Body Composition Changes from Infancy to 4 Years and Associations with Early Childhood Cognition in Preterm and Full-Term Children

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Keywords

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Abstract

Background: Infants born prematurely are at risk for neurodevelopmental complications. Early growth is associated with improved later cognition. The relationship of early proportionality and body composition with later cognition is not well established. **Objectives:** To assess differences in fat-free mass and adiposity (fat mass, percent body fat) changes in preterm and full-term infants through preschool age and examine associations with early childhood cognition. **Methods:** This is a prospective, observational study in an appropriate for gestational age cohort of 71 patients (20 preterm and 51 full-term) from infancy through preschool age. Anthropometric and body composition measurements via air displacement plethysmography were obtained during infancy at term and 3–4 months (preterm corrected ages), and at 4 years. Cognitive testing occurred at 4 years. Associations of body composition changes between visits with cognitive

function were tested using linear regression. **Results:** In the preterm group, higher term to 4-month corrected age percent body fat gains were associated with lower working memory performance ($p = 0.01$), and higher 4-month corrected age to 4-year fat-free mass gains were associated with higher full-scale IQ ($p = 0.03$) and speed of processing performance ($p \leq 0.02$). In the full-term group, higher 4-month to 4-year fat mass gains were associated with lower full-scale IQ ($p = 0.03$). **Conclusions:** Body composition gains during different time periods are associated with varying areas of cognitive function. These findings may inform interventions aimed at optimal growth.

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Introduction

Children born prematurely are at risk for later cognitive deficits. Growth failure after premature birth is a risk factor for poorer neurodevelopment; better infancy growth is associated with improved cognitive and motor function. Increased gains in weight, length, and head circumference both during and after NICU hospitalization are associated with improved neurodevelopment [1, 2].

Children born prematurely are also at risk for long-term metabolic health detriments. In this population the neurodevelopmental benefits of growth can be in competition with the potential harm of rapid growth given its association with later insulin resistance, hypertension, and obesity [3, 4]. Balancing enhanced neurodevelopment with minimized metabolic risk may require interventions that track [5] and target optimal proportionality and quality of weight gain (body composition). For example, improved length gains (a lean growth marker) up to 12 months corrected age (CA) are associated with improved cognition [2], while increased BMI gain (a fat growth marker) from term CA to 18 months CA is associated with later obesity [4]. Notably, however, length and BMI may not accurately reflect lean and fat compartments in infancy and childhood [6, 7].

Children born prematurely have a different body composition at term CA than those born at full term: lower fat-free mass (FFM) and a higher percentage of fat mass (FM) [8, 9]. Comparative reports of later life body composition between children born before term versus full term have varying results [10, 11]. Emerging evidence suggests positive associations between FFM gains, but not FM gains, and later improvements in neurodevelopment. Specifically, greater FFM measurements at term and 4 months CA are associated with faster speed of processing at 4 months CA [12], and greater FFM gains during NICU hospitalization are associated with improved motor and cognitive scores at 12 months CA [13].

We previously reported on differences in body composition growth patterns between term and preterm infants from infancy to preschool age [11]. Associations of body composition beyond infancy with early childhood cognition in preterm infants have not yet been reported. Knowledge regarding the continued influence of growth patterns on later neurodevelopment will inform optimal growth patterns and interventions promoting these patterns.

In this paper, we aimed to test the hypothesis that cognitive function, particularly memory and executive function, are associated with fat-free body mass accretion in preterm and not full-term infants.

Methods

Subjects

Subjects were recruited during infancy from the University of Minnesota Masonic Children's Hospital (preterm, $n = 27$; December 2008 through October 2009) and an ongoing infancy body composition study (full-term, $n = 97$; April 2009 through June 2010) [14]. The initial study explored possible body composition

differences between preterm and full-term infants. Preterm subjects were recruited as a convenience sample. As this was a pilot study, a power analysis was not conducted given no previous studies reporting on similar predictors and outcome variables. Included subjects were born appropriate for gestational age: birth weight between the 10th and 90th percentiles on Fenton preterm growth curves or World Health Organization full-term growth curves. Preterm infants were included if born <35 weeks gestational age (GA) and excluded if they were diagnosed with a condition known to affect growth (e.g., congenital viral infection, chromosomal abnormality). Further group details are in the initial report [8]. The University of Minnesota Institutional Review Board approved the infancy and preschool follow-up studies. Parents gave written consent for their child's participation in each portion of the study.

Reported birth characteristics were GA, birth weight, sex, illness, and nutritional factors from the electronic medical record (preterm) or parental report (full-term). Demographics (maternal highest level of education and race) and feeding practice (breast milk and/or formula) were collected by self-report during the infancy visits.

Protocol

Subjects participated in 3 visits at our outpatient research center. The first, visit 1, was after NICU discharge, near term postmenstrual age for preterm infants, and about 2 weeks after hospital discharge for full-term infants (39–44 weeks postmenstrual age). The next time point, visit 2, was at 3–4 months (preterm CA). Finally, visit 3 or “preschool visit,” was at 4 years.

Anthropometrics and Body Composition

Study staff measured anthropometrics (weight, length or height, and head circumference) and body composition via air displacement plethysmography at all visits. Air displacement plethysmography was completed using the PEA POD at visits 1 and 2 and the BOD POD with Pediatric Option at visit 3 (Cosmed Ltd.; Concord, CA, USA). Body composition via air displacement plethysmography uses a participant's weight, length (visits 1 and 2) or height (visit 3), and volume measurements to calculate body density. Participant FFM, FM, and percent body fat (%BF) are derived from the body density measurement using established density values of FFM and FM [15, 16], as validated in infants and children, including those born prematurely [17–19].

Cognitive Testing

Cognitive testing performed at 4 years included measurements of general intelligence plus specific domains known to be affected in the preterm population: memory, attention, and executive function. All children were able to fully participate in testing.

A trained psychometrist (S.H.) blinded to the children's birth status administered the standardized Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WPPSI-IV; Wechsler, 2012). Age-normed results are: full-scale intelligence quotient (FSIQ), verbal comprehension index, visual spatial index, fluid reasoning index, working memory index (WMI), and processing speed index (PSI).

Four tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were chosen and administered in a standard, scripted format by one of three trained researchers. Tasks chosen test executive functioning related to visual memory, working memory, and speed of processing [20]. Performance differences in later childhood cohorts born preterm versus full term have been reported [21].

Table 1. Participant characteristics and preschool cognitive testing

Variable ^a	Preterm (<i>n</i> = 20)	Full-term (<i>n</i> = 51)	<i>p</i> value ^b
Birth data			
Birth weight, g	1,843 (586)	3,535 (459)	<0.01
Birth weight z-score ^c	0.04 (0.62)	0.47 (0.89)	0.051
Gestational age, weeks	31.9 (2.57)	39.8 (1.03)	<0.01
Demographics			
Male sex	13 (65)	26 (51)	0.31
White race	17 (85)	38 (75)	0.53
Maternal education >high school	14 (70)	45 (88)	0.084
Preterm hospitalization data			
Antenatal steroids	15 (75)	–	–
Day 1 score for neonatal acute physiology ^d	5.5 (2 to 17)	–	–
Head ultrasound abnormal ^e	1 (5)	–	–
Postnatal steroids	0	–	–
Energy deficit, kcal/kg ^f	88.4 (17.8 to 230)	–	–
Protein deficit, g/kg ^g	2.7 (–0.14 to 5.9)	–	–
Visit 1 (near term, preterm corrected age)			
Weight z-score ^c	0.00 (0.85)	0.10 (0.74)	0.61
Length z-score ^c	–0.02 (1.2)	0.27 (0.88)	0.26
Occipitofrontal head circumference z-score ^c	0.92 (0.90)	0.82 (0.90)	0.67
Breast milk, yes ^h	17 (85)	49 (96)	0.13
Visit 2 (3–4 months, preterm corrected age)			
Weight z-score ^c	–0.38 (1.2)	–0.055 (0.89)	0.21
Length z-score ^c	–0.19 (1.2)	0.38 (0.89)	0.029
Occipitofrontal head circumference z-score ^c	0.77 (0.96)	0.75 (0.76)	0.94
Breast milk, yes ^h	7 (35)	32 (63)	0.062
Visit 3 (4 years)			
Weight z-score ^c	–0.41 (1.2)	0.02 (0.84)	0.088
Height z-score ⁱ	–0.45 (0.97)	–0.08 (0.84)	0.12
WPPSI-IV ^j			
Full-scale IQ	98.2 (13.2)	105 (13.0)	0.068
Verbal comprehension index	104 (14.3)	108 (14.7)	0.27
Visual-spatial index	97.7 (14.7)	105 (15.3)	0.067
Fluid reasoning index	97.2 (11.9)	99.2 (12.0)	0.53
Working memory index	98.9 (10.5)	99.2 (12.8)	0.91
Processing speed index	95.4 (12.2)	103 (12.7)	0.022
CANTAB ^j			
Motor screen: average latency, ms	1,553 (311)	1,532 (455)	0.83
Motor screen: error number	1.32 (2.31)	0.73 (1.67)	0.33
Spatial span longest span length	1.68 (1.42)	2.12 (1.47)	0.27
Spatial working memory, 4-box error	6.61 (4.55)	7.85 (6.19)	0.38
Spatial working memory, 6-box error	24.0 (7.91)	28.0 (13.72)	0.15
Spatial working memory, total errors	30.4 (9.22)	35.4 (16.8)	0.14
Delayed match to sample, % correct first try	42 (12)	41 (15)	0.83
Visual evoked potentials ^k			
p100 latency, ms	131 (19.9)	127 (21.4)	0.39

^a Continuous data are reported as means (SD) and categorical data as number yes (%) unless otherwise specified in the row. ^b The *p* value is calculated from 2-sample *t* test for continuous variables, and the Fisher exact test for categorical variables. ^c Calculated for weight, length (visits 1 and 2) or height (visit 3), and head circumference on Fenton or World Health Organization growth chart as appropriate for preterm/full-term status and postmenstrual age. ^d Reported as means (range). ^e One infant had bilateral grade 2 intraventricular hemorrhage without hydrocephalus on serial images. ^f Energy deficit calculated using a 120 kcal/kg/day goal and subtracting or adding actual calories received each day of hospitalization and combined for entire hospitalization (kcal/kg); reported as means (range). ^g Protein deficit calculated using a 3.5 g/kg/day goal and subtracting or adding actual protein received each day of hospitalization and combined for entire hospitalization (g/kg); reported as means (range). ^h Number of infants fed breast milk either exclusively or partially per maternal report. ⁱ Excluding full-term participants without (*n* = 3) or with incomplete (*n* = 1) data. ^j Excluding participants without data (preterm *n* = 1, full-term *n* = 2) or with incomplete data (preterm *n* = 1, full-term *n* = 3). ^k Excluding participants without data (preterm *n* = 1, full-term *n* = 1).

Table 2. Body composition changes between visits

Variable	Preterm ^a (<i>n</i> = 20)	Full-term ^a (<i>n</i> = 51)	<i>p</i> value ^b
Fat-free mass, g/week			
V1-V2 rate	120 (24.2)	120 (32.4)	0.96
V2-V3 rate	39.9 (6.33)	42.6 (6.59)	0.12
Fat mass, g/week			
V1-V2 rate	59.8 (29.7)	90.7 (41.7)	0.001
V2-V3 rate	7.56 (6.89)	8.86 (4.84)	0.45
Percent body fat, %/week			
V1-V2 rate	0.39 (0.36)	0.96 (0.51)	<0.001
V2-V3 rate	-0.03 (0.04)	-0.02 (0.03)	0.57

V1, visit 1 at term or term corrected age (preterm participants); V2, visit 2 at 3–4 months (preterm corrected age); V3, visit 3 at 4 years. ^a Data are reported as means (SD). ^b The *p* value is calculated from a 2-sample *t* test.

Visual Evoked Potentials

Brain speed of processing was also assessed with pattern reversal visual evoked potentials (VEP) via event-related potentials. A previous report of the preterm portion of this cohort showed associations between speed of processing and infancy body composition [12]. A 128-channel sensor net system was used. Event-related potential data were collected and recorded online using Net-Amps amplifiers and the NetStation software (Electrical Geodesics Inc., Eugene, OR, USA). The child's visual response latency (ms), referred to as "p100," was measured at lead 76, the midline occipital active electrode [22].

Data Analysis

Descriptive statistics by preterm versus full-term status were analyzed as mean (SD) or count (percentage) as appropriate for demographic, cognition, and body composition variables. Two-sample *t* tests for continuous variables or Fisher exact tests for categorical variables were run with preterm versus full-term status for all variables to calculate *p* values.

To examine associations between body composition changes and children's performance on each cognitive test, a multivariable linear regression analysis was performed. Exposures were FFM and %BF change from term to 3–4 months (preterm CA) and from 3–4 months (preterm CA) to 4 years. The outcome measures were WPPSI-IV, CANTAB, and VEP performance at 4 years. Covariates known to be associated with children's cognitive performance – sex, race, and maternal education – were included in all models. The exact age at the 4-year visit was additionally adjusted for in the analysis of all the CANTAB variables, as CANTAB results are not age normative. Given our hypothesis that body composition changes would be associated with cognitive testing at 4 years of age in the preterm group, but not the full-term group, the two groups were assessed separately in the regression analyses.

Analyses were performed using SAS (v9.3; SAS Institute, Cary, NC, USA). Statistical significance was defined as *p* < 0.05.

Results

Some participants were lost to follow-up (22 of 27 preterm and 52 of 97 full-term infants participated in visit 3). Preterm and full-term children who did versus those who did not complete visit 3 had no significant group differences in birth weight, GA [13], maternal education, or race (data not shown). Three children (2 preterm, 1 full-term) did not have body composition data collected at visit 3 due to lack of child cooperation. This analysis includes children with body composition data at all visits (preterm *n* = 20, GA 27.0–34.9 weeks; full-term *n* = 51).

Participant characteristics and preschool cognitive testing results are seen in Table 1.

Preterm infants had lower FFM and higher %BF than the full-term infants at visit 1 but similar body composition at visits 2 and 3 (previously reported data not shown) [8, 11]. Body composition accretion from visit 1 to visit 2 was different for the two groups, as shown in Table 2. As compared to full-term infants, from visit 1 to visit 2 the premature infants gained less FM (90.7 vs. 59.8 g/week, *p* = 0.001), less %BF (0.96 vs. 0.39%/week, *p* < 0.001), and similar FFM (120 g/week, *p* = 0.96). The groups had similar body composition changes from visit 2 to visit 3.

Table 3 details significant results of the regression analysis for preterm children.

Early changes in proportionality (%BF) were associated with the preterm children's performance on working memory tests at preschool age: greater gains in %BF from visit 1 to visit 2 were associated with a lower WPPSI-IV WMI score and a higher number of errors in the CANTAB spatial working memory test. Figure 1 illustrates these significant associations found in the preterm but not full-term group. Each percentage point higher %BF per week from visit 1 to visit 2 was associated with a 21-point lower WPPSI-IV WMI at visit 3 (SE 6.3, *p* = 0.005) and 22 more total errors on CANTAB spatial working memory (SE 6.1, *p* = 0.005) in preterm participants.

Later body composition and proportionality changes were associated with preterm children's general cognition (WPPSI-IV FSIQ) and tests of processing speed. Higher FFM gain from infancy to early childhood (visit 2 to visit 3) was positively associated with preschool full-scale IQ and PSI in the preterm group (Fig. 2). For a preterm participant each gram of FFM gained per week from visit 2 to visit 3 was associated with a 0.85-point higher WPPSI-IV FSIQ (SE 0.36, *p* = 0.033) and a 0.95-point higher WPPSI-IV PSI (SE 0.35, *p* = 0.015). Higher FFM gain during this time period was also associated with a 244 ms lower CANTAB delayed match to sample latency

Table 3. Cognitive factors associated with body composition changes in preterm infants at 4 years of age

Variable/test	Percent body fat rate, %/week				Fat-free mass rate, g/week			
	visit 1 to visit 2		visit 2 to visit 3		visit 1 to visit 2		visit 2 to visit 3	
	estimate (SE)	<i>p</i> value	estimate (SE)	<i>p</i> value	estimate (SE)	<i>p</i> value	estimate (SE)	<i>p</i> value
Working memory								
WMI	−20.9 (6.29)	0.005	−18.6 (72.1)	0.80	−0.14 (0.18)	0.47	0.28 (0.43)	0.52
SWM total errors ^a	21.6 (6.08)	0.005	−58.8 (83.7)	0.50	0.22 (0.17)	0.21	0.45 (0.51)	0.40
Full-scale IQ	−5.63 (7.90)	0.49	−62.0 (68.2)	0.38	0.03 (0.18)	0.86	0.85 (0.36)	0.033
Processing speed								
PSI	1.47 (8.15)	0.86	−41.0 (70.3)	0.57	0.07 (0.18)	0.69	0.95 (0.35)	0.015
DMS mean corrected latency ^a	431 (1530)	0.78	7,110 (1,270)	0.59	−13.1 (29.7)	0.67	−244 (43.6)	<0.001
VEP p100 latency	−12.5 (15.8)	0.44	331 (94.8)	0.004	0.27 (0.33)	0.43	0.01 (0.78)	0.99

Multivariable linear regression analysis with adjustment for sex, race (white vs. non-white), and maternal education ($\leq$ high school vs. $>$ high school). Visit 1 at term (preterm corrected age); visit 2 at 3–4 months (preterm corrected age); visit 3 at 4 years. WMI, WPPSI-IV working memory index; SWM, CANTAB spatial working memory; full-scale IQ, WPPSI-IV full-scale intelligence quotient; PSI, WPPSI-IV processing speed index; DMS, CANTAB delayed match to sample; VEP, visual evoked potential. ^aCANTAB analysis additionally adjusted for age at visit 3.

Fig. 1. Rate of percent body fat gain from visit 1 to visit 2 associated with visit 3 working memory testing. **a** WPPSI-IV working memory index. Preterm β (SE) = −20.9 (6.29), p = 0.005, R = 0.51; full-term β (SE) = −5.50 (3.69), p = 0.14, R = 0.15. **b** CANTAB spatial working memory total errors. Preterm β (SE) = 21.6 (6.08), p = 0.005, R = 0.63; full-term β (SE) = 3.61 (5.00), p = 0.47, R = 0.15.

for correct answer (SE 43.6, p < 0.001), i.e. a faster time. Additionally, for each %BF gain per week from visit 2 to visit 3, VEP p100 latency increased by 331 ms (SE 94.8, p = 0.004), i.e. a slower time.

Body composition changes in the preterm children were not associated with other WPPSI-IV subscores or CANTAB spatial span or other delayed match to sample measures (data not shown).

Fig. 2. Rate of fat-free mass gain from visit 2 to visit 3 associated with visit 3 cognitive testing. **a** WPPSI-IV full-scale IQ. Preterm β (SE) = 0.85 (0.36), $p = 0.033$, $R = 0.63$; full-term β (SE) = -0.004 (0.33), $p = 0.99$, $r = 0.03$. **b** WPPSI-IV processing speed index. Preterm β (SE) = 0.95 (0.35), $p = 0.015$, $R = 0.59$; full-term β (SE) = 0.11 (0.32), $p = 0.73$, $R = 0.039$.

In the full-term group later adiposity gains were negatively associated with preschool cognition. Specifically, FM gains from visit 2 to visit 3 were associated only in the full-term group with lower FSIQ ($\beta = -0.92$, SE 0.41, $p = 0.031$), lower PSI ($\beta = -0.77$, SE 0.38, $p = 0.049$), and lower maximum span length on CANTAB spatial span ($\beta = -0.1$, SE 0.04, $p = 0.029$).

Discussion

Early growth is important for preterm children's later cognition. Concern exists regarding potential adverse metabolic consequences of excess growth (i.e., later obesity, hypertension, and insulin resistance). Evidence increasingly supports augmenting lean tissue growth to optimize the competing cognitive and metabolic outcomes [2, 4]. Recent literature specifically suggests that gains in FFM, but not FM, are associated with improved infancy cognition [12, 13]. To our knowledge, this is the first report relating body composition changes beyond infancy with preschool age cognition.

As compared to full-term infants, this heterogeneous group of appropriate for gestational age preterm infants had less FFM and higher %BF at term CA [8]. Then, the preterm group gained significantly less FM and less

%BF but similar FFM from term CA to 3–4 months CA (Table 2), and the groups had a similar body composition [8]. The groups were also similar at 4 years [11]. Except for a slightly lower WPPSI-IV PSI in the preterm group, cognitive testing results including general cognition were normal and similar for both groups, demonstrating a preterm group relatively unaffected by major neurodevelopmental disability.

In the preterm cohort, greater %BF gain (greater FM gain relative to less FFM gain) from term CA to 4 months CA (visit 1 to visit 2) was negatively associated with preschool working memory. Poorer working memory performance has been described in very low birth weight and late preterm infants [21, 23]. These tasks are a function of the dorsolateral prefrontal cortex and hippocampus [21]. Structural changes in these areas are associated with working memory performance in preterm children [24]. These brain areas undergo rapid structural and functional changes during infancy and are vulnerable to stress-related injury including nutritional deprivation [25]. Infancy growth patterns in association with working memory performance have not been previously reported.

Our findings infer that higher adiposity and/or lack of appropriate FFM growth from term to 4 months CA may be detrimental to developmental trajectories in

these brain areas and preterm children's ongoing working memory performance. Weight and length growth during the early infancy/post-NICU discharge time period are recognized as important for later neurodevelopment [4]. Therefore, we suggest that targeting overall growth while minimizing FM and %BF gains may promote improved working memory function development. Working memory and other executive functioning continue to develop beyond preschool age. Longer-term studies are needed to determine persistence of these findings.

Greater infancy to preschool age (visit 2 to visit 3) FFM gains, but not adiposity gains, were associated with improved overall cognition (FSIQ) and processing speed task performance (WPPSI-IV PSI, CANTAB delayed match to sample latency, VEP p100 latency) among the preterm cohort. Differences in processing speed between preterm and full-term children are well known, and our study confirms these findings. Processing speed and general cognition are associated with brain imaging changes. FFM is a reflection of overall protein accretion, which along with growth factors such as insulin-like growth factor-1, is necessary for overall brain growth and myelination [25]. Soria-Pastor et al. [26] studied a group of adolescents born prematurely and found both overall intelligence and processing speed were correlated with decreased brain white matter on MRI. Murray et al. [27] also reported in a group of 7-year-olds born prematurely that decreased processing speed was associated with global brain and white matter abnormalities on MRI.

Our findings indicate that specific body composition changes continue to incur neurodevelopmental benefit beyond infancy. The literature best supports that growth in the first 4 months after discharge from the NICU is associated with improved neurodevelopment. However, Belfort et al. [4] found that higher BMI gains from 4 to 12 months CA were also associated with lower odds of IQ below 85, and Ramel et al. [2] reported that higher linear growth to 12 months CA was associated with improved 24-month CA cognitive performance. The relatively long time between visits 2 and 3 limits a more specific definition of the most beneficial time periods for FFM gain. While one period of growth may be influenced by growth in the prior period [28], we found that growth during each time period was associated with different cognitive changes, pointing to sensitive growth periods for each affected domain. Future studies with more frequent follow-up visits will be important to define these critical periods, particularly as excess growth

during this time frame may incur increased metabolic risk [4].

Our primary aim of the study was to explore the relationship of body composition changes with cognition in the preterm children, yet we also found that increased adiposity during early childhood was associated with poorer cognitive performance in the full-term children. Previous research suggests adequate early growth is important for preschool cognition in full-term appropriate for gestational age children [29], while rapid early growth does not incur additional neurodevelopmental benefit [30] and is, in fact, associated with lower cognitive scores [29]. We suggest increasing adiposity during early childhood may be detrimental to long-term cognitive outcomes and should be monitored more closely.

Our study has some limitations. The preterm group was small and heterogeneous with regard to GA. Also, follow-up at visit 3 was suboptimal for the full-term group, though those seen were similar to those who did not follow up [11]. We were unable, given the sample size, to adjust for additional covariates that may affect body composition or cognition (e.g., nutrition, physical vs. sedentary activity, neonatal illness). Larger studies with additional follow-up visits are important to confirm these preliminary findings.

We report preliminary evidence in a heterogeneous preterm population that body composition changes following NICU discharge – decreased early adiposity and increased later FFM – are associated with enhanced preschool cognitive performance. Lower infancy to preschool adiposity gains may also incur neurodevelopmental benefit in the full-term population. Further research aimed to improve neurodevelopment and minimize metabolic risk will define optimal body composition growth patterns. Ultimately, intervention trials targeting these patterns will inform best practices from the NICU through childhood.

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Disclosure Statement

The authors declare no conflicts of interest.

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