

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

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Key words:

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

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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 2020³. 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 undiagnosed⁶ or misdiagnosed⁷. To decrease morbidity and mortality from this chronic lung disorder, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated⁸. In a number of cross-sectional, population-based surveys⁹⁻¹¹ the GOLD guidelines were used to estimate the prevalence of COPD. One of the first surveys, the confronting COPD International Survey¹², 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) studies¹³. 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 COPD¹⁴. 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 study¹⁰, 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 study¹⁵, 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 population¹⁶ (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 morbidity¹, were used to define the baseline respiratory status of screened subjects. Subjects with either respiratory symptoms, lung function below normal range¹⁷, 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 elsewhere¹⁸⁻²⁰.

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 guidelines²¹ 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 standards²². ECCS reference values were used²³. Variation in spirometer performance was assessed and accounted for. Reversibility²⁴ was assessed 15 minutes after inhalation of 800 µg salbutamol by spacer. At the moment of screening lung function below normal range¹⁷ was defined as bronchodilator FEV₁/VC (Forced Expiratory Volume in one second / Vital Capacity) $\leq$ lower limit of normal (predicted minus 1.64 sd). Reversibility was defined positive if after bronchodilatation the change in FEV₁ (relative to the predicted value) amounted to at least 15%²⁴. In the GOLD-based disease classification²¹ definitions were for obstruction a postbronchodilator

FEV₁/VC<70%, and for reversibility a 12% change of predicted FEV₁ 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 questionnaire²⁵. 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 (dropout², trial participants³). 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 FEV₁ ($p=0.0001$), lower postbronchodilator FEV₁/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 FEV₁ {-241 mL (sd: 303 mL); on average: -48 mL/year} and in postbronchodilator FEV₁/VC {7.1% (sd: 9.9%)}. At-risk subjects demonstrated more reduction of lung function (postbronchodilator FEV₁: -262mL versus -199mL; $p=0.02$) and a lower average postbronchodilator FEV₁/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 FEV₁) 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 FEV₁/VC, but subjects did not become obstructive. Asthmatic subjects at year five (n=21) showed no decrease in lung function or postbronchodilator FEV₁/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 cough¹ 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 cough¹. COPD appears to be an insidiously starting disease. Due to subjects' underperception of disease severity¹² there is a huge underpresentation of early signs of respiratory morbidity²⁶ causing underdiagnosis of COPD in general practice. As smoking cessation can reduce symptoms and prevent progression of disease²⁷, 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 survival²⁷. 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 practice¹³ 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 obstruction³¹. 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 studies³²⁻³⁶, 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 FEV₁, 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, Celli¹¹ 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-bronchodilator³⁷. Celli did not have disposition of reversibility testing, making it impossible to distinguish reversible from irreversible obstruction¹¹. In a recent editorial³⁸, 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.

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Table 3 Obstruction and respiratory morbidity

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Figure 2 The course of FEV₁ and FEV₁/VC in early respiratory morbidity.

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

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

Appendix 3 Trial participants.

Table 1

Algorithm for the classification of chronic respiratory disease (based on the GOLD criteria²¹)

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 FEV₁* ≥ 80%		no	MILD COPD (GOLD I)
or 50% ≤ FEV₁ < 80%		no	MODERATE COPD (GOLD II)
or 30% ≤ FEV₁ < 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 FEV₁ after bronchodilatation with a change of at least 200 mL.

⁺ Obstructive if FEV₁*/VC[#] < 70%

* postbronchodilator forced expiratory volume;

[#] vital capacity

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

	SCREENED SUBJECTS							
	without baseline abnormalities				with baseline abnormalities			
	(N=151)				(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)
<u>Screening criteria</u> 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	
<u>Mucus hypersecretion</u> ⁼	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 FEV₁ (at year 5: n=150, respectively n=299)[#] vital capacity[^] Dutch modified version of the MRC questionnaire[~] FEV₁ / 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 season¹ 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

[~] FEV₁ / VC ≤ lower limit of normal

^{\$} ≥ 15% predicted

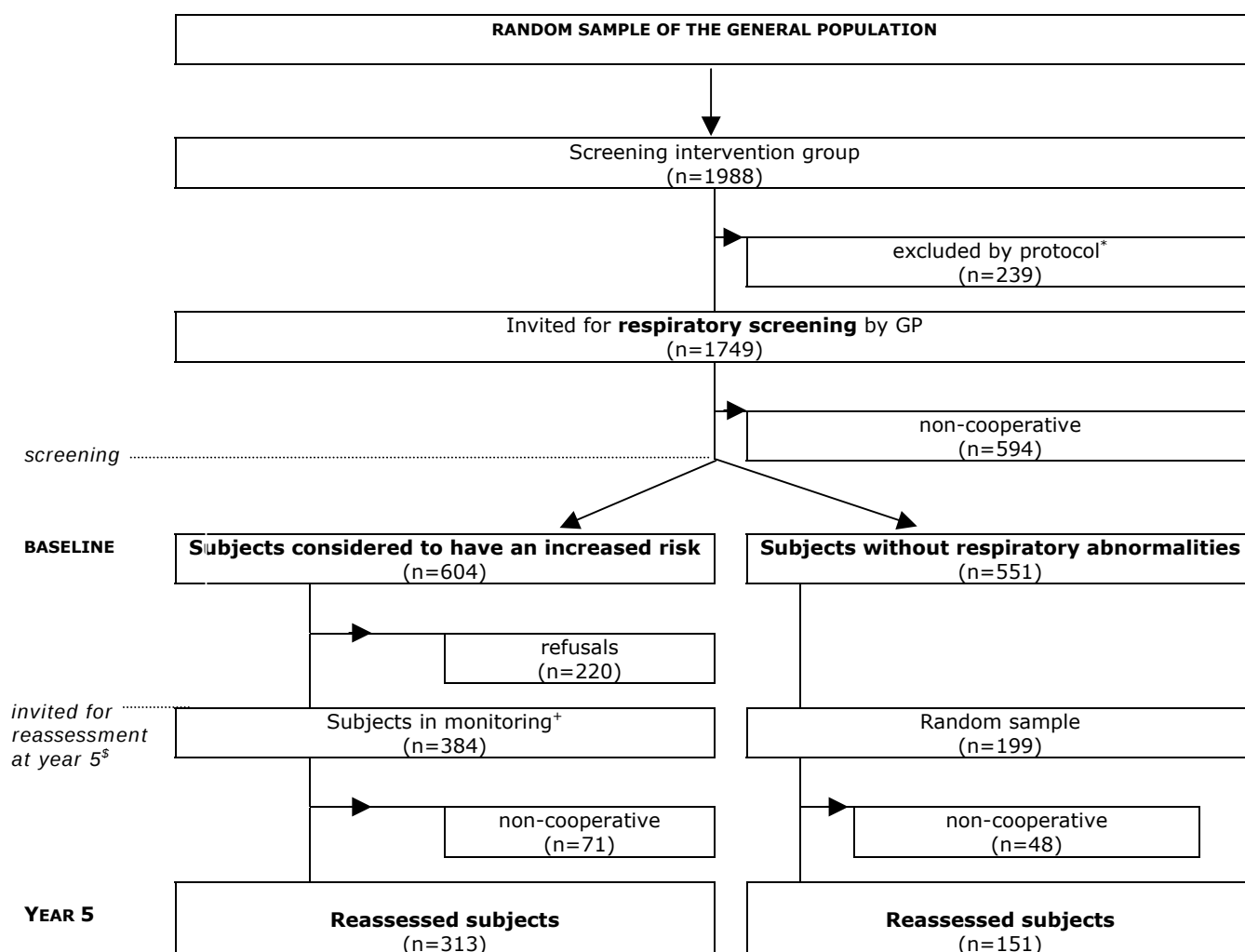
[@] combination of at least two out of three mild early signs (mild obstruction, reversibility, weather-dependent or recurrent productive cough)

⁼ continue production of sputum in winter

[†] [95% confidence intervals]

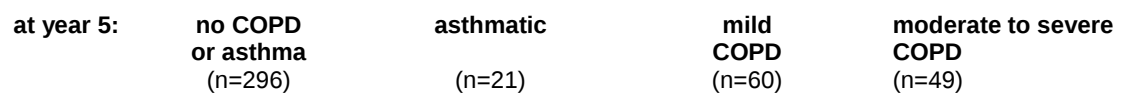
¹ Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

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}

Postbronchodilator FEV₁ (95% CI)

- ◆ = 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	$FEV_1 / VC \leq$ lower limit of normal (predicted minus 1.64 sd)
reversibility	FEV_1 reversibility $\geq 15\%$ predicted
(at least two out of three) mild early signs	$FEV_1 / VC \leq$ predicted value minus 1SD and/or
	FEV_1 reversibility $\geq 10\%$ 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 FEV₁ 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 FEV₁ (p=0.09) or postbronchodilator FEV₁/VC (p=0.96) from placebo treatment. As a consequence, participants of the intervention study were included in the sample.

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