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ORIGINAL ARTICLE

**Asthma and Allergic Rhinitis at 4 Years of Age in
Relation to Fish Consumption in Infancy**

**Per Nafstad, M.D., Ph.D., M.P.H.,^{1,2,*} Wenche Nystad, Ph.D.,¹
Per Magnus, M.D., Ph.D.,¹ and Jouni J. K. Jaakkola, M.D., Ph.D.^{1,3}**

¹Division Epidemiology, Norwegian Institute of Public Health, Oslo, Norway

²Buskerud College, Drammen, Norway

³Environmental Health Program, The Nordic School of Public Health,
Göteborg, Sweden

ABSTRACT

It has been suggested that consumption of fish and polyunsaturated fatty acids could have a protective effect against inflammation in the airways and the development of asthma and other allergic diseases. Our objective was to test the hypothesis that fish consumption during the first year of life decreases the risk of childhood asthma and allergic rhinitis. We assessed the relation between introduction of fish in the diet during the first year of life and risk of asthma and allergic rhinitis in a prospective 4-year cohort study of 2531 Norwegian children. We estimated odds ratios (OR) in logistic regression analysis adjusting for potential confounders. A total of 47.6% children had fish during the first year of life. The adjusted OR for allergic rhinitis was 0.45 (95% confidence interval [CI]=0.28, 0.74) and for asthma 0.84 (95% CI=0.57, 1.22). Fish consumption in the first year of life may reduce the risk of developing asthma and allergic rhinitis in childhood.

Key Words: Asthma; Allergic rhinitis; Fish consumption; Children; Epidemiology.

Asthma and other atopy-related diseases are common among children (1,2) but their causes are still insufficiently understood (2–7). These diseases often start during childhood, and therefore there has

been special interest in their relations to early life events and exposures (2–7). Diet could be of importance for the development of these diseases (8–11). Some studies have suggested that consumption of

*Correspondence: Per Nafstad, Division of Epidemiology, Norwegian Institute of Public Health, P.O. Box 4404 Nydalen, 0403 Oslo, Norway; Fax: 47 23 40 82 52; E-mail: per.nafstad@fhi.no.

fish and polyunsaturated fatty acids could have a protective effect against inflammation in the airways and the development of asthma and other allergic diseases (8–18). We tested the hypothesis that introduction of fish in the diet in the first year of life is related to a lower risk of asthma and allergic rhinitis in children in a prospective 4-year cohort study of Norwegian children.

MATERIAL AND METHODS

Study Population

We analyzed the children from the Oslo Birth Cohort Study, which was initiated in 1992–1993 by recruitment of 3754 newborns. The cohort and results from 1, 2, and 4 years of follow-up has been presented elsewhere (19–22). Information on children's health and environmental exposures were collected by parentally administered questionnaires at birth and when the children were ½, 1, 1½, 2, and 4 years old. The current analysis was based on the 2531 children with complete information on respiratory health at the age of 2 and 4 years. The Norwegian Data Inspectorate had approved the study.

Health Outcomes

The main outcomes of interest were current asthma and allergic rhinitis at the age of 4 years. Current asthma and allergic rhinitis (nose- or eye-related allergy, including hay fever) were defined on the basis of answers to the 4-year follow-up questionnaire. Both outcomes had to be diagnosed by a physician, and current disease meant that the child had to have experienced symptoms of the disease during the previous 12 months. Two secondary outcomes included current atopic dermatitis and gastroenteritis. Current atopic dermatitis was defined analogously with the respiratory outcomes, whereas gastroenteritis was defined as having diarrhea or nausea during the last 4 weeks before the questionnaire was filled in.

Exposure Assessment

The exposure of interest was early introduction to fish in the diet (i.e., during the first 12 months of

life). Exposure information was from the 12-month questionnaire, in which the parents were asked to report at which age (in months) the child was given different kinds of food. No quantitative information was collected on the amount of fish consumption.

Covariates

We obtained information on potential confounders, including other dietary factors from the questionnaires and hospital records. Factors that had been found to be determinants of the outcomes in previous literature and analyses of the present data were considered in the current analyses, together with indicators of socioeconomic status. We considered the following covariates: parental atopy (parental asthma or hay fever), the experience of atopic eczema 0–6 months of age, gender, maternal age at delivery, birth order, uterus-related pregnancy complications, keeping pets at home when the child was born, an episode of lower respiratory tract infections during first year of life, maternal education, family income per year, maternal smoking at the end of pregnancy, and length of breastfeeding. Description and categorization of these variables is presented elsewhere (19–22).

Statistical Methods

We used odds ratio (OR) as the measure of association applying logistic regression analysis to adjust for potential confounding. We elaborated the relations of interest by including different combinations of covariates in the models, as well as in stratified analysis according to parental atopy, length of breastfeeding, early atopic eczema during first 6 months of life, and experience of lower respiratory tract infections. Because of missing values for some of the variables, we explored models with categories for missing values to maintain all cases in the analysis and models without missing values for one or more conditions. The analyses were conducted using the computer program SPSS version 9.0 (23).

RESULTS

We have described the cohort in different stages of the follow-up in recent publications (20–22).

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Briefly, children in the study population at the age of 4 years ($n=2531$) had somewhat older and more educated mothers, and came from families with higher income than children from the original cohort. Otherwise the study population was comparable with the children of the baseline study population for most of the conditions.

Only 0.7% of the children ($n=15$) ate fish during the first 6 months. The corresponding figure was 12.7% ($n=288$) at 9 months of age, and reached 47.6% ($n=1080$) at the age of 12 months (260 with missing information). None of the 15 children who ate fish during the first 6 months of life had symptomatic asthma or allergic rhinitis at age 4 years. Of the children breastfed 0–6 months, 55% had eaten fish during the first year of life compared with 45% of children breastfed for more than 6 months. Among children of atopic and nonatopic parents, the corresponding percentages were 39 and 52%, among children with and without atopic eczema 0–6 months of life 38 and 49%, and among children having an episode of lower respiratory tract infection during first year of life or not 38 and 49%.

The risk of allergic rhinitis was substantially lower in children who had fish during the first year of life (0.025) compared with children who had fish later in life (0.060), with an OR of 0.40 (95% Confidence Interval [CI]=0.25, 0.63) (Table 1). Adjustment for potential confounding did not have any substantial influence (0.45; 0.28, 0.74). The OR in a corresponding model without a separate category for missing information for each variables was 0.44 (95% CI=0.26, 0.75, missing information for 449 children in one or more variables). The associations between the early introduction to fish and the risk of asthma at the age of 4 years were weaker and

statistically significant only in bivariate analysis (see Table 1). The risk of allergic rhinitis among children with missing information on fish intake was 0.065 (OR 1.09, 95% CI=0.63, 1.88) and of asthma 0.088 (OR 1.22, 95% CI=0.75, 1.97). The reference category was no introduction to fish first year of life.

Early introduction to fish in the diet showed a consistent negative association with the risk of allergic rhinitis in different levels of potential modifiers, such as length of breastfeeding, parental atopy, early life atopic eczema, and experience of lower respiratory tract infections (Table 2). Among children breastfed for more than 6 months, introduction to fish in the diet in the first year of life was more strongly associated to the risk of allergic rhinitis than among children with a shorter duration of breastfeeding.

The relation between fish diet and asthma was negative in children of nonatopic parents (OR 0.50; 95% CI=0.30, 0.83), whereas no such relation was present in children of atopic parents (1.00; 0.61, 1.63), as shown in Table 2. Also, the protective effect on asthma was stronger in children who experienced atopic eczema in early life (0.47; 0.23, 0.97) compared with children without early life atopic eczema (0.91; 0.58, 1.42), as well as in children who were breastfed for more than 6 months (0.56; 0.36, 0.87) compared with those breastfed less (0.76; 0.41, 1.39).

The risks of having doctor-diagnosed atopic eczema with symptoms the last year at the age of 4 years was 0.108 among children with early and 0.155 among children with late introduction to fish ($p=0.001$), relative risks: OR 0.66 (0.52, 0.84). Corresponding figures for gastroenteritis during the last 4 weeks were 0.165 and 0.178 ($p=0.43$), relative risks: OR 0.91 (0.73, 1.13).

Table 1. The risk of asthma and allergic rhinitis at the age of 4 years and the crude (c) and adjusted (a) odds ratios (OR) for asthma and allergic rhinitis at the age of 4 years according to introduction of fish ($n=1080$) or not ($n=1191$) during first year of life (reference category: no symptoms). Data from the Oslo birth cohort study.

Introduction of fish during the first year of life		Risk	cOR (95% CI)	aOR (95% CI) ^a
Asthma	No	0.074	1	1
	Yes	0.049	0.65 (0.46–0.92)	0.84 (0.57–1.22)
Allergic rhinitis	No	0.060	1	1
	Yes	0.025	0.40 (0.25–0.63)	0.45 (0.28–0.74)

Adjusted odds ratios were adjusted for parental atopy, atopic eczema 0–6 months of age, gender, parity, birth weight, maternal age at delivery, birth order, uterus-related pregnancy complications, keeping pets at home when the child was born, an episode of lower respiratory tract infections during first year of life, maternal education, family income per year, maternal smoking at the end of pregnancy, and length of breastfeeding.

^aAdjusted odds ratios were estimated with variables including a separate category for missing information.

Table 2. The absolute and relative risk (odds ratio [OR]) (reference category: no symptoms) of asthma and allergic rhinitis at the age of 4 years by introduction of fish during the first year of life in different strata of length of breastfeeding, parental atopy, early life atopic eczema, and lower respiratory tract infections during first year of life.

Introduction of fish during the first year of life		Asthma risk	OR	Allergic rhinitis risk	OR
Length of breastfeeding					
0–6 mo	No	0.080		0.066	
	Yes	0.062	0.76 (0.41–1.39)	0.042	0.62 (0.31–1.25)
>6 mo	No	0.073		0.058	
	Yes	0.042	0.56 (0.36–0.87)	0.017	0.28 (0.15–0.52)
Parental hay fever or asthma					
No	No	0.061		0.044	
	Yes	0.031	0.50 (0.30–0.83)	0.021	0.47 (0.25–0.86)
Yes	No	0.094		0.085	
	Yes	0.093	1.00 (0.61–1.63)	0.035	0.39 (0.20–0.78)
Early life atopic eczema					
No	No	0.047		0.032	
	Yes	0.043	0.91 (0.58–1.42)	0.018	0.56 (0.30–1.04)
Yes	No	0.167		0.190	
	Yes	0.087	0.47 (0.23–0.97)	0.071	0.32 (0.15–0.69)
An episode of lower respiratory tract infection during the first year of life					
No	No	0.053		0.055	
	Yes	0.036	0.67 (0.43–1.05)	0.022	0.39 (0.24–0.66)
Yes	No	0.162		0.083	
	Yes	0.133	0.80 (0.44–1.45)	0.042	0.48 (0.19–1.24)

DISCUSSION

Consistent with the hypothesis, we found that early introduction of fish in the diet was negatively associated with the risk of allergic rhinitis. The corresponding association with the risk of asthma was weaker.

Prospective collection of dietary information before the development of the studied outcomes reduced the possibility of information bias. The two main outcome variables were based on parental responses to questions concerning their child's health. The validity of these outcomes depends on both the accuracy of the diagnostic practice in the study area and parents' responses to the questionnaire. Two types of errors could have occurred: random and systematic errors. There is no reason to believe that any systematic error took place (i.e., that the diagnoses were influenced by introduction

of fish diet). Some random error in the outcome assessment is likely. We required a doctor's diagnosis and we believe that most parents do remember diagnosed diseases among their children. However, the diagnosis of asthma and allergic diseases in this age group includes uncertainties, because objective methods, such as PEF follow-up or spirometry, are not commonly used and the weight of the diagnosis is based on anamnesis. This type of random error would underestimate the protective effect (bias towards the "no effect"), rather than produce a spurious effect. This article focused on respiratory disorders. However, atopic dermatitis, a nonrespiratory atopy-related disorder, showed an association similar to that of the respiratory disorders, whereas gastroenteritis did not. The latter finding provides reassurance that eating fish did not result in general differences in disease reporting related to early introduction of fish diet. None of the children introduced to fish during

the first 6 months of life had asthma or allergic rhinitis at the age of 4 years. However, because of small numbers, this finding provides only weak evidence of the protective or nonprotective direction of the effect.

We were able to adjust for most of the known determinants of these diseases, which reduced the possibility of confounding as an alternative explanation for the observed relations. Early introduction to fish could also indicate that the relevant exposure was consumption of fish during the first 4 years or maternal exposure during pregnancy. Adjusting for one or several other foods, such as cow's milk, yogurt, orange juice, and eggs, did not substantially affect the association between introduction to fish and allergic rhinitis (data not given). However, we cannot totally exclude the possibility of confounding by other dietary habits or lifestyle factors. Conditions such as the experience of early life eczema, parental atopy, duration of breastfeeding, and early life lower respiratory tract infections are both determinants of the studied outcomes and potential modifiers of the relations. We also considered that they could be related to dietary habits. To elaborate these complex relations, we conducted stratified analyses according to these factors. The negative association between introduction to fish was surprisingly consistent in all strata, which reduces the probability that systematic differences in reporting of asthma and allergic rhinitis because of these conditions could explain the negative association.

The present results provide evidence of protective effects of fish consumption on the risk of allergic rhinitis and asthma. The effect estimate was strongest for allergic rhinitis. An explanation for a weaker protective effect on asthma than on allergic rhinitis is that asthma during the first 4 years is probably a heterogeneous condition as to both manifestations and aetiology. The protective effects were consistent in different levels of other determinants of atopic diseases. Two cross-sectional studies of Australian children reported a protective effect of fish consumption. In a study of 4366 school children in Sydney, eating fish more than once per week had a protective effect on bronchial hyperreactiveness (15). In another study of 468 children who had previously reported wheezing, eating of fresh, oily fish was related to a lower risk of current asthma, with an odds ratio of 0.26 (95% CI 0.09–0.72) (13). One could speculate that ingestion of fish leads to a shift in the n-3/n-6 fatty acids balance, which could result in reduced production of inflammatory mediators of importance for the disease development (8,24). However, the

evidence for a biological explanation of these effects is still weak.

In spite of longitudinal design and extensive adjustment for potential confounding, we think that the complexity of measuring dietary habits warrants careful conclusions. Our results suggest that early intake of fish protects against airway diseases in early life. However, it is also possible that fish consumption only reflect other dietary factors or lifestyle factors, making it difficult to separate effects. We think that additional epidemiologic studies with more precise methods of both outcome and exposure assessment together with basic research on mechanism are needed.

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