

Original article

Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood

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Background: Early vitamin supplementation is given routinely to infants in many countries, but it is unclear whether this affects the risk of allergic diseases.

Objectives: We sought to study the association between early-life supplementation of vitamins A and D in water-soluble form or in peanut oil and allergic diseases up to 4 years of age.

Methods: A prospective birth cohort of 4089 newborn infants was followed for 4 years using parental questionnaires repeatedly to collect information on exposure and health. At 4 years, the response rate was 90%, and allergen-specific IgE levels to food and airborne allergens were measured in 2614 of the participating children.

Results: Vitamins A and D were given to 98% of the children in infancy, and vitamins based in peanut oil dominated (90%). Children supplemented with vitamins A and D in water-soluble form during the first year of life had an almost 2-fold increased risk of asthma (adjusted odds ratio [OD], 2.18; 95% CI, 1.45-3.28), food hypersensitivity (adjusted OR, 1.89; 95% CI, 1.33-2.65), and sensitization to common food and airborne allergens (adjusted OR, 1.88; 95% CI, 1.34-2.64) at age 4 years compared with those receiving vitamins in peanut oil. No increased risk of IgE antibodies to peanut was seen in children receiving vitamins in peanut oil.

Conclusion: Supplementation of vitamins A and D in water-soluble form seems to increase the risk of allergic disease up to the age of 4 years compared with supplementation with the same vitamins given in peanut oil.

Clinical implications: Vitamins A and D in oil does not seem to increase the risk of allergic disease during childhood. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Allergic disease, asthma, BAMSE, childhood, fatty acids, prevention, sensitization, vitamin D

Dietary intake has been suggested to exert protective, as well as unfavorable, effects on asthma and allergic diseases. In recent years there has been a focus on the role of vitamins, antioxidants, fruits, and vegetables, as well as fatty acids.¹⁻⁴ For example, early multivitamin supplementation has been reported to increase the risk of asthma and food allergy.⁵ High serum levels of vitamin A have been associated with an increased risk of IgE sensitization, and dietary vitamin D supplementation early in life has been associated with atopy and allergic rhinitis in adulthood.^{6,7} A possible explanation for these findings is that such vitamins might skew the immune system toward a T_H2 response.⁸ Accordingly, vitamin D supplementation during infancy has been associated with a reduced risk of type 1 diabetes.⁹

Recommendations about supplementation with vitamins during early childhood are given in many western countries.¹⁰ In Sweden all infants are recommended a dose of 1000 IE of vitamin A and 400 IE of vitamin D daily from 2 weeks of age up to 5 years of age to prevent vitamin A and D deficiency.¹¹ The vitamins are free of charge during the first 2 years of life and distributed by the Child Health Care units. After the first year of life, the vitamins are recommended to be given during wintertime only. The vitamins can either be water soluble or oil based. At the time of the study, the oil used was refined peanut oil. In general, the oil-based vitamins were recommended because such preparations do not need to be kept cold.

Peanut oil contains omega-6 fatty acids but also a small amount of omega-3 fatty acids.^{12,13} A diet rich in omega-3 fatty acids has been suggested to reduce the risk of several autoimmune diseases, and protective effects have been reported also for allergic diseases.^{14,15} The use of peanut oil in medications and formulas has been associated with an increased risk of sensitization to peanut in some studies, but data are inconclusive.¹⁶⁻¹⁸

The primary aim of the present study was to investigate the association between early supplementation of vitamins

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Abbreviations used

BAMSE: Children, Allergy, Milieu, Stockholm,
Epidemiological survey
OR: Odds ratio

A and D in water-soluble form or based in peanut oil and development of allergic disease up to the age of 4 years.

METHODS

Study design

All newborns in a predefined area of Stockholm, Sweden, were invited to participate in a prospective study (the Children, Allergy, Milieu, Stockholm, Epidemiological survey [BAMSE]) from February 1994 until November 1996. In total, 4089 newborn infants were included, which comprised 75% of all infants born in this area. The study design has been described in detail elsewhere.^{19,20} Data on parental allergy and various exposures were obtained by using parental questionnaires when the infants were newborns (median age, 2 months). At 1, 2, and 4 years of age, the parents answered questionnaires with a focus on symptoms related to allergic diseases in their children, as well as on key exposures and possible confounding factors. Data about breast-feeding, diet, and vitamin supplementation were collected from the 1-year questionnaire. The response rates for the questionnaires were 96%, 94%, and 91%, respectively. The information on supplementation with vitamins A and D was provided in 4 predefined categories (vitamins based in peanut oil, vitamins in water-soluble form, vitamins as a combination of the 2 preparations, and no vitamins).

All children with answered questionnaires ($n = 3670$) at age 4 years 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. Permission for the study was obtained from the Ethics Committee of Karolinska Institutet, Stockholm.

Definition of health outcomes

During the first 2 years of life, *asthma* was defined as at least 3 episodes of wheezing in addition to respiratory symptoms treated with inhaled steroids or signs of bronchial hyperreactivity, such as coughing and wheezing during play or physical strain, without ongoing upper respiratory tract infection. At 4 years of age, asthma was defined as at least 4 episodes of wheezing during the last 12 months or at least 1 episode of wheezing during the same period if the child was taking inhaled steroids.²⁰

Eczema was defined as dry skin in combination with itchy rash for at least 2 weeks with typical localization during the last 12 months, a physician's diagnosis of eczema during the last 24 months, or both.²¹

Allergic rhinitis was defined as sneezing, runny or blocked nose, and/or red itchy eyes after exposure to pollen or pets; a physician's diagnosis of allergic rhinitis during the last 24 months; or both.

Hypersensitivity to food was defined as specific symptoms (ie, atopic dermatitis, urticaria, edema of the lips/eyes, pruritus around the eyes or runny nose, and asthma) after ingestion of common types of food during the last 24 months.

The terms *transient*, *late-onset*, and *persistent disease* were used to assess onset and duration of disease (asthma, eczema, allergic rhinitis, and food hypersensitivity). *Transient disease* denotes children fulfilling the outcome criteria during the first 2 years of life but not later. *Persistent disease* implies that the child fulfilled the outcome criteria both during the first 2 years of life and at 4 years of age.

Late-onset disease denotes that the child only fulfilled disease criteria at age 4 years.

The term *multiple diseases* was defined as at least 2 of the following 3 diseases at the age of 4 years: asthma, eczema, or allergic rhinitis.

For *sensitization*, IgE antibodies against a mixture of common inhalant allergens (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium* species) and common food allergens (cow's milk, hen's egg, cod fish, soy bean, peanut, and wheat) were analyzed with Phadiatop and fx5, respectively. Single allergens were analyzed if Phadiatop or fx5 test results were positive (≥ 0.35 kU_A/L; Pharmacia CAP System, Phadia AB, Uppsala, Sweden). Data of the 7 most common single allergens (milk, egg white, peanut, birch, timothy, cat, and horse) are presented here.²²

Statistical methods

Difference in the distribution of selected characteristics among the 4 groups (vitamins in peanut oil, vitamins in water-soluble form, both preparations, and no vitamins A and D) was tested with the χ^2 test. The association between vitamin A and D supplementation and the selected health outcomes was analyzed with logistic regression. The results are presented as adjusted odds ratios (ORs) with 95% CIs. Several models were tested to identify potential confounders, and finally, the logistic regression model was adjusted for parental allergic disease (defined as physician-diagnosed asthma, hay fever, or both in combination with allergy to furred pets or pollen in 1 or both parents), maternal age (<25 years, ≥ 25 years), maternal smoking (yes, no), breast-feeding (<4 months, ≥ 4 months), and fish consumption ($\leq$ once a month, ≥ 2 –3 times a month) because these covariates were associated with both exposure and health outcomes. Other models were also evaluated, such as a broader definition of heredity, also including eczema among the parents and any allergic disease (asthma, eczema, allergic rhinitis, or allergy to pollen or pets) among older siblings, as well as gestational age, damp housing, and socioeconomic status, but these covariates had a small effect on the risk estimates ($<3\%$).

The Wald test was used to assess interaction between covariates (departure from a multiplicative model). All statistical analyses were performed with STATA Statistical Software (release 8.0; StataCorp, College Station, Tex). Complete information on vitamin A and D consumption at age 1 year and answers on all 4 questionnaires were required for inclusion in the analyses. In total, 3618 (88.5%) children fulfilled these criteria.

RESULTS

Most children (98%) had been given vitamins A and D during the first year of life, and vitamins based in peanut oil dominated (90%). Two hundred thirty-seven (7%) children had received vitamins in water-soluble form, and 73 (2%) had used both alternatives. Only 59 ($<2\%$) children were not given vitamins A and D during the first year of life. The distribution of selected exposure characteristics in relation to supplementation with vitamins A and D is shown in Table I. Some differences were seen among the 4 exposure groups in relation to heredity for allergic disease, maternal smoking, breast-feeding, and fish consumption. Children receiving vitamins A and D in water-soluble form were more exposed to maternal smoking (19% vs 13%, $P = .01$), breast-fed less than 4 months (27% vs 20%, $P = .004$), and had less regular consumption of fish at the age of 1 year (31% vs 19%, $P < .001$).

TABLE I. Distribution of selected exposure characteristics at 2 months and 1 year of age in relation to intake of vitamins A and D in peanut oil, water-soluble form, or both

	Peanut oil (N = 3249; n [%])	Water-soluble form (N = 237; n [%])	Both water and oil (N = 73; n [%])	No AD (N = 59; n [%])
Sex (female)	1617 (50)	110 (46)	34 (47)	27 (46)
Parental allergy*	947 (29)	80 (34)	32 (44)	18 (31)
Maternal smoking†	412 (13)	44 (19)	15 (21)	7 (12)
Socioeconomic status				
Blue collar	513 (16)	48 (20)	10 (14)	16 (27)
White collar	1390 (43)	103 (44)	28 (38)	26 (45)
Self-employed	1301 (40)	84 (35)	35 (48)	16 (28)
Damp housing‡	261 (9)	26 (11)	2 (3)	3 (5)
Gestational age <40 wk	1064 (33)	80 (34)	30 (41)	17 (29)
Maternal age (≤25 y)	240 (7)	14 (6)	6 (8)	6 (10)
Breast-feeding <4 mo	635 (20)	65 (27)	15 (21)	14 (24)
Fish consumption ≤1/mo	611 (19)	74 (31)	17 (23)	15 (25)

*Physician's diagnosis of asthma, hay fever, or both in any parent combined with allergy to furred pet or pollen.

†Maternal smoking during pregnancy or at enrollment.

‡Damage by damp, mold odor, and/or visible mold last year.

TABLE II. Association between consumption of vitamins A and D in water-soluble form compared with in peanut oil up to age 1 years and allergic diseases at 4 years of age

	Vitamins A and D in oil		Vitamins A and D in water-soluble form			
	N	n (%)	N	n (%)	OR _{adj} †	95% CI
Any allergic disease	3249	946 (29)	237	87 (37)	1.28	0.97-1.70
Asthma	3227	203 (6)	236	33 (14)	2.18	1.45-3.28
Eczema	3243	645 (20)	236	56 (24)	1.14	0.82-1.53
Allergic rhinitis	3206	324 (10)	237	32 (14)	1.21	0.81-1.81
Food hypersensitivity	3236	351 (11)	236	48 (20)	1.87	1.32-2.65
Multiple allergic diseases	3249	199 (6)	237	31 (13)	2.03	1.32-3.12

*Reference group.

†OR adjusted for parental allergic disease; maternal age; maternal smoking during pregnancy, at recruitment, or both; fish consumption; and breast-feeding.

compared with children receiving oil-based vitamins. Because of a small number of children receiving both preparations or no vitamins at all, these groups were excluded from further analyses. Children participating in the 4-year follow-up who also gave blood were not more likely to have asthma or eczema than children who did not provide a blood sample (data not shown). The same was true for parental allergy.

Children who had been given vitamins A and D in water-soluble form during the first year of life had an almost 2-fold increased risk of asthma (OR, 2.18; 95% CI, 1.45-3.28) and food hypersensitivity (OR, 1.89; 95% CI, 1.33-2.65) compared with children having received the same vitamins in peanut oil (Table II). No significant associations were seen for the development of eczema and allergic rhinitis (OR of 1.15 [95% CI, 0.83-1.58] and OR of 1.22 [95% CI, 0.82-1.83], respectively). However, for multiple allergic diseases, a 2-fold increased risk was observed (OR, 2.03; 95% CI, 1.32-3.12) among children supplemented with vitamins A and D in water-soluble form compared with those given such vitamins in peanut oil.

The effect of early exposure to vitamins A and D was heterogeneous for different phenotypes of allergic disease

(Table III). Children who regularly received vitamins A and D in water-soluble form during the first year of life had an increased risk of persistent allergic disease up to the age of 4 years compared with children who received vitamins in oil. ORs were 2.70 (95% CI, 1.59-4.60) for persistent asthma, 2.32 (95% CI, 1.32-4.07) for allergic rhinitis, and 2.99 (95% CI, 2.01-4.42) for food hypersensitivity. No association was found between early supplementation of vitamins A and D and occurrence of any transient or late-onset disease.

Associations between early exposure to vitamins A and D and sensitization to the 7 most common allergens in the BAMSE cohort are presented in Table IV. A positive association was seen for supplementation with vitamins A and D in water-soluble form during the first year of life and IgE antibodies to food and airborne allergens (OR of 1.75 [95% CI, 1.20-2.56] and OR of 1.95 [95% CI, 1.33-2.84], respectively). The prevalence of allergen-specific IgE antibodies was considerably lower among children having received peanut oil containing vitamins for all of the 7 tested allergens. The association was statistically significant for sensitization to egg white, horse, cat, and birch allergens.

TABLE III. Daily intake of vitamins A and D in peanut oil compared with vitamins A and D in water-soluble form in relation to allergic diseases at 4 years of age

	Transient				Late onset			Persistent		
	N	n	OR _{adj} *	95% CI	n	OR _{adj} *	95% CI	n	OR _{adj} *	95% CI
Asthma										
Oil based	3221	163	1.00		109	1.00		94	1.00	
Water soluble	234	14	1.22	0.69-2.17	13	1.73	0.95-3.16	19	2.70	1.59-4.60
Eczema										
Oil based	3238	389	1.00		238	1.00		406	1.00	
Water soluble	236	33	1.16	0.78-1.72	18	1.14	0.68-1.90	38	1.20	0.82-1.76
Allergic rhinitis										
Oil based	3175	125	1.00		239	1.00		85	1.00	
Water soluble	235	9	0.91	0.45-1.82	15	0.81	0.47-1.40	17	2.32	1.32-4.07
Food hypersensitivity										
Oil based	3224	439	1.00		168	1.00		182	1.00	
Water soluble	234	32	1.05	0.70-1.56	7	0.64	0.30-1.40	41	2.99	2.01-4.42

*OR adjusted for parental allergic disease; maternal age; maternal smoking during pregnancy, at recruitment, or both; fish consumption; and breast-feeding.

Among children who had received vitamins A and D in peanut oil, 5% were sensitized to peanut compared with 9% of the children who had received oil-based vitamins in water-soluble form ($P = .05$).

The associations between intake of vitamins A and D and the studied outcomes tended to be similar in children with parental allergy compared with those seen in children without parental allergy (data not shown).

DISCUSSION

Most children in this Swedish birth cohort had been given vitamins A and D during the first year of life, and oil-based vitamins dominated. In the present study the prevalence of allergic disease was higher among children supplemented with vitamins A and D in water-soluble form compared with children supplemented with vitamins A and D in peanut oil. Consequently, children supplemented with vitamins A and D in water-soluble form had an increased risk of asthma, food hypersensitivity, and sensitization to common food and inhalant allergens at the age of 4 years. The effect of supplementation with vitamins A and D in water-soluble form was heterogeneous for different phenotypes of allergic disease and was seen particularly for multiple allergic disease and persistent allergic disease during the first 4 years of life.

The effect of supplementation with vitamins A and D in water-soluble form is in agreement with results from a Finnish population-based study in which vitamin D supplementation during the first year of life was a risk factor for atopy and allergic rhinitis later in life.⁷ Furthermore, a study by Milner et al⁵ from the United States indicated that early multivitamin supplementation increased the risk of asthma among black children and food allergies among exclusively formula-fed children. However, it is difficult to compare the studies because the national guidelines regarding vitamin supplementation differed substantially between the countries. It is also unclear in what type of

TABLE IV. Association between intake of vitamins A and D and the 7 most common allergens among children in the BAMSE cohort

	N	≥0.35 kU/L		
		n (%)	OR _{adj} *	95% CI
Food mix				
Oil based	2295	351 (15)	1.00	
Water soluble	159	41 (26)	1.75	1.20-2.56
Phadiatop				
Oil based	2294	333 (15)	1.00	
Water soluble	159	42 (26)	1.95	1.33-2.84
Milk				
Oil based	2290	189 (8)	1.00	
Water soluble	159	21 (13)	1.54	0.94-2.51
Egg white				
Oil based	2291	102 (4)	1.00	
Water soluble	159	17 (11)	2.27	1.30-3.59
Peanut				
Oil based	2288	117 (5)	1.00	
Water soluble	159	14 (9)	1.52	0.84-2.75
Horse				
Oil based	2286	62 (3)	1.00	
Water soluble	159	12 (8)	2.66	1.38-5.12
Cat				
Oil based	2291	115 (5)	1.00	
Water soluble	159	21 (13)	2.57	1.55-4.28
Timothy				
Oil based	2280	124 (5)	1.00	
Water soluble	159	13 (8)	1.37	0.75-2.51
Birch				
Oil based	2277	187 (8)	1.00	
Water soluble	158	26 (17)	1.98	1.25-3.11

*OR adjusted for parental allergic disease; maternal age; maternal smoking during pregnancy, at recruitment, or both; fish consumption; and breast-feeding.

preparation the vitamins were given in the studies from Finland and the United States.

One might speculate that the difference in effect of early supplementation with vitamins A and D given in

water-soluble form or in peanut oil on the development of allergic disease seen in our study is related to a possible preventive effect by the fatty acids in the peanut oil. Such oil contains both omega-6 and omega-3 fatty acids to a proportion of approximately 34:1.^{12,13} Omega-3 fatty acids seem to have anti-inflammatory effects in contrast to omega-6 fatty acids, which might promote inflammation.¹⁴ However, a substantial contribution of omega-3 fatty acids from peanut oil to total daily intake is unlikely, given the low content in the peanut oil. Another possible explanation is that the absorption or the toxicity of vitamins might be different if given in water-soluble form or in oil-based form. The result of a recently performed meta-analysis comparing the toxicity of different forms of retinol indicates that the physical form is a major determinant of toxicity.²³ This has also been discussed in some older studies in which the absorption has been suggested to be better from a water suspension.²⁴ An argument against a negative effect of vitamins A and D if given in water-soluble form is the lack of difference in health outcome between those given vitamins in water-soluble form and the group of children who did not receive any vitamins. However, it should be kept in mind that only very few children did not receive vitamin supplementation, making results in this group uncertain.

During our study period, the oil solution was based on peanut oil. This has recently changed to sunflower oil, mainly because of suspected risk of development of peanut allergy. In our study the risk for sensitization to peanut was not increased for children with regular exposure to peanut oil during the first year of life; on the contrary, a borderline protective effect was observed. This is contrary to the results of some other studies but might be explained by different routes of administration.¹⁷ Furthermore, it is important to distinguish between crude peanut oil and refined preparations. The peanut oil used in the present study was highly refined and thus likely contained no peanut protein.

Residual confounding must be considered in the interpretation of our findings. Children who had received vitamins A and D in water-soluble form were more often exposed to maternal smoking during pregnancy and at 2 months of age, were less breast-fed, and had less regular consumption of fish at the age of 1 year compared with children receiving oil-based vitamins. All of these factors have been suggested to increase the risk for recurrent wheeze or asthma, but all those factors were adjusted for in the analysis.²⁵⁻²⁷ Heredity of allergic disease could be a confounding factor because at the time of the study, it was well known that the oil was produced from peanuts and that peanut oil in baby food had been suggested to increase the risk of sensitization to peanut.¹⁶ Thus atopic families might have selected the water-soluble vitamin supplements, and the association with atopic disease might be due to so-called reverse causation. However, when a very broad definition of heredity was used, including also parental eczema and allergic disease among older siblings, only minor changes of the risk estimates were seen. Although we cannot exclude residual confounding,

the magnitude of the association between vitamins A and D and allergic disease, as well as the consistency of the results, indicate that confounding is unlikely to explain the findings.

The strength of our study is a high response rate for all questionnaires during the 4-year follow-up period, reliable measurements of exposure, and well-defined outcome measures. We also have an appreciable number of children with allergic disease, which enabled allocation into different phenotypes depending on onset and duration of allergic disease. However, a weakness of our study is lack of information about vitamin supplementation after the first year of life, and therefore exposure misclassification related to later exposure cannot be entirely ruled out. Nevertheless, the majority of the children were receiving oil-based vitamins, and if some of them changed during the second year to vitamins in water-soluble form, it should primarily lead to a dilution of the associations between supplementation with vitamins A and D and development of allergic disease.

In conclusion, vitamins A and D in water-soluble form seem to increase the risk of allergic disease up to the age of 4 years compared with supplementation of such vitamins if given in peanut oil. The mechanisms behind these findings are still unclear, and our results have to be confirmed by others before the evidence can be used as a basis for preventive advice.

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