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

Authors and affiliations

Ann D Morgan[1], Chetna Sharma[2], Kieran J Rothnie[1,3], James Potts[1], Liam Smeeth,[3] Jennifer K Quint[1,3]

[1] Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College London, London, UK

[2] Faculty of Medical Sciences, University College London, London, UK

[3] Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author**:** Ann Morgan (a.morgan15@imperial.ac.uk)

Additional administrative information

Systematic review registration number: The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 1 March 2016 (Registration number: CRD42016035932).

Competing interests: none to declare.

Funding: This systematic review was conducted as part of a research degree funded by The British Lung Foundation (RG14-15). LS is supported by a Wellcome Trust Senior Clinical Research Fellowship.

Contributions: Ann Morgan developed the review protocol, including the inclusion and exclusion criteria, the risk of bias assessment tool and the data extraction forms with assistance from Jennifer Quint, acted as first reviewer and prepared the draft paper for publication. Kieran Rothnie contributed to the development of the search strategy and risk of bias assessment tool. Chetna Sharma served as the second reviewer, assisting with the screening, data extraction and risk of bias assessment. James Potts helped with the preparation of the forest plots. All named authors reviewed and commented on draft versions of the paper.

Abstract

Rationale Chronic obstructive pulmonary disease (COPD) has been identified as a risk factor for cardiovascular diseases such as myocardial infarction. The role of COPD in cerebrovascular disease is, however, less certain: although earlier studies have suggested that the risk for stroke is also increased in COPD, more recent investigations have generated mixed results.

Objectives The primary objective of our review was to quantify the magnitude of the association between COPD and stroke. We also sought to clarify the nature of the relationship between COPD and stroke by investigating whether the risk of stroke in COPD varies with age, sex, smoking history and/or type of stroke and whether stroke risk is modified in particular COPD phenotypes.

Methods A search of MEDLINE and EMBASE databases was conducted in May 2016 to identify articles which compared stroke outcomes in people with and without COPD. Studies were grouped by study design to distinguish those which reported prevalence of stroke (cross-sectional studies) from those which estimated incidence (cohort or case–control studies). Additionally, studies were stratified according to study population characteristics, the nature of COPD case definitions, and adjustment for confounding (smoking). Heterogeneity was assessed using the I^2 statistic.

Results We identified 5,484 studies, of which 30 met our pre-defined inclusion criteria. Of the 25 studies which reported prevalence ratios, 11 also estimated prevalence odds ratios (PORs). The level of heterogeneity among these cross-sectional studies did not permit the calculation of pooled ratios, save for a group of four studies which estimated prevalence odds ratios adjusted for smoking (POR=1.51; 95%CI: 1.09–2.09; I^2=45%). All 11 studies which estimated relative risk for non-fatal incident stroke reported increased risk in COPD. Adjustment for smoking invariably reduced the magnitude of the associations.

Conclusion Although both prevalence and incidence of stroke is increased in people with COPD, the weight of evidence does not support the hypothesis that COPD is an independent risk factor for stroke. The possibility remains that COPD is causal in certain subsets of COPD patients and for certain stroke subtypes.

334 words

Introduction

Comorbidities are highly prevalent in chronic obstructive pulmonary disease (COPD) and an important consideration in the management of this heterogeneous disease. More than 95% of people with COPD have at least one comorbidity and over 50% have four or more (1). Cardiovascular diseases (CVDs) rank among the most frequently observed comorbidities in the COPD population and contribute to disease progression, poor clinical outcomes and mortality (2).

Large population-based studies have shown that CVD is not only a common cause of mortality in people with COPD, accounting for up to a third of all deaths (3), but also that the risk of cardiovascular mortality in this population is approximately twice that in the general population (4). Although the underlying reasons are not yet fully understood, there is evidence to suggest that COPD is an independent risk factor for the development of cardiovascular disease, with systemic inflammation providing the mechanistic link between the two (5-7).

The relationship between COPD and individual CVD outcomes has been the subject of several reviews (8-11). Whereas collective evidence points to an approximately twofold increase in the risk of a myocardial infarction (MI) (8, 11) the nature of the association between COPD and stroke is less certain. Earlier study findings are suggestive of an increased risk for stroke in people with COPD (12, 13), but more recent investigations have generated contradictory results (14). In order to clarify the role of COPD in relation to stroke, we performed a further systematic review of the available evidence linking COPD and stroke outcomes in which we report results separately for cross-sectional study designs (which estimate prevalence) and longitudinal cohort studies (which estimate incidence). In addition, we have been able to include a number of recently published population-based studies which investigate, in more detail than before, stroke outcomes by subtype.

Methods

Protocol and registration

In accordance with the PRISMA-P guidelines (15), study objectives, inclusion criteria, search strategies and analysis methods were pre-specified and documented in a protocol, which was registered with the International Prospective Register of Systematic Reviews in March 2016 (PROSPERO registration number: CRD42016035932) and published in the open literature (16).

Study objectives

Our primary objective was to quantify the magnitude of the association between COPD and stroke. Secondary objectives were to determine: 1) whether there is any evidence that the association between COPD and stroke varies with age, sex, smoking history and/or type of stroke (e.g. haemorrhagic versus ischaemic); and 2) whether stroke risk is modified in particular COPD phenotypes, e.g. frequent exacerbators.

Information sources and search strategy

MEDLINE (OVID(R) interface, 1948 onwards) and EMBASE (Ovid interface, 1980 onwards) were searched in May 2016 for articles of potential relevance. Literature search strategies were developed using both Medical Subject Headings (MeSH terms) and free text searching using an appropriate set of key words to delimit the concepts "COPD" or "airflow limitation" and "stroke". These searches were combined using the AND Boolean logic operator. The database search was supplemented by a manual scan of the reference lists of included studies. The search strategies are detailed in the data supplement (see **e-Appendix 1**).

Eligibility criteria

Inclusion criteria were drawn up using the PECOs framework. We included observational studies which 1) employed either a cross-sectional, cohort or case–control design; 2) were conducted in an adult population aged > 35 years; and 3) reported prevalence and/or incidence of cerebrovascular events (stroke) in people with a diagnosis of COPD or evidence of obstructed lung function (FEV_1/FVC ratio < 0.7) and also in a comparator group of individuals without COPD and/or with normal lung function. We also considered secondary analyses of randomised control trials where these met our other inclusion criteria. Accepted definitions for COPD included a physician diagnosis, recording of appropriate ICD-9/ICD-10 codes in healthcare databases, spirometry and self-report. We excluded abstracts, case histories, reviews and commentaries. No language restrictions were applied.

Study selection

Titles and abstracts of all records identified by the database searches were screened by two reviewers. Full texts were retrieved for all titles potentially meeting the pre-defined eligibility criteria. Full-text screening was also conducted by two reviewers. Discrepancies were resolved by discussion with a third reviewer.

Data extraction and quality assessment

Information about study aims, design and setting, characteristics of the study population, COPD and stroke case ascertainment, as well as reported effect measures for the association between COPD and stroke outcomes were extracted for all included studies using a pre-designed form. Online supplementary material was consulted when necessary, and original authors were contacted to clarify and/or obtain numerical data as required.

Included studies were assessed for risk of bias using a tool adapted from the Newcastle–Ottawa scale (17) by the investigators to suit the purposes of this review. The adapted tool (see **e-Appendix 2**) was structured around the three main sources of bias in our included studies: selection of participants; measurement of variables (exposures, outcomes and covariates); and control of confounding. Each domain comprised several items, tailored where appropriate to take account of different study designs. Each item was assigned a risk of bias category as follows: “moderate-to-high risk of bias”, “unclear risk of bias” or “low risk of bias”. Risk of bias assessment was conducted independently by two reviewers on a subset of studies to check the internal validity and consistency of the tool.

Analysis methods

The included studies were grouped according to study design to distinguish studies which estimated prevalence of stroke events in people with COPD versus people without COPD (as a simple percentage or as a prevalence odds ratio (POR)) from those using either a cohort or case–control design to calculate the incidence of stroke, again comparing COPD with COPD-free individuals (as an odds ratio (OR), an incident rate ratio (IRR) or a hazard ratio (HR)). We further grouped studies according to the study population characteristics (general population versus secondary care), the nature of the quality of the exposure case definition (e.g. physician-diagnosed COPD versus self-reported COPD), and the level of control for confounding (i.e. whether or not effect estimates had been adjusted for smoking). Several included studies reported multiple measures and/or conducted

more than one type of analysis, and these are presented separately. The risk of bias assessment was also conducted separately for each analysis type.

Heterogeneity was assessed by means of the I^2 statistic. Given the high level of statistical heterogeneity, it was not deemed appropriate to calculate pooled effect estimates. A narrative synthesis was thus conducted.

Results

Study selection and characteristics

A total of 5,484 articles of potential interest were identified by the database searches (**Figure 1)**. After title and abstract screening, 305 articles, plus another 9 titles identified from reference lists of selected studies, were selected for full-text review. A total of 284 articles were subsequently rejected, leaving 30 studies to form the basis of this review. **Table 1** (13, 14, 18-40) summarises the key characteristics of those studies which report prevalence measures and **Table 2** (13, 14, 23, 37, 39, 41-45) those which estimate incidence. Fuller information is provided in the data supplement (**e-Appendix 3**).

Prevalence of stroke events

Twenty-five studies compared the frequency of stroke events in people with COPD with that in a comparator cohort of individuals without COPD (21 studies) or relative to a general or standard population (4 studies) using a cross-sectional study design; of these, 11 also reported crude or adjusted PORs (**Table 1)**. The majority of the included cross-sectional studies indicated that stroke events are more prevalent in people with COPD than in the general population (**Figure 2**). Only three studies (19, 34, 40) suggest otherwise. Of the 10 studies that reported prevalence ratios (PRs) in excess of 2, three were conducted in outpatient populations (18, 24, 32) and another two were based on self-reported diagnoses of both COPD and stroke (22, 25). Of the 11 studies that also reported PORs, 7 found a significantly increased odds of a stroke event in people with COPD relative to those without (**Figure 3**). PORs ranged in magnitude from 3.34 (95%CI: 3.21–3.48) to 1.05 (95%CI: 0.63–1.77). While the majority of these studies reported effect estimates adjusted for age and sex, only four adjusted for smoking (Figure 3).

The level of heterogeneity among studies reporting prevalence ratios was too large to justify reporting a pooled effect estimate (Figure 2), even when studies were further stratified (see **e-Appendix 4**). However, heterogeneity was lower among the group of four studies which report PORs adjusted for smoking (I^2=45%), implying that smoking may be an important source of the observed heterogeneity. The pooled prevalence OR for this group of studies was estimated at 1.51 (95%CI: 1.09–2.09).

Risk of incident stroke

Eleven studies provided estimates of the relative risk of incident stroke in COPD (**Table 2**); of these, three reported IRRs, seven reported HRs and two reported ORs (in which patients with a prior stroke history were excluded from the analysis). One study reported risk estimates for non-fatal and fatal stroke in the form of a standardised rate ratio (SRR for hospitalisation) and a standardised mortality rate (SMR), respectively (41). The majority of the older incidence studies reported effect estimates for any stroke event (a composite of ischaemic, haemorrhagic and "not specified" stroke); four estimated the relative risk of having a fatal stroke (23, 39, 41, 42). One study reported results for ischaemic strokes only (14). Several of the more recently published large population-based cohort studies estimated relative risks by stroke subtype (43,44,45). The effect of COPD disease severity was investigated in two studies (37,44).

Results of studies which estimated stroke risk in the form of IRRs or HRs are presented in **Figure 4a**, and those that reported either RRs, SRRs or ORs in **Figure 4b**, grouped according to whether effect estimates were adjusted for smoking. Collectively, these studies suggest an increased risk for incident stroke in people with COPD relative to those without. Effect estimates for all stroke ranged from 2.79 (95%CI: 2.56–3.04) to 1.11 (95%CI: 1.02–1.21), but the high degree of heterogeneity prohibited pooling of estimates (I^2>70%). Adjustment for smoking invariably reduced the strength of the association between COPD and stroke; among those studies which reported results unadjusted and adjusted for smoking, unadjusted effect estimates ranged from 1.20 (95% CI: 1.00–1.43) to 2.79 (95% CI: 2.56–3.04) whereas adjusted effect estimates ranged from 1.09 (95% CI: 0.91–1.31) to 1.62 (95% CI: 1.49–1.77). Moreover, in three of five studies (23,37,44) adjustment for smoking not only reduced the magnitude of the relative risk but the effect estimates lost statistical significance.

A number of studies reported effect estimates stratified by either age or gender, or both (13,39,45). These analyses suggested that the effect of COPD on the risk of incident stroke is higher for women and in younger age groups (under 65s). The study by Feary et al., 2010 (13) for example

reported an adjusted HR for stroke of 3.44 (95% CI: 0.85–13.84) in subjects aged 35–44 years (the youngest age group) and a steady reduction in the relative risk for stroke with increasing age, down to 1.10 (95% CI: 0.98–1.23) among the over 75s (Figure 4b).

Three studies reported effect estimates by stroke subtype (43-45). Two reported a greater relative risk for haemorrhagic stroke compared with ischaemic stroke (**Figure 5**). Soderholm et al. (2016) found that the greatest risk was for subarachnoid haemorrhage (SAH) [HR_{SAH}=1.46; 95%CI, 1.16–1.85; HR_{ICH}=1.29; 95%CI, 1.16–1.43; HR_{IS}=1.20; 95%CI, 1.15–1.25], the risk for which did not diminish over the 10 years of follow up, unlike that for ischaemic stroke (IS) and intracerebral haemorrhagic (ICH) stroke which was greatest during the initial two-year period of follow up (45). In contrast, Lin et al. (2015) reported HRs for ischaemic and haemorrhagic stroke of 1.64 (95%CI, 1.49–1.82) and 1.18 (95%CI, 0.89–1.57), respectively (43).

None of our included studies found evidence of a relationship between COPD disease severity and stroke risk (37,44). Only Portegies et al. investigated the influence of exacerbation frequency on stroke risk and reported no difference in risk between frequent and infrequent exacerbators (44). They did however observe a significantly increased risk for stroke in the 7-week period immediately after the onset of a severe acute exacerbation of COPD [adjusted HR=6.6 (95%CI, 2.42–18.2)].

Risk of bias assessment

Figure 6 summarises the results of the risk of bias assessment, displaying for each of the study design categories the proportion of analyses assessed as having a low risk of bias (green) and a moderate-to-high risk of bias (red). Results for individual studies are provided in the supplementary material (see **e-Appendix 5)**. Cross-sectional studies rated reasonably well in terms of the selection of the exposed and unexposed groups but a relatively high proportion of studies relied on self-report and/or were unclear as to whether TIAs were included in the definition of “any stroke”. A significant number were conducted in hospital populations, involving smaller sample sizes and thus fewer stroke events. For the group of incidence studies, the main biases stemmed from the poor control of confounding, of smoking in particular, and the length of follow up.

Discussion

This systematic review finds that strokes are more common in people with COPD than in the general population, and that the risk of experiencing an incident stroke is increased in people with COPD. Although the high level of heterogeneity limited our ability to quantify the magnitude of the increased risk of incident stroke, we suggest that this is relatively modest, and less than that reported for other cardiovascular outcomes such as MI.

The fact that the magnitude of the association between COPD and stroke is attenuated by adjustment for smoking implies that this shared risk factor accounts for much of the elevated risk and that COPD by itself does not confer a large additional risk. Only 2 of the 11 analyses which estimated risk of incident stroke lend support to the hypothesis that COPD is an independent risk factor for stroke (13, 43), and indicates there is heterogeneity in the causal mechanisms underlying the association between COPD and specific cardiovascular diseases.

We found evidence to suggest that the relative risk for stroke declines with increasing age, with the greatest risk occurring in those COPD patients aged under 65 years. There is also some evidence, albeit limited at the present time due to the paucity of studies, that the relative risk for haemorrhagic stroke may be greater than that for ischaemic stroke (44,45). A heightened risk of haemorrhagic stroke, and SAH in particular, is consistent with reports of an increased presence of cerebral small vessel disease in people with COPD, and implies a role for hypoxia and oxidative stress in the pathophysiology of stroke in COPD (46-48). In this context, it is interesting to note that Arboix et al. in their study of stroke registry patients identified COPD as an independent risk factor for ischaemic strokes of atherothrombotic origin (OR=1.40; 96%CI: 1.04–1.93) but not for other types of ischaemic stroke (e.g. lacunar and cardioembolic strokes)(49, 50). While this is consistent with the increased burden of carotid artery plagues of high lipid content seen in people with COPD (46), we are unable to corroborate this finding due to the lack of studies which examine ischaemic stroke outcomes by subtype.

We found no clear evidence that COPD disease severity influences stroke risk (independently of age). However, the role of exacerbations remains a matter of some debate and warrants further investigation. Two studies failed to find an association between exacerbation frequency and stroke risk (44, 51), but others have reported markedly increased risks for stroke in the period immediately following an acute exacerbation relative to periods of more stable disease (44, 52).

Our review serves to highlight several intriguing features of the evidence base linking COPD and stroke. The first is the differential in risk for MI and stroke in COPD (14). While a degree of heterogeneity in the magnitude of the associations between COPD and individual CVDs due to

aetiologic differences is to be expected (53), other factors – such as competing risks – may well be contributing to the observed differential. It is also possible that treatment initiated for early cardiac disease may be preventing subsequent strokes in the COPD population (44).

The second is the observation that while several population-based studies have demonstrated an inverse relationship between lung function impairment as measured by FEV_1 (% predicted) and stroke risk (54-59), few find evidence of a similar relationship with low FEV_1/FVC, a measure which is indicative of airflow obstruction and thus COPD. For example, Howaza et al. (2006), using data from the Atherosclerotic Risk In Communities Study (ARIC) showed that non-smoking white subjects with low FEV_1 (and FVC) were at increased risk of ischaemic stroke; however there was no evidence of an association with the ratio, FEV_1/FVC (56). This finding highlights the need for more research to identify which aspects of impaired lung function are the most important in terms of CVD risks and to characterise the groups at greatest risk. The observed link between FEV_1 and vascular disease may, as some have suggested, imply a role for common early life determinants (60). Alternatively, in terms of the development of vascular and airways disease, events in later life may be more relevant. Several studies have demonstrated increased risks for stroke in subjects with chronic bronchitis (61, 62). This coupled with evidence for increased risk for stroke in the period following a severe exacerbation of COPD might imply that those with more bronchitic COPD, who experience frequent exacerbations and steeper rates of lung function decline, might be at heightened risk for ischaemic stroke.

Strengths and limitations

While the present review benefits from the adoption of a comprehensive search strategy and broad inclusion criteria, there are limitations. The main limitation is the high level of heterogeneity in the included studies, which precludes the calculation of an overall effect estimate.

The main sources of heterogeneity are differences in study population characteristics, coupled with variations in case definitions for both the exposure and outcomes. Studies sourcing individuals from secondary care are likely to have a higher proportion of patients more severe disease and are unlikely to be representative of the COPD patient population as a whole. Case definitions for COPD are highly heterogeneous, ranging from self-report to pulmonary physician diagnoses supported by spirometry. Misclassification of COPD with asthma is likely to represent a significant source of bias, even in studies which purport to use physician diagnoses. Although self-

reported stroke diagnoses might be considered to be more reliable than those for COPD, studies are inconsistent in their definitions of all stroke and stroke subtypes.

The lack of adequate control for confounding, in particular smoking, represents another inherent limitation. Our review includes a number of studies which rely on administrative health care databases, the majority of which do not contain data on smoking. Given that many of our included studies investigated multiple CVD outcomes, not just stroke, we judge the risk of publication basis to be low.

Conclusion

Both prevalence and incidence of stroke is increased in people with COPD. The increased risk for incident stroke is attenuated by adjustment for smoking, suggesting that in the population as a whole COPD is not an independent risk factor for stroke. However, the possibility remains that COPD is a causal factor in certain subsets of COPD patients, and for certain types of stroke. Our review highlights the need for further well controlled and detailed longitudinal cohort studies in order to quantify the nature and magnitude of the risk of different stroke subtypes in people with COPD.

References

1. Vanfleteren LEGW, Spruit MA, Groenen M, Gaffron S, van Empel VPM, Bruijnzeel PLB, Rutten EPA, Op ’t Roodt J, Wouters EFM, Franssen FME. Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine* 2013; 187: 728-735.
2. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, Celli B. Comorbidities and Risk of Mortality in Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine* 2012; 186: 155-161.
3. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; 128(4):2099-2107.
4. Maclay JD, MacNee W. Assessment of cardiovascular comorbidity. European Respiratory Society Monograph 2013, 59:28-49.
5. Man SFP, Van Eeden S, Sin DD. Vascular Risk in Chronic Obstructive Pulmonary Disease: Role of Inflammation and Other Mediators. *Canadian Journal of Cardiology* 2012; 28: 653-661.
6. Roversi S, Roversi P, Spadafora G, Rossi R, Fabbri LM. Coronary artery disease concomitant with chronic obstructive pulmonary disease. *European Journal of Clinical Investigation* 2014; 44: 93-102.
7. Sin DD, Man SFP. Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases?: The Potential Role of Systemic Inflammation in Chronic Obstructive Pulmonary Disease. *Circulation* 2003; 107: 1514-1519.
8. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respiratory Medicine* 2015; 3: 631-639.
9. de Miguel Díez J, Morgan JC, García RJ. The association between COPD and heart failure risk: a review. *International Journal of Chronic Obstructive Pulmonary Disease* 2013; 8: 305-312.
10. Mullerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: Systematic literature review. *Chest* 2013; 144: 1163-1178.
11. Rothnie KJ, Yan R, Smeeth L, Quint JK. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open* 2015; 5:e007824.
12. Doehner W, Haeusler KG, Endres M, Anker SD, MacNee W, Lainscak M. Neurological and endocrinological disorders: Orphans in chronic obstructive pulmonary disease. *Respiratory Medicine* 2011; 105(Suppl. 1): S12-S19.
13. Feary JR, Rodrigues LC, Smith CJ, Hubbard RB. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010; 65:956-962.
14. Yin L, Lensmar C, Ingelsson E, Back M. Differential association of chronic obstructive pulmonary disease with myocardial infarction and ischemic stroke in a nation-wide cohort. *International Journal of Cardiology* 2014; 173: 601-603.
15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015; 4(1): 1-9.
16. Morgan AD SC, Rothnie K, Quint J. Chronic Obstructive pulmonary disease and the risk of stroke: a systematic review protocol. *BMJ Open* 2016; 6(11).
17. Wells G, B Shea, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: The Ottawa Hospital Research Institute (http://www.ohri.ca/programs/clinical_epidemiology/oxfrod.asp; assessed 4 March 2016)

18. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respiratory Research* 2010; 11:122.
19. Antonelli-Incalzi R, Pedone C, Scarlata S, Battaglia S, Scichilone N, Forestiere F, Bellia V. Correlates of mortality in elderly COPD patients: focus on health-related quality of life. *Respirology* 2009; 14: 98-104.
20. Bentsen SB, Rustoen T, Miaskowski C. Prevalence and characteristics of pain in patients with chronic obstructive pulmonary disease compared to the Norwegian general population. *The Journal of Pain* 2011; 12: 539-545.
21. Cazzola M, Calzetta L, Bettoncelli G, Cricelli C, Romeo F, Matera MG, Rogliani P. Cardiovascular disease in asthma and COPD: A population-based retrospective cross-sectional study. *Respiratory Medicine* 2012; 106: 249-256.
22. Cunningham TJ, Ford ES, Rolle IV, Wheaton AG, Croft JB. Associations of self-reported cigarette smoking with chronic obstructive pulmonary disease and co-morbid chronic conditions in the United States. COPD: Journal of Chronic Obstructive Pulmonary Disease 2015; 12(3):276-286.
23. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Annals of Epidemiology* 2006; 16: 63-70.
24. de Lucas-Ramos P, Izquierdo-Alonso JL, Moro JMRG, Frances JF, Lozano PV, Bellon-Cano JM. Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study). *International Journal of COPD* 2012; 7: 679-686.
25. Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *International journal of chronic obstructive pulmonary disease* 2009; 4: 337-349.
26. García-Olmos L, Alberquilla Á, Ayala V, García-Sagredo P, Morales L, Carmona M, de Tena-Dávila MJ, Pascual M, Muñoz A, Salvador CH, Monteagudo JL. Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study. *BMC Family Practice* 2013; 14: 1-8.
27. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: A longitudinal study. *Thorax* 2010; 65: 499-504.
28. Jo YS, Choi SM, Lee J, Park YS, Lee SM, Yim JJ, Yoo CG, Kim YW, Han SK, Lee CH. The relationship between chronic obstructive pulmonary disease and comorbidities: A cross-sectional study using data from KNHANES 2010-2012. *Respiratory Medicine* 2015; 109: 96-104.
29. Lin P-J, Shaya FT, Scharf SM. Economic implications of comorbid conditions among Medicaid beneficiaries with COPD. *Respiratory Medicine* 2010; 104: 697-704.
30. Lindberg A, Larsson LG, Ronmark E, Lundback B. Co-morbidity in mild-to-moderate COPD: Comparison to normal and restrictive lung function. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2011; 8: 421-428.
31. Lopez Varela MV, Montes de Oca M, Halbert R, Muino A, Talamo C, Perez-Padilla R, Jardim JR, Valdivia G, Pertuze J, Menezes AM. Comorbidities and health status in individuals with and without COPD in five Latin American cities: the PLATINO study. *Arch Bronconeumol* 2013; 49: 468-474.
32. Mapel DW, Picchi MA, Hurley JS, Frost FJ, Petersen HV, Mapel VM, Coultas DB. Utilization in copd: Patient characteristics and diagnostic evaluation. *Chest* 2000; 117: 346S-353S.
33. Mapel DW, Dedrick D, Davis K. Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991-1999. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005; 2: 35-41.
34. Miniati M, Monti S, Pavlickova I, Bottai M. Survival in COPD: Impact of Lung Dysfunction and Comorbidities. *Medicine* 2014; 93: e76.

35. Nagorni-Obradovic LM, Vukovic DS. The prevalence of COPD co-morbidities in Serbia: Results of a national survey. *Primary Care Respiratory Medicine* 2014; 24:e14008.
36. Pleasants RA, Ohar JA, Croft JB, Liu Y, Kraft M, Mannino DM, Donohue JF, Herrick HL. Chronic obstructive pulmonary disease and asthma-patient characteristics and health impairment. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2014; 11: 256-266.
37. Schneider C, Bothner U, Jick SS, Meier CR. Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. *European Journal of Epidemiology* 2010; 25: 253-260.
38. Schnell K, Weiss CO, Lee T, Krishnan JA, Leff B, Wolff JL, Boyd C. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: A cross-sectional study using data from NHANES 1999-2008. *BMC Pulmonary Medicine* 2012; 12.
39. Sidney S, Sorel M, Quesenberry Jr CP, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068-2075.
40. van Manen JG, Bindels PJ, CJ IJ, van der Zee JS, Bottema BJ, Schade E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* 2001; 54: 287-293.
41. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005; 128: 2640-2646.
42. Knuiman MW, James AL, Divitini ML, Ryan G, Bartholomew HC, Musk AW. Lung function, respiratory symptoms, and mortality: Results from the Busselton Health Study. *Annals of Epidemiology* 1999; 9: 297-306.
43. Lin HW, Chung CL, Lin YS, Yu CM, Lee CN, Bien MY. Inhaled pharmacotherapy and stroke risk in patients with chronic obstructive pulmonary disease: A nationwide population based study using two-stage approach. PLoS One 2015; 10(7):e010102.
44. Portegies MLP, Lahousse L, Joos GF, Hofman A, Koudstaal PJ, Stricker BH, Brusselle GG, Ikram MA. Chronic Obstructive Pulmonary Disease and the Risk of Stroke: the Rotterdam Study. *American Journal of Respiratory and Critical Care Medicine* 2015; 3: 251-258.
45. Soderholm M, Inghammar M, Hedblad B, Egesten A, Engstrom G. Incidence of stroke and stroke subtypes in chronic obstructive pulmonary disease. *European Journal of Epidemiology* 2016; 31: 159-168.
46. Austin V, Crack PJ, Bozinovski S, Miller AA, Vlahos R. COPD and stroke: are systemic inflammation and oxidative stress the missing links? *Clinical science (London)* 2016; 130: 1039-1050.
47. Dodd JW, Chung AW, Van Den Broek MD, Barrick TR, Charlton RA, Jones PW. Brain structure and function in chronic obstructive pulmonary disease: A multimodal cranial magnetic resonance imaging study. *American Journal of Respiratory and Critical Care Medicine* 2012; 186: 240-245.
48. Lahousse L, Tiemeier H, Ikram MA, Brusselle GG. Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review. *Respiratory Medicine* 2015; 109: 1371-1380.
49. Arboix A, Morcillo C, Garcia-Eroles L, Oliveres M, Massons J, Targa C. Different vascular risk factor profiles in ischemic stroke subtypes: A study from the 'Sagrat Cor Hospital of Barcelona Stroke Registry'. *Acta Neurologica Scandinavica* 2000; 102: 264-270.
50. Arboix A. Cardiovascular risk factors for acute stroke: Risk profiles in the different subtypes of ischemic stroke. *World Journal of Clinical Cases* 2015; 3: 418-429.
51. Windsor CL, Herrett E, Smeeth L, Quint J. The association between exacerbation frequency and stroke risk, in patients with COPD: A matched case-control study. *Thorax* 2014; 69: A214.
52. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091-1097.
53. Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, Smeeth L, Timmis A, Hemingway H. Heterogeneous associations between smoking and a wide range of initial

presentations of cardiovascular disease in 1 937 360 people in England: lifetime risks and implications for risk prediction. *International Journal of Epidemiology* 2015; 44: 129-141.
54. Gulsvik AK, Gulsvik A, Skovlund E, Thelle DS, Mowe M, Humerfelt S, Wyller TB. The association between lung function and fatal stroke in a community followed for 4 decades. *Journal of Epidemiology and Community Health* 2012; 66: 1030-1036.
55. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711-715; discussion 715-716.
56. Hozawa A, Billings JL, Shahar E, Ohira T, Rosamond WD, Folsom AR. Lung function and ischemic stroke incidence: the Atherosclerosis Risk in Communities study. *Chest* 2006; 130: 1642-1649.
57. Strachan DP. Ventilatory function as a predictor of fatal stroke. *BMJ* 1991; 302: 84-87.
58. Truelsen T, Prescott E, Lange P, Schnohr P, Boysen G. Lung function and risk of fatal and non-fatal stroke. The Copenhagen city heart study. *International Journal of Epidemiology* 2001; 30: 145-151.
59. Wannamethee SG, Shaper AG, Ebrahim S. Respiratory function and risk of stroke. *Stroke* 1995; 26: 2004-2010.
60. Dow L, Ebrahim S. Commentary: Lung function and risk of fatal and non-fatal stroke - The Copenhagen City heart study. *International Journal of Epidemiology* 2001; 30: 152-153.
61. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. *Nature Reviews Neurology* 2010; 6: 681-694.
62. Pinol-Ripoll G, De La Puerta I, Santos S, Purroy F, Mostacero E. Chronic bronchitis and acute infections as new risk factors for ischemic stroke and the lack of protection offered by the influenza vaccination. *Cerebrovascular Diseases* 2008; 26: 339-347.

Figures and tables

Table 1: Key characteristics of included studies: prevalence

Study	Study design and setting	Study population	COPD		Stroke outcome	Stroke prevalence (%) COPD v non-COPD unless otherwise stated	PR and/or maximally adjusted POR (95% CI) COPD v non-COPD unless otherwise stated
			No. of subjects	Men (%)			
Agusti et al., 2010 (18)	x-sectional Multi-country	Hospital outpatients (ECLIPSE study cohort)	2,164	65.3%	Any stroke	4.0% v 1.7 %	PR: 2.31 (1.2–4.4)
Antonelli-Incalzi et al., 2009 (19)	Cohort Italy	Hospital outpatients (SaRA study participants)	238	81%	Any stroke	2.3% v 7.0% (at baseline)	PR: 0.34 (0.15–0.81)
Bentsen et al., 2011 (20)	x-sectional Norway	Hospital clinic attendees	100	47%	Any stroke	3.0% v 2.3% (COPD v general population)	PR: 1.33 (0.45–4.33)
Cazzola et al., 2012 (21)	x-sectional Italy	General population (Health Search Database)	25,281	46%	Any stroke	4.2% v 2.0%	PR: 2.05 (1.93–2.18) Adjusted POR (age only): 3.60 (3.42–3.82)
Cunningham et al., 2015 (22)	x-sectional health survey USA	General population (2011 Behavioral Risk Factor Surveillance System survey participants)	33,088	40%	Any stroke	9.7% v 2.8% 7.4% v 2.4% (COPD v age-standardised population)	PR: 3.46 (3.34–3.60)
Curkendall et al., 2006 (23)	Matched cohort Saskatchewan, Canada	General population (administrative healthcare database)	11,493	54%	Any stroke	1. Baseline 4.8% v 3.3% 2. Period 9.6% v 7.9%	1. Baseline PR: 1.45 (1.30–1.62) Adjusted POR (age, sex by matching): 1.47 (1.31–1.64) 2. Period PR: 1.22 (1.14–1.33) Adjusted POR (age, sex by matching): 1.24 (1.15–1.34)
de Lucas-Ramos et al., 2012(24)	Case–control Madrid, Spain	Primary and secondary clinic attendees	970	70.4%	Any stroke	10.0% v 2.9%	PR: 3.45 (1.70–7.01) Adjusted POR (age, sex, HTN,HLD, DM, smoking): 3.22 (1.47–7.04)
Feary et al., 2010 (13)	Cohort UK	General population (THIN primary care database)	29,870	48.1%	Any stroke (inc TIAs)	9.9% v 3.2% (at baseline)	PR: 3.1 (3.0–3.2) POR: 3.34 (3.21– 3.48)
Finkelstein et al., 2009 (25)	x-sectional health survey USA	General population (2002 National Health Interview Survey)	958	46%	Any stroke	8.0% v 3.6%	PR: 2.2 (1.78–2.80) Adjusted POR (SES, health behaviours, comorbidities): 1.5 (1.1–2.1)
Garcia-Olmos et al., 2013 (26)	x-sectional Madrid, Spain	General population (primary care records)	3,124	76%	Any stroke	7.49% v 6.48% (COPD v expected prevalence in general population)	PR: 1.19 (0.89–1.42)
Guerra et al., 2010 (27)	Cohort Tuscon, AR, USA	General population (TESAOD study participants)	294	53.1%	Any stroke	3.1% v 1.1% (on enrolment)	PR: 2.8 (1.22–6.02)
Jo et al.,2015 (28)	Cross-sectional health survey Republic of Korea	General population (KNHANES V survey respondents)	744	100%	Any stroke	2.7% v 1.9% 2.1 % v 1.3% (population weighted)	PR: 1.42 (0.86–2.32) Adjusted POR (age): 1.61 (0.84–3.09)

Lin et al., 2010 (29)	Matched cohort Maryland, USA	General population (Medicaid database)	1,388	20.8%	Any stroke	10.7% v 6.5% (at baseline)	PR: 1.65 (1.35–2.04) Adjusted POR (age, sex by matching) : 1.73 (1.38–2.18)
Lindberg et al., 2011 (30)	Matched cohort Northern Sweden	General population (OLIN study cohort)	933	55%	Any stroke	7.7% v 7.1% (at baseline)	PR: 1.08 (0.79–1.48) Adjusted POR (age, sex, BMI, smoking): 1.05 (0.63–1.77) GOLD stage II-IV v no-COPD
Lopez-Varela et al., 2013 (31)	x-sectional Five Latin American cities	Population based (PLATINO study participants)	759	52%	CVA	3.2% v 2.1%	PR: 1.52 (0.96–2.33)
Mapel et al., 2000 (32)	x-sectional (two cohorts) New Mexico, USA	1. HMO General population (Lovelace Health Plan) 2.UMC Hospital patients	1. HMO 200 2. UMC 200	1. HMO 51% 2. UMC 36%	1. HMO Any stroke 2. UMC Any stroke	1. HMO 4.0% v 3.5% 2. UMC 6.5% v 2.8%	1. HMO PR: 1.14 (0.42–3.09) 2. UMC PR:2.3 (0.84–5.59)
Mapel et al., 2005 (33)	x-sectional (two different time periods) New Mexico, USA	Hospital inpatients (Veterans Administration System)	1. 1992 87,867 2. 1998 70,679	1. 1992 99% 2. 1998 98%	Any stroke	1. 1992 7.5% v 6.8% 2. 1998 7.9% v 7.7%	1. 1992 PR: 1.1 (1.08–1.14) 2. 1998 PR:1.02 (0.97–1.03)
Miniati et al., 2014 (34)	Matched cohort Pisa, Italy	General population	200	89%	Any stroke	1% v 1.5%	PR: 0.66 (0.11–4.00)
Nagorni-Obradovic and Vukovic, 2014 (35)	x-sectional health survey Serbia	General population (household health survey respondents)	653	46.6%	Any stroke	5.4% v 3.8%	PR:1.42 (0.98–1.80) Adjusted POR (age, sex, education, smoking): 1.44 (0.92–2.26)
Pleasants et al., 2014 (36)	x-sectional health survey North Carolina, USA	General population (Behavioral Risk Factor Surveillance System survey participants)	1,948	NR	Any stroke	4.4% v 2.4%	PR: 1.57 (1.16–2.13)
Schneider et al., 2010 (37)	Matched cohort UK	General population (CPRD primary health care database)	35,772	51%	Any stroke (inc TIAs)	6.9% v 5.9% (at baseline)	PR: 1.17 (1.12–1.24) Adjusted OR (age, sex, GP practice): 1.19 (1.12–1.26)
Schnell et al., 2012(38)	x-sectional health survey USA	General population (NHANES study participants)	995	39.9%	Any CVA	9.0% v 4.5%	PR: 1.93 (1.57–2.40)
Sidney et al., 2005(39)	Matched cohort North California, USA	General population (NCKP Medical Care Program subscribers)	45,966	55.4%	Hospitalisation for stroke	1.2% v 0.5% (at baseline)	PR: 2.4 (2.08–2.82) Adjusted POR (age, sex, length of subscription) : 2.44 (2.09–2.85)
Van Manen et al. 2001(40)	x-sectional Western Netherlands	General population (patients registered with 28 GP practices)	290	64%	Any CVA	3.1% v 3.7%	PR: 0.86 (0.39–1.96)
Yin et al., 2014 (14)	Cohort Sweden	General population (national administrative databases)	51,348	44.3%	Ischaemic stroke	4.2% v 1.9% (COPD v general population)	PR: 2.2 (2.07–2.32)

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular attack; DM, diabetes mellitus; HLD, hyperlipidaemia; HTN, hypertension; PR, prevalence ratio; POR, prevalence odds ratio: SES socioeconomic status

Table 2: Key characteristics of included studies: incidence

Study	**Study design and setting**	**Study population**	**COPD**		**Reported effect measures**	**Maximally adjusted effect estimate (95% CI)** COPD v non-COPD unless otherwise specified	**Factors adjusted for (**maximally adjusted estimate**)**
			No. of subjects	**Men (%)**			
Curkendall et al., 2006 (23)	Matched cohort, 1998–2001 Saskatchewan, Canada	General population (administrative health care databases)	11,493	54%	1. OR for any stroke 2. IRR for hospitalisation 3. IRR for fatal stroke	1. Adjusted OR: 1.11 (1.02–1.21) 2. Adjusted IRR: 1.23 (0.68–2.22) 3. Adjusted IRR: 1.24 (0.90–1.71)	1. Age, sex (by matching) plus HTN, HLD, DM, CVDs 2. Age, sex, HTN, HLD, DM, obesity, smoking, CVDs 3. Age, sex (by matching)
Feary et al., 2010 (13)	Cohort, 2005–2007 UK	General population (THIN primary health care databases)	29,870	48.1%	HR for any stroke (inc TIAs)	Crude HR: 2.79 (2.56–3.04)	
Guerra et al., 2010 (27)	Cohort, 1972–1996 Tuscon, AR, USA	General population (TESAOD study participants)	155	61.3%	HR for fatal stroke	Adjusted HR: 6.2 (2.9–13.4) recurrent obstructive v normal spirometry	Age, sex, BMI
Huiart et al., 2005 (41)	Cohort, 1990–1999 Saskatchewan, Canada	General population (administrative healthcare databases)	5,648	53.9%	1. SRR for hospitalisation 2. SMR for fatal stroke	1. SRR: 1.27 (1.16–1.38) 2. SMR: 1.60 (1.36–1.85)	Age, sex, calendar year by indirect standardisation using a standard population
Knuiman et al., 1999 (42)	Cohort, 1969–1995 Busselton, Australia	General population (Busselton Health study participants)	606	64%	HR for fatal stroke, separately for men and women	*Men* Adjusted HR: 0.76 (0.39–1.47) *Women* Adjusted HR: 0.90 (0.44–1.91)	Age, smoking, %FEV_1, other respiratory symptoms, CHD, CVD risk factors
Lin et al., 2015 (43)	Matched cohort, 2004–2006 Taiwan, Province of China	General population (National health insurance database, LHID2005)	10,413	65.8%	1. IRR for any stroke (exc TIAs) 2. HR for any stroke (exc TIAs)	1. Adjusted IRR: 1.79 (1.50–2.13) 2. Propensity score adjusted HR: 1.62 (1.49–1.77)	1. age, sex (by matching) 2. Matching variables plus HTN, HLD, DM , CHD, smoking, alcohol, BMI
Portegies et al., 2015(44)	Cohort, 1990–2012 Ommoord, Rotterdam, The Netherlands	General population (Rotterdam Study participants)	1,566	53.5%	HR for any stroke	Adjusted HR: 1.09 (0.91–1.31)	Age, sex, smoking
Schneider et al., 2010 (37)	Cohort, 1995–2005 UK	General population (CPRD primary health care database)	15,907	NR	IRR for any stroke (inc TIA)	Adjusted IRR: 1.23 (0.79–1.92)	Age, sex, GP practice (by matching)
Schneider et al., 2010 (37)	Nested case–control UK	General population (CPRD primary health care database)	NR	NR	OR for any stroke (inc TIA)	Adjusted OR: 1.13 (0.92–1.38)	Age, sex, GP practice (by matching), plus smoking, BMI, HTN, DM, aspirin use
Sidney et al., 2005 (39)	Matched cohort, 1996–2000 Northern California, USA	Mixed (KPNC Medical Care Program subscribers)	1,010	54.4%	1. RR for hospitalisation 2. RR for fatal stroke	1. Adjusted RR: 1.39 (1.25–1.54) 2. Adjusted RR: 1.35 (1.09–1.66)	1. Age, gender, DM, HTN, HLD, prior CVD 2. Age, gender, DM, HTN, HLD, prior CVD

Soderholm et al., 2016 (45)	Matched cohort, 1996–2000 Sweden	Hospitalised population (Inpatient registers)	103,419	54.2%	HR for hospitalisation	Adjusted HR: 1.24 (1.19–1.28)	SES, country of origin, history of asthma, DM, CVD, rheumatoid arthritis, kidney disease, lupus, length of hospital stay
Yin et al., 2014 (14)	Cohort, 2005–2008 Sweden	General population (national administrative databases)	51,348	44.3%	HR for ischaemic stroke	Fully adjusted HR: 1.09 (1.02–1.17)	Age, sex, SES, medications

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular attack; DM, diabetes mellitus; HLD, hyperlipidaemia; HTN, hypertension; HR, hazard ratio; OR, odds ratio; IRR, incident rate ratio; RR, relative risk; SES socioeconomic status; SMR, standardised mortality ratio;

Figure 1. Flow chart of included studies

Note: some studies were excluded for more than one reason.

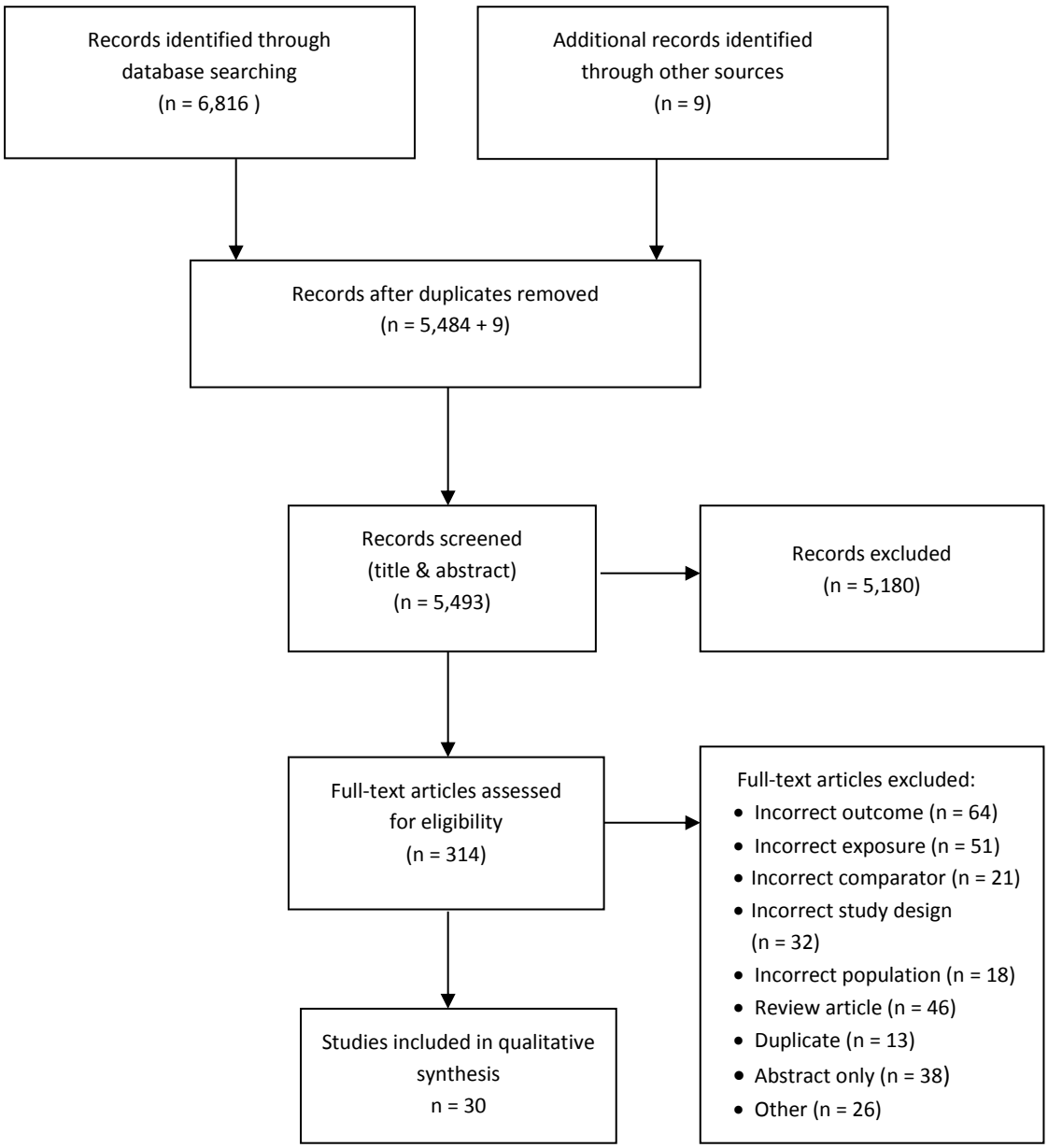
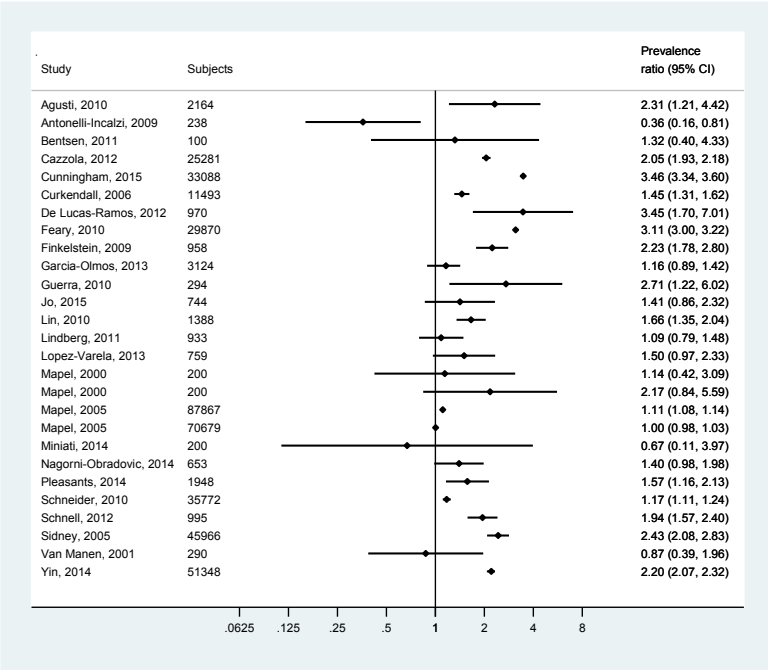
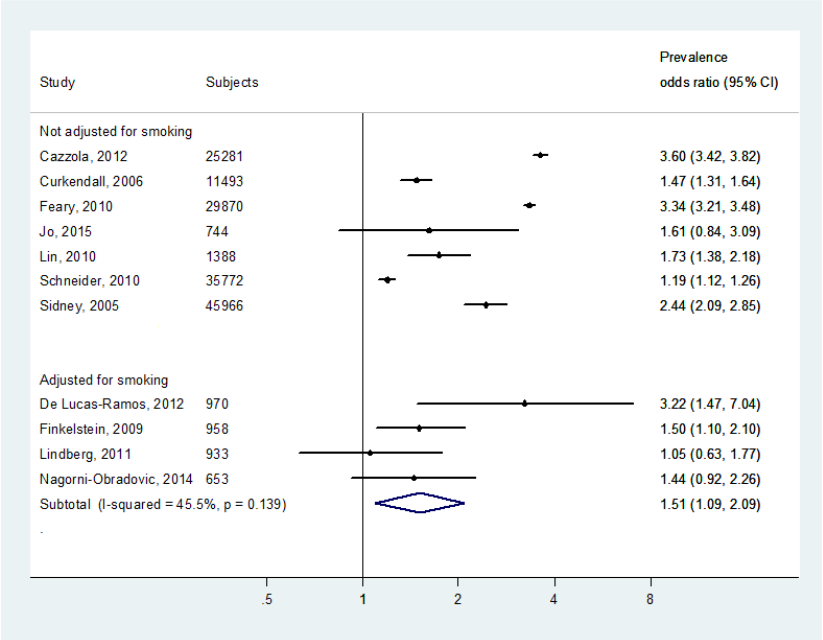


Figure 2: Forest plot showing estimates of the prevalence ratio (PR) for stroke comparing people with and without COPD



Note: Subjects = number of study participants with COPD.

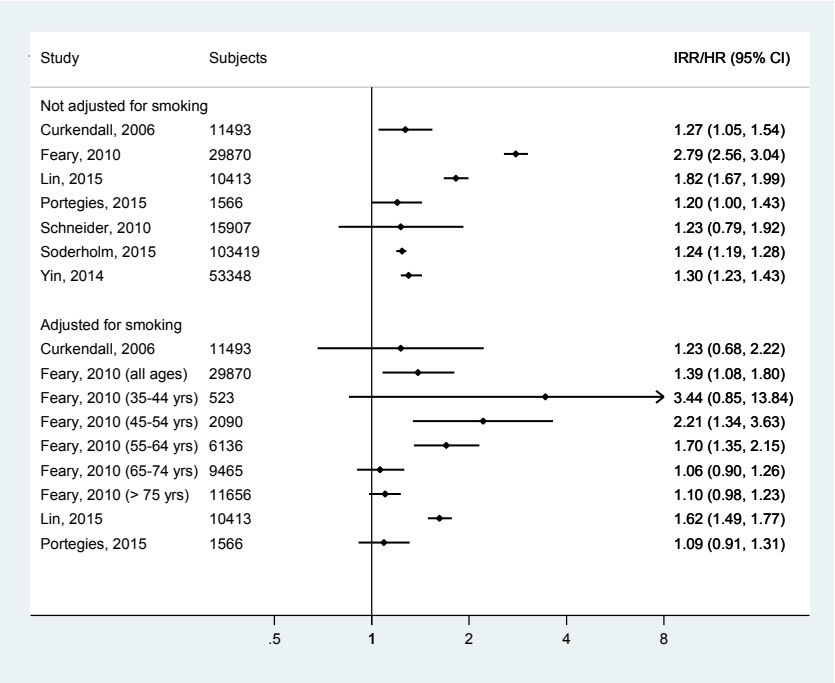
Figure 3: Forest plot showing estimates of the prevalence odds ratio (POR) for stroke comparing people with and without COPD, grouped according adjustment for smoking



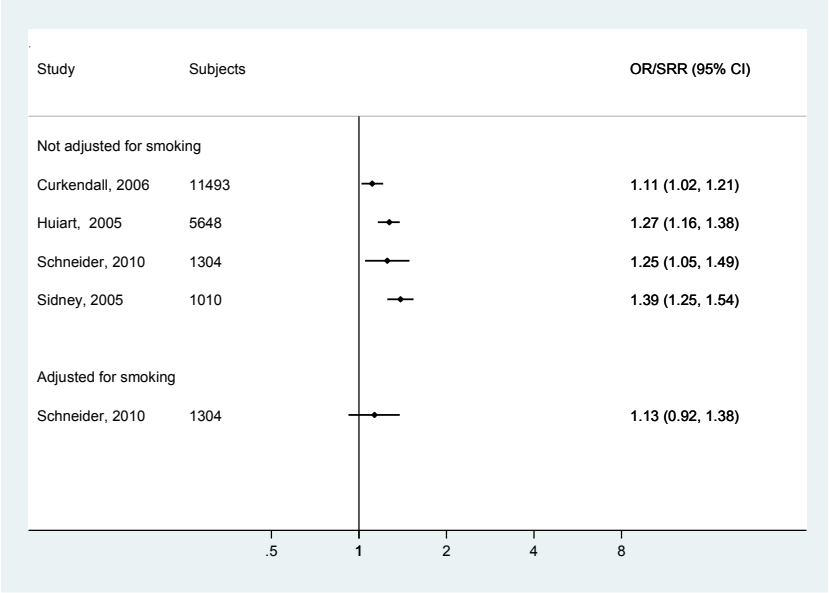
Note: Subjects = number of study participants with COPD.

Figure 4: Forest plot showing relative risks for stroke comparing people with and without COPD, grouped according adjustment for smoking

a) IRRs/HRs

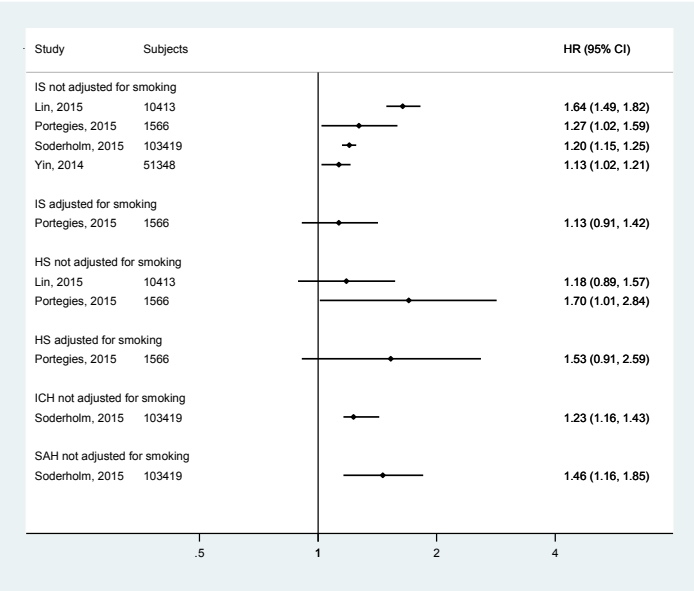


b) RRs/ORs



Note: Subjects = number of study participants with COPD.

Figure 5: Relative risks for stroke, by stroke subtype



Note: Subjects = number of study participants with COPD

Figure 6: Risk of bias assessment results for a) studies which estimate prevalence ratios, b) studies which prevalence odds ratios and c) studies which estimate incidence of stroke events in people with COPD versus people without COPD

Figure 6a: Prevalence ratios (PR)

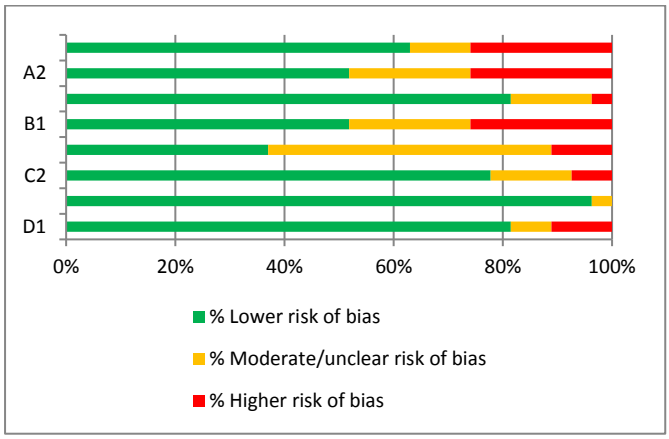


Figure 6b: Prevalence odds ratios **(POR)**

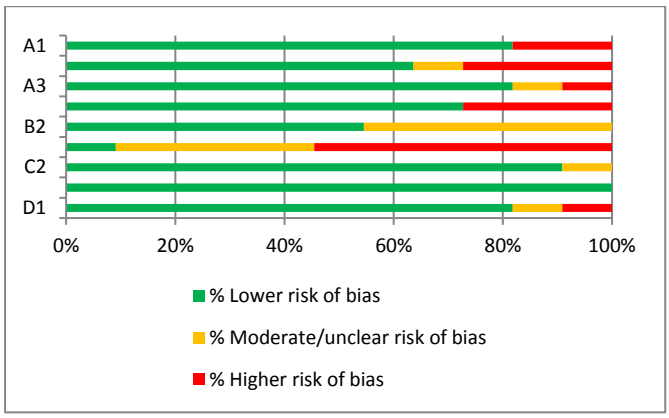
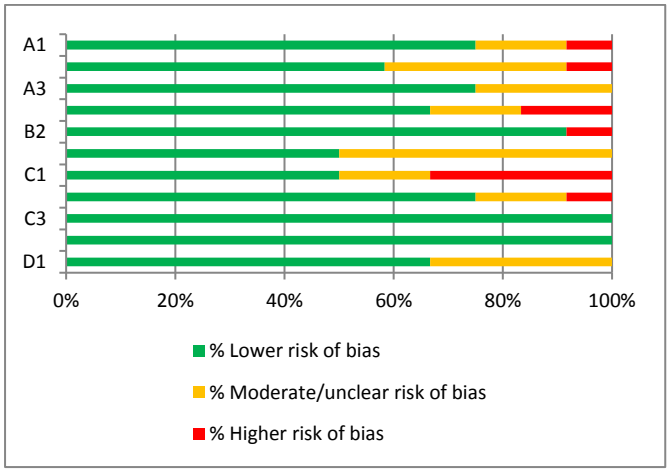


Figure 6c: Incidence (HR, IRR, OR, RR)



Note: The signalling questions employed in the risk of bias assessment vary according to study type and are coded as follows: A1 relates to the representativeness of study population; A2 to the representativeness of exposed individuals; A3 to the representativeness/selection of unexposed individuals; B1 to the ascertainment of exposure; B2 to the assessment of the outcome; B3 to the length of follow up (long enough for outcomes to occur); C1 to adjustment for confounding (appropriate); C2 to the sample size (adequate); C3 to the absence or otherwise of the outcome at study start; and C4 to missing data (appropriate handling) and D1 to other potential sources of bias of concern. See also e-Appendix 5).