

## 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<sup>1</sup> and long gestations<sup>2</sup> 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<sup>2</sup> or by increasing the fetal growth rate.<sup>3-6</sup>

Randomised controlled trials have shown that fish oil can delay spontaneous delivery and prevent recurrence of preterm delivery,<sup>7,8</sup> 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,<sup>7,8</sup> 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.<sup>5,9-12</sup>

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.<sup>13</sup> 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. Frequency of consumption of such meals has been shown to be a strong and independent predictor of variation in erythrocyte n-3 fatty acids.<sup>14</sup> 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 then estimated daily intakes of fish and long chain n-3 fatty acids.<sup>15,16</sup> 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). An alternative strategy is presented on [bmj.com](http://bmj.com).

**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.<sup>17</sup>

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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)

**Covariates**—We used covariates as previously described<sup>13</sup>: sex of infant (girl, boy); smoking (0, 1-9,  $\geq 10$  cigarettes a day) and alcohol consumption (<10 or  $\geq 10$  drinks a week) in pregnancy; maternal age ( $\leq 19$ , 20-29, 30-39,  $\geq 40$  years), parity (0,  $\geq 1$ ), height ( $\leq 159$ , 160-169, 170-179,  $\geq 180$  cm), and pre-pregnant weight ( $\leq 49$ , 50-59, 60-69, 70-79,  $\geq 80$  kg); length of education ( $\leq 7$ , 8-9,  $\geq 10$  years); and whether the mother had a cohabitant (0, 1).

**Statistical analyses**—We decided all analytical conditions a priori. We used the  $\chi^2$  test, analysis of variance, and logistic regression. We included all suspected potential confounders (see covariate list) in the multivariate model simultaneously

## 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. On the basis of the frequency of consumption of fish (table 1), we estimated that, 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.

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 (see [bmj.com](http://bmj.com)). 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 as reference (table 3). The association between intake of fish and risk of fetal growth retardation weakened but was not always fully abolished after adjustment for potential confounding.

## Discussion

### Strengths and weaknesses

Strengths of the study included that exposure data were collected in a concurrent fashion and long before 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. An alternative strategy, based solely on food frequency data, is presented on [bmj.com](http://bmj.com).

**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

Group*	Dichotomous outcomes (No (%))			Continuous outcomes (mean (SD))		
	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)
<b>Statistical tests</b>						
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  $\chi^2$ . ‡Analysis of variance.

### 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.<sup>7 8</sup> 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.<sup>18-21</sup> An association was seen between duration of pregnancy and a biomarker for intake of marine n-3 fatty acids 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.<sup>22</sup>

A case-control study in the same population could not detect any association between seafood intake in pregnancy and risks of preterm birth<sup>23</sup>; unlike the present study, however, this study assessed dietary intake retrospectively after delivery, which may have distorted the results.

Several observational studies have found associations between measures of maternal seafood intake and fetal growth rate.<sup>5 9-12</sup> In the randomised trials, where fish oil was provided after week 16-20 of gestation, no effects were seen on fetal growth rate.<sup>7 8</sup> 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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### 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

**Table 3** 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
<b>Statistical tests</b> (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.

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## Clinical course of hepatitis C virus during the first decade of infection: cohort study

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### Abstract

**Objective** To determine the clinical course of hepatitis C virus in the first decade of infection in a group of patients who acquired their infections on a known date.

**Design** Cohort study.

**Setting** Clinical centres throughout the United Kingdom.

**Participants** 924 transfusion recipients infected with the hepatitis C virus (HCV) traced during the HCV lookback programme and 475 transfusion recipients who tested negative for antibodies to HCV (controls).

**Main outcome measures** Clinical evidence of liver disease and survival after 10 years of infection.

**Results** All cause mortality was not significantly different between patients and controls (Cox's hazards ratio 1.41, 95% confidence interval 0.95 to 2.08). Patients were more likely to be certified with a death related to liver disease than were controls (12.84, 1.73 to 95.44), but although the risk of death directly from liver disease was higher in patients than controls this difference was not significant (5.78, 0.72 to 46.70). Forty per cent of the patients who died directly from liver disease were known to have consumed excess alcohol. Clinical follow up of 826 patients showed that liver function was abnormal in 307 (37.2%), and 115 (13.9%) reported physical signs or symptoms of liver disease. Factors associated with developing liver disease were testing positive for HCV ribonucleic acid (odds ratio 6.44, 2.67 to 15.48), having acquired infection when older (at age  $\geq$  40 years; 1.80, 1.14 to 2.85), and years since transfusion (odds ratio 1.096 per year, 1.00 to 1.20). For patients with severe disease, sex was also significant (odds ratio for women 0.38, 0.17 to 0.88). Of the 362 patients who had undergone liver biopsy, 328 (91%) had abnormal histological results and 35 (10%) of these were cirrhotic.

**Conclusions** Hepatitis C virus infection did not have a great impact on all cause mortality in the first decade of infection. Infected patients were at increased risk of dying directly from liver disease,

particularly if they consumed excess alcohol, but this difference was not statistically significant.

### Introduction

Hepatitis C virus (HCV) is a common cause of liver disease<sup>1</sup> and a major health problem worldwide.<sup>2</sup> Acute infection is rarely diagnosed, and information about the clinical course of HCV infection has come largely from retrospective studies of patients with established liver disease.<sup>3</sup> Such studies exclude people with no clinical evidence of infection, and observations are often biased towards severe disease outcomes. Opportunities for prospective studies of HCV related disease are rare, and the rate of development of chronic liver disease and hepatocellular carcinoma is poorly understood.

In early 1995, the UK Department of Health announced that they would undertake a "lookback" at people who had received blood from donors subsequently found to be infected with the virus when transfusion took place before the introduction of testing of the blood supply for antibodies to HCV.<sup>4</sup> Recipients were identified from hospital records, traced, and offered counselling, serological testing, and treatment for HCV infection. Our study describes the HCV related disease and mortality seen after 10 years of infection.

### Methods

#### Patients

At the end of 1999, 996 transfusion recipients infected with HCV had been traced during the lookback.<sup>5</sup> For most patients, transfusion was the only probable route of infection, but 18 were excluded because exposure to other possible causes meant that the date they acquired the virus was uncertain. Another 54 patients were excluded because of missing or unclear key information or because initial reactivity to antibodies to HCV was not confirmed. Of the remaining 924 eligible patients, 608 (65.8%) were known to be positive for HCV ribonucleic acid and 189 (20.5%) negative for