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Associations of growth and body composition with brain size in preterm infants

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Abstract

Objectives: To assess associations of very preterm infants' brain size at term equivalent age with 1) physical growth from birth to term, and 2) body composition at term.

Study Design: We studied 62 infants born <33 weeks' gestation. At birth and term, we measured weight, length, and calculated body mass index (BMI). At term, infants underwent air displacement plethysmography to determine body composition (fat and fat-free mass) and magnetic resonance imaging to quantify brain size (bifrontal diameter [BFD], biparietal diameter [BPD], transverse cerebellar distance [TCD]). We estimated associations of physical growth (Z-score change from birth to term) and body composition with brain size, adjusting for potential confounders using generalized estimating equations.

Results: Median birth gestational age was 29 weeks (range 24, 32.9). Positive gains in weight and BMI Z-score were associated with increased brain size. Each additional 100g of fat-free mass at term was associated with larger BFD (0.6mm, 95% confidence interval [CI]: 0.2, 1.0), BPD (0.7mm, 95%CI: 0.3, 1.1), and TCD (0.3mm, 95%CI: 0.003, 0.5). Associations between fat mass and brain metrics were not statistically significant.

Conclusions: Weight and BMI gain from birth to term, and lean mass—but not fat—at term, were associated with larger brain size. Factors that promote lean mass accrual among preterm infants may also promote brain growth.

Keywords

preterm; body composition; brain metrics; air displacement plethysmography

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INTRODUCTION

For very preterm infants, the period from birth to term represents a critical window for growth of the body and brain. Greater weight gain in the neonatal intensive care unit (NICU) predicts improved neurodevelopment [1–3], but weight alone is a non-specific marker of nutrient accretion. Distinguishing fat from lean mass accrual characterizes the quality of weight gain and may provide information about brain growth and development. Yet, little is known about how the composition of weight gain during the NICU hospitalization is related to neonatal brain size and future neurodevelopmental risk.

A few small studies have linked lean mass at term equivalent age with improved subsequent neurodevelopment, including faster cognitive processing at 4 months and higher cognitive scores at 1 and 4 years. In contrast, higher fat mass in those studies was associated with either neutral or worse cognitive outcomes [4–6]. Thus, lean mass at term may be a useful biomarker for brain growth and development. Brain size can be quantified using magnetic resonance imaging (MRI) [7], and larger brain size at term predicts better neurodevelopmental outcomes [8,9]. However, studies of body composition and brain size are both sparse and conflicting. One small (N=42) study found that both lean and fat mass correlated positively with cerebellar volume [10], whereas another small study (N=22) found a negative association between fat mass and total brain volume [11]. Both studies are limited by small sample sizes. Further, both assessed brain size only in one region or as total brain volume without considering different regions.

The primary aim of our study was to assess associations of physical growth and body composition with directly measured brain size among very preterm infants at term corrected age. Our underlying hypothesis was that lean mass represents the accretion of nutrients, including protein, required for brain growth. For this study, we hypothesized that higher lean mass—but not fat—at term equivalent would be associated with larger brain size. We also hypothesized that greater weight, length and BMI gains from birth to term would be associated with larger brain size.

SUBJECTS AND METHODS

PARTICIPANTS

We conducted a prospective, longitudinal study of very preterm infants born at a single academic Level III NICU from November 2015 to September 2018. Inclusion criteria were: gestational age <33 weeks at birth; singleton or twins; and no intention to transfer to another hospital after enrollment. Exclusion criteria were: major congenital anomalies; triplets or higher order multiples; and inability to provide informed consent in English. Of 122 infants enrolled, for this analysis we excluded: 27 infants who were unexpectedly transferred and 2 who died after enrollment; 18 infants missing MRI or body composition data; 7 infants whose parents withdrew consent; 4 infants diagnosed with a congenital anomaly after enrollment; and 2 infants who could not undergo body composition analysis due to dependence on continuous respiratory support. Thus, our final sample for this analysis was 62 (Figure 1; online).

This study was approved by the Institutional Review Board of Brigham and Women's Hospital, and all parents of infants who participated in the study provided written consent.

MEASURES

Clinical Data—Clinical data were collected from the electronic health record, including demographics, common comorbidities of prematurity (supplemental oxygen use at 36 weeks postmenstrual age, necrotizing enterocolitis, retinopathy of prematurity, sepsis, patent ductus arteriosus, and intraventricular hemorrhage) defined using standard definitions [12], and severity of illness using the Score for Neonatal Acute Physiology-Perinatal Extension-II (SNAPPE-II) [13].

Anthropometrics—Infants were weighed daily by clinical nursing staff on a calibrated infant scale (Scale-Tronix, Inc, White Plains, NY) to the nearest gram. Two trained NICU dietitians performed all length and head circumference measurements after birth. Length was measured weekly and within 24 hours of the body composition measurement to the nearest 0.1 centimeter on an infant length board (Ellard Instrumentation Ltd, Monroe, WA) using the 2-person method [14]. Head circumference (HC) was measured weekly to the nearest 0.1 centimeter using a non-stretchable tape. Weight, length, HC, and body mass index (BMI) Z-scores were calculated at birth and at term equivalent using the Olsen intrauterine growth reference [15,16].

Body Composition—At term equivalent age, infants underwent body composition measurement using air displacement plethysmography (ADP) in the Peapod Infant Body Composition System (COSMED, Concord, CA). This device directly measures body mass and volume, then uses a two-compartment model to determine fat and fat-free mass from infant-specific equations [17]. The accuracy and precision of the device have been validated for preterm infants [17]. We also calculated Z-scores for lean and fat mass at term using recently published reference data [18], the fat-free mass index (FFMI) using the formula fat-free mass/length^2 (kg/m^2), and the fat mass index (FMI) as fat mass/length^2 (kg/m^2).

Brain Metrics—At term equivalent age, infants underwent brain MRI without sedation [19] using a Siemens Trio 3 Tesla scanner (Erlangen, Germany). T_2-weighted images were acquired with a sagittal T_2 turbo spin echo sequence, with 1 × 1 × 1 mm isotropic voxels, flip angle = 160°, TR = 8630 ms, TE = 133 ms, FOV = 190 × 190 mm, matrix = 192 × 192. Total scan time was approximately one hour per participant. The images were manually AC-PC aligned using 3DSlicer [20] to standardize their 3-dimensional orientation. The aligned images were then used to derive 2D brain metrics in ITKSNAP [21], whereby a single observer manually delineated 3 brain metrics—bifrontal diameter (BFD), biparietal diameter (BPD), and transverse cerebellar diameter (TCD)— in the coronal plane [7] (Figure 2; online). In a subset of 29 infants, reliability of metrics was assessed by a second observer who was blinded to the body composition data. Interrater reliability of all 3 metrics had intraclass correlation coefficients of >0.9. Intrarater reliability had intraclass correlation coefficients of 0.83 (BFD), 0.98 (BPD), and 0.93 (TCD). We chose these 3 metrics from among 8 previously described tissue metrics [7] because these 3 have the highest correlation

with brain tissue volumes, highest intra- and interrater reliability, and are all associated with later neurodevelopmental outcomes [7,9].

STATISTICS

The primary outcome was brain size as determined by brain metrics (BFD, BPD, TCD) at term equivalent age. The primary exposures were 1) measures of body composition at term equivalent age (absolute fat-free and fat mass, body fat percentage, fat-free mass index, fat mass index, fat-free mass Z-score and fat mass Z-score) and 2) Z-score change from birth to term equivalent age of anthropometrics (weight, length, HC and BMI). We quantified associations between exposure and outcome variables using generalized estimating equations to account for non-independence of infants born to the same mother. The model included covariates that we identified a priori as determinants of infant growth, body composition and/or brain size [7,22] including gestational age at birth, birthweight Z-score (as a measure of fetal growth), postmenstrual age at time of outcome measurement, and sex. Further adjusting for severity of illness using the SNAPPE-II score, supplemental oxygen use at 36 weeks, or duration of mechanical ventilation did not substantially change the results, and these variables were not included in the final models. A sensitivity analysis excluding infants with grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia did not substantially alter the results, so all infants were included in the final analysis.

We used IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, New York) and SAS version 9.4 (SAS Inc, Cary, NC) for all analyses.

RESULTS

Participant characteristics are shown in Table 1. Median gestational age at birth was 29.1 weeks (range 24.0, 32.9), and median birth weight Z-score was 0.05. By term equivalent age (median postmenstrual age 39.4 weeks), median weight Z-score fell to −0.6. Length Z-score generally also declined (median −0.9 units) from birth to term, whereas median BMI Z-score change was only −0.02. At term, average body fat percentage was 17.7% ± 5.3% (Table 2). Infants excluded from the analysis had similar distribution of sex and race/ethnicity and similar median gestational age, birthweight, and birthweight z-score, as compared with infants who completed the study (data not shown).

Cross-sectional associations of body composition with brain size at term equivalent age after adjustment for covariates are shown in Table 3. Lean mass was positively associated with all three metrics. Specifically, each additional 100g of lean mass was associated with 0.62 mm larger BFD (95% CI: 0.24, 1.00); 0.70 mm larger BPD (95% CI: 0.27, 1.13); and 0.26 mm larger TCD (95% CI: 0.003, 0.51). To express these values in relation to average brain metric values, they represent 1% of average BFD and BPD, and 0.5% of average TCD. Similar to absolute lean mass, the lean mass Z-score and fat-free mass index showed generally positive associations with brain size, although associations with TCD did not meet statistical significance. Scatterplots of lean mass Z-score and brain metrics are shown in Figure 3; online. Associations of fat mass with each brain metric were positive but not statistically significant. Adiposity, whether measured by body fat percentage, body

fat percent Z-score, fat mass Z-score, or fat mass index, was not statistically significantly associated with any measure of brain size (Table 3).

In a post-hoc analysis comparing infants born <28 weeks' gestation (n=23) with those born ≥28 weeks' gestation (n=39), we found no significant difference between groups in mean lean mass (2.4 ± 0.3 kg vs 2.4 ± 0.4 kg; p=0.98) or lean mass Z-score (−1.5 ± 1.2 vs −1.1 ± 1.4; p=0.24). We also explored effect modification of gestational age category on the association between lean mass and brain metrics, by adding an interaction term between gestational age and the exposure variable in each analysis. None of the interaction terms were statistically significant (p=0.2–0.9).

Longitudinal associations of physical growth from birth to term equivalent age with brain size at term equivalent are shown in Table 4. Weight and BMI Z-score gain were strongly positively associated with all measures of brain size. For each additional Z-score gain in weight, BFD was 2.1 mm (95% confidence interval [CI]: 0.6, 3.7) larger; BPD was 2.6 mm (95% CI: 0.9, 4.3) larger; and TCD was 1.3 mm (95% CI: 0.3, 2.2) larger. To express the associations with weight Z-score gain in relation to average brain metric values, they represent 3% of average BFD and BPD, and 2% of average TCD. Associations between BMI gain and brain metrics were smaller in magnitude but still strongly positive. In contrast, associations of linear growth (Z-score change in body length from birth to term equivalent age) with brain metrics were not statistically significant.

To assess whether brain metrics provided additional information as compared with using head circumference alone to assess brain size, we calculated Pearson correlation coefficients between head circumference Z-score at the time of the MRI and each brain metric. HC Z-score was moderately correlated with brain metrics; r=0.68 with BFD, r=0.60 with BPD, and r=0.50 with TCD (p<0.01 for all correlation coefficients).

DISCUSSION

In a cohort of very preterm infants, we found that more rapid gains in weight and BMI from birth to term equivalent age were associated with larger brain size at term. While weight gain in the NICU is a well-established determinant of neurodevelopmental outcomes [1–3] and predicts brain size at term [10,23], relatively little is known about how the composition of weight gain relates to early brain growth and development. Using a non-invasive technique to accurately differentiate lean from fat mass, we evaluated relationships of weight composition with brain size at term equivalent age. Our main finding was that lean mass—whether measured in absolute value, Z-score, or fat-free mass index—was positively associated with brain size, whereas fat mass was not.

Our finding of a positive association between lean mass and brain size complements the limited literature on body composition and neurodevelopment. In the few studies conducted to date, lean mass at term was linked to faster cognitive processing speed in infancy and to improved cognitive scores at 1 and 4 years old [4–6]. Taken together, these data suggest that lean mass may be a useful biomarker of brain growth, reflecting factors that facilitate the accretion of nutrients into many tissues, including the brain. One such factor is nutrient

intake, particularly protein [24,25] which influences lean mass accrual [26,27] and plays a crucial role in brain developmental processes including neurotransmitter production, cell migration and differentiation, myelination, synaptogenesis, and neuronal growth [28,29]. Prior observational studies of preterm infants found that greater proportion of total energy intake composed of protein in the first few weeks of life was associated with greater lean mass at term equivalent [26]. Similarly, a randomized trial of additional protein and energy intake improved lean mass accretion during the neonatal hospitalization among very low birthweight infants [27]. In addition to nutrient intake, other factors may influence nutrient accretion in the body and brain, including severity of illness [9,30], inflammation [31–33], postnatal steroid administration [34,35], comorbidities such as bronchopulmonary dysplasia [30], and the insulin-like growth factor axis [36,37].

In contrast to lean mass, we found little evidence for an association of adiposity—either fat mass or body fat percent—with brain size in any of the three brain regions we studied. In suggesting no benefit of greater adiposity, our results are consistent with a prior study (N=22) in which greater deep subcutaneous fat mass was associated with *decreased* total brain size [11]. Our results are also consistent with prior studies of fat accrual and neurodevelopmental outcomes, which show no benefit of early fat mass gains or fat mass on neurodevelopmental testing from 4 months through 4 years old [4–6,38]. Our findings contrast, however, with one study (N=42) in which greater fat mass at term equivalent was associated with larger cerebellar size [10]. An important context for our findings is that preterm infants often develop relatively greater adiposity by term equivalent age than term-born infants [39]. Furthermore, preterm infants have elevated risk of adverse cardiometabolic outcomes later in life [40]. Emerging evidence suggests early fat accrual may exacerbate later cardiometabolic risk in both full term and preterm infants [41–43]. The optimal body composition for preterm infants remains unknown, yet our work adds to the growing body of literature suggesting that excess adiposity is not beneficial for brain growth or development.

Two prior MRI-based studies in preterm infants found that faster weight gain velocity prior to term was associated with larger total brain volume and cerebellum [10,23] but neither of those studies addressed the proportionality of weight gain. We noted that gain in BMI—representing weight gain out of proportion to length—predicted larger brain size at term. Unlike older children and adults, BMI in infants is a poor surrogate for fat mass in both preterm infants at birth and full term infants throughout infancy [44,45], although the relationship between BMI gain and adiposity gain in preterm infants is unknown. Nevertheless, in settings where body composition analysis is not available, BMI gain may complement weight gain in providing information about nutritional status in relation to brain growth. Routine BMI assessment can be facilitated by published reference charts for preterm infants [16].

Some authors have suggested that gain in body length may be a better index of lean body mass accretion and organ growth than weight gain [28,31]. In this context, we expected to find an association between linear growth and brain size, but our data showed no association. Similarly, one prior study in the preterm population also found no association between linear growth from birth to term and volume of the total brain, cerebellum, or cortical gray matter

[23]. It is notable that the concept of body length as an indicator of lean mass is largely extrapolated from work in the adult population, where height was found to be a better proxy for lean body mass than weight [46,47]; whereas, studies of preterm infants have shown the opposite, that weight is a better proxy for lean body mass than length is [44]. Prior studies linking linear growth from birth to term with neurodevelopmental outcomes have yielded inconsistent results in preterm infants [3,30,48]. An important caveat is that length measurements are often subject to measurement error [49], which could obscure true associations between linear growth and outcome; in our study, we minimized measurement error by using an infant length board and having only two trained observers perform all measurements.

In this study, we used MRI to directly measure brain size at term equivalent age. As compared with head circumference, MRI is preferred for measuring brain size because MRI distinguishes brain tissue from extra-axial cerebrospinal fluid—which is increased in preterm infants—and is not influenced by head shape [50,51]. Brain growth in the NICU is important because early abnormalities in brain size persist throughout childhood and adolescence, and are associated with long-term outcomes [34,52,53]. In prior studies, the brain metrics we measured at term have been shown to predict later neurodevelopmental outcomes independent of other known risk factors (such as sex, gestational age, severity of illness, maternal education, and overt brain injury) [54,55]. One of those studies compared a contemporary cohort of infants to a historical cohort, and found that the contemporary cohort had 4–10% larger brain metrics and twice as many infants with normal neurodevelopmental outcome at 2 years (68% vs 33%) [55]. However, further research is needed to determine the extent of the impact on neurodevelopment that would be expected from the 1–3% increases in brain size described in our study.

Strengths of our study include direct measurement of brain size using quantitative analysis of high-quality magnetic resonance images, although we acknowledge that more sophisticated volumetric analysis could further clarify precise regions of the brain where growth is associated with greater lean mass accrual. We also measured body composition directly using a highly accurate device specifically validated for preterm infants. However, our study has several limitations. A large proportion of enrolled infants did not complete the study, primarily due to early transfer to lower level units for convalescent care, although we did not find any difference in demographic characteristics among those infants and the remaining infants to suggest that this introduced bias in our results. We did not have data on long-term neurodevelopmental outcomes, although prior studies have shown that brain metrics at term are associated with later outcomes. Finally, this is a single center study and our findings may not be generalizable to other units with different populations or care practices, although our findings regarding weight gain and brain size are consistent with the few prior studies on this topic.

In conclusion, we found that the composition of weight gain from birth to term relates to brain growth; lean mass was associated with larger brain size whereas fat mass was not. While the optimal composition of weight gain for preterm infants remains unknown, our work adds to emerging evidence suggesting the importance of early lean mass accrual to optimize long-term neurodevelopment [4–6]. The beneficial effects of lean mass—in

contrast with fat—are particularly relevant given the striking deficit of lean mass and excess adiposity that preterm infants develop during the NICU hospitalization [39]. It is not yet known whether interventions that improve lean mass accrual could also improve brain growth and neurodevelopment. Nevertheless, body composition is an attractive biomarker of brain growth in preterm infants, particularly since recent advances in technology allow rapid non-invasive testing of body composition in the NICU. Attention to the quality and composition of preterm infants' weight gain, rather than quantity alone, is likely important for optimizing brain growth and neurodevelopment while mitigating risks to later cardiometabolic health.

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ABBREVIATIONS:

ADP	air displacement plethysmography
BFD	bifrontal diameter
BPD	biparietal diameter
BMI	body mass index
FMI	fat mass index
HC	head circumference
FFMI	fat-free mass index
MRI	magnetic resonance imaging
NICU	neonatal intensive care unit
SNAPPE-II	Score for Neonatal Acute Physiology-Perinatal Extension-II
TCD	transverse cerebellar diameter

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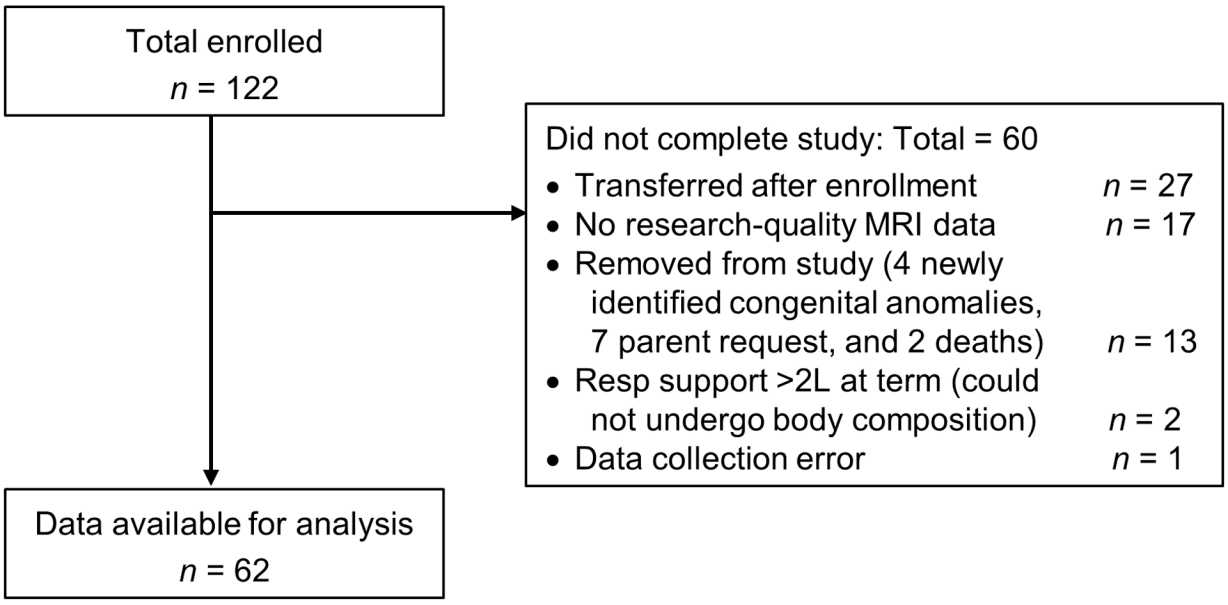

Figure 1.
Flow diagram of study participants.

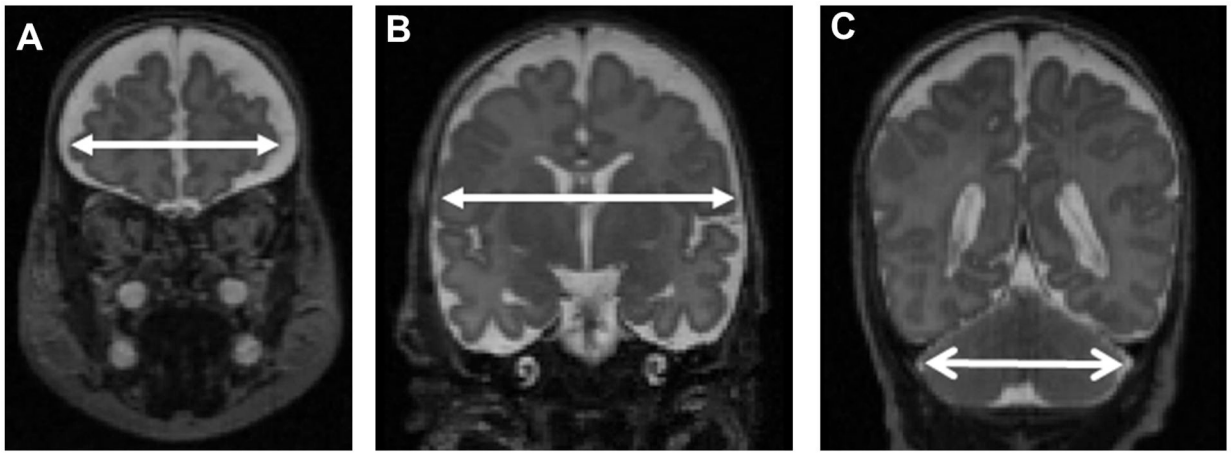

Figure 2.
Example measurements of bifrontal diameter (panel A), biparietal diameter (panel B), and transverse cerebellar diameter (panel C).

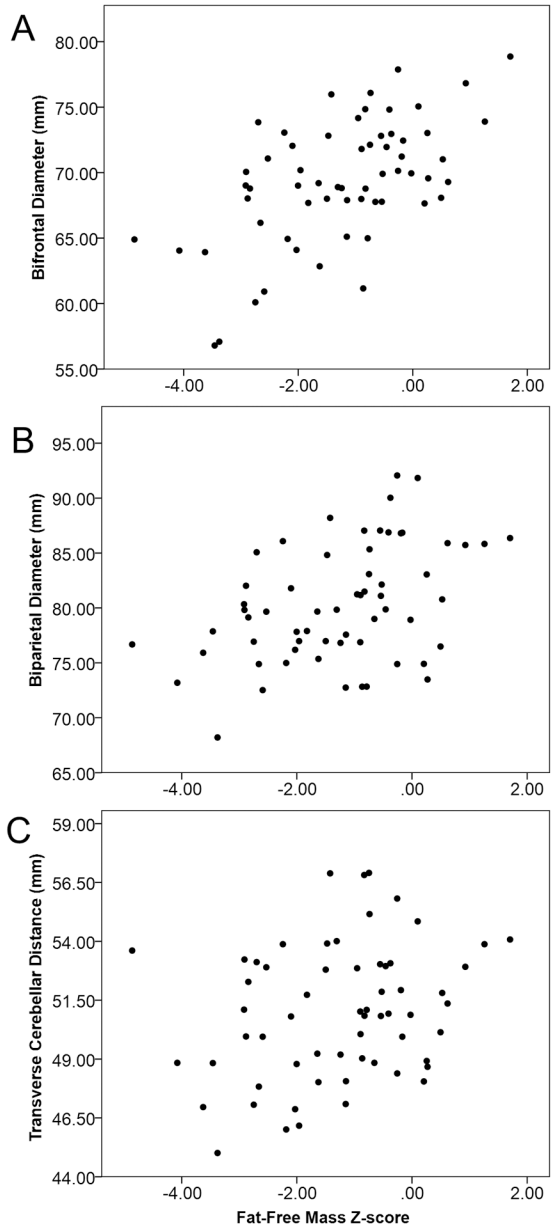

Figure 3.

Unadjusted scatterplots of lean mass Z-score at term equivalent age and brain size measured by 3 brain metrics: bifrontal diameter (panel A), biparietal diameter (panel B), and transverse cerebellar diameter (panel C).

Table 1.

Characteristics of 62 participants.

Characteristic[1]	N (%) or Median (Range)
Male	35 (56%)
Race	
African-American	12 (19%)
Asian	3 (5%)
Caucasian	36 (58%)
Other	11 (18%)
Hispanic ethnicity	12 (19%)
Gestational age at birth (weeks)	29.1 (24.0, 32.9)
Birth weight (g)	1088 (410, 2065)
Birth weight Z-score[2]	0.05 (−3.1, 2.3)
Small for gestational age (birthweight <10%)	11 (18%)
Multiple gestation	18 (29%)
Received antenatal steroids	61 (98%)
SNAPPE-II score	8.5 (0, 48)
Surfactant treatment	40 (65%)
Any mechanical ventilation	40 (65%)
Duration of mechanical ventilation (days)	1 (0, 49)
Supplemental oxygen at 36 weeks	23 (37%)
Postnatal steroids	7 (11%)
Necrotizing enterocolitis Bell stage ≥2	3 (5%)
Culture-proven sepsis	1 (2%)
Patent ductus arteriosus treatment	11 (18%)
Intraventricular hemorrhage grade 3 or 4	4 (6%)

[1] N(%) for categorical data and median (minimum, maximum) for skewed data (gestational age, birthweight, SNAPPE-II score, and duration of mechanical ventilation).

[2] From Olsen 2010 reference charts.

Table 2.

Body composition and brain metrics at term equivalent age (n=62).

Characteristic[1]	Median (Range) or Mean ± Standard Deviation
Postmenstrual age (weeks)	39.4 (35.9, 42.1)
Anthropometrics	
Weight at term (g)	2982 ± 503
Weight Z-score at term[2]	−0.6 (−3.2, 0.7)
Δ weight Z-score (birth to term)[2]	−0.5 (−3.1, 1.8)
Length at term (cm)	47.8 ± 2.6
Length Z-score at term[2]	−0.8 (−4.3, 0.7)
Δ length Z-score (birth to term)[2]	−0.9 (−2.0, 1.4)
Head circumference at term (cm)[3]	34.0 ± 1.5
Head circumference Z-score at term[3]	−0.1 (−2.0, 1.9)
Δ HC Z-score (birth to term)[2]	0.4 (−1.6, 3.1)
Body mass index Z-score at term[2]	0.2 (−1.8, 1.5)
Δ BMI Z-score (birth to term)[2]	−0.02 (−2.8, 2.8)
Body composition	
Fat-free mass (g)	2442 ± 384
Fat-free mass index (kg/m^2)	10.7 ± 1.0
Fat mass (g)	539 ± 207
Fat mass index (kg/m^2)	2.3 ± 0.8
Body fat percentage	17.7 ± 5.3
Brain metrics	
Bifrontal diameter (mm)	69.4 ± 4.7
Biparietal diameter (mm)	80.4 ± 5.3
Transverse cerebellar diameter (mm)	51.0 ± 2.8

[1] N(%) for categorical data, mean ± standard deviation for normally distributed data, or median (minimum, maximum) for skewed data (postmenstrual age, anthropometric Z-scores).

[2] 1 infant was missing weight, length, and body mass index Z-score at term equivalent age due to being measured at 42 weeks, beyond the range covered by the Olsen growth charts.

[3] 2 infants were missing head circumference data at term equivalent age.

Table 3.

Cross-sectional associations of body size and composition with brain size at term equivalent age (n=62).

	Mean (95% confidence interval) increase in brain size.					
	Bifrontal diameter (mm)		Biparietal diameter (mm)		Transverse cerebellar diameter (mm)	
	Estimate	p	Estimate	p	Estimate	p
Fat-free mass (per 100g)	**0.62 (0.24, 1.00)**	**0.001**	**0.70 (0.27, 1.13)**	**0.001**	**0.26 (0.003, 0.51)**	**0.04**
Fat-free mass index (kg/m^2)	**1.41 (0.56, 2.27)**	**0.001**	**1.18 (0.13, 2.23)**	**0.03**	0.34 (−0.20, 0.88)	0.22
Fat-free mass Z-score	**1.39 (0.44, 2.35)**	**0.004**	**1.40 (0.27, 2.54)**	**0.02**	0.53 (−0.10, 1.16)	0.10
Fat mass (per 100g)	0.31 (−0.12, 0.76)	0.17	0.50 (−0.16, 1.16)	0.13	0.36 (−0.01, 0.73)	0.06
Fat mass index (kg/m^2)	0.62 (−0.32, 1.56)	0.20	0.96 (−0.61, 2.54)	0.23	0.81 (−0.06, 1.69)	0.07
Fat mass Z-score	0.46 (−0.18, 1.11)	0.16	0.62 (−0.38, 1.62)	0.22	0.39 (−0.11, 0.89)	0.13
Body fat percent	0.04 (−0.09, 0.16)	0.59	0.10 (−0.12, 0.32)	0.39	0.11 (−0.01, 0.23)	0.07
Body fat **%** Z-score	0.13 (−0.37, 0.63)	0.61	0.33 (−0.52, 1.19)	0.45	0.39 (−0.07, 0.84)	0.09
Weight Z-score	**2.1 (0.60, 3.67)**	**0.006**	**2.60 (0.90, 4.31)**	**0.003**	**1.27 (0.32, 2.22)**	**0.009**
Length Z-score	1.13 (−0.48, 2.74)	0.17	1.48 (−0.32, 3.27)	0.11	0.91 (−0.05, 1.87)	0.06
BMI Z-score	**1.79 (0.69, 2.89)**	**0.001**	**1.95 (0.45, 3.44)**	**0.01**	**0.95 (0.11, 1.79)**	**0.03**
Head circumference Z-score	**2.70 (1.74, 3.67)**	**<0.001**	**3.10 (2.04, 4.16)**	**<0.001**	**1.26 (0.48, 2.04)**	**0.001**

Estimates represent the difference in brain metric measurement associated with one unit difference in each growth or body composition parameter at term equivalent age, adjusted using generalized estimating equations for gestational age at birth, sex, birthweight Z-score, and postmenstrual age at time of brain MRI, and accounting for non-independence of infants born to the same mother.

Table 4.

Longitudinal associations of physical growth from birth to term with brain size at term equivalent (n=62).

	Mean (95% confidence interval) increase in brain size.					
	Bifrontal diameter (mm)		**Biparietal diameter (mm)**		**Transverse cerebellar diameter (mm)**	
Z-score change	**Estimate**	**p**	**Estimate**	**p**	**Estimate**	**p**
Weight	**2.1 (0.6, 3.7)**	**0.006**	**2.6 (0.9, 4.3)**	**0.003**	**1.3 (0.3, 2.2)**	**0.008**
Length	1.1 (−0.6, 2.8)	0.20	1.7 (−0.01, 3.5)	0.05	0.3 (−0.6, 1.3)	0.50
BMI	**1.4 (0.3, 2.5)**	**0.01**	**1.4 (0.03, 2.8)**	**0.04**	**1.0 (0.3, 1.7)**	**0.008**
Head circumference	**1.3 (0.2, 2.4)**	**0.03**	0.8 (−0.7, 2.3)	0.31	**1.2 (0.5, 1.9)**	**<0.001**

Estimates represent the difference in brain metric associated with one Z-score difference in physical growth (change from birth to term equivalent age), adjusted using generalized estimating equations for gestational age at birth, sex, birthweight Z-score, and postmenstrual age at time of brain MRI, and accounting for non-independence of infants born to the same mother.