Thorax Online First, published on September 28, 2007 as 10.1136/thx.2006.068007

Predictive value of lung function below normal range and respiratory symptoms for progression of COPD

Mieke Albers, Tjard Schermer, Yvonne Heijdra, Johan Molema, Reinier Akkermans, Chris van Weel

Key words:
COPD, obstruction, progression, lower limit of normal, GOLD

Abbreviations:

COPD	Chronic Obstructive Pulmonary Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
DIMCA	Detection, Intervention and Monitoring of COPD and Asthma in general practice
FEV_1	Forced Expiratory Volume in one second
VC	Vital Capacity
OR	Odds Ratio
CI	Confidence Interval

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is an insidiously starting disease. Early detection has high priority because of the possibility of early implementation of smoking cessation interventions. An evidence based model for case-finding of COPD is not yet available.

Study Objective: To describe the early development of COPD, and to assess the predictive value of early signs (respiratory symptoms, lung function below normal range, reversibility).

Design and Methods: In a prospective study, based in general practice, formerly undiagnosed subjects (n=464) were assessed at baseline and at year five for respiratory symptoms and pulmonary function. Odds ratio's of early signs were calculated (adjusted for age, gender, packyears at baseline, and smoking behaviour during follow-up), and defined as possible indicators of disease progression.

Results: Over a five year period, the percentage of subjects with obstruction increased from 7.5% (n=35) at baseline to 24.8% (n=115) at year five. Baseline presence of mild early signs and lung function below normal range were related to an increased risk to develop mild to moderate COPD {GOLD I; OR:1.87 (95% CI [1.22-2.87]), respectively GOLD II; OR:2.08 (95% CI [1.29- 3.37]) to 2.54 (95% CI [1.25-5.19])}at year five.

Conclusion: Lung function below normal range and early respiratory signs predict the development and progression of COPD.

Introduction

In the past decades, an increase in prevalence of Chronic Obstructive Pulmonary Disease (COPD) and asthma has been observed[1;2]. Due to demographic changes the global burden of COPD is expected to shift from the sixth leading cause of death in 1990 to the third position by 2020[3]. This evolution is a significant challenge for primary care, as prevalence of COPD is expected to nearly double over the period 1994 to 2015[4;5].

Although it is generally recognized that COPD patients should be identified before the disease becomes substantial, early stage COPD often remains undiagnosed[6] or misdiagnosed[7]. To decrease morbidity and mortality from this chronic lung disorder, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated[8]. In a number of cross-sectional, population-based surveys[9-11] the GOLD guidelines were used to estimate the prevalence of COPD. One of the first surveys, the confronting COPD International Survey[12], confirmed the huge burden to society and, furthermore, identified a significant disparity between subjects' perception of disease severity and the assessed degree of severity.

The hallmark of COPD is the presence of airway obstruction. Recently, the prevalence of undiagnosed airflow obstruction was estimated by reviewing data from thirteen (mainly cross-sectionally designed) studies[13]. Prevalence ranged from three to twelve percent. Furthermore, the GOLD guidelines define a very early stage of COPD, in which subjects are considered to be 'at risk' for COPD[14]. This so called GOLD stage 0 is defined by chronic respiratory symptoms without measurable obstruction. Meanwhile, prospective long-term and population-based studies, focusing on early stage COPD in relation to respiratory disease years later, are scarce [10;15]. In one study[10], the Copenhagen City Heart Study, the authors concluded that GOLD stage 0 was not prognostic for development of COPD. In the Obstructive Lung Disease in Northern Sweden study[15], subjects with respiratory symptoms at study entry showed an increased risk to develop COPD. As this ambiguity warrants further research, the objective of the current study was to investigate the value of early respiratory symptoms and lung function below normal range as indicators for progression of COPD.

Methods

Design

The Detection, Intervention and Monitoring of COPD and Asthma in general practice (DIMCA study) is a prospective cohort study, designed to assess the feasibility of active detection of early stage chronic respiratory disease (COPD, asthma) in the Dutch general population[16] (figure 1). The initial cohort can be regarded as a random sample from the Dutch general population. Adult subjects (20-70 yr.) without a medical history of COPD, asthma or other chronic respiratory disease were included. All subjects took part in a screening program for COPD or asthma at the earliest possible stage of disease. The assessment consisted of a respiratory symptoms questionnaire and lung function measurement. The criteria in the original screening program, further referred to as early signs of respiratory morbidity[1], were used to define the baseline respiratory status of screened subjects. Subjects with either respiratory symptoms, lung function below normal range[17], or a response on salbutamol (reversibility) were at baseline considered to have an increased risk of developing respiratory morbidity. Otherwise, subjects were labelled as having *no abnormalities*. Subsequently, at-risk subjects were invited to participate in a two-year monitoring program. After monitoring, those showing persisting signs and symptoms (of varying severity) were invited for an intervention study with inhaled corticosteroids in a series of three randomized controlled trials. The results of the trials are described elsewhere[18-20].

For the present study subjects were reassessed after five years with regard to their respiratory symptoms and lung function. Invited were (figure 1): all subjects with an increased risk of

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

developing respiratory morbidity who participated in monitoring (n=384), and a random sample of the subjects with no baseline abnormalities (n=199).
The course of respiratory morbidity was operationalised by the change in lung function, reversibility, respiratory symptoms and self-reported smoking behaviour over the five year period. Subjects were classified by COPD stages, as the recently developed GOLD guidelines[21] facilitate such classification. To study whether early signs and symptoms of respiratory morbidity precede development of actual disease, an algorithm based on the GOLD criteria (table 1) was used to allocate subjects to either one of the following categories: asthmatic, at risk for COPD (GOLD 0), mild COPD (GOLD I), moderate COPD (GOLD II), severe COPD (GOLD III) , or not having COPD or asthma.
The medical ethics review board of the University Medical Centre Nijmegen approved the study. Subjects gave their written informed consent.

Measurements

Lung function and reversibility

Lung function was assessed by two trained lung function technicians at two different points in time (at baseline and at year five). Measurements were performed according to the American Thoracic Society standards[22]. ECCS reference values were used[23]. Variation in spirometer performance was assessed and accounted for. Reversibility[24] was assessed 15 minutes after inhalation of 800 µg salbutamol by spacer. At the moment of screening lung function below normal range[17] was defined as bronchodilator FEV_1/VC (Forced Expiratory Volume in one second / Vital Capacity) ≤ lower limit of normal (predicted minus 1.64 sd). Reversibility was defined positive if after bronchodilatation the change in FEV_1 (relative to the predicted value) amounted to at least 15%[24]. In the GOLD-based disease classification[21] definitions were for obstruction a postbronchodilator FEV_1/VC<70%, and for reversibility a 12% change of predicted FEV_1 after bronchodilatation with a change of at least 200 mL.

Respiratory symptoms and smoking behaviour

The occurrence of respiratory symptoms was measured at baseline and at year 5 with the Dutch modified version of the Medical Research Council questionnaire[25]. Chronicity of respiratory symptoms was defined by occurrence of symptoms for more than 3 months per year. Mucus hypersecretion was defined as continuous production of sputum in the winter season. Furthermore, subjects were asked whether they were current smokers, ex–smokers or never-smokers.

Statistical analysis

To describe the course of respiratory morbidity the mean individual change over the 5-year follow-up period in lung function was compared for the group of subjects with no abnormalities versus the group of at-risk subjects. The appropriate univariate statistical tests were used.
The progression of COPD was studied using multinomial logistic modelling. Dependent variable was respiratory morbidity at year five. This outcome was defined by the three categorical levels of absence of COPD or asthma, mild COPD or moderate to severe COPD. Initially obstructed subjects were excluded from the analysis. Odds ratio's of early signs of respiratory morbidity were calculated and defined as possible indicators of disease progression. Due to gained insight, mucus hypersecretion was added to the signs initially defined at the screening. Odds Ratio's were based on adjustment for age, gender, the number of packyears at baseline, and smoking behaviour during the 5-year follow-up period. Following the disease classification at year five (Table 1), categories were compared on lung function and obstruction over the five year period, using confidence limits. The SAS statistical package (version V8.2 for Windows) was used for all analyses. Two-sided P values of < 0.05 were considered to be statistically significant.

Results

The flow of the DIMCA cohort (figure 1; n=1749) showed different rates of nonparticipation. Over the 5-yr period, ten subjects were lost to follow-up due to death (none of them was COPD related). Between the initial (screened) sample and the (on GOLD stage) classified sample at year five there were no signs of selection (dropout[2], trial participants[3]). Five hundred eighty three subjects were invited for reassessment at year five. In the group without respiratory abnormalities (n=199) the response was 76%; in the at-risk group (n=384) the response was 82%.

Symptoms and lung function in screened subjects

The characteristics of the study population, and their evolution over the 5-year period, are given in table 2. At baseline there was no difference in age, gender, height or smoking history between subjects without respiratory abnormalities and at-risk subjects. Both at baseline *and* at the reassessment after five years, at-risk subjects had more symptoms (p=0.001), lower post-bronchodilator FEV_1 (p=0.0001), lower postbronchodilator FEV_1/VC (p=0.0003, respectively p<0.0001), and were more often current smokers (p=0.07, respectively p=0.04) than subjects without baseline abnormalities. Over the 5-year period the overall individual change (n=464) showed a decrease in postbronchodilator FEV_1 {-241 mL (sd: 303 mL); on average: -48 mL/year}and in postbronchodilator FEV_1/VC {7.1% (sd: 9.9%)}. At-risk subjects demonstrated more reduction of lung function (postbronchodilator FEV_1: -262mL versus -199mL; p=0.02) and a lower average postbronchodilator FEV_1/VC (-8.0 versus –5.2; p=0.04).

Respiratory morbidity

The distribution of the respiratory morbidity at year 5 is presented in Table 3. Over the five year period, the percentage of subjects with obstruction increased from 7.5% (n=35) at baseline to 24.8% (n=115) at year five. The change in lung function (postbronchodilator FEV_1) and obstruction over the five year period is presented in figure 2. The group of subjects labelled at year five as not having COPD or asthma (n=296) did not show a decline in lung function. There was a slight but significant decrease in postbronchodilator FEV_1/VC, but subjects did not become obstructive. Asthmatic subjects at year five (n=21) showed no decrease in lung function or postbronchodilator FEV_1/VC. Over the five year period, subjects with mild COPD (n=60) or moderate to severe COPD (n=49) significantly decreased in lung function, and became obstructive as well.

Respiratory morbidity odds ratio's

Assessment of respiratory morbidity at year 5 included 464 subjects (Table 3). The multinomial logistic regression analysis focussed on subjects without COPD or asthma (n=287), mild COPD subjects (n=48) and moderate to severe COPD subjects (n=39). Subjects with obstruction at baseline (n=35) were excluded from the analysis. Odds ratio's of early signs of respiratory morbidity were adjusted for age, gender, number of packyears at baseline and smoking behaviour (Table 4). Results showed that subjects with a baseline presence of mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent productive cough[1] had an increased risk to develop mild COPD (OR:1.87) or moderate COPD (OR:2.08). Baseline presence of lung function below normal range and mucus hypersecretion appeared to be predictive for the development of moderate COPD (OR:2.54, respectively OR:1.88). Female gender was significantly underrepresented in mild COPD (OR:0.54), whereas older age (OR:1.06) and an increased smoking history contributed to the risk on development of moderate COPD (OR:1.06, respectively OR:1.05).

[2] Baseline values of the several follow-up groups (Appendix Table 2)

[3] Trial participants

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

Discussion

The main objective of the current study was to investigate the value of early respiratory symptoms and lung function below normal range as indicators for progression of COPD. In the study period, we observed a substantial increase of morbidity in subjects who were at baseline considered to have an increased risk for development of chronic obstructive airway disease. The most prominent predictors for developing COPD were lung function below normal range and mild early signs of reversibility, weather-dependent cough or shortness of breath, or recurrent productive cough [1]. COPD appears to be an insidiously starting disease. Due to subjects' underperception of disease severity [12] there is a huge underpresentation of early signs of respiratory morbidity[26] causing underdiagnosis of COPD in general practice. As smoking cessation can reduce symptoms and prevent progression of disease[27], early detection has high priority. Additional reason to promote early detection is that treatment of COPD can improve lung function and quality of life of many patients, can reduce admissions to hospital, and might even improve survival[27]. Spirometry is considered the 'gold standard' for detecting obstruction, and provides prognostic information[11;28] as well. As yet, mass *screening* for obstruction is not considered feasible in general practice[13] and until now there is no long-term evidence on its effectiveness. Several studies focused on screening of high-risk groups[29;30], however, screening of high-risk groups will detect only a part of the population with obstruction[31]. For reasons of feasibility and cost-effectiveness it is generally agreed that *case-finding* is the most appropriate tool in reducing underdiagnosis of COPD in general practice. As a first step in the development of an evidence based model for case-finding, risk factors for the detection of early COPD need to be identified. Development of COPD was investigated in several studies[32-36], in which a great variety of *risk factors* (such as middle-age, current or past smoking status, a self-reported history or a general physician's diagnosis of chronic obstructive airway disease, laryngeal height, bronchial hyperresponsiveness, respiratory symptoms, body mass index, accelerated decline in lung function, exercise capacity, occupational exposure, air pollution, asthma, genetic variation and functional status) were used. In the present study, in a population-based sample with initially undiagnosed subjects from general practice, we used prospective data to describe early development of COPD, and to identify risk factors. We used an algorithm, based on the recently developed GOLD guidelines, to relate disease severity at year 5 to the baseline presence of early signs. However, some remarks have to be made. First of all, in the study design, the early signs were fixed by the screening criteria defined at baseline. Due to gained insight, mucus hypersecretion (prominent in former GOLD stage 0) was added to this selection of early signs. Second, subjects were classified on the basis of a cross-sectional measurement at year five. Although a well-defined algorithm was used, classification was *only* based upon post-bronchodilator $FEV_{1,}$ vital capacity (VC), reversibility and respiratory symptoms. In daily practice, however, often additional clinical assessment will be needed to arrive at an undisputed diagnosis, with a reliable disease staging. On the other hand, in the present study reversibility data were used to distinguish between COPD and asthma. Development of COPD was further confirmed by progressive lung function decline, and development of obstruction (figure 2). In his study of the population impact of different definitions of airway obstruction, Celli[11] stated that the rates according to the GOLD guidelines turned out to produce lower estimates than other spirometry-based definitions. This might be explained by the fact that in that study spirometry only was performed pre-bronchodilator[37]. Celli did not have disposition of reversibility testing, making it impossible to distinguish reversible from irreversible obstruction[11]. In a recent editorial[38], Vestbo brought to the attention that GOLD has not attempted to separate 0 COPD from symptomatic asthma. With the algorithm used, including an effort to minimize mislabelling of asthmatic subjects, we use a prudent estimate of prevailing disease at year five. Third, as in regression analysis adjustment was restricted to a limited set of risk factors (age, gender, packyears at baseline, and

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

smoking behaviour during follow-up), not all confounding factors may have been excluded. A further finding concerned the steady (or slightly decreased) percentage of subjects with respiratory signs and symptoms in the at-risk group. The most obvious explanation might be that after assessment of symptoms, the problem is identified and subjects will deal with it.

Over the five year period, the number of subjects with obstruction increased considerably. In other terms, screened subjects, considered to have an increased risk for development of COPD, appeared to have a more than 3-fold risk to actually develop mild or moderate COPD. The most prominent predictor for development of moderate COPD was a baseline presence of lung function below normal range (OR: 2.54). In this cohort of initially undiagnosed subjects, a baseline presence of mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent productive cough showed to be predictive for development of mild COPD (OR:1.87) or moderate COPD (OR:2.08) 5 years later. Furthermore, baseline mucus hypersecretion (in the absence of airflow obstruction without full reversibility) appeared to be predictive (OR: 1.88) for subsequent development of moderate COPD. A prolonged follow-up from early stage COPD onwards, followed by an undisputed clinical diagnosis, may further clarify these relations. In terms of health care, the identification of risk factors for early detection of COPD may contribute to the development of an evidence based model for case-finding. This is specifically of interest for the studied cohort, as these undiagnosed subjects did not present themselves in primary care.

In conclusion, lung function below normal range and early respiratory signs are possible predictors for progression of COPD.. As a result, implementation of GOLD guidelines in general practice may reduce underdiagnosis and undertreatment.

Acknowledgement

The authors like to thank Guido van den Boom. His former support and contribution were basic to the present article. The authors also wish to thank Lea Peters and Joke Grootens for their support in data collection, logistics and generating graphs.

Tables and figures

Table 1

Algorithm for the classification of chronic respiratory disease (based on the GOLD criteria[21])

LUNG FUNCTION	RESPIRATORY SYMPTOMS[$]	REVERSIBILITY[&]	DISEASE CLASSIFICATION	
NO OBSTRUCTION[+]		yes	ASTHMATIC	
	no chronic symptoms	no	NO COPD or ASTHMA	
	chronic symptoms	no	AT RISK FOR COPD	(GOLD 0)
OBSTRUCTION[+]		yes	INADEQUATELY MANAGED ASTHMA	
and **$FEV_1^* \geq 80\%$**		no	MILD COPD	(GOLD I)
or **$50\% \leq FEV_1 < 80\%$**		no	MODERATE COPD	(GOLD II)
or **$30\% \leq FEV_1 < 50\%$**		no	SEVERE COPD	(GOLD III)

Legend

[$] chronic symptoms: cough and sputum production for at least 3 months in each of two consecutive years

[&] Reversibility: a 12% change of predicted FEV_1 after bronchodilatation with a change of at least 200 mL.

[+] Obstructive if $FEV_1^*/VC^\# < 70\%$

[*] postbronchodilator forced expiratory volume;

[#] vital capacity

Table 2 Characteristics (*sd*) of the study population

	SCREENED SUBJECTS							
	without baseline abnormalities (N=151)				with baseline abnormalities (N=313)			
	year 0		year 5		year 0		year 5	
Age	42.9	*(11.2)*	48.0	*(11.2)*	44.0	*(11.5)*	49.2	*(11.5)*
Gender (% female)	50.3		50.3		59.4		59.4	
FEV_1* (ml)	3532	*(833)*	3335	*(806)*	3195	*(795)*	2938	*(802)*
FEV_1 / VC# (%)	84.5	*(8.3)*	79.3	*(7.9)*	81.3	*(9.8)*	73.0	*(8.8)*
Screening criteria[1]								
respiratory symptoms^	-		37.1		88.8		80.5	
lung function < normal range~	-		4.6		16.6		20.8	
reversibility$	-		0.7		2.9		2.9	
mild early signs @	-		9.3		31.6		32.6	
Mucus hypersecretion=	0.7		4.6		14.4		13.7	
Packyears	8.9	*(12.0)*			8.7	*(10.8)*		
Ever smokers (%)	43.1		43.7		32.6		34.2	
Current smokers (%)	31.8		27.2		40.6		36.7	

Legend:
* postbronchodilator FEV_1 (at year 5: n=150, respectively n=299)
# vital capacity
^ Dutch modified version of the MRC questionnaire
~ FEV_1 / VC ≤ lower limit of normal
$ ≥ 15% predicted
@ combination of at least two out of three mild early signs (mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent productive cough)
= continuous production of sputum in the winter season

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

Table 3 Obstruction and respiratory morbidity

	OBSTRUCTED SUBJECTS		RESPIRATORY MORBIDITY		SUBJECT TO ANALYSIS
	baseline	year 5	year 5		
	n	n	n	%	n
no COPD or asthma	9		296	63.8	287
mild COPD	12	60	60	12.9	48
moderate COPD	10	49	49	10.6	39
at risk for COPD	1		7	1.5	
asthmatic	3	6	21	4.5	
Missing			31	6.7	
Total	35	115	464	100	374

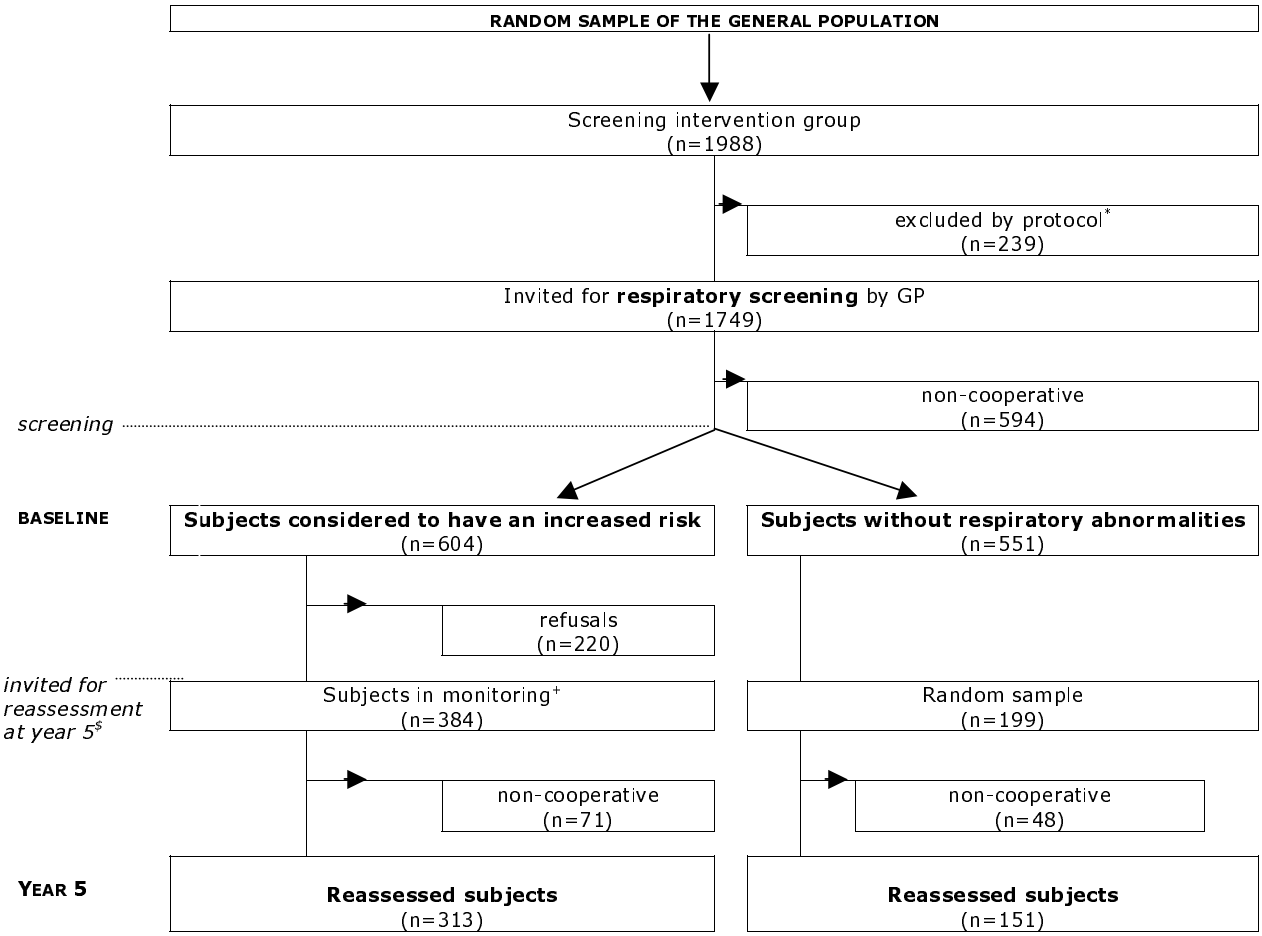
Table 4. Odds ratio's from multinomial regression analysis of early signs as predictors of respiratory morbidity five years later. Analysis was restricted to those 374/464 subjects who were free of 'obstruction' at baseline.
(OR's were adjusted for age, gender, packyears at baseline, and smoking behaviour during follow-up)

	RESPIRATORY MORBIDITY[&] AT YEAR 5 (N=374)			
	MILD COPD (12.8%)		MODERATE COPD (10.4%)	
	OR	*ADJ. OR*	*OR*	*ADJ. OR*
Screening criteria [1]				
- respiratory symptoms[^]	1.30 [0.92-1.83][!]	1.41 0.98-2.01]	0.96 [0.66-1.42]	0.94 [0.61-1.43]
- lung function below normal range[~]	1.45 [0.74-2.86]	1.46 [0.72-2.96]	**2.02** [1.07-3.83]	**2.54** [1.25-5.19]
- reversibility[$]	1.04 [0.38-2.88]	1.02 [0.00-0.03]	0.56 [0.16-1.93]	0.94 [0.25-3.49]
- mild early signs [@]	**1.69** [1.13-2.54]	**1.87** [1.22-2.87]	**1.97** [1.28-3.02]	**2.08** [1.29-3.37]
Mucus hypersecretion[=]	1.35 [0.77-2.36]	1.17 [0.64-2.14]	**2.53** [1.52-4.19]	**1.88** [1.07-3.33]
Smoking behaviour				
- packyears (baseline)		0.99 [0.95-1.02]		**1.05** [1.01-1.08]
- not smoking at year 5		1.23 [0.79-1.92]		1.04 [0.56-1.90]
- smoking at year 5		1.53 [0.96-2.46]		1.81 [0.99-3.30]
- smoking during follow-up		1.31 [0.54-3.17]		0.79 [0.21-2.96]
Age		1.00 [0.97-1.04]		**1.06** [1.01-1.10]
Gender (*female=1*)		**0.54** [0.38-0.76]		1.13 [0.73-1.73]

Legend:
[&] mild COPD (N=48), moderate COPD (n=39)
[^] Dutch modified version of the MRC questionnaire
[~] FEV_1 / VC ≤ lower limit of normal
[$] ≥ 15% predicted
[@] combination of at least two out of three mild early signs (mild obstruction, reversibility, weather-dependent or recurrent productive cough)
[=] continue production of sputum in winter
[!] [95% confidence intervals]

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

Figure 1: Flow chart



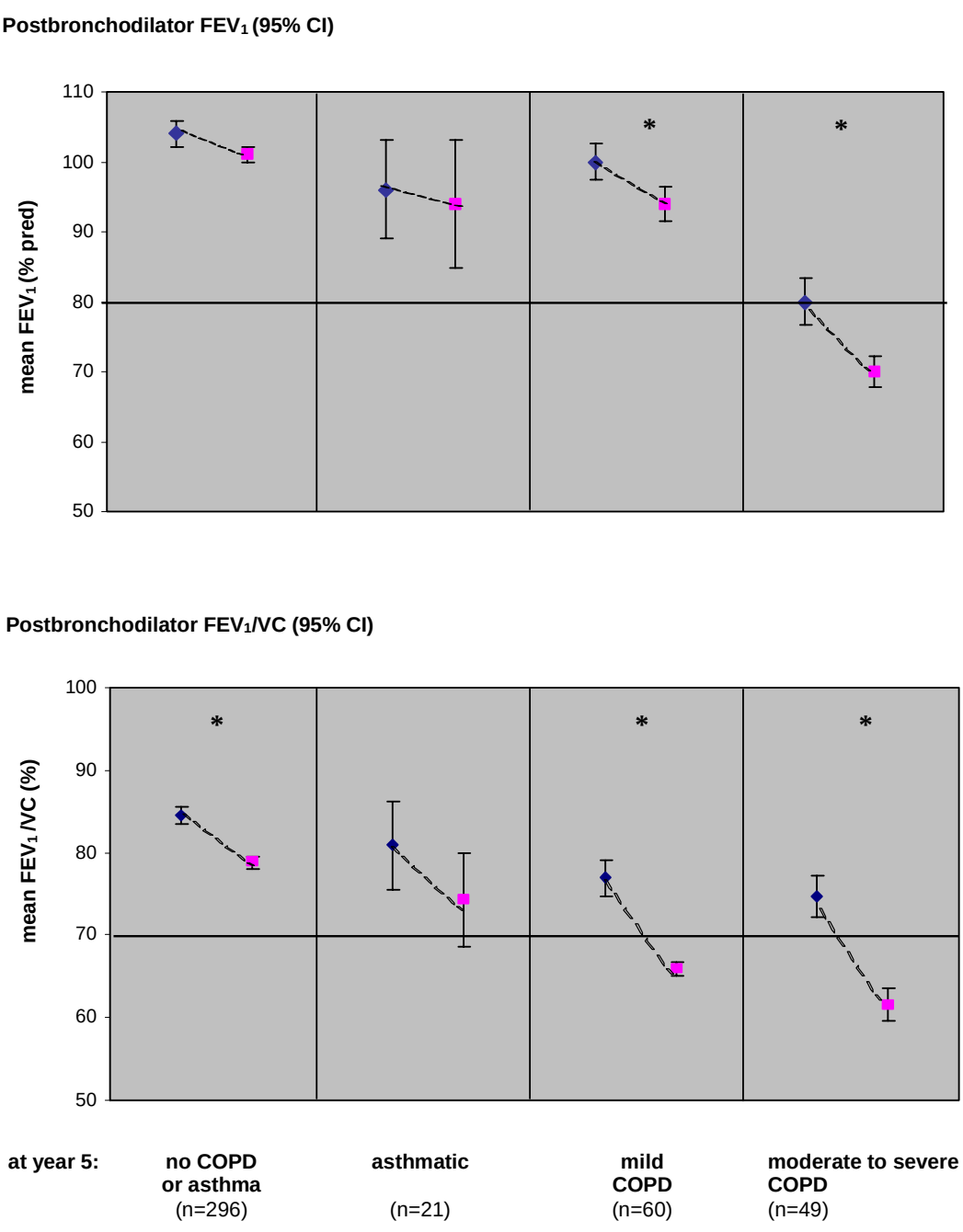
Legend:

* 12% (n=239) was excluded because respiratory disease had already been diagnosed by the GP

$ At year five the follow-up cohort was reduced, envisaging 400 subjects in the at-risk group, and 200 subjects in the group without respiratory abnormalities

\+ a total number of 145 at-risk subjects participated in one of the randomized controlled trials[18;20;39]

Figure 2: The course of FEV_1 and FEV_1/VC in early respiratory morbidity



Legend:

◆ = year 0: mean values with 95% confidence interval

■ = year 5: mean values with 95% confidence interval

* = statistically significant difference between year 0 and year 5

Appendix Table 1 Screening criteria, used to determine the respiratory status of subjects

CRITERIA	
respiratory symptoms	wheezing, dyspnoea, cough (≥ 3 months/year) or an asthma attack or shortness of breath due to an allergic reaction (in the previous 12 months)
lung function below normal range	FEV_1 / VC ≤ lower limit of normal (predicted minus 1.64 sd)
reversibility	FEV_1 reversibility ≥ 15% predicted
(at least two out of three) mild early signs	FEV_1 / VC ≤ predicted value minus 1SD and/or FEV_1 reversibility ≥ 10% predicted and/or weather-dependent (productive) cough or shortness of breath or the occurrence of more than one period of (productive) cough in the previous two years

Appendix Table 2 Baseline values of the respective follow-up groups

	N	Age (yr)	Gender (% female)	Pre-FEV_1[#] (mL)	Packyear (No.)	Smoking status (% ever smokers)
AT-RISK SUBJECTS						
Baseline group	604	43.4	59.9	3058	9.1	32.0
Monitoring group	384	42.9	57.6	3109	8.9	
Reassessed group (year 5)	313	43.9	59.4	3065	8.7	32.6
SUBJECTS WITHOUT ABNORMALITIES						
Baseline group	551	42.9	50.3	3440	7.0	37.4
Reassessed group (year 5)	151	42.9	50.3	3477	8.9	43.1

Legend:
[#] pre-bronchodilator forced expiratory volume

Appendix 3

A total number of 145 at-risk subjects participated in one of the randomized controlled trials (for a period varying between 12 and 30 months), in which inhaled corticosteroids (n=68) were compared to placebo treatment (n=77). The mean individual change in postbronchodilator FEV_1 over the five year period was –352 mL (*sd 287 mL*) in the corticosteroid treated group versus –280 mL (*sd 307 mL*) in the placebo treated group. Based on the individual change over the five year period, corticosteroid treatment did not show a different course in respiratory symptoms, postbronchodilator FEV_1 (p=0.09) or postbronchodilator FEV_1/VC (p=0.96) from placebo treatment. As a consequence, participants of the intervention study were included in the sample.

Reference List

(1) Lofdahl CG. Cost development of obstructive airway disease in Sweden. Eur Respir Rev 1996; 6:113-115.

(2) Tirimanna PR, van Schayck CP, den Otter JJ et al. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract 1996; 46(406):277-281.

(3) Murray CJL, Lopez AD. Alternative visions of the future: projecting mortality and disability, 1990-2020. In: Murray CJL, Lopez AD, editors. The Global Burden of Disease. The Harvard School of Public Health, on behalf of the World Health Organization and the World Bank, 1996: 361-395.

(4) Weel Cv, Smith H, Beasley JW. Family practice research networks. Experience from three countries. J Fam Pract 2000; 49:938-943.

(5) Feenstra TL, van Genugten ML, Hoogenveen RT et al. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001; 164(4):590-596.

(6) Coultas DB, Mapel D, Gagnon R et al. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med 2001; 164(3):372-377.

(7) Tinkelman DG, Price DB, Nordyke RJ et al. Misdiagnosis of COPD and Asthma in Primary Care Patients 40 Years of Age and Over. J Asthma 2006; 43(1):75-80.

(8) Pauwels RA, Buist AS, Calverley PM et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163(5):1256-1276.

(9) de Marco R, Accordini S, Cerveri I et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 2004; 59(2):120-125.

(10) 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(3):329-332.

(11) Celli BR, Halbert RJ, Isonaka S et al. Population impact of different definitions of airway obstruction. Eur Respir J 2003; 22(2):268-273.

(12) Rennard S, Decramer M, Calverley PM et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J 2002; 20(4):799-805.

(13) Coultas DB, Mapel DW. Undiagnosed airflow obstruction: prevalence and implications. Curr Opin Pulm Med 2003; 9(2):96-103.

(14) Fabbri LM, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Respir J 2003; 22(1):1-2.

(15) Lindberg A, Eriksson B, Larsson LG et al. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest 2006; 129(4):879-885.

(16) Van den 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(6):1730-1738.

(17) Pellegrino R, Viegi G, Brusasco V et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26(5):948-968.

(18) van Grunsven P, Schermer T, Akkermans R et al. Short- and long-term efficacy of fluticasone propionate in subjects with early signs and symptoms of chronic obstructive pulmonary disease. Results of the DIMCA study. Respir Med 2003; 97(12):1303-1312.

(19) van den BG, Rutten-van Molken MP, Molema J et al. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. Am J Respir Crit Care Med 2001; 164(11):2057-2066.

(20) Albers M, Schermer T, Van den Boom G et al. Efficacy of Inhaled Steroids in Undiagnosed Subjects at High Risk for COPD. Results of the Detection, Intervention, and Monitoring of COPD and Asthma Program. Chest 2004; 126:1815-1824.

(21) Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.com. Date accessed: December 6, 2006. 2006.

(22) Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(3):1107-1136.

(23) Quanjer PH, Tammeling GJ, Cotes JE et al. 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 [see comments]. Eur Respir J Suppl 1993; 16(s):5-40.

(24) Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. Eur J Respir Dis 1987; 70(3):171-179.

(25) van Schayck CP, Folgering H, den Otter JJ et al. Does the continuous use of bronchodilators mask the progression of asthma or chronic bronchitis? Fam Pract 1992; 9(4):397-404.

(26) Boom Gvd, Tirimanna PRS, Kaptein AA et al. Underpresentation of shortness of breath in the general population. Results of the DIMCA programme. Asthma Gen Pract 1999; 7(1):3-7.

(27) Rennard SI. Treatment of stable chronic obstructive pulmonary disease. Lancet 2004; 364(9436):791-802.

(28) Buffels J, Degryse J, Heyrman J et al. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Chest 2004; 125(4):1394-1399.

(29) Zielinski J, Bednarek M. Early detection of COPD in a high-risk population using spirometric screening. Chest 2001; 119(3):731-736.

(30) Stratelis G, Jakobsson P, Molstad S et al. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Br J Gen Pract 2004; 54(500):201-206.

(31) Albers M, Thoonen B, Dekhuijzen R. Recommended case-finding strategy misclassifies relevant groups of subjects with COPD. Rapid response to: Schayck CP van, JMC Loozen, E Wagena et al: Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ, rapid response 2002;(324):1370.

(32) Celli BR, Cote CG, Marin JM et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. New Engl J Med 2004; 350(10):1005-1012.

(33) Hospers JJ, Postma DS, Rijcken B et al. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. Lancet 2000; 356(9238):1313-1317.

(34) Straus SE, McAlister FA, Sackett DL et al. The accuracy of patient history, wheezing, and laryngeal measurements in diagnosing obstructive airway disease. CARE-COAD1 Group. Clinical Assessment of the Reliability of the Examination-Chronic Obstructive Airways Disease. JAMA 2000; 283(14):1853-1857.

(35) MANNINO DM. Chronic obstructive pulmonary disease: definition and epidemiology. Respir Care 2003; 48(12):1185-1191.

(36) Rijcken B, Schouten JP, Xu X et al. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV1. Am J Respir Crit Care Med 1995; 151:1377-1382.

(37) Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J 2004; 23(4):497-498.

(38) Vestbo J. COPD in the ECRHS. Thorax 2004; 59(2):89-90.

(39) van den BG, Rutten-van Molken MP, Molema J et al. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. Am J Respir Crit Care Med 2001; 164(11):2057-2066.

Predictive value of lung function below normal range and respiratory symptoms for progression of COPD

Mieke Albers, Tjard Schermer, Yvonne Heijdra, Johan Molema, Reinier Akkermans, Chris van Weel

Key words:

COPD, obstruction, progression, lower limit of normal, GOLD

Abbreviations:

COPD	Chronic Obstructive Pulmonary Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
DIMCA	Detection, Intervention and Monitoring of COPD and Asthma in general practice
FEV_1	Forced Expiratory Volume in one second
VC	Vital Capacity
OR	Odds Ratio
CI	Confidence Interval

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is an insidiously starting disease. Early detection has high priority because of the possibility of early implementation of smoking cessation interventions. An evidence based model for case-finding of COPD is not yet available.

Study Objective: To describe the early development of COPD, and to assess the predictive value of early signs (respiratory symptoms, lung function below normal range, reversibility).

Design and Methods: In a prospective study, based in general practice, formerly undiagnosed subjects (n=464) were assessed at baseline and at year five for respiratory symptoms and pulmonary function. Odds ratio's of early signs were calculated (adjusted for age, gender, packyears at baseline, and smoking behaviour during follow-up), and defined as possible indicators of disease progression.

Results: Over a five year period, the percentage of subjects with obstruction increased from 7.5% (n=35) at baseline to 24.8% (n=115) at year five. Baseline presence of mild early signs and lung function below normal range were related to an increased risk to develop mild to moderate COPD {GOLD I; OR:1.87 (95% CI [1.22-2.87]), respectively GOLD II; OR:2.08 (95% CI [1.29- 3.37]) to 2.54 (95% CI [1.25-5.19])}at year five.

Conclusion: Lung function below normal range and early respiratory signs predict the development and progression of COPD.

Introduction

In the past decades, an increase in prevalence of Chronic Obstructive Pulmonary Disease (COPD) and asthma has been observed[1;2]. Due to demographic changes the global burden of COPD is expected to shift from the sixth leading cause of death in 1990 to the third position by 2020[3]. This evolution is a significant challenge for primary care, as prevalence of COPD is expected to nearly double over the period 1994 to 2015[4;5].

Although it is generally recognized that COPD patients should be identified before the disease becomes substantial, early stage COPD often remains undiagnosed[6] or misdiagnosed[7]. To decrease morbidity and mortality from this chronic lung disorder, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated[8]. In a number of cross-sectional, population-based surveys[9-11] the GOLD guidelines were used to estimate the prevalence of COPD. One of the first surveys, the confronting COPD International Survey[12], confirmed the huge burden to society and, furthermore, identified a significant disparity between subjects' perception of disease severity and the assessed degree of severity.

The hallmark of COPD is the presence of airway obstruction. Recently, the prevalence of undiagnosed airflow obstruction was estimated by reviewing data from thirteen (mainly cross-sectionally designed) studies[13]. Prevalence ranged from three to twelve percent. Furthermore, the GOLD guidelines define a very early stage of COPD, in which subjects are considered to be 'at risk' for COPD[14]. This so called GOLD stage 0 is defined by chronic respiratory symptoms without measurable obstruction. Meanwhile, prospective long-term and population-based studies, focusing on early stage COPD in relation to respiratory disease years later, are scarce [10;15]. In one study[10], the Copenhagen City Heart Study, the authors concluded that GOLD stage 0 was not prognostic for development of COPD. In the Obstructive Lung Disease in Northern Sweden study[15], subjects with respiratory symptoms at study entry showed an increased risk to develop COPD. As this ambiguity

warrants further research, the objective of the current study was to investigate the value of early respiratory symptoms and lung function below normal range as indicators for progression of COPD.

Methods

Design

The Detection, Intervention and Monitoring of COPD and Asthma in general practice (DIMCA study) is a prospective cohort study, designed to assess the feasibility of active detection of early stage chronic respiratory disease (COPD, asthma) in the Dutch general population[16] (figure 1). The initial cohort can be regarded as a random sample from the Dutch general population. Adult subjects (20-70 yr.) without a medical history of COPD, asthma or other chronic respiratory disease were included. All subjects took part in a screening program for COPD or asthma at the earliest possible stage of disease. The assessment consisted of a respiratory symptoms questionnaire and lung function measurement. The criteria in the original screening program, further referred to as early signs of respiratory morbidity[1], were used to define the baseline respiratory status of screened subjects. Subjects with either respiratory symptoms, lung function below normal range[17], or a response on salbutamol (reversibility) were at baseline considered to have an increased risk of developing respiratory morbidity. Otherwise, subjects were labelled as having *no abnormalities*. Subsequently, at-risk subjects were invited to participate in a two-year monitoring program. After monitoring, those showing persisting signs and symptoms (of varying severity) were invited for an intervention study with inhaled corticosteroids in a series of three randomized controlled trials. The results of the trials are described elsewhere[18-20].

For the present study subjects were reassessed after five years with regard to their respiratory symptoms and lung function. Invited were (figure 1): all subjects with an increased risk of

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

developing respiratory morbidity who participated in monitoring (n=384), and a random sample of the subjects with no baseline abnormalities (n=199).

The course of respiratory morbidity was operationalised by the change in lung function, reversibility, respiratory symptoms and self-reported smoking behaviour over the five year period. Subjects were classified by COPD stages, as the recently developed GOLD guidelines[21] facilitate such classification. To study whether early signs and symptoms of respiratory morbidity precede development of actual disease, an algorithm based on the GOLD criteria (table 1) was used to allocate subjects to either one of the following categories: asthmatic, at risk for COPD (GOLD 0), mild COPD (GOLD I), moderate COPD (GOLD II), severe COPD (GOLD III) , or not having COPD or asthma.

The medical ethics review board of the University Medical Centre Nijmegen approved the study. Subjects gave their written informed consent.

Measurements

Lung function and reversibility

Lung function was assessed by two trained lung function technicians at two different points in time (at baseline and at year five). Measurements were performed according to the American Thoracic Society standards[22]. ECCS reference values were used[23]. Variation in spirometer performance was assessed and accounted for. Reversibility[24] was assessed 15 minutes after inhalation of 800 µg salbutamol by spacer. At the moment of screening lung function below normal range[17] was defined as bronchodilator FEV_1/VC (Forced Expiratory Volume in one second / Vital Capacity) ≤ lower limit of normal (predicted minus 1.64 sd). Reversibility was defined positive if after bronchodilatation the change in FEV_1 (relative to the predicted value) amounted to at least 15%[24]. In the GOLD-based disease classification[21] definitions were for obstruction a postbronchodilator

FEV_1/VC<70%, and for reversibility a 12% change of predicted FEV_1 after bronchodilatation with a change of at least 200 mL.

Respiratory symptoms and smoking behaviour

The occurrence of respiratory symptoms was measured at baseline and at year 5 with the Dutch modified version of the Medical Research Council questionnaire[25]. Chronicity of respiratory symptoms was defined by occurrence of symptoms for more than 3 months per year. Mucus hypersecretion was defined as continuous production of sputum in the winter season. Furthermore, subjects were asked whether they were current smokers, ex–smokers or never-smokers.

Statistical analysis

To describe the course of respiratory morbidity the mean individual change over the 5-year follow-up period in lung function was compared for the group of subjects with no abnormalities versus the group of at-risk subjects. The appropriate univariate statistical tests were used.

The progression of COPD was studied using multinomial logistic modelling. Dependent variable was respiratory morbidity at year five. This outcome was defined by the three categorical levels of absence of COPD or asthma, mild COPD or moderate to severe COPD. Initially obstructed subjects were excluded from the analysis. Odds ratio's of early signs of respiratory morbidity were calculated and defined as possible indicators of disease progression. Due to gained insight, mucus hypersecretion was added to the signs initially defined at the screening. Odds Ratio's were based on adjustment for age, gender, the number of packyears at baseline, and smoking behaviour during the 5-year follow-up period. Following the disease classification at year five (Table 1), categories were compared on lung function and obstruction over the five year period, using confidence limits. The SAS statistical package (version V8.2 for Windows) was used for all analyses. Two-sided P values of < 0.05 were considered to be statistically significant.

Results

The flow of the DIMCA cohort (figure 1; n=1749) showed different rates of nonparticipation. Over the 5-yr period, ten subjects were lost to follow-up due to death (none of them was COPD related). Between the initial (screened) sample and the (on GOLD stage) classified sample at year five there were no signs of selection (dropout[2], trial participants[3]). Five hundred eighty three subjects were invited for reassessment at year five. In the group without respiratory abnormalities (n=199) the response was 76%; in the at-risk group (n=384) the response was 82%.

Symptoms and lung function in screened subjects

The characteristics of the study population, and their evolution over the 5-year period, are given in table 2. At baseline there was no difference in age, gender, height or smoking history between subjects without respiratory abnormalities and at-risk subjects. Both at baseline *and* at the reassessment after five years, at-risk subjects had more symptoms (p=0.001), lower post-bronchodilator FEV_1 (p=0.0001), lower postbronchodilator FEV_1/VC (p=0.0003, respectively p<0.0001), and were more often current smokers (p=0.07, respectively p=0.04) than subjects without baseline abnormalities. Over the 5-year period the overall individual change (n=464) showed a decrease in postbronchodilator FEV_1 {-241 mL (sd: 303 mL); on average: -48 mL/year}and in postbronchodilator FEV_1/VC {7.1% (sd: 9.9%)}. At-risk subjects demonstrated more reduction of lung function (postbronchodilator FEV_1: -262mL versus -199mL; p=0.02) and a lower average postbronchodilator FEV_1/VC (-8.0 versus –5.2; p=0.04).

Respiratory morbidity

[2] Baseline values of the several follow-up groups (Appendix Table 2)

[3] Trial participants

The distribution of the respiratory morbidity at year 5 is presented in Table 3. Over the five year period, the percentage of subjects with obstruction increased from 7.5% (n=35) at baseline to 24.8% (n=115) at year five. The change in lung function (postbronchodilator FEV_1) and obstruction over the five year period is presented in figure 2. The group of subjects labelled at year five as not having COPD or asthma (n=296) did not show a decline in lung function. There was a slight but significant decrease in postbronchodilator FEV_1/VC, but subjects did not become obstructive. Asthmatic subjects at year five (n=21) showed no decrease in lung function or postbronchodilator FEV_1/VC. Over the five year period, subjects with mild COPD (n=60) or moderate to severe COPD (n=49) significantly decreased in lung function, and became obstructive as well.

Respiratory morbidity odds ratio's

Assessment of respiratory morbidity at year 5 included 464 subjects (Table 3). The multinomial logistic regression analysis focussed on subjects without COPD or asthma (n=287), mild COPD subjects (n=48) and moderate to severe COPD subjects (n=39). Subjects with obstruction at baseline (n=35) were excluded from the analysis. Odds ratio's of early signs of respiratory morbidity were adjusted for age, gender, number of packyears at baseline and smoking behaviour (Table 4). Results showed that subjects with a baseline presence of mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent productive cough[1] had an increased risk to develop mild COPD (OR:1.87) or moderate COPD (OR:2.08). Baseline presence of lung function below normal range and mucus hypersecretion appeared to be predictive for the development of moderate COPD (OR:2.54, respectively OR:1.88). Female gender was significantly underrepresented in mild COPD (OR:0.54), whereas older age (OR:1.06) and an increased smoking history contributed to the risk on development of moderate COPD (OR:1.06, respectively OR:1.05).

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

Discussion

The main objective of the current study was to investigate the value of early respiratory symptoms and lung function below normal range as indicators for progression of COPD. In the study period, we observed a substantial increase of morbidity in subjects who were at baseline considered to have an increased risk for development of chronic obstructive airway disease. The most prominent predictors for developing COPD were lung function below normal range and mild early signs of reversibility, weather-dependent cough or shortness of breath, or recurrent productive cough [1]. COPD appears to be an insidiously starting disease. Due to subjects' underperception of disease severity [12] there is a huge underpresentation of early signs of respiratory morbidity[26] causing underdiagnosis of COPD in general practice. As smoking cessation can reduce symptoms and prevent progression of disease[27], early detection has high priority. Additional reason to promote early detection is that treatment of COPD can improve lung function and quality of life of many patients, can reduce admissions to hospital, and might even improve survival[27]. Spirometry is considered the 'gold standard' for detecting obstruction, and provides prognostic information[11;28] as well. As yet, mass *screening* for obstruction is not considered feasible in general practice[13] and until now there is no long-term evidence on its effectiveness. Several studies focused on screening of high-risk groups[29;30], however, screening of high-risk groups will detect only a part of the population with obstruction[31]. For reasons of feasibility and cost-effectiveness it is generally agreed that *case-finding* is the most appropriate tool in reducing underdiagnosis of COPD in general practice. As a first step in the development of an evidence based model for case-finding, risk factors for the detection of early COPD need to be identified. Development of COPD was investigated in several studies[32-36], in which a great variety of *risk factors* (such as middle-age, current or past smoking status, a self-reported history or a general physician's diagnosis of chronic obstructive airway disease, laryngeal height, bronchial hyperresponsiveness, respiratory symptoms, body mass

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

index, accelerated decline in lung function, exercise capacity, occupational exposure, air pollution, asthma, genetic variation and functional status) were used. In the present study, in a population-based sample with initially undiagnosed subjects from general practice, we used prospective data to describe early development of COPD, and to identify risk factors. We used an algorithm, based on the recently developed GOLD guidelines, to relate disease severity at year 5 to the baseline presence of early signs. However, some remarks have to be made. First of all, in the study design, the early signs were fixed by the screening criteria defined at baseline. Due to gained insight, mucus hypersecretion (prominent in former GOLD stage 0) was added to this selection of early signs. Second, subjects were classified on the basis of a cross-sectional measurement at year five. Although a well-defined algorithm was used, classification was *only* based upon post-bronchodilator $FEV_{1,}$ vital capacity (VC), reversibility and respiratory symptoms. In daily practice, however, often additional clinical assessment will be needed to arrive at an undisputed diagnosis, with a reliable disease staging. On the other hand, in the present study reversibility data were used to distinguish between COPD and asthma. Development of COPD was further confirmed by progressive lung function decline, and development of obstruction (figure 2). In his study of the population impact of different definitions of airway obstruction, Celli[11] stated that the rates according to the GOLD guidelines turned out to produce lower estimates than other spirometry-based definitions. This might be explained by the fact that in that study spirometry only was performed pre-bronchodilator[37]. Celli did not have disposition of reversibility testing, making it impossible to distinguish reversible from irreversible obstruction[11]. In a recent editorial[38], Vestbo brought to the attention that GOLD has not attempted to separate 0 COPD from symptomatic asthma. With the algorithm used, including an effort to minimize mislabelling of asthmatic subjects, we use a prudent estimate of prevailing disease at year five. Third, as in regression analysis adjustment was restricted to a limited set of risk factors (age, gender, packyears at baseline, and smoking behaviour during follow-up), not all confounding factors may have been excluded. A

further finding concerned the steady (or slightly decreased) percentage of subjects with respiratory signs and symptoms in the at-risk group. The most obvious explanation might be that after assessment of symptoms, the problem is identified and subjects will deal with it.

Over the five year period, the number of subjects with obstruction increased considerably. In other terms, screened subjects, considered to have an increased risk for development of COPD, appeared to have a more than 3-fold risk to actually develop mild or moderate COPD. The most prominent predictor for development of moderate COPD was a baseline presence of lung function below normal range (OR: 2.54). In this cohort of initially undiagnosed subjects, a baseline presence of mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent productive cough showed to be predictive for development of mild COPD (OR:1.87) or moderate COPD (OR:2.08) 5 years later. Furthermore, baseline mucus hypersecretion (in the absence of airflow obstruction without full reversibility) appeared to be predictive (OR: 1.88) for subsequent development of moderate COPD. A prolonged follow-up from early stage COPD onwards, followed by an undisputed clinical diagnosis, may further clarify these relations. In terms of health care, the identification of risk factors for early detection of COPD may contribute to the development of an evidence based model for case-finding. This is specifically of interest for the studied cohort, as these undiagnosed subjects did not present themselves in primary care.

In conclusion, lung function below normal range and early respiratory signs are possible predictors for progression of COPD.. As a result, implementation of GOLD guidelines in general practice may reduce underdiagnosis and undertreatment.

Acknowledgement

The authors like to thank Guido van den Boom. His former support and contribution were basic to the present article. The authors also wish to thank Lea Peters and Joke Grootens for their support in data collection, logistics and generating graphs.

Tables and figures

Table 1

Algorithm for the classification of chronic respiratory disease (based on the GOLD criteria[21])

LUNG FUNCTION	RESPIRATORY SYMPTOMS[$]	REVERSIBILITY[&]	DISEASE CLASSIFICATION	
NO OBSTRUCTION[+]		yes	ASTHMATIC	
	no chronic symptoms	no	NO COPD or ASTHMA	
	chronic symptoms	no	AT RISK FOR COPD	(GOLD 0)
OBSTRUCTION[+]		yes	INADEQUATELY MANAGED ASTHMA	
and **FEV_1*≥80%**		no	MILD COPD	(GOLD I)
or **50%≤FEV_1<80%**		no	MODERATE COPD	(GOLD II)
or **30%≤FEV_1<50%**		no	SEVERE COPD	(GOLD III)

Legend

[$] chronic symptoms: cough and sputum production for at least 3 months in each of two consecutive years

[&] Reversibility: a 12% change of predicted FEV_1 after bronchodilatation with a change of at least 200 mL.

[+] Obstructive if FEV_1*/VC# < 70%

[*] postbronchodilator forced expiratory volume;

[#] vital capacity

Table 2 Characteristics (*sd*) of the study population

	SCREENED SUBJECTS							
	without baseline abnormalities (N=151)				with baseline abnormalities (N=313)			
	year 0		year 5		year 0		year 5	
Age	42.9	*(11.2)*	48.0	*(11.2)*	44.0	*(11.5)*	49.2	*(11.5)*
Gender (% female)	50.3		50.3		59.4		59.4	
FEV_1* (ml)	3532	*(833)*	3335	*(806)*	3195	*(795)*	2938	*(802)*
FEV_1 / VC# (%)	84.5	*(8.3)*	79.3	*(7.9)*	81.3	*(9.8)*	73.0	*(8.8)*
Screening criteria[1]								
respiratory symptoms^	-		37.1		88.8		80.5	
lung function < normal range~	-		4.6		16.6		20.8	
reversibility$	-		0.7		2.9		2.9	
mild early signs @	-		9.3		31.6		32.6	
Mucus hypersecretion=	0.7		4.6		14.4		13.7	
Packyears	8.9	*(12.0)*			8.7	*(10.8)*		
Ever smokers (%)	43.1		43.7		32.6		34.2	
Current smokers (%)	31.8		27.2		40.6		36.7	

Legend:

* postbronchodilator FEV_1 (at year 5: n=150, respectively n=299)

vital capacity

^ Dutch modified version of the MRC questionnaire

~ FEV_1 / VC ≤ lower limit of normal

$ ≥ 15% predicted

@ combination of at least two out of three mild early signs (mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent productive cough)

= continuous production of sputum in the winter season

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

Table 3 Obstruction and respiratory morbidity

	OBSTRUCTED SUBJECTS		RESPIRATORY MORBIDITY		SUBJECT TO ANALYSIS
	baseline	year 5	year 5		
	n	n	n	%	n
no COPD or asthma	9		296	63.8	287
mild COPD	12	60	60	12.9	48
moderate COPD	10	49	49	10.6	39
at risk for COPD	1		7	1.5	
asthmatic	3	6	21	4.5	
Missing			31	6.7	
Total	35	115	464	100	374

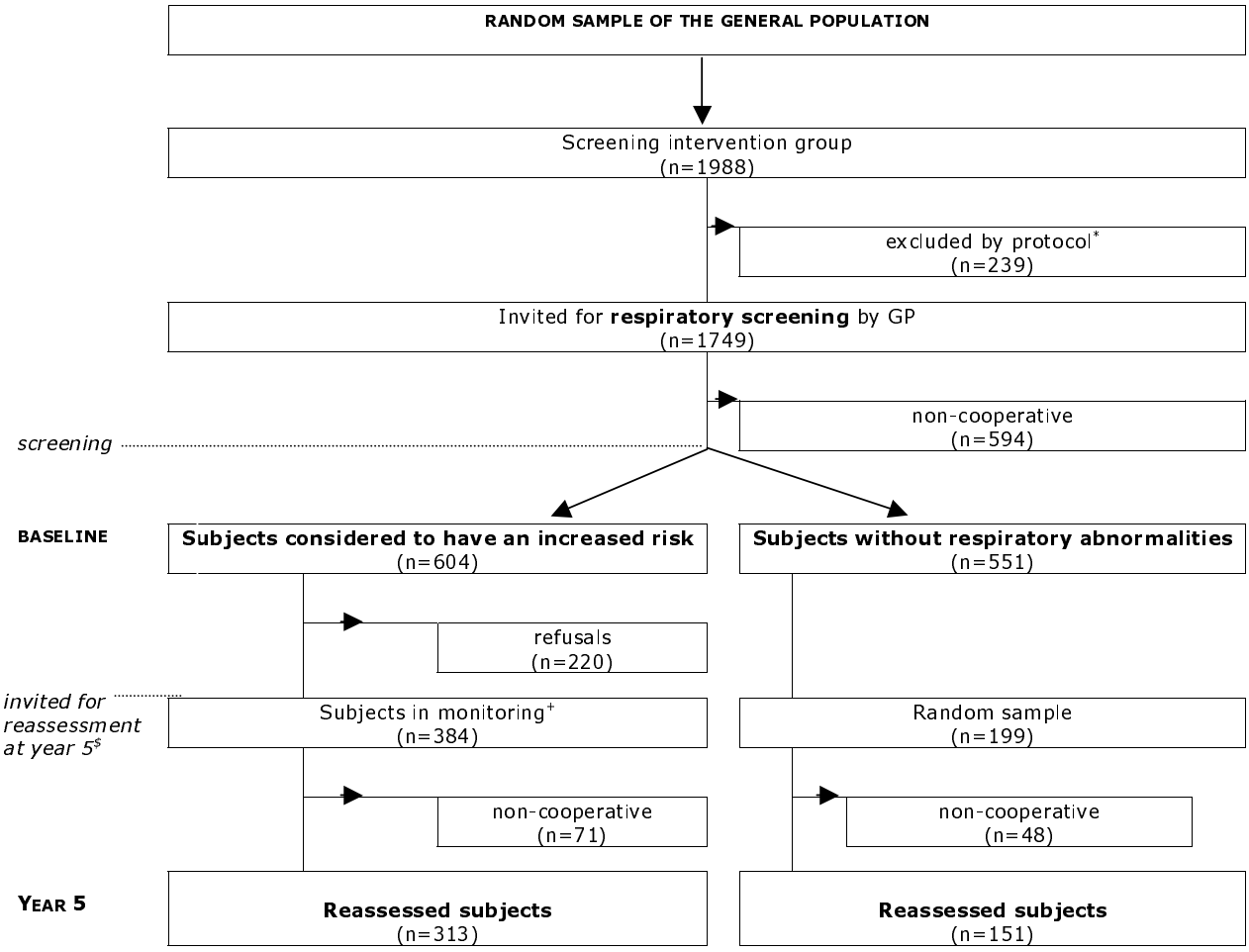
Table 4. Odds ratio's from multinomial regression analysis of early signs as predictors of respiratory morbidity five years later. Analysis was restricted to those 374/464 subjects who were free of 'obstruction' at baseline.
(OR's were adjusted for age, gender, packyears at baseline, and smoking behaviour during follow-up)

	RESPIRATORY MORBIDITY[&] AT YEAR 5 (N=374)			
	MILD COPD (12.8%)		MODERATE COPD (10.4%)	
	OR	*ADJ. OR*	*OR*	*ADJ. OR*
Screening criteria [1]				
- respiratory symptoms[^]	1.30 [0.92-1.83][!]	1.41 0.98-2.01]	0.96 [0.66-1.42]	0.94 [0.61-1.43]
- lung function below normal range[~]	1.45 [0.74-2.86]	1.46 [0.72-2.96]	**2.02** [1.07-3.83]	**2.54** [1.25-5.19]
- reversibility[$]	1.04 [0.38-2.88]	1.02 [0.00-0.03]	0.56 [0.16-1.93]	0.94 [0.25-3.49]
- mild early signs [@]	**1.69** [1.13-2.54]	**1.87** [1.22-2.87]	**1.97** [1.28-3.02]	**2.08** [1.29-3.37]
Mucus hypersecretion[=]	1.35 [0.77-2.36]	1.17 [0.64-2.14]	**2.53** [1.52-4.19]	**1.88** [1.07-3.33]
Smoking behaviour				
- packyears (baseline)		0.99 [0.95-1.02]		**1.05** [1.01-1.08]
- not smoking at year 5		1.23 [0.79-1.92]		1.04 [0.56-1.90]
- smoking at year 5		1.53 [0.96-2.46]		1.81 [0.99-3.30]
- smoking during follow-up		1.31 [0.54-3.17]		0.79 [0.21-2.96]
Age		1.00 [0.97-1.04]		**1.06** [1.01-1.10]
Gender (*female=1*)		**0.54** [0.38-0.76]		1.13 [0.73-1.73]

Legend:
[&] mild COPD (N=48), moderate COPD (n=39)
[^] Dutch modified version of the MRC questionnaire
[~] FEV_1 / VC ≤ lower limit of normal
[$] ≥ 15% predicted
[@] combination of at least two out of three mild early signs (mild obstruction, reversibility, weather-dependent or recurrent productive cough)
[=] continue production of sputum in winter
[!] [95% confidence intervals]

[1] Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

Figure 1: Flow chart



Legend:

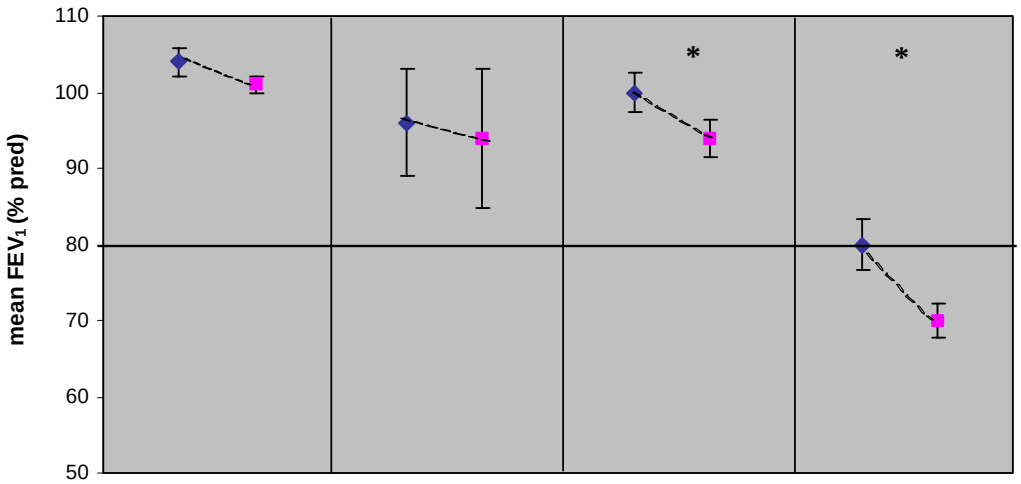
* 12% (n=239) was excluded because respiratory disease had already been diagnosed by the GP

$ At year five the follow-up cohort was reduced, envisaging 400 subjects in the at-risk group, and 200 subjects in the group without respiratory abnormalities

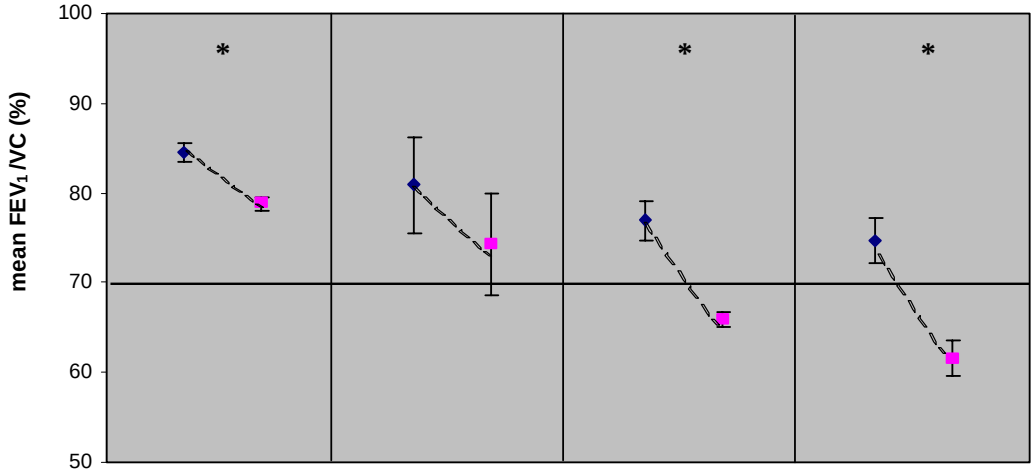
\+ a total number of 145 at-risk subjects participated in one of the randomized controlled trials[18;20;39]

Figure 2: The course of FEV_1 and FEV_1/VC in early respiratory morbidity

Postbronchodilator FEV_1 (95% CI)



Postbronchodilator FEV_1/VC (95% CI)



at year 5:	**no COPD or asthma** (n=296)	**asthmatic** (n=21)	**mild COPD** (n=60)	**moderate to severe COPD** (n=49)

Legend:

◆ = year 0: mean values with 95% confidence interval

■ = year 5: mean values with 95% confidence interval

* = statistically significant difference between year 0 and year 5

Appendix Table 1 Screening criteria, used to determine the respiratory status of subjects

CRITERIA	
respiratory symptoms	wheezing, dyspnoea, cough (≥ 3 months/year) or an asthma attack or shortness of breath due to an allergic reaction (in the previous 12 months)
lung function below normal range	FEV_1 / VC ≤ lower limit of normal (predicted minus 1.64 sd)
reversibility	FEV_1 reversibility ≥ 15% predicted
(at least two out of three) mild early signs	FEV_1 / VC ≤ predicted value minus 1SD and/or
	FEV_1 reversibility ≥ 10% predicted and/or
	weather-dependent (productive) cough or shortness of breath or the occurrence of more than one period of (productive) cough in the previous two years

Appendix Table 2 Baseline values of the respective follow-up groups

	N	Age (yr)	Gender (% female)	Pre-FEV_1[#] (mL)	Packyear (No.)	Smoking status (% ever smokers)
AT-RISK SUBJECTS						
Baseline group	604	43.4	59.9	3058	9.1	32.0
Monitoring group	384	42.9	57.6	3109	8.9	
Reassessed group (year 5)	313	43.9	59.4	3065	8.7	32.6
SUBJECTS WITHOUT ABNORMALITIES						
Baseline group	551	42.9	50.3	3440	7.0	37.4
Reassessed group (year 5)	151	42.9	50.3	3477	8.9	43.1

Legend:

[#] pre-bronchodilator forced expiratory volume

Appendix 3

A total number of 145 at-risk subjects participated in one of the randomized controlled trials (for a period varying between 12 and 30 months), in which inhaled corticosteroids (n=68) were compared to placebo treatment (n=77). The mean individual change in postbronchodilator FEV_1 over the five year period was –352 mL (*sd 287 mL*) in the corticosteroid treated group versus –280 mL (*sd 307 mL*) in the placebo treated group. Based on the individual change over the five year period, corticosteroid treatment did not show a different course in respiratory symptoms, postbronchodilator FEV_1 (p=0.09) or postbronchodilator FEV_1/VC (p=0.96) from placebo treatment. As a consequence, participants of the intervention study were included in the sample.

Reference List

(1) Lofdahl CG. Cost development of obstructive airway disease in Sweden. Eur Respir Rev 1996; 6:113-115.

(2) Tirimanna PR, van Schayck CP, den Otter JJ et al. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract 1996; 46(406):277-281.

(3) Murray CJL, Lopez AD. Alternative visions of the future: projecting mortality and disability, 1990-2020. In: Murray CJL, Lopez AD, editors. The Global Burden of Disease. The Harvard School of Public Health, on behalf of the World Health Organization and the World Bank, 1996: 361-395.

(4) Weel Cv, Smith H, Beasley JW. Family practice research networks. Experience from three countries. J Fam Pract 2000; 49:938-943.

(5) Feenstra TL, van Genugten ML, Hoogenveen RT et al. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001; 164(4):590-596.

(6) Coultas DB, Mapel D, Gagnon R et al. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med 2001; 164(3):372-377.

(7) Tinkelman DG, Price DB, Nordyke RJ et al. Misdiagnosis of COPD and Asthma in Primary Care Patients 40 Years of Age and Over. J Asthma 2006; 43(1):75-80.

(8) Pauwels RA, Buist AS, Calverley PM et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163(5):1256-1276.

(9) de Marco R, Accordini S, Cerveri I et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 2004; 59(2):120-125.

(10) 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(3):329-332.

(11) Celli BR, Halbert RJ, Isonaka S et al. Population impact of different definitions of airway obstruction. Eur Respir J 2003; 22(2):268-273.

(12) Rennard S, Decramer M, Calverley PM et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J 2002; 20(4):799-805.

(13) Coultas DB, Mapel DW. Undiagnosed airflow obstruction: prevalence and implications. Curr Opin Pulm Med 2003; 9(2):96-103.

(14) Fabbri LM, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. Eur Respir J 2003; 22(1):1-2.

(15) Lindberg A, Eriksson B, Larsson LG et al. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest 2006; 129(4):879-885.

(16) Van den 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(6):1730-1738.

(17) Pellegrino R, Viegi G, Brusasco V et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26(5):948-968.

(18) van Grunsven P, Schermer T, Akkermans R et al. Short- and long-term efficacy of fluticasone propionate in subjects with early signs and symptoms of chronic obstructive pulmonary disease. Results of the DIMCA study. Respir Med 2003; 97(12):1303-1312.

(19) van den BG, Rutten-van Molken MP, Molema J et al. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. Am J Respir Crit Care Med 2001; 164(11):2057-2066.

(20) Albers M, Schermer T, Van den Boom G et al. Efficacy of Inhaled Steroids in Undiagnosed Subjects at High Risk for COPD. Results of the Detection, Intervention, and Monitoring of COPD and Asthma Program. Chest 2004; 126:1815-1824.

(21) Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.com. Date accessed: December 6, 2006. 2006.

(22) Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(3):1107-1136.

(23) Quanjer PH, Tammeling GJ, Cotes JE et al. 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 [see comments]. Eur Respir J Suppl 1993; 16(s):5-40.

(24) Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. Eur J Respir Dis 1987; 70(3):171-179.

(25) van Schayck CP, Folgering H, den Otter JJ et al. Does the continuous use of bronchodilators mask the progression of asthma or chronic bronchitis? Fam Pract 1992; 9(4):397-404.

(26) Boom Gvd, Tirimanna PRS, Kaptein AA et al. Underpresentation of shortness of breath in the general population. Results of the DIMCA programme. Asthma Gen Pract 1999; 7(1):3-7.

(27) Rennard SI. Treatment of stable chronic obstructive pulmonary disease. Lancet 2004; 364(9436):791-802.

(28) Buffels J, Degryse J, Heyrman J et al. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Chest 2004; 125(4):1394-1399.

(29) Zielinski J, Bednarek M. Early detection of COPD in a high-risk population using spirometric screening. Chest 2001; 119(3):731-736.

(30) Stratelis G, Jakobsson P, Molstad S et al. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Br J Gen Pract 2004; 54(500):201-206.

(31) Albers M, Thoonen B, Dekhuijzen R. Recommended case-finding strategy misclassifies relevant groups of subjects with COPD. Rapid response to: Schayck CP van, JMC Loozen, E Wagena et al: Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ, rapid response 2002;(324):1370.

(32) Celli BR, Cote CG, Marin JM et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. New Engl J Med 2004; 350(10):1005-1012.

(33) Hospers JJ, Postma DS, Rijcken B et al. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. Lancet 2000; 356(9238):1313-1317.

(34) Straus SE, McAlister FA, Sackett DL et al. The accuracy of patient history, wheezing, and laryngeal measurements in diagnosing obstructive airway disease. CARE-COAD1 Group. Clinical Assessment of the Reliability of the Examination-Chronic Obstructive Airways Disease. JAMA 2000; 283(14):1853-1857.

(35) MANNINO DM. Chronic obstructive pulmonary disease: definition and epidemiology. Respir Care 2003; 48(12):1185-1191.

(36) Rijcken B, Schouten JP, Xu X et al. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV1. Am J Respir Crit Care Med 1995; 151:1377-1382.

(37) Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J 2004; 23(4):497-498.

(38) Vestbo J. COPD in the ECRHS. Thorax 2004; 59(2):89-90.

(39) van den BG, Rutten-van Molken MP, Molema J et al. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. Am J Respir Crit Care Med 2001; 164(11):2057-2066.