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Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study

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Background Reduced lung function has been shown to be a significant predictor of non-fatal ischaemic heart disease, and of mortality due to cardiovascular disease. Fewer studies have analysed the relationship between lung function and risk of fatal or non-fatal stroke. The present study presents results on the relation between forced expiratory volume in one second (FEV_1) and risk of incident and fatal first-ever stroke.

Subjects and Methods The analyses are based on prospective cohort data from 12 878 eligible men and women aged 45–84 years, who participated in the first health examination of the Copenhagen City Heart Study in 1976–1978. The subjects were followed from day of entry until 31 December 1993. During that period 808 first-ever strokes occurred of which 153 were fatal within 28 days. Risk of incident and fatal stroke was estimated by means of Cox hazard regression. The analyses included adjustment for potential confounders: sex, age, smoking, inhalation, body mass index, systolic blood pressure, triglycerides, physical activity in leisure time, education, diabetes mellitus, and antihypertensive treatment.

Results We found an inverse association between FEV_1 and risk of first-time stroke. For each 10% decrease in FEV_1 in percentage of expected, the relative risk (RR) increased 1.05 (95% CI : 1.00–1.09, $P = 0.03$). This represents an approximately 30% higher risk of stroke in the group of people with the lowest lung function as compared to the group with the highest lung function. The association between lung function and risk of fatal stroke resembled that of risk of incident stroke (fatal and non-fatal). The RR was 1.11 (95% CI : 1.03–1.19) for each 10% decrease in FEV_1 in percentage of expected. This represents approximately a doubling of the risk between the highest and lowest lung function groups.

Conclusions This study shows that reduced lung function measured in percentage of predicted FEV_1 is a predictor of first-time stroke and fatal stroke independent of smoking and inhalation. The high risk of fatal first-ever stroke in the group of people with low lung function may be of significance in both the design and interpretation of clinical trials.

Keywords Lung function, FEV_1, cerebrovascular disorders, epidemiology

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Several investigations have shown that reduced lung function is a significant predictor of non-fatal ischaemic heart disease, and of mortality due to cardiovascular disease.[1–9] These studies have all found an inverse association between lung function and cardiovascular disease. Fewer studies have analysed specifically the relationship between lung function and risk of fatal or non-fatal stroke.[6–8,10–13] The link between pulmonary function and risk of stroke is suggested to be mediated via increased susceptibility to infections and increased blood viscosity in people with low lung function. A recent cross-sectional study found that lower pulmonary function was associated with subclinical cerebral infarctions and white matter lesions; structural abnormalities may be precursors of clinical stroke.[14]

A risk factor for stroke occurrence may not exhibit the same strength and relation for risk of fatal stroke. A distinction

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between fatal and non-fatal stroke is therefore warranted, as the effect of reduced pulmonary function may not be the same for these two end-points. Impaired lung function could be an important prognostic factor after a stroke, since survival is both determined by the severity of the stroke and by co-morbidity.[15] In the present paper, we have therefore investigated the effect of reduced forced expiratory volume in one second (FEV_1) on risk of first-ever stroke, and fatal first-ever stroke, in men and women participating in a large cohort study in Copenhagen, Denmark.

Subjects and Methods

Study population

The Copenhagen City Heart Study was initiated in 1976 and included 19 698 people living in Østerbro and Nørrebro in Copenhagen, Denmark. A detailed description of the examinations has been published previously.[16] Briefly, people were chosen randomly within age and sex strata, and invited by letter to three health examinations held in 1976–1978, 1981–1983 and 1991–1994. In all, 371 people died before the initial examination, and of the remaining 19 327 people, there were 5104 (26.4%) non-responders and 14 223 (73.6%) responders. In all 55 people were lost to follow-up; 53 due to emigration, but there was no information regarding the remaining 2 people.

Lung function

The participants had FEV_1 measured at the initial health examination. The electronic spirometer Monaghan N 403 was used. The spirometer measures had an accuracy within 5% of the volume as measured by a water-sealed Collins spirometer, and it was calibrated daily with a one-litre syringe and weekly against a water-sealed Godard spirometer. The technicians performing the measurements had been trained by staff of the pulmonary function laboratory at the State Hospital (Rigshospitalet). The measurements were performed with the subject in a sitting position without the use of a noseclip. Participants were asked to inhale to total lung capacity before beginning the forced expiration. Maximum effort was to be exerted throughout the expiration. Three values were obtained. As a criterion of a correct performance at least two measurements of FEV_1 differing by less than 5% had to be produced. The value from the highest measurement was coded and used in the analyses.

The expected FEV_1 (E FEV_1) were estimated using the following formula including gender, age, and height:[17]

$$\text{E } FEV_1 \text{ women (ml)} = 443 - 30 \times \text{age (yr)} + 23 \times \text{height (cm)}$$

$$\text{E } FEV_1 \text{ men (ml)} = -506 - 38 \times \text{age (yr)} + 35 \times \text{height (cm)}$$

These regressions were based on a subgroup of healthy never-smokers participating in the first health examination. Subsequently the participants were categorized into seven groups according to their FEV_1 in percentage of the expected volume: <50, 50–59, 60–69, 70–79, 80–89, 90–99 and ⩾100%.

Covariates

The following variables were included as potential confounders: gender; smoking (never smokers, ex-smokers, current smokers of 1–10, 11–24, and ⩾25 cigarettes per day); inhalation (yes and no); physical activity in leisure time (nearly completely physically passive or light physical activity <2 h per week, light physical activity 2–4 h per week, light physical activity for >4 h a week or more exhausting physical activity for 2–4 h a week, and exhausting physical activity >4 h a week or regular hard training); educational level (<8, 8–11, or >11 years); presence of diabetes mellitus (yes and no); cholesterol (<8 mmol/l and ⩾8 mmol/l); triglycerides (mmol/l); body mass index (<20, 20–25, 25–30, and ⩾30 kg/m^2), systolic blood pressure (mmHg); antihypertensive treatment (yes and no).

Outcome

The Danish National Hospital Discharge Register and the National Health Service Register of Causes of Death were used to provide information about all participants with regard to hospitalization and death. The International Classification of Diseases, Eighth Revision (ICD-8), codes 430–438 were used to identify people who had had a stroke. The cases were validated by using WHO's definition of stroke; an acute disturbance of focal or global cerebral function with symptoms lasting longer than 24 hours or leading to death with presumably no other reasons than of vascular origin.[18,19] To ensure detection of non-fatal non-hospitalized stroke events the participants were asked at the following study health examinations, i.e. in 1981–1983 and 1991–1994, if they had suffered a stroke.

To distinguish between ischaemic infarct, intracerebral haemorrhages and subarachnoid haemorrhages, either CT- or MR-scan, autopsy, spinal fluid examination, or operation description was necessary. If the scan did not visualize an infarct, but the person had symptoms that met the criteria for the definition of stroke, a diagnosis of ischaemic infarct was made.[20] The diagnosis of stroke was not applied in cases where a scan revealed signs of prior cerebrovascular disease but without history of any symptoms. Unspecified stroke relates to a patient for whom no information on stroke subtype was available.

Fatal first-ever stroke was defined as death after a first-ever stroke within the initial 28 days after stroke onset.

Statistics

Cox hazards regression model was used with age as the underlying time axis. Age limits were set to be 45–85 years by lexis[21] (i.e. a person was in- or excluded in the analyses when the age 45–85 years was reached). The following exclusion criteria were used: participants who did not reach the lower age limit for the analyses (n = 536), people older than 85 years at the beginning of the analyses (n = 34), participants who had a stroke before the initial examination (n = 178), participants with missing values on FEV_1 (n = 315). Of the remaining participants, 254 had had a history of myocardial infarct before the start of the study.

The regression ceofficients were estimated using the maximum likelihood method. The results are given in terms of estimated relative risks (RR). Assumption of proportional hazards was evaluated graphically. Tests for interactions were based on the log likelihood ratio test. Wald's test was used to examine whether the linear regression coefficients betweeen lung function and risk of fatal and non-fatal stroke differed significantly. The statistical software package STATA was used for the calculations.[22]

Results

During the 17-year follow-up 808 strokes occurred among 7097 eligible women and 5781 eligible men, i.e. 6% developed a stroke. There were 412 unspecified strokes (51%), 309 (38%) ischaemic infarcts, 49 (6%) intracerebral haemorrhages, and 38 (5%) subarachnoid haemorrhages. There were 471 (58%) strokes in men, and 337 (42%) strokes in women. Among participants without measurement of FEV_1 21 (7%) developed stroke during the follow-up.

There were differences between participants with high versus low lung function. People with a high lung function were often never-smokers, had ⩾8 years of education, and were more physically active in leisure time (Table 1). Systolic blood pressure also tended to exhibit an inverse relation with lung function as did antihypertensive treatment, tobacco smoke inhalation and diabetes mellitus. Thus, both biological and socioeconomic markers showed an unfavourable association with low lung function.

There was an inverse relation between FEV_1 and risk of first-time stroke in analyses adjusting only for age and sex (Table 2). The risk rose steadily with decreasing FEV_1, especially in women, whereas in men there was a decrease in the risk among those with the lowest lung function. These differences between men and women were not statistically significant (χ^2: 3.73, d.f. = 6; $P = 0.71$). In subsequent analyses the confounding variables were added; first smoking and tobacco smoke inhalation (simple adjustment), then co-morbidities (partial adjustment), and finally lifestyle factors (complete adjustment). The inverse association remained, but few of the categorical values differed significantly from the reference group. The substantial effect of the chosen confounding factors reflects that all of them are well-described risk factors for stroke, and show an unfavourable association with low lung function. The relation between the lung function groups could be expressed log linear, as the log likelihood ratio test for linearity was insignificant (χ^2: 6.72, d.f. = 5; P= 0.24), with an RR of 1.05 (95% CI : 1.00–1.09, $P = 0.03$) for each 10% decrease in FEV_1 in percentage of expected. This reflects an approximately 30% higher risk of stroke between the group of people with the best lung function as compared to the groups with the lowest lung function. In the analysis of men only the RR between the groups was 1.03 (95% CI : 0.98–1.09), while in women it was 1.06 (95% CI : 0.99–1.12). There was no statistically significant interaction between lung function expressed as a linear variable and gender (χ^2: 0.69, d.f. = 1; $P = 0.41$). Exclusion of subarachnoid haemorrhage and intracerebral haemorrhage had no effect, as the RR remained 1.05 (95% CI : 1.01–1.09). In a subsample including only never-smokers the RR was 1.04 (95% CI : 0.92–1.15) for each 10% decrease in FEV_1 in percentage of expected; test for linearity (χ^2: 7.85, d.f. = 5; $P = 0.16$).

Of the 808 strokes that occurred in the participants during the follow-up period 153 (19%) were fatal within 28 days. The association between lung function and risk of fatal stroke resembled that for risk of incident stroke, as the risk increased with decreasing lung function (Figures 1 and 2). The differences between the lung function groups could be expressed as linear (χ^2: 6.04, d.f. = 5; $P = 0.30$), with an RR of 1.11 (95% CI : 1.03–1.19) for each 10% decrease in FEV_1 in percentage of expected. This reflects approximately a doubling of the risk between the highest and lowest lung function groups. After exclusion of intracerebral haemorrhage and subarachnoid haemorrhage the RR between the lung function groups was 1.15 (95% CI : 1.06–1.24); test for linearity (χ^2: 7.02, d.f. = 5; $P = 0.22$).

The difference between the two linear estimates of the RR for fatal and non-fatal stroke, respectively, was not statistically significant (χ^2: 2.98, d.f. = 2; $P = 0.23\%$).

Discussion

The present investigation showed that reduced FEV_1 was significantly associated with increased risk of first-time stroke in analyses with adjustment for several confounding factors including smoking and inhalation. The risk of fatal first-ever stroke was also inversely associated with reduced FEV_1, the RR being even higher. The effect of lung function on risk of stroke was unchanged in analyses excluding haemorrhagic strokes.

The FEV_1 decreases with age and in previous publications from the Copenhagen City Heart Study, the average annual FEV_1 decline among never-smokers between the two first study health examinations was approximately 25–30 ml per year.[17] The decrease was similar to that found in other community studies.[23] As the decline occurs at an almost constant pace in people aged over 30, and as our definition of expected lung function takes gender, age and height into consideration, the results are unbiased with respect to these parameters. On the other hand our study shares the same disadvantages as other prospective studies in that we assume that the subjects remain in the same lung function group throughout the observation period.

The risk associated with reduced FEV_1 was higher for fatal than for incident strokes. The risk between the highest and the lowest lung function group was approximately 100% higher for fatal first-time stroke versus 30% for incident stroke. These results suggest that the equivocal results between the previous investigations may be related to different use of endpoints, where stroke incidence tend to show a weak association.[6,10,12,13] Possible explanations of these findings could be that either stroke patients with impaired lung function have more severe stroke, or they are more likely to suffer from fatal complications to stroke. Thus, the stronger association of FEV_1 with fatal stroke could perhaps be due to a higher complication rate among those with impaired lung function, rather than a higher incidence of cerebrovascular accidents. If stroke patients with low lung function are more susceptible to complications, it may be of importance in clinical trials. Unfortunately, information about stroke severity and complications was unavailable and we are unable to examine this hypothesis.

All our analyses showed that a log-linear expression between the FEV_1 groups could be used, indicating a dose-response relationship. However, the biological mechanism relating impaired lung function to risk of stroke remains unclear. One possible explanation is that the relationship could merely reflect residual confounding from tobacco smoking.[24] In the subsample analysis of never-smokers the RR remained unchanged, which at least partly contradicts this explanation, although the result was not statistically significant, presumably due to the smaller sample size.

Both biological and socioeconomic markers showed an unfavourable association with impaired lung function. Most of

Table 1 Baseline characteristics

Variables	FEV_1[a] as percentage of expected						
	⩾100% n = 2483 (19%)	90–99% n = 2628 (20%)	80–89% n = 2998 (23%)	70–79% n = 2278 (18%)	60–69% n = 1324 (10%)	50–59% n = 622 (5%)	<50% n = 545 (4%)
No. of strokes	136 (17%)	128 (16%)	175 (22%)	163 (20%)	96 (12%)	62 (8%)	48 (6%)
Mean age at entry (years)	56	54	54	55	56	57	59
Sex							
% women	60%	56%	55%	54%	51%	51%	43%
Smoking							
Never-smoker	29%	23%	19%	15%	11%	13%	9%
Ex-smoker	22%	18%	16%	14%	12%	12%	19%
1–10 cig/day	26%	26%	28%	29%	28%	31%	32%
11–25 cig/day	17%	25%	28%	31%	37%	32%	31%
>25 cig/day	6%	8%	9%	11%	12%	12%	9%
Inhalation							
Yes	63%	72%	74%	78%	76%	78%	79%
Education (years)							
<8	41%	44%	47%	52%	59%	64%	68%
8–11	45%	44%	43%	39%	34%	31%	28%
>11	14%	12%	10%	9%	7%	5%	4%
Physical activity in leisure time							
<4 h/wk	71%	76%	73%	75%	80%	79%	86%
Cholesterol							
<8 mmol/l	93%	93%	93%	92%	92%	94%	96%
Diabetes mellitus							
Yes	1%	1%	1%	2%	3%	3%	5%
Antihypertensive treatment							
Yes	11%	10%	13%	12%	14%	18%	18%
Body mass index, kg/m^2	25	25	25	25	26	25	26
Systolic blood pressure, mmHg (SD)	137 (21)	136 (21)	137 (22)	138 (22)	140 (22)	141 (24)	142 (22)
Triglycerides, mmol/l (SD)	1.6 (1)	1.7 (1.3)	1.8 (1.3)	1.8 (1.2)	2.0 (1.4)	1.8 (1.1)	1.8 (1.2)

[a] Forced expiratory volume in one second.

Table 2 Forced expiratory volume in one second (FEV_1) and relative risk (RR) of stroke incidence in men and women

	Men and women[a]		Men[a]		Women[a]	
FEV_1	RR	95% CI	RR	95% CI	RR	95% CI
<50%	1.73	(1.24–2.40)	1.59	(1.04–2.43)	2.07	(1.21–3.52)
50–59%	2.01	(1.24–2.71)	2.00	(1.35–2.97)	2.06	(1.28–3.31)
60–69%	1.40	(1.08–1.82)	1.30	(0.92–1.85)	1.56	(1.05–2.31)
70–79%	1.43	(1.14–1.80)	1.41	(1.04–1.92)	1.47	(1.04–2.07)
80–89%	1.19	(0.95–1.49)	1.29	(0.96–1.75)	1.05	(0.74–1.47)
90–99%	0.96	(0.75–1.22)	0.93	(0.67–1.30)	1.00	(0.70–1.42)
⩾100%	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Simple adjustment[b]		**Partial adjustment[c]**		**Complete adjustment[d]**	
<50%	1.54	(1.10–2.16)	1.30	(0.92–1.83)	1.12	(0.79–1.60)
50–59%	1.80	(1.32–2.43)	1.51	(1.11–2.06)	1.38	(1.01–1.88)
60–69%	1.24	(0.95–1.61)	1.09	(0.83–1.42)	1.00	(0.76–1.31)
70–79%	1.29	(1.02–1.62)	1.18	(0.93–1.48)	1.18	(0.89–1.42)
80–89%	1.10	(0.88–1.38)	0.99	(0.78–1.24)	0.95	(0.75–1.19)
90–99%	0.93	(0.73–1.18)	0.88	(0.69–1.12)	0.86	(0.68–1.10)
⩾100%	1.00	(reference)	1.00	(reference)	1.00	(reference)

Cox regression model adjusted for age.

[a] Adjusted for: age.

[b] Adjusted for: age, sex, smoking and inhalation.

[c] Adjusted for: age, sex, smoking, inhalation, diabetes mellitus, systolic blood pressure, cholesterol, triglycerides.

[d] Adjusted for: age, sex, smoking, inhalation, diabetes mellitus, systolic blood pressure, cholesterol, triglycerides, physical activity in leisure time, education, antihypertensive treatment, and body mass index.

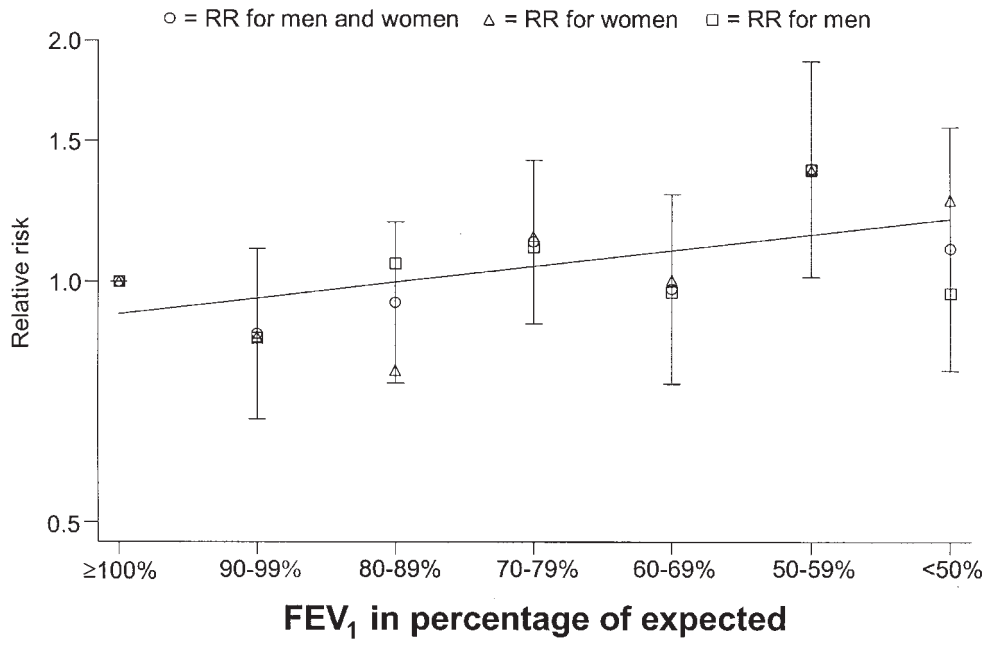

Figure 1 Forced expiratory volume in one second (FEV_1) in percentage of expected and risk of stroke.

Cox regression model adjusted for smoking, inhalation, education, body mass index, physical activity in leisure time, diabetes mellitus, systolic blood pressure, anti-hypertensive treatment, cholesterol, and triglycerides.

RR (Relative Risk). The line is the regression line for men and women combined. The bars indicate the 95% confidence intervals in analyses of men and women combined.

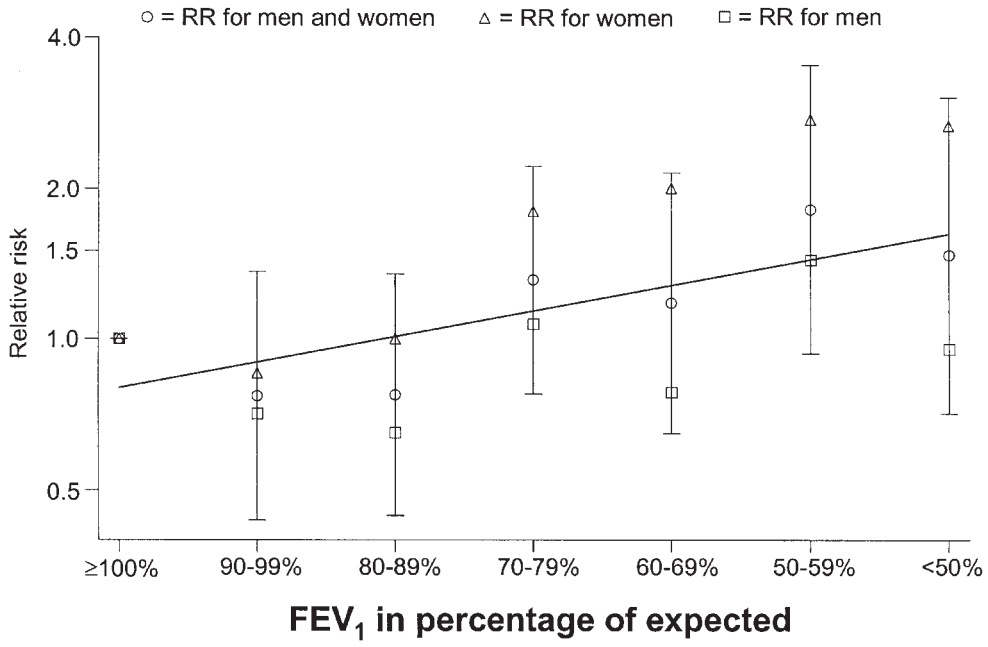

Figure 2 Forced expiratory volume in one second (FEV_1) in percentage of expected and risk of fatal stroke.

Cox regression model adjusted for smoking, inhalation, education, body mass index, physical activity in leisure time, diabetes mellitus, systolic blood pressure, anti-hypertensive treatment, cholesterol, and triglycerides.

RR (Relative Risk). The line is the regression line for men and women combined. The bars indicate the 95% confidence intervals in analyses of men and women combined.

these factors are well-known risk factors for stroke, and the powerful confounding effect of both smoking, tobacco smoke inhalation, co-morbidity, and lifestyle factors was evident in analyses where these variables were consecutively included. Despite this, the relation between lung function and stroke remained statistically significant, indicating that lung function is an independent risk factor for stroke. However, the analyses indicate that the association between lung function and stroke is likely to be confounded by a broad variety of factors.

Other reasons for the observed increased stroke risk in people with reduced lung function may be an increased susceptibility to infections. Recent publications have discussed the possible link between chronic bronchitis,[25] and infection with microbial agents such as *Chlamydia pneumonia*, with the risk of cardiovascular disease and atherogenesis.[26,27] Infection has also been associated with increased risk of cerebrovascular ischaemia.[28,29] Severely impaired lung function is associated with an increase in haematocrit and haemoglobin concentration, which in turn is associated with lower cerebral blood flow[30] and an increased risk of ischaemic stroke.[31,32] Thus the haematocrit could be regarded as a possible intermediary variable. However, there are studies that have not been able to show a statistically significant effect of haemoglobin and hematocrit on risk of stroke.[13,33] Data regarding the participants' levels of haematocrit and haemoglobin were not collected at the study examination. However, it seems unlikely that the possible effects of blood viscosity can explain the entire effect of lung function on risk of stroke as the lung function must be severely impaired before viscosity increases. In this study a modest reduction of FEV_1 was associated with higher risk of stroke, accepting the linear relationship.

These possible biological mechanisms predict that the effect of reduced lung function is likely to be predominantly on risk of ischaemic stroke. However, analyses where patients with intracerebral haemorrhage and subarachnoid haemorrhage were excluded showed no difference of the log-linear risk estimates. It is possible that the low proportion of haemorrhagic stroke events may have provided insufficient statistical power to detect a difference in the effect on stroke subtypes. In addition, our follow-up covers the period where neuroimaging was introduced in Denmark. In the first years of the study few patients had a scan performed, which is reflected by the relatively large proportion of unspecified strokes. Some misclassification is likely to have occurred, which may further have weakened the possibility of demonstrating a differential association between FEV_1 and risk of either ischaemic or heamorrhagic stroke.

This study indicates that reduced FEV_1, expressed as percentage of expected, is a predictor of first-time stroke and fatal stroke independent of smoking and inhalation. The differences between the highest and lowest lung function groups are approximately 30% for incident stroke, and increase to approximately 100% for fatal stroke. Possible explanations for these findings are either more severe strokes in people with low lung function, or an increased susceptibility to complications. Considering the uncertainty about the biological explanation for the results it appears to be premature to use FEV_1 as a screening tool. However, FEV_1 should be considered as a potential confounder or effect modifier in clinical and preventive trials where stroke is the outcome. Further research is needed to clarify the possible biological mechanism connecting reduced lung function with incidence and survival after stroke.

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