Lead Article

Nutrition as a modifiable factor in the onset and progression of pulmonary function impairment in COPD: a systematic review

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**Context:** Chronic obstructive lung disease (COPD) is a progressive lung disease characterized by persistent airflow limitation. An increasing amount of evidence suggests an effect of dietary quality on the risk of COPD in the general population and pulmonary function decline in patients with COPD. **Objective:** The association of dietary intake and nutrient status with COPD risk and onset, as well as pulmonary function decline (change in forced expiratory volume in 1 second, forced vital capacity, or the ratio of the former to the latter) in patients with COPD was investigated in this systematic review. **Data Sources:** The PubMed database was searched by combining terms of pulmonary function or COPD with diet, nutrient status, or nutritional supplementation. **Data Extraction:** Original studies and systematic reviews and meta-analyses were included. Articles obtained were independently screened for relevance on the bases of title and abstract by 2 researchers. Eventually, 89 articles were included in the analysis. **Results:** The unhealthy Western-style diet is associated with an increased risk of COPD and an accelerated decline of pulmonary function. Intake of fruit, vegetables, dietary fibers, vitamins C and E, polyphenols, and β-carotene were individually associated with lower COPD risk, whereas consumption of processed meat was associated with higher COPD risk. Data on the effect of dietary quality on pulmonary function decline in patients with COPD are limited and inconsistent. Strong evidence for beneficial effects on pulmonary function decline was found only for vitamin D supplementation. **Conclusion:** Considering the increasing burden of COPD, more attention should be given to dietary quality as a modifiable factor in disease development and progression in patients with COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), cardiovascular disease, and diabetes are the most common chronic diseases worldwide.[1,2] A poor diet is a modifiable risk factor for cardiovascular disease and diabetes.[3] However, the association between diet and COPD onset and decline in pulmonary function is less established. COPD is characterized by persistent airflow limitation and respiratory symptoms,[4] resulting from thickening of the airway walls causing increased mucus production (chronic bronchitis) or destruction of the alveolar walls (emphysema).[5,6] Prominent respiratory symptoms include dyspnea, cough, and sputum production. Some patients with COPD have frequent exacerbations, defined as acute events that include pulmonary infections and/or respiratory failure that result in worsening of the respiratory symptoms, which may require hospitalization and often aggravate the decline of pulmonary function.[7] Smoking tobacco and air pollution are risk factors for the onset and progression of COPD. There is also increasing evidence for poor diet and malnutrition as additional risk factors.[8,9]

In a Dutch study of patients with COPD, researchers found that, overall, patients consumed a typical Western diet characterized by low intake of vitamins, fruits, vegetables, and fish and high intakes of saturated fat, cured meat, and refined grains.[10] In COPD management, nutrition and metabolism have been topics of scientific research for decades, but that research primarily has been focused on advanced disease, caloric and protein requirements, and extrapulmonary disease progression. Airway and systemic inflammation appear to be associated with disease progression.[11,12] Along with inflammation, oxidative stress in lung tissue is enhanced while the antioxidant capacity is substantially depleted due to overproduction of reactive oxygen species as a result of tobacco smoking, air pollution, and acute exacerbations.[13] Healthy dietary patterns and specific nutrient intake can attenuate pulmonary and related systemic inflammation as well as oxidative stress associated with COPD.[14]

Hence, dietary intake may be beneficial for reducing the risk of COPD onset and for decelerating the rate of pulmonary function decline in patients with COPD.[15] However, a clear overview of the existing evidence for this notion is lacking. Therefore, our objective for this systematic review was to compile and evaluate available evidence regarding the association between dietary intake and plasma or serum nutrient status on the one hand, with the risk and onset of COPD, as well as the progression of pulmonary function decline in COPD on the other.

METHODS

Data source and search strategy

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; see Supplemental Table S1 in the Supporting Information online).[16] A systematic search was conducted of the PubMed database on January 26, 2021, to find relevant articles. The search strategy consisted of terms referring to pulmonary function and COPD, combined with diet, nutrient status, and nutritional supplementation (see Supplemental Appendix 1 in the Supporting Information online for the exact search strategy) and was limited to English written publications of clinical studies; experimental and animal studies were excluded. No time limits were included in the search strategy; PubMed was systematically searched for relevant articles up to January 26, 2021. Observational and interventional studies were included (Table 1). In addition, reference lists of included papers were screened for additional publications.

Study selection and data extraction

Articles identified from the PubMed search were independently screened by 2 researchers (LE.J.v.I. and R.J.H.C.G.B.) for relevance based on title and abstract. Subsequently, relevant full-text articles were assessed for eligibility. Studies were eligible for inclusion if they addressed the association between the risk, onset, or progression of COPD with pulmonary outcome measures (ie, pulmonary function and COPD risk or incidence) on the one hand, and diet, nutrient status, or nutritional supplementation on the other. With respect

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria
Population	Patients with COPD
	General population
Intervention/correlate	Dietary intake
	Nutrient status
	Nutritional supplementation
Comparison	Placebo (only applicable for randomized controlled trials)
Outcome	Risk of COPD
	Pulmonary function (FEV$_1$, FVC, or FEV$_1$/FVC)
	Incidence of COPD
Study design	Cross-sectional studies
	Case-control studies
	Cohort studies
	Randomized controlled trials
	Systematic reviews/meta-analysis

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity.

to nutrient status, only articles reporting nutrient levels in blood were included (papers reporting nutritional status reflecting body composition were excluded). Influence of caloric intake on COPD risk or progression was not examined in this systematic review, because these studies mainly focused on abnormal body composition, not pulmonary function. Original studies as well as systematic reviews/meta-analyses were included. Original studies already summarized in ≥ 1 of the included systematic reviews or meta-analyses (n = 56) were excluded from this review to avoid overrepresentation. Because we included original studies as well as systematic reviews and meta-analyses, the following criteria, adjusted from predefined guidelines and criteria,[17–20] were used to draw conclusions from the included studies: A conclusion of "very strong evidence" was drawn if ≥ 1 systematic review or meta-analysis and/or > 5 original studies reported consistent results. Evidence was considered "strong" if > 3 studies reported consistent results. If < 3 studies reported consistent results, evidence was considered "limited." When contrary results were reported in studies, evidence was considered "inconsistent." A conclusion of "no evidence" was drawn if no studies were found.

RESULTS

Search results

In total, the PubMed search yielded 2517 hits that were assessed for relevance (Figure 1). Subsequently, the full texts of 227 articles were reviewed and, eventually, 89 articles were included on the basis of predefined criteria. A detailed overview of characteristics of the included studies is provided in Table S2 in the Supporting Information online.

Dietary patterns

Generally, 2 dietary patterns are distinguished in nutritional epidemiology. The Western-style diet is characterized by high dietary intake of red and/or processed meats, refined grains, sweets, desserts, and French fries and is generally considered unhealthy.[21] The Mediterranean-style diet is characterized mainly by high dietary intake of fruit, vegetables, fish, and whole-grain products and is often considered prudent or healthy. The Healthy Eating Index–2005 is commonly used to assess adherence to dietary guidelines and to score how healthy a diet is.[22] A meta-analysis showed that the risk of COPD was higher in the highest category than in the lowest category of the unhealthy dietary pattern and, for the healthy/prudent dietary pattern, the risk of COPD was lower in the highest than

in the lowest category.[21] In 2 cross-sectional studies focusing on women, impaired pulmonary function, defined as forced vital capacity (FVC) < 80% and/or forced expiratory volume in 1 second (FEV_1) < 80% of predicted value and/or the ratio of FEV_1 to FVC < 0.7, was positively associated with the Western-style diet, but no association was found with the Mediterranean-style diet.[23,24] In a case-control study, men and women with medium or high adherence to a Mediterranean-style diet were, in a dose-response manner, at a significantly lower risk for development of COPD than those with low adherence.[25] Furthermore, an overall healthy diet, assessed by the Healthy Eating Index–2005, was positively associated with the ratio of FEV_1 to FVC in cross-sectional analyses of the general population.[26]

Data indicating that healthy dietary patterns also positively modulate progression of pulmonary function decline in patients diagnosed with COPD are scarce. In a longitudinal analysis, researchers found that consumption of foods from a healthy diet (defined as fruit, fish, tea, and dairy products) reflected significant higher levels of FEV_1 and FVC in patients with COPD and less decline over a 3-year period.[27] Moreover, a positive association was observed between the Mediterranean-style diet and FEV_1 and FVC among patients with COPD in a cross-sectional study, indicating that a healthier diet is reflected in higher levels of pulmonary function.[28]

Thus, there is very strong evidence for an increased risk for development of COPD when an unhealthy Western-style diet is consumed, whereas adherence to a prudent or Mediterranean-style diet decreases that risk. The potential of diet to modulate pulmonary function decline in patients diagnosed with COPD is less well studied because long-term cohort studies in patients with COPD that include dietary data are scarce. Furthermore, to our knowledge, no clinical trials have investigated the effect of a shift toward a healthy dietary pattern.

Processed meat

A meta-analysis including 5 prospective cohort studies involving individuals of the general population[29] and a large longitudinal cohort study including middle-aged women[30] both showed that consumption of processed meat elevated the risk for development of COPD. These findings correspond with results of a cross-sectional study in the general US population[31] that showed a negative association between processed meat intake and FEV_1 and FVC. Therefore, it can be concluded that there is very strong evidence that increased consumption of processed meat is negatively associated with pulmonary function in the general population and, hence,
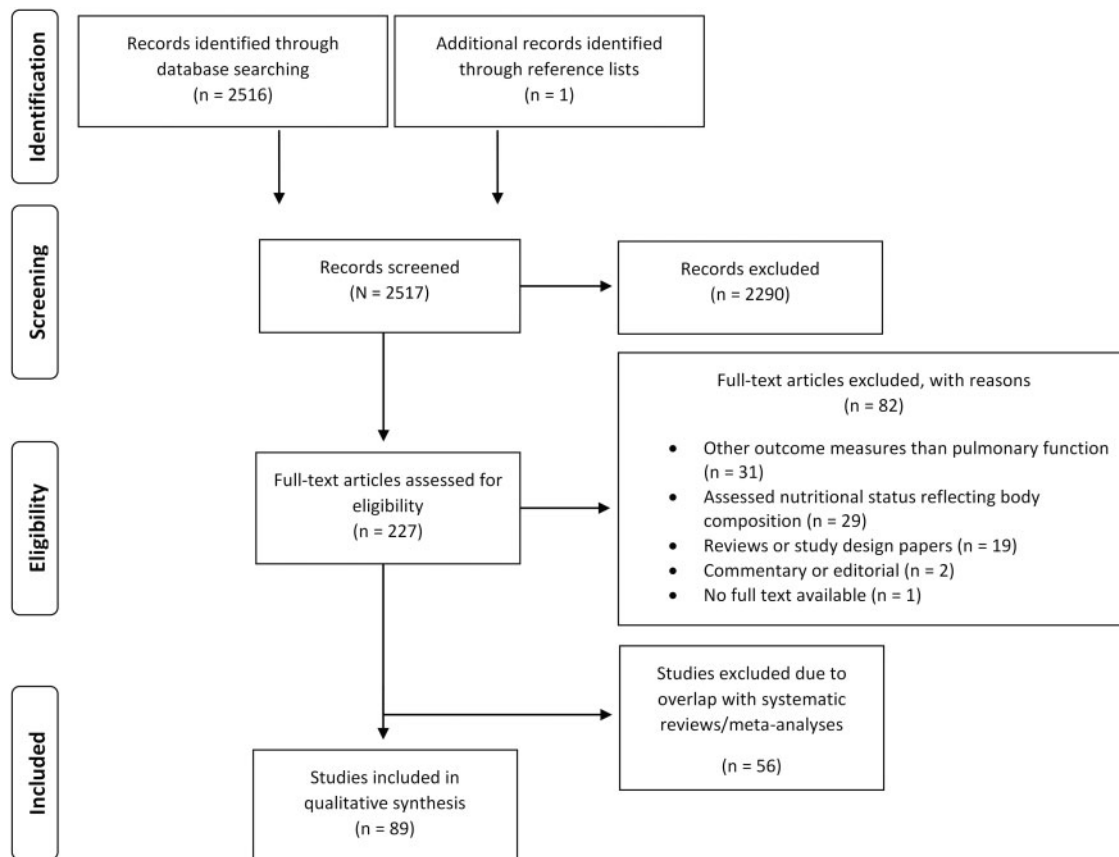
Figure 1 **PRISMA flowchart for selection of included studies.**

an increased risk of COPD. No studies on the effects of processed meat intake on acceleration of pulmonary function impairment in patients with COPD were found; adequate longitudinal studies are required in cohorts of patients with COPD.

Alcohol

The influence of alcohol consumption on the risk of COPD or rate of pulmonary function decline was investigated in 7 cross-sectional[23,32–37] and 2 prospective cohort studies[38,39] in the general population. It was reported that lifetime alcohol consumption and heavy drinking were predictors of lower FEV_1 levels in the general population[23,32,33] and that high alcohol consumption (≥ 350 g/wk) significantly accelerated the decline of FEV_1 over 5 years.[38] In contrast, no correlation between alcohol consumption and FEV_1 and FEV_1 percent predicted was observed in 2 other cross-sectional studies at baseline and after 5 years of follow-up.[34,35] It was also shown that FEV_1 was lower in nondrinkers of alcohol than in light drinkers.[37] Strikingly, low to moderate levels of alcohol drinking, especially of beer and wine, was associated with a lower risk and fewer new cases of COPD over 20 years of follow-up,[36,39]

in contrast to former heavy drinkers, who had significantly increased odds of development of pulmonary obstruction.[36]

Thus, evidence on alcohol consumption relative to COPD is inconsistent. Heavy drinking is associated with pulmonary function decline, whereas mild to moderate consumption may have protective effects in the general population. For the effect of alcohol consumption on pulmonary function decline in patients already diagnosed with COPD, we found no available studies; therefore, adequate longitudinal cohort studies are required.

Fruit and vegetables

The association between fruit and vegetable intake and the risk of COPD was quantitatively evaluated in a meta-analysis including 8 studies that involved 5787 patients with COPD among 244 154 participants from the general population.[40] A significantly lower risk of COPD was observed related to higher fruit and/or vegetable intake. Furthermore, in a cross-sectional analysis, fruit intake was associated with higher FEV_1 and lower COPD risk, whereas no such associations were found for vegetable intake.[41] A cross-sectional study showed

that both fruit and vegetable consumption were positively associated with FEV_1 and FVC in the general population,[31] and a longitudinal study in middle-aged adults showed that especially higher intake of tomato was associated with an attenuated decline in FVC over 10 years but not in FEV_1.[42]

In several studies, patients with COPD had a significantly lower intake of fruit and vegetables than did healthy individuals.[43–45] Also, in a randomized controlled trial (RCT), a dietary shift to a diet rich in fruit and vegetables was associated with higher FEV_1 percent predicted in patients with COPD compared with a diet free of choice.[46]

Overall, there is very strong evidence that dietary fruit and vegetable consumption is associated with a lower risk of COPD in the general population. However, studies on the effect of fruit and vegetable intake on pulmonary function decline in patients diagnosed with COPD are still limited.

Polyphenols

A positive association between polyphenol intake and FEV_1 and FVC was reported in a cross-sectional analysis of a general population.[47] Total intake of catechins, flavonols, and flavones specifically was positively associated with FEV_1.[48] Moreover, greater anthocyanin intake significantly attenuated the annual decline in FEV_1 and FVC in a longitudinal analysis of men in the United States.[49] Furthermore, more frequently drinking green tea, which is rich in polyphenols, was associated with a decreased prevalence of COPD in a cross-sectional analysis of a general population[50] and decreased incidence in older adults in a prospective cohort study after 4.5 years of follow-up.[51]

Likewise, intake of the dietary polyphenol resveratrol was positively associated with FVC in a cross-sectional analysis, but no significant longitudinal change was observed.[52] Remarkably, only intake of white wine, which contains much lower levels of resveratrol than red wine, was associated with higher FEV_1 levels and lower risk of airway obstruction, whereas no association was found with red wine intake. Dietary total antioxidant capacity was positively associated with FEV_1 and FVC in a cross-sectional study of a general population, as well as in premenopausal women or women who never smoked.[31,53] In patients with COPD, total antioxidant capacity in blood appeared to be lower than in healthy control subjects.[45] A RCT including stable patients with COPD showed that supplementation with antioxidant polyphenol-rich pomegranate juice for 5 weeks had no beneficial effects on any pulmonary function parameter.[54]

In summary, very strong evidence is available showing positive effects of polyphenols on the risk of COPD. To date, however, limited evidence is available on the effect of polyphenol intake on pulmonary function impairment in patients diagnosed with COPD. Thus, there is a need for RCTs with long-term follow-up to evaluate the effect of polyphenol supplementation on pulmonary function decline.

Vitamin D

Higher dietary intakes of vitamin D were associated with higher FEV_1 and lower prevalence of COPD in a cross-sectional analysis of a general population.[55] Increased odds of COPD development were reported in a cross-sectional analysis in smokers with a serum 25(OH)D concentration <50 nmol/L compared with smokers with a serum concentration ≥50 nmol/L.[56] Vitamin D deficiency was associated with decreased FEV_1 and FVC in the Korean population,[57] and in another study, researchers reported this association only in men without medical conditions, and not in women.[58] Furthermore, 6 cross-sectional[59–64] studies reported a positive association between serum 25(OH)D concentrations and FEV_1 in a general population, healthy individuals, and adolescents, but no longitudinal change in FEV_1 was observed in healthy individuals.[63] In addition, in prospective analyses, lower 25(OH)D concentrations were associated with a faster decline rate of FEV_1 over 20 years and higher risk of COPD development.[64] Although, together, the results of these studies indicate there is very strong evidence of a positive association between 25(OH)D concentrations and FEV_1, these positive associations were not confirmed in 5 other cross-sectional studies.[55,65–68] In addition, in a prospective cohort study, no association between 25(OH)D concentrations and change in FEV_1 over 5 years was observed.[69]

With respect to the association between vitamin D and pulmonary function decline in patients with COPD, 2 studies reported that dietary intake of vitamin D was lower than recommended.[10,70] Authors of a systematic review and meta-analysis in which a total of 21 studies were included, involving 4818 patients with COPD and 7175 control subjects, reported that serum 25(OH)D levels of patients were significantly lower than in the control group.[71] Correspondingly, mean serum concentrations of 25(OH)D were significantly lower in patients with COPD than in healthy control subjects,[72] and patients with COPD had a higher risk of vitamin D deficiency.[73,74] Furthermore, in 3 cross-sectional studies,[75–77] researchers demonstrated that vitamin D deficiency was inversely associated with absolute FEV_1 or FEV_1 percent predicted or FVC in patients

with COPD. Also, lower vitamin D levels were associated with lower absolute FEV_1 levels in patients with COPD and in healthy control subjects in a cross-sectional analysis, but they were significantly lower in patients with COPD when compared with the control group.[78] According to a longitudinal analysis, vitamin D deficiency (< 20 ng/mL) was associated with a greater rate of FEV_1 percent predicted decline over 1 year.[77] And in 2 cross-sectional studies, no significant correlation was found between serum 25(OH)D levels and absolute FEV_1 levels or FEV_1-to-FVC ratio.[79,80]

With respect to the effect of vitamin D supplementation on pulmonary function, a meta-analysis including 8 RCTs involving 687 patients with COPD showed that neither short-term (<6 mo) nor long-term (>6 mo) vitamin D supplementation inhibited FEV_1 decline.[81] However, an update of this meta-analysis,[82] including 19 RCTs involving 2004 patients with COPD, reported a significant positive effect of vitamin D supplementation on FEV_1; however, the duration of supplementation was not stated. In another RCT, significant improvements were reported in FEV_1 or FVC after vitamin D supplementation in smokers with COPD or vitamin D deficiency only.[83]

The effect of vitamin D on the risk of COPD and pulmonary function decline has been investigated extensively. However, inconsistent evidence is reported on the relationship between vitamin D intake and serum concentrations and the risk of COPD in the general population. Moreover, despite very strong evidence of low dietary intake and serum concentrations of vitamin D in patients with COPD compared with control subjects, evidence on vitamin D's association with pulmonary function decline is not consistent. On the other hand, very strong evidence, based on a large meta-analysis, indicates that vitamin D supplementation has beneficial effects on pulmonary function decline in patients with COPD. Potential effects of vitamin D supplementation are stronger in patients deficient in vitamin D.

Other vitamins

Dietary intake and nutrient status of vitamins C and E as well as β-carotene, a precursor of vitamin A, were positively associated with FEV_1 in cross-sectional studies,[84,85] and higher intake of vitamin C was associated with a reduced risk of COPD in the general population.[86] Moreover, in community-dwelling older adults, dietary intake of vitamin C in smokers was associated with a slower rate of FEV_1 decline, whereas in former smokers, intake of vitamins C, E, or β-carotene was individually associated with an attenuated decline rate and no associations were found relative to never

smokers.[87] Also, in another study, higher serum levels of β-carotene protected against FEV_1 decline over 8 years in the general population.[88] In 2 cross-sectional[89,90] studies, a positive association of vitamin E with FEV_1 and FVC was observed, and in a prospective cohort study[91] with 2 times 2 years of follow-up, a significant decrease in COPD risk was noted with increase in dietary intake of vitamins E and C in the general population. A systematic review of 14 studies showed an association between vitamin intake and the development of COPD. More specifically, intake of vitamins A, C, D, E, and β-carotene was associated with greater pulmonary function in the general population. No clear evidence was found that supplementation with those vitamins by patients with COPD had beneficial effects on FEV_1 (range of duration, 4 wk to 5 y).[92] Individually, daily supplementation with vitamins A, C, and E was associated with higher FEV_1 in a cross-sectional analysis of older adults.[68]

In patients with COPD, dietary intake of vitamins A, B_9, C, and E was lower than recommended,[10,93] and plasma concentrations of these vitamins were lower in patients with COPD than in healthy individuals.[44] Furthermore, serum vitamin A concentrations were lower in patients with moderate to severe COPD than in healthy smokers in a cross-sectional analysis, and FEV_1 and FVC measurements were higher after 30 days of vitamin A supplementation in patients with COPD.[94] In addition, lower vitamin K status was observed in patients with COPD compared with smoking and nonsmoking control subjects, although it was not associated with FEV_1.[95] In 2 RCTs, no effect of vitamin E supplementation was found at 12 weeks and 5 years, respectively, on the rate of annual FEV_1 decline in current male smokers and in patients with COPD.[96,97]

In summary, very strong evidence exists for a positive effect of vitamins C, E, and β-carotene on the risk of COPD in the general population. However, despite lower dietary intake and blood levels of vitamins in patients with COPD than in control subjects, the effect on pulmonary function decline has not yet been longitudinally investigated in these patients.

Fatty acids

Fish and omega-3 polyunsaturated fatty acids are common components of the prudent or healthy dietary pattern. Authors of a systematic review summarized evidence on the role of fatty acid intake in the onset of COPD, but results were not consistent.[98] In addition, in a prospective cohort study, no association between omega-3 polyunsaturated fatty acid intake and the risk of COPD was observed,[99] and 1 cross-sectional study

showed no associations with FEV_1.[41] However, in 2 cross-sectional analyses of current and former smokers, an inverse association between docosahexaenoic acid and the risk of COPD was observed,[100,101] and in 2 cross-sectional studies, dietary intake of fish had a protective association with FEV_1.[68,102] A positive association was also observed between serum docosahexaenoic acid concentration and FEV_1 percent predicted and FVC percent predicted in men.[103] With respect to saturated fatty acid intake, only 1 cross-sectional study was found and the authors reported no effects on the onset of COPD.[104]

In terms of pulmonary function decline in COPD, a significant positive association between intake of pentadecanoic acid and FEV_1-to-FVC ratio was observed in patients with COPD in a cross-sectional study,[105] whereas in another cross-sectional study, no associations between polyunsaturated fatty acid intake and pulmonary function (ie, FEV_1 percent predicted and FVC percent predicted) were observed.[106]

Evidence for the association between dietary intake of fatty acids and the risk and progression of COPD is still very limited and inconsistent and needs to be further elucidated.

Fiber

A reduced risk of COPD in the general population was reported for dietary fiber intake in a systematic review that included 2 longitudinal cohort studies, a case-control study, and a cross-sectional study.[98] Moreover, low fiber intake was associated with reduced outcomes of FEV_1 and thereby an increased risk of COPD, particularly in current and former smokers in a cross-sectional and prospective cohort study.[107,108] In a prospective cohort study, dietary fiber intake was even found to be associated with a long-term 30% reduced risk of COPD development, especially for fruit- and cereal-derived fibers.[109] Accordingly, there is very strong evidence indicating that high intake of dietary fibers reduces the risk of COPD, but we found no studies that reported on the effect of dietary fiber intake on pulmonary function decline in patients with COPD.

DISCUSSION

This systematic review highlights the effect of dietary intake, nutrient status, and nutritional supplementation in the general population on the risk for development and onset of COPD and on progression of pulmonary function decline in patients diagnosed with COPD. Generally, patients with COPD often consume a typical Western-style diet, which is poor in dietary quality, and thus they probably eat more processed meat and fewer fruits and vegetables, and less fiber. This review clearly reveals strong evidence that a Western diet, high consumption of processed meat, and low consumption of fruits, vegetables, and fiber are associated with an increased risk of COPD.

Tobacco-smoke exposure and air pollution enhance oxidant burden and chronic pulmonary and systemic inflammation.[110] Oxidant burden in the respiratory tract is increased by tobacco exposure and by the release of reactive oxygen species from neutrophils and macrophages, attracting inflammatory cells into the lungs and inducing inflammatory responses by activating transcription factors like nuclear factor-κB.[111] Enhanced oxidative stress also results in lung-tissue injury by oxidation of proteins, DNA, and lipids.[112] These processes can contribute to loss of pulmonary function and the onset of COPD. Dietary intake of nutrients with antioxidant or anti-inflammatory properties, like vitamins and fiber, theoretically could attenuate pulmonary function decline, which can reduce the risk of COPD in the general population and disease progression in patients with COPD.

In this systematic review, we found consumption of fruit and vegetables is positively associated with COPD risk in the general population. Intake influences the oxidant and anti-oxidant balance, including that in the respiratory tract, because fruit and vegetables have high content of antioxidant substances (eg, vitamins C and E). Vitamin C is involved in the immune defense and potentially protects against environmental oxidative stress.[113] Moreover, vitamin C deficiency can cause an impaired immune function, rendering patients more susceptible to acute viral or bacterial infections.[113] Furthermore, we found beneficial effects of nutritional fibers, especially cereal fibers and fibers in fruits, on the risk of COPD development. A potential mechanism to explain the inverse association between dietary-fiber intake and COPD risk may be that nutritional fibers modulate the innate immune system and attenuate systemic inflammation via the gut-lung axis.[114] A chronically overactive innate immune response can contribute to accelerated loss of pulmonary function.[115] The gut microbiome plays a pivotal role in functioning of the host immune system. Bacterial fermentation of dietary fibers in the gut results in the production of short-chain fatty acids, such as butyrate, which can modify the immune response by inhibition of macrophage and neutrophil activation, inducing regulatory T cells, and improving microbial composition.[116,117] A previous longitudinal and cross-sectional study demonstrated that high intake of dietary fibers decreased concentrations of pro-inflammatory markers like C-reactive protein and interleukin-6.[118,119]

In contrast to the beneficial effects of fruit, vegetable, and fiber intake, the studies in this review revealed greater consumption of processed meat is identified as potential risk factor in the onset of COPD. This may be due to the potential pro-inflammatory properties and the high concentrations of nitrates, nitrites, and nitrosamine compounds.[120] Nitrites are pro-oxidants and can produce oxidizing reactive nitrogen species such as peroxynitrite, which may amplify inflammatory and oxidative stress processes involved in the lung, leading, for example, to DNA damage, inhibition of mitochondrial respiration, and cell dysfunction.[121] Moreover, processed meat contains advanced glycation end products that can increase inflammation and oxidative stress by activating NF-κB after binding to the cell-surface receptor.[122,123] Long-term persistence of inflammation and reactive nitrogen species may contribute to progressive loss of pulmonary function; however, the underlying mechanisms of processed meat intake in the pathogenesis of COPD remains unclear and needs to be further elucidated.

Micronutrients were not included in this systematic review and, as far as we know, they have not been implicated in the risk of COPD or pulmonary function decline. However, it has been reported that patients with COPD have lower dietary intake of calcium, phosphorus, and iron compared with that of healthy control subjects,[124] and patients with COPD with iron deficiency have less exercise capacity, more frequent exacerbations, and increased COPD severity than do patients with COPD who do not have iron deficiency.[125,126] Whether low mineral status also affects lung function and COPD risk remains to be elucidated.

This systematic review shows that the association between dietary intake and the risk of COPD in the general population has been extensively investigated, but no or few studies are available on the association between nutrition and progression of pulmonary function decline in patients with COPD. The available evidence suggests increased nutritional intake of fruit and vegetables or vitamins C, E, and β-carotene; polyphenols; or dietary fibers could very well play a role in the prevention of COPD. Poor nutrition, in addition to tobacco smoking and air pollution, thus is identified as a modifiable COPD risk factor in the general population. Hence, improving quality of dietary intake and adherence to a healthier diet like the Mediterranean diet should be considered as an important lifestyle adaptation with respect to COPD prevention.

CONCLUSION

Considering the increasing burden of COPD worldwide, the scarce or absent data on the effect of dietary intake, nutrient status, and supplementation on pulmonary function decline in patients with COPD highlight the need for large, longitudinal cohort studies and RCTs with long-term follow-up to clarify the role of nutrition in the progression of pulmonary function decline in this disease. Overall, stimulating a shift toward a healthy Mediterranean dietary pattern during lifestyle counseling in patients with COPD may contribute to attenuated decline of pulmonary function, reduced risk of comorbidities, and improved health-related quality of life.

Supporting Information
The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Items from the PRIMA checklist included in the systematic review.**

Appendix S1 **Details of the database search strategy.**

Table S2 **Results of each cross-sectional, longitudinal cohort study or randomized controlled trial summarized in the systematic review.**

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