Original Article

Effects of rapid growth in early childhood on metabolic and cardiovascular diseases among preschool-aged children

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Background and Objectives: To investigate whether the tempo of weight gain of children during infancy (from birth up to two years of age) or childhood (between two and five years old) is associated with metabolic and cardiovascular disease. **Methods and Study Design:** Cluster sampling was employed to obtain a random sample of preschool children. In total, 1450 children aged five to six years participated in this survey. We obtained data on body weight, height, blood pressure (BP), and serum levels of total cholesterol, triglycerides, glucose, and uric acid, as well as anthropometry at birth and at age 2. **Results:** The prevalence of obesity at five years old was 14.5%. At five years of age, children with rapid growth (change in body mass index, BMI z-score >0.67) during infancy had a higher odds ratio (OR) of childhood obesity (OR: 2.97 [95% CI: 2.15–4.11]) compared to children with non-rapid growth (change in BMI z-score ≤0.67). Also, children with rapid growth during childhood had a higher OR of childhood obesity (OR: 17.90 [95% CI: 12.31–26.04]), higher systolic BP (OR: 2.38 [95% CI: 1.68–3.39]), higher diastolic BP (OR: 2.42 [95% CI: 1.53–3.83]), and higher triglycerides (OR: 4.09 [95% CI: 1.47–11.33]) or hyperuricemia (OR: 2.23 [95% CI: 1.51–3.29]). **Conclusions:** Rapid growth in early childhood is associated with risk factors for both cardiovascular outcomes and metabolic outcomes among preschool children. Developing effective prevention and intervention programs for pre-school children might be important to reduce incidence of long-term metabolic and cardiovascular disease as adults.

Key Words: rapid growth, obesity, blood pressure, children

INTRODUCTION

The prevalence of non-communicable diseases like obesity and cardiovascular disease has reached epidemic proportions globally. Early postnatal rapid growth leads to increased risk of obesity in childhood and potential risk for disease in adulthood, and the greatest variation in rates of weight gain is seen in the first 1–2 years of life.[1] The results of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) showed that early postnatal rapid growth from birth to two years is a risk factor for childhood obesity and may contribute to associations between intrauterine growth restraint and risk of disease in adulthood.[2]

In recent years, the role of the early-life environment in determining later disease risk has been the focus of human studies worldwide. One early study showed that rapid growth after age two is related to increased risk of cardiovascular events later in life,[3] adding to evidence that the pre-school years are a critical period for development of obesity. Our early survey showed a quickly increasing trend in child obesity prevalence from 2006 to 2014 among children aged 5–6 years old.[4] However, there is a lack of research examining the relationship between rapid growth between two and five years, and possible determinants of cardiovascular disease.

Therefore, the aim of this study was to investigate whether the tempo of weight gain during infancy (from birth up to two years of age) or childhood (between two and five years old) was associated with determinants of cardiovascular disease. We also assessed which period of growth is more associated with increased cardiovascular disease risk in pre-school years.

METHODS

Study population and settings

Tianjin is the fourth largest city in China with a population of 14.1 million;[4] it is directly under the administration of the central government of China. One study reported that child obesity data collected in Tianjin appear to be similar to country-level data.[5] A cross-sectional sur-

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vey was carried out in six central urban districts of Tianjin from March to June 2015.[6] Cluster sampling was employed to obtain a random sample of preschool children. Three to six kindergarten schools were randomly selected from each central urban district. In total, about 10% of kindergartens schools were surveyed (26 of 263 schools). In Tianjin, kindergarteners range from 3 to 6 years old. All children aged ≥5 years (n=3547) in selected kindergarten schools were invited to take part in our survey. In total, 3391 (95.6%) children agreed to participate. Health care records for children from birth to five years old have been collected and available in electronic form since 2010.[7,8] We sequentially excluded 1557 children with missing information of weight or length/height at birth or two years old, 24 children who did not have a blood test, and 360 children with other missing variables required for this analysis. In total, 1450 children were included in the analysis.

The study protocols were guided by the Ethical Principles and Guidelines for the Protection of Human Subjects of Research and the study was approved by the Human Subjects Committee of the Tianjin Women's and Children's Health Center. Informed consent was obtained from all parents of these children. The research methods were carried out in accordance with the Declaration of Helsinki.

Measurements

A questionnaire was completed by the children's parents at home. The questionnaire included information on the child's birth date, sex, history of illness status (such as chronic diseases, surgical trauma, and allergy history), current health status (such as pneumonia, diarrhea, and fever over the past two weeks), parents' socioeconomic factors (such as occupation, e.g., 'blue collar, farmer, administrative, service professionals, education/health/technology field, business, or unemployed', education, e.g., 'less than high school', 'completed high school or some college', and 'completed a bachelor or postgraduate degree', and family income, e.g., 'below 70 thousand yuan per year', 'between 70 and 100 thousand yuan per year', 'between 100 and 150 thousand yuan per year', 'above 150 thousand yuan per year'), and parents' history and current health status (such as diabetes, dyslipidemia, and hyperuricemia).

Weight, height, and blood pressure (BP) at five years old were measured by specially trained pediatricians using the standardized protocol at the kindergarten clinic unit. Weight was measured to the nearest 0.01 kg using a digital scale (TCS-60, Tianjin Weighing Apparatus, China). Standing height was measured to the nearest 0.1 cm using a stadiometer (SZG-180, Shanghai Zhengdahengqi, China). Low birth weight was defined as <2500 g. Non-low birth weight was defined as >2500 g. Body mass index (BMI) was calculated by dividing weight in kilograms (kg) by the square of height in meters (m). Z-scores for birth weight-for-gestational age, birth length-for-gestational age, birth weight-for-length for gestational age, and birth BMI-for-gestational age were calculated using our own study population means and standard deviations.[8] Z-scores for weight, height, and BMI were calculated based on the World Health Organization (WHO) child growth standards.[9] In order to make the data more useful for comparison, and to contribute to the understanding of international standard definitions of overweight and obesity, we used BMI to classify each child as "normal," "overweight," or "obese". Normal weight was defined as a BMI less than the 85th percentile for age and sex using the WHO growth reference (<1.035 Z score), overweight was defined as a BMI >85th percentile (≥ 1.035 Z score), and obesity was defined as a BMI >95th percentile (≥1.645 Z score).[9] Sitting BP was measured on the right arm using automated sphygmomanometers (OMRON HBP-1300, OMRON (CHINA) CO., LTD.)[10] after at least five minutes' rest. The fifth Korotkoff sound was adopted for diastolic BP recording. Mean BP was calculated from three readings. High systolic or diastolic BP was defined based on criteria recommended for Chinese children, i.e., systolic or diastolic BP ≥ 95th percentile for age and sex.[11]

All children provided a 0.5 mL peripheral blood sample from the ring finger after at least eight hours of fasting at the kindergarten clinic unit.[12] Blood samples were immediately centrifuged and processed with an automatic device. Serum levels of total cholesterol, triglycerides, glucose, and uric acid were measured enzymatically using an automatic analyzer (RX Daytona; Randox Laboratories Ltd, Antrim, Ireland).[13] Hyperglycemia was defined as a fasting glucose level of 5.6 mmol/L or higher.[14] High total cholesterol and high triglycerides were defined as 5.18 mmol/L or higher and 1.70 mmol/L or higher, respectively.[15] Due to the lack of a practical guideline for hyperuricemia in preschool children, hyperuricemia was defined as 310 μmol/L (5.2 mg/dL, 90th percentile in our sample) or higher.[6]

According to Ong et al.,[16] a Z-score of 0.67 represents the width of each percentile band on standard growth charts (2nd, 10th, 25th, 50th, 75th, 90th, and 98th percentile lines); thus, a weight gain exceeding >0.67 standard deviation (SD) indicates an increase across at least one of these percentile bands. Thus, in our study, rapid growth was defined as an SD of more than 0.67 of BMI gain, and non-rapid growth was defined as an SD of no more than a 0.67 of BMI gain.

Statistical analysis

For statistical analysis, quantitative variables are expressed as the mean (standard deviation) and the variables as frequencies. The normal distribution of variables was evaluated using the Shapiro-Wilk test. Normally distributed variables are reported as the mean ± SD and were compared using the Student's t or one-way analysis of variance (ANOVA); pairwise comparisons were performed by least significance difference (LSD). The Kruskal-Wallis test was performed for variables with non-normal distributions. To compare the difference of general characteristics among rapid growth and non-rapid growth in children, the Chi-square test was used for categorical variables. Binary logistic regression was used to assess the associations between rapid growth and the indicator of metabolic and cardiovascular disease in univariable and multivariable analyses. The confounding factors included children's age, sex, education of parents, family income, and health history of parents. All statistical analyses were performed with PASW for Windows, version 20.0 (Statistics 20, SPSS, IBM, Armonk, NY). A p value of less than 0.05 for a two-tailed test was considered statistically significant.

RESULTS

We recruited 1450 children between five and six years old with an average age of 5.8 (0.3) years old; 52.6% of the children were boys. General characteristics of the study population are presented in Table 1. Boys had higher mean weight (Mean (SD), 22.6 (4.5) kg), mean height (118.2 (5.0) cm) and mean BMI (16.1 (2.3) kg/cm^2) than girls (21.6 (4.2) kg; 116.9 (5.2) cm; 15.7 (2.1) kg/cm^2) at 5 years old. The prevalence of obesity was 14.5% for all children, 17.4% for boys and 11.2% for girls. We analyzed the influence of socioeconomic factors on rapid growth in childhood (Supplementary Table 1). There were no significant differences among the subgroups of family income or parents' history and current health status.

We compared mean Z-scores for body weight, body length, and BMI from birth to five years old (Table 2). Children who showed infant rapid growth were lighter and had a smaller BMI at birth than children who showed non-rapid growth. However, these children had a greater BMI at two years old and five years old than those who showed non-rapid growth. In contrast, there was no difference in weight and length at birth between childhood rapid growth and non-rapid growth. Children who showed childhood rapid growth had a smaller BMI at two years old than those who showed non-rapid growth. These children were taller at two years old, and were heavier, taller, and had greater BMI at five years old than those who showed non-rapid growth. The prevalence of overweight (BMI-for-age ≥85th percentile) and obesity (BMI-for-age ≥95th percentile) at five years old was 33.6% and 22.6% for children who showed infant rapid growth, respectively, and 68.6% and 50.7% for children who showed childhood rapid growth, respectively. In addition, we split the children into two groups: a non-low birth weight group and a low birth weight group. Similar to the above results, among both non-low birth weight and low birth weight groups, children who showed infant rapid growth had a greater BMI at two and five years old than those who showed non-rapid growth. Children who showed childhood rapid growth had a greater BMI at five years old than those who showed non-rapid growth.

The distributions of indices of metabolic and cardiovascular disease stratified by subgroups of rates of growth during infancy and childhood are summarized in Table 3. In our study, children with childhood rapid growth had higher systolic and diastolic BP as well as higher mean concentrations of fasting glucose, serum triglyceride, and serum uric acid. However, there were differences in these variables among children with infant rapid growth.

Table 4 shows the odd ratios (OR) of childhood obesity and indicators of metabolic and cardiovascular diseases at age five stratified by rates of growth during infancy and childhood. After adjustment for all confounding factors, children with childhood rapid growth had a higher odds ratio (OR) of childhood overweight (OR: 2.52 [95% CI: 1.68–3.78]), obesity (OR: 17.90 [95% CI: 12.31–26.04]), high systolic BP (OR: 2.38 [95% CI: 1.68–3.39]), high diastolic BP (OR: 2.42 [95% CI: 1.53–3.83]), and high triglycerides (OR: 4.09 [95% CI: 1.47–11.33]) or hyperuricemia (OR: 2.23 [95% CI: 1.51–3.29]) at age five years compared with children with non-rapid growth during childhood. Children with infancy rapid growth only had a higher odds ratio (OR) of childhood obesity (OR: 2.97 [95% CI: 2.15–4.11]) at age five years compared with children with non-rapid growth during infancy. We also analyzed the risk according to joint four groups of rates of growth during infancy and childhood. Similarly, children with both infant and childhood rapid growth had a higher odds ratio of childhood obesity (OR: 267.74 [95% CI: 116.00–617.96]), high systolic BP (OR: 4.62 [95% CI:

Table 1. Characteristics of study participants

	Boys	Girls	Total	p
No. of subjects	763	687	1450	
Age, y	5.8 (0.3)	5.8 (0.3)	5.8 (0.3)	0.977
Weight at age 5 y, kg	22.6 (4.5)	21.6 (4.2)	22.2 (4.4)	<0.001
Height at age 5 y, cm	118 (5.0)	117 (5.2)	118 (5.1)	<0.001
BMI at age 5 y, kg/cm^2	16.1 (2.3)	15.7 (2.1)	15.9 (2.3)	0.001
Overweight at age 5 y†, %	27.4	20.2	24.0	0.001
Obesity at age 5 y†, %	17.4	11.2	14.5	0.001
Birth				
Weight-for-age z-score	0.08 (0.99)	0.07 (1.08)	0.08 (1.03)	0.862
Length-for-age z-score	0.05 (0.90)	0.02 (0.95)	0.04 (0.92)	0.560
BMI-for-age z-score	0.08 (1.02)	0.08 (1.09)	0.08 (1.05)	0.963
Two years				
Weight-for-age z-score	0.74 (0.93)	0.73 (0.92)	0.73 (0.93)	0.797
Length-for-age z-score	0.76 (1.04)	0.75 (0.97)	0.75 (1.01)	0.906
BMI-for-age z-score	0.40 (1.00)	0.38 (1.01)	0.39 (1.01)	0.752
Five years				
Weight-for-age z-score	0.75 (1.30)	0.45 (1.11)	0.61 (1.23)	<0.001
Length-for-age z-score	0.72 (0.93)	0.60 (0.95)	0.67 (0.94)	0.014
BMI-for-age z-score	0.41 (1.44)	0.12 (1.19)	0.27 (1.34)	<0.001

Data are means (SD) or percent.
†Overweight was defined as weight-for-length ≥ 85th percentile (≥1.035 Z score); Obesity was defined as weight-for-length ≥95th percentile (≥1.645 Z score); Sex-specific weight-for-length percentiles were based on WHO growth reference[9]

Table 2. Mean values of Z scores for age from birth to five years old

	Infant (0–2 years)			Childhood (2–5 years)		
	Non-rapid growth	Rapid growth	p	Non-rapid growth	Rapid growth	p
No. of subjects	902	548		1154	296	
Boy,%	52.2	53.3	0.693	49.5	64.9	<0.001
Birth						
Weight-for-age z-score	0.38 (0.96)	−0.42 (0.95)	<0.001	0.09 (1.01)	0.04 (1.10)	0.485
Length-for-age z-score	0.06 (0.92)	0.01 (0.93)	0.227	0.05 (0.92)	0.01 (0.94)	0.589
BMI-for-age z-score	0.45 (0.91)	−0.53 (0.99)	<0.001	0.08 (1.01)	0.05 (1.18)	0.642
Two years						
Weight-for-age z-score	0.52 (0.85)	1.08 (0.95)	<0.001	0.75 (0.92)	0.67 (0.96)	0.175
Length-for-age z-score	0.86 (0.99)	0.57 (1.01)	<0.001	0.68 (1.00)	1.02 (0.98)	<0.001
BMI-for-age z-score	−0.01 (0.85)	1.04 (0.90)	<0.001	0.47 (0.97)	0.06 (1.07)	<0.001
Non-low birth weight	0.01 (0.85)	1.07 (0.89)	<0.001	0.48 (0.98)	0.08 (1.07)	<0.001
Low birth weight	−0.68 (0.85)	0.38 (0.70)	0.002	0.20 (0.77)	−0.56 (1.13)	0.044
Five years						
Weight-for-age z-score	0.46 (1.16)	0.84 (1.30)	<0.001	0.30 (0.97)	1.81 (1.38)	<0.001
Length-for-age z-score	0.68 (0.94)	0.63 (0.95)	0.315	0.57 (0.92)	1.04 (0.94)	<0.001
BMI-for-age z-score	0.04 (1.24)	0.66 (1.40)	<0.001	−0.09 (1.02)	1.69 (1.46)	<0.001
Non-low birth weight	0.05 (1.24)	0.68 (1.41)	<0.001	−0.09 (1.03)	1.72 (1.45)	<0.001
Low birth weight	−0.84 (0.86)	0.05 (1.04)	0.018	−0.43 (0.85)	0.56 (1.49)	0.026
Overweight at age 5 y†,%	18.2	33.6	0.148	12.6	68.6	<0.001
Normal birth	18.4	34.2	0.189	12.7	69.2	<0.001
Low birth weight	0	20.8	0.102	7.1	42.9	0.016
Obesity at age 5 y†,%	9.5	22.6	<0.001	5.2	50.7	<0.001
Non-low birth weight	9.7	23.3	<0.001	5.3	51.2	<0.001
Low birth weight	0	8.3	0.324	0	28.6	0.004

Data are expressed as means (SD); proportions, %.
†Overweight was defined as BMI-for-age ≥85th percentile (≥1.035 Z score); Obesity was defined as BMI-for-age ≥95th percentile (≥1.645 Z score); Sex-specific BMI-for-age percentiles were based on WHO growth reference [9]

Table 3. The distributions of indices of metabolic and cardiovascular diseases stratified by subgroups

	Group 1§	Group2§	Group 3§	Group 4§	Total	p
Numbers	699	455	203	93	1450	
SBP†	96.5 (10.4)	97.2 (10.8)	99.2 (11.1) ab	106.3 (11.7) abc	97.8 (11.0)	<0.001
DBP†	58.9 (8.0)	58.9 (8.0)	61.1 (9.0) ab	62.8 (8.9) ab	59.5 (8.3)	<0.001
FG†	4.85 (0.37)	4.89 (0.34) a	4.95 (0.35) a	5.00 (0.48) ab	4.89 (0.37)	<0.001
TC‡	4.23 [0.86]	4.21 [0.87]	4.12 [0.82]	4.25 [0.86]	4.21 [0.86]	0.286
TG‡	0.67 [0.33]	0.68 [0.34]	0.69 [0.40]	0.81 [0.47] ab	0.68 [0.35]	0.002
UA‡	234.0 [68.0]	236.0 [62.0]	245.0 [84.0] a	259.0 [68.0] ab	238.0 [68.0]	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FG: fasting glucose; TC: total cholesterol; TG: triglyceride; UA: uric acid.
Data are expressed as means (SD); medians [IQR]; † ANOVA; ‡ Kruskal-Wallis Test.
§Group 1: Infant (0-2 years) Non-rapid growth and Childhood (2–5 years) Non-rapid growth; Group 2: Infant (0-2 years) Rapid growth and Childhood (2–5 years) Non-rapid growth; Group 3: Infant (0-2 years) Non- rapid growth and Childhood (2–5 years) Rapid growth; Group 4: Infant (0-2 years) Rapid growth and Childhood (2–5 years) Rapid growth
a p<0.05 compared with group 1; b p<0.05 compared with group 2; c p<0.05 compared with group 3.

2.73–7.79]), high diastolic BP (OR: 3.03 [95% CI: 1.50–6.13]), or high triglycerides (OR: 10.59 [95% CI: 2.62–42.83]) at age five years compared with children with non-rapid growth during both infancy and childhood.

DISCUSSION

We conducted an observational study using longitudinal data of 1450 healthy participants, aged 5–6 years. We observed a relationship of accelerated gain in BMI Z-score of infancy or childhood with obesity, systolic blood pressure, diastolic blood pressure, triglycerides, and hyperuricemia in preschool children. Furthermore, childhood rapid growth (2–5 years) appears to be more detrimental than infant rapid growth (0–2 years) in terms of cardiovascular and metabolic disease risk.

The relationship between rapid growth and childhood obesity has been investigated in many studies. A population-based prospective cohort study among 5126 children found that higher BMI during infancy was associated with increased risks of obesity among children at the age of 6 years.[17] Ong et al demonstrated that among 848 children born at full-term, infant rapid weight growth in early life was associated with a higher BMI at the age of five years.[16] Other studies also indicated that infant weight gain during infancy is associated with an increased risk of being overweight in preschool children.[18,19] Similar to previous studies, we found that those children with rapid growth (accelerated gain in BMI-z-score) during infancy or childhood had a higher risk of obesity (2.97-fold and 17.9-fold, respectively) at five years of age compared with children with non-rapid growth.

Rapid growth can occur at any stage of growth but is

Table 4. The distributions of indices of metabolic and cardiovascular diseases stratified by subgroups

	Infant (0–2 years) Rapid growth†	*p* for trend	Childhood (2–5 years) Rapid growth‡	*p* for trend	Group 1§	Group2§	Group 3§	Group 4§	*p* for trend
Overweight¶	1.17 (0.80-1.71)	0.428	2.52 (1.68-3.78)	<0.001	1.00	2.24 (1.39-3.61)	4.99 (3.00-8.32)	1.47 (0.61-3.50)	<0.001
Obesity¶	2.97 (2.15-4.11)	<0.001	17.9 (12.3-26.0)	<0.001	1.00	7.31 (3.7-14.4)	32.7 (16.6-64.5)	268 (116-618)	<0.001
High SBP	1.32 (0.96-1.82)	0.088	2.38 (1.68-3.39)	<0.001	1.00	1.04 (0.70-1.53)	1.67 (1.05-2.64)	4.62 (2.73-7.79)	<0.001
High DBP	1.14 (0.73-1.76)	0.563	2.42 (1.53-3.83)	<0.001	1.00	1.15 (0.66-1.98)	2.34 (1.31-4.17)	3.03 (1.50-6.13)	0.002
Hyperglycemia	0.73 (0.33-1.62)	0.432	1.47 (0.63-3.42)	0.376	1.00	0.60 (0.23-1.56)	1.12 (0.40-3.18)	1.48 (0.41-5.37)	0.583
High TC	0.94 (0.63-1.41)	0.768	0.93 (0.56-1.54)	0.775	1.00	0.81 (0.52-1.26)	0.69 (0.36-1.33)	1.26 (0.59-2.69)	0.466
High TG	2.01 (0.73-5.53)	0.175	4.09 (1.47-11.3)	0.007	1.00	1.42 (0.35-5.79)	2.56 (0.56-11.8)	10.59 (2.62-42.8)	0.005
Hyperuricemia	1.09 (0.76-1.57)	0.649	2.23 (1.51-3.29)	<0.001	1.00	1.48 (0.95-2.29)	3.02 (1.87-4.86)	1.83 (0.90-3.72)	<0.001

High SBP: high systolic blood pressure; High DBP: high diastolic blood pressure; High TC: high total cholesterol; High TG: high triglyceride.
Data are expressed as OR (95% CI).
†Reference group: Infant (0–2 years) Non-rapid growth
‡Reference group: Childhood (2–5 years) Non-rapid growth
§Group 1: Infant (0–2 years) Non-rapid growth and Childhood (2–5 years) Non-rapid growth; Group 2: Infant (0–2 years) Rapid growth and Childhood (2–5 years) Non-rapid growth; Group 3: Infant (0–2 years) Non-rapid growth and Childhood (2–5 years) Rapid growth; Group 4: Infant (0–2 years) Rapid growth and Childhood (2–5 years) Rapid growth
Adjusted for children's age, sex, education of parents, family income and health history of parents.
¶Overweight was defined as BMI-for-age ≥85th percentile (≥1.035 Z score); Obesity was defined as BMI-for-age ≥95th percentile (≥1.645 Z score); Sex-specific BMI-for-age percentiles were based on WHO growth reference[9]

most commonly observed in the first 1–2 years of life when infants may show significant rapid growth. Rapid growth is most likely to occur during infancy among low birth weight infants, following a period of growth restriction. Rapid growth of low birth weight children is usually referred to as "catch-up" growth, which is a phenomenon assumed to result from recovery from undernutrition in-utero. These variable growth rates often compensate for intrauterine restraint or enhancement of fetal growth.[1] Children who showed catch-up growth between birth and two years old were fatter (greater BMI and greater percentage body fat derived from skinfold measurements) and had more central fat distribution (larger waist circumference) at five years old than other children.[16] Nutrition is a major contributor to the rate of growth, particularly in early postnatal life. Formula-fed infants grow faster than those who were breast-fed, and this pattern of growth is associated with an increased later risk of obesity and cardiovascular disease.[20] Rapid growth also occurs among non-low birth weight children. Lifestyle factors, such as greater fast food intake[21] and sedentary lifestyle,[22] are likely important for weight gain in childhood. In our study, children who showed infant rapid growth were lighter and had a lower BMI at birth than those who showed non-rapid growth. These children had higher BMIs at two years old and also at five years old compared to other children. However, there was no difference in weight and length at birth between childhood rapid growth and non-rapid growth. Children who showed childhood rapid growth had a smaller BMI at two years old but were heavier and taller and had a greater BMI at five years old than other children. These results suggest an association between growth restraint in fetal and infant rapid growth, and an association between growth restraint before two years old and childhood rapid growth. The rate of weight gain during childhood was more strongly related to childhood obesity risk than weight gain up to two years of age.

Several studies have reported adverse effects of accelerated early weight gain on the cardiovascular profile. Lurbe demonstrated that systolic BP was related to weight gain, and at five years the heaviest children had the highest systolic BP.[23] A study of children aged 13–14 years showed that rapid weight gain during early childhood was predictive of high BP,[24] and another study showed an association with increased risk of elevated BP in adulthood.[25] Likewise, the present study showed that childhood rapid growth was associated with increased systolic BP and with increased diastolic BP. An earlier study demonstrated that both early and late rapid growth is associated with increased systolic BP in adolescence.[26] Another early study showed that change in BMI Z-score at early school age has a weak positive association with adult systolic BP, and that the association between change in BMI Z-score at late school age and systolic BP is positive.[27] However, in the present study, infant rapid growth was not associated with childhood BP. The impact of critical periods on BP during the first two years of life has not been demonstrated consistently and warrants future investigation.

Most studies have focused on the associations of infant weight gain with metabolic outcomes. A cohort study of subjects in Helsinki, Finland reported that increased SD scores for BMI from 2 to 11 years of age was associated with increased fasting plasma insulin, but not with increased serum triglyceride concentrations.[3] Results from a study of 128 subjects suggest that rapid weight gain during infancy predicted the clustering of metabolic risk factors at age 17 years.[28] Another observational study using longitudinal data collected in the Programming Factors for Growth and Metabolism (PROGRAM) study of 217 healthy participants reported that increased weight gain relative to height growth in the first three months of life is associated with reduced insulin sensitivity and serum high density lipoprotein (HDL) cholesterol levels, serum levels of triglycerides, and type two diabetes in early adulthood.[29] In our study, we observed a higher mean concentration of fasting glucose, serum total cholesterol, triglyceride, and serum uric acid to be associated with childhood rapid growth, but not with infant rapid growth. There was a positive association between "unhealthy" dietary patterns (poor in fiber and rich in sodium, fat, and refined carbohydrates) and cardiometabolic alterations in children.[30] Children with "unhealthy" dietary patterns might intake excessive energy and gain more weight during childhood (rapid growth). A previous study found that preschool children whose mothers had worse dietary scores were more likely to follow unhealthier patterns.[31] Within a family context, eating habits develop during the first years of life, and these early diet habits track into later ages and influence current and future health. In the present study, we did not obtain information related to children's diets. Thus, the mechanism of action of diet is still unclear. In future studies, we will collect more information regarding the lifestyle of children and their families. Further studies should focus on the impact of dietary patterns and other lifestyle choices on cardiovascular risk factors in children.

Obesity may be a key risk factor for developing metabolic and cardiovascular diseases among preschool-aged children with rapid growth. During rapid growth, excessive energy intake results in fat accumulation, fat remodeling, and change of gene expression in adipose tissue, which may lead to obesity.[32] Animal studies show that obesity-induced hyperlipidemia, atherosclerosis, hypertension, and metabolic syndrome are related to the neuroendocrine metabolism disorder of the hypothalamus-pituitary-adrenal axis. In rats with a "rapid growth" pattern, the hypothalamic-pituitary-adrenal axis exhibited a lower basal activity but have enhanced sensitivity to chronic stress, leading to increased levels of serum glucose, insulin, insulin resistant index, total cholesterol and low-density lipoprotein-cholesterol, and decreased levels of high-density lipoprotein-cholesterol.[33]

One limitation of our study was that we did not collect data of recent dietary patterns and physical activity. Some studies show that dietary patterns and physical activity are related to childhood obesity.[22,34] In our study, all children ate three meals and exercised regularly in kindergarten schools. Thus, these children are thought to have similar dietary patterns and physical activity. We also did not collect detailed data on feeding status in early infancy or parental BMI, or maternal health during pregnancy, which may weaken the observed associations. Our previous research found that formula-fed children grow more rapidly than breastfed-children.[35] Another study found that maternal pre-pregnancy overweight was associated with greater weight gain of offspring in early infancy.7 In addition, we analyzed the influence of socioeconomic factors on rapid growth in childhood, but found no significant association. Thus far, we have only followed children's growth to 6 years old but our study is ongoing and thus we continue to collect more detailed data. Further studies are needed to explore the comprehensive effects of genetic and living environment factors on rapid growth. Another limitation of our study was that we only used BMI in our analysis. Adiposity measures also include waist circumference, skinfolds, fat mass, and abdominal or visceral fat deposits. Weight gain consists of gain in both fat and lean mass. Further research is needed to explore whether fat or lean mass gain has a greater impact on cardiovascular disease. In addition, we could conduct comparisons to populations of other countries to explore the impact of rapid growth on obesity in different economies, cultures, or ethnicities.

In conclusion, our data suggests that rapid growth in early childhood is associated with increased risk factors for certain cardiovascular and metabolic outcomes among preschool children. Rapid growth from two years old to five years old is more detrimental in this regard than rapid growth in the first two years of life. All children should be monitored for height and weight gain, regardless of birth weight. Developing effective prevention and intervention programs for pre-school children might be an important step in combating the childhood obesity epidemic and reducing the incidence of long-term metabolic and cardiovascular diseases in adults.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Supplementary table 1. Characteristics of socioeconomic factors

	Infant (0–2 years)		*p*	Childhood (2–5 years)		*p*
	Non-rapid growth	Rapid growth		Non-rapid growth	Rapid growth	
Mother's history of diseases†			0.523			0.338
No	1.6	2.0		1.6	2.4	
Yes	98.4	98.0		98.4	97.6	
Father's history of diseases†			0.218			0.104
No	5.2	6.8		4.8	7.1	
Yes	94.8	93.2		95.2	92.9	
Family income, yuan/year ‡			0.109			0.963
≥150,000	29.2	34.4		31.3	30.5	
100,000-<150,000	31.1	31.8		31.2	32.0	
70,000- <100,000	15.5	12.3		14.5	13.6	
<70,000	24.2	21.5		23.0	23.9	

Data are expressed as proportions, %.
†History of diseases such as diabetes, dyslipidemia, and hyperuricemia.
‡US$1=six point six yuan