Association between antioxidant vitamins and asthma outcome measures: systematic review and meta-analysis

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ABSTRACT

Background: Epidemiological studies suggest that dietary intake of vitamins A, C and E may be associated with the occurrence of asthma. A systematic review and meta-analysis was conducted in accordance with MOOSE guidelines to determine whether vitamins A, C and E, measured as dietary intakes or serum levels, are associated with asthma.

Methods: MEDLINE, EMBASE, CINAHL, CAB abstracts and AMED (up to November 2007), conference proceedings and bibliographies of papers were searched to identify studies of asthma, wheeze or airway responsiveness in relation to intakes and serum concentrations of vitamins A, C and E. Pooled odds ratios (OR) or mean differences (MD) with 95% confidence intervals (CI) were estimated using random effects models.

Results: A total of 40 studies were included. Dietary vitamin A intake was significantly lower in people with asthma than in those without asthma (MD −182 μg/day, 95% CI −288 to −75; 3 studies) and in people with severe asthma than in those with mild asthma (MD −344 μg/day; 2 studies). Lower quantile dietary intakes (OR 1.12, 95% CI 1.04 to 1.21; 9 studies) and serum levels of vitamin C were also associated with an increased odds of asthma. Vitamin E intake was generally unrelated to asthma status but was significantly lower in severe asthma than in mild asthma (MD −1.20 μg/day, 95% CI −2.3 to −0.1; 2 studies).

Conclusions: Relatively low dietary intakes of vitamins A and C are associated with statistically significant increased odds of asthma and wheeze. Vitamin E does not appear to be related to asthma status.

METHODOLOGY

Statistical analysis

Data were extracted independently by two authors (SA and JL-B). Dichotomous outcomes are presented as odds ratios (OR) with 95% confidence intervals (CI) and continuous outcomes are presented as mean differences (MD) with 95% CI. Conversions of biochemical units of measurement for the exposures were performed where necessary to allow for comparisons of units across studies.
Identified from searches n = 2624

Excluded after title n = 2305

Included after titles n = 319

Excluded after abstract n = 230

Included after abstracts n = 89

Excluded at full text stage n = 49
Not relevant exposure n = 7
Reviews n = 23
Not pre-specified outcome n = 17
Other n = 2

Included in systematic review n = 40

Insufficient data for meta-analysis n = 3

Included in meta-analysis n = 37

Figure 1 Flow chart for identifying studies.

Where exposure was expressed in quantiles, vitamin levels are expressed as high or low, typically representing a comparison of the lowest with the highest exposure categories.

Meta-analyses were performed to calculate weighted effect measures across studies using random effects models. Heterogeneity between the studies was assessed using $I^2$, and if levels of heterogeneity ($I^2 > 75\%$) existed, then meta-analyses were not performed. Subgroup analyses relating to methods of asthma diagnosis, adult versus children and methodological quality of the studies were conducted to explore reasons for moderate levels of heterogeneity ($I^2 > 50\%$). Analysis was performed using Review Manager 4.2.9 (Version 4.2 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003); $p$ values $< 0.05$ were considered statistically significant. The systematic review was carried out in accordance with the MOOSE guidelines.12

RESULTS

Overview of included studies

From an initial 2624 papers and abstracts identified from the literature searches, 89 had potentially eligible abstracts and 40 met the selection criteria (table 1, fig 1). Twenty-three of these assessed asthma as an outcome,16–19 25 26 28 29 31 32 34–36 40–44 47 48 50–52 and 23 studied biochemical levels in serum or plasma.15–15 17 18 20 21 23 24 26–28 30 31 33 34 38 37 39 42 46 48 50 and 1 assessed the effects of antioxidant levels in sputum.72 Further information about the individual studies is presented in the online supplement.

Methodological quality of the studies

The NOS scores for the 40 studies ranged from 3 to 9, with a median of 6; 26 of the 40 studies (65%) were scored as being of moderate or high level ($\geq 6$) methodological quality.

Dietary intake and serum levels of vitamin A

Overall, 21 papers reported the association of vitamin A or its components on one or more of the outcome measures,15–15 24 25 27–29 31 32 34–36 40 42 45 51 52 of which 11 papers assessed exposure to vitamin A, 15–17 19 20 24 34 36 39 43 45 10 assessed $\beta$-carotene,17 18 22 25 51 52 and 4 assessed carotene.29 31 35 40

The results for $\beta$-carotene, $\alpha$-carotene, retinol and carotene are presented in the online supplement.

Asthma as the outcome

Self-reported dietary intake was significantly reduced in asthma by 182 µg/day (95% CI $-$288.42 to $-$75.25; $F = 0\%$; 8 studies; fig 2). Pooled serum levels were also reduced in asthma (4 studies; all high quality and ascertained asthma using physician diagnosis), though not to the point of statistical significance (by 0.17 mol/l (95% CI $-$0.36 to 0.02); $F = 59\%$; fig 2). However, the direction of the association seemed to differ between adults and children, with pooled serum levels being significantly reduced in the two studies in children (MD $-$0.25 µmol/l, 95% CI $-$0.40 to $-$0.10; fig 2).

Asthma severity as the outcome

Cases of severe asthma had significantly lower dietary intakes of vitamin A (MD $-$344 µg/day (95% CI $-$757.17 to $-$112.64; $F = 0\%$; 2 studies; fig 3) than cases of mild disease. Results of the four studies assessing serum levels showed extreme heterogeneity ($I^2 = 80\%)$ so a pooled analysis was not carried out; however, a subgroup analysis suggested that physician-diagnosed cases of severe asthma (all studies of lower quality and conducted in adults) had significantly lower serum levels of vitamin A (MD $-$0.48 µmol/l, 95% CI $-$0.66 to $-$0.30; $F = 0\%$; 5 studies; fig 3) than cases of mild disease. No relation was seen for self-reported severity of asthma (all conducted in children and of higher quality) (MD $-$0.02, 95% CI $-$0.17 to 0.13; 1 study; fig 3).

Wheeze as the outcome

Although no association was seen between low dietary intakes of vitamin A and wheeze (OR 0.58, 95% CI 0.29 to 1.16; 1 study), low serum levels were significantly associated with a 24% decreased odds of wheeze (95% CI 0.63 to 0.92; 1 study).

Airway reactivity as the outcome

No significant associations were seen for total dietary intake of vitamin A (MD 0.02, 95% CI $-$0.08 to 0.12 per doubling intake).43

Dietary intake and serum levels of vitamin C

A total of 52 papers reported the association with vitamin C.11 14 16 17 19 21–23 26 27–29 32–34 40–44 51 52
Asthma as the outcome

Low levels of dietary vitamin C intake were associated with a significant increase in the relative odds of asthma (OR 1.12, 95% CI 1.04 to 1.20; \( I^2 = 0\% \); 9 studies; fig 4). Meta-analysis of studies reporting serum vitamin C levels and the odds of asthma was not carried out because of extreme levels of heterogeneity (\( I^2 = 94\% \); 2 studies; both studies were of moderate to high quality and used self-reported asthma diagnosis); however, individual studies showed that low levels of serum vitamin C were associated with increased odds of asthma (OR 1.12, 95% CI 1.04 to 1.20 per 1 \( \mu \)mol/L increase; OR 1.01, 95% CI 1.00 to 1.02 per 1 \( \mu \)mol/L increase;\(^6\)).

The mean dietary intake of vitamin C was not significantly different in people with asthma compared with those without asthma (MD \(-8.62\) mg/day, 95% CI \(-19.77\) to \( 2.55\); \( I^2 = 19\% \); 5 studies). Pooled analyses of mean serum levels of vitamin C and asthma status could not be performed owing to high levels of heterogeneity (\( I^2 = 100\% \); 9 studies), primarily relating to one study\(^14\) in which extremely high levels of vitamin C were seen in the control group (mean 272.54 \( \mu \)mol/L). A sensitivity analysis restricted to high-quality studies (NOS \( \geq 8\)) excluded this finding\(^14\) and revealed that people with asthma had mean serum levels that were significantly lower (by 16.8 \( \mu \)mol/L, 95% CI \(-21.5\) to \(-12.1\); \( I^2 = 0\% \); 2 studies), while non-significant reductions were seen in moderate and lower quality studies (fig 5). Subgroup analyses based on age (adult: \( I^2 = 99.5\% \), 6 studies; children: \( I^2 = 94\% \), 2 studies) and method of asthma ascertainment (physician-diagnosed: \( I^2 = 88\% \), 6 studies; self-reported: 1 study; unknown method: 1 study) indicated that these factors did not explain any of the observed heterogeneity.

Asthma severity as the outcome

Similar dietary intake (MD \(-16.13\) mg/day, 95% CI \(-41.02\) to \( 8.76\), \( I^2 = 0\% \); 2 studies) and serum levels (MD \(-5.41\) \( \mu \)mol/L, 95% CI \(-14.17\) to 3.35; \( I^2 = 67\% \); 4 studies) of vitamin C were seen between severe and non-severe asthma.

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**Table 1** Characteristics of the included studies

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*Methodological quality of studies based on the Newcastle-Ottawa Quality Assessment Scale. †Non-parametric data presented in article. ‡Excluded from meta-analysis due to insufficient data. §Constituent of vitamin A or E measured.
Figure 2  Dietary intake (µg/day) and serum levels (µmol/l) of vitamin A and asthma. Mean differences relate to the difference in mean dietary intakes or serum levels of vitamin A. Squares are the difference in means between people with asthma and those without asthma, and bars represent 95% confidence intervals (CI). Negative mean differences indicate lower levels seen in subjects with asthma than in those without asthma. Arrows on the end of bars indicate that the limits are beyond the scale presented.

Figure 3  Dietary intake (µg/day) and serum levels (µmol/l) of vitamin A and asthma severity. Mean differences relate to the difference in mean dietary intakes or serum levels of vitamin A. Squares are the difference in means between people with severe asthma and those without severe asthma, and bars represent 95% confidence intervals (CI). Negative mean differences indicate that lower levels are seen in people with severe asthma than in those with mild asthma. Arrows on the end of bars indicate that the limits are beyond the scale presented.
Figure 4  Dietary intakes (mg/day) of vitamin C and asthma. Odds ratios relate the ratio of odds of low dietary levels of vitamin C in people with asthma compared with those without, and bars represent 95% confidence intervals (CI). Odds ratios <1 indicate that lower dietary levels of vitamin C are seen in people with asthma than in those without asthma. Arrows on the end of bars indicate the limits are beyond the scale presented.

Figure 5  Serum levels (µmol/l) of vitamin C and asthma. Mean differences relate to the difference in mean serum levels of vitamin C. Squares are differences in mean between people with asthma and those without asthma and bars represent 95% confidence intervals (CI). Negative mean differences indicate that lower levels are seen in people with asthma than in those without asthma. Arrows on the end of bars indicate the limits are beyond the scale presented.
Wheeze as the outcome

An increased odds of wheeze was associated with lower dietary intakes of vitamin C (OR 1.10, 95% CI 1.00 to 1.20; \( p = 0.04 \); \( I^2 = 0\% \); 6 studies; fig 6). Extreme levels of heterogeneity were seen between the studies that assessed serum levels of vitamin C and the odds of wheeze (3 studies; \( I^2 = 81\% \)), therefore pooled analyses were not performed. All three studies were of moderate to high quality and assessed wheeze using self-reported questionnaire; however, a subgroup analysis based on age found that no effect was present in adults (OR 0.99, 95% CI 0.97 to 1.01; \( I^2 = 0\% \); 2 studies), but a significant 41% increase in the odds of wheeze was seen in the study that included participants of all ages (95% CI 1.14 to 1.75). Additionally, mean dietary intake (MD 4.70 mg/day, 95% CI −26.6 to 36.0; 1 study) and mean serum vitamin C (MD 0.06 μmol/l, 95% CI −1.00 to 1.12; \( I^2 = 0\% \); 2 studies) were similar in people with and without wheeze.

Airway reactivity as the outcome

Three heterogeneous studies conducted in adults reported the relation between dietary intake of vitamin C and airway reactivity as measured using methacholine challenge. Two studies found evidence of a significant increase in airway reactivity with lower levels of vitamin C (OR 7.14; 95% CI 1.92
Asthma

Dietary intake and serum levels of vitamin E

Twenty-four studies reported the association with vitamin E levels,16 17 21 22 24 25 27–29 31 32 34–36 38–40 43–45 48 49 51 52 of which 4 assessed α-tocopherol in particular.21 23 31 36

Asthma as the outcome

Pooled analyses could not be performed to assess the relation between mean dietary intake (I² = 81%; 5 studies) or mean serum levels (I² = 90%; 6 studies) of vitamin E and asthma due to extreme heterogeneity. All of the studies that measured mean dietary intake of vitamin E were of moderate to high quality and conducted in adults, and therefore only subgroup analyses based on ascertainment of asthma status were conducted. Significantly lower mean levels of dietary vitamin E were associated with asthma in studies which used physician diagnoses (MD 1.20 mg/day, 95% CI -2.29 to -0.11; I² = 0%; 2 studies); however, no significant difference in mean serum vitamin E levels were seen with asthma in studies which used physician diagnoses (MD 0.10 μmol/l, 95% CI -1.17 to 1.57; I² = 47%; 5 studies; fig 7). No relation was seen between the odds of asthma and lower dietary intakes of vitamin E (OR 1.23, 95% CI 0.90 to 1.69; I² = 74%; 6 studies) or serum levels of vitamin E (OR 1.04, 95% CI 0.91 to 1.19; 1 study). All of the studies of the relation between dietary intake of vitamin E and the odds of asthma (6 studies) used self-reported ascertainment of asthma. A subgroup analysis of these studies showed a non-significant trend towards an increased odds of asthma with lower levels of dietary vitamin E (adults: OR 1.25, 95% CI 0.93 to 1.67; p = 0.13; I² = 53%; 4 studies); however, studies were too heterogeneous for comparisons in children (I² = 91%; 2 studies). A subgroup analysis based on quality of the studies did not explain any of the observed heterogeneity between the 6 studies (moderate to high quality: I² = 84%; 3 studies; low quality: I² = 63%; 3 studies).

Asthma severity as the outcome

Significantly lower dietary intake was seen in those with severe asthma (MD -1.20 μg/day, 95% CI -2.29 to -0.11; I² = 0%; 2

Figure 7 Dietary intakes (mg/day) and serum levels (μmol/l) of vitamin E and asthma. Mean differences relate to the difference in mean dietary intake or serum levels of vitamin E. Squares are differences in mean between people with asthma and those without asthma, and bars represent 95% confidence intervals (CI). Negative mean differences indicate that lower levels are seen in people with asthma than in those without asthma. Arrows on the end of bars indicate the limits are beyond the scale presented.
studies) but there was no difference in mean serum levels (MD 
−0.34 μmol/L, 95% CI −3.79 to 2.94; F = 31.5%; 3 studies) 
compared with those with less severe disease.

Wheeze as the outcome
Similar levels of dietary intakes of vitamin E were seen in people 
with wheeze and those without (MD 0.80 μg/day, 95% CI 
−0.23 to 1.83; 1 study). No relation was seen between the odds 
of wheeze and lower serum levels (OR 1.08, 95% CI 0.88 to 1.30; 
1 study) or lower levels of dietary intake (OR 0.90, 95% CI 0.68 
to 1.20; F = 66%; 5 studies).

Airway reactivity as the outcome
No association was seen between the risk of airway reactivity 
and lower dietary intakes of vitamin E (OR 1.06, 95% CI 0.48 to 
2.38; F = 39%; 2 studies; MD −0.08, 95% CI −0.26 to 0.09 per 
doubling intake; 1 study).

DISCUSSION
This systematic review and meta-analysis of the evidence on 
antioxidant vitamin intake and asthma status shows a 
consistent negative association between overall dietary vitamin 
A intake and the odds of asthma and severe asthma, although 
findings for wheeze were less consistent. The mean deficit of 
182 μg vitamin A per day in people with asthma relates to 26% 
and 30% of the latest recommended daily intakes of vitamin A 
for men and women, respectively.54 Additionally, most of the 
studies assessing the association found mean levels of vitamin A 
in people with asthma were below the recommended daily 
intakes. Vitamin A intake was lower in people with severe 
asthma than in those with less severe asthma by the equivalent 
of about half the recommended daily amount (50% in men and 
57% in women). The results for the specific types of vitamin A 
(retinol, α-carotene, total carotenoids and carotene) did not 
generally reach statistical significance at the 5% level; however, 
there was a tendency for increased serum β-carotene levels to be 
associated with reduced odds of asthma.

For vitamin C we found evidence of an increase of 
approximately 12% in the odds of asthma associated with 
lower levels of intake of vitamin C. Results from individual 
studies also suggested that mean serum levels tended to be 
lower in people with asthma. These findings were generally 
supported by the results for wheeze and airway reactivity; 
however, associations with asthma severity were not conclu- 

These findings contrast with those of a recent meta-analysis 
of published studies55 which found no significant association 
between dietary antioxidant intake and asthma or lung 
function. However, this meta-analysis searched only for studies 
in adults published in English language journals and listed in 
only one electronic database, and the meta-analyses were based 

One concern relating to our analysis is that the methods used 
to ascertain levels of the antioxidant vitamins (either through 
dietary intake, plasma and serum or sputum levels) were 
 inconsisent over the range of the studies included. Even within 
 a particular type of ascertainment such as food frequency 
 questionnaires, substantial variation existed between the 
 methods used and the periods covered by the questionnaire, 
 some assessing dietary intake over the last 12 months and some 
 over 6 months. In addition, due to the design of the majority 
of studies included in the review, the levels of antioxidant vitamins 
 were assessed after the onset of asthma. The use of both food 
 frequency questionnaires and of biological levels to estimate 
 dietary intake have recognised strengths and weaknesses, but a 
 major strength of questionnaires is that they measure typical 
 dietary patterns over several months and, while the quantitative 
estimates of intake they provide are relatively imprecise, their 
 ranking of intake is more representative56 and therefore suitable 
 for combination in the meta-analysis of quantile effects. 
 Biochemical levels offer the advantage of objectivity but often 
 reflect only relatively recent intake and may also be subject to 
 homeostatic or other metabolic or excretory influences that 
distort the relation between biological level and dietary intake. 
 For example, levels of vitamin C in peripheral blood show 
 relatively little variation between intakes above the minimum 
 recommended daily intake57 and are therefore less representative 
 of between-subject differences in intake than questionnaire 
 measures. Thus, while dietary and serum measures are 
 correlated for vitamin A,58 vitamin C61 and vitamin E 62 and, in 
 particular, strong correlations have been reported for anti- 
oxidant vitamins in people with asthma,63 these methodological 
differences are still likely to cause some discrepancy in the 
 observed relations between diet and disease.

Most of the studies we analysed did not report adjusted 
 results, so the results from our analyses are primarily based on 
 crude estimates which were either extracted or estimated from 
 these studies and so are subject to the unadjusted effects of 
 confounding factors such as age,27 63 64 socioeconomic status,15 35 
 smoking,66 67 body mass index,68 the effects of correlated intakes 
 of other antioxidant vitamins and, in particular for vitamin E, 
 the effects of total cholesterol and lipid levels. The most 
 common factors adjusted for in the included studies were age 
 (23 studies), sex (18 studies), smoking (active or passive, 16 
 studies) and social class (12 studies); only 6 studies adjusted for 
 the effects of other antioxidant vitamins in their analyses.

Overall, our findings from this systematic review and meta- 
analysis indicate that low levels of vitamin C intake and—to a 
 lesser extent—vitamin A are consistently associated with 
 asthma risk to a degree that, if causal, would be sufficient to 
 be clinically relevant. These findings are plausible, given the 
 recognised anti-inflammatory and antioxidant actions of these 
vitamins.59 However, these conclusions have not been supported 
 by the limited data available from randomised clinical trials of 
dietary supplementation with vitamin C for which a recent 
 Cochrane review concluded that there is no appreciable effect.5

One explanation for this discrepancy would be that the 
 observational data are systematically flawed by biases leading 
to spurious results from meta-analyses,60 and particularly 
publication bias. We attempted to minimise the effects of 
publication bias by performing comprehensive searches that 
 included “grey” literature; however, we were unable to formally 
test for publication bias due to the small numbers of studies 
 included in the meta-analyses. Another possibility is that the 
 observed relation between nutrient intake and disease is not 
causal but arises from correlation with other causally-related 
 nutrients or non-dietary exposures. Alternatively, the observa-

sustained periods of intake than have been tested in randomised trials to date. Reverse causation is also a potential explanation, particularly in severe asthma, but there is no evidence that this occurs in the milder disease that predominated in the studies analysed.

The epidemiological evidence thus suggests that vitamins A and C are linked to asthma. Epidemiological studies and meta-analyses are useful for identifying association between exposures and diseases but cannot reliably establish causation. Further investigations are necessary to account for the observed associations using well-designed randomised controlled trials of vitamin supplementation in asthma. Trials of vitamin C supplementation to date have been disappointing: whether the effect of vitamin A will prove more important to clinical management or whether the observed associations with diet are due to confounding effects will only be resolved by further clinical trials.

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REFERENCES

Safety and effectiveness of home-based pulmonary rehabilitation in COPD

Despite overwhelming evidence to suggest that pulmonary rehabilitation improves health status in patients with chronic obstructive pulmonary disease (COPD), this service is largely underutilised due to poor accessibility. This Canadian multicentre randomised study was designed to compare outpatient pulmonary rehabilitation with self-monitored home-based rehabilitation in improving dyspnoea.

Patients with stable COPD (forced expiratory volume in 1 s <70% predicted) and an MRC dyspnoea score of 2 or more were recruited. 252 patients with similar baseline characteristics were randomly assigned to both groups. Both groups showed statistically and clinically significant improvements in dyspnoea scores (on chronic respiratory questionnaire) at 3 months. Although this was not maintained, the home rehabilitation group was certainly not inferior to the outpatient rehabilitation group at 1 year. Both strategies were similar at 3 months and 1 year in improving 6-minute walking distance, cycling endurance time and health status (as assessed by St George’s Respiratory Questionnaire components). Adverse events were comparable for both groups.

The authors conclude that home-based rehabilitation is safe and not inferior to hospital outpatient rehabilitation in improving dyspnoea, health status and exercise tolerance. They also point out that, despite the fact that no economic analysis was done, the cost implications are likely to be similar for both strategies. However, the results have to be applied cautiously in patients with severe COPD who potentially may benefit the most from home-based rehabilitation, as only a small proportion with severe disease were included in the study. This study alludes to a potential alternative for patients who are unable to access hospital-based pulmonary rehabilitation.


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