Depression is associated with poor prognosis in patients with chronic obstructive pulmonary disease – a systematic review

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ABSTRACT

INTRODUCTION: Patients with depression have significantly increased mortality from somatic disease. The purpose of this article was to review studies that investigate if there is a prognostic association with depression as co-morbidity in patients with chronic obstructive pulmonary disease (COPD). We chose the following outcomes: mortality, suicide behaviour, risk of COPD exacerbation, use of primary care and prescription data.

METHODS: A literature review was performed on 16 December 2014 in PubMed, Embase, OVID Medline and Cochrane for cohort studies. Only studies with mortality and exacerbation/hospital admissions were found. Studies failing to meet relevant criteria in terms of design or/and outcome, and studies with significant methodological faults were excluded.

RESULTS: A total of 22 cohort studies were included. Of these studies, 20 were prospective, one retrospective and one was a combined retro- and prospective study. There was a tendency for studies with more patients and higher methodological quality to show a positive correlation. Sixteen of the studies showed that depression was associated with increased mortality (relative risk (RR): 1.02-3.6) and more COPD exacerbations (RR: 1.3-7.0).

CONCLUSIONS: The results showed that not only is depression a debilitating disease on its own, it also predisposes to COPD exacerbations and increased mortality in patients with COPD. Depression in patients with COPD is underdiagnosed and undertreated, and a stronger focus on the clinical significance of depression as co-morbidity is warranted.

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a condition characterised by airway obstruction that is not fully reversible. The airway obstruction is progressive and associated with an abnormal inflammatory response to obnoxious particles or gasses [1]. Co-morbidity in COPD patients is more a rule than an exception [2], and it poses a substantial risk for mortality, increased frequency of exacerbations and poorer quality of life. In Denmark, 85-90% of COPD cases are caused by smoking [3]. In a Danish cohort followed through 25 years, the absolute risk for developing COPD was 25%, while subclinical COPD was found in 30-40% [4].

A number of studies have investigated how various somatic co-morbidities affect COPD patients' prognoses. In a meta-analysis by Smith et al in 2014, ten of the most common co-morbidities were analysed. The 3 co-morbidities leading to the highest total mortality were lung cancer, cirrhosis and diabetes, with respective hazard ratios of 2.02, 1.68 and 1.54-1.7 [2]. These co-morbidities also proved to have a considerable impact on the number of exacerbations and on quality of life.

Depression is highly prevalent in patients with COPD, even when compared with other chronic diseases such as stroke and cancer [5]. Patients with depression show a high mortality rate for somatic disease. This has been studied extensively in various medical fields, particularly in cardiology. One investigation found that severe depression increases is associated with a three-fold increased relative risk of mortality due to cardiac causes [6]. In a meta-analysis investigating mortality in patients with COPD, a relative risk for mortality of 1.8 was found in patients with depression as co-morbidity [7]. Similar results have been replicated in several studies [8, 9]. It is worth noticing that only 30-40% of the increased mortality is due to suicide.

The prevalence of depression among patients with COPD has been estimated to be between 8% and 80% [2, 10-15]. This significant variation reflects differences in study populations, diagnostic classification systems, and whether questionnaires or clinical interviews were used. Despite the significant prevalence, depression – especially in its milder forms – is possibly under-diagnosed. In an American cross-sectional study from 2005 of 1,334 patients with COPD, only 31% of the patients with depression as co-morbidity and/or anxiety received antidepressive treatment [16]. Studies investigating risk factors for depression in patients with COPD show diverging results. In an Argentinean cohort, Lopez Jove et al found female gender (odds ratio (OR) = 4.14) and dyspnoea (OR = 4.48) to be risk factors, while physical activity (OR = 0.29) was protective. No significant association was found between the severity of COPD and

SYSTEMATIC REVIEW

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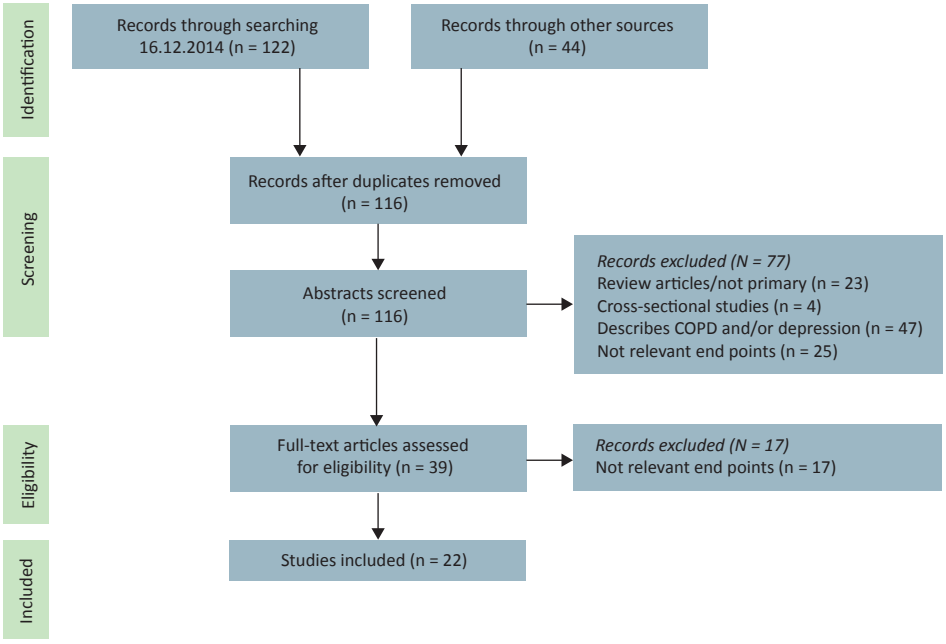
FIGURE 1

PRISMA flow diagram [24].

COPD = chronic obstructive pulmonary disease.



smoking status [17]. Funk et al found the prevalence of depressive symptoms to be increased with both increasing GOLD and The Burden of Obstructive Lung Disease (BOLD) stages [18].

COPD exacerbations are important causes of the significant morbidity and mortality associated with COPD, and exacerbations have been proven to accelerate the progression of COPD [19]. COPD exacerbations are defined by GOLD as an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations; it is acute in onset; and it may warrant a change in regular medication [1]. The frequency of exacerbations is one of the most important determinants for health-related quality of life in COPD patients [20].

KEY POINTS

Patients with depression have a significantly increased mortality from somatic disease, this has been documented in several studies in the field of cardiology.

Depression is very prevalent among patients with chronic obstructive pulmonary disease, even when comparing with other chronic diseases, such as stroke and cancer.

The majority of the studies included showed a positive correlation between co-morbid depression and risk of exacerbation and mortality in patients with chronic obstructive pulmonary disease.

The results reinforce the notion that not only is depression a debilitating disease on its own, but it also increases the morbidity and mortality in patients with chronic obstructive pulmonary disease.

COPD exacerbations are more common than previously presumed. In a prospective cohort study, Seemungal et al found that on average patients with COPD had 2.5-3 exacerbations annually. 50% of the cases were not reported to the researchers, but were discovered by looking through the patients' symptoms diary [20]. The international epidemiologic studies of COPD are characterised by a large variation in prevalence and mortality.

The BOLD initiative conducted an international multi-centre study in which the total prevalence of COPD was found to be 10.1% for stage two or higher COPD. If stage one had been included, the prevalence would have approached 20% [21]. Another large international meta-analysis reported the COPD prevalence to be between 0.2% and 37% [22]. The large variation clearly expresses differences in the diagnostic approach, classification methods and population characteristics. Mortality was found to be 3-111/100,000. This reflects differences in length of patient follow-up, which sequelae were registered for COPD, and differences between patients, for instance in terms of GOLD stage. A Scandinavian retrospective register study found that patients with COPD had a reduction of life expectancy of 8.3 ± 6.8 years [23].

METHODS

Search strategy

The article is based on a review of cohort studies and other review articles. The searches were conducted on

the 16 December 2014. The search was first done at PubMed with the MeSH terms "pulmonary disease, chronic obstructive" AND "prognosis" AND "depression". The same search was repeated in OVID Medline, Cochrane and Embase. Other search words used in various combinations were *COPD, mortality, hospital admission, hospital readmission, exacerbation, health-care use, suicide, depressive disorder primary care* and *drug prescriptions*. Linguistic and methodological limitations were not applied in the searches. For relevant articles, abstracts were reviewed and the articles obtained. Literature references in the chosen studies as well as general review or status articles for COPD were also used to find relevant studies, although this ended up primarily being duplicates, which were removed when the studies were reviewed together.

Study selection

The searches resulted in 136 abstracts, which were reduced to 39 articles after being reviewed (**Figure 1**). The following inclusion criteria were chosen: studies highlighting the prognostic significance of co-morbid depression in patients with COPD in terms of mortality, hospital admission/exacerbations, use of primary care, use of pharmaceuticals and suicide risk; retro- and prospective cohort studies; and studies which used a validated depression scale or structured diagnostic interviews.

Depression was defined as either a depressive episode, a recurrent depressive disorder, or elevated depressive symptoms. Studies deviating in outcomes, study design and studies with significant methodological faults were excluded. We only found studies with mortality and exacerbation/hospital admissions as outcomes.

Of the 39 articles, only 22 met the inclusion criteria: 20 of these studies were prospective cohort studies, one was a retrospective, and one was a combined retrospective and prospective cohort study.

Methodological quality assessment

The studies were reviewed using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies [24]. The checklist consists of 12 points, but since several of these are general and were fulfilled by all the studies, and several of them overlap, we chose the six with largest methodological discriminatory potential, and the ones which could more easily be presented schematically. The included studies were thus assessed by the following six methodological quality criteria: 1) number of patients in the cohort (ideally 30 or more patients per group); 2) generalisability of the cohort (whether the population had specific inclusion or exclusion criteria reducing its external validity); 3) whether 20% or more of the patients were lost during the course of the study; 4) whether the studies controlled for three or more of the following confounders: age, sex, smoking status, co-morbidities and forced expiratory volume in the first second (FEV1); 5) whether clinical outcomes were scored adequately (by a central mortality registry, hospital registry or through an interview with a person who was blinded to the depression status); 6) whether depression was diagnosed through interview or was self-reported. The overview is presented in **Table 1**.

COPD was diagnosed clinically and spirometrically in all the studies except from that of Dalal et al [25] where patients were identified by earlier prescription of at least one medication against COPD, and afterwards verified by checking that the patient had at least one COPD-related International Classification of Diseases (ICD), version nine (ICD-9) diagnosis. Everyone stated that validated depression diagnostic instruments had been used, but there was a consistent lack of depression diagnostic instruments specifically validated to patients with COPD.

Data analysis

The studies presented great heterogeneity in relation to demographics, severity of COPD, whether the condition was stable or characterised by many exacerbations, follow-up and with regard to how depression or depressive traits were diagnosed. For this reason, we have chosen not to summarise the results statistically.

RESULTS

All studies are listed in **Table 2** and **Table 3** which includes an overview of the various study designs and results. The 22 included studies followed between 46 and 26,591 patients (average: 2,120). The cohorts were followed for 2.3 years (range: four weeks to 8.7 years).

Does our attitude as health-care workers contribute to the development of depression in patients with chronic obstructive pulmonary disease?

TABLE 1

Methodologic evaluation of the included studies.

Reference	Generalizability of cohorts	Controlled co-variables
Abrams et al, 2011, USA [26]	War veterans, 97% men, multiple co-morbidities, patients without "acute care status" were excluded	Age, gender, race, smoking status, "illness severity", laboratory values (Na, albumin, urea, haematocrit, leukocytes, arterial $PaCO_2$), ventilatory support treatment, where the patient is admitted from smoking status, age, gender, education level, marital status co-morbidities, exposure to coal or biomass, BODE index
Lou et al, 2014, China [27]	No unusual inclusion or exclusion criteria	Age, gender, race, smoking status, "illness severity", laboratory values (Na, Albumin, urea, haematocrit, leukocytes, arterial $PaCO_2$), ventilatory support treatment, where the patient is admitted from smoking status, age, gender, education level, marital status co-morbidities, exposure to coal or biomass, BODE index
Fan et al, 2007, USA [28]	Emphysema, FEV1/FVC ≤ 0.45, done 6-10 weeks of pulmonary rehabilitation before start of study	Age, gender, lung function/capacity, BODE index, co-morbidities, antidepressants
Ng et al, 2007, Singapore [29]	Only current or former smokers	Age, gender, marital status, length of hospital stay, BMI, FEV1/FVC, PaO_2, $PaCO_2$, duration of COPD, dyspnoea, smoking status, previous readmissions, SGRQ, socioeconomic variables
Gudmundsson et al, 2012, Scandinavia [30]	No unusual inclusion or exclusion criteria	Age, gender, FEV1, health status, smoking status, co-morbidities, treatment, pharmacological treatment
Yohannes et al, 2002, England [31]	Only ≥ 60 yrs and symptomatic disabling COPD	MRADL score, pre-bronchodilator FEV1, BMI, long-term oxygen therapy, age, smoking status
Almagro, 2002, Spain [32]	No unusual inclusion or exclusion criteria	Age, gender, FEV1, functional status, pharmaceuticals, dyspnoea, SGRQ, co-morbidities, readmissions last year, marital status, $PaCO_2$ at discharge
de Voogd et al, 2009, Netherlands [33]	No unusual inclusion or exclusion criteria	Age, gender, marital status, smoking status, FEV1, BMI, Wpeak
de Voogd et al, 2009, Netherlands [34]	No unusual inclusion or exclusion criteria	Age, gender, marital status, smoking status, FEV1, BMI, depressive symptoms, Type D personality, exercise capacity
Yohannes et al, 2005, England [35]	Only age ≥ 60 yrs and previous depression or use of antidepressants	Age, gender, smoking status, social class, FEV1, BMI, co-morbidities, arterial blood gas values, pack-yrs, BPQ, MRADL
Stage et al, 2005, Denmark [36]	Majority women	Age, gender, smoking status, antidepressants, FEV1, corticosteroids
Dalal et al, 2011, USA [25]	No unusual inclusion or exclusion criteria	Age, gender, co-morbidities, pharmaceuticals, medical expenses, "proxies" for COPD severity
Eisner et al, 2010, USA [37]	Only patients > 65 yrs with COPD, anxiety and depression	Age, gender, race, education, income, smoking status, BODE index, COPD severity
Xu et al, 2008, China [38]	Possible predominance of men	Age, gender, smoking status, marital status, education/job, FEV1, dyspnoea, exercise capacity, social support, self-efficacy COPD-related, co-morbidities, type of hospital, respiratory drugs, oxygen therapy, former readmissions
Gudmundsson et al, 2005, Scandinavia [39]	No unusual inclusion or exclusion criteria	Age, smoking status, FEV1, SGRQ
Jennings et al, 2009, USA [40]	Only patients who have completed an outpatient pulmonary rehabilitation program	Age, gender, FEV1, exercise capacity, BMI, treatment (corticosteroids, long-term oxygen), co-morbidities
Quint et al, 2008, England [41]	No unusual inclusion or exclusion criteria	Age, gender, time outdoors, FEV1, FVC, BMI, Smoking history pack-yrs, SGRQ, MRC dyspnoea score
Chen & Narsavage, 2006, Taiwan [42]	73% men and 72% current or former smokers	Age, gender, education, daily functioning, co-morbidities, "severity of illness score", disease-related self-efficacy, perceived family support
Laurin et al, 2009, Canada [43]	Only patients who have participated in a training program for self-control of COPD, outpatients with ≥ 10 pack-yrs Excluded patients ≥ 85 yrs and those who have long-term stay in a nursing home/care home	Age, gender, duration of COPD diagnosis, COPD severity, smoking status, "setting", co-morbidities, monitoring, former hospitalizations
Coventry et al, 2011, England [44]	No unusual inclusion or exclusion criteria	Age, gender, FEV1, smoking status, co-morbidities, previous COPD-related hospitalization
Ito et al, 2012, Japan [45]	No unusual inclusion or exclusion criteria	BMI, GOLD stage, PaO_2, $PaCO_2$, treatment (long oxygen, noninvasive positive pressure ventilation, corticosteroids)
Dahlen & Janson, 2002, Sweden [46]	COPD and asthma	Age, sex, atopic status, treatment, pack-yrs

BMI = body mass index; BODE index = BMI, airflow obstruction, dyspnoea, exercise capacity; BPQ = breathing problems questionnaire; CES-D = Center for Epidemiological Studies depression scale; COPD = chronic obstructive pulmonary disease; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1st sec.; GOLD = global initiative for chronic obstructive lung disease; KPMCP = Kaiser Permanente medical care programme; Medicare = public health insurance system in the USA for the elderly and the disabled; MRADL = Manchester respiratory activities of daily living; MRC dyspnoea scale = medical research council dyspnoea scale; SGRQ = St. George's respiratory questionnaire; Wpeak = peak power output.

TABLE 1, CONTINUED

Lost to follow-up, %	Clinical outcomes scored adequately	Type of depression diagnostic instrument
Not stated	National treatment-register for veterans and hospital registry	Interview
Not stated	Not stated	Self-reported
1.1	Hospital registry and/orinsurance claims data	Self-reported
13.8	Interview with nurse	Self-reported
0	National registry	Self-reported
Not stated	Interview with GP and hospital registry	Self-reported
4.4	Contacted patient or family by telephone and/or data from hospital registry or mortality registry	Interview
0	Municipal registry	Self-reported
0	Municipal registry	Self-reported
0	Hospital registry, and/or contact with GP	Self-reported
0	Danish mortality registry	Interview
Not stated	Insurance claims	Interview
Not stated	Interview with patient, KMCP database	Self-reported
8	Telephone interview with patient	Self-reported
1.4	Telephone interview with patient, verified with hospital registry	Self-reported
Not relevant (retrospective design)	Hospital registry	Self-reported
1.2	Self-reported	Self-reported
6.7	Interview with patient on telephone, at home, or in hospital during readmission Readmission data was confirmed in hospital registry	Interview
Not stated	70% were followed by caseworker and reported to him and repsonsible doctor The patients were also contacted telephonically with a structured interview about exacerbations by a research assistant All data was confirmed with data from a hospital registry Caseworker, nurse and doctor were blinded to patient's depressive status	Interview
0	Home visits by patient by the leader of the research project	Self-reported
10.5	Interview with responsible physician who was blinded to the CES-D score Patients were trained in symptom recognition for COPD exacerbation and instructed to note that in COPD diary	Self-reported
14	Interview with patient confirmed with hospital registry	Self-reported

Eleven of the articles had mortality as outcome, 14 had new acute COPD exacerbations and/or new hospital admissions and three of the articles followed both of these outcomes. The depression severity score was not associated with the risk of mortality or COPD exacerbations in any of the studies.

TABLE 2

General characteristics and results of the included studies: mortality.

Reference Outcome	Patients in cohort, n; average age, yrs	Women, %	Study design	COPD characteristics	Follow-up, yrs	Depression diagnostic instrument, cut-off	Depression, %	Result (95% CI)
Abrams et al, 2011, USA [26]	26,591; 69	3	Prospective cohort	After admission for COPD	0.08 (T)	ICD-9	11.6	
Mortality, OR New HACOPD, HR								1.53 (1.28-1.82) 1.35 (1.18-1.54)
Lou et al, 2014, China [27]	7,787; 62	52	Prospective cohort	Stable COPD	4 (T)	HADS ≥ 8	35	
Mortality, OR								1.35 (1.02-1.68)
Fan et al, 2007, USA [28]	603; 67	36	Prospective cohort	Emphysema	3 (T)	BDI ≥ 10	41	
3-yr mortality, OR 1-yr mortality New HACOPD								2.26 (1.30-3.93) NS NS
Ng et al, 2007, Singapore [29]	376; 72	85	Prospective cohort	After admission for AECOPD	0.86 (M)	HADS ≥ 8	44	
Mortality, OR New HACOPD								2.26 (1.30-3.93) NS
Gudmundsson et al, 2012, Scandinavia [30]	256; 69	43	Prospective cohort	After admission for AECOPD	8.7 (M)	HADS ≥ 8	Not stated	
Mortality								NS
Yohannes et al, 2002, England [31]	137; 73	50	Prospective cohort	Stable COPD	2.5 (T)	BASDEC MADRS Cut-off not stated	Not stated	
Mortality								NS
Almagro, 2002, Spain [32]	135; 72.2	8	Prospective cohort	After admission for AECOPD	1.9 (M)	Yesavage score/ GDS-SF ≥ 11	Not stated	
Mortality, OR								3.6 (1.46-6.59)
de Voogd et al, 2009, Netherlands [33]	121; 62	36	Prospective cohort	Stable COPD, admitted to pulmonary rehabilitation centre	8.5 (T)	BDI ≥ 19	33	
Mortality, OR								1.93 (1.12-3.33)
De Voogd et al, 2009, Netherlands [34]	122; 61	52	Prospective cohort	Stable COPD, admitted to pulmonary rehabilitation centre	7 (T)	HADS ≥ 8	33	
Mortality, HR								1.07 (1.00-1.14)
Yohannes et al, 2005, England [35]	100; 73	52	Prospective cohort	After AECOPD	1 (T)	BASDEC Cut-off not stated	56	
Mortality, OR								1.13 (1.02-1.26)
Stage et al, 2005, Denmark [36]	49; 71	67	Prospective cohort	Stable COPD	2.2 (T)	ICD-10	47	
Mortality, HR								0.2 (0.09-0.82)

AECOPD = acute exacerbation of COPD; BASDEC = brief assessment schedule depression cards; BDI = Beck depression inventory; CES-D = Center for Epidemiological Studies depression scale; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ED = emergency department; GDS = geriatric depression scale; HACOPD = hospital admission for COPD; HADS = hospital anxiety and depression scale; HR = hazard ratio; ICD-9/10 = International Classification of Diseases and Related Health Problems 9th/10th ed.; IRR = incidence rate ratio; M = median; MADRS = Montgomery-Asberg depression rating scale; NS = not significant; OR = odds ratio; SF-36 MH = 36-item short-form health survey of mental health domain; T = total.

Mortality

One of the studies found that depression as co-morbidity reduced mortality, three found no significant correlation and the eight remaining studies found an increased mortality. The study that found depression to be a protective factor was one of the smaller studies with 49 patients. The three studies with most patients all found a positive correlation. A total of seven different diagnostic instruments were used to diagnose depression.

Chronic obstructive pulmonary disease exacerbation

Six of the studies found no significant correlation between COPD exacerbation and depression. The last eight studies found that depression: 1) increased the risk for acute exacerbations of COPD, 2) increased the risk of new hospital admission for COPD, 3) were more often ”frequent exacerbators”, and 4) had a higher risk of having more than one exacerbation. The two studies with the most patients found a positive correlation, but in

both studies patients were followed for relatively short periods of time; four weeks and one year, respectively. Apart from this, there were no clear trends in relation to the size of the studies, length of follow-up or outcomes. There were, however, generally, more studies with low numbers of patients and shorter length of follow-up in this group. A total of eight different instruments were used to diagnose depression.

DISCUSSION

Limitations

The quality and the conclusions drawn were limited by the scarce amount of primary studies carried out and by the fact that they exclusively evaluated mortality and COPD exacerbations. Furthermore, the included studies were characterised by a large degree of heterogeneity since the term "depression" encompassed everything from self-reported elevated symptoms of depression via questionnaires to depression diagnosed by psychiatrists and patients receiving pharmacologic antidepressive therapy.

Five of the 14 studies focusing on COPD exacerbations as an outcome used a definition that was symptomatic and in line with GOLD's official definition [38, 40, 41, 43, 45]. The remaining studies defined COPD exacerbation as hospital admissions, hospital readmissions and/or treatment in an emergency department. Seemungal et al pointed out that COPD exacerbations are underreported [20]. In the study of Xu et al, only 183 of 876 symptom-based COPD exacerbations made patients contact the hospital.

In total, ten different instruments were used for detecting depression. Except for Jennings et al, all the studies state that the instruments used are validated. Jennings et al did not have an independent depression scale from the cohort, but utilised the component concerning mental health of the "36-item short-form health survey". Subsequently, they validated the results against the Beck Depression Inventory in another group of patients. Laurin et al [47] identified the limitations of the different instruments and their cut-off score when interpreting the results of the studies in specific populations. A dichotomous cut-off score where one point separates depression from its absence is questionable, especially with regard to concerns that the usefulness of questionnaires can be affected by cultural background, sex and the participants' disease [46]. To illustrate this, Hayashi et al performed a study where they screened for depression in a COPD population with CES-D and HAS-D. The prevalence of depressive symptoms was 29.8% based on CES-D and 40.5% based on HAS-D [48].

Of the 22 included studies, only Gudmundsson (2005) referred to a study where the depression instrument was validated in a COPD population [39]. The study they refer to does not, however, validate the stated depression instrument against psychiatric diagnostic criteria, but investigated the incidence of depression in the chosen population and the risk factors for developing depression. The review of the literature was done by one of the authors (KS).

Mechanisms of interaction between chronic obstructive pulmonary disease and depression, and implications for future treatment

The underlying processes remain unclear. There are obvious life-changes such as loss of independence, physical invalidity and uncertainty in relation to the COPD and COPD exacerbations. These all contribute to a lowering of the quality of life and can contribute to causing, triggering and prolonging depression. These factors, however, cannot explain the increased prevalence of depression in patients with COPD compared with other, otherwise comparable chronic diseases such as stroke and heart failure. In a study mapping palliative needs in terminal patients with COPD, Kirkegaard et al found that many of the patients are bothered by their own feelings of shame and guilt linked to the diagnosis of COPD and the stigma they experience from the health care and society in general. They hypothesise that this is a contributing factor that may explain the high prevalence of depression in this group [49]. The same findings are shown in several studies performed in various countries. In a Norwegian longitudinal study following a limited number of patients with COPD, the main theme was a "feeling of being exiled in the world of the healthy, because of self-blame and society's stigmatisation of COPD as a self-inflicted disease". The participants experienced feelings of disgrace through subtle blame and a lack of support from their social network, health-care encounters and larger society [50].

A variety of mechanisms have been suggested to explain the correlation, such as systemic inflammation, hypoxia and effects of smoking on the central nervous system [51]. The co-morbidities have traditionally been seen as a result of systemic spread of destructive processes in the lungs, creating a local inflammatory and reparative response, with chain reactions to several other organ systems. Fabbri et al argued that COPD is part of a systemic inflammatory syndrome affecting several organ systems, including the lungs [52, 53]. A number of investigations reported increased levels of cytokines, chemokines and acute-phase proteins in the blood of patients with COPD, especially during COPD exacerbations [54, 55]. It is possible that the correlation between depression and poor prognosis may be caused by smoking, which is very prevalent among patients with COPD. Smoking is a central part of the pathogenesis in the majority of COPD cases in Western countries. In an interest-

TABLE 3

General characteristics and results of the included studies: chronic obstructive pulmonary diasease exacerbations

Reference Outcome	Patients in co-hort, n; aver-age age, yrs	Wo-men, %	Study design	COPD characteristics	Follow-up, yrs	Depression diagnostic instrument, cut-off	Depres-sion, %	Result (95% CI)
Abrams et al, 2011, USA [26]	26,591; 69	3	Prospective cohort	After admission for COPD	0.08 (T)	ICD-9	12	
Mortality, OR								1.53 (1.28-1.82)
New HACOPD, HR								1.35 (1.18-1.54)
Dalal et al, 2011, USA [25]	7,522; 64	63	Combined retro- and prospective cohort	Stable COPD	1 (T)	Use of anti-depres-sants ICD-9	50	
New AECOPD/ New HACOPD, HR								1.60 (1.36-1.88)
Eisner et al, 2010, USA [37]	1,202; 57	57	Prospective cohort	Recently treated for COPD	2.1 (M)	Yesavage score/ GDS-SF ≥ 6	15	
New AECOPD								NS for depression co-morbidity with anxiety Depression not stated as an independent risk factor
Fan et al, 2007, USA [28]	603; 67	36	Prospective cohort	Emphysema	3 (T)	BDI ≥ 10	41	
3-yr mortality, OR								2.26 (1.30-3.93)
1-yr mortality								NS
New AECOPD								NS
Xu et al, 2008, China [38]	469; 66	≥ 33	Prospective cohort	Stable COPD	1 (T)	HADS ≥ 11	9	
New AECOPD/ New HACOPD, IRR								1.72 (1.04-2.85)
Gudmundsson et al, 2005, Scandinavia [39]	406; 69	51	Prospective cohort	After treatment in ED for AECOPD	1 (T)	HADS ≥ 8	29	
New AECOPD/ New HACOPD, OR								NS; 1.09 (0.79-1.50)
Ng et al, 2007, Singapore [29]	376; 72	85	Prospective cohort	After admission for AECOPD	0.86 (M)	HADS ≥ 8	44	
Mortality, HR								1.93 (1.04-3.58)
New HACOPD								NS

AECOPD = acute exacerbation of COPD; BASDEC = brief assessment schedule depression cards; BDI = Beck depression inventory; CES-D = Center for Epidemiological Studies depression scale; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ED = emergency department; GDS = geriatric depression scale; HACOPD = hospital admission for COPD; HADS = hospital anxiety and depression scale; HR = hazard ratio; ICD-9/10 = International Classification of Diseases and Related Health Problems 9th/10th ed.; IRR = incidence rate ratio; M = median; MADRS = Montgomery-Asberg depression rating scale; NS = not significant; OR = odds ratio; SF-36 MH = 36-item short-form health survey of mental health domain; T = total.

ing Danish study of non-smokers with COPD, results showed they had milder disease, that they did not have elevated levels of inflammatory markers and that they had practically the same risk of cardiovascular co-morbidity as the background population. They pointed out that the prevalence of smoking is on the decline in developed countries, and that this group will undoubtedly make up a larger proportion of COPD patients in the future [56].

The systemic inflammation we see, especially in patients with COPD and a smoking history, potentially has interesting therapeutic implications for co-morbid depression. In a newly published meta-analysis, results suggest that anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDS) can reduce depressive symptoms in patients with depression [57]. Several of the pharmaceuticals being used in the treatment of co-morbid conditions to COPD have been observed to affect COPD disease activity. This, among others, applies to statins, ACE inhibitors and peroxisome proliferator-activated receptor (PPAR) antagonists. All the three groups of pharmaceuticals have immunosuppressive or immunomodulatory effects in addition to their primary effects. In the Copenhagen general population study, use of statins was associated with a reduced risk of exacerbations in patients with COPD and a lower C-reactive protein (CRP) , but the correlation did not show for the patients with the most severe degree

TABLE 3, CONTINUED

General characteristics and results of the included studies: chronic obstructive pulmonary diasease exacerbations

Reference Outcome	Patients in co-hort, n; aver-age age, yrs	Wo-men, %	Study design	COPD characteristics	Follow-up, yrs	Depression diagnostic instrument, cut-off	Depres-sion, %	Result (95% CI)
Jennings et al, 2009, USA [40]	194; 67	51	Retrospective cohort	Stable COPD 1 yr after lung rehabilitation	1 (T)	SF-36 MH score ≤ 8	17	
Risk of having ≥ 1 exacerbation, OR								2.80 (1.09-7.21)
Quint et al, 2008, England [41]	169; 71	43	Prospective cohort	Stable COPD	1 (T)	CES-D ≥ 16	9	
With CES-D ≥ 16, %								Frequent exacerbations (≥ 3): 54 Infrequent exacerbations (≤ 2): 35
Chen & Narsavage, 2006, Taiwan [42]	140; 72	27	Prospective cohort	After admission for AECOPD	0.25 (T)	SDS Cut-off not stated	Not stated	
New AECOPD, OR								NS; 1.05 (0.99-1.12)
Laurin et al, 2009, Canada [43]	110; 66	51	Prospective cohort	Previous admission for AECOPD	2 (M)	Anxiety Disordes Interview Schedule IV Confirmed with blinded psychologist	49	
New AECOPD/ New HACOPD, OR								1.56 (1.02-2.38) (only significant for ambulatory setting, not inpatient)
Coventry et al, 2011, England [44]	79; 65	44	Prospective cohort	After admission for AECOPD	1 (T)	HADS ≥ 15	43	
New AECOPD, OR								1.30 (1.06-1.60)
Ito et al, 2012, Japan, [45]	76; 70	9	Prospective cohort	Stable COPD	1 (T)	CES-D score ≥ 16	18	
New AECOPD, OR								NS; 1.85 (0.41-8.38)
Dahlen & Janson, 2002, Sweden [46]	43 (28 asthma, 15 COPD); 65	55	Prospective cohort	After treatment in ED for AECOPD or asthma exacerbation	0.08 (T)	HADS ≥ 8 (anxiety and/ or depression)	40 (anxiety and/or depres-sion)	
New AECOPD/ New HACOPD, OR								7.1 (1.10-50)

of COPD without cardiovascular co-morbidity. Ingebrigtsen et al therefore postulate that statins possibly affect only the risk of exacerbation in patients with COPD and cardiovascular co-morbidity [58].

Several broad-spectrum anti-inflammatory pharmaceuticals for COPD are being developed, such as phosphodiesterase 4 inhibitors, mitogen-activated protein kinase inhibitors and nuclear factor kappa B inhibitors. Large investigations on the possible antidepressive effect of the available pharmaceuticals are lacking and this issue remains an area for possible future research. This is worth considering, given that the studies carried out with the standard antidepressive pharmacologic regimen in COPD patients are inconclusive or have a reduced effect [59, 60].

CONCLUSIONS AND FUTURE CHALLENGES

In all, 16 of the 22 included studies showed that depression is associated with increased mortality (RR: 1.02-3.6) and with more COPD exacerbations (RR: 1.3-7.9). There was a tendency for studies with more patients and higher methodological quality to show a positive correlation.

The studies demonstrate that not only is depression a debilitating disease in itself, it also signalises an increased risk for new COPD exacerbations and increased mortality. Depression in patients with COPD is underdiagnosed and undertreated, and a stronger focus on the clinical significance of co-morbid depression is warranted. The findings underline the recommendations from (among other) The Danish College of General Practitioners' clinical guidelines "COPD in general practice", which state that patients should be screened for co-morbidity, including depression upon diagnosis of COPD, and thereafter at least once annually during control visits [3]. The results can also indicate that the patients with depression as co-morbidity could benefit from more frequent follow-ups on their disease activity, and

possibly from intensification of their antidepressive treatment, pharmacologically as well as psychotherapeutically. Furthermore, our results illustrate the need for facilitating the availability of psychological treatment, both financially and in relation to time, as the COPD patient population is a socioeconomically vulnerable group, which one must assume has a higher threshold for seeking help from the health-care system than other less vulnerable groups. While primary care and somatic health care in general are free in Denmark, psychotherapy provided by psychologists is not, and there is a prohibitively long waiting time and strict criteria for being referred to psychotherapeutic therapy by a psychiatrist.

More research investigating prognostic factors such as development of new somatic illness, use of primary care and use of pharmaceuticals in the COPD population with depression as co-morbidity is needed. Furthermore, there is a lack of studies validating the depression diagnostic instruments in cohorts with COPD, and larger studies evaluating the effect of pharmacologic and non-pharmacologic antidepressive treatments on depression, physical parameters linked to COPD and survival.

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