

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

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8 **Key words:**

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

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19 **Abbreviations:**

20	COPD	Chronic Obstructive Pulmonary Disease
21	GOLD	Global Initiative for Chronic Obstructive Lung Disease
22	DIMCA	Detection, Intervention and Monitoring of COPD and Asthma in general practice
23	FEV <sub>1</sub>	Forced Expiratory Volume in one second
24	VC	Vital Capacity
25	OR	Odds Ratio
26	CI	Confidence Interval

27

27 **Abstract**

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

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

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

38 *Results:* Over a five year period, the percentage of subjects with obstruction increased from 7.5%  
39 (n=35) at baseline to 24.8% (n=115) at year five. Baseline presence of mild early signs and lung  
40 function below normal range were related to an increased risk to develop mild to moderate COPD  
41 {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  
42 (95% CI [1.25-5.19])} at year five.

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

45

## 45 **Introduction**

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

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

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

## 72 **Methods**

### 73 *Design*

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

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

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

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

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

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

## 105 *Measurements*

### 106 *Lung function and reversibility*

107 Lung function was assessed by two trained lung function technicians at two different points in time  
108 (at baseline and at year five). Measurements were performed according to the American Thoracic  
109 Society standards<sup>22</sup>. ECCS reference values were used<sup>23</sup>. Variation in spirometer performance was  
110 assessed and accounted for. Reversibility<sup>24</sup> was assessed 15 minutes after inhalation of 800 µg  
111 salbutamol by spacer. At the moment of screening lung function below normal range<sup>17</sup> was defined  
112 as bronchodilator FEV<sub>1</sub>/VC (Forced Expiratory Volume in one second / Vital Capacity) ≤ lower  
113 limit of normal (predicted minus 1.64 sd). Reversibility was defined positive if after  
114 bronchodilatation the change in FEV<sub>1</sub> (relative to the predicted value) amounted to at least 15%<sup>24</sup>.  
115 In the GOLD-based disease classification<sup>21</sup> definitions were for obstruction a postbronchodilator  
116 FEV<sub>1</sub>/VC < 70%, and for reversibility a 12% change of predicted FEV<sub>1</sub> after bronchodilatation with a  
117 change of at least 200 mL.

### 119 *Respiratory symptoms and smoking behaviour*

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

### 126 *Statistical analysis*

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

130 The progression of COPD was studied using multinomial logistic modelling. Dependent variable  
131 was respiratory morbidity at year five. This outcome was defined by the three categorical levels of  
132 absence of COPD or asthma, mild COPD or moderate to severe COPD. Initially obstructed subjects  
133 were excluded from the analysis. Odds ratio's of early signs of respiratory morbidity were  
134 calculated and defined as possible indicators of disease progression. Due to gained insight, mucus  
135 hypersecretion was added to the signs initially defined at the screening. Odds Ratio's were based on  
136 adjustment for age, gender, the number of packyears at baseline, and smoking behaviour during the  
137 5-year follow-up period. Following the disease classification at year five (Table 1), categories were  
138 compared on lung function and obstruction over the five year period, using confidence limits. The  
139 SAS statistical package (version V8.2 for Windows) was used for all analyses. Two-sided P values  
140 of < 0.05 were considered to be statistically significant.

141

142 **Results**

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

149  
 150 *Symptoms and lung function in screened subjects*

151 The characteristics of the study population, and their evolution over the 5-year period, are given in  
 152 table 2. At baseline there was no difference in age, gender, height or smoking history between  
 153 subjects without respiratory abnormalities and at-risk subjects. Both at baseline *and* at the  
 154 reassessment after five years, at-risk subjects had more symptoms (p=0.001), lower post-  
 155 bronchodilator FEV<sub>1</sub> (p=0.0001), lower postbronchodilator FEV<sub>1</sub>/VC (p=0.0003, respectively  
 156 p<0.0001), and were more often current smokers (p=0.07, respectively p=0.04) than subjects  
 157 without baseline abnormalities. Over the 5-year period the overall individual change (n=464)  
 158 showed a decrease in postbronchodilator FEV<sub>1</sub> {-241 mL (sd: 303 mL); on average: -48  
 159 mL/year} and in postbronchodilator FEV<sub>1</sub>/VC {7.1% (sd: 9.9%)}. At-risk subjects demonstrated  
 160 more reduction of lung function (postbronchodilator FEV<sub>1</sub>: -262mL versus -199mL; p=0.02) and a  
 161 lower average postbronchodilator FEV<sub>1</sub>/VC (-8.0 versus -5.2; p=0.04).

162  
 163 *Respiratory morbidity*

164 The distribution of the respiratory morbidity at year 5 is presented in Table 3. Over the five year  
 165 period, the percentage of subjects with obstruction increased from 7.5% (n=35) at baseline to 24.8%  
 166 (n=115) at year five. The change in lung function (postbronchodilator FEV<sub>1</sub>) and obstruction over  
 167 the five year period is presented in figure 2. The group of subjects labelled at year five as not having  
 168 COPD or asthma (n=296) did not show a decline in lung function. There was a slight but significant  
 169 decrease in postbronchodilator FEV<sub>1</sub>/VC, but subjects did not become obstructive. Asthmatic  
 170 subjects at year five (n=21) showed no decrease in lung function or postbronchodilator FEV<sub>1</sub>/VC.  
 171 Over the five year period, subjects with mild COPD (n=60) or moderate to severe COPD (n=49)  
 172 significantly decreased in lung function, and became obstructive as well.

173  
 174 *Respiratory morbidity odds ratio's*

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

<sup>2</sup> Baseline values of the several follow-up groups (Appendix Table 2)

<sup>3</sup> Trial participants

<sup>1</sup> Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).



187 **Discussion**

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

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<sup>1</sup> Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

235 smoking behaviour during follow-up), not all confounding factors may have been excluded. A  
236 further finding concerned the steady (or slightly decreased) percentage of subjects with respiratory  
237 signs and symptoms in the at-risk group. The most obvious explanation might be that after  
238 assessment of symptoms, the problem is identified and subjects will deal with it.  
239 Over the five year period, the number of subjects with obstruction increased considerably. In other  
240 terms, screened subjects, considered to have an increased risk for development of COPD, appeared  
241 to have a more than 3-fold risk to actually develop mild or moderate COPD. The most prominent  
242 predictor for development of moderate COPD was a baseline presence of lung function below  
243 normal range (OR: 2.54). In this cohort of initially undiagnosed subjects, a baseline presence of  
244 mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent  
245 productive cough showed to be predictive for development of mild COPD (OR:1.87) or moderate  
246 COPD (OR:2.08) 5 years later. Furthermore, baseline mucus hypersecretion (in the absence of  
247 airflow obstruction without full reversibility) appeared to be predictive (OR: 1.88) for subsequent  
248 development of moderate COPD. A prolonged follow-up from early stage COPD onwards,  
249 followed by an undisputed clinical diagnosis, may further clarify these relations. In terms of health  
250 care, the identification of risk factors for early detection of COPD may contribute to the  
251 development of an evidence based model for case-finding. This is specifically of interest for the  
252 studied cohort, as these undiagnosed subjects did not present themselves in primary care.  
253 In conclusion, lung function below normal range and early respiratory signs are possible predictors  
254 for progression of COPD.. As a result, implementation of GOLD guidelines in general practice may  
255 reduce underdiagnosis and undertreatment.

256

#### 257 **Acknowledgement**

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

## Tables and figures

- Table 1** Algorithm for the classification of chronic respiratory disease (based on the GOLD criteria).
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- Figure 1** Flow chart of the initial general population cohort in the DIMCA program, and the follow-up group reassessed at year five.
- Figure 2** The course of FEV<sub>1</sub> and FEV<sub>1</sub>/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 criteria<sup>21</sup>)**

LUNG FUNCTION	RESPIRATORY SYMPTOMS <sup>§</sup>	REVERSIBILITY <sup>&amp;</sup>	DISEASE CLASSIFICATION
<b>NO OBSTRUCTION<sup>+</sup></b>	no chronic symptoms	yes	ASTHMATIC
	chronic symptoms	no	NO COPD or ASTHMA
<b>OBSTRUCTION<sup>+</sup></b> and <b>FEV<sub>1</sub><sup>*</sup> ≥ 80%</b> or <b>50% ≤ FEV<sub>1</sub> &lt; 80%</b> or <b>30% ≤ FEV<sub>1</sub> &lt; 50%</b>		no	AT RISK FOR COPD (GOLD 0)
		yes	INADEQUATELY MANAGED ASTHMA
		no	MILD COPD (GOLD I)
		no	MODERATE COPD (GOLD II)
		no	SEVERE COPD (GOLD III)

*Legend*

<sup>§</sup> chronic symptoms: cough and sputum production for at least 3 months in each of two consecutive years

<sup>&</sup> Reversibility: a 12% change of predicted FEV<sub>1</sub> after bronchodilatation with a change of at least 200 mL.

<sup>+</sup> Obstructive if FEV<sub>1</sub><sup>\*</sup>/VC<sup>#</sup> < 70%

<sup>\*</sup> postbronchodilator forced expiratory volume;

<sup>#</sup> 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 <sub>1</sub> * (ml)	3532	(833)	3335	(806)	3195	(795)	2938	(802)
FEV <sub>1</sub> / VC# (%)	84.5	(8.3)	79.3	(7.9)	81.3	(9.8)	73.0	(8.8)
<u>Screening criteria</u> <sup>1</sup>								
respiratory symptoms <sup>^</sup>	-		37.1		88.8		80.5	
lung function < normal range <sup>~</sup>	-		4.6		16.6		20.8	
reversibility <sup>§</sup>	-		0.7		2.9		2.9	
mild early signs <sup>@</sup>	-		9.3		31.6		32.6	
<u>Mucus hypersecretion</u> <sup>=</sup>								
	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<sub>1</sub> (at year 5: n=150, respectively n=299)

# vital capacity

<sup>^</sup> Dutch modified version of the MRC questionnaire<sup>~</sup> FEV<sub>1</sub> / VC ≤ lower limit of normal<sup>§</sup> ≥ 15% predicted<sup>@</sup> 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)<sup>=</sup> continuous production of sputum in the winter season<sup>1</sup> 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	%	
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

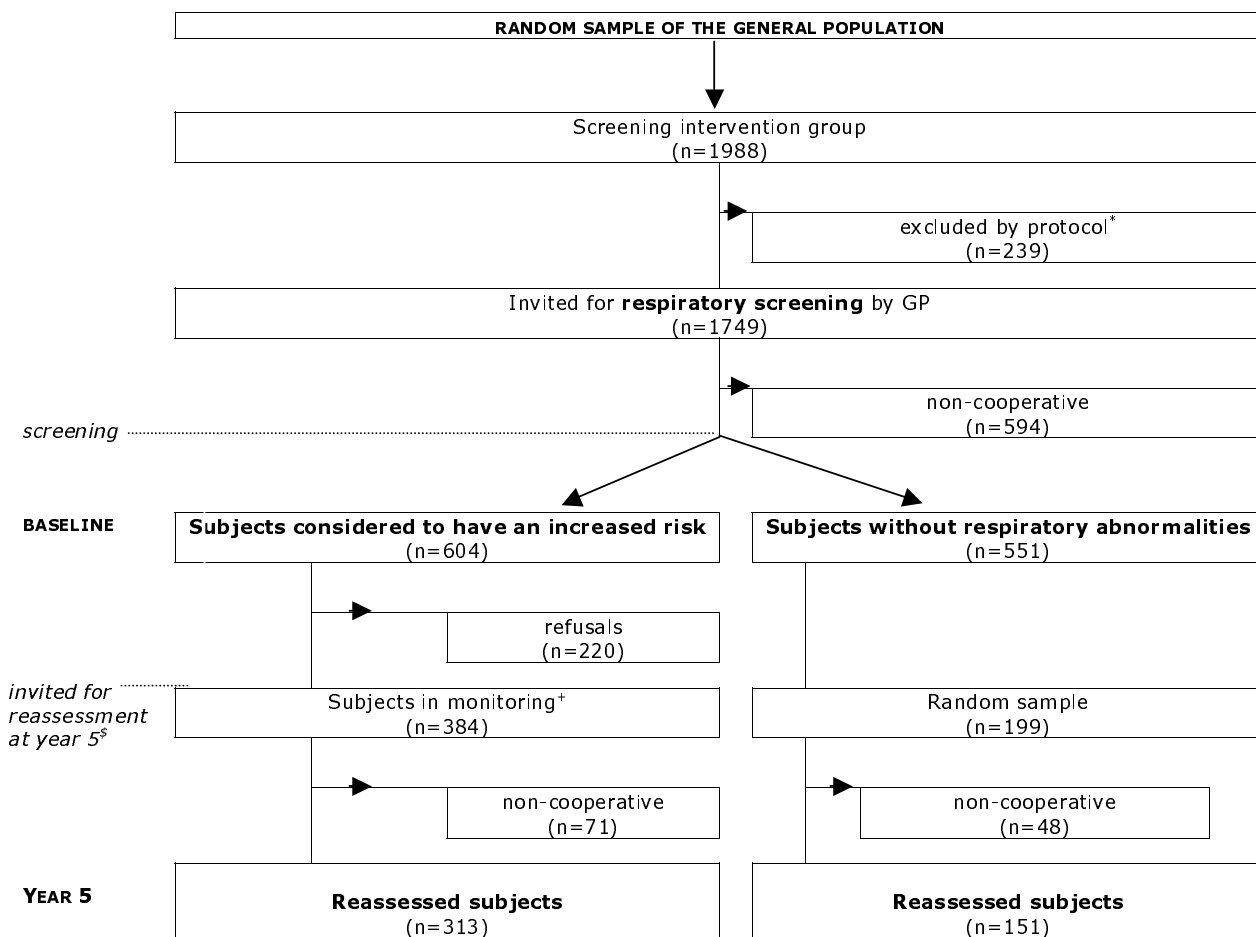
**Table 4.** Odds ratio's from multinomial regression analysis of early signs as predictors of respiratory morbidity five years later. Analysis was restricted to those 374/464 subjects who were free of 'obstruction' at baseline.

(OR's were adjusted for age, gender, packyears at baseline, and smoking behaviour during follow-up)

	RESPIRATORY MORBIDITY <sup>&amp;</sup> AT YEAR 5 (N=374)			
	MILD COPD (12.8%)		MODERATE COPD (10.4%)	
	OR	ADJ. OR	OR	ADJ. OR
Screening criteria <sup>1</sup>				
- respiratory symptoms <sup>^</sup>	1.30 [0.92-1.83] <sup>1</sup>	1.41 [0.98-2.01]	0.96 [0.66-1.42]	0.94 [0.61-1.43]
- lung function below normal range <sup>~</sup>	1.45 [0.74-2.86]	1.46 [0.72-2.96]	<b>2.02</b> [1.07-3.83]	<b>2.54</b> [1.25-5.19]
- reversibility <sup>§</sup>	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 <sup>@</sup>	<b>1.69</b> [1.13-2.54]	<b>1.87</b> [1.22-2.87]	<b>1.97</b> [1.28-3.02]	<b>2.08</b> [1.29-3.37]
Mucus hypersecretion <sup>=</sup>	1.35 [0.77-2.36]	1.17 [0.64-2.14]	<b>2.53</b> [1.52-4.19]	<b>1.88</b> [1.07-3.33]
Smoking behaviour				
- packyears (baseline)		0.99 [0.95-1.02]		<b>1.05</b> [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]		<b>1.06</b> [1.01-1.10]
Gender (female=1)		<b>0.54</b> [0.38-0.76]		1.13 [0.73-1.73]

**Legend:**<sup>&</sup> mild COPD (N=48), moderate COPD (n=39)<sup>^</sup> Dutch modified version of the MRC questionnaire<sup>~</sup> FEV<sub>1</sub> / VC ≤ lower limit of normal<sup>§</sup> ≥ 15% predicted<sup>@</sup> combination of at least two out of three mild early signs (mild obstruction, reversibility, weather-dependent or recurrent productive cough)<sup>=</sup> continue production of sputum in winter<sup>1</sup> [95% confidence intervals]<sup>1</sup> Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1)

**Figure 1:** Flow chart

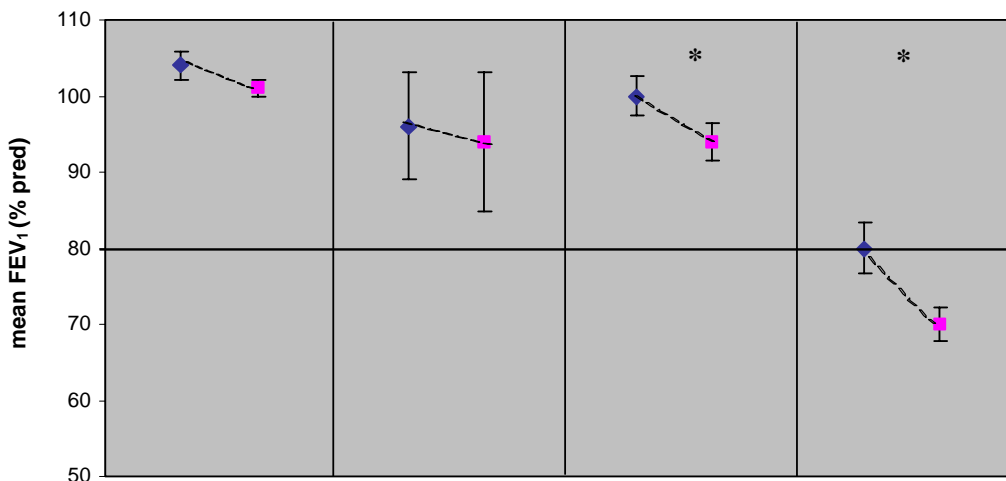


**Legend:**

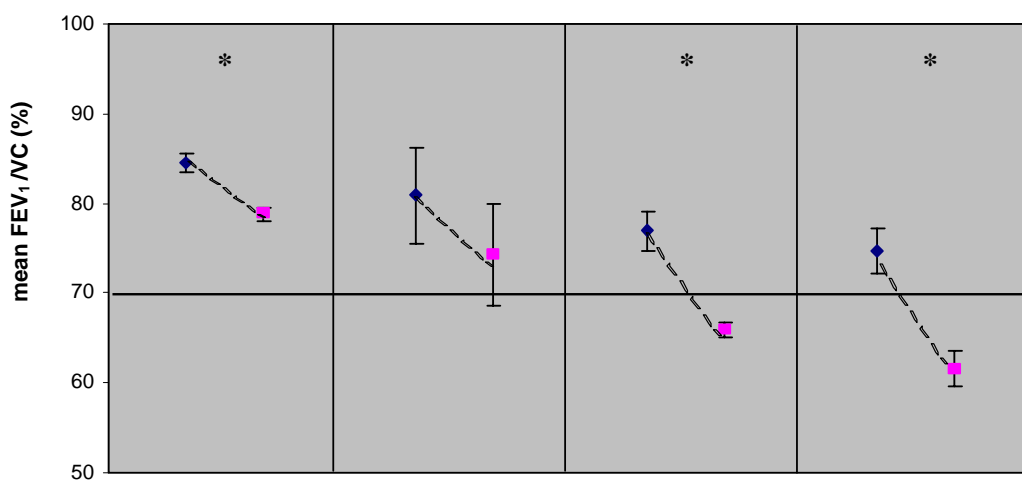
- \* 12% (n=239) was excluded because respiratory disease had already been diagnosed by the GP
- \$ At year five the follow-up cohort was reduced, envisaging 400 subjects in the at-risk group, and 200 subjects in the group without respiratory abnormalities
- + a total number of 145 at-risk subjects participated in one of the randomized controlled trials<sup>18; 20; 39</sup>

Figure 2: The course of FEV<sub>1</sub> and FEV<sub>1</sub>/VC in early respiratory morbidity

Postbronchodilator FEV<sub>1</sub> (95% CI)



Postbronchodilator FEV<sub>1</sub>/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 ( $\geq 3$ 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
	$FEV_1 / VC \leq$ predicted value minus 1SD and/or
(at least two out of three) mild early signs	$FEV_1$ 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 <sub>1</sub> <sup>#</sup> (mL)	Packyear (No.)	Smoking status (% ever smokers)
<b>AT-RISK SUBJECTS</b>						
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
<b>SUBJECTS WITHOUT ABNORMALITIES</b>						
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:

<sup>#</sup> 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<sub>1</sub> 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<sub>1</sub> (p=0.09) or postbronchodilator FEV<sub>1</sub>/VC (p=0.96) from placebo treatment. As a consequence, participants of the intervention study were included in the sample.

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

3

4 *Mieke Albers, Tjard Schermer, Yvonne Heijdra, Johan Molema, Reinier Akkermans, Chris van*  
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6

7

8 **Key words:**

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

10

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19 **Abbreviations:**

20	COPD	Chronic Obstructive Pulmonary Disease
21	GOLD	Global Initiative for Chronic Obstructive Lung Disease
22	DIMCA	Detection, Intervention and Monitoring of COPD and Asthma in general practice
23	FEV <sub>1</sub>	Forced Expiratory Volume in one second
24	VC	Vital Capacity
25	OR	Odds Ratio
26	CI	Confidence Interval

27

27 **Abstract**

28 *Background:* Chronic Obstructive Pulmonary Disease (COPD) is an insidiously starting disease.

29 Early detection has high priority because of the possibility of early implementation of smoking  
30 cessation interventions. An evidence based model for case-finding of COPD is not yet available.

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

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

38 *Results:* Over a five year period, the percentage of subjects with obstruction increased from 7.5%  
39 (n=35) at baseline to 24.8% (n=115) at year five. Baseline presence of mild early signs and lung  
40 function below normal range were related to an increased risk to develop mild to moderate COPD  
41 {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  
42 (95% CI [1.25-5.19])}at year five.

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

45

## 45 **Introduction**

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

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

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

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

71

## 72 **Methods**

### 73 *Design*

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

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

---

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

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

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

102 The medical ethics review board of the University Medical Centre Nijmegen approved the study.

103 Subjects gave their written informed consent.

104

## 105 *Measurements*

### 106 *Lung function and reversibility*

107 Lung function was assessed by two trained lung function technicians at two different points in time  
108 (at baseline and at year five). Measurements were performed according to the American Thoracic  
109 Society standards<sup>22</sup>. ECCS reference values were used<sup>23</sup>. Variation in spirometer performance was  
110 assessed and accounted for. Reversibility<sup>24</sup> was assessed 15 minutes after inhalation of 800 µg  
111 salbutamol by spacer. At the moment of screening lung function below normal range<sup>17</sup> was defined  
112 as bronchodilator FEV<sub>1</sub>/VC (Forced Expiratory Volume in one second / Vital Capacity) ≤ lower  
113 limit of normal (predicted minus 1.64 sd). Reversibility was defined positive if after  
114 bronchodilatation the change in FEV<sub>1</sub> (relative to the predicted value) amounted to at least 15%<sup>24</sup>.  
115 In the GOLD-based disease classification<sup>21</sup> definitions were for obstruction a postbronchodilator

116 FEV<sub>1</sub>/VC<70%, and for reversibility a 12% change of predicted FEV<sub>1</sub> after bronchodilatation with a  
117 change of at least 200 mL.

118

#### 119 *Respiratory symptoms and smoking behaviour*

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

125

#### 126 *Statistical analysis*

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

130 The progression of COPD was studied using multinomial logistic modelling. Dependent variable  
131 was respiratory morbidity at year five. This outcome was defined by the three categorical levels of  
132 absence of COPD or asthma, mild COPD or moderate to severe COPD. Initially obstructed subjects  
133 were excluded from the analysis. Odds ratio's of early signs of respiratory morbidity were  
134 calculated and defined as possible indicators of disease progression. Due to gained insight, mucus  
135 hypersecretion was added to the signs initially defined at the screening. Odds Ratio's were based on  
136 adjustment for age, gender, the number of packyears at baseline, and smoking behaviour during the  
137 5-year follow-up period. Following the disease classification at year five (Table 1), categories were  
138 compared on lung function and obstruction over the five year period, using confidence limits. The  
139 SAS statistical package (version V8.2 for Windows) was used for all analyses. Two-sided P values  
140 of < 0.05 were considered to be statistically significant.



141

142 **Results**

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

149

150 *Symptoms and lung function in screened subjects*

151 The characteristics of the study population, and their evolution over the 5-year period, are given in  
152 table 2. At baseline there was no difference in age, gender, height or smoking history between  
153 subjects without respiratory abnormalities and at-risk subjects. Both at baseline *and* at the  
154 reassessment after five years, at-risk subjects had more symptoms (p=0.001), lower post-  
155 bronchodilator FEV<sub>1</sub> (p=0.0001), lower postbronchodilator FEV<sub>1</sub>/VC (p=0.0003, respectively  
156 p<0.0001), and were more often current smokers (p=0.07, respectively p=0.04) than subjects  
157 without baseline abnormalities. Over the 5-year period the overall individual change (n=464)  
158 showed a decrease in postbronchodilator FEV<sub>1</sub> {-241 mL (sd: 303 mL); on average: -48  
159 mL/year} and in postbronchodilator FEV<sub>1</sub>/VC {7.1% (sd: 9.9%)}. At-risk subjects demonstrated  
160 more reduction of lung function (postbronchodilator FEV<sub>1</sub>: -262mL versus -199mL; p=0.02) and a  
161 lower average postbronchodilator FEV<sub>1</sub>/VC (-8.0 versus -5.2; p=0.04).

162

163 *Respiratory morbidity*

---

<sup>2</sup> Baseline values of the several follow-up groups (Appendix Table 2)

<sup>3</sup> Trial participants

164 The distribution of the respiratory morbidity at year 5 is presented in Table 3. Over the five year  
165 period, the percentage of subjects with obstruction increased from 7.5% (n=35) at baseline to 24.8%  
166 (n=115) at year five. The change in lung function (postbronchodilator FEV<sub>1</sub>) and obstruction over  
167 the five year period is presented in figure 2. The group of subjects labelled at year five as not having  
168 COPD or asthma (n=296) did not show a decline in lung function. There was a slight but significant  
169 decrease in postbronchodilator FEV<sub>1</sub>/VC, but subjects did not become obstructive. Asthmatic  
170 subjects at year five (n=21) showed no decrease in lung function or postbronchodilator FEV<sub>1</sub>/VC.  
171 Over the five year period, subjects with mild COPD (n=60) or moderate to severe COPD (n=49)  
172 significantly decreased in lung function, and became obstructive as well.

173

#### 174 *Respiratory morbidity odds ratio's*

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

---

<sup>1</sup> Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

## 187 **Discussion**

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

---

<sup>1</sup> Screening criteria, used to determine the respiratory status of subjects (Appendix Table 1).

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

236 further finding concerned the steady (or slightly decreased) percentage of subjects with respiratory  
237 signs and symptoms in the at-risk group. The most obvious explanation might be that after  
238 assessment of symptoms, the problem is identified and subjects will deal with it.  
239 Over the five year period, the number of subjects with obstruction increased considerably. In other  
240 terms, screened subjects, considered to have an increased risk for development of COPD, appeared  
241 to have a more than 3-fold risk to actually develop mild or moderate COPD. The most prominent  
242 predictor for development of moderate COPD was a baseline presence of lung function below  
243 normal range (OR: 2.54). In this cohort of initially undiagnosed subjects, a baseline presence of  
244 mild obstruction or reversibility, or a weather-dependent cough or shortness of breath, or a recurrent  
245 productive cough showed to be predictive for development of mild COPD (OR:1.87) or moderate  
246 COPD (OR:2.08) 5 years later. Furthermore, baseline mucus hypersecretion (in the absence of  
247 airflow obstruction without full reversibility) appeared to be predictive (OR: 1.88) for subsequent  
248 development of moderate COPD. A prolonged follow-up from early stage COPD onwards,  
249 followed by an undisputed clinical diagnosis, may further clarify these relations. In terms of health  
250 care, the identification of risk factors for early detection of COPD may contribute to the  
251 development of an evidence based model for case-finding. This is specifically of interest for the  
252 studied cohort, as these undiagnosed subjects did not present themselves in primary care.  
253 In conclusion, lung function below normal range and early respiratory signs are possible predictors  
254 for progression of COPD.. As a result, implementation of GOLD guidelines in general practice may  
255 reduce underdiagnosis and undertreatment.

256

### 257 **Acknowledgement**

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

## Tables and figures

- Table 1** Algorithm for the classification of chronic respiratory disease (based on the GOLD criteria).
- Table 2** Characteristics (*sd*) of the study population.
- Table 3** Obstruction and respiratory morbidity
- Table 4** Odds ratio's from multinomial regression analysis of early signs as predictors of respiratory morbidity five years later.
- Figure 1** Flow chart of the initial general population cohort in the DIMCA program, and the follow-up group reassessed at year five.
- Figure 2** The course of FEV<sub>1</sub> and FEV<sub>1</sub>/VC in early respiratory morbidity.
- Appendix Table 1** Screening criteria, used to determine the respiratory status of subjects.
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**Table 1**

Algorithm for the classification of chronic respiratory disease (based on the GOLD criteria<sup>21</sup>)

LUNG FUNCTION	RESPIRATORY SYMPTOMS <sup>§</sup>	REVERSIBILITY <sup>&amp;</sup>	DISEASE CLASSIFICATION
<b>NO OBSTRUCTION<sup>+</sup></b>		yes	ASTHMATIC
	no chronic symptoms	no	NO COPD or ASTHMA
	chronic symptoms	no	AT RISK FOR COPD (GOLD 0)
<b>OBSTRUCTION<sup>+</sup></b> and <b>FEV<sub>1</sub><sup>*</sup> ≥ 80%</b> or <b>50% ≤ FEV<sub>1</sub> &lt; 80%</b> or <b>30% ≤ FEV<sub>1</sub> &lt; 50%</b>		yes	INADEQUATELY MANAGED ASTHMA
		no	MILD COPD (GOLD I)
		no	MODERATE COPD (GOLD II)
		no	SEVERE COPD (GOLD III)

*Legend*

<sup>§</sup> chronic symptoms: cough and sputum production for at least 3 months in each of two consecutive years

<sup>&</sup> Reversibility: a 12% change of predicted FEV<sub>1</sub> after bronchodilatation with a change of at least 200 mL.

<sup>+</sup> Obstructive if FEV<sub>1</sub><sup>\*</sup>/VC<sup>#</sup> < 70%

<sup>\*</sup> postbronchodilator forced expiratory volume;

<sup>#</sup> 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 <sub>1</sub> * (ml)	3532	(833)	3335	(806)	3195	(795)	2938	(802)
FEV <sub>1</sub> / VC# (%)	84.5	(8.3)	79.3	(7.9)	81.3	(9.8)	73.0	(8.8)
<u>Screening criteria</u> <sup>1</sup>								
respiratory symptoms <sup>^</sup>	-		37.1		88.8		80.5	
lung function < normal range <sup>~</sup>	-		4.6		16.6		20.8	
reversibility <sup>§</sup>	-		0.7		2.9		2.9	
mild early signs <sup>@</sup>	-		9.3		31.6		32.6	
<u>Mucus hypersecretion</u> <sup>=</sup>	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<sub>1</sub> (at year 5: n=150, respectively n=299)

# vital capacity

<sup>^</sup> Dutch modified version of the MRC questionnaire

<sup>~</sup> FEV<sub>1</sub> / VC ≤ lower limit of normal

<sup>§</sup> ≥ 15% predicted

<sup>@</sup> 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)

<sup>=</sup> continuous production of sputum in the winter season

<sup>1</sup> 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	%	
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 <sup>&amp;</sup> AT YEAR 5 (N=374)			
	MILD COPD (12.8%)		MODERATE COPD (10.4%)	
	OR	ADJ. OR	OR	ADJ. OR
Screening criteria <sup>1</sup>				
- respiratory symptoms <sup>^</sup>	1.30 [0.92-1.83] <sup>1</sup>	1.41 0.98-2.01]	0.96 [0.66-1.42]	0.94 [0.61-1.43]
- lung function below normal range <sup>~</sup>	1.45 [0.74-2.86]	1.46 [0.72-2.96]	<b>2.02</b> [1.07-3.83]	<b>2.54</b> [1.25-5.19]
- reversibility <sup>§</sup>	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 <sup>@</sup>	<b>1.69</b> [1.13-2.54]	<b>1.87</b> [1.22-2.87]	<b>1.97</b> [1.28-3.02]	<b>2.08</b> [1.29-3.37]
Mucus hypersecretion <sup>=</sup>	1.35 [0.77-2.36]	1.17 [0.64-2.14]	<b>2.53</b> [1.52-4.19]	<b>1.88</b> [1.07-3.33]
Smoking behaviour				
- packyears (baseline)		0.99 [0.95-1.02]		<b>1.05</b> [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]		<b>1.06</b> [1.01-1.10]
Gender (female=1)		<b>0.54</b> [0.38-0.76]		1.13 [0.73-1.73]

**Legend:**

<sup>&</sup> mild COPD (N=48), moderate COPD (n=39)

<sup>^</sup> Dutch modified version of the MRC questionnaire

<sup>~</sup> FEV<sub>1</sub> / VC ≤ lower limit of normal

<sup>§</sup> ≥ 15% predicted

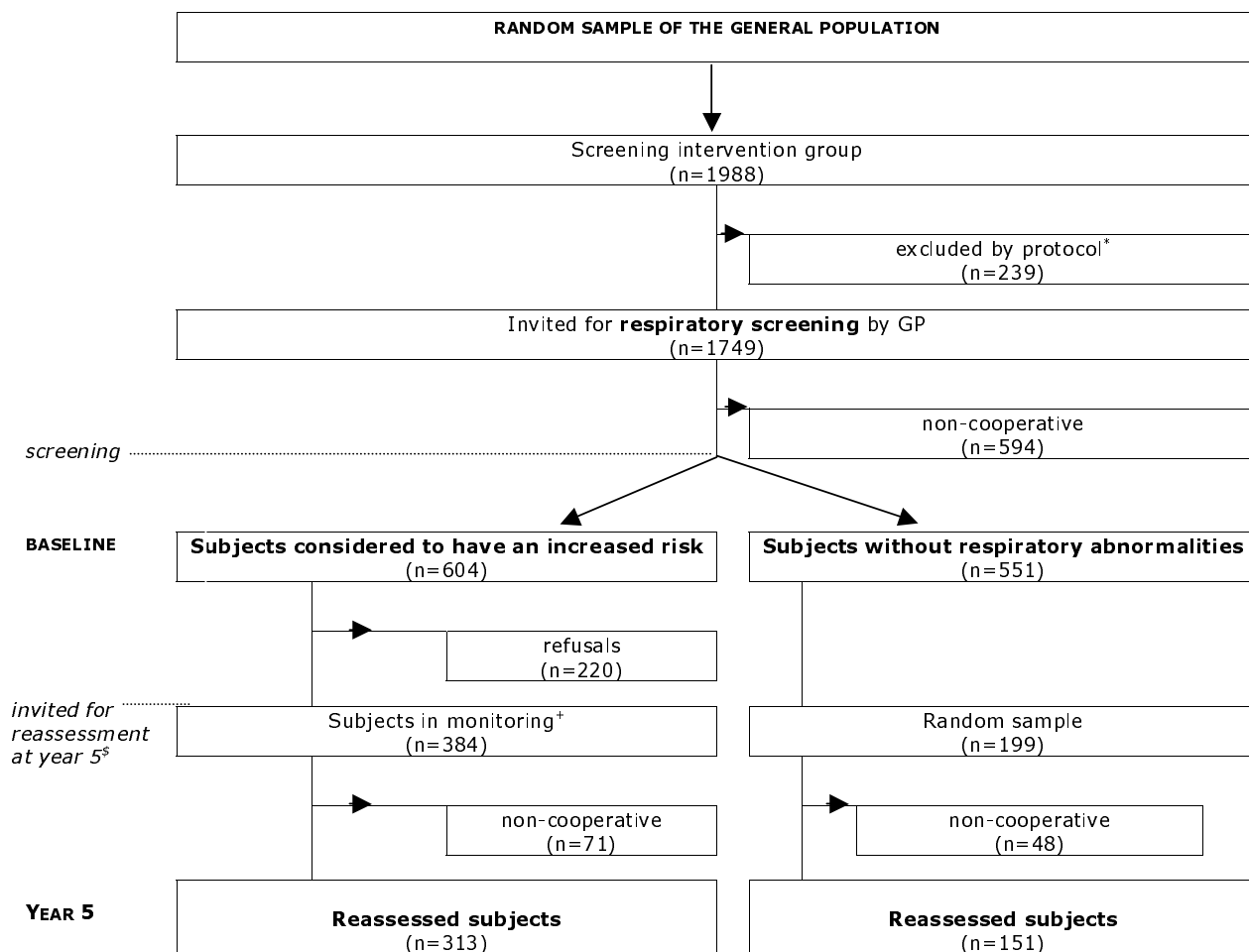
<sup>@</sup> combination of at least two out of three mild early signs (mild obstruction, reversibility, weather-dependent or recurrent productive cough)

<sup>=</sup> continue production of sputum in winter

<sup>1</sup> [95% confidence intervals]

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

**Figure 1:** Flow chart

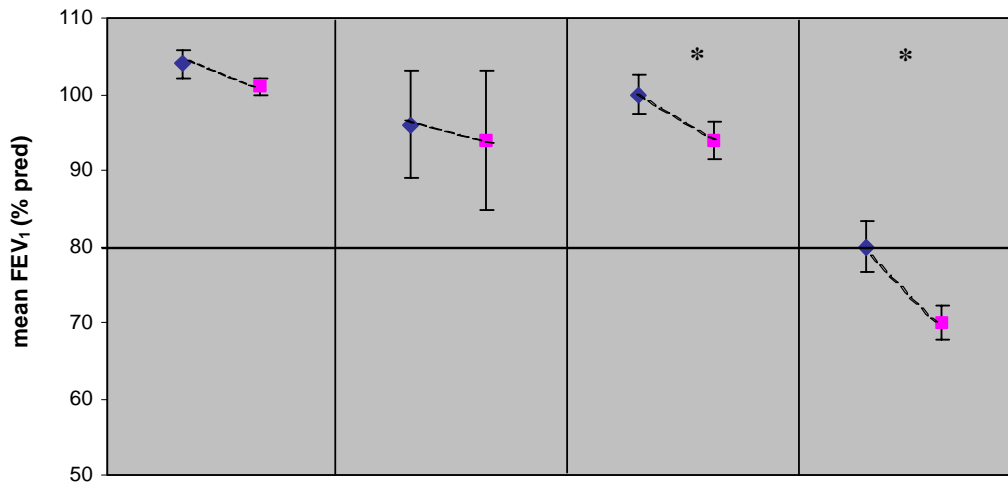


**Legend:**

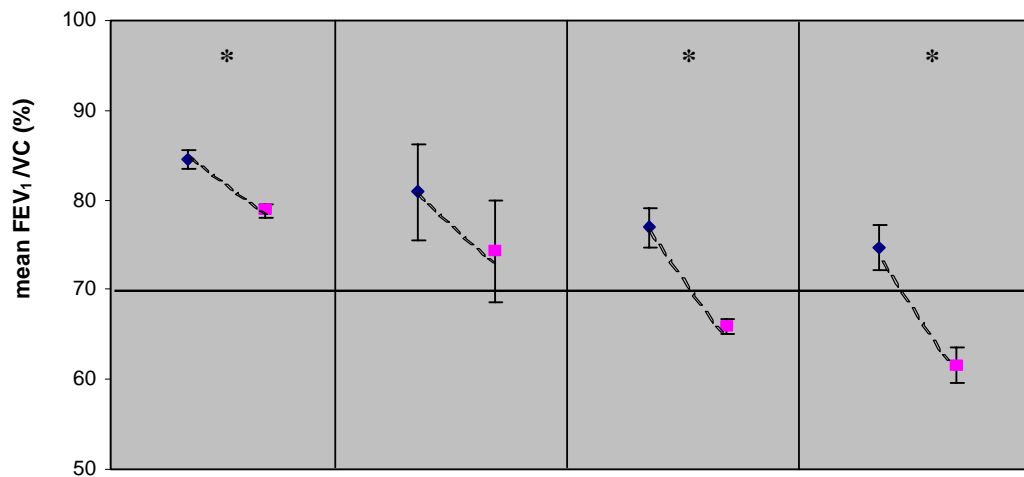
- \* 12% (n=239) was excluded because respiratory disease had already been diagnosed by the GP
- \$ At year five the follow-up cohort was reduced, envisaging 400 subjects in the at-risk group, and 200 subjects in the group without respiratory abnormalities
- + a total number of 145 at-risk subjects participated in one of the randomized controlled trials<sup>18; 20; 39</sup>

**Figure 2: The course of FEV<sub>1</sub> and FEV<sub>1</sub>/VC in early respiratory morbidity**

**Postbronchodilator FEV<sub>1</sub> (95% CI)**



**Postbronchodilator FEV<sub>1</sub>/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 ( $\geq 3$ 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)	$FEV_1 / VC \leq$ predicted value minus 1SD and/or
mild early signs	$FEV_1$ 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 <sub>1</sub> <sup>#</sup> (mL)	Packyear (No.)	Smoking status (% ever smokers)
<b>AT-RISK SUBJECTS</b>						
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
<b>SUBJECTS WITHOUT ABNORMALITIES</b>						
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:

<sup>#</sup> 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<sub>1</sub> 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<sub>1</sub> (p=0.09) or postbronchodilator FEV<sub>1</sub>/VC (p=0.96) from placebo treatment. As a consequence, participants of the intervention study were included in the sample.

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