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Steady Growth in Early Infancy Is Associated with Greater Anthropometry in Indian Children Born Low Birth Weight at Term

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ABSTRACT

Background: Patterns of early growth are associated with later body composition and risk of adult noncommunicable disease but information from low-income countries is limited.

Objectives: The aim of this study was to investigate early growth trajectories and later anthropometric and bone density outcomes among children born term low birth weight (LBW: 1.8–2.5 kg).

Methods: We used data from 902 children from the Delhi Infant Vitamin D Supplementation study of LBW term infants (which collected monthly anthropometry from birth to 6 mo) and who had height, weight, midupper arm circumference (MUAC), midupper arm muscle circumference (MUAMC), subscapular and triceps skinfold thicknesses, tibia and radius bone density measured at age 4–6 y. We investigated how growth in the first 6 mo of life, modeled using the SuperImposition by Translation and Rotation (SITAR) growth curve model, was related to these outcomes. SITAR summarizes each infant's weight and length trajectory in terms of a population mean curve and child-specific growth parameters: size, timing, and intensity. These were included as explanatory variables in linear regression models for the childhood outcomes.

Results: Considering the infant weight and length SITAR parameters jointly, childhood weight was strongly associated with infant length timing [estimated regression coefficient $\beta = 0.25$ (95% CI: 0.10, 0.39)] and with weight size, timing, and intensity [$\beta = 9.01$ (6.75, 11.27), $\beta = -0.25$ (−0.43, −0.07), $\beta = 5.03$ (3.22, 6.84), respectively]. Childhood height was associated only with the length parameters [$\beta = 0.97$ (0.71, 1.23), $\beta = -0.43$ (−0.77, −0.09), $\beta = 11.68$ (8.60, 14.75), respectively]; childhood MUAC, MUAMC, and skinfolds with all parameters; and bone density with none. Overall, delayed and sustained growth in infant weight and length resulted in higher values of all outcomes except bone density, with the period up to 15 wk of age appearing critical for setting childhood anthropometry in this population.

Conclusions: The explanation for the effects of delayed growth and length of the period in which trajectories are set is unclear; however, sustained and delayed growth in early infancy appears to be beneficial for these LBW children at least in the short-term. The trial was registered at clinicaltrials.gov as BT/PR7489/PID/20/285/2006. *J Nutr* 2019;149:1633–1641.

Keywords: DIVIDS, low birth weight, infant growth, childhood size, childhood bone density, SITAR

Introduction

The Developmental Origins of Adult Disease hypothesis is well-supported regarding growth and body composition outcomes as well as for outcomes related to cardiovascular disease, diabetes, and kidney disease (1, 2). Low birth weight (LBW) is generally associated with increased risk of later disease, and rapid postnatal growth may aggravate this risk (2). The timing of catch-up growth, which is defined differently by different researchers (3), and the type of tissue laid down appear important in determining the balance between metabolic load and capacity and thus the risk of adult chronic diseases (2). Causes of LBW differ with respect to high income and low income, so consequences of rapid postnatal growth of LBW infants may also differ; there is fairly limited and inconsistent evidence from low-income countries. There is evidence from India that growth before age 2 y which is faster than expected based on prior growth and the population mean, that is, faster relative growth, carries no excess risk (4). However, faster relative growth in fat mass, measured by bioelectrical impedance, although not in lean mass or length, in later childhood was associated with increased body fat, waist-to-hip ratio, blood pressure, and insulin resistance in adolescence (4). On the other hand, in a study of 5 birth cohorts from low- and middle-income countries, including India, faster relative growth in both length and weight relative to length before age 2 y increased the risk of adult overweight (5).

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Prenatal and early postnatal effects on outcomes related to bone health are less well established than those related to overweight and its consequences. Although it is known that peak bone density, reached in young adulthood, is an important determinant of bone density and osteoporosis in later life (6, 7), there is disagreement as to how peak bone density is affected by in utero and infant factors. LBW has been linked to lower adult bone density and increased risk of hip fracture (6) but a systematic review and meta-analysis showed the association of birth weight with bone density becoming progressively weaker at higher ages (8). Bone density was low in a cohort of young adult Indians (9).

India is undergoing a nutrition and epidemiologic transition and thus has a high burden of both early undernutrition and later overnutrition (10, 11). Rates of LBW are among the highest in the world (12) and stunting and wasting remain prevalent (13). The increasing prevalence of overweight is also a concern, especially because, compared with white Caucasians who have been more frequently the participants in research on early origins of adult disease, Indians tend to have a higher proportion of body fat for a given BMI (11). Because LBW infants are at high risk of later chronic diseases (1), and catch-up growth may be beneficial for short-term health but with unclear effects on longer-term health, it is important to investigate longer-term effects of early growth trajectories of term LBW Indian infants.

Our group has studied a cohort of children born LBW at term between 2007 and 2010. As infants in the Delhi Infant Vitamin D Supplementation (DIVIDS) trial, they were given vitamin D or placebo for the first 6 mo, during which we collected detailed monthly data about their growth and health (14, 15). We obtained further growth and body composition data from them when they were 4–6-y-old (16). By this age, BMI and body composition are strongly correlated with BMI in middle-aged adults (17). In the present study we use data from both the original and the later time points to examine the relation between early growth, that is, weight and length trajectories from birth up to 6 mo of age, as the exposure, and anthropometry, bone structure, and strength at age 4–6 y as the outcomes.

Methods

The DIVIDS cohort

The DIVIDS trial was an individually randomized, double blind, placebo-controlled trial of weekly vitamin D supplementation of Indian infants for the first 6 mo of life (registration BT/PR7489/PID/20/285/2006 on clinicaltrials.gov) (14). The primary outcome was the rate of all inpatient hospital admissions or death. Infants (n = 2079) born at Safdarjung Hospital, New Delhi, were eligible if they were singleton, ≥ 37 weeks of gestation as defined by last menstrual period, birth weight 1.8–2.5 kg, < 48-h-old, living within 15 km of Safdarjung Hospital, and with parents' written or thumbprint informed consent. Exclusion criteria were severe congenital abnormalities, death before age 7 d, intention to live outside the catchment area before the infant reached 6 mo, or lack of consent. Safdarjung Hospital is a large government hospital in South Delhi giving subsidized medical treatment to a low- to middle-income population. At ages 6, 10, 14, 18, 22, and 26 wk, parents brought the infant to the hospital for anthropometry, clinical examination by a doctor, and questionnaires on morbidity, diet, and infant sunlight exposure. The vitamin D treatment resulted in modest but statistically significant increases in anthropometric outcomes at 6 mo (14).

The follow-up of the trial's participants was conducted at the Institute of Home Economics, University of Delhi, from November 2012 to January 2014 (16). All 1489 participants in the original DIVIDS trial (14) who completed follow-up to 6 mo were potentially eligible. A total of 912 children were traced and came for a follow-up visit. Parents and children were invited to the study office on specified days and were provided with either transport or travel reimbursement. Information was collected on: *1*) sociodemographic factors, morbidity history, and sunlight exposure (by interviewer-administered questionnaire); *2*) detailed anthropometry; *3*) body composition via deuterium dilution (in a subset, n = 229); *4*) child motor development using the Ages and Stages Questionnaire, Second Edition (http://agesandstages.com); *5*) quantitative ultrasound measures of bone structure and strength (tibia and radius); and *6*) measurement of vitamin D status from venous blood samples (16).

Outcomes

Anthropometric measures were taken in triplicate using standard methods (18) and included height (measured in cm), weight (kg), midupper arm circumference (MUAC, cm), and triceps and subscapular skinfold thickness (mm). Medians of the triplicate measures were used here (19). Midupper arm muscle circumference (MUAMC, cm) was derived from MUAC and triceps skinfold using standard definitions (18). Bone structure and strength were measured by quantitative ultrasound (Sunlight Omnisense 7000 Bone Sonometer) (20) at the distal radius and midshaft of the tibia. The values were then standardized according to the instrument's Caucasian age- and sex-specific references (hereafter referred to as radius and tibia z scores). At follow-up, the children treated with vitamin D in infancy had slightly lower BMI than those given placebo (16).

Exposures

Duplicate measurements of infant weight (kg) and length (cm) were made at ages 6, 10, 14, 18, 22, and 26 wk, with duplicates averaged. Most infants (64% in the active arm and 67% in the placebo arm) had data at all 6 visits, with only 1% attending < 3 visits.

Covariates

The following covariates were considered for inclusion in the analyses of the childhood outcomes: child's age at measurement, maternal age and parity (categorized as primiparous or other) at birth of the child, duration of predominant breastfeeding, that is breast milk and non-nutritive liquids only (categorized as < 11 wk, 11–17 wk, ≥ 18 wk), family's socioeconomic status (SES) (as indicated by a family asset index score and categorized into fifths according to the distribution of the original trial population) (14), season of bone measurement, and reported usual sun exposure in the past month. Allocated treatment and sex were considered potential effect modifiers of these relations; the robustness of the results to the inclusion of duration of predominant breastfeeding, a possible intermediate factor of the growth trajectories, was examined by excluding it from the models. Allocated treatment and sex were also included in the SITAR models for the weight and length trajectories to account for any systematic differences caused by these variables.

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Supplemental Tables 1–3 and Figures 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
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Abbreviations used: BIC, Bayesian Information Criterion; DIVIDS, Delhi Infant Vitamin D Supplementation; LBW, low birth weight; MUAC, midupper arm circumference; MUAMC, midupper arm muscle circumference; SES, socioeconomic status; SITAR, SuperImposition by Translation and Rotation.

Analysis sample

Nine of the 912 children who attended the follow-up visit did not have all outcome measurements and 1 had missing sun exposure data. Hence, 902 children contributed to the analyses.

Statistical methods

The aim of the analyses was to study whether weight and length trajectories from birth till age 26 wk were associated with the 8 childhood outcomes, after accounting for the original vitamin D intervention and the child's sex. We adopted a 2-step approach to examine this. The first step consisted of modeling each child's weight and length growth trajectories from 0 to 26 wk to extract child-specific differences (random coefficients) from his/her sex-treatment-specific average trajectory. For this step we used the available growth data on the original 2079 infants. The second step related the child-specific random coefficients to the childhood outcomes observed in the 902 children with complete outcome and confounders data. The representativeness of the children contributing to the second step was examined via logistic regression analysis.

Step 1.

We modeled the infant-specific weight and length trajectories using the SuperImposition by Translation and Rotation (SITAR) model (21). SITAR is a nonlinear mixed effects model where the nonlinearity of the relation between the growth dimensions and age at measurement is modeled via a mean cubic spline curve with knots set at quantiles of the age distribution. The mean curve is transformed in 3 distinct ways to make it fit individual growth trajectories, where the transformations – termed size, timing, and intensity – are estimated as subject-specific random coefficients. Size is an up–down shift of the mean curve on the measurement scale (so it represents "average size"), timing is a left–right shift on the age scale reflecting the peak of the growth spurt (with negative values for an early spurt and positive for late), and intensity indicates a stretching or shrinking of the age scale to indicate the velocity of growth (where positive indicates faster growth). Size is measured in units of the measurement, timing is in units of age (wk), and intensity is a fraction or percentage. The formal specification of the model has been described and successfully implemented previously (21–23).

Estimation was by maximum likelihood using the sitar R package (24) with alternative transformations of the age and growth dimensions explored. The Bayesian Information Criterion (BIC) and estimated residual deviance were used to compare the models. The BIC trades off goodness of fit and model complexity. Adding extra knots to the spline curve improves the fit and reduces the deviance, but the BIC requires the reduction in deviance per extra knot to exceed $\log_e(n)$ where n is the sample size. Using these criteria, the best fitting models had age in wk, length in cm, and weight in $\log_e$-transformed kg. Sex, but not allocated treatment, was found to influence the growth trajectories and hence only sex was included in the final models.

Empirical Bayes predictions of the size, timing, and intensity random coefficients of the SITAR models for infant weight and length were derived (25).

Step 2.

Linear regression models were fitted separately to each of the childhood outcomes on the 902 children with complete data, with the random coefficients predicted in step 1 included as the exposures of interest. These analyses were carried out adjusting for the prespecified covariates, initially separately for infant weight and length (Models 1 and 2) and then jointly (Model 3). The contributions of the infant weight and length SITAR random coefficients were assessed via Wald tests.

Because infant weight is log-transformed, it is measured in fractional (or %/100) units (26). Hence, the regression coefficients for weight size in each of the childhood outcome models were divided by 100 to represent the expected change in the outcome per 1% increase in infant size.

To interpret the results, predicted outcome values for each child were calculated from the regression models that included the weight and length SITAR random coefficients, setting the confounders at their reference values [i.e., female, age 5 y, maternal age 25 y, primiparous mother, ≥ 18 wk of (predominant) breastfeeding, summer season, < 1 h/d sun exposure, and middle level of SES]. These fitted values were then ranked into quarters and, for each quarter, weight and length SITAR random coefficients were averaged to identify the growth trajectories of typical children from the 4 groups. To highlight the group differences, the trajectories are plotted relative to the overall mean, that is, after subtracting the mean trajectories for weight and length (these are referred to as "residual trajectories").

Attrition analysis

An indicator of follow-up participation (i.e., contribution to the analyses in step 2) was created and treated as the outcome in a logistic regression model that included all relevant parental and birth characteristics for which (near) complete data were available.

Ethics

Both the original DIVIDS trial and the later follow-up received ethical approval from the Institute of Home Economics, University of Delhi, Sitaram Bhartia Institute of Science and Research, and the London School of Hygiene and Tropical Medicine. Parents provided written or thumbprint informed consent for their child's participation. Children were seen by a medical doctor and provided with treatments or referrals as required. Names and addresses were removed from data sets before analysis.

Results

Step 1

The characteristics of the infants contributing to step 1 are summarized in **Table 1**. By design the average birth weight is low and this is reflected in the birth weight and birth length values standardized to the WHO reference (27). Most infants were predominantly breastfed for > 18 wk.

Figure 1 shows the sex-specific average weight and length trajectories predicted by the SITAR models using the infant growth data, and their respective velocity curves. Girls (thicker solid line) were lighter than boys (lighter solid line) throughout infancy, although weight velocity (dashed lines) peaked at around 6 wk in both sexes (5.8 ± 0.2 and 5.6 ± 0.2 wk for girls and boys, respectively). The 2 sexes were similar in length up to 6 wk but subsequently diverged, whereas length velocity peaked earlier in girls than boys (age at peak velocity 1.9 ± 0.3 and 3.5 ± 0.2 wk, respectively). The details of the fitted SITAR models are in **Supplemental Table 1**, while **Supplemental Figure 1** highlights the extent to which the SITAR random coefficients explain the observed variation in trajectories.

The 2 sets of coefficients derived from fitting the SITAR model separately to the infant weight and length data show strong within-set correlations, as well as between sets: weight size was negatively correlated with weight intensity ($r = -0.57$, $P < 0.001$) and length size with length intensity ($r = -0.77$, $P < 0.001$; **Supplemental Table 2**). In contrast, weight timing and weight intensity ($r = 0.70$, $P < 0.001$), length timing and length size ($r = 0.83$, $P < 0.001$), and weight timing and length timing ($r = 0.45$, $P < 0.001$) were positively correlated (Supplemental Table 2). These correlations led to certain combinations of predicted random coefficients being more prominent.

Step 2

The birth characteristics of the infants contributing to step 2 are summarized in Table 1, next to those used to fit the SITAR growth models (in step 1). At age 4–6 y, the children remained light and short relative to the WHO growth

TABLE 1 Baseline characteristics of the study participants who contributed to the infant growth models (step 1) and the subset that contributed to the childhood outcome models (step 2), DIVIDS cohort[1]

	Included in the growth model	Included in the outcome models
All (%)	2079 (100.0)	902 (100.0)
Vitamin D arm	1039 (50.0)	442 (49.0)
Female	1109 (53.3)	473 (52.4)
Birth weight,[2] kg	2.2 ± 0.2	2.2 ± 0.2
Birth weight *z* score[3]	−2.6 ± 0.4	−2.5 ± 0.4
Birth length,[2] cm	45.6 ± 1.4	45.7 ± 1.4
Birth length *z* score[3]	−2.1 ± 0.8	−2.0 ± 0.8
Maternal age,[4] y	23.5 ± 3.4	23.7 ± 3.3
Maternal parity > 0	947 (45.6)	413 (45.8)
Maternal height,[5] cm	149.5 ± 5.6	149.7 ± 5.5
Maternal BMI,[4,6] kg/m^2	21.1 ± 3.0	21.4 ± 3.1
Duration of predominant breastfeeding		
0–10 wk	712 (34.2)	213 (23.6)
11–17 wk	391 (18.8)	153 (17.0)
≥ 18 wk	976 (47.0)	536 (59.4)
Family SES[7]		
Lowest	416 (20.0)	113 (12.5)
Low	416 (20.0)	134 (14.9)
Middle	416 (20.0)	161 (17.9)
High	416 (20.0)	242 (26.8)
Highest	415 (20.0)	252 (27.9)

[1]Values are means ± SDs or frequency (%). DIVIDS, Delhi Infant Vitamin D Supplementation; SES, socioeconomic status.
[2]Birth weight was affected by 1 missing value, birth length by 5 missing values.
[3]Standardized values calculated using WHO international standards (27).
[4]Maternal age was at infant birth and her BMI from week 6 postpartum.
[5]Maternal height is affected by missing values; there were 1184 available observations.
[6]Maternal BMI is affected by missing values; there were 948 available observations.
[7]Family asset index score and categorized into fifths according to the distribution of the original trial population.

TABLE 2 Childhood characteristics of the study participants who contributed to the childhood outcome models (step 2), DIVIDS cohort[1]

All (%)	902 (100.0)
Age, y	5.0 ± 1.0
Weight, kg	14.3 ± 2.6
Weight *z* score[2]	−1.9 ± 1.0
Height, cm	100.8 ± 8.2
Height *z* score[2]	−1.8 ± 1.0
MUAC, cm	15.6 ± 1.3
MUAMC, cm	13.5 ± 1.1
Triceps skinfold, mm	6.5 ± 1.4
Subscapular skinfold, mm	4.7 ± 1.0
Tibia ultrasound *z* score	−0.5 ± 1.0
Radius ultrasound *z* score	−0.6 ± 1.0
Season	
Mar–Jun (Summer)	226 (25.1)
Jul–Sep (Monsoon)	212 (23.5)
Oct–Feb (Winter)	464 (51.4)
Sun exposure	
Never	60 (6.7)
< 1 h/d	423 (46.9)
1–2 h/d	261 (28.9)
> 2 h/d	158 (17.5)

[1]Values are means ± SDs or frequency (%). DIVIDS, Delhi Infant Vitamin D Supplementation; MUAC, midupper arm circumference; MUAMC, midupper arm muscle circumference.
[2]Standardized values calculated using WHO international standards (27).

standards (27) (**Table 2**). There are no obvious differences between the 2 sets of children in terms of treatment arm, sex, and birth characteristics, although the children followed up at 4–6 y were more likely to have taller/heavier mothers, to have been breastfed for longer, and to be from households with higher SES, as already observed (16). A multivariable logistic regression model for the odds of follow-up participation was fitted to identify the most significant drivers among these predictors. This showed that breastfeeding duration and family SES were the strongest drivers of participation (**Supplemental Table 3**) and should therefore be included in the step 2 analyses to correct any bias from attrition, under a missing at random assumption (28).

The models regressing childhood anthropometric outcomes on the infant weight or length random coefficients (while adjusting for the prespecified covariates) showed strong associations

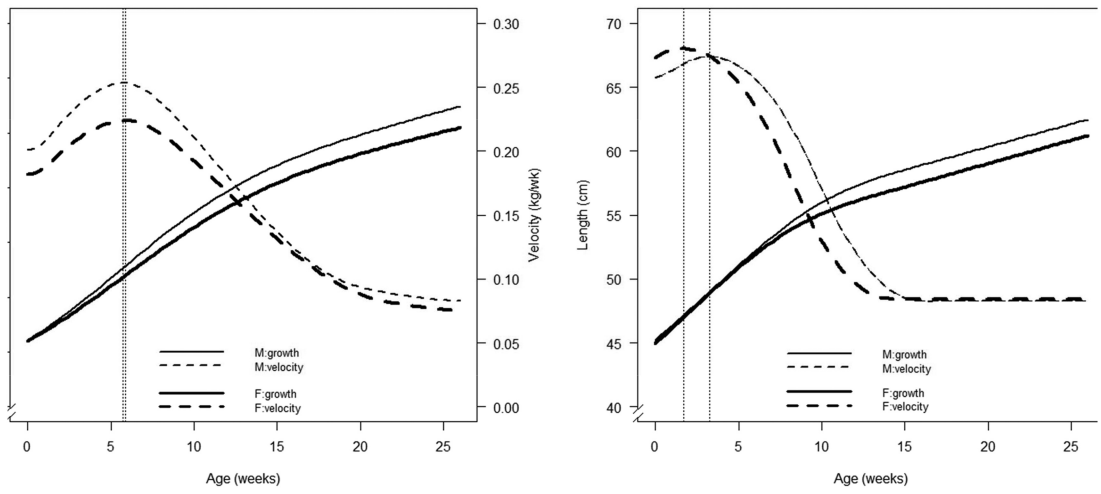

FIGURE 1 Estimated average growth trajectories (solid lines) and velocity trajectories (dotted lines) in infant weight and length by sex; DIVIDS study, $n = 2079$. The mean age at peak velocity was 5.5 ± 0.2 wk in boys and 5.8 ± 0.2 wk in girls; the mean age at peak length velocity was 3.5 ± 0.2 wk in boys and 1.9 ± 0.2 in girls. DIVIDS, Delhi Infant Vitamin D Supplementation.

TABLE 3 Within-dimension mutually adjusted regression models for childhood weight, height, MUAC, MUAMC, triceps and subscapular thickness, childhood tibia, and radius *z* score in terms of features of infant growth, DIVIDS cohort, $n = 902$[1]

Outcome at follow-up (ages 4–6 y)	Growth features[2]	Infant weight (Model 1)		Infant length (Model 2)	
		β (95% CI)	P[3]	β (95% CI)	P[4]
Weight, kg			< 0.001		< 0.001
	Size[5]	9.41 (7.51, 11.30)		0.19 (0.18, 0.29)	
	Timing, wk	−0.17 (−0.33, 0.00)		0.14 (0.00, 0.28)	
	Intensity, %[6]	4.97 (3.51, 6.43)		2.61 (1.50, 3.73)	
Height, cm			< 0.001		< 0.001
	Size[5]	19.61 (15.05, 24.17)		0.97 (0.76, 1.18)	
	Timing, wk	−0.36 (−0.75, 0.03)		−0.25 (−0.55, 0.06)	
	Intensity, %[6]	9.99 (6.48, 13.51)		11.68 (9.25, 14.11)	
MUAC, cm			< 0.001		< 0.001
	Size[5]	4.93 (3.58, 6.29)		0.03 (−0.04, 0.09)	
	Timing, wk	−0.06 (−0.18, 0.05)		0.13 (0.03, 0.23)	
	Intensity, %[6]	2.50 (1.46, 3.55)		0.40 (−0.40, 1.20)	
MUAMC, cm			< 0.001		< 0.001
	Size[5]	4.16 (3.02, 5.30)		0.03 (−0.03, 0.09)	
	Timing, wk	−0.06 (−0.16, 0.04)		0.11 (0.03, 0.20)	
	Intensity, %[6]	2.19 (1.31, 3.07)		0.47 (−0.20, 1.14)	
Triceps skinfold, mm			<0.001		0.13
	Size[5]	2.47 (0.96, 3.98)		−0.02 (−0.09, 0.06)	
	Timing, wk	−0.02 (−0.15, 0.11)		0.07 (−0.04, 0.18)	
	Intensity, %[6]	0.99 (−0.17, 2.15)		−0.23 (−1.09, 0.62)	
Subscapular skinfold, mm			< 0.001		0.009
	Size[5]	1.64 (0.47, 2.82)		−0.04 (−0.09, 0.02)	
	Timing, wk	−0.01 (−0.11, 0.09)		0.10 (0.02,0.19)	
	Intensity, %[6]	0.76 (−0.15, 1.66)		−0.34 (−1.00, 0.32)	
Tibia *z* score			0.04		0.09
	Size[5]	−1.08 (−2.25, 0.09)		−0.04 (−0.10, 0.02)	
	Timing, wk	0.14 (0.04, 0.24)		0.08 (0.00, 0.16)	
	Intensity, %[6]	−1.10 (−2.00, −0.21)		−0.56 (−1.21, 0.09)	
Radius *z* score			0.30		0.29
	Size[5]	0.74 (−0.48, 1.96)		−0.01 (−0.07, 0.04)	
	Timing, wk	−0.02 (−0.12, 0.08)		0.05 (−0.03, 0.14)	
	Intensity, %[6]	0.44 (−0.50, 1.38)		0.03 (−0.65, 0.71)	

[1] Model 1 includes the 3 weight coefficients and Model 2 includes the 3 length coefficients; each model is adjusted for sex, age at measurement, treatment group, maternal age and parity, socioeconomic status, predominant breastfeeding duration, sun exposure, and season of interview. DIVIDS, Delhi Infant Vitamin D Supplementation; MUAC, midupper arm circumference; MUAMC, midupper arm muscle circumference; SITAR, SuperImposition by Translation and Rotation.
[2] SITAR random coefficients.
[3] *P* value from the Wald test for the joint effect of the infant weight SITAR random coefficients.
[4] *P* value from the Wald test for the joint effect of the infant length SITAR random coefficients.
[5] The regression coefficient for size represents a percentage/100 change in Model 1 and a change expressed in cm in Model 2.
[6] The regression coefficient represents a percentage change.

with both for all outcomes, except for triceps skinfold and tibia *z* score, which were only associated with the weight coefficients, and for radius *z* score, which was associated with none (**Table 3**). More specifically, weight size and weight intensity were strongly associated with weight, height, MUAC, and MUAMC; weight size only with triceps and subscapular skinfolds; and weight timing with none of these outcomes (Table 3, Model 1). In contrast, when the 3 infant length random coefficients were included in the model (in place of the weight coefficients), all were strongly related to childhood weight, whereas length size and length intensity were associated with childhood height and only length timing with MUAC, MUAMC, and subscapular skinfold (Table 3, Model 2). All these associations were positive, indicating greater childhood anthropometry with greater infant size and intensity.

None of the random coefficients were significantly associated with radius *z* score. The significant associations with tibia *z* score were positive for weight and length timing and negative for weight intensity (Table 3).

Allocated treatment and sex did not modify any of the results and exclusion of predominant breastfeeding from the models did not change the results.

We next fitted joint models that included both sets of weight and length random coefficients (Model 3 in **Table 4**). Childhood weight was strongly associated with infant length timing and all 3 infant weight random coefficients (the regression coefficients for weight and length timing being of opposite sign). Childhood height was associated with the 3 length random coefficients and with weight size; and childhood MUAC and MUAMC with both weight and length random coefficients (with all the regression coefficients for weight and length being of opposite sign). The results for triceps and subscapular skinfold are consistent with those for MUAC and MUAMC, whereas those for tibia and radius *z* score showed no (or very weak)

TABLE 4 Fully adjusted regression models for childhood anthropometry and bone *z* score in terms of features of infant growth (Model 3), DIVIDS cohort, $n = 902$[1]

		Infant weight		Infant length	
Outcome at follow-up	Growth features[2]	β (95% CI)	P[3]	β (95% CI)	P[4]
Weight, kg			< 0.001		< 0.001
	Size[5]	9.01 (6.75, 11.27)		−0.05 (−0.16, 0.07)	
	Timing, wk	−0.25 (−0.43, −0.07)		0.25 (0.10, 0.39)	
	Intensity, %[6]	5.03 (3.22, 6.84)		−0.44 (−1.79, 0.91)	
Height, cm			< 0.001		< 0.001
	Size[5]	5.48 (0.32, 10.64)		0.97 (0.71, 1.23)	
	Timing, wk	0.25 (−0.16, 0.67)		−0.43 (−0.77, −0.09)	
	Intensity, %[6]	−0.82 (−4.93, 3.30)		11.68 (8.60, 14.75)	
MUAC, cm			< 0.001		< 0.001
	Size[5]	6.66 (5.02, 8.29)		−0.17 (−0.25, −0.09)	
	Timing, wk	−0.22 (−0.35, −0.08)		0.24 (0.13, 0.34)	
	Intensity, %[6]	4.11 (2.81, 5.42)		−2.08 (−3.06, −1.11)	
MUAMC, cm			< 0.001		< 0.001
	Size[5]	5.40 (4.02, 6.77)		−0.13 (−0.20, −0.06)	
	Timing, wk	−0.18 (−0.29, −0.07)		0.20 (0.11, 0.29)	
	Intensity, %[6]	3.39 (2.29, 4.48)		−1.58 (−2.39, −0.76)	
Triceps skinfold, mm			<0.001		0.03
	Size[5]	4.01 (2.18, 5.84)		−0.12 (−0.22, −0.03)	
	Timing, wk	−0.12 (−0.27, 0.03)		0.12 (0.00, 0.24)	
	Intensity, %[6]	2.31 (0.85, 3.77)		−1.62 (−2.71, −0.53)	
Subscapular skinfold, mm			< 0.001		0.005
	Size[5]	3.00 (1.57, 4.40)		−0.13 (−0.20, −0.05)	
	Timing, wk	−0.12 (−0.23,0.00)		0.16 (0.07, 0.25)	
	Intensity, %[6]	1.95 (0.82, 3.08)		−1.48 (−2.32, −0.63)	
Tibia *z* score			0.20		0.48
	Size[5]	−1.06 (−2.48, 0.37)		−0.01 (−0.08, 0.06)	
	Timing, wk	0.12 (0.00, 0.23)		0.04 (−0.06, 0.13)	
	Intensity, %[6]	−1.01 (−2.15, 0.12)		−0.19 (−1.04, 0.66)	
Radius *z* score			0.44		0.42
	Size[5]	1.09 (−0.40, 2.58)		−0.05 (−0.12, 0.03)	
	Timing, wk	−0.06 (−0.18, 0.06)		0.08 (−0.02, 0.17)	
	Intensity, %[6]	0.76 (−0.42, 1.95)		−0.37 (−1.26, 0.52)	

[1]The model includes all 3 weight and all 3 length coefficients and is adjusted for sex, age at measurement, treatment group, maternal age and parity, socioeconomic status, predominant breastfeeding duration, sun exposure, and season of interview. DIVIDS, Delhi Infant Vitamin D Supplementation; MUAC, midupper arm circumference; MUAMC, midupper arm muscle circumference; SITAR, SuperImposition by Translation and Rotation.
[2]SITAR random coefficients.
[3]*P* value from the Wald test for the joint effect of the infant weight SITAR random coefficients.
[4]*P* value from the Wald test for the joint effect of the infant length SITAR random coefficients.
[5]The regression coefficient for size represents the change in outcome per unit percentage/100 change for infant weight and per cm change for infant length.
[6]The regression coefficient represents a percentage change.

associations with the infant size, timing, and intensity random coefficients.

To aid the interpretation of these joint models, given the strong correlations among the random coefficients highlighted above, we graphed the weight and length residual growth trajectories of "typical children," that is, children with combinations of weight and length random coefficients representative of children in each quarter of the outcome being considered. For childhood weight (**Figure 2**A), the trajectories of the 4 typical children show that the infant weight trajectories (solid lines) separate and track from birth, whereas the distinctive feature of their infant length trajectories (dashed lines) is in the timing of their (relative) growth spurt, which occurs later in children in the top quarter of childhood weight. Figure 2B shows the equivalent infant growth plots of children with typical childhood heights. It is not surprising that Figure 2A and B are similar. They both highlight the time from birth to about 15 wk of age as the period when most of the subsequent variability originates, and when children's relative size at age 4–6 y is set. However, these features are more notable in the plots for childhood height, where there is even greater separation among the length trajectories (for the original infant weight and length trajectories see **Supplemental Figure 2**).

Figure 3 shows the infant weight and length trajectories defined by categories of predicted childhood MUAC and subscapular skinfold thickness (equivalent figures for MUAMC and triceps skinfold thickness are shown in **Supplemental Figure 3**). Overall, these figures show similar patterns to those for childhood weight in terms of infant weight trajectories but are less variable in terms of infant length trajectories.

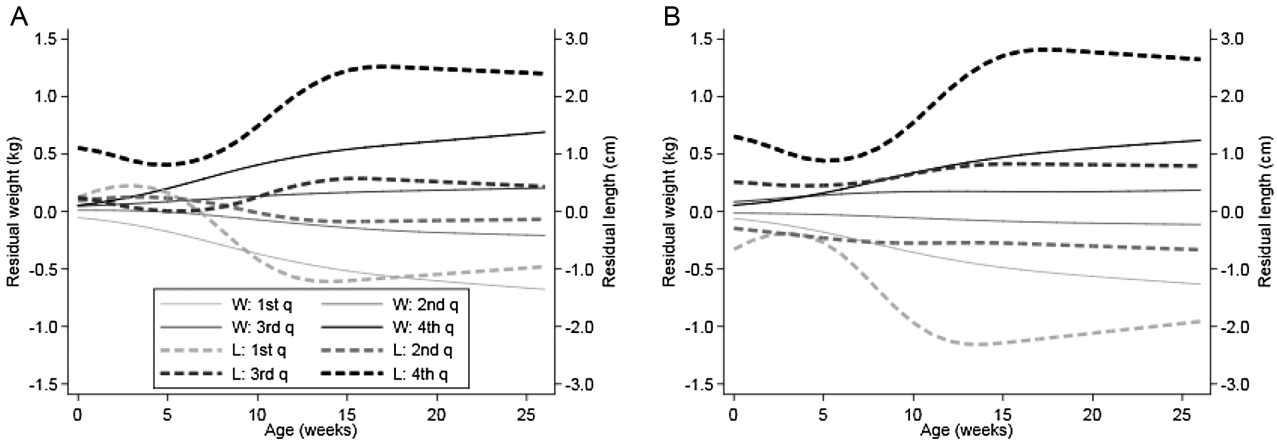

FIGURE 2 Residual W and L trajectories of 4 typical children, chosen according to increasing predicted childhood weight (A) and childhood height (B), DIVIDS study. The residual weights and lengths at each age are the differences between the predicted values for each groups and the population mean. The W and L trajectories of 4 typical children were specified using the mean random coefficients in the predicted quarters of each childhood outcome (at reference values of the confounders: female, age at measurement 5 y, maternal age 24 y, primiparous mother, summer season, < 1 h/d sun exposure, breastfeeding ≥ 18 wk, middle category of family SES). Predictions are based on the SITAR models reported in Supplemental Table 1. The predicted childhood weight of the 4 typical children in the panel is: 12.9, 13.8, 14.4, and 15.3 kg. The predicted childhood height of the 4 typical children in the right panel is: 97.6, 99.9, 101.4, and 103.7 cm. DIVIDS, Delhi Infant Vitamin D Supplementation; L, length; q, quarter; SES, socioeconomic status; SITAR, SuperImposition by Translation and Rotation; W, weight.

Discussion

This study contributes to the literature on how early growth trajectories are associated with later anthropometry and bone health in children born term LBW. Unsurprisingly, greater size and growth intensity in infancy were associated with greater size in childhood. The novel findings relate to the patterns of associations with the SITAR coefficients, which show that later weight and length timing, that is, delayed growth spurts in infancy, were associated with greater values of most childhood outcomes. It should be noted that infant growth in the study was based on the first 6 mo of life and is thus much earlier than the "early" growth usually studied (4, 5). In addition, our results are restricted to LBW term infants. Our study showed a surprising result, which we have not seen previously: the short window, between birth and 15 wk of age, during which the growth trajectories diverged greatly and then were stable until age 4–6 y.

There are inconsistencies across studies on early growth and later disease, in part because of different definitions of rapid postnatal growth and the time period in which it was measured (3, 29). Inconsistencies may also result from different populations studied; for example, the causes of both LBW and fast postnatal weight gain may differ in low- or middle-income countries from those in high-income countries. In reviews

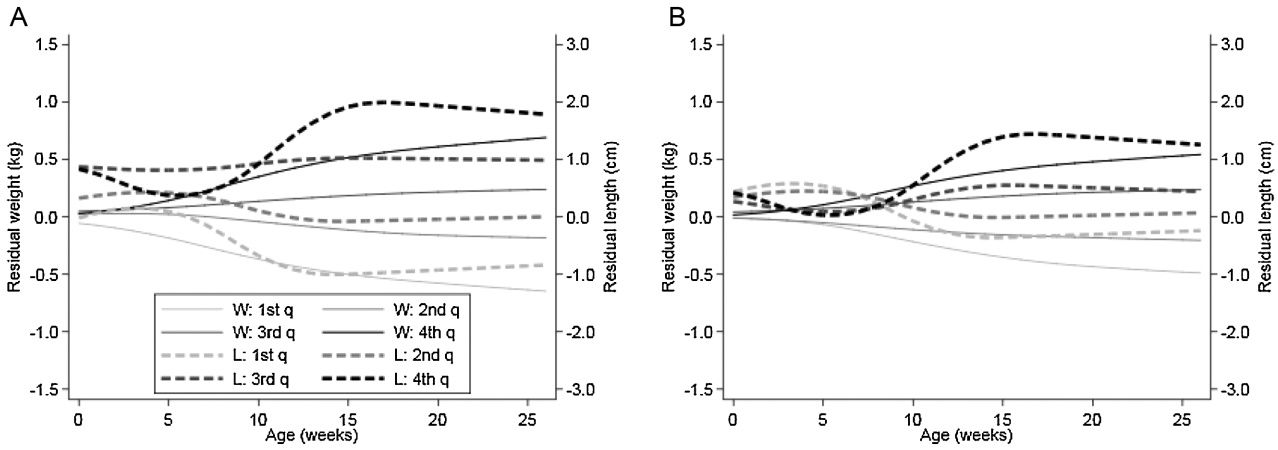

FIGURE 3 Residual W and L trajectories of 4 typical children, classified according to increasing predicted childhood MUAC (A) and childhood subscapular skinfold thickness (B), DIVIDS study. The residual weight and length at each age is the difference between the predicted values for a given combination of random coefficients and the predicted population average. The W and L trajectories of the 4 typical children were specified using the mean random coefficients in the predicted quarters of each childhood outcome (at reference values of the confounders: female, age at measurement 5 y, maternal age 24 y, primiparous mother, summer season, < 1 h/d sun exposure, breastfeeding ≥ 18 wk, middle category of family SES). Predictions are based on the SITAR models reported in Supplemental Table 1. The predicted childhood MUAC of the 4 typical children in the left panel is: 14.9, 15.4, 15.8, and 16.3 cm. The predicted childhood subscapular skinfold thickness of the 4 typical children in the right panel is: 4.5, 4.7, 4.8, and 5.0 mm. DIVIDS, Delhi Infant Vitamin D Supplementation; L, length; MUAC, midupper arm circumference; q, quarter; SES, socioeconomic status; W, weight

including studies from mainly high-income countries, risk of later overweight was increased by rapid infant growth across the birth weight range (29, 30).

In both Swedish (31) and Ethiopian (32) infants, fat-free mass index changed little throughout infancy but fat mass index increased rapidly in the first 2–3 mo of life and then leveled off. Thus, the earlier growth spurts in early infancy, that is, early timing, identified in the current study may have been driven primarily by fat. A recent study from Ethiopia found that fat-free mass accretion in the first 6 mo of life had greater effects on length growth at age 5 y than did early fat mass accretion (33). Thus children with later growth, that is, later timing, may have been putting on proportionally more lean mass with subsequent effects on childhood anthropometry.

Which factors contributed to the differing growth trajectories in infancy is unclear because the study was not designed to collect such information. In some contexts, infant feeding practice could be an important contributor to differences in growth trajectories; duration of predominant breastfeeding was controlled for in the analyses (although it did not change the results). Furthermore, a major effect of infant feeding practice was unlikely in the DIVIDS cohort in which breastfeeding was universal and the median duration of exclusive breastfeeding was 15 wk, and of predominant breastfeeding 20 wk. Vitamin D supplementation in infancy did not affect growth trajectories. Prenatal factors may have played an important role, as illustrated by the divergence of weight trajectories from very early stages, leading to differences in childhood. Which physiological factors, controlled by either genetics or environment, operate during the critical window from birth to 15 wk to affect later growth are unclear but it is possibly relevant that peak weight and length velocity occurred at later times for those who then grew to become heavier and taller.

Researchers in both the United Kingdom and India have previously investigated the associations between early growth and later bone density. Faster growth in infancy and early childhood was associated with greater bone density in older British adults (34, 35) and younger Indian adults (7). Our study provides new data from an LBW cohort with frequent weight and length measurements in infancy; we found no important effect of early growth on bone structure and strength as assessed by ultrasound.

A limitation of our study is that it was originally designed as a trial of vitamin D supplementation, and the timing of the follow-up was determined by external factors, mainly funding. Therefore, our detailed growth data extend only to 6 mo, whereas having data at 2 y would have permitted comparison with previous similar studies. An additional limitation was that, as is common in longitudinal studies in low- and middle-income countries, many children in the DIVIDS cohort were lost by age 4–6 y, so we could not examine the associations with the growth trajectories in the poorest children or those with shorter duration of predominant breastfeeding. However, controlling for the main drivers of attrition in the childhood outcome analyses should have removed most of the impact of selection bias, making the results generalizable to the larger DIVIDS cohort. Strengths of the study include its size, frequent infant growth measurements, and analysis of the SITAR random coefficients, with the latter providing insights into how the different components of growth interact and influence later outcomes.

In conclusion, our results suggest that slower but steadier growth in infancy, and in particular during the first 15 wk, was associated with larger childhood anthropometric values. We interpret these higher outcomes as beneficial in the LBW children, given their persistent growth impairment relative to international standards. However, long-term follow-up is needed to determine whether these relatively short-term gains are associated with beneficial or adverse later effects.

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