# Dietary fibre and fatty acids in chronic obstructive pulmonary disease risk and progression: a systematic review.

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REVIEW

# Dietary fibre and fatty acids in chronic obstructive pulmonary disease risk and progression: a systematic review

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## ABSTRACT

**Dietary intake attracts increasing interest in the risk for and progression of chronic obstructive pulmonary disease (COPD). In particular, dietary fibre and fatty acids have drawn specific attention for their immunomodulating potential. The study aimed to review the current evidence on the potential roles of dietary fibre or fatty acid intake in the risk and progression of COPD. Pubmed, EMBASE, Cochrane Collaboration Database and conference databases for original studies in adults addressing the association between fibre or fatty acid intake and COPD in terms of risk, lung function and respiratory symptoms were searched. Nine articles were included of which four reported on dietary fibre and five on fatty acids. Data of studies could not be pooled because of methodological diversity. Greater intake of dietary fibre has been consistently associated with reduced COPD risk, better lung function and reduced respiratory symptoms. Results on the associations between fatty acids and COPD are inconsistent. Dietary quality deserves further attention in developing COPD prevention and management programs.**

**Key words:** diet, lifestyle, nutrient, nutrition.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; PUFA, polyunsaturated fatty acid.

## INTRODUCTION

An estimated 64 million people suffer from chronic obstructive pulmonary disease (COPD) worldwide, a disease that is associated with high morbidity and mortality.[1] COPD is defined as a preventable and largely lifestyle-induced disease characterized by an abnormal pulmonary inflammatory response resulting in a progressive and partially irreversible airflow limitation.[2] In addition, COPD has been shown to have a profound systemic component characterized by low-grade systemic inflammation and frequent comorbidities.[2]

The disease state of COPD is likely the product of genetic and environmental factors.[3] Although exposure to cigarette smoke is considered the principal environmental risk factor, an estimated 25–45% of COPD patients have never smoked.[4] Only about 20% of smokers eventually develop COPD,[5] and only about 10% of the variability in forced expiratory volume in 1 s ($FEV_1$) is explained by smoking in the general population.[6] It has therefore been suggested that environmental factors other than smoking, such as poor diet and low physical activity level should also be considered as the risk factors for development of COPD. For a comprehensive overview on the effects of physical inactivity on COPD risk, we refer the reader to a recent review by Hopkinson and Polkey.[7] The present systematic review was undertaken to summarize the current knowledge on the effects of specific dietary components with disease-modulating potential on COPD risk and progression. To our knowledge, this has not previously been reviewed systematically.

Nutritional support in COPD management traditionally has a primary focus on malnourished patients. In recent years, however, nutritional research in COPD has also explored associations between dietary patterns and specific dietary components with COPD risk and progression. It has been shown that a diet rich in fruit, vegetables, whole-meal cereals and fish can reduce the risk of COPD, whereas a 'Western diet' rich in refined grains, cured and red meats, desserts, and French fries can increase COPD risk.[8,9] Knowledge on the influence of specific dietary components may ultimately provide the best possible way to optimize dietary recommendations in COPD. Dietary fibre and fatty acids have been shown to influence the immune system in various ways and have been hypothesized to play a role in modulating the pulmonary and systemic inflammatory response in COPD.

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Higher intake of dietary fibre has indeed been associated with improved gut immunity and reduced systemic inflammation. Dietary fibres can be divided into water-soluble and -insoluble fibres.[10] Fermentation of soluble fibres in the large intestine produces short-chain fatty acids, may enhance immune function, through effects on membrane bound (protein coupled receptors) or nuclear receptors (e.g. peroxisome proliferator-activator receptors) and inhibition of the pro-inflammatory nuclear factor-κB.[10–12] Insoluble fibres add bulk to the stool, accelerate intestinal transit times and can also be fermented to a certain degree. However, their health-related mechanisms are less well understood.

Polyunsaturated fatty acids (PUFA) are incorporated in the cell membrane and have been shown to alter membrane-bound enzymes and receptor functioning (e.g. toll-like receptors and interferon-γ receptors). Moreover, n-3 and n-6 fatty acids are metabolized into anti- and pro-inflammatory eicosanoids, respectively.[13] Higher intake of n-3 fatty acids has been put forward as a mechanism to tilt the immune function into a more anti-inflammatory state.

The present systematic review summarizes the current evidence on the potential roles of dietary fibre or specific fatty acids in COPD risk and progression.

## METHODS

### Data sources and search strategy

This systematic review was performed according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14] Relevant articles were searched in Pubmed (through August 2013), EMBASE (1974 through August 2013), Cochrane Collaboration Database (through August 2013), and in conference databases of the European Respiratory Society (2006–2012), American Thoracic Society (2008–2013), European Society for Clinical Nutrition and Metabolism (2003–2012), American Society for Parenteral and Enteral Nutrition (2009–2013), and Experimental Biology (2010–2013). Databases were either systematically searched by combining free terms and subject headings (Mesh or Emtree terms for Pubmed and EMBASE, respectively) when available or were handsearched. The search strategy consisted of terms on dietary fibre and specific fatty acids in combination with relevant COPD-related terms and lung function (see Online Supplement for terms used and search strategies per e-database). In Pubmed and EMBASE, the limits 'humans' and 'adults' were imposed. Additionally, references of retrieved articles were handsearched to find more articles.

### Study selection

Articles identified by the search were first screened by title. Subsequently, the corresponding abstracts of potentially relevant hits were independently screened by two researchers (ELAFW and BvdB) based on selection criteria. The second researcher was blinded for journal, authors, title, publication date and publication language (all abstracts were in English). In case of disagreement, consensus was reached on the selection of studies for full-text assessment. To be included, the studies needed to be original researches in adults addressing the association between dietary fibre or fatty acids with predefined outcome measures (pulmonary function, pulmonary symptoms and/or COPD risk/incidence/prevalence). In case of uncertainty for inclusion of full-text articles or conference abstracts, consensus was reached via a third reviewer. Native speakers were consulted for foreign language articles.

## RESULTS

### Search results

A flowchart of study selection is presented in Figure 1. Briefly, the search in electronic databases yielded 5451 hits from Pubmed, 5562 from EMBASE and 759 from the Cochrane Collaboration Database, from which in total 225 possibly eligible articles were found. Additionally, 16 articles were identified in reference lists. In total, 241 abstracts were judged requiring assessment to their full-text. Subsequently, 88 full-text articles and 42 conference abstracts underwent thorough assessment based on the predefined criteria. Finally, nine articles were included. Of these, four reported data on associations between fibre intake and COPD (Table 1), and five investigated associations between fatty acid intake and COPD (Table 2). At first, the objective was to perform a meta-analysis. However, the studies proved too heterogeneous to allow pooling of results. Hence, we provide a narrative synthesis of the respective studies.

All the studies used a food frequency questionnaire or validated analogues to assess nutrient intake. In addition, all the studies adjusted extensively for possible confounding by known risk factors, including smoking.

### Associations between dietary fibre and COPD

In the large population-based Atherosclerosis Risk in Communities Study comprising 11 897 US men and women aged 44–66 years, higher total dietary fibre intake was cross-sectionally associated with better lung function ($FEV_1$, forced vital capacity (FVC) and $FEV_1$/FVC ratio).[15] Notably, people in the highest quintile of total dietary fibre intake (median 25.0 g/day) had an adjusted 60 mL higher $FEV_1$ compared with people in the lowest quintile (median 10.2 g/day). In addition, higher total dietary fibre intake was associated with lower odds ratios for COPD (odds ratio 0.85, 95% confidence interval 0.68–1.05). COPD was defined as prebronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ of predicted and/or self-reported persisted cough and production of phlegm on most days for at least 3 consecutive months of the year for 2 or more years. Similar data were obtained when investigated for fibre from cereals and fibre from fruit, but not for fibre from vegetables.

Another study by Hirayama *et al.*[16] compared 278 Japanese COPD patients (mean $FEV_1$ 57% of

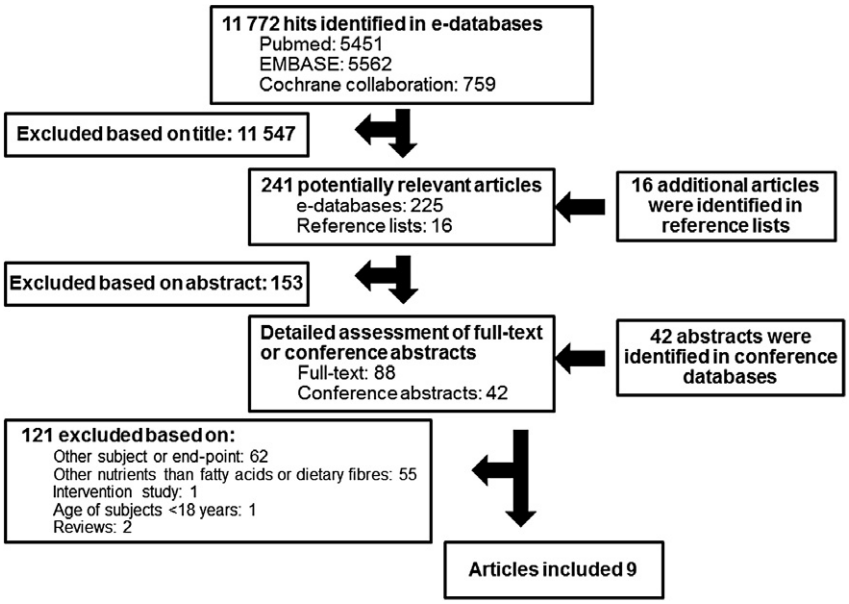


**Figure 1** Flow chart of article selection.

predicted) and 340 community-based non-COPD controls and found that the mean vegetable and fruit intakes of COPD patients were significantly lower. The authors subsequently applied logistic regression analyses to estimate the odds of having COPD across quartiles of nutrient intakes. They found that people who consumed ≥16.1 g total dietary fibre per day had lower odds of having COPD compared with those who consumed <8.8 g total dietary fibre per day (odds ratio 0.49, 95% confidence interval 0.26–0.94). Upon stratification into soluble and insoluble fibre intake, the authors found a similar association for insoluble but not soluble fibre.

Although the earlier referenced data from the Atherosclerosis Risk in Communities Study and the Japanese study may suggest a role for dietary fibre in COPD aetiology, their cross-sectional natures preclude the drawing of any causal inferences. Two other studies, however, applied a prospective design and showed remarkably consistent results. First, in a 5-year prospective population-based cohort of 63 257 middle-aged men and women residing in China and Singapore,[17] higher intake of non-starch polysaccharides was associated with a lower incidence of 'COPD symptoms' (defined as cough and phlegm, both shorter and longer than 3 months). Interestingly, whereas fruit and vitamin C intakes were also associated with lower incident COPD symptoms, these associations disappeared after further adjustment for dietary fibre intake. This suggests that dietary fibre intake may be at least partly responsible for these associations. However, in epidemiological studies, it remains difficult to disentangle associations with dietary fibre intake from for example anti-oxidant intake when they are consumed simultaneously. It should also be taken into account that no pulmonary function data were available in this study, and that the respiratory symptoms designated as 'COPD symptoms' may have reflected respiratory conditions other than COPD.

Another 16-year prospective study by Varraso *et al.*[18] in 111 580 US men and women from the Nurses' Health Study and Health Professionals Follow-up Study identified 832 incident COPD cases by means of a thorough questionnaire and required report of a diagnostic test at diagnosis. This epidemiological COPD definition was validated in a random sample and showed confirmation of diagnosis in up to 88%. It was found that compared with people in the lowest quintile of total dietary fibre intake (median 11.2 g/day), those in the highest quintile (median 28.4 g/day) had a lower adjusted relative risk of newly diagnosed COPD (relative risk 0.67, 95% confidence interval 0.50–0.90). Upon stratification on dietary fibre type, only cereal (primarily insoluble) fibre intake was independently associated with newly diagnosed COPD.

## Associations between fatty acids and COPD

Shahar *et al.*[20] investigated the cross-sectional associations between n-3 fatty acid intake (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), and lung function and COPD status in subjects participating in the population-based Atherosclerosis Risk in Communities Study. It was found that higher fish consumption, and specifically higher total n-3 fatty acid intake, was strongly associated with lower odds for COPD and lower lung function (dose-dependently). No significant findings were obtained in analyses restricted to never-smokers in this study. N-6 fatty acid intake was not reported in this study.

In the cross-sectional population-based Monitoring Project on Risk Factors and Health in the Netherlands-European Prospective Investigation into Cancer and Nutrition (MORGEN-EPIC) study,[21] data on intake of specific fatty acids and lung function were available of 13 820 Dutch men and women aged 20–59 years. The prevalence of COPD (Global

**Table 1** Study characteristics and results of included studies on fibre intake and COPD outcome parameters

| Ref. | Study design, study population, country | *n* | Dietary assessment | Dietary fibre type | Median or mean intake of highest versus lowest group of intake (g/day) | Outcome (difference in lung function, or odds ratio (OR) or relative risk (RR) and 95% confidence interval comparing highest to lowest group of intake) | | *P* for trend across increasing groups of intake | Covariates |
|---|---|---|---|---|---|---|---|---|---|
| [15] | Cross-sectional study on lung function and COPD odds, ARIC, United States | 11 897 | FFQ[¶] (semiquantative) | Total fibre | 25.0 versus 10.2 | $FEV_1$ | +60.2 mL (27.7–92.7)[†] | <0.001[†] | Age, sex, height, height$^2$, study centre, ethnicity, smoking status, pack-years, BMI, occupation, education, diabetes status, traffic density, glycaemic index; vitamins C, D, and E; and omega-3 polyunsaturated fatty acids from both food and supplements, cured meat, other sources of fibre (total fibre intake not adjusted for specific fibre types) |
| | | | | | | FVC | +55.2 mL (18.2–92.3)[†] | 0.001[†] | |
| | | | | | | $FEV_1$/FVC | +0.4% (0.1–0.9)[†] | 0.040[†] | |
| | | | | | | Chronic bronchitis | OR = 0.87 (0.64–1.19) | 0.185 | |
| | | | | | | Spirometry-defined COPD | OR = 0.80 (0.63–1.02) | 0.035[†] | |
| | | | | | | COPD (both definitions) | OR = 0.85 (0.68–1.05) | 0.044[†] | |
| | | | | Fruit | 8.1 versus 0.8 | $FEV_1$ | +65.4 mL (34.4–96.4)[†] | <0.001[†] | |
| | | | | | | FVC | +62.1 mL (26.8–97.4)[†] | 0.002[†] | |
| | | | | | | $FEV_1$/FVC | +0.5% (0.0–0.9) | 0.022[†] | |
| | | | | | | Chronic bronchitis | OR = 0.63 (0.47–0.84)[†] | 0.004[†] | |
| | | | | | | Spirometry-defined COPD | OR = 0.81 (0.64–1.03) | 0.083 | |
| | | | | | | COPD (both definitions) | OR = 0.72 (0.59–0.89)[†] | 0.005[†] | |
| | | | | Cereal | 5.8 versus 1.6 | $FEV_1$ | +48.6 mL (19.5–77.7)[†] | 0.001[†] | |
| | | | | | | FVC | +40.3 mL (7.1–73.4)[†] | 0.016[†] | |
| | | | | | | $FEV_1$/FVC | +0.5% (0.1–1.0)[†] | 0.015[†] | |
| | | | | | | Chronic bronchitis | OR = 0.77 (0.58–1.01) | 0.028[†] | |
| | | | | | | Spirometry-defined COPD | OR = 0.79 (0.64–0.98)[†] | 0.017[†] | |
| | | | | | | COPD (both definitions) | OR = 0.83 (0.69–1.01) | 0.021[†] | |
| | | | | Vegetable[‡] | 7.5 versus 2.2 | $FEV_1$ | NS | NS | |
| | | | | | | FVC | NS | NS | |
| | | | | | | $FEV_1$/FVC | NS | NS | |
| | | | | | | Chronic bronchitis | OR = NS | NS | |
| | | | | | | Spirometry-defined COPD | OR = NS | NS | |
| | | | | | | COPD (both definitions) | OR = NS | NS | |
| [16] | Case–control study on COPD odds, outpatients, Japan | COPD 278 Controls 340 | FFQ (Recall 5 years ago) | Total fibre | ≥16.1 versus ≤8.8 | COPD | OR = 0.49 (0.26–0.95)[†] | 0.160 | Age, gender, BMI, education level, smoking status, pack-years, alcohol intake, life-long physical activity, daily total energy intake |
| | | | | Soluble | ≥3.4 versus ≤1.6 | COPD | OR = 0.58 (0.31–1.10) | 0.271 | |
| | | | | Insoluble | ≥10.8 versus ≤5.9 | COPD | OR = 0.50 (0.26–0.94)[†] | 0.174 | |
| [17] | 5-year prospective cohort study on incident cough and phlegm, SCHS, China and Singapore | 63 257 | FFQ | Non-starch polysaccharides | 11.6 versus 4.7 | Cough + phlegm | OR = 0.61 (0.47–0.78)[†] | <0.001[†] | Age, total energy intake, dialect group, sex, smoking status, age at starting to smoke and cigarettes per day |
| | | | | | | Persistent cough + phlegm[§] | OR = 0.60 (0.43–0.82)[†] | 0.001[†] | |
| [18] | 16-year prospective cohort study on incident COPD; Women: NHS; Men: HPFS, United States | 111 580 | FFQ (Past year) | Total fibre | 28.4 versus 11.2 | COPD | RR = 0.67 (0.50–0.90)[†] | 0.03[†] | Age, sex, smoking status, pack-years, energy intake, US region, physician visits, BMI, physical activity, diabetes, omega-3 PUFA, cured meat intake and fibre type (except for total fibre) |
| | | | | Fruit | 7.6 versus 1.4 | COPD | RR = 0.77 (0.59–1.01) | 0.31 | |
| | | | | Cereal | 9.0 versus 2.2 | COPD | RR = 0.77 (0.59–0.99)[†] | 0.04[†] | |
| | | | | Vegetable | 10.7 versus 3.5 | COPD | RR = 0.92 (0.71–1.18) | 0.89 | |

[†] Statistically significant outcome.
[‡] Exact values not available.
[§] Cough and phlegm for ≥3months/year
[¶] Semiquantative food frequency questionnaire used was a modified version of a validated version.
ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 s; FFQ, Food Frequency Questionnaire; FVC, forced vital capacity; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NA, not available; NS, not significant; SCHS, Singapore Chinese Health Study.

**Table 2** Study characteristics and results of included studies on fatty acid intake and COPD outcome parameters

| Ref. | Study design, study population, country | *n* | Dietary assessment | Dietary fatty acid | Cut-off, median or mean intake of highest versus lowest group of intake (g/day) | Outcome (difference in lung function parameters or odds ratio (OR) and 95% confidence interval comparing highest to lowest group of intake) | | | *P* for trend across increasing groups of intake | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|
| [16,19]†† | Case–control study on breathlessness and COPD odds, Outpatients, Japan | COPD 278<br>Controls 340 | FFQ (recall 5 years ago)¶ | SFA | ≥1.67 versus ≤0.87 | Breathlessness | | OR = 0.92 (0.47–1.82) | 0.730 | Age, gender, BMI, education, alcohol drinking, smoking status, pack-years, daily total energy intake |
| | | | | | ≥1.63 versus ≤0.8 | COPD | | OR = 1.41 (0.68–2.94) | 0.242 | |
| | | | | MUFA | ≥1.48 versus ≤0.82 | Breathlessness | | OR = 0.75 (0.36–1.56) | 0.728 | |
| | | | | | ≥1.43 versus ≤0.81 | COPD | | OR = 1.01 (0.48–2.13) | 0.702 | |
| | | | | PUFA | ≥0.78 versus ≤0.43 | Breathlessness | | OR = 0.53 (0.26–1.09) | 0.025† | |
| | | | | | ≥0.76 versus ≤0.44 | COPD | | OR = 0.48 (0.23–1.01) | 0.002† | |
| | | | | n-3 Fatty acids | ≥0.16 versus ≤0.08 | Breathlessness | | OR = 1.05 (0.54–2.03) | 0.278 | |
| | | | | | ≥0.16 versus ≤0.08 | COPD | | OR = 0.95 (0.46–1.13) | 0.170 | |
| | | | | n-6 Fatty acids | ≥0.64 versus ≤0.33 | Breathlessness | | OR = 0.51 (0.25–1.05) | 0.021† | |
| | | | | | ≥0.63 versus ≤0.34 | COPD | | OR = 0.55 (0.26–1.14) | 0.002† | |
| | | | | n-6 : n-3 Ratio | ≥4.58 versus ≤3.09 (ratio) | Breathlessness | | OR = 0.63 (0.36–1.09) | 0.357 | |
| | | | | | ≥4.54 versus ≤3.08 (ratio) | COPD | | OR = 0.69 (0.38–1.24) | 0.108 | |
| | | | | α-Linolenic acid c18:3 (n-3) | ≥0.16 versus ≤0.80 | COPD | | OR = 0.87 (0.44–1.70) | 0.499 | Age, gender, BMI, education, smoking status, pack-years, life-long physical activity, daily total energy intake |
| | | | | Linoleic acid c18:2 (n-6) | ≥0.42 versus ≤0.22 | COPD | | OR = 1.40 (0.70–2.80) | 0.696 | |
| [20] | Population based cross-sectional study on lung function and COPD odds, ARIC, United States | Current or former smokers 6228 | FFQ (semiquantative) | Eicosapentaenoic acid c20:5 (n-3) + docosahexaenoic acid c22:6 (n-3) | >0.33 versus <0.09 | Men | $FEV_1$ | +29 ml[7–51]† | <0.05† | Pack-years, age, race, height, energy intake, education level |
| | | | | | | | FVC | +11 mL (–13 to 35) | NS | |
| | | | | | | | $FEV_1$/FVC | 0.5% (0.2–0.8)† | <0.05† | |
| | | | | | | Women | $FEV_1$ | +22 mL[8–37]† | <0.05† | |
| | | | | | | | FVC | +22 mL[5–38]† | <0.05† | |
| | | | | | | | $FEV_1$/FVC | 0.3% (0–0.5)† | <0.05† | |
| | | Never-smokers 4179 | | | NA | Men | $FEV_1$ | –8 mL (–36 to 20) | NS | |
| | | | | | | | FVC | –12 mL (–44 to 21) | NS | |
| | | | | | | | $FEV_1$/FVC | 0.1% (–0.3 to 0.4) | NS | |
| | | | | | | Women | $FEV_1$ | +11 mL (–2 to 25) | NS | |
| | | | | | | | FVC | +10 mL (–7 to 26) | NS | |
| | | | | | | | $FEV_1$/FVC | 0.1% (–0.1 to 0.3) | NS | |
| | | Current or former smokers 8960 | | | 0.48 versus 0.05 | Spirometrically detected COPD | | OR = 0.50 (0.32–0.79)† | 0.007† | |
| | | | | | | Chronic bronchitis | | OR = 0.66 (0.52–0.85)† | <0.001† | Age, sex, race, height, weight, pack-years, energy intake and educational level |
| | | | | | | Physician-diagnosed emphysema | | OR = 0.31 (0.18–0.52)† | 0.003† | |
| | | | | | | COPD (any definition) | | OR = 0.59 (0.46–0.75)† | 0.001† | |
| | | | | Linoleic acid c18:2 (n-6) | Lowest versus highest | Airway Obstruction | | OR = 0.8 | NS | |
| | | | | Oleic acid c18:1 (n-9) | Lowest versus highest | Airway Obstruction | | OR = 1.1 | NS | |
| [21] | Cross-sectional study on $FEV_1$ and resp. symptoms/COPD odds, MORGEN, Netherlands | 13 820 | FFQ | α-Linolenic acid c18:3 (n-3) | >1.62 versus <0.84 | $FEV_1$ | | +18.0 mL (–14.3 to 50.2)† | 0.14† | Age, age$^2$, sex, smoking status, pack-years, height, energy intake, vitamin C, BMI, education status |
| | | | | | | Wheeze | | OR = 1.2 (1.0–1.4) | 0.009† | |
| | | | | | | Resp. symptoms‡ | | OR = 1.2 (0.8–1.7) | 0.42 | |
| | | | | | | COPD‡‡ | | OR = 1.07 (0.74–1.55) | 0.49 | |
| | | | | Eicosapentaenoic acid c20:5 (n-3) | >0.07 versus <0.01 | $FEV_1$ | | –22.9 mL (–48.5 to 2.7) | 0.28 | |
| | | | | | | Wheeze | | OR = 1.2 (1.1–1.5)† | 0.005† | |
| | | | | | | Resp. symptoms‡ | | OR = 1.3 (1.0–1.7) | 0.26 | |
| | | | | | | COPD‡‡ | | OR = 0.84 (0.63–1.11) | 0.19 | |
| | | | | Docosapentainoic acid c22:5 (n-3) | >0.017 versus <0.002 | $FEV_1$ | | –24.0 mL (–49.4 to 1.3) | 0.29 | |
| | | | | | | Wheeze | | OR = 1.3 (1.1–1.5)† | 0.008† | |
| | | | | | | Resp. symptoms‡ | | OR = 1.3 (0.9–1.7) | 0.55 | |
| | | | | | | COPD‡‡ | | OR = 0.75 (0.56–0.99)† | 0.11 | |
| | | | | Docosahexaenoic acid c22:6 (n-3) | >0.14 versus < 0.04 | $FEV_1$ | | –39.3 mL (–64.8 to –13.8)† | 0.04† | |
| | | | | | | Wheeze | | OR = 1.2 (1.0–1.4) | 0.007† | |
| | | | | | | Resp. symptoms‡ | | OR = 1.0 (0.8–1.4) | 0.96 | |
| | | | | | | COPD‡‡ | | OR = 0.95 (0.71–1.25) | 0.50 | |
| | | | | Linoleic acid c18:2 (n-6) | >17.9 versus <9.0 | $FEV_1$ | | –38.1 mL (–70.1 to –5.5)† | 0.02† | |
| | | | | | | Wheeze | | OR = 1.1 (0.9–1.4) | 0.27 | |
| | | | | | | Resp. symptoms‡ | | OR = 0.8 (0.6–1.2) | 0.44 | |
| | | | | | | COPD‡‡ | | OR = 0.95 (0.68–1.34) | 0.27 | |

**Table 2** Continued

| Ref. | Study design, study population, country | *n* | Dietary assessment | Dietary fatty acid | Cut-off, median or mean intake of highest versus lowest group of intake (g/day) | Outcome (difference in lung function parameters or odds ratio (OR) and 95% confidence interval comparing highest to lowest group of intake) | | *P* for trend across increasing groups of intake | Covariates |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Eicosadienoic acid c20:2 (n-6) | >0.07 versus <0.02 | $FEV_1$ | −45.4 mL (−74.3 to −16.5)† | 0.04† | |
| | | | | | | Wheeze | OR = 1.1 (0.9–1.3) | 0.32 | |
| | | | | | | Resp. symptoms‡ | OR = 1.4 (1.0–1.9) | 0.13 | |
| | | | | | | COPD‡‡ | OR = 1.85 (1.32–2.58)† | 0.001† | |
| | | | | Eicosatrienoic acid or Dihomo-gamma linolenic acid c20:3 (n-6) | >0.019 versus <0.008 | $FEV_1$ | −14.2 mL (−43.3 to 14.9) | 0.67 | |
| | | | | | | Wheeze | OR = 1.0 (0.8–1.2) | 0.61 | |
| | | | | | | Resp. symptoms‡ | OR = 1.3 (1.0–1.9) | 0.07† | |
| | | | | | | COPD‡‡ | OR = 1.56 (1.12–2.17)† | 0.01† | |
| | | | | Arachidonic acid c20:4 (n-6) | >0.12 versus <0.05 | $FEV_1$ | −41.8 mL (−70.0 to −13.6)† | 0.0005† | |
| | | | | | | Wheeze | OR = 1.1 (0.9–1.3) | 0.16 | |
| | | | | | | Resp. symptoms‡ | OR = 1.1 (0.8–1.5) | 0.49 | |
| | | | | | | COPD‡‡ | OR = 1.63 (1.20–2.22)† | 0.002† | |
| | | | | Docosatetraenoic acid c22:4 (n-6) | >0.017 versus <0.006 | $FEV_1$ | −54.5 mL (−81.6 to −27.4)† | <0.0001† | |
| | | | | | | Wheeze | OR = 1.0 (0.9–1.2) | 0.82 | |
| | | | | | | Resp. symptoms‡ | OR = 1.3 (0.9–1.8) | 0.15 | |
| | | | | | | COPD‡‡ | OR = 1.65 (1.22–2.22)† | 0.001† | |
| | | | | Docosapentaenoic acid c22:5 (n-6) | >0.004 versus < 0.000 | $FEV_1$ | +40.5 mL (14.4–66.6)† | 0.0003† | |
| | | | | | | Wheeze | OR = 1.0 (0.8–1.1) | 0.81 | |
| | | | | | | Resp. symptoms‡ | OR = 1.2 (0.9–1.7) | 0.42 | |
| | | | | | | COPD‡‡ | OR = 0.71 (0.53–0.96)† | 0.036† | |
| | | | | Trans fatty acids | >4.9 versus <2.3 | $FEV_1$ | −19.0 mL (−54 to 16.0) | 0.54 | |
| | | | | | | Wheeze | OR = 1.1 (0.9–1.3) | 0.40 | |
| | | | | | | Resp. symptoms‡ | OR = 1.3 (0.8–1.8) | 0.58 | |
| | | | | | | COPD‡‡ | OR = 1.38 (0.95–2.02) | 0.15 | |
| [22] | Nested-case control study on lung function HCS, Australia | Low-lung function§§ 45 Controls 145 | FFQ (Semiquantative) | SFA | Male = 32.3, Female = 28.0§ | $\%FEV_1$ | NS | NA | Age, gender, smoking status |
| | | | | MUFA | Male = 26.9, Female = 23.8§ | $\%FEV_1$ | NS | | |
| | | | | n-3 Fatty acids | Male = 0.106, Female = 0.092§ | %FEV1 | NS | | |
| | | | | n-6 Fatty acids | Male = 12.1, Female = 11.5§ | $\%FEV_1$ | NS | | |
| [23] | Cross-sectional study on the prevalence of wheeze and bronchitis NHANES II, United states | 9074 | 24-h dietary recall | SFA | 26.0§ | Wheeze | NS | NA | Age, race, sex, pack-years, calories |
| | | | | | | Bronchitis | NS | | |
| | | | | Linoleic acid c18:2 (n-6) | 10.2§ | Wheeze | NS | | |
| | | | | | | Bronchitis | NS | | |
| | | | | Oleic acid c18:1 (n-9) | 27.4§ | Wheeze | NS | | |
| | | | | | | Bronchitis | NS | | |

† Statistically significant outcome.
‡ 'Respiratory symptoms' was defined by having one or more of the following symptoms: chronic cough (defined as cough during the winter time on most days for at least 3 months a year), chronic phlegm (defined as productive cough during the winter time or for at least 3 months a year) or breathlessness (defined as shortness of breath compared with people of same age when walking on level ground).
§ Mean intake.
¶ Excluding cooking oils, margarine, butter, mayonnaise and salad dressings.
†† Findings from the same study population were reported in two separate publications.
‡‡ COPD defined as GOLD stage 2 or higher.
§§ Low-lung function defined as $FEV_1$>80%.

ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 s; FFQ, food frequency questionnaire; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCS, Hunter Community Study; MORGEN, Monitoring Project on Risk Factors and Health in the Netherlands; MUFA, mono-unsaturated fatty acid; NA, not available; NHANES II, National Health and Nutrition Examination Survey; NS, not significant; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Initiative for Chronic Obstructive Lung Disease (GOLD) 2 or higher, no post-bronchodilator data) was 4%. Of the n-3 fatty acids, only DHA was significantly associated with $FEV_1$, but the direction of this association was inverse. Also, higher intake of n-6 fatty acids were generally associated with lower $FEV_1$ and greater odds ratio for COPD. Moreover, it was found that smoking status significantly interacted with the associations between n-6 fatty acids and $FEV_1$; the inverse associations were stronger in smokers compared with non-smokers. In the entire population, α-linolenic acid, EPA, docosapentaenoic acid and DHA (all n-3) intake were all associated with an increased risk of wheeze, and EPA (n-3), eicosadienoic acid (n-6) and eicosatrienoic acid (n-6) intake were positively associated with respiratory symptoms (chronic cough, chronic phlegm and/or breathlessness). Finally, COPD prevalence was negatively associated with docosapentainoic acid (n-3) and docosapentaenoic acid (n-6), and positively with eicosadienoic acid (n-6), eicosatrienoic acid (n-6), arachidonic acid (n-6) and docosatetraenoic acid (n-6) intake.

In the much smaller population-based Hunter Community Study,[22] comprising 195 Australian men and women aged 55–85 years (including 45 subjects with $FEV_1 < 80\%$ of predicted), no cross-sectional associations were found between dietary intake of saturated fatty acids, monounsaturated fatty acids, n-3 PUFA and n-6 PUFA with $FEV_1$, FVC or $FEV_1$/FVC. The study did find that higher fat intake (as a percentage of total energy intake) was associated with lower $FEV_1$ and FVC among men, but from these data, it cannot be concluded that specific fatty acids account for these associations.

In the same population in which Hirayama *et al*. reported data on associations between dietary fibre and COPD,[16] the authors also investigated associations for specific fatty acids that were published in a separate paper.[19] Compared with controls, COPD patients consumed significantly less PUFA, n-6 fatty acids and n-3 fatty acids but similar quantities of saturated fatty acids and mono-unsaturated fatty acids. Significant *P*-values for trends were reported for associations with COPD breathlessness across quartiles of PUFA and n-6 fatty acid intakes, but not n-3 fatty acids or (n-3) : (n-6) ratio. In contrast with the other papers referenced earlier,[20–22] this study excluded fatty acids from cooking oils, margarine, butter, mayonnaise and salad dressings, and may therefore have underestimated actual intake levels.

Finally, another cross-sectional study among 20 322 people aged >30 years from the population-based Second National Health and Nutrition Examination Survey did not find any significant association between oleic acid (n-9) or linoleic acid (n-6) intake with wheezing.[23]

## DISCUSSION

There is growing attention to the influence of an overall poor lifestyle in the increased risk for and progression of COPD, which goes beyond smoking. This review was undertaken to summarize the current data on the relationship between dietary fibre or fatty acids, and COPD risk and progression. At present, the available data indeed suggest a role for dietary fibre in COPD as greater intake of dietary fibre has been associated with better lung function in the general population, lower odds of COPD, and lower risk of incident respiratory symptoms and COPD.

According to the European Food Safety Authority, the current recommendation for dietary fibre intake is 25 g/day, and the actual intake averages between 15 and 30 g/day across European countries.[24] Of the studies, we have reviewed, only those subjects who were in the highest quartile/quintile of dietary fibre intake met this recommendation. The European Food Safety Authority also states that a dietary fibre intake of >25 g/day may be even more beneficial, as it has been consistently shown to reduce the risk of type 2 diabetes, cardiovascular disease and colorectal cancer.[24] There are currently no data available that indicate whether such amounts of dietary fibre intake are also beneficial in terms of reduced COPD risk, or could also be beneficial for COPD progression given the increased risk for diabetes and cardiovascular disease,[25] in particular in earlier disease stages.

In a recent 3-year prospective study in 120 COPD patients, participants were randomized to follow a fruit and vegetable-rich diet or their regular diet. The former group succeeded to increase fruit and vegetable intake, and interestingly, this was associated with a slight improvement in $FEV_1$ over 3 years (by approximately 5% of predicted), whereas the control group was characterized by an expected decline in $FEV_1$ (by approximately 9% of predicted, between-group difference $P = 0.03$).[26] That study was performed against the background of a potential benefit of increased dietary anti-oxidants. However, the results may also have been partly accounted for by the simultaneous increase in dietary fibre intake. The feasibility of increasing fruit and vegetable intake in COPD patients was confirmed in a recent exploratory study.[27]

The Atherosclerosis Risk in Communities Study reported a 60-mL difference in $FEV_1$ between persons in the lowest versus highest quintiles of fibre intake, in favour of the latter.[15] This is a clinically substantial difference because normal $FEV_1$ decline in adults is approximately 30 mL/year,[28] and the $FEV_1$ difference between never-smokers and current smokers is generally around 200 mL.[29] Dietary fibre may therefore be an important modifiable factor to prevent or delay significant lung function decline.

Current evidence is not conclusive about which food items containing dietary fibre are more beneficial for reducing COPD. Two studies found significant associations for fruit and cereal fibre, but not for vegetable fibre.[15,18] However, it is not clear whether this is accountable to soluble or insoluble fibre. Generally, cereals contain mainly water-insoluble fibre but are also a relatively good source of water-soluble fibre (about 25%[10]); fruits contain mainly water-soluble fibre, and vegetables contain water-insoluble fibre.[30] On the contrary, only insoluble fibre was associated with lower COPD odds ratio in the Japanese study,[16] but the small range of soluble fibre intake in that

study (≥3.4 g/day vs ≤1.6 g/day) is a limitation in this respect.

N-6 fatty acids are thought to be more pro-inflammatory than their n-3 counterparts,[13] and it is hypothesized that greater n-3 fatty acid intake and/or lower n-6 : n-3 fatty acid ratios are associated with beneficial outcomes related to COPD. In a cross-sectional analysis of 250 COPD patients, higher intake of α-linolenic acid (n-3) was associated with lower circulating tumour necrosis factor-α concentrations, and higher intake of arachidonic acid (n-6) was related to higher interleukin-6 and C-reactive protein concentrations.[31] However, whereas specific dietary fatty acids may be associated with systemic inflammation in COPD patients, the articles reviewed have inconclusive data with respect to relevant functional outcome measures. In most studies except for one,[20] n-3 fatty acid intake did not seem to be associated with COPD. Remarkably, the median intake of the highest quartile of EPA and DHA in this particular study was considerably higher compared with that in the other studies. Nonetheless, in all studies, n-3 fatty acid intake was far below the current recommendations of 1.6 g/day for men and 1.1 g/day for woman.[32] Protective effects could only become apparent with higher intake levels, which may explain the lack of significant results. Furthermore, it has been suggested that a n-6 : n-3 fatty acid ratio between 1:1 and 4:1 may be most beneficial, whereas current ratios are approximately 16:1 in Western diets.[33] Unfortunately, this hypothesis has not been investigated appropriately yet with respect to COPD outcomes.

Another possibility to assess fatty acid intake would be the use of biomarkers in plasma or in cell membranes. Few studies have used this approach to correlate fatty acid profiles in the body with lung function or COPD outcome parameters. A case–control study reported a three times higher arachidonic acid (C20:4 n-6) to EPA (C20:5 n-3) ratio in erythrocyte membranes in COPD patients compared with healthy subjects.[34] In the Atherosclerosis Risk in Communities Study, plasma fatty acids were measured in a subset of the population of which DHA, but not EPA, was correlated with higher $FEV_1$/FVC ratios and lower COPD risk in smokers.[35] DHA was also found to be associated with higher $FEV_1$ and FVC in a German population.[36] Studies with validated biomarkers seem warranted to clarify the conflicting results with fatty acids and COPD proxies.

PUFA supplementation may have beneficial effects on exercise performance via modulation of transcriptional regulation of impaired skeletal muscle oxidative capacity. PUFA are the natural ligands of the peroxisome proliferator-activator receptors that have been shown to be downregulated in advanced COPD. A randomized, placebo–controlled, clinical trial including 120 patients showed that 9 g of PUFA supplementation daily during an 8-week exercise training program enhanced effects on exercise capacity in patients with severe COPD.[37] Another recent trial including insulin-resistant men receiving high-fat meals showed that PUFA induced less transcriptional downregulation of oxidative pathways than did other high-fat meals rich in short- or medium-chain fatty acids.[38] It is therefore worthwhile to further explore the potential beneficial role of specific PUFA on extrapulmonary manifestations of COPD.

Two studies indicated that smoking status is an important consideration when interpreting associations between fatty acid intake and COPD-related outcomes, as the negative associations with n-6 fatty acids were stronger in smokers than in non-smokers,[21] and positive associations with EPA + DHA were found in ever-smokers.[20] These data may suggest that lower n-6:n-3 ratios may be beneficial particularly in smokers; however, this hypothesis has not been addressed in the current literature.

Limitations of our review are primarily related to methodological quality of the included studies. Although the studies have been extensively adjusted for smoking (most often both smoking status and pack-years smoked), residual confounding factors cannot be ruled out. Albeit to a lesser extent, there could also be residual confounding by socioeconomic status or educational level. As mentioned, we could not perform a meta-analysis. This is primarily a consequence of the large heterogeneity among the available studies rather than a methodological limitation of our review. Finally, we must take into consideration that most studies retrospectively analysed collected data from large epidemiological studies that were not primarily designed to investigate effects of dietary components on COPD-related outcomes. Therefore, confirmation of results in large adequately powered prospective studies primarily designed to examine the effects of specific dietary components on COPD-related outcomes is necessary. Although the required number of subjects of such prospective studies would be large, the measurements required should be widely available, relatively cheap and can easily be incorporated in new initiatives.

In conclusion, current data indicate that changes in dietary composition, in particular with respect to dietary fibre amount, may have beneficial effects in terms of COPD risk and progression. It is worthwhile to further study the underlying mechanisms in order to optimize and specify dietary recommendations in COPD.

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ELAFW, BvdB, HRG and AMWJS designed the systematic review. ELAFW and BvdB conducted the review and wrote the draft of the manuscript. HRG and AMWJS reviewed the manuscript. AMWJS had primary responsibility for the final content. All authors read and approved the final draft of the manuscript. None of the authors have a conflict of interest. There were no funding sources.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Appendix S1** Search strings used in online databases.