# The role of nutrition in asthma prevention and treatment

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*Asthma is a chronic respiratory condition characterized by airway inflammation and hyperreactivity. Prevalence has continued to rise in recent decades as Western dietary patterns have become more pervasive. Evidence suggests that diets emphasizing the consumption of plant-based foods might protect against asthma development and improve asthma symptoms through their effects on systemic inflammation, oxidation, and microbial composition. Additionally, increased fruit and vegetable intake, reduced animal product consumption, and weight management might mediate cytokine release, free radical damage, and immune responses involved in the development and course of asthma. The specific aim of this review paper is to examine the current literature on the associations between dietary factors and asthma risk and control in children and adults. Clinical trials examining the mechanism(s) by which dietary factors influence asthma outcomes are necessary to identify the potential use of nutritional therapy in the prevention and management of asthma.*

## INTRODUCTION

Asthma is a common chronic disorder in which the airways become inflamed and narrow, causing periods of airflow obstruction. Common symptoms during acute episodes include wheezing, coughing, chest tightness, and shortness of breath.[1]

Asthma prevalence has been steadily rising since the 1980s. According to national surveillance data from the Centers for Disease Control, an estimated 6.8 million people had asthma in 1980.[1] This number increased to 25.7 million persons diagnosed in 2010.[1] In children, asthma prevalence was reported to be 3.5% in 1980.[1] Thirty years later, that figure had jumped to 9.5% of children aged 0–17 years.[1,2]

The disease can be fatal. In 2009, the rate of deaths with asthma as the underlying cause per 10,000 persons with asthma was 1.9 in adults and 0.3 in children.[1] The asthma death rate was highest among individuals aged 65 years and older.[2]

The disease is more common in African Americans (11.9% in 2010) than in white Americans (7.8%).[1,2] According to the 2012 National Vital Statistics System and National Health Interview Survey, asthma mortality was also higher in African Americans (24.9%) than white persons (8.4%) in 2010.[1] Persons with a family income below the federal poverty threshold also had higher asthma prevalence.[1,3] In 2010, asthma prevalence was 2.5% higher among individuals with a family income under the federal poverty threshold than

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individuals with a family income at or above the poverty threshold.[1] Holsey et al[4] suggest that disparities in asthma prevalence and mortality can be attributed to lower socioeconomic status and the greater health needs of minority groups. Minority groups are more likely to be uninsured or have nonprivate insurance, and subsequently less likely to receive quality medical care and afford prescription medication. In addition, minority and low-income patients are more likely to report difficulty obtaining appointments and less likely to be seen by an asthma specialist. Socioeconomically disadvantaged individuals are also more likely to consume high-fat foods and fewer fruits and vegetables than individuals with a higher socioeconomic status.[5] These disparities in healthcare and diet quality might explain the increased asthma prevalence in low-income families.

### Current treatment

Current drug treatments for asthma include long-term control treatments, such as inhaled corticosteroids, long-acting beta-agonists,[6] and oral medications.[7] For acute episodes, oral corticosteroids, beta-agonists, and inhaled bronchodilators are used.[8,9] Environmental control measures (eg, humidity regulation, vacuuming, and pest management) can reduce asthma exacerbations due to airborne allergens such as tobacco smoke, particulate matter, pollen, mold, or dust mites.[10,11] Environmental control measures do not, however, address the underlying condition.[12]

### Pathophysiology and role of inflammation

Airway hyperresponsiveness has been linked to the action of granulocytes such as eosinophils, lymphocytes, macrophages, and mast cells.[13,14] During an allergic reaction, these cells trigger smooth muscle contraction in the airways, microvascular leakage, and airway mucus secretion.[15,16]

## DIETARY FACTORS AFFECTING ASTHMA

Several foods and food groups have been shown to influence the development and course of asthma, as described in the sections below.

### Fruit and vegetable intake

Fruit and vegetable consumption may reduce the risk of developing asthma.[17–22] Meta-analyses compared the relative risk of adults and children in the highest intake group for fruits and vegetables with participants in the lowest intake group. High consumption of fruits and vegetables was found to be associated with reduced risk of developing asthma in children and adults.[23,24] This has been noted specifically for apples[18,25] and oranges.[18] Oftentimes, high intake was defined as consumption of fruit once a day,[17,21] or half a cup or less of fruits or vegetables per day.[18–20] Many of the reviewed studies show an association between consuming fruits and vegetables once a day and a higher forced expiratory volume in 1 second ($FEV_1$), reduced odds of asthma, and reduced incidence of wheezing.[23]

Fruits and vegetables can also make asthma symptoms more manageable. Fruits and vegetables have been inversely associated with wheeze symptoms in children. Long-term fruit intake (mean consumption frequency from 2 to 8 years of age) was found to be inversely associated with asthma symptoms (odds ratio [OR] 0.90; 95%CI, 0.82–0.99) and sensitization to inhaled allergens (OR 0.90; 95%CI, 0.82–0.99).[21] A cross-sectional study observed an inverse association between a fruit intake of $\geq$3 times per week and asthma wheeze (OR 0.87; 95%CI, 0.80–0.95) and severe asthma symptoms (OR 0.86; 95%CI, 0.76–0.97) in children aged 6–7 years. The researchers also observed an inverse association with vegetable intake and asthma wheeze (OR 0.88; 95%CI, 0.82–0.94) and severe asthma symptoms (OR 0.88; 95%CI, 0.80–0.97). The inverse association between fruit and vegetable intake with asthma symptoms was also found in adolescents.[26] Adult patients with asthma experience similar protective effects from fruit and vegetable intake. Prior studies have reported findings on the association between asthma control and both cooked and raw vegetables, while some do not specify whether the vegetables reported were cooked or raw. However, a 2013 study on Japanese patients with asthma observed a positive association between 5 or more servings per week of raw vegetables and well-controlled asthma. Iikura et al[27] suggest that the anti-inflammatory effect of flavonoids in vegetables is lost with heating, explaining the particular association between raw vegetable intake and well-controlled asthma. Similar findings were observed in a randomized controlled trial, implementing a diet that included $\geq$5 servings of vegetables and 2 servings of fruits daily or a diet with $\leq$2 servings of vegetables and 1 serving of fruits for 14 days. After the 2-week intervention, patients following the low vegetable and fruit diet displayed lower percentage predicted $FEV_1$ and forced vital capacity (FVC) than their counterparts on the high vegetable and fruit diet.[28] Likewise, high citrus intake (>46.3 g/d) was associated with reduced risk of symptomatic asthma ($P = 0.002$).[29] In addition, a 2017 meta-analysis reported an inverse association between fruit intake and asthma severity ($P < 0.05$) in both adults and children.[24]

Several studies have demonstrated a concomitant reduction in pro-inflammatory cytokines and an

increase in anti-inflammatory markers associated with fruit and vegetable intake. Fruit and vegetable consumption was inversely associated with airway neutrophils in asthmatic adults.[30,31]

### Dairy products and asthma

A 2015 case-control study (n = 678 children) compared children in the highest quartiles of dairy intake (Q3–4; OR = 1.72; 95%CI, 1.19–2.49) with children in the lowest quartiles (Q1–2; OR < 1) and showed a positive association between frequent dairy consumption and odds of developing asthma (OR 1.93; CI, 1.32–2.84).[32] Woods et al[33] observed a positive association between ricotta cheese consumption and concurrent asthma ($P = 0.009$). Similarly, low-fat cheese was positively associated with doctor-diagnosed asthma ($P = 0.04$).

When examining the role of dairy in asthma control, Woods et al[33] also reported a positive association between bronchial hyperreactivity and consumption of ricotta cheese ($P = 0.04$) and low-fat cheese ($P = 0.007$). Haas et al[34] attempted to assess the acute effects of milk on pulmonary function in asthma patients by serving 16 oz. of whole milk, skim milk, or water before assessing lung function.[34] While $FEV_1$ and forced expiratory flow at 50% vital capacity were not affected by milk consumption, a progressive deterioration in pulmonary diffusing capacity of carbon monoxide after whole milk consumption was observed in asthmatic patients ($P < 0.001$).

Acute effects of dairy ingestion were examined in a double-blind, placebo-controlled, crossover study.[35] Participants were randomly assigned to begin either a dairy-free or a control diet for 2 weeks and then challenged with an equivalent of 300 mL cow's milk. $FEV_1$ and peak expiratory flow were measured on the active challenge day. While these measurements were not significantly different on active-challenge vs placebo-challenge days, the dairy challenge triggered asthma symptoms in 8 of the 20 patients, whereas no increase in the severity of symptoms was found in the placebo group.

Another double-blind, placebo-controlled, crossover trial randomly assigned 25 adult patients with mild asthma to ingest either 10 g of powdered whole cow milk or a placebo after avoiding dairy consumption for 5 days prior to this.[36] On average, $FEV_1$ decreased by 3.3% 30 minutes after the cow milk challenge ($P = 0.0007$). Likewise, $FEV_1$/FVC decreased by 2.7% 30 minutes after consumption of the cow milk ($P = 0.0337$) and gradually returned to the baseline value after 7 hours. These small changes, although statistically significant, would likely have little clinical significance. The researchers suggest measurement through conventional spirometry might lack the sensitivity necessary to detect dairy-induced pulmonary changes.

The effects of an 8-week experimental diet free of milk and eggs were assessed in 22 children with asthma. The experimental group experienced a 22% improvement in peak expiratory flow rate, while children following their normal diets experienced a 0.6% decrease ($P < 0.05$).[37] Larger-scale studies of longer duration would help clarify the potential connection between dairy and clinical symptoms.

The mechanisms by which dairy products may influence the development or course of asthma are not clear, but may include responses to milk proteins or milk lipids.[34] Han et al[32] observed a positive association between consumption of dairy products and pro-inflammatory interleukin(IL)-17F concentrations ($P < 0.05$). This correlation suggests an IL-17F–dependent inflammatory pathway might play a mediating role in the development of asthma.

While the current dietary guidelines recommend consuming 3 cups of dairy per day,[38] most adults do not meet this recommendation.[39] Based on the negative correlation between dairy intake and asthma control, these findings suggest that the dietary guideline recommendations for dairy intake should be revisited.

## DIETARY PATTERNS

### Western diet

Western diets typically emphasize the consumption of animal products at the expense of fruits, vegetables, whole grains, and legumes. Asthma prevalence has increased with the westernization of dietary patterns.[40] Urbanization of Latin American countries has resulted in a shift toward Western dietary patterns. Bermudez et al suggested that these dietary changes might play a causative role in the increased prevalence of asthma in Latin American countries.[41] Much of the US population following Western dietary patterns do not meet the daily recommended fruit or vegetable intake and exceed the recommended saturated fat limit.[42,43]

High fat intake and low fiber intake have been associated with airway inflammation and worsened lung function in asthmatic patients. An Australian study (n = 202) found that severe asthmatic patients consumed diets higher in fat and lower in fiber ($P = 0.014$) than their healthy counterparts. These dietary patterns were associated with increased airway eosinophilia ($P < 0.05$), while fiber intake was positively associated with $FEV_1$ ($P < 0.001$).[44] A 2013 study reported that fat intake displayed a positive correlation with airway

eosinophilia ($P = 0.014$) in asthmatic patients. Saturated fat intake was also positively associated with a higher percentage of sputum eosinophils ($P = 0.001$), which correlate with asthma severity and impaired lung function.[45,46] Current dietary guidelines recommend limiting saturated fat intake to <10% of total calories per day,[38] while the American Heart Association recommends reducing saturated fat intake to <7% of total calories per day. However, Americans are exceeding these recommendations by 1%–5%.[43] Likewise, Kim et al[47] found that a high-fat diet (deriving 60% energy from fat) resulted in increased airway hyperresponsiveness via enhanced cytokine production in the lung.

### Plant-based diets

Diets emphasizing fruits, vegetables, and whole grains, while placing less emphasis on high-fat meats and dairy products, have been associated with reduced asthma risk. A case-control study on Peruvian children with asthma (n = 287) reported decreased odds of asthma with increased consumption of fruits, vegetables, legumes, cereals, pasta, rice, and potatoes and reduced meat intake ($P = 0.02$).[48] A similar diet pattern has been shown to reduce the risk of lifetime diagnosis of asthma in children.[49,50]

Mediterranean-style dietary patterns emphasizing plant-based items have also been associated with reduced asthma symptoms in affected children.[49–52] In a study of 158 children with asthma, higher adherence to a Mediterranean diet was associated with greater lung function ($P < 0.05$), $FEV_1$, and FVC (test for trend $P < 0.12$ and $P < 0.06$, respectively) than the children with the lowest adherence.[53] Calatayud-Sáez et al[54] (n = 104 children) reported a significant improvement in asthma attack intensity, infections, hospital admissions, and medication use after a 1-year Mediterranean dietary program. Lv et al[50] also reported that a Mediterranean diet conferred a protective effect on current wheeze in children. Alphantonogeorgos et al[55] (n = 1125 children) observed an inverse association between Mediterranean diet adherence and asthma symptoms ($P < 0.001$). A 2013 systematic review reported negative associations between Mediterranean diet adherence in children and the 3 respiratory outcomes – "current wheeze" ($P = 0.02$), "current severe wheeze" ($P = 0.008$), and "asthma ever" ($P = 0.06$) – when compared with non-Mediterranean in adolescents.

The *2015–2020 Dietary Guidelines for Americans* recommend that Americans consume more fruits and vegetables (1.5–2 cups of fruit and 2–3 cups of vegetables daily) to reduce the risk of developing chronic diseases. However, according to the 2015 Behavioral Risk Factor Surveillance System, only 12.2% of adults meet fruit recommendations and 9.3% meet vegetable intake recommendations.[42] A systematic review by the European Academy of Allergy and Clinical Immunology concluded that the clinical recommendation to increase fruits and vegetables to reduce asthma risk, particularly in children, is supported by the current literature.[56] Asthmatic patients following an 8-week plant-based diet experienced a greater reduction in asthma medication use ($P = 0.02$) and symptom severity ($P = 0.05$), and frequency ($P = 0.033$), than their control counterparts (M. Seltz, PhD, unpublished data, September 2006). Similar clinical improvements in vital capacity, $FEV_1$, and physical working capacity were observed after asthmatic patients adopted a vegan diet for 1 year.[57] A vegan diet is free of animal products and emphasizes the consumption of fruits, vegetables, grains, and legumes. These findings suggest that a plant-based diet provides a potential treatment option for asthmatic patients.

Systemic inflammation is associated with worse clinical outcomes in asthmatic patients.[58,59] However, diets centered on plant-based foods have been shown to reduce pro-inflammatory molecules, while increasing anti-inflammatory markers.[60] Nutrients such as unsaturated fatty acids and antioxidants obtained from plant-based foods have been shown to attenuate inflammation and conditions driven by systemic inflammatory response.[61,62] However, controlled studies are necessary to further explore the link between dietary patterns and asthma symptoms.

## POTENTIAL MECHANISMS

### Antioxidants

Researchers suggest that the antioxidants found in plant foods contribute to reduced airway inflammation and resulting improvements in $FEV_1$[63,64] and FVC.[64] A prospective randomized clinical trial found that increased fruit and vegetable consumption, and subsequently antioxidant intake, is associated with improved lung function.[65] Specifically, flavonoids found in vegetables may confer a protective effect against asthma.[18,19] Romieu and Trenga[66] reviewed the mechanisms by which fruit and vegetable consumption mediate asthmatic symptoms, as described below.

Antioxidants are molecules that scavenge free radicals and reduce them by donating an electron, in order to prevent oxidative damage. The lungs are exposed to endogenous and environmental oxidants, which, if left unbalanced by the antioxidant defense system, can result in oxidative stress and pulmonary dysfunction.[67] Antioxidants prevent, intercept, and repair the effects of

oxidation and cellular damage. Some antioxidants are produced endogenously, while others must be obtained via dietary sources.[68] Dietary antioxidants include vitamins E and C, carotene, ubiquinone, flavonoids, and selenium.[67]

Vitamin E interrupts lipid peroxidation to inhibit oxidant-induced membrane damage in human tissue.[66] γ-Tocopherol, an isoform of vitamin E, also scavenges reactive nitrogen species, which can become elevated with acute neutrophilic inflammation.[69] Additionally, pretreatment of endothelial cells with α-tocopherol inhibits leukocyte recruitment. It also inhibits signal transduction mediator activity and lung inflammation. Thus, plasma α-tocopherol has been positively associated with lung function in patients with and without asthma.[69]

Vitamin C, which is found in vegetables and fruits and is absent in meats, supports the hydration of airway surfaces[65] and scavenges and reduces free radicals.[70] It also acts as a cofactor in several immune-modulating regulatory enzymes.[71] While prostaglandins induce inflammation and bronchoconstriction,[72] vitamin C affects the release of arachidonic acid, a prostaglandin precursor, which impedes prostaglandin E2 ($PGE_2$) synthesis. Vitamin C mediates oxidized vitamin E regeneration, allowing it to act as a chain-breaking antioxidant.[73] It also protects neutrophil membranes after oxidant exposure and stimulates migration to infection sites, improving immune cell function.[71] Vitamin C also plays several roles in immune function by contributing to phagocytosis and lymphocytic function and modulating cytokine and histamine concentrations.[71]

β-Carotene scavenges the highly reactive free radical superoxide anion and reacts directly with peroxyl free radicals,[67] which can otherwise damage proteins and lead to aging.[68] Likewise, other dietary carotenoids (including α-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) are associated with improvements in lung function.[74] In another study, higher serum α-carotene and β-carotene levels were associated with better pulmonary function in older disabled community-dwelling women. The higher concentrations of these carotenoids reflect greater intake of orange and dark green leafy fruits and vegetables.[75]

Flavonoids have been recognized as the major active nutraceutical ingredients in plants, owing to their properties as antioxidants and metal chelators. Flavonoids also exhibit anti-inflammatory and anti-allergic activities.[76] Flavonoids scavenge and suppress the activity of superoxide anion and can chelate iron ions.[66] The latter have been shown to reduce iron absorption during overload and prevent the resulting oxidative damage.[77] Flavonoids might contribute to the positive effect of fruit consumption on asthma.[78]

Selenium is a cofactor for the glutathione peroxidase antioxidant enzyme. Together, this structure reduces hydrogen peroxide and organic peroxide, subsequently preventing lipid peroxidation. Studies have suggested that patients with asthma have a lower concentration of selenium in their plasma ($P < 0.001$)[79] and whole blood ($P < 0.001$)[79] (−4.9; 95%CI, −10.2 to 0.4 ng/mL)[80] when compared with their non-asthmatic counterparts. Likewise, reduced whole blood (−3.3; 95% CI, −5.8 to −0.8 units/g Hb)[80] and red blood cell ($P = 0.0061$)[81] glutathione peroxidase activity has been observed in asthmatic patients. Thus, studies suggest that consuming dietary sources of these antioxidants can protect against the effects of oxidants and prevent inflammation.[82]

Flavonoids and selenium have been shown to confer a protective effect on asthma in a case-control study (720 cases and 980 controls).[25] Likewise, antioxidants can reduce oxidative stress and potentially reduce asthmatic symptoms.[25] Increased magnesium intake is associated with a positive effect on asthma.[83,84] In contrast, a low-salt diet improves pulmonary function in patients with exercise-induced asthma.[85] These listed nutrients, and their respective quantities, can be obtained through a plant-based diet and present a potential method for treating asthma symptoms.

## Fiber, inflammation, and lung function

A study of 598 Dutch children demonstrated an inverse association between whole grain consumption and odds of asthma.Tabak et al[86] also reported similar associations for concurrent wheeze and atopic wheeze with bronchial hyperresponsiveness. Dietary fiber intake has been positively associated with improvements in lung function.[87,88] Kan et al[87] observed that participants in the highest quintile of total fiber intake (median intake of 25 g/d) had higher $FEV_1$ ($P$ for trend $< 0.001$), FVC ($P = 0.001$), $FEV_1$/FVC ratio ($P = 0.040$), predicted $FEV_1$ ($P < 0.001$), and predicted FVC ($P = 0.001$) than those in the lowest quintile of fiber intake (median intake of 10.2 g/d). Likewise, Hanson et al[88] observed similar associations between high dietary fiber consumption (mean intake >17.5 g/d) and higher measurements of $FEV_1$ and FVC ($P = 0.05$ and 0.01, respectively), and mean percent predicted $FEV_1$ and FVC ($P = 0.07$ and 0.02, respectively), when compared with subjects in the lowest quintile of fiber intake (mean intake <10.75 g/d).

The antioxidant and anti-inflammatory effects of whole grains might explain these protective effects.[89] Whole grain consumption is inversely associated with

serum C-reactive protein[90,91] and tumor necrosis factor-α receptor-2.[92] Studies have also shown an inverse association between fiber intake and pro-inflammatory interleukin-6 (IL-6), tumor necrosis factor-α receptor-2,[93] and C-reactive protein.[94] Based on the total fiber intake of participants in the highest quintile (24.7 g/d)[93] and quartile (22.4 g/d),[94] the recommended daily intake (25 g/d for women and 38 g/d for men) can potentially illicit these anti-inflammatory effects.[95] Thus, dietary fiber might greatly influence inflammation and result in improved lung function.

The fiber content of the diet influences the gut microbiome, which produces several metabolites that in turn influence immune and metabolic responses. While airway diseases are commonly associated with gut inflammation,[96] dietary patterns modulate the microbiome composition, thus influencing immunological responses.[92] Changes in signaling in intestinal epithelial cells can alter the microbiota and regulate lung pro-inflammatory responses through modulation of inflammatory cytokine production.[97] Studies suggest that dietary-induced changes in microbiota can mediate lung inflammation.

Gut microbes ferment dietary fiber to produce short-chain fatty acids, which have an immunomodulatory effect.[98] Butyrate is a short-chain fatty acid produced by gut microbiota that reduces inflammatory cytokine expression. Butyrate activates peroxisome proliferator–activated receptor $\gamma$ , which then inhibits nuclear factor $\kappa$B activity – a transcription factor that regulates genes involved in immune inflammatory responses.[44] Short-chain fatty acids also activate G-protein-coupled receptors, which can inhibit immune cell recruitment.[99,100] Thus, consumption of a high-fiber diet is associated with a positive change in gut bacteria that protects against airway allergic responses.[101] A 2013 study (n = 202) observed a positive association between dietary fiber intake in asthmatic patients and $FEV_1$ ($P = 0.001$), FVC ($P = 0.002$), and $FEV_1$/FVC ($P = 0.035$).[44]

Dietary fiber may act through other mechanisms, as well. While hyperglycemia stimulates the release of pro-inflammatory cytokines,[102] dietary fiber has been shown to reduce blood glucose[103] and is associated with higher plasma adiponectin concentrations.[104] Dietary fiber might also prevent inflammation by increasing the thickness of the intestinal barrier, preventing proteins from entering the bloodstream and triggering an immune response.[105] This demulcent effect on the intestinal lining might also explain the anti-inflammatory effects of a high-fiber diet.

While animal products are virtually devoid of fiber, vegan diets tend to emphasize the consumption of high-fiber fruits, vegetables, and whole grains. Thus, a plant-based diet can potentially improve airway inflammation by promoting anti-inflammatory cytokines, improving glucose control, and modulating gut immunologic response.

## Dietary fat

Inflammation associated with immune dysfunction can be observed through elevated sputum IL-6[106] and IL-8, neutrophil influx, and increased gene expression for Toll-like receptor-2 and -4.[107] Consumption of a single, mixed high-fat meal (containing fats of different quality and degree of saturation) increases pro-inflammatory mediator production, including the release of TNF-α and IL-6,[108,109] and activates Toll-like receptor, producing an immune response.[110] Wood et al[110] demonstrated that plasma fatty acid changes positively correlated with changes in sputum % neutrophils and negatively with % $FEV_1$, FVC, $FEV_1$/FVC. These results suggest that various dietary fats may influence airway inflammation. While some unsaturated fats might play a protective role, researchers suggest that saturated fat might induce inflammation. Saturated fatty acids activate pro-inflammatory NFkB and cyclooxygenase-2 expression through Toll-like receptor-4. In contrast, unsaturated fatty acids inhibit this pathway and the subsequent inflammatory response.[111]

Saturated fat activates Toll-like receptor-4, eliciting an immune response and an inflammatory cascade.[112] Participants randomized to a 10-week dietary intervention or combined dietary and exercise intervention reported changed in saturated fat intake of −24 and −30 g/d, respectively ($P \leq 0.01$ for both). Expectedly, reducing dietary saturated fat intake corresponded with a reduction in neutrophilic airway inflammation in male patients with asthma ($r = 0.775$, $P = 0.041$).[113]

High fat diets might also exacerbate inflammation by negatively altering gut bacteria.[114–116] Thus, a low-fat vegan diet limiting added oils and nuts (≈10% energy from fat)[117] might improve asthmatic symptoms by circumventing these inflammatory responses to high fat foods.

*Polyunsaturated fatty acids.* A simultaneous rise in n-6 and decrease in n-3 polyunsaturated fatty acid (PUFA) consumption has been observed with the concurrent increase in children's asthma in the UK.[118,119] A proposed mechanism for this correlation is an observed increase in the pro-inflammatory mediators prostaglandin $E_2$[66,120] and leukotriene B4[66] with increased linoleic acid consumption. Linoleic acid is the most abundant n-6 PUFA in the Western diet and is converted to arachidonic acid, a precursor to both $PGE_2$ and leukotriene B4. $PGE_2$ promotes type 2 T-helper ($T_H2$) cells, which

stimulate inflammatory cytokine production,[120] and immunoglobulin E, stimulating the release of pro-inflammatory mediators and eliciting an allergic response.[121] Leukotriene B4 stimulates neutrophil activation, increases IL-6 production, and may stimulate early gene transcription of other cytokines.[122]

In contrast, n-3 PUFA inhibits the conversion of linoleic acid to arachidonic acid, a $PGE_2$ precursor, thereby circumventing this inflammatory pathway.[120] α-Linolenic acid (an n-3 PUFA) is converted to eicosapentaenoic acid, which can competitively inhibit arachidonic acid metabolism and thereby circumvent the inflammatory cascade.[66] n-3 PUFAs also impede $PGE_2$ formation by inhibiting cyclooxygenase, an enzyme responsible for the conversion of arachidonic acid to $PGE_2$. Thus, increased n-6 and reduced n-3 consumption, as observed in recent Western dietary patterns, might play a role in allergic sensitization.[120] While n-6 PUFAs are commonly derived from plant oils and animal fat, n-3 PUFAs can be obtained from leafy greens, flaxseeds, and walnuts.[123]

## Vitamin D

Several epidemiological studies have suggested a relationship between asthma prevalence and vitamin D insufficiency and deficiency in children. Across all studies, the prevalence of vitamin D deficiency and insufficiency was significantly higher in asthma patients than controls.[6–8] In a sample of 483 asthmatic children in Qatar, only 13.4% had adequate levels of serum vitamin D, and vitamin D deficiency was the strongest of 8 potential predictors of asthma.[124] Checkley et al[125] conducted a cross-sectional study examining asthma prevalence and 25-hydroxyvitamin D levels among 1134 children across 2 different communities in Peru: the urban community of Lima and the rural community of Tumbes. Children who were vitamin D–deficient (<20 ng/mL 25-hydroxyvitamin D) were 5 times as likely to have asthma, whereas those who were vitamin D–insufficient (<30 ng/mL 25-hydroxyvitamin D) were 3 times as likely. There was a significantly higher prevalence of both asthma and vitamin D insufficiency in the urban community of Lima. This suggests that the relationship between vitamin D and asthma may be moderated by ecological factors.[125]

Vitamin D insufficiency is also linked to asthma severity. Multiple studies have found an inverse relationship between serum 25-hydroxyvitamin D3 and childhood asthma control.[126,127] Vitamin D insufficiency has also been associated with increased risk of hospitalization or emergency visits in multiple retrospective and prospective analyses.[128–130] Additionally, vitamin D appears to confer a protective effect beyond that of inhaled corticosteroids[128] and mediated the effects of exposure to airborne particulate matter among urban, obese children.[131]

However, the association between vitamin D and specific markers of asthma severity is less clear. Brehm et al[129] found no significant correlations between vitamin D insufficiency and total immunoglobulin (Ig)E or lung function measures in a sample of Puerto Rican children, suggesting that vitamin D insufficiency is linked to asthma exacerbations through a mechanism other than innate immune response. However, similar studies have found a significant inverse correlation between serum vitamin D levels and total IgE.[130,132] Additionally, serum 25-hydroxyvitamin D3 is linked to airway smooth muscle mass and positively correlated with markers of lung function, including forced expiration and forced vital capacity.[132] These relationships suggest that vitamin D may modulate asthma severity through immunomodulatory effects and airway remodeling (via smooth muscle cell proliferation or hypertrophy).[130,132]

The role of vitamin D extends beyond its well-known role in calcium metabolism. The active form of vitamin D ($1,25[OH]_2D$) plays a key role in both innate and adaptive immunity, and thus may defend against respiratory infections and inflammatory diseases, including asthma.[133–135] Macrophages convert circulating 25-hydroxyvitamin D3 into active 1,25-hydroxyvitamin D3. Active vitamin D then modulates innate immunity by stimulating the expression of the antimicrobial peptide cathelicidin, which acts on bacterial organisms by disintegrating the cell membrane. Vitamin D controls adaptive immunity by reducing the transcription of anti-inflammatory $T_H1$ cytokines and increasing the expression of pro-inflammatory $T_H2$ cytokines, thereby controlling the $T_H1$-$T_H2$ balance.[133] $T_H2$ cytokines include IL-4, IL-5, IL-9, and IL-14, which initiate B-cell activation, eosinophilia, and production of immunoglobulin E.[136] Through up-regulating $T_H2$ expression, vitamin D produces an anti-inflammatory immune response. Vitamin D insufficiency may also stimulate inflammatory responses to nonpathogenic bacteria in the gut, thereby mediating asthma and immune function through the role of vitamin D in the gut microbiome.[137]

## Body weight and asthma

Overweight and obese children are at higher risk of developing asthma than normal-weight youths, with risk increasing as degree of obesity increases.[138,139] BMI is positively associated with worse asthma control in children and adolescents[140] and asthma exacerbation in

adults.[141] Obesity in children is also associated with an increased risk of asthma exacerbation,[142] higher hospital charges, longer hospital stays,[143] and more frequent emergency department visits[144] than non-obese children. Increased inflammation seen in obesity could help explain the link. Adipose tissue releases pro-inflammatory molecules such as IL-6, tumor necrosis factor-$\alpha$, C-reactive protein, and leptin, which contribute to the immune response.[112] Obesity has also been linked to increased systemic leukotriene inflammation in patients with asthma. Leukotrienes are pro-inflammatory substances released from mast cells that play a key role in bronchoconstriction in asthma.[141] Thus, excess adipose tissue might contribute to airway inflammation, exacerbating asthma symptoms.[145]

*Obesity-related vs healthy-weight pediatric asthma.* Not only does obesity increase asthma risk and worsen symptoms, but obesity-related asthma appears to be a separate phenotype of pediatric asthma.[146] "Classic" childhood asthma, in healthy-weight children, is marked by a systemic increase in atopy-associated $T_H2$ cells. Conversely, obesity-related childhood asthma is characterized by increases in $T_H1$ cells.[146–148] This $T_H1$ polarization correlates with reduced pulmonary function.[146] Levels of leptin and its downstream pro-inflammatory cytokine IL-6 also correlate directly with $T_H1$ polarization.[147] Further differentiating the obesity-related asthma phenotype – and potentially helping explain its increased severity – is the negative effect of insulin resistance and dyslipidemia on pulmonary function seen in adolescents.[149,150] Interestingly, obesity-related asthma was previously thought to occur predominantly in adults.[151] However, like type 2 diabetes, it may be that the authors are seeing "adult-onset" asthma in children and teens as the obesity epidemic worsens.

*Weight management interventions for childhood asthma.* Dietary interventions producing weight loss in obese children have been found to elicit improvements in lung function, asthma control,[152] and quality of life, and fewer acute attacks.[153] Overweight/obese adults with asthma placed on a diet intervention showed improvements in asthma control ($P \leq 0.001$) and quality of life ($P = 0.002$).[113] Another dietary intervention study induced a mean weight loss of −14.5% in obese patients with asthma, resulting in significant improvements in lung function ($FEV_1$ $P = 0.009$ and FVC $P < 0.0001$), dyspnea ($P = 0.02$), rescue medication use ($P = 0.03$), and number of exacerbations ($P = 0.001$) compared with the controls.[154]

Weight loss in obese patients can prevent early airway closure and improve ventilatory mechanics.[155] Thus, a potential explanation for these improvements is reduced airway obstruction due to a reduction in obesity-related airway closure as a result of weight loss. Furthermore, a diet that produces weight loss can alleviate excess adiposity, reduce inflammation, and therefore improve lung function. Plant-based diets are particularly effective for weight loss.[156,157]

## CONCLUSION

The prevalence of asthma has risen in recent decades. As Western dietary patterns have become more pervasive, asthma prevalence has increased. Most Americans do not meet the daily recommended fruit or vegetable intake and exceed the recommendations for limiting saturated fat. Thus, recommendations to increase fruit and vegetable consumption, while decreasing saturated fat and dairy intake, are supported by the current literature. Mediterranean and vegan diets emphasizing the consumption of fruits, vegetables, grains, and legumes, while reducing or eliminating animal products, might reduce the risk of asthma development and exacerbation. Fruit and vegetable intake has been associated with reduced asthma risk and better asthma control, while dairy consumption is associated with increased risk and might exacerbate asthmatic symptoms. Dietary components such as antioxidants, fiber, polyunsaturated fatty acids, total and saturated fat, and vitamin D consumption likely affect immune pathways involved in the pathophysiology of asthma. However, intervention trials to assess the prevention and control of asthma by dietary means are necessary to confirm these associations.


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