

e-Appendix 3

Characteristics of included studies (more detailed summaries)

Table e-A3.1 Prevalence studies

Table e-A3.2a Incidence studies where the outcome is all stroke (including hospitalisation for stroke)

Table e-A3.2b Incidence studies where the outcome is fatal stroke

Table e-A3.2c Incidence studies where the outcome is ischaemic stroke

Table e-A3.2d Incidence studies where the outcome is haemorrhagic stroke

Table e-A3.1 Prevalence studies

Study (authors/ country)	Study design and population	COPD diagnostic criteria	Outcomes measured/ stroke definition	No. of subjects		No. of stroke events		Subject characteristics (COPD versus non-COPD unless otherwise stated)	Effect estimate(s) Prevalence COPD v non-COPD (%) and/or POR (95% CI)	Factors adjusted for (studies reporting POR)
				COPD	Non-COPD	COPD	Non-COPD			
<i>Hospitalised populations</i>										
Agusti et al., 2010 Multicountry (46 centres in 12 countries)	Cross-sectional analysis of baseline data collected at recruitment of patients to the ECLIPSE study cohort Study population <i>COPD group</i> : outpatient clinic attendees aged 40–75 years at enrolment, free from other respiratory disorders and inflammatory diseases <i>Non-COPD group</i> : volunteers from general population free from significant disease and normal spirometry	PB spirometry + smoking history (ex or current)	Any stroke Self-report (ATS DLD 78 questionnaire)	2,164 (including 954 with GOLD II, 911 with GOLD III, and 296 with GOLD IV)	582 (337 with smoking history + 245 never smokers)	86	9 (7 in the smoking controls and 2 in the non-smoking controls)	Men: 65.3% (COPD) Mean age (years):63.4 (COPD) v 55.4 (smoking controls) v 54.1 (non-smoking controls) Current smokers: 36% (COPD) v 61% (smoking controls)	<i>All subjects</i> 4% (COPD) v 2% (smoking controls) v 1% (non-smoking controls) <i>Men</i> 3.5% (COPD) <i>Women</i> 4.0% (COPD)	
Antonelli-Incalzi et al., 2009 Italy	Cohort study, 1996–1999 Source population: S.a.R.A study participants; 1,970 outpatients recruited from 24 participating hospital clinics, aged 65 years and over at enrolment between	Symptoms, smoking history, backed by PB spirometry	Any stroke Patient record review	238	1,239	6	87	Men: 81% (COPD) Mean age (years): 72.6 (COPD) Current smokers: 67.6% (COPD)	<i>All subjects</i> 2.3% v 7.0% (at baseline)	
Bentsen et al., 2011 Norway	Cross-sectional survey Source population: 136 subjects, aged over 35 years, attending outpatient clinics for COPD rehabilitation between August 2005 and August 2007 (excluding severely ill patients or those with heart disease); controls of similar age were randomly selected from the general population (n=993)	Pulmonary physician diagnosis of COPD, symptoms + spirometry	Any stroke Self-report	100 (45 of whom reported pain)	968 (333 of whom reported pain)	3	22	Men: 47% (n=45) v 42% (n=333) Mean age (years): 65.0 (n=45) v 57.8 (n=333) Smoking history: NR	<i>All subjects</i> 3.0% v 2.3% (COPD v general population)	Note: analyses confined to the 45 subjects with COPD who reported pain

de Lucas-Ramos et al., 2012 Madrid, Spain	Cross-sectional study Source population: Primary and secondary COPD clinic attendees; controls recruited from smoking cessation clinics at participating centres. Eligible subjects were smokers, aged > 40 years and free from other respiratory conditions	GP diagnosis of COPD confirmed by spirometry and history of smoking	Any stroke Self-report but responses cross-checked with patient records	970 (aged 40 years and over with a history of smoking)	276 (smokers with no history of COPD)	97	8	Men: 70.4% v 73.7% Mean age (years): 64.1 v 59.0 Smoking status (mean pack-years): 65.8 v 34.5	<i>All subjects</i> 10.0% v 2.9% Adjusted POR: 3.22 (1.47–7.04)	Adjusted for age, sex, hypertension, dyslipidaemia, diabetes, smoking
Mapel et al., 2005 New Mexico, USA	Cross-sectional study Source population: Patients treated by the Veterans Administration System hospital (as inpatients) between 1991 and 1999. Study population: Patients with COPD were matched to another Veteran of similar age and sex without a diagnosis of COPD (1:1)	GP diagnosis, identified by means of IDC-9 codes (in any position in the patient treatment file)	Any stroke, identified by means of ICD-9 codes	1. 1992 87,867 2. 1998 70,679	1. 1992 481,812 2. 1998 308,275	1. 1992 6,614 2. 1998 5,472	1. 1992 32,730 2. 1998 23,774	1. 1992 Men: 98.7% v 98.1% Mean age (years): 66.1 v 57.3 2. 1998 Men: 98.1% v 95.7% Mean age (years): 67.8 v 59.8	1. 1992 7.5% v 6.8% 2. 1998 7.9% v 7.7%	
General population										
Cazzola et al., 2012 Italy	Cross-sectional study Source population: Over 900,000 patients aged 14 years and over registered with c 650 GP practices contributing health data to the Health Search database (HSD) at the end of 2009. Study population: 690,489 eligible individuals aged 34 years and over	GP diagnosis; identified by means of ICD-9 codes in primary health care database	Any stroke event, identified by means of ICD-9 codes (430–438)	25,281	1,059	625,467	12,760	Men: 46% (COPD) Aged > 75 years: 44% v 16% Current smokers: 36.5% v 25.5%	<i>All subjects</i> 4.19% v 2.04% Adjusted POR: 3.6 (3.42–3.82) <i>Men</i> 4.76% v 1.95% Adjusted POR: 3.97 (3.69–4.26) <i>Women</i> 9.03% v 2.12% Adjusted POR: 3.48 (3.22–3.77) <i>Aged 35–44 years</i> 0.26% v 0.9% <i>Aged 45–54 years</i> 0.71% v 0.31% <i>Aged 55–64 years</i>	Adjusted for age Adjusted for age Adjusted for age

									1.43% v 1.03% Aged 65–74 years 3.8% v 2.92% Aged 75–84 years 6.17% v 6.91% Aged >85 years 6.88% v 10.29%	
Cunningham et al., 2015 USA	Cross-sectional health survey Source population: 2011 Behavioral Risk Factor Surveillance System (BRFSS) survey) participants (n = 405,856) Participants are aged > 18 years and are considered representative of the non-institutionalised US population	Self-report (reported positively to question: Has a doctor, nurse, or other health professional ever told you that you had COPD, emphysema or chronic bronchitis?)	Any stroke Self-report	33,088	372,498	3,210	10,430	Men: 40.0% v 47.6% Age (% aged 65 years and over): 37.1% v 20.1% Current smokers: 36.7% v 16.0%	<i>All subjects</i> 9.7% v 2.8% (<i>absolute numbers</i>) 7.4% v 2.4% (<i>age adjusted</i>) <i>Never smokers</i> Adjusted PR: 2.2 (1.9–2.5) <i>Former smokers</i> Adjusted PR: 1.6 (1.5–2.8) <i>Current smokers</i> Adjusted PR: 2.0 (1.8–2.4)	. Adjusted for age Adjusted for age Adjusted for age
Curkendall et al., 2006 Saskatchewan, Canada	Retrospective matched cohort, 1998–2001 Study population: all subjects contributing data to provincial healthcare administrative databases who meet inclusion criteria for COPD case definition and are aged > 40 years at diagnosis, matched to subjects with no history of respiratory illness	ICD-9 codes in physician claims or hospital separation data; more than 2 prescriptions for broncho-dilators within 6 months of COPD diagnosis	Any stroke event (identified by ICD-9 codes in hospital records and/or physician outpatient medical records	11,493	22,986 (matched 1:2 on age and sex)	551 (baseline) 1,103 (period)	758 (baseline) 1,816 (period)	Aged 65 or over at COPD diagnosis: 75% Men: 54% (matched) Ever smokers: 80.1% v 52.7% (2003 survey) Underweight: 3.9% v 1.9% (2003 survey)	<i>All subjects (baseline prevalence measures)</i> 4.8% v 3.3% Adjusted POR: 1.47 (1.31–1.64) <i>All subjects (period prevalence measures)</i> 9.6% v 7.9% Adjusted POR: 1.24 (1.15–1.34)	Adjusted for age and sex (by matching) Adjusted for age and sex (by matching)
Feary et al., 2010 UK	Retrospective cohort, 2005–2007 Study population: all subjects registered to UK GP practice contributing data to THIN (primary care database) who meet inclusion criteria for COPD case definition and are aged > 35 years at diagnosis	Read codes in THIN Stratified by disease severity	Any stroke (inc. TIAs) identified by means of Read codes	29,870	1,174,240	2,955	37,342	Men: 48.1% v 51.9% Aged > 65 years: 70.7% v 27.8% Ever smokers: 86.2% v 44.6% Deprivation (highest): 18.2% v 9.0%	<i>All subjects</i> 9.9% v 3.2% (at baseline) Crude POR: 3.34 (3.21–3.48)	

Finkelstein et al., 2009 USA	Cross-sectional health survey Source population: Core 2002 National Health Interview Survey (NHIS) respondents	Emphysema and/or chronic bronchitis (self-report) plus aged over 40 years and with a history of smoking	Any stroke Self-report	958	17,384	77	626	Men: 45.5% (COPD) White: 85.4%; Black: 8.8%; Hispanic: 4.1% (COPD) Mean age: 60.3 years (COPD) Smokers: 46.3% (COPD) BMI>25: 64.3% (COPD)	<i>All subjects</i> 8.0% v 3.6% Crude POR: NR Adjusted POR: 1.5 (1.1–2.1)	Adjusted for socioeconomic factors, health behaviours, selected comorbidities
Garcia-Olmos et al., 2013 Madrid, Spain	Cross-sectional survey, 2007 Study population: patients registered with 129 GP practices (n = 198,670)	GP diagnosis; identified by means of relevant codes in primary care records	Any stroke, identified by means of relevant codes in primary care records	3,124	c 195,487	NR	NR	Men: 76% (COPD) Aged > 40 years: 98% (COPD)	<i>All subjects</i> 7.49% v 6.48% (prevalence in COPD v "expected" prevalence in age-, sex-standardised population)	
Guerra et al., 2010 Tuscon, AR, USA	Cohort study; enrolment in 1972 with periodic follow up until 1996 Study population: Tuscon Epidemiological Study of Airway Obstructive Disease (TESACOD) study participants aged 21–80 years	Spirometry only; subjects grouped into 6 categories depending on spirometric patterns including obstructive and normal	Any stroke Self-report	294	9	1,505	17	Obstructive v normal at enrolment: Men: 53.1% v 43.7% Mean age (years): 60 v 46 Ever smoker: 77% v 53.9%	<i>All subjects</i> 3.1% v 1.1% (at enrolment)	
Jo et al., 2015 Republic of Korea	Cross-sectional survey Study population: KNHANES V survey respondents, 2010–2012 (drawn from 3,800 randomly selected households)	Former or current smoker with FEV ₁ /FVC < 0.7 and aged > 40 years	Any stroke Self-report	744	3,313	20	63	Mean age (years): 65.0 v 55.1 Current smoker: 41.3% v 36.7% Mean BMI: 23.7 v 2.7	<i>All subjects</i> 2.7% v 1.9% (absolute numbers) 2.1% v 1.3% (population weighted) Age-standardised OR: 1.61 (0.84–3.09)	
Lin et al., 2010 Maryland, USA	Retrospective matched cohort, 2001–2003 Source population: 445,000 Medicaid beneficiaries Study population: Subjects aged between 40 and 65 years at study start	COPD diagnosis in claims records identified by means of ICD-9 codes	Any stroke identified by means of ICD-9 codes in claims records	1,388	2,776 (matched 1:2 on age, sex and race)	149	180	Mean age (years): 49 (matched) Men: 20.8% (matched) Smoking status: NR	<i>All subjects</i> 10.7% v 6.5% Adjusted POR: 1.73 (1.38–2.18)	Adjusted for age and sex (by matching)

Lindberg et al., 2011 Sweden	Retrospective matched cohort Source population: OLIN study cohort; 4 adult cohorts re-examined in 2002–2004, with annual follow up from 2005–2011	Spirometry GOLD criteria used to stage COPD patients according to disease severity	Any stroke Self-report (in a structured interview)	933	933 (matched 1:1 on age and gender)	76	70	Men: 55% (matched) Mean age: 65 years (matched) Mean BMI: 26.06 v 26.58 Current smokers: 3.5% v 12.6%	<i>All subjects</i> 7.7% v 7.1% (at baseline) <i>GOLD stage I v non-COPD</i> Adjusted POR: 0.91 (0.56–1.48) <i>GOLD stage (II-IV) v non-COPD</i> Adjusted POR: 1.05 (0.63–1.77)	Adjusted for gender, BMI age and smoking habits
Lopez-Varela et al., 2013 Multi-centre, five Latin American cities	Cross-sectional study Source population: PLATINO study participants (n = 6,711) Study population: 5,314 participants aged over 40 years with spirometry data	Spirometry only; PB FEV ₁ /FVC < 0.7	Any stroke Self-report (in a structured interview)	759	4,555	24	96	Men: 52.3% v 37.4% Mean age (years): 64.1 v 55.0 Mean BMI: 26.8 v 28.3 Smoking status (mean pack years) 19.4 v 9.1	<i>All subjects</i> 3.2% v 2.1%	
Mapel et al., 2000 New Mexico, USA	Cross-sectional study, 1997 1. HMO cohort Source population: Members of the Lovelace Health Plan (n = 174,484) 2. UMC cohort Source population: Adult residents of Bernalillo County treated by University of New Mexico Hospitals and Clinics (n = 15,675)	1. HMO Diagnosis of COPD in discharge summary and administrative data 2. UMC Diagnosis of COPD in discharge summary	1. HMO Any stroke Recorded in discharge summaries and administrative data 2. UMC Any stroke Recorded in discharge summaries	1. HMO 200 (random selection from 1,522 eligible subjects) 2. UMC 200 (random selection from 330 eligible subjects)	1. HMO 200 (matched 1:1 on age and gender) 2. UMC 200 (selected from the NHIS 1995 survey)	1. HMO 8 2. UMC 13	1. HMO 7 2. UMC 6	1. HMO Men: 51% (COPD) Smokers: NR 2. UMC Men: 36% (COPD) Smokers: NR	<i>All subjects</i> 1. HMO 4.0% v 3.5% 2. UMC 6.5% v 2.8%	
Miniati et al., 2014 Pisa, Italy	Matched cohort study, 2001–2003 Source population: Subjects recruited by GPs from a larger cohort enrolled in a Europe-wide case-control study on genetic susceptibility to COPD	Physical examination, spirometry + history of smoking	Any stroke	200	201 (matched 1:1 on age, sex and smoking history)	2	3	Men: 89% v 86% Mean age (years): 66 v 65 Smoking status (mean pack years): 48 v 40	<i>All subjects</i> 1.0% v 1.5% (at baseline)	

Nagorni-Obradovic and Vukovic, 2014 Serbia	Cross-sectional health survey Source population: Household health survey respondents aged > 40 years (n = 10,013)	Self reported history of chronic bronchitis or emphysema: not supported by spirometry	Any stroke Self-reported history of stroke	653	9,360	30	339	Men: 46.6% v 54.4% Mean age (years): 62.8 v 59.3 Smokers: 43.0% v 39.6%	<i>All subjects</i> 5.4% v 3.8% Adjusted POR: 1.44 (0.92–2.26) <i>Men</i> 7.4 % v 4.1 % <i>Women</i> 4.0% v 3.3% <i>40–59 years</i> 2.3% v 1.6% <i>>60 years</i> 7.7% v 6.4%	Adjusted for gender, smoking, age, education,
Pleasant et al., 2014 North Carolina, USA	Cross-sectional survey, 2007 and 2009 Source population: Behavioral Risk Factor Surveillance System (BRFSS) survey participants, aged > 18 years (n = 28,054)	Self reported history of COPD, chronic bronchitis or emphysema:	Any stroke Self-report	1,948	20,024	NR	NR	NR	<i>All subjects</i> 4.4% v 2.4% (age standardized) Adjusted PR: 1.57 (1.16–2.13)	Using the 2000 standard US population Adjusted for age, sex, ethnicity, education, health care, BMI, smoking
Schneider et al., 2010 UK	Retrospective cohort (matched), 1995–2005 Source population: patients registered to a UK GP practice and contributing data to CPRD (primary care database) and aged 40–79 years	GP diagnosis (identified by means of Read codes in CPRD)	Any stroke; identified by Read codes in CPRD, plus either death or hospitalisation within 30 days, and/or new treatment for stroke within 180 days	35,772	35,772 (matched 1:1 on age, sex and GP practice and Index date)	2,454	2,093	Men: 51.3% (matched) 73.3% aged > 60 years at time of COPD diagnosis (matched) Current smokers: 43.3% v 18.0%	<i>All subjects</i> 6.9% v 5.9% (at baseline) Adjusted POR: 1.19 (1.12–1.26)	Adjusted for age, sex, GP practice by matching
Schnell et al., 2012 USA	Cross-sectional health survey, 1999-2008 (joined 5 survey waves) Source population: NHANES study participants, aged > 45 years	Self-report or GP diagnosis of chronic bronchitis or emphysema (asthmatics excluded); no spirometry	Any stroke Self-report	995	14,828	89	682	Men: 39.9% v 47.0 Mean age (years): 62.7 v 60.0 Ever smoker: 68.9% v 52.1 % > 10 pack years: 43.0% v 26.8%	<i>All subjects</i> 8.9% v 4.6%	

Sidney et al., 2005 North Carolina, USA	Retrospective (matched) cohort, 1996–2000 North Carolina Kaiser Permanente (NCKP) Medical Care Program subscribers, aged 40 years and over	ICD-9 codes in hospital discharge or outpatient records plus at least 2 prescriptions for COPD medications within 1 year	Any hospitalised stroke (fatal and non-fatal); identified by ICD9 codes	45,966	45,966 (matched on sex, age and length of NCKP membership)	553	228	Men: 55.4% (matched) Mean age (years): 64.4 years (matched) Current smokers: NR	<i>All subjects</i> 2% v 0.5% (at baseline prevalence) Adjusted POR: 2.44 (2.09–2.85)	Adjusted for age, sex, length of membership (by matching)
Van Manen et al. 2001 Western Netherlands	Cross-sectional survey Source population: patients registered with 28 urban and suburban GP practices in 1996–1997; c 55,000 patients	GP record of either asthma or COPD; airway obstruction confirmed by spirometry	Any stroke Self-report	290	421	9	15	Men: 64.1% v 41.1% Mean age (years): 65.8 v 65.9 Current smokers: NR	<i>All subjects</i> 3.1% v 3.7%	
Yin et al., 2014 Sweden	Prospective cohort, 2005–2008 Source population: Swedish subjects contributing to national administrative databases, which include patient files and prescribing information	Diagnosis of COPD in patient registers (identified by means of ICD codes)	Ischaemic stroke (identified by means of ICD-codes)	51,348	6,743,342	NR	NR	Men: 44.3% v 48.7% Mean age (years): 71.1 v 49.3 Current smokers: NR	<i>All subjects</i> 4.2% v 1.9% (COPD v general population)	

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Disease; NR, not reported; PB, post-bronchodilator; POR, prevalence odds ratio; PR prevalence ratio

Table e-A3.2a Incidence studies where the outcome is all stroke (including hospitalisation for stroke)

Study (authors/ country)	Study design and population	Patient characteristics		COPD diagnostic criteria	Outcomes measured/stroke definition	Mean length of follow up	Effect estimate(s): OR/HR/IRR/RR (crude and maximally adjusted) in COPD v non-COPD (unless otherwise stated) (95% CI)	Factors adjusted for
		COPD	Non-COPD					
Curkendall et al., 2006 Saskatchewan Canada	Retrospective (matched) cohort, 1/1/1998–31/12/2001 Study population: All subjects contributing data to provincial healthcare databases meeting inclusion criteria for COPD case definition and aged > 40 years at diagnosis; matched to subjects with no history of respiratory illness	n = 11,493 Men: 54% Aged > 65 years (at diagnosis): 75% Ever smokers: 80.1% (2003 survey)	n = 22,986 (matched 1:2 on age and sex) Men: 54% Aged > 65 years (at cohort entry): 75% Ever smokers: 52.7% (2003 survey)	ICD-9 codes (491.0–492.8 or 496) in physician claims or hospital separation data; more than two prescriptions for bronchodilators within 6 months of COPD diagnosis	Any stroke event (identified by ICD-9 codes (431–436) in hospital records and/or physician outpatient medical records)	NR; but under 3 years	<i>All subjects</i> Adjusted OR for any stroke: 1.11 (1.02–1.21) Partially adjusted IRR for hospitalisation: 1.27 (1.05–1.54) Adjusted IRR for hospitalisation: 1.23(0.68–2.22)	Adjusted for history of CVD events (including stroke), diabetes, hypertension, hyperlipidaemia Adjusted for age and sex (by matching) Adjusted for age, sex + hypertension, diabetes, hyperlipidaemia, obesity, smoking, history of CVDs
Feary et al., 2010 UK	Retrospective cohort, 2005–2007 Study population: All subjects registered to a UK GP practice contributing data to THIN (primary care database) meeting study inclusion criteria for COPD (including aged > 35 years at COPD diagnosis)	n = 29,870 Men: 48.1% Aged > 75 years (at diagnosis): 39.0% Ever smokers: 86.2%	n = 1,174,240 Men: 51.45% Aged > 75 years (at cohort entry): 13.5% Ever smokers: 44.6%	COPD identified by means of Read codes in patient records	Any stroke event (including TIAs) identified by means of Read codes	895 days	<i>All subjects</i> Crude HR: 2.79 (2.56–3.04) <i>35-44 year-olds</i> Adjusted HR: 3.44 (0.85–13.84) <i>45-54 year-olds</i> Adjusted HR: 2.21 (1.34–3.63) <i>55-64 year-olds</i> Adjusted HR: 1.70 (1.35–2.15) <i>65-74 year-olds</i> Adjusted HR: 1.06 (0.90–1.26) <i>> 75 year-olds</i> Adjusted HR: 1.10 (0.98–1.23)	Adjusted for sex and smoking status

Huiart et al., 2005 Saskatchewan Canada	Population-based cohort study; enrolment 1/1/1990–31/12/1997, with follow up to 31/12/1999 Source population: All residents of Saskatchewan eligible for health insurance coverage (c. 90% of population)	n = 5,648 Men: 53.9% Mean age (years): 73.5 Smoking status: NR	Reference group is a standard Saskatchewan population (age and gender standardised)	Medications-based: patients must have been dispensed at least three COPD medications in any 1-yr period between 1/1/90 and 31/12/97, aged > 55 years, and not have been prescribed asthma medications in the past 5 years	Hospitalisation for any stroke (identified from hospital separation database by means of ICD-9 codes: 430–438)	4.4 years	<i>All subjects</i> Standardised rate ratio (SRR) for hospitalisation: 1.27 (1.16–1.38)	Adjusted for age, gender and calendar year (by indirect standardisation)
Lin et al., 2015 Taiwan, Province of China	Population-based cohort study; enrolment 1/1/04–31/12/04 with follow up to 31/12/2006 Source population: Longitudinal Health Insurance Database (LHID 2005) covers 98% of population; > 50 years	n = 10, 413 Men: 65.8% Aged > 70 years at enrolment: 54.7% Smoking status: NR	n = 41,952 (matched 4:1) Men: 65.8% Aged > 70 years at enrolment: 54.7% Smoking status: NR	Three consensus COPD diagnoses (ICD codes) in patient record in year before treatment and 3 claims for COPD medications	Any stroke event exc. TIAs identified using ICD-9 codes	Stroke patients: 963 days (median) 990 for stroke-free patients	<i>All subjects</i> Crude IRR: 1.79 (1.50–2.13) Partially adjusted HR: 1.82 (1.67–1.99) Fully adjusted HR: 1.65 (1.51–1.79) Propensity adjusted HR: 1.62 (1.49–1.77)	Adjusted for age and sex (matching variables) Adjusted for age and sex + hypertension, hyperlipidaemia, diabetes, CHD As above + smoking, alcohol, BMI
Portegies et al., 2015 Ommoord district, Rotterdam, The Netherlands	Prospective cohort, 1990–2012 Source population: Subjects enrolled in the Rotterdam Study, which started in 1990 with additional enrolments 2000 and 2006, and follow up to 2012	n = 1,566 (538 with COPD at entry) <i>Prevalent COPD</i> Men: 53.5% Mean age (years): 67 Current smokers: 40.1%	n = 11,549 <i>Prevalent COPD</i> Men: 39.6% Mean age (years): 65.8 Current smokers: 21.7%	Spirometry-based case definition, supplemented with search of primary health care records, hospital discharge letters and prescriptions for COPD medications in cases where spirometry not available	Any stroke event (identified in linked primary and secondary care records)	9.6 years	<i>All subjects</i> Partially adjusted HR: 1.20 (1.00–1.43) Adjusted HR: 1.09 (0.91–1.31)	Adjusted for age and sex only Adjusted for smoking as well as age and sex
Schneider et al., 2010 UK	Retrospective cohort, 1995–2005 Source population: Patients registered to a UK GP practice and contributing to CPRD Study population: Subjects with COPD diagnosis recorded 1/1/1995 to 31/12/2005, and	n = 18,361 less those with prior stroke Men: 51.3% Aged > 70 years: 39.6% Ever smoker: 68.6%	n = 18,361 less those with prior stroke Men: 51.3% Aged > 70 years: 39.6% Ever smoker: 36.0%	GP diagnosis (identified by means of diagnostic Read codes in CPRD)	Any stroke (inc. TIAs) identified by means of diagnostic Read codes in CPRD, plus either death or hospitalisation within 30 days, and/or new treatment with	NR	<i>All subjects</i> Partially adjusted IRR: 1.23 (0.79–1.92)	Adjusted for age, sex and GP practice (matching variables only)

	aged 40-79 years matched 1:1 on age and sex and GP practice to COPD-free subjects				standard therapies for stroke within 180 days			
Schneider et al., 2010 UK	Nested case-control study Study population: subjects with stroke, matched 1:4 with subjects with no stroke (random selection from the above study cohort)	N = 598 cases (stroke cases of whom 300 had COPD and 298 were COPD free) Characteristics of this subset not reported	2,260 controls matched 4:1 with subjects with no stroke (of whom 1004 had COPD and 1256 were COPD free)	GP diagnosis (identified by means of diagnostic Read codes in CPRD) Stratified COPD by disease severity (staged by medication history: mild moderate and severe)	Any stroke including TIAs (as above)	NR	<i>All subjects</i> Partially adjusted OR: 1.25 (1.05– 1.49) Adjusted OR: 1.13 (0.92–1.38) <i>Mild COPD v no COPD</i> Partially adjusted OR: 1.28 (0.77–2.15) Adjusted OR 1.22 (0.71 –2.09) <i>Moderate v no COPD</i> Partially adjusted OR: 1.26 (1.05–1.51) Adjusted OR: 1.13 (0.92–1.38) <i>Severe v no COPD</i> Partially adjusted OR: 0.98 (0.47–2.05) Adjusted OR: 1.00 (0.47–2.15)	Adjusted for matching variables Adjusted for matching variables + smoking, BMI, hypertension, aspirin use and diabetes
Sidney et al., 2005 Northern California, USA	Retrospective (matched) cohort: 1996–2000 Source population: Kaiser Permanente (NCKP) Medical Care Program subscribers Study population: Subjects meeting case definition for COPD, matched 1:1 to COPD-free subjects; aged > 40 years	n = 1,010 Men: 55.4% > 70 years: 38.2% Ever smokers: NR	n = 753 Men: 55.4% > 70 years: 38.0% Ever smokers: NR	ICD-9 codes (491, 492, 496) in hospital discharge or outpatient records plus 2 at least two prescriptions for COPD medications within a 12 month period	Any hospitalised stroke (identified by means of ICD9 and ICD 10 codes 431–434 and 436; I60,I61 I63 I64	Mean: 2.75 years COPD; 2.99 years controls	<i>All subjects</i> Age-adjusted IRR:1.51 (1.37– 1.66) Adjusted IRR: 1.39 (1.25–1.54)	Direct age adjustment using 2000 KPNC membership as standard Adjusted for age, gender, diabetes hypertension, hyperlipidaemia, 6-month prior CVD
Soderholm et al., 2016 Sweden	Cohort, 1987–2003 Individuals hospitalised for COPD between 1987 and 2003 aged 40–84 years, identified from the Swedish Inpatient Register	n = 103,419 Men: 54.2% (matched) Mean age (years): 69.9 (matched) SES (non-manual worker): 17.9% Ever smokers: NR	n = 103,419 (matched 1:1 on year of birth, age, sex and county of residence) SES (non-manual worker): 25.0% Ever smokers: NR	Diagnosis (primary or secondary) of COPD in hospital discharge record (identified by means of ICD-9/10 codes)	Any hospitalised stroke identified by means of ICD-9/10 codes	NR	<i>All subjects</i> Adjusted HR: 1.24 (1.19–1.28)	Adjusted for SES, country of origin, history of asthma, diabetes, CVD, rheumatoid arthritis, kidney disease, lupus, length of hospital stay

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Disease; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; SES, socioeconomic status; TIA, transient ischaemic attack

Table e-A3.2b Incidence studies where the outcome is fatal stroke

Study (authors/ country)	Study design and population	Patient characteristics		COPD diagnostic criteria	Outcomes measured/ stroke definition	Mean length of follow up	Effect estimate(s): OR/IRR/HR/RR (crude and maximally adjusted) in COPD v non-COPD (unless otherwise stated) (95%CI)	Factors adjusted for
		COPD	Non-COPD					
Curkendall et al., 2006 Saskatchewan, Canada	Retrospective (matched) cohort, 1/1/1998 to 31/12/2001 Study population: All subjects contributing data to provincial healthcare databases meeting inclusion criteria for COPD case definition and aged > 40 years at diagnosis; matched to subjects with no history of respiratory illness	n = 11,493 Men: 54% Aged > 65 years (at diagnosis): 75% Ever smokers: 80.1% (2003 survey)	n = 22,986 (matched 1:2 on age and sex) Men: 54% Aged > 65 years (at cohort entry): 75% Ever smokers: 52.7% (2003 survey)	ICD-9 codes (491.0-492.8 or 496) in physician claims or hospital separation data; more than two prescriptions for bronchodilators within 6 months of COPD diagnosis	Any fatal stroke event (identified by ICD-9 codes (431–436) in hospital records and/or physician outpatient medical records)	NR; but less than 3 years	<i>All subjects</i> Partially adjusted IRR for fatal stroke: 1.24 (0.90–1.71)	Adjusted for age, sex (matching variables)
Huiart et al., 2005 Saskatchewan, Canada	Population-based cohort study; enrolment 1/1/1990-31/12/1997, with follow up to 31/12/1999 Source population: all residents of Saskatchewan eligible for health insurance coverage (c. 90% of population)	n = 5,648 Men: 53.9% Mean age: 73.5 years Smoking status: NR	Reference group is a standard Saskatchewan population (age and gender standardised)	Medications-based: patients must have been dispensed at least 3 COPD medications in any 1-yr period between 1/1/90 and 31/12/97, aged > 55 years, and not have been prescribed asthma medications in the past 5 years	Stroke mortality; identified by means of ICD-9 codes (431–436) codes in vital registration databases	4.4 years	<i>All subjects</i> Standardised mortality ratio (SMR): 1.60 (1.36–1.85)	Adjusted for age, gender, calendar year (by indirect standardisation)
Guerra et al., 2010 Arizona, USA	Cohort study; enrolment in 1972 with periodic follow up; cause of death ascertained in 2005	n = 294 (recurrent obstructive spirometry) Men: 53.1% Mean age (years): 60 Ever smoker: 77%	n = 1,505 (normal spirometry) Men: 43.7% Mean age (years): 46 Ever smoker: 54%	Spirometry only; subjects grouped into 6 categories depending on spirometric patterns including recurrent obstructive and normal	Fatal stroke Cause of death statistics	NR	<i>All subjects</i> Adjusted HR: 6.2 (2.9–13.4)	Adjusted for age, sex, BMI

<p>Knuiman et. al, 1999 Western Australia</p>	<p>Retrospective population-based cohort, 1969–1995 Source population: Busselton Health Study participants Study population: 2,100 men and 2,177 women who participated in surveys in 1969,1972 or 1975</p>	<p>n = 607</p>	<p>n = 3,670</p>	<p>Symptoms of chronic bronchitis only: cough and/or phlegm production for at least 3 months of year</p>	<p>Stroke mortality Death certificates and relatives; ICD codes 430-438</p>	<p>26 years (1969 survey), 20 years (1975 survey)</p>	<p><i>Men</i> Partially adjusted HR: 0.78 (0.41–1.42) Fully adjusted HR: 0.76 (0.39–1.47) <i>Women</i> Partially adjusted HR: 0.92 (0.44–1.93) Fully adjusted HR: 0.90 (0.44–1.91)</p>	<p>Adjusted for age and smoking only Adjusted for age and smoking, plus other respiratory symptoms, %PFEV₁, CHD, and CVD risk factors</p>
<p>Sidney et al., 2005 Northern California, USA</p>	<p>Retrospective (matched) cohort: 1996–2000 Source population: Kaiser Permanente (NCKP) Medical Care Program subscribers, 1/1/1996 to 31/12/2000 Study population: Subjects meeting case definition for COPD, matched 1:1 to COPD-free subjects; aged 40 years and over</p>	<p>n = 1,010 Men: 55.4% > 70 years: 38.2% Ever smokers: NR</p>	<p>n = 753 Men: 55.4% > 70 years: 38.0% Ever smokers: NR</p>	<p>ICD-9 codes (491, 492, 496) in hospital discharge or outpatient records plus at least two prescriptions for COPD medications within a 12 month period</p>	<p>Any fatal stroke event (identified by means of ICD9 and ICD 10 codes: 431–434 and 436; I60, I61, I63, I64)</p>	<p>Mean: 2.75 years COPD; 2.99 years controls</p>	<p><i>All subjects</i> Age-adjusted IRR: 1.46 (1.21–1.75) Adjusted IRR: 1.35 (1.09–1.66) <i>Men</i> Age-adjusted IRR: 1.09 (0.84–1.41) <i>Women</i> Age-adjusted IRR: 1.47 (1.11–1.94)</p>	<p>Age adjustment is by direct standardisation using 2000 NCKP membership as standard Adjusted RRs are adjusted for age, gender, diabetes hypertension, hyperlipidaemia, 6-month prior CVD</p>

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Disease; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; %PFEV₁, percent predicted FEV₁; SES, socioeconomic status;

Table e-A3.2c Incidence studies where the outcome is ischaemic stroke

Study (authors/ country)	Study design and population	Patient characteristics		COPD diagnostic criteria	Outcomes measured/stroke definition	Mean length of follow up	Effect estimate(s): OR/RR/HR (crude and maximally adjusted) in COPD v COPD-free (unless otherwise stated) (95%CI)	Factors adjusted for
		COPD	Non-COPD					
Lin et al., 2015 Taiwan, Province of China	Population-based cohort study; enrolment 1/1/04-31/12/04 with follow up to 31/12/2006 Source population: Longitudinal Health Insurance Database (LHID 2005) covers 98% of population; > 50 years	n = 10, 413 Men: 65.8% Aged > 70 years at enrolment: 54.7% Smoking status: NR	n = 41,952 (matched 4:1) Men: 65.8% Aged > 70 years at enrolment: 54.7% Smoking status: NR	Three consensus COPD diagnoses (ICD codes) in patient record in year before treatment and 3 claims for COPD medications	Ischaemic stroke (identified by means of ICD codes 433–435)	Stroke patients: 963 days (median) 990 for stroke-free patients	<i>All subjects</i> Adjusted HR: 1.64 (1.49–1.82)	Adjusted for hypertension, hyperlipidaemia, diabetes, CHD
Portegies et al., 2015 Ommoord district, Rotterdam, The Netherlands	Prospective cohort, 1990-2012 Source population: Subjects enrolled in the Rotterdam Study, which started in 1990 with additional enrolments 2000 and 2006, and follow up to 2012	n = 1,566 (538 with COPD at entry) <i>Prevalent COPD</i> Men: 53.5% Mean age (years): 67 Current smokers: 40.1%	n = 11,549 <i>Prevalent COPD</i> Men: 39.6% Mean age (years): 65.8 Current smokers: 21.7%	Spirometry-based case definition, supplemented with search of primary health care records, hospital discharge letters and prescriptions for COPD medications in cases where spirometry not available	Ischaemic stroke event (identified in linked primary and secondary care records using)	9.6 years	<i>All subjects</i> Partially adjusted HR=1.27 (1.02–1.59) Adjusted HR: 1.13 (0.91–1.42)	Adjusted for age and sex Adjusted for smoking as well as age and sex
Soderholm et al., 2016 Sweden	Matched cohort, 1987–2003 Source population: Individuals hospitalised for COPD aged 40-84 years (identified from the Swedish Inpatient Register); matched controls selected from the Total Population Register	n = 103,419 Men: 54.2% (matched) Mean age (years): 69.9 (matched) SES (non-manual worker): 17.9% Ever smokers: NR	n = 103,419 (matched 1:1 on year of birth, age, sex and county of residence) SES (non-manual worker): 25.0% Ever smokers: NR	Diagnosis (primary or secondary) of COPD in hospital discharge record (identified by means of ICD-9/10 codes)	All hospitalised Ischaemic strokes (identified by means of ICD-9/10 codes)	NR	<i>All subjects</i> Adjusted HR: 1.20 (1.15–1.25)	Adjusted for SES, country of origin, history of asthma, diabetes, CVD, rheumatoid arthritis, kidney disease, lupus and length of hospital stay
Yin et al., 2014	Prospective cohort, 2005–2008	n = 51,348	n = 6,743,342	Diagnosis of COPD in patient registers	Incident ischaemic stroke events	3.5 years	<i>All subjects</i> Partially adjusted HR: 1.3	Adjusted for age, sex, SES

Sweden	Source population : All subjects contributing to national administrative databases Study population (COPD group): Subjects aged over 18 years on 1 July 2005 with a diagnosis of COPD and no history of MI or stroke	Men: 44.3% Mean age (years): 71.1 Current smokers: NR	Men: 48.7% Mean age (years): 49.3 Current smokers: NR	(identified by means of ICD codes)	(identified by means of ICD-8/9/10 codes)	(1.19–1.34) Fully adjusted HR: 1.13 (1.02–1.21)	Adjusted for age, sex, SES, medications
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CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Disease; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; SES, socioeconomic status; TIA, transient ischaemic attack

Table e-A3.2d Incidence studies where the outcome is haemorrhagic stroke

Study (authors/ country)	Study design and population	Patient characteristics		COPD diagnostic criteria	Outcomes measured/stroke definition	Mean length of follow up	Effect estimate(s): OR/RR/HR (crude and maximally adjusted) in COPD v COPD-free (unless otherwise stated)	Factors adjusted for
		COPD	Non-COPD					
Lin et al., 2015 Taiwan, Province of China	Population-based cohort; enrolment 1/1/04– 31/12/04 with follow up to 31/12/2006 Source population: Longitudinal Health Insurance Database (LHID 2005) covers 98% of population; > 50 years	n = 10, 413 Men: 65.8% Aged > 70 years at enrolment: 54.7% Smoking status: NR	n = 41,952 (matched 4:1) Men: 65.8% Aged > 70 years at enrolment: 54.7% Smoking status: NR	Three consensus COPD diagnoses (ICD codes) in patient record in year before treatment and three claims for COPD medications	Any haemorrhagic stroke event, identified by means of ICD codes (430– 432)	Stroke patients: 963 days (median) 990 for stroke- free patients	<i>All subjects</i> Adjusted HR: 1.18 (0.89– 1.57)	Adjusted for hypertension, hyperlipidaemia, diabetes, CHD
Portegies et al., 2015 Ommoord district, Rotterdam, The Netherlands	Prospective population- based cohort, 1990-2012 Source population: Subjects enrolled in the Rotterdam Study, which started in 1990 with additional enrolments 2000 and 2006, and follow up to 2012	n = 1,566 (538 with COPD at entry) <i>Prevalent COPD</i> Men: 53.5% Mean age (years): 67.0 Current smokers: 40.1%	n = 11,549 <i>Prevalent COPD</i> Men: 39.6% Mean age (years): 65.8 Current smokers: 21.7%	Spirometry-based case definition, supplemented by search of primary healthcare records, hospital discharge letters and prescriptions for COPD medications in cases were spirometry not available	Any haemorrhagic stroke (identified in linked primary and secondary care records)	9.6 years	<i>All subjects</i> Partially adjusted HR: 1.70 (1.01–2.84) Fully adjusted HR: 1.53 (0.91– 2.59)	Adjusted for age and sex Adjusted for smoking as well as age and sex
Soderholm et al., 2016 Sweden	Cohort (matched) 1987– 2003 Source population: Individuals hospitalised for COPD aged 40–84 years (identified from the Swedish Inpatient Register); controls selected from the Total Population Register	n = 103,419 Men: 54.2% Mean age (years): 69.9 SES (non-manual worker): 17.9% Ever smokers: NR	n = 103,419 (matched 1:1 on year of birth, age, sex, county of residence) SES (non-manual worker): 25.0% Ever smokers: NR	Diagnosis (primary or secondary) of COPD in hospital discharge record (identified by means of ICD-9/10 codes)	All subarachnoid and intracerebral haemorrhagic strokes identified by means of ICD-9/10 codes	NR	<i>All subjects</i> <i>Intracerebral haemorrhage</i> Adjusted HR: 1.23 (1.16–1.43) <i>Subarachnoid haemorrhage</i> Adjusted HR: 1.46 (1.16–1.85)	Adjusted for SES, country of origin, history of asthma, diabetes, CVD, rheumatoid arthritis, kidney disease, lupus, length of hospital stay

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Disease; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; SES, socioeconomic status