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Title: Incidence of stroke and stroke subtypes in chronic obstructive pulmonary disease.

Running title: Stroke in COPD.

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Key words: COPD, stroke, cerebral infarction, intracerebral haemorrhage, subarachnoid haemorrhage.

ABSTRACT

Background

It is uncertain whether the incidence of stroke is increased in patients with chronic obstructive pulmonary disease (COPD), and whether COPD is associated with all subtypes of stroke (i.e. ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage). We evaluated the association between COPD and incidence of stroke in a nation-wide cohort study.

Methods

All individuals between 40 and 84 years of age, hospitalised for COPD between 1987 and 2003 in Sweden were identified in the Swedish hospital discharge register. For each COPD patient (n=103,419), one reference individual was randomly selected from the general population matched for year of birth, sex and county of residence. After excluding subjects with prior stroke, incidence rates during 10 years follow-up were calculated. Hazard ratios (HR) for stroke comparing COPD patients with reference subjects were estimated using Cox regression adjusting for demographics and comorbidities.

Results

Incidence of all-cause stroke (n events=17,402) was significantly increased in COPD patients compared to reference individuals (HR: 1.24, 95% CI 1.19-1.28), especially during the first two years after COPD diagnosis (HR: 1.46, 1.37-1.55). Incidences of ischemic stroke (HR 1.20, 1.15-1.25), intracerebral haemorrhage (HR: 1.29, 1.16-1.43) and subarachnoid haemorrhage (HR: 1.46, 1.16-1.85) were all increased in COPD patients.

Conclusions

Incidences of all stroke subtypes are increased in COPD, especially during the first years after COPD diagnosis. The association was independent of several comorbidities, although residual confounding from smoking and hypertension cannot be excluded. A global evaluation of stroke risk factors seems warranted in patients with COPD.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common disease with an overall prevalence of around 10% in the adult population worldwide and in Sweden.[1, 2] COPD is characterized by chronic airflow limitation in combination with respiratory symptoms, and diagnosis is based on a low ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC).[2] The life time risk of developing COPD has been estimated to 25% in the general population over 35 years,[3] and the disease burden is projected to grow in the next few years.[4]

Stroke is another major health threat, and constitutes one of the most common causes of death and severe disability.[4] Ischemic stroke (IS) is the most common subtype (around 85% of all strokes), whereas intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) are less common (10 and 5% respectively) but associated with very high mortality rates (30-50%).[5] Although some risk factors are shared for all stroke subtypes (e.g. hypertension),[6, 7] several important cardiovascular risk factors are differentially related to IS, ICH and SAH. For example, smoking is a strong risk factor for IS and SAH[6, 7] whereas results have been conflicting for ICH.[6, 8] Diabetes increases the risk of IS and ICH[6] but might be inversely related to SAH,[7] and atrial fibrillation is strongly associated with cardioembolic IS. Also, the mean age in SAH is substantially lower than in IS and ICH.[7, 9]

COPD and reduced lung function are associated with a high prevalence of cardiovascular risk factors, e.g. hypertension, smoking and diabetes.[10-12] However, even after adjustment for a wide range of confounders, and in analyses of non-smokers, reduced lung function (low FEV1 and/or FVC) has been associated with increased risk of cardiovascular disease,[13] including all-cause stroke,[14] IS[15] and SAH,[9] respectively. The underlying reason is unclear, but mechanisms such as extracellular matrix degradation, inflammation and oxidative stress, have been suggested to contribute to both reduced lung function and development of stroke.[13, 15, 9]

The incidence of stroke in COPD has been evaluated in a few studies. Most studies reported a moderate (10-50%) risk increase.[16, 10, 17, 18] However, results have been inconsistent. Feary et al[19] found an almost three-fold increase in stroke incidence, although this high effect was mainly observed in younger age groups, whereas other studies reported no significant association between COPD and stroke after adjustment for comorbidities.[18, 16] Furthermore, previous studies of stroke incidence and COPD made no distinction between stroke subtypes. Hence, it is unclear to what extent COPD is associated with increased risk of stroke, and it is not known how COPD effects the risk of IS, ICH and SAH, respectively. Characterization of these associations could provide a better understanding of disease mechanisms, and improve strategies of stroke prevention in COPD patients.

In a nationwide cohort study in Sweden, we assessed the incidence of stroke subtypes in COPD patients and reference individuals, randomly selected from the general population.

METHODS

Study population

The Centre for Epidemiology, Sweden, identified all individuals between 40 and 84 years of age with a hospital discharge diagnosis of COPD between 1987–2003 in the Swedish hospital discharge register, according to the International Classification of Diseases, Ninth and Tenth revisions (ICD-9: 491–492, 496; ICD-10: J41–J44), either as primary diagnosis (hospitalised because of COPD) or as secondary diagnosis (hospitalised with COPD). A total of 132,017 patients, born 1903–1963, were identified. For each individual with COPD one reference individual was randomly selected from the Total Population Register, matched for sex, year of birth, and county of residence during the year of first hospital discharge listing a COPD diagnosis.

The Swedish Inpatient Register is a hospital discharge registry that was established in 1964 and became nationwide in 1987, covering all hospitals in Sweden. One primary diagnosis and up to seven secondary diagnoses are listed for each patient.[20] Diagnoses are made by physicians at discharge of the patient and contra-signed by board-certified specialists. The registry has a high overall validity and has been used extensively in research purposes.[20] A recent validation study reported that the validity for the diagnosis COPD is acceptable in this register, with less than 10 % of the COPD diagnoses being misclassified or uncertain. No difference in diagnostic validity was observed between COPD listed as main or secondary diagnosis.[21]

All subjects were linked to the Total Population Register to obtain information on country of birth, vital status and date of emigration. Each individual was also linked to The Swedish National Population Censuses of 1980, 1985 and 1990 to obtain information on socioeconomic position (SEP). The SEP groups were combined into three broad categories: manual, non-manual, and other types of occupation. In addition, a category for those outside the workforce (i.e. old age pensioners, housewives, students and unemployed) or with missing information was included.

Exclusions

Among the COPD patients, 682 (0.5%) individuals were excluded because of data irregularities, and 11,131 (8.4%) who died less than 30 days after the date of inclusion (before start of follow-up), were also excluded. Of the reference individuals, 2,678 (2.0%) who died before the start of follow-up and 1,736 (1.3%) who had been hospitalised with a COPD diagnosis prior to inclusion, were excluded.

Subsequently, we excluded all individuals who had a primary or secondary diagnosis of either stroke (ICD-9 codes 430, 431, 434 and 436, and ICD-10 codes I60-I64) or "late effects of cerebrovascular disease" (ICD-9 438, ICD-10 I69.0-I69.4) before or on the start of follow-up. The number of individuals excluded because of prior stroke was 4,715 (4.1%) among reference individuals and 8,624 (7.4%) among COPD patients.

Due to the exclusions, 8,161 (6.2%) COPD patients and 18,785 (14.2%) referents lacked their counterpart and were therefore also excluded. 103,419 case-referent pairs remained.

Outcome and follow-up

Information about all discharges from hospital, 1987-2010, listing stroke (SAH, ICH, IS and stroke not specified as haemorrhage or infarction; ICD-9 codes 430, 431, 434 and 436, and ICD 10-codes I60, I61, I63, I64), were obtained from the Inpatient Register. Follow-up started 30 days after the date of hospital discharge for the COPD subject, for both COPD and referent subjects, and continued until the date of first incident stroke, death, emigration or 10 years after start of follow-up (at most until Dec 31 2010), whichever came first.

Reference individuals diagnosed with COPD during follow-up were censored by the date of the first hospitalisation listing COPD (n=3,787, 3.7% of the reference group). If stroke and COPD occurred at the same date in a referent, the subject was censored.

In the main analysis only stroke as primary diagnosis was included. An additional analysis was also performed, in which all primary and secondary stroke diagnoses were counted as stroke events.

Statistics

Associations between baseline characteristics and COPD-status were evaluated with logistic regression. Incidence rates were calculated for all-cause stroke and for each stroke subtype separately in COPD and reference individuals. Cox regression models internally stratified by year of birth, year of inclusion, sex and county of residence to account for the matched design, were used to calculate hazard ratios (HR) for all-cause stroke and stroke subtypes in COPD compared with the reference group. Models were subsequently adjusted for country of birth, SEP, history of asthma, type 1 and 2 diabetes, hypertension, ischemic heart disease, heart failure, atrial fibrillation, alcohol abuse, rheumatoid arthritis/systemic lupus erythematosus, kidney failure, and total duration of hospital stay before inclusion (0, 1-5, 6-20, or >20 days). Comorbidities were defined according to ICD-9 or ICD-10 codes listed at hospital discharges before inclusion. Covariates were selected a priori based on previous knowledge about risk factors for COPD and stroke.

The proportional hazards assumption was graphically evaluated with log-log plots, and formally assessed with a likelihood ratio test comparing a model with an interaction between COPD-status and follow-up time intervals (0-2, 2-5 and 5-10 years) to a model without this interaction. The HRs for all-cause stroke, IS and ICH, respectively, were not constant over time (p for interaction with time intervals <0.001 for all-cause stroke and IS, 0.035 for ICH). Results are therefore presented for each time interval. The effect of COPD on SAH incidence did not change substantially over time (p=0.47). Interactions between COPD-status and all covariates were tested by comparing a model with the interaction term to a model of main effects, in the first time interval. Statistical analysis was performed using Stata version 12 (StataCorp. 2011. College Station, TX: StataCorp LP.)

Ethics

The study was approved by Lund University Research Ethics Committee (590/2004 and 270/2012).

RESULTS

Baseline characteristics

Mean age (±SD) was 70±10 years (mean year of birth 1925) and 46% of participants were women. Sixty-two percent of COPD patients had COPD as primary diagnosis. Baseline demographics and prevalence of comorbidities are shown in table 1.

Incidence of stroke in COPD versus non-COPD

A total of 17,402 incident strokes (7,945 in COPD and 9,457 in reference individuals) occurred during 1,348,973 person years of follow-up. Median follow-up was 5.1 years (548,938 person years) in COPD patients and 9.7 years (800,034 person years) in reference individuals. Crude incidence of all-cause stroke was 12.9 (95% CI 12.7-13.1) per 1000 person years in all participants, 14.5 (14.2-14.8) in COPD and 11.8 (11.6-12.1) in referents.

Incidence rates and HRs for all-cause stroke and stroke subtypes during the whole follow-up and for three intervals of follow-up time are presented in table 2. The incidence of all-cause stroke was increased in COPD subjects. The effect estimate was largest during the first two years of follow-up and was then attenuated over ten years. The incidences of IS and ICH were also increased in COPD and these associations were similarly attenuated with time; however, after five years of follow-up there was still evidence of a higher incidence of IS in COPD, whereas ICH was no longer significantly associated with COPD. There was evidence of a higher risk of SAH in COPD, and this association did not differ significantly with time.

The association between COPD and all-cause stroke incidence was modified by age, sex, ischemic heart disease, SEP, and total duration of hospital stay, respectively (figure 1). In the separate outcome analyses, effect modification was observed by age (p for interaction<0.001) and total duration of hospital stay (p=0.007) for IS, whereas no significant interactions were present in analyses of ICH or SAH.

Sensitivity analyses

In an analysis including both primary and secondary diagnoses of stroke as outcome (n=20,231), the HRs were similar or slightly higher (all-cause stroke: 1.33; 95% CI:

1.29-1.37, IS: 1.27; 1.22-1.32, after full adjustment) compared to the main analysis and variation over time was similar.

Another sensitivity analysis was performed to evaluate whether COPD diagnosed both as primary and secondary diagnosis, was associated with increased stroke risk. This analysis showed similar or somewhat higher estimates for stroke in those with COPD as secondary diagnosis (HR: 1.43; 95% CI: 1.36-1.51 for the whole follow-up after full adjustment) compared to those with COPD as primary diagnosis (HR: 1.13; 1.08-1.18; p for interaction<0.001). All results from this analysis are shown in Supplementary Table 1.

Hospitalised sample

We performed a subgroup analysis of COPD patients and reference individuals where the reference subject had also been hospitalised prior to inclusion, thus using an in-patient control group. In this analysis, the hazard ratios for all-cause stroke (1.21; 95% CI: 1.16-1.27), IS (1.16; 1.10-1.23), ICH (1.31; 1.13-1.51) and SAH (1.40; 1.00-1.97), were similar compared to the main analysis after full adjustment (Supplementary Table 2). There were no significant differences in hazard ratios for all-cause stroke, ICH or SAH, according to whether the reference individuals were inpatients or non-hospitalized subjects from the general population (p for interaction=0.14, 0.95 and 0.37, respectively). For IS, there was suggested effect modification (p for interaction=0.043). All results from this analysis are given in Supplementary Table 2.

DISCUSSION

In this nationwide cohort study, COPD patients had increased incidences of all subtypes of stroke compared with reference individuals from the general population, even when controlling for several potential confounders. The risk increase for all-cause stroke, IS and ICH, respectively, was highest in the first two years after COPD diagnosis and decreased over ten years, whereas the increased risk of SAH seemed to be unchanged with time.

The moderate increase of total stroke risk in COPD found in this study is consistent with previous findings,[18, 17, 10] although some studies have suggested both higher[19] and lower estimates.[16] The incidence of stroke subtypes in COPD has not previously been assessed, to our knowledge. Studies of lung function in the general population have, however, reported inverse relationships of FEV1 with incidence of IS [15, 22, 23] and SAH[9], respectively.

Although the reasons for the associations of COPD and reduced lung function, with stroke remain unclear, some mechanisms have been suggested. Systemic inflammation[13, 15] and high levels of cholesterol[13] could be of importance for IS development, however, it is unclear to what extent inflammation and plasma lipids are associated with haemorrhagic stroke.[7, 6, 24] Reduced lung function has been suggested to be inversely associated with incident atrial fibrillation.[25, 18] A higher prevalence of atrial fibrillation in COPD could also be a possible cause of the increased risk of IS in COPD. However, our analysis show that COPD and IS are associated even after adjusting for atrial fibrillation. Nevertheless, detection of atrial fibrillation and preventive treatment with anticoagulants in COPD patients could hypothetically reduce the risk of IS.

Many population-based studies have assessed spirometric findings in relation to cardiovascular disease. In most studies, FEV1 or FVC, but not the FEV1/FVC ratio, have been the major determinants of the risk of cardiovascular events.[26, 15] A recent study showed, however, an inverse relationship between FEV1/FVC ratio and incidence of SAH, after adjusting for smoking.[9] Since COPD is defined by a reduced FEV1/FVC ratio, the present results of a persistent effect of COPD on SAH

risk, points in the same direction. Increased degradation of extracellular matrix components due to proteinase-antiproteinase imbalance have been suggested as an important mechanism in both COPD and SAH.[9] A genetic component favouring these processes could hypothetically underlie the increased risk of SAH in COPD.

There was an increased risk for ICH in the first five years of follow-up. Blood pressure is the major risk factor for ICH and it is not previously known how ICH relates to lung function or COPD. Even though the relationship between hypertension and COPD is inconsistent in the literature, with some studies reporting positive associations [11, 12] and other studies no or negative associations [27, 16, 28], it is still possible that hypertension could constitute one link between COPD and ICH. Assessment of blood pressure and treatment of hypertension in COPD patients could be of importance to reduce ICH risk.

The association between COPD and stroke was stronger in younger age groups, which has also been observed in one previous study.[19] However, in the present study, the association of COPD with stroke was significant also in subjects aged >70 years. Since genetic factors might be most important for diseases with early onset, the high effect in the low age-group might reflect the influence of shared genetic factors. Another reason for the interaction with age could be the very low absolute stroke rate among the young.

There are several possible reasons for the stronger association between COPD and stroke in the first years of follow-up. The mortality in COPD patients in the first few years after inclusion was high, and after approximately 5 years, only half of COPD subjects remained in the analysis. It is possible that COPD patients who were susceptible to stroke already had suffered from a stroke event or died after the first years of follow-up. COPD patients still in the analysis at 10 years of follow-up could have a mild COPD, which might contribute to the lower HRs after five years. Preventive measures, such as smoking cessation and anti-hypertensive treatment could potentially have reduced the long-term risks of stroke in COPD patients, but we do not know if these factors were more common in COPD compared to reference subjects.

One study reported that exacerbations of COPD could be associated with increased risk of stroke for the following 49 days.[29] This was found in a large registry of COPD-patients when exacerbation was defined as prescription of antibiotics, but there was no risk increase for stroke using other definitions of exacerbation.[29] Another study reported a non-significant increased risk for stroke in the 30 days after exacerbations compared to the 30 days preceding it.[30] It is uncertain if exacerbations could contribute to a higher stroke risk in the first years, and it needs to be further investigated how exacerbations influence the risk of stroke.

Methodological considerations

Overall, the national discharge registry has high quality and provides valid data of all hospital discharges in Sweden.[20] Validation studies of stroke diagnoses have shown that the proportion identified (sensitivity) is high (88-98%) for data from the 1980s to 1990s[31-33] and 2000s [20, 34]. The positive predictive value has improved over the last 25 years, probably due to increasing use of computed tomography, and was well over 90% in studies from 1999 and 2004 [31, 33, 34, 20]. In the present study, stroke was only included as outcome if listed as primary diagnosis, which should reduce the risk of false positive diagnoses.[34]

COPD diagnoses in the inpatient register have a reasonable validity and less than 10% are considered uncertain or inaccurate.[21] Moreover, all stages of COPD are seen in both primary and secondary diagnosis and no difference in diagnostic validity was observed based on the level of diagnosis, in a recent validation study [21]. In the present study, a total of 3.7% of the reference individuals were censored because they were hospitalised for COPD during follow-up. The prevalence of physician diagnosed COPD in Sweden has been estimated to 3-5% in the general population [35, 36]. This indicates that a large proportion of COPD cases occuring in the reference group was probably identified in the inpatient register. The occurrence of undetected COPD cases in the reference group would, if anything, lead to an underestimation of the association between COPD and stroke.

We included a large number of consecutive COPD patients and the follow-up time was long. The COPD-free comparison group was randomly selected from the general

population. In studies using hospitalised patients in the exposed but not in the non-exposed group, there is hypothetically a risk of a higher detection rate of diagnoses in the hospitalised group. To minimise this effect, follow-up started 30 days after the COPD patient had been discharged from hospital, and those with stroke during admission for COPD were therefore excluded as prevalent stroke cases. Also, symptoms of stroke are most often apparent and the vast majority (>90%)[34] of stroke patients are treated in hospital, regardless of having COPD. Taken together, it is unlikely that ascertainment bias had a substantial impact on the results.

It could also be that hospitalised individuals have worse general health status compared to individuals that have not been hospitalised. In the present study, the reference group was randomly selected from the general population, and some but not all of the references had been hospitalised before inclusion. To address this issue the analysis was adjusted for total duration of hospital stay before inclusion, and in addition, we performed a sensitivity analysis using an in-patient reference group (i.e. only referents that had been hospitalised before inclusion). The associations between COPD and all stroke subtypes were still significant and estimates were similar to the main analysis, when using an in-patient reference group.

One limitation of large-scale registry-based studies is the lack of detailed information about all potential confounders. We do not have information on for example, body mass index, dyspnoea symptoms, cardiovascular treatment, blood pressure levels, and most importantly, smoking. Other studies of the general population in Sweden, which is represented by the reference group in the present study, have shown that around 50% of adults were current or former smokers in the 1990s.[2, 35, 37] In subjects who reported symptoms of COPD, or were diagnosed with COPD according to spirometric findings, the rate of "ever-smoking" was around 75%.[35, 38] The comparison in the present study is not done between a smoking and a non-smoking group; Current smoking rate in COPD patients was 47% in 1992[35] and 34% in 2004[39] in population-based studies from Sweden. The corresponding rates in non-COPD subjects in the same studies were 33% and 13%, respectively.[35, 39] A survey of COPD patients in secondary care (2007) showed that 23% were still smokers[40] compared to national estimates of around 16% (2005) in the whole population (>45 years of age)[37].

Smoking status is strongly related to socioeconomic status, country of birth,[37] and comorbidities, and adjusting for all covariates only slightly reduced the effect estimates in the present analysis. In other studies of lung function and stroke,[15, 14, 23, 22] or COPD and stroke,[16, 19] estimates were only reduced with around 10% by adjustment for smoking. It is also noteworthy that COPD was similarly associated with incidence of ICH, yet it is controversial whether smoking is a risk factor for ICH.[6, 8]. Although we cannot estimate the influence of smoking on the results, we believe it is unlikely that the results could be fully explained by smoking.

Hypertension is an important risk factor for all subtypes of stroke. Hypertension has also been associated with COPD in some studies,[11, 12] whereas in other studies, there have been no association or negative association between hypertension and COPD [27, 16, 28]. Hypertension was not commonly used as a hospital diagnosis and we did not have information on individual blood pressure levels or use of antihypertensive treatments, which would be preferable. However, adjustment for a diagnosis of hypertension did not substantially change the results for the association between COPD and stroke.

In conclusion, incidences of all stroke subtypes are increased in COPD, especially during the first years after COPD diagnosis. The association was independent of several comorbidities, although residual confounding from hypertension and smoking cannot be excluded. A global evaluation of stroke risk factors seems warranted in patients with COPD.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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TABLES

Table 1. Population characteristics and prevalence of comorbidities at baseline.

	COPD	Reference*	P value
Number	103,419	103,419	
COPD classification, %			
Primary diagnosis	61.6		
Secondary diagnosis	38.5		
Age, years, mean±SD	69.9±9.5		
Age distribution, %			
40-54 years	7.8		
55-69 years	34.1		
70-84 years	58.1		
Year of birth, %			
1903-1922	46.2		
1923-1942	46.3		
1943-1963	7.6		
Sex, %			
Men	54.2		
Women	45.8		
Country of birth, %			<0.001
Sweden	88.4	91.2	
Not Sweden	11.6	8.8	
Socioeconomic position, %			<0.001
Non-manual	17.9	25.6	
Manual	28.2	26.6	
Other	9.5	10.4	
Out of workforce/missing	44.4	37.4	
Comorbidities, %			
Atrial fibrillation	6.4	3.1	<0.001
Diabetes	5.4	2.9	<0.001

Hypertension	6.4	3.7	<0.001
Ischemic heart disease	14.0	7.7	<0.001
Heart failure	10.9	2.9	<0.001
Alcohol abuse	4.6	0.9	<0.001
Asthma	13.3	0.9	<0.001
RA/SLE	2.4	1.1	<0.001
Kidney failure	0.6	0.2	<0.001
Total duration of hospital stay, %			<0.001
0 days	32.1	57.3	
1-5	14.9	15.2	
6-20	23.6	18.0	
>20	29.4	13.1	

*Reference subjects were matched to COPD patients 1:1 on year of birth, age, sex and county of residence.

Table 2. Incidence of stroke in COPD compared with controls for the whole follow-up and in three time intervals.

			Follow-up 0-2 years		Follow-up 2-5 years		Follow-up 5-10 years	
	COPD	Reference	COPD	Reference	COPD	Reference	COPD	Reference
N	103,419	103,419	103,419	103,419	76,273	95,020	52,206	81,767
All-cause stroke								
No. of events	7,945	9,457	2,734	1,972	2,618	3,106	2,593	4,379
IR, /1000 py	14.5 (14.2-14.8)	11.8 (11.6-12.1)	15.6 (15.0-16.2)	9.9 (9.5-10.4)	13.7 (13.2-14.3)	11.7 (11.3-12.1)	14.2 (13.6-14.7)	13.0 (12.6-13.4)
HR	1.35 (1.31-1.40)	1	1.60 (1.51-1.69)	1	1.26 (1.19-1.33)	1	1.26 (1.20-1.33)	1
HR[a]	1.24 (1.19-1.28)	1	1.46 (1.37-1.55)	1	1.15 (1.09-1.22)	1	1.16 (1.10-1.22)	1
Ischemic stroke								
No. of events	5,580	6,855	1,801	1,374	1,801	2,158	1,978	3,323
IR, /1000 py	10.2 (9.9-10.4)	8.6 (8.4-8.8)	10.3 (9.8-10.8)	6.9 (6.6-7.3)	9.5 (9.0-9.9)	8.1 (7.8-8.5)	10.8 (10.3-11.3)	9.9 (9.5-10.2)
HR	1.32 (1.27-1.37)	1	1.51 (1.41-1.62)	1	1.24 (1.16-1.32)	1	1.27 (1.19-1.35)	1
HR[a]	1.20 (1.15-1.25)	1	1.37 (1.27-1.47)	1	1.12 (1.05-1.19)	1	1.15 (1.08-1.23)	1
Intracerebral haemorrhage								
No. of events	799	948	269	186	278	318	252	444
IR, per 1000 py	1.46 (1.36-1.56)	1.18 (1.11-1.27)	1.5 (1.4-1.7)	0.9 (0.8-1.2)	1.5 (1.3-1.6)	1.2 (1.1-1.3)	1.4 (1.2-1.6)	1.3 (1.2-1.5)
HR	1.35 (1.22-1.49)	1	1.64 (1.36-1.98)	1	1.34 (1.13-1.58)	1	1.17 (0.99-1.38)	1

HR[a]	1.29 (1.16-1.43)	1	1.56 (1.29-1.89)	1	1.29 (1.08-1.53)	1	1.12 (0.95-1.33)	1
Subarachnoid haemorrhage[b]								
No. of events	175	168	60	42	52	58	63	68
IR, per 1000 py	0.32 (0.27-0.37)	0.21 (0.18-0.24)	0.34 (0.27-0.44)	0.21 (0.16-0.29)	0.27 (0.21-0.36)	0.22 (0.17-0.28)	0.34 (0.27-0.44)	0.20 (0.16-0.26)
HR	1.48 (1.19-1.85)	1	1.58 (1.06-2.34)	1	1.23 (0.84-1.81)	1	1.66 (1.15-2.39)	1
HR[a]	1.46 (1.16-1.85)	1	1.57 (1.05-2.36)	1	1.20 (0.81-1.79)	1	1.65 (1.13-2.40)	1
Stroke, not otherwise specified								
No. of events	1,396	1,486	604	370	487	572	302	574
IR, per 1000 py	2.53 (2.40-2.67)	1.86 (1.77-1.95)	3.4 (3.2-2.7)	1.9 (1.7-2.1)	2.6 (2.3-2.8)	2.2 (2.0-2.3)	1.6 (1.5-1.8)	1.6 (1.5-1.8)
HR	1.49 (1.37-1.60)	1	1.89 (1.66-2.16)	1	1.32 (1.16-1.49)	1	1.26 (1.08-1.47)	1
HR[a]	1.35 (1.24-1.47)	1	1.72 (1.50-1.97)	1	1.20 (10.5-1.36)	1	1.15 (0.98-1.35)	1

IR; incidence rate (95% confidence interval), py; person years, HR; hazard ratio

All models stratified by year of birth, year of inclusion, sex and county of residence.

[a] Adjusted for country of birth, socioeconomic position, history of asthma, diabetes, hypertension, ischemic heart disease, heart failure, atrial fibrillation, alcohol abuse, rheumatoid arthritis/systemic lupus erythematosus, kidney failure and total duration of hospital stay.

[b] Effect of COPD-status not time-dependent.

FIGURES

Fig 1 Association between COPD and stroke by subgroups in the first follow-up time interval (0-2 years).

Supplementary Data

1. Supplementary Table 1
2. Supplementary Table 2

Title: Incidence of stroke and stroke subtypes in chronic obstructive pulmonary disease.

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Supplementary Table 1. The association between COPD and stroke according to level of COPD diagnosis (primary or secondary).

		P interaction	Follow-up 0-2 years	Follow-up 2-5 years	Follow-up 5-10 years
All stroke					
COPD primary diagnosis					
Unadjusted	1.21 (1.17-1.26)		1.41 (1.36-1.52)	1.10 (1.03-1.18)	1.19 (1.11-1.27)
Adjusted*	1.13 (1.08-1.18)	<0.001	1.31 (1.21-1.41)	1.03 (0.96-1.08)	1.10 (1.03-1.18)
COPD secondary diagnosis					
Unadjusted	1.60 (1.53-1.69)		1.91 (1.75-2.08)	1.56 (1.43-1.69)	1.41 (1.29-1.43)
Adjusted*	1.43 (1.36-1.51)		1.68 (1.53-1.84)	1.40 (1.28-1.53)	1.27 (1.16-1.38)
Ischemic stroke					
COPD primary diagnosis					
Unadjusted	1.19 (1.14-1.25)		1.35 (1.23-1.48)	1.09 (1.01-1.19)	1.19 (1.10-1.28)
Adjusted*	1.10 (1.05-1.16)	<0.001	1.24 (1.13-1.37)	1.01 (0.92-1.10)	1.10 (1.02-1.20)
COPD secondary diagnosis					
Unadjusted	1.55 (1.46-1.64)		1.76 (1.58-1.96)	1.49 (1.35-1.65)	1.42 (1.29-1.57)
Adjusted*	1.36 (1.28-1.55)		1.52 (1.36-1.70)	1.32 (1.18-1.46)	1.27 (1.15-1.40)
Intracerebral haemorrhage					
COPD primary diagnosis					
Unadjusted	1.22 (1.08-1.39)		1.47 (1.15-1.88)	1.18 (0.95-1.46)	1.09 (0.89-1.35)
Adjusted*	1.17 (1.02-1.33)	0.0060	1.41 (1.09-1.81)	1.15 (0.92-1.45)	1.02 (0.82-1.27)
COPD secondary diagnosis					
Unadjusted	1.58 (1.35-1.84)		1.93 (1.43-2.60)	1.63 (1.25-2.11)	1.32 (1.01-1.71)
Adjusted*	1.50 (1.29-1.77)		1.85 (1.36-2.52)	1.59 (1.22-2.08)	1.22 (0.93-1.61)
Subarachnoid haemorrhage**					
COPD primary diagnosis					
Unadjusted	1.39 (1.04-1.85)				
Adjusted*	1.34 (0.99-1.81)	0.22			
COPD secondary diagnosis					
Unadjusted	1.62 (1.15-2.85)				
Adjusted*	1.67 (1.17-2.38)				

All models stratified by year of birth, year of inclusion, sex and county of residence.
*Adjusted for country of birth, socioeconomic position, history of asthma, diabetes, hypertension, ischemic heart disease, heart failure, atrial fibrillation, alcohol abuse, rheumatoid arthritis/systemic lupus erythematosus, kidney failure and total duration of hospital stay.
**Effect of COPD not time-dependent.

Supplementary Table 2. The association between COPD and stroke with hospitalised and non-hospitalised reference subjects.

		P interaction	Follow-up 0-2 years	Follow-up 2-5 years	Follow-up 5-10 years
All stroke					
Hospitalised reference subjects					
Unadjusted	1.18 (1.13-1.24)		1.36 (1.26-1.47)	1.10 (1.02-1.18)	1.11 (1.03-1.20)
Adjusted*	1.21 (1.16-1.27)	0.14	1.39 (1.28-1.50)	1.12 (1.04-1.21)	1.14 (1.05-1.24)
Non-hospitalised reference subjects					
Unadjusted	1.55 (1.48-1.62)		1.97 (1.80-2.16)	1.46 (1.35-1.58)	1.40 (1.31-1.52)
Adjusted*	1.28 (1.22-1.35)		1.58 (1.43-1.76)	1.22 (1.12-1.34)	1.18 (1.08-1.29)
Ischemic stroke					
Hospitalised reference subjects					
Unadjusted	1.15 (1.09-1.21)		1.26 (1.15-1.38)	1.09 (1.001-.19)	1.10 (1.01-1.20)
Adjusted*	1.16 (1.10-1.23)	0.043	1.27 (1.15-1.40)	1.09 (0.99-1.19)	1.14 (1.04-1.25)
Non-hospitalised reference subjects					
Unadjusted	1.54 (1.46-1.63)		1.99 (1.78-2.23)	1.44 (1.30-1.58)	1.43 (1.32-1.56)
Adjusted*	1.26 (1.19-1.35)		1.58 (1.39-1.80)	1.18 (1.05-1.32)	1.20 (1.08-1.32)
Intracerebral hemorrhage					
Hospitalised reference subjects					
Unadjusted	1.25 (1.09-1.44)		1.80 (1.39-2.34)	1.04 (0.83-1.31)	1.10 (0.87-1.40)
Adjusted*	1.31 (1.13-1.51)	0.95	1.89 (1.44-2.48)	1.12 (0.87-1.42)	1.08 (0.84-1.39)
Non-hospitalised reference subjects					
Unadjusted	1.46 (1.27-1.68)		1.47 (1.12-1.94)	1.78 (1.39-2.27	1.23 (0.98-1.55)
Adjusted*	1.27 (1.08-1.49)		1.22 (0.89-1.67)	1.63 (1.23-2.16)	1.10 (0.84-1.42)
Subarachnoid haemorrhage**					
Hospitalised reference subjects					
Unadjusted	1.34 (0.97-1.85)				
Adjusted*	1.40 (1.00-1.97)	0.37			

Non-hospitalised reference subjects		
Unadjusted	1.63 (1.20-2.20)	
Adjusted*	1.51 (1.06-2.14)	

All models stratified by year of birth, year of inclusion, sex and county of residence.
*Adjusted for country of birth, socioeconomic position, history of asthma, diabetes, hypertension, ischemic heart disease, heart failure, atrial fibrillation, alcohol abuse, rheumatoid arthritis/systemic lupus erythematosus, kidney failure and total duration of hospital stay.
**Effect of COPD not time-dependent.