BMJ Open

Hospitalisation and mortality outcomes of patients with comorbid COPD and heart failure: a systematic review protocol

Eleanor L Axson,[1] Varun Sundaram,[1,2] Chloe I Bloom,[1] Alex Bottle,[3] Martin R Cowie,[1] Jennifer K Quint[1]

[1]National Heart and Lung Institute, Imperial College London, London, UK
[2]Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA
[3]Dr Foster Unit, Department of Primary Care and Public Health, Imperial College London, London, UK

Correspondence to
Miss Eleanor L Axson;
e.axson@imperial.ac.uk

ABSTRACT

Introduction Chronic obstructive pulmonary disease (COPD) and heart failure (HF) often coexist in patients. Many studies have explored the short-term and long-term outcomes of patients with comorbid COPD and HF; however, there have been discrepancies in their findings.

Methods and analysis In this systematic review, MEDLINE and Embase will be searched using a prespecified search strategy. Randomised controlled trials and studies conducted in the general population that employ analytical or descriptive (longitudinal or case–control) study designs that report odds ratios (ORs), hazard ratios (HRs), or risk ratios (RRs) of mortality or hospitalisation, comparing patients with comorbid COPD and HF with patients with just COPD, will be selected. Screening by title and abstract, then full-text screening will be conducted by two reviewers. The Population, Exposure, Comparator, Outcomes, Study (PECOS) characteristics framework will be used to systemise the data extraction from selected studies. Study quality will be assessed using an adapted version of the Newcastle-Ottawa risk of bias tool. Data extraction and the risk of bias will also be conducted by two reviewers. Given sufficient homogeneity of selected studies, a meta-analysis will be conducted. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria will be used to assess the quality of cumulative evidence.

Dissemination With this review, we hope to improve the understanding of clinical outcomes of patients with comorbid COPD and HF. We intend to publish the results of our review in a peer-reviewed journal and to present our findings at national and international meetings and conferences.

PROSPERO registration number CRD42018089534

BACKGROUND
Rationale

It is estimated that 3 million individuals in the UK have chronic obstructive pulmonary disease (COPD), but that only one-third are currently diagnosed.[1] According to the British Heart Foundation, an estimated 900 000 individuals are living with heart failure (HF) in the UK, estimated to be increasing at a rate of over 25 000 new cases per year.[2 3]

Strengths and limitations of this study

► The main strength of the review is that it is based on a comprehensive search strategy designed to retrieve maximum articles related to our research questions.
► The main limitation of this study is the use of observational studies relying on healthcare databases leading to uncertain validity of the diagnoses of chronic obstructive pulmonary disease (COPD) and heart failure (HF).
► Another limitation is the selection bias in randomised control trials that may skew outcomes.
► Studies have shown that COPD is often undiagnosed in patients with HF, and vice versa, which may impact the implications of our findings.

HF and COPD often coexist in patients. In older community patients with COPD, 20% have comorbid HF, and COPD was diagnosed prospectively in 30% of stable community patients with HF.[4 5] HF and COPD share aetiology, symptoms and the potential to exacerbate the other condition, leading to higher healthcare utilisation costs and mortality in patients with both conditions.[6 7] Recent international guidelines have recommended increased consideration of comorbid conditions when assessing COPD and HF, demonstrating recognition of the influences of comorbidities on disease progression and prognosis.[7 8]

The increased mortality resulting from HF in COPD, and vice versa, could be attributed to the comorbidity itself or potentially to the complex interplay related to the underutilisation of beta-blockers and/or the long-term use of beta-agonists in this population.[9 10] There have been studies that have explored the short-term and long-term outcomes of patients with comorbid COPD and HF; however, there have been discrepancies

in their findings. In this systematic review, we hope to address whether or not having comorbid COPD and HF leads to worse outcomes, as measured by mortality and hospitalisation, compared with having COPD only.

Objectives

The primary aim of this systematic review is to determine if patients with comorbid COPD and HF have worse clinical outcomes than patients with COPD alone. This systematic review has two objectives:

► To assess the mortality rate of patients with comorbid COPD and HF compared with patients with COPD alone.
► To assess the hospitalisation rate of patients with comorbid COPD and HF compared with patients with COPD alone.

METHODS

This protocol has been prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.[11]

Eligibility criteria
Study design/characteristics
We will target randomised controlled trials and observational studies (longitudinal cohorts and case–control). Studies conducted post-1980, from any world region and reported in English will be considered eligible. Animal studies will not be included.

Participants
Our study will ideally draw participants from the general adult population ≥35 years of age.

Exposure
The primary exposure of interest is comorbid COPD and HF. Studies involving an exposed participant group with diagnoses of both COPD and HF will be included in the review. Ideally, both the diagnosis of COPD and HF will be confirmed clinically; however, depending on the number of studies retrieved we will consider studies where COPD is self-reported. Clinical diagnosis of COPD requires spirometry confirmation, with a postbronchodilator forced expiratory volume in 1 s/forced vital capacity ratio of <0.7, indicative of airway obstruction.[12] Clinical diagnosis of HF should meet National Institute for Health and Care Excellence guidelines for the diagnosis of chronic HF.[13]

Comparators (controls)
Studies will be included if they compare outcomes in the exposed group (people with comorbid COPD and HF) with those in a group of 'unexposed' individuals (people with a diagnosis of COPD alone).

Outcome
Studies will be included in the review if one of the primary outcomes is mortality at any time postdiagnosis and/or emergency (unplanned) hospitalisation. Our primary outcomes of interest are respiratory-related deaths and hospitalisations. Should the availability and detail of the literature not allow for cause-specific outcomes alone to be investigated, we will look at all-cause hospitalisation and mortality, broken down by causes as appropriate. We will investigate hospital admission and, if possible, 30-day readmission. Our search strategy has been developed to accommodate all of these outcomes.

Information sources
MEDLINE (Ovid interface, 1980 onwards) and Embase (Ovid interface, 1980 onwards) will be searched for potentially relevant articles using predefined search strategies. The International Prospective Register of Systematic Reviews (PROSPERO) will be searched periodically for ongoing and completed systematic reviews pertaining to comorbid COPD and HF. The Cochrane Central Register of Controlled Trials on *The Cochrane Library* will be searched for trials pertaining to comorbid COPD and HF. Additionally, a manual search of the reference lists of all included studies will be conducted to check for other possibly relevant articles.

Search strategy
Literature searching will include Medical Subject Headings (MeSH) terms and free text using an appropriate set of words to delimit each of 'COPD', 'HF', 'hospitalisation' and 'mortality'. The terms for 'COPD' and 'HF' will be combined using the Boolean logic operator AND. The terms for 'hospitalisation' and 'mortality' will be combined using the Boolean logic operator OR. These two statements will then be combined using the Boolean logic operator AND. For example, ((chronic obstructive pulmonary disease AND heart failure) AND (hospitalisation OR mortality)).

Search terms will be reviewed by at least three people with medical knowledge prior to searching. Strategies will be developed for MEDLINE and then adjusted for use in Embase. Search filters limiting to studies published in 1980 onwards, studies published in English and studies in humans will be used. The literature review searches will be updated at the end of the process. The proposed search terms are listed in table 1.

Study records
Data management
Literature search results will be uploaded and stored in EndNote (V.X8) and duplicates will be removed.

Selection process
First, titles and abstracts of all records identified by the search will be screened independently by two researchers against the predefined eligibility criteria. Disputed records will be included in the full-text screening. Next, the full reports of the articles identified in the first screening as possibly meeting our eligibility criteria will obtained. Online supplementary material will be consulted if the information contained in the main article are not enough to determine fulfilment of the inclusion criteria. Full text screening will

Table 1 Search terms (provisional)

Concept	Search terms
Chronic obstructive pulmonary disease	*MeSH terms:* exp Pulmonary Disease, Chronic Obstructive/exp Emphysema/ exp Pulmonary emphysema/exp Chronic bronchitis/exp Lung diseases, obstructive/ *Free text terms:* COPD, COAD, COBD, AECB, emphysema, chronic bronchitis, obstructive (pulmonary or lung or airway or airflow or bronchitis or respiratory) disease
Heart failure	*MeSH terms:* exp Heart Failure/ exp Ventricular dysfunction, left/ *Free text terms:* heart failure, HF, (chronic or acute) heart failure, CHF, AHF, cardiac failure, left ventricular dysfunction, myocardial failure, congestive heart failure, hospitalised heart failure, HHF, cardiomyopathy
Mortality	*MeSH terms:* exp Mortality/exp Hospital mortality/ *Free text terms:* mortality, death*, all-cause (mortality or death*), cause-specific (mortality or death*), cardiovascular (mortality or death*), respiratory (mortality or death*)
Hospitalisation	*MeSH terms:* exp Hospitalization/ exp Patient admission/exp Patient readmission/ *Free text terms:* hospitali?ation*, hospital admission*, hospital readmission*, patient admission*, patient readmission*, hospital stay*, hospital treatment*, hospital care

AECB, acute exacerbations of chronic bronchitis; COPD, chronic obstructive pulmonarydisease; COAD, chronic obstructive airways disease; COBD, chronic obstructive bronchitis disease; HF, heart failure; MeSH, Medical Subject Headings.

also be conducted independently by two reviewers. Any discrepancies will be resolved through discussion and/or consultation with a third reviewer. A record of reasons for rejection of articles during the full-text stage will be kept.

Data extraction

Information will be extracted from all studies determined to meet the inclusion criteria using a modified version of the prespecified data extraction form used in a previous systematic review.[14] The form will be modified as necessary following testing with the first six selected studies. Online supplementary material and/or authors of the studies will be consulted if the information provided in the main articles is insufficient to complete data extraction. Data extraction will be carried out independently by two reviewers. Discrepancies will be resolved through discussion and/or consultation with a third reviewer.

Data items

The Population, Exposure, Comparator, Outcomes, Study characteristics framework will guide our data-extraction process. Information to be extracted include:

- ▶ Population: characteristics of the study population such as age and sex distribution and the size of the population; the sampling methods used; and the inclusion/exclusion criteria of the study.
- ▶ Exposure: definition of exposure, identification of exposure, number of subjects exposed and any exclusions.
- ▶ Comparators: definition of unexposed individuals, identification of unexposed individuals, number of unexposed individuals and any exclusions.
- ▶ Outcomes: identification of deaths and/or hospitalisations (all-cause, respiratory-specific), number of individuals with the outcome, any exclusions, length of follow-up.
- ▶ Study characteristics: setting, design, period of study, aims, objectives.

We will record unadjusted and maximally adjusted estimates as appropriate, and we will note which covariates were used in adjustment. If results were stratified, these results will be itemised; and if these were not reported, we will seek this information from the study authors.

Outcomes and prioritisation

The primary outcomes of interest are hospitalisation rate and mortality rate of patients with comorbid COPD-HF as compared with patients with COPD alone. We will look at all-cause hospitalisation and mortality, and, if detail permits, CVD/respiratory-specific causes. Studies must report risk ratios (RRs), hazard ratios (HRs) or odds ratios (ORs). We will prioritise randomised controlled trials and observational studies.

Risk of bias assessment (in individual studies)

The majority of established methods and tools for assessing the methodological quality of individual studies were designed for randomised controlled trials and intervention studies. As this study is observational, we will be using a method devised previously,[14] based on the Newcastle-Ottawa scale.[15] Our tool will draw on bias stemming from the selection of participants, the measurement of variables and the control of confounding. Each source of bias will be rated from 'moderate to high risk of bias', 'unclear risk of bias' or 'low risk of bias'. Each component will be assessed independently. Risk of bias assessment will be conducted independently by two reviewers. Discrepancies will be resolved through discussion and/or consultation with a third reviewer.

Data synthesis

We will group studies according to their comparator group, that is to say, by whether the outcomes of patients with comorbid COPD and HF are compared with patients with only COPD. We will use the I^2 statistic to assess the level of statistical heterogeneity of our studies. If we find that our studies have a very high level of heterogeneity ($I^2 > 75\%$), we will conduct a narrative synthesis of the data. If the level of heterogeneity allows, we will conduct a meta-analysis using inverse probability weighting to calculate a pooled effect estimate using the appropriate model

(fixed or random effects based on level of heterogeneity). Should numbers of studies allow, we will analyse studies with adjudicated diagnoses in a separate analysis.

Risk of bias in meta-analysis
We will use funnel plots to assess the likelihood of reporting bias and Begg's test to test for asymmetry. If there is not a sufficient number of studies, we will discuss possible sources of bias across studies and bear this limitation in mind when drawing conclusions.

Confidence in cumulative evidence
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines will be used to assess the quality of evidence for our research questions. Special attention will be paid to methodological flaws and consistency of results between studies. Additional domains will be considered if appropriate. Strength of evidence will be judged as 'high' (further research is unlikely to change our conclusion), 'moderate' (further research is likely to alter our conclusion) or 'low' (further studies are required to answer the research question with a high degree of confidence/increase confidence).

Patient involvement
No patients were involved in the design or analysis of this study.

ETHICS AND DISSEMINATION
We intend to publish the results of our review in a peer-reviewed journal and to present our findings at national and international meetings and conferences.

Limitations
The main limitation of this study is the use of observational studies relying on healthcare databases leading to uncertain validity of the diagnoses of COPD and HF. Additionally, randomised control trials have selection biases that may skew outcomes. COPD and HF share many symptoms, and misdiagnosis may result. Finally, studies have shown that COPD is often undiagnosed in patients with HF, and vice versa, which may impact the implications of our findings.[5 16 17]

CONCLUSION
With this review, we hope to improve the understanding of clinical outcomes of patients will comorbid COPD and HF.

REFERENCES
1. Shahab L, Jarvis MJ, Britton J, et al. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax* 2006;61:1043–7.
2. Donkor A. *British Society for Heart Failure National Heart Failure Audit*. London: National Institute for Cardiovascular Outcomes Research, 2016.
3. Townsend NW, Wickramasinghe K, Bhatnagar P, et al. Coronary Heart Disease Statistics. *British Heart Foundation* 2012.
4. Boschetto P, Fucili A, Stendardo M, et al. Occurrence and impact of chronic obstructive pulmonary disease in elderly patients with stable heart failure. *Respirology* 2013;18:125–30.
5. Boudestein LC, Rutten FH, Cramer MJ, et al. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail* 2009;11:1182–8.
6. Cowie MR, Anker SD, Cleland JGF, et al. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Fail* 2014;1:110–45.
7. Rusinaru D, Saaidi I, Godard S, et al. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol* 2008;101:353–8.
8. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2010 https://www.nice.org.uk/guidance/cg101 (cited 15 Jan 2018).
9. Bermingham M, O'Callaghan E, Dawkins I, et al. Are beta2-agonists responsible for increased mortality in heart failure? *Eur J Heart Fail* 2011;13:885–91.
10. Lipworth B, Skinner D, Devereux G, et al. It is important to distinguish between HFrEF and HFpEF when interpreting these data. *Heart* 2016;102:1934.1–1934.
11. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
12. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. [Webpage]. 2017 http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/ (cited 10 Jan 2018).
13. Chronic heart failure in adults: management. [Webpage]. 2010 https://www.nice.org.uk/guidance/cg108/ (cited 10 Jan 2018).
14. Morgan AD, Sharma C, Rothnie KJ, et al. Chronic obstructive pulmonary disease and the risk of stroke: a systematic review protocol. *BMJ Open* 2016;6:e011898.
15. Wells G, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa: The Ottawa Hospital Research Institute.
16. Almagro P, Lapuente A, Pareja J, et al. Underdiagnosis and prognosis of chronic obstructive pulmonary disease after percutaneous coronary intervention: a prospective study. *Int J Chron Obstruct Pulmon Dis* 2015;10:1353–61.
17. Campo G, Pavasini R, Barbetta C, et al. Predischarge screening for chronic obstructive pulmonary disease in patients with acute coronary syndrome and smoking history. *Int J Cardiol* 2016;222:806–12.