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Pain in patients with COPD: a systematic review and meta-analysis

Eléonore F van Dam van Isselt,[1] Karin H Groenewegen-Sipkema,[2] Monica Spruit-van Eijk, Niels H Chavannes,[1,1] Margot W M de Waal,[1] Daisy J A Janssen,[3] Wilco P Achterberg[1]

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[1]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
[2]Pulmonary Department, Deventer Hospital, Deventer, The Netherlands
[3]Department of Research and Education, CIRO+, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands

Correspondence to
Eléonore F van Dam van Isselt; E.F.vanDamvanIsselt@lumc.nl

ABSTRACT

Objectives: To systematically investigate the prevalence of pain, factors related with pain and pain management interventions in patients with chronic obstructive pulmonary disease (COPD).

Design: Systematic review and meta-analysis.

Data sources and study eligibility criteria: PubMed (MEDLINE), EMBASE, CINAHL and PsychINFO from 1966 to December 2013. Studies were included if they presented clinical data on pain or symptom burden in patients with COPD, or pain as a domain of quality of life (QoL). All types of study designs were included.

Results: Of the 1571 articles that were identified, 39 met the inclusion criteria and were included in this review. Fourteen studies focused on pain and symptom burden (including pain) in patients with COPD and 25 studies focused on QoL using a questionnaire that included a separate pain domain. Reported pain prevalence in high-quality studies ranged from 32 to 60%. Included studies report that pain is more prevalent in patients with COPD compared to participants from the general population. Comorbidity, nutritional status, QoL and several symptoms were related to pain. None of the included studies reported a significant relationship between lung function and pain prevalence or severity. However, studies investigating pain in patients with moderate COPD reported higher pain prevalence compared to studies in patients with severe of very severe COPD.

Conclusions: Although literature on this topic is limited and shows substantial heterogeneity, pain seems to be a significant problem in patients with COPD and is related to several other symptoms, comorbidity and QoL. Data synthesis suggests that pain is more prevalent in patients with moderate COPD compared to patients with severe or very severe COPD. Further research is needed and should focus on determining a more accurate pain prevalence, investigating the relationship between pain prevalence, disease severity and comorbidity and explore implementation and efficacy of pain management interventions in patients with COPD.

Strengths and limitations of this study

- This is the first systematic review on pain in patients with chronic obstructive pulmonary disease (COPD).
- A broad search strategy was used, to minimise the risk of missing any relevant published studies.
- Literature on pain in patients with COPD is limited and included studies that showed great heterogeneity, therefore confounding and selection bias are likely to occur.
- Owing to the search strategy that was used, data on pain as a subdomain of quality of life may not be complete.

airway disease. Both the prevalence and disease severity of COPD are strongly related to age and worldwide, the rate of related morbidity and mortality is rising.[1] COPD represents a major burden for individual patients, healthcare systems and society in terms of healthcare costs.[2] As the disease progresses, health status becomes increasingly impaired. Especially in advanced COPD, patients suffer from high symptom burden, impaired functional capacity and poor quality of life (QoL).[3 4]

Well-known symptoms in COPD are dyspnoea, cough and wheezing, whereas other symptoms such as fatigue, nausea and insomnia are also frequently reported.[5] Recent literature indicates that pain is also a significant symptom in patients with COPD. Two systematic reviews on patients with end-stage COPD[6 7] reported prevalences of pain of 21–77%. Both these reviews reported only on studies including patients with advanced or terminal disease or studies on palliative care in patients with very severe COPD. Less is known about pain in patients with mild-to-moderate disease. In a cross-sectional study on pain in patients with moderate-to-severe COPD, HajGhanbari et al[8] reported that pain is more prevalent among individuals with COPD compared with healthy adults.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, usually progressive

Bentsen et al[9] found similar results, reporting pain in 45% of the patients with moderate COPD compared with 34% in the general population. Other questions remain about pain in COPD. For example, the relationship with disease severity and comorbidity remains unclear[8] and information on the causes and characteristics of pain, and how pain influences functional capacity and QoL, is scarce.[8 9] There are several factors related to COPD that may contribute to a higher pain prevalence in patients with COPD. The systemic inflammatory process, which activates cytokines, may generate chronic and neuropathic pain. Musculoskeletal disorders and comorbidities (including mechanical limitations of chest wall movement due to hyperinflation and osteoporosis) are also considered possible causes of pain in patients with COPD and inactivity may aggravate common age-related comorbidities such as osteoarthritis and low back pain.[8] Improving knowledge on aetiology, characteristics, correlations and impact of pain is important and necessary to improve pain recognition and pain treatment in patients with COPD. It is likely that adequate pain recognition and treatment is important in improving QoL, exercise tolerance and lifelong adherence to physical activity in patients with COPD. Thus, pain seems to be a relevant but poorly understood problem in patients with COPD. Therefore, the aim of this review is to systematically describe and investigate pain in patients with COPD. More specifically, to examine the prevalence of pain and factors related with pain and to identify interventions that may reduce pain in patients with COPD.

METHODS
Electronic searches
We conducted a systematic search using MEDLINE/PubMed (from 1966 to December 2013), EMBASE (from 1980 to December 2013), CINAHL (from 1981 to December 2013) and PsychINFO (from 1980 to December 2013) using the following groups of keywords:
1. Pain, pains, Pain Measurement, Analgesics, analgesic (PubMed), pain, pain assessment, analgesia, analgesic (EMBASE), Pain, analgesia, analgesic (CINAHL), Pain, Aphagia, Back Pain, Chronic Pain, Headache, Myofascial Pain, Neuralgia, Neuropathic Pain, Somatoform Pain Disorder, Analgesia, analgesic (PsychINFO).
2. Pulmonary Disease, Chronic Obstructive, COPD, Lung Diseases, Obstructive, chronic bronchitis, chronic obstructive airway disease, chronic airway obstruction, chronic airway obstructions, COAD, chronic airflow obstruction, chronic airflow obstructions, Pulmonary Emphysema.

Keywords were entered using controlled terms (eg, Medical Subject Headings in Medline) and as free-text word. Within each group the keywords were combined using 'OR' and the two groups were combined using 'AND' (see online supplementary file 1). No language or other restrictions were applied. Reference lists from included studies and reviews were searched by hand to identify additional articles. All articles that were identified by the electronic search were put into a reference database (Reference Manager V.12.0).

Selection of studies
Articles that reported original data on pain in patients with COPD, or assessed pain as a domain of QoL in patients with COPD, were considered eligible. We included all types of study designs (cross-sectional, longitudinal, prospective/retrospective, qualitative/quantitative design). Articles without an (English) abstract, reviews, editorials, conference abstracts and case reports were excluded. Two members of the review team (EFvDvI and KG) independently assessed the titles and abstracts of all potentially relevant publications that were identified from the search. Decisions of the two reviewers about inclusion/exclusion were compared and, in case of disagreement, were resolved by asking a third reviewer (DJAJ) and to achieve consensus. Subsequently, the same two reviewers evaluated the full text of all potentially eligible articles. Decisions about inclusion and exclusion were again compared and, in case of disagreement, resolved by asking the third reviewer in order to achieve consensus.

Data extraction and quality assessment
Details on study design, patients, setting and outcome were recorded by two independent reviewers (EFvDvI and KG). For each study the following items were recorded: author, journal, year of publication, country of origin, design and aim of the study, setting, inclusion and exclusion criteria, response rate, number of patients, patient characteristics (age, forced expiratory volume in 1 s as % of predicted value (FEV_1% predicted), Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade, and gender), pain and QoL instrument used, reported pain prevalence or mean score on the pain domain of the QoL instrument, correlations, limitations and conclusions.

All included articles were ranked for quality according to the Mixed Method Appraisal Tool (MMAT).[10] The MMAT has recently been developed for the appraisal stage of systematic literature reviews that include quantitative, qualitative and mixed methods studies. The MMAT has proven to be an effective and practical quality assessment tool for mixed method review studies.[10] The MMAT consists of four criteria for the appraisal of quantitative (descriptive, randomised and non-randomised) and qualitative studies. Hence, each study design is judged within its methodological domain (table 1). The MMAT scores range from 100% (all four criteria are met) to 25% (one criterion is met). In the present review, quality assessment scores were calculated for all included studies. Ranking according to the MMAT was conducted by two independent reviewers (EFvDvI and KG) and any disagreement in the MMAT scores was resolved by discussion or by asking a third reviewer (DJAJ) for advice to reach consensus.

Table 1 Criteria Mixed Methods Appraisal Tool (MMAT), by Pluye *et al*[10]

Types of mixed methods study components or primary studies	Methodological quality criteria (see tutorial for definitions and examples)	Responses			
		Yes	No	Can't tell	Comments
Screening questions (for all types)	Are there clear qualitative and quantitative research questions (or objectives*), or a clear mixed methods. question (or objectives*)? Do the collected data allow address the research. question (objective)? Eg. consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components) *Further appraisal may be not feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.*				
1. Qualitative	1.1. Are the sources of qualitative data (archives, documents, informants, observations) relevant to address the research question (objective)? 1.2. Is the process for analysing qualitative data relevant to address the research question (objective)? 1.3. Is appropriate consideration given to how findings relate to the context, eg, the setting, in which the data were collected? 1.4. Is appropriate consideration given to how findings relate to researchers' influence, eg, through their interactions with participants?				
2. Quantitative randomised controlled (trials)	2.1. Is there a clear description of the randomisation (or an appropriate sequence generation)? 2.2. Is there a clear description of the allocation concealment (or blinding when applicable)? 2.3. Are there complete outcome data (80% or above)? 2.4. Is there low withdrawal/drop-out (below 20%)?				
3. Quantitative non-randomised	3.1. Are participants (organisations) recruited in a way that minimises selection bias? 3.2. Are measurements appropriate (clear origin, or validity known, or standard instrument: and absence of contamination between groups when appropriate) regarding the exposure intervention and outcomes? 3.3. In the groups being compared (exposed vs non-exposed: with intervention vs without; cases vs controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups? 3.4. Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?				
4. Quantitative descriptive	4.l. Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)? 4.2. Is the sample representative of the population understudy? 4.3. Are measurements appropriate (clear origin, or validity known, or standard instrument)? 4.4. Is there an acceptable response rate (60% or above)?				
5. Mixed methods	5.1. Is the mixed methods research design relevant to address the qualitative and quantitative research questions (or objectives), or the qualitative and quantitative aspects of the mixed methods question (or objective)? 5.2. Is the integration of qualitative and quantitative data (or results*) relevant to address the research question (objective)? 5.3. Is appropriate consideration given to the limitations associated with this integration, eg,the divergence of qualitative and quantitative data (or results*) in a triangulation design? *Criteria for the qualitative component (1.1 to 1.4), and appropriate criteria for the quantitative component (2.1 to 2.4. or 3.1 to 3.4. or 4.1 to 4.4), must be also applied*				

*These two items are not considered as double-barreled items since in mixed methods research, (1) there may be research questions (quantitative research) and or research objectives (qualitative research), and (2) data may be integrated, and/or qualitative findings and quantitative results can be integrated.

Data synthesis and meta-analysis

A meta-analysis was performed concerning the Short-Form health survey (SF)-36_Bodily Pain data.

The SF-36 is a widely used, self-administered, reliable and valid instrument to assess generic health-related QoL.[11] The SF-36 consists of 36 items divided into eight subdomains. The score of each subdomain ranges from 0 to 100, with 100 representing the best quality of life. The questionnaire contains two questions related to pain: the SF-36 bodily pain subdomain (SF-36_BP): 'How much bodily pain have you had during the past (4) week(s)?' (score from 0 (no pain) to 6 (very severe pain)) and 'During the past (4) week(s), how much did pain interfere with your normal work (including both work outside the home and housework)? (score from 0 (not at all) to 5 (extremely)) We performed a meta-analysis with a Forest plot using a Microsoft Excel spreadsheets, as developed by Neyeloff et al.[12] They showed that this method produces a statistically adequate but graphically appealing forest plot summarising descriptive data. We assumed a random-effects model to calculate the mean score on the SF-36_BP item and a 95% CI. The heterogeneity was assessed with the Q statistic and the I^2 index. Meta-analyses and Forest plots using a Microsoft excel spreadsheet were conducted by step-by-step guide focusing on descriptive data analysis.[12] To determine the strength of the linear correlations between lung function ($FEV_1\%$ predicted) and pain prevalence and the SF-36_BP score, we calculated the correlation coefficient between these variables. In case of normally distributed data, Pearson correlation coefficient was calculated. In case of non-normally distributed data a non-parametric test (Spearman's test) was used. We defined statistical significance at $p \leq 0.05$ (two-sided level of significance). In studies that presented only the GOLD grade distribution the mean GOLD grade was calculated and converted into a mean $FEV_1\%$-predicted.

RESULTS

Study selection and characteristics

The electronic systematic search identified 1571 eligible citations (PubMed 1067, EMBASE 379, CINAHL 71, PsychINFO 54). Eight studies were identified using other sources. A total of 1491 citations were excluded based on title and abstract. In total, 88 articles were reviewed in detail. Reasons for exclusion are reported in the PRISMA flowchart (figure 1). Thirty-nine studies met the inclusion criteria and were included in the review (tables 2 and 3).

Fourteen studies focused on pain and symptom burden (including pain) in COPD[5 8 9 13–23] and 25 studies focused on QoL using a questionnaire that included a separate pain domain[4 24–47] (table 2 and 3). The included studies were published between 1995 and 2013. All included studies on symptom burden in COPD were published in the past decade (2000–2013) and studies with a specific focus on pain in COPD were published in the last 5 years (figure 2).

Of the 14 articles on pain and symptom burden in COPD, three reports from Bentsen et al[9 21 22] and two reports from Borge et al[18 20] were based on the same original research study. Ten studies were conducted at the outpatient pulmonary department of a hospital (secondary and tertiary care), one in primary care and three were population-based studies. Most studies on pain and symptom burden (n=10; 71%) had a cross-sectional design. The majority of the included studies on pain as a domain of QoL also used a cross-sectional design (n=17; 68%), seven studies used a prospective design (observational (n=3) and interventional (n=4)) and one study used a retrospective design. Almost all studies (n=21) on pain as a domain of QoL included patients with COPD recruited from an outpatient pulmonary department or hospital/intensive care unit setting (secondary and tertiary care).

Quality assessment

Of the 14 studies on pain and symptom burden in COPD, 10 had a MMAT score of 100%, three scored 75% and one study scored 50% (table 2). Shortcomings in quality included insufficient response rate,[13 14 18 20] or insufficient comparability between participants.[13] Of the 25 studies on pain as a subdomain of QoL, 20 had a score of 75% (n=14) or 100% (n=6). The most frequent shortcoming in quality assessment was an insufficiently or not reported response rate (n=19; table 3).

Pain measurement

Pain was measured using different instruments. Five studies on pain and symptom burden in COPD used the Brief Pain Inventory (BPI), or the body outline diagram of the BPI.[48] The BPI is a self-administered questionnaire used to assess the severity of pain (scale 0–10; cut-off points: mild pain (0–4), moderate pain: (5–6) and severe pain (7–10)) and the impact of pain on daily functioning (scale 0–10) in patients with chronic diseases or conditions. The BPI also contains a body diagram on which patients can indicate the location on which they experienced the most pain.[20 48] In five studies pain was not measured with a specific pain or symptom questionnaire, but a screening question was used, such as: 'Are you generally bothered with pain?'[9] or 'Are you usually free of pain and discomfort?'.[15] Other instruments used include: the McGill Pain Questionnaire (MPQ), the Memorial Symptom Assessment Scale (MSAS), the VOICES questionnaire and the London and Leeds Pain Survey. One study measured pain using a Visual Analogue Scale (VAS).[5]

Pain as a subdomain of QoL was measured using five different instruments: the SF-36 (n=19), the EuroQol-5 Dimensions (EQ-5D; n=3), the Nottingham Health Profile (NHP; n=3), the Health Status Questionnaire (HSQ; n=1) and the Duke Health Profile (DHP; n=1).
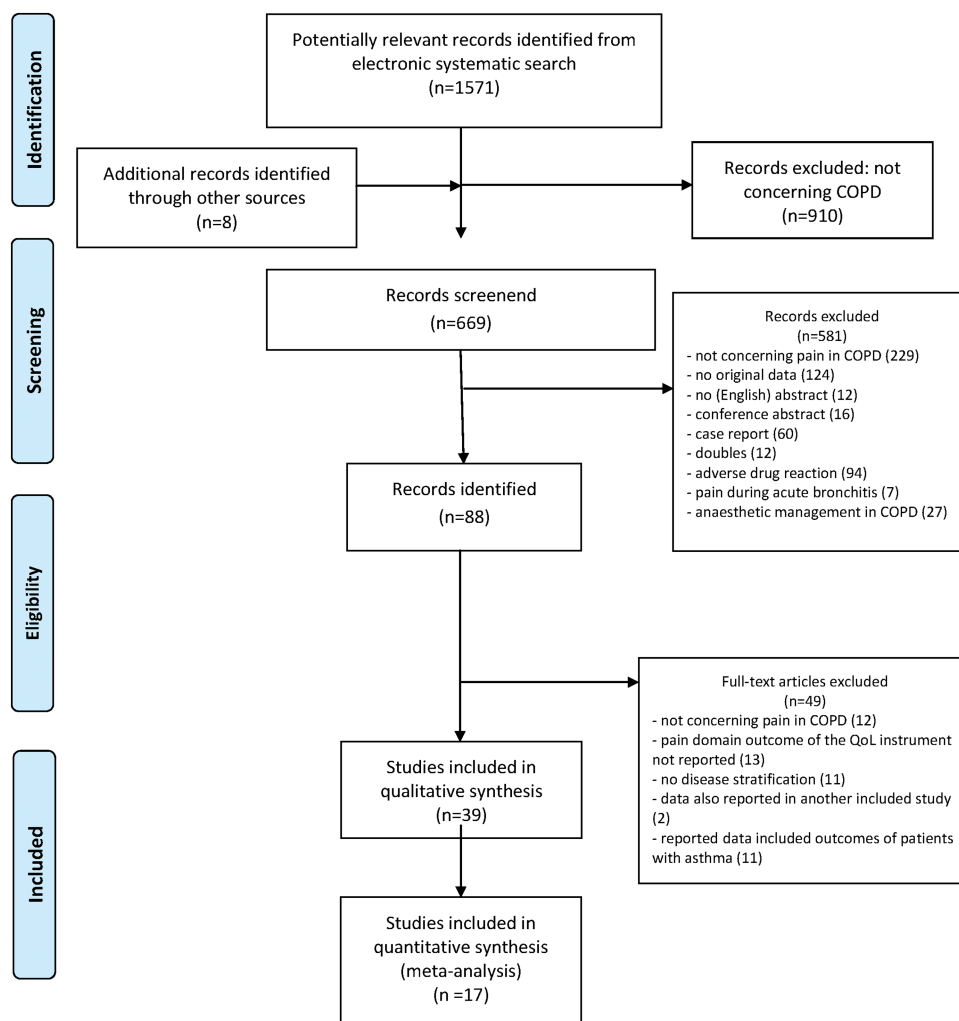
Figure 1 Flow diagram of the inclusion of studies (according to the PRISMA guidelines).

Prevalence of pain

Of the 14 studies on pain and symptom burden, 11 reported the prevalence of pain: range from 21% to 72.1% (figure 3). Studies on prevalence of pain differed in design, setting and patient characteristics. Mean age was 57.9–76.8 years and mean $FEV_1\%$ predicted ranged from 21% to 48%. Three studies did not report the mean $FEV_1\%$ predicted or the GOLD grade of the included patients. The MMAT scores of the studies that reported pain prevalence ranged from 50% to 100%. The reported pain prevalence of the studies with a MMAT score of 100% ranged from 32.4% to 59.8% (figure 3). Five studies investigated the prevalence of pain in patients with COPD compared to participants from the general population,[8] [9] patients with other chronic diseases[5] [23] or patients with lung cancer.[13] Bentsen et al[9] found a pain prevalence in patients with COPD of 45% compared to 34% in the general population (p=0.02) and HajGhanbari et al[8] reported that patients with COPD reported 2.5 times more pain and 3.7 times more interference of pain with daily activities, compared to healthy people. Roberts et al also reported that a higher pain prevalence in patients with COPD compared to patients with other chronic diseases (59.8% vs 51.7%; p=0.001), but in the study conducted by Janssen et al, patients with chronic heart failure reported more pain than patients with COPD (48.8% vs 32.4%, p=0.05).

Of all included studies, 19 used the SF-36, the SF-20 or the SF-8. Of these, 17 reported scores on the bodily pain domain as a mean score (SD). In four of these studies, the SF-36_BP was measured in two separate groups of patients with COPD (cases and controls). A random-effects meta-analysis on the SF-36/20/8_BP data of the 21 studies and groups of patients with COPD, showed a mean score on the SF-36_BP of 66.7 (CI 95% 61.2; 72.2; figure 4). The three studies that used the EQ-5D showed that 45%,[40] 46%[4] and 56%[41] of the patients with COPD reported having any problems on the subdomain pain/discomfort of the EQ-5D, respectively.

Characteristics of pain

Five studies measured pain intensity and interference using the BPI. Mean pain intensity scores ranged from 2.8 to 5.4 points (mild to moderate pain) and mean interference scores ranged from 3.6 to 5.8 points (mild to moderate interference) on a scale from 0 to 10

Table 2 Pain and symptom burden

Author	Aim	Setting and sample	N (patients with COPD)	Mean age in years (SD)	FEV$_1$% of predicted (SD)	GOLD-stage	Pain, symptom, QoL instrument used	Outcome (pain prevalence) (%)	MMAT score
Claessens et al[13]* USA	To compare the course of illness and patterns of care for patients with non-small-cell lung carcinoma (NSCLC) and COPD	Secondary care Patients with severe COPD or stage II of IV NSCLC, recruited on admission to the hospital because of acute illness/ exacerbation	1008	70 (–)	–	–	Screening question: 'How much of the time do you experience pain'?. 'How severe is the pain'	21	50% 3.1:+ 3.2:+ 3.3:– 3.4:–
Elkington et al[14]*** UK	To assess the healthcare needs of patients with COPD in the last year of life	Population based Informants of COPD or emphysema deaths were identified by the Office for National Statistics	209	76.8 (–)	–	–	VOICES	72	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
Rashiq et al[15]** Canada	To determine the associations of Chronic Non Cancer Pain (CNCP) with a wide range of factors in the biological, psychological and social domain	Population based Sample from data from the Canadian National Population Health Survey	2289	–	–	–	Screening question: 'Are you usually free of pain and discomfort'?	34.9	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Blinderman et al[16]* USA	To evaluate the pattern of symptom distress and investigate the relationships among symptoms and measures of comorbidity, physical and mental functioning and QoL in patients with advanced COPD	Secondary care Patients identified by review medical records in outpatients pulmonary department	100	62.2 (10.5)	24.4 (3.9)	–	MSAS SIP MILQ	41	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Lohne et al[17]**** Norway	To evaluate pain experiences of patients with COPD	Tertiary care Patients newly admitted to hospital(tertiary referral centre) for COPD assessment and lung transplantation assessment	16	57.9 (4.1)	21.1 (5.8)	–	Semistructured interview BPI	38	100% 1.1:+ 1.2:+ 1.3:+ 1.4:+
Borge et al[18]** Norway	To explore the relationships between demographic and clinical variables and symptoms for patients with COPD	Secondary care Patients recruited from outpatient pulmonary department of a hospital	154	64.6 (10.2)	59.1 (22.6)	GOLD 1:18.2% GOLD 2:46.8% GOLD 3:25.3% GOLD 4:9.7%	BPI HADS LFS GSDS RQLQ	–	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
White et al[19]** UK	To determine the palliative care needs in patients with advanced COPD	Primary care Patients in care of GP's with diagnosis of COPD, identified from medical records	145	71.6 (9.7)	29.1 (9.5)	–	LLPS MRC HADS CCQ	40	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Janssen et al[5]** Netherlands	To assess severity of symptoms, presence of comorbidities, and current provision of healthcare in outpatients with advanced COPD or chronic heart failure (CHF)	Secondary care Patients recruited from outpatient pulmonary department of 1 academic and 5 general hospitals	105	66.3 (9.2)	34.1 (13.5)	GOLD 1:– GOLD 2:– GOLD 3:26.7% GOLD 4:73.3%	VAS	32.4	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+

Table 2 Continued

Author	Aim	Setting and sample	N (patients with COPD)	Mean age in years (SD)	FEV$_1$% of predicted (SD)	GOLD-stage	Pain, symptom, QoL instrument used	Outcome (pain prevalence) (%)	MMAT score
Bentsen et al[9]** Norway	To evaluate the prevalence and characteristics of pain in patients with COPD compared to a sample from the Norwegian general population	Secondary care Patients: sample of patients with COPD who underwent outpatient PR programme. Controls: age appropriate sample from Norwegian general population	100	65 (9.2)	48.0 (16.0)	GOLD 1:– GOLD 2:53% GOLD 3:31% GOLD 4:16%	Screening question: 'Are you generally bothered with pain?' NRS BPI	45	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Borge et al[20]** Norway	To explore the prevalence and intensity of pain, its location, how demographic and clinical variables may be related to pain and how pain is associated with QoL	Secondary care Patients recruited from outpatient pulmonary department	154	64.6 (10.2)	59.1 (22.6)	GOLD 1:18.2% GOLD 2:46.8% GOLD 3:25.3% GOLD 4:9.7%	BPI RQLQ QOLS	72.1	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
Bentsen et al[21]** Norway	To evaluate the differences in respiratory parameters between patients with COPD who did and did not have pain	Secondary care Sample of patients with COPD who underwent PR programme at the outpatient pulmonary department	100	65 (9.2)	48.0 (16.0)	GOLD 1:– GOLD 2:53% GOLD 3:31% GOLD 4:16%	Screening question: 'Are you generally bothered with pain'? SGRQ	–	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Hajghanbari et al[9]** Canada	To determinate if pain is more common in patients with COPD than in healthy people and if pain is related to physical activity, QoL and comorbidities	Secondary care Patients recruited from caseload of respirologists and PR programmes. Controls recruited from local population	47	70 (6.7)	44.7 (19.2)	–	MPQ BPI TSK SF-36	50	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Bentsen et al[22]** Norway	To examine the prevalence of multiple symptoms in patients with COPD and to examine the relationship between the patients outlook for the future and multiple symptoms	Secondary care Sample of patients with COPD who underwent PR programme at the outpatient pulmonary department	100	66.1 (8.3)	46 (15)	GOLD 1:– GOLD 2 44% GOLD 3:43% GOLD 4:13%	Screening question: 'Are you generally bothered with pain?' BPQ NRS	–	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Roberts et al[23]** USA	To describe chronic pain prevalence among patients with COPD compared with similar patients with other chronic diseases in a managed care population in the USA	Population based Cases and controls selected from members of a regional managed care plan	7952	69.3 (–)	–	GOLD 1:21.5% GOLD 2:55.5% GOLD 3:19.5% GOLD 4:3.5%	Identification of pain was based on both pain diagnosis and management and was assessed using diagnosis and procedure codes from the managed care claims database and outpatient pharmacy information	598	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+

*Prospective cohort study; **cross-sectional study; ***mixed method; ****retrospective post-bereavement study.
BPI, Brief Pain Inventory; BPQ, Breathing Problems Questionnaire; BPI, Brief Pain Inventory; CCQ, Clinical COPD Questionnaire; CHF, chronic heart failure; CNCP, Chronic Non Cancer Pain; COPD, chronic obstructive pulmonary disease; DHP, Duke Health Profile; FEV$_1$, forced expiratory volume in 1 s; GP, general practitioner; life; GSDS, General Sleep Disturbances Scale; HADS, Hospital Anxiety and Depression Scale; LFS, Lee Fatigue Scale; LLPS, London and Leeds Pain Survey; MMAT, Mixed Method Appraisal Tool; MPQ, McGill Pain Questionnaire; MSAS, Memorial Symptom Assessment Scale; MILQ, Multidimensional Index of Life Quality; MMAT, Mixed Method Appraisal Tool; MPQ, McGill Pain Questionnaire; MRC, Medical Respiratory Counsel dyspnoea scale; MSAS, Memorial Symptom Assessment Scale; NHP, Nottingham Health Profile; NRS, Numeric Rating Scale; NSCLC, non-small-cell lung carcinoma; PR, pulmonary rehabilitation; QoL, Quality of Life; QOLS, Quality Of Life Scale; RQLQ: Respiratory Quality of Life Questionnaire; SF-36, Short Form Health Survey-36; SGRQ, St George Respiratory Questionnaire; SIP, Sickness Impact Profile; TSK, Tampa Scale for Kinesiophobia; VAS, Visual Analogue Scale; SF-36, Short-Form health survey-36; VAS, Visual Analogue Scale; VOICES: VOICES questionnaire.

(higher scores indicating more pain intensity/interference). Three studies used the body outline diagram of the BPI to investigate the most prominent locations of the experienced pain.[9] [17] [20] Most frequently reported locations of pain were the shoulders and neck: 33% (n=15),[9] 36.4% (n=56)[20] and 50% (n=8)[17]; lumbar region: 29.2%(n=45)[20] and 47% (n=21)[9] and chest: 17.5% (n=27),[20] 36% (n=16)[9] and 38% (n=6).[17] None of the included studies investigated the type of pain (eg, neuropathic or nociceptive pain) or conducted a comprehensive pain assessment.

Factors related to pain

Of the 14 studies on pain or symptom burden, seven reported factors related to pain or correlations between pain and several variables, such as lung function, comorbidity and other symptoms (table 4).

Four of these studies reported from the same two original studies.[18] [20–22] None of the studies on pain or symptom burden reported a significant relationship between lung function (FEV$_1$% predicted, GOLD grade) and pain prevalence or pain severity. Several studies reported a significant correlation between pain and comorbidity.[8] [21] [23] Bentsen et al[21] reported that comorbidity was a risk factor for pain in patients with COPD; patients with COPD and pain were more likely to report the presence of a comorbidity and had a significantly higher number of comorbidities. However, the study from Borge et al[20] found no significant difference in the number of comorbidities between patients with COPD with and without pain. These conflicting results are also found for the correlation between pain severity and the number of comorbidities[8] [18] (table 4). Other variables that showed a significant correlation with pain presence or pain severity are: QoL, breathlessness, insomnia, fatigue, anxiety, depression and nutritional status (table 4). Of the included studies on pain as a subdomain of QoL, none reported correlations between the SF-36_BP score and variables of interest. Two studies using other QoL instruments, that is, the EQ-5D[40] and the NHP[27] concluded that their analysis showed no significant correlation between pain as a subdomain of QoL and lung function.

Pain management interventions

None of the included studies aimed to investigate the effect of a specific intervention on pain in patients with COPD. Bentsen et al[9] reported that 49% of the participants with pain received treatment with analgesics and 16% received physiotherapy. In a cross-sectional study in patients with advanced COPD, Janssen et al[5] found that 47% of the patients with pain (VAS score >30 mm) reported that their symptoms were addressed. Furthermore, if symptoms were treated, patients reported only moderate satisfaction with symptom treatment. One study on symptom burden in patients with severe COPD in primary care reported that all patients who suffered from pain ever day or pain on most days,

were on prescribed analgesics.[19] Three studies investigated the effect of a pulmonary rehabilitation programme on health status.[32–34] All reported no effect of the intervention on the pain domain of the health status instrument used (two studies used the SF-36, one used the HSQ).

Overall relationship between pain prevalence and disease severity

To determine the relationship between lung function and pain prevalence, we calculated the correlation coefficient between these variables. Of the 11 studies that reported on pain prevalence, seven also reported the mean FEV$_1$% predicted and one study reported the GOLD grade distribution,[23] which was converted to a weighted mean GOLD grade (figure 5). There was a strong correlation between lung function (FEV$_1$% predicted) and pain prevalence; Spearmans r=0.79 (p=0.021). Of the 21 studies and groups that reported SF-36/20/8 scores on the pain domain, 18 reported the mean FEV$_1$% predicted. In three groups of patients only the GOLD grade was reported,[34] [37] which was converted to a weighted mean GOLD grade. No significant correlation was found between the SF-36_BP score and lung function: Pearson's correlation coefficient=0.21 (p=0.37; figure 6).

DISCUSSION

Main findings

The *first* main finding of this systematic review is that pain seems to be a significant clinical problem in patients with COPD, with a reported prevalence in high-quality studies ranging from 32% to 60%. *Second*, literature on pain in patients with is limited; only a few studies with a specific focus on pain in patients with COPD have recently been published. Still, little is known about the causes and characteristics of pain, factors that are related to pain and literature on the effect of interventions aimed at reducing pain in patients with COPD is lacking. *Third*, our data synthesis shows that studies investigating pain in patients with moderate airflow limitation reported a higher pain prevalence compared with studies in patients with severe airflow limitation. This finding could suggest that pain is more prevalent in patients with moderate COPD compared to patients with severe or very severe COPD. However, confounding and selection bias are likely to occur and much remains unclear about the relation between pain and disease severity. *Fourth*, our results suggest a correlation between pain and several other symptoms, such as dyspnoea, insomnia, fatigue, anxiety and depression, QoL and comorbidity.

Strengths and limitations

To our knowledge, this is the first systematic review study on pain in patients with COPD. One strength of this study is that we included all types of studies and used a

Table 3 Pain as a subdomain of quality of life (QoL)

Author	Aim	Setting and sample	N (patients with COPD)	Mean age (SD) in years	FEV$_1$% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Mahler et al[25] (1995)**** USA	To examine longitudinal changes in clinical parameters in patients with COPD	Secondary care Patients recruited from the outpatient pulmonary department of 3 hospitals	110	67 (8)	44 (17)	–	SF-20	38.9 (32.9)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Mahler et al[24] (1995)* USA	To evaluate the SF-36 as an instrument for measuring HRQoL in patients with symptomatic COPD	Secondary care Patients with COPD and no significant comorbidity recruited from an outpatient pulmonary department	50	72 (8)	48.2 (21.9)	GOLD 1:18% GOLD 2: 20% GOLD 3&4: 62%	SF-36	70.5 (24.2)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:−
Hoang Thi et al[26] (1997)**** France	To seek factors predicting HRQoL in patients with severe COPD on LTOT	Primary care Patients on LTOT monitored at home by a region organisation for medical assistance of patients with COPD	61	66.0 (6.4)	–	GOLD 1:– GOLD 2:– GOLD 3&4:100%	DHP	46.6 (38.1)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:−
Monso et al[27] (1998)* Spain	To identify physiological parameters related to QoL in severe patients with COPD using LTOT	Secondary care Patients with COPD on LTOT recruited from outpatient pulmonary department of a university hospital	47	65.2 (8.2)	31.8 (11.9)	GOLD 1:– GOLD 2:– GOLD 3&4:100%	NHP	35.1 (31.6)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:−
Schlenk et al[28] (1998)* USA	To examine HRQoL as measured by the SF-36 across patient populations with chronic disorders and to compare QoL in these participants with normative data on healthy persons	Primary care Sample comprised from 6 studies of persons with chronic disorders. Patients with COPD were recruited from a pilot study designed to determine the effect of home-based PR on HRQoL	13	66.7 (3.7)	–	–	SF-36	58.54 (24.16)	25% 4.1:− 4.2:− 4.3:+ 4.4:−
Hajiro et al[29] (1999)* Japan	To compare categorisations of the level of dyspnoea with the staging of disease severity as defined by the FEV$_1$ in representing how HRQoL is distributed in patients with COPD	Secondary care Patients (100% male) with stable COPD recruited from outpatient pulmonary department of a university hospital	194	70 (8)	41.5 (15.6)	GOLD 1:29% GOLD 2:32% GOLD 3:39% GOLD 4:–	SF-36	65.5 (21.3)	100% 4.1:+ 4.2:+ 4.3:+ 4.4:−
Stavem et al[30] (1999)* Norway	To assess relationships between health status and measures of dyspnoea, lung function and exercise capacity in patients with COPD	Secondary care Patients with COPD recruited from outpatient pulmonary department of a hospital	59	57 (9)	54 (17)	GOLD 1:42% GOLD 2:36% GOLD 3:22% GOLD 4:–	SF-36	64.0 (27.6)	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Gore et al[31] (2000)* UK	To examine if patients with severe COPD are relatively disadvantaged in terms of medical and social care compared to patients with inoperable lung cancer	Secondary care Patients attending for follow-up at the outpatient pulmonary department of a hospital	50	70.5 (5.5)	–	GOLD 1:– GOLD 2:– GOLD 3&4:100%	SF-36	– (only figures presented)	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Kaelin et al[32] (2001)*** USA	To examine the efficacy of a programme using symptom limited interval training combined with strength training on 6MWT, increases in exercise capacity and QoL	Secondary care Patients with primary diagnosis of COPD entering a PR programme at an outpatient pulmonary department	50	68.4 (6.9)	39.5 (11.5)	–	HSQ	pre-PR: 65.9 (26.7) post-PR: 69.5 (21.6) NS	50% 4.1:+ 4.2:+ 4.3:− 4.4:−

Continued

Table 3 Continued

Author	Aim	Setting and sample	N (patients with COPD)	Mean age (SD) in years	FEV$_1$% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Boueri *et al*[33] (2001)*** USA	To evaluate the effects of a 3-week comprehensive PR programme on QoL in patients with COPD	Tertiary care Patients with COPD, referred for PR at the outpatient pulmonary department of a pulmonary tertiary care centre	37	66 (7.3)	29.6 (10.9)	–	SF-36	pre-PR; 77.5 (27.4) post-PR; 83.2 (18.5) p=0.100	75% 4.1:+ 4.1:+ 4.3:+ 4.4:–
de Torres *et al*[34] (2002)*** USA	To investigate the capacity of several of the most frequently used outcome measurements to detect changes after PR in a population of patients with severe COPD who qualified for LVRS	Secondary care 7 hospitals participating in a trial comparing LVRS and standard medical treatment. Population consisted of the first 37 consecutive patients with severe COPD selected for LVRS	37	63 (6)	–	GOLD 1:– GOLD 2:– GOLD 3&4:100%	SF-36	pre-PR:87 (18) post-PR:87 (18) NS	50% 4.1:+ 4.2:+ 4.3:– 4.4:–
Ambrosino *et al*[35] (2002)**** Italy	To evaluate the perceived health and cognitive status in survivors of COPD exacerbations requiring mechanical ventilation	Secondary care Patients (P): patients with COPD at their first episode of acute on chronic respiratory failure requiring mechanical ventilation. Controls (C): stable patients with COPD on LTOT (>6 months) with no previous ICU admission	97 P:63 C:34	 68 (7) 67 (7)	 30 (16) 36 (19)	GOLD 1:– GOLD 2:– GOLD 3&4: 100%	NHP	P:21.2 (28.4) C:13.7 (19.2) p=0.17	50% 3.1:+ 3.2:+ 3.3:– 3.4:–
Sant'Anna *et al*[36] (2003)* Brazil	To assess HRQoL in low an income population of patients with hypoxaemia and COPD receiving LTOT	Tertiary care Patients (P): patients with COPD and LTOT recruited from an outpatient pulmonary department of a tertiary care university hospital Controls (C): patients with COPD but no severe hypoxaemia	69 P:36 C:33	 63.5 (10.8) 63.1 (9.2)	 32.1% (14.4) 35.7% (13.9)	–	SF-36	P:56.9 (32.4) C:68.1 (28.9) NS	75% 3.1:+ 3.2:+ 3.3:– 3.4:+
Van Manen *et al*[37] (2003)* Netherlands	To determine the influence of COPD on HRQoL independent of comorbidity	Primary care Patients (P): patients with COPD and comorbidity Controls(C): patients with COPD and comorbidity	148 P:107 C:41	–	–	GOLD 1:24% GOLD 2:39% GOLD 3&4:37%	SF-36	P:83.6 (23.2) C:88.8 (18.5)	75% 3.1:+ 3.1:+ 3.3:+ 3.4:–
Sato *et al*[38] (2004) */*** Japan	To investigate the responsiveness of the SF-36 in patients with COPD and asthma	Secondary care Patients recruited from the outpatient pulmonary department of an universal hospital	*Cross-sectional* Pre-treatment 152 In-treatment 123 *Longitudinal* 136	 69.1 (7.4) 70.1 (7.3) 69.1 (7.4)	 44.9 (17.3) 49.9 (18.1) 44.9 (17.3)	–	SF-36	*Cross-sectional* Pre-treatment 73.4 (24.3) In-treatment: 80.3 (22.8) p=0.02 *Longitudinal* 73.8 (25.3)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
Katsura *et al*[39] (2005)* Japan	To evaluate the effects of body weight on both generic and disease specific HRQoL of patients with COPD	Secondary care Patients (88% male) with stable COPD recruited from outpatient pulmonary department	83	74.6 (6.4)	53.9 (22.2)	–	SF-36	– (only figures presented)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
Rutten-van Molken *et al*[40] (2006)* Netherlands	To assess the discriminative properties of the EQ-5D with respect to COPD severity according to the GOLD criteria in a large multinational study	Secondary care Patients recruited form an outpatient pulmonary department	1235	64.5 (8.4)	48.8 (12.2)	GOLD 1:0.0% GOLD 2:50.7% GOLD 3:41.8% GOLD 4:7.4%	EQ-5D	– (only figures presented)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–

Continued

Table 3 Continued

Author	Aim	Setting and sample	N (patients with COPD)	Mean age (SD) in years	FEV$_1$% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Punekar et al[41] (2007)* USA, 5 EU countries	To assess and compare health status among patients with COPD presenting for treatment in 6 countries and in 2 healthcare settings using a generic health status instrument	Population based, primary(PC) and secondary care(SC) Physicians were randomly selected. Patient selection: the first 6 consecutive patients diagnosed and treated for COPD presenting for consultation during the next 10 working days	2703 PC: 1381 SC:1322	66 (10.8) 66 (11.3)	–	PC GOLD 1:37% GOLD 2:31% GOLD 3:32% GOLD 4:– SC: GOLD 1:25% GOLD 2:36% GOLD 3:39% GOLD 4:–	EQ-5D	PC Any problems: 53% SC Any problems: 56%	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Bailey et al[42] (2008)** USA	To examine the relationship between improvements in 6MWT and QoL in patients with COPD following a PR programme	Secondary care Patients with COPD that completed an outpatient PR programme	139	68 (11.8)	44.7 (20.0)	–	SF-36	pre-PR; 63.1 (22.4) post-PR; 70.1 (62.5) p=0.212	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
Habraken et al[43] (2009)* Netherlands	To compare self-reported HRQoL data of patients with COPD with GOLD stage 4 and patients with end stage NSCLC	Secondary and tertiary care Patients identified from medical records of the outpatient pulmonary department of 4 hospitals and 1 tertiary pulmonary centre	82	69.5 (6.7)	–	GOLD 1:– GOLD 2:– GOLD 3:– GOLD 4:100%	SF-36	62 (IQR 41–100)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–
Kil et al[14] (2010)* South Korea	To determine the prevalence of depression and examine its impact on HRQoL among older patients with COPD	Secondary care Patients recruited from the outpatient pulmonary department of an academic hospital	91	69.3 (8.2)	58.9 (19.5)	GOLD 1:14.2% GOLD 2:51.7% GOLD 3:29.7% GOLD 4:4.4%	SF-36	63.0 (30.1)	50% 4.1:– 4.2:+ 4.3:+ 4.4:–
Rascon-Anguilar et al[45] (2011)* USA	To evaluate HRQoL in patients with COPD compared with those with both COPD and gastroesophageal reflux disease (GERD) symptoms	Secondary care Patients presenting at the outpatient pulmonary department for routine healthcare: Patients (P): patients with COPD with GERD symptoms. Controls (C): patients with COPD without GERD symptoms	86 P:32 C:54	66.0 (9.9) 68.8 (7.0)	40.7 (17.6) 45.9 (16.0)	–	SF-36	P:51.7 (28.8) C:66.7 (27) p<0.02	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Janssen et al[4] (2011)* Netherlands	To assess health status and care dependency in patients with advanced COPD or CHF and to identify correlates of an impaired health status	Secondary care Patients recruited from outpatient pulmonary department of 1 academic and 5 general hospitals	105	66.3 (9.2)	34.1 (13.5)	GOLD 1:– GOLD 2:– GOLD 3:26.7% GOLD 4:73.3%	SF-36 EQ-5D	SF-36_BP: 70.9 (29.5) EQ-5D: Any problems: 45.7%	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Cedano et al[46] (2012)* Brazil	To evaluate and correlate the QoL of patients with COPD on LTOT with their sociodemographic and clinical characteristics and level of dependence	Secondary care Convenience sample of patients on LTOT followed at the oxygen therapy outpatient pulmonary department	80	69.6 (9.1)	37.4 (14.1)	GOLD 1:– GOLD 2:– GOLD 3:– GOLD 4:100%	SF-36	61.2 (27.4)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–

Table 3 Continued

Author	Aim	Setting and sample	N (patients with COPD)	Mean age (SD) in years	FEV$_1$,% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Arimura et al[47] (2013)* Japan	To evaluate the clinical usefulness of a concise two-question instrument to assess depressive symptoms in patients with COPD and to determine whether the instrument was related to the SF-8	Secondary care Patients recruited as a consecutive sample of clinically stable patients with COPD visiting the outpatient pulmonary department of five hospitals	52	72.7 (7.5)	62.5 (25.7)	GOLD 1:23% GOLD 2:40% GOLD 3:25% GOLD 4:12%	SF-8	52.2 (10.0)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:–

*Cross–sectional study; **retrospective study; ***prospective intervention study (controlled and non-controlled); ****prospective observational study.COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; DHP, Duke Health Profile; EQ-5D, EuroQol-5 Dimensions; FEV$_1$, forced expiratory volume in 1 s; HRQoL, health-related quality of life; HSQ, Health Status Questionnaire; ICU, intensive care unit; MMAT, Mixed Method Appraisal Tool; NSCLC, non-small-cell lung carcinoma; NHP, Nottingham Health Profile; PR, SF-36, Short-Form health survey-36.

broad search method. Therefore, it seems unlikely that the search strategy we used failed to identify relevant published studies. Second, the selection strategy was objective, as it was performed by two, and in case of disagreement, by three individual members of the review team. Third, we were able to conduct a meta-analysis on the SF-36_BP data.

Some limitations also need to be discussed. First, as literature on this topic is scarce, only 14 studies on pain and symptom burden in patients with COPD were included. Moreover, these studies showed substantial heterogeneity in design, setting, patient characteristics and pain measurement instruments used. Selected studies included patients with relatively severe COPD; mean FEV$_1$% predicted ranged from 21% to 48%. These differences in study methods might have influenced the reported pain prevalence and also limit the generalisability of the results. Furthermore, there were differences between the studies in patient selection criteria and the healthcare setting from which the patients were recruited, although most of the studies were conducted in a secondary (outpatient) care setting. Second, the appropriateness of including the SF-36_BP scores in this review is debatable. As our search strategy did not include 'QoL' as a keyword, we included only those studies on QoL that mentioned the keyword 'pain' in the abstract. This implies that our data on pain as a subdomain of QoL may not be complete. Nevertheless, we feel that the reported results do provide important information on this subject.

Interpretation of findings and relation to other literature

The wide range in pain prevalence can be explained by the heterogeneity in study design, setting, patient characteristics and instruments and definitions used to measure pain. We were interested in chronic and/or recurrent pain in patients with COPD. However, as we wanted a broad search method, we used 'pain' instead of 'chronic pain' as a major key word in our search strategy, as many studies do not clearly define pain as being 'chronic' or 'acute'. We did however exclude studies that concerned 'pain during acute bronchitis' (figure 1). Different studies used different definitions of pain and none of the included studies presented longitudinal data on the course of pain. The wide range in pain prevalence can also be explained by differences in the quality assessment score. Three of the studies on pain and symptom burden that reported the prevalence of pain, had quality limitations as identified with the MMAT. Furthermore, in the study conducted by Elkington et al[14] pain prevalence was based on reports of informants of the deceased participants. Agreement between the patient's and the proxy perception of pain is only moderate.[14 49] This by-proxy reporting of symptoms and the fact that the study included only patients in the terminal phase of their disease, could explain the relatively high level of reported prevalence of pain (72%). Claessens et al[13] reported a relatively low

Figure 2 Number of publications on 'pain' and 'symptom burden including pain' in patients with chronic obstructive pulmonary disease.
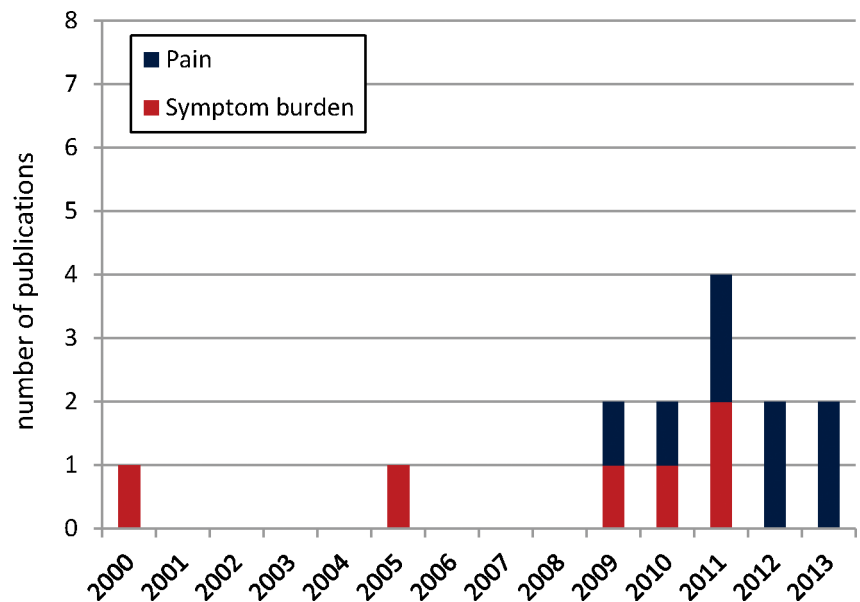
prevalence of pain (21%). However, pain was defined as 'moderately severe or extremely severe pain at least half of the time'. Borge et al[20] found a relatively high prevalence (72%) but used a much lower threshold, as pain was considered to be present in all patients that shaded pain on the body diagram of the BPI. Roberts et al[23] also reported a relatively high pain prevalence of 60%. In their cross-sectional study, recurrent pain-related health-care utilisation (diagnosis and treatment) was considered evidence of chronic pain; data were received from the managed care claims database and from the out-patient pharmacy. Although evidence of chronic pain based on diagnosis and management can be reliable, it should be noted that, in the latter study, 28.6% patients with COPD used short-acting or long-acting opioids, compared with 17% in the control group (patients with other chronic diseases).[23] However, as the reason for prescribing opioids was not stated it is debatable whether opioid prescription was indeed aimed at treating pain, especially as it is also prescribed for chronic dyspnoea in patients with COPD.[50] Therefore, the

reported prevalence of chronic pain in the study of Roberts et al[23] might be an overestimation. The reported prevalence of pain should be interpreted in relation to pain prevalence in the general population, as well as in patients with cancer and other chronic diseases. Recent population-based surveys showed that 25–35% of the adults report chronic pain.[51] In patients with cancer this percentage is higher, as 50% of all patients with cancer experience chronic pain.[51] Thus, the literature indicates that the prevalence of pain in patients with COPD is higher compared with the general population. Results from our meta-analysis on the SF-36_BP data also show that patients with COPD experience more pain compared to the general population: mean score of the SF-36_BP domain in the general US adult population is 75.2 (SD 23.7),[11] which is higher than the mean score we found in our random-effects meta-analysis of the SF-36_BP data in patients with COPD. A higher score on the SF-36_BP domain refers to less pain and better QoL. We were not able to perform a meta-analysis on the results of the included studies that used other QoL

Figure 3 Prevalence of pain. ● prospective cohort study; ◆ cross-sectional study; ■ mixed method; ▲ retrospective postbereavement study. green: Mixed Method Appraisal Tool (MMAT)-score: 100%; orange: MMAT-score: 75%; red: MMAT-score: 50%.
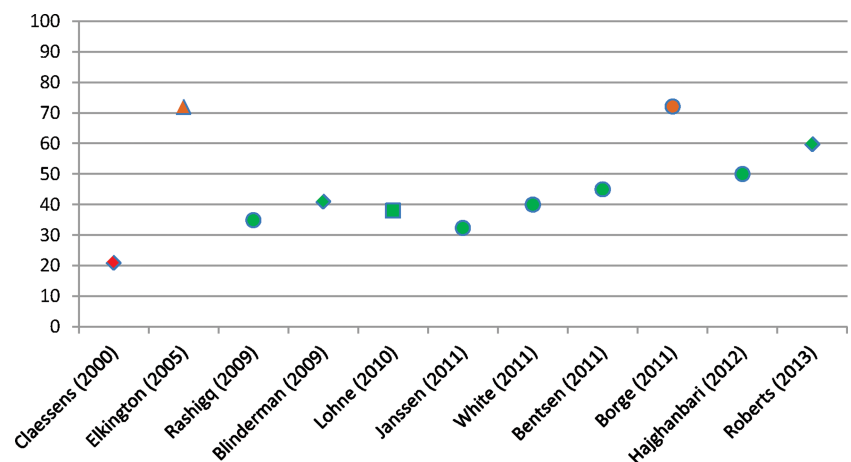
Figure 4 Random effects meta-analysis of studies that examined the mean score on Short-Form health survey-36 (SF-36_BP) in patients with chronic obstructive pulmonary disease. The Forest plot shows the mean scores with 95% CIs for included study populations. The Q statistic was 19.32 with df=20 (p>0.10) and I^2 was 0%. The MMAT scores are shown using different colours: green: MMAT-score: 100%; orange: MMAT-score: 75%; red: MMAT-score: 50%; purple: MMAT-score: 25%.

instruments, because of the very small numbers of studies that used the same instrument (EQ-5D: n=3; NHP: n=2; HSQ: n=1; DHP: n=1). Results from the random-effects meta-analysis of the SF-36_BP scores show substantial heterogeneity. It is very likely, that parts of the heterogeneity is explained by research setting, population, study design, cultural diversity and other, unknown variables.

None of the included studies on pain or symptom burden reported a significant relationship between lung function (measured as $FEV_1\%$ predicted or GOLD grade) and pain prevalence or pain severity.

Table 4 Factors related to pain (presence and severity)

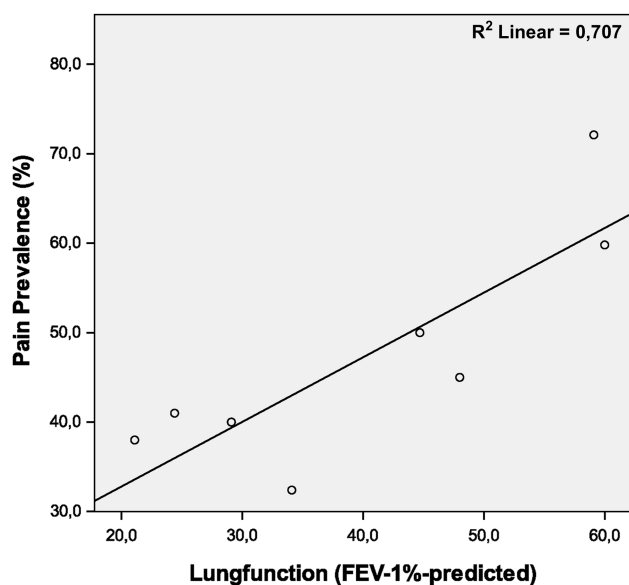| Significant relation	No relation	Conflicting results
HRQoL[20]	age, sex[18] [20–22]	Comorbidity[8] [18] [20–23]
Breathlessness[17] [18] [21]	Lung function[8] [18] [20–23]	
Insomnia[18] [22]	Smoking status[18] [20] [21]	
Fatigue[18]		
Anxiety[18]		
Depression[18] [23]		
Nutritional status[20]		
HRQoL, health-related quality of life.		

Figure 5 Relationship between lungfunction and pain prevalence. Each data point represents a separate study. Correlation coefficient: Spearmans r=0.79 (p=0.021).

Interestingly, when we investigated the correlation between lung function and pain prevalence over all included studies on pain and symptom burden in patients with COPD, a strong correlation was found between lung function and pain prevalence. Studies that investigated prevalence of pain in patients with moderate COPD reported a higher pain prevalence compared with studies in patients with severe and very severe
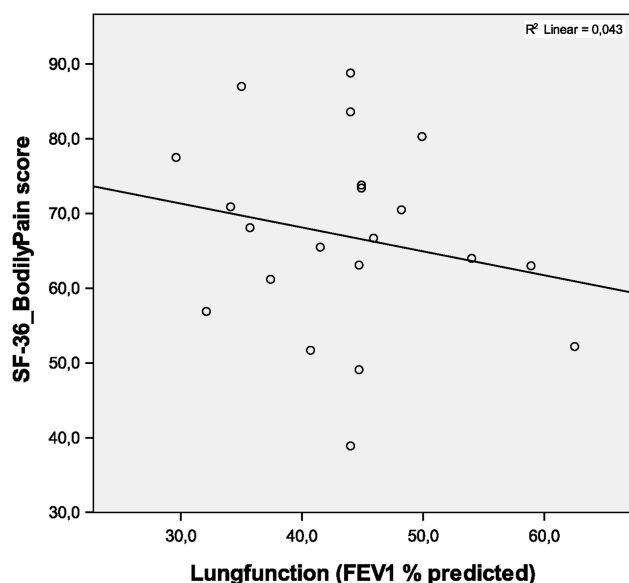
Figure 6 Relationship between lungfunction and Short-Form health survey-36 Bodily Pain (SF-36_BP) score. Each data point represents a separate study. Increasing units on the y-axis (eg, higher SF-36_BP scores) refer to less severe pain and better quality of life. Pearson's correlation coefficient=0.21 (p=0.37).

COPD. This might suggest that pain is more prevalent in patients with moderate COPD compared with patients with severe or very severe COPD. This finding has not previously been reported in literature on pain in patients with COPD. An explanation for this might be found in the hypothesis that when investigating the relationship between lung function and pain, confounding and selection bias are very likely to occur. Possible selection bias and confounding in the included studies might be an explanation for the observed relation between lung function and pain prevalence in the present study. For example, the number and severity of comorbidities may have caused selection bias: patients with very severe COPD and many comorbidities (cardiovascular and musculoskeletal such as osteoporosis) might have already died, or were not able to participate in the studies due to severely limited functional capacity. The number and severity of comorbidities might also have acted as a confounder in the relationship between pain prevalence and disease severity in the included studies. Furthermore, our results can be interpreted in line with a growing body of evidence showing that the correlation between FEV_1, symptoms and impairment of a patient's health status is weak.[52] Hence, in the recently updated GOLD Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD strategy, 2014) the classification of a patient's disease severity requires assessment of symptoms and exacerbation history, in addition to the degree of airflow obstruction. Our results show some evidence for a relationship between pain and comorbidity, although the included studies are not entirely consistent on this topic. Musculoskeletal disorders and comorbidities (including mechanical limitations of chest wall movement due to hyperinflation and osteoporosis) are considered possible causes of pain in patients with COPD.[8 9] However, due to the heterogeneity in the study designs we were unable to conduct a meta-analysis on pain prevalence and lung function controlling for comorbidity. In conclusion, much remains unclear about the relationship between disease severity, pain and comorbidity in patients with COPD and further research on this topic is needed.

We were unable to identify a study that investigated a specific intervention aimed at reducing pain in patients with COPD. The lack of literature on this topic is probably due to the fact that, in general, literature on pain in patients with COPD is scarce and pain seems to be a symptom that is often overlooked; this applies to daily practice and to research on the effect of comprehensive interventions, such as pulmonary rehabilitation (PR) and integrated disease management (IDM). In systematic reviews on PR and IDM in patients with COPD, pain is not mentioned as a patient-centred outcome in the field of symptom management.[53 54] Also, in national and international COPD guidelines there is almost no discussion of pain as part of a comprehensive symptom assessment. For example, the GOLD Global Strategy for Diagnosis, Management, and Prevention of COPD

(GOLD guideline 2014) does not mention chronic pain and discusses opioids only in the context of the relief of dyspnoea. Also, the combined statement on PR of two major international medical societies does not mention pain as a problem in COPD management.[55] Moreover in the Institute for Clinical Systems Improvement (ISCI) guidelines for management of COPD, pain is not discussed. Only the American Thoracic Society (ATS) clinical policy statement on palliative care for patients with respiratory diseases and critical illness includes a separate section on pain management; however, this addresses only dying patients with respiratory diseases and critical illnesses in general.[56]

CONCLUSION AND IMPLICATIONS

Pain in patients with COPD is a significant problem with an estimated prevalence of 32–60%. Literature on this topic is scare, and studies specifically focusing on pain in patients with COPD have only recently been published. Little is known about the factors associated with pain and no literature is available on the effect of interventions aimed at reducing pain in patients with COPD. Studies that investigated pain in patients with moderate airflow limitation reported a higher pain prevalence compared with studies in patients with severe and very severe airflow limitation. This finding might suggest that pain is more prevalent in patients with moderate COPD compared with patients with severe or very severe COPD. However, there was a substantial heterogeneity in patient characteristics and outcome assessment tools. More research on this topic is needed. Standardisation of assessment tools of pain in patients with COPD is needed. Future studies should focus on determining a more accurate prevalence of pain in patients with COPD, also in relationship to disease severity and comorbidity. Research should also pay more attention to the causes, course and characteristics of pain and clinical intervention trials are warranted. Furthermore, adequate pain recognition and treatment in clinical practice is important and pain assessment should be incorporated into regular comprehensive symptom assessment in the clinical care of this group of patients. Finally, pain prevalence and its possible impact on QoL should be discussed in guidelines on COPD in order to raise awareness and recognition of this topic.

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