NUTRITION REVIEWS

Special Article

Fruit and vegetable intake and risk of wheezing and asthma: a systematic review and meta-analysis

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Major bibliographic databases were searched for studies examining the relationship between fruit and vegetable consumption and the risk of wheezing and asthma. Random-effects models were used to pool study results. Subgroup analyses were conducted by fruit and vegetable categories, study design, and age group. Twelve cohorts, 4 population-based case-control studies, and 26 cross-sectional studies published between January 1990 and July 2013 were identified. For the meta-analysis of adults and children, the relative risk (RR) and confidence intervals (CI) when comparing the highest intake group with the lowest intake group were 0.78 (95%CI, 0.70–0.87) for fruit and 0.86 (95%CI, 0.75–0.98) for vegetables. High intake of fruit and vegetables (RR = 0.76; 95%CI, 0.68–0.86 and RR = 0.83; 95%CI, 0.72–0.96) reduced the risk of childhood wheezing. Total intake of fruit and vegetables had a negative association with risk of asthma in adults and children (RR = 0.54; 95%CI, 0.41–0.69). Consuming fruit and vegetables during pregnancy had no association with the risk of asthma in offspring. High intake of fruit and vegetables may reduce the risk of asthma and wheezing in adults and children.

INTRODUCTION

During the past few decades, the prevalence of asthma and the morbidity and mortality associated with this condition have increased worldwide.[1] Asthma is characterized mainly by chronic airway inflammation that adversely affects normal lung function.[1–3] A causal relationship for the development of asthma has not been established; however, interactions between genetic and environmental factors, including diet, are believed to cause sensitivity to allergic diseases. Diet may be a modifiable factor in predisposing individuals to asthma.[1,4] For example, high intakes of salt,[5] a change in the fatty acids component of the diet,[6] and low intakes of fruit and vegetables[7,8] have been related to the development of obstructive lung diseases.

High intake of flavone and flavanone was associated with a lower incidence of asthma.[9] Although flavonoids are considered non-nutritive compounds, many have antioxidant, anti-inflammatory, anticancer, and gastro-, cardio-, and neuro-protective properties, which has led to increased interest in their potential role in the prevention of some chronic diseases.[10–13] High intake of flavonoids such as quercetin, hesperitin, and naringenin has also been associated with a lower risk of asthma.[9,14] Quercetin, which is present in apples, has anti-inflammatory and

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antioxidant capacities and is widely ingested.[15,16] Increasing evidence from cell and animal studies shows that flavonoids have a direct effect on signaling cascades involved in inflammatory cell responses.[17,18]

Understanding dietary effects on wheezing and asthma may aid in the prevention of these chronic diseases. Therefore, a meta-analysis of published epidemiological studies was performed to clarify the relationship between consumption of fruit and vegetables and the risk of wheezing and/or asthma. It was hypothesized that the consumption of fruit and vegetables would be negatively associated with the risk of wheezing and asthma.

METHODS

A systematic review was conducted according to the MOOSE (meta-analysis of observational studies in epidemiology) guidelines.[19] Using the Medline/PubMed, Embase, Cinahl, and Scopus databases, an extensive search was conducted of literature published in English between January 1990 and July 2013 and involving humans. The following key words and medical subject heading (MeSH) were included: asthma [MeSH] or lung function [MeSH] or asthma symptom and/or fruit [MeSH] and/or vegetables. Additional studies were identified from the reference list of selected articles and the Science Citation Index. Two authors extracted data independently (ES, MPM) and two authors (FK, ES) independently performed the quality assessment. To ensure uniformity, a single author checked the extracted data and validity criteria against the original published report. Abstracts of all identified studies were read, and irrelevant papers were excluded. The full texts of the remaining articles were reviewed to determine whether they met the criteria of the proposed study. Studies that met the following criteria were included in the meta-analysis: 1) the study was prospective, case-control, or cross-sectional; 2) fruit and/or vegetable intake was the exposure investigated; 3) the outcome was asthma, asthma symptoms, and/or wheezing; 4) the odds ratio or the relative risk (RR) and the corresponding 95% confidence intervals (CIs) were reported. If the data were duplicated in more than one study, the most recent and complete study was included in the meta-analysis. Data drawn from the literature included the type of study, the country in which the study was performed, sex and age of participants, sample sizes, outcomes, and potential confounders, such as duration of the study and type and amount of fruit and vegetables consumed.

A meta-regression model was used to assess the association between fruit and vegetable intake and risk of wheezing and/or asthma. This analysis was performed for the total number of adults and children together, for the adults and the children separately, and for pregnant women. To examine the risk of wheezing and/or asthma from a specific risk factor, the risk estimate from each study, weighted by the inverse of variance, was pooled. First, a fixed-effects model was used. When significant levels were obtained, the random-effects models of DerSimonian[20] were applied, which consider both within- and between-type study variations. Sensitivity analysis was conducted to examine whether the inclusion criteria affected the pooled estimates.[21,22] Cochran's test for heterogeneity was used to determine whether the studies included in the meta-analysis evaluated the same underlying sizes of the effect.[23] A threshold of $P < 0.1$ was used to identify the presence of heterogeneity (genuine variation in effect sizes). I^2 (an estimate of the proportion of total observed variability due to genuine variation rather than random error within studies) was used to quantify the degree of inconsistency between studies and was considered substantial when I^2 was >50%.[24] As recommended in the MOOSE guidelines, analyses were stratified by key features of the study design to assess the effects on the results.[19] Furthermore, using subgroup analysis, considering for confounding factors and effect modifiers was employed using the recommendations of Nurmatov et al.[25] Primary confounding factors, which considered general characteristics (including age and sex), socioeconomic status (including education and income), environmental factors (such as smoking), and dietary factors, were taken into account. In the sensitivity analyses, secondary confounding factors were also accounted for, specifically physical activity.[25] Statistical analyses were performed with Stata statistical software version 9.1 (Stata Corp., College Station, TX, USA).

RESULTS

The literature search identified 334 potentially relevant publications. After screening the titles and abstracts, 259 were excluded because they were irrelevant or were review articles. The process of study selection is shown in Figure 1. Seventy-six articles were retrieved for further review, of which 34 were excluded. Of the studies excluded, 13 evaluated diet patterns and risk of asthma using factor analysis.[26–38] Another 4 were randomized controlled trials,[39–42] of which 1 investigated the effects of a mixture of fruit, vegetables, fish oil, and probiotics supplement,[41] 1 compared the effects of high intake of vegetables and fruit with low intake,[42] 1 studied lycopene extract from tomato,[40] and 1 investigated the effect of purple passion fruit peel extract on pulmonary function parameters.[39] Five studies reported RRs for the lowest versus the highest intake of fruit and vegetables,[7,8,43–45] 1 considered only supplement use,[46] 2 reported the association of fruit intake and forced expiratory volume in 1 second,[47,48] 1 reported exposure to birch/grass pollen and

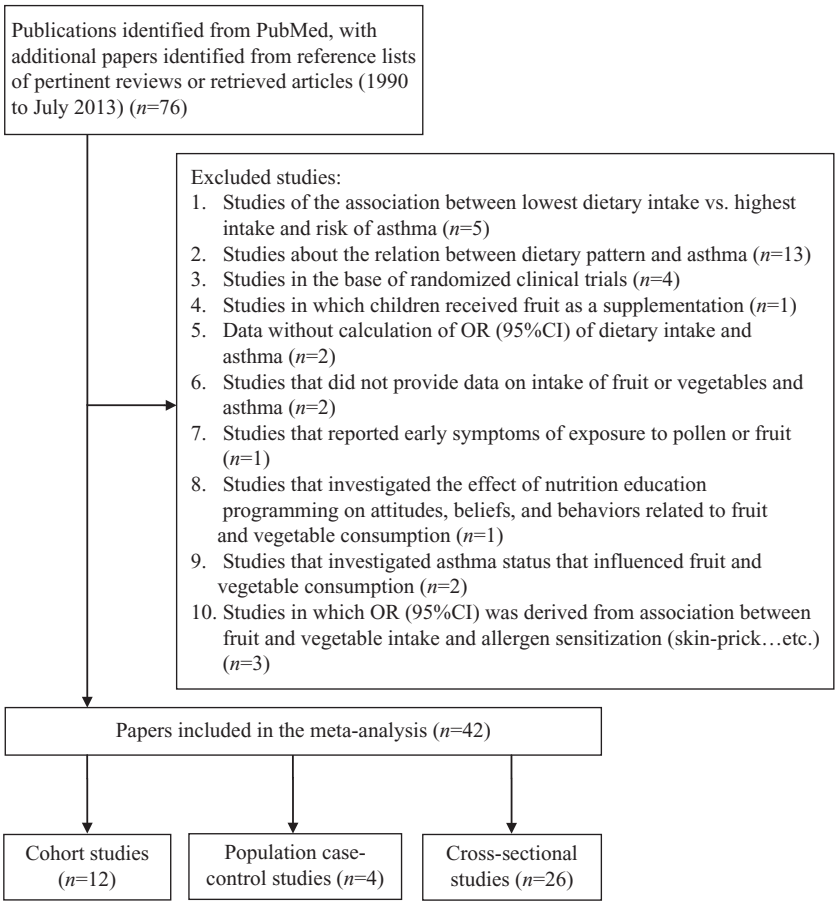

Figure 1 **Summary of screening process to identify studies for meta-analysis.**

tree-nuts of at 1 or 2 years and asthma symptoms at 4 years of age,[49] 2 did not provide sufficient information to allow the calculation of CIs,[38,50] and 1 investigated the effect of nutrition education programs on attitudes, beliefs, and behaviors related to fruit and vegetable consumption.[51] Two studies investigated the influence of asthma status on fruit and vegetable intake,[52,53] and 3 others assessed the effect of fruit and vegetable intake on allergic responses.[54–56]

Forty-two articles fulfilled the inclusion criteria. Table 1 shows the main characteristics of the studies evaluated, including 12 cohort studies,[9,57–67] 4 population-based case-control studies,[68–71] and 26 cross-sectional studies.[72–97] Overall, 93,575 subjects with 11.5 years of follow-up were included from cohort studies, 1,367 cases and 1,833 controls from case-control studies, and 958,457 participants from cross-sectional studies. The International Study of Asthma and Allergies in Childhood questionnaire was used to elicit self-reported respiratory symptoms in studies on children and adolescents.[59,60,64–66,70,73,77–81,83,84,86,89–91] A validated food frequency questionnaire was used for dietary assessment in 23 studies,[59,61,65–68,72,75–77,81,82,84–88,90,91,93,95–97] and a dietary habits questionnaire or food diaries were used in 19 studies.[9,57,58,60,62,64,69–71,73,74,78–80,83,89,92]

RRs from studies that examined an association between fruit and vegetable consumption and wheezing and/or asthma in the total number of adults and children and in subgroup analyses of children were pooled. Furthermore, analyses were performed to determine the association between maternal fruit and vegetable intake during pregnancy and the risk of asthma in offspring.

Adults and children

Fruit and vegetable intake and risk of wheezing. Two cohort studies[58,65] and 13 cross-sectional studies[73,77–81,84–87,90,91,96] evaluated the association between fruit intake and different descriptions of wheezing, including wheeze, wheezy illness, severe wheeze, shortness of breath with wheeze, severe wheeze with atopy, and exercise-related wheeze (Table 2). A strong negative association was found between high fruit intake and wheezing (RR = 0.81; 95%CI, 0.74–0.88), with significant heterogeneity confirmed among included studies (P for heterogeneity <0.0001, $I^2 = 81.9\%$) (Figure 2A). A sensitivity

Table 1 **Cohort studies, population-based case-control studies, and cross-sectional studies included in the meta-analysis of the associations between fruit and vegetable intake and risk of asthma and wheezing.**

Reference	Country	Food measured	Study population	Age	Follow-up (y)	Basis for asthma diagnosis	Method of dietary evaluation	Values or variables contrasted	Adjustments applied
Cohort studies									
Miedema et al. (1993)[57]	Netherlands	Total fruit & solid fruit	793 males	40–59 y	25	Episodes of respiratory symptoms doctor diagnosis	Dietary history	Quartile 4 vs. quartile 1	Age, BMI, energy, smoking
Butland et al. (1999)[58]	United Kingdom	Fresh fruit	5,582 males & 5,770 females	0–33 y	23	Wheezing/whistling in the chest in the past doctor diagnosis	Validated questionnaires	>1 time/wk vs. never	Sex, smoking, social class, vegetable intake
Knekt et al. (2002)[9]	Finland	Orange, apple, grapefruit, onion, white cabbage, berries, & juices	382 (males & females)	30–69 y	20	Questionnaire	Dietary history	Quartile 4 vs. quartile 1	Sex, age
Willers et al. (2007)[59]	Netherlands	Total fruit, citrus/kiwi, apples, fruit juice, total vegetables, & green leafy vegetables	1,212 (mothers & their children)	At birth	5	ISAAC questionnaire	FFQ	>4 times/wk vs. 0–1 time/wk	Maternal age of leaving full-time education, paternal social class, maternal age and smoking during pregnancy, smoking in the home during childhood, energy, maternal asthma and/or atopy, birth weight, presence of older siblings, sex of child, breastfeeding
Willers et al. (2008)[60]	Netherlands	Fruit & vegetables	2,832 (mothers & their children)	3 mo–8 y	8	ISAAC questionnaire	Questionnaire about mother's & child's diets	Daily vs. rare intake	Sex, maternal education, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, maternal supplement use during pregnancy without folic acid and iron, region, intervention or natural history study group
Chatzi et al. (2008)[61]	Spain	Vegetables	507 mothers & 468 children	6.5 y	6.5	Questionnaire about wheeze, whistling, and skin-prick test	FFQ	Weekly or daily consumption vs. never	Gender, parental asthma, maternal social class and education, BMI, energy intake at age 6.5 years

Bacopoulou et al. (2009)[62]	Greece	Fruit & vegetables	2,133 (males & females)	At birth	18	Questionnaire about family history of atopy, detailed information on asthma & doctor-diagnosed asthma	Validated questionnaire	Daily consumption vs. never	
Uddenfeldt et al. (2010)[63]	Sweden	Fruit	8,066 (males & females)	16 y, 30–39 y, & 60–69 y	13	Questionnaire	Questionnaire about frequency of current consumption	Daily consumption vs. never	Sex, heredity, hay fever, smoking, gastro-oesophageal reflux, snoring, physical activity, building dampness, socioeconomic group, BMI
Miyake et al. (2010)[64]	Japan	Total fruit, citrus fruit, apples, total vegetables, green, yellow, and other vegetables	50,004 (mothers & their children)	16–24 mo	2	ISAAC questionnaire	DHQ	Quartile 4 vs. quartile 1	Maternal age, gestation at baseline, education, history of asthma, maternal smoking during pregnancy, age of infant at third survey
Willers et al. (2011)[65]	Netherlands	Fresh fruit & cooked vegetables	2,870 (mothers & their children)	2–3 y & 7–8 y	6	ISAAC questionnaire	Annual FFQ	1 time/wk vs. long-term intake from age 2 to 8 y	Sex, maternal educational, parental atopy, maternal smoking during pregnancy, smoking in the house at 8 years of age, breast feeding, presence of older siblings, birth weight, overweight mother, overweight child at 8 years of age, geographical region and study arm
Erkkola et al. (2012)[66]	Finland	Fruit & vegetables	2,441 (mothers & their children)	0–5 y	5	ISAAC questionnaire	FFQ	Highest vs. lowest quintile	Sex, place of birth, duration of gestation, maternal age at delivery, maternal basic education, smoking during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental asthma, parental allergic rhinitis, atopic eczema by 6 months of age, pets at home by 1 year of age, duration of breastfeeding, and day-care at 1 year of age

Table 1 **Continued**

Reference	Country	Food measured	Study population	Age	Follow-up (y)	Basis for asthma diagnosis	Method of dietary evaluation	Values or variables contrasted	Adjustments applied
Protudjer et al. (2012)[67]	Canada	Fruit & vegetables	476 (males & females)	8–10 y & 11–14 y	6	Skin-prick test ≥3 mm & asthma symptoms	FFQ	Low vs. high score	Breastfeeding, fast food consumption, weight, region of residence, income, physical activity, maternal history of asthma
Population based case-control studies									
Shaheen et al. (2001)[68]	United Kingdom	Apples & onions	607 cases & 864 controls	16–50 y	–	Questionnaire	FFQ	Apples, onions: ≥5 times/wk compared with <once/month	Vitamin C and β-carotene intake
Patel el al. (2006)[69]	United Kingdom	Fruit & vegetables	515 cases & 515 controls	45–75 y	–	Doctor-diagnosed asthma	7-day food diaries	Higher consumption than median intake vs. no consumption	Smoking, social class, BMI, physical activity, education
Pastorino et al. (2006)[70]	Brazil	Fresh fruit & cooked vegetables	141 cases & 387 controls	13–14 y	–	ISAAC questionnaire	Questionnaire about dietary habits	Weekly or daily vs. no consumption	Allergic mother, skin prick test, eczema, rhinitis and prematurity
Mendes et al. (2011)[71]	Brazil	Fruit & vegetables	104 cases & 67 controls	2–1 y	–	Questionnaire	Dietary data collected during the last 30 days	Regular vs. occasional consumption	Race, sex, mechanical ventilation during neonatal period, age at onset of the disease, parental education, household income, presence of pets, family history of asthma or history of allergic rhinitis, exposure to maternal smoking, exclusive breastfeeding, obesity, regular consumption of fish or eggs
Cross-sectional studies									
La Vecchia et al. (1998)[72]	Italy	Vegetables	46,693 (males & females)	≥15 y	–	Questionnaire	FFQ	Highest vs. lowest tertile	Alcohol, smoking, age, sex, education
Forastiere et al. (2000)[73]	Italy	Citrus/kiwi fruit	18,737 (males & females)	6–7 y	–	ISAAC questionnaire	Questionnaire on dietary habits, citrus fruit consumption	5–7 times/wk vs. <1 time/wk	Sex, study area, father's education, household density, parental smoking, dampness or mould, parental asthma

Priftanji et al. (2002)[74]	Albania	Fruit or vegetables	2,653 (males & females)	20–44 y	–	Questionnaire	Questionnaire on dietary habits	At least once/wk	Age, sex, smoking
Ushiyama et al. (2002)[75]	Japan	Fruit & vegetables	2,070 (mothers & their children)	<12 mo	–	Doctor diagnoses	FFQ	Portion sizes (80 kcal)	Family history of asthma, sex, order of birth, age
Woods et al. (2003)[76]	Australia	Fruit & vegetables	1,601 (males & females)	20–44 y	–	ECRHS questionnaire	FFQ	1–2 pieces apples, pears, and berries/day; 2–4 servings leafy greens & tomatoes/day	Age, sex, smoking, BMI, region of birth, family history of asthma, and energy intake
Farchi et al. (2003)[77]	Italy	Fresh fruit, citrus fruit, kiwi, cooked vegetables, salads, tomatoes, & peppers	5,257 (boys & girls)	6–7 y	–	ISAAC questionnaire	FFQ	>4 times/wk vs. never	Sex, study area, paternal education, paternal smoking, parental asthma, dampness or mould in the child's room, household crowding
Awasthi et al. (2004)[78]	India	Fruit & vegetables	3,000 (boys & girls)	13–14 y	–	ISAAC questionnaire	Validated questionnaire	Fruit: ≥3 times/d Vegetables: ≥1 time/wk	Mother's education, antibiotic use in the first year of life, eating pasta or fast-food or meat ≥1/wk, exercise ≥1/wk
Wong et al. (2004)[79]	China	Fruit & vegetables	10,902 (boys & girls)	10 y	–	ISAAC questionnaire	Validated questionnaire	Fruit: ≥1 time/day Vegetable: ≥1 time/wk	Propensity score, sex
Nja et al. (2005)[80]	Norway	Fruit & vegetables	4,585 (boys & girls)	6–16 y	–	ISAAC questionnaire	Validated questionnaire	Daily consumption vs. less than once/wk	Age, sex, area, parental education, parental atopy, exposure to dog and cat, mothers' smoking during pregnancy or first year after delivery
Tabak et al. (2006)[81]	Germany	Citrus fruit & vegetables	598 (boys & girls)	8–13 y	–	ISAAC questionnaire	FFQ	Highest vs. lowest tertile	Mother's education, foreign descent, energy intake
Romieu et al. (2006)[82]	France	Fruit, citrus fruit, apples, leafy vegetables, fruity vegetables,[a] tomatoes, root vegetables,[b] carrots, & cabbage	68,535 females	40–65 y	–	ATS questionnaire	FFQ	Quartile 4 vs. quartile 1	Age, energy intake, BMI, physical activity, smoking, menopausal status, vitamin supplementation use
Garcia-Marcos et al. (2007)[83]	Spain	Fruit & vegetables	20,106 (boys & girls)	6–7 y	–	ISAAC questionnaire	Validated questionnaire	≥3 times/wk vs. once or twice/wk	Sex, obesity, maternal smoking, number of siblings and physical activity

Table 1 **Continued**

Reference	Country	Food measured	Study population	Age	Follow-up (y)	Basis for asthma diagnosis	Method of dietary evaluation	Values or variables contrasted	Adjustments applied
Okoko et al. (2007)[84]	United Kingdom	Fresh apples, apple juice, bananas, & other fruit	2,640 (boys & girls)	5–10 y	–	ISAAC questionnaire	FFQ	>1 serving/day vs. <1 serving/mo	Sex, age, paracetamol exposure, ibuprofen use, supplement use, lived on a farm, mould or mildew in house, finance support, exposure to passive smoking, ethnicity, birth weight, breastfeeding, number of parents living with child, number of children at home, parental education
Chatzi et al. (2007)[85]	Spain	Fruit, vegetables, & fruity vegetables	460 (boys & girls)	6.5 y	–	Questionnaire	FFQ	Highest vs. lowest tertile	Energy intake
Chatzi et al. (2007)[86]	Crete	Fruit & vegetables	690 (boys & girls)	7–18 y	–	ISAAC questionnaire & family history of allergic disease	FFQ	>1 time/day vs. <1 time/day	Age, sex, BMI, parental asthma, number of older siblings
Tsai & Tsai (2007)[87]	Taiwan	Fruit & vegetables	2,218 (boys & girls)	11–12 y	–	ATS questionnaire	FFQ	Daily intake vs. never	Residential districts, gender, physician-diagnosed allergy
Barros et al. (2008)[88]	Portugal	Fruit & vegetables	174 (males & females)	>16 y	–	Doctor diagnosis	FFQ	Fruit: >304.97 g/day vs. <17.51 g/day; Vegetables: >426.63 g/day vs. <211.54 g/day	Gender, age, education, energy intake and corticosteroid use
Garcia et al. (2008)[89]	Colombia	Fruit	3,256 children & 3,829 adolescents	6–7 y and 13–14 y	–	ISAAC questionnaire	Questionnaire on dietary habits	≥3 times/wk vs. occasionally	Acetaminophen and antibiotic use, TV watching, maternal education, presence of cat at home
Takaoka & Norback (2008)[90]	Japan	Fruit, fruit juice, raw vegetables, & cooked vegetables	153 females	Mean, 21 y	–	ISAAC/ECRHS questionnaires, doctor-diagnosed asthma	FFQ	Almost daily vs. never	Age, smoking, parental asthma/allergy, all food items studies
Nagel et al. (2010)[91]	20 countries[c]	Fruit, fruit juice, raw vegetables, & cooked vegetables	50,004 (boys & girls)	8–12 y	–	ISAAC questionnaire	FFQ	≥3 times/wk vs. never/occasionally	Age, sex, smoking exposure, parental atopy, exercise and number of siblings

Lawson et al. (2011)[92]	Canada	Vegetables	4,726 (boys & girls)	11–15 y	–	Doctor diagnosis; wheeze or cough during or after active play; dry cough at night without a cold; visit to doctor, ER, or hospital for wheezing	Validated questionnaire	High vs. low consumption	Age, sex, ethnicity, and socioeconomic status
Rosenlund et al. (2011)[93]	Sweden	Fruit (total fruit, apple, citrus, bananas), vegetables (total vegetables, onions, carrots, tomatoes, cruciferous, & green vegetables)	2,447 (boys & girls)	8 y	–	At least 4 episodes of wheezing in the last year or at least 1 episode of wheezing during the same period in combination with prescribed inhaled steroids used occasionally or regularly	FFQ	Highest vs. lowest tertile	Sex, socioeconomic status, maternal smoking during pregnancy and/or at baseline, BMI, maternal age at baseline, and parental history of allergic disease
Nakamura et al. (2012)[94]	Japan	Fruit & vegetables	452 (boys & girls)	3–6 y	–	ATS-DLD questionnaire	3-day dietary record	Highest vs. lowest tertile	Age, sex, BMI, breastfeeding, history of food allergy, mother's age, parental history of allergy, maternal education level, the number of siblings and household smoking
Rosenkranz et al. (2012)[95]	Australia	Fruit & vegetables	156,035 (males & females)	≥45 years	–	Questionnaire & self-reported information	FFQ	Quintile 5 vs. quartile 1	Age, education, weight status, physical activity, and smoking status
Ellwood et al. (2013)[96]	51 countries[d]	Fruit & vegetables	246,545 adolescents & 143,775 children	6–7 y and 13–14 y	–	ISAAC questionnaire	FFQ	≥3 times/wk vs. never	
Agrawal et al. (2013)[97]	India	Fruit & vegetables	99,574 females & 56,742 males	20–49 y	–	Questionnaire	FFQ	Daily intake vs. never/ occasionally	Age, sex, marital status, education, employment status, religion, geographic region, environmental factors, BMI, smoking status, alcohol, TV watching, other dietary factors

Abbreviations: ATS, American Thoracic Society; ATS-DLD, American Thoracic Society and Division of Lung Diseases of the National Heart, Lung, and Blood Institute; BMI, body mass index; DHQ, diet history questionnaire; ECRHS, the European Community Respiratory Health Survey screening questionnaire; ER, emergency room; FFQ, food frequency questionnaire; ISAAC, International Study of Asthma and Allergies in Childhood questionnaire.

[a] Fruity vegetables: artichoke, avocado, tomatoes, cucumber, green beans, eggplants, bell pepper, and zucchini.

[b] Root vegetables: carrots, beetroot, celeriac, and salsify.

[c] 29 centers in 20 countries (ISAAC Phase II).

[d] 107 centers in 51 countries (ISAAC Phase III).

Table 2 **Meta-analysis of the association between fruit and vegetable intake and risk of wheezing and asthma in studies in adults and children, in children, and in pregnant women.**

Population and analysis type	Pooled effect estimate (95%CI)	*P* heterogeneity	I^2	No. of studies
Adults and children				
Wheeze and fruit				
Overall	0.81 (0.74–0.88)	<0.0001	81.9%	15
By type of study				
Cohort	0.96 (0.84–1.10)	0.38	0.0%	2
Cross-sectional	0.79 (0.72–0.86)	<0.0001	84.1%	13
Subgroup analysis				
Apples	0.64 (0.42–0.98)	0.03	71.9%	2 (CS)
Citrus fruit	0.68 (0.60–0.76)	0.20	35.2%	4 (CS)
Wheeze and vegetables				
Overall	0.89 (0.81–0.98)	<0.0001	82.5%	11
By type of study				
Cohort	1.22 (1.04–1.44)	–	–	1
Cross-sectional	0.86 (0.78–0.94)	<0.0001	81.1%	10
Subgroup analysis				
Tomatoes	0.50 (0.35–0.70)	0.20	40.1%	2 (CS)
Peppers	0.64 (0.32–1.31)	0.52	0.0%	2 (CS)
Asthma and fruit				
Overall	0.84 (0.80–0.90)	<0.0001	70.0%	23
By type of study				
Cohort	0.78 (0.66–0.92)	0.02	65.1%	5
Population based case-control	0.71 (0.60–0.85)	0.65	0.0%	4
Cross-sectional	0.84 (0.83–0.94)	<0.0001	69.5%	14
Subgroup analysis				
Apples	0.84 (0.78–0.91)	0.05	52.8%	7 (1 cohort, 2 PCC, and 4 CS)
Citrus fruit	0.86 (0.78–0.96)	0.04	60.7%	5 (1 cohort, 1 PCC, and 3 CS)
Asthma and fruit and vegetables				
Overall	0.64 (0.41–1.01)	<0.0001	86.5%	4
By type of study				
Cohort	0.60 (0.40–0.90)	–	–	1
Cross-sectional	0.65 (0.37–0.1.16)	<0.0001	88.1%	3
Asthma and vegetables				
Overall	0.88 (0.82–0.95)	<0.0001	83.8%	18
By type of study				
Cohort	0.77 (0.35–1.69)	0.004	88.2%	2
Population-based case-control	0.80 (0.43–1.48)	0.03	72.3%	3
Cross-sectional	0.87 (0.81–0.94)	<0.0001	86.1%	13
Atopy and fruit	0.98 (0.95–1.01)	0.53	0.0%	3 (CS)
Atopy and vegetables	0.99 (0.96–1.01)	0.44	0.0%	3 (CS)
Adults				
Wheeze and fruit	0.69 (0.49–0.96)	0.27	17.5%	2
Overall				
By type of study				
Cohort	0.81 (0.53–1.22)	–	–	1
Cross-sectional	0.57 (0.36–0.90)	–	–	1
Wheeze and vegetables	1.2 (0.86–1.67)	–	–	1
Asthma and fruit	0.77 (0.68–0.87)	<0.0001	84.4%	9
Overall				
By type of study				
Cohort	0.71 (0.61–0.82)	0.27	23.0%	3
Population-based case-control	0.72 (0.60–0.87)	0.70	0.0%	2
Cross-sectional	0.87 (0.76–1.002)	<0.0001	85.1%	4
Subgroup analysis				
Apples	0.77 (0.66–0.90)	0.02	66.1%	5 (1 cohort, 2 PCC, and 2 CS)
Citrus fruit	0.76 (0.56–1.02)	0.01	76.9%	3 (1 cohort, 1 PCC, and 1 CS)
Asthma and vegetables	0.84 (0.74–0.96)	<0.0001	92.7%	6
Overall				

Table 2 **Continued**

Population and analysis type	Pooled effect estimate (95%CI)	*P* heterogeneity	I^2	No. of studies
By type of study				
Population-based case-control	0.88 (0.62–1.25)	–	–	1
Cross-sectional	0.84 (0.73–0.97)	<0.0001	94.2%	5
Children				
Wheeze and fruit				
Overall	0.81 (0.74–0.88)	<0.0001	83.1%	14
By type of study				
Cohort	0.98 (0.86–1.12)	–	–	1
Cross-sectional	0.79 (0.72–0.86)	<0.0001	84.2%	13
Subgroup analysis				
Apples	0.64 (0.42–0.98)	0.03	71.9%	2 (CS)
Citrus fruit	0.69 (0.61–0.77)	0.22	32.3%	4 (CS)
Wheeze and vegetables				
Overall	0.88 (0.79–0.97)	<0.0001	83.7%	10
By type of study				
Cohort	1.22 (1.04–1.44)	–	–	1
Cross-sectional	0.84 (0.76–0.93)	<0.0001	82.4%	9
Subgroup analysis				
Tomatoes	0.50 (0.35–0.70)	0.19	40.1%	2 (CS)
Peppers	0.64 (0.32–1.31)	0.52	0.0%	2 (CS)
Asthma and fruit				
Overall	0.90 (0.86–0.94)	0.21	24.5%	12
By type of study				
Cohort	0.90 (0.83–0.99)	0.55	0.0%	2
Population-based case-control	0.51 (0.23–1.16)	0.36	0.0%	2
Cross-sectional	0.90 (0.85–0.95)	0.13	38.2%	8
Asthma and fruit and vegetables				
Overall	0.57 (0.42–0.77)	0.69	0.0%	2
By type of study				
Cohort	0.60 (0.40–0.90)	–	–	1
Cross-sectional	0.53 (0.33–0.84)	–	–	1
Asthma and vegetables				
Overall	0.91 (0.82–1.00)	<0.0001	69.2%	12
By type of study				
Cohort	0.77 (0.35–1.69)	0.004	88.2%	2
Population-based case-control	0.73 (0.20–2.66)	0.01	85.9%	2
Cross-sectional	0.91 (0.83–0.99)	0.02	57.9%	8
Pregnant women				
Wheeze and fruit	0.94 (0.0.73–1.27)	0.02	70.2%	4 cohort
Wheeze and apples	0.84 (0.48–1.46)	0.06	71.8%	2 cohort
Wheeze and vegetables	0.91 (0.70–1.18)	0.05	61.0%	4 cohort
Asthma and fruit				
Overall	0.94 (0.81–1.08)	0.84	0.0%	3
By type of study				
Cohort	0.92 (0.78–1.08)	0.81	0.0%	2
Cross-sectional	1.01(0.74–1.38)	–	–	1
Asthma and vegetables				
Overall	1.06 (0.72–1.58)	0.05	67.4%	3
By type of study				
Cohort	0.95 (0.81–1.12)	0.31	5.0%	2
Cross-sectional	1.80 (1.06–3.20)	–	–	1

Abbreviations: CS, cross-sectional study; PCC, population-based case-control study.

analysis performed by excluding the three types of wheezing (severe wheeze with allergic sensitization atopy, severe wheeze, and exercise-related wheeze) in two studies[73,80] produced similar results (RR = 0.83; 95%CI; 0.77–0.90). To ensure confounder and effect modification[25] were properly accounted for, sensitivity analysis was performed by including studies that adjusted for both effect modification and at least two primary confounders (general characteristics, socioeconomic status, smoking, and physical activity). Further analysis found

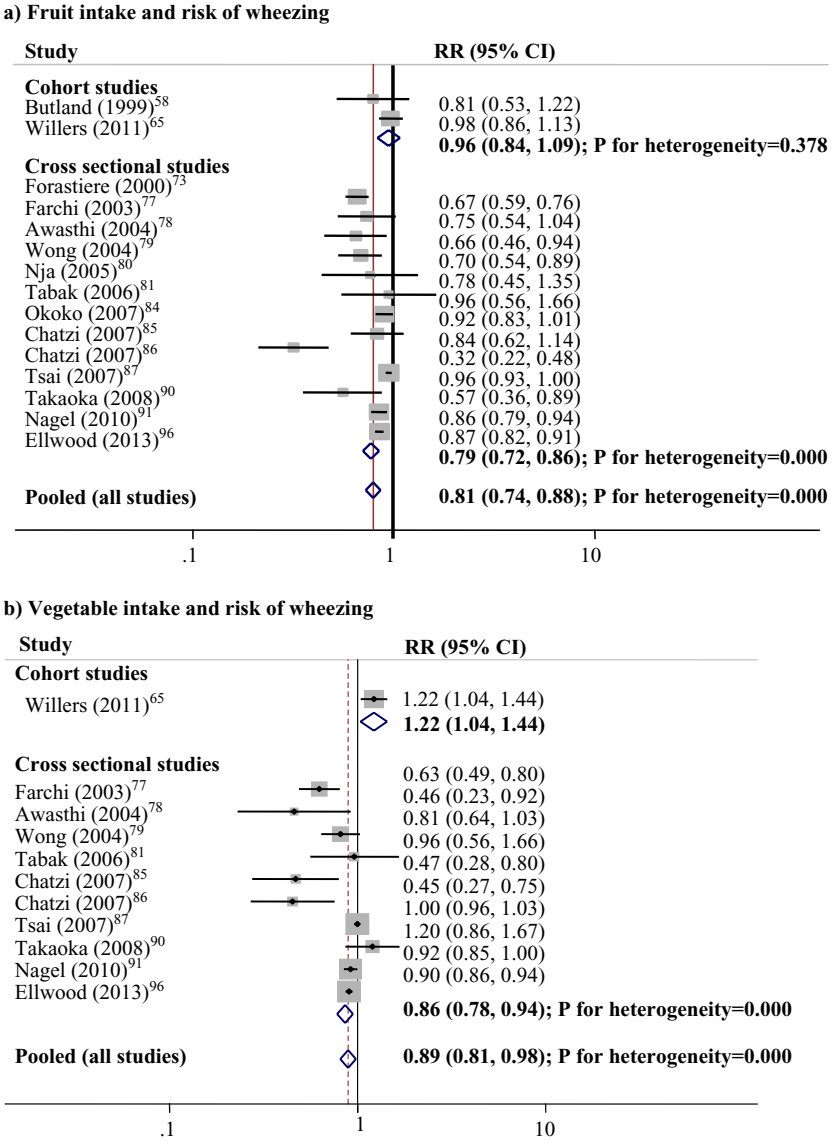

Figure 2 **Forest plots of the association between intake of fruit (a) or vegetables (b) and risk of wheezing.**

the association between fruit intake and wheezing was similar (RR = 0.81; 95%CI, 0.75–0.89; *P* for heterogeneity <0.0001, $I^2 = 82.5\%$).

After stratifying by study type, there was a significant 24% reduction in risk for the cross-sectional studies, whereas results for cohort studies were null. There was also a significant negative association between high intake of apples and citrus fruit and reduced risk of wheezing (Table 2). There was a significant heterogeneity within studies for apple consumption (*P* for heterogeneity = 0.03, $I^2 = 71.9\%$), but not for citrus fruit (*P* for heterogeneity = 0.20, $I^2 = 35.2\%$).

The association between vegetable intake and risk of wheezing was examined in 1 cohort[65] and 10 population-based cross-sectional studies (Table 2).[77–79,81,85–87,90,91,96] Total raw and cooked vegetable consumption was correlated with a significant decrease in risk of wheezing (RR = 0.89; 95%CI, 0.81–0.98; *P* for heterogeneity <0.0001, $I^2 = 82.5\%$) (Figure 2B). Four studies[65,77,90,91] reported inverse associations between cooked vegetables and wheezing, in which the pooled effect of a high intake of cooked vegetables was null (RR = 0.99; 95%CI, 0.81–1.22; *P* for heterogeneity = 0.027, $I^2 = 67.4\%$). A sensitivity analysis, performed by excluding these four studies, also showed raw vegetable consumption significantly decreased the risk of wheezing (RR = 0.70; 95%CI, 0.53–0.94; *P* for heterogeneity <0.0001, $I^2 = 79.3\%$). Furthermore, the sensitivity analysis showed no association between high vegetable intake and reduced risk of wheezing (RR = 0.92; 95%CI, 0.85–1.01; *P* for heterogeneity <0.0001, $I^2 = 82.1\%$). In the subgroup analysis, high tomato intake was negatively associated with the risk of

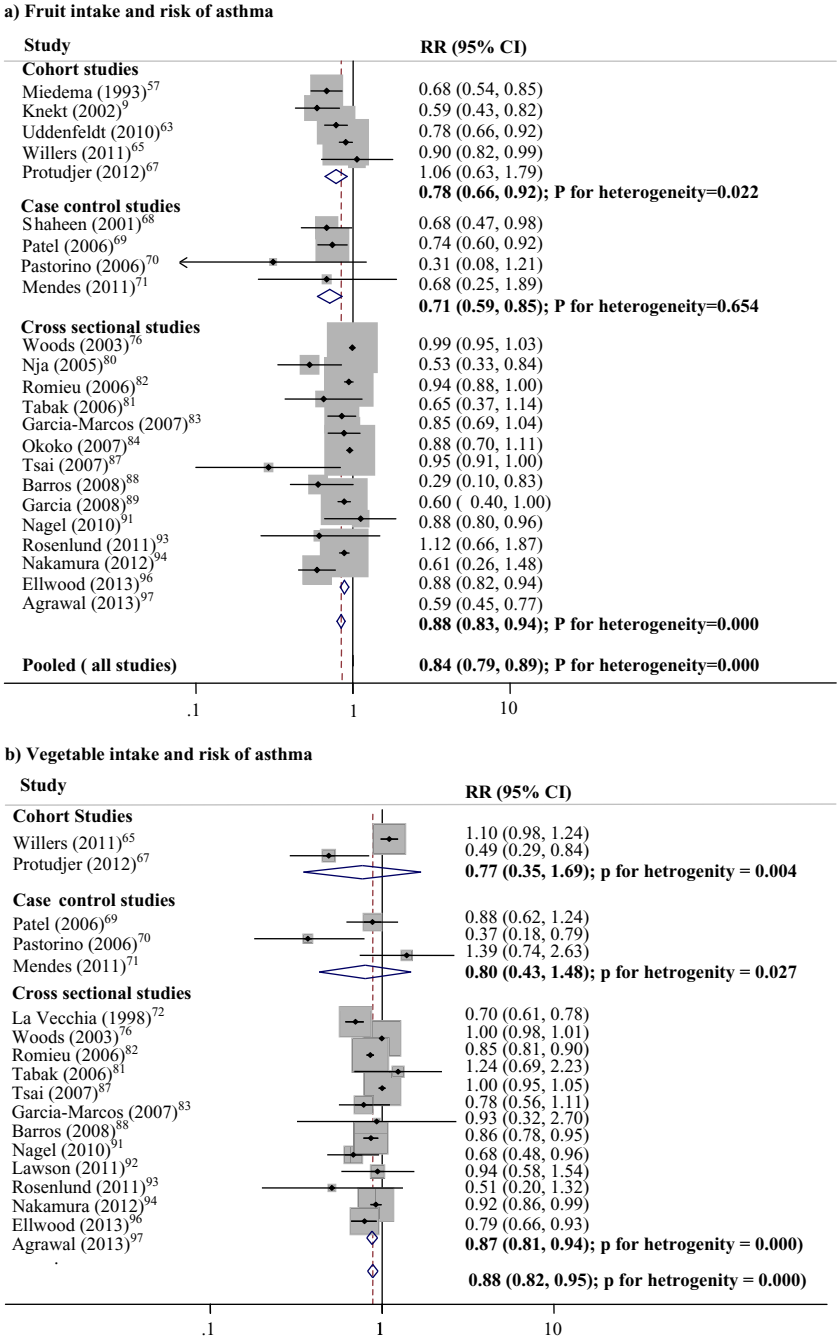

Figure 3 **Forest plots of the association between intakes of fruit (a) or vegetables (b) and risk of asthma.**

wheezing. The findings for high bell pepper intake, however, were null (Table 2).

Fruit and vegetable intake and risk of asthma. Meta-analysis of 5 prospective cohorts,[9,57,63,65,67] 4 population-based case-control studies,[68–71] and 14 cross-sectional studies[76,80–84,87–89,91,93,94,96,97] that evaluated intake of fruit in relation to risk of asthma yielded a significant negative association. The overall RR was 0.84 (95%CI, 0.80–0.90) for the highest fruit intake group compared with the lowest intake group, with significant heterogeneity (*P* for heterogeneity <0.0001, $I^2 = 69.4\%$) (Table 2). A sensitivity analysis performed by excluding severe asthma in one study[96] produced similar results (RR = 0.84; 95%CI, 0.79–0.9). Subgroup analysis by study design yielded a significant negative association between high fruit intake and risk of asthma among population-based case-control studies, cohort studies, and cross-sectional studies (Table 2, Figure 3A). When data were stratified by fruit type, the results remained statistically significant for both high intake of apples and for citrus fruit intake and risk of asthma (Table 2).

Fruit and vegetable consumption in pregnant women and risk of wheezing or asthma in their children. Meta-analysis of 2 cohort studies,[65,67] 3 population-based case-control studies,[69–71] and 13 cross-sectional studies[72,76,81–83,87,88,91–94,96,97] showed that high consumption of vegetables had a modest association with reduced risk of asthma (RR = 0.88; 95%CI, 0.82–0.95; $P < 0.0001$, $I^2 = 83.8$) (Figure 3B). A sensitivity analysis was performed by excluding 2 studies[65,70] on cooked vegetables; there was a significant negative association between high raw vegetable consumption and risk of asthma (RR = 0.87; 95%CI, 0.81–0.94; *P* for heterogeneity <0.0001, $I^2 = 84.1\%$). In subgroup analysis, a null inverse association was found between high vegetable intake and risk of asthma among cohort and population-based case-control studies but significant negative association was found among cross-sectional studies (Table 2).

High consumption of a mixture fruit and vegetables was significantly associated with a decreased risk of asthma (RR = 0.64; 95%CI, 0.41–1.01; *P* for heterogeneity< 0.0001, $I^2 = 86.5\%$).[62,74,80,95]

Data from 3 cross-sectional studies[76,85,86] showed no association between high intake of fruit (RR = 0.98; 95%CI, 0.95–1.01) or vegetables (RR = 0.99; 95% CI, 0.96–1.01) and risk of atopy (Table 2).

Adults

Fruit and vegetable intake and risk of wheezing and asthma. One cohort study[58] and 1 cross-sectional study[90] that examined the association between fruit intake and risk of wheezing in adults showed a reduction in risk of asthma when highest versus lowest intakes were compared (RR = 0.68; 95%CI, 0.49–0.96; *P* for heterogeneity = 0.27, $I^2 = 17.5\%$). One cross-sectional study presented a positive relation between vegetable intake and wheezing (RR = 1.20; 95%CI, 0.86–1.70).[90]

Meta-analysis of 3 cohorts,[9,57,63] 2 population-based case-controls,[68,69] and 4 cross-sectional studies[76,82,88,97] evaluated intake of fruit in relation to risk of asthma and showed a significant negative association, with an overall RR of 0.77 (95%CI, 0.68–0.87; *P* for heterogeneity <0.0001, $I^2 = 84.4\%$) for the highest fruit intake compared with the lowest intake. Analysis by study type showed a negative association for the cohort, population-based case-control, and cross-sectional studies (Table 2). In subgroup analysis, an inverse association was also found between apple or citrus fruit consumption and risk of asthma (RR = 0.77; 95%CI, 0.66–0.90; *P* for heterogeneity = 0.02, $I^2 = 66.1\%$ and RR = 0.76; 95%CI, 0.56–1.02; *P* for heterogeneity = 0.013, $I^2 = 76.9\%$, respectively). Meta-analysis from 1 population-based case-control[69] and 5 cross-sectional[72,76,82,88,97] studies revealed a negative association between high vegetable intake and risk of asthma (RR = 0.84; 95%CI, 0.74–0.96; *P* for heterogeneity <0.0001, $I^2 = 92.7\%$).

The associations between fruit and vegetable consumption of mothers during pregnancy and allergic outcomes in their children were investigate. The pooled RR from 4 cohort studies[59,60,64,66] for fruit and from 4 cohort studies[60,61,64,66] for vegetables showed that maternal consumption of fruit and vegetables during pregnancy was not associated with risk of wheezing (RR = 0.94; 95%CI, 0.73–1.27; *P* for heterogeneity = 0.02, $I^2 = 70.2\%$ for fruit and RR = 0.91; 95%CI, 0.70–1.18; *P* for heterogeneity = 0.05, $I^2 = 61.0\%$ for vegetables) or risk of asthma (RR = 0.94; 95%CI, 0.81–1.08; *P* for heterogeneity = 0.84, $I^2 = 0.0\%$ for fruit and RR = 1.06; 95%CI, 0.72–1.58; *P* for heterogeneity = 0.05, $I^2 = 67.4\%$ for vegetables) in their children. In the pooled analyses of 2 cohorts,[59,64] high intakes of apples during pregnancy and risk of wheezing in children was also null (RR = 0.84; 95%CI, 0.48–1.46; *P* for heterogeneity = 0.06, $I^2 = 71.8\%$) (Table 2).

Children

Fruit and vegetable intake and risk of wheezing and asthma. The pooled RR from 13 cross-sectional studies[73,77–81,84–87,90,91,96] and 1 cohort study[65] conducted for fruit and for 9 cross-sectional studies[77–79,81,85–87,91,96] and 1 cohort study[65] conducted for vegetables indicates a significant negative association between high fruit and vegetable intake and risk of childhood wheezing (RR for fruit = 0.81; 95%CI, 0.74–0.88; *P* for heterogeneity <0.0001, $I^2 = 83.1\%$; and RR for vegetables = 0.88; 95%CI, 0.79–0.97; *P* for heterogeneity <0.0001, $I^2 = 83.7\%$) (Table 2). Again, analyses were pooled separately by children within the end age range of ≤11 years old and by others within the first age range of >11 years old.[70,71,78,80,81,86,87,90–92,96] The reverse association between fruit intake and wheezing was significant for children ≤11 years old (RR = 0.83; 95%CI, 0.74–0.93; *P* for heterogeneity <0.001, $I^2 = 72.8\%$) and for children >11 years old (RR = 0.81; 95%CI, 0.72–0.90; *P* for heterogeneity <0.0001, $I^2 = 83.3\%$). The association was weak for vegetables in children ≤11 years old (RR = 0.91; 95%CI, 0.84–0.99; *P* for heterogeneity <0.001, $I^2 = 74.1\%$) and in children >11 years old (RR = 0.81; 95%CI, 0.65–1.02; *P* for heterogeneity <0.0001, $I^2 = 85.9\%$). In subgroup analysis by food, there was a significant negative association between the risk of wheezing and a high intake of citrus fruit and tomatoes (Table 2). A weak negative association was found between risk of asthma and high intake of fruit (RR = 0.90; 95%CI, 0.86–0.94; *P* for heterogeneity = 0.21, $I^2 = 24.5\%$) and vegetables (RR = 0.91; 95%CI, 0.82–1.0; *P* for heterogeneity <0.0001, $I^2 = 69.2\%$). The significant

inverse association was also found for children >11 years old by fruit (RR = 0.76; 95%CI, 0.65–0.89; *P* for heterogeneity <0.01, I^2 = 64.6%), but not for children ≤11 years old (RR = 0.89; 95%CI, 0.83–0.95; *P* for heterogeneity = 0.88, I^2 = 0.0%), and for children >11 years old by vegetable (RR = 0.92; 95%CI, 0.83–1.02; *P* for heterogeneity <0.003, I^2 = 70.0%) and for children ≤11 years old (RR = 0.86; 95%CI, 0.71–1.04; *P* for heterogeneity <0.004, I^2 = 70.9%). Total fruit and vegetable intake had a statistically significant negative association with risk of asthma in children) (Table 2).

DISCUSSION

This review sought to verify whether fruit and vegetable consumption has a beneficial effect on wheezing and asthma prevention, and if so, which are the most beneficial. The findings show that high intakes of fruits and raw vegetables (most markedly of fruit) are significantly associated with a reduction in the risk of wheezing, while high intake of vegetables had a modest negative association with risk of asthma. This review is unique as it is the first meta-analysis of the relationship between fruit and vegetables and the risk of wheezing and asthma. In a combined analysis of adults and children, individuals in the highest total fruit and vegetable intake category had a 36% lower risk of asthma than individuals in the lowest intake categories. In children, high intake of citrus fruit and tomatoes was negatively associated with the risk of wheezing, and high intake of fruit and vegetables was associated with a reduction in the risk of wheezing and asthma. However, 1 cohort study[65] and 2 cross-sectional studies[81,87] showed a positive relationship between high vegetable consumption and asthma, contradicting these results. One study[66] noted a positive relationship between vegetable intake in pregnant women and the incidence of asthma in their infants. In the subgroup of fruit and vegetables analyses, high intake of citrus fruit and tomatoes was strongly related to the reduction in the risk of wheezing, and there was an inverse association between high intakes of apples and citrus fruit and the risk of asthma. Similarly, 1 study found a strong negative relationship between fruit and vegetable consumption and allergic asthma.[74] An observational study in Australia also showed that the consumption of apples and pears was negatively associated with risk of asthma and bronchial hyperresponsiveness.[76] Pooled analysis by Nurmatov et al.[98] on children aged 10–14 years showed a high intake of fruit but not vegetables reduced the risk of wheezing. The present review showed a negative association between high fruit consumption and risk of wheezing and asthma in children >11 years old and between high fruit consumption and wheezing in children ≤11 years old.

The possible protective effects of fruit and vegetables against some types of cancer, heart disease, diabetes, and asthma have been shown in epidemiological studies[97,99–101] and may be related to the high content of antioxidants in these foods.[102] Antioxidants play a prominent role in ameliorating oxidative damage caused by free radicals. Flavonoids are a large group of polyphenolic metabolites and are abundant in fruit and vegetables.[103] In vitro, flavonoids have biological effects such as free-radical scavenging, modulation of enzymatic activity, and inhibition of cellular proliferation. Therefore, they may have potential antibiotic, antiallergic, antidiarrheal, antiulcer, apoptotic, immune-modulatory, and anti-inflammatory effects.[104–109] In addition, flavonoids may enhance the activities of endogenous antioxidants; they have been shown to lower oxidative stress by inducing the activity of glutathione S-transferase, an enzyme that may protect cells from oxidative pathologies.[110]

Because respiratory airways are highly susceptible to oxidative damage, numerous enzymatic and nonenzymatic antioxidant defense mechanisms are present. Antioxidants may decrease airway inflammation by protecting the airways against oxidants from both endogenous and exogenous sources.

The mixtures of polyphenols in foods are often poorly characterized. For instance, tomatoes contain many polyphenols, such as chlorogenic acid and rutin. The skins of red tomatoes contain naringenin chalcones; tomatoes also contain quercetin.[111] Therefore, investigation of individual food items is warranted.

The present analysis showed a strong negative association between high intake of apples and reduced risk of wheezing and asthma. Lee et al.[16] showed that, among all phenolic phytochemicals in apples, quercetin (the main flavonoid in apples) contributes most to antioxidant activity. Moreover, the vitamin C content of apples provides only 11% of the total antioxidant capacity in apples and compared with vitamin C, flavonoids such as quercetin contribute more to the total antioxidant activity of apples. Because a large proportion of quercetin is in apple peels, consuming apples with skins is recommended.[16]

This meta-analysis is not without limitations. The ability to differentiate between food items with respect to association with asthma was limited. Some analyses were based on only two studies, and there are few prospective studies included. The findings, therefore, are based mostly on cross-sectional studies that are relatively quick and easy but do not permit distinction between cause-and-effect associations. As a result, data are prone to subject recalls and interviewer bias.[112] There are also some defects in adjusting for confounding and modification of effects, which may have introduced bias to the findings.[25] In addition, differing outcome parameters were used in

wheezing and asthma. To prevent bias and to enhance the quality of study, only studies that adjusted for important confounders were included. In addition to the analysis of total adults and children, results were stratified again by study design, range of age in children, and some food items. Moreover, extensive sensitivity analyses were performed by excluding studies that did not meet specific criteria for adjustment or study design. None of these exclusions appreciably changed the overall estimates, which suggests these findings are reliable. High intake of fruit and vegetables was negatively associated with risk of wheezing and asthma in both adults and children. Among the different kinds of vegetables and fruit investigated, citrus fruit and tomatoes displayed the strongest negative association with risk of wheezing, and citrus fruit and apples showed the strongest negative association with risk of asthma.

CONCLUSION

The current study represents a comprehensive systematic review and meta-analysis. The results suggest that a flavonoid-rich diet is negatively associated with wheezing and risk of asthma. Further molecular studies may be necessary to identify possible mechanisms of citrus fruit, apples, and tomatoes in relation to the development of asthma. Moreover, prospective cohort studies with large sample sizes are needed to accurately measure the effects of high fruit and vegetable intake on risk of asthma.

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Declaration of interest. The authors have no relevant interests to declare.

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