Pediatric RESEARCH

POPULATION STUDY ARTICLE

Child-related and parental predictors for thelarche in a general population of girls: the PANIC study

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BACKGROUND: Obesity has been associated with earlier thelarche, whereas other predictors for it remain unclear.
METHODS: We studied child-related and parental predictors for earlier thelarche in 195 girls aged 6–8 years followed up for 2 years. A physician evaluated breast development by inspection and palpation. Body fat percentage (BF%) was measured by dual-energy X-ray absorptiometry, diet by food records, and physical activity and sedentary time by body movement and heart rate monitors. Parental education, smoking, and alcohol consumption and household income were assessed by questionnaires. Gestational age, birth weight, and maternal prepregnancy BMI were obtained from hospital registers. Predictors for thelarche were examined using logistic regression analysis adjusted for age and follow-up time.
RESULTS: The incidence of thelarche during 2 years increased by 11% (OR 1.11, CI 1.06–1.17, $p < 0.001$) for 1 unit increase in baseline BF%. Girls with a smoking parent had a 2.64 (95% CI 1.21–5.77, $p = 0.015$) times higher incidence of thelarche than other girls. The associations of lower parental education and higher maternal prepregnancy BMI with the higher incidence of thelarche were largely explained by BF%. Other possible predictors were not associated with thelarche.
CONCLUSIONS: Higher BF% and exposure to tobacco smoke are independent predictors for earlier thelarche.

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INTRODUCTION

Thelarche is defined as the appearance of glandular breast tissue in girls and is often the first sign of gonadotropin-dependent central puberty.[1] However, thelarche may also be an isolated non-gonadotropin-dependent phenomenon.[2] The age at thelarche has declined during the past decades.[3–5] The causes of this trend are a topic of interest because early sexual maturation may have adverse health and psycho-social consequences in girls.[6–8]

Variations in the timing of puberty in girls are attributable to genetic factors, body composition, and environmental factors.[9–11] However, evidence about pubertal timing in girls comes mostly from studies focusing on menarche instead of thelarche.[9,10] Obese girls have been found to have an earlier thelarche than normal weight girls.[5,12] The timing of thelarche also appears to be earlier in African-American girls than in Caucasian girls and earlier in Caucasian girls than in Asian girls.[4,5] Prenatal or postnatal exposure to tobacco smoke has been observed to be associated with an earlier timing of menarche,[13] but evidence for its relationship with the timing of thelarche is inconsistent.[14–16] Moreover, as far as we are aware, there are no studies on the associations of girls' lifestyle factors, such as physical activity, sedentary time, and diet, or parental alcohol consumption with the timing of thelarche.

More follow-up studies in general population of girls with a clinically verified thelarche are needed to provide reliable evidence on potential predictors for an earlier timing of thelarche. In the present study, we aimed to examine child-related and parental predictors for thelarche during a 2-year follow-up in a general population of prepubertal Caucasian girls aged 6–8 years at baseline.

METHODS

Study design and participants

The current analyses are based on the baseline and 2-year follow-up data from the Physical Activity and Nutrition in Children (PANIC) study, which is a controlled physical activity and dietary intervention study (ClinicalTrials.gov NCT01803776) in a representative population sample of primary school children from the city of Kuopio, Finland. A total of 736 children aged 6–8 years who started the first grade in primary schools in 2007–2009 were invited to participate in the baseline examinations, and 512 (70%) participated: 246 (48%) were girls and 266 (52%) were boys. The participants did not differ in sex distribution, age, or body mass index—standard deviation score (BMI-SDS) from all children who started the first grade in the primary schools of Kuopio in 2007–2009 based on the comprehensive data obtained from the school health examinations. Of the 512 children who participated in the baseline examinations, 440 (86%) attended the 2-year follow-up study in 2009–2011. The exclusion criteria for the present analyses were male gender, non-Caucasian races, diseases, and medications known to affect sexual maturation assessed at baseline and 2-year follow-up as well as palpable breast tissue at baseline. After these exclusions, 195 girls participating in the 2-year follow-up study were included in the present analyses. The Research Ethics Committee of the Hospital

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District of Northern Savo approved the study protocol. All participating children gave their assent, and their parents or caregivers provided a written informed consent.

Assessment of body size and composition

Body height was measured three times by a research nurse using a calibrated wall-mounted stadiometer to an accuracy of 0.1 cm with the children standing in the Frankfurt plane without shoes. The mean of the nearest two values was used in the analyses. Body weight was measured twice using the InBody® 720 bioelectrical impedance device (Biospace, Seoul, Korea) to an accuracy of 0.1 kg with the children having fasted for 12 h, emptied their bladder, and wearing light underwear. The mean of these two values was used in the analysis. BMI was calculated by dividing body weight (kg) with body height (m) squared. BMI-SDS was calculated using the Finnish growth reference data.[17] Normal weight, overweight, and obesity were defined using the age- and sex-specific BMI cut-offs of the International Obesity Task Force (IOTF).[18] Target height was calculated according to Tanner's formula.[19] Body fat percentage was measured using the Lunar® dual-energy X-ray absorptiometry device (Lunar Prodigy Advance, GE Medical Systems, Madison, WI, USA) with the children in the non-fasting state but having emptied their bladder and wearing only light clothing with all metal objects removed. Information on gestational weeks at birth and birth size was obtained from the records of Kuopio University Hospital. Birth height SD and birth weight SD were calculated using Finnish growth references for newborns.[20]

Assessment of secondary sexual characteristics

Pubertal status at baseline and at the 2-year follow-up was evaluated by a trained physician according to Tanner's classification (M1–5 for breast development and P1–5 for pubic hair).[21] Thelarche was defined as at least M2 for breast development.[21]

Assessments of physical activity and sedentary time

Physical activity and sedentary time were assessed using a combined heart rate and body movement monitor called Actiheart® (CamNtech Ltd., Papworth, UK). The participants were requested to wear the monitor continuously for a minimum of 4 consecutive days, including 2 weekdays and 2 weekend days. Moderate-to-vigorous physical activity time was defined as time spent in physical activity exceeding the intensity of 4.0 metabolic equivalents (METs) and sedentary time as time spent in activity ≤1.5 METs excluding sleep. One MET corresponds to the oxygen uptake of 3.5 ml O_2/min/kg and the energy expenditure of 71 J/min/kg.

Assessment of diet

Food consumption and nutrient intake were assessed by food records of 4 predefined consecutive days, including 2 weekdays and 2 weekend days or 3 weekdays and 1 weekend day, that were filled out by the parents.[22] We accepted food records of 4 (97.9%) or 3 (2.1%) consecutive days in the analyses. We used the Baltic Sea Diet Score as a measure of overall diet quality.[23] The Baltic Sea Diet Score is calculated by summing the scores for the quartiles of the consumption of fruit and berries (range 0–3), vegetables (0–3), high-fiber grain products (0–3), low-fat milk (0–3), fish (0–3), and red meat and sausage (3–0) and the ratio of polyunsaturated fatty acids to saturated fatty acids in the diet (0–3) in our study population. The Baltic Sea Diet Score thus ranges between 0 and 21, a higher score indicating better diet quality.

Assessment of parental background

Parental factors were assessed using a structured questionnaire filled out by mothers and fathers at baseline. Parental education was categorized based on either completed or ongoing education of mothers and fathers (vocational school or less, polytechnic, university).[22] Household income was categorized as ≤30,000, 30,001–60,000 and >60,000 €/year.[22] The higher level of education and household income reported by a parent were used in the analyses. In the analyses, parental alcohol consumption (portions/week) was that of the parent who consumed more alcohol. Parental smoking was considered positive if either of the parents reported that he or she was a current smoker. Information on mother's prepregnancy BMI was collected from the birth records of Kuopio University Hospital.

Statistical methods

Statistical analyses were performed using the IBM SPSS Statistics software, Version 24 (IBM Corp. Armonk, NY, USA). Differences and associations were considered statistically significant if $p < 0.05$. Differences in characteristics between girls who achieved thelarche during the 2-year follow-up and girls who did not were studied by T test for independent samples for continuous variables and by Chi-square test for categorical variables. The associations of child-related and parental factors with the incidence of thelarche were investigated using logistic regression analyses adjusted for baseline age and follow-up time and further for body fat percentage.

RESULTS

Altogether 57 (29.0%) of the 195 girls had achieved thelarche during 2-year follow-up. The characteristics of girls without thelarche and girls in whom it was present at the 2-year follow-up are shown in Table 1.

The incidence of thelarche increased by 11% (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.06–1.17, $p < 0.001$) with each single unit increase in baseline body fat percentage after adjustment for baseline age and follow-up time (Table 2). A 1-cm increase in baseline body height was associated with a 21% increase in the incidence of thelarche (OR 1.21, 95% CI 1.11–1.32, $p < 0.001$) adjusted for baseline age and follow-up time. It was associated with a 17% increase in the incidence of thelarche (OR 1.17, 95% CI 1.07–1.28, $p = 0.001$) after additional adjustment for body fat percentage.

Girls whose parents had no more than vocational education had a 3.65 times higher incidence of thelarche (OR 3.65, 95% CI 1.21–11.02, $p = 0.022$) in comparison with those girls whose parents had a university education after adjustment for baseline age and follow-up time (Table 2). This difference was no longer statistically significant after additional adjustment for body fat percentage.

Girls living in homes with the lowest household income had a 2.71 times higher incidence of thelarche (OR 2.70, 95% CI 1.02–7.14, $p = 0.045$) than those girls living in homes with the highest household income (Table 2). This difference was no longer statistically significant after further adjustment for body fat percentage.

Girls whose parent was a smoker at baseline had a 2.64 times higher incidence of thelarche (OR 2.64, 95% CI 1.21–5.77, $p = 0.015$) than girls whose parents were non-smokers after adjustment for baseline age and follow-up time (Table 2). Further adjustment for body fat percentage exerted a minor effect on this difference.

The incidence of thelarche increased by 11% (OR 1.11, 95% CI 1.03–1.20, $p = 0.009$) with each single unit increase in maternal prepregnancy BMI (Table 2). This association was no longer statistically significant after additional adjustment for body fat percentage.

DISCUSSION

In the present study, a higher body fat percentage at the age of 6–8 years predicted an earlier thelarche by the 2-year follow-up.

Table 1. Characteristics.

	Girls without thelarche ($n = 138$)	Girls with thelarche ($n = 57$)	p value
Age (years)			
Baseline	7.5 (0.3)	7.8 (0.3)	<0.001
2-year follow-up	9.6 (0.4)	9.9 (0.4)	<0.001
Body height (cm)			
Baseline	126.1 (5.0)	131.3 (5.2)	<0.001
2-year follow-up	137.5 (5.6)	144.1 (6.0)	<0.001
Body height SDS			
Baseline	−0.1 (0.9)	0.6 (0.9)	<0.001
2-year follow-up	−0.2 (0.9)	0.6 (0.9)	<0.001
Target height SDS	−0.1 (0.7)	0 (1)	0.436
Body weight (kg)			
Baseline	24.7 (3.7)	29.3 (5.4)	<0.001
2-year follow-up	30.9 (5.1)	38.6 (7.9)	<0.001
BMI SDS			
Baseline	−0.5 (1.0)	0.2 (1.0)	<0.001
2-year follow-up	−0.4 (0.9)	0.4 (1.0)	<0.001
Body fat percentage (%)			
Baseline	19.9 (6.3)	25.7 (7.7)	<0.001
2-year follow-up	22.8 (7.1)	29.9 (8.8)	<0.001
Body weight status at baseline, *n* (%)			
Normal weight	130 (94.2)	44 (77.2)	0.002
Overweight	6 (4.3)	9 (15.8)	
Obese	2 (1.4)	4 (7.0)	
Tanner stage of pubic hair at 2-year follow-up, *n* (%)			<0.001
P1	127 (92.0)	40 (71.4)	
P2 or more	11 (8.0)	16 (28.6)	
Gestational weeks at birth (weeks)	40 (1.7)	40 (1.8)	0.252
Birth height SDS	−0.1 (1.0)	−0.1 (0.9)	0.612
Birth weight SDS	−0.1 (1.0)	0.1 (0.9)	0.276
Baltic Sea Diet Score	12.6 (4.1)	11.4 (4.2)	0.102
Sedentary time (h/d)	3.8 (2.2)	4.3 (2.2)	0.177
Moderate-to-vigorous physical activity (h/day)	1.6 (0.9)	1.6 (0.9)	0.586
Parental education, *n* (%)			
University	49 (35.5)	13 (23.2)	0.071
Polytechnic	76 (55.1)	33 (58.9)	
Vocational school or less	13 (9.4)	10 (17.9)	
Household income, *n* (%)			
>60,000 €/y	49 (35.5)	16 (28.1)	0.369
30,001–60,000 €/y	66 (47.8)	27 (47.4)	
≤30,000 €/y	23 (16.7)	14 (24.6)	
Parental smoking (%)			
Yes	37 (28.0)	20 (39.2)	0.143
No	95 (72.0)	31 (60.8)	
Parental alcohol consumption (portions/week)	6.9 (6.8)	7.6 (9.4)	0.545
Maternal prepregnancy BMI	22.9 (3.4)	24.8 (5.7)	0.034

The data are means (standard deviations) for continuous variables and numbers (percentages) for categorical variables. Data on parental smoking and alcohol consumption were available for 183 girls and on birth size and gestational age for 194 girls. Normal weight, overweight, and obesity were defined using the age and sex-specific body mass index cut-offs of the International Obesity Task Force (IOTF).[18]
SDS standard deviation score, *BMI* body mass index.

Moreover, body height at the age of 6–8 years and parental smoking predicted an earlier thelarche even after accounting for body fat percentage. A lower parental education, a lower household income, and a higher maternal prepregnancy BMI were also associated with an earlier timing of thelarche. However, the associations of parental education and maternal prepregnancy BMI with the timing of thelarche were largely and that of household income was partly explained by the girls' body fat percentage. Gestational age, birth weight, physical activity, sedentary time, diet quality, or parental alcohol consumption were not associated with the timing of thelarche.

Our finding of an association between a higher body fat percentage and an earlier timing of thelarche is compatible with the results of earlier studies.[12,24,25] Reinehr and co-workers[24] and Lawn and co-workers[25] used BMI as a measure of obesity, whereas Zhai and co-workers[12] estimated body fat percentage by determining skinfold thicknesses. We measured body fat percentage using dual-energy X-ray absorptiometry, which provides a more precise assessment of the body fat content than achievable with either BMI or skinfold thicknesses. Although low levels of physical activity and an unhealthy diet are major risk factors for adiposity, we found no associations of these lifestyle factors with the earlier timing of thelarche.

Greater adiposity is known to accelerate linear growth in prepubertal children.[26] In our study, girls with thelarche at the 2-year follow-up were taller at the age of 6–8 years than girls without it, but there was no difference in target height between these groups of girls. The association between a higher body height and an earlier timing of thelarche was not accounted for by body fat percentage, suggesting that adiposity does not explain the higher incidence of earlier thelarche in taller girls. However, the finding of an association between a higher body height and an earlier thelarche is consistent with a well-documented delay in childhood growth of late maturing children.[27]

An important observation of our study is that exposure to parental smoking was a strong predictor for earlier thelarche even after controlling for body fat percentage. The results of previous studies suggest that prenatal or postnatal exposure to tobacco smoke is associated with an earlier menarche.[13,15,28–30] However, there are few studies examining the association between exposure to tobacco smoke and the timing of thelarche.[14–16] Windham and co-workers[14] found no association between exposure to prenatal or postnatal cigarette smoking and the timing of thelarche, but Maisonet and co-workers[15] and Brix and co-workers[16] reported that those girls who had been prenatally exposed to tobacco smoke had an earlier thelarche than other girls. Tobacco is known to contain hormonally active compounds that may disrupt the hormonal balance of children and may thus exert an effect on the timing of puberty.[14,30]

A higher maternal prepregnancy BMI has been found to be associated with an earlier timing of menarche and overweight in the offspring.[31,32] According to the study conducted by Lawn and co-workers,[25] a higher maternal prepregnancy BMI was also associated with an earlier timing of thelarche. In our study, the relationship between a higher maternal prepregnancy BMI and the earlier timing of thelarche was largely explained by the girls' body fat percentage. Some studies have reported an association between fetal growth retardation and an earlier pubertal timing.[33,34] We did not observe an association between birth size and gestational age with the incidence of thelarche. In our study, there were only few girls born preterm or small for gestational, which may limit possibilities to detect associations of these characteristics with the earlier timing of thelarche.

Only few previous studies have investigated the associations of socioeconomic status with the timing of thelarche.[11,35] Our findings on a lower parental education and a lower household income being associated with a higher incidence of thelarche are

Table 2. Predictors of earlier thelarche.

	Model 1		Model 2	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Body fat percentage (%)[a]	1.11 (1.06–1.17)	**<0.001**		
Body height (cm)[a]	1.21 (1.11–1.32)	**<0.001**	1.17 (1.07–1.28)	**0.001**
Birth weight (SDS)	1.14 (0.83–1.57)	0.425	0.99 (0.70–1.41)	0.973
Gestational weeks at birth	1.11 (0.90–1.37)	0.333	0.14 (0.91–1.43)	0.252
Sedentary time (h/day)[a]	1.08 (0.93–1.26)	0.314	0.94 (0.78–1.21)	0.476
Moderate-to-vigorous physical activity (h/day)[a]	0.89 (0.93–1.26)	0.533	1.21 (0.78–1.12)	0.379
Baltic Sea Diet Score[a]	0.99 (0.91–1.07)	0.794	0.97 (0.89–1.06)	0.468
Parental education[a]				
University	Reference		Reference	
Polytechnic	1.79 (0.82–3.94)	0.146	1.58 (0.63–3.28)	0.394
Vocational school or less	3.65 (1.21–11.02)	**0.022**	2.39 (0.74–7.68)	0.145
Household income[a]				
>60,000 (€/y)	Reference		Reference	
30,001–60,000 (€/y)	1.51 (0.70–3.27)	0.298	1.62 (0.71–3.69)	0.249
≤30,000 (€/y)	2.70 (1.02–7.14)	**0.045**	2.63 (0.91–7.59)	0.073
Parental alcohol consumption (portions/week)[a]	0.58 (0.28–1.18)	0.130	0.56 (0.26–1.18)	0.125
Parental smoking[a]	2.64 (1.21–5.77)	**0.015**	2.49 (1.11–5.61)	**0.028**
Maternal prepregnancy BMI	1.11 (1.03–1.20)	**0.009**	1.05 (0.96–1.15)	0.319

The data are odds ratios (95% confidence intervals) and their *p* values from logistic regression models adjusted for baseline age and follow-up time (Model 1) and additionally body fat percentage (Model 2). *p* Values <0.05 are in bold.
BMI body mass index, *LM* lean mass.
[a]Variables are from baseline.

in line with these previous studies. However, the previous studies[11,35] used socioeconomic position, whereas we used parental education and a lower household income as indicators of socioeconomic status. In our study, the association of parental education with the timing of thelarche was largely and that of household income was partly explained by the girls' body fat percentage.

A sufficient amount of energy stored in adipose tissue is required for the onset of puberty, especially in girls.[36] Leptin, a hormone produced by adipose tissue, is known to have a permissive role in the onset of puberty in girls.[37,38] The mechanism for the activation of hypothalamus–pituitary–gonadal axis by leptin at the beginning of puberty is indirect, and kisspeptin is believed to be one of the key mediators for leptin's action.[39] Correspondingly, the secular trend of earlier sexual maturation in girls is, at least partly, explained by the increasing prevalence of overweight in children. However, some of the girls in our study population may also have had isolated thelarche. Adiposity has been associated with not only puberty but also isolated thelarche that is thought to be a result of an increased aromatization of adrenal-derived androgens into estrogens in adipose tissue.[2,40] Since the focus of the present study was to investigate predictors for the earlier timing of thelarche, we did not differentiate between isolated thelarche and central puberty.

Strengths and limitations

The strengths of our study include the population sample of girls examined, the prospective study design, the reliable clinical assessment of breast development by a physician, and the careful assessment of child-related and parental predictors for earlier thelarche. The weaknesses of our study are that we lack information on the exact time of thelarche, the parental timing of puberty, and the duration of exposure to tobacco smoke. Another weakness of the study is that the age of the girls varied between 6 and 8 years. Moreover, girls with thelarche were slightly older than those without it. We therefore controlled baseline age and follow-up time in the statistical analyses.

CONCLUSIONS

Our results suggest that a higher body fat percentage and exposure to tobacco smoke are independent predictors for an earlier thelarche.

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AUTHOR CONTRIBUTIONS

J.E.S.J. and T.A.L. contributed to conception and design of the study; A.V. and T.M.S. to the acquisition of data; S.E.S. and A.V. to the analysis of data; and S.E.S., A.V., J.E.S.J., and T.A.L. to the interpretation of data. S.E.S. drafted the article, and all other authors have revised it critically for important intellectual content. All authors have approved this final version to be published.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

REFERENCES

1. Susman, E. J. et al. Longitudinal development of secondary sexual characteristics in girls and boys between ages 9 1/2 and 15 1/2 years. *Arch. Pediatr. Adolesc. Med.* **164**, 166–173 (2010).
2. Johansen, M. L. et al. Pubertal progression and reproductive hormones in healthy girls with transient thelarche. *J. Clin. Endocrinol. Metab.* **102**, 1001–1008 (2017).
3. Marshall, W. A., Tanner, J. M. Variations in the pattern of pubertal changes in girls. *Arch. Dis. Child.* **44**, 291–303 (1969).
4. Herman-Giddens, M. E. et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. *Pediatrics* **99**, 505–512 (1997).
5. Biro, F. M. et al. Onset of breast development in a longitudinal cohort. *Pediatrics* **132**, 1019–1027 (2013).
6. Downing, J. & Bellis, M. A. Early pubertal onset and its relationship with sexual risk taking, substance use and anti-social behaviour: a preliminary cross-sectional study. *BMC Public Health* **9**, 1–11 (2009).
7. Lakshman, R. et al. Early age at menarche associated with cardiovascular disease and mortality. *J. Clin. Endocrinol. Metab.* **94**, 4953–4960 (2009).
8. Copeland, W. et al. Outcomes of early pubertal timing in young women: a prospective population-based study. *Am. J. Psychiatry* **167**, 1218–1225 (2010).
9. Towne, B. et al. Heritability of age at menarche in girls from the Fels Longitudinal Study. *Am. J. Phys. Anthropol.* **128**, 210–219 (2005).
10. Gavela-Pérez, T., Garcés, C., Navarro-Sánchez, P., López Villanueva, L. & Soriano-Guillén, L. Earlier menarcheal age in Spanish girls is related with an increase in body mass index between pre-pubertal school age and adolescence. *Pediatr. Obes.* **10**, 410–415 (2015).
11. Sun, Y., Mensah, F. K., Azzopardi, P., Patton G. C. & Wake, M. Childhood social disadvantage and pubertal timing: a national birth cohort from Australia. *Pediatrics* https://doi.org/10.1542/peds.2016-4099 (2017).
12. Zhai, L. et al. Association of obesity with onset of puberty and sex hormones in Chinese girls: a 4-year longitudinal study. *PLoS ONE* **10**, 1–12 (2015).
13. D´Aloise, A. A., DeRoo, L. A., Baird, D. D., Weinberg, C. R. & Sandler, D. P. Prenatal and infant exposures and age at menarche. *Epidemiology* **24**, 277–284 (2013).
14. Windham, G. C. et al. Age at pubertal onset in girls and tobacco smoke exposure during pre- and postnatal susceptibility windows. *Epidemiology* **28**, 719–727 (2017).
15. Maisonet, M. et al. Role of prenatal characteristics and early growth on pubertal attainment of British girls. *Pediatrics* **126**, e591–e600 (2010).
16. Brix, N. et al. Maternal smoking during pregnancy and timing of puberty in sons and daughters: a population-based cohort study. *Am. J. Epidemiol.* **188**, 47–56 (2018).
17. Saari, A. et al. New Finnish growth references for children and adolescents aged 0 to 20 years: length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann. Med.* **43**, 235–248 (2011).
18. Cole, T. J., Bellizzi, M. C., Flegal, K. M. & Dietz, W. H. Establishing a standard definition for child overweight and obesity worldwide: international survey. *Br. Med. J.* **320**, 1240–1243 (2000).
19. Tanner, J. M., Goldstein, H. & Whitehouse, R. H. Standards for children's height at ages 2-9 years allowing for height of parents. *Arch. Dis. Child.* **45**, 755–762 (1970).
20. Sankilampi, U., Hannila, M. L., Saari, A., Gissler, M. & Dunkel, L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. *Ann. Med.* **45**, 446–454 (2013).
21. Tanner, J. M. *Growth at Adolescence* 2nd edn (Blackwell, Oxford, 1962).
22. Eloranta, A. M. et al. Dietary factors and their associations with socioeconomic background in Finnish girls and boys 6-8 years of age: the PANIC Study. *Eur. J. Clin. Nutr.* **65**, 1211–1218 (2011).
23. Kanerva, N., Kaartinen, N. E., Schwab, U., Lahti-Koski, M. & Männistö, S. The Baltic Sea Diet Score: a tool for assessing healthy eating in Nordic countries. *Public Health Nutr.* **17**, 1697–1705 (2014).
24. Reinehr, T. et al. Effect of weight loss on puberty onset in overweight children. *J. Pediatr.* **184**, 143–150 (2017).
25. Lawn, R. B., Lawlor, D. A. & Fraser, A. Maternal pre-pregnancy BMI, gestational weight gain and daughter's age at menarche: the Avon longitudinal study of parents and children. *Am. J. Epidemiol.* **187**, 677–686 (2017).
26. Holmgren, A. et al. Pubertal height gain is inversely related to peak BMI in childhood. *Pediatr. Res.* **81**, 448–454 (2017).
27. Prader, A. Delayed adolescence. *Clin. Endochrinol. Metab.* **4**, 143–155 (1975).
28. Rubin, C. et al. Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. *Paediatr. Perinat. Epidemiol.* **23**, 492–504 (2009).
29. Shrestha, A., Nohr, E. A., Bech, B. H., Ramlau-Hansen, C. H. & Olsen, J. Smoking and alcohol use during pregnancy and age of menarche in daughters. *Hum. Reprod.* **26**, 259–265 (2011).
30. Behie, A. M. & O'Donnell, M. H. Prenatal smoking and age at menarche: influence of the prenatal environment on the timing of puberty. *Hum. Reprod.* **30**, 957–962 (2015).
31. Deardorff, J. et al. Maternal pre-pregnancy BMI, gestational weight gain, and age at menarche in daughters. *Matern. Child Health J.* **17**, 1391–1398 (2013).
32. Gaillard, R., Felix, J. F., Duijts, L. & Jaddoe, V. W. V. Childhood consequences of maternal obesity and excessive weight gain during pregnancy. *Acta Obstet. Gynecol. Scand.* **93**, 1085–1089 (2014).
33. Lazar, L., Pollak, U., Kalter-Leibovici, O., Pertzelan, A. & Phillip, M. Pubertal course of persistently short children born small for gestational age (SGA) compared with idiopathic short children born appropriate for gestational age (AGA). *Eur. J. Endocrinol.* **149**, 425–432 (2003).
34. Persson, I. et al. Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. *Am. J. Epidemiol.* **150**, 747–755 (1999).
35. Hiatt, R. A. et al. Childhood socioeconomic position and pubertal onset in a cohory of multiethnic girls. *Cancer Epidemiol. Biomark. Prev.* **26**, 1714–1721 (2017).
36. Frisch, R. & Revelle, R. Height and weight at menarche and hypothesis of a critical body weightss and adolescent events. *Science* **169**, 397–399 (1970).
37. Rexford, S. A., Dushay, J., Flier, S. N., Prabakaran, D. & Flier, J. S. Leptin accelerate the onset of puberty in normal female mice. *Endocrinol. Metab.* **99**, 391–395 (1997).
38. Cheung, C. et al. Leptin is a metabolic gate for the onset of puberty in the female rat. *Endocrinology* **138**, 855–858 (1997).
39. Sanchez-Garrido, M. A. & Tena-Sempere, M. Metabolic control of puberty: roles of leptin and kisspeptins. *Horm. Behav.* **64**, 187–194 (2013).
40. Dumic, M., Tajic, M., Mardesic, D. & Kalafatic, Z. Premature thelarche: a possible adrenal disorder. *Arch. Dis. Child.* **57**, 200–203 (1982).