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RESEARCH

Identification and characterization of factors associated with short stature and pre-shortness in Chinese preschool-aged children

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Abstract

Objectives: We aimed to identify and characterize potential factors, both individually and jointly as a nomogram, associated with short stature and pre-shortness in Chinese preschool-aged children.
Methods: Total of 9501 children aged 3–6 years were recruited from 30 kindergartens in Beijing and Tangshan from September to December 2020 using a stratified random sampling method. Effect-size estimates are expressed as odds ratio (OR) and 95% CI.
Results: The prevalence of short stature and pre-shortness in preschool-aged children was 3.9% (n = 375) and 13.1% (n = 1616), respectively. Factors simultaneously associated with the significant risk for short stature, pre-shortness and both included BMI, paternal height, maternal height, birth weight, birth height, latter birth order (≥2) and less parental patience to children. Besides, breastfeeding duration (≥12 months) was exclusively associated with pre-shortness (OR, 95% CI, P: 1.16, 1.01 to 1.33, 0.037), and childhood obesity with both short stature (3.45, 2.62 to 4.54, <0.001) and short stature/pre-shortness (1.37, 1.15 to 1.64, <0.001). Modeling of significant factors in nomograms had descent prediction accuracies, with the C-index being 77.0, 70.1 and 71.2% for short stature, pre-shortness and both, respectively (all P < 0.001).
Conclusions: Our findings indicate the joint contribution of inherited characteristics, nutrition status from the uterus to childhood, and family psychological environment to short stature and pre-shortness in Chinese preschool-aged children. Further validation in other independent groups is warranted.

Key Words

- short stature
- pre-shortness
- preschool-aged children
- factor
- nomogram

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Introduction

Short stature is increasingly recognized as a worldwide public health concern, and it affects about 3% to 11% of children worldwide (1, 2, 3, 4). In China, the prevalence of short stature was estimated to be 3.7% among children from 7 to 18 years of age (4). Short stature is commonly seen in pediatric endocrinology units in routine clinical practice (5). Considering the fact that immediate and effective interventions can improve final adult height, early identification of factors that can predict pre-shortness or short stature in children is crucial to implement timely interventions that may reduce or prevent the occurrence of short stature in adulthood.

The detrimental consequences of short stature have drawn special attention due to its underlying physical and psychosocial impairments from childhood to adulthood, such as cardiometabolic diseases, diabetes and

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psychological functioning problems (6, 7, 8, 9). In clinical practice, pre-shortness is often the major reason for medical appointments, as more and more parents are anxious that children with shorter body height may pursue less higher education, have less employment opportunities, and even have problems with heterosexual relationships (10, 11, 12). Further from clinical aspects, childhood pre-shortness may be a harbinger of short stature in adulthood due to the multifactorial and complex contributions to height gain process. Our recent study indicated that pre-shortness was inclined to be affected by modifiable factors than short stature (13), underscoring the importance of prevention and control at the stage of pre-shortness. Hence, it is of public health and clinical importance to identify and characterize factors associated with short stature and pre-shortness in children and help obtain satisfied final body height in adulthood.

It is generally believed that human height is a complex trait on which inherited and environmental factors act interactively (14, 15). About 20% of short stature is pathological, and 80% is idiopathic due to unknown causes (16). Factors associated with less height gain have been extensively evaluated, yet the results are not often reproducible, especially for modifiable factors (17, 18). For example, some studies have shown that high BMI was positively associated with short stature and pre-shortness (13, 19), whereas others failed to support this claim (20). The reasons for inconsistent results are manifold, possibly due to differences in races or ethnicities, genetic underpinnings, study designs, statistical power, as well as the characteristics of study populations.

To shed some light on the possible reasons and yield more information for future studies, we undertook a large-scale, cross-sectional survey in Chinese preschool-aged children from 30 randomly selected kindergartens in Beijing and Tangshan, aiming to identify and characterize potential factors that were significantly associated with short stature and pre-shortness, both individually and jointly as a nomogram prediction model.

Methods

Study design

The cross-sectional survey was done in Beijing and Tangshan from September to December 2020. The conduct of this survey was reviewed and approved by the Ethics Committee of China–Japan Friendship Hospital and was in compliance with the principles of the Declaration of Helsinki. Parents or guardians of all study children have read and signed informed consent forms prior to participation.

Study children

Study population included preschool-aged children attending junior to senior kindergarten classes at the time of enrollment. Using a stratified cluster random sampling strategy, 4 out of 16 districts in Beijing and 2 out of 7 districts in Tangshan were selected. Within each district, 5 kindergartens were selected, and 30 kindergartens were included finally. Children who are diagnosed to have major illnesses such as chronic kidney disease, hypothyroidism, or congenital heart disease were excluded from the present analysis.

Data collection and quality control

Self-designed questionnaires were sent to the parents or guardians of study children. From children, surveyed data included sex, region, date of birth, time spent on outdoor activities at workdays and weekends, weekly intake frequency of fast food and night meals, picky eating, birth weight, birth height, gestational age, delivery mode, twins or not, birth order, breastfeeding duration and solid food introduction age. Weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) of children were measured by trained healthcare physicians. From parents, self-reported data on age, height, gestational diabetic mellitus, education, family income, and self-rated patience to children were recorded.

Kindergarten teachers were in charge of sending the electronic questionnaires to the parents or guardians of all participating children. Data were exported from electronic questionnaires to a Microsoft Office Excel™ spreadsheet and were strictly checked by trained staff. In case of missing or uncertain records, parents were contacted for the sake of clarity.

Definition of short stature and pre-shortness

Children with height z-scores < −2S.D. are defined as short stature according to age- and sex-specific measures under the China criteria (2009) (21). Children with height z-scores between < −1S.D. and ≥ −2S.D. are defined as pre-shortness.

Definition of other characteristics

For children, BMI was calculated as measured weight divided by height squared (kg/m^2). BMI category was

Table 1 The baseline characteristics of study children.

Characteristics	Children with normal height (n = 7885)	Children with SS (n = 375)	P_1	Children with PSS (n = 1241)	P_2	Children with SS or PSS (n = 1616)	P_3
From children							
Age (months)	55.5 (48.0, 66.7)	55.0 (47.8, 63.7)	0.387	53.8 (47.6, 65.8)	0.002	54.6 (47.6, 65.7)	0.003
Males	4169 (52.9%)	144 (38.4%)	<0.001	510 (41.1%)	<0.001	4169 (52.9%)	<0.001
Region			<0.001		0.001		<0.001
Beijing	5308 (67.3%)	170 (43.5%)		776 (62.6%)		946 (58.6%)	
Tangshan	2577 (32.7%)	205 (54.7%)		464 (37.4%)		669 (41.4%)	
Height (cm)	110 (105, 117)	98 (93, 102)		102 (98, 109)	<0.001	100 (97, 107)	<0.001
Height (s.d.)	0.3 (−0.3, 1.0)	−2.5 (−2.9, −2.2)	<0.001	−1.3 (−1.6, −1.2)	<0.001	−1.5 (−1.9, −1.2)	<0.001
Weight (kg)	19.0 (17.0, 21.0)	15.5 (14.5, 17.5)	<0.001	16.0 (15.0, 18.0)	<0.001	16.0 (15.0, 18.0)	<0.001
BMI (kg/m^2)	15.4 (14.4, 16.5)	16.3 (15.0, 18.1)	<0.001	15.6 (14.6, 16.6)	0.001	15.7 (14.7, 16.8)	<0.001
BMI category			<0.001		0.534		0.001
Non overweight or obesity	5968 (87.9%)	211 (68.7%)		960 (85.2%)		1171 (84.8%)	
Overweight	1098 (15.5%)	68 (24.4%)		167 (14.8%)		235 (16.7%)	
Obesity	819 (12.1%)	96 (31.3%)		114 (10.6%)		210 (15.2%)	
Outdoor activities (hours per day)	1.6 (1.0, 2.3)	1.7 (1.0, 2.4)	0.593	1.6 (1.0, 2.3)	0.898	1.6 (1.0, 2.3)	0.726
Night meals intake frequency			0.368		0.189		0.276
None or once in a while	4648 (58.9%)	233 (62.1%)		700 (56.4%)		933 (57.7%)	
1–2 times weekly	1800 (22.8%)	79 (21.1%)		296 (23.9%)		375 (23.2%)	
3–5 times weekly	762 (9.7%)	28 (7.5 %)		119 (9.6%)		147 (9.1%)	
Every day	675 (8.6%)	35 (9.3%)		126 (10.2%)		161 (10.0%)	
Fast food intake frequency			0.108		0.184		0.159
None or once in a while	5177 (65.7%)	264 (70.4%)		837 (67.4%)		1101 (68.1%)	
1–2 times weekly	2564 (32.5%)	101 (26.9%)		387 (31.2%)		488 (30.2%)	
3–5 times weekly	83 (1.1%)	6 (1.6%)		6 (0.5%)		12 (0.7%)	
Every day	61 (0.8%)	4 (1.1%)		11 (0.9%)		15 (0.9%)	
Picky about food			0.762		0.042		0.06
No	4625 (58.7%)	217 (57.9%)		690 (55.6%)		907 (56.1%)	
Yes	3260 (41.3%)	158 (42.1%)		551 (44.4%)		709 (43.9%)	
Birthweight (kg)	3.4 (3.0, 3.6)	3.1 (2.9, 3.5)	<0.001	3.2 (3.0, 3.5)	<0.001	3.1 (2.9, 3.5)	<0.001
Birth height (cm)	50 (50, 52)	50 (50, 52)	<0.001	50 (49, 51)	<0.001	50 (50, 52)	<0.001
Birth order			<0.001		<0.001		<0.001
<2	4657 (59.1%)	158 (42.1%)		646 (52.1%)		804 (49.8%)	
≥2	3228 (40.9%)	217 (57.9%)		595 (47.9%)		812 (50.2%)	
Twins			0.524		0.164		0.378
No	7691 (99.4%)	367 (99.2%)		1207 (99.8%)		1574 (99.6%)	
Yes	43 (0.6%)	3 (0.8%)		3 (0.2%)		6 (0.4%)	
Gestational age (weeks)			0.056		0.026		0.004
<37	678 (8.6%)	44 (11.7%)		123 (9.9%)		167 (10.3%)	
37–42	7058 (89.5%)	321 (85.6%)		1083 (87.3%)		1404 (86.9%)	
>42	149 (1.9%)	10 (2.7%)		35 (2.8%)		45 (2.8%)	
Delivery mode			0.003		0.275		0.691
Vaginal delivery	4234 (53.7%)	172 (45.9%)		687 (55.4%)		859 (53.2%)	
Cesarean section	3651 (46.3%)	203 (54.1%)		554 (44.6%)		757 (46.8%)	

(Continued)

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Table 1 Continued.

Characteristics	Children with normal height (*n* = 7885)	Children with SS (*n* = 375)	P_1	Children with PSS (*n* = 1241)	P_2	Children with SS or PSS (*n* = 1616)	P_3
Breastfeeding duration (months)			0.99		0.01		0.028
≤12	2752 (65.1%)	131 (34.9%)		387 (31.2%)		518 (32.1%)	
>12	5133 (65.1%)	131 (34.9%)		854 (68.8%)		1098 (67.9%)	
Solid food introduction age (months)			<0.001		0.736		0.014
≤6	5963 (75.6%)	242 (64.5%)		933 (75.2%)		1175 (72.7%)	
>6	1922 (24.4%)	133 (35.5%)		308 (24.8%)		441 (27.3%)	
From parents or guardians							
Gestational diabetes mellitus			0.273		0.992		0.615
No	6849 (91.1%)	333 (92.8%)		1073 (91.1%)		1406 (91.5%)	
Yes	671 (8.9%)	26 (7.2%)		105 (8.9%)		131 (8.5%)	
Maternal height (cm)	175 (172, 178)	172 (170, 175)	<0.001	160 (158, 163)	<0.001	160 (158, 163)	<0.001
Paternal height (cm)	162 (160, 165)	160 (156, 163)	<0.001	172 (170, 175)	<0.001	172 (170, 175)	<0.001
Maternal age at delivery (years)	29.3 (27.0, 32.6)	28.9 (26.7, 33.4)	0.137	29.1 (26.8, 32.6)	0.224	29.0 (26.8, 32.6)	0.087
Paternal age at delivery (years)	30.6 (27.8, 34.2)	30.1 (27.6, 33.4)	0.049	30.2 (27.6, 34.0)	0.134	30.2 (27.6, 33.9)	0.03
Maternal education	29 (27, 33)		<0.001				<0.001
High school degree or below	2451 (31.1%)	200 (53.3%)		2451 (31.1%)	0.001	658 (40.7%)	
Bachelor's degree	4167 (52.8%)	143 (38.1%)		4167 (52.8%)		740 (45.8%)	
Master's degree	1045 (13.3%)	25 (6.7%)		1045 (13.3%)		179 (11.1%)	
Doctor's degree or above	222 (2.8%)	7 (1.9%)		222 (2.8%)		39 (2.4%)	
Paternal education			<0.001		0.002		<0.001
High school degree or below	2726 (34.6%)	207 (55.2%)		496 (40.0%)		703 (43.5%)	
Bachelor's degree	3810 (48.3%)	127 (33.9%)		536 (43.2%)		663 (41.0%)	
Master's degree	955 (12.1%)	23 (6.1%)		152 (12.2%)		175 (10.8%)	
Doctor's degree or above	394 (5.0%)	18 (4.8%)		57 (4.6%)		75 (4.6%)	
Family income (RMB per year)			<0.001		0.216		<0.001
<100,000	2579 (32.7%)	206 (54.9%)		439 (35.4%)		645 (39.9%)	
100,000–300,000	2929 (37.1%)	109 (29.1%)		458 (36.9%)		567 (35.1%)	
>300,000	2377 (30.1%)	60 (16.0%)		306 (24.7%)		404 (25.0%)	
Parental patience to children			<0.001		0.001		<0.001
10 points	972 (12.3%)	45 (12.0%)		121 (9.8%)		166 (10.3%)	
7–9 points	4370 (55.4%)	172 (45.9%)		657 (52.9%)		829 (51.3%)	
4–6 points	2226 (28.2%)	126 (33.6%)		396 (31.9%)		522 (32.3%)	
1–3 points	317 (4.0%)	32 (8.5%)		67 (5.4%)		99 (6.1%)	

Data are expressed as median (interquartile range) or count (percent). *P* value was calculated by the rank-sum test or the Chi-squared test, where appropriate.
PSS, pre-shortness; SS, short stature.

defined as obesity, overweight and non-overweight or obesity according to the China criteria (2009) (22). Time spent on outdoor activities every day was calculated as the sum of time both on workdays × 5 and weekends × 2 divided by 7. Fast food is referred to as food with high energy and low nutrition (e.g. hamburger and french fries), night meal is defined as eating food within 2 h before bedtime. And weekly intake frequency was consistent with fast food and night meals, which were classified as every day, often (three to five times), occasional (one to two times) or none or once in a while. Picky eating was defined as yes or no. Birth order was grouped into <2 and ≥2. Whether twins or not was also recorded. Additionally, gestational age was divided into <37 weeks, 37–42 weeks, and >42 weeks. Delivery mode included vaginal delivery and cesarean section. Breastfeeding duration was classified as <12 months, and ≥12 months according to the mean value. Solid food introduction age was recorded in months.

For parents or guardians, maternal and paternal height were self-reported. Maternal and paternal age at delivery were calculated as the difference between the date of child's birthdate and parents' birthdate. Maternal gestational diabetes mellitus diagnosed by doctors from second-class or above hospitals were recorded. Education was categorized as doctor's degree or above, master's degree, bachelor's degree, and high school degree or below. Family income (RMB per year) was categorized as >300,000, 100,000–300,000 or <100,000. Parental self-rated patience to children was separated into 10 points, 7–9 points, 4–6 points and 1–3 points. Lower points represented less patience to children in their daily life.

Statistical analyses

The distributions of continuous variables between two groups were assessed for normality by the use of the skewness and kurtosis test. Skewed continuous variables are expressed as median (interquartile range) and normally distributed variables as mean (s.d.). Categorical variables are expressed as numbers (percentage). Between-group comparisons were implemented by the *t*-test or rank-sum test or χ^2 test, where appropriate.

To examine whether there is a possible bias arising from different kindergartens, intraclass correlation coefficient (ICC), which is a statistic that can be used to quantify the degree to which observations within a cluster differ from those between clusters,(18) was calculated.

To identify significant factors associated with childhood short stature and pre-shortness, multivariable linear regression analyses using the Stepwise method were first done. Standardized and unstandardized regression coefficients, as well as 95% CI and *P* value were recorded.

Table 2 Multivariable regression analyses of potential contributing factors on height (s.d.) in preschool-aged children

Variables	Unstandardized coef.	95% CI	*P*	Standardized coef.
Age (months)	0.0001	−0.0022 to 0.0023	0.948	0.0007
Males	0.2748	0.2247 to 0.3248	<0.001	0.1107
Region	−0.0079	−0.0859 to 0.0702	0.843	−0.0030
Children BMI (kg/m^2)	−0.0528	−0.0642 to −0.0415	<0.001	−0.0942
Maternal height (cm)	0.0444	0.0390 to 0.0499	<0.001	0.1721
Paternal height (cm)	0.0500	0.0445 to 0.0551	<0.001	0.2072
Birth height (cm)	0.0208	0.0101 to 0.0315	<0.001	0.0413
Birth weight (kg)	0.3973	0.3375 to 0.4572	<0.001	0.1457
Gestational age (weeks)	0.1366	0.0414 to 0.2318	0.005	0.0293
Gestational diabetes mellitus	0.0493	−0.0386 to 0.1371	0.272	0.0114
Birth order	−0.1275	−0.1907 to −0.0643	<0.001	−0.0507
Twins	0.0670	−0.2844 to 0.4185	0.708	0.0038
Breastfeeding duration (months)	−0.0990	−0.1523 to −0.0457	<0.001	−0.0377
Solid food introduction (months)	−0.0034	−0.0625 to 0.0557	0.909	−0.0012
Night meals intake frequency	−0.0273	−0.0535 to −0.0010	0.042	−0.0213
Fast food intake frequency	−0.0627	−0.1097 to −0.0158	0.009	−0.0273
Outdoor activities (hours per day)	0.0098	−0.0098 to 0.0295	0.325	0.0102
Picky about food	−0.1190	−0.1706 to −0.0674	<0.001	−0.0473
Maternal age at delivery (years)	0.0055	−0.0051 to 0.0161	0.306	0.0192
Paternal age at delivery (years)	0.0089	0.0000 to 0.0178	0.049	0.0356
Maternal education	−0.0564	−0.1057 to −0.0071	0.025	−0.0370
Paternal education	0.0205	−0.0345 to 0.0756	0.465	0.0122
Family income (RMB per year)	−0.0287	−0.0636 to 0.0063	0.108	−0.0219
Parental impatience to children	−0.0464	−0.0823 to −0.0104	0.012	−0.0266

Coef, coefficient.

Table 3 Identification of significant contributing factors separately for SS, PSS and SS or PSS using univariate and multivariable logistic regression analyses in preschool-aged children.

Variables	Children with SS			Children with PSS			Children with SS or PSS		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Unadjusted									
Children BMI (per 1 kg/m^2 increase)	1.19	1.15 to 1.23	<0.001	1.03	1.001 to 1.05	0.042	1.07	1.05 to 1.10	<0.001
Paternal height (per 1 cm increase)	0.88	0.86 to 0.90	<0.001	0.90	0.89 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001
Maternal height (per 1 cm increase)	0.89	0.87 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001
Birth weight (per 1 cm increase)	0.48	0.39 to 0.59	<0.001	0.48	0.43 to 0.55	<0.001	0.48	0.43 to 0.53	<0.001
Birth height (per 1 kg increase)	0.94	0.90 to 0.98	0.005	0.92	0.89 to 0.94	<0.001	0.92	0.91 to 0.94	<0.001
Birth order (≥2)	1.98	1.61 to 2.44	<0.001	1.33	1.18 to 1.50	<0.001	1.46	1.31 to 1.62	<0.001
Parental impatience to children	1.32	1.50 to 1.52	<0.001	1.19	1.10 to 1.29	<0.001	1.22	1.13 to 1.31	<0.001
Breastfeeding duration (≥12 months)	Not significant			1.18	1.04 to 1.35	0.01	1.14	1.01 to 1.27	0.028
Picky about food	Not significant			1.13	1.004 to 1.28	0.043	Not significant		
Gestational age (>42 weeks)	Not significant			Not significant			1.24	1.04 to 1.48	0.019
Partially adjusted*									
Children BMI (per 1 kg/m^2 increase)	1.20	1.16 to 1.24	<0.001	1.04	1.01 to 1.07	0.006	1.08	1.06 to 1.11	<0.001
Paternal height (per 1 cm increase)	0.89	0.87 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001
Maternal height (per 1 cm increase)	0.90	0.88 to 0.92	<0.001	0.90	0.89 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001
Birth weight (per 1 cm increase)	0.50	0.40 to 0.61	<0.001	0.50	0.44 to 0.57	<0.001	0.50	0.44 to 0.55	<0.001
Birth height (per 1 kg increase)	0.94	0.90 to 0.98	0.001	0.92	0.90 to 0.94	<0.001	0.92	0.90 to 0.94	<0.001
Birth order (≥2)	1.53	1.22 to 1.92	<0.001	1.26	1.11 to 1.44	<0.001	1.32	1.17 to 1.48	<0.001
Parental impatience to children	1.22	1.06 to 1.41	0.005	1.19	1.09 to 1.29	<0.001	1.20	1.11 to 1.29	<0.001
Breastfeeding duration (≥12 months)	Not significant			1.15	1.01 to 1.31	0.037	Not significant		
Picky about food	Not significant			1.15	1.02 to 1.29	0.028	Not significant		
Gestational age (>42 weeks)	Not significant			Not significant			Not significant		
Multivariable adjusted**									
Children BMI (per 1 kg/m^2 increase)	1.20	1.15 to 1.24	<0.001	1.04	1.01 to 1.07	0.011	1.08	1.06 to 1.11	<0.001
Paternal height (per 1 cm increase)	0.88	0.86 to 0.90	<0.001	0.89	0.88 to 0.91	<0.001	0.89	0.88 to 0.90	<0.001
Maternal height (per 1 cm increase)	0.90	0.88 to 0.92	<0.001	0.90	0.89 to 0.91	<0.001	0.90	0.89 to 0.91	<0.001
Birth weight (per 1 cm increase)	0.45	0.36 to 0.57	<0.001	0.48	0.42 to 0.55	<0.001	0.47	0.42 to 0.53	<0.001
Birth height (per 1 kg increase)	0.93	0.89 to 0.97	0.001	0.91	0.89 to 0.94	<0.001	0.92	0.90 to 0.94	<0.001
Birth order (≥2)	1.65	1.25 to 2.19	<0.001	1.49	1.27 to 1.75	<0.001	1.53	1.32 to 1.76	<0.001
Parental impatience to children	1.26	1.09 to 1.46	0.002	1.21	1.10 to 1.32	<0.001	1.22	1.13 to 1.32	<0.001
Breastfeeding duration (≥12 months)	Not significant			1.16	1.01 to 1.33	0.037	Not significant		
Picky about food	Not significant			Not significant			Not significant		
Gestational age (>42 weeks)	Not significant			Not significant			Not significant		

*Variables under partial adjustment included age, sex and region; **Variables under multivariable adjustment included age, sex, region, time spent on outdoor activities every day, twins, gestational age, delivery mode, gestational diabetes mellitus, solid food introduction age, parental age at delivery, parental education, family income.
PSS, pre-shortness; SS, short stature.

Next, Logistic regression analyses were performed with all the significant possible factors identified by multivariable linear regression analyses at a significant level of 5%. Adjusting for confounders was implemented in a step-by-step manner: (i) without adjustment, (ii) partial adjustment for age, sex, and region, and (iii) multivariable adjustment additionally for time spent on outdoor activities every day, twins, gestational age, delivery mode, gestational diabetes mellitus, solid food introduction age, parental age at delivery, parental education, and family income. Effect-size estimates were expressed as odds ratio (OR) and 95% CI.

Prediction accuracy of significant factors was appraised from both calibration and discrimination aspects. Calibration statistics include Akaike information criterion (AIC), Bayesian information criterion (BIC), -2 log likelihood ratio test, as well as the Hosmer–Lemeshow test. Discrimination statistics include the area under the receiver operating characteristic (ROC) to justify the improvement in prediction performance. Additionally, the net benefit for adding significant factors was justified by decision curve analysis (23).

Finally, on the basis of significant factors for short stature, pre-shortness and both, prediction nomogram models were constructed, and these models were generated by the R language version 3.5.2 for Windows.

Unless otherwise reported, statistical analyses were completed using the STATA software version 14.0 (Stata Corp, TX) for the Windows. Two-sided *P* value of less than 5% was accepted to be statistically significant. Statistical power was estimated using the PS Power and Sample Size Calculations software version 3.0.

Results

Baseline characteristics

Questionnaires were sent to the parents or guardians of 10,441 children initially, and 98% of them (*n*= 10230) returned the questionnaires within scheduled time. Completed questionnaires were strictly reviewed by trained staff, and finally, 9501 of them were deemed eligible for inclusion. The baseline characteristics of 9501 children in this study are shown in Table 1.

In this study, the prevalence of short stature and pre-shortness was 3.9% (*n*= 375) and 13.1% (*n*= 1616), respectively. In addition, the ICC statistic indicated no evidence of potential bias arising from different kindergartens ($P < 0.01$).

Identification of contributing predictors

As shown in Table 2, multivariable linear regression analyses showed that 15 factors were significantly associated with higher height s.d. Six of them were positive, including males, maternal height, paternal height, birth weight, birth height, and gestational age. Nine were negative, including children BMI, latter birth order ≥ 2, breastfeeding duration >12 months, higher night meals and fast food intake frequency, picky eating, paternal age at delivery, maternal education, and less parental patience to children. All significant factors identified by multivariable linear regression analyses were subsequently incorporated into logistic regression analyses except for males, paternal age

Table 4 Prediction accuracy gained by adding the significant factors identified for short stature or pre-shortness in preschool-aged children.

Statistics	Children with SS		Children with PSS		Children with SS or PSS	
	Basic model	Full model	Basic model	Full model	Basic model	Full model
Calibration						
AIC	2650.990	2274.083	6348.298	5603.153	7570.499	6598.163
BIC	2775.393	2445.800	6474.433	5784.255	7697.360	6773.304
LR test ($\chi2$)	283.94		511.88		684.80	
LR test (*P* value)	<0.001		<0.001		<0.001	
HL test (*P* value)	0.454	0.225	0.379	0.304	0.363	0.203
Discrimination						
IDI (*P* value)	<0.001		<0.001		<0.001	
AUROC (*P* value)	<0.001		<0.001		<0.001	

Basic model included age, sex, region, night meals intake frequency, fast food intake frequency, time spent on outdoor activities every day, picky about food, twins, gestational age, delivery mode, gestational diabetes mellitus, solid food introduction age, parental age at delivery, parental education, family income; Full model additionally included parental height, maternal height, birth weight, birth height, BMI, birth orders (≥2) and parental impatience to children for both short stature and short stature or pre-shortness, parental height, maternal height, birth weight, birth height, BMI, birth orders (≥2) , parental impatience to children and breastfeeding duration (>12 months) for pre-shortness.
AIC, Akaike information criterion; AUROC, area under the receiver operating characteristic; BIC, Bayesian information criterion; IDI, integrated discrimination improvement; LR, likelihood ratio; PSS, pre-shortness; SS, short stature.

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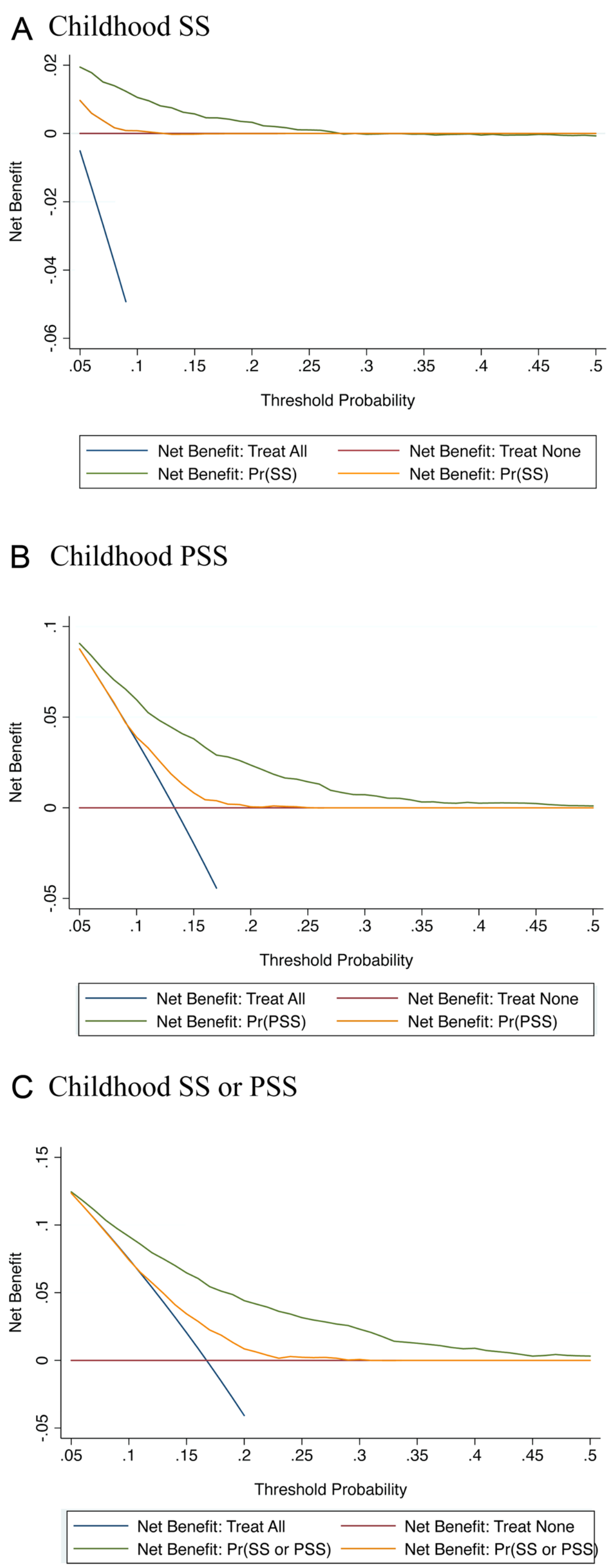

Figure 1
Decision curve analysis for SS, PSS and SS or PSS in preschool-aged children. SS, short stature; PSS, pre-shortness.

at delivery and maternal education that were deemed as confounder factors under adjustment.

As shown in Table 3, after partial and multivariable adjustment, six contributing factors involving children BMI (OR, 95% CI, *P* for short stature: 1.20, 1.15 to 1.24, <0.001), paternal height (0.88, 0.86 to 0.90, <0.001), maternal height (0.90, 0.88 to 0.92, <0.001), birth weight (0.45, 0.36 to 0.57, <0.001), birth height (0.93, 0.89 to 0.97, 0.001), latter birth order (≥2) (1.65,1.25 to 2.19, <0.001) and less parental patience to children (1.26, 1.09 to 1.46, 0.002) were significantly associated with childhood short stature, pre-shortness and both. In addition, breastfeeding duration (>12 months) (OR, 95% CI, *P* for pre-shortness: 1.16, 1.01 to 1.33, 0.037) was significantly correlated to childhood pre-shortness.

Prediction accuracy assessment

The prediction accuracy of the identified factors for short stature, pre-shortness and both was assessed by comparing two models, *viz*. full model (all variables in the survey) and basic model (all variables except the significant factors), from both calibration and discrimination aspects (Table 4). Significant improvement was seen after adding the significant factors under each group classification. For example, as revealed by the –2 log likelihood ratio test, full model and basic model differed significantly in prediction performance under short stature, pre-shortness and both (all $P < 0.0001$). Additionally, decision curve analysis indicated that the net benefits gained by adding the significant factors to the basic model were obvious (Fig. 1).

Prediction of BMI for short stature and pre-shortness

To further interrogate the risk prediction of BMI for childhood short stature, pre-shortness and both, the ordinal Logistic regression analyses were used after multivariable adjustment for confounding factors (Table 5). BMI was analyzed on both continuous and categorical scales. Per 1 kg/m^2 increase in BMI was associated with 19% increased risk of short stature (OR, 95% CI, P: 1.19, 1.15 to 1.23, < 0.001), 3% increased risk of pre-shortness (1.03, 1.001 to 1.05, 0.042) and 7% increased risk of short stature or pre-shortness (1.07, 1.05 to 1.10, < 0.001).

Figure 2 displays the risk prediction of continuous children BMI for childhood short stature, pre-shortness and both under the restricted cubic spline regression analysis after adjusting for age, sex and region. The tendency between children BMI and the risk of childhood short stature were significantly positive, while pre-shortness was not that significant.

When BMI was analyzed on a categorical scale, childhood obesity was significantly associated with short stature (3.45, 2.62 to 4.54, <0.001) and short stature or pre-shortness (1.37, 1.15 to 1.64, <0.001). Childhood overweight was significantly associated with short stature (1.94, 1.45 to 2.61, <0.001). Neither childhood obesity nor overweight had a significant relation with pre-shortness individually.

Prediction nomogram model

Risk prediction nomogram models were constructed for short stature, pre-shortness and both in preschool-aged children on the basis of the identified significant predictors (Fig. 3). The predictive accuracy was good as shown in Supplementary Fig. 1 (see section on supplementary materials given at the end of this article), and the C-index were 77.0 ,70.1 and 71.2% for short stature, pre-shortness and both, respectively (all $P < 0.001$).

Taking the nomogram model for short stature as an example: assuming the BMI of a child is 20 kg/m^2 (50 points), the height of father is 165 cm (85 points), the height of mother is 155 cm (55 points), with birthweight 3 kg (37.5 points), birth height 50 cm (2.5 points), birth order is 2 (15 points), and parental patience to the child is 1 point (15 points), the probability of short stature is estimated to be about 50%.

Discussion

In this large-scale cross-sectional survey of 9501 Chinese preschool-aged children, we aimed to identify and characterize potential factors associated with short stature and pre-shortness. The key finding of this survey was that six factors including children BMI, paternal height, maternal height, birth weight, birth height, birth order and parental patience to children were significantly associated with childhood short stature, pre-shortness, and both. Additionally, breastfeeding duration was a significant predictor for childhood pre-shortness. Furthermore, childhood obesity and overweight were both significantly associated with short stature. To our knowledge, this is so far the first report that has examined the joint contribution of inherited characteristics, nutrition status from the uterus to childhood, and family psychological environment to short stature and pre-shortness in Chinese preschool-aged children.

It is estimated that approximately 80% of the variance in human height is determined by inherited factors (24, 25), with the remaining 20% of variance by environmental factors such as nutrition status and psychological stress (26). Among people affected by short stature, 37% have familial short stature, 27% have a constitutional growth delay, and 17% have both (27, 28, 29), which indicates great inherited patterns of short stature. Our current study supported the claim that short stature and pre-shortness were significantly determined by parental height (13, 30, 31). Undoubtedly, besides inherited factors, the development processes of short stature and pre-shortness are also affected by modifiable environmental factors such as nutrition status and family psychological factors. First, the typical pattern of linear growth faltering begins *in utero* and progresses through early childhood (32), as our study indicated that birth height and birth weight reflecting *in utero* nutrition status were the robust predictors of

Table 5 Prediction of BMI on both continuous and categorical scales for SS, PS and SS or PS by using the ordinal Logistic regression analyses.

Variables	Children with SS			Children with PSS			Children with SS or PSS		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Childrens' BMI (per 1 kg/m^2 increase)	1.19	1.15 to 1.23	<0.001	1.03	1.00 to 1.05	0.042	1.07	1.05 to 1.10	<0.001
Childrens' BMI category									
Childhood obesity	3.45	2.62 to 4.54	<0.001	Not significant			1.37	1.15 to 1.64	<0.001
Childhood overweight	1.94	1.45 to 2.61	<0.001	Not significant			Not significant		
Non overweight or obesity	Reference			Reference			Reference		

P values were calculated after adjusting for age, sex, region, night meals intake frequency, fast food intake frequency, time spent on outdoor activities every day, picky about food, twins, gestational age, delivery mode, gestational diabetes mellitus, solid food introduction age, parental age at delivery, parental education, family income.
PSS, pre-shortness; SS, short stature.

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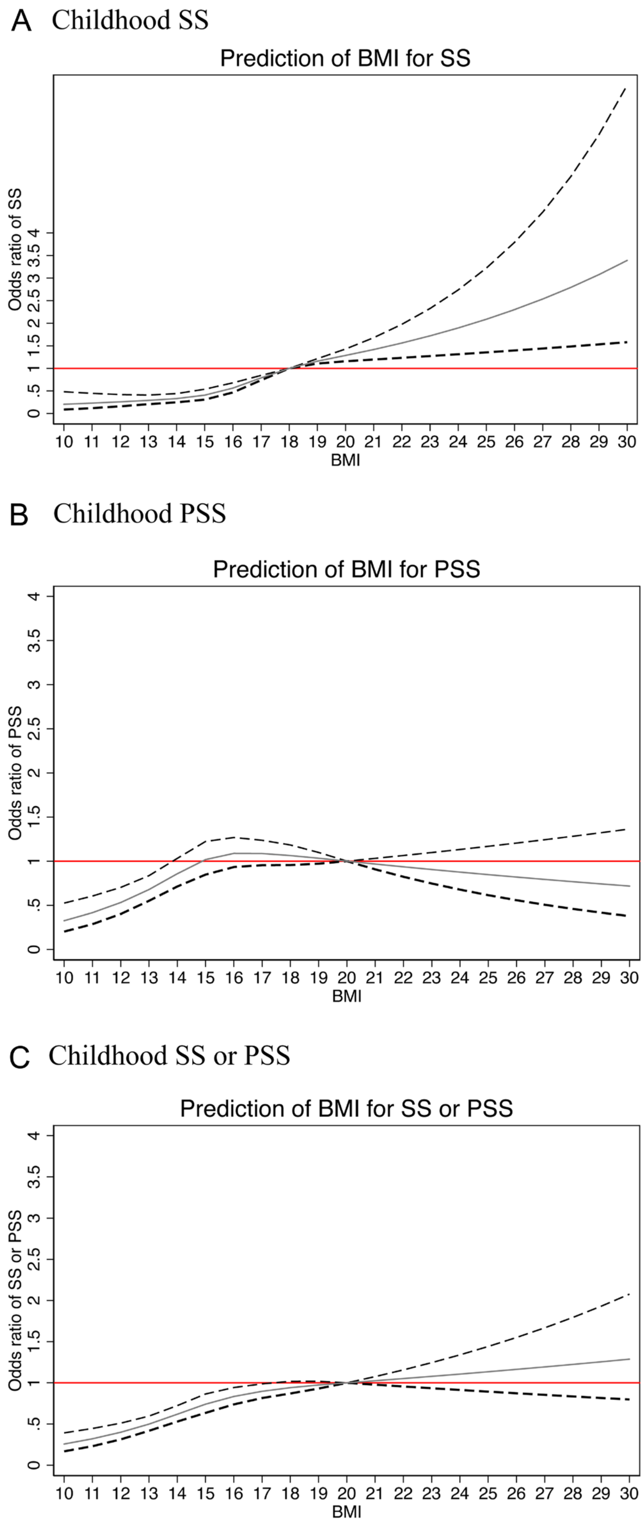

Figure 2
Risk of continuous BMI for SS, PSS, and SS or PSS among preschool children, after adjusting for age, sex and region. SS, short stature; PSS, pre-shortness. Lines with short dashes represent the 95% CI.

both short stature and pre-shortness, consistent with the findings of some previous studies (33, 34). Secondly, we found that children's higher BMI representing better nutrition status had a significantly positive association with short stature and pre-shortness, in agreement with that of most previous studies (13, 19). More importantly, our study reported for the first time that childhood obesity and overweight representing malnutrition status were significantly associated with short stature in preschool-aged children. Although some studies reported that obesity during adolenscence could enhance the precocious puberty and early epiphyseal closure accounting for short stature in adulthood (35); this still could not explain the relationship between obesity or overweight and short stature in the preschool period. We speculated that overweight or obesity representing malnutrition was in fact another form of unbalanced nutrition status which is harmful to linear growth. The precise underlying biological mechanisms need further exploration in future studies. Unfortunately, we failed to support that specifically low children BMI representing undernutrition was positively associated with short stature and pre-shortness as a U-shape between BMI and risk of short stature or pre-shortness. It was possibly because of the very few numbers of children with very low BMI representing undernutrition owing to progressive socioeconomical conditions in Beijing and Tangshan, which caused the lack of statistical power. Therefore, we recommended that children should maintain normal BMI with a balanced nutrition status so as to avoid short stature or pre-shortness.

Several important findings distinguishing the present study merit adequate discussion. First, parental patience to children that could impact childhood psychological health was found to be inversely associated with the occurrence of short stature and pre-shortness. It is well known that parents with less patience are often in an unstable emotional status and irritable, which may create a long-term stressful family environment for children. There is an emerging notion that a stressful environment changes a child's gene expression and hormonal activity and contributes to biological changes that may lead to mental and physical disorders (36). The specific biological mechanisms of the impact of parental impatience on childhood short stature and pre-shortness worth further investigation. Secondly, birth order ≥ 2 was for the first time found to be positively associated with the risk for childhood short stature and pre-shortness. The possible explanation was that latter birth order means larger family size and the association of short stature with large family size was confirmed (37, 38). It is hypothesized that children in the larger families are compatible with deprivation of

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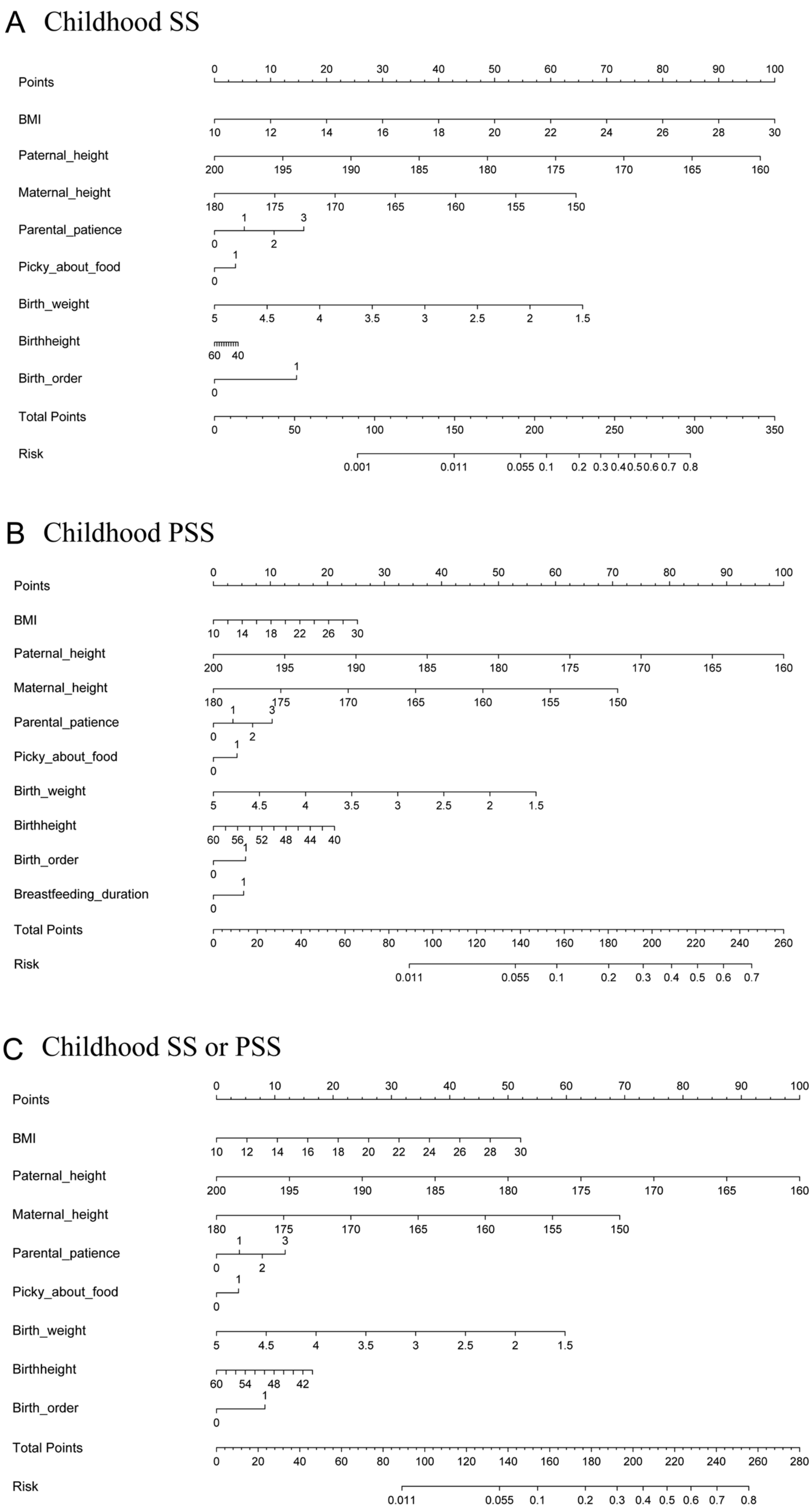

Figure 3
The prediction nomogram models for SS, PSS and SS or PSS in preschool-aged children. SS, short stature; PSS, pre-shortness. Lines with short dashes represent the 95% CI. Here, '0' and '1' of 'Picky_eating' were defined as without picky eating and with picky eating. '0' and '1' of 'Birth_order' represented <2 and ≥2, respectively. '0' and '1' of 'Breastfeeding_duration' were defined as <12 months and ≥12 months according to the mean value. '0', '1', '2', and '3' of 'Parental_patience' represented parental self-rating patience to children separated into 10 points, 7–9 points, 4–6 points, and 1–3 points.

parental care and love, which may affect psychological development or relatively worse family income contributing to limited linear growth of children. Thirdly, we found that breastfeeding duration of more than 12 months was a significant risk factor for pre-shortness that is rarely reported in the literature. Most studies have reported a reduction in the risk of child undernutrition, with evidence for a dose-response relationship between breastfeeding duration and reduced risk (39, 40, 41). However, according to our results and the recommendation of the World Health Organization (WHO) that breastfeeding duration should be more than 6 months (42), we recommend moderate breastfeeding duration between 6 and 12 months. Because human milk may become less nutritional along with changeable components over time (43), excessive long-term breastfeeding may cause undernutrition against the linear growth of children instead.

Limitations

Several possible limitations need to be acknowledged. First, this was a cross-sectional study, precluding further comments on the cause-effect relationship. Secondly, our data were obtained through questionnaires filled in by the parents or guardians of study children, and hence, recall bias cannot be excluded. Thirdly, although children with diagnosed chronic diseases causing pathological short stature were excluded at enrollment, those children not yet been diagnosed could not be excluded merely by the questionnaires.

Conclusions

In conclusion, our findings indicate that short stature and pre-shortness are determined by the joint contribution of multiple potential factors including inherited, nutritional, and psychological factors in Chinese pre-school children. It is helpful in making intervention strategies for preventing short stature or pre-shortness and improving height gain in early childhood. Further explorations are still necessary to clarify the underlying biological mechanisms of short stature or pre-shortness.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0147.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Data availability statement

Data and codes involved in this study are available upon reasonable request.

Author contribution statement

Z Z planned and designed the study and directed its implementation and drafted the protocol; M Y, X D, B Z, and S W obtained statutory and ethics approvals; M Y and B Z contributed to data acquisition; M Y and W N conducted statistical analyses; M Y, X D, B Z and S W did the data preparation and quality control; M Y and W N wrote the manuscript. All authors read and approved the final manuscript prior to submission.

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