

Association between biomarker-quantified antioxidant status during pregnancy and infancy and allergic disease during early childhood: A systematic review

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Recent findings suggest a significant association between the antioxidant status of pregnant women and of their children during the first years of life and the development of allergic disease during childhood. The aim of this review was to identify all studies that estimated the effect of intake of antioxidants in pregnant women and their children on the development of allergic disease during early childhood. A systematic review was conducted of epidemiological studies featuring original peer-reviewed data on the association between dietary antioxidant status and allergic disease during childhood. A systematic search was performed following the Meta-analysis of Observational Studies in Epidemiology Guidelines. A comprehensive search of the literature yielded 225 studies, 18 of which were selected for the extraction of results and were related to antioxidant status and allergic disease. The systematic review included five prospective cohort studies, four cross-sectional studies, and nine case-control studies. Eight studies reported an important association between antioxidant status and asthma onset during childhood. Similarly, wheezing and eczema were studied as an outcome in six and in five studies, respectively. Recent observational studies suggest that a higher intake of antioxidant vitamins, zinc, and selenium during pregnancy and childhood reduces the likelihood of childhood asthma, wheezing, and eczema.

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INTRODUCTION

Allergic disease represents the largest category of chronic disease within pediatrics in most countries and has increased in prevalence since the mid-20th century.¹ Although allergic diseases are associated with genetic factors, environmental elements during pregnancy and the first years of life are also suggested to alter the likelihood of disease development.² A number of environmental elements have been found to interfere with maturation of the immune system, to promote dysfunction of the

immune system, and, finally, to facilitate the development of allergic disease.² Consequently, the rapid increase in the prevalence of allergic disease noted over the past few years may be a combined outcome of altered gene-environment interactions that increase the expression of genetic susceptibility as a result of environmental exposures.

Maternal diet during pregnancy has been listed among the main factors that may influence specific immune maturation events, allergic sensitization, and the incidence of childhood allergic disease.^{3–5} Two

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hypotheses relate the increase in allergic disease to a changing intake of dietary antioxidants. The first proposes that the increase is a consequence of declining intake of dietary antioxidants, which compromises lung antioxidant defenses and increases airway vulnerability to oxidant stress.⁶ The second hypothesis proposes that the increase in allergic disease is a consequence of increased antioxidant intake because of the increased availability of functional and antioxidant-enriched foods. This suppresses secretion of the T-helper type 1 (Th1) cytokine, interferon-gamma, resulting in “antioxidant stress,” which therefore suppresses Th1 differentiation and promotes development of the Th2 phenotype.⁶ As a result, the focus of research for these hypotheses has now moved towards investigation of the role of the fetus and early-life nutrient status in the development of childhood allergic disease.⁷

Several recent reviews have emphasized that the nutritional adequacy of antioxidant nutrients is strongly associated with immune maturation and the onset of pediatric allergies.^{8,9} A recent review summarizes current epidemiological knowledge and reports that most observational studies report potentially beneficial associations between dietary antioxidants and allergic outcomes, but a small minority report potentially adverse associations.⁶ Allan et al.⁶ also emphasized that even though a small number of birth cohort studies have reported potentially beneficial associations between maternal intake of some antioxidants during pregnancy and childhood asthma, there are very limited data suggesting associations between maternal antioxidant intake and childhood atopic dermatitis and allergic disease. Finally, the authors conclude that the results of epidemiological studies suggest associations between the status of antioxidants such as vitamin C, vitamin E, some carotenoids, selenium, and antioxidant-rich fruits and the development of asthma and, to a much lesser extent, atopic dermatitis and allergic disease.⁶

Recent reviews summarize the mechanisms by which the main antioxidants act and interfere with the pathogenesis of allergic disease.^{6,8,10} The main anti-inflammatory effects of vitamin E appear to be mediated by inhibition of protein kinase B and C activity and the subsequent inhibition of the activation and DNA binding of the transcription factor NF- κ B, with consequent effects on the regulation of inflammatory cytokines and other proinflammatory molecules.^{6,10} Vitamin E deficiency also contributes to the pathogenesis of allergic disease by reducing T helper (Th)-cell secretion of interferon-gamma and/or increasing secretion of interleukin-4 or interleukin-5, increasing the production of prostaglandin E₂, downregulating interleukin-4 mRNA expression in human Th cells, and influencing the development of regulatory T cells (Tr cells).⁶ In addition, vitamin C pro-

vides intracellular and extracellular aqueous-phase antioxidant capacity, primarily by scavenging oxygen free radicals and suppressing macrophage secretion of superoxide anions. Flavonoids act mainly as scavengers of the superoxide anion, exhibit singlet oxygen-quenching properties, scavenge lipid peroxyl radicals, and act as chelators of iron ions.⁶ Selenium and a component of glutathione peroxidase play a key role in protecting cells against oxidative damage.⁸ Moreover, both flavonoids and selenium contribute in several ways to the pathogenesis of allergic disease, as depicted in Figure 1.

In light of the above findings, the aim of this systematic review was to assess the impact of maternal antioxidant status during pregnancy (assessed from biological samples) and of early antioxidant status during childhood on the development of allergic disease, including wheezing, asthma, allergic rhinitis, and eczema.

METHODS

Literature search strategy

A systematic review of the existing literature on antioxidant status and allergic disease during childhood was performed. Prior to conducting the search, a review protocol was developed, following standards outlined in the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.¹¹ A systematic, comprehensive, bibliographic search was carried out using the US National Library of Medicine Medline database for the years 1990–2010, utilizing the PubMed interface due to its free access to abstracts. Key words used in Medline included the following: (“respiratory sounds” OR “asthma” OR “rhinitis, allergic, seasonal” OR “rhinitis, allergic, perennial” OR “eczema”) AND (“diet” OR “antioxidants” OR “vitamins” OR “vitamin A” OR “vitamin C” OR “vitamin E” OR “folic acid” OR “beta carotene” OR “flavonoids” OR “selenium”) AND (“maternal nutritional physiological phenomena” OR “pregnancy” OR “child, preschool” OR “child” OR “infant”). Retrieved studies were checked against a list of eligibility criteria, while a manual evaluation of the reference lists of the published research articles and reviews was performed to supplement the electronic searches.

Selection criteria

A priori eligibility criteria were defined to restrict the studies included. Studies were included only if they referred to humans, were published in English after 1990, were epidemiological studies (of any study design), assessed the dietary antioxidant status of the pregnant

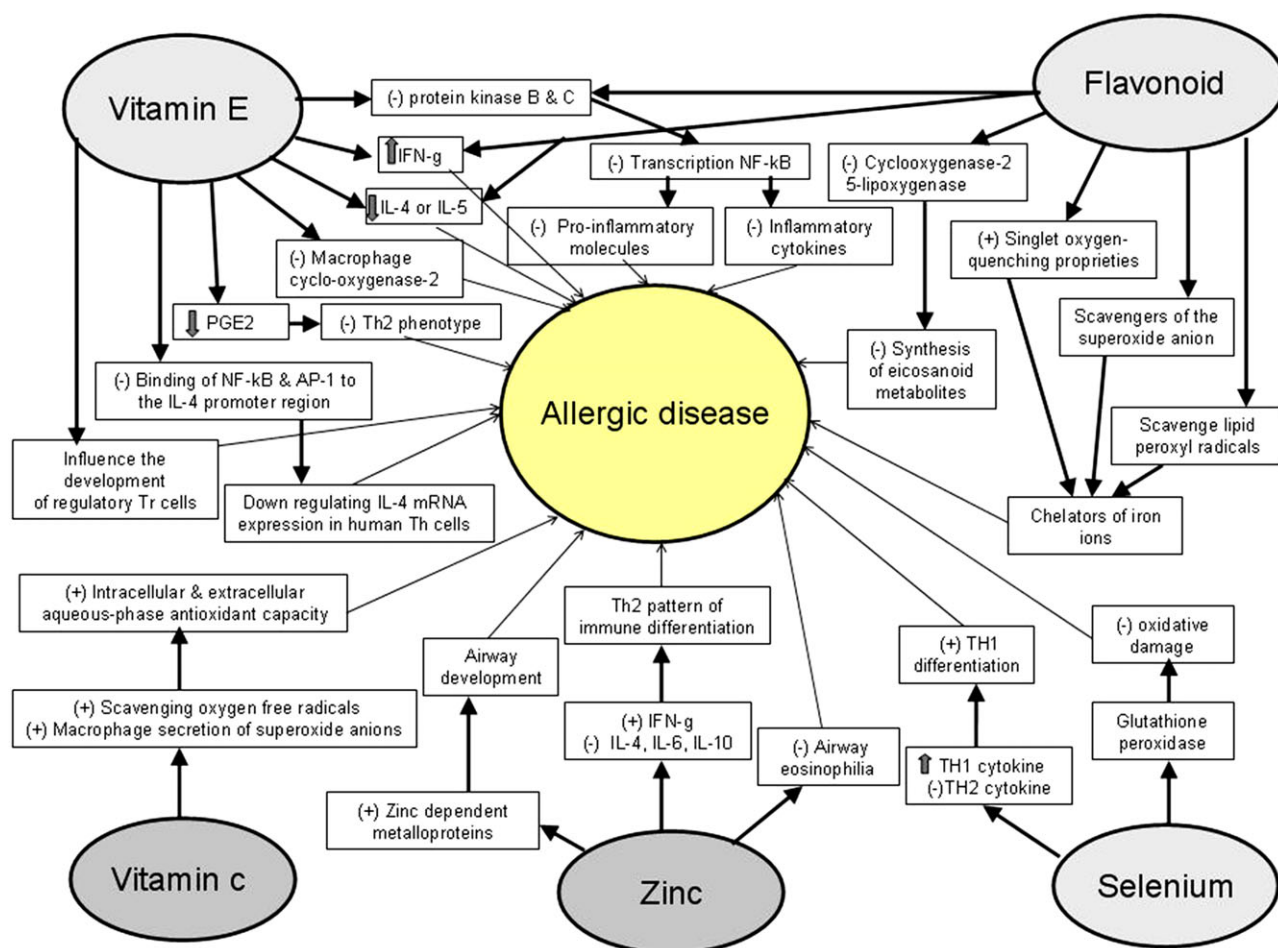


Figure 1 Antioxidants and the development of allergic disease.

mother and/or the child via biochemical indicators, and examined the impact of different levels of antioxidant status on the onset of allergic disease during childhood. Allergic disease included asthma, wheezing, allergic rhinitis, and eczema. Studies that only assessed antioxidant status by self-reported food-frequency questionnaires, 24-hour recalls, and dietary histories were excluded.

Literature screening and data extraction

Prior to inclusion, studies were evaluated by two independent reviewers for relevance to the subject. Study selection was accomplished through four levels of study screening. At level 1 screening, studies were excluded by reviewing the title of the article. At level 2 screening, abstracts of all studies accepted at level 1 were reviewed for relevance. At level 3 screening, the full text was obtained for relevant papers and for any citations for which a decision could not be made from the abstract (level 2 screening). At level 4 screening, a manual search of recent reviews or already-retrieved original articles

was performed, and additional referenced manuscripts were included in the systematic review. A predesigned data collection form was used to extract the data from each study. The following data were extracted: main characteristics of the study, study population, study topic, measures of effect-confidence intervals for each outcome, and adjustment for potential confounders. Any discrepancies in inclusion were resolved by discussion between the reviewers.

RESULTS

Overview of the studies included

The initial analysis resulted in the retrieval of 225 records. Of these, 154 were excluded during the initial screening of manuscript titles and abstracts. Another 57 manuscripts were excluded after examination of the full text. Additionally, four manuscripts were retrieved by searching the reference lists of the reviews and articles retrieved. The flowchart of the procedure is shown in Figure 2. The

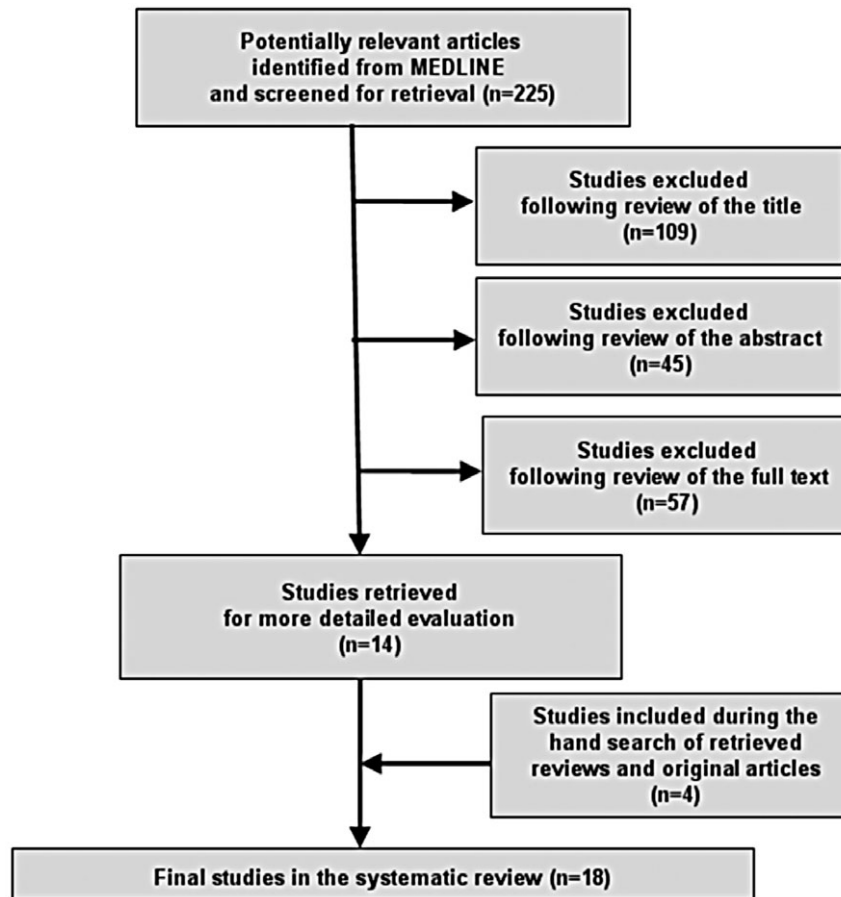


Figure 2 Flow chart of literature search and strategy outcomes.

systematic review included five prospective cohort studies,^{12–16} three cross-sectional studies,^{17–20} and 10 case-control studies.^{21–29} Six studies were conducted in the United Kingdom,^{12–17} two in the United States,^{18,19} three in Turkey,^{22,24,26} two in Japan,^{25,27} one in India,²³ one in Saudi Arabia,²⁸ one in New Zealand,²¹ one in China²⁰ and one in Korea.²⁹ The main characteristics of the studies included in the analysis are shown in Table 1.

Table 2 presents the main findings of the 18 studies included in the review. Twelve studies examined the presence of asthma during childhood as an outcome.^{14–19,22–25,27,28} Wheezing was examined in seven studies^{12–15,20,21,26} and eczema in five studies.^{12–16,29} Moreover, to assess antioxidant status, child serum samples were used as a biochemical marker in 13 studies^{17–29} and maternal blood samples during pregnancy in four studies.^{13–16} Neonatal cord blood samples obtained at birth were used in two studies.^{12,15}

Several antioxidants were examined in the studies included. The antioxidants most commonly examined were vitamin A,^{18,20,23,27,28} vitamin E,^{13,14,18,19,27} vitamin C,^{13,17–19,29} selenium,^{12,15,19,21,24,26} β -carotene,^{18,19,22,28,29} and zinc.^{12,14,24} Other antioxidants included in the studies

reviewed were retinol,^{17,29} α -tocopherol,^{17,22,29} manganese,^{12,24} iron,^{12,24} α -carotene,¹⁸ ascorbic acid,²² cryptoxanthin,¹⁸ lutein,¹⁸ lycopene,¹⁸ copper,^{12,24} 25(OH)-vitamin D,¹⁶ magnesium,¹² lead,¹² and mercury.¹²

Effects of intake of antioxidants on asthma

Kalayci et al.²² showed that antioxidant vitamins are decreased in sera of asthmatic patients, even during the asymptomatic periods of the disease, and Arora et al.²³ reported that vitamin A levels in children with asthma were found to be significantly lower than those in healthy controls (mean $22.14 \pm \text{SD } 5.38 \mu\text{g/dL}$ versus $27.54 \pm \text{SD } 4.83 \mu\text{g/dL}$). The same study reported that the severity of asthma was negatively correlated with serum vitamin A levels ($r = -0.61$, $P = 0.0001$), while children with severe persistent asthma had markedly lower serum vitamin A levels when compared with those suffering from mild intermittent asthma (mean $13.42 \pm \text{SD } 5.19 \mu\text{g/dL}$ versus $24.61 \pm \text{SD } 2.32 \mu\text{g/dL}$).²³ Harik-Khan et al.,¹⁸ found that vitamin C (adjusted odds ratios [AOR] 0.72 per unit increase, 95% confidence interval [CI] 0.55–0.95) and α -carotene (AOR 0.95 per unit increase, 95% CI

Table 1 General characteristics of studies included in the systematic review.

Reference	Study location (duration*), type	Study population	Study topic
Powell et al. (1994) ¹⁷	UK, Sheffield Cross-sectional study	Asthmatic children: <i>n</i> = 37 Healthy children: <i>n</i> = 35	To compare the antioxidant status of children with chronic controlled asthma to that of non-atopic controls
Shaw et al. (1994) ²¹	New Zealand, Kawerau Case-control study	Wheezing: <i>n</i> = 26 Controls: <i>n</i> = 61	To study risk factors for asthma prevalence in Kawerau children aged 8–13 years
Kalayci et al. (2000) ²²	Turkey, Ankara Case-control study	Asthmatic children: <i>n</i> = 14 Controls: <i>n</i> = 12	To investigate the possible changes in antioxidant vitamin levels and their relationship to the oxidant stress produced by asthma
Arora et al. (2002) ²³	India, New Delhi Case-control study	Asthmatic children: <i>n</i> = 35 Controls: <i>n</i> = 29	To assay vitamin A levels among children with asthma and correlate them with asthma severity
Harik-Khan et al. (2004) ¹⁸	USA (1988–1994) Cross-sectional study	Asthmatic children: <i>n</i> = 397 Healthy children: <i>n</i> = 3,696	To examine the relation between vitamin intake and asthma
Kocyigit et al. (2004) ²⁴	Turkey, Zonguldak Case-control study	Asthmatic children: <i>n</i> = 42 Controls: <i>n</i> = 30	To evaluate the status of essential trace elements (Se, Mn, Cu, Zn, and Fe) concentrations in plasma and their effect on oxidative status among patients with childhood asthma
Liao et al. (2004) ²⁵	Taiwan (2001–2002) Case-control study	Asthmatic children: <i>n</i> = 46 Controls: <i>n</i> = 52	To evaluate the influence of chronic inflammation on the total antioxidant status in asthmatic children and matched controls
Rubin et al. (2004) ¹⁹	USA (1988–1994) Cross-sectional study	Asthmatic children: <i>n</i> = 415 Healthy children: <i>n</i> = 5305	To investigate the hypothesis that higher serum levels of vitamins E and C, selenium, and β -carotene decrease the risk of childhood asthma
Shaheen et al. (2004) ¹²	UK (1991–1992) Prospective cohort study	At 30–42 months: <i>n</i> = 2,044 Wheezing: <i>n</i> = 284 At 18–30 months: <i>n</i> = 2,173 Eczema: <i>n</i> = 621	To explore the association between cord concentrations of selenium, zinc, copper, manganese, magnesium, iron, lead, and mercury with wheezing and eczema in children
Martindale et al. (2005) ¹³	UK (1997–1999) Prospective cohort study	Singleton infants: <i>n</i> = 1,924 At 6 months: <i>n</i> = 1,637 Wheezing: <i>n</i> = 313 Atopic dermatitis: <i>n</i> = 362 At 12 months: <i>n</i> = 1,512 Wheezing: <i>n</i> = 233 Atopic dermatitis: <i>n</i> = 290 At 24 months: <i>n</i> = 1,374 Wheezing: <i>n</i> = 210 Atopic dermatitis: <i>n</i> = 358	To test the hypothesis that maternal antioxidant intake during pregnancy influences childhood susceptibility to asthma and atopic disease
Devereux et al. (2006) ¹⁴	UK, Aberdeen (1997–1999) Prospective cohort study	At birth: <i>n</i> = 1,861 infants At 5 years: <i>n</i> = 1,253 children Ever wheezing: <i>n</i> = 254 Ever asthma: <i>n</i> = 157 Doctor-confirmed eczema: <i>n</i> = 359	To assess whether maternal nutrient intake during pregnancy is associated with asthma-related outcomes in children 5 years of age
Kocabas et al. (2006) ²⁶	Turkey, Ankara Case-control study	Children with frequent wheeze: <i>n</i> = 61 Controls: <i>n</i> = 61	To investigate the association between selenium levels and wheezing in children who wheeze frequently
Mizuno et al. (2006) ¹⁹	Japan, Kanagawa Case-control study	Asthmatic children: <i>n</i> = 26 Controls: <i>n</i> = 25	To evaluate vitamin A and E concentrations in well-nourished children with asthma with minimal sign of acute-phase response
Devereux et al. (2007) ¹⁵	UK, Aberdeen (1997–1999) Prospective cohort study	Children at 2 years of age: <i>n</i> = 1,282 Maternal plasma selenium samples: <i>n</i> = 1,867 Wheezing: <i>n</i> = 195 Asthma: <i>n</i> = 65 Cord blood plasma selenium samples: <i>n</i> = 489 Wheezing: <i>n</i> = 63 Asthma: <i>n</i> = 22	To investigate whether wheezing symptoms and asthma in children up to the age of 2 years are associated with plasma selenium
Gale et al. (2008) ¹⁶	UK, Southampton (1991–1992) Prospective cohort study	At birth: <i>n</i> = 466 At 9 months of age: <i>n</i> = 440 Visible eczema on examination: <i>n</i> = 27 Atopic eczema: <i>n</i> = 48 At 9 years of age: <i>n</i> = 178 Atopic eczema: <i>n</i> = 16 Asthma: <i>n</i> = 19	To investigate whether exposure to high maternal concentrations of 25(OH)-vitamin D in pregnancy poses any risk including asthma and atopic eczema to the child
Al Senaidy (2009) ²⁸	Saudi Arabia, Riyadh Case-control study	Asthmatic children: <i>n</i> = 433 Controls: <i>n</i> = 537	To assess the possible association of low serum dietary antioxidants with allergic diseases including asthma
Luo et al. (2010) ²⁰	China (2007–2008) Cross-sectional study	Wheezing: <i>n</i> = 331	To investigate the relation between vitamin A deficiency and infant wheezing
Oh et al. (2010) ²⁹	Korea (2006–2007) Case-control study	Atopic dermatitis: <i>n</i> = 180 Controls: <i>n</i> = 242	To investigate the association of antioxidant nutritional status with risk of atopic dermatitis in young children

*Study duration was not available for all studies.

Table 2 Measures and major findings of studies included in the systematic review.

Reference	Form of atopy	Subject age	Antioxidant(s) measured	Biomarker	Main results	Risk adjustment
Powell et al. (1994) ¹⁷	Asthma	1.5–16 y	Retinol	Child serum samples	<i>Retinol</i> Median levels in $\mu\text{mol/L}$ (IQR) Asthma vs. controls: 1.29 (1.04–1.59) vs. 1.42 (1.28–1.71) $P > 0.05$	None
			Vitamin C		<i>Vitamin C</i> Median levels in $\mu\text{mol/L}$ (IQR) Asthma vs. controls: 57.96 (40.32–70.00) vs. 59.92 (42.98–77.98) $P > 0.05$	
			α -tocopherol		<i>α-tocopherol</i> Median levels in $\mu\text{mol/L}$ (IQR) Asthma vs. controls: 20.87 (14.75–22.97) vs. 21.6 (17.02–25.93) $P > 0.05$	
Shaw et al. (1994) ²¹	Wheezing	8–13 y	Selenium	Child serum samples	<i>Selenium</i> Measured in $\mu\text{g/L}$ for 70+ vs. 60–69 vs. 50–59 vs. <50 OR (95% CI): 1.0 vs. 1.1 (0.2–5.1) vs. 1.9 (0.3–9.7) vs. 3.1 (0.9–11.8) Antioxidant vitamins were decreased in sera of asthmatic children	None
Kalayci et al. (2000) ²²	Asthma	13–15 y	Ascorbic acid, α -tocopherol, β -carotene	Child serum samples	<i>Vitamin A</i> Mean $\pm$ SD in levels in $\mu\text{g/dl}$ Asthma vs. controls: 22.14 ± 5.38 vs. 27.54 ± 4.83 ($P = 0.0001$) Grade 4 asthma vs. grade 1 asthma: 13.2 ± 5.19 vs. 26.87 ± 2.32 Negative correlation between serum vitamin A and severity of asthma: $r = 0.61$, $P = 0.0001$	None
Arora et al. (2002) ²³	Asthma	2–12 y	Vitamin A	Child serum samples	<i>Vitamin A</i> Serum mg/dL AOR (95% CI) per unit increase: 1.004 (0.991–1.017)	
Harik-Khan et al. (2004) ¹⁸	Asthma	6–17 y	Vitamin A	Child serum samples	<i>Vitamin A</i> Serum mg/dL AOR (95% CI) per unit increase: 1.000 (0.999–1.001)	
			Vitamin E		<i>Vitamin E</i> Serum mg/dL AOR (95% CI) per unit increase: 1.000 (0.999–1.001)	
			Vitamin C		<i>Vitamin C</i> Serum mg/dL AOR (95% CI) per unit increase: 0.720 (0.546–0.949)	
			α -carotene		<i>α-carotene</i> Serum $\mu\text{g/dL}$ AOR (95% CI) per unit increase: 0.945 (0.899–0.993)	
			β -carotene		<i>β-carotene</i> Serum mg/dL AOR (95% CI) per unit increase: 0.996 (0.978–1.014)	
			Cryptoxanthin		<i>Cryptoxanthin</i> Serum mg/dL AOR (95% CI) per unit increase: 0.985 (0.962–1.009)	
			Lutein/zeaxanthin		<i>Lutein</i> Serum $\mu\text{g/dL}$ AOR (95% CI) per unit increase: 1.005 (0.988–1.022)	
			Lycopene		<i>Lycopene</i> Serum $\mu\text{g/dL}$ AOR (95% CI) per unit increase: 1.001 (0.990–1.013)	

Kocigigit et al. (2004) ²⁴	Asthma	2–13 y	Selenium	Child serum samples	None	Selenium Mean $\pm$ SD Asthmatic: 59.92 ± 22.91 mg/dL Healthy: 76.50 ± 14.69 mg/dL $P = 0.006$ Manganese Mean $\pm$ SD Asthmatic: 4.43 ± 1.02 mg/dL Healthy: 5.60 ± 1.28 mg/dL $P = 0.043$ Iron Mean $\pm$ SD Asthmatic: 935.61 ± 160.12 mg/dL Healthy: 771.43 ± 189.91 mg/dL $P = 0.001$ Copper Mean $\pm$ SD Asthmatic: $1,400.08 \pm 256.44$ mg/dL Healthy: $1,337.84 \pm 283.23$ mg/dL $P = 0.426$ Zinc Mean $\pm$ SD Asthmatic: 765.72 ± 167.16 mg/dL Healthy: 775.74 ± 106.38 mg/dL $P = 0.812$ Total antioxidant capacity Mean $\pm$ SD Asthmatic: 1.18 ± 0.32 mg/dL Healthy: 1.51 ± 0.54 mg/dL $P = 0.009$ Total antioxidant status Mean $\pm$ SD Asthmatic: 1.189 ± 0.093 Healthy: 1.338 ± 0.241 $P < 0.001$
						Vitamin E
						AOR (95% CI) per 1 SD increase: $0.95 (0.8-1.1)$
						β -carotene
						AOR (95% CI) per 1 SD increase: $0.87 (0.7-1.0)$
						Vitamin C
						AOR (95% CI) per 1 SD increase: $0.81 (0.7-0.9)$
						Selenium
						AOR (95% CI) per 1 SD increase: $0.88 (0.7-1.1)$
Liao et al. (2004) ²⁵	Asthma	5–9 y	Total antioxidant status	Child serum samples	None	
Rubin et al. (2004) ¹⁹	Asthma	4–16 y	Vitamin E	Child serum samples		
			β -carotene			
			Vitamin C			
			Selenium			

Age, sex, race, BMI, passive and active smoke exposure, parental history of asthma and/or hay fever, urban, environment, household crowding, years of education of head of household, childhood history of hay fever and avoidance of pet ownership caused by allergy. Models with vitamin E or β -carotene were also adjusted for total serum cholesterol and triglycerides.

Table 2 Continued

Reference	Form of atopy	Subject age	Antioxidant(s) measured	Biomarker	Main results	Risk adjustment
Shaheen et al. (2004) ¹²	Wheezing, eczema	0–42 mo	Selenium	Neonatal cord blood samples	<i>Selenium</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 0.99 (0.75–1.29) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.77 (0.56–1.05) vs. 1.09 (0.79–1.50) vs. 0.67 (0.45–0.99) -Eczema at 18–30 months AOR (95% CI) per doubling concentration: 0.91 (0.76–1.10)	Confounders: sex, maternal age, parity, gestational age, maternal smoking, maternal educational level, maternal housing tenure, maternal origin, birth weight
					<i>Zinc</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 1.16 (0.93–1.44) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.92 (0.71–1.20) vs. 1.23 (0.97–1.50) vs. 0.94 (0.67–1.31) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 1.10 (0.94–1.28)	
					<i>Copper</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 1.01 (0.84–1.21) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.95 (0.79–1.14) vs. 1.00 (0.80–1.25) vs. 1.00 (0.77–1.29) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 1.00 (0.88–1.14)	
					<i>Manganese</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 0.94 (0.82–1.08) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.96 (0.82–1.13) vs. 0.92 (0.77–1.11) vs. 0.96 (0.80–1.15) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 0.99 (0.89–1.10)	
					<i>Magnesium</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 1.03 (0.77–1.36) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.96 (0.71–1.30) vs. 1.16 (0.83–1.62) vs. 0.72 (0.48–1.08) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 0.99 (0.81–1.21)	
					<i>Iron</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 0.90 (0.80–1.02) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.93 (0.82–1.06) vs. 0.86 (0.75–0.99) vs. 0.95 (0.79–1.14) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 0.90 (0.83–0.98)	
			Lead	Neonatal cord blood samples	<i>Lead</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 1.05 (0.88–1.25) -Transient infant vs. later onset vs. persistent AOR (95% CI): 0.96 (0.78–1.19) vs. 0.92 (0.77–1.09) vs. 1.33 (0.96–1.84) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 0.97 (0.85–1.12)	
					<i>Mercury</i> -Wheezing at 30–42 mo AOR (95% CI) per doubling concentration: 0.99 (0.89–1.11) -Transient infant vs. later onset vs. persistent AOR (95% CI): 1.03 (0.93–1.15) vs. 0.98 (0.86–1.12) vs. 1.04 (0.87–1.25) -Eczema at 18–30 mo AOR (95% CI) per doubling concentration: 1.03 (0.95–1.12)	

Martindale et al. (2005) ¹³	Wheezing, eczema	13–24 mo	Vitamin E	Maternal serum blood sample at 12 th gestational week	<i>Vitamin E intake</i> -Wheezing (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 0.73(0.44–1.21) vs. 0.70 (0.42–1.44) vs. 0.71 (0.43–1.18) vs. 0.79 (0.47–1.31) <i>P</i> for trend = 0.363 -Wheezing in absence of a cold in the 2 nd year of life (1 st third vs. 2 nd third vs. 3 rd third) AOR (95% CI): 1.00 vs. 0.61 (0.35–1.07) vs. 0.47 (0.25–0.86) <i>P</i> for trend = 0.010 -Eczema (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 1.04 (0.69–1.56) vs. 0.83 (0.55–1.24) vs. 0.91 (0.60–1.31) vs. 0.84 (0.55–1.28) <i>P</i> for trend = 0.292 -Eczema in children of atopic mothers group (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 0.77 (0.41–1.44) vs. 0.44 (0.23–0.83) vs. 0.83 (0.45–1.51) vs. 0.41 (0.21–0.80) <i>P</i> for trend = 0.024 <i>Vitamin C intake</i> -Wheezing (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 1.79 (1.00–3.19) vs. 2.50 (1.49–4.39) vs. 1.52(0.83–2.77) vs. 2.25 (1.26–4.02) <i>P</i> for trend = 0.034 -Wheezing in absence of a cold in the 2 nd year of life (1 st third vs. 2 nd third vs. 3 rd third) AOR (95% CI): 1.00 vs. 1.94 (1.09–3.47) vs. 0.93(0.48–1.82) <i>P</i> for trend = 0.288 -Eczema (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 0.94 (0.60–1.47) vs. 1.78 (1.17–2.70) vs. 1.05 (0.68–1.64) vs. 1.41 (0.91–2.18) <i>P</i> for trend = 0.115 -Eczema in children of atopic mothers group (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 0.78 (0.4–1.55) vs. 1.56 (0.82–2.98) vs. 0.82 (0.42–1.61) vs. 1.37 (0.70–2.65) <i>P</i> for trend = 0.395	Sex, maternal age, paternal social class, maternal atopy, maternal smoking, other children in the home and antibiotic use, vitamin C
			Vitamin C		<i>Vitamin C intake</i> -Wheezing (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 1.79 (1.00–3.19) vs. 2.50 (1.49–4.39) vs. 1.52(0.83–2.77) vs. 2.25 (1.26–4.02) <i>P</i> for trend = 0.034 -Wheezing in absence of a cold in the 2 nd year of life (1 st third vs. 2 nd third vs. 3 rd third) AOR (95% CI): 1.00 vs. 1.94 (1.09–3.47) vs. 0.93(0.48–1.82) <i>P</i> for trend = 0.288 -Eczema (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 0.94 (0.60–1.47) vs. 1.78 (1.17–2.70) vs. 1.05 (0.68–1.64) vs. 1.41 (0.91–2.18) <i>P</i> for trend = 0.115 -Eczema in children of atopic mothers group (1 st fifth vs. 2 nd fifth vs. 3 rd fifth vs. 4 th fifth vs. 5 th fifth) AOR (95% CI): 1.00 vs. 0.78 (0.4–1.55) vs. 1.56 (0.82–2.98) vs. 0.82 (0.42–1.61) vs. 1.37 (0.70–2.65) <i>P</i> for trend = 0.395	Sex, maternal age, paternal social class, maternal atopy, maternal smoking, other children in the home and antibiotic use, of vitamin E.

Table 2 Continued

Reference	Form of atopy	Subject age	Antioxidant(s) measured	Biomarker	Main results	Risk adjustment
Devereux et al. 2006 ¹⁴	Asthma, wheezing, eczema	5 y	Vitamin E	Maternal serum samples at 12 th gestational week	<i>Quintiles of vitamin E intake (mg/dl): 2.61–6.21 vs. 6.21–7.07 vs. 7.07–7.89 vs. 7.90–9.15 vs. 9.17–30.8</i> -Ever wheeze AOR (95% CI): 1.00 vs. 0.84 (0.52–1.37) vs. 0.92 (0.57–1.50) vs. 0.50 (0.29–0.85) vs. 0.75 (0.44–1.28) <i>P</i> for trend = 0.07 -Wheeze in last 12 months AOR (95% CI): 1.00 vs. 0.76 (0.43–1.35) vs. 0.75 (0.42–1.34) vs. 0.51 (0.27–0.95) vs. 0.46 (0.24–0.90) <i>P</i> for trend = 0.01 -Wheeze without cold in last 12 months AOR (95% CI): 1.00 vs. 0.50 (0.22–1.15) vs. 0.56 (0.25–1.28) vs. 0.53 (0.23–1.23) vs. 0.22 (0.08–0.62) <i>P</i> for trend = 0.01 -Seen doctor with wheeze in last 12 months AOR (95% CI): 1.00 vs. 0.80 (0.42–1.54) vs. 0.75 (0.39–1.47) vs. 0.58 (0.29–1.18) vs. 0.38 (0.17–0.87) <i>P</i> for trend = 0.02 -Ever asthma AOR (95% CI): 1.00 vs. 0.64 (0.35–1.16) vs. 0.60 (0.33–1.12) vs. 0.59 (0.32–1.10) vs. 0.47 (0.24–0.92) <i>P</i> for trend = 0.04 -Doctor-confirmed asthma AOR (95% CI): 1.00 vs. 0.54 (0.29–0.99) vs. 0.53 (0.28–0.99) vs. 0.48 (0.25–0.93) vs. 0.45 (0.23–0.89) <i>P</i> for trend = 0.02 -Asthma and wheeze in last 12 months AOR (95% CI): 1.00 vs. 0.56 (0.27–1.14) vs. 0.58 (0.28–1.20) vs. 0.61 (0.30–1.26) vs. 0.28 (0.11–0.69) <i>P</i> for trend = 0.02	Maternal age, maternal atopy, maternal smoking, maternal vitamin C intake, father's social class, maternal age of leaving full-time education, deprivation index, birth weight, birth head circumference, birth crown-heel length, child's sex, birth order, breast feeding, use antibiotics by child in 1 st year of life and maternal zinc intake
			Zinc		<i>Quintiles of vitamin zinc intake (mg/dl): 4.44–10.19 vs. 10.19–11.43 vs. 11.43–12.62 vs. 12.63–14.22 vs. 14.25–30.30</i> -Short of breath in last 12 months AOR (95% CI): 1.00 vs. 0.92 (0.42–2.01) vs. 0.57 (0.24–1.37) vs. 0.73 (0.31–1.70) vs. 0.59 (0.15–1.04) <i>P</i> for trend = 0.05 -Short of breath in absence of a cold in last 12 months AOR (95% CI): 1.00 vs. 1.05 (0.39–2.8) vs. 0.47 (0.14–1.55) vs. 0.60 (0.18–1.96) vs. 0.20 (0.04–0.98) <i>P</i> for trend = 0.02 -Ever asthma AOR (95% CI): 1.00 vs. 0.55 (0.30–1.01) vs. 0.59 (0.32–1.07) vs. 0.44 (0.23–0.85) vs. 0.51 (0.27–0.97) <i>P</i> for trend = 0.04 -Current treatment for asthma AOR (95% CI): 1.00 vs. 0.76 (0.41–1.39) vs. 0.60 (0.32–1.14) vs. 0.54 (0.28–1.05) vs. 0.61 (0.32–1.17) <i>P</i> for trend = 0.08 -Asthma and wheeze in last 12 months AOR (95% CI): 1.00 vs. 0.63 (0.32–1.25) vs. 0.54 (0.26–1.10) vs. 0.47 (0.22–1.03) vs. 0.28 (0.12–0.67) <i>P</i> for trend = 0.003 -Ever eczema AOR (95% CI): 1.00 vs. 0.88 (0.57–1.35) vs. 0.74 (0.47–1.15) vs. 0.74 (0.47–1.15) vs. 0.63 (0.40–0.95) <i>P</i> for trend = 0.03 -Doctor-confirmed eczema AOR (95% CI): 1.00 vs. 0.85 (0.55–1.33) vs. 0.83 (0.54–1.30) vs. 0.67 (0.42–1.05) vs. 0.67 (0.43–1.07) <i>P</i> for trend = 0.05 -Current treatment for eczema AOR (95% CI): 1.00 vs. 0.45 (0.25–0.79) vs. 0.61 (0.36–1.05) vs. 0.44 (0.25–0.78) vs. 0.51 (0.29–0.90) <i>P</i> for trend = 0.04	Energy intake, maternal age, maternal atopy, maternal smoking, maternal vitamin C intake, father's social class, maternal age of leaving full-time education, deprivation index, birth weight, birth head circumference, birth crown-heel length, child's sex, birth order, breast feeding, use antibiotics by child in 1 st year of life and maternal vitamin E intake

Kocabas et al. (2006) ²⁶	Wheezing	0.3–5 y	Selenium	Child serum samples	<i>Selenium</i> Mean $\pm$ SD Patients: 61.95 $\pm$ 1.20 μg/dL Controls: 72.71 $\pm$ 1.28 μg/dL $P < 0.001$ <i>Vitamin A</i> Mean $\pm$ SD Asthmatic: 19.41 $\pm$ 7.45 μg/mL Controls: 29.52 $\pm$ 11.34 μg/mL $P < 0.001$ <i>Vitamin E</i> Mean $\pm$ SD Asthmatic: 6.12 $\pm$ 1.83 mg/mL Controls: 5.88 $\pm$ 1.52 mg/mL $P > 0.05$	None
Mizuno et al. (2006) ²⁹	Asthma	Mean age: 5.5 y	Vitamin A	Child serum samples	Asthmatic: 19.41 $\pm$ 7.45 μg/mL Controls: 29.52 $\pm$ 11.34 μg/mL $P < 0.001$	None
Devereux et al. (2007) ¹⁵	Wheezing, asthma	Neonatal follow-up at 1, 2, and 5 y	Selenium	Maternal serum samples at gestational week 12	<i>Maternal plasma selenium</i> AOR (95% CI) per 10 μg/kg increase -Wheeze in last year: 0.86 (0.76–0.97) -Wheeze in the absence of a cold in last year: 0.91 (0.76–1.09) -Seen by family doctor because of wheeze in last year: 0.79 (0.69–0.93) -Doctor-confirmed asthma: 0.92 (0.76–1.12)	Infant gender, maternal atopy, maternal smoking, maternal age at recruitment, maternal parity, birth weight, birth crown–heel length, birth occipitofrontal head circumference, Scottish index of multiple deprivation, use of antibiotics during 1 st year of child's life, and maternal plasma ascorbate
Gale et al. (2008) ¹⁶	Asthma, eczema	At 9 mo and 9 y	25(OH)-vitamin D	Neonatal cord blood samples	<i>Neonatal cord plasma selenium</i> AOR (95% CI) per 10 μg/kg increase -Wheeze in last year: 0.67 (0.47–0.96) -Wheeze in the absence of a cold in last year: 0.978 (0.47–1.30) -Seen by family doctor because of wheeze in last year: 0.62 (0.41–0.93) -Doctor-confirmed asthma: 0.95 (0.57–1.58)	Infant gender, maternal atopy, maternal smoking, maternal age at recruitment, maternal parity, mode of delivery, birth weight, birth crown–heel length, birth occipitofrontal head circumference, Scottish index of multiple deprivation, use of antibiotics during 1 st year of child's life and cord plasma ascorbate
Al Senaidy (2009) ²⁸	Asthma	6–18 y	Vitamin A, β -carotene	Child serum samples	25(OH)-vitamin D (<30 vs. 30–50 vs. 50–75 vs. >75 nmol/L) -At 9 mo (OR [95% CI]) Visible eczema: 1.00 vs. 0.59 (0.14–2.50) vs. 0.79 (0.21–3.00) vs. 3.26 (1.15–9.29) Atopic eczema: 1.00 vs. 1.11 (0.43–2.84) vs. 1.75 (0.73–4.17) vs. 1.62 (0.67–3.89) -At 9 y (OR [95% CI]) Visible eczema: 1.00 vs. 0.71 (0.15–3.39) vs. 0.47 (0.08–2.68) vs. 1.89 (0.51–6.99) Reported asthma: 1.00 vs. 2.05 (0.36–11.80) vs. 2.05 (0.36–11.80) vs. 5.40 (1.09–26.65)	None
Luo et al. (2010) ²⁰	Wheezing	1–31 mo	Vitamin A	Child serum samples	<i>Vitamin A</i> Mean $\pm$ SD Asthmatic: 19.4 $\pm$ 1.1 mg/dL Healthy: 28.9 $\pm$ 0.86 mg/dL $P = 0.0001$ β-carotene Mean $\pm$ SD Asthmatic: 75.1 $\pm$ 0.009 mg/dL Healthy: 87.8 $\pm$ 3.2 mg/dL $P < 0.05$	None
Oh et al. (2010) ²⁹	Atopic dermatitis	Patients' mean age ($\pm$ SD): 5.3 y (± 0.9) Controls' mean age ($\pm$ SD): 5.2 y (± 1.0)	Retinol α -tocopherol β -carotene Vitamin C	Child serum samples	<i>Serum vitamin A</i> (<0.35 vs. 0.35–0.50 vs. 0.50–0.70 μmol/L) -Mild vs. severe wheezing (X^2): 33.49 vs. 33.01 vs. 30.28 $P < 0.001$ -Acute vs. persistent wheezing (X^2): 10.26 vs. 10.41 vs. 9.98 $P < 0.05$ <i>Serum retinol</i> AOR (95%CI) in μmol/L: 0.74 (0.58–0.96) <i>Serum α-tocopherol</i> AOR (95%CI) in μmol/L: 0.64 (0.41–0.98) <i>Serum β-carotene</i> AOR (95%CI) in μmol/L: 0.76 (0.57–1.03) <i>Plasma vitamin C</i> AOR (95%CI) in μmol/L: 0.94 (0.76–1.17)	Monthly household income, parental histories of allergic diseases, the child's age, gender, and body mass index

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; mo, months; OR, odds ratio; SD, standard deviation; μ S, total antioxidant status; X^2 , chi-square; y, years.

0.90–0.99) were significantly associated with asthma severity. Kocyigit et al.²⁴ reported that plasma iron concentrations were higher than plasma selenium and plasma manganese concentrations ($P < 0.001$, $P < 0.001$, and $P < 0.01$, respectively) and plasma selenium and plasma manganese concentrations were lower than plasma iron concentrations ($P < 0.01$, $P < 0.05$, and $P < 0.01$, respectively) in patients when compared with levels in healthy subjects. Accordingly, Rubin et al.¹⁹ found that a standard deviation increase in concentrations of β -carotene (AOR 0.9, 95% CI 0.7–1.0), vitamin C (AOR 0.8, 95% CI 0.7–0.9), and selenium (AOR 0.9, 95% CI 0.7–1.1) was associated with a 10–20% reduction in the prevalence of asthma.

Similarly, Liao et al.²⁵ reported that the serum level of total antioxidant status in asthmatic children was significantly lower than that of controls, and Devereux et al.¹⁴ reported that maternal zinc intake during pregnancy was negatively associated with “asthma ever” status and with active asthma (AOR 0.83, 95% CI 0.71–0.78 and AOR 0.72, 95% CI 0.59–0.89, respectively). The same study found maternal vitamin E intake during pregnancy to be negatively associated with ever developing asthma and with asthma development within the previous year (AOR 0.84, 95% CI 0.72–0.98 and AOR 0.79, 95% CI 0.65–0.95, respectively). Similarly, Mizuno et al.²⁷ found that the mean serum vitamin A concentrations were significantly lower in asthmatic children than in controls (mean $19.41 \pm \text{SD } 7.45$ mg/dL versus $29.52 \pm \text{SD } 11.34$ mg/dL). C-reactive protein and serum vitamin A concentrations were also significantly different between the two groups in the same study. Similarly, Al Senaidy²⁸ found that the serum vitamin A concentration was significantly lower in asthmatic subjects than in healthy control subjects (mean $19.4 \pm \text{SD } 1.1$ mg/dL versus mean $28.9 \pm \text{SD } 0.86$ mg/dL).

On the contrary, Powell et al.¹⁷ reported that children with asthma had no significantly reduced retinol, vitamin C, or α -tocopherol levels when compared with the control group. Among studies that examined the effect of antioxidant status on asthma, one study reported that selenium concentrations in maternal plasma during early pregnancy and in cord plasma were not associated with asthma-like development within the second year of life.¹⁵ In addition, the only study that examined the effect of 25(OH)-vitamin D concentrations during pregnancy (>75 nmol/L) found an increased risk for asthma development at the age of 9 years (AOR 5.40, 95% CI 1.09–26.65) in comparison with children whose mothers had a concentration of 25(OH)-vitamin D below 30 nmol/L.¹⁶

Effects of intake of antioxidants on wheezing

All studies that examined the association between antioxidant status and the development of wheezing symp-

toms during childhood reported an inverse association. More specifically, Shaw et al.²¹ observed that current wheeze was more common in those with low levels of selenium (odds ratio [OR] 3.1, 95% CI 0.9–11.8) in stored serum collected 8 years previously. Moreover, Shaheen et al.¹² reported that cord selenium was negatively associated with persistent wheeze (AOR per doubling concentration, 0.67), while cord iron concentrations were also negatively associated with later-onset wheeze and eczema development (AOR per doubling concentration, 0.86 and 0.90, respectively). In addition to the above, Martindale et al.¹³ suggested that maternal vitamin E intake during pregnancy was negatively associated with wheeze development at age 1–2 years in the absence of a cold (P value for trend, 0.010).

Similarly, Devereux et al.¹⁴ found that maternal vitamin E intake during pregnancy was negatively associated with wheeze development within the previous year (AOR per intake quintile, 0.82; 95% CI 0.71–0.95) and persistent wheezing (AOR per intake quintile, 0.77; 95% CI 0.63–0.93). Kocabaş et al.²⁶ noted that serum selenium levels were lower among patients when compared with healthy subjects (mean $61.95 \pm \text{SD } 1.23$ mg/L versus $72.71 \pm \text{SD } 1.28$ mg/L), and there was a negative correlation between serum selenium levels and the number of wheezing attacks during the previous year ($r = -0.655$, $P < 0.001$). The following year, Devereux et al.¹⁵ reported that maternal plasma selenium concentrations during early pregnancy were inversely associated with wheezing (AOR per 10 mg/kg plasma selenium, 0.86; 95% CI 0.76–0.97) and with consulting a doctor because of wheeze in the second year of life (AOR per 10 mg/kg plasma selenium, 0.79; 95% CI 0.69–0.93). The same study also reported that cord plasma selenium was inversely associated with wheezing and with consulting a doctor because of wheeze in the second year of life (AOR per 10 mg/kg cord selenium, 0.67 [95% CI 0.47–0.96] and 0.62 [95% CI 0.41–0.93], respectively).¹⁵ Finally, Luo et al.²⁰ revealed a significantly higher rate of moderate and severe vitamin A deficiency in the persistent wheezing group than in the acute wheezing group ($P < 0.01$). Moreover, the rate of severe vitamin A deficiency was significantly higher in patients with severe wheezing than in those with mild or moderate wheezing ($P < 0.01$).

Effects of intake of antioxidants on eczema

Shaheen et al.¹² found that cord selenium was negatively associated with persistent wheeze (AOR per doubling concentration, 0.67), and cord iron was negatively associated with later-onset wheeze (AOR per doubling concentration, 0.86) and with eczema (AOR per doubling concentration, 0.90). Similarly, Martindale et al.¹³ reported a negative association between maternal vitamin

E intake and childhood eczema (*P* value for trend, 0.024). Devereux et al.¹⁴ suggested that maternal zinc intake during pregnancy was negatively associated with ever developing eczema and current treatment for eczema at 5 years of age (*P* value for trend, 0.03 and 0.04, respectively). Overall, Oh et al.²⁹ reported a negative association between intakes of antioxidant-related nutrients and atopic dermatitis. Specifically, a reduced allergic disease risk was found with one standard deviation increase of serum α -tocopherol (OR 0.64, 95% CI 0.41–0.98) and retinol (OR 0.74, 95% CI 0.58–0.96) concentrations.

On the other hand, Gale et al.¹⁶ implied that children whose mothers had a 25(OH)-vitamin D concentration of >75 nmol/L during pregnancy had an increased risk of visible eczema at 9 months, of atopic eczema at 9 months, and of visible eczema at 9 years when compared with children whose mothers had a 25(OH)-vitamin D concentration of <30 nmol/L (AOR 3.26, 95% CI 1.15 – 9.29; AOR 1.62, 95% CI 0.67–3.89; and AOR 1.89, 95% CI 0.51 – 6.99, respectively).

DISCUSSION

In this systematic review, a majority of published studies reveal that maternal antioxidant status during pregnancy and a child's intake of antioxidants during the first years of life are inversely associated with the development of allergic disease during childhood. The results presented in this review indicate that the impact of antioxidants on allergic disease is most evident for antioxidant vitamins, zinc, β -carotene, and selenium. Six studies found a positive association between asthma development during childhood and serum antioxidant concentrations in children.^{18,19,23,24,27,28} Similarly, wheezing as an outcome was examined in six studies, which revealed significant associations with antioxidant levels in maternal serum samples,^{16–18} in child serum samples,^{20–26} and in cord blood samples.¹⁵ Finally, five studies found a positive association between antioxidant status and eczema prevalence; antioxidant status was measured in maternal serum samples in three studies,^{13,14,16} in cord blood samples in one study,¹² and in children's serum samples in one study.²⁹

Similarly, recent reviews have highlighted associations between childhood allergic disease and reduced maternal intake of some nutrients during pregnancy. Currently, several cohort studies from populations with differing socioeconomic, genetic, smoking, and dietary profiles have reported low maternal intakes of dietary vitamin E and zinc during pregnancy to be associated with an increased likelihood of childhood allergic disease.¹⁰ Moreover, a number of studies have revealed that the Mediterranean diet, due to its high antioxidant content (predominance of fruit, vegetables, legumes, nuts

and whole-grain cereals) has been associated with a reduced likelihood of asthma, wheezing, and allergic rhinitis.⁹ In parallel, there are studies that found an association between reduced lifetime prevalence of allergic rhinitis and the frequent consumption of grapes, oranges, kiwi fruit, and a high Mediterranean diet score.⁹

In line with the above, recent findings highlight the significance of the prenatal and early infant periods for the development of allergic disease.² Even if allergic disease has a clear genetic basis, it has been reported that a reduced barrier function as well as altered immunity are fundamental to the development of allergic disease.³⁰ More specifically, a suboptimal fetal nutrient status antenatally adversely affects respiratory epithelial and mesenchymal development, resulting in suboptimal early-life airway function, which is associated with an increased risk of wheezing and asthma in later childhood.³¹ A variety of immune cell types and maturational processes that can be altered by antioxidant status through nutrition are involved in the mechanisms of pathogenesis.² Moreover, any suboptimal nutritional deviation of initial encounters between allergen and Th cells towards the Th2 phenotype are likely to be disproportionately exaggerated by the natural immunoregulatory mechanisms that promote further Th-cell differentiation towards the Th2 phenotype and inhibit development of the reciprocal Th1 phenotype.³¹ Conclusively, antioxidants counteract oxidative stress and inhibit the inflammatory response,^{32,33} which might lead to adverse outcomes regarding the form of immune dysfunction and the increased risk of allergic disease in offspring.³⁴

This systematic review focused on studies that assessed dietary antioxidant status by means of biomarkers. Biochemical indicators of dietary intake included maternal and child serum and cord blood samples. One important limitation of these measurements is that these biomarkers reflect recent intake¹¹ and, therefore, might not provide sufficient information on long-term intake, which is the most relevant risk factor for chronic disease. In addition, factors such as exposure to tobacco smoke may decrease serum levels of vitamin C and, therefore, might result in invalid information on antioxidant status as well as altered measurable outcomes.^{35–38} Nevertheless, similar problems exist when assessing nutrient intake based on 24-hour recalls, food-frequency questionnaires, and dietary histories, all of which may provide a poor measurement of daily intake because of a wide variation in intake from day to day; moreover, the use of a food-frequency questionnaire results in random error in the measurement of dietary intake and might lead to the underestimation of the relationship between dietary factors and allergic disease.¹¹

Nearly all studies quantifying the levels of antioxidants in blood have been of cross-sectional or case-

control design, and because allergic diseases are associated with oxidant stress, it is not possible to determine whether low antioxidant levels preceded disease or resulted from disease.⁶ In addition, these studies are also beset by the problem of confounding, because dietary intakes can be associated with age, gender, region, socio-economic status, culture, lifestyle, smoking habit, or ethnicity; furthermore, foods and diets rich in one antioxidant tend to be rich in others, and as a result it is possible that the observed associations are a consequence of confounding by complex social and behavioral factors.³⁹ The number of potential confounding factors for which adjustment is made in studies of antioxidants and allergic disease ranges from a minimal number to a large number of factors.

Several forms of childhood allergic disease are associated with a number of environmental risk factors, most of which can be avoided. Disease prevention, therefore, will be most successful if exposure to the prenatal and neonatal environmental risk factors is avoided.^{2,33} The results of this review indicate that current approaches to identify maternal and neonatal environmental exposures that are correlated with immunotoxicity are inadequate. As a result, recent findings of the inverse associations between intake of antioxidants and childhood allergic disease increase the need for well-designed interventional and/or cohort studies in pregnant women and child populations. Such studies should aim to evaluate and reveal the clear relationship between exposure and disease over an adequate time frame and to obtain insight into the causality of the association after adjusting for several risk factors. Moreover, recent studies report an association between allergic disease and polymorphisms in different genes (interleukin-13, interleukin-4 receptor, catalase, etc.), indicating the need for further investigation of the role of different gene polymorphisms that are involved in the antioxidant defense system and that result in the pathogenesis of allergic disease.^{40,41} Moreover, research could also focus on policy issues that aim to identify effective methods of promoting the consumption of fresh fruits and vegetables, especially among pregnant women and children.

CONCLUSION

The results of this review show that the majority of published studies indicate an association between inadequate antioxidant status in utero and during early childhood and an increase in the risk of allergic disease. Future well-designed interventional cohort studies are needed to confirm these findings, and further work, particularly in children and pregnant women, is required to establish whether dietary intervention with individual nutrients has a role in the prevention or treatment of allergic disease.

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Declaration of interest. The authors have no relevant interests to declare.

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