

Diet and chronic obstructive pulmonary disease: independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study)

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Summary

Background In recent years antioxidants, foods rich in antioxidants (e.g. fruits, vegetables) and fish have been suggested to protect against chronic obstructive pulmonary disease (COPD). There are also indications for a protective effect of whole grain intake and of consuming moderate amounts of alcohol. It is, however, not clear whether the effects of the different dietary factors on COPD are independent of each other and if so, whether their effects are additive.

Objective To gain more insight into the potential protective effect of diet on COPD, we studied fruit, vegetable, fish, alcohol and whole grain consumption simultaneously in relation to pulmonary function and COPD symptoms.

Methods Analysed were cross-sectional data collected in 13 651 men and women aged 20–59 years participating between 1994 and 1997 in the MORGEN study (monitoring project on risk factors and health in The Netherlands). Regression models were adjusted for age, gender, height (for pulmonary function only), smoking, BMI and energy intake.

Results Fruit and whole grain intake showed independent beneficial associations with COPD (P -trend < 0.001). Furthermore, in subjects with low alcohol consumption (1–30 g/day) the forced expiratory volume in 1 s (FEV₁) was higher and the prevalence of COPD symptoms lower than in non-drinkers ($P < 0.001$). The effects of a favourable intake of fruits (> 180 g/day), whole grains (> 45 g/day) and alcohol (1–30 g/day) were largely additive. In the 2998 subjects with a favourable intake of the three foods, the FEV₁ was 139 mL higher and the prevalence of COPD symptoms lower (odds ratio (OR) = 0.44) than in subjects ($n = 1406$) with unfavourable intakes of fruits, whole grains and alcohol ($P < 0.001$). A similar effect was observed in those who had never smoked. Fish and vegetable intake did not show independent beneficial associations with COPD.

Conclusions Our results suggest independent beneficial effects of fruits, whole grains and alcohol on COPD that are largely additive and cannot be explained by smoking habits.

Keywords: diet, pulmonary function, COPD symptoms, cross-sectional study, independent effects, fruits, whole grains, alcohol

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Introduction

In recent years evidence has accumulated that diet may protect from developing chronic obstructive pulmonary disease (COPD). However, until today most epidemiological

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studies have focused on one or a limited number of dietary factors simultaneously. It is therefore not clear whether the effects of the different (groups of) dietary factors on COPD are independent of each other and if so, whether their effects are additive.

A high intake of dietary antioxidants (e.g. vitamin C, vitamin E and β -carotene) [1–7] and of foods rich in antioxidants (e.g. fruits and vegetables) [8–14] and a high fish and/or n-3 fatty acid intake [12,15–18] were observed to be beneficially associated with pulmonary function, COPD symptoms or COPD mortality. Furthermore, indications for a beneficial effect of low alcohol consumption on pulmonary function and chronic lung disease were observed [9,19,20]. Whole grain intake has not been studied in relation to COPD before, but we hypothesized a protective effect based on the results of a study in middle-aged men from three European countries [13].

We studied the independent effects of fruits, vegetables, fish, alcohol and whole grains on pulmonary function and COPD symptoms in 13 651 men and women examined between 1994 and 1997 in the MORGEN study (the monitoring project on risk factors and health in The Netherlands). Earlier, a beneficial association of a high intake of vitamin C and of β -carotene with pulmonary function was observed in the MORGEN study [6].

Methods

Subjects and study design

The MORGEN study is a cross-sectional investigation into the prevalence of (risk factors for) chronic diseases in the Dutch population. Between 1994 and 1997, 17 453 men and women aged 20–59 years were examined through self-administered questionnaires and a physical examination. In Amsterdam and Maastricht each year a new random sample was examined and in a third town, Doetinchem, participants of an earlier study (1987–91) were re-examined. Complete information on diet was available for 17 025 subjects. Of these, 1603 subjects did not perform a lung function measurement due to practical reasons. Of the remaining 15 422 subjects we excluded pregnant women ($n = 83$), those with a technically unacceptable or non-reproducible forced expiratory volume in 1 s (FEV₁) measurement ($n = 1493$) and those with missing values for one or more potential confounders ($n = 187$). Thus, the final study population consisted of 13 651 subjects.

Methods

The general questionnaire contained questions on demographic variables and presence of (risk factors for) chronic diseases. The second questionnaire was a semiquantitative

food frequency questionnaire, developed for the MORGEN study which is part of the EPIC study (European Prospective Investigation into Cancer and Nutrition) [21–23]. The habitual consumption of 178 food items during the last year was estimated and alcohol and energy intake calculated using the 1996 Dutch food composition table [24]. The physical examination included measurement of weight, height and pulmonary function.

Questions on respiratory symptoms were selected from the Dutch part of the European Community Respiratory Health Survey [25,26]. The presence of COPD symptoms was defined as having one or more of the following symptoms: chronic cough (= cough during winter time on most days for at least 3 months a year), chronic phlegm (= productive cough during winter time on most days for at least 3 months a year) or breathlessness (= shortness of breath when walking on level ground with people of the same age).

Pulmonary function measurements were performed by trained paramedics using a heated pneumotachometer (Jaeger, Würzburg, Germany). Subjects were measured in a sitting position while wearing a nose clip. Subjects had to achieve at least three technically acceptable manoeuvres for measuring the FEV₁, of which two had to be reproducible according to European Respiratory Society (ERS) criteria [27]. The maximum value of the reproducible manoeuvres was used in the analysis.

Height (precision 0.5 cm) and weight (precision 0.1 kg) were measured and the body mass index (BMI) calculated (weight/height²). Pack years of cigarette smoking were calculated as the product of the number of years smoked and the average number of cigarettes smoked per day, divided by 20. Educational level was categorized into: low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education) and high (higher vocational or university education). Physical activity was categorized into insufficient = moderate or heavy activity < 3.5 h a week, and sufficient = moderate and heavy activity > 3.5 h a week of which at least 2 h is of heavy activity [28].

Statistical analysis

All analyses were performed using the SAS statistical package (version 6.12, Cary, NC, USA). To study the relation between the FEV₁ and dietary factors, a multiple linear regression model with FEV₁ divided by height squared as the dependent and age, age squared and gender as independent variables was used [6]. The results are presented in its original scale (mL) for a standard height of 1.70 m. Logistic regression analysis was used to study the associations between COPD symptoms and dietary factors. Age, gender, height (for pulmonary function only), pack

years of smoking, BMI and energy intake were considered to be potential confounders.

Fruit consumption also included consumption of fruit juices. Vegetable intake did not include intake of potatoes and legumes. Whole grain intake was defined as intake of wholemeal bread, rye bread and unrefined grains (e.g. brown rice).

First, for each food the association with COPD was studied: crude, adjusted for potential confounders and additionally adjusted for the other foods (independent association). The number of alcohol drinks consumed was categorized into three levels: none or occasional (≤ 1 per week), low (> 1 per week and ≤ 3 per day) and moderate or heavy (> 3 per day). A drink was assumed to contain 10 g of alcohol. Expressed in grams of alcohol consumed per day: level 1 = ≤ 1 , level 2 = 1–30 and level 3 = > 30 g/day. Fruit(juices), vegetable, fish and whole grain intake was divided into quartiles. The adjusted average FEV₁ and prevalence of COPD symptoms was calculated per category of food intake using PROC GLM (option LSMEANS). To adjust for alcohol consumption two dummy variables (1: none vs. low; 2: moderate or higher vs. low) were added to the adjusted models. Fruit, vegetable, fish and whole grain intake were modelled as continuous variables when adjusted for.

Subsequently, additivity of the effects of foods independently associated with COPD was assessed. For this purpose food intake was dichotomized (favourable vs. unfavourable) based on the previous analyses and smoothed spline-plots. For each combination of two foods the joint effect of the foods was compared with the effect expected from the additive effects of the individual foods [29]. That is, subjects with unfavourable intakes of both foods (reference) were compared with subjects with a favourable intake of either one food (individual effects) or both foods (joint effect) and the sum of the two individual effects compared with the observed joint effect. Furthermore, the difference in pulmonary function and prevalence of COPD symptoms between subjects with favourable intakes of all foods independently associated with COPD and subjects with unfavourable intakes of these foods was estimated.

Adjustment for several lifestyle factors (i.e. physical activity level, educational level and nationality) did not cause a relevant change in the studied associations and these factors were therefore not included in the final analysis. Excluding the subjects that had used vitamin supplements daily in the last 12 months (13% of the study population) had no effect on the reported associations; therefore results of the total study population are presented.

Finally, to assess potential residual confounding by cigarette smoking, the main analyses were repeated in those who had, and those who had never smoked separately.

Results

The characteristics of the study population are described in Table 1. Pack years of smoking was inversely associated with the FEV₁ ($\beta = -7.6$ mL/pack year, $P < 0.001$) and positively associated with the prevalence of COPD symptoms (OR = 1.03 per pack year, $P < 0.001$), after adjustment for age, height (for FEV₁ only), gender, BMI and energy intake.

After adjustment for potential confounders, intake of fruit(juices), vegetables and whole grains was positively associated with the FEV₁ and inversely associated with the prevalence of COPD symptoms (Table 2). Fish intake was not associated with COPD. The adjusted FEV₁ was lower in non-drinkers compared with drinkers. The prevalence of COPD symptoms, however, was lower in subjects with a low alcohol consumption (1–30 g/day) compared with both non-drinkers and those with a moderate or heavy alcohol consumption (Table 2).

After additional adjustment for the other four foods, the associations of fruit(juices), whole grains and alcohol with COPD remained largely unchanged (Table 2). For vegetable intake the association with both the FEV₁ and COPD symptoms disappeared, while fish intake showed a weak inverse association with pulmonary function after adjustment for the effects of the other foods (Table 2).

To study the combined effects of fruit (juices), whole grains and alcohol on COPD, a favourable intake of fruit (juices) was defined as an intake > 180 g/day and a favourable intake of whole grains as > 45 g/day. Alcohol consumption was dichotomized into low (favourable) vs. other (= none, moderate or heavy). Figure 1a shows that the effects of a favourable vs. an unfavourable intake of the three foods on pulmonary function were largely additive. For instance, compared with subjects with an unfavourable intake of fruit(juices) and whole grains (f-wg = reference group), subjects with a favourable intake of fruit(juices) and an unfavourable intake of whole grains (F-wg) had a 45 mL higher FEV₁. In subjects with a favourable intake of whole grains and an unfavourable intake of fruit(juices) (f-WG) the FEV₁ was 63 mL higher. Finally, in the group with a favourable intake of both foods (F-WG) the FEV₁ was 101 mL higher compared with the reference group. The joint effect (101 mL) was only marginally smaller than the sum of the individual effects ($45 + 63 = 108$ mL). The effects of fruit(juices) and alcohol and of alcohol and whole grains were also observed to be largely additive (Fig. 1a). Similar results were observed for COPD symptoms (Fig. 1b).

In subjects with a favourable intake of fruit(juices), whole grains and alcohol, the FEV₁ was observed to be 139 mL higher and the prevalence of COPD symptoms lower (OR = 0.44) than in subjects with unfavourable

Table 1. Characteristics of the study population (the MORGEN study)

Variable	Unit	Total <i>n</i> = 13 651		Ever smoked <i>n</i> = 9072		Never smoked <i>n</i> = 4579	
		Mean	SD	Mean	SD	Mean	SD
Age	years	41.2	10.8	42.4	10.2	38.7	11.5
Height	m	1.72	0.09	1.72	0.09	1.72	0.10
BMI	kg/m ²	24.9	3.9	24.9	3.8	24.8	4.0
Smoking	Pack years	10.3	13.8	15.5	14.4	–	–
Energy intake	MJ/day	9.5	2.9	9.6	2.9	9.4	2.9
Fruit(juices)	g/day	248	176	235	170	275	183
Vegetables	g/day	128	53	128	53	128	52
Fish	g/day	9	10	9	10	9	10
Whole grain products	g/day	69	74	68	73	73	77
Alcohol	g/day	13	17	15	19	8	12
FEV ₁	mL	3586	848	3540	838	3676	861

Variable	Category	%	%	%
COPD symptoms*	Yes	16	18	11
Gender	Males	46	47	43
Alcohol consumption	Low	64	64	63
Physical activity	Sufficient	60	58	63
Educational level	Low	44	48	36
Nationality	Dutch	97	97	97

*One or more of following symptoms: chronic cough, chronic phlegm, breathlessness.

intakes of the three foods (Table 3). When stratified according to smoking status the combined effect of the three foods was somewhat smaller in those who had never smoked compared with those who had (Table 3). However, this difference was not statistically significant (interaction-term: $P > 0.40$).

After adjustment for the effects of the other foods, the association of alcohol with COPD was in both those who had smoked and those who had never smoked similar to that given in Table 2 for the total study population. For fruit and whole grain intake, however, the independent association with both the FEV₁ (Fig. 2) and COPD symptoms (results not shown) was somewhat stronger in those who had never smoked than in those who had.

Discussion

Our cross-sectional study showed independent beneficial associations of fruit(juices), whole grains and alcohol with COPD. The effects of a favourable intake of fruits (> 180 g/day), whole grains (> 45 g/day) and alcohol (1–30 g/day) were observed to be largely additive. In subjects with a favourable intake of the three foods

($n = 2998$), the FEV₁ was 139 mL higher and the prevalence of COPD symptoms lower (OR = 0.44) than in subjects ($n = 1406$) with unfavourable intakes of fruit(juices), whole grains and alcohol ($P < 0.001$). Similar, although generally slightly weaker, associations were observed in those who had never smoked. Fish and vegetable intake did not show independent beneficial associations with COPD.

Earlier, data from the MORGEN study were used to study intake of dietary antioxidants (vitamin C, vitamin E and β -carotene) in relation to COPD. A high intake of vitamin C and β -carotene was observed to be positively associated with pulmonary function [6]. Dietary intake of a nutrient is increased by consuming foods rich in this nutrient. However, foods always contain a variety of nutrients and other substances. Since interaction between the different substances may influence the biological effect of a food, it is important to study diet in relation to COPD at the food or food group level as well. Furthermore, knowledge of the effects of foods, instead of nutrients, is of more use for nutritional education. To avoid multiple testing, only foods that had been observed to be related to COPD in earlier studies and/or foods for which a biological

Table 2. The cross-sectional association of individual foods with COPD-related outcomes: crude, adjusted for potential confounders and additionally adjusted for the effects of the other foods (the MORGEN study)

	Intake (g/day)		FEV ₁ (ml)			COPD symptoms (%)		
			Crude	Adj. ¹	Adj. ²	Crude	Adj. ¹	Adj. ²
<i>Fruit(juices)</i>	Mean	Max.						
Quartile 1	73	125	3395	3423	3428	20.5	19.2	18.9
Quartile 2	166	216	3452	3452	3451	15.7	15.9	16.0
Quartile 3	269	331	3506	3494	3493	13.4	14.0	14.2
Quartile 4	485	2078	3491	3474	3471	13.6	13.9	14.1
<i>P-trend</i>			***	***	***	***	***	***
<i>Vegetable</i>	Mean	Max.						
Quartile 1	69	91	3425	3434	3443	17.6	17.7	17.1
Quartile 2	106	120	3465	3464	3467	15.0	15.2	15.0
Quartile 3	136	155	3481	3478	3475	14.2	14.2	14.4
Quartile 4	199	562	3472	3467	3459	16.3	16.0	16.7
<i>P-trend</i>			***	**	—	—	*	—
<i>Whole grains</i>	Mean	Max.						
Quartile 1	2	5	3407	3421	3428	18.9	17.7	17.3
Quartile 2	20	45	3436	3437	3438	17.1	17.3	17.2
Quartile 3	81	115	3491	3488	3483	14.3	14.7	15.0
Quartile 4	175	919	3509	3498	3495	12.9	13.4	13.7
<i>P-trend</i>			***	***	***	***	***	***
<i>Fish</i>	Mean	Max.						
Quartile 1	1	3	3463	3471	3479	16.6	16.3	16.0
Quartile 2	4	7	3449	3452	3453	14.9	14.9	14.8
Quartile 3	9	12	3467	3463	3460	15.3	15.5	15.7
Quartile 4	21	162	3464	3458	3452	16.4	16.4	16.7
<i>P-trend</i>			—	—	*	—	—	—
<i>Alcohol</i>								
Level 1 (<i>n</i> = 3206)	≤1		3410†	3407†	3407†	18.1†	18.2†	18.3†
Level 2 (<i>n</i> = 8670)	> 1, ≤ 30		3485	3476	3475	13.5	14.3	14.4
Level 3 (<i>n</i> = 1775)	> 30		3435†	3484 ^{NS}	3491 ^{NS}	22.8†	18.5†	18.0†

****P*-trend < 0.001; ***P*-trend < 0.01; **P*-trend < 0.05; —, *P*-trend ≥ 0.05; †compared with level 2: *P* < 0.001; NS compared with level 2: *P* ≥ 0.05.

Crude, FEV₁: adjusted for age, height and gender; COPD symptoms: crude.

Adj.¹, Adjusted for age, height (for FEV₁ only), gender, pack years of smoking, BMI and energy intake.

Adj.², Adjusted for potential confounders and the other four foods: alcohol consumption (dummies for none vs. low and for moderate or higher vs. low alcohol consumption) and/or fruit, vegetable, whole grain and fish intake (continuous variables) were added to the adjusted model.

mechanism of action was available, were included in the analyses.

Antioxidants and foods rich in antioxidants, like fruits and vegetables, are thought to protect the airways against oxidant-mediated damage leading to COPD. In the literature there is reasonably consistent evidence for an association between fruit intake and COPD-related outcomes [8–13], but less so for vegetable intake [9,12–14]. This may partly be explained by the low relative validity of dietary assessment methods for measuring vegetable intake

[22,30]. Furthermore, a large part of the vegetables is usually consumed boiled, which leads to loss of vitamin C.

As hypothesized, we observed a beneficial association between whole grain consumption and COPD, which may be due to the antioxidant components of whole grains (e.g. vitamin E, phenolic acids and phytic acid) [31]. The observed beneficial association of a low alcohol consumption with COPD is consistent with earlier findings [9,19,20]. Whether this effect is caused by a direct effect of alcohol or by a confounding effect of ill health among

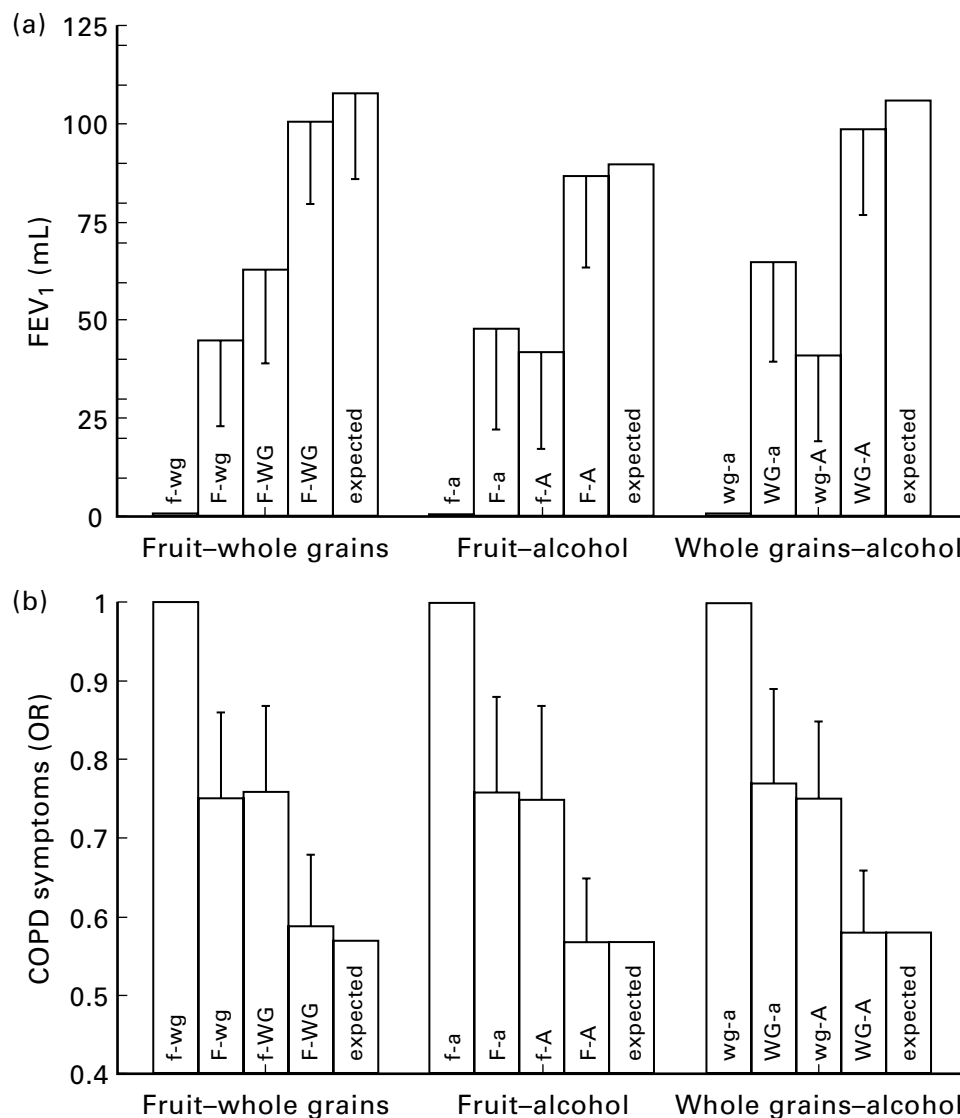


Fig. 1. Additive effects of a favourable vs. an unfavourable intake of fruit(juices) and whole grains, of fruit(juices) and alcohol, and of whole grain and alcohol (the MORGEN study). Favourable intake: F = fruit(juices) > 180 g/day; WG = whole grains > 45 g/day; A = low alcohol consumption (1–30 g/day). Unfavourable intake: f = fruit(juices) ≤ 180 g/day; wg = whole grains ≤ 45 g/day; a = none, moderate or heavy alcohol consumption (≤ 1 or > 30 g/day).

ex-drinkers [32] or by differences in other characteristics between the men in the different categories of alcohol consumption, remains to be clarified. A direct protective effect of alcohol is possible, since various inhibitory effects of alcohol on inflammatory cells have been described [33–36]. Inflammation of the peripheral airways, mainly initiated by inhaled oxidants and free radicals, is one of the main processes in the pathogenesis of COPD. Finally, the lack of an association between fish intake and COPD may be explained by the low level of fish consumption in the Dutch population. The results of earlier studies, that

observed a higher fish consumption, are not conclusive [9,12,13,15–18].

Two important issues when evaluating the observed effects of fruits, whole grains and alcohol are whether the required intake is practically feasible and whether the associated effects are relevant. The definition of a favourable intake used—fruit(juices) > 180 g/day, whole grain products > 45 g/day and low alcohol consumption—is comparable to the Dutch recommendations regarding a healthy diet. This suggests that such an intake can indeed be achieved by a large part of the Dutch population.

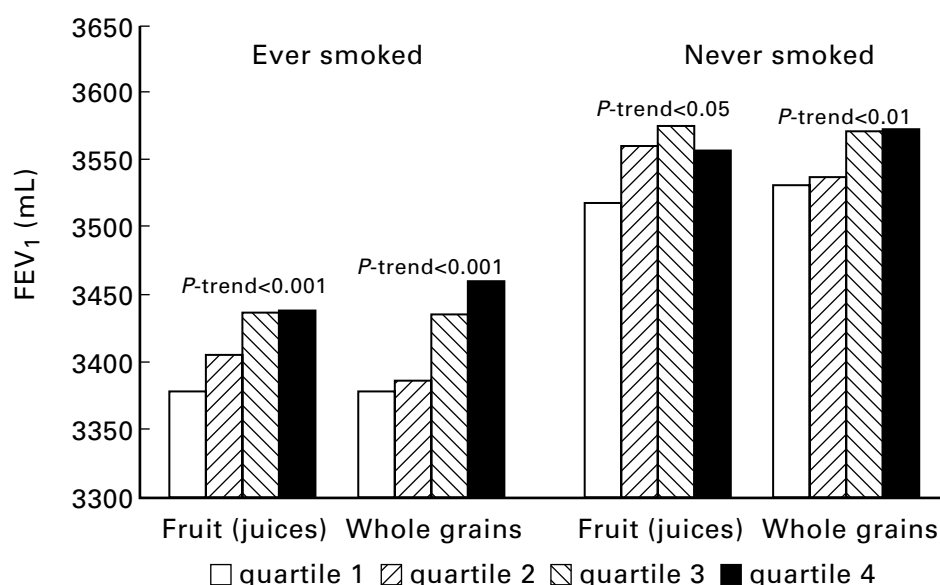


Fig. 2. The independent effect of fruits and whole grains on pulmonary function in those who had smoked and those who had never smoked: adjusted* mean forced expiratory volume in 1 s (FEV₁) per smoking status specific quartile of intake† (the MORGEN study). *Adjusted for age, height, gender, pack years of smoking, BMI, energy intake, alcohol consumption (dummies for none vs. low and for moderate or higher vs. low alcohol consumption), vegetable, fish and whole grain or fruit intake. †Fruit (g/day): those who had smoked q1 < 117, q2 < 199, q3 < 316, q4 < 1724; those who had never smoked q1 < 145, q2 < 246, q3 < 368, q4 < 2078. Whole grains (g/day): those who had smoked q1 < 5, q2 < 42, q3 < 110, q4 < 919; those who had never smoked q1 < 6, q2 < 50, q3 < 125, q4 < 512.

Furthermore, the observed effect on pulmonary function (139 mL in FEV₁) is roughly equivalent to the effect of ageing 5 years or to the effect of smoking one pack of cigarettes per day for 20–25 years [37]. The effect of dietary factors on COPD therefore does involve an important public health impact.

Another important finding of our study is that also in those who had never smoked a beneficial effect of fruits, whole grains and alcohol on pulmonary function and

COPD symptoms was observed. Thus, residual confounding by smoking can not explain the observed effect of diet on COPD totally. It may partly explain the fact that in those who had smoked the observed associations were somewhat stronger, at least with regard to fruit and whole grain intake. Smokers are known to consume less fruits, vegetables and whole grain products and to have lower intakes of vitamin C and β -carotene [38].

Finally, the following methodological concerns need to

Table 3. Difference in FEV₁ and in the prevalence of COPD symptoms between subjects with favourable* vs. unfavourable† intakes of fruit(juices), whole grains and alcohol (the MORGEN study)

	<i>n*/n†</i>	Favourable* vs. unfavourable† intakes of fruit(juices), whole grains and alcohol	
		Difference in FEV ₁ (ml) adjusted‡ (95% CI)	COPD symptoms (OR) adjusted‡ (95% CI)
Total population	2998/1406	139 (108–170)	0.45 (0.38–0.54)
Ever smokers	1888/1023	147 (109–185)	0.44 (0.35–0.54)
Never smokers	1110/383	118 (64–172)	0.53 (0.37–0.76)

*Favourable: for fruit(juices): > 180 g/day; for whole grains: > 45 g/day; for alcohol: low consumption (1–30 g/day).

†Unfavourable: for fruit(juices): ≤ 180 g/day; for whole grains: ≤ 45 g/day; for alcohol: none, moderate or heavy consumption (≤ 1 or > 30 g/day).

‡Adjusted for potential confounders: age, gender, height (for FEV₁ only), pack years of smoking, BMI and energy intake.

be addressed. First, in this cross-sectional study it is not possible to discriminate between a causal relation between dietary factors and COPD and a non-causal association introduced by the fact that people with (symptoms of) COPD changed their diet. However, subjects with COPD symptoms are most likely to change their diet towards a diet that is generally considered to be healthy (i.e. a high intake of fruits, and whole grains and moderate alcohol consumption), causing a dilution of observed associations. A change in diet as a consequence of disease processes is only likely in severe cases of COPD and therefore in a population study, such as ours, less relevant. Also, in a longitudinal study a protective effect of dietary factors on COPD-related outcomes was observed [9]. It is possible that subjects with COPD symptoms have reported their diet differently from symptom-free individuals (information bias). The direction, and therefore the consequence, of such a bias is unclear. Furthermore, selection towards subjects with a better pulmonary function may have occurred, since failure to perform an adequate pulmonary function measurement may be an indicator of impaired respiratory health [39]. However, only minor differences in intake of the studied foods were observed between those with and those without technically acceptable and reproducible FEV₁ measurement (results not shown). Therefore this potential selection is not likely to have influenced the observed associations. Finally, confounding by health-related life-style factors, such as physical activity and educational level, did not explain our results. Residual confounding by other, unmeasured factors remains possible.

In conclusion, we observed independent beneficial associations of fruit, whole grain and alcohol intake with COPD that were largely additive. Since these effects were also observed in those who had never smoked, residual confounding by smoking could not explain our findings totally.

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