

Growth Patterns of Large for Gestational Age Children up to Age 4 Years

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KEY WORDS

growth, preterm, large for gestational age, appropriate for gestational age

ABBREVIATIONS

AGA—appropriate for gestational age

FT—full-term

GA—gestational age

HC—head circumference

LGA—large for gestational age

LOLLIPOP—Longitudinal Preterm Outcome Project

PT—preterm

SGA—small for gestational age

Dr Bocca-Tjeertes had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and was responsible for acquisition, analysis, and interpretation of data, statistical analysis, drafting and critical revision of the manuscript for important intellectual content, administrative, technical, and material support, and obtaining funding; Drs Reijneveld and Bos had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis, and were responsible for statistical analysis, critical revision of the manuscript for important intellectual content, study supervision, and obtaining funding; Dr Kerstjens was responsible for acquisition of data, critical revision of the manuscript for important intellectual content, administrative, technical, and material support, and obtaining funding; Ms Veldman was responsible for analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and administrative, technical, and material support; and Dr de Winter was responsible for analysis and interpretation of data, statistical analysis, and critical revision of the manuscript for important intellectual content.

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WHAT'S KNOWN ON THIS SUBJECT: Preterm (PT) birth is negatively associated with growth. Particularly small for gestational age PT infants are at risk for delays in growth, whereas knowledge about the consequences regarding growth of large for gestational age PT birth is lacking.



WHAT THIS STUDY ADDS: During infancy, growth in height, weight, and head circumference of large for gestational age PT infants was well balanced and sufficient. Subsequently, however, weight gain accelerated and resulted in high BMIs compared with the World Health Organization Multicentre Growth Reference Study population.

abstract

OBJECTIVE: To determine how growth of large for gestational age (LGA) preterm (PT) children was affected by their PT birth and their LGA status.

METHODS: This is a community-based cohort study of 1302 PT and 489 full-term (FT) children, born 2002 and 2003.

RESULTS: We found that growth in height, weight, and head circumference of LGA PT children was well balanced during infancy and that only weight gain accelerated during subsequent years. This led to high BMIs comparable to those of LGA FT children. Being born both LGA and PT resulted in a median growth at the age of 4 years that was 0.1 SD lower for weight ($P = .44$), 0.1 SD lower for height ($P = .48$), and 0.5 SD lower for head circumference compared with LGA FT counterparts ($P = .016$), whereas BMI at age 4 years was equal. Compared with appropriate for gestational age (AGA) PT children, these measures for LGA PT children were 0.9 SD, 0.6 SD, and 0.4 SD (all $P < .001$) higher, respectively. That led to the BMI of LGA PT children at age 4 years being significantly higher (0.9 points, ie, 0.7 SD) than that of AGA PT and also higher (0.6 points, ie, 0.4 SD) than that of AGA FT children.

CONCLUSIONS: The growth patterns of LGA PT-born children are distinctly different from other PT or FT children. In particular, we found substantially greater weight gains and relatively higher BMIs among them, which added to their already increased metabolic risks based on their gestational age. *Pediatrics* 2014;133:e643–e649

Preterm (PT) birth is a predictor of poor growth and long-term growth restriction in both early and moderately PT-born children.^{1–3} On the 1 hand, small for gestational age (SGA) birth (birth weight <10th percentile) as a proxy for intrauterine growth restriction is strongly associated with poor growth.^{4,5} On the other hand, large for gestational age (LGA) birth (birth weight >90th percentile) as a proxy for intrauterine overgrowth is also considered to predict a negative pregnancy outcome⁶ even though knowledge about the consequences of LGA PT birth is lacking.

LGA birth is associated with various risks. First, it leads to complications such as prolonged labor and shoulder dystocia, both of which may lead to asphyxia.⁷ Second, LGA birth frequently occurs in combination with maternal diabetes. Maternal diabetes can result in severe morbidities in the newborn, such as congenital heart disease.⁸ Third, hypoglycemia and iron deficiency are seen more often in LGA newborns and may lead to a higher prevalence of specific cognitive impairments.^{9,10} These findings are based on a limited number of studies on LGA full-term (FT) children. Even less is known about long-term growth in LGA children, particularly in that of PT infants. LGA birth seems to carry the risk for obesity. To date, however, all studies on growth were restricted to FT children.^{11,12}

Considering the likelihood of the risk for various suboptimal outcomes in LGA PTs and the lack of knowledge on the subject, our main aim was to determine how growth was affected by PT birth and LGA status. To achieve this aim we compared absolute gains (number of kg/cm attained per 1-year period and in total) of LGA PT children (LGA PTs) with 3 groups: appropriate for gestational age (AGA) PT children (AGA PTs), LGA FT children (LGA FTs), and AGA FT controls (AGA FTs). Next, we compared them

regarding age-standardized (relative) weight, height, head circumference (HC), and BMI per age-year. We hypothesized that LGA PTs grew more slowly than their counterparts.

METHODS

Study Design, Sampling Procedure, and Power Considerations

This study was part of the so-called LOLLIPOP study (Longitudinal Preterm Outcome Project), a large, community-based cohort study on growth and neurocognitive development in PT children. The LOLLIPOP sample consists of early and moderately PT children born before 36 weeks' gestation and randomly selected FT control subjects who were not matched for any variable. All children were born between January 1, 2002 and December 31, 2003. For every 2 PTs we selected 1 FT control. The children were included during visits to well-child clinics at the age of 4 years.

The cohort size was based on estimates of numbers needed to compile growth curves for PT children in the Netherlands as previously described^{3,13} and led to a planned inclusion of 500 early and 1000 moderately PT-born children. This enabled us to detect a difference in growth restraint between PT- and FT-born children per week gestational age (GA) for boys and girls separately, with power 80% at $P = .05$. For the current study, longitudinal growth data were available for 1301 (77%) PT- (GA 25–36 weeks) and for 489 (77%) FT-born (GA 38–42 weeks) children.

LOLLIPOP was approved by the local institutional review board and written informed consent was obtained from all parents.

Measures and Procedures

GA was expressed as completed weeks of gestation. Children whose GA could not be defined beyond reasonable doubt were excluded.

Data on growth during the children's first 4 years were obtained retrospectively from records kept at the well-child clinics and augmented by data retrieved from hospital records. During their first 4 years, children in the Netherlands routinely have ~15 check-ups at a well-child clinic. The check-ups include the assessment of height, weight, and HC (until the large fontanel is closed). Height and weight are measured with standardized measuring devices. Up to the age of 15 months the children are examined in supine position. From 15 months onward, the children stand upright and wear only socks. Weight is measured undressed. We analyzed more than 38 500 standardized measurements.

Statistical Analysis

We prepared our data by converting birth weights, heights, and HCs to z scores (mean = 0; SD = 1) according to GA, thereby using the FT AGAs derived from our own cohort as the reference group. Next, LGA was defined as a birth weight of more than 1.6 SD above the median (ie, 90th percentile, P90). Children who had a birth weight of more than 1.6 SD below the median (ie, 10th percentile, P10, SGA children) were excluded from the analyses.

To describe longitudinal growth during the first 4 years of life, we assessed the weight, height, and HC of each of the children at birth and their weight and height at calendar ages 1 year (± 30 days), 2 years (± 61 days), 3 years (± 61 days), and 3 years and 10 months (± 91 days). HC was measured up to the age of 1 year (± 30 days), shortly before closure of the large fontanel. Finally, the BMI of each child was calculated with the formula: $BMI = \text{weight}/(\text{height}^2)$. The BMI of the children was also compared with the (WHO) Health Organization Multicentre Growth Reference Study standards to clarify clinical significance.

Longitudinal Absolute Gains and Age-Standardized (Relative) Growth

To compare PT LGA with PT AGA and FT LGA children, we first calculated the absolute gains per group from birth to 4 years. Absolute gains were defined as the number of kilograms or centimeters gained per 1-year period for weight, height, and HC. Relative weight, height, and HC were defined as the z score that the child had reached at a certain age compared with the FT AGAs. In this case, we also expressed age-standardized growth as BMI to determine whether the weight of LGA-born children was proportional to their height. We performed all analyses with and without adjusting for PT birth (ie, the number of weeks born too early). Next, we determined statistical significances, by using *F* tests in analysis of variance.

Influence of PT Birth and LGA Status on Growth

We examined the effects of PT birth and LGA status and the interaction between these factors. Absolute gains and relative weight, height, and HC were analyzed by using *F* tests in analysis of variance. All measures at all ages were analyzed separately using LGA and PT as predictors, together with the interaction between these 2 variables.

All analyses were done with SPSS 19 for Windows (IBM SPSS Statistics, IBM Corporation).

RESULTS

Background Characteristics

The group of PT children consisted of 1302 children, 112 of whom were LGA at birth (Table 1). There were many multiples among them: 373 twins (28.5%) and 20 triplets and quadruplets (1.6%). Within the PT group, LGA children were more likely to be singleton ($P < .001$) and male ($P = .033$). Results are shown for all children combined, as differences by gender became statistically

TABLE 1 Characteristics of the Total Sample: Numbers and Proportions (%) of LGA and AGA as well as PT and FT Children at Birth

	LGA	AGA	PT	FT	P Values ^a	
	N = 193	N = 1597	N = 1301	N = 498	LGA Versus AGA	PT Versus FT
Gender						
Male	110 (57%)	842 (52.7%)	712 (54.7%)	240 (49.1%)	.24	.033
Female	83 (43%)	755 (47.3%)	589 (45.3%)	249 (50.9%)		
Multiple birth						
Singleton	185 (95.5%)	1207 (75.6%)	908 (69.8%)	484 (99.0%)		
Twin	8 (4.1%)	370 (23.2%)	373 (28.7%)	5 (1.0%)	<.001	<.001
Triplet/quadruplet	0 (0%)	20 (1.3%)	20 (1.5%)	0 (0%)		
Maternal height						
< -1 SD	24 (20.9%)	235 (27.1%)	230 (26.7%)	29 (24.2%)		
-1 SD to 1 SD	61 (53.0%)	486 (56.1%)	480 (55.7%)	67 (55.8%)	.10	.75
>1 SD	30 (26.1%)	145 (16.7%)	151 (17.5%)	24 (20.0%)		
Socioeconomic status						
Maternal education level						
Normal/high	140 (73.3%)	1151 (72.3%)	927 (71.6%)	364 (74.6%)		
Low	51 (26.7%)	441 (27.7%)	368 (28.4%)	124 (25.4%)	.77	.21
Family income						
Normal/high	185 (95.9%)	1524 (95.4%)	1238 (95.2%)	471 (96.3%)		
Low	8 (4.1%)	73 (4.6%)	63 (4.8%)	18 (3.7%)	.79	.29

^a Differences were tested by using independent sample *t* tests.

non-significant once weight, height, and HC had been corrected for gender by using gender-specific z scores.

Influence of PT Birth and LGA Status on Growth

During infancy, absolute growth in weight and height was affected most by

PT birth (Table 2). Subsequently, absolute weight gain was primarily influenced by LGA status with variable statistical significance. From 1 to 4 years, LGA PTs gained significantly more weight than their counterparts, be they AGA PTs or LGA FTs (Fig 1A). During the same time frame, by

TABLE 2 Absolute Gains in Weight (kg), Height (cm), and HC (cm), Means (SD) for PT and FT LGA and AGA Children During Ages 0 to 4 Years

	PT		FT		P Values ^a	
	LGA (N = 112)	AGA (N = 1189)	LGA (N = 81)	AGA (N = 408)	PT Versus FT	LGA Versus AGA
Weight						
0 to <1 y	7.4 (1.1)	7.2 (1.0)	6.3 (1.0)	6.4 (1.1)	<.001	.52
1 to <2 y	3.2 (0.8)	3.0 (0.8)	3.0 (0.8)	3.0 (0.8)	.95	.06
2 to <3 y	2.5 (0.8)	2.3 (0.8)	2.5 (0.7)	2.2 (0.7)	.98	.002
3 to <4 y	2.0 (0.7)	1.9 (0.9)	2.1 (0.7)	1.9 (0.9)	.73	.07
Total 0 to <4 y	15.2 (2.1)	14.4 (2.2)	13.8 (1.8)	13.4 (1.9)	<.001	<.001
Height						
0 to <1 y	28.2 (3.2)	30.9 (4.1)	24.6 (2.6)	24.9 (2.8)	<.001*	<.001*
1 to <2 y	13.5 (2.2)	13.4 (2.1)	12.5 (2.2)	12.8 (2.4)	.004	.92
2 to <3 y	9.8 (2.2)	9.6 (2.1)	10.1 (2.0)	9.3 (1.8)	.47	.14
3 to <4 y	6.3 (1.7)	6.5 (1.8)	6.2 (1.6)	6.1 (2.0)	.006	.51
Total 0 to <4 y	57.8 (4.7)	60.2 (5.2)	53.2 (3.8)	53.3 (4.0)	<.001*	<.001*
HC						
0 to <1 y	13.7 (1.7)	14.7 (1.7)	10.5 (1.2)	11.9 (0.9)	<.001	<.001

^a Mutually adjusted.

* Factors PT and LGA significantly interact: $P < .01$

contrast, increases in height in LGA PTs were equal to those of AGA PTs. Both PT groups had greater height gains than FTs, so height gain remained to be more affected by prematurity.

Being born both LGA and PT also affected the increase in HC. Increase in HC was accelerated in PT children and exceeded that of FT children by 2.8 to 3.2 cm during the first year after birth.

Regarding absolute growth, the 2 predictors prematurity and LGA status both influenced gains positively, but they did not modify each other's effects, except for absolute height gain during infancy ($P < .01$).

Relative weight, height, and HC were also affected positively by LGA status and PT birth (Table 3) at all the ages and for all the measures. Correcting for prematurity led to lower estimates of growth failure, differences still reaching statistical significance ($P < .001$ for all measures during the first 2 years of life). Nevertheless, LGA status and PT birth did not modify each other's effect on growth, except for relative height during infancy ($P < .01$). Being born both LGA and PT resulted in a median growth at the age of 4 that was 0.1 SD lower for weight, 0.1 SD lower for height, and 0.5 SD lower for HC compared with LGA FTs, whereas the BMI at age 4 years was equal (Table 4). Compared with AGA PTs, it was 0.9 SD, 0.6 SD, and 0.4 SD higher for the 3 measures, respectively. Even though they were born PT, LGA PTs managed to grow to within the normal range for AGA FTs before the age of 1 year. In particular, their BMI at age 4 years was significantly higher (0.5–0.9 points, ie, ~0.5–1.0 SD) than that of both AGA FTs and AGA PTs (Fig 1B).

Prematurity and LGA status did not modify each other's effects regarding BMI.

DISCUSSION

This study demonstrated that up to the age of 4 years the absolute growth of LGA

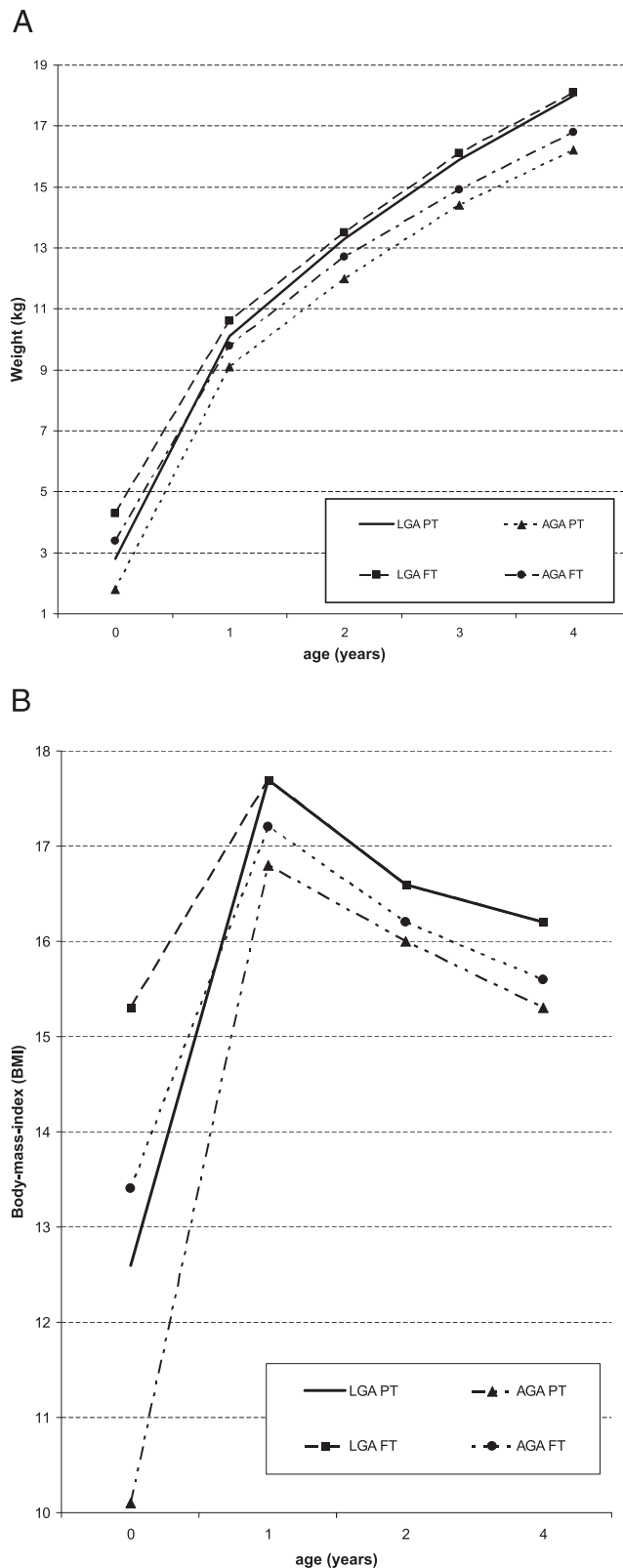


FIGURE 1

A, Weight in kg during ages 0 to 4 years in LGA and AGA PT- and FT-born children. B, BMI during ages 0 to 4 years in LGA and AGA PT- and FT-born children.

TABLE 3 Relative Weight, Height, and HC in Z Scores and Total BMI: Means (SD) in LGA and AGA PT and FT Children During Ages 0 to 4 Years, By Age

	PT LGA		PT AGA		FT LGA	FT AGA	P Values ^a	
	Uncorrected	Corrected	Uncorrected	Corrected			PT Versus FT	LGA Versus AGA
Z weight at age								
0 y	-1.6 (1.1)	1.4 (1.1)	-3.5 (1.1)	-0.5 (1.2)	1.5 (0.7)	-0.3 (0.8)	<.001	<.001
1 y	0.1 (0.9)	0.8 (1.0)	-0.8 (1.1)	-0.3 (1.1)	0.6 (0.9)	-0.1 (1.0)	<.001	<.001
2 y	0.3 (0.9)	0.8 (1.0)	-0.6 (1.1)	-0.2 (1.1)	0.4 (0.8)	-0.1 (1.0)	<.001*	<.001*
4 y	0.4 (1.0)	0.4 (1.0)	-0.5 (1.1)	-0.5 (1.1)	0.5 (1.9)	-0.1 (1.0)	<.001	<.001
Z height at age								
0 y	-1.5 (1.1)	1.5 (1.4)	-3.6 (2.0)	-0.4 (1.8)	0.9 (0.8)	-0.2 (0.9)	<.001*	<.001*
1 y	0.0 (0.9)	0.7 (0.9)	-0.9 (1.1)	-0.2 (1.1)	0.6 (1.0)	-0.1 (1.0)	<.001	<.001
2 y	0.2 (0.8)	0.9 (1.0)	-0.6 (1.0)	0.0 (1.1)	0.6 (0.9)	-0.1 (1.0)	<.001	<.001
4 y	0.3 (1.0)	0.3 (1.0)	-0.3 (1.1)	-0.3 (1.1)	0.4 (1.0)	-0.1 (1.0)	<.001	<.001
Z HC at age								
0 y	-1.8 (1.4)	1.8 (0.9)	-3.4 (1.7)	0.7 (1.0)	1.2 (0.5)	-0.4 (0.9)	<.001	<.001
1 y	0.1 (1.1)	0.5 (0.8)	-0.3 (1.1)	0.1 (0.8)	0.6 (1.4)	-0.1 (0.9)	<.001	<.001

Calendar ages, uncorrected for PT birth and corrected for PT birth, respectively.

^a Mutually adjusted.

* Factors PT and LGA significantly interact: $P < .01$.

TABLE 4 BMI Means (SD) and Z Scores of BMI (SD) of LGA and AGA PT and FT Children During Ages 0 to 4 Years, By Age (Calendar Ages)

	PT LGA	PT AGA	FT LGA	FT AGA	P Values ^a	
					PT Versus FT	LGA Versus AGA
BMI at age						
0 y	12.6 (1.6)	10.2 (1.8)	15.2 (1.2)	13.4 (1.3)	<.001	<.001
1 y	17.7 (1.4)	16.8 (1.5)	17.7 (1.6)	17.2 (1.4)	<.001	<.001
2 y	16.6 (1.3)	16.0 (1.4)	16.6 (1.0)	16.5 (1.3)	<.001	<.001
4 y	16.2 (1.3)	15.3 (1.4)	16.2 (1.1)	15.6 (1.2)	<.001	<.001
Z BMI at age						
0 y	-0.6 (1.2)	-2.4 (1.4)	1.5 (0.9)	0.0 (1.0)	<.001	<.001
1 y	0.4 (1.0)	-0.2 (1.1)	0.4 (1.2)	0.0 (1.0)	.002	<.001
2 y	0.1 (0.9)	-0.3 (1.0)	0.1 (0.8)	0.0 (1.0)	<.001	<.001
4 y	0.4 (1.0)	-0.3 (1.1)	0.4 (0.9)	0.0 (1.0)	<.001	<.001
Z BMI compared with the WHO Multicentre Growth Reference Study standards at age						
0 y	-0.7 (1.3)	-2.6 (1.5)	1.6 (1.0)	0.0 (1.1)	<.001	<.001
1 y	0.9 (1.0)	0.2 (1.2)	0.9 (1.2)	0.4 (1.1)	.002	<.001
2 y	0.7 (1.0)	0.2 (1.1)	0.7 (0.9)	0.6 (1.1)	<.001	<.001
4 y	0.7 (1.0)	0.0 (1.1)	0.7 (0.9)	0.3 (1.0)	<.001	<.001

Z scores were corrected for gender.

^a Mutually adjusted.

PTs was characterized by increases in weight, height, and HC exceeding that of FT children. Adjusted for PT birth (ie, by the number of weeks born too early) their age-standardized (relative) growth during the first years of life was slower than that of AGA children, be they PT or FT. From this perspective, the growth of LGA PTs was equal to the growth of LGA FTs. In particular, we found substantially greater weight gains and higher BMIs in LGA PTs than in AGA PTs and AGA FTs. These findings seem to imply that regarding weight, LGA-born children grew too fast for their GA, which had already exposed

them to an elevated risk for metabolic consequences such as metabolic syndrome.^{14,15} From birth onward, LGA PTs were unsuccessful in maintaining their well-balanced body proportions as their weight gain exceeded their height gain. Consequently, by the age of 4 years they were comparable to LGA FTs.

No significant interaction was found for the predictors LGA status and PT birth, except for absolute height gain during infancy and total height gains. PT birth is reported as a factor that accelerates growth, but this acceleration seems to be restricted to HC particularly.¹⁶ When

having reached adulthood, PT-born infants are on average shorter and lighter than their term-born counterparts.⁵ Previously, LGA-born children were described by Hediger and Eyzaguirre^{6,12} as misbalanced in weight and height in the long-term. Our study confirmed these findings in a much larger sample with a wider range of GAs. Even though we found rapid growth in weight in LGA PTs, their weight gain was independent of their being born PT. It was not an additive effect of LGA status and PT birth.

Weight gain and HC growth were previously described as beneficial to neurocognitive outcome in studies that concerned AGA and SGA PT children.^{4,17,18} This may imply that LGA PTs are relatively less at risk for developmental delays up to the age of 4 years, but this hypothesis requires additional study.

In this study, we used a reference sample from our own cohort. We did not use other references, such as the WHO Multicentre Growth Reference Study standards, except for BMI comparisons. These WHO standards are applicable to many populations, but less so to the Dutch population, being 1 of the tallest in the world. A disadvantage of using the WHO references would be that one could underestimate the sequels of prematurity regarding growth, because

the Dutch PT child would be (close to) normal if median growth is set at the lower median of the WHO references. Moreover, the WHO standards are unlikely the most suitable for PT populations, as they were drawn from a totally different population sample. The reference sample from our own cohort (found to be non-significantly different from the Dutch growth surveys) comprises children born in exactly the same time frame (2002–2003) and similar parts of the Netherlands. They also shared the same neonatal care and feeding strategies of the time.

The major strengths of this study were the large samples of early and moderately PT- and FT-born children as well as its community-based design. We also analyzed growth longitudinally, which is rarely done but gives more insight in distinctive growth patterns as well as catch-up growth.

Our study also had some limitations. First, our cohort consisted of many multiples. Multiple births are associated with fewer LGA births. We included them because many twins are born moderately PT, which is mostly physiologic rather than pathologic and, in the

long-term, multiple births are not associated with poor growth.^{19,20} Second, we were unable to differentiate well-regulated diabetic mothers from unregulated ones and we could not enter diabetes as a predictor in our models. Nevertheless, we knew that many of the mothers of LGA children were not diabetic. In our cohort, therefore, LGA birth and its sequels could not be explained by maternal diabetes alone.

Our study has several implications. First, the growth pattern of LGA PT children differs distinctly from that of AGA PT and FT children. Greater weight gains and relatively high BMIs imply that metabolic consequences such as metabolic syndrome are of specific concern.^{14,15,21} In this study we assessed growth up to the age of 4 years, which is exactly the age span during which children are most likely to develop overweight and obesity that persists into adolescence.²² It may be helpful to specifically use weight-for-height charts to distinguish between catch-up growth, which is expected to take place at least during infancy in PT-born children,^{5,23} and excessive growth during which weight-for-height will

increase and exceed the 50th percentile of the reference population. Growth in LGA children, be they PT or FT, should therefore be monitored closely. Future replication of this study with a larger sample is called for, as growth can be studied more extensively to elucidate the separate and joint effects of LGA and PT birth year by year during early childhood.

CONCLUSIONS

The growth pattern of LGA PT-born children differs distinctly from AGA PT and FT children. In particular, we found substantially greater weight gains and relatively higher BMIs among them, which added to their already increased metabolic risks based on their GA.

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