

ORIGINAL ARTICLE

Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: The Generation R Study

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BACKGROUND/OBJECTIVES: Maternal fish consumption during pregnancy might influence the fetal immune system through anti-inflammatory effects of omega-3 fatty acids, and might affect the risks of childhood asthma and atopy. In Generation R, a prospective cohort study in the Netherlands, we examined the associations of first trimester fish consumption with childhood wheezing and eczema in the first 4 years of life.

METHODS: In total, 2976 mothers completed a 293-item semiquantitative food frequency questionnaire covering dietary intake in the first trimester. The occurrence of wheezing and eczema was yearly assessed by questionnaires.

RESULTS: Median weekly fish consumption was 83 (95% range 0–316) grams per week. We observed no consistent associations of maternal total-, lean- or fatty-fish consumption during pregnancy with the risks of childhood wheezing. Maternal shellfish consumption of 1–13 g per week was associated with overall increased risks of childhood wheezing and eczema (OR 1.20 (1.04, 1.40) and OR 1.18 (1.01, 1.37), respectively). Maternal fatty fish consumption of 35–69 g per week was associated with increased overall risks of childhood eczema (OR 1.17 (1.00, 1.38)), but maternal total- or lean-fish consumption was not.

CONCLUSIONS: During pregnancy, shellfish consumption was associated with increased risks of wheezing and eczema, while fatty fish consumption was associated with a higher risk of eczema only. Maternal total fish or lean fish consumption were not associated with wheezing or eczema. Further studies are needed to replicate these findings and to explore underlying mechanisms.

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Keywords: pregnancy; fish consumption; asthma symptoms; eczema; cohort study; atopy

INTRODUCTION

Specific adverse fetal and infant exposures might lead to the development of asthma and atopic disease.^{1–3} Suboptimal maternal diet during pregnancy is one of these exposures, which might lead to fetal lung development adaptations and to fetal immune system programming.^{3–5} Previous studies investigating maternal diet during pregnancy in relation with childhood asthmatic and atopic diseases mainly focused on vitamins, allergenic foods and fish consumption.⁵ Fish, in particular fatty fish, contains anti-inflammatory n-3 PUFAs, which regulate immune responses and might be protective against atopic diseases and asthma.^{4,6} On the other hand, contaminants of fish might counterbalance the protective effects of n-3 PUFAs when fish consumption is low.⁷ Many observational and interventional studies, explored the associations of maternal fish consumption or fish oil supplementation during pregnancy with the risks of childhood asthma and atopy.^{8–22} Although these studies showed a protective effect on at least one outcome, they were not all able to adjust for potential confounders. Also, previous intervention studies differed in selection of participants, types of intervention and definition of outcome measures. Thus, whether maternal fatty fish consumption or fish oil supplementation has protective effects on the development of atopic diseases in the offspring remains unclear. Furthermore, fish oil supplementation may not have the same effects as fish consumption from normal diet, especially when fish consumption is low.

Therefore, we examined the associations of maternal first trimester fish consumption during pregnancy with the risks of childhood wheezing and eczema in the first 4 years of life in a population-based prospective cohort study among 2796 Dutch mothers and their children with a relatively low fish intake.

MATERIALS AND METHODS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards in Rotterdam.²³ All children were born between April 2002 and January 2006. The study has been approved by the Medical Ethical Committee of the Erasmus Medical Center in Rotterdam (MEC 198.782/2001/31). Written informed consent was obtained from all participants. The present study was performed in Dutch participants only, as the food frequency questionnaire (FFQ) was validated for assessment of dietary intake in a Dutch population. In total, 3433 Dutch mothers were included during pregnancy and fully participated in the postnatal phase of the study. To assess first trimester dietary intake, we selected mothers who were enrolled in the study before a gestational age of 25 weeks ($n=3361$). Information about fish consumption during pregnancy was available in 2969 (88%) of these mothers. We excluded twin pregnancies ($n=42$) to prevent bias due to correlation. Of the remaining 2927 children, we excluded 131 (4%) children of whom we had no information on wheezing and eczema available, leading to a population for analysis of 2796 mothers and children (Figure 1).

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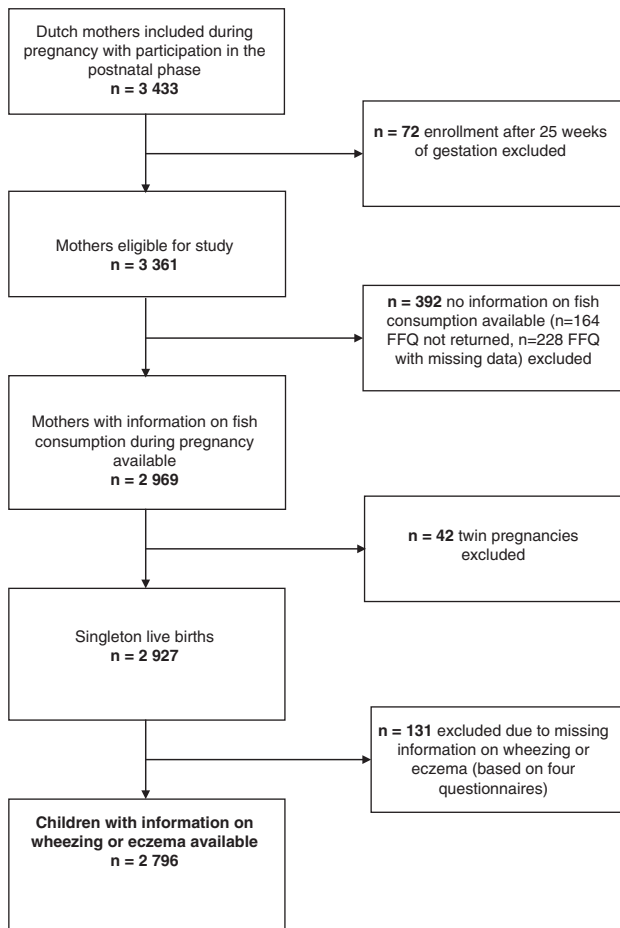


Figure 1. Flow chart of participants included for analysis

Fish consumption during pregnancy

We assessed maternal first trimester dietary intake, including fish consumption using a modified version of the validated semiquantitative FFQ of Klipstein-Grobush *et al.*²⁴ The FFQ was administered at enrollment in the study (median gestational age 13.4 weeks, 95% range 10.1–21.8), as main interest was in the long-term effects of maternal diet during early pregnancy, which might be a critical period for the fetal lung development. The FFQ considered food intake over the prior 3 months, thereby covering dietary intake within the first trimester of pregnancy. The FFQ consists of 293 items structured to meal patterns. Questions include consumption frequency, portion size, preparation method and additions. Portion sizes were estimated using Dutch household measures and colored photographs of foods showing different portion sizes.²⁵ To calculate average daily nutritional values, the 2006 version of the Dutch food composition table was used. Frequency of fish consumption was assessed for total fish consumption and different types of fish. On the basis of the nutrient content and information from previous studies, we assessed consumption of different fish types by seven categories: lean fish (codfish, plaice, catfish, sole fish, tuna, whiting and haddock), moderately fatty fish (trout, anchovy and gurnard), fatty fish (salmon, herring, mackerel, eel, sardines, halibut and bloater), shellfish (crab, lobster, shrimps and mussels), processed fish (fish fingers, fish burgers, crumbed and fried fish), fish derived from liver (haddock liver) and roe (soft and hard roe). For the analysis of total fish, we aggregated all fish consumed, and for the analysis of fatty fish we aggregated moderately fatty fish and fatty fish. Processed fish, roe and fish derived from the liver were not further analyzed. On the basis of the distribution of fish consumption and the number of subjects, we created five categories of total fish consumption (0; 1–69; 70–139; 140–209; and >210 g per week), four categories of lean fish consumption (0; 1–34; 35–69; and >70 g per week), four categories of fatty fish

consumption (0; 1–34; 35–69; and >70 g per week) and three categories of shellfish consumption (0; 1–13; >14 g per week) as previously described.²⁶

Wheezing and eczema symptoms

We obtained information on wheezing (no, yes) and doctor-attended eczema (no, yes) in the last year by questionnaires, adapted from the International Study on Asthma and Allergy in Childhood²⁷ at the ages of 1, 2, 3 and 4 years. Doctor-attended eczema at age 1 refers to eczema between the ages 6 to 12 months. Response rates for the questionnaires at the ages of 1, 2, 3 and 4 years were 71, 76, 72 and 73%, respectively.²⁸

Covariates

Information on maternal age, parity, socio-economical status, history of asthma or atopy, use of periconceptional folic acid supplements, prepregnancy body mass index and pet keeping were obtained by questionnaire, which was completed by the mother at enrollment. Maternal vegetable intake (gram per day) was derived from the FFQ that was administered at enrollment in the study. We used Pearson's correlations to assess whether other food groups were correlated with fish intake. We found a correlation of 0.206 between fish intake and intake of vegetables. Other food groups were not correlated with fish intake (correlations ranged from –0.086 to 0.063). Therefore, we only added consumption of vegetables as a covariate to the model. Socio-economic status was assessed using the highest maternal educational level and household income.²⁹ We used parity as a proxy for siblings, the correlation between those variables was high (Cohen's Kappa=0.87, $P<0.001$). Information about active maternal smoking and alcohol use during pregnancy was obtained by postal questionnaires sent during the first, second and third trimester of pregnancy. Information on maternal psychological distress was obtained by postal questionnaires at 20 weeks of gestation using the Brief Symptom Inventory.³⁰ A global severity index (0–100) was defined, which is a measure of current level or depth of the symptoms of psychological distress, and denotes overall psychological symptoms. Birth weight, gestational age at birth and sex of the children were obtained from midwife and hospital registries at birth. Postal questionnaires at the ages of 6 and 12 months provided information about breastfeeding (ever vs never), daycare attendance and lower respiratory tract infections (pertussis, bronchitis, bronchiolitis or pneumonia). Timing of introduction of complementary feeding of the children was assessed with a FFQ at the age of 14 months.

Statistical analysis

We used generalized estimating equations to analyze the associations of total-, lean- and fatty fish consumption categories with the risks of wheezing and eczema at the ages of 1, 2, 3 and 4 years. With generalized estimating equation analyses, repeatedly measured asthma symptoms over the time can be analyzed, taking the correlation between repeated measurements within the same subject into account. No fish consumption was used as the reference group for all analyses. Furthermore, we examined longitudinal overall effects of maternal fish consumption with wheezing and eczema in the first 4 years of life. All models were first performed unadjusted and subsequently adjusted for potential confounders. Selection of confounders was based on previous studies and univariate analyses. Covariates were included in the models, if the effect estimates changed 5% or more, or if they were strongly related with the outcomes of interest. We performed tests for trends by using consumption of total fish, lean fish and fatty fish in grams per week as a continuous variable in the generalized estimating equation models. As previous studies showed differences in associations of fish consumption during pregnancy with wheezing between children with and without a predisposition for asthma, we tested the interaction of maternal history of asthma or atopy with fish consumption, and stratified the analysis. The percentages of missing values within the population for analysis were lower or near to 10%, except for daycare attendance (17%), folic acid use (17%) and lower respiratory tract infections (35%). To prevent bias associated with missing data, missing values were multiple imputed based on the correlation of the missing variables with other characteristics. Ten imputed data sets were created and analyzed separately after, which results were combined. The statistical analyses were performed using the Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc. Chicago, IL, USA) and SAS 9.2 (SAS institute, Cary, NC, USA).

RESULTS

Population characteristics

Mothers were enrolled in our study at a mean age of 31.8 years (s.d. 4.0) and median pregnancy duration at intake of 13.4 weeks (95% range 10.1–21.8) (Table 1). Average total fish intake was 83 g per week (95% range 0–316). Of all mothers, 523 (18.7%) did not consume any type of fish during pregnancy. In total, 7.0% of the mothers had a weekly total fish consumption of more than 210 g, which is ~1.5 servings per week. Average lean fish intake was 28 g per week (95% range 0–149), average fatty fish intake was 32 g per week (95% range 0–150) and average shellfish intake was 0 g per week (95% range 0–35). Mean total energy intake was 2147 kcal per day (s.d. 498) (Table 1). The prevalence of wheezing declined from 30% at the age of 1 year, to 11% at the age of 4 years, and the prevalence of eczema declined from 23% at the age of 1 year, to 12% at the age of 4 years.

Maternal fish consumption and childhood wheezing

We observed no associations of maternal total fish consumption during pregnancy with childhood wheezing at the ages of 1–4 years (Table 2). Also, we did not observe consistent associations of maternal lean fish consumption with the overall risk of childhood wheezing. At the age of 3 years, we observed an inverse association of higher lean fish intake with wheezing (P for trend <0.01). We did not observe any association between maternal fatty fish consumption during pregnancy with overall and yearly risks of childhood wheezing. Shellfish consumption of 1–13 g per week was associated with an increased risk of wheezing (overall OR 1.20 (95% CI 1.04, 1.40)). Results of the unadjusted analysis are shown in Supplementary Table S1. We additionally stratified the analysis for maternal history of atopy or asthma, but results did not differ between the two groups. Also, P -value for an interactive effect of fish intake and maternal history of atopy or asthma on childhood wheezing was nonsignificant (data not shown).

Maternal fish consumption and childhood eczema

We did not observe associations of maternal total- or lean fish consumption during pregnancy with childhood eczema (Table 3). As compared with no fatty fish consumption, maternal fatty fish consumption of 35–69 g fatty fish per week increased the overall risk of childhood eczema (OR 1.17 (95% CI 1.00, 1.38)). The highest category of fatty fish consumption (>70 g per week) was not associated with eczema (OR 1.06 (95% CI 0.88, 1.38)) and P for trend was 0.68. Shellfish consumption of 1–13 g per week was associated with an increased risk of wheezing (overall OR 1.18 (95% CI 1.01, 1.37)). Results from the fully adjusted models were similar to the results from the unadjusted analysis (Supplementary Table S2). We additionally stratified the analysis for maternal history of atopy or asthma and the effect estimates did not change, although they were no longer statistically significant. P -value for an interactive effect of fish intake and maternal history of atopy or asthma on childhood eczema was nonsignificant (data not shown).

DISCUSSION

In this population-based prospective cohort study of Dutch pregnant women, maternal first trimester total-, lean- and fatty fish consumption were not associated with the risks of childhood wheezing. Also, maternal first trimester total fish and leanfish consumption were not associated with the risks of childhood eczema. Maternal first trimester fatty fish consumption was associated with an increased risk of childhood eczema. We did not find evidence for an interactive effect of maternal history of atopy or asthma and fish intake on wheezing or eczema.

Table 1. Characteristics of the mothers and their children ($n = 2796$)

Maternal characteristics	Observed data set	Imputed data set
Age (years)	31.8 (4.0)	31.8 (4.0)
Gestational age at enrollment (weeks) ^a	13.4 (10.1–21.8)	13.4 (10.1–21.8)
Prepregnancy body mass index	23.1 (3.7)	23.1 (3.7)
Parity (%)		
Nullipara	60.5 (1 691)	60.6 (1 693)
Multipara	39.4 (1 102)	39.4 (1 103)
Missing	0.1 (3)	
Household income (%)		
<2000 euro per month	15.3 (400)	16.0 (446)
≥ 2000 euro per month	84.7 (2 220)	84.0 (2 350)
Missing	6.3 (176)	
Highest education finished (%)		
Primary or secondary	34.9 (971)	35.0 (978)
Higher	65.1 (1 810)	65.0 (1 818)
Missing	0.5 (15)	
Distress during pregnancy (global severity index) ^a	0.12 (0.00–0.71)	0.12 (0.00–0.71)
History of asthma or atopy (%)		
No	61.8 (1 518)	61.8 (1 728)
Yes	38.2 (939)	38.2 (1 068)
Missing	12.1 (339)	
Smoking during pregnancy (%)		
No	78.1 (1 998)	77.5 (2 168)
Until pregnancy was known	9.3 (238)	9.8 (274)
Continued	12.6 (323)	12.7 (354)
Missing	8.5 (237)	
Alcohol use during pregnancy (%)		
No	48.0 (1 204)	47.6 (1 331)
Until pregnancy was known	12.8 (322)	13.4 (374)
Continued	39.1 (981)	39.0 (1 091)
Missing	10.3 (289)	
Folic acid supplementation use (%)		
None	8.3 (192)	8.8 (247)
Postconception start	32.0 (739)	32.1 (898)
Preconception start	59.7 (1 379)	59.1 (1 652)
Missing	17.4 (486)	
Total daily energy intake (kcal)	2 147 (498)	2 147 (498)
Total fish intake (grams/week) ^a	83 (0–316)	83 (0–316)
Fatty fish intake (grams/week) ^a	32 (0–150)	32 (0–150)
Lean fish intake (grams/week) ^a	28 (0–149)	28 (0–149)
Shellfish intake (grams/week) ^a	0 (0–35)	0 (0–35)
Vegetables intake (grams/day) ^a	149 (54–305)	149 (54–305)
Pet keeping (%)		
No	58.5 (1 479)	58.3 (1 630)
Yes	41.5 (1 049)	41.7 (1 166)
Missing	9.6 (268)	
Children's characteristics		
Sex (%)		
Boy	50.1 (1 401)	50.1 (1 401)
Girl	49.9 (1 395)	49.9 (1 395)
Gestational age at birth (weeks) ^a	40.3 (36.0–42.4)	40.3 (36.0–42.4)
Birth weight (grams)	3 513 (544)	3 513 (544)
Breastfeeding (%)		
No	9.0 (248)	9.3 (261)
Yes	91.0 (2 494)	90.7 (2 535)
Missing	1.9 (54)	
Daycare attendance 1st year (%)		
No	30.2 (704)	31.9 (891)
Yes	69.8 (1 626)	68.1 (1 905)
Missing	16.7 (466)	
Lower respiratory tract infections in the 1st year (%)		
No	80.4 (1 466)	78.8 (2 202)
Yes	19.6 (358)	21.2 (594)
Missing	34.8 (972)	
Timing of introduction of complementary feeding (%)		
0–3 months	4.4 (80)	7.7 (216)
3–6 months	56.3 (1 030)	54.9 (1508)
After 6 months	39.3 (719)	38.3 (1072)
Missing	34.6 (967)	

Values are means (s.d.) or valid percentages (absolute numbers). Missings were 13.6% (379) for prepregnancy BMI and 9.4% (264) for global severity index.

^aMedians (95% range).

Table 2. Maternal fish consumption and risks of wheezing

Odds ratios (95% confidence interval) of wheezing (n = 2796)						
	n _{total}	Age 1, n _{cases} = 852	Age 2, n _{cases} = 513	Age 3, n _{cases} = 342	Age 4, n _{cases} = 321	Overall
<i>Total fish consumption (gram/week)</i>						
0	523	Reference	Reference	Reference	Reference	Reference
1–69	728	0.97 (0.74, 1.26)	0.89 (0.65, 1.25)	0.88 (0.57, 1.37)	0.87 (0.56, 1.34)	0.92 (0.77, 1.09)
70–139	908	0.92 (0.71, 1.19)	0.97 (0.72, 1.30)	0.86 (0.59, 1.24)	0.87 (0.56, 1.35)	0.91 (0.77, 1.08)
140–209	442	0.90 (0.65, 1.25)	0.89 (0.61, 1.28)	0.70 (0.45, 1.10)	0.87 (0.55, 1.39)	0.86 (0.70, 1.06)
> 210	195	1.02 (0.66, 1.57)	0.63 (0.38, 1.03)	0.65 (0.34, 1.27)	0.90 (0.43, 1.88)	0.83 (0.62, 1.12)
P for trend ^a		P = 0.77	P = 0.14	P = 0.20	P = 0.74	P = 0.22
<i>Lean fish consumption (gram/week)</i>						
0	980	Reference	Reference	Reference	Reference	Reference
1–34	728	1.22 (0.97, 1.53)	0.97 (0.74, 1.26)	0.86 (0.62, 1.18)	0.82 (0.58, 1.17)	1.02 (0.88, 1.19)
35–69	721	1.04 (0.80, 1.35)	0.79 (0.59, 1.06)	0.67 (0.49, 0.92)*	0.73 (0.52, 1.03)	0.86 (0.73, 1.02)
> 70	367	1.28 (0.92, 1.79)	0.89 (0.62, 1.27)	0.60 (0.39, 0.92)*	0.92 (0.61, 1.39)	0.99 (0.80, 1.23)
P for trend ^a		P = 0.12	P = 0.40	P < 0.01	P = 0.35	P = 0.22
<i>Fatty fish consumption (gram/week)</i>						
0	886	Reference	Reference	Reference	Reference	Reference
1–34	604	0.92 (0.72, 1.17)	1.14 (0.84, 1.55)	1.04 (0.73, 1.49)	1.08 (0.72, 1.63)	1.02 (0.86, 1.19)
35–69	795	0.86 (0.67, 1.12)	1.00 (0.76, 1.33)	0.94 (0.68, 1.29)	0.89 (0.60, 1.31)	0.91 (0.77, 1.08)
> 70	511	0.96 (0.73, 1.26)	0.99 (0.73, 1.35)	0.85 (0.57, 1.25)	0.95 (0.61, 1.48)	0.94 (0.78, 1.15)
P for trend ^a		P = 0.46	P = 0.40	P = 0.27	P = 0.56	P = 0.18
<i>Shellfish consumption (gram/week)</i>						
0	1 686	Reference	Reference	Reference	Reference	Reference
1–13	513	1.19 (0.94, 1.51)	1.26 (0.97, 1.70)	1.22 (0.87, 1.70)	1.11 (0.80, 1.55)	1.20 (1.04, 1.40)*
> 14	597	1.06 (0.85, 1.33)	1.19 (0.90, 1.57)	0.92 (0.65, 1.31)	0.96 (0.70, 1.32)	1.06 (0.92, 1.22)
P for trend ^a		P = 0.47	P = 0.23	P = 0.62	P = 0.74	P = 0.28

Values are odds ratios (with 95% confidence interval) and reflect the associations of fish consumption during pregnancy with wheezing in the offspring, compared with women with no fish consumption, based on generalized estimating equation models. *P-value. <0.05. All models were adjusted for maternal age, parity, highest completed education level, household income, history of asthma or atopy, use of periconceptional folic acid supplements, prepregnancy body mass index, pet keeping, smoking and alcohol use during pregnancy, total daily energy intake, vegetable intake, distress during pregnancy, gestational age at enrollment and child's birth weight, gestational age at birth, sex, breastfeeding, timing of introduction of complementary feeding, daycare attendance in the first year, lower respiratory tract infections in the first year.

^aTests for trend were based on generalized estimating equation models with fish consumption (gram/week) as a continuous variable.

A major strength of the present study is the population-based, prospective cohort design, the detailed information about fish intake, the repeatedly over time measured outcomes, and extensive information on a large number of potential confounders, which were taken into account. The response rate for the Generation R Study was ~61% with a loss to follow up percentage <10% during the first 4 years.²⁹ The nonresponse would lead to biased effect estimates if the associations would be different between those included and not included in the analyses. However, this seems unlikely because biased estimates in large cohort studies mainly arise from loss to follow up rather than from nonresponse at baseline.³¹ We prospectively collected detailed information on consumption of different types of fish, which enabled us to separately analyze the effect of total-, lean- and fatty fish. Nondifferential misclassification of fish consumption might have occurred. However, as mothers were not aware of this specific research question,²⁹ we do not expect that selective reporting had biased our results. We measured the main respiratory symptom outcome in our study using International Study on Asthma and Allergy in Childhood questionnaires. Although this method is validated from the age of 7 years, it is widely accepted in epidemiological studies among younger children^{32–34}, and reliably reflects the incidence of asthma symptoms in young children.³⁵ An earlier Dutch birth cohort study used identical International Study on Asthma and Allergy in Childhood questions, and observed similar prevalences of wheezing based on the International Study on Asthma and Allergy in Childhood questionnaires as in our study.³² In preschool children, a diagnosis of asthma is based on symptoms. Objective

tests, including spirometry or bronchial hyper responsiveness, are difficult to perform in young children and have limited applicability. We did not have objective measurements of atopy such as specific Immunoglobulin E blood or skin prick test measurements. However, we were able to use maternal history of atopy or asthma as a proxy for atopy of the child.

Fish, in particular fatty fish, contains anti-inflammatory n-3 PUFAs, which regulate immune responses and might be protective against atopic diseases and asthma.^{4,6} In our study, we did not observe consistent associations of maternal fish consumption during pregnancy with the risks of childhood wheezing. Furthermore, we observed no associations of maternal total- or lean fish consumption during pregnancy with risks of eczema in the offspring. Surprisingly, we found that some categories of fatty fish consumption increased the risks of childhood eczema. These observations are in contrast to results from previous studies, which mainly, but not consistent, suggest that maternal fish intake during pregnancy protects against the development of childhood asthma and atopy.^{8–22} Observational studies in large cohorts observed lower incidence of eczema in offspring of mothers with the highest fish consumption during pregnancy,^{19,21} but not lower incidences of wheezing or asthma. In the Netherlands, fish consumption is relatively low, which can explain the differences in the observations. The effects found in the other observational studies where among pregnant women with a fish consumption of at least once a week. In our population, only 7% of the mothers had a weekly total fish consumption of more than 210 g, which is ~1.5 servings per week. A previous study in the Netherlands, with similar levels of fish consumption,

Table 3. Maternal fish consumption and risks of eczema

Odds ratios (95% confidence interval) of eczema (n = 2796)						
	n _{total}	Age 1, n _{cases} = 643	Age 2, n _{cases} = 373	Age 3, n _{cases} = 254	Age 4, n _{cases} = 240	Overall
Total fish consumption (gram/week)						
0	523	Reference	Reference	Reference	Reference	Reference
1–69	728	1.06 (0.79, 1.42)	1.08 (0.75, 1.56)	0.89 (0.60, 1.33)	1.01 (0.66, 1.56)	1.03 (0.85, 1.25)
70–139	908	1.16 (0.86, 1.57)	1.12 (0.78, 1.61)	0.84 (0.57, 1.24)	0.89 (0.59, 1.35)	1.06 (0.88, 1.27)
140–209	442	1.03 (0.74, 1.45)	1.17 (0.79, 1.73)	0.79 (0.48, 1.31)	0.88 (0.53, 1.48)	0.96 (0.73, 1.28)
> 210	195	1.02 (0.66, 1.57)	0.95 (0.51, 1.75)	0.91 (0.47, 1.78)	0.88 (0.48, 1.63)	0.96 (0.73, 1.28)
P for trend ^a		P = 0.87	P = 0.96	P = 0.84	P = 0.51	P = 0.73
Lean fish consumption (gram/week)						
0	980	Reference	Reference	Reference	Reference	Reference
1–34	728	1.03 (0.76, 1.40)	1.08 (0.80, 1.46)	1.08 (0.76, 1.59)	1.13 (0.79, 1.61)	1.06 (0.89, 1.27)
35–69	721	1.05 (0.82, 1.36)	1.17 (0.86, 1.58)	0.85 (0.57, 1.26)	0.98 (0.66, 1.46)	1.04 (0.89, 1.22)
> 70	367	1.03 (0.73, 1.46)	1.10 (0.76, 1.59)	0.97 (0.60, 1.57)	0.73 (0.44, 1.21)	0.99 (0.79, 1.24)
P for trend ^a		P = 0.49	P = 0.73	P = 0.67	P = 0.31	P = 0.67
Fatty fish consumption (gram/week)						
0	886	Reference	Reference	Reference	Reference	Reference
1–34	604	1.13 (0.87, 1.46)	1.25 (0.89, 1.77)	1.10 (0.74, 1.61)	1.24 (0.82, 1.87)	1.17 (0.99, 1.38)
35–69	795	1.26 (0.97, 1.64)	1.22 (0.89, 1.66)	1.10 (0.75, 1.61)	0.93 (0.64, 1.35)	1.17 (1.00, 1.38)*
> 70	511	1.02 (0.75, 1.40)	1.21 (0.82, 1.77)	0.95 (0.63, 1.45)	1.04 (0.65, 1.68)	1.06 (0.88, 1.27)
P for trend ^a		P = 0.85	P = 0.58	P = 0.98	P = 0.79	P = 0.68
Shellfish consumption (gram/week)						
0	1 686	Reference	Reference	Reference	Reference	Reference
1–13	513	1.11 (0.85, 1.44)	1.26 (0.93, 1.70)	1.08 (0.75, 1.55)	1.38 (0.96, 2.00)	1.18 (1.01, 1.37)*
> 14	597	1.06 (0.82, 1.37)	1.11 (0.82, 1.51)	0.81 (0.53, 1.23)	0.94 (0.66, 1.36)	1.02 (0.86, 1.21)
P for trend ^a		P = 0.82	P = 0.46	P = 0.92	P = 0.92	P = 0.64

Values are odds ratios (with 95% confidence interval) and reflect the associations of fish consumption during pregnancy with eczema in the offspring, compared with women with no fish consumption, based on generalized estimating equation models. **P*-value. < 0.05. All models were adjusted for maternal age, parity, highest completed education level, household income, history of asthma or atopy, use of periconceptional folic acid supplements, prepregnancy body mass index, pet keeping, smoking and alcohol use during pregnancy, total daily energy intake, vegetable intake, distress during pregnancy, gestational age at enrollment and child's birth weight, gestational age at birth, sex, breastfeeding, timing of introduction of complementary feeding, daycare attendance in the first year, lower respiratory tract infections in the first year.

^aTests for trend were based on generalized estimating equation models with fish consumption (gram/week) as a continuous variable.

also found no effect of maternal fish consumption during the pregnancy on wheezing or asthma.²² It is difficult to determine whether the suggested beneficial effects that were observed in previous observational studies were due to fish consumption and not to other aspects from maternal diet or lifestyle. None of the previous studies that found an association of maternal fish consumption during pregnancy with childhood asthma did take maternal body mass index, folic acid supplement use, alcohol use and distress during pregnancy into account. In our study, adjustment for these potential confounders changed the effect estimates with more than 5%. Randomized intervention studies using fish oil supplementation during pregnancy can avoid the risk of bias due to confounding. To our knowledge, five interventional studies were performed, which addressed this research question. Sample sizes ranged from 65 to 533 pregnant women. Although differences in immunological outcomes in cord blood or infant plasma between those with and without fish oil supplementation were promising, studies were not convincing for differences in clinical outcomes, including asthma or eczema. Only three studies assessed clinical outcomes, of which one study found a protective effect of fish oil supplementation on eczema, but not on asthma,²⁰ and another study found no effect at all.¹⁰ Only one trial, performed in Denmark, observed a lower risk for both asthma and eczema if mothers received fish oil supplementation during pregnancy.¹⁴ Thus, previous intervention studies did not provide consistent evidence for beneficial effects of maternal fish consumption or fish oil supplementation on clinical outcomes, such as asthma or atopic symptoms. Furthermore, due to the

selection of specific participants, such as atopic pregnant women, translating the results to a general population should be done very carefully.

We observed that children from mothers with low fatty fish consumption during pregnancy had higher risks of eczema, compared with women with no fish consumption. The highest category of maternal fatty fish consumption was also not associated with an increased risk of childhood eczema. The association of high maternal fatty fish consumption during pregnancy with higher risks of childhood eczema has not been previously reported. Therefore, replication is needed and any biological explanation is speculative. However, our observations are consistent with the hypothesis that the beneficial effects of n-3 PUFAs may be counterbalanced in part by the harmful impact of pollution of seafood.⁷ Concentration of contaminants is higher in fatty fish and in shellfish than in lean fish, which might explain that the observed associations differ depending on the type of fish. A meta-analysis that compared benefits and risks of fish consumption showed that 15 g per day is a common benefit threshold for several endpoints.⁷ The increased risks that we observed were among women who had a weekly fish consumption below this threshold. Contaminants found in fish include mercury and polychlorinated biphenyls. Regular fatty fish consumption has been associated with increased maternal plasma concentrations of polychlorinated biphenyls,³⁶ and a previous cross-sectional study among adults have showed that higher mercury blood levels were associated with higher risks of eczema.³⁷ To our knowledge, the association of maternal

mercury levels in pregnancy and the risk childhood eczema has not been reported yet.

Another possible explanation might be reverse causation, in case fish consumption is higher among mothers of whom the children are at high risk of eczema. However, fish consumption was only slightly higher among mothers with a history of atopy or asthma. Finally, mothers who frequently consume fish might be more health conscious and report eczema symptoms more frequently. As we did not find similar results for wheezing symptoms, this explanation seems unlikely. Although our results are consistent at the different ages of the child and results reached statistically significant levels of $P < 0.01$, our observations could still be considered a chance finding. Further research is necessary to explore if the observed associations can be replicated.

CONCLUSION

Our results suggest that in a healthy Dutch population, with a relatively low fish intake, first trimester maternal total fish or lean fish consumption is not associated with childhood wheezing or eczema in the first 4 years of life. Maternal fatty fish consumption was associated with a higher risk of eczema, but not with wheezing. Shellfish consumption was associated with increased risks of both wheezing and eczema. Further studies are needed to replicate these findings and to explore underlying mechanisms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol* 2012; **27**: 5–14.
- Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**: 733–743.
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of *in utero* and early-life conditions on adult health and disease. *N Engl J Med* 2008; **359**: 61–73.
- Calder PC, Kremmyda LS, Vlachava M, Noakes PS, Miles EA. Is there a role for fatty acids in early life programming of the immune system? *Proc Nutr Soc* 2010; **69**: 373–380.
- Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005; **115**: 1109–1117, quiz 18.
- Prescott SL, Calder PC. N-3 polyunsaturated fatty acids and allergic disease. *Curr Opin Clin Nutr Metab Care* 2004; **7**: 123–129.
- Gochfeld M, Burger J. Good fish/bad fish: a composite benefit-risk by dose curve. *Neurotoxicology* 2005; **26**: 511–520.
- Calvani M, Alessandri C, Sopo SM, Panetta V, Pingitore G, Tripodi S et al. Consumption of fish, butter and margarine during pregnancy and development of allergic sensitizations in the offspring: role of maternal atopy. *Pediatr Allergy Immunol* 2006; **17**: 94–102.
- Denburg JA, Hatfield HM, Cyr MM, Hayes L, Holt PG, Sehmi R et al. Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. *Pediatr Res* 2005; **57**: 276–281.
- Dunstan JA, Mitoulas LR, Dixon G, Doherty DA, Hartmann PE, Simmer K et al. The effects of fish oil supplementation in pregnancy on breast milk fatty acid composition over the course of lactation: a randomized controlled trial. *Pediatr Res* 2007; **62**: 689–694.
- Furuhjelm C, Warstedt K, Larsson J, Fredriksson M, Bottcher MF, Falth-Magnusson K et al. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr* 2009; **98**: 1461–1467.
- Krauss-Etschmann S, Hartl D, Rzehak P, Heinrich J, Shadid R, Del Carmen Ramirez-Tortosa M et al. Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. *J Allergy Clin Immunol* 2008; **121**: 464–70 e6.
- Lauritzen L, Kjaer TM, Fruekilde MB, Michaelsen KF, Frokiaer H. Fish oil supplementation of lactating mothers affects cytokine production in 2 1/2-year-old children. *Lipids* 2005; **40**: 669–676.
- Olsen SF, Osterdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ et al. 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. *Am J Clin Nutr* 2008; **88**: 167–175.
- Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA et al. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. *BMJ* 2012; **344**: e184.
- Prescott SL, Barden AE, Mori TA, Dunstan JA. Maternal fish oil supplementation in pregnancy modifies neonatal leukotriene production by cord-blood-derived neutrophils. *Clin Sci (Lond)* 2007; **113**: 409–416.
- Romieu I, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fito N, Anto JM et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. *Clin Exp Allergy* 2007; **37**: 518–525.
- Salam MT, Li YF, Langholz B, Gilliland FD. Maternal fish consumption during pregnancy and risk of early childhood asthma. *J Asthma* 2005; **42**: 513–518.
- Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr* 2007; **85**: 530–537.
- Warstedt K, Furuhejm C, Duchon K, Falth-Magnusson K, Fageras M. The effects of omega-3 fatty acid supplementation in pregnancy on maternal eicosanoid, cytokine, and chemokine secretion. *Pediatr Res* 2009; **66**: 212–217.
- Willers SM, Devereux G, Craig LC, McNeill G, Wijga AH, Abou El-Magd W et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax* 2007; **62**: 773–779.
- Willers SM, Wijga AH, Brunekreef B, Kerkhof M, Gerritsen J, Hoekstra MO et al. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Respir Crit Care Med* 2008; **178**: 124–131.
- Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van IJendoorn MH, de Jongste JC et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012; **27**: 739–756.
- Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, Geleijnse JM, Hofman A, Grobbee DE et al. Dietary assessment in the elderly: validation of a semi-quantitative food frequency questionnaire. *Eur J Clin Nutr* 1998; **52**: 588–596.
- Donders-Engelen M. VDHLHK. *Maten Gewichten Codenummers (Measures Weights Code Numbers)*. Vakgroep Humane Voeding, Landbouwwuniversiteit Wageningen en TNO Voeding Zeist: Wageningen; The Netherlands, 2003.
- Heppe DH, Steegers EA, Timmermans S, Breeijen H, Tiemeier H, Hofman A et al. Maternal fish consumption, fetal growth and the risks of neonatal complications: the Generation R Study. *Br J Nutr* 2011; **105**: 938–949.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**: 483–491.
- Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, Moll HA, Hofman A, de Jongste JC et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. *Am J Respir Crit Care Med* 2012; **185**: 731–737.
- Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010; **25**: 823–841.
- Beurs E. *Brief Symptom Inventory*. Leiden: The Netherlands.
- Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006; **17**: 413–418.
- Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M et al. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA Birth Cohort. *Am J Respir Crit Care Med* 2007; **175**: 1078–1085.

- 33 Harpsoe MC, Basit S, Bager P, Wohlfahrt J, Benn CS, Nohr EA *et al*. Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: a study within the Danish National Birth Cohort. *J Allergy Clin Immunol* 2012, pii S0091-6749: 01502–01503.
- 34 Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A *et al*. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; **63**: 974–980.
- 35 Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF *et al*. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996; **25**: 609–616.
- 36 Halldorsson TI, Thorsdottir I, Meltzer HM, Nielsen F, Olsen SF. Linking exposure to polychlorinated biphenyls with fatty fish consumption and reduced fetal growth among Danish pregnant women: a cause for concern? *Am J Epidemiol* 2008; **168**: 958–965.
- 37 Miyake Y, Tanaka K, Yasutake A, Sasaki S, Hirota Y. Lack of association of mercury with risk of wheeze and eczema in Japanese children: the Osaka Maternal and Child Health Study. *Environ Res* 2011; **111**: 1180–1184.

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Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood. The Generation R Study.

Running title:

Maternal fish consumption and atopic symptoms

Supplement Material

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Supplementary Table S1. Maternal fish consumption and risks of wheezing (crude analysis)

Odds ratios (95% confidence interval) of wheezing (n=2796)						
	n_{total}	Age 1 n _{cases} =852	Age 2 n _{cases} =513	Age 3 n _{cases} =342	Age 4 n _{cases} =321	Overall
Total fish consumption						
(gram/week)						
0	523	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-69	728	0.99 (0.77, 1.28)	0.92 (0.69, 1.24)	0.93 (0.65, 1.31)	0.91 (0.61, 1.34)	0.95 (0.82, 1.11)
70-139	908	0.89 (0.69, 1.14)	0.95 (0.72, 1.26)	0.85 (0.59, 1.22)	0.92 (0.63, 1.34)	0.90 (0.78, 1.05)
140- 209	442	0.89 (0.67, 1.18)	0.85 (0.60, 1.21)	0.65 (0.41, 1.02)	0.91 (0.59, 1.38)	0.85 (0.70, 1.02)
>210	195	1.04 (0.71, 1.52)	0.67 (0.41, 1.11)	0.64 (0.35, 1.17)	0.87 (0.48, 1.56)	0.86 (0.67, 1.10)
<i>p for trend¹</i>		<i>p=0.67</i>	<i>p=0.24</i>	<i>p=0.07</i>	<i>p=0.82</i>	<i>p=0.14</i>
Lean fish consumption						
(gram/week)						
0	980	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-34	728	1.23 (0.99, 1.53)	1.02 (0.79, 1.31)	0.88 (0.63, 1.23)	0.88 (0.64, 1.21)	1.07 (0.94, 1.22)
35-69	721	0.99 (0.79, 1.24)	0.77 (0.59, 1.01)	0.61 (0.43, 0.87)**	0.76 (0.52, 1.09)	0.84 (0.73, 0.97)*
>70	367	1.25 (0.95, 1.65)	0.89 (0.65, 1.23)	0.65 (0.43, 1.00)	0.99 (0.67, 1.46)	1.02 (0.86, 1.20)
<i>p for trend¹</i>		<i>p=0.59</i>	<i>p=0.06</i>	<i>p=0.01</i>	<i>p=0.52</i>	<i>p=0.15</i>

Fatty fish consumption						
(gram/week)						
0	886	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-34	604	0.96 (0.76, 1.21)	1.20 (0.91, 1.57)	1.12 (0.81, 1.55)	1.09 (0.77, 1.55)	1.06 (0.92, 1.22)
35-69	795	0.84 (0.68, 1.04)	0.98 (0.75, 1.28)	0.88 (0.62, 1.27)	0.91 (0.64, 1.30)	0.89 (0.78, 1.02)
>70	511	0.97 (0.75, 1.24)	0.98 (0.72, 1.33)	0.81 (0.55, 1.18)	0.95 (0.66, 1.39)	0.95 (0.81, 1.11)
<i>p for trend¹</i>		<i>p=0.50</i>	<i>p=0.57</i>	<i>p=0.15</i>	<i>p=0.63</i>	<i>p=0.18</i>
Shellfish consumption						
(gram/week)						
0	1 686	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-13	513	1.24 (1.00, 1.54)	1.34 (1.03, 1.75)*	1.33 (0.99, 1.80)	1.17 (0.84, 1.63)	1.27 (1.11, 1.45)***
>14	597	1.04 (0.83, 1.30)	1.16 (0.89, 1.51)	0.87 (0.63, 1.22)	0.90 (0.65, 1.23)	1.03 (0.90, 1.19)
<i>p for trend¹</i>		<i>p=0.59</i>	<i>p=0.25</i>	<i>p=0.52</i>	<i>p=0.82</i>	<i>p=0.43</i>

Values are odds ratios (with 95% confidence interval) and reflect the associations of fish consumption during pregnancy with wheezing in the offspring, compared to women with no fish consumption, generalized estimating equation models.

¹Tests for trend were based on generalized estimating equation models with fish consumption (gram/week) as a continuous variable.

*P-value <0.05; **P-value <0.01, ***P-value <0.001

Supplementary Table S2. Maternal fish consumption and risks of eczema (crude analysis)

Odds ratios (95% confidence interval) of eczema (n=2796)						
	n_{total}	Age 1 n _{cases} =643	Age 2 n _{cases} =373	Age 3 n _{cases} =254	Age 4 n _{cases} =240	Overall
Total fish consumption						
(gram/week)						
0	523	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-69	728	0.99 (0.77, 1.28)	0.92 (0.69, 1.24)	0.93 (0.65, 1.31)	0.91 (0.61, 1.34)	0.95 (0.82, 1.11)
70-139	908	0.89 (0.69, 1.14)	0.95 (0.72, 1.26)	0.85 (0.59, 1.22)	0.92 (0.63, 1.34)	0.90 (0.78, 1.05)
140- 209	442	0.89 (0.67, 1.18)	0.85 (0.60, 1.21)	0.65 (0.41, 1.02)	0.91 (0.59, 1.38)	0.85 (0.70, 1.02)
>210	195	1.04 (0.71, 1.52)	0.67 (0.41, 1.11)	0.64 (0.35, 1.17)	0.87 (0.48, 1.56)	0.86 (0.67, 1.10)
<i>p for trend¹</i>		<i>p</i> =0.67	<i>p</i> =0.24	<i>p</i> =0.06	<i>p</i> =0.82	<i>p</i> =0.14
Lean fish consumption						
(gram/week)						
0	980	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-34	728	1.23 (0.99, 1.53)	1.02 (0.79, 1.31)	0.88 (0.63, 1.23)	0.88 (0.64, 1.21)	1.07 (0.94, 1.23)
35-69	721	0.99 (0.79, 1.24)	0.77 (0.59, 1.01)	0.61 (0.43, 0.87)	0.76 (0.52, 1.09)	0.84 (0.73, 0.97)*
>70	367	1.25 (0.95, 1.65)	0.89 (0.65, 1.23)	0.65 (0.43, 1.00)	0.99 (0.67, 1.46)	1.02 (0.86, 1.20)
<i>p for trend¹</i>		<i>p</i> =0.59	<i>p</i> =0.06	<i>p</i>=0.01	<i>p</i> =0.52	<i>p</i> =0.15

Fatty fish consumption						
(gram/week)						
0	886	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-34	604	0.96 (0.76, 1.21)	1.20 (0.91, 1.57)	1.12 (0.81, 1.55)	1.09 (0.77, 1.55)	1.06 (0.92, 1.22)
35-69	795	0.84 (0.68, 1.04)	0.98 (0.75, 1.28)	0.88 (0.62, 1.27)	0.91 (0.64, 1.30)	0.89 (0.78, 1.02)
>70	511	0.97 (0.75, 1.24)	0.98 (0.72, 1.33)	0.81 (0.55, 1.18)	0.95 (0.66, 1.39)	0.95 (0.81, 1.11)
<i>p for trend</i> ¹		<i>p=0.50</i>	<i>p=0.57</i>	<i>p=0.15</i>	<i>p=0.63</i>	<i>p=0.18</i>
Shellfish consumption						
(gram/week)						
0	1 686	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1-13	513	1.24 (1.00, 1.54)	1.34 (1.03, 1.75)	1.33 (0.99, 1.80)	1.17 (0.84, 1.63)	1.27 (1.11, 1.45)*
>14	597	1.04 (0.83, 1.30)	1.16 (0.89, 1.51)	0.87 (0.63, 1.22)	0.90 (0.65, 1.23)	1.03 (0.90, 1.19)
<i>p for trend</i> ¹		<i>p=0.59</i>	<i>p=0.25</i>	<i>p=0.53</i>	<i>p=0.82</i>	<i>p=0.43</i>

Values are odds ratios (with 95% confidence interval) and reflect the associations of fish consumption during pregnancy with eczema in the offspring, compared to women with no fish consumption, based on generalized estimating equation models.

¹Tests for trend were based on generalized estimating equation models with fish consumption (gram/week) as a continuous variable.

*P-value <0.05; **P-value <0.01