Original Article

Effect of omega 3 and omega 6 fatty acid intakes from diet and supplements on plasma fatty acid levels in the first 3 years of life

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Background: The optimal method for conducting omega (n–)3 polyunsaturated fatty acid (PUFA) supplementation trials in children is unknown. Aim: To assess the impact of n–3 and n–6 PUFA intake from the background diet on plasma levels of n–3 and n–6 PUFA in children aged 0-3 years, with and without n–3 supplementation. Methods: Subjects were randomised antenatally to receive either n–3 PUFA supplements and low n–6 PUFA cooking oils and spreads or a control intervention, designed to maintain usual fatty acid intake. Dietary intake was assessed at 18 months by 3–day weighed food record and at 3 years by food frequency questionnaire. Plasma phospholipids were measured at both time points. Associations were tested by regression. Results: N–3 PUFA intake from background diet did not significantly affect plasma n–3 levels. In contrast, n–6 PUFA intake in background diet was positively related to plasma n–6 levels in both study groups. In addition, n–6 PUFA intake from diet was negatively associated with plasma n–3 levels at 18 months and 3 years (–0.16%/g n–6 intake, 95%CI –0.29 to –0.03 and –0.05%/g n–6 intake, 95%CI –0.09 to –0.01, respectively) in the active group, but not in the control group. Conclusion: Interventions intending to increase plasma n–3 PUFA in children by n–3 supplementation should also minimise n–6 PUFA intake in the background diet.

Key Words: omega–3 fatty acids, omega–6 fatty acids, dietary supplements, plasma, dietary intake

INTRODUCTION

There have been several reports of beneficial effects of n–3 fatty acids in the prevention or treatment of human disease. Dietary supplementation aimed at increasing plasma levels of n–3 long-chain polyunsaturated fatty acids (LC-PUFA) has been shown to be beneficial in treatment of depression[1] and developmental coordination disorder[2] in children. Some, but not all, trials of LC-PUFA supplementation in infancy have shown beneficial effects on visual, neural and developmental outcomes.[3] Beneficial effects have also been observed in trials of fish-oil supplements or of diets high in n–3 fatty acids for secondary prevention of adverse cardiovascular outcomes in adults.[4]

Cross-sectional studies in children have also suggested protective effects of n–3 LCPUFAs on asthma[5] although our recent randomised controlled trial of fish oil supplementation during the first five years of life did not show any beneficial effects on the risk of developing asthma by age five years.[6] Furthermore, the negative findings of the intention-to-treat analysis have recently been confirmed by a post-hoc analysis which examined the effect of actual intake of supplements, adjusted for compliance, background dietary intake of n–3 and n–6 LC-PUFA, and plasma n–3 phospholipids measured on three occasions over the five-year study period on respiratory and allergic disease outcomes at age five years.[7] Also, a meta-analysis of randomised controlled trials of fish oil supplementation in people with asthma did not find consistent evidence of any beneficial effects.[8] Hence, the beneficial effects of n–3 LC-PUFA supplementation have been established for some outcomes but not for others.

Interest in the putative protective effects of supplementation with n–3 LC-PUFA continues because the proposed mechanism is the down-regulation of the inflam

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matory leukotriene LT-B4, in which n–3 LC-PUFAs play a role.[9,10] However, n–6 PUFAs tend to compete biochemically with n–3 LC-PUFAs, and thus, may impede their anti-inflammatory effects.[10-13] Evidence that n–6 PUFAs are an independent risk factor for asthma and atopy is largely ecological.[8,14,15] Despite the potential interaction between n–6 and n–3 PUFAs, none of the trials assessed in the Cochrane review attempted to control or examine dietary n–6 PUFA intake in the fish oil supplemented groups.[8]

The impact of background dietary sources of n–6, and n–3, LC-PUFA on plasma levels of n–3 LC-PUFA, which is important in investigations of n–3 LC-PUFA for therapeutic purposes, remains unknown. In our randomised controlled trial of n–3 LC-PUFA supplementation for the prevention of asthma, we did attempt to minimise n–6 LC-PUFA intake from oils and spreads and we measured background dietary intake of n–3 and n–6 LC-PUFA. In this current paper, we use data from the Childhood asthma prevention study (CAPS) clinical trial to investigate the effects of fatty acids in the background diet, in modifying the effect of the n–3 supplement on n–3 levels in plasma phospholipids, as measured at age 18 months and 3 years.

MATERIALS AND METHODS

The study design has been described in detail previously and only key features are presented here. The study was a randomised, parallel-group controlled trial using a factorial design that separately tested two interventions: dietary fatty acid modification and house dust mite avoidance.

The study was approved by the Human Research Ethics Committees of the University of Sydney, Children's Hospital Westmead, and Western and South Western Sydney Area Health Services. Informed consent was obtained from a parent prior to any study related procedure.

Subjects

Between September, 1997 and November, 1999 we recruited pregnant women, whose unborn children were at increased risk of developing asthma, because one or more parents or siblings had asthma or wheeze. We excluded those with a pet cat at home, strict vegetarians, women with a non-singleton pregnancy, and infants born earlier than 36 weeks gestation.[16] We randomised participants, after signed consent was obtained at approximately 36 weeks gestation, into active intervention or control groups for both HDM avoidance and dietary fatty acid modification using a procedure that we have described previously.[16]

Dietary Intervention

The aim of the active diet intervention was to increase the total intake of omega–3 fatty acids and decrease the total intake of omega–6 fatty acids using fish oil supplements, and monounsaturated cooking oils and spreads in preparing children's food. We added the contents of tuna oil 500mg capsules to formula of infants from the time they started bottle-feeding or to solid foods from age six months, whichever was earlier. The capsules contained 37% omega–3 and 6% polyunsaturated fatty acids, 24% monounsaturated fatty acids, 28% saturated fatty acids and 5% minor fatty acids. The dose of long chain PUFAs DHA and EPA were 128 mg and 30 mg, respectively, per capsule. Subjects in the intervention group were also supplied with cooking oils and margarines containing approximately 16% omega–6 fatty acids, 6% omega–3 fatty acids and 40% omega 9 fatty acids.[16]

The control diet was designed to maintain omega–3 and omega–6 polyunsaturated fatty acids at levels currently seen in the Australian population (low omega–3 and high omega–6 intake). The control group were provided 500mg Sunola oil capsules containing 0.3% omega–3 and 7% omega–6 polyunsaturated fatty acids, 82% monounsaturated fatty acids, 9% saturated fatty acids and 1.7% minor fatty acids. The families in the control group were supplied with polyunsaturated cooking oils and margarines containing approximately 40% omega–6, 20% omega 9 and 1.2% omega–3 polyunsaturated fatty acids.

Supplementation with oil capsules began when the child commenced bottlefeeding or at age six months, which ever was earlier. Replacement of usual cooking oils and spreads began when solid foods were introduced to the child's diet.

Dietary Assessment

Dietary assessments at 18 months and three years measured background dietary intake of n–3 and n–6 PUFA including that contributed by the cooking oils and spreads supplied as part of the active diet intervention or control diet.

At age 18 months, data on food consumption were collected using three-day weighed food records including one weekend day. A research dietitian instructed mothers on how to keep records and issued a food record booklet and set of Tanita digital kitchen scales (2.0 kg x 1.0 g). At the end of the recording period, the dietitian visited subjects' homes to collect the records and check them for completeness and accuracy, including brand names of foods and supplements recorded.[17]

Details of the response rate for the WFR have been reported elsewhere.[17] In brief, 90% of 533 participants approached agreed to keep food records and 460 (86%) actually did so. Of these, 36 were excluded either because the records were incomplete, the quality of the data was poor, the child's food intake on these days was atypical due to illness affecting food intake, or because the child was breastfeeding more than twice per day and therefore the quantity of energy and food consumed could not be measured accurately. The final number of WFR analysed for this paper was 424, representing an 80% response rate among those who were asked to keep records.[17]

Food and beverage items and weights (adjusted for leftovers), were checked, coded and entered into the nutrient analysis program (M & H Williams, Sydney, SERVE version 3.95 1998) based on the Australian Composition of Foods (National Foods Authority, Canberra, NUTTAB95 version 3.0 1995) to derive nutrient data for all foods eaten on each eating occasion.[17] Average fatty acid values over the 3 days (g/day) were calculated from a data base of the fatty acid composition of Australian

foods compiled by Mann[18] included in the SERVE nutrient analysis program.

Dietary intakes of n–3 and n–6 PUFA were measured at three years using a semi-quantitative food frequency questionnaire (FFQ).[19,20] The parent, as a proxy for the child was asked to complete the dietary questionnaire describing the usual frequency of selected foods and the quantities of these in relation to a reference serve, consumed by their child over the past year. Average daily intakes of omega–3 and omega–6 fatty acids (g/day) were calculated using the fatty acid food composition data base by Mann.[18] Of 526 subjects approached, 456 (75%) parents completed the FFQ. Fatty acid intake from breastmilk was not quantified, as very few mothers were still breastfeeding their children at 18 months, and none were doing so at 3 years.

Fatty Acid analysis

Plasma samples were collected by venipuncture from children at 18 months (n=393) and 3 years (n=400) and were analysed for plasma phospholipids by gas chromatography at the Flinders Medical Centre, Adelaide. Details of the assay methods have been reported elsewhere.[21] Plasma n–3 and n–6 PUFA for each subject were expressed as a percentage of total fatty acids.

Statistical Analysis

Differences in medians between study groups were tested by the Wilcoxon test. The association between intakes from background diet and plasma levels of fatty acids was assessed using multiple regression, separately for the active intervention and control diet groups, thus taking into account those with and without supplementation with n–3 fatty acids. Results were expressed as regression coefficients to indicate the difference in plasma PUFA levels as per unit intake of PUFA. All statistical analyses were carried out using SAS (Version 9.1).

RESULTS

As previously reported, at 18 months and 3 years plasma n–3 PUFAs were significantly higher, and plasma n–6 PUFAs were substantially and significantly lower, in the active intervention group than in the control group (Table 1).[6,7] Similarly, dietary intake of n–3 was significantly higher and intake of n–6 PUFAs (including that from the supplied cooking oils and spreads, and background diet) significantly lower in the intervention group compared with the control group at both 18 months and 3 years (Table 1).[7] There was no difference in saturated, monounsaturated and total PUFA intake between the two diet groups at either time point. The background diet of subjects in this cohort has been described recently.[22,23]

We found no significant associations between dietary intake of n–3 PUFA and plasma n–3 or plasma n–6 PUFA levels in either the active intervention or control groups at 18 months or three years (Table 2). By contrast, n–6 PUFA levels in the diet were inversely related to n–3 PUFA levels in plasma at 18 months and 3 years in the active dietary intervention group. Among children in the active intervention group, a one gram increase in the dietary intake of n–6 PUFA was associated with a 0.16% decrease in plasma n–3 PUFA levels at 18 months and a 0.05% decrease in plasma n–3 PUFA at three years (Table 2). There was no significant effect of dietary intake of n–6 PUFA on plasma n–3 PUFA levels in the control group.(Table 2) As might be expected, dietary intake of

Table 1. Fatty acid intake and plasma phospholipid proportions by diet intervention group

	Diet Intervention Group				
	Active		Control		
	n	Median (Inter-quartile range)	n	Median (Inter-quartile range)	*p* value‡
At age 18 months					
Background Diet measured by weighed food record (g/day) †					
Saturated Fatty Acids	216	21.50 (17.35 to 26.15)	209	21.30 (16.10 to 26.60)	0.8849
Monounsaturated Fatty Acids	216	13.65 (11.45 to 16.75)	209	12.60 (10.50 to 15.60)	0.0336
Total PUFAs	244	3.60 (2.80 to 4.90)	232	3.65 (2.80 to 4.90)	0.8563
n–3 PUFAs	216	0.40 (0.20 to 0.60)	208	0.20 (0.10 to 0.30)	<0.0001
n–6 PUFAs	216	2.80 (2.20 to 3.45)	208	3.55 (2.50 to 5.15)	<0.0001
n–6:n–3 PUFAs ratio	216	7.25 (5.20 to 11.00)	208	18.33 (13.86 to 26.00)	<0.0001
Plasma (% of total fatty acids)					
n–3 PUFAs	202	6.52 (5.30 to 7.92)	191	4.82 (4.28 to 5.41)	<0.0001
n–6 PUFAs	202	32.56 (30.66 to 33.81)	191	35.06 (33.29 to 36.42)	<0.0001
At Age Three years					
Background Diet measured by food frequency questionnaire (g/day) †					
Saturated Fatty Acids	253	42.73 (33.67 to 55.16)	249	42.73 (33.15 to 57.56)	0.3394
Monounsaturated Fatty Acids	253	34.00 (25.40 to 40.81)	249	32.62 (24.25 to 43.60)	0.6029
Total PUFAs	253	13.85 (10.31 to 17.54)	249	12.44 (9.54 to 16.99)	0.5436
n–3 PUFAs	235	1.28 (0.91 to 1.96)	221	1.18 (0.87 to 1.47)	0.0054
n–6 PUFAs	235	10.58 (7.93 to 14.44)	221	12.21 (15.84 to 8.75)	0.0145
n–6:n–3 PUFAs ratio	235	9.01 (4.89 to 11.80)	221	10.75 (8.24 to 12.75)	<0.0001
Plasma (% of total fatty acids)					
n–3 PUFAs	203	5.67 (5.67 to 7.00)	197	4.61 (4.13 to 5.11)	<0.0001
n–6 PUFAs	203	33.17 (31.72 to 34.67)	197	35.71(34.23 to 37.00)	<0.0001

†Including supplied oils and spreads but not including supplements
‡Difference between intervention groups tested by Wilcoxon Rank Sum Test

Table 2. Effect of background dietary intake of n–3 and n–6 PUFA on plasma phospholipid proportions of these fatty acids by diet intervention group

	Diet intervention Group			
	Active		Control	
Measure of PUFA Intake (g/day)	Difference† in plasma n–3 PUFA (%) per g PUFA intake (95% CI)	Difference† in plasma n–6 PUFA (%) per g PUFA intake (95% CI)	Difference† in plasma n–3 PUFA (%) per g PUFA intake (95% CI)	Difference† in plasma n–6 PUFA (%) per g PUFA intake (95% CI)
Diet at 18 months (WFR)				
n–3 PUFAs	0.05 (–0.98 to 1.08)	–0.60 (–1.79 to 0.59)	0.42 (–0.34 to 1.17)	–1.58 (–3.29 to 0.13)
n–6 PUFAs	–0.16 (–0.29 to –0.03)	0.58 (0.43 to 0.73)	–0.04 (–0.11 to 0.03)	0.37 (0.21 to 0.53)
Diet at three years (FFQ)				
n–3 PUFAs	0.21 (–0.10 to 0.51)	–0.19 (–0.68 to 0.30)	0.39 (0.00 to 0.77)	–0.43 (–1.11 to 0.25)
n–6 PUFAs	–0.05 (–0.09 to –0.01)	0.13 (0.06 to 0.19)	–0.01 (–0.06 to 0.03)	0.08 (0.01 to 0.16)

WFR = Weighed food record
FFQ = Food frequency questionnaire
Results shown in bold are $p < 0.05$
† Regression coefficients are shown. These represent the difference in plasma PUFA levels as per unit intake of PUFA.

n–6 PUFA was positively associated with plasma n–6 PUFA levels in both the active diet intervention and control groups at 18 months and three years, with a stronger association in the active group than the control group on both occasions.

DISCUSSION

The aim of the CAPS active dietary intervention was to maximise n–3 PUFA plasma levels by providing the children with fish oil supplement capsules and minimising known sources of n–6 PUFA intake in the diet, partly by replacement with n–3 PUFA rich spreads and oils. These interventions achieved higher n–3 PUFA and lower n–6 PUFA levels in the diet, as well as in the measured concentrations of plasma phospholipids, in the active intervention group compared to the control group.[7]

Our finding that higher intakes of n–6 fatty acids in the diet, were associated with lower levels of n–3 PUFAs in plasma demonstrates that the effectiveness of n–3 supplementation in increasing plasma n–3 PUFA levels is enhanced by restricting background dietary intake of n–6 PUFA. This finding supports earlier findings that n–6 PUFAs biochemically compete with n–3 PUFAs.[10-13] Volker at al,[12] included subjects with an intake of n–6 PUFAs of less than 10g per day, and found that n–3 LC-PUFA was sufficiently incorporated into the cells at this level of n–6 dietary intake. In our study a much lower intake of n–6 PUFAs from the diet (median intake of 2.80g) had adverse effects on plasma n–3 PUFAs. This suggests that the quantity of n–6 PUFAs in the diet that is needed to minimise down-regulation of plasma n–3 PUFAs may vary for different populations and age groups.

We attempted to minimise the intakes of n–6 PUFAs in the active diet intervention group by providing spreads and oils low in n–6 PUFAs, although we made no attempt to modify other sources of n–6 PUFAs in the diets of these children. N–6 PUFAs are widely distributed in foods in the Australian diet and the most likely sources were fat spreads and cooking oils, fats included in cereal based products (including biscuits, pies, cakes, pastry), meats and fried potatoes.[5,24,25] It is possible that the families chose to use oils and spreads which they purchased themselves, and/or that the children consumed larger amounts of other foods high in n–6 PUFAs. If so, this may have limited the magnitude of the increase in plasma n–3 PUFA in the active diet intervention group. Our findings suggest that decreasing the intake of n–6 PUFAs in order to maximise the effects of supplementation of n–3 PUFAs may require a more intensive intervention than simply supplying low n–6 PUFA oils and spreads.

N–3 PUFA intake from the background diet had no influence on plasma levels of n–3 PUFA in either the active or control diet intervention groups. This is presumably attributable to the very low intakes of n–3 PUFA in the diets of most children, emphasising the importance of supplementation in order to achieve an increase in plasma n–3 PUFA levels.

In this analysis, we used two different measurement tools to assess dietary intakes, each of which has different strengths and applications. WFR, the method we used at 18 months, is generally regarded as the most precise method for measuring quantities of foods and nutrients consumed by individuals[26] but may not fully reflect "usual intakes" of infrequently consumed foods. Thus, intakes of foods high in n–3 and n–6 PUFAs which may be infrequently consumed may have been underestimated by the WFR. By contrast, the FFQ, as used in the CAPS study at age 3 years, attempts to measure 'usual' intake, and often ranks individuals relatively accurately with regard to their usual intakes of selected foods and nutrients. However, its precision in generating point estimates for food and nutrient intakes of individuals tends to be low. [26] The FFQ used in this study has previously been used to rank dietary intake of n–3 and n–6 PUFAs in children,[5, 27] but has not been assessed for its validity in measuring absolute intakes of PUFAs in comparison with another dietary assessment method, or in relation to plasma n–6 PUFAs. Nevertheless, the consistency between our findings of the relationships between dietary intakes and plasma levels of n–3 and n–6 PUFAs at 18 months and three years supports the validity of both dietary assessments for this purpose.

In conclusion interventions intending to increase plasma n–3 PUFA in children by n–3 supplementation should explore methods for reducing the n–6 PUFA intake in background diet to effectively minimise n–6 PUFA intake.

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AUTHOR DISCLOSURES

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Original Article

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從飲食及補充品中攝取 n–3 及 n–6 脂肪酸對出生 3 年內血漿脂酸含量的影響

背景：對年幼兒童，如何實施 n–3 多元不飽和脂酸補充試驗是最合適的，仍然未知。目的：評估 0–3 歲兒童從飲食攝取 n–3 及 n–6 多元不飽和脂酸，及有無補充 n–3 脂肪酸，對血漿中 n–3 及 n–6 多元不飽和脂酸含量的影響。方法：研究對象在出生前被隨機分派到 n–3 多元不飽和脂酸補充和低 n–6 烹調油及抹油組或介入控制組(維持一般的脂肪酸攝取)中。在研究對象 18 個月大及 3 歲時，分別利用三天飲食秤重記錄法及飲食頻率問卷來評估飲食攝取。並在這兩個時間點分析血漿磷脂質，利用迴歸法來測試相關性。結果：從飲食攝取的 n–3 多元不飽和脂酸並不會顯著影響血漿 n–3 脂酸的含量。相反地，兩組幼童從飲食攝取的 n–6 多元不飽和脂酸與血漿 n–6 脂酸的比率有顯著的正相關。此外，在實驗組中從飲食攝取的 n–6 多元不飽和脂酸與 18 個月大及 3 歲時的血漿 n–3 脂酸比率之間呈現負相關（分別是-0.16%/克 n–6 脂酸，95%CI 為-0.29 至-0.03 以及-0.05%/克 n–6 脂酸，95%CI 為-0.09 至-0.01），控制組則無此相關。結論：若想增加兒童血漿中 n–3 多元不飽和脂酸而介入 n–3 脂酸補充，應同時使飲食攝取的 n–6 多元不飽和脂酸降低。

關鍵字：n–3 脂肪酸、n–6 脂肪酸、膳食補充、血漿、膳食攝取