

## ORIGINAL ARTICLE

## Risk of depression in patients with chronic obstructive pulmonary disease and its determinants

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**Background:** Although it has been repeatedly suggested that chronic obstructive pulmonary disease (COPD) is associated with depression, no conclusion has so far been reached. A study was undertaken to investigate whether depression occurs more often in patients with COPD than in controls. The demographic and clinical variables associated with depression were also determined.

**Methods:** Patients with a registered diagnosis of obstructive airway disease in general practice, aged  $\geq 40$  years, forced expiratory volume in 1 second ( $FEV_1$ )  $< 80\%$  predicted,  $FEV_1$  reversibility  $\leq 12\%$ ,  $FEV_1/VC \leq$  predicted  $- 1.64 \times SD$ , and a history of smoking were selected. A random sample of subjects without a registered diagnosis of asthma or COPD aged 40 years or older acted as controls. Depression was assessed using the Centers for Epidemiologic Studies Depression (CES-D) scale.

**Results:** In patients with severe COPD ( $FEV_1 < 50\%$  predicted), the prevalence of depression was 25.0% compared with 17.5% in controls and 19.6% in patients with mild to moderate COPD. When the results were adjusted for demographic variables and comorbidity, the risk for depression was 2.5 times greater for patients with severe COPD than for controls (OR 2.5, 95% CI 1.2 to 5.4). In patients with mild to moderate COPD this increased risk of depression was not seen. Living alone, reversibility of  $FEV_1$  % predicted, respiratory symptoms and physical impairment were significantly associated with the scores on the CES-D scale.

**Conclusion:** Patients with severe COPD are at increased risk of developing depression. The results of this study underscore the importance of reducing symptoms and improving physical functioning in patients with COPD.

Due to the irreversible nature of chronic obstructive pulmonary disease (COPD), the aim of treatment in patients with COPD is not to cure but to reduce symptoms, increase functioning, and improve the patients' quality of life.<sup>1</sup> It has long been suggested that depression is a common emotional disturbance in patients with COPD who are faced with major physical impairment and embarrassing symptoms such as dyspnoea and productive cough. The presence of depression obviously impairs the quality of life, as it may have an effect on emotional, social, as well as physical functioning. However, although some studies have found increased levels of depression in patients with COPD,<sup>2-4</sup> others have not.<sup>5,6</sup> In a recent review on the presence of depression in patients with COPD, it was concluded that no final conclusion could be drawn on the association between COPD and depression since the designs of the studies had major drawbacks, such as the absence of a control group and small sample sizes.<sup>7</sup> The present study uses a large number of patients and a control group to investigate whether depression occurs more often in patients with mild to moderate COPD and those with severe COPD than in controls, and the aspects of COPD particularly related to depression.

## METHODS

## Selection of patients

COPD was defined as a ratio of forced expiratory volume in 1 second to vital capacity ( $FEV_1/VC$ ) before and after inhalation of 400  $\mu g$  salbutamol below the reference ratio minus  $1.64 \times$  standard deviation,  $FEV_1 < 80\%$  predicted, reversibility in  $FEV_1 \leq 12\%$  of predicted  $FEV_1$ , and a history of smoking. These patients were selected from 28 general practices from urban and suburban regions in the western part of the Netherlands in three consecutive steps. (1) Since spirometric tests are not always performed to differentiate between COPD and asthma

in general practice, misclassification of COPD patients can occur, especially in the elderly in whom there is an important overlap between the two entities. All patients registered with a diagnosis of asthma or COPD in their general practice who were aged at least 40 years were therefore selected from the patient lists in each practice. (2) The general practitioners (GPs) were asked to exclude patients who met the following criteria: poor cognitive functioning ( $n=47$ ), a poor mastering of the Dutch language ( $n=46$ ), and presence of an end stage disease ( $n=33$ ). (3) All eligible subjects ( $n=1106$ ) who were willing to participate underwent a lung function test to confirm a diagnosis of COPD and filled in a questionnaire between December 1996 and October 1999 ( $n=659$ , response 60%). Patients who met the criteria for COPD were included ( $n=163$ ). One patient was excluded because of missing data on more than half of the items of the measure for depression. Lung function data and questionnaire data were obtained on the same day.

The study was approved by the medical ethics committee of the Academic Medical Center, University of Amsterdam.

## Selection of controls

A random sample of 676 subjects was taken from 13 general practices who were not diagnosed by the GP as having asthma or COPD and who were aged 40 years or older. These 13 practices were part of and represented the 28 practices from which the patients were selected. Since all Dutch inhabitants have to be registered with a GP, the sample can be considered representative of the general population. An age stratified sample was taken with 178 controls aged 40-60 years and 498 aged 60 years or older. The GPs were asked to exclude persons with poor cognitive functioning ( $n=26$ ), a poor mastering of the Dutch language ( $n=7$ ), or with an end stage disease ( $n=1$ ). All eligible controls ( $n=642$ ) who were willing to participate filled in a questionnaire between April and July 1998

**Table 1** General characteristics of patients and controls

	COPD patients (FEV <sub>1</sub> <50%) (n=60)	COPD patients (FEV <sub>1</sub> 50–80%) (n=102)	Controls (n=359)
Male sex	44 (73.3%)	72 (70.6%)	145 (40.4%)
Low education	52 (88.1%)	85 (85.0%)	274 (80.1%)
Living alone	10 (16.7%)	30 (29.4%)	92 (25.8%)
NHS insurance	45 (75.0%)	77 (76.2%)	246 (68.5%)
Comorbidity	36 (65.5%)	66 (71.0%)	179 (57.0%)
Mean (SD) age (years)	67.8 (8.7)	66.2 (10.3)	65.6 (12.8)
Mean (SD) reversibility FEV <sub>1</sub> (%)	4.2 (4.1)	5.6 (3.9)	–

NHS=National Health Service.

(n=445, response 69%). In addition, all controls with missing data on more than half of the items of the measure for depression were excluded (n=62) as well as controls with self-reported obstructive pulmonary disease (n=24).

### Measurement of depression

The Centers for Epidemiologic Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. Those with a score of 16 or higher on the CES-D were considered possible cases for depression. The CES-D is validated and widely used in epidemiological studies as an indicator for clinical depression in populations.<sup>8</sup> In case less than half of the items on the CES-D were incomplete, missing data were replaced by the mean scores of the valid data of each participant.

### Other research variables

Lung function impairment was assessed by spirometric tests before and after inhalation of 400 µg salbutamol using a pneumotachograph (MasterScope, Jaeger, Germany) according to the European Respiratory Society guidelines for measurement<sup>9</sup> and carried out by trained personnel. FEV<sub>1</sub> was dichotomised into values lower than 50% of the predicted value (severe airway obstruction) and those of 50% of the predicted value or higher (moderate to mild airway obstruction).<sup>10</sup>

To determine the presence of comorbid diseases, all participants were asked to complete a questionnaire on chronic diseases. This questionnaire was developed by Statistics Netherlands and is broadly used in demographic studies in the Netherlands.<sup>11</sup> Diseases included in the questionnaire have a prevalence of more than 2% in the general population and are long lasting by nature. The diseases were described in a way that was easy for patients to understand—for example, “high blood pressure” was used instead of “hypertension”. The following diseases were listed: locomotive diseases (rheumatoid arthritis, arthrosis, slipped disc, disorder of the back for >3 months), hypertension, serious heart diseases or myocardial infarction, sinusitis, migraine, dizziness with falling, ulcer stomach/duodenum, cancer, atherosclerosis, thyroid diseases, diabetes, serious intestinal diseases for >3 months, serious skin diseases, gall bladder diseases, stroke, chronic cystitis, kidney stones, thrombosis, epilepsy, liver diseases, and renal diseases.

In addition, information on the following variables was obtained by questionnaire: sex, age, highest form of education received (low level: primary school, lower vocational training, school for lower general secondary education; high level: pre-university education, high vocational training or university).

Symptoms and physical functioning were assessed using the symptoms and activity components of the St George's Respiratory Questionnaire (SGRQ).<sup>12</sup> The symptoms component is concerned with the frequency and severity of respiratory symptoms, and the activity component is concerned with activities that are limited by breathlessness.

### Analysis of data

The prevalence of depression was determined by calculating the percentage of patients and controls with a score of 16 or

higher on the CES-D. To determine whether the prevalence of depression was higher in patients than in controls, logistic regression analyses were performed in which the results were adjusted for demographic variables and comorbidity. In this model the dependent variable was the score on the CES-D (16 or higher/lower than 16) and the independent variable was the research group (patient/control). Age, sex, education, type of insurance, living conditions, and comorbidity were included as covariates. The relationship between demographic and clinical variables and depression in patients with COPD was assessed by performing logistic regression analyses with the score on the CES-D as dependent variable (16 or higher/lower than 16) and with all demographical variables, comorbidity and COPD related variables (FEV<sub>1</sub>, reversibility of FEV<sub>1</sub>, respiratory symptoms, physical functioning) as independent variables. For these analyses the continuous variables “reversibility of FEV<sub>1</sub> % predicted”, “symptoms”, and “physical functioning” were dichotomised according to the mean ±1 SD. All analyses were carried out using SPSS 8.0.2 for Windows.

## RESULTS

### General characteristics

A total of 162 patients with COPD and 359 controls were included in the study. Their characteristics are shown in table 1. Sixty of the patients had an FEV<sub>1</sub> <50% of the predicted value (37.0%) and thus suffered from severe airway obstruction; 102 patients had an FEV<sub>1</sub> 50–80% of the predicted value (63.0%). In both patient groups the majority were men (73.3%, 70.6%), had a low level of education (88.1%, 85.0%), and had other chronic diseases (65.5%, 71.0%). Fewer of the controls were men (40.4%), had a low level of education (80.1%), or had chronic diseases (57.0%). The mean age of controls (65.6 years) was comparable to that of patients (67.8, 66.2 years).

### Prevalence of depression

In table 2 the results are presented on the prevalence of depression in patients with COPD and in controls. In the COPD patients as a whole, 21.6% had a score of 16 or more on the CES-D scale compared with 25.0% of patients with severe COPD (FEV<sub>1</sub> <50%), 19.6% of those with mild to moderate COPD (FEV<sub>1</sub> 50–80%), and 17.5% of the controls. As demographic variables and comorbidity were thought to be important prognostic variables which could confound the differences in the prevalence of depression between patients and controls, the results were adjusted for these variables. In the multivariate analysis there appeared to be no risk for depression in the total group of COPD patients (OR 1.5, 95% CI 0.8 to 2.6) or in the subgroup of patients with mild to moderate COPD (OR 1.1, 95% CI 0.5 to 2.1), but patients with severe COPD had a 2.5 times greater risk for depression than controls (OR 2.5, 95% CI 1.2 to 5.4).

### Determinants of depression

The prevalence of depression was also calculated in several subgroups of COPD patients (table 3). In these subgroups the

**Table 2** Prevalence of depression in patients with COPD compared with controls

	n	CES-D $\geq 16$	Adjusted OR (95% CI)
COPD (whole group)	162	35 (21.6%)	1.5 (0.8 to 2.6)
Severe COPD (FEV <sub>1</sub> <50% predicted)	60	15 (25.0%)	2.5 (1.2 to 5.4)
Mild to moderate COPD (FEV <sub>1</sub> 50–80% predicted)	102	20 (19.6%)	1.1 (0.5 to 2.1)
Controls	359	63 (17.5%)	1.0

CES-D=Centers for Epidemiologic Studies Depression scale.

Univariate results and results adjusted for sex, age, education, health insurance, living situation, and comorbidity (logistic regression analysis).

**Table 3** Relationship between demographic and disease-related variables and depression (CES-D) in patients with COPD (n=162): prevalence in subgroups and logistic regression analysis

	n	CES-D $\geq 16$	Crude OR (95% CI)	Adjusted OR† (95% CI)
$\geq 65$ years	99	17 (17.2%)	0.5 (0.2 to 1.1)	0.7 (0.2 to 1.9)
<65 years	63	18 (28.6%)	1.0	1.0
Men	116	21 (18.1%)	0.5 (0.2 to 1.1)	0.8 (0.3 to 2.2)
Women	46	14 (30.4%)	1.0	1.0
NHS insurance	122	28 (23.0%)	1.4 (0.5 to 3.4)	1.3 (0.4 to 4.4)
Private insurance	39	7 (17.9%)	1.0	1.0
Low education	137	29 (21.2%)	0.9 (0.3 to 2.7)	0.8 (0.2 to 3.0)
High education	22	5 (22.7%)	1.0	1.0
Living alone	40	15 (37.5%)*	3.1 (1.4 to 6.8)	2.8 (1.0 to 7.8)
Living with others	122	20 (16.4%)	1.0	1.0
Presence comorbidity	102	25 (24.5%)	1.8 (0.7 to 4.5)	2.4 (0.7 to 8.1)
Absence comorbidity	46	7 (15.2%)	1.0	1.0
FEV <sub>1</sub> <50% predicted	60	15 (25.0%)	1.4 (0.6 to 2.9)	0.8 (0.3 to 2.5)
FEV <sub>1</sub> $\geq 50\%$ predicted	102	20 (19.6%)	1.0	1.0
Reversibility $\leq 1.1\%$	29	13 (44.8%)*	4.1 (1.7 to 9.7)	3.7 (1.3 to 11.0)
Reversibility 1.1–12%	133	22 (16.5%)	1.0	1.0
Severe symptoms‡	33	13 (39.4%)*	3.2 (1.4 to 7.3)	2.8 (0.9 to 8.6)
Mild to moderate symptoms	129	22 (17.1%)	1.0	1.0
Severe impaired physical function§	20	10 (50.0%)*	4.7 (1.8 to 12.4)	5.6 (1.6 to 19.9)
Mild to moderate impaired physical function	142	25 (17.6%)	1.0	1.0

\*p<0.01 ( $\chi^2$  test).

†Adjusted for all other variables.

‡Score = 71.98 on symptoms dimension SGRQ (mean + 1 SD).

§Score = 68.69 on activities dimension SGRQ (mean + 1 SD).

prevalence of depression ranged from 15.2% (absence of comorbidity) to 50.0% (severe impaired physical functioning). Depression also occurred often in patients with a reversibility in FEV<sub>1</sub> of  $\leq 1.1\%$  (44.8%), in patients with a score on the symptoms dimension of the SGRQ of  $\leq 71.98$  (39.4%), and in patients who lived alone (37.5%).

Furthermore, with logistic regression analysis the adjusted odds ratio for the independent influence of each demographic and clinical variable on the CES-D was calculated (table 3). It appeared that the risk of depression was significantly increased in patients who lived alone (OR 2.8, 95% CI 1.0 to 7.8), in patients with a reversibility in FEV<sub>1</sub> of  $\leq 1.1\%$  predicted (OR 3.7, 95% CI 1.3 to 11.0), and in patients with COPD with severe impaired physical functioning (OR 5.6, 95% CI 1.6 to 19.9).

## DISCUSSION

In this study we found that the prevalence of depression in COPD patients with severe airways obstruction (FEV<sub>1</sub> <50%) was 25% and that they had a 2.5 times greater risk of depression

than controls who were comparable for demographic variables and the presence of comorbidity. In patients with mild to moderate COPD no increased risk for depression was seen. We also found that living alone, reversibility in FEV<sub>1</sub> % predicted, respiratory symptoms, and physical impairment were related to depression in patients with COPD, whereas age, sex, insurance type, education, FEV<sub>1</sub>, and comorbidity were not.

The CES-D scale which we used as a measure for depression is not designed to determine the presence of clinical depression, but rather the presence of depressive symptoms.<sup>8</sup> Patients with a score of 16 or higher are considered possible cases. The percentage of patients with actual clinical depression may thus have been lower than was found in this study. Nevertheless, patients with a score of 16 or higher do suffer from many depressive symptoms and, for this reason, these patients should be considered for further evaluation or monitoring in clinical practice. Furthermore, an overestimation of actual cases of depression does not influence the estimated risk of depression in patients with COPD as overestimation will be the same in patients and in controls.

Some participants, particularly controls, were excluded because of missing data on the CES-D. As all participants also answered questions on the SF-36 questionnaire, we were able to investigate whether controls with missing data on the CES-D differed from those without missing data with respect to mental health and the mental summary score of the SF-36. It appeared that the mean scores of mental health and the mental summary score for controls with missing data (mean (SD) 52.0 (9.2) and 75.7 (16.0)) were very similar to the mean scores of these dimensions for controls without missing data (51.7 (9.5) and 75.9 (17.4)). This suggests that exclusion of controls with missing data on the CES-D scale will not have influenced the proportion of controls with depressive symptoms in our study.

In subjects with missing data on 10 items or less of the 20 items of the CES-D, the missing data were replaced by the mean values of the valid data. Although this could be considered a rather high cut off point, only a few of these subjects had 5–10 missing items (14 out of 88). Furthermore, when subjects with five or more missing items were excluded, the results did not differ from those obtained when subjects with 10 or more missing items were excluded.

Two items on the CES-D scale may not only indicate a depressive symptom but may also be symptoms of COPD. These items are “I did not feel like eating, my appetite was poor” and “My sleep was restless”. However, when removing the possible effect of COPD on the CES-D score by excluding these two items, an increased risk of depression was still found in patients with severe COPD (OR changed from 2.5 to 2.1). Since these items are not necessarily symptoms of COPD alone and may still be symptoms of depression, at least in some of the patients who suffered from these symptoms, the actual risk estimate of depression in patients with severe COPD would be somewhere between 2.1 and 2.5.

In previous studies the prevalence of depression in patients with COPD ranged from 6% to 46%.<sup>2–6 13–18</sup> This variation in prevalence can be partly attributed to the use of different measures for depression. In the one study that also used the CES-D scale, a prevalence of depression of 29% was found.<sup>13</sup> The reason why depression occurred more often in this study than in our study may be that it included patients with more severe airways obstruction who were eligible for a rehabilitation programme. As disease and demographic characteristics of the patient population included in the study also influence the extent to which depression occurs, the prevalence of depression in patients with COPD does not exist. It is therefore difficult to compare prevalence rates from studies that included different populations.

Since previous studies suffered from several methodological problems such as small sample sizes and the absence of proper control groups, it remained inconclusive whether patients with COPD were more at risk than controls for the development of depression.<sup>7</sup> Furthermore, many studies only included patients with a restricted range of pulmonary function. The results of these studies are only valid for specific patients—for example, those receiving oxygen therapy<sup>2</sup> or with an exacerbation.<sup>18</sup> Another reason for conflicting results between studies is that, in several studies, patients and controls were not comparable with respect to important prognostic factors. In some studies patients and control subjects were only matched on age and sex,<sup>4–6</sup> while other studies also matched on education and social class.<sup>2,3</sup> Furthermore, in some studies patients with comorbidity were excluded<sup>5 16 18</sup> while in others these patients were included.<sup>2 4 6</sup>

Our study did not suffer from these methodological problems as we were able to include a large sample of COPD patients with a broad range of severity of disease and a large number of controls. We were able to adjust our results for a variety of prognostic factors, thereby making patients and controls comparable for demographic variables and comorbidity. We were able to show that COPD was associated with

depression, but that the risk of depression was only increased in patients with severe airways obstruction. Furthermore, as we adjusted our results for the presence of chronic disease, it became clear that comorbidity, which frequently occurs in patients with COPD, is not responsible for the increased risk of depression in these patients.

When we investigated whether demographic and disease related variables were independently associated with depression in patients with COPD, it appeared that living alone, reversibility in FEV<sub>1</sub> % predicted, respiratory symptoms, and physical impairment were related to depression. This suggests that these factors may affect patients in such a way that they become depressed. The perceived severity of the disease thus seems at least as important as the clinically assessed severity of disease for the development of depression. This also suggests that, in preventing depression in COPD patients, it may be important to focus on decreasing symptoms and improving functioning by, for example, medical treatment or rehabilitation programmes. Nevertheless, other factors such as coping must also be responsible as they do not completely determine the presence of depression.

Although there was a trend for an association, FEV<sub>1</sub> was not significantly related to the CES-D score in patients with COPD. Patients with severe COPD had an increased risk of depression compared with controls, while those with mild to moderate COPD were not at an increased risk. This could be explained by the fact that pulmonary function is a predictor for depression, but not a very strong predictor. Its influence may only become apparent when subjects with the greatest difference in pulmonary function are compared—that is, COPD patients with severe airways obstruction and controls with no obstructive airways disease. This implies that this commonly used clinical characteristic is still an important first indicator for the presence of depressive symptoms.

In conclusion, depressive symptoms are common in patients with COPD and those with severe COPD have a 2.5 times greater risk of developing depression than controls. As depression is a disorder which remains easily undiagnosed due to underpresentation and because the symptoms are not very specific, it is important to consider this disorder in patients with COPD. Our findings underscore the importance of reducing symptoms and improving physical functioning in patients with COPD rather than focusing on pulmonary function alone.

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