Fish and polyunsaturated fat intake and development of allergic and nonallergic rhinitis

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Background: Rhinitis is one of the most common diseases in childhood. Fish, polyunsaturated fatty acid (PUFA), and vitamin D intakes have been hypothesized to affect the risk of allergic disease; however, it is unclear whether these are linked to the development of rhinitis.

Objective: We sought to assess potential associations between consumption of fish, dietary n-3 and n-6 PUFAs, and vitamin D at age 8 years and development of allergic rhinitis (AR) and nonallergic rhinitis (NAR) between the ages of 8 and 16 years.

Methods: We included 1970 participants from a birth cohort. Data on dietary intake was obtained from a food frequency questionnaire at age 8 years. The rhinitis definition was based on questionnaires and IgE measures.

Results: The prevalence of rhinitis symptoms at age 8 years was 19% (n = 380). Among the 1590 children without rhinitis symptoms at age 8 years, 21% (n = 337) had AR between ages 8 and 16 years, and 15% (n = 236) had NAR. Regular intake of oily fish and higher long-chain n-3 PUFA intake were associated with a reduced risk of cumulative incidence of NAR (adjusted odds ratio, 0.52 [95% CI, 0.32-0.87] for oily fish; odds ratio, 0.45 [95% CI, 0.30-0.67] for highest vs lowest tertile of long-chain n-3 PUFAs; *P* trend < .001). The results for rhinitis, irrespective of AR and NAR, were in line with the findings for NAR.

Conclusion: Regular consumption of oily fish and dietary long-chain n-3 PUFAs in childhood might decrease the risk of rhinitis, especially NAR, between the ages of 8 and 16 years. (J Allergy Clin Immunol 2015;136:1247-53.)

Key words: *Adolescent, allergic rhinitis, BAMSE, children, diet, fatty acid, fish, nonallergic rhinitis, prospective studies, vitamin D*

Rhinitis is one of the most common chronic diseases in childhood.[1,2] Noninfectious rhinitis can be distinguished into allergic rhinitis (AR) and nonallergic rhinitis (NAR).[3,4] In adolescent populations with rhinitis, about 1 in 4 seem to have NAR.[5] A known risk factor for both AR and NAR is parental allergic disease.[6-8] However, few modifiable risk factors have been identified, especially for NAR.[6]

Changes in dietary habits during the past decades, including fish consumption, have been suggested to play a role in the increase of allergic diseases, including rhinitis.[9,10] Oily fish is rich in long-chain n-3 polyunsaturated fatty acids (PUFAs) and vitamin D, which have been suggested to decrease the risk of allergic disease through their immunomodulatory properties,[11,12] whereas n-6 PUFAs and an increased n-6/n-3 ratio have been suggested to increase the risk.[11]

In some studies, including our birth cohort, regular intake of fish in infancy has been associated with a reduced risk of rhinitis at preschool age[13-16] and up to age 12 years.[17] The incidence of rhinitis is high at school age and during adolescence,[2,18] and therefore it is of interest to examine whether school-age consumption of fish, dietary PUFAs, and vitamin D can affect the risk of rhinitis. Previous studies on fish and PUFA intake in school age have assessed intake at the same time as the outcome, and in these studies fish consumption has not been associated with rhinitis,[19-23] whereas studies on PUFA intake and rhinitis have been inconclusive.[24,25] Although few studies have examined the association between vitamin D status and rhinitis in children, an inverse association between vitamin D status at age 6 years and rhinoconjunctivitis at age 14 years was recently observed in a prospective cohort.[26] In previous studies of the relation between fish, PUFA, and vitamin D consumption and rhinitis in childhood, IgE reactivity to common allergens has rarely been included in the definition of rhinitis, which reduces the possibility of exploring associations for AR and NAR separately.

In our birth cohort with longitudinal data, we examined potential associations between fish intake, including types of fish, dietary n-3 and n-6 PUFAs, and vitamin D, at age 8 years and cumulative incidence of AR and NAR between ages 8 and 16 years.

METHODS

Study design and study population

This study is based on a population-based birth cohort, the Children, Allergy, Milieu, Stockholm, an Epidemiological study (BAMSE), to which 4089 newborns were recruited between February 1994 and November 1996 in Stockholm, Sweden. Baseline information was obtained through a parental questionnaire shortly after birth, and follow-ups have taken place throughout

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Abbreviations used
AA: Arachidonic acid
ALA: α-Linolenic acid
AR: Allergic rhinitis
BAMSE: Children Allergy, Milieu, Stockholm, an Epidemiological study
FFQ: Food frequency questionnaire
LA: Linoleic acid
NAR: Nonallergic rhinitis
OR: Odds ratio
PUFA: Polyunsaturated fatty acid

childhood.[27,28] The most recent follow-up took place at age 16 years; adolescents answered a questionnaire, and the response rate compared with the baseline cohort was 76%.

At 8 and 16 years of age, participants who answered the respective questionnaire were invited to a clinical examination. At the 8-year examination, the child's diet was assessed by using a food frequency questionnaire (FFQ; n = 2614). At both ages 8 (n = 2470 [60%]) and 16 (n = 2547 [62%]) years, participants provided blood samples, which were analyzed for IgE antibodies with ImmunoCAP to common inhalant allergens by using the Phadiatop mix (birch, timothy, and mugwort pollen; cat, dog, and horse dander; and *Cladosporium herbarum* and *Dermatophagoides pteronyssinus*; Thermo Fisher Scientific, Uppsala, Sweden). Blood samples that scored positive for the Phadiatop mix were analyzed for allergen-specific IgE antibodies to the single allergens mentioned above. A technical cutoff was set at an IgE level of 0.35 kU/L or greater, according to the manufacturer's instructions.

Participants with baseline questionnaire data, data on nutrient and total fish intake at age 8 years, and outcome data at age 16 years were included in the present study (n = 1970, 48% of original cohort). Inclusion in the study is described in detail in Fig 1. All parts of BAMSE have been approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden, and informed consent from the study participants has been obtained.

Dietary assessment

Diet at age 8 years was assessed by using an FFQ with 98 foods and beverages frequently consumed in Sweden. The participants were asked to indicate how often on average they had consumed these in the previous 12 months, and 10 response categories were predefined (never, <1 time per month, 1-3 times per month, 1 time per week, 2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, and ≥3 times per day). Most often the FFQ was filled out by a parent (57%) or a parent together with the child (40%). With regard to fish consumption, participants were asked about intake of herring/mackerel and salmon fishes (categorized as oily fish), as well as codfish/pollock/pike, fish fingers, and tuna fish. Intakes of dietary PUFA and vitamin D were computed from the FFQ by multiplying the frequency of consumption of each food item by its nutrient content per serving and summarized over food and beverages by using composition values obtained from the Swedish Food Administration Database.[29] Nutrient intakes were adjusted for total energy intake by using the residuals method.[30] PUFAs assessed were linoleic acid (LA; 18:2n-6), α-linolenic acid (ALA; 18:3n-3), arachidonic acid (AA; 20:4n-6), eicosapentaenoic acid (20:5n-3), docosapentaenoic acid (22:5n-3), and docosahexaeonic acid (22:6n-3).

Definition of outcomes

Rhinitis symptoms at age 8 years. These symptoms included parent-reported sneezing or runny or blocked nose without common cold or flu in the last 12 months and/or nose or eye symptoms in contact with furred pets and/or pollens after 4 years of age.[3]

AR at age 16 years. AR included adolescent-reported sneezing or runny or blocked nose without common cold or flu or in contact with furred pets, pollens, and/or mites in the last 12 months in combination with sensitization to any of the inhalant allergens tested (Phadiatop ≥0.35 kU/L).[3]

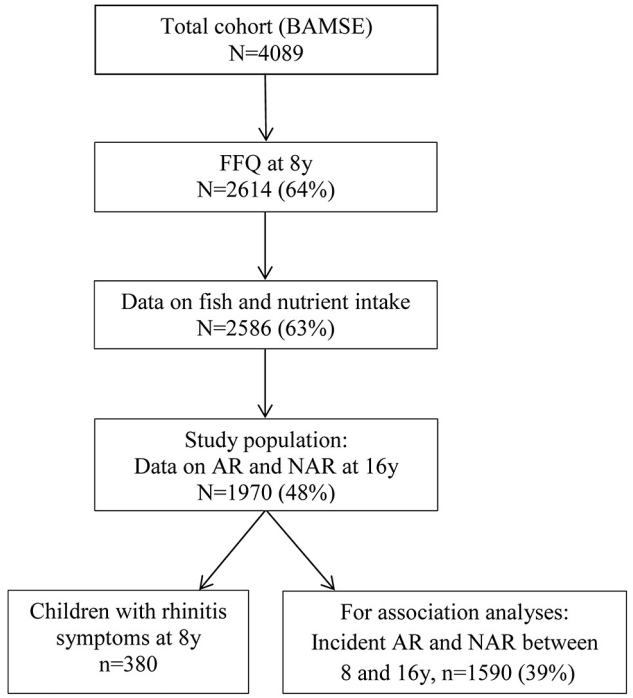

FIG 1. Flow chart of inclusion into the study population and analyses of the cumulative incidence of AR and NAR between ages 8 and 16 years.

NAR at age 16 years. NAR included adolescent-reported symptoms as above with no sensitization (Phadiatop <0.35 kU/L).[3]

Statistical analyses

The distribution of selected background characteristics for the study population and for the total cohort was compared with a 1-sample *t* test. Fish intake was divided into dichotomous variables less than 2 times a week or 2 or more times a week for total fish and less than 1 time a week or 1 or more times a week for oily fish, cod/pollock/pike, and fish fingers. PUFA and vitamin D intakes were divided into tertiles. PUFAs were analyzed as single fatty acids (ALA, LA, and AA) and grouped together to total PUFA, n-6 (LA and AA), and long-chain n-3 (docosahexaeonic acid, eicosapentaeonic acid, and docosapentaenoic acid) PUFAs. We also analyzed the n-6/n-3 ratio. The outcome was analyzed as the cumulative incidence of AR and NAR between ages 8 and 16 years by excluding children with rhinitis symptoms at age 8 years (n = 380, Fig 1), and the reference category consisted of adolescents with no rhinitis symptoms and no sensitization to inhalant allergens at age 16 years. Analyses of associations between exposure and outcome were done with multinomial logistic regression. The results are presented as adjusted odds ratios (ORs) with 95% CIs. Tests for trends in analyses of PUFA and vitamin D intake were performed, assigning the median value of each tertile to all subjects in that tertile, which then was used as a continuous variable in the model.

Traditional potential confounding factors for which we tested were sex, allergic heredity, maternal age, maternal smoking during pregnancy or the child's first months, older siblings and socioeconomic status (baseline questionnaire), breast-feeding duration and fish consumption in infancy (1-year questionnaire), and parental origin, indoor moist, furred pet ownership, parental smoking, socioeconomic status, energy intake, supplement use, and overweight status (8-year questionnaire). In the first step analyses were unadjusted because no factor changed crude ORs by 5% or greater. In a second step food groups (total intake of dairy products, meat, cereals, fruits, and vegetables) were tested as potential confounding factors in analyses of fish intake. No food group changed crude ORs by 5% or greater, and fish analyses were only adjusted for the other types of fish. In addition, in analyses of PUFAs and vitamin D, nutrients were tested as possible

TABLE I. Distribution of selected exposure characteristics in the study population (n = 1970) and among adolescents with incident AR (n = 337) or NAR (n = 236) between ages 8 and 16 years

	Study population*		Incident AR†		Incident NAR‡	
	No.	Percent	No.	Percent	No.	Percent
Male sex	970	49.2	183	54.3	102	43.2
Maternal smoking,§ yes	233	11.8	37	11.0	46	19.5
Maternal age at birth ≤25 y	134	6.8	21	6.2	22	9.3
Breast-feeding ≥4 mo	1578	81.4	271	81.1	188	81.7
Parental origin,‖ outside of Scandinavia	407	20.8	87	25.9	51	21.7
Socioeconomic status, white collar worker	1675	85.9	293	88.3	185	79.4
Allergic heredity,¶ yes	625	32.0	136	40.6	53	22.7
Eczema at age 1 y, yes	312	16.0	60	18.0	27	11.7
Any wheeze at age 1 y, yes	280	14.5	54	16.2	36	15.6
Fish intake at age 1 y, ≥2 times/mo	1560	80.5	252	75.5	188	81.4
Parental smoking,# yes	324	16.6	45	13.4	51	21.8
Obesity at age 8 y,** yes	75	3.8	16	4.8	10	4.2
Supplement use at age 8 y,†† yes	825	42.4	134	40.0	108	46.2
Sensitization to inhalant allergens at age 8 y,‡‡ yes	493	26.3	163	50.6	2	0.9
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Energy intake at age 8 y (kcal)	1910	462	1917	434	1923	500

*Subjects fulfilling the inclusion criteria: baseline questionnaire data, data on nutrient and total fish intake at age 8 years, and outcome data at age 16 years.
†Adolescents fulfilling the inclusion criteria as above and: do not have rhinitis symptoms at age 8 years and have AR at age 16 years.
‡Adolescents fulfilling the inclusion criteria as above and: do not have rhinitis symptoms at age 8 years and have NAR at age 16 years.
§Mother smoked at least 1 cigarette per day at any point of time during pregnancy or the child's first months.
‖Father and/or mother born outside of Scandinavia.
¶Doctor-diagnosed asthma and/or hay fever in combination with reported allergy to pollen or pets in 1 or both parents.
#Any of the parents smoked at least 1 cigarette per day when the child was age 8 years.
**The child had an isoBMI of at least 30 kg/m^2 at age 8 years (age and sex specific cut-off values developed for children under 18 years of age).
††The child used supplements, such as multivitamins, sometimes or regularly at age 8 years.
‡‡The child had at least 1 IgE value of 0.35 kU/L or greater against inhalant allergens at age 8 years.

confounders (total intake of carbohydrates, proteins, saturated fat, monounsaturated fat, total antioxidant capacity, and other exposures in respective analyses). Carbohydrates, monounsaturated fat, vitamin D, and the other group of PUFAs changed crude ORs by 5% or greater and were therefore adjusted for in the respective PUFA intake analysis, and vitamin D analyses were adjusted for carbohydrates, monounsaturated fat, and PUFAs. To control for possible disease-related modification of exposure, we additionally adjusted the analyses for early symptoms of allergic disease (children with reported symptoms of wheeze, eczema, or both during the first 2 years of life). Possible interactions between types of fish, PUFAs, and vitamin D and allergic heredity were tested with the likelihood ratio test. Data analyses were executed with Stata version 11.2 software (StataCorp, College Station, Tex).

RESULTS

There were only minor differences in the distribution of background characteristics between the 1970 adolescents in the study population and the baseline cohort (see Table E1 in this article's Online Repository at www.jacionline.org).

The prevalence of rhinitis symptoms at age 8 years was 19% (n = 380). Among the 1590 without rhinitis symptoms at age 8 years, 337 adolescents (21%) had AR between ages 8 and 16 years, and 236 (15%) had NAR. Adolescents who had AR or NAR had somewhat different background characteristics (Table I). For example, participants with incident AR had a higher prevalence of allergic heredity and more reported eczema in infancy. The largest difference was seen for sensitization to inhalant allergens at age 8 years (ie, 51% with an incidence of AR at age 16 years were sensitized at age 8 years compared with 1% with NAR).

Median intakes of fish and nutrients for the study population, as well as for the adolescents with incident AR or NAR, are described in Table II. At age 8 years, 38% of the study population had a fish intake of 2 times per week or more. Fourteen percent consumed oily fish once a week or more, and the corresponding percentages for cod/pollock/pike and fish fingers were 32% and 38%, respectively. The median intake of total PUFAs was 7.85 g/d, whereas the median intake of vitamin D was 5.12 μg/d. Distribution of disease in relation to fish, PUFA, and vitamin D intake at age 8 years is described in Table E2 in this article's Online Repository at www.jacionline.org. A regular intake of fish at age 8 years was not significantly associated with risk of AR or NAR at the same age (adjusted OR, 1.04 [95% CI, 0.71-1.54] for AR; adjusted OR, 0.80 [95% CI, 0.43-1.48] for NAR).

In multivariate logistic regression analysis there was no apparent association between intake of total fish at age 8 years and cumulative incidence of AR and NAR between the ages of 8 and 16 years (Table III). In analyses based on type of fish, a regular intake of oily fish was associated with a reduced risk of cumulative incidence of NAR between ages 8 and 16 years (adjusted OR, 0.52 [95% CI, 0.32-0.87]), whereas the association with AR was in the same direction but did not reach statistical significance (adjusted OR, 0.78 [95% CI, 0.53-1.15]). There were no evident associations for cod/pollock/pike or fish fingers and AR or NAR. Adjusting for early symptoms of allergic disease to avoid disease-related modification of exposure did not affect the observed ORs (data not shown).

Long-chain n-3 PUFA intake was associated with a significant reduced risk of cumulative incidence of NAR between ages 8 and 16 years (adjusted OR, 0.45 [95% CI, 0.30-0.67] for the highest vs lowest tertile; P trend < .001). In addition, an increased n-6/n-3 ratio was associated with an increased risk of cumulative incidence of NAR (adjusted OR, 1.56 [95% CI, 1.03-2.33] for highest vs lowest tertile; P trend = .032). No significant associations were observed for intake of total PUFA, total n-6 PUFA, and the single fatty acids LA and ALA and cumulative incidence of AR and NAR (Table IV). Additional adjustment for early symptoms of

TABLE II. Consumption of fish and unadjusted PUFAs and vitamin D at age 8 years for the study population (n = 1970) and adolescents with an incident AR (n = 337) and NAR (n = 236) between ages 8 and 16 years

	Study population			Incident AR			Incident NAR		
	Median	IQR	Minimum-maximum	Median	IQR	Minimum-maximum	Median	IQR	Minimum-maximum
Fish intake (times/wk)									
Total fish	1.70	1.23	0-14.6	1.70	1.23	0-7.9	1.63	1.28	0-6
Oily fish	0.47	0.47	0-7.1	0.47	0.47	0-4.5	0.47	0.47	0-3
Cod/pollock/pike	0.47	0.88	0-7	0.47	0.88	0-2	0.47	0.88	0-2
Fish fingers	0.47	0.53	0-7	0.47	0.53	0-7	0.47	0.53	0-2
PUFA intake (g/d)									
Total PUFA	7.85	3.12	3.0-25.1	7.89	2.98	3.2-19.4	7.98	3.28	3.3-16.2
ALA	1.13	0.50	0.4-4.1	1.13	0.47	0.4-3.2	1.15	0.62	0.4-3.1
Long-chain n-3 PUFA*	0.24	0.17	0.01-2.5	0.24	0.16	0.03-0.9	0.21	0.17	0.03-0.8
n-6 PUFA†	6.22	2.45	2.4-20.1	6.28	2.35	2.4-15.9	6.21	2.70	2.7-13.7
LA	6.15	2.43	2.3-20.0	6.20	2.35	2.4-15.9	6.15	2.63	2.7-13.6
AA	0.07	0.03	0.005-0.4	0.07	0.04	0.02-0.4	0.07	0.04	0.02-0.2
n-6/n-3 ratio	4.58	0.76	1.4-11.2	4.62	0.69	2.8-8.5	4.65	0.72	3.1-11.2
Vitamin D intake (μg/d)	5.12	2.58	0.9-17.5	5.11	2.48	1.2-12.2	5.27	2.47	1.1-12.4

*Eicosapentaeonic, docosapentaenoic, and docosahexaeonic acid.
†LA and AA.

TABLE III. ORs of AR or NAR between ages 8 and 16 years*† in relation to fish intake at age 8 years‡ (n = 1590)

	Incident AR		Incident NAR	
	Crude OR§ (95% CI)	Adjusted OR‖ (95% CI)	Crude OR§ (95% CI)	Adjusted OR‖ (95% CI)
Total fish¶				
≥2 Times/wk	1.04 (0.80-1.35)	—	0.98 (0.72-1.32)	—
Oily fish				
≥1 Time/wk	0.78 (0.53-1.14)	0.78 (0.53-1.15)	**0.59 (0.37-0.95)**	**0.52 (0.32-0.87)**
Cod/pollock/pike				
≥1 Time/wk	0.95 (0.72-1.26)	0.93 (0.69-1.25)	1.10 (0.81-1.51)	1.15 (0.82-1.61)
Fish fingers				
≥1 Time/wk	1.21 (0.93-1.57)	1.26 (0.95-1.66)	1.06 (0.79-1.44)	1.04 (0.75-1.44)

P values of .05 or smaller are considered significant and shown in boldface.
*No rhinitis symptoms at age 8 years.
†The reference group in analyses is composed of adolescents without sensitization and rhinitis symptoms at age 16 years.
‡Fish intake at age 8 years is based on answers to an FFQ.
§Unadjusted model.
‖Model including the variables oily fish, cod/pollock/pike, and fish fingers at once.
¶Total fish is the sum of the variables oily fish, cod/pollock/pike, and fish fingers.

allergic disease did not affect the observed results (data not shown). We did not observe any obvious associations between intake of vitamin D and cumulative incidence of AR or NAR between ages 8 and 16 years (Table IV). There were no significant interactions between allergic heredity and intake of fish, PUFAs, and vitamin D with respect to the incidence of AR or NAR (data not shown).

Because the results for AR and NAR pointed in the same direction, we performed *post hoc* analyses by using AR and NAR cases combined to increase the comparability with the results from other studies (Fig 2). The results obtained were comparable with those for NAR in Tables III and IV; regular oily fish intake and dietary long-chain n-3 PUFAs were associated with a decreased risk of cumulative incidence of rhinitis between ages 8 and 16 years (adjusted OR, 0.67 [95% CI, 0.48-0.94] for oily fish; adjusted OR, 0.73 [95% CI, 0.55-0.98] for highest vs lowest tertile of long-chain n-3 PUFA; *P* trend = .034), and the n-6/n-3 ratio was borderline significantly associated with an increased risk of cumulative incidence of rhinitis (adjusted OR, 1.28 [95% CI, 0.96-1.74] for highest vs lowest tertile; *P* trend = .100).

DISCUSSION

In our study of 1970 adolescents from the birth cohort BAMSE, regular intake of oily fish and dietary long-chain n-3 PUFAs measured at age 8 years was associated with a reduced risk of cumulative incidence of NAR between ages 8 and 16 years. In addition, an increased n-6/n-3 ratio was associated with an increased risk of cumulative incidence of NAR. The results for rhinitis, whether AR or NAR, were comparable with those for NAR.

In contrast to our findings, other studies on fish and PUFA consumption in childhood have not observed an association[20,21,23,24] or increased risk[24,25] of rhinitis. Discrepancy between other studies on rhinitis and our findings can be due to a number of factors, including PUFA categorization (total PUFA vs n-3 and n-6 PUFA or single fatty acids). In adults inverse associations between long-chain n-3 PUFAs and rhinitis have been reported,[31,32] although another study did not observe any associations.[33] These studies were all of a cross-sectional design. In our cross-sectional analysis of oily fish intake and AR and NAR at age 8 years, we observed no associations.

Oily fish might influence allergic disease through its content of long-chain n-3 PUFAs. Long-chain n-3 PUFAs have been shown

TABLE IV. ORs of AR or NAR between ages 8 and 16 years*† in relation to dietary PUFA (in grams per day) and vitamin D (in micrograms per day) intake in tertiles at age 8 years (n = 1590)

	Incident AR		Incident NAR	
	Crude OR‡ (95% CI)	Adjusted OR§ (95% CI)	Crude OR‡ (95% CI)	Adjusted OR§ (95% CI)
Total PUFA				
Q2	0.93 (0.68-1.28)	0.88 (0.62-1.25)	0.94 (0.66-1.34)	0.83 (0.56-1.22)
Q3	0.95 (0.69-1.29)	0.85 (0.57-1.28)	0.87 (0.61-1.24)	0.69 (0.43-1.11)
P value for trend‖	.757	.478	.448	.127
ALA				
Q2	0.84 (0.61-1.15)	0.80 (0.55-1.15)	1.08 (0.75-1.54)	1.06 (0.70-1.60)
Q3	0.86 (0.63-1.18)	0.80 (0.50-1.28)	0.98 (0.69-1.41)	0.89 (0.52-1.53)
P value for trend‖	.383	.376	.890	.643
Long-chain n-3 PUFA				
Q2	0.84 (0.61-1.15)	0.87 (0.63-1.20)	**0.64 (0.45-0.90)**	**0.62 (0.44-0.88)**
Q3	0.95 (0.70-1.30)	1.02 (0.72-1.44)	**0.48 (0.33-0.70)**	**0.45 (0.30-0.67)**
P value for trend‖	.794	.922	<.001	<.001
n-6 PUFA				
Q2	0.96 (0.70-1.31)	0.97 (0.66-1.42)	0.98 (0.69-1.40)	0.91 (0.59-1.40)
Q3	0.91 (0.67-1.25)	0.88 (0.54-1.43)	0.91 (0.64-1.30)	0.86 (0.50-1.49)
P value for trend‖	.557	.239	.589	.374
LA				
Q2	0.97 (0.71-1.32)	1.00 (0.68-1.46)	0.98 (0.69-1.40)	0.92 (0.59-1.41)
Q3	0.93 (0.68-1.27)	0.92 (0.57-1.60)	0.91 (0.64-1.30)	0.86 (0.50-1.50)
P value for trend‖	.634	.714	.588	.606
AA				
Q2	0.91 (0.66-1.25)	0.89 (0.64-1.25)	**0.68 (0.48-0.97)**	0.76 (0.52-1.10)
Q3	1.06 (0.78-1.46)	1.01 (0.69-1.49)	0.82 (0.58-1.17)	1.02 (0.66-1.57)
P value for trend‖	.639	.890	.340	.855
n-6/n-3 ratio				
Q2	1.24 (0.91-1.70)	1.22 (0.88-1.68)	**1.47 (1.02-2.11)**	**1.50 (1.02-2.18)**
Q3	1.16 (0.85-1.59)	1.12 (0.79-1.59)	**1.50 (1.04-2.15)**	**1.56 (1.03-2.33)**
P value for trend‖	.343	.511	.031	.032
Vitamin D				
Q2	0.94 (0.69-1.29)	0.96 (0.70-1.33)	0.80 (0.56-1.15)	0.97 (0.67-1.42)
Q3	0.82 (0.60-1.13)	0.85 (0.59-1.21)	0.93 (0.66-1.32)	1.27 (0.85-1.89)
P value for trend‖	.228	.370	.715	.236

P values of .05 or smaller are considered significant and shown in boldface.
*No rhinitis symptoms at age 8 years.
†The reference group in analyses is composed of adolescents without sensitization and rhinitis symptoms at age 16 years.
‡Unadjusted model.
§Model adjusted for intakes of carbohydrates, monounsaturated fatty acids, vitamin D, and the other fatty acids used as exposures at age 8 years.
‖Test for trend with median value of each exposure category.

to decrease the production of inflammatory mediators and increase the level of anti-inflammatory mediators, whereas n-6 PUFAs promote formation of inflammatory mediators.[11] Therefore higher intake of n-6 and lower intake of n-3 PUFAs might lead to a higher risk of inflammation. We observed the strongest associations between oily fish, long-chain n-3 PUFAs, and NAR. NAR does not involve IgE mediation but is a nasal mucosal inflammation caused by nonimmunologic factors, and its specific mechanisms are not fully understood.[34] Allergic heredity and sensitization to inhalant allergens are strong determinants of AR, as observed in a previous report from our cohort, as well as other reports.[3,7,8] In the current study 51% of the adolescents with AR between ages 8 and 16 years were sensitized to inhalant allergens at age 8 years. Thus there might be less room for modifiable factors, such as diet, to influence the risk of AR to a great extent.

Another possible mechanism proposed to link oily fish and allergic disease is through vitamin D, which is known to have immunomodulatory properties.[12] However, we did not observe any associations between dietary vitamin D levels and AR or NAR, which might be because of the general low levels of intake in our subjects. Although the median intake in our study population was slightly higher compared with that of children of the same age in a Swedish national survey (5.1 vs 4.3 μg/d),[35] only 14% reached the Nordic recommendation of an average vitamin D intake of 7.5 μg/d.[36] In addition, dietary intake is only one part that affects vitamin D status, which is highly determined by sun exposure.[12] Therefore most studies on vitamin D levels and allergic disease in childhood have used blood levels of vitamin D, and unfortunately, serum levels were not available in our cohort.

The strengths of the present study include its prospective longitudinal design with repeated data on rhinitis symptoms, which made it possible to study the cumulative incidence of disease. We had the opportunity to distinguish between AR and NAR by including an objective measure of sensitization to inhalant allergens to the outcome definition. We were also able to distinguish between oily and lean fish and consider both vitamin D and types of PUFAs. Moreover, we could account for a large number of potential confounders, such as infant fish intake

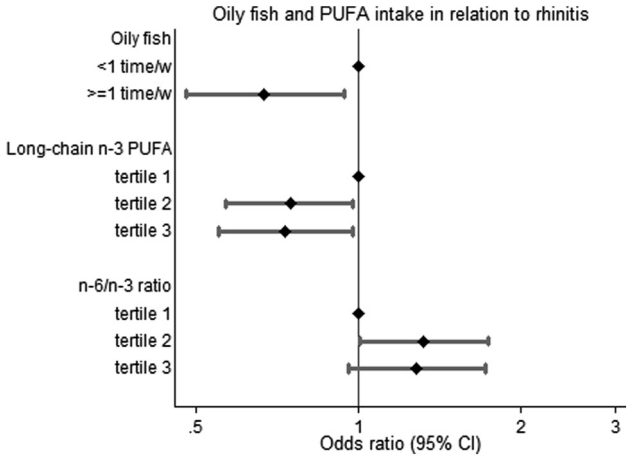

FIG 2. Intake of oily fish and PUFAs at age 8 years in relation to the cumulative incidence of rhinitis between ages 8 and 16 years. Cases of AR and NAR were analyzed together. Adjusted ORs and 95% CIs were obtained by using logistic regression.

and other aspects of childhood diet. Despite this, we cannot rule out that unmeasured factors have introduced residual confounding, such as maternal fish intake during pregnancy, which has been associated with a decreased risk of allergic disease during childhood, although primarily up to preschool age.[37,38]

Limitations include the possibility of selection bias because we include only 48% of the baseline cohort. However, in comparison with the baseline cohort, there are only minor differences in distribution of background factors for our included study population. Another possible limitation is misclassification of the NAR outcome; it is difficult to disentangle true NAR from long-lasting symptoms after an upper respiratory tract infection. However, the definition we use for NAR includes rhinitis symptoms according to the International Study of Asthma and Allergy in Children[18] or symptoms after exposure to pollen or furred animals. Another concern is that the adolescents classified as having NAR might be sensitized to an inhalant allergen that we have not measured, although sensitization was measured with Phadiatop, which includes the 8 most common inhalant allergens in our region. However, some of the adolescents with NAR symptoms might have local AR not captured with Phadiatop.[39] Despite these concerns, the 15% classified as having NAR in our study population correspond to the number suggested by Lieberman and Pattanaik.[40] In total, 36% were classified as having rhinitis (either AR or NAR), which is in line with other studies on adolescents.[41,42]

Misclassification of exposure is also possible. The FFQ is not a perfect tool for assessing food consumption and will probably not capture the absolute intake. Nevertheless, because we categorize intake instead of using the absolute value, this is a minor problem as long as the possible misclassification is nondifferential, which is probable because we study food consumption measured before disease development. In addition, fish consumption in the study population was in line with data from a Swedish national survey for the same age category (1.70 vs 1.75 times per week),[35] whereas PUFA levels were only slightly higher in the included study population compared with those in children of comparable age (8.3 vs 7 g/d).[35]

In conclusion, our study of 1970 subjects from the Swedish birth cohort BAMSE revealed that a regular intake of oily fish and dietary long-chain n-3 PUFAs in childhood might decrease the risk of cumulative incidence of rhinitis between the ages of 8 and 16 years, especially NAR, whereas an increased n-6/n-3 ratio seemed to increase the risk. Although the support from other epidemiologic studies for this association is limited, the association is biologically plausible. However, further studies are needed to disentangle the possible mechanisms behind these observations. Consuming oily fish at least once per week is consistent with the current dietary guidelines to consume varying types of fish at least twice a week. Thus our study provides additional support for these recommendations.

We would like to express our sincere gratitude to all the children and parents contributing to the BAMSE birth cohort. We also thank the BAMSE secretariat for their invaluable work with data collection and management.

Clinical implications: Regular oily fish consumption in childhood might decrease the risk of rhinitis up to age 16 years, possibly because of its content of long-chain n-3 PUFAs.

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TABLE E1. Distribution of selected exposure characteristics in the cohort (n = 4089) and study population (n = 1970)

	Total cohort		Study population*		
	No.	Percent	No.	Percent	95% CI†
Male sex	2065	50.5	970	49.2	47.7-50.8
Maternal smoking,‡ yes	563	13.8	233	11.8	10.8-12.9
Maternal age at birth ≤25 y	319	7.8	134	6.8	6.0-7.7
Breast-feeding ≥4 mo	3116	79.5	1578	81.4	80.2-82.6
Parental origin,§ outside of Scandinavia	707	20.8	407	20.8	19.6-22.0
Socioeconomic status, white collar worker	3323	82.7	1675	85.9	84.7-86.9
Allergic heredity,‖ yes	1200	29.7	625	32.0	30.5-33.5
Eczema at age 1 y, yes	594	15.1	312	16.0	15.0-17.3
Any wheeze at age 1 y, yes	577	14.7	280	14.5	13.4-15.6
Fish intake at age 1 y, ≥2 times/mo	3143	80.1	1560	80.5	79.2-81.7
Parental smoking,¶ yes	597	17.7	324	16.6	15.6-17.7
Obesity at age 8 y,# yes	116	4.4	75	3.8	3.4-4.3
Supplement use at age 8 y,** yes	1082	42.0	825	42.4	41.3-43.4
Sensitization to inhalant allergens at age 8 y,†† yes	637	26.0	493	26.3	25.3-27.2
	Mean	**SD**	**Mean**	**SD**	**95% CI**
Energy intake at age 8 y (kcal)	1905	468	1910	462	1900-1920

*Subjects fulfilling the inclusion criteria: baseline questionnaire data, data on nutrient and total fish intake at age 8 years and outcome data at age 16 years.
†CIs were created by applying finite population correction factor.
‡Mother smoked at least 1 cigarette per day at any point of time during pregnancy or the child's first months.
§Father and/or mother born outside of Scandinavia.
‖Doctor-diagnosed asthma and/or hay fever in combination with reported allergy to pollen or pets in 1 or both parents.
¶Any of the parents smoked at least 1 cigarette per day when the child was age 8 years.
#The child had an isoBMI of at least 30 kg/m^2 at age 8 years (age and sex specific cut-off values developed for children under 18 years of age).
**The child used supplements, such as multivitamins, sometimes or regularly at age 8 years.
††The child had at least 1 IgE value of 0.35 kU/L or greater against inhalant allergens at age 8 years.

TABLE E2. Distribution of disease in relation to fish intake and dietary PUFA and vitamin D at age 8 years

	Incident study population* (n = 1590)		
	No disease†	Incident AR‡	Incident NAR§
Total fish			
<2 Times/wk	482	208	149
≥2 Times/wk	288	129	87
Oily fish			
<1 Time/wk	651	295	213
≥1 Time/wk	119	42	23
Cod/pollock/pike			
<1 Time/wk	527	231	153
≥1 Time/wk	237	99	76
Fish fingers			
<1 Time/wk	486	198	145
≥1 Time/wk	277	136	88
Total PUFA			
Q1 (4.2-7.5)	250	114	82
Q2 (7.5-8.6)	254	108	78
Q3 (8.6-18.8)	266	115	76
ALA			
Q1 (0.6-1.0)	253	123	76
Q2 (1.0-1.2)	253	103	82
Q3 (1.2-3.0)	264	111	78
Long-chain n-3 PUFA			
Q1 (0.02-0.2)	233	110	103
Q2 (0.2-0.3)	270	107	76
Q3 (0.3-3.6)	267	120	57
n-6 PUFA			
Q1 (3.1-5.9)	251	115	80
Q2 (5.9-6.8)	253	111	79
Q3 (6.8-15.1)	266	111	77
LA			
Q1 (3.1-5.8)	251	114	80
Q2 (5.8-6.8)	253	111	79
Q3 (6.8-15.0)	266	112	77
AA			
Q1 (0.02-0.06)	246	109	91
Q2 (0.06-0.08)	278	112	70
Q3 (0.08-0.28)	246	116	75
n-6/n-3 ratio			
Q1 (1.5-4.3)	281	109	66
Q2 (4.3-4.8)	247	119	85
Q3 (4.8-10.9)	242	109	85
Vitamin D			
Q1 (1.5-4.5)	246	117	83
Q2 (4.5-6.0)	263	118	71
Q3 (6.0-24.1)	261	102	82

*No rhinitis symptoms at age 8 years.
†Adolescents without sensitization and rhinitis symptoms at age 16 years (reference group in association analyses).
‡Adolescents with sensitization and rhinitis symptoms at age 16 years.
§Adolescents with no sensitization but rhinitis symptoms at age 16 years.