

Use of multivitamin supplements in relation to allergic disease in 8-y-old children¹⁻³

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ABSTRACT

Background: Multivitamins are frequently consumed by children, but it is unclear whether this affects the risk of allergic disease.

Objective: We sought to study the association between multivitamin supplementation and allergic disease in 8-y-old children.

Design: Data were obtained from a Swedish birth cohort study. Information on lifestyle factors, including use of vitamin supplements, environmental exposures, and symptoms and diagnoses of allergic diseases, was obtained by parental questionnaires. In addition, allergen-specific IgE concentrations of food and airborne allergens were measured in blood samples collected at age 8 y. A total of 2423 children were included in the study. The association between use of vitamin supplements and the selected health outcomes was analyzed with logistic regression.

Results: Overall, no strong and consistent associations were observed between current multivitamin use and asthma, allergic rhinitis, eczema, or atopic sensitization at age 8 y. However, children who reported that they started taking multivitamins before or at age 4 y had a decreased risk of sensitization to food allergens (odds ratio: 0.61; 95% CI: 0.39, 0.97) and tendencies toward inverse associations with allergic rhinitis. In contrast, there was no consistent association among children who started to use multivitamins at or after age 5 y.

Conclusion: Our results show no association between current use of multivitamins and risk of allergic disease but suggest that supplementation with multivitamins during the first years of life may reduce the risk of allergic disease at school age. *Am J Clin Nutr* 2009;90:1693–8.

INTRODUCTION

The escalating rates of asthma and allergic disease seen in the past decades are most evident in industrialized countries and have recently been proposed to partly be a consequence of changed dietary habits characterized by a fall in consumption of fish, fresh fruit, and vegetables rich in antioxidants and minerals (1, 2). Antioxidants—for example, vitamin C, vitamin E, vitamin A, and selenium—have been the most widely studied nutrients with regard to allergic diseases, either as individual nutrients or in analyses assessing fruit and vegetable intakes. A protective role of antioxidants in allergic disease is plausible because of their ability to scavenge free radicals generated by the inflammatory response with can exacerbate the disease process (2, 3). Moreover, epidemiologic studies support an association between antioxidants and asthma as well as allergic disease (4–7).

The consumption of dietary supplements among children has become quite common (8, 9). Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) show that >30% of children in the United States take dietary supplements regularly, with the most frequent use among 4- to 8-y-old children (8). Multivitamins and multiminerals were the most commonly used supplements (18%). Likewise, a Swedish national survey performed in 2003 showed that 33% of the children consumed vitamin supplements, most often multivitamins (9). Information on dietary supplement intake in relation to allergy in children is scarce; however, current evidence indicates that supplementation with antioxidants may have an influence on asthmatic symptoms (10) and lung function in asthmatic children exposed to high levels of ozone or air pollution (11). The relation between vitamin supplement use and health status still remains unclear for most dietary supplements but excessive consumption could be of questionable benefit (12–15).

The aim of the current study was to examine the association between use of multivitamin supplementation and allergic disease in 8-y-old children by using data from a Swedish birth cohort. We further investigated this association in relation to age at first use of multivitamin supplementation.

SUBJECTS AND METHODS

Study design

From February 1994 until November 1996, 4089 newborns were included in a prospective study (BAMSE, Swedish abbreviation for Children, Allergic disease, Milieu, Stockholm, Epidemiology). These infants comprised 75% of all eligible children in a predefined area of Stockholm, Sweden. The study

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design was described in detail elsewhere (16, 17). In brief, information on various background exposures, allergic heredity, and other demographic data were obtained through a parental questionnaire when the children were on average 2 mo old. Questionnaires focusing on symptoms related to allergic disease and on key exposures were also answered by the parents when the children were 1, 2, 4, and 8 y old. The response rates were 96%, 94%, 91%, and 84%, respectively. All children with answered questionnaires at age 8 y were invited to a clinical investigation including blood sampling. Sera of 2470 children (60%) were analyzed for specific IgE to common inhalant and food allergens. At the clinical examination, parents (together with their child) were asked to fill in a food-frequency questionnaire (FFQ) containing questions about 98 foods and beverages frequently consumed in Sweden as well as consumption of vitamin supplements. In total, 2614 families (64%) filled out the FFQ. Most often the FFQ was filled out by a parent (57%) or by a parent together with their child (40%). The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

Assessment of exposures to dietary supplements

Information about vitamin supplementation was collected from the FFQ at age 8 y. The use of vitamin supplements during the past 12 mo was reported to be either regular, occasional, or never. Parents of regular and occasional users further specified what kind of predefined supplement their child had used (multivitamins with minerals, multivitamins without minerals, vitamins A and D combined, vitamin A, vitamin D, vitamin C, and other) and since which year the supplement had been taken by the child. We analyzed ever use of any vitamin supplement or multivitamins as well as age at first use of multivitamins (≤ 4 or ≥ 5 y). Age 4 y was chosen as the cutoff because most children in the analyzes ($n = 1986$) also participated in a clinical examination (including measurement of antibodies to IgE) at age 4 y, and their parents were informed about the results of the IgE test.

Multivitamins were the most frequently used supplements among the children in our study, and most of the brands common in Sweden contain the Recommended Daily Allowance (18) of vitamins A, C, D, and E and the B vitamins (thiamine, riboflavin, niacin, folate, vitamin B-6, and vitamin B-12). Several brands also contain the Recommended Daily Allowance of minerals, mainly iron, zinc, iodine, manganese, chromium, and selenium.

Definition of health outcomes

Assessments of asthma, allergic rhinitis, and eczema were based on the follow-up questionnaire at age 8 y.

Asthma was defined as having ≥ 4 episodes of wheeze in the past 12 mo or ≥ 1 episode of wheeze during the same period in combination with prescribed inhaled steroids occasionally or regularly (17, 19).

Allergic rhinitis was defined as showing symptoms of sneezing, a runny or blocked nose, or itchy, red, and watery eyes after exposure to furred pets or pollen (according to the questionnaire) or having received a physician's diagnosis of allergic rhinitis between the time of the previous questionnaire at age 4 y and the questionnaire at age 8 y (17, 19).

Eczema was defined as dry skin in combination with itchy rash for ≥ 2 wk with typical localization during the past 12 mo and/or a physician's diagnosis of eczema from the age of 4 y (17).

Any allergic disease was indicated if the child had at least one of asthma, allergic rhinitis, or eczema at 8 y of age.

Atopic sensitization was indicated if the child had at least one allergen-specific IgE result of ≥ 0.35 kU/L against common inhalant allergens (Phadiatop: cat, dog, horse, birch, timothy, mugwort, and *Dermatophagoides pteronyssinus* and *Cladosporium* species) and/or food allergens (fx5: cow milk, hen's egg, cod fish, soy bean, peanut, and wheat) using the ImmunoCAP System (Phadia AB, Uppsala, Sweden).

Early symptoms of wheeze was defined as at least one episode of wheeze after 3 mo and up to 1 y of life reported in the parental questionnaire at age 1 y.

Early symptoms of eczema was defined as dry skin, itchy rashes for ≥ 2 wk, and specific localization of rash and/or physician's diagnosis of eczema up to age 1 y reported in the parental questionnaire at age 1 y.

Statistical methods

Differences in the distribution of selected characteristics between the 2 groups (intake of any vitamin supplements vs no use of vitamin supplements) were tested with the chi-square test. The associations between intake of any vitamin supplements or any multivitamins and the selected health outcomes were analyzed with logistic regression. To distinguish between IgE-mediated and non-IgE-mediated disease, analyses were also performed for each outcome in combination with atopic sensitization. All results are presented as adjusted odds ratios (ORs) with 95% CIs. Several models were tested to identify potential confounders, and the final logistic regression model was adjusted for parental history of allergic disease (defined as physician's diagnosis of asthma, hay fever, or both in combination with allergy to furred pets and/or pollen in one or both parents), socioeconomic status (blue collar worker and white collar worker), maternal smoking during pregnancy and/or at baseline (the mother smoked at least one cigarette per day at any point of time during the pregnancy or when the child was ≈ 2 mo old), and breastfeeding (exclusive breastfeeding < 4 or ≥ 4 mo) because these variables changed the OR estimates. Further adjustment for intake of dietary antioxidants, either as selected nutrients (vitamin C, E, D, and A as well as minerals such as selenium and magnesium) or as a total intake of fruit and vegetables, had little effect on the observed ORs and was therefore not included in the final model.

To test for disease-related modification of exposure (reverse causality), we adjusted the model for early symptoms of wheeze and eczema. Moreover, because parents were informed about the result of the IgE-test performed at age 4 y, we also adjusted for atopic sensitization at age 4 y (yes, no). However, this had no major influence on the obtained OR and was therefore not included in the extended model.

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, TX).

To be included in the analyzes, answers on the questionnaires at age 2 mo (baseline data) and 8 y (symptoms of allergic disease)

were required, together with information on vitamin supplement intake at age 8 y (from the FFQ) and information on atopic sensitization at age 8 y. A total of 2423 children fulfilled these criteria.

RESULTS

Children included in the present study were highly representative when compared with the children in the baseline cohort regarding distribution of exposure factors such as sex, parental allergic diseases, socioeconomic status, maternal smoking, and breastfeeding (data not shown). The prevalence of asthma (7.5%), allergic rhinitis (15.3%), and eczema (17.5%) at age 8 y tended to be higher but not significantly different from that of the cohort as a whole (6.3%, 13.3%, and 16.3%, respectively).

In total, 40.3% of the children reported to ever have used any type of vitamin supplement during the past 12 mo (**Table 1**). The most frequently used vitamin supplements were multivitamins with minerals (25.0%), multivitamins without minerals (9.5%), and vitamin C (6.1%). Among children who had taken "other" supplements ($n = 44$), fish oil/omega-3 capsules ($n = 18$) and calcium tablets ($n = 8$) were most frequently used. Supplement use was more frequent among children with parental history of allergic disease (45.0% compared with 38.0%; $P = 0.004$), children with a higher socioeconomic status (41.9% compared with 31.6%; $P = 0.001$), and children with early symptoms of eczema (45.9% compared with 39.1%; $P = 0.034$) (**Table 2**).

The association between intake of any vitamin supplement or multivitamin and allergic disease as well as atopic sensitization in 8-y-old children are shown in **Table 3**. Because multivitamins with minerals and multivitamins without minerals yielded similar ORs, they were combined into one exposure, hereafter called multivitamins. In adjusted models there was no statistically significant association between current use of any vitamin supplement or multivitamins and asthma, allergic rhinitis, eczema, or atopic sensitization at age 8 y. Further adjustment for early symptoms of wheeze or eczema had no major influence on the observed ORs (data not shown).

Among children who used multivitamins during the past 12 mo, we investigated age at first use in relation to allergic disease and atopic sensitization (**Table 4**). On average, the children had

TABLE 1

Current intake of vitamin supplements at age 8 y among children in the BAMSE cohort ($n = 2423$)¹

Supplement	Frequency of intake		
	Regular	Occasional	Ever
	<i>n</i> (%)		
Any vitamin	317 (13.1)	660 (27.2)	977 (40.3)
Multivitamins with minerals	212 (8.7)	393 (16.2)	605 (25.0)
Multivitamins without minerals	78 (3.2)	151 (6.2)	229 (9.5)
Vitamins A + D	22 (0.9)	50 (2.1)	72 (3.0)
Vitamin A	4 (0.2)	1 (0.0)	5 (0.2)
Vitamin D	3 (0.1)	0 (0.0)	3 (0.1)
Vitamin C	25 (1.0)	122 (5.0)	147 (6.1)
Other (eg, fish oil, calcium)	27 (1.1)	26 (1.1)	53 (2.2)

¹ Consumption of vitamin supplements during the past 12 mo. BAMSE, Swedish abbreviation for Children, Allergic disease, Milieu, Stockholm, Epidemiology.

TABLE 2

Distribution of selected exposure characteristics at age 2 mo and symptoms during the first year of life in relation to current intake of vitamin supplements at age 8 y among children in the BAMSE cohort ($n = 2423$)¹

	Use of vitamin supplements		
	<i>n</i> /Total <i>n</i>	Percentage	95% CI
Total	977/2423	40.3	38, 42
Child's sex			
Boy	511/1252	40.8	38, 44
Girl	466/1171	39.8	37, 43
Parental history of allergic disease ²			
No	620/1631	38.0	36, 40
Yes	348/773	45.0	41, 49 ³
Socioeconomic status			
Blue collar worker	115/364	31.6	27, 37
White collar worker	848/2025	41.9	40, 44 ³
Exclusive breastfeeding			
<4 mo	170/443	38.4	34, 43
≥4 mo	785/1928	40.7	39, 43
Maternal smoking during pregnancy and/or at baseline			
No	857/2118	40.5	38, 43
Yes	120/303	39.6	34, 45
Early symptoms of wheeze ⁴			
Yes	151/356	42.4	37, 48
No	806/2018	39.9	38, 42
Early symptoms of eczema ⁵			
Yes	185/403	45.9	41, 51
No	770/1970	39.1	37, 41 ³

¹ Consumption of vitamin supplements during the past 12 mo. BAMSE, Swedish abbreviation for Children, Allergic disease, Milieu, Stockholm, Epidemiology.

² Physician's diagnosis of asthma, hay fever, or both in combination with allergy to furred pets and/or pollen in one or both parents.

³ $P < 0.05$ for difference in frequency of vitamin supplement use between groups (chi-square test).

⁴ At least one episode of wheeze after 3 mo and up to 1 y of life.

⁵ Dry skin, itchy rashes for 2 wk, and more and specific localization of rash and/or physician diagnosis of eczema after 1 y and up to 2 y.

started to use multivitamins at age 5.7 y. Children who started taking multivitamins before or at age 4 y had an inverse association with sensitization to food allergens (OR: 0.61; 95% CI: 0.39, 0.97) as well as tendencies toward inverse associations with allergic rhinitis (OR: 0.62; 95% CI: 0.38, 1.03). These results persisted when early symptoms of wheeze and eczema were added to the model (OR: 0.60; 95% CI: 0.37, 0.96 for sensitization to food allergens; OR: 0.59; 95% CI: 0.34, 1.00 for allergic rhinitis). In contrast, we observed nonsignificant associations with allergic rhinitis (OR: 1.21; 95% CI: 0.91, 1.60) and eczema (OR: 1.24; 95% CI: 0.95, 1.63) among children who started to consume multivitamins at or after the age of 5 y. These associations were somewhat attenuated after adjustment for early symptoms of wheeze and eczema (OR: 1.08; 95% CI: 0.81, 1.45 allergic rhinitis; OR: 1.14; 95% CI: 0.86, 1.51 for eczema).

To distinguish between IgE-mediated and non-IgE-mediated disease, each outcome was also analyzed in combination with atopic sensitization to inhalant or food allergens. The results for asthma, allergic rhinitis, and eczema in combination with atopic sensitization resembled the results described above (data not shown).



TABLE 3

Association between current intake of any vitamin supplements or multivitamins at age 8 y and allergic diseases and atopic sensitization at age 8 y among children in the BAMSE cohort ($n = 2423$)¹

	Use of vitamin supplements			
	No		Yes	
	<i>n</i> /Total <i>n</i>	OR (referent)	<i>n</i> /Total <i>n</i>	OR _{adj} ² (95% CI)
Any vitamin supplement				
Asthma	103/1387	1.0	72/970	0.95 (0.69, 1.31)
Allergic rhinitis	203/1381	1.0	149/974	1.01 (0.80, 1.28)
Eczema	225/1356	1.0	181/952	1.17 (0.93, 1.46)
Any allergic disease ³	403/1352	1.0	304/953	1.06 (0.88, 1.28)
Atopic sensitization	471/1380	1.0	340/967	1.02 (0.85, 1.22)
Inhalant allergens	354/1383	1.0	255/968	0.99 (0.81, 1.20)
Food allergens	276/1381	1.0	193/967	0.99 (0.80, 1.23)
Multivitamins				
Asthma	120/1598	1.0	61/812	0.96 (0.69, 1.33)
Allergic rhinitis	246/1593	1.0	123/815	0.94 (0.74, 1.20)
Eczema	266/1563	1.0	148/797	1.11 (0.88, 1.40)
Any allergic disease ³	481/1560	1.0	249/797	0.99 (0.82, 1.20)
Atopic sensitization	547/1590	1.0	287/811	1.01 (0.84, 1.22)
Inhalant allergens	407/1594	1.0	219/811	1.03 (0.84, 1.26)
Food allergens	324/1591	1.0	159/811	0.94 (0.75, 1.17)

¹ Consumption of any vitamin supplements or multivitamins during the past 12 mo. Atopic sensitization refers to an allergen-specific serum IgE concentration ≥ 0.35 kU/L. BAMSE, Swedish abbreviation for Children, Allergic disease, Milieu, Stockholm, Epidemiology; OR, odds ratio. ORs and 95% CIs were estimated by logistic regression.

² Adjusted for socioeconomic status, parental history of allergic disease, smoking during pregnancy and/or at baseline, and breastfeeding.

³ At least one of asthma, rhinitis, or eczema.

Consumption of multivitamins showed no evidence of statistical interaction with sex, parental allergy, maternal smoking and consumption of fruit and vegetables when tested for asthma ($P = 0.51, 0.27, 0.88$, and 0.34 , respectively), allergic rhinitis ($P = 0.43, 0.91, 0.57$, and 0.41 , respectively), eczema ($P = 0.13, 0.17, 0.89$, and 0.99 , respectively), or atopic sensitization ($P = 0.69, 0.93, 0.96$, and 0.99 , respectively).

DISCUSSION

In our study of 2423 Swedish 8-y-olds, there was no strong and consistent association between use of any vitamin supplement during the past 12 mo and allergic disease. Likewise, no association was observed when multivitamin supplementation was analyzed separately. However, for children who reported that they started to use multivitamins at age ≤ 4 y, we observed an inverse

TABLE 4

Association between age at first use of multivitamins in relation to allergic diseases and atopic sensitization at age 8 y among children in the BAMSE cohort ($n = 2423$)¹

	Age at "first time" intake of multivitamins					
	Never		≤ 4 y		≥ 5 y	
	<i>n</i> /Total <i>n</i>	OR (referent)	<i>n</i> /Total <i>n</i>	OR _{adj} ² (95% CI)	<i>n</i> /Total <i>n</i>	OR _{adj} ² (95% CI)
Asthma	103/1387	1.0	13/181	0.87 (0.47, 1.64)	37/501	0.99 (0.67, 1.47)
Allergic rhinitis	203/1381	1.0	20/182	0.62 (0.38, 1.03) ³	88/504	1.21 (0.91, 1.60)
Eczema	225/1356	1.0	26/177	0.85 (0.54, 1.34)	98/494	1.24 (0.95, 1.63)
Any allergic disease ⁴	403/1352	1.0	44/177	0.73 (0.51, 1.07)	164/495	1.14 (0.91, 1.43)
Atopic sensitization	471/1380	1.0	55/180	0.79 (0.55, 1.12)	185/502	1.10 (0.88, 1.37)
Inhalant allergens	354/1383	1.0	45/180	0.86 (0.59, 1.24)	141/502	1.09 (0.86, 1.38)
Food allergens	276/1383	1.0	25/179	0.61 (0.39, 0.97) ⁵	107/502	1.09 (0.84, 1.41)

¹ Age at first use of multivitamins among current multivitamin users. Atopic sensitization refers to an allergen-specific serum IgE concentration ≥ 0.35 kU/L. BAMSE, Swedish abbreviation for Children, Allergic disease, Milieu, Stockholm, Epidemiology; OR, odds ratio. ORs and 95% CIs were estimated by logistic regression.

² Adjusted for socioeconomic status, parental history of allergic disease, smoking during pregnancy and/or at baseline, and breastfeeding.

³ $P = 0.067$.

⁴ At least one of asthma, rhinitis, or eczema.

⁵ $P < 0.05$.



association for sensitization to food allergens and tendencies toward inverse associations for allergic rhinitis. In contrast, there was no consistent association among children who started to use multivitamins at age ≥ 5 y. The use of vitamin supplements was common, ie, 40% reported having taken any vitamin supplements during the past year. Also, children who used supplements displayed more hereditary traits of allergy, had parents with higher socioeconomic status, and more often had symptoms of eczema during the first year of life when compared with nonusers.

The strengths of the present study included the large number of participants, limited loss to follow-up, and detailed assessment of phenotypes as well as of exposure, including vitamin supplements. However, misclassification of exposure might affect our results. We only asked for the frequency of consumption during the past 12 mo, and parents of vitamin supplement users were asked to remember when the child first started taking the supplements. If parents of children with allergic diseases recall previous supplement use differently from other parents, it may give rise to recall bias. The use of dietary supplements among children as reported in a FFQ has not been validated to our knowledge. FFQs have, however, proven to be adequate when ranking and assessing dietary macronutrient, vitamin D, and calcium intakes in children (20, 21). For adults, on the other hand, a brief questionnaire can accurately and reproducibly capture data on supplement use for frequently consumed products, but it may perform less well for products used less often or more intermittently (22, 23).

The cross-sectional design, which used both exposure and outcome information obtained at 8 y of age, is a drawback of this study. In epidemiologic reports on allergic diseases in childhood, disease-related modification of exposure may be a major bias, which is not always easy to control for and may lead to misinterpretation of the results. This has been discussed in several articles investigating behavioral factors, such as breastfeeding (24), vaccination (25), pet ownership (26), and consumption of specific food items (27) in relation to allergic diseases. Therefore, we cannot exclude a disease-related modification of exposure, ie, that the observed risk estimate was affected by the fact that children started to take dietary supplements (or avoided to do so) because of their allergic symptoms, rather than because of a true effect of dietary supplements on allergic diseases. We tried to investigate this by grouping individuals according to age at the start of multivitamin consumption and by adjusting for early symptoms of wheeze and eczema in the multivariate analyses. These adjustments had no major influence on the observed ORs among children who started to use multivitamins at age 4 y or earlier, whereas the nonsignificant increments in risk observed for allergic rhinitis, eczema, and any allergic disease among children who started to consume multivitamins at age ≥ 5 y were somewhat attenuated. Furthermore, it should be noted that most of the data on other risk factors used in our analyses, such as breastfeeding and parental smoking habits, were obtained before onset of disease.

Multivitamins are the most commonly purchased and regularly used supplement by adults and children (8, 28, 29). Despite this, there is limited evidence on multivitamin use in relation to allergic disease in children. Milner et al (14) reported an increased risk of asthma among infants who consumed multivitamin supplements during the first 6 mo of life, although restricted to black infants. However, they found no association between multivitamin use at 3 y of age and asthma. Likewise, in a Nor-

wegian study, intake of vitamin supplements during the first year of life was associated with a borderline significant increased risk of sensitization at school age (15). In our study there was no increased risk of allergic diseases among children who started to use multivitamins at an early age. Instead, we observed an inverse association with sensitization to food allergens in this group. There may be several explanations for the differences in results. First, the earlier studies investigated the effect of vitamin supplementation during the first year of life, whereas most of the children in the present study started to consume multivitamins after age 1 y. It should be noted, though, that 98% of the children in our study received supplementation of vitamins A and D from 2 wk of age and through the first years of life (17). Second, the composition, dose, and duration of the consumed supplements may differ between the studies. Third, differences in nutritional status between the populations might cause different responses to vitamin supplementation. Fourth, Milner et al did not consider disease-related modification of exposure in their analyses, whereas the Norwegian study excluded children with asthma during the first year of life; thus, their results are less likely to be affected by this potential bias.

An association between use of multivitamins and allergic disease is biologically plausible because of the antioxidant and immunomodulatory properties of certain vitamins. Many of the pathophysiological changes associated with allergic diseases are produced by activated inflammatory cells, which generate an excessive amount of oxygen free radicals. A postulated hypothesis is that antioxidants, because of their ability to quench free radicals, prevent chain reactions that could result in lipid peroxidation and damage to cell membranes, ie, of immune cells (3) or DNA, both of which have been suggested to be involved in the allergic disease process (30, 31). On the other hand, it has been proposed that several antioxidant nutrients can act as pro-oxidants at higher doses through a reduction of transition metal ions (32). Vitamins have also been postulated to exert non-antioxidant immunomodulatory effects (33, 34). Previous research has shown that a variety of vitamins commonly found in multivitamins can cause naive T cells to differentiate toward the extremes of the T helper type 1 and T helper type 2 phenotypes (3, 33), each characterized by different cytokine profiles, which leads to physiologic states that may increase the odds of an allergic response when encountering certain antigens (13, 14, 34, 35).

Overall, the scientific evidence regarding the beneficial or harmful effects of vitamin supplements in relation to allergic diseases appears contradictory. In previous studies in which the effect of single nutrient supplementation has been investigated and found not to be effective, it has been suggested that perhaps a combination of antioxidants would have given different results (36), a finding not supported by the present study. Rather, dose and duration of supplementation seem to be important conditioning factors (37, 38). Furthermore, Feary and Britton (39) propose that perhaps vitamin supplements only work in nutritionally deplete populations and that no additional beneficial effect will occur in well-fed and consequently oversupplemented individuals. The variability in individual susceptibility to oxidative stress may also explain the conflicting results between studies on antioxidant supplementation (40). Hence, the effectiveness of vitamin supplementation is still an unresolved matter that warrants rigorous scientific evaluation (38, 41, 42), and further exploration of the association between vitamin



supplementation and allergic diseases is very important from a public health point of view.

In conclusion, our study of 2423 Swedish boys and girls showed no association between current multivitamin use and risk of allergic disease, but suggests that supplementation with multivitamins in early life may reduce the risk of allergic disease at school age. The cross-sectional nature of the data implies that the findings should be interpreted with caution.

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REFERENCES

1. Ellwood P, Asher MI, Björkstén B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. *ISAAC Phase One Study Group*. *Eur Respir J* 2001;17:436–43.
2. Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994;49:171–4.
3. Webb AL, Villamor E. Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function. *Nutr Rev* 2007;65:181–217.
4. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005;115:1109–17, quiz 1118.
5. Devereux G. Early life events in asthma—diet. *Pediatr Pulmonol* 2007;42:663–73.
6. Hartert TV, Peebles RS. Dietary antioxidants and adult asthma. *Curr Opin Allergy Clin Immunol* 2001;1:421–9.
7. Fogarty A, Britton J. The role of diet in the aetiology of asthma. *Clin Exp Allergy* 2000;30:615–27.
8. Picciano MF, Dwyer JT, Radimer KL, et al. Dietary supplement use among infants, children, and adolescents in the United States, 1999–2002. *Arch Pediatr Adolesc Med* 2007;161:978–85.
9. Enghardt Barbieri H, Pearson M, Becker W. Riksmaten—children 2003: dietary habits and nutrient intake in Swedish children. Uppsala, Sweden: National Food Administration, 2006.
10. Linday LA, Shindlerdecker RD, Tapia-Mendoza J, Dolitsky JN. Effect of daily cod liver oil and a multivitamin-mineral supplement with selenium on upper respiratory tract pediatric visits by young, inner-city, Latino children: randomized pediatric sites. *Ann Otol Rhinol Laryngol* 2004;113:891–901.
11. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. *Am J Respir Crit Care Med* 2002;166:703–9.
12. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 2007;297:842–57.
13. Murr C, Schroecksnadel K, Winkler C, Ledochowski M, Fuchs D. Antioxidants may increase the probability of developing allergic diseases and asthma. *Med Hypotheses* 2005;64:973–7.
14. Milner JD, Stein DM, McCarter R, Moon RY. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. *Pediatrics* 2004;114:27–32.
15. Nja F, Nystad W, Lodrup Carlsen KC, Hetlevik O, Carlsen KH. Effects of early intake of fruit or vegetables in relation to later asthma and allergic sensitization in school-age children. *Acta Paediatr* 2005;94:147–54.
16. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002;13(suppl 15):11–3.
17. Kull I, Bergström A, Melen E, et al. Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. *J Allergy Clin Immunol* 2006;118:1299–304.
18. Nordic Council of Ministers. Nordic nutrition recommendations 2004: integrating nutrition and physical activity. Copenhagen, Denmark: Nordic Council of Ministers, 2004.
19. Östblom E, Lilja G, Pershagen G, van Hage M, Wickman M. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. *Clin Exp Allergy* 2008;38:1325–52.
20. Marshall TA, Eichenberger Gilmore JM, Broffitt B, Stumbo PJ, Levy SM. Relative validity of the Iowa Fluoride Study targeted nutrient semi-quantitative questionnaire and the block kids' food questionnaire for estimating beverage, calcium, and vitamin D intakes by children. *J Am Diet Assoc* 2008;108:465–72.
21. Bertoli S, Petroni ML, Pagliaro E, et al. Validation of food frequency questionnaire for assessing dietary macronutrients and calcium intake in Italian children and adolescents. *J Pediatr Gastroenterol Nutr* 2005;40:555–60.
22. Murphy SP, Wilkens LR, Hankin JH, et al. Comparison of two instruments for quantifying intake of vitamin and mineral supplements: a brief questionnaire versus three 24-hour recalls. *Am J Epidemiol* 2002;156:669–75.
23. Messerer M, Wolk A. Sensitivity and specificity of self-reported use of dietary supplements. *Eur J Clin Nutr* 2004;58:1669–71.
24. Lowe AJ, Carlin JB, Bennett CM, et al. Atopic disease and breastfeeding—cause or consequence? *J Allergy Clin Immunol* 2006;117:682–7.
25. Rosenlund H, Bergström A, Alm JS, et al. Allergic disease and atopic sensitization in children in relation to measles vaccination and measles infection. *Pediatrics* 2009;123:771–8.
26. Almqvist C, Egmar AC, Hedlin G, et al. Direct and indirect exposure to pets—risk of sensitization and asthma at 4 years in a birth cohort. *Clin Exp Allergy* 2003;33:1190–7.
27. Kull I, Bergström A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;61:1009–15.
28. Rock CL. Multivitamin-multimineral supplements: who uses them? *Am J Clin Nutr* 2007;85(suppl):277S–9S.
29. Gardiner P, Buettner C, Davis RB, Phillips RS, Kemper KJ. Factors and common conditions associated with adolescent dietary supplement use: an analysis of the National Health and Nutrition Examination Survey (NHANES). *BMC Complement Altern Med* 2008;8:9.
30. Greene LS. Asthma, oxidant stress, and diet. *Nutrition* 1999;15:899–907.
31. Riedl MA, Nel AE. Importance of oxidative stress in the pathogenesis and treatment of asthma. *Curr Opin Allergy Clin Immunol* 2008;8:49–56.
32. Pearson P, Lewis SA, Britton J, Young IS, Fogarty A. The pro-oxidant activity of high-dose vitamin E supplements in vivo. *BioDrugs* 2006;20:271–3.
33. Long KZ, Santos JI. Vitamins and the regulation of the immune response. *Pediatr Infect Dis J* 1999;18:283–90.
34. Li-Weber M, Giaisi M, Treiber MK, Krammer PH. Vitamin E inhibits IL-4 gene expression in peripheral blood T cells. *Eur J Immunol* 2002;32:2401–8.
35. Averbek M, Gebhardt C, Emmrich F, Treudler R, Simon JC. Immunologic principles of allergic disease. *J Dtsch Dermatol Ges* 2007;5:1015–28.
36. Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. *Thorax* 2004;59:652–6.
37. Riccioni G, D'Orazio N. The role of selenium, zinc and antioxidant vitamin supplementation in the treatment of bronchial asthma: adjuvant therapy or not? *Expert Opin Investig Drugs* 2005;14:1145–55.
38. Huang HY, Caballero B, Chang S, et al. Multivitamin/mineral supplements and prevention of chronic disease. *Evid Rep Technol Assess (Full Rep)* 2006;May:1–117.
39. Feary J, Britton J. Dietary supplements and asthma: another one bites the dust. *Thorax* 2007;62:466–8.
40. Romieu I, Castro-Giner F, Kunzli N, Sunyer J. Air pollution, oxidative stress and dietary supplementation: a review. *Eur Respir J* 2008;31:179–97.
41. Smit HA, Grievink L, Tabak C. Dietary influences on chronic obstructive lung disease and asthma: a review of the epidemiological evidence. *Proc Nutr Soc* 1999;58:309–19.
42. Stanner SA, Hughes J, Kelly CN, Buttriss J. A review of the epidemiological evidence for the 'antioxidant hypothesis'. *Public Health Nutr* 2004;7:407–22.