Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circulation 2007;115;213-220; originally published online Dec 18, 2006;
DOI: 10.1161/CIRCULATIONAHA.106.617811
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Promotion of Faster Weight Gain in Infants Born Small for Gestational Age

Is There an Adverse Effect on Later Blood Pressure?

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Background—Being born small for gestational age is associated with later risk factors for cardiovascular disease, such as high blood pressure. Promotion of postnatal growth has been proposed to ameliorate these effects. There is evidence in animals and infants born prematurely, however, that promotion of growth by increased postnatal nutrition increases rather than decreases later cardiovascular risk. We report the long-term impact of growth promotion in term infants born small for gestational age (birth weight <10th percentile).

Methods and Results—Blood pressure was measured at 6 to 8 years in 153 of 299 (51%) of a cohort of children born small for gestational age and randomly assigned at birth to receive either a standard or a nutrient-enriched formula. The enriched formula contained 28% more protein than standard formula and promoted weight gain. Diastolic and mean (but not systolic) blood pressure was significantly lower in children assigned to standard compared with nutrient-enriched formula (unadjusted mean difference for diastolic blood pressure, −3.2 mm Hg; 95% CI, −5.8 to −0.5; $P=0.02$) independent of potential confounding factors (adjusted difference, −3.5 mm Hg; $P=0.01$). In observational analyses, faster weight gain in infancy was associated with higher later blood pressure.

Conclusions—In the present randomized study targeted to investigate the effect of early nutrition on long-term cardiovascular health, we found that a nutrient-enriched diet increased later blood pressure. These findings support an adverse effect of relative "overnutrition" in infancy on long-term cardiovascular disease risk, have implications for the early origins of cardiovascular disease hypothesis, and do not support the promotion of faster weight gain in infants born small for gestational age. **(*Circulation*. 2007;115:213-220.)**

Key Words: blood pressure ■ follow-up studies ■ gestational age ■ nutrition

Infants born small for gestational age (SGA) are at long-term risk of atherosclerotic cardiovascular disease (CVD)[1] and its risk factors (such as high blood pressure[2]), but whether manipulation of nutrition and growth in infancy can influence these effects is controversial.

Previously, epidemiological associations between greater weight at 1 year of age and a lower risk of later CVD have led to suggestions that promotion of infant growth may be beneficial for later CVD.[3,4] Paradoxically, however, intervention studies in animals indicate that promotion of early growth by a higher nutrient intake increases later cardiovascular risk.[5–8] Recent data in humans are also conflicting. For instance, faster growth in early life was not associated with mortality from CVD in a Finnish cohort[9] but was associated with later cardiovascular risk factors such as endothelial dysfunction,[10] insulin resistance,[11] and dislipidemia[12] in preterm infants. Similarly, in infants born at term, upward

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percentile crossing for weight was associated with higher later blood pressure,[13–15] insulin resistance,[16] and, in 2 systematic reviews, an increased risk of later obesity.[17,18] Promotion of growth in infancy may also be detrimental for later CVD risk. For instance, nutritional supplementation with dried milk powder in infancy has been shown to have an adverse long-term effect on, or program, higher blood pressure in adulthood.[19] However, most previous studies in humans are observational, and there are few randomized studies with long-term prospective follow-up that can inform the optimal management of infants born SGA.

In the present study, we investigated the role of early nutrition and weight gain on later CVD risk using an experimental approach. We studied term infants born SGA, whom it was ethical at the time to assign randomly to a

Received February 8, 2006; accepted October 20, 2006.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.617811**

nutrient-enriched formula that promoted growth (which was thought to be beneficial)[20] or to a standard formula. Our principal and a priori outcome was later blood pressure, an established risk factor for CVD, known to be programmed by early nutrition[21] and to track into adult life.[22]

Methods

Participants

Research nurses recruited infants from 5 hospitals in Cambridge, Nottingham, and Leicester in the United Kingdom between 1993 and 1995.[20] Infants meeting the eligibility criteria (≥37 weeks of gestation, with birth weight below the 10th percentile for gestation and sex according to UK growth charts, and free of congenital abnormalities) were enrolled as soon as possible after birth.[20] Gestational age was determined from the last menstrual period or first trimester ultrasound scan. Infants of mothers who had unequivocally decided to formula-feed were randomly assigned (at a mean age of 4 days; n=299) to receive a standard, term formula (Farley's Ostermilk, Farley's Health Products, a division of HJ Heinz Company Ltd, Stockley Park Uxbridge, UK) or a nutrient-enriched formula (Farley's PremCare). The randomization schedule, generated by random permuted blocks and prepared by a member of the team not involved in data collection, was assigned with the use of sealed envelopes.[20] A reference group of breast-fed infants (≥37 weeks of gestation and birth weight <10th percentile) was also recruited (n=175).[20] Informed written consent was obtained from the parent, and the study was approved by the research ethics committees of each participating center.

Study Design

Formulas were assigned until age 9 months. Anthropometric and demographic information was obtained as described.[20] Social class was based on the occupation of the parent providing the main financial support for the family according to the registrar general's classification.

Composition of Formulas

Both formulas fulfilled the European Community directive for the composition of formulas for term infants. Nutrient-enriched formula contained 28% more protein than standard formula and also more minerals, trace elements, and vitamins to support the projected increase in weigh and length gain (Table 1).

Follow-Up

All children who were alive, traceable, and willing to participate were reviewed in their homes between 1999 and 2002. Ethical approval for the follow-up was obtained from research ethics committees at each center, and written consent was obtained from children's parents or guardians. The derivation of the sample followed up at 6 to 8 years of age is given in the Figure.

All researchers and study participants were blinded to the original dietary assignments. Diastolic and systolic blood pressures were measured with an automated oscillometric device (Accutorr, Datascope Corp, NJ), which has been recommended by the European Society of Hypertension and validated previously with protocols from the US Association for the Advancement of Medical Instrumentation and the British Hypertension Society.[23,24] Mean arterial blood pressure (MAP) was derived automatically from the shape of the blood pressure curve according to the following formula:

$$\text{MAP}=\frac{\text{systolic pressure}+(2\times\text{diastolic pressure})}{3}$$

Measurements were made, after 10 minutes of rest, on 2 occasions 5 minutes apart in the left arm with the use of an appropriately sized cuff,[21] and the average value was obtained. Height and weight were measured by trained observers using a portable stadiometer accurate to 1 mm (Holtain Instruments Ltd, Crymych, UK) and electronic scales accurate to 0.1 kg (Seca, CMS Weight Equipment Ltd, London, UK), respectively.

TABLE 1. Composition of the Trial Diets*

	Term Formula	Nutrient-Enriched Formula
Energy, kJ	284	301
Energy, kcal	68	72
Protein, g	1.4	1.8
Casein	0.6	0.7
Whey	0.9	1.1
Carbohydrate, g	7.0	7.2
Lactose	7.0	6.2
Maltodextrin	0.0	1.0
Fat, g	3.8	4.0
Minerals		
Calcium, mg	39	70
Phosphorus, mg	27	35
Chloride, mg	45	45
Sodium, mg	17	22
Potassium, mg	57	78
Zinc, mg	0.3	0.6
Iron, mg	0.6	0.6
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	0.1	0.2
Folate, μg	3.4	25
C, mg	6.9	15
D, μg	1.0	1.3
E, mg	0.5	1.5
K, μg	2.7	6.0
Biotin, μg	1.0	1.1
Pantothenic acid, mg	0.2	0.4
Carnitine, mg	0.0	1.1
Taurine, mg	5.0	5.1
Choline, mg	4.8	5.1
Osmolality, mOsm/L	300	280

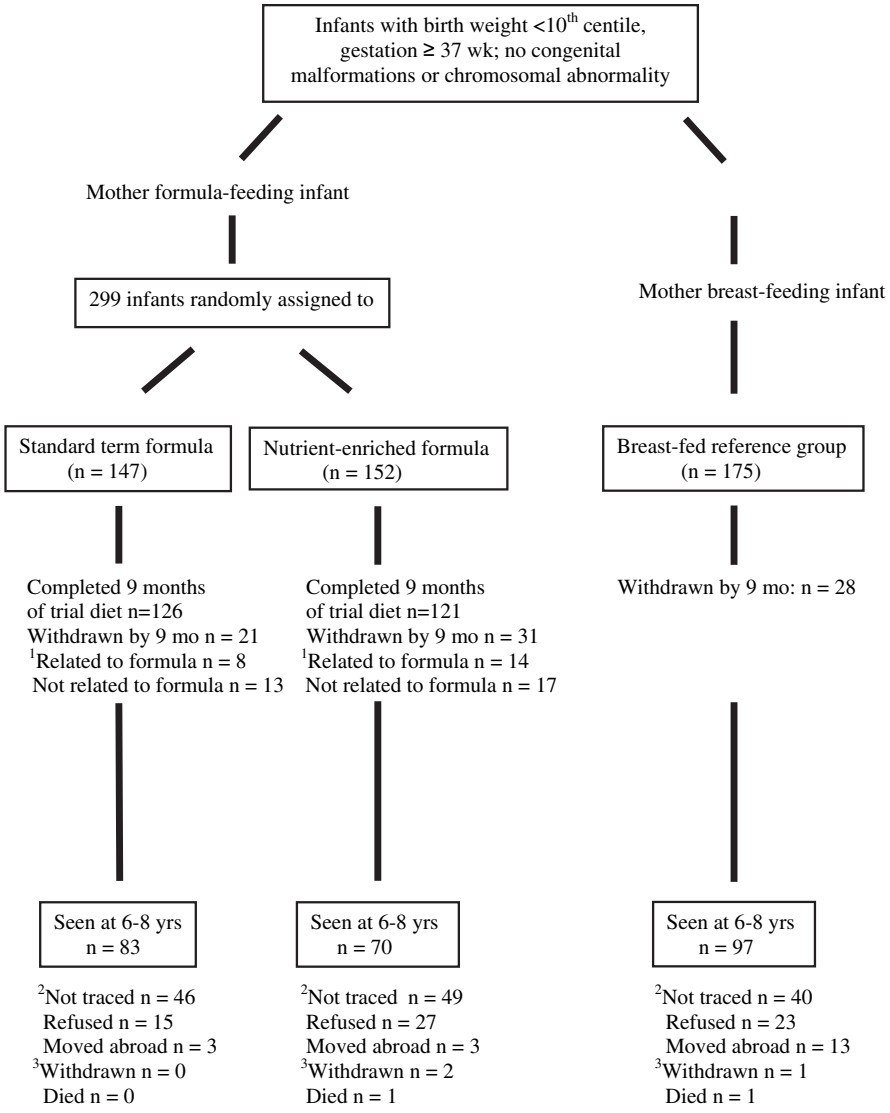
*Values are per 100 mL.

Statistical Analysis

Sample size was based on our previous study[21] and estimated to detect a half SD difference in mean diastolic blood pressure and MAP between randomized formula-fed groups at 80% power and 5% significance[21] (requiring ≈128 subjects). A subset of 153 formula-fed children agreed to participate.

Our outcomes were diastolic blood pressure and MAP, which have been shown previously to be programmed by early nutrition.[21] Secondary outcomes were systolic blood pressure and size at follow-up. Comparisons between (randomized) groups were made with Student t test for continuous variables and χ^2 test for categorical variables. Multiple linear regression analyses were used to adjust differences in outcome between randomized groups for possible baseline differences. Initial analyses were on an intention-to-treat basis and included all children followed up irrespective of whether they complied with the initial diet. Secondary analyses were confined to those who complied with the dietary intervention.

Linear regression analyses were used to assess the influence of growth rate on later blood pressure. In 6 separate regression models,



[1]Withdrawn from the study by the mothers for reasons considered by research nurse to be related to formula (e.g. constipation, vomiting, or feeling 'unsettled' or 'not satisfied' with formula). [2]Not traced or did not reply to initial letter; [3]withdrawn by family doctor (reasons not given).

Derivation of sample.

growth was expressed as the change in weight or length SD score (*z* score) (calculated with the use of percentiles for British infants) from birth to age 9 months, 9 to 18 months, and 18 months to 6 to 8 years. Regression analyses were adjusted for potential confounding factors (age, sex, *z* score for weight and height at 6 to 8 years, and social class). Assumptions of linearity were checked in exploratory analyses with the use of nonparametric statistics and visual inspection of scatterplots.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Main Effect: Comparison of Groups Randomly Assigned to Different Formulas

Children reviewed at 6 to 8 years were representative of the original study population; there were no differences in demographic, anthropometric, or socioeconomic factors in infancy between children who were or were not followed up (Table 2). A greater percentage of boys was reviewed in the nutrient-enriched formula group compared with the standard-formula group (Table 3); this would not be expected to confound our findings because diastolic blood pressure, MAP, and systolic blood pressure did not differ by sex (eg, mean blood pressure=78 [SD 8] mm Hg in boys versus 78 [SD 8] mm Hg in girls; $P=0.6$). There were no other significant differences between randomly assigned dietary groups in anthropometric, socioeconomic, or demographic factors at baseline or at follow-up (Table 3) or in maternal age, anthropometry, education, and incidence of smoking or high blood pressure during pregnancy (data not shown). There were no adverse events reported (reasons for participants withdrawing from the trial are given in the Figure).[20]

At age 6 to 8 years, diastolic blood pressure and MAP were lower in children randomly assigned to standard formula compared with nutrient-enriched formula (for diastolic blood

TABLE 2. Characteristics of Children Who Were and Were Not Followed up at Ages 6 to 8 Years

	Standard Formula vs Nutrient-Enriched Formula Trial		Breast-Fed Reference Group	
	Followed up (n=153)	Not Followed up (n=146)	Followed up (n=97)	Not Followed up (n=78)
Growth				
At birth				
Gestation, wk	39.2 (1.3)	39.2 (1.4)	39.3 (1.5)	39.1 (1.3)
Birth weight, kg	2.6 (0.3)	2.6 (0.3)	2.6 (0.3)	2.5 (0.3)
Birth weight *z* score	−1.7 (0.5)	−1.7 (0.5)	−1.7 (0.5)	−1.7 (0.5)
At enrollment				
Weight, kg	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)
Weight *z* score	−1.79 (0.6)	−1.75 (0.6)	−1.8 (0.5)	−1.8 (0.5)
Length, cm	47.2 (1.9)	47.1 (2.2)	47.9 (1.8)	47.2 (1.8)†
Length *z* score	−1.43 (0.9)	−1.47 (1.0)	−1.1 (0.8)	−1.4 (0.9)‡
Change in weight *z* score enrollment to 9 mo	0.92 (1.0)	0.82 (1.0)	0.88 (0.9)	0.74 (1.0)
Change in length *z* score enrollment to 9 mo	0.81 (1.0)	0.79 (1.1)	0.45 (1.0)	0.40 (0.9)
Demographic				
% Male (n)*	44 (68)	48 (70)	54 (52)	52 (41)
Maternal age, y	26.8 (4.9)	26.4 (5.4)	30.0 (4.4)	28.8 (5.0)
Social class: % nonmanual (n)*	20 (31)	24 (35)	64 (62)	68 (53)
Maternal qualifications*				
% None (n)	30 (46)	39 (57)	3 (3)	4 (3)
% Degree or higher (n)	3 (5)	7 (10)	34 (33)	37 (29)

Data are mean (SD) except *percentage (n) analyzed by χ^2 test. Small loss of n (<10%) for some variables.
Significant differences between those followed up and not followed up: †P=0.01; ‡P=0.02.

pressure: mean difference, −3.2 mm Hg; P=0.02) (Table 4). Similar findings were obtained after adjustment for potential confounding factors (age, sex, *z* score for weight and height at 6 to 8 years, and social class) (Table 4).

There was little evidence that the relation between formula type and later blood pressure differed according to sex (P>0.4 for formula×sex interactions for diastolic blood pressure, MAP, or systolic blood pressure). When stratified by sex, blood pressure tended to be lower in both boys and girls randomized to standard formula versus nutrient-enriched formula (mean difference [95% CI] in boys: diastolic: −2.1 [−6.2 to 2.0] mm Hg, P=0.3; MAP: −2.5 [−6.2 to 1.3] mm Hg, P=0.2; systolic: −1.7 [−6.4 to 3.0] mm Hg, P=0.5; in girls: diastolic: −4.6 [−8.4 to −0.8] mm Hg, P=0.02; MAP: −3.5 [−7.4 to 0.4] mm Hg, P=0.08; systolic: −2.6 [−7.3 to 2.2] mm Hg, P=0.3).

The effect of early diet on later diastolic blood pressure was also evident after the analysis was confined to those who completed the initial diet (137 of 153) (per protocol) and adjustment for potential confounding factors (as above) (mean difference, −3.7 mm Hg; 95% CI, −6.5 to −0.9; P=0.009). Similar findings were obtained for MAP (mean difference, −3.2 mm Hg; 95% CI, −5.9 to −0.5; P=0.02) but not for systolic blood pressure (mean difference, −2.2 mm Hg; 95% CI, −5.5 to 1.0; P=0.2).

Association With Birth Weight

Diastolic blood pressure was lower in infants randomized to standard versus nutrient-enriched formula after adjustment for birth weight for gestational age *z* score (birth weight *z* score) (mean difference, −3.2 mm Hg; 95% CI, −6.0 to −0.6; P=0.02). There was a trend for nutrient-enriched formula to have a greater adverse effect on later blood pressure in those with lower birth weight for gestation; the interaction between nutrient-enriched formula and birth weight *z* score was statistically significant for MAP (P=0.04) but not for systolic (P=0.08) or diastolic blood pressure (P=0.4).

Nonrandomized Analyses

In a secondary analysis, we tested the hypothesis that upward percentile crossing for weight programmed later blood pressure. Infant weight gain was assessed as both a dichotomous and continuous variable.

When infant weight gain was analyzed as a dichotomous variable, diastolic blood pressure was greater in children whose weight *z* score increased between birth and age 9 months (mean [SD]: 63.5 [8.0] mm Hg; n=104) than in those without such acceleration in weight (59.9 [7.1] mm Hg; n=29) (unadjusted mean difference, 3.6 mm Hg; 95% CI, 0.3 to 6.8; P=0.03). Similar findings were obtained after adjustment for potential confounding factors (adjusted mean difference, 3.7 mm Hg; 95% CI, 0.3 to 7.2; P=0.03); for MAP (unadjusted mean difference, 4.6 mm Hg; 95% CI, 1.4 to 7.7; P=0.005; adjusted mean difference, 4.7 mm Hg; 95% CI, 1.5 to 8.0; P=0.005); and for systolic blood pressure (unadjusted mean difference, 5.6 mm Hg; 95% CI, 1.8 to 9.4; P=0.004; adjusted mean difference, 5.1 mm Hg; 95% CI, 1.3 to 9.0; P=0.01).

As a continuous variable, the change in weight *z* score between birth and 9 months was not associated with higher

TABLE 3. Anthropometric and Demographic Characteristics of Children

	Randomized Formula-Fed Groups		
	Standard Formula (n=83)	Nutrient-Enriched Formula (n=70)	Breast-Fed Group (n=97)
In infancy			
Gestation, wk	39.3 (1.4)	39.1 (1.2)	39.3 (1.5)
Birth weight, kg	2.6 (0.3)	2.5 (0.3)	2.6 (0.3)
Birth weight *z* score	−1.65 (0.5)	−1.75 (0.6)	−1.65 (0.5)
Apgar score at 5 min	9.5 (0.7)	9.7 (0.6)	9.0 (1.1)
At enrollment			
Weight, kg	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)
Weight *z* score	−1.77 (0.5)	−1.82 (0.6)	−1.83 (0.5)
Length, cm	47.3 (1.7)	47.1 (2.1)	47.9 (1.8)
Length *z* score	−1.39 (0.8)	−1.45 (1.0)	−1.08 (0.8)
Social class: % nonmanual (n)*	22 (18)	19 (13)	64 (62)
Age 9 mo			
Completed trial diet to 9 mo, % (n)*	88 (73)	91 (64)	93 (90)
Weight, kg	8.2 (1.0)	8.5 (0.9)†	8.3 (0.8)
Weight *z* score	−0.95 (1.1)	−0.67 (1.0)	−0.93 (0.9)
Length, cm	69.6 (2.8)	70.6 (2.7)†	70.1 (2.1)
Length *z* score	−0.66 (1.1)	−0.53 (1.1)	−0.60 (0.8)
Change in weight *z* score enrollment to 9 mo	0.76 (1.1)	1.15 (0.9)†	0.90 (0.9)
Change in length *z* score enrollment to 9 mo	0.73 (1.0)	0.92 (1.1)	0.44 (0.9)
18 mo			
Weight, kg	10.1 (1.3)	10.4 (1.1)	10.6 (1.2)
Weight *z* score	−1.04 (1.1)	−0.81 (1.0)	−0.74 (1.0)
Height, cm	79.6 (3.4)	80.3 (3.0)	81.2 (2.7)
Height *z* score	−0.60 (1.1)	−0.46 (1.1)	−0.29 (0.9)
Change in weight *z* score 9 to 18 mo	−0.06 (0.6)	−0.13 (0.6)	0.20 (0.6)
Change in height *z* score 9 to 18 mo	0.06 (0.7)	0.02 (0.8)	0.28 (0.5)
6–8 y			
% (Proportion) followed up*	56 (83/147)	46 (70/152)	55 (97/175)
% Male (n)*	33 (27)	59 (41)‡	54 (52)
Age, y	6.8 (0.6)	6.7 (0.4)	6.9 (0.8)
Weight, kg	22.0 (4.2)	22.7 (6.1)	22.7 (4.0)
Weight *z* score	−0.27 (1.1)	−0.13 (1.2)	−0.16 (1.2)
Height, cm	117.3 (6.9)	118.1 (6.4)	119.8 (6.6)
Height *z* score	−0.51 (1.1)	−0.31 (1.1)	−0.22 (1.1)
Body mass index	16.0 (1.8)	16.3 (2.9)	16.0 (16.0)
Change in weight *z* score 18 mo to 6–8 y	0.77 (1.0)	0.64 (1.0)	0.62 (0.9)
Change in height *z* score 18 mo to 6–8 y	0.15 (0.8)	0.17 (0.7)	0.16 (0.8)

Data are mean (SD) except *% (n).

Comparison of randomized formula-fed groups all not significant except †P=0.03, ‡P=0.001. Small loss of n (<15%) for some variables.

later diastolic blood pressure (0.7 mm Hg increase per *z* score change; 95% CI, −0.8 to 2.3; P=0.3) but was associated with higher MAP (1.5 mm Hg increase per *z* score change; 95% CI, 0.1 to 3.0; P=0.04) and systolic blood pressure (1.7 mm Hg increase per *z* score change; 95% CI, −0.01 to 3.4; P=0.05) independent of potential confounding factors (as above). Similar observations were obtained after adjustment for confounding factors (as above) together with randomized diet (for diastolic blood pressure: 0.8 mm Hg increase per *z* score change in weight between birth and 9 months; 95% CI, −0.7 to 2.3; P=0.3; MAP: 1.5 mm Hg increase per *z* score change; 95% CI, 0.04 to 3.0; P=0.04; and systolic blood pressure: 1.7 mm Hg increase per *z* score change; 95% CI, −0.08 to 3.4; P=0.06).

TABLE 4. Blood Pressure in Randomized Formula-Fed Groups at Age 6–8 Years

	Unadjusted Blood Pressure, mm Hg					Adjusted Blood Pressure, mm Hg*		
	Standard (n=83)	Nutrient Enriched (n=70)	Mean Difference	95% CI	*P*	Mean Difference	95% CI	*P*
Diastolic	61.3 (8.2)	64.5 (8.3)	−3.2	−5.8 to −0.5	0.02	−3.5	−6.2 to −0.7	0.01
MAP	76.9 (8.3)	79.5 (7.8)	−2.5	−5.1 to 0.1	0.06	−3.0	−5.6 to −0.3	0.03
Systolic	100.5 (10.2)	102.2 (9.8)	−1.7	−4.9 to 1.5	0.3	−2.0	−5.3 to 1.3	0.2

Data are mean (SD) in each formula group.
*Adjusted for age, sex, *z* score for weight and height at 6–8 years, and social class.

Blood pressure at age 6 to 8 years was not associated with acceleration in length between birth and age 9 months or with the change in weight or length *z* score between age 9 and 18 months or between 18 months and 6 to 8 years (data not shown).

Breast-Fed Reference Group

Blood pressure in breast-fed infants (mean [SD]: diastolic, 62.5 [8.6]; MAP, 78.2 [7.8]; systolic, 101.7 [9.4] mm Hg) was similar to infants fed a standard or nutrient-enriched formula. However, exploratory analyses suggested that faster early weight gain also programmed higher later blood pressure in breast-fed children. Thus, breast-fed infants whose weight *z* score increased in the first 9 months (n=76) had higher diastolic blood pressure (mean [SD], 63.1 [8.5] mm Hg) than those whose weight did not (55.6 [6.4] mm Hg; n=11) (mean difference, 7.5 [95% CI, 2.2 to 12.8] mm Hg; $P=0.006$). Similar findings were made for mean and systolic blood pressure ($P<0.02$ for both).

Discussion

In the present prospective experimental study, we found that consumption of a nutrient-enriched formula programmed higher blood pressure in SGA infants. We postulate that these effects, seen up to 8 years after random dietary assignment, were the result of faster weight gain in infancy promoted by the nutrient-enriched diet. Our findings support the concept that early nutrition has a major impact on long-term cardiovascular health in infants born at term, as shown previously in experimental studies in infants born preterm,[11,21] and these findings provide further experimental evidence to support the hypothesis that faster growth in infancy has adverse effects for later blood pressure.[13–15] Therefore, together with evidence from animal studies[5–8] and from studies in preterm infants[10–12] and both SGA[16] and healthy term infants[13–15,17,18] (including 2 systematic reviews for effects on later obesity[17,18]), our findings argue against the promotion of faster weight gain in infants born SGA.

The size of the effect of early diet on later blood pressure (≈3 mm Hg) may amplify with age[25] and for populations is substantial in terms of its potential impact on public health, although the 95% CIs around the point estimate raise the possibility that the effect size could be smaller. Lowering population-wide diastolic blood pressure by only 2 mm Hg, however, would be expected to prevent ≈100 000 myocardial and cerebrovascular events per year in the United States alone.[26] The present study therefore has important implications for infant nutrition policy. Our data indirectly support the promotion of breast-feeding, which is associated with slower weight and length gain in infancy,[27] but, at least in term infants born SGA, discourage the promotion of faster weight gain.

The effect of a nutrient-enriched early diet on later blood pressure appears to be mediated via an effect on the rate of early weight gain. This finding is consistent with detrimental effects of faster growth in infancy on cardiovascular risk factors[5–8] and life span[28] in animals, endothelial dysfunction[10] and insulin resistance[11] in infants born prematurely, and a tendency to obesity in healthy term infants.[17,18,29] Both faster linear growth and faster weight gain have been implicated previously.[10,16,29] Faster weight gain[2,30] and length gain[2] in older children have also been consistently associated with higher later blood pressure. However, these studies have usually estimated growth from the difference in weight *z* score between birth and a point later in childhood or adult life and therefore have not defined the period of postnatal weight gain that has the greatest negative impact on later blood pressure.

Surprisingly, there are relatively few data on the programming effects of weight gain in infancy, which, as the period of most rapid growth, could be particularly influential. A recent Brazilian study showed that faster weight gain in infancy, childhood, or after puberty had exactly the same negative implications for later systolic blood pressure (0.37 mm Hg increase in systolic blood pressure per *z* score increase in weight gain per year).[13] Similarly, faster weight gain in infancy was associated with later systolic blood pressure in prospective studies of adults from Finland[14] and children from the United States.[15] In contrast, a follow-up of a British cohort did not find any effect of infant weight gain on adult blood pressure,[30] whereas a greater fall in ponderal index between 6 and 18 months of age predicted higher systolic blood pressure in adults living in Hong Kong.[31] These previous conflicting findings might be explained by differences in study populations (eg, from a developed or developing country), different ages at follow-up, and the impact of confounding factors associated with an observational study design. In contrast, our experimental study, in which random dietary assignment produced differences in weight and length growth, shows that faster weight gain in infancy programs both higher systolic and diastolic blood pressure later in childhood.

We considered several potential limitations to the interpretation of our data. First, only 51% of the original population was followed up. However, this is unlikely to introduce systematic bias because our sample was representative of those recruited at birth, and subject characteristics of children who were reviewed at age 6 to 8 years did not differ between

randomized groups at birth or at follow-up. Moreover, there is no prior reason why the epidemiological association between acceleration in weight in infancy and later blood pressure should differ between children reviewed and those not reviewed. Similarly, the excess of boys in the nutrient-enriched compared with the standard formula group at follow-up did not affect the findings because there were no sex differences in blood pressure at age 8 years and because the effects of nutrient-enriched formula on later blood pressure were independent of sex.

Second, the applicability of our findings to infants not born SGA is uncertain. Previous studies in animals,[5–8] our data in preterm infants,[10,11] and studies in term infants[17,18] suggest that programming effects of a nutrient-enriched diet and faster weight and length gain on later CVD risk factors, including blood pressure,[13–15] are independent of size at birth. Whether similar effects are seen in infants with appropriate birth weight needs further research, although nutrition intervention studies are more difficult to justify in such groups. Nonetheless, the adverse effect of a nutrient-enriched early diet on later outcome in our study appeared to be greater in babies with lower birth weight, consistent with data from animal studies.[28] Previously, blood pressure has been shown to be lower in breast-fed than formula-fed individuals.[21] That this was not shown here may be because breast-fed infants, when born SGA, also show deleterious (spontaneous) faster postnatal weight gain. In fact, we found a 7.5 mm Hg difference in diastolic blood pressure between 78% of breast-fed infants who showed faster weight gain and those who did not.

Third, we studied children and did not have prospective follow-up into adulthood. Therefore, it is theoretically possible that the positive association between early weight gain and later blood pressure reverses in adult life, although a previous association between faster weight gain in infancy and higher blood pressure in adulthood[14] argues against this hypothesis.

Finally, the present study did not identify mechanisms for the observed effects. Nevertheless, differences in blood pressure between randomized dietary groups were independent of body weight adjusted for height (in regression analyses), a major determinant of blood pressure also strongly influenced by faster weight gain in infancy.[17,18] In fact, as in infants born prematurely,[32] a nutrient-enriched diet did not have long-term effects on height or weight in SGA infants. Furthermore, in accordance with a previous report,[33] only acceleration in weight and not length was associated with higher later blood pressure. This is consistent with our previous findings of a smaller effect of faster early length gain compared with weight gain on later endothelial function.[10]

Previously, we postulated that faster growth programs the metabolic syndrome possibly by an effect on hormonal systems such as insulin-like growth factor-1.[34] Our present findings were consistent with this hypothesis and support an evolutionary conserved mechanism, which suggests that faster early growth can have negative effects on long-term health and, in many species, there is a tradeoff within individuals between accelerated early growth and shorter life span.[5,35] Because the present randomized study addressed infant feeding and not growth, however, the present study cannot determine whether it is faster weight gain itself or infant nutrition (1 determinant of early growth) that is the mechanistic link between nutrient-enriched formula and higher later blood pressure. Thus, the high protein content of the nutrient-enriched formula was designed to fuel faster weight and length gain, and the higher content of other nutrients was calculated to meet the increased nutrient needs for infants growing faster. However, we cannot exclude the possibility that differences between formulas in specific nutrients such as calcium or phosphorus would have been influential for later blood pressure, although there are no convincing studies to suggest this explanation. Nonetheless, the primary role of growth in programming is supported by our preliminary observation that faster weight gain programmed higher blood pressure even in breast-fed infants. Similarly, faster weight gain has been shown to program later obesity independent of protein intake[29] and the method of infant feeding.[36]

Thus, we suggest that, as in animal models,[5–8] the cost of faster growth in infancy is a later increase in cardiovascular risk. Although faster weight gain has short-term advantages for morbidity in infants with low birth weight from low-income countries,[37] whether risk-benefit analysis will lead to similar conclusions in such infants from high-income countries remains uncertain. Importantly, unlike the case for infants born prematurely, a nutrient-enriched diet in infancy did not improve cognitive development at age 18 months in our SGA infants.[38] Clearly, further data are required to inform the debate on the effects of early growth for later cardiovascular outcomes and in particular to explain the discrepancies in findings from some historical cohorts[3,4,9] and more recent observational[13–15] and experimental studies.[11,21] Our findings, however, support the hypothesis that the promotion of faster weight gain has adverse programming effects on later blood pressure, at least in term infants born SGA.

Acknowledgments

We thank Wendy Jenkins, Dee Beresford, Penny Lucas, and Emma Sutton for technical assistance.

Sources of Funding

This study was funded by the Medical Research Council of the United Kingdom. We thank Farley's Health Products (a division of HJ Heinz Company Ltd, Stockley Park Uxbridge, UK) for supplying the trial formulas.

Disclosures

None.

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CLINICAL PERSPECTIVE

Being born small for gestational age is associated with later risk factors for cardiovascular disease, such as high blood pressure. Promotion of postnatal growth has been proposed to ameliorate these effects. There is evidence in animals and infants born prematurely, however, that promotion of growth by increased postnatal nutrition increases rather than decreases later cardiovascular risk. We tested this hypothesis by measuring blood pressure at 6 to 8 years of age in a cohort of children born small for gestational age (birth weight $<$10th percentile) and randomly assigned at birth to receive either a nutrient-enriched formula, which promoted growth, or a standard, control formula. Diastolic and mean arterial blood pressures were found to be significantly lower in children assigned to standard compared with nutrient-enriched formula (unadjusted mean difference for diastolic blood pressure, -3.2 mm Hg; 95% CI, -5.8 to -0.5; $P=0.02$), independent of potential confounding factors. In observational analyses, faster weight gain in infancy was associated with higher later blood pressure. The present study showed that a nutrient-enriched diet in infancy increased later blood pressure with an effect size that is important for the health of populations rather than individuals. These findings are consistent with data from animal models that suggest an adverse effect of relative "overnutrition" in infancy on long-term cardiovascular disease risk, indirectly support the promotion of breast-feeding, which is associated with slower weight gain in infancy, and argue against the promotion of faster weight gain, at least in term infants born small for gestational age.