Chronic Obstructive Pulmonary Disease and the Risk of Stroke

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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.

Results: The MEDLINE and EMBASE databases were searched in May 2016 to identify articles that compared stroke outcomes in people with and without COPD. Studies were grouped by study design to distinguish those that reported prevalence of stroke (cross-sectional studies) from those that estimated incidence (cohort or case–control studies). In addition, 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. We identified 5,493 studies, of which 30 met our predefined inclusion criteria. Of the 25 studies that reported prevalence ratios, 11 also estimated prevalence odds ratios. The level of heterogeneity among the included cross-sectional studies did not permit the calculation of pooled ratios, save for a group of four studies that estimated prevalence odds ratios adjusted for smoking (prevalence odds ratio, 1.51; 95% confidence interval, 1.09–2.09; $I^2 = 45\%$). All 11 studies that estimated relative risk for nonfatal incident stroke reported increased risk in COPD. Adjustment for smoking invariably reduced the magnitude of the associations.

Conclusions: Although both prevalence and incidence of stroke are 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 patients with COPD and for certain stroke subtypes.

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

Author Contributions: A.D.M. developed the review protocol, including the inclusion and exclusion criteria, the risk of bias assessment tool, and the data extraction forms with assistance from J.K.Q., acted as first reviewer, and prepared the draft paper for publication. K.J.R. contributed to the development of the search strategy and risk of bias assessment tool. C.S. served as the second reviewer, assisting with the screening, data extraction, and risk of bias assessment. J.P. helped with the preparation of the forest plots. All named authors reviewed and commented on draft versions of the paper.

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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 more than 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 one-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). 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 more recently published population-based studies that investigate, in more detail than before, stroke outcomes by subtype.

Methods

Protocol and Registration

In accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines (15), study objectives, inclusion criteria, search strategies, and analysis methods were prespecified 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., hemorrhagic vs. ischemic), and (*2*) whether stroke risk is modified in particular COPD phenotypes, for example, in frequent exacerbators.

Information Sources and Search Strategy

MEDLINE (OVID interface, 1948 onward) and EMBASE (OVID interface, 1980 onward) 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 keywords 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 Appendix E1 in the online supplement.

Eligibility Criteria

Inclusion criteria were drawn up using the PECOS (population, exposure, comparison, outcome, study design) framework. We included observational studies that (*1*) employed either a cross-sectional, cohort, or case–control design; (*2*) were conducted in an adult population greater than 35 years of age; 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 randomized control trials where these met our other inclusion criteria. Accepted definitions for COPD included a physician diagnosis, recording of appropriate *International Classification of Diseases* (ICD)-9/ICD-10 codes in health care 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 predefined eligibility criteria. Full-text screening was also conducted by two reviewers. Discrepancies were resolved by discussion with a third reviewer.

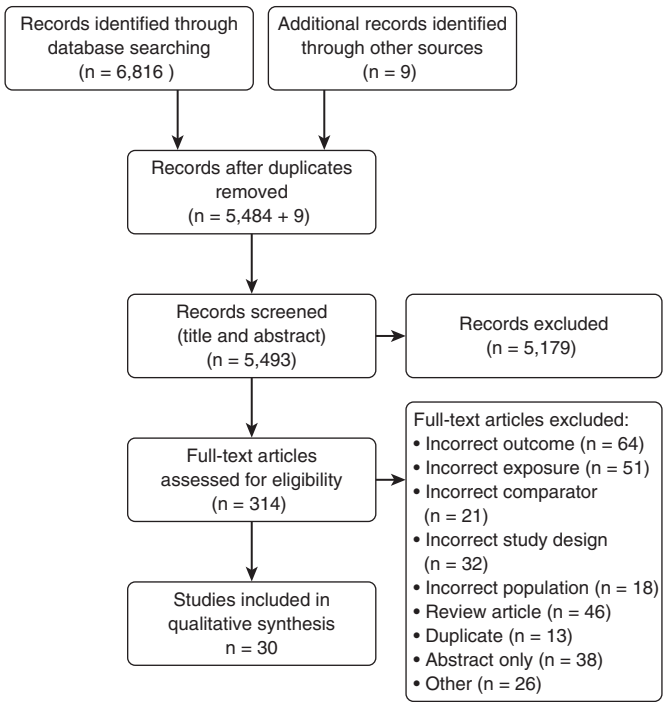

Figure 1. Flow chart of included studies. *Note*: Some studies were excluded for more than one reason.

Table 1. Key characteristics of included studies: prevalence

Study (Ref)	Study Design and Setting	Study Population	COPD		Stroke Outcome	Stroke Prevalence (%)*	PR and/or Maximally Adjusted POR (95% CI)*
			No. of Subjects	Men (%)			
Agusti *et al.*, 2010 (18)	Cross-sectional; multicountry	Hospital outpatients (ECLIPSE Study cohort)	2,164	65.3	Any stroke	4.0 vs. 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 vs. 7.0 (at baseline)	PR: 0.34 (0.15–0.81)
Bentsen *et al.*, 2011 (20)	Cross-sectional; Norway	Hospital clinic attendees	100	47	Any stroke	3.0 vs. 2.3 (COPD vs. general population)	PR: 1.33 (0.45–4.33)
Cazzola *et al.*, 2012 (21)	Cross-sectional; Italy	General population (Health Search Database)	25,281	46	Any stroke	4.2 vs. 2.0	PR: 2.05 (1.93–2.18) Adjusted POR (age only): 3.60 (3.42–3.82)
Cunningham *et al.*, 2015 (22)	Cross-sectional health survey; USA	General population (2011 Behavioral Risk Factor Surveillance System survey participants)	33,088	40	Any stroke	9.7 vs. 2.8 7.4 vs. 2.4 (COPD vs. age-standardized population)	PR: 3.46 (3.34–3.60)
Curkendall *et al.*, 2006 (23)	Matched cohort; Saskatchewan, Canada	General population (administrative health care database)	11,493	54	Any stroke	1. Baseline: 4.8 vs. 3.3 2. Period: 9.6 vs. 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 vs. 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 (including TIAs)	9.9 vs. 3.2 (at baseline)	PR: 3.1 (3.0–3.2) POR: 3.34 (3.21–3.48)
Finkelstein *et al.*, 2009 (25)	Cross-sectional health survey; USA	General population (2002 National Health Interview Survey)	958	46	Any stroke	8.0 vs. 3.6	PR: 2.2 (1.78–2.80) Adjusted POR (SES, health behaviors, comorbidities): 1.5 (1.1–2.1)
García-Olmos *et al.*, 2013 (26)	Cross-sectional; Madrid, Spain	General population (primary care records)	3,124	76	Any stroke	7.49 vs. 6.48 (COPD vs. expected prevalence in general population)	PR: 1.19 (0.89–1.42)
Guerra *et al.*, 2010 (27)	Cohort; Tucson, AR	General population (TESAOD study participants)	294	53.1	Any stroke	3.1 vs. 1.1 (on enrollment)	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 vs. 1.9 2.1 vs. 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	General population (Medicaid database)	1,388	20.8	Any stroke	10.7 vs. 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 vs. 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 vs. no COPD
López Varela *et al.*, 2013 (31)	Cross-sectional; five Latin American cities	Population based (PLATINO Study participants)	759	52	CVA	3.2 vs. 2.1	PR: 1.52 (0.96–2.33)
Mapel *et al.*, 2000 (32)	Cross-sectional (two cohorts); New Mexico	1. HMO: General population (Lovelace Health Plan) 2. UMC: Hospital patients	1. 200 2. 200	1. 51 2. 36	1. Any stroke 2. Any stroke	1. 4.0 vs. 3.5 2. 6.5 vs. 2.8	1. PR: 1.14 (0.42–3.09) 2. PR: 2.3 (0.84–5.59)
Mapel *et al.*, 2005 (33)	Cross-sectional (two different time periods); New Mexico	Hospital inpatients (Veterans Administration system)	1. 1992: 87,867 2. 1998: 70,679	1. 99 2. 98	Any stroke	1. 7.5 vs. 6.8 2. 7.9 vs. 7.7	1. PR: 1.1 (1.08–1.14) 2. PR: 1.02 (0.97–1.03)
Miniati *et al.*, 2014 (34)	Matched cohort; Pisa, Italy	General population	200	89	Any stroke	1 vs. 1.5	PR: 0.66 (0.11–4.00)
Nagorni-Obradovic and Vukovic, 2014 (35)	Cross-sectional health survey; Serbia	General population (household health survey respondents)	653	46.6	Any stroke	5.4 vs. 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)	Cross-sectional health survey; North Carolina	General population (Behavioral Risk Factor Surveillance System survey participants)	1,948	NR	Any stroke	4.4 vs. 2.4	PR: 1.57 (1.16–2.13)
Schneider *et al.*, 2010 (37)	Matched cohort; UK	General population (GPRD primary health care database)	35,772	51	Any stroke (including TIAs)	6.9 vs. 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)	Cross-sectional health survey; USA	General population (NHANES Study participants)	995	39.9	Any CVA	9.0 vs. 4.5	PR: 1.93 (1.57–2.40)
Sidney *et al.*, 2005 (39)	Matched cohort; northern California	General population (NCKP Medical Care Program subscribers)	45,966	55.4	Hospitalization for stroke	1.2 vs. 0.5 (at baseline)	PR: 2.4 (2.08–2.82) Adjusted POR (age, sex, length of subscription): 2.44 (2.09–2.85)

(Continued)

Table 1. (*Continued*)

Study (Ref)	Study Design and Setting	Study Population	COPD		Stroke Outcome	Stroke Prevalence (%)*	PR and/or Maximally Adjusted POR (95% CI)*
			No. of Subjects	Men (%)			
van Manen *et al.*, 2001 (40)	Cross-sectional; western Netherlands	General population (patients registered with 28 GP practices)	290	64	Any CVA	3.1 vs. 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	Ischemic stroke	4.2 vs. 1.9 (COPD vs. general population)	PR: 2.2 (2.07–2.32)

Definition of abbreviations: BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular attack; DM = diabetes mellitus; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GP = general practice; GPRD = General Practice Research Database; HLD = hyperlipidemia; HMO = health maintenance organization; HTN = hypertension; KNHANES V = Korean National Health and Nutrition Examination Survey V; NCKP = Northern California Kaiser Permanente; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OLIN = Obstructive Lung Disease in Northern Sweden; PLATINO = Proyecto Latino Americano de Investigación en Obstrucción Pulmonar; PR = prevalence ratio; POR = prevalence odds ratio; SaRA = Salute Respiratoria nell'Anziano; SES = socioeconomic status; TESAOD = Tucson Epidemiological Study of Airway Obstructive Disease; THIN = The Health Improvement Network database; TIA = transient ischemic attack; UMC = university-affiliated county medical center.
*COPD versus non-COPD unless otherwise stated.

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 predesigned 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* Appendix E2) 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 that 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 vs. secondary care), the nature of the quality of the exposure case definition (e.g., physician-diagnosed COPD vs. 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) summarizes the key characteristics of those studies that report prevalence measures and Table 2 (13, 14, 23, 27, 37, 39, 41–45) those that estimate incidence. Fuller information is provided in the online supplement (Appendix E3).

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 (four 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, seven found significantly increased odds of a stroke event in people with COPD relative to those without (Figure 3). PORs ranged in magnitude from 3.60 (95% confidence interval [CI], 3.42–3.82) to 1.05 (95% CI, 0.63–1.77). Whereas the majority of these studies

Table 2. Key characteristics of included studies: incidence

Study (Ref)	Study Design and Setting	Study Population	COPD		Reported Effect Measures	Maximally Adjusted Effect Estimate (95% CI)*	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 hospitalization 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 (including TIAs)	Crude HR: 2.79 (2.56–3.04)	
Guerra *et al.*, 2010 (27)	Cohort, 1972–1996; Tucson, AR	General population (TESAOD Study participants)	155	61.3	HR for fatal stroke	Adjusted HR: 6.2 (2.9–13.4) recurrent obstructive vs. normal spirometry	Age, sex, BMI
Huiart *et al.*, 2005 (41)	Cohort, 1990–1999; Saskatchewan, Canada	General population (administrative health care databases)	5,648	53.9	1. SRR for hospitalization 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 standardization 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	General population (National health insurance database, LHID2005)	10,413	65.8	1. IRR for any stroke (excluding TIAs) 2. HR for any stroke (excluding 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.*, 2016 (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 (GPRD primary health care database)	15,907	NR	IRR for any stroke (including TIA)	Adjusted IRR: 1.23 (0.79–1.92)	Age, sex, GP practice (by matching)
	Nested case–control; UK	General population (GPRD primary health care database)	NR	NR	OR for any stroke (including 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	Mixed (KPNC Medical Care Program subscribers)	1,010	54.4	1. IRR for hospitalization 2. IRR for fatal stroke	1. Adjusted IRR: 1.39 (1.25–1.54) 2. Adjusted IRR: 1.35 (1.09–1.66)	1. Age, sex, DM, HTN, HLD, prior CVD 2. Age, sex, DM, HTN, HLD, prior CVD
Söderholm *et al.*, 2016 (45)	Matched cohort, 1996–2000; Sweden	Hospitalized population (Inpatient registers)	103,419	54.2	HR for hospitalization	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 ischemic stroke	Fully adjusted HR: 1.09 (1.02–1.17)	Age, sex, SES, medications

Definition of abbreviations: BMI = body mass index; CI = confidence interval; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CVDs = cardiovascular diseases; DM = diabetes mellitus; GP = general practice; GPRD = General Practice Research Database; HLD = hyperlipidemia; HTN = hypertension; HR = hazard ratio; IRR = incident rate ratio; KPNC = Northern California Kaiser Permanente Medical Care Program; LHID2005 = Longitudinal Health Insurance Database 2005; NR = not reported; OR = odds ratio; SES = socioeconomic status; SMR = standardized mortality rate; SRR = standardized rate ratio; TESAOD = Tucson Epidemiological Study of Airway Obstructive Disease; THIN = The Health Improvement Network database; TIA = transient ischemic attack.
*COPD versus non-COPD unless otherwise specified.

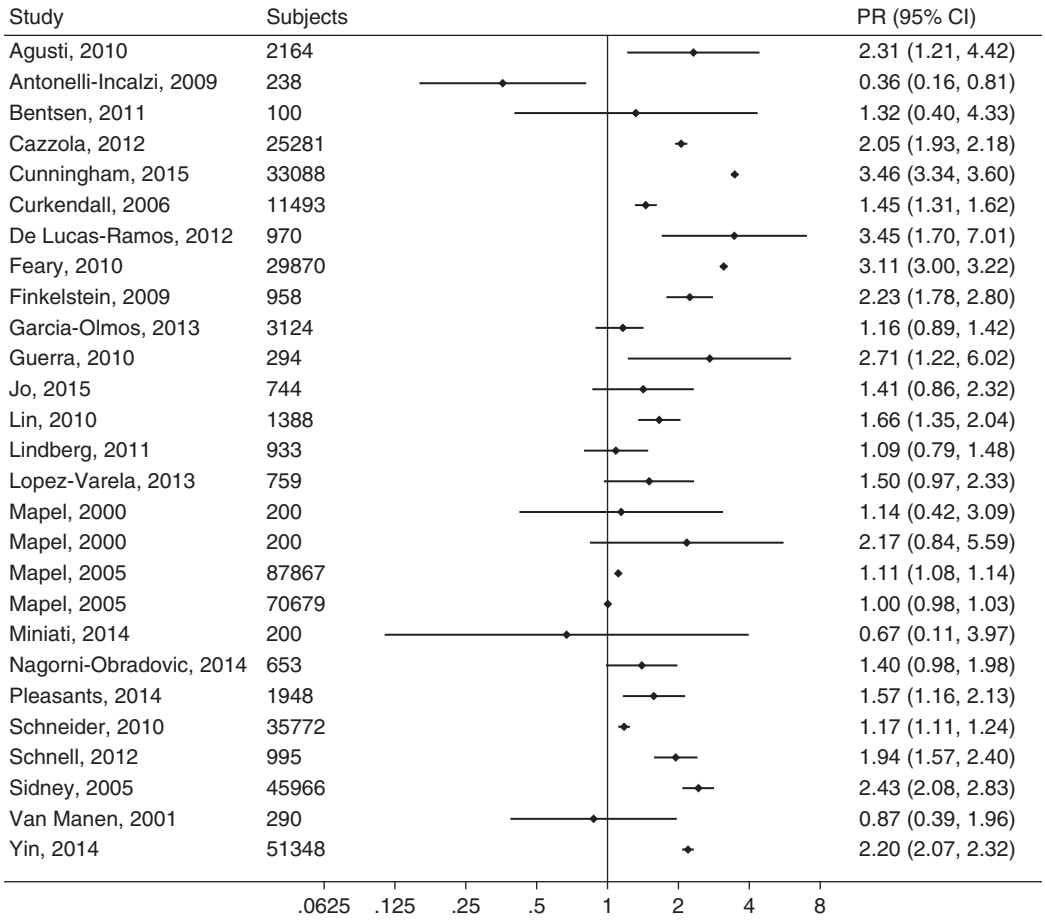

Figure 2. Forest plot showing estimates of the prevalence ratio (PR) for stroke, comparing people with and without chronic obstructive pulmonary disease (COPD). CI = confidence interval; Subjects = number of study participants with COPD.

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 great to justify reporting a pooled effect estimate (Figure 2), even when studies were further stratified (*see* Appendix E4). However, heterogeneity was lower among the group of four studies that 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 nonfatal and fatal stroke in the form of a standardized rate ratio (SRR for hospitalization) and a standardized mortality rate (SMR), respectively (41). The majority of the older incidence studies reported effect estimates for any stroke event (a composite of ischemic, hemorrhagic, and "not specified" stroke); four estimated the relative risk of having a fatal stroke (23, 39, 41, 42). One study reported results for ischemic strokes only (14). Several of the more recently published large population-based cohort studies estimated relative risks by stroke subtype (43–45). The effect of COPD disease severity was investigated in two studies (37, 44).

Results of studies that estimated stroke risk in the form of IRRs or HRs are presented in Figure 4a, and those that reported either ORs or SRRs 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 that 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

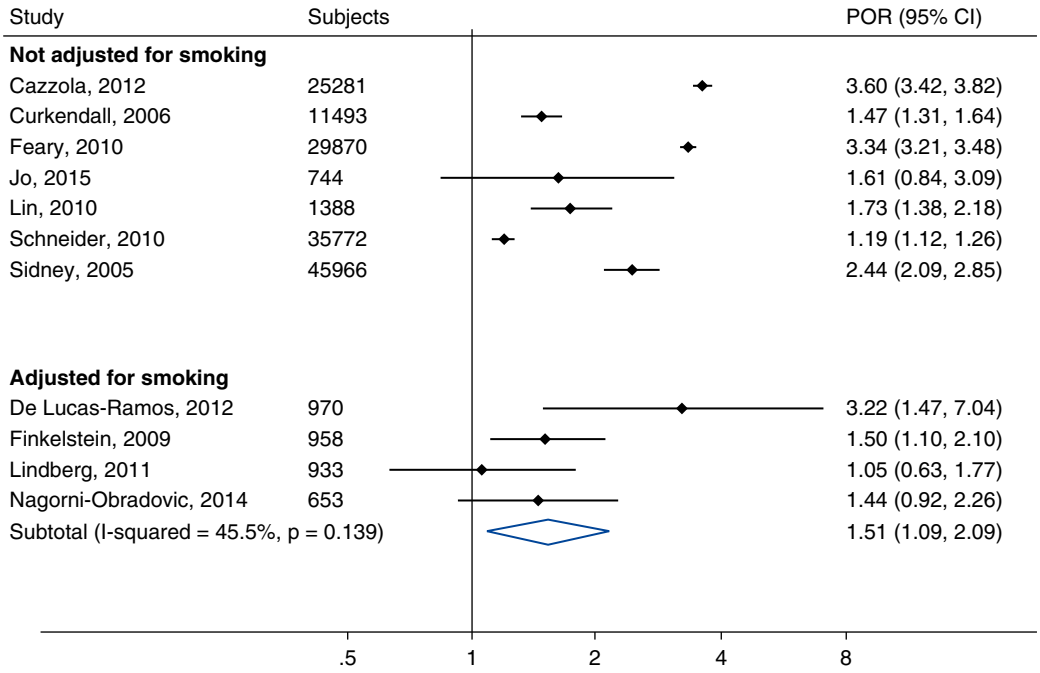

Figure 3. Forest plot showing estimates of the prevalence odds ratio (POR) for stroke, comparing people with and without chronic obstructive pulmonary disease (COPD), grouped according adjustment for smoking. CI = confidence interval; Subjects = number of study participants with COPD.

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 sex, 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 (less than 65 yr). The study by Feary and colleagues (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 those over 75 years of age (Figure 4a).

Three studies reported effect estimates by stroke subtype (43–45). Two reported a greater relative risk for hemorrhagic stroke compared with ischemic stroke (Figure 5). Söderholm and colleagues found that the greatest risk was for subarachnoid hemorrhage (SAH) (HR_{SAH}, 1.46; 95% CI, 1.16–1.85; HR_{ICH}, 1.23; 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 ischemic stroke (IS) and intracerebral hemorrhagic (ICH) stroke, which was greatest during the initial 2-year period of follow-up (45). In contrast, Lin and colleagues reported HRs for ischemic and hemorrhagic 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 severity and stroke risk (37, 44). Only Portegies and colleagues 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 summarizes 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 online supplement (*see* Appendix E5). 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 transient ischemic attacks 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

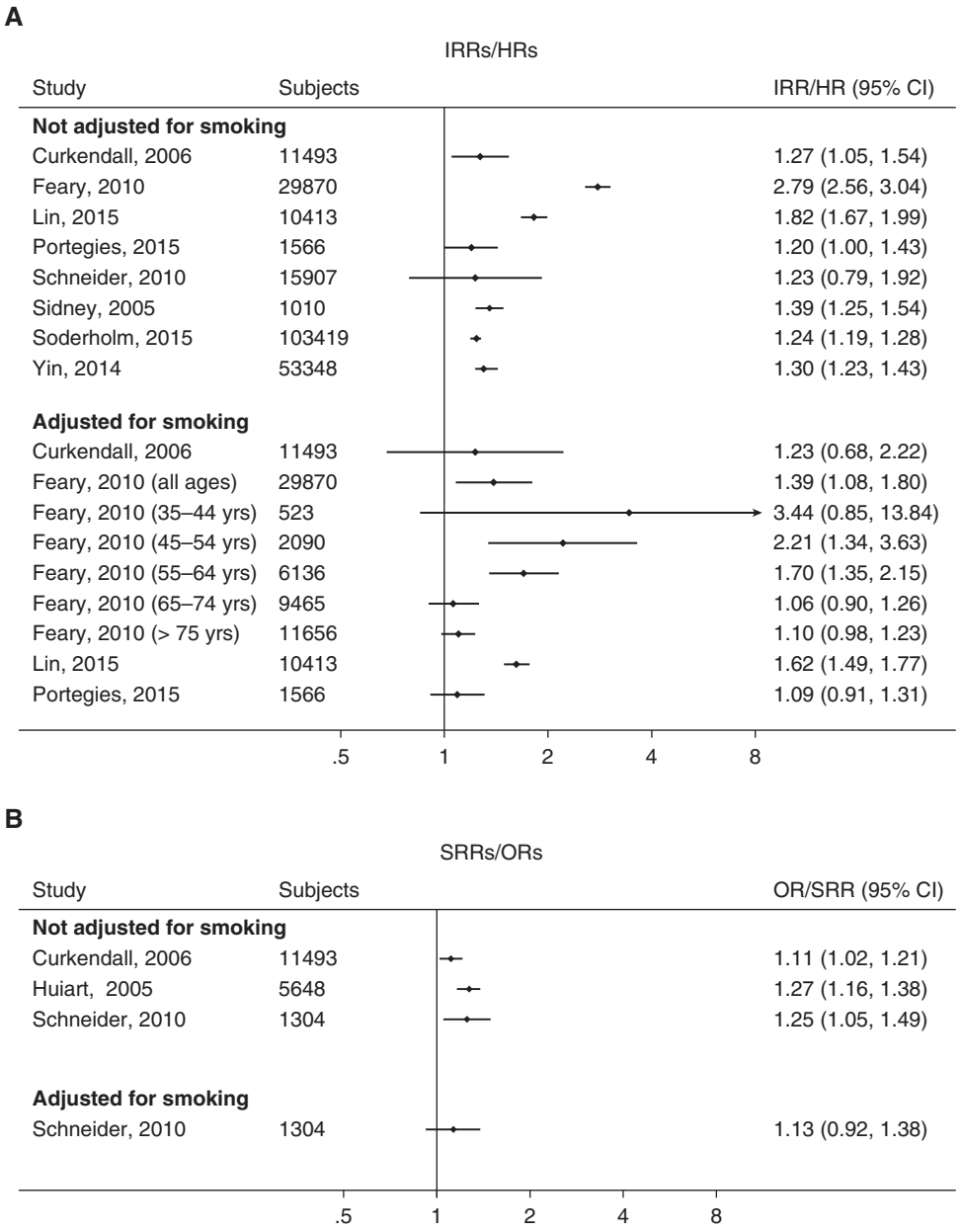

Figure 4. Forest plot showing relative risks for stroke comparing people with and without chronic obstructive pulmonary disease (COPD), grouped according adjustment for smoking. (*A*) IRRs/HRs. (*B*) SRRs/ORs. CI = confidence interval; HR = hazard ratio; IRR = incident rate ratio; OR = odds ratio; SRR = standardized rate ratio; Subjects = number of study participants with COPD.

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 two of the 11 analyses that estimated risk of incident stroke lend support to the hypothesis that COPD is an independent risk factor for stroke (13, 43).

We found evidence to suggest that the relative risk for stroke declines with increasing age, with the greatest risk occurring in those patients with COPD who are less than 65 years of age. There is also some evidence, albeit limited at the present time because of the paucity of studies, that the relative risk for hemorrhagic stroke may be greater than that for ischemic stroke (44, 45). A heightened risk of hemorrhagic 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 and colleagues, in their study of stroke registry patients, identified COPD as an independent risk factor for ischemic strokes of atherothrombotic origin (OR, 1.40; 96% CI, 1.04–1.93) but not for other types

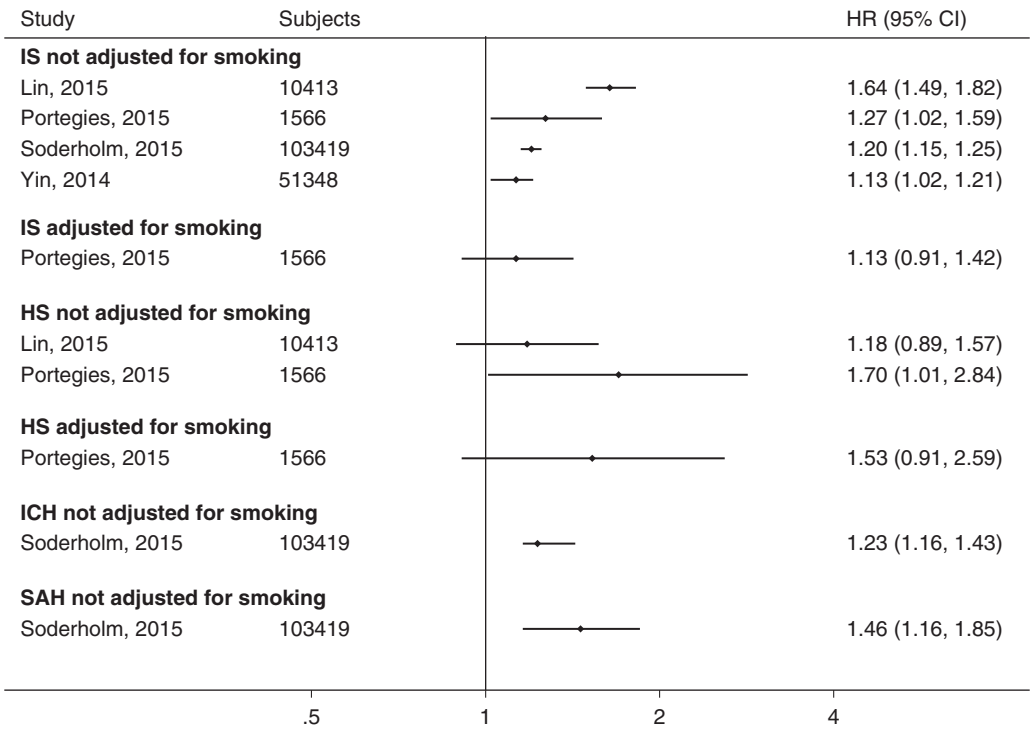

Figure 5. Forest plot showing relative risks for stroke, comparing people with and without chronic obstructive pulmonary disease (COPD), by stroke subtype. CI = confidence interval; HR = hazard ratio; HS = hemorrhagic stroke; ICH = intracerebral hemorrhagic; IS = ischemic stroke; SAH = subarachnoid hemorrhage; Subjects = number of study participants with COPD.

of ischemic stroke (e.g., lacunar and cardioembolic strokes) (49, 50). Although 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 because of the lack of studies that examine ischemic stroke outcomes by subtype.

We found no clear evidence that COPD 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 after 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). Although a degree of heterogeneity in the magnitude of the associations between COPD and individual CVDs due to differences in the causal mechanisms that underpin the associations 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 whereas 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 that is indicative of airflow obstruction and thus COPD. For example, Hozawa and colleagues, using data from the Atherosclerosis Risk in Communities Study (ARIC), showed that nonsmoking white subjects with low FEV_1 (and FVC) were at increased risk of ischemic stroke; however, there was no evidence of an association with the FEV_1/FVC ratio (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 characterize 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 of increased risk for stroke in the period after 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 ischemic 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.

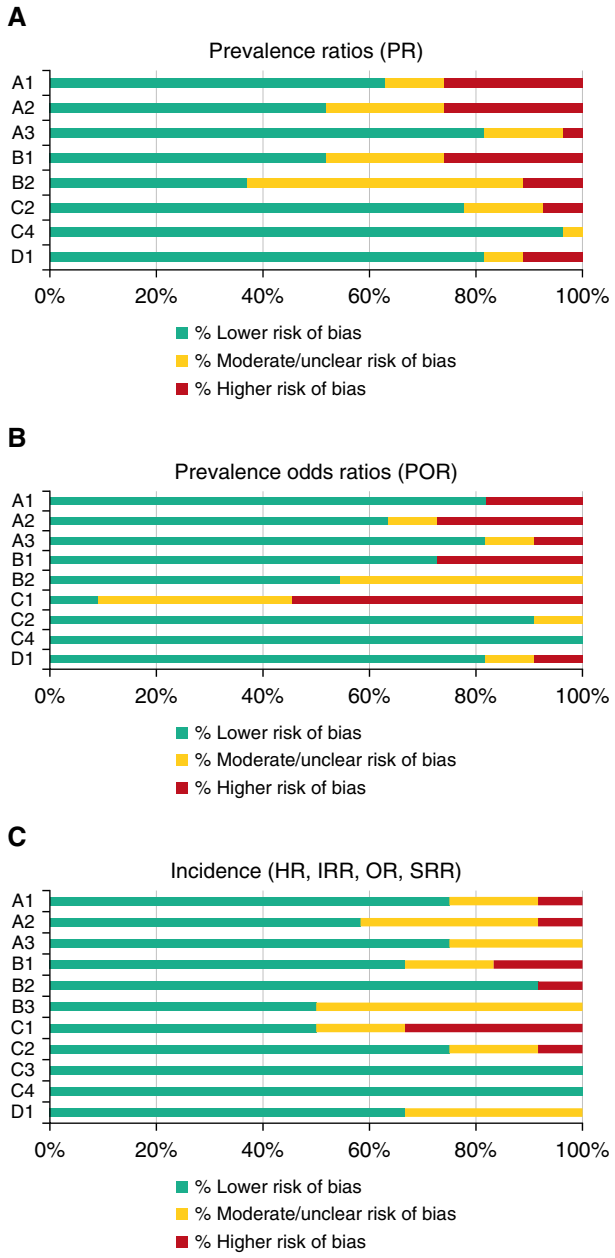

Figure 6. Risk of bias assessment results for (*A*) studies that estimate prevalence ratios, (*B*) studies that estimate prevalence odds ratios, and (*C*) studies that estimate incidence of stroke events in people with chronic obstructive pulmonary disease (COPD) versus people without COPD. (*A*) Prevalence ratios (PRs); (*B*) Prevalence odds ratios (PORs); (*C*) Incidence (hazard ratio [HR], incident rate ratio [IRR], odds ratio [OR], standardized rate ratio [SRR]). *Note*: The signaling 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; C4 to missing data (appropriate handling); and D1 to other potential sources of bias of concern. (*See* also Appendix E5.)

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 with more severe disease and who are unlikely to be representative of the population of patients with COPD 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 that 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 that 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 bias to be low.

Conclusion

Both prevalence and incidence of stroke are 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 patients with COPD, and for certain types of stroke. Our review highlights the need for further well-controlled and detailed longitudinal cohort studies to quantify the nature and magnitude of the risk of various stroke subtypes in people with COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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