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

Emmanouela Sdona¹  | Sandra Ekström^{1,2}  | Niklas Andersson¹  | Jenny Hallberg^{3,4} |
 Susanne Rautiainen^{5,6,7}  | Niclas Håkansson¹  | Alicja Wolk^{1,8}  | Inger Kull^{3,4}  |
 Erik Melén^{1,3,4}  | Anna Bergström^{1,2} 

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

Correspondence

Emmanouela Sdona, MD, PhD, Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-171 77 Stockholm, Sweden.

Email: emmanouela.sdona@ki.se

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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* .083), with reduced odds of incident asthma and increased odds of remittent asthma ($\geq$ 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). In contrast, no association was observed with vegetable intake. A higher dietary TAC (T3 vs. T1) at 8 years was associated with reduced odds of prevalent asthma (OR 0.73; 95% CI 0.58–0.93, *p-trend* .010) and improved lung function development (FEV₁-z +0.11; 95% CI 0.01–0.21, *p-trend* .036 and FVC-z +0.09; 95% CI –0.01–0.20,

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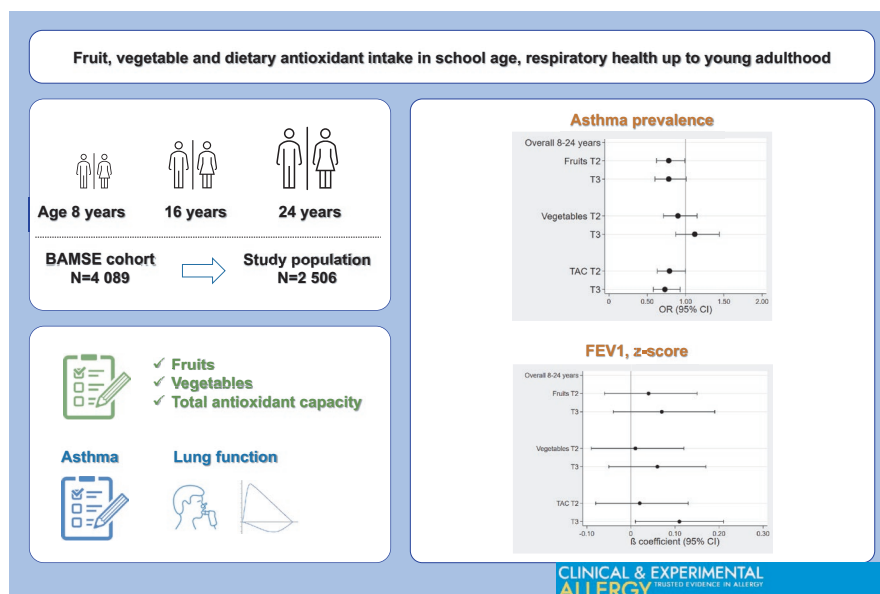
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p-trend .072) up to 24 years. Associations were more pronounced among males, and regarding asthma, participants sensitized to aeroallergens.

Conclusions: Antioxidant intake in school age may improve asthma and lung function up to young adulthood. Although our results should be interpreted with caution, they emphasize the importance of following current dietary guidelines regarding consumption of antioxidant-rich foods as part of a balanced diet.

KEYWORDS

antioxidants, asthma, diet, fruits, lung function



GRAPHICAL ABSTRACT

This longitudinal study of 2506 participants from the population-based birth cohort BAMSE aimed to investigate the association of fruit, vegetable and dietary total antioxidant capacity (TAC) at age 8 years, with repeated measures of asthma and lung function up to 24 years. Diet and asthma were assessed by questionnaires and lung function by spirometry. Results from this study suggest that high fruit and dietary antioxidant intake in school age may improve asthma and lung function up to young adulthood.

1 | 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 life-long 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.⁴⁻⁶ Most longitudinal studies have focused on maternal exposure during pregnancy, reporting lower risk of wheeze or asthma or improved lung function in the offspring.⁷⁻⁹ Fewer studies have examined antioxidant intake

Key Messages

- Antioxidant intake in school age may improve asthma and lung function up to young adulthood.
- Males and participants sensitized to aeroallergens may benefit more from an increased intake.
- General dietary recommendations regarding intake of antioxidant-rich foods may be important for respiratory health.

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.¹¹ Furthermore, although there is some support for an association between high fruit intake and improved lung function in young adulthood from cross-sectional studies,¹² 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.¹³ 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,¹⁴ as well as improved lung function development among children with asthma.¹⁵ 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 on-going 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.¹⁶ 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.¹⁷ 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.¹⁶

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 "≥three times/day".¹⁸ 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) method¹⁹ on the average ORAC content [μmol Trolox equivalents (TE)/day] of age-specific portion sizes.¹⁴ ORAC values were further energy-adjusted using the residuals method.²⁰ Total energy intake was summarized over the whole diet and calculated using food composition data from the Swedish National Food Administration Database²¹ 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.²² 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, Dermatophagoides pteronyssinus [house dust mite] and Cladosporium [mould]) result ($\text{IgE} \geq 0.35 \text{ kU}_A/\text{L}$).

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).²³ 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.²⁴ 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.²⁵ In the multivariable models, we adjusted for sex, total energy intake (kcal·day⁻¹) 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 (StataCorp).

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 $\mu\text{mol TE/day}$, 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 ($\geq$ 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 ($\geq$ 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
Dietary antioxidant intake, median (IQR)	n = 1237	n = 1269	n = 2506	n = 1161	n = 1164	n = 2325	n = 592	n = 383	n = 975
Fruit intake, times/day	1.42 (1.15)	1.35 (1.17)*	1.38 (1.17)	0.64 (0.79)	0.64 (0.79)*	0.64 (0.79)	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, $\mu\text{mol TE/day}$	10,397 (4322)	9611 (4486)*	10,009 (4454)	NA	NA	NA	NA	NA	NA
Asthma cases, n (%)	n = 1237	n = 1269	n = 2506	n = 1205	n = 1226	n = 2431	n = 1113	n = 1045	n = 2158
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	113 (9.4)	74 (6.0)*	187 (7.7)	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)	n = 775	n = 708	n = 1483	n = 668	n = 553	n = 1221	n = 612	n = 485	n = 1097
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 FEV₁ and FVC were calculated using equations from the GLL 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: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; NA, non-applicable; SD, standard deviation; TE, Trolox equivalents.

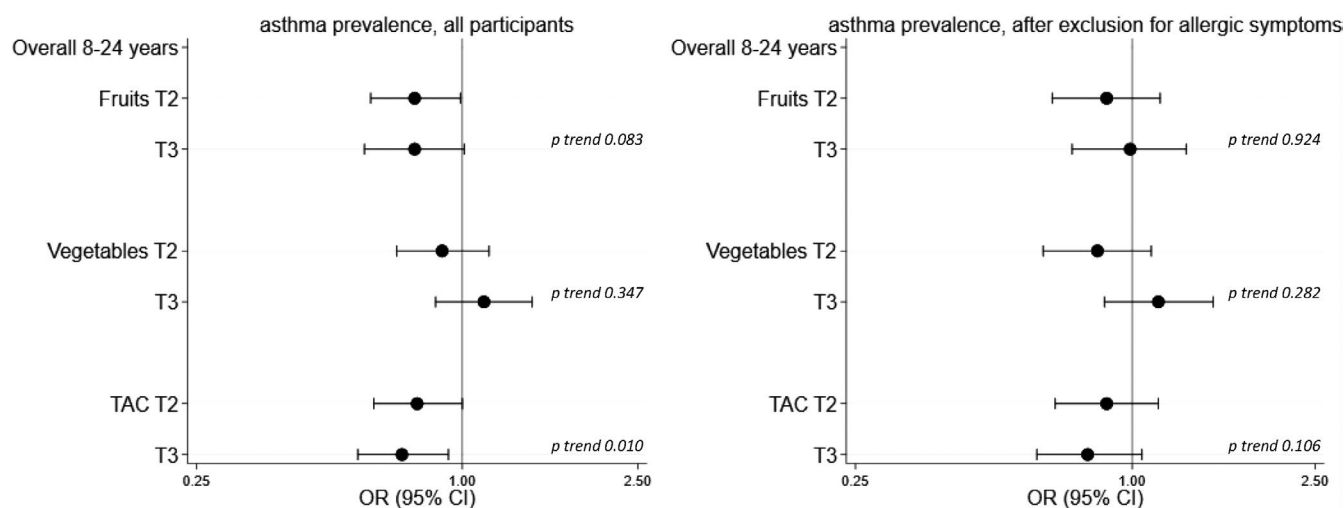


FIGURE 1 Overall associations between antioxidant intake at age 8 years and prevalence of asthma up to 24 years. OR (95% CI): odds ratio (95% confidence interval). Median intakes by tertiles: fruits T1 0.70 (reference), T2 1.37 and T3 2.43 times/day, vegetables T1 1.11 (reference), T2 2.31 and T3 3.75 times/day, TAC T1 6960 (reference), T2 10,007 and T3 13,603 $\mu\text{mol TE/day}$. Analyses for all participants ($n = 2506$) and after exclusion of participants with food-related allergic symptoms (to specific fruits or vegetables, $n = 242$) obtained by generalized estimating equation (GEE) models, 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

TABLE 2 Sex-specific overall associations between antioxidant intake at age 8 years and prevalence of asthma up to 24 years

	Asthma prevalence					
	All participants, OR (95% CI)			After exclusion, OR (95% CI)		
	Females ($n = 1237$)	Males ($n = 1269$)	<i>p</i> -interaction	Females ($n = 1104$)	Males ($n = 1160$)	<i>p</i> -interaction
Fruits	0.95 (0.71–1.27)	0.60 (0.45–0.81)	.017	1.15 (0.83–1.60)	0.73 (0.53–1.01)	.026
Vegetables	1.11 (0.83–1.48)	0.98 (0.73–1.30)	.189	1.15 (0.84–1.59)	1.11 (0.81–1.53)	.536
TAC	0.83 (0.63–1.09)	0.71 (0.54–0.93)	.437	0.89 (0.66–1.21)	0.76 (0.56–1.03)	.446

Note: OR (95% CI): odds ratio (95% confidence interval). Median intakes (<median reference) males: fruits 1.35 times/day, vegetables 2.17 times/day and TAC 9611 $\mu\text{mol TE/day}$, females: fruits 1.42 times/day, vegetables 2.43 times/day and TAC 10,397 $\mu\text{mol TE/day}$. Generalized estimating equations (GEE) models for all participants ($n = 2506$) and after exclusion of participants with food-related allergic symptoms (to specific fruits or vegetables, $n = 242$), adjusted for total energy intake, parental education, ethnicity and history of atopic disease, maternal age at delivery, smoking in pregnancy and/or infancy, and older siblings. *p* interaction between antioxidant intake and sex.

TABLE 3 Overall associations between antioxidant intake at age 8 years and prevalence of asthma up to 24 years, stratified by sensitization status at 8 years

	Asthma prevalence, OR (95% CI)		
	Non-sensitized ($n = 1716$)	Sensitized ($n = 594$)	<i>p</i> -interaction
Fruits	0.98 (0.74–1.31)	0.58 (0.42–0.80)	.014
Vegetables	1.28 (0.96–1.70)	0.91 (0.66–1.25)	.035
TAC	0.99 (0.76–1.30)	0.71 (0.52–0.96)	.109

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 $\mu\text{mol TE/day}$. Generalized estimating equations (GEE) models 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.

24 years. 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 ($\geq$ 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

prevalent asthma among sensitized participants (OR 0.58; 95% CI 0.42–0.80), but not among non-sensitized participants (OR 0.98; 95% CI 0.74–1.31, *p-interaction* .014). Additionally, sensitized participants with higher TAC intake tended to have reduced odds of prevalent asthma compared to non-sensitized participants.

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 ($\geq$ median vs. <median, OR 0.76; 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 ($\geq$ 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).

3.4 | Associations with lung function up to age 24 years

We observed no association between intake of fruits or vegetables at age 8 years and lung function up to 24 years (Table 5). However, a higher TAC intake was associated with increased mean FEV₁-z (T3 vs. T1, +0.11; 95% CI 0.01–0.21, *p-trend* .036) and a tendency to increased mean FVC-z (+0.09; 95% CI –0.01–0.20, *p-trend* .072) up to 24 years.

Age- and sex-specific analyses between TAC intake and lung function are shown in Figure 2. In age-specific analyses, associations were statistically significant at ages 8 years ($\geq$ median vs. <median, FEV₁-z 0.11; 0.02–0.20), 16 years (FEV₁-z 0.13; 0.03–0.23 and FVC-z 0.13; 0.03–0.23) and 24 years (FEV₁-z 0.16; 0.06–0.26 and FVC-z 0.15; 0.05–0.25). In sex-specific analyses, associations tended to be stronger among males, but the interaction terms were not significant.

In analyses of lung function change, we found no interaction between time and TAC, thus no difference in change over time for lung function between the different TAC intake groups (data not shown). In analyses stratified by asthma at age 8 years, there was no significant difference between participants with or without asthma (Table S3). Likewise, no effect modification by aeroallergen sensitisation was observed (data not shown).

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 OR (95% CI)		After exclusion 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 μ mol 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.

TABLE 5 Overall associations between antioxidant intake at age 8 years and lung function up to 24 years ($n = 1483$)

	FEV ₁ z-score β (95% CI)			FVC z-score β (95% CI)			FEV ₁ /FVC % β (95% CI)		
	T2	T3	p-trend	T2	T3	p-trend	T2	T3	p-trend
Fruits	0.04 (−0.06 to 0.15)	0.07 (−0.04 to 0.19)	.243	0.03 (−0.07 to 0.13)	0.06 (−0.05 to 0.18)	.281	0.1 (−0.5 to 0.8)	0.1 (−0.7 to 0.8)	.900
Vegetables	0.01 (−0.09 to 0.12)	0.06 (−0.05 to 0.17)	.268	0.01 (−0.10 to 0.11)	0.09 (−0.02 to 0.20)	.099	0.1 (−0.6 to 0.7)	−0.3 (−1.0 to 0.5)	.442
TAC	0.02 (−0.08 to 0.13)	0.11 (0.01 to 0.21)	.036	0.01 (−0.09 to 0.11)	0.09 (−0.01 to 0.20)	.072	0.1 (−0.5 to 0.8)	0.2 (−0.5 to 0.8)	.638

Note: Median intake in tertiles: fruits: T1 0.70 (reference), T2 1.37 and T3 2.43 times/day, vegetables: T1 1.11 (reference), T2 2.31 and T3 3.75 times/day, TAC: T1 6977 (reference), T2 10,016 and T3 13,501 $\mu\text{mol TE/day}$. Mixed effects linear regression models adjusted for sex, total energy intake, 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 children^{26–29} and adults^{30–32} 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 study^{36,37}; 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

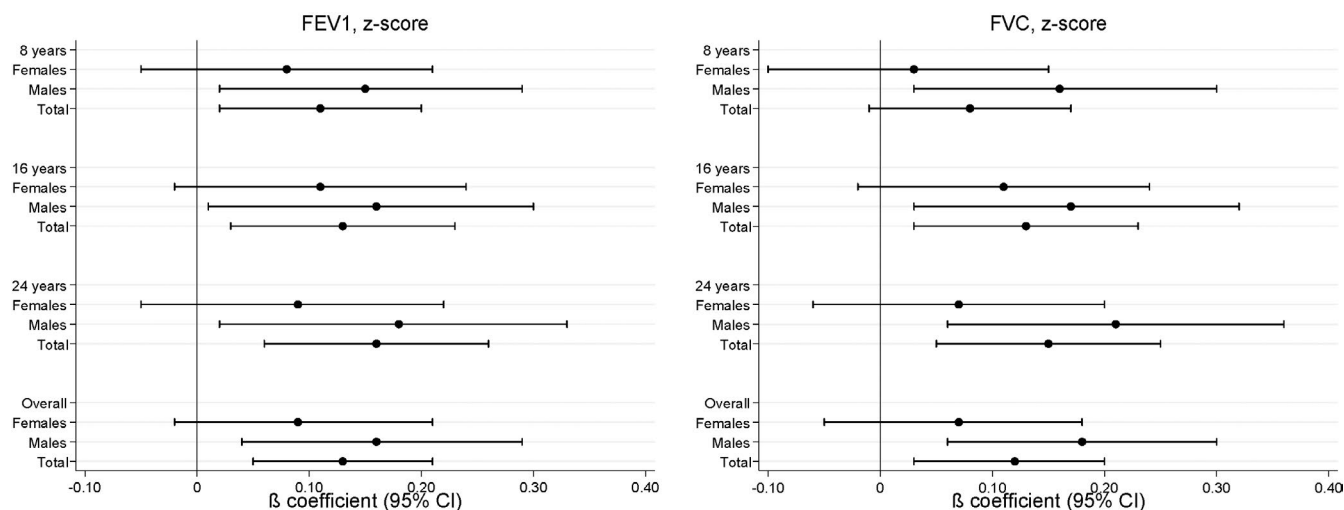


FIGURE 2 Age- and sex-specific associations between TAC intake at age 8 years and lung function up to 24 years. Median TAC intake (<median reference): total 10,016 $\mu\text{mol TE/day}$, females 10,364 $\mu\text{mol TE/day}$ and males 9546 $\mu\text{mol TE/day}$. Analyses for all participants ($n = 1483$, including 775 females and 708 males), obtained by mixed-effects linear regression, adjusted for sex (totals), total energy intake, parental education, ethnicity and history of atopic disease, maternal age at delivery, smoking in pregnancy and/or infancy, and older siblings

In the present study, associations between fruit intake and asthma, and TAC intake and FEV₁ 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.^{48,49} In addition, sex hormones may influence the development of asthma in females.⁵⁰ 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.^{3,51} 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.¹⁶

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.⁵² 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.^{53–55} 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,⁵⁶ while TAC intake from a similar FFQ as in our study has shown reasonable validity in adults.⁵⁷ 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>

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SUPPORTING INFORMATION

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

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The BAMSE participants (total)

N=4 089

Answered questionnaire, food frequency questionnaire (FFQ) and had ± 3 log SD mean energy intake at age 8 years
n= 2 595

Attended clinical examination and had spirometry at age 8 years
n = 1 818

Answered the questionnaires at ages 16 and/or 24 years
Study population
n = 2 506 (1 237 females, 1 269 males)

Attended clinical examination and had spirometry at ages 16 and/or 24 years
Lung function analyses
n =1 483 (775 females, 708 males)

Answered FFQ and had ± 3 log SD mean energy intake at age 16 years
Long-term intake analyses
n= 2 325 (1 161 females, 1 164 males)

Supplementary Material

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

Emmanouela Sdoná, MD, PhD¹, Sandra Ekström, PhD^{1,2}, Niklas Andersson¹, Jenny Hallberg, PhD^{3,4}, Susanne Rautiainen, PhD^{5,6,7}, Niclas Håkansson, PhD¹, Alicja Wolk, PhD^{1,8}, Inger Kull, PhD^{3,4}, Erik Melén, MD, PhD^{1,3,4} and Anna Bergström, PhD^{1,2}

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

Assessment of diet

At the 16-year-follow up, adolescents were asked to fill in a web-based FFQ (1). This meal-based FFQ was designed for adolescents aged 15-18 years. The FFQ included screening questions about intake of fruits/berries and vegetables during the past 12 months. There were six pre-specified response categories for fruits ('never' to '≥2 times/day') and seven for vegetables ('never' to '≥3 times/day'). If participants replied that they ate fruits and berries more than one to two times per week, they were additionally asked which of the following seven fruits/fruit groups they usually ate: bananas, apples/pears, citrus fruits, kiwis, berries, grapes, other fruits. If they replied that they ate vegetables more than one to two times per week, they were additionally asked which of the following 14 vegetables/vegetable groups they usually ate: tomatoes/paprika, cucumbers/lettuce/zucchini, carrots, onion, corn, avocados, cauliflower/cabbage, broccoli, spinach, green peas, beans/lentils/chickpeas, parsnip/rutabaga/celeriac, pickled vegetables, other vegetables.

In order to calculate long-term fruit and vegetable intake, we converted the frequencies of intake of food items to intakes in grams per day. For the 8-year FFQ data, we used information from a Swedish diet survey on children (Riksmaten 2003) on portion size in grams of individual food items and then summarized over fruits and vegetables (4). For the 16-year FFQ data, we used information from the Swedish National Food Agency database on portion size in grams (5), assuming equal frequency of intake of the different fruit and vegetable items, listed under fruit and vegetable groups, respectively, and summarizing the mean of the serving sizes of the different items. Following that, we calculated mean fruit and vegetable intake in grams per day at ages 8 and 16 years, which we defined as long-term intake, and created categories of long-term intake, in tertiles or, when the numbers of participants were small, in two categories divided by the median.

At the 24-year-follow up, young adults were asked to fill in a web-based FFQ including 126 foods and beverages frequently consumed in Sweden. Participants were asked how often, on average, they had consumed fruits and vegetables during the past 12 months. There were four questions on fruit items with nine pre-specified response categories ranging from '1-3 times per month' to ' ≥ 5 times/day' and eight questions on vegetable items with five pre-specified response categories ranging from '1-3 times per month' to '7 times per week or more'. Participants were asked to specify the frequency of consumption of the following fruits/fruit groups, if they were consumed at least once per month: bananas, apples/pears, citrus fruits, other fruits or berries. They were also asked to specify the frequency of consumption of the following vegetables/vegetable groups, if they were consumed at least once per month: vegetables mix, tomatoes/cucumbers/lettuce, spinach/rucola, onions/leeks/garlic, carrots, avocados, broccoli/Brussels sprouts/cabbage, olives. The consumption frequencies were converted into average daily consumption and summarized as fruits and vegetables, respectively. This meal-based FFQ has been validated against doubly labelled water and a web-based seven-day weighed food record (2, 3).

Assessment of lung function

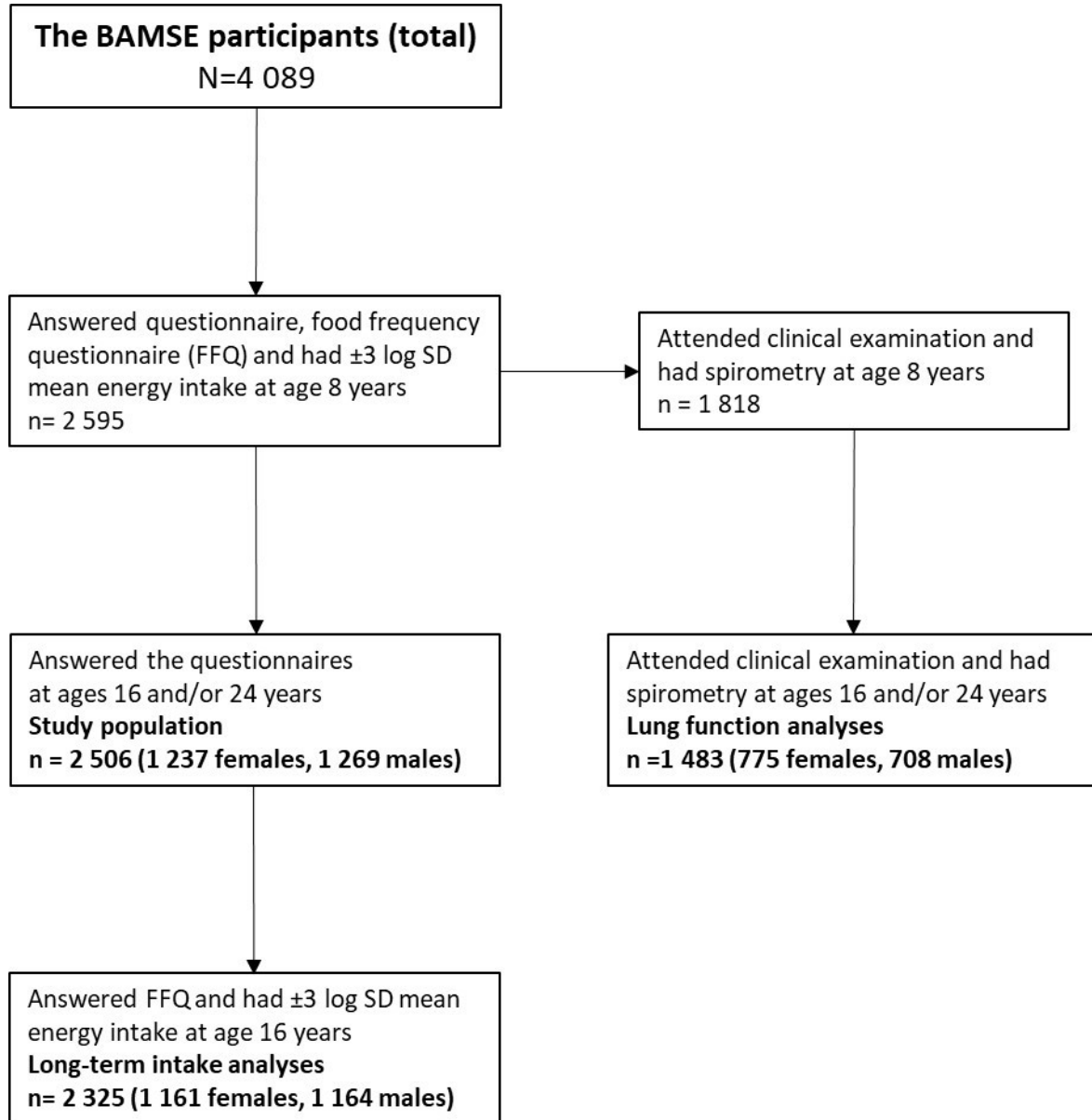
Regarding spirometry measurements, all participants performed repeated maximal expiratory flow volume (MEFV) measurements. The highest values of FEV₁ and FVC were extracted and used for analysis, provided that the subject's effort was accepted as being maximal by the test leader, the MEFV curve passed visual quality inspection and the two highest FEV₁ and FVC readings were reproducible according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (6).

Statistical analyses

Longitudinal analyses take the correlation between repeated measurements on the same individual into account. The models incorporate an interaction between time and exposure to estimate age-specific associations and changes in lung function over time.

Additional adjustment for maternal BMI, prematurity, exclusive breastfeeding, secondhand tobacco smoking, BMI, fish intake, supplement use and physical activity at 8 years, and smoking at 24 years did not influence the results and was not included in the final models.

Figure S1. Flow chart of the study



Due to the longitudinal design of the study, data on the outcome were required from at least one time-point (16 or 24 years). Participants with missing data at one time-point were included in analyses of overall associations, but not in age-specific analyses and analyses of lung function change. Among participants with complete questionnaire and FFQ data at age 8 years, participants with complete questionnaires were 2 431 (1 205 females, 1 226 males) at age 16 years and 2 158 (1 113 females, 1 045 males) at age 24 years. Among participants with complete questionnaire, FFQ and spirometry data at age 8 years, participants with available spirometry data were 1 221 (668 females, 553 males) at age 16 years and 1 097 (612 females, 485 males) at age 24 years.

Table S1. Distribution of selected characteristics in the original cohort and in the study population

	Total cohort n=4 089		Study population n=2 506			Lung function analyses n=1 483		
Selected characteristics	n	%	n	%	95% CI	n	%	95% CI
Male sex	2 065	50.5	1 269	50.6	49.4-51.9	708	47.7	45.7-49.8
Parent with university education	2 161	52.9	1 364	54.5	53.2-55.7	834	56.2	54.2-58.2
Parent born out of Sweden	718	21.1	535	21.4	20.6-22.2	317	21.4	19.9-23.1
Parent with allergic disease	1 200	29.7	776	31.2	30.1-32.4	474	32.2	30.3-34.1
Exclusive breastfeeding $\geq$ 4 months	3 116	79.5	1 999	81.3	80.3-82.2	1 194	82.0	80.3-83.5
Older siblings	1 980	48.4	1 178	47.0	45.8-48.2	674	45.5	43.4-47.5
Maternal smoking in pregnancy and/or infancy	563	13.8	318	12.7	11.9-13.5	185	12.5	11.2-13.9
	mean	SD	mean	SD	95%CI	mean	SD	95%CI
Maternal age (y)	30.7	4.5	30.9	4.5	30.8-31.0	30.9	4.4	30.8-31.1
Maternal BMI ¹ (kg/m ²)	22.9	3.3	22.9	3.2	22.8-23.0	22.8	3.2	22.7-22.9
Birth weight ¹ (g)	3 535	552	3 540	551	3527-3554	3 531	537	3509-3553
Gestational age ¹ (w)	39.5	1.8	39.5	1.8	39.5-39.6	39.5	1.8	39.4-39.6

95% CI: 95% confidence interval created by applying finite population correction factor, SD: standard deviation.

Numbers may not add up to total due to missing. ¹ Variables obtained from the medical birth register.

Table S2. Distribution of demographic, dietary and lifestyle characteristics in the study population in relation to antioxidant intake at age 8 years (n=2 506)

	Fruit and vegetable intake			TAC intake		
	<median	≥median	<i>p-value</i>	<median	≥median	<i>p-value</i>
Male sex, n (%)	683 (54.9)	586 (46.4)	<0.001	703 (56.1)	566 (45.2)	<0.001
Total energy intake, Kcal/day, mean (SD)	1 750 (417)	2 063 (463)	<0.001	1 921 (470)	1 894 (465)	0.146
Parent with university education, n (%)	638 (51.3)	726 (57.5)	0.006	665 (53.0)	699 (55.9)	0.360
Parent born out of Sweden, n (%)	252 (20.3)	283 (22.5)	0.189	245 (19.6)	290 (23.2)	0.026
Parent with allergic disease, n (%)	387 (31.4)	389 (31.1)	0.833	402 (32.2)	374 (30.2)	0.282
Young maternal age (<25 years), n (%)	104 (8.4)	75 (5.9)	0.019	105 (8.4)	74 (5.9)	0.017
Maternal BMI, kg/m ² , mean (SD)	22.9 (3.1)	22.9 (3.4)	0.590	22.9 (3.1)	22.9 (3.3)	0.804
Exclusive breastfeeding (≥4 months), n (%)	996 (81.6)	1 003 (81.0)	0.724	993 (80.9)	1 006 (81.7)	0.644
Maternal smoking in pregnancy and/or infancy, n (%)	171 (13.8)	147 (11.7)	0.113	169 (13.5)	149 (11.9)	0.233
Older siblings, n (%)	561 (45.1)	617 (48.9)	0.057	550 (43.9)	628 (50.2)	0.002
Asthma at age 8 years, n (%)	138 (11.2)	129 (10.3)	0.501	145 (11.6)	122 (9.8)	0.142
Allergy to fruits and vegetables at age 8 years, n (%)	132 (11.6)	110 (9.5)	0.097	138 (11.9)	104 (9.1)	0.028
Overweight/obesity at age 8 years, n (%)	258 (20.7)	246 (19.5)	0.436	221 (17.6)	283 (22.6)	0.002
Physical activity ≥3 times/week at age 8 years, n (%)	172 (13.9)	205 (16.2)	0.095	193 (15.4)	184 (14.7)	0.609
Use of multivitamins at age 8 years, n (%)	529 (43.0)	512 (41.2)	0.342	508 (41.0)	533 (43.2)	0.270
Fish intake ≥2 times/week at age 8 years, n (%)	380 (30.7)	574 (45.6)	<0.001	464 (37.1)	490 (39.3)	0.250

SD: standard deviation, *p*-values were calculated from the chi-square test for categorical variables and *t*-test for continuous variables.

Median intakes: fruit and vegetable 3.84 times/day, TAC 10 009 μmol TE/day.

Table S3. Overall associations between TAC intake (T2 and T3 combined vs reference tertile 1) at age 8 years and lung function up to 24 years, stratified by asthma at age 8 years (n=181)

	FEV ₁ z-score			FVC z-score		
	β (95% CI)			β (95% CI)		
	No asthma	Asthma	<i>p-interaction</i>	No asthma	Asthma	<i>p-interaction</i>
TAC	0.03 (-0.07-0.13)	0.19 (-0.05-0.43)	0.261	0.04 (-0.06-0.13)	0.11 (-0.14-0.37)	0.572

Median TAC intakes: T1 6 977 (reference), T2 and T3 11 404 μmol TE/day. Analyses adjusted for sex, total energy intake, parental education, ethnicity and history of atopic disease, maternal age at delivery and smoking in pregnancy and/or infancy, and older siblings.

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