Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial

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Abstract

Objective To determine whether supplementation of infant formula milk with long chain polyunsaturated fatty acids (LCPUFAs) influences blood pressure in later childhood.
Design Follow up of a multicentre, randomised controlled trial.
Setting Four study centres in Europe.
Participants 147 formula fed children, with a reference group of 88 breastfed children.
Intervention In the original trial newborn infants were randomised to be fed with a formula supplemented with LCPUFAs (n=111) or a formula without LCPUFAs but otherwise nutritionally similar (n=126). In the present follow up study the blood pressure of the children at age 6 years was measured.
Main outcome measures Systolic, diastolic, and mean blood pressure.
Results 71 children in the LCPUFA supplementation group (64% of the original group) and 76 children in the non-supplementation group (60%) were enrolled into the follow up study. The LCPUFA group had significantly lower mean blood pressure (mean difference −3.0 mm Hg (95% confidence interval −5.4 mm Hg to −0.5 mm Hg)) and diastolic blood pressure (mean difference −3.6 mm Hg (−6.5 mm Hg to −0.6 mm Hg)) than the non-supplementation group. The diastolic pressure of the breastfed children (n=88 (63%)) was significantly lower than that of the non-supplemented formula group but did not differ from the LCPUFA formula group.
Conclusions Dietary supplementation with LCPUFAs during infancy is associated with lower blood pressure in later childhood. Blood pressure tends to track from childhood into adult life, so early exposure to dietary LCPUFAs may reduce cardiovascular risk in adulthood.

Introduction

Recent reports have linked breast feeding in infancy to lower blood pressure during childhood. Two longitudinal observational studies of term infants showed that children who were breast fed for at least three months had lower systolic and diastolic blood pressures in later childhood and adolescence than children who were formula fed. This difference remained after adjustment for known confounding variables.[1 2] A study involving preterm infants who had been randomised to be fed with banked breast milk had lower systolic and diastolic blood pressures at the age of 15 years than children who were fed term or preterm formula.[3]

The mechanisms underlying the relation between breast feeding in infancy and blood pressure during childhood are unclear. The study involving preterm infants found no difference in blood pressure of infants who were fed a term formula and infants who were fed a preterm formula that contained additional protein, energy, and minerals, including sodium.[3] Breast milk contains a wide range of substances—trophic substances, hormones, and specific nutrients—that are not included in formulas and that may influence blood pressure.

Considerable interest has been shown recently in the role of long chain polyunsaturated fatty acids (LCPUFAs), as these fatty acids are in breast milk but are not routinely available in formula milks.[4] During the first weeks of life preterm infants and some term infants may not be able to synthesise enough LCPUFAs to meet demand, and therefore infants fed with formula without supplementation may be relatively deficient in LCPUFAs, compared with breast-fed infants. As these fatty acids are preferentially incorporated into neural cell membranes, studies have predominantly focused on the influence of fatty acids on visual and cognitive development.[5 6] However, it is also known that LCPUFAs are incorporated into other cell membranes, including vascular endothelium.[7 8] Several studies have reported lower blood pressure in adults whose diet was supplemented with omega 3 fatty acids, but no published studies have looked at the effect of LCPUFA supplementation on blood pressure in children.[9 10]

In an earlier tolerance study of LCPUFA supplementation and its effect on cognitive development we randomly assigned newborn infants to be fed with a formula containing LCPUFAs or to a formula without LCPUFAs but otherwise nutritionally similar.[6 11] We therefore had the opportunity to further investigate the randomised groups to determine the relation of LCPUFA supplementation in infancy to blood pressure in later childhood.

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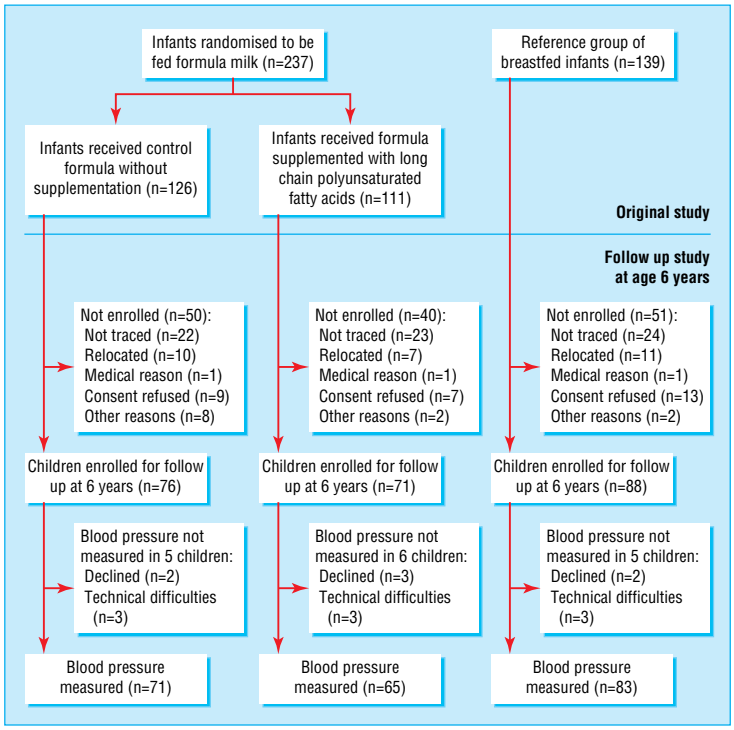
bmj.com 2003;326:953



Flow of participants through the original trial of infant formula feed and the follow up study at age 6 years

Methods

In 1992 six European centres took part in a multicentre, randomised controlled trial of a new infant formula that was supplemented with docosahexaenoic acid and arachidonic acid.[6] Four of the centres that contributed to this original tolerance and safety study agreed to take part in the present follow up study. Each centre (Dundee and Birmingham in the United Kingdom, Leuven in Belgium, and Milan in Italy) had a cohort of 6 year old children who as infants had been randomised to be fed one of the trial formulas and a reference group of breastfed children. Each centre obtained consent from the parent or guardian of the child. The figure shows the numbers of children who participated in the original trial and the follow up study.

The children had all been born between 37 and 42 weeks' gestation and weighed between 2500 g and 4000 g at birth. A computer generated randomisation table was used to assign the infants immediately after birth to a formula supplemented with LCPUFAs or a formula without supplementation. Permutated blocks of six were used, so that after every sixth infant the two groups were numerically balanced. Randomisation was stratified to ensure sex matching. Table 1 shows the composition of the formulas. The LCPUFA source was egg yolk, with approximately 70% of LCPUFAs being esters of phospholipids.

Table 1 Fatty acid composition (g per 100 g of fat) of the two infant formulas

Fatty acid	Formula with LCPUFA supplementation	Formula without supplementation
Linoleic acid	11.5 to 12.8	11.4
α linolenic acid	0.6 to 0.65	0.7
Arachidonic acid	0.3 to 0.4	<0.1
Docosahexaenoic acid	0.15 to 0.25	0

LCPUFA=long chain polyunsaturated fatty acid.

Each of the children was fed the trial formula during the first four months of life. Each month the children's weight, length, head circumference, subscapular skinfold thickness, and mid-arm circumference were measured. Other factors relating to safety and tolerance were also recorded.

In the present follow up study the children and their families were invited to attend a clinic or laboratory in the relevant study centre. During the visits, which took place between April 1998 and March 2000, a demographic and clinical questionnaire was completed and the child's blood pressure measured. Psychological assessments were also done (data not included).

Blood pressure was measured while the child was sitting on a chair with the right arm held in the horizontal position. In all centres staff used an automated blood pressure monitor (OMRON 711 Automatic IS, Omron Healthcare, Hamburg, Germany) with a child cuff (type 40S, 15-22 cm). Systolic, diastolic, and mean blood pressures were recorded as the average of three readings. Throughout both studies research assistants and parents or guardians were blind to the formula each child had received.

Previous studies have shown the standard deviation of childhood blood pressure measurements to be 8 mm Hg, and so we calculated that a sample size of 63 children in each group was needed to detect a difference of 4 mm Hg with a power of 80% at the 0.05 level of significance. We used Student's t test to compare normally distributed variables.

Results

Nearly two thirds (235/376) of the participants in the original tolerance and safety study were recruited to the present study (table 2). The figure shows the reasons for non-enrolment in the present study. Compared with the children from the randomised groups who took part in the follow up study, the children who did not take part had a lower birth weight (mean (SD) 3108 g (411 g) v 3292 g (397 g); P=0.001), length (49.8 cm (2.0 cm) v 50.5 cm (2.6 cm); P=0.04), and mid-arm circumference (10.1 cm (0.9 cm) v 10.5 cm (1.0 cm); P=0.007).

The mean age of the children at the time of blood pressure assessment was 70.1 months (SD 3.5 months). There were no demographic or anthropometrical differences between the two randomised groups at the time of the follow up (table 3). As expected, there were social differences between the formula fed children and the reference group of breastfed children: children who were breast fed had more siblings, fewer smokers in the family, older parents, and fathers who were more educated (table 4).

Six children declined to have their blood pressure measured. In 10 children technical difficulties resulted in unreliable data being obtained, and attempts to repeat the measurements were unsuccessful. The final analysis was on 219 children (65 in the LCPUFA group, 71 in the non-LCPUFA group, and 83 breastfed children).

Diastolic blood pressure was significantly lower in the LCPUFA group than in the non-LCPUFA group

Table 2 Proportions (percentage) of children in the original trial of types of infant formula who took part in the present follow up study

Centre	Formula with LCPUFA supplementation	Formula without supplementation	Breastfed children*	Total
Birmingham	11/14 (79)	6/15 (40)	16/26 (62)	33/55 (60)
Dundee	27/40 (68)	32/50 (64)	30/43 (70)	89/133 (67)
Leuven	19/30 (63)	20/30 (67)	24/38 (70)	63/98 (64)
Milan	14/27 (52)	18/31 (58)	18/32 (56)	50/90 (56)
Total	71/111 (64)	76/126 (60)	88/139 (63)	235/376 (63)

LCPUFA=long chain polyunsaturated fatty acid.
*Reference group.

Table 3 Characteristics of children in the original trial of types of infant formula who were enrolled into the follow up study. Figures are means (SD) except where otherwise indicated

Characteristics	Formula with LCPUFA supplementation (n=71)	Formula without supplementation (n=76)
Demographic characteristics		
Age of mother (years) at follow up	34.2 (5.8)	34.6 (5.4)
Age of mother (years) at completion of education	18.4 (3.4)	18.0 (2.8)
Age of father (years) at follow up	36.1 (5.8)	36.0 (4.7)
Age of father (years) at completion of education	17.7 (3.1)	17.9 (2.6)
No of mothers married or with partner/No of single mothers*	61/8	69/6
No of children in home	2.1 (1.0)	2.0 (0.9)
No of smokers in household	0.82	0.74
Sex ratio (male/female) in group	41/30	37/39
Gestation (weeks)	39.4 (1.5)	39.5 (1.3)
Child's age at assessment (months)	70.1 (3.8)	70.0 (3.1)
Anthropometry at birth		
Weight (g)	3293 (438)	3291 (359)
Crown-heel length (cm)	50.5 (2.8)	50.5 (2.5)
Occipitofrontal circumference (cm)	34.7 (1.4)	34.8 (2.4)
Mid-upper arm circumference (cm)	10.5 (1.1)	10.4 (0.9)
Subscapular skinfold (mm)	4.7 (1.2)	4.6 (0.9)
Triceps skinfold (mm)	4.8 (1.2)	4.8 (0.9)

LCPUFA=long chain polyunsaturated fatty acid.
*Marital status of three mothers not known.

Table 4 Characteristics of children in the original trial of types of infant formula who were enrolled into the follow up study, compared with reference group of breastfed children. Figures are means (SD) except where otherwise indicated

Characteristics	Formula fed children (n=147)	Breast fed children (n=88)	P value
Age of mother (years) at follow up	34.4 (5.6)	35.9 (4.1)	0.031
Age of mother (years) at completion of education	18.2 (3.1)	18.9 (3.6)	0.111
Age of father (years) at follow up	36.0 (5.3)	39.2 (5.1)	0.0001
Age of father (years) at completion of education	17.8 (2.8)	19.5 (4.8)	0.003
No of mothers married or with partner/No of single mothers*	130/14	78/5	0.239
No of children in home	2.1 (1.0)	2.5 (1.2)	0.01
No of smokers in household	0.78 (0.75)	0.35 (0.60)	0.0001

(table 5). Systolic blood pressure was also lower, but not significantly. However, mean blood pressure was significantly lower in the LCPUFA group than in the non-LCPUFA group. The blood pressure of the breastfed children was 92.5 mm Hg systolic (SD 9.7 mm Hg) and 57.5 mm Hg diastolic (SD 8.5 mm Hg). The diastolic pressure of breastfed children was significantly lower than that of the non-LCPUFA group (mean difference −3.4 mm Hg (95% confidence interval −6.8 mm Hg to −0.01 mm Hg; P=0.02)) but did not differ from that of the LCPUFA group.

Discussion

Blood pressure at age 6 years was lower in children who as infants had been fed with a formula supplemented with LCPUFAs than in children who were fed a formula without LCPUFAs. Blood pressure in the reference group of breastfed children was similar to that in the supplemented formula group, but a direct comparison of the two groups is not possible because of confounding variables (including milk composition, age and education of fathers, and family history of smoking).

Table 5 Blood pressure (mm Hg) at age 6 years in children who as infants had been randomised to be fed with formula supplemented with long chain polyunsaturated fatty acids or with formula without supplementation

Blood pressure	Supplemented formula (n=65)	Formula without supplementation (n=71)	Mean difference (95% CI)	P value
Mean	74.8	77.8	−3.0 (−5.4 to −0.5)	0.02
Diastolic	57.3	60.9	−3.6 (−6.5 to −0.6)	0.018
Systolic	92.4	94.7	−2.3 (−5.3 to 0.7)	0.132

Strengths and limitations of the study

The multicentre cohort consisted of children who were born healthy at full term and who were randomised at birth to one of the study formulas. The infants remained on the assigned formula for four months, but data on subsequent diet were not collected. Nearly two thirds of the original group took part in the present study of blood pressure. Social characteristics of the children who did not take part in the follow up study did not differ from those of the participants, but mean weight, length, and mid-arm circumference at birth were all lower in the children who did not participate. The impact of these anthropometrical differences on our results is uncertain. However, it has been shown that the amount of stored LCPUFAs at birth is directly related to birth weight[12]; it could therefore be postulated that the effect of LCPUFA supplementation in lowering blood pressure might have been more marked among the children who did not take part in the present study.

Mechanisms of action

The mechanisms underlying the relation of LCPUFAs to blood pressure remain uncertain. Several studies of adults with hypertension have shown that an increased dietary intake of omega 3 fatty acids is associated with lower blood pressure.[9] A double blind, placebo controlled trial showed that docosahexaenoic acid but not eicosapentaenoic acid lowered ambulatory blood pressure in overweight men.[10] The authors of this trial reported in another study of the same cohort that docosahexaenoic acid enhanced dilatory responses to sodium nitroprusside and attenuated constrictor responses to noradrenaline.[13] These data are supported by animal studies that have shown lower blood pressure in rats that were fed a diet enriched with docosahexaenoic acid, compared with rats on a control diet.[14 15] Data relating omega 6 fatty acids to blood pressure are more limited. One study of weanling male rats showed that systolic blood pressure was inversely related to intake of linoleic acid.[16] In our study the concentration of linoleic acid was similar in the two formulas, and it is uncertain whether the additional arachidonic acid in the trial formula influenced this metabolic pathway.

Implications

Our results support an association between early nutritional intervention and health benefits in later life. Whether the influence of LCPUFAs on blood pressure would have been stronger with a longer period of supplementation is uncertain. A recent animal study noted higher blood pressure in adult rats that were deficient in omega 3 fatty acids in the perinatal period, and this increase in blood pressure was not prevented by later repletion with fatty acids.[17]

Blood pressure is known to track from childhood into adult life, and deviations from normal blood pressure during childhood are amplified in later life.[18] Our findings are therefore relevant to public health strategies aimed at improving the long term health of the population. It has previously been reported that lowering a population's diastolic blood pressure by even a few millimetres can significantly reduce hypertension, coronary heart disease, and stroke.[19 20] These benefits can be achieved by simple dietary measures early in life.

What is already known on this topic

Breast milk contains long chain polyunsaturated fatty acids, and breastfed children have lower blood pressure than children fed with formula milk

Blood pressure differences in childhood are known to carry through into adulthood

Dietary omega 3 fatty acid supplementation can lower blood pressure in adults with hypertension

What this paper adds

Supplementation with long chain polyunsaturated fatty acids in infancy results in lower blood pressure later in childhood

We thank the original investigators in Leuven (E Eggermont) and Milan (M Giovannini) for their contributions. M Smith and A Elliot (Dundee), A McNaughton (Birmingham), H Daniels and M Huybens (Leuven), and L Gianni (Milan) undertook the assessments.

Contributors: JSF and PW designed the study, analysed the data, and contributed to the writing of the paper. JB, PC, and CA discussed the study design, supervised the study in Birmingham, Leuven, and Milan, respectively, and edited the paper. GB was involved in the initial implementation and monitoring of the study.

Funding: Research grant from Milupa (Friedrichsdorf, Germany).

Competing interests: JSF, PW, and CA have received research support from Milupa and other milk formula companies and honorariums for speaking at and attending conferences that were partly or wholly sponsored by these companies.

Ethical approval: All centres obtained ethical approval from the relevant authorities.

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(Accepted 7 March 2003)