Fish Consumption in Infancy and Asthma-like Symptoms at Preschool Age

WHAT'S KNOWN ON THIS SUBJECT: Several studies have reported inverse associations between fish consumption during pregnancy or later childhood and asthma prevalence. However, because fish can also be highly allergenic, the optimal timing of introduction of fish and the adequate amount in infancy remains unclear.

WHAT THIS STUDY ADDS: Introduction of fish between 6 and 12 months but not fish consumption afterward is associated with a lower risk of wheezing whereas no introduction of fish or introduction between 0 and 6 months of life increases the risk of wheezing.

abstract

FREE

OBJECTIVE: To assess whether timing of introduction of fish and the amount of fish consumption in infancy were associated with asthma-like symptoms at preschool age.

METHODS: This study was embedded in the Generation R study (a population-based birth cohort in Rotterdam, Netherlands). At the age of 12 and 14 months, timing of introduction of fish into the infant's diet was assessed. The amount of fish consumption at 14 months was assessed by a semiquantitative food frequency questionnaire. Presence of asthmalike symptoms in the past year was assessed at the child's age of 36 and 48 months.

RESULTS: Relative to no introduction in the first year of life, introduction between age 6 and 12 months was significantly associated with a lower risk of wheezing at 48 months (odds ratio [OR]: 0.64; 95% CI: 0.43–0.94). When compared with introduction between 6 and 12 months, no introduction in the first year and introduction between 0 and 6 months were associated with an increased risk of wheezing at 48 months (OR: 1.57; 95% CI: 1.07–2.31 and OR: 1.53; 95% CI: 1.07–2.19, respectively). The amount of fish at age 14 months was not associated with asthmalike symptoms ($P > .15$).

CONCLUSIONS: Introduction of fish between 6 and 12 months but not fish consumption afterward is associated with a lower prevalence of wheezing. A window of exposure between the age of 6 and 12 months might exist in which fish might be associated with a reduced risk of asthma. *Pediatrics* 2012;130:1060–1068

AUTHORS: Jessica C. Kiefte-de Jong, RD, PhD,[a,b] Jeanne H. de Vries, PhD,[c] Oscar H. Franco, MD, PhD,[d] Vincent W.V. Jaddoe, MD, PhD,[a,b,d] Albert Hofman, MD, PhD,[d] Hein Raat, MD, PhD,[e] Johan C. de Jongste, MD, PhD,[f] and Henriette A. Moll, MD, PhD[b]

[a]The Generation R Study Group, and Departments of [b]Pediatrics, [d]Epidemiology, [e]Public Health, and [f]Pediatrics/Respiratory Medicine, Erasmus Medical Center, Rotterdam, Netherlands; and [c]Department of Human Nutrition, Wageningen, Netherlands

KEY WORDS

fish, wheezing, shortness of breath, complementary feeding, asthma

ABBREVIATIONS

CI—confidence interval
DHA—decosahexaenoic acid
EPA—eicosapentaenoic acid
FFQ—Food Frequency Questionnaire
n-3 PUFA—N-3 polyunsaturated fatty acids
OR—odds ratio
PCBs—polychlorinated biphenyls

Dr Kiefte-de Jong analyzed the data, wrote the first draft of the manuscript, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. She fulfills the criteria as described by the International Committee of Medical Journal Editors (ICMJE) as follows: (1) substantial contributions to conception and design, acquisition of data, and analysis and interpretation of the data; (2) drafting the article; and (3) final approval of the version to be published. Dr de Vries has participated in the acquisition and data analysis of nutritional data. She fulfills the criteria as described by the ICMJE as follows: (1) substantial contributions to acquisition of data, and analysis of the data; (2) critical revision of the paper for important intellectual content; and (3) final approval of the version to be published. Drs Franco, Jaddoe, Raat, Hofman, and de Jongste fulfill the criteria as described by the ICMJE as follows: (1) substantial contribution to interpretation of the data; (2) critical revision of the paper for important intellectual content and (3) final approval of the version to be published. Dr Moll supervised the study. She fulfills the criteria as described by the ICMJE as follows: (1) substantial contributions to conception and design, acquisition of data, and interpretation of the data; (2) critical revisions of the paper for important intellectual content; (3) final approval of the version to be published.

(Continued on last page)

The prevalence of asthma in Westernized countries is increasing.[1] It has been suggested that adoption of a Westernized diet can be one of the reasons related to the increase of asthma.[2] Indeed, we have previously found that a "Western-like" dietary pattern in toddlers was associated with asthmalike symptoms at preschool age.[3] In contrast, we did not find any association with a dietary pattern characterized by high intake of fish, vegetables, and fruit[3] whereas adherence to this diet during pregnancy or at school age has been noted to protect against asthma in previous studies.[4–8] Because we did not find a clear association between a dietary pattern including fish and asthmalike symptoms,[3] we hypothesized that any potential beneficial effect of fish consumption in toddlers may be diluted in our previous study as a result of the dietary pattern approach and therefore deserves additional study. Various studies have suggested that early life exposure of n-3 polyunsaturated fatty acids (n-3 PUFA), a major component in fatty fish, protects against the development of asthma.[2,9,10] In line with this, a recent study reported a beneficial effect of introduction of fish before age 9 months on the development of wheezing at age 4.5 years,[11] whereas another study reported no association between introduction of fish and asthma.[12] However, because fish can also be highly allergenic,[13] the optimal timing of introduction of fish in the infant's diet and the adequate amount remains unclear. We aimed in this study to assess whether timing of introduction of fish in the first year of life and fish consumption afterward were associated with the development of asthmalike symptoms at preschool age.

METHODS

The current study was performed within the Generation R Study, a population-based multiethnic prospective birth cohort in Rotterdam, Netherlands.[14] The cohort includes 7210 children born between April 2002 and January 2006 whose parents provided postnatal consent (Supplemental Fig 2). The Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam, approved the study (MEC 198.782/2001/31). Written informed consent was obtained from all participants.

Timing of the Introduction of Fish and Amount of Fish Consumption in Infancy

From 2003 onward, nutritional data of the child was collected at age 14 months (mean ± SD: 14 ± 2 months) by using a semiquantitative food frequently questionnaire (FFQ), which was validated in Dutch children and has been described in detail previously.[15] Questions from the FFQ on the consumption fish are found in Supplemental Table 6. We divided the fish products into 2 groups on the basis of their fat content: (1) fatty fish defined as >10 g fat per 100 g: herring, mackerel, eel, and salmon; (2) other fish defined as 0 to 10 g fat per 100 g: white fish, fish fingers, squid, flounder, cod, pollack, haddock, tilapia, sole, tuna, whiting, trout, gurnard, perch, plaice, wolf fish, and swordfish.[16] Consumption of fish was categorized as follows: "No consumption," "Less than a half serving per week," and "At least a half serving per week." In addition, intake of 120 g raw fish was counted as one serving of fish.[17] Both at the child's age of 12 and 14 months, parents were asked the following question: "Please indicate how old your child was when you gave him or her fish for the first time." The observed agreement between measurement at 12 and 14 months was 85% with a Cohen's κ of .31. Answers categories included "never given in first year of life," "0 to 3 months," "3 to 6 months," "after 6 months and thereafter." Because of the small number in the group of introduction between 0 and 3 months (n = 7), this was combined with the group "3 to 6 months" into a new category: 0 to 6 months.

Asthmalike symptoms

Information regarding the presence of wheezing and shortness of breath in the past year was obtained by using an age-adapted version of the validated "International Study of Asthma and Allergies in Childhood"[18] questionnaire at the ages of 36 months and 48 months. The observed agreement for wheezing and shortness of breath between measurement by questionnaire and by physician interview in our cohort was 75% (Cohen's κ = .30) and 81% (Cohen's κ = .39), respectively.[19] To establish potential reverse causality, sensitivity analyses were performed with and without exclusion of any asthmalike symptoms at the age of 12 and 24 months. However, because effect estimates were similar, final analyses were performed in all children.

Covariates

Variables possibly related to food consumption and wheezing were considered potential confounders in this study and selected based on previous knowledge and literature.[15,20] Infant's gender, gestational age and birth weight were obtained from obstetric records assessed in midwife practices and hospital registries.[14] Information about maternal age, maternal BMI, parity, educational level, ethnicity, marital status, household income, and any family history of asthma, eczema, allergy to house dust, or hay fever was obtained by questionnaire at enrollment. Maternal smoking and alcohol habits were assessed by questionnaire in each trimester of pregnancy. We assessed maternal dietary fish intake at enrollment using a modified version of the validated semiquantitative FFQ described previously.[21,22] Mother's intake of folic acid was assessed by

questionnaire at enrollment of the study as described earlier.[23] Data on breastfeeding was collected by a combination of delivery reports and postnatal questionnaires at ages 2, 6, and 12 months. Breastfeeding was defined in this study as follows: (1) never, (2) partially through 4 months, (3) exclusively through 4 months.[24] Postnatal questionnaires completed by the mother at age 6 and 12 months included information on any day-care attendance (yes versus no), any vitamin D supplementation (yes versus no), and any history of doctor-attended food allergy and eczema. Weight and height were measured at the child health centers during routine visits around age 48 months. The definition of overweight was established according to international cutoff points for children.[25]

Statistical Analysis

Univariate associations between maternal and child characteristics and timing of introduction of fish were performed with 1-way analysis of variance (continuous variables) and χ^2 test (categorical variables). Logistic regression analyses were used to assess the association between timing of introduction of fish and amount fish consumption and asthmalike symptoms. A crude model was computed followed by a multivariate model adjusting for potential confounders. All analyses on the amount of fish consumption at 14 months were adjusted for total energy intake.[26] To assess whether the association between fish and asthmalike symptoms was different by strata of, for example, ethnicity, history of food allergy, and parental history of atopy; stratified analyses were performed by these groups and statistical interaction was tested by adding the product term of the fish variable multiplied by the stratum (eg, fish consumption × food allergy) as an independent variable to the crude models.

A multiple imputation procedure ($n = 5$ imputations) was performed on all variables to reduce potential bias associated with missing data (Supplemental Fig 2, Supplemental Table 7).[27] Analyses were then performed in each of the 5 imputed data sets separately, and the final results were pooled and presented as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed with PASW Statistics 17.0.

RESULTS

Characteristics of the study population and prevalence of wheezing according to timing of introduction of fish are shown in Tables 1 and 2. A fish-free dietary regimen at age 14 months was reported in only 0.1% of the children. Fish consumption of the children at age 14 months was higher in children introduced to fish in the first year of life relative to those without fish introduction in the first year of life (Fig 1). Timing of introduction of fish showed no similarities with timing of introduction of other foods in the first year of life (Cohen's $\kappa \leq .15$, Supplemental Table 9).

Timing of Introduction of Fish and Asthmalike Symptoms

Children who were introduced to fish between 6 and 12 months had a significantly lower prevalence of wheezing at 48 months than children who were not introduced to fish in the first year of life (Table 3). Symptoms of shortness of breath were less prevalent in children introduced to fish between 6 and 12 months, but this was not statistically significant (Supplemental Table 10). Relative to introduction between 6 and 12 months, both fish introduction between 0 and 6 months and no introduction in the first year of life were associated with an increased prevalence of wheezing and shortness of breath at 48 months (Table 4, Supplemental Table 11). The associations between timing of introduction of fish and asthmalike symptoms were not different within strata of ethnicity, family history of allergic disease, maternal fish consumption during pregnancy, any history of food allergy, eczema, breastfeeding duration, and type of fish consumption at age 14 months ($P_{interaction} > .15$ for all comparisons).

Amount of Fish Servings and Wheezing and Shortness of Breath

No association was found between the amount of fish servings and wheezing and shortness of breath at 36 and 48 months (Table 5, Supplemental Table 7). Fatty fish consumption of less than ½ serving per week was significantly associated with wheezing at 48 months but this association was mainly explained by confounding factors (Table 5).

Results did not differ within strata of ethnicity, maternal fish consumption during pregnancy, any family history of allergic disease, any history of food allergy, eczema, and breast-feeding duration ($P_{interaction} > .20$ for all comparisons).

DISCUSSION

This study showed that introduction of fish between 6 and 12 months, but not the amount of fish servings afterward, was associated with a lower prevalence of wheezing in preschool children. However, no introduction in the first year of life or introduction between 0 and 6 months was associated with an increased prevalence of asthmalike symptoms.

Most studies on fish intake and asthma have assessed maternal fish intake during pregnancy and asthma in the offspring. Both epidemiologic studies and randomized controlled trials showed protective effects of fish and fish fatty acids during pregnancy and asthma in children.[28,29] However, evidence from epidemiologic studies

TABLE 1 Characteristics of the Study Population According to Timing of Introduction of Fish (N = 7210)

	Timing of Introduction of Fish Into the Infant's Diet			
	Between 0 and 6 mo, n = 1281	Between 6 and 12 mo, n = 5498	Never Given in First Year, n = 431	P Value
Mother				
Maternal age at intake (mean ± SD)	29 ± 5	31 ± 5	31 ± 5	<.01
Maternal BMI at intake (mean ± SD)	25.2 ± 4.3	24.6 ± 4.2	24.8 ± 4.2	<.01
Marital status (n, %)				<.01
Married/living together	963 (75)	4835 (88)	372 (86)	
Living alone	318 (25)	663 (12)	59 (14)	
Household income (n, %)				<.01
<2000 euro/mo	816 (64)	2044 (37)	214 (50)	
≥2000 euro/mo	465 (36)	3453 (63)	217 (50)	
Maternal educational level (n, %)				<.01
Low	265 (21)	511 (9)	67 (16)	
Middle	683 (53)	2334 (42)	202 (47)	
High	333 (26)	2653 (48)	162 (36)	
Family history of atopic disease (n, %)	563 (44)	2634 (48)	185 (43)	.05
Smoking during pregnancy (n, %)	421 (33)	1397 (25)	115 (27)	<.01
Alcohol use during pregnancy (n, %)	418 (33)	2420 (44)	151 (35)	<.01
Fish intake in pregnancy in serving/wk (median, interquartile range)	0.6 (0.2–1.2)	0.7 (0.4 -1.1)	0.4 (0–0.9)	<.01
Fatty fish	0.2 (0–0.5)	0.3 (0–0.5)	0.2 (0–0.4)	<.01
Lean fish	0.4 (0–0.7)	0.4 (0.1–0.6)	0.2 (0–0.5)	<.01
Perinatal folic acid supplementation (n, %)	701 (55)	4151 (76)	287 (67)	<.01
Nulliparous (n, %)	572 (45)	3164 (57)	224 (52)	<.01
Child				
Male gender (n, %)	648 (51)	2763 (50)	236 (55)	.26
Birth wt (mean ± SD)	3333 ± 553	3420 ± 562	3446 ± 557	<.01
Gestational age (mean ± SD)	39.7 ± 1.7	39.8 ± 1.8	39.9 ± 1.7	.15
Ethnicity (n, %)				<.01
Dutch or other Western	588 (46)	3709 (67)	256 (59)	
Cape Verdian	74 (6)	142 (3)	17 (4)	
Moroccan	151 (12)	310 (6)	41 (10)	
Antillean or Surinamese	202 (16)	518 (9)	43 (10)	
Turkish	137 (11)	395 (7)	42 (10)	
African	52 (4)	144 (3)	10 (2)	
Other	77 (6)	279 (5)	23 (5)	
Early day-care attendance (n, %)	711 (56)	3501 (64)	250 (58)	.13
Any vitamin D supplementation in first year of life (n, %)	794 (62)	3122 (57)	245 (57)	.08
Any history of food allergy (n, %)	334 (26)	632 (11)	153 (35)	<.01
Breastfeeding (n, %)				<.01
Never	355 (28)	965 (18)	118 (28)	
Partial up to 4 mo of age	641 (50)	3083 (56)	204 (47)	
Exclusive up to 4 mo of age	285 (22)	1450 (26)	109 (25)	
BMI for age z score at 48 mo (mean ± SD)	0.1 ± 0.9	0.1 ± 1.0	0.1 ± 0.9	.85
Overweight at 48 mo (n, %)	233 (18)	1012 (18)	71 (16)	.31

Table represents the pooled results after the multiple imputation procedure.

assessing the effects of fish intake in young children and asthma is scarce and contradictory. Nafstad et al found no significant association between introduction of fish in the first year and any asthma diagnosis.[30] However, Hesselmar et al found a tendency between early fish introduction of fish and asthma (between group-difference of fish introduction: 9 vs 13 months).[12] Another study by Kull et al found that consumption of fish more than once a week in the first year of life was associated with a lower prevalence of asthma.[31] Arvaniti et al[6] and Tabak et al[32] showed that fish intake was associated with a lower prevalence of asthma in older children (>8 years). In contrast, Willers et al showed no association between the amount of fish consumption at age 2 to 3 years and 7 to 8 years and asthma diagnosis at 8 years.[33] Age differences and variation in measuring fish consumption make it difficult to compare our results with previous studies but there seems to be a tendency for a beneficial effect on asthma when fish exposure occurs in the first year of life. Our study suggests that appropriate timing of introduction of fish rather than the amount of fish servings after 12 months is important in the association with wheezing. Underlying mechanisms why fish may protect against asthma are speculative. Fish is a great source of n-3 PUFAs such as decosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Several studies suggest that DHA and EPA have immunoregulatory and/or antiinflammatory properties.[29,34] Lower levels of n-3 fatty acids have been found in asthmatics relative to control subjects,[35] but others found no association between levels of n-3 fatty acids and asthma in schoolchildren aged 8 to 13 years.[36] In addition, the optimal intake of n-3 fatty acids in young children remains controversial. In 2002, the US Institute of Medicine concluded that there is insufficient evidence to provide clear recommendation on n-3 PUFA intake in children,[37] whereas the Technical Committee on Dietary Lipids of the International Life Sciences Institute of North America stated in 2009 that a daily EPA and DHA intake between 250 and 500 mg per day reduces the risk of coronary head disease later in life.[38] The European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies concluded in 2009 that in older infants, DHA intake of 50 to

TABLE 2 Prevalence Rates of Wheezing According to Weekly Intake of Fish and Timing of Introduction of Fish in the Infant's Diet

		Children With Wheezing at 36 mo, *N* = 2480, *n* (%)	Children With Wheezing at 36 mo, *N* = 2439, *n* (%)
Fatty fish consumption at 14 mo			
No fatty fish consumption	4931 (68)	1736 (35)	1710 (35)
Less than ½ serving a week	1910 (27)	622 (33)	611 (32)
At least ½ serving a week	366 (5)	121 (33)	118 (32)
Other fish consumption at 14 mo			
No other fish consumption	2182 (30)	745 (34)	738 (34)
Less than ½ serving a week	2965 (41)	980 (33)	962 (32)
At least ½ serving a week	2063 (29)	755 (37)	740 (36)
Timing of introduction of fish in first year of life			
Never in first year	431 (6)	173 (40)	192 (45)
0–6 mo	1281 (18)	667 (52)	593 (46)
6–12 mo	5498 (76)	1639 (30)	1654 (30)

Table represents the pooled results after the multiple imputation procedure.

100 mg per day can improve visual function but evidence does not permit to define an age specific dietary recommendation for EPA and DHA from 2 years onward.[39] None of the recommendations on EPA and DHA were related to influence on asthma. In line with this, the European Society for Pediatric Gastroenterology Hepatology and Nutrition commented in 2011 on supplementation of n-3 fatty acids to diet of children from 2 years and possible benefits on clinical outcomes.[40] The committee concluded that there is no convincing evidence that supplementation with n-3

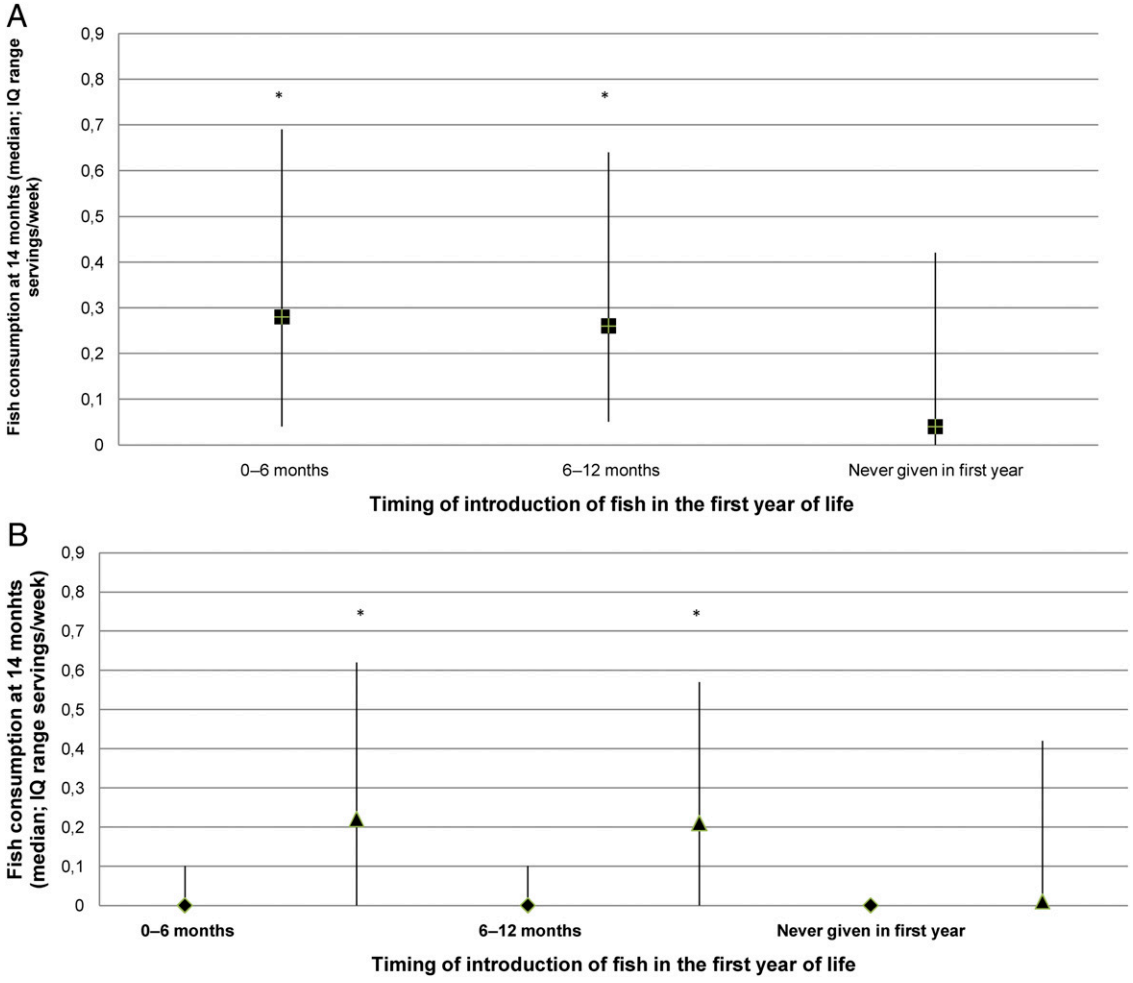

FIGURE 1

A, Fish consumption at 14 months according to timing of introduction of fish in first year of life. *$P < .05$ compared with never given in first year of life. B, Type of fish consumption at 14 months according to timing of introduction of fish in first year of life (*$P < .05$ compared with never given in first year of life. ◆, Fatty fish consumption; ▲, other fish consumption). IQ, interquartile.

TABLE 3 Association Between Timing of Introduction of Fish and Wheezing Symptoms When Compared With No Introduction in First Year of Life

Timing of Introduction of Fish	Univariate Model, OR (95% CI)	*P* Value	Multivariate Model[a], OR (95% CI)	*P* Value
Wheezing age 36 mo				
Never in first year	Reference		Reference	
0–6 mo	1.58 (0.53–4.75)	.33	1.31 (0.53–3.29)	.48
6–12 mo	0.65 (0.40–1.07)	.08	0.72 (0.51–1.03)	.07
Wheezing age 48 mo				
Never in first year	Reference		Reference	
0–6 mo	1.25 (0.65–2.41)	.44	0.98 (0.60–1.59)	.92
6–12 mo	0.58 (0.33–1.02)	.06	0.64 (0.43–0.94)	.03

ORs relative to "never wheezing in the past year" derived from logistic regression with 'never given in first year of life' as reference category after the multiple imputation procedure.

[a] Adjusted for maternal age, maternal BMI, maternal alcohol and smoking during pregnancy, household income, maternal educational background, family history of asthma, eczema, hay fever or allergy to house dust, maternal fish consumption during pregnancy, folic acid supplementation during pregnancy, parity, birth weight, gestational age, infant's gender, infant's ethnicity, breastfeeding duration, early day-care attendance, any vitamin D supplementation in first year of life.

fatty acids has beneficial effects on asthma in children.[40] If n-3 fatty acids are the components in fish that may protect against asthmalike symptoms, one would expect that not only timing of introduction but also the amount of fish consumption and fatty fish in particular determines the effect. This was not the case in our study, which may be explained in several ways. First, timing of introduction of fish may act as a proxy of other lifestyle factors and behaviors; for instance, it may be associated with intake of other foods that may have an influence on asthmalike symptoms. Nonetheless, we have previously demonstrated that timing of introduction of food allergens and a dietary pattern including fish, vegetables, and fruit at age 14 months were not significantly associated with asthmalike symptoms in our cohort.[3,41] Also, the timing of introduction of fish showed no similarities with timing of introduction of other foods (Supplemental Table 9). This raises questions as to whether confounding by other diet factors plays a role. Furthermore, to our knowledge, not many studies have assessed the amount of fish consumption at such a young age and its effect on asthmalike symptoms. Most studies have been carried out in older children or assessed the timing of introduction of fish in the infant's diet rather than the amount of fish consumption afterward. However, Goksor et al[11] showed that early fish introduction, but not the frequency of fish consumption at 12 months, was associated with recurrent wheeze, which is in line with our results. Similar results were also found in the Prevention of Allergy Among Children in Trondheim study.[42] Assessing nutrient intake at very young age is challenging because variation in certain foods can be limited and the diet can be subject to major changes at this age.[43] The lack of significant results on the amount of fish consumption in infancy may be due to the relatively low fish consumption in this age group. Therefore, additional studies on the effect of fish consumption at preschool age are necessary. Third, contamination of fish by, for example, mercury and polychlorinated biphenyls (PCBs) might be an explanation for negative results on fish consumption. Although studies suggest that exposure to these components may have immunologic effects early in life,[44,45] the effect on the development of asthma is indistinct. Fish is the major contributor of mercury consumption,[46] and no association between mercury exposure and wheezing symptoms have been found in preschool children.[46] In addition, a report by the Dutch Institute for Food Safety showed that high mercury intake is not a major problem in Dutch infants.[47] Another study showed that PCBs exposure may both increase and decrease the risk of allergic disease in children.[48] Nonetheless, intake of PCBs and dioxins is due to contributions of many food items; fish contributes 16% to 26% to the total intake of dioxins and PCBs in the Dutch population.[49] Because particularly the intake of fish is relatively low in this population of infants, we think it is unlikely that the intake of mercury, PCBs, and dioxins from fish may have markedly influenced our results.

Finally, given the results related to timing of introduction rather than to quantity of fish intake, there might be a specific window of exposure between

TABLE 4 Association Between Timing of Introduction of Fish and Wheezing Symptoms When Compared With Introduction Between Age 6 and 12 Months

Timing of Introduction of Fish	Univariate Model, OR (95% CI)	*P* Value	Multivariate Model[a], OR (95% CI)	*P* Value
Wheezing age 36 mo				
Never in first year	1.53 (0.93–2.53)	.08	1.38 (0.97–1.97)	.07
0–6 mo	2.43 (1.28–4.60)	.02	1.82 (1.00–3.32)	.05
6–12 mo	Reference		Reference	
Wheezing age 48 mo				
Never in first year	1.72 (0.98–3.03)	.06	1.57 (1.07–2.31)	.03
0–6 mo	2.16 (1.04–4.48)	.04	1.53 (1.07–2.19)	.03
6–12 mo	Reference		Reference	

ORs relative to "never wheezing in the past year" derived from logistic regression with 'never given in first year of life' as reference category after the multiple imputation procedure.

[a] Adjusted for maternal age, maternal BMI, maternal alcohol and smoking during pregnancy, household income, maternal educational background, family history of asthma, eczema, hay fever or allergy to house dust, maternal fish consumption during pregnancy, folic acid supplementation during pregnancy, parity, birth weight, gestational age, infant's gender, infant's ethnicity, breastfeeding duration, early day-care attendance, any vitamin D supplementation in first year of life.

TABLE 5 Association Between Infant Fish Consumption at 14 Months and Asthmalike Symptoms

Fish Consumption	Univariate Model, OR (95% CI)	*P* Value	Multivariate Model[a], OR (95% CI)	*P* Value
Wheezing at age 36 mo				
Total fish consumption				
No fish consumption	Reference		Reference	
Less than ½ serving/wk	1.05 (0.83–1.34)	.65	0.99 (0.77–1.28)	.95
At least ½ serving/wk	1.07 (0.85–1.34)	.53	0.99 (0.80–1.24)	.96
Fatty fish consumption				
No fish consumption	Reference		Reference	
Less than ½ serving/wk	0.89 (0.75–1.06)	.19	0.96 (0.81–1.14)	.62
At least ½ serving/wk	0.91 (0.66–1.24)	.54	1.04 (0.77–1.40)	.80
Other fish consumption				
No other fish consumption	Reference		Reference	
Less than ½ serving/wk	0.95 (0.83–1.08)	.41	0.90 (0.79–1.04)	.15
At least ½ serving/wk	1.10 (0.83–1.46)	.44	0.99 (0.77–1.28)	.95
Wheezing at age 48 mo				
Total fish consumption				
No fish consumption	Reference		Reference	
Less than ½ serving/wk	1.01 (0.85–1.20)	.91	0.94 (0.78–1.13)	.48
At least ½ serving/wk	1.03 (0.81–1.32)	.77	0.94 (0.76–1.18)	.58
Fatty fish consumption				
No fish consumption	Reference		Reference	
Less than ½ serving/wk	0.88 (0.77–0.99)	.04	0.93 (0.82–1.06)	.26
At least ½ serving/wk	0.86 (0.53–1.37)	.48	0.97 (0.61–1.55)	.88
Other fish consumption				
No other fish consumption	Reference		Reference	
Less than ½ serving wk	0.94 (0.78–1.14)	.51	0.89 (0.70–1.13)	.30
At least ½ serving/wk	1.08 (0.82–1.42)	.52	0.96 (0.73–1.26)	.74

ORs relative to "never wheezing in the past year" derived from logistic regression with 'never given in first year of life' as reference category after the multiple imputation procedure.

[a] Adjusted for maternal age, maternal BMI, maternal alcohol and smoking during pregnancy, household income, maternal educational background, family history of asthma, eczema, hay fever or allergy to house dust, maternal fish consumption during pregnancy, folic acid supplementation during pregnancy, parity, birth weight, gestational age, infant's gender, infant's ethnicity, breastfeeding duration, early day-care attendance, any vitamin D supplementation in first year of life.

age 6 and 12 months during which fish may be protective for developing asthma. The idea that a specific window of opportunity exist in the first year of life in which some environmental factors may decrease or increase the risk of asthma has been proposed by others.[50] In addition, others studies suggest that early life exposure to n-3 PUFAs may play a role in the induction of oral tolerance.[51]

We found an increased risk of wheezing when children were not introduced to fish in the first year of life or when they received any fish between 0 and 6 months of life. This may suggest that tolerance to fish is particularly induced with introduction between 6 and 12 months, which may provide some room for beneficial effects of additional components of fish that individually or in combination might be associated with a decreased risk of asthma and asthmalike symptoms.

A limitation of this work is the lack of objective measurement on asthma. The main outcomes in this study were parental-reported asthmalike symptoms. In preschool children, a diagnosis of asthma is based on symptoms of wheezing or shortness of breath[52] because it is complicated to perform lung function measurements in young children. Moreover, the diagnosis of asthma as proposed by current guidelines relies on symptoms rather than measurements.[53]

Although a reasonable level of agreement was seen between timing of introduction of fish assessed at 12 months and at 14 months, misclassification on the timing of fish may occur. If this misclassification is also related to asthmalike symptoms, this would have influenced our results, but this seems unlikely. Also, we did not have data on type of the amount of fish consumed at the moment of introduction. Nevertheless, nutritional assessment can be subject to measurement error, and therefore, repeated measures of n-3 fatty acids in blood during infancy can be useful to shed light on the association between fish consumption and asthma development and whether any potential beneficial effect of the timing of the introduction of fish can be attributed to n-3 fatty acids.

This is an epidemiologic study and thus does not permit final conclusions with respect to the causality of the described associations because residual confounding by other lifestyle factors may exist.

CONCLUSIONS

Introduction of fish between the age of 6 and 12 months but not dietary fish intake at 14 months was associated with a lower prevalence of wheezing at preschool age. A specific window of opportunity between the age of 6 and 12 months might exist in which fish may protect against asthma.

ACKNOWLEDGMENTS

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam; the Municipal Health Service, Rotterdam Metropolitan Area; the Rotterdam Homecare Foundation; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond. We acknowledge the contributions of children and parents, general practitioners, hospitals, and midwives in Rotterdam. Also, we thank Saskia Meyboom, Corine Perenboom, and Els Siebelink of the Department of Human Nutrition, Wageningen University, Netherlands for their contribution in processing the food consumption data.

REFERENCES

1. Matricardi PM. Prevalence of atopy and asthma in eastern versus western Europe: why the difference? *Ann Allergy Asthma Immunol*. 2001;87(6 suppl 3):24–27
2. Robison R, Kumar R. The effect of prenatal and postnatal dietary exposures on childhood development of atopic disease. *Curr Opin Allergy Clin Immunol*. 2010;10(2):139–144
3. Tromp II, Kiefte-de Jong JC, de Vries JH, et al. Dietary patterns and respiratory symptoms in pre-school children: The Generation R Study. *Eur Respir J*. 2012;40(3):681–689
4. Chatzi L, Torrent M, Romieu I, et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax*. 2008;63(6):507–513
5. Chatzi L, Torrent M, Romieu I, et al. Diet, wheeze, and atopy in school children in Menorca, Spain. *Pediatr Allergy Immunol*. 2007;18(6):480–485
6. Arvaniti F, Priftis KN, Papadimitriou A, et al. Adherence to the Mediterranean type of diet is associated with lower prevalence of asthma symptoms, among 10-12 years old children: the PANACEA study. *Pediatr Allergy Immunol*. 2011;22(3):283–289
7. Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP; ISAAC Phase Two Study Group. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two. *Thorax*. 2010;65(6):516–522
8. Chatzi L, Kogevinas M. Prenatal and childhood Mediterranean diet and the development of asthma and allergies in children. *Public Health Nutr*. 2009;12(9A):1629–1634
9. Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM; CAPS Team. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. *Pediatr Allergy Immunol*. 2004;15(6):517–522
10. Oddy WH, de Klerk NH, Kendall GE, Mihrshahi S, Peat JK. Ratio of omega-6 to omega-3 fatty acids and childhood asthma. *J Asthma*. 2004;41(3):319–326
11. Goksör E, Alm B, Thengilsdottir H, Pettersson R, Åberg N, Wennergren G. Preschool wheeze—impact of early fish introduction and neonatal antibiotics. *Acta Paediatr*. 2011;100(12):1561–1566
12. Hesselmar B, Saalman R, Rudin A, Adlerberth I, Wold A. Early fish introduction is associated with less eczema, but not sensitization, in infants. *Acta Paediatr*. 2010;99(12):1861–1867
13. Hajeb P, Selamat J. A contemporary review of seafood allergy. *Clin Rev Allergy Immunol*. 2012;43(3)365–385
14. Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol*. 2010;25(11):823–841
15. Kiefte-de Jong JC, De Vries JH, Bleeker SE, et al. Socio-demographic and lifestyle determinants of early life dietary patterns: the Generation R Study. *Br J Nutr*. 2012, In press
16. Netherlands Nutrition Center. *Nevo: Dutch food composition database 2006*. The Hague, The Netherlands: Netherlands Nutrition Centre; 2006
17. Donders-Engelen M, Heijden van der L, Hulshof KF. *Maten, gewichten en codenummers*. Wageningen, the Netherlands: Human Nutrition of TNO and Wageningen University; 2003
18. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483–491
19. Mohangoo AD, de Koning HJ, Hafkamp-de Groen E, et al. A comparison of parent-reported wheezing or shortness of breath among infants as assessed by questionnaire and physician-interview: The Generation R study. *Pediatr Pulmonol*. 2010;45(5):500–507
20. Caudri D, Wijga A, A Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124(5):903–10.e1–7
21. Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, et al. Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. *Eur J Clin Nutr*. 1998;52(8):588–596
22. Heppe DH, Steegers EA, Timmermans S, et al. Maternal fish consumption, fetal growth and the risks of neonatal complications: the Generation R Study. *Br J Nutr*. 2011;105(6):938–949
23. Timmermans S, Jaddoe VW, Mackenbach JP, Hofman A, Steegers-Theunissen RP, Steegers EA. Determinants of folic acid use in early pregnancy in a multi-ethnic urban population in The Netherlands: the Generation R study. *Prev Med*. 2008;47(4):427–432
24. Sonnenschein-van der Voort AM, Jaddoe VW, van der Valk RJ, et al. Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms. *Eur Respir J*. 2012;39(1):81–89
25. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240–1243
26. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 1997;65(suppl 4):1220S–1228S; discussion 1229S–1231S
27. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393
28. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clin Rev Allergy Immunol*. 2011;41(1):36–66
29. Klemens CM, Berman DR, Mozurkewich EL. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG*. 2011;118(8):916–925
30. Nafstad P, Nystad W, Magnus P, Jaakkola JJ. Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. *J Asthma*. 2003;40(4):343–348
31. Kull I, Bergström A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy*. 2006;61(8):1009–1015
32. Tabak C, Wijga AH, de Meer G, Janssen NA, Brunekreef B, Smit HA. Diet and asthma in Dutch school children (ISAAC-2). *Thorax*. 2006;61(12):1048–1053
33. Willers SM, Wijga AH, Brunekreef B, et al. Childhood diet and asthma and atopy at 8 years of age: the PIAMA birth cohort study. *Eur Respir J*. 2011;37(5):1060–1067
34. Iwami D, Nonomura K, Shirasugi N, Niimi M. Immunomodulatory effects of eicosapentaenoic acid through induction of regulatory T cells. *Int Immunopharmacol*. 2011;11(3):384–389
35. Kitz R, Rose MA, Schubert R, et al. Omega-3 polyunsaturated fatty acids and bronchial inflammation in grass pollen allergy after allergen challenge. *Respir Med*. 2010;104(12):1793–1798
36. Rodríguez-Rodríguez E, Perea JM, Jiménez AI, Rodríguez-Rodríguez P, López-Sobaler AM, Ortega RM. Fat intake and asthma in Spanish schoolchildren. *Eur J Clin Nutr*. 2010;64(10):1065–1071
37. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academy Press; 2002/2005

38. Harris WS, Mozaffarian D, Lefevre M, et al. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr*. 2009;139(4):804S–819S
39. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. *EFSA J*. 2010;8:1461
40. Agostoni C, Braegger C, Decsi T, et al; ESPGHAN Committee on Nutrition. Supplementation of N-3 LCPUFA to the diet of children older than 2 years: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2011;53(1):2–10
41. Tromp II, Kiefte-de Jong JC, Lebon A, et al. The introduction of allergenic foods and the development of reported wheezing and eczema in childhood: the Generation R study. *Arch Pediatr Adolesc Med*. 2011;165(10):933–938
42. Oien T, Storrø O, Johnsen R. Do early intake of fish and fish oil protect against eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. *J Epidemiol Community Health*. 2010;64(2):124–129
43. Grummer-Strawn LM, Scanlon KS, Fein SB. Infant feeding and feeding transitions during the first year of life. *Pediatrics*. 2008; 122(suppl 2):S36–S42
44. Vas J, Monestier M. Immunology of mercury. *Ann N Y Acad Sci*. 2008;1143:240–267
45. Dietert RR, Zelikoff JT. Early-life environment, developmental immunotoxicology, and the risk of pediatric allergic disease including asthma. *Birth Defects Res B Dev Reprod Toxicol*. 2008;83(6):547–560
46. 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 (8):1180–1184
47. van Asselt ED, de Mul A, Traag WA, van Klaveren JD. *Inname aan zware metalen en nitraat door jonge kinderen (Consumption of heavy metals and nitrate in young children)*. Wageningen: Wageningen Universiteit en Researchcentrum, Instituut voor Voedselveiligheid; 2008
48. Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants. *Environ Health Perspect*. 2010;118 (10):1429–1433
49. Baars AJ, Bakker MI, Baumann RA, et al. Dioxins, dioxin-like PCBs and non-dioxin-like PCBs in foodstuffs: occurrence and dietary intake in the Netherlands. *Toxicol Lett*. 2004; 151(1):51–61
50. Becker A, Chan-Yeung M. Primary asthma prevention: is it possible? *Curr Allergy Asthma Rep*. 2008;8(3):255–261
51. Brandtzaeg P. Food allergy: separating the science from the mythology. *Nat Rev Gastroenterol Hepatol*. 2010;7(7):380–400
52. Koopman LP, Brunekreef B, de Jongste JC, Neijens HJ. Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma. *Pediatr Allergy Immunol*. 2001;12(3):118–124
53. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008;32(4):1096–1110

(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2012-0875

doi:10.1542/peds.2012-0875

Accepted for publication Jul 24, 2012

Address correspondence to: Henriëtte A. Moll, MD, PhD, Department of Pediatrics, Erasmus Medical Center, Dr. Molewaterplein 60, 3015 GJ Rotterdam, the Netherlands. E-mail: h.a.moll@erasmusmc.nl

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *Oscar H. Franco has received a grant from Pfizer nutrition to establish a center on aging research, ErasmusAGE; the other authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: This phase of the Generation R Study was supported by the Erasmus Medical Center, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (Zon Mw) and Europe Container terminals Besloten Vennootschap. Funders had no role in study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit the manuscript.

Fish Consumption in Infancy and Asthma-like Symptoms at Preschool Age

Jessica C. Kiefte-de Jong, Jeanne H. de Vries, Oscar H. Franco, Vincent W.V. Jaddoe, Albert Hofman, Hein Raat, Johan C. de Jongste and Henriette A. Moll

Pediatrics 2012;130;1060
DOI: 10.1542/peds.2012-0875 originally published online November 12, 2012;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Fish Consumption in Infancy and Asthma-like Symptoms at Preschool Age

Jessica C. Kiefte-de Jong, Jeanne H. de Vries, Oscar H. Franco, Vincent W.V. Jaddoe, Albert Hofman, Hein Raat, Johan C. de Jongste and Henriette A. Moll

Pediatrics 2012;130;1060
DOI: 10.1542/peds.2012-0875 originally published online November 12, 2012;