Journal of the International Neuropsychological Society (2015), **21**, 126–136

doi:10.1017/S1355617715000077

Physical Growth in the Neonatal Intensive-Care Unit and Neuropsychological Performance at Preschool Age in very Preterm-Born Singletons

Sarah Raz,[1] Angela K. DeBastos,[1] Julie Bapp Newman,[2] Brittany N. Peters,[1] Andrew M. Heitzer,[1] Jamie C. Piercy,[1] AND Daniel G. Batton[3]

[1]Department of Psychology and the Merrill Palmer Skillman Institute, Wayne State University, Detroit, Michigan
[2]Division of Pediatric Neuropsychology, Children's National Medical Center, Washington, District of Columbia
[3]Department of Pediatrics, Southern Illinois University Medical School, Springfield, Illinois

(RECEIVED April 2, 2014; FINAL REVISION January 12, 2015; ACCEPTED January 13, 2015; FIRST PUBLISHED ONLINE March 5, 2015)

Abstract

We studied the associations between early postnatal growth gains and neuropsychological outcome in very preterm-born children. Specifically, we wished to establish whether relationships exist between gains in head circumference (relative to gains in body-weight or length), from birth to hospital discharge, and intellectual, language, or motor, performance at preschool age. We used data from 127 preschoolers, born <33 weeks, all graduates of the William Beaumont Hospital Neonatal Intensive-Care Unit (NICU) in Royal Oak, MI. Cognitive, motor, and language outcomes were evaluated using the Wechsler Preschool and Primary Scales of Intelligence-Revised, Peabody Developmental Scales – 2nd Edition, and the Preschool Language Scale – 3rd Edition, respectively. Differences between *Z*-scores at birth and hospital discharge, calculated for three anthropometric measures (head circumference, weight, length), were variables of interest in separate simultaneous multiple regression procedures. We statistically adjusted for sex, socioeconomic status, birth weight, length of hospitalization, perinatal complications, and intrauterine growth. Examination of the relationships between anthropometric indices and outcome measures revealed a significant association between NICU head growth and global intelligence, with the *Z*-difference score for head circumference accounting for a unique portion of the variance in global intelligence ($\eta_p^2 = .04$). Early postnatal head growth is significantly associated with neuropsychological outcome in very preterm-born preschoolers. To conclude, despite its relative brevity, NICU stay, often overlapping with the end of 2nd and with the 3rd trimester of pregnancy, appears to be a sensitive developmental period for brain substrates underlying neuropsychological functions. (*JINS*, 2015, *21*, 126–136)

Keywords: Infant, Premature, Intensive care, Neonatal, Body size, Body height, Body weight, Neuropsychological tests

INTRODUCTION

The relationships between postnatal growth and neuropsychological outcome in very preterm-born children are of significant interest to developmental neuropsychologists. Yet most research efforts have focused on ante-, or perinatal, risk factors that may alter the course of development. The rate of early postnatal physical growth, as reflected by gains in weight, length, and especially head circumference, from birth to hospital discharge, may have relevance to subsequent neuropsychological functioning. Physical growth rate, in the neonatal intensive-care unit (NICU), may be either an independent causal factor that determines cognitive, language, and motor outcome, or a marker of the quality of the recovery from adverse antenatal and perinatal conditions. However, the etiology of postnatal physical growth delay or inhibition is far from obvious, and the possibility of multiple etiologies must be taken into account. In the very-preterm-born infant, the growth period during stay in the NICU corresponds to an antenatal period in the full-term infant, roughly overlapping with the third trimester of pregnancy and the latter part of the second trimester. As noted by Ehrenkranz et al. (2006), nonnutritional factors (e.g., preexisting/prenatal medical conditions) contribute to the development of growth failure during NICU hospitalization, yet delays in regaining birth weight and low nutrient intake also play a major role.

Correspondence and reprint requests to: Sarah Raz, Developmental Neuropsychology Laboratory, the Merrill-Palmer Skillman Institute, Wayne State University, 71 E. Ferry, Detroit, Michigan 48202. E-mail: sarahraz@wayne.edu

The study of postnatal anthropometric data obtained from children born preterm, conducted in the past two decades, involved examination of head size (Charkaluk et al., 2011; Cheong et al., 2008; Cooke, 2005; Kuban et al., 2009; Kurdahi Badr, Bookheimer, Purdy, & Deeb, 2009; Raz, Newman, DeBastos, Peters, and Barron, 2014; Rijken et al., 2007), body-length or stature (e.g., Heinonen et al., 2008, Ramel et al., 2012; Raz et al., 2014), and body-weight (e.g., Heinonen et al., 2008; Kan et al., 2008). In this at-risk population, anthropometric indices reflecting physical growth during single (e.g., Raz et al., 2014) or multiple (e.g., Cooke, 2006) developmental stages, spanning from hospital discharge (e.g., Ramel et al., 2012) to adolescence (e.g., Cooke, 2006), have been shown to be associated with neuropsychological outcome. Follow-up periods ranged from infancy (e.g., Ramel et al., 2012) to preschool or school-age (Cooke, 2006; Cooke & Foulder-Hughes, 2003; Kan et al., 2008; Peterson, Taylor, Minich, Klein, & Hack, 2006; Raz et al., 2014). While head growth is closely associated with MRI-based measurements of brain growth (Cheong et al., 2008), the nature of the relationships between body-length or weight and neuropsychological functioning seems less straightforward. Ramel and colleagues (2012) suggested that lean body mass, and, therefore, linear growth, is closely linked to organ growth and differentiation (including the brain), and that this relationship is stronger than that observed between fat mass (and, therefore, weight gain) and organ growth. In their recent 2-year follow-up investigation they found that body-length at 4 and 12 months accounted for variance in 24-month cognitive development, over and above the variance explained by weight and head circumference.

In the current investigation of very preterm-born children, we wished to study the relationship between preschool outcome and the earliest gains observed in postnatal head growth, relative to other indices of physical growth. To determine whether there was a unique relationship between head growth and neuropsychological outcome, we evaluated change in head size, from birth to hospital discharge, compared to changes in body-weight and length during the same period. Neuropsychological functioning was evaluated in the intellectual, language, and motor domains. Inspection of the relevant literature revealed that out of four studies of early physical growth, one was an infancy (Ehrenkranz et al., 2006), while three (Cooke, 2006; Franz et al., 2009; Kan et al., 2008) were preschool or school-age, follow-up studies. Ehrenkranz et al. (2006) completed a developmental evaluation of 490 extremely low birth weight infants between 18 and 22 months corrected age. They documented a significant relationship between growth velocity (rate of weight and head circumference gain) before hospital discharge and the likelihood of both neurodevelopmental impairment and Mental or Psychomotor Developmental index < 70 (Bayley II-R). They concluded that growth velocity during NICU hospitalization in extremely low birth weight infants exerts a significant statistical effect on neurodevelopmental outcome in toddlerhood. Kan et al. (2008) examined intellectual and motor outcome associations with gains in weight during NICU hospitalization in a sample of 179 8-year-old extremely preterm-born children. Outcome measures were adjusted for biological and social risk variables. The investigators reported that neither 8-year IQ scores (WISC-III) nor the Movement ABC binary centile score (<15 *vs.* ≥ 15) were related to change between birth and discharge in weight *Z*-scores. Developmental outcome associations with in-hospital gains in head circumference could not be determined due to missing hospital data.

Adjusting for social class and degree of intrauterine growth restriction, Cooke (2006) found, in a sample of 194 very low birth-weight (<1500 g) school-age children born in the early 1980s (therefore receiving NICU services during the presurfactant era), a correlation between occipito-frontal circumference difference scores (change in head circumference *Z*-score between birth and discharge), and TOMI scores (indexing minor motor impairment), but not WISC-III IQ scores. Franz et al. (2009) studied neurological, motor, and cognitive outcome in 219 very low birth weight preschoolers with gestational age <30 weeks. The sample included cases with severe perinatal intracranial hemorrhage (ICH) and periventricular leukomalacia. Statistical analyses showed a relationship between reduction in risk for abnormal neurological examination and increase in weight and head circumference deviation scores, from birth to hospital discharge, based on normative data. Catch-up growth of head circumference, but not weight, from birth to discharge was also associated with reduction in risk for impaired mobility. While an increase in weight *SD* units was related to an increase in the K-ABC Mental Processing composite score, only a nonsignificant trend for a relationship was observed between head circumference *SD* scores and the same global intelligence index.

In summary, from the above mentioned three studies of NICU growth and preschool/school-age outcome in preterm-born children, two (Cooke, 2006; Franz et al., 2009) examined in-hospital gains in head circumference. While only the latter study was conducted on a cohort receiving NICU services during the surfactant era, neither reported significant relationships between head growth and standardized neuropsychological outcome measures. From the two studies that examined in-hospital weight gains, Franz et al. (2009) reported a significant association with intellectual measures, while Kan et al. (2008) could not demonstrate relationships between NICU weight gain and neuropsychological functioning. The link between neuropsychological outcome and in-hospital gains in linear growth was not examined in any of these studies.

Given the limited body of knowledge available about the relationships between early postnatal growth and longer-term developmental outcome, we examined neuropsychological performance in a very preterm-born preschool singleton sample, while focusing on two concrete objectives. First, we wished to evaluate whether associations exist between early head growth gains (relative to other physical growth indices) and performance in multiple neuropsychological outcome domains, including verbal and non-verbal intelligence, receptive and expressive language, and both fine and gross motor skills. Notably, language performance has not been investigated in any of the three preschool/school age follow-up studies reviewed above. Second, in light of the above-described findings that attributed special predictive significance to early linear growth (Ramel et al., 2012), we wanted to establish the presence of relationships between gains in body-length, during NICU stay, and preschool outcome, in addition to evaluating gains in weight and head circumference. None of the above-mentioned studies that focused on early postnatal growth gains (Cooke, 2006; Franz et al., 2009; Kan et al., 2008) included an examination of the link between developmental outcome and linear growth. Finally, we evaluated the aforementioned associations in a middle class sample to minimize the influence of potentially confounding socioeconomic factors on neuropsychological outcome. Thus, generalizability to lower strata was traded-off to achieve improved internal validity.

METHODS

Participants

Outcome data were available for 134 very preterm (gestational age ≤32 6/7 weeks), singleton birth, preschoolers who were graduates of the William Beaumont Hospital (WBH) NICU in Royal Oak MI. At WBH NICU, resuscitation is attempted for all infants with an estimated gestational age ≥23 0/7 weeks (Batton, DeWitte, & Pryce, 2011). The children were born between 1996 and 2001 and evaluated between July 2002 and July 2007. Seven children were removed from this sample: two with cerebral palsy (CP), two with ICH grade >2, one with both CP and ICH grade >2, and two with intracranial pathology other than ICH. We excluded moderate or severe CP and ICH as such pathologies may involve distinct causal mechanisms (e.g., Truwit, Baarkovich, Koch, & Ferriero, 1992) with independent effects on neuropsychological functioning (e.g., Hou et al., 2010; Raz et al., 1995) that may, in turn, confound the hypothesized statistical effects of head growth. Altogether, 127 cases were available for study, accounting for approximately 21% of the relevant NICU cohort. However, missing anthropometric data at birth or discharge somewhat lowered the number of cases available for discrete analyses of in-hospital growth. Thus, NICU head growth could not be calculated for six children, weight gain for one case, while linear growth could not be computed for eight children. For the total sample of 127 available children, gestational age ranged from 23 0/7 to 32 6/7 weeks (mean ± *SD* = 29.61 ± 2.70 weeks) and birth weight from 365–2830 g (mean ± *SD* = 1363.68 ± 516.11 g). Gestational age was determined by maternal dates and confirmed by early prenatal ultrasound in >95% of cases. The mean gestational age (± *SD*) of 29.1 (±2.8) weeks and birth weight (± *SD*) of 1359 (±508.5) g for the NICU singleton cohort was similar to that of our sample.

The catchment area of WBH NICU includes primarily middle class strata, residing in suburban Detroit. Approximately 85% of admissions were covered by private medical insurance, whereas 15% were insured through Medicaid. These data are consistent with our sample's composition, where the mean Hollingshead (1975) socioeconomic status (SES) score (± *SD*) was 47.61 ±12.44 on a scale with an upper limit of 66. The portion of the 1996–2001 NICU singleton cohort (≤32 6/7 weeks) that could not be recruited for study was comprised of 12.82% African Americans and 57.40% males, while our sample included 9.4% African Americans ($Z = 1.40$; $p < .30$) and 57.85% males ($Z = -.017$; $p < .98$).

Riddle and DonLevy's (2010) gestational age-specific reference norms were used to derive head circumference and body-length *Z*-scores at birth, while the reference norms by Kramer et al. (2001) were used to calculate *Z*-scores for birth weight. For all three indexes of NICU growth gain, the age-, and sex-specific means and *SD*'s by Olsen and colleagues (2010) were used to derive *Z*-scores for discharge up to 41 weeks conceptional age, while the CDC 2000 growth chart data (Kuczmarski et al., 2002) were used to derive *Z*-scores for infants ≥42 weeks. In selecting reference norms for anthropometric variables measured at birth, we preferred the use of reference data with a racial distribution (Caucasian *vs*. minority) that was similar to that observed in our sample and the NICU cohort from which it was obtained. The discharge reference norms were more representative of the U.S. population at large.

Of the 121 participants with head growth data available, the difference between head circumference *Z*-scores, at birth and discharge (*Z*-difference), was ≥0 for 86 cases and <0 for 35 cases. Thus, for the preponderance of the very preterm-born cases (71%), head circumference at discharge yielded lower *Z*-scores than head circumference measured at birth. This observation probably reflects, in part, a relative slowing of the overall rate of head growth in the early postnatal period in this very preterm born subsample. Conversely, in 29% of our sample the rate of head growth "accelerated" during in-hospital stay, as these children attained a higher *Z* (and centile) score at discharge than at birth. One hundred one of the 121 children with available head growth data were recruited through a follow-up study of preterm children in the preschool years (30 with head circumference *Z*-difference ≥ 0 and 71 with *Z*-difference <0), whereas 20 of the children were recruited through a related, concurrent study on the preschool outcome of mild ICH (5 with head circumference *Z*-difference ≥0 *vs*. 15 with *Z*-difference <0). Age range at recruitment and participation rates differed somewhat between the studies (4–6 years for the prematurity follow-up and 3–5 years for the ICH study, with participation rates of 64% and 56% of contactable families, respectively). Nonetheless, the proportion of children with and without in-hospital head growth gains did not differ by recruitment mechanism/study (Yates corrected $\chi^2[1] = .024$; $p = .88$).

According to maternal report, one child sustained a head injury without loss of consciousness. In seven cases, the family reported seizure history, yet only two required anti-seizure medication. One mother reported drinking a glass of wine per day, while 17 mothers reported cigarette

Table 1. Demographic and sociofamilial characteristics

Characteristic	Mean ± *SD*/ frequency (*N* = 121)[a]
Adjusted age (months)	60.82 ± 8.60
Gender (M : F)	70: 51 [57.85 : 42.15]
Race (W : O)	86: 35 [71.08 : 28.92]
SES	47.47 ± 12.57
Maternal VIQ[b]	105.85 ± 14.78 (105)
Mother's education (years)	15.30 ± 2.38 (120)
Father's education (years)	15.14 ± 2.90 (117)

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. In the case of missing data, number of subjects used in calculating group means and *SD*s is provided in parentheses. Percentages are provided in brackets.

[a] A single case was missing all parental background information.

[b] Prorated parental Verbal IQ based on three subtests (Vocabulary, Similarities, and Information) of the Wechsler Adult Intelligence Scale—III (Wechsler, 1997); Testing was completed on the biological mothers in all cases.

M = male, F = female; W = White, O = Other (1 Asian, 15 African Americans, 2 African American/Asian, 6 Asian/Caucasian, 2 African American/Caucasian, 8 Hispanic/Caucasian; 1 American Indian/Caucasian); SES = socioeconomic status (Hollingshead's (1975) Four Factor Index of Social Status).

smoking, during pregnancy. Detailed information about each child's socio-demographic characteristics, pre-, peri-, and neonatal background, as well as exposure to diagnostic and treatment procedures, was obtained from hospital records. Tables 1–3 provide summary statistics of background characteristics for 121 participants with available head circumference measures.

Neuropsychological Assessment

Children were evaluated in one or two sessions, depending upon each child's attention span. The examiners were graduate students trained extensively in developmental neuropsychological assessment. To prevent bias in administration and scoring, they were kept unaware of the child's perinatal status. All testing and perinatal background data were obtained in compliance with the regulations of the Human Investigation Committees of Wayne State University and WBH. Intellectual functioning was assessed using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989). Due to time constraints, four of the five subtests from the Verbal (VIQ) subscale (Information, Similarities, Vocabulary, and Comprehension) and four of the five subtests from the Performance (PIQ) subscale (Geometric Design, Mazes, Block Design, and Picture Completion) were administered to each child. Motor skills were assessed using the Peabody Developmental Motor Scales (PDMS-2; Folio & Fewell, 2000). This instrument has precise scoring criteria and is normed on a large, stratified sample (Maring & Elbaum, 2007). The PDMS-2 is a comprehensive, standardized measure of gross and fine motor skills that yields Total, Gross, and Fine Motor (TM, GM, and FM, respectively) scales. The GM subtests are appropriate for preschoolers and include Stationary (equilibrium and balance), Locomotion (crawling, walking, running, hopping,

Table 2. Antenatal Perinatal and neonatal factors

Background characteristic	Mean ± *SD*/ frequency
Antenatal factors	
Abruption of the placenta	9 [7.44]
Chorioamnionitis (histological)	32 [26.45]
Diabetes [a]	9 [7.44]
HELLP syndrome[b]	6 [4.96]
Hypertention in pregnancy	45 (120) [37.50]
Intrauterine growth (*Z* score)[c]	−.09 ± .91 (120)
IUGR classification (<10th centile)[c]	11 [9.09]
Membranes ruptured >12 hrs[d]	31 (120) [25.83]
Mother's age at delivery (yrs)	31.16 ± 4.61
Smoking during pregnancy[e]	17 [14.05]
Vaginal bleeding (abnormal)	50 [41.32]
Total antenatal complications[f]	1.58 ± 1.07 (118)
Perinatal factors	
Abnormal presentation [g]	39 [32.23]
Birth weight (g)*	1,374 ± 527
Birth length (cm)	38.73 5.04
Birth length *Z* score	−.05 ± .99
Birth head circumference (cm) ***	26.89 ± 3.32
Birth head circumference *Z* score***	−.01 ± 1.02
Cesarean section	64 [52.89]
Forceps	4 [3.31]
General anesthesia	11 [9.09]
Gestational age (weeks)[h]	29.64 ± 2.67
Nuchal Cord	1 (120) [.82]
5 minute Apgar	8.21 ± .90
Total perinatal complications[i]	1.71 ± 1.15
Neonatal factors	
Anemia at birth[j]	18 (120) [15.00]
Apnea	100 [83.33]
Bronchopulmonary dysplasia (BPD)	47 [38.84]
Days hospitalization	56.21 ± 42.50
Discharge head circumference *Z*-score***	−.37 ± 95
Discharge length z-score	−1.15 ± 1.32 (115)
Discharge weight z-score***	−1.02 ± .85 (120)
Hyaline membrane disease (HMD)[k]	84 [69.42]
Hyperbilirubinemia [l]	25 [20.66]
Hypermagnesemia	10 [8.26]
Hypotension [m]	4 [3.31]
Intracranial hemorrhage (ICH)[n]	21 [17.35]
Meconium aspiration	4 [3.31]
Necrotizing enterocolitis (NEC)[o]	4 [3.31]
Patent ductus arteriosus (PDA)[p]	48 [39.67]
Persistent pulmonary stenosis (PPS)	6 [5.00]
Pneumothorax	6 [5.00]
Retinopathy of prematurity (ROP)[q]	21 [17.35]
Sepsis (initial or acquired)[r]	19 [15.70]
Thrombocytopenia	13 [10.74]
Total neonatal complications[s]	3.44 ± 2.22
Total nonrespiratory neonatal complications[t]	1.24 ± 1.43 (120)
Total ante-, peri-, and neonatal complications	6.77 ± 2.80 (118)

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. In the case of missing data, number of subjects used in calculating group means and *SD*s is provided in parentheses. Percentages are provided in brackets.

[a] Includes both gestational diabetes and diabetes mellitus.

[b] Hemolysis, elevated liver enzymes and low platelets.

[c] A *Z* score expressing the deviation of an infant's birth weight from the mean weight of his/her gestational age group, at delivery, according to norms published by Kramer et al. (2001). Intrauterine growth restriction (IUGR) classification was created by using the 10th percentile as a cutoff.

[d] Time from spontaneous or artificial rupture of membranes to delivery.

[e] Smoking behavior: 5 cases ≤ 5 cigarettes, 2 cases 10 cigarettes, 3 cases 20 cigarettes per day, 7 cases no available information.

[f] Total antepartum complications includes maternal hypertension, chorioamnionitis, maternal diabetes, HELLP syndrome, membranes ruptured > 12 hours, multiple gestation, smoking during pregnancy, abnormal vaginal bleeding, IUGR, and placental abruption.

[g] Includes various atypical presentations such as breech or transverse lie.

[h] As determined by obstetrician; >95% of cases were corroborated by antenatal ultrasound.

[i] Total perinatal complications include abnormal presentation, C section, forceps, general anesthesia, nuchal cord, and fetal tachycardia.

[j] Hematocrit <40%.

[k] Based on a chest roentgenogram and clinical evaluation.

[l] Peak bilirubin ≥ 12 mg/dl

[m] Requiring treatment

[n] Documented on the basis of cranial ultrasound: 16 cases with Grade 1 and 5 with grade 2.

[o] Documented by radiographic changes, positive stool guiacs and abdominal distention.

[p] Diagnosed by clinical manifestations and echocardiographic information.

[q] Severity diagnoses: 9 with Grade II, 2 with Grade III, 9 with Grade III+, 1 with Grade IV.

[r] Established by positive blood culture.

[s] Total neonatal complications includes anemia, apnea, hyaline membrane disease, BPD, hyperbilirubinemia, hypermagnesemia, hypotension, ICH, necrotizing enterocolitis, PDA, persistent pulmonary stenosis, pneumothorax, retinopathy of prematurity, sepsis, and thrombocytopenia.

[t] Total nonrespiratory complications includes anemia, hypotension, ICH, meconium aspiration, NEC, ROP, initial or acquired sepsis, thrombocytopenia.

Table 3. Antenatal and neonatal diagnostic and intervention procedures

Diagnostic and intervention procedure	Mean ± *SD*/ frequency
Antenatal magnesium sulfate[a]	72 (118) [61.02]
Antenatal steroids [b]	106 (118) [89.83]
Neonatal cranial ultrasound	117 (120) [97.50]
Neonatal steroids	20 [16.53]
Surfactant administration	55 [45.45]
Days respiratory support [c]	35.87 ± 49.59
Days ventilation	12.51 ± 23.24
Home on O_2	17 [14.05]

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. In the case of missing data, number of subjects used in calculating group means and *SD*s is provided in parentheses. Percentages are provided in brackets.

[a] Magnesium sulfate, administered to inhibit preterm labor and/or control seizures in preeclampsia.

[b] Betamethasone, to promote fetal lung maturation

[c] Including mechanical ventilation, continuous positive airway pressure (CPAP), nasal cannulae, and oxyhood.

and jumping) and Object Manipulation (catching, throwing, and kicking). The FM subtests include Grasping (from one hand grasp to bilateral manipulation) and Visual-Motor Integration (reaching and grasping, building with blocks and copying designs). We used the Preschool Language Scale (PLS-3; Zimmerman, Steiner, & Pond, 1992) to assess language skills. The PLS-3, an extensively standardized instrument, includes tasks assessing linguistic skills in the areas of semantics, morphology, syntax, integrative language and pre-literacy competencies. The test provides scores for Total Language (TL), and two subscales assessing receptive and expressive language: Auditory Comprehension (AC) and Expressive Communication (EC).

General Statistical Considerations

The variable of interest was the difference between head circumference *Z*-score at birth and hospital discharge (*Z*-difference). The *Z*-score at each of the time points was computed as the deviation of attained head circumference from age-specific group means. For comparison purposes, the *Z*-difference was also calculated for weight and length; each of the three scores was then entered into a separate regression models as a predictor of interest (see Table 4). To examine associations between the *Z*-difference scores for each of the three anthropometric variables and neuropsychological performance, we used simultaneous multiple regression analyses. Several variables that may potentially confound the outcome effect of our variables of interest were added to the model as "covariates." We reasoned that, in addition to including basic demographic measures such as sex and socioeconomic status (SES; Hollingshead, 1975), prominent early risk factors should be considered. We, therefore, included birth weight, days hospitalization, the total number of complications, and the intrauterine growth *Z*-score (the distance of an infant's birth weight, in *SD* units, from gestational age-, and sex-specific means provided by Kramer et al., 2001) as covariates. To reduce the number of predictors as well as decrease the number of categorical variables and interaction terms, the total number of complications was used in lieu of individual risk factors. To alleviate multicollinearity, variables that strongly correlated with selected predictors were excluded. Such correlations were observed between birth weight and gestational age, (Pearson's $r[125] = .84$) or hospitalization days and oxygenation or ventilation days ($r[125] = .96$ and .82, respectively, all p's $< .001$).

Global outcome scales, including the WPPSI-R FSIQ, The PLS-3 TL, and the PDMS-2 TMQ were used as dependent variables. When significant associations were documented between anthropometric indices and a global outcome measure, subscale analyses were conducted using Bonferroni correction to adjust for the number of subscales. In computing the scores for each dependent measure, age corrected for extent of prematurity, rather than chronological age, was used. To corroborate the significant outcome effects of our anthropometric predictors, we conducted supplemental analyses in which we examined the statistical interaction between the separate *Z*-scores observed at birth and at discharge. The multiplicative interaction term, when added to the separate *Z*-scores, represents the unique contribution of the combined distinct pattern of the two *Z*-scores, over and above the separate direct predictive contribution of each *Z*-score. Thus, the significance test for the interaction term has been viewed as an alternative to the test of

Table 4. Results of three simultaneous multiple regression analyses with weight, length, or head circumference as predictors

		Weight (Model I)				Length (Model II)				Head circumference (Model III)			
Scale	Source	F	df	*Beta*	*p*	F	df	*Beta*	*p*	F[6]	df	*Beta*	*p*
FSIQ	Anthropometric index (*Z*-difference)	2.76	1,115	–.16	.10	.76	1,108	–.08	.38	4.45[+]	1,108	–.19	.04
										$\eta_p^2 = .04$			
	Sex	1.83		.11	.18	.96		.09	.33	.76		.08	.39
	Days hospitalization	3.19		–.26	.08	4.53		–.33	.36	2.91		–.26	.09
	SES	14.64		.31	.000	12.44		.30	.001	12.03		.29	.001
	Total complications	.04		–.02	.83	.00		.00	.99	.00		.00	.97
	Birth weight	2.32		–.26	.13	2.00		–.25	.16	1.62		–.23	.21
	Intrauterine growth *Z* score	10.50		.41	.002	7.44		.33	.007	9.72		.40	.002
VIQ	Anthropometric index (*Z*-difference)	.98	1,115	–.10	.32	1.51	1,108	–.12	.22	3.73	1,108	–.18	.06
										$\eta_p^2 = .033$			
	Sex	2.94		.15	.09	1.36		.11	.25	1.45		.11	.23
	Days hospitalization	2.54		–.25	.11	3.58		–.30	.06	1.38		–.19	.24
	SES	8.10		.25	.005	7.2		.24	.008	7.31		.24	.008
	Total complications	.25		.06	.61	.37		.08	.54	.33		.07	.57
	Birth weight	.45		–.12	.50	.61		–.15	.43	.19		–.08	.66
	Intrauterine growth *Z* score	2.94		.23	.09	2.39		.20	.12	3.09		.24	.08
PIQ	Anthropometric index (*Z*-difference)	4.54	1,115	–.20	.035	.37	1,108	–.05	.54	2.59[+]	1,108	–.16	.08
		$\eta_p^2 = .044$											
	Sex	.36		.05	.55	.19		.04	.66	.08		.03	.77
	Days hospitalization	2.19		–.22	.14	3.23		–.27	.07	3.06		–.26	.08
	SES	14.97		.31	.000	12.10		.29	.001	11.06		.28	.001
	Total complications	.96		–.11	.33	.46		–.08	.50	.33		–.07	.57
	Birth weight	4.03		–.34	.05	3.00		–.31	.09	2.94		–.31	.09
	Intrauterine growth *Z* score	16.45		.51	.000	10.57		.40	.002	12.86		.46	.001
TL	Anthropometric index (*Z*-difference)	4.39[1]	1,114	–.21	.04	.59[3]	1,107	–.07	.44	1.91	1,108	–.13	.17
		$\eta_p^2 = .037$											
	Sex	2.65		.14	.11	2.36		.14	.13	2.73		.16	.10
	Days hospitalization	.94		–.15	.33	1.06		–.16	.31	.36		–.10	.55
	SES	12.51		.30	.001	12.49		.31	.001	9.24		.27	.003
	Total complications	.04		–.02	.84	.10		–.04	.75	.07		.03	.79
	Birth weight	1.04		–.18	.31	.63		–.15	.43	.08		–.06	.77
	Intrauterine growth *Z* score	5.29		.31	.02	1.93		.18	.17	2.14		.20	.15
EC	Anthropometric index (*Z*-difference)	2.66	1,115	–.16	.10	.20	1,108	–.04	.66	.76	1,108	–.08	.39
	Sex	1.80		.12	.18	1.70		.12	.19	1.67		.12	.20
	Days hospitalization	.74		–.14	.39	.76		–.14	.38	.64		–.13	.42
	SES	11.10		.29	.001	10.98		.30	.001	10.02		.29	.002
	Total complications	.19		–.05	.66	.42		–.08	.52	.08		–.03	.78
	Birth weight	1.29		–.21	.26	1.00		–.19	.32	.82		–.17	.37
	Intrauterine growth *Z* score	4.37		.28	.04	1.76		.17	.19	2.83		.23	.09

Table 4: (*Continued*)

		Weight (Model I)				Length (Model II)				Head circumference (Model III)			
Scale	Source	F	df	*Beta*	*p*	F	df	*Beta*	*p*	F^{6}	df	*Beta*	*p*
AC	Anthropometric index (*Z*-difference)	4.73^{2} $\mathbf{\eta_p^2 = .040}$	1,114	–.22	.03	$.87^{4}$	1,107	–.09	.35	2.44^{5+}	1,107	–.15	.12
	Sex	4.10		.18	.045	3.51		.18	.06	2.52		.15	.11
	Days hospitalization	.54		–.12	.46	.70		–.14	.41	.18		–.07	.67
	SES	8.06		.25	.005	8.25		.26	.005	7.79		.25	.006
	Total complications	.21		.06	.64	.19		.06	.66	.20		.06	.66
	Birth weight	.08		–.05	.77	.00		–.00	.99	.13		.00	.98
	Intrauterine growth *Z* score	3.38		.25	.07	.87		.12	.35	1.48		.17	.23
TM	Anthropometric index (*Z*-difference)	1.39	1,114	–.11	.24	1.26	1,107	–.10	.26	$.71^{+}$	1,107	–.08	.40
	Sex	.51		.06	.47	.17		.04	.67	.83		.08	.36
	Days hospitalization	5.14		–.35	.03	5.36		–.36	.02	5.05		–.36	.03
	SES	8.17		.24	.005	7.72		.24	.006	7.27		.23	.008
	Total complications	1.42		–.14	.235	1.14		–.13	.29	.73		–.10	.40
	Birth weight	2.18		–.26	.14	2.14		–.27	.14	1.31		–.22	.25
	Intrauterine growth *Z* score	6.64		.33	.011	4.94		.28	.03	4.71		.29	.03
FM	Anthropometric index (*Z*-difference)	2.16	1,115	–.14	.14	.62	1,108	–.07	.43	1.15^{+}	1,108	–.10	.28
	Sex	1.85		.12	.18	1.77		.12	.19	2.18		.14	.14
	Days hospitalization	2.05		–.22	.15	1.57		–.20	.21	2.10		–.23	.14
	SES	10.10		.27	.002	10.93		.29	.001	9.41		.27	. 003
	Total complications	1.15		–.13	.28	1.24		–.14	.27	.45		–.08	.50
	Birth weight	1.89		–.25	.17	1.18		–.20	.28	.89		–.18	.35
	Intrauterine growth *Z* score	3.69		.25	.06	1.69		.17	.20	2.01		.19	.16
GM	Anthropometric index (*Z*-difference)	.50	1,114	–.07	.48	1.17	1,107	–.10	.28	$.14^{+}$	1,107	–.03	.71
	Sex	.001		.00	.97	.13		–.03	.71	.07		.02	.79
	Days hospitalization	5.01		–.35	.03	6.27		–.40	.01	4.79		–.35	.03
	SES	3.15		.15	.08	2.42		.13	.12	2.59		.14	.11
	Total complications	.88		–.11	.35	.54		–.09	.46	.57		–.09	.45
	Birth weight	.80		–.16	.37	1.29		–.21	.26	.53		–.14	.47
	Intrauterine growth *Z* score	5.43		.31	.02	5.22		.29	.02	4.22		.28	.04

Note. Outcome measures: Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Total Language (TL), Expressive Communication (EC), Auditory Comprehension (AC), Total Motor (TM), Fine Motor (FM), and Gross Motor (GM).

[+] There was a significant interaction between sex and head circumference *Z* difference score observed for several outcome measures, including FSIQ, PIQ, TM, FM, GM and AC ($p < .05$). Because the departure from additivity appeared to be an artifact of differences between the sex-specific ranges and means of the *Z*- difference scores for males and females in our sample, as explained below, the results for the reduced model, without the interactions, are presented above. Specifically, the *Z*-difference scores (head circumference *Z* score at discharge subtracted from head circumference *Z* score at birth) calculated for the male subsample ranged from a value that was more than an *SD* higher than the corresponding value for female infants (*Z*-difference = 3.27 vs. 2.23, respectively), to a value that was more than 2.5 *SD* units higher than the corresponding value for female infants (*Z*- difference = –1.42 vs. –4.06, respectively). Because of the nature of our sample composition (particularly the absence of male representation amongst infants with more accelerated NICU head growth), it is not surprising that the average (standardized) head circumference growth gain in males between birth and discharge was significantly lower than that of their female counterparts (mean head circumference z-difference score (± *SD*) = .66 ± .84 and –.05 ±1.28 for males and females, respectively (t [119] = –3.68, $p < .000$).

[1] A single case with studentized residual value of –3.60 was removed from the analyses of TL

[2] A single case with studentized residual value of –3.86 was removed from the analyses of AC

[3] A single case with studentized residual value of –3.51 was removed from the analyses of TL

[4] A single case with studentized residual value of –3.80 was removed from the analyses of AC

[5] A single case with studentized residual value of –3.85 was removed from the analyses of AC

[6] A single case with large leverage (> .29) was removed from all analyses in Model III.

significance for difference scores in regression models (Laird & Weems, 2011).

Before using the reduced model, interactions between the single categorical variable, sex, and anthropometric indices of postnatal growth—most importantly NICU head growth—were evaluated. Because essentially all the six participants who had made substantial head growth gains (head circumference growth gains from 1.5 to 4.07 *SD*s) in our sample happened to be female, with no male representation at the upper end of the distribution, the presence of interaction effects between sex and NICU head growth on outcome was evaluated both with and without these cases. Finally, SES was imputed for a single case with missing SES values *via* regression procedure, using the parents' years of education as a predictor.

RESULTS

Table 4 displays regression analyses with each anthropometric variable entered separately as a continuous dimension (Models I–III). As Table 4 shows, SES and adequacy of antenatal growth (intrauterine growth *Z*-score) were the predictors most consistently associated with our outcome measures. While in all three models SES explained a significant share of the variance in all outcome measures except GM, antenatal growth accounted for a significant share of the variance in the FSIQ, PIQ, TM, and GM in all three models, and for variance in TL and EC only in Model I. In terms of our predictors of interest, following adjustment for the six covariates, the *Z*-difference score for head circumference accounted for a unique portion of the variance in the FSIQ. Neither the VIQ nor the PIQ subscales met the required $p = .025$ significance threshold. When weight, in lieu of head circumference, *Z*-difference was entered into multiple regression models as the variable of interest, this anthropometric variable accounted for a unique portion of the variance in TL. None of the two language subscales met the required.025 significance threshold, though a trend ($p < .03$) was observed for AC. The *Z*-difference score for length did not explain outcome variance in any of our neuropsychological outcome measures. Of interest, none of the three difference scores was found to be significantly associated with motor indices.

To further corroborate the significant associations observed between head circumference and the FSIQ (Model III), and between body-weight and TL (Model I), we conducted two supplemental analyses where the difference score in each of these two models was substituted for the multiplicative interaction between the two anthropometric indices used in computing the difference (the *Z*-score at birth and the *Z*-score at discharge; see Laird & Weems, 2011 for statistical discussion). The first supplemental analysis yielded a significant interaction between head circumference *Z*-scores at birth and at discharge for the FSIQ ($F[1,108] = 3.82$; $p = .05$)[1], thus corroborating the association between head growth and global cognitive skills reported in Table 4 (Model III). The second supplemental analysis yielded no significant interaction between body-weight at birth and at discharge for TL ($F[1,114] = .01$; $p < .92$), hence failing to support the significant findings from Model I difference score analyses.

It should be noted that, although we found a significant sex by NICU head growth interaction effect on the FSIQ ($p = .03$; see Table 4, Model III), these relationship appeared to be linked to the different distributions of head circumference growth gains in the two sexes, in our particular sample of preschoolers. The average standardized birth-to-discharge change in head circumference was significantly greater in female neonates relative to their male counterparts (mean head circumference *Z*-difference ± *SD* = $-.05 \pm 1.28$ and $.66 \pm .84$, respectively ($t[119] = -3.68$; $p < .000$). After removal of the six females with the highest head circumference growth gains, outside the male group range (i.e., head circumference *Z*-difference <–1.5), the two-way interaction between sex and the head circumference difference *Z*-score was no longer significantly associated with the FSIQ ($p < .18$). Notably, the head circumference difference *Z*-score remained significantly associated with the FSIQ in the reduced model, even in the smaller subsample with the six most negative difference scores (i.e., highest gains in NICU head growth) excluded ($F[1,103] = 8.42$; $p = .005$).

DISCUSSION

We found that in very preterm-born infants, head growth in the NICU was associated with preschool outcome, particularly in the cognitive domain. This relationship was observed even after statistical adjustment for ante-, peri-, and neonatal risk factors, as well as socio-demographic variables. NICU stay represents a brief period in human development, averaging only 8 weeks (Table 2). Yet increase in head circumference *Z*-score from birth to discharge was significantly associated with higher global intellectual performance in the preschool years. In contrast, change in *Z*-scores reflecting birth-to-discharge gain in body-weight, or length, was unrelated to neuropsychological outcome.

Our findings are consistent, in part, with the results reported by Ehrenkranz et al. (2006) in a younger cohort of extremely low birth weight infants followed to 22 months corrected age. Similar to our analyses, the investigators also statistically adjusted for multiple sociodemographic variables and potential perinatal confounders. The observed relationships between in-hospital rate of head growth and infant mental development (Bayley Mental Development Index <70), in the study by Ehrenkranz and colleagues, is compatible with our findings of an association between change in head circumference and preschool intellectual performance. Ehrenkranz et al. concluded that growth velocity in extremely low birth weight infants during NICU hospitalization exerts a significant, and probably independent, effect on

---

[1] Analysis without the 14 cases whose discharge age was ≥42 weeks resulted in somewhat weaker association with FSIQ (F $[1, 96 = 3.56$; $p < .06$), consistent with reduced sample size.

neurodevelopmental outcome at 18–22 months of age. However, their report of an association between NICU growth in head circumference and motor skills in infancy is inconsistent with our negative findings for this outcome domain, perhaps because of differences between the two samples in age at follow-up.

Contrary to expectations, no relationships were observed between gains in body-length and preschool cognitive, language, or motor skills. These negative findings seem inconsistent with the notion that early gains in lean body mass (and, therefore, linear growth) are closely related to organ (including brain) growth and differentiation (Ramel et al., 2012). Although in our earlier, cross-sectional, study (Raz et al., 2014), we found some support for Ramel et al.'s expectation that functional outcome will be linked to length measurements, the current results did not lend support to their thesis. The absence of significant relationships between early postnatal linear growth and neuropsychological functioning at preschool age may be partly due to reduced accuracy of length measurements in newborns, likely associated with the difficulty in keeping children fully stretched-out and still (WHO Multicentre Growth Reference Study Group, 2006).

Our findings are partly consistent with the results reported by Franz et al. (2009) who followed-up 219 very preterm-born infants to preschool age. Using the same anthropometric indices of growth rate as in the current study (birth-to-discharge change in weight or head circumference *SD* scores), they found that global cognitive outcome was significantly associated with in-hospital weight gain, with a similar trend for head circumference. Because the associations between physical growth indices and neurodevelopment were exceeded by the consequences of severe ICH, the authors concluded that improving early neonatal growth could ameliorate long-term outcome in extremely preterm infants, though the effects may be small. Nonetheless, it should be noted that even a small effect is worthy of mention in the context of the relative brevity of NICU stay.

In contrast with our inability to demonstrate a relationship between physical growth in the NICU and motor outcome, Franz and colleagues (2009) reported that in-hospital head growth was an important predictor of motor examination ratings. The inclusion criteria for their sample were similar to ours in terms of age at follow-up, but the two samples differed in gestational age (<30 weeks in Franz et al.) and birth weight (Franz et al. had an upper limit of 1500 g while we allowed birth weight to vary), with our sample having a wider range on both dimensions. Most importantly, 11% of participants in the study by Franz et al. had severe perinatal brain lesions.

As reported above, neither postnatal head growth, nor linear growth or weight gain accounted for variance in motor skills. However, examination of the findings presented in Table 4 reveals that a significant portion of the variance in gross motor functioning was explained by adequacy of intrauterine growth, within each of the three linear models, regardless of the specific anthropometric measure chosen to index NICU physical growth. It should be noted here that consistent with the available body of literature (e.g., Kronenberg, Raz, & Sander, 2006; Lohaugen et al., 2013), reduced antenatal growth was associated with lower scores on multiple outcome measures. Furthermore, associations with outcome measures were observed more consistently for intrauterine, than for postnatal (NICU), growth. Nonetheless, the finding that antenatal, but not early postnatal, reduced body-growth is associated with lower gross motor performance may be explained by the relatively increased sensitivity of motor systems to developmental disruption *in utero*. Although myelination is predominantly a post-term process and continues at least until the end of the second year of life, myelination of various regions involved in motor functions begins *in utero*, perhaps as early as the end of the first trimester. While myelination appears in the inferior cerebellar peduncles at 25 weeks, the posterior limb of the internal capsule begins its myelination process by 35 weeks gestation, with preterm infants showing earlier internal capsule myelination than more mature infants (Battin & Rutherford, 2002). The very early myelination of motor regions is likely to render motor functioning in preterm-birth children increasingly vulnerable to antenatal risk. Indeed, in a recent study Faebo Larsen, Hvas Mortensen, Martinussen, and Nybo Andersen (2013) found that developmental coordination disorder is associated with lower gestational age and with suboptimal antenatal growth. Unlike motor skills, intellectual functions appear to be linked to growth deficits during both the antenatal and early postnatal periods, at least in our sample of preterm-born preschoolers. Our data may, therefore, suggest a more extended vulnerability period of cognitive functions to early growth deficits and concomitant risk factors. Because this sample was comprised of very preterm infants, a preponderance of the time span between birth and NICU discharge was, in fact, parallel to the third trimester of pregnancy. One may speculate that in a completed, full-term, pregnancy vulnerability of intellectual outcome to risk factors associated with early growth deficits may proceed well into the midst or end of the third trimester, while the peak sensitivity of motor skills to risk factors associated with growth deficits occurs earlier. Nonetheless, replication of the current findings is needed to support the notion of relatively extended vulnerability of cognitive functions to growth delay.

We found that lower SES, even within the restricted range of our preponderantly middle class sample, was associated with reduced performance across outcome domains, including motor functioning. As evident from Table 4, SES was more consistently associated with outcome measures than any other predictor in our regression models. The ubiquitous impact of SES, extending even to a neurological disorder such as CP, has been demonstrated in a Swedish national cohort study (Hjern & Thorngren-Jerneck, 2008). This group speculated that SES is merely a proxy for difficult to document antenatal biological risk factors such as compromised placental exchange, nutritional deficits, or intrauterine infections. However, SES effects on neurocognitive function, as well as on brain structure and function, are likely mediated by more than one mechanism. In addition to antenatal factors associated with adverse biological influences *in utero*, one should also take into account factors like parental care and cognitive stimulation in infancy and childhood (Hackman & Farah, 2008; Hackman, Farah, & Meaney, 2010; Lawson, Duda, Avants, Wu, & Farah, 2013; Noble, McCandliss, & Farah, 2007).

The limitations of this study include unknown reliability of anthropometric indices, derived from medical records data. However, unreliability should have resulted, if anything, in reduced associations between our growth indices and preschool-age performance measures. Perinatal and neonatal medical risk data were also retrospectively obtained. Since our participants were assessed at preschool age, it is yet to be determined whether anthropometric variables reflecting growth in the NICU have similar associations with outcome measures in older children. Moreover, early growth indices may ultimately show stronger associations with select cognitive processing tasks with greater sensitivity to early growth rate. Finally, the anatomical and functional brain correlates of anthropometric variables associated with early postnatal growth gains have yet to be established. The study of MRI-based cerebral morphometry or activation during neonatal intensive care hospitalization may help elucidate the neural mechanisms underlying the physical growth and behavioral outcome associations observed here in very preterm-born children.

ACKNOWLEDGMENTS

The authors thank Tammy Swails, Amanda Shoemaker, Jacquie Perry, and Sarah Meachen for their help in data collection. The testing of the subjects was funded in part by the Merrill-Palmer Skillman Institute. There are no known conflicts of interest concerning this manuscript.

REFERENCES

Battin, M., & Rutherford, M.A. (2002). Imaging the preterm infant. In M.R. Rutherford (Ed.), *MRI of the neonatal brain* (Chapter 3) Philadelphia: WB Saunders.

Batton, D.G., DeWitte, D.B., & Pryce, C.J. (2011). One hundred consecutive infants born at 23 weeks and resuscitated. *American Journal of Perinatology*, *28*, 299–304. doi:10.1055/s-0030-1268714

Charkaluk, M.L., Truffert, P., Marchand-Martin, L., Mur, S., Kaminski, M., & Ancel, P.Y., … the Epipage study group (2011). Very preterm children free of disability or delay at age 2: Predictors of schooling at age 8. *Early Human Development*, *87*, 297–302. doi:10.1016/j.earlhumdev.2011.01.033

Cheong, J.L.Y., Hunt, R.W., Anderson, P.J., Howard, K., Thompson, D.K., Wang, H.X., … Doyle, L.W. (2008). Head growth in preterm infants: Correlations with magnetic resonance imaging and neurodevelopmental outcome. *Pediatrics*, *121*, e1534–e1540.

Cooke, R.W.I. (2005). Perinatal and postnatal factors in very preterm infants and subsequent cognitive and motor abilities. *Archives of Disease in Childhood Fetal and Neonatal Edition*, *90*, F60–F63.

Cooke, R.W.I. (2006). Are there critical periods for brain growth in children born preterm? *Archives of Disease in Childhood Fetal and Neonatal Edition*, *91*, F17–F20.

Cooke, R.W., & Foulder-Hughes, L. (2003). Growth impairment in the very preterm and cognitive and motor performance at 7 years. *Archives of Disease in Childhood*, *88*, 482–487.

Ehrenkranz, R.A., Dusick, A.M., Vohr, B.R., Wright, L.L., Wrage, L.A., & Poole, W.K. (2006). Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*, *117*, 1253–1261. doi:10.1542/peds.2005–1368

Fabo Larsen, R., Hvas Mortensen, L., Martinussen, T., & Nybo Andersen, A.M. (2013). Determinants of developmental coordination disorder in 7-year-old children: A study of children in the Danish National Birth Cohort. *Developmental Medicine and Child Neurology*, *55*, 1016–1022.

Folio, M.R., & Fewell, R.R. (2000). *Peabody Developmental Motor Scales-Second Edition*. Austin, TX: Pro-Ed, Inc.

Franz, A.R., Pohlandt, F., Bode, H., Mihatsch, W.A., Sander, S., Kron, M., & Steinmacher, J. (2009). Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. *Pediatrics*, *123*, e101–e109. doi:10.1542/peds.2008-1352

Hackman, D.A., & Farah, M.J. (2008). Socioeconomic status and the developing brain. *Trends in Cognitive Science*, *13*, 65–70.

Hackman, D.A., Farah, M.J., & Meaney, M.J. (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews – Neuroscience*, *11*, 651–659.

Heinonen, K., Räikkönen, K., Pesonen, A.-K., Kajantie, E., Andersson, S., Eriksson, J.G., … Lano, A. (2008). Prenatal and postnatal growth and cognitive abilities at 56 months of age: A longitudinal study of infants born at term. *Pediatrics*, *121*, e1325–e1333. doi:10.1542/peds.2007–1172

Hjern, A., & Thorngren-Jerneck, K. (2008). Perinatal complications and socio-economic differences in cerebral palsy in Sweden – A national cohort study. *BMC Pediatrics*, *8*, 49.

Hollingshead, A.B. (1975). *A four factor index of social status*. Unpublished working paper. New Haven, CT: Department of Sociology, Yale University.

Hou, M., Sun, D.R., Shan, R.B., Wang, K., Yu, R., Zhao, J.H., … Jiang, Y.P. (2010). Comorbidities in patients with cerebral palsy and their relationship with neurologic subtypes and gross motor function classification system level. *Chinese Journal of Pediatrics*, *48*, 351–354.

Kan, E., Roberts, G., Anderson, P., & Doyle, L.W., the Victorian Infant Collaborative Study Group (2008). The association of growth impairment with neurodevelopmental outcome at eight years of age in very preterm children. *Early Human Development*, *84*, 409–416.

Kramer, M.S., Platt, R.W., Wen, S.W., Joseph, K.S., Allen, A., Abrahamowicz, M., … Breart, G. (2001). A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*, *108*, E35. doi:10.1542/peds.108.2.e35

Kronenberg, M.E., Raz, S., & Sander, C.J. (2006). Neurodevelopmental outcome in children born to mothers with hypertension in pregnancy: The significance of suboptimal intrauterine growth. *Developmental Medicine and Child Neurology*, *48*, 200–206.

Kuban, K.C., Alfred, E.N., O'Shea, T.M., Paneth, N., Westra, S., Miller, C., … Leviton, A. (2009). Developmental correlates of head circumference at birth and two years in a cohort of extremely low gestational age newborns. *The Journal of Pediatrics*, *155*, 344e–349e. doi:10.1016/j.jpeds.2009.04.002

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., … Johnson, C.L. (2002). 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. *Vital and Health Statistics*, 1–190.

Kurdahi Badr, L., Bookheimer, S., Purdy, I., & Deeb, M. (2009). Predictors of neurodevelopmental outcome for preterm infants with brain injury: MRI, medical and environmental factors. *Early Human Development*, *85*, 279–284.

Laird, R.D., & Weems, C.F. (2011). The equivalence off regression models using difference scores and models using separate scores for each informant: Implications for the study of informant discrepancies. *Psychological Assessment*, *23*, 388–397.

Lawson, G.M., Duda, J.T., Avants, B.B., Wu, J., & Farah, M.J. (2013). Associations between children's socioeconomic status and prefrontal cortical thickness. *Developmental Science*, *16*, 641–652.

Lohaugen, G.C., Ostgard, H.F., Andreassen, S., Jacobsen, G.W., Vik, T., Brubakk, A.M., … Martinussen, M. (2013). Small for gestational age and intrauterine growth restriction decreases cognitive function in young adults. *Journal of Pediatrics*, *163*, 447–453.

Maring, J.R., & Elbaum, L. (2007). Concurrent validity of the early intervention developmental profile and the Peabody Developmental Motor Scale-2. *Pediatric Physical Therapy*, *19*, 116–120.

Noble, K.G., McCandliss, B.D., & Farah, M.J. (2007). Socioeconomic gradients predict individual differences in neurocognitive abilities. *Developmental Science*, *10*, 464–480.

Olsen, I.E., Groveman, S.A., Lawson, M.L., Clark, R.H., & Zemel, B.S. (2010). New intrauterine growth curves based on United States data. *Pediatrics*, *125*, e214–e224. doi:10.1542/peds.2009-0913

Peterson, J., Taylor, H.G., Minich, N., Klein, N., & Hack, M. (2006). Subnormal head circumference in very low birth weight children: Neonatal correlates and school-age consequences. *Early Human Development*, *82*, 325–334.

Ramel, S.E., Demerath, E.W., Gray, H.L., Younge, N., Boys, C., & Georgieff, M.K. (2012). The relationship of poor linear growth velocity with neonatal illness and two-year neurodevelopment in preterm infants. *Neonatology*, *102*, 19–24. doi:10.1159/000336127

Raz, S., Lauterbach, M.D., Hopkins, T.L., Porter, C.L., Riggs, W.W., & Sander, C.J. (1995). Severity of perinatal cerebral injury and developmental outcome: A dose response relationship. *Neuropsychology*, *9*, 91–101.

Raz, S., Newman, J.B., DeBastos, A.K., Peters, B.N., & Batton, D.G. (2014). Postnatal growth and neuropsychological performance in preterm-birth preschoolers. *Neuropsychology*, *28*, 188–201.

Riddle, W., & DonLevy, S.C. (2010). Generating expected growth curves and Z-scores for premature infants. *Journal of Perinatology*, *30*, 741–750.

Rijken, M., Wit, J.M., Le Cessie, S., & Veen, S., Leiden Follow-Up Project on Prematurity (2007). The effect of perinatal risk factors on growth in very preterm infants at 2 years of age: The Leiden Follow-Up Project on Prematurity. *Early Human Development*, *83*, 527–534.

Truwit, C.L., Barkovich, A.J., Koch, T.K., & Ferriero, D.M. (1992). Cerebral palsy: MR findings in 40 patients. *AJNR American Journal of Neuroradiology*, *13*, 67–78.

Wechsler, D. (1989). *Wechsler Preschool and Primary Scale of Intelligence-Revised*. San Antonio, TX: The Psychological Corporation.

WHO Multicentre Growth Reference Study Group (2006). Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. *Acta Paediatrica Supplement*, *450*, 38–46.

Zimmerman, I.L., Steiner, V.G., & Pond, R.E. (1992). *Preschool Language Scale-Third Edition*. San Antonio, TX: The Psychological Corporation.