

## Antioxidant intake and allergic disease in children

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### Clinical & Experimental Allergy

#### Summary

**Background** Antioxidant intake may reduce the risk of allergic disease by protecting against oxidative tissue damage. Major sources of antioxidants in the Western world are fruits, vegetables (vitamin C,  $\beta$ -carotene,  $\alpha$ -tocopherol), meat and milk (selenium, magnesium, zinc). Children may exclude or eat less of some fruits and vegetables due to cross-reactivity between pollen and these foods, complicating assessment of causal relationships. **Objective** To investigate the association between dietary antioxidant intake and allergic disease, taking potential reverse causation into account.

**Methods** Data on 2442 8-year-old children from the Swedish birth cohort study BAMSE were analysed. Children with completed parental questionnaires on exposures and health, including a food-frequency questionnaire and who provided a blood sample were included. Associations between antioxidant intake during the past year and current allergic disease were analysed using logistic regression.

**Results** An inverse association was observed between intake of  $\beta$ -carotene and rhinitis ( $OR_{adj}$ , highest vs. lowest quartile, 0.67, 95% CI 0.49–0.93). Magnesium intake was inversely related to asthma ( $OR_{adj}$ , 0.65, 95% CI 0.42–1.00) and atopic sensitisation ( $OR_{adj}$ , 0.78, 95% CI 0.61–1.00). Following exclusion of children who avoided certain fruits, vegetables or milk due to allergic symptoms ( $n = 285$ ), the inverse association remained between magnesium intake and asthma ( $OR_{adj}$ , 0.58, 95% CI 0.35–0.98), whereas all other associations became non-significant.

**Conclusion and clinical relevance** Diet modifications due to allergy may affect the antioxidant intake and needs to be considered when investigating the relationship between diet and allergic disease. Magnesium intake seems to have a protective effect on childhood asthma.

**Keywords** antioxidants, asthma, diet, eczema, minerals, reverse causation, rhinitis, sensitisation, vitamins

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#### Introduction

A decreased dietary antioxidant intake may have contributed to the increased prevalence of allergic diseases in the recent decade. Antioxidant vitamins, such as vitamin C,  $\beta$ -carotene (precursor of vitamin A) and  $\alpha$ -tocopherol, are involved in redox-reactions and act by scavenging reactive oxygen-free radicals that in turn could lead to inflammation. Minerals, such as selenium and zinc, are important cofactors to enzymes that take part in redox-reactions, whereas magnesium has an important influence on electrical potential across cell membranes and bronchodilates smooth muscle [1–3].

Epidemiological studies on dietary antioxidant intake and allergy in children are inconclusive [4–8]. Among 5-year-olds, intake of  $\beta$ -carotene was associated with a reduced risk of atopy [4]. In the same age group, a low vitamin A intake was related to an increased prevalence of atopic dermatitis, whereas a high vitamin E intake had a protective effect on atopic dermatitis [8]. Among 12-year-olds, a high vitamin E intake had a protective effect on asthma [6]. A protective effect of asthma has also been associated with a high vitamin A intake and a high vitamin C intake in teenagers [5].

Among the minerals possessing an antioxidative effect, a low intake of magnesium has been associated

with asthma and wheeze at 12 years of age [6]. One study observed no association between antioxidant intake and allergy in children [7]. A recent meta-analysis based on children and adults supported a protective effect on asthma by intake of vitamin E and vitamin A [9]. Major sources of antioxidants in the western world are fruits and vegetables (vitamin C,  $\alpha$ -tocopherol,  $\beta$ -carotene), meat and milk (selenium, magnesium, and zinc) [10–12]. Of these food groups, high consumption of fruit and vegetables has been inversely related to allergic disease in several studies [13–15]. In a previous report from the prospective Swedish birth cohort BAMSE, we observed an inverse association between high intake of fruit and childhood allergic disease; however, our data also indicated that disease-related modification of diet contributed to this association [13]. Whether such bias also contributes to the associations between dietary antioxidant intake and childhood allergic disease has not been investigated. Therefore, the aim of this study was to investigate the association between intake of dietary antioxidant, such as vitamin C,  $\beta$ -carotene,  $\alpha$ -tocopherol, selenium, magnesium, and zinc, and current allergic disease, taking disease-related modification of diet into consideration.

## Methods

### Study design

A prospective birth cohort of 4089 new-born infants (BAMSE) was established among children born between February 1994 and November 1996, comprising 75% of all eligible children in predefined areas of Stockholm, Sweden. The study design has been described elsewhere [16]. In brief, information on various background exposures, allergic heredity, socio-economy, and other demographic data were obtained through a parental questionnaire when the children were on average 2-months-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 years old. The response rates were 96%, 94%, 91%, and 84%, respectively. All children with answered questionnaires at age 8 years were invited to a clinical investigation including blood sampling. Sera of 2470 children (60%) were analysed for specific IgE (Immunoglobulin E) antibodies to common inhalant and food allergens. The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

### Assessment of nutrient intake

At the clinical examination at age 8 years, parents (together with their child) answered a food-frequency questionnaire (FFQ), including 98 food items and

beverages commonly consumed in Sweden. In total, 2614 families (64%) filled out the FFQ. Most often, it was filled out by a parent (57%) or by a parent together with the child (40%). The FFQ was transformed into nutrients by multiplying the frequency of consumption of each food item by its nutrient content per serving, using composition values obtained from the Swedish National Food Agency Database [17], and summarized over foods and beverages. Nutrient intake was energy-adjusted using the residuals method [18]. In this study, we investigated vitamin C,  $\beta$ -carotene (precursor of vitamin A),  $\alpha$ -tocopherol, selenium, magnesium, and zinc.

### Definition of health outcomes

Assessment of current allergic disease was based on the follow-up questionnaire at age 8 years and has been used previously [13].

*Rhinitis* was defined as prolonged sneezing or a runny or blocked nose, without a common cold at the same time, in the last 12 months prior to the questionnaire at age 8 years.

*Asthma* was defined as having at least four episodes of wheezing in the last 12 months prior to the questionnaire at 8 years, or at least one episode of wheezing during the same period in combination with prescribed inhaled steroids occasionally or regularly.

*Eczema* was defined as dry skin in combination with an itchy rash for at least 2 weeks with typical localization during the last 12 months prior to the questionnaire at age 8 years, and/or a physician's diagnosis of eczema from the age of 7 years.

*Atopic sensitisation* was indicated if the child had at least one allergen-specific IgE-result of  $\geq 0.35$  kU<sub>A</sub>/L against common inhalant allergens: cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium* species (Phadiatop<sup>®</sup>) and/or common food allergens: cows' milk, hens' egg, cod fish, soy bean, peanut, and wheat (fx5<sup>®</sup>), using the ImmunoCAP System (Phadia AB, Uppsala, Sweden), analysed in blood samples obtained at the 8-year follow-up.

### Statistical methods

Associations between antioxidant intake and the health outcomes were estimated by odds ratios (ORs) and 95% confidence intervals (CIs) computed from logistic regression. To distinguish between IgE-mediated and non-IgE-mediated disease, analyses were also performed for each outcome in combination with atopic sensitisation (from blood sample analyses). Potential confounders were included in the model, if they changed the crude OR with more than 5% [parental history of allergic disease (defined as physician-diagnosed asthma and/or

hay fever in combination with allergy to furred pets and/or pollen in one or both parents)], or if they were considered to be traditional risk factors for allergic disease (sex, parental socioeconomic status), maternal smoking during pregnancy and/or at baseline (at least one cigarette per day), iso-BMI (age-adjusted BMI) [19], and vitamin supplementation (during the past 12 months). Differences in proportions between groups of consumption were tested using the chi-square test. Test for linear trend was calculated using a continuous term including the medians of each quartile. Values were considered significant at a *P*-value of less than 0.05. In a second step, to examine potential effects of disease-related modification of diet (reverse causation), we excluded children who reported food-related allergic symptoms (wheezing, itchy eyes and/or runny nose, oral allergy syndrome, eczema, urticaria, or diarrhoea/vomiting) from specific fruits, vegetables (apple, peach, kiwi, avocado, banana, fresh carrot, or any other specified fruit or vegetable) or milk, and/or who avoided any of these food items due to allergic symptoms.

To be included in the analyses, answers on the questionnaires at age 2 months (baseline data), and 8 years were required, together with a completed FFQ at age 8 years (where calculations of total energy and nutrient intake were possible) and information on atopic sensitisation at age 8 years. In total, 2442 children fulfilled these criteria. All statistical analyses were performed using STATA Statistical Software (release 11.0; Stata-Corp, College Station, TX, USA).

## Results

Children included in this study were highly representative when compared with children in the baseline cohort regarding distribution of exposure factors, such as sex, parental allergic disease, socioeconomic status, maternal smoking and breastfeeding (data not shown). However, the prevalence of asthma (7.4%), rhinitis (15.4%), and eczema (14.0%) at age 8 years in the study group appeared somewhat higher when compared with the cohort as a whole (6.3%, 13.3%, and 12.9%, respectively), but did not differ significantly.

The mean intake of different antioxidants were: vitamin C, 98.4 mg (SD  $\pm$  36.9);  $\alpha$ -tocopherol, 7.1 mg (SD  $\pm$  1.2);  $\beta$ -carotene, 2.1 mg (SD  $\pm$  1.2); selenium, 35.0  $\mu$ g (SD  $\pm$  6.3); magnesium, 303.1 mg (SD  $\pm$  29.7); and zinc, 10.3 mg (SD  $\pm$  1.4). Intakes of selected antioxidants were above the recommended daily intake (RDI) in Sweden [20]. The major food sources of the antioxidants consumed by the 8-year-old Swedish children are presented in Table 1. Vitamin C,  $\alpha$ -tocopherol and  $\beta$ -carotene are mostly derived from fruit juices and citrus fruits, as well as fat spreads and carrots. Milk is the major source for selenium, magnesium, and zinc.

**Table 1.** The three major sources (%) of different antioxidants among 8-year-old children in the BAMSE study (N = 2442)

|                                       |                          |              |                         |       |
|---------------------------------------|--------------------------|--------------|-------------------------|-------|
| <i>Vitamin C</i>                      | Juice                    | Citrus fruit | Apples, pears           | Other |
|                                       | 20.0                     | 11.3         | 9.3                     | 59.4  |
| <i><math>\alpha</math>-tocopherol</i> | Fat spreads              | Tomatoes     | Apples, pears           | Other |
|                                       | 12.4                     | 8.3          | 4.7                     | 74.6  |
| <i><math>\beta</math>-carotene</i>    | Carrots                  | Tomatoes     | Meat dishes*            | Other |
|                                       | 51.6                     | 7.4          | 7.0                     | 34.0  |
| <i>Selenium</i>                       | Dairy prod. <sup>†</sup> | Meat dishes* | Egg dishes <sup>‡</sup> | Other |
|                                       | 34.0                     | 11.4         | 9.4                     | 45.2  |
| <i>Magnesium</i>                      | Dairy prod. <sup>†</sup> | Meat dishes* | Potatoes                | Other |
|                                       | 29.0                     | 5.0          | 4.5                     | 61.5  |
| <i>Zinc</i>                           | Dairy prod. <sup>†</sup> | Meat dishes* | Pasta                   | Other |
|                                       | 29.0                     | 21.1         | 3.1                     | 46.8  |

\*Meat dishes include dishes with minced meat, porc, beef, or veal.

<sup>†</sup>Dairy products include milk, chocolate milk, sour milk, and yoghurt.

<sup>‡</sup>Egg dishes include egg, omelette, pancake, and waffles.

The distribution of different potential confounding factors in relation with the mean antioxidant intake is presented in Table 2. Intake of vitamin C,  $\alpha$ -tocopherol and  $\beta$ -carotene was higher among girls, than among boys. The intake of  $\beta$ -carotene was also higher in children of white-collar workers, as well as in children of non-smoking mothers. Moreover, overweight children (iso-BMI  $\geq$  25 kg/m<sup>2</sup>) had higher intakes of vitamin C,  $\beta$ -carotene, magnesium, and zinc compared to normal weight children (iso-BMI < 25 kg/m<sup>2</sup>).

Table 3a–b presents the associations between dietary antioxidant intake and current allergic disease in children. Among the vitamins (Table 3a), an inverse association was observed between intake of  $\beta$ -carotene and rhinitis (OR<sub>adj</sub>, highest vs. lowest quartile, 0.67, 95% CI 0.49–0.93, *P* for trend 0.035). In total, 237 children reported allergic symptoms related to at least one of six pre-specified fruits or vegetables (apple, peach, kiwi, banana, avocado, fresh carrot) or any other fruit or vegetable (citrus fruit, strawberry, and tomato were the most commonly listed food items), or avoided these food items due to such symptoms. When those children were excluded from the analysis, because they might have changed their diet as a result of allergic symptoms, the inverse association between  $\beta$ -carotene and rhinitis became non-significant.

Among the minerals (Table 3b), magnesium intake was inversely related to asthma (OR<sub>adj</sub>, highest vs. lowest quartile, 0.65, 95% CI 0.42–1.00, *P* for trend 0.039) and atopic sensitisation (OR<sub>adj</sub>, highest vs. lowest quartile, 0.78, 95% CI 0.61–1.00, *P* for trend 0.041). No consistent dose-response relation could be observed for any of the other antioxidants. Milk is a major source of the studied minerals and could cause allergic symptoms. This could result in a falsely protective effect from

Table 2. Mean intake of different dietary antioxidants in relation to potential confounding factors among 8-year-old children in the BAMSE study (N = 2442)

| Potential confounders                            | No. of children | Mean intake of antioxidants |        |                                |        |                              |        |                            |        |                             |        |                        |        |
|--------------------------------------------------|-----------------|-----------------------------|--------|--------------------------------|--------|------------------------------|--------|----------------------------|--------|-----------------------------|--------|------------------------|--------|
|                                                  |                 | Vitamin C mg<br>(Mean ± SD) | P      | α-tocopherol mg<br>(Mean ± SD) | P      | β-carotene mg<br>(Mean ± SD) | P      | Selenium µg<br>(Mean ± SD) | P      | Magnesium mg<br>(Mean ± SD) | P      | Zinc mg<br>(Mean ± SD) | P      |
| All children                                     | 2442            | 98.4 ± 36.9                 |        | 7.1 ± 1.2                      |        | 2.1 ± 1.2                    |        | 35.0 ± 6.3                 |        | 303.1 ± 29.7                |        | 10.3 ± 1.4             |        |
| Sex                                              |                 |                             |        |                                |        |                              |        |                            |        |                             |        |                        |        |
| Boy                                              | 1255            | 95.4 ± 36.7                 | <0.001 | 6.9 ± 1.2                      | <0.001 | 2.0 ± 1.2                    | <0.001 | 34.8 ± 6.2                 | <0.001 | 302.0 ± 28.8                | 0.132  | 10.3 ± 1.3             | 0.496  |
| Girl                                             | 1187            | 101.5 ± 36.9                |        | 7.2 ± 1.2                      |        | 2.2 ± 1.3                    |        | 35.2 ± 6.5                 |        | 304.1 ± 30.5                |        | 10.3 ± 1.4             |        |
| Parental allergic disease                        |                 |                             |        |                                |        |                              |        |                            |        |                             |        |                        |        |
| Yes                                              | 775             | 99.7 ± 37.2                 | 0.218  | 7.0 ± 1.2                      | 0.167  | 2.0 ± 1.2                    | 0.076  | 34.7 ± 6.2                 | 0.076  | 301.8 ± 28.8                | 0.167  | 10.3 ± 1.3             | 0.203  |
| No                                               | 1648            | 97.7 ± 36.8                 |        | 7.1 ± 1.3                      |        | 2.1 ± 1.3                    |        | 35.1 ± 6.4                 |        | 303.6 ± 30.1                |        | 10.3 ± 1.4             |        |
| Parental socioeconomic status*                   |                 |                             |        |                                |        |                              |        |                            |        |                             |        |                        |        |
| Blue-collar                                      | 391             | 95.8 ± 37.0                 | 0.133  | 7.1 ± 1.2                      | 0.096  | 1.7 ± 1.1                    | <0.001 | 35.8 ± 7.1                 | <0.001 | 304.9 ± 30.9                | 0.004  | 10.5 ± 1.4             | 0.048  |
| White-collar                                     | 2044            | 98.8 ± 36.8                 |        | 7.0 ± 1.3                      |        | 2.1 ± 1.3                    |        | 34.8 ± 6.2                 |        | 302.8 ± 29.4                |        | 10.3 ± 1.3             |        |
| Maternal smoking during pregnancy or at baseline |                 |                             |        |                                |        |                              |        |                            |        |                             |        |                        |        |
| Yes                                              | 304             | 98.2 ± 37.8                 | 0.917  | 7.0 ± 1.3                      | 0.141  | 1.8 ± 1.1                    | <0.001 | 3.05 ± 6.2                 | <0.001 | 303.3 ± 31.3                | 0.811  | 10.3 ± 1.3             | 0.616  |
| No                                               | 2136            | 98.4 ± 36.8                 |        | 7.1 ± 1.2                      |        | 2.1 ± 1.3                    |        | 35.0 ± 6.4                 |        | 303.1 ± 29.4                |        | 10.3 ± 1.4             |        |
| Iso-BMI†                                         |                 |                             |        |                                |        |                              |        |                            |        |                             |        |                        |        |
| <25                                              | 1918            | 97.2 ± 36.9                 | 0.002  | 7.1 ± 1.2                      | 0.243  | 2.1 ± 1.2                    | 0.153  | 34.5 ± 6.0                 | <0.001 | 300.2 ± 28.9                | <0.001 | 10.2 ± 1.3             | <0.001 |
| ≥ 25                                             | 524             | 102.8 ± 36.9                |        | 7.0 ± 1.3                      |        | 2.0 ± 1.2                    |        | 36.6 ± 7.2                 |        | 313.6 ± 30.1                |        | 10.7 ± 1.4             |        |
| Vitamin supplements the past 12 months           |                 |                             |        |                                |        |                              |        |                            |        |                             |        |                        |        |
| Yes                                              | 1383            | 98.8 ± 36.8                 | 0.641  | 7.2 ± 1.3                      | <0.001 | 2.0 ± 1.3                    | 0.335  | 34.8 ± 6.2                 | 0.422  | 302.2 ± 30.8                | 0.336  | 10.3 ± 1.4             | 0.026  |
| No                                               | 1026            | 98.1 ± 36.7                 |        | 7.0 ± 1.2                      |        | 2.1 ± 1.2                    |        | 35.0 ± 6.4                 |        | 303.4 ± 28.6                |        | 10.4 ± 1.3             |        |

\*3<sup>rd</sup> category (consisting of students, unemployed, housewives/men) not shown because of low numbers.†Iso-BMI is an age-adjusted measure of BMI (kg/m<sup>2</sup>) used up to 18 years of age.

Table 3. Associations between intake of different dietary antioxidants and current allergic disease among 8-year-old children in the BAMSE cohort (N = 2442)

|                                                                                                                                                                                     | Quartiles of intake* |     |          |                  |          |                  |           |                  | P for trend |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----|----------|------------------|----------|------------------|-----------|------------------|-------------|--|
|                                                                                                                                                                                     | 1                    |     | 2        |                  | 3        |                  | 4         |                  |             |  |
|                                                                                                                                                                                     | n/N†                 | Ref | n/N†     | OR (95% CI)‡     | n/N†     | OR (95% CI)‡     | n/N†      | OR (95% CI)‡     |             |  |
| a) Association between selected vitamins and current allergic disease. Children who reported food-related allergic symptoms from fruit or vegetables were excluded (n = 237)        |                      |     |          |                  |          |                  |           |                  |             |  |
| Vitamin C intake                                                                                                                                                                    |                      |     |          |                  |          |                  |           |                  |             |  |
| Mean intake/day ± 1 SD                                                                                                                                                              | 57±11                |     | 83±7     |                  | 106±7    |                  | 147±28    |                  |             |  |
| All children§                                                                                                                                                                       | 592                  |     | 597      |                  | 598      |                  | 595       |                  |             |  |
| Rhinitis                                                                                                                                                                            | 106/591              | 1.0 | 89/597   | 0.81 (0.60–1.11) | 91/596   | 0.85 (0.62–1.17) | 82/592    | 0.75 (0.54–1.03) | 0.108       |  |
| Asthma                                                                                                                                                                              | 50/588               | 1.0 | 39/594   | 0.77 (0.50–1.19) | 41/595   | 0.82 (0.53–1.27) | 46/592    | 0.93 (0.61–1.42) | 0.864       |  |
| Eczema                                                                                                                                                                              | 82/578               | 1.0 | 79/580   | 0.75 (0.53–1.04) | 86/582   | 0.79 (0.57–1.10) | 76/579    | 0.81 (0.58–1.12) | 0.275       |  |
| Atopic sensitisation                                                                                                                                                                | 215/588              | 1.0 | 188/593  | 0.81 (0.63–1.03) | 211/590  | 0.98 (0.77–1.25) | 206/589   | 0.94 (0.73–1.19) | 0.960       |  |
| After exclusion§                                                                                                                                                                    |                      |     |          |                  |          |                  |           |                  |             |  |
| Rhinitis                                                                                                                                                                            | 72/525               | 1.0 | 64/543   | 0.86 (0.60–1.23) | 70/542   | 0.97 (0.68–1.40) | 58/532    | 0.80 (0.55–1.17) | 0.349       |  |
| Asthma                                                                                                                                                                              | 29/522               | 1.0 | 30/540   | 1.02 (0.60–1.73) | 33/541   | 1.16 (0.69–1.96) | 33/534    | 1.19 (0.71–2.00) | 0.455       |  |
| Eczema                                                                                                                                                                              | 72/509               | 1.0 | 64/531   | 0.82 (0.57–1.18) | 66/533   | 0.81 (0.56–1.16) | 62/517    | 0.78 (0.54–1.13) | 0.218       |  |
| Atopic sensitisation                                                                                                                                                                | 166/521              | 1.0 | 150/539  | 0.83 (0.64–1.08) | 185/536  | 1.14 (0.88–1.48) | 165/529   | 0.99 (0.76–1.28) | 0.597       |  |
| α-tocopherol intake                                                                                                                                                                 |                      |     |          |                  |          |                  |           |                  |             |  |
| Mean intake/day ± 1 SD                                                                                                                                                              | 5.6±0.5              |     | 6.6±0.2  |                  | 7.4±0.2  |                  | 8.7±0.8   |                  |             |  |
| All children§                                                                                                                                                                       | 596                  |     | 597      |                  | 592      |                  | 597       |                  |             |  |
| Rhinitis                                                                                                                                                                            | 98/595               | 1.0 | 92/597   | 0.95 (0.69–1.30) | 100/591  | 1.10 (0.80–1.50) | 78/593    | 0.83 (0.60–1.16) | 0.420       |  |
| Asthma                                                                                                                                                                              | 51/593               | 1.0 | 37/593   | 0.73 (0.47–1.13) | 46/588   | 0.99 (0.65–1.52) | 42/595    | 0.90 (0.58–1.39) | 0.903       |  |
| Eczema                                                                                                                                                                              | 79/580               | 1.0 | 85/579   | 1.07 (0.77–1.50) | 81/578   | 1.02 (0.73–1.43) | 78/582    | 0.97 (0.69–1.36) | 0.781       |  |
| Atopic sensitisation                                                                                                                                                                | 212/591              | 1.0 | 185/593  | 0.82 (0.64–1.05) | 212/586  | 1.06 (0.83–1.35) | 211/590   | 1.06 (0.83–1.35) | 0.301       |  |
| After exclusion§                                                                                                                                                                    |                      |     |          |                  |          |                  |           |                  |             |  |
| Rhinitis                                                                                                                                                                            | 58/523               | 1.0 | 63/535   | 1.12 (0.76–1.64) | 78/539   | 1.44 (1.00–2.09) | 65/545    | 1.18 (0.80–1.73) | 0.268       |  |
| Asthma                                                                                                                                                                              | 29/522               | 1.0 | 22/532   | 0.77 (0.43–1.36) | 36/536   | 1.37 (0.82–2.29) | 38/547    | 1.45 (0.87–2.41) | 0.049       |  |
| Eczema                                                                                                                                                                              | 61/509               | 1.0 | 66/521   | 1.05 (0.72–1.53) | 73/528   | 1.16 (0.80–1.67) | 64/539    | 0.97 (0.67–1.42) | 0.955       |  |
| Atopic sensitisation                                                                                                                                                                | 159/519              | 1.0 | 148/531  | 0.89 (0.68–1.17) | 178/534  | 1.18 (0.90–1.53) | 181/541   | 1.22 (0.94–1.58) | 0.048       |  |
| β-carotene intake                                                                                                                                                                   |                      |     |          |                  |          |                  |           |                  |             |  |
| Mean intake/day ± 1 SD                                                                                                                                                              | 767±206              |     | 1447±225 |                  | 2324±281 |                  | 3707±1072 |                  |             |  |
| All children§                                                                                                                                                                       | 598                  |     | 594      |                  | 599      |                  | 591       |                  |             |  |
| Rhinitis                                                                                                                                                                            | 114/595              | 1.0 | 87/594   | 0.73 (0.53–0.99) | 90/599   | 0.78 (0.57–1.06) | 77/588    | 0.67 (0.49–0.93) | 0.035       |  |
| Asthma                                                                                                                                                                              | 55/592               | 1.0 | 41/592   | 0.75 (0.49–1.14) | 40/594   | 0.78 (0.51–1.21) | 40/591    | 0.81 (0.53–1.25) | 0.354       |  |
| Eczema                                                                                                                                                                              | 91/583               | 1.0 | 81/579   | 0.88 (0.64–1.22) | 73/583   | 0.78 (0.56–1.10) | 78/574    | 0.86 (0.62–1.20) | 0.082       |  |
| Atopic sensitisation                                                                                                                                                                | 229/596              | 1.0 | 192/589  | 0.78 (0.62–1.00) | 201/591  | 0.85 (0.67–1.08) | 198/584   | 0.86 (0.67–1.10) | 0.422       |  |
| After exclusion§                                                                                                                                                                    |                      |     |          |                  |          |                  |           |                  |             |  |
| Rhinitis                                                                                                                                                                            | 71/515               | 1.0 | 67/544   | 0.87 (0.61–1.25) | 69/554   | 0.91 (0.64–1.31) | 57/529    | 0.78 (0.54–1.15) | 0.270       |  |
| Asthma                                                                                                                                                                              | 32/512               | 1.0 | 33/543   | 0.99 (0.60–1.64) | 34/550   | 1.10 (0.66–1.82) | 26/532    | 0.90 (0.52–1.54) | 0.774       |  |
| Eczema                                                                                                                                                                              | 71/504               | 1.0 | 67/531   | 0.87 (0.61–1.25) | 62/539   | 0.79 (0.54–1.14) | 64/516    | 0.87 (0.60–1.26) | 0.434       |  |
| Atopic sensitisation                                                                                                                                                                | 169/515              | 1.0 | 165/539  | 0.90 (0.70–1.18) | 171/546  | 0.95 (0.73–1.24) | 161/525   | 0.94 (0.72–1.23) | 0.138       |  |
| b) Association between selected minerals and current allergic disease. Children who reported food-related allergic symptoms from fruits, vegetables or milk were excluded (n = 285) |                      |     |          |                  |          |                  |           |                  |             |  |
| Selenium intake                                                                                                                                                                     |                      |     |          |                  |          |                  |           |                  |             |  |
| Mean intake/day ± 1 SD                                                                                                                                                              | 27±3                 |     | 33±1     |                  | 37±1     |                  | 43±4      |                  |             |  |
| All children§                                                                                                                                                                       | 597                  |     | 596      |                  | 597      |                  | 592       |                  |             |  |
| Rhinitis                                                                                                                                                                            | 93/595               | 1.0 | 75/594   | 0.76 (0.54–1.06) | 107/597  | 1.19 (0.87–1.62) | 93/590    | 1.02 (0.74–1.41) | 0.387       |  |
| Asthma                                                                                                                                                                              | 52/593               | 1.0 | 32/590   | 0.58 (0.37–0.93) | 44/596   | 0.80 (0.52–1.22) | 48/590    | 0.90 (0.59–1.36) | 0.849       |  |
| Eczema                                                                                                                                                                              | 93/584               | 1.0 | 72/581   | 0.75 (0.54–0.95) | 80/579   | 0.83 (0.60–1.15) | 78/575    | 0.82 (0.59–1.14) | 0.303       |  |
| Atopic sensitisation                                                                                                                                                                | 224/593              | 1.0 | 187/585  | 0.76 (0.60–0.97) | 203/594  | 0.85 (0.67–1.08) | 206/588   | 0.89 (0.70–1.13) | 0.461       |  |
| After exclusion§                                                                                                                                                                    |                      |     |          |                  |          |                  |           |                  |             |  |
| Rhinitis                                                                                                                                                                            | 63/502               | 1.0 | 56/539   | 0.78 (0.53–1.14) | 70/532   | 1.08 (0.75–1.56) | 62/522    | 0.96 (0.65–1.40) | 0.831       |  |
| Asthma                                                                                                                                                                              | 34/501               | 1.0 | 26/538   | 0.69 (0.41–1.18) | 25/531   | 0.66 (0.39–1.13) | 34/521    | 0.95 (0.58–1.56) | 0.819       |  |
| Eczema                                                                                                                                                                              | 68/492               | 1.0 | 59/528   | 0.79 (0.54–1.14) | 63/514   | 0.85 (0.59–1.23) | 61/509    | 0.84 (0.58–1.22) | 0.470       |  |
| Atopic sensitisation                                                                                                                                                                | 169/500              | 1.0 | 159/530  | 0.83 (0.63–1.08) | 156/530  | 0.81 (0.62–1.06) | 160/519   | 0.87 (0.66–1.13) | 0.302       |  |

(continued)

Table 3 (continued)

|                                    | Quartiles of intake* |     |                  |                          |                  |                          |                  |                          | P for trend |
|------------------------------------|----------------------|-----|------------------|--------------------------|------------------|--------------------------|------------------|--------------------------|-------------|
|                                    | 1                    | Ref | 2                | OR (95% CI) <sup>‡</sup> | 3                | OR (95% CI) <sup>‡</sup> | 4                | OR (95% CI) <sup>‡</sup> |             |
|                                    | n/N <sup>†</sup>     |     | n/N <sup>†</sup> |                          | n/N <sup>†</sup> |                          | n/N <sup>†</sup> |                          |             |
| <b>Magnesium intake</b>            |                      |     |                  |                          |                  |                          |                  |                          |             |
| Mean intake/day $\pm$ 1 SD         | 266 $\pm$ 15         |     | 293 $\pm$ 6      |                          | 312 $\pm$ 5      |                          | 341 $\pm$ 17     |                          |             |
| All children <sup>§</sup>          | 599                  |     | 600              |                          | 595              |                          | 588              |                          |             |
| Rhinitis                           | 91/598               | 1.0 | 103/599          | 1.15 (0.84–1.58)         | 86/593           | 0.94 (0.68–1.30)         | 88/586           | 1.02 (0.73–1.41)         | 0.806       |
| Asthma                             | 57/595               | 1.0 | 42/596           | 0.71 (0.46–1.08)         | 37/592           | 0.61 (0.40–0.95)         | 40/586           | 0.65 (0.42–1.00)         | 0.039       |
| Eczema                             | 95/584               | 1.0 | 78/586           | 0.80 (0.57–1.11)         | 68/580           | 0.68 (0.48–0.95)         | 82/569           | 0.83 (0.60–1.16)         | 0.223       |
| Atopic sensitisation               | 231/589              | 1.0 | 200/597          | 0.77 (0.60–0.98)         | 191/590          | 0.73 (0.57–0.93)         | 198/584          | 0.78 (0.61–1.00)         | 0.041       |
| <i>After exclusion<sup>§</sup></i> |                      |     |                  |                          |                  |                          |                  |                          |             |
| Rhinitis                           | 59/506               | 1.0 | 69/526           | 1.17 (0.80–1.70)         | 56/533           | 0.87 (0.59–1.29)         | 67/530           | 1.16 (0.79–1.71)         | 0.710       |
| Asthma                             | 40/505               | 1.0 | 24/524           | 0.55 (0.32–0.93)         | 28/532           | 0.62 (0.37–1.02)         | 27/530           | 0.58 (0.35–0.98)         | 0.056       |
| Eczema                             | 78/495               | 1.0 | 57/514           | 0.68 (0.47–0.99)         | 51/520           | 0.59 (0.40–0.86)         | 65/514           | 0.76 (0.53–1.10)         | 0.107       |
| Atopic sensitisation               | 174/498              | 1.0 | 152/524          | 0.75 (0.58–0.98)         | 157/529          | 0.77 (0.59–1.01)         | 161/528          | 0.81 (0.62–1.06)         | 0.145       |
| <b>Zinc intake</b>                 |                      |     |                  |                          |                  |                          |                  |                          |             |
| Mean intake/day $\pm$ 1 SD         | 8.7 $\pm$ 0.6        |     | 9.9 $\pm$ 0.3    |                          | 10.7 $\pm$ 0.2   |                          | 12.0 $\pm$ 0.9   |                          |             |
| All children <sup>§</sup>          | 596                  |     | 601              |                          | 597              |                          | 588              |                          |             |
| Rhinitis                           | 94/592               | 1.0 | 78/601           | 0.81 (0.58–1.13)         | 92/597           | 0.95 (0.69–1.31)         | 104/586          | 1.17 (0.86–1.60)         | 0.240       |
| Asthma                             | 45/590               | 1.0 | 30/599           | 0.65 (0.40–1.06)         | 51/593           | 1.10 (0.72–1.68)         | 50/587           | 1.08 (0.70–1.66)         | 0.363       |
| Eczema                             | 98/579               | 1.0 | 74/583           | 0.73 (0.52–1.01)         | 64/587           | 0.60 (0.42–0.84)         | 87/570           | 0.89 (0.64–1.22)         | 0.326       |
| Atopic sensitisation               | 221/590              | 1.0 | 185/597          | 0.76 (0.60–0.97)         | 198/590          | 0.82 (0.65–1.05)         | 216/583          | 0.98 (0.77–1.24)         | 0.968       |
| <i>After exclusion<sup>§</sup></i> |                      |     |                  |                          |                  |                          |                  |                          |             |
| Rhinitis                           | 60/496               | 1.0 | 61/550           | 0.93 (0.64–1.37)         | 65/534           | 1.00 (0.68–1.46)         | 65/514           | 1.09 (0.74–1.59)         | 0.616       |
| Asthma                             | 35/498               | 1.0 | 19/548           | 0.48 (0.27–0.85)         | 36/531           | 0.93 (0.57–1.51)         | 29/514           | 0.76 (0.45–1.27)         | 0.636       |
| Eczema                             | 75/485               | 1.0 | 59/533           | 0.69 (0.48–1.00)         | 49/526           | 0.56 (0.38–0.82)         | 68/499           | 0.88 (0.61–1.27)         | 0.379       |
| Atopic sensitisation               | 168/495              | 1.0 | 154/547          | 0.77 (0.59–1.00)         | 160/527          | 0.82 (0.63–1.07)         | 162/510          | 0.90 (0.69–1.17)         | 0.526       |

\*Energy-adjusted nutrients.

<sup>†</sup>n/N = number of cases/Total number of children.<sup>‡</sup>Adjusted for sex, parental socioeconomic status, maternal smoking during pregnancy and/or at baseline, iso-BMI, parental history of allergic disease and vitamin supplementation.<sup>§</sup>All children = 2442. Exclusions were made of children who reported food-related allergic symptoms to specific fruits, vegetables, or milk.

these minerals in relation to allergic disease. Therefore, in addition to the exclusion described above, children who reported allergic symptoms from milk or avoided milk due to such symptoms (in total 285 children), were also excluded in the analyses of mineral intake. After exclusion, the inverse association observed between magnesium intake and asthma remained (OR<sub>adj</sub>, highest vs. lowest quartile, 0.58, 95% CI 0.35–0.98, P for trend 0.056). Moreover, the inverse associations observed in the lower quartiles between intake of magnesium and zinc in relation to allergy remained after the exclusion.

To distinguish between IgE-mediated and non-IgE-mediated allergic disease, each outcome was combined with atopic sensitisation to common food and inhalant allergens. Tables 4a–b shows the association between antioxidant intake and current allergic disease combined with atopic sensitisation at age 8 years. Results are presented for the highest vs. the lowest tertile of intake. Among the vitamins, (Table 4a) an inverse association was observed between intake of vitamin C and

eczema (OR<sub>adj</sub>, highest vs. lowest tertile, 0.62, 95% CI 0.39–1.00, P for trend 0.092), and  $\beta$ -carotene and rhinitis (OR<sub>adj</sub>, highest vs. lowest tertile, 0.63, 95% CI 0.43–0.92, P for trend 0.033), both in combination with atopic sensitisation. After exclusion of children who avoided or reported allergic symptoms from certain fruits and vegetables, only the association between vitamin C and IgE-mediated eczema remained (OR<sub>adj</sub>, highest vs. lowest tertile, 0.56, 95% CI 0.31–1.00, P for trend 0.150). Among the minerals (Table 4b) magnesium intake was inversely related to asthma (OR<sub>adj</sub>, highest vs. lowest tertile, 0.52, 95% CI 0.31–0.87, P for trend 0.003) and eczema (OR<sub>adj</sub>, highest vs. lowest tertile, 0.53, 95% CI 0.32–0.87, P for trend 0.008), both combined with atopic sensitisation. When children who avoided or reported symptoms from fruits, vegetables or milk were excluded, these inverse associations remained for magnesium intake in relation to IgE-mediated asthma (OR<sub>adj</sub>, highest vs. lowest tertile, 0.46, 95% CI 0.24–0.89, P for trend 0.010) and IgE-mediated

**Table 4.** Associations between intake of different dietary antioxidants and current allergic disease combined with atopic sensitisation among 8-year-old children in the BAMSE cohort (N = 2442)

|                                                                                                                                                                                     | The highest vs. the lowest tertile*           |                          |             |                                                    |                          |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------|-------------|----------------------------------------------------|--------------------------|-------------|
|                                                                                                                                                                                     | n/N <sup>†</sup><br>All children <sup>§</sup> | OR (95% CI) <sup>‡</sup> | P for trend | n/N <sup>†</sup><br>Children excluded <sup>§</sup> | OR (95% CI) <sup>‡</sup> | P for trend |
| a) Associations between selected vitamins and current allergic disease. Children who avoided or reported allergic symptoms from fruits or vegetables were excluded a) (n = 237)     |                                               |                          |             |                                                    |                          |             |
| <i>Vitamin C</i>                                                                                                                                                                    |                                               |                          |             |                                                    |                          |             |
| Rhinitis and no sens                                                                                                                                                                | 33/782                                        | 0.80 (0.46–1.40)         | 0.655       | 27/703                                             | 0.74 (0.41–1.35)         | 0.304       |
| Rhinitis and sens                                                                                                                                                                   | 74/782                                        | 0.71 (0.48–1.04)         | 0.109       | 49/703                                             | 0.79 (0.49–1.28)         | 0.467       |
| Asthma and no sens                                                                                                                                                                  | 20/782                                        | 0.77 (0.36–1.64)         | 0.682       | 18/705                                             | 0.82 (0.36–1.87)         | 0.742       |
| Asthma and sens                                                                                                                                                                     | 43/782                                        | 0.94 (0.56–1.57)         | 0.980       | 30/705                                             | 1.41 (0.71–2.77)         | 0.398       |
| Eczema and no sens                                                                                                                                                                  | 77/767                                        | 1.02 (0.65–1.61)         | 0.766       | 70/689                                             | 1.00 (0.62–1.61)         | 0.366       |
| Eczema and sens                                                                                                                                                                     | 54/767                                        | 0.62 (0.39–1.00)         | 0.092       | 35/689                                             | 0.56 (0.31–1.00)         | 0.150       |
| <i>α-tocopherol</i>                                                                                                                                                                 |                                               |                          |             |                                                    |                          |             |
| Rhinitis and no sens                                                                                                                                                                | 43/782                                        | 1.50 (0.82–2.73)         | 0.159       | 41/721                                             | 1.69 (0.90–3.18)         | 0.201       |
| Rhinitis and sens                                                                                                                                                                   | 65/782                                        | 0.72 (0.48–1.06)         | 0.215       | 51/721                                             | 1.06 (0.65–1.71)         | 0.751       |
| Asthma and no sens                                                                                                                                                                  | 17/782                                        | 1.03 (0.48–2.20)         | 0.769       | 17/721                                             | 1.46 (0.63–3.35)         | 0.178       |
| Asthma and sens                                                                                                                                                                     | 34/782                                        | 0.89 (0.53–1.51)         | 0.946       | 30/721                                             | 1.61 (0.85–3.03)         | 0.215       |
| Eczema and no sens                                                                                                                                                                  | 73/772                                        | 0.94 (0.59–1.51)         | 0.786       | 66/712                                             | 0.85 (0.51–1.40)         | 0.300       |
| Eczema and sens                                                                                                                                                                     | 60/772                                        | 1.04 (0.64–1.68)         | 0.787       | 49/712                                             | 1.29 (0.74–2.27)         | 0.404       |
| <i>β-carotene</i>                                                                                                                                                                   |                                               |                          |             |                                                    |                          |             |
| Rhinitis and no sens                                                                                                                                                                | 34/776                                        | 0.74 (0.42–1.27)         | 0.551       | 28/701                                             | 0.66 (0.36–1.22)         | 0.263       |
| Rhinitis and sens                                                                                                                                                                   | 78/776                                        | 0.63 (0.43–0.92)         | 0.033       | 54/701                                             | 0.83 (0.51–1.33)         | 0.488       |
| Asthma and no sens                                                                                                                                                                  | 18/778                                        | 0.78 (0.37–1.65)         | 0.821       | 15/703                                             | 0.87 (0.38–2.00)         | 0.965       |
| Asthma and sens                                                                                                                                                                     | 34/778                                        | 0.75 (0.44–1.27)         | 0.324       | 20/703                                             | 0.83 (0.40–1.70)         | 0.640       |
| Eczema and no sens                                                                                                                                                                  | 73/756                                        | 0.98 (0.62–1.54)         | 0.785       | 65/683                                             | 0.92 (0.56–1.49)         | 0.594       |
| Eczema and sens                                                                                                                                                                     | 43/756                                        | 0.68 (0.42–1.10)         | 0.081       | 33/683                                             | 0.75 (0.43–1.32)         | 0.143       |
| b) Association between selected minerals and current allergic disease. Children who reported food-related allergic symptoms from fruits, vegetables or milk were excluded (n = 285) |                                               |                          |             |                                                    |                          |             |
| <i>Selenium</i>                                                                                                                                                                     |                                               |                          |             |                                                    |                          |             |
| Rhinitis and no sens                                                                                                                                                                | 39/781                                        | 1.04 (0.60–1.82)         | 0.693       | 34/699                                             | 1.24 (0.66–2.34)         | 0.380       |
| Rhinitis and sens                                                                                                                                                                   | 91/781                                        | 0.97 (0.66–1.42)         | 0.607       | 53/699                                             | 0.82 (0.51–1.31)         | 0.619       |
| Asthma and no sens                                                                                                                                                                  | 23/780                                        | 1.25 (0.61–2.54)         | 0.380       | 18/697                                             | 1.10 (0.51–2.41)         | 0.617       |
| Asthma and sens                                                                                                                                                                     | 44/780                                        | 0.76 (0.45–1.28)         | 0.461       | 26/697                                             | 0.86 (0.45–1.64)         | 0.523       |
| Eczema and no sens                                                                                                                                                                  | 68/763                                        | 0.74 (0.47–1.17)         | 0.203       | 62/681                                             | 0.82 (0.50–1.34)         | 0.461       |
| Eczema and sens                                                                                                                                                                     | 59/763                                        | 0.84 (0.53–1.34)         | 0.653       | 40/681                                             | 0.83 (0.47–1.47)         | 0.604       |
| <i>Magnesium</i>                                                                                                                                                                    |                                               |                          |             |                                                    |                          |             |
| Rhinitis and no sens                                                                                                                                                                | 38/777                                        | 1.26 (0.70–2.29)         | 0.561       | 33/699                                             | 1.80 (0.91–3.54)         | 0.196       |
| Rhinitis and sens                                                                                                                                                                   | 77/777                                        | 0.85 (0.58–1.26)         | 0.254       | 52/699                                             | 0.90 (0.57–1.44)         | 0.461       |
| Asthma and no sens                                                                                                                                                                  | 20/775                                        | 1.12 (0.48–2.62)         | 0.722       | 17/697                                             | 0.90 (0.37–2.19)         | 0.967       |
| Asthma and sens                                                                                                                                                                     | 32/775                                        | 0.52 (0.31–0.87)         | 0.003       | 20/697                                             | 0.46 (0.24–0.89)         | 0.010       |
| Eczema and no sens                                                                                                                                                                  | 88/760                                        | 1.11 (0.71–1.72)         | 0.852       | 76/682                                             | 0.99 (0.61–1.59)         | 0.688       |
| Eczema and sens                                                                                                                                                                     | 51/760                                        | 0.53 (0.32–0.87)         | 0.008       | 37/682                                             | 0.48 (0.27–0.85)         | 0.014       |
| <i>Zinc</i>                                                                                                                                                                         |                                               |                          |             |                                                    |                          |             |
| Rhinitis and no sens                                                                                                                                                                | 33/778                                        | 0.90 (0.51–1.60)         | 0.392       | 28/686                                             | 1.13 (0.59–2.18)         | 0.515       |
| Rhinitis and sens                                                                                                                                                                   | 92/778                                        | 1.23 (0.85–1.78)         | 0.113       | 51/686                                             | 1.03 (0.65–1.63)         | 0.924       |
| Asthma and no sens                                                                                                                                                                  | 23/777                                        | 1.50 (0.64–3.54)         | 0.964       | 20/684                                             | 1.24 (0.49–3.16)         | 0.306       |
| Asthma and sens                                                                                                                                                                     | 45/777                                        | 1.00 (0.61–1.66)         | 0.026       | 23/684                                             | 0.62 (0.33–1.17)         | 0.163       |
| Eczema and no sens                                                                                                                                                                  | 71/772                                        | 0.76 (0.49–1.18)         | 0.046       | 61/670                                             | 0.81 (0.50–1.30)         | 0.285       |
| Eczema and sens                                                                                                                                                                     | 68/772                                        | 1.01 (0.64–1.60)         | 0.101       | 47/670                                             | 0.93 (0.54–1.59)         | 0.771       |

\*Energy-adjusted nutrients. The reference group consists of non-sensitized children without any allergic symptoms/diagnoses.

<sup>†</sup>n/N = number of cases/Total number of children.<sup>‡</sup>Adjusted for sex, maternal smoking during pregnancy and/or at baseline, parental history of allergic disease, parental socioeconomic status, iso-BMI, and vitamin supplementation.<sup>§</sup>All children, N = 2442. Children who avoided or reported allergic symptoms from fruits, vegetables, or milk were excluded from the analyses.

eczema ( $OR_{adj}$ , highest vs. lowest tertile, 0.48, 95% CI 0.27–0.85,  $P$  for trend 0.014).

In our study, 40% of the children used vitamin supplements during the past 12 months. To further avoid confounding, we performed the analyses described above in non-users of vitamin supplements, with comparable results, although with wider confidence intervals (data not shown).

## Discussion

In this study on 2442 8-year-old boys and girls in Sweden, we observed an inverse association between high intake of  $\beta$ -carotene and rhinitis. Furthermore, inverse associations were also seen between high magnesium intake and asthma, as well as atopic sensitisation. To evaluate potential disease-related modification of diet, children who avoided or reported allergic symptoms to fruits, vegetables, and (in analyses of minerals) milk, were excluded from the analyses. After exclusion, the association between  $\beta$ -carotene and rhinitis was weaker and became non-significant, whereas the association between magnesium intake and asthma remained statistically significant. Moreover, magnesium intake was inversely associated with asthma and eczema when combined with atopic sensitisation. An inverse association was also observed for intake of vitamin C and eczema combined with atopic sensitisation. Our findings indicate that disease-related modification of diet may affect the nutrient intake, particularly for antioxidants originating from foods that might cross-react with birch-pollen, such as carrots and apples.

The strengths of the current study include the large number of participants, detailed information on food intake, and detailed outcome assessment including information on atopic sensitisation measured in serum. Of the children in the baseline cohort, 60% were included in the analyses of antioxidants and allergic disease at age 8 years. The distribution of sex, parental allergic disease, and socioeconomic status among these children was comparable to the distribution among all children in the cohort. The prevalence of asthma, rhinitis, and eczema was somewhat higher among the included children, but did not differ significantly. The intake of antioxidants was based on total food consumption assessed by a FFQ. Misclassification of exposure could affect our results, because parents and children might find it difficult to remember the frequency of food consumption during the last year. However, validity of FFQ's has been proven to be relatively good [21, 22]. The FFQ used in this study has been validated using Spearman correlation in adults by comparing 14 repeated 24-h-recalls with correlation coefficients for vitamin C 0.81,  $\alpha$ -tocopherol 0.57,  $\beta$ -carotene 0.51, selenium 0.75, magnesium 0.73, and zinc

0.56 [20]. Moreover, if misclassification of exposure is non-differential between children with allergy and other children, it would primarily lead to underestimation of the true association. In addition, the intake of antioxidants was comparable to that observed in a Swedish national survey [10]. Girls consumed more vitamin C,  $\alpha$ -tocopherol, and  $\beta$ -carotene than boys, whereas no difference was seen for consumption of minerals. This could refer to the consumption of fruits and vegetables that has previously been reported to be significantly higher among girls in this cohort [13]. Although our analyses would have been strengthened by blood biomarkers of antioxidant intake, this was not available for the subjects in our study.

Use of vitamin supplementation was not included in the estimation of antioxidant intake. The use of vitamin supplements was about 40% in this group of 8-year-olds, with multivitamins as the pre-dominant type [23]. All analyses were adjusted for use of vitamin supplements. Moreover, when we confined our analyses to children who did not use vitamin supplements, comparable results were obtained. Antioxidants, and other sources with antioxidative capacity, may be added to foods as preservatives. For example, Ascorbic acid added to a food (e.g. jam) will contribute to the food's vitamin C level and therefore be included in the food composition database. In contrast, the antioxidative effect of sulfites (which is added to, for example, dried fruit) will not be included. However, the effect of potential confounding of preservatives on the association between antioxidants and allergic disease is likely to be small.

Although we performed our analyses in a prospective cohort, the information on both antioxidant intake and allergic symptoms was collected at age 8 years. This cross-sectional design is a major limitation of the study and it is important that the results are interpreted within this context. Moreover, given the large number of comparisons made in this study, some of our statistically significant findings may have been due to chance. Disease-related modification of diet (reverse causation), i.e. that children changed their diet due to the allergic disease, might affect our results [13]. We examined the potential effects of this bias by excluding children who reported food-related allergic symptoms from specific fruits, vegetables, and (in the analyses of minerals) milk, or who avoided these food items due to allergic symptoms. After this, the results of  $\beta$ -carotene intake in association with rhinitis were no longer significant, whereas the association between magnesium intake and asthma remained. Children with allergic disease may modify their diet for several reasons [13], for example, due to allergic symptoms caused by cross-reactivity between specific foods (such as apples and carrots) and inhalant allergens [13, 24]. Over 50% of the  $\beta$ -carotene

is derived from carrots, whereas about 20% of the magnesium comes from milk intake. Thus, different antioxidants may be differently sensible to reverse causation depending on how many foods they are derived from.

Before exclusion of children, we observed an inverse association between  $\beta$ -carotene intake and rhinitis. These results are consistent with previous studies in children that did not account for disease-related modification of diet. Results from a study among British 5-year-olds showed that  $\beta$ -carotene intake was associated with a reduced risk of allergic sensitisation at 5 and 8 years of age [4]. Similarly, intake of  $\beta$ -carotene was inversely associated with atopic dermatitis in 5-year-old Korean children [8]. No association was observed between dietary intake of  $\beta$ -carotene and asthma outcomes in a recent meta-analysis [25]. In a German Case-control study on adults,  $\beta$ -carotene intake was associated with a higher prevalence of hay fever [26]. Disease-related modification of diet was not considered in any of the previous studies on antioxidant intake and allergic disease.

Our finding of an inverse association between magnesium intake and asthma was comparable to the results reported from a cross-sectional study among 12-year-old children from Saudi Arabia where low intake of magnesium was related to wheezy illness [6]. Moreover, low magnesium intake has been associated with decreased lung volumes and flows in American teenagers, especially in asthmatics [27], whereas a low dietary magnesium intake among adults was associated with bronchial hyper reactivity [28]. In addition, a recent Dutch birth cohort study observed that asthma was less common in children with high serum magnesium levels

[29]. In contrast, some studies show no association between magnesium intake and asthma [30, 31]. A double-blind random controlled trial that included 16 weeks of supplementation with vitamin C and magnesium to adult asthmatics gave no evidence of beneficial effects of any supplement on any outcome measure of asthma control [32]. Despite this, magnesium intake may have a beneficial effect on asthma due to its relaxing effect on bronchial smooth muscle function [3, 27].

In summary, diet modification due to allergy may affect the antioxidant intake, especially if the antioxidants originate from foods that are cross-reacting with birch-pollen. This needs to be considered when investigating the relationship between diet and allergic disease. In this study, magnesium intake seems to have a protective effect on childhood asthma, even after consideration of reverse causation.

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