



POPULATION STUDY ARTICLE

Body mass index growth trajectories, early pubertal maturation, and short stature

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BACKGROUND: Childhood body mass index (BMI) trajectory classes are rarely linked to early puberty risk, particularly among Chinese children. We estimated early puberty risk across BMI trajectory classes, investigated factors contributing to pubertal development, and examined differences in final adult height between children exhibiting early and nonearly pubertal maturation across the classes.

METHODS: The Taiwan Children Health Study recruited 10-year-old children in 2010 from 14 Taiwanese communities and resurveyed them at age 11, 12, and 18 years. The study comprised 3109 children (50.4% boys) with available data for BMI (age 6–11 years) and pubertal stages (age 11, 12, and 18 years).

RESULTS: Classes 1–4 were persistently healthy weight, rapid BMI growth, chronically overweight/obese, and early transient overweight/obese. Children in class 3 exhibited the highest risk of early pubertal maturation. Puberty genetic score, low sleep quality, and high fat-free mass collectively explained 15% of the variance in Tanner stages among class 3 children. Early pubertal maturation was considered to cause short and tall stature in boys and girls, respectively.

CONCLUSIONS: Modifying sleep quality and fat-free mass may reduce early puberty risk in children with chronic overweight/obesity. Vigorous physical activity may reduce adiposity and increase the final adult height in the children.

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INTRODUCTION

The increasing global prevalence of childhood obesity and its effects on pubertal maturation have attracted considerable attention.¹ Among Chinese school-age children, the rates of overweight and obesity have increased from 1% in 1985 to 20% in 2014.² By contrast, the mean age at puberty has shown a decreasing trend since 1979.^{3,4} Recent large-scale studies on Chinese children have indicated that the age at spermatarche has decreased by 2 years,³ and the age at menarche has decreased by 0.8 years.⁴ The increasing prevalence of childhood obesity and decreasing ages of pubertal maturation have raised concerns regarding the critical period during which an increase in body mass index (BMI) has been frequently observed in the case of early pubertal maturation.⁵ Relatively extensive studies have demonstrated that British children with early voice change and early menarche appeared to experience rapid childhood BMI growth.^{6,7} In a Chinese study, infant BMI trajectory classes were associated with earlier pubertal onset, but the childhood BMI trajectory classes were rarely linked to early puberty. Whether childhood BMI trajectory classes differently affect pubertal timing in Chinese children warrants further investigation, particularly in Chinese boys.

Overall, the median age of menarche in Asian and Pacific Island children (12.2 years) has been reported to be earlier than in the Caucasian population (12.8 years).⁸ Conversely, Asian children do not experience pubertal maturation as rapidly as do children in Caucasian and Hispanic ethnic groups. The underlying reason for

the discordant timing in puberty across racial or ethnic strata remains unclear, but several theories have been proposed. The onset of puberty has been reported to be affected by genetics,⁹ nutrition,¹⁰ body composition,¹¹ and environmental factors.¹² Although nongenetic factors explain <50% of the variance in pubertal timing,⁹ they can be modified to prevent the early onset of puberty. The effects of most nongenetic factors on pubertal timing have been scattered in multiple literature reviews,^{9–12} but they have not been combined to determine the proportion of the variance that they collectively explain in pubertal development stages.

The relationship between pubertal maturation and final adult height has been studied in the past decade; however, conclusive results for both sexes have not been obtained.¹³ In British and Spanish girls, early menarche or early puberty were reported to potentially reduce the final adult height.^{13–15} When only boys were examined,¹³ one of these studies did not demonstrate a significant relationship between pubertal maturation and final adult height. Pubertal maturation and final adult height varied with ethnicity and geographical regions. However, the effect of pubertal maturation on final adult height has not been explored in the Chinese population. We conducted a nationwide longitudinal study (Taiwan Children Health Study [TCHS]) in 14 representative communities in Taiwan. Our aim was to estimate the risks of early pubertal maturation for each growth trajectory class in Chinese children and to estimate the contribution of pubertal genes, background, lifestyle, and body composition in the explanation of

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the variation in pubertal development stages. Finally, we examined the differences in final adult height between children exhibiting early and nonearly pubertal maturation across the classes.

Research gaps

- (1) Little is known about whether childhood BMI trajectory classes differently affect pubertal timing in Chinese children, particularly in Chinese boys.
- (2) Although genetic factors, nutrition, body composition, and environmental factors have been reported to affect the onset of puberty, they have not been combined to determine the proportion of the variance that they collectively explain in pubertal developmental stages.
- (3) The effect of pubertal maturation on final adult height has not been explored in the Chinese population.

Hypotheses

- (1) Children with higher BMI across various trajectory classes might experience earlier onset of puberty compared with children with normal BMI.
- (2) Nongenetic factors might explain a larger proportion of the onset of puberty than genetic factors.
- (3) Children with early puberty have a shorter adult height than those with normal puberty.

METHODS

Study design and data collection

We used data from the TCHS, which is a nationwide longitudinal study.^{16–19} The TCHS comprised two cohorts consisting of 7930 children from 14 representative Taiwanese communities. The first cohort enrolled children aged 12 years in 2007, and the second cohort enrolled children aged 10 years in 2010. The present study focused on the second cohort with an open-cohort design because it provided adiposity exposures and pubertal outcomes. Children in this cohort were resurveyed at the ages of 11, 12, and 18 years. Children (and their parents) who provided written informed consent and completed a written questionnaire were included. The TCHS protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of National Taiwan University Hospital.

Early pubertal maturation

Puberty outcomes were assessed at age 11, 12, and 18. We used the Tanner-derived composite stage²⁰ to derive sex-specific pubertal stages. It had schematic drawings of the five stages of secondary sexual characteristics (pubic hair and breast development for girls and pubic hair and genital development for boys). The two sex characteristics were combined and averaged to create a single score.²¹ According to previous literature,²² early pubertal maturation was defined as the onset of puberty stages at a younger age than the median age for that stage. We then defined early pubertal maturation by referencing median age provided by two large-scale population-based Chinese studies.^{22,23} In boys, voice change before the age of 13 years was defined as early voice change.⁷ The onset of menarche before the age of 12.43 years was defined as early menarche.²³

Difference between near final height and target height

The height at the age of 18 years and parental heights were reported by the participants (18 years old) and their parents. The

difference between near final height (near FH) and target height (TH) was defined as the TH (in cm) subtracted from the near FH (in cm). The near FH was defined as the height at 18 years old. The TH was determined using the corrected midparental height (CMH) method.²⁴ The CMH method has been widely used to predict TH (H_{mid}). The TH for boys is $H_{mid} = (H_{father} + H_{mother} + 13 \text{ cm})/2$, and that for girls is $H_{mid} = (H_{father} + H_{mother} - 13 \text{ cm})/2$. H_{father} and H_{mother} represent the heights of the father and mother, respectively.

Adiposity measures

Body weights and heights at the age of 10–12 years were measured annually from 2010 to 2012. Data from earlier years were required to determine the BMI trajectories; the weights and heights were retrospectively retrieved from the children's primary school health records. Self-reported weights and heights at age 18 years were obtained through telephone interviews. The BMI (kg/m^2) was calculated using the heights and weights reported and transformed into BMI z-scores according to the World Health Organization growth standards.²⁵ The BMI data were transformed into standardized BMI z-scores according to the Taiwanese growth standards for school-age children and adolescents. The prevalence of overweight and obesity was defined according to Taiwanese growth charts. A child being overweight was defined by a BMI between the 85th and 95th percentile of age- and sex-specific BMI, and childhood obesity was defined by BMI ≥ 95 th percentile of age- and sex-specific BMI according to the growth charts for children.

Fat mass and fat-free mass were determined using a medical body composition analyzer (IOI 353; Jawon Medical, Korea); the measurements were based on bioelectrical impedance. The flexible tape was used to measure the waist circumference (in cm) midway between the lowest rib and iliac crest, and the hip circumference (in cm) was measured at the level of the maximal posterior extension of the buttocks. The waist-to-hip ratio (%) was defined as the waist circumference divided by the hip circumference.¹⁷ Adiposity measures, except for BMI, were transformed into sex- and age-specific z-scores by using the TCHS cohort method.¹⁸

Other puberty-related factors

A review study indicated that genetic factors could determine 50–80% of the variation in pubertal timing.⁹ The intake of animal foods has been associated with earlier sexual development, whereas vegetable protein intake is related to delayed maturation.¹⁰ Fu et al.²⁶ reported that early menarche may be associated with higher speed fitness, leg and muscle power, and lower physical stamina. A recent study indicated that early menarche might have a short-term effect on sleep in adolescent girls.²⁷ Therefore, we included not only demographic factors but also genetic factors, dietary intake, sleep quality, and physical fitness.

Factors that have been documented as contributors to pubertal development, such as genetic factors, physical fitness, nutrition, body composition, and environmental factors, were included in the analysis. Eleven pubertal candidate single-nucleotide polymorphisms (SNPs) have been reported in meta-analyses of genome-wide association studies or studies on children. In our previous studies, we used DNA samples from the oral mucosa to identify these SNPs.^{16,18} Their allele dosage and their association with pubertal maturation are listed in Supplemental Table E1. Coefficients were applied to obtain the weighted allele dosage and calculate a genetic score for each child.

Standardized physical fitness tests consisted of an 800-m sprint, a jump-and-reach test, sit ups, and a sit-and-reach test.¹⁷ Based on the combination of these fitness indicators, we calculated a physical fitness index for each child. Other puberty-related factors, such as sleep quality, dietary intake, and demographic characteristics, were reported by children or their parents. The detailed procedures were previously published in one of our studies.¹⁷

Data analysis

Children whose childhood adiposity and sexual maturation status were available and that did not have any missing values were included in the statistical analyses. Subgroup analyses were conducted to clarify the sex-specific relationship between growth trajectory and early pubertal maturation.

Linear regression was used to analyze the effects of each SNP dosage. The SNP dosage in an individual was multiplied by the regression coefficient of the SNP for the associated pubertal developmental stage obtained from the regression analysis. The sum of the multiplied SNP doses in children was calculated to obtain the genetic score.

Individual BMI z-scores were used to determine each personalized trajectory across the ages of 6–12 years. The latent growth mixture model (LGMM) was applied to identify heterogeneous classes. To determine the number of classes, the Akaike¹⁷ information criterion, Bayesian information criterion (BIC) test, and Lo–Mendell–Rubin (LMR) test were used. Lower scores on these tests are preferred. Children were assigned to one of the four trajectory classes according to the highest posterior probability they exhibited. The reason for establishing four trajectory classes in the present study has been described in our previous studies.^{17,19} In brief, lower BIC test values, with significant results in the LMR test for a k class model compared with a k-1 class model, suggested that the model fitted the data adequately when an additional latent class was included (Table E2). LGMM analysis was conducted using the Mplus software version 7 (www.statmodel.com).

Generalized estimating equations (GEEs) have been widely applied for repeated-measures data in clinical trials and biomedical studies. The GEE approach is suitable when data of the same individual at distinct time points are used to investigate the correlation between exposures and outcomes. In our data, we used a GEE to fit a marginal model that examined the relationship between adiposity growth and early pubertal maturation. The marginal model was adjusted for parental education, family income, and birthweight.

GLMs are used for repeated-measures analysis of variance.²⁸ We used a GLM to relate the difference between near FH and TH (in cm) to trajectory classes and pubertal maturation. The Fisher’s protected least significant difference (LSD) method was used for post hoc multiple comparisons. The LSD method was used to calculate confidence intervals (CIs) for all pairwise differences among the means.²⁹

A linear mixed-effects model was used for identifying the critical contributions of pubertal developmental stages. For the mixed-effects model, a general and simple method was recommended for computing two types of R^2 values. Marginal R^2 values described the proportion of variance explained by the fixed-effects alone, and the conditional R^2 values described the proportion of variance explained by the fixed-effects plus the random factors. Only the marginal R^2 values were used because their proportion of variance is explained by potential contributions without time-varying factors.³⁰

Overweight and obesity were defined using the SAS software version 9.4 (www.sas.com). LGMM analysis was conducted using the Mplus software version 7 (www.statmodel.com). Other analyses were conducted using the R software (version 3.6.0).

RESULTS

The open-cohort study population comprised of 3457 children (Table 1). In all, 2879 and 3109 children were surveyed at age 11 and 12 years, respectively (Tables E3-1 and Tables E3-2). They were assigned to one among four latent BMI trajectory classes for which they exhibited the highest posterior probability (Fig. 1); the results were consistent with those of our previous studies.^{17,19} The distribution of children in the four classes was 48%, 20%, 29%, and

Table 1. Characteristic of the children in Taiwan Children Health Study.

Characteristics	3457 with available puberty data and BMI trajectory data	
	n or mean	% or SD
Baseline data		
At age 11 years	2867	82.9
At age 12 years	590	17.1
Sex (boys)	1746	50.5
Age (years)	11.3	0.5
Birthweight (kg)	3127.3	466.1
Breastfeeding (yes)	815	49.2
Household cigarette smoke (yes)	1192	50.1
Parental education		
High school or below	1713	49.8
College or university	1420	41.3
Post-graduate school	305	8.9
Family Income		
<600,000	1615	47.0
600,001–1,000,000	1235	35.9
>1,000,001	588	17.1
Height		
Fathers height (cm)	169.7	7.5
Mothers height (cm)	159.1	5.4
BMI (kg/m ²)	19.5	3.8
Trajectory classes		
Class 1	1651	47.7
Class 2	688	20.0
Class 3	1023	29.6
Class 4	95	2.7
Early pubertal maturation (boys)		
Voice breaking	61	4.2
Tanner stage 1	473	26.5
Tanner stage 2	967	55.4
Tanner stage 3	267	15.3
Tanner stage 4	46	2.6
Tanner stage 5	3	0.2
Early pubertal maturation (girls)		
Early menarche	352	24.4
Tanner stage 1	189	11.0
Tanner stage 2	1109	64.8
Tanner stage 3	360	21.0
Tanner stage 4	49	2.9
Tanner stage 5	4	0.2
Critical contributions of pubertal developmental stages		
Genetic index (score, 10 ⁻²)	5.3	1.6
Sleep quality index (score)	5.1	2.8
Fat-free mass (kg)	33.9	6.1
Adult height at 18 years (cm)	166.1	8.5

All data are presented as mean ± standard deviation (SD) or numbers (%). The number of participants do not add up to the total number because of missing data

3% in the persistently healthy weight (class 1), rapid BMI growth (class 2), chronically overweight/obese (class 3), and early transient overweight/obese (class 4) classes, respectively. The prevalence of early pubertal maturation in boys and girls was 11.6% and 9.8%,

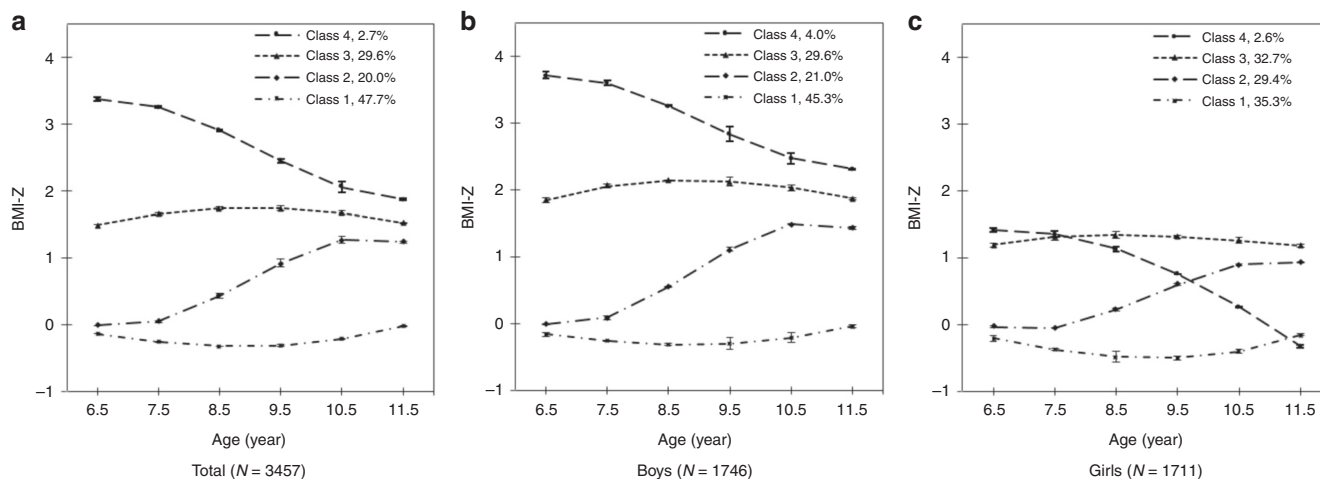


Fig. 1 Longitudinal BMI z-score trajectory classes estimated using latent growth mixture modeling.

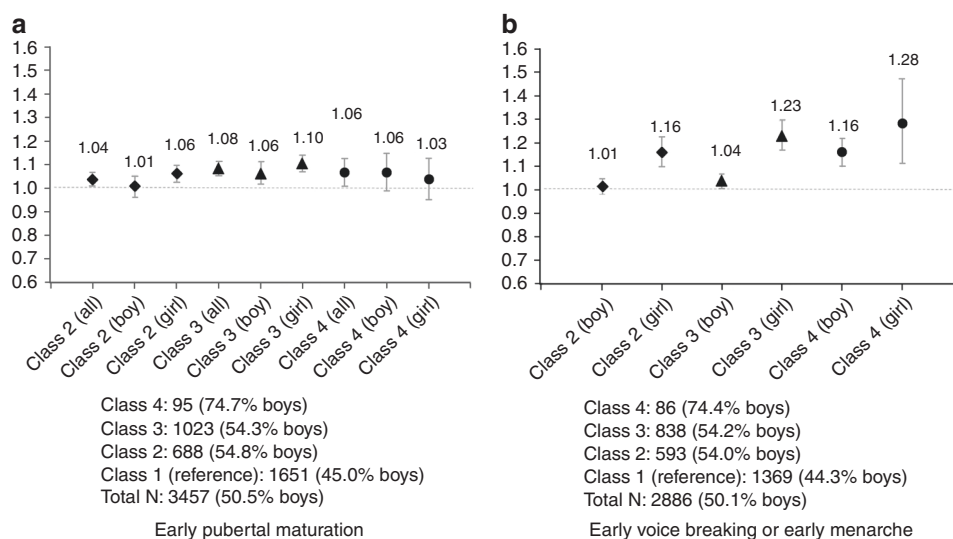


Fig. 2 Risk of early pubertal maturation in each trajectory class compared with the normative growth class. Reference class = class 1 (the normative growth class); OR = odds ratio, adjusted for parental education, family income, and birthweight; CI = confidence interval; and BMI = body mass index (kg/m^2).

respectively, at the age of 11 years and 24.1% and 6.6%, respectively, at the age of 12 years. Between the age of 11 and 12 years, 4.1–12.1% of boys experienced a voice change (early voice change), and 24.2–31.7% of girls experienced menarche (early menarche).

BMI trajectory and pubertal maturation

Figure 2 presents the effect of BMI trajectory classes on pubertal progression, with respect to early pubertal maturation (Fig. 2a) and to early voice change and early menarche (Fig. 2b). Class 2 (rapid BMI growth) exhibited a higher risk of early pubertal maturation than did class 1 (persistently healthy weight) (odds ratio [OR] = 1.04, 95% confidence interval [CI]: 1.01–1.06). The results of the subgroup analysis revealed that girls but not boys in class 2 were more likely to experience early maturation (OR = 1.06, 95% CI: 1.03–1.10) than those in class 1. Moreover, the risk of early menarche was higher in class 2 than in class 1 (OR = 1.16, 95% CI: 1.10–1.22). Figures E1 and E2 were used to confirm the main finding (Fig. 2). Figures E1 and E2 demonstrate the risk of early pubarche and early telarche/gonadarche (respectively) in each trajectory class compared with the normative growth class using

Tanner stages for pubic hair and breast or genital region. In Fig. E1, children in BMI trajectory classes 3 and 4 both had significantly increased risk of early pubic hair maturation. Class 4 children have the highest risk of early pubarche, especially the girls. While in Fig. E2, class 3 girls have the highest risk of early telarche, whereas class 2 and 3 boys have the highest risk of early gonadarche.

Children in class 3 (chronically overweight/obese) exhibited the highest risk of early pubertal maturation than those in class 1 (OR = 1.08, 95% CI: 1.05–1.11) (Fig. 2a). An additional sex-based subgroup analysis revealed that boys (OR = 1.06, 95% CI: 1.02–1.11) and girls (OR = 1.10, 95% CI: 1.07–1.14) in class 3 exhibited the highest risk of early pubertal maturation. The risk of early voice change in boys (OR = 1.04, 95% CI: 1.01–1.07) and the risk of early menarche in girls (OR = 1.23, 95% CI: 1.17–1.30) were higher in class 3 than in the other classes (Fig. 2b).

Children in class 4 (early transient overweight/obese) exhibited a higher risk of early pubertal maturation than those in class 1 (OR = 1.06, 95% CI: 1.01–1.03) (Fig. 2a). In the subgroup analysis (Fig. 2b), boys (OR = 1.16, 95% CI: 1.10–1.22) in class 4 exhibited the highest risk of early voice change, and girls in class 4 exhibited the highest risk of early menarche (OR = 1.28, 95% CI: 1.11–1.47).

Table 2. Critical contributors to pubertal developmental stages (class 3, $N = 1015$).

Parameter	Genetic score (G)			Poor sleep quality (P)			Fat-free mass (F)			Marginal ^a R^2	Conditional ^a R^2
	Estimate	Std. error	P value	Estimate	Std. error	P value	Estimate	Std. error	P value		
Total											
Genetic score (G)	0.10	0.02	2.0×10^{-10}							0.03	0.34
Poor sleep quality (P)				0.05	0.01	6.0×10^{-11}				0.03	0.39
Fat (F)							0.05	4.0×10^{-3}	2.0×10^{-16}	0.11	0.47
G + P	0.10	0.02	1.7×10^{-9}	0.05	0.01	1.5×10^{-10}				0.07	0.39
P + F				0.04	0.01	2.5×10^{-7}	0.04	4.6×10^{-3}	2.0×10^{-16}	0.10	0.47
G + F	0.12	0.02	9.9×10^{-15}				0.05	4.1×10^{-3}	2.0×10^{-16}	0.16	0.48
G + P + F	0.12	0.02	2.9×10^{-13}	0.04	0.01	1.1×10^{-7}	0.04	4.4×10^{-3}	2.0×10^{-16}	0.15	0.47
Boys											
Genetic score (G)	0.06	0.02	0.01							0.01	0.30
Poor sleep quality (P)				0.06	0.01	8.3×10^{-7}				0.03	0.35
Fat (F)							0.07	0.01	2.0×10^{-16}	0.18	0.47
G + P	0.05	0.02	0.05	0.06	0.01	7.4×10^{-7}				0.04	0.36
P + F				0.03	0.01	1.3×10^{-3}	0.06	0.01	2.0×10^{-16}	0.17	0.46
G + F	0.04	0.02	0.10				0.06	0.01	2.0×10^{-16}	0.18	0.47
G + P + F	0.03	0.02	0.21	0.04	0.01	1.1×10^{-3}	0.06	0.01	2.0×10^{-16}	0.17	0.46
Girls											
Genetic score (G)	0.06	0.03	0.03							0.01	0.35
Poor sleep quality (P)				0.05	0.01	5.4×10^{-6}				0.03	0.38
Fat (F)							0.06	0.01	2.0×10^{-16}	0.15	0.47
G + P	0.08	0.03	0.01	0.05	0.01	3.0×10^{-6}				0.04	0.38
P + F				0.04	0.01	2.1×10^{-4}	0.05	0.01	2.5×10^{-14}	0.14	0.45
G + F	0.07	0.03	0.02				0.06	0.01	2.0×10^{-16}	0.16	0.47
G + P + F	0.07	0.03	0.01	0.04	0.01	1.2×10^{-4}	0.05	0.01	2.3×10^{-14}	0.16	0.46

^aThe marginal R^2 described the proportion of variance explained by the fixed-effects alone, and the conditional R^2 described the proportion of variance explained by fixed-effects and random factors

Factors contributing to pubertal development in class 3

We further analyzed in detail the contributors to pubertal staging in the trajectory class with the highest early pubertal maturation risk, namely class 3. Regression coefficients between pubertal developmental stages and contributions are listed in Table 2 and Table E4-3. The contributions were categorized as background, lifestyle, and body composition. To identify critical contributions in each category, marginal R^2 and P values were used. Higher R^2 and lower P values were preferred. The genetic score, sleep quality, and fat-free mass explained 3%, 3%, and 11% of the variance in the pubertal developmental stages, respectively. For example, the regression coefficients of the genetic risk score with the outcome implied that for each 1% increase in the genetic score, we observed a 0.1 increase in the regression coefficient in the Tanner stage ($P = 2.0 \times 10^{-10}$). Children with poor sleep quality (Pittsburgh Sleep Quality Index [PSQI] ≥ 7) had earlier Tanner stages than those with a high or normal quality of sleep (PSQI < 7) by 0.05 stages ($P = 6.0 \times 10^{-11}$). For each 1-kg increase in fat-free mass, we observed a 0.05 increase in the regression coefficient in the Tanner stage ($P = 2.0 \times 10^{-16}$). In total, 15% of the variance for pubertal developmental stages was explained by combining genetic score, poor sleep quality, and fat-free mass. Combining all the critical contributors explained 17% and 16% of the variance in the pubertal developmental stages in boys and girls, respectively, in class 3.

Effects of BMI trajectory and early pubertal maturation on the difference between near FH and TH

Figure 3 presents the interaction effects of BMI trajectory classes and pubertal maturation on the difference between near FH and TH. In classes 1–3, children with early pubertal maturation exhibited a smaller difference between near FH and TH than

did those with normal pubertal maturation (–0.24 to –0.99 cm). In class 4, children with early pubertal maturation exhibited a greater difference between near FH and TH than those with normal pubertal maturation (8.12 cm). An additional sex-based subgroup analysis revealed similar results in boys. However, girls in classes 1–3 with early pubertal maturation appeared to have a taller stature than did those with normal pubertal maturation.

Normal-weight early mature children (class 1) had a worse near FH compared to their TH, whereas early mature children in classes 2–4 were taller than their TH. Compared to normal maturer, early maturer had a decrease height gain, while subgroup analysis showed that this was true only for boys, as early maturer girls in classes 1–3 had an increased height gain compared to normal maturer. All early menarche children in class 4 overcame their target much more than normal maturer children, regardless of gender.

DISCUSSION

Using a suitable statistical technique, namely LGMM, we identified the following four BMI trajectory classes in Taiwanese children aged 6–12 years:^{17,19} persistently healthy weight, rapid BMI growth, chronically overweight/obese, and early transient overweight/obese. From the results, children with chronic overweight/obesity clearly exhibited the highest risk of early pubertal maturation. Moreover, genetic scores, sleep quality, and fat-free mass was considered critical factors contributing to early pubertal developmental stages. To our knowledge, this is the first study to describe the long-term effects of various growth patterns and early pubertal maturation on near FH as well as to analyze the critical contributors to pubertal stages.

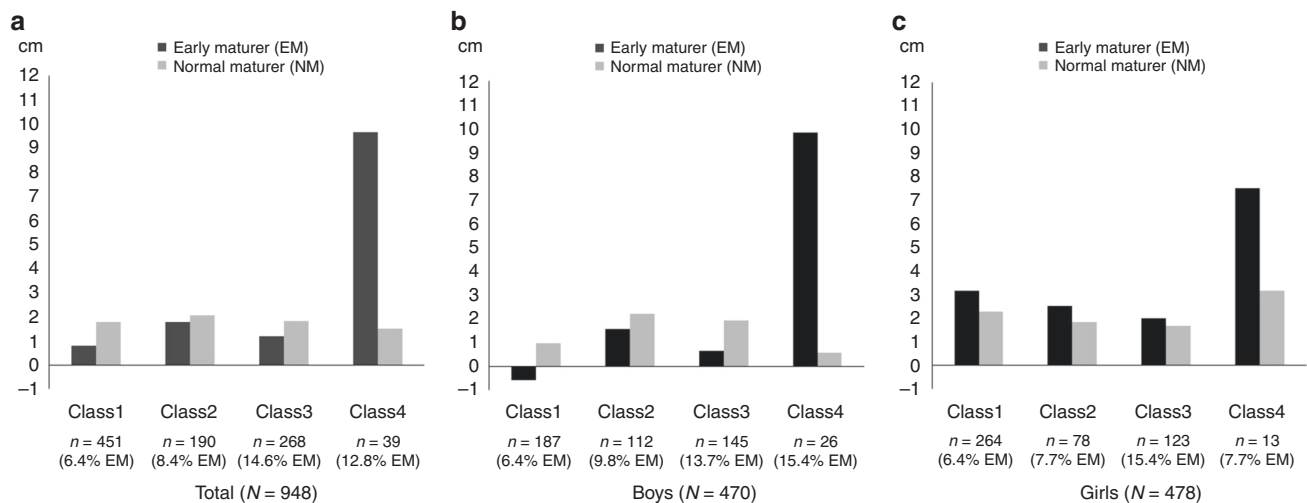


Fig. 3 Difference in height between early and normal pubertal maturers at age 18 years. Height difference = actual height at 18 years old – target height; target height for boys (in cm) = (father’s height + mother’s height + 13) ÷ 2; target height for girls (in cm) = (father’s height + mother’s height – 13) ÷ 2.

Two studies have retrospectively described BMI growth by categories based on the timing of secondary sexual characteristics in the British population.^{6,7} They have reported that boys with earlier voice change experienced a rapid weight gain between the age of 2 and 14 years;⁷ girls with earlier menarche also presented an acute gain in BMI from birth to 7 years old.⁶ Similar findings were reported in a prospective US cohort in which a positive correlation was observed between the rapid gain in BMI and the risk of early pubertal initiation among boys.³¹ The findings of the current study support the idea that rapid BMI growth (class 2) is significantly associated with an increase in the risk of early pubertal maturation in girls but not in boys (Fig. 2b). Ethnicity affected the relationship between rapid BMI growth and the risk of early pubertal maturation.^{32,33} In our study, Figs. E1 and E2 were used to confirm the main finding (Fig. 2). In Fig. E1, children in BMI trajectory classes 3 and 4 both had significantly increased risk of early pubic hair maturation. While in Fig. E2, only girls in BMI trajectory class 3 suffered from an increased risk of early breast maturation. The effects of adiposity on different stages and tempo of pubertal development might vary by gender. In girls, the glandular breast tissue appearance is the initial sign of estrogenic activity, whereas the onset of pubic hair growth is attributable to the onset of adrenal gland and androgen production. Sometimes, breast development does not necessarily indicate the onset of central puberty in every case, because it could also be an effect of estrogens derived from adipose tissue. Previous Chinese studies also revealed that the effects of obesity on onset and velocity of puberty growth might be different.^{3,34} While obesity triggers an earlier onset of puberty, it does not necessarily influence the later stage of pubertal growth, such as spermatheca.

When we compared our findings to those of previous studies, we highlighted that a chronically overweight/obese status exhibited the highest risk of early pubertal maturation in Chinese children. A chronically overweight/obese status implies that persistently high BMI growth is more likely to cause early pubertal maturation. In addition to long-term BMI changes, body composition plays a critical role in pubertal onset.^{7,16,32,35} In the present study, when both girls and boys were examined, fat mass and fat-free mass appeared to exert the strongest effect on pubertal developmental stages (Supplementary Table E4-3). However, when girls and boys were examined separately, the strong relationship between fat mass and pubertal developmental stages was observed only in girls (Supplementary Table E4-3). The differences in the fat and fat-free distribution during the pubertal

years are sex-related.^{32,35} These findings were similar to those of previous studies, which demonstrated that girls gain relatively large amounts of fat mass during pubertal years,^{35,36} whereas boys acquire relatively large amounts of fat-free mass.³⁵ Previous studies have also indicated that girls generally exhibit an excess of gynoid fat pattern and fat deposition on the hips and thighs during puberty, whereas boys may exhibit an android fat distribution and fat deposition on the abdomen.^{32,35}

In the present study, genetic scores, low sleep quality, and fat-free mass were critical contributors to pubertal developmental stages in the chronically overweight/obese class. According to our literature review, this is the first study to combine these critical contributors to explain 15% of the variance in the pubertal stages. Although several identified SNPs have been reported to underlie pubertal timing and secondary sexual characteristics,³⁷ they did not explain >1% of the variance in the pubertal stages in both sexes in the present study. This may imply that lifestyle and environmental factors play crucial roles in pubertal development.^{12,38,39} The present study combined genetic scores and lifestyle factors to explain 4% of the variance in the pubertal stages. Moreover, previous studies have frequently indicated that body composition is a critical contributor to pubertal timing.^{7,16,32,35} When body composition was included in the prediction model in the present study, the fat-free mass explained >15% of the variance in pubertal stages in both sexes. An increase in fat-free mass (by ~1 kg) per year elevated 0.07 and 0.06 pubertal stages in boys and girls, respectively. A slight increase in fat mass (by ~1 kg) per year increased 0.04 pubertal stages only in girls.

Previous studies have assumed that a reduced final adult height might be explained by early puberty.^{13–15} Our findings were inconsistent with these assumptions and indicated that children with early pubertal maturation in classes 1–3 exhibited a similar difference between near FH and TH. Contrary to the assumption, our finding revealed that children with early pubertal maturation in class 4 exhibited a greater difference between near FH and TH than those with normal pubertal maturation. When boys and girls were examined separately, our findings demonstrated that most boys with early pubertal maturation in classes 1–3 did not achieve midparental heights. The relationship between pubertal maturation and final adult height in boys remains unclear.¹³ By contrast, most previous studies have reported consistent findings that early menarche in girls is likely to have lower final adult height. Our findings according to which girls with early pubertal maturation

had a greater difference between near FH and TH than those with normal pubertal maturation in classes 1–4 were inconsistent with those of previous studies.^{13–15} Moreover, the near FHs of boys and girls in class 4 with early pubertal maturation were greater than their midparental heights. Although children in class 4 were more likely to enter puberty early, they took actions to grow taller and faster. According to our previous findings, children in class 4 engaged in relatively high levels of moderate to vigorous physical activity during their prepubertal childhood.¹⁷ Other studies have reported a possible mechanism to explain that phenomenon stating that the determination of exercise training volume and intensity may inhibit the secretion of luteinizing and follicle-stimulating hormones as well as estrogen and progesterone,⁴⁰ delay pubertal timing and bone aging,⁴⁰ and provide more space for height growth.

This study has multiple strengths. The first was the study's longitudinal design; it included children up to the age of 18 years with repeated measurements of BMI and outcomes of pubertal maturation. It was also the first to use LGMM to examine the effects of heterogeneous BMI trajectory classes on early pubertal maturation in Chinese children. Pubertal developments are complex processes and are characterized by changes involving hormonal, physical, and cognitive factors.⁴¹ By using comprehensive measurements of multiple factors related to puberty, we explored the critical factors contributing to describe pubertal stages.²⁴ Moreover, we tested our hypothesis using three outcomes (pubertal stage, the timing of voice change for boys, and age of menarche for girls), and the results from these outcomes were consistent, thus confirming the robustness of our findings. This study may be valuable to clinicians because critical genetic, background-related, and lifestyle-related factors may explain the percentage of variance in early pubertal maturation. We also used stratified analysis to observe the near FHs and to provide clinical information on short stature prevention. However, our study was limited by the fact that we did not include the timing of maternal menarche as a covariate. Nonetheless, we included the genetic score as a covariate, which can solve this inherited issue. Moreover, our study was limited by the lack of reference median age at voice breaking for the Chinese population. Instead, we determined early voice breaking by referring to a British study.⁷ Because body weight and height data were based on participant self-report, the data may appear on record bias. The other limitation of our study was that the assessment of pubertal development was directly reported by the children. In large-scale epidemiological studies, direct examination of participant to determine pubertal stages is not easily practical. However, we have invited a pediatric endocrinologist to participate in the validation study to provide standardized assessment of pubertal development.⁴² There is consistent agreement for pubertal stage between children self-report and physician inspection.

Among chronically overweight children, boys with early pubertal maturation happened to have a reduced height gain, whereas girls with early pubertal maturation were much taller than their THs compared to normally mature girls. Children with transient overweight had the highest risk or early voice breaking (boys) or early menarche (girls) and, regardless of gender, reached a higher near FH compared to their targets. Chronically overweight boys are encouraged to engage physical activity to reduce their adiposity and to increase the near FH.

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AUTHOR CONTRIBUTIONS

H.-Y.F. contributed to the statistical analysis, interpretation of data, manuscript writing, and data management. R.-H.H. contributed to critically revising this manuscript for intellectual content. C.Y. reviewed the study design and contributed to the interpretation of data. Y.-C.C. and Y.L.L. contributed to the cohort data collection and supervised the study.

ADDITIONAL INFORMATION

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