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Chronic obstructive pulmonary disease and the risk of stroke: a systematic review protocol

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ABSTRACT

Introduction: There is good evidence to suggest that chronic obstructive pulmonary disease (COPD) increases the risk of ischaemic heart disease, in particular myocardial infarction (MI). The relationship between stroke and COPD, however, is not as well established, and studies conducted to date have generated conflicting results.

Methods and analysis: MEDLINE and Embase will be searched for relevant articles using a prespecified search strategy. We will target observational studies conducted in the general population that employ either a longitudinal cohort or case–control study design to estimate ORs, HRs or incident rate ratios for the association between COPD and a subsequent first stroke. Both stages of screening, title and abstract followed by full-text screening, will be conducted independently by two reviewers. The Population, Exposure, Comparator, Outcomes, Study characteristics (PECOS) framework will be used to systematise the process of extracting data from those studies meeting our selection criteria. Study quality will be assessed using an adapted version of the Newcastle-Ottawa risk of bias tool. The data extraction and the risk of bias assessment will also be conducted in duplicate. A meta-analysis will be considered if there is sufficient homogeneity across selected studies or groups of studies. If a meta-analysis is not justified, a narrative synthesis will be conducted. Selected Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria will be used to assess the quality of the cumulative evidence.

Dissemination: Currently ranking second and fourth in the list of global causes of mortality, respectively, stroke and COPD are important non-communicable diseases. With this review, we hope to clarify some of the current uncertainty that surrounds the COPD–stroke relationship and in turn improve understanding of the nature of the role of COPD in comorbid stroke.

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Strengths and limitations of this study

- This review benefits from a comprehensive search strategy, designed to retrieve as many articles relevant to our primary and secondary research questions as possible. In particular, we have broadened our scope to include studies which examine the relationship between impaired lung function and stroke, as well as that between a chronic obstructive pulmonary disease (COPD) diagnosis and stroke.
- This review is not unique in the sense that other researchers have examined the evidence linking COPD and stroke. However, it does seek to build on and extend previous work by including a number of new studies and by distinguishing prevalent and incident stroke events more explicitly than has hitherto been attempted.
- The main limitation, inherent in observational studies which rely on administrative healthcare databases, is uncertainty in the validity of the ascertainment of the exposure (diagnosis of COPD) and the outcomes (stroke case definition).

progressive airflow limitation and concomitant respiratory symptoms. Prevalence estimates vary between countries but generally lie in the range 5–10%.[1] Rates of COPD rise steeply with increasing age and are generally higher in men than in women. Smoking is considered to be the main risk factor, but exposure to airborne irritants and genetic predisposition are likely contributory factors.[1]

Comorbidities are a defining feature of COPD. More than 95% of patients with COPD have at least one comorbidity and over 50% have four or more coexisting diseases.[2] Cardiovascular diseases (CVDs) are especially prevalent among patients with COPD and are considered to contribute substantially to COPD disease progression, low quality of life, poor clinical outcomes and all-cause mortality in this group of patients.[3]

Both cerebrovascular disease (stroke) and ischaemic heart disease (IHD) have been

BACKGROUND
Rationale

Chronic obstructive pulmonary disease (COPD) is a common debilitating inflammatory lung condition characterised by

shown to be associated with COPD.[4–7] Whereas the latter association has been well documented and there is, for instance, good evidence to suggest that COPD increases the risk of myocardial infarction (MI) approximately twofold,[6] that between stroke and COPD has not been subject to the same level of scrutiny. This is despite the fact that stroke is one of the most common causes of death and severe disability worldwide, second only to IHD.[8]

Those studies which have examined the association between COPD and stroke risk have generated conflicting results.[9–11] Attempts have been made to review the available evidence linking COPD and stroke,[4 6 12 13] typically as part of broader systematic reviews looking a range of CVD outcomes. In a largely narrative review of cohort and case–control studies, Müllerova et al[4] were unable to find sufficient cumulative evidence to support the hypothesis that COPD is an independent risk factor for stroke. More recently, Chen et al[6] have attempted to quantify the magnitude of the associations between CVD outcomes and COPD, based on a much larger evidence base (29 studies) and using a more rigorous review methodology. For stroke outcomes, a meta-OR of 1.32 (95% CI 0.99 to 1.76; 16 datasets) was calculated, providing only weak evidence for an increased risk for all stroke in COPD. However, as the authors themselves acknowledge, their analysis is compromised by a heavy reliance on cross-sectional studies which restricts assessment of the temporality of the association.

In the present systematic review, it is our intention to examine the evidence base linking stroke and COPD. By extending the work of previous reviewers in a number of key respects, we hope to clarify some of the uncertainty that currently surrounds the nature of the relationship between COPD and the risk of stroke. In the first instance, we intend to expand the evidence base for the review by including a number of recently published large, population-based observational studies. These new studies are likely to provide valuable insight given that they are longitudinal in nature and also consider, for the first time, outcomes by stroke subtype (ie, ischaemic (atherothrombotic, cardioembolic and lacunar infarcts) or haemorrhagic (intracerebral and subarachnoid) stroke). The latter is of particular interest given the possibility that COPD may increase the risk for certain types of stroke more than others. Arboix et al,[14] for example, report a significant association between COPD and atherothrombotic ischaemic strokes but not cardioembolic strokes, lacunar infarcts or ischaemic strokes of unusual aetiology.

In addition to exploring the COPD–stroke association by stroke subtype, we will attempt to group studies by study design, separating those cross-sectional studies that estimate prevalence from studies that estimate stroke risk (as incident events). Third, we will also review the evidence linking stroke risk to lung function, as measured by forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and the ratio, FEV_1/FVC.

Objectives

The primary aim of the systematic review is to determine whether people with COPD are at greater risk of a subsequent cerebrovascular event (stroke) than those without COPD.

Secondary research questions include the following:

► Is there any evidence that the association between COPD and stroke varies with age, sex, smoking history, medication history and/or type of stroke (eg, haemorrhagic vs ischaemic stroke)?
► Is COPD an independent risk factor for stroke?
► Is stroke risk modified in particular COPD phenotypes, for example, in frequent exacerbators and/or in those with more severe disease?
► Is the magnitude of the association between COPD and subsequent stroke generally lower, higher or similar to that observed between COPD and MI?

METHODS

This protocol has been prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.[15]

Eligibility criteria

Study design/characteristics: Our target will be observational studies that use either a longitudinal cohort (prospective and retrospective) or a case–control study design. While recognising the limitation of cross-sectional study designs in terms of assessment of temporality, we will also consider cross-sectional studies which estimate stroke prevalence, and/or ORs for stroke, in COPD versus COPD-free patient groups. We will also include studies which are secondary analyses of a randomised control trial (RCT) where these meet our other inclusion criteria.

Participants: Our study populations will ideally be drawn from the general adult population but restricted to those aged 35 years and over. If necessary and appropriate, studies involving a hospitalised patient population will also be included. Studies conducted post 1980, from any world region and reported in any language will be considered as eligible.

Animal studies will not be included.

Exposure: The primary exposure of interest is COPD. Thus, studies involving an exposed participant group whose members have a confirmed clinical diagnosis[i] of COPD will be included in the review. Depending on the number of studies retrieved, we will also consider studies in which COPD diagnosis relies on self-report.

Studies in which the exposure status is assessed in terms of spirometry alone will also form part of the

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[i]According to GOLD, a diagnosis of COPD should be considered in any patient who has dyspnoea, chronic cough or sputum production and a history of exposure to known risk factors. A clinical diagnosis requires confirmation by spirometry: a postbronchodilator FEV_1/FVC ratio of <0.7 is considered indicative of airway obstruction and thus COPD.[1]

review. In adults with 'normal' lung function, the value of the FEV_1/FVC ratio lies between 0.7 and 0.8; a value of <0.7 indicates impaired lung function, and more precisely, airflow obstruction. Other measures of lung function, FEV_1 and FVC, are less specific and low values can indicate either obstructed or restricted airflow.

Comparators (controls): In order to be eligible for inclusion, studies must compare outcomes in a group of exposed individuals (people with a diagnosis of COPD or evidence of impaired lung function) with a group of unexposed individuals, that is, people without COPD or normal lung function.

Outcomes: Studies will be included in the review if one of the primary outcomes is objective or self-reported stroke. A stroke is conventionally defined as a focal disturbance of cerebral function of vascular origin lasting more than 24 hours. When the disturbance is of a transient nature, and does not appear to cause lasting neurological damage and clinical symptoms, it is referred to as a transient ischaemic attack or a TIA. Strokes are further subdivided into ischaemic and haemorrhagic strokes. Accounting for 85% of all strokes, ischaemic strokes are by far the more common. Haemorrhagic strokes, while less prevalent, are associated with higher mortality rates (30–50%).

In the case of those studies which meet our primary inclusion criteria, and for which data are available, we will assess a number of additional outcomes. Secondary outcomes of interest include MI and stroke subtypes. We will also report the results of any stratified analyses which estimate stroke risk in subpopulations of potential interest.

Information sources

The two main biomedical-related databases, MEDLINE (Ovid interface, 1948 onwards) and Embase (Ovid interface, 1980 onwards), will be searched for potentially relevant articles using predefined search strategies (see *Search strategy*). To ensure research saturation, the electronic database search will be supplemented by a manual search of the reference lists of all included studies to check for additional potentially relevant studies.

The International Prospective Register of Systematic Reviews (PROSPERO) will also be periodically checked for ongoing and completed systematic reviews that deal with COPD and comorbidities.

Search strategy

Literature search strategies will be based on both MeSH terms (Medical Subject Headings) and free text (natural language) searching using an appropriate set of key words to delimit the concepts 'COPD' and 'stroke'. These searches will be combined using the AND Boolean logic operator.

The list of proposed search terms will be reviewed by a number of people with medical knowledge and any necessary adjustments made prior to running the search. The search strategy will be developed in the first instance for MEDLINE and then adapted for use with Embase. No search filters will be applied. The proposed search terms are listed in table 1.

The literature searches will be updated at the end of the review exercise.

Study records

Data management: Literature search results will be uploaded to EndNote (V.7) and duplicate records removed.

Selection process: The selection of studies for inclusion in the review will be conducted in two stages. First, titles and abstracts of all records identified by the database searches will be screened by the primary researcher against the predefined eligibility criteria (see above) in order to identify a subset of potentially relevant studies. A second reviewer will repeat this exercise on a proportion of records (approximately half) and any discrepancies resolved by discussion. To reduce the risk of missing potentially relevant studies, a deliberately lenient approach will be adopted for this first level of screening (by title and abstract).

We will obtain full reports for all titles that appear to meet our eligibility criteria, or where there is uncertainty. Full text screening will be also conducted by two reviewers, with the primary researcher screening all reports and the second reviewer approximately one half. Online supplementary material will be consulted if the information provided in the main published article is insufficient to assess whether or not the inclusion criteria are met. Any discrepancies will be resolved by discussion and/or consultation with a third reviewer with specific expertise in COPD. A record will be kept of the reasons for rejection of articles during the full-text screening process.

Table 1	Search terms (provisional)
Concept	**Search terms**
COPD	*MeSH terms*: exp Pulmonary Disease, Chronic Obstructive/; 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; lung or respiratory or ventilatory) function
Stroke	*MeSH terms*: exp Stroke/; Stroke, Lacunar/; *Free text terms*: stroke; CVA; TIA; cerebrovascular (disease or event or accident or attack or injury); cerebral ischaemia; transient ischaemic attack; ischaemic stroke (atherothrombotic, cardioembolic, lacunar infarction); haemorrhagic stroke (intracerebral, subarachnoid)

AECB, acute exacerbation of chronic bronchitis; COAD, chronic obstructive airways disease; COBD, chronic obstructive bronchial disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischaemic attack.

Data extraction: Information will be extracted from all selected studies using a prespecified data extraction form designed by the primary reviewer (see online supplementary table S1). The form will be piloted on the first six selected studies and refined as necessary. Online supplementary material will be consulted and/or authors contacted if the information provided in the original published articles is insufficient to complete the extraction.

As with screening, data extraction will be carried out in duplicate on a proportion of selected records to reduce the risk of errors and introducing bias (around a quarter). Similarly, any discrepancies will be resolved by discussion and/or consultation with the third reviewer.

Data items
We will use the Population, Exposure, Comparator, Outcomes, Study characteristics (PECOS) framework to systematise our data extraction. Within each of these five domains, information will be recorded on the following items:
- Study characteristics: setting, design, period of study, aims and objectives;
- Population: characteristics of the study population (including size, sex and age distribution, ethnicity), recruitment and sampling methods, inclusion/exclusion criteria);
- Exposure: exposure status definition and identification, number of exposed subjects, any exclusions;
- Comparators: identification and definition of unexposed individuals, number of unexposed subjects, any exclusions;
- Outcomes: definition and identification of primary (stroke) and secondary outcomes (stroke subtypes, MI), number of subjects, any exclusions, length of follow-up.

In terms of the effect estimates for the association between COPD and stroke, we will record both the unadjusted and the maximally adjusted estimates. Details of the covariates measured and adjusted for will also be noted. Results of any additional stratified analyses, for example, by age group, gender or severity of COPD, will be itemised when these have been conducted. If stratified effect estimates of interest are not reported in the published article, this information will be sought from the study authors.

Outcomes and prioritisation
The primary clinical outcome of interest is first recorded stroke post a COPD diagnosis. We will prioritise those studies with a longitudinal study design that calculate effect estimates as either HRs or incidence rate ratios, but will also consider those studies that report ORs if it can be determined that subjects had not had a stroke event prior to the start of the study period.

Outcomes disaggregated by type of stroke—ischaemic (atherothrombotic, cardioembolic, lacunar infarct), haemorrhagic (intracerebral, subarachnoid) and/or TIA

—will be recorded for those studies which report such information. When risk of MI is also reported for the same cohort of patients, this will also be noted.

Risk of bias assessment (in individual studies)
There are several established methods and tools for assessing the methodological quality of individual studies.[16] However, the majority of these have been designed with the needs of RCT and healthcare interventions in mind and have limited application to observational studies. For this reason, we plan to devise our own risk of bias assessment tool, drawing on the Newcastle-Ottawa scale[17] and structured around three main sources of bias (domains):
- selection of participants;
- measurement of variables (exposures, outcomes and covariates);
- control of confounding.

Each component of our chosen domains will be assigned a risk of bias category from the following: 'moderate to high risk of bias', 'unclear risk of bias' or 'low risk of bias'. We will consider each component of our tool separately and will not attempt to assign our included studies an overall score.

Risk of bias assessment will be conducted independently by two reviewers on a quarter of the selected studies and disagreements will be resolved in the first instance by discussion and then through consultation with a third reviewer. On completion of this process, the remaining studies will be assessed for risk of bias by one reviewer.

Data synthesis
For the purposes of data synthesis, we will group studies according to both outcome definition (ie, prevalent vs incident stroke) and exposure definition, that is to say, we will distinguish studies which evaluate stroke risk in COPD versus non-COPD patients and those that compare the incidence of stroke in people with impaired lung function with those with normal lung function (as measured by FVC, FEV_1 or FEV_1/FVC). Our primary analysis will consider all strokes (as a composite outcome); depending on the number of retrieved studies, analyses by stroke subtype will be also conducted. Depending on the characteristics of the included studies, we will consider stratifying our results according to one or more additional criteria, for instance, by population (general vs hospitalised) and exposure ascertainment (physician diagnosis vs self-report).

If we find our included studies (or groups of studies) are sufficiently homogenous in terms of design, study population and outcomes, we will conduct a meta-analysis (using inverse variance weighting) to calculate a pooled effect estimate. We will use the I^2 statistic to assess the level of statistical heterogeneity and to guide our choice of model (fixed or random effects model). If however we find that level of heterogeneity ($I^2 > 75\%$) precludes such an approach, a narrative synthesis will be conducted, to include summary tables

detailing study characteristics, participants, exposure status and outcomes, and effect estimates.

Risk of bias in meta-analysis

Given sufficient numbers of studies, we will use funnel plots to assess the likelihood of outcome reporting bias (publication and other reporting biases) and a Begg's test to test for asymmetry. If however this is not possible we will discuss possible sources of bias across studies and bear this limitation in mind when drawing our conclusions.

Confidence in cumulative evidence

The quality of evidence for our primary and secondary research questions will be assessed using those domains of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines[18] that are pertinent to observational studies, notably those relating to methodological flaws within the component studies and the consistency of results across different studies. Additional domains may be considered if deemed 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).

ETHICS AND DISSEMINATION

Ethical review is not required as this study is a systematic review. It is our intention to submit the results of our review for peer-reviewed publication and to present our findings at national and international meetings and conferences.

Both stroke and COPD are important chronic non-communicable diseases, currently ranking second and fourth in the list of causes of global mortality, respectively.[8] With this review, we hope to contribute to the existing knowledge base for both conditions, but principally to an improved understanding of the nature of the role of COPD in comorbid stroke.

been reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.

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