Infant Growth after Preterm Birth and Neurocognitive Abilities in Young Adulthood

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Objectives To examine whether faster growth from birth to term (40 postmenstrual weeks) and during the first year thereafter was associated with better neurocognitive abilities in adults born preterm with very low birth weight (VLBW; <1500 g).

Study design Weight, length, and head circumference data of 103 VLBW participants of the Helsinki Study of Very Low Birth Weight Adults were collected from records. Measures at term and at 12 months of corrected age were interpolated. The participants underwent tests of general neurocognitive ability, executive functioning, attention, and visual memory at mean age of 25.0 years.

Results Faster growth from birth to term was associated with better general neurocognitive abilities, executive functioning, and visual memory in young adulthood. Effect sizes in SD units ranged from 0.23-0.43 per each SD faster growth in weight, length, or head circumference (95% CI 0.003-0.64; *P* values <.05). After controlling for neonatal complications, faster growth in head circumference remained more clearly associated with neurocognitive abilities than weight or length did. Growth during the first year after term was not consistently associated with neurocognitive abilities.

Conclusions Within a VLBW group with high variability in early growth, faster growth from birth to term is associated with better neurocognitive abilities in young adulthood. Neurocognitive outcomes were predicted, in particular, by early postnatal head growth. *(J Pediatr 2014;165:1109-15)*.

Individuals born prematurely (<37 gestation weeks) and/or with very low birth weight (VLBW, <1500 g) show poorer neurocognitive functioning in childhood,[1-3] adolescence,[3-6] and young adulthood,[3,4,7-10] compared with term-born peers. However, neurocognitive differences between preterm and term-born individuals are relatively modest, and a large proportion of preterm individuals fare well. Although the degree of prematurity and immaturity-associated illnesses and complications may directly account for some of these differences, growth after preterm birth may have an independent effect on neurocognitive abilities.

Among preterm infants, faster growth from birth to childhood,[11-16] before discharge[17,18] and term age,[19] and during the first year after term[20] is associated with better childhood neurocognitive abilities. Very few studies have examined whether these effects persist into adulthood. These studies have shown that better general neurocognitive abilities are associated with faster growth from term to 4 months corrected age (CA) in 18-year-olds born prematurely with low birth weight (≤2500 g),[21] lack of growth restriction from birth to 3 months CA in 19-year-olds born appropriate for gestational age (AGA) but very preterm (<32 gestational weeks) or with VLBW,[22] and catch-up growth from birth to 12 months CA in preterm small for gestational age (SGA) individuals aged 17-28 years.[23]

We tested whether, in VLBW individuals, faster growth in weight, length, and head circumference from preterm birth to term and from term to 12 months CA is associated with better general neurocognitive ability, executive functioning, attention, and visual memory in young adulthood.

AGA	Appropriate for gestational age
CA	Corrected age
PIQ	Performance IQ
SGA	Small for gestational age
VIQ	Verbal IQ
VLBW	Very low birth weight

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Methods

The original cohort of the Helsinki Study of Very Low Birth Weight Adults, described previously[24] in detail, consisted of 335 VLBW infants born consecutively between January 1978 and December 1985 and discharged alive (survival rate 70.7%) from the Neonatal Intensive Care Unit of Children's Hospital at Helsinki University Central Hospital in Finland. In 2004-2005, 255 subjects residing in the greater Helsinki area were invited to the first clinical follow-up visit[24] and 166 participated. Of them, 113 participated in the second follow-up visit, which included neurocognitive testing in 2007-2008.[7,25] We excluded participants who reported neurosensory impairments (2 with blindness, 6 with cerebral palsy, and 2 with developmental disability). This resulted in 103 participants for the current study: 89 were born very preterm (<32 + 0 weeks + days gestation) and 14 moderately preterm (32 + 0 − 36 + 6 weeks + days); 37 (36%) were born SGA (birth weight for gestational age ≤−2 SD).[26] All participants gave their written informed consent, and the Ethics Committee for Children and Adolescents' Diseases and Psychiatry at the Helsinki University Central Hospital approved the study protocol.

Weight, length, and head circumference measurements came from hospital and child welfare clinic records. To obtain measures at term (40 + 0 weeks + days postmenstrual age), we interpolated between true measurements, provided a measurement had been made within 28 days. The median time period between term and the closest true measurement point was 1 day for weight and 4 days for length and head circumference. We interpolated size at 12 months (52 weeks) CA if a measurement had been made within 42 days, allowing a wider range to increase sample size. The median time period between 12 months CA and the closest true measurement point was 15 days for weight and 16 days for length and head circumference.

We converted size at birth and at term into *z* scores by sex and age according to Finnish charts.[26] Finnish infant growth charts from that time[27,28] provide *z* scores for length and head circumference and a percentage score of current weight in relation to expected weight for sex and CA. Therefore, we converted length and head circumference at 12 months CA into *z* scores by sex and age, whereas weight at 12 months was first converted into percentage scores for sex and age and thereafter, to facilitate comparison of effect sizes, into *z* scores within the VLBW cohort.

Four subtests[7] of the Wechsler Adult Intelligence Scale III[29] measured general neurocognitive ability: vocabulary, digit span, similarities, and block design. Five tests measured executive functioning, attention, and visual memory: phonetic (words beginning with letters S and P) and categorical (animal, vegetable/fruit names) verbal fluency,[30] the Rey-Osterrieth Complex Figure test,[31] the Trail Making Test,[32] the Bohnen version of the Stroop test,[33] and the Conners' Continuous Performance Test.[34]

Sex (male/female), gestational age (weeks), date of birth for calculating age at neurocognitive testing (years), time period between closest true measurement point and term/12 months CA (days), and neonatal complications and illnesses (septicemia, bronchopulmonary dysplasia, indomethacin treatment, surgery because of patent ductus arteriosus, blood exchange transfusion because of hyperbilirubinemia, each yes/no; intraventricular hemorrhage, grade; and duration of ventilator treatment, days) were extracted from medical records. Twenty-five participants lacked data on intraventricular hemorrhage and were considered a separate group when dummy coding the covariate. As young adults, participants reported highest education of either parent (categorized according to Statistics Finland).

Statistical Analyses

In linear regression models, we used neurocognitive test scores and their composite scores as outcomes in young adulthood. First, we performed logarithmic, square, or square root variable transformations on neurocognitive test scores to attain normality and then converted the scores into *z* scores (mean = 0, SD = 1). We used similarities, vocabulary, and digit span scores to estimate verbal IQ (VIQ), block design scores to estimate performance IQ (PIQ), and VIQ and PIQ to estimate overall IQ according to Finnish norms which correct for sex and age.[29] We utilized principal component analysis with Varimax rotation to reduce the number of executive functioning, attention, and visual memory outcomes. We included the first 4 components as they explained 75% of the variation, and only their eigenvalues were greater than 1.0 (**Table I**; available at www.jpeds.com). The components were named verbal flexibility (on which higher scores reflected better performance especially on Fluency and Stroop tasks), visual memory (higher scores on Rey-Osterrieth Complex Figure scores), visual flexibility (higher scores on Trail Making Test), and impulsivity (lower Conners' Continuous Performance Test reaction times and more commission errors).

As main predictors of neurocognitive ability, we used infant growth in weight, length, and head circumference from: (1) birth to term; and (2) from term to 12 months CA. Following the lead of Adair et al[35] and Osmond et al,[36] we used standardized residual change scores from linear regression models, in which body size *z* scores at term were regressed on the corresponding measure at birth and body size *z* scores at 12 months CA were regressed on the corresponding measure at term, creating uncorrelated residuals that reflect growth conditional on previous history.[35-38] This approach was chosen so that differences in the duration of growth periods or earlier growth patterns would not interfere with interpretation of the results.[35-38] In supplementary analyses, we used body size *z* scores at birth, at term, and at 12 months CA to predict neurocognitive outcome variables. We considered *P* values <.05 significant.

All analyses on growth from birth to term were adjusted for size at birth, and analyses on growth from term to 12 months CA were adjusted for size at term. To control