Supplement

Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry

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Contents

Lung function

Information on lung function was obtained from the physical health examination, obtained from a trained healthcare professional according to internal standard operating procedures in spirometry performance in the Copenhagen General Population Study. In the first 14 625 participants, spirometry was performed using a Vitalograph (Maids Moreton, Buckinghamshire, United Kingdom), and in the remaining participants, it was performed using an EasyOne Spirometer (ndd Medical Technologies, Zurich, Switzerland). It was necessary to replace the Vitalograph, as it stopped functioning in 2005. The Vitalograph was calibrated daily with a 1-L syringe and the EasyOne Spirometer was verified regularly with a 3-L syringe, as recommended by the manufacturers. Spirometry was performed in a standing position without the use of a nose-clip under strict instructions from a healthcare professional. Only pre-bronchodilator measurements of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were performed. FEV_1 and FVC were typically measured with at least three sets of values. A valid spirometry performance was based on at least two measurements differing by less than 5% and a correct visual inspection of the spirometry curves. Only the highest measurements of FEV_1 and FVC were used. Predicted values of FEV_1, FVC, and FEV_1/FVC were calculated separately for the two spirometers using internally derived reference values based on a subsample of healthy asymptomatic (i.e. without dyspnoea, chronic mucus hypersecretion, cough, or wheezing) never-smoking individuals without any chronic disease with age and height as covariates separately for men and women. Presence of chronic disease was determined according to the questionnaire and the national Danish Patient Registry and included among others respiratory disease, cardiovascular disease, diabetes, and cancer. In total, predicted values were based on 11 288 individuals aged 20-100 years from the Copenhagen General Population Study and the Copenhagen City Heart Study, another Danish population-based prospective cohort study with similar form of recruitment. The lower limit of normal (LLN) of FEV_1/FVC, defined as the bottom 5th percentile of the predicted value, was calculated as the mean value minus 1.645 standard deviations.

Chronic respiratory symptoms

Information on chronic respiratory symptoms was obtained from the questionnaire and confirmed at the day of attendance by a healthcare professional together with the participant. Chronic respiratory symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Dyspnoea was defined as an affirmative response to at least one of the following questions: “Do you get breathless when hurrying on level ground or walking up a slight hill?”, “Do you get breathless when walking on level ground with people of the same age?”, “Do you stop for a breath when walking on level ground in your own tempo?”, “Do you occasionally wake up at night because of breathlessness or troubled breathing?”, “Do you get breathless when taking a bath or getting dressed?”, “Do you get breathless while seated and/or at rest?”, and “Are you often bothered by breathlessness?”. A value of the modified Medical Research Council dyspnoea scale $\geq$2 was defined as an affirmative response to at least one of the following questions: “Do you get breathless when walking on level ground with people of the same age?”, “Do you stop for a breath when walking on level ground in your own tempo?”, and “Do you get breathless when taking a bath or getting dressed?”. Night-time dyspnoea was defined as an affirmative response to the question: “Do you occasionally wake up at night because of breathlessness or troubled breathing?”. Chronic mucus hypersecretion was defined as an affirmative response to the question: “Do you cough up phlegm from the lungs in the morning and/or during the day as long as three consecutive months each year?”. Wheezing was defined as an affirmative response to the question: “Do you occasionally have whistling or wheezing while breathing?”. Cough was defined as an affirmative response to the question: “Do you occasionally cough during activity?”.

Potential confounders

Information on potential confounders was obtained from the questionnaire, physical health examination, blood samples, and the national health registries we have in Denmark. Precise age and sex was obtained from the national Danish Civil Registration System. Smoking status was defined as never, former, or current smoking. Cumulative tobacco consumption was calculated in pack-years based on information on age at smoking initiation and cessation, duration of tobacco consumption, and amount of consumed tobacco (number of daily consumed cigarettes, cheroots, and cigars and grams of weekly consumed pipe tobacco); i.e., a pack-year was 20 cigarettes or equivalent smoked daily for a year. FEV_1 % predicted was calculated as indicated above. Occupational exposure was defined as an affirmative response to the question: “Have you for longer periods of your working life been exposed to dust or fumes?”. Environmental tobacco smoke was reported as exposure to passive smoking in hours per day. Fever or infection within the past 4

weeks was if individuals reported fever, bronchitis, or urinary tract infections up to 4 weeks before the day of enrolment. Body mass index was calculated as measured weight divided by measured height squared (kg/m^2). Plasma cholesterol was measured using standard hospital assays. Systolic and diastolic blood pressures were measured using automated equipment. Alcohol consumption was reported in units per week and converted to grams (1 unit = 12 g of alcohol). Information on cardiovascular diseases, including ischaemic heart disease (International Classification of Diseases [ICD]-8: 410-414 and ICD-10: I20-I25), stroke (ICD-8: 432-435 and ICD-10: I60, I61, I63-I64, G45), heart failure (ICD-8: 427.09-427.11 and ICD-10: I50), and atrial fibrillation (ICD-8: 427.93-427.94 and ICD-10: I48), was obtained from the national Danish Patient Registry defined as all inpatient and outpatient hospital contacts. Information on diabetes was based on self-report, nonfasting plasma glucose >11 mmol/L, use of antidiabetic medication, and/or all inpatient and outpatient hospital contacts from the national Danish Patient Registry (ICD-8: 249-250 and ICD-10: E10-E14). Information on cancer, excluding non-melanoma skin cancer cases, was obtained from the national Danish Cancer Registry, which records all cancer forms in Denmark. Cancer included both a history of cancer and active cancer.

Table S1. Detailed characteristics of lung function and chronic respiratory symptoms in individuals in the Copenhagen General Population Study without known airway disease.*

	$FEV_1/FVC \geq 0.70$		$FEV_1/FVC < 0.70$	
	No symptoms (n=52 999)	**Symptoms (n=30 890)**	**No symptoms (n=7076)**	**Symptoms (n=6990)**
FEV_1 predicted – %	101 (92-109)	96 (86-105)†	90 (80-100)†	81 (68-92)†
FVC predicted – %	101 (93-110)	96 (87-106)†	107 (96-118)†	98 (84-110)†
FEV_1/FVC	0.79 (0.76-0.83)	0.79 (0.75-0.82)†	0.67 (0.63-0.69)†	0.66 (0.61-0.68)†
FEV_1/FVC <LLN – no. (%)	563 (1)	446 (1)†	5318 (75)†	5479 (78)†
FEV_1 predicted ≥80% – no (%)	50 349 (95)	26 796 (87)†	5271 (74)†	3612 (52)†
FEV_1 predicted 50-79% – no (%)	2626 (5)	4030 (13)†	1730 (24)†	3014 (43)†
FEV_1 predicted 30-49% – no (%)	19 (<1)	60 (<1)†	70 (1)†	345 (5)†
FEV_1 predicted <30% – no (%)	5 (<1)	4 (<1)	5 (<1)†	19 (<1)†
Dyspnoea – no (%)	0 (0)	23 133 (75)†	0 (0)	5315 (76)†
mMRC ≥2 – no. (%)	0 (0)	4937 (16)†	0 (0)	1513 (22)†
Night-time dyspnoea – no. (%)	0 (0)	2115 (7)†	0 (0)	392 (6)†
Chronic mucus hypersecretion – no. (%)	0 (0)	5279 (17)†	0 (0)	1799 (26)†
Wheezing – no. (%)	0 (0)	9744 (32)†	0 (0)	2752 (39)†
Cough – no. (%)	0 (0)	7432 (24)†	0 (0)	1815 (26)†

*Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Data presented as number (percent). FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. LLN=the lower limit of normal.
†P<0.05 for comparison with individuals with FEV_1FVC ≥0.70 and no symptoms at baseline examination, obtained from Wilcoxon rank-sum or Pearson χ^2 tests.

Table S2. Healthcare utilisation according to lung function and chronic respiratory symptoms in individuals in the Copenhagen General Population Study without known airway disease.*

	FEV_1/FVC ≥0.70		FEV_1/FVC <0.70	
	No symptoms (n=52 999)	**Symptoms (n=30 890)**	**No symptoms (n=7076)**	**Symptoms (n=6990)**
Acute bronchitis/pneumonia episodes for the past 10 years				
None – no. (%)	45 367 (86)	22 257 (72)†	5884 (83)†	4733 (68)†
1-5 – no. (%)	7493 (14)	8071 (26)†	1169 (17)†	2063 (30)†
≥6 – no. (%)	139 (<1)	562 (2)†	23 (<1)	194 (3)
General practitioner visits in the past 12 months				
0-1 time – no. (%)	27 135 (51)	11 192 (36)†	3216 (45)†	2331 (33)†
2-3 times – no. (%)	17 093 (32)	10 580 (34)†	2341 (33)	2343 (34)†
4-5 times – no. (%)	5848 (11)	5264 (17)†	971 (14)†	1303 (19)†
>5 times – no. (%)	2923 (6)	3854 (12)†	548 (8)†	1013 (14)†
Specialised practitioner visits in the past 12 months				
0-1 time – no. (%)	42 748 (81)	22 884 (74)†	5408 (76)†	5053 (72)†
2-3 times – no. (%)	6830 (13)	5068 (16)†	1131 (16)†	1248 (18)†
4-5 times – no. (%)	1773 (3)	1506 (5)†	274 (4)†	366 (5)†
>5 times – no. (%)	1648 (3)	1432 (5)†	263 (4)†	323 (5)†

*Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Data presented as number (percent). FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity.
†P<0.05 for comparison with individuals with FEV_1FVC ≥0.70 and no symptoms at baseline examination, obtained from Wilcoxon rank-sum or Pearson χ^2 tests.

Table S3. Characteristics according to lung function and chronic respiratory symptoms in individuals in the Copenhagen General Population Study with known airway disease that were excluded.*

	FEV_1/FVC ≥0.70		FEV_1/FVC <0.70	
	No symptoms (n=1555)	**Symptoms (n=4769)**	**No symptoms (n=520)**	**Symptoms (n=3447)**
At baseline examination				
Age – yr	54 (46-65)	56 (47-66)‡	65 (55-72)‡	67 (58-75)‡
Men – no. (%)	684 (44)	1649 (35)‡	264 (51)‡	1564 (45)
FEV_1 predicted – %	97 (89-106)	92 (82-102)‡	81 (70-91)‡	67 (53-81)‡
FVC predicted – %	99 (91-108)	94 (84-103)‡	100 (89-111)	86 (73-100)‡
FEV_1/FVC	0.78 (0.74-0.82)	0.77 (0.74-0.81)	0.64 (0.60-0.68)‡	0.62 (0.54-0.67)‡
FEV_1/FVC <LLN – no. (%)	30 (2)	141 (3)‡	452 (87)‡	3100 (90)‡
Current smokers – no. (%)	135 (9)	786 (16)‡	73 (14)‡	959 (28)‡
Former smokers – no (%)	605 (39)	1965 (41)	286 (55)‡	1809 (52)‡
Tobacco consumption – pack-yr†	10.7 (4.5-23.8)	15.0 (6.0-30.0)‡	18.4 (7.5-33.0)‡	30.0 (15.3-46.4)‡
Occupational exposure – no. (%)	113 (7)	739 (16)‡	40 (8)	754 (22)‡
Environmental tobacco smoke – no. (%)	221 (14)	1010 (21)‡	73 (14)	605 (18)‡
Fever or infection within the past 4 weeks – no. (%)	50 (3)	410 (9)‡	11 (2)	351 (10)‡
Body mass index – kg/m^2	25.0 (22.9-27.5)	26.8 (24.0-30.2)‡	24.6 (22.5-26.5)‡	25.8 (23.4-28.8)‡
Plasma cholesterol – mmol/L	5.5 (4.8-6.2)	5.6 (4.9-6.3)‡	5.6 (5.0-6.3)‡	5.6 (4.8-6.3)‡
Systolic blood pressure – mmHg	137 (124-152)	138 (125-153)	145 (129-159)‡	142 (130-158)‡
Diastolic blood pressure – mmHg	84 (76-90)	84 (76-90)	84 (77-91)	84 (76-90)
Alcohol – units/week	7 (3-14)	6 (2-13)‡	10 (4-17)‡	8 (3-16 ‡
Cardiovascular disease – no. (%)	113 (7)	581 (12)‡	73 (14)‡	767 (22)‡
Diabetes – no. (%)	51 (3)	277 (6)‡	21 (4)	248 (7)‡
Cancer – no. (%)	95 (6)	293 (6)	53 (10)‡	411 (12)‡
Exclusion criteria				
Previous inpatient/outpatient hospital contact with COPD – no. (%)	146 (9)	614 (13)‡	129 (25)‡	1387 (40)‡
Previous inpatient/outpatient hospital contact with asthma – no. (%)	448 (29)	1361 (29)	190 (37)‡	950 (28)
Self-reported asthma – no. (%)	866 (56)	3400 (71)‡	297 (57)	1995 (58)
Self-reported treatment with airway medication – no. (%)	773 (50)	2973 (62)‡	277 (53)	2478 (72)‡
During follow-up				
Exacerbation hospitalisations – no (%)	30 (2)	406 (9)	50 (10)	1774 (51)
Pneumonia hospitalisations – no (%)	95 (6)	562 (12)	78 (15)	1298 (38)
Respiratory deaths – no (%)	4 (<1)	53 (1)	5 (1)	237 (7)
Deaths – no (%)	95 ()	454 (10)	62 (12)	977 (28)

*Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Data presented as median and 25th and 75th percentiles, or number (percent). FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. LLN=the lower limit of normal.
†Only for current and former smokers.
‡P<0.05 for comparison with individuals with FEV_1FVC ≥0.70 and no symptoms at baseline examination, obtained from Wilcoxon rank-sum or Pearson χ^2 tests.

Table S4. Detailed characteristics of lung function and chronic respiratory symptoms in individuals in the Copenhagen General Population Study with known airway disease that were excluded.*

	$FEV_1/FVC \geq 0.70$		$FEV_1/FVC < 0.70$	
	No symptoms (n=1555)	**Symptoms (n=4769)**	**No symptoms (n=520)**	**Symptoms (n=3447)**
FEV_1 predicted – %	97 (89-106)	92 (82-102)‡	81 (70-91)‡	67 (53-81)‡
FVC predicted – %	99 (91-108)	94 (84-103)‡	100 (89-111)	86 (73-100)‡
FEV_1/FVC	0.78 (0.74-0.82)	0.77 (0.74-0.81)	0.64 (0.60-0.68)‡	0.62 (0.54-0.67)‡
FEV_1/FVC <LLN – no. (%)	30 (2)	141 (3)‡	452 (87)‡	3100 (90)‡
FEV_1 predicted ≥80% – no (%)	1422 (91)	3759 (79)‡	273 (53)‡	883 (26)‡
FEV_1 predicted 50-79% – no (%)	130 (8)	975 (20)‡	231 (44)‡	1824 (53)‡
FEV_1 predicted 30-49% – no (%)	3 (<1)	32 (1)‡	15 (3)‡	629 (18)‡
FEV_1 predicted <30% – no (%)	0 (0)	3 (<1)	1 (<1)	111 (3)‡
Dyspnoea – no (%)	0 (0)	3153 (66)‡	0 (0)	2764 (80)‡
mMRC ≥2 – no. (%)	0 (0)	1093 (23)‡	0 (0)	1381 (40)‡
Night-time dyspnoea – no. (%)	0 (0)	764 (16)‡	0 (0)	585 (17)‡
Chronic mucus hypersecretion – no. (%)	0 (0)	1204 (25)‡	0 (0)	1258 (37)‡
Wheezing – no. (%)	0 (0)	3299 (69)‡	0 (0)	2441 (71)‡
Cough – no. (%)	0 (0)	2209 (46)‡	0 (0)	1591 (46)‡

*Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Data presented as number (percent). FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. LLN=the lower limit of normal.
†P<0.05 for comparison with individuals with FEV_1FVC ≥0.70 and no symptoms at baseline examination, obtained from Wilcoxon rank-sum or Pearson χ^2 tests.

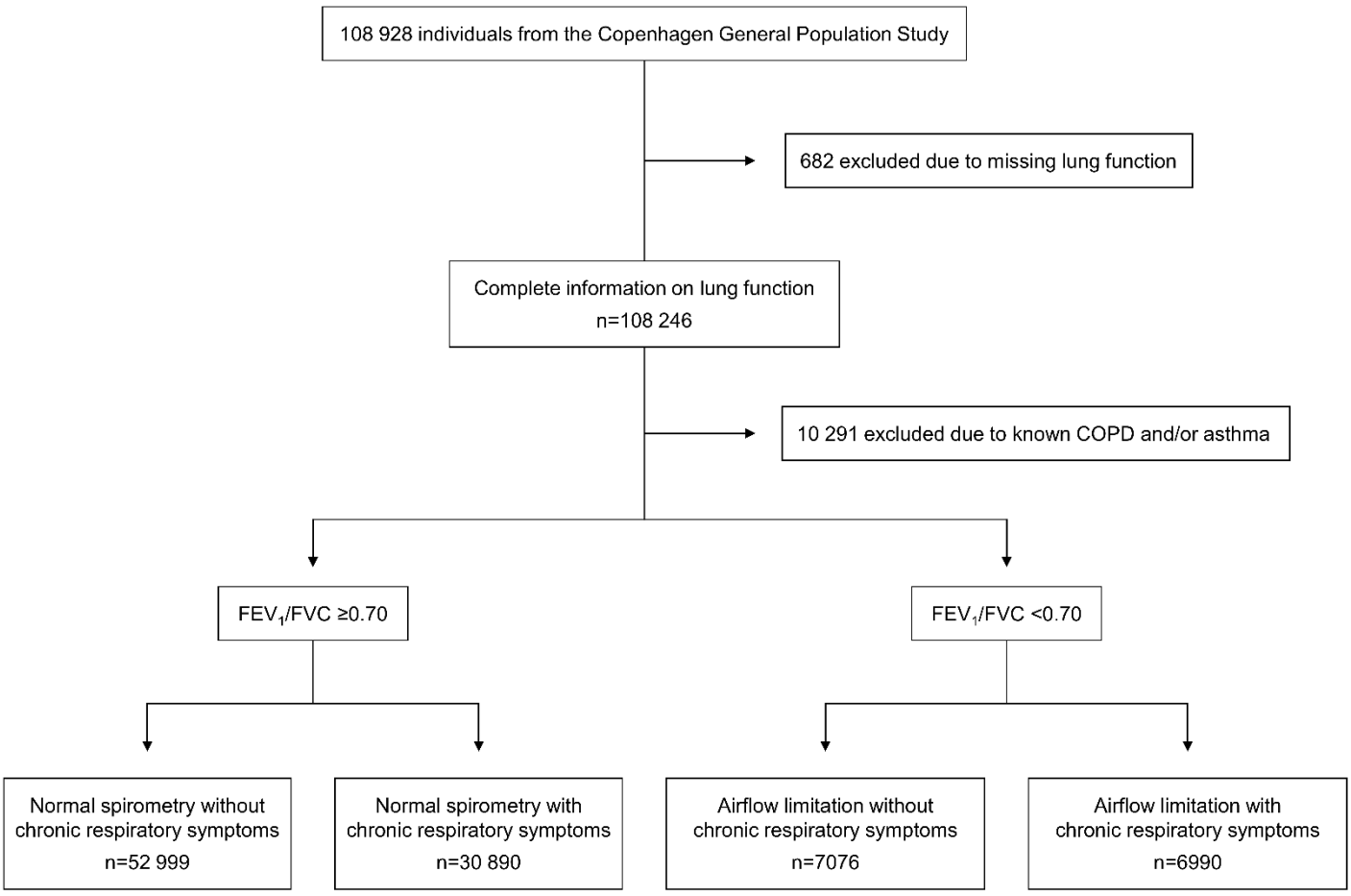
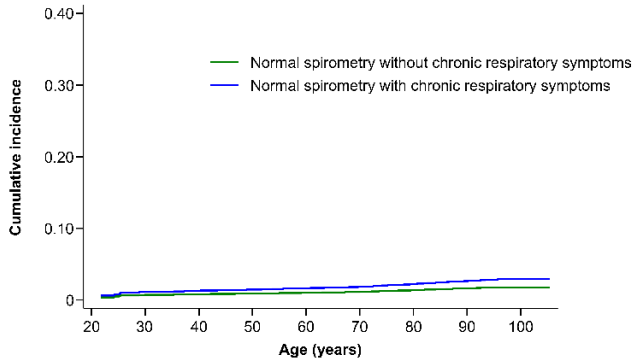


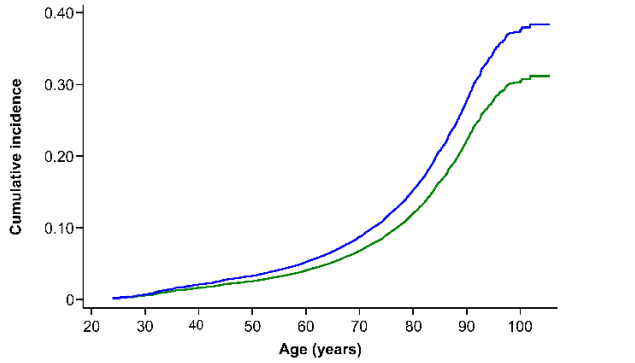
Figure S1. Flowchart. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity.

Exacerbation hospitalisations



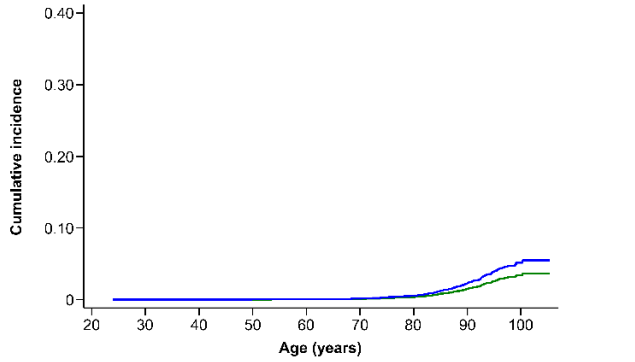
	No. of individuals/events	SHR (95% CI)	P-value
Normal spirometry without chronic respiratory symptoms	52 999/97	1 [Reference]	
Normal spirometry with chronic respiratory symptoms	30 890/203	1.63 (1.26-2.12)	<0.001

Pneumonia hospitalisations



	No. of individuals/events	SHR (95% CI)	P-value
Normal spirometry without chronic respiratory symptoms	52 999/1604	1 [Reference]	
Normal spirometry with chronic respiratory symptoms	30 890/1713	1.30 (1.20-1.40)	<0.001

Respiratory mortality



	No. of individuals/events	SHR (95% CI)	P-value
Normal spirometry without chronic respiratory symptoms	52 999/94	1 [Reference]	
Normal spirometry with chronic respiratory symptoms	30 890/163	1.53 (1.16-2.01)	0.002

Figure S2. Cumulative incidences and risk of respiratory hospitalisations and death according to chronic respiratory symptoms in individuals with normal spirometry without known airway disease. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Cumulative incidences and subhazard ratios (SHRs) with 95% confidence intervals (CIs) were obtained from competing risk analyses using Fine & Gray regression model with competing events being all-cause mortality and emigration. P-values were from Wald's tests. Analyses were multivariable adjusted, that is, for age (as timescale), sex, and pulmonary and non-pulmonary related confounders, including smoking status, cumulative tobacco consumption, forced expiratory volume in 1 second (FEV_1) % predicted, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure, and atrial fibrillation), diabetes, and cancer.

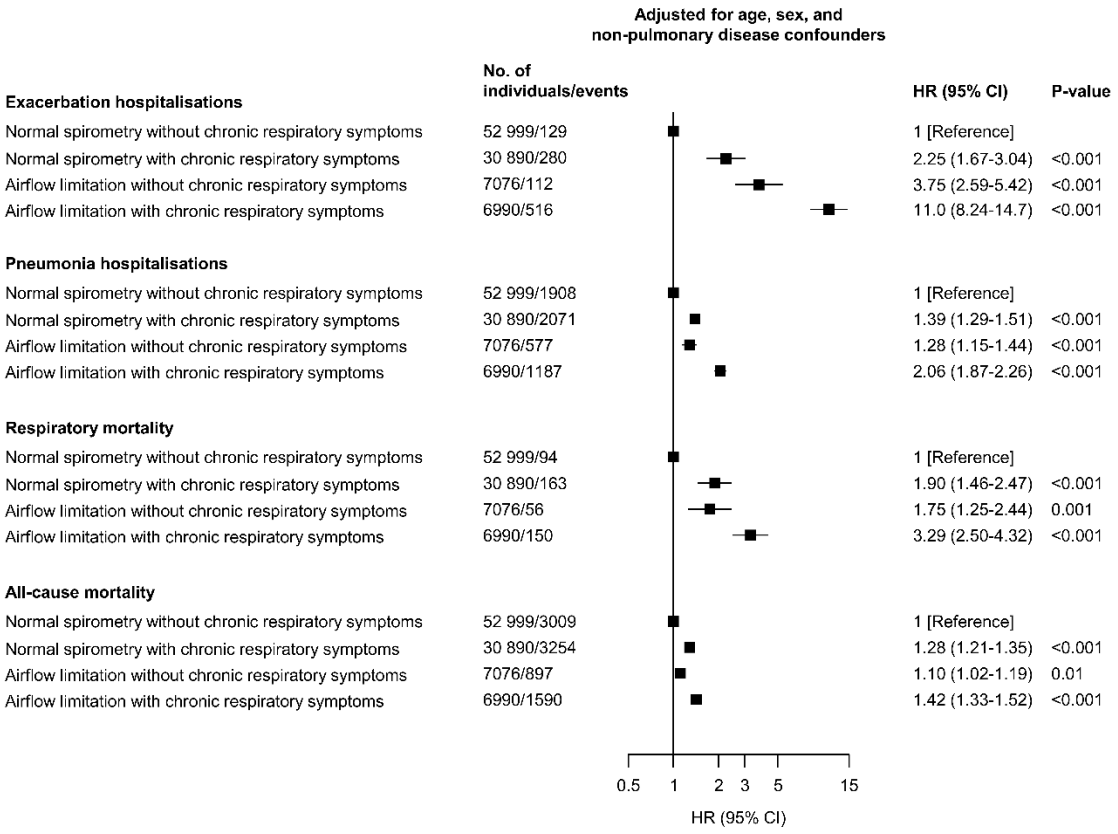


Figure S3. Risk of respiratory hospitalisations and death according to lung function and chronic respiratory symptoms in individuals without known airway disease. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained from Cox proportional regression model. P-values were from Wald's tests. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Analyses were multivariable adjusted for non-pulmonary disease related confounders, that is, for smoking status, cumulative tobacco consumption, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure, and atrial fibrillation), diabetes, and cancer.

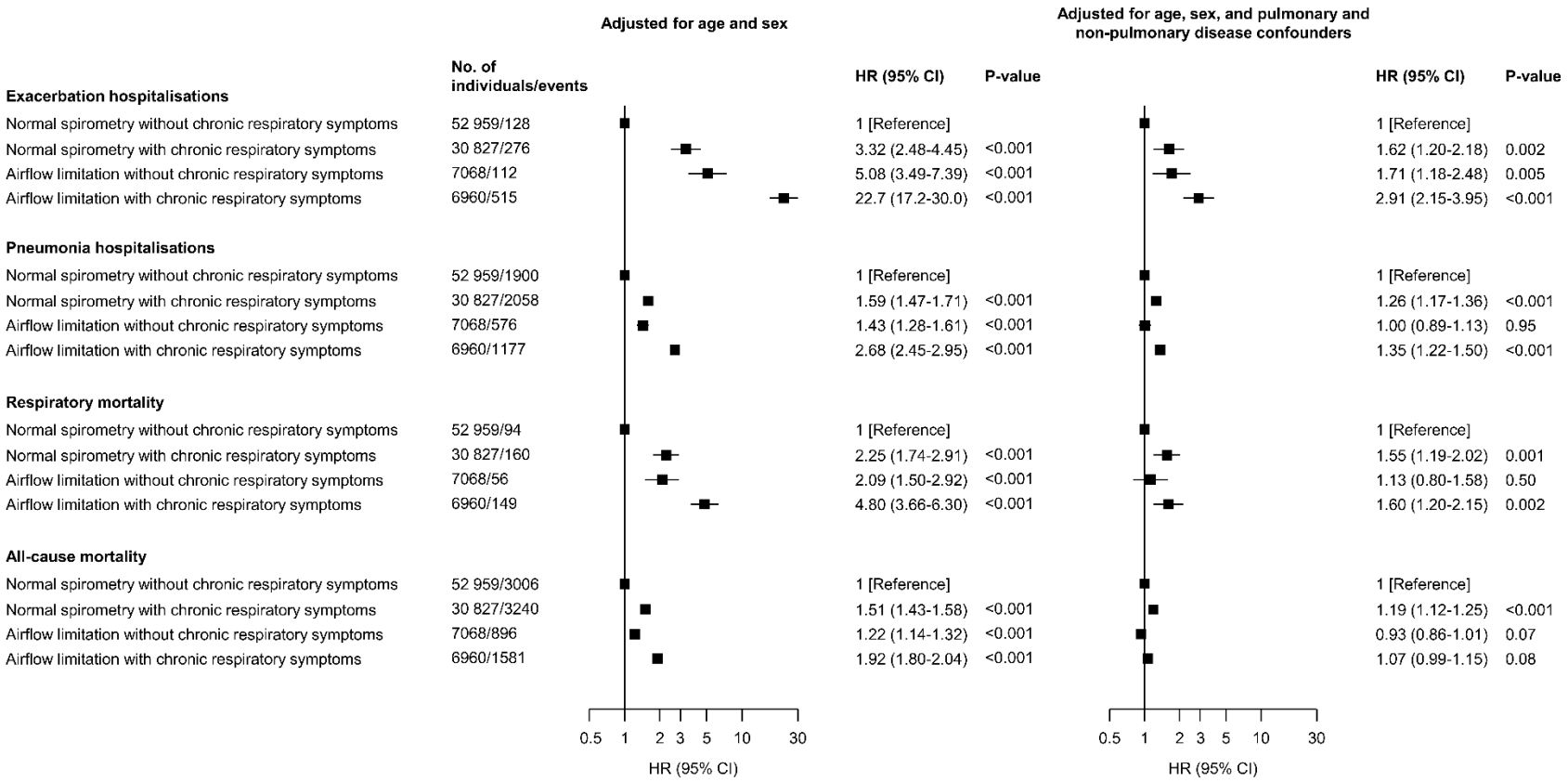


Figure S4. Risk of respiratory hospitalisations and death according to lung function and chronic respiratory symptoms in individuals without known airway disease. Individuals with interstitial lung disease excluded (International Classification of Diseases [ICD]-8: 515-517 and ICD-10: J84, J60-J70). Information was obtained from the national Danish Patient Registry defined as all inpatient and outpatient hospital contacts. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained from Cox proportional regression model. P-values were from Wald's tests. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Pulmonary and non-pulmonary disease related confounders included smoking status, cumulative tobacco consumption, forced expiratory volume in 1 second (FEV_1) % predicted, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure, and atrial fibrillation), diabetes, and cancer.

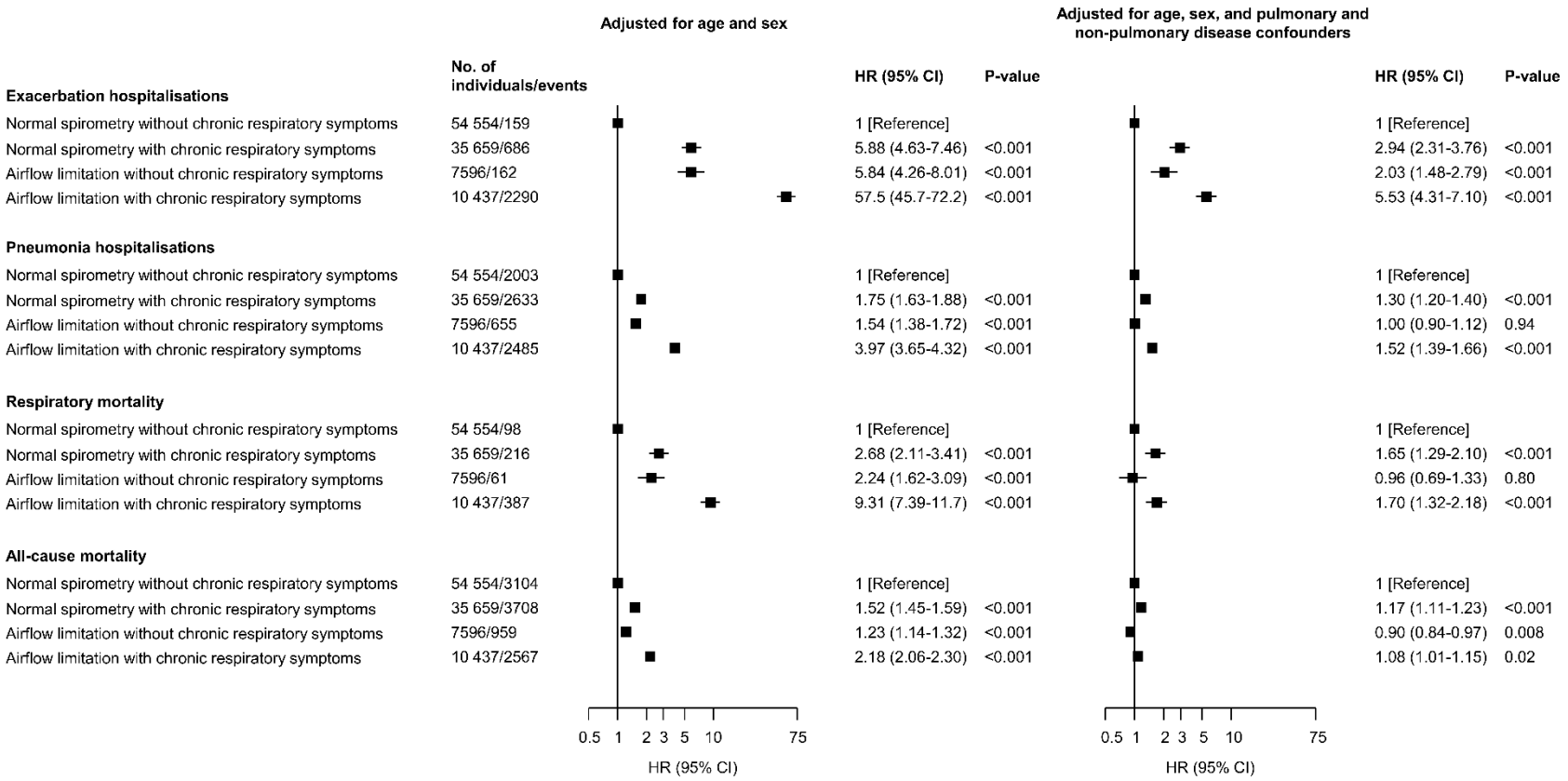


Figure S5. Risk of respiratory hospitalisations and death according to lung function and chronic respiratory symptoms in individuals <u>with and without known airway disease</u>. Information was obtained from the national Danish Patient Registry defined as all inpatient and outpatient hospital contacts. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained from Cox proportional regression model. P-values were from Wald's tests. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Pulmonary and non-pulmonary disease related confounders included smoking status, cumulative tobacco consumption, forced expiratory volume in 1 second (FEV_1) % predicted, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure, and atrial fibrillation), diabetes, and cancer.

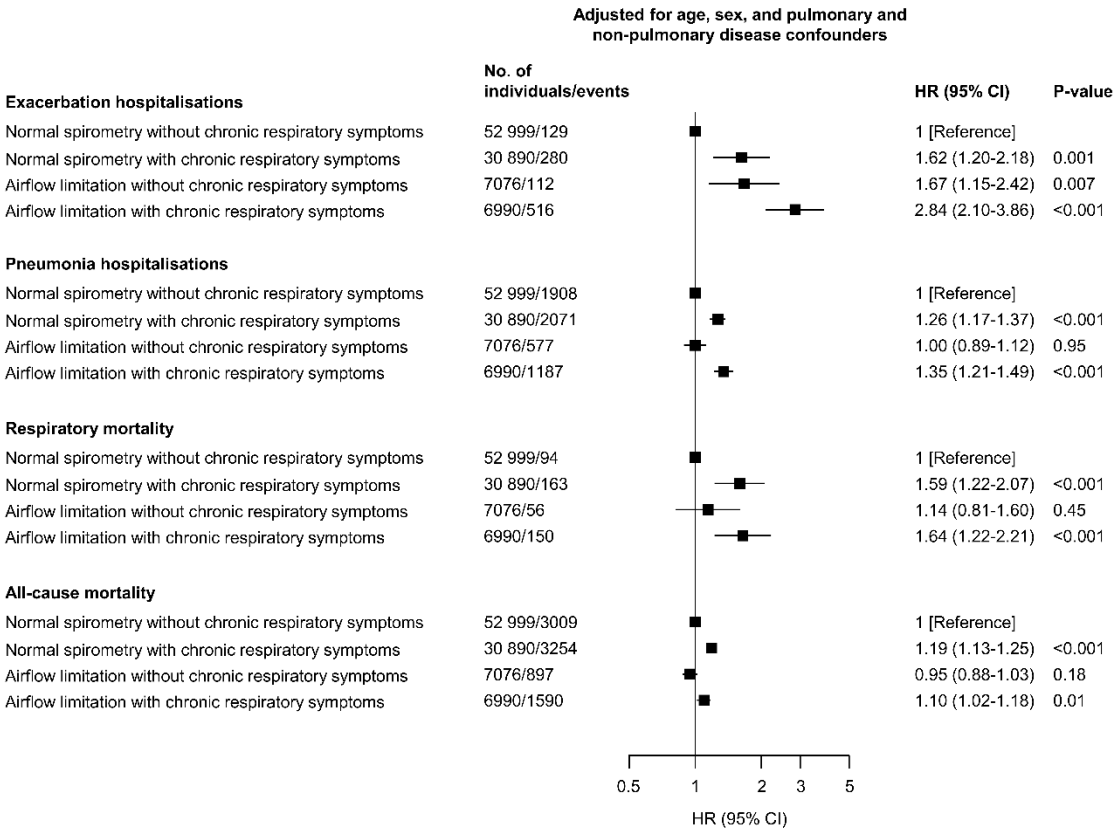


Figure S6. Risk of respiratory hospitalisations and death according to lung function and chronic respiratory symptoms in individuals without known airway disease. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing, and cough. Hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained from Cox proportional regression model. P-values were from Wald's tests. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Pulmonary and non-pulmonary disease related confounders included type of spirometer, smoking status, cumulative tobacco consumption, forced expiratory volume in 1 second (FEV_1) % predicted, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure, and atrial fibrillation), diabetes, and cancer.