Papers

Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study

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Abstract

Objective To determine the relation between intake of seafood in pregnancy and risk of preterm delivery and low birth weight.
Design Prospective cohort study.
Setting Aarhus, Denmark.
Participants 8729 pregnant women.
Main outcome measures Preterm delivery and low birth weight.
Results The occurrence of preterm delivery differed significantly across four groups of seafood intake, falling progressively from 7.1% in the group never consuming fish to 1.9% in the group consuming fish as a hot meal and an open sandwich with fish at least once a week. Adjusted odds for preterm delivery were increased by a factor of 3.6 (95% confidence interval 1.2 to 11.2) in the zero consumption group compared with the highest consumption group. Analyses based on quantified intakes indicated that the working range of the dose-response relation is mainly from zero intake up to a daily intake of 15 g fish or 0.15 g n-3 fatty acids. Estimates of risk for low birth weight were similar to those for preterm delivery.
Conclusions Low consumption of fish was a strong risk factor for preterm delivery and low birth weight. In women with zero or low intake of fish, small amounts of n-3 fatty acids—provided as fish or fish oil—may confer protection against preterm delivery and low birth weight.

Introduction

It is important to identify modifiable causes of preterm delivery and fetal growth retardation, which are strong predictors of infants' later health and survival. Observations of high birth weights[1] and long gestations[2] in the fish eating community of the Faroe Islands suggested that intake of seafood rich in long chain n-3 fatty acids can increase birth weight by prolonging gestation[2] or by increasing the fetal growth rate.[3–6]

Fish oil has been shown in randomised trials[7 8] and animal experiments[9 10] to have the potential to delay spontaneous delivery and prevent preterm delivery, but the minimum amount of n-3 fatty acids needed to obtain this effect remains to be determined. No detectable effects on fetal growth rate were seen in these trials,[7 8] but fish oil was provided only in the second half

of pregnancy, and several observational studies have found direct associations between measures of seafood intake in pregnancy and fetal growth rate.[5 11–14]

We investigated these issues in a cohort of women in whom seafood intake in early pregnancy was assessed prospectively by a questionnaire method.[15] We tested whether a low intake of seafood in early pregnancy is a risk factor for preterm delivery and low birth weight and whether it is associated with a lower fetal growth rate. We related the findings to quantified intakes of fish and long chain n-3 fatty acids.

Methods

We invited all pregnant women receiving routine antenatal care in Aarhus, Denmark, to complete self administered questionnaires in weeks 16 and 30 of gestation. The study base has been described in detail elsewhere.[16] During 1992-6 the questionnaire administered at 16 weeks contained questions about intake of fish and fish oil. Only singleton, live born babies without detected malformations were included in the analysis. The local scientific-ethical committee approved the protocol, and we used an informed consent form.

Exposure variables

In Denmark fish is eaten mainly as part of a hot meal, in an open sandwich, or cold in a green salad or pasta salad.[15] Frequency of consumption of such meals has been shown to be a strong and independent predictor of variation in erythrocyte n-3 fatty acids, without taking into consideration whether the meals contained fat or lean fish.[15] We posed four questions: "How often did you eat: (*a*) fish in a hot meal, (*b*) bread with fish, (*c*) green salad or pasta salad with fish, and (*d*) fish oil as a supplement?" The women were asked to understand the term "fish" as including roe, prawn, crab, and mussel and to let the responses represent the period from when they first knew they were pregnant until completion of the questionnaire. Each question had six predefined response categories: never, less than once a month, 1-3 times a month, 1-2 times a week, 3-6 times a week, every day.

We quantified daily intakes of fish and long chain n-3 fatty acids on the basis of the following assumptions. (Contribution of long chain n-3 fatty aids from foods of non-marine origin—for example, offal meat—was considered negligible.) The six frequency

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Table 1 Frequency of consumption of meals containing fish by 8729 women. Values are number (percentage). Women who took fish oil were excluded

Meal type	Never	<1 per month	1-3 per month	1-2 per week	3-6 per week	Every day	Total
Hot meal	999 (11.4)	2700 (30.9)	3851 (44.1)	1140 (13.1)	32 (0.4)	0	8722 (100)
Sandwich	601 (6.9)	1425 (16.3)	3196 (36.6)	2698 (30.9)	711 (8.1)	92 (1.1)	8723 (100)
Salad	3515 (40.3)	3111 (35.7)	1766 (20.2)	299 (3.4)	24 (0.3)	4 (0.0)	8719 (100)

categories corresponded to 0, 0.5, 2, 4, 20, and 28 servings per 28 days. Each serving of a hot fish meal provided 144 g fish and 1627 µg n-3 fatty acids, a fish sandwich provided 29 g fish and 431 µg n-3 fatty acids, and a fish salad provided 50 g fish and 149 µg n-3 fatty acids. These values were mainly derived from work done by the Danish Veterinary and Food Administration on portion sizes, distributions of fish species in meals, and food tables for the Danish population.[17 18] We defined six groups of exposure, with the lowest group consuming no fish and the other five groups being fifths of the remaining participants (designated QUANT0, QUANT1, QUANT2, QUANT3, QUANT4, QUANT5).

To avoid the uncertainties of the above assumptions we adopted a priori an alternative analytical strategy, which was based solely on the raw food frequency variables ("food frequency strategy"), and which could still provide a strong test of the hypotheses. To limit the number of variables considered simultaneously, we restricted analyses to the 1304 women who had eaten no fish salad and who had consumed hot meals and open sandwiches with fish with the same frequency. To secure substantial exposure contrasts, we defined four comparison groups with reasonable sample sizes in such a way that both the defining variables increased progressively: women who had consumed fish as a hot meal and as open sandwiches (*a*) zero times, (*b*) more than zero but less than once a month, (*c*) 1-3 times a month, and (*d*) once or more often a week (designated FREQ0, FREQ1, FREQ2, and FREQ3).

Outcome variables

We assessed gestational age by early ultrasonography in 71% of participants, and otherwise from menstrual data or best clinical judgment. We defined low birth weight as <2500 g and preterm as delivery before 259 days. We assessed intrauterine growth retardation below the 10th centile and birth weight expected from gestational age from the infant's birth weight, gestational age, and sex, on the basis of a Danish standard.[19]

Covariates

We used covariates as previously described[16]: sex of infant (girl, boy); smoking (0, 1-9, ≥10 cigarettes a day) and alcohol consumption (<10 or ≥10 drinks a week) in pregnancy; maternal age (≤19, 20-29, 30-39, ≥40 years), parity (0, ≥1), height (≤159, 160-169, 170-179, ≥180 cm), and pre-pregnant weight (≤49, 50-59, 60-69, 70-79, ≥80 kg); length of education (≤7, 8-9, ≥10 years); and whether the mother had a cohabitant (0, 1).

Statistical analyses

The study hypothesis could be tested in many different ways with our data, so we decided all analytical conditions a priori. This avoided data dependent analyses and kept preconditions for interpreting P values and confidence intervals as valid as possible for an observational study with self selected rather than randomised allocation to levels of exposure. We used the χ^2 test, analysis of variance, and logistic regression. We included all suspected potential confounders (see covariate list) in the multivariate model simultaneously.

Table 2 Occurrences of low birth weight, preterm delivery, and intrauterine growth retardation, and mean birth weight, gestation length, and birth weight adjusted for gestation length, according to quantified daily intake of long chain n-3 fatty acids

	Dichotomous outcomes (No (%))			Continuous outcomes (mean (SD))		
Group*	Low birth weight	Preterm delivery	Intrauterine growth retardation	Birth weight (g)	Gestation (days)	Adjusted birth weight (g)
QUANT0 (n=282)	20 (7.1)	20 (7.1)	23 (8.2)	3432 (589)	278.8 (14.3)	3466 (490)
QUANT1 (n=1723)	54 (3.1)	71 (4.1)	152 (8.8)	3543 (543)	281.7 (11.9)	3494 (486)
QUANT2 (n=1618)	52 (3.2)	61 (3.8)	116 (7.2)	3572 (559)	281.8 (12.4)	3521 (481)
QUANT3 (n=1890)	34 (1.8)	45 (2.4)	96 (5.1)	3592 (498)	282.2 (10.4)	3532 (446)
QUANT4 (n=1419)	35 (2.5)	50 (3.5)	91 (6.4)	3581 (521)	282.2 (11.3)	3520 (455)
QUANT5 (n=1775)	37 (2.1)	52 (2.9)	94 (5.3)	3617 (518)	282.4 (11.0)	3550 (457)
Statistical tests						
Between groups (P value)	<0.001†	0.001†	0.001†	0.001‡	0.001‡	0.004‡
Linear trend (P value)	<0.001	0.003	0.001	0.001	0.001	0.001

*See text for definitions of the six groups. †Pearson χ^2. ‡Analysis of variance.

Table 3 Occurrences of potential confounders according to quantified daily intake of long chain n-3 fatty acids. Values are percentages (numbers)

Group*	Smoker	High school	Primiparous	Single	<50 kg	<1.6 m	Teenager
QUANT0	40.7 (112/275)	34.2 (92/269)	58.5 (165/282)	7.6 (21/276)	6.5 (18/275)	10.1 (27/268)	6.7 (19/282)
QUANT1	30.2 (508/1683)	44.1 (736/1669)	59.3 (1022/1723)	5.8 (98/1697)	5.2 (88/1700)	7.7 (131/1695)	1.9 (32/1723)
QUANT2	23.0 (363/1576)	56.2 (876/1560)	56.4 (912/1618)	4.9 (78/1593)	4.7 (75/1590)	6.2 (99/1604)	1.2 (19/1618)
QUANT3	19.0 (353/1851)	67.3 (1244/1849)	50.6 (956/1890)	3.9 (72/1865)	3.1 (57/1861)	5.1 (94/1861)	0.3 (6/1890)
QUANT4	21.1 (293/1391)	67.4 (931/1382)	47.9 (680/1419)	2.7 (38/1395)	3.3 (46/1399)	6.1 (85/1399)	0.6 (8/1419)
QUANT5	18.3 (315/1724)	69.9 (1201/1719)	49.6 (880/1775)	4.5 (78/1741)	4.2 (73/1749)	5.7 (100/1748)	0.4 (7/1775)

*See text for definitions of the six groups.

Results

Of 8998 women returning the 16 week questionnaire, 8729 (97%) had not consumed fish oil supplements—results refer to this restricted group. Mean birth weight was 3577 (SD 531) g, and duration of gestation was 280.0 (11.5) days. Low birth weight occurred in 2.7% (232/8707), preterm delivery in 3.4% (299/8707), and intrauterine growth retardation in 6.6% (572/8705) of participants. Table 1 shows unidimensional distributions of the three food frequency variables. On average, women consumed 15.8 (SD 13.9) g fish and 0.182 (0.161) g long chain n-3 fatty acids a day. Covariate distributions, assessed in a larger sample from the same population, have been published.[16]

Estimated mean daily intakes for the six exposure groups QUANT0 to QUANT5 were 0, 3.3, 8.0, 13.4, 18.0, and 38.4 g fish; and 0, 0.038, 0.092, 0.146, 0.216, and 0.445 g long chain n-3 fatty acids. Low birth weight, preterm birth, and intrauterine growth retardation all tended to decrease with increasing fish consumption, and mean birth weight, duration of gestation, and birth weight adjusted for gestational age tended to increase with increasing fish consumption (table 2). These associations were mainly apparent at the lower end of the exposure scale—this was particularly the case for preterm birth and mean duration of gestation.

Smokers, primiparous women, teenagers, and women with low weight, short stature, and without high school education and cohabitant occurred more frequently in the low exposure groups (table 3). The impression that the decline in risk occurred mainly at the lower end of the exposure distribution was confirmed on examination of adjusted odds ratios for low birth weight and preterm birth, with the highest intake group (QUANT5) as reference (table 4). The association between intake of fish and risk of fetal growth retardation weakened but was not always fully abolished after adjustment for potential confounding.

Alternative strategy
Table 5 defines the comparison groups of the food frequency strategy. Estimated mean daily intakes in the four groups FREQ0 to FREQ3 were 0, 3.1, 12.4, and 44.3 g fish; and 0, 0.037, 0.147, and 0.537 g long chain n-3 fatty acids. Occurrence of low birth weight and preterm delivery both decreased significantly and progressively across the four groups, as frequency of fish consumption increased (table 6). Intrauterine growth retardation exhibited a similar, but non-significant, pattern. Mean birth weight, duration of gestation, and

Table 4 Crude and adjusted* odds ratios (95% CI) for low birth weight, preterm delivery, and intrauterine growth retardation according to quantified daily intake of long chain n-3 fatty acids (n=7902). The highest intake group (QUANT5) is used as reference

Group†	Low birth weight	Preterm delivery	Intrauterine growth retardation
QUANT0:			
Crude	4.37 (2.43 to 7.87)	2.95 (1.67 to 5.20)	1.52 (0.91 to 2.55)
Adjusted	3.22 (4.73 to 6.00)	2.69 (1.49 to 4.84)	1.14 (0.67 to 1.98)
QUANT1:			
Crude	1.61 (1.02 to 2.55)	1.61 (1.09 to 2.37)	1.73 (1.31 to 2.28)
Adjusted	1.31 (0.82 to 2.10)	1.48 (0.99 to 2.21)	1.45 (1.09 to 1.94)
QUANT2:			
Crude	1.69 (1.07 to 2.68)	1.48 (0.99 to 2.21)	1.41 (1.05 to 1.90)
Adjusted	1.54 (0.97 to 2.46)	1.44 (0.96 to 2.16)	1.31 (0.97 to 1.77)
QUANT3:			
Crude	0.98 (0.60 to 1.61)	0.90 (0.59 to 1.38)	1.02 (0.76 to 1.38)
Adjusted	0.99 (0.60 to 1.63)	0.90 (0.59 to 1.39)	1.03 (0.76 to 1.40)
QUANT4:			
Crude	1.12 (0.67 to 1.88)	1.28 (0.83 to 1.96)	1.16 (0.85 to 1.59)
Adjusted	1.16 (0.69 to 1.94)	1.31 (0.85 to 2.01)	1.25 (0.91 to 1.72)
QUANT5:			
Reference	1.0	1.0	1.0
Statistical tests (dietary variable modelled as five indicator variables)			
Crude (P value)	0.0003	<0.0001	0.0003
Adjusted (P value)	0.004	0.003	0.09

*Adjusted for maternal smoking, alcohol consumption, age, parity, height, pre-pregnant weight, length of education, and cohabitant status (see text).
†See text for definitions of six groups.

birth weight adjusted for gestational age all increased significantly across the four groups.

Risks of low birth weight and preterm delivery were significantly increased in the lowest group compared with the highest group, even after adjustment for potential confounding, with odds ratios of 3.57 (95% confidence interval 1.14 to 11.14) for low birth weight and 3.60 (1.15 to 11.20) for preterm delivery, with the high intake group (FREQ3) as reference (table 7). The association between risk of intrauterine growth retardation and the dietary variable got much weaker and tended to be abolished after adjustment for confounding.

Discussion

Low consumption of seafood was a strong risk factor for preterm delivery and low birth weight. The associations were strongest below a daily intake of 0.15 g long chain n-3 fatty acids or 15 g fish.

Strengths and weaknesses
Strengths of the study included that exposure data were collected in a concurrent fashion and long before

Table 5 Frequencies of hot meals and sandwiches containing fish consumed by the 3515 women who never ate salad with fish (seven were missing on one or both of the other two variables) and definition of groups for comparison

	Sandwiches						
Hot meals	Never	<1 per month	1-3 per month	1-2 per week	3-6 per week	Every day	Total
Never	282*	143	186	99	14	4	728
<1 per month	100	301†	481	237	55	5	1179
1-3 per month	75	203	511‡	383	97	11	1280
1-2 per week	17	33	58	141§	51§	8§	308
3-6 per week	1	1	0	4§	6§	0§	12
Every day	0	0	0	0§	0§	0§	0
Total	475	681	1236	864	223	28	3507

*Group FREQ0. †Group FREQ1. ‡Group FREQ2. §Group FREQ3.

Table 6 Occurrences of low birth weight, preterm delivery, and intrauterine growth retardation, and mean birth weight, mean gestation length, and mean birth weight adjusted for length of gestation, according to frequency of fish intake

	Dichotomous outcomes (No (%))			Continuous outcomes (mean (SD))		
Group*	Low birth weight	Preterm delivery	Intrauterine growth retardation	Birth weight (g)	Gestation (days)	Adjusted birth weight (g)
FREQ0 (n=282)	20 (7.1)	20 (7.1)	23 (8.2)	3432 (589)	278.8 (14.3)	3466 (490)
FREQ1 (n=301)	12 (4.0)	14 (4.7)	27 (9.0)	3522 (576)	280.3 (12.8)	3513 (554)
FREQ2 (n=511)	13 (2.5)	18 (3.5)	30 (5.9)	3554 (512)	281.5 (10.9)	3512 (451)
FREQ3 (n=210)	4 (1.9)	4 (1.9)	13 (6.2)	3656 (536)	283.4 (10.8)	3561 (486)
Statistical tests						
Between groups (P value)	0.005†	0.03†	0.3†	<0.001‡	<0.001‡	0.2‡
Linear trend (P value)	0.001	0.003	0.2	<0.001	<0.001	0.04

*See text and table 5 for definitions of comparison groups. †Pearson χ^2. ‡Analysis of variance.

occurrence of outcome among more than 8000 women, that exposure categories and other analytical conditions were decided a priori, and that analyses took account of nine potential confounding factors.

The main weakness of the study, as with any observational study, was the possibility of confounding that was not adjusted for. Adjustment had little impact on measures of association, but confounding by unmeasured factors cannot be ruled out.

Another weakness was that the assumed values for portion sizes, distributions of fish species in meals, and food contents of nutrients are only approximations to the true values. Imprecise estimates of quantified intake of n-3 fatty acids are thus inevitable. Although this imprecision is unlikely to explain the steep decline in risk at the low end of the exposure distribution, it may contribute to the observed "bending" of the relation if imprecision increases with increasing exposure, a possibility that cannot be ruled out.

Alternative strategy

The alternative strategy was free of these assumptions as it simply used the questions on food frequency to define four groups with large differences in exposure; the questions had been shown to be strong and mutually independent predictors of n-3 fatty acids measured in erythrocytes in the same population.[15] It is therefore reassuring that this strategy corroborated the finding of a steep decline in risk across the lowest exposure groups, although with only four groups it was not pos-

What is already known on this topic

Long chain n-3 fatty acids in amounts above 2 g a day may delay spontaneous delivery and prevent recurrence of preterm delivery

Large studies have not been carried out to determine to what extent low consumption of n-3 fatty acids is a risk factor for preterm delivery

The dose-response relation has not been described

What this study adds

Low consumption of fish seems to be a strong risk factor for preterm delivery and low birth weight in Danish women

This relation is strongest below an estimated daily intake of 0.15 g long chain n-3 fatty acids or 15 g fish

sible to draw conclusions about levelling off at high exposures.

Comparisons with other studies

Overall, the findings agree with the randomised trials showing that consumption of fish oil in pregnancy can increase birth weight by prolonging gestation and reduce the risk of recurrence of preterm delivery.[7 8] The finding that the dose-response relations were strong at low exposures corroborates two earlier studies. A reduction in early delivery was seen in women who had received only 0.1 g n-3 fatty acids (along with other substances) a day from week 20 of gestation.[20–23] An association was seen between duration of pregnancy and a biomarker for intake of marine n-3 fatty acids (fatty acids measured in erythrocyte lipids) in Danish women, whereas no such association could be detected in Faroese women with a substantially higher intake, suggesting a stronger association at low exposures.[24]

A case-control study in the same population could not detect any association between seafood intake in pregnancy and risks of preterm birth[25]; unlike the present study, however, this study assessed dietary intake retrospectively after delivery, which may have distorted the results and led to the null finding.

Several observational studies have found associations between measures of maternal seafood intake and fetal growth rate.[5 11–14] In the randomised trials, where fish oil was provided after week 16-20 of

Table 7 Crude and adjusted* odds ratios (95% CI) for low birth weight, preterm delivery, and intrauterine growth retardation according to fish intake (n=1159). The highest intake group (FREQ3) is used as reference

Group†	Low birth weight	Preterm delivery	Intrauterine growth retardation
FREQ0:			
Crude	4.06 (1.34 to 12.01)	3.79 (1.26 to 11.38)	1.28 (0.61 to 2.71)
Adjusted	3.57 (1.14 to 11.14)	3.60 (1.15 to 11.20)	1.01 (0.45 to 2.26)
FREQ1:			
Crude	1.60 (0.49 to 5.27)	2.34 (0.75 to 7.30)	1.44 (0.70 to 2.96)
Adjusted	1.39 (0.41 to 4.67)	2.09 (0.66 to 6.62)	1.26 (0.59 to 2.66)
FREQ2:			
Crude	1.26 (0.40 to 3.96)	1.59 (0.52 to 4.85)	1.01 (0.51 to 2.03)
Adjusted	1.25 (0.39 to 3.94)	1.58 (0.52 to 4.83)	1.02 (0.50 to 2.08)
FREQ3:			
Reference	1.00	1.00	1.00
Statistical tests (dietary variable modelled as three indicator variables)			
Crude (P value)	0.004	0.03	0.5
Adjusted (P value)	0.02	0.06	0.8

*Adjusted for maternal smoking, alcohol consumption, age, parity, height, pre-pregnant weight, length of education, and cohabitant status (see text).
†See text and table 5 for definitions of comparison groups.

gestation, no effects were seen on fetal growth rate.[7 8] The observational data could therefore possibly be explained either by effects of n-3 fatty acids exerted before week 16-20 or by effects of other substances in seafood. Our study could substantiate neither of these two possibilities, as the associations between seafood consumption in early pregnancy and fetal growth rate tended to disappear after adjustment for potential confounders.

Randomised controlled trials to examine the dose-response relations between long chain n-3 fatty acids and timing of delivery and preterm risk are warranted.

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