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Association between insulin-like growth factor-1 and systolic blood pressure in children and adolescents with short stature

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Abstract

The relationship between insulin-like growth factor-1 (IGF-1) and systolic blood pressure (SBP) is controversial in adults and children. The purpose of this study was to investigate the relationship between the IGF-1 standard deviation score (IGF-1 SDS) and SBP in children with short stature. A cross-sectional analysis including 1315 children with short stature was conducted from March 2013 to October 2020. We estimated IGF-1, blood pressure and other laboratory tests, and anthropometric indicators were also evaluated. Subgroup analyses of the pubertal stage, sex, growth hormone levels, thyroid hormone levels, fasting blood glucose levels, and triglyceride levels were performed. A positive association between the IGF-1 SDS and SBP was observed by univariate analysis ($p < .001$). We further found a nonlinear association between the IGF-1 SDS and SBP. The inflection point for the curve was found at an IGF-1 SDS level of −2.91. In multivariate piecewise linear regression, there was a positive association between the IGF-1 SDS and SBP when the IGF-1 SDS was greater than −2.91 (β 1.56, 95% CI: 0.91, 2.22; $p < .001$). However, we did not observe a significant relationship between the IGF-1 SDS and SBP when the IGF-1 SDS level was less than −2.91 (β −0.95, 95% CI −3.17, 1.28; $p = .379$). This association was consistent across subgroup analyses. The present study demonstrated that there is a nonlinear relationship between the IGF-1 SDS and SBP in children with short stature. Increased serum IGF-1 levels were associated with elevated SBP when the IGF-1 levels reached the inflection point.

1 | INTRODUCTION

Blood pressure is a very important physiological indicator reflecting the state of vascular function, and elevated blood pressure is the main risk factor for cardiovascular disease (CVD).[1,2] Several studies have shown that childhood blood pressure status can predict adult blood pressure.[3,4] In addition, a previous study explored the relevant factors affecting children's blood pressure and found that body height and body mass are the key factors determining children's blood pressure.[5] Many studies focus on the relationship between height and blood pressure in adults and have shown increased blood pressure with shorter stature.[6,7] However, there is increasing evidence that there is also a relationship between height and blood pressure in children.[8,9] Therefore, these studies suggest that it is particularly important to explore blood pressure levels and related factors, especially in children and adolescents with short stature.

The growth process of children and adolescents is complex and controlled by growth hormone (GH), thyroid hormone, sex hormone, and other growth factors.[10] As an important growth factor, insulin-like growth factor-1 (IGF-1) has been proven to be a good biochemical marker for evaluating normal growth and growth disorders.[11] In addition to promoting bone growth, IGF-1 can also promote lipolysis and improve insulin sensitivity and plays an important role in glucose and lipid metabolism, which is related to the risk of metabolic syndrome and CVD.[12,13] Furthermore, a study demonstrated that polymorphisms in the IGF-1 gene are associated with the risk of myocardial infarction, strengthening the link between IGF-1 and CVD.[14] However, there are inconsistent results in this area, with some reports showing a positive correlation between IGF-I levels and cardiovascular risk factors, while others show a negative correlation, particularly with regard to blood pressure.[15] This phenomenon may be because IGF-1 not only has functions in microvascular protection and vasodilation[16,17] but also induces angiogenesis and promotes the migration and proliferation of smooth muscle cells in vitro, and the overexpression of IGF-I can increase vasoconstriction.[18,19]

Conflicting reports concerning the relationship between blood pressure and IGF-1 highlight the complexity of understanding the vascular function of IGF-1.[20–25] These findings include positive,[20] negative,[21] or neutral[22] relationships between blood pressure and IGF-1 in adults. Additionally, in children, inconsistent results for blood pressure and IGF-1 have been reported.[23–25] A neutral[23] or positive relationship[24] was observed between blood pressure and IGF-1 in healthy children. Furthermore, cross-sectional analysis indicates an inverse association between blood pressure and IGF-1 in 64 children.[25]

Previous studies have reported the relationship between IGF-1 and blood pressure in different populations, including patients with hypertension or diabetes, hemodialysis patients, and healthy individuals.[26–29] However, there is limited research on IGF-1 and blood pressure in children with short stature, who are more likely to develop CVD. The purpose of this study was to explore the relationship between IGF-1 and blood pressure in Chinese children with short stature.

2 | METHODS

2.1 | Study participants

The subjects of this study were patients who visited the Endocrine Department of the Affiliated Hospital of Jining Medical University between March 2013 and October 2020 due to their short stature. The study was conducted among 1315 children, 912 males and 403 females, with an average age of 10.4 ± 3.6 years. Participants whose height was more than two standard deviations (SD) lower than the average of the same race, age, and sex were included in the study. Subjects with chronic diseases, with skeletal dysplasia, with thyroid dysfunction, small for gestational age and with other known causes

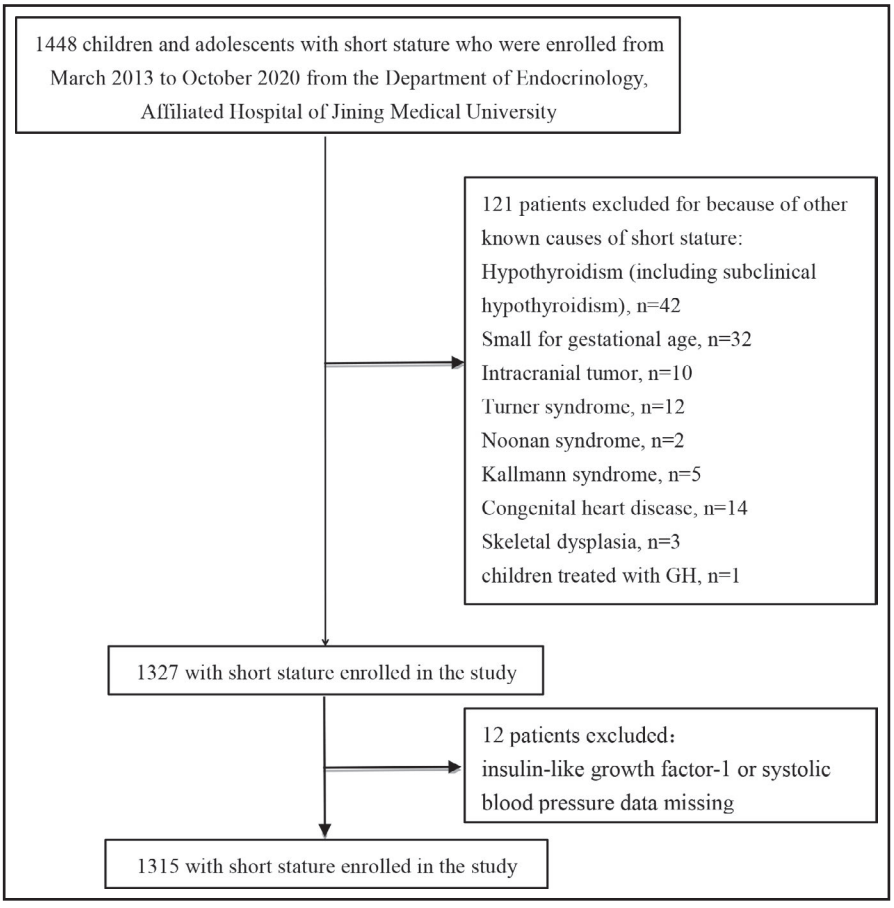

FIGURE 1 Flow chart of the study population

of short stature, including Noonan syndrome and Turner syndrome or subjects who have received either GH or antihypertensive treatment, were all excluded from this analysis. The flow chart of the study selection process is shown in Figure 1.

Ethics approval was obtained from the Ethics Committee of the Affiliated Hospital of Jining Medical University. All procedures were carried out in accordance with the moral standards of the Helsinki Declaration. We obtained written informed consent from the guardians representing our study participants.

2.2 | Anthropometric measurements

Anthropometric measurements for the study were performed in a quiet and warm room using standard anthropometric procedures. A stadiometer (Nantong Best Industrial Co, Ltd.) was used to measure height to the nearest 0.1 cm. Each child stands barefoot on the platform of the height meter. The heel, sacrum and both shoulder blades are close to the column of the height meter, and the horizontal board of the height meter is up at the top of the child's head. For the weight measurement, the children wore light clothes and were barefoot; each child stood naturally in the center of the weight measurement plate and maintained a stable body position, and an electronic scale (Wuxi Weigher Factory Co, Ltd.), accurate to 0.1 kg, measured his or her weight. The standard deviation scores (SDS) of height and BMI were calculated according to the values of normal Chinese children.[30,31]

Puberty was assessed by professional physicians. Pubertal breast development in girls was evaluated by examination combined with palpation; in boys, the volume of the testicles is determined by palpation and testicular meter—that is, the testis is palpated and compared with the most similar bead on the orchid meter. Tanner stage was used to evaluate the sexual development of children.[32] Pubertal development was classified as follows: prepubertal: Tanner 1; early pubertal: Tanner 2–3; late pubertal: Tanner 4–5.

After 10 min of sedentary rest, clothing that covered the cuff was removed. The right arm blood pressure was measured three times using an electronic sphygmomanometer (Omron HBP-1300). The cuff size was based on the length and circumference of the upper arm and was chosen to be as large as possible without having the elbow skin crease obstruct the stethoscope.[33] The average of the three measurements was used for statistical analysis. The criteria for hypertension followed the age- and sex-specific blood pressure reference standard for Chinese children and adolescents. Hypertension was defined as an average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥ 95th percentile for sex and age.[34] The mean arterial pressure (MAP) was calculated as DBP plus one-third of the pulse pressure.

2.3 | Laboratory measurements

Overnight fasting blood samples were collected from all children for measuring laboratory parameters. Serum IGF-1 concentrations were measured by a chemiluminescence assay (DPC IMMULITE 1000 analyzer; SIEMENS) that had intra- and interassay CVs of 3.0% and 6.2%, respectively. Two stimulating tests were performed for GH (500 mg of levodopa for those weighing more than 30 kg or 250 mg of levodopa for those weighing <30 kg, orally, and 0.1 U/kg of insulin, subcutaneously). Blood samples were collected 0, 30, 60, 90, and 120 min after administration to obtain serum GH concentrations at each time point. A chemiluminescence method was used to assess the GH concentration (ACCESS2; Beckman Coulter). The intra- and interassay CVs were 3.5% and 5.8%, respectively. Thyroid function, including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH), was tested using a luminescence immunoassay system (Cobas e602, Roche). Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were analyzed by an autobiochemical analyzer (Cobas c702, Roche). For the reliability of the study, the IGF-1 SDS was calculated using the reference values of healthy children of the same age and sex.[35]

2.4 | Statistical analysis

Continuous variables are presented as the mean ± standard deviation or median (interquartile range). Categorical variables are displayed as numbers and percentages. Univariate analysis and multiple regression analysis were used to explore the relationship between the IGF-1 SDS and SBP. Then, to detect nonlinear associations between the IGF-1 SDS and SBP, smooth curve fitting was conducted. Smooth curve fitting was also used to analyze the relationship between IGF-1 and DBP, MAP and hypertension, and subgroup analysis of IGF-1 and SBP. Finally, a multivariate piecewise linear regression was further applied to estimate the threshold association of the IGF-1 SDS and SBP according to the smoothing plot. The log likelihood ratio test was also performed to compare the one-line linear regression model with a two-piecewise linear model to examine the statistical significance. A two-sided $p < .05$ was considered statistically significant in all analyses. Statistical analysis was performed with R 3.6.1 (https://www.R-project.org) and EmpowerStats (https://www.empowerstats.com; X&Y Solutions, Inc).

3 | RESULTS

3.1 | General characteristics of the study population

In total, 1315 eligible subjects (912 males and 403 females) were identified. The general characteristics of the study subjects are summarized in Table 1. The mean age of the patients was 10.4 ± 3.6 years. The mean height SDS of the children was −2.89 ± 0.73. Of the study population, 868 (66.01%) subjects were prepubescent. The median IGF-1 SDS and mean SBP levels were

TABLE 1 Clinical and biochemical characteristics

	All
Number	1315
Sex (male %)	912 (69.35%)
Age (years)	10.4 ± 3.6
Height (cm)	125.71 ± 17.79
Height SDS	−2.89 ± 0.73
Body weight (kg)	27.80 ± 11.32
BMI (kg/m^2)	17.87 ± 3.50
BMI SDS	0.04 (−0.80 to 0.95)
IGF-1 (ng/ml)	168.00 (98.18–252.00)
IGF-1 SDS	−0.99 (−1.79 to −0.14)
SBP (mmHg)	105.30 ± 12.01
DBP (mmHg)	62.42 ± 8.57
FPG (mmol/L)	4.75 ± 0.62
TG (mmol/L)	0.75 ± 0.42
TC (mmol/L)	3.86 ± 0.73
HDL-C (mmol/L)	1.39 ± 0.30
LDL-C (mmol/L)	2.10 ± 0.59
HR (bpm)	90.28 ± 12.41
Peak GH (ng/ml)	6.96 (4.66–10.76)
FT3 (pmol/L)	6.41 ± 1.05
FT4 (pmol/L)	17.49 ± 2.70
TSH (mIU/L)	2.94 ± 1.37
Hypertension	
No	1186 (90.19%)
Yes	129 (9.81%)
Pubertal stage	
Prepubertal (%)	868 (66.01%)
Early pubertal (%)	422 (32.09%)
Late pubertal (%)	25 (1.90%)

Note: Continuous variables are presented as the mean ± standard deviation or median (interquartile range). Categorical variables are displayed as number (percentage).

Abbreviations: BMI SDS, body mass index standard deviation scores; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; HDL-C, high density lipoprotein-cholesterol; Height SDS, height standard deviation scores; HR, heart rate; IGF-1 SDS, insulin like growth factor-1 standard deviation scores; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyrotrophic hormone.

−0.99 (−1.79 to −0.14) and 105.30 (12.01) mmHg, respectively. One hundred twenty-nine (9.81%) of the subjects had hypertension in the present study.

3.2 | Factors associated with SBP of the study population

In univariate analysis, the association between clinical parameters and SBP was determined. As shown in Table 2, we observed a significant positive association between the IGF-1 SDS and SBP ($p < .001$). In addition, other variables, including age, height SDS, weight, BMI SDS, FPG, TG, FT3, and puberty stage, remained positively associated with SBP (all $p < .05$), whereas the relationship between sex, FT4, and SBP was negative ($p < .05$). However, the relationships between SBP and TC, LDL-C, HDL-C, peak GH, TSH, and heart rate (HR) were not significant in the study (all $p > .05$).

TABLE 2 Association between SBP and different variables

Variables	β	(95% CI)	p Value
Age (years)	1.52	(1.36, 1.68)	<.001
Height SDS	1.06	(0.28, 1.84)	.008
Body weight (kg)	0.57	(0.52, 0.62)	<.001
BMI SDS	0.69	(0.18, 1.19)	.009
IGF-1 SDS	2.26	(1.77, 2.76)	<.001
FPG (mmol/L)	2.36	(1.29, 3.44)	<.001
TG (mmol/L)	3.50	(1.89, 5.12)	<.001
TC (mmol/L)	−0.07	(−0.99, −0.85)	.889
HDL-C (mmol/L)	−1.49	(−3.76, 0.79)	.201
LDL-C (mmol/L)	−0.09	(−1.24, 1.07)	.882
HR ((bpm)	0.01	(−0.05, 0.06)	.815
Peak GH (ng/ml)	0.05	(−0.07, 0.16)	.406
FT3 (pmol/L)	0.96	(0.33, 1.58)	.003
FT4 (pmol/L)	−0.55	(−0.79, −0.30)	<.001
TSH (mIU/L)	−0.19	(−0.67, 0.29)	.435
Sex			
Male	Reference		
Female	−4.09	(−5.48, −2.69)	<.001
Pubertal stage			
Prepubertal (%)	Reference		
Early pubertal (%)	8.57	(7.25, 9.88)	<.001
Late pubertal (%)	13.09	(8.62, 17.57)	<.001

Note: $p < .05$ is considered to be statistically significant.

Abbreviations: BMI SDS, body mass index standard deviation scores; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; HDL-C, high density lipoprotein-cholesterol; Height SDS, height standard deviation scores; HR, heart rate; IGF-1 SDS, insulin like growth factor-1 standard deviation scores; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyrotrophic hormone.

3.3 | The results of nonlinearity of the IGF-1 SDS and SBP

In the present study, smooth curve fitting was conducted to analyze the nonlinear relationship between the IGF-1 SDS and SBP. The results showed that the relationship between the IGF-1 SDS and SBP was nonlinear after adjusting for potential confounding factors, including age, sex, BMI, HR, TG, FPG, peak GH, FT3, FT4, TSH, and pubertal stage. An inflection point was observed in the present study, indicating two stages of change between the IGF-1 SDS and SBP (Figure 2). Furthermore, a one-linear regression and two-piecewise

linear regression were performed to determine the best fit model according to *p* for the log likelihood ratio test.

As shown in Table 3, in the one-linear regression, we observed that the IGF-1 SDS was independently positively associated with SBP after adjusting for confounding variables (β 1.22, 95% CI 0.66, 1.78; $p < .001$). Using two-piecewise linear regression, the results revealed that the inflection point of the IGF-1 SDS was −2.91. Specifically, there was a significant positive association between the IGF-1 SDS and SBP when the IGF-1 SDS was greater than −2.91 (β 1.56, 95% CI: 0.91, 2.22; $p < .001$). However, a significant relationship between the IGF-1 SDS and SBP was not observed when the level of the IGF-1 SDS was lower than −2.91 (β −0.95, 95% CI −3.17, 1.28; $p = .379$). The differential linear regression and piecewise linear regression were evaluated by the log likelihood ratio test. A value of *p* less than .05 means that a piecewise linear function is more suitable for observation; otherwise, the linear function is better. The results showed that the *p* for the log likelihood ratio test was less than .05 ($p = .048$); therefore, the two-piecewise linear regression for fitting the association between the IGF-1 SDS and SBP can accurately represent the relationship.

Subgroup analysis assessed the relationship between IGF-1 and SBP by smooth curve fitting according to the puberty stage, sex, GH levels, thyroid hormone (including FT3, FT4, and TSH) levels, FPG levels, and TG levels in additional files: (Figures S1–S5). The association between IGF-1 and SBP was consistent across subgroup analyses.

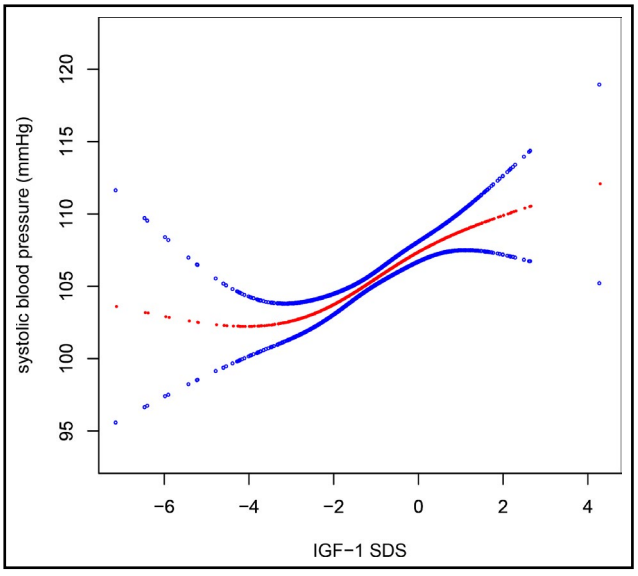

FIGURE 2 The relationship between the IGF-1 SDS and SBP by smooth curve fitting. Adjustment variables: age, sex, BMI, HR, TG, FPG, peak GH, FT3, FT4, TSH, and pubertal stage. BMI, body mass index; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; HR, heart rate; IGF-1 SDS, insulin-like growth factor-1 standard deviation score; SBP, systolic blood pressure; TG, triglyceride; TSH, thyroid stimulating hormone

4 | DISCUSSION

The present study demonstrated a significant positive relationship between the IGF-1 SDS and SBP in children with short stature. Interestingly, we further explored the nonlinear relationship between the IGF-1 SDS and SBP. More specifically, there was a positive relationship between the IGF-1 SDS and SBP when the IGF-1 SDS was greater than −2.91, whereas a significant relationship between the IGF-1 SDS and SBP was not observed when the level of the IGF-1 SDS was lower than −2.91.

The present study suggested that SBP increases with increasing IGF-1 in children with short stature. Among adults, there is conflicting evidence about whether high IGF-I levels can have a protective or detrimental effect on blood pressure.[12,15] Inconsistent results for blood pressure and IGF-1 have also been reported in children.[23–25] A previous study found that the association between IGF-1 and SBP was not significant in healthy children early in life.[23] In addition, Sesso and colleagues[25] conducted a cross-sectional analysis in 64 children and observed that IGF-1 was negatively associated with SBP. The sample size of this study was small, and only correlation analysis was performed without adjusting for confounding factors. Our findings are consistent with the results of a recently reported study,[24] a prospective longitudinal study conducted in a primary care facility of 521 children in Girona, which showed that IGF-1 is positively associated with SBP. These conflicting results may be attributed to differences in population characteristics, sample size, and confounder adjustment. Importantly, these studies explored only the linear relationship between IGF-1 and SBP and did not further investigate the nonlinear relationship between IGF-1 and SBP.

TABLE 3 Threshold effect analysis for the relationship between the IGF-1 SDS and SBP

	SBP	
Models	**Adjusted β (95% CI)**	***p* Value**
Model I		
One line slope	1.22 (0.66, 1.78)	<.001
Model II		
Turning point	−2.91	
<−2.91 slope 1	−0.95 (−3.17, 1.28)	.379
>−2.91 slope 2	1.56 (0.91, 2.22)	<.001
LRT test	0.048	

Note: Model I, linear analysis; Model II, non-linear analysis. LRT test, logarithmic likelihood ratio test. (*p*-value < .05 means Model II is significantly different from Model I, which indicates a non-linear relationship); Adjustment variables: age, sex, BMI, HR, TG, FPG, peak GH, FT3, FT4, TSH, and pubertal stage. $p < .05$ is considered to be statistically significant.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; HR, heart rate; IGF-1 SDS, insulin like growth factor-1 standard deviation scores; SBP, systolic blood pressure; TG, triglyceride; TSH, thyrotrophic hormone.

In the present study, we further observed the nonlinear relationship between IGF-1 and SBP by smoothing curve fitting. When the level of the IGF-1 SDS exceeds a certain range, the relationship between IGF-1 and SBP is significant. This is consistent with a previous report that the relationship between IGF-1 and SBP is due to high levels of IGF-1,[15,24] but in their study, they did not obtain the range of IGF-1 levels. Our study shows that when the level of the IGF-1 SDS is greater than −2.91, there is a positive association between IGF-1 and SBP in children and adolescents with short stature. The potential mechanism of this phenomenon may be that overexpression of IGF-1 in vascular smooth muscle cells leads to an increase in vascular contractility,[18] while low IGF-1 concentration may lead to loss of the anti-inflammatory and endothelial protective functions of IGF-1.[15] Additionally, the lower proportion of bioavailable IGF-1, which controls microcirculation and vascular resistance, and lower bioavailability of GH, which controls muscle mass, likely cause the relative thinning of microcirculation, which is the cause of hypertension in children who rapidly gain muscle mass.[36,37] These results support that the increase of BP in growing children and adolescents may be due to the increase in the GH level, which overbalances the available IGF-1 level.[38] Under these conditions, IGF-1 may not be sufficient to provide sufficient distal angiogenesis for increased muscle mass, leading to hypertension. However, when the level of the IGF-1 SDS is greater than −2.91, the possible mechanism of the increase in SBP requires further study.

Height is significantly associated with pulse wave velocity and blood pressure.[6–9,39] Thus, the underlying mechanisms mediating the effects of IGF-1 on SBP are complex. As a growth factor, GH/IGF-1 is also involved in the regulatory action of the development of the heart and maintenance of its structure. GH/IGF-1 can also cause fluid retention and an increased plasma volume, which may affect blood pressure and heart geometry.[40] Additionally, shorter individuals have poor hemodynamics because the early appearance of systolic reflections causes aortic stiffness.[41] Furthermore, in addition to the increased SBP due to reflected waves and arteriosclerosis in shorter people, another potential height-related effect is the hydrostatic force exerted by the blood column extending between the middle brachial artery and brain.[42] Therefore, more attention should be given to the blood pressure level of children with short stature.

According to the hypertension guidelines, when considered separately, higher SBP and DBP are associated with an increased risk of CVD. However, higher SBP is consistently associated with an increased risk of CVD after adjusting or stratifying DBP. By contrast, the association between DBP and CVD risk was not consistent after adjustment or stratification for SBP.[33] Therefore, we mainly analyzed the relationship between IGF-1 and SBP. Additionally, we analyzed the relationship between IGF-1 and DBP and MAP (Figures S6), and the result trends were consistent. Several studies have shown that the childhood blood pressure status can predict adult blood pressure[3,4] and that childhood hypertension is associated with hypertension during adulthood, and thus, a long-term prospective of cardiovascular health. Therefore, we analyzed IGF-1 and hypertension (Figures S7) and found that the result trends were consistent.

Serum IGF-1 levels fluctuate throughout life. The IGF-1 level in childhood increases with age, reaches its peak in adolescence, and then decreases with age throughout adulthood.[43] To increase the accuracy and reliability of the study results, IGF-1 was standardized in our analysis, that is, the IGF-1 SDS was used. In a recently reported longitudinal study with 521 children aged 8.8 ± 0.1 years in north-eastern Spain, a positive association was observed between IGF-1 and SBP[20]; however, although the authors adjusted for age and sex, this did not protect against IGF-1 fluctuations.

The main strength of our study was that we explored the relationship between IGF-1 and SBP in a large sample size of children with short stature. The incidence of short stature in China is approximately 3%,[44] and in this population, there is a greater risk of cardiovascular and blood pressure problems. In addition, the present study revealed a nonlinear relationship between IGF-1 and SBP rather than the simple linear relationship obtained by previous studies. Another major strength of our study is that the IGF-1 SDS is used to analyze the relationship between IGF-1 and SBP, which can increase the accuracy and reliability of our study.

On the other hand, several potential limitations of the present study should also be considered. First, the nature of the cross-sectional analysis of the present study does not allow us to infer causality. Second, in this study, a nonlinear relationship between IGF-1 and SBP was found in children with short stature. This result may not be applicable to other populations, and there may be different relationships between IGF-1 and SBP in other populations, which is worthy of further investigation. Finally, further investigation is necessary to follow up on the IGF-1 SDS and SBP changes to determine whether this relationship remained or changed after GH treatment.

5 | CONCLUSION

In conclusion, the present study identified that there is a nonlinear relationship between the IGF-1 SDS and SBP in children with short stature. Increased serum IGF-1 levels were associated with elevated SBP when the IGF-1 levels reached the inflection point. The results will contribute to understanding the relationship between IGF-1 and SBP in children with short stature.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Q. Z performed the studies and drafted the manuscript. M. Z. revised the manuscript. Y. C. helped with the statistical analysis. H. S. interpreted the data for the study. B. B. participated in the study

concept and design, revising it critically for important intellectual content and final approval of the published version. All the authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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