


Dietary total antioxidant capacity in early school age and subsequent allergic disease

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Summary

Background Dietary antioxidant intake has been hypothesized to influence the development of allergic diseases; however, few prospective studies have investigated this association.

Objective Our aim was to study the association between total antioxidant capacity (TAC) of the diet at age 8 years and the subsequent development of asthma, rhinitis and sensitization to inhalant allergens between 8 and 16 years, and to assess potential effect modification by known risk factors.

Methods A total of 2359 children from the Swedish birth cohort BAMSE were included. Dietary TAC at age 8 years was estimated by combining information on the child's diet the past 12 months from a food frequency questionnaire with a database of common foods analysed with the oxygen radical absorbance capacity method. Classification of asthma and rhinitis was based on questionnaires, and serum IgE antibodies were measured at 8 and 16 years.

Results A statistically significant inverse association was observed between TAC of the diet and incident sensitization to inhalant allergens (adjusted odds ratio: 0.73, 95% confidence interval: 0.55–0.97 for the third compared to the first tertile, *P*-value for trend = 0.031). Effect modification by traffic-related air pollution exposure was observed, with a stronger association between dietary TAC and sensitization among children with low traffic-related air pollution exposure (*P*-value for interaction = 0.029). There was no evidence for effect modification by *GSTP1* or *TNF* genotypes, although these results should be interpreted with caution. No clear associations were observed between TAC and development of rhinitis or asthma, although a significant inverse association was observed for allergic asthma (OR_{adj} 0.57, 95% CI 0.34–0.94).

Conclusions and Clinical Relevance Higher TAC of the diet in early school age may decrease the risk of developing sensitization to inhalant allergens from childhood to adolescence. These findings indicate that implementing an antioxidant-rich diet in childhood may contribute to the prevention of allergic disease.

Keywords allergy, asthma, BAMSE, children, interaction, sensitization, total antioxidant capacity

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Introduction

Asthma, rhinitis and sensitization in children and adolescents are public health concerns [1, 2]. The aetiology is likely to be multifactorial, and exposures during fetal life such as maternal diet in pregnancy have been suggested to influence the development [3–6]. While asthma is rather common throughout childhood, the

prevalence of rhinitis and that of sensitization to inhalant allergens increase from early school age to adolescence [7–10]. Therefore, it is of interest to investigate whether the child's diet in school age may influence the subsequent risk of allergic diseases.

Airway and systemic inflammation as well as oxidative stress are recognized mechanisms involved in the pathogenesis of asthma and allergic diseases [11].

Antioxidants reduce reactive oxygen species (ROS) and epidemiological studies have reported inverse associations between diets rich in antioxidants and allergic diseases; however, results are inconsistent and previous studies on school age intake have often been cross-sectional [12–17].

Most studies on antioxidants and allergic disease have considered dietary intake or serum levels of individual vitamins and minerals rather than a combined antioxidant measure [18]. The antioxidant system is complex and involves a wide range of exogenous dietary compounds with antioxidative properties working in synergy with each other [19]. Total antioxidant capacity (TAC) of the diet aims to assess the combined activity of all antioxidants [19], and may thereby provide a better estimate than measuring amounts of single compounds as previously done. TAC can be estimated from food frequency questionnaires by summarizing known TAC values of different food items [20]. To our knowledge, there are no previous studies investigating whether total dietary antioxidant intake has a preventive role in allergic disease development among children.

Air pollution exposure (e.g. from road traffic or second hand tobacco smoke) can increase airway inflammation and oxidative stress [21], and has been associated with reduced lung growth as well as asthma in children [22–25]. Dietary antioxidants might counteract oxidative stress and inflammation induced by air pollutants [26]. Also, the response to both air pollution exposure [27] and dietary antioxidant intake [28] might be modified by genetic susceptibility of pro-inflammatory and antioxidant enzyme genes. For example, children carrying specific variants in the *glutathione S-transferase pi 1 (GSTP1)* gene may constitute a susceptible population at increased risk of asthma associated with air pollution [27]. It is therefore of high relevance to study interactions between antioxidant intake, air pollution exposure and genetic variants, which very few studies have previously examined.

The aim of this study was to examine the association between the TAC of the diet in early school age and subsequent development of asthma, rhinitis and sensitization to inhalant allergens. Effect modifications by air pollution exposure and genetic polymorphisms were also investigated.

Materials and methods

Study design and study population

The BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) study is a longitudinal, population-based prospective birth cohort including 4089 children born between 1994 and 1996

in Stockholm [29]. Baseline information was obtained through parental questionnaires when the children were 2 months old. Follow-up questionnaires were answered by the parents at 1, 2, 4 and 8 years (response rates 96%, 94%, 91% and 84%, respectively) and by the teenagers themselves at age 16 years (response rate 76%). Clinical examinations including blood sampling were performed at age 4, 8 and 16 years. Blood samples were analysed for specific IgE antibodies with ImmunoCAP (Phadia AB, Uppsala, Sweden) to common inhalant allergens using the Phadiatop[®]-mix (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *Cladosporium*) [9]. Genotype data for single nucleotide polymorphisms (SNPs) in *glutathione S-transferase pi 1 (GSTP1)* and *tumour necrosis factor (TNF)* were available for 982 subjects (children with asthma symptoms and controls) as previously described [30]. At the 8 years clinical examination, diet was assessed using a food frequency questionnaire (FFQ) ($n = 2614$) [15]. Most often the FFQ was filled out by a parent (57%) or by a parent together with the child (40%). To be included in this study, answers on the questionnaires at baseline, 8 years and 16 years were required, together with a completed FFQ and a mean energy intake within ± 3 log standard deviations (SD). In total, 2359 children (1179 boys and 1180 girls) fulfilled these criteria (see Fig. S1 in the supporting information). The study was approved by the ethical review board of Karolinska Institutet, Stockholm, Sweden (2010/1474-31/3) and written informed consent from the study participants has been obtained.

Assessment of total antioxidant capacity of the diet

The FFQ contained questions about 98 foods and beverages frequently consumed in Sweden. Children were asked how often, on average, they had consumed each type of food or beverage during the past 12 months. There were 10 pre-specified response categories ranging from 'never' to ' ≥ 3 times/day'. TAC estimates [μmol Trolox equivalents/day (TE/day)] were calculated using an established and validated assay [20, 31]. TAC estimates of the items from the FFQ was extracted from a database of common foods in the United States analysed with the oxygen radical absorbance capacity (ORAC) method [31]. Individual TAC estimates were calculated by multiplying the average frequency of consumption of each food item by ORAC content (μmol TE/g) of age-specific portion sizes [32] and further energy-adjusted using the residuals method [33]. Overall, in the 98-item FFQ there were 35 food items (including 20 fruit and vegetable items) with available ORAC values. There was no available information on TAC values from dietary supplements.

Assessment of air pollution from road traffic

Exposure to ambient air pollution was estimated based on a methodology described in detail elsewhere [34, 35]. In brief, the method entails geocoding of children's residential and school addresses and using historical emission databases together with dispersion models. For this study, emissions from local road traffic were included using traffic derived nitrogen oxides (NO_x) as a marker of exhaust particles. NO_x exposure at age 8 years was defined as the average concentration to which the child was exposed during 12 months prior the date of answering the 8-year follow-up questionnaire.

Definition of health outcomes

Assessment of asthma and rhinitis were based on the parental questionnaire at age 8 years and on the adolescent questionnaire at age 16 years.

Asthma definition. report of at least two of the following three conditions: symptoms of wheeze in the last 12 months, ever doctor's diagnosis of asthma, and asthma medicine occasionally or regularly last 12 months [36].

Onset of asthma between age 8 and 16 years was defined as fulfilling the definition of asthma at age 16 years, but not at age 8 years.

Rhinitis definition. report of sneezing, runny or blocked nose without common cold or flu in the last 12 months, and/or nose or eye symptoms after contact with furred pets and/or pollens after 4 years of age for rhinitis at 8 years of age, or after contact with furred pets, pollens in the last 12 months for rhinitis at 16 years of age [37]. Onset of rhinitis between 8 and 16 years of age was defined as fulfilling the definition of rhinitis at 16 years, but not at 8 years of age.

Sensitization. specific IgE result of ≥ 0.35 kU_A/L against any of the *inhalant allergens* [37]. *Inhalant allergens* were further subdivided into *outdoor allergens* (birch, timothy, mugwort, *Cladosporium*) and *indoor allergens* (cat, dog, horse, *Dermatophagoide* *pteronyssinus*). Onset of sensitization between 8 and 16 years of age was defined as fulfilling the definition of sensitization at 16 years but not at 8 years of age.

Allergic asthma definition at 16 years of age. a combination of asthma and sensitization against any inhalant allergen. Onset of allergic asthma between 8 and 16 years of age was defined as fulfilling the definition of allergic asthma at 16 years without asthma at 8 years independent of sensitization status at 8 years of age [38].

Allergic rhinitis definition at 16 years. a combination of rhinitis and sensitization against any inhalant allergen. Onset between 8 and 16 years was defined as allergic rhinitis at 16 years without rhinitis at 8 years independent of sensitization status at 8 years [37].

The genetic polymorphisms investigated in this study are SNPs in pro-inflammatory (TNF, $n = 5$ SNPs including -308G/A) and antioxidant enzyme (GSTP1, $n = 6$ SNPs including Ile105Val) genes that were available in our cohort [30].

Statistical analyses

One-sample *t*-test with finite population correction was used to test for differences in the distribution of baseline characteristics between the study population and the original cohort. The distribution of selected exposure characteristics by tertiles of TAC (linear relationship not assumed) was compared by the chi-square test (categorical covariates) and analysis of variance (ANOVA) (continuous covariates). Multivariate logistic regression was used to analyse associations between dietary TAC in tertiles, at age 8 years and the onset of the health outcomes between ages 8 and 16 years. The results are presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Tests for trends were performed by assigning the median value of dietary TAC within each tertile and tested as a continuous variable in the model.

A factor was considered to be a confounder and was included in the model if it changed the crude OR with $\geq 5\%$ and made a significant difference in a likelihood ratio test (LRT) (P for inclusion < 0.05), or if it was considered to be a traditional risk factor for allergic disease. The final model was adjusted for sex, parental history of allergic disease, parental socio-economic status and early maternal smoking. Parental smoking, BMI status, or diet (vitamin D, omega-3 fatty acids, omega-6 fatty acids or dietary supplements) at age 8 years did not influence the observed OR and were not included in the final model. The definitions of all potential confounders tested for are found in the supporting information.

To control for possible reverse causality (i.e. that the disease would have influenced the exposure), we performed a sensitivity analysis, excluding children who reported allergic symptoms related to at least one of six pre-specified fruits or vegetables (apple, peach, kiwi, banana, avocado, fresh carrot) or any other fruit or vegetable (citrus fruit, strawberry, and tomato were the most commonly listed food items), and/or who avoided any of these food items because of allergic symptoms, as these children might have changed their diet as a result of allergic symptoms at age 8 years [39]. Onset

was additionally redefined to not having the specific outcome of interest at age 4 and 8 years, as well as to not having any of the outcomes (asthma, rhinitis, or sensitization) at 8 years. Further, we additionally adjusted for early symptoms of allergic disease (children with reported symptoms of wheeze and/or eczema during the first 2 years of life, see Definitions of health outcomes in the supporting information).

Effect modification on the association between TAC of the diet (dichotomized) and sensitization to inhalant allergens by sex, parental history of allergic disease, dietary supplement use, parental smoking at 8 years, exposure to NO_x at 8 years (divided into tertiles) were assessed. Genotypes of the antioxidant and inflammatory genes *GSTP1* and *TNF* (using dominant coding) were also assessed. A LRT between the model with and without the interaction term was used to test the null hypothesis of no interaction. Data analyses were made with STATA 13 software (StataCorp, College Station LP, TX, USA).

Results

The major contributors to dietary TAC among 8-year-olds were fruits (39.8%), juices and jam (15.8%), and whole grains (12.1%) (Fig. 1).

The 2359 children included in the study were comparable to the 4089 children in the baseline cohort with no major differences in distribution of baseline characteristics such as sex, parental history of allergic disease and early maternal smoking (Table S1 in the supporting information). The mean TAC intake was 10405.4 μmol TE/day, which corresponds to two servings of apples

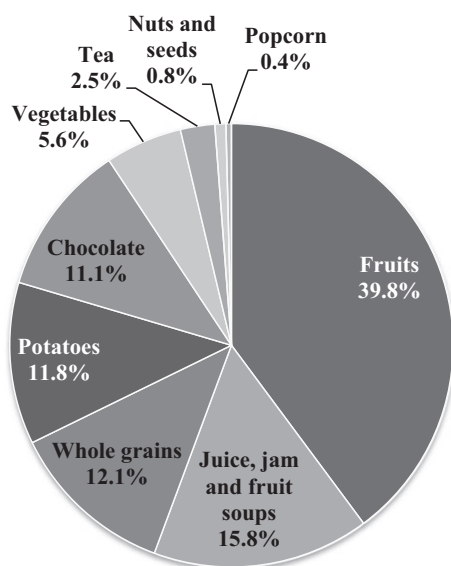


Fig. 1. Contributors to food frequency questionnaire (FFQ)-based total antioxidant capacity (TAC) of diet estimate among 8-year-olds in the BAMSE birth cohort.

per day. Boys had a significantly lower dietary TAC compared to girls ($P < 0.001$). Furthermore, there was a difference in mean intake of vitamin D, omega-3 and omega-6 fatty acids across tertiles of dietary TAC (Table 1). Significantly lower intakes of vitamin D were found in children in the highest tertile of dietary TAC. Children who reported allergic symptoms related to fruits and vegetables were significantly more frequent in the lowest tertile of dietary TAC, 13% compared to 9% among children in the highest tertile.

The number of adolescents with onset of allergic diseases between 8 and 16 years (compared to children at risk at 8 years) were 191/2088 (9%) for asthma, 646/1811 (36%) for rhinitis, 428/1563 (27%) for sensitization to inhalant allergens, 109/1844 (6%) for allergic asthma and 337/1602 (21%) for allergic rhinitis.

To assess the association between TAC of the diet and incident allergic disease between 8 and 16 years of age, we performed multivariate logistic regression analyses. Higher dietary TAC was statistically significantly inversely associated with incident sensitization to inhalant allergens (OR_{adj} 0.73, 95% CI 0.55–0.97 for third tertile compared to the first tertile, P -value for trend = 0.031) (Table 2). Further, the association with incident sensitization to inhalant allergens was only significant for outdoor allergens, while no statistically significant association was observed for indoor allergens. When investigating the association between dietary TAC and incident allergic asthma a statistically significant inverse association was observed (OR_{adj} 0.57, 95% CI 0.34–0.94 for third tertile compared to the first tertile, P -value for trend = 0.029) (Table 2). Dietary TAC was not statistically significantly associated with incident rhinitis.

In all further analysis, the second and third tertiles were combined due to few numbers of cases in each tertile for some of the studied outcomes. When the association between TAC of the diet and incident sensitization to inhalant allergens was assessed in this way, the association remained significant (OR_{adj} 0.73, 95% CI 0.57–0.93). After additional adjustment for dietary supplement use and dietary intakes of omega-3, omega-6 fatty acids and vitamin D at 8 years of age similar results were observed (OR_{adj} 0.70, 95% CI 0.55–0.90). Restriction to children who did not use any supplements showed similar results (OR_{adj} 0.69, 95% CI 0.51–0.94). Furthermore, TAC of the diet was also associated with incident asthma (OR_{adj} of 0.73, 95% CI 0.54–1.01) when analysing the second and third tertile vs. the first tertile. A similar OR estimate was observed for allergic asthma (OR_{adj} 0.67, 95% CI 0.44–1.02).

In sensitivity analyses, potential impact from change in fruit and vegetable intake due to allergic symptoms at age 8 years was investigated by excluding children who reported avoidance of pre-specified fruits or vegetables

Table 1. Characteristics of the study population in relation total antioxidant capacity (TAC) of the diet ($n = 2359$)

Selected exposure characteristics	Tertiles of the TAC of the diet*			P-value [†]
	T1 $n = 787$	T2 $n = 786$	T3 $n = 786$	
ORAC, $\mu\text{mol TE/day}$, median (min–max)	6969 (1768–8637)	10 077 (8644–11 510)	13 624 (11 516–33 097)	
Boys, %	57.2	48.5	44.3	<0.001
Parental history of allergic disease, %	33.3	31.6	29.2	0.20
Parental socio-economic status [‡] , %	84.3	85.3	86.5	0.48
Early maternal smoking, %	14.1	12.0	12.0	0.34
Parental smoking at 8 years, %	17.4	17.3	17.8	0.97
NO _x exposure at 8 years \geq median, %	47.4	50.6	52.0	0.19
Dietary supplement use at 8 years, %	42.0	41.4	43.7	0.65
Omega-3 intake (g/day) [§] , mean (SD)	1.5 (0.32)	1.5 (0.36)	1.4 (0.34)	0.009
Omega-6 intake (g/day) [§] , mean (SD)	6.5 (1.27)	6.7 (1.32)	6.5 (1.40)	0.004
Vitamin D intake ($\mu\text{g/day}$) [§] , mean (SD)	5.6 (1.71)	5.3 (1.78)	5.0 (1.45)	<0.001
Reported allergic symptoms related to fruits and vegetables intake at 8 years, %	13.2	9.0	9.4	0.017

*Total antioxidant capacity intake ($\mu\text{mol Trolox equivalents/day}$) as measured with oxygen radical absorbance capacity assay, energy-adjusted to 1900 kcal/day.

[†]P-values were calculated from the chi-square test for categorical variables and ANOVA for continuous variables.

[‡]Percent white-collar workers.

[§]Energy-adjusted to 1900 kcal/day.

ORAC, oxygen radical absorbance capacity; TE/day, Trolox equivalents per day; SD, standard deviations.

($n = 228$). After this restriction, the association for sensitization to inhalant allergens was similar (OR_{adj} 0.75, 95% CI 0.58–0.96). Furthermore, similar results were observed when we restricted the analysis to those not having the specific outcome of interest at 4 and 8 years (OR_{adj} 0.73, 95% CI 0.57–0.93) or to those not having any of the allergic outcomes (asthma, rhinitis or sensitization to inhalant allergens) at 8 years (OR_{adj} 0.72, 95% CI 0.55–0.94). Moreover, adjustment for early symptoms of allergic disease did not have any impact on the association (OR_{adj} 0.73, 95% CI 0.57–0.93).

The association between dietary TAC and incident sensitization to inhalant allergens was further examined in stratified analyses. These analyses (Table 3) indicated that there was a significant association confined to children exposed to the lowest levels of traffic-related NO_x (OR_{adj} 0.58, 95% CI 0.38–0.88), with a significant LRT for interaction term in the model ($P = 0.029$).

The test for interaction remained significant after exclusion of children who reported avoidance of pre-specified fruits or vegetables due to allergic symptoms (OR_{adj} 0.62, 95% CI 0.40–0.96, LRT P -value for interaction = 0.05). Sex, parental heredity, dietary supplement use, and parental smoking did not modify the association between dietary TAC and incident sensitization to inhalant allergens. In addition, the tests for interaction between key *GSTP1* and *TNF* genotypes and dietary TAC in association with sensitization to inhalant allergens were not significant (Table S2 in the supporting information).

Discussion

In this study of 2359 adolescents from the birth cohort BAMSE, we observed an inverse association between dietary TAC and incident sensitization to inhalant allergens between age 8 and 16 years. The association was modified by air pollution exposure, where a stronger inverse association between dietary TAC and incident sensitization to inhalant allergens was observed among children with low exposure to traffic-related NO_x. In addition, our results suggest that TAC of the diet may be of importance for the development of asthma symptoms in conjunction with sensitization to common airborne allergens.

To our knowledge, this is the first prospective study investigating the association between intakes of dietary antioxidants in childhood and development of allergic disease. However, consistent with our observations some previous cross-sectional studies have also observed an inverse association between diets rich in antioxidants and allergic disease in children [14, 40, 41] and adults [42, 43]. Although potential reverse causation could not be addressed in these studies.

As dietary antioxidants might inhibit oxidative stress induced by air pollutants [26], we examined the potential interactions with traffic-air pollution exposure and parental smoking. An inverse association between dietary TAC and sensitization was particularly found in children exposed to low levels of traffic air pollution with a significant interaction effect. An inverse

Table 2. Association between the TAC of the diet and new onset of allergy related disease between 8 and 16 years of age, multivariable adjusted model*

	Tertiles of the TAC of the diet [†]								
	T1			T2			T3		
	n/N	Ref	n/N	OR	95% CI	n/N	OR	95% CI	P-value for trend [‡]
Asthma	72/668	1.0	58/691	0.74	0.52–1.07	57/690	0.73	0.50–1.05	0.091
Rhinitis	200/565	1.0	232/599	1.18	0.92–1.50	200/611	0.91	0.71–1.16	0.378
Sensitization to inhalant allergens	158/496	1.0	124/500	0.73	0.55–0.96	131/534	0.73	0.55–0.97	0.031
Sensitization to outdoor allergens	106/496	1.0	73/500	0.66	0.47–0.92	82/534	0.71	0.51–0.98	0.041
Sensitization to indoor allergens	80/496	1.0	71/500	0.90	0.63–1.28	70/534	0.83	0.59–1.18	0.306
Allergic asthma	42/578	1.0	37/615	0.79	0.49–1.27	28/617	0.57	0.34–0.94	0.029
Allergic rhinitis	112/490	1.0	114/531	0.97	0.70–1.34	104/550	0.80	0.58–1.11	0.179

*Adjusted for sex, parental history of allergic disease, early maternal smoking and parental socio-economic status.

[†]Total antioxidant capacity intake (μmol Trolox equivalents/day) as measured with oxygen radical absorbance capacity assay, energy-adjusted to 1900 kcal/day.

[‡]P-value for trend was calculated by assigning the median value of dietary TAC within each tertile to all subjects in that tertile, and then, it was used and tested as a continuous variable in the model.

n/N, number of new cases/total number of children; Ref, reference group; OR, odds ratio obtained from multivariate logistic regression model; 95% CI, 95% confidence interval.

Table 3. Association between the TAC of the diet and new onset of sensitization to inhalant allergens between 8 and 16 years of age; stratified analyses

	Tertiles of the TAC of the diet*					LRT P-value for interaction
	T1		T2 and T3 combined			
	n/N	Ref	n/N	OR [†]	95% CI	
Girls	59/218	1.0	133/590	0.80	0.56–1.15	0.480
Boys	99/278	1.0	122/444	0.67	0.49–0.93	
No parental heredity	91/355	1.0	165/756	0.84	0.63–1.14	0.094
Parental heredity	67/141	1.0	90/278	0.54	0.35–0.82	
No dietary supplement use	104/290	1.0	151/586	0.65	0.48–0.89	0.356
Dietary supplement use	54/199	1.0	97/431	0.80	0.54–1.19	
No parental smoking [‡]	133/408	1.0	208/842	0.72	0.55–0.93	0.850
Parental smoking	23/82	1.0	43/184	0.80	0.43–1.45	
NO _x exposure [§] , T1	65/162	1.0	81/315	0.58	0.38–0.88	0.029
NO _x exposure, T2	47/144	1.0	83/344	0.66	0.42–1.02	
NO _x exposure, T3	41/177	1.0	86/346	1.12	0.73–1.73	

*Total antioxidant capacity intake (μmol Trolox equivalents/day) as measured with oxygen radical absorbance capacity assay, energy-adjusted to 1900 kcal/day.

[†]Adjusted for sex, parental history of allergic disease, early maternal smoking and parental socio-economic status if the factor was not the one stratified for.

[‡]Parental smoking at 8 years of age.

[§]NO_x exposure at 8 years of age, divided in tertiles.

n/N, number of new onset cases/total number of children; Ref, reference group; OR, odds ratio obtained from multivariate logistic regression model; 95% CI, 95% confidence interval; LRT, likelihood ratio test.

Bold text indicates a statistically significant difference with a p-value less than 0.05

association was also found in the strata of children with non-smoking parents, although the CIs were overlapping and the interaction P-value was not statistically significant. Similarly, others have found that high TAC of the diet suggestively plays a favourable role in asthmatic children with non-smoking parents [44]. Moreover, high TAC of the diet has been associated with increased lung function among premenopausal and

never smoking women [45]. It is possible that dietary antioxidant intake may protect against allergic sensitization in conditions of low oxidative stress, while high intakes of dietary antioxidants may not be enough to counteract the high oxidative stress and inflammatory burden caused by higher exposure to air pollution [45, 46]. A recent study in a cohort of animal laboratory workers showed that individuals with higher levels of

oxidative stress at baseline were more likely to develop allergic sensitization after allergen exposure, as indicated by higher serum levels of 4-hydroxynonenal-modified proteins (indicating oxidative stress) and lower expression of heme oxygenase-1 (indicating reduced antioxidant capacity) at baseline in those who later developed allergic sensitization [47]. Polymorphisms in genes related to oxidative stress and inflammation may modify the response to oxidative stress by causing oxidant/antioxidant imbalance. *GSTP1* polymorphisms interacting with traffic-air pollution exposure have been associated with increased risk of childhood asthma [27] and further interaction with *TNF* has shown increased risk of sensitization in children [30]. A cumulative effect of genetic susceptibility in *glutathione S-transferase mu 1 (GSTM1)*, *GSTP1* and *NAD(P)H dehydrogenase, quinone 1 (NQO1)* polymorphisms and low dietary vitamin C intake has been associated with decreased lung function in asthmatic children [28]. The apparent protective effect of antioxidant intake on sensitization in our cohort was not modified by *GSTP1* or *TNF* genotypes; however, these results should be interpreted with caution due to the small study sample with information on genotypes.

Strengths of the current study include the prospective longitudinal design where the information on dietary intake was collected before the outcome. Previous studies have focused on intake of fruits, vegetables and individual antioxidants. The TAC estimate reflects the whole antioxidant network in diet taking synergistic and antagonistic effects between compounds into account. The 35 food items with available TAC values included the major sources of antioxidant-rich foods. It is important to point out that the TAC of diet estimate reflects contributions from only foods; thus, our results are not generalizable to dietary supplements. However, the use of individual supplements for the prevention or treatment of asthma or allergies has not been supported by previous clinical trials [46]. We were able to account for several potential confounding factors such as tobacco smoke and traffic air pollution. We were also able to investigate potential effect modification by these factors, which have typically not been addressed in many dietary studies on asthma and allergy [46, 48]. Despite this, residual and unmeasured confounding cannot be excluded.

Some limitations of this study should be acknowledged. Our study population comprised 58% of the baseline cohort, which could impact the generalizability of the results. However, we observed that the baseline lifestyle characteristics were similar as in the original cohort. In addition, the mean fruit and vegetable intake (important contributors to dietary TAC) in the present study was comparable with a Swedish population-based survey in children [49]. Misclassification of exposure

may be present, as ORAC values were available for 35 of the 98 items in our FFQ. However, information was available for important major dietary antioxidant sources including fruits, vegetables, whole grains, nuts, and chocolate [31]. There was no ORAC-TAC data available for lentils, but consumption of lentils and beans is low in this population. Furthermore, there was no ORAC-TAC estimate available for dairy products, although dairy products are not considered to be major antioxidant sources. Another potential weakness is that the FFQ has not been validated in children. However, the validity has been investigated for a FFQ that is similar to the one used in the current study and a correlation of 0.27 (95% CI 0.06–0.46) was observed between plasma ORAC measurements and FFQ-based ORAC estimates [20]. Although our analyses would have been strengthened by blood biomarkers of antioxidant intake, this was not available for the participants in our study. Exposure misclassification is likely to be non-differential as exposure was measured before the outcome and would primarily result in attenuation of the effect estimates. Relatively high numbers of new onset rhinitis and sensitization to inhalant allergens between 8 and 16 years of age were found in our study and the misclassification of rhinitis is possible as we used questionnaire-based information. However, the prevalence of rhinitis and that of sensitization are in line with other studies on adolescents [7, 50–52], and sensitization was objectively measured through blood samples. Despite the prospective design, our data cannot determine whether a high antioxidant intake possibly prevents or just delays the development of sensitization. Due to the large number of tests performed in this study, we cannot exclude the possibility that some of our findings may be due to false positives.

In conclusion, in this study of 2359 adolescents from the Swedish birth cohort BAMSE a high dietary TAC in early school age appeared to decrease the risk of developing sensitization to inhalant allergens between 8 and 16 years of age. Further prospective studies and randomized trials are needed to understand whether a diet high in antioxidants prevents allergic disease development.

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Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Data S1 Definition of health outcomes. Data S2 Definition of potential confounders.

Figure S1. Flow chart of the inclusion to the study population and number of children with serum IgE and genetics data available in the current study.

Table S1. Distribution of baseline characteristics among children in the original BAMSE cohort and among children included in the analyses.

Table S2. Association between the TAC of the diet and new onset of sensitization to inhalant allergens between 8 and 16 years of age, adjusted model^a stratified by genotype.