow-up of girls that were part of the district health and nutrition examination from 0-4 years of age in 1983-1984 in Niakhar district of Senegal	Stunted vs. Not Stunted: Stunting defined as at least one length measurement done in 1983-1984 (between 6-18 months of age) below -2 Z-scores of the NCHS/WHO reference (1983)	Height for age from health and nutrition examination study records	Breast Tanner stage at visit	Assessed by researchers at visits every 6 months	Distribution of breast Tanner stage at each adolescent visit by stunting status, P-value from ANOVA	Percent distribution of breast Tanner stage by year (p value): 1996 (NS): Stunted: B1 64.5%, B2 32.3%, B3 3.2%, B4 0%, B5 0% Non-Stunted: B1 54.4%, B2 35.6%, B 9.4%, B4 0%, B5 0% 1997 (NS): Stunted: B1 27.6%, B2 25.0%, B3 32.9%, B4 14.5%, B5 0% Not Stunted: B1 32.7%, B2 27.4%, B3 28.6%, B4 10.2%, B5 1.1% 1998 (NS, p=0.07) Stunted: B1 12.3%, B2 23.1%, B3 29.2%, B4 33.8%, B5 1.5% Not Stunted: B1 12.5%, B2 24.6%, B3 32.4%, B4 20.7%, B5 9.8% 1999 (NS): Stunted: B1 2.9%, B2 7.4%, B3 10.3%, B4 39.7%, B5 39.7% Not Stunted: B1 5.7%, B2 5.3%, B3 16.7%, B4 30.8%, B5 41.4%	None

Boyne, 2010, Jamaica	Prospective cohort	140 girls who were seen at all scheduled visits between birth and 11 years Age 11 years at follow-up Vulnerable Windows Cohort Study, pregnant women were recruited in 1992-1993 at University Hospital of the West Indies, Kingston,Jamaica for birth cohort.	Gain in weight, height and BMI measured from 0-6 months, 6-24 months and 2-8 years. Growth was defined as the amount by which the size at the end of the time interval exceeded that which would have been predicted by linear regression using the measurements available at the beginning of the interval (conditional measures, uncorrelated)	Weight and crown heel length measured within 24 hours of delivery; height and weight measured by trained study staff at visits	Breast Tanner stage at 11 year visit	Breast Tanner stage assessed every 6 months starting at age 8 years by trained nurses (visual only, no palpation)	Multiple regression analyses to examine the relationships among child's growth and body composition and the stage of puberty with outcomes and predictors in standardized form, so that the regression coefficients were effectively correlation coefficients.	Correlations between the size at birth and growth of Afro-Caribbean girls their stage of breast development at age 11 years: Weight: 0-6 months: 0.15 6m-2y: 0.12 BMI: 0-6 months: 0.13 6m-2y: 0.15 Height: 0-6 months: 0.11 6m-2y: 0.02 P≥.05 for all correlations	Age at clinic visit

Maisonet, 2010, United Kingdom	Prospective cohort	1316 singleton, term girls (37-42 weeks gestation) with consistent pubertal staging and birth size data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Weight-for-age SD scores and BMI SDS calculated using girls' 1990 British growth reference. Assessed change in weight and BMI SDS for each interval of interest (0-2 months, 2-9 months, 9-20 months and 0-20 months)	Health records (weight and length measured at 2,9, and 20 months by health professionals as part of routine infant health surveillance program)	Age at transition to Breast Tanner stage ≥2 or ≥3	Breast Tanner stage reported by girls or mothers at repeated pubertal self-assessments between 8-14 years of age *Girls with inconsistent responses were excluded from analyses	Interval-censored parametric survival model for age at transition to breast Tanner stage ≥2 or ≥3 assuming a normal distribution (Diff <0 indicates earlier breast development)	Adjusted difference for age at entry to breast Tanner stage ≥2: Weight SDS change 0-2 mo: Diff = -0.22, 95% CI=-0.35,-0.09 Weight SDS change 2-9 mo: Diff = -0.05, 95% CI=-0.16,0.05 Weight SDS change 9-20 mo: Diff = -0.25, 95% CI=-0.39,-0.11 Weight SDS change 0-20 mo: Diff = -0.19 (-0.29,-0.10), p = 0.00 Adjusted difference for age at entry to breast Tanner stage ≥3: Weight SDS change 0-2 mo: Diff = -0.13, 95% CI=-0.24,-0.02 Weight SDS change 2-9 mo: Diff = -0.13, 95% CI=-0.22,-0.04) Weight SDS change 9-20 mo: Diff = -0.18, 95%CI=-0.30,-0.06 Weight SDS change 0-20 months: Diff=-0.19, 95% CI=-0.27, -0.11 Adjusted difference for age at entry to breast Tanner stage ≥2: BMI SDS change 0-2 mo: Diff = -0.09, 95% CI=-0.18,-0.00 BMI SDS change 2-9 mo: Diff = -0.02, 95% CI= -0.10,0.07 BMI SDS change 9-20 mo: Diff = -0.10, 95% CI=-0.19,-0.00 BMI SDS change 0-20 months: Diff=-0.10, 95% CI=-0.18, -0.02	Maternal age at menarche, previous live birth, maternal race or ethnicity, smoking during pregnancy, maternal prepregnancy BMI, maternal age at delivery, maternal education, birthweight, birth length and weight or BMI SDS change in prior previous interval

Adjusted difference for age at entry to breast Tanner stage ≥3:
BMI SDS change 0-2 mo: Diff = -0.04, 95% CI=-0.11,0.04
BMI SDS change 2-9 mo: Diff = -0.07, 95% CI=-0.14,0.01
BMI SDS change 9-20 mo: Diff = -0.08, 95% CI=-0.17,-0.00
BMI SDS change 0-20 months: Diff=-0.10, 95% CI=-0.17, -0.03

Wang, 2012, United States	Prospective cohort	305 term girls Age 10-15 years at first report of pubertal status, followed annually until TS5 or max of 5 years Adolescent follow-up of subset of the North Carolina Infant Feeding Study, infants born 1978-1982	Change in weight gain Z-score (age- and sex-specific weight z-scores calculated at each observation time using LMSGrowth software and data from the CDC 2000 growth charts) in time intervals - 0-6 months - 6-12 months - 1-2 years	Weight recorded by nurse at birth. Nurse measured weight of child at follow-up visits at 6 weeks, 3 months, 6 months, 1 year, 1.5 years, 2 years, 3 years, 4 years and 5 years of age.	Breast Tanner stage at first adolescent report, categorized for analysis as >2 or >3	Daughter self-report at first adolescent survey when available	Parametric survival analyses with log normal distribution for age at report of breast Tanner stage >2 or >3 (girls were either left or right censored at age of TS report) (β<0 indicates earlier age at attainment of breast stage)	Regression coefficient in adjusted log-normal survival analyses of time to Breast Stage >2 Weight gain 0-6 months: β=-0.05, 95% CI=-0.07, -0.02 Weight gain 6-12 months: β= -0.05, 95% CI=-0.09, -0.01 Weight gain 1-2 years: β= -0.05, 95% CI=-0.09, -0.02 Regression coefficient in adjusted log-normal survival analyses of time to Breast Stage >3 Weight gain 0-6 months: β=-0.02, 95% CI=-0.05, 0.01 Weight gain 6-12 months: β= -0.05, 95% CI=-0.09, -0.01 Weight gain 1-2 years: β= -0.03, 95% CI=-0.07, 0.00	Birthweight, weight gain (change in Z-score) from 0-6 months, 6-12 months, 1-2 years, 2-5 years, maternal pre-pregnancy weight, maternal age at delivery and race (race for TS>3 model only due to small cell counts).

Hui, 2012, Hong Kong	Prospective cohort	3208 term girls with feasible pubertal staging Followed up to age 13 years Children of 1997, population representative Hong Kong Chinese birth cohort	Sex-specific growth trajectories for weight from birth to 12 months from latent class analyses: TI: below average birthweight, slow weight gain in first year TII: below average birthweight, stable weight gain in first year TIII: average birth weight, fast weight gain in first year TIV: average birthweight, stable weight gain in first year TV: high birthweight, fast weight gain in first year	Weight measurements from medical record linkage to well-baby checks. Used measure closest to 1 month, 3 months, 9 months and 12 months to interpolate weight at these exact ages. Used latent class analysis to construct sex-specific weight growth trajectories from birth to 12 months.	Age at pubertal onset, defined as the earliest age when breast Tanner stage 2 was recorded	Link to the Student Health Service record, where Tanner stage was assessed by a doctor visually on a biannual basis from age 7 years	Multivariable interval-censored survival analysis to examine association between infant growth (trajectories) and age at pubertal onset (TR<0 indicates earlier development)	Time ratio (95% CI) for age at pubertal onset, unadjusted model: TI: TR=1.020, 95% CI=1.006, 1.034 TII: TR=1.005, 95% CI=0.992,1.018 TIII: TR=1.001, 95% CI=0.987,1.015 TIV: Referent TV: TR=0.992, 95% CI=0.977-1.006 Time ratio (95% CI) for age at pubertal onset, mediation model including height and BMI in childhood: TI: TR=0.982, 95% CI=0.969-0.996 TII: TR=0.991, 95% CI=0.979-1.004 TIII: TR=1.011, 95% CI=0.998-1.025 TIV: Referent TV: TR=1.020, 95% CI=1.006-1.035 Sobel test for mediation p<0.001	None (none changed effect estimates by 5%) Mediation models adjusted for body size in childhood (closest to age 7)

German, 2015, United States	Prospective cohort	659 girls with complete data Followed up to age 15.5 years National Institutes of Health Study of Early Child Care and Young Development (SECCYD), children enrolled at 1 year of age in 1991 and followed prospectively until 15.5 years of age	Height and BMI SDS at 15 months	Measured by researchers at study visits	Age at breast Tanner stage 2	Breast Tanner assessed by researchers annually	Pearson's product-moment correlation coefficients used to determine the linear association between auxological parameters and age at stages of pubertal development	Height SDS significantly inversely associated with age at thelarche started at age 15 months (r=-0.2, p=0.0001). The correlation strength increased with age. BMI SDS was significantly correlated with thelarche age starting at 36 months (r=-0.27, p=0.001). At 15 months, correlation coefficient is inverse but not significant. Pubertal progression through the Tanner stages did not correlate with height or BMI at any age.	None

Aydin, 2017, Turkey	Retrospective cohort	84 girls 6-9 years Children approaching pubertal age with medical records at the Well Child Clinic of Istanbul University Faculty of Medicine from birth to 5 years of age	Height, weight and BMI SDS according to national standards for each visit between 1 and 60 months of age Change in BMI SDS for each 3-6 month interval between 0 and 36 months Accelerated weight gain (AWG) = gain in weight ≥0.67 SDS Accelerated height gain (AHG): gain in height ≥0.67 SDS	Height and weight measured by trained nurses at child visits at ages 1, 2, 3, 4, 5, 6, 9, 12, 15 and 18 months and every 6 months until 4 years of age, with a final visit at age 5 years.	Breast Tanner stage at visit, assessed by visual inspection and palpation.	Physician assessment	Repeated mixed measures model used to examine longitudinal anthropometric data between prepubertal and pubertal children. Multivariable logistic regression models to examine associations between pubertal signs and accelerated early growth, adjusted for BW SDS< gestational age, current age, height, weight and BMI SDS	"Girls with breast development had higher weight and BMI SDS values than the girls without breast development starting at 9 months of age, but differences only reached statistical significance at 18 months of age for weight SDS and BMI SDS (P=0.05 and P=0.05) and at the study visit for weight, height and BMI SDS (P=0.001, P=0.01, and P=0.002). Additionally, girls with breast development were more likely to have AWG between 6 and 15 months of age (p=0.05)" Note: most analyses used "first pubertal sign" as the outcome, which was a mixture of breast and pubic hair development (not included here)	Mixed models included anthropometric measures at all visits. Logistic model for AWG adjusted for BW SDS gestational age, current age, height, weight and BMI SDSs.

Supplemental Table 2.6. Studies of infant size or growth and timing of menarche

Author, Location, Year	Study Design	Study Population (N, Age range, Name)	Exposure	Exposure source	Outcome	Outcome source	Statistical method	Results	Covariates
Berkey, 2000, United States	Prospective cohort	67 girls Followed up to 18 years Harvard Longitudinal Studies of Child Health and Development, females born in the 1930s and 1940s to women who were enrolled during their first trimester of pregnancy while obtaining prenatal care at the Boston Lying-In Hospital	BMI at 1-2 years Height at 1-2 years	Calculated from measured height and weight at semi-annual visits	Age at menarche, continuous	Not specified, assume self-reported by girl at annual follow-up visit (reported to nearest month)	Pearson correlation between age at menarche with BMI, height and diet measures in childhood.	Correlation for BMI from 1-2 years and age at menarche = -0.08 (p>.05) Correlation for height from 1-2 years and age at menarche: -0.35 (p<0.05)	None *Results for height at 1-2 year and BMI 1-2 years in multivariable linear regression model are not shown (assuming these variables were removed during stepwise algorithm)

Adair, 2001, Philippines	Prospective cohort	966 girls with complete information on birth characteristics and anthropometry at 8 years Age 14-15 years at follow-up Cebu Longitudinal Health and Nutrition Survey, infants born in 1984-1984 from women in randomly selected urban and rural barangays in Metro Cebu, Philippines.	7 groups characterized by birth weight (cut at median, 3kg), birth length (cut at median, 49cm) and postnatal growth to 6 months (fast vs. slow, defined as a weight and/or length increment above/below the sample median, respectively): Long/light/slow Long/light/fast Long/heavy/slow Long/heavy/fast Short/light/slow Short/light/fast Short/heavy	Measured by project staff soon after birth and at 6 month visit	Age at menarche, continuous	Girl's self-report of month and year of first menses from interview at 10-11 and 14-15 years	Parametric Weibull models to estimate associations between birth characteristics and age at menarche, with premenarcheal girls treated as right censored (~5%) (HR>1 indicates earlier menarche)	Multivariable results (HR and t-statistic from Weibull) from 7-group model with Short/Heavy at birth as reference group: Long/Light/Slow: 1.33 (1.61), p≥.10 Long/Light/Fast: 1.78 (4.16), p<.01 Long/Heavy/Slow: 1.28 (1.68), p<.10 Long/Heavy/Fast: 1.46 (2.87), p<.01 Short/Light/Slow: 1.24 (1.40), p≥.10 Short/Light/Fast: 1.40 (2.80), p<.01)	Gestational age, BMI at 8 years, Skinfold thickness at 8 years, Mother's height, Mother's age at menarche, Total energy intake at 8 years, Low fat (<10%) consumption at 8 years, SES

Benefice, 2001, Senegal	Prospective cohort	406 girls measured from 1995-1999 Mean age 11.4±0.5 years in 1995 and 15.4±0.5 years in 1999 Adolescent follow-up of girls that were part of the district health and nutrition examination from 0-4 years of age in 1983-1984 in Niakhar district of Senegal	Stunted vs. Not Stunted: Stunting defined as at least one length measurement done in 1983-1984 (between 6-18 months of age) below -2 Z-scores of the NCHS/WHO reference (1983)	Height for age from health and nutrition examination study records	Presence of menarche at each visit	Self-reported by girls every 6 months over 4-year follow-up. If girls did not understand, their mother was asked.	Distribution of menarche status at each adolescent visit by stunting status, P-value from t-test	Percent distribution of menarche status by year (p value): 1996 (NS): Stunted: 100% pre-menarche Non-Stunted: 98.8% pre, 1.3% post 1997 (NS): Stunted: 97.4% pre, 2.6% post Not Stunted: 97.4% pre, 2.6% post 1998 (NS, p=0.08) Stunted: 93.8% pre, 6.2% post Not Stunted: 85.9% pre, 14.1% post 1999 (NS): Stunted: 61.2% pre, 38.8% post Not Stunted: 63.3% pre, 36.1% post	None

dos Santos Silva, 2002, United Kingdom	Prospective cohort	2008 girls with menarche and early life data Followed up to 48 years MRC National Survey of Health and Development studies, birth cohort born first week of March 1946	Growth in infancy, defined as the difference in ranks between the height at 2 years estimated by the random coefficients model and birthweight and grouped into tertiles for analysis Growth in body composition, defined as the difference in ranks between the BMI at 2 years estimated by the random coefficients model and birthweight and grouped into tertiles for analysis	Hospital record for birthweight or height and weight measured by study staff at follow-up (2,4,6,7, years)	Age at menarche	Reported by mother when daughter was 15 or recalled by participant at 48 year-old follow-up visit if not available at 15 years (17%)	Mean difference in rank change or absolute measure by menarche group (early: <11.75 years, average: 11.75-14.25, late: >14.25 years) Multivariable Weibull models for age at menarche, using standardized rank change in height or BMI from random coefficient model in tertiles as predictor (HR>1 indicates earlier menarche)	Mean height at age 2 in cm (SD) by menarche: Early: 85.7 (4.5) Average: 84.8 (4.8) Late: 83.7 (4.7) Mean BMI at age 2 (SD) by menarche: Early: 17.5 (2.1) Average: 17.7 (2.5) Late: 17.6 (2.3) HR for age at menarche from Weibull models (first tertile is the reference for all): Rank change in length 0-2 years, model 1: Second: HR=1.23, 95% CI 1.02, 1.42 Third: HR=1.60, 95% CI 1.28, 1.87 p for trend<0.001 Rank change in length 0-2 years, mediation model Second: HR=1.01, 95% CI 0.86, 1.24 Third: HR=1.04, 95% CI 0.74, 1.36 p for trend=0.74 Rank change in BMI 0-2 years, model 1: Second: HR=1.21, 95% CI 0.97, 1.44 Third: HR=1.34, 95% CI 1.07, 1.57 p for trend=0.01 Rank change in BMI 0-2 years, mediation model: Second: HR=1.21, 95% CI 1.03, 1.52 Third: HR=1.41, 95% CI 1.16, 1.74 p for trend<0.001	Length model 1: Birthweight Length mediation model: Birthweight, height rate from 2-4 years,height rate from 4-7 years, BMI rank changes from 0-2 years, BMI rate from 2-6 years BMI model 1: Birthweight, rank changes in height from 0-2 years, height rate from 2-4 years, height rate from 4-7 years BMI mediation model: Birthweight, length rank changes from 0-2 years, height rate from 2-4 years, height rate from 4-7 years, BMI rate from 2-6 years *Note: random coefficients model for height includes mother's height, mother's age at birth, birth order, father's manual occupation and no. of younger siblings. Model for BMI includes father's manual occupation.

Sloboda, 2007, Australia	Prospective cohort	776 girls with menarche data Age 12-14 years at follow-up Western Australian Pregnancy (Raine) Cohort, women enrolled during pregnancy in 1989-1990	BMI at 1 year Height at 1 and 2 years	Measured at study visits	Age at menarche	Self-report on puberty questionnaire or censored at age at last follow-up if no menarche reported	Continuous data summarized using medians, IQ ranges and ranges Kaplan-Meier survival probabilities to estimate probability of reaching menarche Multivariable Cox regression models to evaluate association between fetal and postnatal growth and age at menarche	Stated in text that BMI at 1 year and height at 1 and 2 years were not associated with age at menarche (data not shown)	Not stated

Ong, 2009, United Kingdom	Prospective cohort	2715 singleton girls with age at menarche data Mean age at follow-up: 12.9 years (IQR 12.8-13.0) Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Weight, length and BMI Z-scores at birth, 2, 9 and 19 months were calculated using British 1990 growth reference and actual age at measurement Infancy weight gain and length gain were calculated as the difference in weight or length Z-score between those ages.	Birth weight as recoded in delivery room, birth length measured by staff, weight and length at ages 2, 9 and 19 months extracted from local child health database (collected as part of routine infant health surveillance program)	Age at menarche, categorized as: <12 12-13 >13	Reported by girl at adolescent visit (~13 years of age). Some missing data on age at first menstruation were imputed from similar data collected at 11 year visit.	Means (SD) of early-life measures by age at menarche group; P for trend, adjusted for age. Multiple regression models were performed to test the linear associations between infant body size, infant weight gain and infant length gain with age at menarche (<12, 12-13 or 13+) as a continuous variable. The effect of conditional infancy weight gain between birth-9 months on menarche <12 years were analyzed by logistic regression.	Size at 2 months (Mean, SD) by girls' age at menarche (p trend): Weight (kg) (P for trend=0.9): <12: 4.81 (0.02) 12-13: 4.78 (0.02) >13Y: 4.81 (0.02) Length (cm) (P for trend=0.6): <12: 56.9 (0.1) 12-13: 56.7(0.1) >13Y: 56.9 (0.1) BMI (P for trend=0.9): <12: 14.8 (0.04) 12-13: 14.9(0.1) >13Y: 14.9 (0.1) Size at 9 months: Weight (kg) (P for trend=<.001): <12 : 8.91 (0.04) 12-13: 8.76 (0.04) >13: 8.73 (0.03) Length (cm) (P for trend=0.1): <12: 71.5(0.1) 12-13: 71.2 (0.1) >13: 71.2 (0.1) BMI (P for trend=0.007): <12 :17.5 (0.1) 12-13: 17.3(0.1) >13: 17.3 (0.1) Size at 19 months: Weight (kg) (P for trend=<.001): <12: 11.58 (0.06) 12-13: 11.40 (0.06) >13: 11.31 (0.04) Length (cm) (P for trend=<.001):	Age and mother's education. Multivariable model adjusted for mother's education, smoking in pregnancy, birth order and breastfeeding Logistic regression model included birthweight SD score.

				<12: 83.0(0.2) 12-13: 83.0 (0.2) >13: 82.5 (0.1) BMI (P for trend=0.09): <12:16.9 (0.1) 12-13: 16.7 (0.1) >13: 16.7 (0.1)	Girls with earlier menarche showed faster rates of weight gain between ages 0-2 months (p for trend=0.006) and 2-9 months (p for trend<.0001), but not from 9-19 months (p>.05) (Figure 1A). Girls with earlier menarche had faster rate of length gain from 2-9 months (P=0.006) and 9-19 months (P=0.004), but not from 0-2 months (Figure 1B). In multivariable models, weight gain from 0-2 months and 2-9 months were still significantly associated with menarche group. Associations between infancy length gain and menarche were largely explained by infancy weight gain (p≥.05 when adjusted for infancy weight gain). OR from logistic regression model for menarche <12 years: Change in weight SDS 0-9 months: OR=1.34, 95% CI 1.21, 1.49

Terry, 2009, United States	Prospective cohort	262 women 38-46 years at follow-up Follow-up in 2001-2006 of subset of women from New York site of the CPP birth cohort (born 1959-1963)	Weight and length at 4m and 12m Within-cohort percentile rank change in height and weight from 0-4 months and 4-12 months	Measured by study staff at visits and interpolated at 4 months, 12 months and 7 years using cubic splines	Age at menarche, continuous and dichotomized as: ≤12 years >12 years	Self-reported by adult participant	Univariate associations using correlation coefficients for continuous variables, chi-square tests and analysis of variance to compare averages across subgroups Multivariable linear regression models using age for age at menarche (β<0 indicates earlier menarche).	Mean weight at 4 months in kg by menarche status (p=0.99): ≤12 years: 6.13 (0.75) >12 years: 6.13 (0.81) Mean weight at 12 months in kg by menarche status (p=0.39): ≤12 years: 9.67 (1.17) >12 years: 9.55 (1.02) Mean length at 4 months in cm by menarche status (p=0.80): ≤12 years: 61.72 (3.0) >12 years: 61.63 (2.68) Mean length at 12 months in cm by menarche status (p=0.89): ≤12 years: 73.74 (3.08) >12 years: 73.80 (3.13) β for 10-percentile change in weight from 0-4 months from linear regression model: Partially adjusted β=0.04, 95% CI= -0.04, 0.13 Fully adjusted parsimonious model: β=-0.01, 95% CI= -0.13, 0.10 β for 10-percentile change in weight from 4-12 months from linear regression model: Partially adjusted β=-0.09, 95% CI= -0.19, 0.01	Partially adjusted model for weight change, 0-4 months: birthweight Partially adjusted model for weight change, 4-12 months: birthweight and weight change from 0-4 months Fully adjusted parsimonious model: Birth weight, percentile change in weight, birth length, percentile change in height, family SES at age 7, maternal age at menarche

Fully adjusted parsimonious model: β=-0.15, 95% CI= -0.27, -0.02

β for 10-percentile change in height from 0-4 months from linear regression model: Fully adjusted parsimonious model: β=0.00, 95% CI= -0.12, 0.13

β for 10-percentile change in height from 4-12 months from linear regression model: Fully adjusted parsimonious model: β= 0.08, 95% CI= -0.04, 0.20

Karaolis-Danckert, 2009, Germany	Prospective cohort	87 term, singleton girls with birthweight>2500 g, height measurements at 6 and 13 years of age and at least 5 measures between these ages, anthropometrics at 24 months, complete data on maternal characteristics and age at menarche At least 13 years of age Subset of the DONALD (Dortmund National and Anthropometric Longitudinally Designed) Study started in 1985 (40-50 infants age 3-6 mos enrolled annually)	Weight gain from 0-2 years, defined by difference in SDS-score: - Rapid: SDS >0.67 - Normal: SDS≤0.67 Sex- and age-independent SDS scores were calculated by using the German reference surveys for weight and BMI and then internally standardized to this data by age and sex	Birthweight abstracted from standardized document given to all pregnant women in Germany, weight at age 2 years measured to nearest 0.1kg by study staff at visit	Age at menarche, continuous	Girls or their parents are asked if menarche occurred since previous visit, and if so, which month and year	Linear mixed-effects regression models (PROC MIXED) were used to construct longitudinal models of age at menarche (β<0 indicates earlier age at menarche).	Adjusted β from linear regression model: Rapid weight gain from 0-2 years (>0.67SDS vs normal weight gain): β=-0.82, SE=0.25, p=0.002 Adjusted β from pathway linear regression model: Rapid weight gain from 0-2 years (>0.67SDS vs normal weight gain): β=-0.60, SE=0.26, p=0.02 Interaction between birthweight and rapid weight gain: Low birthweight and rapid weight gain experienced menarche 1.68 years (SE=0.35) earlier than children with a bwt ≥3000g and normal weight gain (referent).	Maternal overweight and birthweight Pathway model additionally adjusted for BMI SD score 1 year before ATO Noted that adjustment for gestational age did not change results (data not shown)

Salsberry, 2009, United States	Prospective cohort	2,667 non-Hispanic white (1448) and African-American girls (1219) born before 1998 who were at least 8 years of age by 2006 interview and had reported age of menarche. Followed up to 20 years 1986-2006 waves of the Children of the NLSY79 (National Longitudinal study of Youth, women born between 1957-1964)	Estimated BMI and height at 2 years of age, calculated from longitudinal statistical techniques as polynomial functions of age for each race-timing group	Height and weight at each follow-up, measured by interviewer (75%) or reported by mom or girl	Age at menarche in months, which was categorized into 3 groups based on <25th percentile, 25--75th percentile and >75th percentile for race: - Early: <141 months for White girls, <133 months for African American girls - Middle: 141-157 months for White girls, 133-152 months for African American girls - Late: >157 months for White girls, >152 months for African American girls	Year and month of menarche reported by mothers of girls 8-13 years and daughters at 14 years and older at biennial interviews	Estimates from random coefficient models were used to predict height and BMI by age and age relative to menarche for girls in each race-timing group. The standard errors of these estimates were used to construct 95% Cis around height and BMI for each age. These CIs were used to identify at which ages significant differences in predicted height and BMI occurred across race-timing groups.	Predicted BMI (95% CI) as a function of chronological age by race-timing group: African American girls at 2 years Early: 17.4 (17.0, 17.7) Middle: 16.7 (16.5, 17.0) Late: 16.6 (16.3, 16.8) White girls at 2 years Early: 16.3 (16.0, 16.6) Middle: 16.3 (16.1, 16.5) Late: 16.2 (16.0, 16.5) Predicted Height (in) (95% CI) as a function of chronological age by race-timing group: African American girls at 2 years Early: 32.6 (32.3, 32.9) Middle: 32.3 (32.2, 32.5) Late: 32.3 (32.1, 32.6) White girls at 2 years Early: 32.5 (32.3, 32.7) Middle: 32.4 (32.3, 32.6) Late: 32.6 (32.4, 32.8)	Height or BMI at other time points (3, 4, 5, 6, 7, 8 and 20 years)

			Weight and height Z-scores from 1984 at average 19.4 months) calculated based on 2006 WHO curves and categorized as ≤0, 0.01-1, 1.01-2, and >2. Growth from 0-19.4 months was assessed as the change in Z-score between time periods, with the birthweight Z-score calculated using Williams curve.					Adjusted PR for weight-for-age Z-score at 19.4 months: ≤0: Referent 0.01-1: PR=1.43, 95% CI=1.16, 1.77 1.01-2: PR=1.54, 95% CI= 1.20, 1.98 ≥2: PR=1.53, 95% CI= 0.97, 2.37 Adjusted PR for height-for-age Z-score at 19.4 months: ≤0: Referent 0.01-1: PR=1.24, 95% CI=1.02, 1.52 1.01-2: PR=1.35, 95% CI=0.98,1.86 ≥2: PR=1.48, 95% CI=0.77, 2.84 Adjusted PR for weight-for-height Z-score at 19.4 months: ≤0: Referent 0.01-1: PR=1.39, 95% CI=1.09, 1.78 1.01-2: PR=1.53, 95% CI=1.18, 1.99 ≥2: PR=1.49, 95% CI=0.99, 2.07	
Mesa, 2010, Brazil	Prospective cohort	2083 women with menarche data Age 23-24 years at follow-up 2004-2005 follow-up of women from the 1982 Pelotas Birth Cohort Study	Change in Z-scores were defined as catch-down (≤0.67), normal (-0.669-0.669) and catch-up (≥0.67).	Weight measured at birth, height and weight measured at follow-up visits.	Age at menarche in years, categorized as <12 and ≥12 years	Self-report by participant in adulthood	Multivariable-adjusted Poisson regression with a robust variance estimative to obtain prevalence ratios (PR>1 indicates early menarche)	Adjusted PR for change in weight-for-age Z-score from birth-19.1 months: Catch-down: Referent Normal: PR=1.27, 95% CI=0.91, 1.78 Rapid: PR=1.75, 95% CI=1.27, 2.43 Inference for change in weight Z-score is the same across birthweight tertiles.	Family income, skin color, smoking during pregnancy, pre-gestational maternal BMI and breastfeeding duration

Boyne, 2010, Jamaica	Prospective cohort	140 girls who were seen at all scheduled visits between birth and 11 years At least 11 years at follow-up Vulnerable Windows Cohort Study, pregnant women were recruited in 1992-1993 at University Hospital of the West Indies, Kingston,Jamaica for birth cohort.	Gain in weight, height and BMI measured from 0-6 months, 6-24 months and 2-8 years. Growth was defined as the amount by which the size at the end of the time interval exceeded that which would have been predicted by linear regression using the measurements available at the beginning of the interval (conditional measures, uncorrelated)	Weight and crown heel length measured within 24 hours of delivery; height and weight measured by trained study staff at visits	Age at menarche	Menstrual history was taken at each visit (biannual)	Multiple regression analyses to examine the relationships among child's growth and body composition and the stage of puberty with outcomes and predictors in standardized form, so that the regression coefficients were effectively correlation coefficients.	Correlations between the size at birth and growth of Afro-Caribbean girls and age at menarche at age 11 years: Height: 0-6 months: 0.02 6m-2y: -0.02 Weight: 0-6 months: -0.11 6m-2y: -0.08 BMI: 0-6 months: -0.16 6m-2y: -0.11 P≥.05 for all correlations	Age at clinic visit

Maisonet, 2010, United Kingdom	Prospective cohort	1316 singleton, term girls (37-42 weeks gestation) with consistent pubertal staging and birth size data Age 8-14 years at follow-up Avon Longitudinal Study of Parent and Children, born April 1991-December 1992	Weight-for-age SD scores and BMI SDS calculated using girls' 1990 British growth reference. Assessed change in weight and BMI SDS for each interval of interest (0-2 months, 2-9 months, 9-20 months and 0-20 months)	Health records (weight and length measured at 2,9, and 20 months by health professionals as part of routine infant health surveillance program)	Age at menarche	Month and year of menarche, reported girls at pubertal self-assessments between 8-14 years of age. Girls with inconsistent responses were excluded from analyses	Interval-censored parametric survival model for age at menarche assuming a normal distribution (Diff <0 indicates earlier menarche)	Adjusted difference for weight change models and age at menarche: Weight SDS change 0-2 mo: Diff = -0.07 (-0.17,0.03), p = 0.15 Weight SDS change 2-9 mo: Diff = -0.19 (-0.27,-0.11), p = 0.00 Weight SDS change 9-20 mo: Diff = -0.14 (-0.24,-0.03), p = 0.01 Weight SDS change 0-20 mo: Diff = -0.19 (-0.26,-0.12), p = 0.00 Adjusted difference for BMI change models and age at menarche: BMI SDS change 0-2 mo: Diff = -0.04 (-0.10,0.03), p = 0.26 BMI SDS change 2-9 mo: Diff = -0.09 (-0.15,-0.03), p = 0.00 BMI SDS change 9-20 mo: Diff = 0.02 (-0.09,0.05), p = 0.61 BMI SDS change 0-20 mo: Diff = -0.07 (-0.13,-0.01), p = 0.03	Maternal age at menarche, previous live birth, maternal race or ethnicity, smoking during pregnancy, maternal prepregnancy BMI, maternal age at delivery, maternal education, birthweight, birth length and weight or BMI SDS change in prior previous interval

Chevalley, 2011, Switzerland	Prospective cohort	115 women with body size data at birth (96 at 1 year) Mean age 20.4 at follow-up Follow-up of pre-pubertal girls participating in an RCT of calcium-enriched foods and bone mass growth (enrolled at mean 7.9 years, followed up to 20.4 years. Exclusion criteria at enrollment were ratio of weight/height <3rd or >97th percentile, physical signs of puberty, chronic disease, malabsorption, bone disease and regular use of medication)	Body weight, standing height and BMI at birth and 1 year (converted to Z-scores) and change in Z-score or body size from birth to 1 year	Obtained retrospectively at baseline from questionnaires sent to parents and pediatricians	Age at menarche, continuous and dichotomized at the median (12.9 years)	Self-reported by daughter at interview at visits (8.9 years, 10 years, 12.4 years, 16.4 years)	Univariate linear regression analysis examining association between BMI Z-score at birth and 1 year or change in BMI Z-score from birth to 1 year and age at menarche Z-score. Differences in anthropometric characteristics between earlier and later menarche (dichotomized at the median) assessed by unpaired t-tests or by Wilcoxon signed rank test.	Linear regression of BMI at 1 year Z-score predicting age at menarche Z-score: β = -0.026, 95% CI=-0.237, 0.184, R-squared = 0.01 Linear regression of change in BMI Z-score from birth to 1 year predicting age at menarche Z-score: β = -0.048, 95% CI=-0.328, 0.232, R-squared = 0.01 Mean (SD) of anthropometric characteristics at 1 year by median age at menarche (12.9 years): Weight (kg), p=0.408: Earlier: 9.1 (0.9) Later: 9.3 (1.0) Standing height (cm), p=0.819 Earlier: 73.9 (3.2) Later: 74.0 (3.6) BMI, p=0.317 Earlier: 16.7 (1.1) Later: 17.0 (1.6) Mean (SD) of gain in anthropometric characteristics from birth-1 year by median age at menarche: Weight (kg), p=0.506: Earlier: 6.0 (0.8) Later: 6.1 (1.0) Standing height (cm), p=0.810 Earlier: 24.7 (2.6) Later: 24.9 (3.9) BMI, p=0.907 Earlier: 3.8 (1.6) Later: 3.9 (1.9)	None

Wang, 2012, United States	Prospective cohort	305 term girls Age 10-15 years at first report of pubertal status, followed annually until TS5 or max of 5 years Adolescent follow-up of subset of the North Carolina Infant Feeding Study, infants born 1978-1982	Change in weight gain Z-score (age- and sex-specific weight z-scores calculated at each observation time using LMSGrowth software and data from the CDC 2000 growth charts) in time intervals 0-6 months 6-12 months 1-2 years	Weight recorded by nurse at birth. Nurse measured weight of child at follow-up visits at 6 weeks, 3 months, 6 months, 1 year, 1.5 years, 2 years, 3 years, 4 years and 5 years of age.	Age at menarche, continuous	Date of menarche reported by daughter on annual surveys (started in 1992 at age 10-15, followed for max of 5 years)	Univariate linear model for age at menarche. Multivariable-adjusted parametric survival analyses with log normal distribution for age at menarche (β<0 indicates earlier menarche)	Univariable linear regression results: Weight gain 0-6 months: β=-0.06, SE=0.07, p>0.05 Weight gain 6-12 months: β=-0.26, SE=0.12, p<0.05 Weight gain 1-2 years: β=-0.28, SE=0.13, p<0.05 Regression coefficient in adjusted log-normal survival analyses of time to menarche Weight gain 0-6 months: β=-0.03, 95% CI=-0.05, -0.02 Weight gain 6-12 months: β= -0.05, 95% CI= -0.08, -0.03 Weight gain 1-2 years: β= -0.04, 95% CI= -0.06, -0.01	Birthweight, weight gain (change in Z-score) from 0-6 months, 6-12 months, 1-2 years, 2-5 years, maternal pre-pregnancy weight and race.
German, 2015, United States	Prospective cohort	659 girls with complete data Followed up to age 15.5 years National Institutes of Health Study of Early Child Care and Young Development (SECCYD), children enrolled at 1 year of age in 1991 and followed prospectively until 15.5 years of age	Height and BMI SDS at 15 months	Measured by researchers at study visits	Age at menarche	Assuming reported by child at annual follow-up visits	Pearson's product-moment correlation coefficients used to determine the linear association between auxological parameters and age at menarche.	Height SDS significantly inversely associated with age at menarche started at age 54 months (r=-0.16, p=0.014). At 15 months, correlation coefficient is inverse but not significant. The correlation strength increased with age. BMI SDS was significantly correlated with menarche age starting at 54 months (r=-0.16, p=0.016). At 15 months, correlation coefficient is inverse but not significant.	None

Salgin, 2015, South Africa	Prospective cohort	922 girls of black South African origin included in menarche analysis Followed up to age 18 years Birth to Twenty, prospective birth cohort of singleton births between late April 1990-early June 1990 in Johannesburg-Soweto, South Africa	Infancy weight gain calculated as change in weight SDS from birth to 1 year. Catch-up growth defined as gain in weight SDS >0.67. Catch-down growth defined as weight SDS<-0.67. Others categorized as "no rapid change"	Birthweight extracted from hospital record, weight and length measured by study staff at home visits at age 1 and 2 years	Age at menarche, continuous	Reported in full years by female subjects and their parents annually from age 9 years	Data were analyzed for normality using the Kolmogorov-Smirnov test and log-transformed to a normal distribution to allow use of analysis of variance to assess differences in age at menarche between girls with different patterns of weight gain during infancy. Mean values for age at menarche were adjusted for covariates.	Mean (SD) age at menarche by infancy weight gain pattern (p<0.001): Catch-up: 12.5 (0.1) No rapid change: 12.6 (0.1) Catch down: 13.1 (0.1) Association persisted after adjustment for smoking during pregnancy, birth order, gestational age, formula-milk feeding and household SES (p=0.005)	Smoking during pregnancy, birth order, gestational age, formula-milk feeding and household SES

Aurino, 2017, India, Peru, Vietnam	Prospective cohort	2001 girls with birthweight data 12 years at follow-up Young Lives cohort of Indian, Peruvian and Vietnamese girls born in 2001-2002, recruited at ~1 year and followed up to 12 years	BMI and height Z-score at 1 year calculated using WHO international reference standards	Assumed height and weight measured at enrollment	Age at menarche, continuous	Self-reported in years by girls in 2013, when ~12 year of age	Difference in mean BMI and height Z-scores at 1 year by menarche status using t-tests	Mean (SD) of BMI Z-score at 1 year by menarche status at visit: Full sample (p=<0.001): Pre-menarche: -0.08 (1.28) Menarche: 0.13 (1.21) India (p=<0.001): Pre-menarche: -0.99(1.07) Menarche: -0.64 (1.00) Peru (p=0.242): Pre-menarche: -0.78(1.20) Menarche: 0.88 (1.13) Vietnam (p=0.031): Pre-menarche: -0.47(0.88) Menarche: -0.33 (0.94) Mean (SD) of Height Z-score at 1 year by menarche status at visit: Full sample (p=<0.001): Pre-menarche: -1.11 (1.20) Menarche: -0.79 (1.19) India: Pre-menarche : -1.06(1.32) Menarche: -0.72 (1.28) Peru (p=<0.001): Pre-menarche: -1.18(1.18) Menarche: -0.92 (1.28) Vietnam (p=<0.001): Pre-menarche: -1.06(1.16) Menarche: -0.70 (1.04)	None

								Mean (SD) anthropometrics by menarche status: Weight (kg) 4 months: <12y: 6.54 (0.89), ≥12y: 6.40 (0.79) Weight (kg) 12 months: <12y: 9.90 (1.24), ≥12y: 9.61 (1.23) Height (cm) 4 months: <12y: 62.79 (3.27), ≥12y: 62.26 (2.73) Height (cm) 12 months: <12y: 74.43 (3.11), ≥12y: 73.70 (3.17)	
Flom, 2017, United States	Prospective cohort	1126 women with age at menarche data Age 39-49 years at follow-up The Early Determinants of Mammographic Density Study, 2008 adult follow-up of female participants in the CHDS and Boston and Providence sites of NCPP birth cohorts (pregnancies 1959-1966)	Weight and length gain during 2 infancy periods: 0-4 months and 4-12 months - Percentile rank change in weight or length - Conditional growth (standardized residuals from regressing current percentiles against previous percentiles) - Pattern: Rapid (increasing ≥2 CDC percentiles; Rapid (staying within 2 CDC percentiles); Slow (decreasing ≥2 CDC percentiles)	Length and weight measured at clinic visits (NCPP) or extracted from medical records (CHDS). Interpolated weight and length at 4 months (using measures from 3.1-5.4 months); 12 months (using measures from 10.1-15 months) and 4 years (3.7-4.7 years) using cubic splines.	Age at menarche, continuous and categorized as: <12 years ≥12 years	Self-report by woman in adulthood	Multivariable logistic regression for early menarche (<12 y), GEE models and linear random effect models for age at menarche (continuous) using percentile rank change, conditional growth and pattern models (β<0 or OR>1 indicates earlier menarche).	Adjusted percentile rank change logistic regression model, OR for early menarche (<12y): 10-unit increase in percentile rank in change in weight, 0-4 months: OR=1.06, 95% CI=0.97, 1.16 10-unit increase in percentile rank change in weight, 4-12 months: OR=1.1, 95 % CI=1.01, 2.27 10-unit increase in percentile rank change in height, 0-4 months: OR=1.17, 95% CI=1.05, 1.29 10-unit increase in percentile rank change in height, 4-12 months: OR=1.08, 95% CI=0.98, 1.19 Adjusted percentile rank change linear regression model: 10-unit increase in	Birthweight, birthlength, percentile rank change in weight and height from 0-4 months, 4-12 months and 1-4 years, maternal age at menarche

							percentile rank change in weight, 0-4 months: β=-0.09, 95% CI= -0.15, -0.04 10-unit increase in percentile rank change in weight 4-12 months: β=-0.09, 95% CI= -0.15, -0.02 10-unit increase in percentile rank change in height, 0-4 months: β=-0.04, 95% CI= -0.10, 0.01 10-unit increase in percentile rank change in height, 4-12 months: β=-0.05, 95% CI= -0.11, 0.01 Inference was similar when conditional growth or growth pattern models were used and in sibling subset.

Supplemental Table 2.7. NIH quality assessment of included studies

Article	1. Research question	2. Study population	3. Participation rate	4. Subject selection	5. Sample size	6. Temporality	7. Timeframe	8. Levels of Exposure	9. Exposure assessment	10. Repeat exposure assessment	11. Outcome assessment	12. Outcome blinded	13. Loss to follow-up	14. Confounding
Miller et al, 1972	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	No, ~60% of original cohort was followed up at 22 years	No
Zacharias et al, 1976	Yes	Yes	Yes (62%)	Yes	No	Unclear	Yes	No	Unclear	NA	Yes	No	Yes, 7% were lost	No
Billewicz et al, 1981	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, self-report but based on regular follow-up	No	Yes	No
Fledelius, 1982	Yes	No	Not stated	Not stated	No	Yes	Yes	No	Yes	NA	Yes	No	Not stated	No
Westwood et al, 1983	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	NA	Yes, clearly defined but based on recall	No	No	No
Roberts et al, 1986	Yes	Yes	Unknown - response rate not given	Yes	No	No	Unclear - don't have age breakdown of subjects	Not stated	Yes, but based on parent recall	NA	No - mix of recall and status quo	No	NA	No
Stark, 1989	Yes	Yes	Not provided	Yes	No	Yes	Yes	Not clear	Yes	NA	Yes, self-report	No	Not stated	No
Prapas et al, 1989	No	No	Unknown - response rate not given	Unknown - details not given	No	No	Yes	Yes	Yes, but based on recall	NA	Yes, but based on recall	No	NA	No
Moisan et al, 1990	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes, but based on	NA	Yes, but based on recall	No	Yes	No

									parent recall					
Frisancho et al, 1994	Yes	Not clear	Not stated	Not stated	No	Yes	Yes	No	Yes	NA	Unclear	Unclear	Not stated	No
St. George et al, 1994	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but based on recall	No	Yes	No
Bhargava et al, 1995	Yes	Yes	Not stated	Yes	Yes - power calculation given for anthropometric analyses	Yes	Yes, though unclear if all girls had outcome	No	Yes	NA	Yes	Not stated	Not stated	No
Cooper et al, 1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but based on maternal recall	No	No, response for menarche question 71%. Compared responders and non-responders for early-life characteristics	Birth order adjusted for, not birth length. Mutually adjusted regression for birthweight and weight at 7 years
Powls et al, 1996	Yes	Yes	Not stated	Unknown where 60 controls that were not part of original study came from	No	Yes	Could have missed earlier pubertal onset	No	Yes	NA	Yes	Not stated	Not stated	No
Bacallao et al, 1996	Yes	Yes	Not stated	Not stated	No	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	Not stated	No
Amador et al, 1996	Yes	Yes	Not stated	Not stated	No	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	Not stated	No
Leger et al, 1997	Yes	Yes	Yes (58%)	Yes	No	Yes	Yes	No	Yes	NA	Not stated	No	No (33 lost%)	No
Persson et al, 1999	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	No - no description of why so much missing from	Yes	No	No

										medical record				
Tenhola et al, 2000	Yes	Yes	Yes	Yes	No	Yes	Yes if focus is early menarche	No	Yes, but did not look at differences based on weight/height independently	NA	Not stated	Not stated	Not stated how many participated in 5y and 12y follow-ups	No
Berkey et al, 2000	Yes	Yes	Not stated	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Not stated	Yes, loss to follow-up close to 50%	No - no adjustment for size at birth; adjusted for later size
Ford et al, 2000	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NA	Yes	Not stated	Depended on the group (30% loss in NBW, 8% in VLBW)	No
Peralta-Carcelen, 2000	Yes	Yes	Yes	Yes	No	Only for case group	Could have missed earlier pubertal onset	No	Exposure measured different for cases and controls	NA	Yes	Yes for breast Tanner	NA (cross-sectional)	No
Saigal, 2001	Yes	Yes	Not provided	No (ELBW and controls recruited at different time)	No	Yes	Yes	No	Unclear how exposure assessed in controls	NA	Unclear	No	Yes (86-91% follow-up)	No
Adair, 2001	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	No	No (69% of cohort were interviewed for 14-15 year questionnaire)	Yes
Ghirri, 2001	Yes	No - not enough	Not stated	Yes	No	Yes	Yes	No	Yes	NA	Yes	No	NA	No

		details given about selection of study groups												
Benefice, 2001	Yes	Yes	Yes, though not at all visits	Yes	No	Yes	Longer follow-up needed for menarche	No	Yes	Yes	Yes	No	~70% of initial cohort were found again in 1995	No
Koziel & Jankowska et al, 2002	Yes	Yes	Not stated	Yes	No	Yes	Yes	No	Yes	NA	Yes	No	NA	No
dos Santos Silva et al, 2002	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes, though could have looked at infant growth as continuous exposure	Yes, though some infants had more measures than others to contribute to random effects model	Yes	No - 17% of participants had menarche recalled in adulthood instead of in adolescence	No	Yes (84% followed)	Yes
Delemarre-van de Waal, 2002	Yes	No	Not stated	Not stated	No	Yes	Not clear	Yes	Yes	NA	Yes	Not clear	Not provided	No
Hack, 2003	Yes	Yes	Not stated	No, VLBW and controls recruited differently	No	Yes	Yes	No	Unclear how assessed for controls	NA	Unclear how assessed	No	No, 64% of controls followed and 78% of cases	No
Romundstad et al, 2003	Yes	Yes	Yes	Yes, though exclusion of perinatal conditions that may influence birth weight could affect results	No	Yes	Yes	Yes	Yes	NA	Yes, though some misclassification could be introduced due to missing data on months	No	Yes (90%)	No. Gestational age controlled for, and parental height in a subset.

Windham et al, 2004	Yes	Yes	Yes	Yes, though picked based on earlier inclusion	No	Yes	Yes	No	Yes	NA	Yes - though digit preference	No	Not provided	No
Veening et al, 2004	Yes	Yes	Not provided	Yes	No	Yes	Yes	No	Yes	NA	Yes	Unclear	Not provided	No
Trentham-Dietz et al, 2005	Yes	Yes	Yes	Yes	No	No	Limited number of girls with menarche	Yes	No - parent recall	NA	Yes	No	NA	No
van Weissenbruch et al, 2006	Yes	Yes	Not provided	Yes	No	Yes	Yes	No	Yes	NA	Yes	Unclear		
Tam et al, 2006	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	No	No; 156/215 were interviewed at age 15	No; only BMI Z-score at 8 years controlled for.
Sloboda et al, 2007	Yes	Yes	Details not provided in this publication	Yes	No	Yes	Yes, though more details about age at censor could have been provided	Yes	Yes	NA	Yes	No	No; 55% of original cohort of girls included in analysis	Yes
Vandeloo et al, 2007	Yes	Yes	Yes	Yes	No	Yes?	Unclear	Yes	Unclear	NA	Unclear	Unclear	NA	No - all variables associated in univariate analyses thrown into same model
Blell et al, 2008	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	NA	Yes - but based on recall when 50 years	No	Yes	No - univariable models shown only

Bosch et al, 2008	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No - parent recall (small, normal, tall)	No	Yes	No	Yes - LTFU right around 20%	No
Chaudhari et al, 2008	Yes	Yes	Not stated	Yes	No	Yes	Unclear - % with menarche not given	No	Yes	NA	Yes - based on parent report	No	Not stated	No
Opdahl et al, 2008	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	No	No	No
Windham et al, 2008	Yes	Yes	Details not provided in this publication	No - selected for birth weight	No	Yes	Yes	Yes	Yes	NA	Yes - adult recall	No	Not stated	Yes
Salsberry et al, 2009	Yes	Yes	Details not provided in this publication	Yes	No	Yes	Yes	Yes	Yes	NA	Yes - mix of parent and self-recall	No	Yes (90% of eligible sample included)	No
Rubin et al, 2009	Yes	Yes	Yes, though eligilibility criteria not clear	Yes	No	Yes	Yes - if early menarche is focus	Yes	Yes	NA	Yes, but based on different percentage of questionnaire completion at each age	No	Yes - ~80% of participants completed at least one puberty questionnaire	Only in pre-pregnancy BMI analysis
Labayen et al, 2009	Yes	Yes	Details not provided in this publication	Yes	Yes - sample size needed given	Yes	Yes	Yes	Yes	NA	Yes, but reported to nearest year only	No	NA, but less than 80% included in analyses due to missing data	No
Semiz et al, 2009	Yes	Yes	Not stated	Yes	Yes - target sample size given	No	Age range sufficient, but unclear how	Not stated	Not stated	NA	Unclear	No	NA, but unclear why degree of missing data so high	No

							analyzed							
Keim et al, 2009	Yes	Yes	Details not provided in this publication	No - selected for birth weight	No	Yes	Yes	Yes	Yes	NA	Yes, but recalled in adulthood	No	Not stated	Yes
Ong et al, 2009	Yes	Yes	Not stated	Yes	No	Yes	Yes - though 50% still pre-menarche	Yes	Yes	NA	Yes, but use of imputed data	No	Not stated	No - unclear if infant growth associations adjusted for birth weight
Terry et al, 2009	Yes	Yes	Yes, among those traced	Yes	Yes	Yes	Yes	Not for maternal measure, yes for birth and infancy measures	Yes	NA	Yes, but based on adult recall	No	No, high loss to follow-up, but those lost didn't differ by most measures	Yes
Karaolis-Danckert, 2009	Yes	Yes	Not stated	Yes, but excluded low birthweight babies	No	Yes	Yes	No	Yes	NA	Yes, but pre-menarche girls may have been excluded. Also mixture of parent and self-report	No	Not clearly stated, but appears to be>20% based on missing data	No (maternal factors; birthweight always adjusted for later growth)
Espetvedi Finstad, 2009	Yes	Yes	Not stated	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but recalled in adulthood	No	NA (cross-sectional)	No
Mesa, 2010	Yes	Yes	Not stated	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but recalled in adulthood	No	No	Yes, though no adjustment for birth size
Boyne, 2010	Yes	No - age range not clear	Not stated	Yes	No	Yes	Unclear - age of participants	Yes	Yes	NA	Unclear how outcome was assessed	Not stated	No, high loss to follow-up, but those lost didn't differ	No

							not stated, unclear if any were censored						by most measures	
Epplein, 2010	Yes	Yes	Not stated	No - some girls were selected 5-7 years after initial recruitment	No	Only for linked data	Yes	Yes	Mixture of recall and record data	NA	Yes	No	NA (cross-sectional)	No
Maisonet, 2010	Yes	Yes	Depends on analysis	Yes, but excluded preterm babies and many without infancy measures	No	Yes	Unclear - mean age of participants not given	Yes	Yes	NA	Yes, but mixture of parent/daughter report	No	Not provided	Yes
Christensen, 2010	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes, but self-report	NA	Yes, but mixture of parent/daughter report	No	Not provided	Yes
Morris, 2010	Yes	Yes	Not stated	Not stated	No	No	Yes	Yes	Yes, but self-report	NA	Yes, but self-report	No	NA (cross-sectional)	Yes, though adjusted for later size in multivariable model
Ruder, 2010	Yes	Yes	Not stated	Not stated	No	No	Yes	Yes	No, use of self-report and maternal report	NA	No, mix of prospective and retrospective data	No	Not stated	No
Olivo-Marston, 2010	Yes	Yes	Not stated	Yes	No	No	Yes	Yes	Yes, but maternal report	NA	Yes, clinician assessment (though without palpation)	Yes	NA (cross-sectional)	No, didn't have information on gestational age or parent characteristics. Adjusted for height and BMI at visit.

Cho, 2010	Yes	Yes	Not stated	Yes	No	No	Yes	Yes	Yes, but maternal report	NA	Yes, but self-report	No	NA (cross-sectional)	No
Shrestha, 2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Self-report, ~50% to nearest year only and 50% with month and year	No	No, 72% of participants were asked follow-up information on age at menarche	Yes
Boynton-Jarrett, 2011	Yes	Yes	Not provided	Yes	No	No	Yes	Yes	Yes, but maternal report	NA	Yes, but self-report in categories	No	NA (cross-sectional)	Yes, though adjusted for variables later in life course
Chevalley, 2011	Yes	Yes	Not provided	Yes	Mo	Yes	Yes	Yes	No, use of maternal/ pediatrician report	NA	Yes, but self-report	No	Not provided	No
Orden, 2011	Yes	Yes	Not provided	Unclear how schools were selected	No	No	Yes	Yes	Yes, but maternal report	NA	Yes, but status quo	No	NA (cross-sectional)	No
Papadimitriou, 2011	Yes	No	Not provided	Unclear how controls were selected	No	Yes	Yes	Yes	Yes	NA	Unclear is physician palpation was assessed in all groups	Unclear	NA (cross-sectional)	No
Wehkalampi, 2011	Yes	Yes	Not provided	Ye	No	Yes	Yes	No	Yes	NA	Yes, but self-report	No	Not stated, but less than 80% of original cohort included in analyses	No
Szwed, 2012	Yes	No	Not provided	Not stated	No	Yes	Yes	Yes	Yes	NA	No, excluded girls <17 years	No	NA (cross-sectional)	No
Reagan, 2012	Yes	Yes	Not provided	No (African-American and white samples selected differently)	No	Yes	Yes	Yes	Yes, maternal report but near time of birth	NA	No, mix of parent report and self-report	No	Yes, though only 78% included in analyses due to missing data	Yes, though also adjusted for pre-pubertal BMI
Wang, 2012	Yes	Yes	Not provided	Yes, but convenience sample	No	Yes	Yes	Yes	Yes, but maternal exposures were	NA	No, mix of parent report and self-report	No	No, 30% lost to follow-up	Yes, though no adjustment for

									self-reported					length/height
Oh, 2012	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes, but maternal report	NA	No, mix of parent report and self-report	No	NA (cross-sectional)	No
Hui, 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Unclear (doctors may have had access to earlier records)	Yes	Yes
Dossus, 2012	Yes	Yes	No (20%)	Yes	No	No	Yes	Yes	Yes, but self-report. Excluded pre-term for birthweight analysis	NA	Yes, but self-report. Excluded early and late menarche	No	Not provided	Yes, though could be over-adjusted
D'Aloisio, 2013	Yes	Yes	Not provided	Yes	No	No	Yes	Yes	Yes, but self-report	NA	Yes, but self-report	No	NA (cross-sectional)	Yes
Sorensen, 2013	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but self-report	No	NA	Yes by design
Deardorff, 2013	Yes	Yes	Not provided	Yes	No	Yes	Yes	Yes	Yes, but self-report	NA	Yes, but self-report	No	Not reported, though only 64% included in analyses due to missing data	Yes
Hernandez, 2013	Yes	Yes	Not provided	Yes	No	Yes	Needed longer follow-up	No	Yes	NA	Unclear how outcome was assessed	Unclear	No, only 41/71 (57.8%) completed 3 years of follow-up	No
Jahanfar, 2013	Yes	Yes	Not provided	Yes	No	No	Yes	Not stated	Not stated	NA	Yes, but self-report	No	NA (cross-sectional)	No
Kale, 2014	Yes	Yes	Not provided	No (differences by site)	No	Yes	Yes	No	Yes, but maternal report in adolescence	NA	Yes	Unclear	Not reported	No

Zhang & Hartman, 2014	Yes	Yes	Not provided	No - excluded all pre-menarche girls	No	No	Yes	Yes	Yes, but maternal report in adolescence	NA	Yes, but self-report	No	NA (cross-sectional)	No, adjusted for adolescent body size in all analyses
Gavela-Perez, 2015	Yes	Yes	Not provided	Yes	No	Yes	Yes	Yes	Yes, but maternal report in adolescence	NA	Yes, but self-report	No	Yes	No
Meulenijzer, 2015	Yes	No	Not provided	Not provided	No	No	Yes	Yes	Yes, but maternal report in adolescence	NA	Yes, but self-report	No	NA (cross-sectional)	No
German, 2015	Yes	Yes	Not provided	Not provided	No	Yes	Yes	Yes	Yes	NA	Yes	Unclear	No (71% followed up through 15.5 y)	No
Salgin, 2015	Yes	Yes	Not provided	Yes	No	Yes	Yes	No	Yes	NA	Yes	No	No (68% followed up through 18 years)	Yes
Behie & O'Donnell, 2015	Yes	Yes	Not provided	Not provided	No	Yes	Yes, though a lot of censoring	Yes	Yes, but parent report	NA	Yes, but parent report	No	No (61% included in analysis)	No, adjusted for adolescent body size in all analyses
Wells, 2016	Yes	Yes	No (30%)	Yes	No	No	Yes	Yes	Yes, but self-report	NA	Yes, but self-report	No	NA (cross-sectional)	No
Mariansdatter, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes, but self-report	NA	Yes, but self-report	No	Yes (83%)	No
Krzyzanowska, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but self-report	No	Not stated	No
Schulte, 2016	Yes	Yes	Not provided	Yes	No	Yes	Yes	No	Yes	NA	Yes, but mix of parent and self-report	No	Not stated	By design
Kubo, 2016	Yes	Yes	Not provided	Yes	No	Yes	Yes	Yes	Yes, but self-report	NA	Yes	Unclear	Yes	Yes
Aydin, 2017	Yes	Yes	No (31.4 %)	Yes	NO	Yes	Early breast development only	Yes	Yes	NA	Yes	Unclear	NA (retrospective)	No (maternal factors; birthweight always adjusted for

														later growth)
Aurino, 2017	Yes	Yes	Not provided	Yes (by country)	No	Yes	Yes, early menarche only	Yes	No, different sources of birthweight information	NA	Yes, but self-report	No	Yes (5.2%)	Yes, though no birthlength, gestational age or maternal body size data
Flom, 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but self-report	No	NA	Yes
Workman & Kelly, 2017	Yes	Yes	Not provided	Yes	No	No	Yes	Yes	Yes, but self-report	NA	Yes, but self-report	No	NA (cross-sectional)	No
Kelly, 2017	Yes	Yes	Not provided	Yes	No	Yes	Yes, early menarche only	Yes	Yes, but self-report	NA	Yes, but mother report	No	Not provided	No
Lawn et al, 2018	Yes	Yes	Not provided	Yes	No	Yes	Yes	Yes	Yes	NA	Yes, but self-report	No	No but no difference	Yes
Kubo et al, 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Unclear	NA (retrospective)	Yes

Supplemental Table 2.8. Newcastle-Ottawa Scale quality assessment of included studies

Cohort Studies (also used for cross-sectional studies, with follow-up replaced by response rate)

Article	1. Representativeness of the exposed cohort	2. Selection of the non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest was not present at start of study	5. Comparability of cohorts on the basis of design or analysis	6. Assessment of outcome	7. Follow-up long enough for outcomes to occur	8. Adequacy of follow-up for cohorts (modified for adequacy of response rate for cross-sectional studies)	Total score (Max 9)
Miller et al, 1972	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	No analytic controls (0)	Not clear (0)	Yes (1)	60% followed up, no comparison provided (0)	5
Zacharias et al, 1976	Volunteers (0)	Same as exposed (1)	Unclear (0)	Yes (1)	No analytic controls (0)	Self-report? (0)	Yes (1)	Subjects loss to follow-up less than 20% (1)	4
Billewicz et al, 1981	Limited description provided (0)	Same as exposed (1)	Unclear (0)	Yes (1)	No analytic controls (0)	Self-report (0)	Yes (1)	Subjects loss to follow-up less than 20% (1)	4
Fledelius et al, 1982	Details not provided (0)	Details not provided (0)	Hospital record (1)	Yes (1)	Not enough information to determine(0)	Self-report (0)	Yes(1)	Not provided (0)	3
Westwood et al, 1983	Somewhat representative (1)	Drawn from same community as exposed (1)	Hospital record (1)	Yes (1)	Matched on factors like SES and race (1), but no statistical controls	Self-report (0)	Yes (1)	Significant number of subjects lost (70%), comparison provided of those studied vs. not studied (1)	6
Roberts et al, 1986	Somewhat representative (1)	Drawn from same community as exposed (1)	Parent self-report (0)	No (0)	Controlled for birth order and family size (1), no control for birth length or parent size	Self-report (0)	Unclear (no age range, given, 0)	No response rate given (0)	3
Stark, 1989	Representative (1)	Same as exposed (1)	Records (1)	Yes (1)	Comparable on design, no analytic controls (1)	Self-report (0)	Yes (1)	Loss to follow-up rate not provided (0)	6
Prapas et al, 1989	Students, not clearly defined who participated (0)	Same as exposed (1)	Self-report (0)	No (0)	Limited design or analytic controls (0)	Self-report (0)	Yes (1)	No response rate given (0)	2

Frisancho et al, 1994	Details not provided (0)	Same as exposed (1)	Records (1)	Yes (1)	No analytic controls (0)	Unclear (0)	Yes (1)	Not provided (0)	4
St. George et al, 1994	Somewhat representative (1)	Same as exposed (1)	Records (1)	Yes (1)	No analytic controls (0)	Self-report (0)	Yes (1)	Subjects loss to follow-up less than 20% (1)	6
Bhargava et al, 1995	No description; unclear if all LBW infants were selected (0)	Same as exposed (1)	Hospital record (1)	Yes (1)	Matched on parental height, education and SES (1), not analytic controls	Self-report (0)	Unclear (not clear how many were right censored and actually followed to age 14) (0)	Loss to follow-up not shown (0)	4
Cooper et al, 1996	Representative (1)	Same as exposed (1)	Health visitor or midwife record (1)	Yes (1)	Controlled for birth order and SES, not for birth length, other early-life variables (1)	Maternal report (0)	Yes(1)	Response rate for this analysis (71%), did compare responders with non-responders (1)	7
Powls et al, 1996	Details not provided (0)	Some were same as exposed, details on other sources of controls not clear (0)	Hospital record (1)	Yes (1)	Matched on age, sex and school (1), no analytic controls	Clinical rating for breast development (1), self-report for menarche (0)	No(0) - for menarche	Response rate not given (0)	3-4
Bacallao et al, 1996	Details not provided, <2500g were excluded (0)	Same as exposed (1)	Obstetric card (1)	Yes (1)	No analytic controls (0)	Unclear (0)	Yes (1)	Follow-up rate not provided (0)	4
Bacallao et al, 1996	Details not provided, <2500g were excluded (0)	Same as exposed (1)	Obstetric card (1)	Yes (1)	No analytic controls (0)	Unclear (0)	Yes (1)	Follow-up rate not provided (0)	4
Leger et al, 1997	Representative (1)	Same as exposed (1)	Birth registry (1)	Yes (1)	Design comparable, no analytic controls (1)	Unclear (0)	Yes (1)	67% followed (0)	6
Persson et al, 1999	Representative (1)	Same as exposed (1)	Hospital record (1)	Yes (1)	Comparable based on design (1), limited analytic controls(0)	Medical record (1)	Yes(1)	Menarche data missing for many participants, no description of differences between those with and without menarche data	7

								in medical record (0)	
Tenhola et al, 2000	Representative (1)	Same as exposed (1)	Hospital record (1)	Yes (1)	Comparable based on design (1), limited analytic controls(0)	Self-report (0)	No(0) - for menarche	~25% of SGA subjects did not participate, did not differ from those that did based on birth measures(1)	6
Berkey et al, 2000	Selected - "likely to maintain residence near Boston and committed to having their child in a long term study" (0)	Same as exposed (1)	Measured by doctor (1)	Yes (1)	Comparable on design, inappropriate analytic control for later growth, unclear averaging of measures(1)	Self-report (0)	Yes(1)	Almost 50% loss to follow-up; did not differ by birth size (0)	5
Ford et al, 2000	Selected survivors (0)	Same as exposed (1)	Hospital record (1)	Yes (1)	VLBW group older than other groups, no analytic controls (0)	Self-report (0)	Yes(1)	Loss to follow-up differed by group, 30% in NBW (0)	4
Peralta-Carcelen et al, 2000	Selected survivors (0)	Drawn from a different source (0)	Medical record for cases, recall for controls (0)	No (0)	Matched on age, sex, race and SES (1), no analytic controls	Self-report for menarche (0), clinician assessment for breast TS(1)	Yes(1)	82.6% response rate for cases, not given for controls (0)	2-3
Saigal et al, 2001	Selected survivors (0)	Drawn from a different source (0)	Medical records for cases, not stated for controls (0)	Yes (1)	Matched on age, sex and SES (1), no analytic controls	Self-report (0)	Yes (1)	>80% follow-up rate for cases and controls (1)	4
Adair, 2001	Representative (1)	Same as exposed (1)	Measured by study staff (1)	Yes (1)	Comparable on design and adjusted for appropriate confounders. Results shown with and without adjustment for	Self-report (0)	Yes (1)	Response rate for 14-15 year follow-up 69%, did compare characteristics of those lost with participants (1)	8

					characteristics at 8 years (2)				
Ghirri, 2001	No description; unclear if all SGA infants were selected (0)	Same as exposed (1)	Hospital record (1)	Yes (1)	Comparable on design, no analytic controls (1)	Self-report(0)	Yes(1)	Response rates not given(0)	5
Benefice, 2001	Representative (1)	Same as exposed (1)	Measured by study staff (1)	Yes (1)	Comparable on design, no analytic controls (1)	Self-report (0)	No(0) - for menarche	Yes, coverage at least 80% for most visits, differences examined (1)	6
Koziel & Jankowska, 2002	Representative (1)	Same as exposed (1)	Birth records (1)	Yes (1)	Comparable on design, controlled for SES only and BMI at 14 years (1)	Self-report(0)	Yes(1)	Response rate details not stated (0)	6
dos Santos Silva, 2002	Representative (1)	Same as exposed (1)	Birth records (1)	Yes (1)	Comparable on design, control for maternal factors in random coefficient model, no information on birth length or gestational age (1)	Self-report(0)	Yes(1)	Yes, 84% follow-up, differences assessed(1)	7
Hack, 2003	Selected (0)	Drawn from a different source (0)	Birth records for exposed, unclear for non-exposed (0)	Yes (1)	Ascertained and followed differently, no analytic controls (0)	Assume self-report (0)	Yes (1)	Follow-up 78% of cases and 64% for controls, did compare those that were and were not followed (0)	2

Romundstad, 2003	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Exclusion of prenatal conditions could bias low birthweight group. Did control for gestational age and maternal factors in a subset (1)	Self-report(0)	Yes(1)	Yes, 90% response (1)	7
Delemarre-van de Waal, 2002	No description (0)	Same as exposed (1)	Medical records (1)	No (0)	Details not provided, no analytic controls (0)	Clinical report (1)	No (0)	Not provided (0)	3
Windham, 2004	Representative (1)	Same as exposed (1)	Measured at birth (1)	Yes (1)	Comparable on design, some analytic controls (1)	Self-report(0)	Yes(1)	Yes, 80% response, comparison of those that did and did not participate (1)	7
Veening, 2004	Details not provided (0)	Same as exposed (1)	Medical records (1)	Yes (1)	Comparable on design, no analytic controls (1)	Clinical report (1)	Yes (1)	Yes, 90% follow-up (1)	7
Trentham-Dietz, 2005	Representative (1)	Same as exposed (1)	Parent self-report (0)	No (0)	Cross-sectional study, no analytic controls (0)	Self-report(0)	No(0)	Cross-sectional study, 60% response rate (0)	2
van Weissenbruch, 2004	Details not provided (0)	Same as exposed (1)	Medical records (1)	Yes (1)	Comparable on design, no analytic controls (1)	Not stated (0)	Yes (1)	Not stated (0)	5
Tam, 2006	Unclear is subset is representative(0)	Same as exposed (1)	Medical records (1)	Yes (1)	Limited analytic control (1)	Self-report(0)	Yes(1)	No, 72.5% followed up at 15 years, no description of whether those followed were different than those lost (0)	5
Sloboda, 2007	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	EBW controlled for several maternal factors, not clear what other factors were adjusted for in analyses (1)	Self-report(0)	Yes (1)	55% of original girls in this analysis, no description of differences between those lost and those participated (0)	6

Vandeloo, 2007	Representative (1)	Same as exposed (1)	Unclear (0)	No (0)	Design and modeling strategy not clear (0)	Not clear (0)	Not clear (0)	Participation rate 100% (1)	3
Blell, 2008	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Comparable on design, no analytic controls (1)	Self-report (0)	Yes (1)	~50% participation, those who participated differed from those lost (0)	6
Bosch, 2008	Representative (1)	Same as exposed (1)	Parent self-report (0)	Yes (1)	Comparable on design, no analytic controls (1)	Self-report(0)	Yes(1)	20% LTFU, no comparison of those lost vs. those participated (0)	
Chaudhari, 2008	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Design comparable, no analytic controls (1)	Parent-report (0)	Not clear (0)	Not provided (0)	5
Opdahl, 2008	Representative (1)	Same as exposed (1)	Measured at birth (1)	Yes (1)	Design comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	77.6% of girls attended adolescent follow-up; not comparison of those that did and did not participate (0)	6
Windham, 2008	Representative (1)	Selection criteria for adult follow-up different (0)	Parent self-report (0)	Yes (1)	Controlled for maternal factors in analysis (1)	Self-report(0)	Yes(1)	Not provided (0)	4
Salsberry, 2009	Representative (1)	Same as exposed (1)	Mix of parent report and study measurement (0)	Yes (1)	Design comparable, limited analytic controls (1)	Self or parent report (0)	Yes (1)	90% of eligible girls included (1)	6
Rubin, 2009	Representative (1)	Same as exposed (1)	Medical records for birth weight (1), self-report for pre-pregnancy BMI (0)	Yes (1)	Design comparable, analytic controls only in logistic regression analysis (1)	Self or parent report (0)	Yes for early menarche, not for full range (1)	~80% completed at least one puberty questionnaire; compared differences between non-responders and respondents (1)	6 or 7
Labayen, 2009	Representative (1)	Same as exposed (1)	Health booklet (1)	No (0)	Design comparable, controlled for factors later in life (1)	Self-report (0)	Yes(1)	<80% included due to large amount of missing data (0)	5

Semiz, 2009	Representative (1)	Same as exposed (1)	Parent self-report (0)	No (0)	Not enough information to determine(0)	Self-report(0) for menarche, clinical assessment for breast Tanner but unclear how it was used in analysis (0)	Yes(1)	NA, but response rate not given (0)	3
Keim, 2009	Representative (1)	Selection criteria for adult follow-up different (0)	Parent self-report (0)	Yes (1)	Controlled for maternal factors in analysis (1)	Self-report in adulthood (1)	Yes (1)	Not provided (0)	5
Ong, 2009	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Design comparable, more analytic controls needed (1)	Self-report (0)	50% of girls still did not reach menarche; unclear how included if <13 years (0)	Participation rate at visit not given. Examined differences between girls in analysis (70%) and singleton girls not included (0)	5
Terry, 2009	Representative (1)	Same as exposed (1)	Parent report for maternal weight, medical records for others (1)	Yes (1)	Design comparable and adequate controls (1)	Self-report(0)	Yes(1)	Low follow-up, but differences examined (0)	5 or 6
Karaolis-Danckert, 2009	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Design comparable, more analytic controls needed (1)	Self-report(0)	Yes(1)	Not provided (0)	6
Espetvedt Finstad, 2009	Selected (0)	Same as exposed (1)	Medical records (1)	No (0)	Exclusion criteria could be associated with birthweight, more analytic controls needed (0)	Self-report(0)	Yes(1)	Participation rate not provided (0)	3
Mesa, 2010	Representative (1)	Same as exposed (1)	Measured by study staff (1)	Yes (1)	Design comparable, more analytic controls needed (1)	Self-report(0)	Yes(1)	22.6% lost to follow-up, some comparison provided (0)	6

Boyne, 2010	Representative (1)	Same as exposed (1)	Measured by study staff (1)	Yes (1)	Design comparable, more analytic controls needed (1)	Self-report for menarche, measured for breast development but unclear how assessed (0)	Unclear (0) - no mention of censored data	Low follow-up, but differences examined (0)	5
Epplein, 2010	Representative (1)	Same as exposed (1)	Recall and record linkage (0)	No (0)	Design comparable, more analytic controls needed (1)	Self-report (0)	Yes(1)	Participation rate not provided (0)	4
Maisonet, 2010	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Design comparable, appropriate controls (2)	Self and parent-report (0)	Unclear (0)	Detail not provided, but few girls with infancy measures (0)	6
Christensen, 2010	Representative (1)	Same as exposed (1)	Maternal report (0)	Yes (1)	Design comparable, appropriate controls (2)	Self and parent-report (0)	Yes (1)	Compared characteristics of respondents vs non-respondents (1)	7
Morris, 2010	Volunteers (0)	Same as exposed (1)	Recalled in adulthood (0)	No (0)	Potential survivorship bias in design, some analytic controls (1)	Self-report (0)	Yes (1)	NA, participation rate not provided (0)	3
Ruder, 2010	Not stated, but likely not representative since RCT (0)	Same as exposed (1)	Recalled (0)	Yes (1)	Original cohort excluded extremes of height and weight, limited analytic controls (1)	Self-report(0)	Yes(1)	Not provided (0)	4
Olivo-Marston, 2010	Representative (1)	Same as exposed (1)	Parent recall (0)	No (0)	Design comparable, limited analytic controls (1)	Clinical rating for breast development (1)	Yes (1)	NA, participation rate not provided and a lot of missing data for TS (0)	5
Cho, 2010	Representative (1)	Same as exposed (1)	Parent recall (0)	No (0)	Design comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	NA, participation rate not provided (0)	4

Shrestha, 2011	Not stated (0)	Same as exposed (1)	Self-report (0)	Yes (1)	Design comparable, controlled for maternal factors (2)	Self-report(0)	Yes(1)	72% of girls completed follow-up survey, did not compare those that did and did not participate (0)	5
Boynton-Jarrett, 2011	Selected - nurses (0)	Same as exposed (1)	Maternal recall (0)	No (0)	Design comparable, controlled for maternal factors (2)	Self-report (0)	Yes (1)	Not provided (0)	4
Chevalley, 2011	Selected - RCT volunteers (0)	Same as exposed (1)	Maternal/pediatrician report (0)	Yes (1)	Exposure source not clear, no analytic controls (0)	Self-report (0)	Yes (1)	Not provided (0)	3
Orden, 2011	Not provided (0)	Same as exposed (1)	Maternal recall (0)	No (0)	Cross-sectional study, no analytic controls (0)	Self-report (0)	Yes (1)	NA, participation rate not provided (0)	2
Wehkalampi, 2011	Selected - survivors (0)	Same as exposed (1)	Hospital records (1)	Yes (1)	Matched, no analytic controls (1)	Self-report (0)	Yes (1)	Not provided (0)	5
Szwed, 2012	Not provided (0)	Same as exposed (1)	Medical records (1)	No (0)	More recruitment details needed, no analytic controls (0)	Self-report (0)	Yes (1)	NA, participation rate not provided (0)	3
Reagan, 2012	Representative (1)	Same as exposed (1)	Maternal report (0)	Yes (1)	Appropriate selection, controlled for pre-pubertal BMI in all analyses (1)	Maternal and self-report(0)	Yes(1)	78% of those eligible were included in this analysis, but compared those that did and did not participate and found no differences (1)	6
Wang, 2012	Selected (volunteers) (0)	Same as exposed (1)	Study measures, except for maternal BMI (1)	Yes (1)	Appropriate analytic controls, but excluded preterm (1)	Maternal and self-report(0)	Yes (1)	70% of cohort was follow-up, though N for analyses was much smaller. Compared those that were and were not followed-up	6

								with minimal differences (1).	
Oh, 2012	Not provided (0)	Same as exposed (1)	Maternal recall (0)	No (0)	Cross-sectional study, limited analytic controls (0)	Maternal and self-report(0)	Yes (1)	93% agreed to participate, though only 60% were included in analyses due to missing data (1)	3
Hui, 2012	Representative (1)	Same as exposed (1)	Medical records (1)	Yes (1)	Representative cohort, appropriate covariates, though did exclude pre term (2)	Clinical report (1)	Yes (1)	88% of cohort members were included in analysis (1)	9
Dossus, 2012	Representative (1)	Same as exposed (1)	Self-report (0)	No (0)	Excluded pre-term in birthweight analysis, may have over-adjusted models (0)	Self-report (0)	Yes (1)	Approximately 80% did each questionnaire, those included didn't differ from those excluded (1)	4
D'Aloisio, 2013	Selected (0)	Same as exposed (1)	Self-report (0)	No (0)	Cross-sectional study, appropriate controls (1)	Self-report (0)	Yes (1)	Participation rate not provided (0)	3
Sorensen, 2013	Representative of twins (1)	Same as exposed (1)	Medical records (1)	No (0)	Appropriate (2)	Self-report (0)	Yes (1)	86.2% response rate (1)	8
Deardorff, 2013	Representative (1)	Same as exposed (1)	Self-report (0)	Yes (1)	Appropriate (2)	Self-report (0)	Yes (1)	Loss to follow-up not reported, but 35.5% not included due to missing data (0)	6
Hernandez, 2013	Representative (1)	Same as exposed (1)	Self-report (0)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Not clear (0)	No (0)	>40% LTFU, though not different in baseline characteristics	5

								from those followed (1)	
Jahanfar, 2013	Representative of twins (1)	Same as exposed (1)	Not provided (0)	No (0)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	NA, participation rate not provided (0)	4
Kale, 2014	Representative (1)	Same as exposed (1)	Self-report (0)	Yes (1)	Appropriate, only crude analyses for birthweight presented (1)	Clinical report (1)	Yes (1)	Loss to follow-up not reported (0)	6
Zhang & Hartman, 2014	Representative (1)	Same as exposed (1)	Maternal report (0)	No (0)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	Cross-sectional study, response rate not reported (0)	4
Gavela-Perez, 2015	Representative (1)	Same as exposed (1)	Maternal report (0)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	96% follow-up rate (1)	6
Meulenijzer, 2015	Representative (1)	Same as exposed (1)	Maternal report (0)	No (0)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	Cross-sectional study, response rate not reported, 42% excluded due to missing data (0)	4
German, 2015	Not provided (0)	Same as exposed (1)	Measured by researchers (1)	Yes (1)	Cohort comparable, limited analytic controls (1)	Clinical report (1)	Yes (1)	71% followed, no comparison of those that were and were not followed (0)	6
Salgin, 2015	Representative (1)	Same as exposed (1)	Hospital record/study measures (1)	Yes (1)	Appropriate (2)	Self-report (0)	Yes (1)	69% followed, no comparison of those that were and were not followed (0)	7
Behie, 2015	Representative (1)	Same as exposed (1)	Parent report (0)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Parent report (0)	Yes, for early menarche (1)	61% included in analysis, no comparison (0)	5
Wells, 2016	Selected (volunteers) (0)	Same as exposed (1)	Self-report (0)	No (0)	Exclusion criteria could be associated with birthweight, more analytic controls needed (0)	Self-report (0)	Yes (1)	30% response rate (0)	2

Mariansdatter, 2016	Representative (1)	Same as exposed (1)	Self-report (0)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	83% follow-up rate, differences examined (1)	6
Krzyzanowska, 2016	Representative (1)	Same as exposed (1)	Medical record (1)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	Not provided (0)	6
Schulte, 2016	Selected, twin pairs with TTTS (0)	Same as exposed (1)	Medical record (1)	Yes (1)	Control by design (2)	Self-report (0)	Yes (1)	Not provided (0)	6
Kubo, 2016	Representative (1)	Same as exposed (1)	Self-report (0)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Clinical report (1)	Yes (1)	Follow-up rate not provided. 86.7% of girls included in analysis (missing data excluded), no difference between those included and excluded (1)	7
Aydin, 2017	Volunteers (0)	Same as exposed (1)	Medical record (1)	No (0)	Cohorts comparable, limited analytic controls (1)	Clinical report (1)	Early breast development only (1)	Participation rate low (0)	5
Aurino, 2017	Representative (1)	Same as exposed (1)	Mix of medical record and self-report (0)	Yes (1)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Early menarche only (1)	Only 5.2% lost to follow-up, no difference in exposure (1)	6
Flom, 2017	Representative (1)	Same as exposed (1)	Medical record (1)	Yes (1)	Appropriate (2)	Self-report (0)	Yes (1)	86.3% of traced women participated (1)	8
Workman & Kelly, 2017	Representative (1)	Same as exposed (1)	Self-report (0)	No (0)	Cohorts comparable, limited analytic controls (1)	Self-report (0)	Yes (1)	Participate rate not provided. 88% included in analysis (missing excluded), girls excluded more likely to be non-Hispanic black (1)	5
Kelly, 2016	Representative (1)	Same as exposed (1)	Maternal report (0)	Yes (1)	Cohorts comparable, analytic controls not appropriate for birthweight (1)	Mother report (0)	Early menarche only (1)	Not provided (0)	5

Lawn et al, 2018	Representative (1)	Same as exposed (1)	Self-report and medical record (1)	Yes (1)	Cohorts comparable, appropriate controls (2)	Self-report (0)	Yes (1)	No difference between those that were and were not lost to follow-up in early-life data (1)	8
Kubo et al, 2018	Representative (1)	Same as exposed (1)	Medical record (1)	Yes (1)	Cohorts comparable, appropriate controls (2)	Medical record (1)	Yes (1)	N/A (retrospective cohort) (1)	9

Case-Control Studies

Article	**1. Is the case definition adequate?**	**2. Representativeness of the cases**	**3. Selection of Controls**	**4. Definition of Controls**	**5. Comparability of cases and controls on the basis of the design or analysis**	**6. Ascertainment of exposure**	**7. Same method of ascertainment for cases and controls**	**8.Non-Response rate**	**Total score (Max 9)**
Moisan et al, 1990	Yes, self-report (0)	All girls with menarche in cohort (1)	Nested from cohort (1)	No reported menarche (1)	Cases and controls are from same source population (nested). (1) Unclear if analyses were adjusted (0)	Self-report (0)	Yes (1)	High response rate in both groups (1)	5
Papadimitriou, 2011	Yes, self-report (0)	Potential for selection bias (0)	Details not provided (0)	Breast development after age 9 (1)	Unclear if cases and controls are comparable based on design (0)	Medical records (1)	Unclear (0)	Not provided (0)	2

Appendix C Additional background information for Chapter 3

Appendix C.1. Early-life exposure constructs

Primary Exposures of Interest		
Exposure of Interest	**Definition**	**Scale**
Maternal pre-pregnancy BMI	BMI of mother before pregnancy with LEGACY daughter, calculated from the maternal report of height and usual weight before pregnancy with LEGACY daughter.	Continuous Categorical: <18.5, 18.5 to <25, 25 to <30, ≥30
Maternal weight gain during pregnancy	Amount of weight gained during pregnancy with LEGACY daughter as reported by mother at baseline	Categorical: < 10 lbs, 10-14 lbs, 15-19 lbs, 20-29 lbs, 30-39 lbs, 40-49 lbs, ≥50 lbs
Gestational weight gain adequacy per 2009 IOM guidelines	Based on the maternal report of pre-pregnancy BMI and gestational weight gain, created categories based on modified 2009 IOM guidelines (based on collection of gestational weight gain in LEGACY) for singleton and multiple pregnancies (see **Appendix C.2**): -Inadequate -Adequate -Excessive	Categorical
Recreational physical activity during pregnancy	Recreational physical activity during pregnancy as reported by mother at baseline: -Inactive, no walking or other regular exercise -Mostly inactive, equivalent to walking about half a mile or less every day -Somewhat active, equivalent to walking about 1 mile every day -Active, equivalent to walking about 2 miles every day -Highly active, equivalent to walking about 3 or more miles every day	Categorical
Physical activity at home during pregnancy	Physical activity level at home during pregnancy as reported by mother at baseline: -Mostly sitting -Active housework most of the time with little sitting -Heavy manual work at home	Categorical
Physical activity at work during pregnancy	Physical activity level at work during pregnancy as reported by mother at baseline: -Not working -Mostly sitting and standing -Mostly walking with some sitting and standing -Mostly heavy labor with some walking and standing and little sitting	Categorical
Birth weight in kg	Birth weight of the daughter as reported by mother at baseline. Birthweight was reported in grams or in lbs/oz and converted to kilograms.	Continuous Categorical: <2.5kg, 2.5 to <3kg, 3 to

		<3.5kg, 3.5 to <4kg, ≥4kg
Birthlength in cm	Birthlength of the daughter as reported by mother at baseline. Birthlength was reported in centimeters or inches and converted to centimeters.	Continuous Categorical (quartiles)
Additional Early-life Factors		
Gestational age in weeks	Weeks or months that pregnancy lasted as reported by LEGACY mom at baseline. Pregnancy length reported in months was converted to weeks (Conversion to weeks = [length in months*4] + 4, i.e. 9 months = 40 weeks). For those that did not know the pregnancy length, some reported the number of days born before or after the due date. Gestational age in weeks was then calculated assuming that the due date corresponded to 40 weeks.	Continuous Categorical: <37 weeks vs. ≥37 weeks
Birth order	Birth order of the LEGACY daughter based on the number of reported prior pregnancies lasting at least 6 months and resulting in a live birth by LEGACY mom at baseline	Continuous Categorical: First-born vs. not
Multiple pregnancy	Singleton vs. multiple pregnancy, based on maternal report at baseline	Dichotomous
Gestational diabetes	Diabetes or high blood sugar during pregnancy as reported by mother at baseline	Dichotomous
Gestational hypertension or toxemia/pre-eclampsia	Hypertension or high blood pressure or toxemia or pre-eclampsia during pregnancy as reported by mother at baseline	Dichotomous
Maternal age at birth	Mom's age in years at birth of LEGACY daughter	Continuous Categorical: <30, 30-39, ≥40

Appendix C.2. 2009 Institute of Medicine recommendations for total weight gain during pregnancy by pre-pregnancy BMI and modified range used to define adequate gestational weight gain for LEGACY

Pre-pregnancy BMI	Singleton Gestation		Multiple Gestation	
	IOM recommended weight gain in lbs	Range used to define adequate weight gain in lbs in LEGACY	IOM recommended weight gain in lbs	Range used to define adequate weight gain in lbs in LEGACY
Underweight (<18.5 kg/m^2)	28-40	30-39.9	No recommendation	Not included (set to missing, n=2)
Normal weight (18.5-24.9 kg/m^2)	25-35	20-39.9	37-54	>30
Overweight (25.0-29.9 kg/m^2)	15-25	15-29.9	31-50	30-49.9
Obese (≥30 kg/m^2)	11-20	10-19.9	25-42	20-39.9

Appendix C.3. Advantages and disadvantages of the methods for modeling breast development in LEGACY

	Advantages	Disadvantages
Study subset		
Full cohort	Increased precision No bias resulting from subgroup selection Can control for more confounding factors in larger sample size	Measurement error on the outcome for girls that already reached puberty at baseline, which is related to age (Recalled age at pubertal events is older as girls are further from puberty) Cannot assess mediation by pre-pubertal body size
Subset with pre-pubertal BMI available	Not selecting directly on age or outcome, which could result in bias Can examine mediation by pre-pubertal BMI	Measurement error on the outcome for girls for girls that already reached puberty at baseline, which is related to age (Recalled age at pubertal events is older as girls are further from puberty) Less precision than using full cohort
Subset with prospective data based on age cut-off at baseline	Limited bias due to recall of outcome since limiting to (mostly) prospective data Not selecting based on observed outcome (if selecting all girls reported to be pre-pubertal at baseline, those with early development would be more likely to be excluded which could induce bias) Can examine mediation by pre-pubertal BMI	Less precision Potential for selection bias if younger girls at baseline differ from full cohort in characteristics related to pubertal timing Able to control for fewer confounders due to small cell counts in subset
Subset with clinical breast Tanner stage data	Limited measurement error on the outcome as 1) clinical breast TS is considered the gold standard for assessing breast development and 2) inter-rater reliability for clinical TS in LEGACY is very high Not selecting based on observed outcome	Less precision Potential for selection bias if girls that are more developed are less likely to agree to participate in clinical TS measures May not be generalizable to other LEGACY sites Able to control for fewer confounders due to small cell counts in subset
Modeling option		
Option 1: - Girls with breast development at first visit	No additional assumptions are made regarding pubertal timing	Does not take advantage of collected data on age at breast development

are left censored at first visit age - Girls with breast development during follow-up are interval censored (age at last visit with no development, age at first visit with development) - Girls without breast development at last visit are right censored at age of last report of no development	The only option that is not a mixture of PDS and Tanner (since only PDS has recalled age)	Must use parametric model with all types of censoring patterns Cannot accommodate left and interval censoring and left truncation Percentage of left censored girls differs between Tanner and PDS models (higher for PDS)
Option 2: - Recalled age at breast development is imputed as though it were observed for left censored girls - Girls with breast development during follow-up are interval censored (age at last visit with no development, age at first visit with development) - Girls without breast development at last visit are right censored at age of last report of no development	Use of recalled age allows for a more precise estimate of the age at breast development for left censored girls and takes advantage of this data Can be directly compared with Option 1 to determine the influence that use of recalled age has on the results	Cannot accommodate left and interval censoring and left truncation Semi-parametric Cox model cannot accommodate interval censoring Percentage of left censored girls differs between Tanner and PDS models (higher for PDS) Could be bias from measurement error on the outcome by using recalled age for left censored girls (recalled age increases with time from development)
Option 3: - Recalled age at breast development is imputed as though it were observed for left censored girls - Midpoint of interval is imputed as though it were observed for interval censored girls - Girls without breast development at last visit are right censored at age of last report of no development	Use of recalled age allows for a more precise estimate of the age at breast development for left censored girls and takes advantage of this data Since only using right censored data, can run both a parametric Weibull model or a semi-parametric Cox proportional hazards model With a semi-parametric Cox model, can accommodate left truncation (i.e. allow everyone to be at risk starting at age 5)	Could be bias from measurement error on the outcome by using recalled age for left censored girls (recalled age increases with time from development) Makes additional assumption about the timing of breast development for interval censored girls (which may not be appropriate over long intervals).

Option 4: - Recalled age at breast development is imputed as though it were observed for left censored girls and interval censored girls - Girls without breast development at last visit are right censored at age of last report of no development	Not affected by the length of the interval for interval censored Schema is consistent for left censored and interval censored girls Since only using right censored data, can run both a parametric Weibull model or a semi-parametric Cox proportional hazards model With a semi-parametric Cox model, can accommodate left truncation (i.e. allow everyone to be at risk starting at age 5)	Could be bias from measurement error on the outcome by using recalled age for both left and interval censored girls (recalled age increases with time from development, so would expect this would matter more for left censored girls) Recalled age is based on PDS, so makes more sense to use this on a PDS model. Tanner model may be more sensitive to bias from measurement error since it may use reports of recalled age at a later follow-up visit

Appendix C.4. Comparison and interpretation of the different methods for modeling breast development in LEGACY

Comparison	If Similar:	If Different:
Full cohort vs. subset with pre-pubertal data	Use of subset with pre-pubertal data does not affect inference	Possible selection bias in terms of who has pre-pubertal data Could be due to smaller amount of bias on outcome in subset with pre-pubertal data - look at difference in age distribution
Full cohort vs. "prospective" subset	Inclusion of older girls does not bias the effect estimate Confounding did not drive estimates for young cohort	Likely due to use of retrospective data Possible selection bias in terms of who is in the prospective cohort Possible confounding in "prospective" cohort since can adjust for fewer variables with smaller sample size
Full cohort vs. subset with clinical Tanner	Measurement error of the outcome does not drive association	Likely due to use of mother-reported data Possible selection bias in terms of who has clinical Tanner data Possible confounding in subset with clinical Tanner since can adjust for fewer variables with smaller sample size
Modeling Option 1 vs. Modeling Option 2	Use of recalled age for left censored girls does not affect inference - can use either model	Could be due to measurement error of the outcome when using recalled data. Would expect a likely bias towards the null (heavier girls more likely to have early puberty and be left censored; since BMI likely on causal pathway, could bias towards null) Could compare these modeling options again in subset of girls that were not overweight and see if difference is smaller in this subgroup
Modeling Option 2 vs. Modeling Option 3	Use of midpoint for interval censored girls does not affect inference - can use either model	Assumption that puberty occurred at midpoint of interval may not be valid - use Option 2
Modeling Option 2/3 vs. Modeling Option 4	Use of recalled age for interval censored girls does not affect inference - can use either model	Likely due to measurement error in recalled age or possible wide interval - do sensitivity analyses to explore
Option 1: Breast Tanner models vs Breast PDS models	Exposure-outcome association is robust to use of PDS or Tanner	Exposure may be associated with differential reporting of breast development based on method. Consider adjusting estimates for sensitivity and specificity of measure
Option 3 or 4: Parametric Weibull model vs. semi-parametric Cox model	Assumption of Weibull distribution is reasonable	Weibull distribution may not be a good fit for the data - consider other distributions

Appendix D Supplemental tables for Chapter 3

Supplemental Table 3.1. Descriptive characteristics of the LEGACY Girls Study cohort by maternal pre-pregnancy body mass index

	BMI <18.5 (N=47)	BMI 18.5-24.9 (N=676)	BMI 25-29.9 (N=179)	BMI ≥30 (N=96)
Early-life characteristics				
Maternal age at birth (Mean±SD)	30.8 ± 5.9	32.4 ± 5.2	32.4 ± 5.6	31.5 ± 6.0
Maternal height, m (Mean±SD)	1.7 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
Maternal pre-pregnancy weight, kg (Mean±SD)	49.9 ± 4.8	58.6 ± 5.9	72.8 ± 8.0	92.6 ± 14.5
Gestational weight gain (n, %)				
<10 lbs	2 (4.3)	6 (0.9)	4 (2.2)	15 (15.6)
10-14 lbs	3 (6.4)	19 (2.8)	14 (7.8)	5 (5.2)
15-19 lbs	6 (12.8)	46 (6.8)	20 (11.2)	12 (12.5)
20-29 lbs	10 (21.3)	221 (32.7)	53 (29.6)	26 (27.1)
30-39 lbs	11 (23.4)	188 (27.8)	45 (25.1)	17 (17.7)
40-49 lbs	7 (14.9)	101 (14.9)	24 (13.4)	10 (10.4)
≥50 lbs	6 (12.8)	84 (12.4)	17 (9.5)	6 (6.3)
Missing	2 (4.3)	11 (1.6)	2 (1.1)	5 (5.2)
Gestational weight gain adequacy based on the 2009 IOM guidelines (n, %)				
Inadequate (below guidelines)	20 (42.6)	79 (11.7)	20 (11.2)	13 (13.5)
Adequate (within guidelines)	11 (23.4)	417 (61.7)	73 (40.8)	18 (18.8)
Excessive (above guidelines)	12 (25.5)	164 (24.3)	83 (46.4)	58 (60.4)
Missing	4 (8.5)	16 (2.4)	3 (1.7)	7 (7.3)
Maternal recreational physical activity during pregnancy (N, %)				
Inactive, no walking or other regular exercise	4 (8.5)	70 (10.4)	27 (15.1)	25 (26.0)
Mostly inactive, equivalent to walking about half a mile or less every day	10 (21.3)	131 (19.4)	56 (31.3)	27 (28.1)
Somewhat active, equivalent to walking about 1 mile every day	11 (23.4)	169 (25.0)	32 (17.9)	10 (10.4)
Active, equivalent to walking about 2 miles every day	18 (38.3)	255 (37.7)	62 (34.6)	33 (34.4)
Highly active, equivalent to walking about 3 or more miles every day	4 (8.5)	50 (7.4)	2 (1.1)	1 (1.0)
Missing	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Maternal physical activity at home during pregnancy (N, %)				
Mostly sitting	4 (8.5)	129 (19.1)	39 (21.8)	28 (29.2)
Mostly walking and standing, with some sitting	18 (38.3)	265 (39.2)	78 (43.6)	36 (37.5)
Active housework most of the time with little sitting	24 (51.1)	275 (40.7)	62 (34.6)	30 (31.3)
Heavy manual work at home	0 (0.0)	4 (0.6)	0 (0.0)	1 (1.0)
Missing	1 (2.1)	3 (0.4)	0 (0.0)	1 (1.0)

Maternal physical activity at work during pregnancy (N, %)				
Not working	13 (27.7)	120 (17.8)	41 (22.9)	28 (29.2)
Mostly sitting and standing	13 (27.7)	282 (41.7)	74 (41.3)	35 (36.5)
Mostly walking with some sitting and standing	20 (42.6)	244 (36.1)	60 (33.5)	28 (29.2)
Mostly heavy labor with some walking and standing and little sitting	1 (2.1)	29 (4.3)	4 (2.2)	4 (4.2)
Missing	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.0)
Maternal physical activity during pregnancy, 2nd trimester (N, %)				
Stayed the same	32 (68.1)	489 (72.3)	133 (74.3)	64 (66.7)
Substantially increased	2 (4.3)	36 (5.3)	10 (5.6)	6 (6.3)
Substantially decreased	13 (27.7)	151 (22.3)	36 (20.1)	26 (27.1)
Gestational diabetes during pregnancy with LEGACY daughter (N, %)				
Yes	4 (8.5)	32 (4.7)	19 (10.6)	19 (19.8)
No	42 (89.4)	636 (94.1)	158 (88.3)	74 (77.1)
Missing	1 (2.1)	8 (1.2)	2 (1.1)	3 (3.1)
Gestational hypertension, toxemia or pre-eclampsia during pregnancy with LEGACY daughter (N, %)				
Yes	2 (4.3)	30 (4.4)	20 (11.2)	20 (20.8)
No	44 (93.6)	636 (94.1)	157 (87.7)	73 (76.0)
Missing	1 (2.1)	10 (1.5)	2 (1.1)	3 (3.1)
Type of gestation (N, %)				
Multiple	2 (4.3)	36 (5.3)	5 (2.8)	2 (2.1)
Singleton	45 (95.7)	635 (93.9)	173 (96.7)	92 (95.8)
Missing	0 (0.0)	5 (0.7)	1 (0.6)	2 (2.1)
Birth order (Mean±SD)	1.5 ± 0.7	1.7 ± 0.9	1.9 ± 1.0	2.1 ± 1.2
Birth order, dichotomized (N, %)				
First-born	29 (61.7)	324 (47.9)	78 (43.6)	30 (31.3)
Not first-born	18 (38.3)	347 (51.3)	100 (55.9)	64 (66.7)
Missing	0 (0.0)	5 (0.7)	1 (0.6)	2 (2.1)
Gestational age in weeks (Mean±SD)	39.1 ± 1.9	39.0 ± 2.2	39.1 ± 2.0	39.0 ± 1.6
Gestational age, categorized (N, %)				
<37 weeks	4 (8.5)	89 (13.2)	18 (10.1)	8 (8.3)
≥37 weeks	43 (91.5)	585 (86.5)	161 (89.9)	87 (90.6)
Missing	0 (0.0)	2 (0.3)	0 (0.0)	1 (1.0)
Intrauterine smoke exposure (N, %)				
Yes	2 (4.3)	7 (1.0)	6 (3.4)	4 (4.2)
No	45 (95.7)	669 (99.0)	173 (96.7)	92 (95.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Birthweight, g (Mean±SD)	3173.4 ± 624.8	3264.3 ± 584.3	3368.7 ± 562.3	3430.0 ± 525.0

Birthweight, categorized (N, %)				
<2500g	3 (6.4)	59 (8.7)	11 (6.2)	4 (4.2)
2500-2999g	9 (19.2)	130 (19.2)	23 (12.9)	14 (14.6)
3000-3499g	24 (51.1)	252 (37.3)	66 (36.9)	36 (37.5)
3500-3999g	8 (17.0)	182 (26.9)	56 (31.3)	26 (27.1)
≥4000g	3 (6.4)	50 (7.4)	19 (10.6)	16 (16.7)
Missing	0 (0.0)	3 (0.4)	4 (2.2)	0 (0.0)
Birthlength, cm (Mean±SD)	50.3 ± 3.4	50.5 ± 3.7	50.5 ± 3.7	51.1 ± 2.9
Birthlength categorized (N, %)				
<48.25	3 (6.4)	78 (11.5)	17 (9.5)	7 (7.3)
48.25-50.74	18 (38.3)	174 (25.7)	53 (29.6)	27 (28.1)
50.75-53.24	15 (31.9)	144 (21.3)	31 (17.3)	17 (17.7)
≥53.25	7 (14.9)	199 (29.4)	55 (30.7)	32 (33.3)
Missing	4 (8.5)	81 (12.0)	23 (12.9)	13 (13.5)
Ponderal index at birth, kg/m^3 (Mean±SD)	25.5 ± 3.8	25.6 ± 5.3	26.7 ± 8.5	25.6 ± 4.0
Ponderal index at birth, categorized (N, %)				
<22.98	12 (25.5)	163 (24.1)	35 (19.6)	23 (24.0)
22.98-25.21	10 (21.3)	147 (21.8)	40 (22.4)	15 (15.6)
25.22-28.11	11 (23.4)	144 (21.3)	33 (18.4)	30 (31.3)
≥28.12	10 (21.3)	141 (20.9)	48 (26.8)	15 (15.6)
Missing	4 (8.5)	81 (12.0)	23 (12.9)	13 (13.5)
Baseline characteristics				
Age at baseline (Mean±SD)[a]	10.2 ± 2.3	10.0 ± 2.4	9.9 ± 2.3	9.6 ± 2.5
BMI-for-age percentile at baseline, (Mean±SD)[a]	38.0 ± 29.6	46.2 ± 29.0	60.5 ± 30.1	71.6 ± 29.2
BMI-for-age percentile at baseline, categorized (N, %)a				
≥85th BMI-for-age percentile	3 (6.4)	75 (11.1)	48 (26.8)	43 (44.8)
<85th BMI-for-age percentile	44 (93.6)	569 (84.2)	121 (67.6)	47 (49.0)
Missing	0 (0.0)	32 (4.7)	10 (559.0)	6 (6.3)
History of breast cancer in a first- or second-degree relative (N, %)				
BCFH+	23 (48.9)	352 (52.1)	94 (52.5)	46 (47.9)
BCFH-	24 (51.1)	324 (47.9)	85 (47.5)	50 (52.1)
BOADICEA lifetime risk score (Mean±SD)	14.1 ± 4.5	14.7 ± 4.8	14.9 ± 4.9	13.5 ± 3.8
Study site				
Philadelphia	5 (10.6)	112 (16.6)	18 (10.1)	15 (15.6)
New York	8 (17.0)	117 (17.3)	33 (18.4)	15 (15.6)
Utah	8 (17.0)	121 (17.9)	26 (14.5)	11 (11.5)
Ontario	10 (21.3)	118 (17.5)	24 (13.4)	15 (15.6)
Northern California	16 (34.0)	208 (30.8)	78 (43.6)	40 (41.7)
Race/ethnicity				
Non-Hispanic white	24 (51.1)	466 (68.9)	92 (51.4)	45 (46.9)
Non-Hispanic black	5 (10.6)	29 (4.3)	18 (10.1)	22 (22.9)

Hispanic	6 (12.8)	100 (14.8)	54 (30.2)	20 (20.8)
Asian/Pacific Islander	9 (19.2)	67 (9.9)	8 (4.5)	4 (4.2)
Other or mixed race/ethnicity	3 (6.4)	14 (2.1)	7 (3.9)	5 (5.2)
Maternal education				
Some college, vocational or technical school or less	11 (23.4)	158 (23.4)	56 (31.3)	48 (50.0)
Bachelor's degree	20 (42.6)	250 (37.0)	65 (36.3)	28 (29.2)
Graduate degree	15 (31.9)	253 (37.4)	54 (30.2)	15 (15.6)
Missing	1 (2.1)	15 (2.2)	4 (2.2)	5 (5.2)
Paternal education				
Some college, vocational or technical school or less	18 (38.3)	189 (28.0)	66 (36.9)	53 (55.2)
Bachelor's degree	14 (29.8)	205 (30.3)	49 (27.4)	20 (20.8)
Graduate degree	13 (27.7)	255 (37.7)	48 (26.8)	10 (10.4)
Missing	2 (4.3)	27 (4.0)	16 (8.9)	13 (13.5)
Maternal age at menarche (Mean±SD)	13.4 ± 1.6	12.9 ± 1.5	12.4 ± 1.5	11.7 ± 1.5
Maternal age at menarche, categorized				
<12 years	5 (10.6)	98 (14.5)	48 (26.8)	41 (42.7)
12-13 years	21 (44.7)	384 (56.8)	96 (53.6)	38 (39.6)
≥14 years	21 (44.7)	183 (27.1)	26 (14.5)	12 (12.5)
Missing	0 (0.0)	11 (1.6)	9 (5.0)	5 (5.2)

[a]Age at pilot baseline visit for girls with pilot data (N=21)

Supplemental Table 3.2. Descriptive characteristics of the LEGACY Girls Study cohort by breast cancer family history

	BCFH+ (N=530)	BCFH- (N=501)
Early-life characteristics		
Maternal age at birth (Mean±SD)	32.8 ± 5.1	31.5 ± 5.7
Maternal height, m (Mean±SD)	1.6 ± 0.1	1.6 ± 0.1
Maternal pre-pregnancy weight, kg (Mean±SD)	64.3 ± 12.9	63.7 ± 13.7
Maternal pre-pregnancy BMI (Mean±SD)	23.8 ± 4.8	23.7 ± 5.0
Maternal pre-pregnancy BMI, categorized (N, %)		
<18.5	23 (4.3)	24 (4.8)
18.5 to <25	352 (66.4)	324 (64.7)
25 to <30	94 (17.7)	85 (17.0)
≥30	46 (8.7)	50 (10.0)
Missing	15 (2.8)	18 (3.6)
Gestational weight gain (n, %)		
<10 lbs	15 (2.8)	12 (2.4)
10-14 lbs	24 (4.5)	18 (3.6)
15-19 lbs	43 (8.1)	43 (8.6)
20-29 lbs	174 (32.8)	142 (28.3)
30-39 lbs	132 (24.9)	132 (26.4)
40-49 lbs	68 (12.8)	77 (15.4)
≥50 lbs	53 (10.0)	60 (12.0)
Missing	21 (4.0)	17 (3.4)
Gestational weight gain adequacy based on the 2009 IOM guidelines (n, %)		
Inadequate (below guidelines)	77 (14.5)	55 (11.0)
Adequate (within guidelines)	265 (50.0)	254 (50.7)
Excessive (above guidelines)	157 (29.6)	160 (31.9)
Missing	31 (5.9)	32 (6.4)
Maternal recreational physical activity during pregnancy (N, %)		
Inactive, no walking or other regular exercise	74 (14.0)	54 (10.8)
Mostly inactive, equivalent to walking about half a mile or less every day	130 (24.5)	105 (21.0)
Somewhat active, equivalent to walking about 1 mile every day	105 (19.8)	117 (23.4)
Active, equivalent to walking about 2 miles every day	188 (35.5)	191 (38.1)
Highly active, equivalent to walking about 3 or more miles every day	31 (5.9)	26 (5.2)
Missing	2 (0.4)	8 (0.4)
Maternal physical activity at home during pregnancy (N, %)		
Mostly sitting	98 (18.5)	111 (22.2)
Mostly walking and standing, with some sitting	207 (39.1)	196 (39.1)
Active housework most of the time with little sitting	219 (41.3)	181 (36.1)

Heavy manual work at home	2 (0.4)	3 (0.6)
Missing	4 (0.8)	10 (2.0)
Maternal physical activity at work during pregnancy (N, %)		
Not working	106 (20.0)	105 (21.0)
Mostly sitting and standing	222 (41.9)	191 (38.1)
Mostly walking with some sitting and standing	183 (34.5)	174 (34.7)
Mostly heavy labor with some walking and standing and little sitting	17 (3.2)	22 (4.4)
Missing	2 (0.4)	9 (1.8)
Maternal physical activity during pregnancy, 2nd trimester (N, %)		
Stayed the same	382 (72.1)	355 (70.9)
Substantially increased	26 (4.9)	28 (5.6)
Substantially decreased	120 (22.6)	111 (22.2)
Missing	2 (0.4)	7 (1.4)
Gestational diabetes during pregnancy with LEGACY daughter (N, %)		
Yes	43 (8.1)	35 (7.0)
No	479 (90.4)	451 (90.0)
Missing	8 (1.5)	15 (3.0)
Gestational hypertension, toxemia or pre-eclampsia during pregnancy with LEGACY daughter (N, %)		
Yes	39 (7.4)	35 (7.0)
No	483 (91.1)	449 (89.6)
Missing	8 (1.5)	17 (3.4)
Type of gestation (N, %)		
Multiple	19 (3.6)	26 (5.2)
Singleton	506 (95.5)	464 (92.6)
Missing	5 (0.9)	11 (2.2)
Birth order (Mean±SD)	1.8 ± 0.9	1.8 ± 1.0
Birth order, dichotomized (N, %)		
First-born	239 (45.1)	231 (46.1)
Not first-born	286 (54.0)	259 (51.7)
Missing	5 (0.9)	11 (2.2)
Gestational age in weeks (Mean±SD)	39.0 ± 2.1	39.0 ± 2.2
Gestational age, categorized (N, %)		
<37 weeks	62 (11.7)	58 (11.6)
≥37 weeks	459 (86.6)	434 (86.6)
Missing	9 (1.7)	9 (1.8)
Intrauterine smoke exposure (N, %)		
Yes	13 (2.5)	6 (1.2)
No	513 (96.8)	487 (97.2)
Missing	4 (0.8)	8 (1.6)
Birthweight, g (Mean±SD)	3302.3 ± 574.0	3294.0 ± 593.6

Birthweight, categorized (N, %)		
<2500g	44 (8.3)	34 (6.8)
2500-2999g	86 (16.2)	93 (18.6)
3000-3499g	196 (37.0)	192 (38.3)
3500-3999g	154 (29.1)	125 (25.0)
≥4000g	45 (8.5)	49 (9.8)
Missing	5 (0.9)	8 (1.6)
Birthlength, cm (Mean±SD)	50.4 ± 3.4	50.7 ± 3.8
Birthlength categorized (N, %)		
<48.25	57 (10.8)	49 (9.8)
48.25-50.74	150 (28.3)	127 (25.4)
50.75-53.24	106 (20.0)	109 (21.8)
≥53.25	149 (28.1)	151 (30.1)
Missing	68 (12.8)	65 (13.0)
Ponderal index at birth, kg/m^3 (Mean±SD)	26.0 ± 6.1	25.6 ± 5.5
Ponderal index at birth, categorized (N, %)		
<22.98	116 (21.9)	122 (24.4)
22.98-25.21	121 (22.8)	96 (19.2)
25.22-28.11	112 (21.1)	113 (22.6)
≥28.12	113 (21.3)	105 (21.0)
Missing	68 (12.8)	65 (13.0)
Baseline characteristics		
Age at baseline (Mean±SD)[a]	10.1 ± 2.5	9.8 ± 2.3
BMI-for-age percentile at baseline, (Mean±SD)[a]	52.1 ± 30.4	49.4 ± 30.5
BMI-for-age percentile at baseline, categorized (N, %)[a]		
≥85th BMI-for-age percentile	91 (17.2)	83 (16.6)
<85th BMI-for-age percentile	410 (77.4)	396 (79.0)
Missing	29 (5.5)	22 (4.4)
BOADICEA lifetime risk score (Mean±SD)	17.9 ± 4.7	11.1 ± 0.4
Study site		
Philadelphia	90 (17.0)	63 (12.6)
New York	80 (15.1)	95 (19.0)
Utah	78 (14.7)	95 (19.0)
Ontario	90 (17.0)	89 (17.8)
Northern California	192 (36.2)	159 (31.7)
Race/ethnicity		
Non-Hispanic white	352 (66.4)	298 (59.5)
Non-Hispanic black	29 (5.5)	49 (9.8)
Hispanic	100 (18.9)	84 (16.8)
Asian/Pacific Islander	38 (7.2)	50 (10.0)
Other or mixed race/ethnicity	11 (2.1)	20 (4.0)
Maternal education		

Some college, vocational or technical school or less	139 (26.2)	148 (29.5)
Bachelor's degree	190 (35.9)	183 (36.5)
Graduate degree	181 (34.2)	165 (32.9)
Missing	20 (3.8)	5 (1.0)
Paternal education		
Some college, vocational or technical school or less	168 (31.7)	171 (34.1)
Bachelor's degree	164 (30.9)	134 (26.8)
Graduate degree	166 (31.3)	167 (33.3)
Missing	32 (6.0)	29 (5.8)
Maternal age at menarche (Mean±SD)	12.7 ± 1.6	12.7 ± 1.5
Maternal age at menarche, categorized		
<12 years	96 (18.1)	104 (20.8)
12-13 years	281 (53.0)	277 (55.3)
≥14 years	135 (25.5)	112 (22.4)
Missing	18 (3.4)	8 (1.6)

[a]Age at pilot baseline visit for girls with pilot data (N=21)

Supplemental Table 3.3. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal pre-pregnancy BMI and GWG, categorized by the 2009 IOM guidelines, and the onset of breast development for the overall cohort and girls age <8 years at baseline

	Overall cohort					***Girls <8 years at baseline***				
		Unadjusted		Adjusted[a]			Unadjusted		Adjusted[b]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Gestational weight gain adequacy by the modified 2009 IOM guidelines										
Below guidelines	132	0.994 (0.961, 1.027)	1.05 (0.81, 1.36)	1.003 (0.969, 1.038)	0.98 (0.74, 1.29)	27	1.021 (0.933, 1.112)	0.86 (0.45, 1.65)	1.031 (0.949, 1.121)	0.79 (0.42, 1.48)
Within guidelines	513	Reference	Reference	Reference	Reference	130	Reference	Reference	Reference	Reference
Exceeding guidelines	313	**0.968 (0.946, 0.992)**	**1.28 (1.07, 1.54)**	0.981 (0.958, 1.006)	1.16 (0.96, 1.41)	80	0.956 (0.907, 1.007)	1.38 (0.95, 2.02)	0.969 (0.914, 1.028)	1.27 (0.81, 1.98)
Maternal pre-pregnancy BMI and GWG guidelines										
BMI<25 and did not exceed guidelines	521	Reference	Reference	Reference	Reference	122	Reference	Reference	Reference	Reference
BMI<25 and exceeded guidelines	173	0.982 (0.955, 1.009)	1.15 (0.93, 1.43)	0.980 (0.953, 1.007)	1.18 (0.94, 1.47)	40	**0.915 (0.855, 0.979)**	**1.92 (1.18, 3.14)**	**0.917 (0.857, 0.980)**	**1.92 (1.17, 3.16)**
BMI≥25 and did not exceed guidelines	124	0.977 (0.930, 1.026)	1.20 (0.81, 1.77)	0.989 (0.942, 1.037)	1.10 (0.75, 1.61)	35	**0.906 (0.846, 0.971)**	**2.06 (1.26, 3.35)**	0.935 (0.870, 1.005)	1.65 (0.99, 2.78)
BMI≥25 and exceeded guidelines	140	**0.942 (0.913, 0.972)**	**1.59 (1.25, 2.03)**	**0.957 (0.928, 0.988)**	**1.41 (1.10, 1.82)**	40	0.949 (0.887, 1.016)	1.47 (0.90, 2.40)	0.957 (0.889, 1.031)	1.39 (0.80, 2.41)

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).
[b]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).

Supplemental Table 3.4. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal physical activity during pregnancy and the onset of breast development with adjustment for GWG for the overall cohort and girls age <8 years at baseline

	Overall cohort[a]		Girls <8 years[b]	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Recreational physical activity				
Inactive, no walking or other regular exercise	0.977 (0.941, 1.015)	1.20 (0.89, 1.63)	**0.933 (0.873, 0.998)**	**1.70 (1.02, 2.83)**
Mostly inactive, equivalent to walking about half a mile or less every day	1.006 (0.976, 1.038)	0.95 (0.74, 1.22)	1.012 (0.951, 1.077)	0.91 (0.56, 1.47)
Somewhat active, equivalent to walking about 1 mile every day	1.010 (0.983, 1.038)	0.93 (0.75, 1.15)	1.008 (0.949, 1.071)	0.94 (0.59, 1.51)
Active or highly active, equivalent to walking 2 miles or more every day	Reference	Reference	Reference	Reference
Physical activity at home				
Mostly sitting	1.013 (0.981, 1.046)	0.90 (0.70, 1.17)	0.974 (0.912, 1.041)	1.22 (0.74, 2.02)
Mostly walking and standing, with some sitting	Reference	Reference	Reference	Reference
Active housework most of the time with little sitting or heavy manual labor	1.019 (0.995, 1.044)	0.86 (0.70, 1.04)	0.994 (0.942, 1.048)	1.05 (0.70, 1.57)
Physical activity at work				
Not working outside the home	**1.033 (1.003, 1.063)**	**0.77 (0.61, 0.98)**	**1.089 (1.021, 1.163)**	**0.52 (0.31, 0.86)**
Mostly sitting and standing	Reference	Reference	Reference	Reference
Mostly walking or heavy labor	1.004 (0.980, 1.028)	0.97 (0.80, 1.18)	1.016 (0.964, 1.070)	0.89 (0.59, 1.33)

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other), maternal education (some college or less, Bachelor's degree, graduate degree), maternal pre-pregnancy BMI (continuous) and gestational weight gain (<20lbs, 20-29 lbs, 30-39lbs, 40-49lbs, ≥50lbs).
[b]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree), maternal pre-pregnancy BMI (continuous) and gestational weight gain (<20lbs, 20-29 lbs, 30-39lbs, 40-49lbs, ≥50lbs).

Supplemental Table 3.5. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between size at birth and the onset of breast development for the overall cohort and girls age <8 years at baseline

	Overall cohort					***Girls <8 years at baseline***				
		Adjusted for weight and length only[a]		Multivariable-adjusted[b]			Adjusted for weight and length only[a]		Multivariable-adjusted[c]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Birthweight										
<2500g	62	1.003 (0.955, 1.053)	0.98 (0.67, 1.43)	0.989 (0.937, 1.045)	1.09 (0.70, 1.70)	17	1.057 (0.925, 1.210)	0.67 (0.25, 1.77)	1.054 (0.904, 1.229)	0.66 (0.20, 2.21)
2500-2999g	157	1.008 (0.975, 1.041)	0.94 (0.73, 1.22)	1.013 (0.982, 1.046)	0.90 (0.69, 1.16)	38	0.997 (0.927, 1.073)	1.02 (0.60, 1.74)	1.012 (0.935, 1.100)	0.91 (0.49, 1.69)
3000-3499g	345	Reference	Reference	Reference	Reference	91	Reference	Reference	Reference	Reference
3500-3999g	247	1.012 (0.988, 1.037)	0.91 (0.75, 1.10)	1.010 (0.986, 1.034)	0.92 (0.76, 1.12)	57	1.006 (0.940, 1.076)	0.96 (0.59, 1.56)	0.993 (0.932, 1.058)	1.06 (0.64, 1.74)
≥4000g	79	0.981 (0.938, 1.025)	1.16 (0.82, 1.64)	0.997 (0.953, 1.043)	1.03 (0.71, 1.48)	22	0.967 (0.876, 1.067)	1.28 (0.62, 2.61)	0.981 (0.882, 1.092)	1.16 (0.50, 2.70)
Per 500g increase	890	0.996 (0.984, 1.008)	1.03 (0.94, 1.13)	1.000 (0.987, 1.014)	1.00 (0.90, 1.12)	225	0.988 (0.958, 1.020)	1.09 (0.87, 1.37)	0.987 (0.950, 1.026)	1.11 (0.81, 1.50)
Birthlength										
<48.25	104	1.012 (0.973, 1.052)	0.91 (0.67, 1.24)	1.011 (0.970, 1.054)	0.91 (0.65, 1.28)	28	1.085 (0.980, 1.202)	0.55 (0.26, 1.16)	1.051 (0.951, 1.161)	0.68 (0.31, 1.47)
48.25-50.74	276	Reference	Reference	Reference	Reference	64	Reference	Reference	Reference	Reference
50.75-53.24	213	0.997 (0.970, 1.025)	1.03 (0.83, 1.27)	0.988 (0.962, 1.015)	1.10 (0.88, 1.37)	58	1.058 (0.983, 1.138)	0.67 (0.39, 1.15)	1.028 (0.961, 1.101)	0.81 (0.47, 1.37)
≥53.25	297	0.994 (0.967, 1.022)	1.05 (0.85, 1.29)	0.991 (0.965, 1.017)	1.08 (0.88, 1.33)	75	1.009 (0.931, 1.094)	0.93 (0.52, 1.68)	1.020 (0.952, 1.093)	0.86 (0.50, 1.48)
Per 1 cm increase	890	0.998 (0.994, 1.002)	1.02 (0.99, 1.05)	0.998 (0.994, 1.002)	1.02 (0.99, 1.05)	225	1.001 (0.991, 1.009)	1.00 (0.93, 1.07)	1.005 (0.998, 1.013)	0.96 (0.91, 1.02)
Ponderal index										
<22.98	234	1.002 (0.974, 1.032)	0.98 (0.79, 1.23)	0.994 (0.967, 1.023)	1.05 (0.83, 1.32)	56	1.015 (0.946, 1.088)	0.90 (0.54, 1.49)	1.009 (0.943, 1.079)	0.94 (0.55, 1.59)
22.98-25.21	216	Reference	Reference	Reference	Reference	57	Reference	Reference	Reference	Reference
25.22-28.11	222	1.003 (0.973, 1.033)	0.98 (0.78, 1.24)	1.003 (0.974, 1.034)	0.97 (0.76, 1.24)	63	1.008 (0.948, 1.072)	0.94 (0.60, 1.47)	0.993 (0.939, 1.062)	1.05 (0.62, 1.78)
≥28.12	218	1.009 (0.980, 1.038)	0.93 (0.75, 1.17)	1.009 (0.981, 1.038)	0.93 (0.74, 1.17)	49	0.982 (0.910, 1.059)	1.14 (0.66, 1.96)	0.961 (0.901, 1.026)	1.36 (0.82, 2.25)
Per 1 kg/m^3 increase	890	1.000 (0.998, 1.003)	1.00 (0.98, 1.02)	1.001 (0.998, 1.003)	0.99 (0.98, 1.01)	225	0.999 (0.996, 1.002)	1.01 (0.99, 1.03)	0.998 (0.996, 1.000)	1.02 (1.00, 1.03)

[a]Mutually adjusted for birthweight and birthlength. Categorical model adjusted for other measure as continuous variable.

[b]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other), maternal education (some college or less, Bachelor's degree, graduate degree), maternal pre-pregnancy BMI (continuous), gestational weight gain (<20lbs, 20-29 lbs, 30-39lbs, 40-49lbs, ≥50lbs) and gestational age in weeks.
[c]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree), maternal pre-pregnancy BMI (continuous), gestational weight gain (<20lbs, 20-29 lbs, 30-39lbs, 40-49lbs, ≥50lbs) and gestational age in weeks.

Supplemental Table 3.6. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between birthweight and birthlength groups and the onset of breast development for the overall cohort and girls age <8 years at baseline

	Overall cohort					***Girls <8 years at baseline***				
		Adjusted for weight and length only[a]		Multivariable-adjusted[b]			Adjusted for weight and length only[a]		Multivariable-adjusted[c]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Birthweight & birthlength groups, defined by the median										
Long/light	164	0.973 (0.933, 1.016)	1.23 (0.89, 1.71)	0.976 (0.939, 1.014)	1.22 (0.90, 1.66)	42	0.990 (0.883, 1.110)	1.07 (0.47, 2.44)	1.015 (0.926, 1.111)	0.89 (0.44, 1.81)
Long/heavy	347	0.985 (0.948, 1.023)	1.13 (0.84, 1.51)	0.983 (0.945, 1.018)	1.15 (0.87, 1.53)	91	1.020 (0.918, 1.134)	0.87 (0.41, 1.85)	1.038 (0.955, 1.128)	0.75 (0.40, 1.42)
Short/light	278	0.992 (0.951, 1.035)	1.06 (0.77, 1.47)	0.989 (0.951, 1.028)	1.10 (0.80, 1.51)	70	1.007 (0.903, 1.123)	0.95 (0.43, 2.09)	1.024 (0.934, 1.123)	0.83 (0.41, 1.68)
Short/heavy	101	Reference	Reference	Reference	Reference	22	Reference	Reference	Reference	Reference

[a]Mutually adjusted for birthweight and birthlength. Categorical model adjusted for other measure as continuous variable.

[b]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other), maternal education (some college or less, Bachelor's degree, graduate degree), maternal pre-pregnancy BMI (continuous), gestational weight gain (<20lbs, 20-29 lbs, 30-39lbs, 40-49lbs, ≥50lbs) and gestational age in weeks.

[c]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree), maternal pre-pregnancy BMI (continuous), gestational weight gain (<20lbs, 20-29 lbs, 30-39lbs, 40-49lbs, ≥50lbs) and gestational age in weeks.

Supplemental Table 3.7. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between maternal pre-pregnancy BMI, recreational physical activity during pregnancy and GWG in girls with a BMI less than the 85th percentile for age

	Subset of cohort with pre-pubertal BMI measures, excluding girls with BMI-for-age percentile ≥85					***Girls <8 years at baseline, excluding girls with BMI-for-age percentile ≥85***				
		Multivariable-adjusted[a]		Additional adjustment for daughter's body size[b]			Multivariable-adjusted[c]		Additional adjustment for daughter's body size[d]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Maternal pre-pregnancy BMI										
<18.5	25	1.031 (0.987, 1.077)	0.77 (0.53, 1.12)	1.027 (0.983, 1.072)	0.80 (0.55, 1.16)		*Those with BMI<18.5 are in referent group due to small numbers			
18.5 to <25	346	Reference	Reference	Reference	Reference	141	Reference	Reference	Reference	Reference
25 to <30	70	0.975 (0.928, 1.024)	1.25 (0.81, 1.92)	0.977 (0.930, 1.026)	1.22 (0.79, 1.88)	34	0.992 (0.933, 1.055)	1.07 (0.64, 1.81)	1.016 (0.954, 1.083)	0.87 (0.50, 1.51)
≥30	28	0.973 (0.923, 1.026)	1.27 (0.81, 1.99)	0.980 (0.930, 1.032)	1.19 (0.76, 1.87)	16	0.981 (0.898, 1.071)	1.18 (0.56, 2.51)	1.008 (0.919, 1.017)	0.93 (0.41, 2.10)
Continuous (per kg/m^2)	469	**0.996 (0.992, 0.999)**	**1.04 (1.01, 1.07)**	**0.996 (0.993, 1.000)**	**1.03 (1.00, 1.07)**	191	0.997 (0.991, 1.002)	1.03 (0.98, 1.08)	0.999 (0.993, 1.005)	1.01 (0.96, 1.06)
Recreational physical activity[b]										
Inactive, no walking or other regular exercise	50	0.975 (0.925, 1.028)	1.24 (0.78, 1.98)	0.971 (0.921, 1.023)	1.29 (0.81, 2.06)	22	0.952 (0.892, 1.016)	1.54 (0.87, 2.71)	**0.938 (0.883, 0.997)**	**1.78 (1.03, 3.08)**
Mostly inactive, equivalent to walking about half a mile or less every day	110	0.994 (0.962, 1.028)	1.05 (0.78, 1.41)	0.992 (0.959, 1.026)	1.07 (0.80, 1.44)	47	1.027 (0.962, 1.100)	0.79 (0.45, 1.40)	1.022 (0.955, 1.093)	0.82 (0.45, 1.51)
Somewhat active, equivalent to walking about 1 mile every day	109	1.018 (0.984, 1.054)	0.85 (0.63, 1.16)	1.014 (0.978, 1.052)	0.88 (0.64, 1.21)	44	1.019 (0.957, 1.086)	0.85 (0.48, 1.47)	1.012 (0.951, 1.077)	0.90 (0.51, 1.58)
Active or highly active, equivalent to walking 2 miles or more every day	200	Reference	Reference	Reference	Reference	78	Reference	Reference	Reference	Reference
Gestational weight gain[b]										
<20lbs	71	0.987 (0.944, 1.032)	1.12 (0.76, 1.66)	0.988 (0.944, 1.034)	1.11 (0.75, 1.65)	26	0.944 (0.868, 1.028)	1.66 (0.80, 3.48)	0.948 (0.873, 1.029)	1.64 (0.78, 3.42)
20-29 lbs	137	Reference	Reference	Reference	Reference	63	Reference	Reference	Reference	Reference
30-39 lbs	129	0.985 (0.951, 1.021)	1.14 (0.83, 1.56)	0.986 (0.952, 1.022)	1.13 (0.83, 1.54)	51	**0.917 (0.860, 0.977)**	**2.17 (1.25, 3.76)**	**0.922 (0.864, 0.984)**	**2.10 (1.18, 3.73)**
40-49 lbs	70	0.958 (0.918, 1.000)	1.45 (1.00, 2.12)	0.961 (0.919, 1.005)	1.42 (0.96, 2.09)	27	**0.906 (0.843, 0.975)**	**2.40 (1.25, 4.61)**	**0.903 (0.840, 0.971)**	**2.54 (1.29, 4.99)**
≥50 lbs	48	0.956 (0.911, 1.004)	1.48 (0.96, 2.26)	0.958 (0.912, 1.007)	1.45 (0.94, 2.23)	20	0.927 (0.841, 1.023)	1.96 (0.82, 4.66)	0.917 (0.835, 1.007)	2.21 (0.94, 5.21)

Maternal pre-pregnancy BMI and GWG[a]										
BMI<25 and <30 lbs	160	Reference	Reference	Reference	Reference	61	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	201	0.979 (0.949, 1.010)	1.20 (0.919, 1.57)	0.980 (0.949, 1.012)	1.20 (0.91, 1.58)	77	**0.910 (0.853, 0.970)**	**2.32 (1.32, 4.07)**	**0.912 (0.856, 0.972)**	**2.31 (1.31, 4.10)**
BMI≥25 and <30lbs	48	0.974 (0.916, 1.035)	1.26 (0.74, 2.15)	0.975 0.917, 1.037)	1.25 (0.73, 2.12)	28	0.940 (0.872, 1.013)	1.73 (0.91, 3.31)	0.965 (0.896, 1.040)	1.38 (0.70, 2.72)
BMI≥25 and ≥30 lbs	46	**0.947 (0.898, 0.997)**	**1.61 (1.02, 2.54)**	0.953 (0.905, 1.005)	1.51 (0.95, 2.39)	21	0.932 (0.840, 1.034)	1.87 (0.75, 4.70)	0.963 (0.863, 1.075)	1.41 (0.52, 3.83)

[a]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).
[b]Adjusted for everything in [a] plus daughter's BMI-for-age percentile between age 5-7 years and interaction between BMI-for-age percentile and centered age at BMI measure.
[c]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree). Model for GWG also adjusted for maternal pre-pregnancy BMI (continuous).
[d]Adjusted for everything in [b] plus daughter's BMI-for-age percentile between age 5-7 years and interaction between BMI-for-age percentile and centered age at BMI measure

Supplemental Table 3.8. Sensitivity analyses for associations between maternal pre-pregnancy BMI and GWG and the onset of breast development for the overall cohort by modeling strategy using mother-reported Sexual Maturation Scale (SMS)

		Mother SMS Model 1[a]		Mother SMS Model 2[b]		Mother SMS Model 3[c]		
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	Cox model: HR (95% CI)
Maternal pre-pregnancy BMI[d]								
<18.5	46	**1.055 (1.011, 1.101)**	0.65 (0.46, 0.92)	1.037 (0.999, 1.077)	0.73 (0.53, 1.02)	**1.039 (1.001, 1.078)**	**0.72 (0.53, 0.99)**	0.74 (0.54, 1.00)
18.5 to <25	649	Reference	Reference	Reference	Reference	Reference	Reference	Reference
25 to <30	174	0.993 (0.956, 1.032)	1.06 (0.78, 1.44)	0.986 (0.955, 1.018)	1.13 (0.86, 1.49)	0.986 (0.955, 1.018)	1.13 (0.86, 1.48)	1.16 (0.92, 1.47)
≥30	90	0.967 (0.930, 1.006)	1.30 (0.95, 1.79)	0.968 (0.933, 1.003)	1.33 (0.97, 1.81)	0.968 (0.934, 1.003)	1.32 (0.97, 1.80)	**1.34 (1.04, 1.74)**
Continuous (per kg/m^2)	959	**0.997 (0.994, 0.999)**	**1.03 (1.01, 1.05)**	0.998 (0.995, 1.000)	1.02 (1.00, 1.04)	0.998 (0.995, 1.000)	1.02 (1.00, 1.04)	**1.02 (1.01, 1.04)**
Gestational weight gain[e]								
<20lbs	149	0.984 (0.949, 1.021)	1.14 (0.85, 1.53)	0.989 (0.960, 1.018)	1.10 (0.86, 1.41)	0.989 (0.960, 1.018)	1.10 (0.86, 1.41)	1.06 (0.85, 1.32)
20-29 lbs	301	Reference	Reference	Reference	Reference	Reference	Reference	Reference
30-39 lbs	247	0.976 (0.948, 1.006)	1.21 (0.96, 1.53)	0.985 (0.959, 1.012)	1.14 (0.90, 1.44)	0.986 (0.959, 1.012)	1.13 (0.90, 1.43)	1.16 (0.96, 1.40)
40-49 lbs	138	0.975 (0.942, 1.008)	1.23 (0.94, 1.61)	0.987 (0.956, 1.018)	1.12 (0.86, 1.47)	0.987 (0.957, 1.018)	1.12 (0.86, 1.46)	1.11 (0.88, 1.40)
≥50 lbs	106	**0.963 (0.927, 1.000)**	**1.36 (1.00, 1.84)**	**0.968 (0.940, 0.996)**	**1.33 (1.03, 1.70)**	**0.968 (0.940, 0.997)**	**1.32 (1.03, 1.69)**	**1.26 (1.00, 1.58)**
Maternal pre-pregnancy BMI and GWG[d]								
BMI<25 and <30 lbs	306	Reference	Reference	Reference	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	378	0.986 (0.961, 1.011)	1.12 (0.92, 1.37)	0.992 (0.969, 1.015)	1.07 (0.88, 1.31)	0.992 (0.970, 1.015)	1.07 (0.88, 1.30)	1.08 (0.91, 1.28)
BMI≥25 and <30lbs	144	0.988 (0.945, 1.033)	1.10 (0.77, 1.57)	0.988 (0.953, 1.023)	1.11 (0.82, 1.51)	0.988 (0.954, 1.024)	1.11 (0.82, 1.50)	1.15 (0.88, 1.50)
BMI≥25 and ≥30 lbs	113	**0.946 (0.911, 0.982)**	**1.56 (1.16, 2.10)**	**0.950 (0.918, 0.984)**	**1.55 (1.15, 2.09)**	**0.951 (0.919, 0.984)**	**1.54 (1.14, 2.07)**	**1.57 (1.21, 2.03)**

[a]Girls with maternal report of TS≥2 at first completed growth and development questionnaire were left-censored at age of questionnaire completion. Girls that transitioned from TS1 to TS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last questionnaire were mom reported TS1 and end of the interval defined as age at first questionnaire where mom reported TS≥2. Girls without a maternal report of TS≥2 during follow-up were right censored at age of last questionnaire where mom reported TS1. This is the primary model used in the analyses and shown in Table 3.2. It is included here for easy comparison across models.

[b]Recalled age at breast development imputed as though observed for left-censored girls. Interval and right-censored girls are entered as in Model 1.

[c]Recalled age at breast development imputed as though observed for left-censored girls and midpoint of interval imputed as though observed for interval-censored girls. Right-censored girls are entered as in Model 1.

[d]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree).

[e]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other), maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).

Supplemental Table 3.9. Sensitivity analyses for associations between maternal pre-pregnancy BMI and GWG and the onset of breast development for the overall cohort by modeling strategy using mother-reported Pubertal Development Scale (PDS)

	Mother PDS Model 1[a]		Mother PDS Model 2[b]		Mother PDS Model 3[c]			Mother PDS Model 4[d]		
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	Cox model: HR (95% CI)	TR (95% CI)	HR (95% CI)	Cox model: HR (95% CI)
Maternal pre-pregnancy BMI[d]										
<18.5	1.039 (0.997,1.082)	0.73 (0.52,1.03)	1.013 (0.975,1.052)	0.90 (0.65,1.24)	1.017 (0.979,1.056)	0.87 (0.63,1.20)	0.91 (0.68,1.22)	1.007 (0.966,1.050)	0.94 (0.67,1.33)	0.97 (0.74,1.27)
18.5 to <25	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
25 to <30	0.989 (0.959,1.021)	1.09 (0.84,1.41)	0.986 (0.957,1.016)	1.12 (0.88,1.44)	0.986 (0.958,1.016)	1.12 (0.88,1.44)	1.16 (0.95,1.42)	0.986 (0.957,1.016)	1.12 (0.88,1.44)	1.15 (0.96,1.37)
≥30	0.981 (0.940,1.023)	1.17 (0.83,1.66)	0.976 (0.938,1.016)	1.23 (0.88,1.72)	0.977 (0.940,1.017)	1.21 (0.87,1.68)	1.25 (0.98,1.62)	0.974 (0.935,1.014)	1.24 (0.89,1.74)	1.26 (1.00,1.58)
Continuous (per kg/m^2)	0.998 (0.995,1.000)	1.02 (1.00,1.04)	0.999 (0.996,1.001)	1.01 (0.99,1.04)	0.999 (0.996,1.001)	1.01 (0.99,1.04)	**1.02 (1.00,1.03)**	0.999 (0.996,1.001)	1.01 (0.99,1.04)	**1.02 (1.00,1.03)**
Gestational weight gain[e]										
<20lbs	0.975 (0.940,1.012)	1.23 (0.91,1.66)	0.989 (0.961,1.018)	1.10 (0.86,1.40)	0.989 (0.961,1.017)	1.10 (0.87,1.40)	1.05 (0.86,1.29)	0.990 (0.962,1.019)	1.09 (0.86,1.38)	1.04 (0.87,1.25)
20-29 lbs	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
30-39 lbs	0.975 (0.949,1.002)	1.23 (0.99,1.54)	0.989 (0.962,1.017)	1.10 (0.87 1.39)	0.990 (0.962 1.017)	1.09 (0.86,1.38)	1.11 (0.93,1.33)	0.994 (0.967,1.023)	1.05 (0.83,1.32)	1.06 (0.90,1.24)
40-49 lbs	**0.961 (0.929,0.994)**	**1.39 (1.06,1.84)**	0.983 (0.952,1.014)	1.16 (0.89,1.51)	0.982 (0.952,1.013)	1.17 (0.90,1.52)	1.15 (0.93,1.41)	0.984 0.953,1.015)	1.15 (0.88,1.49)	1.12 (0.93,1.35)
≥50 lbs	**0.956 (0.920,0.992)**	**1.46 (1.06,2.00)**	**0.971 (0.943,0.999)**	**1.28 (1.01,1.64)**	**0.970 (0.943,0.999)**	**1.29 (1.01,1.64)**	1.22 (0.99,1.51)	**0.970 (0.942,0.999)**	**1.28 (1.01,1.62)**	1.17 (0.96,1.42)
Maternal pre-pregnancy BMI and GWG[d]										
BMI<25 and <30 lbs	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	0.982 (0.958,1.007)	1.16 (0.95,1.43)	0.994 (0.970,1.017)	1.06 (0.86,1.29)	0.994 (0.971,1.018)	1.05 (0.86,1.28)	1.06 (0.91,1.25)	0.996 (0.972,1.020)	1.04 (0.85,1.27)	1.04 (0.90,1.20)
BMI≥25 and <30lbs	0.994 (0.957,1.032)	1.05 (0.77,1.43)	0.994 (0.962,1.027)	1.05 (0.80,1.38)	0.995 (0.964,1.028)	1.04 (0.79,1.37)	1.10 (0.88,1.37)	0.993 (0.960,1.027)	1.06 (0.81,1.39)	1.10 (0.90,1.35)
BMI≥25 and ≥30 lbs	**0.948 (0.911,0.986)**	**1.56 (1.13,2.15)**	**0.957 (0.922,0.993)**	**1.45 (1.05,1.99)**	**0.957 (0.922, .993)**	**1.45 (1.06,1.98)**	**1.49 (1.16,1.90)**	**0.960 (0.924,0.997)**	**1.40 (1.02,1.91)**	**1.38 (1.11,1.73)**

[a]Girls with maternal report of PDS≥2 at first completed growth and development questionnaire were left-censored at age of questionnaire completion. Girls that transitioned from PDS1 to PDS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last questionnaire were mom reported PDS1 and end of the interval defined as age at first questionnaire where mom reported PDS≥2. Girls without a maternal report of PDS≥2 during follow-up were right censored at age of last questionnaire where mom reported PDS1.

[b]Recalled age at breast development imputed as though observed for left-censored girls. Interval and right-censored girls are entered as in Model 1.

[c]Recalled age at breast development imputed as though observed for left-censored girls and midpoint of interval imputed as though observed for interval-censored girls. Right-censored girls are entered as in Model 1.

[d]Recalled age at breast development imputed as though observed for left-censored and interval-censored girls. Right-censored girls are entered as in Model 1.
[e]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other) and maternal education (some college or less, Bachelor's degree, graduate degree).
[f]Adjusted for race (Non-Hispanic white Non-Hispanic black, Hispanic, Asian, Other), maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).

Supplemental Table 3.10. Comparison of models using mother-reported Sexual Maturation Scale (SMS) vs. Pubertal Development Scale (PDS) for associations between maternal pre-pregnancy BMI and GWG and the onset of breast development in girls <8 years of age

		Mother SMS Model 1[a]		Mother PDS Model 1[b]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Maternal pre-pregnancy BMI[c]					
<25	163	Reference	Reference	Reference	Reference
25 to <30	44	0.977 (0.921, 1.037)	1.19 (0.76, 1.86)	0.987 (0.934, 1.044)	1.11 (0.71, 1.72)
≥30	29	0.927 (0.853, 1.008)	1.77 (0.96, 3.26)	0.944 (0.871, 1.022)	1.58 (0.84, 2.98)
Continuous (per kg/m^2)	236	**0.995 (0.992, 0.999)**	**1.04 (1.01, 1.07)**	0.996 (0.992, 1.000)	1.03 (1.00, 1.06)
Gestational weight gain[d]					
<20lbs	34	0.938 (0.869, 1.013)	1.64 (0.91, 2.94)	0.960 (0.894, 1.031)	1.40 (0.78, 2.52)
20-29 lbs	74	Reference	Reference	Reference	Reference
30-39 lbs	62	**0.928 (0.872, 0.986)**	**1.78 (1.12, 2.86)**	0.953 (0.899, 1.010)	1.49 (0.93, 2.40)
40-49 lbs	32	**0.919 (0.854, 0.988)**	**1.92 (1.08, 3.40)**	**0.918 (0.863, 0.976)**	**2.02 (1.22, 3.37)**
≥50 lbs	29	0.923 (0.844, 1.009)	1.85 (0.93, 3.67)	0.942 (0.872, 1.019)	1.63 (0.86, 3.10)
Maternal pre-pregnancy BMI and GWG[c]					
BMI<25 and <30 lbs	67	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	93	**0.907 (0.848, 0.970)**	**2.11 (1.28, 3.48)**	**0.929 (0.878, 0.983)**	**1.83 (1.15, 2.89)**
BMI≥25 and <30lbs	41	**0.910 (0.839, 0.987)**	**2.05 (1.13, 3.72)**	0.939 (0.875, 1.008)	1.67 (0.94, 2.95)
BMI≥25 and ≥30 lbs	30	**0.907 (0.826, 0.996)**	**2.11 (1.04, 4.28)**	0.933 (0.856, 1.016)	1.77 (0.88, 3.54)

[a]Girls with maternal report of TS≥2 at first completed growth and development questionnaire were left-censored at age of questionnaire completion. Girls that transitioned from TS1 to TS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last questionnaire were mom reported TS1 and end of the interval defined as age at first questionnaire where mom reported TS≥2. Girls without a maternal report of TS≥2 during follow-up were right censored at age of last questionnaire where mom reported TS1. This is the primary model used in the analyses and shown in Table 3.2. It is included here for easy comparison across models.

[b]Girls with maternal report of PDS≥2 at first completed growth and development questionnaire were left-censored at age of questionnaire completion. Girls that transitioned from PDS1 to PDS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last questionnaire were mom reported PDS1 and end of the interval defined as age at first questionnaire where mom reported PDS≥2. Girls without a maternal report of PDS≥2 during follow-up were right censored at age of last questionnaire where mom reported PDS1.

[c]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree).

[d]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).

Supplemental Table 3.11. Comparison of models using mother-reported Sexual Maturation Scale (SMS), mother-reported Pubertal Development Scale (PDS) and clinical Tanner scale for associations between maternal pre-pregnancy BMI and GWG and the onset of breast development in girls from New York and Utah sites with clinical Tanner assessment available

		Mother SMS Model 1[a]		Mother PDS Model 1[b]		Clinical Tanner Model 1[c]	
	N	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Maternal pre-pregnancy BMI[d]							
<18.5	16	1.033 (0.968, 1.102)	0.78 (0.47, 1.29)	1.027 (0.967, 1.091)	0.80 (0.48, 1.33)	1.008 (0.943, 1.078)	0.93 (0.52, 1.68)
18.5 to <25	209	Reference	Reference	Reference	Reference	Reference	Reference
25 to <30	52	0.958 (0.905, 1.014)	1.40 (0.89, 2.21)	1.000 (0.955, 1.047)	1.00 (0.68, 1.46)	0.972 (0.930, 1.016)	1.28 (0.87, 1.88)
≥30	25	0.971 (0.900, 1.047)	1.26 (0.70, 2.28)	1.012 (0.942, 1.088)	0.90 (0.50, 1.65)	0.993 (0.933, 1.058)	1.06 (0.61, 1.84)
Continuous (per kg/m^2)	302	0.996 (0.991, 1.001)	1.03 (0.99, 1.07)	0.999 (0.994, 1.004)	1.01 (0.97, 1.05)	0.997 (0.993, 1.001)	1.03 (0.99, 1.07)
Gestational weight gain[e]							
<20lbs	59	0.993 (0.946, 1.042)	1.06 (0.73, 1.55)	0.958 (0.913, 1.006)	1.43 (0.96, 2.12)	0.969 (0.926, 1.014)	1.32 (0.89, 1.96)
20-29 lbs	100	Reference	Reference	Reference	Reference	Reference	Reference
30-39 lbs	67	0.995 (0.945, 1.048)	1.04 (0.70, 1.55)	0.980 (0.934, 1.027)	1.19 (0.80, 1.76)	0.999 (0.954, 1.045)	1.01 (0.68, 1.51)
40-49 lbs	44	0.988 (0.936, 1.043)	1.10 (0.72, 1.68)	**0.948 (0.902, 0.997)**	**1.56 (1.04, 2.33)**	0.996 (0.953, 1.042)	1.03 (0.70, 1.53)
≥50 lbs	29	0.965 (0.894, 1.041)	1.33 (0.73, 2.41)	0.988 (0.908, 1.075)	1.11 (0.54, 2.26)	0.969 (0.882, 1.064)	1.32 (0.58, 3.00)
Maternal pre-pregnancy BMI and GWG[d]							
BMI<25 and <30 lbs	110	Reference	Reference	Reference	Reference	Reference	Reference
BMI<25 and ≥30 lbs	112	0.997 (0.958, 1.038)	1.02 (0.75, 1.40)	1.000 (0.964, 1.038)	1.00 (0.73, 1.36)	1.005 (0.962, 1.049)	0.96 (0.65, 1.40)
BMI≥25 and <30 lbs	49	0.969 (0.911, 1.031)	1.28 (0.79, 2.08)	1.019 (0.963, 1.079)	0.85 (0.53, 1.36)	0.979 (0.928, 1.033)	1.20 (0.75, 1.92)
BMI≥25 and ≥30 lbs	28	0.932 (0.861, 1.009)	1.73 (0.92, 3.25)	0.961 (0.888, 1.040)	1.39 (0.72, 2.71)	0.985 (0.932, 1.042)	1.14 (0.70, 1.85)

[a]Girls with maternal report of TS≥2 at first completed growth and development questionnaire were left-censored at age of questionnaire completion. Girls that transitioned from TS1 to TS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last questionnaire were mom reported TS1 and end of the interval defined as age at first questionnaire where mom reported TS≥2. Girls without a maternal report of TS≥2 during follow-up were right censored at age of last questionnaire where mom reported TS1. This is the primary model used in the analyses. It is included here for comparison across this subset with clinical Tanner data.

[b]Girls with maternal report of PDS≥2 at first completed growth and development questionnaire were left-censored at age of questionnaire completion. Girls that transitioned from PDS1 to PDS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last questionnaire were mom reported PDS1 and end of the interval defined as age at first questionnaire where mom reported PDS≥2. Girls without a maternal report of PDS≥2 during follow-up were right censored at age of last questionnaire where mom reported PDS1.

[a]Girls that were TS≥2 as assessed by a trained clinical rater at their first clinic visit with clinical Tanner staging available were left censored at age at visit. Girls that transitioned from TS1 to TS≥2 during follow-up were interval-censored with the start of the interval defined as the age at last clinic visit where TS1 as assessed by trained clinical rater and end of the interval defined as age at first clinic visit where TS≥2 as assessed by trained clinical rater. Girls without an assessment of TS≥2 by a trained clinical rater during follow-up were right censored at age at last visit where TS1 as assessed by trained clinical rater.

[d]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree).

[e]Adjusted for maternal education (some college or less, Bachelor's degree, graduate degree) and maternal pre-pregnancy BMI (continuous).

Appendix E Supplemental tables and figures for Chapter 4

Supplemental Table 4.1. Adjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between weight-for-age and length-for-age Z-scores at different ages across infancy and the onset of breast development

	Model 1[a] - Weight only		Model 2[a] - Length only		Model 3[b] - Weight and Length	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Weight-for-age Z-score, 0 months	**0.968 (0.943, 0.994)**	**1.30 (1.04, 1.62)**			0.973 (0.946, 1.001)	1.25 (0.99, 1.57)
Weight-for-age Z-score, 2 months	**0.981 (0.963, 0.999)**	**1.16 (1.01, 1.35)**	–	–	0.999 (0.980, 1.019)	1.01 (0.86, 1.18)
Weight-for-age Z-score, 4 months	**0.976 (0.959, 0.994)**	**1.22 (1.05, 1.41)**	–	–	0.992 (0.974, 1.010)	1.07 (0.92, 1.25)
Weight-for-age Z-score, 6 months	**0.976 (0.958, 0.994)**	**1.22 (1.05, 1.43)**	–	–	0.986 (0.966, 1.006)	1.12 (0.95, 1.33)
Weight-for-age Z-score, 9 months	**0.971 (0.952, 0.989)**	**1.28 (1.09, 1.52)**	–	–	0.983 (0.966, 1.001)	1.15 (0.99, 1.34)
Weight-for-age Z-score, 12 months	**0.972 (0.953, 0.992)**	**1.26 (1.07, 1.50)**	–	–	**0.983 (0.967, 0.999)**	**1.15 (1.01, 1.32)**
Length-for-age Z-score, 0 months			0.988 (0.945, 1.001)	1.10 (0.99, 1.22)	0.992 (0.981, 1.004)	1.06 (0.97, 1.17)
Length-for-age Z-score, 2 months	–	–	**0.979 (0.960, 0.999)**	**1.19 (1.01, 1.39)**	0.980 (0.959, 1.000)	1.18 (1.00, 1.40)
Length-for-age Z-score, 4 months	–	–	**0.963 (0.945, 0.983)**	**1.36 (1.16, 1.59)**	**0.968 (0.948, 0.989)**	**1.31 (1.10, 1.55)**
Length-for-age Z-score, 6 months	–	–	**0.972 (0.954, 0.991)**	**1.26 (1.07, 1.47)**	**0.979 (0.959, 1.000)**	**1.19 (1.00, 1.41)**
Length-for-age Z-score, 9 months	–	–	**0.969 (0.953, 0.986)**	**1.30 (1.12, 1.51)**	**0.977 (0.960, 0.995)**	**1.21 (1.04, 1.41)**
Length-for-age Z-score, 12 months	–	–	**0.975 (0.958, 0.993)**	**1.23 (1.06, 1.42)**	0.983 (0.966, 1.000)	1.15 (1.00, 1.33)

*Z-scores calculated using 2000 CDC growth charts as reference. Estimates for each age are from separate models.
[a]Estimates adjusted for gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

Supplemental Table 4.2. Unadjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between rates of weight and length gain during infancy and the onset of breast development in the LEGACY Girls Study

	Model 1[a] - Weight only		Model 2[a] - Length only		Model 3[a] - Weight and Length	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	**0.973 (0.952, 0.994)**	**1.32 (1.05, 1.65)**	–	–	0.983 (0.966, 1.001)	1.14 (0.99, 1.31)
Change in length Z-score, 0-12 months	–	–	**0.978 (0.959, 0.997)**	**1.19 (1.02, 1.38)**	0.984 (0.966, 1.003)	1.13 (0.97, 1.31)
Change in weight Z-score, 0-6 months	**0.979 (0.960, 0.998)**	**1.18 (1.02, 1.37)**	–	–	0.985 (0.965, 1.006)	1.12 (0.95, 1.32)
Change in weight Z-score, 6-12 months	0.969 (0.940, 1.000)	1.27 (1.00, 1.63)	–	–	0.976 (0.948, 1.006)	1.21 (0.95, 1.53)
Change in length Z-score, 0-6 months	–	–	0.978 (0.958, 1.000)	1.18 (1.00, 1.39)	0.984 (0.962, 1.007)	1.13 (0.95, 1.34)
Change in length Z-score, 6-12 months	–	–	0.985 (0.960, 1.011)	1.12 (0.92, 1.37)	0.987 (0.961, 1.013)	1.11 (0.90, 1.36)
Change in weight Z-score, 0-2 months	0.991 (0.969, 1.014)	1.07 (0.90, 1.27)	–	–	1.005 (0.983, 1.027)	0.97 (0.82, 1.14)
Change in weight Z-score, 2-4 months	**0.937 (0.899, 0.977)**	**1.66 (1.19, 2.32)**	–	–	**0.951 (0.911, 0.992)**	**1.49 (1.05, 2.10)**
Change in weight Z-score, 4-6 months	0.988 (0.944, 1.035)	1.10 (0.76, 1.57)	–	–	0.982 (0.926, 1.042)	1.15 (0.72, 1.82)
Change in weight Z-score, 6-9 months	**0.940 (0.902, 0.979)**	**1.66 (1.18, 2.32)**	–	–	**0.941 (0.902, 0.981)**	**1.65 (1.16, 2.35)**
Change in weight Z-score, 9-12 months	0.998 (0.957, 1.041)	1.02 (0.73, 1.43)	–	–	0.995 (0.951, 1.042)	1.04 (0.72, 1.51)
Change in length Z-score, 0-2 months	–	–	0.986 (0.962, 1.011)	1.11 (0.93, 1.33)	0.985 (0.961, 1.009)	1.12 (0.94, 1.35)
Change in length Z-score, 2-4 months	–	–	**0.949 (0.915, 0.984)**	**1.50 (1.14, 1.99)**	**0.960 (0.923, 0.998)**	**1.38 (1.02, 1.87)**
Change in length Z-score, 4-6 months	–	–	1.011 (0.972, 1.051)	0.92 (0.68, 1.24)	1.015 (0.977, 1.055)	0.89 (0.66, 1.20)
Change in length Z-score, 6-9 months	–	–	0.974 (0.949, 1.000)	1.23 (1.00, 1.51)	0.985 (0.961, 1.009)	1.14 (0.93, 1.39)
Change in length Z-score, 9-12 months	–	–	0.999 (0.962, 1.037)	1.01 (0.76, 1.36)	1.014 (0.976, 1.053)	0.89 (0.65, 1.22)

*Z-scores calculated using 2000 CDC growth charts as reference

[a]Estimates adjusted for weight and length Z-scores at birth and change in previous intervals.

Supplemental Table 4.3. Adjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between rates of weight and length gain during infancy and the onset of breast development in the LEGACY Girls Study using the 2006 WHO growth charts as the reference population.

	Model 1[a] - Weight only		Model 2[a] - Length only		Model 3[a] - Weight and Length	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	**0.974 (0.953, 0.996)**	**1.24 (1.03, 1.50)**	–	–	0.984 (0.966, 1.002)	1.15 (0.98, 1.34)
Change in length Z-score, 0-12 months	–	–	**0.983 (0.968, 0.999)**	**1.15 (1.01, 1.31)**	0.988 (0.973, 1.003)	1.11 (0.97, 1.26)
Change in weight Z-score, 0-6 months	0.983 (0.964, 1.002)	1.15 (0.98, 1.35)	–	–	0.991 (0.972, 1.012)	1.08 (0.91, 1.28)
Change in weight Z-score, 6-12 months	**0.967 (0.935, 1.000)**	**1.33 (1.00, 1.78)**	–	–	0.972 (0.939, 1.006)	1.27 (0.95, 1.71)
Change in length Z-score, 0-6 months	–	–	**0.980 (0.964, 0.996)**	**1.19 (1.03, 1.36)**	0.983 (0.966, 1.000)	1.16 (1.00, 1.34)
Change in length Z-score, 6-12 months	–	–	0.991 (0.968, 1.014)	1.08 (0.89, 1.31)	0.993 (0.971, 1.015)	1.06 (0.88, 1.29)
Change in weight Z-score, 0-2 months	0.991 (0.971, 1.010)	1.08 (0.92, 1.27)	–	–	1.005 (0.986, 1.025)	0.96 (0.82, 1.12)
Change in weight Z-score, 2-4 months	**0.946 (0.909, 0.985)**	**1.59 (1.13, 2.24)**	–	–	**0.959 (0.919, 0.999)**	**1.44 (1.00, 2.08)**
Change in weight Z-score, 4-6 months	0.988 (0.933, 1.046)	1.11 (0.68, 1.80)	–	–	0.991 (0.934, 1.051)	1.08 (0.65, 1.80)
Change in weight Z-score, 6-9 months	**0.937 (0.891 , 0.986)**	**1.77 (1.12, 2.78)**	–	–	**0.944 (0.896, 0.995)**	**1.68 (1.03, 2.73)**
Change in weight Z-score, 9-12 months	1.008 (0.960, 1.059)	0.93 (0.61, 1.42)	–	–	0.987 (0.935, 1.042)	1.13 (0.69, 1.83)
Change in length Z-score, 0-2 months	–	–	0.991 (0.971, 1.067)	1.08 (0.92, 1.26)	0.989 (0.971, 1.008)	1.09 (0.94, 1.27)
Change in length Z-score, 2-4 months	–	–	**0.955 (0.928, 0.984)**	**1.48 (1.14, 1.90)**	**0.961 (0.932, 0.991)**	**1.41 (1.08, 1.84)**
Change in length Z-score, 4-6 months	–	–	1.010 (0.976, 1.045)	0.92 (0.69, 1.23)	1.013 (0.979, 1.048)	0.90 (0.67, 1.20)
Change in length Z-score, 6-9 months	–	–	0.976 (0.948, 1.004)	1.23 (0.96, 1.59)	0.985 (0.958, 1.013)	1.15 (0.89, 1.48)
Change in length Z-score, 9-12 months	–	–	1.002 (0.969, 1.036)	0.99 (0.74, 1.31)	1.015 (1.006, 1.025)	0.88 (0.64, 1.21)

*Z-scores calculated using 2006 WHO growth charts as reference

[a]Estimates adjusted for weight and length Z-scores at birth, change in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

Supplemental Table 4.4. Adjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between weight-for-length Z-scores and change in weight-for-length Z-scores during infancy and the onset of breast development

	TR (95% CI)	HR (95% CI)
Size models[a]		
Weight-for-length Z-score, 0 months	0.994 (0.983, 1.004)	1.05 (0.97, 1.15)
Weight-for-length Z-score, 2 months	1.002 (0.995, 1.010)	0.98 (0.93, 1.04)
Weight-for-length Z-score, 4 months	1.001 (0.993, 1.008)	1.00 (0.94, 1.05)
Weight-for-length Z-score, 6 months	0.998 (0.988, 1.008)	1.02 (0.94, 1.10)
Weight-for-length Z-score, 9 months	0.997 (0.988, 1.006)	1.02 (0.95, 1.10)
Weight-for-length Z-score, 12 months	0.994 (0.985, 1.004)	1.05 (0.97, 1.13)
Growth models[b]		
Change in weight-for-length Z-score, 0-12 months	1.003 (0.983, 1.023)	0.98 (0.83, 1.15)
Change in weight-for-length Z-score, 0-6 months	1.004 (0.985, 1.023)	0.97 (0.83, 1.13)
Change in weight-for-length Z-score, 6-12 months	1.002 (0.977, 1.027)	0.99 (0.81, 1.20)
Change in weight-for-length Z-score, 0-2 months	1.014 (0.998, 1.031)	0.89 (0.78, 1.02)
Change in weight-for-length Z-score, 2-4 months	0.999 (0.971, 1.027)	1.01 (0.81, 1.27)
Change in weight-for-length Z-score, 4-6 months	0.987 (0.954, 1.020)	1.11 (0.85, 1.46)
Change in weight-for-length Z-score, 6-9 months	0.998 (0.973, 1.024)	1.02 (0.82, 1.25)
Change in weight-for-length Z-score, 9-12 months	1.002 (0.968, 1.038)	0.98 (0.74, 1.30)

*Z-scores calculated using 2000 CDC growth charts as reference

[a]Estimates adjusted for gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

[b]Estimates adjusted for weight-for-age Z-score at birth, length-for-age Z-score at birth, change in weight-for-length Z-scores in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain

Supplemental Table 4.5. Sensitivity analyses for the associations between rates of weight and length gain during infancy and the onset of breast development excluding infants at increased risk of rapid infant growth

	Excluding preterm[a]		Excluding birthweight<2500g[b]		Excluding multiples[c]	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	0.985 (0.968, 1.002)	1.14 (0.98, 1.32)	0.986 (0.969, 1.002)	1.13 (0.98, 1.30)	0.985 (0.969, 1.002)	1.13 (0.98, 1.31)
Change in length Z-score, 0-12 months	0.992 (0.974, 1.009)	1.07 (0.93, 1.25)	0.989 (0.971, 1.008)	1.09 (0.94, 1.28)	0.989 (0.971, 1.007)	1.10 (0.94, 1.28)
Change in weight Z-score, 0-6 months	0.994 (0.974, 1.014)	1.05 (0.89, 1.25)	0.994 (0.975, 1.014)	1.05 (0.89, 1.24)	0.990 (0.971, 1.010)	1.09 (0.92, 1.28)
Change in weight Z-score, 6-12 months	0.977 (0.949, 1.007)	1.21 (0.94, 1.57)	0.978 (0.951, 1.006)	1.21 (0.94, 1.55)	0.978 (0.950, 1.008)	1.21 (0.94, 1.55)
Change in length Z-score, 0-6 months	**0.978 (0.959, 0.998)**	**1.20 (1.02, 1.42)**	**0.977 (0.957, 0.997)**	**1.22 (1.03, 1.44)**	0.981 (0.961, 1.001)	1.18 (1.00, 1.39)
Change in length Z-score, 6-12 months	1.001 (0.975, 1.028)	0.99 (0.76, 1.24)	1.001 (0.974, 1.028)	1.00 (0.79, 1.26)	0.995 (0.969, 1.023)	1.04 (0.83, 1.31)
Change in weight Z-score, 0-2 months	1.000 (0.980, 1.021)	1.00 (0.84, 1.18)	1.000 (0.980, 1.020)	1.00 (0.85, 1.18)	1.003 (0.983, 1.024)	0.98 (0.83, 1.35)
Change in weight Z-score, 2-4 months	0.968 (0.929, 1.008)	1.32 (0.93, 1.44)	0.969 (0.931, 1.009)	1.31 (0.92, 1.44)	**0.961 (0.925, 0.999)**	**1.40 (1.00, 1.97)**
Change in weight Z-score, 4-6 months	1.008 (0.954, 1.064)	0.94 (0.59, 1.49)	1.004 (0.952, 1.059)	0.97 (0.61, 1.53)	0.991 (0.939, 1.045)	1.09 (0.68, 1.72)
Change in weight Z-score, 6-9 months	**0.948 (0.903, 0.994)**	**1.62 (1.03, 2.52)**	**0.951 (0.909, 0.996)**	**1.57 (1.03, 2.39)**	**0.945 (0.902, 0.990)**	**1.66 (1.08, 2.56)**
Change in weight Z-score, 9-12 months	1.002 (0.955, 1.050)	0.99 (0.64, 1.51)	1.001 (0.956, 1.047)	0.99 (0.66, 1.50)	1.007 (0.962, 1.054)	0.94 (0.63, 1.42)
Change in length Z-score, 0-2 months	0.983 (0.961, 1.005)	1.15 (0.96, 1.38)	0.985 (0.963, 1.007)	1.14 (0.95, 1.36)	0.986 (0.964, 1.009)	1.12 (0.94, 1.35)
Change in length Z-score, 2-4 months	**0.951 (0.917, 0.986)**	**1.54 (1.13, 2.10)**	**0.948 (0.915, 0.982)**	**1.58 (1.16, 2.19)**	**0.953 (0.919, 0.988)**	**1.51 (1.10, 2.07)**
Change in length Z-score, 4-6 months	1.018 (0.980, 1.058)	0.86 (0.61, 1.19)	1.012 (0.974, 1.051)	0.90 (0.65, 1.26)	1.014 (0.975, 1.054)	0.89 (0.63, 1.25)
Change in length Z-score, 6-9 months	0.985 (0.953, 1.018)	1.15 (0.85, 1.54)	0.982 (0.951, 1.014)	1.18 (0.88, 1.57)	0.983 (0.953, 1.014)	1.17 (0.88, 1.55)
Change in length Z-score, 9-12 months	1.039 (0.996, 1.083)	0.71 (0.48, 1.04)	1.035 (0.996, 1.076)	0.73 (0.51, 1.05)	1.027 (0.987, 1.068)	0.79 (0.55, 1.13)

*Z-scores calculated using 2000 CDC growth charts as reference

[a]N=21 preterm girls excluded. Estimates adjusted for weight and length Z-scores at birth, change in weight and length in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian).

[b]N=13 girls with birthweight <2500g excluded. Estimates are adjusted as described in [a]

[c]N=13 girls from multiple gestations excluded. Estimates are adjusted as described in [a]

Supplemental Table 4.6. Adjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between rates of weight and length gain during infancy and the onset of breast development in girls with a BMI at baseline less than the 85th percentile for age

	Model 1[a] - Weight only		Model 2[a] - Length only		Model 3[a] - Weight and Length	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	**0.977 (0.956, 0.997)**	**1.23 (1.02, 1.49)**	–	–	0.991 (0.964, 1.019)	1.08 (0.85, 1.38)
Change in length Z-score, 0-12 months	–	–	**0.978 (0.961, 0.996)**	**1.21 (1.03, 1.42)**	0.983 (0.961, 1.006)	1.16 (0.95, 1.42)
Change in weight Z-score, 0-6 months	0.979 (0.958, 1.000)	1.20 (0.99, 1.45)	–	–	0.988 (0.960, 1.016)	1.11 (0.87, 1.43)
Change in weight Z-score, 6-12 months	0.976 (0.947, 1.005)	1.24 (0.95, 1.62)	–	–	0.989 (0.955, 1.024)	1.10 (0.81, 1.50)
Change in length Z-score, 0-6 months	–	–	**0.978 (0.960, 0.997)**	**1.21 (1.03, 1.43)**	0.983 (0.961, 1.006)	1.16 (0.95, 1.41)
Change in length Z-score, 6-12 months	–	–	0.985 (0.957, 1.014)	1.14 (0.88, 1.47)	0.987 (0.957, 1.017)	1.12 (0.86, 1.47)
Change in weight Z-score, 0-2 months	0.984 (0.961, 1.008)	1.14 (0.93, 1.40)	–	–	1.005 (0.978, 1.033)	0.96 (0.76, 1.22)
Change in weight Z-score, 2-4 months	**0.961 (0.923, 1.000)**	**1.41 (0.99, 1.99)**	–	–	0.978 (0.938, 1.020)	1.22 (0.84, 1.78)
Change in weight Z-score, 4-6 months	0.978 (0.922, 1.038)	1.21 (0.72, 2.03)	–	–	0.983 (0.927, 1.042)	1.17 (0.69, 1.60)
Change in weight Z-score, 6-9 months	**0.934 (0.890, 0.981)**	**1.84 (1.18, 2.88)**	–	–	0.971 (0.924, 1.020)	1.33 (0.82, 2.15)
Change in weight Z-score, 9-12 months	1.017 (0.973, 1.063)	0.86 (0.58, 1.28)	–	–	1.012 (0.960, 1.068)	0.89 (0.54, 1.48)
Change in length Z-score, 0-2 months	–	–	0.985 (0.961, 1.009)	1.14 (0.93, 1.40)	0.983 (0.958, 1.009)	1.16 (0.93, 1.44)
Change in length Z-score, 2-4 months	–	–	**0.949 (0.916, 0.983)**	**1.59 (1.16, 2.18)**	**0.951 (0.916, 0.987)**	**1.57 (1.12, 2.21)**
Change in length Z-score, 4-6 months	–	–	1.029 (0.989, 1.071)	0.77 (0.54, 1.11)	1.032 (0.993, 1.074)	0.75 (0.52, 1.08)
Change in length Z-score, 6-9 months	–	–	**0.947 (0.924, 0.970)**	**1.68 (1.31, 2.15)**	**0.952 (0.926, 0.979)**	**1.59 (1.21, 2.10)**
Change in length Z-score, 9-12 months	–	–	1.010 (0.973, 1.048)	0.92 (0.65, 1.30)	1.015 (0.978, 1.054)	0.86 (0.60, 1.24)

*Z-scores calculated using 2000 CDC growth charts as reference. N=177 girls with a BMI-for-age percentile <85th at baseline.
[a]Estimates adjusted for weight and length Z-scores at birth, change in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

Supplemental Table 4.7. Time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between rates of weight and length gain during infancy and the onset of breast development with adjustment for daughter's pre-pubertal body size

	Subset with BMI between 5-7[a]		With adjustment for BMI[b]	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	**0.984 (0.970, 0.997)**	**1.15 (1.02, 1.29)**	0.986 (0.971, 1.001)	1.12 (0.99, 1.28)
Change in length Z-score, 0-12 months	**0.980 (0.963, 0.998)**	**1.18 (1.01, 1.37)**	**0.981 (0.962, 1.000)**	**1.17 (1.00, 1.37)**
Change in weight Z-score, 0-6 months	0.982 (0.963, 1.002)	1.16 (0.98, 1.38)	0.987 (0.968, 1.008)	1.11 (0.94, 1.32)
Change in weight Z-score, 6-12 months	0.989 (0.961, 1.018)	1.14 (0.97, 1.35)	0.988 (0.958, 1.019)	1.10 (0.85, 1.43)
Change in length Z-score, 0-6 months	**0.977 (0.955, 1.000)**	**1.21 (1.00, 1.47)**	**0.975 (0.953, 0.999)**	**1.23 (1.01, 1.49)**
Change in length Z-score, 6-12 months	0.987 (0.959, 1.016)	1.12 (0.88, 1.42)	0.988 (0.960, 1.018)	1.10 (0.86, 1.41)
Change in weight Z-score, 0-2 months	0.992 (0.972, 1.013)	1.06 (0.90, 1.26)	1.000 (0.975, 1.025)	1.00 (0.82, 1.23)
Change in weight Z-score, 2-4 months	0.964 (0.925, 1.005)	1.36 (0.96, 1.94)	0.966 (0.928, 1.007)	1.33 (0.94, 1.90)
Change in weight Z-score, 4-6 months	0.973 (0.915, 1.033)	1.27 (0.75, 2.13)	0.975 (0.917, 1.036)	1.24 (0.73, 2.09)
Change in weight Z-score, 6-9 months	0.965 (0.915, 1.017)	1.37 (0.86, 2.19)	0.957 (0.906, 1.012)	1.46 (0.89, 2.39)
Change in weight Z-score, 9-12 months	1.005 (0.958, 1.054)	0.96 (0.63, 1.45)	1.007 (0.955, 1.061)	0.94 (0.60, 1.48)
Change in length Z-score, 0-2 months	0.981 (0.959, 1.005)	1.17 (0.96, 1.41)	0.979 (0.955, 1.003)	1.19 (0.98, 1.45)
Change in length Z-score, 2-4 months	0.962 (0.923, 1.002)	1.39 (0.98, 1.97)	0.961 (0.921, 1.002)	1.40 (0.98, 2.01)
Change in length Z-score, 4-6 months	1.003 (0.957, 1.052)	0.97 (0.65, 1.45)	1.007 (0.962, 1.055)	0.94 (0.64, 1.39)
Change in length Z-score, 6-9 months	0.983 (0.944, 1.024)	1.16 (0.81, 1.65)	0.988 (0.949, 1.029)	1.11 (0.78, 1.58)
Change in length Z-score, 9-12 months	1.007 (0.959, 1.057)	0.94 (0.62, 1.44)	1.014 (0.965, 1.065)	0.89 (0.58, 1.36)

*Z-scores calculated using 2000 CDC growth charts as reference. N=185 girls with pre-pubertal BMI data

[a]Estimates adjusted for weight and length Z-scores at birth, change in weight and length in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

[b]Estimates adjusted as described in [a] with additional adjustment for BMI-for-age percentile and interaction between BMI-for-age percentile and centered age at BMI measurement.

Supplemental Table 4.8. Adjusted time ratios (TR), hazard ratios (HR) and 95% confidence intervals (CIs) for associations between rates of weight and length gain during infancy and the onset of breast development using inverse probability weighting to adjust for subset selection bias

	IPW Model 1[a]		IPW Model 2[b]	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	0.978 (0.949, 1.008)	1.18 (0.95, 1.48)	0.984 (0.960, 1.008)	1.15 (0.93, 1.42)
Change in length Z-score, 0-12 months	0.989 (0.963, 1.017)	1.09 (0.88, 1.34)	0.993 (0.971, 1.016)	1.06 (0.87, 1.29)
Change in weight Z-score, 0-6 months	0.983 (0.960, 1.006)	1.13 (0.96, 1.34)	0.988 (0.965, 1.011)	1.11 (0.92, 1.35)
Change in weight Z-score, 6-12 months	0.971 (0.930, 1.014)	1.25 (0.90, 1.36)	0.985 (0.949, 1.021)	1.14 (0.83, 1.57)
Change in length Z-score, 0-6 months	0.988 (0.955, 1.022)	1.09 (0.85, 1.40)	0.987 (0.961, 1.014)	1.12 (0.89, 1.39)
Change in length Z-score, 6-12 months	0.990 (0.955, 1.027)	1.08 (0.81, 1.43)	0.999 (0.967, 1.032)	1.01 (0.76, 1.33)
Change in weight Z-score, 0-2 months	0.994 (0.965, 1.024)	1.04 (0.85, 1.29)	0.999 (0.975, 1.023)	1.01 (0.84, 1.23)
Change in weight Z-score, 2-4 months	**0.952 (0.909, 0.998)**	**1.44 (1.02, 2.04)**	**0.956 (0.919, 0.995)**	**1.47 (1.05, 2.06)**
Change in weight Z-score, 4-6 months	1.026 (0.956, 1.101)	0.83 (0.49, 1.40)	1.028 (0.952, 1.109)	0.79 (0.41, 1.52)
Change in weight Z-score, 6-9 months	0.949 (0.899, 1.002)	1.54 (0.95, 2.51)	0.957 (0.910, 1.006)	1.51 (0.91, 2.50)
Change in weight Z-score, 9-12 months	1.020 (0.967, 1.075)	0.85 (0.55, 1.32)	1.027 (0.976, 1.080)	0.78 (0.48, 1.26)
Change in length Z-score, 0-2 months	0.992 (0.963, 1.022)	1.06 (0.86, 1.32)	0.997 (0.970, 1.026)	1.02 (0.81, 1.29)
Change in length Z-score, 2-4 months	0.956 (0.902, 1.013)	1.40 (0.91, 2.15)	0.955 (0.910, 1.002)	1.49 (0.98, 2.26)
Change in length Z-score, 4-6 months	1.031 (0.978, 1.087)	0.79 (0.54, 1.18)	1.021 (0.970, 1.075)	0.84 (0.54, 1.30)
Change in length Z-score, 6-9 months	**0.955 (0.925, 0.987)**	**1.46 (1.11, 1.91)**	**0.958 (0.929, 0.989)**	**1.49 (1.12, 1.98)**
Change in length Z-score, 9-12 months	1.030 (0.987, 1.075)	0.78 (0.55, 1.11)	1.036 0.995, 1.077)	0.72 (0.49, 1.05)

*Z-scores calculated using 2000 CDC growth charts as reference

[a]Estimates adjusted for weight and length Z-scores at birth and change in weight and length in previous intervals
[b]Estimates adjusted for weight and length Z-scores at birth, change in weight and length in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain
(BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

Supplemental Table 4.9. Sensitivity analyses based on outcome assessment and modeling strategy for the associations between rates of weight and length gain during infancy and the onset of breast development

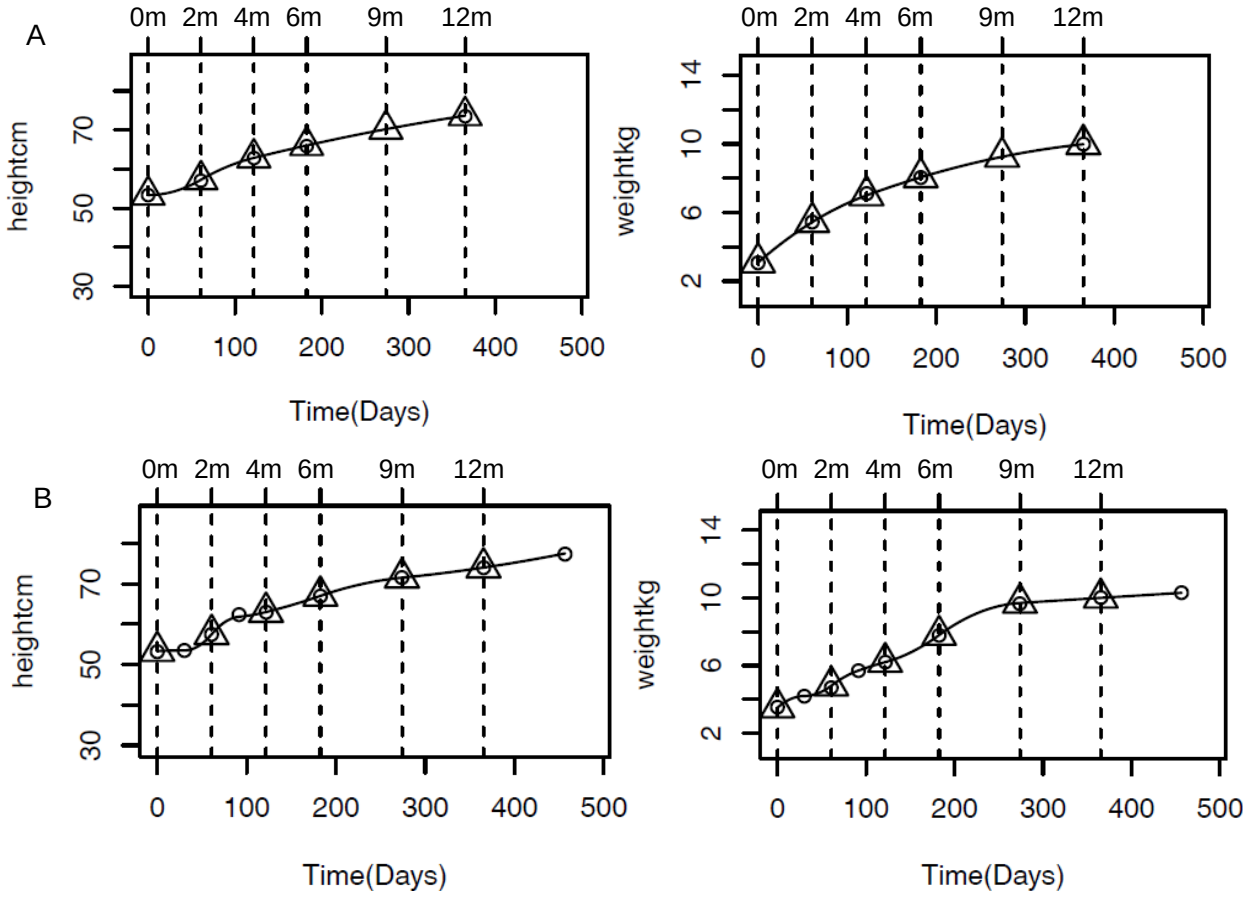
	Excluding inconsistent girls[a]		Model using SMS with recalled data		Model using PDS	
	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)	TR (95% CI)	HR (95% CI)
Change in weight Z-score, 0-12 months	0.988 (0.961, 1.015)	1.12 (0.87, 1.45)	0.991 (0.977, 1.005)	1.09 (0.95, 1.24)	1.001 (0.988, 1.034)	0.99 (0.88, 1.12)
Change in length Z-score, 0-12 months	0.989 (0.967, 1.012)	1.10 (0.90, 1.36)	0.993 (0.978, 1.008)	1.07 (0.93, 1.22)	1.004 (0.989, 1.020)	0.96 (0.83, 1.10)
Change in weight Z-score, 0-6 months	0.991 (0.965, 1.017)	1.09 (0.86, 1.39)	1.005 (0.985, 1.026)	0.96 (0.81, 1.13)	0.995 (0.977, 1.014)	1.04 (0.88, 1.25)
Change in weight Z-score, 6-12 months	0.984 (0.951, 1.018)	1.21 (0.94, 1.55)	0.992 (0.964, 1.021)	1.08 (0.83, 1.40)	1.007 (0.981, 1.033)	0.94 (0.74, 1.19)
Change in length Z-score, 0-6 months	0.984 (0.964, 1.005)	1.16 (0.96, 1.40)	**0.978 (0.960, 0.996)**	**1.21 (1.07, 1.52)**	1.005 (0.987, 1.023)	0.96 (0.81, 1.14)
Change in length Z-score, 6-12 months	0.993 (0.965, 1.022)	1.04 (0.83, 1.31)	1.006 (0.983, 1.030)	0.95 (0.77, 1.18)	1.004 (0.980, 1.028)	0.97 (0.77, 1.21)
Change in weight Z-score, 0-2 months	1.004 (0.977, 1.032)	0.96 (0.75, 1.23)	1.007 (0.989, 1.026)	0.94 (0.81, 1.10)	1.011 (0.992, 1.030)	0.90 (0.75, 1.08)
Change in weight Z-score, 2-4 months	0.971 (0.936, 1.007)	1.32 (0.93, 1.89)	0.985 (0.952, 1.020)	1.14 (0.84, 1.54)	0.982 (0.949, 1.016)	1.20 (0.85, 1.68)
Change in weight Z-score, 4-6 months	1.011 (0.957, 1.067)	0.90 (0.54, 1.52)	1.048 (0.990, 1.110)	0.66 (0.41, 1.07)	0.977 (0.930, 1.027)	1.26 (0.77, 2.06)
Change in weight Z-score, 6-9 months	0.961 (0.911, 1.014)	1.49 (0.86, 2.56)	1.015 (0.965, 1.067)	0.88 (0.57, 1.36)	0.992 (0.950, 1.036)	1.08 (0.70, 1.65)
Change in weight Z-score, 9-12 months	0.999 (0.948, 1.054)	1.01 (0.59, 1.72)	1.007 (0.970, 1.006)	0.94 (0.65, 1.35)	1.000 (0.961, 1.041)	1.00 (0.68, 11.47)
Change in length Z-score, 0-2 months	0.989 (0.966, 1.012)	1.11 (0.90, 1.37)	0.996 (0.976, 1.016)	1.04 (0.88, 1.23)	1.009 (0.991, 1.028)	0.82 (0.76, 1.10)
Change in length Z-score, 2-4 months	**0.953 (0.919, 0.987)**	**1.59 (1.13, 2.23)**	**0.958 (0.932, 0.983)**	**1.45 (1.16, 1.83)**	0.984 (0.953, 1.017)	1.17 (0.85, 1.61)
Change in length Z-score, 4-6 months	1.025 (0.989, 1.063)	0.79 (0.55, 1.12)	0.996 (0.968, 1.026)	1.03 (0.80, 1.33)	1.030 (0.989, 1.073)	0.75 (0.50, 1.11)
Change in length Z-score, 6-9 months	0.979 (0.940, 1.019)	1.24 (0.83, 1.87)	0.990 (0.961, 1.019)	1.10 (0.84, 1.42)	1.000 (0.972, 1.028)	1.00 (0.76, 1.32)
Change in length Z-score, 9-12 months	1.011 (0.973, 1.050)	0.90 (0.61, 1.33)	1.029 (0.998, 1.025)	0.76 (0.56, 1.02)	1.009 (0.972, 1.049)	0.91 (0.63, 1.32)

*Z-scores calculated using 2000 CDC growth charts as reference

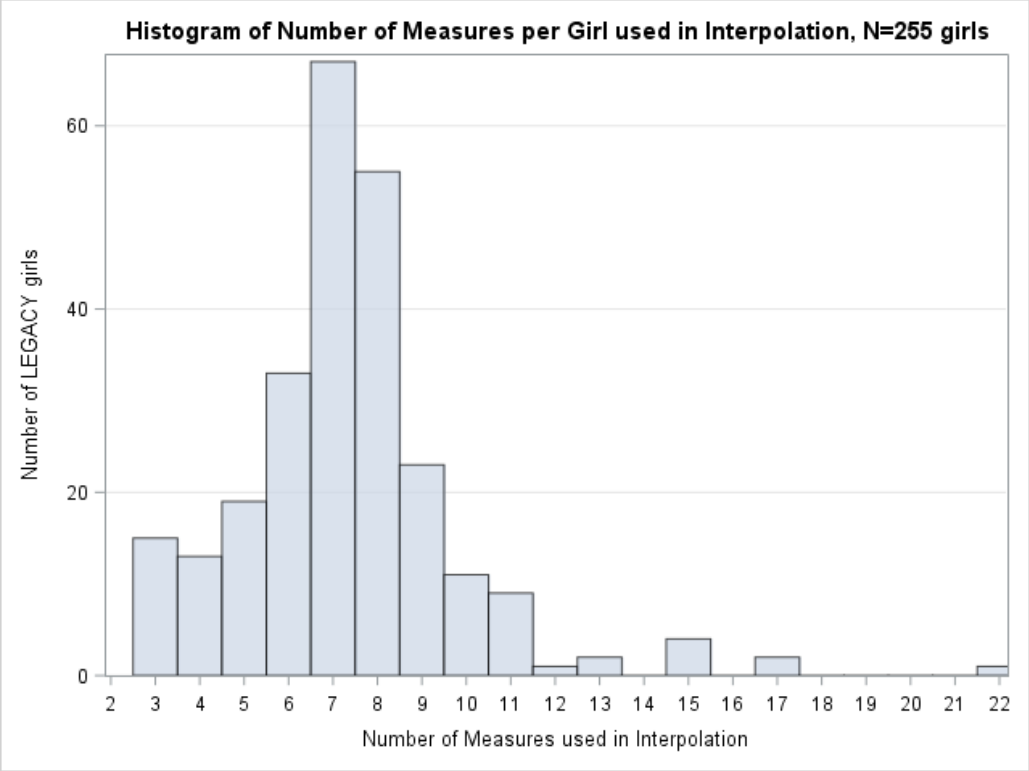
Estimates adjusted for weight and length Z-scores at birth, change in weight and length in previous intervals, gestational age in weeks, maternal pre-pregnancy BMI and gestational weight gain (BMI<25 and GWG<30lbs, BMI<25 and GWG≥30 lbs, BMI≥25 and GWG<30 lbs, BMI≥25 and GWG≥30), and race/ethnicity (Hispanic, Non-Hispanic Black or Mixed race/ethnicity, Non-Hispanic White, Asian)

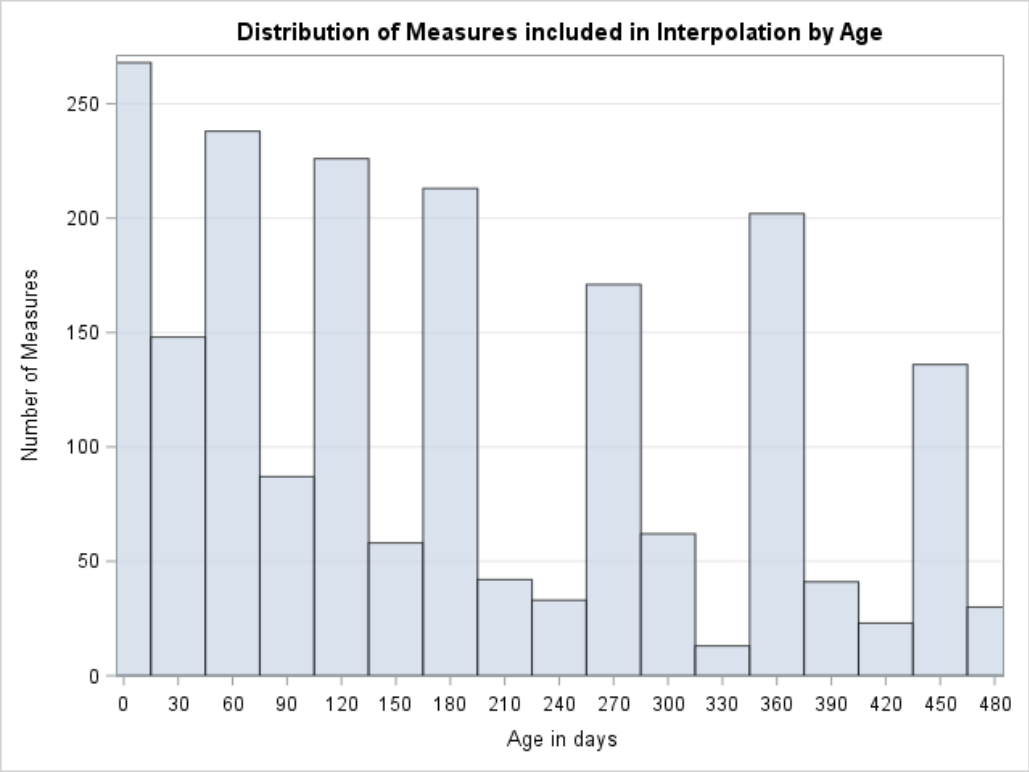
[a]N=22 girls excluded

Supplemental Figure 4.1. Examples of individual quadratic spline interpolation of infancy height and weight data. *Height and weight data shown for two individuals. Circles represent observed data points. Triangles represent interpolated data points at 0 months, 2 months, 4 months, 6 months, 9 months and 12 months. Individual A had 5 observed data points to contribute to the interpolation. Individual B had 9 observed data points to contribute to the interpolation.*

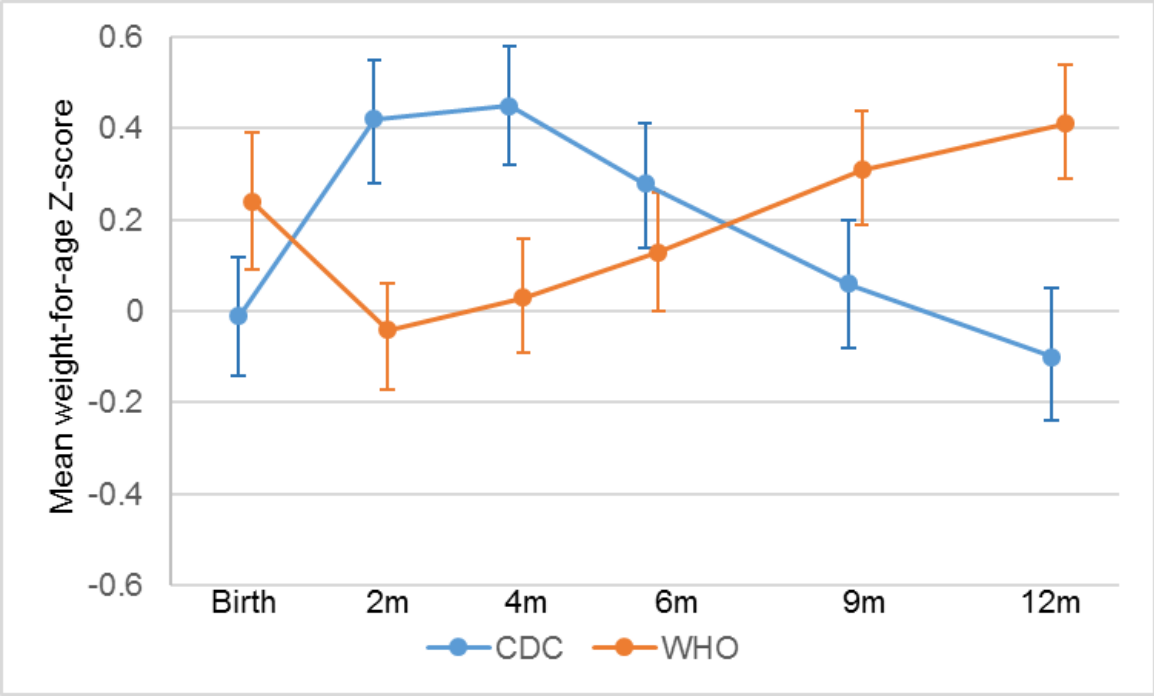


Supplemental Figure 4.2. Histograms of data availability for infant growth interpolation

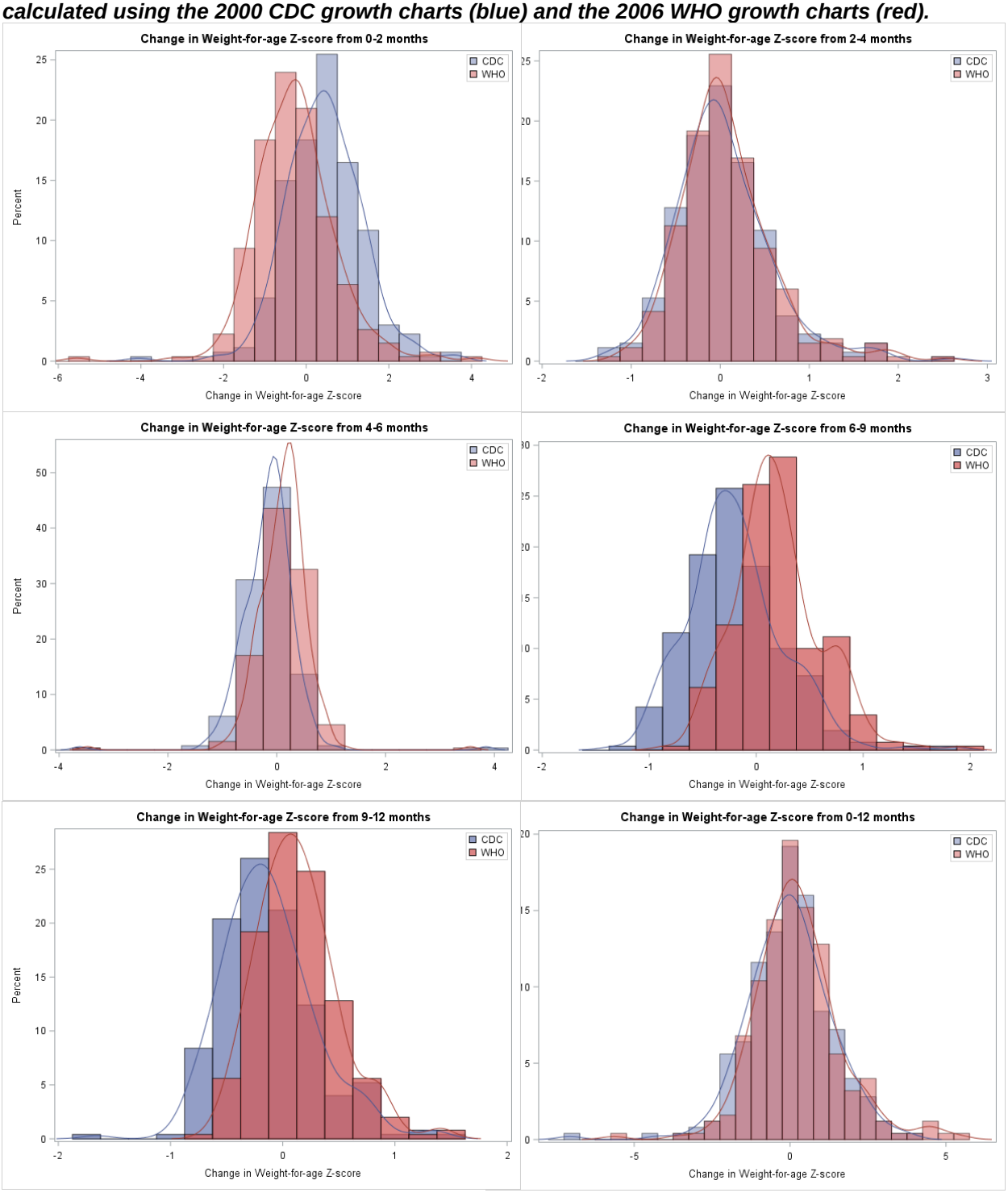




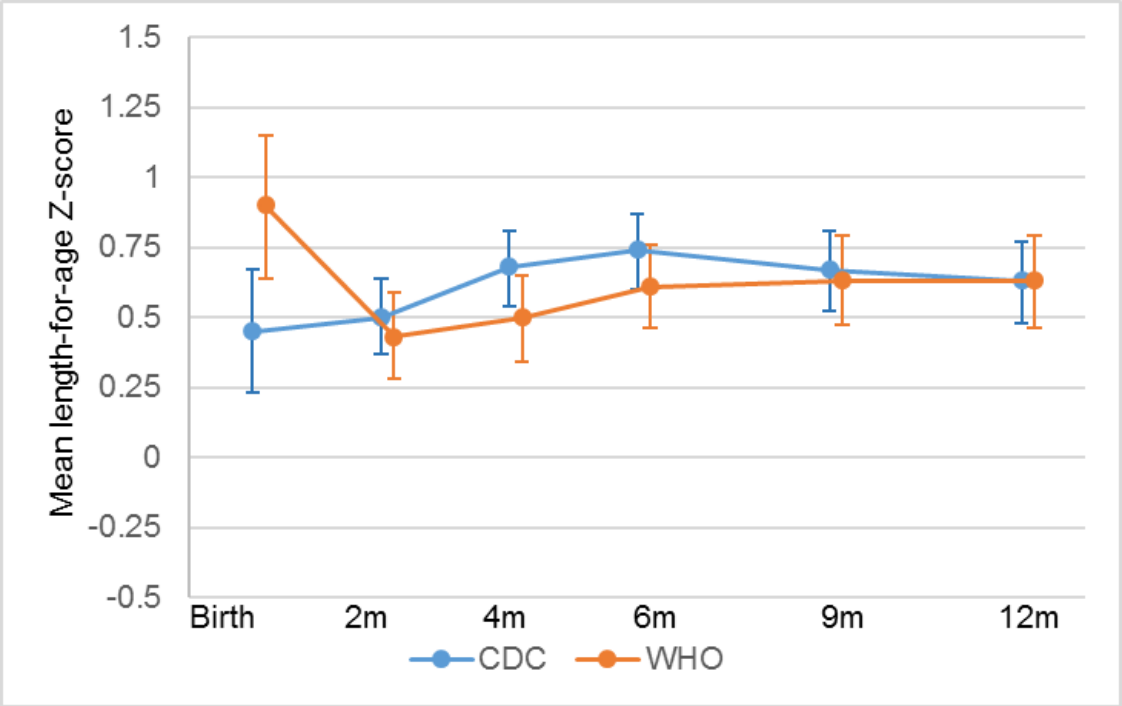
Supplemental Figure 4.3. Mean weight-for-age Z-scores and 95% confidence intervals by age calculated using the 2000 CDC growth charts and the 2006 WHO growth charts. *The means are connected by lines to better identify the CDC and WHO patterns. At each age, means and error bars are slightly offset to distinguish the groups from one another.*



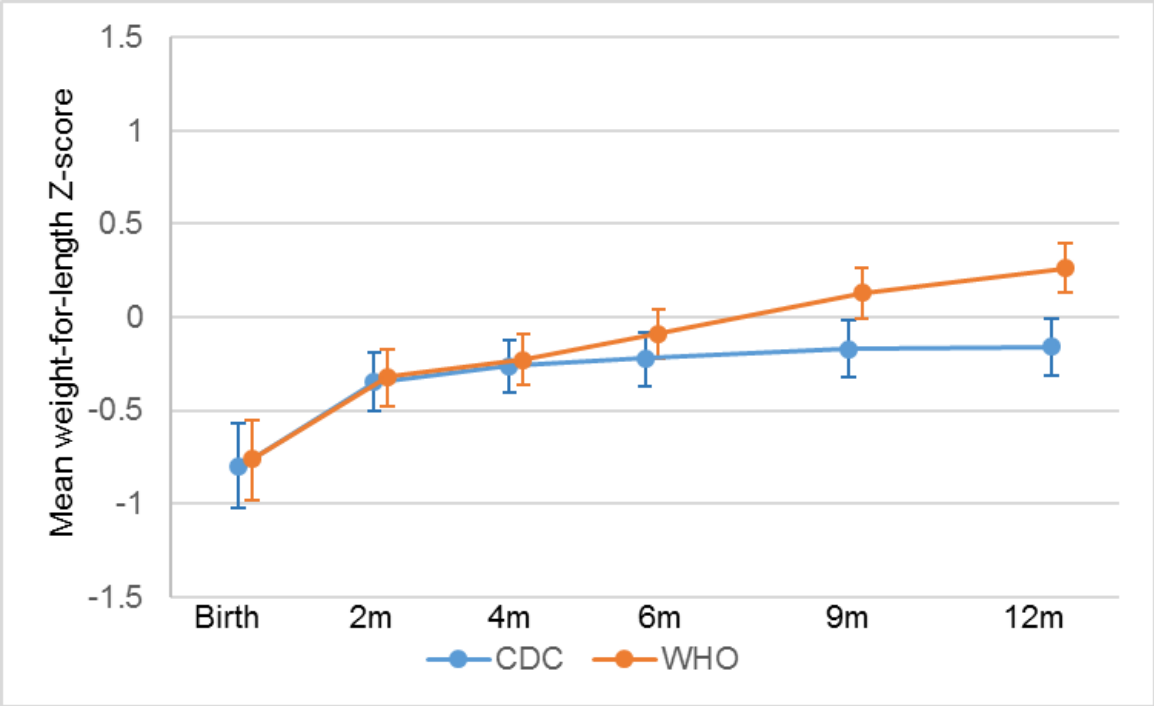
Supplemental Figure 4.4. Histograms of change in weight-for-age Z-scores for each age interval calculated using the 2000 CDC growth charts (blue) and the 2006 WHO growth charts (red).



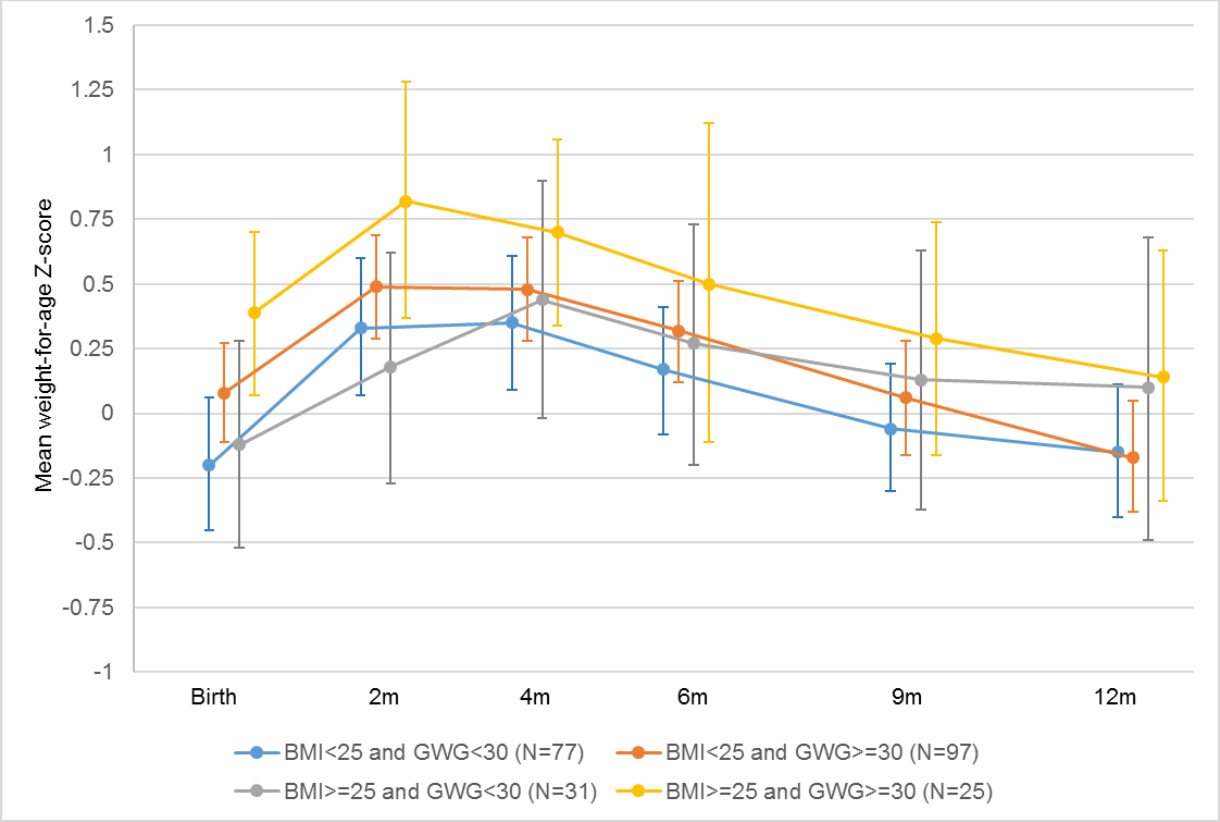
Supplemental Figure 4.5. Mean length-for-age Z-scores and 95% confidence intervals by age calculated using the 2000 CDC growth charts and the 2006 WHO growth charts. *The means are connected by lines to better identify the CDC and WHO patterns. At each age, means and error bars are slightly offset to distinguish the groups from one another.*



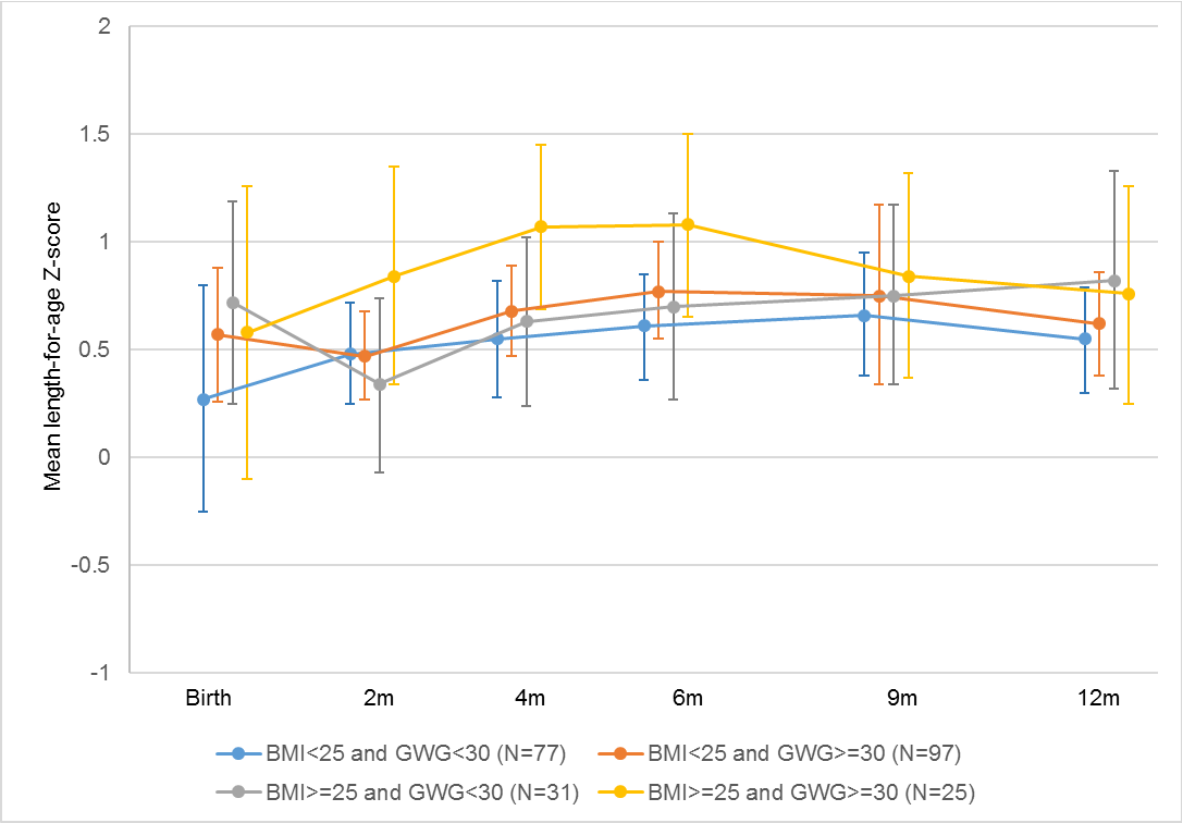
Supplemental Figure 4.6. Mean weight-for-length Z-scores and 95% confidence intervals by age calculated using the 2000 CDC growth charts and the 2006 WHO growth charts. *The means are connected by lines to better identify the CDC and WHO patterns. At each age, means and error bars are slightly offset to distinguish the groups from one another.*



Supplemental Figure 4.7. Mean weight-for-age Z-scores and 95% confidence intervals through infancy by maternal pre-pregnancy body mass index and gestational weight gain. *The means are connected by lines to better identify the different groups. At each age, means and error bars are slightly offset to distinguish the groups from one another. Z-scores were calculated using the 2000 CDC growth charts.*

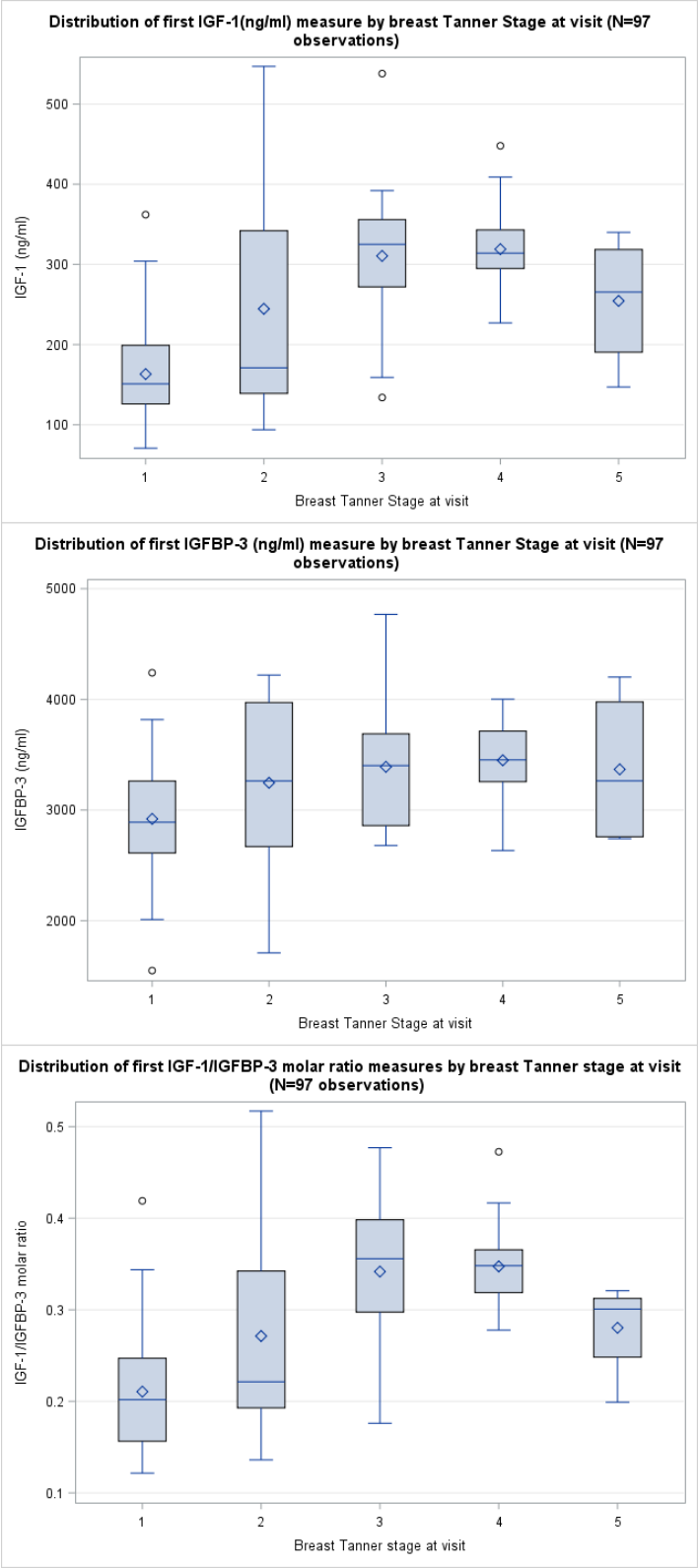


Supplemental Figure 4.8. Mean length-for-age Z-scores and 95% confidence intervals through infancy by maternal pre-pregnancy body mass index and gestational weight gain. *The means are connected by lines to better identify the different groups. At each age, means and error bars are slightly offset to distinguish the groups from one another. Z-scores were calculated using the 2000 CDC growth charts.*

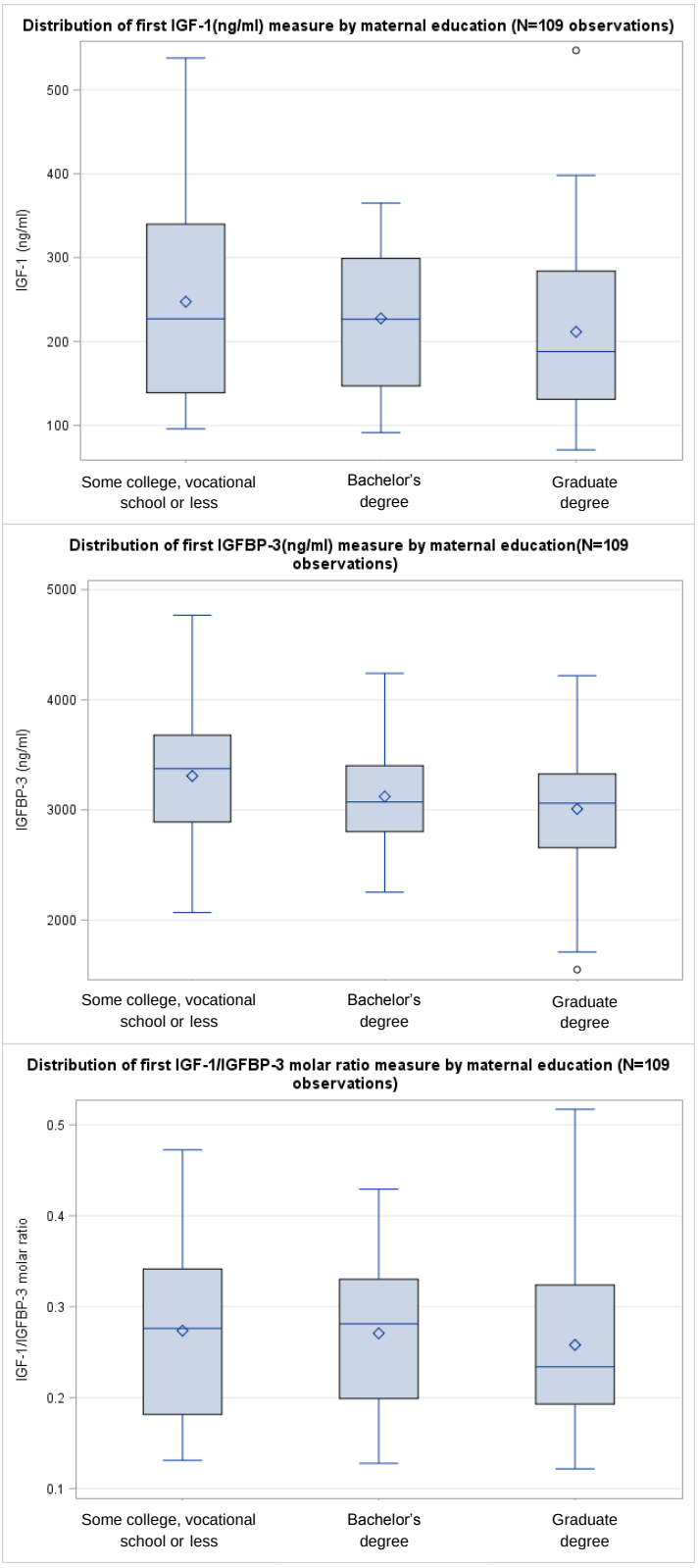


Appendix F Supplemental tables and figures for Chapter 5

Supplemental Figure 5.1. Boxplots of first serum biomarker measures by breast Tanner stage at visit (N=97 girls)



Supplemental Figure 5.2. Boxplot of first IGF-1/IGFBP-3 molar ratio by maternal education (N=109 girls)



Supplemental Table 5.1. Descriptive characteristics of the LEGACY Girls Study New York site by serum availability (N=177 girls)

	At least 1 serum IGF-1/IGFBP-3 measure* (N=109)	**No serum IGF-1/IGFBP-3 measures (N=68)**
Early-life characteristics		
Maternal age at birth (Mean±SD)	33.0 ± 6.3	33.8 ± 4.8
Maternal height, m (Mean±SD)	1.6 ± 0.1	1.6 ± 0.1
Maternal pre-pregnancy weight, kg (Mean±SD)	63.3 ± 11.1	62.0 ± 12.7
Maternal pre-pregnancy BMI (Mean±SD)	23.8 ± 4.2	23.5 ± 5.4
Maternal pre-pregnancy BMI, categorized (N, %)		
<18.5	3 (2.8)	5 (7.4)
18.5 to <25	71 (65.1)	46 (67.7)
25 to <30	23 (21.1)	10 (14.7)
≥30	9 (8.3)	6 (8.8)
Missing	3 (2.8)	1 (1.5)
Gestational weight gain (n, %)		
<10 lbs	5 (4.6)	0 (0.0)
10-14 lbs	6 (5.5)	1 (1.5)
15-19 lbs	5 (4.6)	13 (19.1)
20-29 lbs	33 (30.3)	24 (35.3)
30-39 lbs	23 (21.1)	15 (22.1)
40-49 lbs	16 (14.7)	9 (13.2)
≥50 lbs	17 (15.6)	5 (7.4)
Missing	4 (3.7)	1 (1.5)
Gestational weight gain adequacy based on the 2009 IOM guidelines (n, %)		
Inadequate (below guidelines)	14 (12.8)	15 (22.1)
Adequate (within guidelines)	54 (49.5)	30 (44.1)
Excessive (above guidelines)	37 (33.9)	21 (30.9)
Missing	4 (3.7)	2 (2.9)
Maternal recreational physical activity during pregnancy (N, %)		
Inactive, no walking or other regular exercise	19 (17.4)	7 (10.3)
Mostly inactive, equivalent to walking about half a mile or less every day	26 (23.9)	21 (30.9)
Somewhat active, equivalent to walking about 1 mile every day	19 (17.4)	23 (33.8)
Active, equivalent to walking about 2 miles every day	36 (33.0)	15 (22.1)
Highly active, equivalent to walking about 3 or more miles every day	7 (6.4)	2 (2.9)
Missing	2 (1.8)	0 (0.0)

Maternal physical activity at home during pregnancy (N, %)		
Mostly sitting	30 (27.5)	21 (30.9)
Mostly walking and standing, with some sitting	35 (32.1)	28 (41.2)
Active housework most of the time with little sitting	40 (36.7)	18 (26.5)
Heavy manual work at home	1 (0.9)	1 (1.5)
Missing	3 (2.8)	0 (0.0)
Maternal physical activity at work during pregnancy (N, %)		
Not working	27 (24.8)	14 (20.6)
Mostly sitting and standing	46 (42.2)	31 (45.6)
Mostly walking with some sitting and standing	32 (29.4)	20 (29.4)
Mostly heavy labor with some walking and standing and little sitting	2 (1.8)	2 (2.9)
Missing	2 (1.8)	1 (1.5)
Maternal physical activity during pregnancy, 2nd trimester (N, %)		
Stayed the same	65 (59.6)	47 (69.1)
Substantially increased	12 (11.0)	4 (5.9)
Substantially decreased	30 (27.5)	17 (25.0)
Missing	2 (1.8)	0 (0.0)
Gestational diabetes during pregnancy with LEGACY daughter (N, %)		
Yes	10 (9.2)	8 (11.8)
No	94 (86.2)	60 (88.2)
Missing	5 (4.6)	0 (0.0)
Gestational hypertension, toxemia or pre-eclampsia during pregnancy with LEGACY daughter (N, %)		
Yes	10 (9.2)	5 (7.4)
No	94 (86.2)	62 (91.2)
Missing	5 (4.6)	1 (1.5)
Type of gestation (N, %)		
Multiple	7 (6.4)	4 (5.9)
Singleton	99 (90.8)	64 (94.1)
Missing	3 (2.8)	0 (0.0)
Birth order (Mean±SD)	1.6 ± 0.7	1.8 ± 1.0
Birth order, dichotomized (N, %)		
First-born	54 (49.5)	30 (44.1)
Not first-born	52 (47.7)	38 (55.9)
Missing	3 (2.8)	0 (0.0)
Gestational age in weeks (Mean±SD)	38.9 ± 2.4	38.7 ± 2.5
Gestational age, categorized (N, %)		
<37 weeks	16 (14.7)	9 (13.2)
≥37 weeks	91 (83.5)	59 (86.8)

Missing	2 (1.8)	0 (0.0)
Intrauterine smoke exposure (N, %)		
Yes	4 (3.7)	1 (1.5)
No	103 (94.5)	67 (98.5)
Missing	2 (1.8)	0 (0.0)
Birthweight, g (Mean±SD)	3232.4 ± 681.3	3213.3 ± 618.7
Birthweight, categorized (N, %)		
<2500g	13 (11.9)	7 (10.3)
2500-2999g	17 (15.6)	11 (16.2)
3000-3499g	35 (32.1)	26 (38.2)
3500-3999g	34 (31.2)	19 (27.9)
≥4000g	9 (9.0)	4 (4.0)
Missing	1 (0.9)	1 (1.5)
Birthlength, cm (Mean±SD)	51.3 ± 3.6	49.5 ± 4.0
Birthlength categorized (N, %)		
<48.25	8 (7.3)	8 (11.8)
48.25-50.74	20 (18.4)	25 (36.8)
50.75-53.24	22 (20.2)	11 (16.2)
≥53.25	32 (29.4)	16 (23.5)
Missing	27 (24.8)	8 (11.8)
Baseline characteristics		
Age at baseline (Mean±SD)	9.8 ± 2.4	9.0 ± 2.3
BMI-for-age percentile at baseline, (Mean±SD)	63.1 ± 29.0	54.5 ± 31.1
BMI-for-age percentile at baseline, categorized (N, %)		
≥85th BMI-for-age percentile	31 (28.4)	11 (16.2)
<85th BMI-for-age percentile	77 (70.6)	43 (63.2)
Missing[a]	1 (0.9)	14 (20.6)
Breast cancer family history in a first- or second-degree relative (N, %)		
BCFH+	44 (40.4)	37 (54.4)
BCFH-	65 (59.6)	31 (45.6)
BOADICEA lifetime risk score (Mean±SD)	13.8 ± 4.4	13.7 ± 4.0
Race/ethnicity (N, %)		
Non-Hispanic white	43 (39.5)	41 (60.3)
Non-Hispanic black	14 (12.8)	6 (8.8)
Hispanic	43 (39.5)	14 (20.6)
Asian/Pacific Islander	4 (3.7)	6 (8.8)
Other or mixed race/ethnicity	5 (4.6)	1 (1.5)
Maternal education (N, %)		
Some college, vocational or technical school or less	37 (33.9)	7 (10.3)
Bachelor's degree	30 (27.5)	28 (41.2)
Graduate degree	42 (38.5)	33 (48.5)

Paternal education (N, %)		
Some college, vocational or technical school or less	29 (26.6)	15 (22.1)
Bachelor's degree	32 (29.4)	23 (33.8)
Graduate degree	36 (33.0)	29 (42.7)
Missing	12 (11.0)	1 (1.5)
Maternal age at menarche (Mean±SD)	12.7 ± 1.7	12.6 ± 1.5
Maternal age at menarche, categorized (N, %)		
<12 years	27 (24.8)	16 (23.5)
12-13 years	55 (50.5)	40 (58.8)
≥14 years	25 (22.9)	12 (17.7)
Missing	2 (1.8)	0 (0.0)

*The participating guardian for 2 girls with serum measures is not the biological mother and early-life data is missing for these girls.
[a]More participants without serum samples participated in LEGACY by phone/mail and did not attend in-person clinic visits. They did not give blood or have body measures taken.

Supplemental Table 5.2. Difference in mean levels of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio by birthweight with and without adjustment for infant weight gain

	IGF-1 (ng/ml)		***IGFBP-3 (ng/ml)***		***IGF-1/IGFBP-3 molar ratio****	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
	Without adjustment for infant weight gain					
Birthweight (per 500g increase)	-15.64 (-42.43, 11.16)	-12.61 (-38.37, 13.15)	-29.58 (-241.24,182.08)	-32.55 (-244.41,179.30)	-0.02 (-0.05,0.01)	-0.01 (-0.04,0.01)
	With adjustment for infant weight gain[c]					
Birthweight (per 500g increase)	-4.61 (-37.49, 28.27)	-4.47 (-35.55,26.62)	-120.16 (-378.08,137.75)	-118.23 (-376.75,140.27)	0.01 (-0.03,0.04)	0.01 (-0.02,0.04)

Models include 29 girls with birthweight, infant growth and all covariate data.

*Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

[a]Adjusted for maternal pre-pregnancy BMI (continuous), weight-for-age or length-for-age Z-score at birth, age at blood draw (centered) and quadratic of age at blood draw (centered)

[b]Adjusted for maternal pre-pregnancy BMI (continuous), weight-for-age or length-for-age Z-score at birth, age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit (TS1 vs. TS2+) and BMI-for-age percentile at visit (centered)

[c]Change in weight-for-age Z-score from 0-12 months (continuous)

Supplemental Table 5.3. Associations between maternal, birth and infant factors and square-root transformed IGF-1 and IGF-1/IGFBP-3 molar ratio

	Square root of IGF-1 (ng/ml)			***Square root of IGF-1/IGFBP-3 molar ratio****		
	Model 2		p for intx with BCFH[a]	Model 2		p for intx with BCFH[a]
	β (SE)	P>t		β (SE)	P>t	
Maternal pre-pregnancy BMI (per 1 kg/m^2)[b]	0.06 (0.007)	0.26	0.38	0.00 (0.002)	0.85	0.06
Maternal recreational physical activity during pregnancy[c]			0.82			0.16
Inactive, no walking or other regular exercise	-1.04 (0.66)	0.12		-0.02 (0.02)	0.21	
Mostly inactive, equivalent to walking about half a mile or less every day	-0.50 (0.54)	0.35		0.01 (0.01)	0.70	
Somewhat active, equivalent to walking about 1 mile every day	0.02 (0.57)	0.97		0.00 (0.02)	0.84	
Active or highly active, equivalent to walking about ≥2 miles every day	Reference	-		Reference	-	
Gestational weight gain[c]			0.33			0.60
<20 lbs	0.13 (0.68)	0.85		0.01 (0.02)	0.58	
20-29 lbs	Reference	-		Reference	-	
30-39lbs	0.87 (0.53)	0.11		**0.04 (0.01)**	**0.01**	
40-49lbs	0.55 (0.63)	0.39		0.02 (0.02)	0.20	
≥50 lbs	0.69 (0.71)	0.33		0.01 (0.02)	0.47	
Maternal pre-pregnancy BMI and GWG[b]			0.15			0.17
BMI<25 and <30 lbs	Reference	-		Reference	-	
BMI<25 and ≥30 lbs	0.59 (0.55)	0.28		0.02 (0.02)	0.16	
BMI≥25 and <30lbs	0.49 (0.66)	0.47		0.00 (0.02)	0.91	
BMI≥25 and ≥30 lbs	1.54 (0.79)	0.05		0.04 (0.02)	0.10	
Birthweight (per 500g increase)[d]	**-0.44 (0.21)**	**0.04**	0.08	-0.01 (0.01)	0.11	0.42
Birthlength (per 1cm increase)[d]	0.007 (0.08)	0.93	0.16	-0.001 (0.002)	0.82	0.62
Growth from 0-12 months[e]						
Change in weight-for-age Z-score	0.55 (0.43)	0.20	0.30	**0.03 (0.01)**	**0.01**	0.57
Change in length-for-age Z-score	0.08 (0.48)	0.87	0.79	0.02 (0.02)	0.28	0.07
Growth from 0-6 months[e]						
Change in weight-for-age Z-score	0.05 (0.51)	0.92	0.42	0.01 (0.02)	0.48	0.40
Change in length-for-age Z-score	-0.16 (0.41)	0.70	0.73	-0.01 (0.01)	0.59	0.55
Growth from 6-12 months[f]						
Change in weight-for-age Z-score	1.39 (0.70)	0.05	0.27	**0.07 (0.02)**	**0.002**	0.42
Change in length-for-age Z-score	0.21 (0.55)	0.70	0.96	0.03 (0.02)	0.12	0.10

*Molar ratio = IGF-1(ng/ml)*0.1307 divided by IGFBP-3 (ng/ml)*0.03478

[a]P for interaction from F test from Model 2

[b]Adjusted for age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit and BMI-for-age percentile at visit (centered)

[c]Adjusted for age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit, BMI-for-age percentile at visit (centered) and maternal pre-pregnancy BMI

[d]Adjusted for maternal pre-pregnancy BMI (continuous), preterm, age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit and BMI-for-age percentile at visit (centered)
[e]Adjusted for maternal pre-pregnancy BMI (continuous), weight-for-age or length-for-age Z-score at birth, age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit (TS1 vs. TS2+) and BMI-for-age percentile at visit (centered)

[f]Adjusted for maternal pre-pregnancy BMI (continuous), weight-for-age or length-for-age Z-score at birth, change in weight-for-age or length-for-age Z-score from 0-6 months, age at blood draw (centered) and quadratic of age at blood draw (centered), breast Tanner stage at visit (TS1 vs. TS2+) and BMI-for-age percentile at visit (centered)