

## Supplement

### **Young and middle-aged adults with airflow limitation according to lower limit of normal but not fixed ratio have high morbidity and poor survival: a population-based prospective cohort study**

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## Spirometry

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 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 manufacturer. 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<sub>1</sub>) and forced vital capacity (FVC) were performed. FEV<sub>1</sub> 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<sub>1</sub> and FVC were used. Predicted values of FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC were calculated separately for the two spirometers using internally derived reference values based on a subsample of healthy asymptomatic (i.e. without chronic mucus hypersecretion, dyspnoea, wheezing, or cough) 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 comprehensive 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.

## Symptoms

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?”. 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?”. 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?”.

## Characteristics and potential confounders

Smoking status was defined as never, former, or current smoking. Cumulative tobacco consumption was defined as tobacco consumed through smoking and measured in pack-years based on information on the duration of tobacco smoking and current amount of consumed tobacco: one pack-year was 20 cigarettes or the equivalent (e.g. cigars, cheroots, pipe) smoked daily for a year. Use of airway medication was defined as an affirmative response to the question: “Do you take any kind of medication for asthma and/or bronchitis (including sprays and/or dry powders) daily or almost daily?”. Asthma was based on self-report or a previous inpatient/outpatient hospital contact due to asthma (International Classification of Diseases [ICD]-8:493 and ICD-10:J45-J46), obtained from the National Danish Patient Registry. Allergy was defined present if the participants reported “Asthma”, “Hay fever”, or “Eczema” as a reaction to “Food, medication, grass, flower, animal hair, or other allergens”. Severity of airflow limitation was assessed using predicted values of FEV<sub>1</sub>. Inflammatory biomarkers in blood (i.e. C-reactive protein, fibrinogen, leucocytes, neutrophils, and eosinophils) and plasma cholesterol, glucose, and triglycerides were measured using standard hospital assays. Analyses were subjected to daily precision testing by using internal quality control material and monthly accuracy testing by using an external control quality programme. Number of acute bronchitis or pneumonia episodes in the last 10 years was self-reported and included only those leading to a doctor’s consultation and/or absence from work. Number of visits to the general practitioners office in the last 12 months was self-reported and included any type of visits. Body mass index was calculated as measured weight divided by measured height squared (kg/m<sup>2</sup>). Familial

predisposition for asthma was defined as an affirmative response to the question: “Do your biological parents or biological siblings have asthma?”. Childhood asthma, hay fever, or eczema was defined as an affirmative response to the question: “As a child, did you have asthma, hay fever, or eczema?”. Occupational exposure to dust/fumes was defined as an affirmative response to the question: “Have you for longer periods of your working life been exposed to dust or fumes?”. Daily exposure to passive smoking was reported as hours of exposure per day. Socioeconomic status was based on level of education, reported as years attending school, and income, reported as annual household income. Alcohol consumption was reported in units per week and converted to grams (1 unit = 12 g). Diabetes was based on self-report, nonfasting plasma glucose >11 mmol/L, use of antidiabetic medication, and/or previous inpatient/outpatient hospital contact with diabetes (ICD-8:249-250 and ICD-10:E10-E14), obtained from the National Danish Patient Registry. Systolic and diastolic blood pressure was measured using automated equipment. Physical activity was reported according to hours per week and degree of activity in leisure-time. Use of cholesterol lowering medication was defined as an affirmative response to the question: “Do you take any kind of medication for high cholesterol daily or almost daily?”.

**TABLE S1** Unadjusted comorbidities, severity of disease, and healthcare use among 95 288 individuals according to clinical groups of airflow limitation in the Copenhagen General Population Study

	No AFL	AFL	Potentially underdiagnosed AFL			Potentially overdiagnosed AFL		
	(n=78 779)	(n=12 365)	(n=1056)	P vs. No AFL	P vs. AFL	(n=3088)	P vs. No AFL	P vs. AFL
<b>Use of airway medication – no. (%)</b>	3246 (4)	2154 (17)	83 (8)	<0.0001	<0.0001	224 (7)	<0.0001	<0.0001
<b>Asthma – no. (%)</b>	4157 (5)	2026 (16)	130 (12)	<0.0001	0.001	203 (7)	0.002	<0.0001
<b>Allergy – no. (%)</b>	22 016 (28)	3468 (28)	365 (35)	<0.0001	<0.0001	672 (22)	<0.0001	<0.0001
<b>Symptoms</b>								
Chronic mucus hypersecretion – no. (%)	5690 (7)	2275 (18)	112 (11)	<0.0001	<0.0001	385 (12)	<0.0001	<0.0001
Dyspnoea – no. (%)	23 090 (29)	5716 (46)	342 (32)	0.03	<0.0001	1283 (42)	<0.0001	<0.0001
mMRC ≥2 – no. (%)	5281 (7)	2056 (17)	55 (5)	0.05	<0.0001	457 (15)	<0.0001	0.01
Night-time dyspnoea – no. (%)	2522 (3)	749 (6)	55 (5)	<0.0001	0.26	113 (4)	0.16	<0.0001
Wheezing – no. (%)	11 360 (14)	3939 (32)	284 (27)	<0.0001	0.001	535 (17)	<0.0001	<0.0001
Cough – no. (%)	8426 (11)	2620 (21)	213 (20)	<0.0001	0.44	342 (11)	0.50	<0.0001
Any symptom – no. (%)	31 252 (40)	7437 (60)	529 (50)	<0.0001	<0.0001	1573 (51)	<0.0001	<0.0001
<b>Degree of airflow limitation</b>								
FEV <sub>1</sub> % predicted ≥80 – no. (%)	71 763 (91)	6151 (50)	841 (80)	<0.0001	<0.0001	2292 (74)	<0.0001	<0.0001
FEV <sub>1</sub> % predicted 50-79 – no. (%)	6907 (9)	5167 (42)	212 (20)	<0.0001	<0.0001	777 (25)	<0.0001	<0.0001
FEV <sub>1</sub> % predicted 30-49 – no. (%)	98 (<1)	923 (7)	3 (<1)	0.15	<0.0001	19 (<1)	<0.0001	<0.0001
FEV <sub>1</sub> % predicted <30 – no. (%)	11 (<1)	124 (1)	0 (0)	0.70	0.001	0 (0)	0.51	<0.0001
<b>Levels of inflammatory biomarkers</b>								
C-reactive protein – mg/L	1.4 (1.0-2.2)	1.5 (1.0-2.7)	1.4 (0.9-2.0)	0.02	<0.0001	1.5 (1.0-2.6)	<0.0001	0.75
Fibrinogen – µmol/L	10.5 (9.2-12.2)	11.0 (9.6-12.9)	10.0 (8.8-11.7)	<0.0001	<0.0001	11.3 (9.9-13.0)	<0.0001	<0.0001

Leucocytes – x 10 <sup>9</sup> /L	7.0 (6.0-8.1)	7.3 (6.2-8.6)	7.4 (6.3-8.6)	<0.0001	0.40	7.0 (6.0-8.1)	0.95	<0.0001
Neutrophils – x 10 <sup>9</sup> /L	4.0 (3.3-4.9)	4.3 (3.5-5.3)	4.2 (3.4-5.2)	<0.0001	0.15	4.1 (3.4-5.0)	<0.0001	<0.0001
Eosinophils – x 10 <sup>9</sup> /L	0.16 (0.11-0.24)	0.18 (0.12-0.27)	0.17 (0.11-0.26)	0.006	0.01	0.17 (0.11-0.26)	<0.0001	0.0001
<b>Number of acute bronchitis or pneumonia episodes in the last 10 years</b>								
None – no. (%)	61 962 (79)	8333 (67)	775 (73)	<0.0001	<0.0001	2242 (73)	<0.0001	<0.0001
1-5 – no. (%)	15 675 (20)	3409 (28)	261 (25)	<0.0001	0.046	783 (25)	<0.0001	0.01
≥6 – no. (%)	1142 (1)	623 (5)	20 (2)	0.23	<0.0001	63 (2)	0.008	<0.0001
<b>Number of visits to the GPs office in the last 12 months</b>								
None – no. (%)	17 050 (22)	2191 (18)	243 (23)	0.28	<0.0001	496 (16)	<0.0001	0.03
Once – no. (%)	18 047 (23)	2368 (19)	262 (25)	0.14	<0.0001	501 (16)	<0.0001	<0.0001
Twice or more – no. (%)	43 682 (55)	7806 (63)	551 (52)	0.03	<0.0001	2091 (68)	<0.0001	<0.0001

Data presented as median (25th and 75th percentiles) or number (%). P values obtained from Wilcoxon rank-sum test or Pearson  $\chi^2$  test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) ≥0.70 and FEV<sub>1</sub>/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV<sub>1</sub>/FVC ≥0.70 and FEV<sub>1</sub>/FVC <LLN, potentially overdiagnosed AFL was defined as FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub>/FVC ≥LLN, and AFL was defined as FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub>/FVC <LLN. GP = general practitioner. mMRC = modified Medical Research Council dyspnoea scale.

**TABLE S2** Age- and sex adjusted respiratory and cardiovascular outcome related potential confounders among 95 288 individuals according to clinical groups of airflow limitation in the Copenhagen General Population Study

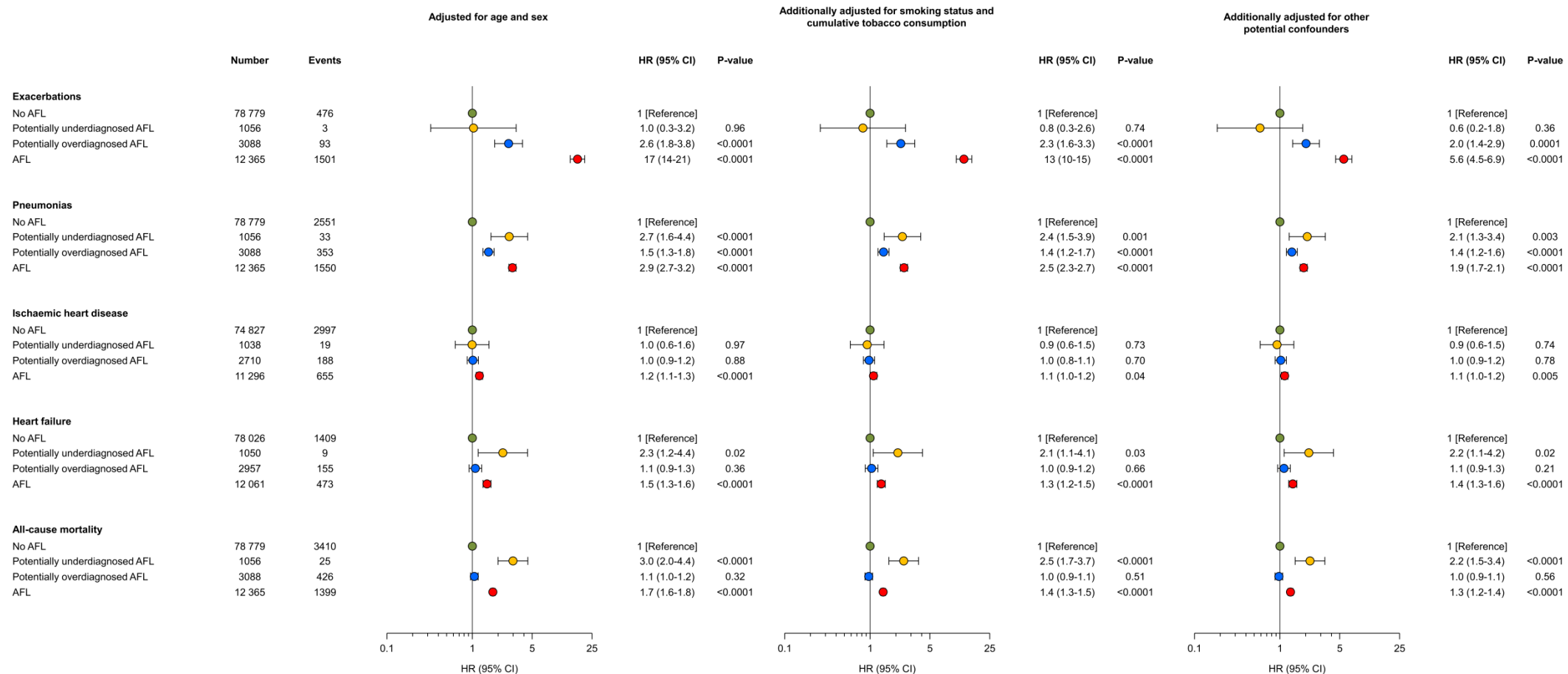
	No AFL	AFL	Potentially underdiagnosed AFL			Potentially overdiagnosed AFL		
	(n=78 779)	(n=12 365)	(n=1056)	P vs. No AFL	P vs. AFL	(n=3088)	P vs. No AFL	P vs. AFL
Body mass index (kg/m <sup>2</sup> )	26	25	26	0.0003	0.004	25	<0.0001	0.02
Familial predisposition for asthma (%)	17	24	22	<0.0001	0.21	17	0.35	<0.0001
Childhood asthma, hay fever, or eczema (%)	13	18	15	0.008	0.04	15	0.04	0.001
Occupational exposure to dust/fumes (%)	9.8	14	12	0.02	0.17	8.8	0.06	<0.0001
Daily exposure to passive smoking (%)	18	19	19	0.25	0.88	15	0.0002	<0.0001
Poor socioeconomic status (%)	7.4	8.9	11	0.009	0.13	6.0	<0.0001	<0.0001
Alcohol (g/week)	130	135	128	0.59	0.049	122	<0.0001	<0.0001
Diabetes (%)	4.3	4.1	3.0	0.15	0.21	3.2	<0.0001	0.001
Systolic blood pressure (mmHg)	142	140	140	0.002	0.29	141	0.004	0.78
Diastolic blood pressure (mmHg)	84	84	83	0.005	0.61	83	<0.0001	<0.0001
Physical inactivity (%)	5.9	9.1	6.6	0.30	0.004	6.7	0.03	0.001
Use of cholesterol lowering medication (%)	12	12	9.0	0.06	0.02	11	0.04	0.001
Plasma cholesterol (mmol/L)	5.6	5.5	5.5	0.001	0.71	5.5	<0.0001	0.003
Plasma triglycerides (mmol/L)	1.69	1.65	1.67	0.65	0.45	1.59	<0.0001	0.007

Percentages are age- and sex adjusted, obtained from logistic regression models. Means are age- and sex adjusted, obtained from linear regression models. P-values obtained from Wald test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) ≥0.70 and FEV<sub>1</sub>/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV<sub>1</sub>/FVC ≥0.70 and FEV<sub>1</sub>/FVC <LLN, potentially overdiagnosed AFL was defined as FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub>/FVC ≥LLN, and AFL was defined as FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub>/FVC <LLN.

**TABLE S3** Unadjusted respiratory and cardiovascular outcome related potential confounders among 95 288 individuals according to clinical groups of airflow limitation in the Copenhagen General Population Study

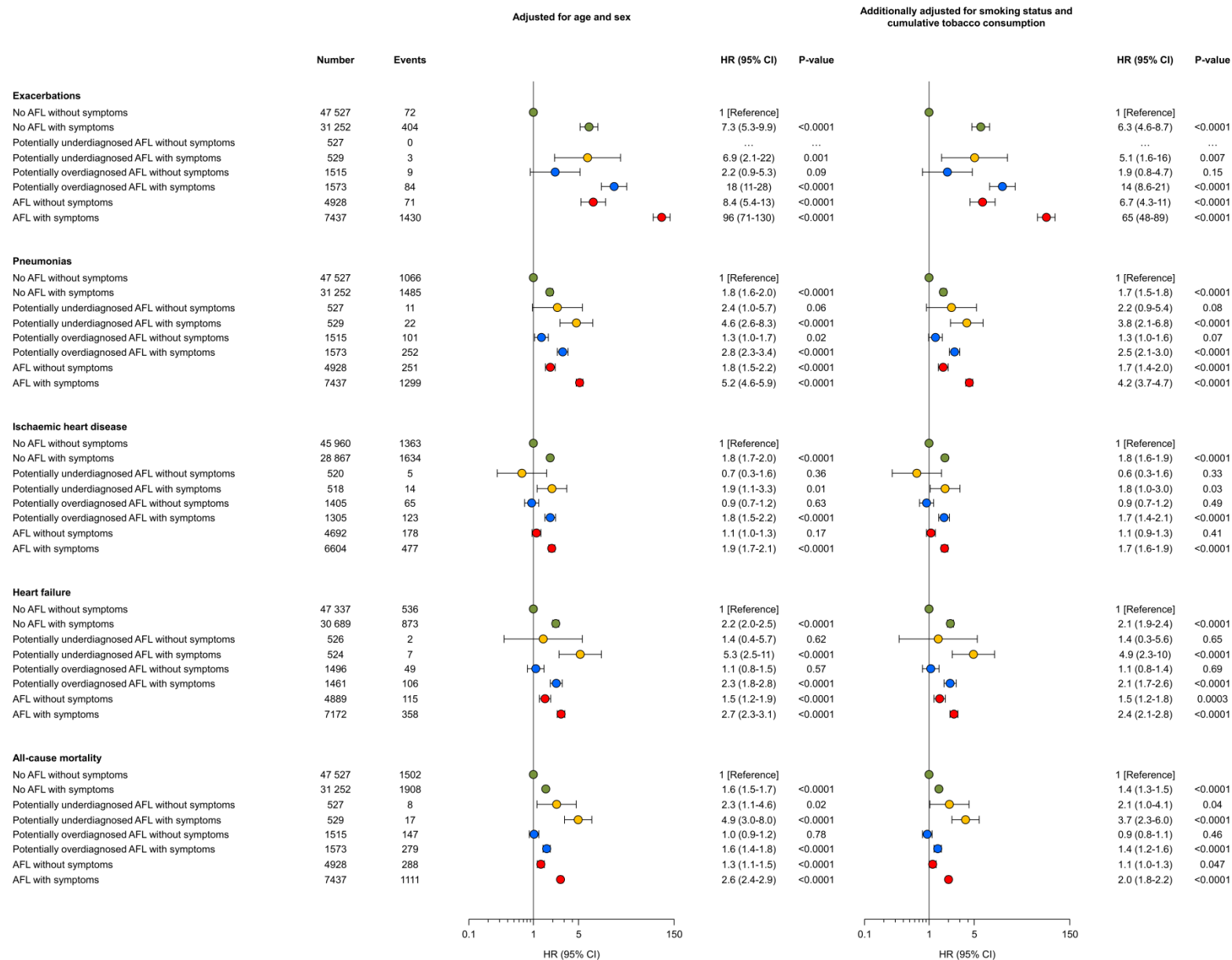
	No AFL	AFL	Potentially underdiagnosed AFL			Potentially overdiagnosed AFL		
	(n=78 779)	(n=12 365)	(n=1056)	P vs. No AFL	P vs. AFL	(n=3088)	P vs. No AFL	P vs. AFL
<b>Body mass index – kg/m<sup>2</sup></b>	26 (23-29)	25 (23-28)	25 (22-27)	<0.0001	0.0002	25 (23-28)	<0.0001	0.35
<b>Familial predisposition for asthma – no. (%)</b>	13 433 (17)	2696 (22)	275 (26)	<0.0001	0.001	437 (14)	<0.0001	<0.0001
<b>Childhood asthma, hay fever, or eczema – no. (%)</b>	10 714 (14)	1801 (15)	234 (22)	<0.0001	<0.0001	256 (8)	<0.0001	<0.0001
<b>Occupational exposure to dust/fumes – no. (%)</b>	7615 (10)	1816 (15)	114 (11)	0.22	0.001	269 (9)	0.08	<0.0001
<b>Daily exposure to passive smoking – no. (%)</b>	14 232 (18)	2175 (18)	242 (23)	<0.0001	<0.0001	336 (11)	<0.0001	<0.0001
<b>Poor socioeconomic status – no. (%)</b>	5102 (6)	1560 (13)	23 (2)	<0.0001	<0.0001	530 (17)	<0.0001	<0.0001
<b>Alcohol – g/week</b>	96 (48-180)	108 (48-204)	72 (30-144)	<0.0001	<0.0001	108 (48-192)	<0.0001	0.68
<b>Diabetes – no. (%)</b>	3156 (4)	661 (5)	14 (1)	<0.0001	<0.0001	182 (6)	<0.0001	0.23
<b>Systolic blood pressure – mmHg</b>	139 (125-154)	142 (129-158)	130 (120-142)	<0.0001	<0.0001	149 (135-162)	<0.0001	<0.0001
<b>Diastolic blood pressure – mmHg</b>	84 (76-91)	84 (76-91)	82 (75-89)	<0.0001	<0.0001	83 (76-90)	0.02	0.03
<b>Physical inactivity – no. (%)</b>	4695 (6)	1052 (9)	80 (8)	0.03	0.30	177 (6)	0.60	<0.0001
<b>Use of cholesterol lowering medication – no. (%)</b>	8516 (11)	2029 (16)	35 (3)	<0.0001	<0.0001	672 (22)	<0.0001	<0.0001
<b>Plasma cholesterol – mmol/L</b>	5.6 (4.9-6.3)	5.6 (4.8-6.3)	5.3 (4.6-6.0)	<0.0001	<0.0001	5.6 (5.0-6.4)	<0.0001	0.0001
<b>Plasma triglycerides – mmol/L</b>	1.38 (0.96-2.05)	1.41 (1.00-2.06)	1.26 (0.89-1.92)	<0.0001	<0.0001	1.38 (0.99-2.00)	0.60	0.08

Data presented as median (25th and 75th percentiles) or number (%). P values obtained from Wilcoxon rank-sum test or Pearson  $\chi^2$  test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) ≥0.70 and FEV<sub>1</sub>/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV<sub>1</sub>/FVC ≥0.70 and FEV<sub>1</sub>/FVC <LLN, potentially overdiagnosed AFL was defined as FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub>/FVC ≥LLN, and AFL was defined as FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub>/FVC <LLN.

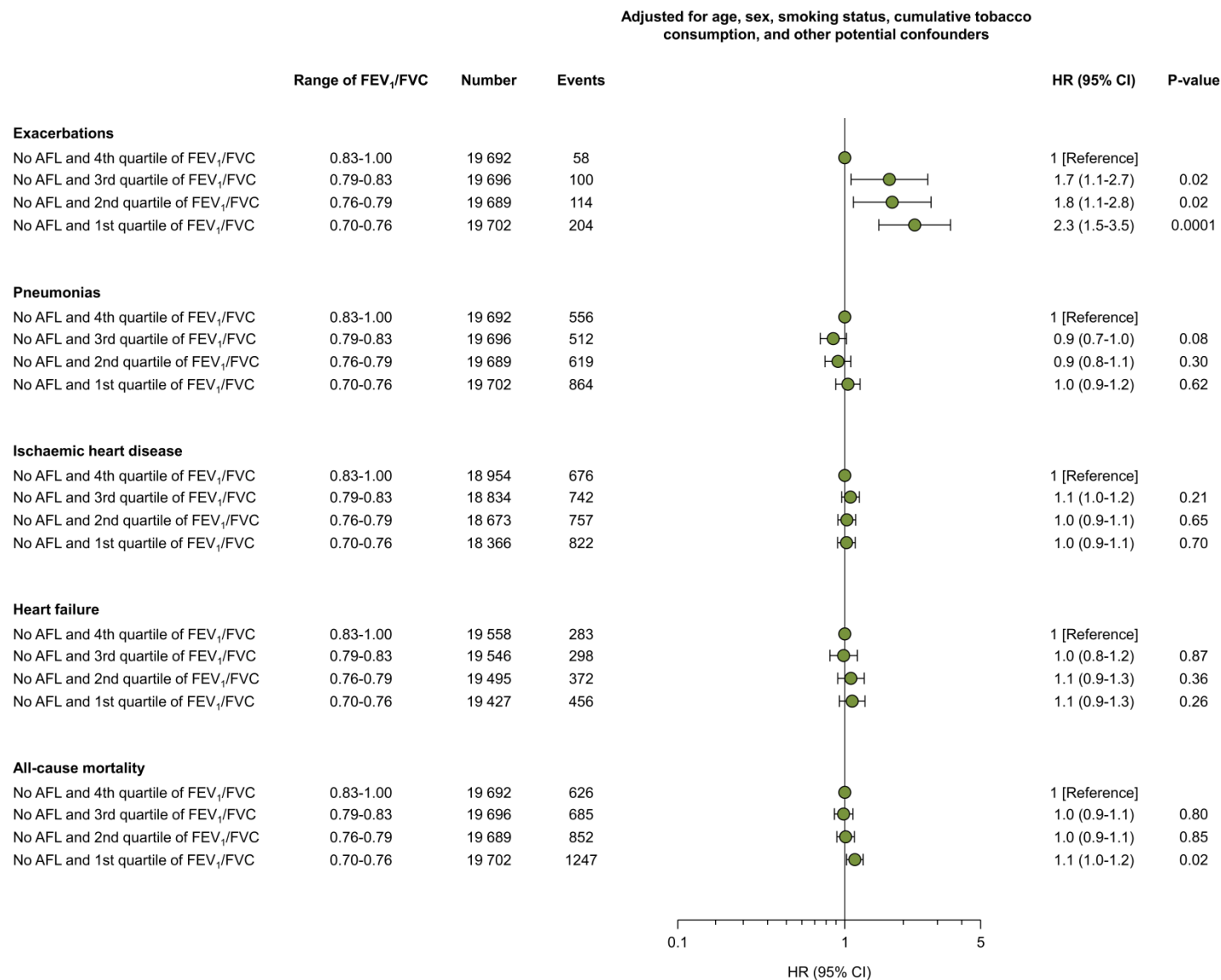


**Figure S1. Prognosis according to different criteria for airflow limitation with adjustment for other potential confounders.** Risk of exacerbations and pneumonias was assessed using multiple failure-time analysis; otherwise, a single failure-time analysis was used. P-values obtained from Wald test. Other potential confounders for exacerbations and pneumonias included use of airway medication, asthma, allergy, body mass index, familial predisposition for asthma, childhood asthma, hay fever, or eczema, occupational exposure to dust/fumes, daily exposure to passive smoking, physical activity, and socioeconomic status. Other potential confounders for ischaemic heart disease and heart failure included diabetes, body mass index, systolic and diastolic blood pressure, plasma cholesterol, plasma triglycerides, alcohol consumption, use of cholesterol lowering medication, physical activity, and socioeconomic status. Other potential confounders for all-cause mortality included all of the mentioned. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second ( $FEV_1$ )/forced vital capacity (FVC)  $\geq 0.70$  and  $FEV_1/FVC \geq$  lower limit of normal (LLN), potentially underdiagnosed AFL was defined as  $FEV_1/FVC \geq 0.70$  and  $FEV_1/FVC < LLN$ , potentially overdiagnosed AFL was defined as  $FEV_1/FVC < 0.70$  and  $FEV_1/FVC \geq LLN$ , and AFL was defined as  $FEV_1/FVC < 0.70$  and  $FEV_1/FVC < LLN$ . CI = confidence interval. HR = hazard ratio.





**Figure S2. Prognosis according to different criteria for airflow limitation and presence of symptoms.** Risk of exacerbations and pneumonias was assessed using multiple failure-time analysis; otherwise, a single failure-time analysis was used. P-values obtained from Wald test. Presence of symptoms was defined as at least one of the following respiratory symptoms: chronic mucus hypersecretion, dyspnoea, wheezing, or cough. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second ( $FEV_1$ )/forced vital capacity (FVC)  $\geq 0.70$  and  $FEV_1/FVC \geq$  lower limit of normal (LLN), potentially underdiagnosed AFL was defined as  $FEV_1/FVC \geq 0.70$  and  $FEV_1/FVC < LLN$ , potentially overdiagnosed AFL was defined as  $FEV_1/FVC < 0.70$  and  $FEV_1/FVC \geq LLN$ , and AFL was defined as  $FEV_1/FVC < 0.70$  and  $FEV_1/FVC < LLN$ . CI = confidence interval. HR = hazard ratio.



**Figure S3. Prognosis of individuals without airflow limitation according to quartiles of FEV<sub>1</sub>/FVC.** Risk of exacerbations and pneumonias was assessed using multiple failure-time analysis; otherwise, a single failure-time analysis was used. P-values obtained from Wald test. Other potential confounders for exacerbations and pneumonias included use of airway medication, asthma, allergy, body mass index, familial predisposition for asthma, childhood asthma, hay fever, or eczema, occupational exposure to dust/fumes, daily exposure to passive smoking, physical activity, and socioeconomic status. Other potential confounders for ischaemic heart disease and heart failure included diabetes, body mass index, systolic and diastolic blood pressure, plasma cholesterol, plasma triglycerides, alcohol consumption, use of cholesterol lowering medication, physical activity, and socioeconomic status. Other potential confounders for all-cause mortality included all of the mentioned. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC)  $\geq 0.70$  and FEV<sub>1</sub>/FVC  $\geq$  lower limit of normal (LLN). CI = confidence interval. HR = hazard ratio.