Catch-up growth in small-for-gestational-age term infants: a randomized trial[1–3]

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ABSTRACT

Background: Small-for-gestational-age (SGA) term infants are at risk of long-term growth deficits.

Objective: The objectives were to test the hypothesis that postnatal growth in SGA term infants can be altered by dietary intervention and to examine whether there is a critical window for nutritional programming of the growth trajectory during the first 9 mo postnatally.

Design: Healthy term (gestation ≥37 wk) infants with birth weights below the 10th centile were randomly assigned to receive standard term formula (TF; n = 147) or nutrient-enriched formula (EF; n = 152) for the first 9 mo; 175 breast-fed SGA term infants formed a reference group. The main outcome measures were weight, length, and occipitofrontal head circumference (OFC) at 9 and 18 mo.

Results: The infants fed the EF showed greater gains in length by 9 (1.1 cm; 95% CI: 0.38, 1.79) and 18 (1.0 cm; 0.25, 1.83) mo and in OFC by 9 (0.5 cm; 0.1, 0.9) and 18 (0.6 cm; 0.2, 1.1) mo than did infants fed the TF; the differences were larger in females. The dietary effects were independent of the pattern of growth retardation. Breast-fed infants showed greater gains in weight and OFC by 18 mo than did infants fed the TF; however, these differences disappeared after adjustment for age, parental size, and birth order.

Conclusions: Linear growth and OFC gains in SGA term infants improve after nutritional intervention during the first 9 mo of life and the effects persist for ≥9 mo beyond the intervention period. Further information on whether catch-up growth is beneficial or detrimental to long-term outcomes is required before public health interventions can be recommended. *Am J Clin Nutr* 2001;74:516–23.

KEY WORDS Term infants, small-for-gestational-age infants, catch-up growth, postnatal nutrition, randomized trial, infant formulas, United Kingdom

INTRODUCTION

Small-for-gestational-age (SGA) term infants who have undergone fetal growth restriction are a major focus of current research. These infants are known to be at risk of long-term growth deficits (1) and, most importantly, epidemiologic evidence suggests that they may be at greater risk of adult degenerative diseases, notably ischemic heart disease (2) and hypertension and type 2 diabetes (3). Whether these outcomes can be influenced by improving early nutrition in these vulnerable infants is unclear.

Most authors have suggested that the windows for achieving catch-up growth in SGA infants are the first 6 mo of life for weight and the first 9 mo of life for length (a period when breast milk or formula would be the predominant part of the infant's diet). This suggestion raises the possibility that there might be a critical period for setting the long-term growth trajectory (4–8). However, the influence of dietary intervention during this period has received little attention.

We previously reported in a small nonrandomized study that breast-fed SGA infants had significantly greater gains in weight, length, and head circumference during the first year than did infants fed a standard term infant formula (9). In that study, the advantage in catch-up growth for the breast-fed group began to emerge in the first 2 wk postpartum. One factor that we hypothesized might have contributed to these findings is that breast milk early in lactation may have a higher protein content than does infant formula. Protein is the dietary factor most highly associated with growth rate in mammals. Attempts to promote rapid growth by providing extra energy without additional protein are likely to be unsuccessful because excess energy is deposited as fat. There is some evidence that when this approach is adopted in SGA infants, the infants eventually down-regulate their milk volume intake and catch-up growth is not achieved (10).

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TABLE 1
Composition of the trial diets[1]

	TF (Farley's OsterMilk)[2]	EF (Farley's PremCare)[2]
Energy		
(kJ)	284	301
(kcal)	68	72
Protein (g)	1.45	1.85
Casein (g)	0.56	0.72
Whey (g)	0.89	1.13
Carbohydrate (g)	6.96	7.24
Lactose (g)	6.96	6.20
Maltodextrin (g)	—	1.04
Fat (g)	3.82	3.96
Minerals		
Calcium (mg)	39	70
Phosphorus (mg)	27	35
Chloride (mg)	45	45
Sodium (mg)	17	22
Potassium (mg)	57	78
Zinc (mg)	0.34	0.60
Iron (mg)	0.65	0.65
Copper (μg)	42	57
Iodine (μg)	4.5	4.5
Manganese (μg)	3.4	5.0
Vitamins		
Retinol (μg)	100	100
Thiamine (μg)	42	95
Riboflavin (μg)	55	100
B-6 (μg)	35	80
B-12 (μg)	0.14	0.2
Folate (μg)	3.4	25
C (mg)	6.9	15
D (μg)	1.0	1.3
E (mg)	0.48	1.5
K (μg)	2.7	6.0
Biotin (μg)	1.0	1.1
Pantothenic acid (mg)	0.23	0.40
Carnitine (mg)	—	1.1
Taurine (mg)	5.0	5.1
Choline (mg)	4.8	5.1
Osmolality (mOsmol/L)	300	280

[1] Values are per 100 mL. TF, standard term formula; EF, nutrient-enriched formula.

[2] Farley Health Products (A division of HJ Heinz Company Ltd), Stockley Park, Uxbridge, United kingdom.

The strategy of providing extra protein with only sufficient extra energy for protein utilization has already been adopted in the design of special formulas used to achieve high growth rates in hospitalized preterm infants. We also applied this concept successfully in the design of formula to promote catch-up growth in preterm infants after hospital discharge (11) and now extend the use of the same formula in the present study for the nutrition of SGA term infants. This formula contains almost 30% more protein than do most standard formulas; in addition, this formula has a significantly higher protein-to-energy ratio and contains more calcium, phosphorus, trace elements, and vitamins.

The current study tested the hypothesis that the growth of SGA infants can be altered by dietary manipulation during the first 9 mo postnatally. Testing this hypothesis is a necessary prerequisite for investigating whether catch-up growth is beneficial or detrimental to the long-term outcome of SGA infants.

SUBJECTS AND METHODS

Subjects

Infants were recruited from 5 hospitals in Cambridge, Nottingham, and Leicester in the United Kingdom between 1993 and 1995, with follow-up at 18 mo completed in 1997. All infants were born at term (≥37 wk gestation) and had birth weights below the 10th centile for gestation and sex according to UK growth charts. Infants with congenital abnormalities known to affect growth or development were ineligible. Mothers were approached only after they had unequivocally decided not to breast-feed and had commenced formula feeding; they were given information about the study and then telephoned later at home to see whether they wished to participate; 199 infants formed the experimental group.

A reference group of infants whose mothers had decided to breast-feed was also recruited (n = 175). All infants in the reference group were born at ≥37 wk gestation and had a birth weight below the 10th centile. If the mother changed to formula feeding within 2 wk of delivery, the infant was withdrawn from the study. The duration of exclusive and partial breast-feeding was recorded. Informed consent was obtained from the parent or guardian of each infant and the study was approved by the ethical committees of each of the participating centers.

Study design

The non-breast-fed infants were randomly assigned to receive either standard term formula (TF group; n = 147) or nutrient-enriched formula (EF group; n = 152) and commenced the trial diet within the first week of life. The randomization schedule was generated by random permuted blocks with the assignments in sealed envelopes; the subjects were stratified by race (white or Asian) and by birth weight centile (below or above the 5th centile for gestation age and sex). Randomization assignments were prepared by a member of the team who was not involved in subsequent aspects of the study.

The formulas were color-coded and the code was held by Farley Health Products and not revealed to the investigators until after the preliminary data analysis. Parents and study personnel were therefore blinded to the dietary allocation throughout the study, follow-up, and initial data analyses.

Composition of formulas

The composition of the formulas is shown in **Table 1**. Both the TF and EF were supplied by Farley Health Products (a division of HJ Heinz Co Ltd, Stockley Park, Uxbridge, United Kingdom) and fulfilled the European Community directive for the composition of formulas for term infants (12). The EF (PremCare) contained nearly 30% more protein in relation to energy than did the TF (OsterMilk) and contained more calcium, phosphorus, trace elements, and vitamins to support the projected increased growth.

Outcome measures

Growth

The primary outcome measures were changes in weight, length, and occipitofrontal head circumference (OFC) between enrollment and 9 and 18 mo of age. However, measurements were also made at 6, 12, and 24 wk. Unclothed infants were weighed to the nearest 10 g with a portable digital scale. OFC and midupper arm circumference were measured with a nonstretchable lasso tape, and length was measured with a horizontal stadiometer, both to the next highest millimeter. Calipers (Holtain Ltd, Croswell, Crymych, United

Kingdom) were used to measure triceps and subscapular skinfold thicknesses. All measurements were made by research nurses who underwent an initial period of training by a senior research nurse and who were checked regularly during the study. To support secondary explanatory analyses, parental weights and heights were obtained by parental recall at the 6-wk appointment. Maternal head circumference was measured by the research nurse and paternal head circumference was measured by either the research nurse or, after instruction, by the mother.

Food tolerance

Details on the frequency and consistency of stools (on a 5-point scale of hard, formed, mushy, runny, or watery) and the presence of blood and troublesome constipation were collected at 12 and 26 wk. The amount of time spent crying in a 24-h period and whether the mother thought the infant had colic were also recorded. When an infant was withdrawn from the study, the research nurse tried to ascertain whether this was related to the trial diet.

Safety

At each visit, information was collected on the infant's general health, eg, the frequency of upper respiratory tract infections, chest infections requiring antibiotics, gastroenteritis, the number of visits to the hospital or to the family physician, and the number of courses of antibiotics taken. The presence of eczema, wheeze, and asthma was also recorded. Demographic and obstetric data were collected at the time of randomization.

Statistics

We calculated that one hundred forty-four infants per group would permit detection of a difference in outcome measures of one-third the SD with 80% power at 5% significance. To attain this number at 9 and 18 mo follow-up we recruited 150 subjects per group.

Differences between the 2 formula-fed groups were compared by using Student's *t* test or the Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. To avoid multiple comparisons of repeated measures, growth between interim points during the study period was examined by using the change in weight, length, or OFC over different time intervals. The change in weight, length, and OFC between interim points was examined by using multiple linear regression analysis. We attempted to see all infants for follow-up at 18 mo regardless of whether they had completed 9 mo of the trial diet. All analyses were performed with the investigators blinded to the identity of the formulas, on an intention-to-treat basis. Differences between the formula-fed groups and the breast-fed reference group were compared by using analysis of variance with post hoc pairwise comparisons with Dunnett's test where appropriate. We tested formally for an interaction between diet and sex on gain in weight, length, and OFC between enrollment and 9 and 18 mo by entering the interaction term "formula × sex" into the regression models simultaneously with the separate variables (formula and sex) and size at enrollment.

We also explored whether the differences in size between breast-fed infants and formula-fed infants at 18 mo could be explained by genetic or socioeconomic differences between the groups rather than by diet. Factors included in the models were the infant's sex, size at enrollment, birth order, and age at follow-up; parental size; social class; and maternal education and support (living with partner, single but supported financially, or single and unsupported). SPSS software (version 8.0; SPSS Inc, Chicago) was used for the analyses.

RESULTS

Randomized trial

The baseline characteristics of the study groups are shown in **Table 2**. The study profile, including the number of subjects withdrawn during the study, is depicted in **Figure 1**. There were no significant differences in the proportion of infants withdrawn from each formula group or in the number of subjects withdrawn by their parents or clinicians; 87% of the TF infants and 80% of the EF infants completed the 9 mo diet. The mean (±SD) ages at 9 and 18 mo of follow-up were similar in both groups: 40 ± 2 compared with 40 ± 3 wk at 9 mo and 80 ± 4 compared with 80 ± 4 wk at 18 mo, respectively.

Outcome measures

Growth

There were no significant differences between the 2 formula-fed groups in weight or OFC at 9 or 18 mo of age (**Table 3**) or in triceps and subscapular skinfold thicknesses. However, the EF group was longer than the TF group at both 9 and 18 mo: by 1.0 cm (95% CI: 0.25, 1.64; $P = 0.008$) at 9 mo and by 0.8 cm (−0.004, 1.61; $P = 0.051$) at 18 mo.

The EF infants also had greater gains in length and OFC between enrollment and both 9 and 18 mo (**Table 4**). A greater proportion of the EF than of the TF group had a length above the 50th centile by 18 mo (32% compared with 21%; $P = 0.06$). Further analyses showed that the difference in OFC between the EF and TF groups was established by 12 wk [0.85 cm (95% CI: 0.7, 1.0) greater in the EF group; $P < 0.001$]; beyond this period, the difference decreased slightly but remained significant at 18 mo. The difference in length gain between the EF and TF groups was established by 26 wk [1.1 cm (0.30, 1.73) greater in the EF group; $P = 0.005$] and was maintained but did not increase beyond this time point. The greater gain in length in the EF group remained significant after adjustment for sex: by 0.75 cm (0.12, 1.37; $P = 0.02$) between enrollment and 9 mo and by 0.80 cm (0.04, 1.5; $P = 0.04$) between enrollment and 18 mo. There was no significant interaction between parental height and diet on linear growth between enrollment and 18 mo of age.

It was apparent that differences in growth between the 2 formula-fed groups were greater in girls than in boys at 9 and 18 mo. Compared with girls fed the TF, girls fed the EF were significantly longer at 9 mo (69.8 ± 2.5 compared with 68.6 ± 2.3 cm; $P = 0.006$) and had significantly greater gains in weight, length, and OFC up to 9 mo and in length and OFC up to 18 mo (**Table 5**). In boys, there were no significant differences in any variables between diet groups. The coefficient for the interaction between formula and sex was positive in all cases and significant for the gain in length at 9 mo (1.33; $P = 0.04$). Thus, the effect on linear growth between birth and 9 mo in the EF group was significantly greater in girls than in boys. Four infants who did not complete 9 mo of the trial diet were seen at the 9-mo follow-up and 7 infants who did not complete 9 mo of the trial diet were seen at the 18-mo follow-up. Exclusion of these noncompleters did not alter the findings significantly.

The test for an interaction between size at enrollment and diet on gains in weight, length, and OFC up to 18 mo of age—to examine whether the effect of diet varied according to the degree of growth restriction—showed that the interaction terms were not significant for weight, length, or OFC. The ponderal index [wt (g)/length^3 (cm)] at birth showed a significant negative

TABLE 2
Baseline characteristics of the 2 formula-fed groups and the breast-fed reference group[1]

	Randomized formula-fed groups		
	TF (n = 145)	EF (n = 151)	Breast-fed reference group (n = 175)
Male (%)	41.5 (61)	50.7 (77)	53.1 (93)
Gestation (wk)	39.4 ± 1.39[2]	39.0 ± 1.26	39.17 ± 1.45
Birth weight (kg)	2.60 ± 0.28	2.53 ± 0.30	2.57 ± 0.29
Birth weight (SD score)	−1.67 ± 0.46	−1.71 ± 0.60	−1.67 ± 0.51
Enrollment			
Weight (kg)	2.57 ± 0.30	2.50 ± 0.30	2.51 ± 0.27
Length (cm)[3]	47.28 ± 2.05	47.03 ± 2.05	47.61 ± 1.86[4]
OFC (cm)	33.0 ± 1.2	32.7 ± 1.3	33.0 ± 1.3
Ponderal index (g/cm^3)[3]	24.77 ± 3.63	24.33 ± 2.44	23.88 ± 2.49[5]
Mothers with PIH (%)[6]	3.4	2.0	9.1
Mothers with PET (%)	6.8	11.8	14.9
Maternal weight (kg)	56.2 ± 10.4 (137)	57.5 ± 10.6 (130)	59.0 ± 11.5 (157)
Maternal height (cm)	160.0 ± 6.0 (137)	159.4 ± 11.8 (130)	161.5 ± 6.6 (157)
Maternal OFC (cm)	54.4 ± 1.9 (137)	54.5 ± 2.4 (130)	54.9 ± 1.9 (154)
Paternal weight (kg)	75.5 ± 12.1 (130)	76.1 ± 13.2 (117)	74.8 ± 11.4 (153)
Paternal height (cm)	174.9 ± 8.3 (130)	175.5 ± 12.2 (120)	177.0 ± 7.5 (154)
Paternal OFC (cm)[7]	57.1 ± 1.8 (116)	57.2 ± 2.8 (95)	58.1 ± 3.0 (135)[8]
Maternal age (y)[7]	26.4 ± 4.9	26.8 ± 5.4	29.5 ± 4.7[8]
Maternal education (%)			
No qualifications[6]	37.9	32.2	3.4
Degree or higher qualification[6]	4.1	5.9	35.6
Social classes 1 and 2 (%)[6]	14.2	12.7	56.3
Maternal smoking during second and third trimesters (%)			
None	51.7	55.3	83.9
1–10/d	30.6	27.0	12.6
>10/d[6]	17.7	17.8	3.4
Paternal smoking (%)			
None	45.8	50.7	66.3
1–10/d	22.2	18.2	17.2
>10/d	31.9	31.1	16.6

[1] PIH, pregnancy-induced hypertension; PET, hypertension with proteinuria or edema; OFC, occipitofrontal head circumference; TF, standard term formula; EF, nutrient-enriched formula.
[2] $\bar{x}$ ± SD; n in parentheses.
[3] $P < 0.05$ (ANOVA).
[4] Significantly different from the EF group, $P < 0.05$ (Dunnett's post hoc test).
[5] Significantly different from the TF group, $P < 0.05$ (Dunnett's post hoc test).
[6] $P < 0.05$ (chi-square test).
[7] $P < 0.001$ (ANOVA).
[8] Significantly different from the TF and EF groups, $P < 0.005$ (Dunnett's post hoc test).

association with gains in weight, length, and OFC between birth and 18 mo, suggesting that infants who were longer and thinner at birth showed greater postnatal growth. However, there was no interaction between the ponderal index and diet; thus, the effect of diet on postnatal growth did not differ significantly according to the pattern of growth restriction.

Food tolerance

Similar proportions of infants in the TF and EF groups, respectively, received solids at 6 wk (2.8% compared with 3.8%), 12 wk (64% compared with 57%), and 26 wk (96% compared with 98%). There were no significant differences between the 2 groups in stool consistency or in the incidence of colic, constipation, or blood in the stools at 12 or 26 wk. Infants fed the EF passed a greater number of stools per week than did the TF group: a median of 10 compared with 7 at 12 wk (P = 0.008) and of 14 compared with 9.5 at 26 wk (P = 0.008). Of the 31 infants in the EF group and of the 21 infants in the TF group withdrawn from the study because they did not complete 9 mo of the formula diet, the formula was considered by the research nurse to be a possible, probable, or definite cause of withdrawal in 14 (45%) infants in the EF group and in 8 (38%; NS) infants in the TF group. Reasons for withdrawal included constipation, vomiting, or a feeling of being "unsettled" or "not satisfied" with the formula.

Safety

There were no significant differences between groups in the incidence of upper respiratory tract infections, chest infections, gastroenteritis, or visits to the hospital or to the family physician during the diet period (0–9 mo) or between 9 and 18 mo. A similar proportion from each group was reported to have wheeze, asthma, or eczema.

Comparison of the formula-fed infants with the breast-fed reference group

One hundred thirty-seven of the 175 breast-fed infants originally recruited completed 18 mo of follow-up. As expected, the mothers of the breast-fed infants were significantly older, were of

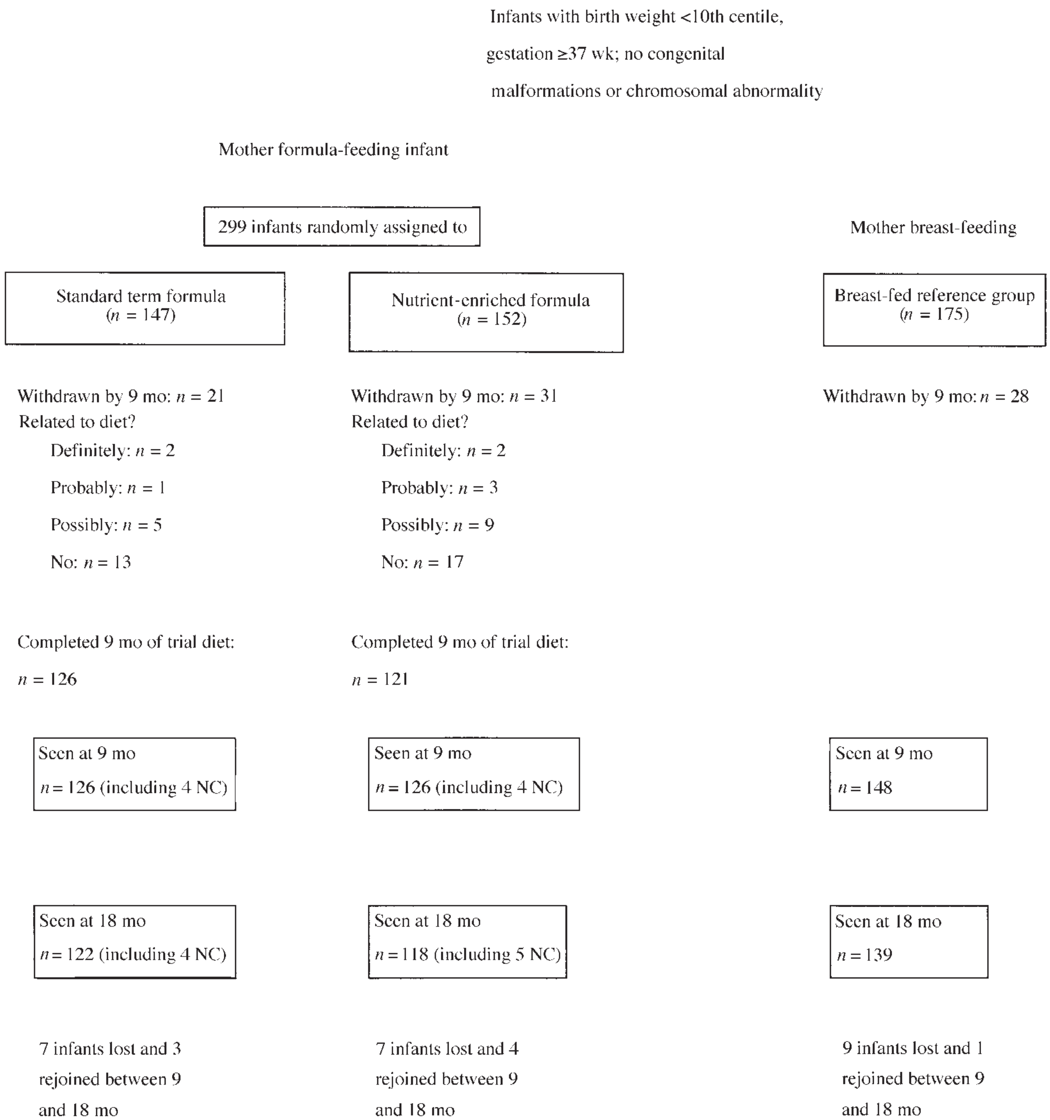

FIGURE 1. Profile of trial. NC, noncompleter.

a higher social class, and had more educational qualifications than did the mothers of the formula-fed infants. Furthermore, the mothers of the breast-fed infants were more likely to have developed either pregnancy-induced hypertension or preeclampsia during pregnancy. The parents of the breast-fed infants were less likely to smoke and paternal OFC was significantly greater in the breast-fed group (Table 2). The breast-fed infants were significantly less likely to have started eating solid foods at 12 wk (32%) than were the formula-fed infants, but 99% were eating solid foods by 26 wk. The median duration of exclusive breast-feeding was 12 wk (25th and 75th centiles: 8 and 16 wk) and the total duration of breast-feeding was 29 wk (25th and 75th centiles: 16 and 52 wk).

Anthropometric measurements for the breast-fed infants are shown in Table 3. Compared with the EF group, the breast-fed group was significantly longer at enrollment. There were no significant differences in weight, length, or OFC between breast-fed and formula-fed infants at 9 mo. The breast-fed infants had a greater gain in OFC than did the TF group [difference of 0.4 cm (95% CI: 0.05, 0.83; P = 0.02)], whereas the EF group had a greater gain in length than did the breast-fed infants over this period [difference of 1.2 cm (95% CI: 0.55, 2.0; $P < 0.001$)]. By 18 mo, the breast-fed infants had a significantly greater weight, length, and OFC than did the TF group and a greater length than did the EF group. The mean age at 18 mo of follow-up was greater in the breast-fed infants than in both formula-fed groups (82 ± 5 compared with 80 ± 4 wk; $P \leq 0.05$). However, after adjustment for sex and age at follow-up, the breast-fed infants also had significantly greater gains in weight [by 0.29 kg (95% CI: 0.013, 0.56; P = 0.04] and in OFC [by 0.42 cm (95% CI: 0.1, 0.73; P = 0.009] between enrollment and 18 mo than did the TF group. Gains in weight, length, and OFC did not differ significantly between breast-fed infants and the EF group. The differences between breast-fed infants and the TF group were similar in boys and girls.

After adjustment for social class, maternal education and support, parental size, and infant's sex, size at enrollment, age at follow-up, and birth order, there were no significant differences in weight, length, or OFC between breast-fed infants and either formula-fed group. The factors in these models that independently

TABLE 3
Anthropometric data for the 2 formula-fed groups and the breast-fed reference group[1]

	Randomized formula-fed groups		
	TF (n = 145)	EF (n = 151)	Breast-fed reference group (n = 175)
Weight (kg)			
Birth	2.60 ± 0.28	2.53 ± 0.30[2]	2.57 ± 0.29
Enrollment	2.57 ± 0.30	2.50 ± 0.30	2.51 ± 0.27
6 wk	3.86 ± 0.46	3.87 ± 0.48	3.91 ± 0.47
12 wk	5.08 ± 0.59	5.21 ± 0.69	5.11 ± 0.52
26 wk	7.08 ± 0.79	7.22 ± 0.85	7.04 ± 0.74
9 mo	8.23 ± 0.97 (126)	8.37 ± 0.96 (121)	8.24 ± 0.82 (148)
18 mo[3]	10.09 ± 1.15 (122)	10.24 ± 1.14 (118)	10.49 ± 1.13[2] (139)
Length (cm)			
Enrollment[4]	47.3 ± 2.1	47.0 ± 2.1	47.6 ± 1.9[5]
6 wk	52.6 ± 1.9	52.7 ± 2.3	52.9 ± 2.8
12 wk	57.2 ± 2.0	57.3 ± 2.4	57.7 ± 2.0
26 wk	64.4 ± 2.6	65.4 ± 3.1[2]	65.2 ± 2.2
9 mo	69.5 ± 2.9 (126)	70.5 ± 2.7[2] (121)	69.9 ± 2.3 (148)
18 mo[6]	79.3 ± 3.2 (122)	80.1 ± 3.1[2] (118)	80.9 ± 2.2[2,5] (139)
OFC (cm)			
Enrollment	33.5 ± 1.2	33.2 ± 1.2	33.2 ± 1.1
6 wk	37.0 ± 1.3	37.0 ± 1.3	37.1 ± 1.1
12 wk	39.4 ± 1.3	39.5 ± 1.5	39.5 ± 1.1
26 wk	42.8 ± 1.4	42.9 ± 1.5	43.1 ± 1.4
9 mo	45.2 ± 1.5 (126)	45.3 ± 1.5 (121)	45.3 ± 1.3 (148)
18 mo	47.5 ± 1.5 (122)	47.8 ± 1.5 (118)	48.0 ± 1.4[2] (139)

[1] $\bar{x}$ ± SD; n in parentheses. OFC, occipitofrontal head circumference; TF, standard term formula; EF, nutrient-enriched formula.
[2] Significantly different from the TF group, $P < 0.05$.
[3] $P = 0.02$ (ANOVA).
[4] $P = 0.03$ (ANOVA).
[5] Significantly different from the EF group, $P < 0.05$.
[6] $P < 0.001$ (ANOVA).

influenced later size were age at follow-up, size at enrollment, parental size, and birth order. There were no significant interactions between maternal smoking during pregnancy or maternal preeclampsia and diet on growth between enrollment and 18 mo.

DISCUSSION

Randomized trial

Term SGA infants randomly assigned to receive EF for the first 9 mo of life were longer at 9 and 18 mo and showed a greater gain in body length and head circumference up to 18 mo of age compared with those who received TF. These findings showed that catch-up growth during the first months of postnatal life in SGA term infants was altered with nutritional intervention and that the effects of the nutritional intervention persisted for at least 9 mo beyond the period of intervention. The findings are also consistent with, though do not prove, the hypothesis that the critical period for programming of the growth trajectory in SGA term infants includes early postnatal life.

The analyses suggested that most of the gains in length in the EF group occurred during the first 6 mo of life; beyond this time, the difference between groups was maintained but did not increase. This finding concurs with previous reports, highlighting the importance of trying to achieve catch-up growth in the first 6–9 mo of life (4–8, 13). The greater gain in OFC in the EF than in the TF group was established by 12 wk. Nevertheless, although the major effect of the EF was seen during the first 6 mo, we cannot tell from our data whether continuing the EF beyond 6 mo was important for maintaining the advantage in growth.

Whether the observed growth differences are biologically significant or will persist beyond the end of study (6–18 mo) or further into childhood or adulthood remains to be determined. The difference in length of ≈1 cm between the groups at 9 mo amounted to about one-third of the SD or 6.7% of the population variation, which could be relevant in terms of a population even though a 1-cm increase in height for an individual does not appear to be a dramatic change. In rats, McCance (14) showed that a brief dietary manipulation in the suckling period had lifetime "programming" effects on growth trajectory and adult size and that the size difference became amplified progressively with age. Whether such amplification occurs in humans is an important question to be addressed in our follow-up.

We chose birth weight below the 10th centile as our criterion for growth retardation. Although commonly used, this cutoff is open to criticism in that it groups infants who may be small for familial or ethnic reasons with those who are pathologically growth retarded. We found no significant interaction between parental height and diet on linear growth between enrollment and 18 mo, suggesting that the response to the diet was no less in those who were considered small for familial reasons.

It is surprising, given that catch-up growth occurs while infants are receiving formula almost exclusively, that the influence of manipulating the diet has received such little attention as a potential means of improving growth. Twenty years ago, Ounsted and Sleigh (15) reported faster postnatal growth in breast-fed, SGA term infants than in infants fed formula. Davies (7) found no significant growth differences between SGA term infants fed either banked human milk or formula with different protein contents.

TABLE 4
Gains in weight, length, and occipitofrontal head circumference (OFC) between enrollment and 9 and 18 mo of follow-up by diet group[1]

	Randomized formula-fed groups		
Gains	TF	EF	Difference (95% CI)
Enrollment to 9 mo			
n	126	121	—
Weight (kg)	5.66 ± 0.92[2]	5.87 ± 0.89	0.22 (−0.010, 0.45)
Length (cm)	22.3 ± 3.0	23.4 ± 2.6	1.1[3] (0.38, 1.8)
OFC (cm)	11.6 ± 1.8	12.1 ± 1.4	0.5[3] (0.1, 0.9)
Enrollment to 18 mo			
n	122	118	—
Weight (g)	7.51 ± 1.13	7.76 ± 1.10	0.25 (−0.032, 0.54)
Length (cm)	32.0 ± 3.2	33.0 ± 2.9	1.0[3] (0.25, 1.82)
OFC (cm)	13.9 ± 1.8	14.5 ± 1.5	0.63[3] (0.20, 1.1)
9 to 18 mo			
Weight (g)	1.95 ± 0.61	1.85 ± 0.62	0.1 (−0.06, 0.26)
Length (cm)	9.84 ± 1.94	9.51 ± 2.32	0.34 (−0.22, 0.89)
OFC (cm)	2.36 ± 0.80	2.35 ± 0.73	0.01 (−0.19, 0.21)

[1] TF, standard term formula; EF, nutrient-enriched formula.
[2] $\bar{x}$ ± SD.
[3] Significant difference between groups, $P \leq 0.01$.

Brooke and Kinzey (10) randomly assigned SGA term infants to be fed high- or standard-energy-containing formula. They found that the high-energy-fed group down-regulated their intake so that, by 2 mo, energy intakes were similar between the 2 groups.

Simply increasing the energy intake of SGA infants via dietary fat or carbohydrate is therefore unlikely to improve growth. For this reason, the EF used in the present study was designed to provide a modestly higher amount of energy but a significantly higher amount of protein and a higher protein-energy ratio than the TF. The observed growth benefit may have resulted solely from this difference in energy and protein contents. However, the EF also contained more zinc, calcium, phosphorus, and vitamins than did the TF, which may partly explain the greater linear growth in the EF group. Indeed, zinc supplementation in isolation was shown to improve catch-up growth in SGA infants (16).

Interestingly, the effect of the EF on growth was greater in girls than in boys and there was a significant interaction between diet and sex on length at 9 mo. Most studies of nutritional intervention in animals and preterm humans have found that males are more sensitive to early malnutrition than are females. However, the poorer response or inability of the boys in the present study to respond to the EF may be further evidence of their high-risk status; indeed, it is possible that boys might require more extreme nutritional intervention than do girls. A study with a larger sample size would be required to resolve this issue.

Some authors suggest that the potential for catch-up growth depends on the type of growth retardation, perhaps reflecting the timing of the underlying intrauterine insult (7, 17, 18). Thus, infants with disproportionate growth retardation (a low ponderal index at birth) have been reported to show good catch-up in weight, whereas those with proportionate growth retardation have been reported to remain shorter and lighter and to have a lower head circumference up to 4 y of age. In our study, infants with a lower ponderal index at birth had significantly greater gains in weight, length, and OFC by 18 mo of age. However, the effect of the EF on growth during this period did not vary according to the severity of growth retardation or the ponderal index at birth. Therefore, it would be difficult to select groups of infants who would be expected to benefit most from nutritional supplementation on the basis of their size-for-gestation or pattern of growth retardation.

TABLE 5
Gains in weight, length, and occipitofrontal head circumference (OFC) between enrollment and 9 and 18 mo of follow-up in the 2 formula-fed groups by sex[1]

	Boys			Girls		
Gains	TF	EF	Difference (95% CI)[2]	TF	EF	Difference (95% CI)
Enrollment to 9 mo						
n	51	65	—	75	56	—
Weight (kg)	6.10 ± 1.02[3]	6.08 ± 0.91	0.02 (−0.34, 0.37)	5.36 ± 0.72	5.63 ± 0.80	0.27[4] (−0.002, −0.53)
Length (cm)	23.5 ± 3.6	23.6 ± 2.7	0.07 (−1.0, 1.22)	21.5 ± 2.2	23.1 ± 2.5	1.6[4] (0.8, 2.4)
OFC (cm)	12.0 ± 2.4	12.4 ± 1.5	0.4 (−0.4, 1.1)	11.4 ± 1.0	11.8 ± 1.1	0.4[4] (0.06, 0.8)
Enrollment to 18 mo						
n	45	61	—	77	57	—
Weight (kg)	7.94 ± 1.24	7.90 ± 1.04	0.04 (−0.4, 0.5)	7.26 ± 1.0	7.61 ± 1.14	0.35 (−0.014, 0.72)
Length (cm)	32.8 ± 3.7	33.0 ± 2.9	0.2 (−1.1, 1.4)	31.5 ± 2.8	33.1 ± 3.0	1.6[4] (0.6, 2.6)
OFC (cm)	14.1 ± 2.6	14.7 ± 1.5	0.5 (−0.3, 1.3)	13.8 ± 1.1	14.4 ± 1.5	0.6[4] (0.2, 1.1)

[1] TF, standard term formula; EF, nutrient-enriched formula.
[2] None of the differences were significant.
[3] $\bar{x}$ ± SD.
[4] Significant difference between groups, $P \leq 0.05$.

In recent years, evidence from retrospective epidemiologic studies has been interpreted as suggesting that growth retardation is associated with many adverse outcomes later in life (2, 3) and that this effect is amplified in those individuals who become overweight during adult life (19). This scenario might call into question the advisability of promoting catch-up growth in infants who may have been programmed for an adverse long-term outcome in utero. In general, it is suggested that these adverse effects are amplified by adult obesity rather than by increases in height, which was the major effect seen in our study; we found no evidence that the EF made infants fatter. However, we plan to conduct a follow-up study to assess the effect of improved early growth on later health outcomes, including markers for ischemic heart disease and type 2 diabetes.

Comparison of the formula-fed infants with the breast-fed reference group

The differences in social class and maternal educational attainment between the formula-fed and breast-fed reference groups were as expected. Mothers who breast-fed were more likely to have developed hypertension or preeclampsia during pregnancy but were less likely to have smoked than were the mothers of the formula-fed infants, suggesting that the underlying cause of the infants' growth retardation might well differ between the 2 groups. This in itself might influence the potential for catch-up growth or the response to diet, although we found no significant interaction between either maternal smoking during pregnancy or history of preeclampsia and diet on growth up to 18 mo of age. Parents of breast-fed infants were also taller and had larger OFCs, suggesting that the growth potential of breast-fed infants might be greater than that of formula-fed infants. Without adjustment for confounding factors, breast-fed infants were significantly heavier and longer and had greater gains in weight and OFC by 18 mo of age than did the TF group; most of this size difference occurred between 9 and 18 mo. In contrast, there were no significant differences between breast-fed infants and the EF group. However, differences between the TF group and the breast-fed infants were diminished and were no longer significant after adjustment for age at follow-up, size at enrollment, parental size, and birth order.

These findings suggest that the breast-fed, SGA term infants grew well. Infants who received a standard TF showed less catch-up in weight, length, and OFC by 18 mo of age; however, this finding may reflect the lower genetic growth potential and social circumstances. The EF group had growth rates similar to those of breast-fed infants despite a genetic growth potential and environment comparable with that of the TF group. Nineteen of the breast-fed infants originally recruited were excluded from follow-up because their mothers did not breast-feed for ≥2 wk. Growth data were not collected for these infants; therefore, we cannot exclude the possibility of a selection bias in favor of faster growing infants remaining in the study (assuming that poor infant growth may have caused the mothers to stop breast-feeding).

Conclusion

Formula-fed SGA term infants show improved linear growth and gains in OFC when fed EF rather than the standard TF during the first 9 mo of life. These results show that early growth in these infants is amenable to dietary manipulation. Our findings also have potentially important biological implications because they suggest that the effect of the improved diet persists for ≥9 mo after the period of intervention, thus providing preliminary experimental evidence that the growth trajectory might be subject to nutritional programming in humans. This hypothesis needs further testing at follow-up. Our findings also raise the question of whether standard term formulas provide adequate nutrition to formula-fed SGA infants. However, further information on the long-term consequences of early catch-up growth in these infants is required before general public health interventions can be recommended.

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