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Does early nutrition in infants born before term programme later blood pressure?

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Abstract

Objectives—To test whether nutrition early in infants' development programmes later blood pressure and whether the reported relation between low birth weight and later high blood pressure is due to poor nutrition or growth before full term.

Design—Prospective randomisation of preterm infants to early diets differing greatly in nutrient content in four parallel multicentre trials, with blinded follow up 7·5-8 years later.

Setting—Neonatal units at Cambridge, Ipswich, King's Lynn, Norwich, and Sheffield.

Subjects—758 children weighing under 1850 g at birth.

Main outcome measure—Blood pressure at age of 7·5-8 years.

Results—There were major differences in nutrient intake from randomised diets (preterm formula v standard formula and preterm formula v donor breast milk; in each case with or without mother's milk), but follow up showed no differences in later

blood pressure. Individual subjects showed large variation in protein and energy intakes and in growth performance, including degrees of growth failure seldom seen in utero, but these factors were also unrelated to later blood pressure.

Conclusion—Extremes of nutritional intake and growth performance in preterm infants do not programme later blood pressure at 7·5-8 years of age. These findings do not support the hypothesis that high blood pressure has early nutritional origins. We suggest that the long term rise in blood pressure reported in individuals who had low birthweight (at full term) is not, as previously speculated, due to poor fetal nutrition or growth as such.

Introduction

The possibility that nutrition in early life could influence propensity to adult disease¹ is of great concern to public health. This idea originates from the more general concept in developmental biology

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recently redefined by Lucas as programming,² the process whereby a stimulus or insult when applied at a critical or sensitive period of development results in a long term or permanent effect on the structure or function of the organism. Animal evidence for programming during critical periods of development dates back over 100 years³; that early nutrition could operate in this way⁴ is supported by numerous experimental studies in animals.^{2,4,5} Corresponding evidence in humans has been more difficult to obtain. Our approach is to conduct formal long term prospective outcome studies of individuals randomly assigned to their early diet.^{6,7} Recent retrospective epidemiological studies have linked possible markers of early nutrition, notably size at birth or in infancy, with cardiovascular disease or its risk factors in adult life.^{8,9} Several investigators have shown that babies born small have higher blood pressure in later life.^{9,10}

Barker *et al* suggested that small size at birth reflects suboptimal fetal nutrition and argued that nutritional intervention during pregnancy might favourably influence later blood pressure.¹¹ Since 1982 we have explored the hypothesis that early nutrition programmes later blood pressure in a large multicentre study of preterm infants born in the third or late second trimester. Their diets were strictly randomly assigned until they reached, on average, full term, and their blood pressure was measured at 7.5-8 years of age. This study allowed us to extricate the effects of nutrition before term from other factors that might have influenced later blood pressure had these infants remained in utero. Furthermore, when premature babies reach the equivalent of full term they have often developed severe growth failure,⁶ commonly compounded by pre-existing growth retardation at birth,¹² which would enable us to examine effects on later blood pressure of extremes of growth failure seldom seen in the fetus born at term.

Subjects and methods

We enrolled 926 infants with birth weights under 1850 g admitted to the neonatal units in Cambridge, Ipswich, King's Lynn, Norwich, and Sheffield between 1982 and 1985.⁶ Ethical approval was obtained in each centre. No parent refused consent, and only babies with major congenital anomalies were excluded.

DIETS

Four parallel randomised trials were conducted. In three centres the infants of mothers who chose not to provide breast milk were randomly allocated to pasteurised banked breast milk donated by unrelated lactating women or to a nutrient enriched preterm formula (Farley's Osterpremi, Crookes Health Care) as their sole diet (trial 1). The infants of mothers who provided breast milk (trial 2) were randomly allocated to banked breast milk or preterm formula as a supplement in volumes according to the mother's success in providing breast milk (median intake of mother's milk was 53% of total enteral feed volume (lower and upper quartiles 17% and 91%)). In the two remaining centres, infants were randomly allocated to a standard "term" formula (Farley's Ostermilk) or to the above preterm formula as sole diets (trial 3) or, when mothers provided their breast milk (trial 4), as supplements to mother's milk (median intake of breast milk 39% (5% and 76%)). The trials can be treated independently or combined (see below), still preserving randomisation. The infants were randomised to diets within 48 hours of birth by means of sealed envelopes as previously described.⁶

Table I shows the protein, energy, and sodium contents of the diets. Compared with standard formula, the preterm formula was also enriched in vitamins,

zinc, and copper.¹³ The assigned diets were given until the infant weighed 2000 g or was discharged home, whichever was sooner. For infants fed maternal milk, protein and energy intakes were estimated from 4935 complete 24 hour collections of milk. Average nutrient values were obtained from 600 samples of pooled banked breast milk. In addition, 200 infants required a period of parenteral nutrition. Total protein and energy consumed from all sources was calculated (per kg body weight) and averaged over hospital stay.

TABLE I—Nutritional contents of trial diets

	Banked breast milk*	Mother's milk	Standard term formula	Preterm formula
Protein (g/100 ml)	1.1	1.5	1.45	2.0
Sodium (mmol/l)	7.2	11.0	8.3	19.6
Energy (MJ/100 ml)	0.192	0.259	0.284	0.334

*Mean values determined analytically by us.

BODY WEIGHT

Trained staff weighed the infants daily in hospital. To assess the relation between failure to gain weight and later blood pressure three further variables were calculated: weight gain (g/kg/day) on each diet after birth weight had been regained⁴; change in standard deviation of body weight from expected mean weight (derived from Gairdner-Pearson growth data¹⁴) between birth and hospital discharge (or discontinuation of total diet), incorporating our own birthweight centiles for preterm infants¹² (a baby with a birth weight 1 SD below the mean and a discharge weight 3 SD below the mean would have a change in standard deviation of -2 SD); and standard deviation of body weight from expected weight at hospital discharge, representing a summation of both intrauterine and extrauterine growth failure.

FOLLOW UP

Extensive demographic and clinical data were collected from the 782 subjects who were followed up at 7.5-8 years of age, representing 99% of survivors still in Britain. Blood pressure was recorded in 758 of the subjects followed up and was measured three times. Since the first reading was significantly higher (by a mean of 4.4 mm Hg) than subsequent ones, the last two values were averaged for the analyses. An automated device (Accutor Datascope) was used to measure blood pressure in most subjects (553), but a conventional sphygmomanometer was used when two of the devices became unavailable. Small differences in values obtained were accounted for in the analyses. Study data were analysed with Student's *t* test and regression analysis.

Results

Table II summarises demographic data. Birth weight (range 663-1847 g), gestation, social class,⁷ sex ratio,

TABLE II—Characteristics of 758 preterm infants. Values are numbers (percentages) unless stated otherwise

Mean (SD) birthweight (g)	1404 (293)
Mean (SD) gestation (weeks)	31.1 (2.7)
Males:females	376:382
Social class:	
I	49 (6)
II	128 (17)
III non-manual	70 (9)
III manual	307 (41)
IV	95 (13)
V	34 (4)
Other	75 (10)
Required intravenous feeding*	200 (26)
Ventilated for > 24 h	296 (39)
Neurologically impaired at follow up	56 (7)

*Feeding with amino acids with or without lipids.

TABLE III—Blood pressure in children aged 7·5–8 years in relation to randomised infant diet

Diets	No of subjects	Mean (SD) blood pressure (mm Hg)	
		Systolic	Diastolic
<i>Trial 1</i>			
Banked breast milk	66	98·7 (7·9)	61·0 (7·5)
Preterm formula	60	98·6 (9·5)	61·7 (7·3)
95% Confidence interval for difference		–3·0 to 3·2	–3·2 to 2·0
<i>Trial 2</i>			
Banked breast milk and mother's milk	133	99·3 (9·6)	61·4 (7·2)
Preterm formula and mother's milk	146	99·2 (9·8)	61·8 (7·3)
95% Confidence interval for difference		–2·2 to 2·4	–2·2 to 1·2
<i>Trial 3</i>			
Standard formula	68	103·4 (10·1)	60·4 (7·9)
Preterm formula	65	101·8 (10·8)	59·2 (8·0)
95% Confidence interval for difference		–1·6 to 5·8	–1·6 to 3·9
<i>Trial 4</i>			
Standard formula and mother's milk	111	100·4 (9·6)	59·8 (7·0)
Preterm formula and mother's milk	109	102·7 (9·5)	59·6 (7·0)
95% Confidence interval for difference		–4·9 to 0·2	–1·7 to 2·0
<i>All trials</i>			
Banked breast milk or standard formula*	378	100·2 (9·5)	60·7 (7·3)
Preterm formula*	380	100·6 (10·0)	60·7 (7·4)
		–1·7 to 1·1	–1·1 to 1·0

*With or without mother's milk.

TABLE IV—Systolic blood pressure according to diet in boys, girls, and children born small for their gestational age (birth weight <10th centile)

Diets	Boys	Girls	Children born small
<i>Trial 1</i>			
Banked breast milk:			
No of subjects	31	35	25
Mean (SD) blood pressure (mm Hg)	98·7 (8·5)	98·6 (7·5)	99·6 (7·2)
Preterm formula:			
No of subjects	25	35	21
Mean (SD) blood pressure (mm Hg)	98·1 (9·7)	98·9 (9·5)	101·8 (10·7)
95% Confidence interval for difference	–4·3 to 5·5	4·3 to 3·8	–7·5 to 3·1
<i>Trial 2</i>			
Banked breast milk and mother's milk:			
No of subjects	76	57	37
Mean (SD) blood pressure (mm Hg)	98·3 (9·2)	100·7 (10·2)	101·0 (11·3)
Preterm formula and mother's milk:			
No of subjects	80	66	52
Mean (SD) blood pressure (mm Hg)	100·5 (8·9)	97·7 (10·7)	98·1 (9·9)
95% Confidence interval for difference	–5·1 to 0·6	–0·7 to 6·8	–1·6 to 7·4
<i>Trial 3</i>			
Standard formula:			
No of subjects	35	33	23
Mean (SD) blood pressure (mm Hg)	103·7 (10·3)	103·0 (10·1)	100·9 (11·8)
Preterm formula:			
No of subjects	23	42	24
Mean (SD) blood pressure (mm Hg)	99·5 (11·4)	103·0 (10·3)	98·7 (12·0)
95% Confidence interval for difference	–1·6 to 10·0	–4·7 to 4·8	–4·7 to 9·3
<i>Trial 4</i>			
Standard formula and mother's milk:			
No of subjects	48	63	43
Mean (SD) blood pressure (mm Hg)	99·2 (9·9)	101·2 (9·3)	98·4 (9·3)
Preterm formula and mother's milk:			
No of subjects	48	51	42
Mean (SD) blood pressure (mm Hg)	101·6 (9·5)	104·0 (9·4)	102·5 (10·7)
95% Confidence interval for difference	–6·1 to 1·4	–6·3 to 0·7	–8·4 to 0·2
<i>All trials</i>			
Banked breast milk or standard formula*:			
No of subjects	190	188	128
Mean (SD) blood pressure (mm Hg)	99·6 (9·6)	100·9 (9·4)	99·8 (10·0)
Preterm formula*:			
No of subjects	186	194	139
Mean (SD) blood pressure (mm Hg)	100·4 (9·5)	100·7 (10·4)	100·1 (10·7)
95% Confidence interval for difference	–2·8 to 1·1	–1·8 to 2·2	–2·7 to 2·3

*With or without mother's milk.

TABLE V—Distribution of energy and protein intake and of growth of infants during hospital stay

	Centile				
	10th	25th	50th	75th	90th
Energy intake (MJ/kg/day)	0·313	0·356	0·410	0·456	0·510
Protein intake (g/kg/day)	1·8	2·0	2·3	2·6	3·0
Change in relative weight*	–2·4	–1·8	–1·3	–0·8	–0·2
Steady state weight gain (g/kg/day)†	9·5	12·1	14·5	16·9	19·7
Standard deviations from expected weight at discharge from hospital	–3·3	–2·9	–2·3	–1·5	–0·7

*Difference between number of standard deviations from expected birth weight and number of standard deviations from expected weight at discharge from hospital: negative value represents a fall.

†Weight gain after regaining birth weight.

proportion requiring intravenous feeding, and days on assigned diets did not differ between randomised groups.

ANALYSES ACCORDING TO DIET

Table III shows the main comparisons for the four parallel randomised trials. There were no differences in diastolic or systolic pressure in any trial. We also combined all four trials (preserving randomisation) to compare children fed low nutrient diets for preterm infants (donor milk or standard formula used alone or with mother's milk) with those fed the enriched preterm formula (alone or with mother's milk). There were no differences in blood pressure between these two groups.

Table IV shows that systolic blood pressure was unaffected by diet in major subgroups: boys, girls, children born small for their gestational age (birth weights <10th centile). Diastolic pressure was also unrelated to diet (results not shown). Early diet in babies with short gestation (>32 weeks) and prolonged hospital stay (28–120 days; median 42 days) did not affect later blood pressure.

The tendency to lower systolic values seen in the centres using banked breast milk reflected the use of non-automated devices to measure blood pressure in these centres (see methods section). This did not, however, affect comparisons within trials. Regression analysis with adjustment for the type of machine used did not reveal any dietary effect on blood pressure.

EPIDEMIOLOGICAL (NON-RANDOMISED) ANALYSES

Table V shows protein and energy intakes during hospital stay (median 30 days; maximum 120 days). There were considerable differences in macronutrient intake between individual infants, reflecting differences in randomised enteral diets and the variation in feed tolerance in these high risk infants. The infants also showed great variation in postnatal growth: 10% showed a fall in relative weight between 2·4 SD below expected birth weight and 4·1 SD below expected weight at discharge from hospital. Steady state weight gain (regressed best fit) after birth weight had been regained varied twofold between the 10th and 90th centiles, and the variation in the range was more than threefold. When the infants were discharged home close to term (mean 37 weeks' gestation) their weights showed extreme variation (full range 2·0 SD above to 5·4 SD below expected weight), reflecting the combined effects of in utero and postnatal (but pre-term) growth.

The five intake and growth variables tested in table V showed no association with systolic and diastolic blood pressure at 7·5–8 years of age even after adjustment for possible confounding factors including gestation, size for gestation, device used to measure blood pressure, sickness variables (patent ductus and duration of mechanical ventilation), and anthropometric indices at 7·5–8 years (mid-arm circumference, height, and body mass index). Table VI shows this lack of association.

Our conclusions were unaffected when analyses were confined to a low risk group, which excluded 56 infants with neurological impairment and those who had required ventilatory assistance. In previous analyses we showed that body weight at 7·5–8 years was positively related to both blood pressure at this age and to early growth.¹⁵ However, adjustment for body weight at 7·5–8 years did not significantly alter our findings here.

Discussion

Our data do not support the hypothesis that early nutrition programmes later blood pressure. The

TABLE VI—Protein and energy intake and indices of growth of 758 infants (divided by quartiles to give about 180–190 subjects in each subgroup) in relation to blood pressure at 7.5–8 years of age

	Mean (SD) blood pressure (mm Hg)	
	Systolic	Diastolic
Protein intake (g/kg/day):		
<1.9	101.0 (10.2)	60.3 (7.4)
1.9–2.1	100.9 (9.9)	60.5 (6.9)
2.2–2.6	100.4 (9.5)	60.7 (7.9)
>2.6	99.8 (9.6)	60.7 (7.8)
Energy intake (MJ/kg/day):		
<0.334	100.7 (10.1)	60.6 (7.5)
0.334–0.390	100.4 (9.8)	60.3 (7.0)
0.391–0.451	100.8 (9.2)	60.4 (7.8)
>0.451	100.0 (10.0)	60.9 (7.5)
Change in relative weight*:		
<–1.7	100.8 (9.0)	60.2 (7.3)
–1.7 to –1.1	100.2 (10.1)	60.2 (8.2)
–1.2 to –0.7	100.0 (9.9)	60.7 (7.0)
>–0.7	100.5 (10.7)	60.8 (7.4)
Steady state weight gain (g/kg/day)†:		
<12	100.2 (9.6)	59.9 (7.7)
12–14	100.4 (10.4)	60.2 (7.4)
15–17	100.2 (10.0)	60.9 (8.4)
>17	99.3 (9.6)	60.7 (6.9)
Standard deviations from expected weight at discharge from hospital		
<–2.8	100.2 (10.1)	60.3 (7.5)
–2.8 to –2.1	100.1 (10.2)	60.5 (7.5)
–2.2 to –1.4	99.8 (10.0)	59.7 (7.4)
>–1.4	101.4 (9.3)	61.4 (7.4)

*Difference between number of standard deviations from expected birth weight and number of standard deviations from expected weight at discharge from hospital: negative value indicates a fall.

†Weight gain after regaining birth weight.

relation between small size at birth and later raised blood pressure observed by some investigators^{7–10} had suggested an adverse effect of poor fetal nutrition, and hence growth, on long term regulation of blood pressure. The public health and clinical implication of this, in terms of achieving optimal nutrition in the fetus, has stimulated large investment in research in fetal nutrition. Reduced fetal growth, however, might be associated with non-nutritional factors that could explain the later outcomes. In order to test whether poor nutrition or poor growth before full term are critical factors for long term programming of blood pressure it was important to find a model in which these factors could be extricated from other influences on the fetus (for example, those provided by a deranged intrauterine environment). Our study of preterm infants in many respects provides this opportunity, but we did not find that nutritional or growth deficits before full term, even when extreme, programmed blood pressure 7.5–8 years later.

RATIONALE OF STUDY

In our recent analysis of birth weights of babies born before 34 weeks' gestation from this cohort we found that reduced size for gestation was not associated with raised blood pressure at 7.5–8 years of age—indeed, we found the opposite trend.¹⁵ Therefore, we hypothesised that the critical window for programming blood pressure might be late in gestation, beyond the time of birth of these preterm infants. We tested this in three ways.

Diet

At follow up we examined the blood pressures of children who had been assigned to different diets between preterm birth and, on average, full term (>37 weeks after mother's previous menstruation). We believe that this large randomised study is unique. There were substantial differences between groups in intakes of energy, protein, sodium, calcium, phosphorus, iron, zinc, copper, and several micro-nutrients,¹³ which were reflected by significant differences in early growth.⁶ If any one of these dietary components (such as protein or sodium) programmed later blood pressure then differences between groups might have been expected, yet none was seen. Indeed, we found no effect of early sodium intake on blood

pressure in these children at 18 months of age.¹⁶ There was also no difference in blood pressure between feed groups within large subpopulations previously shown to be most vulnerable to the effects of early diet,⁷ notably infants with retarded growth before birth and male infants.^{7,17} Earlier interim analysis had showed that boys in one subgroup (fed standard formula) had higher systolic blood pressure, but this was not confirmed here. In a balanced combination of our four trials, preserving randomisation and comparing low nutrient with high nutrient diets, we found no difference in blood pressure at 7.5–8 years despite the sample size (758 subjects) allowing us to detect a change of only 1.8 mm Hg in systolic pressure between groups at 5% significance and 80% power.

Protein and energy intake

We examined the two major components of nutrition, protein and energy intake, in relation to later blood pressure. Diets for the preterm infants differed greatly in protein and energy content (table I). Moreover, because of the difficulties feeding these infants, actual achieved protein and energy intakes in individuals averaged over hospital stay were even more variable, the lowest values resulting in changes in body composition seen in malnutrition.¹⁸ However, later blood pressures seemed unaffected by such large differences in intake.

Early growth

We assessed growth from birth (mean 31 weeks' gestation) to attainment, on average, of full term. During this time body weight status in 20% of our cohort fell, in relation to growth charts for preterm infants, by between 2 SD and 4 SD, providing an opportunity to explore the long term consequences of a degree of growth failure rarely seen in utero. Even extreme growth failure was not associated with programmed changes in later blood pressure. Failure to gain body length, common in preterm infants,⁶ was also unrelated to later blood pressure (unpublished results). Furthermore, the standard deviation of body weight from mean expected weight for age at discharge from hospital (a measure of the combined impact of prenatal and postnatal growth to near term) varied greatly, from 2 SD above to over 5 SD below the mean. This massive range of growth performance did not seem to influence later blood pressure.

COMPARISON WITH OTHER STUDIES

We considered why our findings might not have supported previous suggestions of the early nutritional origins of high blood pressure¹¹ based on its epidemiological association with low birth weight. Possibly 7.5–8 years of age was too early to detect a dietary effect since early influences on later blood pressure may be amplified throughout life.¹⁹ Nevertheless, "tracking" for blood pressure has been observed even from infancy,²⁰ and some studies have shown a relation between birth weight (in full term babies) and childhood blood pressure.⁹ Continued follow up of our cohort will resolve this. As in other studies, adjustment for current weight did not affect our findings.

Preterm infants might be demographically atypical, although social class distribution in our cohort (table II) was similar to that of the British population.²¹ Arguably, preterm infants might be intrinsically abnormal with an unusual pattern of blood pressure programming. However, if children with congenital defects are excluded (as was the case in our study) there is no evidence that premature babies are generally abnormal; rather, their postnatal illnesses usually reflect complications of immaturity. Moreover, our conclusions were unaffected even in infants who remained well (never needed respiratory assistance)

Clinical implications

- Epidemiological studies have shown that low birth weight, possibly indicating poor early nutrition, is associated with high blood pressure in later life
- Infants born prematurely were given controlled diets that varied in nutritional content until the time when they would normally have been born
- Infants showed extremes of nutrient intake and poor growth that would seldom occur in fetuses that were born at full term
- There was no association between early nutrition or growth and blood pressure measured at 7.5-8 years of age
- These results do not support nutritional intervention for pregnant women in order to prevent high blood pressure in their offspring

and who were subsequently neurologically unimpaired. Also, we calculate that Whincup's values for systolic blood pressure (based on two readings) in children aged 5-7 born at term²² were the same as those obtained by us with our first two readings (mean 104 mm Hg in each case). The reasons for growth retardation here might differ from those in full term infants. However, we wished to test if early nutritional or growth deficits in themselves programmed blood pressure; in that respect our cohort was uniquely suitable.

In previous studies of birth weight and later blood pressure, growth to full term occurred in utero; in our study part of this growth occurred postnatally. As a result of some complex interaction, possibly involving the placenta,²³ high blood pressure may be programmed only if poor nutrition and growth occur in utero. Alternatively, poor fetal growth may be associated with adverse non-nutritional factors such as hypoxia that could programme blood pressure. Regardless of mechanism, our data generate a new hypothesis, that preterm delivery of the growth retarded fetus (often practised when fetal morbidity is likely) could be beneficial by removing it from an adverse environment for blood pressure programming. Even if this is substantiated, however, the many risks of preterm delivery might outweigh any advantage.

CONCLUSION

This study does not negate the idea of nutritional programming. Indeed, our evidence from the same cohort of subjects shows that nutrition during a brief period before term may have profound long term consequences.^{2,7,17,24} Furthermore, our work does not challenge the observed association between birth weight (at full term) and later blood pressure, but it does not suggest that early growth failure or inadequate nutrition is in itself the explanation. If size at birth and later high blood pressure are causally related and not explained by unidentified confounding demographic factors then the wider search for aetiological clues must include further exploration of the relation between fetus and placenta and of the intrauterine environment found with retardation of fetal growth. However, in our view, it would be premature to devise nutritional interventions for mother or fetus in an attempt to prevent later hypertension.

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BMJ audit: Time to decisions and publication

Between 1 January 1994 and 30 June 1994 we met our target of making a decision on a paper within 56 days for 88% of all papers submitted and for 64% of those we eventually accepted. This is a small improvement on comparable figures of 86% and 62% in the last six months of 1993. We accepted 76% within 66 days (74% in the last six months of 1993), and the average time to accept a paper was 48 days (50 days in the previous six months). We met our target of 14 days to reject a paper that we did not referee 40% of the time (the same as the previous six months); 84% were rejected within 24 days (the same as the previous six months), and the average time to reject such papers was 18 days (the same as the previous six months).

We met our target of publishing original papers within eight weeks of acceptance in only 13% of cases (27% in the last six months of 1993); 24% were published within 10 weeks (66% in the previous six months); 57% within 12 weeks (85% in the previous six months); and 85% within 16 weeks