Pediatric RESEARCH

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Early body composition changes are associated with neurodevelopmental and metabolic outcomes at 4 years of age in very preterm infants

Katie M. Pfister[1], Lei Zhang[2], Neely C. Miller[3], Ellen C. Ingolfsland[1], Ellen W. Demerath[4] and Sara E. Ramel[1]

BACKGROUND: Very preterm (VPT) infants are at-risk for altered growth, slower speed of processing (SOP), and hypertension. This study assesses the relationship between postnatal body composition (BC), neurodevelopment (indexed by SOP), and blood pressure (BP) in VPT infants.

METHODS: Thirty-four VPT infants underwent weekly measurements and BC testing until discharge and post-discharge at 4 mos CGA and 4 yrs. At post-discharge visits, SOP was assessed using visual evoked potentials and the NIH Toolbox; BP was also measured.

RESULTS: In-hospital rate of weight, length and fat-free mass (FFM) gains were associated with faster SOP at 4 yrs. Higher rate of gains in weight and FFM from discharge to 4 mos CGA were associated with faster SOP at 4 mos CGA, while higher fat mass (FM) gains during the same time were positively associated with BP at 4 yrs. BC at 4 yrs nor gains beyond 4 mos CGA were associated with outcomes.

CONCLUSIONS: In VPT infants, early FFM gains are associated with faster SOP, whereas post-discharge FM gains are associated with higher BPs at 4 yrs. This shows birth to 4 mos CGA is a sensitive period for growth and its relation to neurodevelopmental and metabolic outcomes. Close monitoring and early nutritional adjustments to optimize quality of gains may improve outcomes.

Pediatric Research (2018) 84:713–718; https://doi.org/10.1038/s41390-018-0158-x

BACKGROUND

Postnatal growth and body composition of preterm infants is altered compared to intra-uterine gains such that by term corrected gestational age (CGA), preterm infants have lower fat-free mass (FFM) and higher fat mass (FM) compared to term counterparts.[1–3] Long-term neurodevelopment in preterm infants is affected in part by nutritional status and growth during hospitalization and early infancy. In particular, weight gain, head growth, linear growth, and FFM gains during hospitalization and up to 4 months CGA are associated positively with gross neurodevelopment at 18–24 months, whereas growth beyond 4 months CGA has been shown to have minimal associations with neurodevelopmental outcomes.[4–6] Early aggressive nutrition is also associated with brain development and outcomes at 12–24 months.[7–10] This early, postnatal time period appears to be a sensitive stage for growth as it relates to the brain and neurodevelopment in preterm infants. Very preterm (VPT) infants are particularly vulnerable given that most or all of their third trimester, a period of marked brain development, is spent ex-utero.

One aspect of neurodevelopment particularly affected in preterm infants is speed of processing (SOP). SOP is delayed in preterm infants during early and mid-childhood.[11,12] Processing speed goes on to affect daily functioning, academics, and behavior through its mediation of executive functioning and attention[12,13] and is also related to full-scale IQ.[11]

Our group previously published a pilot study showing that higher FFM at term and 4 months CGA is associated with faster SOP at 4 months CGA in a small group of preterm infants born <35 weeks.[6] SOP, which reflects both synaptic integrity and myelination, is easily tested in infants and children using visual evoked potentials (VEPs). Latency to the peak of the P100 waveform indexes neuronal processing speed and maturation of the visual system and shortens (speeds up) throughout the third trimester, infancy, and early childhood as the visual pathway develops. These factors, as well as low intra-subject variability and ease of administration, make VEP a useful tool in assessing early brain development in at-risk infants and children.[14] Older children are also able to complete task-based testing that assesses SOP.

Additionally, preterm infants are at-risk for long-term metabolic abnormalities including hypertension;[15] however, whether early catch-up growth and/or body composition changes alter this risk remains unclear.[16] In preterm infants, some studies have shown that high BMI and weight gain during the first 12–18 months of life increases the risk of obesity during later childhood.[17,18] Lapillionne et al.[8] summarized a number of studies that show early growth of preterm infants is not associated with later hypertension, particularly under 8 months of age, while gains after this time period showed associations. Very few studies have evaluated the effect of in-hospital growth, and particularly body composition, on long-term metabolic outcomes.

[1]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA; [2]Clinical and Translational Science Institute, University of Minnesota, Minneapolis, MN, USA; [3]Center for Neurobehavioral Development, University of Minnesota, Minneapolis, MN, USA and [4]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA

Correspondence: Katie M. Pfister (Pfis0019@umn.edu)

Received: 9 February 2018 Revised: 9 February 2018 Accepted: 7 June 2018
Published online: 21 August 2018

The objective of the present study was to prospectively follow a cohort of very preterm infants (<32 weeks at birth) from birth to 4 years to evaluate the association between early body composition and long-term neurodevelopment, as assessed by SOP, as well as metabolic outcomes, as assessed by blood pressure (BP).

METHODS

Thirty-four VLBW preterm infants were recruited from the University of Minnesota Masonic Children's Hospital Neonatal Intensive Care Unit between April 2011 and November 2012. Inclusion criteria included birth weight <1500 g, gestational age at birth <32 weeks, and size appropriate for gestational age (birth weight between the 10th and 90th percentile on the Fenton Curve[19]). Infants were excluded if there was presence of a congenital metabolic disease that would affect growth. The University of Minnesota Institutional Review Board approved the protocol and informed consent was obtained from a parent within the first 5 days of life.

Inpatient data

Infants had weekly inpatient anthropometrics recorded and, once able to tolerate room air for >5 min, also underwent weekly body composition testing (median day of life 24.5 and median CGA 33.2 weeks). Weight was recorded to the nearest 1 g, supine length was measured using an infant length board (Perspective Enterprises; Portage, MI), and OFC was measured with a flexible cloth tape measure (length and OFC recorded to the nearest 0.1 cm). Body composition was measured using air-displacement plethysmography (PEA POD, COSMED, Ltd.; Concord, CA), which provides a validated measurement of infant body composition, including preterm infants.[20] Briefly, infant weight to the nearest 0.1 g and volume were measured using the PEA POD and were used to calculate body density using known age and sex-specific FFM density values.[21] A detailed description of the PEA POD's measurement procedures, design, and operating principles are described elsewhere.[22–25]

Data collected as covariates included nutritional intake and markers of illness. Caloric intake (kcal/kg/d) and protein intake (g/kg/d) were recorded by a NICU dietician. Cumulative nutritional deficit or surplus for the hospitalization was calculated from goals of 120 kcal/kg/d of energy and 4 g/kg/d of protein. Illness severity was measured using the Score for Neonatal Acute Physiology-II (SNAP-II), a validated illness severity and mortality risk score for neonates,[26] on day 1. Also recorded was worst grade of intraventricular hemorrhage and retinopathy of prematurity, as well as number of days on positive airway pressure, oxygen, antibiotics, and IV/oral steroids.

Outpatient data

Body composition (again via air-displacement plethysmography using the PEA POD (COSMED, Ltd.) for infants and BOD POD with Pediatric Option (COSMED, Ltd.; Concord, CA) at 4 years) and VEPs were recorded at 4 months CGA and 4 years old. At 4 years old, children were also assessed using the NIH Toolbox Pattern Comparison Processing Speed Test Ages 3–6 (NTPST)[27] and blood pressure was measured using a Datascope Accutor Plus non-invasive automatic oscillometric blood pressure monitor. The average of two blood pressure measurements was used for analysis. At the 4 month CGA visit, a 64-electrode Sensor Net was used for VEP data acquisition; at the 4 year visit a 128-channel net was used. Nets are designed using an elastic tension structure with electrodes positioned in a geodesic pattern. Infants were seated in a darkened room and presented a visual stimulus of a pattern-reversing black-and-white checkerboard, presented by E-Prime software (Psychology Software Tools, Sharpsburg, PA). The pattern was comprised of ~1.5 × 1.5 cm individual checks (1.4 × 1.4°) with two reversals per second for 50 trials. It was displayed on a 20″ ViewSonic Graphics Series G225f monitor (ViewSonic, Walnut, CA) with a screen that was 39 cm wide × 29 cm tall so that the viewing field subtended to 33.4 × 23.5° at a viewing distance of 60 cm. A research assistant, hidden behind the monitor and a cloth screen, provided auditory stimuli to keep the participants' attention on the monitor if needed.[14] Pattern-reversal VEP data was collected and recorded from ongoing EEG using the Geodesic EEG System 200 (Electrical Geodesics, Inc. (EGI), Eugene, OR), and NetStation 4.4.2 software (EGI) was used to measure scalp impedances (accepted if <50 KΩ) and process the data (re-referenced to the vertex, amplified with a 0.1–100 Hz bandpass and digitized at 250 Hz).

Using NetStation 4.4.2 analysis software (EGI), EEG data were filtered with a 30-Hz lowpass filter, segmented to 500 ms periods starting 100 ms before the stimulus presentation, and baseline corrected to the average prestimulus voltage. Segments were then hand-edited for movement artifact, eye movement, and poor recordings. Per center protocol,[28] trials were excluded if the number of electrodes rejected was >16% and participants with <12 accepted trials (out of 50) were excluded from further analysis (mean number of accepted trials at 4 months and 4 years was 35.7 and 38, respectively). For accepted trials, bad data on individual electrode was replaced using spherical spline interpolation and the average waveform at each electrode was calculated and re-referenced to the average reference. Latency of the P100 component was measured at Oz (at 4 months, the average of leads O1 and O2 were used to approximate Oz). If an individual electrode did not have an identifiable P100, data were treated as missing.

Data analysis

Multiple linear regression was performed to assess the relationship between body composition and anthropometric measurements and SOP (using latency to P100 on the VEP, where shorter (smaller) latency indicates faster processing, and raw score from NTPST, where a higher score means faster processing) in all patients who had a 4 month VEP and longitudinal SOP data at 4 years. Covariates adjusted were CGA at visit and birth gestational age, as well as ROP stage for VEPs; we were unable to adjust for other clinical factors given the small sample size. Slope estimates with standard errors and *p*-values were calculated. The associations between clinical factors (caloric and protein deficits, SNAP-II score, and days of antibiotics, steroids, and positive-pressure ventilation) and SOP were assessed using Pearson partial correlation coefficients for nutritional deficits and SNAP-II, and Spearman partial correlation for steroid, antibiotic, and positive-pressure ventilation exposure due to skewed distribution of data. For analysis of the relationship between body composition and blood pressure, linear regression analysis was performed, adjusting for sex, gestational age at birth, age at visit, and 4-year length. All analyses were performed using SAS (V9.4; SAS Institute, Cary, NC). Statistical significance was defined as $p \le 0.05$.

RESULTS

Infant characteristics for participants are included in Table 1. Of the 34 infants enrolled in the NICU with inpatient data, 28 returned for the 4 month visit and had adequate VEP data for analysis. Of those infants, 14 returned at 4 years for longitudinal SOP, body composition, and blood pressure testing. There were 6 infants who were followed in the NICU, missed the 4 month visit, and returned at 4 years for BC and BP analysis, and thus were included in that portion of the analysis only (Fig. 1). There were some statistical differences in characteristics between that group of 6 infants who missed the 4 month visit and those who attended—they were younger at birth (26.2 weeks (SD 2.05) vs 29.0 weeks (SD 1.14), $p = 0.013$) and experienced more complications of prematurity with higher rates of ROP (3 (50%) vs 1 (5.9%), $p = 0.03$)

Table 1. Descriptive characteristics of 34 very preterm infants

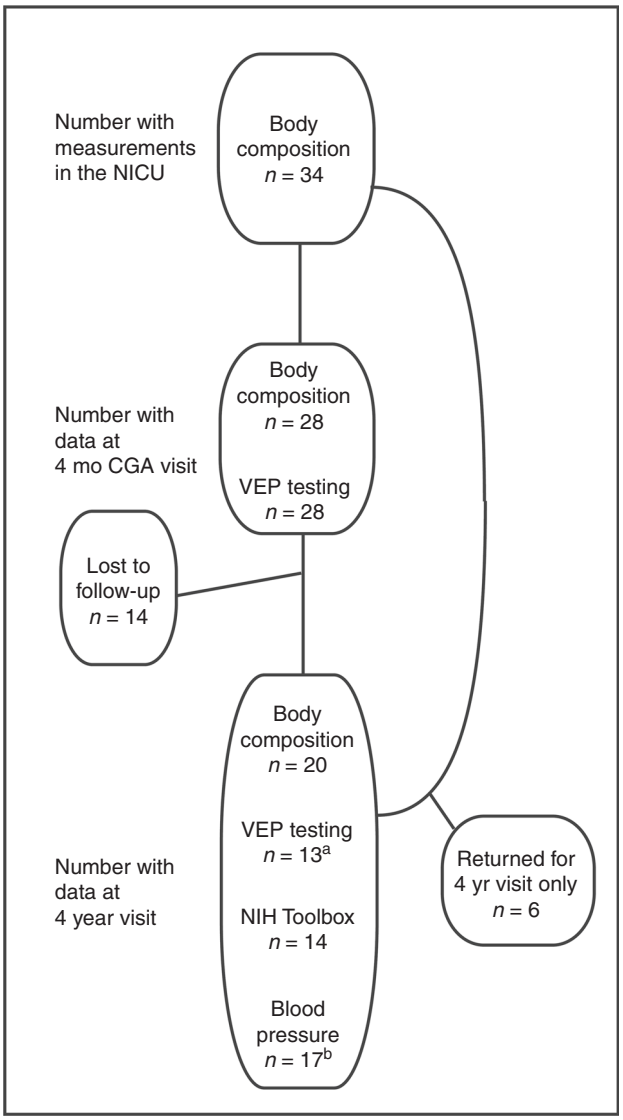
	Data[a]
Gestational age at birth (weeks)	28.2 (2.17)
Sex (male)	19 (55.9%)
Maternal race (non-Hispanic white)	26 (76.5%)
Birth weight (g)	1094 (257.8)
Birth length (cm)	36.56 (3.16)
Birth head circumference (cm)	25.75 (2.34)
Calorie deficit at discharge (kcal)	1018 (727.1)
Protein deficit at discharge (g)	43.39 (23.79)
Inpatient days	69.24 (28.02)
Age at first body composition testing (days)[b]	24.5 (2–122)
CGA at first body composition testing (weeks)[b]	33.2 (30.1–40.5)
SNAP score at day 1	10.32 (8.22)
Postnatal steroids (days)	0 (0–68)
Antibiotic use (days)	7 (0–75)
Positive-pressure use (days)	15 (0–114)
Intraventricular hemorrhage > grade 1	7 (20.6%)
Retinopathy of prematurity > stage 1	8 (23.5%)
Chronic lung disease[c]	9 (26.5%)

[a]Continuous variables expressed as mean (standard deviation) and categorical variables as *n* (percentage). Skewed data reported as median (range)
[b]Excluding two participants who could not have inpatient body composition testing due to oxygen need
[c]Chronic lung disease defined as oxygen need at ≥36 weeks CGA

and chronic lung disease (5 (83.3%) vs 1 (5.9%), $p = 0.012$), higher caloric deficits (1759 kcal (SD 969) vs 674 kcal (SD 541), $p = 0.003$), longer NICU stays (95.3 days (SD 31.5) vs 58.4 days (SD 16.4), $p = 0.02$) and more days on positive-pressure ventilation (55.8 days (SD 40) vs 16.1 days (SD 13.4), $p = 0.02$). As expected, mean P100 latency decreased over time: (163 ms at 4 months CGA and 123 ms at 4 years). Early P100 latency did not predict later processing speeds (VEP or NTPST) in this small group of subjects.

Speed of processing at 4 months CGA and body composition
After adjusting for CGA at visit, GA at birth and ROP stage, higher rate of weight ($p = 0.04$, $r^2 = 0.65$) and FFM ($p = 0.05$, $r^2 = 0.65$) gains (g/wk) between term and 4 months CGA were associated with shorter latency to P100 (or faster SOP) (Table 2). Absolute weight and FFM at 4 months were also associated with shorter P100 latencies (slope estimate (SD) −0.02 (0.01), $p = 0.015$, $r^2 = 0.64$ and slope estimate (SD) −0.023 (0.01), $p = 0.05$, $r^2 = 0.60$, respectively). Conversely, fat mass and %body fat changes had no associations with SOP at 4 months.

Speed of processing at 4 years and body composition
There were no significant associations between body composition at any age and P100 latency at 4 years after adjusting for age at visit, GA at birth, and ROP. However, early body composition changes were positively associated with processing speed as assessed by the NTPST after adjusting for age at visit and GA at birth. This was seen only in early gains in lean body mass: higher inpatient (birth to discharge) rates of increase in weight (g/wk), length (cm/wk), and FFM (g/wk) were positively associated with SOP on the NTPST (respective *p*-values: $p = 0.03$, $p = 0.05$, $p = 0.03$; respective r^2 values: $r^2 = 0.39$, $r^2 = 0.34$, $r^2 = 0.39$) (Table 2). Neither body composition at 4 years, nor rates of gains from 4 months to 4 years were associated with SOP at 4 years.



[a]One child of the 14 with longitudinal SOP testing had inadequate VEP data,so 13 used for analysis
[b]BP data not able to be obtained on 3 participants due to cooperation

Fig. 1 Flow diagram of study subject participation

Relationship of clinical factors to SOP
We explored the relationship between several clinical factors and their relationship with SOP at 4 months CGA and 4 years (adjusting for age at measurement and birth GA). Several clinical factors strongly correlated with early SOP: in-hospital caloric and protein deficits, as well as number of days of steroids and antibiotics had the strongest correlations; however, these were no longer significant by 4 years (Table 3).

Blood pressure at 4 years and body composition
Faster gains in FM and percent body fat (%BF) between term and 4 months CGA were associated with increased systolic blood pressure (SBP) at 4 years of age (FM $p \le 0.01$, $r^2 = 0.78$ and %BF $p = 0.01$, $r^2 = 0.68$) (Table 2). Higher absolute FM at 4 months CGA was also associated with increased SBP and diastolic blood pressure (DBP) at 4 years of age (4 month SBP: slope estimate (SD)

Table 2. The relationship of body composition and anthropometric changes with speed of processing and blood pressures

	VEP at 4 months CGA[a]		VEP at 4 years[a]		4 year NIH Toolbox Processing Speed Test[b]		Systolic blood pressure at 4 years[c]	
Rate of change epoch	Slope (SE)	*p*-value	Slope (SE)	*p*-value	Slope (SE)	*p*-value	Slope (SE)	*p*-value
Inpatient								
Weight (g/wk)	0.04 (0.91)	0.96	0.84 (1.48)	0.58	0.78 (0.31)	**0.03**	−0.88 (0.64)	0.19
Length (cm/wk)	116.5 (139.6)	0.41	−37.56 (254.3)	0.89	95.6 (43.2)	**0.05**	−71.22 (92.6)	0.46
OFC (cm/wk)	4.7 (229.5)	0.98	47.08 (312.6)	0.88	134.3 (73.2)	0.09	25.54 (145.7)	0.86
FFM (g/wk)	0.007 (1.26)	0.99	0.68 (1.99)	0.74	0.90 (0.36)	**0.03**	0.43 (0.82)	0.61
FM (g/log (wk))	−0.024 (0.16)	0.88	−0.078 (0.19)	0.69	0.089 (0.06)	0.17	−0.084 (0.09)	0.36
%BF (g/log (wk))	−1.74 (9.5)	0.86	0.75 (11.76)	0.95	4.09 (4.18)	0.35	−4.585 (4.81)	0.36
Term to 4 mo CGA								
Weight (g/wk)	−0.31 (0.14)	**0.04**	0.36 (0.28)	0.24	−0.13 (0.1)	0.26	0.22 (0.14)	0.16
Length (cm/wk)	−4.67 (42.9)	0.99	−1.23 (44.89)	0.98	−23.7 (16.7)	0.19	6.69 (21.05)	0.76
OFC (cm/wk)	−105.9 (75.9)	0.18	213.6 (125.7)	0.13	50.1 (60.8)	0.43	−66.47 (56.09)	0.27
FFM (g/wk)	−0.43 (0.21)	**0.05**	0.57 (0.32)	0.12	−0.11 (0.14)	0.47	0.039 (0.19)	0.84
FM (g/log (wk))	−0.32 (0.26)	0.24	−0.13 (0.95)	0.89	−0.29 (0.21)	0.2	0.83 (0.19)	**0.002**
%BF (g/log(wk))	−8.3 (32.08)	0.7	22.91 (62.9)	0.73	−11.78 (13.18)	0.39	45.56 (14.93)	**0.01**
4 mo CGA to 1 yr								
Weight (g/wk)			0.3 (0.63)	0.65	−0.17 (0.25)	0.5	0.37 (0.28)	0.22
Length (cm/wk)			41.9 (162.9)	0.81	39.6 (75.1)	0.61	14.53 (94.45)	0.88
OFC (cm/wk)			−41.77 (464.2)	0.93	−206.2 (141)	0.2	−98.14 (254.1)	0.71
1 to 2 yr								
Weight (g/wk)			−1.56 (1.79)	0.43	0.25 (0.66)	0.72	−0.43 (0.29)	0.19
Length (cm/wk)			127.9 (314.5)	0.7	−62.8 (107.5)	0.58	−19.06 (142.7)	0.9
OFC (cm/wk)			435.2 (521.3)	0.45	231.8 (251.3)	0.39	481.78 (273.9)	0.13
2 to 4 yr								
Weight (g/wk)			−1.95 (1.47)	0.26	0.27 (0.43)	0.55	−0.2 (0.38)	0.61
Length (cm/wk)			−671.5 (316.4)	0.09	−82.8 (157.3)	0.61	105.92 (160.7)	0.53
OFC (cm/wk)			−2686.3 (1778.5)	0.21	214.6 (684.8)	0.76	892.75 (750.96)	0.27
4 mo to 4 yr								
Weight (g/wk)			0.83 (2.04)	0.7	0.58 (0.4)	0.18	0.24 (0.5)	0.64
Length (cm/wk)			−50.34 (389.1)	0.9	73.66 (150.7)	0.64	−1.53 (248.1)	0.99
OFC (cm/wk)			21.88 (2859.9)	0.99	−63.65 (963.75)	0.95	965.35 (984.8)	0.35
FFM (g/wk)			1.87 (1.96)	0.39	0.48 (0.62)	0.46	0.96 (0.94)	0.33
FM (g/log (wk))			−2.88 (3.3)	0.41	0.54 (0.52)	0.32	−0.08 (0.75)	0.91
%BF (g/log (wk))			88.9 (522.76)	0.87	78.93 (80.17)	0.35	−160.2 (129.56)	0.24

[a]Adjusted for birth gestational age (bGA), CGA at visit and ROP
[b]Adjusted for bGA and CGA at visit
[c]Adjusted for sex, bGA, CGA at visit, and length

0.03 (0.01), $p = 0.04$, $r^2 = 0.40$; 4 month DBP: slope estimate (SD) 0.02 (0.006) $p = 0.03$, $r^2 = 0.64$). Neither growth nor body composition changes prior to term nor after 4 months CGA were associated with SBP or DBP at 4 years of age.

DISCUSSION

In very preterm infants, goals of ex-utero growth and nutritional status are meant to mimic in utero conditions;[29] yet preterm infants continue to have altered body composition at term CGA compared to their term counterparts.[1–3] Further, they often have subnormal neurodevelopment[30] and are at-risk for hypertension[8] and other metabolic concerns. The present study shows that increased early growth and lean body mass gains (rather than catch up after 4 months CGA) are associated with faster speed of processing during infancy and early childhood in VPT infants. In addition, we report that early gains in adiposity are associated with higher blood pressure at 4 years.

Neurodevelopmental outcomes

Like other studies[4,5,17] our results show birth to 4 months CGA to be a critically sensitive time period for growth and nutrition and their relation to neurodevelopmental outcomes in preterm infants. In particular, increased inpatient rate of gain in weight, length (a surrogate for FFM) and FFM go on to positively affect SOP at 4 years of age. Daily life and school-related functions are affected by processing speed, as it impacts executive functioning skills and the ability to take in information and respond to it properly.

As shown by the r^2 values, 65% of the variance of P100 latency (or SOP) at 4 months is accounted for by early FFM gains, birth gestational age, CGA at visit, and ROP. By 4 years, this value decreases, yet it is noteworthy that early FFM remains significantly

Table 3. Relationship of clinical factors to SOP

		Calorie deficit	Protein deficit	SNAP score day 1	Steroid days	Antibiotic days	Positive-pressure days
4 month VEP	Correlation	0.47	0.49	−0.06	0.44	0.55	0.39
	p-value	**0.016**	**0.01**	0.77	**0.02**	**0.004**	**0.05**
4 year VEP	Correlation	0.47	−0.31	−0.14	0.18	0.41	−0.38
	p-value	0.167	0.38	0.7	0.63	0.25	0.28
NIH Toolbox SOP	Correlation	−0.43	−0.09	−0.28	−0.51	−0.24	−0.14
	p-value	0.21	0.8	0.42	0.13	0.51	0.70

associated with 4 year SOP given the number of exposures and experiences that influence neurodevelopment and could diminish the effect.

Other clinical factors, such as nutritional deficits and exposure to steroids, antibiotics and positive-pressure ventilation also appear to affect early brain development, as assessed by SOP. However, it seems these factors are overcome with time, as they were no longer associated with SOP by 4 years of age. This is unlike early FFM gains, which had an ongoing association. FFM indexes organ growth[31] and protein accretion.[32] Protein status affects neuronal growth and differentiation, particularly during the rapid synaptogenesis occurring during the third trimester, thus impacting the scaffolding of the brain on which further growth and development is based.[33] Some of the illness factors mentioned above are associated with inflammation (steroid need representing lung inflammation and antibiotics as a surrogate for inflammation related to sepsis). Illness and inflammation affect neurodevelopment through white matter injury[34,35] and suppression of insulin-like growth factor 1 (IGF-1), a protein important for neuronal growth and differentiation.[36,37] Based on our results, it is possible the effects of inflammation on brain development may be partly overcome by improved scaffolding from early protein gains.

Metabolic outcomes

We also found increased gains in adiposity between term and 4 months CGA to be associated with higher blood pressure at 4 years of age, whereas body composition changes prior to term did not show the same relationship to later blood pressure. Previous studies have mostly only looked at the association between early weight gain and later blood pressure, which have minimal associations, and linear growth, which may have some association.[8] Body composition better represents the quality of growth, which is more likely to be related to metabolic outcomes. As shown by the r^2 values, FM gains from discharge to 4 months CGA (along with birth gestational age, age at visit, and length at 4 years) account for 78% of the variance in BP at 4 years, showing the clear impact on this outcome.

Metabolic outcomes, such as blood pressure, of formerly preterm infants are becoming an important topic of research. Much of the literature up until now has focused on IUGR term infants; however, this is not necessarily a comparable population to preterm infants undergoing altered extra-uterine growth. Though multiple large studies and reviews have shown that preterm infants are at-risk for elevated blood pressure,[15,38,39] reduced insulin sensitivity,[40] and increased low-density lipoprotein,[15] the influence of growth, diet, and neonatal illness on these outcomes are just now being evaluated. While the association between early body composition and later body composition or other metabolic markers was not within the scope of this paper, we have previously shown that FFM accretion between 1 and 2 weeks and 3–4 months CGA in preterm infants is related to preschool lean body mass, and this may lower the risk of later adverse metabolic outcomes.[41] Thus, a focus on inpatient gains and optimizing individual early nutrition plans and growth so that minimal catch-up growth post-discharge is needed may help minimize long-term metabolic risk. In addition, our findings highlight the importance of monitoring quality of weight gain after discharge to allow optimization of neurodevelopment and diminish later metabolic risk.

One strength of this study is the group of VPT infants studied, as infants born <32 weeks are at the highest risk for growth and neurodevelopmental derangements. Further strengths are the longitudinal evaluation of both metabolic and neurodevelopmental outcomes; the length of follow-up out to 4 years, a time when outcomes are more predictive of adulthood outcomes; as well as data showing the influence of in-hospital body composition, growth, and nutrition on long-term outcomes, a time period that has received less focus in the literature. The more we understand about the influence early changes and interventions have on long-term outcomes, the better we will be able to optimize our care of this neonatal population. The small cohort size is a weakness of this study, and larger longitudinal studies are needed to support the results. Also, a few of the sickest infants initially recruited in the study were unable to be included in the BC/SOP analysis due to continued oxygen requirement at 4 months of age (and thus unable to undergo body composition or SOP testing). This remains a population with lacking data due to inability to study their body composition, and yet a population at highest risk of altered body composition and suboptimal neurodevelopment. Body composition studies that include these infants would greatly add to the literature.

In summary, body composition is an important biomarker to follow in VPT infants and early body composition changes have long-lasting effects. Monitoring quality of weight gain in early infancy, and focusing early nutritional interventions on weight gain prior to 4 months and on FFM rather than FM gains may improve neurodevelopmental and metabolic outcomes.

ACKNOWLEDGEMENTS

The support for this study was provided by the Amplatz McQuarrie Scholar Award through the Department of Pediatrics at the University of Minnesota and NIH Grant P30 DK50456 to the Minnesota Obesity Center at the University of Minnesota and the Mayo Clinic.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Simon, L. et al. Determinants of body composition in preterm infants at the time of hospital discharge. *Am. J. Clin. Nutr.* **100**, 98–104 (2014).
2. Johnson, M. J., Wootton, S. A., Leaf, A. A. & Jackson, A. A. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. *Pediatrics* **130**, e640–e649 (2012).

3. Ramel, S. E. et al. J Body composition changes in preterm infants following hospital discharge: comparison with term infants. *Pediatr. Gastroenterol. Nutr.* **53**, 333–338 (2011).
4. Belfort, M. B. et al. Infant growth before and after term: effects on neurodevelopment in preterm infants. *Pediatrics* **128**, e899–e906 (2011).
5. Ramel, S. E. et al. The relationship of poor linear growth velocity with neonatal illness and two year neurodevelopment in preterm infants. *Neonatology* **102**, 19–24 (2012).
6. Pfister, K. M., Gray, H. L., Miller, N. C., Demerath, E. W. & Georgieff, M. G. Exploratory relationship of fat-free mass to speed of brain processing in preterm infants. *Pediatr. Res.* **74**, 576–583 (2013).
7. Coviello, C. et al. Effects of early nutrition and growth on brain volumes, white matter microstructure and neurodevelopmental outcome in preterm newborns. *Pediatr. Res.* **83**, 102–110 (2018).
8. Lapillonne, A. & Griffin, I. J. Feeding preterm infants today for later metabolic and cardiovascular outcomes. *J. Pediatr.* **162**(3 Suppl 1), S7–S16 (2013).
9. Stephens, B. E. et al. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics* **123**, 1337–1343 (2009).
10. dit Trolli, S. E., Kermorvant-Duchemin, E., Huon, C., Bremond-Gignac, D. & Lapillone, A. Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. *Early Hum. Dev.* **88**(Suppl11), S25–S29 (2012).
11. Gnigler, M. et al. Very preterm children are at increased risk of reduced processing speed at 5 years of age, predicted by typical complications of prematurity and prenatal smoking. *Acta Paediatr.* **104**, e124–e129 (2015).
12. Mulder, H., Pitchford, N. J. & Marlow, N. Processing speed mediates executive function difficulties in very preterm children in middle childhood. *J. Int. Neuropsychol. Soc.* **17**, 445–454 (2011).
13. Mulder, H., Pitchford, N. J. & Marlow, N. Processing speed and working memory underlie academic attainment in very preterm children. *Arch. Dis. Child. Fetal Neonatal Ed.* **95**, F267–F272 (2010).
14. McCullough, D. L. in *Infant EEG and Event-Related Potentials* (ed de Haan, M.) 41–76 (Psychology Press, London, 2007).
15. Parkinson, J. R. C., Hyde, M. J., Gale, C., Santhakumaran & Modi, N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. *Pediatrics* **131**, e1240–e1263 (2013).
16. Pfister, K. M. & Ramel, S. E. Optimizing growth and neurocognitive development while minimizing metabolic risk in preterm infants. *Curr. Pediatr. Rep.* **2**, 269–275 (2014).
17. Belfort, M. B., Gillman, M. W., Buka, S. L., Casey, P. H. & McCormick, M. C. Preterm infant linear growth and adiposity gain: trade-offs for later weight status and intelligence quotient. *J. Pediatr.* **163**, 1564–1569.e2 (2013).
18. Casey, P. H. et al. Evolution of obesity in a low birth weight cohort. *J. Perinatol.* **32**, 91–96 (2012).
19. Fenton, T. R. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. *BMC Pediatr.* **3**, 13 (2003).
20. Roggero, P. et al. Evaluation of air-displacement plethysmography for body composition assessment in preterm infants. *Pediatr. Res.* **72**, 316–320 (2012).
21. Foman, S. J., Haschke, F., Ziegler, E. E. & Nelson, S. E. Body composition of reference children from birth to age 10 eyars. *Am. J. Clin. Nutr.* **35**(5 Suppl), 1169–1175 (1982).
22. Urlando, A., Dempster, P. & Aitkens, S. A new air displacement plethysmograph for the measurement of body composition in infants. *Pediatr. Res.* **53**, 486–492 (2003).
23. Sainz, R. D. & Urlando, A. Evaluation of a new pediatric air-displacement plethysmograph for body-composition assessment by means of chemical analysis of bovine tissue phantoms. *Am. J. Clin. Nutr.* **77**, 364–370 (2003).
24. Yao, M., Nommsen-Rivers, L., Dewey, K. & Urlando, A. Preliminary evaluation of a new pediatric air displacement plethysmograph for body composition assessment in infants. *Acta Diabetol.* **40**(Suppl 1), S55–S58 (2003).
25. Ma, G. et al. Validation of a new pediatric air-displacement plethysmograph for assessing body composition in infants. *Am. J. Clin. Nutr.* **79**, 653–660 (2004).
26. Richardson, D. K., Corcoran, J. D., Escobar, G. J. & Lee, S. K. S. N. A. P.-I. I. and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J. Pediatr.* **138**, 92–100 (2001).
27. Weintraub, S. et al. Cognition assessment using the NIH Toolbox. *Neurology* **80** (11Suppl 3), S54–S64 (2013).
28. DeBoer T., Scott L. S., & Nelson C. A. in *Methodological Handbook for Research Using Event-Related Potentials* (ed Handey, T.) 263–297 (The MIT Press, Cambridge, MA, 2005).
29. American Academy of Pediatrics, Committee on Nutrition. in *Pediatric Nutrition Handbook* 5th edn (ed Kleinman, R.) 23–55 (American Academy of Pediatrics, Elk Grove Village, IL, 2004).
30. Aarnoudse-Moens, C. S., Weisglas-Kuperus, N., van Goudoever, J. B. & Oosterlaan, J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* **124**, 717–728 (2009).
31. Skullerud, K. Variations in the size of the human brain. Influence of age, sex, body length, body mass index, alcoholism, Alzheimer changes, and cerebral atherosclerosis. *Acta Neurol. Scand.* **102**(Suppl c), 1–94 (1985).
32. Forbes, G. B. Relation of lean body mass to height in children and adolescents. *Pediatr. Res.* **6**, 32–37 (1972).
33. Fuglestad, A., Rao, R. & Georgieff, M. in *Handbook of Developmental Cognitive Neuroscience* 2nd edn (eds Nelson, C. A., Luciana, L.) 623–642 (MIT Press, Cambridge, MA, 2008).
34. Wu, Y. W. & Colford, J. M. Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA* **284**, 1417–1424 (2000).
35. Shah, D. K. et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J. Pediatr.* **153**, 170–175 (2008).
36. Hansen-Pupp, I. et al. Circulatory insulin like growth factor-I and brain volumes in relation to neurodevelopmental outcomes in very preterm infants. *Pediatr. Res.* **74**, 564–569 (2013).
37. Lee, K. H., Calikoglu, A. S., Ye, P. & D'Ercole, A. J. Insulin-like growth factor-I (IGF-I) ameliorates and IGF binding protein-1 (IGFBP-1) exacerbates the effects of undernutrition on brain growth during early postnatal life: studies in IGF-I and IGFBP-1 transgenic mice. *Pediatr. Res.* **45**, 331–336 (1999).
38. de Jong, F., Monuteaux, M. C., van Elburg, R. M., Gillman, M. W. & Belfort, M. B. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension* **59**, 226–234 (2012).
39. Kerkhof, G. F., Breukhoven, P. E., Leunissen, R. W. J., Willemsen, R. H. & Hokken-Koelega, A. C. S. Does preterm birth influence cardiovascular risk in early adulthood? *J. Pediatr.* **161**, 390–396 (2012).
40. Tinnion, R., Gillone, J., Cheetham, T. & Embleton, N. Preterm birth and subsequent insulin sensitivity: a systematic review. *Arch. Dis. Child.* **99**, 362–368 (2014).
41. Scheurer, J. M. et al. Body composition trajectories from infancy to preschool in children born preterm versus full-term. *J. Pediatr. Gastroenterol. Nutr.* **64**, e147–e153 (2017).