

Original article

Fish consumption during the first year of life and development of allergic diseases during childhood

Background: Fish consumption during infancy has been regarded as a risk factor for allergic disease but later evidence suggests a protective role. However, methodological limitations in the studies make conclusions uncertain. The aim of this study was to assess the association between fish consumption during the first year of life and development of allergic diseases by age 4.

Methods: A prospective birth cohort of 4089 new-born infants was followed for 4 years using parental questionnaires at ages 2 months, 1, 2 and 4 years to collect information on exposure and health effects. The response rate at 4 years was 90%. A clinical investigation was performed at age 4 years, which included blood sampling for analysis of specific IgE to common food and airborne allergens.

Results: Parental allergic disease and onset of eczema or wheeze during the first year of life delayed introduction of fish in the child's diet. After exclusion of such children to avoid disease-related modification of exposure, regular fish consumption during the first year of life was associated with a reduced risk for allergic disease by age 4, OR_{adj} 0.76 (95% CI 0.61–0.94) and sensitization, OR_{adj} 0.76 (0.58–1.0). The reduced risk appeared most pronounced for multiple disease, OR_{adj} 0.56 (0.35–0.89). IgE-sensitization to fish was only present among 18 of the 2614 children.

Conclusion: Regular fish consumption before age 1 appears to be associated with a reduced risk of allergic disease and sensitization to food and inhalant allergens during the first 4 years of life.

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In recent decades consumption of omega-3 polyunsaturated fatty acid has decreased, whereas the consumption of vegetable oil-based products, rich in omega-6 polyunsaturated fatty acid, has increased (1, 2). Omega-3 fatty acids, prevalent in fish and especially in oily fishes, seem to have anti-inflammatory effects in contrast to omega-6 fatty acids which seem to promote inflammation (3, 4). Changes in the fatty acid content of the diet have been proposed to contribute to the increased prevalence of allergic diseases among children (5–8). For several autoimmune diseases such as rheumatoid arthritis, Crohn's disease and ulcerative colitis the omega-3 fatty acids appear to be beneficial in both prevention and treatment (2, 3).

Fish consumption has been associated with a decreased risk of childhood asthma and rhinitis in some studies but the evidence is not conclusive (9–12). In parallel, to reduce the risk for allergic diseases in children parents in many countries have been advised to postpone the introduction of fish for infants with heredity of allergy or early symptoms of allergic diseases (13). In Sweden, allergy-preventive advice regarding avoidance of egg and

fish during the first year of life has been given to families with allergic disease during 1979–2001 (14). If such recommendations are followed, a bias resulting from disease-related modification of exposure is likely to be introduced in aetiological epidemiological studies. However, such bias has not been controlled for in previous studies on this topic.

The aim of this study was to investigate the association between fish consumption during the first year of life and development of allergic diseases by age 4 in a prospective birth cohort (BAMSE) controlling for disease-related modification of exposure.

Materials and methods

Study design

A prospective birth cohort of 4089 new-born infants was established in Stockholm during 1994–1996, comprising 75% of all eligible children in a predefined area of Stockholm. The study has been described in detail elsewhere (15, 16). When the infants were new-born (median age 2 months) data on allergic heredity and various

exposures were obtained by parental questionnaires. Information on diet, including consumption and time for introduction of fish was collected at age 1. At 1, 2 and 4 years of age the parents answered questionnaires with the main focus on symptoms related to allergic diseases and key exposures. The response rates for the questionnaires were 96%, 94% and 90%, respectively. All children with questionnaire data at 4 years of age ($n = 3670$) were invited to a clinical investigation including blood sampling. A total of 2965 children agreed to participate, and blood samples were collected from 2614 children (64%). Permission for the study was obtained from the Ethics Committee of Karolinska Institutet, Stockholm.

Classification of exposure and outcomes

Fish consumption. The questionnaire at age 1 requested the child's age (in months) when fish was first introduced in the diet as well as current fish consumption. Fish consumption was specified in five predefined categories (never, once a month, two to three times a month, once a week and more than once a week).

Asthma. Asthma at age 4 years was defined as at least four episodes of wheezing during the last 12 months or at least one episode of wheezing during the same period, if the child was on inhaled steroids (17).

Eczema. Atopic eczema at age 4 years was defined as dry skin in combination with itchy rash for at least 2 weeks, with typical localization, during the last 12 months and/or doctors' diagnosis of eczema during the last 24 months (18).

Allergic rhinitis. Allergic rhinitis at age 4 years was defined as sneezing, running or blocked nose and/or red itchy eyes after exposure to pollen or pets and/or doctors diagnosis of allergic rhinitis during the last 24 months.

Multiple allergic diseases. At least two of the following diseases, asthma, eczema or allergic rhinitis at the age of 4 years.

Persistent allergic disease. Implies that the child fulfilled the outcome criteria both during the first 2 years of life and at 4 years of age.

Sensitization. The blood samples obtained at age 4 were analysed for IgE antibodies against inhalant (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *Cladosporium herbarium*) and food (milk, egg, fish, soy, peanut and wheat) allergens with Phadiatop® and Foodmix®. Furthermore, specific IgE to fish allergens was analysed with ImmunoCAP (Pharmacia CAP System™, Uppsala, Sweden). An IgE antibody level ≥ 0.35 kU_A/l was considered as positive (19).

Statistical methods

The association between fish consumption and the selected health outcomes was analysed with logistic regression and results are presented as adjusted odds ratios (ORs) with 95% confidence intervals (95% CI). Fish consumption was analysed both in its five original categories from the questionnaire and as a dichotomized variable (never or $\leq$ once a month and ≥ 2 –3 times a month). Age for introduction of fish in months was analysed as a dichotomized variable according to the mean age, 8.3 months. To identify potential confounders, several models were tested and finally adjustments were made for parental allergic disease (none, single, double), maternal

age (< 25 years, ≥ 25 years), maternal smoking (no/yes) and breast-feeding (< 4 months, ≥ 4 months) as these variables affected the odds ratio by 10% or more. Heredity was defined as doctor-diagnosed asthma and/or allergic rhinitis and/or eczema in any parent or both. Complete information on fish consumption and answered questionnaires at age 2 months, 1, 2 and 4 years were available for 3619 children (89%), who formed the basis for the analyses.

To avoid disease-related modification of exposure the data were analysed in three steps. Firstly, the effect of fish consumption was analysed in the whole cohort. Secondly, children with onset of eczema during the first year of life were excluded ($n = 545$). Thirdly, children with onset of eczema and/or recurrent wheeze during the first year of life were excluded ($n = 640$). To test for interaction Wald test was used and chi-square test for test of trend.

All statistical analyses were performed with STATA, Statistical Software: release 8.0 (College Station, TX, USA).

Results

Certain exposure characteristics in relation to age at introduction of dietary fish

The mean age for introduction of fish in the child's diet was 8.3 months. However, some groups of children revealed a higher age for introduction of fish in the diet, such as children with heredity for allergic diseases, and children with recurrent wheeze or symptoms of eczema during the first year of life (Table 1). In Table 1 selected exposure characteristics are presented in relation to fish consumption.

At age 1 year, 80% of the children consumed fish two to three times a month or more. Three hundred and forty-nine children (10%) had never had fish at this age, while 369 (10%) had fish once a month or less, 670 (19%) two to three times a month, 1282 (35%) once a week, and 949 (26%) more than once a week.

Association between dietary fish at 12 months of age and allergic diseases at age 4

Children who consumed fish during the first year of life had a reduced risk of allergic diseases at age 4 (Table 2). A dose-dependent reduced risk was observed for all outcomes (asthma, eczema, allergic rhinitis and sensitization) ($P < 0.001$). An inverse association was also observed in analyses based on age at introduction of fish. Children receiving fish between 3 and 8 months of age had a reduced risk for asthma (OR_{adj} 0.73, 95% CI 0.55–0.97), eczema (OR_{adj} 0.77, 0.64–0.92), allergic rhinitis (OR_{adj} 0.77, 0.60–0.97), and sensitization (OR_{adj} 0.78, 0.64–0.95) compared with children introduced to fish at 9 months or older.

Association between dietary fish at 12 months of age and allergic diseases at age 4, excluding infants with early development of disease

To avoid bias due to disease-related modification of exposure, children with eczema and/or recurrent wheeze

Table 1. Distribution of selected exposure characteristics at birth, breastfeeding, recurrent wheeze and eczema in relation to age of introduction and amount of fish in the child's diet at 12 months of age

	Age for introduction of fish (in months)		Fish regularly (two to three times a month or more)		
	Mean	95% CI	N*	n† (%)	95% CI
Sex					
Female	8.3	8.2–8.4	1789	1430 (80)	78.0–81.7
Male	8.3	8.2–8.4	1830	1471 (80)	78.4–82.1
Heredity‡					
None	7.9	7.8–8.0	1877	1574 (84)	82.1–85.5
Any	8.8	8.7–8.9	1374	1057 (77)	74.6–79.1
Double	9.1	8.8–9.4	346	251 (73)	67.5–77.2
Mother's age (years)					
<25	8.0	7.7–8.3	267	202 (76)	70.0–80.7
≥25	8.4	8.3–8.4	3351	2698 (81)	79.1–81.8
Socioeconomic status (SEI)					
Blue collar	7.9	7.7–8.1	588	466 (79)	75.7–82.5
White collar	8.3	8.3–8.5	1547	1254 (81)	79.0–83.0
Self employed	8.5	8.3–8.6	1436	1147 (80)	77.7–81.9
Maternal smoking during pregnancy or at 2 months					
No	8.4	8.3–8.5	3140	2518 (80)	78.7–81.6
Yes	7.8	7.6–8.0	478	382 (79)	76.0–83.4
Breastfeeding					
<4 months	7.6	7.4–7.8	730	590 (81)	77.8–83.6
≥4 months	8.5	8.4–8.6	2885	2308 (80)	78.5–81.4
Recurrent wheeze at age 1					
No	8.3	8.2–8.4	3483	2804 (81)	79.1–81.8
Yes	8.7	8.2–9.2	135	96 (71)	62.7–78.6
Eczema at age 1					
No	8.2	8.1–8.3	3072	2540 (83)	81.3–84.0
Yes	9.0	8.8–9.3	545	360 (67)	61.9–70.0

*Total number of children.

†Number of children with specific trait.

‡Doctor-diagnosed asthma and/or allergic rhinitis and/or eczema in any parent (any) or both (double).

during the first year of life were excluded. In analyses excluding children with symptoms of eczema during the first year of life (Table 3), a reduced risk was observed of eczema, allergic rhinitis, any allergic disease and sensitization for children with fish consumption ≥ 2 times per month compared with ≤ 1 time per month. Excluding also children with recurrent wheeze during the first year of life had little effect on the observed risk estimates, although it affected the confidence intervals, so that the results for eczema (OR_{adj} 0.78, 95% CI 0.60–1.00) and sensitization (OR_{adj} 0.76, 0.58–1.00) became borderline statistically significant.

The risk reduction associated with regular fish consumption at age 1 appeared particularly pronounced for more severe allergic disease measured as persistent allergic disease (persistent eczema, OR_{adj} 0.48, 0.32–0.68 and persistent rhinitis OR_{adj} 0.43, 0.23–0.79, respectively) and multiple allergic disease, i.e. two or three diseases (OR_{adj} 0.56, 0.35–0.89).

Table 4 shows the association between fish consumption and allergic diseases or sensitization in relation to

Table 2. Association between reported fish in the diet of the child at 12 months of age and allergic diseases at age 4

Fish consumption																			
Never*	Once a month						Two to three times a month						Once a week				≥Once a week		<i>P</i> _{trend}
	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>OR</i> _{adj} [†]	95% CI	<i>N</i>	<i>n</i>	<i>OR</i> _{adj} [†]	95% CI	<i>N</i>	<i>n</i>	<i>OR</i> _{adj} [†]	95% CI	<i>N</i>	<i>n</i>	<i>OR</i> _{adj} [†]	95% CI	
Asthma	348	35	364	34	0.94	0.57–1.56	666	51	0.82	0.54–1.29	1275	79	0.66	0.43–1.01	942	48	0.55	0.34–0.87	0.003
Eczema	349	105	367	85	0.72	0.51–1.00	668	150	0.71	0.53–0.95	1281	227	0.54	0.41–0.70	947	174	0.57	0.43–0.76	<0.001
Allergic rhinitis	344	70	362	42	0.52	0.34–0.79	662	72	0.51	0.35–0.73	1267	120	0.47	0.32–0.62	940	69	0.34	0.24–0.49	<0.001
Any allergic disease‡	349	158	369	123	0.61	0.45–0.84	670	209	0.58	0.45–0.76	1282	355	0.50	0.39–0.64	949	245	0.46	0.35–0.60	<0.001
Phadiatop	238	61	263	45	0.62	0.39–0.94	475	75	0.56	0.39–0.82	981	127	0.49	0.34–0.69	651	82	0.44	0.30–0.64	<0.001
Fx5	238	61	263	50	0.69	0.45–1.05	475	80	0.61	0.41–0.88	918	127	0.48	0.43–0.68	652	88	0.47	0.33–0.69	<0.001
Sensitization§	238	84	263	72	0.70	0.48–1.02	475	113	0.59	0.42–0.83	918	202	0.54	0.39–0.74	651	141	0.53	0.38–0.74	<0.001

*Reference category $OR = 1$.

†Adjusted for parental allergic disease, maternal age, maternal smoking and breastfeeding.

‡At least one of the following diseases at age 4, asthma, eczema or allergic rhinitis.

§Phadiatop or fx5 with IgE antibody levels ≥ 0.35 kU_A/l.

Table 3. Association between reported fish in the child's diet at 12 months of age and allergic diseases at 4 years of age among all children and after exclusion of children with eczema and asthma during the first year of life

	Fish consumption		Fish consumption			
	≤1 per month*		≥2–3 per month			
	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	OR _{adj} †	95% CI
All children						
Asthma at 4	712	69	2883	178	0.68	0.51–0.92
Eczema at 4	716	190	2896	551	0.69	0.57–0.84
Rhinitis at 4	706	112	2869	261	0.57	0.45–0.73
Any allergic disease‡	718	281	2901	809	0.65	0.54–0.77
Sensitization§	501	156	2044	456	0.66	0.53–0.82
Children with eczema during the first year of life excluded						
Asthma at 4	527	38	2528	133	0.76	0.52–1.11
Eczema at 4	531	98	2536	358	0.76	0.60–0.98
Rhinitis at 4	522	58	2512	172	0.63	0.46–0.86
Any allergic disease	535	161	2540	577	0.72	0.58–0.88
Sensitization	365	83	1787	336	0.80	0.61–1.05
Children with eczema and/or recurrent wheeze during the first year of life excluded						
Asthma at 4	506	24	2454	112	1.02	0.65–1.62
Eczema at 4	510	92	2462	345	0.78	0.60–1.00
Rhinitis at 4	501	56	2437	162	0.60	0.43–0.83
Any allergic disease	511	145	2465	546	0.76	0.61–0.94
Sensitization	348	82	1728	326	0.76	0.57–1.00

*Reference category OR = 1.

†Adjusted for parental allergic disease, maternal age, maternal smoking and breastfeeding.

‡At least one of the following diseases at age 4, asthma, eczema or allergic rhinitis.

§Phadiatop or fx5 with IgE antibody levels ≥0.35 kU_A/l.

parental allergic disease. There were no clear or consistent differences in risk estimates for allergic disease in children with or without heredity for allergic disease. However, a reduced risk of sensitization related to regular fish consumption was only seen in children without parental allergy (OR_{adj} 0.52, 0.35–0.76).

Using a stricter definition of allergic disease, i.e. IgE mediated or not (20), comparable associations between fish consumption and all investigated outcomes were observed regardless of sensitization, with the possible exception of any allergic disease and eczema, where a stronger protective effect was suggested in those with sensitization to common inhalant or food allergens, OR_{adj} 0.51, 0.31–0.84 and OR: 0.52, 0.30–0.91, respectively (Table 5). Risk estimates appeared similar for those with IgE antibodies to food allergens and inhalant allergens (data not shown).

At 4 years only 18 of 2614 children exhibited IgE antibodies to fish (0.7%). Children with IgE antibodies to fish had a higher mean age for introduction, 10 months compared with 8.4 months among children without specific IgE antibodies ($P = 0.01$). Children who were introduced to fish before 8 months of age had a reduced risk of specific IgE to fish (OR_{adj} 0.17, 0.04–0.64) compared with children who started with fish after this age. After exclusion of children with eczema and/or recurrent wheeze at 1 year the corresponding estimates were (OR_{adj} 0.27, 0.04–1.47). The results must be interpreted with caution due to small numbers of children sensitized to fish.

Table 4. Association between reported fish in the child's diet at 12 months of age and asthma, eczema, rhinitis and sensitization at age 4 among children with and without heredity for allergic disease (children fulfilling criteria for eczema and/or wheeze at age 1 excluded)

	No heredity				Heredity				<i>P</i> -interaction†
	<i>N</i>	<i>n</i>	OR _{adj} *	95% CI	<i>N</i>	<i>n</i>	OR _{adj} *	95% CI	
Asthma at 4 years									
≤ 1 per month	237	8	1.00‡		269	16	1.00‡	0.60–1.84	0.90
≥2–3 per month	1381	47	0.98	0.45–2.11	1073	65	1.04		
Eczema at 4 years									
≤ 1 per month	239	29	1.00‡		271	63	1.00‡	0.50–0.96	0.27
≥2–3 per month	1385	158	0.93	0.61–1.42	1077	187	0.69		
Rhinitis at 4 years									
≤ 1 per month	235	20	1.00‡		266	36	1.00‡	0.41–0.94	0.77
≥2–3 per month	1371	69	0.56	0.33–0.95	1066	93	0.62		
Any allergic disease at 4 years§									
≤ 1 per month	239	49	1.00‡		272	96	1.00‡	0.53–0.94	0.45
≥2–3 per month	1387	248	0.84	0.60–1.18	1078	298	0.70		
Sensitization at 4 years¶									
≤ 1 per month	167	47	1.00‡		181	35	1.00‡	0.76–1.72	<0.01
≥2–3 per month	952	161	0.52	0.35–0.76	776	165	1.14		

*Adjusted for maternal age, maternal smoking and breastfeeding.

†Wald test, $P < 0.05$.

‡Reference group OR = 1.

§At least one of the following diseases at age 4, asthma, eczema or allergic rhinitis.

¶Phadiatop or fx5 with IgE antibody levels ≥0.35 kU_A/l.

Table 5. Association between reported fish in the child's diet at 12 months of age and asthma, eczema, rhinitis at age 4 among children with and without sensitization (children fulfilling criteria for eczema and/or wheeze at age 1 excluded)

Fish consumption	No sensitization				Sensitization*				P-interaction
	N	n	OR _{adj} †	95% CI	N	n	OR _{adj} †	95% CI	
Asthma at 4 years									
≤ 1 per month	266	14	1.00‡		82	6	1.00	0.46–2.96	0.46
≥2–3 per month	1398	54	0.77	0.45–2.11	324	27	1.17		
Eczema at 4 years									
≤ 1 per month	266	42	1.00		81	24	1.00	0.30–0.91	0.14
≥2–3 per month	1399	187	0.86	0.59–1.24	326	60	0.52		
Rhinitis at 4 years									
≤ 1 per month	259	22	1.00	7	82	19	1.00	0.30–1.01	0.90
≥2–3 per month	1386	67	0.58	0.35–0.96	322	46	0.55		
Any allergic disease at 4 years§									
<1 per month	511	145	1.00		266	65	1.00	0.31–0.84	0.09
≥2–3 per month	2465	546	0.84	0.62–1.15	1402	286	0.51		

*Phadiatop or fx5 with IgE antibody levels ≥0.35 kU_A/l.

†Adjusted for maternal age, maternal smoking, heredity for allergic disease and breastfeeding.

‡Reference group OR = 1.

§At least one of the following diseases at age 4, asthma, eczema or allergic rhinitis.

Discussion

In this prospective cohort study, we observed a reduced risk of asthma, eczema, allergic rhinitis and sensitization at age 4 years among children who consumed fish at least twice a month during the first year of life. After exclusion of children with early symptoms of eczema and/or recurrent wheeze, to control for disease-related modification of exposure, a reduced risk was indicated primarily for eczema, allergic rhinitis and sensitization. The risk reduction seemed to be most pronounced for allergic rhinitis. The lower risk for sensitization was only seen in children without heredity for allergic disease.

The strengths of our study include the large sample size and the population-based design, reasonable numbers of exposed children, and fairly detailed data for fish consumption. We have also been able to assess a large number of potential confounders. After testing several models only parental allergic disease, maternal age, maternal smoking during pregnancy or at enrolment and breastfeeding were identified as confounders. Despite this, we cannot entirely rule out that other, unmeasured dietary factors such as use of cooking oil and intake of trans fatty acids may affect our findings. Furthermore, children with early symptoms of allergic disease or parental allergy had a later introduction of fish in the diet and consumed less fish at 12 months of age. This clearly shows that disease-related modification of exposure and parental allergy need to be controlled in epidemiological studies on fish consumption and allergic disease. However, excluding children with very early symptoms of eczema or recurrent wheeze may be a limitation with regard to generalization of data. The fact that some of our associations, such as the reduced risk of sensitization, in children with regular fish consumption

were seen in children without heredity for allergic disease speaks against a residual confounding effect by parental allergy.

One weakness of our study is the absence of data about maternal diet during pregnancy and lactation as fatty acids may be stored for a long time in the human body. But it is probable that the diet of the child reflects the diet in the family and thus regular fish consumption at age 1 may serve as a proxy for the maternal dietary habits during pregnancy and lactation. It would also have strengthened the study if the exposure assessment had been more precise regarding both amount and type of ingested fish, but such information was not available.

Although, the potential association between early fish consumption and allergy has been addressed in several studies, data are not conclusive (8–11). In a Norwegian birth cohort, Nafstad et al. reported a reduced risk of asthma and allergic rhinitis among children who consumed fish during the first year of life (11). However, they did not account for disease-related modification of exposure. The association between omega-3 fatty levels and allergic disease, measured as asthma and atopy, has not been confirmed in some cross-sectional studies among teenagers and adults (21, 22).

In recent years several intervention studies with fish oil supplementation during pregnancy have been published, suggesting an immunomodulating effect (23–25). This is supported in our study where a protective effect of fish consumption on sensitization was indicated.

It is possible that dietary polyunsaturated fatty acids might influence the development of allergic sensitization by increasing the formation of prostaglandin E₂, which in turn promotes a Th2 response and stimulates the formation of IgE (1). There is only limited evidence regarding supplementation with fish oil during childhood. In a

recent publication of the 3-year follow up of the Australian Childhood Prevention Study, there was a 10% significant reduction in the prevalence of atopic cough associated with such supplementation, but with no effect on other manifestations of allergic disease (26). Intervention with supplementation of omega-3 has not been shown to reduce the severity of concurrent allergic disease in several studies (27, 28). However, in a study from Cardiff, UK supplementation of fish oil markedly reduced the severity of exercise-induced bronchoconstriction in elite athletes (29).

IgE sensitization to fish was rare at age 4 years. Only 18 of 2614 tested children had specific IgE antibodies to fish, indicating that fish is probably not an important allergen in the population. This is supported by results of others. In a population-based cohort of children followed up to 7 years of age, only one of 2061 children had a positive skin prick test to cod (30). A low prevalence of sensitization to fish has also been reported from Germany, where less than 1% of children up to 17 years of age had a positive skin prick test to herring (31).

The discrepancy between the marked effects on fish consumption and onset of allergic disease in epidemiological studies compared with the generally limited effects seen in intervention studies may have several explanations. Firstly, the role of polyunsaturated fatty acids in the pathogenesis of allergic disease remains unclear, e.g. absolute and relative quantities of different polyunsaturated

and saturated fatty acids may be important. Secondly, it is possible that regular fish consumption is a parallel phenomenon to other exposures and lifestyle factors that may protect from onset of allergic disease. Fish consumption in early life might be a proxy for a lifestyle that reduces the risk of allergic disease. Thirdly, to our knowledge no other previous epidemiological studies have controlled for disease-related modification of exposure. In many populations, parental allergy and early symptoms of allergy are likely to alter both the time for introduction of fish and regular consumption, such as in our cohort.

In conclusion our results indicate that early and regular fish consumption at 1 year of age is associated with a reduced risk of allergic disease (primarily allergic rhinitis and eczema), and sensitization to food and airborne allergens at 4 years of age in children. A risk reduction was also seen for severity of allergic disease such as persistent disease or multiple allergic disease at the age of 4. Sensitization to fish is rare, even among those with early introduction to fish.

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