

# Dietary Factors and Risk of Chronic Obstructive Pulmonary Disease: a Systemic Review and Meta-Analysis

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Received: 29 January 2019

Accepted: 29 June 2019

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**Background:** The relationship between dietary pattern and the risk of chronic obstructive pulmonary disease (COPD) has been described; however, the exclusive role of dietary factors remains controversial. Hence, we conducted this systematic meta-analysis to clarify the role of some nutrients and antioxidant vitamins in the risk of COPD.

**Materials and Methods:** PubMed, Embase, and Scopus databases were searched for studies evaluating the associations between COPD outcome measures, symptoms, and mortality, and intake of fruits and vegetables, fiber, fish, n-3 or n-6 fatty acids, and antioxidant vitamins in adults. The random-effect model meta-analyses were used to pool the results.

**Results:** Ten cohort, six case-control, and 20 cross-sectional studies were identified. The pooled relative risks (RRs) of the COPD and confidence intervals (CIs) for the highest intake group compared with the lowest intake group were 0.74 (95% CI: 0.65-0.85) for fruit, 0.65 (95% CI: 0.55-0.78) for dietary fiber, 0.71 (95% CI: 0.58-0.85) for fish, and 0.89 (95% CI: 0.76-0.99) for vitamin C. No association was observed between the risk of COPD and the intake of vegetables, n-3 fatty acids, vitamin E, and  $\beta$ -carotene; however, it was associated with n-6 fatty acids 1.06 (95% CI: 0.87-1.30).

**Conclusion:** The results suggested that a higher intake of fruits, probably dietary fiber, and fish reduce the risk of COPD.

**Key words:** COPD; Antioxidant Vitamins; Fruit; Vegetables; Dietary Fiber; Fatty Acids

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global public health problem and is a major cause of morbidity and mortality in developed and developing countries; according to estimations, it is the eighth cause of disability-adjusted life-years (DALYs) in 2016 in all age groups, and with an aging population, COPD prevalence is believed to increase (1-4). COPD is a preventable disease characterized by progressive airflow limitation, which only can be partially reversible. Smoking is the principal cause of

COPD, but not all smokers develop the disease (2). Besides genetic factors, environmental exposures and dietary habits have been suggested as etiological factors for the risk of COPD (5-7). Additionally, the increased oxidative burden, as a major source in the pathogenesis of COPD, plays a critical role in lung injury and airway remodeling. One of the primary treatment targets of COPD is an improvement in the quality of life. In this regard, evidence highlights the importance of dietary modifications as

antioxidant sources in the prevention and management of COPD (8, 9).

Several studies have suggested that specific foods and dietary supplements may be beneficial in COPD prevention and management (10, 11). Specific antioxidants (e.g., vitamins C and E), as well as foods rich in antioxidants (e.g., fruit and vegetables), appear to modulate lung function positively, airway damage, and COPD development and symptoms (12, 13). A recent review reported that a high intake of dietary fiber is associated with reduced COPD risk (14). In addition, fish and fatty acid consumption have both been directly correlated with respiratory symptoms of COPD (15). Omega-3 polyunsaturated fatty acids (n-3 PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), appear to have anti-inflammatory effects; however, there is contradictory evidence regarding the inverse association between intake of n-3 PUFAs and the risk of COPD and mortality (16). These findings have not yet been quantified in a comprehensive review or pooled using meta-analysis techniques. A recent review reviewed randomized controlled trials (RCTs) on the relationship between dietary pattern (nutritional supplementation) and the risk of COPD, in which no relationship was found between these two factors (17, 18). Thus, this study systematically investigated the association between some nutrients, including fruits, vegetables, fatty acids, and the antioxidant vitamins and the risk of COPD.

## MATERIALS AND METHODS

Both the systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the current study (19).

### Search strategy and eligibility criteria

We searched PubMed (Medline), Embase, and Scopus databases for studies published in English from January 1990 to November 2018 on the associations between COPD outcomes and the intake of fish, fruits and vegetables,

fiber, fatty acids (n-3 and n-6), and antioxidant vitamins (C, E, and  $\beta$ -carotene) in adults. Additional studies were identified by searching the reference list of the retrieved articles and the Science Citation Index manually.

The following medical subject heading (MeSH) terms and/or keywords were used: "COPD", "emphysema", "chronic bronchitis" (as COPD outcomes), "COPD symptoms (including cough, phlegm, breathlessness, and dyspnea), or "COPD mortality"; and "diet", "fish", "fatty fish", "fruit", "citrus fruit", "vegetables", "dietary fiber", "fatty acid", "n-3 fatty acids", "n-6 fatty acids", "omega-3 fatty acid", "omega-6 fatty acid", "essential fatty acid", "EFA (essential fatty acid)", "polyunsaturated fatty acid", "docosahexaenoic acid", "eicosapentaenoic acid", "fish oil", "vitamin E", "vitamin C", " $\beta$ -carotene", " $\alpha$ -tocopherol", and "ascorbic acid". After retrieving the articles, prospective, case-control, cross-sectional, irrelevant, and duplicate studies, except for the most relevant articles were excluded. The extracted studies were independently inspected by two authors (ESR and MPM). Discrepancies were resolved by consensus, or, if needed, by arbitration from a senior author. We read the abstracts of all the remaining studies to exclude relevant articles. Studies that (i) only investigated the association between dietary supplementation among COPD patients, (ii) reported an association between blood levels of nutrients and risk of COPD, (iii) conducted diet pattern analyses, (iv) provided no data on relative risks (RRs) and or odds ratios (ORs), (v) reported duplicated data from another study, and (vi) provided no contrast between intake categories (Fig. 1) were also excluded. The full texts of the remaining articles were reviewed to determine the inclusion criteria and check the reported RR, OR, confidence intervals (CIs), or the required data to compute the COPD outcomes and symptoms to compare the high and low intake categories. The Critical Appraisal Skills Programme (CASP) was used to critically appraise the included observational studies (20).

### Data extraction

The following information was extracted from the included studies: publication date, type of study, author's name, country, sample size, year of enrollment, participants' characteristics, food items, dietary assessment methods, year of study, follow-up duration, potential confounding factors that accounted for COPD outcomes and symptoms, and smoking status.

### Data analysis and statistical methods

To conduct the meta-analysis, OR estimates from case-control and cross-sectional studies, and the risk or rate ratios from cohort studies, were assumed to be valid estimates of RR. RR estimates were pooled using the DerSimonian and Laird method through a weighted average of the log RR and considering random-effects. Heterogeneity for each pooled estimate was assessed using the Cochran's Q-test. Heterogeneity was considered as  $P \leq 0.1$  for the Q statistic and regarded significant when  $I^2$  was  $>50\%$ . Both the Begg's rank correlation test and Egger's regression model were used for assessing the publication bias. Analyses were conducted using Stata 13 software (Stata Corp LP, College Station, TX).

## RESULTS

The characteristics of the ten cohort studies (15, 21-29), six case-control studies (30-35), and 20 cross-sectional studies (36-55) included in the meta-analysis of the associations between dietary factors and the risk of COPD are shown in Table 1. Therefore, 36 publications were assessed in detail (Fig. 1).

Included studies had been conducted in different geographical areas as follows: eight studies in Asia (25, 27, 31-33, 35, 48, 55), 19 studies in Europe (22-24, 28-30, 34, 36, 38, 42, 43, 44-47, 49, 51, 52, 54), eight studies in the United States (15, 26, 37, 39-41, 50, 53) and one study in seven countries in Asia, Europe, and North America (Table 1). The characteristics of the included studies are displayed in Table 1. Most studies had been adjusted for age, sex, BMI, energy intake, smoking status, and social history.

To assess usual dietary intake, 28 studies had used food frequency questionnaires (FFQ), of which two studies had used FFQ and a 24-hour recall, three studies had used the crosscheck dietary method, one study had assessed with only 24-hour recall, and one study had used weighted household food records.

In the final analyses, the following number of studies had reported data for the associations between the risk of COPD (outcomes and symptoms) or mortality and the following dietary factors: seven for fruits (22, 25, 28, 30, 32, 54, 56), six for vegetables (25, 28, 30, 32, 46, 54), three for fruits & vegetables (28, 31, 35), five for fiber intake (25, 26, 29, 32, 53), six for n-3 fatty acids (15, 22, 32, 33, 36, 39), four for n-6 fatty acids (15, 32, 33, 36), two for linolenic acids (32, 36), three for linoleic acid (22, 32, 36), seven for fish (15, 21, 24, 37, 39, 47, 52), six for vitamin C (27, 32, 34, 35, 37, 55), five for vitamin E (27, 34, 35, 44, 45), and six for  $\beta$ -carotene (27, 32, 34, 35, 44, 45).

The pooled analysis of seven studies showed a 26% reduction in the risk of COPD (symptom and outcomes) that was significantly associated with high fruit intake without heterogeneity (Table 2 and Fig. 2a). In this regard, the results of sensitivity analysis of the study design for three cohort studies (22, 25, 28) were: RR=0.71, 95% CI: 0.63- 0.79;  $I^2$ : 0.0%, heterogeneity P-value: 0.8; for two population case-control studies (30, 32) were: RR= 0.59, 95% CI: 0.33- 1.06;  $I^2$ : 50%, heterogeneity P-value: 0.2; and for two cross-sectional studies (54, 56) were: RR= 0.88, 95% CI: 0.72- 1.07;  $I^2$ : 27%, heterogeneity P-value: 0.2. In addition, in the subgroup meta-analysis for five included studies reporting an association between fruits intake and COPD outcomes (22, 28, 30, 32, 54) or three studies regarding symptoms (25, 32, 56), there were no changes in the pooled effect estimates as displayed in Table 2. Meta-analysis on the association between COPD mortality and higher fruit consumption also showed a significant reduction in the risk of COPD mortality (RR=0.53; 95% CI: 0.39-0.74;  $I^2$ : 0.0%; heterogeneity P-value: 0.65) (Table 2).

When the highest intake category of vegetables was compared with the lowest intake category, the pooled RR

was null for the associated COPD symptoms and outcomes (Table 2). Following stratification by study design as a sensitivity analysis, the pooled RRs for two cohort studies (25, 28) were 0.85, 95% CI: 0.74-0.97; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.5; for two population case-control studies (30, 32) were 0.54, 95% CI: 0.33-0.87; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.6 and for two case-control studies (46, 54) were 0.92, 95% CI: 0.52-1.62; I<sup>2</sup>: 96%; heterogeneity P-value: <0.001. No association was found in two studies that had investigated vegetable intake and the risk of COPD mortality (21, 24). In addition, there was no association between COPD risk and the total intake of fruits and vegetables (Table 2).

A meta-analysis of the relationship between dietary fiber consumption and COPD risk (symptoms and outcomes), showed a 35% reduction in COPD risk (Table 2 and Fig. 2c). In this regard, stratification by study type showed a 39% reduction in the COPD risk in three cohort studies (RR=0.61; 95% CI: 0.54-0.68; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.9) (25, 26, 29). The pooled analysis for the association between COPD outcomes and dietary fiber intake also indicated a significant reduction in outcomes (RR=0.65; 95% CI: 0.49-0.91; I<sup>2</sup>: 77%; heterogeneity P-value: 0.01) (26, 29, 32, 53).

Among six studies investigating n-3 fatty acids, there were no associations between their high intake and risk of either COPD outcomes alone or both COPD symptoms and outcomes (Table 2). Similarly, the subgroup analysis according to study design exhibited no relationship between these factors as follows: two cohort studies (RR=1.00; 95% CI: 0.79-1.27; I<sup>2</sup>: 41%; heterogeneity P-value: 0.2) (15, 22); two population case-control studies (RR=0.79; 95% CI: 0.49-1.27; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.7) (32, 33) and two cross-sectional studies ((RR=0.74; 95% CI: 0.39-1.38; I<sup>2</sup>: 90%; heterogeneity P-value: 0.001) (36, 39). The pooled analysis of n-3 fatty acids and COPD symptoms indicated a positive relationship (Table 2) (33, 36). Also, there was an association between Linolenic acids intake and COPD risk (RR=1.02; 95% CI: 0.74-1.41; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.6). Of four studies investigating n-6 fatty acids, there were positive associations between their

intake and risk of COPD (Table 2). Studies that specifically had investigated linoleic acids also displayed positive associations with COPD risk (RR=1.25; 95% CI: 0.88-1.77; I<sup>2</sup>: 52.5%; heterogeneity P-value: 0.1).

The pooled analysis of three studies on fish intake showed a 35% reduction in the risk of COPD (RR=0.65; 95% CI: 0.52-0.82; I<sup>2</sup>: 72%; heterogeneity P-value: 0.03). There was also a decrease in the risk of COPD by analysis of the included studies on both symptoms and outcomes (RR=0.71; 95% CI: 0.58-0.85; I<sup>2</sup>: 76%; heterogeneity P-value: 0.002); a considerable heterogeneity among these studies was observed. High fish intake was not associated with the risk of COPD mortality (21, 24); however, a significant decrease (19%) in the risk of COPD had been reported considering symptoms alone (RR=0.81; 95% CI: 0.71-0.92; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.73) (Table 2) (47, 52).

The pooled estimation was not significant regarding studies on the association of high intakes of vitamin E and risk of both COPD symptoms and outcomes (RR=0.85; 95% CI: 0.72-1.0; I<sup>2</sup>: 60%; heterogeneity P-value: 0.04) (Table 2 and Fig. 2d). The detailed analysis based on COPD symptoms, outcomes, or mortality is shown in Table 2. High intake of  $\beta$ -carotene was not associated with a risk of COPD in either the pooled analysis (Table 2) or after stratification by the study types, RR=0.99; 95% CI: 0.99-1.0; I<sup>2</sup>: 0.0%; heterogeneity P-value: 0.9 for population case-control studies (32, 34, 35) and RR=0.83; 95% CI: 0.74-0.93; I<sup>2</sup>: 0.0%; heterogeneity P-value: <0.001 for cross-sectional studies (44, 45). In addition, a high intake of vitamin C was associated with a reduced risk of COPD according to six studies, yet with a substantial heterogeneity (Table 2). The similar results were identified in subgroup analysis based on study design, RR=0.81; 95% CI: 0.55-1.17; I<sup>2</sup>: 51%; heterogeneity P-value: 0.1 for three population case-control studies (32, 34, 35) and RR=0.86; 95% CI: 0.76-0.99; I<sup>2</sup>: 85%; heterogeneity P-value: 0.01 for cross-sectional studies (37, 55).

The distribution of the funnel plot and Egger's regression analysis did not show asymmetry. The cumulative analyses showed consistency of the findings over time (Figures not shown).



Table 1. Characteristics of studies included in the meta-analysis of the association between dietary factors and COPD

Author name, year	Country	Sample Size	Year of Enrollment	Follow up (y)	Sex	Age(y)	Food items studied	Dietary evaluation	Contrast	Adjustment
<b>Cohort studies</b>										
Miedema et al., 1993(22)	Netherlands	793	1960	25	M	40-59	Fruit and fatty acids	Cross-check dietary method	Quartile 4 compared with quartile 1	Age, smoking, BMI, energy intake
Carey et al., 1998 (23)	United Kingdom	2,171	1984-1985	7	M/F	18-73	Fresh fruit	FFQ	4.5-5 times/d compared with never	Region, social class, smoking
Tabak et al., 1998 (21)	Seven Countries (Finland, Italy, Greece, former Yugoslavia, Japan, United States and Serbia)	12,763	1958-1964	25	M	40-59	Fish, n-3, n-6, EPA, DHA fatty acids, total fruit and vegetables, citrus fruit, other fruit, flavonoids, vitamins C, E and $\beta$ -carotene	1, 4, and 7 day records from 16 different cohorts	The log of 10% of the mean of each food item intake	Energy intake, BMI
Waldia et al., 2002 (24)	Finland, Italy and Netherlands	2,917	1958-1964	20	M	50-69	Fruit, vegetables, fish, vitamins C, E and $\beta$ -carotene	Cross-check method	Highest vs. the lowest tertile	Country, age, smoking
Buller et al., 2004 (25)	Singapore	63,257	1993-1998	5	M/F	45-74	Fruit, Non-starchy vegetables, fish, soy, isoflavonoids, vitamins C, E and $\beta$ -carotene	FFQ	Highest vs. the lowest quartile or tertile	Age, sex, ethnicity, energy intake, smoking
Varraso et al., 2010 (26)	USA	111,580	1984-2000	16	M/F	40-74	Total fiber, cereals fiber, fruit fiber, vegetable fiber	FFQ	Highest vs. the lowest quintile	Age, sex, smoking, energy intake, BMI, US region, physician visits, physical activity, diabetes, intakes of omega-3 and cured meat.
Varraso et al., 2015 (15)	USA	120,175	1984-1998		M/F	F: 30-55 M: 40-75	Fish, n-3, n-6, EPA, DHA fatty acids,	FFQ	<1 vs $\geq$ 4 serving/wk	Age, smoking, race-ethnicity, physician visit, US region, educational, menopausal status, BMI, physical activity, multivitamin use, and energy intake, and modified prudent and Western dietary patterns.
Joshi et al., 2015 (27)	Korea	7106	2001-2006	6	M/F	40-69	vitamins C, E and $\beta$ -carotene	FFQ	Highest vs. the lowest quartile	age, sex, marriage status, BMI, history of asthma and tuberculosis, energy, and smoking.
Kaluza et al., 2017 (28)	Sweden	44,335	1998-2012	13.2	M	45-79	Fruit, vegetables	FFQ	Highest vs. the lowest quintile	age, education, BMI, physical activity, smoking(status and pack-years), energy intake, alcohol consumption and modified recommended food score and non-recommended food score
Kaluza et al., 2018 (29)	Sweden	45,058	1998-2012		M	45-79	Dietary fiber	FFQ	FFQ	age, education, BMI, physical activity, smoking(status and pack-years), energy intake, alcohol consumption

Author name, year	Country	Sample Size	Year of Enrollment	Follow up (y)	Sex	Age(y)	Food items studies	Dietary evaluation	Contrast	Adjustment
<b>Population case-control studies</b>										
Chen et al., 2001 (34)	United Kingdom	364/374	1995	-	MF	25-65	vitamins C, E and $\beta$ -carotene	FFO	Highest vs. the lowest quartile	age, sex, BMI, working status, energy intake, colinine levels, and smoking (pack years)
Watson et al., 2002 (30)	United Kingdom	150/116	-	-	MF	>45	Fruit and vegetables	Validated FFO	Highest vs. the lowest tertile	Age, BMI, vegetable intake
Cellk et al., 2006 (31)	Turkey	40/36	2003-2004	-	M	Mean: cases:57.73 controls: 55.25	Fruit and vegetables, n-3 and n-6 fatty acids	Aitizona FFO (AFFO)	>3times/day compared with never/rarely intake	Age, sex, smoking
Hirayama et al., 2009 (32)	Japan	278/340	2006	-	MF	50-75	Fruit and vegetables, fiber, n-3 and n-6 fatty acids, vitamin C and $\beta$ -carotene	Validated FFO	$\geq 7$ times /d compared with almost never	Age, gender, BMI, education level, alcohol intake, smoking, physical activity, daily intake of red meat, chicken and fresh fish.
Hirayama et al., 2010 (33)	Japan	278/340	2006	-	MF	50-75	Fatty acids, isoflavones (genistein and daidzein)	Validated FFO	Highest vs. the lowest quartile	Age, gender, BMI, education level, alcohol intake, smoking, physical activity, daily intake of red meat
Lin et al., 2010 (35)	Taiwan	34/43	2005-2006	-	MF	$\geq 50$	Fruit, vegetables, vitamins C, E and total carotenoids	FFO	Fruit and vegetables: frequency/mo; Vitamins: mg/d	Age, sex, BMI, smoking, carbohydrate intake, protein intake
<b>Cross-sectional studies</b>										
Schwartz et al., 1990 (37)	USA	9,074	1976-1980 (NHANES II)	-	MF	$\geq 30$	Fish and vitamin C	FFO and 24hr recall	High vs. low intake	Age, race, sex, smoking (pack years), total calories
Strachan et al., 1991 (38)	United Kingdom	1,357current smoker/1,502non-smokers	1984-1985	-	MF	18-69	Fresh fruit and fruit juice	Validated FFO	> once /d compared with never	Age, sex, height, smoking, region, household socioeconomic group
Shahar et al., 1994 (39)	USA	8,960	1986-1989	-	MF	45-64	Fish and n-3 fatty acids	FFO	Highest vs. the lowest quartile	Age, sex, race, height, weight, energy intake, educational levels, smoking (status and pack years)

Author name, year	Country	Sample Size	Year of Enrollment	Follow up (y)	Sex	Age(y)	Food items studies	Dietary evaluation	Contrast	Adjustment
<b>Cross-sectional studies</b>										
Schwartz et al., 1994 (40)	USA	2,526	1971-1975 (NHANES I)	-	MF	30-70	Fish	FFQ and 24hr dietary recall	Fish: Portion/wk VII C: Highest vs. the lowest tertile	Age, sex, height, smoking, race, employment
Sharp et al., 1994 (41)	USA	6,346	1965-1968	-	M	45-68	Fish	FFQ	High ( $\geq 2$ times/wk) vs. low ( $< 2$ times/wk) fish intake	Age, height, smoking, energy intake, education level, body weight.
Britton et al., 1995 (42)	United Kingdom	2,633	January to May 1991	-	MF	18-70	Vitamins C and E	FFQ	Vit C: $> 40.2$ mg from 99.2 (mean) and Vit E: $> 2.2$ mg from 6.2	Age, sex, height, mean allergen skin wheal diameter, smoking (status and pack years)
Dow et al., 1996 (43)	United Kingdom	178	June 1991 - March 1992	-	MF	70-96	Vitamins C and E	FFQ	Increase of each mg/d for vitamin E	Age, sex, height, smoking, energy intake, vitamin C intake
Rautalahti et al., 1997 (44)	Finland	7,286	1985-1988	-	M	50-69	Vitamins E and $\beta$ -carotene	FFQ	High vs. low frequency intake	
Grievink et al., 1998 (45)	Netherlands	6,555	1994-1995	-	MF	20-59	Vitamins C, E and $\beta$ -carotene	FFQ	90 <sup>th</sup> vs. 10 <sup>th</sup> percentile of antioxidant intake	Age, sex, energy intake, smoking (pack years), antioxidant intake
La Vecchia et al., 1998 (46)	Italy	46,693	1993	-	MF	$\geq 15$	Vegetables	FFQ	Highest vs. the lowest tertile	Age, sex, alcohol intake, smoking, education.
Fluge et al., 1998 (47)	Norway	4,300	1991	-	MF	20-44	Fish	FFQ	$> 1$ time/wk compared with $< 1$ time/wk	Age, sex, BMI, occupation, smoking
Hu et al., 1998 (48)	China	3,085	1989	-	MF	35-64	Vitamin C	3-day weighed household food record	Increase of 100 mg/d from mean (151.1) daily vitamin C intake	Age, sex, height, weight, education, smoking
Tabak et al., 1999 (49)	Finland, Italy and Netherlands	Finland: 1,248; Italy: 1,386; Netherlands: 691	1960s	-	M	40-59	Fish	Cross-check dietary method	Highest vs. the lowest quartile	Height, age, smoking, BMI, alcohol intake, and energy intake



Author name, year	Country	Sample Size	Year of Enrollment	Follow up (y)	Sex	Age (y)	Food items studies	Dietary evaluation	Contrast	Adjustment
<b>Cross-sectional studies</b>										
Hu et al., 2000 (50)	USA	18,162	1988-1994	-	MF	≥ 17	Vitamins C, E and β-carotene	24hr dietary recall	Increase of 111 mg/d from mean (15:1) vitamin C and >0.1 α-TE/d vitamin E intake	Age, sex, height, age <sup>2</sup> , race, BMI, income, smoking, total caloric and fat intake
Tabak et al., 2001 (51)	Netherlands	13,651	1994-1997	-	MF	20-59	Fruit and vegetables,	FFQ	Highest vs. the lowest quartile	Age, sex, height, smoking, BMI, energy intake
Kelly et al., 2003 (52)	UK (Scotland)	1,146	1995	-	MF	16-64	Fruit, vegetables, and fish	Questionnaire	At least once/d compared with never or rarely intake	Age, sex, height, age <sup>2</sup> , height <sup>2</sup> , smoking, social class, activity level.
Kan et al., 2008 (53)	USA	11,897	1987-1989	-	MF	44-66	Fiber	FFQ	Highest vs. the lowest quintiles	Age, sex, height, height <sup>2</sup> , study center, ethnicity, smoking (status and pack years), BMI, occupation, education, diabetes status, traffic, energy intake, glycemic index, micronutrients from food and supplements, cured meat, and fiber intake
McKeever et al., 2008 (36)	Netherlands	13,820	1994-1997	-	MF	20-59	n-3, and n-6 fatty acids	FFQ	Highest vs. the lowest quintiles	Age, age <sup>2</sup> , sex, smoking, height, energy intake, vitamin C, BMI, education.
Vukovic et al., 2010 (54)	Serbia	14,522	2006	-	MF	>20	Fruit and vegetables	Questionnaire	Every da intake compared with Less than every day	Age, sex, education, settlement type
Park et al., 2016 (55)	Korea	3,283	2012	-	MF	≥40	Vitamin C	FFQ	Highest vs. the lowest quartile	age, sex, Univariate and multivariate analysis

Table 2. Meta-analysis of the association between dietary intake and the risk of COPD

	Pooled estimate RR (95%CI)*	P heterogeneity	I <sup>2</sup>	No of studies
<b>Fruit</b>				
COPD symptoms and outcomes	0.74 (0.65- 0.85)	0.1	44%	7
COPD Outcomes	0.74 (0.62- 0.90)	0.04	59%	5
COPD symptoms	0.73 (0.61- 0.88)	0.6	0.0%	3
COPD mortality	0.53 (0.39- 0.74)	0.7	0.0%	2
<b>Vegetables</b>				
COPD Symptoms & Outcomes	0.82 (0.65- 1.04)	<0.001	82%	6
COPD Outcomes	0.79 (0.60- 1.05)	<0.01	85%	5
COPD Symptoms	0.71 (0.39- 1.3)	0.1	72%	2
COPD mortality	1.1 (0.93- 1.2)	0.7	0.0%	2
<b>Total fruit and vegetables</b>				
COPD Outcomes	0.80 (0.60- 1.1)	<0.001	85%	3
<b>Dietary fiber</b>				
COPD Symptoms & Outcomes	0.65 (0.55- 0.78)	0.01	69%	5
COPD Outcomes	0.65 (0.49- 0.91)	0.01	77%	3
<b>n-3 fatty acids</b>				
COPD Symptoms & Outcomes	0.86 (0.66- 1.11)	0.002	74%	6
COPD Outcomes	0.83 (0.67- 1.03)	0.004	72%	6
COPD Symptoms	1.2 (1.0- 1.4)	0.7	0.0%	2
<b>n-6 fatty acids</b>				
COPD Symptoms & Outcomes	1.06 (0.87- 1.30)	0.14	45%	4
COPD Outcomes	1.04 (0.76- 1.41)	0.1	55%	4
COPD symptoms	0.83 (0.38- 1.86)	0.03	80%	2
<b>Fish</b>				
COPD Symptoms & Outcomes	0.71 (0.58- 0.85)	0.002	76%	5
COPD Outcomes	0.65 (0.52- 0.82)	0.03	72%	3
COPD Symptoms	0.81 (0.71- 0.92)	0.7	0.0%	2
COPD mortality	0.96 (0.92- 1.0)	0.8	0.0%	2
<b>Vitamin E</b>				
COPD Symptoms & Outcomes	0.85 (0.72- 1.0)	0.04	60%	5
COPD Outcomes	0.79 (0.66- 0.96)	0.1	56%	4
COPD Symptoms	0.93 (0.76- 1.2)	0.1	67%	2
COPD mortality	0.95 (0.86- 1.1)	0.4	0.0%	2
<b>β-carotene</b>				
COPD Symptoms & Outcomes	0.91 (0.78- 1.05)	<0.001	95.4%	6
COPD Outcomes	0.92 (0.76- 1.1)	<0.001	92%	5
COPD Symptoms	0.88 (0.63- 1.3)	0.001	91%	2
COPD mortality	0.63 (0.35- 1.1)	0.4	0.0%	2
<b>Vitamin C</b>				
COPD Outcomes	0.89( 0.76- 0.99)	0.002	73%	6
COPD mortality	0.55 (0.3- 1.0)	0.9	0.0%	2

\*The overall pooled risk ratio (RR) of COPD risk and the confidence intervals (CIs) for the groups with the highest versus the lowest levels of intake

\*\* Population case-control

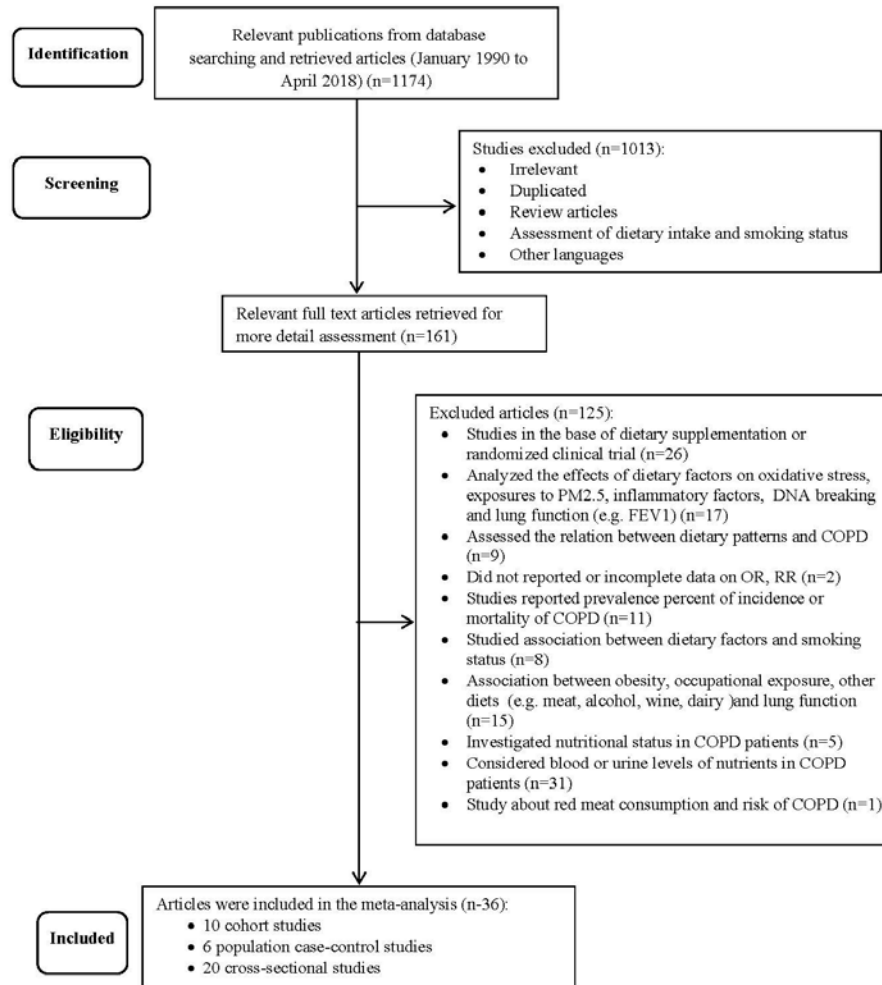
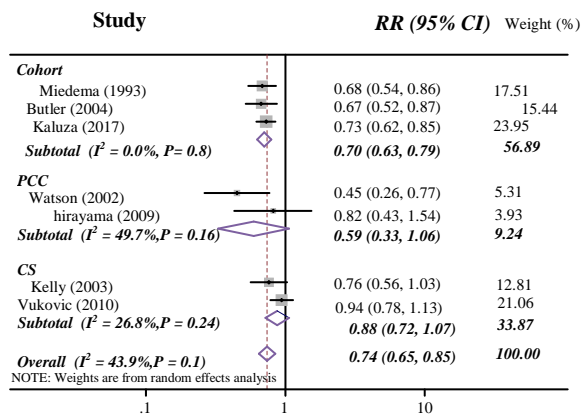
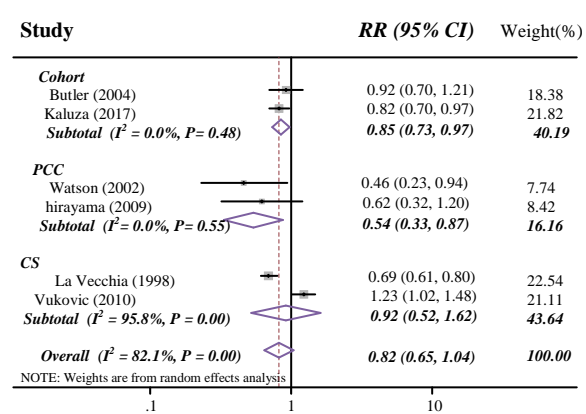


Figure 1. Study selection stages.

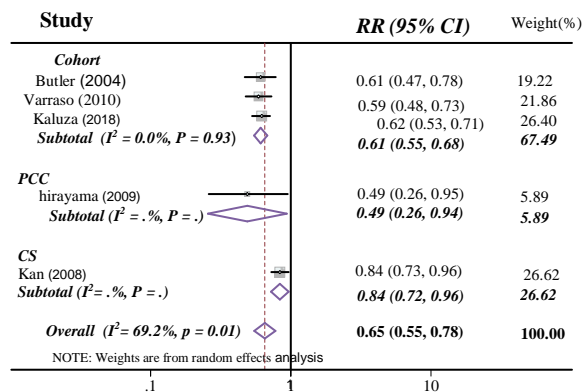
**a) Fruits**



**b) Vegetables**



## c) Fiber



## d) Vitamin E

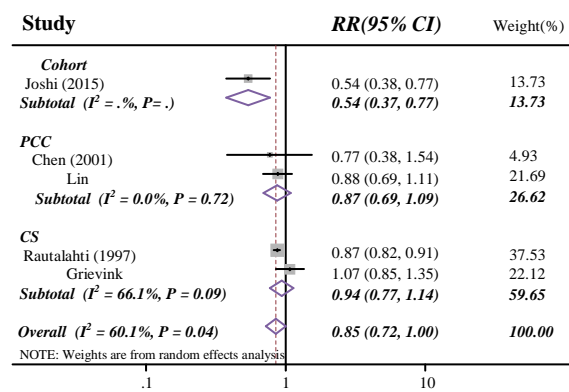


Figure 2. Forest plots of the association between intake of fruit (a), vegetables (b), dietary fiber (c), and vitamin E (d) and COPD outcomes and symptom.

## DISCUSSION

There has been growing interest in the effects of foods and nutrients with antioxidant or anti-inflammatory properties on lung function or COPD symptoms (33). These investigations are mainly epidemiologic studies with inconsistent results.

This study was intended to systematically review all epidemiologic evidence related to the association between some antioxidant and anti-inflammatory dietary factors and COPD. The results showed that ample consumption of fruit significantly reduced the risk of COPD outcomes and symptoms. In addition, subgroup analyses by study design, as a sensitivity analysis, similarly supported the results obtained through a meta-analysis of longitudinal studies. Fiber intake reduced the risk of COPD outcomes and symptoms according to cohort studies, whereas n-3 and n-6 fatty acids intakes were not associated with the risk of COPD. The findings also indicated that high vitamin E intake significantly reduced the risk of COPD outcomes and symptoms.

According to epidemiological studies, diets rich in fruits, vegetables, and vitamins protect against chronic diseases, such as cardiovascular disease and cancer. Fruits and vegetables are rich in several types of vitamins and bioactive components (57). It has been reported that

increased oxidative stress is a potential pathogenic factor for COPD (58). Therefore, it is suggested that the negative association between fruits and vegetables intake and COPD-related outcomes might be partly due to the antioxidant properties of these nutrients, such as vitamin C, flavonoids, and carotenoids (26, 59). Previous studies have supported the protective effect of flavonoids on COPD symptoms (25, 60). These compounds may protect against oxidant-mediated damage that leads to COPD (27). Although these antioxidants can be found in almost all fruits and vegetables, fruits have higher levels of antioxidants (61). This difference suggests a possible explanation for the observation that the association between COPD and high fruit intake was stronger than high vegetable intake.

Notably, longitudinal studies support the negative association between fiber intake and COPD that can be related to anti-inflammatory properties of dietary fiber (26). In agreement with our findings, some prospective studies supported strong associations between long-term increased fruits and fiber intake and health conditions (62). Fiber intake is associated with lower levels of C-reactive protein and pro-inflammatory cytokines and higher levels of some anti-inflammatory cytokines, such as adiponectin (63, 64). Lignans, which are constituents of dietary fibers

and whole grains, inhibit type I-IV allergic inflammation and pro-inflammatory enzymes (65); however, the exact mechanism underlying dietary anti-inflammatory activity of fiber is unclear (26).

A healthy lifestyle, and a healthy diet, in particular, might be another explanation for the observed association between fruits intake and COPD related outcomes (66). Given that significant results were observed in longitudinal and cross-sectional studies, and also the included studies were mostly adjusted for several indicators of a healthy lifestyle (e.g., smoking, alcohol consumption, physical activity, and energy intake), the findings suggested that factors associated with a healthy lifestyle may not substantially affect the relationship between fruits, vegetables, and fiber intake and the risk of COPD. Another underlying issue regarding the association observed in this study might be the confounding effects of smoking. It has reported that smokers have lower intakes of fruit, vegetables, and whole grain products; on the other hand, they higher need vitamin C and  $\beta$ -carotene (66). The extent to which residual confounding factors influenced the results might not be significant, as most of the included studies had reported adjusted effect sizes; however, it cannot be concluded that underlying factors related to a healthy diet or the residual confounding effect of smoking may affect the observed associations.

The findings showed that vitamin E reduced the risk of COPD symptoms; however, no associations were found in pooled analysis of both symptoms and outcomes. This antioxidant vitamin may protect the lungs from oxidative damage caused by smoking or air pollution. Vitamin E is a free radical scavenger found in tissue membrane, as well as intracellular and extracellular lung fluids. In extracellular lung fluid and lipid membranes, vitamin E converts oxygen radicals and lipid peroxy radicals to less reactive forms (67). A negative relationship was also observed between the intake of vitamin C and the risk of COPD. In this study, the interaction between these vitamins had not been investigated, and their synergic effects had not been

quantified. Additionally, considering the biological interaction between vitamins C and E, the extent to which the protective effect of vitamin E is related to that of vitamin C is unresolved (68).

The results of the meta-analysis did not support the association between the intake of unsaturated fatty acids (n-3 and n-6 fatty acids) and the risk of COPD. Observational studies have been conducted based on the hypothesis that n-6 fatty acids could stimulate the production of pro-inflammatory eicosanoids, while anti-inflammatory n-3 fatty acids might promote the metabolism of these molecules into less biologically active eicosanoids, such as leukotriene B5 (69).

The current study had some limitations. Some analyses were based on only two studies, and few prospective studies were included. Furthermore, the null findings suggest that the effect of any individual nutrient in reducing the risk of COPD may be too small to detect; however, when several nutrients are consumed together, the cumulative effect may be sufficient for detection (17). Although some articles were cross-sectional studies, but the cohort study, which included in the pooled analysis studies, exhibited logical outcomes. Another limitation of this meta-analysis was the heterogeneity identified in some of the pooled analyses, which may be attributed to the sample sizes, small number of the studies included, or the distribution of effective modifiers that were not investigated in the primary studies and could not be detected. Studying an overall dietary approach rather than specific foods or nutrients is effective in investigating the association between dietary patterns and diseases more comprehensively. However, this study revealed a strong negative association with taking fruits and the risk of COPD (70).

Our results support nutritional interventions encouraging taking fruits, and probably fish, and dietary fiber, which can reduce the risk of COPD outcomes and symptoms significantly.

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