



Self-reported intake of fruit and vegetables and risk of chronic obstructive pulmonary disease: A nation-wide twin study

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ABSTRACT

Background: Although smoking is the major risk factor for chronic obstructive pulmonary disease (COPD) many patients with obstructive lung function suggesting COPD are never-smokers. Therefore, other lifestyle factors have been suggested as risk factors.

Aims: i) To examine the association between self-reported intake of fruit and vegetables and risk of COPD and ii) to examine whether the association between these traits are due to underlying genetic factors.

Methods: 12,449 twins, aged 40–80, from the Danish Twin Registry were recruited. The participants completed a questionnaire on medical history and lifestyle factors and participated in clinical examination. COPD was defined according to ATS/ERS recommendations. Multivariate logistic regressions were used to estimate the risk of COPD in individuals with a low intake of fruit and vegetables. Co-twin control analyses were performed to examine whether the association between fruit and vegetables and COPD is explained by genetic factors. Self-reported physician-diagnosed asthmatic individuals were excluded.

Results: Of the 11,458 individuals were included in the analyses, 48% of the participants were males. Mean age was 58.9 (years) $\pm$ SD 9.6, mean BMI (kg/m^2) 26.6 $\pm$ SD 4.4.

A multivariate logistic regression, including sex, age and BMI showed that both smoking, no and heavy drinking and physical inactivity were independent predictors of COPD. There was a significant frequency-dependent association between intake of fruit and vegetables and increased risk of COPD. Conditional logistic regression analyses showed that the association might be controlled by genetic factors.

Conclusions: This study shows that low intake of fruit and vegetables is associated with an increased risk of COPD and the association might be under influence of genetic factors.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide with great impact on public health in terms of increasing prevalence, comorbidity and mortality [1]. Smoking is a by far the strongest risk factor for decline in lung function [2,3] and chronic bronchitis [4,5]. Early studies have suggested that 80–90% of COPD cases are caused by smoking [6]. However, more recent studies have suggested that only around half of the continuous smoking population develop COPD [7,8]. Thus, COPD cannot solely be explained by smoking. Air pollution from either cooking, biomass fuels or occupational exposures have been suggested to account for 20% of COPD cases

[9,10] with $\alpha 1$ -antitrypsin deficiency only accounting for 1–2% [11].

It is now recognized that oxidative stress induced by smoking plays a major role in the development of COPD [12]. A study showed that the total antioxidant capacity of the diet is inversely associated with plasma concentration of high-sensitivity C-reactive protein [13] and furthermore, that the antioxidant capacity is markedly reduced in patients with COPD [14]. A previous prospective study found that fruit, but not vegetables had a protective effect against COPD mortality [15]. Another study showed that intake of fruit was inversely associated with reduced cough with phlegm [16]. A recent Swedish prospective study found that high consumption of fruit and vegetables is associated with a reduced incidence of COPD in both smokers and ex-smokers, but not never-

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smokers [17]. Although an increasing number of studies examining the association between life style factors and COPD are being published, the majority, if not all, define airway obstruction by fixed FEV₁/FVC-ratio < 0.70 and not a FEV₁/FVC-ratio below the lower limit of normal as suggested by the European Respiratory Society/American Thoracic Society (ERS/ATS) [18].

Twin studies have shown that the individual susceptibility to chronic bronchitis [19] and COPD [20] is explained to some extent by genetic factors. Furthermore, there is a moderate to strong genetic contribution to the individual difference in life style factors, i.e. the heritability for smoking is 69% and a healthy diet is 32% [21]. Twin pairs discordant for a given exposure can be used to investigate if an association between the exposure and disease is due to underlying genetic factors [22]. Thus, the aims of this study were i) to examine the association between self-reported intake of fruit and vegetables and COPD in a population-based twin study, and ii) to examine if the association between the intake of fruit and vegetables and COPD is due to genetic or environmental factors.

2. Methods

2.1. Study participants

12,449 twin individuals born 1931–1961 included in the Infrastructure Initiative 2008–2011 were recruited. This nation-wide umbrella study has previously been described in details [23]. Briefly, the survey included two cohorts: The Middle Age Danish Twin study follow-up (MADT-cohort), consisting of 2402 individuals born 1931–1952 and The Middle Age Danish Twin Study (MIDT-cohort) consisting of 10,281 individuals born 1931–1969 and who are not included in the MADT-cohort. The participant rate was 62% for the MADT cohort and about 40% for the MIDT cohort.

Questionnaire data were available for 12,449 individuals and lung function data were available for 11,219 individuals (90%). All individuals with self-reported physician-diagnosed asthma were excluded prior to any analyses, $n = 991$ (8%). Thus, we included 11,458 individuals for the analyses.

2.2. Questionnaire data

Data on life style factors and respiratory symptoms were obtained from a questionnaire which was filled out by the participants at home and brought along for the clinical examination. Respiratory symptoms were defined as shortness of breath at rest or during exercise, cough with or without sputum, chronic bronchitis (cough and sputum in at least 3 months in 2 consecutive years), nocturnal awakening due to shortness of breath or chest tightness. Self-reported physician-diagnosed asthmatic individuals were excluded prior to analyses.

2.2.1. Life style factors

Smoking status was assessed asking questions regarding daily units smoked and duration of smoking in years. The effect of smoking was estimated by creating categorical variable: current, former and never smoking. Alcohol consumption was measured based on self-reported weekly intake of types of beverage and then summarized to a total of units per week. Following the recommendations for alcohol consumption set by the Danish Health Authority [24] the variable was categorized into 'no consumption', 'moderate consumption' (1–13 units/week for women and 1–20 units/week for men), and 'high consumption' (≥ 14 units/week for women and ≥ 21 units/week for men).

Dietary habits were based on the self-reported frequency of consuming a) fruit, b) raw vegetables, c) boiled vegetables, d) fruit juice, and e) vegetable juice on a 8-point scale: 1 = never, 2 = once or less monthly, 3 = twice monthly, 4 = once weekly, 5 = 2–3 times weekly, 6 = once daily, 7 = 2–3 times daily, and 8 = four or more times daily. Thus, a participant could be ascribed a diet score between 5 and 40

points. The effect of diet was assessed in the analyses as a continuous variable and a categorical variable. Based on the 8-point scale the following four categories for the frequency of intake of fruit and vegetables were defined for the main analyses: *never*, *monthly*, *weekly*, and *daily*.

For the purpose of sensitivity analyses, the five diet variables were subsequently recoded in three different ways; 1) categorized into five groups: never, monthly, weekly, once daily, and ≥ 2 times daily, 2) categorized into six groups: never, monthly, weekly, once daily, 2–3 times daily and ≥ 4 times daily and 3) treated as continuous variables with the score for each item. Physical activity was assessed using four questions on the frequency and intensity of physical activity at work and home. For each question the participant could choose between 'never', 'yearly', 'monthly', 'weekly', and 'daily'. The scores for all four questions were summarized and subsequently dichotomized into 'physical inactive' and 'physical active'.

2.2.2. Zygosity assessment

Twin zygosity was determined by a questionnaire method using four questions on similarity. The overall misclassification using this method is as low as 4% when compared with genetic marker analysis and thus regarded as a valid classification method [28].

2.3. Clinical examination

Height and weight were measured without shoes and in light clothing twice and then averaged.

2.3.1. Spirometry and definition of airway obstruction

The pre-bronchodilator lung function test was performed using a Spiroson-AS ultrasonic flowmeter (ECO Medics AE, Dürnten, Switzerland) and according to ERS/ATS guidelines for spirometry [25]. The Global Lung Initiative 2012 was used as reference values for FEV₁, FVC, and FEV₁/FVC-ratio [26] and airway obstruction was defined as FEV₁/FVC-ratio below lower limit of normal, which in this epidemiological study corresponds to a z-score for FEV₁/FVC-ratio of -1.96 [26]. We followed the recommendations from ERS/ATS and defined COPD by the presence of respiratory symptoms (at least one of the above-mentioned symptoms) and airways obstruction [27].

Furthermore, to enable comparison with other studies we did sensitivity analyses in which airways obstruction was defined as FEV₁/FVC-ratio < 0.70.

2.3.2. Statistical analyses

Data were analysed with the statistical package STATA 14.0 (StataCorp LP, College Station, Texas, USA). Chi-square and t-tests were used to compare the baseline characteristics in the non-COPD and COPD group. A categorical age variable was defined and the study sample was divided into 4 age groups: 40–50, 51–60, 61–70, and 71–80. BMI was categorized into: *underweight* (< 18.5), *normal weight* (18.5–25), *overweight* (> 25–30), and *obese* (> 30).

First, univariate logistic regressions were used to identify potential risk factors for COPD; sex, age, BMI, smoking, alcohol consumption, physical activity, and intake of fruit and vegetables. Second, the association between self-reported intake of fruit and vegetables and risk of COPD was assessed in a multiple logistic regression with sex, age, BMI, smoking, alcohol consumption, physical activity as covariates. Conditional logistic regression analyses were applied to compare the risk of COPD in the twin with a low intake of the various fruit and vegetable categories compared with the co-twin with a high intake. Low intake was defined as a weekly consumption or less. A different OR in DZ twins compared with MZ twins suggests that the association between fruit and vegetables and COPD is controlled by underlying genetic factors.

Data were analysed with the statistical package STATA 14.0 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station,

Table 1

Baseline characteristics of the total sample, non-COPD and COPD populations.

	Total sample (n = 11,458)	Non-COPD (n = 11,169)	COPD# (n = 289)	P-value
Sex (male), No. (%)	5548 (48%)	5399 (48%)	149 (52%)	NS
Age, mean (SD)	58.9 (9.6)	58.4 (9.6)	61.8 (8.6)	*
Body Mass Index (BMI), mean (SD)	26.6 (4.4)	26.6 (4.4)	25.6 (4.6)	*
Smoking, n (%)				
Never smoking	4842 (43)	4822 (43)	20 (7)	*
Former smoking	4262 (37)	4169 (38)	93 (32)	NS
Current smoking	2273 (20)	2098 (19)	175 (61)	*
Alcohol, n (%)				
No consumption	1587 (14)	1530 (14)	57 (20)	NS
Moderate intake	8574 (75)	8403 (75)	171 (59)	*
High intake	1297 (11)	1236 (11)	61 (21)	*
Intake of fruit and vegetables*				
Total score, mean (SD)	21.6 (4.4)	21.6 (4.3)	19.6 (4.8)	*
Fruit, mean score (SD)	6.1 (1.3)	6.1 (1.3)	5.4 (1.6)	*
Raw vegetables, mean score (SD)	5.2 (1.5)	5.2 (1.5)	4.4 (1.9)	*
Boiled vegetables, mean score (SD)	5.2 (1.1)	5.2 (1.1)	4.9 (1.2)	*
Fruit juice, mean score (SD)	3.7 (1.9)	3.7 (1.9)	3.4 (1.9)	NS
Vegetables juice, mean score (SD)	1.6 (1.2)	1.6 (1.2)	1.6 (1.3)	NS
Physical activity, n (%)				
Active	3180 (28)	3141 (28)	39 (13)	*
Inactive	8278 (72)	8028 (72)	250 (87)	

COPD defined as FEV₁/FVC < LLN + at least one respiratory symptom.

T-tests were used for continuous variables and chi-square-tests for categorical variables.

*Based on self-reported frequency of consuming fruit and vegetables on a 8-point scale ranging from 0 to 8 (never to ≥ 4 times/daily) for each category. * Significant p-values after Bonferroni-correction. The percentages are for available data and not the total number.

TX: StataCorp LP).

3. Results

3.1. Baseline characteristics

In total, 11,448 individuals were included of whom 48% were male and the mean age was 58.9 ± 9.6 years and BMI was 26.6 ± 4.4 kg/m².

289 (2.5%) individuals had COPD and differed from the non-COPD individuals as they were older, 61.8 ± 8.6 years vs. 58.4 ± 9.6 years, respectively, $p < 0.001$, included a higher proportion of current smokers; 51% vs. 19%, $p < 0.001$, and a higher proportion of heavy drinkers; 21% vs. 11%, $p < 0.001$, and were more physically inactive 87% vs. 72%, $p < 0.001$.

The total diet score was significantly lower in the COPD group compared with the non-COPD group, 19.6 ± 4.8 vs. 21.6 ± 4.3 , respectively, $p < 0.001$. The significantly lower score was present for all diet categories except vegetables juice (Table 1).

3.2. Predictors of COPD

In multivariate logistic regression models, we identified a number of predictors of COPD: increased age, underweight (compared with normal weight), OR = 3.04 (1.46–6.30), $p < 0.01$, former and current smoking, OR = 4.82 (2.96–7.85) and OR = 16.72 (10.45–26.77), respectively, $p < 0.001$.

A U-shaped association between alcohol consumption and risk of COPD was observed: individuals with no and high consumption had an increased risk of COPD compared with individuals with a moderate consumption, OR = 1.53 (1.10–2.11), $p < 0.05$ and OR = 1.46 (1.07–2.00), $p < 0.05$, respectively (Table 2).

3.3. Dietary habits and COPD

Table 3 shows a multiple logistic regression adjusted for sex, age, BMI, smoking, alcohol consumption and physical activity. Individuals with a low intake of fruit compared to those with a daily intake (reference) were at greater risk of COPD; weekly, OR = 1.65 (1.25–2.18),

Table 2

Predictors of COPD in a random population of 11,458 individuals.

	COPD (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Total sample	289 (2.5)		
Sex			
Male	149 (2.7)	Reference	Reference
Female	140 (2.4)	0.88 (0.69–1.11)	0.95 (0.73–1.24)
Age			
40–50	35 (1.2)	Reference	Reference
51–60	84 (2.5)	2.12 (1.42–3.16)	1.83 (1.22–2.76)
61–70	125 (3.3)	2.82 (1.93–4.11)	2.63 (1.78–3.87)
71–80	45 (4.4)	2.88 (1.83–4.53)	2.54 (1.59–4.07)
BMI			
Normal weight	124 (2.9)	Reference	Reference
Underweight	10 (11.8)	4.51 (2.29–8.85)	3.04 (1.49–6.19)
Overweight	108 (2.2)	0.77 (0.59–1.00)	0.76 (0.57–1.02)
Obese	46 (2.2)	0.76 (0.54–1.07)	0.73 (0.51–1.05)
Smoking			
Never	20 (0.4)	Reference	Reference
Former	93 (2.2)	5.38 (3.32–8.70)	4.82 (2.97–7.82)
Current	175 (7.7)	20.11 (12.61–32.06)	16.72 (10.51–26.60)
Alcohol consumption			
Moderate intake	171 (2.0)	Reference	Reference
No intake	57 (3.6)	1.86 (1.37–2.54)	1.53 (1.09–2.14)
High intake	61 (4.7)	2.43 (1.79–3.28)	1.46 (1.07–2.00)
Physical activity			
Active	39 (1.2)	Reference	Reference
Inactive	250 (3.0)	2.52 (1.79–3.54)	1.81 (1.28–2.57)

Significant results are printed in bold.

$p < 0.001$, monthly, OR = 2.31 (1.51–3.56), $p < 0.001$ and never, OR = 2.48 (1.06–5.81), $p < 0.05$. The same pattern was observed for raw vegetables, weekly, OR = 1.41 (1.05–1.88), $p < 0.05$, monthly, OR = 1.75 (1.18–2.60), $p < 0.01$, and never, OR = 2.39 (1.54–3.73), $p < 0.001$.

3.4. Co-twin control analyses

The association between intake of fruit and vegetables and COPD was further examined in conditional logistic regression analyses in which the risk of COPD within twin pairs discordant for low intake was compared (Table 4). In all twin pairs, the twin with low intake of fruit

Table 3
Association between intake of fruit and vegetables and risk of COPD in 11,458 adult twins.

	COPD No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI) [§]
Fruit, n (%)			
Daily	155 (1.8)	Reference	Reference
1–3 times/week	95 (4.1)	2.33 (1.80–3.02)	1.65 (1.25–2.19)
1–2 times/month	32 (7.7)	4.52 (3.05–6.69)	2.32 (1.49–3.61)
Never	7 (9.9)	5.96 (2.44–14.52)	2.48 (1.03–6.00)
Raw vegetables, n (%)			
Daily	91 (1.6)	Reference	Reference
1–3 times/week	119 (2.8)	1.71 (1.30–2.25)	1.41 (1.05–1.89)
1–2 times/month	142 (4.2)	2.80 (1.92–4.08)	1.75 (1.17–2.62)
Never	36 (8.3)	5.48 (3.62–8.29)	2.39 (1.49–3.85)
Boiled vegetables, n (%)			
Daily	94 (2.0)	Reference	Reference
1–3 times/week	163 (2.7)	1.35 (1.04–1.75)	1.22 (0.46–1.59)
1–2 times/month	26 (3.7)	1.84 (1.18–2.86)	1.34 (0.84–2.12)
Never	5 (5.5)	2.79 (1.12–6.98)	1.21 (0.46–3.18)
Fruit juice, n (%)			
Daily	53 (2.1)	Reference	Reference
1–3 times/week	77 (2.1)	1.06 (0.74–1.51)	1.17 (0.81–1.70)
1–2 times/month	94 (2.7)	1.33 (0.95–1.86)	1.28 (0.90–1.81)
Never	64 (3.4)	1.66 (1.14–2.41)	1.15 (0.78–1.71)
Vegetable juice, n (%)			
Daily	12 (4.4)	Reference	Reference
1–3 times/week	17 (2.4)	0.50 (0.23–1.06)	0.56 (0.25–1.24)
1–2 times/month	40 (1.8)	0.36 (0.19–0.70)	0.41 (0.20–0.82)
Never	216 (2.7)	0.56 (0.31–1.01)	0.56 (0.30–1.06)

[§]Adjusted for sex, age, BMI, smoking, alcohol consumption and physical activity. Significant results are printed in bold.

Table 4
Co-twin control analysis – risk of COPD in monozygotic and dizygotic twin pairs discordant for low intake of self-reported fruit and vegetables.

	All twins OR (95% CI)	MZ twins OR (95% CI)	DZ twins OR (95% CI)	P-value
Fruit	2.62 (1.38–4.96)	0.80 (0.21–2.98)	3.50 (1.60–7.68)	0.06
Raw	1.88 (1.02–3.44)	0.60 (0.14–2.51)	2.60 (1.25–5.39)	0.07
vegetables	1.48 (0.87–2.51)	2.50 (0.49–12.89)	1.29 (0.73–2.27)	0.29
Boiled	1.38 (0.72–2.62)	0.80 (0.21–2.98)	2.00 (0.90–4.45)	0.57
vegetables	0.43 (0.11–1.66)	0.50 (0.05–5.51)	0.50 (0.09–2.73)	0.19
Fruit juice				
Vegetable juice				

Conditional logistic regression estimating the risk of COPD in the twin with low intake of the various fruit and vegetable categories compared with the co-twin with high intake. P-value for difference in OR in MZ vs. DZ twins. Significant results are printed in bold.

and raw vegetables had an increased risk of COPD compared with the co-twin with a high intake, OR = 2.62 (1.38–4.96) and 1.88 (1.02–3.44), respectively, which support the results from the logistic regressions. When applying the same analyses in MZ and DZ twin separately, the DZ twin with low intake of fruit and vegetables had an increased risk of COPD compared with the co-twin, OR = 3.50 (1.60–7.68) and OR = 2.60 (1.25–5.39), respectively, which suggests that the association might be due to underlying genetic factors as the difference in risk estimates was only borderline significant.

Table 5 show the resemblance between MZ and DZ twins discordant for low intake of fruit and vegetables.

3.5. Sensitivity analyses

The inverse association between the intake of fruit and vegetables and risk of COPD was robust even in several sensitivity analyses. When

recoded into five categories (never, monthly, weekly, once daily, and ≥ 2 times daily) the results did not change the findings from the main analysis (Table S1), whereas recoding into six categories (never, monthly, weekly, once daily, 2–3 times daily and ≥ 4 times daily), the increased risk of COPD remained statistically significant for only the ‘monthly’ and ‘never’-groups (Table S2). Table S3 shows two independent multivariate logistic regressions in which the diet scores are included as continuous variables. First, we found that each increase of 1 unit in total diet score was associated with a significant decrease in risk of COPD. Further, when the total score was decomposed into scores for the five diet items, the same pattern was found for fruit, raw and boiled vegetables. Table S4 shows multivariate logistic regressions revealing the same pattern between intake of fruit and raw vegetables and risk of COPD when defined as a FEV₁/FVC-ratio < 0.70 + respiratory symptoms as when defined by lower limit of normal. The risk estimates were lower when using fixed ratio for the COPD diagnosis compared to lower limit of normal in spite of a higher number of cases.

4. Discussion

In this nation-wide twin study, we found that the risk of COPD is decreased in individuals with a daily intake of fresh fruit and raw vegetables compared with those with a weekly intake or less, whereas fruit and vegetable juice seem not to have any effect. These findings are in line with previous studies [29–32]. A Korean prospective study found that high intake of antioxidant vitamins C and E was associated with increased levels of FEV₁ and FVC [32] and two independent prospective studies in US men and women, Varraso et al. found that diet rich in fruits, vegetables and fish may reduce the risk of self-reported COPD [30,31]. In a 20-year prospective study investigating the impact of diet and COPD mortality, Walda et al. found that only fruit had a protective effect and not vegetables or fish [15].

Shaheen and co-workers found that a “prudent” pattern (high intake of fruit, vegetables, oily fish and whole meal) was positively associated with FEV₁, FVC in both men and women, whereas a higher FEV₁/FVC-ratio was only found in men [29]. While the majority of studies have defined airway obstruction as a FEV₁/FVC-ratio < 0.70, Shaheen et al. defined airway obstruction as a FEV₁/FVC-ratio below lower limit of normal. However, the identification of cases seems to be solely based on airway obstruction, as they do not mention inclusion of respiratory symptoms. To our best knowledge, our study is the first to assess the association between fruit and vegetables and COPD defined according to the current recommendations: the presence of airway obstruction (FEV₁/FVC-ratio below lower limit of normal) plus respiratory symptoms [27,33].

A sensitivity analysis showed that the association was weaker when using FR-COPD compared with LLN-COPD and this in spite of less power. Another study has showed that the association between telomere length and COPD was stronger and more significant when using LLN to diagnose COPD than was FR [34].

Oxidative stress due to smoking and air pollution over a longer period induces inflammation which can result in local airway remodelling which is thought to be responsible for accelerated decline in lung function [12,35–37] [38]. A study of 218 individuals with chronic airway obstruction with a history of COPD and/or asthma from the general population suggested that the dietary antioxidants vitamin C, β -Cryptoxanthin, β -Carotene, Lutein/zeaxanthin, and Lycopene are positively associated with FEV₁ [39]. In a prospective study of a random population of men and women, Carey et al. reported that the intake of fruit and vegetables did not impact the decline in lung function during a 7-year period. [40], which is in contrast to a 5-year prospective study by Butland et al., who found that the intake of fruit, vegetables, vitamin C and E seems to reduce the lung function decline [41]. Furthermore, they reported that the protective effect was found for hard fruit rather than soft juice, which is in line with our results indicating that only fresh fruit and raw vegetables, but not fruit and vegetable juice seem to

Table 5
Resemblance between monozygotic and dizygotic twin pairs for low intake of fruit and vegetables.

	MZ			DZ		
	Total pairs (n)	Concordant pairs (n)	Discordant pairs (n)	Total pairs (n)	Concordant pairs (n)	Discordant pairs (n)
Fruit	3254	271	987	2395	171	770
Raw vegetables	3200	883	1397	2357	627	1094
Boiled vegetables	3226	1245	1318	2375	868	1012
Fruit juice	3193	1958	1015	2349	1417	774
Vegetable juice	3161	3028	128	2318	2221	93

play a role.

The results from the study by Butland et al. are supported by a more recent study of two unselected Inuit populations by Baines and co-workers, who found that the intake of fruit and vegetables is positively correlated with FEV₁ and FVC [42]. Only few randomized controlled trials (RCT) have assessed the effect of diet on clinical outcome in COPD patients [43,44]. A 12-weeks RCT including 81 patients with moderate-to-severe COPD showed that the patients were able to comply with a dietary intervention, but no improvements were observed in airway inflammation of systemic oxidative stress [43].

However, another RCT including 120 COPD patients with varying severity showed that patients randomized to a diet rich in fruit and vegetables improved in lung function assessed by FEV₁ compared with the control group over a 3-year period [44]. Early studies have suggested that exhaled hydrogen peroxide, a biomarker of oxidative stress, is associated with COPD exacerbations [45,46], and a more recent RCT has shown that intake of fruit and vegetables reduces asthma exacerbations [47].

Although an increasing number of studies examining the impact of diet and COPD are added to the literature, more studies are needed. However, there is a more convincing research suggesting the beneficial effect of fruit and vegetables on asthma in both children [48] and adults [49].

It is reasonable to believe that the association between fruit and vegetables and COPD can be explained by other behavioural and genetic factors. An individual who displays a healthy lifestyle in terms of following a diet rich on fruit, vegetables and fish is more likely to be physically active, be a non-smoker and have a moderate consumption of alcohol and thus confound the association between diet and COPD. Therefore, studies investigating this association should preferably take these other life style factors into account.

Other studies have addressed the important question on why some individuals have a healthy lifestyle, while others have not [21]. The same research group have shown that heritability of several lifestyle factors range from 32% (diet) to 69% (smoking) in this present population. A Swedish twin study showed that the susceptibility to smoking and chronic bronchitis displayed a genetic overlap of 14% [50]. Our findings suggested that the association between fruit and raw vegetables might be partly controlled by genetic factors, although this needs further investigation to draw a firm conclusion.

This large, nation-wide twin study has a number of strengths. First, it differs from other comparable studies by its unselected population of both men and women with an age span from 40 to 80 years. Second, we have used the recommended definition to diagnose COPD covering both lung function measurement and assessment of respiratory symptoms. Third, we have data on relevant possible confounders such as BMI, smoking, alcohol consumption and physical activity included as covariates in the analyses. Fourth, as we have included twin individuals we had the possibility to examine whether the association between self-reported intake of fruit and vegetables and COPD is influenced by genetic factors. Lastly, various sensitivity analyses confirmed the robustness of our data.

Our study also has some limitations. The cross-sectional design does not allow assessment of the causal association between dietary habits

and COPD. However, our findings add new knowledge as we have defined COPD according to the current recommendation. Moreover, in the co-twin control analyses we were able to test if low intake of fruit and vegetables is associated with an increased risk of COPD in a 1:1 matched pair, which is a unique study design as the twin pairs are alike regard to many unknown factors and hence, the risk of residual confounding is reduced.

Another limitation is that we only had data on self-reported intake of various fruit and vegetables and not any specific measurements of antioxidant load/oxidative stress. However, the aim of this study was to examine the association of dietary habits and risk of COPD. Although we have adjusted for major and independent confounders, we cannot completely rule out residual confounding. One important confounder being socioeconomic status, which is known to be associated with an increased risk of COPD [50]. However, the level of socioeconomic status is shown to be under strong genetic influence [51] and since the same associations were observed in the co-twin control analyses, the reliability of our main findings is increased.

In conclusion, this large, nation-wide population study of adult twins aged 40–80, individuals with a self-reported weekly intake of fresh fruit and raw vegetables or less are at greater risk of COPD. Although controlling for many factors in the co-twin control analyses, the underlying mechanism for the association between intake of fruit and vegetables and COPD remains open and needs further investigation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2018.09.013>.

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Sensitivity analyses I – IV – for online material

Table S1. Sensitivity analysis I - categorical diet item divided into five groups and risk of COPD.

	COPD, N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)§
Fruit, n (%)			
>2 daily	79 (1.5)	Reference	Reference
Once daily	76 (2.2)	1.48 (1.08-2.04)	1.14 (0.82-1.60)
1-3 times/week	95 (4.1)	2.77 (2.05-3.75)	1.77 (1.26-2.45)
1-2 times/month	32 (7.7)	5.37 (3.52-8.20)	2.48 (1.53-4.00)
Never	7 (9.9)	7.09 (2.87-17.51)	2.66 (1.08-6.60)
Raw vegetables, n (%)			
>2 daily	30 (1.7)	Reference	Reference
Once daily	61 (1.6)	0.91 (0.58-1.41)	0.75 (0.47-1.19)
1-3 times/week	119 (2.8)	1.60 (1.07-2.40)	1.15 (0.74-1.78)
1-2 times/month	42 (4.2)	2.62 (1.62-4.23)	1.42 (0.83-2.41)
Never	36 (8.3)	5.13 (3.08-8.53)	1.94 (1.07-3.52)
Boiled vegetables, n (%)			
>2 daily	10 (1.5)	Reference	Reference
Once daily	84 (2.1)	1.44 (0.74-2.78)	1.35 (0.69-2.64)
1-3 times/week	163 (2.7)	1.85 (0.98-3.52)	1.58 (0.82-3.04)
1-2 times/month	26 (3.7)	2.52 (1.21-5.27)	1.74 (0.81-3.70)
Never	5 (5.5)	3.83 (1.28-11.47)	1.57 (0.50-4.96)
Fruit juice, n (%)			
>2 daily	9 (2.3)	Reference	Reference
Once daily	44 (2.1)	0.88 (0.43-1.82)	1.07 (0.51-2.28)
1-3 times/week	77 (2.1)	0.95 (0.47-1.91)	1.24 (0.60-2.57)
1-2 times/month	94 (2.8)	1.19 (0.60-2.39)	1.36 (0.66-2.78)
Never	64 (3.4)	1.49 (0.73-3.02)	1.22 (0.59-2.55)
Vegetable juice, n (%)			
>2 daily	2 (4.4)	Reference	Reference
Once daily	10 (4.8)	1.12 (0.24-5.28)	1.18 (0.20-6.94)
1-3 times/week	17 (2.4)	0.55 (0.12-2.44)	0.64 (0.12-3.57)
1-2 times/month	40 (1.8)	0.40 (0.09-1.69)	0.47 (0.09-2.49)
Never	216 (2.7)	0.61 (0.15-2.53)	0.64 (0.12-3.35)

§Adjusted for sex, age, BMI, smoking, alcohol consumption and physical activity. Significant results are printed in bold.

Table S2. Sensitivity analysis II - categorical diet item divided into six groups and risk of COPD.

	COPD, N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)§
Fruit, n (%)			
ñ4 times daily	16 (1.7)	Reference	Reference
2-3 times daily	63 (1.5)	0.87 (0.50-1.51)	0.93 (0.53-1.63)
Once daily	76 (2.2)	1.33 (0.77-2.27)	1.07 (0.61-1.89)
1-3 times/week	95 (4.1)	2.48 (1.45-4.23)**	1.66 (0.93-2.97)
1-2 times/month	32 (7.7)	4.80 (2.61-8.84)***	2.34 (1.19-4.60)*
Never	7 (9.9)	6.34 (2.32-17.32)***	2.51 (0.90-6.67)
Raw vegetables, n (%)			
ñ4 times daily	4(1.3)	Reference	Reference
2-3 times daily	26 (1.8)	1.43 (0.50-4.13)	1.90 (0.64-5.61)
Once daily	61 (1.6)	1.23 (0.44-3.40)	1.27 (0.45-3.62)
1-3 times/week	119 (2.8)	2.17 (0.80-5.88)	1.94 (0.69-5.48)
1-2 times/month	42 (4.4)	3.55 (1.26-10.00)	2.41 (0.81-7.13)
Never	36 (8.3)	6.94 (2.43-19.83)	3.28 (1.07-10.03)*
Boiled vegetables, n (%)			
ñ4 times daily	3 (1.5)	Reference	Reference
2-3 times daily	7 (1.5)	1.00 (0.26-3.92)	1.05 (0.26-4.18)
Once daily	84 (2.1)	1.44 (0.45-4.59)	1.39 (0.43-4.52)
1-3 times/week	163 (2.7)	1.86 (0.59-5.87)	1.64 (0.51-5.25)
1-2 times/month	26 (3.7)	2.52 (0.76-8.43)	1.80 (0.53-6.10)
Never	5 (5.5)	3.84 (0.90-16.42)	1.63 (0.36-7.28)
Fruit juice, n (%)			
ñ4 times daily	4 (4.4)	Reference	Reference
2-3 times daily	5 (1.7)	0.37 (0.10-1.40)	0.37 (0.09-1.48)
Once daily	44 (2.1)	0.45 (0.16-1.28)	0.55 (0.18-1.65)
1-3 times/week	77 (2.2)	0.49 (0.17-1.36)	0.64 (0.22-1.88)
1-2 times/month	94 (2.8)	0.61 (0.22-1.70)	0.69 (0.24-2.04)
Never	64 (3.4)	0.76 (0.28-2.14)	0.63 (0.21-1.87)
Vegetable juice, n (%)			
ñ4 times daily	1 (11.1)	Reference	Reference
2-3 times daily	1 (2.7)	0.22 (0.01-3.94)	0.21 (0.01-4.26)
Once daily	10 (4.8)	0.41 (0.05-3.57)	0.43 (0.06-3.15)
1-3 times/week	17 (2.4)	0.20 (0.02-1.68)	0.23 (0.03-1.64)
1-2 times/month	40 (1.8)	0.14 (0.02-1.18)	0.17 (0.02-1.54)
Never	216 (2.7)	0.22 (0.03-1.78)	0.23 (0.03-2.09)

§Adjusted for sex, age, BMI, smoking, alcohol consumption and physical activity. Significant results are printed in bold.

Table S3. Sensitivity analyses III & IV - The association between 1) total diet item scores and risk of COPD and 2) category diet scores and risk of COPD.

	Crude OR (95% CI)	Adjusted OR (95% CI) [§]
Total diet score	0.91 (0.88-0.93)	0.96 (0.94-0.99)
Fruit	0.71 (0.66-0.76)	0.83 (0.77-0.91)
Raw vegetables	0.75 (0.70-0.80)	0.87 (0.80-0.94)
Boiled vegetables	0.83 (0.76-0.91)	0.91 (0.83-1.01)
Fruit juice	0.92 (0.86-0.98)	0.98 (0.92-1.04)
Vegetable juice	1.02 (0.91-1.13)	1.04 (0.93-1.15)

Multivariate linear regression analyses of **1)** total diet score and **2)** the five diet items as a continuous variable based on the score for each item and risk of COPD.

[§]Adjusted for sex, age, height, BMI, smoking, alcohol consumption and physical activity. Significant results are printed in bold.

Table S4. Sensitivity analysis IV - Association between intake of fruit and vegetables and risk of COPD defined as FEV₁/FVC-ratio <0.70 plus respiratory symptoms.

	COPD, N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)§
Fruit, n (%)			
<i>Daily</i>	435 (5.1)	<i>Reference</i>	<i>Reference</i>
1-3 times/week	217 (9.4)	1.94 (1.64-2.30)	1.50 (1.25-1.81)
1-2 times/month	49 (14.1)	3.08 (2.30-4.13)	1.89 (1.37-2.62)
Never	13 (18.3)	4.21 (2.20-8.04)	2.03 (1.05-3.95)
Raw vegetables, n (%)			
<i>Daily</i>	252 (4.5)	<i>Reference</i>	<i>Reference</i>
1-3 times/week	293 (6.8)	1.54 (1.30-1.84)	1.27 (1.05-1.52)
1-2 times/month	93 (9.8)	2.30 (1.79-2.96)	1.52 (1.16-1.99)
Never	76 (17.5)	4.51 (3.40-5.98)	2.06 (1.49-2.85)
Boiled vegetables, n (%)			
<i>Daily</i>	254 (5.5)	<i>Reference</i>	<i>Reference</i>
1-3 times/week	397 (6.7)	1.22 (1.04-1.44)	1.17 (0.98-1.39)
1-2 times/month	59 (8.4)	1.56 (1.16-2.10)	1.36 (0.99-1.86)
Never	9 (9.9)	1.88 (0.94-3.79)	1.02 (0.47-2.19)
Fruit juice, n (%)			
<i>Daily</i>	143 (5.6)	<i>Reference</i>	<i>Reference</i>
1-3 times/week	179 (5.1)	0.91 (0.72-1.14)	1.06 (0.84-1.35)
1-2 times/month	221 (6.5)	1.16 (0.93-1.44)	1.19 (0.95-1.50)
Never	178 (9.5)	1.76 (1.39-2.21)	1.30 (1.02-1.66)
Vegetable juice, n (%)			
<i>Daily</i>	20 (7.9)	<i>Reference</i>	<i>Reference</i>
1-3 times/week	48 (6.9)	0.86 (0.52-1.32)	0.95 (0.53-1.70)
1-2 times/month	110 (4.9)	0.60 (0.36-0.98)	0.74 (0.43-1.25)
Never	533 (6.6)	0.83 (0.52-1.32)	0.91 (0.55-1.50)

§Adjusted for sex, age, BMI, smoking, alcohol consumption and physical activity. Significant result are printed in bold.