Fish consumption in infancy and development of allergic disease up to age 12 y[1–3]

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ABSTRACT

Background: Fish intake in infancy has been associated with reduced risk of allergic disease in early childhood, but it is unknown whether this effect remains as children grow older.

Objective: We studied the possible effect of fish consumption in infancy on prevalent and incident allergic disease up to the age of 12 y.

Design: A total of 3285 children from a prospective Swedish birth cohort (Children, Asthma, Milieu, Stockholm, Epidemiology) were included in the current analyses. At 1, 2, 4, 8, and 12 y, parental questionnaires were used to obtain information on lifestyle factors, environmental exposures, and symptoms of allergic disease. The frequency of fish intake in infancy was assessed in the 1-y questionnaire. Serum immunoglobulin (Ig) E concentrations associated with common allergens were obtained at age 8 y. Generalized estimating equations and multivariate logistic regression were used to examine associations between fish consumption in infancy and prevalent and incident allergic disease at ages 1–12 y, including sensitization and IgE-associated disease at age 8 y.

Results: At 1 y of age, 80% of the children consumed fish regularly (ie, ≥2 times/mo). From 1 to 12 y of age, regular fish consumption in infancy reduced overall risks of prevalent and incident allergic disease [adjusted OR (95% CI) after restriction to children without early symptoms of allergic disease was 0.74 (0.60, 0.90) ($P = 0.003$) for prevalent rhinitis and 0.78 (0.63, 0.97) ($P = 0.028$) for prevalent eczema.

Conclusion: Regular fish consumption in infancy may reduce risk of allergic disease up to age 12 y. *Am J Clin Nutr* 2013;97:1324–30.

INTRODUCTION

Omega-3 fatty acids have been hypothesized to lower risk of allergic disease through their immunological effect (1). Intervention studies have suggested that supplementation with omega-3 fatty acids or fish oil during pregnancy might induce immunologic changes that are transferred to the fetus, which may have a beneficial effect on allergic disease during the first years of life (2–4). However, supplementation studies in infancy and childhood have shown more inconsistent results (2).

Fish is a major source of long-chain omega-3 fatty acids. Maternal fish intake during pregnancy has been reported to reduce risk of allergic outcomes, including sensitization, in infants and children (5–10). Fish consumption in infancy has been studied as the time of introduction in some studies and as the frequency of intake in other studies. In most studies, fish in the child's diet has been associated with reduced risk of eczema, rhinitis, wheeze, and asthma up to preschool age (11–18). However, there have also been reports of no association with allergic disease (19). Parents in many countries, including in the United States and Sweden, have previously been advised to delay the introduction of fish for infants at increased risk of allergic disease (eg, having heredity for or early symptoms of allergic disease) (20, 21). If such recommendations were followed, leading to delayed introduction and, thereby, a lower intake of fish in these children, this disease-related modification of exposure may bias studies on fish consumption in infancy. Therefore, most recent studies on early fish consumption have taken the disease-related modification of exposure into account in different ways (11, 13–18). Today, such recommendations are not given (22, 23), and fish is considered a healthy food. In Sweden, all children are recommended to consume fish 2–3 times/wk from the age of 1 y (24), and a Swedish national survey showed a mean consumption of 1.7 times/wk in 8-y-olds (25). To evaluate the effect of fish consumption in infancy on the subsequent health of a child, it is important to take the child's current fish consumption into account, but to our knowledge, this has not been done in previous studies.

The population-based birth cohort study Children, Asthma, Milieu, Stockholm, Epidemiology (BAMSE), in which children have been followed by repeated parental questionnaires, offered an opportunity to evaluate the effect of fish consumption in infancy and risk of allergic disease up to age 12 y, with adjustment for the child's fish intake at age 8 y. We previously reported that regular fish intake in infancy was associated with reduced risk of allergic disease at 4 y of age in this birth cohort (18). The aim of the current analyses was to investigate the possible effect of early fish consumption on prevalent and incident allergic disease

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[2] Supported by the Stockholm County Council, the Swedish Research Council, the Swedish Research Council Formas, the Swedish Heart and Lung Foundation, the Swedish Asthma and Allergy Association, and the Swedish Foundation for Health Care Science and Allergy Research.

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Received June 21, 2012. Accepted for publication February 28, 2013. First published online April 10, 2013; doi: 10.3945/ajcn.112.045377.

Supplemental Material can be found at:
http://ajcn.nutrition.org/content/suppl/2013/05/13/ajcn.112.045377.DCSupplemental.html

up to the age of 12 y, with disease-related modification of exposure and diet in school age taken into account. We were also able to investigate the association between early fish consumption and allergic disease in relation to IgE sensitization at 8 y of age. In addition, we examined the association between fish intake in school age and incident allergic disease at age 12 y.

SUBJECTS AND METHODS

Study design and study population

This longitudinal study was based on the population-based, prospective birth cohort BAMSE. A total of 4089 newborns were recruited between February 1994 and November 1996 in a predefined area of Stockholm, Sweden. The study design has been described in detail elsewhere (26). In brief, information on several background exposures, allergic heredity, socioeconomic status, and other demographic data were obtained by using a parental questionnaire when the mean age of the children was 2 mo (baseline). When children reached 1, 2, 4, and 8 y of age, parents received a mailed questionnaire that focused on key exposures and symptoms of asthma, rhinitis, and eczema. Response rates were 96%, 94%, 91%, and 84%, respectively. In 2008, when the children were 12 y (age range: 11–14 y), a parental questionnaire was sent out on one occasion, which explained the diversity in age compared with previous follow-ups. The response rate was 82% at this follow-up.

Families who answered the questionnaire at age 8 y were invited to a clinical examination that included blood sampling. The blood of 2470 children (60%) were analyzed for IgE antibodies to 8 common inhalant (Phadiatop) and 6 common food allergens [fx5; Thermo Fischer Scientific (formerly Phadia AB)]. All parts of the BAMSE study have been approved by the ethics committee of Karolinska Institutet, Stockholm, Sweden.

Assessment and definition of fish consumption

Information on the frequency of fish consumption at age 1 y was retrieved from the 1 y follow-up. The following 5 frequency categories were predefined: never, 1 time/mo, 2–3 times/mo, 1 time/wk, and >1 time/wk. Fish intake at 8 y of age was assessed by using a food-frequency questionnaire that contained questions about the frequency of consumption of 5 fish items, including both fatty and lean fish. Participants were asked how often, on average, they had consumed each item over the past year, and the frequencies for all fish items were then added together. The food-frequency questionnaire was filled in by the parents together with the child at the clinical examination at age 8 y.

Definition of health outcomes

All health outcomes were based on parental questionnaires despite sensitization, which was based on blood samples from 8 y of age.

Asthma at 1 and 2 y of age was defined as ≥3 episodes of wheeze in combination with inhaled steroids or signs of bronchial hyperreactivity without concurrent upper respiratory infection. asthma at 4, 8, and 12 y of age was defined as ≥4 episodes of wheeze in the past 12 mo or at least one episode in the same time period in combination with occasional or regular use of prescribed inhaled steroids (27). Rhinitis at 1 and 2 y of age was defined as prolonged rhinitis symptoms for ≥2 mo in the past 12 mo; rhinitis at 4, 8, and 12 y of age was defined as prolonged sneezing or a runny or blocked nose without a common cold in the past 12 mo (27). Eczema was defined as dry skin in combination with an itchy rash for ≥2 wk at typical localization (at 1, 2, and 4 y of age: face or arm/leg-extension surfaces or arm/leg flexures or wrist/ankle flexures; at 8 and 12 y of age: face or arm/leg flexures or wrist/ankle or neck) in the past 12 mo or doctor's diagnosis of eczema during the past 12 mo at 1, 2, and 8 y or cortisone ointment during the past 12 mo at 4 y (27). Incident disease was defined as fulfilling the diagnosis of disease at the respective age, as previously described, without fulfilling the definition at any previous follow-up. Sensitization at 8 y of age was defined as at least one allergen-specific IgE result ≥0.35 kU/L against inhalant allergens (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarium*) or food allergens (cow milk, hen egg, cod fish, soy bean, peanut, and wheat).

The terms IgE associated and non–IgE associated were used if the child fulfilled the criteria of a specific allergic disease at age 8 y and was or was not sensitized to any of the tested allergens, respectively.

Statistical analyses

Data analyses were made with STATA 11.2 software (StataCorp LP). Generalized estimating equations with an unstructured matrix were used to assess the association between fish intake at age 1 y and specific health outcomes during childhood. The generalized estimating equation model calculates population average risks by taking the correlation within individuals into account and provides estimates when missing observations are unequally spaced (28). The model incorporates an interaction between time and exposure to evaluate the effect of exposure over time (28). Fish intake at age 1 y was analyzed in its 5 original categories from the questionnaire as well as a dichotomized variable with categories ≤1 time/mo (irregular) and ≥2–3 times/mo (regular). Multivariate logistic regression was used to analyze associations between fish intake at age 1 y and sensitization outcomes at 8 y of age and fish intake at age 8 y in relation to incident allergic disease between ages 8 and 12 y. Fish intake at age 8 y, divided into tertiles, was analyzed on the basis of reported consumption. Results are presented as adjusted ORs with 95% CIs. Final models were adjusted for sex, parental history of allergic disease (doctor diagnosis of asthma or hay fever in combination with a reported allergy to pollen or pets in one or both parents), and maternal smoking (≥1 cigarette/d at any time point during the pregnancy or when the child was an infant) on the basis of a priori knowledge. Additional adjustments were made for socioeconomic status, breastfeeding duration, maternal age, overweight and parental smoking at age 8 y, as well as childhood diet at age 8 y (fish, vitamin D, total energy, and use of a dietary supplement). However, none of the factors changed the observed ORs, and therefore, additionally tested factors were not included in the final model. To control for possible disease-related modification of exposure, we restricted analyses to children without symptoms of wheeze or eczema during the first year of life (hereafter, denoted as early symptoms of allergic disease). To test for a possible interaction between fish consumption and

TABLE 1
Distribution of selected exposure characteristics in all children in the BAMSE birth cohort and children included in the current analyses[1]

Selected characteristics	Total cohort (n = 4089)	Children included in the current analyses (n = 3285)
Sex: M	2065 [50.5 (49.0, 52.0)]	1664 [50.6 (48.9, 52.4)]
Maternal age at birth: ≤25 y	319 [7.8 (7.0, 8.6)]	231 [7.0 (6.2, 7.9)]
Breastfeeding: ≥4 mo	3116 [79.5 (78.2, 80.8)]	2644 [80.6 (79.3, 82.0)]
Parental history of allergic disease[2]: yes	1200 [29.7 (28.3, 31.1)]	1007 [30.9 (28.3, 32.5)]
Maternal smoking[3]: yes	563 [13.8 (12.7, 14.8)]	431 [13.1 (12.0, 14.3)]
Socioeconomic status: white collar worker	3323 [81.6 (80.4, 82.8)]	2724 [83.2 (81.9, 84.5)]
Fish intake at 1 y: ≥2–3 times/mo	3143 [80.1 (78.9, 81.3)]	2621 [79.8 (78.4, 81.2)]

[1] All values are n [% (95% CI)]. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology.
[2] Doctor-diagnosed asthma or hay fever in combination with reported allergy to pollen or pets in one or both parents.
[3] Mother smoked ≥1 cigarette/d at any point in time during pregnancy or when the child was an infant.

early symptoms of allergic disease and parental history of allergic disease, Wald's test was used. In addition, analyses were stratified by the presence of early symptoms and parental history of allergic disease.

Children were included in the analyses if information from the baseline questionnaire, data on fish intake at age 1 y, and data on at least one of the outcomes (asthma, rhinitis, or eczema) at age 12 y was available (n = 3285). Of these children, 2314 subjects had information on sensitization, and 2456 subjects had information on fish intake at 8 y of age.

RESULTS

The 3285 children included in our analyses were comparable with children in the baseline cohort (ie, the 4089 children recruited to BAMSE at a mean age of 2 mo) regarding distribution of sex, maternal age, breastfeeding duration, parental history of allergic disease, maternal smoking, socioeconomic status, and fish consumption at age 1 y (**Table 1**). In addition, there were no differences in the prevalence of obesity and intake of dietary supplements at age 8 y between children included in our analyses and all children in the cohort followed up to 8 y of age [4.4% (95% CI: 3.6%, 5.2%) obese children in the cohort compared with 4.3% (95% CI: 3.5%, 5.0%) obese children included in our analyses, and 42.0% (95% CI: 40.1%, 43.9%) of the children in the cohort used supplements sometimes or regularly compared with 41.9% (95% CI: 39.9%, 43.8%) of children included in our analyses].

The mean (±SD) age of fish introduction was 8.3 ± 2.3 mo. At 1 y of age, 80% of the children consumed fish regularly (ie, ≥2 times/mo), and the mean consumption was 1.0 ± 0.7 times/wk. Parental allergic disease and early onset of allergic disease delayed the introduction of fish in the child's diet and predicted lower intake at age 1 y ($P < 0.001$) (data not shown). The prevalence of parental allergic disease and of eczema at age 1 y differed significantly between children with lower than higher fish consumption at 1 y of age (*see* Supplemental Table 1 under "Supplemental data" in the online issue). In addition, children with higher fish consumption at age 1 y had a significantly higher median intake of vitamin D at age 8 y (*see* Supplemental Table 1 under "Supplemental data" in the online issue). In contrast, there were no differences in relation to other background factors tested, including fish intake at age 8 y. At age 8 y, the mean consumption of fish was 1.9 ± 1.1 times/wk, and the median consumption was 1.6 times/wk (IQR: 1.2 times/wk).

The prevalence and incidence of asthma, rhinitis, and eczema at different ages are presented in **Table 2**. The prevalence of asthma was quite consistent over time, whereas the prevalence of rhinitis increased, and the prevalence of eczema decreased somewhat during school age. The incidence of the diseases followed the same patterns. The prevalence of asthma at 12 y was 7%, whereas the prevalence of rhinitis and eczema were 21% and 12%, respectively. The incidence of asthma, rhinitis, and eczema at 12 y of age (defined as fulfilling the definition at age 12 y but not at any previous time point) was 3%, 13%, and 5%, respectively, over a 4-y period.

TABLE 2
Distribution of health outcomes in children up to 12 y of age in the BAMSE birth cohort (n = 3285)[1]

	Prevalent cases	Incident cases
Asthma [n (%)]		
1 y of age	125 (4)	125 (4)
2 y of age	187 (6)	118 (4)
4 y of age	213 (7)	119 (4)
8 y of age	200 (6)	94 (3)
12 y of age	218 (7)	83 (3)
Rhinitis [n (%)]		
1 y of age	116 (4)	116 (4)
2 y of age	128 (4)	100 (3)
4 y of age	353 (11)	314 (11)
8 y of age	430 (14)	245 (10)
12 y of age	681 (21)	295 (13)
Eczema [n (%)]		
1 y of age	504 (15)	504 (15)
2 y of age	610 (19)	320 (12)
4 y of age	616 (19)	214 (9)
8 y of age	397 (13)	98 (5)
12 y of age	392 (12)	94 (5)

[1] Prevalent cases were defined as the total number of cases at the respective follow-up occasion. Incident cases were defined as the first-time outcome in the respective age without fulfilling the definition at any previous time point. Percentages were calculated in relation to the total number of subjects who contributed to the analyses at the respective occasion. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology.

TABLE 3
Association between fish intake in infancy and allergic disease up to 12 y of age in the BAMSE birth cohort (overall effect from 0 to 12 y of age)[1]

	Fish intake at age 1 y					
	Never (reference)	1 time/mo[2]	2–3 times/mo[2]	1 time/wk[2]	>1 time/wk[2]	*P*-trend
Asthma	1.00	0.61 (0.43, 0.88)	0.74 (0.55, 1.00)	0.49 (0.37, 0.65)	0.54 (0.40, 0.74)	≤0.001
Rhinitis	1.00	0.76 (0.59, 0.98)	0.75 (0.60, 0.94)	0.57 (0.46, 0.70)	0.53 (0.43, 0.66)	≤0.001
Eczema	1.00	0.59 (0.46, 0.76)	0.58 (0.47, 0.72)	0.44 (0.36, 0.54)	0.43 (0.35, 0.54)	≤0.001

[1] All values are ORs; 95% CIs in parentheses. Values were obtained by using generalized estimating equation analyses. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology.
[2] Adjusted for parental history of allergic disease, sex, maternal smoking during pregnancy or when the child was an infant.

Children who consumed fish at age 1 y had an overall reduced risk of prevalent asthma, rhinitis, and eczema up to age 12 y (**Table 3**). Reduced risks were dose dependent for all outcomes ($P < 0.001$). Additional adjustment for fish intake at 8 y of age did not change the observed results (data not shown). To evaluate the possible influence of a disease-related modification of exposure, we restricted analyses to children without early symptoms of allergic disease ($n = 2404$). After this restriction, associations were attenuated but still significant for rhinitis [adjusted OR (95% CI) for highest compared with lowest intakes: 0.63 (0.46, 0.87); *P*-trend < 0.001] and with borderline significance for eczema [adjusted OR (95% CI) for highest compared with lowest intakes: 0.74 (0.52, 1.03); *P*-trend = 0.008], whereas for asthma, the association became weaker [adjusted OR (95% CI) for highest compared with lowest intakes: 0.81 (0.48, 1.37); *P*-trend = 0.303].

When fish consumption at age 1 y was classified into irregular (≤1 time/mo) or regular intake (≥2–3 times/mo), children who consumed fish regularly had overall reduced risk of prevalent asthma (adjusted OR: 0.71; 95% CI: 0.57, 0.87; $P = 0.001$), rhinitis (adjusted OR: 0.68; 95% CI: 0.59, 0.79; $P < 0.001$), and eczema (adjusted OR: 0.61; 95% CI: 0.52, 0.70; $P < 0.001$) at 1–12 y of age (**Figures 1–3**). Reduced risks were consistent over all time points; however, estimates for eczema gradually became less significant and were nonsignificant at 12 y of age (Figure 3). In analyses of incident allergic disease, overall significant reduced risks were observed for asthma (adjusted OR: 0.80; 95% CI: 0.65, 0.98; $P = 0.034$), rhinitis (adjusted OR: 0.74; 95% CI: 0.63, 0.86; $P < 0.001$), and eczema (adjusted OR: 0.63; 95% CI: 0.55, 0.73; $P < 0.001$) at 1–12 y of age (Figures 1–3).

When analyses were restricted to children without early symptoms of allergic disease [Figures 1–3, "overall(2)"], comparable results were obtained for prevalent rhinitis (adjusted OR: 0.74; 95% CI: 0.60, 0.90; $P = 0.003$) and eczema (adjusted OR: 0.78; 95% CI: 0.63, 0.97; $P = 0.028$), whereas the association became nonsignificant for asthma (adjusted OR: 0.89; 95% CI: 0.63, 1.27; $P = 0.521$). In analyses of incident disease, the OR remained significant for rhinitis (adjusted OR: 0.78; 95% CI: 0.63, 0.95; $P = 0.017$), whereas it was nonsignificant for asthma (adjusted OR: 0.85; 95% CI: 0.61, 1.19; $P = 0.348$) and eczema (adjusted OR: 0.87; 95% CI: 0.70, 1.08; $P = 0.204$). There was no significant interaction between fish intake and early symptoms of allergic disease for any outcomes ($P > 0.05$ for all outcomes). Stratification by parental history of allergic disease did not show any large differences between strata in overall risk reduction for asthma, rhinitis, and eczema, and *P*-interaction values were nonsignificant (data not shown).

In multivariate logistic regression, regular fish intake at age 1 y was associated with reduced risk of sensitization to inhalant and/or food allergens at 8 y of age (adjusted OR: 0.78; 95% CI: 0.63, 0.96). When the analysis was restricted to children without early symptoms of allergic disease, the association became nonsignificant (adjusted OR: 0.98; 95% CI: 0.73, 1.30; $P = 0.867$). To distinguish between IgE-mediated and non-IgE-mediated allergic disease, each allergic disease was combined with sensitization. Associations between fish intake at age 1 y and allergic disease IgE-associated and non-IgE-associated disease at 8 y of age compared with in children without allergic disease and sensitization are shown in **Table 4**. In these analyses, the association appeared to be stronger for IgE-associated asthma and eczema than for non-IgE-associated asthma and eczema. Thus, significant reduced risks of IgE-associated asthma, rhinitis, and eczema at age 8 y for children who consumed fish regularly at age 1 y were seen (Table 4). In addition, there was decreased risk of non-IgE-associated rhinitis but not for

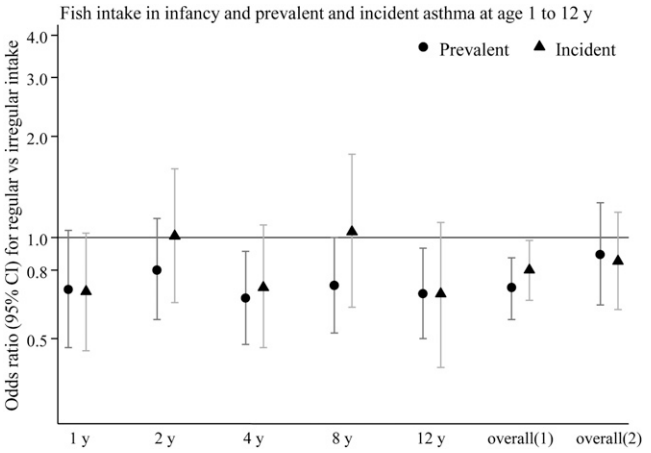

FIGURE 1. Regular fish intake in infancy (≥2–3 times/mo compared with <1 time/mo) in relation to prevalent (circles) and incident (triangles) asthma up to 12 y of age in children in the BAMSE birth cohort ($n = 3285$). ORs (95% CIs) were obtained by using generalized estimating equation analyses and adjusted for sex, parental history of allergic disease, and maternal smoking during pregnancy or when the child was an infant. ORs are presented for each specific age. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology; overall(1), ORs for the entire time period; overall(2), analysis was restricted to children without symptoms of wheeze or eczema during the first year of life.

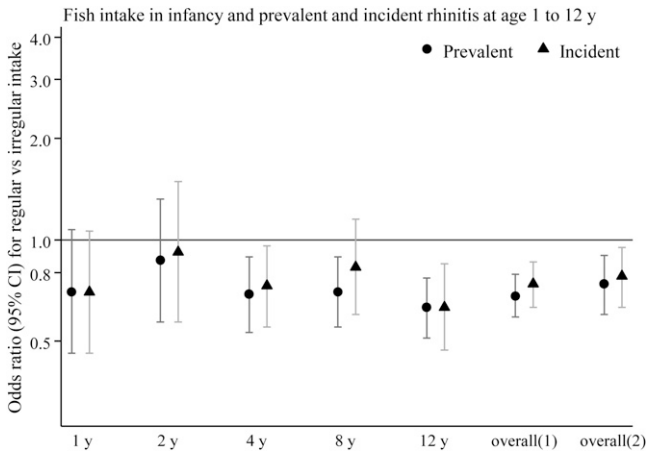

FIGURE 2. Regular fish intake in infancy (≥2–3 times/mo compared with <1 time/mo) in relation to prevalent (circles) and incident (triangles) rhinitis up to 12 y of age in children in the BAMSE birth cohort (n = 3285). ORs (95% CIs) were obtained by using generalized estimating equation analyses and adjusted for sex, parental history of allergic disease, and maternal smoking during pregnancy or when the child was an infant. ORs are presented for each specific age. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology; overall(1), ORs for the entire time period; overall(2), analysis was restricted to children without symptoms of wheeze or eczema during the first year of life.

non-IgE-associated asthma or eczema. When analyses were restricted to children without early symptoms of allergic disease, associations with IgE-associated asthma, rhinitis, and eczema became nonsignificant.

In the 2456 children with information on fish intake at age 8 y, we examined the association with incident allergic disease at age 12 y. No significant associations were observed for asthma (highest compared with lowest tertiles of intake: adjusted OR: 1.12; 95% CI: 0.62, 2.05; P-trend = 0.693), rhinitis (highest compared with lowest tertiles of intake: adjusted OR: 1.20; 95% CI: 0.85, 1.70; P-trend = 0.302), or eczema (highest compared with lowest tertiles of intake: adjusted OR: 0.82; 95% CI: 0.47, 1.46; P-trend = 0.500). Additional adjustment for fish intake at age 1 y had no major influence on the obtained results (data not shown).

DISCUSSION

For the first time to our knowledge, we were able to examine how fish intake in infancy affects the development of allergic disease over the first 12 y of life, both as prevalent and incident disease. In our population-based cohort that included 3285 Swedish children born in 1994–1996 followed from birth and onwards, we were also able to take into account the disease-related modification of exposure as well as fish intake in school-aged children. Children with a regular fish intake at age 1 y had an overall reduced risk of prevalent and incident allergic disease, in particular rhinitis and eczema, up to age 12 y. In contrast, we observed no significant association between fish intake at age 8 y and incident allergic disease at age 12 y.

Strengths of the study included its prospective design, large number of participants with a minor loss to follow-up, and detailed and repeated assessment of outcomes through questionnaires, which made it possible to study both prevalent and incident disease through childhood and objective measurements of sensitization through allergen-specific IgE analyses in blood. Moreover, we were able to assess a large number of potential confounders, including vitamin D and childhood diet at 8 y of age. Despite this, we could not rule out that unmeasured factors, such as other parts of an infant diet that contributed with omega-3 fatty acids (eg, rapeseed oil), may have affected our findings. Our analyses were limited by the absence of information on maternal diet, and therefore, we could not exclude the possibility that a child's fish intake in infancy may act as a marker for maternal intake during pregnancy of these foods. Nevertheless, our findings made it very unlikely that infant fish intake leads to greater risk of childhood allergic disease, which was previously believed.

A misclassification of exposure is a possible source of bias in epidemiologic studies (29). However, in our study, parents were asked, when the child was aged 1 y, how often the child consumed fish at the same age, which minimized risk of misclassification of exposure. One limitation with our exposure assessment is that we could not distinguish between types of fish consumed. Such analyses would have been interesting because lean and fatty fish have different contents of fatty acids and might affect risk of allergic disease differently.

A more important concern is risk of disease-related modification of exposure, which is an important factor to consider in epidemiologic studies (30, 31). In our analyses, we observed that early symptoms of allergic disease in the child and parental history of allergic disease affected fish consumption at 1 y of age. We tried to take such bias into account by restricting the analyses to children without symptoms of wheeze or eczema during the first year of life. Although these analyses showed that the disease-related modification of exposure affected our results to some extent, the consumption of fish in infancy also reduced risk of rhinitis and eczema during childhood in the restricted analyses. In addition, after stratification by parental history of allergic disease, no major differences were seen between strata, which indicated an independent effect of infant fish consumption on the subsequent development of allergic disease.

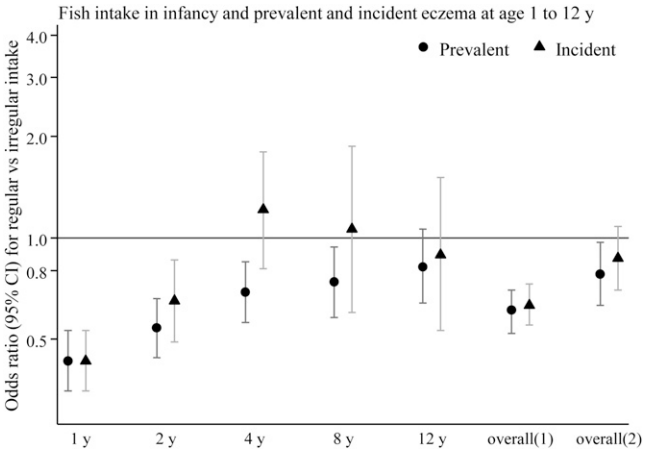

FIGURE 3. Regular fish intake in infancy (≥2–3 times/mo compared with <1 time/mo) in relation to prevalent (circles) and incident (triangles) eczema up to 12 y of age in children in the BAMSE birth cohort (n = 3285). ORs (95% CIs) were obtained by using generalized estimating equation analyses and adjusted for sex, parental history of allergic disease, and maternal smoking during pregnancy or when the child was an infant. ORs are presented for each specific age. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology; overall(1), ORs for the entire time period; overall(2), analysis was restricted to children without symptoms of wheeze or eczema during the first year of life.

TABLE 4
Association between fish intake in infancy and allergic disease associated with sensitization at 8 y of age before and after restriction to children without early symptoms of allergic disease in the BAMSE birth cohort (n = 2314)[1]

	Fish intake at age 1 y				
	≤1 time/mo		≥2–3 times/mo		
	n/*N*	Reference	*n*/*N*	Adjusted OR (95% CI)[2]	Adjusted OR (95% CI)[3]
Asthma and no sensitization	12/457	1.00	42/1845	0.82 (0.41, 1.62)	0.57 (0.24, 1.37)
Asthma and sensitization[4]	38/457	1.00	75/1845	0.51 (0.33, 0.78)	0.73 (0.35, 1.50)
Rhinitis and no sensitization	31/459	1.00	74/1849	0.50 (0.32, 0.79)	0.36 (0.21, 0.63)
Rhinitis and sensitization[4]	61/459	1.00	185/1849	0.70 (0.50, 0.97)	0.98 (0.58, 1.67)
Eczema and no sensitization	40/446	1.00	129/1811	0.70 (0.47, 1.03)	0.74 (0.47, 1.24)
Eczema and sensitization[4]	45/446	1.00	99/1811	0.51 (0.34, 0.75)	0.84 (0.41, 1.71)

[1] ORs (95% CIs) were obtained by using logistic regression analyses. BAMSE, Children, Asthma, Milieu, Stockholm, Epidemiology; *n*, number of children with the outcome in the exposure category; *N*, total number of children in the exposure category.

[2] Adjusted for parental history of allergic disease, sex, and maternal smoking during pregnancy or when the child was an infant

[3] Restricted to children without wheeze or eczema during the first year of life (n = 2404). Adjusted for parental history of allergic disease, sex, and maternal smoking during pregnancy or when the child was an infant.

[4] Sensitization was classified as the occurrence of IgE antibodies to any of 8 inhalant or 6 food allergens at 8 y of age.

In line with our findings of reduced risk of allergic disease for infants with regular fish consumption, a protective effect of weekly fish intake at age 1 y on eczema at age 2 y, which remained after the exclusion of children with an onset of eczema at <1 y of age, was reported in a Norwegian study (17). In a cohort from Western Sweden, an association was observed between fish intake in infancy and reduced risk of eczema at 1 y of age and of allergic rhinitis and recurrent wheeze at 4.5 y of age (11–13). In addition, in other studies, fish intake in infancy was also shown to decrease risk of allergic disease in preschool ages (14–16). In the Dutch birth cohort Prevention and Incidence of Asthma and Mite Allergy, no association was observed between weekly fish intake at 2 y of age and differences in asthma or wheeze prevalence at age 3 y in univariate analyses (19). Differences in results might have been due to the amount of different types of fish consumed, definitions of outcomes, and the advice given to parents regarding fish consumption in infancy may have differed depending on which country the different cohorts took place in and the birth years of participating children.

To our knowledge, regular fish consumption in infancy and allergic disease associated with IgE sensitization in school age has not been studied before. In our analyses, regular fish intake in infancy was associated with decreased risk of IgE-associated asthma, rhinitis, and eczema at 8 y of age. However, when analyses were restricted to children without early symptoms of allergic disease, reduced risk of IgE-associated asthma, rhinitis, and eczema became nonsignificant. Despite this, it is biologically plausible that the effect was seen mainly for IgE-associated disease because fish is a major source of omega-3 fatty acids, which have an inhibitory effect on prostaglandin E_2, which leads to a decreased formation of IgE (1). Because of their immunological effect, omega-3 fatty acids have been hypothesized to lower risk of allergic diseases (1). In intervention studies, it has been observed that omega-3 fatty acids and fish-oil supplementation during pregnancy may have induced immunologic changes in cord blood and in the fetus and also seemed to have a beneficial effect on allergic disease during the child's first years of life (2–4). However, supplementation studies in infancy and childhood have shown inconsistent results (2). Few epidemiologic studies in children have been able to distinguish between the consumption of fatty and lean fish, and results have been inconclusive (12, 17, 32). Explanations for the discrepancy in interventions and observational studies might be the differing amounts of omega-3 ingested or the quantities of omega-3 intake in relation to intakes of other fatty acids (eg, omega-6). Alternatively, compounds other than the fatty acids in fish, such as certain proteins or vitamins, might explain the association with allergic disease. Moreover, regular fish intake may be a proxy for a generally healthy lifestyle that may protect from allergic disease. However, when fish intake at age 8 y was taken into account, it did not affect reduced risks we observed for fish intake at 1 y of age on allergic disease up to age 12 y. If our results reflect a biologic mechanism that relates infant fish intake to the development of allergic disease, it seems likely that the mechanism would apply to multiple populations.

In conclusion, our analyses of 3285 Swedish children indicates that regular fish consumption early in life may reduce overall risk of allergic disease up to 12 y of age, particularly risks of rhinitis and eczema.

We thank all children and parents participating in the BAMSE cohort as well as Eva Hallner, André Lauber, and the rest of the staff involved in the study.

The authors' responsibilities were as follows—MW: initiated the BAMSE project; JM, IK, and AB: designed the study; IK: supervised the data collection; JM: conducted statistical analyses and wrote the manuscript; IK, HR, NH, AW, EM, MW, and AB: provided comments on the manuscript; and all authors: interpreted data and approved the final manuscript. None of the authors had a conflict of interest.

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