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Body Composition Changes and Catch-up Growth in Pre-pubertal Children with Short Stature: A Longitudinal Retrospective Cross-sectional Cohort Study

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What is already known on this topic?

Differentiating whether a child with pre-pubertal short stature will achieve normal height or remain short before the pubertal growth spurt is challenging. While growth hormone deficiency is associated with reduced skeletal muscle mass (SMM), longitudinal studies comparing body composition in those achieving versus failing catch-up growth are lacking.

What this study adds?

This study examined body composition changes in pre-pubertal children with short stature, distinguishing those who achieved normal height from those who remained short before the pubertal growth spurt. Differences in SMM index (SMMI) growth emerged as important, highlighting the need for possible early therapeutic intervention in cases with poorer SMMI increase.

Abstract

Objective: Predicting whether children with pre-pubertal short stature will achieve catch-up growth to a normal height or remain short remains a clinical challenge. As body composition plays a vital role in growth, we aimed to compare longitudinal body composition changes in children with short stature who either achieved normal height by the onset of the growth spurt or remained short.
Methods: This longitudinal, retrospective, cross-sectional, cohort study analyzed anthropometric and body composition data of children aged 8 and 12 years, allowing for both longitudinal tracking and cross-sectional comparisons. Participants were categorized into three groups: short-to-short statured (short stature at 8 and 12 years, n = 177), short-to-normal statured (short stature at age 8 and normal stature at 12, n = 90), and control (normal stature at both ages, n = 7,195). Height, weight, body fat mass (BFM), skeletal muscle mass (SMM), body mass index (BMI), BFM index (BFMI), and SMM index (SMMI) were assessed. Growth variations were examined using a difference-in-difference estimator.
Results: Cross-sectional analysis showed the short-to-short group had significantly lower weight, BFM, SMM, BMI, BFMI, and SMMI compared to controls at both ages. Longitudinally, the short-to-normal group exhibited significantly greater increases in height [0.87

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and 0.95 standard deviation scores (SDS) for boys and girls, respectively], weight (0.59 and 0.68 SDS), and SMMI (0.75 and 0.50 SDS) compared to the short-to-short group. However, BFMI increases were not significant.

Conclusion: Children with pre-pubertal short stature who achieved a normal height showed the most significant increase in SMMI. Children with lower increases in SMMI may require further assessment for continued short stature.

Keywords: Anthropometric data, body composition, catch-up growth, children and adolescents, short stature, skeletal muscle mass

Introduction

Short stature, defined as a height that is >2 standard deviations (SDs) below the population mean for age and sex, is a frequent reason for referral to pediatric endocrinologists (1,2). Timely evaluation and treatment of the causes of short stature are critical determinants of final adult height. In children with idiopathic short stature (ISS), early puberty or delayed treatment initiation until after puberty can lead to a shortened duration of growth hormone (GH) therapy and a reduction in final adult height (3). Similarly, starting the therapy at a younger age, before the onset of puberty, considerably increases the final adult height in individuals with ISS, GH deficiency (GHD) and Turner syndrome and those born small for gestational age (SGA) (4,5,6). Therefore, clinicians must distinguish whether a child with short stature would likely overcome this condition naturally, such as in those with constitutional delay of growth and puberty (CDGP), or will exhibit persistent short stature.

As interest in the impact of body composition on growth patterns in children and adolescents has increased, a previous cross-sectional analysis of the body composition of individuals with short stature revealed that their fat-free mass (FFM) index was considerably lower (7). However, there is a scarcity of longitudinal studies analyzing the differences in body composition between those whose pre-pubertal short stature persists into pubertal age and those with a short stature who achieved a normal height. Moreover, there is growing interest in employing bioelectrical impedance analysis (BIA) for body composition assessment in clinical settings due to its cost-effectiveness, simplicity, and non-invasiveness (7). In addition, BIA has consistently demonstrated excellent test-retest reliability and moderate to strong correlations with dual-energy X-ray absorptiometry (DXA), particularly in pediatric and adolescent cohorts, thereby establishing it as an affordable, convenient, and highly reproducible method for evaluating body composition in clinical practice (8). In the present study, we conducted a longitudinal analysis using data from Korean children and adolescents to compare the changes in body composition among those whose pre-pubertal short stature persisted into pubertal age, those who achieved a normal height and a control group with a normal height.

Methods

Study Sample

The GP Cohort Study, conducted by GP Co., Ltd. in Gwangmyeong City, Gyeonggi Province, Republic of Korea, is an ongoing mixed longitudinal research study involving Korean students. The study involves students aged 7-18 years from elementary, middle and high schools in Korea, specifically in Gyeonggi Province, with approximately 35 schools participating annually. Data collection occurs biannually in schools, where examiners use the stadiometer and octapolar multi-frequency biometric impedance analyzer (Inbody models J10 and J30, Inbody, Seoul, Korea) to measure students' height, weight and body composition following a standard protocol. Height measurements were taken using a stadiometer in accordance with the Centers for Disease Control and Prevention guidelines, whereas body composition assessments followed the manual provided by InBody Inc. (7,8,9). Participants were instructed to stand for five minutes before the examination, and the examination was conducted if at least two hours had passed since the last meal. Before the examination, participants were instructed to use the restroom, wash their hands thoroughly, and return. Examinations were preferably conducted in the morning at schools, and apart from assisting participants in adopting the standard standing posture for the examination, there was no physical contact between the subjects and the examiners during the examination.

For the original GP Cohort Study data collection, written informed consent was obtained from both the legal guardians and the students themselves prior to participation. Students eligible for physical and body composition measurements with consent from their guardians and themselves were included (8). We excluded those whose measurements could not be taken or who refused participation. Since its commencement on January 1, 2013, the study has gathered 649,330 data points from 110,648 children and adolescents (58,135 boys and 52,513 girls born between 1998 and 2020, as of December 31, 2023).

Short stature was defined as a height more than -2 SD scores (SDSs) below the population mean for age and sex, whereas normal stature was defined as a height between -2 SDS and 2 SDS for age and sex (6). The children were categorized into the following three groups based on their stature at ages 8 and 12 years: short-to-short statured (SS) group comprising children with a short stature at both 8 and 12 years of age (177 children; 94 boys and 83 girls); short-to-normal statured (SN) group, comprising children who had a short stature at 8 years of age but achieved a normal height at 12 years of age (90 children; 47 boys and 43 girls); and control group, including children with a normal stature at both 8 and 12 years of age (7,195 children; 3,675 boys and 3,520 girls).

The present study was approved by the Institutional Review Board of Yonsei University Health System, Severance Hospital (approval no: 4-2023-1470, date: 28.12.2023), and the requirement for obtaining informed consent from the participants was waived because this investigation was a de-identified retrospective study.

Measurement of Anthropometric Parameters and Body Composition

The participants' height (cm), weight (kg), body fat mass (BFM, kg) and skeletal muscle mass (SMM, kg) were measured to determine their body mass index (BMI), BFM index (BFMI) and SMM index (SMMI), which were calculated as follows.

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{Height\ (m)^2}$$

$$BFMI\ (kg/m^2) = \frac{BFM\ (kg)}{Height\ (m)^2}$$

$$SMMI\ (kg/m^2) = \frac{SMM\ (kg)}{Height\ (m)^2}$$

The anthropometric measurements and indices were calibrated based on the GP growth chart for Korean children and adolescents and are presented as the SDS specific to age and sex (9).

Statistical Analysis

Descriptive statistics of the SDS of height, weight, body composition and their indices are presented as mean with standard errors for age and sex. In our analysis, we examined and compared the changes in height, weight and body composition from ages 8 to 12 years between the SS, SN and control groups. Pairwise comparisons among the three groups were made using independent-sample t-tests. We used a difference-in-difference (DID) estimator to examine the growth variations among the three groups. To compute the estimator, first, we determined the mean changes in height, weight and body composition from ages 8 to 12 within one group (D_1). Second, we calculated the corresponding changes within another group (D_2). Finally, we computed the difference between these changes ($\delta_{12} = D_1 - D_2$). Statistical significance was established by estimating the DID estimator in the DID regression model.

All statistical evaluations were conducted using Python, version 3.9.7 (Python Software Foundation, Wilmington, Delaware, USA) and R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). A p value of less than 0.05 was deemed to indicate statistical significance.

Results

Cross-sectional Analysis of Height, Weight, and Body Composition in SS, SN, and Control Group at Pre-pubertal and Early Pubertal Stages

In the cross-sectional analysis, the boys in the SS group consistently showed significantly lower weight, BFM, SMM, BMI, BFMI and SMMI at both 8 and 12 years of age than the boys in the control group (Tables 1 and 2 and Appendix Tables A1 and A2). Changes of mean height, weight, and BFM, SMM SDS at ages 8 and 12 across in both sex is described in Figure 1. To illustrate, at 8 years of age, the boys in the SS group were, on average, 12.08 cm (2.66 SDS) shorter and 7.00 kg (1.76 SDS) lighter, and their BFM and SMM were lower by 2.26 (0.83 SDS) and 2.76 (2.05 SDS) kg, respectively. In addition, their BMI, BFMI and SMMI were 1.14 (0.53 SDS), 0.75 (0.46 SDS) and 0.45 (0.86 SDS) kg/m² lower, respectively, than the boys in the control group. At 12 years of age, the boys in the SS group were, on average, 18.47 cm (2.75 SDS) shorter and 15.46 kg (1.73 SDS) lighter, and their BFM and SMM were lower by 3.34 (0.51 SDS) and 7.14 (2.17 SDS) kg, respectively. Furthermore, their BMI, BFMI and SMMI were 1.98 (0.62 SDS), 0.26 (0.07 SDS) and 1.22 (1.33 SDS) lower, respectively, than the boys in the control group.

The boys in the SN and SS groups showed a similar growth pattern and body composition at 8 years of age. Minimal non-significant differences in height (0.85 cm, 0.25 SDS), weight (0.05 kg, 0.10 SDS), BFM (-0.12 kg, 0.05 SDS), SMM (0.06 kg, 0.11 SDS), BMI (-0.19 kg/m², -0.03 SDS), BFMI (-0.12 kg/m², 0.02 SDS) and SMMI (-0.03 kg/m², -0.04 SDS) were observed between the SN and SS groups. However, by the age of 12 years, the SN and SS groups showed significant differences in most parameters. The boys in the SS group were 7.48 cm (1.12 SDS) shorter and 6.05 kg (0.70 SDS) lighter, and their BFM and SMM were lower by 0.93 (0.11

SDS) and 3.03 (0.98 SDS) kg, respectively, than those of the boys in the SN group. Moreover, the SS group had lower BMI (0.92 kg/m², 0.27 SDS) and SMMI (0.67 kg/m², 0.70 SDS) than the SN group. Interestingly, the difference in BFMI (-0.05 kg/m², -0.07 SDS) between the boys in the SS and SN groups was not significant.

In the cross-sectional analysis of the girls, those in the SS group consistently exhibited significantly lower weight, BFM, SMM, BMI, BFMI and SMMI at both 8 and 12 years of age than the girls in the control group (Tables 1 and 2 and Appendix Tables A1 and A2). To illustrate, at 8 years of age, the girls in the SS group were, on average, 12.11 cm (2.65

Table 1. Mean height, weight, and body composition SDS at ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

Age (years)	8			12		
	Control	SN	SS	Control	SN	SS
Boys						
Height SDS (SE)	0.05 (0.88)	-2.36 (0.34)	-2.61 (0.41)	0.33 (0.86)	-1.30 (0.48)	-2.42 (0.32)
Weight SDS (SE)	0.12 (1.02)	-1.54 (0.73)	-1.64 (0.87)	0.37 (1.07)	-0.67 (0.94)	-1.36 (0.73)
BFM SDS (SE)	0.11 (1.08)	-0.67 (0.78)	-0.72 (0.90)	0.24 (1.09)	-0.16 (1.12)	-0.27 (0.98)
SMM SDS (SE)	0.14 (0.96)	-1.81 (0.59)	-1.92 (0.69)	0.33 (0.94)	-0.87 (0.62)	-1.84 (0.52)
BMI SDS (SE)	0.12 (1.06)	-0.44 (0.81)	-0.41 (0.91)	0.26 (1.09)	-0.09 (1.17)	-0.36 (1.00)
BFMI SDS (SE)	0.11 (1.09)	-0.34 (0.82)	-0.36 (0.95)	0.18 (1.09)	0.05 (1.17)	0.12 (1.06)
SMMI SDS (SE)	0.18 (1.04)	-0.72 (0.86)	-0.68 (0.96)	0.27 (1.02)	-0.35 (0.79)	-1.06 (0.73)
Girls						
Height SDS (SE)	-0.02 (0.87)	-2.34 (0.28)	-2.67 (0.47)	0.33 (0.84)	-1.37 (0.42)	-2.65 (0.49)
Weight SDS (SE)	0.02 (0.93)	-1.43 (0.69)	-1.75 (0.68)	0.20 (0.96)	-0.70 (0.79)	-1.70 (0.95)
BFM SDS (SE)	-0.00 (0.98)	-0.57 (0.81)	-0.89 (0.78)	0.10 (0.99)	-0.27 (0.91)	-0.97 (1.09)
SMM SDS (SE)	0.04 (0.89)	-1.82 (0.49)	-2.01 (0.69)	0.25 (0.93)	-0.98 (0.61)	-1.98 (0.78)
BMI SDS (SE)	0.03 (0.97)	-0.33 (0.81)	-0.53 (0.78)	0.06 (1.00)	-0.14 (0.94)	-0.66 (1.08)
BFMI SDS (SE)	0.00 (0.99)	-0.20 (0.86)	-0.50 (0.84)	0.04 (0.99)	-0.03 (0.95)	-0.56 (1.17)
SMMI SDS (SE)	0.08 (0.96)	-0.78 (0.79)	-0.82 (0.92)	0.11 (1.00)	-0.36 (0.87)	-0.90 (1.04)

SDS: standard deviation score, SN: short-to-normal statured group, SS: short-to-short statured group, BFM: body fat mass, SMM: skeletal muscle mass, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index, SE: standard error

Table 2. Differences of mean height, weight, and body composition SDS at ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

Age (years)	8			12		
	Control-SN	Control-SS	SN-SS	Control-SN	Control-SS	SN-SS
Boys						
Height SDS (CI)	**2.41 (2.39-2.43)**	**2.66 (2.63-2.69)**	**0.25 (0.22-0.28)**	**1.63 (1.61-1.65)**	**2.75 (2.73-2.77)**	**1.12 (1.09-1.15)**
Weight SDS (CI)	**1.66 (1.63-1.70)**	**1.76 (1.70-1.82)**	**0.10 (0.03-0.17)**	**1.04 (0.99-1.08)**	**1.73 (1.68-1.78)**	**0.70 (0.63-0.76)**
BFM SDS (CI)	**0.77 (0.73-0.81)**	**0.83 (0.77-0.89)**	0.05[N] (-0.02-0.13)	**0.40 (0.35-0.46)**	**0.51 (0.44-0.58)**	**0.11 (0.02-0.19)**
SMM SDS (CI)	**1.94 (1.91-1.97)**	**2.05 (2.01-2.10)**	**0.11 (0.06-0.17)**	**1.20 (1.17-1.23)**	**2.17 (2.14-2.21)**	**0.98 (0.93-1.02)**
BMI SDS (CI)	**0.56 (0.52-0.60)**	**0.53 (0.47-0.59)**	-0.03[N] (-0.11-0.04)	**0.35 (0.29-0.41)**	**0.62 (0.55-0.68)**	**0.27 (0.18-0.35)**
BFMI SDS (CI)	**0.45 (0.41-0.49)**	**0.46 (0.40-0.53)**	0.02[N] (-0.06-0.09)	**0.14 (0.08-0.19)**	0.07[N] (-0.00-0.14)	-0.07[N] (-0.16-0.02)
SMMI SDS (CI)	**0.90 (0.86-0.94)**	**0.86 (0.80-0.93)**	-0.04[N] (-0.12-0.04)	**0.62 (0.58-0.66)**	**1.33 (1.28-1.38)**	**0.70 (0.64-0.77)**
Girls						
Height SDS (CI)	**2.31 (2.30-2.33)**	**2.64 (2.61-2.68)**	**0.33 (0.29-0.37)**	**1.70 (1.68-1.73)**	**2.98 (2.95-3.02)**	**1.28 (1.24-1.32)**
Weight SDS (CI)	**1.44 (1.41-1.48)**	**1.76 (1.72-1.81)**	**0.32 (0.26-0.38)**	**0.90 (0.86-0.94)**	**1.90 (1.83-1.97)**	**1.00 (0.92-1.08)**
BFM SDS (CI)	**0.57 (0.52-0.61)**	**0.89 (0.83-0.95)**	**0.32 (0.26-0.39)**	**0.37 (0.32-0.42)**	**1.07 (1.00-1.15)**	**0.70 (0.62-0.79)**
SMM SDS (CI)	**1.86 (1.83-1.88)**	**2.05 (2.00-2.10)**	**0.19 (0.13-0.24)**	**1.24 (1.20-1.27)**	**2.23 (2.18-2.29)**	**1.00 (0.93-1.06)**
BMI SDS (CI)	**0.36 (0.32-0.40)**	**0.56 (0.51-0.62)**	**0.20 (0.13-0.27)**	**0.19 (0.15-0.24)**	**0.72 (0.64-0.80)**	**0.52 (0.43-0.61)**
BFMI SDS (CI)	**0.21 (0.16-0.25)**	**0.51 (0.45-0.56)**	**0.30 (0.22-0.37)**	**0.07 (0.02-0.12)**	**0.60 (0.52-0.68)**	**0.53 (0.43-0.62)**
SMMI SDS (CI)	**0.87 (0.83-0.91)**	**0.90 (0.84-0.97)**	**0.03[N] (-0.04-0.11)**	**0.47 (0.43-0.52)**	**1.01 (0.93-1.08)**	**0.53 (0.45-0.62)**

[N]Statistically insignificant.
SDS: standard deviation score, SN: short-to-normal statured group, SS: short-to-short statured group, BFM: body fat mass, SMM: skeletal muscle mass, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index, CI: 95% confidence interval

SDS) shorter and their body weight, BFM and SMM were lower by 6.73 (1.77 SDS), 2.35 (0.89 SDS) and 2.61 (2.05 SDS) kg, respectively, than those of the girls in the control group. Their BMI, SMMI and BFMI were also lower by 1.19 (0.56 SDS), 0.84 (0.51 SDS) and 0.46 (0.90 SDS) kg/m² than those of the girls in the control group. At 12 years of age, the girls in the SS group were, on average, 16.34 cm (2.98 SDS) shorter, and their body weight, BFM and SMM were lower by 13.15 (1.90 SDS), 4.47 (1.07 SDS) and 5.08 (2.23 SDS) kg, respectively. In addition, their BMI, SMMI and BFMI were lower by 1.88 (0.72 SDS), 1.00 (0.60 SDS) and 0.71 (1.01 SDS) kg/m², respectively, than those of the girls in the control group.

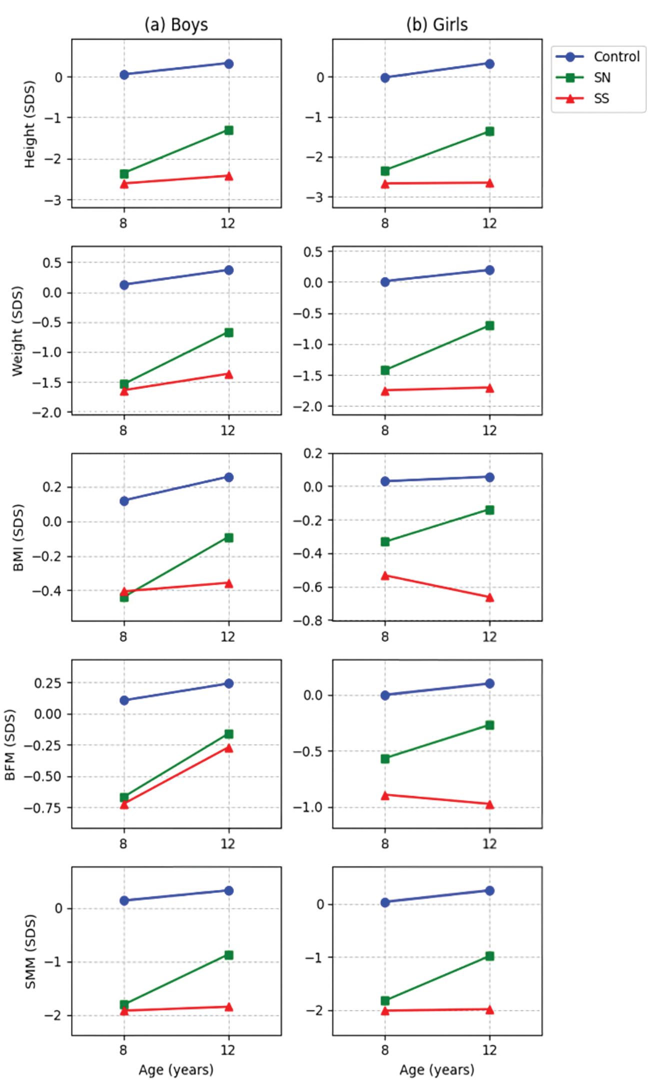

Figure 1. Changes of mean height, weight, and body composition at ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

SN: short-to-normal statured group, SS: short-to-short statured group, BMI: body mass index, BFM: body fat mass, SMM: skeletal muscle mass, SDS: standard deviation score

When comparing the parameters between the girls in the SN and SS groups, it was observed that, unlike the boys, the girls in the SN group were already taller (1.21 cm & 0.33 SDS) and heavier (0.96 kg & 0.32 SDS) and had greater BFM (0.77 kg & 0.32 SDS) and SMM (0.15 kg & 0.19 SDS) by the age of 8 than the girls in the SS group. Moreover, their BMI (0.39 kg/m² & 0.20 SDS) and BFMI (0.47 kg/m² & 0.30 SDS) were also significantly higher. These discrepancies became more pronounced by 12 years of age. The girls in the SS group were shorter (7.17 cm & 1.28 SDS) and lighter (6.50 kg & 1.00 SDS), and their BFM and SMM were lower by 2.69 (0.70 SDS) and 2.24 (1.00 SDS) kg, respectively. Furthermore, their BMI and BFMI were lower by 1.34 (0.52 SDS) and 0.87 (0.53 SDS) kg/m², respectively. Notably, compared to girls in the SN group, the difference in SMMI was not significant at 8 years of age (0.00 kg/m² & 0.03 SDS), but it became significant by 12 years of age (0.38 kg/m² & 0.53 SDS).

Differences in Longitudinal Growth Trajectories of Height, Weight, and Body Composition Among SS, SN, and the Control Group from Pre-pubertal to Early Pubertal Stages

To assess the longitudinal differences in the height, weight and body composition growth across the SS, SN and control groups, we used the DID estimator (Table 3, Figure 2 and Appendix Table A3). This estimator computes these variances by assessing the changes in SDS between 8 and 12 years of age within each group. When comparing the data between the boys in the SS and control groups, the SDS changes in most parameters were not significant, except for the SMMI SDS change of 0.46 SDS. Conversely, the boys in the SN group demonstrated significantly greater increases in height (0.78 SDS), weight (0.62 SDS), BFM (0.37 SDS) and SMM (0.75 SDS) compared to the control group. Furthermore, when compared to the SS group, the boys in the SN group showed significantly greater increases in height (0.87 SDS), weight (0.59 SDS), SMM (0.86 SDS) and SMMI (0.75 SDS).

Similar trends were observed among the girls. When comparing the values between the girls in the SS and control groups, no significant differences were found in the SDS changes of any parameter. Conversely, the girls in the SN group displayed notable growth discrepancies with the control group. The SN group showed significantly greater increases in height (0.61 SDS), weight (0.54 SDS), SMM (0.62 SDS) and SMMI (0.39 SDS) than the control group. When compared to the SS group, the SN group exhibited significantly greater increases in height (0.95 SDS), weight (0.68 SDS), SMM (0.81 SDS) and SMMI (0.50 SDS).

Table 3. Comparison of height, weight, and body composition SDS changes between ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

	Difference			Difference-in-difference		
	Control	SN	SS	Control-SN	Control-SS	SN-SS
Boys						
Height SDS (CI)	**0.28 (0.27-0.28)**	**1.05 (1.03-1.08)**	**0.19 (0.15-0.22)**	**-0.78† (-1.03- -0.53)**	0.09 (-0.26-0.44)	**0.87† (0.67-1.07)**
Weight SDS (CI)	**0.25 (0.23-0.26)**	**0.87 (0.81-0.93)**	**0.27 (0.20-0.35)**	**-0.62† (-0.93- -0.32)**	-0.03 (-0.45-0.40)	**0.59† (0.18-1.01)**
BFM SDS (CI)	**0.13 (0.12-0.15)**	**0.51 (0.44-0.57)**	**0.45 (0.36-0.54)**	**-0.37* (-0.69- -0.06)**	-0.32 (-0.76-0.12)	0.05 (-0.42-0.53)
SMM SDS (CI)	**0.19 (0.18-0.20)**	**0.94 (0.90-0.98)**	**0.07 (0.02-0.13)**	**-0.75† (-1.02- -0.47)**	0.12 (-0.27-0.50)	**0.86† (0.56-1.17)**
BMI SDS (CI)	**0.14 (0.13-0.15)**	**0.35 (0.28-0.42)**	**0.05 (-0.04-0.14)**	-0.21 (-0.52-0.10)	0.09 (-0.35-0.53)	0.30 (-0.19-0.79)
BFMI SDS (CI)	**0.08 (0.07-0.09)**	**0.39 (0.32-0.46)**	**0.47 (0.38-0.57)**	-0.31 (-0.63-0.00)	-0.40 (-0.84-0.05)	-0.08 (-0.59-0.42)
SMMI SDS (CI)	**0.09 (0.08-0.10)**	**0.37 (0.32-0.43)**	**-0.37 (-0.46- -0.29)**	-0.28 (-0.58-0.02)	**0.46* (0.05-0.88)**	**0.75† (0.33-1.16)**
Girls						
Height SDS (CI)	**0.36 (0.35-0.37)**	**0.97 (0.94-0.99)**	**0.02 (-0.03-0.07)**	**-0.61† (-0.87- -0.35)**	0.34 (-0.02-0.70)	**0.95† (0.74-1.16)**
Weight SDS (CI)	**0.18 (0.17-0.19)**	**0.72 (0.67-0.78)**	**0.04 (-0.04-0.13)**	**-0.54† (-0.83- -0.25)**	0.14 (-0.27-0.54)	**0.68† (0.27-1.08)**
BFM SDS (CI)	**0.10 (0.09-0.11)**	**0.30 (0.24-0.36)**	**-0.08 (-0.18-0.01)**	-0.20 (-0.50-0.11)	0.18 (-0.24-0.60)	0.38 (-0.09-0.85)
SMM SDS (CI)	**0.22 (0.21-0.23)**	**0.84 (0.80-0.88)**	**0.03 (-0.04-0.10)**	**-0.62† (-0.90- -0.34)**	0.19 (-0.20-0.58)	**0.81† (0.48-1.13)**
BMI SDS (CI)	**0.03 (0.02-0.04)**	**0.19 (0.13-0.26)**	**-0.13 (-0.22- -0.04)**	-0.17 (-0.47-0.14)	0.16 (-0.26-0.58)	0.32 (-0.15-0.80)
BFMI SDS (CI)	**0.04 (0.03-0.05)**	**0.17 (0.11-0.24)**	**-0.06 (-0.16-0.04)**	-0.14 (-0.44-0.17)	0.09 (-0.33-0.52)	0.23 (-0.26-0.73)
SMMI SDS (CI)	**0.03 (0.01-0.04)**	**0.42 (0.36-0.48)**	**-0.08 (-0.18-0.02)**	**-0.39* (-0.69- -0.09)**	0.10 (-0.31-0.52)	**0.50* (0.03-0.96)**

†p value < 0.01, *p value < 0.05.

SDS: standard deviation score, SN: short-to-normal statured group, SS: short-to-short statured group, BFM: body fat mass, SMM: skeletal muscle mass, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index, CI: 95% confidence interval

Discussion

The present study is the first to analyze and compare the longitudinal body composition changes between Korean children with a pre-pubertal short stature who maintained their short stature and those who attained a normal stature by early puberty. The cross-sectional analysis indicated that children in the SS group had significantly lower values for weight, BFM, SMM, BMI, BFMI, and SMMI compared to the control group at both assessed ages. In a longitudinal perspective, the SN group showed significantly larger increases in height (0.87 SDS for boys and 0.95 SDS for girls), weight (0.59 SDS for boys and 0.68 SDS for girls), and SMMI (0.75 SDS for boys and 0.50 SDS for girls) than the SS group, while there was no significant difference in BFMI between the groups.

To facilitate early intervention by clinicians, the present study focused on data collected before the period of late puberty, establishing the ages of 8 and 12 years as benchmarks for pre-pubertal and early pubertal stages, respectively. The rationale for selecting these age benchmarks is twofold. First, a child with a short stature who did not achieve a normal height by early puberty may have a persistent short stature or reduced final adult height. Even among children with CDGP, which are typically known to be able to naturally overcome their short stature, some of them may not reach their predicted adult height, particularly if the puberty onset is delayed (10). This suggests that, regardless of whether the short stature is due to an underlying organic cause or related to CDGP, the children who do not exhibit a normal growth pattern before the onset of puberty may experience a reduction in final adult height. Therefore, analyzing the growth patterns up to the early pubertal stage will facilitate timely interventions. Second, our prior research on the pubertal growth spurt within the GP cohort dataset used in this study, utilized the age of onset of the growth spurt (AGOS) as an indirect indicator of puberty onset. The findings revealed that the AGOS, within one SD of the normal distribution, was 10.17 ± 0.61 and 8.57 ± 0.68 years for boys and girls, respectively. Consequently, these age ranges were considered indicative of puberty onset, leading to the selection of the ages 8 and 12 years as the respective age thresholds for this study (9).

In this context, the children were categorized into three groups based on their stature at 8 and 12 years of age. Our findings showed that both boys and girls in the SS group were significantly shorter and lighter and had significantly lower BFM, SMM, BMI, BFMI, and SMMI at 8 and 12 years of age than the control group. However, the children with pre-pubertal short stature exhibited distinct growth patterns, with the differences between those who remained short-statured and those who achieved a normal stature becoming more pronounced over time. When assessing the growth differences across groups, the SN group demonstrated

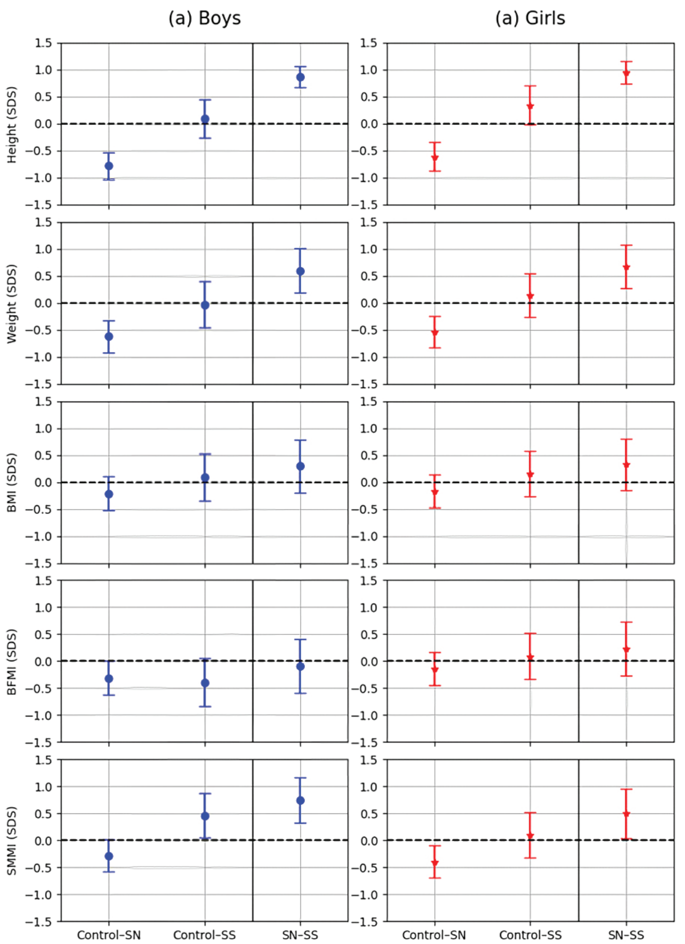

Figure 2. Comparison of height, weight, BMI, BFMI, and SMMI changes between ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

SN: short-to-normal statured group, SS: short-to-short statured group, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index

significantly greater increases in height, weight, BFM and SMM than the control group. Additionally, compared to the SS group, the SN group exhibited greater increases in height, weight, SMM and SMMI. A significant difference in SMMI was observed between the boys in the SS and control groups, whilst no significant differences were found between girls in the SS and control groups. Overall, the SN group exhibited significantly greater increases in height, weight and SMM than the SS and control groups, with consistent trends observed in both sexes.

In the present study there was a significant difference in SMMI between the SN and SS groups, which is consistent with the results of a previous case-control study analyzing the body composition of preschool children with short stature (11). Short stature results from diverse etiologies, and numerous factors associated with lower SMMI have been identified among them. From the perspective of GH action, low SMMI in children with short stature can often be attributed to impaired skeletal muscle cell proliferation and myocyte differentiation resulting from reduced GH/IGF-1 axis activity, particularly in cases of GHD. This finding aligns with the results of a previous study conducted in China involving a similar age group (mean age of 10.00 ± 3.42 years). In that study, SMMI, measured using chest computed tomography (CT), was positively associated with serum GH peak and IGF-1 levels. Low peak GH and IGF-1 levels were identified as independent predictors of reduced SMMI in children with short stature (12,13). Consistent with these observations, studies investigating ISS also highlight reduced lean body mass in affected children. A case-control study involving preschool-age children with unexplained short stature reported significantly lower fat-free mass (FFM) and SMM compared to height-matched normal controls (11). Notably, SMMI was lower in children with short stature despite similar BMI values, suggesting a relative deficit in muscle tissue potentially linked to early-life growth impairment. In addition, the other factors contributing to a short stature may include a low lean body mass, as observed in individuals with ISS, decreased SMM due to malnutrition, including inadequate protein intake, and muscle wasting associated with chronic illnesses, including chronic kidney disease and cystic fibrosis (14,15,16). Importantly, however, there is a lack of direct statistical data linking endocrine abnormalities or chronic illnesses causally to short stature and reduced SMMI gain and so caution should be exercised when interpreting these associations. Furthermore, another plausible and often overlooked explanation is that many of the children with short stature might have been born SGA, either with low birthweight or low birth length, predisposing them to persistent short stature and reduced muscle mass later in life. Emerging research indicates that children with short stature who were born SGA may have reduced SMM compared to their peers. Persistent short stature in children born SGA is frequently associated with significant deficits in muscle mass. Schweizer et al. (17) studied 34 short prepubertal children born SGA (mean age approximately 7.3 years; height SDS approximately -3.3) and reported that these children exhibited significantly reduced muscle mass and impaired muscle function. Similarly, Rojo-Trejo et al. (18) compared 44 term-born SGA children aged 6-11 years to 57 appropriate-for-gestational-age peers. The SGA group demonstrated consistently lower measures of muscle and bone mass, including significantly lower appendicular skeletal muscle mass index and total body bone mineral content and density ($p \leq 0.005$).

Although these factors may all contribute to persistently low SMMI in children with short stature, it is important to recognize that many cases of short stature remain unexplained and are likely influenced by environmental factors. Indeed, more than half of short-stature cases are not associated with systemic diseases, endocrine disorders, or chromosomal abnormalities (19). Environmental factors, including socio-economic status, malnutrition, and lack of physical activity, have been widely studied and are commonly recognized as contributing factors (20,21).

Therefore, regardless of whether the cause of short stature is clearly identified, we believe it is essential to analyze a child's body composition to monitor children with persistently low SMMI. The individuals who consistently exhibit a low SMMI and short stature should receive increased attention and care, as they may be at risk for growth problems. This comprehensive approach ensures that both pathological causes and environmental influences are thoroughly evaluated, allowing for a better understanding of the underlying aetiology and potential presence of concurrent metabolic disorders associated with low SMMI (22,23).

The present study has a few limitations. The first limitation is that, although we adhered to the standard guidelines provided by InBody Co., Ltd. for BIA measurements, certain factors, such as the inability to uniformly control the hydration status or electrolyte balance across all individuals and the absence of temperature measurements, present challenges (24). Despite these challenges, BIA offers several advantages as a method for assessing body composition. Although alternative methodologies, including magnetic resonance imaging, CT and DXA are available, BIA stands out due to its simplicity, non-invasiveness and cost-effectiveness, making it particularly suitable for large-scale studies (25,26). Recent studies on multi-frequency BIA devices indicate reduced susceptibility to errors and the excellent reproducibility of these devices, supporting their reliability for use in longitudinal observations across children and adolescent populations (27,28). Another limitation of our study is that we longitudinally analyzed the body composition characteristics in children with pre-pubertal short stature persisting into the early pubertal stage, which did not encompass the entire age spectrum of children and adolescents, including the age the final adult height was achieved. Furthermore, since our cohort study was conducted in Gwangmyeong City, Gyeonggi Province, it may not fully represent the characteristics of the entire Korean population, potentially limiting the generalizability of our findings. Finally, in this study, the diminished gain in SMMI observed in the SS group, which failed to achieve normal height by early puberty, was initially interpreted as suggestive of growth failure. However, although our definitions of prepuberty and early puberty were based on AGOS obtained from previous research involving the same cohort (7,9), the absence of key parameters, including measured parental height, Tanner stage, bone age estimation, birth history (including gestational age, birth weight, and birth length), and height velocity, limits our ability to conclusively attribute these findings to true growth failure (2,10). Notably, our prior research on pubertal changes in body composition within the same cohort demonstrated that boys typically exhibit an earlier age at peak FFM velocity and a higher velocity compared to girls (7). This suggests a potentially greater variability in SMMI depend on pubertal staging in boys, particularly among those with CDGP. Consequently, without these additional parameters, distinguishing true pathological short stature from normal variants such as CDGP or familial short stature remains challenging. Therefore, future studies should incorporate these critical factors to enable a more precise and objective classification. Additionally, we plan to follow this cohort into late adolescence and adulthood to determine whether early pubertal SMMI trajectories are predictive of final adult height, thereby clarifying whether the observed differences reflect transient variations or enduring growth outcomes.

However, the greatest strength of our study lies in its being, to the best of our knowledge, the first longitudinal population-based study to demonstrate significant differences in SMMI among children with a pre-pubertal short stature that persists into early puberty, children with a pre-pubertal short stature who achieved a normal height, and children with a normal height. We are continuously collecting new participants' height, weight, and body composition data each year while expanding the geographical range of our subjects. We are also incorporating additional clinically relevant parameters, such as parental height, Tanner staging, bone age estimation, birth history (including gestational age, birth weight, and birth length), and height velocity into our data collection. In future study, by conducting longitudinal analyses on subjects who have reached their final adult height, we aim to evaluate the broader scope of data and understand how changes in body composition during different stages of pubertal development influence height growth. This comprehensive approach will enable a more detailed analysis of the impact of body composition on final adult stature.

In conclusion, our study could serve as a foundation for using longitudinal body composition assessment to identify high-risk children with short stature. The most significant increase in SMMI was observed in children who improved to normal height from pre-pubertal short stature. Children with lower increases in SMMI may require further assessment for continued short stature.

Conclusion

This study analyzed anthropometric and body composition changes in children with pre-pubertal short stature who either achieved normal height or remained short by early puberty. Children who achieved normal height demonstrated greater increases in SMMI, height, and weight, with SMMI being the most significant factor in body composition trajectory than those who remained short. Lower increases in SMMI may indicate a need for further evaluation and potential intervention for persistent short stature.

Ethics

Ethics Committee Approval: The present study was approved by the Institutional Review Board of Yonsei University Health System, Severance Hospital (approval no: 4-2023-1470, date: 28.12.2023).

Informed Consent: Written informed consent was obtained from both the legal guardians and the students themselves prior to participation.

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Footnotes

Authorship Contributions

Concept: Junghwan Suh, Jihun Kim, Design: Junghwan Suh, Jihun Kim, Data Collection or Processing: Dohyun Chun, Analysis or Interpretation: Dohyun Chun, Literature Search: Seo Jung Kim, Writing: Dohyun Chun, Seo Jung Kim, Junghwan Suh, Jihun Kim.

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Availability of Data and Materials: The data that support the findings of this study are available from GP Co., Ltd. but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of GP Co., Ltd.

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