Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial[1–4]

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ABSTRACT

Background: Evidence suggests that asthma is rooted in the intrauterine environment and that intake of marine n−3 polyunsaturated fatty acids (n−3 PUFAs) in pregnancy may have immunomodulatory effects on the child.

Objective: Our aim was to examine whether increasing maternal intake of n−3 PUFAs in pregnancy may affect offspring risk of asthma.

Design: In 1990, a population-based sample of 533 women with normal pregnancies were randomly assigned 2:1:1 to receive four 1-g gelatin capsules/d with fish oil providing 2.7 g n−3 PUFAs (n = 266); four 1-g, similar-looking capsules/d with olive oil (n = 136); or no oil capsules (n = 131). Women were recruited and randomly assigned around gestation week 30 and asked to take capsules until delivery. Among 531 live-born children, 528 were identified in registries and 523 were still alive by August 2006. Diagnoses from the International Coding of Diseases version 10 were extracted from a mandatory registry that recorded diagnoses reported from hospital contacts.

Results: During the 16 y that passed since childbirth, 19 children from the fish oil and olive oil groups had received an asthma-related diagnosis; 10 had received the diagnosis allergic asthma. The hazard rate of asthma was reduced by 63% (95% CI: 8%, 85%; P = 0.03), whereas the hazard rate of allergic asthma was reduced by 87% (95% CI: 40%, 97%; P = 0.01) in the fish oil compared with the olive oil group.

Conclusion: Under the assumption that intake of olive oil in the dose provided here was inert, our results support that increasing n−3 PUFAs in late pregnancy may carry an important prophylactic potential in relation to offspring asthma. *Am J Clin Nutr* 2008;88: 167–75.

INTRODUCTION

Although the cause of asthma remains enigmatic (1), several different lines of evidence point toward the possibility that asthma may be rooted in the intrauterine environment of the person (2). The ratio between Th1 and Th2 cells of the immune system are of crucial importance in asthma (3), and the critical period of establishment of the Th1-Th2 balance lies in the early life period (4). Further, most asthma cases are apparent in early childhood, and several maternal and birth characteristics are associated with offspring risk of asthma. Maternal smoking (5), infections (6, 7), and antibiotic use (8) during pregnancy are all associated with increased risk of atopic diseases in the offspring, and so have low birth weight (8), preterm delivery (9), and cesarean delivery (10)

Maternal diet may also matter. Antioxidants (11), vitamin D (12), vitamin A (13), folate (14), and food-born pollutants (15) have been implicated. The most promising dietary factor in relation to asthma might, however, be the marine n−3 polyunsaturated fatty acids (n−3 PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which may affect immune function through several different mechanisms. The incorporation of EPA and DHA in cell membranes leads to decreased availability of arachidonic acid and increased competition for both the cyclooxygenase and lipoxygenase enzymes, resulting in decreased synthesis of arachidonic acid–derived eicosanoids (2, 16–19). Prostaglandin E2 (PGE2) is reduced, which in turn may alter the balance of Th1 and Th2 cytokines, and so is the production of leukotrienes (20), which play an important role in asthma (21).

Two retrospective observational studies have supported the possibility that marine n−3 PUFAs in pregnancy might prevent against offspring atopy (22, 23), and so have 3 recent prospective studies (24–26); whereas 1 large prospective study could not substantiate the hypothesis (27). So far, the randomized controlled trials (RCTs) (28–30) in the field have been too small (*n*

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[2] The study sponsor was not involved in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

[3] Supported by the European Union FP6 consortium, Early Nutrition Programming Project (EARNEST; project No. FOOD-CT-2005-007036), The Danish Obesity Research Centre by grant 2101-06-0005 from the Danish Strategic Research Council, The Lundbeck Foundation (grant R13-A907), and The Danish Medical Research Council (grant 271-07-0289).

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Received March 17, 2008.

Accepted for publication April 8, 2008.

< 100) and have had too short of a follow-up period to evaluate this question in a meaningful way; their findings on biochemical indexes, however, suggest a beneficial effect of fish oil.

In 1990, we conducted an RCT with fish oil supplementation among 533 pregnant women. Taking fish oil was associated with longer gestation (31), affected the maternal thromboxane and prostacyclin production (32), and increased the concentrations of n−3 PUFAs in umbilical blood and tissues (33). The aim of the present study was to examine the hypothesis that these children also have a reduced risk of being diagnosed with asthma during their childhood and early adolescence.

SUBJECTS AND METHODS

Study population and data collection

The trial was based in the main midwife clinic in the city of Aarhus, Denmark, which covers a well-defined geographic area. The regional ethics committee approved the original protocol. We wrote to all women scheduled to attend the routine midwife assessment at week 30 from November 1989 until July 1990, explained the study, and invited them to participate. We excluded women with a history of placental abruption in a previous pregnancy or a serious bleeding episode in the present pregnancy. Other exclusion criteria were multiple pregnancies, allergy to fish, and regular use of fish oil or prostaglandin inhibitors. The women were interviewed at entry about lifestyle factors and after delivery about compliance and side effects. Information was also available from a routine self-administered questionnaire in week 16 of gestation, from birth certificates and hospital records, and from a postpartum questionnaire.

Ethics

In 1989, we were granted permission from the Scientific Ethical Committee System to conduct the trial. In 2006, we asked the National Board of Health for permission to undertake the present study. Because the study technically is a pure registry linkage study, there was no requirement or need, according to Danish law of regulations, to contact the Scientific Ethical Committee System for obtaining permission.

Intervention products

The active treatment was four 1-g gelatin capsules daily providing Pikasol fish oil (Lube Ltd, Hadsund, Denmark): 32% EPA and 23% DHA, together with 2 mg tocopherol/mL added to prevent autooxidation of EPA and DHA. This corresponds to ≈2.7 g marine n−3 PUFA/d. One control group received four 1-g capsules of olive oil daily (72% oleic acid and 12% linoleic acid), and the second control group received no supplement. The gelatin capsules and their boxes looked identical. We included the olive oil control group mainly to reduce the risk of "contamination" caused by self-supplementation with fish oil or by increased fish consumption. We chose olive oil rather than other fats for these reasons: because we could find no biological evidence suggesting an effect of oleic acid on length of gestation, because a plant oil high in linoleic acid would be more likely to interact with endogenous eicosanoid metabolism, and because olive oil was more likely to appeal to the women than a preparation consisting mainly of saturated fat. Nevertheless, the appropriateness of olive oil had been questioned, so we included a second control group who received no supplement. The original trial was dimensioned to enable detection of a difference in mean birth weight of 200 g between the fish oil and olive oil groups at type I and type II error rates of 0.05 and 0.2, respectively.

Randomization and steps taken to optimize compliance

Women were randomly assigned to 3 groups in the ratio of 2:1:1, described in detail earlier (31). Various measures were taken to optimize and assess compliance and to reduce contamination. Before trial entry we made sure that each woman understood that she might be allocated to any 1 of the 3 groups. Boxes of capsules were handed out at the entry interview and all 3 later visits; the subjects were asked to return the boxes each time so that the number of capsules taken could be estimated (by weighing the boxes).

Food intake at baseline

A simple food-frequency questionnaire was applied at random assignment that enabled stratification into 3 categories: women with low, medium, and high habitual intake of fish (31).

Offspring asthma

All citizens in Denmark receive a unique 10-digit personal identification number with a link from mother to child and vice versa. We used this as entry to extract information from the National Patient Registry (NPR) about the children. The NPR is a mandatory national hospital discharge registry, which for many years has recorded virtually all discharge diagnoses for hospitalizations in Denmark (34). From 1994 it also recorded diagnoses from ambulatory visits. The registry also records emergency room visits resulting in an asthma diagnosis. Most asthma diagnoses in the registry are likely to have been given by general pediatricians or pediatricians subspecialized in pulmonology. The NPR introduced the International Coding of Diseases version 10 (ICD-10) in 1994. For each child we extracted information about the following diagnoses given during the period from birth of the child in 1990 until August 2006: ICD-10 codes DJ45 (asthma); DJ450 (allergic asthma); DJ451 (asthma bronchiale nonallergicum); DJ458 (asthma of mixed type); DJ459 (asthma without specification); DJ469 (status asthmaticus); DJ301–304 (allergic rhinitis); DL200, DL208, DL208A, and DL209 (atopic dermatitis); and the corresponding ICD-8 codes 49300, 49301, 49302, 49308, 49309, and 69100. The information included the contact date with the health care system which had resulted in one of these diagnoses. The asthma diagnoses of the NPR have recently been validated (35).

Analytic strategy

We had decided a priori to test the study hypothesis by comparing the fish oil group with the olive oil group. This decision was taken because we assumed the latter to meet the main criteria for a placebo regimen, ie, that olive oil in the dose provided is inert in relation to the endpoint under study and that masking was efficient in that group (these assumptions are discussed and substantiated in "Discussion"). First, we would compare them with respect to occurrences of any type of asthma in the offspring (primary hypothesis) and, second, with respect to occurrences of allergic asthma (secondary hypothesis). All analyses were planned as intention to treat. Because data were available, we decided to also examine occurrences of asthma in the group in

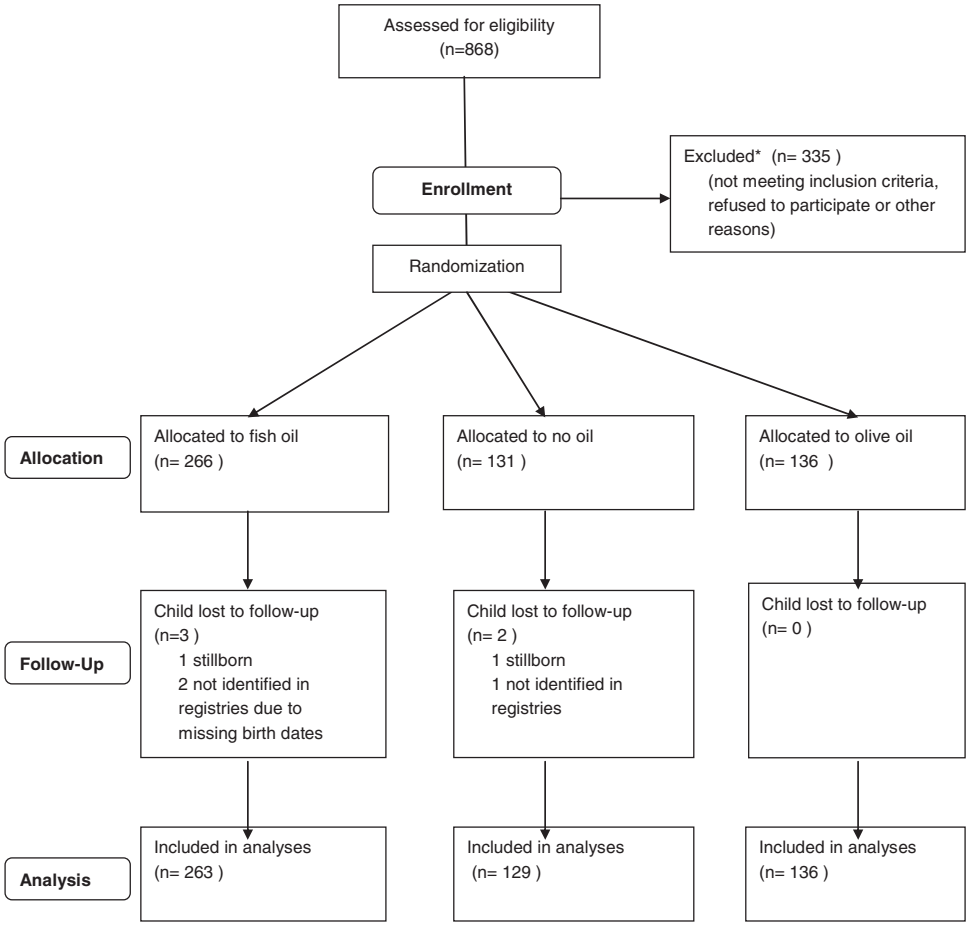

FIGURE 1. Flow chart of 16-y follow-up of offspring from a randomized controlled trial of fish oil supplementation in pregnancy. *Baseline characteristics of participants and nonparticipants are available from earlier publications (29, 31).

which mothers were allocated to receive no oil capsules; however, this was not part of our a priori hypothesis. At a reviewer's suggestion, we also undertook an analysis in which we expanded the asthma diagnosis to also cover 2 other allergy-relevant diagnoses, ie, atopic dermatitis and allergic rhinitis.

Statistical methods

We used a Cox regression model with age as the underlying time variable and time of first asthma diagnosis as event time, the latter being censored at 1 August 2006 or time of death, whichever came first. The statistical software package SAS 9.1.3 (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Child identification 16 y later

Of the 533 randomly assigned fetuses, 531 children were born alive. Of these children, 528 were identified in registries and 522 were still alive by August 2006 (**Figure 1**). Causes of postnatal death included malformations (4), accident (1), and metabolic disease (1). Three of these deaths occurred in the fish oil group and 3 in the no oil group.

F1

Asthma occurrences in the fish oil group compared with the olive oil group

Eight occurrences of asthma (any type) were observed in the fish oil group ($n = 263$) and 11 in the olive oil group ($n = 136$), corresponding to a hazard rate ratio (fish oil compared with olive oil) of 0.37 (95% CI: 0.15, 0.92) (**Table 1**; **Figure 2**, upper left). The number of children with a diagnosis of allergic asthma was 2 in the fish oil group and 8 in the olive oil group, corresponding to a hazard rate ratio of 0.13 (95% CI: 0.03, 0.60) (Table 1; Figure 2, upper right). When the asthma diagnoses were expanded to also comprise other allergic manifestations, we found 11 occurrences of asthma (all types), atopic dermatitis, or allergic asthma in the fish oil group ($n = 263$) and 13 in the olive oil group ($n = 136$), corresponding to a hazard rate ratio (fish oil compared with olive oil) of 0.43 (95% CI: 0.19, 0.96) (**Table 2**; Figure 2, lower left). We found 6 occurrences of allergic asthma, atopic dermatitis, or allergic rhinitis in the fish oil group ($n = 263$) and 10 in the olive oil group ($n = 136$), corresponding to a hazard rate ratio (fish oil compared with olive oil) of 0.31 (95% CI: 0.11, 0.84) (Table 2; Figure 2, lower right).

T1-F2

T2

Asthma occurrences in the fish oil group compared with the olive oil group stratified by baseline intake of fish

The hazard rate ratios for all types of asthma (fish oil compared with olive oil) were 0.13 (95% CI: 0.01, 1.29), 0.54 (95% CI: 0.16,

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TABLE 1
Asthma and allergic asthma diagnoses in each randomization group during 16-y follow-up of offspring from a randomized controlled trial with fish oil supplementation in pregnancy[1]

		Asthma (all types)		Allergic asthma	
	Children followed up	Cases	Hazard rate ratio (95% CI)[2]	Cases	Hazard rate ratio (95% CI)[2]
	n	*n*		*n*	
Olive oil	136	11	1 (ref)	8	1 (ref)
Fish oil	263	8	0.37 (0.15, 0.92)	2	0.13 (0.03, 0.60)
P			0.03		0.01
No oil	129	3	0.29 (0.08, 1.03)	0	—
P			0.06		
Overall homogeneity test					
P			0.05		—

[1] Ref, reference.
[2] Assessed with Cox regression analysis.

1.87), and 0.36 (95% CI: 0.06, 2.17) in the low, middle, and high fish consumers, respectively. None of the associations were statistically significant (**Table 3**). When the asthma diagnoses were expanded to also comprise other allergic manifestations, the hazard rate ratios for asthma (all types), atopic dermatitis, or allergic asthma (fish oil compared with olive oil) were 0.10 (95% CI: 0.01, 0.87), 0.63 (95% CI: 0.21, 1.87), and 0.54 (95% CI: 0.11, 2.69) in the low, middle, and high fish consumers, respectively.

Asthma occurrences in the no oil group

Children of mothers in the no oil group were remarkably similar to the children whose mothers had received fish oil. Three occurrences of asthma (all types) were observed in the no oil group ($n = 129$), corresponding to a hazard rate ratio of 0.29 (95% CI: 0.08, 1.03) compared with the olive oil group (Table 1). When the asthma diagnoses were expanded to also comprise

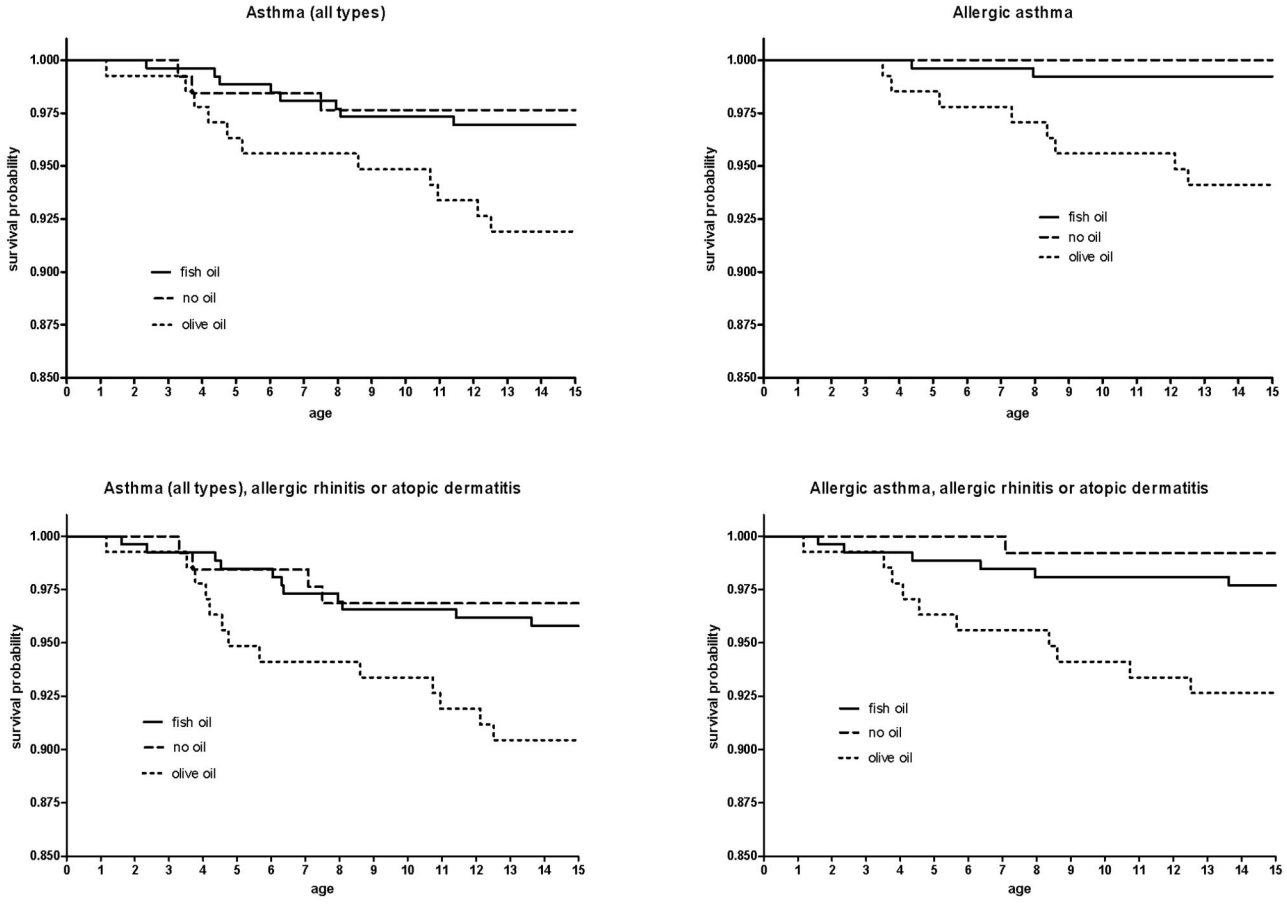

FIGURE 2. Sixteen-year follow-up of offspring from a randomized controlled trial with fish oil supplementation in pregnancy. Kaplan-Meier survival curves show occurrences of asthma-related diseases recorded in the National Patient Registry, stratified by randomization group. The 4 graphs show occurrences of asthma (all types); allergic asthma; asthma (all types), allergic rhinitis, or atopic dermatitis; and allergic asthma, allergic rhinitis, or atopic dermatitis.

TABLE 2
Asthma-related diagnoses in each randomization group during 16-y follow-up of offspring from a randomized controlled trial with fish oil supplementation in pregnancy[1]

		Asthma (all types), atopic dermatitis, or allergic rhinitis		Allergic asthma, atopic dermatitis, or allergic rhinitis	
	Children followed up	Cases	Hazard rate ratio (95% CI)[2]	Cases	Hazard rate ratio (95% CI)[2]
	n	*n*		*n*	
Olive oil	136	13	1 (ref)	10	1 (ref)
Fish oil	263	11	0.43 (0.19, 0.96)	6	0.31 (0.11, 0.84)
P			0.04		0.02
No oil	129	4	0.32 (0.11, 0.99)	1	0.10 (0.01, 0.81)
P			0.05		0.03
Overall homogeneity test					
P			0.05		0.008

[1] Ref, reference.
[2] Assessed with Cox regression analysis.

other allergic manifestations, the hazard rate ratio for asthma (all types), atopic dermatitis, or allergic asthma (no oil compared with olive oil) was 0.32 (95% CI: 0.11, 0.99), whereas the hazard rate ratio for allergic rhinitis, atopic dermatitis, or allergic asthma (no oil compared with olive oil) was 0.10 (95% CI: 0.01, 0.81) (Table 2). Stratification of these contrasts into the low, middle, and high fish consumers resulted in small numbers of cases, and none of the associations were significant (Table 3 and **Table 4**); the hazard rate ratios for all types of asthma (no oil compared with olive oil) were 0.33 (95% CI: 0.04, 3.20), 0.22 (95% CI: 0.3, 1.89), and 0.33 (95% CI: 0.03, 3.13), respectively (Table 3).

DISCUSSION

Compared with the placebo group, when the mothers had received supplements of olive oil in pregnancy, we found that

TABLE 3
Asthma and allergic asthma diagnoses stratified by baseline fish intake in each randomization group during 16-y follow-up of offspring from a randomized controlled trial with fish oil supplementation in pregnancy[1]

		Asthma (all types)		Allergic asthma	
	Children followed up	Cases	Hazard rate ratio (95% CI)[2]	Cases	Hazard rate ratio (95% CI)[2]
	n	*n*		*n*	
Low baseline fish intake					
Olive oil	24	3	1 (ref)	2	1 (ref)
Fish oil	58	1	0.13 (0.01, 1.29)	1	0.20 (0.02, 2.23)
P			0.08		0.19
No oil	24	1	0.33 (0.04, 3.20)	0	—
P			0.34		—
Overall homogeneity test					
P			0.16		—
Medium baseline fish intake					
Olive oil	81	5	1 (ref)	3	1 (ref)
Fish oil	150	5	0.54 (0.16, 1.87)	1	0.18 (0.02, 1.73)
P			0.33		0.14
No oil	74	1	0.22 (0.03, 1.89)	0	—
P			0.17		—
Overall homogeneity test					
P			0.27		—
High baseline fish intake					
Olive oil	31	3	1 (ref)	3	1 (ref)
Fish oil	55	2	0.36 (0.06, 2.17)	0	—
P			0.27		—
No oil	31	1	0.33 (0.03, 3.13)	0	—
P			0.33		—
Overall homogeneity test					
P			0.45		—

[1] Ref, reference.
[2] Assessed with Cox regression analysis.

TABLE 4
Asthma-related diagnoses stratified by baseline fish intake in each randomization group during 16-y follow-up of offspring from a randomized controlled trial with fish oil supplementation in pregnancy[1]

		Asthma (all types), atopic dermatitis, or allergic rhinitis		Allergic asthma, atopic dermatitis, or allergic rhinitis	
	Children followed up	Cases	Hazard rate ratio (95% CI)[2]	Cases	Hazard rate ratio (95% CI)[2]
	n	*n*		*n*	
Low baseline fish intake					
Olive oil	24	4	1 (ref)	3	1 (ref)
Fish oil	58	1	0.10 (0.01, 0.87)	1	0.13 (0.01, 1.25)
P			0.04		0.08
No oil	24	2	0.50 (0.09, 2.71)	1	0.32 (0.03, 3.07)
P			0.42		0.32
Overall homogeneity test					
P			0.05		0.15
Medium baseline fish intake					
Olive oil	81	6	1 (ref)	4	1 (ref)
Fish oil	150	7	0.63 (0.21, 1.87)	4	0.54 (0.14, 2.17)
P			0.41		0.39
No oil	74	1	0.18 (0.02, 1.51)	0	—
P			0.12		—
Overall homogeneity test					
P			0.17		—
High baseline fish intake					
Olive oil	31	3	1 (ref)	3	1 (ref)
Fish oil	55	3	0.54 (0.11, 2.69)	1	0.18 (0.02, 1.72)
P			0.45		0.14
No oil	31	1	0.32 (0.03, 3.11)	0	—
P			0.33		—
Overall homogeneity test					
P			0.56		—

[1] Ref, reference.
[2] Assessed with Cox regression analysis.

asthma occurred at lower rates during the first 15–16 y of life in children whose mothers had received supplements of fish oil. This pattern was robust to expanding the diagnosis to also comprise 2 other allergic manifestations, atopic dermatitis and allergic rhinitis. Narrowing the diagnosis to allergic asthma tended to strengthen the associations and so did restricting to children whose mothers had reported a low habitual fish intake at random assignment.

Strengths of our study include that it was a population-based, placebo-controlled RCT (31) of good quality [for an independent evaluation, *see* Szajewska et al (36)] and done in a setting (Denmark) where successful tracking and registry-based follow-up during 16 y could be accomplished. Of 533 fetuses randomly assigned, 531 children were born alive and 528 were identified in registries by August 2006; 522 were recorded as still alive 16 y after random assignment, leaving little room for selection bias as an explanation of our findings. We used the mandatory Danish NPR to ascertain cases with asthma. We extracted information on all encounters within the Danish hospital system (typically a hospitalization or an ambulatory consultation at a hospital) that had resulted in the recording of an asthma diagnosis. A recent validation study found good agreement between the central recordings of asthma events in the NPR and the information that could be extracted from the medical records with a sensitivity of an asthma diagnosis in the registry of 90% and a specificity of 99% (35). Ascertaining cases this way, however, has most likely led to underdetection of milder cases treated outside the Danish Hospital System, which may explain the relatively low occurrence in the placebo group children of 8% (11 of 136). However, the consequential overrepresentation of the more serious cases may render our findings suggestive of a preventive effect of fish oil more clinically relevant. The threshold for contacting the hospital given asthma or related symptoms may vary systematically according to factors such as parents' education, age, and sibship size. This may result in variable efficiency in the detection of true asthma events. However, because our study was a RCT, the degree and nature of misclassification of the asthma event is likely to be similar across trial groups, and such (nondifferential) misclassification of diagnoses cannot explain the observed differential occurrences of asthma across trial groups. This type of misclassification may even have attenuated our measure of effect.

A fundamental assumption of our design was that olive oil, which we used as placebo, is inert in relation to the endpoints studied. We know of no reports of increased occurrences of asthma in populations in the Mediterranean countries where olive oil intake is generally much higher than the dose given in the present trial (10–20 g/d compared with 4 g/d). Furthermore, we are not aware of evidence that specific substances in olive oil given in the present doses can increase the risk of asthma or have other immunologic effects. The main constituent of olive oil, oleic acid, can be produced in the mammalian body. Olive oil also provides linoleic acid, which can undergo elongation and desaturation to arachidonic acid, which in turn is a precursor for several

potent mediators of the inflammatory process such as leukotrienes (21). However, we estimated the amount provided in the olive oil to be <3% of the average daily linoleic acid intake in Denmark at that time, 0.4 g/d compared with 15.0 g/d (the corresponding intake figures for oleic acid were 3 g/d compared with 30 g/d) (31). By contrast, the fish oil supplement provided 2.7 g marine n−3 PUFA/d, raising the average intake of this nutrient by a factor of ≈10.

The main function of the placebo in the present trial was to counter tendencies of participants in the control group to increase their intake of marine n−3 PUFAs by their own initiative. Such contamination bias, which is a problem well known from open trials, would otherwise tend to dilute and abolish any possible true effects of the intervention being tested. Masking worked relatively well in the placebo group (31). In a questionnaire sent postpartum, only 48% of women in the placebo group identified correctly that they had been receiving olive oil, whereas 50% reported that they either did not know or that they (erroneously) believed they had been receiving fish oil (the corresponding figures for women allocated fish oil were 85% and 14%).

In the trial design we also included a second control group who received no oil supplement, but who went through all the same procedures (recruitment, informed consent, random assignment, and follow-up) as did the oil groups. This was mainly done to be on the safe side if evidence later appeared to suggest that olive oil is not inert in the doses provided. Because data from the no oil group were available, we did examine occurrences of asthma among the children in the no oil group (although this was not part of the a priori hypotheses). Interestingly, these children exhibited diagnostic patterns remarkably similar to children in the fish oil group, although asthma occurrence in the no oil group was not significantly different from occurrence seen in the olive oil group. In our view, the most likely explanation for this finding is contamination bias, as explained earlier. Several factors may have induced a belief in trial participants that increasing intake of n−3 PUFAs, either by increasing fish intake or by taking fish oil, would benefit their own or their children's health. The scientific ethical committee requested that each woman in the trial, before giving her consent, be informed about the original study hypothesis, which was that fish oil would reduce risk of preterm delivery and low birth weight. In addition, at the time of conducting the trial, findings of low occurrences of heart disease in Greenland Inuit were in the media several times and are likely to have stimulated a general public awareness in Denmark about the potential health benefits of consuming marine foods or oils. Finally, the fish oil preparation we used in the trial (Pikasol) had been successfully marketed and was widely available for purchase.

Our finding of lower occurrences of asthma in children of mothers who received supplements of marine n−3 fatty acids in pregnancy is in line with 2 retrospective (22, 23) and 3 prospective (24–26) studies. One large prospective study (27), using biomarkers for maternal and fetal exposures to fatty acids, did not show any clear inverse association between prenatal n−3 PUFAs and atopic diseases; however, that study was limited to diseases occurring in the early childhood period and focused on wheezing and eczema as endpoints. The RCTs in the field have mainly been explanatory trials undertaken in high-risk populations and focused on biochemical endpoints (28–30). They have had short follow-up periods and most likely been underpowered (<100) to study the putative preventive effect of fish oil on disease endpoints. Nevertheless, those RCTs have been important because they have documented effects on biochemical measures of relevance to asthma, including that fish oil modifies neonatal leukotriene production by cord blood–derived neutrophils (20).

It is biologically plausible that increasing the intake of marine n−3 PUFAs in the third trimester of pregnancy could have a preventive effect against asthma in the offspring. The marine n−3 PUFAs, EPA and DHA, may affect fetal immune function through many different mechanisms (2). The incorporation of EPA and DHA in cell membranes leads to decreased availability of arachidonic acid and to increased competition for both the cyclooxygenase and lipoxygenase enzymes, resulting in decreased synthesis of arachidonic acid–derived eicosanoids (16). Marine n−3 PUFAs may also be converted to resolvins and neuroprotectins with antiinflammatory and neuroprotective properties (17–19). PGE2 production is reduced, which in turn may contribute to altering the balance of Th1 and Th2 cytokines and to reducing the production of immunoglobulin E. The leukotriene production, which is known to play a role in asthma pathogenesis (21), is also reduced (20).

The initial finding from the present trial was that supplementation with marine n−3 PUFAs appeared to be associated with longer gestations in the mothers (31), a pattern observed in 2 later trials (37, 38) and several animal experiments (39, 40). A Danish prospective observational study has even suggested that, in women with zero or a low intake of marine n−3 PUFAs, small increments in intake may lead to substantial reductions in the risks of both preterm and early preterm delivery (41, 42). It is therefore interesting that recent evidence has linked preterm delivery to asthma in the offspring in several different ways. Spontaneous preterm delivery was associated with intrauterine inflammation (43), and asthma appears to occur at increased rates in children born preterm (9). In a recent study, under conditions simulating inflammation, supplementation with marine n−3 PUFAs decreased PGE2 and PGF2α production in cultured decidual cells (44). The reduction in prostaglandin production was associated with a decreased expression of microsomal prostaglandin E synthases 1 and 2; the researchers suggested that this may be one mechanism by which n−3 PUFA supplementation could delay delivery. We hypothesize that intrauterine inflammation and low maternal intake of n−3 PUFAs may interact in creating conditions that can trigger preterm delivery or may lead to an increased propensity in the newborn to become asthmatic later in life, or do both simultaneously. If the intrauterine processes leading to asthma in the offspring truly do share mechanisms with the processes initiating spontaneous delivery, it is possible that the period shortly before delivery might be the time window during which dietary n−3 PUFAs are exerting their putative protective effect against asthma in the offspring.

We have limited data to evaluate the dose-response relations between maternal intake of n−3 PUFAs and offspring asthma. Our observation of a reduced occurrence of asthma in the no oil group (if our contention is correct that this was due to participant-initiated increase in n−3 PUFA intake) may be taken to support that relatively low doses are sufficient to confer protection. The inverse association between fish oil and risk of any type of asthma became nonsignificant when restricting the analysis to women reporting low habitual intake of fish at baseline, but the association tended, if anything, to become stronger. This may

also suggest that the dose-response curve is steepest in the lower end of the exposure distribution.

In conclusion, our data are compatible with the hypothesis that an increased intake of marine n−3 PUFAs in the third trimester may confer protection against asthma in the offspring. Clearly, there is a need for both large RCTs with long follow-ups as well as mechanistic studies to examine this further. Trials should also be undertaken that test the potential immunomodulatory effects on the offspring of various doses of n−3 PUFAs supplemented during various time windows during gestation.

We are grateful for the constructive comments made by the peer-reviewers and for the helpful discussions of our results with Harold S Hansen (Faculty of Pharmaceutical Sciences, University of Copenhagen) and with members of the EU FP6 consortium EARNEST.

The author's responsibilities were as follows—SFO: was involved in the conduct of the original trial, initiated the follow-up of the offspring, had the lead role in interpreting the data and in the writing of the report, and is the guarantor of the study; MLØ: was involved in establishing the follow-up of the offspring, did the statistical analyses, and participated in the interpreting of the results and in the writing of the report; JDS: was involved in the conduct of the original trial and participated in the interpreting of the results and the writing of the report; LMM: was involved in establishing the follow-up of the offspring and participated in the interpreting of the results and the writing of the report; DR: was involved in establishing the follow-up of the offspring and participated in the interpreting of the results and the writing of the report; NJS: was involved in the conduct of the original trial and participated in the interpreting of the results and the writing of the report; TBH: was involved in the conduct of the original trial and participated in the interpreting of the results and the writing of the report. None of the authors had a personal or financial conflict of interest.

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