Asthma

Beneficial Roles of Citrus

Executive Summary

Sandy Barros and Filomena Valim

- Lung disease is the number three killer in America, responsible for one in seven deaths (American Lung Association).
- > 35 million Americans are living with chronic lung disease such as asthma, emphysema and chronic bronchitis.
- Asthma is a respiratory disease characterized by episodes or attacks of inflammation and narrowing of the small airways in response to asthma triggers. It is responsible for 14 billion dollars in medical expenses and indirect costs and approximately 5,000 deaths annually.

Types of asthma:

- ***Allergic (extrinsic) asthma:*** characterized by symptoms that are triggered by an allergic reaction. It is the most common form of asthma, affecting over 50% of the 20 million asthma sufferers.
- ***Non-Allergic (intrinsic) asthma:*** triggered by factors not related to allergies. It is triggered by other factors such as anxiety, stress, exercise, cold air, dry air, hyperventilation, smoke, viruses or other irritants. **In non-allergic asthma, the immune system is not involved in the reaction.**

The two most widely used tests to assess lung function are:

- **FEV_1** (forced expiratory volume in 1 second)
- **FVC** (forced expiratory vital capacity)

- Role of Nutrition:

Available evidence in the literature on diet and asthma falls in two broad categories:

– Epidemiological studies examining the role of differences in dietary intake of specific nutrients in explaining the distribution and incidence of asthma

– Intervention studies utilizing dietary or parenteral (intravenous) supplementation to modify the disease.

- Effects of selected nutrients:

Potassium:

–No association was noted between potassium intake and wheezing or bronchitis in adults 30 years of age or older (NHANES II).

–Low potassium intake was associated with deficits in FEV_1 and FVC in girls 11-19 years old.

–Flows tended to be lower than normal in both boys and girls, although results were statistically significant only for FEV_1 for girls.

Magnesium:
–There is some evidence that in stable asthma (defined as not requiring oral corticosteroid or request for asthma treatment in the previous two months), magnesium supplementation (300 mg/day) may have an effect on asthma control. The Daily Value for magnesium is 400 mg.
–Low magnesium intake was associated with small deficits in lung function in children.

Fruit and vitamin C:
–Epidemiological studies have consistently demonstrated lower levels of pulmonary function in individuals who consume lower levels of vitamin C or foods containing this vitamin.
–Plasma vitamin C levels in asthmatic subjects have been found consistently to be lower in both adults and children.
–The Zutphen study suggested that fruit, but not specifically vitamin C intake was inversely related to the subsequent development of chronic non-specific lung disease.

Recent studies on diet and respiratory health:

- Substantial body of evidence indicates that nutrition influences respiratory health.
- In recent population-based studies, decreased lung function was associated with low levels of antioxidant intake and serum levels of antioxidants. Carotenoids, vitamin C and vitamin E may play a role in respiratory health.
- A study by McKeever et al. (2002) suggests that a high dietary intake of vitamin C, or of foods rich in vitamin C, may reduce the rate of loss of lung function in adults.
- In a cross-sectional study of 2,650 school-age children in England and Wales, the level of FEV_1 was positively associated with the frequency of fresh fruit consumption.
- Patel et al. (2006), results showed that symptomatic asthma in adults was associated with a low dietary intake of fruit, the antioxidant nutrients vitamin C and manganese, and low plasma vitamin C levels. These findings suggest that diet may be a potentially modifiable risk factor for the development of asthma.

The Children's Health Study:

- Fruit, juice, and vegetable intakes were relatively low among the study's participants compared with the recommendations for 5 servings of fruit and vegetables per day.
- On average, boys and girls consumed 1.5-2 servings of vegetables per day, about 1 serving of fruit per day, and 0.8 servings of fruit juice per day.
- Among girls, lung volume and measures of flow showed deficits associated with low vitamin C intake.
- Among boys, low total vitamin C intake was associated with deficits in lung function compared with those with higher vitamin C intake.
- Low intakes of all fruit juices, orange juice, and other fruit juices were associated with significant deficits in FVC and FEV_1 among boys. The deficits among boys with asthma were large enough to be potentially clinically significant.

The Third National Health and Nutrition Examination Survey (NHANES III)

- Examined a random national population sample of the United States with oversampling of minorities and children.

- Except for vitamin C, none of the serum concentrations of antioxidants differed significantly between participants with asthma and participants who never had asthma (20 years or older).
- Serum concentrations of vitamin C, a-carotene, b-carotene, and b-cryptoxanthin were associated with asthma diagnosis (children 6-17 years old). Low levels of vitamin C and a-carotene were predictive of asthma.
- This study strengthens a growing body of data indicating that vitamin C plays a role in the development or expression of asthma in children.
- Other studies, besides NHANES, have shown that asthmatic patients have been reported to have-lower-than-normal concentrations of vitamin C in their plasma and blood leukocytes, which suggest that asthma could be associated with chronic lower concentration of vitamin C.

Flavonoids:

- Fresh fruits, a main source of vitamin C are also a source of other nutrients such as flavonoids, and vitamins A and E, which may also have a beneficial effect on pulmonary health.
- Knekt et al. (2002) found that the incidence of asthma was lower at higher total flavonoid intakes. The strongest associations were noted from flavonoids found in apple and oranges.
- A glass of 100% orange/grapefruit juices provides significant quantities of hesperidin and naringin, as well as some quercetin.

Citrus juices as part of a life-long diet strategy that highlights the intake of naturally nutrient dense foods may have a beneficial effect on lung health and other inflammation related diseases.

As reported below, scientific studies have concluded that asthmatic patients have lower than normal concentrations of vitamin C in their plasma. **Citrus juices are a healthy and flavorful way to increase vitamin C intake in asthmatic patients.**

For a more detailed and referenced review of this topic, please continued reading below

Asthma
Beneficial Roles of Citrus
Literature Review
Sandy Barros and Filomena Valim

1- INTRODUCTION:

According to the American Lung Association (www.lungusa.org) lung disease is the number three killer in America, responsible for one in seven deaths. Lung disease and other breathing problems are the number one killer of babies younger than one year old. Today, more than 35 million Americans are living with chronic lung disease such as asthma, emphysema and chronic bronchitis.

Asthma is a respiratory disease characterized by episodes or attacks of inflammation and narrowing of the small airways in response to asthma triggers.

The prevalence of asthma and associated atopy (a hereditary allergy characterized by symptoms produced upon exposure to the exciting antigen without inoculation) has increased substantially over the past 30 years in most developed countries and appears to have risen in developing countries in relation to the degree of affluence of the population.

According to the Asthma and Allergy Foundation of America (http://www.aafa.org), 20 million Americans have asthma. Asthma is a chronic disease and one of the most common and costly in America. It is responsible for 14.6 million missed days of school each year, making asthma the leading cause of school absenteeism. It is also responsible for 14.5 million missed days of work for adults each year, a 100 million days of restricted physical activity for children and adults each year, 1.9 million emergency room visits, 14 billion dollars in medical expenses and indirect costs and approximately 5,000 deaths annually.

References linking the subject asthma and citrus have been prevalent in our Media Monitoring Reports since December 2003 with the most recent reference appearing in May 2006 issues of the reports. As a result of these references, the subject was chosen for the development of a white paper.

1.1- Types of Asthma:

The two types of asthma according to the Asthma and Allergy Foundation of America are*:*

- **Allergic (extrinsic) asthma:** characterized by symptoms that are triggered by an allergic reaction. Allergic asthma is an airway obstruction and inflammation that is partially reversible with medication. Allergic asthma is the most common form of asthma, affecting over 50% of the 20 million asthma sufferers. Many of the symptoms of allergic and non-allergic asthma are the same (coughing, wheezing, shortness of breath or rapid breathing, and chest tightness). However, allergic asthma is triggered by inhaled allergens such as dust mite allergen, pet dander, pollen, mold, etc., resulting in asthma symptoms.

- **Non-Allergic (intrinsic) asthma:** triggered by factors not related to allergies. Like allergic asthma, non-allergic asthma is characterized by airway obstruction and inflammation that is at least partially reversible with medication, however, symptoms in this type of asthma are not associated with an allergic reaction. Non-allergic asthma is triggered by other factors such as anxiety, stress, exercise, cold air, dry air, hyperventilation, smoke, viruses or other irritants. **In non-allergic asthma, the immune system is not involved in the reaction.**

Allergic and non-allergic asthma are primarily a chronic inflammatory disease of the airways. This means that people with asthma have inflamed airways which causes two secondary symptoms:

(1) The bronchi, the airway branches leading to the lungs, become overly reactive and more sensitive to all kinds of asthma triggers such as allergens, cold and dry air, smoke and viruses.

(2) The lungs have difficulty-moving air in and out, which is called airflow obstruction. Together, these symptoms cause the tertiary symptoms, the coughing, wheezing, tight chest and worse.

Chronic obstructive pulmonary disease (COPD) is a term referring to two lung diseases, chronic bronchitis and emphysema, that are characterized by obstruction to airflow that interferes with normal breathing. Chronic bronchitis is the inflammation and eventual scarring of the lining of the bronchial tubes. Emphysema begins with the destruction of air sacs (alveoli) in the lungs where oxygen from the air is exchanged for carbon dioxide in the blood. Both of these conditions frequently co-exist, hence physicians prefer the term COPD. It does not include other obstructive diseases such as asthma.

1.2- Lung function tests:

Defining and measuring asthma is difficult, and studies have used many different outcome measures including asthma symptoms, self-reported diagnosed asthma, lung function, and airway hyperresponsiveness.

The two most widely used tests to assess lung function are:

- **FEV_1 (forced expiratory volume in 1 second)**

The FEV_1 is the volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity. It reports the largest value of three technically satisfactory maneuvers. The start of the forced expiration is obtained by linear extrapolation of the steepest part of the volume-time diagram, as shown in Figure 1.

FEV_1 is by far the most frequently used index for assessing airway obstruction, bronchoconstriction or bronchodilatation.

FEV_1 is expressed as a percentage of the vital capacity. It is the standard index for assessing and quantifying airflow limitation.

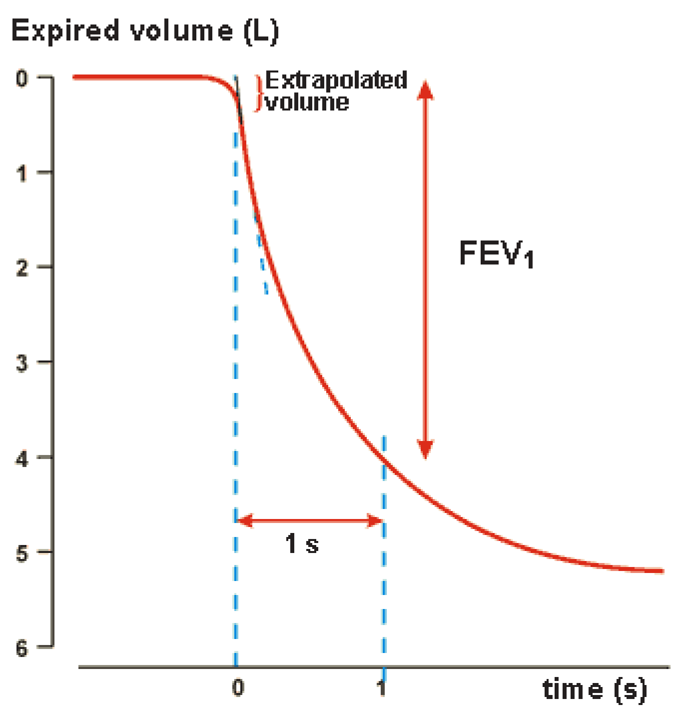

Figure 1 – Graphical representation of the FEV_1 (http://www.spirxpert.com/indices7.htm)

- **FVC (forced expiratory vital capacity)**

FVC is defined as the volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume. This measurement is performed during forceful exhalation; the preceding maximal inhalation need not be performed forcefully. The volume assessed is the forced expiratory vital capacity (FEVC), commonly called forced vital capacity (FVC), see Figure 2. The maneuver is almost invariably performed in conjunction with the assessment of the FEV_1 and of maximum expiratory flow-volume curves.

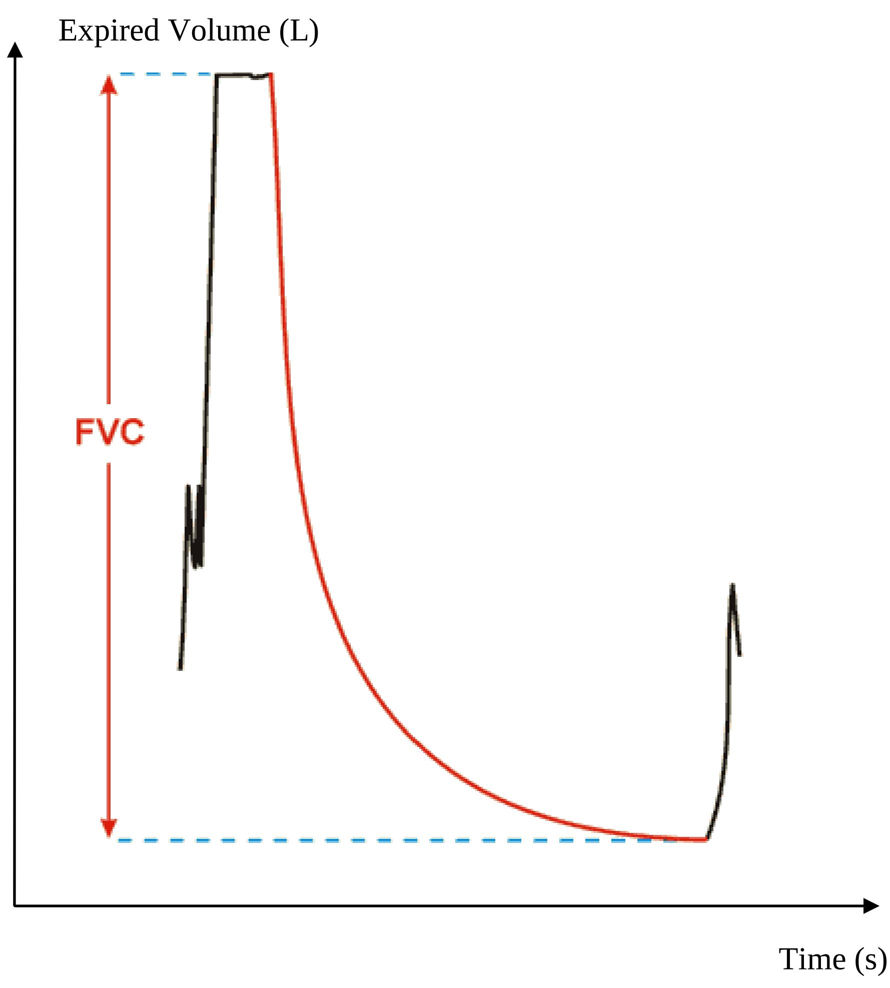

Figure 2- Graphical representation of FVC (http://www.spirxpert.com/indices5.htm)

- **FEV1/FVC** -- This is the percentage of the vital capacity that is expired in the first second of maximal expiration. In healthy individuals the FEV1/FVC is usually around 70%. In patients with obstructive lung disease FEV1/FVC decreases and can be as low as 20-30% in severe obstructive airway disease.

2- ROLE OF NUTRITION:

Although the explanation for the rise in asthma prevalence in developed countries is not known, it has coincided with a marked change in the diet of these nations. Diet is an environmental factor that changes rapidly with the shift from a rural subsistence to an urban lifestyle, and from a controlled to a free market economy. The hypotheses that an alteration in the diet of nations may be causing the changes in the prevalence of asthma was initially proposed by Burney (1987) and later developed by Seaton et al. (1994), and has since attracted a great deal of interest.

Available evidence in the literature on diet and asthma falls in two broad categories: epidemiological studies examining the role of differences in dietary intake of specific nutrients in explaining the distribution and incidence of asthma; and intervention studies utilizing dietary or parenteral (intravenous) supplementation to modify the disease. The role of diet is complex because some dietary factors can trigger asthma attacks whereas others may prevent such attacks (Baker & Ayres, 2000).

Fogarty & Britton (2000) published a review article regarding the role of diet in the etiology of asthma. The review considered the published evidence for the effects of individual nutrients on asthma and the possibilities for treatment. The evidence reviewed is derived from various sources including several large, cross-sectional studies that explored the role of nutrient intake in asthma by using dietary questionnaires to measure intake of food constituents, and different methods of measuring diseases and outcomes in different populations. The datasets used by the authors and specific data reviewed were extracted from the following:

- The First National Health and Nutrition Examination Study (NHANES I).

  This study measured forced expiratory flow rate in 1 second (FEV_1) in 2526 randomly sampled adults aged 30-70 years from the USA (Schwartz & Weiss, 1994).
- The Second National Health and Nutrition Examination Survey (NHANES II) (Schwartz & Weiss, 1990).

  NHANES II assessed the relationship between dietary intake and respiratory symptoms in 9074 adults aged 30 years and older.

- The MOGEN Study.

  This study was a cross sectional investigation of the prevalence of risk factors for chronic diseases using self-administered questionnaires and a physical examination in a randomly selected sample of the Dutch population aged 20-59 years from three towns in the Netherlands (Amsterdam, Doetinchem, and Maastricht). The study measured FEV_1 and FVC in 6555 subjects (Grievink et al., 1998).

- The Nurses' Health Study.

  It contained dietary questionnaire data on 77866 women aged 34-68 years, followed since 1980. This is the only prospective study to use diagnosed asthma as an endpoint (Troisi et al., 1995).

- The Zutphen Study.

  This study followed 793 middle-aged men in the town of Zutphen in the Netherlands from 1960 to 1985. Interviews with a dietitian were used to assess diet and to determine an endpoint of chronic non-specific lung disease, a diagnosis based on episodes of respiratory symptoms lasting more than 3 months, or a diagnosis of asthma, chronic bronchitis or emphysema (Miedema et al., 1993).

- Fogarty & Britton (2000) also included their own study that assessed bronchial reactivity and spirometry in 2633 subjects in an adult population aged 18-70 years from Nottingham, United Kingdom.

All of these datasets have been used to address dietary and other hypotheses relating to asthma. Different investigators analyzing individual nutrient effects have not always adjusted for effects of other nutrients shown to be related to the outcome in question in other studies. It is therefore sometimes unclear whether effects seen consistently in different datasets are perhaps likely to be valid.

The effects of selected nutrients evaluated in this review, as well as other recent publications, are as follows:

Potassium:

Potassium is the main intracellular cation and has a role in maintaining the trans-membrane potential that influences nerve conduction and muscle tone.

No association was noted between potassium intake and wheezing or bronchitis in adults 30 years of age or older participating in the NHANES II survey (Schwartz & Weiss, 1990).

Gilliland et al. (2002) investigated measures of airflow rates based on the physiological roles of potassium and other ions on children's lung function. The authors examined cross-sectional dietary data and pulmonary function test from 2566 children aged 11-19 years old during 1998-99. Among girls, low potassium intake was associated with deficits in FEV_1 and FVC. Flows tended to be lower than normal in both boys and girls, although results were statistically significant only for FEV_1 for girls.

Magnesium:

Magnesium is a predominantly intracellular cation that plays a part in the maintenance of the resting potential across cell membranes and therefore modulates bronchial tone and diameter (Gilliland et al., 2002). It is also an essential co-factor for enzymes that require ATP (adenosine triphosphate), has an anti-inflammatory effect (Cairns & Kraft, 1996), and is involved in the syntheses and replication of RNA and DNA (Weising & Bellorin-Font, 1998).

Developing epidemiological evidence that dietary magnesium may be of relevance in the etiology of asthma has coincided with an increasing consideration of benefits of intravenous magnesium in the treatment of other diseases, such as myocardio infarction (Woods et al., 1992) and eclampsia (seizure activity) (Saunders & Hammersley, 1995). Magnesium supplementation may also have a role in the management of bronchial asthma (Bruner et al., 1995).

There is some evidence that in stable asthma (defined as not requiring oral corticosteroid or request for asthma treatment in the previous two months), magnesium supplementation (300 mg/day) may have an effect on asthma control (Rylander et al., 1997). The Daily Value for magnesium is 400 mg.

Gilliland et al. (2002) also investigated the effect of dietary magnesium on children's lung function. They found that the intake of magnesium was higher in boys than in girls; however, both had intakes that were substantially lower than the Recommended Dietary Allowance (RDA) for this age group (410 mg/day for boys, 360 mg/day for girls). Less than 14% of the boys and 12% of the girls had adequate intake of magnesium. The author's findings indicated that low magnesium intake was associated with small deficits in lung function in children. Although the magnitude of the deficits are small for individual persons, low magnesium intake is prevalent in the general population of children, and the lung function deficits associated with low magnesium may have a substantial impact on respiratory health at the population level.

Fruit and vitamin C:

Oxidizing free radicals are thought to play a significant role in mediating the pathogenesis of both asthma and Chronic Obstructive Pulmonary Disease (COPD), and this has given rise to the hypothesis that relative deficiencies of dietary antioxidants such as vitamin C, vitamin E and selenium may increase susceptibility to these diseases. Studies have shown that oxidative stress is high among people with asthma (Ford et al., 2004), therefore, it is reasonable to hypothesize that people with asthma may need additional antioxidant protection.

Epidemiological studies have consistently demonstrated lower levels of pulmonary function in individuals who consume lower levels of vitamin C or foods containing this vitamin. Cross-sectional studies of randomly selected populations have shown positive associations between fresh fruit consumption and lung function in national surveys of 9003 adults (Strachan et al., 1991) and 2650 children (Cook et al., 1997), with a larger effect on FEV_1 in a subset of subjects who reported wheeze in the latter study.

Similarly, evidence supporting the hypothesis that vitamin C influences lung function is available from large cross-sectional studies, although the effect was relatively weak. Data from the NHANES I population from the United States demonstrated a 40 mL difference in FEV_1 between the highest and lowest tertiles of vitamin C intake, although not for vitamin C-rich vegetables (Schwartz & Weiss, 1994).

A study by Britton et al. (1995) in Nottingham, United Kingdom, provided consistent results, with a 25 mL higher FEV_1 for each standard deviation of 40 mg in vitamin C intake. A similar effect was seen in the MORGEN study, with a 53 mL increase in FEV_1 between the 10^{th} and the 90^{th} percentiles of vitamin C intake, and to a lesser extent in a study of 3085 adults from China, in which an increase of 100 mg of vitamin C/day was associated with a rise of 22 mL in FEV_1 (Hu et al., 1998).

Plasma vitamin C levels in asthmatic subjects have been found consistently to be lower in both adults (Olusi et al., 1979) and children (Aderele et al., 1985). Raised levels of serum vitamin C appear to be associated with higher lung function (Ness et al., 1996), lower frequencies of self-reported wheezing and bronchitis in NHANES II (Schwartz & Weiss, 1990). Thus, the cross-sectional data on the effect on asthma of dietary fruit and vitamin C intake, and serum vitamin C levels as a marker of intake consistently show a benefit with higher levels of consumption of fruit and food containing vitamin C. However, data from prospective longitudinal studies of the development of asthma and pulmonary disease show different effects of the consumption of fruit and vitamin C. The Zutphen study suggested that fruit, but not specifically vitamin C intake was inversely related to the subsequent development of chronic non-specific lung disease. A prospective study of 2171 adults without a history of chronic respiratory disease over a 7-year period showed a more marked fall in FEV_1 in subjects who reduced their fresh fruit consumption the most, compared with those who did not change their dietary fruit intake after adjustment for region, social class and smoking (Carey et al., 1998).

However, the Nurses' Health Study demonstrated no relationship between dietary vitamin C intake and the subsequent incidence of asthma in a cohort of 77866 women (Troisi et al., 1995). The discrepancy between this study and the Zutphen Study may be explained by the difference in the gender of the subjects and the different outcome measures used. Furthermore, the Zutphen Study used a chronic non-specific lung disease outcome encompassing a wider range of diseases, particularly in a group consisting of a large proportion of smokers. Alternatively, a protective effect of fruit may be attributable to fruit constituents other than vitamin C.

3- RECENT STUDIES ON DIET AND RESPIRATORY HEALTH:

A substantial body of evidence indicates that nutrition influences respiratory health. Much of the nutrition research has focused on the intake of fruits, vegetables, and antioxidant micronutrients, because the lung is subject to a wide range of oxidant insults and because antioxidant defenses play an important role in protecting the lung from damage.

A growing, but as yet inconsistent body of evidence indicates, that a low dietary intake of fruits and antioxidants, including vitamins A, C, and E, is associated with obstructive airway conditions and with deficits in adult lung function assessed by spirometric measurements of FEV_1 and forced vital capacity (FVC).

In recent population-based studies, decreased lung function was associated with low levels of antioxidant intake and serum levels of antioxidants (Schunemann et al., 2002 & McKeever et al., 2002). Schunemann et al. (2002) studied the association of FEV_1 and FVC as a percentage of the predicted values of the FEV_1 and FVC, respectively and the intakes of several carotenoids in a random sample of 1,616 men and women aged 35-79 years, and free from respiratory disease. Their findings support the hypothesis that carotenoids, vitamin C and vitamin E may play a role in respiratory health. In a separate study by McKeever et al. (2002), the authors investigated the relationship between decline in lung function and dietary intakes of magnesium, vitamin C, and other antioxidant vitamins in a general population cohort. Their study suggests that a high dietary intake of vitamin C, or of foods rich in vitamin C, may reduce the rate of loss of lung function in adults and thereby help to prevent COPD.

Patel et al. (2006) undertook a study to assess the independent association of several antioxidant nutrients with asthma in adults. The case-control study was performed in 515 adults with physician diagnosed asthma using dietary data obtained from 7-day food diaries. The results showed that symptomatic asthma in adults was associated with a low dietary intake of fruit, the antioxidant nutrients vitamin C and manganese, and low plasma vitamin C levels. These findings suggest that diet may be a potentially modifiable risk factor for the development of asthma.

Few population-based studies have investigated the relation between intake of antioxidants and lung function during childhood. The existing evidence among children is consistent with the findings in adults, but it suggests that the assessment of the source of antioxidant intake may be important in defining the role of specific antioxidant vitamins, including vitamin C. In a cross-sectional study of 2,650 school-age children in England and Wales, the level of FEV_1 was positively associated with the frequency of fresh fruit consumption and more weakly associated with green vegetables and salad consumption (Cook et al., 1997). However, FEV_1 was not associated with serum levels of vitamin C, suggesting that other micronutrients in fruit were important.

Gilliland et al. (2003) investigated the relation between children's pulmonary function and intake of fruits, vegetables, juices, and vitamins A, C, and E by examining cross-sectional data from the Children's Health Study (1997-1998). The Children's Health Study is a 10-year longitudinal study of respiratory health in schoolchildren. Beginning in the 1997-1998 school year, dietary data were collected using a validated food frequency questionnaire. These questionnaires were completed by children who ranged in age from 11 to 19 years. The majority of the participants were non-Hispanic whites from middle-class families with health insurance. Total juice intake was defined as the total daily servings of orange, apple, and other juices.

Fruit, juice, and vegetable intakes were relatively low among the study's participants compared with the recommendations for 5 servings of fruit and vegetables per day. On average, boys and girls consumed 1.5-2 servings of vegetables per day, about 1 serving of fruit per day, and 0.8 servings of fruit juice per day. The authors found that both lung volume and measures of flow showed deficits associated with low vitamin C intake among girls. Among boys, low total vitamin C intake was associated with deficits in lung function compared with those with higher vitamin C intake. Significant differences were found in the FVC, FEV_1, and FEF_{25-75} (forced expiratory flow between 25% and 75%

of the forced vital capacity). The same lung function tests were significantly lower in girls who had intake in the lowest decile compared with higher vitamin C intakes.

Low intakes of all fruit juices, orange juice, and other fruit juices were associated with significant deficits in FVC and FEV_1 among boys. The deficits among boys with asthma were large enough to be potentially clinically significant.

3.1- NHANES III Database Studies:

The Third National Health and Nutrition Examination Survey (NHANES III) examined a random national population sample of the United States with oversampling of minorities and children. Participants undertook health questionnaires completed by adult caretakers where appropriate, and a sub-sample underwent physical examination, were tested for pulmonary function, and had blood samples taken to measure serum vitamins.

Ford et al. (2004) compared antioxidant concentrations among people with and without asthma using data from NHANES III. The analysis was comprised of 16,541 participants: 771 participants with current asthma, 352 participants with former asthma, and 15,418 participants who never had asthma. The three groups did not differ by age, race or ethnicity. Analyses were limited to participants aged 20 years or older. Except for vitamin C, none of the serum concentrations of antioxidants differed significantly between participants with asthma and participants who never had asthma. The age adjusted mean vitamin C concentrations in patients with asthma was significantly lower than that among participants without asthma.

Harik-Khan et al. (2004) used the NHANES III data set to analyze whether serum vitamin concentrations, specifically vitamins A, C, E and carotenoids were associated with a clinical diagnosis of asthma when other factors such as body weight, socioeconomic status, passive smoke exposure, urban environment, and ethnicity were taken into account. The authors used linked information from the questionnaire, physical examination, and laboratory data for participants aged 6-17 years. Overall, for 5,433 participants between the ages of 6 and 17 years, the question, “Has a doctor ever said that your child has asthma?” was answered. For these children, technically reportable serum vitamin measurements were available for 4,427 (81%). For these 4,427 participants, one or more items of the physical examination or sociodemographic information were missing for 334, leaving a final study population of 4,093 children for whom measurements were complete. Of these children, 2,072

(50.6%) were girls, and 397 (9.7%) had a physician diagnosis of asthma. Of the latter group, 278 children (70%) have current asthma.

Analyses comparing children with asthma versus children without asthma confirmed previous findings that environmental and socioeconomic factors were associated with asthma. These asthma risk factors included male gender, family history of asthma or hay fever, smaller household size, unemployed head of household, lower educational status of head of household, female head of household, and urban environment. Serum concentrations of vitamins A and E were not different between asthmatics and nonasthmatics. However, significant differences were present for serum concentrations of vitamin C, α-carotene, β-carotene, and β-cryptoxanthin. The authors did not find any difference in ascorbic acid dietary intake, calculated from the recall interview of the last 24 hours, or in the intake of supplemental minerals and vitamins between asthmatics and nonasthmatics. After statistical adjustment for potentially confounding socioeconomic factors, only low vitamin C and α-carotene serum levels were predictive of asthma.

This study strengthens a growing body of data indicating that vitamin C plays a role in the development or expression of asthma in children. It is the first large childhood study that has relied on serum vitamin levels rather than food frequency questionnaires and has also controlled for several other potentially confounding characteristics.

Vitamin C is a water-soluble antioxidant present in normal concentrations in the airway and alveolar (tiny air sacs in the lungs) lining fluid. As an antioxidant, vitamin C can modify oxidative insults from inhaled agents, infectious agents, or cellular inflammation. In several studies, large acute doses of vitamin C (>1.0 g) have been found to have a beneficial effect on airways reactivity. The evidence of benefit of vitamin C supplementation as a treatment for chronic asthma was inconclusive in two recent literature reviews (Bielory & Gandhi, 1994; Kaur et al., 2001). Other short-term studies support the use vitamin C in treating asthma and allergies (Hatch, 1995; Monteleone & Sherman, 1997).

Harik-Khan et al. (2004) also analyzed the relation between asthma and antioxidant dietary intake and vitamin supplementation by using the available NHANES III intake of dietary ascorbic acid and of supplemental vitamins and minerals. No difference was found between children with and without asthma regarding those two measures. This suggests a discrepancy between the interview data (dietary intake) and serum vitamin C level. One possible explanation of this fact is that the recall data are flawed and do not reflect true vitamin C intake. Alternatively, it is possible that in asthma patients, metabolism or excretion of vitamin C is different. For example, it may be that increases in the level of oxidative stress due to inflammation lead to lower levels of serum vitamin C (Winklhofer-Roob et al., 1997).

Harik-Khan et al. (2004) concluded that low levels of serum vitamin C are associated with an increased risk of asthma. The authors also pointed out that since this study's findings are descriptive rather than experimental, caution must be used when inferring causal relations. The consistency of the relation of low vitamin C levels across different studies with varied population samples, age groups, methods of ascertaining disease state, and nutritional intake strengthens the validity of the association. However, the strength of the association is not constant across all studies.

A previous study of 51 African asthmatic children and matched controls found that asthmatics had lower plasma ascorbic acid levels and that there was a positive correlation between vitamin C concentrations and socioeconomic class among children with asthma (Aderele et al., 1985). This finding was attributed to higher intake of fruits by children in the higher socioeconomic groups.

Another study of 14 asthmatic children from Turkey showed decreased serum levels of vitamin C as well as of β-carotene and vitamin E compared with 12 normal controls (Kalayci et al., 2000).

Forastiere et al. (2000) found in a large Italian population sample of children aged 6-7 years, that a history of frequent winter consumption of citrus and kiwi fruits, rich in vitamin C, was associated with protection from respiratory symptoms over the following 12 months. In the Italian diet citrus fruit (consumed largely in winter) is the most important source of vitamin C. Kiwi fruit was included in the item because of its high vitamin C content and its widespread consumption in recent years. No clear dose response was observed, and the protective effect was evident even among children who ate such fruits only once or twice a week. A stronger effect was observed among children with a history of asthma.

Asthmatic patients have been reported to have-lower-than-normal concentrations of vitamin C in their plasma and blood leukocytes, which suggests that asthma could be associated with chronic lower concentration of vitamin C. However, providing asthmatic patients with vitamin C supplements has yielded conflicting results (Hatch, 1995).

Furthermore, cross-sectional and case-control studies suggest a protective effect of vitamin C on airway hyperreactivity and wheezing. Results, however, should be interpreted with caution, and it is premature to conclude that vitamin C is a critical nutrient. Fresh fruits, a main source of vitamin C are also a source of other nutrients such as flavonoids, and vitamins A and E, which may also have a beneficial effect on pulmonary health.

Flavonoids are a family of polyphenols specially found in fruits and vegetables. They are also well known for having antioxidant properties, and have anti-allergic and anti-inflammatory effects. It has been suggested that certain flavonoids have beneficial effects on asthma (Garcia et al., 2005).

Knekt et al. (2002) studied flavonoid intake and risk of chronic diseases. The authors found that the incidence of asthma was lower at higher total flavonoid intakes. They found that this association was due to the intakes of quercetin (3.9-4.7 mg/day), hesperitin (15.4-26.8 mg/day) and naringenin (4.7-7.7 mg/day). The intake values shown above for each flavonoid are the highest quartile intakes for men and women, respectively. The strongest associations were noted for apple and oranges.

Reported values for quercetin, hesperitin and naringenin for oranges, orange juices, grapefruit and grapefruit juices are shown in Table 1. The data obtained from the USDA Database for the flavonoid content of selected foods (2003) reflect most of the analytical procedures which convert the glycosides to aglycones and results are reported as aglycones. However, when the individual glycosides were determined, the values for glycosides were converted into aglycone forms using conversion factors based on molecular weights.

Table 1 – Selected flavonoids values for oranges, orange juice, grapefruit and grapefruit juice.

Flavonoid **(mg/100g edible portion)**	**Oranges**	**Orange Juice**	**Grapefruit**	**Grapefruit Juice**
Quercetin	0.9[a]	0.90 – 1.34[b]	0.5	0 – 0.147
Hesperitin	31.0 – 41.4	3.61 – 39.2	1.5	0 – 34.93
Naringenin	0 – 6.37	1.47 – 6.37	53	9.67 –62.58

Data from USDA Database for the flavonoid content of selected foods - 2003

(a) Arabbi et al., 2005. (b) Careri et al., 2000.

Based on the data reported in Table 1, a glass of 100% orange/grapefruit juices provides significant quantities of hesperidin and naringin, as well as some quercetin. The body further metabolizes hesperidin and naringin into hesperitin and naringenin, compounds that may be related to a lower asthma risk.

4- ANTIHISTAMINIC EFFECTS OF CITRUS COMPOUNDS AND ASTHMA:

Antihistamines (AH) have been evaluated as potential therapies for asthma for more than 50 years. With first-generation compounds, side effects prevented effective dosing. The usual doses of currently used (non-sedating) AH, such as fexofenadine or loratadine, have little or no beneficial effects on asthma (Nelson, 2003).

Various studies were conducted during the 1980s through the early 1990s regarding the antihistaminic effects of vitamin C. In the rat, acute stress induces a rapid mobilization of tissue ascorbate, *de novo* synthesis of ascorbate in the liver, and a rise in plasma and urinary ascorbate levels, culminating in elevated total/body ascorbate levels. In human beings, the enhanced metabolism of ascorbic acid after stress results in a rapid fall in ascorbic stores because of the body's inability to synthesize ascorbate *in vivo*. Chatterjee et al. (1975) have postulated that ascorbate mobilization during stress may be a natural defense mechanism for the detoxification of excess histamine.

Johnston et al. (1992) studied the antihistaminic effects and complications of supplemental vitamin C intake. Participants consumed a single placebo capsule daily during the initial week of the study. During weeks 2 and 3, they consumed 500 mg of L-ascorbate daily in a single dose. At weeks 4 through 5, the daily dosage level was increased to 2,000 mg taken as a divided dose. During the final week of the study, two placebo capsules were taken daily. At the end of the six-week double-blind, placebo-controlled protocol, the authors found that the mean total plasma vitamin C value rose significantly (46%) over the baseline value after 2-weeks of vitamin C supplementation of 500 mg per day. However, mean total plasma vitamin C values at the 500-mg dosage, the 2,000-mg dosage, and the 1-week withdraw period did not differ significantly. The mean reduced ascorbic value was significantly greater than the baseline value at the 2,000-mg dosage only. Blood histamine levels did not rise significantly during the week-long, placebo controlled withdrawal period. Hence, the antihistamine properties of vitamin C appear to be related to reduced ascorbic acid levels in plasma, not total vitamin C levels.

5- CONCLUSIONS:

One hypothesis to explain the increasing prevalence of asthma is that decreasing dietary intake of antioxidants may lead to an increased vulnerability of the pulmonary airways to reactive oxygen specimens (Seaton et al., 1994). The extent to which diet may have an impact on either the etiology or the severity of asthma is a question that has generated much interest (Hubbard & Fogarty, 2006).

Although a wide range of nutrients appears to have an effect on asthma outcomes in cross-sectional studies, evidence from longitudinal studies and randomized clinical trials are far less consistent or conclusive (McKeever & Britton, 2004).

However, our literature search has pointed out the following observations:

Vitamin C:

Epidemiological studies have consistently demonstrated lower levels of pulmonary function in individuals who consume lower levels of vitamin C or foods containing this vitamin.

Similarly, evidence supporting the hypothesis that vitamin C influences lung function is available from large cross-sectional studies, although the effect was relatively weak.

Plasma vitamin C levels in asthmatic subjects have been found consistently to be lower in both adults and children. Raised levels of serum vitamin C appear to be associated with higher lung function, lower frequencies of self-reported wheezing and bronchitis in NHANES II.

A study in Nottingham, United Kingdom showed that for each standard deviation of 40 mg in vitamin C intake, a consistent increase of 25 mL in FEV_1 was observed. A similar effect was seen in the MORGEN study, with a 53 mL increase in FEV_1 between the 10^{th} and the 90^{th} percentiles of vitamin C intake, and to a lesser extent in a study of 3085 adults from China, in which an increase of 100 mg of vitamin C/day was associated with a rise of 22 mL in FEV_1.

Gilliland et al. (2003) studied the daily average intake of vegetables, fruits and juices (servings/day) among boys and girls from the Children’s Health Study. They found that low intakes of all fruit juices, orange juice, and other fruit juices were associated with significant deficits in FVC and FEV_1 among boys. In a clinical study situation, the deficits among boys with asthma were large enough to be potentially significant.

Potassium:

In a study by Gilliland et al. (2003), cross-sectional dietary data and pulmonary function test were obtained from 2,566 children. Among girls, low potassium intake was associated with deficits in FEV_1 and FVC. Flows tended to be lower in both boys and girls, although results were statistically significant only for FEV_1 for girls.

Magnesium:

There is some evidence that in stable asthma, magnesium supplementation (300 mg/day) may have an effect on asthma control (Rylander et al., 1997).

Gilliland et al. (2003) found indications that low magnesium intake was associated with small deficits in lung function in children. They also found that, although the magnitude of the deficits are small for individual persons, low magnesium intake is prevalent in the general population of children, and the lung function deficits associated with low magnesium may have a substantial impact on respiratory health at the population level.

An interpretation of the above stated evidence is that diet may play an important role in asthma. A logical and possibly efficient approach to realizing the beneficial effect of diet to an individual and population's lung health is probably dietary manipulation to increase intake of naturally nutrient rich foods in a balanced diet throughout life. There is a general consistency in the evidence that an unhealthy diet seems to be associated with an increase risk of asthma and/or chronic obstructive pulmonary disease. Natural foods having nutrients, which have been shown to provide beneficial effects in lung health, such as citrus juices and fruit should be an integral part of a balanced diet.

Orange juice is an excellent source of vitamin C, as well as a good source of potassium and contains other minerals and compounds such as, magnesium and flavonoids that have been shown to have possible beneficial effects on lung health.

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