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Original Article

Analysis of the distribution of adult height standard deviation scores in relation to prepubertal height standard deviation scores using longitudinal growth data

—Investigation of the catch-up rates of children with short stature to attain normal adult height—

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Highlights

- Of children with short stature at prepuberty, 58.4% attained adult height.
- Of children with tall stature at prepuberty, 67.3% of them had normal adult height.
- Children with prepubertal height SDS of ≤ –2.5 SD may not attain normal adult height.

Abstract. Using the longitudinal growth data of 13,809 individuals in the Akita Prefecture, the percentage distributions of their adult height (AH) standard deviation scores (SDS) in relation to their prepubertal height SDS were obtained. The AH SDS increased with negative prepubertal height SDS and decreased with positive prepubertal height SDS, showing that a greater amount of change was associated with a greater interval of the prepubertal height SDS from the mean. The proportions of individuals who achieved normal AH stratified by prepubertal height SDS were as follows: 67.1%, in the group with prepubertal height SDS of –2.5 < to ≤ –2.0 SD, 46.0% in the group with –3.0 < to ≤ –2.5 SD, 75.2% in the group with +2.0 ≤ to < +2.5 SD, and 55.1% in the group with +2.5 ≤ to < +3.0 SD. Of all participants with short stature at prepuberty, 58.4%, 33.8%, 8.3%, and 0% of those with prepubertal height SDS of ≤ –2.0 SD, ≤ –2.5 SD, ≤ –3.0 SD, and ≤ –3.5 SD attained normal AH, respectively. On average, it is difficult for children with prepubertal height SDS of ≤ –2.5 SD to attain normal AH.

Key words: natural growth, short stature, tall stature, adult height, catch-up

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Introduction

In Japan, GH therapy in individuals with short stature has been approved for the treatment of GH deficiency (GHD), Turner syndrome, achondroplasia or hypochondroplasia, short stature associated with chronic renal failure, short stature born small for gestational age (SGA), Prader-Willi syndrome and Noonan syndrome. However, approximately 15 to 20% of children with short stature who are diagnosed with these disorders receive GH therapy, even at the National Center for Child Health and Development, where several pediatric patients with severe short stature are treated (1). More than 80% of short children are considered to have idiopathic short stature (ISS), which is not treated as a disorder.

In 2007, pediatric endocrinologists from various countries including Japan, the United States, and Europe discussed the definition, diagnosis, and treatment of ISS. The results were published in a Consensus Statement (2), that is now recognized as the international standard for ISS.

Reports on the natural history of idiopathic short stature in children are limited because of the need to include a large number of individuals with normal height for appropriate epidemiological research. Karlberg *et al.* (3) analyzed the data (from birth to 18 yr) on the growth of 4,888 children born around 1974 in Sweden; the data were collected in 1992. They reported that the correlation between child height and adult height gradually became stronger from birth to 8 yr and that the probability of having adult height SDS of ≤ –2.0 SD for children with height SDS of –3.0 SD at age 8 was 63%.

In Japan, Komatsu *et al.* (4) analyzed the longitudinal growth data of children born in Akita Prefecture between April 1975 and March 1976 and reported that 60.2% of boys with short stature and 56.3% of girls with short stature during prepuberty had a height SDS of > –2.0 SD at the age of 17 yr.

In this study, we cleaned these same data from Akita Prefecture and performed a more detailed analysis to determine and compare the percent distributions of adult-height SDS in relation to prepubertal height SDS. We mainly investigated the proportion of children with short stature catching up to attain normal adult height.

Subjects and Methods

This study included 13,813 participants (6,798 males and 7,015 females) who were born in Akita Prefecture between April 1975 and March 1976. Prepubertal height was defined as height at the age of 6 yr, and adult height was defined as height at the age of 17 yr. The data were cleaned as follows. For the ages of 6 and 7 yr, the height that seemed natural on the growth curve was used as the prepubertal height (height at the age of 6 yr in **Fig. 1(a)** and height at the age of 7 yr in **Fig. 1(b)**). Similarly, for the ages of 16 and 17 yr, the height that seemed natural on the growth curve was used as the adult height (the height at the age of 16 yr in **Fig. 2(a)** and the height at the age of 17 yr in **Fig. 2(b)**). Specifically, the growth rates between the ages of 6 and 7 yr and between 16 and 17 yr were calculated. If the values were outside the normal range, the participants were selected and evaluated. The data of eighty-two participants were cleaned. The mean adult height was 171.3 ± 5.7 cm for the male participants and 158.4 ± 5.1 cm for the female participants.

The mean ± SD of the heights of 81,451 male and 84,084 female participants was calculated every month and used as the standard value to calculate the height SDS. The prepubertal and adult height SDS were divided into groups at intervals of 0.5 SD from –3.5 SD to +3.5 SD, and height SDS of ≤ –3.5 SD and ≥ +3.5 SD were each categorized as one group. The prepubertal and adult height SDS were confirmed to follow a normal distribution in males and females.

This study was approved by the ethical review board of the Japan Medical Association (R4-24).

Results

The proportions of the adult short stature (≤ –2.0 SD), adult normal stature (–2.0 SD to +2.0 SD), and adult tall stature (≥ +2.0 SD) cases were determined for each prepubertal height SDS group for male and female participants as shown in **Figs. 3(a)** and **3(b)**. The frequency of achieving normal adult height decreased with decreasing prepubertal height SDS for short participants and with increasing prepubertal height SDS for tall participants. In the group with prepubertal height SDS of –2.5 < to ≤ –2.0 SD, 62.4% of males and 70.5% of females became adults with normal stature. In the group with prepubertal height SDS of +2.0 ≤ to < +2.5 SD, 68.9% of males and 80.1% of females became adults with normal stature. There were no significant differences between the proportions of adult males and females with short, normal, and tall statures for each prepubertal height SDS group (χ^2 test). The male and female participants were combined to secure enough number of participants with tall and short statures for further analysis.

Fig. 4 shows the proportions of the adult height SDS groups for each prepubertal height SDS group. The section outlined in bold red indicates the adult group with the same height SDS as the prepubertal height SDS group. The groups with negative prepubertal height SDS tended to have more participants with higher adult height SDS, whereas the groups with positive prepubertal height SDS tended to have more participants with lower adult height SDS.

As shown in **Fig. 5**, a plot was created with the mean height SDS for the prepubertal height SDS groups on the x-axis and the mean, ± 1 SD, and ± 2 SD of the adult height SDS on the y-axis for each prepubertal height SDS group from –3.5 SD to +3.5 SD. The adult height SDS increased with negative prepubertal height SDS and decreased with positive prepubertal height SDS. The farther the prepubertal height SDS was from 0 SD, the

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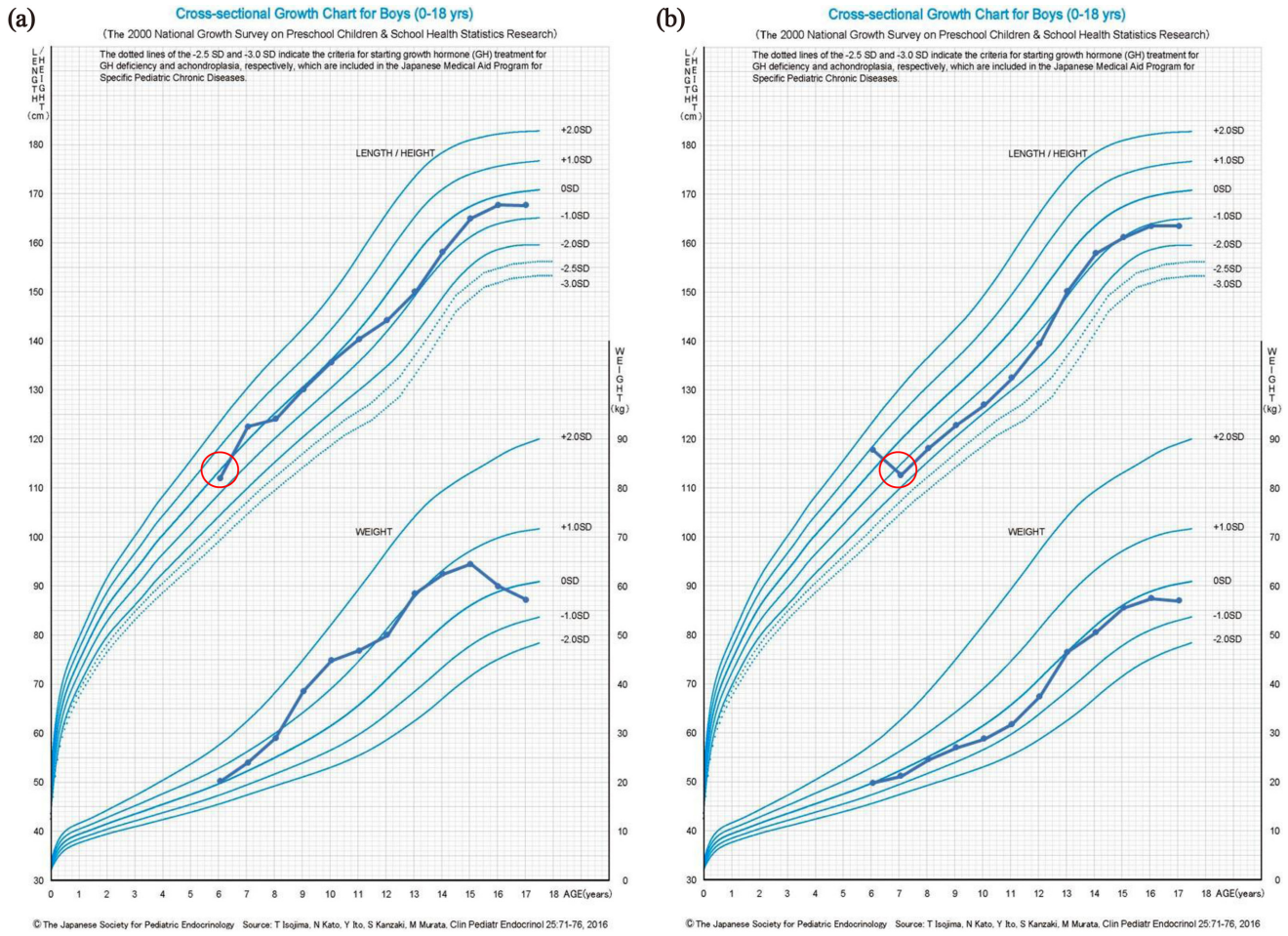

Fig. 1. (a) The measurement at the age of 7 yr was considered unnatural on the growth curve, and the measurement at the age of 6 yr was used as the prepuberty height. (b) The measurement at the age of 6 yr was considered unnatural on the growth curve, and the measurement at the age of 7 yr was used as the prepubertal height.

greater the amount of change. The mean difference in the height SDS from prepuberty to adulthood was +0.51 SD for the group with prepubertal height SDS of –2.5 < to ≤ –2.0 SD, +0.59 SD for the group with prepubertal height SDS of –3.0 < to ≤ –2.5 SD, and +0.69 SD for the group with prepubertal height SDS of –3.5 < to ≤ –3.0 SD. The mean amount of change was –0.73 SD for the group with prepubertal height SDS of +2.0 ≤ to < +2.5 SD, –0.80 SD for the group with prepubertal height SDS of +2.5 ≤ to < +3.0 SD, and –0.95 SD for the group with prepubertal height SDS of +3.0 ≤ to < +3.5 SD.

In **Fig. 4**, the proportions of adults (male and female combined) with short stature (blue), normal stature (yellow), and tall stature (purple) are shown for each prepubertal height SDS group using different colors. All the participants with short prepubertal stature (height SDS of ≤ –3.5 SD) became adults with short stature. However, normal adult height was attained by 13.3% of the group with prepubertal height SDS of –3.5 < to ≤ –3.0 SD (male: 20% [n=1], female: 10% [n=1]), 46.0% of the group with prepubertal height SDS of –3.0 < to ≤ –2.5 SD (male: 46.2%, female: 45.8%), and 67.1% of the group with prepubertal height SDS of –2.5 < to ≤ –2.0 SD (male: 62.4%, female: 70.5%).

Thirty percent of the participants with tall prepubertal stature (height SDS ≥ +3.5 SD) attained normal adult height (male: 33.3% [n=2], female: 25.0% [n=1]). Similarly, 38.1% of the participants with prepubertal height SDS of +3.0 ≤ to < +3.5 SD (male: 22.2%, female: 50.0%), 55.1% of the participants with prepubertal height SDS of +2.5 ≤ to < +3.0 SD (male: 55.6%, female: 54.5%), and 75.2% of the participants with prepubertal height SDS of +2.0 ≤ to < +2.5 SD (male: 68.9%, female: 81.1%) attained normal adult height.

Of all participants with short stature with prepubertal height SDS of ≤ –2.0 SD (119 males, 162 females), 58.4% achieved normal adult height SDS (male: 55.4%, female: 60.5%). Of the short participants with prepubertal height SDS of ≤ –2.5 SD, 33.8% attained normal adult height (male: 38.2%, and female: 30.0%). Of the short participants with prepubertal height SDS of ≤ –3.0 SD, 8.3% attained normal adult height (male: 12.5% [n=1], female: 6.3% [n=1]). None of the participants (0%) with prepubertal height SDS of ≤ –3.5 SD attained normal adult height.

Of all participants with tall stature with prepubertal height SDS of ≥ +2.0 SD, 67.3% attained normal adult height (male: 62.0%, female: 72.7%). Of the

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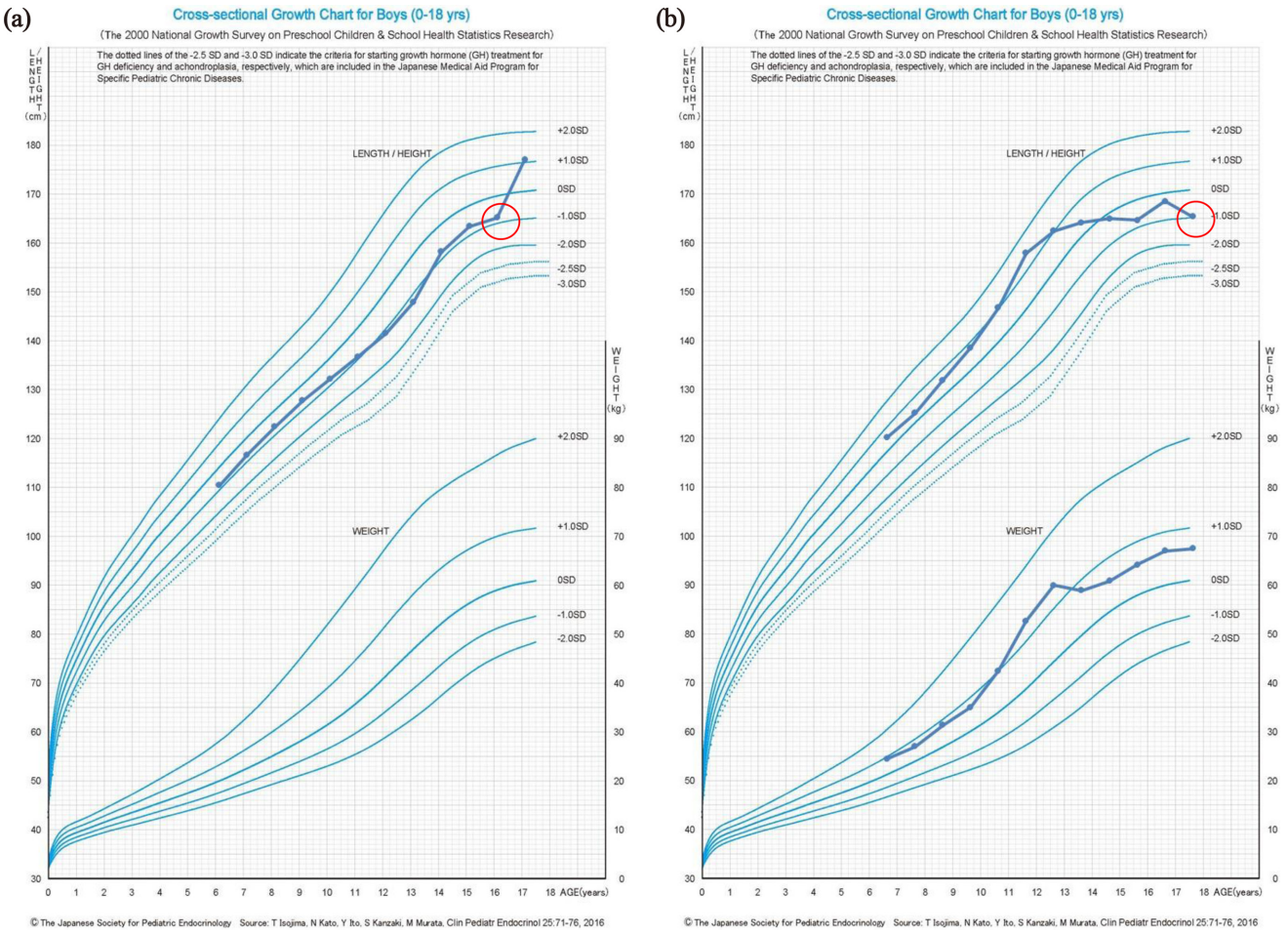

Fig. 2. (a) The measurement at the age of 17 yr was considered unnatural on the growth curve, and the measurement at the age of 16 yr was used as the adult height. (b) The measurement at the age of 16 yr was considered unnatural on the growth curve, and the measurement at the age of 17 yr was used as the adult height.

tall participants with prepubertal height SDS of ≥ +2.5 SD, 49.5% had normal adult height SDS (male: 48.3%, female: 51.0%). Of the tall children with prepubertal height SDS of ≥ +3.0 SD, 35.5% had normal adult height SDS (male: 26.7%, female: 43.8%). Of the tall participants with prepubertal height SDS of ≥ +3.5 SD, 30.0% had normal adult SDS (male: 33.3%, female: 25.0%).

Of the 281 participants who had short stature during prepuberty, only one male participant had an adult height SDS greater than 0 SD.

Discussion

The participants in the current study grew up in an era where GH therapy was approved for pituitary dwarfism (current GHD). However, the GH extracted from the human pituitary gland had to be imported from overseas, which limited the supply and forced some patients to be waitlisted. For this reason, it is doubtful that the participants of this study received GH therapy. Therefore, this longitudinal study is likely to have included untreated cases of GHD and SGA short stature, although this is expected to be a small number. According to a report by the Foundation for Growth Science (5), 2.4% of children with short stature born between 1972 and 1991 (boys: 3.2% and girls:1.6%) received GH therapy for GHD, a common type of GH-treated short stature. Additionally, an epidemiological survey conducted in Kobe showed that 2.5% of pediatric cases of short stature were SGA short stature, which is an indication for GH therapy (6). With the inclusion of rare diseases such as chromosomal abnormalities and skeletal dysplasia, more than 90% of the children with short stature in this study were considered to have ISS.

Using longitudinal height data from this era in the Akita Prefecture, we analyzed the distribution of adult height SDS for each prepubertal height SDS group. Due to the data cleaning of the data for the ages 6–7 yr and 16–17 yr, the results in this study were slightly different from those in a previous report (4), but normal adult height was attained by 55–60% of the participants with short stature. Of the participants with tall stature, approximately 62% of the males and 72% of the females attained normal adult height. Females with tall stature were slightly more likely to attain normal adult height, which may reflect the high incidence of precocious puberty in girls.

Changes in height SDS, as shown in Fig. 5, occurred

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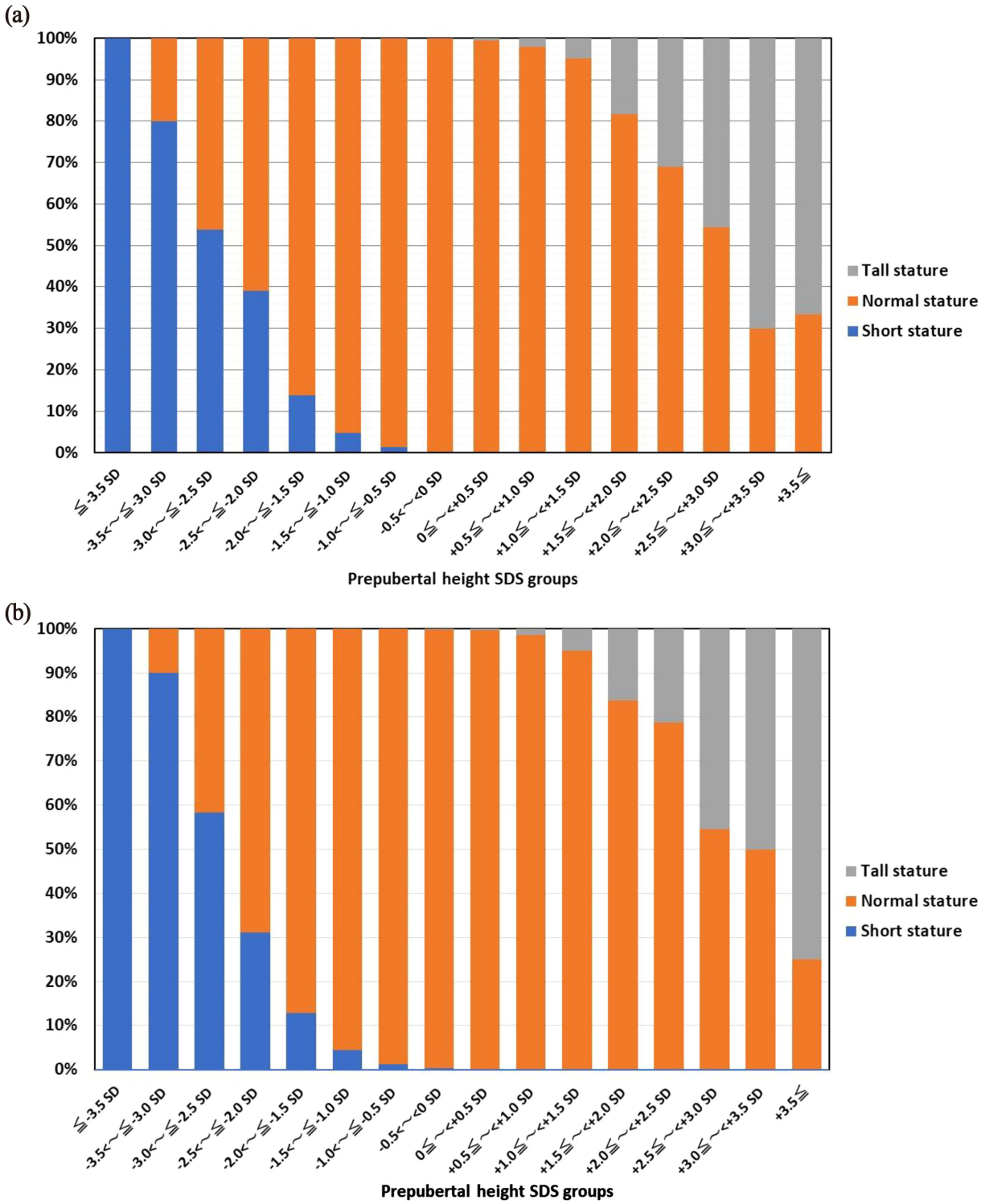

Fig. 3. (a) Distribution of tall, normal and short statures at adult height in males stratified by prepubertal height SDS groups. (b) Distribution of tall, normal and short statures at adult height in females stratified by prepubertal height SDS groups.

during puberty. It has also been reported that the quantitative change in height SDS during puberty is negatively correlated with height SDS at 6 yr (7). Since the age at onset of puberty is negatively correlated with height, weight, and height SDS at 6 yr, taller and heavier children enter puberty earlier and shorter and lighter children enter puberty later (8). It has also been shown that the age at pubertal growth spurt has a significant positive correlation with the quantitative change in height SDS from 6 to 17 yr (7). Consequently, shorter children at 6 yr tend to increase their adult height SDS by entering puberty later, and taller children at 6 yr tend to decrease their adult height SDS by entering puberty earlier.

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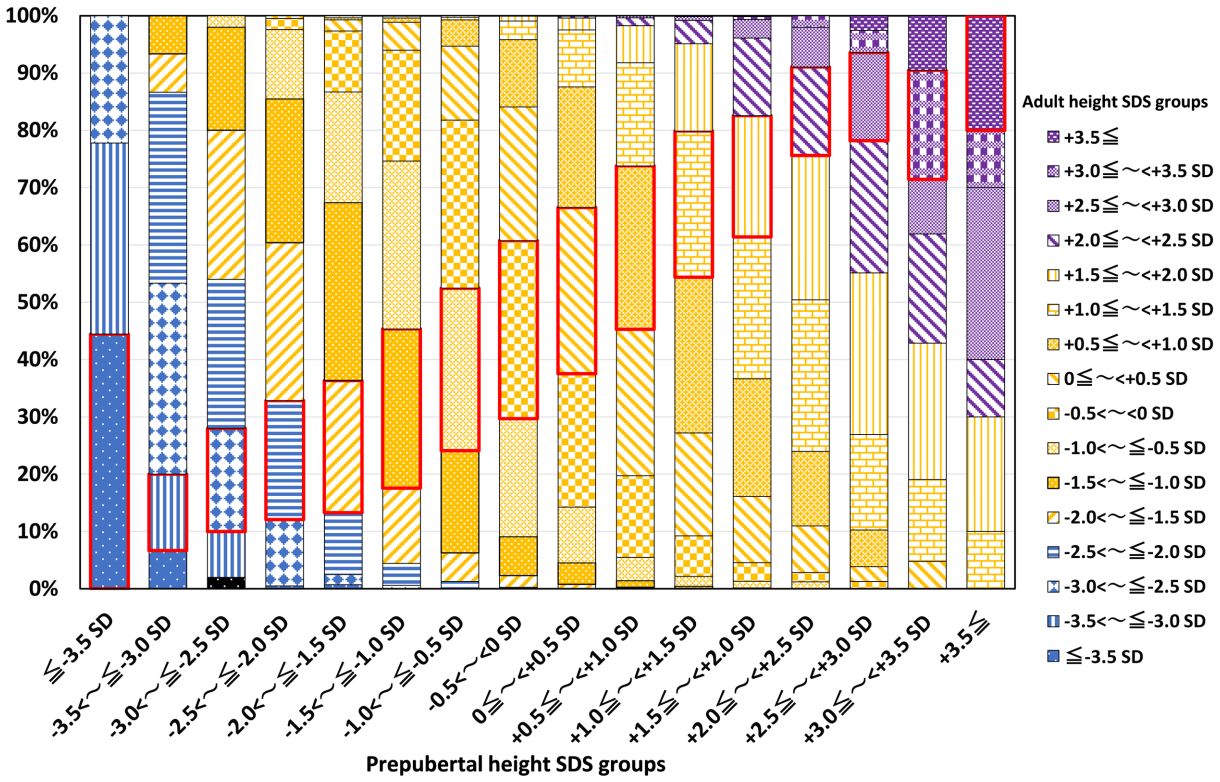

Fig. 4. Distribution of adult height SDS stratified by prepubertal height SDS group. The section outlined in bold red indicates the group with the same height SDS as the prepubertal height SDS. The blue, yellow, and purple sections represent adult short stature, adult normal stature, and adult tall stature, respectively.

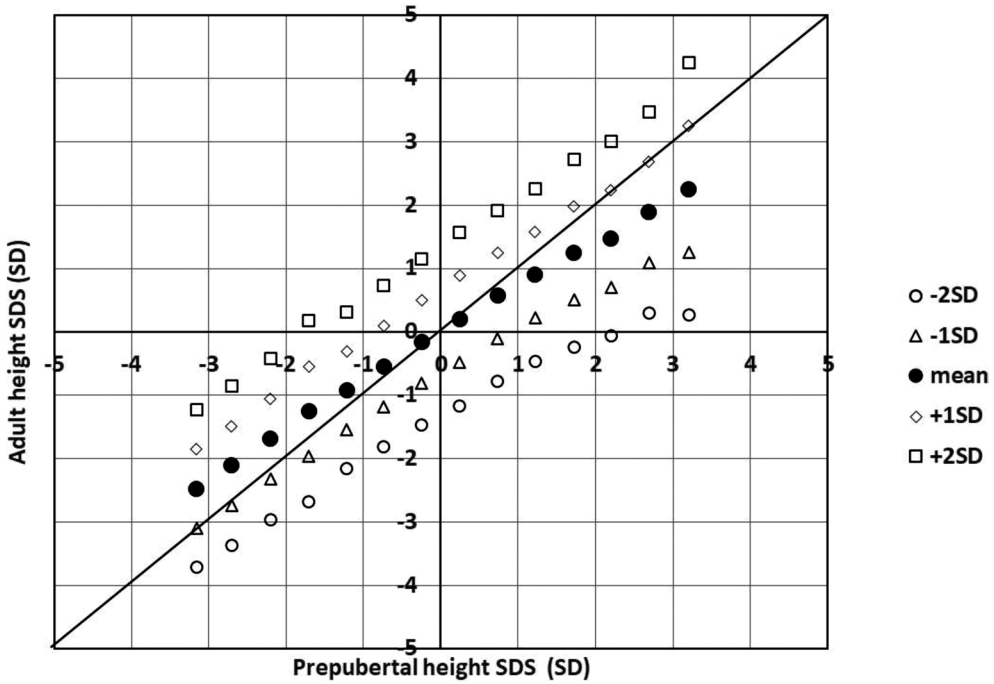

Fig. 5. The mean, ± 1 SD and ± 2 SD of adult height SDS stratified by prepubertal height SDS group.

Of the children with short stature, the proportion who attained normal adult height decreased with decreasing prepubertal height SDS. The proportion was 33.8% for individuals with prepubertal height SDS of ≤ –2.5 SD, approximately half of the rate of individuals with prepubertal height SDS of ≤ –2.0 SD, and 8.3% for individuals with prepubertal height SDS of ≤ –3.0 SD. This indicates that approximately 70% of children with

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prepubertal height SDS of ≤ –2.5 SD and approximately 90% of those with prepubertal height SDS of ≤ –3.5 SD will become adults with short stature. For the groups with negative prepubertal height SDS, height SDS tended to increase from prepuberty to adulthood, and the amount of change was greater in the groups with lower prepubertal height SDS. In the group with prepuberty height SDS of –2.5 < to ≤ –2.0 SD, the mean height SDS was –2.20 SD, and the mean amount of change from prepuberty to adulthood was +0.51 SD, indicating that, on average, this group attained normal adult height. However, in the group with prepuberty height SDS of –3.0 < to ≤ –2.5 SD, the mean height SDS was –2.70 SD and the mean amount of change from prepuberty to adulthood was +0.59 SD, indicating that, on average, this group did not attain normal adult height.

Of the children who had short stature during prepuberty, only one male participant had an adult height SDS of > 0 SD. For this particular case, puberty began later than usual at approximately 14 yr of age. Late onset of puberty normally leads to limited pubertal growth. However, this was considered a rare case with significant pubertal growth based on rapid increments in body weight and body mass index. Therefore, it is generally considered difficult for prepubertal children with short stature to grow taller than the average adult height.

Conflict of interests: The authors declare no conflicts of interest.

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