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Body mass index rebound and pubertal timing in girls with and without a family history of breast cancer: the LEGACY girls study

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Abstract

Background: Heavier body mass index (BMI) is the most established predictor of earlier age at puberty. However, it is unknown whether the timing of the childhood switch to heavier BMI (age at BMI rebound) also matters for puberty.

Methods: In the LEGACY Girls Study ($n = 1040$), a longitudinal cohort enriched with girls with a family history of breast cancer, we collected paediatric growth chart data from 852

girls and assessed pubertal development every 6 months. Using constrained splines, we interpolated individual growth curves and then predicted BMI at ages 2, 4, 6, 8 and 9 years for 591 girls. We defined age at BMI rebound as the age at the lowest BMI between ages 2 and 8 years and assessed its association with onset of thelarche, pubarche and menarche using Weibull survival models.

Results: The median age at BMI rebound was 5.3 years (interquartile range: 3.6–6.7 years). A 1-year increase in age at BMI rebound was associated with delayed thelarche (HR = 0.90; 95% CI = 0.83–0.97) and menarche (HR = 0.86; 95% CI = 0.79–0.94). The magnitude of these associations remained after adjusting for weight between birth and 2 years, was stronger after adjusting for BMI at age 9, and was stronger in a subset of girls with clinically assessed breast development.

Conclusions: Earlier BMI rebound is associated with earlier pubertal timing. Our observation that BMI rebound may be a driver of pubertal timing in girls with and without a family history of breast cancer provides insight into how growth and pubertal timing are associated with breast cancer risk.

Key words: Growth, puberty, BMI, adiposity rebound

Key Messages

- Body mass index (BMI) is an established predictor of pubertal timing, but most studies only study BMI at a single time point.
- The BMI rebound is the sharp increase in BMI after a period of decline that occurs between the ages of 3–8 years.
- In a longitudinal cohort of girls we show a strong and persistent association between earlier age at BMI rebound and earlier pubertal timing, independent of body size at prior ages or body size close to the onset of puberty.
- We demonstrate that when fat accumulation starts matters for pubertal timing in addition to how much (BMI) and how fast or slow (BMI velocity).

Introduction

Larger body size is an established predictor of early age at girls' puberty.[1,2] Most studies have focused on body size at a singular time point either during infancy[3–6] or in childhood,[7–11] and few have taken a longitudinal approach from birth to puberty.[2] One exception is the joint analysis of the Project VIVA and PROBIT cohorts, which concluded that the onset of puberty is influenced by a 'two-hit program',[12,13] with the first hit exerted through height during the infancy–childhood transition (ages 6–12 months) and the second occurring at the childhood–juvenility transition (ages 5–7 years) based on body mass index (BMI) and its rebound.[12,13]

The BMI rebound, the term given to the sharp increase in BMI after a period of decline, typically occurs between the ages of 3–8 years.[14] Despite debate as to whether this pattern reflects biology or a statistical artefact,[15] there is growing evidence that timing of BMI rebound is an important predictor of thelarche (onset of breast development) and menarche.[16] The BMI rebound occurs during adrenarche, when adrenal androgens start to rise.[17] As with early BMI rebound, early adrenarche is associated with earlier pubertal development.[18,19] Thus, these two characteristics of middle childhood may hint at underlying hormonal programming relevant to pubertal timing.

To date, it is unknown whether absolute BMI, the rate of change in BMI (BMI velocity) or timing of that change (BMI rebound) are each associated independently with pubertal timing. To answer these questions, we used growth data from paediatric growth charts and prospective puberty data assessed every 6 months in the LEGACY Girls Study cohort[20] to model growth during the childhood slow growth period (ages 2–8 years), and examined whether absolute BMI, BMI velocity, and age at BMI rebound were associated with pubertal timing.

Methods

Study sample

The LEGACY Girls Study[20] (www.legacygirlsstudy.org) enrolled 1040 girls primarily between the ages of 6–16 years (median age = 10 years) at five study sites in the

USA (New York City, NY; Philadelphia, PA; Salt Lake City, UT; San Francisco Bay Area, CA) and Canada (Toronto, ON). Girls born between 1995–2007 were enrolled from 2011–13 and followed until mid-2016.[20] The study received internal review board approval from each institution, which included obtaining consent from mothers/guardians and assent from girls, This analysis was conducted under Columbia University Internal Review Board (IRB) protocol AAAC5578. At enrolment, about half of the girls had a family history of breast cancer defined as having one or more first- or second-degree relatives diagnosed with breast cancer. Using pedigree data collected at baseline, we calculated an absolute risk score for breast cancer based on the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA; Web program v3; University of Cambridge, Cambridge, UK).[21,22]

Data collection

We assessed pubertal outcomes and other variables using questionnaires and measuring height and weight, with most items collected every 6 or 12 months through in-person visits. Mothers/guardians completed questionnaires for girls of all ages. At baseline, mothers/guardians reported their daughter's race and ethnicity, birthweight, maternal age at daughter's birth, gestational weight gain, age at maternal menarche and maternal education. Pubertal development was assessed through the Growth and Development Questionnaire, which included the Pubertal Development Scale (PDS)[23] (questions enquiring about stages of breast and pubic hair development and age at menarche) and the Sexual Maturation Scale (SMS)[24] (drawings showing the five Tanner stages of breast and pubic hair development).

Growth data: we measured height and weight twice at each in-person visit and averaged the two measures for analysis. Due to the design of the study, the earliest measurements were taken between ages 6–16 years, the age range at study enrolment. To assess growth from birth until age at enrolment, we collected growth charts and records from the participants' paediatricians, extracting age, height and weight. Because we were interested in capturing the BMI rebound for this analysis, we included girls with growth measurements between ages 2 and 8 years, and also girls with measurements up to age 9, so that we could include a measure of pre-pubertal body size in adjusted models. Of the 1040 girls in the cohort, we received 852 growth charts. From those charts, 591 girls had height and weight recorded between the ages of 2 and 9 years. Birthweight and birth length data were available for 576 and 507 of the 591 girls, respectively.

Interpolated growth: using constrained smoothing B-splines,[25] we fitted individual growth curves for height and weight for each girl. We forced the height curves to be monotonic. Using the fitted growth curves, we estimated height, weight and BMI at ages 2, 4, 6, 8 and 9 years for each girl. If a target age was outside the range of observed ages for a girl, we extrapolated her growth measure using the same fitted growth curve, but only when the extrapolation window (i.e. between the target age and its nearest observed age) was not longer than 180 days. We implemented this restriction to avoid large extrapolation errors. This resulted in the following sample sizes: 341 for BMI at age 2 years, 445 for BMI at age 4, 513 for BMI at age 6, 474 for BMI at age 8 and 395 for BMI at age 9. Correlations between height and weight measured at the nearest whole year and interpolated values at each age ranged from 0.67 to 0.95 (Supplementary Table S1, available as Supplementary data at *IJE* online).

BMI rebound: The BMI rebound is the sharp increase in childhood BMI after a period of decline. From the estimated growth curves, we identified the age at the lowest BMI for each girl between the ages of 2 and 8 years. If the age at the lowest BMI was less than 3 years, we categorized these girls as not having a rebound. For girls whose lowest BMI was age 3 years or after, their age at rebound was set equal to the age at the lowest BMI. We created an indicator variable for the absence or presence of BMI rebound, and an age at BMI rebound variable, centred at the mean.

Puberty: the outcomes were: thelarche (breast development onset), pubarche (pubic hair development onset) and menarche. At two LEGACY sites, New York and Utah, trained female research staff or a physician performed standardized clinical breast Tanner staging, with palpation. We have previously shown the PDS to have better accuracy than the SMS in relation to clinical breast Tanner staging[26] and, therefore, chose this measure as the primary outcome.

Statistical analyses

We used Weibull survival models to examine the associations between growth measurements and age at thelarche, pubarche and menarche. The number of left-, interval- and right-censored events were respectively 262, 261 and 66 for thelarche; 217, 219 and 151 for pubarche; and 87, 204 and 286 for menarche. Weibull models consider the mixture of censoring and yield hazard ratios (HR), with HRs greater than 1 indicating greater hazards of having started puberty at a given age. Correlations within siblings were accounted for using robust standard error estimations.

Absolute body size: using the Centers for Disease Control and Prevention (CDC) references and

corresponding program in SAS,[27] we converted these measures to z-scores for height, weight and BMI. We first modelled the associations of birthweight and BMI, and height and weight z-scores at ages 2, 4, 6 and 8 years separately with the onset of each pubertal outcome, adjusted for race/ethnicity. We then expanded the model with birthweight to include z-scores at age 2, 4, 6 and 8 years, one at a time. This way, at a given age we adjusted the associations for birthweight and body size *z*-score in all previous age periods, but not in subsequent age periods. Height models were also adjusted for birth length.

Growth velocity: we calculated BMI, height and weight velocity by the change in body size z-scores between the target ages. For example, we approximated BMI velocity between ages 2 and 4 years by subtracting the BMI z-score at age 2 years from the BMI z-score at age 4 years. Using the Weibull model, we evaluated the association between velocity at different ages with each pubertal outcome, while adjusting for race/ethnicity, birthweight and growth between previous age periods, but not in subsequent age periods.

BMI rebound: we modelled the association between BMI rebound and pubertal milestones using a set of nested models. Model 1 was unadjusted, including only the binary indicator of whether a BMI rebound was observed between ages 2 and 8 years and the age at rebound. Model 2 expanded Model 1 by adjusting for race/ethnicity. We further adjusted for birthweight (Model 3), change in weight z-scores between birth and age 2 years (Models 4 and 5) and BMI z-score at age 9 years (Models 6 and 7). We tested for interactions with breast cancer family history by including a cross-product term between the BOADICEA risk score and both the BMI rebound indicator variable and the age at rebound variable in Model 2. We also assessed interactions with study site to account for contextual differences across the sites.

In sensitivity analyses, we assessed thelarche using the SMS as assessed by mothers/guardians and clinicians. Because we know BMI around the onset of puberty is a strong predictor of pubertal timing, we also restricted our sample to those not overweight (<85th percentile according to the CDC growth references) at enrolment into the study.

Results

The median age at BMI rebound was 5.3 years (interquartile range 3.6–6.7 years). The predicted median ages at thelarche, pubarche and menarche for the study sample were 9.7, 10.7 and 12.8, respectively.

Table 1 compares sample characteristics between girls with and without a BMI rebound, with an early (<5.3 years) or late (≥5.3 years) age at BMI rebound, and those with and without growth chart data. A greater proportion of Hispanic girls had a late rather than an early BMI rebound, whereas a greater proportion of Black girls had an early rather than a late BMI rebound. Girls with a BMI rebound had larger CDC standardized BMI z-scores than girls without rebound, particularly girls who had an early BMI rebound. A greater proportion of girls had early BMI rebound if they had a family history of breast cancer compared with girls without a family history of breast cancer. The sub-sample of girls with growth chart data between the ages of 2 and 9 years had higher birthweights and BMI at baseline than girls without these data.

Table 2 shows the associations of body size at ages 2, 4, 6 and 8 years and growth velocity between birth and ages 2, 4, 6 and 8 with age at thelarche, pubarche and menarche. Greater growth in weight and BMI starting from age 2 were associated with earlier thelarche. Height was not associated with the timing of thelarche. For pubarche, greater growth in BMI and weight at 8 years and between ages 6 and 8 years were associated with earlier onset. Taller height at ages 4 and 6 years and faster height velocity between ages 4 and 6 were associated with earlier pubarche. For menarche, greater growth in weight and height at ages 6 and 8 years were associated with earlier onset. Faster height velocity between ages 4 and 6 years and between ages 6 and 8 years were also associated with earlier menarche. Faster BMI velocity between ages 2 and 4 was associated with earlier menarche.

A later age at BMI rebound was associated with delayed thelarche and menarche (Table 3). Specifically, with a 1-year increase in age at BMI rebound, there was a 10% decreased likelihood of thelarche (HR = 0.90; 95% CI = 0.83–0.97) and a 14% decreased likelihood of menarche (HR = 0.86; 95% CI = 0.79–0.94). These HRs translate to a 1–2 month delay in pubertal age per 1 year delay in BMI rebound. The magnitude of association for both these outcomes remained relatively stable after adjusting for birthweight and change in weight from birth to age 2. These associations were stronger after adjusting for BMI at age 9, indicating that even in girls with the same prepubertal BMI (an established predictor of pubertal timing), the BMI rebound was still associated with their age at thelarche and menarche. The results remained unchanged when restricting the analyses to girls who were not overweight (BMI percentile <85) at baseline (data not shown). Further adjustment for maternal factors, including maternal age at daughter's birth, gestational weight gain, maternal age at menarche and maternal education did not materially alter the HR estimates (data not shown). There was no association between BMI rebound and age at pubarche.

Table 1 Sample Characteristics between girls: with and without a Body mass Index (BMI) rebound, with an early (<5.3) or late (≥5.3) age at BMI rebound, and with and without growth chart data

	BMI rebound		Age at rebound (cut at median 5.3 years)		Growth data available	
	Rebound	No rebound	Early age at rebound	Late age at rebound	No growth data	Growth data
N	481	109	191	290	477	591
	n (%) or mean (SD)		*n* (%) or mean (SD)		*n* (%) or mean (SD)	
Race/ethnicity						
Hispanic	79 (16.4)	8 (7.3)	23 (12.0)	56 (19.3)	109 (22.9)	87 (14.7)
Black	37 (7.7)	9 (8.3)	21 (11.0)	16 (5.5)	33 (6.9)	46 (7.8)
Non-Hispanic White	311 (64.7)	75 (68.8)	122 (63.9)	189 (65.2)	282 (59.1)	387 (65.5)
Asian	42 (8.7)	11 (10.1)	19 (10.0)	23 (7.9)	40 (8.4)	53 (9)
Other	12 (2.5)	6 (5.5)	6 (3.1)	6 (2.1)	13 (2.7)	18 (3.1)
Geographical site						
Philadelphia	94 (19.5)	15 (13.8)	33 (17.3)	61 (21)	50 (10.5)	109 (18.4)
New York	89 (18.5)	22 (20.2)	35 (18.3)	54 (18.6)	65 (13.6)	112 (19)
Utah	74 (15.4)	9 (8.3)	25 (13.1)	49 (16.9)	95 (19.9)	83 (14)
Ontario	81 (16.8)	29 (26.6)	40 (20.9)	41 (14.1)	82 (17.2)	110 (18.6)
California	143 (29.7)	34 (31.2)	58 (30.4)	85 (29.3)	185 (38.8)	177 (30)
Body size						
Birthweight (g)	3256 (604)	3357 (485)	3281 (616.3)	3239 (597)	3315 (580)	3276 (585)
Birth length	50.5 (3.4)	50.4 (3.8)	50.5 (3.6)	50.4 (3.8)		
BMIz[a] at age 2	−0.60(1.8)	−0.14 (2.3)	0.10 (2.2)	−0.43 (2.5)		
BMIz at age 4	0.63 (1.0)	0.02 (1.8)	0.05 (2.0)	−0.002 (1.59)		
BMIz at age 6	−0.66 (1.0)	−0.19(2.3)	0.13 (2.7)	−0.42 (2.0)		
BMIz at age 8	0.50 (1.7)	0.02 (1.5)	0.41 (1.5)	−0.19 (1.4)		
BMIz at ge 9	0.50 (0.84)	−0.05 (1.1)	0.33 (1.0)	−0.23 (1.2)		
BMIz at baseline	−0.13 (1.19)	0.10 (1.20)	0.14 (1.10)	−0.30 (1.22)	−0.57 (1.20)	−0.82 (1.19)
Family history of breast cancer						
None	241 (50.8)	46 (42.2)	89 (47.3)	152 (53.2)	227 (48)	288 (49.3)
1st degree	87 (18.4)	18 (16.5)	36 (19.2)	51 (17.8)	117 (24.7)	105 (18)
2nd degree	146 (30.8)	45 (41.3)	63 (33.5)	83 (29)	129 (27.3)	191 (32.7)
Maternal age at menarche	12.7 (1.6)	12.7 (1.5)	12.5 (1.6)	12.8 (1.5)	12.7 (1.5)	(1.5)

[a]Body mass index z-score.

There were no statistically significant interactions between age at BMI rebound and breast cancer family registry, race/ethnicity or study site. The magnitude of the associations was stronger using clinical assessments of thelarche. For example, the HR for the association between BMI rebound and earlier thelarche, adjusted for race/ethnicity, was 0.90 (0.83–0.97) using PDS and was 0.83 (0.72–0.94) using clinical assessment, respectively (Supplementary Table S2, available as Supplementary data at *IJE* online).

Figure 1 illustrates how an acceleration in BMI rebound can affect pubertal timing with implications for breast cancer risk. The Breakthrough Generations Study[28] demonstrated that girls who reach thelarche before age 10 are at 20% increased risk for breast cancer. The clinical relevance of a 1.2-month acceleration in thelarche due to a 1-year acceleration in BMI rebound translates to 20% more girls at 20% increased risk for breast cancer. Our logic is as follows. In the current LEGACY sample, the median age at thelarche is 9.8 years and median age at BMI rebound is 5.8 years. Of these, 62% of girls reached thelarche before age 10 and are thus at 20% increased risk for breast cancer. If the proportion of girls that reached BMI rebound at age 7.3 years were to reach it at age 6.3 years instead, then their age at thelarche would shift from 10.1 to less than 10 (a 1.2-month difference). This would shift 20% of girls into the zone of 20% increased risk of breast cancer.

Discussion

This study adds to the sparse evidence base regarding the influence of body size and growth on puberty in distinct periods of childhood, not just infancy; and it has implications for understanding early life risk factors (BMI and pubertal timing) for breast cancer. We demonstrated that a later age at BMI rebound was associated with delayed

Table 2 Associations between body size and growth velocity with the age at thelarche, pubarche and menarche

	Thelarche HR (95% CI)	Pubarche HR (95% CI)	Menarche HR (95% CI)
Birthweight (per 100 g)[a]	1.04 (1.02–1.055)	1.00 (0.99–1.00))	1.00 (0.99–1.00)
BMI[b]			
BMI at age 2	1.03 (0.97–1.09)	1.04 (0.96–1.13)	0.96 (0.86–1.08)
BMI at age 4	1.04 (0.92–1.18)	0.96 (0.86–1.06)	1.11 (0.95–1.3)
BMI at age 6	1.15 (1.01–1.32)	1.07 (0.97–1.17)	1.12 (0.85–1.48)
BMI at age 8	1.11 (0.90–1.36)	1.21 (1.06–1.38)	1.24 (0.82–1.88)
BMI velocity[c]			
2 to 4	1.02 (0.95–1.1)	0.98 (0.90–1.06)	1.12 (1.01–1.25)
4 to 6	1.11 (0.99–1.25)	1.07 (0.98–1.16)	1.11 (0.90–1.37)
6 to 8	1.04 (0.90–1.21)	1.15 (1.02–1.30)	1.18 (0.88–1.6)
Weight[d]			
Weight at age 2	0.96 (0.89–1.04)	0.97 (0.87–1.08)	1.04 (0.91–1.18)
Weight at age 4	1.06 (1.00–1.12)	1.01 (0.91–1.13)	1.01 (0.84–1.22)
Weight at age 6	1.01 (0.97–1.05)	1.04 (0.94–1.14)	0.98 (0.95–1.02)
Weight at age 8	1.28 (1.01–1.63)	1.45 (1.18–1.79)	1.53 (1.14–2.07)
Weight velocity[e]			
0 to 2	0.96 (0.89–1.04)	0.97 (0.87–1.07)	1.04 (0.91–1.18)
2 to 4	1.06 (1.00–1.12)	1.01 (0.91–1.12)	1.01 (0.84–1.22)
4 to 6	1.01 (0.97–1.05)	1.04 (0.95–1.14)	0.98 (0.95–1.02)
6 to 8	1.28 (1.00–1.64)	1.44 (1.17–1.78)	1.54 (1.14–2.07)
Birth length	1.04 (1.01–1.08)	1.00 (0.97–1.03)	1.00 (0.97–1.04)
Height[f]			
Height at age 2	1.03 (0.97–1.08)	1.01 (0.98–1.05)	1 (0.97–1.04)
Height at age 4	0.99 (0.84–1.16)	1.24 (1.04–1.48)	1 (0.78–1.29)
Height at age 6	1.18 (0.91–1.52)	1.55 (1.12–2.15)	1.53 (1.06–2.21)
Height at age 8	0.91 (0.81–1.03)	0.95 (0.61–1.48)	1.52 (1.17–1.98)
Height velocity[g]			
0 to 2	1.03 (0.97–1.08)	1.01 (0.98–1.04)	1.01 (0.97–1.04)
2 to 4	0.97 (0.83–1.15)	1.10 (0.92–1.32)	1.04 (0.82–1.31)
4 to 6	1.11 (0.87–1.42)	1.4 (1.00–2.00)	169 (1.14–2.51)
6 to 8	0.91 (0.80–1.03)	0.91 (0.62–1.32)	1.46 (1.08–1.98)

[a]Model 1: adjusted for race/ethnicity.

[b]Model 2: body mass index (BMI) z-score at each age is adjusted for birthweight and race/ethnicity and then modelled progressively including BMI at the preceding age.

[c]Model 3: BMI velocity at each age is adjusted for birthweight and race/ethnicity and then modelled progressively including BMI velocity between the preceding age periods.

[d]Model 4: weight z-score at each age is adjusted for birthweight and race/ethnicity and then modelled progressively including weight at the preceding age.

[e]Model 5: weight velocity at each age is adjusted for birthweight and race/ethnicity and then modelled progressively including weight velocity between the preceding age periods.

[f]Model 6: height z-score at each age is adjusted for birthweight and race/ethnicity and then modelled progressively including height at the preceding age.

[g]Model 7: height velocity at each age is adjusted for birthweight and race/ethnicity and then modelled progressively including height velocity between the preceding age periods.

onset of breast development and menarche. The age at BMI rebound was associated with pubertal timing independent of childhood BMI (at age 9), an established risk factor for early puberty.[9,29]

We observed an average age of 6 and a median age of 5.3 for BMI rebound, in line with national studies [mean (SD)=5.6(0.89)].[16] We confirmed the findings seen in Chinese girls that earlier adiposity rebound is associated with earlier thelarche.[30] Our findings between later rebound and later age at menarche confirm findings from a 1970s birth cohort in New Zealand that found a correlation of 0.37.[16] In the present study, 82% of girls had a BMI rebound compared with only 47% of girls in the NICHD Study of Early Child Care and Youth Development,[13] which found that thelarche and menarche occurred significantly earlier in girls with a BMI rebound compared with those without. Our analyses differed from the NICHD study in that we considered age at BMI

Table 3 Association [hazard ratio (95% confidence interval)] between age at body mass index (BMI) rebound (per 1-year increase) and age at thelarche, pubarche and menarche

	BMI rebound			BMI rebound and weight change 0 to 2		BMI rebound and BMIz at age 9	
Model	1	2	3	4	5	6	7
Thelarche							
N	589	589	575	336	336	384	384
No rebound	1.19 (0.98–1.58)	1.24 (0.93–1.65)	1.14 (0.85–1.53)	1.14 (0.84–1.55)	1.16 (0.85–1.58)	1.1 (0.78–1.60)	1.1 (0.73–1.53)
Age at rebound (per 1 year)	**0.90 (0.83–0.97)**	**0.90 (0.83–0.97)**	**0.91 (0.84–0.98)**	**0.87 (0.78–0.97)**	**0.87 (0.78–0.96)**	**0.90 (0.82–0.99)**	0.95 (0.85–1.06)
Pubarche							
N	587	587	573	335	335	382	382
Nor ebound	1.01 (0.78–1.31)	1.05 (0.81–1.40)	1.04 (0.80–1.34)	0.98 (0.73–1.33)	0.99 (0.73–1.35)	0.99 (0.72–1.38)	0.94 (0.67–1.32)
Age at rebound (per 1 year)	0.96 (0.9–1.03)	0.95 (0.88–1.02)	0.94 (0.87–1.01)	0.90 (0.80–1.01)	0.89 (0.80–1.00)	0.93 (0.86–1.01)	0.96 (0.88–1.04)
Menarche							
N	589	589	575	336	336	384	384
No rebound	0.83 (0.54–1.29)	0.85 (0.55–1.30)	0.86 (0.55–1.34)	0.87 (0.56–1.35)	0.88 (0.57–1.35)	0.86 (0.52–1.40)	0.82 (0.51–1.30)
Age at rebound (per 1 year)	**0.87 (0.79–0.95)**	**0.86 (0.79–0.94)**	**0.85 (0.77–0.93)**	**0.75 (0.65–0.88)**	**0.76 (0.65–0.88)**	**0.85 (0.78–0.94)**	**0.90 (0.81–1.00)**

Model 1: crude.
Model 2: adjusted for race/ethnicity.
Model 3: Model 2 additionally adjusted for birthweight.
Model 4: Model 3 restricted to girls with data on body mass index (BMI) at age 2.
Model 5: Model 4, additionally adjusted for weight change from birth to age 2 years.
Model 6: Model 3 restricted to girls with data on BMI at age 9.
Model 7: Model 6 additionally adjusted for BMI at age 9.
Significant results are bolded.

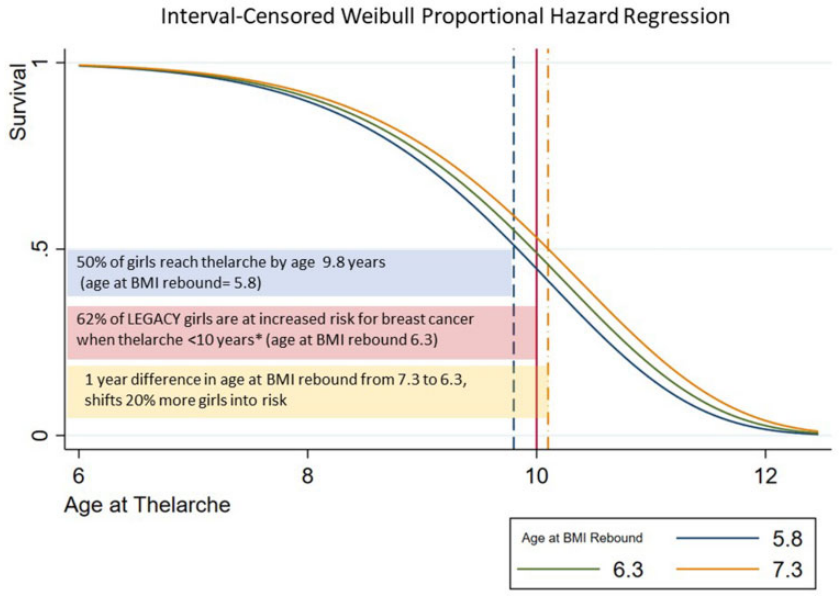

Figure 1 Impact of accelerated body mass index (BMI) rebound and thelarche on breast cancer risk. We calculated the median age at thelarche (9.8 years) and BMI rebound (5.8 years) in the LEGACY study sample. From the Breakthrough Generations Study[28] we know that girls who reach thelarche before age 10 are at 20% increased risk for breast cancer. In the LEGACY sample, 62% of girls reached thelarche before age 10 and are thus at 20% increased risk for breast cancer. If the girls who reached BMI rebound at age 7.3 were instead to reach it at age 6.3, then their age at thelarche would shift from 10.1 to less than 10 (a 1.2-month difference). This would shift 20% more girls into the zone of 20% increased breast cancer risk

rebound in addition to whether or not a rebound occurred. When we only considered the presence vs absence of a BMI rebound, then we observed delayed thelarche and no association with age at menarche (data not shown).

The present results support that the age at BMI rebound was associated with timing of puberty irrespective of birthweight and weight between birth and age 2 years, suggesting that its association is not a function of tracking or compensating for growth at earlier ages. The finding that BMI during older compared with younger ages is more strongly associated with pubertal timing is consistent with other studies.[12,13] Our study is the first to demonstrate that BMI rebound is associated with pubertal milestones in girls with and without a family history of breast cancer.

BMI rebound captures the transition from a period of stable to increasing accumulation of fat mass.[14] The strong and persistent association of age at BMI rebound with age at thelarche and menarche, independent of body size at prior ages or body size close to the onset of puberty, strengthens the conclusion that when fat accumulation starts matters for pubertal timing in addition to how much fat accumulation (BMI) and how fast or slow (BMI velocity). The possibility remains that both growth and pubertal timing reflect a common underlying genetic susceptibility, as suggested by a recent study that found an association of the BMI rebound and early puberty only among girls with genetic predisposition to early puberty.[31] It is also possible that the BMI rebound that we detect is not a biological but rather a mathematical artefact. Bogin, a critic of the conceptualization of the adiposity rebound, argues that the BMI decreases before the rebound not because of fat, but because of the proportion of leg length to overall height.[15,32] Future studies need to determine whether the age at BMI rebound can be modified by diet and physical activity in young children with underlying genetic risk for early puberty and/or breast cancer. Future studies should also consider other measures of adiposity, such as % body fat, given that BMI is only a proxy; however we focused on BMI since it is most translatable to medical settings.

The BMI rebound, which occurs during the childhood to juvenility transition, may be a marker for adrenarche, the rise in adrenal androgens, that is a precursor to pubertal development.[13,17] If this is the case, then our findings are also consistent with studies that show that an earlier age at adrenarche accelerates pubertal timing.[19,33] The concurrent increase in androgens and adipose tissues may lead to peripheral conversion of androgens into oestrogens, explaining earlier thelarche and menarche in girls with earlier BMI rebound.[19] However, it is unclear why BMI rebound was not associated with pubarche in the present study, given that is it also driven by androgens.

Our study has many strengths including the use of growth chart data which provided objective measures to complement the measurement of height and weight. The high collection rate of growth chart data suggests that future life course epidemiological studies may not need to rely as heavily on self-reported measures. Even though we did not have complete growth data on all girls at every age, our interpolation methods yielded high correlations with measured values (Supplementary Table S2, available as Supplementary data at *IJE* online). One limitation in the growth data was incomplete data on birth length; however, adjusting only for birthweight in girls who also had birth length data did not change estimates when both covariates were in the model (data not shown). Unlike other studies, we assessed the pubertal outcomes prospectively every 6 months; most studies assessed it at selected ages[12] or annually.[13] The gold standard for pubertal assessment is clinically assessed Tanner staging; our results were even stronger in the subset of girls with these clinical data as a result of the greater sensitivity, but lower specificity, of the PDS when compared with clinical Tanner staging.[26,34] The study population was a diverse sample in terms of race/ethnicity and included a large proportion of girls with a breast cancer family history, which enabled us to examine interactions with both factors. Age at BMI rebound was an important risk factor for girls with and without breast cancer family history.

In conclusion, we observed a 1–2-month delay in the ages at of onset of breast development and menarche with every 1-year increase in age at BMI rebound. Whereas BMI has long been the most established predictor of pubertal timing,[1] we found that timing of the BMI increase may be an important earlier predictor of pubertal timing and could be determined at paediatric visits which collect growth chart data at annual visits. This would have lasting impact for adolescent health as well as lifelong breast cancer risk.

Supplementary data

Supplementary data are available at *IJE* online.

Ethics approval

All participating institutions (Columbia University Medical Center, Cancer Prevention Institute of California, Lunenfeld Tanenbaum Research Institute of Sinai Health System, Huntsman Cancer Institute at University of Utah, Fox Chase Cancer Center, Children's Hospital of Pennsylvania, and the University of Pennsylvania) obtained institutional review board approval to conduct the study. Mothers/guardians provided written informed consent, and girls provided assent based on institutional standards.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author Contributions

L.C.H. conceptualized the set of analyses presented in this study, conducted the data analysis and interpretation and drafted the initial manuscript. M.B.T., E.M.J., I.L.A., M.B.D., S.S.B. and A.R.B. conceptualized the design of the overall parent study. M.B.T., E.M.J., T.H.M.K., I.L.A., J.A.K., M.B.D., S.S.B., A.R.B., W.K.C., L.A.S., R.L.S., C.J.F., K.O.T., M.L.W. participated in the collection and assembly of data analysis and interpretation and manuscript writing for this paper. Y.W., T.W., M.G. and A.P.A. participated in the analysis and interpretation of the data and reviewed and revised the manuscript. Y.W. and A.S.W. participated in the analysis and interpretation of data and manuscript writing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

None declared.

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