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Reduced pubertal growth in children with obesity regardless of pubertal timing

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Abstract. Childhood obesity affects both pubertal growth and pubertal timing. We evaluated pubertal timing-mediated effects of childhood obesity on pubertal growth. This retrospective, representative-population-based cohort study included 6,733 boys and 6,916 girls born between April 1975 and March 1976 in Akita Prefecture, Japan. Individual changes in height standard deviation score between 7 and 17 years (ΔHtSDS), body mass index Z-score at 7 years (BMIZ), and estimated age at peak height velocity (ÂPHV) were used as surrogate indicators of pubertal growth, childhood obesity and pubertal timing, respectively. ÂPHV-mediated effect of BMIZ on ΔHtSDS was evaluated, and non-ÂPHV-mediated effect was calculated. Based on BMIZ, participants were categorized into three groups (underweight, normal-weight and obese groups), and the differences in ΔHtSDS between obese and normal-weight or underweight groups and ratios of non-ÂPHV-mediated effect were determined. ΔHtSDS values in the obese group were lower by 1.23 in boys and 1.17 in girls than those in the underweight group and by 0.87 in boys and 0.85 in girls than those in the normal-weight group. Non-ÂPHV-mediated effect on the reduced ΔHtSDS in the obese group compared to the underweight and normal-weight groups accounted for 68% and 71% in boys and 59% and 64% in girls, respectively. Thus, childhood obesity is associated with reduced pubertal growth regardless of pubertal timing. This reduced pubertal growth observed in children with obesity could be more affected by non-pubertal timing-mediated effect rather than pubertal timing-mediated effect.

Key words: Pubertal growth, Childhood obesity, Pubertal timing, General population, Age at peak height velocity

PUBERTY induces a dramatic change in height. A pubertal increase in height, called growth spurt, accounts for 17%–18% of adult height [1]. Puberty shows the second-highest period of growth in the infancy-childhood-puberty growth model, the most accepted human growth model [2]. The wide individual variation in pubertal timing is associated with childhood and adult heights. Previous studies have reported that children with early puberty were taller during childhood and have similar or slightly shorter adult height than those with normal or later maturation [3-6].

Children with obesity manifest a specific growth pattern with regard to height, that is accelerated linear growth during childhood, reduced height gain during puberty, and normal or near-normal adult height [7-11]. Childhood obesity can also alter pubertal timing. There is clear evidence that childhood obesity is associated with early pubertal timing in girls, such as early breast development and age of pubarche and menarche [3, 10, 12-17]. In boys, this concept remains controversial: some studies indicated the relationship between obesity and early puberty [18-20], whereas others indicated the association between obesity and late maturation [9, 13, 14]. One study suggested early puberty for overweight and late puberty for obesity [21]. In a recent study using another growth model, children who are overweight and obese in both sexes underwent early puberty compared with children with normal weight and who are underweight [11].

Several studies have investigated the relationship between childhood obesity and pubertal growth; however, it remains unclear how childhood obesity affects pubertal growth in terms of pubertal timing. This study aims to evaluate pubertal timing-mediated effects of

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childhood obesity on pubertal growth.

Participants and Methods

The study was approved by the institutional review board of the National Center for Child Health and Development on 19 November 2018 (permit no: 1991).

This retrospective representative-population-based cohort study included 13,649 school children (6,733 boys and 6,916 girls) born between April 1975 and March 1976 in Akita Prefecture, Japan. The Japanese Ministry of Internal Affairs and Communications reported that the number of births in the region was ~17,500 during the same period, elementary and junior high schools had an ~100% attendance rate and 95% of junior high school graduates advanced to senior high school in 1990. Nationwide research shows that children living in Akita Prefecture are taller and have a higher frequency of obesity than those living other regions; however, Japan is mostly a monoethnic country and there is practically little difference in height between this region and the entire country.

Trained school staff measured the individual height and weight in underwear to the nearest 0.1 cm with a stadiometer and nearest 0.1 kg with a standardized weight scale, respectively, in accordance with the Japanese law, referred to as the School Health and Safety Act [22]. Measurements were taken annually for 11 consecutive years (from ages 7 to 17 years). The individual body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared. Individual height standard deviation scores (HtSDS) at 7 and 17 years and BMI Z-score at 7 years (BMIZ) were calculated on the basis of respective Japanese standard values [23, 24]. Individual changes in height (ΔHt) and HtSDS between 7 and 17 years (ΔHtSDS) were calculated as follows:

ΔHt = Ht at 17 years – Ht at 7 years

ΔHtSDS = HtSDS at 17 years – HtSDS at 7 years

In this study, individual ΔHtSDS was used as a surrogate indicator of pubertal growth to clarify the effect of childhood obesity on pubertal growth because the ages of 7 and 17 are usually considered as pre- and post-pubertal stage, respectively, and height SDS does not significantly change between mid-childhood and the onset age of puberty. The participants were categorized into the following three groups on the basis of BMIZ: underweight, <5th percentile; normal-weight, ≥5th percentile and ≤95th percentile; obese, >95th percentile.

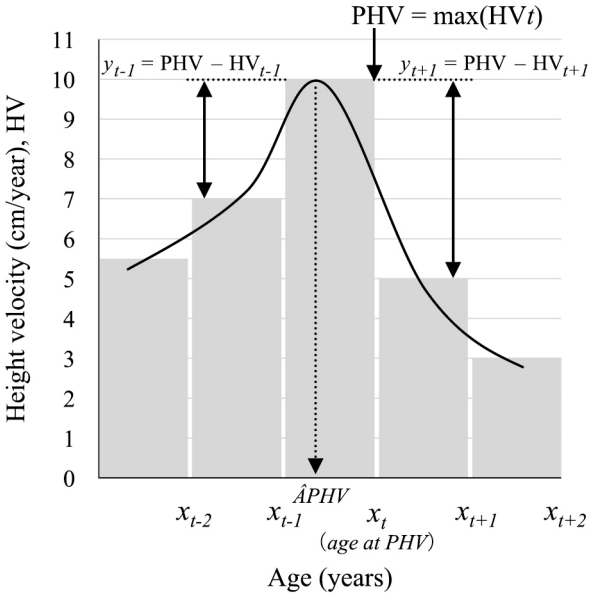


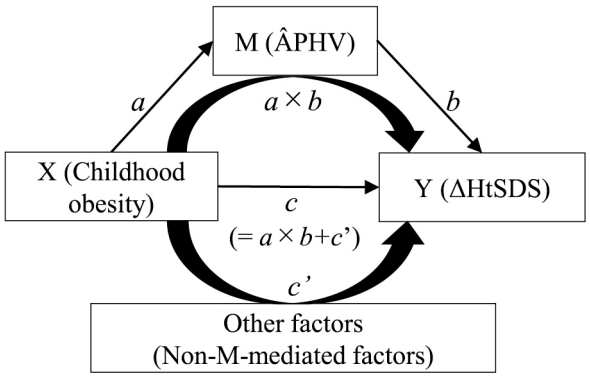
Fig. 1 Method of calculating individual estimated age at peak height velocity (ÂPHV) using the formula $x_t - \{y_{t+1}/(y_{t-1} + y_{t+1})\}$ was used. The solid line represents the assumed curve of HV.

Estimated Age at Peak Height Velocity (Fig. 1)

The estimated age at peak height velocity (ÂPHV) was considered as a surrogate indicator of pubertal timing, because it is a marker of pubertal somatic maturation and it occurs at mid-puberty after acceleration phase before deceleration phase. Individual ÂPHV was calculated as follows: First, height velocity (HV) was calculated as the difference in height between two age points, 1 year apart. Second, peak HV (PHV) was defined as the maximum HV. Finally, ÂPHV was determined on the basis of the difference between PHV and the HVs 1 year before and after the child's age at PHV. The following formula was used: $x_t - \{y_{t+1}/(y_{t-1} + y_{t+1})\}$, where x_t is age at PHV, y_{t-1} is the absolute value of the difference between PHV and HV 1 year before the age at PHV, and y_{t+1} is the absolute value of the difference between PHV and HV 1 year after the age at PHV.

Statistical Analysis

The differences in ÂPHV, Ht and HtSDS at 7 and 17 years, ΔHt, and ΔHtSDS among underweight, normal-weight, and obese groups were assessed using one-way analysis of variance (ANOVA), followed by Bonferroni's *post-hoc* comparisons test. Fig. 2 illustrates mediation framework for our hypothetical model. We first evaluated if ÂPHV met statistical conditions that were necessary for a mediator using the following three steps: 1)



1) X → Y (Y = intercept + c X)
2) X → M (M = intercept + a X)
3) X, M → Y (Y = intercept + b M + c' X)

Non-M-mediated effect of X on Y = c'
M-mediated effect of X on Y = $a \times b = c - c$'

Fig. 2 Mediation framework for our hypothetical model. *a*: Effect of X (Childhood obesity) on M (ÂPHV), *b*: Effect of M (ÂPHV) on Y (ΔHtSDS), *c*: Total effect of X on Y, *c*': Non-M-mediated effect of X on Y. Abbreviations: ÂPHV, estimated age at peak height velocity; ΔHtSDS; change in height standard deviation score between 7 and 17 years, that is (HtSDS at 17 years–HtSDS at 7 years).

establish that X (childhood obesity) is significantly associated with Y (ΔHtSDS), 2) establish that X is significantly associated with M (ÂPHV), and 3) establish that M is independently associated with Y after controlling for X. The non-parametric bootstrap technique with 2000 replications was conducted to estimate the 95% corrected confidence interval (CI) [25, 26]. Thereafter, we performed mediation analysis to quantify the percent of the relationship between childhood obesity and ΔHtSDS through the mediator (ÂPHV: $a \times b$), and through non-ÂPHV-mediated effect (c'). The percent of the non-ÂPHV-mediated effect was calculated using the formula: 100 – the percent of the ÂPHV-mediated effect. In the mediation analysis, simple linear regression with 'a common slope' can be used (Fig. 3A), if comparison groups (obese and normal-weight or underweight groups) met the following two conditions [26]: i) There are significant differences in Y among X even after controlling the effect of M, which indicates partial mediation of X on Y through M, and ii) There are no interactions between X and M, which indicates the equal effect of M on Y across the values of X (if there is a significant interaction, the effect of M on Y is a function of X and it changes as the value of X changes.).

Stata 14.2 software (StataCorp, Texas, USA) was used for all analyses. All statistical tests were two tailed, and a p value of <0.05 was considered statistically significant.

Results

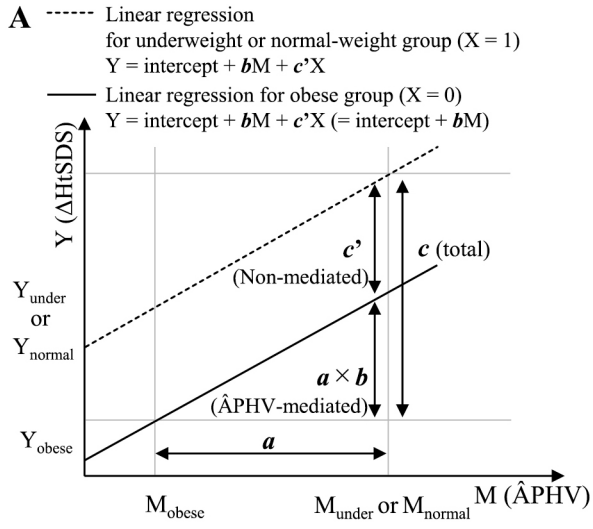
Individual ÂPHV values were evenly distributed for both sexes (Supplementary Fig. 1). Overall, mean ± SD of ÂPHV was 12.77 ± 1.03 years for boys and 10.88 ± 1.01 years for girls. Of the 6,733 boys, 2.3%, 94.6% and 3.1% and of the 6,916 girls, 2.6%, 94.6% and 2.8% were underweight, normal-weight and obese, respectively. Table 1 shows a comparison of the descriptive variables and p value by one-way ANOVA among the three groups. Significant differences were observed in Ht and HtSDS at 7 years, ΔHt, ΔHtSDS, and ÂPHV in both sexes, but there were no differences in Ht and HtSDS at 17 years in both sexes. In the obese group, boys and girls were 6.66 and 6.55 cm taller, respectively, at 7 years than those in the underweight group and 5.10 and 4.58 cm taller, respectively, than those in the normal-weight group. However, the three groups had similar height at 17 years in both sexes because ΔHt was smaller in the obese group and larger in the underweight group. ÂPHV in the obese group was earlier than that in the underweight group by 0.88 years in boys and 1.15 years in girls, and earlier than that in the normal-weight group by 0.57 years in boys and 0.74 years in girls.

Childhood obesity was significantly associated with ΔHtSDS in both sexes (all $p < 0.001$, compared to underweight and normal-weight groups). In addition, childhood obesity was significantly associated with ÂPHV in both sexes (all $p < 0.001$). ÂPHV was independently associated with ΔHtSDS after controlling for childhood obesity in both sexes (all $p < 0.001$). Next, the differences in ΔHtSDS among underweight, normal-weight, and obese groups remained significant even after controlling for the effect of ÂPHV ($F_{(2,6729)} = 112.83$, $p < 0.001$, for boys; $F_{(2,6912)} = 103.69$, $p < 0.001$, for girls). There was no interaction between the groups and ÂPHV ($F_{(2,6727)} = 1.22$, $p = 0.297$ for boys; $F_{(2,6910)} = 1.78$, $p = 0.169$ for girls). The two conditions (i and ii) were met, and ÂPHV-mediated ($a \times b$), non-ÂPHV-mediated (c'), and total (c) effects of obese group on ΔHtSDS compared to underweight and normal-weight groups are described in Fig. 3B. For boys, ΔHtSDS in the obese group was less by 1.23 (95% CI = 1.05, 1.39, $p < 0.001$) than that in underweight group, and the non-ÂPHV-mediated effect accounted for 68%. ΔHtSDS in the obese group was less by 0.87 (95% CI = 0.76, 0.99, $p < 0.001$) than that in the normal-weight group, and the non-ÂPHV-mediated effect accounted for 71%. For girls, ΔHtSDS in the obese group was less by 1.17 (95% CI = 1.01, 1.32, $p < 0.001$) than that in the underweight group, and the non-ÂPHV-mediated effect accounted for 59%. ΔHtSDS in the obese group was less by 0.85 (95% CI = 0.74, 0.97, $p < 0.001$) than that in the underweight group,

Table 1 Descriptive values of participants overall and in each group

Boys	Oveall (*n* = 6,733)	Underweight (*n* = 155)	Normal-weight (*n* = 6,368)	Obese (*n* = 210)	*p* value
BMI (kg/m^2) at 7 years	15.89 (1.76)	13.17 (0.40)	15.75 (1.26)	22.28 (2.16)	
BMIZ	–0.06 (0.83)	–2.09 (0.50)	–0.08 (0.69)	+2.05 (0.29)	
ÂPHV (years)	12.77 (1.03)	13.09 (1.01)	12.78 (1.02)	12.21 (1.08)	<0.001*
Ht (cm) at 7 years	122.22 (5.03)	120.54 (5.25)	122.10 (4.94)	127.20 (5.00)	<0.001*
Ht (cm) at 17 years	171.33 (5.63)	171.49 (6.08)	171.30 (5.61)	172.16 (5.69)	0.091
ΔHt (cm)	49.11 (3.91)	50.94 (3.95)	49.20 (3.81)	44.96 (4.22)	<0.001*
HtSDS at 7 years	–0.04 (1.04)	–0.39 (1.07)	–0.06 (1.02)	+0.96 (1.03)	<0.001*
HtSDS at 17 years	+0.11 (0.97)	+0.13 (1.05)	+0.10 (0.97)	+0.25 (0.98)	0.085
ΔHtSDS	**+0.15 (0.78)**	**+0.52 (0.77)**	**+0.17 (0.76)**	**–0.71 (0.82)**	**<0.001***
Girls	Oveall (*n* = 6,916)	Underweight (*n* = 176)	Normal-weight (*n* = 6,545)	Obese (*n* = 195)	*p* value
BMI (kg/m^2) at 7 years	15.80 (1.84)	12.98 (0.30)	15.69 (1.37)	22.30 (2.84)	
BMIZ	–0.07 (0.82)	–1.97 (0.31)	–0.09 (0.69)	+2.00 (0.31)	
ÂPHV (years)	10.88 (1.01)	11.30 (0.92)	10.89 (1.00)	10.15 (1.02)	<0.001*
Ht (cm) at 7 years	121.64 (4.97)	119.59 (5.15)	121.56 (4.88)	126.14 (5.28)	<0.001*
Ht (cm) at 17 years	158.45 (5.05)	157.96 (5.87)	158.46 (5.02)	158.27 (5.27)	0.371
ΔHt (cm)	36.80 (4.00)	38.36 (4.06)	36.90 (3.89)	32.13 (4.64)	<0.001*
HtSDS at 7 years	0.00 (0.91)	–0.42 (0.93)	–0.01 (0.89)	+0.80 (0.95)	<0.001*
HtSDS at 17 years	+0.08 (0.96)	–0.02 (1.11)	+0.08 (0.96)	+0.04 (1.00)	0.362
ΔHtSDS	**+0.08 (0.69)**	**+0.41 (0.70)**	**+0.09 (0.67)**	**–0.76 (0.83)**	**<0.001***

Note: The values indicate mean (SD). The *p* values of one-way ANOVA were described when comparing among the underweight, normal-weight, and obese groups. * indicats $p < 0.001$ by Bonferrini's *post-hoc* comparisons test between two groups. BMIZ, BMI Z-score at 7 years; ÂPHV, estimated age at peak height velocity; Ht, height; HtSDS, height standard deviation socre; ΔHt, changes in height between 7 and 17 years; ΔHtSDS, changes in height standard deviation score between 7 and 17 years.



B

	Underweight versus obese (95% CI)		Normal-weight versus obese (95% CI)	
Boys				
a	0.88		0.57	
b	0.45	(0.44, 0.47)	0.45	(0.44, 0.47)
c'	0.84	(0.70, 0.98)	0.62	(0.52, 0.71)
a* × *b	0.39	(0.29, 0.48)	0.25	(0.19, 0.32)
c	1.23	(1.05, 1.39)	0.87	(0.76, 0.99)
Girls				
a	1.15		0.74	
b	0.42	(0.41, 0.44)	0.42	(0.41, 0.44)
c'	0.69	(0.56, 0.82)	0.55	(0.45, 0.64)
a* × *b	0.48	(0.39, 0.56)	0.31	(0.25, 0.37)
c	1.17	(1.01, 1.32)	0.85	(0.74, 0.97)

Fig. 3 A. Linear regression model of ÂPHV on ΔHtSDS between obese and underweight or normal-weight groups. B. Summary of ÂPHV-mediated and non-ÂPHV-mediated effects. The linear regression model that was applicable in our mediation analysis is described in Fig. 3A, including ÂPHV- ($a \times b$), non-ÂPHV-mediated (c'), and total (c) effects of obese group on ΔHtSDS compared to underweight or normal-weight group. These effects are summarized in Fig. 3B. a: Difference between M_{obese} and M_{under} or M_{normal}; b: the common slope of the regression lines in underweight, normal-weight and obese groups; c': difference between Y_{obese} and Y_{under} or Y_{normal}; c: $a \times b + c$', indicating the total effect of obesity on ΔHtSDS, where $a \times b$ is ÂPHV-mediated effect and c' is non-ÂPHV-mediated effect on ΔHtSDS. Abbreviations: ÂPHV, estimated age at peak height velocity; ΔHtSDS, change in height standard deviation score between 7 and 17 years, that is (HtSDS at 17 years–HtSDS at 7 years); M_{under}, mean ÂPHV in underweight group; M_{normal}, mean ÂPHV in normal-weight group; M_{obese}, mean ÂPHV in obese group; Y_{under}, y-intercept of the regression line in underweight group, Y_{normal}, y-intercept of the regression line in normal-weight group, Y_{obese}, y-intercept of the regression line in obese group.

and the ÂPHV-mediated effect accounted for 64%. When mediation analysis was performed using BMIZ for X as a continuous variable, higher BMIZ was associated with lower ΔHtSDS both with and without ÂPHV mediation. (Supplementary Table 1).

Discussion

We found that childhood obesity is significantly associated with low pubertal growth, both with and without the mediation of pubertal timing. This reduced pubertal growth observed in children with obesity could be more affected by non-pubertal timing-mediated effect rather than pubertal timing-mediated effect, although childhood obesity is associated with early puberty and reduced pubertal height growth [11]. To the best of our knowledge, this is the first study that showed that children with obesity have reduced pubertal growth regardless of their pubertal timing.

Earlier studies with a small number of patients demonstrated that children with obesity tended to be tall during childhood [27-29]. He and Karlberg first reported the association between childhood obesity and reduced pubertal growth in Swedish general population [8]. They showed that each increased unit of BMI gain during childhood is associated with an increase in height gain during childhood of 0.23 cm in boys and 0.29 cm in girls and a decrease in height gain in adolescence by 0.88 cm in boys and 0.51 cm in girls. Holmgren *et al.* reported pubertal height gain in relation to the highest BMI SDS value between 3.5 and 8 years of age using QEPS, a novel growth model in a Swedish cohort [11]. A higher childhood BMI SDS was associated with earlier puberty and less pubertal height gain, resulting in similar adult height between overweight/obese and normal weight/underweight children. Children with obesity undergo early puberty with less pubertal height gain, which is consistent with our results. This reduction in pubertal height gain is both related to and not related to pubertal timing. It is of note that non-pubertal timing-mediated effects of childhood obesity could have a more important impact on the reduced pubertal growth compared with pubertal timing-mediated effect.

To date, there is little information regarding what type of factors contribute to non-pubertal timing-mediated effect of childhood obesity on reduced pubertal growth. We believe that one of the reasons is inappropriate bone maturation. Studies have reported advanced bone age during childhood in children with obesity and in individuals who become overweight during young adolescence [7, 30]. Bone age is an index of bone maturation and is useful in predicting adult height [31] and is accelerated or retarded by several factors, such as nutrition status and alterations in the secretion of growth, thyroid, and sex hormones. Childhood obesity is positively associated with serum dehydroepiandrosterone sulfate concentrations at 7 years in both sexes [32], and adiposity is associated with increased aromatization of steroids in adipose tissue, leading to increased conversion of androgen to estrogen [33, 34]. Leptin, whose concentration in blood is increased in obesity and is positively correlated with fat mass, might act as a skeletal growth factor to promote the differentiation and proliferation of growth plate chondrocytes [35, 36]. The levels of estrogens and their metabolites increase in girls with obesity, suggesting that obesity is associated with increased extraglandular estrogen production before the onset of puberty [37]. Considering these factors, early closure of epiphyses because of advanced bone maturation during childhood could be one of the main reasons for reduced pubertal growth in children with obesity. Further studies are vital to determine the underlying mechanisms.

Age at peak height velocity, an index of 'somatic' maturation, is an auxological component and is often used in large-scale research as a non-intrusive equivalent indicator of pubertal maturation in both sexes. Puberty can also be assessed by pubertal 'sexual' maturation, such as Tanner stage, which is defined by the enlargement of testes and penis, breast budding, and pubarche. Actually, the relationship between childhood obesity and pubertal timing should be discussed from a viewpoint of both somatic maturation and sexual maturation. In girls, childhood obesity is definitely associated with early somatic and sexual maturation. In boys, three previous reports and our study using an assessment of somatic maturation have revealed the apparent association between childhood obesity and early puberty [10, 11, 18]. One study showed no difference in age at peak height velocity between obese and normal weight groups [17]. However, to date, there is no study suggesting the relationship between childhood obesity and late somatic maturation. Meanwhile, there is no consensus on the relationship between childhood obesity and sexual maturation. Two studies using an assessment of testicular volume showed earlier puberty in children with obesity [19, 20]; the Danish study, during ~15 years, linked the secular trend in earlier onset of puberty indirectly to increased childhood obesity during the same period [19]. On the other hand, two studies revealed the association between childhood obesity and late sexual maturation [13, 14]. Reinehr T *et al.*, in the assessment of testicular volume, reported BMI SDS reduction in children who are overweight is associated with early onset of puberty, suggesting late pubertal sexual maturation in boys with obesity [38]. Taken together, we speculate that childhood obesity in girls accelerates both pubertal somatic and

sexual maturation, whereas in boys, it accelerates somatic maturation but decelerates sexual maturation. Further in-depth longitudinal researches are needed to confirm this relationship.

This study has several limitations. First, individual ΔHtSDS was used as a surrogate indicator of pubertal growth although it is not an exact indicator of pubertal growth. Pubertal growth often indicates pubertal height gain, which can be defined in three different ways: 1) height growth at the age of onset of sexual maturation to adult height, 2) height growth at the age of takeoff on growth chart to adult height, and 3) the value of integral of the only increase in height velocity during puberty compared to childhood. However, in this study, we used ΔHtSDS as a surrogate indicator of pubertal growth to elucidate whether pubertal growth in children with obesity is reduced when comparing children without obesity. In fact, the same indicator (height changes between the age of 8 and 18 years) was used in a previous research for the same purpose [8]. Second, we did not analyze our data in terms of sexual maturations. As mentioned before, individual age at peak height velocity is an index of pubertal somatic maturation and is often used as a marker of pubertal timing in large-scale studies. In a clinical setting, pubertal status is defined as Tanner stages, which are indices of pubertal sexual maturation. However, there was no data about Tanner stages in this study probably due to its intrusiveness. We used individual estimated age at peak height velocity for pubertal timing considering it is equivalent for both sexes. Third, we defined cutoff values for childhood obesity as 95th percentiles, although the BMI cutoff values for childhood obesity have not been determined in Japan [39]. There are three major criteria for international definition of children with obesity: World Health Organization (WHO) references, International Obesity Task Force (IOTF) references, and US Center for Disease Control and Prevention (CDC) recommendations [40-42]. We believe that our BMI cutoff values of 19.54 and 19.80 corresponding to the 95th percentile values at 7.0 years in boys and girls, respectively, are acceptable compared with the BMI cutoff values of 19.0 and 19.8 in WHO references, 20.63 and 20.51 in the IOTF references, and 19.15 and 19.68 in CDC recommendations for the same age. Finally, the data analyzed in this study was from one geographical area in Japan. However, Japan is mostly a monoethnic country and this was one of the largest Japanese children's longitudinal cohort studies. The mean of ÂPHV in this study was almost equal to that in a previous Japanese study [43] and individual ÂPHV values were evenly distributed for both sexes. Despite these limitations, we believe that this study has shown for the first time that children with obesity have reduced pubertal growth regardless of pubertal timing.

Conclusion

On the basis of the Japanese general population, childhood obesity is significantly associated with reduced pubertal growth, both with and without the mediation of pubertal timing. This reduced pubertal growth observed in children with obesity could be more affected by non-pubertal timing-mediated effect rather than pubertal timing-mediated effect.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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