Associations between infant growth and pubertal onset timing in a multiethnic prospective cohort of girls

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Abstract

Background: Early puberty increases risk of adverse health conditions throughout the life course. US girls are experiencing earlier puberty without clear reasons. Studies suggest early life factors, such as infant growth, may influence pubertal timing. We assessed the associations between infant growth and onset of breast development (thelarche), pubic hair development (pubarche), and menarche in girls.

Methods: A prospective cohort of girls born at a Kaiser Permanente Northern California medical facility in 2005–11 was used. Weight-for-age z-scores were calculated at birth and 24 months. Difference in z-scores greater than 0.67 represent rapid “catch-up” growth, less than -0.67 represent delayed “catch-down” growth, and between -0.67 and 0.67 represent “normal” growth. Pubertal onset was measured using clinician-assessed sexual maturity ratings (SMRs) and defined as the age at transition from SMR 1 to SMR 2+ for both thelarche and pubarche. SMR data was collected through June 2020. Menarche was analyzed as a secondary outcome. Weibull and modified Poisson regression models were used. Models were adjusted for potential confounders.

Results: There were 15,196 girls included in the study. Approximately 30.2% experienced catch-up growth, 25.8% experienced catch-down growth, and 44% had normal growth. Girls with catch-up growth had increased risk of earlier thelarche (hazard ratio = 1.26, 95% confidence interval (CI): 1.18, 1.35), pubarche (1.38, 95% CI: 1.28, 1.48), and menarche (< 12y, relative risk = 1.52, 95% CI: 1.36, 1.69) compared to those with normal growth, after adjusting for covariates. These associations were partially mediated by childhood body mass index. Catch-down growth was associated with later pubertal onset.

Conclusions: Girls who experience infant catch-up growth have higher risk of earlier pubertal development compared to girls with normal growth and the associations are partially explained by childhood obesity. This information may help clinicians to monitor girls who are at high risk of developing earlier.

Keywords: Adolescent health, Infant development, Childhood overweight, Puberty

Background

Girls in the U.S. are experiencing puberty earlier, compared with just a few decades ago [1]. This trend is an important public health concern because early puberty in girls is associated with higher risks of adverse mental and physical health conditions throughout the life course [2–5]. Childhood obesity is a known predictor...
of pubertal timing; however, it alone does not explain the trend toward earlier puberty as children with normal body mass index (BMI) are also experiencing similar trends [6]. Because sexual developmental events are part of a continuum that begins during intrauterine life, perinatal factors likely influence the programming of pubertal maturation [7].

Previous studies have reported that infant catch-up growth is associated with earlier puberty [8–13]. However, these studies have several methodological limitations. First, many of these studies focused on self-reported age at menarche. Girls’ pubertal transitions take place over several years, often starting with thelarche, typically followed by pubarche, acne, a growth spurt, and then menarche. Despite occurring late in the pubertal process, menarche is often used as the only pubertal marker. Recent studies have reported that timing of thelarche and pubarche may be more important risk factors for adverse outcomes such as depression, substance abuse, and delinquency in adolescents [14–16] than age at menarche, thus examining pubertal onset as an outcome is also important. Second, few previous studies have used clinician-assessed sexual maturity ratings (SMRs), also known as Tanner stages, an established gold standard 5-point staging system for breast and pubic hair development [17]. Among previous studies that used SMRs, only one conducted in China used clinician-assessed SMRs [18], while others were self-reported [10, 13]. Lastly, many studies did not include important covariates of infant weight gain and pubertal development, such as maternal gestational weight gain (GWG), prior livebirths, or childhood obesity [19–21]. Since infant catch-up growth is strongly associated with GWG [19, 20] and childhood obesity [22, 23], it is important to include these variables in the analysis. We addressed these limitations by conducting a prospective study using a large, racially/ethnically diverse cohort of girls from Northern California and comprehensive clinical data.

**Methods**

**Cohort selection**

A birth cohort of mother-daughter pairs were identified from the Kaiser Permanente Northern California (KPNC) electronic health record (EHR) system and were followed until June 30, 2020. KPNC is an integrated health care delivery system serving over 4.4 million members in Northern California. KPNC members are representative of the general population of Northern California with regard to ethnicity and education [24, 25]. Eligibility for the girls included: singleton and full-term (>36 weeks gestation) birth at a KPNC medical facility between 2005 and 2011, continuous KPNC membership during the follow-up period, with coverage gaps of ≤90 days, availability of childhood BMI measurement (5–6 years old), at least one SMR assessment (details described below) between ages 5 and 18 years, and weight measurements at birth and within two weeks of their second birthday. Exclusion criteria include: girls with medical conditions affecting growth and development, such as adrenal tumors and congenital adrenal hyperplasia (n=478) and mothers with extreme BMI (<15 kg/m² or >60 kg/m²) (n=12). The final cohort consisted of 15,196 mother-daughter pairs. All the data were obtained from the KPNC EHR system and administrative databases.

**Exposure**

Infant growth was measured as weight trajectory patterns and calculated using change in weight-for-age z-scores between birth and 24 months. Z-scores were determined using age- and sex-specific Centers for Disease Control and Prevention year 2000 standard population distributions [26]. A change in z-score was categorized as “catch-up” growth when >0.67; “catch-down” growth when < -0.67; and “normal” growth for change in z-scores ranging between -0.67 and 0.67. A z-score of 0.67 has been used previously to indicate clinically-significant catch-up or catch-down growth [27].

**Outcomes**

Starting in 2010, KPNC pediatricians and family physicians began documenting in the EHR 5-point SMR [17] (1 = no development; 5 = full maturation) as part of routine pediatric checkups starting at age 6 years. At KPNC, breast SMRs are determined using palpation and visual inspection, while pubic hair SMRs are assessed using visual inspection. We have confirmed the validity of using the KPNC EHR system SMR data in a previous study [28]. In the present study, our primary outcomes of interest were age at transition from SMR 1 (prepubertal) to SMR 2+ for breast (thelarche) and pubic hair (pubarche). Given the study design, we are unable to observe the exact ages at these transitions. However, using the information obtained from observed SMRs at routine checkups, standard statistical methods can be applied to estimate age at onset distributions and measures of association between covariates and age of thelarche and pubarche.

Girls who indicated having gotten their menses before 12 years, the current average age of menarche in the United States, were categorized as having ‘earlier’ menarche [29]. Menarche data was collected using responses from KPNC health check-up questionnaires. Questions about menses are asked at Well-Child 10–12 Years (“Has your daughter started menstruating?”) and Well-Teen (“Have you started your period?”) check-ups.
Girls were considered to have earlier menarche if they responded “Yes” before age 12 years. Girls who responded “No” before or after 12 years were considered to have normal/later menarche. Girls who responded “Yes” after age 12 years and had no data before 12 years were excluded from analyses to prevent misclassification.

**Covariates**

BMI percentiles [26] were calculated using girls’ weight and height obtained from clinic visits between the ages 5 and 6 years old.

In our analyses, we adjust for clinically relevant covariates that have been associated with infant anthropometric measurements and later pubertal development. These include GWG [30, 31], maternal age at delivery (years) [32, 33], socioeconomic status (maternal education [high school or less, some college, college graduate, postgraduate]) [34, 35], prior livebirths (0, 1, 2+) [36, 37], breastfeeding duration (never, <6 months, ≥6 months) [38, 39], girl’s race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, and other/unknown) [1, 37], birthweight (grams) [40, 41], and gestational age (weeks) [32, 37]. Maternal GWG was calculated as delivery weight (kg) minus periconceptional weight (kg). Periconceptional weight is the weight measured closest to conception and was selected from recorded weights up to a year prior to conception. Delivery weight was measured closest to the delivery date within 45 days prior to delivery. GWG was categorized in accordance with Institute of Medicine guidelines as “below”, “excessive” or “met” [42].

**Statistical analysis**

Nonparametric estimates of the cumulative distributions of age at pubertal onset were calculated and stratified by infant growth category (Figs. 1 and 2) [43]. Analyses of infant growth in relation to age of thelarche and pubarche, with covariate adjustment, used parametric survival (Weibull) regression models, providing maximum likelihood estimates of hazard ratios and time ratios (TR) with 95% confidence intervals [44]. TR estimates represent the ratio of the median time to event for a given level of the exposure variable in relation to its reference level. Estimation of age at onset distributions and Weibull regression parameters accommodated left, right and interval censoring. Girls were considered left-censored if they had already transitioned to SMR 2+ at the time of the first SMR exam. They were right-censored at the time of their last exam if they had not transitioned to SMR 2+ or had only 1 assessment at SMR 1. Girls who had an exam with an assessment of SMR 1 and a later assessment of SMR 2+ were considered interval-censored, as the exact age at transition between the SMR 1 and 2+ assessments is unknown. Such censoring is a commonly encountered problem which is inherent to study designs where the presence of an event can only be assessed periodically (e.g. at clinic visits spaced over time), and it is a
feature of most studies of pubertal transitions. Statistical estimation and inference techniques for censored time to event data are standard and well-developed, and we have applied such procedures in our analyses. Given that censoring only impacts the approach to estimation of the cumulative age distribution and regression model parameters (e.g. hazard ratio), interpretation of analysis results is the same whether there is or is not censoring during cohort follow-up.

Modified Poisson regression models were used to model menarche comparing earlier menarche (age < 12 years) to normal/later menarche (referent), for point and interval rate ratio estimation (i.e. ratio of proportions with earlier menarche). All the models were adjusted for the same covariates as above.

As a secondary analysis, we considered whether changes in weight at particular age periods were more likely to be associated with age at pubertal onset. We examined weight changes from birth to 2 months, 2 to 9 months, and 9 to 19 months by examining associations between continuous change in weight for age z-scores at each timepoint with each outcome (thelarche, pubarche, menarche) in separate models using girls with measurements in all three time intervals. We also examined race/ethnicity and GWG as potential effect modifiers by using a cross-product term of each variable with infant growth patterns. Additional secondary analyses assessed the mediating effects of childhood BMI (percentiles), with point and interval estimation of the percent of the infant growth effect mediated by BMI, expressed as the ratio of the natural indirect infant growth effect divided by the total effect. The natural indirect effect through a mediator is quantified by using regression models to estimate how infant growth affects childhood BMI, and how this change would in turn affect age at pubertal transition. Estimates are provided for the effects of catch-up growth vs normal and for catch-down growth vs normal assuming the Weibull regression model for infant growth and childhood BMI in relation to age at pubarche and thelarche (dependent variables) with censoring, and a linear regression model relating infant growth to childhood BMI (dependent variable) [45, 46]. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Model Fit
Point and interval estimates of the gamma shape parameter indicated that the Weibull distribution assumption (gamma shape parameter = 1) is quite reasonable for analyses of pubarche, with an estimated gamma shape parameter of 1.07 (95% CI: 0.93, 1.21). The Weibull model fit in analyses of thelarche is not as good, with estimated shape parameter of 0.76 (95% CI: 0.66, 0.85). We note, however, that survival curves do not cross-over, and that our TR and HR estimates are interpreted as infant growth effects averaged over the ages of pubertal onset, with any slight departures from proportionality not impacting this
interpretation. We also note that regression parameters from the more general gamma distribution are very difficult to interpret, and that fitting time-stratified Weibull regression models to obtain HR estimates for specific age-intervals in order to capture heterogeneity across age (e.g. <8, 8–9, 9–10…) is not an option given the heavy left and interval censoring (pubertal status is unknown at the beginning of each fixed age interval). The approach taken here is reasonable, with proper interpretation as age-averaged effects.

**Missing data**
Approximately 25.1% of girls had missing information on at least one covariate: maternal education ($n=202, 1.3\%$), prior livebirths ($n=14, 0.1\%$), GWG ($n=2,634, 17.3\%$), and breastfeeding duration ($n=2,925, 19.2\%$). Multiple imputation was used for handling missingness, using the chained equation technique to generate 50 imputed datasets [47]. The discriminant function method was used to impute missing values for the four categorical variables, with imputation based on the following covariates: infant growth patterns, birth year, maternal age at delivery, maternal education, prior livebirths, birthweight, gestational age, race/ethnicity, GWG, breastfeeding duration, and childhood overweight/obesity status (binary). Regression analyses, outlined above, were performed on each of the imputed datasets, with results combined using Rubin’s rules [48], providing valid point and interval estimates appropriately accounting for the uncertainty in imputing the missing data.

**Ethics approval**
This project was approved by the KPNC Institutional Review Board.

**Results**

**Participant characteristics**
Of the 15,196 girls in the study, 30.2% experienced infant catch-up growth, 25.8% catch-down growth, and 44.0% normal growth (Table 1). Girls with catch-up growth were more likely to be obese/overweight, be non-White, and have a lower gestational age than their counterparts. Girls with catch-down growth had the highest average birthweight. Among girls with information on breast development, 14.5% were left-censored (already had transitioned to stage 2+) and 57.8% were right censored (did not transition to stage 2+ during the study period), and among girls with pubic hair data, 10.6% and 67.1% were left- and right-censored, respectively.

**Primary analyses**

**Infant growth patterns and thelarche**
After adjusting for confounders, girls with infant catch-up growth were more likely to experience earlier thelarche (HR: 1.26, 95% CI: 1.18, 1.35; TR: 0.97, 95% CI: 0.97, 0.98) compared with girls with normal growth (referent). This time ratio corresponds to approximately 3 months earlier breast development. On the other hand, girls with catch-down growth were more likely to experience later thelarche (HR: 0.84, 95% CI: 0.78, 0.90; TR: 1.02, 95% CI: 1.01, 1.03), or approximately 2 months later breast development onset, compared to the referent (Table 2).

**Infant growth patterns and pubarche**
Similar to the thelarche models, girls with catch-up growth were more likely to experience earlier pubarche (HR: 1.38, 95% CI: 1.28, 1.48; TR: 0.97, 95% CI: 0.96, 0.97), and girls with catch-down growth were more likely to experience later pubarche (HR: 0.80, 95% CI: 0.74, 0.87; TR: 1.02, 95% CI: 1.02, 1.03), compared with the referent. This corresponds to approximately 4 months earlier and 3 months later pubic hair development, respectively (Table 3).

**Infant growth patterns and menarche**
Girls with catch-up growth had 1.5 times the odds of experiencing earlier menarche (relative risk [RR]: 1.52, 95% CI: 1.36, 1.69), while girls with catch-down growth were less likely to have earlier menarche compared to the referent (RR: 0.82, 95% CI: 0.71, 0.94) (Table 4).

**Secondary analyses**

**Effects of weight change at different periods in early life**
Change in weight-for-age z-scores between birth and 2 months was associated with risk of earlier thelarche (HR: 1.12, 95% CI: 1.04, 1.21), earlier pubarche (HR: 1.17, 95% CI: 1.08, 1.28), and earlier menarche (RR: 1.08, 95% CI: 0.96, 1.23). Change in z-scores between 2 and 9 months were also associated in the thelarche (HR: 1.11, 95% CI: 1.03, 1.20), pubarche (HR: 1.11, 95% CI: 1.03, 1.21), and menarche (RR: 1.22, 95% CI: 1.09, 1.36) models. Association between growth patterns between 9–19 months and pubertal onset were weakest (Table 5).

**Effect modification by race/ethnicity**
There was some evidence of interaction between infant growth and race/ethnicity in pubarche models ($p=0.06$). Among Black girls, those with catch-up growth had almost twice the risk of experiencing earlier pubarche compared to those with normal growth (HR: 1.69, 95% CI: 1.24, 2.32). Similarly, risk of earlier pubarche was also greater in girls experiencing catch-up growth among API
Table 1  Distribution of Characteristics by Infant Growth Patterns: KPNC Puberty Study (2010–2020), N = 15,196

| Infant Growth Patterns | Catch-up growth (n=4,589) | Catch-down growth (n=3,915) | Normal growth (n=6,692) | P value |
|------------------------|---------------------------|----------------------------|-------------------------|---------|
|                        | N (%)                     | N (%)                      | N (%)                   |         |
| **Maternal Characteristics** |                           |                            |                         |         |
| Age at delivery (years)a | 30.3 (5.5)                | 31.0 (5.0)                 | 30.6 (5.2)              | <0.001  |
| Gestational weight gain |                           |                            |                         |         |
| Exceeds                | 2,040 (44.5)              | 1,889 (48.3)               | 3,031 (45.3)            | 0.001   |
| Met                    | 1,158 (25.2)              | 932 (23.8)                 | 1,730 (25.9)            |         |
| Below                  | 596 (13.0)                | 417 (10.7)                 | 769 (11.5)              |         |
| Missing                | 795 (17.3)                | 677 (17.3)                 | 1,162 (17.4)            |         |
| Prior livebirths       |                           |                            |                         |         |
| 0                      | 2,417 (52.7)              | 1,617 (41.3)               | 3,201 (47.8)            | <0.001  |
| 1                      | 1,399 (30.5)              | 1,531 (39.1)               | 2,336 (34.9)            |         |
| 2+                     | 770 (16.8)                | 762 (19.5)                 | 1,149 (17.2)            |         |
| Missing                | 3 (0.1)                   | 5 (0.1)                    | 6 (0.1)                 |         |
| Education              |                           |                            |                         |         |
| High school or less    | 1,192 (26.0)              | 840 (21.5)                 | 1,522 (22.7)            | <0.001  |
| Some college           | 1,393 (30.4)              | 1,124 (28.7)               | 1,888 (28.2)            |         |
| College graduate       | 1,242 (27.1)              | 1,232 (31.5)               | 1,998 (29.9)            |         |
| Postgraduate           | 706 (15.4)                | 667 (17.0)                 | 1,190 (17.8)            |         |
| Missing                | 56 (1.2)                  | 52 (1.3)                   | 94 (1.4)                |         |
| Breastfeeding duration |                           |                            |                         |         |
| Not breastfed          | 403 (8.8)                 | 220 (5.6)                  | 414 (6.2)               | <0.001  |
| < 6 months             | 1,472 (32.1)              | 935 (23.9)                 | 1,887 (28.2)            |         |
| ≥ 6 months             | 1,818 (39.6)              | 2,016 (51.5)               | 3,106 (46.4)            |         |
| Missing                | 896 (19.5)                | 744 (19.0)                 | 1,285 (19.2)            |         |
| Girl’s Characteristics  |                           |                            |                         |         |
| Gestational age (weeks)a | 38.9 (1.1)                | 39.5 (1.0)                 | 39.2 (1.1)              | <0.001  |
| Birthweight (grams)a   | 3164.4 (370.4)            | 3645.1 (466.3)             | 3381.0 (394.9)          | <0.001  |
| Childhood BMI ≥85th percentile | 1,963 (42.8) | 522 (13.3)               | 1,412 (21.1)            | <0.001  |
| Race/ethnicity         |                           |                            |                         |         |
| White                  | 1,477 (32.2)              | 1,545 (39.5)               | 2,551 (38.1)            | <0.001  |
| Black                  | 384 (8.4)                 | 172 (4.4)                  | 361 (5.4)               |         |
| Hispanic               | 1,362 (29.7)              | 875 (22.3)                 | 1,613 (24.1)            |         |
| Asian/Pacific Islander | 984 (21.4)                | 973 (24.9)                 | 1,596 (23.8)            |         |
| Other/unknown          | 382 (8.3)                 | 350 (8.9)                  | 571 (8.5)               |         |

BMI: body mass index, KPNC: Kaiser Permanente Northern California

*a Values are expressed as mean (standard deviation)

Table 2  Association Between Infant Growth Patterns and Timing of Thelarche: KPNC Puberty Study (2010–2020)

| Infant Growth Patterns | N | Unadjusted |Adjusteda |
|------------------------|---|------------|-----------|
|                        |   | TR (95% CI)| HR (95% CI)| TR (95% CI)| HR (95% CI) |
| Catch-up               | 4,514 | 0.98 (0.97, 0.98) | 1.24 (1.16, 1.33) | 0.97 (0.97, 0.98) | 1.26 (1.18, 1.35) |
| Catch-down             | 3,854 | 1.01 (1.01, 1.02) | 0.89 (0.83, 0.96) | 1.02 (1.01, 1.03) | 0.84 (0.78, 0.90) |
| Normal                 | 6,586 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |

CI: confidence interval, HR hazard ratio, KPNC Kaiser Permanente Northern California, TR time ratio

*a Adjusted for maternal age, education, prior livebirths, GWG, and girl’s birthweight, gestational age, breastfeeding duration, and race
These results correspond with approximately 6, 4, 4, and 2 months earlier pubarche compared to the referent. Girls with catch-down growth were more likely to experience delayed pubarche, however associations were not significant among Asian/Pacific Islander girls (Table 6).

**Mediating role of childhood BMI**
Mediation by BMI was observed for the associations between catch-up growth (vs. normal) and thelarche and between catch-down growth (vs. normal) and thelarche; the percentages mediated by BMI were 67.8% (95% CI: 40.5, 95.1) and 71.8% (95% CI: 34.7, 100), respectively.

Childhood BMI had a weaker mediating effect in pubarche models (catch-up: 43.6%, 95% CI: 29.0, 58.3; catch-down: 45.5%, 95% CI: 22.7, 68.3) and menarche models (catch-up: 55.5%, 95% CI: 40.4, 70.7), with the exception of catch-down growth and menarche, which was fully mediated (100%, 95% CI: 22.4, 100).

### Discussion

#### Principal findings
In this racially and ethnically diverse cohort of girls, we observed that catch-up growth from birth to 24 months, and especially between birth and 9 months, was associated with earlier pubertal onset, while catch-down growth was inversely associated. These associations were independent of important confounders such as maternal age, education, prior livebirths, GWG, girl's birthweight, gestational age, breastfeeding status, and race/ethnicity. Childhood BMI partially mediated observed associations. These data suggest that there may be other mechanisms between early life growth patterns and timing of puberty independent of childhood BMI.

#### Strengths of the study
A major strength of the current study is the use of the EHR system, which allowed us to build a large longitudinal birth cohort that would have otherwise taken many years and tremendous amount of resources to conduct. Additionally, all the data were clinically and objectively assessed, including infant weight and length measures, pubertal stage data assessed by pediatricians, maternal

### Table 3  Association Between Infant Growth Patterns and Timing of Pubarche: KPNC Puberty Study (2010–2020)

| Infant Growth Patterns | N  | Unadjusted TR (95% CI) | HR (95% CI) | Adjusteda TR (95% CI) | HR (95% CI) |
|------------------------|----|----------------------|-------------|----------------------|-------------|
| Catch-up               | 4,484 | 0.96 (0.96, 0.97) | 1.39 (1.30, 1.49) | 0.97 (0.96, 0.97) | 1.38 (1.28, 1.48) |
| Catch-down             | 3,837 | 1.02 (1.01, 1.03) | 0.83 (0.77, 0.90) | 1.02 (1.02, 1.03) | 0.80 (0.74, 0.87) |
| Normal                 | 6,562 | 1.00 (Reference)   | 1.00 (Reference) | 1.00 (Reference)   | 1.00 (Reference) |

CI confidence interval, HR hazard ratio, KPNC Kaiser Permanente Northern California, TR time ratio

a Adjusted for maternal age, education, prior livebirths, GWG, and girl's birthweight, gestational age, breastfeeding duration, and race

### Table 4  Association Between Infant Growth Patterns and Risk of Earlier (age < 12) Menarche: KPNC Puberty Study (2010–2020)

| Infant Growth Patterns | N  | Unadjusted RR (95% CI) | RR (95% CI) | Adjusteda RR (95% CI) | RR (95% CI) |
|------------------------|----|----------------------|-------------|----------------------|-------------|
| Catch-up               | 1,873 | 1.56 (1.41, 1.73) | 1.52 (1.36, 1.69) | 1.52 (1.36, 1.69) | 1.52 (1.36, 1.69) |
| Catch-down             | 1,655 | 0.83 (0.73, 0.95) | 0.82 (0.71, 0.94) | 0.82 (0.71, 0.94) | 0.82 (0.71, 0.94) |
| Normal                 | 2,861 | 1.00 (Reference)   | 1.00 (Reference) | 1.00 (Reference)   | 1.00 (Reference) |

CI confidence interval, KPNC Kaiser Permanente Northern California, RR relative risk

a Adjusted for maternal age, education, prior livebirths, GWG, and girl's birthweight, gestational age, breastfeeding duration, and race

### Table 5  Association Between Infant Growth Patterns and Puberty at Different Early Age Periods: KPNC Puberty Study (2010–2020)

| Change in weight z-scores | Thelarchea | Pubarchea | Menarchea |
|---------------------------|------------|-----------|-----------|
|                           | N          | HR (95% CI) | N          | HR (95% CI) | N          | RR (95% CI) |
| Birth to 2 months         | 2,784      | 1.12 (1.04, 1.21) | 2,772      | 1.17 (1.08, 1.28) | 1,136      | 1.08 (0.96, 1.23) |
| 2 to 9 months             | 2,784      | 1.11 (1.03, 1.20) | 2,772      | 1.11 (1.03, 1.21) | 1,136      | 1.22 (1.09, 1.36) |
| 9 to 19 months            | 2,784      | 1.03 (0.95, 1.12) | 2,772      | 1.07 (0.97, 1.17) | 1,136      | 1.08 (0.95, 1.24) |

CI confidence interval, HR hazard ratio, KPNC Kaiser Permanente Northern California, RR relative risk

a Adjusted for maternal age, education, prior livebirths, GWG, and girl's birthweight, gestational age, breastfeeding duration, and race
### Table 6  Association Between Infant Growth Patterns and Timing of Pubarche, Stratified by Race/Ethnicity: KPNC Puberty Study (2010–2020)

| Infant Growth Patterns | White | Black | Hispanic | Asian/Pacific Islander | Other/Unknown |
|------------------------|-------|-------|----------|------------------------|---------------|
|                        | N     | HR<sup>a</sup> | 95% CI   | N     | HR<sup>a</sup> | 95% CI   | N     | HR<sup>a</sup> | 95% CI   | N     | HR<sup>a</sup> | 95% CI   |
| Catch-up               | 1,437 | 1.38 (1.22, 1.56) | 375 | 1.69 (1.24, 2.32) | 1,321 | 1.23 (1.06, 1.42) | 970 | 1.42 (1.20, 1.67) | 381 | 1.76 (1.35, 2.30) |
| Catch-down             | 1,504 | 0.80 (0.70, 0.92) | 170 | 0.52 (0.35, 0.78) | 853 | 0.78 (0.66, 0.92) | 963 | 0.87 (0.73, 1.03) | 347 | 0.85 (0.64, 1.13) |
| Normal                 | 2,487 | 1.00 (Reference) | 351 | 1.00 (Reference) | 1,583 | 1.00 (Reference) | 1,580 | 1.00 (Reference) | 561 | 1.00 (Reference) |

<sup>a</sup> Adjusted for maternal age, education, prior livebirths, GWG, and girl's birthweight, gestational age, and breastfeeding duration.
weights before and during pregnancy, and other demographic and clinical data. Availability of these data and large and diverse study population extends and strengthens the evidence base for identified risk factors of early puberty by using a large, diverse cohort of mother-daughter pairs.

**Limitations of the data**

There are limitations to this study that are worth noting. First, reliance on data from the EHR system meant that detailed data were not available on potentially relevant factors. For instance, we did not have measurements of biomarkers, diet or physical activity. Second, we did not have exact date of menarche as we used well-child questionnaire data that provided binary responses only and as such had a greater chance of outcome misclassification. Third, over 50% of the cohort was right-censored, or did not have information on age at SMR 2+

These girls were still very young at their most recent breast (mean 8.1 years, standard deviation = 1.5) and pubic hair (mean = 8.4, standard deviation = 1.6) SMR assessments. Heavy censoring can result in lower statistical power and precision, as reflected by wider confidence intervals which were not observed in our primary analyses. Additionally, associations were unchanged when only considering girls with interval-censored outcomes (Table 7), therefore high rates of right-censoring did not impact the results of the current study. Lastly, there was moderate imprecision in estimations of mediation effects, as seen by the wide confidence intervals.

**Interpretation**

In the United States the average age at menarche (12 to 13 years) has remained fairly constant for several decades [49]. However, U.S. girls are now experiencing earlier thelarche and pubarche. Compared to a seminal study published by Herman-Giddens in 1997 [50], our 2013 study demonstrated that US girls are experiencing thelarche up to two years earlier [1]. Childhood obesity is a known predictor of pubertal timing in girls, however, it does not fully explain the trend toward early puberty, as children with normal BMI are also experiencing earlier pubertal onset [6]. Several previous studies have demonstrated that girls with catch-up growth from birth to about age 2 years experienced earlier pubertal timing [8, 9, 12, 51]. In a longitudinal study of 215 German children, those with catch-up growth between birth and 24 months experienced earlier puberty (measured as pubertal growth spurt, age at peak height velocity, and menarche), all independent of pre-pubertal BMI [9]. A more recent population-based cohort study in Denmark also found that an increase in weight z-score from 0 to 12 months was associated with earlier pubertal development (self-reported SMR and other hallmarks) [8]. In a racially and ethnically diverse cohort of 262 girls in New York, Terry et al. reported that catch-up growth from ages 4 months to 1 year and from ages 1 year to 7 years were associated with earlier age at menarche [12]. Similarly, in a UK-based prospective study of 2,715 girls, Ong et al., reported that catch-up growth between 0 and 2 months and also 2 and 9 months were associated with earlier age at menarche, while subsequent weight gain between 9 and 19 months was not associated with age at menarche. Our findings are consistent with and expand on these observations by using clinician-assessed longitudinal SMR data and including multiple pubertal markers in a large, ethnically diverse sample.

Our study may also provide some knowledge regarding a potential source of racial/ethnic differences in the timing of pubertal development. Our recent study reported that median age of thelarche among Black girls is 8.8 years, compared to 9.7 years among white girls, nearly a one-year difference [1]. Menarche among Black girls used to occur later than white girls less than a century ago [52, 53]. Perinatal factors such as excessive GWG and catch-up growth appear to affect minority populations disproportionately [54–56], as we also demonstrated in our data. The differences in the prevalence of these underlying factors may at least partially explain the striking racial/ethnic differences in the average timing of pubertal maturation.

The associations between infant growth and pubertal onset may be explained by a few potential underlying mechanisms. In the current study we found that 44–100% of the associations were mediated by childhood BMI, a proxy for adiposity. Girls with greater percent body fat are more likely to have higher concentrations of leptin and insulin: two metabolic hormones that may alter sexual development by regulating the hypothalamic–pituitary–gonadal and hypothalamic–pituitary–adrenal axes [57, 58]. Estrogen produced in fat cells may also trigger an

**Table 7** Unadjusted Associations Between Infant Growth Patterns and Pubertal Onset in Interval-Censored Girls: KPNC Puberty Study (2010–2020)

| Infant Growth Patterns | Thelarche | Pubarche |
|------------------------|----------|---------|
|                        | N        | HR (95% CI) | N        | HR (95% CI) |
| Catch-up               | 1,250    | 1.28 (1.17, 1.40) | 1,062    | 1.35 (1.23, 1.49) |
| Catch-down             | 1,049    | 0.86 (0.79, 0.94) | 775      | 0.84 (0.75, 0.93) |
| Normal                 | 1,850    | 1.00 (Reference) | 1,486    | 1.00 (Reference) |

CI: confidence interval, HR: hazard ratio, KPNC Kaiser Permanente Northern California
earlier pubertal onset [2]. Some studies also suggest that individuals born small for gestational age experience an enhanced and/or prolonged ‘minipuberty’ – a temporary activation of the hypothalamic-pituitary–gonadal axis in the first year of life—compared to those born appropriate for gestational age [59, 60]. Size for gestational age and infant growth patterns are highly correlated and these early life growth-related factors may influence the programming of the hypothalamic-pituitary–gonadal axis and its functionality later in life.

Conclusions

Our findings provide important information for clinicians and parents that girls who experience catch-up growth during this susceptible period may be at higher risk of early pubertal development. High risk girls may benefit from maintaining healthy weight through healthy diet and physical activities as childhood obesity is a known and modifiable risk factor of early puberty. Further research is needed to identify other mechanisms through which early-life growth is associated with earlier puberty.

Abbreviations

API: Asian & Pacific Islander; BMI: Body Mass Index; CI: Confidence Interval; EHR: Electronic Health Record; GWG: Gestational Weight Gain; HR: Hazard Ratio; KPNC: Kaiser Permanente Northern California; RR: Relative Risk; SMR: Sexual Maturity Rating; TR: Time Ratio.

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Authors’ contributions

AK conceptualized and designed the study, obtained funding, drafted the initial manuscript, and contributed to the revisions of the final manuscript. SA extracted data, created the database for analysis, analyzed the data, helped draft the initial manuscript, and contributed to the revisions of the final manuscript. CPQ advised on statistical analyses and interpretation of the results and contributed to the revisions of the final manuscript. LHK, JD, LCG, and AF provided scientific and clinical advice on the study design, interpretation of the data, and contributed to the revisions of the final manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to our institutional policy. Individuals who are interested in accessing the data may contact the corresponding author regarding [or to discuss or set up] a data use agreement.

Declarations

Ethics approval and consent to participate

Study approval and waiver of consent was obtained from the KPNC Institutional Review Board. Parental consent was not required because when individuals enroll as Kaiser members, they sign a consent that allows their and their dependent’s EHR data to be used for research purposes. The KPNC Institutional Review Board does not require consent for data-only studies. This study was conducted in accordance with prevailing ethical principles.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Bird FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, Deardorff J, Herrick RL, Succop PA, Haith RA, et al. Onset of breast development in a longitudinal cohort. Pediatrics. 2013;132(6):1019–27.
2. Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, Sharpe RM, Skakkebaek NE, Toppari J. Public health implications of altered puberty timing. Pediatrics. 2008;121(Suppl 3):S218-230.
3. Downing J, Bellis MA. Early pubertal onset and its relationship with sexual risk taking, substance use and anti-social behaviour: a preliminary cross-sectional study. BMC Public Health. 2009;9:446.
4. Udry JR. Age at menarche, at first intercourse, and at first pregnancy. J Biosoc Sci. 1979;11(4):433–41.
5. Dossus L, Allen N, Kaaks R, Beral V, Czernichow S, Clavel-Chapelon F, Abnet CC, Boutron-Roer K, Clavel-Chapelon C, Fournier A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;127(2):442–51.
6. Rosenfeld RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–8.
7. Grumbach M, Styne D: Puberty: Ontogeny, Neuroendocrinology, Physiology, and Disorders. In: William’s Textbook of Endocrinology. 10th edn. Edited by al. Lfe. Philadelphia: Saunders; 2003. p. 1115–286.
8. Hvidt JB, Brix N, Ernst A, Louridsen LLB, Ramlau-Hansen CH. Size at birth, infant growth, and age at pubertal development in boys and girls. Clin Epidemiol. 2019;11:873.
9. Karalis-Dankert N, Buyken AE, Sonntag A, Kroke A. Birth and early life influences on the timing of puberty onset: results from the DONALD (DOrtmund Nutritional and Anthropometric Longitudinally Designed) Study. Am J Clin Nutr. 2009;90(6):1559–65.
10. Maisonet M, Christiansen KY, Rubin C, Holmes A, Flanders WD, Heron J, Ong KK, Golding J, McGeehan MA, Marcus M. Role of prenatal character-istics and early growth on pubertal attainment of British girls. Pediatrics. 2010;126(3):e591–600.
11. Silva IDS, De Stavola BL, Mann V, Kuh D, Teitelbaum S, Windham GC, Deardorff J, Herrick RL, Succop PA, Haith RA, et al. Onset of breast development in a longitudinal cohort. Pediatrics. 2013;132(6):1019–27.
12. Terry MB, Ferris JS, Tehranifar P, Wei Y, Flom JD. Birth weight, postnatal growth, and age at menarche. Am J Epidemiol. 2002;155(2):405–12.
13. Wang Y, Dinse GE, Ragan WJ. Birth weight, early weight gain and pubertal maturation: a longitudinal study. Pediatr Obes. 2012;7(2):101–9.
14. Bodicoat DH, Schoemaker MJ, Jones ME, McFadden E, Griffin J, Ashworth A, Swerdlow AJ, Morrow J, King E, Sharpe RM, Skakkebaek NE, Toppari J. Public health implications of altered puberty timing. Pediatrics. 2008;121(Suppl 3):S218-230.
15. Schoemaker MJ, Jones ME, Allen N, Kaaks R, Beral V, Czernichow S, Clavel-Chapelon F, Abnet CC, Boutron-Roer K, Clavel-Chapelon C, Fournier A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;127(2):442–51.
16. Rosenfeld RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–8.

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17. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1966;41(235):291–303.

18. Hui L, Wong M-Y, Lam TH, Leung GM, Schooling CM. Infant growth and onset of puberty: prospective observations from Hong Kong’s “Children of 1997” birth cohort. Ann Epidemiol. 2012;22(11):43–50.

19. Subhan FB, Colman I, McCargar L, Bell RC, Team AS. Higher pre-pregnancy BMI and excessive gestational weight gain are risk factors for rapid weight gain in infants. Matern Child Health J. 2017;21(8):1396–407.

20. Gibby CL, Palacios C, Campos M, Lim E, Banna J. Associations between gestational weight gain and rate of infancy weight gain in Hawai‘i and Puerto Rico WC participants. BMC obesity. 2018;5(1):41.

21. Deardoff J, Berry-Millett R, Rehkopf D, Luecke E, Lahiff M, Abrams B. Maternal pre-pregnancy BMI, gestational weight gain, and age at menarche in daughters. Matern Child Health J. 2013;17(8):1391–8.

22. Stettler N, Zemel BS, Kumanya S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. Pediatrics. 2002;109(2):194–9.

23. Taveras EM, Rifas-Shiman SL, Belfort MB, Kleinman KP, Oken E, Gillman MW. Weight status in the first 6 months of life and obesity at 3 years of age. Pediatrics. 2009;123(4):1177–83.

24. Gordon NP. How does the Adult Kaiser Permanente Membership in Northern California Compare with the Larger Community? In: Oakland: Kaiser Permanente Division of Research; 2006.

25. Gordon NP. Similarity of the Adult Kaiser Permanente Membership in Northern California to the Insured and General Population in Northern California. Statistics from the 2007 California Health Interview Survey. In: Kaiser Permanente Northern California Division of Research, 2012.

26. Kuczynski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Selfridge-Field D, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002;246(1):1–190. PMID: 12043359.

27. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunford DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ. 2000;320(7240):967–71.

28. Kubo A, Deardoff J, Laurent CA, Ferrara A, Greenspan LC, Quesenberry CP, Kushi LH. Associations Between Maternal Obesity and Pregnancy Hyperglycemia and Timing of Puberty Onset in Adolescent Girls: A Population-Based Study. Am J Epidemiol. 2018;187(1):1362–9.

29. Shen Y, Varma DS, Zhang Y, Boc J, Hu H. Age at menarche and depression: results from the NHANES 2005–2016. PeerJ. 2019;7:e7150.

30. Diesel JC, Eckhardt CL, Day NL, Brooks MM, Arslanian SA, Bodnar LM. Gestational weight gain and offspring longitudinal growth in early life. Ann Nutr Metab. 2015;67(1):49–57.

31. Lawn RB, Lawlor DA, Fraser A. Associations between maternal prepregnancy body mass index and gestational weight gain and daughter’s age at menarche: the Avon Longitudinal Study of Parents and Children. Am J Epidemiol. 2018;187(4):677–86.

32. Bille M, Pollard TM, Pearce MS. Predictors of age at menarche in the Newcastle Thousand Families Study. J Bone Sci. 2008;40(4):583–75.

33. Chen X-K, Wen SW, Fleming N, Demisce K, Rhoads GG, Walker M. Teenage pregnancy and adverse birth outcomes: a large population based retrospective cohort study. Int J Epidemiol. 2007;36(2):368–73.

34. Deardorf J, Abrams B, Ekvuweni P, Rehkoph D. Socioeconomic status and age at menarche: an examination of multiple indicators in an ethnically diverse cohort. Ann Epidemiol. 2004;14(10):727–33.

35. Wijlaars LP, Johnson L, van Jaarsveld CH, Wardle J. Socioeconomic status and weight gain trajectory in infancy. Pediatrics. 2015;135(1):111–9.

36. Morris D, Jones M, Soeremark M, Ashworth A, Swerdlov A. Determinants of age at menarche in the UK: analyses from the Breakthrough Generations Study. Br J Cancer. 2010;103(11):1760–4.

37. Pesch MH, Pinti CM, Lumeng JC, McCaffrey H, Tan CC. Mother and Infant Predictors of Rapid Infant Weight Gain. J Clin Pediatr. 2019;58(8):1515–21.

38. Aghaee S, Deardorff J, Greenspan LC, Quesenberry CP, Kushi LH, Kubo A. Breastfeeding and timing of pubertal onset in girls: a multiethnic prospective cohort study. BMC Pediatr. 2019;19(1):277.

39. Carling SJ, Demment MM, Kjølhaed CL, Olson CM. Breastfeeding duration and weight gain trajectory in infancy. Pediatrics. 2015;135(1):111–9.

40. Xiong X, Wightkin J, Magnus JH, Pridjian G, Acuna JM, Buekens P. Birth weight and infant growth: optimal infant weight gain versus optimal infant weight. Matern Child Health J. 2007;11(1):57–63.

41. Council NR. Weight gain during pregnancy: reexamining the guidelines: National Academies Press; 2010.

42. Turnbull BW. The empirical distribution function with arbitrarily grouped, censored and truncated data. J Roy Stat Soc: Ser B (Methodol). 1976;38(3):290–5.

43. Hosmer DW Jr, Lemeshow S, M. Applied Survival Analysis: Regression Modeling of Time-to-Event Data. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2008.

44. Fulcher IR, Tchetgen ET, Williams PL. Mediational analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013;18(2):137.

45. Van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE (TNO report PG/YGZ/99:054). Leiden, Niederlande: TNO Prevention Center, 1999.

46. Rubin DB. Inference and missing data. Biometrika. 1976;63(3):581–92.

47. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med. 1982;306(17):1933–5.

48. Herman-Giddens ME. The decline in the age of menarche in the United States: should we be concerned? J Adolesc Health. 2007;40(3):201–3.

49. Taveras EM, Rifas-Shiman SL, Belfort MB, Kleinman KP, Oken E, Gillman MW, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997;100(4):505–12.

50. Ong KK, Emmett P, Northstone K, Golding J, Rogers I, Ness AR, Wells JC, Dunger DB. Infant weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab. 2009;94(5):1527–32.

51. McDowell MA, Brody DJ, Hughes JP. Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. J Adolesc Health. 2007;40(3):227–31.

52. Herman-Giddens ME. The decline in the age of menarche in the United States: should we be concerned? J Adolesc Health. 2007;40(3):201–3.

53. Taveras EM, Gillman MW, Kleinman K, Rich-Edwards JW, Rifas-Shiman SL. Racial/ethnic differences in early-life risk factors for childhood obesity. Pediatrics. 2010;125(4):686–95.

54. Hedderson MM, Darbinian JA, Ferrara A. Disparities in the risk of gestational diabetes by race-ethnicity and country of birth. Paediatr Perinat Epidemiol. 2010;24(5):441–8.

55. Fulcher IR, Tchetgen ET, Williams PL. Mediational analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013;18(2):137.

56. Alibrandi A, Wasniewska M, Aversa T: Minipuberty in born small for gestational age. Pediatr Res. 2008;121(Suppl 3):S208-217.

57. Remer TM, Manz F. Role of nutritional status in the regulation of adrenarche. J Clin Endocrinol Metab. 1999;84(11):3936–44.

58. Kaplowitz PB. Link between body fat and the timing of puberty. Pediatr Res. 2008;63(2):188–93.

59. Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997;100(4):505–12.

60. Pepe G, Calafiore M, Veltre MR, Conca D, Valenzise M, Mondello I, Alibrandi A, Wasniewska M, Aversa T. Minipuberty in born small for gestational age infants: A case control prospective pilot study. Endocrinology 2022;1–9.

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