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

S Allen, J R Britton, J A Leonardi-Bee

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 intake does not appear to be related to asthma status.

Diet has been widely implicated in the aetiology of cardiovascular disease1 2 and other disorders, but the role of diet in the aetiology of respiratory diseases is less clearly defined. Over the past 15 years many observational epidemiological studies have reported associations between diet and asthma, and particularly for the antioxidant vitamins A, C and E. However, randomised controlled trials of vitamin supplementation in asthma thus far have been inconclusive.3−5 In view of this apparent inconsistency between the observational and experimental data,7 we have attempted to determine the magnitude of the overall associations of these vitamins estimated by the observational studies by carrying out a systematic review and meta-analysis to provide pooled quantitative estimates of the likely magnitude of the effect of dietary intake and blood levels of antioxidant vitamins on a range of measures of asthma and asthma severity.

METHODS

Systematic review methods
A comprehensive search of the MEDLINE (1950 to November 2007), EMBASE (1980 to November 2007), CINAHL (1982 to November 2007) and AMED (1985 to November 2007) was conducted to identify all published comparative epidemiological studies assessing the relation between antioxidant vitamins and asthma status. Search terms were selected under guidance from the Centre for Reviews and Dissemination and the Airways Group Specialist search terms.8 Reference lists from identified relevant studies and previous reviews were scanned and checked for further studies. Abstracts were identified through searching CAB abstracts database (1973 to November 2007) and American Thoracic Society conferences (2005–2007). No language restrictions were applied.

The exposures of interest were measures of dietary intake or of objective levels of vitamins in body fluids of the antioxidant vitamins A, C and E. The primary outcome measure used was asthma (physician-diagnosed, self-reported physician-diagnosed or defined as exercise-induced bronchospasm/constriction); secondary outcomes included wheeze, airway reactivity and asthma severity. Studies using spirometry or symptoms of cough and breathlessness as their main outcomes were excluded as these outcomes are likely to be relatively non-specific to asthma.

Two authors (SA and JL-B) reviewed the titles and then the abstracts, excluding irrelevant papers after each stage. Disagreements were resolved by discussion. The full text of the remaining papers was sought and the following exclusion criteria applied: reviews, duplicated studies, those without relevant outcomes and those in which no quantitative results or p values were presented, inability to source the text. Included studies were assessed for methodological quality using the Newcastle-Ottawa Scale for Quality Assessment (NOS).9 The median score of 6 was used to distinguish moderate and high quality studies from poorer quality studies.

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.10
of the papers studied the effects of measures of dietary intake,^16^-19 23 25 27 29 31 32 34-36 40-45 47-52 23 studied biochemical levels in serum or plasma^15^-15 17 18 20 21 23 24 26-28 30 31 33 34 36-37 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 (>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 35 36 38-40 48 51 52 of which 11 papers assessed exposure to vitamin A,^15^-17 19 20 24 25 34 43 45 10 assessed β-carotene,^17 18 22 25 31 38 43 45 2 assessed α-carotene,^17 18 6 assessed retinol^15^-20 26 36 40 31 52 and 4 assessed carotene.^39 31 35 40 45 49 52 The results for β-carotene, α-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; I^2 = 0%; 3 studies; fig 2). Pooling 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 0.10 μmol/l (95% CI 0.58 to 0.66; I^2 = 0%; 1 study), OR 0.58, 95% CI 0.29 to 1.16; 1 study). 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 –575.17 to –112.64; I^2 = 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; I^2 = 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).^45

### Dietary intake and serum levels of vitamin C

A total of 32 papers reported the association with vitamin C,^11 14 16 17 19 21-25 20 27-30 32-34 40 44 49 51 52

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**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,^15^-15 24 25 27-29 31 35 36 38-40 48 51 assessed asthma and wheeze,^45^-49 2 assessed airway reactivity^20 51 and 1 assessed both asthma and airway reactivity.^22 Twenty-six
Asthma

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 1.00, 95% CI 0.98 to 1.02 per 1 µmol/l increase; \( I^2 = 0\% \); 2 studies), while non-significant reductions were seen in moderate and lower quality studies (\( I^2 = 84\% \), 2 studies) and method of ascertainment (physician-diagnosed: \( I^2 = 99.5\% \), 6 studies; self-reported: 1 study; unknown method: 2 studies) and method of 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 µmol/l, 95% CI −14.17 to 3.35; \( I^2 = 67\% \); 4 studies) of vitamin C were seen between severe and non-severe asthma.

Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Exposure</th>
<th>Dietary component measured</th>
<th>Methodological quality score</th>
<th>Geographical area</th>
<th>Population</th>
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<td>Australia</td>
<td>Adult</td>
</tr>
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</table>

*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 lower levels 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dietary intake of vitamin C (mg/day) and asthma</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio (random) 95% CI</td>
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<td></td>
<td>Exposed group</td>
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<tr>
<td>01 Case-control studies</td>
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<tr>
<td>Hijazi 2000</td>
<td>1.79 (0.86, 3.70)</td>
</tr>
<tr>
<td>Patel 2006</td>
<td>1.12 (1.03, 1.22)</td>
</tr>
<tr>
<td>Shaheen 2001</td>
<td>1.09 (0.75, 1.58)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.13 (1.04, 1.23)</td>
</tr>
<tr>
<td>Test for heterogeneity: χ² = 1.57, df = 2 (p = 0.46), P = 0%</td>
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<tr>
<td>Test for overall effect: Z = 2.84 (p = 0.004)</td>
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<tr>
<td>02 Cross-sectional studies</td>
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<tr>
<td>Burns 2007</td>
<td>1.04 (0.69, 1.56)</td>
</tr>
<tr>
<td>Huang 2001</td>
<td>1.82 (0.88, 3.77)</td>
</tr>
<tr>
<td>Omenaas 2003</td>
<td>0.68 (0.36, 1.32)</td>
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<tr>
<td>Romieu 2004a</td>
<td>1.59 (0.91, 2.77)</td>
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<td>Romieu 2004b</td>
<td>1.04 (0.69, 1.57)</td>
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<tr>
<td>Woods 2003</td>
<td>1.08 (0.76, 1.53)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1.11 (0.90, 1.37)</td>
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<tr>
<td>Test for heterogeneity: χ² = 5.85, df = 5 (p = 0.32), P = 14.5%</td>
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<td>Test for overall effect: Z = 0.96 (p = 0.34)</td>
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<td>03 Cohort studies</td>
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<tr>
<td>Troisi 1999</td>
<td>0.90 (0.57, 1.44)</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>Test for overall effect: Z = 0.44 (p = 0.66)</td>
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<tr>
<td>Total (95% CI)</td>
<td>1.12 (1.04, 1.21)</td>
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<tr>
<td>Test for heterogeneity: χ² = 8.31, df = 9 (p = 0.50), P = 0%</td>
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<td>Test for overall effect: Z = 2.80 (p = 0.004)</td>
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</table>

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Serum levels of vitamin C (µmol/l) and asthma</th>
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<tbody>
<tr>
<td></td>
<td>Mean difference (random) 95% CI</td>
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<td>Exposed group</td>
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<tr>
<td>01 High quality studies (NOS ≥ 8)</td>
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<tr>
<td>Aderle 1985</td>
<td>-17.04 (−21.99, −12.09)</td>
</tr>
<tr>
<td>Baker 1999</td>
<td>-14.50 (−30.27, 1.27)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>-16.81 (−21.53, −12.09)</td>
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<tr>
<td>Test for heterogeneity: χ² = 0.09, df = 1 (p = 0.76), P = 0%</td>
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<td>Test for overall effect: Z = 6.98 (p &lt; 0.00001)</td>
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<td>02 Medium quality studies (NOS = 6 or 7)</td>
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<td>Kelly 1999</td>
<td>-6.00 (−19.52, 7.52)</td>
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<td>Picado 2001</td>
<td>-4.00 (−53.97, 45.97)</td>
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<td>Powell 1994</td>
<td>-1.96 (−12.70, 8.78)</td>
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<tr>
<td>Shidler 2005</td>
<td>-25.56 (−26.46, 5.26)</td>
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<td>Subtotal (95% CI)</td>
<td>-31.28 (−28.06, 5.52)</td>
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<td>Test for heterogeneity: χ² = 26.99, df = 3 (p &lt; 0.000001), P = 88.9%</td>
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<td>Test for overall effect: Z = 1.31 (p = 0.19)</td>
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<tr>
<td>Mainous 2000</td>
<td>0.51 (−0.87, 1.89)</td>
</tr>
<tr>
<td>Vural 2000</td>
<td>-16.47 (−21.97, −10.97)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>-7.76 (−24.40, 8.87)</td>
</tr>
<tr>
<td>Test for heterogeneity: χ² = 34.45, df = 1 (p &lt; 0.000001), P = 97.1%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.91 (p = 0.36)</td>
<td></td>
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</tbody>
</table>
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; $I^2 = 0\%$; 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 (8 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
to 25.0; MD $-0.12$, 95% CI $-0.22$ to $-0.03$ per doubling in intake), but no association was seen in the other study (OR $1.04$, 95% CI $0.76$ to $1.43$). Dietary intake and serum levels of vitamin E

Twenty-four studies reported the association with vitamin E levels, of which 4 assessed α-tocopherol in particular. Asthma as the outcome

Pooled analyses could not be performed to assess the relation between mean dietary intake ($I^2 = 81%$; 5 studies) or mean serum levels ($I^2 = 90%$; 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 $1.91$ mg/day, 95% CI $2.51$ to $1.31$; $I^2 = 0%$; 4 studies; fig 7), however no effect was seen for self-reported asthma status (MD $0.20$ mg/day; 95% CI $0.72$ to $0.32$; 1 study; fig 7). All of the studies that measured serum levels of vitamin E were of high quality, so subgroup analyses based on age and ascertainment of asthma were conducted. Age did not explain the observed heterogeneity (adults: MD $3.12$, 95% CI $2.53$ to $8.76$, $I^2 = 89%$, 4 studies; children: MD $0.00$, 95% CI $-0.02$ to $0.02$, $I^2 = 0%$; 2 studies), and 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 $1.57$; $I^2 = 47%$, 5 studies; fig 7). However, significantly increased levels of vitamin E were seen in the study which did not define asthma status (MD $9.10$ μmol/l, 95% CI $6.34$ to $11.86$; 1 study; 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 $1.69$; $I^2 = 74%$; 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 $1.67$; $I^2 = 53%$; 4 studies); however, studies were too heterogeneous for comparisons in children ($I^2 = 91%$; 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: $I^2 = 84%$, 3 studies; low quality: $I^2 = 63%$, 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 $-0.11$; $I^2 = 0%$; 2 studies).
studies) but there was no difference in mean serum levels (MD
$-0.34 \text{ mmol/l}, 95\% \text{ CI } -3.79 \text{ to } 2.94; P = 31.5\%; 3 \text{ 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 \( \mu \text{g/day}, 95\% \text{ CI}
-0.23 \text{ to } 1.33; 1 \text{ 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 \text{ 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 \text{ studies}; \text{ MD } -0.08, 95\% \text{ CI } -0.26 \text{ to } 0.09 \text{ per}
doubling intake; 1 \text{ 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 \( \mu \text{g 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.\(^\text{54}\) 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, \( \alpha \)-carotene, total carotenoids and carotene) did not
generally reach statistical significance at the 5\% level; however,
there was a tendency for increased serum \( \beta \)-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-
sive. Measures of vitamin E were, however, generally unrelated
to asthma status, although significantly lower mean dietary
intakes (by approximately 2 \( \mu \text{g/day, about } 20\% \text{ of the daily}
recommended intake of vitamin E) were seen in studies of
people with physician-diagnosed asthma.

These findings contrast with those of a recent meta-analysis
of published studies\(^\text{55}\) 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
on a combined outcome of asthma or wheeze. The present
study was conducted with higher methodological rigor, in
accordance with the MOOSE guidelines,\(^\text{12}\) used more compre-
sensive sources and search strategies and, where possible,
validated search terms.\(^\text{56} - 57\)

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
inconsistent 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 representative\(^\text{58}\) 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 intake\(^\text{59}\) 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,\(^\text{60}\) vitamin C\(^\text{61}\) and vitamin E\(^\text{62}\) and, in
particular, strong correlations have been reported for anti-
oxidant vitamins in people with asthma,\(^\text{63}\) 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
covariables such as age,\(^\text{63} - 65\) socioeconomic status,\(^\text{13} - 35\)
smoking,\(^\text{66} - 68\) body mass index,\(^\text{47}\) 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—for 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.\(^\text{59}\) 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.\(^\text{8}\)
One explanation for this discrepancy would be that the
observational data are systematically flawed by biases leading
to spurious results from meta-analyses,\(^\text{45}\) 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-
tion may reflect a causal association arising from dietary intakes
during early life that tend to track into adulthood, or from more
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 degree 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.

**Funding:** This study was internally funded by the University of Nottingham. The study sponsor had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

**Competing interests:** None.

**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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