Antenatal and Postnatal Growth and 5-Year Cognitive Outcome in Very Preterm Infants

**WHAT’S KNOWN ON THIS SUBJECT:** Better postnatal growth, especially head growth, associates with better cognitive development in preterm infants. Suboptimal postnatal growth is more common in infants with poor antenatal growth than in infants with normal growth.

**WHAT THIS STUDY ADDS:** Good weight gain and head circumference growth until 2 years was associated with better 5-year cognitive outcome in non–small for gestational age infants. Good head circumference growth around term age benefits the cognitive outcome of small for gestational age infants.

**OBJECTIVES:** To study how antenatal growth affects cognitive outcome in very preterm infants and to determine whether there is an association between growth in any particular time period between birth and 5 years of age and cognitive outcome. Small for gestational age (SGA) and non-SGA infants were analyzed separately, because antenatal growth may affect postnatal growth.

**METHODS:** Very low birth weight (<1501 g) infants born between 2001 and 2006 and infants born at ≥32 gestational weeks between 2004 and 2006 who were treated at Turku University Hospital (n = 181) were followed. Weight, length, and head circumference (HC) of the infants were measured at 9 time points between birth and 5 years. The growth was determined as a z score change between measurement points. Cognitive development was assessed at 5 years of age with the Wechsler Preschool and Primary Scales of Intelligence–Revised. The association between growth and full-scale IQ (FSIQ) was studied.

**RESULTS:** Growth in length and height was not associated with 5-year cognitive outcome. However, weight (r = 0.18, P = .04) and HC growth (r = 0.25, P = .01) between birth and 2 years of corrected age correlated to FSIQ in non-SGA children. In SGA children, HC growth (r = 0.33, P = .03) around term age correlated to FSIQ.

**CONCLUSIONS:** Cognitive outcome was similar in SGA and non-SGA very preterm infants. Growth affected cognition positively in both subgroups, but the critical time period was different.
Very low birth weight (VLBW) preterm infants are at risk for cognitive problems \(^1\)–\(^5\) and growth failure.\(^6\)–\(^8\) Sub-optimal growth at the time of discharge is still a common phenomenon despite advances in treatment and nutrition regimens.\(^9\)–\(^11\) and growth delay, especially in weight\(^8\),\(^12\),\(^13\) and length,\(^8\),\(^14\),\(^15\) usually remains a problem that tends to ease in childhood\(^14\),\(^15\) and adulthood.\(^7\),\(^16\) Extreme prematurity\(^10\),\(^11\),\(^17\) and being small for gestational age (SGA)\(^7\),\(^15\),\(^18\)–\(^20\) are seen as specific risk factors in this growth lag. Male gender,\(^4\),\(^7\),\(^16\) critical morbidity\(^5\),\(^9\),\(^15\),\(^21\) and of course a parent’s shortness\(^15\),\(^16\),\(^22\),\(^23\) are other important predictors of later poor growth in very preterm infants.

Recently there have been attempts to define the critical growth period for neurodevelopment in preterm infants.\(^10\),\(^24\),\(^25\) Prenatal, and even more for neurodevelopment in preterm childhood.\(^14\),\(^23\),\(^28\) If preterm age may be associated with neurodevelopment in infancy,\(^10\),\(^17\),\(^25\) or between birth and term equivalent age\(^10\),\(^17\),\(^25\) or between term and 1 year of age.\(^3\) A few studies have found evidence that length gain until 2 years of age may be associated with neurodevelopment in childhood.\(^14\),\(^25\),\(^28\) If preterm boys lack catch-up growth in height, this is found to predict impaired intellectual outcome.\(^1\),\(^18\)

Head growth reflects brain size\(^29\) and is a useful predictor of later neurodevelopment.\(^10\) Head growth during the first weeks\(^25\) and months,\(^14\) up to 2 years of life,\(^4\),\(^14\),\(^30\)–\(^32\) has been shown to be especially important for preterm infants’ cognitive abilities. Head size later in childhood has also been associated with cognition,\(^1\),\(^12\),\(^24\)

To gain a better understanding of the optimal postnatal growth and its relevance to the cognitive outcome of preterm infants, we need studies with comprehensive prospective follow-up of growth with several measurement points and standardized cognitive testing in a representative preterm population. Prenatal growth is an important factor to take into consideration, which can be achieved by separately analyzing SGA and non-SGA preterm infants. There are just a few studies\(^22\),\(^23\),\(^26\),\(^27\) that look at the association between postnatal growth patterns and cognition for these 2 groups separately (Supplemental Table 3). In these studies, the focus has often been on the catch-up growth of SGA infants, ignoring the pattern of postnatal growth for non-SGA infants, and therefore the results leave many questions unanswered.\(^22\),\(^27\) Furthermore, the treatment of preterm infants has improved in the past decade, including better nutritional support.

Our aim was to assess the relationship between growth and cognition in a cohort of very preterm infants born between 2001 and 2006. We wanted to see whether there is a particular time window for postnatal growth in weight, length, or head circumference (HC) between birth and 5 years of age that affects the cognitive outcome of preterm infants at 5 years of age, and if so to see whether the timing differs in SGA and non-SGA populations.

**METHODS**

**Study Subjects**

This study is part of a regional, prospective, and multidisciplinary follow-up study of very preterm infants: PIPARI (development and functioning of VLBW infants from infancy to school age). There were 274 infants who met our inclusion criteria; they were born between 2001 and 2006 with a birth weight <1501 g or between 2004 and 2006 with a gestational age (GA) <32 weeks (very low GA), treated at Turku University Hospital, and from Finnish or Swedish-speaking families living in the catchment area to enable psychological assessment.\(^32\) Infants with severe congenital anomalies or a diagnosed syndrome affecting their development were excluded. Forty-one (15%) died, 9 (4%) of the families refused to participate, and the number of later dropouts was 23 (10%). One infant (0.5%) on long-lasting oral corticosteroid therapy was excluded because of its potential effects on growth. Regarding the psychological assessment at 5 years, 2 (1%) infants were tested too late, and the tests of 17 (6%) infants were unsuccessful. The final cognitive outcome was available for 181 infants. Children without an evaluation of cognitive outcome (dropouts included) were more likely to have mothers with lower levels of education \(P = .002\) and to have a diagnosis of cerebral palsy \(P = .009\) than children with an evaluation of cognitive outcome. No differences were found between these groups in the incidence of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), sepsis or meningitis, brain pathology, or SGA status.

**Nutrition Regimen**

We have followed international guidelines in early nutrition, starting parenteral amino acids and lipids on the first day of life. All infants were given breast milk at least until discharge. The breast milk fortification was started when 150 mL/kg per day was reached and continued until the infant reached the weight of 3.5 kg. Solid food and meat were added at 4 and 5 months of age, respectively. Vitamin D and iron were supplemented from 2 and 3 weeks of age, respectively. Baby food was replaced by normal family food ∼1 year after birth.
Assessment of Growth

Trained nurses measured the infants in the hospital and at the follow-up clinic until 2 years of corrected age (CA), and thereafter in the well baby clinics. After birth, weight was measured daily, crown–heel length twice a month, and HC weekly until discharge. Weight was measured to the nearest 0.01 kg with an infant scale (MeWa GmbH, Schwerin, Germany) until the age of 2 years of CA and thereafter to the nearest 0.1 kg. The child was usually lying supine during height measurement up to 2 years of age, after which the child was standing. HC was measured by a soft, unstretchable tape, which was changed regularly. Available data were collected from hospital records; the measurements at 5 years of age were collected by a questionnaire from nurses in the well baby clinics. SGA status was defined as a birth weight < −2.0 SD, and non-SGA was between −2.0 and +2.0 SD. In the non-SGA group, 98% of the infants were classified as appropriate for gestational age (AGA); 2 infants with birth weight z scores of +2.2 and +2.6 were included in this group.

Assessment of Cognitive Development

A psychologist assessed the cognitive outcome of the children at 5 years (−1 week to 2 months) with a short version of the Wechsler Preschool and Primary Scales of Intelligence–Revised. This test is standardized in Finland. The subtests for information, sentences, arithmetic, block design, geometric design, and picture completion were used, and the full-scale IQ (FSIQ) was estimated. FSIQ was used as a continuous variable (mean 100, SD 15).

Assessment of Brain Pathology

A cranial ultrasound was performed by the attending neonatologist for all infants at the ages of 3–5 days and 7–10 days after birth, 1 month after birth, and monthly until discharge. An MRI examination of the brain was performed at corrected term age. The infants were categorized into 3 groups according to the most pathologic brain findings by ultrasound or MRI.

Statistical Analysis

Growth was assessed using the measures of weight, length, and HC at birth, 36 weeks’ GA (±7 days), 40 weeks’ GA (±7 days, term age), 1 month, (±7 days), 2 months (±7 days), 4 months (±7 days), 1 year (±7 days), 2 years (±7 days), and 5 years (±2 months). Age was corrected for prematurity until 2 years. To determine the particular growth period we evaluated growth in short periods, in sequential order, from each age to the following age points: between 36 weeks’ GA and term age and between 1 and 2 months. Growth was also evaluated over longer periods systematically, from birth and then from 36 weeks’ GA to all measurement points. We calculated z scores to indicate the number of SDs by which the measurements differed from the mean at a specific age. The growth parameters before 40 weeks’ GA were converted to these z scores according to Finnish growth charts. These growth charts are in clinical practice for growth assessment and based on live-born infants. We used the World Health Organization growth curves from term to 5 years of age to improve the comparability and generalizability of our data. Vermont Oxford Network definitions were used for neonatal diagnoses. A diagnosis of cerebral palsy was confirmed by a pediatrician at the 2-year follow-up visit. Associations between the categorical predictors and the continuous response variables were studied using the Kruskal–Wallis test. Univariate associations between 2 continuous variables were studied with Spearman’s correlation coefficient (r). The association between the background variables (GA, gender, NEC, BPD, brain pathology, and the mother’s education) and growth was analyzed. Associations between the z score change of growth and FSIQ were studied by using regression analysis, controlling for gender, GA, and the mother’s educational level. A statistically significant result was defined as \( P < 0.05 \).

RESULTS

The descriptive data including cognitive outcome and birth growth data are presented in Table 1 for SGA and non-SGA infants separately. Our cohort consisted of 33% SGA infants and 67% non-SGA infants. Most of the SGA infants (68%) had disproportional growth failure with head sparing, suggesting that those infants might have had growth restrictions before birth.

Determinants of Growth

Gender, GA, and brain pathology significantly determined long-term growth patterns in the whole study cohort. Girls gained more weight between birth and 1 year (\( P = .006 \)) and 2 years’ CA (\( P = .007 \)). Higher GA correlated with better growth before term equivalent age (weight: \( r = 0.73, P < .0001, \) length: \( r = 0.56, P < .0001, \) HC: \( r = 0.42, P < .0001 \)) and also up to 5 years of age (weight: \( r = 0.55, P < .0001, \) length: \( r = 0.44, P < .0001, \) HC: \( r = 0.25, P = .02 \)). The infants with a normal brain MRI at term age gained more weight between birth and 5 years of age than did the infants with brain pathology (\( P = .02 \)).

Growth Patterns

Figure 1 presents the cumulative percentage of SGA infants whose body growth exceeded −2.0 SD in each growth measure to describe the catch-up growth of these growth-restricted
infants. The growth measurements for SGA and non-SGA children between birth and 5 years of age are presented in Supplemental Table 4. Because the growth of preterm infants might be inconsistent over short time periods, the percentage of postnatal growth restriction (weight, length, HC < −2.0 SD) is also presented in Supplemental Table 4.

Growth and Cognitive Outcome

Body growth over a long period, between birth and 5 years of age, did not associate with cognitive outcome. Postnatal weight gain and growth in HC between birth and 2 years of age was associated with improved cognitive outcome in non-SGA children (see Table 2 for detailed information). Postnatal growth in length did not correlate to FSIQ (Table 2). Interestingly, in SGA infants only good HC growth after 36 weeks’ GA in shorter periods, until 4 months of age (P = .03), was associated with higher FSIQ at 5 years of age (see Supplemental Table 5).

When the study infants were studied as a whole group, only HC growth was associated with FSIQ (Table 2). FSIQ at the age of 5 years increased by 2.5 (95% confidence interval [CI], 0.67–4.33, P = .008) for each z score increase in the HC between birth and 1 year of CA, by 3.6 (CI, 0.95–6.15, P = .007) between term equivalent age and 1 year of CA, by 2.5 (CI, 0.45–5.70, P = .02) between term equivalent age and 2 years’ CA after adjustments for GA, gender, and the mother’s education.

DISCUSSION

We studied the impact of antenatal (SGA) and postnatal growth on cognition at 5 years of age in a cohort of 181 very preterm infants using comprehensive growth data. Furthermore, we analyzed whether there is an association between growth during any particular time period between birth and 5 years of age and cognitive outcome at 5 years of age, to discover whether

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Descriptive Data for the Study Cohort and Their Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGA Children (n = 59)</td>
</tr>
<tr>
<td></td>
<td>Mean (min, max) SD or %</td>
</tr>
<tr>
<td>Multiple birth</td>
<td>29</td>
</tr>
<tr>
<td>GA, wk d/7*</td>
<td>30/6/7 (25 5/7, 35 6/7) 2 4/7</td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
</tr>
<tr>
<td>Birth wt, g</td>
<td>1090 (400, 1500) 285</td>
</tr>
<tr>
<td>Z scorea</td>
<td>−3.0 (−5.0, −2.0) 0.8</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>36 (27, 38) 3.6</td>
</tr>
<tr>
<td>Z scorea</td>
<td>−2.3 (−7.8, 1.0) 1.6</td>
</tr>
<tr>
<td>Birth HC, cm</td>
<td>27 (20, 31) 2.4</td>
</tr>
<tr>
<td>Z scorea</td>
<td>−1.9 (−5.3, 0.3) 1.2</td>
</tr>
<tr>
<td>Antenatal corticosteroids*</td>
<td>86</td>
</tr>
<tr>
<td>Apgar score at 5 min*</td>
<td>7.2 (2, 10) 1.7</td>
</tr>
<tr>
<td>Sepsis or meningitis</td>
<td>20</td>
</tr>
<tr>
<td>BPD</td>
<td>10</td>
</tr>
<tr>
<td>NEC</td>
<td>2</td>
</tr>
<tr>
<td>Brain pathology</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
</tr>
<tr>
<td>Minor</td>
<td>32</td>
</tr>
<tr>
<td>Major</td>
<td>39</td>
</tr>
<tr>
<td>FSIQ</td>
<td>99 (42, 133) 17.6</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3</td>
</tr>
<tr>
<td>Length of mother, cm</td>
<td>166 (153, 181) 5.6</td>
</tr>
<tr>
<td>HC of mother, cm</td>
<td>55 (52, 58) 1.5</td>
</tr>
<tr>
<td>Length of father, cm</td>
<td>180 (154, 197) 6.8</td>
</tr>
<tr>
<td>HC of father, cm</td>
<td>58 (54, 63) 1.5</td>
</tr>
</tbody>
</table>

* Statistically significant difference was found between these groups in addition to difference in birth wt z score.
there is a particular growth period significant for brain development. We found differences in the growth profiles of SGA and non-SGA infants. In non-SGA children, good weight gain and growth in HC between birth and 2 years' CA was associated with better cognitive outcome at 5 years of age, but this was not the case in SGA infants. Consistently, Latal-Hajnal et al26 found that good weight gain up to 2 years' CA was associated with better cognitive outcome in non-SGA but not in SGA infants. However, they did not find HC growth to associate with cognitive outcome. Hack et al31 also showed that the HC at 8 months' CA was associated with cognition for all VLBW infants (ie, without separating them into SGA and AGA groups) at 8 to 9 years of age.

We found that good HC growth around term age was associated with improved cognition in SGA infants. Similarly, Stathis et al42 found that poor HC growth between birth and 4 months' CA was associated with impaired 6-year cognition in extremely low birth weight infants. Frisk et al27 showed that cognition was better in the SGA infants with good postnatal HC growth than in SGA infants with a small HC at birth and at 9 months of age. Brandt22 also found that the SGA infants with HC catch-up growth until 1 year of age had higher intelligence scores than those without HC catch-up growth. After controlling for gender, GA, and the mother's education, we found that 5-year FSIQ improved by 2.5 for each z score increase in HC between term equivalent age and 2 years' CA.

Our study suggests that the most significant time period for HC growth in SGA infants is around term age. This implies that nutrition at home after discharge from hospital warrants additional evaluation, especially for SGA infants. We hypothesized that good

### TABLE 2 Correlations Between Growth From Birth to 2 Years of CA and 5-y Cognition

<table>
<thead>
<tr>
<th>Time Period From Birth</th>
<th>Wt</th>
<th>Length</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGA</td>
<td>Non-SGA</td>
<td>All</td>
</tr>
<tr>
<td>To 36 wk GA</td>
<td>-0.12</td>
<td>0.22*</td>
<td>0.08</td>
</tr>
<tr>
<td>To term age</td>
<td>-0.25</td>
<td>0.21*</td>
<td>0.03</td>
</tr>
<tr>
<td>To 1 mo</td>
<td>-0.14</td>
<td>0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>To 2 mo</td>
<td>-0.07</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>To 4 mo</td>
<td>-0.13</td>
<td>0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>To 1 y</td>
<td>-0.003</td>
<td>0.18</td>
<td>0.06</td>
</tr>
<tr>
<td>To 2 y</td>
<td>-0.07</td>
<td>0.18*</td>
<td>0.04</td>
</tr>
</tbody>
</table>

In this table are shown correlations (Spearman’s correlation coefficient) according to z score changes in wt, length, HC, and FSIQ. Correlations are presented separately for SGA, non-SGA, and all study children (both SGA and non-SGA children). Age was corrected for prematurity.

* Correlation was statistically significant (P < .05).

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**FIGURE 2**

Correlation between HC growth and cognitive outcome. The x-axis presents the z score change of HC between birth and 2 years of CA. The y-axis shows the FSIQ. The horizontal lines at FSIQ 85 and FSIQ 70 mark slightly below normal and significantly below normal, respectively.
growth in weight and length in SGA infants would be related to better cognitive outcome, but we did not find an association between weight and length growth and cognitive outcomes in SGA children. In the non-SGA infants, no single time period for growth was more significant than any other. Instead, consistent growth in weight and HC until 2 years’ CA was significant for good cognitive outcome for non-SGA infants. This is an important result because benefits of weight gain in non-SGA infants are also questioned.43 The relationship between length growth and cognitive outcome has been controversial10,14,19 in recent publications. In this study good growth in length was not associated with better outcome. The deviation from normal expected growth was most common at 36 weeks’ GA. At term age, almost all infants, including non-SGA infants, had HCs > –2.0 SD. The weight and length were > –2.0 SD in most infants at 1 year of CA. Although SGA infants had catch-up growth, they remained lighter (z score mean –0.8 vs 0.0) and shorter (–0.4 vs 0.0) and had smaller HCs (–0.4 vs 1.0) than non-SGA infants at 5 years of age. Postnatal growth restriction at 5 years of age was rare in our study cohort compared with some earlier studies: 3% vs 15%10 for weight, 3% vs 6%15 for height, and 1% vs 26%10 for HC. It must be noted that different studies report growth in preterm infant populations at different GAs or birth weights. There is also variation in the definition of intrauterine growth restriction, because some studies use a birth weight <10th percentile and others < –2.0 SD. In addition, causes of intrauterine and postnatal growth restriction vary, as do individual growth rates and styles.15 Furthermore, some infants classified as non-SGA at birth could have been subject to growth restriction in utero and thus had not achieved their genetic growth potential before birth. Growth references and age corrections also vary between studies, along with the age points and methods for evaluation of cognitive outcome. However, because we compared the postnatal growth of SGA and non-SGA very preterm infants and the effect of postnatal growth on their cognitive outcome, we concluded that the differences between growth charts used may not be significant. Yet it is also important to indicate that the cognitive outcome was described by the FSIQ and that this global measure is only 1 aspect of cognitive capacity and does not describe the neuropsychological profile. One limitation of our study is the lack of full-term non-SGA infants for comparison. Measurement of infants is error-sensitive, and without standardized methods there would be significant variability between measurers. At 5 years of age children were measured by trained nurses at well baby clinics. The Finnish National Institute for Health and Welfare has produced a detailed manual of methods for measuring children correctly, and the use of these standardized methods is mandatory. Therefore, it is unlikely that the obtained measurements were not reliable. According to Howe et al,44 routinely collected length, height, and weight measures from child health records are comparable, with no systematic bias, supporting their use in clinical practice and research. Cognitive outcome was similar in SGA and non-SGA preterm born children. Therefore, we assume that postnatal growth in this very preterm cohort, for whom malnourishment was unlikely, was sufficient for brain development. We found that good growth in weight and HC until 2 years’ CA in non-SGA children and good HC growth around term age in SGA infants was associated with better cognitive outcome. Therefore, our results emphasize the importance of growth evaluation as part of the developmental follow-up of very preterm infants. In addition, optimal postdischarge nutrition might especially benefit SGA infants.

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**BITS, BOTS, AND PEOPLE:** When I get an email asking me to claim money from a bank account in Nigeria or make contact with a long lost relative currently living in Bulgaria, I am fairly confident these are fake, and probably automatically generated. They are deleted without much thought. When a news organization reports that Twitter erupted over events someplace, I am less sure how to interpret the news. It would appear that social media sites are easily manipulated. As discussed in The New York Times (August 11, 2013), robotic programs, or “bots”, have become increasingly sophisticated and have been used to discredit political opponents, shape news stories, influence buying habits, and even find love. Bots for social media, often called socialbots, can be programmed to tweet and retweet. They have oddities, specific histories, matching accounts on multiple social media sites, and sleep cycles, making them hard to detect as non-human. Amazingly, some researchers estimate that only 35 percent of the average Twitter user’s followers are real people.

Approximately half of all Internet traffic already comes from nonhuman sources like bots. Computer scientists in Brazil recently revealed that a popular journalist on Twitter was actually a bot they had created. While that does not sound terrible, a respected ranking site classified the make-believe journalist as having more online “influence” than Oprah Winfrey. Others have stolen Twitter hashtags of political opponents and flooded the internet with inappropriate messages—forcing Twitter, per protocol, to shut down the hashtag. The effect was to silence the opponents.

Dating sites are not immune to the effects of bots. When a large on-line dating company bought a smaller service, they redesigned the site. The result was a sharp decline in the number of bots, but also members using the site. Evidently, the bots, which had automatically liked postings and had sent flirtatious emails, made the site seem safe and full of love—if only robotic love.

Now when I read or hear anything about social media, I take what I hear with a grain (or more) of salt and ask myself, how likely is this real or generated automatically?

*Noted by WVR, MD*
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