Fruit, vegetable and dietary antioxidant intake in school age, respiratory health up to young adulthood

Emmanouela Sdona1 | Sandra Ekström1,2 | Niklas Andersson1 | Jenny Hallberg3,4 | Susanne Rautiainen5,6,7 | Niclas Håkansson1 | Alicja Wolk1,8 | Inger Kull3,4 | Erik Melén1,3,4 | Anna Bergström1,2

1Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
2Centre for Occupational and Environmental Medicine, Stockholm, Sweden
3Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
4Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden
5Global and Sexual Health, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
6Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA
7Astrid Lindgrens Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
8Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Abstract

Background: Dietary antioxidants may protect the lung against oxidative damage and prevent chronic respiratory disease. We aimed to investigate fruit, vegetable and antioxidant intake (measured as total antioxidant capacity, TAC) at age 8 years in relation to asthma and lung function up to 24 years.

Methods: In this study of 2506 participants from a Swedish birth cohort, diet was assessed using food frequency questionnaires. Information on asthma was collected by questionnaires, and lung function was measured by spirometry at ages 8, 16 and 24 years. Generalized estimating equations and mixed effect models were used to assess overall, age- and sex-specific associations.

Results: After adjustment for confounders, a higher fruit intake at age 8 years was associated with a tendency to reduced odds of prevalent asthma (T3 vs. T1, OR 0.78; 95% CI 0.60–1.01, p-trend 0.083), with reduced odds of incident asthma and increased odds of remittent asthma (≥median, OR 0.76; 95% CI 0.58–0.99 and OR 1.60; 95% CI 1.05–2.42, respectively) up to 24 years. Comparable, but non-significant, odds ratios were observed in analyses of long-term fruit intake (mean intake at ages 8 and 16 years). Generalized estimating equations and mixed effect models were used to assess overall, age- and sex-specific associations.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. Clinical & Experimental Allergy published by John Wiley & Sons Ltd.
**Introduction**

Asthma is a common chronic respiratory disease affecting both children and adults. Asthma usually starts in childhood, and although some outgrow their disease, a large proportion will suffer from lifelong symptoms, reduced quality of life and long-term lung function deficits.\(^1\)\(^,\)\(^2\) However, asthma may also debut in adulthood, and while it is more common among males in early childhood, it becomes more common among females after puberty.\(^3\)

Several epidemiological studies have investigated the potential modulatory effect of diet on respiratory health and suggested that diets rich in antioxidants may protect the lung against oxidative damage and prevent chronic respiratory disease.\(^4\)\(\text{-}^6\) Most longitudinal studies have focused on maternal exposure during pregnancy, reporting lower risk of wheeze or asthma or improved lung function in the offspring.\(^7\)\(\text{-}^9\) Fewer studies have examined antioxidant intake during childhood. A study from the Dutch PIAMA birth cohort found inverse associations between childhood fruit intake and asthma symptoms up to age 8 years,\(^10\) and similar results were observed in a Japanese cohort followed from age 7 to 10 years for the onset...
of respiratory allergic symptoms. Furthermore, although there is some support for an association between high fruit intake and improved lung function in young adulthood from cross-sectional studies, there is a lack of prospective studies on antioxidant intake in childhood with follow-up beyond school age.

Since single antioxidants may not reflect the total antioxidant power of diet, total antioxidant capacity (TAC) has been used as a cumulative measure of antioxidants consumed in the whole diet and as a proxy to describe overall diet quality. Previous studies from the Swedish BAMSE birth cohort have shown that increased TAC in school age may be associated with reduced risk of allergic asthma up to adolescence, as well as improved lung function development among children with asthma. However, it is still unclear if the protective effect of antioxidant intake on asthma and lung function extends beyond childhood.

The aim of this study was to investigate the association of fruit, vegetable and antioxidant intake measured as TAC, at age 8 years with repeated measures of asthma and lung function up to age 24 years.

2 | METHODS

2.1 | Study population and study design

The study was conducted within the ongoing population-based birth cohort BAMSE, to which 4089 newborn children (75% of eligible population) were recruited from 1994 to 1996 from predefined areas of Stockholm, Sweden. When the children were on average 2 months old (baseline), parents completed questionnaires on background factors. Follow-up questionnaires on symptoms of allergic diseases and selected exposures were sent out and answered at 1, 2, 4, 8, 12, 16 and 24 years of age. At ages 4, 8, 16 and 24 years, participants were invited to clinical examinations, which included anthropometric measurements, lung function testing and blood sampling using standardized methods. Sera have been analysed for specific IgE to common inhalant and food allergens. Diet was assessed by food frequency questionnaires (FFQs) at ages 8, 16 and 24 years. In total, at the 24-year follow-up, 3064 (75% of original cohort) young adults answered the questionnaire, 2270 (56%) participated in the clinical examination, and 2234 (55%) provided blood samples.

The study was approved by the Ethics Committee of Karolinska Institute, Stockholm, Sweden, and written informed consent was obtained from parents up to 8 years and participants at 16 and 24 years of age.

2.2 | Assessment of diet

Diet at age 8 years was assessed using a FFQ including 98 foods and beverages frequently consumed in Sweden. The FFQ was answered by a parent (57%) or by a parent together with the child (40%) and included five fruit items (oranges/citrus fruits, apples/pears, bananas, other fruits and berries) and 13 vegetable items (onion/leek, white/red cabbage, cauliflower, broccoli/brussels sprouts, spinach/kale, rutabaga/beetroot, green peas, pea soup/puree, brown/white beans/soya lentils, lettuce, tomatoes, cucumbers and carrots). Participants indicated how often, on average, they had consumed each type of food item during the past 12 months using 10 pre-specified response categories ranging from "never" to "six times/day". The consumption frequencies were converted into average daily consumption and summarized as fruits and vegetables, respectively.

Individual TAC estimates were obtained by combining the information on frequency of consumption of specific food items with information from a database of common foods analysed with the oxygen radical absorbance capacity (ORAC) method on the average ORAC content [μmol Trolox equivalents (TE)/day] of age-specific portion sizes. ORAC values were further energy-adjusted using the residuals method. Total energy intake was summarized over the whole diet and calculated using food composition data from the Swedish National Food Administration Database and the same age-specific portion sizes as for the calculation of TAC. Overall, in the 98-item FFQ, there were 35 food items (including all fruits and vegetables) with available ORAC values.

Diet at ages 16 and 24 years was assessed using web-based FFQs including 107 and 126 food items, respectively, and consumption of fruits and vegetables was calculated for each age (see online supplement). However, TAC was not available based on these questionnaires.

2.3 | Assessment of asthma and aeroallergen sensitization

Participants were considered to have asthma if they had at least two of the following three criteria, based on parental (age 8 years) and participant (16 and 24 years) questionnaire responses: symptoms of wheeze and/or breathing difficulties in the last 12 months, ever doctor’s diagnosis of asthma, asthma medicine occasionally or regularly in the last 12 months. Prevalent cases (primary outcome) were defined as the total number of cases at the respective follow-up occasion. Incident cases (secondary outcome) were defined as cases with first-time outcome at the respective age without fulfilling the definition of the outcome at the previous follow-up. Remittent cases (secondary outcome) were defined as cases without the outcome at the respective age but fulfilling the definition of the outcome at the previous follow-up. Sensitization to airborne allergens was analysed based on blood samples collected at ages 8, 16 and 24 years and defined as a positive Phadiatop (cat, dog, horse, timothy, birch, mugwort, Dermatophagoïdes pteronyssinus [house dust mite] and Cladosporium [mould]) result (IgE ≥0.35 kU A/L).
2.4 | Assessment of lung function

Lung function (primary outcome) was tested according to ATS/ERS spirometry criteria at age 8 years using a 2200 Pulmonary Function Laboratory (SensorMedics), 16 years using a Jaeger MasterScreen-IOS system (CareFusion Technologies) and 24 years using a Vyaire Vyntus system (Vyaire Medical). The same spirometry test protocol was used at all time-points. Z-scores for forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were computed for each participant, using the GLI reference equations. Pre-bronchodilator measurements were used.

2.5 | Statistical analyses

Intake of fruits, vegetables and TAC at age 8 years was divided into tertiles, and when numbers were small (in stratified analyses and analyses of incidence and remission), it was dichotomized (by the median). Longitudinal associations were analysed by generalized estimating equation (GEE) models with an unstructured matrix for dichotomous outcomes, and by mixed-effects linear regression with a random intercept, an unstructured correlation matrix and restricted maximum likelihood estimation for continuous outcomes. Tests for trend were performed by assigning the median values of exposure variables within each tertile and tested as a continuous variable in the model.

Potential confounding factors were identified from existing literature. In the multivariable models, we adjusted for sex, total energy intake (kcal-day) at 8 years, parental education (elementary school, high school, university), parental ethnicity (born in or outside of Sweden), parental history of atopic disease (yes/no), maternal age at delivery <25 years (yes/no), maternal smoking in pregnancy and/or infancy (yes/no) and older siblings (yes/no). Fruit and vegetable intakes were mutually adjusted through inclusion in the same multivariable model. Variables additionally adjusted, which did not influence the results and were not included in the final models are listed in the supplement.

We stratified analyses with prevalent asthma by sex and aeroallergen sensitization, and lung function analyses additionally by asthma at age 8 years and tested possible reverse causation (i.e. that the disease would have influenced the exposure) by excluding children who reported allergic symptoms related to fruits or vegetables, and/or who avoided any of these due to allergic symptoms at age 8 years. We also performed sensitivity analyses, including long-term fruit and vegetable intake, defined as mean intake in grams/day at ages 8 and 16 years, and adjusting for intake at 24 years.

Participants with baseline questionnaire data, data on fruit, vegetable and TAC intake at age 8 years with a mean energy intake within ±3 log SD and information on asthma at 8, 16 and/or 24 years were included in the study population (n = 2506); participants with anthropometric measurements and spirometry results at 8, 16 and/or 24 years were included in lung function analyses (n = 1483). The 12-year follow-up was not included, due to lung function data not being available. The flow chart of the study is shown in Figure S1. All analyses were performed using the statistical software STATA V.16.

3 | RESULTS

The study population (n = 2506) was comparable to the original cohort (n = 4089) with regard to distribution of selected characteristics, apart from higher proportions of parents with university education (54.5% vs. 52.9%) and allergic disease (31.2% vs. 29.7%) and participants exclusively breastfed ≥4 months (81.3% vs. 79.5%) (Table S1). Additionally, in lung function analyses (n = 1483), there were lower proportions of males (47.7% vs. 50.5%)—due to higher loss-to-follow-up rate at 24 years—and participants with older siblings (45.5% vs. 48.4%).

Descriptive information on dietary antioxidant intake, asthma and lung function, as well as the number of participants with available data at each time-point, is shown in Table 1. At age 8 years, median intake of fruits was 1.4 times/day, vegetables 2.3 times/day and TAC 10,009 μmol TE/day, with females having higher mean intakes compared to males. The higher intake among females persisted at ages 16 and 24 years. Prevalence of asthma at ages 8, 16 and 24 years was 10.7%, 14.2% and 14.6%. At age 8 years, the prevalence was higher among males (12.7% vs. 8.6%), while no significant differences by sex were observed at ages 16 and 24 years. Asthma incidence at age 16 years was higher among females (9.4% vs. 6.0%), whereas there were no significant differences for asthma incidence at age 24 years and for asthma remission. Mean absolute lung function values (FEV1 and FVC) more than doubled from 8 to 16 years and continued to increase from 16 to 24 years, apart from FEV1 among females which did not change significantly.

Participants with higher fruit and vegetable intake (≥ median) had similar distribution of various dietary, lifestyle and demographic characteristics compared to those with lower intake, apart from a higher energy and fish intake (Table S2). Moreover, they were more often females, had a parent with university education and had less often a young mother at baseline. Participants with higher TAC intake (≥ median) had a similar distribution by sex and maternal age, but were also more often overweight/obese, had a parent born out of Sweden and older siblings.

3.1 | Associations with prevalent asthma up to age 24 years

Overall associations between antioxidant intake at age 8 years and prevalent asthma up to 24 years are displayed in Figure 1. Participants with higher fruit intake tended to have reduced odds of prevalent asthma (T3 vs. T1, OR 0.78; 95% CI 0.60–1.01, p-trend .083) up to 24 years. In contrast, no association was observed with vegetable intake. A higher TAC intake was associated with reduced odds of prevalent asthma (OR 0.73; 95% CI 0.58–0.93, p-trend .010) up to
### TABLE 1  Descriptive information on dietary antioxidant intake and asthma lung function from 8 to 24 years of age

|                          | 8 years |                                     | 16 years |                                     | 24 years |                                     |
|--------------------------|---------|--------------------------------------|----------|--------------------------------------|----------|--------------------------------------|
|                          | Females | Males | Total  | Females | Males | Total  | Females | Males | Total  | Females | Males | Total  |
| **Dietary antioxidant intake, median (IQR)** |         |       |        |         |       |        |         |       |        |         |       |        |
| Fruit intake, times/day  | 1.42 (1.15) | 1.35 (1.17)* | 1.38 (1.17) | 1.00 (1.36) | 0.64 (1.36)* | 0.64 (1.36) | 0.99 (1.14) | 0.70 (1.12)* | 0.86 (1.15) |         |       |        |
| Vegetable intake, times/day | 2.43 (1.80) | 2.17 (1.85)* | 2.32 (1.83) | 1.00 (1.36) | 0.64 (1.36)* | 0.64 (1.36) | 2.06 (1.47) | 1.57 (1.23)* | 1.84 (1.37) |         |       |        |
| Total antioxidant capacity, μmol TE/day | 10,397 (4322) | 9611 (4486)* | 10,009 (4454) | NA | NA | NA | NA | NA | NA |         |       |        |
| **Asthma cases, n(%)** |         |       |        |         |       |        |         |       |        |         |       |        |
| Prevalent                | 106 (8.6) | 161 (12.7)* | 267 (10.7) | 181 (15.0) | 164 (13.4) | 345 (14.2) | 178 (16.0) | 137 (13.1) | 315 (14.6) |         |       |        |
| Incident                 | NA | NA | NA | NA | NA | NA | 60 (5.4) | 46 (4.4) | 106 (4.9) |         |       |        |
| Remittent                | NA | NA | NA | 37 (3.1) | 54 (4.4) | 91 (3.7) | 58 (5.2) | 63 (6.0) | 121 (5.6) |         |       |        |
| **Lung function measurements, mean (SD)** |         |       |        |         |       |        |         |       |        |         |       |        |
| FEV$_1$, ml              | 1729 (252) | 1820 (277)* | 1773 (268) | 3485 (423) | 4486 (655)* | 3939 (735) | 3509 (416) | 4721 (644)* | 4045 (802) |         |       |        |
| FEV$_1$, z-score          | 0.45 (0.94) | 0.37 (0.92) | 0.41 (0.93) | −0.05 (0.88) | −0.05 (0.97) | −0.05 (0.92) | −0.17 (0.83) | −0.37 (0.92)* | −0.26 (0.88) |         |       |        |
| FVC, ml                  | 1987 (291) | 2145 (337)* | 2062 (324) | 4055 (498) | 5397 (783)* | 4663 (928) | 4163 (514) | 5834 (830)* | 4902 (1068) |         |       |        |
| FVC, z-score             | 0.62 (0.90) | 0.58 (0.91) | 0.60 (0.91) | 0.18 (0.86) | 0.17 (0.96) | 0.18 (0.91) | 0.03 (0.84) | −0.10 (0.88)* | −0.03 (0.86) |         |       |        |
| FEV$_1$/FVC, %           | 87.2 (5.3) | 85.1 (6.0)* | 86.2 (5.7) | 86.2 (6.0) | 83.4 (6.5)* | 84.9 (6.4) | 84.5 (5.8) | 81.2 (6.1)* | 83.1 (6.2) |         |       |        |

Note: Z-scores for FEV$_1$ and FVC were calculated using equations from the GLI reference, according to age, sex and height. * statistically significant difference (p < .05) between males and females, calculated by Mann–Whitney U test and t-test for continuous variables, as appropriate, and Chi-square test for categorical variables. Percentages were calculated in relation to the total number of subjects who contributed to the analyses at the respective occasion. Numbers may not add up to total due to missing. Participants were considered to have asthma if they had at least two of the following three criteria: ever doctor’s diagnosis of asthma, symptoms of wheeze/breathing difficulties and/or asthma medicine occasionally or regularly in the last 12 months. Prevalent cases: total number of cases at the respective age, incident cases: cases with first-time outcome at the respective age without the outcome at the previous follow-up, remittent cases: cases without the outcome at the respective age but having the outcome at the previous follow-up.

Abbreviations: FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; NA, non-applicable; SD, standard deviation; TE, Trolox equivalents.
However, after exclusion of children who reported allergic symptoms related to any fruit or vegetable at age 8 years (n = 242), the odds ratio became non-significant (OR 0.80; 95% CI 0.62–1.05, p-trend .106). In age-specific analyses, TAC intake was inversely associated with prevalent asthma at ages 8 years (OR 0.72; 95% CI 0.53–0.99, p-trend .046) and 16 years (OR 0.72; 95% CI 0.54–0.96, p-trend .026), while a non-significant odds ratio was observed at 24 years (OR 0.75; 95% CI 0.56–1.01, p-trend .060).

An association between fruit intake and prevalent asthma was observed among males (≥median vs. < median, OR 0.60; 95% CI 0.45–0.81), but not females (OR 0.95; 95% CI 0.71–1.27, p-interaction .017) (Table 2). After exclusion of children with food-related allergic symptoms, the interaction term between fruit intake and sex remained significant (p-interaction .026).

In stratified analyses by Aeroallergen sensitization status (Table 3), a higher fruit intake was associated with reduced odds of
3.2 | Associations with incident and remittent asthma up to age 24 years

A higher fruit intake at age 8 years was associated with reduced odds of incident asthma (OR 0.58; 95% CI 0.58–0.99) and increased odds of remittent asthma (OR 1.60; 95% CI 1.05–2.42). After exclusion of children with food-related allergic symptoms, the association with asthma incidence remained unchanged (OR 0.76; 95% CI 0.57–1.00) (Table 4).

In contrast, no associations were observed with intake of vegetables. Further, participants with higher TAC intake tended to have reduced odds of asthma incidence (OR 0.82; 95% CI 0.64–1.05) and increased odds of asthma remission (OR 1.31; 95% CI 0.90–1.91).

3.3 | Long-term fruit and vegetable intake

Among the 2506 study participants, 2325 had data on fruit and vegetable intake at age 16 years and 975 at 24 years. In analyses of long-term fruit intake (mean intake at ages 8 and 16 years), we observed comparable odds ratios to the analyses of fruit intake at 8 years, but with somewhat wider, and non-significant, confidence intervals for prevalent (T3 vs. T1, OR 0.83; 95% CI 0.63–1.10, p-trend .219), incident (≥median vs. <median, OR 0.77; 95% CI 0.58–1.01) and remittent asthma (OR 1.47; 95% CI 0.95–2.27). Further adjustment for fruit intake at age 24 years had no major influence on the results (data not shown). No association was observed between long-term vegetable intake and prevalent or incident asthma; however, an inverse association between long-term vegetable intake and remittent asthma was observed (OR 0.60; 95% CI 0.39–0.91).

4 | DISCUSSION

In this study of 2506 young adults from the population-based birth cohort BAMSE, a higher fruit intake at age 8 years was associated with a tendency to reduced odds of prevalent asthma, with reduced odds of incident asthma and increased odds of remittent asthma up to age 24 years. In contrast, no association was observed with vegetable intake. The cumulative action of dietary antioxidants, measured as a higher TAC of the diet, was associated with reduced odds of prevalent asthma and increased mean FEV₁. In sex-specific analyses, associations between fruit and TAC intake were more pronounced among males. However, due to the large number of associations tested, results should be interpreted with caution.

### Table 4 Overall associations between antioxidant intake at age 8 years and incidence and remission of asthma up to 24 years

|                          | All participants | After exclusion |
|--------------------------|------------------|-----------------|
|                          | OR (95% CI)      | OR (95% CI)     |
|                          | Incidence        | Remission       | Incidence | Remission       |
| Fruits                   | 0.76 (0.58–0.99) | 1.60 (1.05–2.42)| 0.76 (0.57–1.00)| 1.44 (0.89–2.33) |
| Vegetables               | 0.99 (0.76–1.28) | 0.73 (0.49–1.09)| 1.00 (0.76–1.31)| 0.73 (0.46–1.15) |
| TAC                      | 0.82 (0.64–1.05) | 1.31 (0.90–1.91)| 0.82 (0.63–1.06)| 1.32 (0.86–2.04) |

Note: OR (95% CI): odds ratio (95% confidence interval). Median intakes (<median reference): fruits 1.38 times/day, vegetables 2.32 times/day and TAC 10,009 μmol TE/day. Generalized estimating equations (GEE) models for all participants and after exclusion of participants with food-related allergic symptoms (to specific fruits or vegetables, n = 242), adjusted for sex, total energy intake, parental education, ethnicity and history of atopic disease, maternal age at delivery, smoking in pregnancy and/or infancy, and older siblings.
To our knowledge, this is the first prospective study to investigate the association between antioxidant intake in childhood and asthma and lung function up to young adulthood. Several epidemiological studies in children26–29 and adults30–32 have demonstrated a reduced risk of asthma in relation to a high fruit and vegetable intake, but most have been cross-sectional, thus limiting causal inference and being unable to address incidence and remission of disease. The results from our study are in agreement with previous studies that a potential association seems to be stronger for fruits compared to vegetables.4 Fruits contain a complex mixture of bioactive compounds with antioxidant and immunomodulatory properties, such as vitamins, minerals and polyphenols, that are able to enhance endogenous antioxidant systems, scavenge free radicals produced in the inflammation process and protect the airways against endogenous and exogenous sources of oxidative stress.5 Additionally, fruits are rich in fibres, which by inducing changes in the gut microbiome, might impact on immune responses and lung disease.33 Therefore, the additive and synergistic effects of the different nutrients present in fruits may be responsible for their potent antioxidant activity.34 Higher diversity of vegetable consumption has recently been associated with decreased risk of asthma in school-aged children.35 Potential contamination of vegetables by pollutants, such as cadmium, which have been associated with increased risk of asthma, could contribute to the absence of association with vegetables in the study36,37; however, this question was not possible to address with our data. The inverse association observed between long-term vegetable intake and remittent asthma could be due to chance, as it was not consistent with the analyses of intake at 8 years.

TAC reflects the sum of dietary antioxidant intake, taking synergistic effects into account, and correlates with plasma total antioxidant capacity.38 Consistent with lung function trajectories up to adulthood,39 we observed relatively stable coefficients for the association of high TAC intake and increased mean FEV1 and FVC across ages, which suggest general effects on lung growth rather than on airway obstruction specifically. A previous study from the BAMSE cohort on TAC intake in school age has shown improved lung function development up to adolescence among children with asthma.15 In the present study, we observed no significant difference among participants with and without asthma, which may be explained by the longer duration between exposure and outcome and the lower number of participants compared to the previous study. In this study, we did not observe associations between fruit or vegetable intake and lung function. Previous epidemiological studies in adults have shown positive associations between dietary antioxidants (measured as specific nutrients, antioxidant-rich foods or TAC) and lung function, but conflicting results regarding effect modification by life stage, genetic susceptibility and environmental sources of oxidative stress.40–45 In a longitudinal study from the UK,46 reduction in fresh fruit intake during a 7-year period, but not average intake, was related to decrease in lung function, suggesting reversible and not progressive effects, although this was not supported by subsequent studies.47
In the present study, associations between fruit intake and asthma, and TAC intake and FEV\textsubscript{1} and FVC were more pronounced in males compared to females. Males had a lower dietary antioxidant intake at both ages 8 and 16 years. Sex differences in the same direction as in our study have previously been described, suggesting that oxidative stress may be associated with airflow limitation in males. In addition, sex hormones may influence the development of asthma in females.

At younger ages asthma is more prevalent among boys, whose lung function development continues up to young adulthood, whereas females reach the peak lung function earlier in life and in general have a later onset of asthma. Furthermore, effect modification by aeroallergen sensitization status for fruit intake and prevalent asthma has been observed in our study, and male sex has been associated with increased risk of Ig-E sensitization to airborne allergens up to young adulthood.

Diet modifications due to allergy to fruits and vegetables, and cross-reactivity between some fruit and vegetable and pollen allergens, might affect intake and need to be considered in studies of diet and allergic disease. In our study, exclusion of children with food-related allergic symptoms attenuated the association between TAC intake and prevalent asthma, indicating that parts of the observed association may be due to disease-related modification of consumption. However, the association between fruit intake and incident asthma remained after the exclusion, suggesting less influence of disease-related modification of consumption on incident disease. An alternative explanation for the attenuated associations is the exclusion of sensitized participants, among whom associations seemed to be stronger.

Strengths of our study include the population-based design, long follow-up time with limited loss to follow-up, repeated dietary assessment and lung function testing using standardized methods. Despite our study population comprising 61% of the original cohort, we observed comparable baseline characteristics. To assess exposure, we examined fruits, vegetables and TAC to capture different antioxidant components of the diet. Fruit and vegetable intake was below recommended levels, as only 29% of the children in our study consumed at least five portions per day at age 8 years. This, as well as lower intakes at age 16 years, particularly among boys, is in line with previous studies. Misclassification of exposure in this longitudinal study is likely to be non-differential, as exposure assessment preceded the outcome. Thus, the true associations may be underestimated. However, repeated assessment of dietary intake may better capture long-term dietary intake and reduce exposure misclassification, although the different designs of the FFQs make comparisons over time difficult to interpret. A weakness of our study is that long-term TAC was not available, and TAC did not include all food items but the most important ones. Validity of FFQs recording fruit and vegetable intake among children and adolescents has been reported to be relatively good, while TAC intake from a similar FFQ as in our study has shown reasonable validity in adults. Additionally, asthma definition was based on information collected by questionnaires administered 8 years apart, which might have led to some misclassification of the outcome and over time. Although our analyses were adjusted for several potential confounders, residual confounding cannot be completely ruled out.

In conclusion, results from this longitudinal study suggest that fruit and dietary antioxidant intake in school age may influence asthma and lung function development up to young adulthood, particularly among males. Median intakes of fruits and vegetables at age 8 years in the highest compared to the lowest tertile differed more than threefold. Our results are generally in line with WHO recommendations to consume at least five servings or 400 g per day of fruits and vegetables as part of a balanced diet. Therefore, our findings emphasize the importance of following current
recommendations for the general population and highlight the need for further studies using repeated dietary assessment and biomarkers of dietary intake from childhood up to young adulthood.

ACKNOWLEDGMENTS
The authors would like to thank the children and parents participating in the BAMSE cohort and all staff involved in the study through the years.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ETHICAL APPROVAL STATEMENT
The study was approved by the Swedish Ethical Review Authority (approval number 2016/1380-31/2), and written informed consent was obtained from the parents up to 8 years and participants at 16 and 24 years of age.

AUTHOR CONTRIBUTIONS
ES and AB designed the study, AB, EM and IK supervised the data collection, JH participated in the data collection, ES performed the statistical analyses, all authors interpreted the data, ES wrote the first draft of the manuscript, AB edited the first draft, and all authors have read, critically reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID
Emmanouela Sdona https://orcid.org/0000-0001-7329-4212
Sandra Ekström https://orcid.org/0000-0002-2060-8190
Niklas Andersson https://orcid.org/0000-0001-9785-7462
Susanne Rautiainen https://orcid.org/0000-0001-7193-6082
Niclas Håkansson https://orcid.org/0000-0001-7673-5554
Alicja Wolk https://orcid.org/0000-0001-7387-6845
Inger Kull https://orcid.org/0000-0001-6096-3771
Erik Melén https://orcid.org/0000-0002-8248-0663
Anna Bergström https://orcid.org/0000-0002-7981-6314

REFERENCES
1. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson C. The association between childhood asthma and adult chronic obstructive pulmonary disease. Thorax. 2014;69(9):805-810.
2. Tagiyeva N, Devereux G, Fielding S, Turner S, Douglas G. Outcomes of childhood asthma and wheezy bronchitis. A 50-year cohort study. Am J Respir Crit Care Med. 2016;193(1):23-30.
3. Fuchs O, Bahmer T, Rabe K, von Mutius E. Asthma transition from childhood into adulthood. Lancet Respir Med. 2017;5(3):224-234.
4. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol. 2011;127(3):724-733.
5. Seyyedrezazadeh E, Moghaddam M, Ansarink, Vafa M, Sharma S, Kolahdooz F. Fruit and vegetable intake and risk of wheezing and asthma: a systematic review and meta-analysis. Nutr Rev. 2014;72(7):411-428.
6. Hosseini B, Berthon B, Wark P, Wood L. Effects of fruit and vegetable consumption on risk of asthma, wheezing and immune responses: a systematic review and meta-analysis. Nutrients. 2017;9(4):341.
7. Willers S, Devereux G, Craig L, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. Thorax. 2007;62(9):773-779.
8. Chatzi L, Torrent M, Romieu I, et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. Thorax. 2008;63(6):507-513.
9. Bédard A, Northstone K, Holloway J, Henderson A, Shaheen S. Maternal dietary antioxidant intake in pregnancy and childhood respiratory and atopic outcomes: birth cohort study. Eur Respir J. 2018;52(2):1800507.
10. Willers S, Wijga A, Bruneckreef B, et al. Childhood diet and asthma and atopy at 8 years of age: the PIAMA birth cohort study. Eur Respir J. 2011;37(5):1060-1067.
11. Kusunoki T, Takeuchi J, Morimoto T, et al. Fruit intake reduces the onset of respiratory allergic symptoms in schoolchildren. Pediatr Allergy Immunol. 2017;28(8):793-800.
12. García-Larsen V, Amigo H, Bustos P, Bakolis I, Rona R. Ventilatory Function in Young Adults and Dietary Antioxidant Intake. Nutrients. 2015;7(4):2879-2896.
13. Puchau B, Zulei M, González de Echávarri A, Hermána H, Hermosdorff M, Martinez J. Dietary total antioxidant capacity: a novel indicator of diet quality in healthy young adults. J Am Coll Nutr. 2009;28(6):648-656.
14. Gref A, Rautiainen S, Gruzieva O, et al. Dietary total antioxidant capacity in early school age and subsequent allergic disease. Clin Exp Allergy. 2017;47:751-759.
15. Sdona E, Hallberg J, Andersson N, et al. Dietary antioxidant intake in school age and lung function development up to adolescence. Eur Respir J. 2020;55(2):1900990.
16. Melén E, Bergström A, Kull I, et al. Male sex is strongly associated with IgE-sensitization to airborne but not food allergens: results up to age 24 years from the BAMSE birth cohort. Clin Transl Allergy. 2020;10(15):15. https://doi.org/10.1186/s13601-020-00319-w
17. Ballardini N, Bergström A, Kull I, et al. Resolved allergen-specific IgE sensitization among females and early poly-sensitization among males impact IgE sensitization up to age 24 years. Clin Exp Allergy. 2021;51(6):849-852.
18. Rosenlund H, Kull I, Pershagen G, Wolk A, Wickman M, Bergström A. Fruit and vegetable consumption in relation to allergy: disease-related modification of consumption? J Allergy Clin Immunol. 2011;127(5):1219-1225.
19. Wu X, Beecher G, Holden J, Haytowitz D, Gebhardt S, Prior R. Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. J Agric Food Chem. 2004;52:4026-4037.
20. Willett W, Howe G, Kushli L. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997;65(4 Suppl):S1205-S1228.
21. Bergström L, Kyllberg E, Hagnan U, Eriksson H, Bruce A. The food composition database KOST: the National Administration’s information system for nutritive values of food. Vår Föda. 1991;43:439-447.
22. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. Lancet Respir Med. 2014;2(2):131-140.
23. Wang G, Hallberg J, Um Bergström P, et al. Assessment of chronic bronchitis and risk factors in young adults: results from BAMS. Eur Respir J. 2020;57:2002120.
24. Quanjer P, Stanojevic S, Cole T, et al. Multi-ethnic reference values for spirometry for the 3-95-year age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343.
25. Nurmatov U, Nwaru B, Devereux G, Sheikh A. Confounding and effect modification in studies of diet and childhood asthma and allergies. *Allergy*. 2012;67(8):1041-1059.

26. Chatzi L, Apostolaki G, Bibakis I, et al. Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax*. 2007;62(8):677-683.

27. Nagel G, Weinmayr G, Kleiner A, García-Marcos L, Strachan D, Protudjer J, Sevenhuysen G, Ramsey C, Kozyrskyj A, Becker Bacopoulou F, Veltsista A, Vassi I, et al. Can we be optimistic about asthma in childhood? A Greek cohort study. *J Asthma*. 2009;46(2):171-174.

28. Shafeen S, Sterne J, Thompson R, Songhurst C, Margetts B, Burney P. Dietary antioxidants and asthma in adults: population-based case-control study. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1823-1828.

29. Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. *Thorax*. 2006;61(3):209-215.

30. Butland B, Strachan D, Anderson H. Fresh fruit intake and asthma symptoms in young British adults: confounding or effect modification by smoking? *Eur Respir J*. 1999;13(4):744-750.

31. McKenzie C, Tan J, Macia L, Mackay C. The nutrition-gut immune axis and allergic diseases. *Immunol Rev*. 2017;278(1):277-295.

32. Wolfe K, Kang X, He X, Dong M, Zhang Q, Liu R. Cellular antioxidant capacity estimates in Swedish women. *Eur J Epidemiol*. 2020;52:104–114. https://doi.org/10.1007/s10654-020-01068-y

33. Whitehead I, Wadsworth J, Chinn S. Asthma and respiratory symptoms in the 1958 British birth cohort. *Am J Respir Crit Care Med*. 2008;178(6):517-522.

34. Shaheen S, Jameson K, Syddall H, et al. The relationship of dietary patterns with adult lung function and COPD. *Eur Respir J*. 2010;36(2):277-284.

35. Di Giuseppe R, Arcari A, Serafini M, et al. Total dietary antioxidant capacity and lung function in an Italian population: a favorable role in premenopausal/never smoker women. *Eur J Clin Nutr*. 2012;66(1):61-68.

36. García-Larsen V, Potts J, Omenaas E, et al. Dietary antioxidants and 10-year lung function decline in adults from the ECRHS survey. *Eur Respir J*. 2017;50(6):1602286.

37. Bentley A, Kröthevsky S, Harris T, et al. Dietary antioxidants and forced expiratory volume in 1 s decline: the Health, Aging and Body Composition study. *Eur Respir J*. 2012;39(4):979-984.

38. Garcia-Larsen V, Thawer N, Charles D, et al. Dietary intake of flavonoids and ventilatory function in European adults: a GA²LEN study. *Nutrients*. 2018;10(1):95.

39. Moreno-Macias H, Romieu I. Effects of antioxidant supplements and nutrients on patients with asthma and allergies. *J Allergy Clin Immunol*. 2014;133(5):1237-1244.

40. Mavridis A, Fehily A, Elwood P. Diet, lung function, and lung function decline in a cohort of 2512 middle aged men. *Thorax*. 2000;55(2):102-108.

41. Ochs-Balch H, Grant B, Muti P, et al. Oxidative stress and pulmonary function in the general population. *Am J Epidemiol*. 2005;162(12):1137-1145.

42. Okubo H, Shafeen S, Ntani G, et al. Processed meat consumption and lung function: modification by antioxidants and smoking. *Eur Respir J*. 2014;43(4):972-982.

43. Almqvist C, Worm M, Leynaert B. Working group of GA²LEN WP 2.5 Gender. Impact of gender on asthma in childhood and adolescence: a GA²LEN review. *Allergy*. 2008;63(1):47-57.

44. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med*. 2019;7:358-364.

45. Rosenlund H, Magnusson J, Kull I, et al. Antioxidant intake and allergic disease in children. *Clin Exp Allergy*. 2012;42(10):1491-1500.

46. Lynch C, Kristjansdottir A, Te Velde S, et al. Fruit and vegetable consumption in a sample of 11-year-old children in ten European countries—the PRO GREENS cross-sectional survey. *Public Health Nutr*. 2014;17(11):2436-2444.

47. Albani V, Butler L, Traill W, Kennedy O. Fruit and vegetable intake: change with age across childhood and adolescence. *Br J Nutr*. 2017;117(5):759-765.

48. Livsmedelsverket. Riksmaten ungdom 2016-17. Så äter ungdomar i Sverige: 2018.

49. Vereecken C, Maes L. A Belgian study on the reliability and relative validity of the Health Behaviour in School-Aged Children food-frequency questionnaire. *Public Health Nutr*. 2003;6:581-588.

50. Rautiainen S, Serafini M, Morgenstern R, Prior R, Wolk A. The validity and reproducibility of food-frequency questionnaire-based total antioxidant capacity estimates in Swedish women. *Am J Clin Nutr*. 2008;87:1247-1253.

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.