Title

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Journal

American Journal of Epidemiology, 187(7)

ISSN

0002-9262

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Publication Date

2018-07-01

DOI

10.1093/aje/kwy040

Peer reviewed

American Journal of Epidemiology

Vol. 187, No. 7
DOI: 10.1093/aje/kwy040
Advance Access publication: March 15, 2018

Original Contribution

Associations Between Maternal Obesity and Pregnancy Hyperglycemia and Timing of Puberty Onset in Adolescent Girls: A Population-Based Study

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Initially submitted September 25, 2017; accepted for publication February 26, 2018.

Early puberty is associated with adverse health outcomes. We investigated whether in utero exposure to maternal obesity is associated with daughters' pubertal timing using 15,267 racially/ethnically diverse Kaiser Permanente Northern California members aged 6–11 years with pediatrician-assessed Tanner staging (2003–2017). We calculated maternal body mass index (BMI; weight (kg)/height $(m)^2$) during pregnancy from the electronic health record data. Using a proportional hazards model with interval censoring, we examined the associations between maternal obesity and girls' pubertal timing, as well as effect modification by race/ethnicity and mediation by prepubertal BMI. Maternal obesity (BMI ≥30) and overweight (BMI 25–29.9) were associated with earlier onset of breast development in girls (hazard ratio (HR) = 1.39 (95% confidence interval (CI): 1.30, 1.49) and HR = 1.21 (95% CI: 1.13, 1.29), respectively), after adjustment for girl's race/ethnicity, maternal age, education, parity, and smoking during pregnancy. There was interaction by race/ethnicity for associations between maternal obesity and girls' pubic hair onset: Associations were strongest among Asian and non-Hispanic white girls (HR = 1.53 (95% CI: 1.24, 1.90) and HR = 1.34 (95% CI: 1.18, 1.52), respectively) and absent for African-American girls. Adjustment for girl's prepubertal BMI only slightly attenuated associations. Our results suggest the importance of maternal metabolic factors during pregnancy in the timing of girls' puberty and potential differences in the associations by race/ethnicity.

developmental origins of health and disease; health disparities; obesity; puberty

Abbreviations: BMI, body mass index; BR, breast; CI, confidence interval; CYGNET, Cohort Study of Young Girls' Nutrition, Environment, and Transitions; EHR, electronic health record; GDM, gestational diabetes mellitus; HR, hazard ratio; KPNC, Kaiser Permanente Northern California; PH, pubic hair.

Early onset of puberty has been linked with adverse health consequences. In girls, it is associated with adverse emotional and behavioral outcomes, including higher risk of anxiety, depression, body dissatisfaction, early initiation of sexual activity, and adolescent pregnancy (1–5). Later in life, there is evidence of increased risk of cardiac conditions, all-cause mortality, and breast and reproductive cancers (2, 6–9). We have demonstrated that the average age of puberty onset among girls has declined significantly in the United States over the past few decades (10). Although childhood obesity is a known risk factor for early puberty, the average age at onset of breast development has declined during this same time period even in nonoverweight girls, suggesting that childhood obesity alone does not explain the trend (10).

There are substantial racial/ethnic differences in the timing of pubertal onset and development (11, 12). African-American girls experience earlier puberty onset than non-Hispanic white girls despite the fact that their menarche tended to occur later than that of whites less than a century ago (13, 14). The proportion of 6-year-old African-American girls with breast development *tripled* from 6% to 18% over the past few decades (10, 15), suggesting that environmental or lifestyle factors may play an explanatory role. We recently reported that the median age at onset of breast development among African-American girls is currently 8.8 years, as compared with 9.7 years among whites—a nearly 1-year difference (10). These differences in the timing of puberty onset may have pronounced negative implications for the health of ethnic minorities, both in adolescence and into adulthood, leading to wider health disparities in the future (11, 16, 17). Data are limited regarding the race- and ethnicity-specific risk factors for early puberty, because most previous studies were small and/or homogeneous in their racial/ethnic composition.

Several studies have found that maternal obesity is associated with younger age at menarche in daughters (18–21). However, little is known regarding the associations between maternal pregnancy factors and timing of puberty onset. It is also unknown whether there are racial/ethnic differences in the associations between prenatal metabolic factors and girls' pubertal timing. Maternal obesity and other metabolic conditions affect minority populations disproportionately (22–24), and differences in the prevalence of these underlying factors may at least partially explain the observed racial/ethnic difference in the timing of pubertal development.

We thus examined these associations using a large and racially/ethnically diverse cohort of mother-daughter pairs in Northern California, drawn from the membership of Kaiser Permanente Northern California (KPNC), a large, integrated health-care delivery system.

METHODS

Participants

We created a cohort of mother-daughter pairs using the KPNC electronic health records (EHRs). Among all girls born in KPNC between 2003 and 2006 with continuous KPNC membership (no gap in KPNC insurance coverage >90 days) up to the last date of follow-up (March 2017), we identified those with at least 1 Tanner stage assessment made at age 6 years or more, at least 1 recorded prepubertal body mass index (BMI) value, and information on maternal BMI during the index pregnancy. We excluded girls with a diagnosed condition that affects pubertal development centrally or peripherally, such as hypothalamic hamartoma; Langerhans cell histiocytosis; gonadal, adrenal, or germ-cell tumors; congenital adrenal hyperplasia; or McCune-Albright syndrome.

Measurements

Exposure variables. Maternal BMI. For determination of maternal BMI during pregnancy, we used maternal weight measured at the time of the α-fetoprotein test, generally at 16–18 weeks' gestation (95%). If this weight was not available, we used the first weight measured after conception (5%; median gestational age, 9.2 weeks (range, 0–16 weeks)). Using the height recorded in the EHR, we calculated BMI as weight in kilograms divided by squared height in meters. We categorized women as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), or obese (BMI ≥30.0).

Maternal blood glucose level during pregnancy. Pregnancy glucose values were obtained from the KPNC gestational diabetes mellitus (GDM) registry (25). Within KPNC, 96% of pregnant women are screened using a 50-g, 1-hour oral glucose challenge test around the 28th week of gestation, in accordance with American Diabetes Association recommendations (26). If the glucose challenge test result is abnormal, a diagnostic 100-g, 3-hour oral glucose tolerance test is performed. Women were identified as having GDM according to the Carpenter and Coustan thresholds (26). We categorized women according to results of the glucose challenge test into the blood glucose categories <140 mg/dL and ≥140 mg/dL; women with a glucose concentration greater than or equal to 140 mg/dL were further stratified by the presence of GDM.

Outcomes (thelarche and pubarche). At KPNC, systematic documentation of Tanner stage, the 5-stage puberty onset scale developed by Marshall and Tanner (27), was adopted as a routine part of pediatric appointments in 2006. As with documentation of BMI and growth charts, the information is entered into the EHR. A girl's stage of breast development is assessed by the pediatrician using palpation and visual inspection, and pubic hair is assessed using visual inspection. These EHR-based Tanner data have been validated using "gold standard" measures, described in the Discussion section. For this study, onset of breast (BR) and pubic hair (PH) development were coded separately as "no onset" (stage 1) or "onset" (stage 2 or higher). *Thelarche* is defined as transition from BR1 to BR2+. *Pubarche* is defined as transition from PH1 to PH2+.

Covariates. Girls' weight and height information obtained from the KPNC EHR was used to calculate girls' BMIs. Percentiles and z scores were determined using the appropriate age- (and sex-) specific Centers for Disease Control and Prevention year 2000 standard population distribution and were examined continuously and categorically (<85th percentile vs. ≥85th percentile) (28). BMI at the last documented Tanner stage 1 assessment (i.e., prepubertal), or within 60 days prior to or after that assessment, was used as the "prepubertal" BMI. In addition, girls' birth weights and gestational ages at birth were obtained from the EHRs.

Maternal and girls' demographic, clinical, and lifestyle information was also extracted from the KPNC EHR. Girl's race/ethnicity was categorized as African-American, Hispanic, Asian, non-Hispanic white, or other (primarily multiracial). Maternal education was categorized as high school or less, some college (<4 years), 4 years of college, or graduate school or higher. Maternal age at girl's birth (in years) was analyzed continuously. Maternal parity was coded as 0, 1, or ≥2. Coding of the variable on maternal smoking during pregnancy used questions asking women whether they currently smoked. Women were categorized as smokers if they consistently responded "yes" to multiple smoking questions during the pregnancy.

Statistical analyses

Analyses used Weibull regression, which is both an accelerated failure time model and a proportional hazards regression model with accommodation of left, right, and interval censoring (29). Interval censoring resulted from assessing pubertal stage at clinic examinations only; the exact time of transition from a recorded Tanner stage 1 at an examination to a recorded stage 2 by the time of the following examination was unknown.

The time interval in which pubarche or thelarche occurred was defined as falling between the last examination with pubertal assessment of stage 1, with no previous assessment of stage 2+, and the first examination at pubertal stage 2+. A subject was considered left-censored if she had already transitioned to stage 2+ at the time of the baseline examination and right-censored if she had not transitioned by the time of the last examination or did not have a follow-up Tanner assessment. Regression analyses provided 2 estimates of the association (and 95% confidence interval) between a covariate and the outcome of time to puberty onset: the time ratio and the hazard ratio. The time ratio is interpreted as the ratio of the median times to an event for a given level of a covariate

Table 1. Baseline Characteristics of Girls and Their Mothers in a Study of Maternal Pregnancy Metabolic Factors and the Timing of Puberty Onset ($n = 15,267$), According to Maternal Body Mass Index During Pregnancy, California, 2003–2017

Characteristic	Maternal BMI During Pregnancy[a]								*P* Value
	Underweight ($n = 165$ Pairs)[b]		Normal Weight ($n = 6,468$ Pairs)		Overweight ($n = 4,835$ Pairs)		Obese ($n = 3,799$ Pairs)		
	No. of Pairs	%	No. of Pairs	%	No. of Pairs	%	No. of Pairs	%	
Maternal Characteristics									
Age at delivery, years[c]	27.9 (5.2)		29.9 (5.1)		30.5 (5.2)		30.3 (5.3)		<0.0001
Pregnancy glucose concentration, mg/dL[c]									<0.0001
<140 (normoglycemia)	146	90.1	5,295	83.2	3,709	78.3	2,622	72.2	
≥140 (hyperglycemia)	16	9.9	1,069	16.8	1,025	21.7	1,011	27.8	
Gestational diabetes mellitus	3	1.9	301	4.8	347	7.4	383	10.7	<0.0001
Parity[d]									<0.0001
0	108	65.5	3,342	51.7	1,976	40.9	1,406	37.1	
1	46	27.9	2,178	33.7	1,728	35.8	1,309	34.5	
≥2	11	6.7	946	14.6	1,129	23.4	1,079	28.4	
Education[d]									<0.0001
High school or less	55	33.9	1,675	26.3	1,588	33.4	1,446	38.7	
Some college (<4 years)	43	26.5	1,665	26.1	1,327	27.9	1,283	34.4	
College/university	35	21.6	1,698	26.7	1,039	21.9	627	16.8	
Graduate school or higher	29	17.9	1,334	20.9	799	16.8	377	10.1	
Smoking during pregnancy (yes)	7	4.2	254	3.9	261	5.4	208	5.5	
Girls' Characteristics									
Race/ethnicity									<0.0001
Non-Hispanic white	35	21.2	2,374	36.7	1,805	37.3	1,411	37.1	
Asian	78	47.3	1,958	30.3	818	16.9	321	8.5	
Hispanic	23	13.9	1,192	18.4	1,395	28.9	1,234	32.5	
African-American	12	7.3	254	3.9	302	6.3	420	11.1	
Other	17	10.3	690	10.7	515	10.7	413	10.9	
Prepubertal BMI									<0.0001
<85th percentile	152	92.1	5,284	81.7	3,235	66.9	1,804	47.5	
≥85th percentile	13	7.9	1,184	18.3	1,600	33.1	1,995	52.5	
Birth weight, g[c]	3,072.2 (471.2)		3,270.4 (484.5)		3,399.4 (528.0)		3,455.2 (599.2)		<0.0001

Abbreviation: BMI, body mass index.

[a] BMI was calculated as weight (kg)/height (m)^2. BMI categories: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥30.0).

[b] Number of mother-daughter pairs.

[c] Values are expressed as mean (standard deviation).

[d] Values in subgroups do not sum to total because of missing data.

compared with the referent level. The hazard ratio is interpreted as a ratio of the risk of transitioning from BR1/PH1 to BR2+ or PH2+ for a given level of a covariate compared with the referent level. All models adjusted for girl's race/ethnicity, maternal age at delivery, education, parity, and smoking during pregnancy.

The mediating roles of girls' prepubertal BMI and birth weight were assessed by comparing the coefficients from models with and without these variables, as well as adjusting for the other confounders mentioned above. Effect modification by girl's race/ethnicity was evaluated by including a cross-product term. Stratified analyses were conducted if the *P* value for effect modification was less than 0.05. Because of the evidence of effect modification by race/ethnicity in associations between maternal obesity and timing of pubarche, we have presented stratified results for this analysis only. All analyses used SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Participant characteristics

A total of 15,267 mother-daughter pairs were included in the analysis, among whom 14,760 pairs had data on breast Tanner stage and 14,063 had data on pubic hair Tanner stage. Table 1

Table 2. Association Between Maternal Body Mass Index During Pregnancy and Onset of Breast Development in Daughters (n = 14,760), California, 2003–2017

Maternal BMI During Pregnancy[a,b]	No. of Pairs	Time Ratio[c]	95% CI	Hazard Ratio[c]	95% CI
Underweight	161	1.03	1.00, 1.06	0.75	0.58, 0.97
Normal weight	6,261	1.00	Referent	1.00	Referent
Overweight	4,671	0.98	0.97, 0.99	1.21	1.13, 1.29
Obese	3,667	0.97	0.96, 0.97	1.39	1.30, 1.49

Abbreviations: BMI, body mass index; CI, confidence interval.
[a] BMI was calculated as weight (kg)/height (m)^2. BMI categories: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥30.0).
[b] P for trend < 0.0001.
[c] Adjusted for girl's race/ethnicity and maternal age, education, parity, and smoking during pregnancy.

shows the baseline characteristics of the mothers and girls, stratified by maternal BMI category. Obese women were more likely to have GDM, higher parity, and less education than those who were not obese ($P < 0.0001$). Daughters of obese women were more likely to be overweight and to have greater birth weight ($P < 0.0001$). Approximately 15% of girls were left-censored for the breast development analyses, and 13% were left-censored for the pubic-hair development analyses. Approximately 50% of the girls were right-censored for breast analyses and 64% for pubic hair analyses.

Primary analyses

Association between maternal obesity and timing of breast development. Table 2 presents results from the hazard regression model assessing associations between maternal pregnancy BMI and the timing of onset of breast development among the 14,760 girls with Tanner breast stage data. After adjustment for covariates, there was a strong association between maternal BMI and the hazard of earlier breast development onset. Daughters of obese mothers were more than 30% more likely to experience earlier breast onset than those whose mothers had normal BMIs (hazard ratio (HR) = 1.39, 95% confidence interval (CI): 1.30, 1.49). Daughters of underweight women were less likely to have early breast onset (HR = 0.75, 95% CI: 0.58, 0.97). The corresponding time ratios for obese women versus underweight women translated into approximately 7 months' difference in the timing of breast onset between these 2 groups, adjusting for covariates.

Association between maternal obesity and timing of pubic hair development. Table 3 presents results from assessment of associations between maternal pregnancy BMI and the timing of girls' pubic hair onset among the 14,063 girls with Tanner pubic hair data. Because there was evidence of effect modification ($P = 0.007$), the results were stratified by girl's race/ethnicity. After adjustment for covariates, there were significant associations between maternal obesity (BMI ≥30) and earlier timing of pubarche in all racial/ethnic groups except African Americans. The associations were particularly stronger among Asians and persons in the "other" category; Asian girls with obese mothers were at approximately 50% higher risk of experiencing earlier pubic hair onset than Asian girls with a normal-weight mother (HR = 1.53, 95% CI: 1.24, 1.90), with a corresponding time ratio of 0.96 (95% CI: 0.94, 0.98)—5 months' earlier onset than in the referent group (data not shown in the table). The associations between maternal overweight (BMI 25–29.9) and earlier timing of pubarche were significant among non-Hispanic whites and Asians. On the other hand, the association was not significant among Hispanics, and among African Americans there was a significant inverse association (HR = 0.70, 95% CI: 0.48, 1.00).

Association between pregnancy glucose level and timing of breast and pubic hair onset. We examined the associations between maternal pregnancy hyperglycemia (blood glucose concentration ≥140 mg/dL) and the timing of breast and pubic hair onset (Table 4). There was a significant association between hyperglycemia *without* GDM and earlier onset of breast development (HR = 1.12, 95% CI: 1.03, 1.21), after adjustment for the covariates and maternal BMI. On the other hand, the association between hyperglycemia *with* GDM and breast onset and the association between hyperglycemia regardless of GDM status and pubic hair onset were not significant (Table 4).

Secondary analyses: mediation by girls' obesity and birth weight

Inclusion of girl's BMI attenuated the effect estimates for the maternal obesity–puberty onset associations, but they remained significant. For instance, the hazard ratio for the association between maternal obesity and early breast onset, also adjusting for girl's BMI, was 1.22 (95% CI: 1.13, 1.31), which was attenuated from that produced by the model without this variable (Table 2). Similarly, the associations with pubic hair onset were attenuated after the inclusion of girl's BMI. For instance, among Asians, the hazard ratio from the model including girl's BMI was 1.32 (95% CI: 1.06, 1.64)—still significant, yet attenuated from the model without girl's BMI (Table 3). There was no attenuation from inclusion of the birth weight variable: The hazard ratio for maternal obesity and onset of breast development, adjusting for girl's birth weight, was 1.39 (95% CI: 1.29, 1.49), which was nearly identical to that from the model without birth weight (Table 2). For hyperglycemia analyses, inclusion of girl's BMI or birth weight did not change the associations (data not shown).

DISCUSSION

To our knowledge, this was one of the largest population-based studies to date to have examined the associations between

Table 3. Association Between Maternal Body Mass Index During Pregnancy and Onset of Pubic Hair Development (n = 14,063), by Girl's Race/Ethnicity, California, 2003–2017

Maternal BMI During Pregnancy[a]	Total No. of Pairs	Daughter's Race/Ethnicity															
		Non-Hispanic White			African-American			Hispanic			Asian			Other			
		No. of Pairs	HR[b]	95% CI	No. of Pairs	HR[b]	95% CI	No. of Pairs	HR[b]	95% CI	No. of Pairs	HR[b]	95% CI	No. of Pairs	HR[b]	95% CI	
Underweight	147	31	1.07	0.56, 2.03	9	1.73	0.33, 9.04	20	0.97	0.42, 2.24	72	0.86	0.57, 1.28	15	0.09	0.01, 0.72	
Normal weight	5,996	2,213	1.00	Referent	227	1.00	Referent	1,098	1.00	Referent	1,813	1.00	Referent	645	1.00	Referent	
Overweight	4,439	1,654	1.20	1.07, 1.34	273	0.70	0.48, 1.00	1,292	1.04	0.91, 1.20	742	1.31	1.14, 1.51	478	1.17	0.95, 1.44	
Obese	3,481	1,296	1.34	1.18, 1.52	383	1.11	0.79, 1.57	1,131	1.24	1.07, 1.43	294	1.53	1.24, 1.90	377	1.70	1.36, 2.14	
Total	14,063	5,194			892			3,541			2,921			1,515			

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] BMI was calculated as weight (kg)/height (m)^2. BMI categories: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥30.0).
[b] Adjusted for maternal age, education, parity, and smoking during pregnancy.

maternal pregnancy metabolic factors and the timing of puberty onset in a cohort of racially/ethnically diverse girls. Our findings suggest that maternal obesity is an independent risk factor for early breast and pubic hair development in girls. Further, pregnancy hyperglycemia may also increase the risk of earlier breast development. The association between maternal obesity and earlier appearance of pubic hair may vary by race/ethnicity. Associations were not fully mediated by girl's prepubertal BMI, suggesting that independent pathways of in utero exposure to maternal overnutrition may influence girls' hormonal development.

The Healthy People 2020 program emphasizes the importance of improving adolescent health because "the behavioral patterns established during these developmental periods help determine young people's current health status and their risk for developing chronic diseases during adulthood" (30). Early onset of puberty in girls is associated with numerous immediate and long-term adverse psychological and physiological outcomes (2). Our identification of potentially modifiable upstream risk factors for early puberty can inform preventive measures and interventions designed to reduce this risk.

Pregnancy represents a critical period of development and susceptibility ("window of susceptibility"). Sexual developmental events in females involve maturation of the ovaries (gonadarche) and the adrenal gland (adrenarche) through 2 hormonally distinct processes (the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-adrenal axis) (31). Thelarche is often one of the indications of gonadarche, and pubarche often follows adrenarche. These events are part of a continuum that begins during intrauterine life and extends through the completion of sexual maturation. It is therefore biologically plausible that in utero factors may affect the development of these hormonal processes, thereby programming the timing of sexual maturation later in life.

Our results support a number of hypotheses that were generated from our previous study examining 421 adolescent girls followed longitudinally, from which we reported that in utero exposure to obesity during pregnancy and gestational diabetes were associated with earlier timing of pubarche (25). Although we observed an association between maternal pregnancy factors and timing of onset only for pubic hair, we had hypothesized that there would also be an association with breast development. Thelarche, the initial appearance of breast tissue in girls, normally indicates gonadotropin-driven ovarian estrogen production (31). We reasoned that in utero exposure to maternal hyperglycemia and obesity would be associated with the earlier timing of thelarche via adiposity in the girls, as adipose tissue produces the hormone estrogen, an important component of gonadarche (31). Further, leptin, a hormone produced by adipocytes, is directly correlated with fat mass; recent studies have suggested that leptin may play an important role in pubertal development (32–34). Although we could not measure estrogen or leptin levels in the current study, our results support the hypothesis that girls' prepubertal obesity at least partially mediates the association between maternal obesity/hyperglycemia and the timing of breast onset. The observed independent associations may be explained by factors other than obesity, including insulin resistance or cortisol, both of which play important roles in the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes (35), affecting the timing of breast development.

Table 4. Associations Between Maternal Hyperglycemia During Pregnancy and the Timing of Breast and Pubic Hair Development in Daughters, by Gestational Diabetes Mellitus Status, California, 2003–2017

Maternal Screening Glucose Concentration, mg/dL	Breast Development			Pubic Hair Development		
	No. of Pairs	HR[a]	95% CI	No. of Pairs	HR[a]	95% CI
<140 (normoglycemia)	11,364	1.00	Referent	10,839	1.00	Referent
≥140 (hyperglycemia)						
Without GDM	1,846	1.12	1.03, 1.21	1,753	1.02	0.93, 1.11
With GDM	977	1.06	0.95, 1.18	931	1.04	0.92, 1.17

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; HR, hazard ratio.
[a] Adjusted for race/ethnicity, maternal age, education, parity, smoking during pregnancy, and body mass index.

We were able to test our hypothesis that the results might vary by race/ethnicity because of our large sample and diverse study population. Our results presented evidence that the associations between maternal obesity and timing of pubarche may vary by race/ethnicity and that the association may be stronger in Asians. Our finding corroborates previous findings demonstrating that Asians tend to have increased risks of weight-related conditions at lower BMIs than whites, Hispanics, or African Americans (36, 37). Epidemiologic studies have shown that there is a relationship between BMI and diabetes risk in Asians, but this risk is shifted to lower BMI values (36). One possible explanation for this shift is the difference in the amount of body fat or rate of abdominal obesity in Asians. Compared with Caucasians with the same BMIs, Asians tend to have 3%–5% higher total body fat (38) and South Asians tend to have a higher prevalence of abdominal obesity (39). We did not have measures of body fat or body composition for this study. Further investigation examining how adiposity, body composition, or obesity-related hormones may influence the timing of puberty is warranted.

Animal and human studies have shown that exposure to maternal hyperglycemia and obesity may cause persistent changes in offspring metabolism, such as in utero hyperinsulinemia, pancreatic β-cell secretory capacity, abnormal insulin signaling in insulin-sensitive tissues, and abnormal development of the hypothalamus and adrenal gland, all displaying associations with aberrant control of energy regulation and obesity (40–48). We hypothesize that these mechanisms may underlie associations between maternal obesity, hyperglycemia, and girls' timing of pubarche. Our data demonstrating a stronger association between maternal obesity and early onset of pubarche in Asians suggest that early pubarche may be a surrogate for metabolic dysregulation and that these adolescents may be at higher risk of prediabetes, diabetes, or metabolic syndrome later in life. Clinicians should monitor adolescents with early onset of pubarche closely to prevent the development of metabolic dysregulation.

Lastly, we observed that subclinical maternal hyperglycemia (i.e., hyperglycemia that did not meet criteria for GDM) was significantly associated with early thelarche; however, the association between GDM and thelarche did not reach statistical significance. This was contrary to our hypothesis that maternal hyperglycemia would be associated with earlier timing of *pubarche*, a potential surrogate for metabolic dysregulation. This finding is nonetheless noteworthy because it represents a future opportunity for upstream intervention designed to slow the ever-accelerating timing of puberty in girls. At KPNC, women who are diagnosed with GDM are generally encouraged to monitor their gestational weight gain carefully via a healthier diet and increased physical activity. Although the results must be replicated, our findings demonstrating no association between women with GDM and early onset of puberty suggest that this intervention with women with GDM has been successful in reducing the risk of early puberty in offspring. At KPNC, several intervention studies have targeted women with GDM or obesity with the aim of controlling gestational weight gain in an effort to reduce intergenerational transmission of obesity and diabetes (49, 50). Examination of the effectiveness of such interventions in influencing the timing of puberty and metabolic dysregulation in offspring is warranted.

Our findings should be interpreted with caution, given a few limitations. First, Tanner data were extracted from the EHR. Although pediatrician-assessed Tanner stage may not be as high-quality as assessments conducted by a pediatric endocrinologist, we conducted a validation study to assure that the KPNC Tanner data we used were of high quality. We compared the EHR-based Tanner stages of the girls who participated in the aforementioned prospective study of adolescent girls (the Cohort Study of Young Girls' Nutrition, Environment, and Transitions (CYGNET) (25, 51, 52)) with the Tanner stages obtained for research purposes. In CYGNET, we rigorously trained staff in Tanner stage assessment, followed by observation of the assessments by a board-certified pediatric endocrinologist (L.C.G.), ensuring that the Tanner data collected from this study were of the highest quality. In a comparison of CYGNET clinic assessments with KPNC pediatrician assessments (selecting those done within 6 months of study visits ($n = 217$)), the weighted κ value was 0.66 (95% CI: 0.61, 0.72) for breast development and 0.65 (95% CI: 0.59, 0.71) for pubic hair development (A.K., C.A.L., L.C.G., and L.H.K., unpublished data, 2017). Because the KPNC pediatrician and CYGNET Tanner assessments did not occur at the same time, this level of agreement is notable, strongly suggesting acceptable levels of agreement and reasonable validity of the use of routine pediatric assessments in research. Pediatrician-assessed Tanner stage is more reliable than self-reported or parent-reported assessments—methods commonly used in previous studies (53).

The second limitation was that information on maternal weight was captured during pregnancy, rather than before pregnancy, because the EHR that currently captures prepregnancy weight

was implemented after these girls were born. For the present analysis, we used an established GDM registry which routinely records weight at the time of α-fetoprotein testing. It is possible that some women had rapid gestational weight gain during the first trimester and we were not able to capture this change. In future studies, investigators should examine the role of gestational weight gain and racial/ethnic differences to better understand the interplay of overnutrition, race/ethnicity, and pubertal timing. Such knowledge may explain why we observed an inverse association between maternal obesity and risk of earlier pubarche only among African Americans.

Lastly, we did not have more detailed information about race/ethnicity. For instance, we did not have detailed information as to who comprised the category "other," and we lacked more granular information on subgroups within certain racial/ethnic groups (e.g., Japanese, Chinese, etc., within the Asian group).

In conclusion, our findings suggest that the theory of "windows of susceptibility" over the life course provides an important conceptual framework for understanding how intrauterine exposures may influence the health of offspring. Development of strategies for slowing the trend toward earlier sexual maturation in girls by designing upstream interventions to manage obesity and hyperglycemia among women who are pregnant or planning to become pregnant may hold promise for preventing the adverse, intergenerational effects of these conditions.

ACKNOWLEDGMENTS

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We thank Dr. Amy J. Markowitz (University of California, San Francisco Clinical and Translational Research Career Development Program), Elaine Kurtovich (Kaiser Permanente Division of Research), and Sara Aghaee (Kaiser Permanente Division of Research) for help in the preparation of the manuscript.

This work was supported by the National Institutes of Health (grants K07CA166143 and KL2TR000143 to A.K.).

Conflict of interest: none declared.

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