Parental Obesity and Offspring Pubertal Development: Project Viva

Izzuddin M. Aris, PhD[1,2,3], Sheryl L. Rifas-Shiman, MPH[1], Ling-Jun Li, PhD[1,4,5], Abby F. Fleisch, MD[6,7], Marie-France Hivert, MD[1,8], Michael S. Kramer, MD[2,9,10], and Emily Oken, MD[1,11]

Objective To investigate the association of preconception parental obesity (body mass index [BMI] ≥30 kg/m^2) with offspring pubertal development.

Study design Among 1377 children from a prospective prebirth cohort in Boston, we examined markers of puberty (age at peak height velocity [PHV], age at menarche, self-reported pubertal development score), and adrenarche (pictograph Tanner pubic hair staging). We used multivariable regression models to examine associations of maternal and paternal obesity with offspring pubertal indices, and applied marginal structural models to estimate the controlled direct effect not mediated by offspring prepubertal BMI.

Results The prevalence of paternal obesity alone, maternal obesity alone, and biparental obesity were 10.5%, 10.1%, and 5%, respectively. After adjusting for demographic and socioeconomic factors, parental heights and maternal age at menarche, maternal obesity alone (vs neither parent with obesity) was associated with earlier age at PHV (β −0.30 years; 95% CI -0.57, −0.03) and higher early adolescent pubertal score (0.29 units; 0.10, 0.48) in boys, but not with pubertal or adrenarchal outcomes in girls. Paternal obesity alone was not associated with any outcomes in either boys or girls. Biparental obesity was associated with earlier age at PHV in boys and earlier menarche in girls. Using marginal structural models with stabilized inverse probability weighting, maternal obesity alone had significant controlled direct effects on age at PHV (−0.31 years; −0.62, 0.00) and on pubertal score (0.22 units; 0.00, 0.44) in boys, independent of prepubertal BMI.

Conclusion Maternal, but not paternal, obesity is associated with earlier pubertal development in boys, and such association is independent of prepubertal BMI. *(J Pediatr 2019;215:123-31)*.

Puberty is a time of psychological and biological transition from childhood to adulthood, which normally starts at ages 9-14 years in boys and at ages 8-13 years in girls.[1] Earlier onset of puberty is associated with an increased risk of adverse health outcomes later in life, including type 2 diabetes, cardiovascular disease, and cancer.[2-4]

Although excessive childhood adiposity is a well-known risk factor for earlier onset of puberty,[5] less attention has been paid to the role of in utero factors (such as maternal obesity, a cause of fetal over-nutrition and predictor of childhood overweight/obesity) on pubertal development in the offspring. Studies investigating this relationship have reported inconsistent findings. Some observed that higher maternal prepregnancy body mass index (BMI) is associated with earlier age at menarche,[6,7] and others found no associations.[8] Furthermore, recent data suggest that the father's preconception health and lifestyle can affect a child's health, perhaps mediated by epigenetic changes passed on via sperm.[9]

As parental BMI is a strong predictor of offspring BMI,[10] which in turn affects pubertal development,[5] the association of maternal and/or paternal BMI with offspring pubertal development is presumed to be mediated through the offspring's prepubertal BMI. Previous studies[6-8,11-14] have attempted to estimate direct effects of maternal BMI on offspring pubertal development using a traditional approach: simply adjusting for offspring BMI in a regression model. The drawbacks to this approach, however, are 2 fold: (1) direct effects estimated using this approach are subject to collider-stratification bias if common causes of offspring BMI and pubertal timing (eg, birth weight) are not controlled for[15]; (2) these mediator-outcome confounders are likely affected by maternal BMI itself, creating a problem known as exposure-induced

BMI	Body mass index
MSM	Marginal structural model
PHV	Peak height velocity
PDS	Pubertal development scale
SITAR	SuperImposition by Translation and Rotation

From the [1]Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [2]Department of Obstetrics and Gynecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [3]Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore, Singapore; [4]Division of Obstetrics and Gynecology, KK Women's and Children's Hospital, Singapore; [5]Obstetrics and Gynecology Academic Clinical Program, Duke-NUS Medical School, Singapore; [6]Pediatric Endocrinology and Diabetes, Maine Medical Center, Portland, ME; [7]Center for Outcomes Research and Evaluation, Maine Medical Center Research Institute, Portland, ME; [8]Diabetes Unit, Massachusetts General Hospital, Boston, MA; [9]Department of Pediatrics, McGill University Faculty of Medicine, Montreal, Canada; [10]Department of Epidemiology, Biostatistics and Occupational Health, McGill University Faculty of Medicine, Montreal, Canada; and [11]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

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confounding[16] (**Figure 1**; available at www.jpeds.com). It has been reported previously that controlling for exposure-induced confounders through conventional regression methods yield biased direct effect estimates.[17,18] To circumvent these problems, improved statistical approaches are required.

We used data from a prebirth cohort in Boston to examine associations of parental obesity with offspring pubertal developmental markers. We hypothesized that maternal obesity, would be a stronger risk factor for earlier pubertal development than paternal obesity, and its association would be largely indirect (ie, mediated through the offspring's prepubertal BMI).

Methods

Project Viva is an ongoing study of pre- and perinatal influences on maternal, fetal, and child health.[19] Briefly, we recruited eligible pregnant women during their first prenatal appointment between April 1999 and November 2002 from obstetric practices at Atrius Harvard Vanguard Medical Associates in eastern Massachusetts. Mothers provided written informed consent at enrollment and follow-up visits, and children provided verbal assent at the midchildhood and early adolescent visits. The Institutional Review Board of Harvard Pilgrim Health Care approved the project in line with ethical standards established by the Declaration of Helsinki. Of 2128 live singleton births, this analysis is limited to the 1377 (64.7%) children who had at least 1 measure of pubertal development.

Exposure: Parental Obesity Status

Mothers reported their prepregnancy weight, height, and father's weight and height via questionnaires and interviews at recruitment. We calculated parental BMI as self-reported weight divided by height squared and categorized parental obesity status as follows: neither parent with obesity (prepregnancy and paternal BMI <30 kg/m^2), paternal obesity alone (prepregnancy BMI <30 kg/m^2, and paternal BMI ≥30 kg/m^2), maternal obesity alone (prepregnancy BMI ≥30 kg/m^2 and paternal BMI <30 kg/m^2), or biparental obesity (prepregnancy and paternal BMI ≥30 kg/m^2).

Mediator: Offspring Prepubertal BMI

We used weight and height data from research visits and medical records during midchildhood (median 6.8 years; IQR 6.1-7.3)[20,21] to calculate offspring prepubertal BMI and we derived age- and sex-specific BMI z scores using the World Health Organization Child Growth Standards.[22]

Outcomes: Pubertal Developmental Markers

Age at Peak Height Velocity. We estimated the age at peak height velocity (PHV) using longitudinal height data obtained from research visits and medical records (range: 3-45 height measurements per child; average: 12 height measurements per child; age range: 2.5-18.3 years). We fit subject-specific height growth curves using the SITAR (SuperImposition by Translation and Rotation) growth model.[23] Briefly, SITAR uses a shape-invariant natural cubic spline curve and a nonlinear random-effects model to estimate a population average height growth curve for the entire sample and each subject's deviation from the population average curve as random effects, termed as size, timing, and velocity. Conceptually, these random effects define how much taller or shorter each child is (size), how much earlier or later the child experiences PHV (timing), and how much faster or slower the child's height growth is (velocity) relative to the population average. We assessed the optimal model using the Bayesian information criterion. We estimated the age at PHV for each child by differentiating the individually predicted height curves and locating the maximum inflection point during adolescence for each individually differentiated curve, where the derivative equals to zero.[24] We fitted these models with the SITAR package in R v.3.4.4 (R Core Team, Vienna, Austria).

Age at Menarche. We obtained data on age at menarche from a series of parent-reported questionnaires that were distributed approximately annually between the ages of 9 and 11 years, and at the early adolescent visit (12.9; 12.0-16.4 years). Briefly, mothers indicated whether their daughters had attained their first menstrual period (yes or no) and the month and year of its occurrence.

Pubertal Score. We evaluated pubertal development at the early adolescent visit via a validated written pubertal development scale (PDS) filled out by parents. The PDS has been strongly correlated with physician breast Tanner staging in girls[25] and pubic hair staging in boys.[26] PDS questions for boys include 4 items: voice deepening, facial and body hair growth, acne, and growth spurt. PDS questions for girls include 5 items: breast development, body hair growth, acne, growth spurt, and menarche. The response options for each item (except for menarche) were "not yet started" (1 point), "barely started" (2 points), "definitely started" (3 points), "seems complete" (4 points), and "I don't know" (coded as missing). A "yes" answer on the menarche question receives 4 points, and a "no" answer receives 1 point. We derived a pubertal score for each participant by summing the point values and averaging across all items as detailed previously.[27]

Pubic Hair Staging. At the early adolescent research visit, we obtained self-reported pubic hair staging in boys and girls through questionnaires using Tanner criteria for stage of maturation with descriptions accompanied by pictographs.[28,29]

Covariates

Socioeconomic Status. We obtained data on mother's and father's highest education, and annual household income level via questionnaires and interviews at recruitment. We categorized parental educational attainment (neither parent university-educated, only mother or only father

university-educated, or both parents university-educated) and annual household income level (≤USD $70 000 or >USD $70 000). We extracted data on census tract percent below poverty at the time of delivery from 2000 US Census data.[30]

Other Maternal Factors. Mothers reported their age, smoking history, and age at first menstrual period via questionnaires at enrollment and at the early adolescent visit. We obtained results of a 2-stage clinical prenatal glycemic screening (ie, a nonfasting 50 g 1-hour glucose challenge test followed, if abnormal [≥140 mg/dL], by a 100-g 3-hour oral glucose tolerance test) and categorized women as having normoglycemia, isolated hyperglycemia, impaired glucose tolerance, or gestational diabetes, based on criteria previously detailed.[31] We used measured prenatal weights recorded in the outpatient medical records and self-reported prepregnancy weight to calculate gestational weight gain in the first 2 trimesters. We also extracted data on parity from outpatient prenatal records.

Child Factors. Mothers reported their child's race/ethnicity, which we categorized as white, black, Hispanic, Asian, or other. We extracted data on infant sex and birth weight from hospital medical records. We calculated length of gestation in days by subtracting the date of the last menstrual period from the date of delivery. We used the result from the second trimester ultrasound estimate of gestational duration if it differed from the last menstrual period estimate by more than 10 days. As the World Health Organization growth standards do not provide gestational age-specific means and SDs for birth weight, we calculated birth weight-for-gestational-age z scores from a US national reference.[32] At the 6-month visit, mothers reported the extent of breastfeeding or formula feeding in the first 6 months using interviewer-administered questionnaires. We grouped infants into the following categories: formula only (fed with formula milk only since birth), weaned from breastmilk (initiated breastfeeding at birth but discontinued completely before 6 months of age), mixed milk feeding (fed with some breastmilk throughout the first 6 months, but also supplemented with formula before 6 months), or breastmilk only (fed with breastmilk only since birth).[33]

Statistical Analyses

We used linear regression to examine associations of parental obesity with age at PHV and pubertal score, and we used ordinal logistic regression to examine associations with pubic hair staging. The proportional odds assumption was confirmed. We used parametric maximum-likelihood survival models to estimate associations with age at menarche[34]; this method allowed us to examine time to menarche (the event of interest) and avoid the bias that would arise from excluding girls who have not achieved menarche by the early adolescent visit (n = 269/605; 44.4%). For all analyses, we applied the following models: model 1 adjusted for age at outcome (only for pubertal score and pubic hair stage, to improve precision of the effect estimate); model 2 adjusted for the same covariates as model 1 but added mother's and father's educational level and height; neighborhood census tract percent below poverty; household income; maternal age at enrollment, smoking history, parity, age at menarche; and child race/ethnicity. We estimated variance inflation factors in our models. The values show a low level of multicollinearity for the adjusted covariates (**Table I**; available at www.jpeds.com).

In addition, we used marginal structural models (MSMs; model 3), which can overcome the problems of collider-stratification bias and exposure-induced confounding,[15-18] to estimate the controlled direct effect (ie, the magnitude of association not mediated by BMI z score at midchildhood). We fit these models using inverse probability weighting. Briefly, we first calculated exposure weights (for parental obesity status) based on a multinomial logistic regression model that included only covariates in model 2, with mediator weights (for midchildhood BMI z score) based on a linear regression model that included the exposure, covariates in model 2, and exposure-induced confounders (gestational weight gain in first 2 trimesters, maternal glucose tolerance status, gestational age at delivery, birth weight-for-gestational age z score, and infant feeding type in the first 6 months). As the mediator is a continuous variable, we estimated the weights using a probability density function according to previously reported procedures.[35] We stabilized these weights by multiplying by the marginal probability of the observed exposure (for exposure weights) or the probability density function of the observed mediator conditional on the exposure (for mediator weights), and truncated them at the 1st and 99th percentiles. Finally, we estimated the controlled direct effect by fitting regression models for each pubertal outcome on parental obesity and midchildhood BMI z score, while adjusting for baseline and exposure-induced confounders by weighting on the product of the stabilized exposure and mediator weights for each individual. We also compared direct effect estimates derived from MSMs with those derived using the traditional approach (ie, simply adjusting for offspring BMI in a regression model).

For all analyses, we used chained equation multiple imputation to impute values for missing exposure (n = 65) or covariate (n = 572) data. We generated 50 imputed data sets for the 1377 offspring with at least 1 pubertal outcome and combined the imputed data sets using MI ESTIMATE in Stata (StataCorp LP, Austin, Texas). The imputation model included all exposures, outcomes, and covariates under study. Lastly, to assess robustness of our study findings, we repeated all analyses in subjects without missing exposure or covariate data (n = 740). We decided a priori to conduct all analyses separately in boys and girls, given the known sex differences in pubertal development.[36] We performed all analyses using Stata v 15.1 software (StataCorp LP).

Results

Cohort Description

Compared with families with neither parent with obesity, those with biparental obesity were less educated (34.3% vs

Table II. Characteristics of study population according to parental obesity status (n = 740)*

Characteristics	No parental obesity (n = 565)	Paternal obesity alone (n = 75)	Maternal obesity alone (n = 65)	Biparental obesity (n = 35)	*P* value†
Baseline confounders					
Maternal age at enrollment (y)	33.2 ± 4.3‡	32.5 ± 4.7	32.2 ± 5.3	33.3 ± 4.7	.18
Maternal age at menarche (y)	12.8 ± 1.4	12.9 ± 1.4	12.0 ± 1.5	12.0 ± 1.2	<.01
Annual income >USD $70 000	416 (73.6)‡	44 (58.7)	31 (47.7)	19 (54.3)	<.01
Census tract % below poverty (%)	8.2 ± 7.8	7.5 ± 6.8	11.4 ± 9.5	7.7 ± 6.2	.01
Nulliparous	274 (48.5)	35 (46.7)	29 (44.6)	11 (31.4)	.26
Smoking history					.85
Never smoked	401 (71.0)	53 (70.7)	44 (67.7)	22 (62.9)	
Smoked before pregnancy	124 (21.9)	15 (20.0)	14 (21.5)	9 (25.7)	
Smoked during pregnancy	40 (7.1)	7 (9.3)	7 (10.8)	4 (11.4)	
Mother's height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	.91
Mother's BMI (kg/m^2)	23.0 ± 2.8	24.0 ± 3.2	34.2 ± 4.1	35.3 ± 4.4	<.01
Educational attainment					<.01
Neither parent university educated	50 (8.9)	21 (28.0)	28 (43.1)	12 (34.3)	
Father only university educated	37 (6.6)	7 (9.3)	6 (9.2)	2 (5.7)	
Mother only university educated	71 (12.6)	13 (17.3)	7 (10.8)	9 (25.7)	
Both parents university educated	407 (72.0)	34 (45.3)	24 (36.9)	12 (34.3)	
Father's height (m)	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	.74
Father's BMI (kg/m^2)	25.2 ± 2.5	32.6 ± 2.5	25.8 ± 2.7	33.6 ± 2.9	<.01
Child race/ethnicity					<.01
White	434 (76.8)	53 (70.7)	38 (58.5)	22 (62.9)	
Black	40 (7.1)	11 (14.7)	14 (21.5)	7 (20.0)	
Hispanic/Asian/others	91 (16.1)	11 (40.7)	13 (20.0)	6 (17.1)	
Male sex	294 (52.0)	34 (45.3)	33 (50.8)	15 (42.9)	.55
Exposure-induced confounders					
Abnormal glucose tolerance status (IH, GIGT, GDM)	76 (13.5)	17 (22.7)	20 (30.8)	9 (25.7)	<.01
GWG in first 2 trimesters (kg)	9.5 ± 3.2	9.5 ± 3.7	6.8 ± 5.1	7.1 ± 5.6	<.01
Gestational age at delivery (wk)	39.6 ± 1.6	39.9 ± 1.4	39.6 ± 1.7	39.5 ± 2.0	.48
Birth weight-for-gestational age z score (SD units)	0.19 ± 0.93	0.40 ± 1.07	0.28 ± 0.84	0.40 ± 0.97	.17
Infant feeding type in the first 6 mo					.01
Breastmilk only	185 (32.7)	17 (22.7)	13 (20.0)	4 (11.4)	
Mixed milk feeding	165 (29.2)	20 (26.7)	15 (23.1)	9 (25.7)	
Weaned from breastmilk	168 (29.7)	28 (37.3)	30 (46.1)	16 (45.7)	
Formula milk only	47 (8.3)	10 (13.3)	7 (10.8)	6 (17.1)	
Mediator					
BMI z score at midchildhood (SD units)	0.38 ± 1.01	0.85 ± 1.00	1.24 ± 1.29	1.41 ± 1.31	<.01

GDM, gestational diabetes; *GIGT*, gestational impaired glucose tolerance; *GWG*, gestational weight gain; *IH*, isolated hyperglycemia.
*Sample size restricted to subjects without missing exposure and covariate data, and with at least 1 pubertal outcome.
†*P* values calculated using χ^2 tests for categorical variables and 1-way ANOVA for continuous variables.
‡Values represent mean ± SD or n (%).

72.0% with a maternal and paternal university degree) and had a lower household income (54.3% vs 73.6% with annual income above $70 000), with mothers from these families more likely to have had earlier age at menarche (12.0 vs 12.8 years) and abnormal glucose tolerance during pregnancy (25.7% vs 13.5%) (Table II). Compared with children from families with neither parent with obesity, those from families with biparental obesity were more likely to be of black race/ethnicity (20.0% vs 7.1%), exclusively formula fed in the first 6 months (17.1% vs 8.3%), and had higher midchildhood BMI z score (mean 1.4 vs 0.4 SD units) (Table II). As expected, compared with boys, girls had an earlier age at PHV (11.2 vs 13.1 years), higher pubertal development score in early adolescence (2.9 vs 2.2 units), and were more likely to have a higher pubic hair stage at early adolescence (26.9% vs 14.5% at stage 5) (Table III). Mean (SD) age at menarche was 12.1 (1.1) years among girls who have achieved menarche by the early adolescent visit (n = 336; 55.5%).

Associations of Parental Obesity with Pubertal Development in Boys

After adjusting for confounders (model 2), maternal obesity alone (vs neither parent with obesity) was associated with younger age at PHV (β −0.30 years; 95% CI -0.57, −0.03) and higher pubertal score (0.29 units; 0.10, 0.48), but not with pubic hair stage (OR 1.53; 0.83, 2.82). In MSMs (model 3), maternal obesity alone had significant controlled direct effects on age at PHV (−0.31 years; −0.62, 0.00) and pubertal score (0.22 units; 0.00, 0.44). The controlled direct effect can be interpreted as follows: boys of mothers with obesity will attain PHV earlier (by 0.31 years) and have higher pubertal score (by 0.22 units) than boys of parents neither of whom have obesity, if their BMI z scores at midchildhood are fixed at the mean. Similar findings for the direct effects were observed using the traditional approach (age at PHV: −0.24 years [-0.48, 0.00]; pubertal score: 0.24 units [0.06, 0.43]). Significant associations (model 2: −0.41 years; −0.76, −0.06) and controlled direct effects (model 3:

Table III. Pubertal characteristics in boys vs girls

Pubertal Outcomes	Boys		Girls		*P* value (boys vs girls)*
	n	Mean ± SD or %	n	Mean ± SD or %	
Age at peak height velocity (y)	629	13.1 ± 0.9	615	11.2 ± 1.0	<.01
Age at menarche (y)	—	—	336	12.1 ± 1.1	—
Early adolescent measures					
Pubertal score	584	2.2 ± 0.7	552	2.9 ± 0.7	<.01
Tanner pubic hair stage					<.01
Stage 1	21	3.9	12	2.4	
Stage 2	85	15.9	52	10.3	
Stage 3	149	27.8	118	23.3	
Stage 4	203	37.9	188	37.2	
Stage 5	78	14.5	136	26.9	

*P values calculated using χ^2 tests for Tanner pubic hair stage and 2-sample t test for age at peak height velocity and pubertal score.

−0.30 years; −0.56, −0.03) of biparental obesity (vs neither parent with obesity) were observed with age at PHV, but not with pubertal score or pubic hair stage (Figure 2). However, paternal obesity alone (vs neither parent with obesity) was not associated with, nor had significant controlled direct effects on, any pubertal outcomes in any models (Figure 2).

Associations of Parental Obesity with Pubertal Development in Girls

In adjusted models (model 2) and MSMs (model 3), neither maternal nor paternal obesity alone (vs neither parent with obesity), were significantly associated with any pubertal outcomes (Figure 3). Biparental obesity (vs neither parent with obesity) was associated with age at menarche (hazard ratio 2.17; 95% CI 1.35, 3.49) but not with age at PHV, pubertal score, or pubic hair stage in adjusted models (model 2). The hazard ratio can be interpreted as follows: girls of parents with obesity will have twice the risk of achieving menarche earlier than girls of parents neither of whom have obesity. In MSMs (model 3), biparental obesity had no significant controlled direct effects (1.49; 0.75, 2.96) on age at menarche. However, a significant direct effect was observed (1.77; 1.04, 3.02) when using the traditional approach, which may likely reflect a biased finding.

Complete Case Analyses

Our complete case analyses showed similar patterns of associations of parental obesity with pubertal outcomes as those observed after multiple imputation in both boys and girls (Table IV and Table V; available at www.jpeds.com).

Discussion

We observed differential associations of parental obesity with offspring pubertal development. Compared with boys with neither parent with obesity, those with maternal but not paternal obesity had earlier pubertal development (earlier age at PHV and higher pubertal score in early adolescence). These associations were independent of prepubertal BMI z score but were not seen in girls.

Our observations in boys build upon previous work by Houndsgaard et al and Brix et al, which reported that sons of mothers with obesity were predisposed to earlier sexual maturation and pubertal timing (earlier age of attaining pubic hair development, regular shaving, voice change, acne, and first nocturnal emission) than sons of normal-weight mothers.[37,38] Our null results in girls are also consistent with findings from the Collaborative Perinatal Project.[8] Other investigators, however, have reported associations between maternal obesity and earlier age at menarche, adrenarche, and thelarche in girls.[6,7,13,14] Differing methods of exposure measurement and outcome ascertainment (eg, self-report of adrenarchal staging in our study, which has led to bias vs objective measurements in other studies[14]) or differences in confounding structures in different cohorts may account for some of this heterogeneity in findings. In addition, the clinical relevance of an altered age at PHV or pubertal score should be explored further. Past studies have shown that a 1-year difference in age at PHV or 1-unit change in pubertal score are linked to behavioral disorders,[39] hormonal changes associated with cancer risk,[40] and cardiovascular disease mortality[41] in adulthood. Our observed differences in age at PHV of 0.3 years and in pubertal score of 0.2 units among boys of mothers with obesity in this study may potentially have similar, albeit smaller, health consequences.

As maternal obesity is associated with child obesity and excess child adiposity is a strong risk factor for earlier pubertal onset,[5] we further explored pathways from maternal obesity to offspring pubertal development through prepubertal BMI and found evidence of a direct effect (ie, not mediated by prepubertal BMI) in boys. This suggests that maternal obesity may exert "programming" effects on pubertal development in male offspring, perhaps through exposure to high levels of leptin—an adipokine postulated to have a permissive role in pubertal initiation[42]—or other hormones.[43] Genetic heritability might also explain part of the observed association between maternal obesity alone and pubertal development in boys, as past studies indicate an overlap of genes involved in adiposity and pubertal timing,[44] with some of these genes mainly affecting male subjects.[45]

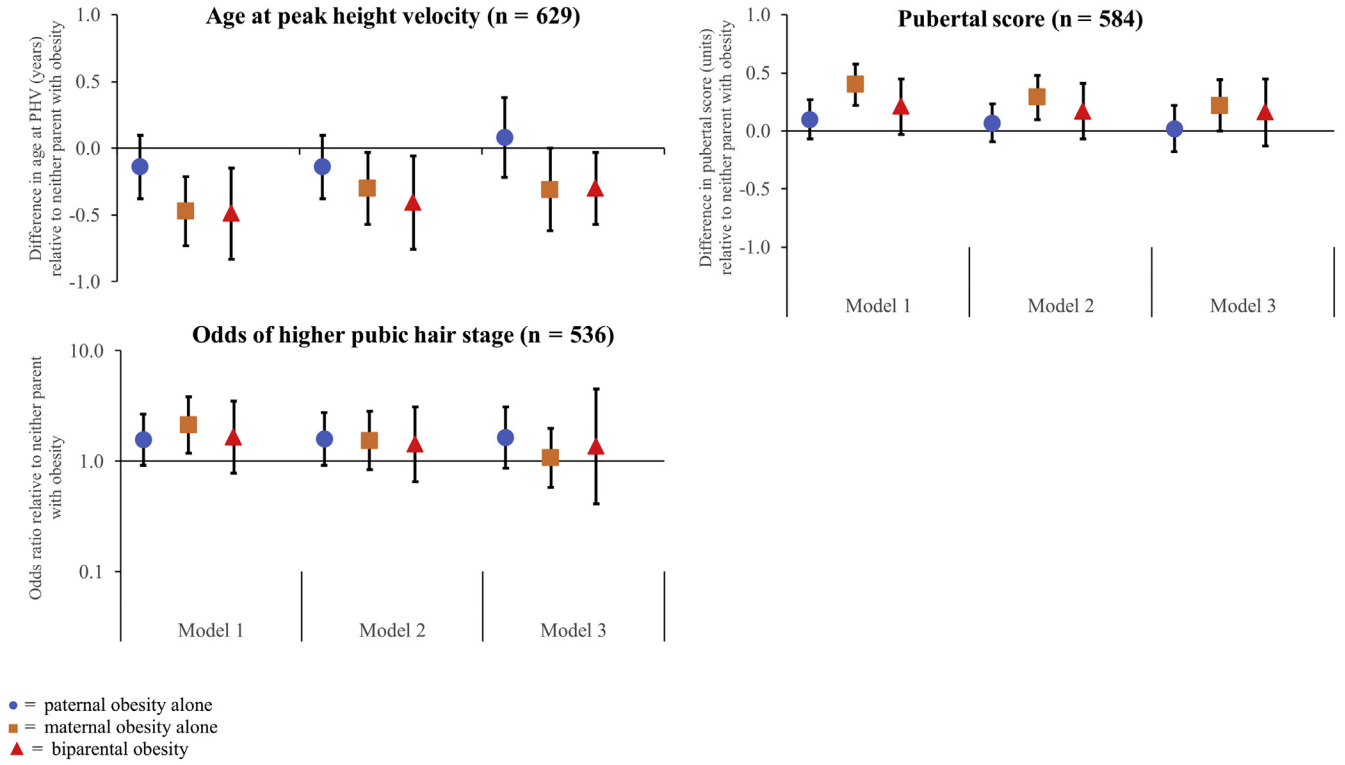

Figure 2. Associations of parental obesity with pubertal development in boys (with multiple imputation). All estimates are relative to neither parent with obesity. The β estimates can be interpreted as the difference in age at PHV or pubertal score for a given parental obesity status. The OR can be interpreted as the odds of attaining a higher pubic hair stage for a given parental obesity status. Model 1: adjusted for age at outcome (only for pubertal score and pubic hair stage). Model 2: Model 1 + mother's and father's educational level and height, neighborhood census tract percent below poverty, household income, maternal characteristics (age at enrollment, smoking history, parity, age at menarche), and child race/ethnicity. Model 3: Marginal structural model that controls for covariates in model 2 and maternal gestational weight gain in the first 2 trimesters, glucose tolerance status, gestational age at delivery, child birth weight-for-gestational age z score, infant feeding type in the first 6 months, and BMI z score at midchildhood.

Past studies have reported inconsistent results regarding the mediating role of prepubertal BMI. Although some reported associations of maternal obesity with offspring pubertal development independent of prepubertal BMI,[7,12-14] others observed effects that were largely indirect (ie, mediated through prepubertal BMI).[6,11] A major limitation of these studies is the use of a traditional regression approach to identify direct effects (ie, adjusting for offspring BMI as if it were a confounder) with risk of collider-stratification bias[15] and does not appropriately control for exposure-induced confounders.[16] Unlike previous studies, our MSM approach to mediation appropriately controls for these confounders through inverse probability weighting and provides more valid estimates of direct effects than traditional approaches.[17,18]

Recent research suggests that paternal lifestyle at conception, such as diet and obesity status, can subsequently affect offspring health.[9] For example, animal experiments have described programming effects of paternal preconceptional exposure to a high-fat diet on offspring metabolic function,[46] and epidemiologic studies have reported paternal obesity as a significant risk factor for offspring overweight/obesity independent of maternal BMI.[47] It is postulated that paternal factors likely exert programming effects on offspring health through epigenetic alterations to the father's sperm.[48] It is possible that paternal obesity alters time to pubertal maturation via the same pathways. In contrast, we found that paternal obesity alone had no association with pubertal development in either boys or girls, suggesting that "programming" effects on offspring pubertal development, if any, were unlikely to occur through the father.

Sex hormone alterations may explain the sex differences we observed in associations between maternal obesity and offspring pubertal development.[49] In both sexes, pubertal onset is typically driven by an increase in the pulsatile secretion of gonadotrophin releasing hormone, which stimulates the release of follicle-stimulating and luteinizing hormones and in turn, triggering production of testosterone (in boys) and estradiol (in girls).[49] It is possible that testosterone production from the testis is more sensitive to early life exposures as compared with sex steroids that are adrenal or ovarian in origin. Further studies are clearly warranted.

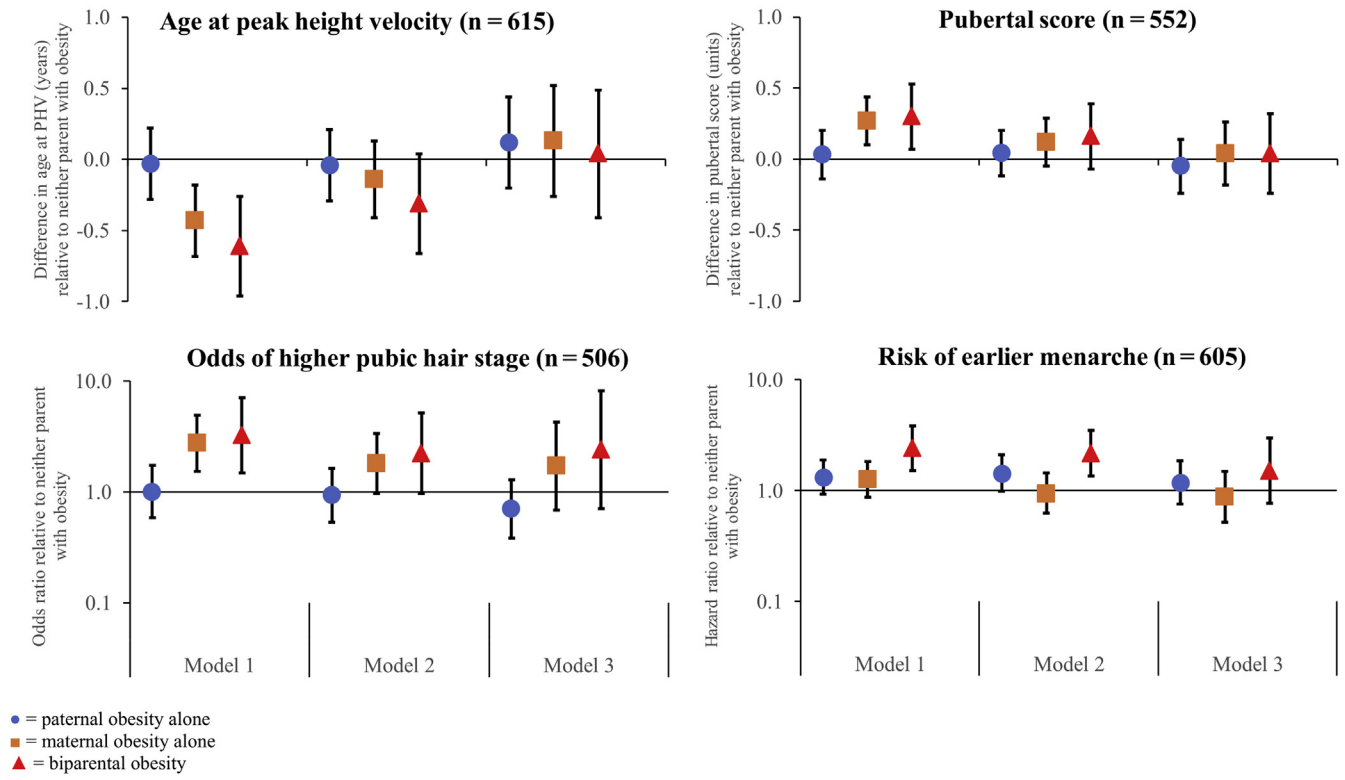

Figure 3. Associations of parental obesity with pubertal development in girls (with multiple imputation). All estimates are relative to neither parent with obesity. The β estimates can be interpreted as the difference in age at PHV or pubertal score for a given parental obesity status. The OR can be interpreted as the odds of attaining a higher pubic hair stage for a given parental obesity status. The hazard ratio can be interpreted as the risk of achieving menarche earlier for a given parental obesity status. Model 1: adjusted for age at outcome (only for pubertal score and pubic hair stage). Model 2: Model 1 + mother's and father's educational level and height, neighborhood census tract percent below poverty, household income, maternal characteristics (age at enrollment, smoking history, parity, age at menarche), and child race/ethnicity. Model 3: Marginal structural model that controls for covariates in model 2 and maternal gestational weight gain in the first 2 trimesters, glucose tolerance status, gestational age at delivery, child birth weight-for-gestational age z-score, infant feeding type in the first 6 months, and BMI z score at midchildhood.

Strengths of our study include its prospective study design, multiple indicators of pubertal development, long-term follow-up, and wide range of covariates (including mothers' age at menarche) obtained by highly trained staff using standardized protocols. Our study also benefits from the use of repeated height measures from early childhood to late adolescence to estimate the age at PHV as a measure of pubertal timing in boys and girls, which has been shown to be a reliable indicator of pubertal development.[50]

Our study is not without limitations. First, mothers self-reported their and the father's weights and heights. We previously conducted a validation study comparing self-reported prepregnancy weight with clinically measured weight in medical records within 3 months before the last menstrual period and found a strong correlation (r = 0.99) between self-reported and objectively-measured BMI.[51] However, we are unable to do the same for father's BMI. Thus, our null findings for paternal obesity may reflect exposure misclassification. Further studies using objectively measured paternal BMI are warranted to better understand the role of paternal obesity on offspring pubertal development. Second, we used self-reported measures of adrenarchal staging and parent-reported measures of pubertal score instead of pubertal assessment by physical examination. Past studies have showed a high degree of concordance between self- and physician assessments of pubic hair development.[52] Moreover, our findings were consistent across different pubertal indicators, including PHV, further suggesting the reliability of the reported measures. Lastly, our findings may not be generalizable to other ethnic groups and populations from different settings, because many of our participants were white and university educated.

In conclusion, our findings suggest that maternal obesity is significantly associated with earlier pubertal development independent of prepubertal BMI in boys and provide support for maternal obesity as an indicator of identifying children who are likely to experience earlier pubertal development in adolescence. Developing upstream interventions to support young women in achieving healthy weight in early adulthood prior to pregnancy, may hold promise for slowing the trend toward earlier pubertal maturation,[53] and possibly

for reducing the risk of adverse health outcomes related to these risk factors. ■

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Reprint requests: Izzuddin M. Aris, PhD, Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401E, Boston, MA 02215. E-mail: Izzuddin_Aris@harvardpilgrim.org

Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Growth in Patients with Gonadal Dysgenesis Receiving Fluoxymesterone

Johanson AJ, Brasel JA, Blizzard RM. J Pediatr 1969;75:1015-21.

Short stature, the most common feature in Turner syndrome, is caused by haploinsufficiency of the SHOX gene located on the distal short arm of the X chromosome. In this retrospective study, the authors describe a cohort of 26 female patients, mean age 13.3 years, with gonadal dysgenesis (sex chromosomes consistent with Turner syndrome) who received fluoxymesterone, a nonaromatizable androgen, for 7-32 months. This group demonstrated a significant increase in growth rate and adult height in comparison with 21 patients receiving estrogen. Interestingly, at the time growth hormone was not believed to be effective at increasing height in girls with Turner syndrome.

Fifty years later, what is different? Growth hormone is now the mainstay of treatment for short stature, with early initiation around 4-6 years of age allowing for an increased adult height into the lower normal range for adult women.[1] Oxandrolone, another nonaromatizable androgen, has fewer virilizing side effects than fluoxymesterone[2] and is currently used as adjunctive therapy with growth hormone for increasing adult height, particularly in cases of delayed diagnosis with severe short stature.[3]

It is important to realize that quality of life in adults with Turner syndrome is unaffected by previous growth hormone treatment, but hearing impairment and delayed pubertal induction after age 15 years are associated with lower quality of life scores.[4] Promoting early growth permits starting estrogen treatment at a similar age to peers. Therefore, although attention to growth is important, it is essential to consider other aspects of care for these girls.

Anisha Gohil, DO
John S. Fuqua, MD
Indiana University School of Medicine
Riley Hospital for Children
Indianapolis, Indiana

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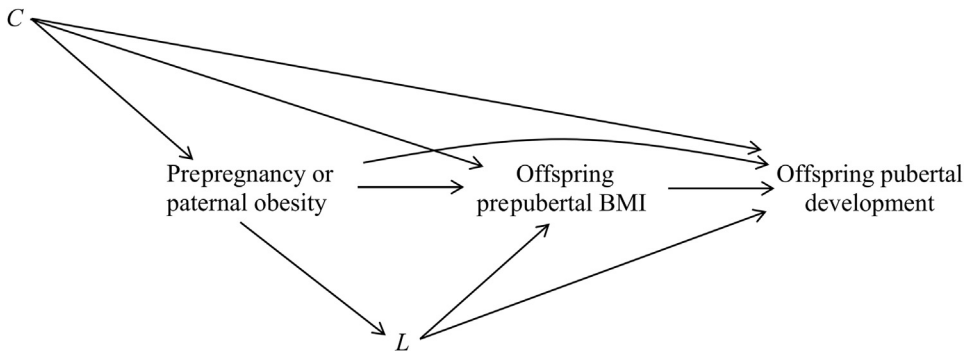

Figure 1. Directed acyclic graph illustrating the relationships of maternal prepregnancy and paternal obesity, offspring prepubertal BMI, and pubertal development. "C" represents confounders for parental obesity and offspring pubertal development (eg, maternal age at menarche, parental socioeconomic status). "L" represents confounders for offspring prepubertal BMI and pubertal development (eg, birth weight) that are also affected by parental obesity (ie, exposure-induced confounders).

Table I. Variance inflation facto values for covariates included in the same model

	Variance inflation factor	
Covariates	**Boys**	**Girls**
Maternal age at enrollment (y)	1.37	1.27
Maternal age menarche (y)	1.11	1.12
Annual income >USD $70 000	1.40	1.30
Census tract % below poverty	1.22	1.34
Nulliparous	1.26	1.19
Smoking history (vs never smoked)		
Smoked before pregnancy	1.14	1.08
Smoked during pregnancy	1.15	1.10
Mothers' height (m)	1.12	1.10
Parental education level (vs both nonuniversity educated)		
Father only university educated	1.75	1.61
Mother only university educated	1.14	1.07
Both university educated	1.23	1.23
Fathers' height (m)	1.09	1.20
Child race/ethnicity (vs white)		
Black	1.30	1.30
Hispanic/Asian/others	1.17	1.19
Parental obesity status (vs neither parent with obesity)		
Paternal obesity alone	1.10	1.06
Maternal obesity alone	1.16	1.22
Biparental obesity	1.07	1.16

Table IV. Associations of parental obesity with pubertal development in boys (complete case analysis)

Pubertal Outcomes	Model 1*	Model 2†	Model 3‡
Age at PHV (y; n = 376)	β [95% CI]		
Neither parent with obesity	Ref	Ref	Ref
Paternal obesity alone	−0.02 [−0.35,0.31]	0.00 [−0.34,0.34]	0.09 [−0.32,0.50]
Maternal obesity alone	−0.48 [−0.82,−0.14]	−0.31 [−0.67,0.04]	−0.43 [−0.78,−0.08]
Biparental obesity	−0.55 [−1.04,−0.07]	−0.50 [−0.99,0.00]	−0.37 [−0.71,−0.02]
Pubertal score (units; n = 376)	β [95% CI]		
Neither parent with obesity	Ref	Ref	Ref
Paternal obesity alone	0.13 [−0.08,0.34]	0.05 [−0.16,0.26]	−0.02 [−0.24,0.19]
Maternal obesity alone	0.39 [0.17,0.60]	0.25 [0.03,0.47]	0.17 [−0.15,0.48]
Biparental obesity	0.13 [−0.18,0.44]	0.07 [−0.24,0.38]	−0.08 [−0.26,0.10]
Odds of higher pubic hair stage (n = 345)	Odds ratio [95% CI]		
Neither parent with obesity	ref	ref	Ref
Paternal obesity alone	1.38 [0.69,2.73]	1.07 [0.52,2.20]	0.86 [0.48,1.56]
Maternal obesity alone	1.84 [0.90,3.75]	1.25 [0.59,2.66]	0.87 [0.46,1.65]
Biparental obesity	1.26 [0.46,3.40]	0.94 [0.33,2.70]	0.55 [0.18,1.63]

*Adjusted for age at outcome (only for pubertal score and pubic hair stage).
†Model 1 + parental height and education level; neighborhood census tract percent below poverty; household income level; maternal age at enrollment, smoking history, age at menarche, parity; and child race/ethnicity.
‡Marginal structural model that controls for covariates adjusted in Model 2 and maternal gestational weight gain in the first two trimesters, glucose tolerance status, gestational age at delivery; child birth weight-for-gestational age z-score, feeding type in the first 6 months, and BMI z score at midchildhood.

Table V. Associations of parental obesity with pubertal development in girls (complete case analysis)

Pubertal Outcomes	Model 1*	Model 2†	Model 3‡
Age at PHV (y; n = 364)	β [95% CI]		
Neither parent with obesity	ref	ref	Ref
Paternal obesity alone	−0.10 [−0.41,0.22]	0.01 [−0.30,0.31]	0.12 [−0.28,0.52]
Maternal obesity alone	−0.42 [−0.78,−0.07]	0.01 [−0.36,0.37]	0.29 [−0.23,0.80]
Biparental obesity	−0.60 [−1.04,−0.16]	−0.16 [−0.60,0.28]	0.39 [−0.32,1.10]
Pubertal score (units; n = 364)	β [95% CI]		
Neither parent with obesity	ref	ref	ref
Paternal obesity alone	0.06 [−0.14,0.26]	0.04 [−0.16,0.24]	−0.03 [−0.29,0.23]
Maternal obesity alone	0.36 [0.14,0.58]	0.16 [−0.08,0.39]	0.01 [−0.34,0.37]
Biparental obesity	0.32 [0.04,0.59]	0.11 [−0.18,0.39]	−0.02 [−0.44,0.41]
Odds of higher pubic hair stage (n = 333)	Odds ratio [95% CI]		
Neither parent with obesity	ref	ref	ref
Paternal obesity alone	1.16 [0.62,2.20]	1.02 [0.53,1.96]	0.86 [0.42,1.74]
Maternal obesity alone	3.87 [1.80,8.33]	2.54 [1.09,5.90]	3.12 [0.57,17.05]
Biparental obesity	4.67 [1.75,12.46]	3.14 [1.08,9.17]	2.85 [0.62,13.05]
Risk of earlier menarche (n = 336)	Hazard ratio [95% CI]		
Neither parent with obesity	ref	ref	ref
Paternal obesity alone	1.31 [0.83,2.06]	1.38 [0.84,2.26]	1.10 [0.60,2.03]
Maternal obesity alone	1.50 [0.99,2.28]	1.11 [0.70,1.77]	0.64 [0.32,1.29]
Biparental obesity	2.37 [1.32,4.25]	2.00 [1.17,3.43]	0.87 [0.38,1.95]

*Adjusted for age at outcome (only for pubertal score and pubic hair stage).
†Model 1 + parental height and education level; neighborhood census tract percent below poverty; household income level; maternal age at enrollment, smoking history, age at menarche, parity; and child race/ethnicity.
‡Marginal structural model that controls for covariates adjusted in model 2 and maternal gestational weight gain in the first 2 trimesters, glucose tolerance status, gestational age at delivery; child birth weight-for-gestational age z score, feeding type in the first 6 months, and BMI z score at midchildhood.