Insulin-like growth factor I concentrations in infancy predict differential gains in body length and adiposity: the Cambridge Baby Growth Study[1–3]

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ABSTRACT

Background: Formula milk–fed infants show faster rates of growth and weight gain than do breastfed infants, and they have higher concentrations of insulin-like growth factor I (IGF-I).

Objective: Our objective was to determine the influence of IGF-I concentrations on gains in weight, length, body mass index (BMI), and adiposity in the first year of life.

Design: IGF-I concentrations were measured in 953 capillary blood samples from 675 unselected infants at ages 3 and 12 mo. These infants were born between 2002 and 2008 in one center and were participating in a prospective longitudinal birth cohort. Weight, length, and 4 skinfold thicknesses as an indicator of adiposity were measured at ages 0, 3, and 12 mo. Analyses were adjusted for age and sex.

Results: Infants who were formula milk–fed had higher IGF-I concentrations at 3 mo, and they showed greater gains in weight, length, BMI, and adiposity between age 3 and 12 mo. IGF-I concentrations at 3 mo were unrelated to subsequent overall weight gain ($P = 0.5$). However, higher IGF-I concentrations at age 3 mo predicted greater subsequent gains in body length ($P < 0.001$ and $P = 0.007$ in formula milk–fed and breastfed infants, respectively) and slower gains in BMI ($P < 0.001$ and $P = 0.004$, respectively) and adiposity ($P = 0.03$ and $P = 0.003$, respectively).

Conclusions: Our findings support a key role for IGF-I in the partitioning of overall infant weight gain into statural growth compared with adiposity. In formula milk–fed infants, higher IGF-I concentrations may lead to faster gains in length; however, other mechanisms likely explain their faster gains in weight, BMI, and adiposity. *Am J Clin Nutr* 2009;90:156–61.

INTRODUCTION

Recent studies have shown that weight gain and growth in utero and during infancy have important consequences on health in later life (1, 2). Faster weight gain during infancy is associated with increased risks of subsequent obesity and related metabolic traits. In Western settings, formula milk–fed infants show greater gains in weight and length compared with breastfed infants (3), and in later childhood these individuals have increased risks of obesity (4). However, infant body weight does not distinguish between gains in length and adiposity, and overall infant weight gain may therefore represent a crude assessment of obesity risk. Furthermore, little is yet known about the regulation of differential gains in body fat and body length in normal infants.

Insulin-like growth factor I (IGF-I) plays a major role in the regulation of human growth during infancy and childhood (5). Rare deleterious mutations in IGF-I or its receptor result in severe intrauterine growth retardation and in marked postnatal reduction in statural growth (6). During early infancy IGF-I generation is directly regulated by nutrition (5). Thereafter, a gradual transition to regulation of IGF-I by growth hormone occurs around the ages of 6–12 mo, which is coincident with a rise in concentrations of growth hormone binding protein, a putative marker of growth hormone (GH) receptor numbers (7, 8).

We hypothesized that IGF-I during early infancy could represent a key mediator between nutritional status and subsequent growth. In particular, higher IGF-I concentrations could regulate the partitioning of overall gains in infant body weight into greater statural growth compared with lesser gains in adiposity.

SUBJECTS AND METHODS

Study design

The current study is part of a large ongoing birth cohort study examining the prenatal and postnatal determinants of infancy weight gain and adiposity. Mothers who attended a single antenatal center in Cambridge, United Kingdom, were included. Mothers aged <16 y or who were unable to give informed consent were excluded. Mothers were approached and recruited at their first antenatal clinic appointment during early pregnancy by trained pediatric research nurses. Offspring were monitored during infancy. Weight, length, and skinfold thicknesses were measured at 0, 3, and 12 mo by the research nurses.

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At the time of the current analysis, the cohort included 1526 infants born between August 2001 and July 2008. The data set was based on a subcohort of 675 infants born between September 2002 and May 2008 who provided a total of 953 capillary blood samples for measurement of IGF-I concentrations in a mixed cross-sectional longitudinal design (278 infants had IGF-I concentrations measured at both 3 and 12 mo). At age 3 mo, IGF-I concentrations were measured in 566 samples, and at age 12 mo, IGF-I concentrations were measured in only 387 samples. Of the 675 infants with any IGF-I measurement, 674 had growth measurements at birth, 641 at 3 mo, and 497 at 12 mo. Compared with the other infants in the birth cohort study without IGF-I measurements, the 675 infants with measured IGF-I concentrations were no different in weight or length at birth or at any time during infancy. Details of their weights, lengths, and skinfold thicknesses at birth, 3 mo, and 12 mo are shown in **Table 1**.

The study was approved by the Cambridge local research ethics committee, and all mothers gave informed written consent.

Anthropometric measurements and blood samples

Infant weight, length, and skinfold thicknesses were measured at birth and at each research clinic visit by trained pediatric research nurses. Weight was measured to the nearest 1 g by using electronic scales. Supine length was measured to the nearest 0.1 cm by using a Kiddimeter (Holtain Ltd, Crosswell, Pembs, United Kingdom). Skinfold thickness was measured in triplicate at 4 sites (triceps, subscapular, flank, and quadriceps) by using a Holtain Tanner/Whitehouse Skinfold Caliper (Holtain Ltd). Mode of infant feeding (breast milk only or formula milk) at age 3 mo was assessed by a questionnaire completed by the parents at that clinic visit. Dried capillary blood-spot samples were collected onto filter paper by heel prick during visits at age 3 and 12 mo (Tenderfoot; Elitech UK, Barkhamstead, United Kingdom) and stored at −20°C until assay.

Assays

IGF-I and IGF binding protein 3 (IGFBP-3) concentrations were measured in capillary blood-spot samples from filter paper as described previously (9). Briefly, for IGF-I measurement, 2 blood-spot disks were punched out from the dried sample and extracted with 400 μL of acidifying buffer. The extracted IGF-I was measured by using a specific radioimmunoassay (Mediagnost, Tübingen, Germany) according to the manufacturer's instructions. The interference of IGFBPs was avoided by addition of excess IGF-II. The intra-assay variability for measurement of filter disk samples was 7.1% at 124 ng/mL IGF-I, and the interassay variability was 7.9% at 330 ng/mL IGF-I (9). For IGFBP-3 measurement, one blood-spot disk was punched out of the dried sample and extracted in 1 ml of a buffer at neutral pH. IGFBP-3 concentration was measured with a specific radioimmunoassay described elsewhere (10). CVs for filter disk samples were 9.6% at 3298 ng/mL and 4.6% at 4359 ng/mL for intra- and interassay variance, respectively (9). The stability of IGF-I and IGFBP-3 in dried blood spots on filter paper stored at −20°C has been proven by repeated measurement of a reference sample for 60 mo.

Calculations and statistics

Body mass index (BMI) was calculated as weight (kg)/height squared. Age and sex-appropriate SD scores (SDS) for weight, height, and BMI at each visit were calculated [SDS = (individual measurement − population mean)/population SD] and were adjusted for actual age at each visit. Measurements of skinfold thickness at each anatomical site were used to derive separate internal SDS, adjusted for age and sex, and an overall skinfold SDS was calculated as the mean SDS of the 4 sites as an indicator of adiposity.

Longitudinal analyses relating IGF-I or IGFBP-3 concentrations at age 3 mo to subsequent growth rates between ages 3 and 12 mo were performed by using multiple linear regression with age, sex, type of milk feeding, and concurrent weight gain included as covariables; materially similar findings were also seen without these covariables (data not shown). To further exclude the possibility of confounding, these longitudinal analyses were also performed stratified by milk feeding groups.

Analyses of determinants of IGF-I or IGFBP-3 concentrations at ages 3 and 12 mo were restricted to the 278 infants with

TABLE 1
Body size at birth and 3 and 12 mo by sex[1]

	Boys (n = 349)	Girls (n = 325)	t Test
Birth			
Gestation (wk)	39.9 ± 1.6	39.9 ± 1.5	$P = 0.99$
Weight (kg)	3.59 ± 0.50	3.43 ± 0.52	$P < 0.001$
Length (cm)	51.8 ± 2.5	50.9 ± 2.5	$P < 0.001$
3 mo	(n = 339)	(n = 305)	
Weight (kg)	6.5 ± 0.8	5.8 ± 0.7	$P < 0.001$
Length (cm)	62.0 ± 2.4	60.3 ± 2.4	$P < 0.001$
BMI (kg/m^2)	16.9 ± 1.3	16.0 ± 1.4	$P < 0.001$
Sum of skinfold thicknesses (mm)	44.4 ± 7.6	43.3 ± 8.2	$P = 0.1$
12 mo	(n = 263)	(n = 245)	
Weight (kg)	10.3 ± 1.1	9.6 ± 1.1	$P < 0.001$
Length (cm)	76.8 ± 2.6	75.0 ± 2.6	$P < 0.001$
BMI (kg/m^2)	17.5 ± 1.3	17.0 ± 1.4	$P < 0.001$
Sum of skinfold thicknesses (mm)	45.7 ± 8.5	46.6 ± 9.4	$P = 0.2$

[1] Values are means ± SDs.

complete data at both time points. Analysis of variance was used to test differences in infant body size and IGF-I concentrations by sex and between infant feeding groups. Multiple linear regression was used to test associations between IGF-I concentrations and variables of body size and growth, with adjustment for sex and age by co-entering those variables in the models.

RESULTS

Breastfeeding compared with formula feeding at age 3 mo

Infants who received any formula milk at age 3 mo were not different in body size or adiposity at age 3 mo compared with breastfed infants; however, they were markedly heavier, taller, and had larger BMI and adiposity by age 12 mo (n = 497, adjusted for age and sex; **Figure 1**).

IGF-I concentrations at age 3 mo are related to subsequent growth

IGF-I concentrations at age 3 mo showed no association with subsequent weight gain between ages 3 and 12 mo [B (regression coefficient) ± SE = −0.001 ± 0.002 SDS · ng^{-1} · mL, P = 0.5; n = 402, adjusted for age, sex, and type of milk feeding at 3 mo]. However, independent of overall weight gain, infants with higher IGF-I concentrations at age 3 mo showed subsequent greater gains in length between 3 and 12 mo ($P < 0.001$; **Figure 2,** top) and lesser gains in BMI ($P < 0.001$; not shown) and adiposity ($P < 0.001$; Figure 2, bottom). These associations were independent of the type of milk feeding at age 3 mo, which was included in the above models. Furthermore, on stratification by type of milk feeding, similar associations with subsequent gains in length, BMI, and adiposity were seen separately within breastfed and formula milk–fed subgroups (**Table 2**).

IGFBP-3 concentrations at age 3 mo also showed similar, but weaker, associations with subsequent gains in length (P = 0.06), BMI (P = 0.03), and adiposity ($P < 0.001$) between ages 3 and 12 mo (adjusted for sex, age, overall weight gain, and type of milk feeding).

Determinants of IGF-I concentrations

IGF-I and IGFBP-3 concentrations at ages 3 and 12 mo are shown for the 278 infants with measurements at both time points, which were stratified by sex and milk feeding group at 3 mo (**Table 3**). Boys and girls had similar IGF-I and IGFBP-3 concentrations at age 3 mo, but by 12 mo girls had higher IGF-I and IGFBP-3 concentrations than boys among both breastfed and formula milk–fed groups. There was a significant interaction between sex and age in IGF-I concentrations ($P < 0.001$), which reflects the decline in IGF-I concentrations between ages 3 and 12 mo in boys (paired t test: $P < 0.001$) but a rise in girls ($P < 0.001$). IGF-I concentrations at age 3 mo were higher in boys and girls who were formula milk–fed compared with those who were breastfed and remained higher at age 12 mo in boys. There were no differences in IGFBP-3 concentrations between milk feeding groups.

IGF-I concentrations showed positive cross-sectional associations with body weight, BMI, and adiposity at ages 3 and 12 mo and with body length at age 12 mo but not at age 3 mo (**Table 4**). IGFBP-3 concentrations were positively associated with BMI and adiposity at age 3 but not at age 12 mo and with length at age 12 mo but not at age 3 mo. Inverse associations with birth weight were seen with IGF-I concentrations at age 3 mo (B ± SE = −6.0 ± 2.3 ng · mL^{-1} · kg^{-1}, P = 0.009) and at age 12 mo (−6.3 ± 2.8, P = 0.03). However, birth weight was unrelated to IGFBP-3 concentrations at age 3 mo (P = 0.5) or at age 12 mo (P = 0.3).

DISCUSSION

In a well-characterized UK birth cohort study, we observed that formula milk feeding at age 3 mo was associated with

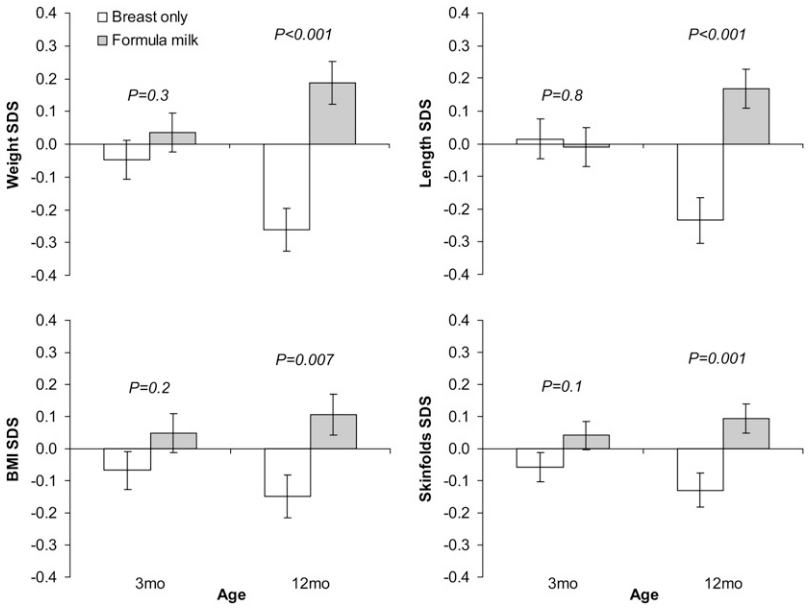

FIGURE 1. Mean (±SE) SD scores (SDS) for weight, length, BMI, and skinfold thicknesses at ages 3 and 12 mo in exclusively breastfed and formula milk–fed infants (n = 497). P values are shown for comparisons between milk feeding groups at each time point, adjusted for age and sex.

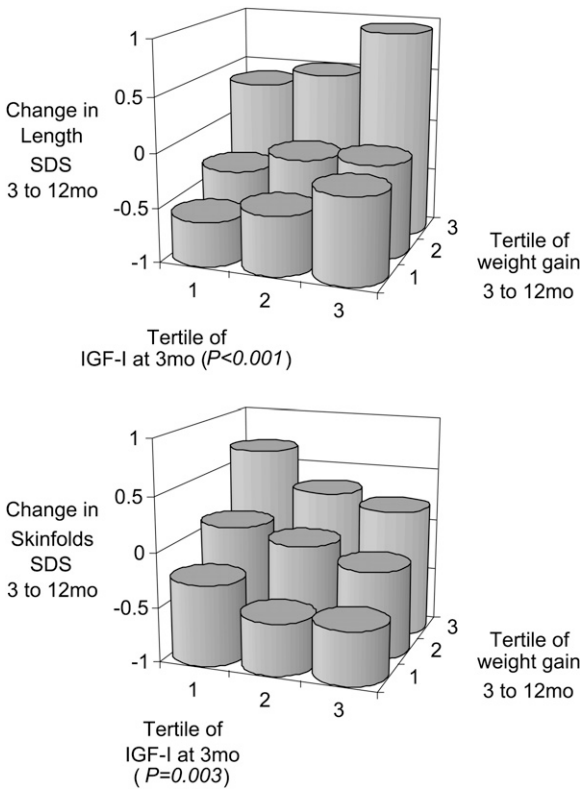

FIGURE 2. Differential effects of insulin-like growth factor I (IGF-I) concentration at age 3 mo on subsequent statural growth [top; mean change in length SD score (SDS)] between ages 3 and 12 mo and on adiposity (bottom; mean change in skinfold thicknesses SDS) between ages 3 and 12 mo. *P* values are shown for linear trend with an IGF-I tertile (n = 402, adjusted for overall weight gain at age 3–12 mo and for type of milk feeding at age 3 mo).

subsequent marked increases in body weight, length, BMI, and adiposity at age 12 mo compared with breastfed infants. Formula milk–fed infants also had higher capillary blood-spot IGF-I concentrations, and although these had apparently little effect on overall weight gain, infants with higher IGF-I concentrations showed subsequently greater gains in body length and lesser gains in BMI and adiposity. These findings support the hypothesis that IGF-I might regulate the partitioning of overall weight gain into statural growth compared with adiposity in infants.

A previous large Danish birth cohort also reported that IGF-I concentrations at age 3 mo were higher in formula milk–fed infants than in breastfed infants (11). A nutritional regulation of circulating IGF-I concentrations by dairy protein has been suggested by observational studies in older children (12, 13) and also by recent experimental data in infants (14). Previous studies have also found positive associations between infancy IGF-I concentrations and body size. In the large Danish birth cohort, IGF-I and IGFBP-3 concentrations were positively associated with gains in weight and length from birth to age 3 mo (11). In another study of 142 Danish infants, IGF-I concentrations at age 9 mo showed modest associations with body weight, and by age 10 y, IGF-I concentrations were positively associated with weight, height, and BMI but not with skinfold thicknesses (15). Our novel longitudinal analyses allowed us to discriminate between the apparent positive effects of IGF-I concentrations on statural growth in infancy and their apparent negative effects on gains in BMI and adiposity.

Previous longitudinal studies in children have similarly shown that higher IGF-I concentrations at age 5 y predict faster statural growth between ages 5 and 10 y (16). Circulating and locally produced IGF-I promotes long-bone growth by stimulating chondrocyte proliferation and maturation at the growth plate (17). IGF-I is also a key promoter of skeletal muscle formation and growth during prenatal and postnatal life (18, 19). In addition to its effects on bone and muscle growth, IGF-I has also been shown to promote adipocyte differentiation and lipid accumulation in vitro (20). Such observations have led other investigators to propose that IGF-I may promote rather than reduce infant adiposity (14, 21). However, in our study, IGF-I appeared to protect against gains in BMI and adiposity within breastfed and formula milk–fed groups separately, and we found no association at all between IGF-I concentrations and overall weight gain. Therefore, whereas higher IGF-I concentrations might well explain the more rapid statural growth of formula milk–fed infants (22), other mechanisms, such as higher insulin concentrations, could explain the relatively rapid gains in infant weight, BMI, and adiposity associated with formula milk–feeding.

We acknowledge that our study included only a minority of all births in our center. The prevalence of exclusive breastfeeding at age 3 mo in our sample was high (43%) compared with only 21% at age 6 wk for the United Kingdom as a whole (23), but it is comparable with data in other established UK cohort studies, eg, 46% at age 3 mo in the Avon Longitudinal Study of Parents and

TABLE 2
Changes in SD scores for length, BMI, and adiposity between ages 3 and 12 mo by tertiles of insulin-like growth factor I (IGF-I) concentrations at age 3 mo in infants who were fed breast milk only (n = 167) or who received formula milk (n = 221)[1]

	Tertiles of IGF-I at 3 mo			
Changes in	1	2	3	*P* trend
Length (breastfed)	−0.33 ± 0.08	−0.13 ± 0.08	+0.06 ± 0.13	0.007
Length (formula-fed)	−0.10 ± 0.09	+0.09 ± 0.08	+0.36 ± 0.08	<0.001
BMI (breastfed)	+0.11 ± 0.07	−0.08 ± 0.07	−0.25 ± 0.11	0.004
BMI (formula-fed)	0.22 ± 0.08	0.05 ± 0.07	−0.18 ± 0.07	<0.001
Skinfold thickness (breastfed)	+0.08 ± 0.09	−0.16 ± 0.09	−0.43 ± 0.15	0.003
Skinfold thickness (formula-fed)	0.28 ± 0.09	−0.06 ± 0.08	−0.01 ± 0.08	0.03

[1] Displayed values are mean ± SE changes in SD score, with adjustment for overall weight gain, age, and sex. There was no significant interaction between type of feeding and tertile of IGF-I for changes in length, BMI, or skinfold thicknesses.

TABLE 3
Capillary blood-spot insulin-like growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3) concentrations (ng/mL) at ages 3 and 12 mo by sex and type of milk feeding[1]

	Boys		Girls	
	Breastfed (n = 61)	Formula milk–fed (n = 92)	Breastfed (n = 57)	Formula milk–fed (n = 68)
IGF-I concentrations				
3 mo	43.7 ± 16.2	55.4 ± 21.6[2]	37.3 ± 14.6	51.0 ± 21.1[2]
12 mo	38.8 ± 15.4	47.6 ± 21.4[2]	56.0 ± 26.2[3]	59.9 ± 26.3[3]
IGFBP-3 concentrations				
3 mo	1630 ± 415	1700 ± 370	1677 ± 316	1804 ± 490
12 mo	1796 ± 418	1844 ± 449	2111 ± 502[3]	2089 ± 475[3]

[1] Values are means ± SDs. Data are restricted to the 278 infants with IGF-I measurements at ages 3 and 12 mo. There was a significant interaction between sex and age on IGF-I concentrations ($P < 0.001$), which reflects the decline in IGF-I concentrations between 3 and 12 mo in boys (paired t test: $P < 0.001$) but a rise in girls ($P < 0.001$). There was no such interaction on IGFBP-3 concentrations.
[2] Significantly different from breastfed, $P < 0.01$.
[3] Significantly different from boys, $P < 0.01$.

Children (3). Furthermore, the differences in weight and length SD scores at age 12 mo between breastfed and formula milk–fed infants were nearly identical in our current study to the Avon Longitudinal Study of Parents and Children (3). Adiposity was estimated from skinfold thickness measurements, which is an imprecise measure of total body fat in infants and does not estimate lean mass, and we had no assessment of muscle or bone mass. However, we saw consistent associations with BMI or skinfold measures, and it is unlikely that any systematic errors in skinfold-thickness measurements could have contributed to these associations with the type of milk feeding or IGF-I concentrations. We also recognize that our associations between IGF-I concentrations at age 3 mo and length gain are limited to the infancy period under observation. In other studies, IGF-I concentrations at ages 7–8 y predicted subsequent childhood height velocity (16), and IGF-I therapy in older children promotes statural growth (24). With regard to body composition, short-term IGF-I therapy for 3–10 mo in children with congenital IGF-I deficiency leads to a reduction in subcutaneous fat (25); however, long-term IGF-I therapy has been reported to markedly increase body adiposity in children, which suggests a possible adipogenic effect of IGF-I (26). In adult cohort studies, lower circulating IGF-I concentrations and shorter stature have been associated with increased visceral fat and risks of type 2 diabetes and cardiovascular disease (27, 28). Therefore, continued higher weight gain relative to height gain may be a risk factor for type 2 diabetes and cardiovascular disease.

During childhood, girls have higher IGF-I concentrations than boys (13, 29), although, curiously, this sexual dimorphism reverses in adult life (28). As in our current study, other studies have found no sex differences in IGF-I concentrations at age 3 mo (11). We now show that a sexual dimorphism in both IGF-I and IGFBP-3 concentrations appears between ages 3 and 12 mo. During infancy there is a major change in the regulation of IGF-I generation, which gradually comes more under the control of GHs. The appearance of a sex difference in IGF-I and IGFBP-3 concentrations between ages 3 and 12 mo might reflect the gradual postnatal emergence of GH regulation of growth, as GH sensitivity is influenced by sex and sex steroid concentrations (30, 31). In contrast to the sex differences in both IGF-I and IGFBP-3 concentrations, formula milk feeding was associated with higher concentrations of IGF-I but not of IGFBP-3, which indicates that infant milk feeding affects free IGF-I concentrations and IGF-I bioavailability.

In conclusion, our findings support the hypothesis that IGF-I has a key anabolic role in regulating the partitioning of overall infant weight gain into statural growth compared with adiposity. Higher IGF-I concentrations may contribute to the faster growth in length in formula milk–fed infants; however, other mechanisms are likely to explain the faster gains in weight, BMI, and adiposity in formula milk–fed infants.

TABLE 4
Cross-sectional correlations between insulin-like growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3) concentrations and body size at ages 3 and 12 mo[1]

	Weight	Length	BMI	Skinfold thickness
IGF-I concentrations				
3 mo	0.19[2]	0.01	0.25[2]	0.23[2]
12 mo	0.25[2]	0.18[3]	0.21[3]	0.14[3]
IGFBP-3 concentrations				
3 mo	0.15[3]	0.01	0.21[2]	0.14[3]
12 mo	0.22[2]	0.23[2]	0.12	0.03

[1] Data are restricted to the 278 infants with IGF-I measurements at both 3 and 12 mo. Standardized regression coefficients are displayed and adjusted for sex and age.
[2] $P < 0.001$.
[3] $P < 0.05$.

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The authors' responsibilities were as follows—KKO, MBR, IAH, CLA, and DBD: study concept and design; ML and KW: data acquisition; KKO: statistical analyses; KKO, ML, MBR, KW, IAH, CLA, and DBD: interpretation of the data; KKO and DBD: drafting of the manuscript; and KKO, ML, MBR, KW, IAH, CLA, and DBD: critical review of the manuscript. None of the authors had a personal or financial conflict of interest.

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