# Growth of Preterm-born Children



Inger Bocca-Tjeertes

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Stellingen behorende bij het proefschrift

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1. Groei bij vroeggeboren kinderen is afhankelijk van de zwangerschapsduur en het geboortegewicht (dit proefschrift).
2. Vroeggeboorte zorgt voor een kortdurende inhaalgroei die de groeiachterstand vanwege de vroeggeboorte gedeeltelijk compenseert (dit proefschrift).
3. De groep kinderen met een groeivertraging op de lange termijn bestaat uit kinderen met een laag-, normaal-, of hoog geboortegewicht voor de zwangerschapsduur en niet alleen uit kinderen met een groeivertraging bij de geboorte (dit proefschrift).
4. Het volgen van groei en het interpreteren van de bevindingen kan vereenvoudigd worden als men de geboortegewichtgroep bepaalt en meeneemt in de conclusie (dit proefschrift).
5. De in dit proefschrift gepresenteerde groeidiagrammen bieden op dit moment de beste leidraad voor het volgen van groei bij vroeggeboren kinderen geboren in de westerse wereld (dit proefschrift).
6. Het risico voor ontwikkelingsachterstanden op de leeftijd van 4 jaar lijkt gerelateerd te zijn aan het geboortegewicht van vroeggeboren kinderen (dit proefschrift).
7. Als we wisten wat we deden, heette het geen onderzoek (Einstein).
8. Kinderen groeien met sprongen, vooral die van de bovenburen (Van Broeckhoven).
9. Het geduld van een moeder is als tandpasta. Hoeveel je er ook van gebruikt, er is altijd nog een beetje over (Saores).
10. Voor ik kinderen kreeg had ik drie theorieën over het opvoeden van kinderen. Nu heb ik drie kinderen en geen enkele theorie (vrij naar Wilmot).
11. Well behaved women rarely make history (Thatcher).

Inger Bocca-Tjeertes, oktober 2013

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RIJKSUNIVERSITEIT GRONINGEN

# Growth of Preterm-born Children

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Inger Femke Astra Bocca-Tjeertes

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# 1

## General introduction and outline of the thesis

*Inger F.A. Bocca-Tjeertes*

## Background

Growth can be seen as a biomarker for the general well-being of a child. It is also one of the accessible outcomes of early preterm birth (before 32 weeks of gestation) or moderately preterm birth (between 32 and 36 weeks of gestation). Recent studies showed that preterm birth is associated with poorer growth in the short and long-term.[1-4] Prematurity thus seems to affect growth directly, although growth is influenced by many other factors, such as genetic and hormonal profiles, morbidity, and social conditions.[2] Knowledge about growth and how it affects preterms children over the entire range of preterm gestation is scarce.

Over the last decades, survival rates of preterm infants have increased significantly as neonatal care has evolved.[5] In the Netherlands, 8% of all live born children are born with a gestational age (GA) of 37 weeks or less.[6] This number is still rising because of various reasons, among others that women, continue to give birth at higher ages, rates of maternal obesity and diabetes mellitus increase, and artificial reproduction is becoming more frequent.[7] Over the last years, management of extremely preterm born children, including those under 25 weeks of gestation, has also changed in favour of actively treating the newborn. This means that long-term care for preterm-born children will expand over the next years.

The aim of this thesis is to describe normal growth in preterm-born children and to determine growth and its influence on development in (pre)term children according to their birth weight, gestational age, and type of fetal growth restriction.

## Growth in general

Postnatal growth can be divided in stages. The first one is infancy. Infancy is a very important period during which growth is mainly influenced by feeding and insulin.[8] Beyond infancy, other hormones, such as growth hormone, play more important roles.[9] Chronic disease, genetic potential, ethnicity, nutrition, congenital malformations or syndromes also influence growth. Although so many factors influence growth, it is still possible to predict a height range in which a healthy newborn will end when it's an adult. It therefore seems that growth is very steady and only externally influenced up to some point.

## Growth assessment and monitoring in the Netherlands

In the Netherlands, routine growth assessments are done at preventive child health care centers (PCHC). Children have about fifteen well-child visits to the PCHC from birth to age 4 years, though this system is currently in revision.[10] 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 onwards, the children stand upright and wear only socks. Weight is measured undressed. The growth measures are then plotted on a (cross-sectional) growth chart and interpreted by a youth physician.

There is a different follow-up program for preterm-born children depending on the need for admission to a tertiary Neonatal Intensive Care Unit (NICU). Preterm children that were admitted to NICUs have extra check-ups during a mostly 2-years follow-up by neonatologists. Preterm children that were admitted to other neonatal wards are mostly seen by pediatricians after their hospital admission. Even so, whereas preterm follow-up is becoming more structured currently, there was no standardized follow-up program during the study period. PCHC and hospitals don't share patient files, so growth assessments are not routinely combined to optimize their interpretation.[11] Monitoring growth and, moreover, decision making based on growth, are challenging as one needs reference charts that actually represent growth. Optimally, growth is monitored using longitudinal growth charts designed for preterm-born children. Reference charts that are currently used are based on either data of fullterm children, birth weight data, or estimated fetal weights. These charts fail to represent actual growth in preterm-born children.[12] Next to this, there is no uniformity among doctors for the use of a specific type of reference chart. For instance, youth physicians used fullterm charts, endocrinologists birth weight charts and neonatologists either one of those.

## Preterm birth and growth

Preterm birth is associated with being smaller and lighter at birth, and with poorer growth after birth. Most studies and data about growth of preterms concern only early preterm-born children. Children born early preterm (GA<32 weeks) or children born with very low birth weights (VLBW) are consistently shown to be at risk for poor growth and long-term growth restriction.[1-4] By contrast, data about growth in moderately preterm-born children (GA 32-36 weeks), who comprise 85% of all preterm-born children, are scarce. This also holds true for children born with high birth weights for their gestation (large-for-gestational age, LGA) and for children born growth-restricted compared to GA. (small-for-gestational age, SGA)

## General interventions to promote growth

Interventions to promote growth generally mainly focus on feeding strategies and on growth hormone administration. These efforts may have important effects and side-effects. On the one hand poor growth and growth restriction may be prevented. On the other hand, children may be put up for additional metabolic risks if overgrowth is facilitated by, for example, enriched feeding.

Preterm-born children are already exposed to metabolic risks purely based on their gestational age.[8,13] It is therefore important to monitor growth frequently and to gain more insight in normal growth in preterm-borns.

By stimulating growth we hope to reach a more favourable developmental outcome.[14-17] However, it is still largely unknown if weight gain is directly related to better developmental achievements, or whether this better development is defined multifactorial. In that case weight gain might be a reflection of other factors, such as less illness, or less neurological damage. We also do not know whether catch-up growth in HC is equal to normal functional brain development, but it most likely is not.

## Growth and its influence on development

Growth affects developmental outcomes, in addition to having effects on metabolic and endocrine outcomes.[14-17] In preterm-born children, the lower a child's gestational age, the higher the risk for developmental delay is.[18] Again, intrauterine growth restricted children are evidently more at risk for additional adverse developmental outcomes compared to their GA matched full-grown counterparts. [14-17]

Catch-up growth is a period of accelerated growth causing a child's z-score to incline towards the median of the reference group. There are indications that catch-up growth is associated with better long-term development.[14-17] Catch-up growth can occur in all growth domains but is probably most influential in head circumference growth when considering the effects of growth on developmental outcome. Although it remains unclear which growth pattern is most associated with developmental delay, it seems at least favourable to have sufficient or even catch-up growth as a preterm-born child.[14-17]

## Main aim and research questions

The main aim of this thesis was to gain more evidence on growth in preterm-born children and its determinants and consequences. Therefore, we assessed normal growth in preterm-born children and its influence on development in (pre)term children according to their birth weight, gestational age, and type of fetal growth restriction. In addition, we aimed to gain a more precise tool for growth monitoring and more uniformity by compiling longitudinal growth for preterm children.

The specific research questions were (between brackets, it is indicated which chapters focus on each question):

1. What is normal growth for moderately-preterm born children? How often does growth restriction occur in the long-term and can it be predicted? (Chapter 2).
2. How is weight, height and head circumference (HC) distributed in preterm-born children during ages 0-4 years when classified by gender and gestational age? (Chapter 3).
3. How do preterm-born SGA children grow compared to their preterm-born and fullterm-born counterparts? (Chapter 4).
4. What are the effects of growth restricted preterm birth on growth and development? Are there any differences when children are classified by their type of growth restriction? (Chapter 5).
5. How do preterm-born LGA children grow compared to their preterm-born and fullterm-born counterparts? Are they at greater risk for developmental delays? (Chapter 6).

## The study sample

The study was based on a stratified sample that was drawn from a community-based cohort of 45,446 children born in 2002-03. This longitudinal cohort study is known as "LOLLIPOP" (Longitudinal Preterm Outcome Project) but in Dutch it is known as "Pinkeltje."

The LOLLIPOP sample consists of early and moderately preterm children born before 36 weeks' gestation and randomly selected fullterm controls that were included during their last visit to the PCHC at age four. This inclusion age was chosen for optimal inclusion rates based on the fact that it involves a check-up including a vaccination at which 97% of all children show up.[19] The cohort size was based on estimates of numbers needed to compile growth curves for preterm children in the Netherlands. These estimates led to a planned inclusion of 500 early and 1000 moderately preterm-born children. This planned inclusion would enable us to detect a difference in growth restraint between preterm and fullterm-born children per week GA for boys and girls separately, with power 80% at $P$ =.05. We enriched the sample with early preterm-born children from five of the ten NICUs in the Netherlands because the data collection via only PCHCs would not lead to the inclusion of the planned number of early preterm children.

Data on growth during the children's first four years were obtained retrospectively from records kept at the PCHC and augmented by data retrieved from hospital records. We analyzed more than 38,500 standardized measurements and these were all used to compile longitudinal growth charts. The measurements used in any other analysis were grouped in periods around a certain age. For these analyses, we had access to an average of 9.9 measurements per child. Data on predictors of growth were obtained from the medical records and a parental questionnaire that was designed for this study.

Postnatal growth was mostly measured as gain in weight, height and head circumference. These measures lead to analyses on absolute gains (absolute growth, i.e. number of kilograms or centimetres gained in a time period), on relative growth (position on growth-chart, $z$-score, and

change of *z*-scores), and on growth restriction (measure below -2SD compared to the reference population at any time).

We used the Dutch four-year version of the Ages and Stages Questionnaire (ASQ) to assess development at the age of four. The ASQ is a parent-completed developmental screening tool. Its reliability and validity has been documented in at least two studies.[20,21] The ASQ assesses development in five domains: communication, fine motor, gross motor, problem-solving ability, and personal-social functioning. The scores on each domain add up to an ASQ total-problems score. A score of >2 SDs below the mean score for the Dutch reference group was considered to indicate developmental delay.

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# 2

## Growth and predictors of growth restraint in moderate preterms aged 0-4 years.

*Inger F.A. Bocca-Tjeertes, Jorien M. Kerstjens, Sijmen A. Reijneveld, Andrea F. de Winter, Arend F. Bos*

Pediatrics 2011;128:e1187-94.

### What's known on this subject

Early preterms often show growth restraint. Studies on small groups of moderate preterms report that they too are at risk. Both poor somatic growth and excessive weight gain can lead to long-term complications.

### What this study adds

This longitudinal study of 1123 children demonstrated that at age four growth regarding height and weight of moderate preterms was restricted twice as often as term-borns. Small-for-gestational age at birth and short mothers were identified as predictors of growth restraint.

## Abstract

***Objective:*** To describe growth in moderate preterms, to determine the prevalence of growth restraint at the age of four, and to identify predictors of growth restraint. We hypothesized that growth in moderate preterms differs from growth in term-borns and that growth restraint is more prevalent in the former.

***Patients and Methods:*** A community-based, cohort study of 1123 moderate preterms (gestational age 32-35$^{+6}$ weeks), born between January 2002 and June 2003.

***Results:*** On average, we found that moderate preterms were shorter and weighed less at each assessment during the first four years of life than their term-born counterparts. Thirty-two boys (5.6%) and 18 girls (3.8%) were growth restricted in height and 21 boys (3.4%) and 27 girls (5.8%) in weight. Their growth in head circumference (HC) was normal compared to term-borns. In addition, growth restraint was associated with being small-for-gestational age (SGA) at birth (for height: odds ratio (OR) 7.7, 95%-confidence interval (CI) 2.9-20.4; for weight: OR 9.5, 95%CI 3.9-23.1), and maternal height below -1 SD (for height: OR 4.9, 95%CI 2.6-10.2; for weight: OR 2.6, 95%CI 1.3-5.2). Poor HC growth was associated with a low level of maternal education (OR 5.3, 95%CI 1.4-20.8).

***Conclusions:*** Growth in moderate preterms indeed significantly differs from term-borns. Predictors at birth are SGA, maternal height below -1 SD, and a low level of maternal education. The fact that growth in moderate preterms may lag behind warrants close monitoring during routine practice. Additional research on prevention of growth restraint is called for.

## Introduction

Worldwide, 5 to13% of all children are born preterm.[1-4] They form a relatively large group with serious medical, social, and economic implications for their parents, health care, and society.[1] A large majority, over 85%, are moderate preterms.[2,3]

Growth in *early* preterms (gestational age [GA] <32 weeks) is studied widely. Findings consistently show that the prevalence of growth restraint in these preterms is higher (10 to over 20%) compared to a term-born population (2%).[5-7] Evidence also points to the persistence of intrauterine growth restraint in early preterms, as well as growth restraint starting after birth due to feeding problems, infections, and other neonatal complications. Poor growth in infancy puts the individual at risk for growth restraint in adulthood and for metabolic complications.[5-13]

In contrast, despite the preponderance of *moderate* preterms (GA 32-35$^{+6}$ weeks), longitudinal information on their growth is scarce.[2,3] Moderate preterms are born at the time when growth velocity is at its highest point ever. During these four weeks they gain much weight in the intrauterine environment.[7] Although evidence is lacking, it is likely that moderate preterms miss this peak, which may subsequently lead to growth restraint, at least during the first years of life. Lack of information on growth also implies that the impact of factors such as being small-for-gestational age (SGA) and maternal stature are not yet fully understood.

Our first aim was a longitudinal description of growth in height, weight, and head circumference (HC) in moderate preterms. The second aim was to identify factors at birth that could serve as predictors of growth restraint at the age of four. We hypothesized that the percentage of growth restricted moderate preterms would be greater compared to term-borns. Furthermore, we expected that the predictors of growth restraint identified at birth would add to the prediction of growth restraint at age four.

## Methods

### *Study design*

Our study population was a subsample of the so-called Lollypop study. Lollypop (Longitudinal Preterm Outcome Project) is an extensive cohort study on growth, development, and general health of preterm infants, registered as: controlled trials.com ISRCTN80622320. The design of the Lollypop study is described in detail elsewhere.[14,15] In short, the Lollypop cohort consists of a large community-based sample of in total 1690 early and moderate preterm children born before 36 weeks of gestation, and 634 randomly selected term-born controls. The study combines retrospective data from medical records and parental questionnaires with measurements of height, weight, and HC of moderate preterms.

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

### *Sampling procedure*

Figure 1 provides an overview of the sampling procedure for moderate preterms. The sample comprised almost all children born in Northern, Central, Eastern, and Southern regions of the country. Thirteen preventive child health care services (PCHCs) in 2005 and 2006, covering approximately 25% of all children in the Netherlands, sampled all preterm children born between 01-01-2002 and 31-05-2003 at GA of 36 weeks or less, during a routine well-child visit at age four. Attendance at this age was 97%.[16] Out of 45,446 children, 1,468 children were eligible based on their GA. We excluded children with major congenital malformations and syndromes, but neurological abnormalities were allowed (Figure 1). We concluded that this sample was fairly representative of the general population, based on national birth records.

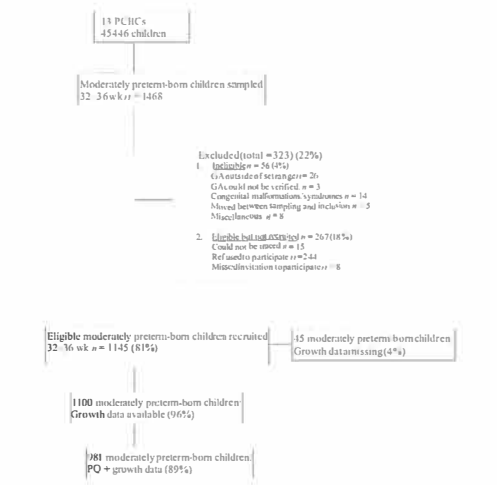


**FIGURE 1**
**Sampling overview of the Lollypop. PCHC indicates preventive child health care services, MP moderately preterm born children, PQ, parental questionnaires, MR, medical records**

We recruited 1145 (response: 81%) moderate preterms, and we collected growth data on 1123 of them (98%). When children were aged four years, 981 (89%) parents completed the questionnaires. Mothers in the non-response group were more often of non-Dutch origin and had a slightly lower social-economic-status (SES) based on their level of education compared to responders. Apart from this, we found no significant differences by response status.

### *Measures and procedure*

In more than 95% of the cases gestational age was based on the date of last menstruation and confirmed by early ultrasound measurements. If not, estimates based on last menstrual date were checked with clinical estimates of gestation after birth. Children whose gestational age could not be defined beyond reasonable doubt were excluded.

Data on growth were obtained from records on routine assessments in both hospital and PCHC settings from birth onwards. During their first four years children routinely have about fifteen well-child check-ups where height, weight, and HC (the latter until the large fontanel is closed), are assessed. Height and weight was measured using standardized measuring devices on every location. Up to the age of 15 months, the child was lying supine. From 15 months onwards, the child was standing. Weight was measured unclothed.

On average, for each PCHC assessment growth values were missing for 20% of all children. Due to the larger number of assessments per child, we resolved this by estimating weight, height, and HC from the nearest measure available with the formula: (Zx) = r*(Zy) (Z-score at age x =

correlation times Z-score at age y, in which y represents the youngest age). In this way we reduced the number of missing values to 3.0%. Longitudinal graphs of each child were drawn based on SD scores, to be able to correct registration errors.

### *Factors influencing growth*

Data on predictors of growth were obtained from medical records and parental questionnaires. SGA was defined as a birth weight of less than -2 SD according to the Kloosterman Dutch intrauterine growth curves.[17] Maternal height was asked for in the parental questionnaire and measured while the mother was standing and wearing stockings. Paternal height was measured as well, but the majority of the fathers did not attend when we measured child and mother. We therefore excluded paternal height from our analyses. In addition, the questionnaire provided data on ethnicity (based on the mother's country of birth), (the amount of) smoking during pregnancy, the mother's level of education, family-income, duration of breast-feeding, multiple pregnancy, and conception by in-vitro-fertilization/intra-cytoplasmic sperm injection (IVF/ICSI).

### *Statistical analysis*

Firstly, to describe growth during the first four years of life, we assessed each child's height, weight, and HC at birth, on the day of the lowest postnatal weight during the first week of life, and at ages 1 month, 3 months (±1 week), 6 months (±2 weeks), 12 months (±2 weeks), 2 years (±1 month), 3 years (±1 month), and between 3.5 and 4 years. HC was measured up to the age of 12 months, shortly before closure of the large fontanel, since the majority of HC growth occurs prior to age one year. Weight at birth was converted to SD-scores according to the Dutch Kloosterman curve, height and HC according to the Usher and McLean curves.[17,18] Growth restraint after birth was defined as more than 2 SD-scores below the median growth of the Dutch population, derived from the 4th Dutch nation-wide growth survey.[19,20] We also collected (growth) data on a control group of term-borns. We compared this control group to the 4th Dutch growth survey and found these groups to be very comparable. We therefore decided to refer to this growth survey which concerns a larger sample of term-borns.

Secondly, we assessed potential predictors for growth restraint, at the age of four for height and weight, and at the age of one for HC, using logistic regression. Factors that were univariately associated with growth restraint at $p<0.20$, or factors that are, according to the literature, associated with growth restraint, were subsequently included in a multivariate (stepwise backward) logistic regression model. Factors in the latter category for the child were: GA, SGA, gender, IVF/ICSI , part of a multiple birth, breast-feeding during first six months of life, and for the mother: height, age, ethnicity, level of education, smoking during pregnancy, and family income.[10,21-24] Appropriate-for-gestational age (AGA) children were also analyzed separately to clarify any differences between AGA and SGA children. All analyses were done with SPSS for Windows (release 16, SPSS, www.spss.com).

## Results

### *Growth*

For the 1123 moderate preterms as a group, weight, height, and HC at birth was adequate. The occurrence of growth restraint in weight, height or HC at birth (2.3% in a general population) was statistically comparable to the reference group of term-borns. Mean GA was $34^{+0}$ weeks (SD 1.0) and mean birth weight 2230 grams (SD 468). Our sample contained many multiples (29.6%) of whom 94.0% were twins. Of the singletons, 2.8% were SGA, of the multiples this was 2.6%. **Table 1** provides detailed information on maternal and child characteristics. Overall, less than 2.0% data was lacking (except for maternal height, 7.0%).

Following birth, at a mean age of 5.3 days, moderate preterms showed an average 8.0% maximum decrease in their birth weight while, during the first weeks of life, their height and HC did not change. After the initial decrease, weight increased within a narrow range up to the age of six months. From then on the range became wider and remained stable between the ages of two to four years. This pattern was similar for boys and girls, although girls' means were lower than boys' means. Mean weights and heights at ages 1, 2, and 3 years are presented in Appendix 1a/b. At the age of four (mean 3.9 years) moderate preterm boys weighed 16.9 ± 2.3 kg (mean ± SD) and girls weighed 16.0 ± 2.4 kg. Compared to term-born boys, who weighed 17.2 ± 2.1 kg, preterm boys were 0.15 SD lighter ($p$=.09); compared to term-born girls, who weighed 16.7 ± 2.05 kg, preterm girls were 0.25 SD ($p$<.01) lighter.

The increase in height showed a similar distribution for boys and girls but the ranges remained stable over the entire period. Absolute height was again lower in girls. At four years, the mean height for boys was 104 ± 4.3 cm and 103 ± 4.1 cm for girls. This was 0.3 SD ($p$<.01) shorter compared to the term-born group from the national growth survey[19] (105.1 ± 4.0 cm) for boys and 0.2 SD ($p$=.04) for girls (103.7 ± 4.1 cm).

**Table 1:** Maternal and child characteristics

| | Boys | Girls | Total |
|---|---|---|---|
| N | 637 (57.0%) | 486 (43.0%) | 1123 (100%) |
| Gestational Age | | | |
| 32 | 73 (11.5%) | 58 (11.9%) | 131 (11.7%) |
| 33 | 131 (20.6%) | 98 (20.2%) | 229 (20.4%) |
| 34 | 173 (27.2%) | 135 (27.8%) | 308 (27.4%) |
| 35 | 260 (40.8%) | 195 (40.1%) | 455 (40.5%) |
| Maternal height | | | |
| <-2SD | 38 (6.0%) | 35 (7.2%) | 73 (6.5%) |
| -2SD – -1SD | 109 (17.1%) | 88 (18.1%) | 197 (17.5%) |
| -1SD – +1SD | 376 (59.0%) | 278 (57.2%) | 654 (58.2%) |
| 1SD – 2SD | 56 (8.8%) | 36 (7.4%) | 92 (8.2%) |
| > 2SD | 11 (1.7%) | 5 (1.0%) | 16 (1.4%) |
| Unknown | 47 (7.4%) | 44 (9.1%) | 91 (8.1%) |
| Smoking during pregnancy | | | |
| No | 483 (75.8%) | 378 (77.8%) | 861 (76.7%) |
| 1-5 | 64 (10.0%) | 38 (7.8%) | 102 (9.1%) |
| 6-10 | 44 (6.9%) | 29 (6.0%) | 73 (6.5%) |
| > 10 | 31 (4.9%) | 31 (6.4%) | 62 (5.5%) |
| Ethnicity | | | |
| Dutch | 580 (91.1%) | 453 (93.2%) | 1033 (92%) |
| Ex Colonial | | | |
| *Dutch Antillean/Aruban* | 2 (0.3%) | 1 (0.2%) | 3 (0.3%) |
| *Surinam* | 5 (0.8%) | 5 (1.0%) | 10 (0.9%) |
| Labor Immigrant: | | | |
| *Turkish* | 4 (0.6%) | 1 (0.2%) | 5 (0.4%) |
| *Moroccan* | 9 (1.4%) | 3 (0.6%) | 12 (1.1%) |
| Other Non-Dutch: | | | |
| *Asian* | 8 (1.3%) | 6 (1.2%) | 14 (1.2%) |
| *African* | 6 (0.9%) | 4 (0.8%) | 10 (0.9%) |
| *Other* | 23 (3.6%) | 13 (2.7%) | 36 (3.2%) |
| Maternal Age | | | |
| < 20 | 10 (1.6%) | 5 (1.0%) | 15 (1.3%) |
| 20 - 35 | 565 (88.7%) | 428 (88.1%) | 993 (88.4%) |
| > 35 | 61 (9.6%) | 50 (10.3%) | 111 (9.9%) |
| Family income | | | |
| Low | 51 (8.0%) | 28 (5.8%) | 79 (7.0%) |
| Moderate/High | 578 (90.7%) | 448 (92.2%) | 1026 (91.4%) |
| Maternal level of education | | | |
| Low | 203 (31.9%) | 147 (30.2%) | 350 (31.2%) |
| Moderate/High | 425 (66.7%) | 329 (67.7%) | 754 (67.1%) |
| IVF/ICSI | | | |
| No | 588 (92.3%) | 437 (89.9%) | 1025 (91.3%) |
| Yes | 42 (6.6%) | 44 (9.1%) | 86 (7.7%) |
| Birth weight: Median (SD) | 2291 (475) | 2172 (448) | 2240 (468) |
| SGA (< P2) | | | |
| No | 614 (96.4%) | 479 (98.6%) | 1093 (97.3%) |
| Yes | 23 (3.6%) | 7 (1.4%) | 30 (2.7%) |
| Multiple* | | | |
| No | 461 (72.4%) | 330 (67.9%) | 791 (70.4%) |
| Yes | 176 (27.7%) | 156 (32.1%) | 332 (29.6%) |
| Breast feeding (first 6 months) | | | |
| No | 545 (85.7%) | 426 (87.7%) | 971 (86.5%) |
| Yes | 85 (13.4% | 53 (10.9%) | 138 (12.3%) |

* The group of multiples consisted mainly of twins (94.0%), the remainder being triplets and quadruplets (6.0%)

HC growth was also similar for boys and girls. Again the girls' means were lower than boys'. The ± 2 SD scores varied very little over time. At the age of one year, boys had a mean HC of 47.0 ± 1.3 cm and girls 45.6 ± 1.3 cm, which was comparable to the reference group.

In short, the overall picture was a stable shift towards the lower side for weight and height attainment. HC growth was rapid after an initial period of growth failure, resulting in comparable HC at age one year.

### *Growth restraint and predictors*

At the age of four, in comparison to 2.3% of the term-borns from the national growth survey,[19] we found growth restraint in height in 50 children (4.6%, $p$=.02; SGA n=8, AGA n=42) i.e. 32 boys (5.6%, $p$=.05) and 18 girls (3.8%, $p$=.35).[25] We found an opposite gender distribution for weight: 48 children (4.4%, $p$=.04; SGA n=7, AGA n=41) were underweight, i.e. 21 (3.4%, $p$=.52) boys and 27 (5.8%, $p$=.02) girls. Growth restraint of HC was present in 10 children (1.2%, $p$=.28).

We found several factors at birth that predicted growth restraint (**Table 2**). In particular, SGA and maternal height below -1 SD were predictors of growth restraint in height and weight. Maternal age over 35 years also increased the child's risk of growth restraint. Of all the socio-economic variables, we found that only a low level of maternal education was associated with poor HC growth. None of the other categories revealed significant associations, with the exception of ex-Dutch colonial ethnicity.

**Table 2:** Results of univariate logistic regression analyses for low height, weight, and head circumference (HC): crude odds ratios (OR), 95%-confidence intervals (CI), and p-values.

| | **Height 4y < -2SD OR (95% CI)** | **Weight 4y < 2SD OR (95% CI)** | **HC 1y < -2SD OR (95% CI)** |
|---|---|---|---|
| GA | | | |
| 35 vs: | 1 | 1 | 1 |
| 32&33 | 1.1 (0.6-2.1) | 1.2 (0.6-2.4) | 1.0 (0.3-1.9) |
| 34 | 1.0 (0.5-2.0) | 0.7 (0.3-1.5) | 0.3 (0.04-2.7) |
| Gender (girls vs. boys) | 1.4 (0.8-2.5) | 0.6 (0.3-1.0) | 3.0 (0.6-14.3) |
| Ethnicity | | | |
| Dutch vs.: | 1 | 1 | 1 |
| ex-Colonial | 6.7 (1.7-25.3)** | 7.3 (1.9-27.4)** | 10.3 (1.2-91)* |
| Labor immigrant | 1.6 (0.2-12.4) | 1.7 (0.2-13.5) | 9.3 (1.1-81)* |
| Other non-Dutch | 1.3 (0.4-4.3) | 1.9 (0.7-5.6) | - |
| Maternal age | | | |
| 20 – 35 years vs.: < 20 years | 1 | 1 | 1 |
| > 35 years | 1.8 (0.2-14.0) | 1.6 (0.2-12.6) | - |
| | 2.2 (1.0-4.6)* | 0.6 (0.2-2.0) | 2.2 (0.5-10.4) |
| Maternal height -1SD - +1SD vs.: | 1 | 1 | 1 |
| < -2SD | 8.5 (3.8-18.9)** | 3.4 (1.5-4.1)** | - |
| > -2SD < -1SD | 5.1 (2.6-10.2)** | 2.6 (1.3-5.2)** | 12.3 (2.5-60.0)* |
| > 1SD - < 2SD | - | 0.7 (0.2-3.0) | - |
| > 2SD | - | - | - |
| Low maternal education level | 1.6 (0.9-2.9) | 1.0 (0.5-1.9) | 5.3 (1.4-20.6)* |
| Low Family income | 1.5 (0.6-3.9) | 0.9 (0.3-3.0) | - |
| Maternal smoking | | | |
| no vs.: | 1 | 1 | 1 |
| 1-5 sig/d | 0.9 (0.3-2.7) | 1.4 (0.5-3.6) | 1.3 (0.2-10.4) |
| 6-10 sig/d | 0.6 (0.2-2.7) | 1.9 (0.7-5.1) | 1.8 (0.2-14.6) |
| > 10 sig/d | 1.5 (0.5-4.4) | 1.8 (0.6-5.2) | 2.1 (0.3-17.4) |
| IVF/ICSI (no vs. yes | 0.8 (0.2-2.6) | 1.4 (0.6-3.7) | 1.2 (0.2-9.9) |
| SGA (yes vs. no) | 7.2 (2.9-17.7)** | 9.3 (3.9-22.1)** | - |
| Multiple (no vs. yes) | 1.2 (0.7-2.2) | 1.9 (0.9-3.2) | 2.6 (0.7-9.0) |
| Breastfeeding, yes vs. no | 0.5 (0.3-1.1) | 0.7 (0.3-1.5) | 1.2 (0.2-9.8) |

* $p < 0.05$; ** $p < 0.01$

**Table 3:** Factors associated with poor growth at age 4 years (height and weight) and 1 year (head circumference). Crude and adjusted # odds ratios (ORs), 95% confidence intervals (CI), and p-values.

| | **height 4y < -2SD OR (95% CI)** | **weight 4y < -2SD OR (95% CI)** | **HC 1y < -2SD OR (95% CI)** |
|---|---|---|---|
| SGA, unadjusted | 7.2 (2.9-17.7) ** | 9.3 (3.9-22.1) ** | |
| SGA, adjusted | 7.7 (2.9-20.4) ** | 9.5 (3.9-23.1) ** | |
| Maternal height, unadjusted | | | |
| >= -1SD | 1 | 1 | |
| >= -2SD < -1SD | 5.1 (2.6-10.2) ** | 2.6 (1.3-5.2) ** | |
| < -2SD | 8.5 (3.8-18.9) ** | 3.4 (1.5-4.1) ** | |
| Maternal height, adjusted | | | |
| >= -1SD | 1 | 1 | |
| >= -2SD < -1SD | 4.9 (2.4-9.9) ** | 2.6 (1.3-5.3) ** | |
| < -2SD | 7.0 (2.9-16.5) ** | 2.8 (1.1-7.4) * | |
| Maternal educational level, unadjusted (low vs. higher) | | | 5.3 (1.4-20.6) ** |
| Maternal educational level, adjusted (low vs. higher) | | | 5.3 (1.4-20.8)** |

# Adjusted for gestational age, ethnicity, maternal education level (low vs. moderate/high), family income (low vs. moderate/high), smoking during pregnancy (categorical), maternal age (categorical), IVF/ICSI (no vs. yes), gender, being part of a multiple (singletons vs. twins and vs. triplets/quadruplets) and breastfeeding during first 6 months of life (no vs. yes).

All significant factors in univariate analyses remained as independent predictors for growth restraint in the multivariate model (**Table 3**), except ethnicity and maternal age. SGA and short maternal height were most predictive for poor height and weight attainment in the long-term, whereas a low level of maternal education was the only predictive factor for HC growth. Analyses were repeated for AGA children only. This did not yield any different findings.

## Discussion

This study demonstrated that moderate preterm birth was associated with poor longitudinal growth outcomes. At the age of four the risk for being underweight and/or comparatively short was substantially higher in moderate preterms compared to term-borns. We also found several predictive factors as early as at birth that could be helpful in identifying moderate preterms at risk of growth restraint.

Longitudinal height and weight attainment was inadequate in approximately 5% of all moderate preterms. We found growth restraint 2.5 times more often in moderate preterms than in term-borns. The group of children that showed growth restraint consisted mainly of AGA children with poor longitudinal growth and some SGA children with lack of catch-up growth. Our findings are in line with Santos et al., who found growth restraint in 4 to 9% late preterm-born children at the age of two.[26] Our data extend their findings to the age of four and our sample was considerably larger.

We found that the HC of moderate preterms did not significantly differ from term-borns. At the end of the first year of life, only 1.2% of all moderate preterms had a HC below -2 SD. HC growth, however, did not occur during the first weeks. Evidence on whether this temporary delay in HC growth was associated with impaired neurodevelopmental outcome, is lacking.[27,28] Further research is needed to elucidate this issue.

The predictors at birth that could help to identify children at highest risk for growth restraint (height and/or weight) were maternal height below -1 SD and SGA. Predictors for AGA children were comparable to those for the total group of moderate preterms which is highly relevant for clinical practice. Small maternal height is a well-known risk factor for poor height gain in a normal population.[21] This obviously also holds true for moderate preterms. Surprisingly, we found that in moderate preterms short lengths of mothers were also associated with poor weight gain, albeit less strongly so than poor height attainment. To our knowledge this has not been reported previously for preterms. SGA had the strongest association with growth restraint. This reflects the lack of catch-up growth in this specific subgroup as was also found among early preterms.[5,6]

Poor growth of HC during the first year was only a[sso]ciated with a low level of maternal education as was described previously in term infants.[8,22] Low maternal education might be associated with a low maternal HC,[22] suggesting that the association we found has a genetic origin. We did not measure maternal HC, so this explanation needs additional study. We found no association between a low maternal education and poor height and weight gain. Similar findings were reported recently.[22]

We did not find other socio-economic and demographic factors, including smoking during pregnancy that influenced growth. Some of such factors, as low family income, maternal age, and multiple birth, were associated with preterm birth,[3] but apparently they exerted no influence on long-term growth, except through gestational age. With the social support system in the Netherlands, malnutrition associated with SES is extremely rare. Smoking during pregnancy often precedes low birth weight,[29] but not in our sample, and neither did it influence long-term growth.

Other factors that we expected to influence growth, such as a lower gestational age, breast feeding during the first six months, gender, and IVF/ICSI, were not identified as predictors of growth restraint in our cohort. Breast-fed children weighed less than formula-fed children at the age of four, but the difference only reached significance at $p$=.06. A consistent finding in term-born populations is that breast-feeding prevents overweight in adulthood.[24,30] It is unknown whether long-term growth in moderate preterms is affected by feeding practices. Finally, conception by artificial reproduction techniques did not implicate poor growth even though others have reported that it is associated with lower birth weight.[23]

Major strengths of this study were our large sample of moderate preterms, the community-based design, and the use of multiple sources of information. We analyzed growth longitudinally. This is rarely done; most growth studies only use cross-sectional data. Finally, we had an inclusion rate of over 80% and sufficient growth data on virtually all children.

Our study had some limitations. Firstly, we found small differences in SES between responders and non-responders. Nevertheless, this is unlikely to have affected our findings since SES was not associated with long-term growth (weight and height). Secondly, we used the 4$^{th}$ Dutch nation-wide growth survey as our reference.[19] It is based on children born shortly before 1997, whereas our cohort consisted of children born between 2002 and 2003. Height and HC have not increased since 1997, but weight has.[31] We could thus have underestimated growth restraint in weight of moderate preterms. Finally, retrospectively collected data on smoking during pregnancy may be biased. However, Jaspers et al. showed maternal recall of smoking during pregnancy to be good, even over a 10-years follow-up.[32]

Our findings imply that there is an urgent need to closely monitor growth in moderate preterms since they are at risk of growth restraint. In particular, this concerns those children whose mothers are short, who were SGA, and whose mother had a low education level. Additional research is needed to prevent the short-term and long-term consequences of growth outside the normal range, and its metabolic consequences. This may lead to optimization of feeding strategies for moderate preterms and prevent both undernourishment in the neonatal period and overly rapid weight gain in the succeeding months.

## Conclusion

In this large, longitudinal study, growth of moderate preterms significantly differed from growth of term-borns since approximately 5% of the moderate preterms were short and/or underweight at the age of four. For the total group up to age four, means for height and weight were below those of term-borns, except at birth. HC growth was normal in the long-term. Maternal height < -1 SD and SGA were two factors present at birth that could be helpful in identifying the children at highest risk of growth restraint regarding height and/ or weight. Only HC growth was influenced by a low level of maternal education. The development of descriptive, longitudinal growth charts for preterms could be a useful tool to identify growth outside the normal range and thus reduce subsequent complications of growth restraint.[8,33]

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# 3

## Growth of preterm and fullterm children aged 0-4 years: integrating median growth and variability in growth charts

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## Abstract

***Objectives:*** Information about normal growth across the entire range of preterm gestational age (GA) is incomplete, but needed to adequately monitor growth of early and moderate preterms. Our aim was to assess the distribution of height, weight, and head circumference (HC) in preterms for ages 0-4 years, by GA and gender. Second, to construct growth reference charts for preterm-born children, again by GA and gender, for monitoring growth in clinical practice.

***Study design:*** Community-based cohort study covering a quarter of the Netherlands.
1690 preterms (GA, 25-35$^{+6}$ weeks) and a random sample of 634 fullterm controls (GA 38-41+6) born 01-01-2002 – 31-12-2003, were followed from birth till age 4, providing 38,553 standardized measurements. *Height, weight* and *HC* were regularly assessed during routine well-child-visits and retrospectively collected.

***Results:*** At all ages, the median height and weight of preterms was lower compared with fullterm children. Growth depended on the child's GA. Increase in HC showed an early catch-up and was similar to fullterm children by the age of one. Height, weight, and HC were more variable in boys, particularly in the very preterm children.

***Conclusions:*** At 0-4 years the growth of preterms differed from fullterm children and depended on their GA. The greater variability of growth in boys suggests that they are more vulnerable to the complications of preterm birth that influence growth. The growth charts are the most precise tools currently available for monitoring growth in preterms.

## Introduction

Over the last decade, the neurodevelopmental outcome and social implications of preterm birth have been studied widely.[1-3] Nevertheless, the consequences of preterm birth for growth are not yet fully understood. Early preterm-born children (early preterms, GA < 32 weeks) are known for their ability to catch up on growth. Nevertheless, they have relatively high rates of growth restraint of below -2SD (10%-20%) for long-term growth.[4,5]

More recently, moderately preterm born children (moderate preterms, GA 32-36 weeks) were also found to differ from fullterm children regarding growth.[6] Although the prevalence of growth restraint was less than in early preterms (approximately 5%), former moderate preterms were, on average, shorter and weighed less than fullterm children.[6] Growth within the normal fullterm range may have both a favorable effect on neurodevelopmental outcomes and on the prevention of metabolic syndrome in preterms.[7,8]

Our knowledge of the normal ranges of growth across the entire range of preterm GAs is incomplete. Ideally, growth in preterms should be comparable with fullterms if pre- and postnatal feeding is adequate. However, 'normal' feeding, based on feeding practices in fullterm children, may never be achieved in preterms. The "normal ranges", derived from the growth curves for fullterm children, are likely to be poor substitutes for monitoring growth in preterms. The usefulness of other growth curves currently available, such as those of Guo et al.[9-11] is also limited. Firstly, the specific preterm growth charts are often based on cross-sectional birth data. Secondly, consensus is lacking on the correction for prematurity. In practice, preterms' calendar age is often adjusted for GA. For example, a preterm-born child at a GA of 32 weeks and a calendar age of 8 weeks is treated as a newly born fullterm (regarding anthropometric and neurodevelopmental data). This adjustment, however, depends on untested assumptions. Moreover, growth until term age is then derived from intrauterine growth.[9-13] Adequate growth curves for early and moderate preterms are needed, because poor growth is an indication for interventions such as specific feeding strategies or growth hormone therapy. Moreover, without adequate growth curves excessive weight gain might go unnoticed.

Our aim was to assess the median (P50) growth and the variation around the P50 regarding height, weight, and HC of preterms for ages 0-4 years, by GA and gender. Our second aim was to construct growth reference charts, again by GA and gender, for monitoring growth in preterms in clinical practice.

## Methods

### *Sample*

This study was part of Lollipop (Longitudinal Preterm Outcome Project), a study of growth, development, and the general well-being of preterm children.[6,14] The Lollipop cohort consists of a community-based sample of early and moderate preterm children (born before 36 weeks of gestation) and randomly selected fullterm controls seen at preventive child healthcare centers (PCHCs) at the age of four. Attendance at this age was 97%. The sample comprised children born in Northern, Central, Eastern, and Southern regions of the Netherlands. Thirteen PCHCs participated, covering approximately 25% of the population. Oversampling of early preterm infants was done by 5 tertiary NICUs covering a larger portion of the Netherlands. These NICUs sampled all early preterm infants, discharged alive from their unit. The sampling was done for children born between 01-01-2002 and 31-12-2003.

The cohort size was based on estimates of numbers needed to compile growth curves for preterm children in the Netherlands. This led to a planned inclusion of 500 early preterms and 1000 moderate preterms which enabled us to detect a difference in growth restraint, i.e. below the 10$^{th}$ percentile of fullterm children of 10% (i.e. 20% instead of 10%) between fullterms and preterms per week of GA, separately for boys and girls, with power 80% at $P$=0.05. In the present study we used a sample of 1690 preterm children with a GA of 25-36 weeks and 634 fullterm children.

We excluded children with major congenital malformations and syndromes. Children with neurological abnormalities were allowed but were very few. We concluded that this sample was fairly representative of the normal population, based on national birth records.[3] We refer to our previous studies for details on the characteristics and sampling of this cohort.[6,14]

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

### *Measures and procedure*

We collected data on growth for ages 0-4.5 years from hospital records and from records kept by the PCHCs visited by the children. Hospitals included tertiary NICUs as well as regional hospitals. We analyzed 38,553 standardized growth measurements. The number of measurements averaged over all children was 9.9. For early preterms, this was 11.5, for moderate preterms 9.8, and for fullterm children 7.3. Height and weight were measured using standardized measuring devices at each location. Up to the age of 15 months, the child was measured lying supine. From 15 months onwards, the child was measured standing. Weight was measured unclothed. In order to detect any registration and data-entry errors we checked all data, for each child separately, for extreme values in the growth curves. In case of multiple sources for one measurement, in particular occurring neonatally, we cross-checked all sources.

Factors known to potentially influence prenatal and/or postnatal growth were obtained from the medical records. Non-responding mothers were more often of non-Dutch origin and had a slightly lower socioeconomic status, measured by level of education, than respondents. Apart from this, we found no significant differences by response status.

GA was expressed as completed weeks of gestation. In more than 95% of the cases we calculated GA by using the last menstrual date, confirmed by early ultrasound measurements. Otherwise, clinical estimates based on last menstrual date were checked against clinical estimates after birth. Children whose GA we could not define beyond reasonable doubt were excluded from the analyses prior to drawing the sample for the present study.

### *Analysis*

We first described the sociodemographic and perinatal characteristics of the sample. Next, we assessed median growth and the variability in growth of preterm children regarding height and weight for the first 4 years of life and regarding HC for the first 1.5 years of life, per week of GA and by gender. Regarding all outcomes, measurements for the additional half year that we collected were only used to assess median growth and its variability adequately at the highest age intervals. For this analysis, we constructed separate growth models for height, weight, and HC based on the data of all preterms, by gender. We did not exclude multiples from our analyses nor did we adjust the models for multiple births.

We modeled *weight* with the LMS model, for ages 0-4 years. In this model, three parameters vary with age: the median (P50, M-curve), the coefficient of variation (CV, S-curve) and the $\lambda$ parameter from the Box-Cox transformation, which models skewness in the data (L-curve). Firstly, a model was fitted to the data of each week separately to obtain a general comprehension of the age-dependent references. After initial model exploration in GAMLSS,[15,16] we found that the age transformation log(age+0.2) yielded a minimum deviance in both boys and girls, if combined with the penalized smoother (ps).[17] We selected penalized splines with degrees of freedom being: df($\mu$)=4, df($\sigma$)=1, and df($\nu$)=1 on the basis of the worm plot.[18]

Next, we modeled *height* for the ages 0-4 years. Given calendar age and GA we assumed that height would follow a normal distribution. After initial model exploration in GAMLSS,[17,18] we found that the age transformation log(age+0.2) yielded a minimum deviance in both boys and girls, in combination with the penalized smoother,[19] and analyzing height in the original scale. We chose penalized splines with df($\mu$)=4, and df($\sigma$)=1 on the basis of the worm plot.[18] and Q-statistics.[19]

We modeled *HC* for ages 0-1.5 years assuming that it also followed a normal distribution depending on age and GA. The further procedure was similar to that for height. See **Appendix 1** for the resulting formulas for weight, height, and HC. The analyses assume that the sample is representative at each time point. Since the average participation rate was very high, the potential for any systematic bias was limited. Moreover, as far as we are aware, the reasons for missed visits were unrelated to the outcomes.

Finally, we integrated the data on median values, variation, and in the case of weight also skewness, into growth curves by means of an age grid for GAs 25-36 weeks, by gender. These formed the basis of the 12 growth charts that we constructed for boys and for girls.

## Results

**Table 1** contains the sociodemographic and perinatal characteristics of the sample and shows that our cohort consisted of more than 90% Caucasian mothers. The sample contained many multiples (30%), mostly twins (96%) and some triplets and quadruplets (4%).

**Table 1:** Characteristics of the sample used for the development of growth charts.

| | early preterms | moderate preterms | term born children | Total |
|---|---|---|---|---|
| N | 612 (26.2%) | 1123 (48.0%) | 605 (25.8%) | 2340 (100%) |
| Gender | | | | |
| boy | 314 (51.3%) | 637 (56.7%) | 300 (49.6%) | 1251 (53.5%) |
| Gestational Age | | | | |
| 25-27 | 99 (16.2%) | | | 99 (4.2%) |
| 28-29 | 186 (30.4%) | | | 186 (8.0%) |
| 30-31 | 327 (53.5%) | | | 327 (14.0%) |
| 32-33 | | 360 (32.1%) | | 360 (15.4%) |
| 34 | | 308 (27.4%) | | 308 (13.2%) |
| 35 | | 455 (40.5%) | | 455 (19.4%) |
| 38 | | | 101 (16.7%) | 101 (4.3%) |
| 39 | | | 152 (25.1%) | 152 (6.5%) |
| 40 | | | 216 (35.7%) | 216 (9.2%) |
| 41 | | | 136 (22.5%) | 136 (5.8%) |
| Maternal height | | | | |
| < -2SD | 31 (5.5%) | 75 (7.3%) | 35 (6.3%) | 141 (6.0%) |
| -2SD – -1SD | 128 (22.8%) | 199 (19.2%) | 91 (16.4%) | 418 (17.9%) |
| -1SD – +1SD | 346 (61.7%) | 652 (63.1%) | 361 (64.9%) | 1359 (58.1%) |
| 1SD – 2SD | 52 (9.3%) | 92 (8.9%) | 64 (11.5%) | 208 (8.9%) |
| > 2SD | 4 (0.7%) | 16 (1.5%) | 5 (0.9%) | 25 (1.1%) |
| Ethnicity | | | | |
| Indigenous Dutch | 539 (94.2%) | 1033 (92.0%) | 575 (94.8%) | 2186 (93.4%) |
| Former Dutch colony | 5 (0.9%) | 13 (1.2%) | 1 (0.2%) | 19 (0.8%) |
| Labour immigrant | 8 (1.4%) | 17 (1.5%) | 9 (1.6%) | 34 (1.5%) |
| Other Non-Dutch | 20 (3.5%) | 60 (5.3%) | 20 (3.5%) | 100 (4.3%) |
| Birth weight | | | | |
| Mean (SD) | 1297 (362) | 2241 (467) | 3549 (503) | 2332 (933) |
| SGA (< P2) | | | | |
| Yes | 32 (5.2%) | 30 (2.7%) | 12 (2%) | 74 (3.2%) |

In 8.1% of all cases, maternal height was unknown.
In 2.8% of all cases, ethnicity was unknown.
SGA was based on birth weight and compared to the Kloosterman curves, defined as a birth weight of more than 2SD below the mean birth weight.

Subsequently, we applied the growth models to weight, height, and HC for each GA from 25-36 and from 38-42 weeks, by gender. Regarding *weight*, the initial model per gestational week fitted the data poorly. This was due to a diminishing difference in weight gain between preterm and fullterm children, which apparently could not be modeled by an additive combination of age and GA. Therefore we added an interaction term between age and GA to the initial model. This allowed both the M and S-curves to vary smoothly over the GAs. We present the results in **Figure 1a/b**. In the entire (calendar) age-range studied, i.e. 0-4 years, median weights were lower for the former preterms across all GAs. Weight gain depended on GA since it declined with decreasing GA compared with fullterms. This pattern was the same for boys and girls. Variability, expressed as coefficient of variation, however, was greater in boys than in girls, especially at the lower GAs.

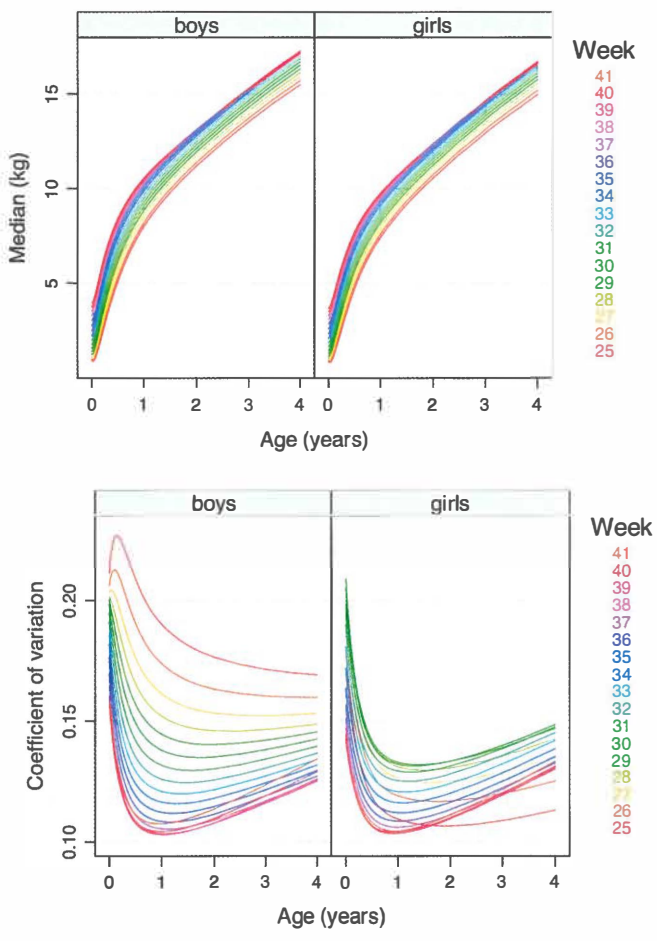



**Figure 1a/b**: Growth in weight by gestational age and gender, ages 0-4 years: fitted median (p50; upper part, a) and coefficient of variation (lower part, b) curves

Regarding *height*, the initial model per gestational week could be integrated into one common model, but in general there were fewer cases below the P50 than expected, especially for the boys. Allowance for skewness varying by age, however, did not yield a better fit. As can be seen in **Figure 2a/b**, the median heights of preterms were lower for all GAs for the entire age-range studied, i.e. 0-4 years (calendar ages of more than 4 years are not shown). Height depended on GA; it decreased with decreasing GA compared with fullterms. Growth patterns of boys and girls did not differ although variability, expressed as standard deviation, was greater in boys than in girls, especially at lower GAs.

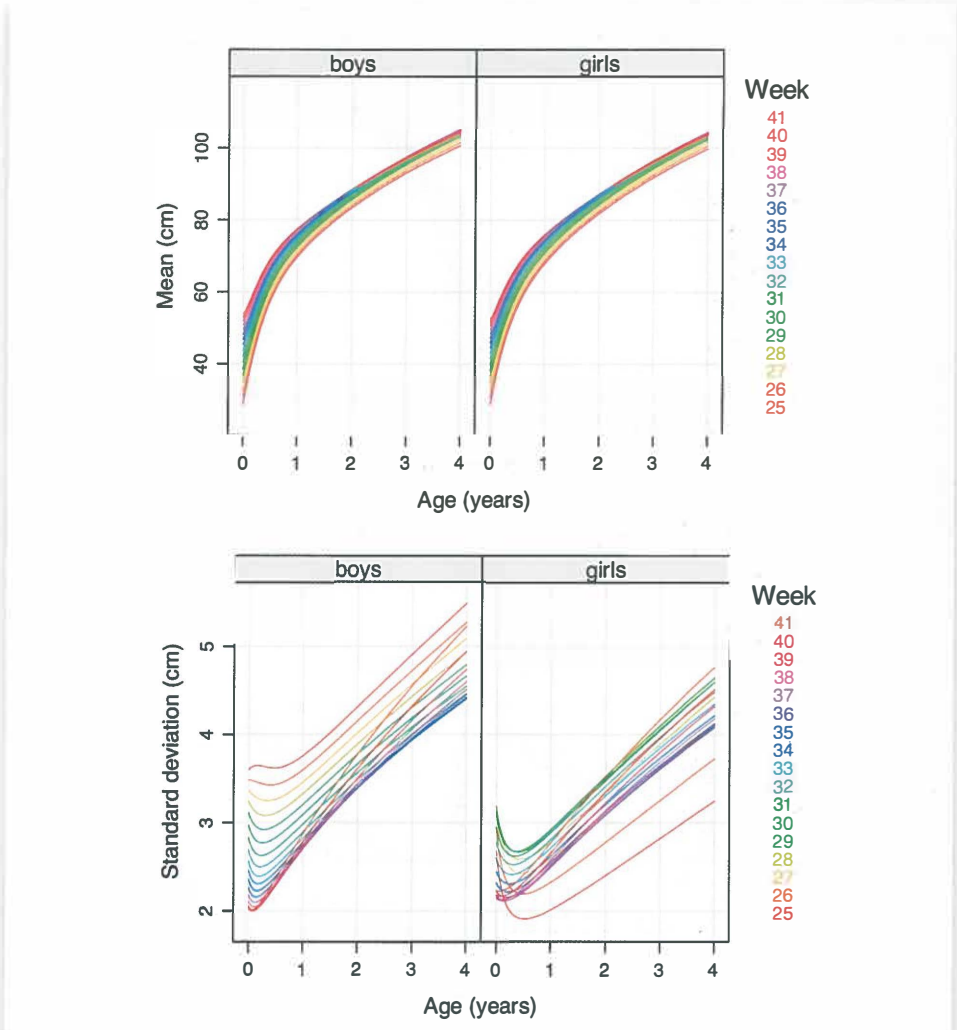
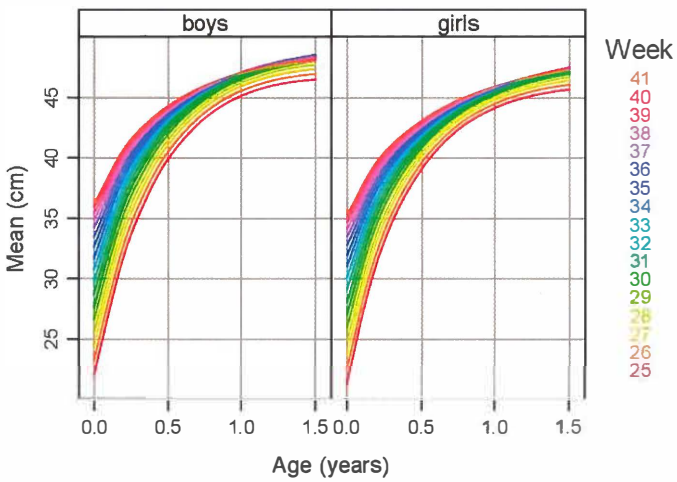



**Figure 2a/b**: Growth in length/height by gestational age and gender, ages 0-4 years: fitted median (p50; upper part, a) and standard deviation (lower part, b) curves.

Regarding *HC*, the initial model per gestational week fitted poorly. Therefore, as in the case of weight, we added an interaction term to the model between age and GA. We present the results in Figure 3a/b. The median growth in HC was lower in preterms during the first months of life. After this initial difference, however, growth in HC was comparable to fullterms. The figures per week of GA suggest that the growth of HC in-utero is reduced after week 34 of gestation. This was the same for both sexes. Variability, expressed as standard deviation, was again greater in boys than in girls, especially at the lower GAs.



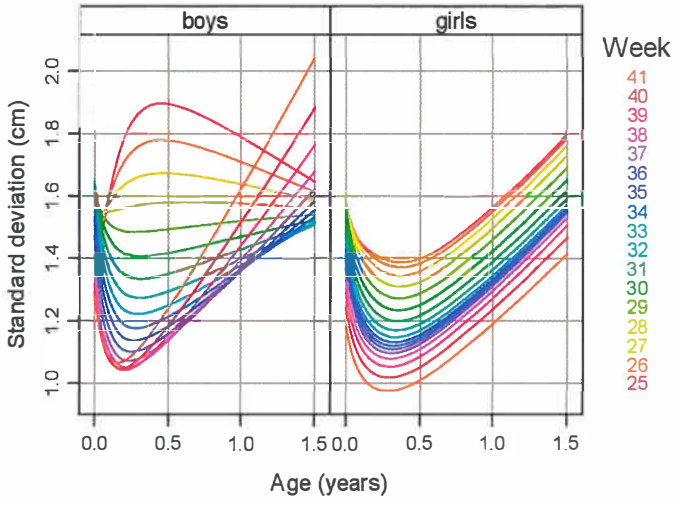




**Figure 3a/b**: Growth in head circumference by gestational age and gender, ages 0-1 years: fitted median (p50; upper part, a) and coefficient of variation (lower part, b) curves.

Finally, we integrated the L, M, and S-curves into growth curves for preterms, by GA week and by gender for ages 0-15 months. The full range of these 24 growth curves can be accessed at: http://www.tno.nl/content.cfm?context=thema&content=inno_case&laag1=891&laag2=902&item_id=1141&Taal=2. At this site similar curves are also available for fullterm children. The data underlying these curves as well as curves for ages 0-4 years are available from the authors.

## Discussion

This study demonstrated that median growth of early and moderately preterm children differed from fullterm children. Being born before 37 weeks' gestation substantially lowered the height, weight, and head circumference attained by a child at age 4. The lower the GA was, the lower the median value (percentile 50). The medians of the distributions increased continuously with increasing GAs from 25-36 weeks. On the one hand, we found that the absolute differences in centimeters or kilograms were approximately constant up to the age of 4 years, implying that the relative differences decreased. On the other hand, the differences in head circumference (measured in centimeters) diminished with age, and were small from the calendar age of six months onwards. For all three measures of growth, variability was greater in boys than in girls, particularly for the lower GAs. This study provides the most precise growth curves that are available for preterms.

Increases in weight and height for the ages 0-4 years were similar for children of different GAs. Thus, on the absolute scale there was no catch-up growth. Of course, when expressed as a percentage of the height or weight attained, the difference between the GAs groups diminished over time. It is shown consistently that early preterms have a higher prevalence of growth restraint.[4,5] Recently, this was also reported for moderate preterms.[6]

We found that the HC of preterm children, at the end of the first year, was comparable with fullterm children. Growth in HC tapers off towards the end of pregnancy and is followed by accelerated growth for the first six months after birth, during which time preterms grow more rapidly than fullterms. Other recent studies reported similar findings.[20,21] Perhaps HC growth in late pregnancy is prevented by the mother since uneventful birth depends on the HC of the fetus not being too large. Presumably, this restrictive mechanism is lacking in preterms causing HC growth not to be reduced.

We found greater variability in growth by GA among boys compared with girls. The greatest gender differences concerned the lower GAs, i.e. 30 weeks and less. Possibly this finding was a reflection of the fact that preterm boys are more susceptible than girls to those complications of preterm birth that influence growth. Other studies show a higher prevalence of predictors of abnormal growth in early preterms boys. [22,23] This explanation requires additional study.

It is well known that maternal height is associated with the child's (target) height and that short mothers (maternal height below -1SD) are more likely to have short offspring in a general population.[24] The effects of short maternal height are partly mediated through SGA birth.[25] This obviously also holds true for preterm-born children. Recently, growth in early and moderately preterm-born infants was found to be largely affected by maternal height.[6] In itself however, to our knowledge, short maternal height is not associated with preterm birth, so we did not adjust for maternal height.

A poor maternal nutritional status is associated with a lower birth weight of the offspring,[26] which might theoretically explain some of the lower weight and height of preterms. However, maternal nutritional status is generally good in the Netherlands, also in case of low socioeconomic

status in the Netherlands because of the well-developed social welfare system. It is therefore unlikely that this had a large influence on birth weights or longitudinal growth in our cohort.

The major strengths of our study were the use of longitudinal data from a large, representative community based sample including the entire range of preterm gestational ages, which provides more valid estimates of longitudinal growth of preterms than both the Niklasson and World Health Organization (WHO) charts did. The Niklasson charts have been constructed from birth weights and postnatal growth after term. The WHO charts have been mainly based on cross-sectional data regarding only healthy fullterm children of breastfeeding, non-smoking mothers living in optimal conditions for growth. The latter does not apply to most preterm-born infants. For every week of GA, from 25-36 weeks and for boys and girls separately, we constructed easy-to-use growth charts. We constructed the charts by integrating all the GAs in one model. This stabilized the estimates per GA and yielded easy-to-read, smoothed growth charts. An additional strength of our approach was that postnatal growth was not derived from growth in utero as it was in the approach of Guo et al.[9-11] Our findings clearly show that the assumption that growth in utero is similar to growth ex utero does not hold.

We also recognize some limitations. As already mentioned, our cohort consisted of over 90% Caucasian mothers. Recent studies suggested that growth charts for newborns based on data from Caucasian children, can also be used for populations of other ethnic and socio-economic backgrounds.[27,28] However, additional research is needed to support this generaliziblilty.

We did not exclude multiples from our analyses nor did we adjust the models for multiple birth, but growth patterns may vary between multiples and singletons, in particular in the first 2 years of life.[29] In the long-term, the influence of multiple birth on growth outcome is less clear than during infancy or slightly beyond, and is not associated with long-term growth restriction.[6,30] Additional research on growth patterns of preterm multiples compared with singletons might clarify this issue further.

This study has several implications. It is important to recognize that preterms will not follow growth patterns of fullterm-born children, even when corrected for gestational age. Normal growth charts are thus not useful for monitoring growth in the relatively large group of preterms. Moreover, the weight, height, and HC attained differed substantially by GA but also within a GA group. This implies an urgent need to monitor growth closely for each preterm child. Our charts portray the normal variation between children depending on their GAs. Abnormal growth in preterms can thus be identified more precisely in Caucasian populations in industrialized countries and probably also in African-American populations.[27,28] This may lead to a better targeted treatment regimen of interventions. It may also offer opportunities to optimize feeding strategies for preterm infants.

Additional research is needed to understand optimal growth and how it is influenced in preterms as preterms form such a substantial part of all children. This may help to prevent the short-term and long-term consequences of less than optimal growth, including its potential metabolic consequences.

## Conclusion

Attained weight, height, and HC are heavily dependent on GA. Variability is greater in boys, suggesting a greater vulnerability to the complications of preterm birth that influence growth. The growth charts we constructed are the most useful tool for monitoring growth in preterm children.

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## Appendix 1:

All functions for growth were programmed in R (www.r-project.org). The R code for fitting the common models was:

**Weight**

```
library(gamlss)
data <- boys
data2 <- data.frame(data,
            t.age = log(data$age+0.2),
            WE = data$GA-40,
            int = (data$GA-40)*(log(data$age+0.2)))
fit.wgt <- gamlss(
  wgt ~ ps(t.age,df=4)+ps(WE,df=1)+ps(int,df=1),
  sigma.formula = ~ ps(t.age,df=1)+ps(WE,df=1)+ps(int,df=1),
  nu.formula = ~ ps(t.age,df=1),
  data = data2, family = BCCG)
```

**Height**

```
fit.hgt <- gamlss(
  hgt ~ ps(t.age,df=4)+ps(WE,df=1)+ps(int,df=1),
  sigma.formula = ~ ps(t.age,df=1)+ps(WE,df=1)+ps(int,df=1),
  data = data2, family = NO)
```

**Head circumference**

```
fit.hc  <- gamlss(
  hc  ~ ps(t.age,df=4)+ps(WE,df=1)+ps(int,df=2),
  sigma.formula = ~ ps(t.age,df=2)+ps(WE,df=1)+ps(int,df=1),
  data = data2, family = NO)
```

The degrees of freedom were identical for boys and girls.

# 4

## Growth in small-for-gestational age preterm-born children from 0-4 years: the role of both prematurity and SGA status

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## 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=1648 preterm-born (gestational age <36 weeks, 57 SGA) and 605 term-born (12 SGA). We defined SGA as a birth weight less than -2SD (P 2.3) compared to counterparts matched for gestational age. Height, weight, and head circumference (HC) were obtained from medical records and translated to z-scores. We defined growth restriction as height or weight less than -2SD 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: -0.2 to -1.0). By contrast, preterm SGA children's z-scores were still -1.5 to -2.0. HC growth was less affected by prematurity and SGA birth (z-scores at 1 year: -0.2 to -1.4). Catch-up growth mainly took place during infancy. Approximately 40% of all preterm SGAs showed growth restriction at four 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% to 11%) persists in growth restriction (growth below the second percentile, P2.3).[1] 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. 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 four. 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 four.

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 1648 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 0-4 years were retrospectively obtained from records in Preventive Child Health Care centres and augmented by data retrieved from hospital records. During their first four years, children in the Netherlands routinely have about fifteen 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 of more than 2SD below the median (P2.3). Height and HC at birth were converted to z-scores according to the Usher and McLean curves.[12]

#### i. Longitudinal absolute gains and relative growth

To compare PT-SGA with PT-AGA and FT-SGA children, we calculated absolute gains during ages 0 to 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.

#### ii. 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 more than 2 SD below the median growth of the FT-AGAs from our cohort. We tested statistical significance using chi-square tests.

#### iii. 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 1648 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*<.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).

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

| | AGA | SGA | Total |
|---|---|---|---|
| **N** | 2196 (97.0%) | 69 (3.0%) | 2265 (100%) |
| **Gestational age** (in 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%) |
| Moderately 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%) |

### *Growth of preterm SGA children*

During infancy, i.e. the first year after birth, absolute *weight* gain of PT-SGAs was 700 g less than that of PT-AGAs (**Table 2**). During the subsequent years, their mean absolute increase in weight was 200-500 g per year less (*P*<.01). During infancy, *height* gain of PT-SGAs was 3.7 cm greater than that of PT-AGAs (*P*<.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 to 4 cm (**Table 2**).

**Table 2**: Absolute gains in weight (kg), height (cm) and head circumference, means and (standard deviations), for preterm (PT) and fullterm (FT) children during ages 0 to 4 years.

| | **Preterm** | | **Fullterm** | | ***P* values@** | |
|---|---|---|---|---|---|---|
| | SGA (n=57) | AGA (n=1591) | SGA (n=12) | AGA (n=605) | PT vs. FT | SGA vs. AGA |
| **Weight** (ages): | | | | | | |
| 0 to <1y | 6.5 (1.0) | 7.3 (1.1) | 6.6 (1.1) | 6.4 (1.1) | <.001* | <.001* |
| 1 to- <2y | 2.5 (0.7) | 3.0 (0.8) | 2.5 (0.5) | 3.0 (0.8) | .93 | <.001 |
| 2 to <3y | 1.8 (0.6) | 2.3 (0.8) | 2.4 (0.6) | 2.3 (0.8) | .27 | .003 |
| 3 to <4y | 1.7 (0.7) | 1.9 (0.9) | 1.6 (0.4) | 2.0 (0.9) | .71 | .035 |
| **Height** (ages): | | | | | | |
| 0 to <1y | 34.2 (3.6) | 30.5 (4.1) | 27.0 (2.2) | 24.9 (2.8) | <.001 | <.001 |
| 1 to <2y | 13.3 (2.2) | 13.4 (2.2) | 11.5 (0.5) | 12.8 (2.3) | .001 | .67 |
| 2 to <3y | 9.0 (1.6) | 9.6 (2.2) | 9.0 (1.4) | 9.4 (1.9) | .32 | .11 |
| 3 to <4y | 6.7 (2.2) | 6.6 (1.8) | 6.8 (2.1) | 6.3 (1.9) | .005 | .53 |
| **Head circumference** (ages): | | | | | | |
| 0 to <1y | 16.7 (2.2) | 14.6 (1.7) | 13.3 (0.0) | 11.2 (1.4) | <.001 | <.001 |

@ Mutually adjusted

* Factors PT and SGA significantly interact: *P* <.01

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**).

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

| | PT-SGA | | PT-AGA | | FT-SGA | FT-AGA | *P* values@ | |
|---|---|---|---|---|---|---|---|---|
| | Uncorrected | *Corrected* | Uncorrected | *Corrected* | | | PT vs. FT | SGA vs. AGA |
| **Weight at age:** | | | | | | | | |
| 0y | -5.2 (0.7) | *-2.2 (0.8)* | -3.2 (1.2) | *-0.3 (1.3)* | -2.5 (0.8) | 0.0 (0.9) | <.001 | <.001 |
| 1y | -2.4 (0.9) | *-1.9 (1.0)* | -0.7 (1.1) | *-0.1 (1.1)* | -0.9 (0.9) | 0.0 (1.0) | <.001 | <.001 |
| 2y | -2.1 (1.0) | *-1.7 (1.1)* | -0.5 (1.0) | *-0.0 (1.1)* | -1.0 (0.9) | 0.0 (1.0) | <.001 | <.001 |
| 4y | -1.7 (1.0) | *-1.7 (1.0)* | -0.3 (1.1) | *-0.3 (1.1)* | -1.0 (0.6) | 0.0 (1.0) | <.001 | <.001 |
| **Height at age:** | | | | | | | | |
| 0y | -6.1 (2.0) | *-2.6 (1.8)* | -3.2 (2.0) | *-0.1 (1.8)* | -1.7 (1.0) | 0.0 (1.0) | <.001 | <.001 |
| 1y | -2.3 (1.1) | *-1.7 (1.1)* | -0.8 (1.1) | *-0.1 (1.1)* | -0.6 (1.0) | 0.0 (1.0) | <.001 | <.001 |
| 2y | -1.7 (1.1) | *-1.3 (1.2)* | -0.5 (1.0) | *0.1 (1.1)* | -0.8 (0.9) | 0.0 (1.0) | <.001 | <.001 |
| 4y | -1.4 (1.0) | *-1.4 (1.0)* | -0.3 (1.1) | *-0.3 (1.1)* | -0.8 (0.8) | 0.0 (1.0) | <.001 | <.001 |
| **HC at age:** | | | | | | | | |
| 0y | -5.7 (2.3) | *-1.0 (1.3)* | -3.2 (1.6) | *0.9 (1.0)* | -1.2 (0.4) | 0.1 (0.9) | <.001 | <.001 |
| 1y | -1.2 (1.2) | *-0.7 (1.0)* | -0.3 (1.1) | *0.1(0.8)* | -0.6 (1.1) | 0.0 (1.0) | .07 | <.001 |

@ mutually adjusted, for uncorrected ages.

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).

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

| | **Preterm** | | **Fullterm** | | ***P* values**[@] | |
|---|---|---|---|---|---|---|
| | SGA (n=44) | AGA (n=1237) | SGA (n=11) | AGA (n=555) | PT vs. FT | SGA vs. AGA |
| **Weight** (ages): | | | | | | |
| 1y | 32 (72.7%) | 134 (10.8%) | 0 (0%) | 6 (1.3%) | <.001* | <.001* |
| 2y# | 25 (55.6%) | 75 (6.2%) | 0 (0%) | 4 (0.9%) | <.001* | <.001* |
| 3y# | 22 (53.7%) | 58 (4.5%) | 1 (10%) | 3 (0.6%) | <.001* | <.001* |
| 4y | 22 (38.6%) | 72 (5.0%) | 1 (9.1%) | 3 (0.5%) | <.001* | <.001* |
| **Height** (ages): | | | | | | |
| 1y | 29 (67.4%) | 155 (12.6%) | 0 (0%) | 5 (1.8%) | .06* | <.001* |
| 2y# | 21 (46.7% | 87 (7.3%) | 0 (0%) | 4 (1.5%) | <.001* | <.001* |
| 3y# | 15 (37.5%) | 54 (4.2%) | 0 (0%) | 4 (1.3%) | .001* | <.001* |
| 4y | 17 (30.4%) | 75 (5.2%) | 1 (9.1%) | 12 (2.2%) | .002* | <.001* |
| **HC** (ages): | | | | | | |
| 1y | 11 (26.8%) | 52 (4.4%) | 0 (0.0%) | 8 (2.2%) | .12 | <.001 |

@ Mutually adjusted
* Factors PT and SGA significantly interact: P <.05
# Age at which some children (15-25%) missed the assessment

*Influence of preterm birth on growth*

Preterms gained approximately 500 g more weight, 6 cm more height and 3.5cm 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*=.12) (**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 to 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. Although weight gains during infancy were less than that of AGAs and height gains exceeded that of AGAs, SGAs grew approximately 400 g per year less in the years following infancy and their height gains did no longer 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 to 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, it was affected most by prematurity (**Table 5**). Absolute increases in weight and in height were also affected in case of SGA, but only during infancy. We found no significant interaction of prematurity with SGA status, except for absolute gains during infancy and during ages 2 to 3 years.

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

| **Absolute gains**; effect sizes from ***multiple linear regression*** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Weight** | | **Height** | | **HC** | |
| Age (years) | Factor | Beta | *P* | Beta | *P* | Beta | *P* |
| 0 to <1# | PT | .351 | **<.001** | .493 | **<.001** | .305 | **<.001** |
| | SGA | -.099 | **<.001** | .130 | **<.001** | .188 | .22 |
| | PT * SGA | -.136 | **.009** | .053 | .42 | .003 | .99 |
| 1 to <2 | PT | .001 | .96 | -.097 | **.001** | | |
| | SGA | -.113 | **<.001** | -.013 | .67 | | |
| | PT * SGA | .014 | .83 | .098 | .36 | | |
| 2 to <3 | PT | -.022 | .42 | .029 | .32 | | |
| | SGA | .013 | .82 | -.045 | .12 | | |
| | PT * SGA | -.095 | **<.001** | -.016 | .86 | | |
| 3 to <4 | PT | -.009 | .71 | .071 | **.005** | | |
| | SGA | -.050 | **.033** | .016 | .53 | | |
| | PT * SGA | .015 | .79 | -.039 | .58 | | |
| **Relative growth**; effect sizes from ***multiple linear regression*** | | | | | | | |
| 0 | PT | -.772 | **<.001** | -.624 | **<.001** | -.347 | **<.001** |
| | SGA | -.188 | **<.001** | -.183 | **<.001** | -.213 | **<.001** |
| | PT * SGA | .044 | .146 | -.068 | .112 | -.105 | .32 |
| 1 | PT | -.291 | **<.001** | -.268 | **<.001** | -.144 | **<.001** |
| | SGA | -.148 | **.004** | -.099 | **.142** | -.116 | **<.001** |
| | PT * SGA | .096 | .064 | -.219 | **<.001** | -.048 | .48 |
| 2 | PT | -.209 | **<.001** | -.187 | **<.001** | | |
| | SGA | -.242 | **<.001** | -.205 | **<.001** | | |
| | PT * SGA | -.073 | .17 | -.059 | .45 | | |
| 4 | PT | -.143 | **<.001** | -.113 | **<.001** | | |
| | SGA | -.206 | **<.001** | -.179 | **<.001** | | |
| | PT * SGA | -.049 | .34 | -.055 | .30 | | |
| **Growth restriction**; effect sizes from ***multivariate logistic regression*** | | | | | | | |
| | | OR (95%CI) | *P* | OR (95%CI) | *P* | OR (95%CI) | *P* |
| 1$ | PT | | | | | 2.0 (0.9-4.3) | .07 |
| | SGA | | | | | 9.5 (3.6-25.5) | **<.001** |
| | PT * SGA | | | | | 8.0 (3.8-16.4) | **<.001** |
| 4 | PT | 9.6 (3.0-30.7) | **<.001** | 2.4 (1.3-4.5) | **.005** | | |
| | SGA | 18.4 (1.8-192.5) | **.015** | 4.4 (0.5-37.4) | .17 | | |
| | PT * SGA | 0.65 (0.1-7.3) | .65 | 1.8 (0.2-16.5) | .61 | | |

Beta: standardized regression coefficient, *P*: significance

# 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.

$ For example: at age 1 year, SGA at birth is significantly associated with growth restriction in head circumference. There is also a significant interaction of prematurity and SGA status (OR 8.0, $P < .001$).

Relative growth was affected by both predictors (**Table 5**) at all the ages and for all measures. Interactions were found only during infancy.

Growth restriction for weight and height was significantly associated with both prematurity and SGA status with odds ratios of 2.4 to 18.4 (**Table 5**). There were multiple 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; $P<.001$). 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 four, 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 incomplete and restricted to the first year after birth. The lack of further catch-up growth resulted in growth restriction. In fact, approximately 38% of all PT-SGAs remained too thin and 30% too short or both at the age of four, 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 four. This was even more evident in the PT-SGA group. This confirms findings of Hack et al on over 200 very low birth weight children at the age of 20 years.[3] Apparently, height gain is more preserved than weight gain during the first years after preterm SGA birth.

HC growth in PT-AGAs children did not differ from that of FT-AGAs, 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 and Kaur previously reported accelerated HC growth in preterms in a much smaller sample.[13,14] 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 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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# 5

## Growth and development in symmetrical and asymmetrical growth restricted preterm-born children

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### What's known on this subject

Fetal growth restriction, particularly in preterm children, is associated with delayed development and poor growth. Knowledge about the consequences of fetal growth restriction if classified by symmetry is lacking, especially in preterm-born children.

### What this study adds

In preterm children, symmetrical and asymmetrical growth restriction at birth results in poorer growth later in life. Both groups are at considerable risk of developmental delay because their long-term development is independent of their head circumference at birth.

## Abstract

***Objective***: To determine how symmetrical (proportionate) and asymmetrical (disproportionate) growth restriction influence growth and development in preterms from birth to four years.

***Design/Methods***: Community-based cohort study of 810 children consisting of 86 symmetrical growth restricted (SGR), 61 asymmetrical growth restricted (AGR), and 663 non-growth restricted (NGR) preterms, born during 2002 and 2003. Symmetrical growth restriction was defined as a birth weight (BW) below the 16$^{th}$ percentile (-1 SD) in comparison to fullterms and a head circumference (HC) z score not exceeding the infant's BW z score by > 1 SD. Asymmetrical growth restriction was defined as a HC z score exceeding that for BW by > 1 SD as a proxy of brain-sparing. Developmental delay was assessed by the Ages-and-Stages-Questionnaire at four.

***Results***: Longitudinal gains in weight and height were similar for SGRs and AGRs and less in comparison to NGRs. At four, z scores for weight were -1.1 for SGRs and -0.7 for AGRs versus -0.3 for NGRs. Z scores for height were -0.8 and -0.5 versus -0.2. Gains in HC were 2 cm more in SGRs, but at one year they were -0.2 versus 0.2 (AGRs) and 0.1 (NGRs). Developmental delay increased with odds ratios of 2.5 (95% confidence intervals, 1.1-6.0) for SGRs and 2.1 (95% confidence intervals, 0.7-5.9) for AGRs.

***Conclusions***: Weight and height gains were similar for AGRs and SGRs but poorer compared to NGRs. SGRs caught up on HC. Developmental delay was more likely in growth restricted preterms and independent of HC at birth.

## Introduction

Small-for-gestational age (SGA) birth is associated with neurological sequels, [1-3] even though children born SGA are known for their ability to catch up on weight and height.[4,5] Nevertheless, in 10% of fullterm (FT) children and in up to 40% of preterm (PT) children this catch-up is insufficient.[6,7] Regarding head circumference (HC) SGAs, despite some catch-up, also persist in having smaller heads in comparison to children born appropriate-for-gestational age (AGA).[7] In PT-born children in particular, being SGA is associated with poorer neurodevelopmental outcomes on e.g., motor and cognitive functions, communication skills, and behavioral conduct.[3,8]

We distinguish two types of growth restriction: proportionate or symmetric growth restriction (SGR) and disproportionate or asymmetric growth restriction (AGR).[9,10] It is assumed that symmetry or asymmetry depends on the timing and the origin of fetal growth restriction. During early pregnancy adversities such as viral infections or genetic abnormalities will presumably result in SGR.[9,10] The effect of placental insufficiency and/or severe nutritional deprivation depends on its onset during pregnancy. If it occurs during early pregnancy it may lead to SGR.[9,10] Conversely, if it occurs during late pregnancy it may lead to AGR. In AGR, which is more common in late pregnancy, the child's weight is disproportionate to its HC due to brain-sparing.[9,10] An explanation for apparent growth restriction may be the constitutionally small child.[9] All forms of growth restriction can result in spontaneous or artificial PT birth.[9-11]

Although there is a considerable body of evidence on growth and development in SGA infants, longitudinal studies on growth and development in growth-restricted children after classification at birth for symmetry in growth, are scarce. Early prediction of outcomes and specific therapies can only be offered confidently if backed by sufficient and solid evidence on the specific subgroup of PT-born children concerned.

Our primary aim was to describe absolute gains and relative growth in weight, height, and HC from birth to the age of four in PT-born children who were either SGR or AGR at birth compared to PT-born non-growth restricted (NGR) controls. Additionally, we aimed to determine what type of growth restriction had affected development most at four. We expected that long-term growth and development would be poorest in SGR children.

## Methods

### *Study design, sampling procedure, and power considerations*

This study was part of the Longitudinal Preterm Outcome Project (LOLLIPOP), a large, community-based cohort study on growth and neurocognitive development in PT children in the Netherlands. The LOLLIPOP sample consists of early and moderate PTs born before 36 weeks' gestation and randomly selected FT controls, born between 1 January 2002 and 31 December 2003. The children were included during visits to well-child clinics at the age of four. For the present study we selected 810 PT-born children for whom data were available on HC at birth and on development at four. Regarding their development this subsample was comparable to the group of PT-born children for whom no HC measures were available at birth - differences were tested using the chi-square test. We classified the selected children according to the type of growth restriction based on their weight and HC at birth.

The review board of University Medical Center Groningen approved LOLLIPOP and written informed consent was obtained from all parents.

### *Measures and procedure*

Gestational age was expressed as the number of completed weeks of gestation. Children whose gestational age could not be defined beyond reasonable doubt were excluded.

Data on growth during the first four years after birth were obtained retrospectively from the medical records kept by the preventive child health care centers and augmented by data retrieved from hospital records. During their first four years, children in the Netherlands routinely have about fifteen well-child check-ups. The check-ups include assessment of height, weight, and HC (the latter until closure of the large fontanel). Height and weight is measured with standardized measuring devices, i.e. an infantometer or stadiometer. Up to the age of 15 months the children are examined while supine. Thereafter the children stand upright in their socks. They are weighed unclothed. We analyzed an average of 9.9 standardized measurements per child.

We prepared our data by converting birth weights (BWs), heights, and HCs to z scores (mean = 0, SD = 1) according to gestational age using the medians and SDs of the FT controls in the LOLLIPOP cohort.[12] Classifications by type of growth restriction were made as follows: SGR was defined as a BW > 1 SD below the median (< 16$^{th}$ percentile, P 16) corrected for gestational age and a HC at birth comparable to the child's BW, i.e. not exceeding the BW by > 1 SD (**Table 1**). Asymmetrical growth restriction (AGR) was defined as any BW > 1 SD less than the corresponding HC, as a proxy of brain-sparing. In case a BW was higher than the P 16 (> - 1 SD) and any HC not exceeding the BW by > 1 SD, the child was classified as NGR.

**Table 1**: classification of growth restriction according to body proportion using birth weight (BW) and head circumference (HC) for symmetrical growth restricted (SGR) and asymmetrical growth restricted (AGR) children.

| | BW | HC |
|---|---|---|
| SGR (n=86) | <-1SD | <-1SD or less than 1SD higher than BW |
| AGR (n=61) | Any BW | >1SD higher than BW |
| NGR (n=663) | BW > -1SD | Any HC less than 1SD higher than BW |

The Dutch four years version of the Ages and Stages Questionnaire (ASQ) was used to measure development at four. It is a parent-completed developmental screening tool. Its reliability and validity has been documented.[12-14] The ASQ measures development in five domains: communication, fine and gross motor ability, problem-solving ability, and personal-social functioning. The scores on each domain add up to an ASQ total score. We considered an ASQ total score of > 2 SDs below the mean score for the Dutch reference group as a sign of developmental delay. For more detailed information on sampling and procedures we refer to our previous publications.[5,7,15-17]

*Statistical analysis*

i. Longitudinal absolute gains and relative growth

To describe longitudinal growth during the first four years of life we assessed each child's weight and height at birth and HC within the first week of life, and again at calendar ages one year (± 30 days), two years (± 61 days), three years (± 61 days), and between three years and ten months (± 91 days). HC was measured up to the age of one year (± 30 days), i.e. shortly before closure of the large fontanel.

In order to compare SGR with AGR and NGR PT-born children, we first calculated absolute gains and relative weights, heights, and HCs from birth to four years. Absolute gains were defined as the number of kilograms or centimeters gained during a one year period. Relative weights, heights, and HCs were defined as the z score that a child had reached at a certain age compared to the NGR FT-born children from our own cohort (data not shown). Next, we calculated relative growth, defined as the change in z score, also during a one year period. We performed all analyses with and without adjustment for prematurity (i.e. the number of weeks born too early). We determined the statistical significances for all groups using *F* tests in ANOVA.

ii. Development of growth restricted preterm-born children

We compared the long-term development of growth restricted PT-born children, be they SGR or AGR, to that of their PT-born NGR counterparts by assessing the proportion of children with abnormal total scores on the ASQ. We used multiple logistic regression models adjusted for maternal height, multiple birth, gender, and socio-economic status for these analyses. For socio-economic status we used maternal education level (high/normal versus low) and family income (high/normal versus low). The factors that were significantly associated ($P < .15$) with abnormal ASQ total scores in the univariate analyses were included in the multivariate models. Within these models, we corrected for gestational age differences by analyzing early PT versus moderate PT birth.

All analyses were done with SPSS for Windows (SPSS 19, www.spss.com).

## Results

*Background characteristics*

Our study group consisted of 810 PT-born children, 147 of whom were growth restricted at birth (**Table 2**). Symmetrical growth restriction occurred more often than asymmetrical growth restriction, 10.8% versus 7.6%, respectively.

**Table 2:** Characteristics of the total sample and proportions (% of the group) for symmetrical growth restricted SGR, asymmetrical growth restricted (AGR) and non growth restricted (NGR) children at birth. The % have been rounded.

| | SGR | AGR | NGR | Total |
|---|---|---|---|---|
| **N** | 86 (10.8%) | 61 (7.5%) | 663 (81.8%) | 810 (100%) |
| **Gestational age** (in weeks) | | | | |
| 25-31 | 31 (9.9%) | 26 (8.3%) | 255 (81.7%) | 312 (100%) |
| 32-35 | 55 (11.0%) | 35 (7.0%) | 408 (81.9%) | 498 (100%) |
| **Gender** | | | | |
| female | 43 (11.4%) | 24 (6.4%) | 310 (82.2%) | 377 (100%) |
| male | 43 (9.9%) | 37 (8.5%) | 353 (81.5%) | 433 (100%) |
| **Multiples/singletons** | | | | |
| singletons | 65 (11.8%) | 46(8.3%) | 442 (79.9%) | 553 (100%) |
| twins | 19 (7.9%) | 15 (6.3%) | 206 (85.8%) | 240 (100%) |
| triplets/quadruplets | 2 (11.7%) | 0 (0%) | 15 (88.3%) | 17 (100%) |
| **Maternal Height** | | | | |
| <-1SD | 20 (12.9%) | 12 (10.8%) | 123 (79.4%) | 155 (100%) |
| -1SD - +1SD | 27 (10.1%) | 13 (4.9%) | 228 (85.1%) | 268 (100%) |
| > +1SD | 9 (9.7%) | 10 (7.7%) | 74 (79.6%) | 93 (100%) |
| **Socioeconomic status** | | | | |
| *Maternal education level* | | | | |
| normal/high | 70 (11.8%) | 40 (6.8%)* | 481 (81.4%) | 591 (100%) |
| low | 16 (7.3%) | 21 (9.6%)* | 181 (83.0%) | 218 (100%) |
| *Family income* | | | | |
| normal/high | 80 (10.4%) | 58 (7.5%) | 634 (82.1%) | 772 (100%) |
| low | 6 (15.9%) | 3 (7.9%) | 29 (76.3%) | 38 (100%) |

* $P < .05$

*Growth in growth restricted preterm-born children*

We compared absolute gains in weight and height in SGR and AGR PT-born children to those of the NGR PT-born control group from birth to four years of age (**Table 3**). Relative gains in weight and height in SGRs and AGRs was greater than in NGRs. The two groups caught up towards the median of the NGR PT-born control group (**Table 3**).

**Table 3**: Absolute gains in weight (kg), height (cm) and head circumference, means and (standard deviations), and relative growth (delta z-scores) for symmetrical (SGR) and asymmetrical growth restricted (AGR), and non growth restricted (NGR) preterm children during ages 0 to 4 years.

| | Growth restricted | | | | Non growth restricted (NGR) | | *P* values | |
|---|---|---|---|---|---|---|---|---|
| | SGR (n=86) | | AGR (n=61) | | (n=663) | | SGR vs. AGR | |
| | Absolute | Relative | Absolute | Relative | Absolute | Relative | Absolute | Relative |
| **Weight (ages):** | | | | | | | | |
| 0 to <1y | 6.9 (1.1) | 2.9 (0.9) | 7.1 (0.9) | 2.9 (0.9) | 7.3 (1.1) | 2.6 (1.2) | .26 | .74 |
| 1 to- <2y | 2.7 (0.7) | 0.2 (0.5) | 2.9 (0.7) | 0.3 (0.5) | 3.0 (0.8) | 0.3 (0.6) | .11 | .47 |
| 2 to <3y | 2.1 (0.7) | 0.1 (0.4) | 2.2 (0.7) | 0.1 (0.3) | 2.3 (0.8) | 0.1 (0.4) | .68 | .24 |
| 3 to <4y | 1.8 (0.7) | 0.1 (0.3) | 1.8 (0.8) | 0.1 (0.4) | 1.9 (0.9) | 0.1 (0.4) | .79 | .76 |
| Total gains | 13.4 (2.0) | 3.2 (1.0) | 14.1 (2.1) | 3.3 (1.2) | 14.6 (2.2) | 2.9 (1.4) | .05 | .80 |
| **Height (ages):** | | | | | | | | |
| 0 to <1y | 32.4 (3.4) | 3.5 (1.4) | 31.7 (4.6) | 3.1 (2.0) | 30.8 (4.0) | 2.7 (1.7) | .39 | .31 |
| 1 to <2y | 13.0 (2.1) | 0.4 (0.7) | 13.1 (1.8) | 0.3 (0.6) | 13.4 (2.1) | 0.3 (0.7) | .87 | .41 |
| 2 to <3y | 9.2 (1.9) | 0.2 (0.5) | 9.2 (2.0) | 0.1 (0.5) | 9.6 (2.0) | 0.1 (0.5) | .89 | .49 |
| 3 to <4y | 6.9 (1.6) | 0.1 (0.4) | 6.7 (1.9) | 0.1 (0.5) | 6.5 (1.7) | 0.0 (0.4) | .61 | .67 |
| Total gains | 61.3 (4.6) | 4.1 (1.6) | 60.8 (5.5) | 3.6 (2.2) | 60.0 (5.1) | 3.1 (1.9) | .57 | .22 |
| **Head circumference (ages):** | | | | | | | | |
| 0 to <1y | 17.5 (2.4) | 5.8 (2.4) | 15.5 (2.9) | 3.8 (2.7) | 15.9 (2.4) | 4.3 (2.3) | **<.001** | **<.001** |

At ages one to four, however, their absolute and relative growth never significantly exceeded that of NGRs and no further catch-up was evident. This resulted in significantly lower z scores for all measures (**Table 4**). At four median weights and heights for AGRs and SGRs were 0.3 to 0.8 SDs lower, compared to those of NGRs, with worst outcomes for SGRs.

**Table 4**: Relative weight, height, and HC in z-scores: means and (standard deviations) during ages 0 to 4 years, by age (calendar ages, uncorrected for prematurity and *corrected for prematurity,* respectively).

| | **Growth restricted** | | | | **Non growth restricted (NGR)** | | ***P* values** | |
|---|---|---|---|---|---|---|---|---|
| | **SGR (n=86)** | | **AGR (n=61)** | | **n=663** | | **SGR vs. AGR** | |
| | Uncorrected | *Corrected* | Uncorrected | *Corrected* | Uncorrected | *Corrected* | Uncorrected | *Corrected* |
| **Weight at age:** | | | | | | | | |
| 0y | -4.4 (0.9) | *-1.5 (1.0)* | -4.1 (1.3) | *-1.1 (1.3)* | -3.2 (1.1) | *-0.3 (1.1)* | .07 | **.036** |
| 1y | -1.6 (1.1) | *-1.0 (1.2)* | -1.2 (1.1) | *-0.6 (1.2)* | -0.7 (1.0) | *-0.1 (1.0)* | .06 | .06 |
| 2y | -1.4 (1.1) | *-1.0 (1.2)* | -0.9 (1.1) | *-0.5 (1.2)* | -0.4 (1.0) | *0.0 (1.0)* | **.023** | **.024** |
| 4y | -1.1 (1.1) | *-1.1 (1.1)* | -0.7 (1.2) | *-0.7 (1.2)* | -0.3 (1.1) | *-0.3 (1.1)* | .06 | .06 |
| **Height at age:** | | | | | | | | |
| 0y | -4.8 (1.6) | *-1.5 (1.5)* | -4.3 (2.4) | *-1.0 (2.4)* | -3.4 (1.9) | *-0.2 (1.7)* | .20 | .20 |
| 1y | -1.7 (1.2) | *-1.0 (1.2)* | -1.1 (1.1) | *-0.4 (1.2)* | -0.8 (1.0) | *-0.1 (1.1)* | **.007** | **.008** |
| 2y | -1.2 (1.0) | *-0.7 (1.1)* | -0.8 (1.0) | *-0.2 (1.2)* | -0.4 (1.0) | *0.2 (1.1)* | **.016** | **.018** |
| 4y | -0.8 (1.1) | *-0.8 (1.1)* | -0.5 (1.1) | *-0.5 (1.1)* | -0.2 (1.0) | *-0.2 (1.0)* | .10 | .10 |
| **HC at age:** | | | | | | | | |
| 0y | -6.6 (2.7) | *-1.4 (1.6)* | -4.2 (3.2) | *0.1 (2.2)* | -4.6 (2.4) | *-0.1 (1.5)* | **<.001** | **<.001** |
| 1y | -0.7 (1.1) | *-0.2 (0.9)* | -0.2 (1.1) | *0.2 (0.9)* | -0.3 (1.0) | *0.1 (0.8)* | **.006** | **.012** |
| 4y | -0.4 (1.0) | *-0.4 (1.0)* | 0.2 (1.2) | *0.2 (1.2)* | 0.2 (1.0) | *0.2 (1.0)* | **.003** | **.003** |

On comparing the two growth restricted groups we found that absolute gains in weight and height were comparable during the first four years of life. Starting with lower z scores at birth, median growth of SGRs at four was still 0.3 to 0.4 SDs lower than that of AGRs.

Regarding HC, SGRs showed accelerated growth in comparison to AGRs and NGRS. From a lower starting point, the absolute gains and the increase in z scores were largest for SGRs. By and large, these measures were mostly similar for AGRs in comparison to NGRs. Despite their rapid growth, the HCs of SGRs were still 0.3 to 0.4 SDs lower than those of AGRs and NGR after correction for prematurity ($P$ = .006).

*Associations with developmental delay according to type of growth restriction*

At birth, growth restricted PTs, be they SGRs or AGRs, had an increased risk of developmental delay at the age of four as measured by the ASQ total score compared to their NGR counterparts matched for gestational age (**Table 5**). After adjustment for confounders, the odds ratio (OR) for developmental delay for PTs born SGR was 2.5 (95% confidence interval, CI, 1.1-5.9, $P < 0.05$). Although not statistically significant, the OR for PTs born AGRs, still pointed in the direction of an increased risk of developmental delay compared to NGR PT-born children; the OR was 2.1 (95% CI, 0.7-6.0) and $P = .16$.

**Table 5:** Proportion of the group (%) with normal and abnormal ASQ total scores and logistic regression analyses for abnormal ASQ total scores.

| | Total ASQ score | | Crude OR (95% CI, *P-values*)* | Adjusted OR (95% CI, *P-values*)@ |
|---|---|---|---|---|
| | normal | abnormal | | |
| **Logistic regression analyses::** | | | | |
| *Birthweight group:* | | | | |
| No GR (n = 663) | 603 (91.0%) | 60 (9.0%) | 1.0 | 1.0 |
| Symmetrical GR (n = 86) | 74 (86.0%) | 12 (14.0%) | 1.63 (0.84 - 3.17, *P* =.15) | 2.54 (1.10 - 5.88, *P* =.028) |
| Asymmetrical GR (n = 61) | 51 (83.6%) | 10 (16.4%) | 1.97 (0.95 - 4.08, *P* =.07) | 2.11 (0.74 - 5.99, *P* = .16) |

@ Adjusted for differences in gestational age, gender, maternal height, and maternal education level

## Discussion

We demonstrated that up to the age of four, SGR and AGR PT-born children failed to catch up on weight and height sufficiently, nor could they keep up with the growth velocity of their NGR counterparts. The HC growth of SGRs exceeded that of AGRs and NGRs, but still remained lower at the age of one. Our results also showed that growth restriction at birth was associated with poorer developmental outcome at four, independent of the child's HC at birth. Growth restricted PT children who were classified by symmetry have not been studied often and we managed to provide answers to several questions.

In SGRs and AGRs, after correcting for prematurity, growth was characterized by comparable absolute and greater relative gains in weight and height during infancy, followed by failure to catch up sufficiently during subsequent years. On the measures both groups had poorer outcomes in comparison to NGRs. This means that although the etiology of intrauterine growth restriction differs, any underlying pathology or time of onset can result in poorer long-term growth [18,19]. In comparison to NGRs, all children, be they growth restricted or not, caught up on weight and height during infancy, but failed to keep this up during subsequent years. This is in line with the concept of "transient catch-up growth" described by Harding et al. [20] It also reflects that long-term outcomes of gains in weight and height beyond the end of the first year could turn out considerably less favorable.

Contrastingly, for SGRs in comparison to AGRs and NGRs, growth in HC was characterized by accelerated growth. The AGR and NGR groups, after correcting for prematurity, were born with a HC normal for their gestational age. SGRs, born with smaller heads, showed spectacular catch-up growth in HC at the end of their first year. Nonetheless, they failed to catch up completely with their AGR and NGR counterparts. Recently, this phenomenon was also reported for FT SGRs.[21] From this perspective, gestational age did not seem to play a major role in HC growth in SGRs.

Developmental delay at the age of four was more likely in case of both symmetrical and asymmetrical growth restriction at birth. The risk for developmental delay increased more than two-fold in the two groups, even after adjustment for confounders. Much to our surprise, we were unable to demonstrate a difference in the risk of developmental delay between the two growth restricted groups. We offer three explanations for the heightened risk of long-term developmental delay. The first explanation being that the catch-up on weight and height in the two groups was insufficient to fully guarantee their normal development, as we found that SGRs and AGRs had similar growth patterns in weight and height. This growth pattern did not facilitate gains that caught up completely with the median of NGRs from birth to four years, and catch-up was associated with a more favorable developmental outcome.[3,22-24]

Second, we speculate that the accelerated HC growth seen in SGRs and their catch-up approaching, but not actually reaching, the medians of AGRs and NGRs, safeguarded these children from additional developmental delay. Based on their HC at birth as a proxy of brain-sparing, we expected less developmental delay in AGRs. A normal HC at birth combined with appropriate HC

growth during the first year, has been shown to protect against poorer developmental outcome, especially in PT children.[3,22-24] Despite normal HC growth in AGRs, this was not the case for the AGRs in our sample. Developmental delay was independent of birth-HC. Accelerated growth of HC in SGRs possibly reflected postnatal brain-sparing. Recently, Klaric et al. reported that in AGRs slower HC growth precedes poorer developmental outcome.[24] Accelerated HC growth may have the opposite effect.

The third explanation may be that fetal growth restriction caused irreversible damage to the developing brain. As a consequence, in case of AGR, brain-sparing was insufficient to fully prevent the child from developmental delay. Nevertheless, evidence on the exact mechanisms of growth and development in growth restricted PT-born children does not as yet allow us to fully understand their outcomes. Further research is needed.

The major strengths of this study were its large sample of growth restricted PT-born children over the entire range of GAs and its community-based design. Moreover, we analyzed growth longitudinally and assessed development using a validated, easy to fill-out developmental screener.[25]

Our study also had some limitations. First, no data on fetal growth were available to us. Therefore, we were unable to differentiate AGRs from normal children with a large HC, nor SGRs from constitutionally small children. Even so, we expect that the proportion of misclassified children was small. Second, we used a rather broad definition of symmetrical growth restriction, i.e. a BW < P 16. This definition could have been stricter by using a BW < P 10 or even < P 2.3. A stricter definition might have led to larger differences.

Our study has several implications. Growth restricted children should be closely monitored as they seem to have an additional risk of growth restriction in both weight and height as well as developmental delay, irrespective of the type of growth restriction or its origin. As developmental delay at the age of four was independent of the child's HC at birth, we might need to take this into account when counseling parents on developmental outcomes in growth restricted children.

Further research is needed to elucidate the effects of growth restriction in PT-born children. Possibly growth restricted children should not be classified by symmetry. It underestimates the sequels of growth restricted birth in AGRs and it also underestimates the ability of catch-up growth in HC and possible developmental protection in SGRs. From this perspective, preventing fetal growth restriction might be the key to preventing poor outcomes in PT-born children.

## Conclusion

Gains in weight and height were similar in SGR and AGR PT-born children and poorer than that of NGR PT-born children. The accelerated HC growth of preterm-born SGR children facilitated its catch-up. Developmental delay was more likely in growth restricted PT-born children and was independent of HC at birth.

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# 6

## Longitudinal growth and development of large for gestational age preterm and fullterm-born children

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### What's known on this subject

Preterm birth is negatively associated with development and growth. Particularly small-for-gestational age (SGA) preterms are at risk for delays in development and growth, whereas knowledge about the consequences of large-for-gestational age (LGA) preterm birth is lacking.

### What this study adds

During infancy, growth in height, weight, and head circumference of LGA preterms was well-balanced and sufficient. Subsequently, however, weight gain accelerated and resulted in high body-mass indices. LGA birth in preterm and fullterm children resulted in less developmental delay.

## Abstract

***Objective***: To determine how growth of large-for-gestational age (LGA) preterm children was affected by their preterm birth and LGA status and to assess the association of LGA birth with developmental delay.

***Patients and Methods***: A community-based cohort study of 1302 preterm (PT) and 489 fullterm (FT) children, born between January 2002 and June 2003.

***Results***: We found that growth in height, weight, and head circumference (HC) of LGA PTs was well-balanced during infancy and that weight gain accelerated during subsequent years. This led to high body-mass indices (BMIs) comparable to those of LGA FTs. In the same gestational age group, being born LGA was associated with a better developmental outcome than being born AGA. Compared to the AGA FT reference group, the crude odds ratio (OR) for developmental delay was 0.2 (95% confidence interval (CI), 0.03–1.74) for LGA FTs, whereas it was 1.2 (95% CI, 0.51–2.97) for LGA PTs and 2.2 (95% CI, 1.38–3.58) for AGA PTs. After adjusting for confounders, LGA birth still reduced the risk of developmental delay.

***Conclusions***: The growth patterns of LGA preterm-born children are distinctly different from other PT or FT children. In particular, we found substantially greater weight gains and relatively higher BMIs in the group that had already been exposed to metabolic risks based on its gestational age. The development of LGA children was less affected than that of AGA children. Birth weight and sufficient increase in HC may have been beneficial to their development.

## Introduction

Preterm birth is negatively associated with various neurodevelopmental outcomes such as motor skills, problem solving, and communication.[1-3] Preterm birth is also a predictor of poor growth and even long-term growth restriction in both early and moderately preterm-born children.[4-6] On the one hand, SGA birth (birth weight <10$^{th}$ percentile) as a proxy for intrauterine growth restriction, is strongly associated with both developmental delay and poor growth.[7,8] On the other hand, LGA birth (birth weight >90$^{th}$ percentile) as a proxy for intrauterine overgrowth, is also considered to predict a negative outcome[9] even though knowledge about the consequences of LGA preterm 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.[10] 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.[11] Third, hypoglycemia and iron deficiency are seen more often in LGA newborns and may lead to a higher prevalence of specific cognitive impairments.[12,13] These findings are based on a limited number of studies on LGA FT children. It remains unclear whether these risks do indeed compromise development of LGA children in later life. Even less is known about growth in LGA children, particularly in that of PTs. LGA birth seems to carry the risk of obesity. To date, however, all studies on growth were restricted to FT children.[14,15]

Considering the likelihood of the risk of 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 preterm birth and LGA status. Our second aim was to assess the association of LGA at birth in PTs and FTs with their development at four years of age. To achieve these aims we compared absolute gains and relative growth in weight, height, HC, and BMIs in LGA PT children (LGA PTs) with three groups: appropriate-for-gestational age (AGA) PT children (AGA PTs), LGA FT children (LGA FTs), and AGA FT controls (AGA FTs). Developmental was assessed by the Ages and Stages Questionnaire (ASQ) at 48 months. We hypothesized that LGA PTs grew more slowly and showed more developmental delay 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 controls. All children were born between 1 January 2002 and 31 December 2003. For every two PTs we selected one FT control. The children were included during visits to well-child clinics at the age of four.

The cohort size was based on estimates of numbers needed to compile growth curves for PT children in the Netherlands, as previously described [4,16] and led to a planned inclusion of 500 early and 1000 moderately preterm-born children. This enabled us to detect a difference in growth restraint between PT and fullterm-born children per week GA for boys and girls separately, with power 80% at $P$ =.05. For the present study, longitudinal growth data as well as developmental data, were available for 1302 PT (GA 25-36 weeks) and 489 FT children.

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

### *Measures and procedure*

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

Data on growth during the children's first four years were obtained retrospectively from records kept at the well-child clinics and augmented by data retrieved from hospital records. During their first four years, children in the Netherlands routinely have about fifteen 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 onwards, the children stand upright and wear only socks. Weight is measured undressed.

We analyzed more than 38500 standardized measurements with an average of 9.9 measurements per child.

We used the Dutch four-year version of the Ages and Stages Questionnaire (ASQ) to assess development at the age of four. The ASQ is a parent-completed developmental screening tool. Its reliability and validity has been documented in at least two studies.[17,18] The ASQ assesses development in five domains: communication, fine motor, gross motor, problem-solving ability, and personal-social functioning. The scores on each domain add up to an ASQ total-problems score. A score of >2 SDs below the mean score for the Dutch reference group was considered to indicate developmental delay. For more detailed information on sampling and procedures please refer to our previous publications.[1,4,12,16,19]

*Statistical analysis*

We prepared our data by converting birth weights, heights, and HCs to *z* scores (mean = 0; SD = 1) according to gestational age 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 (i.e. 90$^{th}$ percentile, P90). Children with a birth weight of more than 1.6 SD below the median (i.e. 10$^{th}$ percentile, P10, SGA children) were excluded from there analyses. Finally, the BMI of each child was calculated with the formula: BMI = weight/ (height$^2$).

In order to describe longitudinal growth during the first four 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 one year (± 30 days), two years (± 61 days), three years (± 61 days), and three years and 10 months (± 91 days). HC was measured up to the age of one year (± 30 days), shortly before closure of the large fontanel.

i. Longitudinal absolute gains and relative growth

To compare PT LGA with PT AGA and FT LGA children, we first calculated the absolute gains per group from birth to four years. Absolute gains were defined as the number of kilograms or centimeters gained per one year period for weight, height, and HC. Relative growth was 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 relative growth as BMI to determine whether the weight of LGA-born children weight was proportional to their height. We performed all analyses with and without adjusting for PT birth (i.e. the number of weeks born too early). Next, we determined statistical significances, using *F* tests in ANOVA.

ii. Influence of preterm 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 growth were analyzed using *F* tests in ANOVA. All measures at all ages were analyzed separately using LGA and PT as predictors, together with the interaction between these two variables.

iii. Development of LGA-born children

To compare the long-term development of LGA PTs and FTs to their counterparts matched for gestational age, we assessed the proportion of children with abnormal total scores on the ASQ. In these analyses, we used multivariate logistic regression models in which we also adjusted for maternal height, multiple birth, gender, and socio-economic status. For the latter, we included maternal education level (high/normal vs. low) and family income (high/normal vs. low). The characteristics that were univariately significantly associated ($P$<.15) with abnormal ASQ total scores were included in the multivariate models.

All analyses were done with SPSS 19 for Windows (www.spss.com).

## 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 amongst them: 373 twins (28.5%) and 20 triplets and quadruplets (1.6%). Within the PT group, LGA children were more likely to be singleton, male, and moderately preterm-born (*P*<.01).

**Table 1**: Characteristics of the total sample: numbers and proportions (%) of appropriate and large-for-gestational age children at birth

| | AGA | LGA | Total |
|---|---|---|---|
| **N** | 1598 (89.2%) | 193 (10.8%) | 1791 (100%) |
| **Gestational age** (in weeks) | | | |
| 25-31 | 436 (95.8%) | 19 (4.2%) | 455 (100%) |
| 32-35 | 754 (89.0%) | 93 (11.0%) | 847 (100%) |
| 38-41 | 408 (83.4%) | 81 (16.6%) | 489 (100%) |
| **Gender** | | | |
| Early preterms | | | |
| female | 222 (97.4%) | 6 (2.6%) | 228 (100%) |
| male | 214 (94.3%) | 13 (5.7%) | 227 (100%) |
| Moderate preterms | | | |
| female | 325 (89.8%) | 37 (10.2%) | 485 (100%) |
| male | 429 (88.5%) | 56 (11.5%) | 362 (100%) |
| Fullterms | | | |
| female | 209 (83.9%) | 40 (16.1%) | 249 (100%) |
| male | 199 (82.9%) | 41 (17.1%) | 240(100%) |
| **Multiples/singletons** | | | |
| Early preterms | | | |
| singletons | 287(94.7%) | 16 (5.3%) | 303 (100%) |
| twins | 142 (97.9%) | 3 (2.1%) | 145 (100%) |
| triplets/quadruplets | 7 (100%) | 0 (0%) | 7 (100%) |
| Moderately preterms | | | |
| singletons | 518 (85.5%) | 88 (14.5%) | 606 (100%) |
| twins | 223 (97.8%) | 5 (2.2%) | 228 (100%) |
| triplets/quadruplets | 13 (100%) | 0 (0%) | 13 (100%) |
| Fullterms | | | |
| singletons | 403 (83.3%) | 81 (16.7%) | 484 (100%) |
| twins | 5 (100.0%) | 0 (0%) | 5 (100%) |
| triplets/quadruplets | 0 (0%) | 0 (0%) | 0 (0%) |
| **Maternal Height** | | | |
| Preterms | | | |
| <-1SD | 370 (95.9%) | 16 (4.1%) | 386 (100%) |
| -1SD - +1SD | 66 (95.7%) | 3 (4.3%) | 69 (100%) |
| > +1SD | 691 (88.6%) | 89 (11.4%) | 780 (100%) |
| Fullterms | | | |
| <-1SD | 63 (94.0%) | 4 (6.0%) | 67 (100%) |
| -1SD - +1SD | 387 (82.9%) | 80 (17.1%) | 467 (100%) |
| > +1SD | 21 (95.5%) | 1 (4.5%) | 22 (100%) |
| **Socioeconomic status** | | | |
| *Maternal education level* | | | |
| Preterms | | | |
| normal/high | 850 (91.6%) | 78 (8.4%) | 928 (100%) |
| low | 336 (91.3%) | 32 (8.7%) | 368 (100%) |
| Fullterms | | | |
| normal/high | 302 (83%) | 62 (17.0%) | 364 (100%) |
| low | 105 (84.7%) | 19 (15.3%) | 124 (100%) |
| *Family income* | | | |
| Preterms | | | |
| normal/high | 1075 (91.4%) | 101 (8.6%) | 1176 (100%) |
| low | 60 (95.2%) | 3 (4.8%) | 63 (100%) |
| Fullterms | | | |
| normal/high | 376 (83.7%) | 73 (16.3%) | 449(100%) |
| low | 13 (72.3%) | 5 (27.7%) | 18 (100%) |

### *Influence of preterm 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 influenced mainly by LGA status. From one to four years, LGA PTs gained significantly more weight than their counterparts, be they AGA PTs or LGA FTs. During the same time frame, by contrast, increases in *height* in LGA PTs were equal to those of AGA PTs. Both preterm groups had greater height gains than FTs, so height gain remained to be more affected by prematurity.

**Table 2**: Absolute gains in weight (kg), height (cm) and head circumference, means, and SDs for preterm and fullterm large and appropriate-for-gestational age children during ages 0 to 4 years

| | Preterm | | Fullterm | | *P* values@ | |
|---|---|---|---|---|---|---|
| | LGA (n=112) | AGA (n=1189) | LGA (n=81) | AGA (n=408) | PT vs. FT | LGA vs. AGA |
| **Weight** (ages): | | | | | | |
| 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** (ages): | | | | | | |
| 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*** |
| **Head circumference** (ages): | | | | | | |
| 0 to <1 y | 13.7 (1.7) | 14.7 (1.7) | 10.5 (1.2) | 11.9 (0.9) | **<.001** | **<.001** |

@ Mutually adjusted
* Factors PT and LGA significantly interact: *P* <.01

LGA – large-for-gestational age
AGA – appropriate-for-gestational age

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.

No significant interaction was found for either of the two predictors, except for absolute height gain during infancy.

Relative growth was affected by LGA status and PT birth at all the ages and for all the measures **(Table 3)**.

**Table 3:** Relative weight, height, and HC in *z* scores and total BMI; means and (SDs) in large and appropriate-for-gestational age preterm and fullterm children during ages 0 to 4 years, by age (calendar ages, uncorrected for preterm birth and *corrected for preterm birth,* respectively)

| | PT-LGA | | PT-AGA | | FT-LGA | FT-AGA | *P* values@ | |
|---|---|---|---|---|---|---|---|---|
| | *Uncorrected* | *Corrected* | *Uncorrected* | *Corrected* | | | PT vs. FT | LGA vs. 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** |

@ mutually adjusted
* Factors PT and LGA significantly interact: *P* <.01

LGA – large-for-gestational age
AGA – appropriate-for-gestational age

Nevertheless, LGA status and PT birth did not interact except for relative increase in height during infancy. Being born both LGA and PT resulted in a median growth at the age of four that was 0.1 SD lower for weight, 0.1 SD lower for height, and 0.5 SD lower for HC compared to LGA FTs, whereas the BMI at four years was equal (**Table 4**). Compared to AGA PTs, it was 0.9 SD, 0.6 SD, and 0.4 SD higher for the three measures, respectively. Even though they were born preterm, LGA PTs managed to grow to within the normal range for AGA FTs before the age of one year. In particular, their BMI at age one was significantly higher (0.5-0.9 points, i.e. approximately 1 SD) than that of both AGA FTs and AGA PTs.

**Table 4**: Total BMI; means in large and appropriate-for-gestational age preterm and fullterm children during ages 0 to 4 years, by age (calendar ages).

| | PT-LGA | PT-AGA | FT-LGA | FT-AGA | *P* values@ | |
|---|---|---|---|---|---|---|
| | | | | | PT vs. FT | LGA vs. AGA |
| **BMI at age:** | | | | | | |
| 0 y | 12.5 (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 |

@ mutually adjusted

LGA – large-for-gestational age
AGA – appropriate-for-gestational age

### *Association of preterm LGA birth with developmental delay*

LGA children, be they PT or FT, had a decreased risk of developmental delay as measured by the ASQ total score compared to their matched AGA counterparts at the age of four (**Table 5**). After adjusting for confounders, odds ratios (OR) were no longer significant, but still indicated a lower risk of developmental delay.

**Table 5**: Number and proportions (% of the group concerned) for children with normal and abnormal Ages and Stages Questionnaire total scores and logistic regression analyses for abnormal total scores.

| | Total ASQ score | | Crude OR (95% CI) | Adjusted OR (95% CI)@ |
|---|---|---|---|---|
| | normal | abnormal | | |
| **Logistic regression analyses** | | | | |
| *Birth weight group* | | | | |
| FT-AGA (n = 408) | 387 (94.9%) | 21 (5.1%) | 1 (reference) | 1 (reference) |
| FT-LGA (n = 81) | 80 (98.8%) | 1 (1.2%) | 0.2 (0.13 – 0.74) | 0.6 (0.07 – 4.95) |
| PT-AGA (n = 1189) | 1061 (89.2%) | 128 (10.8%) | 2.2 (1.38 – 3.58)[1] | 0.9 (0.39 – 1.92) |
| PT-LGA (n = 112) | 105 (93.8%) | 7 (6.2%) | 1.2 (0.51 – 2.97) | 0.4 (0.13 – 1.55) |

1. $P < .01$

@ Adjusted for gender, multiple birth, maternal height, maternal education level, and family income

LGA – large-for-gestational age
AGA – appropriate-for-gestational age
PT – preterm
FT - fullterm

## Discussion

This study demonstrated that up to the age of four years the absolute growth of LGA PTs was characterized by increases in weight, height, and HC exceeding that of FT children. Adjusted for PT birth, i.e. by the number of weeks born too early, their 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 seemed to imply that LGA-born children, regarding weight, grew too fast for their gestational age, due to which they had already been exposed to an elevated risk of metabolic consequences such as metabolic syndrome.[20,21] From birth onwards, LGA PTs were unsuccessful in maintaining their well-balanced body proportions as their weight gain exceeded their height gain. Consequently, by the age of four 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. Preterm birth is reported as a factor that accelerates growth, especially in HC.[22] Previously, LGA-born children were described by Hegiger and Eyzaguirre [9,15] as misbalanced in weight and height in the long-term. Our study confirmed these finding in a much larger sample with a wider range of gestational ages. 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.

Within the same gestational age group, our results also showed that at the age of four being born LGA was associated with better developmental outcome than being born AGA. In both PT and FT children developmental delay was less likely in case of a higher birth weight. Although weight gain and HC growth were previously described as beneficial to neurocognitive outcome in studies that concerned AGA and SGA PT children [7,23,24], this study is the first to assess the influence of birth weight, weight gain, and increase of HC on developmental outcome in LGA PTs up to the age of four.

We offer several explanations for the more favorable developmental outcome of LGA children. First, the comparatively better outcome of the LGA group possibly reflects that their birth weight and growth during the first year after birth protects them from a poor developmental outcome, especially in the PT group. This is in line with reports on better development in SGA-born children, who show rapid catch-up growth in weight.[23,24] Second, a more favorable development may also be due to the fact that a large proportion of LGA children were born moderately PT. Being born within this gestational age range may be a precursor of a poorer neurodevelopmental outcome,[1] but it may also protect the child from an ongoing unfavorable intrauterine situation of high glucose intake and possible deposits. Moderately PT LGA birth may lead to fewer complications during labor, as birth weights are lower compared to LGA FTs. Nevertheless, knowledge of the exact mechanisms of growth and development in preterm LGA children is all but lacking and requires further research.

The major strengths of this study were the large samples of early and moderately PT and fullterm-born children as well as its community-based design. We analyzed growth longitudinally and assessed neurodevelopment using a validated, easy to fill-out, developmental screener. [25]

Our study also had some limitations. First, our cohort consisted of many multiples. Multiple births are associated with fewer LGA births and with a negative effect on developmental outcome. We included them because many twins are born moderately PT, which is mostly physiological rather than pathological and, in the long-term, multiple births are not associated with poor growth.[26,27] 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 PTs and FT children. Greater weight gains and relatively high BMIs imply that metabolic consequences such as metabolic syndrome are of specific concern.[20,21] In this study we assessed growth up to the age of four years, which is exactly the age-span during which children are most likely to develop overweight and obesity that persists into adolescence.[28] Growth in LGA children, be they PT or FT, should therefore be monitored closely. Second, the development of LGA-PTs seems to be less affected than it is in AGA PTs. Although we expected LGA-born children to have a poorer developmental outcome than their AGA counterparts, we did not find this in our sample. Even though further research is needed to elucidate the influence of PT and LGA birth and the role of maternal diabetes, there seems to be no added risk in being born both LGA and PT.

## Conclusion

The growth pattern of LGA PT-born children differs distinctly from AGA PTs and FT children. In particular, we found substantially greater weight gains and relatively high BMIs. This seemed to imply that the LGA-born children grew too fast for their gestational age, due to which they had already been exposed to an elevated risk of metabolic consequences such as metabolic syndrome. The development of LGA children is less affected than that of AGA children. Birth weight and sufficient increase of HC may be beneficial to their development.

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# 7

## General Discussion

*Inger Bocca-Tjeertes*

The aim of this thesis was to describe normal growth in preterm-born children and to determine growth and its influence on development in (pre)term children according to their birth weight, gestational age, and type of fetal growth. The research questions were:

1. What is normal growth for moderately-preterm born children? How often does growth restriction occur in the long-term and can it be predicted? (Chapter 2).
2. How is weight, height and head circumference (HC) distributed in preterm-born children during ages 0-4 years when classified by gender and gestational age? (Chapter 3).
3. How do preterm-born SGA children grow compared to their preterm-born and fullterm-born counterparts? (Chapter 4).
4. What are the effects of growth restricted preterm birth on growth and development? Are there any differences when children are classified by their type of growth restriction? (Chapter 5).
5. How do preterm-born LGA children grow compared to their preterm-born and fullterm-born counterparts? Are they at greater risk for developmental delays? (Chapter 6).

In the discussion, our main research questions will be answered first. Then, we will focus on main outcomes by classifying outcomes according to a child's GA, birth weight, or type of fetal growth restriction. Next we compared and discussed our outcomes with those in other recent studies. Finally, we will focus on some important implications and future perspectives of our studies for the monitoring and management of growth in preterm-born children.

**Main Findings**

1. *What is normal growth for moderately-preterm born children? How often does growth restriction occur in the long-term and can it be predicted?*

Most moderately preterm-born children had sufficient growth that allowed them to grow within normal fullterm ranges. Median growth however, was lowered and moderately preterm-born children had at average poorer long-term growth. This poorer growth resulted in a two-fold increase of children that were growth restricted at age 4 years. Children who were born SGA or who had a short mother (maternal height <-1SD) were at greatest risk for the persistence or development of growth restriction in the long-term. Other growth related predictors were not associated with growth restriction in the long-term in moderately preterm-born children.

2. *How is weight, height and head circumference (HC) distributed in preterm-born children during ages 0-4 years when classified by gender and gestational age?*

Being born before 37 weeks' gestation substantially lowered the height, weight, and head circumference attained by a child at age 4. The lower the GA, the lower the median growth (percentile 50) was. This median growth increased continuously with increasing GAs from 25 up to 36 weeks. We found that the absolute differences in centimeters (height) or kilograms

(weight) were approximately constant up to the age of 4 years, implying that the relative differences decreased, but no sufficient catch-up growth occurred. The differences in head circumference (measured in centimeters), however diminished with age, and were small from the calendar age of six months onwards. At the age of four the risk for being underweight and/or comparatively short was substantially higher in preterms compared to fullterms. For all three measures of growth, variability was greater in boys than in girls, particularly for children with the lower GAs.

We made longitudinal growth charts for boys and girls separately for every week of preterm gestation. These charts graphically represent growth of preterm-born children.

3. *How do preterm-born SGA children grow compared to their preterm-born and fullterm-born counterparts?*

Even though SGA preterm-born children showed the ability of catch-up growth, it was mainly limited to the first year after birth and it was insufficient to grow within normal ranges in the long-term. SGA preterm-born children were affected by both prematurity and growth restriction at birth. Both factors independently had their negative effects on growth in weight, height, and HC of these children. Compared to their preterm-born counterparts, SGA preterm children had poorer growth which dramatically increased the number of children with long-term growth restriction from about 5% in weight and height and 4% in HC to 39% in weight, 30% in height and 27% in HC. Compared to their fullterm-born counterparts, growth of SGA preterm children was considerably more affected and this group had a four-fold increase in growth restriction.

4. *What are the effects of growth restricted preterm birth on growth and development? Are there any differences when children are classified by their type of growth restriction?*

The classification of intrauterine growth restricted children according to symmetry showed that growth and development at age 4 were independent of a child's HC at birth. We found that both groups had similar growth with incomplete catch-up and similar two-fold increase in the risk for developmental delay. Growth restriction, whether symmetrical or asymmetrical, puts the preterm-born child at risk for poor growth as well as for developmental delay.

5. *How do preterm-born LGA children grow compared to their preterm-born and fullterm-born counterparts? Are they at greater risk for developmental delays?*

Their relatively high birth weights and good growth during the first years of life seemed to protect LGA preterm-born children from developmental delay, be they preterm- or fullterm-born. LGA preterm-born children had their own distinctive growth pattern. Combining the sequels of preterm and LGA birth, they were not able to maintain their relatively good body proportions which they were born with. LGA preterm-born children started their life with a birth length that related to the accompanying birth weight. They were thus not overweight

at birth. However, in the following years, they gained more weight than height resulting in high BMIs. Compared to their counterparts, LGA preterm-born children grew mostly like LGA fullterm children. Their high BMI had put them at risk for metabolic consequences that they were already at risk for by being born preterm.

## General discussion

*Growth according to gestational age; general growth of preterm-born children*

Preterm birth affects growth at least up to middle childhood. Being born before 37 weeks' gestation substantially lowers the weight, height, and head circumference attained by a child and the risk for being underweight and/or comparatively short is substantially higher in preterm-born compared to fullterm-born children at the age of 4 **(Chapter 2 and 3)**. HC seems to be the least affected growth measure. (**Figures 1, 2, and 3**).

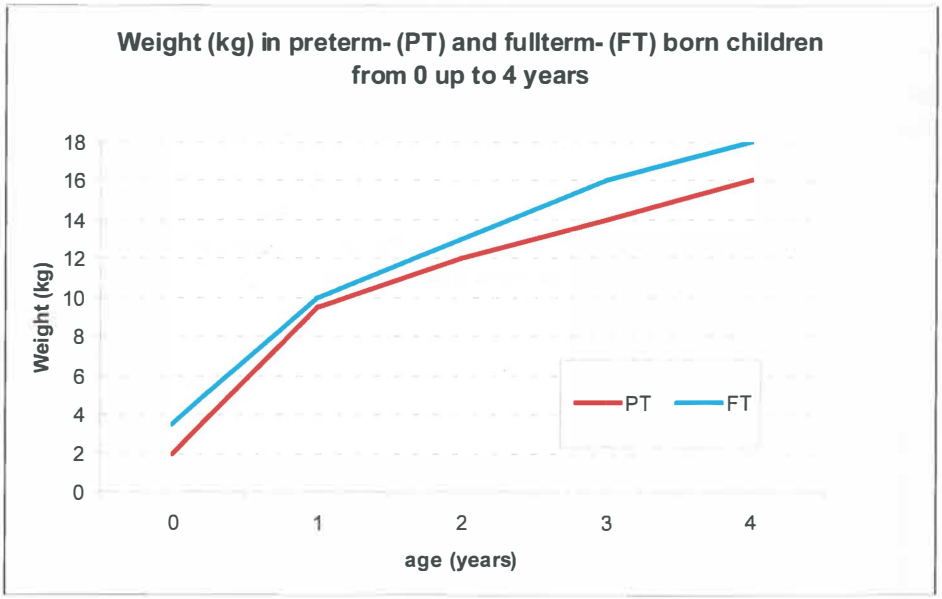


**Figure 1**: Median weight (kg) for fullterm (FT) and preterm (PT) children from 0-4 years (rough sketch).

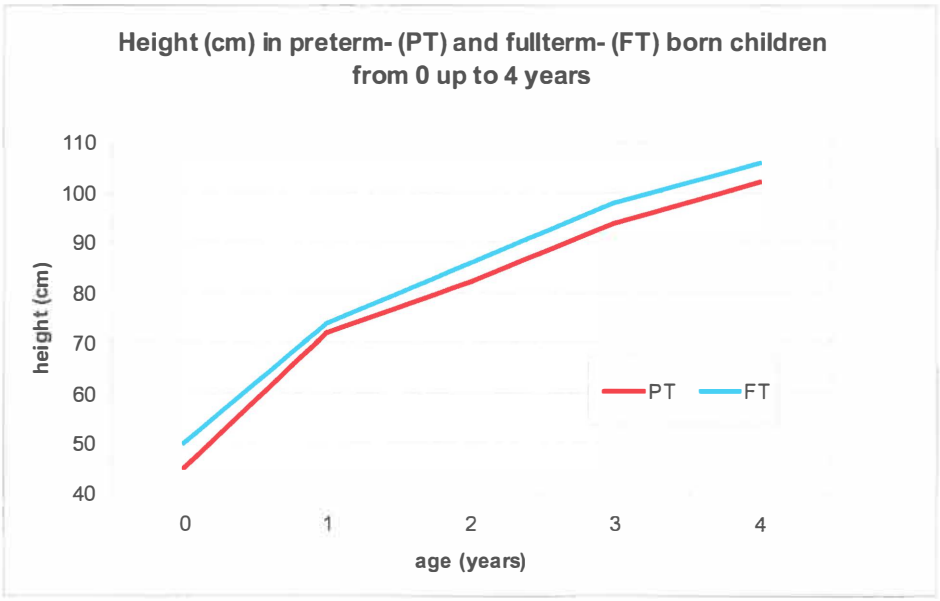


**Figure 2**: Median height (cm) for fullterm (FT) and preterm (PT) children from 0-4 years (rough sketch).

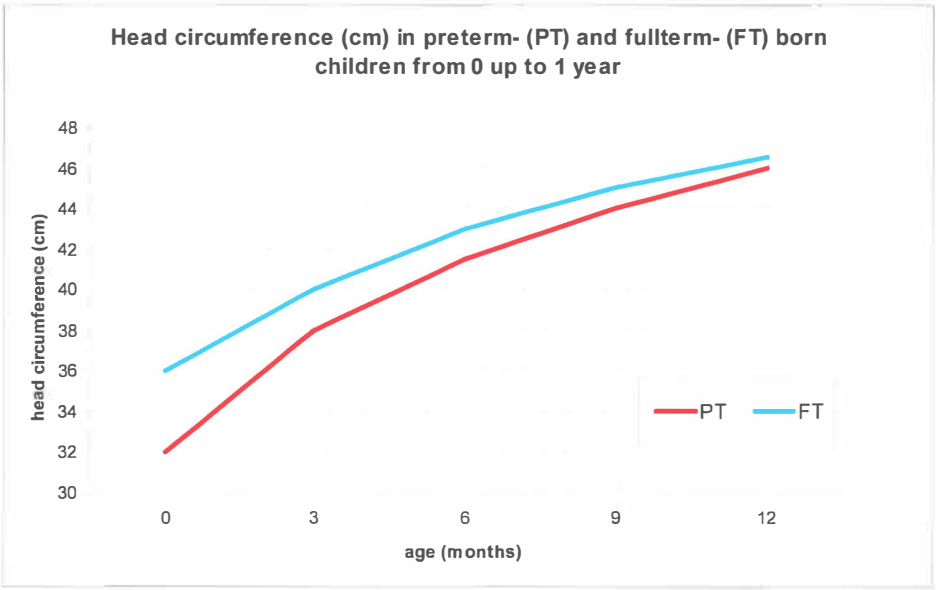


**Figure 3**: Median head circumference (cm) in fullterm (FT) and preterm (PT) children from 0-1 years; m = month (rough sketch).

Although about 95% of all preterm-born children in our cohort grew within normal ranges of fullterm-born children, their median growth was less and the proportion of the group with severe growth restriction at age 4 increased over two-fold, i.e. 5% (**Figure 4**). The children who were growth restricted at age 4 were both appropriate-for-age children with poor longitudinal growth and small-for-gestational age children with lack of catch-up growth. So, not only can growth restriction persist, but preterm-born children can also develop growth restriction more easily than fullterm-born children.

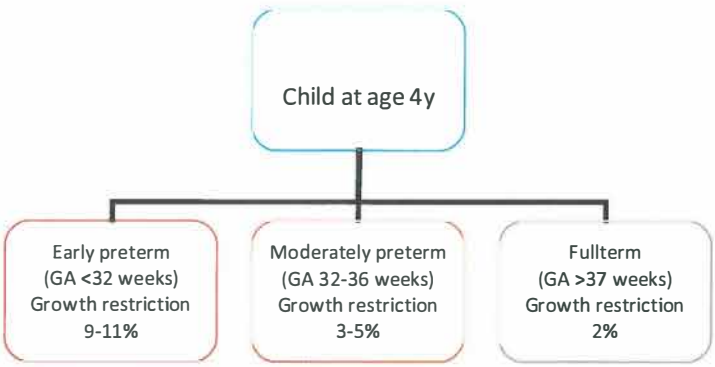


**Figure 4**: Growth restriction: overview according to gestational age.

Although median growth was lower but still within normal full-term ranges for most preterm-born children, it is not easy to predict growth of the *individual* preterm-born child. We found a few independent predictive factors at birth that could be helpful in identifying *moderately* preterm-born children at greatest risk of growth restraint (**Chapter 2**). Children at highest risk for growth restraint (height and/or weight) were those with a maternal height below -1 SD and those born SGA. Poor growth of HC during the first year was associated only with a low level of maternal education. This had been described for term infants as well.[1] Having a short mother and SGA birth have been reported to influence growth in *early* preterm-born children as well [2-6]. Some predictors, such as gestational age, maternal age, and ethnicity, may in fact be somewhat collinear, i.e. are strongly interrelated, which may affect the selection of variables in multivariable models if based on only p-values. Moreover, chronic disease(s) and problems such as feeding difficulties and infections, will probably be more important in this low gestational age group.[7]

We found greater variability among boys compared to girls regarding growth conditional on GA. The greatest gender differences concerned the lower GAs, i.e. 30 weeks and less. Possibly this finding was a reflection of the fact that preterm boys are more susceptible than girls to those complications of preterm birth that influence growth.[8] In the long term, boys were more likely to be comparatively short and girls were more often comparatively thin.

The WHO advises doctors to treat preterm-born children as though they were born fullterm,[9] but our findings refute this advice. In our study, preterm-born children do not follow

growth patterns of fullterm-born children, even when corrected for gestational age. The growth patterns of preterm born children in our study were dependent on GA. The lower the child's GA was, the further its growth deviated from the median growth of fullterm-born children. Therefore, we compiled growth charts for every week of preterm gestation, for boys and girls separately. These charts have several advantages compared to other charts. By using growth curves based on fullterm-born children, one may overestimate undergrowth as growing in the lower regions of the fullterm charts may just be normal for the specific GA the child was. Of course, a (pre)-term child should not grow under its potential weight and height ranges as undergrowth not only puts the individual at risk for infections and metabolic complications[10-12], but also can influence its developmental outcome negatively.[13] Undergrowth itself, or it's sequels, may affect quality of life.[14] At the other end of the growth spectrum, one may also miss overgrowth in the preterm-born child. The consequences of too rapid growth or too much catch-up growth may lead to metabolic complications as well.[10-12] Either one of these misinterpretations may lead to wrong decision-making and potentially harmful treatments.

Most doctors use growth charts that were compiled for fullterm-born children, which makes decision making based on actual growth even more challenging. Growth charts for fullterm-born children have several disadvantages for use in preterm-born children. They are either compiled using cross-sectional data of fullterm-born children, or by using birth weight data and they do not represent actual growth of preterm-born children. The WHO charts were compiled by data of healthy, breast-fed children of healthy, non-smoking women living in optimal conditions for growth.[15] These conditions mostly do not apply to the average preterm population. Although growth of preterm-children might be beneficially influenced by, for example feeding practices in the future, the developed charts currently are the instrument to most precisely monitor growth of preterm-born children in Caucasian populations in industrialized countries and probably also in African-American populations.[16]

### *Associations of growth with birth weight*

Preterm-born children whom were born with either fetal growth restriction (birth weight below P2.3-16 for GA, SGA) or fetal overgrowth (birth weight above P90 for GA, LGA) followed a distinctly different postnatal growth pattern when compared to their counterparts born with a normal birth weight (**Figures 5, 6, and 7, and Chapters 4, 5, and 6**). Postnatal growth of preterm-born children is known to be influenced by fetal growth.[17,18]

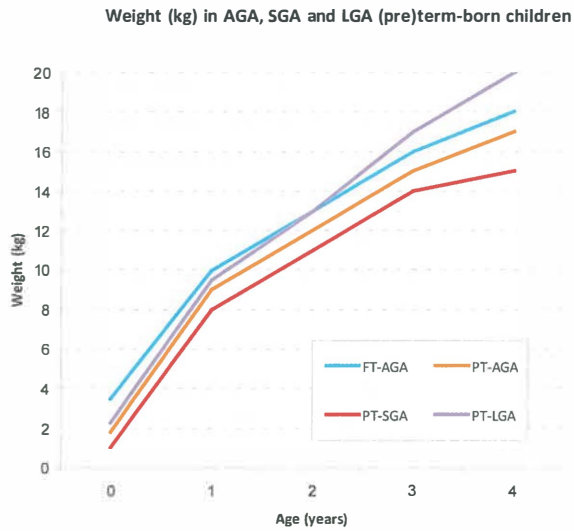


**Figure 5**: Median weight in kg for fullterm (FT) appropriate-for-gestational-age (AGA), preterm (PT) AGA, small-for-gestational-age (SGA) and large-for-gestational-age (LGA) born children from 0-4 years (rough sketch)

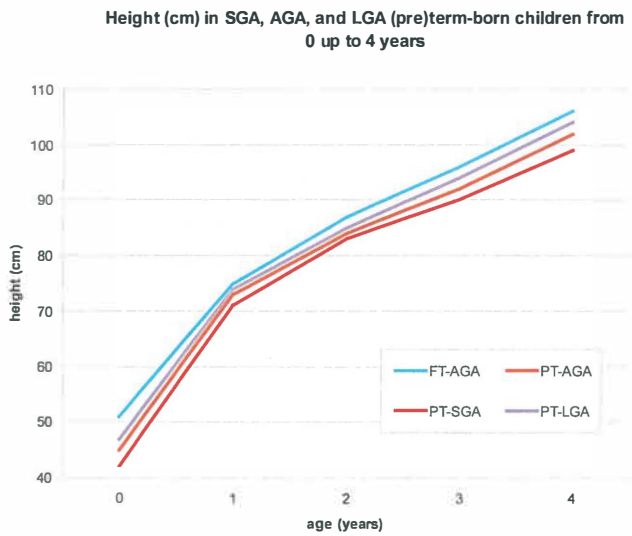


**Figure 6**: Median height in cm for fullterm (FT) appropriate-for-gestational-age (AGA), preterm (PT) AGA, small-for-gestational (SGA) and large-for-gestational-age (LGA) born children from 0-4 years (rough sketch)

SGA birth negatively affected the already restrained growth of preterm-born children, particularly in HC, leading to a unique pattern of HC growth during the first year after birth (**Figure 7**). In our sample, growth of preterm SGA children was characterized by incomplete catch-up growth. Catch-up growth only occurred in the first year after birth. The lack of further catch-up growth resulted in continued growth restriction. In fact, approximately 40% of all preterm SGA children remained too thin and 30% too short, with some of them being both, at the age of four, compared to about 5% of all preterm AGA children and 9% of all fullterm SGA children that remained too thin and or too short. (**Figure 8**). Apparently, height gain is more preserved than weight gain after preterm SGA birth, as was found earlier by Hack et al. and Hediger et al.[2,19]

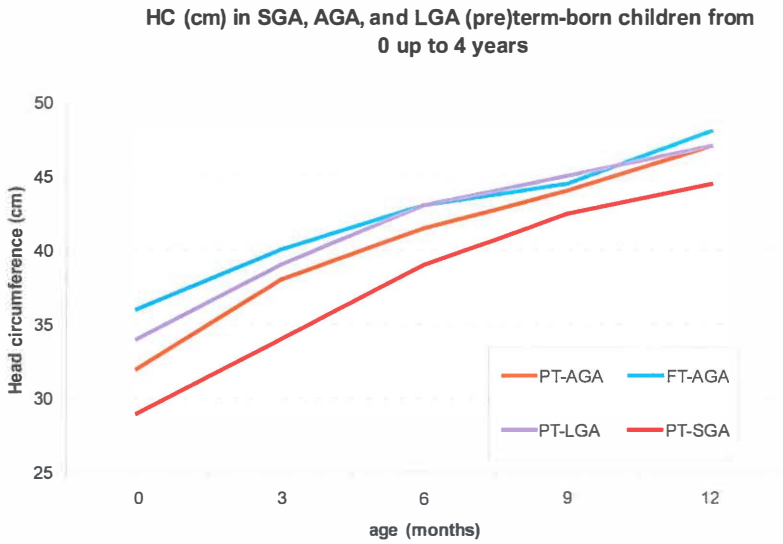


**Figure 7**: Median HC in cm for fullterm (FT) appropriate-for-gestational-age (AGA), preterm (PT) AGA, small-for-gestational (SGA) and large-for-gestational-age (LGA) born children from 0-4 years (rough sketch)

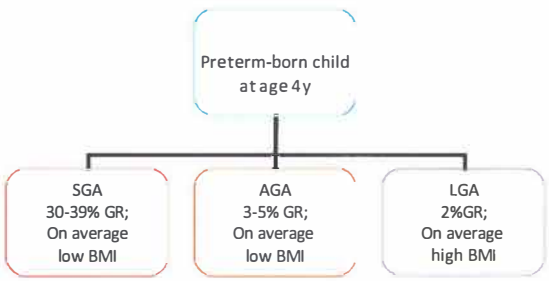


**Figure 8**: Overview of the most important growth outcomes according to birth weight (GR = growth restriction, BMI= body mass index):

The degree of symmetry of growth at birth hardly affected growth outcomes (**Chapter 5**). Both symmetrical growth restricted and asymmetrical growth restricted preterm children failed to sufficiently catch-up on growth in weight and height or even keep up with the growth velocity of their non-growth-restricted counterparts. When corrected for prematurity, growth was characterized by accelerated growth during infancy and failure to further catch-up during subsequent years in both symmetrical and asymmetrical growth restricted children. Symmetrical and asymmetrical growth restriction are believed to have different aetiologies. The asymmetrical form, generally known as late or disproportionate growth restriction, is consistently described as 'saver,' as it evolves in a shorter period of time, namely mostly late pregnancy.[20,21] Our findings however indicate that any underlying pathology or time of onset of fetal growth restriction can accomplish poorer long-term growth, and that in fact the label 'saver' is a misnomer. In growth restricted children, be they symmetrical or asymmetrical, HC growth was still the least affected measure.

There are several explanations for the distinctly different growth patterns of preterm-born children with growth restriction at birth. First, intrauterine growth restriction may result in irreversible disturbances of the growth hormone-IGF axis that prevents the child from *post*natal catch up.[22,23] Second, these children are highly susceptible to (neonatal) complications that negatively affect growth.[24,25] 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.[2,19] Per volume unity, fat weighs less than the fat-free mass. This leads to a relatively lower weight in the growth restricted child because of the relative lack of muscle. Although the effects of fetal growth restriction are visible in both height and weight gain, those in weight gain are thus more outspoken.

Our finding that general growth was equally affected in symmetrical and asymmetrical growth restricted children partially fills another gap in the evidence on postnatal growth after fetal growth restriction. We speculate that growth in utero is already influenced in such a negative way, resulting in growth restriction, that it is not (totally) reversible after birth. It is striking that even asymmetrical growth restriction leads to these high degrees of growth failure in the first years of life in preterm-born children.

At the other end of the prenatal growth spectrum, fetal overgrowth, we found that growth of LGA preterm children was characterized by catch-up growth for all measures when compared to fullterm children (**Figures 5-8**). However, their growth was misbalanced with height attainment being less than weight attainment. That resulted in high BMIs that were comparable to BMIs of fullterm LGA children. This implies that the LGA born child grows too fast for its gestational age. Its gestational age in itself already gave an elevated risk for metabolic consequences such as metabolic syndrome.[10,12,23] Now postnatal overgrowth may add to this risk. Even though rapid growth in weight was more outspoken in LGA preterm than in LGA fullterm children, this weight gain was not simply a footing of the effects of preterm birth and LGA status.

*Associations of fetal growth with developmental delay*

Fetal growth restriction increased the risk for developmental delay over two-fold, both in case of symmetrical and of asymmetrical growth restriction at birth. This increased risk remained after adjustment for confounders such as gestational age, gender, and socio-economic status (**Chapter 5**).

Growth and development thus seem to be associated. Intrauterine growth restricted preterm-born children had high rates of growth restriction following insufficient growth. Developmental delay may be dependent on absolute weight at birth, i.e. the higher the birth weight, the less likely developmental delay is. Other studies reported associations between HC growth and developmental delay as well as associations between weight gain and developmental delay in growth restricted children. These studies point in the same direction, the poorer the children's growth, the poorer their development.[13,26-29] Although this relation between (poor) growth and (poor) development seems likely, it may be that both just have similar causes.

In our sample, developmental delay at age 4 was twice more likely in case of growth restricted birth, be it symmetrical or asymmetrical. A first explanation for this similarity may be that growth during infancy in both groups was insufficient to fully protect adequate development, as we found that symmetrical and asymmetrical growth restricted children have similar poor gains in weight and height, which is known to be suboptimal for good development. [13,26-29] Second, developmental delay was independent of HC at birth. We speculate that the accelerated HC growth of symmetrical growth restricted children protected these children from (further) developmental delay as did their attempt of catch-up growth towards the medians of asymmetrical and non-growth restricted children, which has been show to be beneficial. [30,31]

An explanation for the accelerated HC growth that we found may be postnatal brain sparing. Klaric et al. recently reported that slower HC growth precedes poorer developmental outcome in asymmetrical growth restricted children.[32] Faster HC growth may have the opposite effect. Another explanation may be that fetal growth restriction causes irreversible damage to the developing brain, while brain sparing is insufficient to fully prevent developmental problems in case of AGR. Both groups of growth restricted children were more likely to have developmental delay than non growth restricted children at age 4, so there seems to be a considerable extra risk of growth restricted birth next to preterm birth for both growth and development.

LGA birth, however, was associated with better developmental outcome than AGA birth within the same gestational age group (**Chapter 6**). Developmental delay was less likely in case of a higher birth weight, in both preterm and fullterm children. Although weight gain and HC growth were previously described as beneficial for neurocognitive outcome in studies that concerned AGA and SGA preterm children [13,30,32],we did not expect LGA children to have such benefit of their birth status, as LGA birth is almost entirely seen as a negative pregnancy outcome, with more problems related to pregnancy, labour, and neonatal morbidity.[33-36]

In our sample, LGA preterm-born children were not more likely to have developmental delay than their *fullterm* AGA counterparts, despite their prematurity. Prematurity is associated with developmental delay over the entire range of preterm gestation[37] whereas LGA birth seemed

to diminish this effect. The more favourable development may be due to the fact that birth protected them from an ongoing unfavourable intrauterine situation of high glucose intake and possible deposits which may lead to congenital heart disease, but also to hypoglycaemia in the newborn.[38,39] The latter tends to strongly influence development as well.[40]

Preterm LGA birth may also lead to less complications of labour, as birth weights are lower compared to LGA fullterm children. In combination with a high birth weight and sufficient growth, this time of labour may have protected the child from developmental delay. These explanations form a useful target for further research.

Overall, preterm birth influences development. This influence can either be magnified by growth restricted birth or diminished by LGA birth. The birth weight of a child is not only important for its growth, but also for its development. Considering a child's birth weight could give direction in counselling parents on developmental outcome.

*Summary*

In summary we found that growth in preterm-born children differed from that of fullterm children. It was dependent of a child's gestational age and body proportions at birth. Catch-up growth was seen in preterm-born children, but it was mostly limited to the first year after birth. Growth was mostly insufficient to provide catch-up towards the median for children that were growth restricted at birth compared to their AGA preterm-born counterparts. Even so, preterm children born with an appropriate birth weight for their gestational age were also at risk for growth restriction in the long-term.

Both ends of the birth weight spectrum had different consequences regarding development of preterm-born children. Growth restriction resulted in a two-fold increase of the risk for developmental delay whereas fetal overgrowth did not.

**Strengths and limitations**

Major strengths of our study were its community-based design, the inclusion of over 2500 children over the entire range of (preterm) gestation, and the large number of assessments per child. By comparing these children with their fullterm counterparts from the same cohort, we were able to answer many questions on many topics regarding growth and the association of growth and development.

Our study also has some limitations. First, we obtained data from medical records and parental questionnaires. This may have caused some underestimation of certain effects due to incomplete or imprecise recordings or parental recollections. Recent research has shown that mothers are very capable of recalling data from their pregnancy period, so we do not feel that this strongly affected our data,[41] but the lack of accuracy may have been greater than in standardised research conditions.

Second, inclusion was done in a preventive child health care setting at the age of four. This may have led to exclusion of severely ill children as they are mostly seen by paediatricians in stead of youth physicians. We did however conclude that our cohort was representative for the community it was extracted from, based on the national birth records. We also know from another recent study that over 97% of all children visit the preventive child health care services at the inclusion age. [42]

Third, information on determinants was collected at age 3 years 9 months or was recorded at birth. Apparently, that excludes the measurement of some potentially relevant predictors such as maternal weights and maternal diabetes, long-term fetal growth, hormone levels, and metabolic profiles.

**Implications**

Our study has four important implications for four domains: increasing awareness on the distinctly different growth of preterm-born children; monitoring longitudinal growth dependent on a child's gestational age and body proportions at birth; increasing awareness on the extra risks of fetal growth restriction for poor growth and developmental delay next to preterm birth; and increasing awareness of the effects of fetal overgrowth on growth and development in preterm-born children. Apparently, in all cases the increased awareness should preferably lead to actions to optimize the situation concerned.

First, our findings imply that preterm-born children, despite largely improved neonatal care and feedings strategies, fail to grow as fullterm children and therefore should not be seen as fullterm children, this being in contrast to what WHO advices. If neonatologists, paediatricians, youth physicians and parents follow the WHO advice, they may overlook the possibility of (irreversible) adverse effects of preterm birth on long-term growth. Currently, we are not able to feed preterm-born children in the neonatal period as they would have been fed in a favorable intrauterine situation. We also cannot optimally influence morbidity and other growth-influencing factors either.[43] even so, it is likely that the damage that happens in an unfavorable intrauterine situation might be partially reversible.[22]

We should enable the preterm-born child to follow its own 'optimal' growth pattern. Growth in preterm-born children non optimal compared to that of full-term children as it is mainly misbalanced, i.e. growth in fat mass is greater than in muscles mass.[19] Although preventing underweight is important for preventing infections and negative developmental outcomes, it may not be necessary for a preterm-born child to grow within the exact ranges of fullterm children.

Second, growth in preterm-born children is highly dependent on gestational age and body proportions at birth. More than in fullterm children it is necessary for proper monitoring of growth to look at the individual child and take the child's birth characteristics into account. Growth can be monitored most precisely by using a growth chart that is based on longitudinal growth of a reference group matched by gestational age, as provided in this thesis. The use of such charts is already promoted by others.[16,44] Of course, we need to keep these charts updated for secular

trends may be observed in this specific group. As evidence mounts on the best feeding practices in preterm-born children, one may also expect these charts to (slightly) differ from the current situation in the future.

If growth of preterm-borns is monitored in a better way by GA specific growth charts, then this offers many opportunities for optimization of growth of the children concerned. This in particular relates to monitoring later in childhood. When a child is born, doctors and parents are highly aware of the child's gestational age and birth weight. When the child grows older however, this awareness diminishes though it remains very important for optimal growth counselling. In this respect, we need to encourage all medical professionals to optimize assessment and administration of birth characteristics as this is mostly forgotten in groups that are not known to be at risk for suboptimal growth, e.g. LGA preterm-born children. Future studies should involve the efficacy of these measures.

Third, birth weight, as a proxy of fetal growth restriction or fetal overgrowth, is related to the risk for developmental delay in preterm-born children. In our study, fetal overgrowth had no negative consequences for development and might even be protective, but fetal growth restraint did. The latter put the preterm-born child at (extra) risk for developmental delay, independent of its type or origin. Taking into account that prematurity is known to have a negative influence on a child's development, our study provides additional information that can be helpful in counselling parents and in providing care.

In preventing long-term consequences of improper management of growth in preterm-born children, we may benefit from focusing on specific precursors such as birth weight. There are four instances which cause a child to be at increased risk for metabolic consequences. The first two are fetal growth restriction and fetal overgrowth as they are both predictors of adverse metabolic consequences. In this study, we assessed growth up to the age of four years, which is exactly during the ages at which a child is most likely to develop overweight and obesity that persists into adolescence.[45] Third, preterm children that are born with appropriate-for gestational age birth weights can also be affected by poor growth and even develop growth restriction. Fourth, and probably most importantly, preterm-born children can be affected by misbalanced growth. In all preterm children, a high fat mass may go undetected as a child's weight may be normal. The latter form of suboptimal growth might be the hardest to detect. Misbalanced growth might alter in time. In (preterm) children, we should prevent growth that is either too slow, too rapid, or too misbalanced by monitoring growth very closely and altering feeding strategies per individual child when necessary. Future perspectives should focus on educating health care professionals who regularly deal with preterm-born children. We need a shift towards individualised treatment of children based on their birth characteristics and thereby prevention of under- and overgrowth. For future studies, it would be very important to unravel mechanism of growth as well as its consequences. In every individual, healthy aging starts already during pregnancy and early infancy.

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## English summary

*General introduction*

The main aim of the research reported in this thesis was to describe normal growth in preterm-born children and to determine growth and its influence on development in (pre)term children according to their birth weight, gestational age, and type of fetal growth restriction. Over the last decades, survival rates of preterm infants have increased significantly as neonatal care has evolved. This number is still rising because of various reasons. This means that long-term care for preterm-born children will expand over the next years.

Growth can be seen as a biomarker for the general well-being of a child. It is also one of the accessible outcomes of early preterm birth (before 32 weeks of gestation) or moderately preterm birth (between 32 and 36 weeks of gestation). Recent studies showed that preterm birth is associated with poorer growth in the short- and long-term. Prematurity thus seems to affect growth directly, although growth is influenced by many other factors as well, such as genetic and hormonal profiles, morbidity, and social conditions. Knowledge about growth of preterms and how prematurity affects their growth over the entire range of preterm gestational ages is scarce.

Postnatal growth can be divided in stages. The first one is infancy. Infancy is a very important period during which growth is mainly influenced by feeding and insulin. Next, beyond infancy, other hormones, such as growth hormone, play more important roles. Chronic disease, genetic potential, ethnicity, nutrition, congenital malformations or syndromes also influence growth. Although so many factors influence growth, it is still possible to predict a height range in which a healthy newborn will end when it's an adult. It therefore seems that growth is very steady and only externally influenced up to some point.

Preterm birth is associated with being smaller and lighter at birth, and with poorer growth after birth. Most studies and data about growth of preterms concern only early preterm-born children. Children born early preterm and children born with very low birth weights (VLBW) have consistently been shown to be at risk for poor growth and long-term growth restriction. In contrast, data about growth in moderately preterm-born children, who comprise 85% of all preterm-born children, are scarce. This also holds true for children born with high birth weights for their gestation (large-for-gestational age, LGA) and for children born growth-restricted (small-for-gestational age, SGA).

Interventions to promote growth generally focus on feeding strategies and on growth hormone administration. These efforts may have important effects and side-effects. On the one hand poor growth and growth restriction may be prevented. On the other hand, children may be exposed to additional metabolic risks if overgrowth is facilitated by, for example, enriched feeding. This adds to the metabolic risk already caused by preterm birth purely based on a shorter gestational age. It is therefore important to monitor growth frequently and to gain more insight in normal growth in preterm-borns.

By stimulating growth we hope to reach a more favourable developmental outcome. It is, however, still largely unknown if weight gain is directly related to better developmental achievements, or whether this better development is determined multifactorially. In that case weight gain might be a reflection of other factors, such as less illness, or less neurological damage. We also do not know whether catch-up growth regarding head circumference (HC) is equal to normal functional brain development.

The main aim of this thesis, i.e. to describe normal growth in preterm-born children and to determine growth and its influence on development in (pre)term children according to their birth weight, gestational age, and type of fetal growth restriction, led to the following research questions:

1. What is normal growth for moderately-preterm born children? How often does growth restriction occur in the long-term and can it be predicted? (Chapter 2).
2. How is weight, height and head circumference (HC) distributed in preterm-born children during ages 0-4 years when classified by gender and gestational age? (Chapter 3).
3. How do preterm-born SGA children grow compared to their preterm-born and fullterm-born counterparts? (Chapter 4).
4. What are the effects of growth restricted preterm birth on growth and development? Are there any differences when children are classified by their type of growth restriction? (Chapter 5).
5. How do preterm-born LGA children grow compared to their preterm-born and fullterm-born counterparts? Are they at greater risk for developmental delays? (Chapter 6).

The thesis was based on a stratified sample that was drawn from a community-based cohort of 45,446 children born in 2002-03. This longitudinal cohort study is known as "LOLLIPOP" (**Lo**ngitudina**l** **P**reterm **O**utcome **P**roject) but in Dutch it is known as "Pinkeltje." The LOLLIPOP sample consists of early and moderately preterm children born before 36 weeks' gestation and randomly selected fullterm controls that were included during their last visit to the PCHC at age four. The cohort size was based on estimates of the numbers needed to compile growth curves for preterm children in the Netherlands. This led to a planned inclusion of 500 early and 1000 moderately preterm-born children, in order to detect a difference in growth restraint between preterm and fullterm-born children per week gestational age (GA ) for boys and girls separately, with power 80% at $P$ =.05. We enriched the sample with early preterm-born children from five of the ten NICUs in the Netherlands because the data collection via only PCHCs would not lead to the inclusion of the planned number of early preterm children.

Data on growth during the children's first four years were obtained retrospectively from records kept at the PCHC and augmented by data retrieved from hospital records. Data on predictors of growth were obtained from the medical records and from a parental questionnaire that was designed for this study. We used the Dutch four-year version of the Ages and Stages Questionnaire (ASQ) at the age of four as a parent-completed developmental screening tool.

*Growth of moderately-preterm born children, prevalence and prediction of growth restriction in de long-term*

Most moderately preterm-born children had sufficient growth that allowed them to grow within normal fullterm ranges. Median growth however, was lowered and moderately preterm-born children had at average poorer long-term growth. This poorer growth resulted in a two-fold increase of children that were growth restricted at age 4 years. Children who were born SGA or who had a short mother (maternal height <-1SD) were at greatest risk for the persistence or development of growth restriction in the long-term. Other growth related predictors were not associated with growth restriction in the long-term in moderately preterm-born children.

*Weight, height and HC distribution in preterm-born children by gender and gestational age*

Being born before 37 weeks' gestation substantially lowered the height, weight, and head circumference attained by a child at age 4. The lower the GA, the lower the median growth (percentile 50) was. This median growth increased continuously with increasing GAs from 25 up to 36 weeks. We found that the absolute differences in centimeters (height) or kilograms (weight) were approximately constant up to the age of 4 years, implying that the relative differences decreased, but no sufficient catch-up growth occurred. The differences in head circumference (measured in centimeters), however diminished with age, and were small from the calendar age of six months onwards. At the age of four the risk for being underweight and/or comparatively short was substantially higher in preterms compared to fullterms. For all three measures of growth, variability was greater in boys than in girls, particularly for children with the lower GAs.

We made longitudinal growth charts for boys and girls separately for every week of preterm gestation. These charts graphically represent growth of preterm-born children.

*Distinct growth of preterm-born SGA children*

Even though SGA preterm-born children showed the ability of catch-up growth, this was mainly limited to the first year after birth and it was insufficient to grow within normal ranges in the long-term. SGA preterm-born children were affected by both prematurity and growth restriction at birth. Both factors independently had their negative effects on growth in weight, height, and HC of these children. Compared to their preterm-born counterparts, SGA preterm children had poorer growth. This dramatically increased the number of children with long-term growth restriction from about 5% in weight and height and 4% in HC to 39% in weight, 30% in height and 27% in HC. Compared to their fullterm-born counterparts, growth of SGA preterm children was considerably more affected and this group had a four-fold increase in growth restriction.

*Effects of growth restricted preterm birth on growth and development by type of growth restriction*.

A classification of intrauterine growth restricted children according to symmetry (either disproportionate/asymmetrical or proportionate/symmetrical growth restriction, regarding head circumference and weight) showed that growth and development at age 4 were independent of

a child's symmetry at birth. We found that both the asymmetrical and the symmetrical group had similar growth with incomplete catch-up growth and a similar two-fold increase in the risk for developmental delay. Growth restriction, whether symmetrical or asymmetrical, puts the preterm-born child at risk for poor growth as well as for developmental delay.

*Distinct effects of preterm large-for-gestational age (LGA) birth on growth and development*.
LGA preterm-born children had their own distinctive growth pattern. Combining the sequels of preterm and LGA birth, they were not able to maintain their relatively good body proportions which they were born with. LGA preterm-born children started their life with a birth length that related to the accompanying birth weight. They were thus not overweight at birth. However, in the following years, they gained more weight than height resulting in at average high BMIs. Compared to their counterparts, LGA preterm-born children grew mostly like LGA fullterm children. Their high BMI had put them at risk for metabolic consequences that they were already at risk for by being born preterm. Their relatively high birth weights and good growth during the first years of life seemed to protect LGA preterm-born children from developmental delay, be they preterm- or fullterm-born.

*Implications and future perspectives*
Our study has four important implications: increasing awareness on the distinctly different growth of preterm-born children; monitoring longitudinal growth dependent on a child's gestational age and body proportions at birth; increasing awareness on the extra risks of fetal growth restriction for poor growth and developmental delay next to preterm birth; and increasing awareness of the effects of fetal overgrowth on growth and development in preterm-born children. Apparently, in all cases the increased awareness should preferably lead to actions to optimize the situation concerned.

First, our findings imply that preterm-born children, despite largely improved neonatal care and feedings strategies, fail to grow as fullterm children. They should therefore not be treated according to the growth guidelines for fullterm children, this being in contrast to what WHO advises. If neonatologists, paediatricians, youth physicians and parents follow the WHO advice, they may overlook the risk of (irreversible) adverse effects of preterm birth on long-term growth. Currently, we are not able to feed preterm-born children in the neonatal period as they would have been fed in a favorable intrauterine situation. We also cannot optimally influence morbidity and other growth-influencing factors either. Even so, it is likely that the damage that happens in an unfavorable intrauterine situation might be partially reversible.

Second, growth in preterm-born children is highly dependent on gestational age and body proportions at birth. More than in fullterm children it is necessary for proper monitoring of growth to look at the individual child and take the child's birth characteristics into account. Growth can be monitored most precisely by using a growth chart that is based on longitudinal growth of a reference group matched by gestational age, as provided in this thesis. The use of such charts

is already promoted by others as these support the optimization of the growth of the children concerned. Of course, we need to keep these charts updated, as secular trends in growth may be observed in this specific group.

Third, birth weight, as a proxy of fetal growth restriction or fetal overgrowth, relates to the risk for developmental delay in preterm-born children. In our study, fetal overgrowth had no negative consequences for development and might even be protective, but fetal growth restraint had. The latter puts the preterm-born child at (extra) risk for developmental delay, independent of its type or origin. Taking into account that prematurity is known to have a negative influence on a child's development, our findings can be helpful in counselling parents and in providing care.

Fourth, in (preterm) children, we should prevent growth that is either too slow, too fast, or too misbalanced by monitoring growth very closely. We may benefit from focusing on specific precursors such as birth weight and from altering feeding strategies per individual child when necessary. In every individual, healthy ageing starts already during pregnancy and early infancy.

## Nederlandse samenvatting

### *Introductie*

Het hoofddoel van het onderzoek dat in dit proefschrift gepresenteerd wordt is het beschrijven van normale groei bij vroeggeboren kinderen en het bepalen van groei en de invloed hiervan op de ontwikkeling als deze wordt onderverdeeld op basis van zwangerschapsduur, geboortegewicht en het soort van foetale groeivertraging. In de laatste decennia is het aantal overlevende vroeggeboren kinderen sterk gestegen omdat de neonatale zorg beter werd. Het aantal vroeggeboren kinderen neemt ook nog steeds toe om verschillende redenen. Dit betekent dat de lange termijnzorg voor voeggeborenen in de nabije toekomst alleen maar zal toenemen.

Groei kan gezien worden als een biomarker voor het algemeen welzijn van een kind. Het is daarnaast ook één van de makkelijkst meetbare uitkomsten van ernstige (een zwangerschapsduur van minder dan 32 weken) en milde (een zwangerschapsduur van 32 tot 36 weken) vroeggeboorte. Recente studies hebben laten zien dat vroeggeboorte geassocieerd is met slechtere groei op de korte- en lange termijn. Vroeggeboorte lijkt groei direct te beïnvloeden, hoewel groei op zijn beurt wordt beïnvloed door vele factoren zoals genetische en hormonale profielen, ziekte en sociale omstandigheden. Kennis over groei bij vroeggeboren kinderen en hoe vroeggeboorte de groei beïnvloedt over de hele range van premature zwangerschappen is erg zeldzaam.

Postnatale groei kan worden onderverdeeld in periodes. De eerste daarvan is de zuigelingenperiode. Het eerste jaar na de geboorte is een erg belangrijke periode waarin groei voornamelijk wordt beïnvloed door voeding en insuline. Na de zuigelingenperiode spelen andere hormonen, zoals groeihormoon, een steeds belangrijker rol. Daarnaast beïnvloeden chronische ziekte, genetisch potentieel, etniciteit, voeding, congenitale afwijkingen en syndromen de groei. Hoewel vele factoren de groei reguleren en beïnvloeden, is het nog steeds mogelijk om een lengterange te voorspellen waarin een gezonde pasgeborene terecht zal komen als volwassene. Het lijkt dus dat groei op zich erg stabiel is en maar in bepaalde mate de beïnvloedbaar is van buitenaf.

Vroeggeboorte is geassocieerd met een kleinere geboortelengte en een lager geboortegewicht, maar ook met slechtere groei na de geboorte. De meeste studies over groei bij vroeggeborenen beperken zich tot de ernstig vroeggeboren kinderen. Bij deze groep, evenals bij de groep geboren met een zeer laag geboortegewicht (<1500g) is herhaaldelijk aangetoond dat er een verhoogde kans is op slechte groei en op groeivertraging (groei minimaal 2 standaarddeviaties onder het gemiddelde) op de lange termijn. Maar data over de mild vroeggeborenen, die 95% van de groep vroeggeborenen uitmaken, zijn veel schaarser. Dit is ook zo voor de kinderen die weliswaar vroeggeboren zijn maar met een hoog geboortegewicht voor hun gestatieduur (macrosomen, large-for-gestational age, LGA) of juist een laag geboortegewicht voor hun zwangerschapsduur (dysmaturen, small-for-gestational age, SGA).

Interventies om groei te stimuleren focussen veelal op voedingsstrategieën en het toedienen van groeihormoon. Deze pogingen om groei te stimuleren kunnen belangrijke effecten maar ook bijwerkingen hebben. Aan de ene kant zou slechte groei mogelijk voorkomen kunnen worden, maar aan de andere kant worden de kinderen wel blootgesteld aan metabole risico's als bijvoorbeeld hun voeding verrijkt wordt. Deze metabole risico's worden vervolgens opgeteld bij de metabole risico's die de kinderen puur op basis van hun vroeggeboorte al liepen. Het is daarom belangrijk om groei scherp te controleren en daarnaast meer kennis te verwerven in de normale groei van vroeggeborenen.

Met het stimuleren van groei hoopt men een betere ontwikkeling te kunnen bewerkstelligen. Het is echter nog grotendeels onbekend of een toename in gewicht ook direct gerelateerd is aan betere cognitieve ontwikkeling, of dat die ontwikkeling multifactorieel bepaald wordt. In dat geval zou gewichtstoename ook een uiting kunnen zijn van andere factoren, zoals minder ziekte, of minder neurologische schade. We weten tot slot ook niet of inhaalgroei in schedelomtrek (SO) gelijk staat aan een normale hersenontwikkeling.

Het hoofddoel van dit proefschrift, het beschrijven van normale groei bij vroeggeborenen en het bepalen van groei en de invloed hiervan op ontwikkeling bij vroeggeboren kinderen op basis van hun gestatieduur, geboortegewicht en soort van foetale groeivertraging, leidde tot de volgende onderzoeksvragen:

6. Wat is normale groei voor mild vroeggeboren kinderen? Hoe vaak komt groeivertraging op de lange termijn voor en kan deze voorspeld worden? (Hoofdstuk 2).
7. Hoe zijn gewicht, lengte en SO verdeeld bij vroeggeboren kinderen van 0 tot 4 jaar als ze worden geclassificeerd op basis van zwangerschapsduur en geslacht? (Hoofdstuk 3).
8. Hoe groeien vroeggeboren dysmature kinderen vergeleken met hun vroeggeboren en op tijd geboren leeftijdsgenoten? (Hoofdstuk 4).
9. Wat zijn de gevolgen van groeivertraagde vroeggeboorte op groei en ontwikkeling? Zijn er verschillen aan te tonen als deze kinderen worden onderverdeeld op basis van het soort groeivertraging? (Hoofdstuk 5).
10. Hoe groeien vroeggeboren LGA kinderen vergeleken met hun vroeggeboren en op tijd geboren leeftijdsgenoten? Hebben zij een groter risico voor ontwikkelingsachterstanden? (Hoofdstuk 6).

Dit proefschrift is gebaseerd op een gestratificeerd sample (monster) van een community-based cohort van 45.446 kinderen die geboren werden in 2002-03. Deze longitudinale cohort studie staat internationaal bekend als "LOLLIPOP" (**Lo**ngitudina**l** **P**reterm **O**utcome **P**roject) maar in het Nederlands als "Pinkeltje." Het Pinkeltje cohort bestaat uit ernstig- en mild vroeggeboren kinderen (alle zwangerschapsduren onder de 36 weken) en random geselecteerde op tijd geboren kinderen die allen geïncludeerd werden op het consultatiebureau toen ze bijna 4 jaar oud waren. De grootte van het cohort werd gebaseerd op schattingen van het aantal kinderen dat nodig was

om groeicurven voor Nederlandse vroeggeboren kinderen te maken. Deze schattingen leidden tot een geplande inclusie van 500 ernstig- en 1000 mild vroeggeboren kinderen, opdat verschillen in groei konden worden gedetecteerd tussen op tijd en vroeggeboren kinderen voor elke week van vroeggeboorte voor jongens en meisjes apart. De onderzoeksgroep werk verrijkt met ernstig vroeggeboren kinderen van 5 van de 10 Intensive Cares voor pasgeborenen (NICUs) in Nederland omdat er anders te weinig ernstig vroeggeboren kinderen konden worden geïncludeerd.

Gegevens over groei tijdens de 1e 4 levensjaren werden overgenomen uit de dossiers van de ziekenhuizen en die van de jeugdgezondheidszorg. Daarnaast werd gebruik gemaakt van diezelfde dossiers en een speciaal ontworpen oudervragenlijst om factoren die groei kunnen beïnvloeden vast te stellen. Om ontwikkelingsachterstanden op de leeftijd van 4 jaar te kunnen vaststellen gebruikten we de Nederlandse versie van de 4-jaars Ages and Stages Questionnaire (ASQ), een ontwikkelingsvragenlijst die de ouders zelf invulden.

*Groei van mild vroeggeboren kinderen, prevalentie en voorspelling van groeivertraging op de lange termijn.*

De meeste mild vroeggeboren kinderen waren voldoende in staat om te groeien en haalden ook waarden die binnen de normaalwaarden voor op tijd geboren kinderen vielen. Hun gemiddelde groei echter was lager en mild vroeggeboren kinderen hadden gemiddeld een slechtere groei op lange termijn. Deze slechtere groei resulteerde in een vertweevoudiging van het aantal kinderen met groeivertraging op de leeftijd van 4 jaar ten opzichte van op tijd geboren kinderen. Dysmature kinderen en kinderen met een kleine moeder (moederlengte <-1SD) hadden de meeste kans op groeivertraging op de lange termijn. Andere groeivoorspellende factoren waren niet geassocieerd met groeivertraging op de lange termijn in de groep van mild vroeggeboren kinderen.

*Gewicht, lengte en SO spreiding bij vroeggeboren kinderen op basis van geslacht en zwangerschapsduur.*

Geboren worden voor de 37e zwangerschapsweek verlaagde de verworven lengte, het gewicht en schedelomtrek op de leeftijd van 4 jaar aanzienlijk. Hoe korter de zwangerschapsduur, hoe lager de gemiddelde groei was (50e percentiel, P50). Die gemiddelde groei liep continu op bij een toenemende zwangerschapsduur tussen de 25 en 37 weken. We vonden ook dat de absolute afstanden in centimeters (lengte) of kilogrammen (gewicht) ongeveer constant bleven tot de leeftijd van 4 jaar wat betekent dat de relatieve afstanden wel minder groot werden maar er onvoldoende inhaalgroei was. De onderlinge afstanden bij de schedelomtrek (gemeten in centimeters) namen bij een oplopende leeftijd wel af en waren klein vanaf de (kalender)leeftijd van 6 maanden. Op de leeftijd van 4 jaar was het risico voor het hebben van ondergewicht of een te kleine lengte aanzienlijk groter bij vroeggeboren kinderen ten opzichte van op tijd geboren kinderen. Voor alle 3 meetwaarden was de variabiliteit bij jongens groter dan bij meisjes, vooral bij extreem korte zwangerschapsduren.

We hebben longitudinale groeidiagrammen gemaakt voor zowel jongens als meisjes voor elke week zwangerschapsduur van 25-36 weken. Deze diagrammen vertegenwoordigen de daadwerkelijke groei van vroeggeboren kinderen.

*Specifieke groei van vroeggeboren dysmaturen*
Hoewel vroeggeboren dysmaturen het vermogen hadden om inhaalgroei te vertonen, was deze inhaalgroei beperkt tot het 1e levensjaar en onvoldoende om binnen de normaalwaarden te groeien op de lange termijn. Vroeggeboren dysmaturen hadden zowel last van hun prematuriteit als van hun dysmaturiteit. Beide factoren hadden onafhankelijk van elkaar hun negatieve effect op groei in gewicht, lengte en schedelomtrek bij deze kinderen. Ten opzichte van hun vroeggeboren leeftijdsgenoten vertoonden de vroeggeboren dysmaturen slechtere groei. Dit verhoogde het aantal kinderen met groeivertraging dramatisch van ongeveer 5% in gewicht en lengte en 4% in schedelorntrek tot 39% in gewicht, 30% in lengte and 27% in schedelomtrek. Ten opzichte van op tijd geboren dysmaturen was de groei van vroeggeboren dysmaturen aanzienlijk slechter wat een verviervoudiging van het aantal kinderen met groeivertraging ten gevolg had.

*Effecten van dysmature vroeggeboorte op groei en ontwikkeling afhankelijk van het type groeivertraging.*
Classificatie van bij de geboorte groeivertraagde kinderen op basis van hun lichaamsverhoudingen (ofwel disproportionele/asymmetrische of proportionele/symmetrische groeivertraging vastgesteld op basis van schedelomtrek en gewicht bij de geboorte) laat zien dat groei en ontwikkeling op de leeftijd van 4 jaar onafhankelijk waren van de lichaamsverhoudingen bij de geboorte. We vonden dat symmetrisch als asymmetrisch groeivertraagde kinderen zowel dezelfde groei hadden met incomplete inhaalgroei als een vertweevoudiging van het risico voor ontwikkelingsachterstanden. Groeivertraging, hetzij symmetrisch, hetzij asymmetrisch, zorgt voor extra risico's voor de groei en de ontwikkeling voor het vroeggeboren kind.

*Specifieke effecten van macrosome vroeggeboorte op groei en ontwikkeling.*
Macrosome vroeggeboren kinderen hadden ook een specifiek groeipatroon. De gevolgen van vroeggeboorte e macrosomie combinerend, waren de kinderen niet in staat hun relatief goede lichaamsverhoudingen bij de geboorte te behouden. Macrosome vroeggeborenen hadden bij de geboorte een lichaamslengte die in verhouding stond tot hun hoge geboortegewicht voor de zwangerschapsduur en hadden dus geen overgewicht. Toch kwamen de kinderen in de daaropvolgende jaren veel aan terwijl ze niet zo hard groeiden in de lengte wat resulteerde in gemiddeld hoge body-mass-indices (BMIs). Ten opzichte van hun leeftijdsgenoten groeiden macrosome vroeggeboren het meest vergelijkbaar met op tijdgeboren macrosomen. Hun hoge BMI verhoogt het risico voor metabole gevolgen waar ze ook al risico voor hebben op basis van hun vroeggeboorte. Het relatief hoge geboortegewicht en de goede groei lijken de macrosome kinderen wel te beschermen tegen ontwikkelingsachterstanden, of ze nou vroeggeboren zijn of niet.

*Implicaties and vooruitzichten*

Ons onderzoek heeft vier belangrijke implicaties: het verhogen van het inzicht in het specifiek groeien van vroeggeboren kinderen; het monitoren van groei op een longitudinale manier op basis van de zwangerschapsduur en het geboortegewicht; het verhogen van het inzicht in de bijkomende effecten van foetale groeivertraging op groei en ontwikkeling; en daarnaast het verhogen van het inzicht in de gevolgen van foetale overgroei voor zowel de groei als de ontwikkeling bij vroeggeboren kinderen. In alle gevallen zou deze verhoogde opmerkzaamheid idealiter leiden tot optimalisatie van de betreffende situatie.

Ten eerste impliceren onze bevindingen dat vroeggeboren kinderen, ondanks sterk verbeterde zorg en voedingsstrategieën, niet in staat zijn te groeien als op tijd geborenen. Ze zouden dan ook niet behandeld moeten worden volgens de groeirichtlijnen voor op tijd geboren kinderen, in tegenstelling tot wat de WHO adviseert. Als dit wel gebeurt, lopen neonatologen, kinderartsen, jeugdartsen en ouders het risico op het niet signaleren van (onomkeerbare) gevolgen van vroeggeboorte op de (lange termijn) groei. Zoals het er nu voor staat kunnen we vroeggeboren kinderen nog niet voeden zoals zij in een gunstige intra-uteriene omgeving gevoed zouden zijn via de placenta. We kunnen ook ziektes en andere groei beïnvloedende gebeurtenissen niet (geheel) voorkomen. Het lijkt hoe dan ook wel zo dat de schade die in de ongunstige intra-uteriene omgeving is opgelopen deels omkeerbaar is.

Ten tweede is de groei bij vroeggeboren kinderen sterk afhankelijk van de zwangerschapsduur en de lichaamsverhoudingen bij de geboorte. Voor het goed monitoren van groei is het nog belangrijker dan bij op tijd geboren kinderen om naar het individuele kind te kijken en daar de geboortegegevens bij te betrekken. De groei kan vervolgens het beste worden vervolgd op speciale groeidiagrammen gebaseerd op longitudinale groei van een referentiegroep van vroeggeboren kinderen die overeenkomstig is in zwangerschapsduur en geslacht, zoals die ook worden gepresenteerd in dit proefschrift. Het gebruik van deze diagrammen wordt al geadviseerd door anderen omdat deze diagrammen bijdragen aan het verbeteren van de groei van de betrokken kinderen. Natuurlijk moeten we niet vergeten de diagrammen te blijven updaten omwille van het nog te verwachten effect van seculiere trends in deze specifieke groep kinderen.

Ten derde is het geboortegewicht, als uiting voor foetale groeivertraging of overgroei, gerelateerd aan het risico voor ontwikkelingsachterstanden bij vroeggeboren kinderen. In ons onderzoek had foetale overgroei geen negatieve consequenties voor ontwikkeling -en zou zelfs beschermend kunnen zijn-, maar foetale groeivertraging had deze negatieve consequenties wel degelijk. Deze groeivertraging zorgt voor extra risico voor ontwikkelingsachterstanden onafhankelijk van welke vorm van groeivertraging. Als men er vanuit gaat dat vroeggeboorte op zich invloed heft op de ontwikkeling zouden deze bevindingen een handvat kunnen bieden bij de voorlichting van de ouders van de kinderen evenals bij de adequate zorg.

Ten vierde zouden we bij (vroeggeboren) kinderen moeten voorkomen dat hun groei te snel, te langzaam of te ongebalanceerd verloopt door die groei nauwkeurig te vervolgen. We zouden ons voordeel kunnen doen door te focussen op specifieke precursors zoals geboortegewicht en, waar nodig, voedingsstrategieën te wijzigen voor het individuele kind. In elk individu start "healthy ageing" al tijdens de zwangerschap en de vroege kinderjaren.

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## About the Author

Inger Bocca-Tjeertes was born on 8 August 1979 in Hilversum, the Netherlands. She was raised in a family of 3 girls, which resulted in highly developed chatting skills. Always wanted to become a doctor, she received her Master's degree in Medicine in 2001. Two years later, she passed her Medical Exams with credit at Maastricht University. As a pediatric resident, she worked at the Neonatal Intensive Care Unit in Groningen, where she met Jorien Kerstjens and Arend Bos. Interrupting her residency for having more time for her young children, she was fortunate to receive the invitation for becoming a PhD-student within the LOLLIPOP study group, the results of which are presented in this thesis. Next to this Academic challenge, she worked as a Youth Physician in Drenthe.
After finishing this research trajectory, Inger will complete her pediatric residency in the Unveristy Medical Center Groningen, for which she is very grateful.

Inger is married to Gianni Bocca. They have 3 daughters: Anne (2007), Meinke (2008), and Isabelle (2011). Besides Pediatrics and her family, Inger is passionate about skiing, shopping, coffee, and visiting Italy. It is her wish to become a pediatrician and continue doing research in growth of preterm-born children.

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## Abbreviations

*AGA - appropriate-for-gestational age*
*AGR- asymmetrical growth restriction*
*BMI - body-mass index*
*CI - confidence interval*
*FT - fullterm*
*GA - gestational age*
*HC - head circumference*
*ICSI - intra-cytoplasmic sperm injection*
*IVF - in vitro fertilization*
*LGA - large-for-gestational age*
*Lollipop – Longitudinal Preterm Outcome Project*
*NGR – non-growth restriction*
*NICUs – neonatal intensive care units OR - odds ratio*
*PCHCs – preventive child health care services*
*PT - preterm*
*SD - standard deviation*
*SES - socio-economic status*
SGA - small-for-gestational age
*SGR – symmetrical growth restriction*

## Epiloog

De groeidiagrammen die uit dit proefschrift zijn voortgekomen zijn opgenomen in de AJN/NVK richtlijn nazorg vroeg/SGA-geboorte 2012.

De groeidiagrammen zijn tevens kosteloos te downloaden via www.tno.nl/groei

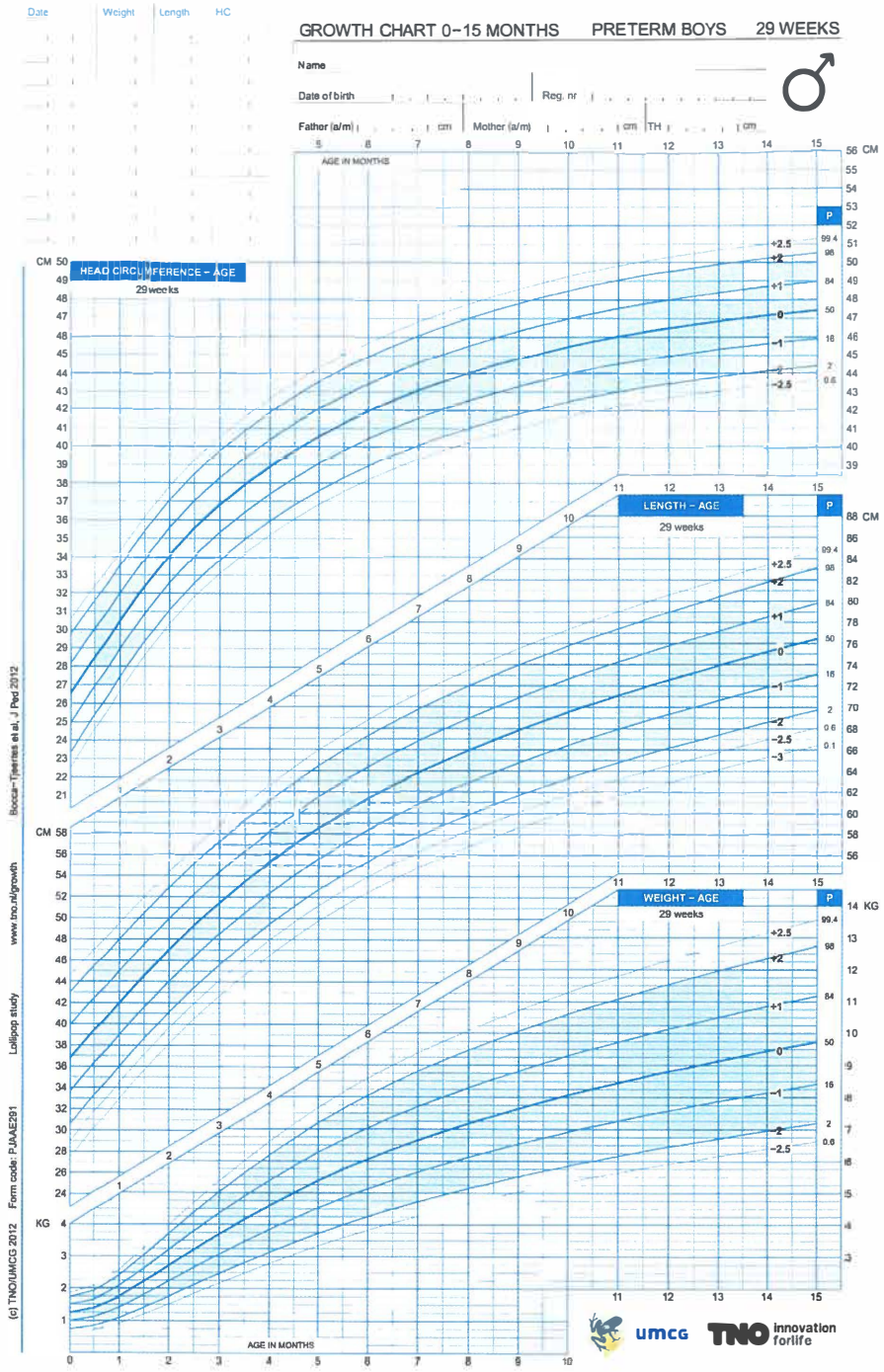


Figure 1: Growth chart for preterm-born boys of 29 weeks' gestation from 0 up to 15m.

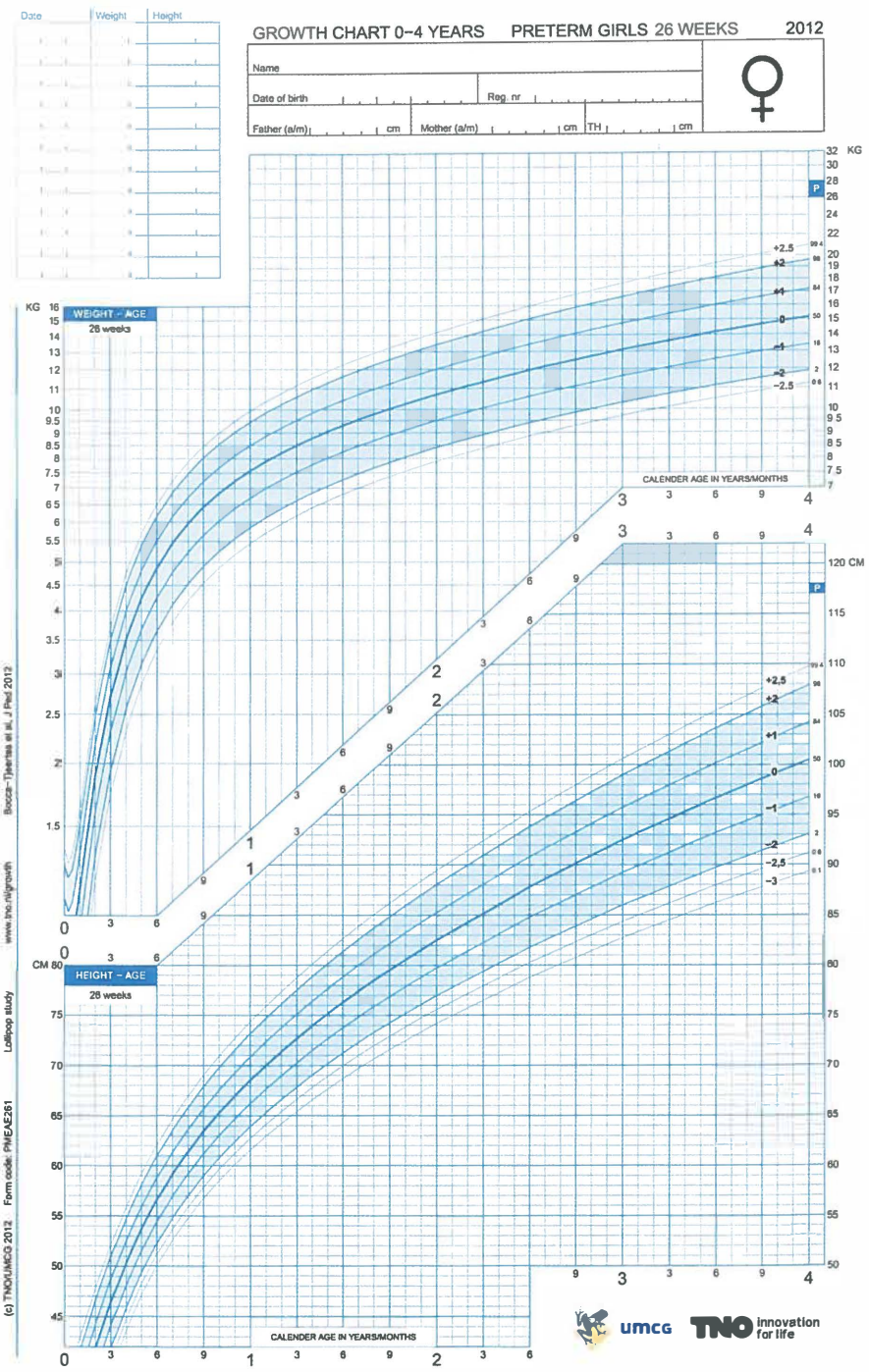


Figure 2: Growth chart for preterm-born girls of 26 weeks' gestation from birth up to 4y.