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# Duration of pregnancy in relation to seafood intake during early and mid pregnancy: prospective cohort

Sjurdur F. Olsen[1], Marie Louise Østerdal[1], Jannie Dalby Salvig[2], Ulrik Kesmodel[3]
Tine Brink Henriksen[4], Morten Hedegaard[5] and Niels Jørgen Secher[6]

[1]*Maternal Nutrition Group, Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, DK-2300, Copenhagen S, Denmark;* [2]*Department of Gynaecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark;* [3]*Department of Epidemiology, University of Aaarhus, Aarhus, Denmark;* [4]*Department of Paediatrics, Aarhus University Hospital, Aarhus, Denmark;* [5]*Department of Gynaecology and Obstetrics, H:S Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [6]*Department of Gynaecology and Obstetrics, H:S Hvidovre, University of Copenhagen, Copenhagen, Denmark*

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**Abstract.** We examined the association between exposure to seafood intake during two periods of pregnancy on the one hand and risks of preterm delivery and postterm delivery on the other. In a prospective cohort of 8729 pregnant Danish women, we assessed frequency of fish meals during the first and second trimester of pregnancy by questionnaires completed around gestation weeks 16 and 30, respectively. When fish intake was based solely on intake reported for the early period of pregnancy, mean gestation length was shorter by 3.91 (95% CI: 2.24–5.58) days and odds of preterm delivery were increased 2.38 (1.23–4.61) times in those who never consumed fish (n = 308) vs. those who consumed both fish as main meal and fish in sandwiches at least once per week (n = 785). These measures were similar when fish intake was based solely on intake reported for mid-pregnancy. In the subgroup of women reporting same intake in the two trimesters, those who never consumed fish (n = 165) had 8.57 (5.46–11.7) days shorter mean gestation and 19.6 (2.32–165) times increased odds of preterm delivery, compared to high fish consumers (n = 127); odds of elective and postterm delivery were *reduced* by a factor 0.33 (0.11–1.02) and 0.34 (0.12–0.95), respectively, in zero fish consumers. All analyses were adjusted for potential confounding by factors such as maternal smoking, height, and prepregnant weight. We conclude that never consuming fish in the first two trimesters of pregnancy was an extremely strong risk factor for preterm delivery but was also associated with reduced risks of elective delivery and postterm delivery.

**Key words:** Fish intake, Pregnancy duration, Prospective cohort

## Introduction

Pregnancy duration varies greatly between women, and very little is known about what causes this variation [1]. Clarification of the causes has great public health implications. Preterm delivery (i.e. delivery earlier than 3 weeks before expected date of delivery) is the main problem in obstetrics today, as it accounts for 70% of perinatal mortality and nearly half of long-term neurological morbidity [2, 3]. On the other hand, postterm delivery (i.e. delivery 2 weeks after expected date of delivery) is associated with increases in perinatal complications, including a higher risk of having elective delivery [4].

It has been hypothesised that an increased intake of long chain *n*-3 fatty acids, abundant in fat from fish, can delay timing of spontaneous delivery, possibly by influencing the prostaglandins involved in the initiation of delivery [5] or through an 'anti-arrhythmic' effect on the myometrial activity [6, 7]. The hypothesis has been supported by some [8–10] but not all [11–14] randomised controlled trials [15], and by some [16, 17] but, again, far from all [18–24] observational studies.

In one large prospective observational study in Aarhus we found low consumption of seafood in pregnancy to be associated with shorter gestations and to be a risk factor for preterm birth in Danish women [17]. Three ensuing prospective studies, undertaken in Bristol, Reykjavík and Boston, could not confirm these findings. One reason for the discrepancy, mentioned by the authors [21, 23, 24], may be that the three studies, contrary to the Aarhus study, were unable to clearly define a group of women with zero fish intake.

In the Aarhus cohort, we assessed frequency of fish meals during the first and second trimester of pregnancy by questionnaires completed around gestation weeks 16 and 30, respectively [17]. Because the second trimester exposure data were not available at the time of our first report, the analyses presented were solely based on the first trimester exposure data. We have now reanalysed the Aarhus cohort data, taking second trimester intake into account.

The present paper addresses four issues. We examine whether seafood intake reported closer to the expected date of delivery might be more closely associated with various measures of pregnancy duration (the timing of spontaneous delivery, preterm delivery, and early preterm delivery, which is delivery earlier than 6 weeks before expected date of delivery) than intake reported earlier; this would indicate a relatively fast effect of long chain *n*-3 fatty acids on timing of delivery [7]. We examine the association between various levels of seafood intake and measures of pregnancy duration in women who reported to have the same intake of seafood during the two periods of pregnancy; less misclassification in the exposure might be expected in such women. We examine the risk of preterm delivery in women with zero fish intake during a prolonged period of pregnancy; this question could not be addressed with data from any of the three other cohorts mentioned [21, 23, 24]. Finally, we examine if seafood intake is associated with increased risk of elective and postterm delivery; this possibility has been suggested by some earlier trials with fish oil [8, 9].

## Population and methods

All pregnant women attending routine antenatal care in Aarhus, Denmark, were invited to complete self-administered questionnaires in gestation weeks 16 and 30; the study base has been described in detail elsewhere [17, 25]. During 1992–1996 the questionnaire contained questions regarding intake of fish and fish oil. Only singleton, live born babies without detected malformations were included in the analysis. Women reporting intake of fish oil supplements were excluded.

### *Exposure variables*

In Denmark fish is mainly eaten as part of a hot meal, open sandwich, or cold in a green or pasta salad [26]. Frequencies by which such meals are consumed in the study population (Aarhus) have been shown to be strong and independent predictors of variation in erythrocyte *n*-3 fatty acids, without considering whether the meals contained fat or lean fish [26]. Four questions were therefore posed: *How often did you eat* (1) *fish in a hot meal*, (2) *bread with fish*, (3) *green salad or pasta salad with fish, and* (4) *fish oil as a supplement*. The women were asked to understand the term 'fish' as also comprising roe, prawn, crab and mussel. Each question had six predefined response categories: *never, less than once per month, 1–3 times per month, 1–2 times per week, 3–6 times per week, every day*. In the 16-week questionnaire, women were asked to let their responses represent the period from when they knew they were pregnant and until completing the questionnaire, whereas in the 30-weeks questionnaire, women were asked to let their responses cover the period from around gestation week 18 until completing the 30-week questionnaire.

To limit the number of variables simultaneously at play, analyses were in the earlier report [17] restricted to those 1304 women who had eaten no fish salad. However, because measures of association between the remaining fish variables and pregnancy duration tended to be similar across levels of fish salad intake, and because the salad intake level in itself did not appear to be a determinant of timing of spontaneous delivery (data not shown), the salad intake level was in this report disregarded in the formation of exposure groups. To secure substantial exposure contrasts, four comparison groups with reasonable sample sizes were defined in such a way that both the defining variables increased progressively: women who had consumed fish as hot meal *and* as open sandwiches (1) zero times, (2) more often, but less than once per month, (3) 1–3 times per month, and (4) once or more often per week. Women consuming fish as hot meal and as open sandwich at different frequencies were excluded in order to obtain maximum contrast between the exposure groups and to ensure a monotonously increasing exposure intensity across the exposure groups.

### *Outcome variables*

Gestational age was assessed by early ultrasound in 71%, else from menstrual data or best clinical judgment. Preterm delivery was defined as delivery before 259 days; early preterm delivery was delivery before 238 days. Postterm delivery was defined as delivery at day 294 or later.

### *Co-variates*

In all models, the following variables were included as covariates: Sex of infant (0, 1); maternal smoking (0, 1–9, 10 + cigarettes per day) and alcohol consumption ( < 1, 1 + drinks per week in pregnancy); maternal age ( < 20, 20–29, 30–39, 40 + years), parity (0, 1 +), height ( < 160, 160–169, 170–179, 180 + cm) and pre-pregnant weight ( < 50, 50–59, 60–69, 70–79, 80 + kg); and maternal educational length ( < 8, 8–9, 10 + years). Elective delivery, defined as induced vaginal delivery or elective caesarean section, was taken into account in some models.

### *Statistical analyses*

Odds ratios were assessed from a logistic regression model including dummy variables representing each fish intake level. The highest intake group was the referent. We adjusted for joint confounding by including the variables (see co-variate list) as explanatory variables simultaneously in the models. Trend tests for Odds ratios were performed by including the fish intake levels coded as 1,2,3,4 and testing the significance of this variable. Differences in continuous outcome were assessed using a linear regression model, and hazard ratios were assessed from a Cox regression model, regarding elective delivery a censoring event [27]. The Cox regression model assumes independent censoring: that is, women who have elective deliveries must not differ from the remaining women with respect to the (unobserved) uncensored gestational age.

For preterm delivery and early preterm delivery, also the Cochran–Armitage test for trend in binomial proportions was performed.

Observations with missing values of any of the confounders were deleted from the data set prior to fitting the regression models. That is, the 'crude' and 'adjusted' estimates are based on the same data set. In any analysis, no more than 11% of subjects were excluded due to missing values. The presented percentages are based on the full data set.

### *Ethics*

The protocol was approved by the local Scientific Ethics Committee. An informed consent form was used.

## Results

### *Analyses based solely on dietary information reported in the 16-weeks questionnaire*

When the analyses were based on frequencies of fish meals reported for the first period, pregnancy duration was shortened by 3.9 (95% CI: 2.2–5.6) days and odds of preterm and early preterm delivery were increased by a factor 2.4 (95% CI: 1.2–4.6) and 7.1 (95% CI: 1.5–34), respectively, in women consuming fish as warm meal and as sandwich zero times vs. at least once per week (Table 1). The corresponding hazard ratio for spontaneous delivery was 1.4 (1.2–1.6). Figure 1 shows Kaplan–Meier survival curves, stratified on the fish intake groups.

### *Analyses based solely on dietary information reported in the 30-weeks questionnaire*

When the analyses were based on frequencies of fish meals reported for the second period (Table 2), pregnancy duration was shortened by 3.1 days (95% CI: 1.4–4.8) and odds of preterm and early preterm delivery were increased by a factor 2.4 (95% CI: 1.2–4.8) and 2.2 (95% CI: 0.5–9.5) respectively in women consuming fish as warm meal and as sandwich zero times vs. at least once per week. The corresponding hazard ratio was 1.3 (95% CI: 1.1–1.5). For all measures of association, the 95% CIs for these estimates overlapped greatly with the corresponding estimates based on frequencies reported for the first period (Table 1).

### *Analyses based on women reporting constant intake in the two questionnaires*

If we restricted the sample to women who had given identical responses to all three questions about frequencies of fish meals, it was reduced to 764 women (Table 3). In this subset of the women, pregnancy duration was shortened by 8.6 days (95% CI: 5.5–11.7) and odds of preterm delivery were increased by a factor 20 (95% CI: 2.3–165), respectively, in women consuming fish as warm meal and as sandwich zero times vs. at least once per week (a confounder adjusted Odds ratio of early preterm delivery could not be estimated due to zero numbers in some of the critical cells). Imprecision of preterm birth Odds ratio estimates in this reduced sample should, however, be noted. The corresponding hazard ratio of spontaneous delivery was 1.9 (95% CI: 1.4–2.5). Figure 2 shows Kaplan–Meier survival curves, stratified on the fish intake groups. When the criterion of reporting constant intake in the two questionnaires was applied, all estimates of association tended to be strengthened substantially compared to the earlier analyses (Tables 1 and 2). The 95% CIs for difference in pregnancy duration between the highest and lowest exposure groups did not overlap with the corresponding estimates obtained for the first and second periods separately, whereas the CIs for the hazard ratio and for Odds ratio of preterm delivery overlapped marginally (Table 3 vs. Tables 1 and 2).

### *Relation between fish intake and risks of postterm delivery and elective delivery*

Consuming zero fish was associated with a reduced risk of postterm delivery, both when fish intake was assessed in gestation week 16 and 30 (Table 4). When the criterion of constant fish intake during the two periods was applied, the Odds ratio was 0.34 (95% CI: 0.12–0.95) (Table 4, panel C). Zero fish intake tended also to be associated with reduced risk of elective delivery when fish intake was assessed in weeks 16 and 30, respectively (Table 4, panels A, B), although none of the confounder adjusted estimates were statistically significant.

**Table 1.** Fish intake in the first trimester of pregnancy in relation to risk of preterm delivery, risk of early preterm delivery, mean gestational age and hazard rate of spontaneous delivery. Only women who had consumed hot fish meals and fish sandwiches with the same frequencies are included

| Fish intake | Number of subjects[a] | Preterm delivery %[a] | Early preterm delivery %[a] | | Preterm delivery Odds ratio[b] (95% CI) | Early preterm delivery Odds ratio[b] (95% CI) | Gestational age Mean difference[b] (95% CI) | Gestational age Hazard ratio[c] (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Zero intake | 308 | 7.14 | 1.95 | Crude | 2.46 (1.33,4.56) | 4.57 (1.09,19.3) | −4.26 (−5.86, −2.66) | 1.39 (1.20,1.60) |
| | | | | Adj.† | 2.38 (1.23,4.61) | 7.09 (1.50,33.5) | −3.91 (−5.58,−2.24) | 1.38 (1.18,1.60) |
| < Each month | 683 | 4.39 | 1.02 | Crude | 1.37 (0.78,2.41) | 2.71 (0.70,10.5) | −1.72 (−2.94, −0.50) | 1.11 (0.99,1.24) |
| | | | | Adj.† | 1.28 (0.72,2.30) | 3.11 (0.77,12.5) | −1.42 (−2.67, −0.18) | 1.10 (0.98,1.23) |
| Each month | 1511 | 2.51 | 0.20 | Crude | 0.78 (0.46,1.33) | 0.52 (0.10,2.56) | −0.47 (−1.49,0.56) | 1.09 (0.99,1.19) |
| | | | | Adj.† | 0.78 (0.46,1.34) | 0.53 (0.11,2.64) | −0.47 (−1.49,0.55) | 1.10 (1.00,1.21) |
| Each week | 785 | 3.18 | 0.38 | Crude | 1 (ref.) | 1 (ref.) | 0 (ref.) | 1 (ref.) |
| | | | | Adj.† | 1 (ref.) | 1 (ref.) | 0 (ref.) | 1 (ref.) |
| Trend test | | $p < 0.001$* | $p < 0.001$* | Crude | $p = 0.001$** | $p = 0.003$** | $p < 0.001$** | $p < 0.001$** |
| | | | | Adj.† | $p = 0.008$** | $p = 0.002$** | $p < 0.001$** | $p < 0.001$** |

†Adjusted for infant sex and maternal smoking, alcohol consumption, age, parity, height, pre-pregnant weight and educational length.
*Cochran–Armitage trend test (one-sided).
**Test performed in a (multivariate) regression model including the fish intake levels coded as 1,2,3,4.
[a]Based on full data set (n = 3287).
[b]Based on reduced data set with information on confounders (n = 3016).
[c]Based on reduced data set with information on confounders and whether the delivery was spontaneous or elective (n = 2923).

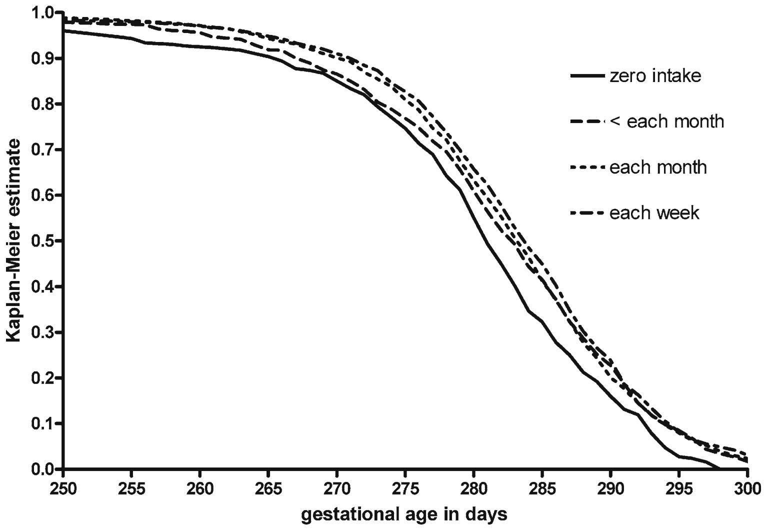


**Figure 1.** Kaplan–Meier survival curves stratified by level of fish intake, recorded in week 16 of gestation.

## Discussion

Never consuming fish in the first two trimesters of pregnancy appeared to be a strong risk factor for preterm delivery in Danish women, and all measures of association tended to become stronger when the sample was restricted to women reporting identical intake in the two periods.

The latter may simply reflect reduced misclassification due to the use of repeated measurements [28]. It is possible that the subset of women who reported (three to four months apart) the same frequencies for both periods may be particularly well suited as a study group to examine relationship between self reported dietary exposures and pregnancy outcome, when the primary interest is not to identify the periods in pregnancy during which the putative dietary factor is exerting its action; compared to other women, they may have more stable lifestyle and be more capable to reporting accurately regarding their dietary intake.

Our study had several strengths. The obstetrical data derived from a highly specialised university ward and can be assumed to be of good quality. We were able to account for the differential occurrences of elective deliveries across the exposure groups, by applying Cox regression which regarded elective delivery as a censoring event. The fish intake questions have earlier been validated against biomarkers in the study population (Aarhus) [26]. We had dietary data for two separate periods in pregnancy, which enabled us to focus on women with constant intake. We were able to adjust for a number of important potential confounding factors.

Weaknesses of our study include that we had no information on other dietary factors than fish, or on other potentially important confounders such as nausea or vomiting during pregnancy which may be associated with fish intake. Moreover, the restrictions we applied reduced the sample size substantially; nevertheless we were able to detect strong associations. We are, however, aware that preterm birth odds ratio estimates in our reduced sample should be interpreted with care due to very wide CIs, but we believe that the tendency in these estimates form an important message. And finally, because of the fact that this was an observational study, we cannot eliminate potential confounding by factors we were unable to adjust for in the analysis.

After our first report (based on the same data as here but not taking second trimester seafood exposure into account) [17], three reports have attempted to replicate our findings. One was based on 10,040 women from the ALSPAC birth cohort in Bristol [21]. The authors replicated, as closely as was possible with their data, our earlier analytic strategy and analyses [17] and, notably, they were unable to detect any association with length of gestation or preterm risk. However, women were asked in week 32 of gestation to complete a questionnaire which included three questions regarding frequency of meals with white fish; other fish; or shell fish, and response options ranged from never or rarely; once in 2 weeks, 1–3 times per week, 4–7 times per week, or more than once a day. With the results from the present study in mind [17], the possibility cannot be rejected that the relatively brief time period represented by the exposure measure, and the fact that the researchers were unable to identify a very low or zero exposure group beyond the criterion 'less than twice a month', could have undermined the possibility to detect any association in these data. A much smaller study undertaken in a population with a large proportion of high fish consumers (Reykjavík), was based on 491 women who completed a food frequency questionnaire after delivery [24].

**Table 2.** Fish intake in the second trimester of pregnancy in relation to risk of preterm delivery, risk of early preterm delivery, mean gestational age and hazard rate of spontaneous delivery. Only women who had consumed hot fish meals and fish sandwiches with the same frequencies are included

| Fish intake | Number of subjects[a] | Preterm delivery %[a] | Early preterm delivery %[a] | | Preterm delivery Odds ratio[b] (95% CI) | Early preterm delivery Odds ratio[b] (95% CI) | Gestational age Mean difference[b] (95% CI) | Gestational age Hazard ratio[c] (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Zero intake | 304 | 7.24 | 1.64 | Crude | 2.78 (1.47,5.26) | 1.93 (0.51,7.23) | −3.96 (−5.57, −2.34) | 1.36 (1.18,1.58) |
| | | | | Adj.† | 2.38 (1.18,4.78) | 2.17 (0.50,9.46) | −3.12 (−4.83, −1.40) | 1.28 (1.09,1.50) |
| < Each month | 677 | 4.14 | 1.03 | Crude | 1.48 (0.81,2.70) | 1.50 (0.47,4.75) | −1.15 (−2.42,0.11) | 1.08 (0.96,1.21) |
| | | | | Adj.† | 1.36 (0.73,2.53) | 1.73 (0.52,5.72) | −0.89 (−2.18,0.40) | 1.06 (0.94,1.20) |
| Each month | 1546 | 2.59 | 0.45 | Crude | 0.81 (0.46,1.44) | 0.46 (0.13,1.58) | 0.12 (−0.94,1.18) | 1.01 (0.92,1.11) |
| | | | | Adj.† | 0.80 (0.45,1.41) | 0.50 (0.14,1.75) | 0.04 (−1.02,1.10) | 1.03 (0.93,1.13) |
| Each week | 715 | 2.94 | 0.70 | Crude | 1 (ref.) | 1 (ref.) | 0 (ref.) | 1 (ref.) |
| | | | | Adj.† | 1 (ref.) | 1 (ref.) | 0 (ref.) | 1 (ref.) |
| Trend test | | $p < 0.001$* | $p = 0.04$* | Crude | $p < 0.001$** | $p = 0.11$** | $p < 0.001$** | $p < 0.001$** |
| | | | | Adj.† | $p = 0.006$** | $p = 0.13$** | $p < 0.001$** | $p = 0.009$** |

†Adjusted for infant sex and maternal smoking, alcohol consumption, age, parity, height, pre-pregnant weight and educational length.
*Cochran–Armitage trend test (one-sided).
**Test performed in a (multivariate) regression model including the fish intake levels coded as 1,2,3,4.
[a]Based on full data set (n = 3242).
[b]Based on reduced data set with information on confounders (n = 2965).
[c]Based on reduced data set with information on confounders and whether the delivery was spontaneous or elective (n = 2879).

**Table 3.** Fish intake in the first and second trimester of pregnancy in relation to risk of preterm delivery, risk of early preterm delivery, mean gestational age and hazard rate of spontaneous delivery. Only including women reporting same intake in the two trimesters, and only including women who had consumed hot fish meals and fish sandwiches with the same frequencies

| Fish intake | Number of subjects[a] | Preterm delivery %[a] | Early preterm delivery %[a] | | Preterm delivery Odds ratio[b] (95% CI) | Early preterm delivery Odds ratio[b] (95% CI) | Gestational age Mean difference[b] (95% CI) | Gestational age Hazard ratio[c] (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Zero intake | 165 | 9.70 | 2.42 | Crude | 13.6 (1.78,104.8) | Undefined | −7.60 (−10.4, −4.77) | 1.81 (1.40,2.33) |
| | | | | Adj.† | 19.6 (2.32,165.2) | | −8.57 (−11.7, −5.46) | 1.90 (1.42,2.53) |
| < Each month | 150 | 2.00 | 0.67 | Crude | 2.67 (0.27,26.0) | Undefined | −2.14 (−5.01,0.72) | 1.20 (0.93,1.56) |
| | | | | Adj.† | 3.25 (0.32,32.7) | | −2.64 (−5.61,0.32) | 1.22 (0.93,1.60) |
| Each month | 322 | 2.17 | 0 | Crude | 2.46 (0.29,20.6) | Undefined | −1.83 (−4.31,0.65) | 1.14 (0.91,1.43) |
| | | | | Adj.† | 2.67 (0.32,22.6) | | −2.12 (−4.59,0.34) | 1.18 (0.94,1.48) |
| Each week | 127 | 1.57 | 0 | Crude | 1 (ref.) | Undefined | 0 (ref.) | 1 (ref.) |
| | | | | Adj.† | 1 (ref.) | | 0 (ref.) | 1 (ref.) |
| Trend test | | $p < 0.001$* | $p = 0.001$* | Crude | $p < 0.001$** | – | $p < 0.001$** | $p < 0.001$** |
| | | | | Adj.† | $p < 0.001$** | – | $p < 0.001$** | $P < 0.001$** |

†Adjusted for infant sex and maternal smoking, alcohol consumption, age, parity, height, pre-pregnant weight and educational length.
*Cochran–Armitage trend test (one-sided).
**Test performed in a (multivariate) regression model including the fish intake levels coded as 1,2,3,4.
[a]Based on full data set (n = 764).
[b]Based on reduced data set with information on confounders (n = 705).
[c]Based on reduced data set with information on confounders and whether the delivery was spontaneous or elective (n = 686).

**Table 4.** Fish intake in pregnancy in relation to risk of postterm delivery and risk of elective delivery. Only women who had consumed hot fish meals and fish sandwiches with the same frequencies are included. Panel A, B and C reflect fish intake in the first trimester, the second trimester, and both the first and second trimester, respectively; moreover, in panel C, only women reporting same intake for the two trimesters are included

| Fish intake | Postterm delivery %[a] | | Postterm delivery Odds ratio[b] (95% CI) | | Elective delivery %[c] | | Elective delivery Odds ratio[b] (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| *Panel A: Grouping based on fish intake recorded in week 16 of gestation* | | | | | | | | |
| Zero intake | 6.49 | Crude | 0.55 | 0.33,0.93 | 3.97 | Crude | 0.69 | 0.36,1.33 |
| | | Adj.† | 0.57 | 0.33,0.98 | | Adj. | 0.69 | 0.35,1.36 |
| < Each month | 10.69 | Crude | 0.83 | 0.59,1.17 | 6.45 | Crude | 1.06 | 0.68,1.63 |
| | | Adj.† | 0.85 | 0.60,1.20 | | Adj. | 1.01 | 0.65,1.59 |
| Each month | 10.99 | Crude | 0.90 | 0.68,1.19 | 5.46 | Crude | 0.78 | 0.53,1.15 |
| | | Adj.† | 0.88 | 0.67,1.17 | | Adj. | 0.77 | 0.52,1.14 |
| Each week | 11.97 | Crude | 1 | | 6.24 | Crude | 1 | |
| | | Adj.† | 1 | | | Adj. | 1 | |
| Trend test | $p = 0.01$* | Crude | $p = 0.03$** | | $p = 0.21$* | Crude | $p = 0.67$** | |
| | | Adj.† | $p = 0.06$** | | | Adj. | $p = 0.58$** | |
| *Panel B: Grouping based on fish intake recorded in week 30 of gestation* | | | | | | | | |
| Zero intake | 4.61 | Crude | 0.34 | 0.18,0.63 | 4.38 | Crude | 0.63 | 0.33,1.21 |
| | | Adj.† | 0.40 | 0.21,0.77 | | Adj. | 0.67 | 0.33,1.33 |
| < Each month | 10.78 | Crude | 0.89 | 0.63,1.26 | 6.81 | Crude | 1.02 | 0.66,1.57 |
| | | Adj.† | 0.93 | 0.65,1.34 | | Adj. | 0.99 | 0.63,1.56 |
| Each month | 11.13 | Crude | 0.94 | 0.70,1.25 | 6.15 | Crude | 0.87 | 0.59,1.26 |
| | | Adj.† | 0.90 | 0.68,1.21 | | Adj. | 0.84 | 0.57,1.23 |
| Each week | 11.61 | Crude | 1 | | 7.36 | Crude | 1 | |
| | | Adj.† | 1 | | | Adj. | 1 | |
| Trend test | $p = 0.003$* | Crude | $p = 0.005$** | | $p = 0.09$* | Crude | $p = 0.41$** | |
| | | Adj.† | $p = 0.04$** | | | Adj. | $p = 0.50$** | |
| *Panel C: Grouping based on fish intake recorded in week 16 and 30 of gestation; only women reporting same intake for the two trimesters are included* | | | | | | | | |
| Zero intake | 4.24 | Crude | 0.33 | 0.13,0.83 | 3.68 | Crude | 0.35 | 0.13,0.95 |
| | | Adj.† | 0.34 | 0.12,0.95 | | Adj. | 0.33 | 0.11,1.02 |
| < Each month | 9.33 | Crude | 0.68 | 0.31,1.48 | 6.76 | Crude | 0.64 | 0.27,1.52 |
| | | Adj.† | 0.71 | 0.31,1.64 | | Adj. | 0.57 | 0.23,1.44 |
| Each month | 12.73 | Crude | 1.01 | 0.54,1.89 | 6.13 | Crude | 0.54 | 0.26,1.14 |
| | | Adj.† | 0.95 | 0.50,1.80 | | Adj. | 0.51 | 0.24,1.09 |
| Each week | 12.60 | Crude | 1 | | 10.48 | Crude | 1 | |
| | | Adj.† | 1 | | | Adj. | 1 | |
| Trend test | $p = 0.002$* | Crude | $p = 0.007$** | | $p = 0.02$* | Crude | $p = 0.07$** | |
| | | Adj.† | $p = 0.04$** | | | Adj. | $p = 0.08$** | |

†Adjusted for infant sex and maternal smoking, alcohol consumption, age, parity, height, pre-pregnant weight and educational length.
*Cochran–Armitage trend test (one-sided).
**Test performed in a (multivariate) regression model including the fish intake levels coded as 1, 2, 3, 4.
[a]Based on full data set (n = 3287, 3242, 764 in panels A, B and C, respectively).
[b]Based on reduced data set with information on confounders (as in Tables 1–3).
[c]Based on dataset with information on whether the delivery was spontaneous or elective (n = 3186, 3148, 745 in panels A, B and C, respectively).

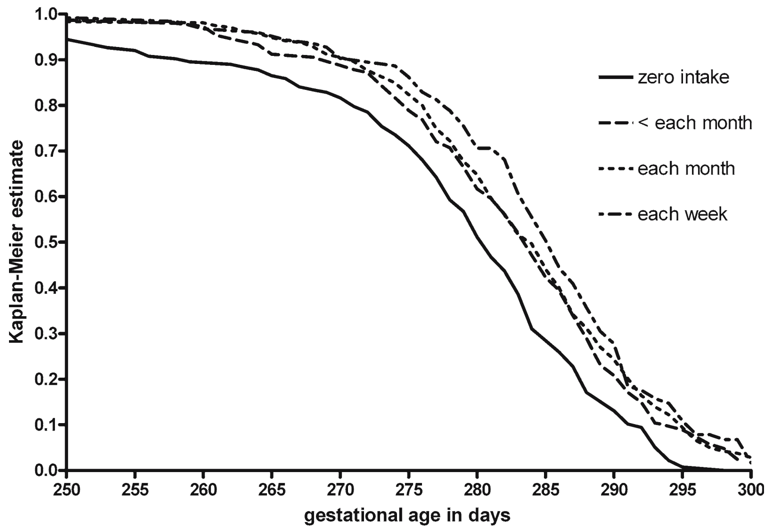


**Figure 2.** Kaplan–Meier survival curves stratified by level of fish intake, recorded in week 16 and 30 of gestation; only women reporting same intake in the two trimesters are included.

Women were asked to report on frequency of warm fish meals and fish meals as bread spread or starters in pregnancy, in categories of 4–6 times per week, 2–3 times per week, 4–6 times per month, or rarer. The authors reported that pregnancy duration was not associated with fish intake. Again, however, it was not possible to identify a zero group with the questions posed; the authors stated that only 1% never consumed any fish in this population. The most recent study was based on the Viva birth cohort in Boston [23]. It comprised 2109 women who were asked twice in pregnancy, by the end of the first and second trimester, respectively, to complete a 130-item food frequency questionnaire. Four questions asked about intake during the past months of canned tune fish; shrimps, lobster, scallops, clamps; dark meat fish; and others. Response options ranged from never or less than once per month, and up to one or more servings per day. Fish intake assessed at neither point in time was related to length of gestation. However, with the data at hand the researchers were unable to clearly identify a zero exposure group at each point in time, and they did not take advantage of using both questionnaires to identify a subgroup of women with constant low intake over a prolonged period, as was done in the present analysis.

Our study could not substantiate that seafood intake assessed closer to the expected date of delivery was more closely associated with the timing of delivery than intake assessed earlier. The pattern observed could not, however, reject the possibility that the putative effect of $n$-3 fatty acids on timing of delivery is fast and of short duration [7]. Under the assumption that this is actually the case, intake reported for the first and second trimester could well be equally predictive of intake shortly before delivery, and one would also expect the predictive power to increase when the first and second trimester assessments agreed. Matters could well be more complex than that. There could be both slow and fast effects, depending on the extent to which the woman's body stores of $n$-3 fatty acids are depleted.

We also found that both the risk of postterm delivery and of elective delivery was raised in the high fish strata, a pattern which agrees with the hypothesis that marine $n$-3 fatty acids delay timing of spontaneous delivery. However, this finding also indicates [4] that one should enjoin great caution if a recommendation of increased fish consumption is to be used in the prevention of preterm delivery and its associated complications. Another issue to consider in this respect is the findings by other researchers indicating that contaminants from fish may have the potential to harm foetal brain development [29].

In conclusion, never consuming fish in the first two trimesters of pregnancy appeared to be an extremely strong risk factor for preterm delivery in Danish women, but was simultaneously associated with reduced risks of elective delivery and postterm delivery. Future observational studies of impact of fish intake in pregnancy on timing of spontaneous delivery should make sure to assess exposures during broad time windows of pregnancy and to include and clearly identify women who never consume fish or consume fish very rarely. Correspondingly, future randomised controlled trials of effect of fish oil supplementation on pregnancy duration should make every effort possible to optimise compliance to allocated treatment regimens as well as to secure efficient masking particularly in the control group, the latter to prevent self supplementation with fish oil and thereby maintenance of the low exposure status in the control group.

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*Address for correspondence:* Sjurdur F Olsen, Department of Epidemiology, Institute of Public Health, University of Aarhus, Vennelyst Boulevard 6, DK-8000 Århus C, Denmark
Phone: +45 89 42 60 97
E-mail: sfo@soci.au.dk