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Preterm infant linear growth and adiposity gain: tradeoffs for later weight status, and IQ

Mandy B. Belfort, MD MPH[1], **Matthew W. Gillman, MD SM**[2], **Stephen L. Buka, ScD**[3], **Patrick H. Casey, MD**[4], and **Marie C. McCormick, MD ScD**[5]

[1]Division of Newborn Medicine, Boston Children's Hospital

[2]Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute

[3]Department of Epidemiology, Brown University

[4]Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital

[5]Department of Society, Human Development, and Health, Harvard School of Public Health

Abstract

Objective—Among preterm infants, to examine tradeoffs between cognitive outcome and overweight/obesity at school age and in young adulthood in relation to infancy weight gain and linear growth.

Study design—We studied 945 participants in the Infant Health and Development Program, an 8-center study of preterm (≤37 weeks), low birth weight (≤2500 grams) infants from birth to 18 years. Adjusting for maternal and child factors in logistic regression, we estimated the odds of overweight/obesity (BMI ≥85th percentile at age 8 or ≥25 kg/m^2 at age 18) and in separate models, low IQ (<85) per z-score change in infant length and BMI from term to 4 months, 4-12 months, and 12-18 months.

Results—More rapid linear growth from term to 4 months was associated with lower odds of IQ<85 at age 8 (OR 0.82, 95% CI 0.70, 0.96), but a higher odds of overweight/obesity (OR 1.27, 95% CI 1.05, 1.53). More rapid BMI gain in all 3 infant time intervals was also associated with a higher odds of overweight/obesity, and from 4-12 months with a lower odds of IQ <85 at age 8. Results at age 18 were similar.

Conclusions—In preterm, low birth weight infants born in the 1980's, faster linear growth soon after term was associated with better cognition but also with a higher risk of overweight/obesity at 8 and 18 years of age. BMI gain over the entire 18 months after term was associated with later risk of overweight/obesity, with less evidence for a benefit to IQ.

Please address correspondence and reprint requests to: Dr. Mandy Brown Belfort, Boston Children's Hospital Division of Newborn Medicine, Hunnewell 438, 300 Longwood Avenue, Boston, MA 02115, mandy.belfort@childrens.harvard.edu, Phone: 617-355-6027 Fax: 617-730-0486 .

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In the United States, over 12% of births are preterm (<37 weeks gestation) (1). Despite intensive nutritional support, at the time of discharge home from the neonatal intensive care unit (NICU), most preterm infants are considerably lighter and shorter than their full term peers at birth (2, 3), but by school age, a majority reaches a similar weight and height (4, 5). Thus, on average, weight gain and linear growth are accelerated for preterm relative to full term infants.

Because brain and somatic growth are correlated, optimizing growth after NICU discharge is highly relevant to preterm infants, and more rapid weight gain during this time period appears to benefit neurodevelopment (6-8). Few studies, however, have distinguished linear growth from gain in weight relative to length, which is important because disproportionate weight gain may be harmful to other aspects of health. Specifically, in full term children, rapid weight gain (9, 10) and gain in weight-for-length (11) in infancy are strongly and consistently associated with later obesity, but only 2 studies (12, 13) have examined the impact of early weight gain on obesity-related outcomes in preterm infants. Although both found positive associations, neither distinguished weight gain proportional to linear growth from excess weight gain.

Differentiating linear growth from disproportionately rapid weight gain may be particularly important to guide nutritional support that will maximize neurodevelopment while minimizing the risk of later obesity in preterm infants. One relevant study (14) found that more rapid linear growth but not body mass index (BMI) gain from term (40 weeks postmenstrual age) to 4 months was associated with a better motor outcome at 18 months, with no follow-up beyond infancy. Another (15) found that both linear growth and excess gain in weight-for-length in the first year of life were associated with a higher IQ at school age, although differences were relatively small and clinically relevant categories (e.g. normal vs. low IQ) were not examined, nor was there follow-up beyond early school age.

Clues to optimizing preterm infant growth after NICU discharge may come from examining both neurodevelopmental and obesity-related outcomes in the same cohort. The aim of this study was to examine associations of infant gain in body mass index (BMI, kg/m^2) and linear growth from term to 18 months with (1) overweight or obesity and (2) IQ <85 at ages 8 and 18 years in a cohort of children born preterm and low birth weight (<2500 grams). We hypothesized that linear growth but not BMI gain would positively impact IQ whereas more BMI gain would lead to greater overweight and obesity.

Methods

We performed an observational analysis of participants in the Infant Health and Development Program (IHDP), an 8-center longitudinal study of preterm (≤37 completed weeks gestation) and low birth weight (≤2500g) infants. In 1984 and 1985, IHDP recruited infants to participate in a randomized trial of an early child development intervention for which the primary outcomes were cognitive development, behavior, and health status. Details of recruitment and follow up and study results have been reported through age 18 years (16-19). Institutional review boards from all participating centers granted approval and caregivers gave written informed consent.

For this analysis, of the original 1060 IHDP participants, we included the 945 with data for IQ or BMI at 8 or 18 years and 2 consecutive infant BMI measurements (term and 4 months or 4 and 12 months or 12 and 18 months). In total, 941 participants were included in the age 8 analyses and 645 in the age 18 analyses. Details about participant flow are shown in Figure 1 (available at www.jpeds.com).

IHDP study staff weighed and measured participants at term and at 4, 12, and 18 months corrected for prematurity (chronologic age in days minus the number of days by which the participant was born prior to 40 weeks) using a calibrated infant balance scale and recumbent length board (20). At age 8 years, study staff weighed children and measured them with a Ross stadiometer. At age 18 years, participants reported their own height and weight in a structured interview. To measure general intelligence, trained assessors administered the Weschler Intelligence Scale for Children-III (WISC-III) at age 8 and the Weschler Abbreviated Scale of Intelligence (WASI) at age 18.

Study staff collected data from the neonatal and maternal medical record and through interviews and questionnaires regarding parental and child demographic, social, economic, and health information. Maternal obesity was noted if the mother reported her pre-pregnancy weight as over 200 pounds. Gestational age was estimated using a modification of the Ballard assessment (21). Maternal intelligence was measured using the Peabody Picture Vocabulary Test-R when the child was 18 months old.

Statistical analyses

We converted all infant measurements to z-scores based on the World Health Organization growth standards (22) which were designed to reflect optimal growth in infancy. Primary predictors were BMI gain and linear growth from term to 4 months, 4 to 12 months, and 12 to 18 months corrected for prematurity, defined as the z-score change between time points.

All age 8 and 18 measurements were converted to percentiles based on Centers for Disease Control and Prevention growth charts (23). Primary outcomes were weight status (underweight, overweight/obesity) and low IQ. We defined underweight at age 8 as BMI percentile <5 and at age 18, BMI <18.5 kg/m^2; and overweight/obesity at age 8 as BMI percentile of ≥85 and at age 18, BMI ≥25 kg/m^2. We also examined short stature, defined as height <2.5th percentile. We defined low IQ as WISC-III or WASI score <85, which is 1 standard deviation below the population mean of 100.

Using multinomial logistic regression, we estimated the odds of underweight vs. normal weight, overweight/obesity vs. normal weight, and in separate models, short stature vs. not and low IQ vs. IQ ≥85, with 95% confidence intervals (CI's), adjusting for child age, sex, and gestational age; and maternal age, education, smoking in pregnancy; and annual household income. As we have done previously (14), we additionally adjusted the 4 to 12 month growth analyses for term to 4 month growth and size at 4 months in the same measurement. Similarly, we adjusted the 12 to 18 month growth analyses for term to 4 month and 4 to 12 month growth, and size at 12 months. We adjusted all analyses for the IHDP study group (intervention vs. control) and the cognitive analyses for maternal IQ.

To examine possible confounding by neonatal complications, we repeated the same analyses after excluding participants with any of the following: 5 minute Apgar score <5; bronchopulmonary dysplasia; necrotizing enterocolitis; or grade 3 or 4 intraventricular hemorrhage and repeated the same analyses. To examine potential effect modification by fetal growth status, we performed analyses stratified by small for gestational age (SGA), defined as birth weight <10th percentile for gestational age based on a contemporary national reference (24) vs. non-SGA. Only 4 participants were large for gestational age (>90th percentile) and we included them in the non-SGA group. We used SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Participant characteristics are shown in Table 1 (available at www.jpeds.com). The mean (SD) gestational age was 33 (2.6) weeks and birth weight 1800 (455) grams. Just over one third were SGA and almost 20% had a neonatal complication. Figure 2 shows participants' BMI and length z-scores at term, 4, 12, and 18 months. In our sample, BMI was higher than the reference population at term, but fell below by 4 months. At 12 months, BMI was similar to the reference population, and was slightly higher at 18 months. Length was below the reference population at term, even lower at 4 months, and increased somewhat by 12 months but remained below the reference population through 18 months.

Table II (available at www.jpeds.com) shows Pearson correlations of the infant size and growth measures. BMI and length were weakly positively correlated at term and 4 months, and not correlated at 12 and 18 months. BMI gain and linear growth were not correlated from term to 4 months, but from 4-12 and 12-18 months, they were negatively correlated,

Tables III and IV show the primary outcomes at 8 and 18 years. At 8 years, 20.4% of participants were overweight or obese and at 18 years, 30.6% were overweight or obese. At 8 years, 35.9% had a full scale IQ score <85 and the proportion was similar (31.7%) at 18 years.

Table V shows the adjusted odds of underweight, overweight/obesity, short stature, and full scale IQ <85 at 8 and 18 years. More rapid linear growth from term to 4 months was associated with lower odds of IQ<85 [odds ratio (OR) 0.82, 95% CI 0.70, 0.96], but higher odds of overweight/obesity (OR 1.27, 95% CI 1.05, 1.53). Infant BMI gain in all 3 time intervals was associated with higher odds of overweight/obesity at age 8 [term to 4 months odds ratio (OR) 1.36 per additional z-score BMI gain, 95% CI 1.14, 1.62; 4 to 12 months OR 1.66, 95% CI 1.33, 2.06; and 12 to 18 months OR 2.00, 95% CI 1.53, 2.61]; and from 4 to 12 months with somewhat lower odds of IQ<85 (OR 0.81, 95% CI 0.68, 0.96). Associations with age 18 outcomes were similar in magnitude and direction. Linear growth from term to 4 months and 4-12 months and BMI gain from 4-12 months were associated with lower odds of short stature at age 8 but not 18 years.

After excluding infants with neonatal complications, associations of infant BMI gain and linear growth with age 8 and 18 outcomes were similar to the full cohort in magnitude and direction, although CI's were somewhat wider. Associations were also similar for SGA and non-SGA participants, although CI's were wide (data not shown).

Discussion

In this study, we found that more rapid BMI gain and linear growth in infancy were associated with better cognition, but also with a greater risk of overweight/obesity at age 8, with similar effects seen at age 18. These results suggest important trade-offs to consider with respect to optimal growth targets for preterm, low birth weight children after NICU discharge.

Our study extends prior work linking early rapid weight gain with later obesity and cognition in two ways. First, although most researchers have examined full term populations, we studied a preterm, low birth weight cohort. We found some similarities to studies of full term children, but also important differences. Consistent with studies of full term children(9, 10), our results suggest that preterm infants are also vulnerable to the obesogenic effects of early rapid weight gain out of proportion to linear growth. This finding is notable in the context of epidemic child obesity (25), with an obesity prevalence that is similar among preterm and full term children (13, 26).

In terms of cognition, however, preterm infants appear to be different from their full term counterparts. Other studies including ours (27) and a subsequent meta-analysis (28) found that in healthy, full term populations, rapid weight gain after birth was not associated with better cognition later in life, although few studies have separated weight gain from linear growth. In contrast, in our preterm, low birth weight cohort, we found that more rapid linear growth in the months after term – developmentally equivalent to the months after a full term birth – may be of substantial benefit to later cognition. It is possible that for the preterm, low birth weight infant, the months after term represent a sensitive period for that may be particularly important for neurodevelopment after a period of prenatal (29) and/or postnatal (2, 3) growth restraint.

A second way that our study extends prior work is in differentiating linear growth from BMI gain after NICU discharge. In our study, even though early (term to 4 months) linear growth was associated with substantially lower odds of IQ<85 at 8 and 18 years, in contrast, BMI gain during the same time period did not appear to benefit cognition, but was associated with higher odds of overweight/obesity. These findings are consistent with another study (14) of preterm infants <33 weeks' gestation, which found an association of linear growth but not BMI gain from term to 4 months with the Bayley motor score at 18 months. Thus, even though early linear growth appears to be important for later cognition, our results suggest that excess early weight gain out of proportion to linear growth may contribute to later obesity, without cognitive benefits.

In our study, early (term to 4 months) linear growth appeared to benefit later cognition, but notably it was also associated with modestly higher odds of overweight/obesity. This finding raises the possibility that supporting optimal brain growth may come at a cost with respect to later cardio-metabolic health. A similar tradeoff was apparent with greater BMI gain from 4 to 12 months, which was associated with higher odds of overweight/obesity, but also with lower odds of IQ<85 at 8 years.

Defining optimal linear growth and BMI gain will require balancing the magnitude of effects on cardio-metabolic health and cognition, as well as the value that clinicians and families place on the different outcomes. In addition to obesity and cognition, an important consideration with respect to early linear growth is its impact on adult height. In our study, more rapid linear growth in infancy appeared protective against short stature at age 8 but not at age 18, suggesting that additional catch-up in linear growth occurred after age 8. Other relevant outcomes to consider include risk for re-hospitalization, which may be greater for low birth weight children with slow weight gain (30, 31), and asthma which in one study (32) was more prevalent in low birth weight children with high vs. low BMI in adolescence.

Children in our study had a higher BMI and were shorter at term than the WHO reference population of full term children at birth. This finding is consistent with studies that directly measured body composition at term using either air displacement plethysmography (33, 34) or DXA(35) and found a greater fat mass and lower fat free mass in preterm children vs. full term children. This difference may reflect excess non-protein energy that is stored as fat in growing preterm infants (36). In one study that followed children after NICU discharge (33) by 3 to 6 months of age, fat mass and fat free mass were similar between preterm and full term children, whereas in our cohort at 4 months, both BMI and length were substantially below the reference population. This difference may reflect the fact that anthropometric measurements only partially account for differences in direct measures of body composition (37). Also, our cohort was born in the 1980's when nutritional practices were different, for example nutrient enriched postdischarge formulas were not in routine use. Specific determinants of early fat accumulation and lean body mass growth, such as composition and fortification of formula and expressed milk (38), energy expenditure (39), and oral-motor feeding skills (40) represent potential targets for intervention during this developmentally sensitive period.

Strengths of our study include a multi-center cohort with availability of detailed growth data at several time points after term, and later IQ and BMI measures in the same cohort. IQ and BMI measured at age 8 and 18 years are strongly correlated with adult outcomes (41, 42). One limitation is reliance on self-report of weight and height at age 18 years. Although highly correlated with direct measures (43), self-reported weight and height may underestimate the prevalence of overweight and obesity (44). We were reassured that in our study, exposure-outcome relationships were similar to those using direct measurements at age 8. We controlled for a number of relevant covariates, but as in any observational study, there may be residual confounding by unmeasured factors. In particular, both slow early weight gain and poor cognitive outcomes could occur as a result of neonatal brain injury or other complications of preterm birth, although excluding children with such complications did not materially change our results. Finally, IHDP included a large proportion of infants from poor households, and mothers of low educational status and of minority race and ethnicity, possibly limiting generalizability to more affluent, educated, and non-minority populations.

In conclusion, we found in a cohort of preterm, low birth weight infants born in the 1980's that early linear growth after term was associated with a better cognitive outcome, but also with a higher risk for overweight/obesity later in life. Excess weight gain out of proportion to linear growth from term through 18 months was associated with later overweight/obesity, with less evidence for a substantial cognitive benefit. These tradeoffs represent important considerations for pediatricians and other clinicians who monitor growth and provide nutritional care for preterm infants.

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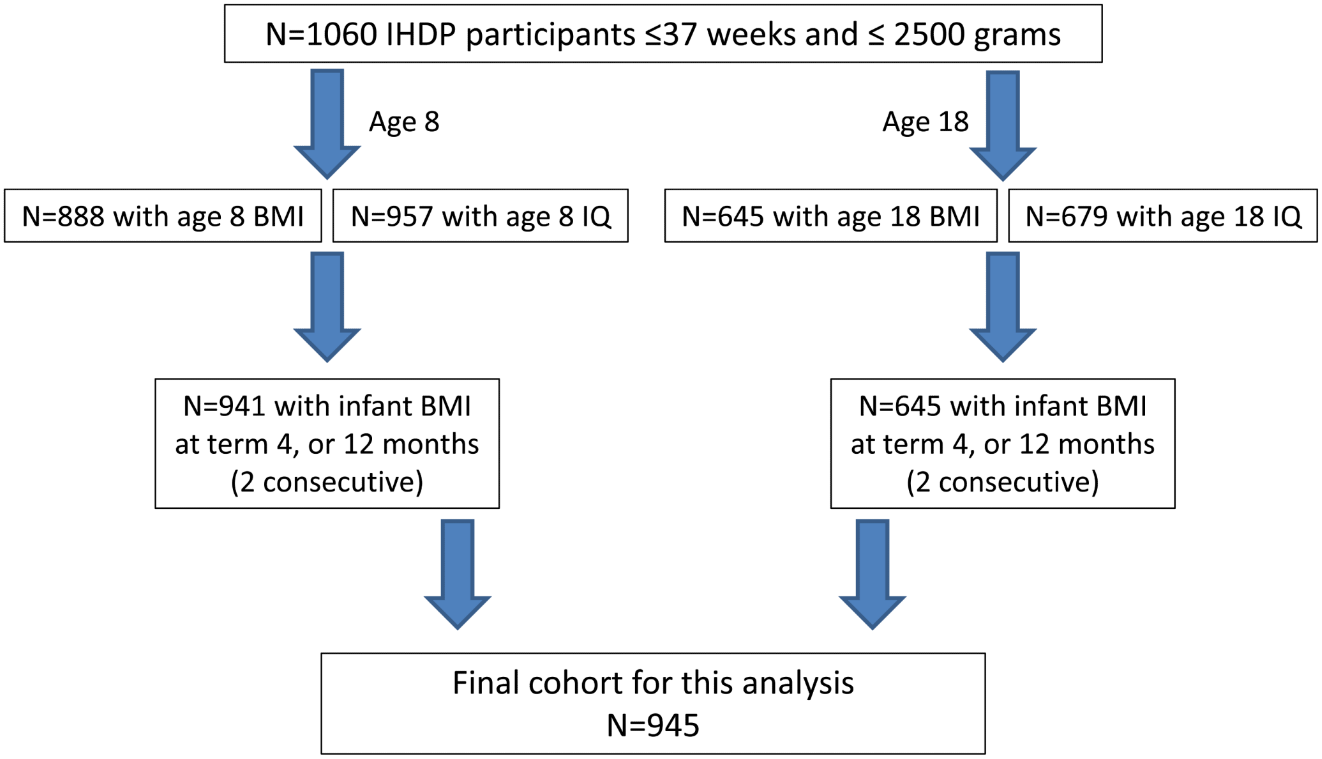

Figure 1.
Participant flow

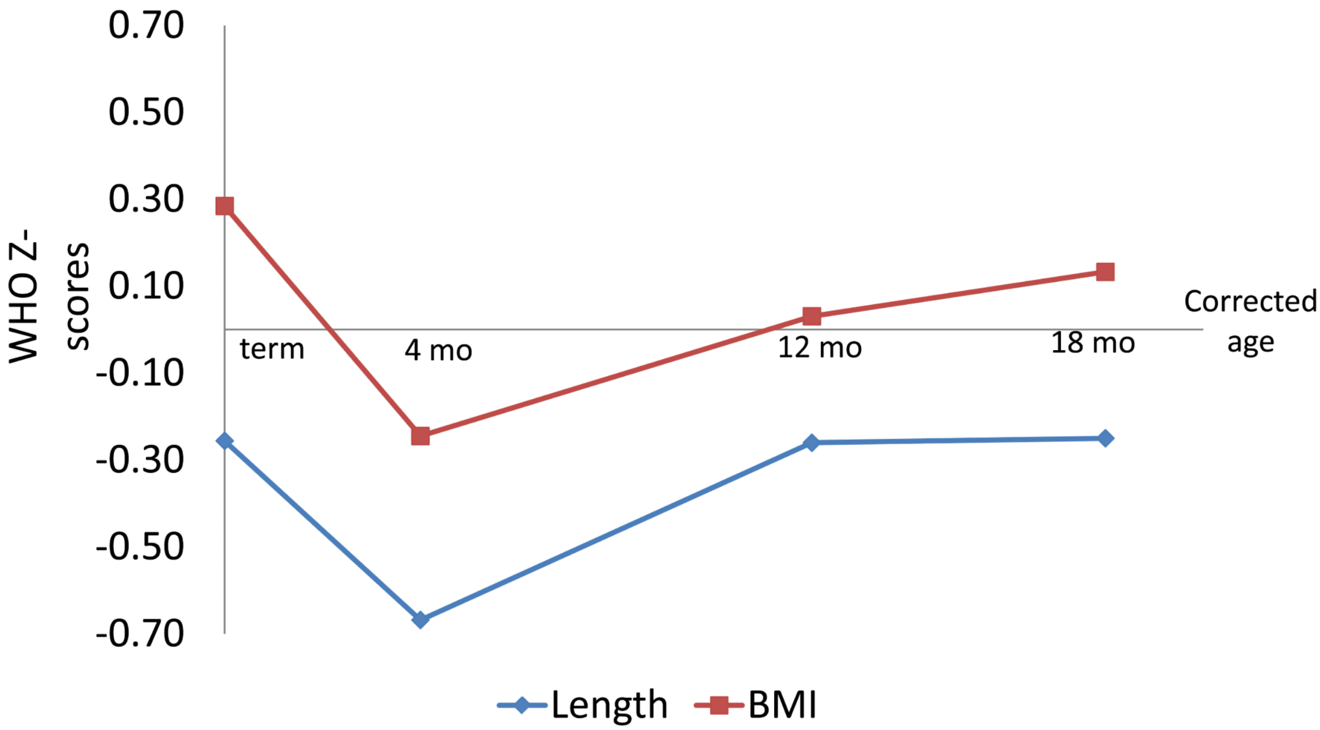

Figure 2.

Participant body mass index (BMI) and length z-scores at term, 4, 12, and 18 months corrected age. A z-score of 0 represents the mean for the reference population.(45)

Table 1

Characteristics of 945 IHDP participants

Maternal	**Mean (SD) or number (%)**
Age (years)	25.0 (6.0)
Maternal IQ	81 (22)
Preeclampsia or eclampsia	150 (17%)
Obese (>200 lbs before pregnancy)	33 (3.5%)
Smoked during pregnancy	610 (32%)
Education	
< high school diploma	342 (35%)
high school graduate	261 (29%)
at least some college	297 (33%)
Annual household income	
<$15,000	230 (25%)
$15,000 to <$35,000	286 (32%)
≥$35,000	266 (30%)
missing	118 (13%)
Race	
Black	475 (53%)
White	333 (37%
Hispanic	92 (10%)
Child/young adult	Mean (SD) or number (%)
Gestational age (weeks)	33.0 (2.6)
Birth weight (g)	1800 (455)
Male	440 (49%)
<32 weeks gestation	245 (27%)
SGA	327 (36%)
NICU complications*	170 (19%)

*chronic lung disease, necrotizing enterocolitis, intraventricular hemorrhage grade III or IV, or 5 minute Apgar score <5

Table 2

Correlations of infant size and growth variables

	BMI z-score				BMI z-score change		
	Term	**4 months**	**12 months**	**18 months**	**Term-4 months**	**4-12 months**	**12-18 months**
Length z-score	*Pearson correlation coefficients and p-values*						
Term	0.19	0.12	0.08	0.08	−0.10	−0.04	−0.00
	p<0.0001	p=0.004	p=0.02	p=0.02	p=0.003	p=0.2	p=1.0
4 months	0.16	0.13	0.17	0.15	−0.06	0.04	−0.02
	p<0.0001	p<0.0001	p<0.0001	p<0.0.001	p=0.08	p=0.3	p=0.5
12 months	0.02	0.25	0.04	0.16	0.16	−0.22	0.16
	p=0.6	p<0.0001	p=0.2	p<0.0001	p<0.0001	p<0.0001	p<0.0001
18 months	−0.02	0.23	0.21	0.00	0.19	−0.04	−0.28
	p=0.5	p<0.0001	p<0.0001	p=0.9	p<0.0001	p=0.3	p<0.0001
Length z-score change							
Term to 4 months	−0.07	−0.02	0.07	0.05	0.06	0.09	−0.02
	p=0.03	P=0.6	p=0.04	p=0.10	p=0.09	p=0.005	p=0.6
4-12 months	−0.18	0.13	−0.18	−0.00	0.25	−0.32	0.23
	p<0.0001	p=0.0001	p<0.0001	p=1.0	p<0.0001	p<0.0001	p<0.0001
12-18 months	−0.07	−0.03	0.25	−0.23	0.04	0.28	−0.64
	p=0.03	p=0.3	p<0.0001	p<0.0001	p=0.21	p<0.0001	p<0.0001

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Table 3

Participant size and weight and height status at 8 and 18 years

	8 years (n=871)		18 years (n=633)	
	Native unit	**Percentile***	**Native unit**	**Percentile***
	Mean (SD)			
BMI	16.7 (2.7) kg/m^2	53.5 (29.9)	24.0 (4.9)kg/m^2	59.8 (28.8)
Height	127.1 (5.9) cm	44.3 (28.9)	168.0 (10.8) cm	45.2 (31.5)
Weight status†	*Number (%)*			
Underweight	49 (5.6%)		42 (6.6%)	
Healthy weight	644 (73.9%)		397 (62.7%)	
Overweight	104 (11.9%)		130 (20.5%)	
Obese	74 (8.5%)		64 (10.1%)	
Short stature‡	42 (4.4%)		33 (3.5%)	

*based on CDC growth charts

†based on percentile cut points at age 8 and BMI cut points at age 18

‡height <2.5th percentile for age and sex

Table 4

Participant IQ at 8 and 18 years

	8 years (n=936)	**18 years (n=669)**
	Mean (SD) or number (%)	
Full scale IQ	90.6 (18.0)	91.8 (16.4)
Low full scale IQ (<85)	336 (35.9%)	212 (31.7%)
Performance IQ	89.9 (17.4)	92.4 (15.8)
Low performance IQ (<85)	379 (40.3%)	195 (29.1%)
Verbal IQ	92.7 (17.9)	92.5 (16.6)
Low verbal IQ (<85)	293 (31.3%)	198 (29.6%)

Table 5

Associations of infant growth with weight and height status and IQ category at 8 and 18 years

	Weight status (vs. normal weight)†				**Height status**		**Full scale IQ**	
	Age 8		**Age 18**		**Age 8**	**Age 18**	**Age 8**	**Age 18**
	Adjusted odds ratios (95% confidence intervals)							
BMI z-score change*	Underweight	Overweight/obese	Underweight	Overweight/obese	Short† (vs. not short)		<85 vs. ≥85	
Term-4 months	0.44	1.36	0.66	1.40	1.05	1.05	0.92	1.11
	(0.33, 0.59)	(1.14, 1.62)	(0.50, 0.89)	(1.16, 1.69)	(0.85, 1.30)	(0.92, 1.21)	(0.80, 1.06)	(0.92, 1.33)
4-12 months	0.44	1.66	0.70	1.28	0.74	0.90	0.81	0.85
	(0.30, 0.63)	(1.33, 2.06)	(0.48, 1.01)	(1.02, 1.60)	(0.57, 0.96)	(0.76, 1.05)	(0.68, 0.96)	(0.69, 1.06)
12-18 months	0.73	2.00	0.75	1.67	0.74	1.03	1.02	0.86
	(0.47, 1.13)	(1.53, 2.61)	(0.48, 1.17)	(1.28, 2.18)	(0.53, 1.03)	(0.85, 1.26)	(0.82, 1.26)	(0.67, 1.11)
Length z-score change*								
Term-4 months	0.73	1.27	0.67	1.19	0.65	0.98	0.82	0.78
	(0.54, 0.98)	(1.05, 1.53)	(0.48, 0.93)	(0.98, 1.43)	(0.52, 0.82)	(0.85, 1.14)	(0.70, 0.96)	(0.65, 0.95)
4-12 months	0.62	1.10	0.68	1.09	0.65	0.93	1.07	1.15
	(0.42, 0.90)	(0.89, 1.37)	(0.45, 1.02)	(0.88, 1.36)	(0.50, 0.86)	(0.79, 1.11)	(0.89, 1.29)	(0.92, 1.44)
12-18 months	0.60	0.94	0.88	0.90	0.77	0.91	0.84	1.07
	(0.41, 0.88)	(0.73, 1.20)	(0.57, 1.37)	(0.70, 1.16)	(0.55, 1.06)	(0.75, 1.11)	(0.68, 1.03)	(0.83, 1.38)

Estimates adjusted for child age, sex, and gestational age; and maternal age, education, smoking in pregnancy; and annual household income.

*based on WHO growth standards

†based on percentile cut points at age 8 and BMI cut points at age 18

‡height <2.5th percentile for age and sex