



The effect of serum levels of vitamin C on asthmatic children: a systematic review

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ABSTRACT

Introduction: Asthma is a chronic inflammatory airway disorder that is distinguished by coughing, wheezing, and dyspnea. It is the most common chronic disease among children. Epidemiological trials have suggested that there may be a correlation between vitamin C intake and the incidence of asthma. Specifically, according to these studies, a rapid increase in the occurrence of asthma may be caused by a decreased intake of dietary antioxidants and various vitamins such as vitamin C. A systematic review was performed to determine the role that vitamin C, in terms of both dietary intake and serum levels, had on asthma in children.

Methods: PubMed and Scopus databases were searched for studies that provide information on the effects of vitamin C on asthma in children aged between 1 and 17 years. The inclusion criteria specified that the studies involved needed to be cohort and case series involving at least ten patients. Exclusion criteria were non-English articles, case reports, and articles involving children who were aged below or above the age 1 and 17 respectively.

Result: A total of 13 studies involving 6503 patients met the inclusion criteria. Dietary vitamin C intake was lower in people with asthma than in those without asthma. Lower quantity dietary intakes and serum levels of vitamin C were also associated with increased incidents of asthma.

Conclusion: According to the extracted data, a relatively low dietary intake of vitamin C is associated with an increased risk of asthma and wheezing. Moreover, asthmatic patients who consumed vitamin C exhibited an improvement in their diseases.

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Introduction

Recognized as a chronic inflammatory disease that results in reversible airway bronchoconstriction or bronchospasm, asthma is one of the world's most common chronic diseases (1,2). It is believed that over 300 million people suffer from asthma worldwide, and experts predict that this number will increase to 400 million by 2025. Between 2002

and 2007, asthma cost the US around \$3,300 per asthmatic patient each year in medical expenses, missed school and working days, and early deaths. In 2009, approximately one in ten children (10%) and one in twelve adults (8%) had asthma. Women were more likely than men, and boys more likely than girls, to have asthma. In 2010, 3 out of

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5 children who had asthma had reported cases of asthma attacks in the previous 12 months (3). Between 2001 and 2009, the greatest increase in asthma rates was among black children (almost a 50% rise). While asthma affects all age groups, it often commences in childhood and is most prevalent among children (4,5).

Despite the fact that vitamin C was discovered as far back as the 1900s, its role against various diseases has yet to be fully understood (6). It is one of the key antioxidant vitamins that constructs the extracellular fluid lining the lung, and pulmonary dysfunction is associated with low vitamin C intake (7). Adults and children with asthma tend to exhibit lower concentrations of vitamin C when compared to normal subjects (8,9). In addition, studies have reported that the intake of vitamin C can reduce the duration of colds, alleviate the symptoms of asthma, and reduce pulmonary dysfunctions (10-13).

In the 1940s, vitamin C was used to treat asthma for the first time. The use of vitamin C in this manner was controversial among physicians. While some studies demonstrated that vitamin C was useful for their asthmatic patients, others found no such effect (14,15). Some studies have confirmed that vitamin C can protect against the lung inflammation that results from both endogenous and exogenous oxidative responses through oxidant stress (16,17). Furthermore, a recent meta-analysis of three randomized trials on vitamin C and exercise-induced bronchoconstriction revealed that vitamin C demonstrates some effects on some phenotypes of asthma (17-19).

Overall, over the past two decades, many epidemiological investigations have established associations between vitamin C and asthma. This systematic review was inspired by previous research findings that suggested that asthma could be improved through the intake of vitamin C. As a result, this study sought to evaluate the evidence pertaining to the possible effect of vitamin C administration on asthmatic patients.

Methods

Search strategy and selection of articles

To review the literature, PubMed and Scopus databases were searched, based on the PRISMA guidelines, using the following search terms: (vitamin C OR ascorbic acid OR ascorb* AND asthma AND child*), (“vitamin C” OR ascorbic acid OR ascorb* AND asthma), (vitamin C OR “ascorbic acid” OR ascorb* AND “broncho constriction”) and (vitamin C OR ascorbic acid OR ascorb* OR antioxidant AND asthma AND children), separately.

The final search was conducted in May 2015. The titles and abstracts of the articles identified through the initial search were examined, and

irrelevant articles were omitted. The full texts of the remaining articles were reviewed to detect studies that did not meet the inclusion criteria of this systematic review. The reference lists of the relevant articles were also reviewed to identify any additional citations that may be of relevance to the literature review. Since a variety of different factors were assessed in the selected studies, it was not easy to compare these factors. All the articles were evaluated in terms of the inclusion criteria of the present study. The titles and/or abstracts of the identified studies were initially evaluated. Following that, the full texts of all articles that met the inclusion criteria were assessed.

The manual search and other sources

The cross-reference search of the bibliography of relevant articles and the reference lists of all primary studies and review articles were reviewed to find studies that had not been identified via the computerized search. Data about authors, publication data, country, patient characteristics (age range), number of tests, and control group participants, vitamin C dosage, and the result of related vitamin C effects on asthma were extracted. After the removal of any duplicate studies, only 17 met the inclusion criteria, which were case-control studies (Table 1). The search procedure was summarized in a PRISMA chart, and this is presented in Figure 1.

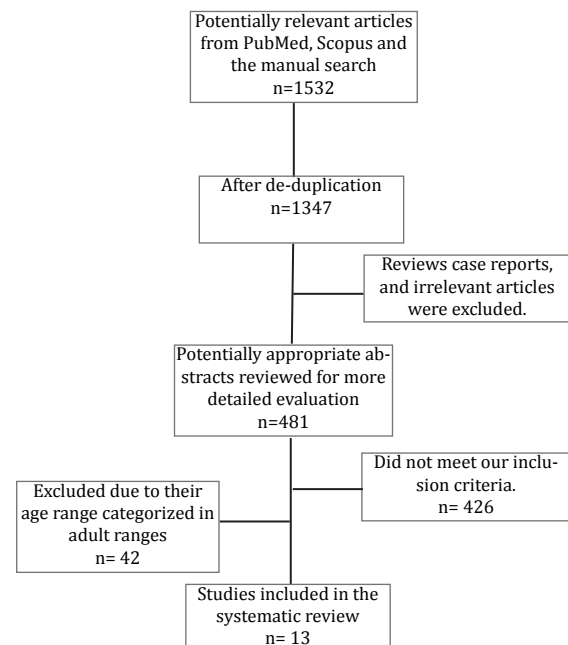


Figure 1. Flowchart of the screening process of articles in the current study

Types of studies, participants, and interventions

Intervention studies, randomized and non-randomized, and placebo-controlled and case-control studies that provided information on the

Table 1. Data extraction from included studies investigated the effect of vitamin C on asthmatic children.

| Author Country Year | No. of asthmatic children | No. of health control | Age range | Vitamin C dosage/ follow-up | Main findings | Study design | Diagnosed asthma |
|-----------------------------------|---------------------------------|-----------------------------|------------------------|---|--|---------------------------------------|---|
| Shanmugasundaram India 2001 | 210 | 180 | 5-10 y | 100 mg per day | Significant reductions in vitamin C concentrations in plasma and GSH in blood in asthma children | Case control | Episodes wheezing, dyspnea or difficult breathing |
| Al-Abdulla Iraq 2010 | 98 | 121 | 1-12 y | Serum measurements | Asthmatic children during exacerbation of their asthma have significant lower serum levels of antioxidant compounds like vitamin C as compared with the controls. | Case controlled prospective study | During acute attack |
| Hemila Finland 2011 | 60 | - | 7.0-8.2 y and 8.3-10 y | 0.2 grams daily and placebo for 6-week | The effect of vitamin C on the childhood asthma control test and FEV1 was significantly modified by age | Cross-over trial | Moderate persistent asthma |
| Harik-Khan USA 2003 | 278 | 3815 | 6-17 y | Ascorbic acid intake was obtained from the dietary | Low vitamin C and intakes are associated with asthma risk in children | Random national population | Physician-diagnosed asthma |
| Sienra-Monge USA 2004 | 59 | 58 | M= 8.9 y | 250 mg/day 12 weeks | Data suggest that vitamin C supplementation above the minimum dietary requirement in asthmatic children and provide some protection against the nasal acute inflammatory response to ozone | Double-blind intervention study | Moderate and severe asthma |
| Forastiere Italy 2000 | 4104 | 18737 | 6-7 y | Fruit intake (categorized as less than once per week, 1-2 per week, 3-4 per week, and 5-7 per week) | The consumption of fruit rich in vitamin C, even at a low level of intake, may reduce wheezing symptoms in childhood, especially among already susceptible individuals. | A random national population sampling | Occurrence of wheezing symptoms over the intervening period |
| Kalayci Turkey 2000 | 14 | 12 | | Serum measurements | Vitamin C was significantly lower in asthmatics at remission compared to controls and it decreased even during the asymptomatic periods of the disease | Case control | During an asthma attack and remission |
| Aderele Nigeri 1985 | 51 | 51 | 1-5 y | Plasma concentration | The mean ascorbic acid level of asthmatics was significantly lower than that of controls. | Case control | |
| Nakamura Japan 2012 | 37 | 415 | 3-6 y | Intake of dietary vitamin | Children with high intakes of vitamin C may be associated with a reduced prevalence of asthma. asthma was significantly associated with low intakes of vitamin C | Case control, questionnaire | Allergy history |

| Author Country Year | No. of asthmatic children | No. of health control | Age range | Vitamin C dosage/ fol- low-up | Main findings | Study design | Diagnosed Asthma |
|---------------------------|---------------------------------|-----------------------------|------------------------|-------------------------------------|---|---|---|
| Romieu Mexico 2002 | 94 | 64 | 6-16 y | 250 mg/day 12weeks | The results suggest that vitamin C had a protective effect against peak expiratory flow decrements after exposure to ozone | Case control | Moderate and severe |
| Romieu Mexico 2004 | 415 | 7,436 | 2-5 y And 6-16 y | 60 mg/day | No increase was observed in children aged 2-5 years. Low vitamin C intake was marginally related to self-reported current wheezing in children aged 6-16 years. | Cross-sectional | Self-reported asthma or wheezing |
| Rubin USA 2004 | 415+ 433 | 5,305 | 4-16 y | Serum measurements | Vitamin C was significantly associated with a lower risk of prevalent asthma | Cross-sectional, multi-stage, complex sample survey | Prevalent asthma, possible asthma and/or wheeze |
| Anderson 1983 | 16 | - | M=9.5 y | 1 g/ per day for 6 months | Injection of ascorbic acid had no detectable effects on the degree of exercise-induced bronchoconstriction | Case control | Exercise-induced bronchoconstriction |

No; number; y; year; mg: milligram; FEV1; forced expiratory volume in one second.

effect of vitamin C on asthma symptoms were included in this systematic review. Studies on children of either gender who were aged from 1-17 years of age were eligible.

Studies were considered for inclusion if they involved children with chronic stable asthma, seasonal asthma, or exercise-induced bronchospasm. In addition, in order to develop clear and identical measures by which studies involving young asthma patients could be assessed, we considered trials that involved asthma physician diagnosis, self-reported physician diagnosis, or those that were defined as exercise-induced bronchospasm/constriction. Secondary outcomes included wheezing, airway reactivity, and asthma severity. Studies using spirometry or symptoms of breathlessness as their main outcomes were excluded because these outcomes are likely to be relatively non-specific to asthma.

Furthermore, vitamin C studies, which reported outcomes on patients with asthma separately as a sub-group, were also considered for inclusion. In addition, the interventions or oral administration of vitamin C were considered as a single dose or as multiple doses for a period. Vitamin C supplementation was compared to placebo or "standard care." Furthermore, we considered health outcomes related to diet and dietary patterns among the population aged 1 to 17 years. The included studies were assessed for methodologi-

cal quality using the Newcastle-Ottawa Scale for Quality Assessment (NOS).

Articles involving less than ten patients, published before 1983, case reports or non-English articles, and those that described patients with diseases such as malnutrition or FTT, pneumonia, and acute bronchitis were excluded from this study.

Results

Overview of included studies

From an initial 1532 papers and abstracts identified during the initial literature search, after deleting the duplicate and irrelevant articles, 481 studies were determined to have potentially eligible abstracts, and 47 met the selection criteria. Of these, only 13 met the inclusion criteria (Figure 1, PRISMA chart).

The population size of the included studies ranged between 6503-36194 asthmatic/control, and the age of the patients and controls ranged from 1-17 years. Moreover, dietary vitamin C intake was lower in people with asthma than in those without asthma (Table 1). Lower quantity dietary intakes and serum levels of vitamin C were also associated with increased odds of asthma.

Discussion

We identified and reviewed 17 randomized controlled trials that evaluated the use of vitamin C

supplements for the treatment of asthma symptoms via single dose, short-term and long-term administration, or dietary fruit intakes. As a result of the differences between the methodologies and results of the studies involved, it was not possible to pool the results. However, a comparison between the studies did find that vitamin C serum concentration in asthmatic children was lower than those of healthy children. Furthermore, there was a general consensus that fruits that are rich in vitamin C reduce some symptoms of asthma and the prevalence of asthmatic attacks.

An analysis of the data accumulated via the National Health and Nutrition Examination Survey (NHANES) revealed an association between dietary vitamin C intake and evidence of pulmonary dysfunction in the general population of the United States. Low vitamin C intake is associated with increased symptoms of asthma and wheezing (20,21). Furthermore, a study by Olusi et al. reported that adult asthmatic patients have lower than normal concentrations of vitamin C in their plasma and blood leukocytes (8). Similarly, an increase of 1 standard deviation in serum concentrations of vitamin C and other non-enzymatic antioxidants, such as β -carotene and selenium, was associated with a reduction in asthma prevalence in a study involving US children (22).

Several investigations have found that taking dietary supplements with extra vitamin C above the normal dietary intake benefits the modulation of acute respiratory effects in healthy adults or asthmatic adults when exposed to oxidative air pollutants (23-25). However, most of these studies have been conducted in a laboratory setting with strict controls in place in terms of age, gender, exercise, and dietary intake in adult subjects. Furthermore, these studies have aimed to investigate the benefits that an additional dose of supplementary antioxidants has in terms of lung function. As such, there is limited data available that specifically describes the effects of vitamins C and E consumed via a normal daily diet on asthma symptoms in children (1).

In comparison to other vitamins, the effects of Vitamin C on asthma symptoms has been more widely investigated. Through several case-control and cross-sectional studies the association between vitamin C and a decreased risk of asthma has been demonstrated (1-4, 6,7); however, in the only available substantive longitudinal study, vitamin C intake was found to have no effect on asthma incidence (8). In randomized trials, vitamin C, in combination with other antioxidants, protects against ozone-induced bronchoconstriction in asthma (1,9,10); however, evidence confirming the effect of vitamin C alone is much less conclusive (11,12). We have recently reported the largest randomized pla-

cebo-controlled clinical trial of vitamin C to date; involving 201 patients randomized to vitamin C or placebo for 16 weeks. This study did not find any association between vitamin C intake and asthma control (13).

In their systematic review and meta-analysis of 32 observational studies involving children and adults, Allen and colleagues reported that a low dietary intake of vitamin C was significantly correlated with slightly increased odds of asthma (26). Moreover, Aderele et al. found that plasma ascorbic acid level was positively correlated with a vulnerability to viral respiratory tract infections and a low level of vitamin C in asthmatic patients, which would make them more prone to infections and acute asthmatic attacks (9). Similarly, Harik-Khan et al. concluded that low vitamin C intake is associated with an increased risk of asthma in children (27). However, through a meta-analysis, GAO et al. concluded that a higher dietary intake of antioxidants was not associated with a lower risk of asthma. The researchers involved in this study did not support the assumption that nutritional intake of vitamin C has an effect on the risk of asthma (28).

Conclusion

The review of the studies that examine vitamin C intake and asthma did not conclusively find that vitamin C supplements can reduce the incidence of asthma. However, in light of the fact that vitamin C is a low-cost supplement that is safe for human consumption, it seems reasonable to recommend that it is prescribed to asthmatic children to alleviate the severity of asthma symptoms. Further research on the possible effects of vitamin C on asthma is required. Specifically, large multicenter randomized controlled trials are recommended.

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Conflict of Interest

The authors declare no conflict of interest.

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