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Miscellaneous

Maternal pre-pregnancy obesity and timing of puberty in sons and daughters: a population-based cohort study

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Abstract

Background: In many countries, an increased prevalence of obesity in pregnancy has coincided with a declining pubertal age. We aimed to explore the potential effect of maternal pre-pregnancy overweight and obesity on timing of puberty in sons and daughters.
Methods: Between 2012 and 2018, 15 819 of 22 439 invited children from the Danish National Birth Cohort, born 2000–03, provided half-yearly information from the age of 11 years on the pubertal milestones: Tanner stages, voice break, first ejaculation, menarche, acne and axillary hair. We estimated adjusted mean monthly differences (with 95% confidence intervals) in age at attaining the pubertal milestones for children exposed to maternal pre-pregnancy obesity [body mass index (BMI) $\geq$30.0 kg/m^2] or overweight (BMI 25.0 to 29.9 kg/m^2) with normal weight (BMI 18.5 to 24.9 kg/m^2) as reference. In mediation analysis, we explored whether childhood BMI at age 7 years mediated the associations.
Results: Maternal pre-pregnancy obesity was associated with earlier age at attaining most pubertal milestones in sons, and pre-pregnancy overweight and obesity were associated with earlier age at attaining all pubertal milestones in daughters. When combining all pubertal milestones, pre-pregnancy obesity [sons: −1.5 (−2.5, −0.4) months; daughters: −3.2 (−4.2, −2.1) months] and overweight [daughters only: −2.6 (−3.3, −1.8) months] were associated with earlier timing of puberty. The associations in sons were completely mediated by higher childhood BMI and partly so in daughters.

Conclusions: Maternal pre-pregnancy obesity appears to lower timing of puberty through childhood obesity in sons and mainly through other mechanisms in daughters.

Key words: Obesity, adiposity, maternal exposure, prenatal exposure delayed effects, puberty, menarche

Key Messages

- Maternal pre-pregnancy obesity was associated with earlier age at voice break, pubic hair development, axillary hair and acne in sons.
- Maternal pre-pregnancy obesity and overweight were associated with earlier age at menarche, breast development, pubic hair development, axillary hair and acne in daughters.
- These associations seemed to be mediated through childhood obesity in sons and partly so in daughters.

Introduction

A secular trend toward earlier age at menarche and onset of breast development has been observed in many countries, whereas a secular trend is less certain in boys.[1–8] Early puberty has been related to increased risk for diseases later in life, such as obesity, diabetes, cardiovascular diseases, breast cancer and testicular cancer,[9–12] whereas late puberty has been related to impaired semen quality, longer time-to-pregnancy, asthma and neuropsychiatric diseases.[10,13–15] This calls for identification of possible modifiable causes of altered timing of puberty. The secular trend toward earlier timing of puberty has coincided with an increasing prevalence of obesity.[16] This ecological association raises the question as to whether maternal obesity is linked to earlier pubertal development in sons and daughters. Maternal obesity could potentially influence timing of puberty through higher childhood body mass index (BMI), as maternal pre-pregnancy obesity is a risk factor for obesity in her children,[17–19] and childhood obesity may lead to insulin resistance and hyperinsulinaemia.[20] Hyperinsulinaemia has been suggested to be a triggering mechanism for earlier puberty,[20–22] consistently observed in obese girls and to some extent also in obese boys.[23]

In daughters, epidemiological studies support an association between maternal pre-pregnancy obesity and earlier age at menarche[24–29] and, recently, also onset of breast and pubic hair development.[27,30,31] These associations seem to be partly mediated by childhood BMI in some[26,27,30] but not all studies.[24,25] However, studies on sons are lacking, and the only study so far had only recalled data on timing of voice break, first nocturnal ejaculation, acne and regular shaving as pubertal milestones, and the potential mediating role of childhood BMI is still unknown.[32]

In this cohort study, we explore the potential effect of maternal pre-pregnancy obesity, measured by BMI, on the timing of puberty in sons and daughters in terms of a range of pubertal milestones. We also quantify the potential mediating role of childhood BMI. We hypothesize that maternal pre-pregnancy obesity is associated with earlier timing of puberty in sons and daughters, partly mediated through childhood obesity in both sexes.

Methods

Population

In this population-based cohort study, we used information from the Puberty Cohort, nested within the Danish National Birth Cohort (DNBC).[33] The DNBC holds information on approximately 92 000 mothers and their children born from 1996 to 2003. Mothers were interviewed by computer-assisted telephone interviews during pregnancy at 17 and 32 weeks of gestation, and at 6 and 18 months postpartum. Self-administered follow-up questionnaires were sent to the families 7 and 11 years after the birth.

Children eligible for being sampled for the Puberty Cohort were live-born singletons born during 2000–03, whose mothers participated in the first interview in the DNBC and had not withdrawn by May 2012 ($n = 56\,641$). In May 2012, we sampled 22 439 children from the DNBC to constitute the Puberty Cohort.[34] From August 2012, these children were invited to provide self-reported, half-yearly information on pubertal milestones, using web-based questionnaires, from the age of 11.5 years until full pubertal maturity (defined as Tanner Stage 5 for breast and pubic hair development in girls and Tanner Stage 5 for genital and pubic hair development in boys). End of follow-up for this study was January 2018. A total of 14 756 children replied to at least one questionnaire.

Furthermore, 10 665 of the invited children gave identical information on their pubertal milestones during the 11-year follow-up in the DNBC. When these data were added, a total of 15 819 children in the Puberty Cohort (7696 sons and 8123 daughters) were followed up on pubertal development at least once (participation rate 70%). The children returned on average 5.7 (range: 1 to 13) questionnaires, resulting in a total of 89 898 questionnaires.

Exposure: maternal pre-pregnancy BMI

During the first interview in the DNBC, the mothers gave information on their height and pre-pregnancy weight, and these were converted to BMI and categorized as follows: underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and obese (≥30.0 kg/m^2).[35]

Outcomes: pubertal milestones in children

The half-yearly, web-based questionnaires used for data collection included questions on current status of the pubertal milestones: first ejaculation (yes/no; if yes: year and months), voice break (no/yes; sometimes/yes; definitively), menarche (yes/no; if yes: year and months), acne (yes/no), axillary hair (yes/no) and Tanner stages[36,37] for pubic hair development and genital or breast development (Stages 1 through 5). To collect information on Tanner stages, we used the Sexual Maturation Scale which includes illustrations and a short description of each of the Tanner stages.[38]

Covariates

The potential confounders were chosen a priori, based on a directed acyclic graph created after a literature review (Supplementary Figure 1, available as Supplementary data at *IJE* online)[39,40]: alcohol consumption in first trimester, smoking in first trimester, maternal age at menarche and parental cohabitation were retrieved from the first interview in the DNBC; highest educational class of parents was classified according to the International Standard Class of Occupation and Education codes (ISCO-88 and ISCED) and retrieved from Statistics Denmark; and parity and maternal age at delivery were retrieved from the Danish National Birth Registry.[41] All confounders were categorized as shown in Table 1. For subanalyses, we included gestational weight gain and duration of exclusive breastfeeding retrieved from the third interview in the DNBC as well as the total difficulties score (scored by the Strengths and Difficulties Questionnaire: SDQ)[42] retrieved from the 7-year questionnaire in the DNBC. The total difficulties score (ranging from 0 to 40) is the sum of four behavioural scales: the emotional, conduct, hyperactivity and peer problems scale.[42] A higher difficulties score indicates higher psychosocial stress. For a maternal-paternal comparison, paternal BMI was retrieved from the 7-year questionnaire as information on paternal BMI during pregnancy was not collected. For mediation analysis, childhood BMI (continuous, kg/m^2) was derived from the children's height and weight reported by their mothers during the DNBC's 7-year follow-up.

Statistical analysis

The Puberty Cohort consists of samples from 27 subgroups of 12 different exposures hypothesized to be important for timing of puberty, including maternal pre-pregnancy BMI, and a random sample of 8000 children.[34] To account for this non-random sampling regimen, we employed sampling weights computed from the sampling fractions from each of the 28 sampling frames, which has been described in detail elsewhere.[34] Due to loss to follow-up, we further employed selection weights.[43] These were estimated using logistic regression on participation status (yes/no) with both pre-pregnancy BMI and the covariates used in the main analysis as explanatory variables. Finally, the selection weights and sampling weights were combined by multiplication and used to reweight all analyses.

Since the information on puberty was collected half-yearly, the outcome information was censored: the outcome was left-censored if the milestone was already attained by the first questionnaire, interval-censored if the milestone was attained between two questionnaires and right-censored if the milestone was not attained by the last questionnaire. Thus, we used a parametric regression model for censored data based on the normal distribution fitted by maximum likelihood estimation.[44] The assumption of normally distributed residuals was inspected by plotting the cumulative incidence function based on the normal distribution against the non-parametric distribution based on the Turnbull Estimator, and the assumption of independent variance was checked by further stratifying the plots on levels of the covariates.[45,46] The data were found compatible with these assumptions (data not shown).

In the main analysis, we estimated the mean age at attaining the pubertal milestones as a function of pre-pregnancy BMI in categories with normal weight as the reference. We also analysed pre-pregnancy BMI as a continuous variable (in units of 10 kg/m^2) to estimate the difference in months at attaining a given pubertal milestone per 10-unit higher pre-pregnancy BMI. Categorical covariates were included in the model as indicator variables, whereas maternal age at delivery (continuous) was

Table 1. Maternal and childhood characteristics according to pre-pregnancy BMI in 15 602[a] children in the Puberty Cohort, Denmark, 2012–18

	Pre-pregnancy BMI				
	<18.5 ($n=1056$) No. (%)	18.5 to 24.9 ($n=9656$) No. (%)	25.0 to 29.9 ($n=3305$) No. (%)	≥30.0 ($n=1585$) No. (%)	Missing No. (%)
Smoking in first trimester					53 (0.3)
Non-smoker	683 (64.7)	6973 (72.5)	2414 (73.2)	1139 (72.1)	
1-10 daily cigarettes	303 (28.7)	2139 (22.2)	679 (20.6)	331 (20.9)	
>10 daily cigarettes	69 (6.5)	504 (5.2)	205 (6.2)	110 (7.0)	
Alcohol in first trimester[b]					22 (0.1)
0 units per week	609 (57.7)	4660 (48.4)	1767 (53.5)	1007 (63.6)	
1 unit per week	302 (28.6)	3128 (32.5)	1016 (30.8)	418 (26.4)	
>1-3 units per week	113 (10.7)	1272 (13.2)	385 (11.7)	108 (6.8)	
>3 units per week	31 (2.9)	578 (6.0)	135 (4.1)	51 (3.2)	
Maternal age of menarche					118 (0.8)
Earlier than peers	174 (16.6)	2121 (22.1)	1048 (31.9)	599 (38.0)	
Same time as peers	611 (58.2)	5601 (58.5)	1828 (55.7)	825 (52.3)	
Later than peers	265 (25.2)	1854 (19.4)	405 (12.3)	153 (9.7)	
Maternal age at delivery in years[c]	29.9 (4.7)	30.8 (4.4)	30.5 (4.3)	30.2 (4.2)	6 (0.0)
First child	518 (49.1)	4989 (51.7)	1564 (47.3)	777 (49.0)	
Second or later child	538 (50.9)	4667 (48.3)	1741 (52.7)	808 (51.0)	
Highest educational class of parents					31 (0.2)
High-grade professional	263 (24.9)	2561 (26.6)	631 (19.1)	194 (12.3)	
Low-grade professional	283 (26.8)	3291 (34.2)	1097 (33.3)	465 (29.4)	
Skilled worker	290 (27.5)	2443 (25.4)	1002 (30.4)	549 (34.7)	
Unskilled worker	172 (16.3)	1088 (11.3)	505 (15.3)	343 (21.7)	
Student	36 (3.4)	206 (2.1)	42 (1.3)	21 (1.3)	
Economically inactive	12 (1.1)	47 (0.5)	20 (0.6)	10 (0.6)	
Cohabitation of parents					9 (0.1)
Do not live together	35 (3.3)	199 (2.1)	56 (1.7)	29 (1.8)	
Live together	1021 (96.7)	9449 (97.9)	3248 (98.3)	1556 (98.2)	
Gestational weight gain in kg[c]	15.1 (5.2)	15.5 (5.3)	14.4 (6.6)	10.7 (8.1)	2438 (15.6)
Duration of exclusive breastfeeding					2274 (14.6)
0 months	34 (3.7)	347 (4.2)	187 (6.6)	161 (11.5)	
<4 months	252 (27.7)	1901 (23.2)	863 (30.4)	503 (36.1)	
≥4 months	625 (68.6)	5938 (72.5)	1787 (63.0)	730 (52.4)	
Total SDQ[d]	5 (3, 8)	5 (3, 8)	5 (3, 8)	6 (3, 9)	
Child BMI at 7 years[c]	14.9 (1.6)	15.5 (1.6)	16.0 (1.8)	16.5 (2.1)	4693 (30.1)

[a]15 602 of 15 819 children with non-missing information on maternal pre-pregnancy BMI (217 missing).
[b]1 unit = 12 g of alcohol.
[c]Values are expressed as mean (standard deviations).
[d]Values are expressed as median (25th percentile, 75th percentile).

included as a second-order polynomial variable. Finally, we estimated the overall association between pre-pregnancy BMI (categorical and continuous) and all pubertal milestones using Huber-White robust variance estimation as a way to reduce the risk of type 1 errors due to multiple testing of correlated pubertal milestones.[47,48] Specifically, the overall association was obtained by modelling age at attaining all the pubertal milestones simultaneously, while we allowed the coefficients for the covariates and the intercept to vary for each pubertal milestone but constrained the coefficient for pre-pregnancy BMI to be common across all pubertal milestones. To explore potential mediation of gestational weight gain, duration of exclusive breastfeeding and the child's psychosocial stress (measured by the total difficulties score at 7 years using the Strengths and Difficulties Questionnaire),[24,27,49–52] we repeated the main analysis but also adjusted for either of these three variables in three subanalyses, and we expected the associations to attenuate after adjustment. As there was some missing information on these three variables, we also restricted the main analysis to having information on these variables to assess the potential bias due

to missing information (Model 1 in Supplementary Tables 1–3, available as Supplementary data at *IJE* online).

Mediation analysis was performed to assess how much of the potential total effect of pre-pregnancy BMI (continuous, per 10 kg/m^2) on timing of puberty was mediated through childhood BMI (the natural indirect effect) and through other unspecified mechanisms (the natural direct effect). We used a regression-based approach described in VanderWeele 2016.[53] When using this approach, the investigator has to specify the index level (30 kg/m^2 for this analysis) and reference level (20 kg/m^2 for this analysis) for the continuous exposure, pre-pregnancy BMI. An advantage of this approach to mediation analysis is that it incorporates interaction between mediator and exposure into the analysis. As the mediation analysis depended on information on height and weight from the 7-year questionnaire, selection weights for this analysis were estimated for participating in both the 7-year follow-up and the Puberty Cohort. The 95% confidence intervals (CI) were bootstrapped with 1000 replications.[54]

Finally, we conducted a maternal-paternal comparison where we compared the adjusted association between maternal pre-pregnancy BMI (in 10 kg/m^2) and overall timing of puberty with the adjusted association between paternal BMI (in 10 kg/m^2) and overall timing of puberty with and without mutual adjustment.[55]

Analyses were performed in STATA 15.1 MP software (Statacorp, College Station, TX) and R (x64 3.3.1). Robust standard errors were used in all analyses to account for clustering of siblings and the use of selection and sampling weights.

Results

Background characteristics

Pre-pregnancy obese mothers were more likely to be heavy smokers, to drink less alcohol, to have earlier age at menarche, to be less educated, to have smaller gestational weight gain, to breastfeed less and to have heavier children than normal weight mothers (Table 1). Mothers of participating children were more likely to be normal weight, non-smokers, moderate alcohol drinkers, non-parous, more educated and breastfeeding than mothers of non-participating children (data now shown).

Main analysis

In sons, maternal pre-pregnancy obesity (BMI $\geq$30.0 kg/m^2) was associated with earlier age at attaining pubic hair development, voice break, axillary hair and acne, whereas a weaker tendency toward earlier genital development and first ejaculation was observed with confidence intervals overlapping the null (Table 2). Dose-dependent relations across BMI groups were observed, although most of the confidence intervals for the estimates for maternal overweight (BMI 25.0 to 29.9 kg/m^2) and underweight (BMI $<$18.5 kg/m^2) included the null. When combining all milestones to a single estimate in sons using Huber-White robust variance estimation, maternal pre-pregnancy obesity was overall associated with 1.5 (95% CI: 0.4, 2.5) months earlier pubertal development. Maternal pre-pregnancy underweight was associated with 1.3 (95% CI: 0.1, 2.4) months later pubertal development in sons. When pre-pregnancy BMI was analysed as a continuous variable, sons attained all pubertal milestones 1.2 (95% CI: 0.5, 1.9) months earlier per 10-unit increase in pre-pregnancy BMI (Table 3).

In daughters, maternal pre-pregnancy obesity was associated with earlier age at attaining all pubertal milestones (Table 2). Maternal pre-pregnancy overweight (BMI 25.0 to 29.9 kg/m^2) was also associated with earlier age at attaining all pubertal milestones, and the associations were of close to similar strengths as for pre-pregnancy obesity. When combining the estimates for all pubertal milestones in daughters, maternal pre-pregnancy obesity was associated with 3.2 (95% CI: 2.1, 4.2) months earlier timing of puberty, and maternal pre-pregnancy overweight was associated with 2.6 (95% CI: 1.8, 3.3) months earlier timing of puberty. No clear pattern was observed for maternal pre-pregnancy underweight, and when combining all milestones, no association (0.0 months (95% CI: -1.2, 1.2)) was found for pre-pregnancy underweight. When pre-pregnancy BMI was analysed as a continuous variable and all pubertal milestones were combined, daughters attained all pubertal milestones 3.1 (95% CI: 2.4, 3.8) months earlier per 10-unit increase in pre-pregnancy BMI (Table 3).

When restricting the main analysis (pre-pregnancy BMI, continuous) to having information on either gestational weight gain, duration of exclusive breastfeeding or total difficulties score at age 7 years, the results remained essentially unchanged, indicating no bias due to missing information (Model 1 in Supplementary Tables 1–3, available as Supplementary data at *IJE* online). When further adjusting for gestational weight gain, the results became slightly accentuated in sons, but remained essentially unchanged in daughters (Model 2 in Supplementary Table 1, available as Supplementary data at *IJE* online). When adjusting for either duration of exclusive breastfeeding or the total difficulties score, the results remained essentially unchanged for both sons and daughters (Model 2 in Supplementary Tables 2 and 3, available as Supplementary data at *IJE* online).

Table 2. Mean age difference in timing of puberty in months as a function of pre-pregnancy BMI categories, the Puberty Cohort, Denmark, 2012–18

			Crude and adjusted mean age difference in months					
		Normal weight (Ref)	Underweight (BMI <18.5)		Overweight (BMI 25.0 to 29.9)		Obese (BMI ≥30.0)	
Pubertal milestones	No.[a]	Mean age[b]	Crude	Adjusted (95% CI)[c]	Crude	Adjusted (95% CI)[c]	Crude	Adjusted (95% CI)[c]
Sons								
Tanner Genital stage 2	7469	10.9	0.3	0.4 (−1.5, 2.4)	−0.9	−0.7 (−2.0, 0.5)	−0.6	−0.4 (−2.1, 1.2)
Tanner Genital stage 3	7469	12.5	0.0	0.4 (−1.4, 2.1)	−0.7	−0.4 (−1.6, 0.8)	−0.8	−0.3 (−1.9, 1.2)
Tanner Genital stage 4	7469	13.7	1.3	1.7 (−0.1, 3.6)	−1.0	−0.6 (−1.8, 0.6)	−1.0	−0.2 (−1.7, 1.4)
Tanner Genital stage 5	7469	15.7	1.3	2.1 (−0.6, 4.9)	−1.2	−0.7 (−2.5, 1.1)	−1.6	−0.8 (−3.1, 1.6)
Tanner Pubic Hair stage 2	7473	11.3	0.4	0.3 (−1.4, 2.0)	−0.4	−0.2 (−1.3, 1.0)	−1.3	−1.1 (−2.6, 0.5)
Tanner Pubic Hair stage 3	7473	12.8	0.7	1.0 (−0.5, 2.5)	−1.3	−0.9 (−1.9, 0.1)	−2.3	−1.7 (−3.1, −0.4)
Tanner Pubic Hair stage 4	7473	13.6	1.3	1.5 (0.0, 3.1)	−0.9	−0.5 (−1.5, 0.5)	−2.4	−1.7 (−3.0, −0.4)
Tanner Pubic Hair stage 5	7473	14.8	0.9	1.6 (−0.5, 3.7)	−1.8	−1.2 (−2.5, 0.1)	−2.8	−2.0 (−3.6, −0.3)
Axillary hair	7478	13.3	1.0	1.2 (−0.7, 3.2)	−1.4	−0.9 (−2.1, 0.4)	−5.4	−4.4 (−6.1, −2.7)
Acne	7478	12.3	1.4	1.7 (0.0, 3.4)	−1.9	−1.5 (−2.7, −0.4)	−2.9	−2.5 (−4.0, −0.9)
Voice break	7274	13.0	1.1	1.7 (−0.1, 3.5)	−1.0	−0.5 (−1.8, 0.7)	−2.9	−2.2 (−3.8, −0.6)
First ejaculation	7465	13.3	1.1	1.3 (−0.4, 3.1)	−0.4	−0.2 (−1.3, 1.0)	−0.5	−0.4 (−2.0, 1.2)
All milestones combined[d]	7274	–	0.9	1.3 (0.1, 2.4)	−1.0	−0.6 (−1.5, 0.2)	−2.0	−1.5 (−2.5, −0.4)
Daughters								
Tanner Breast stage 2	7892	10.0	2.2	2.1 (−0.1, 4.3)	−6.2	−4.9 (−6.7, −3.2)	−8.7	−6.9 (−9.3, −4.4)
Tanner Breast stage 3	7892	11.8	0.4	0.3 (−1.3, 1.8)	−4.5	−3.7 (−4.8, −2.6)	−5.4	−4.2 (−5.6, −2.8)
Tanner Breast stage 4	7892	13.1	1.1	0.8 (−0.8, 2.5)	−3.6	−2.8 (−3.9, −1.8)	−4.6	−3.5 (−4.9, −2.1)
Tanner Breast stage 5	7892	16.1	−1.1	−1.3 (−4.2, 1.7)	−5.8	−4.6 (−6.5, −2.6)	−7.5	−5.7 (−8.3, −3.1)
Tanner Pubic Hair stage 2	7893	11.3	0.1	−0.3 (−1.6, 1.0)	−1.8	−1.3 (−2.2, −0.5)	−1.5	−0.8 (−2.0, 0.4)
Tanner Pubic Hair stage 3	7893	12.5	0.1	−0.3 (−1.6, 0.9)	−2.5	−2.0 (−2.9, −1.2)	−2.5	−1.8 (−3.0, −0.7)
Tanner Pubic Hair stage 4	7893	13.5	0.3	−0.2 (−1.8, 1.4)	−2.0	−1.5 (−2.6, −0.4)	−2.6	−1.9 (−3.4, −0.4)
Tanner Pubic Hair stage 5	7893	15.6	−2.5	−2.8 (−5.2, −0.4)	−3.1	−2.4 (−4.0, −0.7)	−5.8	−4.7 (−6.9, −2.5)
Axillary hair	7898	12.0	−0.1	−0.3 (−2.1, 1.4)	−3.0	−2.6 (−3.8, −1.4)	−3.1	−2.4 (−4.0, −0.9)
Acne	7898	11.5	1.1	1.0 (−0.9, 3.0)	−2.0	−1.4 (−2.7, −0.2)	−4.0	−3.1 (−4.9, −1.4)
Menarche	7890	13.1	0.4	0.3 (−1.1, 1.7)	−3.2	−2.3 (−3.2, −1.4)	−4.4	−3.1 (−4.2, −2.0)
All milestones combined[d]	7890	–	0.3	0.0 (−1.2, 1.2)	−3.2	−2.6 (−3.3, −1.8)	−4.1	−3.2 (−4.2, −2.1)

[a]As some sons and daughters gave information on some but not all pubertal milestones, different number of observations were used for each outcome.
[b]Crude mean age in years at attaining pubertal milestones for sons and daughters of normal-weight mothers (BMI 18.5 to 24.9).
[c]Adjusted for alcohol consumption and smoking in first trimester, highest educational class of parents, maternal age at menarche, maternal age at delivery, parity and cohabitation of parents during pregnancy.
[d]Estimated using Huber-White robust variance estimation.

Mediation analysis

We found antagonistic interaction between pre-pregnancy BMI and childhood BMI for most milestones in daughters but not in sons; the association between higher pre-pregnancy BMI and earlier timing of puberty attenuated (and eventually reversed) with higher childhood BMI in daughters (Supplementary Table 4, available as Supplementary data at *IJE* online). In sons, the associations (the total effects) between pre-pregnancy BMI and timing of puberty were completely mediated through childhood BMI (the natural indirect effects) (Figure 1; Supplementary Table 5, available as Supplementary data at *IJE* online). In daughters, around one-third of the total effects were mediated through childhood BMI (the natural indirect effects) (Figure 2; Supplementary Table 5, available as Supplementary data at *IJE* online).

Maternal-paternal comparison

In the maternal-paternal comparison, the timings of puberty for sons and daughters were associated with paternal as well as with maternal BMI, both with and without mutual adjustment (Table 4).

Discussion

Principal findings

We found that maternal pre-pregnancy obesity was associated with earlier timing of puberty in both sons and daughters. These associations seemed to be mainly mediated by higher childhood BMI in sons but mainly through other mechanisms in daughters.

Table 3. Mean age difference in timing of puberty in months per 10-kg/m^2 increase in pre-pregnancy BMI, the Puberty Cohort, Denmark, 2012–18

		Age difference[a]	
Pubertal milestones	No.[c]	Unadjusted Mean	Adjusted[b] Mean (95% CI)
Sons			
Tanner Genital stage 2	7469	−1.3	−0.2 (−1.3, 0.9)
Tanner Genital stage 3	7469	−2.4	−0.4 (−1.5, 0.6)
Tanner Genital stage 4	7469	−2.6	−0.6 (−1.6, 0.4)
Tanner Genital stage 5	7469	−4.0	−1.2 (−2.7, 0.4)
Tanner Pubic Hair stage 2	7473	−1.7	−0.6 (−1.6, 0.5)
Tanner Pubic Hair stage 3	7473	−2.4	−1.4 (−2.3, -0.4)
Tanner Pubic Hair stage 4	7473	−2.3	−1.4 (−2.3, -0.5)
Tanner Pubic Hair stage 5	7473	−3.3	−1.6 (−2.7, -0.4)
Axillary hair	7478	−2.5	−3.0 (−4.2, -1.9)
Acne	7478	−2.2	−2.2 (−3.3, -1.2)
Voice break	7274	−3.1	−1.3 (−2.4, -0.2)
First ejaculation	7465	−1.6	−0.7 (−1.7, 0.4)
All milestones combined[d]	7274	−1.6	−1.2 (−1.9, -0.5)
Daughters			
Tanner Breast stage 2	7892	−4.5	−7.3 (−9.0, -5.5)
Tanner Breast stage 3	7892	−3.6	−4.3 (−5.3, -3.3)
Tanner Breast stage 4	7892	−3.6	−3.7 (−4.6, -2.8)
Tanner Breast stage 5	7892	−5.9	−5.4 (−7.0, -3.7)
Tanner Pubic Hair stage 2	7893	−0.5	−1.1 (−1.9, -0.3)
Tanner Pubic Hair stage 3	7893	−1.3	−2.1 (−2.9, -1.3)
Tanner Pubic Hair stage 4	7893	−1.8	−1.7 (−2.7, -0.8)
Tanner Pubic Hair stage 5	7893	−3.4	−3.0 (−4.4, -1.6)
Axillary hair	7898	−1.7	−2.7 (−3.7, -1.6)
Acne	7898	−2.8	−2.6 (−3.8, -1.4)
Menarche	7890	−4.1	−3.1 (−3.8, -2.3)
All milestones combined[d]	7890	−4.0	−3.1 (−3.8, -2.4)

[a]Change in age (β) in months at attaining pubertal milestones per 10-kg/m^2 increase in pre-prengnancy BMI with 95% confidence interval.

[b]Adjusted for alcohol consumption and smoking in first trimester, highest educational class of parents, maternal age at menarche, maternal age at delivery, parity and cohabitation of parents during pregnancy.

[c]As some sons and daughters gave information on some but not all pubertal milestones, different number of observations were used for each outcome.

[d]Estimated using Huber-White robust variance estimation.

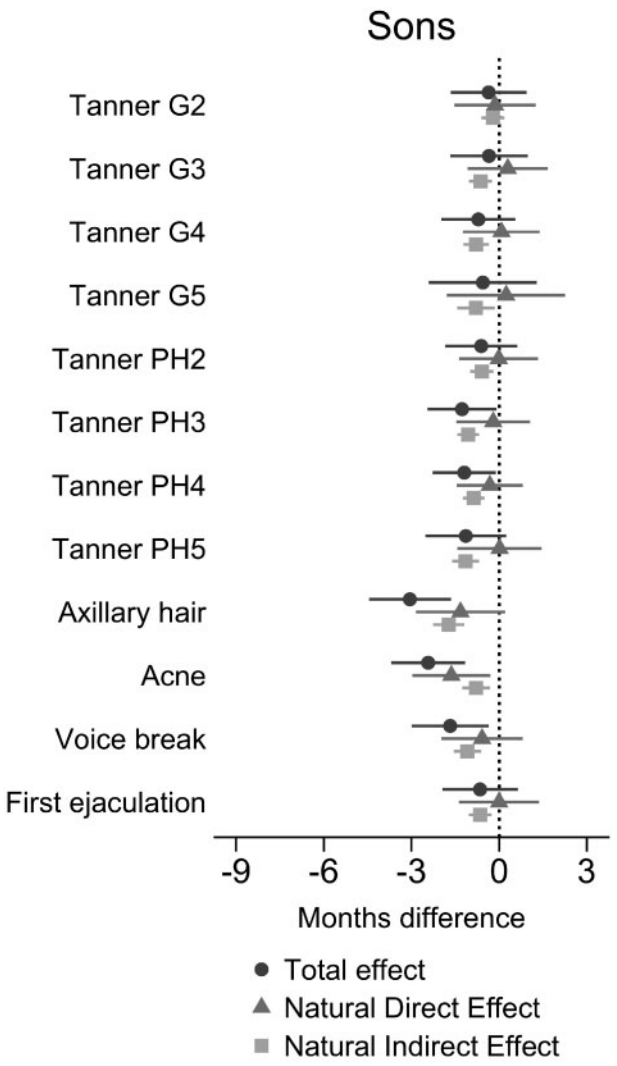

Figure 1. Total effects, natural direct effects and natural indirect effects as mean monthly difference in age at attaining the pubertal milestones with 95% confidence intervals for a pre-pregnancy BMI of 30 kg/m^2 with 20 kg/m^2 as reference among sons. Adjusted for alcohol consumption and smoking in first trimester, highest educational class of parents, maternal age at menarche, maternal age at delivery, parity, and cohabitation of parents during pregnancy. Tanner G2-5, Tanner Genital stage 2–5; Tanner PH2-5, Tanner Pubic Hair stage 2–5.

Strengths and limitations

This study was among the largest on this topic. We used a wide range of pubertal markers that were collected during the course of puberty, we employed selection weights to reduce potential selection bias, we had detailed information on potential important confounders and we employed mediation analysis and a maternal-paternal comparison to gain insight into the potential mechanisms at play.

Our study was limited by the late start of follow up, leaving the earliest milestones left-censored. This will induce error if the assumption of normally distributed residuals is violated. However, we found residuals compatible with the normal distribution. BMI derived from self-reported height and weight is not a perfect measure of BMI measured by health care professional (but with correlation coefficient in adults >0.9),[56] and maternal BMI and childhood BMI at 7 years capture fat mass with some measurement error (correlation coefficient in White boys is 0.86, White girls is 0.96 and White adult women is 0.87).[57,58] This measurement error is most likely non-differential with regard to pubertal development in the children. Hence, the total effect will most likely be biased toward the null. Likewise, the indirect effect will also likely be biased toward the null due to measurement error of the mediator, and consequently, the direct effect will be biased away

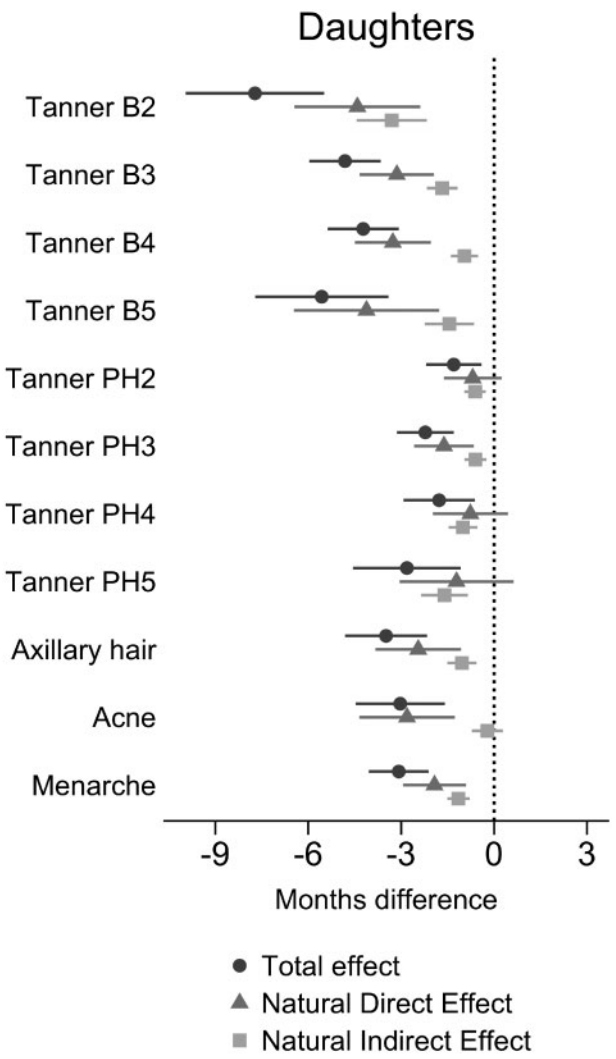

Figure 2. Total effects, natural direct effects and natural indirect effects as mean monthly difference in age at attaining the pubertal milestones with 95% confidence intervals for a pre-pregnancy BMI of 30 kg/m^2 with 20 kg/m^2 as reference among daughters. Adjusted for alcohol consumption and smoking in first trimester, highest educational class of parents, maternal age at menarche, maternal age at delivery, parity and cohabitation of parents during pregnancy. Tanner B2-5, Tanner Breast stage 2-5; Tanner PH2-5, Tanner Pubic Hair stage 2–5.

from the null.[59] We may, therefore, underestimate the proportion mediated. We have previously found moderate agreement between Tanner stages collected by self-report and by clinical examination.[60] However, the measurement error introduced by self-reporting is most likely non-differential, resulting in conservative estimates.[61] The exception is Tanner Breast Stage 2 among obese girls who may take fat tissue for breast tissue.[62] This may explain the stronger associations for Tanner Breast Stages than other pubertal milestones in daughters, but cannot necessarily explain our results for other milestones, such as menarche. In the maternal-paternal comparison, the use of paternal BMI obtained at the 7-year follow-up of the children, as a surrogate for paternal BMI before pregnancy, introduces at least some misclassification. Nevertheless, the associations between paternal BMI and timing of puberty calls for thorough consideration of residual confounding.[55] Several genetic variants have now been associated with both adiposity and timing of puberty.[63] Although we have partly removed this confounding by adjustment for maternal age at menarche, we cannot exclude the possibility of residual confounding. Genetic variants associated with adiposity only may cause residual confounding through high childhood obesity.[64,65] Residual confounding may also be present from eating and leisure-time habits that may be adopted by the children, affecting timing of puberty through childhood BMI. Because these genetic variants related to adiposity and lifestyle habits would likely act through childhood BMI, only the indirect effects may be biased, whereas the direct effects need not necessarily be biased.

Comparison with other studies

Only a single study on sons has been published so far.[32] It found that pre-pregnancy obesity was associated with earlier age at regular shaving but not with age of voice break,

Table 4. Maternal-paternal comparison in 4750 sons and 4897 daughters, the Puberty Cohort, Denmark, 2012–18

	Overall age difference in months at puberty according to BMI (per 10 kg/m^2)[a]	
	Parental BMI in separate models: Estimate (95% CI)[b]	Parental BMI in same model: Estimate (95% CI)[b]
Sons ($n = 4750$)		
Pre-pregnancy BMI	−1.3 (−2.2, −0.3)	−1.0 (−1.9, 0.0)
Paternal BMI at 7 years	−2.2 (−3.3, −1.1)	−2.0 (−3.1, −0.9)
Daughters ($n = 4897$)		
Pre-pregnancy BMI	−3.2 (−4.1, −2.3)	−2.8 (−3.7, −1.9)
Paternal BMI at 7 years	−3.1 (−4.2, −2.0)	−2.5 (−3.6, −1.3)

[a]Estimated using Huber-White robust variance estimation.

[b]Adjusted for alcohol consumption and smoking in first trimester, highest educational class of parents, maternal age at menarche, maternal age at delivery, parity and cohabitation of parents during pregnancy.

first nocturnal ejaculation and acne.[32] Further, a slight attenuation after adjusting for the sons' BMI at 19 years was observed. However, this study was limited by collecting information on the sons' BMI and puberty at 19 years, which introduces some measurement error.[32] Our study used information collected during the course of pregnancy, childhood, and puberty, and we found that maternal pre-pregnancy obesity was associated with earlier timing of puberty. Moreover, the entire association seemed to be mediated through childhood BMI. If these associations are causal, this would indicate that a potential advancing effect of maternal pre-pregnancy BMI on timing of puberty in sons could be reduced or even eliminated through preventive actions against obesity in childhood.

In daughters, maternal pre-pregnancy obesity has been associated with earlier age at menarche[24–29] and earlier onset of breast and pubic hair development,[27,30,31] which is in line with our results. Former studies either reported evidence of some mediation by childhood BMI[26,27,30] or no mediation.[24,25] This discrepancy may be due to a relatively small study population[25] or a heterogeneous ethnic population[24] in the studies that reported no mediation. Our results support a partly mediating role of childhood BMI in daughters.

Interpretation

Gestational weight gain may mediate some of the association between pre-pregnancy BMI and timing of puberty, as gestational weight gain has been related to earlier timing of puberty in daughters.[24,27] When adjusting for gestational weight gain, our associations slightly accentuated in sons but remained largely unchanged in daughters. Hence, differences in gestational weight gain seems to be an unlikely mediator for the observed associations. Overweight and obese mothers may be less likely to breastfeed than normal weight mothers,[49] and shorter duration of breastfeeding has been associated with earlier age at menarche in girls.[50] Thus, duration of breastfeeding could also be a mediator for the observed associations, but our data did not support this hypothesis. Psychosocial stress in the children may also have a mediatory role in the associations.[51,52] Including the total difficulties score measured at 7 years in the model did not indicate that psychosocial stress was a mediator of the relation between maternal pre-pregnancy obesity and timing of puberty in sons and daughters. Finally, accumulation of endocrine disruptors in maternal fat tissue may also mediate the observed association,[32,66] although we had no empirical data to support this.

The maternal-paternal comparison showed similar associations for both paternal and maternal BMI. This may suggest residual confounding if a programming role of paternal BMI can be ruled out.[67,68] A programming role of paternal BMI is supported by a study in rodents, which showed that paternal obesity induced by a high-fat diet before conception led to increased weight and insulin resistance in the offspring,[69] and human studies corroborate this potential link.[70] In turn, both obesity in childhood and insulin resistance are likely causally related to earlier puberty.[20–23] If paternal BMI programmes the sperm, we similarly cannot rule out that maternal pre-pregnancy BMI may affect timing of puberty through similar programming of the oocyte before conception.[71]

If the observed associations in our study reflect causal relations, pre-pregnancy obesity may also cause earlier pubertal development in other Western populations, although estimated effect sizes may vary due to different distributions of other component causes of timing of puberty.

Conclusions

This study suggests that maternal pre-pregnancy obesity may advance timing of puberty through childhood obesity in sons and mainly through other unknown mechanisms in daughters. An increasing prevalence of pre-pregnancy obesity, or environmental causes of that obesity, could at least be part of the explanation for the secular trend toward earlier timing of puberty.

Supplementary Data

Supplementary data are available at *IJE* online.

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