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### Birth Weight, Infant Growth, and Childhood Body Mass Index: Hong Kong's Children of 1997 Birth Cohort

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# Birth Weight, Infant Growth, and Childhood Body Mass Index

## Hong Kong's Children of 1997 Birth Cohort

L. L. Hui, MPhil; C. Mary Schooling, PhD; Shirley Sze Lee Leung, MBBS; Kwok Hang Mak, MBBS; Lai Ming Ho, PhD; Tai Hing Lam, MD; Gabriel M. Leung, MD

**Objective:** To investigate the association between birth weight, infant growth rate, and childhood adiposity as a proxy for adult metabolic or cardiovascular risk in a Chinese population with a history of recent and rapid economic development.

**Design:** Prospective study in a population-representative birth cohort.

**Setting:** Hong Kong Chinese population.

**Participants:** Six thousand seventy-five term births (77.5% successful follow-up).

**Main Exposures:** Birth weight and growth rate (change in the weight  $z$  score) at ages 0 to 3 and 3 to 12 months.

**Main Outcome Measure:** Body mass index (BMI) (calculated as the weight in kilograms divided by the height in meters squared)  $z$  score at about age 7 years.

**Results:** Each unit increase in the weight  $z$  score at ages 0 to 3 and 3 to 12 months increased the BMI  $z$  score by 0.52 and 0.33, respectively. Children in the highest birth weight and growth rate tertiles had the highest BMI  $z$  scores. In the lowest birth weight tertile, increases in the weight  $z$  score at ages 0 to 3 months had a larger effect on the BMI  $z$  score in boys (mean difference, 0.88; 95% confidence interval 0.69-1.07) than in girls (mean difference, 0.52; 95% confidence interval, 0.33-0.71); these differences by birth weight, growth rate at ages 0 to 3 months, and sex were significant ( $P = .007$ ).

**Conclusions:** Faster prenatal and postnatal growth were associated with higher childhood BMI in a population with a recent history of rapid economic growth and relatively low birth weight, suggesting that maximal growth may not be optimal for metabolic risk. However, there may be a developmental trade-off between metabolic risk and other outcomes.

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**D**ESPITE 2 DECADES OF intensive research, the role of fetal and infant growth in metabolic and cardiovascular disease remains controversial with the underlying physiological pathways only beginning to be elucidated. Poor fetal growth alone or in combination with poor infant growth,<sup>1</sup> accelerated infant growth,<sup>2,3</sup> and poor fetal growth followed by accelerated infant growth<sup>4</sup> have been variously implicated as possible detrimental pathways leading to adult metabolic and cardiovascular disease. Although much attention has been focused on low birth weight as the causative factor, evidence from experiments designed to test this hypothesis have highlighted the role of nutritionally driven postnatal growth as a possible missing link in the observed relation

between birth weight and adult metabolic disease.<sup>5,6</sup>

To date, the observational evidence in human studies suggests that both higher birth weight and faster infant growth are associated with childhood obesity<sup>7</sup> with lifelong adverse consequences<sup>8</sup> because obesity tends to track into adulthood<sup>8</sup> where it is a well-established risk factor for cardiovascular disease.<sup>9,10</sup> In adults, the cardiovascular risks associated with excess adiposity are evident even in very lean persons.<sup>11</sup> This relation may be less obvious in children<sup>12</sup>; nevertheless, there is evidence from long-term longitudinal studies that higher body mass index (BMI) (calculated as the weight in kilograms divided by the height in meters squared) in childhood is associated with adult adiposity<sup>13</sup> and cardiovascular mortality,<sup>14</sup> possibly because childhood adiposity is associated

with earlier pubertal maturation<sup>13</sup> that in turn is associated with adult cardiovascular risk.<sup>15</sup> Although premature cardiovascular disease is more common in men,<sup>16</sup> there is little examination of whether birth weight or infant growth (singly or jointly) have different effects by sex, with some suggestions that faster infant growth may be more detrimental in boys<sup>17</sup> and inconsistent evidence for low birth weight.<sup>18-20</sup> To our knowledge, 1 previous study<sup>21</sup> has investigated for effect modification by sex in the relation of infant growth to childhood obesity, but no previous study has examined for effect modification by sex in the joint relation of birth weight and infant growth rate to childhood adiposity. Moreover, these questions are even less clearly answered in developed, nonwestern populations such as that in Hong Kong, China, which currently has a gross domestic product per head similar to western Europe and North America but whose population has had a much more rapid history of economic development over essentially 2 or 3 generations<sup>22,23</sup> and as such may be a sentinel for other rapidly developing nations. Typically in these rapidly developed, nonwestern populations, babies have lower birth weights<sup>24-26</sup> and overall rates of adult cardiovascular disease,<sup>16,27,28</sup> although current rates of pediatric overweight are within the wide range reported in North America and Europe.<sup>29,30</sup> Importantly, from these populations there is increasing evidence that the effect of some risk factors may be time and place dependent.<sup>31-35</sup> Using a contemporary, large, population-based Chinese birth cohort, we examined whether the effect of birth weight and infant growth (singly and jointly) on childhood adiposity varied by sex.

## METHODS

### CHILDREN OF 1997 BIRTH COHORT

We used data from a population-based Hong Kong birth cohort (n=8327) that covered 88.0% of all of the births between April 1, 1997, and May 31, 1997. This birth cohort was initially established to investigate the health effect of secondhand smoke exposure.<sup>36-39</sup> Families were recruited at the Maternal and Child Health Centres, which parents of all newborns are encouraged to attend for free well-baby developmental checkups, physical examinations, and vaccinations until age 6 years. At recruitment, information on socioeconomic status (parental education and type of housing), birth characteristics (birth weight, birth order, sex, gestational age, and method of delivery), patterns of infant feeding, and secondhand smoke exposure was collected using a self-administered questionnaire in Chinese. In September 2005 to May 2006, all of the weight and length or height measurements recorded at each well-baby care visit were retrieved from the Maternal and Child Health Centres. Using record linkage on the unique birth certificate number, weight and height measurements taken at the Department of Health's Student Health Service (with 95.2% population coverage at age 7 years) for school-aged children were also obtained. All of the weights and lengths or heights were measured by trained nurses and recorded to the nearest 0.1 kg and 0.1 cm, respectively.

The study was reviewed by and received approval from the University of Hong Kong–Hospital Authority Hong Kong West Cluster Joint Institutional Review Board and the Ethics Committee of the Department of Health, Government of the Hong Kong SAR, Hong Kong, China.

## EXPOSURES

### Birth Weight

Sex-specific birth weight z scores were calculated relative to the 2006 World Health Organization (WHO) growth standards.<sup>40</sup> Only full-term births ( $\geq 37$  weeks) were included because there is increasing evidence that prematurity per se is associated with metabolic risk.<sup>41</sup>

### Growth Rate

The infant growth rate was defined in terms of the change in the weight z score, ie, standard deviation score, from birth to age 3 months and from ages 3 to 12 months because we expected accelerated growth to be evident by age 3 months.<sup>42</sup> For comparability with other studies, accelerated infant growth was defined as a change greater than 0.67 in the z score.<sup>43</sup> The weight z score was calculated relative to the 2006 WHO growth standards<sup>40</sup> because the postnatal weight of Hong Kong infants matches the new WHO standard closely.<sup>40,44</sup> We used the akima package in R version 2.3.1 statistical software (R Development Core Team, Vienna, Austria) to interpolate the WHO standards onto a daily scale so that all of the weight z scores were calculated at exact daily ages. The closest available weight measurements to age 3 months (within ages 2-4 months) and 12 months (within ages 9-15 months) were used.

## CHILDHOOD ANTHROPOMETRIC OUTCOMES

The main outcome was adiposity at about age 7 years proxied by age (using the exact age in days) and the sex-specific BMI z score relative to the 2000 Centers for Disease Control and Prevention growth charts<sup>45</sup> because the new WHO standards do not yet extend to age 7 years. For comparability with other studies, we also defined childhood overweight and childhood obesity as a BMI for age and sex corresponding to an adult BMI of 25 or 30 or more, respectively, using the International Obesity Taskforce cutoffs.<sup>30</sup> Thus, in this study, overweight children included those who were obese. The International Obesity Taskforce standards were interpolated to obtain cutoffs for overweight and obesity at each age in days using the akima package in R version 2.3.1 statistical software. Not all of the weight and height measurements were taken exactly at age 7 years; the closest measurement between ages 5.5 and 8.5 years was used.

## STATISTICAL ANALYSIS

Initial analysis revealed that the relations of birth weight and infant growth rates to childhood BMI z scores were fairly linear, which was maintained when using z-score tertiles to investigate the shape of the relation. We therefore used multivariable linear regression to assess the association of growth rate at ages 0 to 3 months, growth rate at ages 3 to 12 months, birth weight (as continuous variables or tertiles), and sex with the childhood BMI z score at about age 7 years, adjusted for potential confounders. Whether infant growth had different associations with adiposity at age 7 years by sex or birth weight (ie, effect modification) was assessed from the significance of interaction terms. We similarly used multivariable logistic regression models to assess the association of birth weight, accelerated infant growth, and sex with childhood overweight (including obesity).

Potential confounders considered were the z score for the infant's weight at age 3 months, birth order (first, second, third, or more), gestational age (as a continuous variable representing complete weeks based on the date of the last menstrual period), maternal smoking during pregnancy (yes or no), whether the infant was breastfed (either partially or exclusively) during the first

**Table 1. Baseline Characteristics by Growth Rate Tertile at Ages 0 to 3 and 3 to 12 Months for 6075 Members of the Hong Kong Children of 1997 Birth Cohort**

Characteristic	Participants, No.	Participants in Growth Rate Tertile, %					
		Ages 0-3 mo			Ages 3-12 mo		
		Slow, First (n=2026)	Medium, Second (n=2024)	Fast, Third (n=2025)	Slow, First (n=2026)	Medium, Second (n=2024)	Fast, Third (n=2025)
Sex							
Male	3203	33.3	33.3	33.3	33.3	33.3	33.3
Female	2872	33.4	33.3	33.3	33.4	33.3	33.3
Birth weight tertile							
First <sup>a</sup>	2139	15.3	31.4	53.3	27.6	32.8	39.6
Second <sup>b</sup>	1781	32.2	35.7	32.1	32.8	33.5	33.7
Third <sup>c</sup>	2155	52.2	33.3	14.5	39.5	33.7	26.8
Gestational age, wk							
37	481	17.9	27.2	54.9	24.7	33.1	42.2
38	1371	25.2	33.2	41.6	30.9	32.5	36.6
39	1836	33.4	35.1	31.4	34.5	32.9	32.6
≥ 40	2387	41.1	33.2	25.7	35.6	34.2	30.2
Birth order							
1	2841	32.4	34.5	33.1	29.1	33.2	37.7
2	2412	33.0	32.4	34.6	37.4	33.2	29.4
≥ 3	607	39.4	32.5	28.2	37.7	34.1	28.2
Breastfeeding for 4 wk							
No	3601	34.8	33.4	31.8	32.5	33.4	34.1
Yes	2238	30.8	33.4	35.7	34.8	33.0	32.2
Highest parental education attainment, grade							
≤ 9th	1716	36.5	32.6	30.9	37.8	32.5	29.7
10th-11th	2601	33.9	33.9	32.1	31.5	34.0	34.5
≥ 12th	1546	28.8	33.6	37.6	31.6	33.0	35.4
Maternal smoking during pregnancy							
No	5641	33.2	33.5	33.2	33.5	33.2	33.3
Yes	228	37.7	30.3	32.0	28.9	37.3	33.8

<sup>a</sup>The mean birth weight was 2.8 kg.

<sup>b</sup>The mean birth weight was 3.2 kg.

<sup>c</sup>The mean birth weight was 3.6 kg.

4 weeks of life (yes or no), highest parental education (≤ 9th grade, 10th-11th grade, or ≥ 12th grade), and growth rate in the other period (at ages 0-3 months or 3-12 months; as a continuous variable). However, after preliminary analysis, birth order, feeding type, parental education, and maternal smoking were not included because they did not change the estimates for the effect of growth (at ages 0-3 months or 3-12 months), birth weight, or sex on childhood BMI by more than 5.0%<sup>46</sup> in the sample as a whole or stratified by sex and birth weight. Information on childhood lifestyle is not available for this cohort, so potential confounders or mediators such as diet and physical activity could not be considered. Statistical analyses were performed using R version 2.3.1 statistical software.

## RESULTS

Among all of the 8327 cohort members, there were 7834 full-term and 441 preterm births and 52 with gestational age missing. The BMI at about age 7 years was available for 6496 full-term births (82.9% of all full-term members), among whom 6075 (77.5% of all full-term members) had weight recorded at ages 3 and 12 months. Those included in the analysis quite closely matched those full-term births with incomplete data (n = 1759), and bias should thus be small. For housing and sex, the Cohen

effect sizes<sup>47</sup> were negligible (< 0.10). Effect sizes for education (0.13) and parity (0.11) were slightly larger but still acceptable.

The average growth rates in tertiles were similar in girls and boys (the mean z scores in each tertile at ages 0-3 months were -0.65, 0.26, and 1.17 in boys and -0.63, 0.27, and 1.13 in girls; the mean z scores in each tertile at ages 3-12 months were -0.67, 0.01, and 0.71 in boys and -0.49, 0.10, and 0.71 in girls). For both sexes, faster growth in either infant period was more common in infants with lower birth weight and lower gestational age (**Table 1**). Having more-educated parents was associated with accelerated growth at ages 0 to 3 months but not at ages 3 to 12 months. The prevalence of overweight (including obesity) at age 7 years (mean [SD] age, 7.03 [0.36] years) was 15.3% and was more common in boys (17.5%) than in girls (12.9%). Overweight (including obesity) at about age 7 years was also more prevalent in the children with faster infant growth rates at ages 0 to 3 months (11.9%, 15.3%, and 18.7% in the first, second, and third growth rate tertiles, respectively) or at ages 3 to 12 months (14.8%, 14.4%, and 16.8% in the first, second, and third growth rate tertiles, respectively). Obesity was less common (3.8%) and again was more prevalent in children who had grown faster

**Table 2. Change in Body Mass Index z Score at Age 7 Years per Unit Increase in Weight z Score at Ages 0 to 3 and 3 to 12 Months**

Participants	Change in Childhood BMI z Score (95% CI) <sup>a</sup>	P Value for Interaction		
		Growth Rate and Sex <sup>b</sup>	Growth Rate and Weight z Score at Baseline <sup>b</sup>	Growth Rate, Weight z Score at Baseline, and Sex <sup>b</sup>
Ages 0-3 mo				
All	0.50 (0.46-0.53)	.07	.001	.007
Boys	0.52 (0.47-0.57)	NA	.02	NA
Girls	0.47 (0.41-0.52)	NA	.03	NA
Ages 3-12 mo				
All	0.33 (0.28-0.37)	.04	.24	.17
Boys	0.30 (0.24-0.36)	NA	.38	NA
Girls	0.38 (0.31-0.45)	NA	.39	NA

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by the height in meters squared); CI, confidence interval; NA, not applicable.

<sup>a</sup>Models were adjusted for infant's sex (omitted for sex-stratified models), gestational age (as a continuous variable), z score for weight at baseline (birth weight and weight at age 3 months for growth at ages 0 to 3 months and 3 to 12 months, respectively), and growth rate in the other period (as a continuous variable).

<sup>b</sup>Growth rate indicates the change in the weight z score during the relevant period, ie, ages 0 to 3 months or ages 3 to 12 months.

**Table 3. Changes in Body Mass Index z Score at Age 7 Years for Birth Weight Groups by Growth Rate Tertiles at Ages 0 to 3 Months<sup>a</sup>**

Growth Rate <sup>b</sup>	Birth Weight Groups					
	Low		Medium		High	
	Participants, No.	BMI z Score (95% CI)	Participants, No.	BMI z Score (95% CI)	Participants, No.	BMI z Score (95% CI)
Ages 0-3 mo						
All						
Slow, first tertile	327	1 [Reference]	574	0.33 (0.18 to 0.48)	1125	0.70 (0.57 to 0.84)
Medium, second tertile	671	0.29 (0.14 to 0.43)	636	0.70 (0.55 to 0.85)	717	1.02 (0.87 to 1.16)
Fast, third tertile	1141	0.71 (0.58 to 0.85)	571	1.10 (0.95 to 1.25)	313	1.37 (1.20 to 1.55)
Boys						
Slow, first tertile	182	1 [Reference]	291	0.48 (0.27 to 0.69)	595	0.76 (0.57 to 0.96)
Medium, second tertile	367	0.37 (0.16 to 0.57)	300	0.81 (0.60 to 1.02)	400	1.10 (0.90 to 1.31)
Fast, third tertile	574	0.88 (0.69 to 1.07)	291	1.25 (1.04 to 1.47)	203	1.47 (1.24 to 1.71)
Girls						
Slow, first tertile	145	1 [Reference]	283	0.16 (-0.04 to 0.37)	530	0.62 (0.43 to 0.82)
Medium, second tertile	304	0.19 (-0.01 to 0.40)	336	0.57 (0.36 to 0.77)	317	0.93 (0.72 to 1.13)
Fast, third tertile	567	0.52 (0.33 to 0.71)	280	0.92 (0.71 to 1.13)	110	1.25 (0.99 to 1.51)

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by the height in meters squared); CI, confidence interval.

<sup>a</sup>Adjusted for gestational age (as a continuous variable), growth rate at ages 3 to 12 months (as a continuous variable), and sex if appropriate.

<sup>b</sup>Growth rate was defined in terms of the change in the weight z score.

at ages 0 to 3 months (2.9%, 4.0%, and 6.0% in the first, second, and third growth rate tertiles, respectively).

Faster weight gain at ages 0 to 3 months or at ages 3 to 12 months was independently associated with a higher BMI z score at age 7 years, adjusted for infant's sex, gestational age, z score for weight at baseline, and growth rate in the other period (**Table 2**). Growth at ages 0 to 3 months had a larger effect. There was some evidence that the associations between the growth rate at ages 0 to 3 months and childhood BMI varied with birth weight ( $P = .001$ ) and with the combination of both sex and birth weight ( $P = .007$ ). However, this heterogeneity did not persist for growth at ages 3 to 12 months, where there was evidence of a different effect only by sex ( $P = .04$ ). To display these relations, **Table 3** shows the adjusted joint association of tertiles of birth weight and growth at ages 0 to 3 months with BMI at about age 7 years using the lowest birth weight and growth

rate tertile as the reference for boys and girls separately and together. In each birth weight category, a higher growth rate increased the BMI z score in childhood. Moreover, boys with lower birth weight who experienced fast growth at ages 0 to 3 months had at least the same increase in BMI than boys with higher birth weight with slow growth, although the pattern was less distinct in girls. Nevertheless, the children with the highest birth weight and fastest infant growth from birth to age 3 months had the highest BMI at age 7 years. However, this was a relatively small number of children because fast growth was common in the lower-birth-weight infants and slow growth was much more common in the high-birth-weight infants.

Finally, **Table 4** shows the odds ratios for overweight (including obesity) at age 7 years jointly by birth weight tertile, sex, and accelerated growth. Compared with girls without accelerated growth at ages 0 to 3 months, in each

**Table 4. Odds Ratios and Associated 95% Confidence Intervals of Being Overweight at Age 7 Years for Birth Weight Groups by Accelerated Growth at Ages 0 to 3 and 3 to 12 Months and Sex<sup>a</sup>**

Growth and Sex	Birth Weight Group					
	Low		Medium		High	
	Participants, No. (Overweight, %)	OR (95% CI)	Participants, No. (Overweight, %)	OR (95% CI)	Participants, No. (Overweight, %)	OR (95% CI)
Growth at ages 0-3 mo						
Girls without accelerated growth	491 (9.2)	1 [Reference]	655 (11.0)	1.24 (0.83-1.85)	863 (16.3)	2.00 (1.38-2.90)
Girls with accelerated growth	525 (9.9)	1.12 (0.73-1.72)	244 (15.6)	1.96 (1.22-3.15)	94 (23.4)	3.32 (1.85-5.95)
Boys without accelerated growth	572 (8.4)	0.92 (0.59-1.42)	606 (15.0)	1.79 (1.22-2.64)	1015 (18.1)	2.31 (1.61-3.30)
Boys with accelerated growth	551 (19.2)	2.50 (1.71-3.66)	276 (26.8)	3.98 (2.62-6.05)	183 (31.1)	4.97 (3.16-7.83)
Growth at ages 3-12 mo						
Girls without accelerated growth	802 (9.0)	1 [Reference]	775 (11.9)	1.67 (1.19-2.35)	866 (16.5)	3.11 (2.24-4.32)
Girls with accelerated growth	214 (11.7)	1.48 (0.90-2.43)	124 (14.5)	2.54 (1.43-4.53)	91 (22.0)	5.46 (3.03-9.82)
Boys without accelerated growth	922 (13.6)	1.63 (1.19-2.23)	760 (17.8)	2.66 (1.93-3.65)	1065 (19.4)	3.65 (2.68-4.97)
Boys with accelerated growth	201 (14.4)	1.93 (1.20-3.12)	122 (24.6)	4.71 (2.86-7.77)	133 (25.6)	5.95 (3.66-9.68)

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Odds ratios were adjusted for gestational age (as a continuous variable) and growth rate at another period (as a continuous variable). Accelerated infant growth was defined as a change greater than 0.67 in the z score.

birth weight category (odds ratios, 1.00, 1.24, and 2.00 for low, medium, and high birth weight, respectively), girls with accelerated growth had an increased risk of being overweight or obese at age 7 years (odds ratios, 1.12, 1.96, and 3.32 for low, medium, and high birth weight, respectively). The risks were greater for boys with accelerated growth at ages 0 to 3 months (odds ratios, 2.50, 3.98, and 4.97 for low, medium, and high birth weight, respectively). The same observation was made for the growth rate at ages 3 to 12 months. The highest risk of overweight or obesity was among boys with higher birth weight with accelerated growth.

#### COMMENT

Consistent with previous findings,<sup>2,7,21,43,48,49</sup> in this understudied population with scarce appropriate data, higher birth weight and faster infant weight growth were associated with higher BMI at age 7 years. In addition, we found that faster early weight growth (at ages 0-3 months) had a larger effect on childhood BMI and that early fast growth was more strongly associated with higher BMI in boys with lower birth weight but not girls with lower birth weight. Moreover, infants with lower birth weight were also more likely to grow fast than infants with higher birth weight. Nevertheless, the relatively small number of infants of either sex with higher birth weight who grew fast had the highest BMI at age 7 years and were most likely to be overweight or obese.

Seventy-eight percent of the eligible birth cohort members were included, and most of the exclusions (76.1%) were owing to missing BMI at age 7 years. However, the participants analyzed were no different from the excluded ones in terms of birth weight, growth rate in infancy, or socioeconomic status, suggesting that the availability of anthropometric data was not owing to any known attributes of the infants or their families. Although the mean (SD) birth weight (3.18 [0.44] kg) was lower than the WHO standards,<sup>44</sup> it was very similar to that obtained from comprehensive routine data for Hong Kong (3.20 [0.45] kg).<sup>50</sup> We

do not have parental BMI, which is a risk factor for childhood overweight.<sup>51</sup> However, there is no evidence that growth rate during infancy is related to paternal or maternal<sup>43</sup> BMI. Similarly, we do not have childhood lifestyle factors that are associated with overweight such as physical activity and diet, so we could not examine whether these lifestyle factors are also related to birth weight or infant growth and whether these childhood lifestyle factors mediate or confound the associations of higher birth weight and faster infant growth with higher childhood BMI. We proxied overweight and obesity at age 7 years by BMI because we do not have other, better measures such as body composition.<sup>52</sup> It is possible that greater muscle mass and heavier build may explain some of the higher BMIs in the babies with higher birth weight, although both lean mass and body fat in children are usually positively associated with birth weight.<sup>53</sup> However, greater muscle mass or heavier build is unlikely to explain the differences in BMI by postnatal growth rate. Our cohort was largely fed formula milk.<sup>54</sup> The small number of exclusively breastfed babies in this cohort makes it difficult to assess whether the effect of growth rate on childhood overweight and obesity is the same in exclusively breastfed babies. Finally, we do not have cognitive outcomes for this cohort. There is some evidence that lower birth weight and poor infant growth can adversely affect cognitive development,<sup>55-57</sup> possibly due to impaired neural development or a trade-off between growth and cognitive development.<sup>58</sup> Thus, we cannot rule out the possibility that low birth weight and slow growth could have other adverse consequences even in this setting.

Overall, our findings are similar to those of other studies examining the independent effect of higher birth weight and faster infant growth on childhood adiposity.<sup>7</sup> The 2 previous large studies<sup>2,21</sup> that examined the joint effect of birth weight and infant growth rate did not find any evidence of different effects by birth weight; however, these studies lacked statistical power because they used a dichotomous outcome (childhood overweight or obesity status) and a large number of groups of birth weight and

growth rate. Other previous studies<sup>43</sup> have postulated but not shown that the effect of faster growth on childhood BMI is greater in infants with lower birth weight. Another previous study<sup>17</sup> found that fast infant or childhood growth had a larger effect on childhood adiposity in boys, but the study was limited by a low follow-up rate and growth periods available; we were able to clarify that early infant growth has the largest effect on childhood adiposity.

Most investigation into the effects of faster postnatal growth on metabolic risk has been from the perspective of infant growth as an outcome of or in combination with detrimental restricted intrauterine growth, either within the thrifty phenotype paradigm<sup>59</sup> or more recently within a predictive adaptive response or mismatch paradigm.<sup>60</sup> However, most of the investigation and supporting evidence has been from animal models.<sup>60</sup> In contrast, our study provides some evidence that in infant boys, accelerated early infant growth has a greater effect on adiposity in boys with lower birth weight than in boys with higher birth weight. Our results provide little evidence of a similar effect in girls and as such suggest that some sex specificity might be needed in these models. Further follow-up of this Chinese birth cohort for later cardiovascular risk factors such as blood pressure is planned. We believe this resource will provide more insight into how postnatal growth influences metabolic risk.

There has been little investigation of the physiological pathways by which higher birth weight, within the normal range, should be associated with childhood adiposity.<sup>61</sup> There are physiological pathways by which increased insulin sensitivity in adipose tissue in early postnatal life<sup>62,63</sup> in animals with fetal growth restriction might play a role in the association between rapid infant growth and later adiposity; however, these pathways would mainly apply to children born small. A detrimental effect of faster infant growth regardless of birth weight requires a different explanation. Development of the hypothalamic circuit regulating food intake and hence adiposity in later life<sup>64</sup> may continue to infancy with a narrow developmental window in the first 2 weeks of postnatal life<sup>65</sup> with susceptibility to disruption by overfeeding.<sup>66</sup> To what extent this is affected by the leptin surge during early postnatal life<sup>67,68</sup> and to what extent leptin or any other determinants of these hypothalamic circuits are environmentally driven are not yet clear. However, disruption of hypothalamic circuit development and leptin levels by early overfeeding could result in poorer appetite control in later life. Leptin levels may also be suppressed by androgens,<sup>69</sup> which would be consistent with relatively greater effects of early growth on childhood BMI in boys because the 0- to 3-month age period coincides with the stage of "minipuberty" involving high levels of sex hormones in boys.<sup>70,71</sup> However, although sex-specific effects were part of our initial hypothesis rather than a post hoc test, we cannot rule out the possibility that these differences are chance findings.

## CONCLUSIONS

Although much attention has focused on the detrimental metabolic consequences of low birth weight, in a large representative Chinese birth cohort, higher birth weight and faster growth particularly in the first 3 months of life

were both associated with higher BMI in early childhood at about age 7 years. Faster growth in the early postnatal period also had a larger effect on BMI at age 7 years in boys with lower birth weight. Nevertheless, the small number of high-birth-weight babies with fast infant growth had the highest BMI at age 7 years. Lower-birth-weight boys were more sensitive to the potentially detrimental effects of accelerated growth in early postnatal life, possibly due to levels of sex hormones differing between the sexes at this age. Although early accelerated infant growth may account for some of the prevalence of childhood overweight (including obesity), overweight is but 1 developmental outcome. Whether lower birth weight or slow infant growth are risk factors for other developmental outcomes such as cognitive skills needs to be assessed.

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