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Original Contribution

Associations Between Maternal Pregravid Obesity and Gestational Diabetes and the Timing of Pubarche in Daughters

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We investigated whether in utero exposure to maternal pregravid obesity and/or gestational diabetes mellitus (GDM) was associated with early puberty in girls. We used data from a longitudinal study of 421 mother-daughter pairs enrolled in an integrated health services organization, Kaiser Permanente Northern California (2005–2012). Girls aged 6–8 years were followed annually through ages 12–14 years. Onset of puberty was assessed using study clinic-based Tanner staging. We examined associations of self-reported pregravid obesity and maternal GDM with timing of the daughter's transition to pubertal maturation stage 2 or above for development of breasts and pubic hair, using accelerated failure time regression models with interval censoring to estimate time ratios and hazard ratios and corresponding 95% confidence intervals. Maternal obesity (pregravid body mass index (BMI; weight (kg)/height $(m)^2$) ≥30) was associated with a daughter's earlier transition to breast and pubic hair stage 2+ in comparison with girls whose mothers had pregravid BMI <25. These associations were attenuated and not statistically significant after adjustment for covariates. Girls whose mothers had both pregravid BMI ≥25 and GDM were at higher risk of an earlier transition to pubic hair stage 2+ than those whose mothers had neither condition (adjusted time ratio = 0.89, 95% confidence interval: 0.83, 0.96; hazard ratio = 2.97, 95% confidence interval: 1.52, 5.83). These findings suggest that exposure to maternal obesity and hyperglycemia places girls at higher risk of earlier pubarche.

gestational diabetes; intergenerational disease transmission; life-course epidemiology; obesity; prenatal exposure delayed effects; pubarche; puberty; thelarche

Abbreviations: BMI, body mass index; CI, confidence interval; CYGNET, Cohort Study of Young Girls' Nutrition, Environment, and Transitions; GDM, gestational diabetes mellitus; HR, hazard ratio; KPNC, Kaiser Permanente Northern California; PH2+, pubic hair stage 2+.

A trend towards earlier onset of puberty has been observed among girls in the United States over the past few decades (1–3). In a 2013 study, Biro et al. (3) found that white girls experienced breast development (thelarche) 4 months earlier than those in a study published only 15 years before (2). In addition, the proportion of 6-year-old African-American girls who had already begun to develop breasts or pubic hair increased 2- to 3-fold (4). Early puberty is associated with adverse health outcomes for girls and women over the life course, including obesity, type 2 diabetes, insulin resistance, metabolic syndrome, polycystic ovarian syndrome, and cancer (5–10).

Early-life determinants of the timing of pubertal maturation are not well known. Sexual developmental events in females involve maturation of the ovaries (gonadarche) and the adrenal gland (adrenarche) through 2 hormonally distinct processes (11). Thelarche (first budding of breasts) is often one of the indications of gonadarche, and pubarche (first appearance of pubic hair) 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 likely that early-life factors play important roles in the programming of sexual maturation, as well as later metabolic patterns. Intrauterine growth retardation and small size

for gestational age have been identified as early-life risk factors for premature adrenarche (12, 13). In addition, in a large cohort of adolescent girls, Maisonet et al. (14) recently found that daughters of obese and overweight mothers reported earlier stages of breast development and menarche than daughters of women who had a normal pregravid weight. Other early-life factors such as primiparity, smoking during pregnancy, and rapid weight gain during infancy were also associated with earlier timing of pubertal onset and menarche in that study (14), corroborating results from other studies that have found an association between rapid infant weight gain and earlier onset of menarche (12, 15). These studies indicate the importance of early-life factors influencing the timing of pubertal development in girls.

The incidence of gestational diabetes mellitus (GDM) and the prevalence of obesity among women of reproductive age have increased during the last several decades (13, 16, 17). The adrenal cortex has receptors for insulin and growth factors, and previous studies have suggested that increased levels of insulin in girls may boost androgen production from the adrenal glands, triggering adrenarche (18–21). Daughters of women whose pregnancies were complicated by GDM or obesity are at higher risk of insulin resistance and development of diabetes in the future (22, 23). Since rapid infant weight gain, which appears to be related to earlier pubertal development (12, 14, 15), is a known risk factor for insulin resistance (24, 25), pregnancy obesity and GDM may also influence the timing of puberty onset in the offspring through a similar mechanism. Therefore, we conducted analyses examining the associations between pregravid obesity and GDM in mothers and the timing of thelarche and pubarche in their daughters, using data from a longitudinal study of a multiethnic cohort of girls drawn from the membership of a large integrated health-care delivery system in Northern California.

METHODS

This study was conducted as part of the National Institute of Environmental Health Sciences/National Cancer Institute Breast Cancer and the Environment Research Program, which included 3 collaborative epidemiologic studies examining environmental and other factors that influence pubertal maturation (26). The present analysis was carried out within one of these prospective cohort studies, the Cohort Study of Young Girls' Nutrition, Environment, and Transitions (CYGNET). CYGNET investigates pubertal maturation in the diverse membership of a health maintenance organization, Kaiser Permanente Northern California (KPNC). Written informed consent and assent were obtained from parent and child participants, respectively, and the study protocol was approved by the Kaiser Permanente Institutional Review Board.

Participants and procedure

The CYGNET investigators recruited 444 girls and their caregivers (96% mothers) from KPNC members in the San Francisco Bay Area, Northern California. The study protocol has been described in detail previously (27). Briefly, girls were enrolled in the study at age 6–7 years at recruitment (a handful were 8 years of age at the time of baseline examination) and were ethnically diverse (see Table 1). Girls were members of the KPNC health-care system at birth (1997–1999) and at recruitment (2005–2006). At each annual study visit (mean duration of follow-up in this analysis was 5.4 years; range, 1–7 years), anthropometric measurements were taken, and pubertal staging for breast and pubic hair development was assessed based on the methods of Biro et al. (1) and Marshall and Tanner (28), using palpation for assessment of breast stage and visual inspection for assessment of pubic hair. Other data, such as information on demographic and lifestyle factors, were collected through annual interviews conducted with caregivers and with the girls themselves when they were old enough to provide their own information (ages 10–14 years).

Measurements

Exposure variables. Maternal pregravid body mass index. Maternal pregravid body mass index (BMI) was calculated as weight (in kilograms) divided by squared height (in meters) from self-reported prepregnancy weight and height data, obtained from the CYGNET questionnaire completed at enrollment. We categorized women's pregravid BMI as normalweight (BMI <25.0), overweight (BMI 25.0–<30.0), or obese (BMI ≥30.0).

Maternal GDM. Each girl's medical record was linked to her mother's medical record. In the KPNC system, 96% of pregnancies are screened for GDM using a 50-g, 1-hour oral glucose challenge test (screening test), in accordance with American Diabetes Association recommendations (29). If the screening test result is abnormal, a diagnostic 100-g, 3-hour oral glucose tolerance test is performed. Pregnancy glucose values were obtained from the KPNC GDM registry (13). The validity of plasma glucose results obtained from our laboratory is supported by previously published data (30–33). GDM was defined according to the Carpenter and Coustan thresholds (29) for the diagnostic test, as 2 or more values meeting or exceeding the following plasma glucose cutpoints: fasting glucose 95 mg/dL; 1-hour glucose 180 mg/dL; 2-hour glucose 155 mg/dL; and 3-hour glucose 140 mg/dL.

Outcomes (onset of thelarche and pubarche). Pubertal maturation staging was assessed by means of the gold-standard method for epidemiologic studies: 5-stage Tanner staging (28) conducted by trained personnel. Research staff were trained and certified for these assessments by a pediatric endocrinologist (L.G.). For this study, onset of breast development and pubic hair development were coded separately for each study visit as "no onset" (stage 1) or "onset" (stage 2 or above).

Covariates. Girl's BMI. The study clinic visit included several anthropometric measurements. Height was measured to the nearest 0.1 cm using a mounted wall stadiometer, with the participant in stocking feet and head in the neutral position. Weight was measured without shoes and in light clothing and was rounded to the nearest 0.5 kg. These measurements were used to calculate BMI, and associated percentiles and z scores were determined for the appropriate age- (and sex-) specific Centers for Disease and Control and Prevention year 2000 standard population distribution. As covariates, we included baseline BMI and BMI immediately prior to puberty onset

Table 1. Baseline Characteristics of Study Participants and Mothers by Maternal Gestational Diabetes Status and Pregravid Body Mass Index, CYGNET, San Francisco, California, 2005–2012

Characteristic	GDM Status						Pregravid BMI[a]								
	No GDM			GDM			<25.0			25.0–<30			≥30.0		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Mother-daughter pairs	390	94		27	6		68	18		104	27		55	214	
Girls' characteristics															
Age, years															
6	93	97		3	3		49	53		24	26		19	21	
7	291	92		24	8		162	56		79	27		48	17	
8	6	100		0	0		3	60		1	20		1	20	
Race/ethnicity															
White	170	94		10	6		118[b]	70		31	18		20	12	
Asian	47	92		4	8		42	81		9	17		1	2	
Latina	91	91		9	9		32	38		35	42		17	20	
African-American	82	95		4	5		22	27		29	36		30	37	
Tanner stage 2+															
Breast development	28	7		2	7		12	6		8	8		8	12	
Pubic hair	29	8		2	8		9[b]	4		7	7		10	15	
Girl's BMI															
Normal-weight (<25)	284	95		15	5		171[b]	61		68	24		40	14	
Overweight (25–<30)	54	90		6	10		27	49		18	33		10	18	
Obese (≥30)	52	90		6	10		16	31		18	35		18	35	
% body fat			18.9 (8.7)			21 (10.5)			17.5[b] (8.1)			20.0 (9.7)			21.3 (9.5)
Waist:height ratio			0.49[c] (0.05)			0.51 (0.05)			0.48[b] (0.04)			0.49 (0.06)			0.50 (0.06)
Birth weight, g			3,373 (539)			3,396 (849)			3,335 (546)			3,415 (535)			3,458 (690)
Maternal characteristics															
Age at delivery, years			32.6 (5.9)			33.0 (5.0)			33.4 (5.2)			32.5 (5.8)			30.7 (7.2)
Education															
High school diploma or less	63[c]	86		10	14		26[b]	46		16	29		14	25	
Some college	109	94		7	6		41	37		39	35		30	27	
College degree/university	127	96		5	4		86	67		27	21		16	12	
Postgraduate study	84	94		5	6		57	68		20	24		7	8	
Annual household income															
<$50,000	76	93		6	7		23[b]	32		24	33		26	36	
≥$50,000	313	94		21	6		191	61		80	26		41	13	

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CYGNET, Cohort Study of Young Girls' Nutrition, Environment, and Transitions; GDM, gestational diabetes mellitus; SD, standard deviation.

[a] Weight (kg)/height $(m)^2$.

[b] $P < 0.01$ (χ^2 test for categorical variables and *t* test/ANOVA for continuous variables).

[c] $P < 0.05$ (χ^2 test for categorical variables and *t* test/ANOVA for continuous variables).

separately; because the results were similar, we used baseline BMI, since data on this variable were available for a larger number of girls than BMI more proximal to puberty onset.

Other covariates. Girls' and mothers' demographic information and maternal age at menarche were obtained from the CYGNET questionnaires. Girl's race/ethnicity was assessed using the primary caregiver's report at baseline, and was coded into mutually exclusive categories as African-American or black, Hispanic or Latina, Asian, or non-Hispanic white. Girl's birth weight was obtained from the KPNC electronic databases. Caregivers reported annual household income at baseline. Income was dichotomized into "lower" (<$50,000/year) and "higher" (≥$50,000/year) income. Maternal age at menarche was defined categorically as age in years (<12, 12–<13, 13–<14, or ≥14).

Statistical analyses

Analyses of maternal GDM and pregravid obesity in relation to pubarche and thelarche 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 (34). Interval censoring resulted from assessing pubertal stage at study examinations only; the exact time of transition for a girl who was at stage 1 at one examination and at stage 2 at 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 or greater. A study participant was considered left-censored if she had already transitioned to stage 2 or higher at the time of baseline examination and right-censored if she had not transitioned by the time of the last examination. Regression analyses provided 2 estimates of association (and 95% confidence intervals) between a covariate and the outcome of time to pubertal onset. The time ratio is interpreted as the ratio of the median (or any other quantile) time-to-event for a given level of a covariate to the referent level. The hazard ratio is interpreted as the risk of transitioning to Tanner breast development stage 2+ or pubic hair stage 2+ (PH2+) for a given level of a covariate compared with the referent level. The associations between maternal GDM and prepregnancy obesity and pubertal onset were examined for breast and pubic hair development in separate analyses, without adjustment as well as with adjustment for known confounders, such as girl's race/ethnicity, mother's age at menarche, and household income.

Effect modification between maternal GDM and obesity was evaluated by including a cross-product term. The mediating roles of girl's BMI and birth weight were tested by comparing the coefficients between models with and without these variables, also adjusting for other confounders mentioned above. If the observed association was attenuated substantially (>10% of the effect estimate) after the inclusion of a potential mediator, this was taken to indicate that the variable may mediate the association (35). All analyses used SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Participant characteristics

Of the 444 participants enrolled at baseline, we excluded 27 mother-daughter pairs who were missing information on GDM status and 58 pairs who were missing data on pregravid BMI. The analyses comparing those pairs that were included with those that were excluded did not demonstrate substantial differences in the distributions of the exposure or outcome variables (data not shown). Table 1 shows the baseline characteristics of these study pairs, stratified by GDM status and pregravid BMI category. Daughters of women whose pregnancies were complicated by GDM were more likely to have a greater waist:height ratio, and their mothers were likely to have lower educational attainment than those without GDM. Daughters of women who had pregravid BMI ≥30 were more likely to be Hispanic or African-American, to have greater BMI and waist:height ratio, and to have transitioned to PH2+ by the time of the baseline examination. Mothers with pregravid obesity were younger, less educated, and of lower income than women without it.

Primary analyses

Associations between pregravid obesity and GDM and onset of thelarche. In crude analyses, daughters of women who were obese prior to pregnancy were more likely to have transitioned to breast development stage 2+ than those with pregravid BMI <25 (Table 2). The corresponding time ratio of 0.96 (95% confidence interval (CI): 0.93, 0.99) translates to an approximately 4-month difference in the estimated median age at onset of thelarche between these groups. However, the associations were attenuated and not statistically significant after adjustment for race/ethnicity, household income, and maternal age at menarche. There was no association between maternal GDM and timing of thelarche.

Associations between pregravid obesity and GDM and onset of pubarche. Without adjustment for covariates, girls whose mothers were obese prior to pregnancy had a higher risk of an earlier transition to PH2+ than those whose mothers had pregravid BMI <25 (hazard ratio (HR) = 2.08, 95% CI: 1.53, 2.82). The corresponding time ratio of 0.92 (95% CI: 0.88, 0.95) translates to an approximately 11-month difference in the estimated median age at onset of pubarche between these groups. Daughters of overweight mothers also had a younger age of transition to PH2+ (HR = 1.47, 95% CI: 1.12, 1.93; time ratio = 0.95, 95% CI: 0.92, 0.99 (approximately 7 months earlier)) than those whose mothers had pregravid BMI <25, and there was a dose-effect relationship between pregravid BMI and onset of pubarche ($P < 0.0001$). However, associations were attenuated and no longer statistically significant after adjustment for race/ethnicity, household income, and maternal age at menarche. There was no association between maternal GDM and onset of pubarche (Table 3).

Interaction between pregravid BMI and maternal GDM. Lastly, we evaluated possible interactions between maternal pregravid obesity and GDM (Table 4). The test for interaction suggested a possible interaction for pubarche ($P = 0.08$) but not thelarche ($P = 0.77$). After adjustment for race/ethnicity,

Table 2. Results From Survival Analysis of the Associations Between Maternal Gestational Diabetes and Pregravid Obesity and Girls' Thelarche (Onset of Breast Development), CYGNET, San Francisco, California, 2005–2012

Variable	Unadjusted				Adjusted[a]			
	TR	95% CI	HR	95% CI	TR	95% CI	HR	95% CI
Pregravid BMI[b]								
<25	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25–<30	0.98	0.95, 1.01	1.24	0.94, 1.62	0.99	0.96, 1.02	1.15	0.85, 1.56
≥30	0.96	0.93, 0.99	1.39	1.02, 1.91	1.00	0.97, 1.04	0.96	0.66, 1.39
P for trend	0.002		0.002		0.57		0.78	
GDM								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.00	0.95, 1.05	1.01	0.65, 1.57	1.02	0.97, 1.06	0.85	0.54, 1.35

Abbreviations: BMI, body mass index; CI, confidence interval; CYGNET, Cohort Study of Young Girls' Nutrition, Environment, and Transitions; GDM, gestational diabetes mellitus; HR, hazard ratio; TR, time ratio.

[a] Adjusted for race/ethnicity, household income, and maternal age at menarche.

[b] Weight (kg)/height $(m)^2$.

household income, and maternal age at menarche, there was a significant increase in risk of an earlier transition to PH2+ for girls whose mothers had both GDM and pregravid BMI ≥25 in comparison with the referent group (those with no GDM and with pregravid BMI <25). Those girls on average transitioned to PH2+ substantially earlier than the referent girls (time ratio = 0.89, 95% CI: 0.83, 0.96). The hazard of having transitioned to PH2+ was approximately 3-fold (HR = 2.97, 95% CI: 1.52, 5.83) in this group, compared with the referent group. There was no effect of the association between maternal pregravid obesity and GDM on thelarche in our data.

Supplemental analysis

To evaluate whether the effect of the interaction between maternal obesity and GDM on the timing of girl's pubarche was mediated by girl's obesity or birth weight, we conducted analyses including girl's baseline BMI or birth weight as a mediator. Inclusion of girl's BMI (baseline or proximal to pubarche) or birth weight had only a modest impact on the effect estimates. Compared with the group whose mothers were without GDM and had pregravid BMI <25, the hazard ratio for transition to PH2+ among daughters of those with pregravid obesity *and* GDM was 2.53 (95% CI: 1.27, 5.05) when girl's baseline BMI was included in the model; this finding was somewhat attenuated from that obtained in the model without either girl's BMI or birth weight (HR = 2.97, 95% CI: 1.52, 5.83). When girl's later BMI was included, the results were more similar to those from the model without inclusion of BMI (HR = 2.79, 95% CI: 1.29, 6.01). Similarly, the hazard ratio for the same association including birth weight (HR = 3.16, 95% CI: 1.59, 6.30) was not substantially different from that excluding girl's BMI and birth weight, suggesting that these variables did not fully explain the observed association.

Table 3. Results From Survival Analysis of the Associations Between Maternal Gestational Diabetes and Pregravid Obesity and Girls' Puberarche (Onset of Pubic Hair), CYGNET, San Francisco, California, 2005–2012

Variable	Unadjusted				Adjusted[a]			
	TR	95% CI	HR	95% CI	TR	95% CI	HR	95% CI
Pregravid BMI[b]								
<25	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25–<30	0.95	0.92, 0.99	1.47	1.12, 1.93	0.98	0.95, 1.01	1.20	0.89, 1.62
≥30	0.92	0.88, 0.95	2.08	1.53, 2.82	0.97	0.94, 1.01	1.27	0.89, 1.81
P for trend	<0.0001		<0.0001		0.42		0.82	
GDM								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.99	0.93, 1.05	1.09	0.71, 1.70	0.98	0.93, 1.03	1.24	0.79, 1.94

Abbreviations: BMI, body mass index; CI, confidence interval; CYGNET, Cohort Study of Young Girls' Nutrition, Environment, and Transitions; GDM, gestational diabetes mellitus; HR, hazard ratio; TR, time ratio.

[a] Adjusted for race/ethnicity, household income, and maternal age at menarche.

[b] Weight (kg)/height $(m)^2$.

Table 4. Adjusted[a] Results From Survival Analysis of the Combined Effects of Maternal Gestational Diabetes and Pregravid Obesity on Girls' Puberty Onset, CYGNET, San Francisco, California, 2005–2012

BMI[b] and GDM Status	Breast Development				Pubic Hair			
	TR	95% CI	HR	95% CI	TR	95% CI	HR	95% CI
BMI <25								
No GDM	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
GDM	0.98	0.91, 1.06	1.22	0.54, 2.74	0.99	0.91, 1.08	1.06	0.48, 2.36
BMI ≥25								
No GDM	0.98	0.96, 1.01	1.18	0.88, 1.57	0.98	0.95, 1.01	1.19	0.90, 1.56
GDM	1.01	0.94, 1.08	0.93	0.47, 1.85	0.89	0.83, 0.96	2.97	1.52, 5.83

Abbreviations: BMI, body mass index; CI, confidence interval; CYGNET, Cohort Study of Young Girls' Nutrition, Environment, and Transitions; GDM, gestational diabetes mellitus; HR, hazard ratio; TR, time ratio.

[a] Adjusted for race/ethnicity, household income, and maternal age at menarche.

[b] Weight (kg)/height $(m)^2$.

DISCUSSION

In this multiethnic cohort of mother-daughter pairs, we observed that daughters of mothers who had both pregravid obesity and GDM were more likely to experience an earlier transition to PH2+ than girls whose mothers had no GDM and a BMI <25 prior to pregnancy. This association was independent of race/ethnicity, household income, and maternal age at menarche, and it was not explained by girl's BMI or birth weight. Mothers' pregravid obesity or GDM did not appear to influence their daughters' age at onset of thelarche.

Animal and human studies have demonstrated that maternal GDM and obesity lead to 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 (14, 36–43). Therefore, it is plausible that in utero exposure to GDM and obesity through fetal hyperinsulinemia may alter time to adrenarche. Although our study did not measure premature adrenarche (often determined by a high level of dehydroepiandrosterone sulfate and other adrenal androgens) as an outcome, pubarche, or the appearance of pubic hair, is one of the physical signs of adrenarche. Our results extend previous findings that early-life factors such as intrauterine exposure to maternal obesity probably alter metabolic programming in female offspring, putting them at higher risk of future chronic conditions related to metabolic dysregulation.

Although we hypothesized that in utero exposure to maternal GDM and obesity would also be associated with the timing of thelarche via adiposity in the girls, we did not observe the association after adjustment for other factors known to influence thelarche. It is possible that the underlying metabolic pathways that influence age at onset of pubarche versus thelarche are differentially affected by maternal obesity or GDM. From a methodological perspective, classification of breast development is more difficult to assess than pubic hair, in part because of the influence of adiposity. This may have led to nondifferential misclassification and therefore no association with breast development (35). The observed null finding may also have been due to effect modification by race/ethnicity. We adjusted the results for income and maternal age at menarche to control for hereditary and socioeconomic factors. The strongest attenuation was seen with inclusion of race/ethnicity, suggesting the importance of race/ethnicity's role in both prevalences of pregravid obesity and GDM and girl's pubertal onset. Unfortunately, we did not have enough statistical power to conduct analyses stratified by race/ethnicity, an important variable that has been shown to interact with relationships between prenatal factors and birth outcomes in previous studies (44–46). We did conduct stratified analyses comparing whites with nonwhites and comparing lower household income (<$50,000/year) with higher income (≥$50,000/year). Although neither of these analyses showed differences in the effect estimates between the groups (data not shown), we cannot preclude the possibility of effect modification by race/ethnicity in full-powered studies. Future studies that include diverse and large study populations should examine the role of race/ethnicity to shed more light on the interplay among these important variables.

While our findings represent important additions to the existing evidence regarding the risk factors for early pubarche, they should be interpreted with caution. First, maternal pregravid weight and height were self-reported. However, because of the unique availability of linkage of child medical records with maternal records at KPNC, we were able to compare, in a subgroup, self-reported height and weight data with height and weight recorded during pregnancy (measured at the time of α-fetoprotein testing) in the electronic medical record. The results were similar (for PH2+ analysis comparing pregravid BMI ≥30 with pregravid BMI <25, HR = 1.13 (95% CI: 0.70, 1.83) using self-reported BMI vs. HR = 1.32 (95% CI: 0.83, 2.11) using BMI from medical records), making it unlikely that self-reporting per se biased the results. Second, we did not have information on intrauterine growth retardation, which is known to be associated with timing of pubarche. We did examine the potential mediating roles of birth weight and gestational age, as well as small size for gestational age; however, inclusion of these variables did not change the effect estimates substantially. Lastly, due to the small sample size, we may not have been able to detect significant associations, especially in stratified analyses such as the one shown in Table 4. It is unlikely that we observed a strong

association between maternal pregravid obesity and GDM and timing of pubic hair development only by chance. However, these results should be interpreted with caution and be replicated to confirm the associations. These limitations—possible measurement error in pregravid BMI, lack of information on intrauterine growth retardation, and a relatively small sample size—do not influence the major strengths of this study. These strengths include its prospective design, the use of objective glucose measurements to define GDM, and the use of gold-standard assessments of pubertal staging in an ethnically diverse sample. Few studies provide the opportunity to examine these questions in such a data-rich setting.

In summary, in this ethnically diverse study of mother-daughter pairs, maternal pregravid obesity, particularly in the presence of GDM, was found to be a strong risk factor for early onset of pubarche in girls, and the association was not fully mediated by girl's prepubertal obesity or birth weight. A similar association was not seen for thelarche. The concept of windows of susceptibility over the life course provides an important conceptual framework for understanding how prenatal exposures may influence the health of offspring, which may continue over generations. We found an association between in utero exposure to maternal obesity and GDM and the female offspring's metabolic programming, manifested as early onset of pubarche. Our finding suggests that there may be strategies for slowing down 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.

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