Epidemiological studies on the relation between diet and COPD

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Stellingen

1. Een hoge fruitinname is invers geassocieerd met het voorkomen/optreden van COPD. *(dit proefschrift).*

2. Recent epidemiologisch onderzoek bevestigt het gepostuleerde beschermende effect van het eten van vis tegen COPD niet. *(dit proefschrift)*

3. De waargenomen associaties tussen voedingsfactoren en COPD kunnen niet volledig worden verklaard door effecten van roken. *(dit proefschrift)*

4. De bevindingen van dit promotieonderzoek naar voeding en COPD ondersteunen de huidige Nederlandse richtlijnen voor een gezonde voeding. *(dit proefschrift)*

5. Het ontbreken van een statistische methode om op een valide manier groepen mensen met verschillende voedingspatronen te onderscheiden, is een belangrijke beperking van huidig epidemiologisch onderzoek naar de relatie tussen voeding en chronische ziekten.

6. Bij het reviewen van artikelen voor wetenschappelijke tijdschriften zou de identiteit van de auteurs bij de reviewers onbekend moeten zijn.

7. "Beestachtig" gedrag is niet *on*menselijk.
   (denk aan ex-Joegoslavië, Liberia, Ruanda, Tsjetsjenië...)

8. Het is onterecht dat intelligent werk zoveel meer gewaardeerd en beter beloond wordt dan (emotioneel) zwaar, vies of eentonig werk.

9. Eigen-wijsheid is een goede eigenschap, zeker voor een onderzoeker.

Stellingen behorend bij het proefschrift 'Epidemiological studies on the relation between diet and COPD' van Cora Tabak. Wageningen, 24 mei 2000

Abstract

Epidemiological studies on the relation between diet and COPD

Ph.D. thesis. Nat. Inst. of Public Health and the Environment in Bilthoven, Environmental and Occupational Health Group of the Univ. Utrecht (address till mid 2000: Wageningen Univ.) and the Netherlands Inst. of Health Sciences, Rotterdam, the Netherlands.

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Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality around the world. In the early 1990's several dietary factors were suggested to protect against COPD, based on proposed biological mechanisms and a small number of epidemiological studies. Antioxidants (e.g. vitamin C and E, ß-carotene, flavonoids) and foods rich in antioxidants (e.g. fruits, vegetables, whole grains) may protect the airways against oxidant-mediated damage. Alcohol and n-3 fatty acids (mainly present in fish) are thought to have anti-inflammatory effects.

To gain more insight into the relation between diet and COPD, we analysed data from two large-scale population-based epidemiological studies. Data from the Seven Countries Study (1960-1990) allowed us to study the relation longitudinally in an international setting. However, less sophisticated methods than available today were used to examine mainly ever-smoking middle-aged and older men. In the cross-sectional MORGEN-study (1993-1997), Dutch men and women (20-59 yr.) with a large variation in smoking habits were examined using modern, high-quality methods. All associations were adjusted for age, height (for pulmonary function only), gender, smoking, body mass index and total energy intake.

In the 16 cohorts of the Seven Countries Study, we observed an inverse ecological association of 25-yr COPD mortality with baseline fruit and fish consumption. At the individual level, not energy-adjusted baseline fruit and vitamin E intake were inversely associated with 20-yr COPD mortality in men from three European countries. Alcohol consumption showed a U-shaped curve with 20-yr COPD mortality, with the lowest rate in light drinkers (>1.4, ≤30 g/day). This U-shaped curve was supported by cross-sectional data on alcohol and pulmonary function. In all three countries, men with intake of both fruits and vegetables above the median had a higher pulmonary function (FEV_1 or $FEV_{0.75}$) than those with a low intake of both foods. Finally, bread intake was positively associated with pulmonary function in the three countries.

In participants of the MORGEN-study, intake of catechins, flavonols and flavones was positively associated with the FEV_1 and inversely associated with the prevalence of chronic cough and breathlessness. Catechin intake, not derived from tea, was independently associated with both the FEV_1 and all studied COPD symptoms. Flavonol and flavone intake, however, was independently associated with chronic cough only. At the food group level, solid fruit (=apples, pears), but not tea, intake was beneficially associated with COPD. Furthermore, we observed independent beneficial associations of a favourable intake of fruits and whole grains (above the median) and alcohol (1-30 g/day) with COPD. The 2578 subjects with a favourable intake of all three foods had a 139 ml higher FEV_1 and a lower prevalence of COPD symptoms (OR = 0.44) compared to those with unfavourable intakes of the three foods. This was also observed in never smokers.

The studies described in this thesis mainly suggest a protective effect of a high intake of fruits and whole grains and of light alcohol consumption (up to 3 drinks/day) against COPD. Causality of the observed relations is supported by an apparently temporal relation and by plausible biological mechanisms. Smoking did not seem to explain our findings. Confounding by other health related lifestyle factors can, however, not be excluded. The observed effect of dietary factors was estimated to reduce COPD with 10 to 30% at the population level and is, if causal, certainly of public health relevance.

Contents

Chapter 1

General Introduction

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality around the world. COPD rates may decrease in the coming decades due to a decreasing prevalence of smoking since the 1960's. However, at the moment rates are still rising, especially in women and very old men. In the early 1990's several dietary factors were suggested to be related to COPD, based on proposed biological mechanisms of action and a small number of epidemiological studies. The PhD-project described in this thesis, was designed to gain more insight in the potential protective effect of diet on COPD. In the general introduction first a description will be given of COPD (definition, pathogenesis, risk factors, diagnosis and occurrence) and of the biological mechanisms for the proposed effects of dietary factors. Secondly an outline of the thesis will be given.

COPD

Definition

COPD is a disease state characterised by chronic airway obstruction. Three disorders incorporated and often co-existing in COPD are: chronic bronchitis, small airways disease (also called chronic bronchiolitis) and emphysema.[1] Chronic bronchitis is characterised by chronic or recurrent hypersecretion of mucus in the large airways[2] caused by enlargement of subepithelial glands and leading to symptoms of chronic productive cough.[1] Chronic bronchitis, thus defined, contributes little to airway obstruction. Small airways disease is mainly characterised by inflammatory processes leading to obstruction of peripheral airways with a diameter smaller than 2 to 3 mm.[1,3] Finally, emphysema is defined as permanent abnormal enlargement of airspaces distal to terminal bronchioles (also called parenchym destruction), with destruction of their walls and without obvious fibrosis.[4] There are indications that small airways disease is involved in the development of centrolobular emphysema, one of the main subtypes of emphysema.[5] Both small airways disease and emphysema cause chronic airway obstruction that is slowly progressive and largely irreversible.

Pathogenesis

The pathogenesis of COPD is complex. A large number of cells (macrophages, lymphocytes, platelets, mast cells, neutrophils, eosinophils, fibroblasts, epithelial and endothelial cells) and their secretions are involved, Although insight into the different pathological processes leading to COPD increases rapidly, much is still unclear. Inflammation of the peripheral airways, mainly initiated by inhaled oxidants and free

radicals, is one of the main processes. During inflammation, inflammatory cells (e.g. macrophages, neutrophils, mast cells) become activated and produce reactive oxygen species and inflammatory mediators, such as histamine, prostaglandins and leukotrienes.[6] Many inflammatory mediators have chemotactic activity causing the influx of more inflammatory cells into the lungs.[6] As will be discussed later, several dietary factors are thought to protect against oxidant-mediated damage and/or to reduce airway inflammation.

Risk factors

Patients with COPD usually have smoked cigarettes for 20 years or more.[7] Cigarette smoke contains many oxidants and free radicals that can cause direct damage to the pulmonary tissue. Indirectly, cigarette smoking may lead to oxidative damage through reactive oxygen species generated by accumulated and activated inflammatory cells.[8] Besides smoking, occupational exposure and α_1-antitrypsin deficiency are known risk factors for COPD.[9] A potential protective effect on COPD has been suggested for a high intake of dietary antioxidants, fish fatty acids and light alcohol consumption (see further).

Diagnosis

COPD is often diagnosed late in the course of the disease. Patients seek medical attention when they start to experience breathing difficulties. By that time moderate-to-severe airflow limitation can often be observed.[9] To diagnose and assess the severity of COPD, measurement of the Forced Expiratory Volume in one second (FEV_1) by spirometry is recommended.[7] Chest radiography can be diagnostic of severe emphysema and is recommended in order to rule out other diseases.[7]

Occurrence

COPD rates vary strongly between countries.[9] Data from the WHO[10] regarding mortality from asthma and COPD in 1994/1995 in men and women aged 65-74 years show that rates were lowest in Greece, Canada, France and Spain (< 50 per 100.000) and highest in Russia and Hungary and Poland (>200 per 100.000), with the Netherlands, the US and the UK taking intermediate positions. In all countries, the rates were higher in men than in women. The contribution of asthma to the mortality rates is likely to be low in this age-range.

Current COPD mortality and morbidity rates are a reflection of smoking behaviour 20 to 40 years ago.[11] Since the 1960's COPD rates are rising throughout the world, due to the fact that many men and women started smoking during and after World War II. Since the 1960's the prevalence of smoking has decreased. However, the

decrease was smaller in women than in men and no change was observed in those over 65. As a consequence, an increase in COPD mortality rates is mainly observed in women and in very old men, while in some countries the rates seem to level off or even decrease among younger men.[11-14]

In the Netherlands, in 1994, diseases of the respiratory system were the third largest cause of death (8%). In both men and women, COPD mortality increased between 1979 and 1994. Standardised to the total Dutch population, the COPD mortality rate increased in this period from ± 13 to ± 24 per 100.000 per year in women. In men the rate increased from ± 42 per 100.000 in 1979 to ± 59 per 100.000 in 1989, after which the COPD mortality levelled off.[15]

Table 1: Prevalence (per 1000) of reduced pulmonary function and selected COPD symptoms in the Netherlands (Source: ELON, 1996)[16]

	prevalence per 1000 age (years)			
	30-39	40-49	50-59	60-69
Reduced FEV_1 (< 70% of predicted)				
men	12	18	48	110
women	4	14	19	42
Chronic cough when getting up				
men	89	110	140	160
women	92	130	130	120
Chronic phlegm when getting up				
men	85	110	130	170
women	29	95	140	92
Breathlessness when walking at own pace				
men	17	22	20	65
women	19	52	50	40

The prevalence of pulmonary function clearly below reference levels (FEV_1 < 70% of predicted) in the Netherlands in 1996 increased with age and was higher in men than in women. The prevalence of COPD symptoms was similar in men and women, but increased with age in men and not in women (table 1).

Biological mechanisms for the proposed effects of dietary factors

Antioxidants

In the lungs several intracellular and extracellular antioxidant defence mechanisms protect the tissues against oxidant-mediated damage. Free radical scavenging systems either eliminate oxidants or prevent their conversion into more

toxic species. Dietary factors involved in these systems are the antioxidant (pro)-vitamins vitamin E, ß-carotene and vitamin C and cofactors of antioxidant enzyme systems, such as selenium.[17] Vitamin E or α-tocopherol (α-TH) is a lipid soluble antioxidant that occurs in membranes and lipoproteins. It terminates the chain reaction of lipid peroxidation by scavenging oxygen radicals and intermediate peroxyl radicals ($RO_2\cdot$) :

$$\alpha\text{-TH} + RO_2\cdot \quad \text{---}> \quad RO_2H + \alpha\text{-T}\cdot$$

The α-tocopherol radical (α-T·) is much less reactive in oxidising polyunsaturated fatty acids[18,19] and can be converted back to α-tocopherol by vitamin C.[20,21] The main dietary sources of vitamin E are vegetable oils, seeds, nuts, whole grains and wheat germ.[22] β-carotene, the main carotenoid with provitamin A activity, is also present in tissue membranes.[17] It acts as a scavenger of singlet oxygen and reacts with peroxyl radicals to inhibit lipid peroxidation, possibly in synergistic interaction with vitamin E.[23] The green outer layers of vegetables are good sources of ß-carotene just as yellow and red fruits and vegetables.[24]

Vitamin C or ascorbic acid is water-soluble and widely available in both extracellular and intracellular fluids. Vitamin C can protect biomembranes from lipid peroxidation either directly by scavenging oxygen and peroxyl radicals or indirectly by the regeneration of α-tocopherol. [23,25] However, also pro-oxidant properties of ascorbic acid have been reported.[17] Fresh fruits and green leafy vegetables are rich sources of vitamin C.[24]

Selenium is a cofactor of the glutathione redox cycle. This is an important reducing mechanism for intracellular hydroperoxides, such as hydrogen peroxide (H_2O_2). The key enzyme in the redox cycle is glutathione-peroxidase, a tetrameric protein with four atoms of selenium.[17] Copper, zinc and manganese are cofactors of a group of intracellular metaloenzymes called superoxide dismutases. These enzymes catalyse the dismutation of the superoxide anion ($O_2\cdot$-) into hydrogen peroxide, which can subsequently be reduced by catalase or peroxidases into non-toxic substances.[17] Rich sources of selenium are fish, meat and grains.[24]

Plant foods that contain the mentioned antioxidant nutrients, such as fruits, vegetables and grains, also contain non-nutrients like flavonoids.[26-28] The flavonoids comprise of a large group of polyphenols (over 4000 different flavonoids have been identified) that can be categorised into: flavonols, flavones, catechins, anthocyanidins, flavanones and isoflavonoids. Some flavonoids have been observed to be potent antioxidants.[26,27] However, flavonoids are also known to inhibit the

production of oxygen radicals, leukotrienes, prostaglandins and other pro-inflammatory mediators by activated inflammatory cells.[26] Both the antioxidant and the anti-inflammatory activities of flavonoids may help to prevent COPD. The main dietary sources of flavonoids are tea, fruits and vegetables.[26]

N-3 fatty acids

Fish oils are rich in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A high intake of EPA and DHA is thought to have anti-inflammatory effects in the lungs, because of the influence of these fatty acids on the arachidonic acid metabolism (see figure 1).

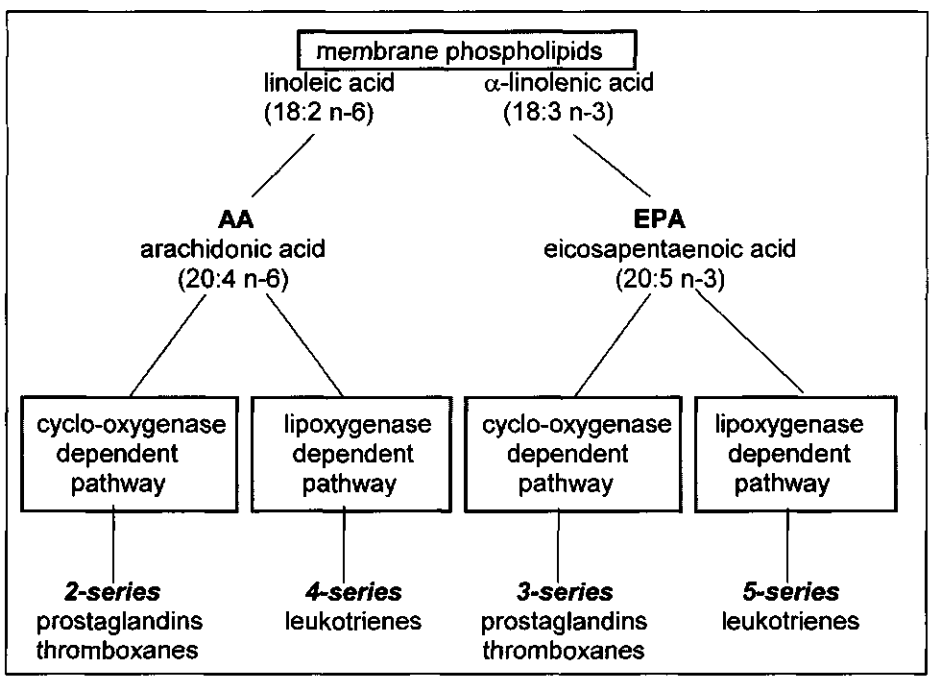

Figure 1: The role of n-3 and n-6 fatty acids in eicosanoid production

Arachidonic acid (AA), a n-6 fatty acid, is present in the phospholipid layer of cell membranes. Under Western dietary conditions, it is the major precursor fatty acid of pro-inflammatory mediators called eicosanoids. Eicosanoids is a collective term for prostaglandins (PG, thromboxanes and leukotrienes (LT). As shown in Figure 1 arachidonic acid derived eicosanoids are from the 2- and 4-series (e.g. PGE2 and LTB4).

A diet rich in fish(oils) has been shown to increase the EPA and DHA content of the membrane phospholipids.[29,30] Under these conditions, EPA and DHA may competitively inhibit the use of arachidonic acid as a substrate for eicosanoid production. Eicosanoids derived from EPA are of the 3- and 5-series (e.g. PGE3 and LTB5).

Since eicosanoids of the 3- and 5- series are biologically less active and thus have a diminished pro-inflammatory capacity compared to eicosanoids from the 2- and 4-series, a high intake of EPA and DHA may reduce airway inflammation.[31-33]

Alcohol

Several inhibitory effects of alcohol on inflammatory cells have been observed. Alcohol has been observed to inhibit PMN delivery to inflammatory sites[34,35] in a dose-dependent manner,[34] possibly by diminishing the required adherence of these cells to the endothelium.[35] Reduced production of TNF by macrophages, known to stimulate PMN adhesion to endothelial cell surfaces, may be involved in this process. Acute alcohol intoxication, was observed to reduce TNF concentrations in lung fluid after bacterial challenge.[36] Both chronic alcoholism and mild intoxication have furthermore been observed to decrease the production of eicosanoids,[37,38] possibly through an inhibiting effect on cyclo-oxygenase and lipoxygenase[38] (see figure 1).

More research is needed to establish whether alcohol consumption suppresses airway inflammation in a dose-dependent way. If so, low alcohol consumption may be beneficial by reducing airway inflammation, while heavy alcohol consumption may be detrimental by suppressing inflammatory and immune processes to such an extent that the defence mechanisms of the lungs are compromised.

This thesis

Rationale

Epidemiological findings of a potential protective effect of dietary factors on COPD in the early 1990's led to the start of this PhD-project in 1994. Beneficial associations with COPD related outcomes had been observed for vitamin C[39], fruits[40,41] and n-3 fatty acids.[42-44] However, also negative findings had been reported for vitamin C,[40,45] ß-carotene,[40] vegetables[40,45] and fish.[40] Alcohol consumption has been studied in relation to COPD since the late 1960's. Early observations indicated that heavy alcohol consumption might have deleterious effects on the lungs, mainly on the basis of studies in alcoholics.[46-48] Indications for a beneficial effect of low alcohol consumption were also observed.[40,49,50]

Aim and global operationalisation

The aim of this thesis was to gain more insight into the potential protective effect of diet on COPD. Studied in relation to COPD were: intake of n-3 fatty acids, vitamin C, vitamin E, ß-carotene and/or flavonoids as well as consumption of alcohol, fruits, vegetables, whole grains and fish. The choice of these dietary factors was based on the presence of a plausible biological mechanism of action and/or previous epidemiological findings (see earlier) and on the availability of data on intake of these dietary factors from two large scale population-based epidemiological studies: The Seven Countries Study and the MORGEN-study.

Data from the Seven Countries Study allowed us to study the longitudinal association between baseline diet and long-term COPD mortality (up to 25 years) in an international setting. Furthermore, in three countries the cross-sectional association between diet and pulmonary function could be studied. The Seven Countries Study was designed to investigate primarily cardiovascular diseases. Since pulmonary function is an important risk factor for cardiovascular diseases, every effort was made to measure pulmonary function as accurately as possible. However, the baseline and 5 and 10-year follow-up measurements were performed between 1960 and 1970 with less sophisticated methods than available today and only middle-aged and older men were examined with a very large proportion of smokers.

The MORGEN-study (1993-1997) was designed to examine risk factors for chronic diseases, including COPD, in the Dutch population. A large number of men and women over a wide age-range (20-59 years) were examined using modern high-quality methods to determine diet, pulmonary function and a large number of potential confounding variables. Furthermore, there was a large variation in smoking habits in the study population, which contained a substantial number of never smokers. An important limitation compared to the Seven Countries Study was, however, its cross-sectional design.

Outline

Using data from the Seven Countries Study and the MORGEN-study the following associations were studied:

- the ecological association between diet and 25-yr COPD mortality in 16 cohorts of middle-aged men from the USA, Japan and five European countries *(Ch. 2)*
- the longitudinal association between diet and 20-yr COPD mortality in middle-aged men from Finland, Italy and the Netherlands *(Ch. 3 and 4)*
- the cross-sectional relation between diet and pulmonary function in middle-aged men from Finland, Italy and the Netherlands *(Ch. 4 and 5)*

- the cross-sectional association of intake of catechins, flavonols and flavones with pulmonary function and COPD symptoms in Dutch adults (*Ch. 6)*
- the cross-sectional association between intake of fruits, vegetables, whole grains, fish and alcohol with pulmonary function and COPD symptoms in Dutch adults: independent effects (*Ch. 7*)

In chapter 8 a general discussion of the results will be given.

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Chapter 2

Fruit and fish consumption: a possible explanation for population differences in COPD mortality (The Seven Countries Study)

Published as:

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Abstract

Background: The aim was to investigate whether average intake of antioxidants, fruits, vegetables and fish may help to explain international differences in COPD mortality. We used information on baseline diet and the 25-yr COPD mortality rate of the 16 population-based cohorts of middle-aged men participating in the Seven Countries Study.

Methods: Dietary information was collected at baseline in small random samples of each cohort. In 1987 the reported foods were bought locally and analysed chemically. After 25 years of follow-up the underlying cause of death of those who died was established centrally. COPD mortality rate ratios were calculated, for a change equivalent to 10% of the overall mean consumption of a dietary factor.

Results: We observed independent inverse associations between 25-yr COPD mortality and baseline consumption of fruits (rate ratio = 0.49, 95%CI = 0.36 to 0.67) and fish (rate ratio = 0.97, 95%CI = 0.93 to 1.00), after adjustment for potential confounders. COPD mortality showed no statistically significant association with intake of antioxidants or vegetables. Fruit and fish consumption together explained about 67% of the variance in the COPD mortality rates of the cohorts.

Conclusions : Fruit and fish consumption may partly explain population differences in COPD mortality. This is in accordance with suggestions for a relation of fruit and fish consumption with COPD observed in studies in individuals.

Introduction

Although cigarette smoking is the primary risk factor for Chronic Obstructive Pulmonary Disease (COPD) in individuals[1], at the population level the relation between smoking and COPD is less clear. In Japan, for instance, smoking prevalence is high, whereas the COPD mortality rate is considerably lower than in most other countries.[2,3] This indicates that other factors apart from smoking influence COPD-rates.

One such factor could be diet. Several epidemiological studies have suggested that dietary antioxidants, fruits and fish may protect the airways against oxidant-mediated damage leading to COPD.[4-14] Studied outcome measures were ventilatory function, respiratory symptoms and long term incidence of chronic lung disease.

Dietary factors involved in antioxidant defence mechanisms of the lungs are antioxidant (pro)vitamins, such as vitamin C, vitamin E and ß-carotene, and cofactors of antioxidant enzymes, such as selenium.[15] Also non-nutritive compounds present in the diet, such as flavonoids, have antioxidant capacities.[16] The potential protective effect of fruits and vegetables may be due to their high antioxidant activity.[12]

Fish oils are thought to have anti-inflammatory effects, because of the influence of the n-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on arachidonic acid metabolism.[12,17] EPA and DHA may competitively inhibit the use of arachidonic acid as a substrate for the production of pro-inflammatory mediators like prostaglandins and leukotrienes. Derived from EPA, these mediators have diminished biological activities compared to the corresponding arachidonic acid-derived mediators.

To investigate whether average intake of antioxidants, fruits, vegetables and fish may help to explain population differences in COPD mortality, we conducted an ecological analysis using information on baseline diet and the 25-yr COPD mortality rate in the 16 cohorts of the Seven Countries Study.

Materials and methods

Study population

Between 1958 and 1964 12,763 men aged 40-59 years from 16 different cohorts were enrolled in the Seven Countries Study. Eleven cohorts consisted of men living in rural parts of Finland, Italy, Greece, former Yugoslavia and Japan. Two cohorts consisted of railroad employees in the USA and Italy, one of workers in a large co-operation in Serbia (Zrenjanin), one of university professors in Belgrade and one of inhabitants of a small industrial town in the Netherlands. Other characteristics of the cohorts have been described in detail.[18]

Examinations

Dietary information was collected at baseline (between 1959 and 1964 for 14 cohorts and around 1970 for Rome Railroad and Ushibuka) in small random samples (8-49) of each cohort, using the 7-day record method in 14 of the cohorts, a 4-day record in Ushibuka and a 1-day record in the US cohort.

In 1985 and 1986 the original dietary intake data were recoded by one dietician in a standardised way and summarised in 16 food groups including vegetables, fruits and fish.[19] For the present analysis the fruit group was decomposed in solid fruits (= apples, pears), citrus fruits and other fruits (= soft fruits, conserved fruits, fruit juice). In 1987, foods representing the baseline diet were bought locally and sent by air in cooling boxes to the Netherlands. Within one day after arrival, the foods were cleaned and combined into equivalent food composites representing the average food consumption of each cohort. These were subsequently homogenised, freeze-dried and stored at -20°C until analysed. Part of the food equivalent composites was not frozen and oxalic acid was added to this part to preserve vitamin C.

Vitamin C was determined fluorometrically[20] within ten days after arrival. Determination of ß-carotene was done using high-performance liquid chromatography followed by spectrophotometric measurements.[21] Vitamin E was extracted according to Grimm and Tiews[22] and determined chromatographically[23]. Selenium was determined according to Welz and Melcher[24] and flavonoids according to Hertog et al.[25] Total lipids were isolated according to Osborne and Voogt.[26] Fatty acids were determined gas chromatographically.[27] Use of different columns made identification possible of the n-6 and the n-3 fatty acids.

In all members of the cohorts data were collected on age, smoking, height, weight and work related physical activity at baseline and on smoking and respiratory symptoms after 10 years of follow-up. Summarised values per cohort were used in the analyses.

Information on smoking, height, weight and work related physical activity was collected in a standardised way.[18] Body Mass Index (BMI, weight/height^2) was calculated and work related activity level was divided into four categories (1=bedridden, 2=sedentary, 3=moderately active, 4=hard physical work) using information on occupation and usual activities, including part-time jobs and notable non-occupational exercise.

The prevalence of respiratory symptoms was determined in all cohorts except the US railroad cohort. Subjects were interviewed by a trained physician using a modified version of the Medical Research Council's questionnaire[28] on respiratory symptoms. Age-adjusted prevalence rates were calculated using the direct method with the age distribution of the whole study population as standard.

Mortality follow-up

The vital status of the men was determined after 25 years of follow-up. Only 56 men (0.4%) were lost to follow-up. The underlying cause of death of those who died was established centrally by two investigators (HB and AM). They reviewed information from clinical records, from family doctors, specialists, relatives and from other useful sources, collected by local investigators. Usually the official cause of death from the death certificate was not considered or only used as a preliminary indication. Primary mortality was coded according to the 8th revision of the International Classification of Diseases. COPD mortality rates (ICD 491-493) were adjusted for age using the direct method, with the age distribution of the whole study population as standard.

Statistical methods

All analyses concern inter-cohort comparisons. The number of deaths from COPD per cohort was assumed to have a Poisson distribution, considering the fact that we deal with count data where the number of deaths is small in relation to the number of observations. Poisson regression was carried out[29,30] with 25-yr COPD mortality as the dependent variable and dietary factors and potential confounders as independent variables. The natural logarithm of the cohort size was used as an offset, that is, an independent variable with a regression coefficient of one. To correct for overdispersion standard errors were multiplied by a scale factor obtained by dividing the residual variance of the model by the residual degrees of freedom.

Five potential confounders, measured at baseline, were considered: age, total energy intake, prevalence of cigarette smoking, work related activity level and BMI. BMI was considered because in individual-level analysis of the Dutch cohort[8] baseline BMI was found to be inversely associated with 25-yr CNSLD incidence. Adjustment for age or work related activity level did not cause a relevant change in any of the studied associations and these factors were therefore not used in the final analysis. Emphasis is given to models containing the dietary factor of interest and one potential confounder, namely the potential confounder that caused the largest change in the estimated regression coefficient of the dietary factor. Subsequently all three confounders where adjusted for, realising however that in this case the number of parameters in the model relative to the total number of observations (n = 16) is quite large.

The antilog of the estimated regression coefficient represents the mortality rate ratio for a one-unit change in the independent variable. For all dietary factors and BMI, rate ratios were presented for a change equivalent to 10% of the mean value of the variable for all cohorts combined and for the smoking variables for a 10%

change in smoking prevalence. The interpretation of the presented rate ratios is best explained with an example. The average baseline intake of vitamin E for all cohorts combined was 15 mg. The presented rate ratio for the unadjusted association between vitamin E and COPD mortality of 0.97 (table 2) indicates that if the average intake were to increase with 1.5 mg (= 10%) the 25-yr COPD mortality rate would be expected to decrease with 3%.

The proportion of explained variance (R^2) of the final model could not directly be derived from the Poisson regression analyses. Therefore the Pearson's product-moment correlation coefficient (R) was determined for the relation between the observed and the expected (on the basis of the Poisson regression model) number of COPD deaths in the cohorts and the R^2 calculated. To obtain normality a square root transformation was first performed on both observed and expected COPD mortality.

All presented correlation coefficients are Spearman correlation coefficients. All tests were two-sided and p-values smaller than 0.05 were considered to be statistically significant.

Results

During 25 years of follow-up 273 men died with COPD as the underlying cause of death, resulting in an overall age-adjusted COPD mortality rate of 2.1%. The 25-yr age-adjusted COPD mortality rate was relatively low in Japan and Belgrade and relatively high in three other cohorts of former Yugoslavia; Slavonia, Zrenjanin and Velika Krsna (table 1). The age-adjusted prevalence of respiratory symptoms after 10 years of follow-up (table 1) showed a strong ecological association with 25-yr age-adjusted COPD mortality ($r = 0.67$, $p = 0.006$).

The COPD mortality rate in the 16 cohorts showed no statistically significant association with the baseline prevalence of cigarette smoking. The association tended to be inverse (figure 1). Similar results were observed for the association between COPD mortality and the prevalence of heavy smoking (>20 cigarettes/day) at baseline (rate ratio = 0.69, 95%CI = 0.45 to 1.04) and the smoking prevalence after 10 years of follow-up (rate ratio = 0.87, 95%CI = 0.60 to 1.30). Furthermore baseline smoking prevalence showed a non-significant inverse association with the prevalence of respiratory symptoms after 10 years of follow-up ($r = -0.21$, $p = 0.45$). Individual level analyses showed a 2.4 times higher risk of dying from COPD during the 25-yr follow-up period for baseline smokers compared to non-smokers (95%CI = 1.8 to 3.2), after adjustment for country.

Table 1: 25-yr COPD mortality and prevalence of respiratory symptoms after 10 years of follow-up (*The Seven Countries Study*).

cohort	code	country	No of men at baseline	10 yrs follow-up: prevalence of respiratory symptoms rate (%)*	25-yr COPD mortality	
					N	rate (%)*
US Railroad	US	USA	2,571	n.a.	40	1.5
Crevalcore	CV	Italy	993	42.8	15	1.5
Montegiorgio	MO		719	56.8	20	2.9
Rome Railroad	RO		768	27.0	10	1.4
Dalmatia	DA	ex-Yugoslavia	671	19.6	14	1.8
Slavonia	SL		696	24.1	46	5.8
Zrenjanin	ZR		516	33.0	22	4.4
Velika Krsna	VK		511	33.2	34	6.3
Belgrade	BE		536	6.4	1	0.1
Zutphen	ZU	Netherlands	878	17.2	14	1.6
East Finland	EF	Finland	817	34.4	15	1.9
West Finland	WF		860	21.3	13	1.4
Tanushimaru	TJ	Japan	508	2.3	2	0.4
Ushibuka	UJ		502	1.8	5	1.0
Crete	CR	Greece	686	16.3	15	2.3
Corfu	CO		529	15.1	7	1.3
Total			12,763	23.4	273	2.1

*age-adjusted

Average BMI at baseline ranged from 21.8 to 26.6 kg/m^2 with an overall mean of 24.0, and was not significantly associated with COPD-mortality (rate ratio = 0.66, 95%CI = 0.37 to 1.18). Average energy intake at baseline (range 9.6-15.8 MJ/day (2.3-3.8 Mcal/day), overall mean 12.6 MJ/day (3.0 Mcal/day)) was positively associated with COPD-mortality, with a rate ratio of 1.24 (95%CI = 1.04 to 1.49).

In the univariate analysis, 25-yr COPD mortality was inversely associated with baseline fruit consumption (figure 2), solid fruit showing the strongest association (table 2). After adjustment for total energy intake, total and solid fruit consumption remained significantly associated with COPD mortality. No association was observed between COPD mortality and consumption of vegetables. Of the antioxidant nutrients studied vitamin C and selenium showed a significant inverse association with COPD mortality, but these associations were no longer significant after adjustment for total energy intake (table 2). Subsequent adjustments for baseline smoking prevalence and BMI did not alter the associations in table 2 in a relevant way.

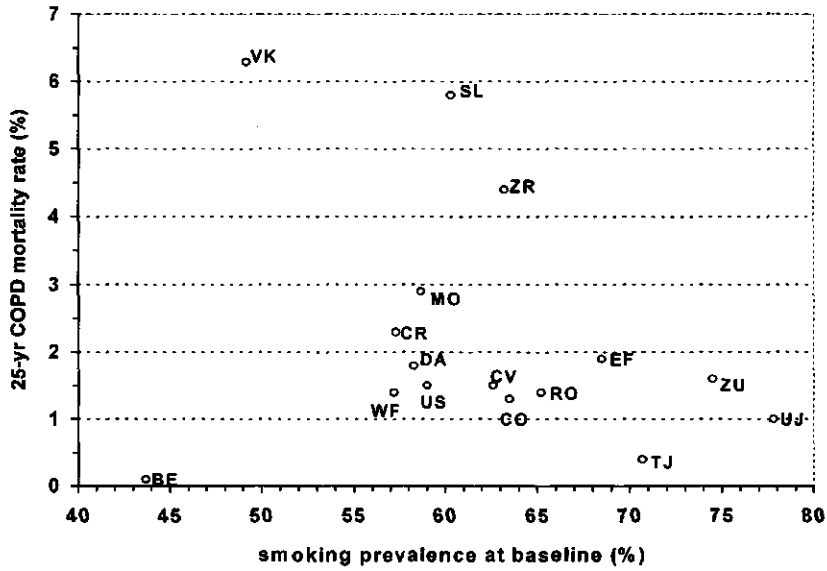

Figure 1: **Association between smoking prevalence at baseline and 25-yr COPD mortality (the Seven Countries Study).** rate ratio = 0.78, 95%CI = 0.49 to 1.25 (for 10% change in smoking prevalence). For codes: see Table 1.

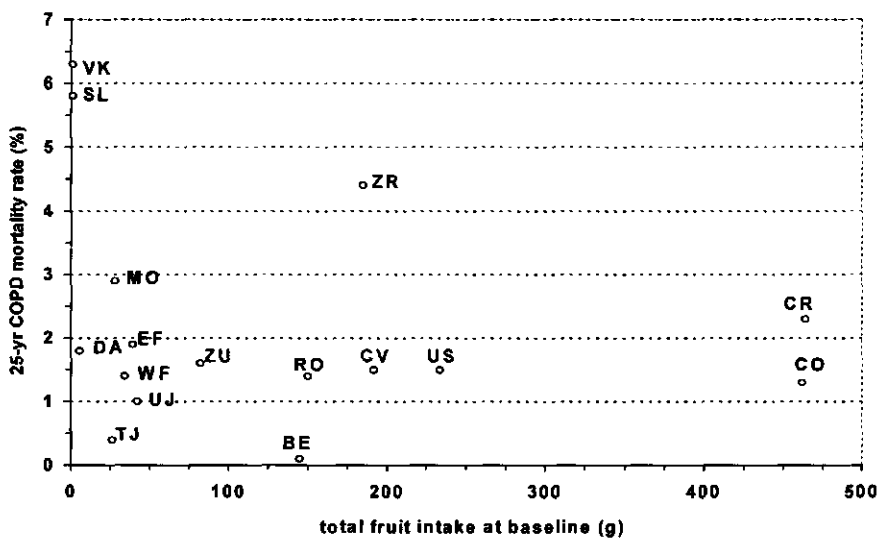

Figure 2: **Association between total fruit consumption at baseline and 25-yr COPD mortality (the Seven Countries Study).** rate ratio = 0.52, 95%CI = 0.38 to 0.73 (for 10% change in overall mean fruit consumption = 13.1 gram). For codes: see Table 1.

Table 2: Association between intake of antioxidants, fruits and vegetables at baseline and 25-yr COPD-mortality (The Seven Countries Study).

		25-yr COPD-mortality			
		crude		adjusted for energy intake	
	10% of mean intake	rate ratio	95%CI	rate ratio	95%CI
Nutrients					
Vitamin E	1.5 mg	0.97	0.86 to 1.07	0.96	0.85 to 1.05
ß-carotene	0.2 mg	1.01	0.93 to 1.11	1.01	0.94 to 1.08
Vitamin C*	7.4 mg	0.33	0.11 to 0.98	0.50	0.16 to 1.78
Selenium*	7.0 mg	0.26	0.08 to 0.83	0.36	0.11 to 1.16
Flavonoids	2.7 mg	1.01	0.96 to 1.07	1.01	0.96 to 1.06
Foods					
Total vegetables	18.2 g	0.99	0.86 to 1.16	1.06	0.93 to 1.21
Total fruits*	13.1 g	0.52	0.38 to 0.73	0.57	0.37 to 0.88
Citrus fruits*	1.8 g	0.88	0.78 to 0.99	0.94	0.79 to 1.13
Solid fruits*	2.5 g	0.71	0.61 to 0.84	0.68	0.52 to 0.88
Other fruits*	8.8 g	0.77	0.59 to 1.02	0.84	0.64 to 1.12

* for these variables analyses were performed on log-transformed values; the log of 10% of the mean intake (see table) was used to calculate the rate ratios.

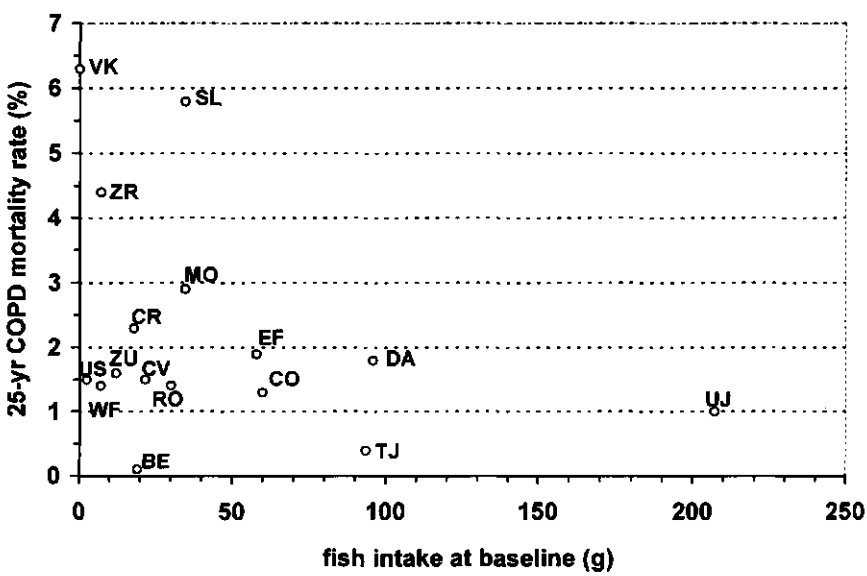

Figure 3: **Association between fish consumption at baseline and 25-yr COPD mortality (the Seven Countries Study).** rate ratio = 0.98, 95%CI = 0.93 to 1.02 (for 10% change in overall mean fish consumption = 4.4 gram). For codes: see Table 1.

An inverse association between fish consumption and COPD mortality is suggested by figure 3. This association almost reached statistical significance after adjustment for BMI, its main confounder (table 3). The intake of EPA and DHA correlated strongly with fish consumption (R = 0.77, P = 0.005) and showed, after adjustment for BMI, a statistically significant inverse association with COPD mortality (table 3). Subsequent adjustments of associations in table 3 for baseline smoking prevalence and total energy intake did not alter the results in a relevant way.

Table 3: Association between intake of different fatty acids and fish at baseline and 25-yr COPD-mortality (The Seven Countries Study).

		25-yr COPD-mortality			
	10% of mean intake	crude rate ratio	95%CI	adjusted for BMI rate ratio	95%CI
Nutrients					
n-6 fatty acids	1.5 g	1.04	0.91 to 1.18	1.12	0.97 to 1.29
n-3 fatty acids	0.3 g	1.00	0.90 to 1.11	0.96	0.86 to 1.08
EPA and DHA	0.1 g	0.97	0.89 to 1.05	0.92	0.84 to 0.99
Foods					
Fish	4.4 g	0.98	0.93 to 1.02	0.96	0.92 to 1.00

In a model containing fruit and fish consumption and smoking prevalence, the association with COPD mortality remained essentially unchanged for fish (rate ratio = 0.97, 95%CI = 0.93 to 1.00) and total fruit consumption (rate ratio = 0.49, 95%CI = 0.36 to 0.67). Smoking prevalence remained unassociated with COPD mortality (rate ratio = 1.11, 95%CI = 0.75 to 1.63). Subsequent adjustments for total energy intake and BMI did not alter these results. Total fruit consumption explained about 57% of the variance in the 25-yr COPD mortality rates of the cohorts. Fish consumption explained an additional 10%.

Discussion

We observed independent inverse associations between average baseline consumption of fruits and fish and long term mortality from COPD in the 16 cohorts of the Seven Countries Study. Fruit and fish consumption together explained about 67% of the variance in the COPD mortality rates of the cohorts. Baseline smoking prevalence showed no clear association with COPD mortality in this ecological study.

General advantages of ecological studies are the much larger variation in exposure (here dietary intake) between-populations than within-populations and

relatively small measurement errors in exposure assessment. The use of dietary intake and mortality data collected in the cohorts, instead of food disappearance data and national statistics, and the availability of individual-level information on potential confounders adds strength to our study. However, its important to bare in mind that on the basis of observations at the population-level, no causal inferences can be made about individual-level phenomena.[31] When ecological data are used to test an etiological hypothesis, the findings therefore need to be judged in the light of both a plausible biological mechanism of action and consistency with results of individual-level studies designed to test the same hypothesis.

We are not aware of other ecological studies on the relation between diet and COPD. Our results concerning fruit and COPD are in agreement with recent individual-level studies. In a random sample of British adults winter fruit consumption was positively associated with ventilatory function[7], and in the Dutch cohort of the Seven Countries Study 25-yr incidence of chronic lung disease was inversely associated with baseline consumption of total and solid fruits[8]. The association between fruit consumption and COPD is thought to be due to a protective effect of the antioxidant vitamin C[7,11], which is suggested by several epidemiological studies[4,6,11]. However, in accordance with the individual-level results from the Dutch cohort[8], we observed that COPD was strongly associated with the consumption of solid fruits, while the association with citrus fruits and vitamin C was less clear. This suggests that, besides vitamin C, other components of fruits may be involved.

The potential protective effect of fish consumption is thought to be due to the anti-inflammatory effects of EPA and DHA.[12,17] After adjustment for BMI, fish consumption and intake of EPA and DHA were inversely associated with COPD mortality. Results of individual-level studies, however, are not conclusive. In cross-sectional studies a positive association was observed between fish consumption and ventilatory function[5,10] and an inverse association between the combined intake of EPA and DHA and COPD was found[9]. In the Dutch cohort[8] no association was observed between baseline intake fish or EPA and DHA and 25-yr incidence of chronic lung disease. This may be due to the low level of intake (average EPA and DHA intake 220 mg/day), but Shahar and co-workers[9] observed their association at similar levels of intake (average 247 mg/day). Further studies are needed to elucidate this issue.

Cigarette smoking is well established as the primary risk factor for COPD in individuals. Individual-level data of the Dutch cohort showed, for example, a strong positive association between baseline smoking and 20-yr mortality from CNSLD.[32] In our ecological analyses, however, baseline prevalence of smoking showed no clear association with the 25-yr COPD mortality rate in the 16 cohorts.

The validity of our data on COPD mortality appears to be good. Great effort has been put into ascertaining the comparability of the mortality data between countries. The primary cause of death was established centrally and based mainly on additional sources of information besides death certificates. Additional individual level analyses showed a clear difference in 25-yr COPD mortality between smokers and non-smokers at baseline. Furthermore, the COPD mortality rates of the cohorts are comparable with results of other longitudinal studies conducted in the same period[33-34] and also accord with data provided by the WHO[2,35]. The validity of our COPD mortality data is further supported by the strong association with the prevalence of respiratory symptoms after 10 years of follow-up. A similar association on the individual level has been reported earlier.[36] A concern might be that the prevalence of smoking in 1960 does not reflect smoking prevalence during the 25-year follow-up period. However, additional analyses showed that baseline smoking prevalence was strongly associated with smoking prevalence after 10 years of follow-up and smoking prevalence after 10 years of follow-up still showed an inverse non-significant association with 25-yr COPD mortality. The prevalence of heavy smoking showed no clear association with COPD mortality also. It is possible that detailed information on the duration of smoking might have revealed a relationship with COPD mortality.

The discrepancy between observed individual-level associations and our ecological association on smoking and COPD may therefore be explained by cross-level bias. In this context the term "bias" is misleading. Through the differential distribution of extraneous risk factors, or individual-level effect modifiers across populations[37], there may truly be no positive association between smoking prevalence and COPD mortality at the population-level. This is supported by the situation in Japan, as reported by Aoki [3], with a high prevalence of smoking and a relatively low mortality from COPD, which is conform our findings in the Japanese cohorts Ushibuka and Tanushimaru.

A few other methodological concerns need to be addressed. Although in our study we used the term COPD (defined as chronic bronchitis and emphysema), asthma does contribute to the mortality rates. The three conditions show overlap in clinical features[38] and especially with methods available in the 1960s it is difficult to discern between asthma and COPD. In our study chronic bronchitis or emphysema was often noted as the secondary cause of death in cases where asthma was reported as the underlying cause of death. Also considering the fact that the number of asthma cases was small, we decided against excluding them from the analyses.

It may be questioned whether food consumption around 1960 is a good indicator for average food consumption during 25-yr of follow-up. The characteristic food

consumption patterns of the seven countries changed during 25-yr of follow-up, but the relative position of the countries in the distribution of different foods, including fruits and fish, was maintained.[19] Therefore, this type of bias is probably small.

Work related activity level can be seen as a proxy for socio-economic status. Since adjustment for work related activity level did not alter the associations studied, socio-economic status cannot explain our findings. However, confounding by other, unmeasured, factors such as for instance air pollution can not be excluded.

We conclude that fruit and fish consumption may partly explain international differences in COPD mortality. This is in accordance with suggestions for a relation between fruit and fish consumption and COPD observed in individual-level studies.

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Chapter 3

Diet and 20-year COPD mortality in middle-aged men from three European countries

Submitted as:

Walda IC, Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A, Nissinen A, Feskens EJM and Kromhout D. Diet and 20-year mortality of chronic obstructive pulmonary disease in the Finnish, Italian and Dutch cohorts of the Seven Countries Study.

Abstract

Background: Several recent cross-sectional surveys demonstrated a protective effect of a high intake of antioxidants, fruit, vegetables and fish on outcomes related to chronic obstructive pulmonary disease (COPD). The objective of the present prospective study was to investigate the association between selected dietary factors and 20-yr COPD mortality in middle-aged men from three European countries.

Methods: Baseline individual information on diet was collected around 1970 using the cross-check dietary history method in Finland (n=1248), Italy (n=1386) and the Netherlands (n=691). The dietary factors studied were fruit, vegetables, fish and antioxidants (vitamin C, vitamin E and ß-carotene). After 20 years of follow-up the underlying cause of death of those who died was established centrally. Survival analyses were performed using the Cox Proportional Hazards Model.

Results: During 20 years of follow-up 73 men died from COPD. After adjustment for age, pack years of smoking and country, inverse relationships were observed between the baseline intake of fruit (relative risk (RR) = 0.49, 95%CI = 0.26 to 0.93) and of vitamin E (RR = 0.51, 95%CI = 0.27 to 0.99) with 20-yr COPD mortality. Additional adjustment for total energy intake resulted in marginally higher estimated RR's for fruit (RR = 0.56, 95%CI = 0.29 to 1.09) and vitamin E intake (RR = 0.66, 95%CI = 0.31 to 1.42).

Conclusion: Our results suggest a protective effect of intake of fruit and of vitamin E on dying from COPD.

Introduction

Several risk factors for the development of chronic obstructive pulmonary disease (COPD) have been identified, among which cigarette smoking is the most important one.[1] High levels of free radicals in cigarette smoke cause direct (tissue oxidation) and indirect (release of oxidising agents and enzymes) damage to lung tissue.[2,3] However, the fact that not all smokers develop significant airflow obstruction suggests that other factors are also involved.

Diet is one of the potential factors. Several recent cross-sectional surveys demonstrated a protective effect of the intake of fruit[4,5,6] and vegetables[5,7] on pulmonary function[4,5,6] and respiratory symptoms[7], which suggests that these dietary factors may have a protective effect on COPD. The high antioxidant concentration of fruits and vegetables is thought to be responsible for their potential protective effect. Recent cross-sectional studies focusing on dietary intake of antioxidants and indicators of COPD showed a protective effect of the intake of vitamin C,[8,9,10,11] vitamin E[12,13] and ß-carotene[10,13], mainly on lung function[8-12] and in one study on respiratory symptoms.[13]

To our knowledge, only two longitudinal studies on the association between diet and COPD have been performed. In the Zutphen Study an inverse relationship was observed between baseline consumption of total and solid fruit and 25-yr incidence of chronic lung disease.[14] However, Miedema and co-workers did not observe a relationship with intake of antioxidants. Carey and colleagues observed that a decreasing frequency of fresh fruit consumption over a period of 7 years was accompanied by a decrease in pulmonary function.[6] However, in this study no relationship between change in lung function and the average level of fruit intake over the 7-yr period was found.

In addition to the above-mentioned dietary factors with antioxidant capacities, it has also been suggested that fish consumption protects against development of COPD. The anti-inflammatory effects of n-3 polyunsaturated fatty acids,[15-17] of which fish is the main source,[18] are thought to be responsible for this protection.

To our knowledge, the present study is the first prospective study that focused on the association between diet and COPD mortality. We investigated the relationship of baseline individual intake of fruit, vegetables, antioxidants and fish with 20-yr COPD mortality. Data of Finnish, Italian and Dutch cohorts of the Seven Countries Study were combined to provide a wide range in dietary intake.

Materials and methods

Study population

From 1958 to 1964 sixteen population samples of middle aged men (40 - 59 years) from seven countries have been enrolled and examined at baseline for the Seven Countries Study.[19] During the second and third round (5 and 10 years of follow-up respectively) dietary data were obtained in the Finnish, Italian and Dutch cohorts. Also 20-year follow-up mortality data were collected.

In the present study two Finnish, two Italian and one Dutch cohort of the Seven Countries Study are involved. In Finland one cohort was located in the east, in Ilomantsi, a rural area close to the Russian border. The other Finnish cohort was situated in the south-western part of the country, in Pöytyä and Mellilä. Two cohorts of Italian men participated in the study. One consisted of men living in the village of Crevalcore, which is located in the Po Valley. The participants of the other Italian cohort were inhabitants of Montegiorgio, a small country village in central Italy. The fifth cohort was located in Zutphen, a small commercial town in the centre-east of the Netherlands.

In 1959 in Finland 1,675 men were examined, about 98 percent of the total eligible population of men born from 1900 to 1919. After 10 years, 612 men in East Finland and 694 men in West Finland were re-examined, respectively 91 percent and 93 percent of the surviving men. Complete dietary information was obtained from 590 men in East Finland and 670 men in West Finland. In Zutphen a random sample of 4 out of each 9 eligible men was drawn in 1960. Invited were 1088 men of which 872 men participated in both the medical examination and the dietary survey (80 percent). In 1970 625 men were re-examined, of which 558 participated in individual dietary surveys. In both Italian cohorts 99 percent of the eligible men participated in 1960 (n=1712). In 1970, 570 participants in Montegiorgio and 753 men in Crevalcore were examined. From respectively 551 and 584 men complete dietary information was obtained.

Data collection

Individual dietary surveys were carried out around 1970 in all cohorts, except in Montegiorgio, where this survey took place in 1965. The dietary data gathered in 1965 in this Italian cohort were used as an approximation for dietary intakes in 1970. Individual dietary intake was estimated by the cross-check dietary history method.[20] Although this method was adapted to the local situation in the specific country, the methodology was comparable for the three countries. The cross-check dietary history method provides information about the usual food consumption pattern during six to twelve months preceding the interview. The first part of the method

concerns questions about the foods used at breakfast, lunch, dinner and between the meals. This, to assess the usual food consumption pattern of a person during weekdays and weekends. For the second part of the survey a checklist with a number of foods was used. The frequencies and amounts consumed were recorded for the different food groups. The information about the food pattern was compared with the information from the checklist. In all cohorts the dietary interviews were carried out by experienced dieticians and nutritionists. The food intake was converted into energy and nutrient intake using the computerised versions of the local food tables for the three different countries.[21-24] Also individual intakes of antioxidants (vitamin C, ß-carotene and vitamin E) were calculated for the separate cohorts, using the local food tables.

In all cohorts information on age, height, weight and smoking status of the participants was collected in a standardised way.[25] Body Mass Index (BMI) was calculated from measurements of body weight (kg) and height (m). Current smoking status was assessed using a standardised questionnaire. Possible answers were: current smoker, former smoker and never smoker. Current or former smokers were asked to report the amount of cigarettes they smoked or used to smoke daily. The number of years smoked was estimated by assuming that in all cohorts the men started smoking at the age of 16 such as known for the Dutch cohort. Pack years of smoking were calculated as the product of the number of years smoked and the number of packs of cigarettes smoked per day. It was assumed that a pack of cigarettes contained 25 cigarettes.

The vital status of the participants was recorded during 20 years of follow-up. The underlying cause of death from those who died was established centrally by two investigators. They reviewed the information from clinical records, from family doctors, specialists and relatives and from other useful sources collected by local investigators. Usually the official cause of death was not considered or only used as a preliminary indication. Primary mortality was coded according to the 8th revision of the International Classification of Diseases (ICD) of the World Health Organisation.[26] The ICD codes 491 to 493 refer to death from chronic bronchitis, lung emphysema and asthma respectively.

Statistical analyses

The Cox Proportional Hazards Model (SAS Procedure PHREG)[27,28] was used to assess the relationship between the consumption of the selected dietary variables and 20-yr COPD mortality, since this method takes into account the unequal lengths of time that each participant has been observed.

Except for fish consumption, the dietary variables were ranked into tertiles. Fish consumption was divided into categorical intakes of 0, 1 - 20 and more than 20 g/day. To be able to assess the effect of high fish consumption also an alternative ranking was used: 0, 1 - 20, 21 - 40 and more than 40 g/day. In the analyses the potential confounders age, pack years of smoking and country were taken into account. Total energy intake and BMI at baseline are other potential confounders that were considered. Adjustment for country was carried out by calculating a pooled relative risk (RR), using the strata option of the PHREG procedure that allows baseline hazards to vary between countries. The same method was used for the analyses in which adjustment for cohort instead of country was carried out. Stratified analyses for each country, which could have given insight into differences in potential protective effect of dietary factors between countries, were not possible due to small numbers of COPD deaths within the countries. Excluding men who died in the first years of the follow-up period could correct for possible influences of a different diet in COPD patients and healthy participants. However, this exclusion was not carried out to maximise statistical power. In case of fish consumption additional analyses were carried out with adjustment for ethanol intake.

All analyses were performed using the SAS statistical package version 6.11 (Cary, USA). The term statistically significant refers to p-values lower than 0.05 (two-sided tests).

Results

Table 1 presents general characteristics of the study population. Of the total research group only 21.3 percent were never smokers, 50.9 percent were current smokers and 27.8 percent were former smokers in 1970. Out of the total study population of 2917 men, 1712 men (58.7 percent) died during twenty years of follow-up, among which 73 deaths from COPD. The overall COPD mortality rate was 171.1 per 100.000 person years with the highest rate in the Netherlands (224.2/100.000 person years) and the lowest rate in Italy (135.6 per 100.000 person years). Among never smokers the COPD mortality rate was 62 per 100.000 person years, in former smokers this rate reached 182 per 100.000 person years and 216 per 100.000 person years was the COPD mortality rate among current smokers.

We observed a wide range in dietary intake (table 2). Mean daily total energy intake ranged from 11.0 MJ in the Netherlands to 15.6 MJ in Finland. Daily intake of vegetables (181 g) and vitamin E (15.5 mg) was highest in the Dutch cohort. Fish consumption, however, was lowest in the Netherlands (16.5 g/day) and highest in

Finland (39.6 g/day). Vitamin C intake was lowest in Italy (43.0 mg/day) and highest in the Netherlands (95.7 mg/day).

Table 1: General characteristics of the Finnish, Italian and Dutch cohorts of the Seven Countries Study (1970)

	Finland *n=1227*	**Italy** *n=1132*	**Netherlands** *n=558*
Age in years (mean, (SD))	59.1 (5.5)	59.3 (4.9)	59.6 (5.4)
BMI* in kg/m^2 (mean, (SD))	24.7 (3.8)	26.0 (3.9)	25.1 (2.7)
Cigarette smoking			
current (%)	50.4	50.8	52.0
former (%)	29.7	19.5	40.3
never (%)	19.8	29.7	7.7
Twenty years of follow-up			
Number of deaths	769	628	315
Number of COPD# deaths	31	23	19

* Body Mass Index
\# Chronic Obstructive Pulmonary Disease

Table 2: *Daily intake of selected nutrients and foods in the Finnish, Italian and Dutch cohorts of the Seven Countries Study (1970)*

	Finland *n=1227* mean (SD)	**Italy** *n=1132* mean (SD)	**Netherlands** *n=558* mean (SD)
Energy intake (MJ)	15.6 (4.7)	12.3 (3.3)	11.0 (2.2)
Ethanol (g)	6.6 (13.1)	82.1 (57.7)	9.4 (13.5)
Vitamin C (mg)	91.4 (35.4)	43.0 (24.4)	95.7 (44.5)
β-carotene (mg)	2.0 (1.9)	0.9 (0.5)	1.2 (0.3)
Vitamin E (mg)	7.0 (2.5)	8.5 (3.1)	15.5 (6.4)
Fruit (g)	175 (185)	153 (167)	170 (129)
Vegetables (g)	79 (60)	68 (53)	181 (58)
Fish (g)	39.6 (46.6)	19.7 (20.8)	16.5 (18.6)

Survival analyses, adjusting for age, pack years of smoking and country, revealed that the baseline intake of fruit and of vitamin E was inversely related to 20-yr COPD mortality (table 3). The adjusted RR between the highest and lowest tertile was 0.49 (95%CI = 0.26 to 0.93) for fruit and 0.51 for vitamin E (95%CI = 0.27 to 0.99). Additional adjustment for total energy intake resulted in marginally higher estimated RR's for fruit (RR = 0.56; 95%CI = 0.29 to 1.09) and vitamin E intake (RR = 0.66;

95%CI = 0.31 to 1.42). Adjustment for BMI showed similar effects, but less pronounced.

The analyses did not show a relationship between COPD mortality and the intake of vegetables, fish, vitamin C and ß-carotene (table 3). Additional adjustment for ethanol intake did not alter the estimated RR's for fish consumption and COPD mortality in a relevant way. Analyses with the alternative classification of fish consumption (0, 1 - 20, 21 - 40, >40 g/day) also did not show an association between fish consumption and COPD mortality (not shown). Adjustment for cohort instead of country resulted in similar results (not shown).

Table 3: The relation between tertiles of baseline intake of dietary factors and 20-yr COPD mortality in 2917 middle-aged men from Finland, Italy and the Netherlands

	adjusted for age, pack years and country*			**adjusted for** age, pack years, country* and energy intake		
Dietary factors	$RR_{2,1}$	$RR_{3,1}$ (95%CI)	p-trend	$RR_{2,1}$	$RR_{3,1}$ (95%CI)	p-trend
Fish (g)**	0.83	1.04 (0.54-2.03)	0.70	0.83	1.10 (0.57-2.14)	0.56
Fruit (g)	1.01	0.49 (0.26-0.93)	0.04	1.08	0.56 (0.64-1.83)	0.11
Vegetables (g)	0.77	0.91 (0.44-1.85)	0.67	0.83	1.08 (0.52-2.26)	0.98
Vitamin C (mg)	0.92	0.80 (0.40-1.61)	0.53	1.07	1.08 (0.51-2.28)	0.84
Vitamin E (mg)	0.68	0.88 (0.47-1.63)	0.58	0.75	1.04 (0.55-1.96)	0.99
ß-carotene (mg)	0.64	0.51 (0.27-0.99)	0.04	0.75	0.66 (0.31-1.42)	0.28

* adjusted for country by calculating a pooled risk ratio, allowing baseline hazards to vary between countries

** Fish intake in categories (0/ 0-20 / >20 g/day)

$RR_{2,1}$ = relative risk of middle vs. lowest tertile

$RR_{3,1}$ = relative risk of highest vs. lowest tertile

tertile limits- fruit: <77, >191; vegetables: <52, >107; vitamin C: <57, >92; ß-carotene: <0.9, >1.5; vitamin E: <6.4, >9.0

Discussion

The results of the present 20-yr follow-up study demonstrated inverse associations between the baseline habitual intake of fruit and of vitamin E and the risk that middle aged men will die from COPD after adjustment for age, pack years of smoking and country. Additional adjustment for total energy intake resulted in marginally higher estimated RR's, however the confidence interval widened and included one. No association with COPD mortality was observed for the consumption of vegetables and fish and for the intake of vitamin C and ß-carotene.

Random misclassification of exposure may have occurred by using the cross-check history method to obtain information on diet. This random misclassification can vary between the selected dietary factors. The validity and reproducibility of this method is reported by Block[29] and Bloemberg and colleagues.[30] Random misclassification of exposure results in bias of relative risks towards one,[31] thus in the present study random misclassification may have led to underestimation of RR's. Baseline values of exposure (diet) and potential confounders (e.g. smoking) may have changed during the follow-up period of 20 years. Huijbregts and colleagues demonstrated an increase of fruit consumption in the survivors during 20 years of follow-up in a subsample of the present study.[32] Since this increase was highest in the reference group, the lowest fruit tertile, this may have given an underestimation of the effect of fruit. On the other hand, overestimation of this effect may have occurred due to residual confounding by smoking, since, in accordance with earlier studies,[33, 34] the present study showed lower dietary intake of fruit among smokers than among non-smokers. Further, although in our study we used the term COPD (defined as chronic bronchitis and emphysema), asthma does contribute to the mortality rates. However, chronic bronchitis or emphysema was often noted as the secondary cause of death in cases where asthma was reported as the underlying cause of death. Also considering the fact that the number of asthma cases was small, we decided against excluding them from the analyses.

The estimated RR's both for fruit and vitamin E intake remained on a similar level after additional adjustment for total energy intake besides age, pack years of smoking and country. Although statistical significance was no longer present, these results suggest a protective effect of these dietary factors on dying from COPD.

Our findings regarding vitamin C are in contrast with the reasonably consistent evidence in literature for a positive association between intake of vitamin C and pulmonary function.[8-11] However, reported associations regarding other COPD related outcomes like respiratory symptoms[10,35] and airway obstruction[36] are less consistent. The only longitudinal study that investigated the relationship between intake of vitamin C and chronic lung disease, demonstrated no association between baseline intake of vitamin C and 25-yr chronic lung disease incidence in the Dutch cohort of the Seven Countries Study, which is in accordance to our findings.[14] However, in the present prospective study the Zutphen cohort is one of the five cohorts we used in our analyses.

With regard to fruit consumption our results are in agreement with the results of several cross-sectional studies,[4-6] but not with other studies that did not show a relationship between fruit intake and pulmonary function[12] or respiratory symptoms[7]. However, our findings are in agreement with the results of the longitudinal study

performed by Miedema and colleagues,[14] who observed an inverse association between baseline consumption of total and solid fruit and 25-yr chronic lung disease incidence in the Dutch cohort of the Seven Countries Study which remained also after adjustment for age, smoking habits, BMI and energy intake. A relationship between 25-yr incidence of chronic lung disease and consumption of citrus fruits, which contain large quantities of vitamin C, was not observed by Miedema and co-workers. These findings, together with our results, support the suggestion that other fruit components than the antioxidant vitamin C may have a protective effect on the development of emphysema and chronic bronchitis, e.g. flavonoids, which have strong antioxidant capacities.[37,38] Because no specified information on foods that contain flavonoids, e.g. onions and red wine, could be derived from the dietary questionnaires, analyses with flavonoids could not be performed.

Our results considering the antioxidant vitamin E are in agreement with the results of two cross-sectional studies, one showing an inverse association between intake of vitamin E and respiratory symptoms[13] and one demonstrating a positive association between intake of vitamin E and pulmonary function[12]. In contrast, two other cross-sectional studies did not show a relationship between intake of vitamin E and pulmonary function.[9,10] Thus, the evidence for a potential protective effect of vitamin E on COPD is inconsistent.

Our observations did not show an association between fish consumption and COPD mortality, which is not in accordance with the hypothesis that intake of n-3 fatty acids prevents the development of chronic bronchitis and lung emphysema. It is not likely that this discrepancy is due to the level of intake in our study population (mean daily intake of 27.4 g), because Shahar and colleagues[16] showed an inverse relationship between incidence of COPD and consumption of fish at similar levels of intake (1.9 servings/week or 85 - 142 g. fish/week).

In summary, our results suggest a protective effect of intake of fruit and of vitamin E on dying from COPD. However, recommendations in relation to fruit consumption and vitamin E intake can not be given because of inconsistency in the results of epidemiological studies.

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Chapter 4

Alcohol consumption in relation to 20-yr COPD mortality and pulmonary function

Submitted as:

Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A, Nissinen A, Feskens EJM, Heederik D, Kromhout D. Alcohol consumption in relation to 20-yr COPD mortality and pulmonary function.

Abstract

Background: Alcohol consumption shows a U-shaped relation with all-cause and cardiovascular mortality. Indications for a protective effect of light-to-moderate alcohol consumption on Chronic Obstructive Pulmonary Disease (COPD) morbidity suggest a similar relation with COPD mortality.

Methods: We fit a Cox proportional hazard model to data on baseline alcohol consumption (1970) and 20-yr COPD mortality from 2953 middle aged men in Finland, Italy and the Netherlands. Concurrently, we studied pulmonary function in relation to none and light alcohol consumption (≤3 drinks/day) in Finland and the Netherlands and in relation to moderate-to-heavy alcohol consumption in Italy, using multiple linear regression. All regression models were adjusted for age, height (for pulmonary function only), BMI, smoking, energy intake and country.

Results: A smoothed spline-plot showed a U-shaped relation between alcohol and COPD mortality. Compared to non- and occasional drinkers (≤1drink/week), the relative risk of COPD mortality was 0.60 (95%CI = 0.33 to 1.09) in light drinkers (>1 drink/week, ≤3 drinks/day) and 1.25 (95%CI = 0.47 to 3.31) in moderate-to-heavy drinkers. In Finland and the Netherlands alcohol consumption was positively associated with pulmonary function. Non-drinkers had a respectively 64 ml (95%CI = -12 to 141) lower $FEV_{0.75}$ and a 94 ml (95%CI = 2 to 186) lower FEV_1 compared to occasional and light drinkers. In Italy, very heavy drinkers (> 12 drinks/day) had a 98 ml (95%CI = 8 to 187) lower $FEV_{0.75}$ than moderate-to-heavy drinkers (>3, ≤12 drinks/day).

Conclusions: We observed a U-shaped curve between alcohol consumption and 20-yr COPD mortality in middle aged men that was supported by cross-sectional data on alcohol and pulmonary function.

Introduction

Several epidemiological studies have reported lower overall mortality rates in light-to-moderate drinkers compared to those not consuming alcohol, while overall mortality seems to increase with higher levels of alcohol consumption.[1-3] The lower cardiovascular disease mortality observed in drinkers of up to several drinks per day compared to non-drinkers[2-7] partly explains the beneficial effect of alcohol. However, also when mortality from cardiovascular diseases was excluded, mortality from other causes was observed to be lower in those consuming up to three drinks per day compared to non-drinkers.[1, 3]

Another important cause of death is Chronic Obstructive Pulmonary Disease (COPD) defined as chronic bronchitis and emphysema. There are indications for a beneficial effect of light-to-moderate alcohol consumption on pulmonary function[7] and 25-yr incidence of chronic lung disease.[8] Furthermore, a beneficial effect of alcohol consumption on the prevalence and extent of emphysema, determined by autopsy, was suggested.[9] Heavy alcohol consumption is thought to have deleterious effects on the lungs, mainly on the basis of studies in alcoholics.[10-12]

To our knowledge the relation between alcohol consumption and long-term COPD mortality has not been studied before. Based on present knowledge, we hypothesised a U-shaped relation. To test this hypothesis we used data on alcohol consumption around 1970 and 20-yr COPD mortality in 2953 middle aged men from Finland, Italy and the Netherlands gathered in the Seven Countries Study. Concurrently, we determined whether cross-sectional data on pulmonary function and alcohol consumption in the three countries indicated a similar effect of alcohol consumption on COPD.

Material and methods

Subjects and study design

Around 1960 sixteen population samples of men aged 40-59 years from seven countries have been enrolled and examined at baseline for the Seven Countries Study.[13] The vital status of the participants was recorded during 30-yrs of follow-up and the men were re-examined at 5 and 10 year after baseline. In table 1 the data-collection in the Finnish, Italian and Dutch cohorts in the 3 examination rounds have been summarised. For all other cohorts data on alcohol consumption and/or pulmonary function was not available.

In Finland one cohort was situated in rural east Finland, close to the Russian border, and the other in a rural area in the west of Finland. The Italian cohorts

Table 1: Data-collection at baseline and at the re-examinations after 5 and 10 years of follow-up in the Finnish, Italian and Dutch participants of the Seven Countries Study.

	Finland	Italy	Netherlands
Examination 1 (baseline)			
Year of examination	1959	1960	1960
Age-range (yr.)	40-59	40-59	40-59
No of examined men	1,677	1,712	872
Response rate (%)	98	99	80
Data on alcohol consumption (n)	-------	------	------
Data on pulmonary function (n)	1,614	1,646	------
Examination 2 (5 year follow-up)			
Year of examination	1964	1965	1965
Age-range (yr.)	45-64	45-64	45-64
No of examined men	1,531	1,548	778
Response rate (% of survivors)	97	95	93
Data on alcohol consumption (n)	-------	1,539	721
Data on pulmonary function (n)	1,491	1,394	694
Examination 3 (10 year follow-up)			
Year of examination	1969	1970	1970
Age-range (yr.)	50-69	50-69	50-69
No of examined men	1,363	1,335	701
Response rate (% of survivors)	95	88	91
Data on alcohol consumption (n)	1,306	592*	615
Data on pulmonary function (n)	1,325	1,069	------

----- data not available * only measured in Crevalcore

consisted of men living in Montegiorgio and Crevalcore, two rural villages in respectively central and northern Italy. The fifth cohort comprised of men from Zutphen, a small commercial town in the east of the Netherlands.

Complete data on alcohol consumption around 1970 (for Montegiorgio alcohol consumption in 1965 was used as a proxy for alcohol consumption in 1970), COPD-mortality between 1970 and 1990 and potential confounders was available for 2,953 men in the three countries. Complete data on alcohol consumption, pulmonary function and potential confounders was available for 1248 Finnish men in 1969 and for respectively 1386 and 691 men in Italy and the Netherlands in 1965.

Methods

Food intake, including consumption of alcoholic beverages, was estimated using the cross-check dietary history method. This method provides information about the usual food consumption pattern six to twelve months preceding the interview.[14] All interviews were carried out by extensively trained dieticians and nutritionists.

Although the dietary history method was adapted to the local situation in each specific country, the methodology was comparable. The nutrient intake, including alcohol, was assessed using computerised versions of the local food tables for the three different countries.[15-18]

The underlying cause of death of those who died during follow-up was established centrally by two investigators (HB and AM). They reviewed information from clinical records, from family doctors, specialists, relatives and from other useful sources, collected by local investigators. Usually the official cause of death from the death certificate was not considered or only used as a preliminary indication. Primary mortality was coded according to the 8th revision of the International Classification of Diseases (COPD = ICD 491-493).

Pulmonary function was measured by spirometry. Equipment and protocols differed between the countries, but were identical among cohorts in a country, as described earlier.[19] In short; Forced Expiratory Volume in 0.75 seconds ($FEV_{0.75}$) was measured in Finland and Italy. In both countries a noseclip was used, but the Finnish subjects were measured in a sitting and the Italian subjects in a standing position. In the Dutch cohort of Zutphen, Forced Expiratory Volume in one second (FEV_1) was measured with subjects sitting in an upright position. In all countries the $FEV_{0.75}$ or FEV_1 was established in three attempts.

Information on age, height, weight and smoking was collected in a standardised way.[13] Body Mass Index (BMI) was calculated (weight/height^2). Pack years were calculated as the product of the number of years smoked and the number of packs of cigarettes smoked per day (for details see ref. 19). A package of cigarettes was assumed to contain 25 cigarettes.

Statistical Analyses

To assess the longitudinal relation between baseline alcohol consumption (around 1970) and 20-yr COPD mortality GAIM-software[20] was used to fit an additive Cox's proportional hazards model, fitting alcohol and pack years of smoking as cubic smoothing splines with 8 degrees of freedom. Relative risks were calculated from the smoothed coefficients by taking the exponent after subtracting the value of the smoothed coefficient for the reference group (the non-drinkers).

Subsequently, the number of alcohol drinks consumed was categorised into 5 levels: none, ≤ 1 per week (occasional), > 1 per week and ≤ 3 per day (light), > 3 and ≤ 9 per day and > 9 per day. A drink was assumed to contain 10 grams of alcohol. The Cox Proportional Hazard Model (SAS procedure PHREG) was now used to determine the relative risk of COPD mortality in the different categories of alcohol consumption, again with the non-drinkers as a reference.

In analyses concerning COPD mortality, age, body mass index (BMI), energy intake, pack years of smoking and country were considered as potential confounders. In the model used for smoothing the mortality data, country was included as a categorical variable. In the subsequent analyses adjustment for country was carried out by calculating a pooled relative risk, using the strata option of the PHREG option (SAS) that allows baseline hazards to vary between countries. Although we used the term COPD, defined as chronic bronchitis and emphysema, asthma does contribute to the mortality rates. Considering the overlap in clinical features[21] and the fact that in our study chronic bronchitis or emphysema was often noted as the secondary cause of death in the small number of cases where asthma was reported as the underlying cause of death, we decided against excluding them from the analysis. Finally, due to the small numbers of COPD deaths in the separate countries a stratified analysis could not be performed.

The relation between alcohol consumption and pulmonary function was studied in the separate countries. In Finland and the Netherlands alcohol consumption was generally low (mean < 1 drink/day, more than 95% with ≤ 3 drinks/day) and in Italy generally high (mean > 8 drinks/day, more than 85% with > 3 drinks/day). Therefore, none, occasional and light alcohol consumption was studied in relation to pulmonary function in Finland and the Netherlands and moderate to heavy alcohol consumption (> 3 drinks per day) was studied in relation to pulmonary function in Italy. The statistical package S-plus (2000) was used to create a smoothed spline-curve. We used a model with $FEV_{0.75}$ /HT2 or FEV_1 /HT^2 as the dependent and age (years) as an independent variable.[19] Potential confounders considered in these analyses were: BMI, energy intake and pack years of smoking. Pack years of smoking was added to the model as a smoothing spline-variable. In Finland and Italy associations were adjusted for cohort. For ease of interpretation the results are presented age-adjusted and in its original scale (FEV_1 or $FEV_{0.75}$ in ml) for a man of average height (1.70 meters).

In all analyses energy intake was defined as the energy derived from fats, carbohydrates and proteins, and not from alcohol. To study whether the effect of alcohol was independent of that of other dietary factors potentially associated with COPD (i.e. vitamin C, vitamin E, ß-carotene, fruits, vegetables and fish) these variables were added to the adjusted models. Analyses stratified by smoking status (non-, former or current smoker) were not possible due to small numbers in several cells.

Results

Alcohol consumption around 1970 and 20-yr COPD mortality

Alcohol consumption around 1970 was relatively low in Finland and the Netherlands (mean < 1 drink/day) and relatively high in Italy (mean > 8 drinks/day). During 20-yrs of follow-up 1,729 men or 58.6% of the study population died. Seventy-three (2.5%) of the men died from COPD, with rates varying from 2.0 to 3.4% between the three countries (table 2).

Table 2: Description of the study population for the analyses on baseline alcohol consumption (around 1970) and 20-yr COPD mortality in middle aged men from three European countries.

	Finland *n = 1260* mean (SD)	**Italy** *n = 1135* mean (SD)	**Netherlands** *n = 558* mean (SD)	**Total** *n = 2953* mean (SD)
Alcohol (g/day)	6.5 (13.0)	82.1 (57.7)	9.4 (13.5)	36.1 (52.0)
Smoking (pack years)	21.4 (17.0)	13.8 (13.9)	20.2 (15.2)	18.2 (15.9)
Age (yr.)	59.1 (5.5)	59.3 (4.9)	59.6 (5.4)	59.3 (5.3)
BMI (m/kg^2)	24.8 (3.8)	26.0 (3.9)	25.1 (2.7)	25.3 (3.7)
Energy intake (MJ)*	15.4 (4.6)	9.9 (2.7)	10.7 (2.2)	12.4 (4.4)
	deaths n (%)	deaths n (%)	deaths n (%)	deaths n (%)
Total mortality	784 (62.2)	630 (55.5)	315 (56.5)	1729 (58.6)
COPD mortality	31 (2.5)	23 (2.0)	19 (3.4)	73 (2.5)

* energy derived from fats, carbohydrates and proteins, and not from alcohol.

In never, former and current smokers at baseline, the 20-yr COPD mortality rate was 0.6, 1.7 and 2.2 per 1000 person years, respectively. After adjustment for age, BMI and energy intake, pack years of smoking was positively associated with COPD mortality (RR = 1.08 per 5 pack years, 95%CI = 1.01 to 1.16). Alcohol consumption was positively associated with smoking, with the average number of pack years smoked increasing from 14.7 in non-drinkers to 22.1 in those consuming >9 drinks per day or with 1.9 pack years per category of alcohol consumption (95%CI = 1.3 to 2.5)

Figure 1 gives both the smoothed curve and a bargraph of the adjusted relative risk of dying from COPD for those consuming alcohol compared to non-drinkers at baseline. In those consuming more than 9 drinks per day (not shown in figure 1) the RR was 1.14 (95%CI = 0.33 to 3.89). A U-shaped curve was observed, with the lowest risk for those with a light alcohol consumption (= >1.4 and ≤ 30 g/day).

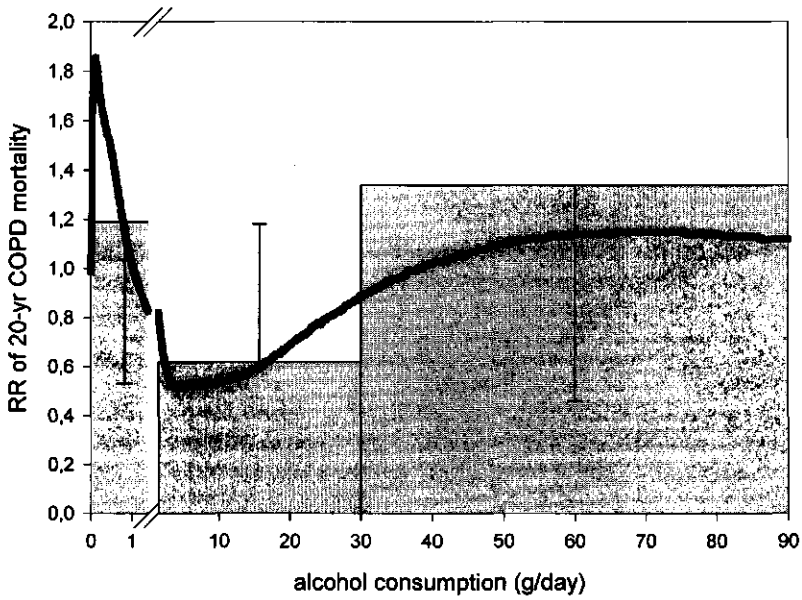


Figure 1: **Smoothed spline-curve and bargraph of the adjusted relative risk of dying from COPD during 20-years of follow-up for middle aged drinkers (up to 9 alcoholic drinks (=90 g) per day) compared to non-drinkers at baseline.** Adjustments were made for age, body mass index, pack years of smoking (smoothed) and energy intake. In non-drinkers 21 cases were observed (9196 personyears), in occasional drinkers 8, in light drinkers 20 and in those consuming 30-90 g/day 15 cases were observed

Compared to the non- and occasional drinkers, the relative risk of 20-yr COPD mortality was 0.60 (95%CI = 0.33 to 1.09) in the light drinkers and 1.25 (95%CI = 0.47 to 3.31) in those with a higher alcohol consumption, after adjustment for all potential confounders. Additional adjustment for the effects of intake of antioxidant vitamins, vegetables or fish had no effect. However, adjustment for fruit intake changed the observed RR's to 0.68 (95%CI = 0.36 to 1.26) and 1.58 (95%CI = 0.54 to 4.64), respectively. The energy-adjusted fruit consumption was on average 98, 186 and 202 g/day for the three compared groups. Finally, after exclusion of deaths in the first 3 years of follow-up, to evaluate the potential effect of subjects with advanced COPD at baseline refraining from drinking, the RR's were 0.59 (95%CI = 0.32 to 1.08) and 1.18 (95%CI = 0.42 to 3.30).

Alcohol and pulmonary function at baseline

The relation between alcohol consumption and pulmonary function was studied in 1186 Finnish men (examined in 1969) and 667 Dutch men (examined in 1965) consuming up to 3 drinks per day (=30 g). Furthermore, 1183 Italian men (examined in 1965) consuming more than 3 drinks per day were studied. The average alcohol consumption was 4.2, 5.3 and 98.9 g/day in Finland, the Netherlands and Italy, respectively. The Finnish men were on average 5 years older than the Dutch and Italian men (table 4).

Table 4: Description of the study populations for the cross-sectional analyses on alcohol consumption and pulmonary function in middle aged men from three European countries.

	Finland, 1969 *n = 1186* mean (SD)	**Italy, 1965** *n = 1183* mean (SD)	**Netherlands, 1965** *n = 667* mean (SD)
Alcohol (g/day)	4.2 (6.5)	98.8 (54.6)	5.3 (7.2)
Smoking (pack years)	21.1 (16.7)	15.4 (15.1)	19.2 (13.8)
Age (yr.)	59.1 (5.5)	54.5 (5.0)	54.8 (5.5)
Height (m)	1.70 (0.06)	1.66 (0.06)	1.74 (0.07)
BMI (kg/m^2)	24.8 (3.8)	25.7 (3.8)	24.7 (2.7)
Energy intake (MJ)*	15.2 (4.5)	10.1 (2.5)	12.3 (2.7)

* energy derived from fats, carbohydrates and proteins, and not from alcohol.

Table 5: Mean (SE) level of pulmonary function according to alcohol consumption in middle aged men from three European countries.

alcohol consumption (g/day)	**Finland, 1969** $FEV_{0.75}$ (ml)* n	mean	(SE)	**Netherlands, 1965** FEV_1 (ml)* n	mean	(SE)	**Italy, 1965** $FEV_{0.75}$ (ml)* n	mean	(SE)
0	461	2661	(31)	265	2776	(36)	--	--	--
> 0, ≤ 1.4	166	2720	(51)	40	2946	(94)	--	--	--
> 1.4, ≤ 30	387	2702	(34)	236	2855	(39)	--	--	--
> 30, ≤ 90	--	--	--	--	--	--	627	2855	(26)
>90	--	--	--	--	--	--	556	2839	(27)

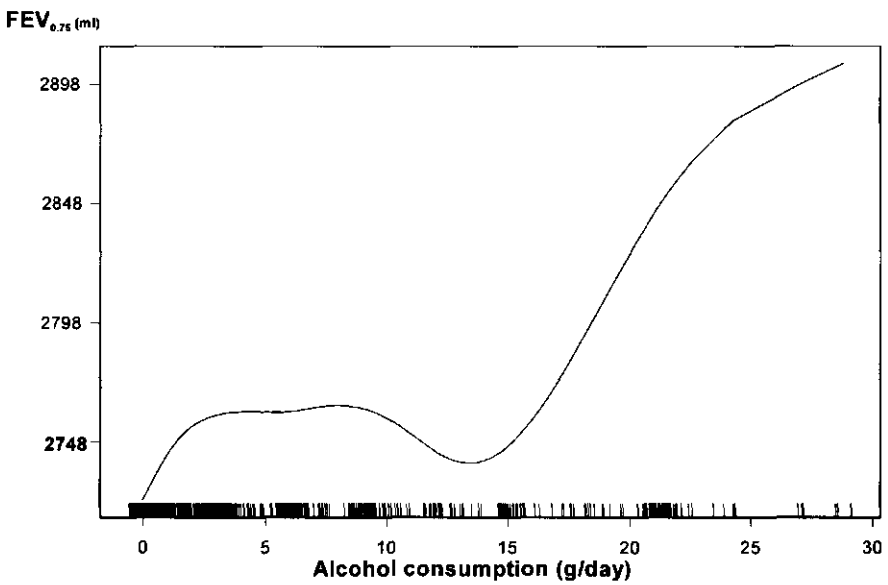
* mean $FEV_{0.75}$ or FEV_1 values adjusted for height and age and presented in its original scale (ml) for a man of average height (1.70 m)

Cigarette smoking (per pack year) was inversely associated with the $FEV_{0.75}$ in Finland (ß = -5.3 ml, 95%CI = -7.6 to -3.0) and Italy (ß = -5.8 ml, 95%CI = -8.2 to -3.4) and with the FEV_1 in the Netherlands (ß = -5.6 ml, 95%CI = -8.9 to -2.4). Smoking was positively associated with alcohol consumption: the average number of

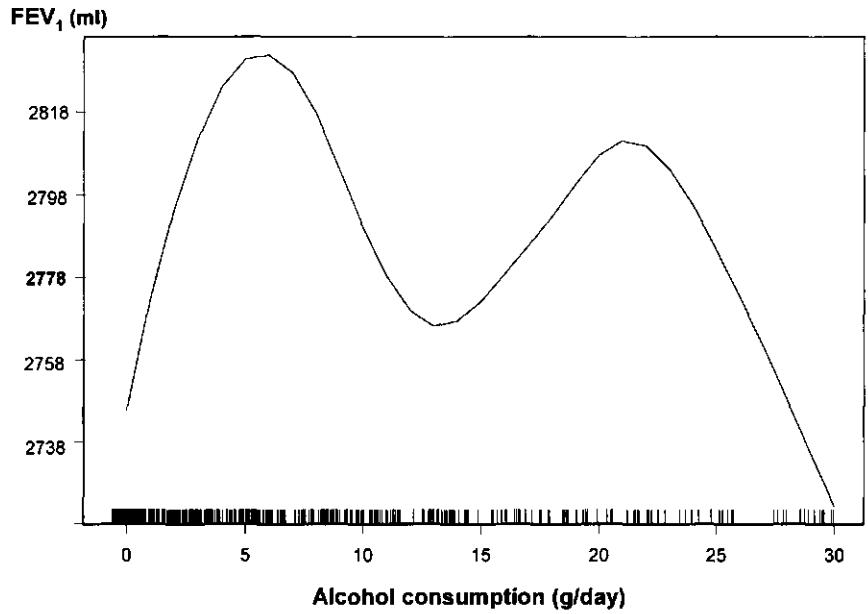
pack years smoked was 18.9 and 16.9 in the non-drinkers and 23.7 and 20.8 in light drinkers in Finland and the Netherlands, respectively. In Italy those consuming less than 9 drinks per day smoked on average 13.2 pack years and those with a higher alcohol consumption on average 17.9 pack years.

Table 5 gives the mean level of FEV_1 or $FEV_{0.75}$ for the different categories of alcohol consumption. The smoothed spline curves in figure 2 indicate that in Finland and the Netherlands pulmonary function was higher in occasional and light drinkers (>0 and ≤ 30 g/day) compared to non-drinkers. In Finland the observed difference in $FEV_{0.75}$ was 64 ml (95%CI = -12 to 141) and in the Netherlands the observed difference in FEV_1 was 94 ml (95%CI = 2 to 186). In Italy, very heavy drinkers had a lower $FEV_{0.75}$ than moderate-to-heavy drinkers (>3, ≤12 drinks/day) (figure 2). The observed difference in $FEV_{0.75}$ was 98 ml (95%CI = 8 to 187).

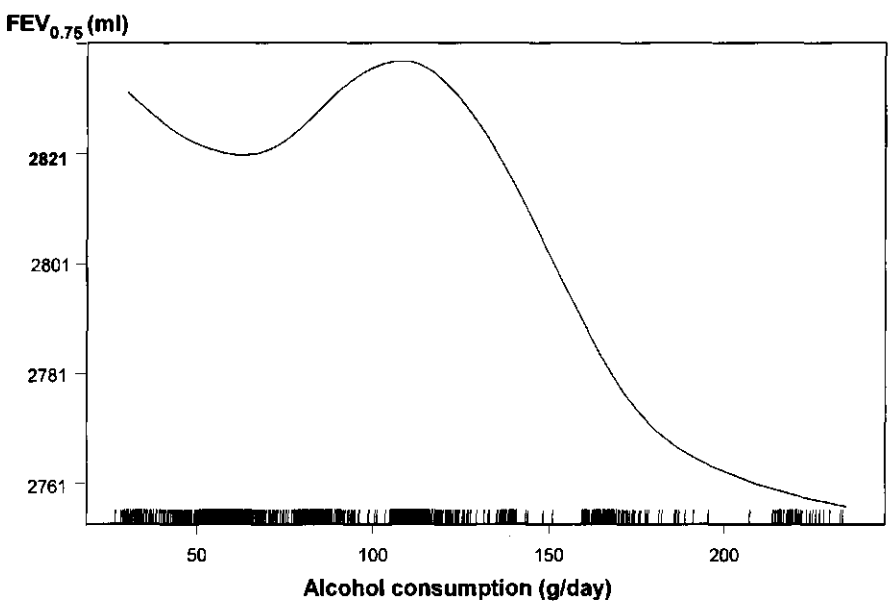
Figure 2: **Alcohol consumption in relation to pulmonary function in middle aged men from three European countries.** Adjustments were made for age, height, smoking, energy intake, body mass index and cohort (for Finland and Italy only).



A: Finland (n = 1186), mean adjusted $FEV_{0.75}$ = 2748 ml.



B: the Netherlands (n = 667), mean adjusted FEV_1 = 2778



C: Italy (n = 1163: excluded are 20 subjects with alcohol consumption >240 g/day, mean adjusted $FEV_{0.75}$ = 2821 ml)

Finally, additional adjustment for intake of other dietary factors (antioxidant vitamins, fruits, vegetables or fish) or only including the men aged 50-64 years (the age-range included in all three countries) did not alter the association between alcohol and pulmonary function in the Netherlands or Italy. In Finland, however, adjustment for fruit intake reduced the observed effect from 64 to 51 ml (95%CI = -31 to 133), while excluding those aged 64 to 69 years reduced the effect to 53 ml (95%CI = -31 to 137).

Discussion

We observed a U-shaped curve between baseline alcohol consumption and 20-yr COPD mortality in middle aged men from Finland, Italy and the Netherlands, with the lowest risk in those with a light alcohol consumption (>1 drink/wk and ≤3 drinks/day). Compared to the non- and occasional drinkers, the relative risk of 20-yr COPD mortality was 0.60 (95%CI = 0.33-1.09) in the light drinkers and 1.25 (95%CI = 0.47-3.31) in those with a higher level of alcohol consumption, after adjustment for potential confounders. A similar effect of alcohol consumption was observed for pulmonary function. In the two countries with a generally low alcohol consumption, pulmonary function was higher in occasional and light (up to 3 drinks per day) compared to non-drinkers. The observed differences were 64 ml in $FEV_{0.75}$ (95%CI = -12 to 141) in Finland and 94 ml in FEV_1 (95%CI = 2 to 186) in the Netherlands. In Italy with a generally high alcohol consumption, the $FEV_{0.75}$ was 98 ml (95%CI = 8 to 187) lower in very heavy drinkers (>12 drinks/day) compared to moderate-to-heavy drinkers (>3 and ≤12 drinks/day).

To our knowledge no prior longitudinal study has focused on alcohol consumption and COPD mortality. Thun, et al.[3] reported no consistent association between death from the wider category of all respiratory causes and alcohol consumption. Unfortunately the data were not shown. In a study by Doll, et al.[1] 13-yr mortality from all respiratory causes in male British doctors seemed to be lower in those consuming 1 to 21 drinks per week (1.3 to 1.7 per 1000 men) compared to non-drinkers (2.0 per 1000 men) and seemed to increase at higher levels of alcohol consumption (2.5 to 3.5 per 1000 men). This is well in accordance with our findings.

In the Dutch cohort a lower risk of 25-yr incidence of chronic lung disease in men with a light-to-moderate alcohol consumption compared to non-drinkers was reported earlier.[8] Also in other studies indications for a beneficial effect of alcohol consumption on COPD related outcomes were observed.[7,9] In two large epidemiological studies no cross-sectional association between light-to-moderate alcohol consumption and airway obstruction was observed.[7,22] However, in these

studies the results were not shown for non-drinkers and occasional drinkers separately.

Our data on COPD mortality did not show a detrimental effect of heavy alcohol consumption. In those consuming more than 9 drinks per day the COPD mortality rate was comparable to the rate in the non-drinkers. Studies in alcoholics, showing a high prevalence of obstructive lung disease, have suggested a detrimental effect of heavy alcohol consumption on the lungs.[10-12] Possibly we were unable to detect an increase in COPD mortality risk in subjects with very high intakes (e.g. > 12 drinks per day), as suggested by the pulmonary function data in Italy, due to the relatively small number of observations in this range of alcohol consumption.

Whether the beneficial effect of light alcohol consumption compared to not drinking alcohol regularly is caused by a direct effect of alcohol or by a confounding effect of *ill*-health among ex-drinkers[23] 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.[24-27] Theoretically it is also possible that subjects with advanced COPD at baseline refrained from drinking alcohol. The result would be a higher COPD mortality among non-drinkers in the first years of follow-up. To address this, we repeated the analysis after excluding deaths in the first three years of follow-up. The difference in COPD mortality between non- and occasional drinkers and light drinkers remained, however, unchanged.

Cigarette smoking, the main risk factor for COPD, is positively associated with alcohol consumption,[2-4] also in the present study. Therefore, residual confounding by smoking may partly obscure the positive effect of light alcohol consumption and may lead to over-estimation of the negative effect of heavier alcohol consumption on COPD. Unfortunately the numbers of never smokers in these study populations were too small to limit the analyses to this subgroup.

In the final models we adjusted for intake of dietary factors potentially associated with COPD[28] and observed a small confounding effect of fruit on the association between alcohol consumption and COPD mortality and on the association between alcohol and pulmonary function in Finland. However, residual confounding by fruit or the other dietary factors due to misclassification of dietary intake cannot be excluded.

In conclusion, we observed a U-shaped curve between alcohol consumption and 20-yr COPD mortality in middle aged men that was supported by cross-sectional data on alcohol and pulmonary function. The lowest COPD mortality, and the highest level of pulmonary function, was observed in men with a low alcohol consumption (up to 3 drinks per day).

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Chapter 5

Dietary factors and pulmonary function: a cross-sectional study in middle-aged men from three European countries

Published as:

Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A, Nissinen A, Feskens EJM, Heederik D, Kromhout D. Dietary factors and pulmonary function: a cross-sectional study in middle-aged men from three European countries. Thorax 1999;54:1021-1026.

Abstract

Background: Results of epidemiological studies relating individual dietary factors to COPD are inconsistent. To evaluate the cross-sectional association of dietary factors with pulmonary function, we used data collected in middle-aged men from three European countries.

Methods: The data were collected in the 1960's in Finland (n=1248), Italy (n=1386), and the Netherlands (n=691). Dietary intake was estimated using the cross-check dietary history method. Pulmonary function ($FEV_{0.75}$ or FEV_1, here called FEV) was measured by spirometry. Associations were adjusted for age, height, smoking, BMI, alcohol consumption and energy intake.

Results: FEV was positively associated with intake of vitamin E in Finland, fruits in Italy and ß-carotene in the Netherlands. In all three countries, men with intake of both fruits and vegetables above the median had a higher FEV than those with a low intake of both foods. The difference in FEV ranged from 110 to 169ml before and from 53 to 118ml after energy adjustment. FEV differences for intake of three antioxidants above vs. below the median ranged from 61 to 181ml before and from -35 to 58ml after energy adjustment. Fish intake was not associated with FEV.

Conclusions: In three European countries a high intake of fruits and vegetables was positively associated with pulmonary function. A high intake of all three antioxidants tended to be positively associated with pulmonary function before, but not after adjustment for energy intake. Associations of individual antioxidant factors with pulmonary function were not consistent across countries.

Introduction

Several epidemiological studies have investigated the relation between diet and Chronic Obstructive Pulmonary Disease (COPD). A possible protective effect against the development of respiratory symptoms, diagnosed COPD or a decline in pulmonary function has been observed for dietary antioxidants[1-9] and/or fruits[10-13] and for n-3 fatty acids and/or fish intake.[14-16] Antioxidants and foods rich in antioxidants, like fruits, are thought to protect the airways against oxidant-mediated damage[17], while the n-3 fatty acids mainly present in fish are thought to have anti-inflammatory effects through their influence on the arachidonic acid metabolism.[18]

The results of studies investigating the relation between antioxidant factors and COPD related outcomes are not consistent. The results vary by the different outcomes studied, whether intake or plasma-levels of antioxidants were studied and whether only dietary intake of antioxidants or also intake from supplements was included.

Observed associations between intake of antioxidants from diet only and pulmonary function are reasonably consistent with regard to vitamin C and fruit intake.[1-3,6,8-13] The two studies[3,8] not observing a statistically significant association of pulmonary function with vitamin C and fruit or fruit and vegetable intake were characterised by a small number of subjects (n=178)[3] or cases (=obstruction, n=95)[8]. With regard to dietary intake of vitamin E or ß-carotene the results of different studies are not consistent. Dow et al.[3] observed a positive association between vitamin E intake and pulmonary function, but no association was observed in two other studies.[2,6] ß-carotene was positively associated with FEV_1 and FVC in the study by Grievink et al.[6], but not in the one by Chuwers, et al.[5]

The magnitude of the effect of individual dietary factors on pulmonary function observed so far is small.[19] Therefore, a small amount of misclassification of dietary intake may have a substantial effect on the studied associations. Furthermore, one dietary factor with antioxidant capacity may not be a good indicator of the antioxidant status in the lungs related to diet. Therefore, it may be better to study the joint effect of several antioxidant factors on pulmonary function.

In the 1960's data on pulmonary function and diet were collected in Finland, Italy and the Netherlands according to the Seven Countries Study protocol.[20] We studied pulmonary function in relation to dietary intake of antioxidant (pro-)vitamins, fruits, vegetables and fish. Furthermore the hypothesis was tested whether the joint effect of either fruits and vegetables or the antioxidant vitamins was more consistent across the countries than effects observed with the individual dietary factors.

Materials and methods

Study population

Around 1960 sixteen population samples of men aged 40-59 years from seven countries were enrolled and examined at baseline for the Seven Countries Study.[20] The men were re-examined 5 and 10 years after baseline. A summary of the data-collection in the three countries is given in table 1.

Table 1: Data-collection at baseline and at the re-examinations after 5 and 10 years of follow-up in the Finnish, Italian and Dutch participants of the Seven Countries Study.

	Finland	Italy	Netherlands
Examination 1 (baseline)			
Year of examination	1959	1960	1960
Age range (yr.)	40-59	40-59	40-59
No. of examined men	1,677	1,712	872
Response rate (%)	98	99	80
Data on diet (n)	-------	------	------
Data on pulmonary function (n)	1,614	1,646	------
Examination 2 (5 year follow-up)			
Year of examination	1964	1965	1965
Age range (yr.)	45-64	45-64	45-64
No. of examined men	1,531	1,548	778
Response rate (% of survivors)	97	95	93
Data on diet (n)	-------	1,539	721
Data on pulmonary function (n)	1,491	1,394	694
Used in present analysis (n)		1,386	691
Examination 3 (10 year follow-up)			
Year of examination	1969	1970	1970
Age range (yr.)	50-69	50-69	50-69
No. of examined men	1,363	1,335	701
Response rate (% of survivors)	95	88	91
Data on diet (n)	1,306	592*	615
Data on pulmonary function (n)	1,325	1,069	------
Used in present analysis (n)	1,248		

---- = data not available * only measured in Crevalcore

Information on pulmonary function and dietary intake was only available for the two Finnish cohorts in 1969 and for the two Italian and the Dutch cohort in 1965. In Finland one cohort was situated in rural east Finland, close to the Russian border, and the other in a rural area in the west of Finland. The Italian cohorts consisted of men living in Montegiorgio and Crevalcore, two rural villages in respectively central

and northern Italy. The fifth cohort comprised of men from Zutphen, a small commercial town in the east of the Netherlands.

Complete data on diet, pulmonary function, and potential confounders was available on 1248, 1386 and 691 men in Finland, Italy and the Netherlands, respectively. In these countries data on pulmonary function were missing for respectively 29, 149 and 28 men. Some men were excluded from spirometry because they suffered from severe conditions, including COPD, as judged by the examining physician. The men with missing lung function data had a lower energy intake than those with a complete record in all three countries and energy-adjusted intake of fruits and/or vitamin C tended to be lower.

Examinations

Food intake was estimated using the cross-check dietary history method, providing information about the usual food consumption pattern six to twelve months preceding the interview.[21] All interviews were carried out by extensively trained dieticians and nutritionists. Although the dietary history method was adapted to the local situation in each specific country, the methodology was comparable. The nutrient intake was assessed using computerised versions of the local food tables for the three different countries.[22-24]

Pulmonary function was measured by spirometry. Equipment and protocols differed between the countries, but where identical among cohorts in one country. In Finland Forced Expiratory Volume in 0.75 seconds ($FEV_{0.75}$) was measured with a McKerrow spirometer. Subjects were measured in a sitting position and with use of a noseclip. The $FEV_{0.75}$ was established in three attempts. In Italy $FEV_{0.75}$ was measured with a Pulmonor Jones spirometer. The subjects were standing and a noseclip was used. The highest value for $FEV_{0.75}$, produced in two or three attempts, has been used in the analyses. In the Netherlands, Forced Expiratory Volume in one second (FEV_1) was measured with a Godart Pulmotest by one technician.[25] Subjects were measured sitting in an upright position. The mean of the two highest values FEV_1, established in three attempts, was used. Assuming that the relation with diet is not different for $FEV_{0.75}$ and FEV_1, the term FEV, without further specification, will be used.

Information on age, height, weight, smoking and work related physical activity was collected in a standardised way.[20] BMI was calculated (weight/ $height^2$) and work related activity level was defined as 1=bedridden, 2=sedentary, 3=moderately active and 4=hard physical work. Pack years of smoking were calculated as the product of the number of years smoked and the number of packs of cigarettes smoked per day. Former and current smokers indicated the number of cigarettes smoked: 1-4, 5-9,

10-19, 20-29, ≥ 30 cigarettes/day and the midpoints of these categories (2, 7, 15, 25, 35) were used in the calculations. Former smokers were also asked to indicate how many years ago they stopped smoking. It was assumed that in all cohorts the men started smoking at the age of 16, as known for the Zutphen cohort. A package of cigarettes was assumed to contain 25 cigarettes.

Statistical Analyses

The cross-sectional relation between FEV and dietary factors was analysed using multiple linear regression analysis. Several models for the dependence of FEV on height and age were evaluated. Considered were models with FEV, its logarithm or FEV divided by height squared (FEV/ HT^2) as the dependent variable and different forms and combinations of height and/or age as the independent variables. Selection of the 'best' model was based on model simplicity, on the percentage of explained variance and on inspection of residuals. The most parsimonious model with FEV/HT^2 as the dependent and age as an independent variable was chosen. In Finland and Italy all associations were adjusted for cohort. For ease of interpretation the results are presented age-adjusted and in its original scale (FEV in ml) for a man of average height (1.70 m).

Fruit consumption was defined as intake of all fresh and canned fruits and fruit juices. Vegetable intake did not included intake of potatoes and legumes. Individual dietary factors were studied as continuous variables, since in analyses using quintiles of intake no indications for non-linear relationships with FEV were observed. High antioxidant intake was defined as intake of all three antioxidants above the median, and low antioxidant intake as intake of the three antioxidants below the median. Likewise high and low intake of fruits and vegetables was defined as intake of both foods respectively above or below the median.

Smoking, BMI, alcohol consumption and energy intake were considered to be potential confounders. Energy intake was defined as the energy not derived from alcohol. To adjust for energy intake both the energy adjusted dietary factor and energy intake were included in the model according to Rothman.[26] Analyses stratified by smoking status (never, former, current smokers) were not possible due to small numbers in several cells. All analyses were performed using the SAS statistical package (windows version 6.11, Cary, USA).

Results

Intake of the different dietary factors showed a broad range across countries. Intake of vegetables, for instance, was highest in the Netherlands (mean = 176 g)

and lowest in Italy (mean = 53 g). The Finnish men were on average 5 years older than the Italian and Dutch men (table 2).

Smoking was inversely associated with FEV in all countries (ß = -5 to -6 ml/packyr, p<0.001). Energy intake was positively associated with FEV, after adjustment for smoking, alcohol consumption, BMI and work related activity level, in Finland (ß = 14 ml/MJ, p<0.001) and in Italy (ß = 34 ml/MJ, p<0.001), but not in the Netherlands (ß = 5 ml/MJ, p=0.54). Energy intake showed a positive association with vitamin E intake in all three countries and with vitamin C intake in Finland and Italy (r = 0.34-0.73, p<0.001).

Table 2: Characteristics of the study population examined in 1969 in the Finnish and in 1965 in the Italian and Dutch cohorts of the Seven Countries study.

	Finland *n = 1248* mean (SD)	**Italy** *n = 1386* mean (SD)	**Netherlands** *n = 691* mean (SD)
Age (yr.)	59.0 (5.5)	54.5 (5.0)	54.8 (5.5)
Height (m)	1.70 (0.06)	1.66 (0.06)	1.74 (0.07)
Smoking (pack years)	21.4 (17.0)	15.1 (15.0)	19.5 (13.9)
BMI (kg/m^2)	24.7 (3.8)	25.8 (3.8)	24.8 (2.7)
Alcohol (g)	6.5 (13.0)	86.8 (58.3)	6.8 (12.5)
Total Energy Intake (MJ)	15.6 (4.7)	12.5 (3.1)	12.4 (2.7)
Energy excl. alcohol (MJ)	15.4 (4.6)	10.0 (2.6)	12.2 (2.8)
FEV* (ml)	2703 (733)	2742 (719)	2960 (699)
Vitamin C (mg)	91.7 (35.3)	45.9 (24.0)	91.8 (39.5)
Vitamin E (mg)	6.7 (2.4)	** 9.9 (3.6)	17.9 (6.6)
ß-carotene (mg	2.0 (1.9)	** 0.8 (0.6)	1.1 (0.4)
Fruits (g)	174 (183)	191 (180)	152 (109)
Vegetables (g)	79 (60)	53 (50)	176 (69)
Fish (g)	39 (46)	21 (20)	17 (23)

* In Finland and Italy $FEV_{0.75}$ was measured and in the Netherlands FEV_1
** n = 1356

In table 3 the results of the regression analyses relating individual dietary factors to FEV are given. FEV was positively associated with intake of vitamin E and vitamin C (p = 0.05) in Finland, vitamin C, vitamin E and fruits in Italy and ß-carotene in the Netherlands, after adjustment for smoking, alcohol consumption and BMI. After subsequent adjustments for energy intake the FEV remained positively associated with intake of vitamin E in Finland, fruits in Italy and ß-carotene in the Netherlands (table 3).

From the data in table 2 and 3 the increase in FEV per SD increase in intake can be calculated. After adjustment for smoking, alcohol consumption and BMI (model b)

for vitamin C the FEV increased with 37 ml per SD (95%CI = -0.3 to 74) in Finland and with 53 ml (95%CI = 19 to 87) per SD in Italy. Similar figures with regard to vitamin E intake were respectively 93 (95%CI = 56 to 129) and 52 (95%CI = 15 to 89) ml/SD in Finland and Italy. Per SD increase in fruit intake the FEV increased with 68 ml (95%CI = 28 to 107) in Italy, with 59 ml (95%CI = -22, 140) in Finland and with 21 ml (95%CI = -23 to 65) in the Netherlands.

Table 3: The cross-sectional association between FEV[1] and intake of antioxidants (ml/mg), fruits (ml/g) or vegetables (ml/g) in middle-aged men from Finland (n = 1248), Italy (n = 1386) and the Netherlands (n = 691).

	Antioxidants			Foods	
	Vitamin C ß (95%CI)	Vitamin E ß (95%CI)	ß-carotene ß (95%CI)	Fruits ß (95%CI)	Vegetables ß (95%CI)
Finland					
model a	1.3 (0.3 to 2.4)	40 (25 to 55)	1 (-18 to 21)	0.2 (0.0 to 0.4)	0.1 (-0.5 to 0.7)
model b	1.0 (-0.0 to 2.1)	39 (24 to 54)	-3 (-22 to 16)	0.3 (-0.1 to 0.8)	-0.0 (-0.6 to 0.6)
model c	-0.5 (-1.7 to 0.7)	22 (1 to 44)	-16 (-36 to 4)	0.0 (-0.4 to 0.5)	-0.5 (-1.1 to 0.2)
Italy					
model a	2.4 (1.0 to 3.8)	14 (4 to 25)	26 (-31 to 82)	0.4 (0.2 to 0.6)	0.5 (-0.2 to 1.2)
model b	2.2 (0.8 to 3.6)	15 (4 to 25)	29 (-27 to 86)	0.4 (0.2 to 0.6)	0.5 (-0.2 to 1.2)
model c	1.0 (-0.5 to 2.5)	-3 (-15 to 10)	1 (-56 to 58)	0.3 (0.1 to 0.5)	0.2 (-0.5 to 0.9)
Netherl.					
model a	0.9 (-0.2 to 2.1)	-3 (-10 to 4)	155 (41 to 270)	0.3 (-0.1 to 0.7)	0.5 (-0.1 to 1.2)
model b	0.7 (-0.4 to 1.8)	-3 (-9 to 4)	144 (31 to 257)	0.2 (-0.2 to 0.6)	0.5 (-0.1 to 1.1)
model c	0.7 (-0.4 to 1.8)	-7 (-15 to 2)	141 (27 to 255)	0.2 (-0.2 to 0.6)	0.5 (-0.1 to 1.1)

a adjusted for height and age
b adjusted for height, age, smoking, BMI and alcohol consumption
c adjusted for height, age, smoking, BMI, alcohol consumption and energy intake
[1] In Finland and Italy $FEV_{0.75}$ was measured and in the Netherlands FEV_1

In all three countries, FEV was higher in men with intake of fruits and vegetables above the median compared to those with intake of both foods below the median, after adjustment for smoking, BMI and alcohol intake (table 4). Subsequent adjustment for energy intake reduced the observed difference in FEV in Finland (110 -> 53 ml) and Italy (169 -> 118 ml), but not in the Netherlands (111 -> 110 ml). In subjects with intake of vitamin C, vitamin E and ß-carotene above the median compared to those with intake of all three antioxidants below the median, the FEV tended to higher before, but not after adjustment for energy intake (table 5).

Table 4: Cross-sectional association between FEV (ml) and the combined intake of fruits and vegetables in middle-aged men in three European countries.

	Difference in FEV_1 between men with intake above vs. below the median		
	fruits ß (95%CI)	vegetables ß (95%CI)	both foods# ß (95%CI)
Finland			
median intake	*117 g*	*65 g*	
above/below median n =	*624/624*	*622/626*	*375/ 377*
model a	117 (44, 190)	48 (-25, 121)	130 (38, 220)
model b	113 (33, 193)	27 (-46, 100)	110 (11, 210)
model c	77 (-4, 158)	-10 (-83, 64)	53 (-50, 156)
Italy			
median intake	*150 g*	*42 g*	
above/below median n =	*657/729*	*691/695*	*278/ 316*
model a	125 (44, 206)	84 (11, 157)	194 (83, 305)
model b	121 (40, 202)	70 (-3, 143)	169 (56, 281)
model c	95 (14, 176)	48 (-24, 121)	118 (4, 232)
Netherlands			
median intake	*131 g*	*165 g*	
above/below median n =	*344/347*	*340/351*	*189/ 196*
model a	45 (-43, 134)	97 (9, 185)	131 (18, 244)
model b	28 (-59, 116)	84 (-3, 172)	111 (-3, 224)
model c	29 (-59, 117)	83 (-4, 170)	110 (-4, 224)

\# comparing the men with intake of both fruits and vegetables *above* the median to the men with intake both foods *below* the median
a adjusted for height and age
b adjusted for height, age, smoking, BMI and alcohol consumption
c adjusted for height, age, smoking, BMI, alcohol consumption and energy intake

Fish intake showed no clear association with FEV. After adjustment for all potential confounders the association was inverse and borderline significant in Finland (ß = -0.87 ml/g, 95%CI = -1.73 to 0.00), while in the Netherlands no association was observed (ß = -0.90 ml/g, 95%CI = -2.78 to 0.97). In Italy the association was positive and borderline significant before (ß = 1.52, 95%CI = -0.17 to 3.22), but not after (ß = 0.61, 95%CI = -1.11 to 2.33) adjustment for energy intake.

Intake of potatoes and margarine or oils, foods containing vitamin C or vitamin E, was not associated with FEV. Bread consumption, however, was positively associated with FEV after adjustment for all potential confounders in Finland (ß = 0.35 ml/g, SE = 0.17), Italy (ß = 0.41 ml/g, SE = 0.17) and the Netherlands (ß = 0.57 ml/g, SE = 0.32). Average bread consumption was 253 g (SD = 134), 348 g (SD =

Table 5: Cross-sectional association between FEV (ml) and the combined intake of antioxidants in middle-aged men in three European countries.

	Difference in FEV (ml) between men with intake above vs. below the median			
	vitamin C ß (95%CI)	vitamin E ß (95%CI)	ß-carotene ß (95%CI)	antioxidants# ß (95%CI)
Finland				
median intake	*87 mg*	*6.4 mg*	*1.37 mg*	
above/below n =	*624/624*	*624/624*	*624/624*	*284/ 280*
model a	96 (23 to 169)	132 (58 to 205)	59 (-14 to 132)	206 (96 to 315)
model b	83 (10 to 157)	125 (53 to 198)	40 (-33 to 112)	181 (71 to 291)
model c	5 (-76 to 85)	23 (-67 to 112)	6 (-67 to 79)	48 (-110 to 197)
Italy				
median intake	*42 mg*	*9.4 mg*	*0.65 mg*	
above/below n =	*692/694*	*678/678*	*678/678*	*380/ 362*
model a	63 (-7 to 133)	34 (-40 to 108)	45 (-26 to 117)	63(-48 to 174)
model b	58 (-11 to 128)	34 (-40 to 108)	52 (-20 to 123)	61 (-51 to 173)
model c	10 (-61 to 81)	-62 (-143 to 18)	24 (-47 to 96)	-35 (-158 to 871)
Netherlands				
median intake	*87 mg*	*17.6 mg*	*1.07 mg*	
above/below n =	*344/347*	*345/346*	*345/346*	*110/ 116*
model a	9 (-80 to 97)	-67 (-155 to 22)	138 (50 to 227)	95 (-59 to 249)
model b	9 (-79 to 96)	-60 (-147 to 28)	138 (51 to 225)	108 (-42 to 257)
model c	7 (-81 to 94)	-92 (-189 to 5)	136 (49 to 224)	58 (-116 to 233)

comparing the men with intake of all three antioxidants *above* the median to the men with intake of all three antioxidants *below* the median

a adjusted for height and age

b adjusted for height, age, smoking, BMI and alcohol consumption

c adjusted for height, age, smoking, BMI, alcohol consumption and energy intake

150) and 220 g (SD = 89) per day for Finland, Italy and the Netherlands, respectively.

When only men aged 50-64 years, the age-range included in all three countries, where used in the analyses the observed associations remained essentially unchanged in Finland. In Italy and the Netherlands the observed associations between individual dietary factors and FEV were generally somewhat stronger in the older subgroup. As a result intake above vs. below the median of both fruits and vegetables was statistically significantly associated with FEV in the Netherlands (ß = 151 ml, SE = 69).

Discussion

In middle-aged men from three European countries, the observed difference in FEV between men with high vs. low intake of both fruits and vegetables (joint effect) ranged from 110 to 169 ml before and from 53 to 118 ml after adjustment for energy intake. Likewise in men with a high intake of vitamin C, vitamin E ànd ß-carotene compared to those with low antioxidant intake a 61 to 181 ml difference was observed before and a -35 to 58 ml difference after adjustment for energy intake. Observed associations between individual dietary factors and pulmonary function were not consistent across the countries. After adjustment for all potential confounders, FEV was positively associated with intake of vitamin E in Finland, intake of fruits in Italy and intake of ß-carotene in the Netherlands.

The joint effect of fruits and vegetables, as defined here, may be less susceptible to misclassification of dietary intake and may reflect the effect of a more relevant difference in exposure, resulting in the more consistent and stronger association with pulmonary function across the countries. The groups that were compared to evaluate the joint effect were not extreme in their fruit or vegetable intake. The larger joint effect is therefore not caused by a larger difference in the fruit consumption between the compared groups alone.

Our results concerning the combined intake of vitamin C, vitamin E and ß-carotene are less clear. In the three countries antioxidant intake tended to be positively associated with FEV before, but not after adjustment for energy intake. Energy intake was strongly and positively associated with pulmonary function in Finland and Italy, with a substantial effect on all observed associations. Energy intake is, however, not a known risk factor for COPD. It is strongly associated with physical activity, but physical activity, even training, does not affect lung volumes.[27] Energy intake may stand for another, unknown, factor associated with diet and pulmonary function, but in this case the factor may be an intermediate factor and not a confounder. Therefore, it is unclear whether the results are more valid either adjusted or unadjusted for energy intake.

In contrast to other studies,[14-16] but in accordance with a study on the relation between fish consumption and 25-yr incidence of chronic lung disease in the Dutch cohort[11], we observed no clear association between fish intake and pulmonary function.

Surprisingly, intake of bread was positively associated with FEV in all three countries, with an increase of 47 to 62 ml FEV per SD increase in intake. An association between whole grain consumption and chronic diseases has been described by Slavin, et al.,[28] one of the proposed biological mechanisms of action being through the antioxidant capacity of several components of whole grains,

including vitamin E. It would be interesting to study the relation between the intake of whole grain products and COPD. Unfortunately, in our study information on the intake of the different types of bread, e.g. white vs. wholemeal bread, was not available.

A number of methodological aspects need to be addressed. First of all, this study was cross-sectional in nature and therefore a temporal relation between diet and pulmonary function cannot be established. Due to the relatively small number of subjects in the different countries, especially in the Netherlands, the power of our study may not be sufficient to detect small effects. Furthermore, although we adjusted for pack years of cigarette smoking, residual confounding by smoking cannot be excluded. Unfortunately it was not possible to repeat the analyses separately in the never smokers due to small numbers. Also confounding by other health related lifestyle factors cannot be excluded, although work related physical activity, which can be seen as an indicator of socio-economic status, could not explain the observed associations (results not shown).

The equipment used in the 1960's for measuring pulmonary function was less sophisticated than modern equipment. However, several studies performed in the 1960's meet the current ATS reproducibility criteria.[29,30] Due to the differences in equipment and procedures used in the different countries and due to the fact that in the Netherlands the FEV_1 was measured and not the $FEV_{0.75}$, the level of FEV can not be compared between countries. Comparisons among men within the three separate countries are, however, valid.

Vitamin C intake relative to the amount of fruits and vegetables ingested was low in Italy compared to Finland and the Netherlands. In the Netherlands potatoes (not included in vegetable intake) are the main source of vitamin C, while for Finland this can be explained by the consumption of unpealed potatoes and vitamin C-rich forest berries. The relative amount of vitamin C derived from fruits is, therefore, likely to be highest in Italy. Other constituents of fruits, like for instance flavonoids may also have a beneficial effect on pulmonary function. Whether this may explain the stronger association between vitamin C and pulmonary function observed in Italy is, however, speculative. Unfortunately information on the flavonoid intake of the studied men in 1965/1970 was not available.

In the different countries 4 to 10% of the men were excluded from the analyses due to missing pulmonary function data. Selection towards men with a better pulmonary function may have occurred, since men with a severe illness, including severe COPD, were excluded from spirometry. Furthermore, failure to perform an adequate pulmonary function measurement can be an indicator of impaired respiratory health.[31] Since energy-adjusted fruit and/or vitamin C intake tended to be

lower in men with missing pulmonary function data, this selection may have caused these associations to be attenuated.

In conclusion, intake of both fruits and vegetables above the median intake was positively associated with pulmonary function in three European countries. Intake of the three studied antioxidants (vitamin C, vitamin E and ß-carotene) above the median tended to be positively associated with pulmonary function before, but not after adjustment for energy intake. The associations of the individual dietary factors with pulmonary function were not consistent across countries. We postulate that the larger and more consistent joint effect of fruit and vegetable intake on pulmonary function might be the result of studying a more relevant and more stable difference in exposure.

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Chapter 6

COPD and intake of catechins, flavonols and flavones (the MORGEN-study)

Submitted as:

Tabak C, Arts ICW, Smit HA, Heederik D, Kromhout D. COPD and intake of catechins, flavonols and flavones (the MORGEN-study)

Abstract

Background: A protective effect of flavonoids against chronic lung disease has been suggested. To test this hypothesis we studied intake of catechins, flavonols and flavones in relation to pulmonary function and COPD symptoms.

Methods: The study population consisted of 13,651 men and women aged 20-59 years from three Dutch cities examined in 1994-1997. Dietary intake was estimated using a semi-quantitative food frequency questionnaire and flavonoid intake calculated using specific food composition tables. Pulmonary function (FEV_1) was measured by spirometry. The presence of COPD symptoms was determined by questionnaire. Associations were adjusted for age, height (for FEV_1 only), gender, smoking, body mass index and energy intake and presented for the fifth vs. the first quintile of intake.

Results: Average catechin, flavonol and flavone intake was 58 mg (SD=46) with tea and apples as the main sources. Total catechin, flavonol and flavone intake was positively associated with the FEV_1 (ß= 44 ml, 95%CI = 18 to 69) and inversely associated with chronic cough (OR = 0.80, 95%CI = 0.66 to 0.97) and breathlessness (OR = 0.74, 95%CI = 0.58 to 0.94). Catechin intake was independently associated with both the FEV_1 (ß = 130 ml, 95%CI = 101 to 159) and all three COPD symptoms (OR = 0.60 to 0.72, $p<0.001$), while flavonol and flavone intake was independently associated with chronic cough only. Solid fruit (=apples, pears), but not tea, intake was beneficially associated with COPD.

Conclusions: The results of this first study on intake of catechins, flavonols and flavones in relation to COPD, suggest a beneficial effect of a high intake of catechins and of solid fruits. Further research is required to confirm our findings.

Introduction

Recent epidemiological evidence has suggested a protective effect of diets rich in flavonoids against cardiovascular diseases and possibly cancer.[1-4] A protective effect of flavonoids against chronic lung disease has been hypothesised by Miedema, et al.[5] They suggested that the stronger association with 25-yr incidence of asthma and COPD observed for solid fruits (=apples, pears) than for other types of fruits, may be due to the high level of flavonoids in apples.

Flavonoids are polyphenols naturally occurring in plant foods. The main sources in a western type diet are tea, fruits and vegetables.[6] Flavonoids have been observed to have both anti-inflammatory and anti-oxidative effects. By inhibiting lipoxygenase and cyclo-oxygenase, two enzymes involved in the arachidonic acid metabolism, flavonoids have been shown to reduce the production of two classes of pro-inflammatory factors (i.e. prostaglandins and leukotrienes)[4,7-9] involved in the pathogenesis of COPD. Furthermore, a high intake of other dietary antioxidants, e.g. vitamin C, has been observed to be beneficially associated with COPD related outcomes.[10]

For three of the six flavonoid subclasses, i.e. catechins, flavonols and flavones, data on their content in food are available.[11-14] To determine whether they are protective against COPD, we studied intake of these flavonoids in relation to pulmonary function and COPD symptoms using data from 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).

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. Each year a new random sample of men and women aged 20-59 years from three towns (Amsterdam, Doetinchem and Maastricht) was examined through self-administered questionnaires and a physical examination. Between 1994 and 1997, 17,530 subjects were studied. Due to practical reasons 2,430 of these subjects did not perform a lung function measurement. Furthermore, those with missing data on diet (n = 394) or potential confounders (n = 198), those with a technically unacceptable or non-reproducible FEV_1 measurement (n = 775) and pregnant women (n = 82) were excluded. 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 semi-quantitative food frequency questionnaire, developed for the MORGEN-study which is part of the EPIC study (European Prospective Investigation into Cancer and Nutrition).[15-17] The habitual consumption of 178 food items during the last year was estimated. Solid fruit intake (=apples, pears) was calibrated using data from a single 24-hour recall collected in a sample (n = 2689) of the MORGEN-population.[18] Vitamin C, ß-carotene and energy intake were calculated using the 1996 Dutch food composition table[19] and intake of the studied flavonoids was calculated using specific food composition tables.[11-14] The physical examination included measurement of weight, height and pulmonary function.

Questions on COPD symptoms were selected from the Dutch part of the European Community Respiratory Health Survey.[20-21] Chronic cough and chronic phlegm were defined as coughing/bringing up phlegm during winter time on most days for at least three months a year and breathlessness as 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, Germany). Subjects were measured in a sitting position and with use of a noseclip. Subjects had to achieve at least three technically acceptable manoeuvres for measuring the forced expiratory volume in one second (FEV_1), of which two had to be reproducible according to ERS criteria.[22] The maximum value of the reproducible manoeuvres was used in the analysis.

Height (precision: 0.5cm) and weight (precision 0.1kg) were measured and the Body Mass Index (BMI) calculated (weight/height^2). 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.

Statistical analysis

All analyses were performed using the SAS statistical package (version 6.12, Cary, USA). The relation between FEV_1 and dietary factors was studied using a multiple linear regression model with FEV_1 divided by height squared as the dependent, and age, age squared and gender as independent variables.[23] The lung function results are presented in their original scale (ml) for an individual with a standing height of 1.70m. Logistic regression analysis was used to study the association between COPD symptoms and dietary factors. Potential confounders considered were: age, gender, height (for pulmonary function only), BMI, alcohol consumption, energy intake and smoking. Adding pack years and pack years

squared to the models gave the best fit. Adjustment for alcohol consumption did not cause a relevant change in any of the studied associations and this factor was therefore not used in the final analysis. Adjustment for educational level was not performed, since this is likely to lead to over-adjustment of the studied associations.

Tea is the main dietary source of the studied flavonoids. To reduce the correlation between catechin intake and that of flavonols and flavones (from r>0.90 to r=0.55), thereby allowing evaluation of independent effects, the intake of these substances from other sources than tea was calculated.

All analyses were performed using quintiles of intake, since non-linearity was observed. Four dummy-variables, with the lowest quintile of intake as the reference, were added to the models and the difference in FEV_1 and COPD symptoms presented for the fifth vs. the first quintile. To study the independent effects of catechins and of flavonols and flavones not derived from tea, the representing variables were added to the models simultaneously.

A beneficial association of vitamin C and ß-carotene intake with the FEV_1 in the MORGEN-study, was reported earlier.[23] No associations were observed with COPD symptoms. To assess potential confounding by these variables on the studied associations, they were added to the adjusted models. Finally, no clear effect modification by smoking status (current, former, and never smokers) was observed and the stratified results are, therefore, not presented.

Results

The characteristics of the study population are described in table 1. Mean FEV_1 was 3.6 litres and 16% of the subjects reported one ore more COPD symptoms. The average number of pack years smoked was 10.3 (table 1).

Table 1: Description of the study population (n = 13651: the MORGEN-study)

	Mean	SD		%
Age (yr.)	41.2	10.8	Gender (males)	46
Height (m)	1.72	0.09	Cough (yes)	6
BMI (kg/m^2)	24.9	3.9	Phlegm (yes)	8
Smoking (pack years)	10.3	13.8	Breathlessness (yes)	6
Energy intake (MJ)	9.5	3.9	One or more COPD symptoms (yes)	16
FEV_1 (ml)	3586	869		

Average catechin, flavonol and flavone intake was 58 mg/day (SD = 46). The main sources of catechins were tea (72%), apples (12%) and chocolate (4%), and

the main sources of flavonols and flavones were tea (47%), apples (14%) and onions (14%). Intake of catechins and intake of flavonols and flavones were highly correlated (r > 0.90). To be able to study the independent effects, we calculated the intake of catechins (mean = 12 mg/day, SD = 6) and of flavonols and flavones (mean = 8 mg/day, SD = 4) from other sources than tea (r = 0.55).

Catechin, flavonol and flavone intake was positively associated with age (ß = 0.30 mg/year), gender (ß = 14.6 mg) and energy intake (ß= 1.6 mg/MJ) and inversely associated with BMI (ß = -0.57 mg/(m/kg^2)) and pack years of smoking (ß = -0.55 mg/py) (p<0.001). Smoking was inversely associated with the FEV_1 (ß = -7.6 ml/py) and positively associated with COPD symptoms (OR = 1.03 per py) (p<0.001).

Table 2: Mean FEV_1 and prevalence of COPD symptoms by quintiles of catechin and/or flavonol and flavone intake (the MORGEN-study)

	1	2	3	4	5
	Quintiles of catechin, flavonol and flavone intake				
Subjects (n)	2730	2730	2731	2730	2730
Median intake (mg)	15	28	44	68	117
FEV_1 (ml)*	3390	3471	3474	3473	3497
Cough (%)	12	11	8	7	7
Phlegm (%)	10	8	7	7	7
Breathlessness (%)	8	5	5	6	5
	*Quintiles of catechin intake***				
Subjects (n)	2730	2730	2731	2730	2730
Median intake (mg)	5.2	8.2	10.9	14.0	24.0
FEV_1 (ml)*	3364	3424	3488	3502	3526
Cough (%)	13	9	8	7	8
Phlegm (%)	11	8	7	6	7
Breathlessness (%)	9	6	5	4	5
	*Quintiles of flavonol and flavone intake***				
Subjects (n)	2730	2730	2731	2730	2730
Median intake (mg)	4.5	6.3	7.8	9.6	12.8
FEV_1 (ml)*	3397	3442	3477	3503	3485
Cough (%)	12	9	8	8	8
Phlegm (%)	9	7	7	7	8
Breathlessness (%)	8	5	5	5	6

* adjusted for age, height and gender and presented for a standard height of 1.70m
** from other sources than tea

In table 2 the mean FEV_1 and the prevalence of COPD symptoms is given per quintile of catechin and/or flavonol and flavone intake. In further analyses subjects in the first and fifth quintile of intake were compared. The difference between the median intake in these quintiles was 102 mg for total catechin, flavonol and flavone

intake and respectively 14.8 and 8.3 mg for catechin and for flavonol and flavone intake not derived from tea.

Total intake of catechins, flavonols and flavones was positively associated with the FEV1 (ß = 106 ml) and inversely associated with all COPD symptoms (OR = 0.54 to 0.57) before adjustment for smoking. Adjustment for pack years of smoking, strongly reduced the size of the observed effect estimates, to ß = 44 ml for the FEV_1 and OR = 0.74 to 0.90 for COPD symptoms. The association with the prevalence of chronic phlegm was no longer statistically significant (table 3).

Table 3: Difference in FEV_1 (ml)* and prevalence of COPD symptoms between subjects with high vs. low intake of catechins, flavonols and flavones (the MORGEN-study)

		fifth vs. first quintile of catechin, flavonol and flavone intake	
		adjusted1	adjusted2
FEV_1 (ml)*	ß (95%CI)	106 (81 to 131)	44 (18 to 69)
Cough	OR (95%CI)	0.54 (0.44 to 0.65)	0.80 (0.66 to 0.97)
Phlegm	OR (95%CI)	0.71 (0.58 to 0.86)	0.95 (0.77 to 1.16)
Breathlessness	OR (95%CI)	0.57 (0.45 to 0.72)	0.74 (0.58 to 0.94)

* results are presented for a standard height of 1.70m
adjusted1: adjusted for age, height (for FEV_1 only), gender, BMI and energy intake
adjusted2: additional adjustment for smoking (pack years and pack years^2)

Table 4 shows the results of the analyses on the independent effects of catechins and of flavonols and flavones not derived from tea. After adjustment for all potential confounders and for flavonol and flavone intake, catechin intake showed a beneficial association with the FEV_1 (ß = 130 ml) and all COPD symptoms (OR = 0.60-0.72). Flavonol and flavone intake was independently associated with the prevalence of chronic cough only (OR = 0.77).

Additional adjustment for ß-carotene intake did not alter the associations regarding the FEV_1, presented in table 3 and 4, in a relevant way. Adjustment for vitamin C intake reduced the effect of total catechin, flavonol and flavone intake from 44 to 27 ml (95%CI = 1 to 53) and the independent effect of catechin intake from 130 to 122 ml (95%CI = 92 to 152).

Consumption of tea (per 200 ml), the main source of the studied flavonoids, was not associated with FEV_1 (ß = 0.3 ml, p = 0.92) or the prevalence of COPD symptoms (OR = 0.98, p = 0.33), after adjustment for all potential confounders. Intake of solid fruits (mean = 55 g/day, SD = 46) was positively associated with the FEV_1 (29 ml/SD, p<0.001) and inversely associated with the prevalence of COPD

symptoms (one or more: OR = 0.79 per SD, p<0.001). Similar, although slightly weaker, associations were observed with the intake of respectively citrus and other fruits.

Table 4: Independent effects of high vs. low intake of catechins and of flavonols and flavones on the FEV_1 (ml)* and the prevalence of COPD symptoms (the MORGEN-study)

	fifth vs. first quintile of	
	Catechin intake**	Flavonol and flavone intake**
*FEV_1 (ml)**		
crude (ß, 95%CI)	155 (126 to 184)	7 (-21 to 35)
adjusted1 (ß, 95%CI)	167 (138 to 197)	12 (-17 to 35)
adjusted2 (ß, 95%CI)	130 (101 to 159)	-4 (-32 to 24)
Cough		
crude (OR, 95%CI)	0.70 (0.57 to 0.86)	0.76 (0.62 to 0.94)
adjusted1 (OR, 95%CI)	0.57 (0.46 to 0.71)	0.69 (0.56 to 0.86)
adjusted2 (OR, 95%CI)	0.72 (0.58 to 0.90)	0.77 (0.62 to 0.96)
Phlegm		
crude (OR, 95%CI)	0.61 (0.49 to 0.76)	1.12 (0.89 to 1.39)
adjusted1 (OR, 95%CI)	0.50 (0.40 to 0.63)	1.07 (0.86 to 1.34)
adjusted2 (OR, 95%CI)	0.60 (0.47 to 0.75)	1.16 (0.93 to 1.46)
Breathlessness		
crude (OR, 95%CI)	0.54 (0.42 to 0.70)	1.12 (0.87 to 1.44)
adjusted1 (OR, 95%CI)	0.59 (0.47 to 0.76)	0.88 (0.68 to 1.14)
adjusted2 (OR, 95%CI)	0.69 (0.52 to 0.90)	0.94 (0.72 to 1.22)

* results are presented for a standard height of 1.70m
** from other sources than tea
adjusted1: adjusted for age, height (for FEV_1 only), gender, BMI and energy intake
adjusted2: additional adjustment for smoking (pack years and pack years^2)

Discussion

Our study was the first to investigate the association of catechin, flavonol and flavone intake with COPD. Intake of the studied flavonoids was positively associated with the FEV_1 (ß = 44 ml) and inversely associated with chronic cough (OR = 0.80) and breathlessness (OR = 0.74). Catechin intake (not derived from tea) showed strong beneficial associations with both FEV_1 (ß = 130 ml) and all COPD symptoms (OR= 0.60 to 0.72), independent of the effects of flavonols and flavones. The latter were only independently associated with cough. Of the main dietary sources of the studied flavonoids, solid fruit (=apples, pears) intake was, but tea consumption was not, beneficially associated with COPD.

Both for catechins and for flavonols and flavones anti-inflammatory and antioxidant activity has been observed and a beneficial effect on COPD seems theoretically equally likely.[24] We only observed an effect of catechins and not of

flavonols and flavones. Furthermore, since tea is the main dietary source of the studied flavonoids, a beneficial effect of tea consumption on COPD would be expected, even when this effect would be based on the effect of catechins alone. The fact that we did not observed such an association could indicate that the observed effect of the catechins is not causal. A substance which intake, from other foods than tea, is related to that of the catechins may confound the association.

A few parallels with associations between other dietary factors and COPD can, however, be observed. In the literature there is reasonably consistent evidence for a beneficial effect of vitamin C, a hydrophilic antioxidant, on COPD.[10] For vitamin E (lipophylic) the evidence is scarce and inconsistent,[10] despite an equally plausible mechanism of action.[25] In line with this, we observed a beneficial effect of the catechins which are hydrophilic, but not with the lipophylic flavonols and flavones.[24] Furthermore, other fruits and chocolate are the main dietary sources of catechins besides tea and apples. For flavonols and flavones main remaining dietary source is vegetable intake. It may not be coincidental that in contrast to fruits, the evidence for a beneficial association of vegetables with COPD is scarce.[10]

The two catechins that contribute 60% to the catechin content of tea, and are rare in other foods, are (-) - epigallocatechin gallate (ECGg) and (-) - epicatechine gallate (ECg). In vitro, the antioxidant capacities of these catechins were observed to be equal to or stronger than that of the other catechins present in tea.[7,26] However, if ECGg and ECg are less biologically active (in vivo) than other catechins, this would be an alternative explanation for the fact that no association with tea was observed.

Residual confounding by smoking habits does not seem to explain our findings, since in never smokers similar associations were observed between intake of the studied flavonoids and COPD (results not shown). Finally, 15 mg of catechins is present in 2 apples or 30 grams of plain chocolate. If valid, the associated increase in FEV_1 (130 ml), is roughly equivalent to the effect of smoking 1 pack of cigarettes per day during ±17 years and to the effect of an increase in age of 4 to 6 years.[27, 28]

In conclusion, this study on intake of catechins, flavonols and flavones in relation to COPD, suggests a beneficial effect of a high intake of catechins. However, the fact that we observed no association with tea consumption raises the question whether the association is causal. Surprising was also the lack of association between COPD and flavonol and flavone intake. Other studies are required to confirm our findings and to get more insight into the biological effects of different flavonoids.

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Chapter 7

Diet and COPD: independent beneficial effects of fruit, whole grain, and alcohol consumption (the MORGEN-study)

Submitted as:

Tabak C, Smit HA, Heederik D, Ocké MC, Kromhout D. Diet and COPD: independent beneficial effects of fruit, whole grain, and alcohol consumption.

Abstract

Background: To gain more insight into the potential protective effect of diet on Chronic Obstructive Pulmonary Disease (COPD), we studied the independent effects of fruits, vegetables, whole grains, fish and alcohol on 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: The effects of a favourable intake of fruits and whole grains (above the median) and alcohol (1-30g/day) on COPD were observed to be largely independent of each other. The 2578 subjects with a favourable intake of fruits, whole grains and alcohol had a 139 ml higher FEV_1 ($p<0.001$) and a lower prevalence of COPD symptoms (OR = 0.44, $p<0.001$) than those with unfavourable intakes of the three dietary factors (n = 1602). This effect was also observed in never smokers. Fish intake was not, and vegetable intake was not independently, associated with COPD.

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

Introduction

In recent years evidence has accumulated that diet may protect from developing Chronic Obstructive Pulmonary Disease (COPD). However, until today most epidemiological studies have focused on one or only a few dietary factors simultaneously. It is, therefore, not clear whether the effects of the different (groups of) dietary factors on COPD are independent of eachother.

A high intake of dietary antioxidants (e.g. vitamin C, vitamin E and ß-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 yet been studied in relation to COPD, but an effect may be expected due to the fact that the bran and germ of grains are rich in antioxidant substances.[21]

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 ß-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 (1987-1991) were re-examined. Complete information on diet was available for 17,025 subjects. Of these, 1,603 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 FEV_1 measurement (n = 1,493) 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 semi-quantitative food frequency questionnaire, developed for the MORGEN-study which is part of the EPIC study (European Prospective Investigation into Cancer and Nutrition).[22-24] 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.[25] 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.[26,27] 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 three months a year), chronic phlegm (= productive cough during winter time on most days for at least three 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, Germany). Subjects were measured in a sitting position while wearing a noseclip. Subjects had to achieve at least three technically acceptable manoeuvres for measuring the FEV_1, of which two had to be reproducible according to ERS criteria.[28] The maximum value of the reproducible manoeuvres was used in the analysis.

Height (precision 0.5cm) and weight (precision 0.1kg) were measured and the Body mass index (BMI) calculated (weight/height^2). 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 categorised into: low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education) and high (higher vocational or university education). Physical activity was categorised into insufficient=moderate or heavy activity less than 3.5 hours a week, and sufficient=moderate and heavy activity more than 3.5 hours a week of which at least 2 hours of heavy activity.[29]

Statistical Analyses

All analyses were performed using the SAS statistical package (version 6.12, Cary, USA). To study the relation between the FEV_1 and dietary factors, a multiple linear regression model with FEV_1 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 an individual with a standing height of 1.70m.

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 individual association with COPD was studied. Alcohol consumption was categorised into: none (< 1 g/day), low (1-30 g/day) and moderate or heavy (>30 g/day). For fruit, vegetable, fish and whole grain intake subjects in the highest and the lowest decile of intake were compared with respect to level of FEV_1 and prevalence of COPD symptoms.

To study the independent effect of foods associated with COPD, food intake was dichotomised: fruits, vegetables, whole grains into above vs. below the median and alcohol into low vs. other. The relation between each dichotomous variable and COPD was adjusted for the effects of the other foods. To adjust for fruit, vegetable or whole grain intake dummy variables representing quintiles of intake were added to the model. To adjust for alcohol, two dummy variables (1: none vs. low, 2: moderate or higher vs. low alcohol consumption) were added. Furthermore, we compared the FEV_1 and the prevalence of COPD symptoms between subjects with favourable intakes (low alcohol consumption and intake above the median of the other dietary factors) and subjects with unfavourable intakes (none, moderate or heavy alcohol consumption and intake below the median of the other dietary factors). To assess the potential confounding effect of cigarette smoking, we also performed these analyses in never and ever smokers (adjusted for pack years) separately.

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.

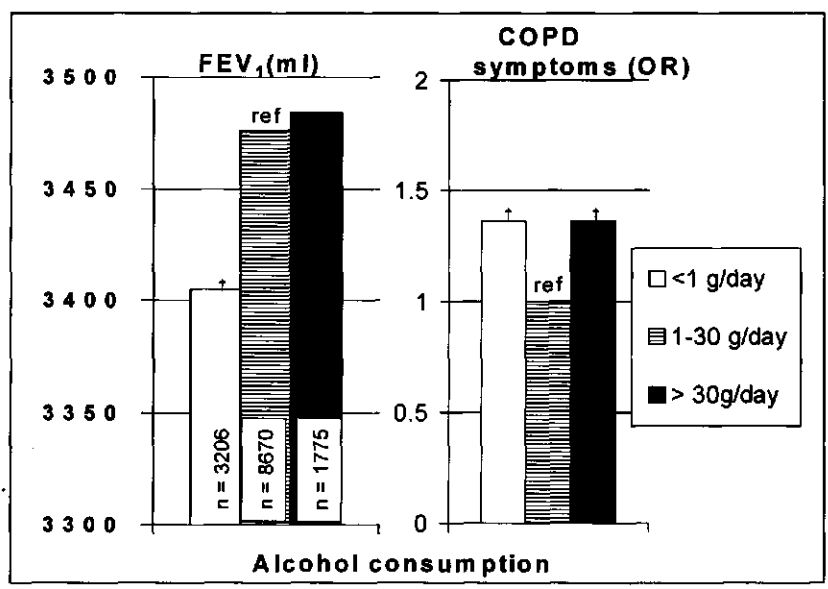
Results

The characteristics of the study population are described in table 1.

Table 1: Characteristics of the study population (the MORGEN-study)

variable	total *n = 13651* mean (SD)	ever smokers *n = 9072* mean (SD)	never smokers *n = 4579* mean (SD)
Age (yr.)	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/m2)	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)	9.5 (2.9)	9.6 (2.9)	9.4 (2.9)
Fruit(juices) (g)	248 (176)	235 (170)	275 (183)
Vegetables (g)	128 (53)	128 (53)	128 (52)
Fish (g)	9 (10)	9 (10)	9 (10)
Whole grains (g)	69 (74)	68 (73)	73 (77)
Alcohol (g)	13 (17)	15 (19)	8 (12)
FEV_1 (ml)	3586 (848)	3540 (838)	3676 (861)
variable	**%**	**%**	**%**
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.



† $p < 0.001$: compared to reference category (ref)

Figure 1: **Adjusted* cross-sectional association between alcohol consumption and COPD (the MORGEN-study).** Adjustments were made for age, gender, height (for FEV_1 only), pack years of smoking, BMI and energy intake

Pack years of smoking was inversely associated with the FEV_1 (ß = -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 other confounders.

The FEV_1 was lower in non-drinkers compared to drinkers. The prevalence of COPD symptoms, however, was lower in subjects with a low alcohol consumption compared to both non-drinkers and those with a moderate or heavy alcohol consumption (figure 1). Therefore, in further analyses alcohol consumption was dichotomised into low vs. other (= none, moderate or heavy).

A high intake of fruit(juices), vegetables or whole grains and a low alcohol consumption was associated with a higher FEV_1 and a lower prevalence of COPD symptoms (table 2). Fish intake was not associated with COPD.

Table 2: Cross-sectional association between intake of individual dietary factors and COPD related outcomes (the MORGEN-study).

	High vs. low food intake*†					
	cut-offs	difference in FEV_1 (ml)			COPD symptoms (OR)		
Foods	(g/day)	adj.[1]	adj.[2]	(95%CI)	crude	adj.[2]	(95%CI)
Fruit(juices)†	<64, >474	152	80	(39-120)	0.50	0.56	(0.45-0.70)
Vegetables†	<68, >198	57	43	(5-80)	0.77	0.71	(0.58-0.88)
Whole grains†	1, >170	152	114	(76-153)	0.54	0.62	(0.50-0.78)
Fish†	<1, >18	21	9	(-27- 45)	1.13	1.14	(0.93-1.41)
Alcohol*	----	66	43	(27-59)	0.63	0.74	(0.67-0.81)

* for alcohol compared groups are: 1-30 g alcohol per day (low) versus otherwise
† compared groups: highest vs. lowest decile of intake
adj.[1] adjusted for age, height and gender
adj.[2] adjusted for age, height (for FEV_1 only), gender, pack years of smoking, BMI and energy intake

After adjustment for the other three foods, the associations of fruit(juices), whole grains and alcohol with COPD remained largely unchanged. For vegetable intake the association with both the FEV_1 and COPD symptoms disappeared (table 3). The sum of the independent effects of a favourable intake of fruit(juices), whole grains and alcohol was 127 ml (= 39 + 54 + 34) in FEV_1 and for COPD symptoms the odds ratio can be calculated to be 0.48 (= 0.78 * 0.79 * 0.77).

In subjects with intake of fruit(juices) and whole grains above the median and low alcohol consumption (favourable intakes), the FEV_1 was observed to be 139 ml higher and the prevalence of COPD symptoms lower (OR = 0.44) than in subjects with intake of fruit(juices) and whole grains below the median and none, moderate or heavy alcohol consumption (unfavourable intakes). A favourable intake of the three

foods was also beneficially associated with the FEV_1 and with COPD symptoms in never smokers (table 4).

Table 3: Difference in FEV_1 and the prevalence of COPD symptoms associated with a favourable* vs. an unfavourable† intake of individual foods, before and after adjustment for the effects of the other foods (the MORGEN-study)

Foods	n*/ n†	median (g/day)	Difference in FEV_1 (ml) adj.[1]	adj.[2] (95%CI)	Difference in COPD symptoms (OR) adj.[1]	adj.[2] (95%CI)
Fruit(juices)	6827 / 6827	216	46	39 (23 - 55)	0.76	0.78 (0.71-0.86)
Vegetables	6827 / 6827	120	23	7 (-8 - 23)	0.90	0.97 (0.88-1.08)
Whole grains	6827 / 6827	45	64	54 (38 - 70)	0.75	0.79 (0.72-0.88)
Alcohol	8687 / 4967	---	43	34 (17 - 50)	0.74	0.77 (0.70-0.85)

* favourable: for fruit(juices) and whole grains defined as intake *above* the median, for alcohol defined as low consumption (1-30 g/day)

† unfavourable: for fruit(juices) and whole grains defined as intake *below* the median, for alcohol defined as none, moderate or heavy consumption

adj.[1] adjusted for age, height (for FEV_1 only), gender, pack years of smoking, BMI and energy intake

adj.[2] dummies for quintiles of intake of fruit, vegetable and/or whole grain intake and/or for none vs. low and for moderate or higher vs. low alcohol consumption were added to the adjusted model.

Table 4: Adjusted[1] difference in FEV_1 and prevalence of COPD symptoms between subjects with favourable* vs. unfavourable† intakes of fruits, whole grains and alcohol (the MORGEN-study).

	n* /n†	Difference in FEV_1 (ml) adj.[1] (95%CI)	Difference in COPD symptoms (OR) adj.[1] (95%CI)
Total population	2578/ 1602	139 (109-170)	0.44 (0.37-0.53)
ever smokers	1746/ 1095	143 (105-181)	0.42 (0.34-0.52)
never smokers	830/ 527	114 (63-165)	0.61 (0.42-0.88)

* favourable: for fruit(juices) and whole grains defined as intake *above* the median, for alcohol defined as low consumption (1-30 g/day)

† unfavourable: for fruit(juices) and whole grains defined as intake *below* the median, for alcohol defined as none, moderate or heavy consumption

adj.[1] adjusted for age, height (for FEV_1 only), gender, pack years of smoking, BMI and energy intake

Discussion

Our cross-sectional study showed that the beneficial effects of fruit(juices), whole grains and alcohol on COPD related outcomes were largely independent of each

other. In the subgroup of subjects with intake of fruit(juices) and whole grains above the median and low alcohol consumption (favourable intakes), the FEV_1 was 139 ml higher and the prevalence of COPD symptoms lower (OR = 0.44) than in those with unfavourable intakes of the three foods. Similar, although slightly weaker, associations were observed in never smokers. Fish intake was not associated with COPD, while the effect of vegetable intake was not independent of that of fruits, whole grains and alcohol.

Antioxidants and foods rich in antioxidants, like fruits and vegetables, are thought to protect the airways against oxidant-mediated damage leading to COPD.[30] 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.[23,31] Furthermore, a large part of the vegetables is usually consumed boiled, which leads to loss of vitamin C. In line with our findings on fruit and vegetable intake (when not adjusted for other foods), in the MORGEN-study a high intake of vitamin C and ß-carotene was observed to be positively associated with pulmonary function.[6]

As hypothesised, 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).[21] The observed beneficial association of a low alcohol consumption with COPD is consistent with earlier findings,[9,19,20] although the underlying biological mechanism is still unclear. 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]

Another important finding of our study is that also in never smokers a beneficial effect of fruits, whole grains and alcohol on pulmonary function and the prevalence 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 ever smokers the observed associations were somewhat stronger. Smokers are known to consume less fruits, vegetables and whole grain products and to have lower intakes of vitamin C and ß-carotene.[32] On the other hand, the potential protective effect of diet may be larger in smokers due to the higher exposure of their lung tissue to oxidants.

The definition of a favourable intake used; above the median for fruit(juices) (fruit alone > 129 g/day, fruit and fruit juices > 216 g/day) and whole grain products (> 45 g/day) and low alcohol consumption, is comparable with 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. Furthermore, the observed effect on pulmonary function (a 139 ml in FEV_1), is roughly equivalent to the effect of an increase in age of 5 years and to smoking 1 pack of cigarettes per day during 20 to 25 years.[33] The effect of dietary factors on COPD therefore does involve an important public health impact.

A number of methodological concerns needs to be addressed. First of all, this study was cross-sectional and therefore a temporal relation between diet and pulmonary function cannot be established. 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.[34] However, only minor differences in intake of the studied foods were observed between those with and without technically acceptable and reproducible FEV_1 measurement (results not shown). Therefore this potential selection is not likely to have influenced the observed associations. Finally, confounding by health related lifestyle 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 beneficial associations of fruits, whole grain and alcohol intake with COPD that were largely independent of eachother. Since these effects were also observed in never smokers, residual confounding by smoking could not explain our findings totally.

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Chapter 8

General discussion

The aim of this thesis was to gain more insight into the relation between diet and Chronic Obstructive Pulmonary Disease (COPD).

Data from two large-scale epidemiological studies, the Seven Countries Study and the MORGEN-study, were considered to be complimentary for this purpose. Data from the Seven Countries Study allowed us to study the relation between diet and COPD related outcomes longitudinally in an international setting. However, the Seven Countries Study was not designed to investigate COPD and the main measurements (1960-1970) were performed with less sophisticated methods than available today. Furthermore, only middle-aged and older men were examined with a very large proportion of smokers. The MORGEN-study (1993-1997) was designed to examine COPD in the Dutch population. Both men and women of a wide age-range (20-59 years) were examined using modern high-quality methods and there was a large variation in smoking habits in the study population. An important limitation compared to the Seven Countries Study was, however, its cross-sectional design.

Studied were COPD mortality (Chapters 2-4), pulmonary function (Chapters 4-7) and COPD symptoms (Chapters 6 and 7) in relation to three groups of dietary factors: antioxidants and foods rich in antioxidants (vitamin C, vitamin E, ß-carotene, flavonoids, fruits, vegetables and/or whole grains/bread), n-3 fatty acids and fish, and alcohol.

Main findings

The studies described in this thesis mainly suggest a protective effect of a number of plant-based foods, i.e. fruits, whole grains and alcohol, against COPD. Fruit intake was inversely associated with long-term COPD mortality both at the ecological and at the individual level. Furthermore, the combined fruit and vegetable intake and also bread intake showed consistent positive associations with pulmonary function in three countries. Alcohol consumption showed a U-shaped relation with 20-yr COPD mortality, with the lowest rate in men with a light alcohol consumption (>1 drink/week, ≤3 drinks/day). This U-shaped curve was supported by cross-sectional data on alcohol consumption and pulmonary function. Finally, a high intake of fruits and whole grains and light alcohol consumption (up to 3 drinks/day), were observed to be independently and beneficially associated with both pulmonary function and COPD symptoms.

Intake of catechins was also suggested to be beneficially associated with COPD. However, for intake of flavonols and flavones and for the main dietary source of the studied flavonoids (i.e. tea) no effect was observed. Inconsistent associations with

COPD were observed for vitamin C, ß-carotene and vitamin E intake. Finally, fish intake was not, and vegetable intake was not independently, associated with COPD.

Comparison of findings with literature

A detailed review of the epidemiological evidence regarding the relation between diet and COPD has recently been published.[1] For antioxidants, foods rich in antioxidants, fish and n-3 fatty acids, the evidence will be summarised here and compared with the findings described in this thesis. The association between intake of individual dietary antioxidants and COPD in the MORGEN-study has been reported earlier by Grievink, et al. [2] However, at that time only data from 1994 and 1995 were available. In this section also the results using data from all four years (1993-1997) will be discussed. Finally, a more detailed description of the literature on alcohol consumption and COPD will be given, since this dietary factor was not included in the review.

Antioxidants and related foods

Vitamin C

There's reasonably consistent evidence indicating an association between dietary intake of vitamin C and pulmonary function in the literature. [2-6] The reported increases in FEV_1 (ml) per mg vitamin C range from 0.2 to 1.3. Although Dow, et al.[5] observed no statistically significant association between vitamin C intake and pulmonary function, the size of the observed effect is comparable to that observed in the other studies (0.7 ml/mg). The reported associations regarding vitamin C and COPD symptoms are not consistent.[2,7]

We observed no associations between dietary vitamin C intake and COPD mortality in middle-aged men participating in the Seven Countries Study. Vitamin C intake was positively associated with pulmonary function in two of the three countries in which this association could be studied. The observed effects were relatively large, with respectively 2.2 and 1.0 ml $FEV_{0.75}$ per mg vitamin C. The association was, however, only statistically significant without adjustment for energy intake and it is unclear whether the results are more valid with or without energy adjustment. In Dutch men and women participating in the MORGEN-study between 1993 and 1997, vitamin C intake (10th vs. 1st decile) was positively associated with the FEV_1 (ß = ±0.6 ml/mg) as described earlier by Grievink, et al.[2] for 1994 and 1995. When using data from four years, having one or more symptoms of COPD was observed to be inversely associated with vitamin C intake (OR = 0.57).

Vitamin E

The observed relationships of vitamin E intake with COPD reported in the literature are inconsistent.[2,4,5,8]

The studies described in this thesis also showed no consistent associations between vitamin E intake and different COPD related outcomes. Baseline vitamin E intake was associated with long-term COPD mortality at the individual, but not at the ecological level. Furthermore, the association of vitamin E intake with pulmonary function depended on the country studied and on whether or not adjustments for energy intake were made. Finally, vitamin E intake was not associated with COPD symptoms or pulmonary function in Dutch participants to the MORGEN-study.

ß-carotene

The relationships between ß-carotene intake and COPD observed in different studies,[2,8-10] including the ones described in this thesis, are inconsistent.

We observed no association between ß-carotene intake and COPD mortality in middle-aged men. In the Netherlands, ß-carotene intake was positively associated with pulmonary function both in middle-aged men (Dutch cohort of the Seven Countries Study) and in men and women aged 20-59 years (MORGEN-study). In the MORGEN-study ß-carotene intake was furthermore inversely associated with the prevalence of COPD symptoms (using data from four years). In middle-aged men from two other European countries ß-carotene intake was, however, not associated with pulmonary function.

Catechins, flavonols and flavones

In the MORGEN-study we observed independent beneficial associations of catechin intake (not derived from tea) with the FEV_1 (fifth vs. first quintile: ß = 130 ml) and with the prevalence of chronic cough, chronic phlegm and breathlessness (OR = 0.60-0.72). Flavonol and flavone intake was only independently associated with chronic cough. Of the main dietary sources of the studied flavonoids solid fruit, but not tea, intake was beneficially associated with COPD.

Miedema, et al.[9] earlier reported a beneficial association between solid fruit consumption and 25-yr incidence of chronic lung disease and suggested that the effect may be due to the high flavonoid contents of these fruits. To our knowledge, intake of flavonoids has not been studied in relation to COPD before.

Fruits and vegetables

Fruit intake appears to be protectively associated with pulmonary function.[11-13] In cross-sectional studies a difference in FEV_1 of 79 to 188 ml was observed between

high and low fruit consumption, depending among other things on the definition for high and low fruit consumption used and on whether adults or children were studied. In the only reported longitudinal study no association between fruit intake and annual change in FEV_1 was observed during a 7-year follow-up period.[13] Vegetable intake has not been observed to be associated with pulmonary function.[3,5,12] A protective effect of vegetable intake on COPD symptoms was observed.[14] However, in middle-aged Dutch men, 25-yr incidence of chronic lung disease was inversely associated with baseline consumption of fruits and especially solid fruits, but not with vegetable intake. Considering the age of the men and the high proportion of smokers (75%) at baseline, the endpoint in this study most likely involved COPD and not asthma.[9]

Our findings regarding fruit consumption and pulmonary function are fairly consistent. The energy-adjusted association between fruit consumption and pulmonary function in middle-aged men was only positive in one of the three countries in which this association could be studied. Without adjustment for energy intake a trend towards a positive association could, however, be observed in all three countries. Moreover, the combined fruit and vegetable intake was positively associated with pulmonary function in all three countries (intake of both foods above vs. below the median intake: 110 -169 ml before and 53 -118 ml after adjustment for energy intake). Furthermore, in Dutch participants of the MORGEN-study, fruit intake (above vs. below the median (= 216 g/day)) was positively and independently associated with both pulmonary function and COPD symptoms (respectively ß = 39 ml and OR = 0.78). Our findings regarding fruit consumption and COPD mortality (both at the ecological and at the individual level) further support a protective effect of high fruit consumption against COPD.

Vegetable intake was not observed to be (independently) associated with any of the studied COPD outcomes.

Whole grains and bread

Surprisingly, in middle-aged men from Finland, Italy and the Netherlands pulmonary function (FEV_1 or $FEV_{0.75}$) was observed to be positively associated with bread consumption (ß = 0.35 to 0.57 ml/mg). We hypothesised that in this case bread intake may be considered to be an indicator of whole grain intake. Whole grains are rich in antioxidant substances[15] and may therefore be hypothesised to protect against COPD. An independent protective association of whole grain intake (above vs. below the median (= 45 g/day) with both the FEV_1 (ß = 54 ml) and COPD symptoms (OR = 0.79) was indeed observed in Dutch participants to the MORGEN-study. To our knowledge this association has not been studied before.

N-3 fatty acids and fish

Several studies have reported beneficial effects of fish or n-3 fatty acid intake against COPD, but at closer inspection it seems questionable whether such an effect actually exists.[7,16-18] Only in one study[7] confounding by other dietary factors associated with COPD was taken into account and as a result the observed association was no longer statistically significant. Furthermore, in two studies[17,18] the observed associations with pulmonary function were only statistically significant in subgroups and in the only individual-level longitudinal study that has been published, no association was observed with 25-yr incidence of chronic lung disease.[9] Finally, after 1994 only two studies[12,19] have reported (negative findings) on fish intake and COPD. This is surprising, considering the growing interest involving diet and COPD. Publication bias, negative results not being published, may explain this phenomenon.

We only observed a relatively weak association between fish intake and COPD mortality in our ecological study. This association was only statistically significant after adjustment for one of the potential confounders. In cross-sectional studies on fish intake and pulmonary function or COPD symptoms and in a longitudinal study on fish intake and 20-yr COPD mortality no associations were observed.

Alcohol consumption

Until today almost all studies focused on the potential detrimental effect of heavy alcohol consumption on COPD. Reported associations not adjusted for smoking will be ignored here. Banner,[20] and Emergil, et al.[21] observed a decreased diffusion capacity in alcoholics, in contrast to Lyon et al.[22] Garshick et al.[23] observed detrimental associations between alcohol consumption and both pulmonary function and COPD symptoms in a study including a large number of alcoholics. A detrimental effect of heavy alcohol consumption is also suggested by studies in non-alcoholic populations. In one study an inverse association between alcohol consumption and FEV_1 was observed only when the heavy drinkers (> 350 g/week) were included in the analyses.[24] In another study especially the frequency of intoxication with alcohol was observed to be positively associated with respiratory symptoms.[25] Finally, in a group of policemen with a relatively high alcohol consumption (mean 33 ± 29: 10% with alcohol consumption > 70 g/day) an inverse association between alcohol consumption and FEV_1 was observed.[26]

With regard to light-to-moderate alcohol consumption, the results of different studies are inconclusive. In one study alcohol consumption was positively associated with COPD symptoms and inversely associated with pulmonary function.[27] The latter association was only statistically significant in the heavy

smokers, raising the question whether residual confounding by smoking may have occurred. In another study moderate alcohol consumption was observed to be inversely associated with total lung capacity, but not with measures of airway obstruction, like the FEV_1 .[28] In two large cross-sectional studies, by Cohen et al.[29] and Sparrow et al,[30] no association was observed between alcohol consumption and airway obstruction. Cohen, et al.[29], however, did observe indications for a protective association between alcohol and airway restriction (FVC as %pred.). Furthermore, a lower 25-yr incidence of asthma and COPD was observed in drinkers compared to non-drinkers[9] and a lower alcohol consumption in subjects with compared to subjects without small airways disease[31]. Finally, a beneficial effect of alcohol consumption on the prevalence and extent of emphysema, determined by autopsy, was suggested by Pratt, et al.[32]

We observed a U-shaped curve between alcohol consumption and 20-yr COPD mortality in middle-aged men from three European countries, with the lowest risk in men with a light alcohol consumption (> 1 alcoholic drink per week and ≤ 3 drinks per day (= >1.4 and ≤ 30 g/day)). Furthermore, in middle-aged men from Finland and the Netherlands, respectively the $FEV_{0.75}$ and the FEV_1 were observed to be higher in light drinkers (up to 3 drinks per day) compared to non-drinkers. Italian men with a very heavy alcohol consumption (> 12 drinks/day) had a lower $FEV_{0.75}$ than men with a moderate to heavy alcohol consumption (> 3 and ≤ 12 drinks/week). In the Dutch participants of the MORGEN-study, those with light alcohol consumption (≥ 1, ≤ 30 g/day) had a higher FEV_1 and a lower prevalence of COPD symptoms than non-drinkers. Consuming more alcohol (> 30 g/day) was not associated with a lower FEV_1. However, a higher prevalence of COPD symptoms was observed in subjects with moderate or heavy alcohol consumption compared to those with light alcohol consumption.

Concluding remarks

Studies described in the literature and in this thesis give the most consistent indications for a protective effect of fruit consumption on COPD. With regard to vitamin C intake there are also strong indications, although the results are somewhat more variable, especially for outcomes other than pulmonary function. The protective effect of a high intake of catechins and whole grains and of light alcohol consumption described in this thesis, needs to be confirmed in other studies. Finally, the relation of vitamin E and ß-carotene intake with COPD remains unclear and considering all the evidence, an independent protective effect of vegetable or fish consumption seems unlikely. However, in most studies the level of fish intake was

moderate and a beneficial effect of high fish consumption can not be excluded. The size of the observed effects, and its public health relevance will be discussed later.

Causality of the relation between diet and COPD

Most of the studies performed on diet and COPD had a cross-sectional design. An important question is whether the observed associations are causal.

Plausible biological mechanism

Causality is supported by the availability of a plausible biological mechanism of action. For the studied dietary factors these mechanisms are described in Chapter 1.

Misclassification of exposure

For the antioxidant vitamins, especially ß-carotene and vitamin E, the present evidence on a protective effect on COPD is inconsistent. This may indicate that a protective effect of these dietary factors does not exist. However, especially if the effects are small, the inconsistent evidence may be the result of biases in performed studies, such as measurement errors in dietary intake or plasma levels of the dietary factors. Furthermore, dietary intake and even plasma levels may not be a good indicator of the presence of the studied dietary factors or their metabolites in the lower airways. Vitamin E, for instance, is a lipid soluble antioxidant that occurs in membranes and lipoproteins. A more valid measure of the exposure may therefore be the amount of vitamin E present in these structures in the lower respiratory tract. Methods to perform such measurements are available (e.g. BAL). Kelly, et al.,[33] for instance, recently reported lower levels of vitamin C and α-tocopherol in the lower airways of asthmatic patients compared to controls, while the plasma levels were similar in the two groups.

Temporal relation

The only indisputable criterion for causality is that the cause (relevant exposure) must precede the effect (occurrence of the disease) in time.[34] In cross-sectional studies it is usually impossible to discern between a causal relation and a non-causal association for instance introduced by the fact that people with (symptoms of) COPD changed their diet. However, also the few performed longitudinal studies show protective associations of dietary factors with COPD related outcomes (Miedema, et al.[9] and Ch 2, 3 and 4). In the Dutch cohort of the Seven Countries Study the relation between baseline diet and 25-yr incidence of chronic lung disease remained unaltered when the men with asthma or COPD diagnosed during the first

two years were excluded from the analysis.[9] This indicates, as was observed, that the food consumption of men with preclinical disease at baseline was not different from the baseline food consumption of cases diagnosed in later years. In the 1960's, when the Seven Countries Study was performed, knowledge on the health effects of diet was much more limited than today. However, even today only a limited number of people are conscious of the potential protective effect of diet on COPD. It is therefore unlikely that participants of the MORGEN-study have changed their diet as a consequence of (preclinical) COPD. This is further supported by the fact that symptoms of COPD only become manifest late in the course of the disease.

Confounding by smoking habits and other health related lifestyle factors

Another issue when establishing causality is the potential influence of confounding factors.

It is known that smokers tend to eat less fruits, vegetables and whole grain products and have lower intakes of vitamin C and ß-carotene and a higher intake of alcohol than non-smokers.[35,36] The higher exposure of smokers to free radicals and other oxidants in cigarette smoke also causes a higher demand for antioxidants to protect the cells. Due to the lower intake and the higher turnover, smokers have lower plasma levels of vitamin C[37] and ß-carotene.[36]

Even when adjustments for smoking habits are performed, in most studies adjustments were made for smoking status and/or pack years of cigarette smoking, the potential for residual confounding by smoking remains. This can only be excluded by studying lifelong non-smokers. Strachan et al.[11] observed a positive association between pulmonary function and fruit consumption in this subgroup and in the MORGEN-study a joint effect of intake of fruits, vegetables and whole grains above the median and light alcohol consumption on pulmonary function was also observed in never smokers (Chapter 7). In these studies residual confounding by cigarette smoking cannot explain observed associations between diet and COPD completely.

Another potential source of confounding is healthy lifestyle. A high intake of antioxidants, fruits, vegetables and whole grains is generally considered 'healthy' and may reflect a healthy lifestyle in general, responsible for the observed protective effect. This is difficult to establish. A healthy diet is a component of a healthy lifestyle and it is likely that at least part of the effect of a healthy lifestyle is mediated through diet. Whether this is also the case in relation to COPD is unclear. On the other hand, other health related lifestyle factors, such as indoor air pollution, may confound the relation between diet and COPD. Adjusting for an indicator of healthy lifestyle, such as educational level, does not resolve this issue. If adjustment for educational level

reduces the effect of diet, this can also be the result of over-adjustment when diet is an intermediate of healthy lifestyle or it may indicate that healthy lifestyle was confounding the association between diet and COPD. In the MORGEN-study the joint effect of fruits, vegetables, whole grains and alcohol in never and current smokers, was independent of educational level and physical activity. Also in other studies where associations between diet and COPD related outcomes were adjusted for indicators of socio-economic status, no appreciable effect was observed. [3,4,6,8,11-14,16-18] However, socio-economic status is a very complex concept and probably not reflected accurately by one indicator such as educational level.

In conclusion, there seems to be a temporal relation between diet and COPD that can not totally be explained by confounding effects of smoking. The existence of biologically plausible mechanisms of action for the different dietary factors (see Chapter 1) add to the evidence that the relations between different dietary factors and COPD are causal. However, confounding by other health related lifestyle factors besides smoking can not be excluded.

Public health relevance

Another issue that needs to be discussed is the potential public health relevance of the observed effects of dietary factors on COPD. If the public health relevance is very small, further study of the relation between diet and COPD and establishing the causality of the association, becomes less important. The estimated values presented here only give an indication of the potential public health effect of dietary factors, since interactions between different risk factors were not taken into account. For instance, in the Dutch cohort of the Seven Countries Study the percentage of never-smokers is low. If the effect of the studied dietary factor only occurs in smokers, the estimated public health effect in this population is likely to be over-estimated in populations with a lower prevalence of smoking.

The observed effect of dietary factors on pulmonary function roughly ranges from 50 to 150 ml in FEV_1, depending on the studied factors and the compared intakes. When expressed as a percentage of the average FEV_1 in a population, a 100 ml increase in FEV_1 seems small. In the MORGEN-population 100 ml is, for instance, equal to 3.9% of the average FEV_1 (3.6 litres). However, in healthy adults 100 ml is equivalent to the decrease in FEV_1 associated with ageing 3 to 5 years[38-41] and to the effect of smoking 1 pack of cigarettes per day during 10 to 20 years.[38,42,43] Furthermore, a 100 ml increase in the average FEV_1 or $FEV_{0.75}$, was estimated to be associated with a reduction in the prevalence of airway obstruction (< 70%pred) from 2.6 to 2.0% (= -23%) in the MORGEN-population and from respectively 14.8 to 12.2

(-18%) and 11.6 to 9.2% (-21%) in middle-aged men from Finland and Italy studied in the Seven Countries Study (see Appendix).

Also data with regard to COPD mortality and the prevalence of COPD symptoms show that the observed effects of different dietary factors, if causal, may certainly be of public health relevance (see Appendix). In middle-aged participants of the Seven Countries Study a shift of all men in the lowest tertile of fruit or vitamin E intake to the highest tertile of intake, was estimated to reduce the number of COPD mortality cases during 20-years of follow-up with 28 and 20% for fruit and vitamin E, respectively. A more realistic shift in exposure for these dietary factors, namely from the lowest to the middle and from the middle to the highest tertile of intake, was still estimated to prevent respectively 21 and 14% of the COPD mortality. In this population, a shift in alcohol consumption of all men with a very light(< 1 alcoholic drink per wk) to a light (> 1 drink per week and < 3 drinks per day) alcohol consumption was estimated to reduce COPD mortality with 15%. With regard to the prevalence of COPD symptoms in the MORGEN-population, a favourable in stead of an unfavourable intake of fruits, whole grains or alcohol (see chapter 7) was calculated to be associated with a reduction in prevalence of 11 to 12%. A favourable in stead of an unfavourable intake of all three foods was associated with a 28% reduction in COPD symptoms.

If causal, the observed effect of diet is estimated to reduce COPD with 10 to 30% at the population level. A relatively small individual effect may thus constitute a large public health effect.

Conclusions

The studies described in this thesis suggest a protective effect of several dietary factors against COPD. Of the antioxidant factors the most consistent evidence was observed for an association between fruit consumption and COPD. A potential protective effect of catechin and whole grain intake on COPD has not been reported earlier and needs to be confirmed in further studies. Our results do not support a protective effect of moderate levels of N-3 fatty acid or fish intake against COPD. Finally, a protective effect of light alcohol consumption was suggested.

Causality of the observed relations is supported by an apparently temporal relation and by the existence of plausible biological mechanisms of action. Smoking could not explain our findings. Confounding by other health related lifestyle factors can, however, not be excluded. If causal, the observed effect of diet on COPD is certainly of public health relevance.

Final considerations and future studies

Adult and childhood diet

A 'healthy' diet in adult life may reflect dietary habits in childhood and thereby the growth and development of the lungs. A study among three generations of Dutch women showed a resemblance between mothers and their adult daughters in nutrition knowledge (r = 0.30-0.35) and in dietary habits.[44,45] The strongest associations between the youngest and the middle generation was observed for fish intake (r = 0.41) and the consumption of sweet and savoury snacks (r = ± 0.30). The latter association (for savoury snacks) was also observed between the older and the middle generation (r = 0.35).

This implies that besides the larger social context also the dietary habits of the family of origin influences the diet of adults. Associations between adult diet and risk of COPD may, therefore, partly be a reflection of the relation between diet and lung development in childhood. If so, attention should focus on improvement of both childhood and adult diet in the prevention of COPD.

A first step to elucidate this issue may be to determine whether young adults with a favourable diet in childhood (e.g. high intake of fruits) have a better pulmonary function than young adults with a less favourable childhood diet.

Dietary patterns

Until today COPD has been studied in relation to specific nutrients (e.g. vitamin C) or specific foods or food groups (e.g. fruits). This gives information on the biological mechanisms through which diet may affect COPD and on whether an increase in intake of nutrients through a higher consumption of specific foods may lead to the intended physiological effect. However, a particular food is often consumed at the expense of another one. To learn more about the impact of many foods and their interactions simultaneously, it is important to study dietary patterns in relation to disease. An advantage of this approach is that it can be used to identify groups at which preventive actions, like nutritional education, may be targeted.

One approach to establish dietary patterns is to use pre-determined criteria, based on available knowledge. In a sense this is what we did in the MORGEN-study when comparing subjects with a favourable intake of fruits, whole grains and alcohol with those with unfavourable intakes of the three foods. The most obvious methods to establish dietary patterns based on a large number of dietary factors and without using prior knowledge on the relation between diet and health are cluster or factor analysis. However, when using standard cluster analyses on dietary data of the MORGEN-study, we were unable to establish clearly separate clusters. When using factor-analyses, a similar problem occurred. Assigning subjects to one factor was

considered arbitrary, since subjects were observed to load highly on more than one factor. It would, however, be relevant to investigate whether these methods can be enhanced to select subgroups with clearly distinct dietary patterns.

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Summary

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterised by airflow obstruction due to chronic bronchitis and/or emphysema. It is an important cause of morbidity and mortality around the world. In the coming decades, COPD rates may decrease due to a decreasing prevalence of smoking since the middle of the 1960's. However, at the moment rates are still rising, especially in women and very old men.

In the early 1990's several dietary factors were suggested to be related to COPD, based on proposed biological mechanisms of action and a small number of epidemiological studies. Antioxidants (e.g. vitamin C, vitamin E and ß-carotene) and foods rich in antioxidants (e.g. fruits, vegetables) are thought to protect the airways against oxidant-mediated damage. For alcohol inhibitory effects on inflammatory cells have been observed and n-3 fatty acids (mainly present in fish) may have anti-inflammatory effects through their influence on the arachidonic acid metabolism.

Methods

To gain more insight into the relation between diet and COPD, we analysed data from two large-scale population-based epidemiological studies. Data from the Seven Countries Study (SCS: 1960-1990) allowed us to study the relation longitudinally in an international setting. However, the main measurements (1960-1970) were performed with less sophisticated methods than available today and only middle-aged or older, mainly ever smoking, men were examined. The MORGEN-study (1993-1997) was designed to examine the prevalence of (risk factors for) chronic diseases (including COPD) in the Dutch population. Men and women in a broad age-range (20-59 yr.) and with a large variation in smoking habits were examined using modern high-quality methods. An important limitation was, however, its cross-sectional design.

COPD mortality, pulmonary function (forced expiratory function in one (= FEV_1) or in 0.75 seconds ($FEV_{0.75}$)) and/or COPD symptoms (breathlessness, chronic cough and chronic phlegm) were studied in relation to intake of antioxidants and foods rich in antioxidants, n-3 fatty acids and/or fish, and alcohol. Age, height, gender, smoking, body mass index and total energy intake were considered to be potential confounding variables.

Results

Diet and 25-yr COPD mortality (SCS: ecological association)

In the 16 cohorts of the Seven Countries Study (from Europe, the VS and Japan), we observed an inverse ecological association of 25-yr COPD mortality with baseline consumption of fruit (rate ratio (=RR) 0.49, 95%CI = 0.36 to 0.67) and fish (RR =

0.97, 95%CI = 0.93 to 1.00). The RR's were calculated for a change equal to 10% of the overall mean intake (= 13.1 g for fruits and 4.4 g for fish). COPD mortality was not associated with intake of vitamin C or E, ß-carotene or vegetables. **(Ch. 2)**

Diet and 20-yr COPD mortality (SCS)

In 2953 men of two Finnish, two Italian and the Dutch cohort, we studied the association between baseline diet and 20-yr COPD mortality at the individual level. Fruit and vitamin E intake were inversely associated with COPD mortality, with respectively RR = 0.49 (95%CI = 0.26 to 0.93) and RR = 0.51 (95%CI = 0.27 to 0.99) before and RR = 0.56 (95%CI = 0.29 to 1.09) and RR = 0.66 (95%CI = 0.31 to 1.42) after energy adjustment. No association was observed for vitamin C, ß-carotene, vegetables and fish. **(Ch. 3)** A smoothed spline-plot showed a U-shaped curve of baseline alcohol consumption with COPD mortality in the 5 cohorts. Compared to non- and occasional drinkers, the RR was 0.60 (95%CI = 0.33 to 1.09) in light drinkers (>1 alcoholic drink/week, ≤ 3 drinks/day) and 1.25 (95%CI = 0.47 to 3.31) in those with a higher level of alcohol consumption. **(Ch. 4)**

Diet and pulmonary function (SCS)

We furthermore studied the association between diet and pulmonary function ($FEV_{0.75}$ or FEV_1 here called FEV) in 1969 in the Finnish men (n=1248) and in 1965 in the Italian (n=1386) and Dutch (n=691) men. In occasional and light drinkers compared to non-drinkers, the FEV was 64 ml (95%CI = -12 to 141) higher in Finland and 94 ml (95%CI =2 to 186) higher in the Netherlands. In Italy, the FEV was 98 ml (95%CI = 8 to 187) lower in very heavy drinkers (> 12 drinks/day) compared to moderate-to-heavy drinkers (>3, <12 drinks/day). **(Ch. 4)** The associations of fruit, vegetable, vitamin C, vitamin E and ß-carotene intake with pulmonary function were not consistent across the countries. However, in all three countries men with intake of both fruits and vegetables above the median had a higher FEV than those with a low intake of both foods. The difference in FEV ranged from 110 to 169 ml before and from 53 to 118 ml after energy adjustment. Furthermore, bread consumption was positively associated with pulmonary function, with ß = 0.35 to 0.57 ml/g. Fish intake was not associated with FEV. **(Ch. 5)**

Diet and COPD (MORGEN-study)

In 13,651 men and women who participated between 1994 and 1997 in the MORGEN-study, we studied the association of dietary factors with pulmonary function and COPD symptoms. Total catechin, flavonol and flavone intake was positively associated with the FEV_1 (ß = 44 ml, 95%CI = 18 to 69) and inversely

associated with chronic cough (OR = 0.80, 95%CI = 0.66 to 0.97) and breathlessness (OR = 0.74, 95%CI = 0.58 to 0.94). Catechin intake was independently associated with both the FEV_1 (ß = 130 ml, 95%CI = 101 to 159) and all three COPD symptoms (OR = 0.60-0.72, $p<0.001$), while flavonol and flavone intake was independently associated with chronic cough only. Solid fruit (=apples, pears), but not tea, intake was beneficially associated with COPD. **(Ch. 6)**

Furthermore, we observed independent beneficial effects of a favourable intake of fruits and whole grains (above the median) and alcohol (1-30 g/day) on pulmonary function and COPD symptoms. The 2578 subjects with a favourable intake of all three foods had a 139 ml higher FEV_1 (95%CI = 109 to 170) and a lower prevalence of COPP symptoms (OR = 0.44, 95%CI = 0.37 to 0.55) compared to those with an unfavourable intake of the three foods. In never smokers a favourable intake of the three foods was associated with a 114 ml higher FEV_1 (95%CI = 63 to 165) and with a lower prevalence of COPD symptoms (OR= 0.61, 95%CI = 0.42 to 0.88). Fish intake was not, and vegetable intake was not independently, associated with COPD. **(Ch. 7)**

Discussion and conclusions

The studies described in this thesis suggest a protective effect of several dietary factors against COPD. Of the antioxidant factors the most consistent evidence was observed for a protective effect of high fruit consumption. A potential protective effect of catechins or whole grain intake on COPD has not been reported earlier and needs to be confirmed in further studies. Our results do not support a protective effect of moderate levels of n-3 fatty acid or fish intake against COPD. Finally, a protective effect of light alcohol consumption (up to 3 drinks/day) was suggested.

Causality of the observed relations is supported by an apparently temporal relation and by the existence of plausible biological mechanisms. Smoking could not totally explain our findings. Confounding by other health related lifestyle factors can, however, not be excluded. The observed effect of diet was estimated to reduce COPD with 10 to 30% at the population level and, if causal, it is certainly of public health relevance. **(Ch.8)**

Samenvatting

Aandoeningen van de luchtwegen: gebruikte termen

In Nederland wordt de term CARA (Chronische Aspecifieke Respiratoire Aandoeningen) gebruikt als verzamelnaam voor astma, chronische bronchitis en emfyseem. Dit zijn longaandoeningen waarbij er een vernauwing optreedt van de luchtwegen. Dit wordt ook wel luchtwegobstructie genoemd. Het gevolg is benauwdheid tijdens (lichte) inspanning en in ernstige gevallen ook in rust. Een belangrijk kenmerk van astma zijn aanvallen van kortademigheid waartussen de longfunctie min of meer normaal is. Bij chronische bronchitis en emfyseem is er sprake van blijvende obstructie van de luchtwegen. In de engelse literatuur, en ook steeds vaker in Nederland, wordt daarom de term COPD (chronic obstructive pulmonary disease) gebruikt om chronische bronchitis en emfyseem aan te duiden.

COPD

COPD is de derde doodsoorzaak in Nederland na hart- en vaatziekten en kanker. De belangrijkste oorzaak van COPD is het langdurig roken van sigaretten. Omdat het aantal rokers in de afgelopen tientallen jaren is afgenomen, verwacht men dat het optreden van COPD in de komende decennia zal gaan afnemen. Op het moment is er nog sprake van een stijgende trend, vooral bij vrouwen en bij mannen op hoge leeftijd.

Voeding en COPD

In het begin van de jaren '90 zagen onderzoekers dat COPD minder vaak voorkwam bij mensen die veel fruit aten of een hoge vitamine C inname hadden. Fruit bevat veel vitamine C en dit is een ***anti***-oxidant. Oxidanten zijn stoffen, o.a. rijkelijk aanwezig in sigarettenrook, die de luchtwegen en andere lichaamsweefsels kunnen beschadigen. Antioxidanten als vitamine C kunnen oxidanten onschadelijk maken, en daardoor mogelijk de luchtwegen beschermen. COPD leek ook minder vaak voor te komen bij mensen die veel vis aten. Verder waren er aanwijzingen dat mensen met een lage tot matige alcohol consumptie een lager risico hadden om COPD te krijgen dan niet-drinkers. Biologisch gezien was dit te verklaren door een remmende werking van alcohol en bepaalde vetten in vis (n-3 vetzuren) op ontstekingen die optreden in de luchtwegen van rokers.

Om meer te weten te komen over het effect van antioxidanten (o.a. vitamine C en E en ß-caroteen), voedingsmiddelen rijk aan antioxidanten (o.a. fruit en groente), vis en alcohol op het optreden van COPD, werden gegevens van twee grote epidemiologische onderzoeken bestudeerd. De resultaten hiervan zijn beschreven in hoofdstuk 2 t/m 7 van dit proefschrift. In hoofdstuk 8 volgt een beschouwing van de resultaten uitlopend in de conclusies.

Hoofdstuk 2

Rond 1960 werden 16 groepen mannen (in totaal ± 13000 mannen) van middelbare leeftijd uit 7 landen (5 Europese landen, Japan en de VS) onderzocht. Bij een klein aantal mannen van iedere groep werd de voeding nagevraagd om een grof beeld te krijgen van de voedingsgewoonten in de verschillende groepen. Voor iedere man die tussen 1960 en 1985 overleed, werd de doodsoorzaak vastgesteld. In groepen die rond 1960 veel fruit en vis aten, bleek de sterfte aan COPD in de daarop volgende 25 jaar relatief laag te zijn. Er werd geen verband gevonden tussen de vitamine C, vitamine E, ß-caroteen of groente inname en de sterfte aan COPD.

Hoofdstuk 3

Rond 1970 werd bij 2953 Finse, Italiaanse en Nederlands mannen, die aan het onderzoek uit hoofdstuk 2 hadden deelgenomen, de voedingsgewoonten nagevraagd. Het risico om aan COPD te overlijden tussen 1970 en 1990, bleek lager te zijn in mannen met een hoge fruit of vitamine E inname. Er werd geen verband gevonden tussen vitamine C, ß-caroteen, groente of visinname en sterfte aan COPD.

Hoofdstuk 5

Rond 1965 werd bij 1248 Finse, 1386 Italiaanse en 691 Nederlandse mannen, die aan het onderzoek uit hoofdstuk 2 hadden deelgenomen, de longfunctie en de voedingsgewoonten bepaald. In alle drie de landen bleken mannen met een bovengemiddelde inname van zowel fruit als groente een betere longfunctie te hebben dan mannen met een lage fruit en groente inname. Ook het eten van veel brood leek gunstig voor de longfunctie in de drie landen. Er werd geen duidelijk verband gevonden voor vis, vitamine C, vitamine E of ß-caroteen.

Hoofdstuk 4

In dit hoofdstuk werden de analyses uit hoofdstuk 3 en 5 uitgevoerd voor alcohol. Mannen die rond 1970 een lage tot matige alcohol consumptie hadden (meer dan 1 glas alcohol per week, maar minder dan 3 glazen per dag) bleken een lager risico te hebben om in de daarop volgende 20 jaar aan COPD te overlijden in vergelijking met zowel niet-drinkers als mannen die meer dan 3 glazen alcohol per dag gebruikten. Bovendien hadden de mannen met een lage tot matige alcohol consumptie de beste longfunctie.

Hoofdstuk 6 en 7

Tussen 1993 en 1997 werden mannen en vrouwen van 20-59 jaar uit Amsterdam, Doetinchem en Maastricht onderzocht. Bij 13,651 personen werden er gegevens verzameld over hun voeding, hun longfunctie en of ze last hadden van luchtwegklachten (hoesten, slijm opgeven en kortademigheid).

Naast vitamine C en ß-caroteen bevatten plantaardige producten minder bekende antioxidanten, zoals de flavonoiden. Flavonoiden komen met name voor in appels en thee. In hoofdstuk 6 wordt beschreven dat mensen die veel appels en peren aten, een betere longfunctie bleken te hebben en minder last van luchtwegklachten. Ook één type flavonoiden, de catechines, leek te beschermen tegen COPD. Voor thee en voor twee andere typen flavonoiden werd geen effect gevonden.

Verder bleek een bovengemiddelde inname van fruit en volkorenproducten samen te gaan met een betere longfunctie en minder luchtwegklachten. Ook een lage alcohol consumptie (tot 3 glazen per dag) leek te beschermen tegen COPD. Er werd geen duidelijk effect van groente of vis gevonden (zie hoofdstuk 7).

Beschouwing van de resultaten (zie hoofdstuk 8)

De resultaten beschreven in dit proefschrift suggereren een beschermend effect van met name fruit, volkoren producten en alcohol tegen COPD. Een mogelijk beschermend effect van fruit is ook door andere onderzoekers gevonden. Er is meer onderzoek nodig om de beschermende effecten van een hoge inname van catechines en volkoren-producten en een lage tot matige alcoholconsumptie te bevestigen.

Het zal de lezer opvallen dat er staat dat de resultaten een effect van voeding *suggereren.* Zaken als meetfouten en verstorende variabelen (b.v. rookgedrag) kunnen de resultaten vertekenen, ook al is op allerlei (statistische) manieren geprobeerd de kans hierop zo klein mogelijk te maken.

Veel fruit en volkorenproducten eten en matig zijn met alcohol maakt deel uit van de Nederlandse aanbevelingen voor een goede voeding. Met andere woorden, de resultaten van dit proefschrift ondersteunen de bestaande aanbevelingen, die gebaseerd zijn op kennis over de beschermende effecten van voeding tegen andere chronische ziekten

Appendix

Calculation of the public health relevance of the observed effects of diet on COPD

To estimate the public health relevance of observed effects of diet on COPD related outcomes, three methods were used:

1. **The change in the prevalence of airway obstruction in a population when the average FEV_1 or $FEV_{0.75}$ increases with 100 ml.**

   Airway obstruction: FEV_1 or $FEV_{0.75}$ below 70% of the predicted value
   Method: 100 ml was added to individual FEV_1 or $FEV_{0.75}$ values

   Applied to:
   a. $FEV_{0.75}$ in 1,248 men (50-69 yr.) from Finland (Ch. 4, 5)
   b. $FEV_{0.75}$ in 1,386 men (45-64 yr.) from Italy (Ch. 4, 5)
   c. FEV_1 in 9072 ever and 4579 never smoking Dutch adults (20-59 yr.)(Ch. 6, 7)

   Regression-equations used to determine predicted values:
   a. in never smokers (n = 239):
      pred= 6153 - 165.4*age + 1.006*age^2 - 135.3*HT + 1148*HT^2 - 86.83*cohort
   b. in never smokers (n = 458):
      pred= -4497 + 134.4*age + 1.629*age^2 + 2100*HT + 530.5*HT^2 -264.8*cohort
   c. in never smokers without COPD symptoms (n = 4091):
      pred= 4599 + 7.721*age - 0.317*age^2 - 4240*HT + 2526*HT^2 - 568.1*gender

   Results:

   prevalence of obstruction (%):

	observed	+ 100ml	change in prevalence
a.	14.8	12.2	-18%
b.	11.6	9.2	-21%
c.	2.6	2.0	-23%

2. Population Attributive Risk (PAR):

$$\frac{Pe\,(RR - 1)}{Pe(RR - 1) + 1}$$ with Pe = the proportion exposed in the total population

This measure can only be used for a dichotomous exposure variable (0,1). (see: US Department of Health and Human services: a report of the Surgeon General. Rockville, 1987)

3. Preventable proportion (PP): $\sum P_iR_i - \sum P_i^*R_i / \sum P_iR_i$

Example:

	Quartiles of an exposure variable			
	0	1	2	3
RR (=R_i)	8	4	2	1
Prevalence (=P_i)	0.25	0.25	0.25	0.25
Prevalence* (=P_i^*)	0	0.50	0.25	0.25

$$PP = \frac{0.25*4 + 0.25*2 + 0.25*1}{0.25*1 + 0.25*2 + 0.25*4 + 0.25*8} = 0.47$$

In the example the preventable proportion is 47% with a shift in exposure of one category to the right. (see: Wahrendorf J. Int J Cancer 1987;40:625-28)

In short, they estimate the effect of a shift in exposure for either a dichotomous exposure variable (exposed yes -> no: PAR) or a categorical variable with different levels of exposure of which a proportion of subjects in each category moves to a more favourable level of exposure (PP). When the prevalence in the non-exposed is known (P1), an odds ratio (OR) can be transformed into a RR, since RR = OR / (1 + P1 (OR - 1).

These methods were applied to:

a. 20-yr COPD mortality in 2953 men aged 50-69 years (Ch. 3 and 4)

	compared	RR	Pe	PAR
Fruit	lowest vs. highest tertile	1.79	0.50	0.28
Vit. E	lowest vs. highest tertile	1.52	0.50	0.20
Alcohol	< 1 drink/wk vs. > 1 pw and ≤ 3 pd	1.67	0.27	0.15

PP for a shift from lowest- to middle and middle to highest- tertile :

	RR's			
	tertile 1	*tertile 2*	*tertile 3*	PP
Fruit	1.79	0.93	1.00	0.21
Vitamin E	1.52	1.33	1.00	0.14

b. the prevalence of COPD symptoms in 13,651 Dutch adults (Ch 7)

		OR	P1	RR	PAR
Fruit	below vs. above the median	1.28	6.7%	1.26	0.12
Whole grain	below vs. above the median	1.27	6.8%	1.25	0.11
Alcohol	low vs other[1]	1.30	8.6%	1.27	0.12
Overall	all favourable vs unfavourable[2]	2.27	10.6%	2.00	0.28

[1] n = 8669 vs. 4982 [2] n = 1602 vs. 2578

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