# Detection of COPD

# in smokers

**Omslagfoto**

De Rode Brug over de Vecht
Het bekende oriëntatiepunt
In de ongepolijste Utrechtse wijk
Waar onze 'doorrookte' praktijk gevestigd is

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**Detection of COPD in smokers**

Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Thesis with a summary in Dutch
Proefschrift met een samenvatting in het Nederlands

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# Detection of COPD in smokers

# Opsporen van COPD bij rokers

(met een samenvatting in het Nederlands)

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. W.H. Gispen, in gevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 11 mei 2006 des ochtends te 10.30 uur

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Thesis Committee

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*Voor mijn moeder*
*en schoonvader*
*Ter nagedachtenis*
*aan mijn vader*
*en schoonmoeder*

# 1

# General introduction

## Introduction

*Mr. Green, 50 years of age, a friendly man with an oversized belly, sells flowers on the market. Last months he experienced increasing difficulty to work all day because of tiredness. For this reason he visits the GP. He complains of coughing, particularly in the morning. He smoked all his life and is unable to quit smoking since smoking is "the only pleasure that keeps him going". According to his medical record, his attendance rate was low in the previous ten years. He visited the practice several times because of musculoskeletal problems, and two times for bronchitis. The latter was treated with a course of antibiotics. The GP considers a diagnosis of COPD and spirometry is performed. Mr. Green has moderate COPD (FEV1 59% of predicted).*

Tiredness and coughing are frequently presented to the GP. Mr. Green visited his GP because of slowly progressive complaints and functional impairment. He was known to the GP as a heavy smoker. According to his medical record Mr. Green presented bronchitis two times in the previous years and apparently COPD was not considered at that time. The prevalence of undetected COPD is likely to be considerable. The early stages of the disease are however often missed. Since there is no cure for COPD and smoking cessation may improve the prognosis by normalizing lung function decline, the medical history of Mr. Green raises several questions. What is the prevalence of undiagnosed COPD? Is it possible to recognize COPD earlier by means of easily obtainable patient characteristics? And most importantly, is the current practice of recognizing of COPD in symptomatic high risk patients justified, should active case-finding be recommended in all smokers attending the GP for lower respiratory tract complaints, or should we even screen all smokers in the population at large to decrease the future burden of COPD? To answer these questions knowledge is needed with respect to the prevalence of undiagnosed COPD and its determinants, the incidence of COPD and its characteristics, the impact of airflow limitation and functional limitations on quality of life in subjects with undiagnosed COPD, and the cost-effectiveness of early detection followed by smoking cessation interventions. These issues are addressed in this thesis.

### Prevalence of undiagnosed COPD and its determinants

The comparison of prevalence rates of COPD is hampered by different definitions for COPD applied. [1-6] In this thesis we use the widely accepted criteria of the Global Initiative for Chronic Obstructive Lung Disease Guidelines to define Chronic Obstructive Pulmonary Disease (COPD), i.e. a *post*bronchodilator FEV1/FVC ratio <0.7. [7, 8] The prevalence of physician-diagnosed COPD in the U.K was 1.4% among women and 1.7% among men [10], and in The Netherlands 1.7% for women and 2.4% for men. [11]

In patients, not necessary smokers, aged 18-75 years, attending the GP with persistent cough, the prevalence of previously undiagnosed COPD was 7% [12] while in a random selection of smokers aged 35-70 years visiting the GP the prevalence of undiagnosed COPD was 18%. [5]
In the population at large in the U.S., the prevalence of COPD varies from about 3% in never smokers to 14% in both male and female current smokers. [9] Prevalence rates increase with age from 8% in male smokers 46-47 years of age to over 40% in male smokers aged 76-77 years.[3] In a Dutch study in the adult population at large - the DIMCA project - the overall prevalence of undiagnosed asthma and COPD was approximately 8%. [13] In three studies in middle-aged smokers - published after the start of our study - the prevalence of undiagnosed COPD defined according to the GOLD criteria varied between 14% and 29%.[1-3] In several different studies in smokers the prevalence of pre-bronchodilator airflow limitation is presented, which is not according to GOLD criteria. [4-6]
Since the prevalence of undiagnosed COPD appears to be considerable, screening spirometry in smokers 45 years or older during a clinical encounter was advocated by some experts.[14] However, screening of all middle-aged smokers seems not feasible because of the high costs involved. [5] Screening of a subgroup of smokers with a high prevalence of COPD identified e.g. by means of easily obtainable patient characteristics would be more efficient. A diagnostic rule in order to identify those smokers with a high risk of having undiagnosed COPD would be helpful. However, such a rule is not available.

**Incidence of COPD and its determinants**
So far, only two studies addressed the incidence of COPD - in smokers and non smokers -according to the criteria of the GOLD Guidelines for COPD. [15, 16] In a Swedish study the 10-year cumulative incidence of moderate COPD (GOLD II) in symptomatic male smokers aged 51-52 years was about 25% while in a Danish study the 15 years cumulative incidence of COPD (GOLD stage 1 or up) in symptomatic smokers was 20%. [15, 16] Many different determinants of COPD have been reported in the literature such as smoking, gender, indoor and outdoor air pollution, chronic respiratory symptoms or frequent respiratory tract infections, a reduced lung function at young adulthood and familial obstructive airways disease.[7, 8.] Nevertheless, their combined value for the estimation of absolute risk of future COPD in smokers is largely unknown. Only one prediction rule for COPD in the population at large, the so called Tecumseh index or risk for developing COPD has been developed and validated. [17, 18, 19] In the latter study the combination of age, gender, smoking habits and degree of lung function identified a large proportion of those who will develop COPD – defined by FEV1 <65% predicted - over a 15 year period.

However, according to this model spirometry is needed while screening spirometry in the adult population at large does not seem a feasible strategy. A better option is probably a prediction rule based on readily obtainable patient characteristics. Feasible algorithms estimating the probability of developing COPD in the clinically most relevant group of smokers are however not available.

**Impact of functional limitations by dyspnoea and airflow limitation on quality of life in middle-aged smokers**

Dyspnoea is the main symptom limiting daily activities in patients with clinical significant COPD. In most guidelines however, the severity of COPD is based on airflow limitation, i.e. the level of forced expiratory volume in one second (FEV1). [7, 8] Importantly, the correlation between airflow limitation and health related quality of life is modest.[20-25] Limitations of physical functioning due to dyspnoea rather than pulmonary function is correlated with quality of life. [26] The knowledge of the impact of dyspnoea or airflow limitation on quality of life in patients with early stages of COPD is however limited.[22] To evaluate the benefits and harms of screening for undiagnosed, predominantly mild COPD, knowledge of the impact of early disease on quality of life is needed. Quality of life questionnaires provide a valid and standardized estimate of the overall impact of airflow limitation and could complement spirometric measurements in the baseline assessment of patients in routine practice. [27] However, in the daily management of smokers - whether or not having COPD - there is a need for a simple and standardized instrument in order to assess functional limitations. The MRC dyspnoea scale could be a more feasible substitute for a quality of life questionnaire. However, in middle-aged smokers little is known about the association between limitations of physical functioning as measured by the MRC dyspnoea scale and airflow limitation on the one hand and quality of life on the other.

**Cost-effectiveness of screening for undiagnosed COPD**

In smokers with physician diagnosed COPD, the implementation of increased smoking cessation intervention is considered cost-effective compared to current practice since short counseling by the GP could generate life-years and even net savings. [11] In addition, also smoking cessation interventions directed towards smokers in the population at large is estimated to be cost-effective compared to current practice.[28] Considering the high prevalence of undiagnosed COPD and the still increasing burden of the disease, the question is whether the recommended strategies in the literature of early detection of undiagnosed COPD in smokers could be cost-effective.[14, 5]

The costs and benefits of detection followed by treatment of previously undiagnosed COPD - screening of smokers in the population at large or case finding in smokers visiting the GP for lower respiratory tract complaints followed by smoking intervention - compared to current practice are unknown.

**Outline of the thesis**

The thesis focused on undiagnosed COPD in current smokers. We restricted our study to early detection of COPD in male smokers 40-65 years of age, because of the higher prevalence of COPD in males, and the expected smaller benefit in elderly smokers due to the absence of a significant number of undiagnosed severe disease and the higher risk of false positive diagnosis in the elderly. [29-31]

In a cross-sectional study in 1998 among smokers without physician diagnosed asthma or COPD, we examined the prevalence of undetected COPD in male smokers 40-65 years old. (Chapter 2) In addition we examined the development of a diagnostic rule based on patient characteristics in order to recognize mild COPD (GOLD I) in daily practice (Chapter 3).

In a 5-year follow-up study, we studied the incidence of moderate COPD (GOLD II) in male smokers aged 40-65 years (Chapter 4) and the development of a rule in order to predict which smokers develop moderate COPD (Chapter 5). In addition we addressed the question whether quality of life in middle-aged smokers – whether or not having early COPD - correlated with limitations of physical functioning by dyspnoea rather than with airflow limitation (Chapter 6).

To answer the question whether early detection of COPD in middle-aged smokers followed by smoking interventions is cost-effective compared to current practice, we combined the findings of our studies, estimates of the effectiveness of smoking cessation interventions and results from former analyses about smoking cessation programs directed towards the general population and towards patients with known COPD as well (Chapter 7).

Finally, in the general discussion the findings of our study are presented followed by a discussion of the pros and cons of screening for COPD in middle-aged smokers (Chapter 8).

## References


1 Stratelis G, Jakobsson P, Molstad S, Zetterstrom O. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Br J General Practice 2004;54:201-206.

2 Tzanakis N, Anagnostopoulos U, Filditaki V, Christaki P, Siafakas N, on behalf of the COPD group of the Hellenic Thoracic Society. Prevalence of COPD in Greece. Chest 2004;125:892-900.

3 Lundback B, Lindberg A, Lindstrom M, et al. Not 15 but 50% of smokers develop COPD? Report from the Obstructive Lung Disease in Northern Sweden Studies. Respir Med 2002;97:115-122.

4 Clotet J, Gomez-Arbonez X, Ciria C, Albalad JM. Spirometry is a good method for detecting and monitoring chronic obstructive pulmonary disease in high-risk smokers in primary health care. Arch Bronconeumol 2004;40:155-159.

5 Van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370-1375.

6 Zielinski J, Bednarek M, and Know the Age of Your Lung Study Group. Early detection of COPD in a high-risk population using spirometric screening. Chest 2001;119:731-736.

7 Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-1276.

8 Fabbri LM, Hurd SS,, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Resp J 2003;22:1-2.

9 Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data form the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160:1683-1689.

10 Soriano JR, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000;55:789-794.

11 Hoogendoorn M, Feenstra T, Hoogenveen R, van Geneugten M. A health policy model for COPD: effects of smoking cessation. Institute for Medical Technology Assessment, 2003. Report number 03.68.

12 Thiadens HA, De Bock GH, Dekker FW, et al. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. BMJ 1998;316:1286-1290.

13 Van de Boom G, Van Schayck CP, Van Molken MP, et al. Active detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. Am J Respir Crit Care Med 1998;158:1730-1738.

14 Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146-61.

15 Lindberg A, Jonsson A-J, Rönmark E, Lundgren R, Larsson L-G, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 2005;127:1544-1552.
16 Vestbo J, Lange P. Can GOLD stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2002;166:329-332.
17 Higgins MW, Keller JB, Becker, et al. An index of risk for Obstructive Airways Disease. Am Rev Respir Dis 1982 ;125 :144-151.
18 Higgins MW, Keller JB, Landis R, et al. Risk of chronic obstructive pulmonary disease. Collaborative assessment of the validity of the Tecumseh Index of Risk. Am Rev Respir Dis 1984 ; 130 :380-385.
19 Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow study. Am Rev Respir Dis 1986:134:1011-1019.
20 Wilson IB, Cleary PD. Linking clinical variables with health related quality of life. JAMA 1995;273:59-65.
21 Wijnhoven HAH, Kriegsman DMW, Hesselink AE, Penninx BWJH, de Haan, M. Determinants of different dimensions of disease severity in asthma and COPD ; pulmonary function and health related quality of life. Chest 2001; 119:1034-1042.
22 Antonell-Incalzi R, Imperiale C, Bellia V, et al. Do GOLD stages of COPD severity really correspond to difference in health status ? Eur Respir J 2003;22:444-449.
23 Bestall JC, Garrod PR, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581-586.
24 Kerstjens HAM. The GOLD Classification has not advanced understanding of COPD. Am J Respir Crit Care Med 2004;170:212-213.
25 Mahler DA, Mackowiak JI. Evaluation of the Short-Form 36-Item questionnaire to measure health-related quality of life in patients with COPD. Chest 1995;197:1585-1589.
26 Hajiro T, Nishimura K, Tsukoni M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnoea vs disease severity in indicating the health-related quality of life of patients with COPD. Chest 1999;116:1632-1637.
27 Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax 2001;56:880-887.
28 Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Mölken MPMH. Cost-effectiveness analysis of face-to-face smoking cessation interventions by professionals. Institute for Medical Technology Assessment, 2003. Report number 03.67.
29 Dickinson JA, Meaker M, Searle M, Ratcliffe G. Screening older patients for obstructive airways disease in a semi-rural practice. Thorax 1999;54:501-505.
30 Crocket A. Screening older patients for obstructive airways disease. Thorax 1999;54:472-473.
31 Hardie JA, Buist AS, Vollmer WM, et al. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Resp J 2002;1117-1122.

2

# Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old

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**Abstract**

**Background.** Airflow obstruction in smokers is often diagnosed relatively late. Earlier detection of airflow obstruction and smoking cessation may result in significant health gain.
**Objective**. To determine the prevalence of previously undetected persistent airflow obstruction according to WHO/GOLD criteria in male smokers aged 40 to 65 years and its correlation with age, smoking history and the presence of coughing**.**
**Methods.** In a cross-sectional study among 805 male smokers aged 40-65 years spirometry was performed according to ATS recommendations. In participants with low lung function (FEV1<85% predicted) a bronchodilator test was performed
**Results.** In 702 participants (mean age 50 years (SD 6.6), mean number of pack years 24.7 (SD 9.6)) with acceptable spirometric curves, previously undetected airflow obstruction was found in 210 subjects (29.9%; 95% CI 26.5-33.4): mild airflow obstruction (GOLD stage I) in 182 subjects (25.9%; 22.7-29.3) and moderate airflow obstruction (GOLD stage II) in 28 (4.0%; 2.7-5.7). In the older age group (≥ 55 years) airflow obstruction (GOLD 1 or higher) was found in 45% versus 21% in the youngest age group (40-44 years). In subjects with ≥ 30 pack years the prevalence of airflow obstruction was 45% vs. 20% among those with <20 pack years. In smokers reporting coughing the prevalence was 47% vs. 25% in those not reporting this symptom.
**Conclusion.** The prevalence of undetected persistent airflow obstruction in middle-aged smokers is high. Targeted screening therefore, especially in smokers aged 40-65 years needs to be considered.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major health problem. Of all cases of COPD 80-90% are supposed to be caused by smoking.[1 2] However, only 10 to 15% of smokers will develop COPD.[2] The estimated prevalence of COPD, defined as a FEV1/FVC ratio <0.7, in the general population in the U.S. varies from about 3% in never smokers to 14% in both male and female current smokers.[3] Only a small proportion of patients with COPD is diagnosed as such by their general practitioner. The prevalence of physician-diagnosed COPD in the UK was 1.4% among women and 1.7% among men.[4] Persons with undetected COPD usually have relatively mild lung function impairment [5] but early detection of undiagnosed airflow obstruction is relevant since the benefit of smoking cessation has also been shown in patients with early stages of COPD.[6]

Using different criteria to define airflow obstruction in the past hampered the comparison of the prevalence rates of different studies. After publication of the WHO Guidelines on COPD (GOLD) in 2001 and the subsequently yearly updates a more uniform classification has been advocated worldwide which is now widely accepted.[7 8] Unlike earlier guidelines on COPD, the GOLD classification includes a relatively novel early stage of COPD: GOLD stage I, defined by a decreased FEV/FVC ratio (<0.7) in combination with a FEV1 within the normal range (≥80% predicted). Classification of more advanced stages is still based on FEV1 measurements. Although knowledge of the magnitude of the prevalence of undetected persistent airflow obstruction is important, the number of available studies using the GOLD criteria is small.[9-11] Several other studies suffer from limitations, such as large differences in the definition of COPD applied [12-15] or not using postbronchodilator lung function measurements.[13, 16, 17]

The aim of the study was to determine the prevalence of undetected airflow obstruction according to the GOLD classification in a cohort of male smokers aged 40 to 65 years without known obstructive lung disease or any other pulmonary condition.

## Methods

This study describes the first part of the IJsselstein Study, a cohort study in a small city in the center of the Netherlands, aimed to assess the prevalence and determinants of undetected airflow obstruction in middle aged smokers. The first part of the study was conducted in 1998 and follow-up measurements were performed from 2003 onwards. Our study focused on a population with a known high risk to develop airflow obstruction, i.e. middle-aged male smokers without lung medication or diagnosed lung disease.

*Study population.* All men (n=3985) aged 40 to 65 years enlisted with a GP in IJsselstein were asked by letter if they smoked one or more cigarettes per day during the previous 12 months, and if so, whether they were willing to participate in a study to identify undetected airflow obstruction. Subjects with documented lung disease (222, 5.6%) were excluded. A total of 2596 of the 3763 men without previously documented lung disease returned the form (69%). Among the 2596 respondents 978 (37.7%) subjects reported to be current smokers. Sixty 'current' smokers were excluded at the first examination because of smoking cessation since more than 12 months (33), smoking only pipe or cigars (17) or because of reporting a lung disease yet (10). Thus the eligible population consisted of 918 (35.4%) current cigarette smokers without known lung disease. Eventually, 805 of the 918 eligible subjects (87.7%) attended the first survey.

*Spirometry.* In all participants spirometry was performed using a hand-held spirometer (Vitalograph 2170). Each subject had to perform at least three acceptable forced vital capacity maneuvers while sitting. The results were shown on a computer screen and the procedure was supported by computer software (Spirotrack). When the FEV1 predicted was less than 85% a bronchodilator test was performed by inhalation of two puffs of terbutaline 250 mcg by an inhalation chamber. When the FEV1 predicted, after an interval of 15 minutes, was still less than 85% an additional bronchodilator test (at least 30 minutes after inhalation of two puffs of ipratropium bromide 20 mcg) was performed on another day within a month. All measurements were performed by one experienced and especially trained nurse practitioner. The spirometer was calibrated with a 1-litre syringe at least once a week. Two investigators (RMMG, APES) independently assessed the quality of the flow-volume curves and time-volume curves according to the criteria of the American Thoracic Society.[18] In case of disagreement, a final assessment was made by a lung physiologist. The maneuvers with the largest sum of FEV1 and FVC were used in this analysis.
Airflow obstruction was classified according to the 2003 update of the WHO/GOLD criteria.[7 8] According to these guidelines COPD is defined by a FEV1/FVC ratio <0.7.

The severity of COPD is distinguished in 4 stages:

- Mild (GOLD stage I): FEV1 predicted ≥80%.
- Moderate (GOLD stage II): 50%≥ FEV1 predicted <80%.
- Severe (GOLD stage III): 30%≥ FEV1 predicted <50%.
- Very severe (GOLD stage IV): FEV1 predicted <30% (or <50% with signs of chronic respiratory failure).

All cut-off values refer to postbronchodilator measurements. A total of 128 subjects performed a prebronchodilator FEV1 predicted <85%. Among them were 30 of the 158 subjects with prebronchodilator GOLD I. Postbronchodilator GOLD I was found in 25 (83.3%) of the 30 subjects with prebronchodilator GOLD I.

*Questionnaire*.The Airways Questionnaire (AQ20), a short questionnaire to measure health-related quality of life among patients with chronic obstructive pulmonary disease, was filled in by the participants before the pulmonary function test.[19] The item concerning coughing (do you have coughing spells in day-time, yes/no) was included in the current analysis.

*Statistical methods.* Predicted values of FEV1 and FVC were computed using the regression equations of the European Coal and Steel Community (ECSC).[20] Statistical analyses were performed using the statistical package SPSS 10.0.

**Table 1. Characteristics of a cohort middle aged male smokers (n=702)**

| Characteristic | Mean | SD or 95% CI |
|---|---|---|
| Age (years) | 50.0 | 6.6 |
| Height (cm) | 178.8 | 6.9 |
| Weight (kg) | 81.7 | 12.0 |
| BMI (kg/m2) | 25.5 | 3.4 |
| Pack-years | 24.7 | 9.6 |
| FVC (litres) | 5.1 | 0.9 |
| FVC predicted (%) | 110 | 15 |
| FEV1 (litres) | 3.7 | 0.7 |
| FEV1 predicted (%) | 99 | 14 |
| FEV1/FVC ratio | 0.73 | 0.07 |
| GOLD Stage I | 25.9% (n=182) | 22.7-29.3 |
| GOLD stage II | 4.0% (n=28) | 2.7-5.7 |

SD: Standard Deviation; 95% CI: 95% Confidence Interval; BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in one second

## Results

*General characteristics.* All participants (805) underwent spirometry. A total of 103 participants (12.8%) produced an unacceptable spirometric curve. Among subjects with and without acceptable curves, no relevant differences in the characteristics listed in table 1 were found. The data of the 702 participants with acceptable curves were used for the analysis. The characteristics of the 702 participants are shown in Table 1.
The mean age was 50.0 years (SD 6.6) and the mean number of cigarette pack years 24.7 (SD 9.6). The mean FVC predicted and FEV1 predicted was 110% (SD 15) and 99% (SD 14), respectively, and the mean FEV1/FVC ratio was 0.73 (SD 0.07).

*Prevalence of airflow obstruction.* Airflow obstruction was found in 210 subjects (29.9%; 95% CI; 26.5-33.4).(Table 1) In 182 subjects (25.9%; 22.7-29.3) the airflow obstruction was mild (GOLD stage I). Prebronchodilator moderate airflow obstruction (GOLD stage II) was found in 53 participants (7.5%; 5.7-9.8). Postbronchodilator GOLD stage II was found in 28 subjects (4.0%; 2.7-5.7), including one participant who met GOLD stage III criteria. No one met GOLD stage IV criteria.

*Determinants of airflow obstruction.* The prevalence of previously undetected airflow obstruction was associated with age, smoking history and coughing. (Table 2) In participants aged 55 years or over the prevalence rates of GOLD stage I and GOLD stage II were higher than in subjects aged 40-44 years, 38% vs. 19% and 7% vs. 2%, respectively.

**Table 2. Patients' characteristics and prevalence of previously undetected airflow obstruction in (n=702) middle aged male smokers**

| Characteristic (n) | | GOLD I (n=182) | GOLD II (n=28) |
|---|---|---|---|
| Age | 40-44 yrs (178) | 19% (34) | 2% (4) |
| | 45-49 yrs (175) | 23% (40) | 1% (2) |
| | 50-54 yrs (169) | 24% (40) | 5% (9) |
| | ≥ 55 yrs (180) | 38% (68) | 7% (13) |
| Pack years | <20 yrs (204) | 19% (39) | 1% (2) |
| | 20-29 yrs (318) | 23% (74) | 4% (14) |
| | ≥ 30 yrs (180) | 38% (69) | 7% (12) |
| Coughing | Absent (553) | 23% (127) | 2% (13) |
| | Present (149) | 37% (55) | 10% (15) |

GOLD I: GOLD /COPD stage I; GOLD II: GOLD/COPD stage II

Correspondingly, in subjects aged 55 years or over, FEV1/FVC ratio and FEV1 (% predicted) were lower than among subjects aged 40-44 years, 0.70 vs. 0.75 and 96% vs.100%, respectively. Among participants who smoked 30 pack years or over, the prevalence rates of GOLD stage I and GOLD stage II were higher than in subjects who smoked less than 20 pack years, 38% vs. 19% and 7% and 1%, respectively. Correspondingly, in smokers who smoked 30 pack years or over, FEV1/FVC ratio and FEV1 (% predicted) were lower than among smokers who smoked less than 20 pack years, 0.69 vs. 0.75 and 95% vs. 101%, respectively. In smokers reporting coughing, the prevalence rates of GOLD stage I and GOLD stage II were higher than in smokers not reporting coughing, 37% vs. 23% and 10% vs. 2%, respectively. Correspondingly, in smokers reporting coughing, the FEV1/FVC ratio and FEV1 (% predicted) were lower than among smokers not reporting coughing, 0.70 vs. 0.74 and 95% vs. 100%, respectively.

## Discussion

In a population of male smokers - 40 to 65 years old - not known with obstructive lung disease the prevalence rates of previously undetected COPD stage I and stage II according to the GOLD criteria were 25.9% and 4.0%, respectively. The prevalence rates of both GOLD I and GOLD II were associated with age, the number of pack years and the presence of coughing.

Some limitations of our study should be considered. First, our study included only men because of limited resources and the known higher smoking rate and prevalence rate of airflow obstruction in men. In the Netherlands the smoking rate of men is 40% in those aged 35-49 years and 31% in those aged 50-64 years; in women these figures are 34% and 23%, respectively.[21] Because of the increasing smoking rate of Dutch women in recent decades, one may expect that the prevalence rate of airflow obstruction in female smokers will rise and will likely become similar to the prevalence rate of the Dutch male smokers in the near future.[13 21] Second, we performed bronchodilator testing in subjects with FEV1 % predicted <85% only. Although our study was designed to assess airflow obstruction according to a widely used clinical criterion (postbronchodilator FEV1 predicted <80%), we have - in retrospect - decided to use the GOLD criteria for COPD, published after we conducted our measurements. The GOLD criteria are currently widely accepted and can be relatively easily applied, although the one-dimensional severity grading – i.e. based on lung function – is discussed.[22] According to the GOLD guidelines, bronchodilator testing should be performed in all subjects with airflow obstruction, i.e. also in subjects with GOLD I (FEV1/FVC <0.7 and FEV1 ≥80% predicted). In 30 of the 157 subjects with prebronchodilator GOLD I a bronchodilator test was performed and only in 5 subjects (5/30; 16.7%) postbronchodilator spirometry was normal. Extrapolating this finding to the remaining 127 subjects with prebronchodilator GOLD I who did not perform a bronchodilator test, implies that 21 of the 127 subjects (16.7%) should have produced postbronchodilator normal spirometry. Thus, 161 rather than 182 subjects would have been diagnosed as GOLD I, giving a slightly lower estimated prevalence rate of GOLD I (22.9% rather than 25.9%).

One of the strengths of our study is that the survey was performed in a population representative for the Dutch population at large. For example, 35% (918) of those who returned the questionnaire on smoking habits, were current smokers, a figure comparable to the expected proportion of smokers (35-36%) in men, aged 40-65 years, in the Netherlands.[21] In addition a rather high proportion (87.7%) of the eligible male smokers participated. Thus, selective response seems unlikely.

In literature the prevalence rates of airflow obstruction vary widely because of differences in the study populations, especially concerning to age, smoking habits and health status, as well as using different reference values or various definitions of airflow obstruction. For example, in several studies pre-bronchodilator FEV1 was used to define COPD, which is not according to GOLD criteria.[12-14, 16 17] Notably, in our study the prevalence rate of *prebronchodilator* GOLD II (7.5%) was 3.5% higher than the prevalence rate of *postbronchodilator* GOLD II (4.0%). Since publication of the GOLD guidelines, as far as we know, only in 3 studies previously undetected postbronchodilator airflow obstruction defined according to the GOLD guidelines (FEV1/FVC ratio <0.7) in middle-aged male smokers was reported. In a Greek study [10] a prevalence rate of 12% was observed while the prevalence rates in two Swedish studies varied from 8% (46-47 yr.) and 24% (61-62 yr.) [11] to 29%, respectively. [9] The latter prevalence rate was similar to the findings of our study.

A clear distinction between COPD and asthma is not possible in all subjects with airflow obstruction, even when the GOLD criteria for COPD are used. We found a significant bronchodilator response, i.e. an improvement of FEV1 both larger than 12% predicted and exceeding 200 ml, in 10 subjects. [20] In 4 of those 10 participants we observed postbronchodilator airflow obstruction, thus fulfilling criteria of both asthma and COPD while 6 subjects performed normal spirometry.

In general practice active detection or airflow obstruction by means of spirometry in smokers should be encouraged and smokers with newly diagnosed airflow obstruction should be offered smoking cessation intervention. However, there are no evidence-based guidelines how GPs can effectively identify airflow obstruction in smokers. Different strategies are advocated such as case finding among smokers attending the GP as well as screening in smokers aged 45 years or over who report smoking during a clinical encounter.[13 23] When case finding in our study was limited to symptomatic smokers, approximately 70% of the smokers with GOLD I (127/182) and about 50% of the subjects with GOLD II (13/28) would be missed. (Table 2) In several countries spirometry in primary care has been advocated and is facilitated in recent years. In the Netherlands most GPs can order lung function testing in diagnostic centers or in hospitals and in a minority of the general practices spirometers on-site and well-trained nurse practitioners are available. In the UK 2004 General Practice contract the focus on respiratory disease is increased and the use of spirometry in order to actively detect airflow obstruction is encouraged.[24] We conclude that the prevalence of undetected persistent airflow obstruction is high. Targeted screening therefore, especially in smokers aged 40-65 needs to be considered.

**Acknowledgements**

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The study has been approved by the ethics committee of the University Medical Center Utrecht and has conformed to the principles embodied in the Declaration of Helsinki.

**References**

1 American Thoracic Society. Standards for the diagnosis and care of patients with chronic pulmonary disease. Statement of the American Thoracic Society. Am J Respir Crit Care Med 1995;152:S77-S120.

2 American Thoracic Society. Cigarette smoking and health. Am J Respir Crit Care Med 1996;153:861-865.

3 Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data form the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160:1683-1689.

4 Soriano JR, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000;55:789-794.

5 Coultas DB, Mapel D, Gagnon RC, Lydick E. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med 2001;164:372-377.

6 Anthonissen NR, Connett JE, Murra RP for the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166: 675-679.

7 Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-1276.

8 Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Resp J 2003;22:1-2.

9 Stratelis G, Jakobsson P, Molstad S, Zetterstrom O. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Br J General Practice 2004;54:201-206.

10 Tzanakis N, Anagnostopoulos U, Filditaki V, Christaki P, Siafakas N, on behalf of the COPD group of the Hellenic Thoracic Society. Prevalence of COPD in Greece. Chest 2004;125:892-900.

11 Lundback B, Lindberg A, Lindstrom M, et al. Not 15 but 50% of smokers develop COPD? Report from the Obstructive Lung Disease in Northern Sweden Studies. Respir Med 2002;97:115-122.

12 Clotet J, Gomez-Arbonez X, Ciria C, Albalad JM. Spirometry is a good method for detecting and monitoring chronic obstructive pulmonary disease in high-risk smokers in primary health care. Arch Bronconeumol 2004;40:155-159.

13 Van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370-1375.
14 Zielinski J, Bednarek M, and Know the Age of Your Lung Study Group. Early detection of COPD in a high-risk population using spirometric screening. Chest 2001;119:731-6.
15 Viegi G, Pedreschi M, Pistelli F, et al. Prevalence of airways obstruction in a general population. European Respiratory Society vs. American Thoracic Society Definition. Chest 2000;117:339S-345S.
16 Sobradelli V, Miravetles M, Gabriel R, et al. Geographic variations in prevalence and underdiagnosis of COPD. Results of the IBERPOC multicentre epidemiological study. Chest 2000;118:981-989.
17 De Marco, R, Accordini S, Cerveri I, et al, for the European Community Respiratory Health Survey (ECRHS) Study Group. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 2004;59:120-125.
18 American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-1136.
19 Hajiro T, Nishimura K, Jones PW, et al. A novel, short and simple questionnaire to measure health related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1874-1878.
20 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC, on behalf of the working party 'Standardization of lung function testing'. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;6:(suppl):5-40.
21 DEFACTO, voor een rookvrije toekomst, jaarverslag 2001. [Dutch Foundation for a smokefree future, year report, 2001].
22 Kerstjens HAM. The GOLD Classification has not advanced understanding of COPD. Am J Respir Crit Care Med 2004;170:21-23.
23 Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146-1161.
24 BMA/NHS Confederation. New 2004 GMS contract. www.bma.org.uk/ap.nsf/content/splashpage

3

# Are patient characteristics helpful in detecting mild COPD (GOLD I) in daily practice?

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**Abstract**

**Objective.** To determine whether in a high risk group of middle-aged male current smokers, patient characteristics are useful to detect mild COPD (GOLD stage I).
**Methods.** In a cross-sectional study in the population at large among male smokers, aged 40-65 years, without documented lung disease, spirometry was performed according to the American Thoracic Society criteria. Medical records were scrutinized to collect patient characteristics. Multiple logistic regression analysis was used to identify independent determinants for mild COPD defined according to the GOLD criteria for COPD.
**Results.** A total of 567 subjects participated. COPD, defined by a FEV1/FVC ratio <0.7, was detected in 170 subjects (30.0%, 95% CI 26.2-33.9%). In 149 subjects (26.3%; 22.7-30.1%) the COPD was mild (GOLD stage I) and in 21 subjects (3.7%; 2.3-5.6%) moderate (GOLD stage II). Only age and cough were independently associated with the presence of mild COPD. The ability of these determinants to discriminate between subjects with or without mild COPD was relatively poor (ROC area 0.65).
**Conclusion.** Our results indicate that patient characteristics are not helpful to detect mild COPD (GOLD stage I) in middle-aged male smokers.

**Introduction**

Chronic Obstructive Pulmonary Disease (COPD) is a major health problem. The estimated prevalence of COPD, defined as a FEV1/FVC ratio <0.7, in the population at large in the U.S. varies from about 3% in never smokers to 14% in both male and female current smokers.[1] In only a small proportion of patients COPD is detected as such by their primary care physician. For example, the prevalence of physician-diagnosed COPD in the UK is 1.4% among women and 1.7% among men.[2] The diagnostic criteria for COPD according to the GOLD guidelines are currently widely accepted, although the one-dimensional severity grading – i.e. only based on lung function – is discussed.[3-5] Relatively novel in the GOLD Guidelines is GOLD stage I (mild COPD) defined by an abnormal FEV1/FVC (<0.7) ratio but with an FEV1 above 80 % predicted. Identifying subjects with early stages of COPD is important since treatment of early COPD by intensive smoking cessation programs has proven to be effective.[6] There is no consensus regarding an optimal screening strategy. Screening strategies involving all elderly smokers (>65 year) has been criticized because of the lack of evidence of a significant number of undiagnosed severe disease, the risk of false positive diagnosis and the smaller benefit of smoking cessation.[7-9] Screening in the younger age group (<40 year) is not recommended because of the low prevalence of COPD. Various authors advocate targeted screening, e.g. spirometry in smokers 45 years or older who report smoking during a clinical encounter.[10, 11] However, screening of all middle-aged smokers seems not feasible because of shortage of resources. Screening of a subgroup of smokers with a high prevalence of COPD identified e.g. by means of easily obtainable patient characteristics would be more efficient. Therefore, the aim of the present study was to determine whether in a high risk group of middle-aged male

**Methods**

This study was part of the IJsselstein Study, a cohort study, aimed to assess the prevalence and determinants of undetected COPD in middle-aged smokers. Subjects with COPD were offered smoking cessation interventions. The study was conducted between 1998 and 2003.smokers, patient characteristics can be used to mild COPD (GOLD stage I).

*Study population.* In 1998 all men (n=3985) aged 40 to 65 years, enlisted with a GP in IJsselstein, a small city in the center of the Netherlands, were asked by letter if they smoked one or more cigarettes a day during the previous 12 months and if so whether they were willing to participate in a study to identify determinants of COPD.
Subjects with documented lung disease, i.e. a diagnosis of asthma, COPD or any other chronic pulmonary condition reported in the GP medical records, (222/3985, 5.6%) were excluded. A total of 2596 of the 3763 men without previously documented lung disease responded (69%). Among the 2596 respondents 978 (37.7%) reported to be current smokers. At the start of the 1998 survey sixty (6.1%) 'current' smokers were excluded because of smoking cessation more than 12 months (33) or because they only smoked pipe or cigars (17); 10 subjects were excluded since they reported a chronic lung disease not recorded in the GP medical records (10). Thus the eligible population consisted of 918 current cigarette smokers without known chronic lung disease (35.4%). Eventually, 805 of these 918 eligible subjects (87.7%) attended the 1998 survey. During the examinations spirometry was performed, a short questionnaire was filled in by the participants and smoking history, height and weight were assessed by a nurse practitioner.
*Spirometry.* In all participants spirometry was performed using a hand-held spirometer (Vitalograph 2170). Each subject had to perform at least three acceptable forced vital capacity maneuvers while sitting. The results were shown on a computer screen and the procedure was supported by computer software (Spirotrack). When FEV1 predicted was less than 85% the bronchodilator response was tested by inhalation of two puffs of terbutaline 250 mcg through an inhalation chamber in order to exclude previous unrecognized asthma. When FEV1 predicted, after an interval of 15 minutes, was still less than 85% an second bronchodilator test (after an interval of at least 30 minutes after two puffs of ipratropium bromide 20 mcg), was performed on another day within a month. All measurements were performed by one experienced and especially trained nurse practitioner. The spirometer was calibrated with a 1-litre syringe at least once a week. Two investigators (RMMG, APES) independently assessed the quality of the flow-volume curves and time-volume curves according to the criteria of the American Thoracic Society.[12] In case of disagreement, a final assessment was made by a lung physiologist. The tracings with the largest sum of FEV1 and FVC were used in this analysis. In total 702 participants performed an adequate lung function test.

COPD was classified according to the 2003 update of the WHO/GOLD criteria.[3, 4] According to these guidelines COPD is defined by a FEV1/FVC ratio <0.7. The severity of COPD is distinguished in 4 stages:

- Mild (GOLD stage I): FEV1 predicted ≥80%.
- Moderate (GOLD stage II): 50%≥ FEV1 predicted <80%.
- Severe (GOLD stage III): 30%≥ FEV1 predicted <50%.
- Very severe (GOLD stage IV): FEV1 predicted <30% (or <50% with signs of chronic respiratory failure).

All cut-off values refer to postbronchodilator measurements.

*Medical records*. All GPs were using computer based medical records. From these medical records the following items were extracted retrospectively:

- Number of clinical encounters because of lower respiratory tract complaints or because of any other reason in the previous 12 months.
- Number of prescription of antibiotics because of lower respiratory tract complaints in the previous 12 months.

A clinical encounter because of lower respiratory tract complaints was defined as the presence of one of the following items in the medical records:

- A diagnosis of acute or chronic bronchitis, pneumonia or lower respiratory tract infection.
- Symptoms such as coughing, dyspnoea, phlegm production or wheezing, without specific diagnosis.

A diagnosis recorded by a primary or secondary care physician in the patient records or in the medical correspondence was classified as present. In total 135 of 702 (19.2%) medical records were missing, 60 (8.5%) records because one GP refused to participate and 75 (10.7%) records because the participants were removed from the practice list by the time we inspected the medical records.

*Questionnaire*. The Airways Questionnaire (AQ20), a short questionnaire to measure health-related quality of life among patients with chronic obstructive pulmonary disease, was filled in by the participants before the pulmonary function test.[13] The item concerning coughing (do you have coughing spells in the day-time, yes/no) was included in the current analysis.

*Data analysis*. The data analysis was performed in the 567 subjects with complete medical records. The association between all aforementioned determinants and the presence of COPD was assessed using univariable logistic regression analysis. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated in subjects with mild COPD (GOLD I) using subjects with normal spirometry as the reference group. Determinants with a univariable p-value of <0.15 were entered together in a multivariable logistic regression model to assess which determinant was independently associated with the presence of mild COPD. In order to retain a more reduced model only the strongest determinants of the presence of COPD were selected, excluding determinants with a p-value >0.05 from the multivariable model.
The reliability (goodness of fit) of the model was assessed by means of the Hosmer & Lemeshow test.[14] The ability of the model to discriminate between subjects with or without mild COPD was quantified using the area under the Receiver Operator Characteristic curve (ROC area).[15] The ROC area is a parameter to summarize discriminative ability of a prediction model and can range from 0.5 (no discrimination) to 1.0 (perfect discrimination). A value ≥0.7 is considered to be reasonable and >0.8 as good.
All statistical analyses were performed using the statistical package SPSS (SPSS for Windows, version 11.0, SPSS INC.).

**Table 1. General characteristics of a cohort male smokers aged 40-65 yrs**

| Characteristic | Mean (SD) † | | | |
|---|---|---|---|---|
| | Total (n=567) | Normal spirometry (n=397) | GOLD I (n=149) | GOLD II (n=21) |
| Age (yrs) | 50.2 (6.6) | 49.2 (6.2) | 52.3 (6.8) | 53.5 (6.6) |
| Smoking history (yrs) | 31.6 (9.0) | 30.5 (8.7) | 34.1 (9.3) | 36.4 (7.2) |
| Pack years of smoking | 24.8 (9.6) | 23.4 (8.7) | 28.2 (11.2) | 27.3 (5.3) |
| BMI ($kg/m^2$) | 25.6 (3.4) | 25.8 (3.4) | 25.1 (3.4) | 25.6 (3.2) |
| FVC (litres) | 5.1 (0.9) | 5.0 (0.8) | 5.4 (0.8) | 4.3 (0.7) |
| FVC (% predicted) | 110 (14) | 108 (14) | 117 (13) | 94 (12) |
| FEV1 (litres) | 3.7 (0.7) | 3.9 (0.7) | 3.5 (0.5) | 2.6 (0.4) |
| FEV1 (% predicted) | 100 (14) | 103 (13) | 95 (10) | 70 (7) |
| FEV1/FVC ratio | 0.73 (0.07) | 0.77 (0.04) | 0.65 (0.04) | 0.60 (0.05) |
| Reversibility (FEV % predicted)‡ | 5.3% (4.3) | - | 5.8 (4.1) | 4.0 (4.7) |
| GP contact (≥1) for all reasons previous 12 months | 60% | 61% | 55% | 71% |
| GP contact (≥1) for LRT complaints previous 12 months | 18% | 16% | 22% | 33% |
| Antibiotics (≥1 prescription) for LRT complaints previous 12 months | 11% | 9% | 14% | 14% |
| Cough | 19% | 14% | 29% | 48% |

† Mean (Standard deviation), unless else stated; BMI: body mass index; LRT: lower respiratory tract; ‡ Reversibility was tested in 45/149 subjects with GOLD I and 20/21 of subjects with GOLD II

## Results

General characteristics of the participants are shown in table 1. The mean age was 50.2 years (SD 6.6) and the mean number of pack years of smoking was 24.8 years (9.6). The mean FVC and FEV1 (% predicted) were 110% (14) and 100% (14), respectively. Cough was reported by 19% of the subjects. Normal spirometry was found in 397 of the 567 subjects (70.0%; 95% CI 66.1-73.8%) while COPD (GOLD stage I or up) was established in 170 participants (30.0%, 95% CI 26.2-33.9%). In 149 subjects (26.3%, 22.7-30.1%) the COPD was mild (GOLD stage I) and in 21 subjects (3.7%, 2.3-5.6%) moderate (GOLD stage II). No one met the criteria for severe COPD (GOLD stage III or IV).

**Table 2. Association between patient characteristics and mild COPD (GOLD I) in smokers, aged 40-65 yrs, and ability (ROC area) of combinations of characteristics to discriminate between subjects with and without GOLD 1**

| Characteristic | | N (546) | Mild COPD (GOLD I; n=149) | |
|---|---|---|---|---|
| | | | OR (95% CI) unadjusted | OR (95% CI) adjusted |
| Age | 40-44 yrs | 138 | 1.0† | 1.4 (1.2-1.7) (per 5 years) |
| | 45-49yrs | 137 | 1.4 (0.8-2.5) | |
| | 50-54 yrs | 130 | 1.5 (0.9-2.8) | |
| | ≥55 yrs | 141 | 3.2 (1.9-5.6) | |
| Pack years | <20 | 159 | 1.0† | |
| | 20-29 | 252 | 1.2 (0.7-2.0) | |
| | ≥30 | 135 | 3.0 (1.8-5.0) | |
| GP contact (≥1) for all reasons, previous 12 months | | 323 | 0.8 (0.5-1.1) | |
| GP contact (≥1) for LRT complaints, previous 12 months | | 96 | 1.5 (0.9-2.4) | |
| Antibiotics (≥1 prescription) for LRT complaints previous 12 months | | 57 | 1.5 (0.8-2.7) | |
| Cough | | 100 | 2.4 (1.5 -3.8) | 2.3 (1.5-3.7) |
| *ROC area* | | | | *0.65 (0.59-0.70)* |

Reference group: subjects without COPD (n=397); N: number of subjects positive for the determinant; CI: confidence interval; LRT: lower respiratory tract †: Reference category

In table 2 unadjusted and adjusted odds ratios for potential determinants of mild COPD are presented. In the univariate analysis age, pack years of smoking and cough were associated with previously undetected mild airflow obstruction (GOLD I) while in the multivariate analysis only age and cough independently correlated with the presence of GOLD I.

Entering these two variables in a prediction model resulted in an area under curve (ROC area) of 0.65 (95% CI 0.59-0.70).

The number of pack years of smoking was strongly correlated with age and did not increase the ROC area. Although the model showed a good fit, indicated by a non-significant Hosmer and Lemeshow test ($p>0.5$), a prediction rule was not developed because of the relatively poor performance of the combination of the determinants (ROC area 0.65) to predict the presence of undetected mild COPD.

**Discussion**

In our study among 567 male middle-aged smokers only age and cough were independently associated with the presence of previously undetected mild COPD (GOLD I). Combining these determinants did not satisfactorily predict the presence of mild COPD (ROC area 0.65).

The difficulty to predict GOLD I by means of patient characteristics is at least partly attributable to the fact that undetected mild COPD is often asymptomatic.(Table 1) These findings are in line with previous reports indicating that mild and even moderate COPD remains to a large extent asymptomatic and that a FEV1 decline up to 50% of predicted does not correlate well with symptoms or other patient characteristics.[16-17]

Some limitations of our study should be considered. First, only men were included. Because of the increased smoking rate of women in recent decades, the prevalence of (undetected) COPD in female smokers is rising.[18] The proportion of middle-aged female patients visiting the GP for respiratory complaints compared to middle-aged male patients is about 40 % higher.[19] In addition, the prevalence of reported respiratory complaints is higher in female smokers than in male smokers. [20] Therefore, patient characteristics, such as respiratory complaints, could possibly be more helpful to detect mild COPD in female than in male smokers. Second, 805 subjects participated in our study and 702 of them (87.2%) produced an acceptable spirometric curve according to ATS criteria which is comparable with other studies.[10] There were no relevant differences in the characteristics, listed in table 1, of subjects with and without acceptable curves. Third, of the 702 subjects with acceptable spirometric curves, 567 medical records (80%) could be collected. For obvious reasons our analysis was restricted to those smokers with complete medical records. Importantly, however, age, pack years and lung function parameters were comparable in subjects with and without retrievable medical records. Finally, age, cough and $\geq$1 GP contact for lower respiratory tract complaints in the previous 12 months were independently associated with the presence of previously undetected moderate COPD (GOLD II) (data not shown). In contrast to our finding regarding GOLD stage I, it is likely that patient characteristics are useful to identify smokers with moderate COPD (GOLD II). The prevalence of GOLD II however in our sample was too low to develop such a prediction rule.

The major strength of our study is that a large proportion of the eligible male smokers in a small town with a population representative of the Dutch population, participated. In addition, we collected patient characteristics in general practices without special instruction to record medical history, in order to make the results of our study applicable to general practices at large in the Netherlands. Finally we used the currently widely accepted GOLD criteria to define COPD including postbronchodilator values.
As far as we know, no other studies have been performed in the population at large aimed to develop a prediction rule based on patient characteristics in order to select middle-aged smokers for screening spirometry. In the literature several screening strategies are advocated, e.g. screening spirometry by primary care physicians among smokers aged >45 years old, with or without lower respiratory tract complaints.[10, 11] According to our study, patient characteristics are of little use to select smokers for screening spirometry in order to identify mild COPD (GOLD stage I). Identifying subjects with mild COPD is important since further deterioration of the COPD to GOLD stage II was assessed in 20% of the subjects with GOLD stage I after 5 years in our study and treatment of early COPD by intensive smoking cessation programs has proven to be effective.[6] More studies are needed to assess cost-effectiveness and feasibility of various screening approaches in smokers to arrive at the optimal screening strategy.
Our results indicate that patient characteristics are not helpful to detect mild COPD (GOLD stage I) in middle-aged male smokers.

**Acknowledgments**
We thank the GPs from IJsselstein who voluntarily participated in this study. The study was funded by the Dutch Asthma Foundation (Reference number 3.4.01.93).
The study was approved by the ethics committee of the University Medical Center Utrecht.

**References**

1 Mannino DM, Gagnon RC, Petty TL, et al. Obstructive lung disease and low lung function in adults in the United States: data form the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160:1683-1689.
2 Soriano JR, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000;55:789-794.
3 Pauwels RA, Buist S, Calverley PMA, et al. on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-1276.
4 Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Resp J 2003;22:1-2.
5 Kerstjens HAM. The GOLD Classification has not advanced understanding of COPD. Am J Respir Crit Care Med 2004;170:21-23.
6 Anthonissen NR, Connett JE, Murra RP for the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-679.
7 Dickinson JA, Meaker M, Searle M, et al. Screening older patients for obstructive airways disease in a semi-rural practice. Thorax 1999;54:501-505.
8 Crocket A. Screening older patients for obstructive airways disease. Thorax 1999;54:472-473.
9 Hardie JA, Buist AS, Vollmer WM, et al. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Resp J 2002;1117-1122.
10 Van Schayck CP, Loozen JMC, Wagena E, et al. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370-1375.
11 Ferguson GT, Enright PL, Buist AS, et al. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146-1161.
12 American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-1136.
13 Hajiro T, Nishimura K, Jones PW, et al. A novel, short and simple questionnaire to measure health related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1874-1878.
14 Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley & Sons, Inc. 1989:140-145.
15 Hanley JA, McNeil BJ. The meaning and use of the area under receiver operating characteristics ROC) curve. Radiology 1982;143:29-36.
16 Vestbo J, Lange P. Can GOLD stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2002;166:329-332.

17 Antonelli-Incalzi R, Imperiale C, Belia V, et al. Do GOLD Stages of COPD severity really correspond to differences in health status? Eur Respir J 2003;22:444-449.
18 DEFACTO, voor een rookvrije toekomst, jaarverslag 2001. [Dutch Foundation for a smokefree future, year report, 2001].
19 Cardol M, Dijk L van, Jong JD de, et al.Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: huisartsenzorg: wat doet de poortwachter ? Utrecht, Bilthoven: NIVEL, Rijksinstituut voor Volksgezondheid en Milieu, 2004.
20 Langhammer A, Johnson R, Holmen J, et al. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord – Trondelag Health Study (HUNT). J Epidemiol Community Health 2000;54:917-922.

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# Incidence and determinants of moderate COPD (GOLD II) in male smokers aged 40-65 years: 5 year follow-up study

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**Abstract**

**Background**. Chronic Obstructive Pulmonary Disease (COPD) is a major health problem with an estimated prevalence of 10-15% among smokers. The incidence of moderate COPD, defined according to the GOLD criteria, is largely unknown.
**Aim.** To determine the cumulative incidence of moderate COPD (FEV1/FVC <0.7 and FEV1 <80% predicted) and its association with patient characteristics in a cohort of male smokers.
**Design.** Prospective cohort study.
**Setting.** The city of IJsselstein, a town in the center of The Netherlands.
**Methods.** Smokers, aged 40-65 years, enlisted with a local GP were invited to participate in a study to identify undetected COPD. Among 399 smokers with normal spirometry (n=292) or mild COPD (FEV1/FVC <0.7 and FEV1 ≥ 80% predicted, n=107) at baseline in 1998, follow-up measurements were conducted in 2003.
**Results.** After a mean follow-up of 5.2 years 33 participants developed moderate COPD (GOLD II), i.e. an estimated cumulative incidence of 8.3% (95% CI 5.8-11.4) and an average annual incidence of 1.6%. No one developed severe airflow obstruction. The risk of developing moderate COPD in smokers with baseline mild COPD (GOLD I) was 5 times higher than in those with baseline normal spirometry (1 in 5 vs. 1 in 25). In multivariate analysis age, starting of smoking in childhood, cough and ≥ 1 GP contact for lower respiratory tract complaints at baseline were independently associated with incident moderate COPD.
**Conclusion.** In a cohort of middle-aged male smokers the estimated cumulative incidence of moderate COPD (GOLD II) in 5 years was relatively high (8%). Age, childhood smoking, cough as well as ≥ 1 GP contact for lower respiratory tract complaints were independently associated with incident moderate COPD.

**How this fits in**

*What do we know?*
Chronic Obstructive Pulmonary Disease (COPD) is a major health problem with an estimated prevalence of 10-15% among smokers. Incidence of COPD is largely unknown.

*What does this paper add?*
The estimated 5-years incidence of moderate COPD is approximately 8% in a population of middle-aged male smokers. Age, childhood smoking (≤ 15 years of age), cough as well as ≥ 1 GP contact for lower respiratory tract complaints are independently associated with incident moderate COPD.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major health problem. Tobacco smoking is by far its major cause. About 10 to 15% of all smokers develop COPD.[1] Adult smokers, who were exposed to tobacco smoke or other air pollutants during childhood, are at increased risk of developing COPD.[1, 2, 3] The susceptibility developing COPD is influenced by still largely unknown genetic factors. [1] Lifelong smokers die on average about 10 years earlier than lifelong non-smokers. [4] About 25% of the excess mortality among smokers is accounted for by lung cancer and COPD. Smoking cessation at an early stage of COPD is the only intervention that substantially improves the prognosis by normalizing lung function decline and decreasing all-cause mortality.[4-6] Therefore early detection of undetected airflow obstruction is advocated. [7] Some authors recommend screening spirometry in all smokers, 45 years or older, attending a GP [8] while other authors recommend case-finding among symptomatic smokers attending their GP.[7] However, the optimal cost-effective strategy (targeting all or specific subgroups of smokers) and the screening frequency is unknown. Knowledge of the prevalence and incidence of COPD as well as its determinants is needed to assess whether targeted screening in – a subgroup of – smokers could be useful. In several studies the prevalence of COPD in smokers was assessed.[9] However, only few studies addressed the incidence of COPD and - as far as we know - in only one study the criteria of the GOLD Guidelines for COPD were used. Therefore we performed a 5 years follow-up study among male smokers to determine the cumulative incidence of moderate COPD defined according to the GOLD criteria and its association with patient characteristics.

## Methods

This study was part of the IJsselstein Study, a cohort study, aimed to assess the prevalence, incidence and patient characteristics of undetected airflow obstruction in middle-aged smokers. The study was conducted between 1998 and 2003.

*Study population.* In 1998, subjects, enlisted with a GP in IJsselstein, a small town in the center of The Netherlands, were asked by letter if they smoked one or more cigarettes per day during the previous 12 months, and if so, whether they were willing to participate in a study to identify undetected airflow obstruction. Eventually, 702 male smokers, aged 40-65 years, participated in this screening study and performed adequate spirometry as well. Details of the first part of the study were published elsewhere. [9] In 2003, a follow-up survey was performed.

A total of 101 subjects (14%) were ineligible due to non-participation of one of the GPs (65) or because of removal of the practice list, death or severe illness (36). In addition follow-up measurements were refused by 165 of the 601 eligible subjects (27%). Eventually, 436 of the 601 eligible subjects (73%) participated in the follow-up survey. The incidence of moderate COPD (GOLD II) was computed in 399 subjects with normal spirometry or mild COPD (GOLD I) at baseline, excluding 10 subjects with baseline GOLD II and 27 participants not performing an acceptable lung function test at the follow-up survey. The study was approved by the ethics committee of the University Medical Center Utrecht.

*Spirometry.* In all participants spirometry was performed by a hand-held spirometer. At the baseline survey in 1998 a Vitalograph spirometer was used and at the follow-up surveys in 2003 -because of logistic reasons - a Jaeger spirometer. Details of the procedure in 1998 were described elsewhere. [9] Briefly, each subject had to perform at least three acceptable forced vital capacity maneuvers while sitting. The results were shown on a computer screen and the procedure was supported by computer software. If the FEV1 was less than 85% of predicted, the bronchodilator response was tested 15 minutes after inhalation of four puffs of salbutamol 100 mcg through an inhalation chamber. In subjects older than 60 years the bronchodilator response was tested 30 minutes after inhalation of two puffs of ipratropium bromide 20 mcg. Experienced and especially trained lung function assistants employed by a primary care diagnostic center performed all measurements. The spirometer was calibrated daily with a 1-litre syringe at the start of a series of measurements. Two investigators (RMMG, APES) independently assessed the quality of the flow-volume curves and time-volume curves according to the criteria of the American Thoracic Society. [10] According to these criteria the maneuvers with the largest sum of FEV1 and FVC were used in this analysis. Predicted values of FVC and FEV1 were computed using the regression equations of the European Coal and Steel Community (ECSC). [11]
Before each lung function test, height and weight were measured and smoking history was assessed.

*Definition of COPD.* After the publication of the WHO Guidelines on COPD (GOLD) in 2001 and its yearly updates afterwards, a uniform classification has been advocated worldwide. [1, 2] According to the GOLD guidelines COPD is defined by a postbronchodilator FEV1/FVC ratio <0.7. The severity of COPD can be distinguished in 4 stages according to postbronchodilator FEV1 values:

- mild (GOLD stage I): FEV1 predicted ≥ 80%;
- moderate (GOLD stage II): 50%≥ FEV1 predicted <80%;
- severe (GOLD stage III): 30%≥ FEV1 predicted <50%;
- very severe (GOLD stage IV): FEV1 predicted <30% (or <50% with signs of chronic respiratory failure).

*Questionnaires.* Symptoms at baseline were assessed by the AQ20 questionnaire, a short questionnaire to measure health-related quality of life among patients with chronic obstructive pulmonary disease. The AQ20 consisted of 20 items concerning the impact of chest trouble such as coughing and dyspnoea at mild to moderate exertion on every day life. [12] In this part of the study only the item concerning coughing was. The family history was assessed by the Dutch language version of the Modified Medical Research Council for Respiratory Symptoms (MMRC) questionnaire. [13]

*Medical records.* All general practitioners used computer based medical records. From these medical records the number of clinical encounters because of lower respiratory tract complaints was extracted retrospectively. A clinical encounter because of lower respiratory tract complaints was defined as the presence of one of the following items in the medical records:

- A diagnosis of acute or chronic bronchitis, pneumonia or lower respiratory tract infection.
- Symptoms such as cough, dyspnoea, phlegm production or wheezing, without specific diagnosis.

In total 17 of 399 (4.3%) medical records were missing because of removal of the practice list by the time we inspected the medical records.

*Statistics.* Patient characteristics, significantly associated with the incidence of moderate COPD in the univariate analysis, were entered in a multivariate logistic regression model. Both forward and backward multiple logistic regression analysis was performed to assess patient characteristics independently associated with the incidence of moderate COPD. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated. The missing data (4.3%) from the medical records concerning the GP contacts for lower respiratory tract complaints were imputed using SPSS software. All statistical analyses were performed using the statistical package SPSS (SPSS for Windows, version 11.0, SPSS INC.).

**Table 1: Baseline characteristics of a cohort of male smokers aged 40-65 years**

| Characteristic | Overall† (n=399) | Normal spirometry† (n=292) | GOLD I† (n=107) |
|---|---|---|---|
| Age (yrs) | 50.0 (6.4) | 49.2 (6.2) | 52.3 (6.5) |
| Smoking history (yrs) | 31.3 (8.5) | 30.5 (8.2) | 33.5 (8.9) |
| Pack years of smoking | 24.1 (8.7) | 23.2 (8.5) | 26.6 (8.7) |
| BMI ($kg/m^2$) | 25.4 (3.3) | 25.5 (3.4) | 25.1 (3.2) |
| Family history of obstructive lung disease | 38% | 39% | 37% |
| Parental smoking | 88% | 87% | 91% |
| Childhood smoking (≤ 15 years of age) | 39% | 36% | 46% |
| Cough | 21% | 18% | 29% |
| ≥1 GP contact for LRT complaints, previous 12 months | 17% | 16% | 23% |
| FVC % predicted | 111 (13) | 109 (13) | 118 (11) |
| FEV1 % pred | 102 (12) | 104 (12) | 97 (10) |
| FEV1/FVC ratio | 0.74 (0.06) | 0.77 (0.05) | 0.66 (0.03) |

†Mean (SD) unless stated else; GOLD I: COPD stage I according to GOLD criteria; BMI: Body Mass Index; LRT: lower respiratory tract; FVC and FEV1: Forced Vital Capacity and Forced Expiratory Volume in one second

## Results

*General characteristics.* Baseline characteristics of the cohort are described in Table 1. The mean age was 50.0 years (SD 6.4), the mean pack years of smoking 24.1 (8.7) and mean smoking history 31.3 years (8.5). The mean FVC and FEV1 (% predicted) were 111% (SD 13) and 102% (12), respectively. The mean follow-up period was 5.2 yrs. The cumulative incidence of GOLD II (moderate COPD) was estimated at 8.3% (33/399; 95% CI 5.8-11.4%). The average annual incidence was 1.6%. No one developed GOLD III or IV (severe or very severe COPD).

*Determinants of incidence of GOLD II.* The cumulative incidence of GOLD II in subjects with baseline mild COPD (GOLD I) was approximately 5 times the incidence among those with baseline normal spirometry (19.6% vs. 4.1%). (Table 2)
The incidence of GOLD II was significantly associated with higher age, heavy smoking as well as starting of smoking in childhood (≤ 15 years of age) (Table 2).

**Table 2. Five-year cumulative incidence of moderate COPD (GOLD II) in middle-aged smokers**

| Characteristic | (Cases/*n*) | GOLD II (%) | *P*-value† |
|---|---|---|---|
| Overall | All (33/399) | 8.3 | |
| Baseline spirometry | normal (12/292) | 4.1 | <0.001 |
| | GOLD I (21/107) | 19.6 | |
| Age (yrs) | 40-44 (3/99) | 3.0 | 0.011 |
| | 45-49 (6/97) | 6.2 | |
| | 50-54 (9/108) | 8.3 | |
| | 55-65 (15/95) | 15.8 | |
| Pack years of smoking | <20 (4/109) | 3.7 | 0.011 |
| | 20-29 (15/198) | 7.6 | |
| | ≥ 30 (14/92) | 15.2 | |
| Family history of obstructive lung disease | Absent (20/238) | 8.4 | 0.9 |
| | Present (12/149) | 8.1 | |
| Parental smoking | Absent (2/40) | 5.0 | 0.4 |
| | Present (27/292) | 9.2 | |
| Childhood smoking | absent (11/245) | 4.5 | 0.002 |
| | present (22/154) | 14.3 | |
| Cough | absent (19/315) | 6.0 | 0.002 |
| | present (14/84) | 16.7 | |
| ≥1 GP contact for LRT complaints, previous 12 months | absent (21/329) | 6.4 | 0.003 |
| | present (12/70) | 17.1 | |

Cases: number of subjects with GOLD II; *n*: number of subjects positive for the characteristic; GOLD II: COPD stage II according to GOLD criteria; LRT: lower respiratory tract; † Chi-square test for association or trend

In addition, the incidence was higher in symptomatic smokers, either reporting cough in the questionnaire or presenting lower respiratory (LRT) symptoms to the GP (Table 2). The highest incidence was found in smokers with GOLD I at baseline reporting cough (29.0%; 9/31) while the lowest incidence was assessed in smokers with normal spirometry at baseline not reporting cough (2.9%; 7/239). A family history of obstructive lung disease (asthma, bronchitis or emphysema) was not associated with the incidence of GOLD II.

**Table 3. Association between baseline characteristics and incidence of GOLD II (n=33) in middle-aged smokers (n=399): unadjusted and adjusted odds ratios (OR)**

| Characteristic | | OR unadjusted (95% CI) | OR adjusted (95% CI) | *P*-value |
|---|---|---|---|---|
| Age | 40-44 | 1.0† | 1.8 (1.2-2.6) | 0.002 |
| | 45-49 | 2.1 (0.5-8.7) | (per 5 years) | |
| | 50-54 | 2.9 (0.8-11.1) | | |
| | 55-65 | 6.0 (1.7-21.5) | | |
| Pack years of smoking ‡ | <20 | 1.0† | | |
| | 20-29 | 2.1 (0.7-6.6) | | |
| | ≥30 | 4.7 (1.5-14.9) | | |
| Childhood smoking (≤15 years of age) (y/n) | | 3.5 (1.7-7.5) | 3.3 (1.5-7.3) | 0.002 |
| Cough (y/n) | | 3.1 (1.5-6.5) | 2.2 (1.0-4.8) | 0.05 |
| ≥1 GP contact for LRT complaints, previous 12 months (y/n) | | 3.0 (1.4-6.5) | 2.8 (1.3-6.4) | 0.01 |

CI: Confidence Interval; LRT: lower respiratory tract; † reference category; ‡ not included in multivariate analysis

In the multivariate analysis age, childhood smoking, cough and ≥1 GP contact for LRT complaints at baseline were independently associated with the incidence of GOLD II. Smoking history was not associated with GOLD II when age and childhood smoking were included (Table 3).

## Discussion

*Summary of main findings.* The five-year cumulative incidence of moderate COPD (GOLD II (moderate COPD) in a cohort of male smokers, either with normal spirometry or mild COPD (GOLD I) at baseline, was 8.3% (95% CI 5.8-11.4%), i.e. an average annual incidence of 1.6%. The incidence of GOLD II was 5 times higher in subjects with baseline GOLD I than in those with baseline normal spirometry. Patient characteristics, independently associated with incident GOLD II, were increasing age, childhood smoking (≤ 15 year of age), cough and ≥1 GP contact for LRT complaints at baseline.

*Strengths and limitations.* Some limitations of our study should be considered. First, only men were included. Sex differences in lung vulnerability to tobacco smoking are under discussion, therefore the estimated incidence rate of moderate COPD in our study in male smokers can not be generalized to female smokers. [14-17] Second, 702 subjects participated in the baseline survey and 436 in the second survey. In subjects only participating in the baseline survey the prevalence of GOLD II at baseline was slightly higher (4.0% vs. 2.4%) and FEV1 predicted was slightly lower (98% vs. 102%) than in those attending both surveys. This may indicate that a slightly higher

proportion of subjects with relatively poorer lung function tended to discontinue participation. Considering that non-participation in the baseline survey as well could have been higher in the smokers with poorer lung function, the estimated 8.3% incidence is likely conservative. Third, to assess the potential bias because of using different spirometers at baseline (Vitalograph) and follow-up measurements (Jaeger) we compared the change in FEV1 in a subset of 171 subjects who performed an additional lung function test in 2002 with the Vitalograph spirometer. The change in FEV1 between the baseline and additional tests, both performed with the Vitalograph spirometer, was similar to the change in FEV1 between the baseline and the follow-up tests, performed with the Vitalograph and Jaeger spirometer respectively (63.5 ml/yr vs. 60.6 ml/yr, T-test for the difference $p$=0.6).
One of the strengths of our study is that the survey was performed in a population representative for the Dutch population at large. For example, 35% of the subjects in the population at large who returned the questionnaire on smoking habits at the baseline survey were current smokers, a figure similar to the expected proportion of smokers (35-36%) in men, aged 40-65 years, in The Netherlands. [18] Moreover a rather high proportion (87.7%) of the eligible smokers participated. Thus selective response seems unlikely. In addition, all subjects with a new diagnosis of moderate COPD performed postbronchodilator lung function measurements, as recommended by the GOLD guidelines.

*Relationships to existing literature.* A limited number of studies has provided incidence rates of COPD.[19-22] In a Finnish study the average annual incidence of COPD (FEV1/FVC<0.6) among male smokers aged 40-64 years was about 0.5%.[19] In a Polish study the average annual incidence of COPD (FEV1<65% predicted) in male smokers aged 41-60 years was 1.2-1.6 %. [20] Using different definitions of COPD as well as prebronchodilator lung function values in those studies is hampering the comparison of the annual incidence estimates of those studies and ours. In a more recent study the 10-year cumulative incidence of moderate COPD (GOLD II) in male smokers aged 51-52 years was about 25% which is comparable to our 5-year incidence in male smokers 50-54 years old.[22]
Unsurprisingly, the incidence of COPD in our study in smokers was associated with age and smoking history, i.e. pack years, in the univariate analysis. [1, 8] In the multivariate analysis pack years of smoking disappeared when age and childhood smoking were included. Several different determinants of COPD such as childhood smoking, respiratory symptoms, a family history of obstructive lung disease and parental smoking are addressed below. [1, 23, 24]

First, in a study of Patel et al. childhood smoking was an independent risk factor of doctor diagnosed obstructive airways disease in women but not in men. [23] In contrast, in our study in men, childhood smoking was an independent risk factor of GOLD II which can possibly be explained using different definitions of airflow obstruction. Supporting the increased risk of COPD by childhood smoking in both sexes is the finding in a prognostic study that cigarette smoking both in boys and in girls, 10 to 18 years of age, is associated with mild airflow obstruction and slowed growth of lung function.[24] Second, Vestbo et al. found a similar incidence of GOLD II - 7.4% vs. 6.7% - in symptomatic and asymptomatic smokers with normal baseline spirometry while we found a three times higher incidence of GOLD II - 9.3% vs. 2.9% - in symptomatic than in asymptomatic smokers.[25] A true association between bronchitic symptoms, such as cough or sputum production, and the incidence of GOLD II is supported by the results of a Swedish study which found a significant association between each bronchitic symptoms and the incidence of GOLD II after adjustment for possible confounders. [22] Third, in our study no association between a family history of obstructive lung disease and the incidence of GOLD II was found. A true association between a positive family history and the development of airflow obstruction can be missed either by poor recall in subjects filling in questionnaires or by smaller family size in contemporary generation compared with earlier generations. Fourth, in an European study parental smoking, especially fathers' smoking was related to a poorer lung function among smoking and non-smoking adults, aged 20-44 years. [26, 27] However, we found no significant association between parental smoking and the incidence of GOLD II, probably by a lack of contrast, since in our study parental smoking during childhood was reported by almost 90% of the subjects.

*Clinical implications.* Early identification of COPD is important since smoking cessation at an early stage of COPD is the only intervention that substantially improves the prognosis by normalizing lung function decline and decreasing all-cause mortality.[4-6] In our study in middle-aged male smokers the overall estimated cumulative 5-year incidence of moderate COPD (GOLD II) was relatively high (8%). The incidence was even higher in those who smoked before the age of 16 or had lower respiratory complaints.

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## References


1 Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-1276.

2 Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Resp J 2003;22:1-2.

3 Gauderman, WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004;351:1057-1067.

4 Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519-1533.

5 Anthonissen NR, Connett JE, Murra RP, for the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166: 675-679.

6 Anthonissen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connet JE, for the Lung Health Study Research Group. The Effects of smoking cessation intervention on 14.5-year mortality. Ann Int Med 2005;142:233-239.

7 Van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370-1375.

8 Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146-1161.

9 Geijer RMM, Sachs APE, Hoes AW, Salomé PL, Lammers J-WJ, Verheij TJM. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. Family Practice 2005, 22:485-489.

10 American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-1136.

11 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC, on behalf of the working party 'Standardization of lung function testing'. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;6:(suppl):5-40.

12 Krzyzanowski M, Hajiro T, Nishimura K, Jones PW, et al. A novel, short and simple questionnaire to measure health related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1874-1878.

13 Thiadens HA. Diagnosing asthma or COPD in patients with persistent cough: variations on a theme (Thesis). Leiden: University of Leiden, 1999.

14 Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex differences in lung vulnerability to tobacco smoking. Eur Respir J 2003;21:1017-1023.

15 Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender differences in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. Eur Respir J 1997;10:822-827.

16 Kerstjens HAM, Rijckens, B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures and fallacies. Thorax 1997;52:820-827.
17 Volmer WM, Enright P, Pedula KL, et al. Race and gender differences in the effects on lung function. Chest 2000;117:764-772.
18 DEFACTO, voor een rookvrije toekomst, jaarverslag 2001. [Dutch Foundation for a smoke free future, year report, 2001].
19 Huhti, E, Ikkala J, A follow-up study on respiratory symptoms and ventilatory function in a middle-aged rural population. Eur J Resp Dis 1980:61:33-45.
20 Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow study. Am Rev Respir Dis 1986:134:1011-1019.
21 Lundback B, Gulsvik A, Albers M, et al. Epidemiological aspects and early detection of chronic obstructive airways diseases in the elderly. Eur Respir J 2003;21:Suppl.40 3S-9S.
22 Lindberg A, Jonsson A-J, Rönmark E, Lundgren R, Larsson L-G, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 2005;127:1544-1552.
23 Patel, BD, Luben RN, Welch AA, et al. Childhood smoking is an independent risk factor for obstructive airways disease in women. Thorax 2004;59:682-686.
24 Gold DR, Wang X, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 1996;335:931-937.
25 Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic pulmonary disease? Am J Respir Crit Care Med 2002;166:329-332.
26 Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. Thorax 2004; 59:295-302.
27 De Marco, R, Accordini S, Cerveri I, et al, for the European Community Respiratory Health Survey (ECRHS) Study Group. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 2004;59:120-125.

5

# Which smokers develop COPD? A prediction rule

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**Introduction**

Tobacco smoking is the main risk factor for COPD (Chronic Obstructive Pulmonary Disease) and approximately 15 % of smokers aged 40 years or over will eventually develop COPD. It is more attractive to early identify smokers with an increased risk for future COPD by means of readily obtainable patient characteristics, than to perform repeated spirometry in all smokers. The aim of our study was to develop an easily applicable prediction rule based on clinical variables in order to identify smokers with an increased risk of developing COPD within 5 years.

**Patients, methods and results**

In 1998 all male smokers, enlisted with a local general practice in IJsselstein, a city in the center of The Netherlands, and unknown with airflow limitation, were invited for spirometry performed according to the criteria of the American Thoracic Society. Baseline characteristics [1] were assessed with questionnaires and by scrutinizing the GP electronic medical records of the participants.[2, 3] In 2003 follow-up spirometry was performed in 436 of the 601 subjects (72%) with adequate baseline spirometry and without moderate COPD at baseline. 27 participants were excluded because of inadequate follow-up spirometry. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Baseline characteristics, independently associated with the incidence of moderate COPD in multivariate logistic regression analysis (p-value<0.05), were included in a prediction rule. [4] Internal validation of the rule was performed by means of bootstrapping using S+ software, version 6.0. The regression coefficients, adjusted by the bootstrap method, were transformed to scores, dividing all coefficients by the coefficient with the lowest value and rounding the scores to the nearest integer. Statistical analyses were performed with the statistical package SPSS (SPSS for Windows, version 12.0, SPSS INC.). Data from the missing medical records (4.2%) were imputed using the linear regression method available in SPSS.

The mean age of the 399 participants was 50.0 years (range 40-65) and the mean number of pack years of smoking 24. The cumulative incidence of moderate COPD after a mean follow-up period of 5.2 yrs was 8.3% (n=33). Independent predictors of moderate COPD, i.e. age, cough, starting smoking before 16 years of age as well as one or more GP consultations because of lower respiratory tract (LRT) complaints in the previous 12 months before the baseline survey, were included in the prediction rule. The rule, adjusted by bootstrapping, showed a reasonable discriminative ability (ROC area 0.72) and a satisfactory goodness of fit (Hosmer & Lemeshow test, $p$=0.6). The score of the rule ranged from 0 to 5 points. The predicted probability of developing moderate COPD increased from 2% (0-1 point), 7% (2 points), 16% (3 points) to 35% (4-5 points).

**Table 1. Regression coefficients, risk scores of independent predictors and discriminative ability of a prediction rule to identify incident moderate COPD in 399 male smokers 40-65 years of age**

| Predictors | | Regression coefficients† (SE) | Risk score (0-5) |
|---|---|---|---|
| age | 45-49 | 0.7 (0.7) | 1 |
| | 50-54 | 0.9 (0.7) | 1 |
| | 55-65 | 1.6 (0.7) | 2 |
| cough | | 0.7 (0.4) | 1 |
| childhood smoking (≤15 yr) | | 1.0 (0.4) | 1 |
| ≥1 GP contact for LRT complaints in previous 12 months | | 0.9 (0.4) | 1 |
| ROC area† | | 0.72 (95% CI 0.63-0.82) | |
| *Performance of prediction rule with risk score of ≥ 2 points* | | | |
| % of smokers with risk score of ≥ 2 points | | 55% (218/399) | |
| sensitivity | | 79% (26/33) | |
| 1-specificity | | 52% (192/366) | |
| positive predictive value | | 12% (26/218) | |
| negative predictive value | | 96% (174/181) | |

† adjusted for over-optimism using bootstrapping

Taking a cut-off of ≥ 2 points would identify as much as 79% (26/33) of the smokers actually developing moderate COPD (sensitivity) in the next 5 years, and 52% (194/366) of the smokers not developing moderate COPD. The cumulative incidence of moderate COPD after 5 years in subjects with ≥ 2 points was 12% (26/218) vs. 4% (7/181) in subjects with < 2 points.

**Comment**

A prediction rule, based on a few readily obtainable clinical variables, can identify most smokers who develop moderate COPD within 5 years, and could be helpful in daily practice to target smoking cessation strategies. The rule should be validated in female smokers.

**What is already known on this topic?**

Smoking status, age and initial FEV1 are independent predictors of future COPD. [5]

**What this study adds**

Clinical variables (age, cough, childhood smoking and recent GP contact because of lower respiratory tract complaints) can enable physicians to identify 80% of the smokers who will develop moderate COPD within 5 years.

**References**

1. Geijer RMM, Sachs APE, Hoes AW, Salomé PL, Lammers J-WJ, Verheij TJM. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. Fam Practice 2005;22:485-489.
2. Thiadens HA. Diagnosing asthma or COPD in patients with persistent cough: variations on a theme (Thesis). Modified Medical Research Questionnaire. Leiden; University of Leiden, 1999.
3. Krzyzanowski M, Hajiro T, Nishimura K, Jones PW, et al. A novel, short and simple questionnaire to measure health related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1874-8.
4. Geijer RMM, Sachs APE, Verheij TJM, Salomé PL, Lammers J-WJ, Hoes AW. Incidence and determinants of moderate COPD (GOLD II) in male smokers aged 40-65 years: 5 year follow-up study. Br J Gen Practice 2006; accepted.
5. Higgins MW, Keller JB, Landis R, et al. Risk of chronic obstructive pulmonary disease. Collaborative assessment of the validity of the Tecumseh Index of Risk. Am Rev Respir Dis 1984;130:380-385.

6

# Quality of life in smokers: focus on functional limitations rather than on lung function?

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**Abstract**

**Background**. The GOLD classification of severity of COPD is based solely on obstruction and does not capture physical functioning. We hypothesized that the MRC dyspnoea scale would correlate better with quality of life than the level of airflow limitation.
**Aim.** To study the associations between limitations in physical functioning (MRC dyspnoea scale) or airflow limitation (GOLD COPD stages) on the one hand and quality of life on the other.
**Methods.** Male smokers aged 40-65 without a prior diagnosis of COPD, enlisted with a general practice in a town in the centre of The Netherlands participated in this study. Quality of life was assessed by means of a generic (SF-36) and a disease specific questionnaire (QOLRIQ).
**Results.** A total of 395 subjects (mean age 55.4 years, pack years 27.1) performed adequate spirometry and completed the questionnaires. Limitations of physical functioning according to the MRC dyspnoea score were found in 25.1% (99/395) of the participants, and obstruction in 40.2% (159/395). The extent of limitations of physical functioning correlated more strongly with all quality of life components than the severity of airflow limitation. Also in multivariate logistic regression analysis the limitations of physical functioning were more strongly related to all quality of life components.
**Conclusion.** In middle-aged smokers the MRC dyspnoea scale is more strongly associated with quality of life than the severity of airflow limitation. Future staging systems of severity of COPD should capture this and not rely on $FEV_1$ alone.

## Introduction

There are several ways to assess the severity of chronic obstructive pulmonary disease (COPD). In almost all guidelines the classification of the severity of COPD is based on airflow limitation alone, i.e. the level of forced expiratory volume in one second (FEV1) without reference for instance to the severity of respiratory symptoms. [1, 2] Importantly, the correlation between airflow limitation and health related quality of life, i.e. an individual's satisfaction or happiness with domains of life insofar as these affect or are affected by health, is modest. [3-8] Dyspnoea is the main symptom limiting functional status in patients with chronic obstructive pulmonary disease (COPD). Functional status is the individuals' ability to perform normal daily activities in the different domains of life. [3] Limitations of the functional status measured on a dyspnoea-scale seem to be more strongly correlated with quality of life than pulmonary function.[9] In addition, patients usually attend the physician because of worsening of respiratory symptoms and not because of lung function decline. Therefore some authors have criticized the one-dimensional grading of COPD severity based on pulmonary function alone, as proposed by the GOLD Guidelines.[7]

In the daily management of smokers, including those with early phases of COPD, there is a need for a simple and standardized instrument to assess health related quality of life to facilitate targeted smoking cessation interventions. The Medical Research Council (MRC) dyspnoea scale possibly represents a useful instrument, because of its ability to categorize patients with severe COPD in terms of their disability. [6] The relationship of the MRC dyspnoea scale with quality of life in smokers at risk of developing COPD or with early stages of COPD, however, is unknown, as is the association of airflow limitation with quality of life in this large population. The aim of our study was to study these associations.

## Methods

In 1998, 702 male smokers, aged 40-65 years, enlisted with a general practice in IJsselstein, a town in the center of The Netherlands, participated in a screening study to identify undetected airflow obstruction. Only men were included because of the higher prevalence of COPD in males than in females as well as because of limited resources. [10] In 2003, a follow-up survey was performed. A total of 601 subjects (86% of 702) were still eligible, the lower number being mainly due to non-participation of one of the GPs.

Eventually, 436 of the 601 eligible individuals (73%) participated in the second survey. The study was approved by the ethics committee of the University Medical Center Utrecht.

*Spirometry* was performed by means of a hand-held Jaeger spirometer. Details of the procedure were described elsewhere. [10] Briefly, each subject had to perform at least three acceptable forced vital capacity maneuvers while sitting. The results were shown on a computer screen and the procedure was supported by computer software. If the FEV1 was less than 85% of predicted, the bronchodilator response was tested 15 minutes after inhalation of four puffs of salbutamol 100 mcg through an inhalation chamber. In subjects aged 60 years or over, the bronchodilator response was tested 30 minutes after inhalation of two puffs of ipratropium bromide 20 mcg. Experienced and especially trained lung function assistants employed by a primary care diagnostic center performed all measurements. The spirometer was calibrated daily with a 1-litre syringe at the start of a series of measurements. Two investigators (RMMG, APES) independently assessed the quality of the flow-volume curves and time-volume curves according to the criteria of the American Thoracic Society. [11]
Predicted values of FVC and FEV1 were computed using the regression equations of the European Coal and Steel Community (ECSC). [12]
According to the GOLD guidelines COPD is defined by a postbronchodilator FEV1/FVC ratio <0.7. [1,2] The severity of COPD can be distinguished in 4 stages according to postbronchodilator FEV1 values:

- Mild (GOLD stage I): FEV1 predicted ≥ 80%.
- Moderate (GOLD stage II): 50%≥ FEV1 predicted <80%.
- Severe (GOLD stage III): 30%≥ FEV1 predicted <50%.
- Very severe (GOLD stage IV): FEV1 predicted <30% (or <50% with signs of chronic respiratory failure).

Before each lung function test, height and weight were measured and the body mass index (kg/m2) was calculated. The number of pack years was computed as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years of smoking.

*Functional limitations* were assessed by a Dutch language version of the MRC dyspnoea scale [13]. The MRC dyspnoea scale measures limitations caused by dyspnoea graded at five levels from grade 1 "Not troubled with breathlessness except with strenuous exercise" to grade 5, "Too breathless to leave the house" (Appendix). The scale has been used for many years and is simple to administer.[14] Chronic cough was considered present if the patient responded yes to the question whether he was coughing almost every day for the previous 3 months.

*Co-morbidity*, defined as a diagnosis of cardiovascular, musculoskeletal or renal disease, cancer or diabetes mellitus, was extracted from the GP medical records. A disease was classified as present when a diagnosis by a primary or secondary care physician was found in the records or in the medical correspondence. In total 17 of 409 (4.2%) medical records were missing.

Generic *quality of life* was assessed by means of the Short Form Health Survey questionnaire (SF-36) and disease specific quality of life by means of the Quality Of Life in Respiratory Illness Questionnaire (QOLRIQ).[15, 16] Both self-administered questionnaires were completed at home in the four weeks before the survey. The SF-36 is composed of 36 questions, organized into eight multi-item scales: physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The scores were linearly transformed to a 0 to 100 scale, with higher scores indicating a better quality of life. The SF-36 is broadly used and validated. [15, 17, 18] The disease specific quality of life questionnaire was developed and validated for patients with mild to moderate asthma or COPD treated primarily in general practice. It comprises 55 items classified into a total score and seven subscales: breathing problems, physical problems, emotions, general activities, situations triggering or enhancing breathing problems, daily and domestic activities and social activities, relationships, and sexuality. For every item, patients were asked to answer, on a 7-point Likert-type scale, to what degree they were troubled because of pulmonary complaints. The response categories of all items ranged from 1 (not troubled at all) to 7 (very much troubled). In case of missing data, less than 50% of missing items were allowed per subscale, and one missing subscale was allowed for the calculation of the total score. The total score of the QOLRIQ and subscales scores of both questionnaires were computed by adding the item scores and dividing the sum by the number of valid items. The scores of the QOLRIQ were transformed in such a way that a lower score indicates a reduced quality of life in order to facilitate the comparison of the scores of the QOLRIQ with the scores of the SF-36.

*Statistical analysis*
Spearman's correlation coefficients ($r_s$) were determined to quantify the correlation of the MRC dyspnoea scale and GOLD staging (independent variables) with the components of the quality of life questionnaires (dependent variables). The MRC scores were recoded in value 0 = not troubled by breathlessness, value 1 = MRC grade I-II and value 2 = MRC grade III-V while GOLD stages were recoded in value 0 = no airflow limitation including GOLD stage 0, value 1 = GOLD stage I and value 2 = GOLD stage II (Appendix). There were no participants with GOLD stage III or IV. The component scores of both quality of life questionnaires appeared to be skewed to the right, indicating that a significant proportion of respondents had filled in the maximum score. The scores could not be normalized using any form of transformation. Therefore, the SF-36 and QOLRIQ component scores were dichotomized around a cut-off of the maximum score minus the minimal important difference: SF-36 high score (96-100: value 0) vs. low score (≤ 95: value 1) and QOLRIQ high score (6.5-7: value 0) vs. low score (≤ 6.5: value 1). The cut-offs of 95 points (SF-36) and 6.5 points (QOLRIQ) were chosen since the minimal important difference is considered to be 5 points for the SF-36 and 0.5 points for the QOLRIQ. [19, 20] In logistic regression analysis we assessed the association of the MRC scores and GOLD stages with the separate dichotomised quality of life component scores. Regression equations were computed with each separate quality of life component score being the outcome measure.

**Table 1. Patients' characteristics and quality of life scores of 395 middle-aged male smokers**

| Characteristics | | Mean (SD) or % |
|---|---|---|
| Age (years) | | 55.4 (6.3) |
| Smoking history (pack years) | | 27.1 (19.3) |
| No employment/retired | | 29% |
| Living alone | | 9% |
| Co-morbidity† | | 27% |
| Chronic cough | | 23% |
| BMI | | 26.6 (3.8) |
| FEV1 (L) | | 3.5 (0.7) |
| FEV1 % predicted | | 98 (16) |
| Lung function | No airflow limitation | 59.7% |
| | Mild COPD (GOLD I) | 29.6% |
| | Moderate COPD (GOLD II) | 10.6% |
| Functional limitations by dyspnoea | None | 74.9% |
| | Mild (MRC I-II) | 17.7% |
| | Moderate or severe (MRC III-V) | 7.3% |
| Generic QOL components ‡ (range 0-100) SF-36 | Physical functioning | 86.3 (17.7) |
| | Role functioning (physical) | 85.9 (29.5) |
| | Bodily pain | 83.3 (22.5) |
| | General health | 66.1 (18.8) |
| | Vitality | 68.3 (19.2 |
| | Social functioning | 87.9 (18.4) |
| | Role functioning (emotional) | 88.9 (26.9) |
| | Mental health | 78.4 (16.4) |
| Disease specific QOL components‡ (range 1-7) QOLRIQ | Total score | 6.5 (0.5) |
| | Breathing problems | 6.1 (0.8) |
| | Physical problems | 6.4 (0.7) |
| | Emotions | 6.5 (0.7) |
| | General activities | 6.6 (0.8) |
| | Situations triggering or enhancing breathing problems | 6.7 (0.6) |
| | Daily and domestic activities | 6.5 (0.6) |
| | Social activities, relationships, sexuality | 6.8 (0.5) |

† Co-morbidity denotes cardiovascular disease, diabetes mellitus, musculoskeletal disease, cancer, renal disease ‡ Higher scores indicate a better quality of life

**Table 2. Univariate (multivariate) association of limitations by dyspnoea and airflow limitation with QOL in middle-aged male smokers**

| Quality of life components | Limitations by dyspnoea graded by MRC scale | | Airflow limitation graded by GOLD staging | |
|---|---|---|---|---|
| **Generic questionnaire (SF-36)** | Univariate (multivariate) OR | 95% CI | Univariate (multivariate) OR | 95% CI |
| Physical functioning | 8.8 (8.4) | 4.8-16.0 | 1.4 (1.3) | 1.2-1.7 |
| Role functioning (physical) | 2.9 (2.9) | 2.0-4.1 | 1.0 (0.8) | 0.8-1.2 |
| Bodily pain | 1.7 (1.7) | 1.2-2.5 | 1.0 (1.0) | 0.9-1.2 |
| General health | 7.0 (7.0) | 1.0-47.1 | 1.1 (1.0) | 0.8-1.6 |
| Vitality | 8.2 (8.3) | 1.2-55.2 | 1.0 (1.0) | 0.7-1.4 |
| Social functioning | 2.1 (2.1) | 1.5-3.0 | 1.1 (1.0) | 0.9-1.3 |
| Role functioning (emotional) | 2.3 (2.5) | 1.6-3.4 | 0.9 (0.8) | 0.7-1.1 |
| Mental health | 2.7 (2.6) | 1.5-4.8 | 1.2 (1.1) | 1.0-1.5 |
| **Disease specific questionnaire (QOLRIQ)** | | | | |
| Total score | 6.2 (6.0) | 3.9-9.7 | 1.4 (1.3) | 1.2-1.7 |
| Breathing problems | 3.9 (3.7) | 2.3-6.5 | 1.7 (1.5) | 1.4-2.1 |
| Physical problems | 4.5 (4.5) | 2.9-7.0 | 1.1 (1.0) | 0.9-1.4 |
| Emotions | 4.8 (4.7) | 3.2-7.2 | 1.2 (1.1) | 1.0-1.5 |
| General activities | 3.3 (3.2) | 2.3-4.7 | 1.2 (1.0) | 1.0-1.5 |
| Situations triggering or enhancing breathing problems | 3.0 (2.9) | 2.1-4.3 | 1.3 (1.2) | 1.0-1.6 |
| Daily and domestic activities | 11.4 (11.1) | 6.5-19.9 | 1.4 (1.3) | 1.1-1.6 |
| Social activities, relationships, sexuality | 3.6 (3.5) | 2.4-5.4 | 1.3 (1.2) | 1.0-1.7 |

Values are odds ratio's obtained from logistic regression analysis using MRC scale and GOLD stages as independent variables and dichotomized scores of the QOL components as separate dependent variables

## Results

A total of 395 male smokers – 91% of the 436 participants – performed adequate spirometry and completed the questionnaires. Twenty seven subjects (6%) did not perform adequate spirometry and 14 participants (3%) did not sufficiently complete the questionnaires. The mean age of the participants was 55.4 years (SD 6.3) and the mean smoking history 27.1 pack years (SD 19.3) (Table 1). Limitations of physical functioning due to dyspnoea – MRC dyspnoea grade I to V - were found in 25.1% (99/395) of the participants, and COPD in 40.2% (159/395) (Table 1). The MRC dyspnoea scale correlated moderately ($r_s$=0.52) with the overall score of the disease-specific questionnaire while the severity of airflow limitation correlated weakly ($r_s$ =0.22) with this score (data not shown).

The MRC dyspnoea scale was weakly to moderately correlated to all separate component scores of both questionnaires ($r_s$ = 0.19-0.58) while airflow limitation was only weakly associated with all component scores of the disease-specific questionnaire ($r_s$ =0.12-0.28) and some component scores of the generic questionnaire ($r_s$ = 0.13-0.20). The MRC scale correlated best with quality of life components measuring impairment in daily activities, i.e. 'physical functioning' from the generic questionnaire ($r_s$ =0.53) and 'daily and domestic activities' from the disease specific questionnaire ($r_s$ =58). In addition, in logistic regression analysis MRC dyspnoea scale was more strongly related to all quality of life components than airflow limitation (Table 2). For example, the odds ratio (OR) of having a worse score of the 'physical functioning' component of the SF-36 was approximately 9 times higher in subjects with moderate or severe limitations on the dyspnoea scale than in those with mild limitations on this scale (OR 8.8; 95% CI 4.8-16.0), while the corresponding odds ratio was only slightly higher (1.4; 1.2-1.7) in patients with moderate compared to those with mild COPD according to the GOLD criteria. (Table 2) The odds ratios of the multivariate analysis were quite similar to those of the univariate analysis (Table 2).

**Discussion**

In our cohort of male smokers 45 to 70 years of age, of whom 40% had mild or moderate COPD (GOLD I or II), quality of life was more strongly associated with functional limitations measured by the MRC dyspnoea scale than with the severity of airflow limitation defined according to the GOLD staging of COPD. To our knowledge this is the first study to show this association in a general population of smokers at risk for COPD or with early disease.

Quality of life was measured with a generic questionnaire (SF-36) as well as with a disease specific questionnaire (QOLRIQ). The SF-36 is commonly used and has been demonstrated to be reliable, responsive and valid in COPD. [8, 19, 22] The Dutch version of the SF-36 has proven to be a reliable and valid instrument for use in studies of chronic disease populations in The Netherlands. [15] The SF-36 component scores of our study in middle-age smokers were highly similar to the scores derived from two random samples from the Dutch population, supporting the finding that early COPD does not markedly affect quality of life. [15] Reliability and validity of the QOLRIQ has been tested in stable primary care patients with asthma or COPD. [16, 22] Limitations in physical functioning were measured with the MRC dyspnoea scale. The MRC dyspnoea scale is widely used and has been demonstrated to be valid compared to alternative clinical dyspnoea ratings such as the baseline dyspnoea index (BDI), dyspnoea components of the St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ). [23]

Some limitations of our study must be addressed. Most smokers without a prior diagnosis of COPD experienced milder disease. Therefore, our results cannot be inferred to patients with severe COPD. Nonetheless, in subjects with severe COPD too, the level of dyspnoea has been shown to be more closely related to quality of life than the FEV1. [8, 9, 20, 21] Second, our cohort consisted of male smokers only. In general, most but not all studies report lower quality of life in females with COPD compared to males with COPD. [4, 5, 17, 24] In smoking and non-smoking women, higher frequencies of respiratory symptoms are reported than in men. Moreover, women visit the GP more frequently for respiratory symptoms. [25-29] Therefore, it seems likely that the independent association of the MRC dyspnoea scale with quality of life will be found in female smokers as well. Third, 236 (59.7%) participants had no airflow limitation. Theoretically in those with airflow limitation the results could be different compared to those without airflow obstruction. Limiting the analysis to the subjects with airflow obstruction only, however, yielded similar associations. Finally, 9% of the participants did not perform adequate spirometry or did not complete the questionnaires. These 41 individuals did however not differ from the included participants with respect to the characteristics presented in Table 1.

Several earlier studies addressed the association of the level of dyspnoea and lung function with quality of life. In subjects with moderate and severe COPD - GOLD stage II and over – quality of life was more strongly associated with the level of dyspnoea than with disease severity based on lung function. [8, 9, 20, 30] To our knowledge, only one study was conducted in subjects with early COPD - GOLD 0-II. Its conclusion that the transition from GOLD stage 0 to II did not correspond with important differences in health status, is in line with our results. [5] In other studies co-morbidity was related to impairment in quality of life independently of the severity of COPD. [17, 24]
The one-dimensional grading of COPD severity based on pulmonary function alone has been criticized [7] since patients do not visit the GP because of a low lung function but because of respiratory complaints and functional limitations. The GOLD classification of COPD lacks an index quantifying the impact of respiratory symptoms on physical functioning such as the NYHA classification in patients with heart disease. Therefore, some authors have proposed a multidimensional severity index for moderate or severe COPD including pulmonary function, BMI, dyspnoea and exercise capacity. [31] The current use of the GOLD staging system in patient care is meant not only to diagnose COPD but also to grade the impact of the disease on functioning of patients, and to guide treatment. From many studies it has become clear that the mono-dimensional grading with FEV1 misses to a large

extent the impact of the level of dyspnoea on the individual patient as well as other aspects of the disease.
Assessing changes in both physical functioning by means of the MRC dyspnoea scale and in lung function is needed in day-to-day practice in order to guide medical treatment, and in particular smoking cessation intervention, of individual patients either at risk for COPD or with diagnosed COPD.
In conclusion, in middle-aged smokers limitations of physical functioning due to breathlessness as measured by the MRC dyspnoea scale are more strongly associated with quality of life than the severity of airflow limitation. Future staging systems of severity of COPD should capture this and not rely on $FEV_1$ alone.

**Acknowledgements**
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**Appendix. Grading of limitations of physical functioning by dyspnoea (MRC scale) and airflow limitation (GOLD staging)**

| Grade | | Value† |
|---|---|---|
| - | No breathlessness at all | 0 |
| MRC I | Not troubled with breathlessness except with strenuous exercise | 1 |
| MRC II | Troubled by breathlessness when hurrying on the level or up a slight hill | |
| MRC III | Walks slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level | 2 |
| MRC IV | Stops for breath after walking 100 yards or after a few minutes on the level | |
| MRC V | Too breathless to leave the house or breathless when dressing | |
| - | No airflow limitation | 0 |
| GOLD I | Mild airflow limitation | 1 |
| GOLD II | Moderate airflow limitation | 2 |

† Value: recoded grade of limitations by dyspnoea and airflow limitation used in logistic regression

## References


1. Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-76.
2. Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Resp J 2003;22:1-2.
3. Wilson IB, Cleary PD. Linking clinical variables with health related quality of life. JAMA 1995;273:59-65.
4. Wijnhoven HAH, Kriegsman DMW, Hesselink AE, Penninx BWJH, de Haan, M. Determinants of different dimensions of disease severity in asthma and COPD ; pulmonary function and health related quality of life. Chest 2001; 119:1034-42.
5. Antonell-Incalzi R, Imperiale C, Bellia V, et al. Do GOLD stages of COPD severity really correspond to difference in health status ? Eur Respir J 2003 ;22 :444-449.
6. Bestall JC, Garrod PR, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581-6.
7. Kerstjens HAM. The GOLD Classification Has Not Advanced Understanding of COPD. Am J Respir Crit Care Med 2004;170;212-213.
8. Mahler DA, Mackowiak JI. Evaluation of the Short-Form 36-Item questionnaire to measure health-related quality of life in patients with COPD. Chest 1995;197:1585-1589.
9. Hajiro T, Nishimura K, Tsukoni M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnoea vs disease severity in indicating the health-related quality of life of patients with COPD Chest 1999;116:1632-1637.
10. Geijer RMM, Sachs APE, Hoes AW, Salomé PL, Lammers J-WJ, Verheij TJM. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. Family Practice 2005;22:485-489.
11. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
12. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC, on behalf of the working party 'Standardization of lung function testing'. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;6:(suppl):5-40.
13. Thiadens HA. Questionnaire. Diagnosing asthma or COPD in patients with persistent cough: variations on a theme (Thesis). Leiden: University of Leiden, 1999.
14. Fletcher CM (Chairman). Standardized questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ 1960;2:1665.
15. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in

community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.
16. Maille AR, Koning CJ, Zwinderman AH, et al. The development of the 'Quality-of-life for Respiratory Illness Questionnaire (QOLRIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respir Med 1997;91:297-309.
17. Van Manen JG, Bindels PJE, Dekker FW, et al. The influence of COPD on health-related quality of life independent of the influence of co-morbidity. J Clin Epidemiol 2003;56:1177-84.
18. Curtis, JR, Patrick DL. The assessment of health status among patients with COPD. Eur Resp J 2003;21:Suppl 41:36S-45S.
19. Van Stel HF, Maillé R, Colland VT, Everaerd W. Interpretation of change and longitudinal validity of the quality of life for respiratory illness questionnaire (QOLRIQ) in inpatient pulmonary rehabilitation. Quality Life Research 2003;12:133-145.
20. Hajiro T, Nishimura K, Tsukoni M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:785-790.
21. Viramontes JL, O'Brien B. Relationships between symptoms and health-related quality of life in chronic lung disease. Gen Inter Med 1994;9:46-48.
22. Maillé AR. Quality of life in asthma and COPD. Development of a disease-specific questionnaire (Thesis). Amsterdam: University of Amsterdam 2000.
23. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnoea in patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 1998;158:1185-1189.
24. Ferrer M, Alonso J, Morera J, Marrades R, et al. Chronic obstructive pulmonary disease and health-related quality of life. Ann Int Med 1987;127:1072-1079.
25. Engström CP, Persson LO, Larsson S, Sullivan M. Health-related quality of life in COPD: why both disease-specific and generic measures should be used. Eur Respir J 2001;18:69-76.
26. Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex differences in lung vulnerability to tobacco smoking. Eur Respir J 2003:1017-1023.
27. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. J Epidemiol Community Health 2000;54:917-922.
28. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax. 1997;52:820-7.
29. Braspenning JCC, Schellevis, FG, Grol RPTM (red.). Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Kwaliteit huisartsenzorg belicht. NIVEL/WOK, 2004
30. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T. Stages of disease severity and factors that affect the health status of patients with chronic obstructive disease. Resp Medicine 2000;94:841-846.
31. Celli BR, Cote CG, Marin JM, et al. The Body-Mass Index, Airflow Obstruction, Dyspnoea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. N Engl J Med 2004;350:1005-1012.

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# Screening for COPD in middle-aged smokers: unfavorable balance between costs and effects

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**Abstract**

**Aim**. To evaluate the costs and effects of two strategies of early detection of COPD - screening and case-finding - in middle aged smokers, followed by a smoking cessation intervention.
**Methods.** Costs and effects of current practice were compared with a screening and a case finding strategy followed by a smoking cessation intervention. Based on a combination of estimates concerning the prevalence of unrecognized COPD in smokers and estimates of the effectiveness of smoking cessation interventions, the costs per detected COPD case and costs per additional quitter were calculated. It was assumed that 25% of all newly detected patients with COPD receive intensive smoking cessation counseling plus bupropion (IC) or short GP counseling (SC).
**Subjects.** Smokers, 45-64 years of age, in The Netherlands, not diagnosed with airflow limitation, in the population at large (screening) or visiting the GP for lower respiratory tract complaints (case finding).
**Results.** A more active approach will offer a substantial increase in the additional number of newly detected COPD in one year: approximately 195,000 in the screening strategy and over 78,000 in the case finding strategy. Detecting one new patient with COPD was estimated to cost €91 according to the screening strategy and €48 according to the case finding strategy.
The costs per quitter following *intensive counseling* were €5,375 in the screening strategy and €3,945 in the case finding strategy which is markedly lower than the costs per quitter following *short counseling*, i.e. €11,216 for screening and €5,628 for case finding. Overall, the case finding variants showed a more favorable balance of costs and effects than the corresponding screening variants. The costs per quitter in the case-finding variants were considerably lower (€3,945 – 5,628) than the costs per quitter of the screening variants (€5,375 - €11,216).
**Conclusion.** Screening for COPD in middle-aged smokers can not be recommended. Case finding seems an attractive alternative, provided that intensive counseling is logistically possible and drug treatment, including nicotine replacement therapy, is reimbursed.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major and still increasing health problem with a high morbidity and mortality. During the next decades, morbidity and mortality are expected to rise further mainly as a result of the past and current burden of smoking and the ageing of the population. [1] Given the high prevalence of undiagnosed COPD in smokers [2], and the proven benefits of smoking cessation on lung function decline and to a lesser extent on mortality [3, 4], several strategies of early detection of COPD have been advocated to diminish the future burden of COPD. [5, 6] Among these early detection strategies are screening of the smoking population at large or case-finding in general practice (i.e. lung function assessment in those presenting to a physician with lower respiratory tract symptoms). In addition, such strategies might be targeted at smokers within a certain age category. This may be especially attractive since a suitable test that is acceptable for the public is available and that smoking cessation interventions in smokers in the population at large and in smokers with known COPD in particular, are estimated to be cost-effective. [7, 8] However, it is unknown whether active screening for or case finding of COPD, followed by subsequent smoking cessation intervention is a cost effective strategy as well. Moreover, the question remains whether early detection and subsequent stop-smoking counseling exhibits a better balance between costs and effects than smoking cessation programs directed towards the general public or directed towards known patients with COPD. Thus, the additional costs of finding a patient with previously unknown COPD, and the benefits due to the fact that the smoking cessation treatment is aimed at a previously undiagnosed patient with COPD instead of an average smoking individual or a known patient with COPD should be weighed. For that purpose we combined data from recent studies on effectiveness of screening and case-finding programs on detecting new COPD patients with 1) estimates of the prevalence of unrecognized COPD in smokers, 2) estimates of the effectiveness of smoking cessation interventions and 3) results from available analyses on the effects of smoking cessation programs directed towards the general population and towards patients with known COPD. In short, the aim of this study was to evaluate the costs and effects of two strategies of early detection and treatment of COPD – screening and case-finding, followed by subsequent smoking cessation intervention - in terms of costs per new COPD case diagnosed and costs per additional quitter.

**Methods**

Four active scenarios were considered which differ in terms of (a) the strategy used to detect individuals with COPD and b) the smoking cessation interventions applied. The search strategies used were screening and case finding, the smoking cessation interventions were intensive counseling or short counseling. Because of the current shift from short counseling by GPs to intensive counseling by practice nurses in general practice in The Netherlands, we analyzed cost-effectiveness of these two interventions. It was assumed that one of the four scenarios was implemented for a period of one year.

*Screening* included one-time spirometry in smokers 45-64 years of age in the population at large, while c*ase finding* was defined as a one-time spirometry test in smokers 45-64 years of age visiting the GP because of lower respiratory tract complaints (LRT).
*Intensive counseling* (IC) was defined as counseling by a trained nurse for a total length of 90 minutes, after a brief stop advice from a GP, in combination with bupropion treatment for a period of nine weeks.
*Short counseling* (SC) included counseling by a general practitioner or a GP assistant in one or two consultations with a total length of 12 minutes. [7]
*COPD* was defined according to the WHO/GOLD criteria by a postbronchodilator FEV1/FVC ratio <0.7. [9, 10]

In order to calculate the costs and effects of the scenarios, the following approach was used. First, the size of the populations eligible for screening and case finding was estimated, as well as the numbers of newly detected individuals with COPD (number of cases) in both search strategies. Second, taking the estimated numbers of newly detected COPD cases into account, the effect of the smoking interventions (numbers of quitters) was estimated. Third, the costs of finding the new COPD cases and the costs of smoking interventions were calculated. Fourth, estimates were obtained of costs per new COPD case and costs per quitter. Finally, the impact of the various parameters on the outcome measures was assessed in a sensitivity analysis.

*Numbers of cases*

The estimated number of subjects with newly diagnosed COPD in current practice in the year 2000 was based on the incidence rates per 5-year age classes and the number of inhabitants in The Netherlands in these specific age classes. [8, 11] The number of spirometry tests needed to diagnose COPD in general practice was calculated by multiplying the number of cases detected in current practice with 2.5, as the prior chance of COPD in a patient with suspected disease was at least as high as in the case finding model (~40%): to find one smoker

with COPD in current practice a 2.5 fold number of spirometry tests is needed. [2]
The numbers of smokers eligible for the screening and case finding strategies were based on demographic data from Statistics Netherlands and on smoking rates published yearly by the Dutch Foundation for a Smoke Free Future. [11, 12] The % of smokers without physician diagnosis of asthma or COPD, the % of smokers invited for spirometry that actually undergo these measurements, the % smokers visiting the GP for LRT complaints each year as well as the prevalence of unrecognized COPD were derived from our recent screening study in male smokers aged 40-65 years.[2] The proportion of female smokers visiting the GP for LRT complaints was calculated by multiplying the estimated rate in men by 1.33.[2, 13] The proportion of smokers actually performing spirometry in the case finding strategy was based on a study in smokers randomly selected in general practice. [6]

*Numbers of quitters*
The estimate of effectiveness of IC combined with bupropion in terms of 12 months continuous abstinence rates (17.2%; 95% CI 14.0-20.4) was based on a review of 4 randomized trials [14] while the estimate of the effectiveness of SC (7.9%: 4.7-11.1) was derived from a Dutch randomized controlled trial.[15] The additional abstinence rates – 12.5% for IC and 3.2% for SC - were calculated by subtracting the twelve months abstinence rate of patients with known COPD in current practice (4.7%) from these abstinence rates. [7]
The numbers of additional quitters were calculated by multiplying the number of cases with the estimated proportion prepared to quit (0.25 ± 0.10) and subsequently with the additional abstinence rate. The proportion of smokers prepared to quit was based on the results from former analyses about smoking cessation programs in the general population and among patients with known COPD.[7, 8]

*Costs*
Costs were calculated as the product of units of resource utilization and estimates of unit cost. Unit costs data were derived from different sources and translated to the price level in 2000 using the consumer price indices reported in the Dutch manual for cost research and, when needed, converted from US dollars to euros on the basis of purchasing power parity (Appendix 1-2). [7, 16-20] The cost categories included direct medical and indirect non medical costs.

The direct medical costs were:

- Costs of spirometry and bronchodilator tests.
- Costs of administration and organization.
- Smoking cessation intervention costs.
- Additional costs.

The indirect non medical costs were:

- Time spent by the participants, included time involved with the tests, traveling time.
- Transportation costs.

The unit costs of *spirometry and bronchodilator tests* were based on reimbursement fees. [17]

*Costs of administration and organization* of the screening strategy, including the costs involved in contacting all subjects, sending reminders and scheduling appointments, were valued equal to the reimbursement fees for administration and organization of screening programs in The Netherlands. [17]

The estimates of the *costs of smoking cessation intervention* were derived from a former cost-effectiveness analysis. [7] Total smoking cessation costs in current practice were computed by multiplying the number of detected cases in the models with the estimated proportion (0.013) using the 'mix' of interventions carried out in current practice, and subsequently with the estimated mean costs of this mix.[7]

The estimated *additional costs* in subjects with newly detected COPD due to increased utilization of health care resources other than the costs of the scheduled visits were negligible according to a former study. [18] Finding new COPD patients will likely generate additional costs due to influenza immunization, since vaccination is indicated in patients with COPD. However, including these costs would also imply that one would need to include the benefits from these vaccinations. As this is outside the scope of this study, we did not include vaccination-related costs and benefits.

*Time costs* of wage earners and participants without paid work were valued equally, according to the net hourly wages of the working participants.[17] We assumed that in the screening strategy spirometry was performed in primary care diagnostic services or hospital-based laboratories and in the case finding strategy by on-site equipment in the general practices. The time needed for a spirometry test was estimated at 15 minutes while for bronchodilator testing 30 additional minutes were included.

The costs of transportation were included in the screening strategy only, since patients in the case finding strategy already visited the GP for another reason. The mean traveling distance to hospital-based laboratories and transportation costs were based on the guidelines for cost research in health care, taking 30 minutes for an average of 14 km. [19, 20]

*Costs per new case of COPD and costs per quitter*
To calculate the costs per case, the numbers of cases were computed by multiplying the numbers of smokers actually performing spirometry in a specific search strategy with the estimated proportion of cases of that strategy. The costs per case were calculated by dividing the detection costs by the number of cases.
Whether the costs per detected case are acceptable critically depends on the health gains and potential cost savings associated with detecting a case of COPD. It is assumed that such gains lie in offering the detected cases a smoking cessation intervention. Based on the costs of these interventions we could calculate the additional (i.e. compared to current practice) cost per quitter by dividing the additional scenario costs by the number of additional quitters. The additional scenario costs were computed by subtracting the costs involved with diagnosing of COPD and with smoking cessation therapy in usual care, from the total costs of a specific scenario. The estimates of the costs per quitter were subsequently compared with published estimates of the costs per quitter in the general population and the cost per quitter in patients with known COPD. [7, 8] The comparisons on the basis of costs per quitter were considered to be sufficient for prioritization of smoking cessation strategies. For comparison with other strategies, estimates may be needed of costs per life year gained or costs per quality adjusted life year gained. Here these estimates were only mentioned in the discussion with reference to a dynamic Dutch population model of COPD progression developed by the National Institute of Public Health and the Environment (RIVM) in The Netherlands and the Institute for Medical Technology Assessment (IMTA) of the Erasmus University of Rotterdam. [8]

*Sensitivity analysis*
A stochastic sensitivity analysis was carried out in which the various parameters underlying the calculations (the various proportions - described in the section about the number of cases and the number of quitters – and the estimates of costs) were varied simultaneously to assess the impact of the variation on the main outcome measures, i.e. the costs per additional case and costs per additional quitter. All proportions (transformed to a log scale) were varied within their 95% confidence intervals - based on the numbers of observations – while the estimates of costs were varied within a margin of ±10%.
We analyzed for which parameters the outcome measures were most sensitive by ordering the standardized coefficients from a regression analysis (using the observations from the stochastic sensitivity analysis) using the main outcome measures as the dependent variables and the variables which were surrounded by uncertainty as independent variables.

**Table 1. Estimates of the number of eligible smokers, spirometry tests to be performed, new COPD cases detected and costs of detection**

| | Eligible smokers (n) | Spirometry tests (n) | New COPD cases (n) | Costs of detection |
|---|---|---|---|---|
| Screening | 1,161,887† | 627,419 (0.54 x 1,161,887) | 207,048 (0.33 x 627,419) | €18.6 million |
| Case finding | 243,996 (0.21 x 1,161,887) | 231,796 (0.95 x 243,996) | 90,401 (0.5 x 231,796) | €4.5 million |
| Current practice | - | 30,083 | 12,033 | €0.8 million |

† 3,862,655= [number of inhabitants in The Netherlands aged 45-64 years in 2000] x 0.32 [proportion of smokers in 2000] x 0.94 [proportion without diagnosed asthma or COPD], year 2000

## Results

*Numbers of cases and costs per case*

In Table 1 the numbers of eligible smokers, the numbers of spirometry tests to be performed, newly detected COPD cases and the costs of detection are presented. The number of the eligible smokers aged 45-64 years was estimated at 1,161,887.

In the screening model the proportion of smokers actually performing spirometry was estimated at 0.54, while the proportion of undiagnosed COPD among them was estimated at 0.33. Consequently, the estimated number of new cases of COPD according to the *screening* strategy was approximately 207,000 (i.e. the product of these 3 figures). Of these individuals 86% can be expected to have mild COPD and 14% moderate COPD. The total detection costs of the screening model were estimated at €18.6 million. Of these about €9 million were related to the tests, €7 million to the time and transportation of the tested subjects, and €2.6 million to administration and organization. The specific cost components are shown in Appendix 1.

In the *case finding* model 21% of the 1,161,887 eligible smokers aged 45-64 years can be expected to visiting the general practice in one year for lower respiratory tract (LRT) complaints, i.e. 243,996 patients. Since the expected proportion of these smokers actually performing spirometry was 0.95 and the estimated proportion of undiagnosed COPD in smokers visiting the GP for LRT complaints was 0.39, the number of newly detected COPD in the *case finding* model was around 90,000. (Table 1) Of these individuals 74% would be classified as having mild and 26% as moderate COPD. Now, the total detection costs were estimated at approximately € 4.5 million, of which about €3.5 million are related to the tests and only €1 million to the time and the transportation of the tested individuals.

The number of patients with newly diagnosed COPD according to *current practice* in the year 2000 was estimated at about 12,000, while an estimated total of around 30,000 spirometry tests were needed to diagnose these cases. The yearly detection costs of the current practice strategy were estimated at approximately €0.8 million.

**Table 2. Additional (i.e. compared to current practice) costs of detection and the number of additional COPD cases detected in the screening and case finding strategy, year 2000**

| Strategy | Additional costs of detection strategy | Additional cases (n) | Costs per case (95% CI) |
|---|---|---|---|
| Screening | €17.8 million | 195,015 | €91 (69 - 105) |
| Case-finding | €3.7 million | 78,368 | €48 (34 - 88) |

In Table 2 the additional detection costs, i.e. the detection costs of the screening or case finding strategies minus the detection costs in current practice, and the additional number of cases, i.e. the number of COPD cases detected according to those strategies minus the number of cases detected according to current practice, are shown. The costs per additionally detected COPD case in the screening model (€91) were higher than in the case finding model (€48).

**Table 3. Additional (i.e. compared to current practice) costs of the scenarios (total of costs involved in the detection of new COPD cases and costs related to smoking interventions) and additional quitters, year 2000**

| Scenario | Additional costs of scenario | Additional quitters (n) | Costs per quitter (95% CI) |
|---|---|---|---|
| Screening + IC | €34.7 million | 6,470 | €5,375 (4,347 - 6,979) |
| Screening + SC | €18.6 million | 1,656 | €11,216 (5,975 - 59,530) |
| Case-finding + IC | €11.1 million | 2,825 | €3,945 (3,113 - 5,214) |
| Case-finding + SC | €4.1 million | 723 | €5,628 (2,810 - 31,810) |

IC: intensive counseling + bupropion, SC: short counseling

*Numbers of quitters and costs per quitter*

In Table 3 the additional costs (including those related to smoking cessation interventions) of the scenarios as well as the additional number of quitters are presented. According to the screening scenarios, the number of individuals receiving anti-smoking therapy was estimated at 51,762, and the number of quitters at 6,470 when applying intensive counseling (IC) and 1,656 when applying short counseling (SC). As expected, the scenario costs were higher for the screening variant including IC (€34.7 million) than for the one including SC (€18.6 million). Nonetheless, the costs per quitter were lower in the screening variant including IC (€5,375) than in the one including SC (€11,216).

According to the case finding scenarios, the number of individuals receiving anti-smoking therapy was estimated at 22,600 and the number of additional quitters at 2,825 when applying IC and 723 when applying SC. Again, the total scenario costs were higher in the variant including IC (€11.1 million) than in the one including SC (€4.1 million) and again, the costs per quitter were lower in the case finding variant including IC (€3,945) than in the one including SC (€5,628).

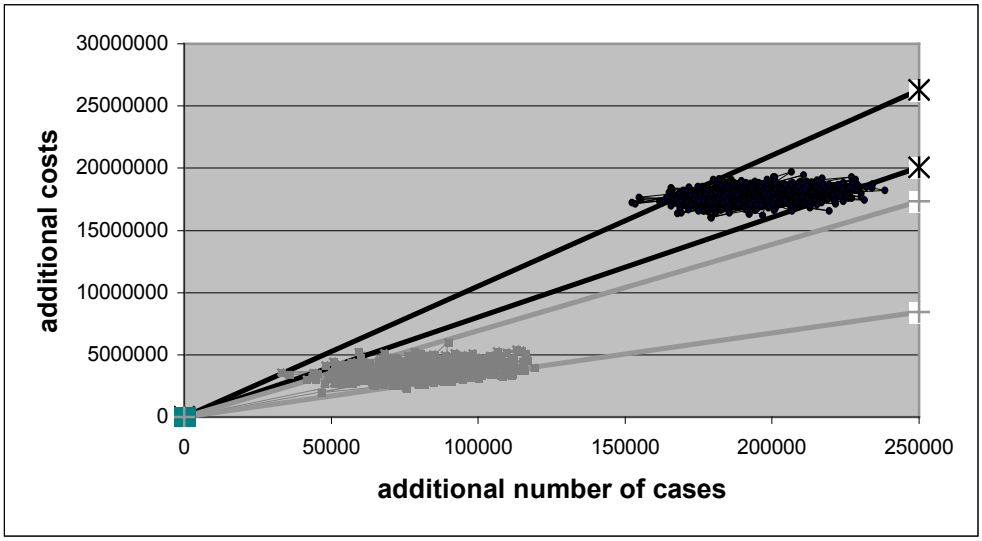
*Sensitivity analysis for cost-effectiveness*

The multivariate regression analysis showed that the outcome measure 'costs per case' was most sensitive for changes in the assumed prevalence of undiagnosed COPD. Figure 1 presents the results from 1000 random draws from the various uncertainty distributions in terms of the additional detections costs of the models and the additional numbers of cases found. The dots refer to the model in comparison to current practice and the straight lines represent the 95% confidence intervals for the costs per newly detected COPD case.

The outcome measure 'costs per quitter' was most sensitive for changes in the assumed additional abstinence rates of the smoking cessation interventions and to a lesser extent for changes in the proportion of smokers prepared to quit and the prevalence of undiagnosed COPD. Figure 2 presents the results from 1000 random draws from the various uncertainty distributions in terms of the additional costs of the four scenarios including the costs of the smoking cessation treatments and the additional numbers of quitters.

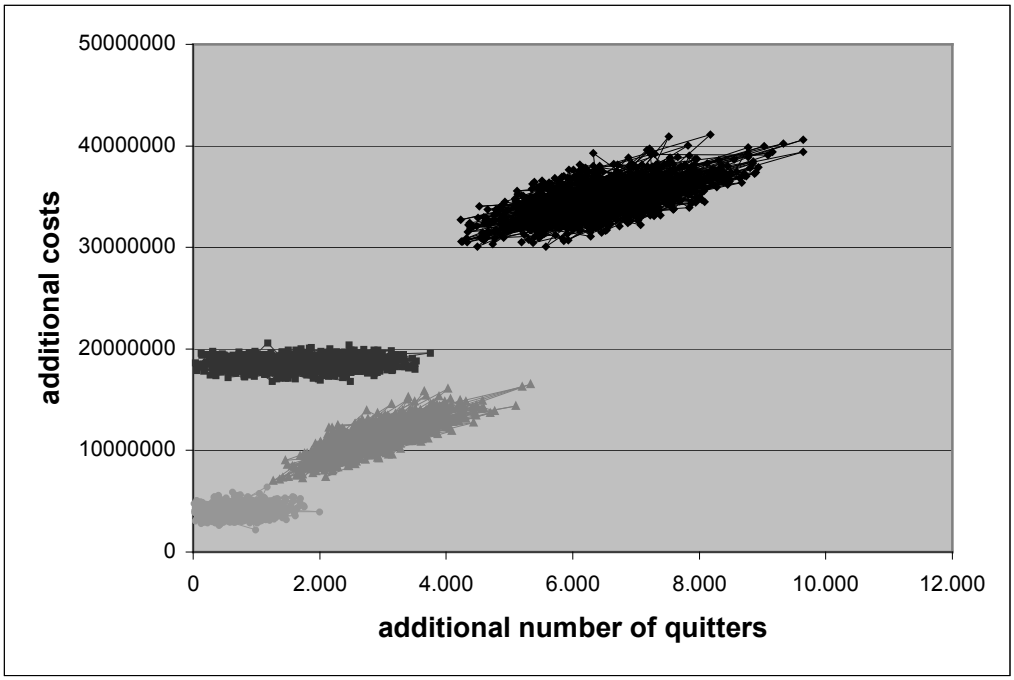
Both outcome measures were not particularly sensitive for changes in any of the relevant parameters.

**Figure 1. Costs per case: uncertainty distributions in terms of additional costs of detection, and additional numbers of cases found**




Black * (lines) = screening compared to current practice (95% CI); Grey + (lines) = case finding compared to current practice (95% CI)

**Figure 2. Costs per quitter: uncertainty distributions in terms of additional costs of scenarios including costs of detection and smoking cessation interventions, and additional quitters**




Top-down: 1) screening + intensive counseling 2) screening + short counseling 3) case finding + intensive counseling 4) case finding + short counseling

## Discussion

In comparison with current practice, the estimated additional costs of detecting one subject with COPD in middle-aged smokers were limited in both the screening and the case finding model, €91 and €48, respectively. The costs per quitter following intensive counseling (€5,375 for screening, €3,945 for case finding) were markedly lower than the costs per quitter following short counseling (€11,216 for screening, €5,628 for case finding). The costs per quitter in the case finding variants were lower than in the corresponding screening variants.

Several aspects of our study deserve further discussion. First, the distribution of the severity of undiagnosed COPD reflects the Dutch situation with a relatively high proportion of undiagnosed mild COPD (86%). In different populations with higher proportions of undiagnosed moderate and severe COPD, the balance between the benefits and costs of early detection and treatment will be better. Second, to reduce the costs of screening and case finding, we considered some modifications of the scenarios.

When for example bronchodilator testing was excluded, the costs per quitter would decrease in the screening variants by 15-28% and in the case finding variants by 16-45%. This reduction was due to the increase of the number of COPD cases by about 3.5% and the proportional increase of the number of quitters combined with a substantial decrease of the costs. Doing so, a small proportion of smokers (3.5%) falsely receives a diagnosis of COPD and is 'falsely' offered smoking cessation intervention as well. Another possibility to reduce the costs is to replace bupropion by nortriptyline. The costs of nortriptyline compared to bupropion are markedly lower (€13 vs. €69 per month, price level 2002) while long term abstinence rates seem comparable (nortriptyline vs. placebo OR 2.8; 95% CI 1.7-4.6; bupropion vs. placebo OR 2.1; 1.8-2.4) [21] Prescribing nortriptyline during nine weeks in stead of bupropion would substantially reduce the costs per quitter treated with intensive counseling, with approximately €1,000 from €3,945 to €2,945, assuming the 12 months' additional abstinence rate of nortriptyline is similar to the abstinence rate of bupropion.[14] Disadvantages of prescribing nortriptyline as a first-line drug for nicotine addiction in general practice are, however, the concerns about potential side-effects, the step-up therapy needed, and the absence of an official approval for a tobacco dependence indication.[22] In a third variant, performing spirometry in general practice by on-site equipment would decrease the costs of the screening plus IC with around 20%. However, even then the case finding variant plus IC would be less expensive because of the costs of administration and organization of the screening strategy and its lower yield of new cases.

To our knowledge, our study is the first formal analysis to report the costs and effects of different strategies of early detection of COPD in middle-aged smokers. Earlier studies of smoking interventions were directed towards patients with physician diagnosed COPD. [8] Several studies in other patient domains reported costs per COPD (and sometimes asthma) case or costs per quitter. Of the studies evaluating a screening strategy, the costs per detected case with asthma or COPD in a Dutch screening study (DIMCA) in the population at large, aged 25-70 years, were US$ 953, which was considerable higher than in our study (€91) partly due to the 4 times higher prevalence of airflow obstruction of our study among middle-aged male smokers.[17] In a Dutch study evaluating a case finding strategy among smokers visiting the general practice at random, the estimated costs – including time costs of the practice assistant and of the equipment only - per detected case were €5 to €10, i.e. markedly lower than the costs per detected case in our analysis (€48). This can be explained by the fact that we included the costs related to the time of the tested individuals, as well as the costs involved with bronchodilator testing. [6]

In our study the costs per quitter following short counseling - €5,628 for the case finding scenario and €11,216 for the screening scenario - were approximately 10 to 15 times as high as the reported costs per quitter following a short counseling program directed towards smokers in the population at large (€443) or towards patients with known COPD (€700).[1, 7]. These differences are largely attributable to the high costs involved with the detection of undiagnosed COPD combined with the low yields of short counseling.

Notably, the uncertainty intervals of the costs of the short counseling variants were wide due to the sensitivity of the outcome 'costs per quitter' for changes of the abstinence rates of the smoking cessation interventions combined with the relatively small number of quitters when applying short counseling (Table 3). Therefore, an early detection scenario including short counseling appeared to have an unfavorable balance between effects and costs. In addition, the uncertainty intervals of the costs per quitter of the intensive counseling variants were smaller (Table 3) in comparison with the corresponding intervals of the short counseling variants, indicating that the outcome 'costs per quitter following intensive counseling' was less sensitive to the change of the abstinence rates than the outcome 'cost per quitter following short counseling'.

Of the four scenarios under study, the case finding variant including IC best approximates the cost-effectiveness - in terms of costs per quitter – of smoking cessation programs directed towards known patients with COPD. In the latter program costs per life-year gained were considerable less than the often (e.g. in breast cancer screening) used limit of €20,000 in The Netherlands. So far, evidence for the cost-effectiveness of case finding and subsequent treatment of previously unrecognized COPD in smokers - in terms of costs per life year gained or quality adjusted life year gained - is however lacking and further studies are needed.

Implementation of a case finding scenario in general practice directed towards middle-aged smokers visiting the GP for LRT complaints would imply that approximately 200,000 extra spirometry test are to be performed in the first year, i.e. about 30 per general practice of 2350 patients. Appropriate reimbursement fees would be a prerequisite for the implementation of such a scenario. Another potential problem concerning implementation is the use of bupropion as essential part of the intensive counseling program. In several countries bupropion and nicotine replacement therapy are not reimbursed which could hamper a proper uptake of intensive counseling.

In conclusion, screening for COPD in middle-aged smokers can not be recommended. Case finding seems an attractive alternative, provided that intensive counseling is logistically possible and drug treatment, including nicotine replacement therapy, is reimbursed.

## References


1 Hoogendoorn M, Rutten-van Mölken MPMH, Hoogenveen RT, et al. A dynamic population model of disease progression in COPD. Eur Respir J 2005;26:223-233.

2 Geijer RMM, Sachs APE, Hoes AW, Salomé PL, Lammers J-WJ, Verheij TJM. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. Family Practice 2005:22:485-459.

3 Anthonissen NR, Connett JE, Murra RP for the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-679.

4 Anthonissen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connet JE, for the Lung Health Study Research Group. The effects of smoking cessation intervention on 14.5-year mortality. Ann Int Med 2005;142:233-239.

5 Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146-1161.

6 Van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370-1375.

7 Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Mölken MPMH. Cost-effectiveness analysis of face-to-face smoking cessation interventions by professionals. Institute for Medical Technology Assessment, 2003. Report number 03.67.

8 Hoogendoorn M, Feenstra T, Hoogenveen RT, Van Genugten M, Rutten-van Mölken MPMH. A health policy model for COPD: effects of smoking cessation. Institute for Medical Technology Assessment, 2003. Report 03.68.

9 Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-1276.

10 Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Resp J 2003;22:1-2.

11 Statistics Netherlands. Statline [online database]. (www.cbs.nl/en/figures/statline)

12 DEFACTO, voor een rookvrije toekomst, jaarverslag 2001. [Dutch Foundation for a Smoke Free Future, year report, 2001].

13 Braspenning JCC, Schellevis, FG, Grol RPTM (red.). Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Kwaliteit huisartsenzorg belicht. NIVEL/WOK, 2004.

14 Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2002, Issue 2. Art. No.: CD000031.

15 Pieterse ME, Seydel ER, de Vries H, Mudde AN, Kok GJ.Effectiveness of a minimal contact smoking cessation program for Dutch general practitioners: a randomized controlled trial. Prev Med 2000;32:182-190.

16 OECD in figures. Statistics on the member countries. Paris, 2001.

17 Van den Boom G, Van Schayck CP, Rutten-van Mölken MPMH, et al. Active detection of Chronic Obstructive Pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. Am J Respir Crit Care Med 1998;158:1730-1738.
18 Van den Boom G, Rutten-van Mölken MPMH, Folgering H, Van Weel C, Van Schayck CP. The economic effects of screening for obstructive airways disease. Prev Med 2000;30:302-308.
19 Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardization of costs: the Dutch Manual of Costing in economic evaluations. Pharmcoeconomics 2002;20:443-454.
20 Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Handleiding kostenonderzoek, methoden en standaardkostprijzen voor economische evaluaties in de gezondheidszorg. Geactualiseerde versie 2004. Diemen: College voor Zorgverzekeraars, 2004.
21 Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2004, Issue 4. Art. No.: CD000031.
22 Wagena EJ, Knipschild P, Zeegers MP. Should nortriptyline be use as a first-line aid to help smokers quit? Results from a systematic review and meta-analysis. Addiction 2005;100:317-326.

**Appendix 1. Detection costs of screening (case finding) and current practice, price level 2000**

| Costs component | Screening (*case finding*) (number) | Current practice (number) | Unit costs † | Costs of screening (*case finding*) (x $10^6$) | Costs of current practice |
|---|---|---|---|---|---|
| Spirometry tests | 627,419 *(231,796)* | 30,083 | €9.94 | €6.2 *(€2.3)* | €299.000 |
| Bronchodilator tests | 229,008 *(98,513)* | 12,785 | €11.93 | €2.7 *(€1.2)* | €152.000 |
| Time of spirometry and to get to the test (hour) | 470,564 *(57,949)* | 22,562 | €9. 82 | €4.6 *(€0.6)* | €222.000 |
| Time of bronchodilator tests (hour) | 114,504 *(49,257)* | 6,393 | €9.82 | €1.1 *(€0.5)* | €63.000 |
| Transportation (km) | 8,783,863 *(0)* | 421,155 | €0.15 | €1.3 *(€0)* | €63.000 |
| Administration + organization (participant) | 627,419 *(0)* | 0 | €4.10 | €2.6 *(€0)* | €0 |
| Detection costs (total) | | | | €18.6 *(€4.5 )* | €800.000 |

† Unit costs: translated to price level year 2000 using the consumers price indices, and when appropriate converted from US dollars to euros on basis of purchasing power parity [8, 18-20]

**Appendix 2. Smoking intervention costs and total costs of screening (case finding) and current practice, price level 2000**

| | Screening *(case finding)* + intensive counseling † | Screening *(case finding)* + short counseling † | Mix of interventions used in current practice † |
|---|---|---|---|
| Number of cases following intervention | 51,762 *(22,600)* | 51,762 *(22,600)* | 2795 *(1220)* |
| Smoking intervention costs | €17.3 million *(€7.5 million)* | €1.1 million *(€0.5 million)* | €315.000 *(€137.000)* ‡ |
| Total costs of screening scenario | €35.9 million *(€12.1 million)* | €19.7 million *(€5.0 million)* | €1.1 million *(€0.9 million)* ‡ |

† Unit costs per participant: €334 (intensive counseling), €21 (short counseling), €113 (mix of interventions in current practice), price level year 2000 [8, 18-20]) ‡ Costs of current practice in screening (case finding) population

# 8

# General discussion

## Should we screen smokers for COPD?

**Introduction**

Chronic Obstructive Pulmonary Disease (COPD), formerly known as lung emphysema and chronic bronchitis, is a major health problem. It currently is the fourth leading cause of death in the world and a further increase in prevalence and mortality is expected. [1] Since 80 to 90 % of the cases of COPD are caused by smoking, and severe COPD has a considerable impact on quality of life and is accompanied by increased morbidity and mortality, the possibility of early detection of COPD in smokers has been debated for many years. Both screening (irrespective of lower respiratory tract complaints) and case finding (limited to those presenting certain lower respiratory tract complaints to a physician) strategies have been proposed to improve early identification of the illness and to diminish the future burden of COPD. Several candidate populations for a screening strategy by means of spirometry have been advocated in the available literature. These include:

- All subjects not known to their GP with diagnosed airways disease. [2]
- Smokers in the population at large. [3]
- Smokers in the population at large, > 39 years of age, with a smoking history of > 10 pack-years. [4]
- Patients ≥ 45 years old who report smoking of cigarettes (current smokers and those who quit during the previous year) to primary-care providers. [5]

Case finding strategies have been proposed in several clinical guidelines, but, again the populations in which case finding (i.e. spirometry to detect possible COPD) is recommended varies considerably and include any patient visiting a physician:

- With symptoms of cough, sputum production or dyspnoea, and/or a history of exposure to risk factors for the disease (GOLD Guidelines). [1]
- Similar to GOLD recommendations but limited to patients aged 35 years and over [6], or limited to those aged 40 years and older. [7]

In this thesis, screening is defined as spirometry testing in current smokers in the population at large, not known to the general physician (GP) with obstructive airways disease while case-finding is defined as performing spirometry in current smokers visiting the GP for lower respiratory tract symptoms. Since COPD is very rare before the age of 40-45 years and early detection and (intensive) smoking cessation programs in the middle-aged is considered crucial to lower the burden of COPD in later life, the studies in this thesis were restricted to those aged 45-64 years.[8]

The aim of the studies presented in this thesis was to provide additional evidence to facilitate the discussions on the (dis)advantages of screening for COPD among middle-aged smokers. In this chapter the findings of our studies relevant to that discussion are presented briefly and the pros and cons of screening are discussed on the basis of the screening criteria of Wilson and Jungner.[9]

**Screening for COPD: main findings of our study**

The thesis provides the following results relevant for the screening debate:

- The prevalence of undiagnosed COPD in middle-age male smokers is high (29.5%). Subjects with previously undetected COPD predominantly experience mild airflow obstruction (87%) while only a small proportion has moderate obstruction (13%) and no one experiences severe airflow limitation (Chapter 2).
- The 5-year cumulative incidence of moderate COPD in middle-age male smokers is considerable (8.3%). The incidence is approximately 5 times higher in subjects with mild COPD (19.6%) compared to those without airflow limitation (4.1%) at baseline (Chapter 4).
- Patient characteristics are not helpful to recognize patients with prevalent mild disease (GOLD stage I) (Chapter 3). In contrast, most smokers who will develop moderate COPD (GOLD stage II) within 5 years (79%) can be identified by means of four readily obtainable characteristics (Chapter 5). However, using these characteristics falsely identifies also a marked proportion (52%) of those who will not develop COPD, as high-risk patients..
- The impact of mild and moderate airflow limitation per se on quality of life in smokers is relatively small. Functional limitations due to dyspnoea rather than the level of airflow limitation are associated with a lower quality of life (Chapter 6).
- Despite the high prevalence of undiagnosed COPD and the considerable incidence of moderate COPD, the balance between costs and benefits of screening for COPD in all middle-aged smokers followed by smoking cessation therapy seems unfavorable. (Chapter 7).

**Screening for COPD: criteria of Wilson & Jungner**

In this section the relevant findings of our studies and results from earlier studies are discussed to evaluate whether the criteria for screening for disease proposed by Wilson and Jungner are currently fulfilled.

1. *The condition sought should be an important health problem.*[+] Without doubt COPD meets this criterion. Morbidity and mortality due to COPD are expected to increase further in the following decades. As a result of demographic changes, COPD prevalence in The Netherlands is estimated to increase from 21/1000 in 1994 to 33/1000 in 2015 for men and from 10/1000 to 23/1000 for women. Anticipated changes in smoking behavior will reduce the projected prevalence to 29/1000 for men, but will increase it to 25/1000 for women. [10] In addition, COPD is an independent risk factor of lung cancer [11] and cardiovascular disease. [12-14]

2. *Treatment of the disease at an early stage should be of more benefit than treatment started at a later stage.*[+]Treatment of COPD includes smoking cessation therapy and drug treatment, and is targeted at different outcome measures as lung function decline, exacerbation frequency, quality of life as well as mortality. In smokers with mild and moderate COPD, the Lung Health Study was the first study to demonstrate prospectively that intensive smoking cessation intervention compared to usual care improves the prognosis by normalizing lung function decline. [15] After 5 year of follow-up there were no significant differences between the usual care and the smoking intervention group for all-cause mortality, lung cancer or hospitalizations for respiratory diseases, although smoking cessation per se was associated with significant reductions of fatal and non fatal cardiovascular disease. [16] After 15 year of follow-up however a small beneficial effect on all-cause mortality was found. The hazard ratio for mortality in the usual care group compared with the smoking intervention group was 1.18 (95% CI, 1.02 to 1.37). The absolute risk reduction was 1.55 per 1000 person-years (p= 0.03), i.e. 645 persons needed to be treated during 1 year to prevent one death (NNT=645). [17] To our knowledge, in patients with severe COPD the benefit of smoking cessation intervention compared to usual care, on lung function or on mortality has not been established yet. Nonetheless, a small effect of inhaled corticosteroids on exacerbation frequency has been seen. [18] In addition, compared with placebo, patients with moderate and severe COPD (mean FEV1 58%, SD 19) assigned to inhaled corticosteroids had a lower risk of all cause mortality (hazard ratio 0.73; 0.55-0.96, NNT=189). [19]

In conclusion, although formally the effects of smoking cessation intervention in smokers with early stages of COPD has not been compared with the effects of smoking interventions at more advanced stages of COPD, it is likely that the long-term benefits of smoking cessation (interventions) are higher in smokers with earlier stages of COPD, the more since other relevant disease, notably cardiovascular disease, could be prevented as well. Thus, this criterion is likely to be met. [20]

3. *The natural course (from susceptibility to precursor, early disease, and advanced disease) should be adequately understood.*[+/-]The susceptibility of smokers to develop COPD and its natural course is poorly understood. [21] Ferguson et al. stated that COPD meets this criterion (the disease, if not detected early, would go on to cause substantial morbidity or mortality). [4] However, we feel that this criterion is only partially met, since it has not been established in prognostic studies whether and to what extent patients with early stages of COPD - particularly GOLD stage 0 and to a minor extent GOLD stage I - will move upward to clinically significant COPD stages. Genotype-environment interactions are likely to be essential contributors to the development of COPD but seem to explain the accelerated decline in FEV1 in only a minority of patients. [22, 23]. It can be questioned whether chronic respiratory symptoms (GOLD stage 0) predicts clinically significant COPD (GOLD stage II and up) in smokers. [24] However, in our study we found a three times higher incidence of GOLD II in symptomatic than in asymptomatic smokers [Chapter 4] which is in line with the results of a Swedish study. [25] In contrast, there is some evidence that GOLD stage I is, indeed, a predictor of rapid decline of FEV1 in (male) smokers but not in ex-smokers.[15, 26, 27] In addition, a second study concluded that middle-aged smokers were at no evident risk of functional deterioration if their FEV1/VC ratio was normal.[ 28] In line with this, we found an approximately 5 times higher incidence of moderate COPD in those with baseline mild COPD, i.e. with an abnormal FEV1/FVC ratio alone, than in those with baseline normal spirometry (Chapter 4).

4. *There should be a recognizable early stage*, *and there should be a suitable test and the test should be acceptable to the population.*[+] Since spirometry fulfils both criteria, the two criteria are discussed together in this section. Early stages of COPD are difficult to detect without spirometry, due to the low discriminative ability of patients characteristics such as smoking history or age, or the poor recall of determinants related to family history or childhood.[29-36]

The association between respiratory symptoms and physical signs on the one hand, and early stages of COPD on the other is inconsistent. [24, 37-39] In line with these findings, patient characteristics were not helpful to recognize subjects with mild COPD in our cross-sectional study (Chapter 3). However, in our longitudinal study (Chapter 5) approximately 80% of those developing moderate COPD at five years could be predicted by a rule based on patient characteristics (age, childhood smoking, cough, GP contacts for lower respiratory tract complaints). So far, no readily obtainable biomarkers in sputum, blood or urine to identify individuals with COPD have been reported in the literature. [40, 41] In contrast, spirometry is a reliable and reproducible method to recognize early stages of COPD. [42] The risk of false positive and false negative results during spirometry can be reduced by means of an adequate quality assurance program. The sensitivity and specificity of lung function tests is not known because the traditional reference standard (pathologic examination of lung tissue) is not feasible in adequately powered studies. A new potential reference standard, high-resolution CT lung scan, may offer more opportunities.[42, 43] Spirometry is a reliable, reproducible and relatively simple non-invasive test. There are no relevant side effects of spirometry. Thus, this criterion is met.

5. *There should be adequate facilities for diagnosis and for treatment of abnormalities detected.*[-] A nationwide screening program in smokers 45-64 years of age with an interval of 5 years would likely generate at least 150,000 extra spirometry tests per year (Chapter 7). In the Netherlands most GPs can currently order lung function testing in primary care facilities or hospital based laboratories while in a minority of the general practices spirometers are available on site. An increasing number of primary care physicians is supported by nurse practitioners trained in the management of patients with asthma and COPD as well as in smoking cessation interventions. Most primary care physicians are familiar with the short counseling smoking cessation method. Drugs (nicotine replacement therapy, antidepressants) for smoking cessation are available, but not used optimally since the expenses are not fully reimbursed. The new 2006 health insurance law in The Netherlands will encourage on-site spirometry and smoking cessation interventions in general practice since appropriate reimbursement fees and the introduction of fee-for-service payment have become available. However, there is currently insufficient capacity of easily accessible facilities to test and treat such large numbers of smokers. It would likely take at least 3 years to train sufficient numbers of nurses to provide the required capacity, provided adequate funding is made available.

Since the necessary facilities to diagnose and treat such large numbers of smokers are currently not available, and expenses for nicotine replacement therapy and some antidepressants are not reimbursed, this criterion is currently not met.

6. *Screening should be repeated at intervals determined by the natural history of the disease.*[+]Tracking of lung function, i.e. repeated measurements of lung function, has potential advantages over a single test such as reducing the effect of outliers resulting in a abnormal first spirometry test. [44] A period of at least two years with regular measurements of FEV1 is needed to diagnose individuals with a substantial increase in the annual rate of decline of FEV1. [45] However it is not known at which interval lung function should be repeated when the results of the first spirometry test in a high-risk patient are normal. Infrequent testing may delay identification of lung function abnormality while more frequent testing with a less-than-optimal spirometry quality assurance program will increase the false positive rate. In a consensus statement 3- to 5-year intervals are recommended. [4] In our cross-sectional study in middle-aged Dutch smokers we predominantly detected subjects with mild COPD and no one with severe COPD (Chapter 2). In addition, in our prognostic study, the 5-year incidence of moderate COPD was approximately 8% (Chapter 4). Therefore, an interval of 5 years seems adequate. A less shorter interval would increase the costs while additional benefits are unlikely.

7. *The chance of physical or psychological harm to those screened should be less than the chance of benefit.*[+] The health impact of undiagnosed airflow obstruction was studied in a national sample of United States adults.[46] Of subjects with undiagnosed airflow obstruction 90% had mild FEV1 impairment. The occurrence of symptoms and self-reports of adverse effect on health and functional status increased with increasing FEV1 impairment, particularly when FEV1 fell below 50% of predicted. The latter finding was confirmed in another study in which progression of COPD from stage 0 to stage 2 did not correspond to any meaningful difference in health status. [47] In line with these finding we found that mild and moderate airflow limitation per se has a relatively small impact on quality of life in smokers, and that quality of life depends more strongly on physical limitations due to dyspnoea than on the level of airflow limitation (Chapter 6). Differences in health care resource utilization between the screened subjects and controls were not found in the DIMCA study. [48]

Therefore, the chance of benefit from smoking cessation at an early stage of COPD is likely to outweigh the chance of potential harm of being diagnosed with COPD.

8. *The cost of a screening program should be balanced against the benefits it provides.*[-] In a Dutch case finding study in smokers visiting the GP, detecting one patient with a $FEV_1$ <80% of predicted would cost €5 to €10 depending on the number investigated. In this study only direct costs – of equipment and time of practice assistant - were calculated while no bronchodilator test was performed. [49] In a Dutch screening study (DIMCA) in the population at large the costs involved in the detection of one person with previously undetected asthma or COPD were US$953. [1] In a U.S. screening study in a random sample of the population at large the costs of detecting one new patient with airflow limitation ranged from approximately US$500 to $1000 depending on the definition of airflow limitation. [45] Compared to other diseases these costs per detected case were relatively low. [50] The National Lung Health Education Program (United States) has recommended using office spirometry to screen for sub-clinical lung disease in smokers 45 years or older during a clinical encounter. [4] The costs and benefits of the latter recommendation have not been evaluated yet. Much of the available evidence of the effectiveness of screening is from studies that included smoking cessation interventions, making it difficult to determine the effects of screening spirometry alone. In our cost-benefit analysis the estimated costs of detecting one subject with COPD in middle-aged smokers were acceptable both in the screening and in the case finding model, €91 and €48 respectively (Chapter 7). These costs could easily be outweighed by savings when a new diagnosis of COPD would only slightly improve smoking cessation rates.[5] However, there is no convincing evidence that spirometry, as an isolated intervention enhances smoking cessation.[51, 52] In our analysis the costs per quitter treated with intensive counseling (€5,375 for the screening strategy, €3,945 for the case finding strategy) were markedly lower than the costs per quitter treated with short counseling (€11,216 for the screening strategy, €5,628 for the case finding strategy). In addition, the screening variants showed a less favorable cost-effectiveness ratio than the corresponding case finding variants. Also, in comparison with previously published costs per quitter treated with intensive counseling - €2,700 for diagnosed COPD or €2,240 for smokers in the general population- the screening variant (€5,375) showed a less favorable balance of costs and effects in terms of costs per quitter than the case finding variant (€3,945). [54, 55]

**Conclusion**

Pros and cons of screening are summarized in table 1. The major arguments in favor of screening are the continuing increasing prevalence of COPD and its associated extensive disability, the likely larger benefit of smoking cessation interventions on lung function decline and to a lesser extent on mortality in those with early disease compared to those with more advanced disease, and the availability of a suitable and acceptable test. The main arguments against screening include the detection of a large number of smokers with mild COPD and minor impairments, the development of clinically significant COPD in only a relatively small proportion of these newly detected cases, and the markedly less favorable balance between costs and effects of a screening strategy followed by smoking intervention in comparison with a case-finding strategy, or in comparison with smoking cessation interventions directed towards smokers in the population at large or towards smoking patients with physician diagnosed COPD. Spirometry and smoking cessation facilities in The Netherlands are, not surprisingly, currently not appropriate for a nationwide screening. It would likely take at least 3 years to develop the necessary logistics, assuming adequate resources.

In the last 50 years the smoking rates in men reduced from approximately 80% in 1950 to 31% in 2004 while in women smoking rates slightly increased from approximately 10% in 1950 to 25% in 2000.[53] Smoking cessation intervention directed towards smokers in the population at large as well as towards smokers with physician diagnosed COPD, is considered to be cost-effective since implementation of short GP counseling generates gains in life-years and net savings.[54, 55]. Although in the short term smoking cessation will cause savings, in the long term it may lead to increased costs due to longevity. [56] However, since the society is concerned with health and willing to spend money on added life-years, discouraging the uptake of smoking should be further stressed and smoking cessation further encouraged. Therefore, smoke-free workplace policies should be further implemented, and free nicotine replacement therapy for nicotine addicts willing to quit, has to become available, just as free methadone for heroin addicts. In conclusion, in general practice intensifying smoking cessation interventions targeted at smokers with a high risk of developing COPD using readily obtainable patient characteristics (aged 55-64 years, smoking before the age of 16 years, cough, and a recent GP contact for lower respiratory tract complaints) should be encouraged. Health care resources should preferably be applied to facilitate additional measures to prevent uptake of smoking or encourage smoking cessation in the population at large or, the latter also, in smokers with physician diagnosed COPD, rather than to develop COPD screening programs in 'healthy' smokers.

**Table 1. Pros and cons of spirometry screening for COPD and smoking cessation interventions in middle-aged smokers**

| Pros | Cons |
|---|---|
| High prevalence, morbidity and mortality | Detection of a large number of smokers with mild COPD and minor impairments only |
| Increasing burden of disease due to aging and past burden of smoking | Development of clinical significant COPD in a modest proportion of subjects with mild COPD |
| Likely benefit of smoking cessation in those with early COPD (normalizing lung function decline and small effect on mortality) | Costs per quitter after screening are markedly higher than costs per quitter in general population or among patients with known COPD |
| Absence of clinical markers and biomarkers of early COPD | Inconsistent evidence of benefit of spirometry per se on quit rate |
| Availability of a reliable, suitable and acceptable test | Smokers with the highest risk of developing clinical significant COPD will likely not participate |
| Optimal screening interval is not known; 5-year interval seems adequate. | Facilities in The Netherlands currently not appropriate for nationwide screening. |
| Chance of benefit likely outweighs chance of potential harm | |

## References


1. Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Am J Respir Crit Care Med 2001;163:1256-1276. [Yearly updated www.goldcopd.com ]
2. Van den Boom G, Van Schayck CP, Rutten van- Molken MPMH, et al. Active detection of chronic obstructive pulmonary disease and asthma in the general population. Am J Respir Crit Care 1998 ;158 :1730-1738.
3. Calverley PMA. COPD. Early detection and intervention. Chest 2000;117:365S-371S.
4. Zieliński J, Bednarek M, and the Know the Age of Your Lung Study Group. Early detection of COPD in a high-risk population using spirometric screening. Chest 2001;119:731-736.
5. Ferguson GT, Enright PL, Buist S, Higgins MW. Office spirometry for lung health assessment in adults. A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146-1161.
6. NICE Guideline. Chronic Obstructive Pulmonary Disease: 2004. [ www.nice.org.uk]
7. Geijer RMM, Thiadens HA, Smeele IJM, et al. NHG-Standaard COPD en astma bij volwassenen: diagnostiek. Huisarts Wet 2001;44:58-68. [Dutch College of General Practitioners. Guideline on COPD and asthma in adults: diagnostics. General Practitioner & Science 2001;44:58-68]. [ http://nhg.artsennet.nl/ ]
8. Dickinson JA, Meaker M, Searle M, Ratcliffe G. Screening older patients for obstructive airways disease in a semi-rural practice. Thorax 1999;54:501-505.
9. Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Papers 34. World Health Organization, Geneva:1968.

10. Feenstra TL, van Geneugten MLL, Hoogenveen RT, Wouters EF, Rutten-van Mölken MPMH. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease. Am J Respir Med Care 2001;164:590-596.
11. Wasswa-Kintu S, Gan WQ, Man SFP, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax 2005:60:570-575.
12. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest 2005;128:2640-2646.
13. Rutten FH, Cramer M-JM, Grobbee DE, at al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005; Epub ahead of print.
14. Knuiman MW, James AL, Divitini ML, Ryan G, Bartholomew HC, Musl AW. Lung function, respiratory symptoms and mortality: results from the Busselton Health Study. Ann Epidemiol 1999;9:297-306.
15. Anthonissen NR, Connett JE, Murra RP for the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166: 675-679.
16. Anthonisen NR, Connett JE, Enright PL, Manfreda J, and the Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002;166;333-339.
17. Anthonissen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connet JE, for the Lung Health Study Research Group. The effects of smoking cessation intervention on 14.5-years mortality. Ann Int Med 2005;142:233-239.
18. Alsaeedi A, Sin D, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. Am J Med 2002;113:50-64.
19. Sin DD, Wu L, Anderson JA, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. Thorax 2005;60:992-997.
20. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519-1533.
21. Croxton TL, Weinman GG, Senior RM, et al. Clinical research in chronic obstructive pulmonary research. NHLBI workshop summary. Am J Resp Crit Care Med 2003;167:1142-1149.
22. Sandford AJ, Silverman EK. Chronic Obstructive Pulmonary Disease I: Susceptibility factors for COPD the genotype-environment interaction. Thorax 2002;57:736-741.
23. Sandford AJ, Chagani T, Weir IR, Connett JE, Anthonissen NR, Paré PD. Susceptibility genes for rapid decline of lung function in the Lung Health Study. Am J Respir Crit Care Med 2001;163:469-473.
24. Vestbo J, Lange P, Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2002;166:329-32.
25. Lindberg A, Jonsson A-J, Rönmark E, Lundgren R, Larsson L-G, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 2005;127:1544-1552.
26. Burrows B, Knudson RJ, Camilli AE, Lyle SK, Lebowitz MD. The 'horse racing effect' and predicting decline in forced expiratory volume in one second from screening spirometry. Am Rev Respir Dis 1987;135:788-793.

27. Petty TL. COPD in perspective. Chest 2002:121:116S-120S.
28. Stanescu D, Sanna, A, Veriter C, Robert A. Identification of smokers susceptible to development of chronic airflow limitation. A 13-year follow-up. Chest 1998;114:416-425.
29. Higgins MW, Keller JB, Landis R, et al. Risk of chronic obstructive pulmonary diseas. Collaborative assessment of the validity of the Tecumseh Index of Risk. Am Rev Respir Dis 1984 ; 130 :380-385.
30. Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow study. Am Rev Respir Dis 1986:134:1011-1019.
31. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease.BMJ. 1991;303:671-675.
32. Gilliland FD, Berhane K, Yu-Fen L, Rappaport EB, Pters JM. Effects of early onset asthma and in utero exposure to maternal smoking in childhood lung function. Am J Respir Care Med 2003;167:917-924.
33. Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1730-1738.
34. Kanner RE, Anthonissen NR, Connett JE, for the Lung Health Study Research Group. Lower respiratory illnesses promote FEV1 decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:359-364.
35. Donaldson GC, Seemungal TAR, Bhowmik, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic pulmonary disease. Thorax 2002;57:874-852.
36. Prescott E, Vestbo J. Socioeconomic status and chronic obstructive pulmonary disease. Thorax 1999;54:737-741.
37. Badgett RG, Tanaka, DJ, Hunt DK, et al. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical finding alone? Am J Med 1993;94:188-196.
38. Shin C, Lee S, Abbott RD, et al. Respiratory symptoms and undiagnosed airflow obstruction in middle-aged adults. Chest 2004;126:1234-1240.
39. Mannino DM, Etzel RA, Flanders WD. Do the medical history and physical examination predict low lung function? Arch intern Med 1993;153:1892-1897.
40. Franciosi L, Page CP, Celli BR, et al. Markers of disease severity in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2005;[Epub ahead of print]
41. Tzortzaki EG, Tsoumakidou M, Makris D, Siafakas NM. Laboratory markers for COPD in 'susceptible' smokers. Clinica Chimica Acta 2005; [Epub ahead of print]
42. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC, on behalf of the working party 'Standardisation of lung function testing'. Lung volumes and forced ventilatory flows. Report working party standardisation of lung function tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;6:(suppl):5-40.

43. Remy-Jardin M, Edme J-L, Boulenguez C, Remy J, Mastora I, Sobaszek A. Longitudinal follow-up study of smoker's lung with thin-section CT in correlation with pulmonary function tests. Radiology 2002;222:261-270.
44. Hankinson, JL, Wagner, GR. Medical screening using periodic spirometry for detection of chronic lung disease. Occup Med 1993;8:353-361**.**
45. Tirimanna PRS, Akkermans RP, Van Schayck, CP, et al. The detection of a rapid decline in FEV1 at an early stage: the duration and number of measurements needed for an accurate estimation of the decline in FEV1. In: Tirimanna PRS. Active detection of obstructive airways disease in the genera; population [Thesis]. Katholieke Universiteit Nijmegen, Nijmegen, 1997.
46. Coultas DB, Mapel D, Gagnon RC, Lydick E. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med 2001;164:372-377.
47. Antonelli-Incalzi, Imperiale C, Bellia V, et al. Do GOLD stages of COPD severity really correspond to differences in health status? Eur Respir J 2003;22:444-449.
48. Van den Boom G, Rutten-van Mölken MPMH, Folgering H, Van Weel C, Van Schacyk CP. The economic effects of screening for obstructive airways disease: an economic analysis of the DIMCA program. Prev Med 2000;30:302-308.
49. Van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:370-375.
50. Van Schayck CP, Chavannes NH. Detection of asthma and chronic obstructive pulmonary diseases in primary care. Eur Resp J 2003;21 (Suppl 39): 16S-22S.
51. Badgett RG, Tanaka DJ. Is screening for chronic obstructive pulmonary disease justified? Prev Med 1997;26:466-472.
52. Humerfelt, S, Eide, GE, Kvale, G, et al. Effectiveness of postal smoking cessation advice: a randomized controlled trial in young men with reduced FEV1 and asbestos exposure. Eur Respir J 1998;11:284-290
53. DEFACTO, voor een rookvrije toekomst, jaarverslag 2004. [Dutch Foundation for a Smoke Free Future, year report 2004]. [ www.stivoro.nl ]
54. Hoogendoorn M, Rutten-van Mölken MPMH, Hoogenveen RT, et al. A dynamic population model of disease progression in COPD. Eur Respir J 2005;26:223-233.
55. Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Mölken MPMH. Cost-effectiveness analysis of face-to-face smoking cessation interventions by professionals. Institute for Medical Technology Assessment, 2003. Report number 03.67.
56. Barendregt JJ, Bonneux L, Van der Maas PJ. The health care costs of smoking. N Engl J Med 1997;337:1052-1057.

# 9

# Summary

In the introduction **(Chapter 1),** we describe some major issues concerning Chronic Obstructive Pulmonary Disease (COPD). COPD, formerly known as lung emphysema or 'chronic bronchitis', is a major and still increasing health problem with a high morbidity and mortality. During the next decades, morbidity and mortality are expected to rise further which is due to the past and current burden of smoking, and the ageing of the population. The prevalence of physician-diagnosed COPD in The Netherlands is estimated at 1.7% for women and 2.4% for men. Among the patients with known COPD 28% experience mild, 54% moderate and 18% (very) severe airflow limitation. In the population at large in the U.S., the prevalence of COPD varies from about 3% in never smokers to 14% in both male and female current smokers. Prevalence rates increase with age from 8% in male smokers 46-47 years of age to over 40% in male smokers aged 76-77 years. The prevalence of undiagnosed COPD is likely even higher than the prevalence of physician diagnosed COPD, i.e. the so-called top of the iceberg phenomenon. In middle-aged smokers the prevalence of undiagnosed COPD is estimated at 14% - 29%.

Smoking is the main risk factor for COPD, and for this it is a largely preventable disease provided smoking cessation is timely achieved. COPD is however often diagnosed relatively lately. Earlier detection of airflow obstruction and smoking cessation may result in significant health gain. This raises several questions. Is the prevalence of undiagnosed COPD actually as high as expected? Is it possible to recognize subjects with undiagnosed COPD by means of easily obtainable patient characteristics? Which subjects with undiagnosed airflow obstruction are at risk for clinical significant COPD? What is the impact of undiagnosed airflow limitation on quality of life? And most important, is the usual diagnostic work-up in general practice, limited to patients with a high risk of COPD only, justified or should we recommend a more active approach like case-finding in all smokers attending the GP for lower respiratory tract complaints or even screening of all smokers in the population at large?

In this thesis several issues regarding the active detection of undiagnosed COPD in current smokers are discussed. The study was conducted between 1998 and 2003 among middle-aged male smokers in IJsselstein, a town in the center of The Netherlands.

In this thesis COPD is defined according to the GOLD guidelines as a postbronchodilator FEV1/FVC ratio <0.7. The severity of COPD is distinguished in 4 stages according to postbronchodilator FEV1 values:

- Mild (GOLD stage I): FEV1 predicted ≥ 80%.
- Moderate (GOLD stage II): 50%≥ FEV1 predicted <80%.
- Severe (GOLD stage III): 30%≥ FEV1 predicted <50%.
- Very severe (GOLD stage IV): FEV1 predicted <30% (or <50% with signs of chronic respiratory failure).

In a cross-sectional study **(Chapter 2)** among smokers without physician diagnosed asthma or COPD, the prevalence of undetected COPD in middle-aged smokers was high. In 702 participants with a mean age of 50 years and a mean number of pack years of 25, previously undetected airflow obstruction was found in 210 subjects (30%). Mild airflow obstruction (GOLD stage I) was assessed in 182 subjects (26%) and moderate airflow obstruction (GOLD stage II) in 28 individuals (4%). In the older age group (≥55 years) the prevalence of airflow obstruction was approximately twice as high as in the youngest age group (40-44 years). In smokers reporting coughing the prevalence was 47% vs. 25% in those not reporting this symptom. Concluding, the prevalence of undetected persistent airflow obstruction in middle-aged smokers is high.

To determine whether patient characteristics are helpful to detect the smokers with mild COPD (GOLD stage I) we analyzed the medical records of 567 subjects who participated in the previously described cross-sectional study **(Chapter 3)**. In total 135 of 702 (19.2%) medical records were missing, 60 (8.5%) records because one GP refused to participate and 75 (10.7%) due to removal of the participants from the practice list by the time we inspected the medical records. A total of 149 out of 567 subjects (26%) had mild COPD. In the univariate logistic regression analysis age, pack years of smoking and cough were associated with previously unrecognized mild airflow obstruction (GOLD stage I) while in the multivariate analysis only age and cough were independently related to the presence of GOLD stage I. The ability of these determinants to discriminate subjects without COPD from those with mild COPD was relatively poor. Therefore no prediction rule was developed. These results indicate that patients' characteristics are not helpful to recognize mild COPD (GOLD stage I) in middle-aged male smokers.

To determine the cumulative 5-year incidence of moderate COPD and its association with patients' characteristics among the 399 smokers without airflow limitation (n=292) or with mild COPD (n=107) at baseline in 1998 who performed adequate spirometry at both occasions, follow-up measurements were conducted in 2003 (**Chapter 4).**

After a mean follow-up of 5.2 years 33 participants developed moderate COPD (GOLD stage II), i.e. an estimated cumulative incidence of 8.3% and an average annual incidence of 1.6%. No one developed severe airflow obstruction (GOLD stage III or IV) . The risk of developing moderate COPD in smokers with baseline mild COPD (GOLD stage I) was 5 times higher than in those with baseline normal spirometry (1 in 5 vs. 1 in 25). Age, childhood smoking (smoking before the age of 16 years), cough as well as ≥ 1 GP contact for lower respiratory tract complaints were independently associated with incidence of moderate COPD. Concluding, in a cohort of middle-aged male smokers the estimated cumulative incidence of moderate COPD (GOLD stage II) in 5 years was relatively high.

In view of the limited health care resources, identifying smokers with an increased risk of developing COPD by means of readily obtainable patient characteristics is more feasible than repeated spirometry in all smokers. Based on patients characteristics identified in Chapter 4 we developed a prediction rule in order to identify smokers with an increased risk of developing moderate COPD **(Chapter 5)**. We analyzed the patient characteristics of the 399 male smokers without moderate COPD who participated in the baseline and follow-up survey in 1998 and 2003. At baseline the mean age of the 399 participants was 50.0 years (range 40-65) and a mean number of 24 pack years. Independent predictors of moderate COPD - age, cough, smoking before the age of 16 years, and ≥ 1 recent GP consultations because of lower respiratory tract (LRT) complaints - were included in the prediction rule. The rule, adjusted for over optimism by bootstrapping, showed a reasonable discriminative ability and a satisfactory goodness of fit. The score of the rule ranged from 0 to 5 points. The predicted probability of developing moderate COPD increased from 2% (0-1 point), 7% (2 points), 16% (3 points) to 35% (4-5 points). Taking a cut-off of ≥ 2 points would identify as much as 79% (26/33) of the smokers actually developing moderate COPD (sensitivity) in the next 5 years, and 52% (194/366) of the smokers not developing moderate COPD. The cumulative incidence of moderate COPD after 5 years in subjects with ≥ 2 points was 12% (26/218) vs. 4% (7/181) in subjects with < 2 points.

As discussed above, early detection of airflow limitation in middle-aged smokers will identify large numbers of 'healthy' subjects with mild airflow obstruction. It is not known whether in smokers at risk for COPD or with early stages of COPD quality of life is correlated with pulmonary function or with physical limitations due to dyspnoea. This issue is discussed in **Chapter 6**. We examined the associations between airflow limitation graded by the GOLD COPD staging or limitations in physical functioning as measured by the MRC dyspnoea scale on the one hand and quality of life on the other.

In 2003 a total of 395 subjects performed adequate spirometry and completed a generic and disease-specific quality of life questionnaire. The mean age of the participants was 55 years and the mean smoking history 27 pack years. Limitations of physical functioning measured by the MRC dyspnoea scale was found in 25.1% (99/395) of the individuals, and COPD in 40.2% (159/395). The MRC dyspnoea scale correlated more strongly with all quality of life component scores than the GOLD severity staging. Also in logistic regression analysis the MRC dyspnoea scale was more strongly related to all separate quality of life components. For example, the odds ratio (OR) of having a worse score of the 'physical functioning' component of the SF-36 was approximately 9 times higher in subjects with moderate or severe limitations on the dyspnoea scale than in those with mild limitations on this scale (OR 8.8; 95% CI 4.8-16.0), while the corresponding odds ratio was only slightly higher (1.4; 1.2-1.7) in patients with moderate compared to those with mild COPD according to the GOLD criteria.
Concluding, in middle-aged smokers limitations of physical functional due to breathlessness as measured by the MRC dyspnoea scale are more strongly associated with quality of life than the severity of airflow limitation. Future staging systems of severity of COPD should capture this and not rely on $FEV_1$ alone.
To evaluate the costs and effects of early detection of COPD in smokers, 45-64 years of age, unknown with airflow limitation, costs and effects of current practice were compared with a screening strategy - in the population at large - and a case finding strategy – in smokers visiting the GP for lower respiratory tract complaints - followed by a smoking cessation intervention (intensive counseling + bupropion or short counseling) (**Chapter 7**). Based on a combination of estimates concerning the undiagnosed prevalence of COPD in smokers and estimates of the effectiveness of smoking cessation interventions, the costs per case and costs per additional (i.e. compared to current practice) quitter were calculated. A more active approach was expected to offer a substantial increase in the additional number of newly detected COPD in one year: approximately 195,000 according to the screening strategy and over 78,000 according to the case finding strategy. Detecting one new patient with COPD was estimated to cost €91 concerning the screening strategy and €48 concerning the case finding strategy. The costs per quitter treated with intensive counseling (€5,375 for screening, €3,945 for case finding) were markedly lower than the costs per quitter treated with short counseling (€11,216 for screening, €5,628 for case finding). Additionally, the case finding variants showed a more favorable balance of costs and effects than the corresponding screening variants. Also, in comparison with previously reported costs per quitter treated with intensive counseling - directed towards smokers with known COPD (€2,700) or towards smokers in

general (€2,240) – the screening variant (€5,375) showed a less favorable balance of costs and effects than the case finding variant (€3,945). In conclusion, screening for COPD in middle-aged smokers can not be recommended. Case finding seems an attractive alternative, provided that intensive counseling is logistically possible and drug treatment, including nicotine replacement therapy, is reimbursed. Finally, in the general discussion **(Chapter 8)** we evaluate the pros and cons of screening for COPD in middle-aged smokers.

We have examined the issue of undetected COPD in middle-aged smokers, particularly its size and its clinical characteristics, the impact of early stages of COPD on quality of life, the development of clinical significant COPD and its determinants, and finally the cost-effectiveness of strategies of early detection of COPD. In summary, our main conclusions and recommendations are:

- The prevalence of undetected COPD in middle-aged smokers is high (30%). Smokers with undetected disease predominantly experience mild airflow obstruction (87%). Patient characteristics however are not helpful to detect those smokers mild COPD (GOLD stage I).
- The 5-year cumulative incidence of moderate disease (GOLD stage II) is considerable (8%). Age, smoking before the age of 16, coughing as well as ≥ 1 GP contact for lower respiratory tract complaints are independently associated with incident moderate disease. These clinical variables can enable physicians to identify approximately 80% of the smokers who will develop moderate COPD.
- In smokers at risk for COPD or with early stages of the disease, limitations of physical functional due to breathlessness as measured by the MRC dyspnoea scale are more strongly associated with quality of life than the severity of airflow limitation. Future staging systems of severity of COPD should capture this and not rely on $FEV_1$ alone.
- Screening for COPD in middle-aged smokers can not be recommended. Case finding seems an attractive alternative, provided that intensive counseling is logistically possible and drug treatment, including nicotine replacement therapy, is reimbursed.
- In general practice intensifying smoking cessation interventions targeted at smokers with a high risk of developing COPD using readily obtainable patient characteristics (aged 55-64 years, smoking before the age of 16 years, cough, and a recent GP contact for lower respiratory tract complaints) should be encouraged.
- Health care resources should preferably be applied to facilitate additional measures to prevent uptake of smoking or encourage smoking cessation in the population at large or, the latter also, in smokers with physician diagnosed COPD, rather than to develop COPD screening programs in 'healthy' smokers.

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# Samenvatting

## Inleiding

Roken is de belangrijkste risicofactor voor Chronic Obstructive Pulmonary Disease (COPD), een longziekte die beter bekend is onder de naam longemfyseem of 'chronische bronchitis'. COPD is een longaandoening die bij 10 tot 15% van de rokers optreedt. De eerste klacht die kan duiden op de aanwezigheid van COPD is de bekende 'rokershoest'. Niet alle rokers die hoesten hebben echter ook daadwerkelijk COPD en lang niet alle rokers met COPD hoesten. Een tweede symptoom van COPD is kortademigheid bij inspanning. Dit symptoom ontstaat pas 20 tot 25 jaar na het begin van het roken en wordt veroorzaakt doordat de longblaasjes – de plaats waar de zuurstofopname uit de lucht plaatsvindt - en het longweefsel door een chronisch ontstekingsproces als gevolg van het roken kapot gaan. Daarbij raken de luchtwegen (bronchiën) verstopt door de ontsteking en de overmatige productie van slijm. Uiteindelijk kan de ziekte leiden tot ernstige beperkingen zoals ernstige benauwdheid bij alledaagse bezigheden als wassen en aankleden.

In het beginstadium van de ziekte hebben de meeste mensen met COPD echter weinig of geen klachten. In dat stadium kan COPD alleen opgespoord worden door het meten van de longfunctie: het meten van de hoeveelheid lucht die je in 1 seconde met kracht kunt uitademen (de 'FEV1') en de hoeveelheid lucht die je met kracht maximaal kunt uitademen (de 'FVC'). Terwijl andere door roken veroorzaakte aandoeningen zoals hart- en vaatziektes behandeld kunnen worden met medicijnen (bloedverdunners, cholesterolremmers, bloeddrukmedicijnen) of operaties (dotteren) zijn er voor COPD nauwelijks behandelingen die het beloop van de ziekte daadwerkelijk gunstig beïnvloeden. Het enige middel om het beloop van de ziekte af te remmen, is stoppen met roken. Tijdige opsporing van COPD gevolgd door een stoppen met roken behandeling kan resulteren in een aanzienlijke gezondheidswinst.

In dit proefschrift, getiteld 'Opsporing van COPD bij rokers', worden de resultaten besproken van 6 studies die uitgevoerd zijn tussen 1998 en 2003 in IJsselstein bij mannelijke rokers tussen de 40 en 65 jaar. Via de huisartsen in IJsselstein werden alle mannelijke patiënten die rookten en die niet bekend waren met COPD of astma uitgenodigd om deel te nemen aan een bevolkingsonderzoek naar COPD. In 1998 en in 2003 werd bij hen de longfunctie gemeten. Daarnaast vulden zij vragenlijsten in met vragen over de aanwezigheid van longziektes in de familie, over luchtwegklachten in hun jeugd en in de voorafgaande jaren , het rookgedrag en de kwaliteit van leven.

**Hoe vaak komt niet eerder vastgesteld COPD bij rokers voor?**
Bij 3 op de 10 rokers van middelbare leeftijd werd niet eerder vastgesteld COPD gevonden (Hoofdstuk 2). In het merendeel van de gevallen ging het om een lichte vorm van de aandoening. Slechts 1 op de 5 deelnemers meldde de klacht hoesten (Hoofdstuk 3). Rokers met een milde of matige ernstige vorm van COPD rapporteerden vaker hoesten, respectievelijk 1 op de 3 en 1 op de 2 personen. Opvallend was dat het totale aantal contacten met de huisarts en het aantal antibiotica kuren voor 'bronchitis' bij rokers mét en zonder COPD gelijk was. Rokers met COPD onderscheidden zich van rokers zonder de aandoening doordat ze gemiddeld ouder waren en vaker de klacht hoesten meldden. Met hulp van deze 2 kenmerken kon echter onvoldoende onderscheid gemaakt worden tussen personen mét en zonder COPD (Hoofdstuk 3).

**Welke rokers krijgen een ernstiger vorm van COPD?**
Na een periode van vijf jaar werd 1 op de 12 rokers die deelnamen aan het onderzoek in 1998, matig ernstig COPD gevonden. Van matig ernstig COPD is sprake als de longfunctie 20% tot 50% minder is in vergelijking met de gebruikelijke longfunctie voor iemand van dezelfde leeftijd (Hoofdstuk 4). Rokers met een lichte vorm van COPD in 1998 hadden een 5 keer zo groot risico op het krijgen van matig ernstig COPD als rokers met een normale longfunctie in 1998. Anders gezegd, 1 op 5 personen met licht COPD (20%) in 1998 had 5 jaar later matig ernstig COPD tegen slechts 1 op de 25 personen met een normale longfunctie (4%) in 1998. Andere risicofactoren voor het ontwikkelen van matig ernstig COPD waren een hogere leeftijd, de aanwezigheid van luchtwegklachten als hoesten bij de meting in 1998, en roken voor de leeftijd van 16 jaar. Met behulp van deze patiënten kenmerken konden 4 van de 5 rokers die matig ernstig COPD ontwikkelden geïdentificeerd worden maar werd ook 1 op de 2 rokers die geen matig ernstig COPD kregen, onterecht gekenmerkt als roker met een verhoogd risico (Hoofdstuk 5).
Opvallend was dat in deze betrekkelijk gezonde groep mannelijke rokers van middelbare leeftijd, de kwaliteit van leven sterker negatief beïnvloed werd door beperkingen van dagelijkse bezigheden als gevolg van benauwdheid dan door de verminderde longfunctie (Hoofdstuk 6).

**Actieve opsporing van COPD?**

Zoals duidelijk is geworden uit het voorafgaande, is het moeilijk om rokers met een vroeg stadium van COPD op te sporen aan de hand van klachten of andere kenmerken. De meeste rokers met een vroeg stadium van de ziekte hebben (nog) geen klachten van de aandoening of komen niet met die klachten naar de dokter. De ziekte komt vaker voor bij rokers naarmate ze ouder worden en langduriger en zwaarder gerookt hebben. Met hulp van deze kenmerken kunnen rokers met een vroeg stadium van de ziekte echter onvoldoende goed opgespoord worden. Daarom wordt al langer gediscussieerd over actieve opsporing van COPD. Twee methoden worden hierbij vaak genoemd:

- een bevolkingsonderzoek door middel van longfunctiemeting bij voorbeeld bij alle rokers tussen de 45 en 64 jaar;
- actieve opsporing bij rokers tussen de 45 en 64 jaar die de huisarts bezoeken met luchtwegklachten.

Op basis van ons onderzoek en van andere studies, hebben wij berekend hoeveel nieuwe rokers met COPD met een bevolkingsonderzoek of actieve opsporing in de huisartsenpraktijk opgespoord zouden kunnen worden en hoeveel dat zou kosten (Hoofdstuk 7). Het opsporen van rokers met COPD heeft weinig zin als ze vervolgens niet begeleid worden bij het stoppen met roken. Daarom hebben we ook berekend hoeveel van de nieuwe rokers met COPD zouden stoppen als ze behandeld zouden worden met 2 verschillende interventies:

- een langdurige begeleiding bestaande uit meerdere consulten met een totale lengte van 90 minuten, ondersteund met medicijnen gedurende 9 weken;
- een kortdurende begeleiding bestaande uit 1 tot 2 consulten met een totale lengte van 12 minuten.

Met een bevolkingsonderzoek bij rokers van 45 tot 64 jaar zullen naar schatting 195.000 nieuwe gevallen van COPD opgespoord worden in één jaar. Met actieve opsporing onder rokers met luchtwegklachten in de huisartspraktijk zal dat aantal ongeveer 78.000 zijn. Het opsporen van één nieuwe roker met COPD kost naar schatting €91 in geval van een bevolkingsonderzoek en €48 in geval van actieve opsporing in de huisartspraktijk. De kosten per nieuwe patiënt met COPD die ten minste 1 jaar stopt met roken, zijn aanmerkelijk lager bij langdurige begeleiding ondersteund met medicijnen dan bij kortdurende begeleiding. Hoewel met een bevolkingsonderzoek meer nieuwe gevallen van COPD opgespoord worden, is actieve opsporing in de huisartsenpraktijk financieel aantrekkelijker. Dit komt doordat de organisatie van een bevolkingsonderzoek extra kosten met zich meebrengt en het aantal nieuwe gevallen met COPD bij een bevolkingsonderzoek verhoudingsgewijs lager is dan bij de actieve opsporing in de huisartsenpraktijk.

**Belangrijkste conclusies en aanbevelingen**

- Bijna 1 op de 3 rokende mannen van middelbare leeftijd heeft COPD zonder dat dat bekend is. Het gaat dan meestal om een lichte vorm van de aandoening. Patiënten kenmerken zoals een hogere leeftijd of hoest klachten zijn niet behulpzaam om deze rokers met lichte vormen van COPD op te sporen.
- Ongeveer 1 op de 12 rokende mannen van middelbare leeftijd ontwikkelt matig ernstig COPD binnen 5 jaar. Bij rokers zonder longfunctieafwijkingen is dit risico 1 op de 25 (4%) en bij personen met een lichte vorm van COPD 1 op de 5 (20%). Risicofactoren voor het ontwikkelen van matig ernstig COPD zijn een hogere leeftijd, roken voor de leeftijd van 16 jaar en luchtwegklachten. Deze risicofactoren kunnen dokters helpen om bijna 80% van diegene die matig ernstig COPD krijgen, te identificeren.
- Bij rokers van middelbare leeftijd wordt de kwaliteit van leven meer beïnvloed door beperkingen van dagelijkse bezigheden als gevolg van benauwdheid dan door de verminderde longfunctie.
- Een bevolkingsonderzoek naar COPD bij rokers van middelbare leeftijd kan niet aanbevolen worden. Actieve opsporing bij rokers die de huisarts bezoeken met luchtwegklachten lijkt een aantrekkelijk alternatief op voorwaarde dat laagdrempelige en langdurige rookstop begeleiding mogelijk is en behandeling van nicotine verslaving met medicijnen vergoed wordt.
- Langdurige rookstop begeleiding gericht op rokers met een verhoogd risico op het krijgen van COPD (leeftijd 55-64 jaar, leeftijd 45-54 jaar in combinatie met roken voor de leeftijd van 16 jaar, of luchtwegklachten) en gericht op rokers die al bekend zijn met COPD, dient meer nadruk te krijgen.
- Het is zinvoller om aanvullende maatregelen te nemen gericht op de hele bevolking met als doel roken te voorkómen en te ontmoedigen dan het ontwikkelen en uitvoeren van een bevolkingsonderzoek naar COPD bij ‘gezonde’ rokers.

## Other publications by the author

Dirksen WJ, Geijer RMM, De Haan, Kolnaar BGM, Mercks JAM, Romeijnders ACM, Dijkstra RH, Van der Laan JR. NHG-Standaard Astma bij kinderen. Huisarts Wet 1992;35:130-143.

Lamers HJ, Van Dongen AM, Jamin R, Brühl PhC, Dijkstra RH, Geijer RMM. NHG-Standaard Acute diarree. Huisarts Wet 1993;36:294-299.

Lantinga H, Ek JW, Nijman FC, Antonietti-Barels IH, Nijssen JP, Bos D, Meulenberg FAEM, Geijer RMM. NHG-Standaard Psoriasis. Huisarts Wet 1994;37:111-119.

Geijer RMM, Meulenberg FAEM, Ek JW, et al. Effectiviteit van lokale medicamenteuze therapie bij psoriasis – een literatuurstudie. Huisarts Wet 1994;37:243-247.

Crobach MJJS, Jung HP, Toorenburg-Beijer B, Van der Wal J, Van Leeuwen JTh, Van Puijenbroek EP, Van der Laan JR, Geijer RMM. NHG-Standaard Allergische en hyperreactieve rhinitis. Huisarts Wet 1995;38:216-227.

Rooijackers-Lemmens E, Van Wijngaarden JJ, Opstelten W, Broen A, Romeijnders ACM, Geijer RMM. NHG-Standaard Otitis externa. Huisarts Wet 1995;38:265-271.

Walma EP, Backx HCA, Besselink RAM, Hamstra PWJ, Hendrick JMA, Kootte JHA, Van Veelen AWC, Vink R, Geijer RMM. NHG-Standaard Hartfalen. Huisarts Wet 1995;38:471-487.

Geijer RMM, Thomas S, Rosmalen CFH. De diagnostiek van astma bronchiale en chronisch obstructief longziekte door de huisarts. Ned Tijdschr Geneeskd 1995;139:2512-2513.

Thomas S, Geijer RMM, Van der Laan, Wiersma Tj [red]. NHG-Standaarden voor de huisarts II. Wetenschappelijke Uitgeverij Bunge; Utrecht, 1996.

Appelman CLM, Bruinsma M, Collette C, Geijer RMM. NHG-Standaard Cervixuitstrijken [eerste herziening]. Huisarts Wet 1996;39:134-141.

Geijer RMM. Onrust rond de pil - Pleidooi voor een conservatief voorschrijfbeleid. Huisarts Wet 1996;39:110-112.

Thomas S, Geijer RMM. Actualiseringsronde NHG-Standaarden 1995-1996 – Wijzigingen in de standaarden M31-M60. Huisarts Wet 1997;40:114-124.

Geijer RMM, Thiadens HA, Smeele IJM, Van der Zwan AAC, Sachs APE, Bottema BJAM, Van Hensbergen W, Van Schayck CP, Van Weel C, Rosmalen CFH. NHG-Standaard COPD en astma bij volwassenen: diagnostiek. Huisarts Wet 1997;40:416-429.

Geijer RMM, Van Schayck CP, Van Weel C, Sachs APE, Van der Zwan AAC, Bottema BJAM, Smeele IJM, Thiadens HA, Van Hensbergen W, Rosmalen CFH. NHG-Standaard COPD: behandeling. Huisarts Wet 1997;40:430-442.

Geijer RMM, Van Hensbergen W, Bottema BJAM, Van Schayck CP, Sachs APE, Smeele IJM, Thiadens HA, Van Weel, C, Van der Zwan AAC, Rosmalen CFH. NHG-Standaard Astma bij volwassenen: behandeling. Huisarts Wet 1997;40:443-445.

Dirksen WJ, Geijer RMM, De Haan M, De Koning G, Flikweert S, Kolnaar BGM. NHG-Standaard Astma bij kinderen [eerste herziening]. Huisarts Wet 1998;40:130-143.

Wempe PA, Ponsioen BP, Hinloopen R, Flikweert S, Geijer RMM. NHG-Standaard Subfertiliteit (eerste herziening). Huisarts Wet 1998;40:533-541.

Flikweert S, Hemrika DJ, Geijer RMM, Evers JLH, Hinloopen RJ, Leerentveld RA, Ponsioen BP, Wempe PA, Zweers DJ. Landelijke Transmurale Afspraak: Subfertiliteit. Huisarts Wet 1998;40:542-544.

Geijer RMM, Van Essen-Zandvliet EEM, Flikweert S, Brinkhorst G, De Haan M, Roorda RJ, De Koning G, Dirksen WJ, Van Suijlekom-Smit LJA, Kolnaar BGM. Landelijke Transmurale Afspraak: Astma bij kinderen. Huisarts Wet 1998;40:144-146.

Geijer RMM, Burgers JS, Van der Laan JR, Wiersma Tj, Rosmalen CFH, Thomas S [red.]. NHG-Standaarden voor de huisarts I. Wetenschappelijke Uitgeverij Bunge; Utrecht, 1999.

Geijer RMM, Rikken SA. Afname van aantal recepten voor de 3$^{de}$ generatiepil. Ned Tijdschr Geneeskd 2000;144:2069-2070.

Geijer RMM, Sachs APE, Hoes AW, Salomé PL, Lammers J-WJ, Verheij TJM. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. Family Practice 2005;22:485-489.

Geijer RMM, Sachs APE, Verheij TJM, Salomé PL, Lammers J-WJ, Hoes AW. Incidence and determinants of moderate COPD (GOLD II) in male smokers aged 40-65 years: 5 year follow-up study. Br J Gen Practice 2006, accepted.

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Vier jaar onderzoek doen, betekent 4 jaar bezig zijn met één ziekte, en dat is een luxe en een schril contract met de waan van elke dag in een huisartsenpraktijk maar tegelijkertijd ook een prima combinatie. Ik heb het met veel plezier gedaan maar ben ook erg blij dat het nu afgerond is.
Prof. dr. TJM Verheij, beste Theo, ik wil je bedanken voor de continuïteit en stabiliteit van je begeleiding. Ik geloof niet dat jij op enig moment bij alle kleine en grotere hobbels op de route van een dergelijk onderzoek, in paniek bent geraakt, in ieder geval niet voor mij waarneembaar. Grote bewondering heb ik voor het feit dat je naast het reilen en zeilen van de afdeling huisartsgeneeskunde van het Julius Centrum nog een dag met je voeten op de werkvloer staat (in de huisartsenpraktijk) en daarnaast ook nog een periode als interim manager van Leidsche Rijn Gezondheidscentra gefunctioneerd hebt.
Prof. dr. AW Hoes, beste Arno, je bent, kort gezegd, briljant en toch een aardige kerel. Voortdurend de grote lijn in het oog houdend, een feilloos gevoel voor de zere plekken, en een goed zicht op de samenhang van de verschillende bouwstenen waaruit het proefschrift bestaat. Je hebt onmiskenbaar bijgedragen aan de kwaliteit van de artikelen.
Dr. APE Sachs, beste 'wishing the impossible' Alfred: overdrachtelijk bedoeld, wishing the impossible was één van de vele creatieve suggesties voor de titel van een artikel. Bedankt voor je vele positieve en enthousiasmerende bijdragen ('dit wordt jouw jaar'). Waardevol was ook je voortdurende aandacht voor het 'stressen' van de kernboodschap of de nieuwswaarde van een artikel. Verder heb ik erg genoten van je verhalen uit de praktijk. Van mevrouw Bakema bijvoorbeeld die altijd op dinsdag naar de kaartclub ging maar niet op die ene dinsdag na het overlijden van haar man en toen de deur open moest doen voor een jonge vrouw die haar man al jaren op die gewraakte dinsdagavonden verwende (© APE Sachs).

Prof. dr. B van Hout, beste Ben, een gecompliceerde bevalling in een weekend in februari per telefoon en mail leidde uiteindelijk tot een mooi artikel. In de week daarna beviel je partner gelukkig zonder complicaties van een gezonde zoon.
Dank ook voor de gezelligheid van mijn collega's op kamer 6.101 van het Straténum waar tussen de dozen met piekstroommeters, zakjes met vezels en stapels vragenlijsten een stakerige eenzame plant met treurig afhangende bladeren probeert te overleven op restanten koffie en thee.
In deze mierenhoop van nijvere promovendi was het plezierig vertoeven, en werd lief en leed gedeeld van de geboorte van kinderen en het overlijden van ouders, verhuizingen en verbouwingen, en moeilijke keuzes tussen het gezin, de praktijk of de wetenschap.
Globaal huisvest kamer 6.101 twee soorten wetenschappers:

- Huisartsen van 'onbestemde' leeftijd, vrijwel allemaal mannen die als de kinderen gaan puberen of het huis al uit zijn en de praktijk routine is geworden een 'boekje' gaan schrijven, een understatement voor ten minste 4 jaar ploeteren;
- jonge, veelal vrouwelijke, huisartsen die het krijgen van kinderen en de huisartsenpraktijk proberen te combineren met het schrijven van zo'n 'boekje'.

Een gemeenschappelijk streven van de promovendi op kamer 6.101 is het bestrijden van die zaken die het leven voor veel mensen zo aangenaam maken. Zo worden de uitwassen van onze fast food cultuur aangepakt met vezels (René Bijkerk) terwijl het diabetisch genootschap andere kwalijke gevolgen van de hedendaagse levensstijl, door hen verbasterd tot 'metabool syndroom', de wereld uit probeert te helpen, te beginnen bij de suiker patiënt (Ryckel van Bruggen, Paul Jansen, Maarten Brinkhuizen, Mariëlle van Avendonk, Frits Cleveringa en voorheen Lex Goudswaard). Ook de genieters van de tabakscultuur moeten het ontgelden (Lidewij Broekhuizen, ondergetekende). En alsof dit allemaal nog niet genoeg is worden er ook pogingen ondernomen om de burger te vrijwaren van een genadige acute hartdood en het minder genadige chronisch hartlijden als gevolg van al deze slechte leefgewoontes (Onno van der Spoel, Madeleine Bruins Slot, Hans Kelder, Frans Rutten. Pieta Bruggink). Professorale buitenbeentjes moeten er ook zijn, Wim Opstelten runde tot voor kort een éénmansbedrijfje in gordelroos tot hij weggelokt werd door de concurrent.
Verder ben ik dank verschuldigd aan Frances Verheij die een uitstekend georganiseerd databestand had achtergelaten bij het begin van de studie. Ik dank Rutger van Petersen voor het verwerken van alle nieuwe data en Pieter Zanen voor zijn adviezen en de hulp bij het inlezen en interpreteren van de longfunctie gegevens. Peter Zuithoff was onmisbaar bij alle statistische analyses waarvan de bootstrap, 'het jezelf aan de lus van je laars uit de modder omhoog trekken' wel de meest interessante was.

De medeauteurs (Prof. dr. J-WJ Lammers, dr. M Kuyvenhoven, Prof. dr. HAM Kerstjens, NPA Zuithoff) ben ik erkentelijk voor hun waardevolle bijdragen en verfrissende invalshoek.
Het onderzoek had nooit kunnen plaatsvinden zonder hulp van de longfunctieassistentes van Saltro, die de afspraken met de deelnemers planden en zich de longen uit het lijf hebben geblazen tijdens het instrueren van de deelnemers.
Ten slotte bedank ik natuurlijk alle deelnemers, die vrijwillig hun adem en tijd ter beschikking hebben gesteld aan de wetenschap.

Gelukkig is hij die zulke collega's (Niek de Grunt, Anneke Kramer, Licky Zydower, Corine Visser), praktijkassistentes (Natascha van de Berg, Nicole de Jong, Lilian de Raadt, Rianne Fris) en praktijkondersteuners (Tinka Schuurman, Renie Knoester) heeft: zonder morren kon ik een paar weken vrij nemen van de praktijk om begin 2006 de laatste puntjes op de i te zetten.
Ma, uiteindelijk was jij degene die zei waarom ga je geen geneeskunde studeren, daar waar ik aan iets abstracts als sterrenkunde dacht.
Otto, mijn broer en Jan, met wie ik al bevriend ben vanaf het kippenproject op de studentenetage IBB $21^{IV}$, fijn dat jullie bereid waren als paranimf op te treden en het feest mee te organiseren.
En thuis, Nel, de laatste maanden waren de weekenden en avonden ronduit ongezellig maar gelukkig heb je daar ondanks of dankzij je eigen drukke werkzaamheden weinig last van gehad en is er nu weer tijd voor gezelliger zaken. Thijs, al weer bijna 2 jaar een uitwonende student maar gelukkig nog wekelijks over de vloer. Wie weet ben jij ook nog eens te verleiden tot een promotieproject. Sam, je laatste jaar op het VWO, het einde van dit promotiegedoe is strak gepland voor de start van jouw eindexamen.

**Curriculum vitae**

Roeland Geijer was born in Leiden, The Netherlands, at August 7, 1954. After graduating secondary school at Katholieke Scholengemeenschap de Breul in Zeist (gymnasium-B) in 1972, he started Medical School at the University of Utrecht, The Netherlands. Fulfilling his alternative military service he worked in a drug treatment center for heroin addicts in Rotterdam (Opo Hoso) in 1980 and 1981. Afterwards he worked some years in different drug treatment centers in Rotterdam between 1981 and 1985. Funded by the Community Health Service in Rotterdam he conducted a study to examine the effects of acupuncture on detoxification of heroin addicts in the prison of Rotterdam in the same period. In 1985 and 1986 he participated in the general practitioners training at the University of Utrecht. Afterwards he worked a year for a drug treatment center in Amsterdam and several years as GP in Amsterdam, Rotterdam en Utrecht. From 1991 to 2002 he worked for the Dutch College of General Practitioners setting guidelines for general practice. In 1995 he settled as a general practitioner in a multi-handed practice established by Niek de Grunt and Anneke Kramer, in Utrecht overlooking the 'Rode Brug' (see cover). In 2002 he started the work described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (supervised by Prof. dr. TJM Verheij and Prof. dr. AW Hoes).