Growth of infants and young children born small for gestational age: growth restriction accompanied by overweight

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Abstract

Objectives: To compare growth profiles of children born small for gestational age (SGA) with those born the appropriate size for gestational age (AGA), and examine expected growth patterns for SGA in early childhood.

Methods: A survey on 23,871 SGA children was conducted in Shanghai. Data were collected at 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 60 months of age (+30 days). A check-up included assessments of weight, height, and head circumference.

Results: At 5 years old, weight, height, and head circumference were lower in SGA children compared with AGA children. The proportions of overweight and obesity of SGA children at 4 to 18 months after birth were significantly higher than those in AGA children, with higher proportions in boys than in girls. There was no correlation between overweight at 5 years old and overweight before 2 years old in SGA children.

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Conclusions: Children born SGA remain shorter and lighter, with a smaller head circumference at 5 years old compared with AGA children. At 4 to 18 months after birth, there is a high incidence of overweight and obesity in SGA children. Overweight and obesity in SGA boys are more serious than those in SGA girls.

Introduction

Children born small for gestational age (SGA) are defined as a birth weight below the 10th percentile for gestational age, or defined as more than 2 standard deviations (SDs) below the mean for weight and/or length. SGA occurs in approximately 3% of live-born newborns worldwide. Children born the appropriate size for gestational age (AGA) are defined as the 10th to 90th percentiles of mean weight for the same gestational age. Children who are born SGA have increased risks of mortality and morbidity in the neonatal period,[1] as well as higher rates of learning disability and a greater risk of a range of diseases later in life, including cardiometabolic and renal conditions.[2]

SGA is associated with foetal growth restriction in which the genetic growth potential is not reached because of disturbances in the supply of nutrients and oxygen *in utero*. Foetal growth restriction can not only lead to adverse foetal growth patterns, but is also associated with development of some metabolic syndromes later in life. This foetal response has been termed developmental programming or the developmental origins of health and disease.[3]

Most children who are born SGA are known for their ability to have catch-up growth. However, the pattern of their catch-up growth is different from that of children who are premature with a low birth weight.[4] Children who are born SGA and show catch-up growth have a greater risk of developing cardiovascular and metabolic disease in later life. These metabolic disorders include dyslipidaemia, insulin resistance, and type II diabetes.[5–8] The underlying mechanisms generating the different growth patterns and metabolic profiles in this situation are not well understood.

This study aimed to compare growth profiles of children who were born SGA with those who were born AGA, and to describe the distribution of overweight and obesity based on health examination survey data in Shanghai. We assessed correlations between overweight at 5 years old and overweight at other ages, and documented the expected growth pattern for SGA in early childhood.

Material and methods

Study design and sampling procedure

This study was part of a large, community-based, general social survey on growth and development in children aged younger than 6 years old in Shanghai. The sample comprised children born between 1 January, 2004 and 1 January, 2010, and covered all 18 districts in Shanghai. The study protocol was approved by Shanghai Children's Hospital Ethics Committee. All of the patients provided verbal informed consent.

By definition, children with birth weight below the 10th percentile were classified as SGA and those born after 37 weeks were defined as full-term. Gestational age is expressed as the number of completed weeks of gestation. Children whose gestational age could not be defined beyond reasonable doubt were excluded. We also excluded children with conditions that would affect growth, such as heart disease, chronic nephritis, tuberculosis, persistent hepatitis, chronic bronchitis, and asthma. Finally, the total sample that met these criteria consisted of 23,871 children. We concluded that this sample was fairly representative of the population.

Measures and procedure

Data on growth during the first 6 years after birth were retrospectively obtained from medical records kept at maternal and child health institutions and nurseries during a 6-month period between September 2014 and March 2015. During their first 6 years, children had 12 health check-ups. Data were collected at the following age points: 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 60 months of age (+30 days). The check-up included assessment of height, weight, and head circumference (HC). Up to age 24 months, the child was measured lying in the supine position. From 24 months onward, the child was measured standing. Weight was measured unclothed. Height and HC were measured to 1-mm accuracy and weight was measured to 0.01 kg. The study was undertaken by trained surveyors who had knowledge of uniform technical standards and methods of operation. To detect any registration and data entry errors, we checked all of the data by maternal and child health networks.

To control for group differences and to scale the values for comparison across age groups, we converted birth weight, height, and HC to z-scores (mean $= 0$, SD $= 1$), using the medians and SDs of normal children (control) in Shanghai according to gestational age. We chose the body mass index (BMI) to categorize overweight or obesity because of its strong correlation with blood pressure, lipoprotein levels, and leptin levels. Even after accounting for the triceps skinfold thickness of children, BMI for age provides additional information on adult adiposity.[9] Up to 24 months of age, BMI was calculated as weight (kg)/body length^2 (m). From 24 months onward, BMI was calculated as weight (kg)/height^2 (m). Overweight was defined as >1 SD and obesity was defined as >2 SD according to the BMI standard of the World Health Organisation (WHO) (2006).[10]

Statistical analysis

We first assessed the median growth and variability in growth for weight, height, and HC from birth to 60 months, per month of age and by sex. Relative weight, height, and HC were defined as the z-score that a child had reached at a certain age compared with AGA controls (data not shown). We then calculated the proportion of overweight and obesity at different ages. We assessed correlations between overweight at 5 years old and overweight at other ages. Growth curves for weight, height, and HC by sex were created based on longitudinal growth data of the sample.

The z-score and BMI are described by mean and standard deviation. Overweight and obesity are shown by frequency and percentage. The t-test was used to evaluate the differences between SGA and AGA. The significance level was set at $P < 0.05$. The Spearman correlation coefficient was used in correlation analysis between overweight at different ages. Epidata3.1 (EpiData Association, Odense, Denmark) for a personal computer was used for data entry. PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Background characteristics

Our study group consisted of 728,602 children born in Shanghai of whom 23,871 were born SGA. The overall prevalence of SGA in this sample was 3.28%. SGA occurred more often in girls than in boys (Table 1)

Growth in children born SGA

Figure 1 shows the median z-scores of weight, height, and HC of SGA boys from 0 to 60 months. During the first 36 months, the z-scores of weight and height increased, which indicated that SGA boys experienced catch-up growth and narrowed the gap with normal children. However, there was a decline in these variables thereafter, which resulted in significantly lower z-scores at 60 months old compared with those at 36 months old ($P < 0.05$). The growth pattern was also pronounced in SGA girls (Figure 2). There were no significant differences in z-scores between SGA boys and

girls (data not shown). At age 5 years, weight and height of SGA children were 0.38 SD and 0.67 SD, respectively, which were significantly lower than those in AGA children (both $P < 0.05$). With regard to HC, the coefficient tended to be approximately -1 SD, with an average of -0.69 SD at 5 years old. During the follow-up period, the height z-score curve was located under the weight z-score curve. The gap between these curves was 0.01 to 0.57 SD, with an average of 0.30 SD. The catch-up growth of SGA children appeared to be disproportional. Catch-up in height was less compared with weight, which indicated a potential problem of obesity in these children.

Overweight and obesity in children born SGA

Figure 3 shows the median BMI of SGA boys at each age point plotted with the BMI standards of the WHO. The changing tendency of BMI over time was the same between SGA boys and AGA boys. The

Table 1. Characteristics of the total sample and proportions (% of the group) for small for gestational age children at birth

Characteristic	Total	Boys	Girls
Total	23871 (100)	9805 (44.1)	14066 (58.9)
Gestational age, weeks			
37	2805 (11.8)	1200 (42.8)	1605 (57.2)
38	4043 (16.9)	1707 (42.2)	2336 (57.8)
39	5291 (22.2)	2073 (39.2)	3218 (60.8)
40	10971 (46.0)	4538 (41.4)	6433 (58.6)
41	761 (3.1)	287 (37.7)	474 (62.3)
42	0	0	0
Birth weight			
ELBW	4 (0.02)	2 (50.0)	2 (50.0)
VLBW	81 (0.34)	45 (55.6)	36 (44.4)
LBW	10715 (44.9)	4472 (41.7)	6243 (58.3)
BW $\geq$2500 g	13071 (54.8)	5289 (40.5)	7782 (59.5)
Region			
Urban	3920 (16.4)	1586 (40.5)	2334 (59.5)
Suburbs	19951 (83.6)	8219 (41.2)	11732 (58.8)

Values are n (%).
ELBW, extremely low birth weight; VLBW, very low birth weight; LBW, low birth weight; BW, birth weight.
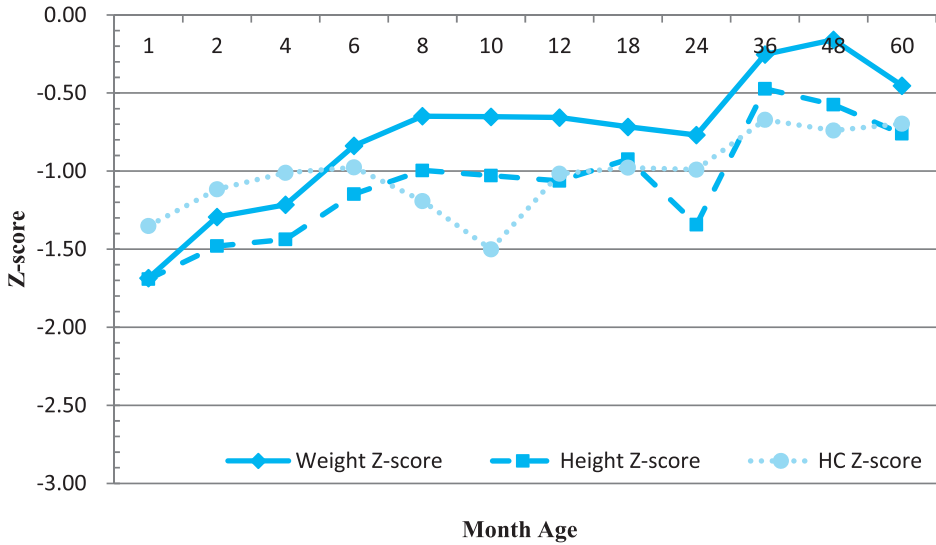
Figure 1. Median z-score curves for weight-for-age (full line), height-for-age (broken line), and head circumference-for-age (dotted line) in small for gestational age boys

Figure 2. Median z-score curves for weight-for-age (full line), height-for-age (broken line), and head circumference-for-age (dotted line) in small for gestational age girls

BMI increased with age before 8 months, and slowly decreased after this time. This trend was also observed in SGA girls (Figure 4). Between 4 to 18 months, the median curve of SGA was located between 0 SD and 1 SD of the WHO standards in both sexes. This indicated more fat accumulation in SGA children than in AGA children during this period. In boys, the peak in BMI was at 8 months old (17.81 ± 1.58 kg/m^2) and in girls it was at 10 months old (17.38 ± 1.42 kg/m^2).
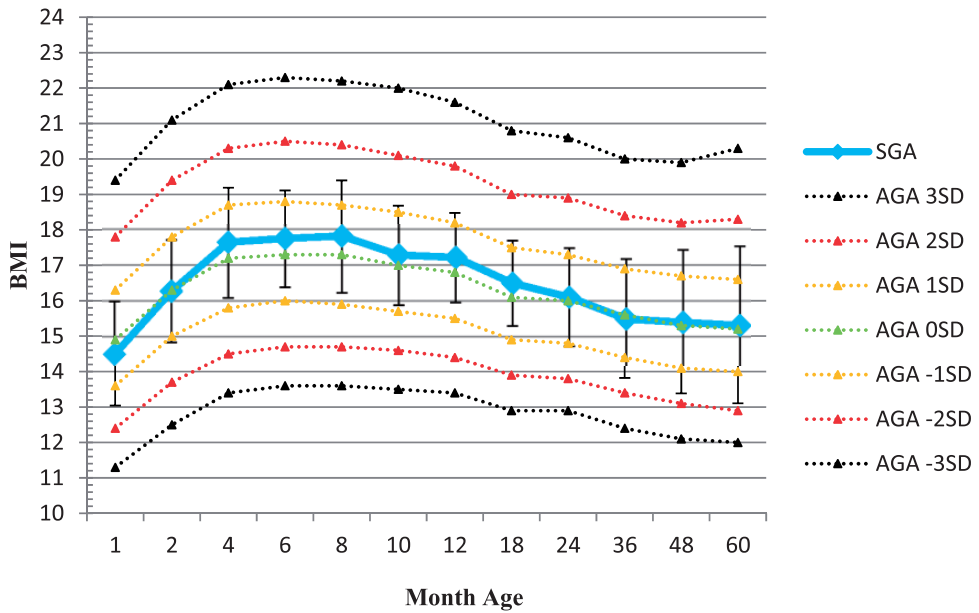
Figure 3. Comparison of body mass index between small for gestational age boys and the World Health Organisation standard. The full line represents median body mass index for age in small for gestational age boys and the dotted lines represent the WHO standard for appropriate size for gestational age boys
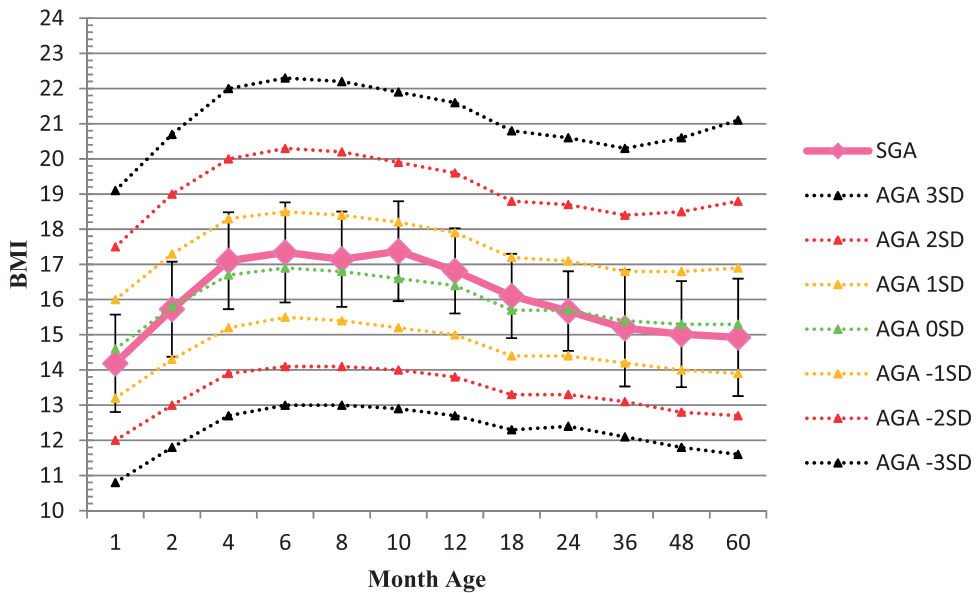

Figure 4. Comparison of body mass index between small for gestational age girls and the World Health Organisation standard. The full line represents median body mass index for age of small for gestational age girls and dotted lines represent the World Health Organisation standard for appropriate size for gestational age girls
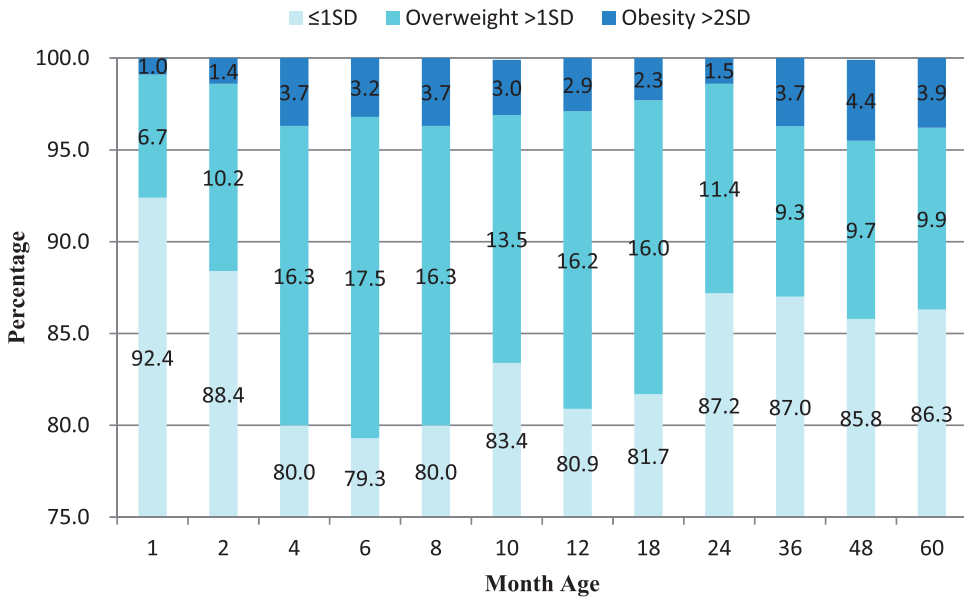
Figure 5. Distribution of overweight and obesity in small for gestational age boys. Numbers in bars represent proportions (% of the group)

Figures 5 and 6 show the distribution of overweight and obesity in SGA children. In SGA boys, the proportion of overweight at 4 to 18 months of age was significantly higher than that in SGA girls (P < 0.05), with a mean rate of 16.0%. In SGA girls, the proportion of overweight from 4 to 12 months of age showed a mean rate of 14.8%. The proportion of obesity at 4 to 18 months of age was a mean of 19.1% in SGA boys and 16.3% in SGA girls

Correlations between overweight at different ages

Correlations between overweight at 5 years old and overweight at other ages are shown in Table 2. Because the proportion of overweight was significant at 4 to 18 months of age, we chose six age points to analyse: 4, 12, 18, 24, 36, and 48 months. There were no significant correlations between overweight at 5 years old and overweight before 2 years old in SGA children. However, a moderate correlation was

observed between overweight at 5 years old and overweight at 3 years old in SGA children (boys: $r_s = 0.437$, P < 0.001; girls: $r_s = 0.531$, P < 0.001). Overweight at 5 years old was highly correlated with overweight at 4 years old (boys and girls: $r_s = 0.624$, P < 0.001).

Discussion

In this population-based study of children who were born SGA, we showed persistent associations of birth weight with growth status in infancy and early childhood to 60 months of age. Children who were born SGA tended to remain lighter and shorter with a smaller HC. Children who were born SGA also had accelerated growth during the first 36 months, but never completely caught up. The average weight and height of SGA children increased from below −1.28 SD at birth to −0.3 to −0.8 SD at 60 months. The catch-up growth of SGA children was disproportional. Catch-up growth in height
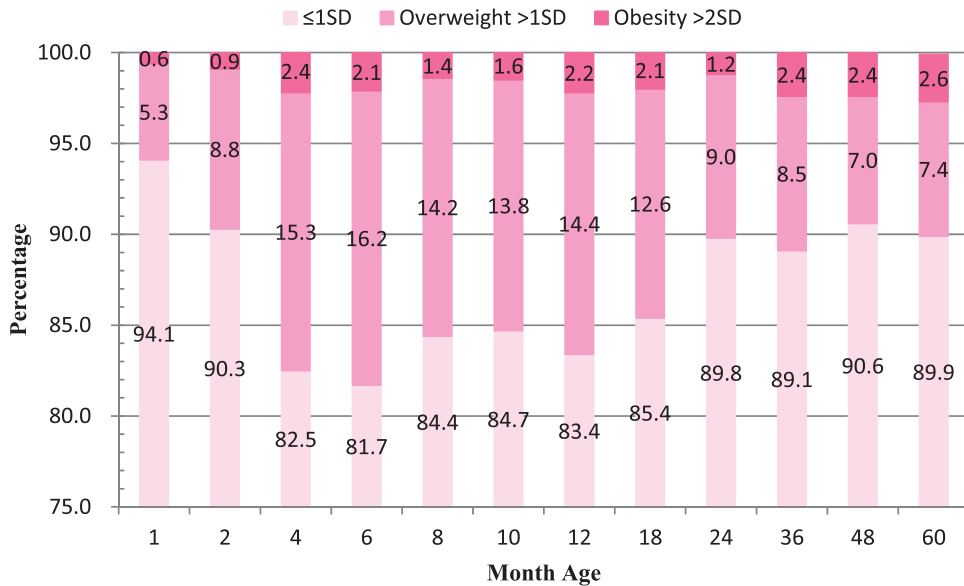
Figure 6. Distribution of overweight and obesity in small for gestational age girls. Numbers in bars represent proportions (% of the group)

Table 2. Correlations between overweight at 5 years old and overweight at other ages

Age (months)	SGA boys		SGA girls	
	r_s	P	r_s	P
4	0.258	0.576	0.136	0.390
12	0.192	0.239	0.139	0.534
18	0.218	0.604	0.091	0.779
24	0.218	0.604	0.360	0.572
36	0.437	<0.001	0.531	<0.001
48	0.624	<0.001	0.624	<0.001

SGA, small for gestational age.

was less than that with weight. This finding indicates more attention should be paid to overweight and obesity in SGA.

In SGA children, the BMI increased with age before 8 months, and slowly decreased after this time, which was similar to AGA children. We did not observe an advance of adiposity rebound in SGA children compared with AGA children. A previous study showed adiposity rebound corresponded to the second rise in the BMI curve, which occurred at 5 to 7 years old.[11] The typical pattern of adiposity rebound is a low BMI followed by an increased BMI level after this rebound. An early adiposity rebound reflects accelerated growth and is associated with an increased risk of overweight.[12] Children who have adiposity rebound at a younger age are predisposed to have more metabolic
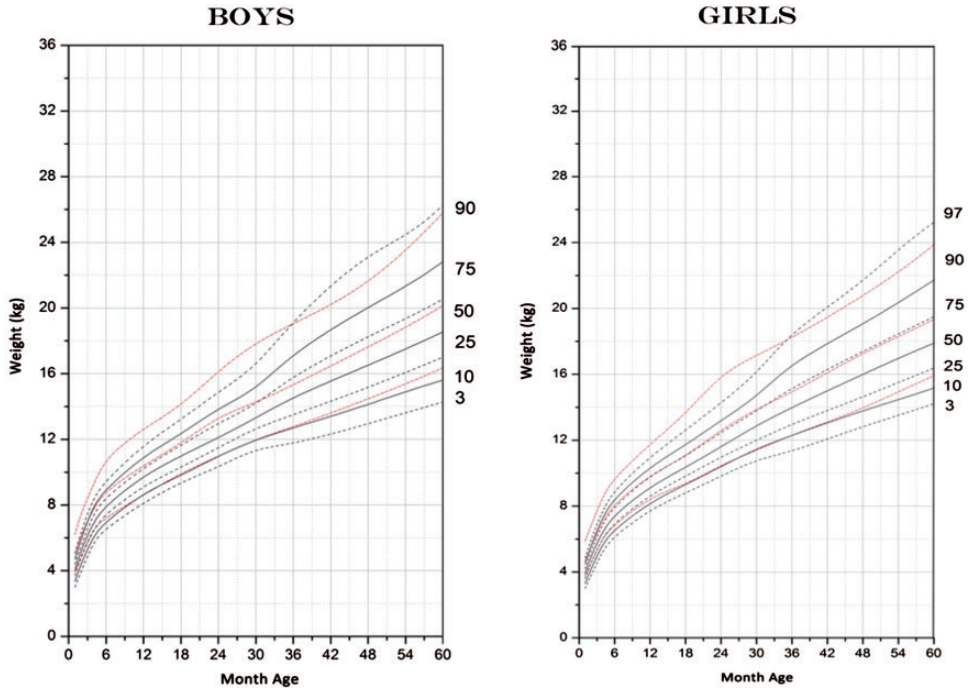
Figure 7. Weight-for-age growth curves for small for gestational age children. Black lines from the top down represent the 97th, 90th, 75th, 50th, 25th, 10th, and 3rd percentiles of weight of small for gestational age children. Red lines from the top down represent the 97th, 50th, and 3rd percentiles of weight of appropriate size for gestational age children

syndromes in future development.[13,14] In our study, the occurrence time of adiposity rebound in SGA children was not different compared with that in AGA children. However, the BMI of SGA children was higher than that in AGA children. Between 4 to 18 months, the BMI of SGA children was higher than that of AGA children, with the median curve located between 0 and 1 SD of the WHO standards. This was also the period when SGA children experienced catch-up growth. Overweight and obesity in SGA boys were more serious than those in SGA girls. Children born SGA experience obvious catch-up growth in the first 2 years after birth and erase the growth deficit. However, catch-up growth is associated with an increased risk of later chronic diseases.[15] SGA children with compensatory catch-up growth in the first year of life show mild disturbance of glucose tolerance associated with a lower insulinogenic index at 4 years old, which suggests impairment of β-cell function.[16] SGA girls who experience catch-up growth in childhood develop an ensemble that includes not only central adiposity, hyperinsulinaemia, and hypoadiponectinaemia, but also hyperleptinaemia, dyslipidaemia, and faster bone maturation before starting puberty.[17] In our study, catch-up growth of SGA children was accompanied by overweight and obesity. Whether metabolic disorders in SGA are caused by catch-up growth or accompanied overweight and obesity is unclear. Research has shown that fat mass is the only significant predictor of insulin sensitivity, whereas birth length and birth weight are not.[18] We suggest that catch-up growth should not
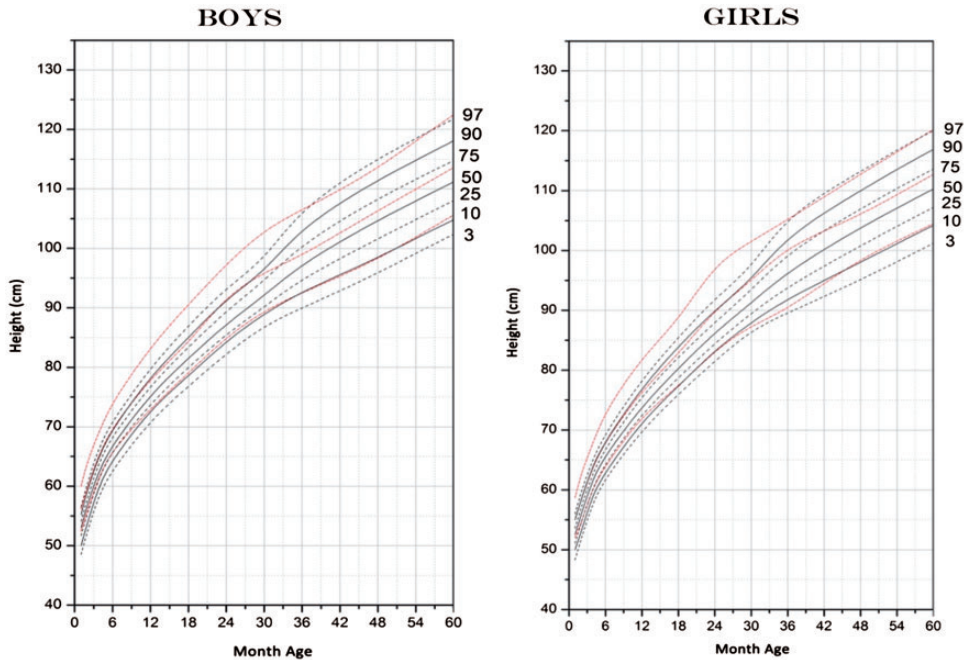
Figure 8. Height-for-age growth curves for small for gestational age children. Black lines from the top down represent the 97th, 90th, 75th, 50th, 25th, 10th, and 3rd percentiles of height of small for gestational age children. Red lines from the top down represent the 97th, 50th, and 3rd percentiles of height of appropriate size for gestational age children

extend to overgrowth or misbalanced growth, and that weight gain in SGA children needs to be controlled within reasonable limits. The possible metabolic risks that accompany growth that is too rapid should be prevented.

Surprisingly, we were unable to show a correlation between overweight at 5 years old and overweight in the first 2 years after birth. However, after 3 years old, overweight was significantly correlated with overweight at 5 years old. We speculate that the lack of correlation before 3 years old was because the age points were close to each other. Our study suggests that if SGA children are still overweight after catch-up growth, they are more likely to develop weight problems and be exposed to metabolic diseases in later life. Freedman et al. showed that overweight 2- to 5-year-olds were > four times as likely to

become overfat adults as were children with a BMI < 50th percentile.[9] More attention should be paid to caloric intake in these children. Despite the weak correlations between overweight before 3 years old, whether catch-up growth would affect fat distribution in the body is unclear. Lourdes et al. showed visceral fat excess by 6 years old in SGA children who experienced catch-up growth.[19] Furthermore, rapid catch-up growth in very low birth weight children leads to changes in abdominal fat distribution at 3 years old.[20] Whether this change in fat distribution leads to metabolic disorders in later life requires further research.

Conditions that are experienced in early life play an important role in the long-term health of individuals.[21] Alterations in development due to impaired, excessive, or imbalanced growth, both *in utero* and
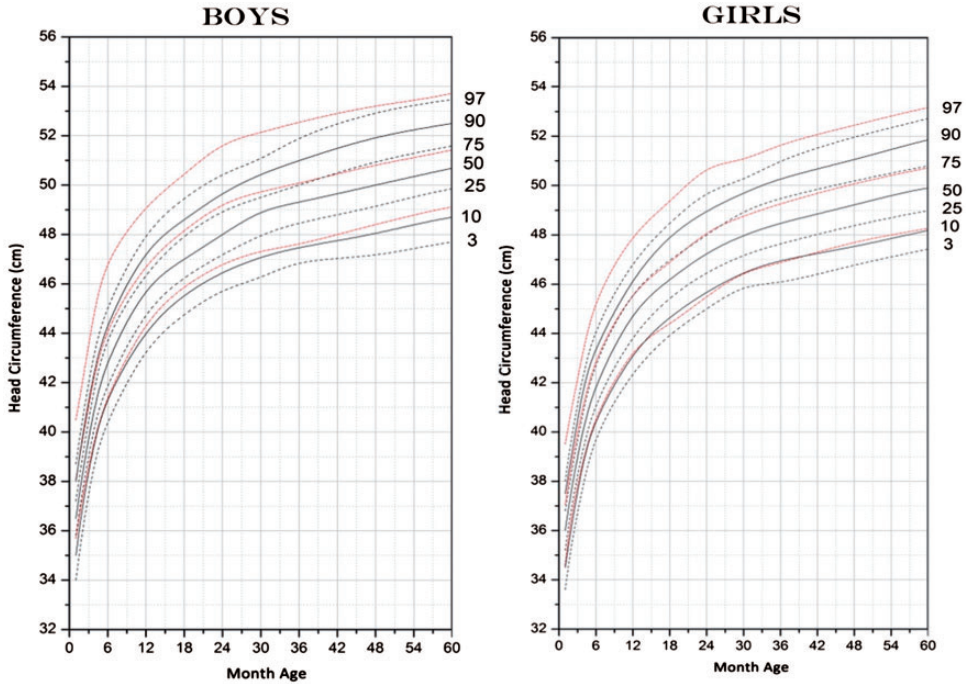
Figure 9. Head circumference-for-age growth curves for small for gestational age children. Black lines from the top down represent the 97th, 90th, 75th, 50th, 25th, 10th, and 3rd percentiles of head circumference of small for gestational age children. Red lines from the top down represent the 97th, 50th, and 3rd percentiles of head circumference of appropriate size for gestational age children

during critical periods, can lead to the permanent changes in structure and physiological programming.[22,23] An insufficient nutritional supply *in utero* in SGA children may change early life programming and imprinting, leading to an atypical growth model.[24] SGA children are at a high risk of developing metabolic disorders in adulthood and may have their own growth trajectory. Current knowledge of the normal ranges of growth across the entire range of SGA gestational ages is incomplete. The growth curve derived from the growth charts for AGA is likely to be a poor substitute for monitoring growth in SGA. Without targeted standards, excessive weight gain might go unnoticed, which may lead to obesity, cardiovascular disease, diabetes, and other health problems.

Adequate growth charts for SGA are required. Therefore, we constructed separate growth charts for weight, height, and HC based on data of our sample in those who had complete longitudinal growth data (Figures 7–9). Because of the large sample of our study, we consider that these growth curves are fairly representative.

Major strengths of this study are its large sample of SGA children over the entire range of ages and its community-based design. Furthermore, we analysed growth longitudinally and assessed development using a validated, easy to fill out, developmental screener.

There are also some limitations in our study. First, no data on foetal growth were available. Therefore, we were unable to detect the foetal origin of growth

restrictions. Growth trajectories of SGA children might vary from different foetal growth patterns. The optimal growth of different types of SGA might not be the same. Second, there were no data of metabolic diseases in our sample. The relations between growth restriction and overweight and metabolic disorders in later life are of particular interest for further research.

Children who are born SGA should be closely monitored because they appear to have an additional risk of growth restriction, as well as developmental delay. Catch-up growth in SGA children is important for erasing the deficit at birth, but should not extend to overgrowth or misbalanced growth. The possible metabolic risks that accompany rapid growth should be prevented. In summary, preventing foetal growth restriction might be important for preventing poor outcomes in SGA children.

Conclusions

Children who are born SGA remain shorter and lighter with a smaller HC at 5 years old compared with AGA children. Catch-up growth of SGA is unbalanced. At age 4 to 18 months there is a high incidence of overweight and obesity among SGA children. Overweight and obesity in SGA boys are more serious than those in SGA girls. There are no associations between overweight at 5 years old and overweight in the first 2 years after birth.

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