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Growth in Small-for-Gestational-Age Preterm-Born Children from 0 to 4 Years: The Role of both Prematurity and SGA Status

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Key Words
Growth · Early preterm · Moderately preterm · Late preterm · Small for gestational age · Appropriate for gestational age · Growth restriction

Abstract
Background: Fullterm small-for-gestational-age children (SGAs) are known for their ability to catch up on growth. Nevertheless, increased risk of growth restriction remains. Evidence on preterm SGA children's growth is lacking. ***Objective:*** To determine absolute gains in height and weight, relative growth, and growth restriction in preterm SGAs from 0 to 4 years and how prematurity and SGA status affect these measures. ***Design/Methods:*** Community-based cohort study, n = 1,648 preterm-born (gestational age <36 weeks, 57 SGA) and 605 term-born (12 SGA). We defined SGA as a birth weight less than –2 SD (P 2.3) compared to counterparts matched for gestational age. Height, weight, and head circumference were obtained from medical records and translated to *z*-scores. We defined growth restriction as height or weight less than –2 SD compared to fullterm appropriate-for-gestational-age children (AGAs). ***Results:*** Absolute height and weight gains were similar, but the relative growth of preterms and fullterms differed. Preterm AGAs and fullterm SGAs, although not reaching it, caught up towards the fullterm AGA median (*z*-scores at 4 years: –0.3 to –1.0). By contrast, preterm SGA children's *z*-scores were still –1.4 to –1.7. Head circumference growth was less affected by prematurity and SGA birth (*z*-scores at 1 year: 0.1 to –0.7). Catch-up growth mainly took place during infancy. 30–39% of all preterm SGAs showed growth restriction at 4 years. ***Conclusions:*** Growth in preterm SGAs is affected considerably by the joint effects of preterm birth and SGA status, resulting in a high proportion of growth restriction.

Introduction

Growth in fullterm small-for-gestational-age children (FT-SGAs), who account for 2.3% of all term-born children, is of particular concern. FT-SGAs are known for their ability to catch up on growth, but a significant proportion (9–11%) persists in growth restriction (growth below the second percentile, P 2.3) [1, 2]. Growth restriction in early childhood is prevalent in early (10–20%) as well as moderately (5%) preterm-born infants [3, 4]. Evidence points to the persistence of intrauterine growth restriction, but growth restriction may also start after birth due to feeding problems, infections, and other neonatal complications [5, 6].

SGA birth is seen in 2–8% of all preterm children (PT-SGAs) [3, 7], but longitudinal information about their growth and how it relates to that of preterm-born appropriate-for-gestational-age children (PT-AGAs) is scarce.

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As yet, evidence backing high-impact interventions such as growth hormone therapy in PT-SGAs is lacking [8]. Such therapies can only be offered confidently if they are supported by sufficient sound evidence gathered as evolves knowledge of growth in preterm SGAs and AGAs.

We aimed to compare growth in height, weight, and head circumference (HC) of PT-SGAs to both PT-AGAs and FT-SGAs longitudinally up to the age of 4. We were interested in both the absolute gains in height and weight, and relative growth, expressed as *z*-scores. Our second aim was to assess the influences of preterm and SGA birth on growth and growth restriction longitudinally. We expected growth of PT-SGAs to be affected more than that of PT-AGAs because of the continued effects of prematurity and SGA birth, thus resulting in a higher percentage of PT-SGAs with persisting growth restriction.

Methods

Study Design, Sampling Procedure, and Power Considerations

This study was part of the Lollipop study (Longitudinal Preterm Outcome Project), a large, community-based cohort study on growth and neurocognitive development in preterm children. The Lollipop sample consists of early and moderately preterm children born before 36 weeks' gestation and randomly selected fullterm controls, all born between 01.01.2002 and 31.12.2003. The children were enrolled during well-child visits at Preventive Child Health Care centres at age 4.

Cohort size was based on estimates of numbers needed to compile growth curves for preterm children in the Netherlands. For the present study, longitudinal growth data were available for 1,648 preterm and 617 fullterm children. We excluded children with major congenital malformations and syndromes. Children with neurological abnormalities were allowed but were very few.

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

Measures and Procedure

Data on growth from 0 to 4 years were retrospectively obtained from records in Preventive Child Health Care centres and augmented by data retrieved from hospital records. During their first 4 years, children in the Netherlands routinely have about 15 well-child check-ups. These include the assessment of height, weight, and HC (the latter until the large fontanel is closed). We measured height and weight with standardized measuring devices, i.e. an infantometer or stadiometer. Up to the age of 15 months, we examined the children in supine position. From 15 months onwards, the children stood upright and wore socks. Weight was measured undressed. We analyzed over 38,500 standardized measurements with an average of 9.9 measurements per child.

Gestational age was expressed as completed weeks of gestation. For more detailed information on sampling and procedures, we refer to our previous publications [4, 9, 10].

Statistical Analysis

We prepared our data by converting birth weights to *z*-scores (mean = 0, SD = 1) according to gestational age using the Dutch Kloosterman curve [11]. SGA was defined as a birth weight >2 SD below the median (P 2.3). Height and HC at birth were converted to *z*-scores according to the Usher and McLean curves [12].

Longitudinal Absolute Gains and Relative Growth

To compare PT-SGA with PT-AGA and FT-SGA children, we calculated absolute gains during ages 0–4 years. These were defined as the number of kilograms or centimetres gained per 1-year period. Relative growth was defined as the *z*-score that the child had reached at a certain age compared with the FT-AGAs from our own cohort. Boys and girls were analyzed separately in this part of the analyses. All analyses were done using both calendar ages and ages corrected for prematurity. We determined statistical significance using F tests in ANOVA.

Proportion of Children with Growth Restriction

We assessed the proportion of growth-restricted children in height, weight or HC. Growth restriction after birth was defined as >2 SD below the median growth of the FT-AGAs from our cohort. We tested statistical significance using χ^2 tests.

Influence of Preterm Birth and SGA Status on Growth

Finally, we assessed the effect of prematurity and SGA status as well as their interaction on absolute growth, relative growth and growth restriction. The first two analyses were performed using linear regression, the third using logistic regression. In all models, SGA, preterm, and SGA · preterm were included as predictors. All analyses were done with SPSS 19 for Windows [www.spss.com].

Results

Background Characteristics

The group of preterm children consisted of 1,648 children of whom 57 were SGA at birth (table 1). Table 1 represents combined data of preterm and fullterm children by birth weight group. Mean gestational age was 32 weeks (SD = 2.5 weeks, range 26–36 weeks). This group contained many multiples, 482 twins (30.3%) and 29 triplets and quadruplets (1.8%). Of the singletons, 4.4% were SGA, of the multiples this was 1.4% ($p < 0.01$). Boys were more often SGA than girls. Furthermore, very preterm-born infants (GA 28–31 weeks) were more often SGA than both extremely preterm (GA 26–27 weeks) and moderately preterm-born infants (GA 32–35 weeks).

Growth of Preterm SGA Children

During infancy, i.e. the first year after birth, absolute *weight* gain of PT-SGAs was 800 g less than that of PT-AGAs (table 2). During the subsequent years, however, their mean absolute increase in weight was 200–500 g per year less ($p < 0.01$). During infancy, height gain of PT-

Table 1. Characteristics of the total sample and proportions (% of the group) for AGA and SGA children at birth

	AGA	SGA	Total
Number (%)	2,196 (97.0)	69 (3.0)	2,265 (100)
Gestational age, weeks			
26–28	158 (94.0)	10 (6.0)	168 (100)
29–31	400 (95.2)	20 (4.8)	420 (100)
32–33	327 (96.2)	13 (3.8)	340 (100)
34–35	706 (98.1)	14 (1.9)	720 (100)
38–41	605 (98.1)	12 (1.9)	617 (100)
Gender			
Early preterms			
Female	275 (96.8)	9 (3.2)	284 (100)
Male	283 (93.1)	21 (6.9)	304 (100)
Moderate preterms			
Female	453 (99.1)	6 (0.9)	459 (100)
Male	580 (96.5)	21 (3.5)	601 (100)
Fullterms			
Female	309 (98.4)	5 (1.6)	314 (100)
Male	296 (97.7)	7 (2.3)	303(100)
Multiples/singletons			
Early preterms			
Singletons	351 (92.4)	29 (7.6)	380 (100)
Twins	194 (99.5)	1 (0.5)	195 (100)
Triplets/quadruplets	13 (100)	0 (0)	13 (100)
Moderate preterms			
Singletons	729 (97.2)	21 (2.8)	750 (100)
Twins	288 (98.0)	6 (2.0)	294 (100)
Triplets/quadruplets	16 (100)	0 (0)	16 (100)
Fullterms			
Singletons	601 (98.2)	11 (1.8)	612 (100)
Twins	4 (80.0)	1 (20.0)	5 (100)
Triplets/quadruplets	0 (0)	0 (0)	0 (0)

SGAs was 3.7 cm greater than that of PT-AGAs ($p < 0.01$), but beyond infancy it was similar. Only during infancy absolute gains in height in PT-SGAs exceeded that of FT-SGAs, by 7.2 cm, respectively, whereas weight gains were equal. In the period following infancy, FT-SGAs grew at least as much as their PT-SGA counterparts. The HC growth of PT-SGAs exceeded that of both PT-AGAs and FT-SGAs by 3–4 cm (table 2).

During infancy, PT-SGAs had greater mean growth increases for weight, height, and HC than PT-AGAs (table 3). This means that relative growth in PT-SGAs was greater than in PT-AGAs. Even so, the *z*-scores for weight and height remained –1.3 to –2.6 SD at all ages. Regarding HC, PT-SGAs had a greater relative growth than PT-AGAs. However, both groups caught up and had *z*-scores of 0.1 to –0.7 SD at age 1 (table 3).

Growth restriction occurred frequently in PT-SGAs, shortness occurred less frequently than underweight (table 4). The proportion of children with growth restriction was greatest within the group of preterm SGAs (approximately 39% for weight, 30% for height, and 27% for HC).

Influence of Preterm Birth on Growth

Preterms gained approximately 500 g more weight, 6 cm more height and 3.5 cm more HC than fullterms during infancy (table 2). During ages 1–4 however, absolute gains in weight and height of preterms and fullterms were similar.

Prematurity had an influence on relative growth at all ages and on all measures, except for HC at the age of 1 year ($p = 0.07$) (table 3). Although relative growth during infancy was greater in preterm children, we found no further catch up in the subsequent years. Preterm children obtained *z*-scores that were 0.1–2.6 SD lower than fullterms, even after correction for prematurity.

Prematurity also had effect on growth restriction. This was most outspoken for weight (table 4).

Influence of SGA Status on Growth

Absolute gains in weight and height of SGAs, be they preterm or fullterm, were affected by their SGA birth. Weight gains during infancy were less than those of AGAs, whereas height gains exceeded those of AGAs. SGAs grew approximately 400 g per year less in the years following infancy and their height gains did not exceed that of their AGA counterparts (table 2).

The influence of SGA on relative growth was more outspoken (table 3). If *z*-scores of PT-SGAs were corrected for numbers of weeks born too early, they were still 0.8–2.5 SDs lower than those of AGAs, illustrating that SGA status significantly influenced all the growth measures at all the ages we investigated.

Growth restriction was also consistently negatively influenced by SGA status (table 4).

Combined Effects of Prematurity and SGA Status

Regarding absolute growth, weight and height gains during infancy were affected most by prematurity (table 5). For age 2–3, we found a significant interaction of prematurity with SGA status regarding weight.

Relative growth was affected by both predictors (table 5) at all the ages and for all measures. For prematurity, these effects were largest during infancy. Again interactions were found at age 1 regarding height.

Growth restriction for weight and height was significantly associated with both prematurity and SGA status with odds ratios of 2.4–18.4 (table 5). There were multiple

Table 2. Absolute gains in weight (kg), height (cm) and HC (means ± SDs) for preterm and fullterm children during ages 0–4 years

	Preterm (PT)		Fullterm (FT)		p values[a]	
	SGA (n = 44)	AGA (n = 1,248)	SGA (n = 10)	AGA (n = 494)	PT vs. FT	SGA vs. AGA
Weight at ages						
0 to <1 year	6.5±1.0	7.3±1.1	6.6±1.1	6.4±1.1	<0.001*	<0.001*
1 to <2 years	2.5±0.7	3.0±0.8	2.5±0.5	3.0±0.8	0.93	<0.001
2 to <3 years	1.8±0.6	2.3±0.8	2.4±0.6	2.3±0.8	0.27	0.003
3 to <4 years	1.7±0.7	1.9±0.9	1.6±0.4	2.0±0.9	0.71	0.035
Height at ages						
0 to <1 year	34.2±3.6	30.5±4.1	27.0±2.2	24.9±2.8	<0.001	<0.001
1 to <2 years	13.3±2.2	13.4±2.2	11.5±0.5	12.8±2.3	0.001	0.67
2 to <3 years	9.0±1.6	9.6±2.2	9.0±1.4	9.4±1.9	0.32	0.11
3 to <4 years	6.7±2.2	6.6±1.8	6.8±2.1	6.3±1.9	0.005	0.53
HC at age						
0 to <1 year	16.7±2.2	14.6±1.7	13.3±0.0	11.2±1.4	<0.001	<0.001

[a] Mutually adjusted. * Factors PT and SGA significantly interact: $p < 0.01$.

Table 3. Relative growth in *z*-scores for weight, height and HC (means ± SDs) during ages 0–4 years by age (calendar ages, uncorrected for prematurity and corrected for prematurity, respectively)

	PT-SGA		PT-AGA		FT-SGA	FT-AGA	p values[a]	
	uncorrected	corrected	uncorrected	corrected			PT vs. FT	SGA vs. AGA
Weight at ages								
0 years	–5.2±0.7	–2.2±0.8	–3.2±1.2	–0.3±1.3	–2.5±0.8	0.0±0.9	<0.001	<0.001
1 year	–2.4±0.9	–1.9±1.0	–0.7±1.1	–0.1±1.1	–0.9±0.9	0.0±1.0	<0.001	<0.001
2 years	–2.1±1.0	–1.7±1.1	–0.5±1.0	0.0±1.1	–1.0±0.9	0.0±1.0	<0.001	<0.001
4 years	–1.7±1.0	–1.7±1.0	–0.3±1.1	–0.3±1.1	–1.0±0.6	0.0±1.0	<0.001	<0.001
Height at ages								
0 years	–6.1±2.0	–2.6±1.8	–3.2±2.0	–0.1±1.8	–1.7±1.0	0.0±1.0	<0.001	<0.001
1 year	–2.3±1.1	–1.7±1.1	–0.8±1.1	–0.1±1.1	–0.6±1.0	0.0±1.0	<0.001	<0.001
2 years	–1.7±1.1	–1.3±1.2	–0.5±1.0	0.1±1.1	–0.9±0.9	0.0±1.0	<0.001	<0.001
4 years	–1.4±1.0	–1.4±1.0	–0.3±1.1	–0.3±1.1	–0.8±0.8	0.0±1.0	<0.001	<0.001
HC at ages								
0 years	–5.7±2.3	–1.0±1.3	–3.2±1.6	0.9±1.0	–1.2±0.4	0.1±0.9	<0.001	<0.001
1 year	–1.2±1.2	–0.7±1.0	–0.3±1.1	0.1±0.8	–0.6±1.1	0.0±1.0	0.07	<0.001

[a] Mutually adjusted for uncorrected ages.

ages where these two factors moderated each other's effects. At 1 and 3 years, prematurity was not significantly associated with growth restriction in height, while the combination of preterm and SGA birth was. This also holds true for HC at 1 year as prematurity and SGA status interacted significantly (OR 8.0; $p < 0.01$). Regarding the proportion of children with growth restriction in height and weight, however, there was no interaction in the long term.

Discussion

This study demonstrated that up to the age of 4, PT-SGAs gained less height and weight in comparison to both PT-AGAs and FT-SGAs. HC growth in PT-SGAs was accelerated during infancy, as was the case in PT-AGAs. PT-SGAs did not catch up on their growth in the same way as did PT-AGAs and FT-SGAs. Catch-up growth was in-

Table 4. Number and proportion (% of the group) of children with growth restriction for weight, height and HC during ages 0–4 years (uncorrected)

	Preterm (PT)		Fullterm (FT)		p values[a]	
	SGA (n = 57)	AGA (n = 1,448)	SGA (n = 11)	AGA (n = 555)	PT vs. FT	SGA vs. AGA
Weight at ages						
1 year	32 (72.7%)	134 (10.8%)	0 (0%)	6 (1.3%)	<0.001*	<0.001*
2 years[b]	25 (55.6%)	75 (6.2%)	0 (0%)	4 (0.9%)	<0.001*	<0.001*
3 years[b]	22 (53.7%)	58 (4.5%)	1 (10%)	3 (0.6%)	<0.001*	<0.001*
4 years	22 (38.6%)	72 (5.0%)	1 (9.1%)	3 (0.5%)	<0.001*	<0.001*
Height at ages						
1 year	29 (67.4%)	155 (12.6%)	0 (0%)	5 (1.8%)	<0.001*	<0.001*
2 years[b]	21 (46.7%	87 (7.3%)	0 (0%)	4 (1.5%)	<0.001*	<0.001*
3 years[b]	15 (37.5%)	54 (4.2%)	0 (0%)	4 (1.3%)	0.001*	<0.001*
4 years	17 (30.4%)	75 (5.2%)	1 (9.1%)	12 (2.2%)	0.002*	<0.001*
HC at age						
1 year	11 (26.8%)	52 (4.4%)	0 (0.0%)	8 (2.2%)	0.12	<0.001

* Factors PT and SGA significantly interact: $p < 0.01$.
[a] Mutually adjusted. [b] Age at which some children missed the assessment.

complete and restricted to the first year after birth. The lack of further catch-up growth resulted in growth restriction. In fact, approximately 40% of all PT-SGAs remained too thin and 30% too short or both at the age of 4, compared to about 5% of all PT-AGAs and 9% of all FT-SGAs.

Relative growth was affected by preterm and SGA birth. In fullterms, relative growth is mostly balanced. In the preterm groups in this study, however, both relative growth in height and weight were affected, the latter even more than the former. We found more often that preterm children were too thin than too short at age 4. This was even more evident in the PT-SGA group. This confirms findings of Hack et al. [3] on over 200 very low birth weight children at the age of 20 years. Apparently, height gain is more preserved than weight gain during the first years after preterm SGA birth.

HC in PT-AGA children did not differ from that of FT-AGAs at age 1, due to accelerated growth during infancy. Regarding the proportion of children that were growth restricted in HC, the combination of preterm and SGA birth affected HC growth more than SGA status itself. This might explain why outcomes for HC in PT-SGAs were better than in FT-SGAs. Prematurity itself is reported as a factor which accelerates growth in HC. Both Cockerill et al. [13] and Kaur et al. [14] previously reported accelerated HC growth in preterms in a much smaller sample. This may be due to brain-sparing which becomes more evident in severe growth restriction [15].

We offer several explanations for the distinctive growth patterns in PT-SGAs. First, intrauterine growth restriction may result in irreversible postnatal disturbances of the growth hormone-IGF axis that prevents the child from catching up [16]. Second, these children are highly susceptible to neonatal complications that influence growth [17]. Third, total body weight may be less as these children are at risk of a mismatch between growth in fat and muscles. Gain in muscle mass is known to be more affected than gain in fat mass [18]. This might explain why PT-SGAs were often more underweight rather than small. Growth may also be influenced by chronic disease or by genetic factors as was reported recently [19]. Nevertheless, further research on the exact mechanisms of growth in PT-SGAs is needed.

Major strengths of this study were its large sample size, its community-based design, and the longitudinal approach. Our study also had some limitations. First, our large sample contained relatively few term SGAs. Second, birth weight was compared to the Kloosterman curves to convert birth weight to SD scores [11]. The Kloosterman curves are relatively old which may lead to an underestimation of the number of SGA children, because of secular trends. Over the last four decades, however, median birth weight has increased very little (up to 150 g) whereas median height increased by 1 cm [20, 21]. Next, our cohort consisted of many multiples. Multiple births are associated with SGA birth, but in our cohort, multiples were SGA less often. Moreover, twins are mostly not growth restricted at

Table 5. Effects of preterm birth and SGA on absolute gains, relative growth and growth restriction; effects of prematurity (PT), SGA and their interaction (PT · SGA) during ages 0–4 years (uncorrected)

Age, years	Factor	Weight		Height		HC	
		β	p	β	p	β	p
Absolute gains; effect sizes from multiple linear regression							
0 to <1[a]	PT	0.351	<0.001	0.493	<0.001	0.305	<0.001
	SGA	–0.099	<0.001	0.130	<0.001	0.188	0.22
	PT · SGA	–0.136	0.009	0.053	0.42	0.003	0.99
1 to <2	PT	0.001	0.96	0.097	0.001		
	SGA	–0.113	<0.001	–0.013	0.67		
	PT · SGA	0.014	0.83	0.098	0.36		
2 to <3	PT	–0.022	0.42	0.029	0.32		
	SGA	0.013	0.82	–0.045	0.12		
	PT · SGA	–0.095	<0.001	–0.016	0.86		
3 to <4	PT	–0.009	0.71	0.071	0.005		
	SGA	–0.050	0.033	0.016	0.53		
	PT · SGA	0.015	0.79	–0.039	0.58		
Relative growth; effect sizes from multiple linear regression							
0	PT	–0.772	<0.001	–0.624	<0.001	–0.347	<0.001
	SGA	–0.188	<0.001	–0.183	<0.001	–0.213	<0.001
	PT · SGA	0.044	0.146	–0.068	0.112	–0.105	0.32
1	PT	–0.291	<0.001	–0.268	<0.001	–0.144	<0.001
	SGA	–0.148	0.004	–0.099	0.142	–0.116	<0.001
	PT · SGA	0.096	0.06	–0.219	<0.001	–0.048	0.48
2	PT	–0.209	<0.001	–0.187	<0.001		
	SGA	–0.242	<0.001	–0.205	<0.001		
	PT · SGA	–0.073	0.17	–0.059	0.45		
4	PT	–0.143	<0.001	–0.113	<0.001		
	SGA	–0.206	<0.001	–0.179	<0.001		
	PT · SGA	–0.049	0.34	–0.055	0.30		
Age, years	Factor	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Growth restriction; effect sizes from multivariate logistic regression							
1[b]	PT					2.0 (0.9–4.3)	0.07
	SGA					7.5 (3.7–15.6)	<0.001
	PT · SGA					8.0 (3.8–16.4)	<0.001
4	PT	9.6 (3.0–30.7)	<0.001	2.4 (1.3–4.5)	0.005		
	SGA	18.4 (1.8–192.5)	0.015	4.4 (0.5–37.4)	0.17		
	PT · SGA	0.65 (0.1–7.3)	0.65	1.8 (0.2–16.5)	0.61		

β = Standardized regression coefficient; p = significance.

[a] For example, in the first year after birth, absolute growth for weight is significantly affected by prematurity, but not by SGA birth, nor is there a statistically significant interaction of prematurity and SGA status.

[b] For example, at age 1 year, SGA at birth is significantly associated with growth restriction in HC. There is also a significant interaction of prematurity and SGA status (OR 10.3, $p < 0.001$).

birth [22, 23] and multiple birth is not associated with growth restriction [4, 24]. Finally, our study had a retrospective design. Even so, we are confident that our data are reliable, because measurements were done with standardized equipment and techniques, by professionals that were trained for measuring children. In short, our findings indicate that growth of PT-SGAs was affected by both prematurity and SGA status to the extent that it resulted in poor growth outcomes. The lack of catch up in HC and weight is a matter of concern for PT-SGAs because both measures are specifically related to neurodevelopmental outcome [25]. The first year of life seems to be the most important

for gaining weight and height in preterm children. Our findings imply, therefore, that strategies to improve growth in preterm children should focus on early infancy.

Conclusion

Preterm SGA-born children seem to follow a distinctive growth pattern, combining the effects of prematurity and SGA status. Growth outcomes were poor for PT-SGAs in particular, with poorest outcomes for weight and best outcomes for HC.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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