ARTICLE

Prenatal and Postnatal Growth and Cognitive Abilities at 56 Months of Age: A Longitudinal Study of Infants Born at Term

Kati Heinonen, PhD[a], Katri Räikkönen, PhD[a], Anu-Katriina Pesonen, PhD[a], Eero Kajantie, MD, PhD[b], Sture Andersson, MD, PhD[b,d], Johan G. Eriksson, MD, PhD[c], Anja Niemelä, MD[e], Timo Vartia, MD[e], Juha Peltola, MD[e], Aulikki Lano, MD[e]

Departments of [a]Psychology and [c]Public Health, University of Helsinki, Helsinki, Finland; [b]National Public Health Institute, Helsinki, Finland; [d]Department of Pediatrics, Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland; [e]Department of Child Neurology, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Both prenatal and postnatal growth may affect the development of cognitive abilities. Prematurity and small body size at birth in epidemiologic samples have been found to have adverse effects on cognitive development.

What This Study Adds

Even within children born at term, fetal and childhood growth are of major importance in laying the foundations of individual differences in cognitive abilities.

ABSTRACT

OBJECTIVE. The aim of the study was to investigate whether weight, length, BMI (kilograms per meter squared), and head circumference at birth and their postnatal growth are associated with cognitive abilities at 56 months of age among infants born at term.

PATIENTS AND METHODS. Our sample was composed of 1056 Finnish children born at term, ($37^{0/7}$ to $41^{6/7}$ weeks) free of any major impairments. Weight, length, and head circumference were measured at birth and at 5, 20, and 56 months of age, and BMI was calculated. We assessed cognitive abilities by conducting tests of general reasoning, visual-motor integration, verbal competence, and language comprehension at 56 months of age.

RESULTS. Firstly, for every 1 SD lower in weight or BMI at birth, general reasoning and/or visual-motor integration was >1.20 points lower, and for every 1 SD lower in length or head circumference at birth, abilities across all of the cognitive domains were >1.31 points lower. Second, for every 1 SD slower gain in weight or BMI from birth to 5 months, general reasoning and visual-motor integration decreased by >0.97 points; for every 1 SD slower gain in length from 5 to 20 months and from 20 to 56 months, respectively, visual-motor integration, and verbal competence and language comprehension decreased by >1.03 points; and for every 1 SD slower increase in head circumference from birth to 5 months and from 5 to 20 months, respectively, visual-motor integration and language comprehension decreased by >1.17 points. Third, tests for nonlinear relationships revealed that, in some cases, large body size and faster growth were also associated with lower scores in cognitive tests.

CONCLUSIONS. Our findings suggest that, even within the range of children born at term, prenatal and postnatal growth in body size are associated with individual differences in cognitive abilities.

www.pediatrics.org/cgi/doi/10.1542/peds.2007-1172

doi:10.1542/peds.2007-1172

The work does not report the results of a clinical trial.

Key Words
birth size, growth, cognitive abilities, postnatal growth, term born

Abbreviations
UC—unstandard coefficient
CI—confidence interval
IGF—insulin-like growth factor

Accepted for publication Nov 13, 2007

Address correspondence to Kati Heinonen, PhD, Department of Psychology, PO Box 9, FI-00014 University of Helsinki, Helsinki, Finland. E-mail: kati.heinonen@helsinki.fi

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Together with genetic and environmental influences provided by the parents, both prenatal and postnatal growth may affect the development of cognitive abilities. Prematurity and small body size at birth in epidemiologic samples, including infants born prematurely and infants whose gestational age is not reported, have been found to have adverse effects on cognitive development.[1–9] Furthermore, infants with suboptimal postnatal growth may perform less well in cognitive tests.[3,4,10–14] It is less clear whether variations in prenatal and postnatal growth among infants born at term affect cognitive functioning. Thus, the major objective of this study was to test in a sample of 1056 Finnish children born at term ($37^{0/7}$ to $41^{6/7}$ weeks) the hypothesis that a smaller body size at birth and faster somatic growth from birth to 5, 20, and 56 months of age are associated with lower levels of cognitive abilities at 56 months.

METHODS

The study cohort was composed of infants participating in the Arvo Ylppö Longitudinal Study.[15,16] From a total of 15 311 deliveries in the 7 maternity hospitals in the county of Uusimaa, Finland, we identified all of the infants born live between March 15, 1985, and March 14, 1986, who were followed up at a neonatal ward of the obstetric unit or transferred to the NICU of the Hospital for Children and Adolescents, Helsinki University Central Hospital, within 10 days of their birth. The population ranged from severely ill preterm infants to infants born at term requiring only brief inpatient observation. In total there were 1535 infants, that is, >10% of the newborns in the area, who were admitted to the neonatal ward for follow-up or treatment during the predetermined period. In addition, 658 infants born during the same period but not admitted to the neonatal ward were prospectively randomly recruited from the 3 largest maternity hospitals in the study area; the neonate born after every second hospitalized infant was selected. Thereafter, the participants were invited to clinical follow-up visits at 5, 20, and 56 months of age. The study protocol was approved by the ethical committees of each participating hospital, and the parent(s) gave their informed consent.

Of the 2193 infants selected for the Arvo Ylppö study, 1599 infants born at term (<37 weeks or >42 weeks) survived to the 56-month follow-up. We excluded 104 because of major impairments and/or mental retardation (ie, major congenital malformations, chromosomal abnormalities, grade 2–4 cerebral palsy,[17] deafness or a hearing defect requiring a hearing aid, epilepsy, and/or with developmental delay at 56 months of age). Finally, there were no follow-up data available at the 56-month visit for 439 infants. Altogether, the participants of the current study were 1056 children born at term and free of major impairments and/or mental retardation (see Fig 1). Of the 602 admitted children, 77 were admitted for observation without any diagnosis. Among the more prevalent diagnoses were respiratory problems (n = 197: 8 had respiratory distress syndrome, 65 had meconium aspiration syndrome, 28 had pneumothorax or other air leakage, and 96 had transient tachypnea or another neonatal respiratory condition), neonatal jaundice (n = 140: 17 had neonatal hemolytic disease, 9 had peak bilirubin levels of 20–25 mg/dL, and 1 had a peak bilirubin level >25 mg/dL), suspected sepsis (n = 50: 16 had a positive blood culture), maternal infection (n = 47), fetal distress (n = 42), hypoglycemia (n = 24, blood glucose <2.2 mmol/L in 2 consecutive measurements), maternal hypertensive disorder (n = 14), and infant feeding problems (n = 13). Less prevalent (n < 10) diagnoses included fetal blood loss or hemorrhage, minor anomalies such as clubfoot, and miscellaneous diagnoses such as torsion of the testis and pyelonephritis.

Of the infants born at term without any major impairment, those who provided follow-up data at 56 months of age (n = 1056) did not differ from those who were lost to the follow-up (n = 439) in gender (P = .18), multiple pregnancy (P = .57), or in the mother's height (P = .46). However, infants lost to the follow-up were more likely to have been admitted to the neonatal ward (P = .002), to come from less educated families (P = .001), to have had younger mothers (P = .007), mothers who smoked more during the pregnancy (P < .001), and whose gestational length was shorter and body size at birth smaller (Ps < .04).

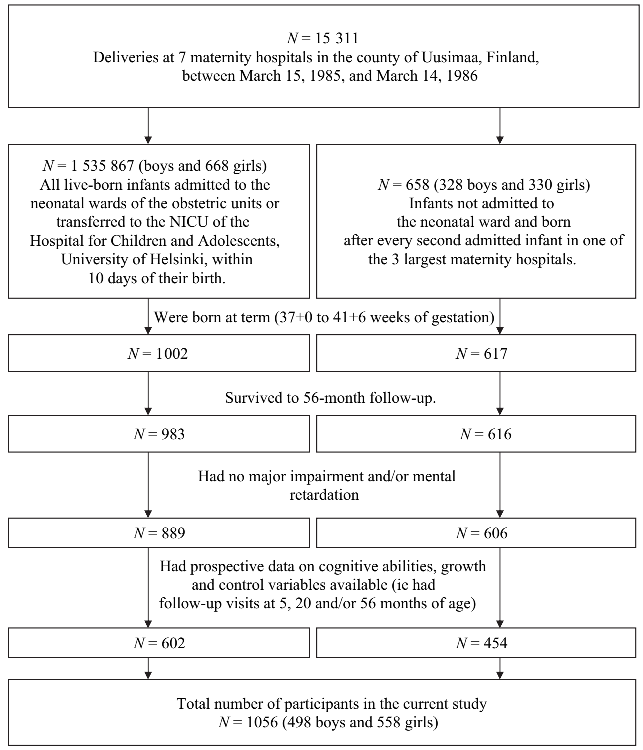

FIGURE 1
Selection of the participants.

Body Size at Birth and in Infancy and Childhood

Data on the newborns' date of birth, weight (grams), length (centimeters), and head circumference (centimeters) were extracted from the birth records, and the BMI was calculated (kilograms per meter squared). The same anthropometric measures were taken during the clinical visits at 5, 20, and 56 months. Because the clinical visits were arranged on working days, not all of the families were able to arrange to be there on the day when the child was exactly 5, 20, or 56 months old. Thus, all of the anthropometric measurements were corrected for exact age (mean: 5 months and 3 days, 20 months and 6 days, and 56 months and 16 days, respectively; SD: 9, 15, and 14 days, respectively) by linear regression.

Growth

The growth variables were the standardized residuals from the linear regression models of body size. Body size at each time point was regressed on corresponding measures at all of the earlier time points, thus creating completely uncorrelated residuals reflecting growth conditional on previous history. For example, weight gain from 20 months to 56 months of age, conditional on weight gain to 20 months of age, was calculated by saving the residuals from the regression model of weight SD scores at 56 months on weight at birth, at 5 months, and at 20 months. The residuals provided information on whether growth by a particular age was faster or slower than would have been predicted from previous measurements (see also ref 18).

Gestational Age

Gestational age was determined primarily from the date of the mother's last menstrual period and ultrasound examination. All of the infants were given a Dubowitz examination.[19] When there was a difference in the estimates of >2 weeks, the Dubowitz clinical maturity assessment results were used.

Cognitive Assessments at 56 Months

During the clinical follow-up visit, 1 member of a team of 4 trained pediatricians gave cognitive-ability tests to the children.[15] First, general reasoning was measured on the Columbia Mental Maturity Scale.[20] This is a nonverbal cognitive-ability test consisting of 100 cards displaying sets of 3 to 5 drawings from which the child has to select the 1 that is different from or unrelated to the others. Second, visual-motor integration was measured on the Beery scale[21]; the child is asked to copy geometrical figures. Third, verbal competence was measured by administering a Finnish translation of the verbal competence test devised by Kiese and Kozielski.[22] It is composed of 82 picture-naming tasks and is similar to the Peabody picture vocabulary test[23] that is frequently used to assess verbal intelligence. Fourth, language comprehension was assessed on the Logopädisher Sprachverständnis Test devised by Wettstein,[24] which includes a set of standard toys with which the child is asked to follow the actions verbally requested by the examiner. All of the cognitive test scores were corrected for exact age at measurement.

Confounders

The following data were derived from hospital records and maternal interviews at birth and at 5 months of age: the child's gender, breastfeeding at 5 months of age (1 = full, 2 = partial, 3 = finished, and 4 = never breast fed), maternal smoking during pregnancy (0, 1–5, 6–10, or >10 cigarettes per day), multiple pregnancy (singleton versus multiple), parental education (from I = elementary school to IV = university education; the average of the mother's and the father's educational level was used), maternal age at delivery, and her self-reported height.

Statistical Analysis

Body size at birth and at 5, 20, and 56 months of age was converted into *z* scores (mean: 0; SD: 1) by gender. The raw scores in the cognitive ability tests were also standardized (mean: 100; SD: 15) to make achievements in the ability tests comparable. The standardized scores for body size measures and in the cognitive ability tests represent the difference from the mean value for the sample of children participating in the current study and who were born at term free of any major impairment and/or mental retardation.

Multiple linear regression analyses were used to test the effect of body size at birth and at 5, 20, and 56 months and growth from birth to 5, 20, and 56 months of age (ie, growth conditional on previous history) on the child's cognitive abilities. Because these relationships are not necessarily linear,[25] to test the potential U-shape relationships, we used multiple linear regression analyses and analyses of covariance. In the former, the U-shaped relationships were modeled via squared terms, and in the latter, polynomial contrasts were computed for body size at birth, achieved body size, and growth to 56 months grouped into 8 deciles.

RESULTS

Table 1 shows the characteristics of the main variables in the 2 groups, those admitted to the neonatal ward and those not admitted. The infants in the first group were lighter, thinner, and had a smaller head circumference at birth, but the 2 groups did not differ in anthropometric measures after birth or in their cognitive-ability test scores. The admitted infants were born earlier (mean: 39.2, SD: 1.4 weeks versus mean: 39.6, SD: 1.1 weeks), were less likely to be singletons (n = 578 [96.0%] vs n = 446 [98.2%]), came from less educated families (mean: 2.3, SD: 0.9 vs mean: 2.4, SD: 0.9), and were breastfed for a shorter period of time (n = 65 [10.8%], n = 207 [34.4%], n = 299 [49.7%], n = 31 [5.1%] vs n = 75 [16.5%], n = 139 [30.6%], n = 237 [52.2%], n = 3 [0.7%] for the solely, partly, finished, and never breastfed, respectively) (Ps < 0.05). The groups did not differ in gender distribution (females: n = 333 [55.3%] vs n = 225 [49.6%]), maternal age (mean: 29.8 years, SD: 5.3 years versus mean: 29.4 years, SD: 4.7 years), height (mean: 164.7 cm, SD: 5.5 cm versus mean: 164.7 cm, SD: 5.3 cm), or maternal smoking during pregnancy (n = 488 [81.1%], n = 41 [6.8%], n = 41 [6.8%], and n = 32 [5.3%] vs n = 387 [85.2%], n = 21 [4.6%], n = 31 [6.8%], and n = 15 [3.3%] for 0, 1–5, 6–10, and >10 cigarettes per day, respectively; Ps > .05). Because some of the conditions in the admitted group may affect cognitive development, ie, hyperbilirubinemia, sepsis, a low 5-minute Apgar score (<4), and hypoglycemia, we also compared the infants with any of these conditions (n = 53) with admitted infants with any of the other conditions and with the rest of the sample in terms of cognitive abilities. The groups did not differ in any of the cognitive ability tests (Ps > .24). Therefore, we present a pooled analysis.

Furthermore, gender-specific analyses indicated that the girls were smaller than the boys in body size at each age (Ps < .001). They performed better in verbal competence (unstandard coefficient [UC]: 2.35; 95% confidence interval [CI]: 0.49 to 4.20) but less well in general reasoning (UC: −4.16; 95% CI −5.96 to −2.35), visual-motor integration (UC: −2.77; 95% CI −4.60 to −0.93), and language comprehension (UC: −4.09; 95% CI −5.92 to −2.26). Finally, even after the gender difference was controlled for, better results were achieved by children with a higher gestational age (general reasoning: UC: 0.88, 95% CI: 0.17 to 1.59; visual-motor integration: UC: 1.28, 95% CI 0.57 to 1.99; verbal competence: UC: 0.99, 95% CI: 0.26 to 1.71), who had been breastfed for longer (verbal competence: UC: 5.77, 95% CI: 0.77 to 10.77, never versus partial), who were singletons (verbal competence: UC: −5.32, 95% CI: −10.18 to −0.46; visual-motor integration: UC: −6.24 95% CI −11.19 to −1.30), whose mothers had smoked less during pregnancy (general reasoning: UC: −4.65, 95% CI:

TABLE 1 **Characteristics of the Sample by Admission to the Neonatal Ward for Follow-up or Treatment During the First 10 Days**

Characteristic	Admitted to the Neonatal Ward		Not Admitted to the Neonatal Ward	
	n	Mean (SD)	*n*	Mean (SD)
At birth				
Weight, kg	602	3.5 (0.6)	454	3.6 (0.5)[a]
Length, cm	602	50.1 (2.6)	454	50.4 (2.0)
Head circumference, cm	602	35.1 (1.6)	454	35.4 (1.4)[a]
BMI, kg/m^2	602	13.8 (1.5)	454	14.2 (1.1)[a]
At 5 mo				
Weight, kg	591	7.3 (0.9)	448	7.4 (0.9)
Length, cm	586	65.7 (2.6)	443	65.9 (2.3)
Head circumference, cm	583	43.0 (1.3)	444	42.9 (1.2)
BMI, kg/m^2	582	16.9 (1.5)	443	17.0 (1.4)
At 20 mo				
Weight, kg	574	11.8 (1.4)	423	11.8 (1.3)
Length, cm	561	84.2 (3.0)	410	84.2 (3.0)
Head circumference, cm	572	48.9 (1.5)	429	48.9 (1.4)
BMI, kg/m^2	559	16.6 (1.3)	406	16.6 (1.3)
At 56 mo				
Weight, kg	593	18.4 (2.7)	444	18.2 (2.4)
Length, cm	585	108.4 (4.4)	441	108.3 (4.4)
Head circumference, cm	587	51.9 (1.4)	447	51.8 (1.3)
BMI, kg/m^2	583	15.6 (1.5)	439	15.5 (1.3)
Cognitive abilities				
General reasoning	589	100.1 (15.1)	447	99.8 (14.7)
Visual-motor integration	585	99.2 (14.9)	436	100.9 (14.9)
Verbal competence	563	100.8 (14.9)	428	99.3 (14.8)
Language comprehension	576	99.9 (15.0)	435	99.9 (14.9)

[a] P value was <.05.

−8.35 to −0.95; visual-motor integration: UC: −6.10, 95% CI: −10.26 to −1.94, nonsmokers versus infants of mothers smoking >10 cigarettes per day), and came from better-educated families (all cognitive test scores, UC: >1.55, 95% CI: 0.56 to 4.80). Neither the mother's age nor her height (Ps > .06) predicted the child's cognitive abilities.

Gender and gestational age were introduced as confounders in the first step (model I), followed in the second step by status of admission to the neonatal ward, breastfeeding, smoking during pregnancy, multiple versus singleton pregnancy, parental education, and maternal age and height (model II). All of the results were also run without controlling for admission to hospital and adding maternal weight at delivery as an additional covariate into model 2. These changes did not alter the results and, thus, are not discussed further.

Relative Body Size at Birth and at 5, 20, and 56 Months and Cognitive Abilities at 56 Months

As Fig 2 shows, after adjustment for gender and gestational age (model I), and further for the other covariates (model 2), the children who were lighter, shorter, and had a smaller head circumference at birth performed significantly worse in the cognitive ability tests at 56 months of age, with a few exceptions. The figure also shows similar trends regarding the achieved body size measures at 5, 20, and 56 months.

The visual-motor-integration test scores were lower by 1.35 to 1.91 points (95% CIs: 0.41 to 2.52, both models) for each 1-SD-lower BMI at birth and at 5 and 20 months. General reasoning was lower by 0.79 to 0.89 points (95% CIs: 0.01 to 1.67, model 2) for each 1-SD-lower BMI at 5, 20, and 56 months of age.

Growth and Cognitive Abilities at 56 Months

When all of the confounders were controlled for, a slower gain in weight and in BMI from birth to 5 months was associated with worse performance in general reasoning and visual-motor integration (see Table 2). A slower growth in height from 5 to 20 months was associated with worse performance in visual-motor integration and from 20 to 56 months with worse verbal competence and language comprehension. A slower growth in head circumference from birth to 5 months and from 5 to 20 months predicted worse performance in visual-motor integration, and from 5 to 20 months it predicted worse performance in language comprehension. Furthermore, even after postnatal growth was controlled for, the birth-size measures generally had the largest and most consistently positive effects on cognitive abilities. The birth-size measures were most systematically associated with visual-motor integration.

Furthermore, the analyses were rerun after the exclusion of infants with weight <2.5 kg at birth (n = 48) and, thereafter, of those with neonatal hyperbilirubinemia, sepsis, a low 5-minute Apgar score, and/or

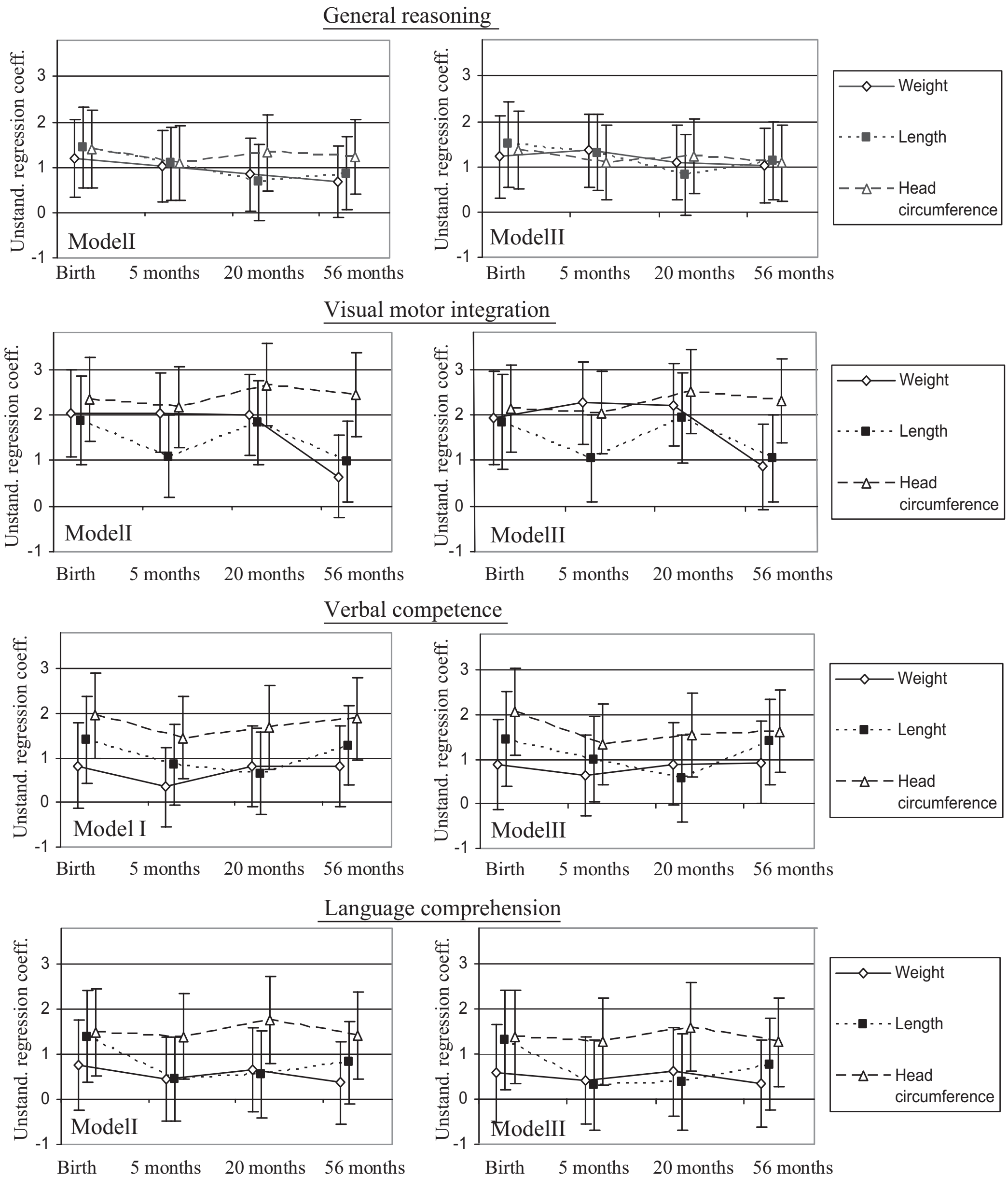

FIGURE 2
Body size measures as predictors of cognitive abilities. The horizontal lines represent unstandardized regression coefficients (ie, mean change in test scores for 1 SD increase in growth indicator), and the vertical lines represent the upper and lower bounds of the 95% CIs. Model I was adjusted for gender and gestational age. Model II was further adjusted for admission to the neonatal ward, breastfeeding, smoking during pregnancy, multiple/singleton pregnancy, parental education, maternal age, and height.

hypoglycemia ($n = 53$). These exclusions had a minimal effect on the results.

U-Shaped Relationships Between Body Size at Birth and at 5, 20, and 56 months and Growth and Cognitive Abilities at 56 Months

Figure 3 reveals the following U-shaped relationships when all of the confounders had been controlled for: weight (Fig 3A), head circumference (Fig 3B), and BMI at 20 (Fig 3C) and 56 months (Fig 3E) showed U-shaped relationships with visual-motor integration; weight at 56 months showed U-shaped relationships with general reasoning (Fig 3D); and growth in BMI from 5 to 20 months showed U-shaped relationships with visual-motor integration (Fig 3F). These relationships show that both a small and a large body size, and slower and faster growth, were associated with worse cognitive test performance.

DISCUSSION

In our sample of 1056 Finnish children born at term, those of a smaller relative size at birth and ≤56 months of age fared generally worse in cognitive ability tests at 56 months. Different periods and measures of somatic growth may cause different effects on later cognitive abilities: a slower gain in weight and BMI seems to be

TABLE 2 **Differences in Cognitive Ability Scores at 56 Months of Age According to SD Score Decreases in Anthropometric Variables**

Growth Variable	General Reasoning, Unstandardized Regression Coefficient (95% CI)		Visual-Motor Integration and Functioning, Unstandardized Regression Coefficient (95% CI)		Verbal Competence, Unstandardized Regression Coefficient (95% CI)		Language Comprehension, Unstandardized Regression Coefficient (95% CI)	
	Model I Adjusted for Gender and Gestational Age	Model II Full Model	Model I Adjusted for Gender and Gestational Age	Model II Full Model	Model I Adjusted for Gender and Gestational Age	Model II Full Model	Model I Adjusted for Gender and Gestational Age	Model II Full Model
Weight								
At birth	1.79 (0.22 to 3.37)[a]	1.85 (0.18 to 3.52)[a]	3.47 (1.72 to 5.22)[c]	3.23 (1.38 to 5.08)[b]	1.64 (−0.11 to 3.40)	1.59 (−0.27 to 3.46)	1.16 (−0.67 to 2.99)	0.72 (−1.27 to 2.72)
Growth from birth to 5 months	0.70 (−0.14 to 1.53)	1.08 (0.25 to 1.90)[b]	1.58 (0.66 to 2.50)[c]	1.93 (1.01 to 2.84)[c]	0.10 (−0.84 to 1.04)	0.41 (−0.52 to 1.35)	0.21 (−0.76 to 1.18)	0.26 (−0.73 to 1.25)
Growth from 5 to 20 months	0.05 (−0.77 to 0.86)	0.12 (−0.70 to 0.93)	0.34 (−0.57 to 1.24)	0.45 (−0.46 to 1.35)	0.68 (−0.23 to 1.60)	0.51 (−0.40 to 1.42)	0.36 (−0.58 to 1.30)	0.30 (−0.67 to 1.27)
Growth from 20 to 56 months	−0.11 (−0.93 to 0.72)	0.14 (−0.67 to 0.95)	−1.02 (−1.92 to −0.11)[a]	−0.71 (−1.60 to 0.18)	0.53 (−0.39 to 1.45)	0.63 (−0.27 to 1.54)	−0.29 (−1.24 to 0.66)	−0.25 (−1.21 to 0.71)
Length/height: at birth	0.52 (0.12 to 0.91)[b]	0.58 (0.16 to 1.00)[a]	0.84 (0.40 to 1.28)[c]	0.84 (0.38 to 1.32)[c]	0.71 (0.28 to 1.15)[c]	0.77 (0.30 to 1.24)[b]	0.57 (0.12 to 1.01)[b]	0.55 (0.05 to 1.04)[a]
Growth from birth to 5 months	0.49 (−0.42 to 1.39)	0.81 (−0.10 to 1.71)	0.10 (−0.90 to 1.11)	0.25 (−0.76 to 1.26)	0.30 (−0.71 to 1.30)	0.56 (−0.45 to 1.57)	−0.03 (−1.00 to 1.07)	0.05 (−1.01 to 1.12)
Growth from 5 to 20 months	−0.22 (−1.05 to 0.61)	−0.11 (−0.94 to 0.72)	1.18 (0.25 to 2.10)[a]	1.29 (0.35 to 2.22)[b]	−0.25 (−1.17 to 0.67)	−0.30 (−1.22 to 0.62)	−0.13 (−1.09 to 0.82)	−0.17 (−1.15 to 0.81)
Growth from 20 to 56 months	0.39 (−0.45 to 1.22)	0.53 (−0.31 to 1.36)	−0.79 (−1.71 to 0.14)	−0.59 (−1.52 to 0.33)	1.59 (0.67 to 2.51)[c]	1.57 (0.65 to 2.49)[b]	1.01 (0.06 to 1.97)[a]	1.03 (0.05 to 2.01)[a]
Head circumference:								
At birth	0.83 (0.24 to 1.43)[b]	0.78 (0.17 to 1.40)[a]	1.53 (0.87 to 2.18)[c]	1.34 (0.67 to 2.02)[c]	1.40 (0.74 to 2.07)[c]	1.47 (0.78 to 2.15)[c]	0.81 (0.12 to 1.50)[a]	0.67 (−0.06 to 1.39)
Growth from birth to 5 mo	0.61 (−0.24 to 1.46)	0.66 (−0.18 to 1.49)	1.37 (0.45 to 2.29)[b]	1.46 (0.55 to 2.38)[b]	0.58 (−0.37 to 1.52)	0.48 (−0.45 to 1.41)	0.79 (−0.19 to 1.77)	0.75 (−0.25 to 1.74)
Growth from 5 to 20 mo	0.73 (−0.14 to 1.60)	0.56 (−0.29 to 1.41)	1.47 (0.53 to 2.42)[b]	1.29 (0.36 to 2.23)[b]	0.77 (−0.19 to 1.74)	0.60 (−0.35 to 1.55)	1.24 (0.23 to 2.25)[b]	1.17 (0.16 to 2.18)[a]
Growth from 20 to 56 mo	−0.01 (−0.83 to 0.82)	−0.14 (−0.96 to 0.67)	0.21 (−0.69 to 1.11)	0.22 (−0.67 to 1.12)	0.43 (−0.49 to 1.34)	0.12 (−0.78 to 1.02)	0.06 (−1.01 to 0.89)	−0.16 (−1.13 to 0.80)
BMI								
At birth	0.45 (−0.18 to 1.08)	0.40 (−0.26 to 1.05)	1.10 (0.40 to 1.80)[b]	0.86 (0.13 to 1.58)[a]	0.11 (−0.59 to 0.80)	0.03 (−0.70 to 0.75)	0.07 (−0.65 to 0.79)	−0.11 (−0.88 to −0.66)
Growth from birth to 5 mo	0.64 (−0.18 to 1.46)	0.97 (0.16 to 1.79)[a]	1.85 (0.95 to 2.76)[c]	2.20 (1.30 to 3.10)[c]	−0.32 (−1.24 to 0.61)	−0.004 (−0.96 to 0.88)	0.16 (−0.78 to 1.09)	0.24 (−0.72 to 1.19)
Growth from 5 to 20 mo	0.20 (−0.85 to 1.05)	0.27 (−0.56 to 1.11)	−0.04 (−0.98 to 0.91)	0.09 (−0.84 to 1.02)	0.93 (−0.03 to 1.88)	0.88 (−0.06 to 1.82)	0.31 (−0.66 to 1.28)	0.35 (−0.63 to 1.34)
Growth from 20 to 56 mo	−0.08 (−0.93 to 0.78)	0.14 (−0.70 to 0.97)	−0.51 (−1.44 to 0.42)	−0.24 (−1.15 to 0.68)	−0.07 (−1.00 to 0.87)	0.08 (−0.84 to 1.00)	−0.72 (−1.68 to 0.25)	−0.62 (−1.60 to 0.35)

Birth size, growth rates from birth to 5 months, from 5 to 20 months, and from 20 to 56 months are considered simultaneously. The growth variables are expressed as standardized residuals of regression of size at each age stage on size at previous age stage(s), that is, growth conditional on history. The full model includes adjustments for gender, gestational age, admission to the neonatal ward, breastfeeding, smoking during pregnancy, multiple/singleton pregnancy, parental education, maternal age at delivery, and maternal height.

[a] *P* value is <.05.

[b] *P* value is <.01.

[c] *P* value is <.001.

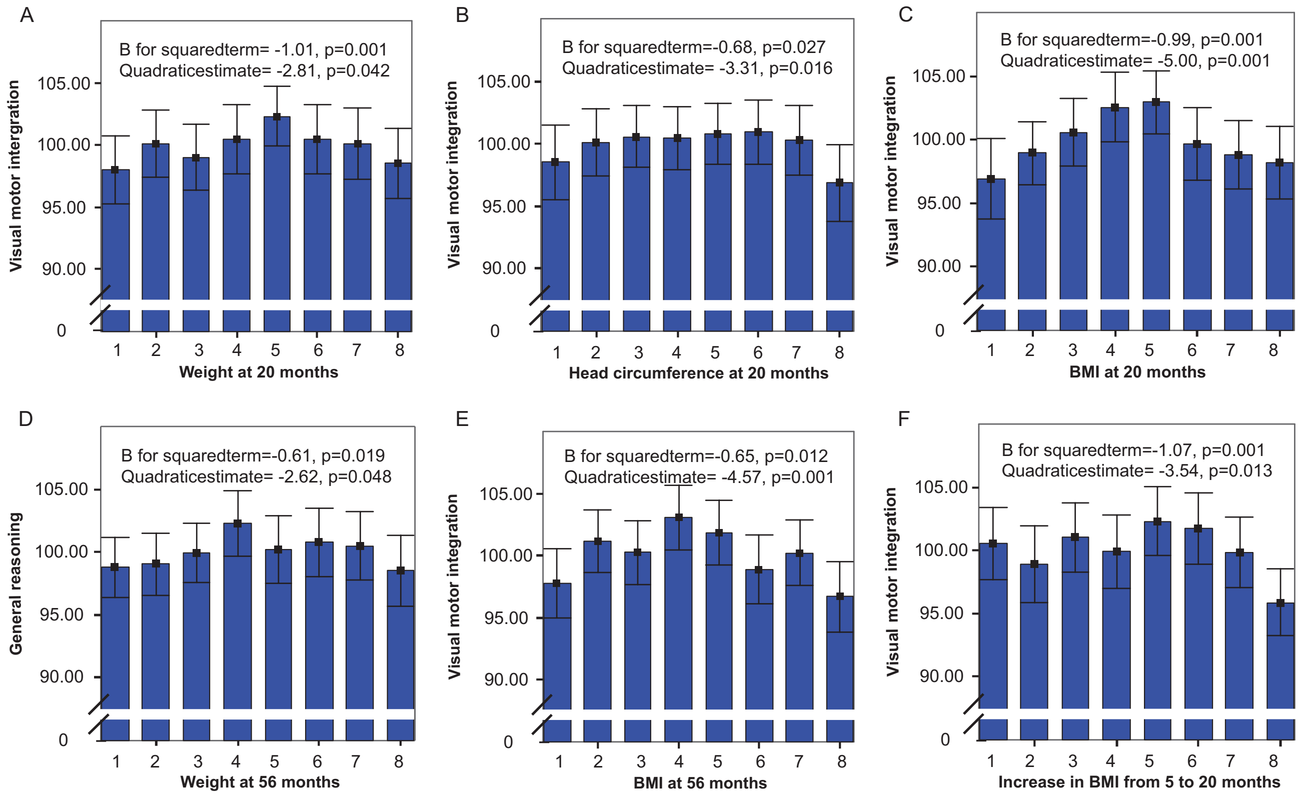

FIGURE 3
Multiple linear regression analyses (squared terms of body size measures) and analyses of covariance (polynomial contrast) testing the curvilinear relationships between body size at birth, at 5, 20, and 56 months and growth and cognitive abilities at 56 months.

negative in its effects during the early months, and a slower gain in head circumference seems to extend its effects from birth until near the second birthday, whereas a slower gain in length seems to play a role after the first months. As far as the different cognitive domains were concerned, general reasoning and visual-motor integration seemed to be predominantly predicted by growth in infancy, whereas growth later in childhood mattered more for the development of verbal competence and language comprehension. Our findings also revealed that, in a few cases, a larger body size and faster growth were associated with lower scores on cognitive tests.

One of the major strengths of this study is that anthropometric measures were available at different points of early childhood development, thereby making it possible to detect the periods of growth that are the most critical. A further advantage is that we had measures of gestational age available, thus allowing us to investigate whether growth predicted cognitive abilities among children born at term. We also had information on several factors known to be associated with cognitive abilities, which allowed us to test whether body size has independent effects.

There are limitations to our study. Two thirds of the infants participating in the Arvo Ylppö Longitudinal Study were admitted to the neonatal ward. Those in the admitted group were born smaller and earlier, came from less educated families, and were breastfed for a shorter time. However, the morbidity of the cohort hospitalized in Finland in the mid-1980s was lower than that of newborns admitted to the hospital today. A large proportion of our admitted group suffered from problems of a transient nature, an indication of this being that there were no differences in somatic growth up to 56 months or in cognitive abilities between the admitted and the notadmitted groups. The majority of the admitted infants had no diagnosed illness and were on the ward for observation or because of common problems of neonatal adaptation. Moreover, excluding those who suffered from a condition with potential cognitive consequences and those with a low birth weight (<2.5 kg) had no significant effect on the results. Loss to follow-up is also inevitable and introduces a potential selection bias. Although the participants in the current study did not differ in many variables from those lost to follow-up, they had better-educated parent(s), older mothers, a longer gestational length, and a larger birth size. The results, therefore, should not be generalized to all children born at term and may rather be more characteristic of children growing up in more affluent environments. The loss of "high-risk" infants could have led to the underestimation of an association, and the loss of participants may have undermined the ability to detect an association. Thus, loss to follow-up may have reduced rather than amplified our ability to detect significant associations in general.

Our findings showing associations between smaller relative body size and worse subsequent cognitive abilities are in accordance with the majority of previous findings,[18,26–32] and extend them in significant ways. Of the previous studies on children born at term, to our knowledge, 3 have focused solely on weight,[30–32] 1 solely on head circumference,[18] and none on length or BMI at birth. In our cohort, head circumference had the most striking effect on the measures of cognitive abilities.

With regard to postnatal growth, to our knowledge only 2 previous studies have focused on samples born at term.[18,26] Gale et al[18] demonstrated that, whereas slower growth in head circumference from birth to 1 year was related to lower verbal and performance IQ at the ages of 4 and/or 8 years, growth from 1 to 8 years was not. Silva et al[26] showed that slower growth in height and head circumference from 5 to 10 years predicted worse general cognitive abilities at the age of 10 years. Furthermore, weight gain from birth to the age of 10 years had a small negative effect on cognitive abilities.[26] Our results suggesting that slower growth in early childhood predicts worse cognitive abilities are, thus, in general agreement with earlier findings. However, when their clinical significance is evaluated, it should be kept in mind that the associations found were relatively modest. Measurements of body size are, nevertheless, crude measurements of conditions during childhood, and any association gives a hint of a biologically significant relationship. We also tested the possibility that the associations were nonlinear. Some previous studies indicate that birth weight may show an inverse U-shaped relationship with later cognitive abilities.[25] There is also evidence that faster weight gain from birth to 10 years[26] and after 15 years may be inversely associated with cognitive performance.[12] Thus, whereas the majority of the associations that we found point to linear relationships, this was not the case for all of them. There was no evidence of nonlinear association between birth size and cognitive abilities, but there was some evidence of a U-shaped association between postnatal growth and cognitive abilities. Our study, thus, contributes significantly to the current literature in showing that both a smaller body size and slower growth and a greater body size and faster growth may be related to lower scores on tests of cognitive ability.

There are no known biological mechanisms linking growth with cognitive development. Growth during the early years of life is a robust indicator of a broad range of adversities acting through multiple causal pathways.[33] Insulin-like growth factor (IGF)-1[34,35] mediates the effects of the growth hormone and has a significant role in somatic growth regulation and organ development. IGF-1 levels in childhood have been found to be related to verbal competence in a population-based sample of children[34] and among children born small for gestational age and treated with a growth hormone.[36] Thus, it is hypothesized that IGF-1 also has an impact on brain development.

CONCLUSIONS

To conclude, we found clear evidence that, even within children born at term, fetal and childhood growth is of major importance in laying the foundations of individual differences in cognitive abilities.

ACKNOWLEDGMENTS

This study was supported by grants from the Academy of Finland, the Emil Aaltonen Foundation, the University of Helsinki, the Juho Vainio Foundation, the Signe and Arne Gyllenberg Foundation, the Wihuri Foundation, the Pediatrics Research Fund, and The Ministry of Research and Technology of the Federal Republic of Germany.

REFERENCES

1. Sørensen HT, Sabroe S, Olsen J, Rothman KJ, Gillman MW, Fischer P. Birth weight and cognitive function in young adult life: historical cohort study. *BMJ.* 1997;315(7105):401–403
2. Ronalds GA, De Stavola BL, Leon DA. The cognitive cost of being a twin: evidence from comparisons within families in the Aberdeen children of the 1950s cohort study. *BMJ.* 2005;331(7528):1306
3. Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T. Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. *Pediatr Res.* 2001;50(1):91–96
4. Pearce MS, Deary IJ, Young AH, Parker L. Growth in early life and childhood IQ at age 11 years: the Newcastle Thousand Families Study. *Int J Epidemiol.* 2005;34(3):673–677
5. Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T. Birth characteristics and different dimensions of intellectual performance in young males: a nationwide population-based study. *Acta Paediatr.* 2003;92(10):1138–1143
6. Bergvall N, Iliadou A, Tuvemo T, Cnattingius S. Birth characteristics and risk of low intellectual performance in early adulthood: are the associations confounded by socioeconomic factors in adolescence or familial effects? *Pediatrics.* 2006;117(3):714–721
7. Geva R, Eshel R, Leitner Y, Valevski AF, Harel S. Neuropsychological outcome of children with intrauterine growth restriction: a 9-year prospective study. *Pediatrics.* 2006;118(1):91–100
8. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. *Pediatrics.* 2005;115(6):1645–1651
9. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA.* 2002;288(6):728–737
10. Gale CR, O'Callaghan FJ, Godfrey KM, Law CM, Martyn CN. Critical periods of brain growth and cognitive function in children. *Brain.* 2004;127(Pt 2):321–329
11. Montgomery SM, Ehlin A, Sacker A. Pre-pubertal growth and cognitive function. *Arch Dis Child.* 2006;91(1):61–62
12. Richards M, Hardy R, Kuh D, Wadsworth ME. Birthweight, postnatal growth and cognitive function in a national UK birth cohort. *Int J Epidemiol.* 2002;31(2):342–348
13. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. *Pediatrics.* 2006;118(3):1078–1086
14. Cooke RW. Are there critical periods for brain growth in children born preterm? *Arch Dis Child Fetal Neonatal Ed.* 2006;91(1):F17–F20
15. Lano A. *The Value of Neonatal Neurological Assessment in Predicting*

Neurodevelopmental Problems at Preschool Age. Helsinki, Finland: University of Helsinki; 2002
16. Riegel K, Ohrt B, Wolke D, Österlund K. *Die Entwicklung Gefährdet Geborener Kinder bis zum Funften Lebensjahr: Die Arvo Ylppö-Neugeborenen-Nachfolgestudie in Sudbayern und Sudfinnland*. Stuttgart, Germany: Ferdinand Enke Verlag; 1995
17. Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954–1970. I. Analyses of general changes. *Acta Paediatr.* 1975;64(2):187–192
18. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN. The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. *Pediatrics.* 2006;118(4):1486–1492
19. Dubowitz LMS, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr.* 1970;77(1):1–10
20. Burgemeister BB, Blum LH, Lorge I. *The Columbia Mental Maturiturity Scale* (manual). New York, NY: Yonkers-on-Hudson; 1954
21. Beery KE. Revised Administration, Scoring, and Teaching Manual for the Developmental Test of Visual-Motor Integration. Cleveland, OH; Toronto, Canada: Modern Curriculum Press; 1982
22. Kiese C, Kozielski PM. *Aktiver Wortschatztest fur drei- bis sechsjährige Kinder.* Weinheim, Germany: Beltz; 1979:AWST 3–6
23. Dunn LM, Markwardt FC. *Peabody Individual Achievement Test*. Circle Pines, MN: American Guidance Service; 1970
24. Wettstein P. *LSVT: Logopädischer Sprachverständnis-Test*. Zurich, Switzerland: Heilpädagogisches Seminar; 1983
25. Shenkin SD, Starr JM, Deary IJ. Birth weight and cognitive ability in childhood: a systematic review. *Psychol Bull.* 2004;130(6):989–1013
26. Silva A, Metha Z, O'Callaghan FJ. The relative effect of size at birth, postnatal growth and social factors on cognitive function in late childhood. *Ann Epidemiol.* 2006;16(6):469–476
27. Jefferis BJ, Power C, Hertzman C. Birth weight, childhood socioeconomic environment, and cognitive development in the 1958 British birth cohort study. *BMJ.* 2002;325(7359):305
28. Lawlor DA, Bor W, O'Callaghan MJ, Williams GM, Najman JM. Intrauterine growth and intelligence within sibling pairs: findings from the Mater-University study of pregnancy and its outcomes. *J Epidemiol Community Health.* 2005;59(4):279–282
29. Martyn CN, Gale CR, Sayer AA, Fall C. Growth in utero and cognitive function in adult life: follow up study of people born between 1920 and 1943. *BMJ.* 1996;312(7043):1393–1396
30. Matte TD, Bresnahan M, Begg MD, Susser E. Influence of variation in birth weight within normal range and within sibships on IQ at age 7 years: cohort study. *BMJ.* 2001;323(7308):310–314
31. Paz I, Laor A, Gale R, Harlap S, Stevenson DK, Seidman DS. Term infants with fetal growth restriction are not at increased risk for low intelligence scores at age 17 years. *J Pediatr.* 2001;138(1):87–91
32. Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. *JAMA.* 2000;283(5):625–632
33. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser.* 1995;854:1–452
34. Gunnell D, Miller LL, Rogers I, Holly JM. Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of Parents and Children. *Pediatrics.* 2005;116(5). Available at: www.pediatrics.org/cgi/content/full/116/5/e681
35. van Dam PS, Aleman A, de Vries WR, et al. Growth hormone, insulin-like growth factor I and cognitive function in adults. *Growth Horm IGF Res.* 2000;10(suppl B):S69–S73
36. van Pareren YK, Duivenvoorden HJ, Slijper FS, Koot HM, Hokken-Koelega AC. Intelligence and psychosocial functioning during long-term growth hormone therapy in children born small for gestational age. *J Clin Endocrinol Metab.* 2004;89(11):5295–5302

Prenatal and Postnatal Growth and Cognitive Abilities at 56 Months of Age: A Longitudinal Study of Infants Born at Term

Kati Heinonen, Katri Räikkönen, Anu-Katriina Pesonen, Eero Kajantie, Sture Andersson, Johan G. Eriksson, Anja Niemelä, Timo Vartia, Juha Peltola and Aulikki Lano

Pediatrics 2008;121;e1325-e1333
DOI: 10.1542/peds.2007-1172