

Original article

Omega-3 and omega-6 fatty acid exposure from early life does not affect atopy and asthma at age 5 years

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Background: The Childhood Asthma Prevention Study was a randomized controlled trial conducted in children with a family history of asthma in whom omega-3 fatty acid supplementation and restriction of dietary omega-6 fatty acids did not prevent asthma, eczema, or atopy at age 5 years.

Objective: We sought to examine the relation of all measures of omega-3 and omega-6 polyunsaturated fatty acids with outcomes at age 5 years in the whole birth cohort, regardless of randomization group.

Methods: Plasma fatty acids were measured at 18 months, 3 years, and 5 years. Compliance with the fatty acid supplements was estimated every 6 months. Dietary intake was assessed at 18 months by means of weighed-food record and at 3 years by means of food-frequency questionnaire. At age 5 years, 516 children were examined for wheeze and eczema (questionnaire) and atopy (skin prick tests, $n = 488$). Multiple logistic regression was used to evaluate associations between exposures and outcomes.

Results: Plasma levels of omega-3 or omega-6 fatty acids were not associated with wheeze, eczema, or atopy at age 5 years ($P = .11-.96$). Overall, fatty acid exposure, measured as plasma

levels, dietary intake, and compliance with supplements, was not associated with any respiratory or allergic outcomes ($P = .35-.59$).

Conclusion: This observational analysis of the cohort, using the full range of observed variation in omega-3 and omega-6 fatty acid exposure, supports the negative findings of the randomized controlled trial.

Clinical implications: Modification of dietary polyunsaturated fatty acids in early childhood is not helpful in preventing atopy and asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, allergy and immunology, birth cohort, child, eczema, omega-3 fatty acids, omega-6 fatty acids, primary prevention

The recent increase in asthma and allergic diseases has partly been attributed to environmental changes, such as dietary intake of polyunsaturated fatty acids. Some observational and ecologic studies showed beneficial associations between dietary intake of oily fish, which is rich in omega-3 fatty acids, and asthma and allergic diseases in childhood.¹⁻³ However, others have not been able to replicate this,⁴⁻⁶ and some studies have shown the contrary.^{7,8} A Cochrane meta-analysis of randomized controlled trials with a duration of more than 4 weeks conducted in individuals with established asthma concluded that there is no consistent effect of omega-3 polyunsaturated fatty acid supplementation on asthma symptoms, asthma medication use, lung function, or bronchial hyperresponsiveness in adults or children.⁹ However, before the Childhood Asthma Prevention Study (CAPS),¹⁰ there had been no previous trials designed to establish the effect of omega-3 fatty acids in the primary prevention of asthma in children.

In CAPS, children were randomized to the active or control arms of a diet intervention. The active diet group received fish oil supplements high in omega-3 polyunsaturated fatty acids along with fat spreads and cooking oils to minimize omega-6 polyunsaturated fatty acid intake, whereas the control group received oil supplements and cooking oils and spreads high in omega-6 polyunsaturated fatty acids. At age 5 years, the active diet intervention had no effect on the prevalence of atopy or asthma.¹¹ Subjects in the active intervention group had a significantly higher proportion of omega-3 fatty acids and a lower proportion

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Abbreviations used

CAPS: Childhood Asthma Prevention Study

DHA: Docosahexaenoic acid

EPA: Eicosapentaenoic acid

FFQ: Food-frequency questionnaire

WFR: Weighed-food record

of omega-6 fatty acids in plasma than the control group. However, these differences were relatively small, and it is plausible that they were not large enough to yield detectable differences in the prevalence of atopy or asthma. To explore further the relationship between fatty acid exposure and these outcomes, we examined all sources of variation in omega-3 and omega-6 levels, including observed plasma levels, compliance with supplements, and dietary intake at ages 18 months and 3 years in relation to outcomes at age 5 years. If an absence of association was found in this *post hoc* analysis, this would add strength to the negative conclusion of the randomized controlled trial. On the other hand, if there was an association between observed fatty acid exposure and outcomes, this might justify a further trial with more vigorous modification of fatty acid intake in the intervention group.

METHODS

Study design and subjects

CAPS is a randomized controlled trial designed to test the effectiveness of interventions to reduce house dust mite levels and to increase the intake of omega-3 fatty acids through a supplement, both separately and in combination, on the presence of asthma and allergic diseases. The design of the study, sample recruitment, criteria for inclusion, and data collection procedures have been described in detail elsewhere.¹⁰ In brief, pregnant women whose unborn child had at least 1 parent or sibling with current asthma or frequent wheeze were recruited antenatally and randomized to one of 4 study groups before the first home visit at 36 weeks' gestation. Six hundred sixteen subjects born between September 1997 and November 1999 were enrolled.

Diet intervention

The aim of the active diet intervention was to increase the total intake of omega-3 polyunsaturated fatty acids and decrease the total intake of omega-6 polyunsaturated fatty acids by using fish oil capsules and monounsaturated cooking oils and spreads for use in preparing the children's food. The oil capsules contained 500 mg of tuna fish oil, which comprised 37% omega-3 polyunsaturated and 6% omega-6 fatty polyunsaturated acids, 24% monounsaturated fatty acids, 28% saturated fatty acids, and 5% minor fatty acids, and the cooking oils and margarines contained approximately 16% omega-6 fatty acids, 6% omega-3 fatty acids, and 40% omega-9 fatty acids.

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 diet group was provided 500 mg of Sunola oil (Crisco-Meadow Lea Foods Inc, Sydney, Australia) 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 control group received 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 bottle-feeding or at age 6 months, whichever was earlier. Replacement of usual cooking oils and fat spreads began when solid foods were introduced to the child's diet.

Assessment of respiratory and atopic outcomes

Clinical outcome assessments were performed at ages 18 months, 3 years, and 5 years. Parents were interviewed about symptoms and diagnoses relevant to asthma and allergic disease by using a *pro forma* questionnaire, and the children were examined.

Atopy was measured with skin prick tests to the inhalant allergens *Dermatophagoides pteronyssinus* (house dust mite), cockroach, cat, *Alternaria alternata*, rye grass, and a grass mix and the ingested allergens salmon, peanut, cow's milk, egg, and tuna (Hollister-Stier, Spokane, Wash). Glycerin and histamine (6 mg/mL) were used as negative and positive controls, respectively. The weal size was measured at 10 minutes as the mean of the largest diameter and its perpendicular, each measured to the nearest millimeter. Weal sizes of 2 mm or larger and sizes larger than those produced by the negative control were defined as positive.

At age 5 years, spirometric function was measured as previously described.¹¹

Subjects were defined as having recent wheeze if the parent reported any period of wheezing in the last 18 months at the 18-month and 3-year assessments and in the last 12 months at the 5-year assessment.

Atopy was defined as the presence of any one or more positive allergen skin prick test results.

Probable current asthma at age 5 years was defined as a parental report of any wheeze in the previous 12 months in addition to either of the following conditions: a parental report of diagnosed asthma at 18 months, 3 years, or 5 years or a greater than 12% increase in FEV₁ after bronchodilator at 5 years.

Eczema was defined as the presence of flexural eczema on inspection or by parental report of a history of itchy rash coming and going for a period of 3 months or more together with a history of seeking medical care for eczema and/or using steroid or emollient creams in the last 18 months at the 18-month and 3-year assessments and in the last 12 months at the 5-year assessment.

Assessment of dietary intake

Dietary intake of fatty acids was measured at 18 months by using a 3-day weighed-food record (WFR), which is described in detail elsewhere.¹² In brief, parents described, weighed, and recorded all foods and beverages consumed by their child over a 3-day period (2 weekdays and 1 weekend day). These weights were adjusted for the amount of leftovers. Food and beverage items and weights were entered into the nutrient database (SERVE version 3.95; M&H Williams, Sydney, Australia) based on Australian Composition of Foods (NUTTAB95 version 3.0; National Foods Authority, Canberra, Australia) to determine average daily nutrient intakes. Average daily fatty acid intakes were calculated from a database of the fatty acid composition of Australian foods.¹³ Omega-3 and omega-6 polyunsaturated fatty acid intakes were calculated in grams per day.

Dietary intake of fatty acids was measured at 3 years by using a semiquantitative food-frequency questionnaire (FFQ) modified from one developed by the Commonwealth Scientific and Industrial Research Organisation, Division of Human Nutrition, Adelaide, South Australia, and applied previously in children.² 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 serving consumed by their child over

the past year. Average daily intakes of omega-3 and omega-6 polyunsaturated fatty acids in grams were calculated by using the same database of fatty acid composition of Australian foods as that used for analyses of the WFR.¹³

Assessment of omega-3 and omega-6 levels in plasma

Blood was collected at ages 18 months, 3 years, and 5 years for measurement of plasma phospholipids by means of gas chromatography. Results for omega-3 and omega-6 polyunsaturated fatty acids were expressed as percentages of total fatty acids.

Assessment of compliance

Oil capsule supplements were given to subjects in the early stages of the study in blister packs and from March 2000 in bottles. From the time bottles were introduced, consumption of oil capsules was estimated at 6-month intervals by measuring the difference in the weight of bottles of capsules dispensed and returned and dividing by the capsule weight. Because subjects were expected to consume 1 capsule per day, the number of capsules consumed was divided by the number of days to estimate the percentage compliance over this period. Compliance was averaged over the duration of the study.

Omega-3 and omega-6 fatty acid exposure from diet, capsules, and plasma

Omega-3 and omega-6 intake from supplements was calculated from the dose of omega-3 and omega-6 contained in the capsules (in grams) that the child was randomized to receive multiplied by the average capsule compliance of that child over the study period.

Plasma omega-3 and omega-6 levels were measured as a percentage of total fatty acids, and the levels were averaged over the 3 measurement occasions.

Statistical analysis

Comparison of the difference between the mean levels of the exposure variables by active or control dietary study group was done with *t* tests.

Multiple logistic regression was used to test 2 models for the association of wheeze, atopy, eczema, and probable current asthma at age 5 years with omega-3 and omega-6 exposure variables. In the first model the exposure variables were plasma omega-3 and omega-6 levels at 18 months, 3 years, and 5 years. In the second model the exposure variables included plasma omega-3 and omega-6 levels at 18 months, 3 years, and 5 years and dietary intake at 18 months and 3 years and capsule intake over the 5 years. The likelihood ratio test from the logistic regression was used to test whether all the variables in each model predicted the clinical outcome for that model. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs), along with *P* values.

All analyses were performed with SAS version 9.1 (SAS, Inc, Chicago, Ill).

Ethics approval for this study was obtained from the ethics committees of the Children's Hospital at Westmead; The South Western, Western, and Central Sydney-area Health Services; and the University of Sydney.

RESULTS

Outcome data at age 5 years were available for 516 participants (83.8% of the 616 randomized subjects). Of these, 375 (72.6%) completed the spirometry, and 488 (94.6%) had skin prick tests. Blood samples were taken

from 393 (71.5%) at 18 months, 400 (75.5%) at 3 years, and 396 (76.7%) at 5 years. WFRs were available for 424 (77.1%) subjects at 18 months, and FFQs were completed by 456 (86.0%) subjects at 3 years. Compliance information was available for all 516 children at 5 years. Complete information on outcomes at 5 years, blood samples at the 3 occasions, diet intake at 2 occasions, and compliance was available for 189 subjects. There was no difference in plasma fatty acid levels or levels of omega-3 or omega-6 fatty acids from dietary intake between the groups with complete and incomplete data, although a difference was seen in the percentage complying with taking the supplements (58.9% vs 49.7%, respectively). Children with incomplete data were slightly more likely to have mothers with a history of asthma and parents with fewer years of education and to have been exposed to environmental tobacco smoke than the children with complete data ($P = .01-.04$).

As we have previously shown, plasma omega-3 levels were significantly higher and plasma omega-6 levels were significantly lower in the active diet intervention group at 18 months, 3 years, and 5 years when compared with levels in the control group ($P < .0001$).¹¹ This was also the case for dietary intake of omega-3 and omega-6 from both the WFR and FFQ (Table I). Average oil capsule compliance over the 5 years was about 6% higher for those in the control group than in the active group ($P = .03$).

There was no association between plasma levels of omega-3 or omega-6 at 18 months, 3 years, or 5 years with respiratory and allergic outcomes at 5 years (individual $P > .05$, model $P = .11-.96$; Table II).

Omega-3 and omega-6 fatty acid intake from the diet at 18 months and 3 years and from fatty acid supplementation throughout the 5 years were not related to respiratory and allergic outcomes at 5 years (individual $P > .05$, model $P = .39-.85$; data not shown).

The overall effect of omega-3 and omega-6 fatty acid exposure based on information on plasma levels and intakes from diet and trial supplements were included as predictors of clinical outcomes. This revealed no association with any clinical outcomes (model $P = .35-.59$, Table III). Adjusting for potential confounders and excluding those with incomplete data did not change the odds ratios.

DISCUSSION

We found no association between plasma levels of omega-3 or omega-6 polyunsaturated fatty acids at 18 months, 3 years, and 5 years and the prevalence of asthma or wheezing illness, eczema, or atopy at 5 years. Furthermore, the overall effect of omega-3 and omega-6 fatty acids, based on information about plasma levels, intake from supplements, and intake from diet revealed no association with these clinical outcomes. These negative results strengthen the main result from the randomized controlled trial, in which an intervention to increase omega-3 fatty acids and decrease omega-6 fatty acids

TABLE I. Descriptive statistics for fatty acid exposure variables in the diet intervention and control groups

Variable	Units	Total N	Diet intervention group						Difference		t test P value
			Active			Control					
			n	Mean	SD	n	Mean	SD	Mean	95% CI	
Plasma omega-3	% Total fatty acid										
18 mo		393	202	6.737	1.899	191	5.032	1.214	1.705	1.387 to 2.023	<.0001
3 y		400	203	6.044	1.486	197	4.789	1.238	1.255	0.986 to 1.524	<.0001
5 y		396	202	5.863	1.316	194	5.049	1.088	0.814	0.575 to 1.053	<.0001
Average 18 mo, 3 y, 5 y*		511	260	6.154	1.342	251	4.992	1.059	1.162	0.952 to 1.373	<.0001
Plasma omega-6	% Total fatty acid										
18 mo		393	202	32.512	2.804	191	34.996	2.752	−2.484	(−3.035 to −1.932)	<.0001
3 y		400	203	33.132	2.557	197	35.625	2.303	−2.493	(−2.972 to −2.014)	<.0001
5 y		396	202	33.596	1.984	194	35.397	1.834	−1.801	(−2.179 to −1.424)	<.0001
Average 18 mo, 3 y, 5 y*		511	260	33.149	1.976	251	35.255	1.899	−2.106	(−2.443 to −1.769)	<.0001
Ratio plasma omega-3/omega-6	Ratio of % total fatty acid										
18 mo		393	202	0.210	0.064	191	0.146	0.041	1.424†	1.344 to 1.509	<.0001
3 y		400	203	0.185	0.053	197	0.136	0.043	1.353†	1.285 to 1.425	<.0001
5 y		396	202	0.176	0.047	194	0.144	0.036	1.219†	1.163 to 1.279	<.0001
Average 18 mo, 3 y, 5 y*		511	260	0.187	0.046	251	0.142	0.036	1.305†	1.254 to 1.359	<.0001
WFR omega-3 (18 mo)	g/d	424	216	0.458	0.315	208	0.231	0.251	0.227	0.172 to 0.281	<.0001
WFR omega-6 (18 mo)	g/d	424	216	3.457	2.677	208	4.283	2.808	−0.826	(−1.350 to −0.303)	.0021
FFQ omega-3 (3 y)	g/d	456	235	1.510	0.780	221	1.271	0.555	0.238	0.113 to 0.363	.0002
FFQ omega-6 (3 y)	g/d	456	235	11.749	5.615	221	12.802	5.575	−1.053	(−2.084 to −0.023)	.0452
Average oil capsule compliance	% Full compliance	539	275	50.244	31.009	264	55.757	28.636	−5.513	−10.570 to −0.457	.0324
Capsule omega-3	g/d	539	275	0.093	0.057	264	0.001	0.0004	0.092	0.085 to 0.099	<.0001
Capsule omega-6	g/d	539	275	0.015	0.009	264	0.020	0.010	−0.004	−0.006 to −0.003	<.0001

*Average levels over the 3 assessments, including all recordings. One child might have participated only on 1 or 2 occasions.

†Geometric mean difference.

from birth to 5 years of age did not have any effect on the prevalence of atopy or asthma at 5 years.¹¹

Some observational studies have demonstrated an association between a high dietary intake of fish and a reduced prevalence of asthma or atopic disease. Peat et al¹ showed that in a population of 1217 seven- to 11-year-old children of mainly Asian decent, eating fish at least once a week decreased the odds of bronchial hyperresponsiveness by 0.35-fold (0.1-0.9). In another study of 486 children 8 to 11 years of age, those who ate oily fish (high in omega-3 fatty acids) more than once a week were less likely to have current asthma than those who ate nonoily fish or no fish at all (OR, 0.26; 95% CI, 0.09-0.72), although fish intake was not associated with wheeze and bronchial hyperresponsiveness.² Other more recent studies do not support the hypothesis of a protective role of omega-3 fatty acids in children⁶ or adults.^{7,14} However, it is possible that cross-sectional studies might be subject to bias and confounding because fish consumption could be a marker for other influential dietary, socioeconomic, and lifestyle factors.

There are few randomized controlled studies on the effect of omega-3 fatty acid supplementation as treatment in children with established asthma. Nagakura et al¹⁵ presented the results of a trial suggesting that dietary

supplementation with fish oil rich in the omega-3 polyunsaturated fatty acid is beneficial for children with asthma; however, the 10-month trial was performed in an environment in which exposure to inhalant allergens and diet were strictly controlled. On the contrary, Hodge et al¹⁶ gave 8- to 12-year-old children with asthma dietary enrichment of omega-3 polyunsaturated fatty acids over 6 months, which increased the plasma levels of these fatty acids but had no effect on the clinical severity of asthma in the study children. These 2 studies were included in a Cochrane meta-analysis of 9 randomized controlled trials conducted in adults and children with established asthma, which concluded that there is no consistent effect of omega-3 polyunsaturated fatty acid supplementation on asthma symptoms, asthma medication use, lung function, or bronchial hyperresponsiveness.⁹ One reason for the diverse results in different trials might be the dose given. In the trial by Nagakura et al,¹⁵ daily doses were matched for body weight, eicosapentaenoic acid (EPA; 7.0–26.8 mg/kg body weight), and docosahexaenoic acid (DHA; 7.3–11.5 mg/kg body weight), whereas in the Hodge trial the children were given 720 mg of EPA and 480 mg of DHA daily. These doses were used with the intention of treating established asthma and were much higher than the doses administered in CAPS (ie, 30 mg of EPA and

TABLE II. Association of omega-3 and omega-6 plasma fatty acids at 18 months, 3 years, and 5 years and allergic or respiratory outcomes at 5 years (n = 257)

Outcome	Exposure	OR	95% CI	Overall <i>P</i> value
Wheeze	Plasma omega-3			.49
	18 mo	1.00	0.82-1.21	
	3 y	0.92	0.68-1.25	
	5 y	0.82	0.61-1.13	
	Plasma omega-6			
	18 mo	1.05	0.95-1.17	
Atopy	3 y	0.94	0.83-1.07	.96
	5 y	0.95	0.80-1.12	
	Plasma omega-3			
	18 mo	0.93	0.78-1.13	
	3 y	1.06	0.80-1.39	
	5 y	1.08	0.82-1.43	
Eczema	Plasma omega-6			.61
	18 mo	1.00	0.91-1.09	
	3 y	1.05	0.93-1.18	
	5 y	0.99	0.85-1.15	
	Plasma omega-3			
	18 mo	0.93	0.73-1.18	
Probable current asthma	3 y	1.15	0.84-1.58	.11
	5 y	0.92	0.66-1.29	
	Plasma omega-6			
	18 mo	1.01	0.90-1.13	
	3 y	0.91	0.79-1.04	
	5 y	1.03	0.86-1.23	
Probable current asthma	Plasma omega-3			.11
	18 mo	0.78	0.60-1.03	
	3 y	1.08	0.77-1.52	
	5 y	0.88	0.62-1.25	
	Plasma omega-6			
	18 mo	1.04	0.92-1.17	
	3 y	0.86	0.75-1.00	
	5 y	0.94	0.78-1.14	

Multiple logistic regression with the likelihood ratio test was used to evaluate whether all variables included in the model predict the clinical outcome.

128 mg of DHA), in which the aim was to prevent atopy and asthma. It might be argued that we could have found a significant effect if the daily dose of omega-3 fatty acids had been increased as the children grew older or had we been able to further reduce omega-6 intake in the background diet. However, the dose of omega-3 fatty acid we used is 3 times the adequate intake level for children in the revised Nutrient Reference Values for Australia and New Zealand,¹⁷ and it is highly unlikely that more interventions would be practical, given the lower compliance with the fish oil supplement and the moderate omega-6 intakes in the background diet of the active group despite the provision of low omega-6 spreads and oils to this group.

Our study is the only randomized controlled trial of the effect of polyunsaturated long-chain fatty acids on the primary prevention of atopy and asthma up to the age of 5 years. The strengths of our study are several, including the 5-year duration of the trial conducted from birth and the information available about omega-3 and omega-6 fatty acid exposure from plasma fatty acid measures on 3 occasions, data on compliance with supplements every 6

months, and dietary intake collected at 2 separate occasions using 2 distinct methods. The most direct measure of exposure to omega-3 and omega-6 fatty acids in the study population is the plasma levels of fatty acids. It is possible that some variation in overall fatty acid exposure is not reflected in these 3 single-point-in-time measures, which is why we have estimated the actual intake of omega-3 and omega-6 fatty acids from supplements as the product of the dose in the capsules that the child was randomized to receive and the average compliance over the study period. Yet we cannot exclude the possibility that parents might have been using the capsules for themselves or other family members or might have discarded the contents of the bottle. Those in the control group recorded slightly higher levels of compliance (55.8%) than those in the active group (50.2%), which might be due to the fact that the omega-3 oil capsules had a slight fish smell and taste.

We acknowledge that there is a potential for effect attenuation in this study and that measurement error in the dietary assessments and the infrequent plasma measurements might have limited our ability to detect an

TABLE III. Association of omega-3 and omega-6 fatty acid levels in plasma and fatty acid intakes from diet and supplements to allergic and respiratory outcomes at 5 years (n = 189)

Outcome	Exposure	OR	95% CI	Overall P value
Wheeze	Plasma omega-3 (18 mo)	0.91	0.69-1.18	.533
	Plasma omega-3 (3 y)	1.07	0.72-1.57	
	Plasma omega-3 (5 y)	0.74	0.51-1.07	
	Plasma omega-6 (18 mo)	1.01	0.89-1.16	
	Plasma omega-6 (3 y)	0.94	0.79-1.11	
	Plasma omega-6 (5 y)	0.98	0.80-1.20	
	WFR omega-3	1.08	0.31-3.79	
	WFR omega-6	1.05	0.92-1.19	
	FFQ omega-3	1.28	0.74-2.21	
Atopy	FFQ omega-6	0.97	0.90-1.05	.592
	Plasma omega-3 (18 mo)	0.84	0.66-1.08	
	Plasma omega-3 (3 y)	1.37	0.95-1.97	
	Plasma omega-3 (5 y)	1.08	0.77-1.51	
	Plasma omega-6 (18 mo)	1.00	0.88-1.13	
	Plasma omega-6 (3 y)	1.08	0.92-1.28	
	Plasma omega-6 (5 y)	0.89	0.73-1.08	
	WFR omega-3	0.58	0.17-1.90	
	WFR omega-6	1.01	0.89-1.14	
Eczema	FFQ omega-3	1.14	0.68-1.90	.587
	FFQ omega-6	1.00	0.93-1.07	
	Plasma omega-3 (18 mo)	0.85	0.62-1.17	
	Plasma omega-3 (3 y)	1.06	0.69-1.64	
	Plasma omega-3 (5 y)	0.87	0.57-1.33	
	Plasma omega-6 (18 mo)	0.95	0.81-1.11	
	Plasma omega-6 (3 y)	0.86	0.70-1.05	
	Plasma omega-6 (5 y)	0.96	0.76-1.22	
	WFR omega-3	1.14	0.29-4.59	
Probable current asthma	WFR omega-6	1.01	0.86-1.18	.354
	FFQ omega-3	0.65	0.32-1.34	
	FFQ omega-6	1.00	0.91-1.10	
	Plasma omega-3 (18 mo)	0.73	0.52-1.03	
	Plasma omega-3 (3 y)	1.20	0.77-1.86	
	Plasma omega-3 (5 y)	0.83	0.54-1.27	
	Plasma omega-6 (18 mo)	1.08	0.91-1.28	
	Plasma omega-6 (3 y)	0.90	0.74-1.10	
	Plasma omega-6 (5 y)	0.99	0.78-1.25	
	WFR omega-3	0.62	0.11-3.40	
	WFR omega-6	0.93	0.79-1.10	
	FFQ omega-3	1.56	0.84-2.89	
	FFQ omega-6	0.97	0.88-1.06	

Multiple logistic regression adjusted for capsule omega-3 and capsule omega-6 intake. The likelihood ratio test was used to evaluate whether all variables included in the model predict the clinical outcome.

association between fatty acid exposures and outcomes. However, we believe that the measurements of plasma levels, dietary intake, and data on compliance together provide a rigorous estimate of fatty acid exposure and complement the treatment assignment analysis reported in the primary study article. Small differences in the characteristics of those with complete and incomplete data for the analyses in this article did not influence the associations between exposure and respiratory outcomes, and thus selection bias did not influence our findings.

We also accept that the effect of variation in dietary exposure to fatty acids might be less in this cohort with presumed strong genetic risk factors for asthma. However,

it is in a high-risk cohort such as this one that preventive interventions are most needed, and therefore the negative findings are relevant to policy and practice.

In conclusion, this study found no overall beneficial effect of omega-3 fatty acid exposure by using information on plasma levels and intakes from diet and supplements over the first 5 years of life on atopy or asthma at age 5 years. These negative results strengthen the key finding from the randomized controlled trial, in which no significant difference was observed in respiratory or allergic outcomes between the intervention and control diet groups, despite a significant difference in the levels of omega-3 and omega-6 fatty acids over the study period.¹¹

The implication of our results is that on the basis of current evidence, fatty acid supplementation in infants cannot be recommended as an effective measure for the primary prevention of asthma. Other hypotheses to explain the apparent protective association between oily fish consumption and asthma among children, such as influential dietary, socioeconomic, and lifestyle factors, should be further explored.

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