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Early View

Original article

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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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Key words: airway obstruction, forced expiratory volume, spirometry, pneumonia, heart failure, mortality.

Take home message: Poor prognosis in young and middle-aged adults with airflow limitation according to LLN but not fixed ratio.

Abstract

A presumed consequence of using a fixed ratio for the definition of airflow limitation (AFL) has been overdiagnosis among older and underdiagnosis among younger individuals. However, the prognosis of younger individuals with potentially underdiagnosed airflow limitation is poorly described. We hypothesized that potential underdiagnosis of AFL at younger age is associated with poor prognosis.

We assigned 95 288 participants aged 20-100years from the Copenhagen General Population Study into: individuals without AFL with forced expiratory volume in 1second (FEV_1)/forced vital capacity (FVC)≥0.70 and ≥lower limit of normal (LLN) (n=78 779,83%); individuals with potentially underdiagnosed AFL with FEV_1/FVC≥0.70 and <LLN (n=1056,1%); individuals with potentially overdiagnosed AFL with FEV_1/FVC<0.70 and ≥LLN (n=3088,3%); and individuals with AFL with FEV_1/FVC<0.70 and <LLN (n=12 365,13%). We assessed risk of exacerbations, pneumonias, ischaemic heart disease, heart failure, and all-cause mortality. Median follow-up was 6.0years (range:2days-11years).

Compared to individuals without AFL, individuals with potentially underdiagnosed AFL had an increased risk of morbidity and mortality with age and sex adjusted hazard ratios of 2.7(95% CI:1.7-4.5) for pneumonias, 2.3(1.2-4.5) for heart failure, and 3.1(2.1-4.6) for all-cause mortality.

Young and middle-aged adults with AFL according to LLN but not fixed ratio experience increased respiratory and cardiovascular morbidity and early death.

Introduction

Underdiagnosis of chronic obstructive pulmonary disease (COPD) is substantial and associated with poor prognosis, also among asymptomatic individuals[1]. Yet, presence of airflow limitation with a low ratio of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) can be easily determined using spirometry[2,3]. Although spirometry use is not recommended for screening of asymptomatic adults, it is encouraged for clinicians to pursue active case-finding in high-risk populations to detect COPD early before severe airflow limitation develops[4]. However, the appropriate definition of airflow limitation is heatedly debated. On the one hand, the use of a fixed ratio, i.e. $FEV_1/FVC < 0.70$, is a simple approach in a busy daily clinical setting[2,3]; on the other hand, the fixed ratio does not account for the normal age-dependent decline in lung function, which leads to a lower ratio of FEV_1/FVC with increasing age[5]. Thus, a presumed consequence of using a fixed ratio would be overdiagnosis among older and underdiagnosis among younger individuals[5,6], especially the latter situation is worrisome, as it may hamper smoking cessation advice and initiation of early treatment. Instead of the fixed ratio, it has been recommended to use the lower 5^{th} percentile of the predicted value for FEV_1/FVC, i.e. $FEV_1/FVC <$ lower limit of normal (LLN), as such an approach will not be prone to an age-dependent variation in lung function and will also be able to account for other biological differences such as gender and race[7,8]. Previous studies have mainly focused on the prognosis of older individuals with potentially overdiagnosed airflow limitation ($FEV_1/FVC < 0.70$ and $\geq$LLN). However, the prognosis of younger individuals with potentially underdiagnosed airflow limitation ($FEV_1/FVC \geq 0.70$ and <LLN) is poorly described.

In the present study, we investigated the prognosis of potentially underdiagnosed airflow limitation in younger individuals from the general population, as defined by the LLN but not the fixed ratio. We hypothesized that potential underdiagnosis of airflow limitation at younger age is associated with poor prognosis. For this purpose, we used the Copenhagen General Population Study including 95 288 randomly selected individuals aged 20-100 years.

Methods

Study design and participants

We recruited 95 288 individuals aged 20-100 years from the Copenhagen General Population Study, a Danish population-based prospective cohort study initiated in November 26, 2003 with ongoing enrolment[1]. In the present study, we had information until July 10, 2013. In Denmark, all individuals are assigned a unique identification number at birth or immigration and recorded in the National Danish Civil Registration System. Based on age and sex, individuals living in the Capital Region of Denmark were randomly selected from the National Danish Civil Registration System to reflect the adult white Danish population of Danish descent by using the unique identification number. Response-rate was approximately 45%. All participants completed a comprehensive questionnaire, underwent a physical health examination, and provided blood for biochemical analyses. Questionnaires were reviewed at the day of attendance by a healthcare professional together with the participant. The study was approved by Herlev and Gentofte Hospital and the regional ethics committee (H-KF-01-144/01) and conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Formation of the clinical groups

Lung function was determined using spirometry with pre-bronchodilator measurements of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Spirometry use in the Copenhagen General Population Study has undergone a rigorous validation process before[9]. Predicted values were calculated using internally derived reference values based on a subsample of 11 288 healthy asymptomatic never-smoking individuals with age and height as covariates separately for men and women[9]. Detailed description of spirometry procedure and questions used to assess characteristics can be found in the Supplement. The lower limit of normal (LLN), defined as the bottom 5^{th} percentile of the predicted value for FEV_1/FVC, was calculated as the mean value minus 1.645 standard deviations. According to different criteria for airflow limitation, individuals were assigned into one of four exclusive subgroups (Figure 1):

1) No airflow limitation: individuals with $FEV_1/FVC \geq 0.70$ and ≥LLN.
2) Potentially underdiagnosed airflow limitation: individuals with $FEV_1/FVC \geq 0.70$ but <LLN.
3) Potentially overdiagnosed airflow limitation: individuals with $FEV_1/FVC < 0.70$ but ≥LLN.
4) Airflow limitation: individuals with $FEV_1/FVC < 0.70$ and <LLN.

Outcomes

Severe exacerbations of obstructive lung disease, i.e. either COPD or asthma related, (International Classification of Diseases [ICD]-8:491-493 and ICD-10:J41-J46) and pneumonias (ICD-8:480-486 and ICD-10:J12-J18) were defined as acute emergency department visits or

hospital admissions with the mentioned primary diagnosis. Ischaemic heart disease (ICD-8:410-414 and ICD-10:I20-I25) and heart failure (ICD-8:427.09-427.11 and ICD-10:I50) were defined as inpatient and outpatient hospital contacts with the mentioned primary or secondary diagnosis. Information was obtained from the National Danish Patient Registry, which covers all public and private Danish hospitals, recorded until November 10, 2014. Denmark used the ICD-8 until January 1, 1994, and proceeded directly to ICD-10 after this date. Information on vital status was obtained from the National Danish Civil Registration System, recorded until November 14, 2014. As follow-up was done using the above register linkage based on the unique identification number provided to everyone at birth or immigration, no person was lost to follow-up, and individuals who emigrated were censored at the date of emigration (n=376). All diagnoses recorded in the registries are made by a medical doctor according to national law.

Statistical analyses

Wilcoxon rank-sum and Pearson $\chi 2$ tests were used for comparisons. Since age differed substantially between the clinical groups, we have used logistic- and linear regression models to account for this in the clinical attributes; however, unadjusted differences are also provided. Kernel density estimation was used to illustrate the age distribution within the clinical groups. Cox proportional hazard models were used to determine the prognosis. For exacerbations and pneumonias, we carried out multiple failure-time analysis using the Andersen-Gill approach, meaning that individuals were at risk of recurrent events. Otherwise, an approach with single failure-time analysis was used. We used analyses with left truncation and age as the underlying timescale. Due to the findings with regard to pneumonia and heart failure, we also carried out competing risk analysis using the methods proposed by Fine and Gray with the competing event

being all-cause mortality. Since an approach with multiple failure-time analysis does not work using Fine and Gray, we instead used an approach with single failure-time analysis. Kaplan-Meier analysis was used for all-cause mortality. Area-proportional Venn diagrams were also created[10]. In the sensitivity analyses, we included other outcome related potential confounders, stratified according to presence of relevant symptomatology (i.e. chronic mucus hypersecretion, dyspnoea, wheezing, and/or cough), and restricted the analyses to individuals without airflow limitation according to quartiles of FEV_1/FVC. Detailed description of questions used to assess potential confounders and symptoms can be found in the Supplement. All analyses were performed using STATA/SE 13.1 for Windows (StataCorp, College Station, Texas, US) and a two-sided P-value <0.05 was considered as significant.

Results

Among 95 288 participants, 78 779 (83%) individuals did not have airflow limitation, 1056 (1%) individuals had potentially underdiagnosed airflow limitation, 3088 (3%) individuals had potentially overdiagnosed airflow limitation, and 12 365 (13%) individuals had airflow limitation (Figure 1). Among individuals with potentially underdiagnosed airflow limitation, 76% were aged 20-50 years, whereas this fraction was 33% among individuals without airflow limitation (Figure 2). Individuals with potentially underdiagnosed airflow limitation constituted 3% among younger individuals aged 20-50 years and <0.5% among older individuals aged 50-100 years. Median follow-up was 6.0 years (range: 2 days to 11 years). During this period, we observed 2073 severe exacerbations of obstructive lung disease, 4487 pneumonias, 3859 ischaemic heart disease events, 2046 heart failures, and 5260 deaths. Since the main purpose was to investigate individuals with potentially underdiagnosed airflow limitation, the analyses including individuals

with potentially overdiagnosed airflow limitation and individuals with airflow limitation are provided in the Supplement.

Compared to individuals without airflow limitation, individuals with potentially underdiagnosed airflow limitation were younger with a median age of 45 versus 56 years and more often current smokers with a prevalence of 28 versus 15% (Table 1); however, the difference in cumulative tobacco consumption was small (16 versus 14 pack-years). After taking age and sex into account and compared to individuals without airflow limitation, individuals with potentially underdiagnosed airflow limitation had a higher prevalence of asthma (10 versus 5.2%), respiratory symptoms (54 versus 40%), and airway medication use (8.6 versus 4.2%) (Table 2). Furthermore, 80% had a mild form of airflow limitation with FEV_1 % predicted $\geq$80%. Only minor differences could be observed in concentrations of inflammatory biomarkers in blood and previous utilization of healthcare compared to individuals without airflow limitation. Results were similar without adjustment (Table S1).

Individuals with potentially underdiagnosed airflow limitation had an increased risk of pneumonias, heart failure, and all-cause mortality but not of exacerbations of obstructive lung disease or ischaemic heart disease compared to individuals without airflow limitation (Figures 3 and S1). Age and sex adjusted hazard ratios (HRs) were 2.7 (95% confidence interval [CI]: 1.7-4.5) for pneumonias, 2.3 (1.2-4.5) for heart failure, and 3.1 (2.1-4.6) for all-cause mortality (Figure 3, left panels). After additional adjustment for smoking status and cumulative tobacco consumption, the risk estimates were similar (Figure 3, right panels). The increased risk of pneumonia and heart failure persisted in a competing risk analysis with the competing event being all-cause mortality (Figure 4). Only minor overlaps could be observed among individuals with potentially underdiagnosed airflow limitation experiencing pneumonia, heart failure, and/or

death (Figure 5). In sensitivity analyses, after additional adjustment for other potential confounders, risk estimates were similar (Tables S4 and S5 and Figure S1, right panels). Furthermore, after stratification according to presence of respiratory symptoms, risk estimates were slightly attenuated for asymptomatic individuals and were higher for symptomatic individuals (Figure S2). Lastly, among individuals without airflow limitation, those in the 1st quartile of FEV_1/FVC (range: 0.83-1.00) had an increased risk of exacerbations of obstructive lung disease and all-cause mortality but not of pneumonias, ischemic heart disease, or heart failure compared to those in the 4th quartile of FEV_1/FVC (0.70-0.76) (Figure S3); suggesting that even within the range of normal lung function, there seems to be an association of lower lung function with poor prognosis.

Individuals with potentially overdiagnosed airflow limitation had an increased risk of exacerbations and pneumonias but not of ischaemic heart disease, heart failure, or all-cause mortality compared to individuals without airflow limitation despite adjustment for potential confounders (Figure S1). Age and sex adjusted HRs were 2.6 (95% CI: 1.8-3.8) for exacerbations and 1.5 (1.3-1.8) for pneumonias (Figure S1, left panels). After stratification according to presence of respiratory symptoms, risk estimates were slightly attenuated for asymptomatic individuals and higher for symptomatic individuals (Figure S2). In addition, symptomatic individuals also had an increased risk of ischaemic heart disease, heart failure, and all-cause mortality.

Discussion

In a large sample from the general population, we found that younger individuals with airflow limitation defined using the LLN criterion but not the fixed ratio criterion had a 2.7-fold risk of pneumonias, a 2.3-fold risk of heart failure, and a 3.1-fold risk of all-cause mortality.

Only 12% of individuals with potentially underdiagnosed airflow limitation reported to have asthma. During follow-up, these individuals did not have an increased risk of COPD or asthma related exacerbations compared to individuals without airflow limitation. A likely explanation is that these non-asthmatic individuals may have underdeveloped lungs. Normal lung development is characterized by a rapid increase in lung function during childhood and peaks in adulthood around the ages of 20-25 years replaced by the plateau phase with preservation of maximally attained lung function for approximately 10 years before being subjected to a steady decline with increasing age; therefore, airflow limitation among these young individuals may be due to an insufficient peak of lung function in adulthood[11-14]. Underdeveloped lungs with low maximally attained lung function in young adulthood is a risk factor for respiratory disease in older age and can even through normal lung function decline lead to development of COPD later in life[15].

Alternatively, individuals with potentially underdiagnosed airflow limitation may be a mixed clinical group not only consisting of those with presence of or predisposition to develop respiratory disease but also those with heart disease, as these individuals during follow-up also displayed an increased risk of heart failure compared to individuals without airflow limitation. Heart failure has long been associated with airflow limitation and it can often be a diagnostic challenge among patients with respiratory disease[16-18]. Thus, by using LLN among young individuals, we may perhaps not only identify those with increased risk of future respiratory

disease but also future heart disease. Furthermore, among individuals experiencing an event with pneumonia, heart failure, and/or death during follow-up, the Venn diagram only showed relatively limited overlap, which clearly indicates heterogeneity in outcome and suggests that different disease entities may be at play as the cause of poor prognosis.

Previous studies have mainly focused on older individuals with potentially overdiagnosed airflow limitation and not on younger individuals with potentially underdiagnosed airflow limitation. Overall, individuals with airflow limitation according to the LLN but not the fixed ratio seem to be a group with an increased risk of future disease[19-22]. In the European Community Respiratory Health Survey, these individuals had an increased risk of developing FEV_1 predicted <80% and hospital service utilization due to breathing problems after 9 years of follow-up[20]. In the third National Health and Nutrition Examination Survey, the same clinical group had the highest risk estimate of 4.0 with regard to risk of all-cause mortality during up to 18 years of follow-up; however, the group only comprised 20 individuals and statistical significance was not achieved[21]. In the Lung Health Study, there was not an overall difference in annual exacerbation rate compared to those without airflow limitation over a 5 year of annual follow-up; however, in the last year of follow-up, a noticeable increase could be observed, perhaps indicating development or progression of early COPD[19]. Furthermore, in the same cohort, there was no difference in decline of lung function[19], suggesting absence of accelerated lung function decline, which usually characterizes COPD[23].

Individuals with airflow limitation according to the fixed ratio but not the LLN have mostly been observed with an increased risk of COPD related exacerbations and all-cause mortality in previous studies[19,21,24,25]. In the present study, we found an increased risk of exacerbations of obstructive lung disease but not of all-cause mortality. These individuals seem to have clinical

findings compatible with COPD[19,25-28], and using the fixed ratio compared to the LLN among older individuals also seems to correlate better with the clinical diagnosis and prognosis of COPD[29]. Thus, based on previous studies and taken together with the present findings, it seems that these individuals may have undiagnosed COPD.

Strengths of the present study include a large sample randomly selected from the general population with information on spirometry and a long and complete follow-up time with clinically relevant outcomes. Furthermore, we had a large number of individuals with discrepant definition of airflow limitation according to the LLN and the fixed ratio.

A major limitation of our study is the lack of post-bronchodilator measurements preventing us from classifying the type of airflow limitation. Thus, some may have reversible form of airflow limitation indicating asthma and some may have irreversible form of airflow limitation indicating COPD or asthma-COPD overlap. However, it was very clear that individuals with potentially under- and overdiagnosed airflow limitation in the present study had an increased risk of respiratory outcomes, and the possible misclassification due to lack of post-bronchodilator measurements would only tend to attenuate our findings rather than exaggerate them. Another limitation is that the results may not be transferable to other ethnicities besides white European ancestry.

In conclusion, defining airflow limitation according to the LLN instead of the fixed ratio at younger age seems to identify individuals with an increased risk of respiratory and cardiovascular morbidity and early death. Clinicians regularly doing spirometry in younger individuals should apply LLN for the diagnosis of airflow limitation, assuming focus is on identifying a vulnerable population with subsequent high morbidity and mortality.

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Contributors: YÇ and PL had full access to all of the data in the study and had final responsibility for the decision to submit for publication. YÇ, SA, BGN, JV, and PL contributed to the study concept and design. YÇ, SA, BGN, JV, and PL collected, analysed, or interpreted the data. YÇ wrote the draft manuscript. YÇ, SA, BGN, JV, and PL revised the manuscript for important intellectual content. YÇ did the statistical analyses. BGN and PL obtained funding. BGN provided administrative, technical, or material support. PL supervised the study.

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TABLE 1 Baseline characteristics of 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
Age – years	56 (47-66)	64 (55-72)	45 (41-50)	<0.0001	<0.0001	73 (67-80)	<0.0001	<0.0001
Men – no. (%)	35 037 (44)	6182 (50)	434 (41)	0.03	<0.0001	1230 (40)	<0.0001	<0.0001
FEV_1 predicted – %	98 (89-108)	80 (66-91)	90 (82-98)	<0.0001	<0.0001	91 (80-102)	<0.0001	<0.0001
FVC predicted – %	99 (90-108)	99 (85-11)	104 (94-112)	<0.0001	<0.0001	101 (88-113)	<0.0001	<0.0001
FEV_1/FVC – %	79 (76-83)	64 (60-67)	71 (70-72)	<0.0001	<0.0001	69 (68-70)	<0.0001	<0.0001
Smoking status								
Never-smokers – no. (%)	36 152 (46)	2988 (24)	416 (39)	<0.0001	<0.0001	1034 (33)	<0.0001	<0.0001
Formers smokers – no. (%)	30 584 (39)	5500 (44)	345 (33)	<0.0001	<0.0001	1518 (49)	<0.0001	<0.0001
Current smokers – no. (%)	12 007 (15)	3863 (31)	294 (28)	<0.0001	0.02	533 (17)	0.002	<0.0001
Cumulative tobacco consumption* – pack-years	14 (5-27)	27 (14-42)	16 (6-28)	0.04	<0.0001	21 (9-37)	<0.0001	<0.0001

Data presented as median (25th and 75th percentiles) or number (%). P values obtained from Wilcoxon rank-sum test or Pearson χ^2 test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN.
*Only calculated for former and current smokers.

TABLE 2 Age- and sex adjusted 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**
Use of airway medication (%)	4.2	17	8.6	<0.0001	<0.0001	6.4	<0.0001	<0.0001
Asthma (%)	5.2	18	10	<0.0001	<0.0001	8.0	<0.0001	<0.0001
Allergy (%)	27	31	28	0.40	0.08	28	0.43	0.004
Symptoms								
Chronic mucus hypersecretion (%)	7.4	17	14	<0.0001	0.06	9.4	<0.0001	<0.0001
Dyspnoea (%)	30	44	39	<0.0001	0.004	33	0.001	<0.0001
mMRC ≥2 (%)	7.1	14	10	0.003	0.02	8.0	0.02	<0.0001
Night-time dyspnoea (%)	3.2	6.0	5.3	0.0002	0.37	3.6	0.28	<0.0001
Wheezing (%)	14	33	24	<0.0001	<0.0001	20	<0.0001	<0.0001
Cough (%)	11	22	18	<0.0001	0.0003	13	<0.0001	<0.0001
Any symptom (%)	40	59	54	<0.0001	0.001	46	<0.0001	<0.0001
Degree of airflow limitation*								
FEV_1 % predicted ≥80 (%)	97	50	80	<0.0001	<0.0001	74	<0.0001	<0.0001
FEV_1 % predicted 50-79 (%)	8.8	42	20	<0.0001	<0.0001	25	<0.0001	<0.0001
FEV_1 % predicted 30-49 (%)	0.1	7.5	0.3	0.15	<0.0001	0.6	<0.0001	<0.0001
FEV_1 % predicted <30 (%)	0.1	1.0	0	0.70	0.001	0	0.51	<0.0001
Concentrations of inflammatory biomarkers in blood								

C-reactive protein (mg/L)	2.4	2.8	2.5	0.32	0.05	2.3	0.28	<0.0001
Fibrinogen (µmol/L)	11.0	11.2	11.1	0.32	0.08	10.9	0.005	<0.0001
Leucocytes (x 10^9/L)	7.2	7.6	7.6	<0.0001	0.71	7.3	0.08	<0.0001
Neutrophils (x 10^9/L)	4.2	4.5	4.5	<0.0001	0.82	4.3	0.02	<0.0001
Eosinophils (x 10^9/L)	0.19	0.21	0.21	0.001	0.26	0.20	0.0002	0.001
Number of acute bronchitis or pneumonia episodes in the last 10 years								
None (%)	79	67	73	<0.0001	<0.0001	73	<0.0001	<0.0001
1-5 (%)	20	28	25	0.0002	0.02	25	<0.0001	0.001
≥6 (%)	1.4	4.9	2.2	0.09	0.0002	1.7	0.34	<0.0001
Number of visits to the GPs office in the last 12 months								
None (%)	21	19	20	0.25	0.31	20	0.21	0.07
Once (%)	23	21	21	0.26	0.64	20	0.01	0.88
Twice or more (%)	56	61	59	0.05	0.32	59	0.009	0.06

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_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN. GP = general practitioner. mMRC = modified Medical Research Council dyspnoea scale.

*Since FEV_1 % predicted is already age- and sex adjusted, no further adjustment was performed. P values obtained from Pearson χ^2 test.

Figure legends

Figure 1. Definition of airflow limitation and differences between the lower limit of normal and the fixed ratio criteria.

Panel A: A theoretical depiction based on two different criteria for airflow limitation, the fixed ratio and the lower limit of normal (LLN). *Panel B:* Assignment of individuals from the Copenhagen General Population Study to different criteria for airflow limitation. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥LLN, potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN.

Figure 2. Age distribution within clinical groups of airflow limitation.

Age distribution illustrated using Kernel density estimation. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥LLN, potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN.

Figure 3. Prognosis of individuals with potentially underdiagnosed airflow limitation.

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. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN) and potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN. CI = confidence interval. HR = hazard ratio.

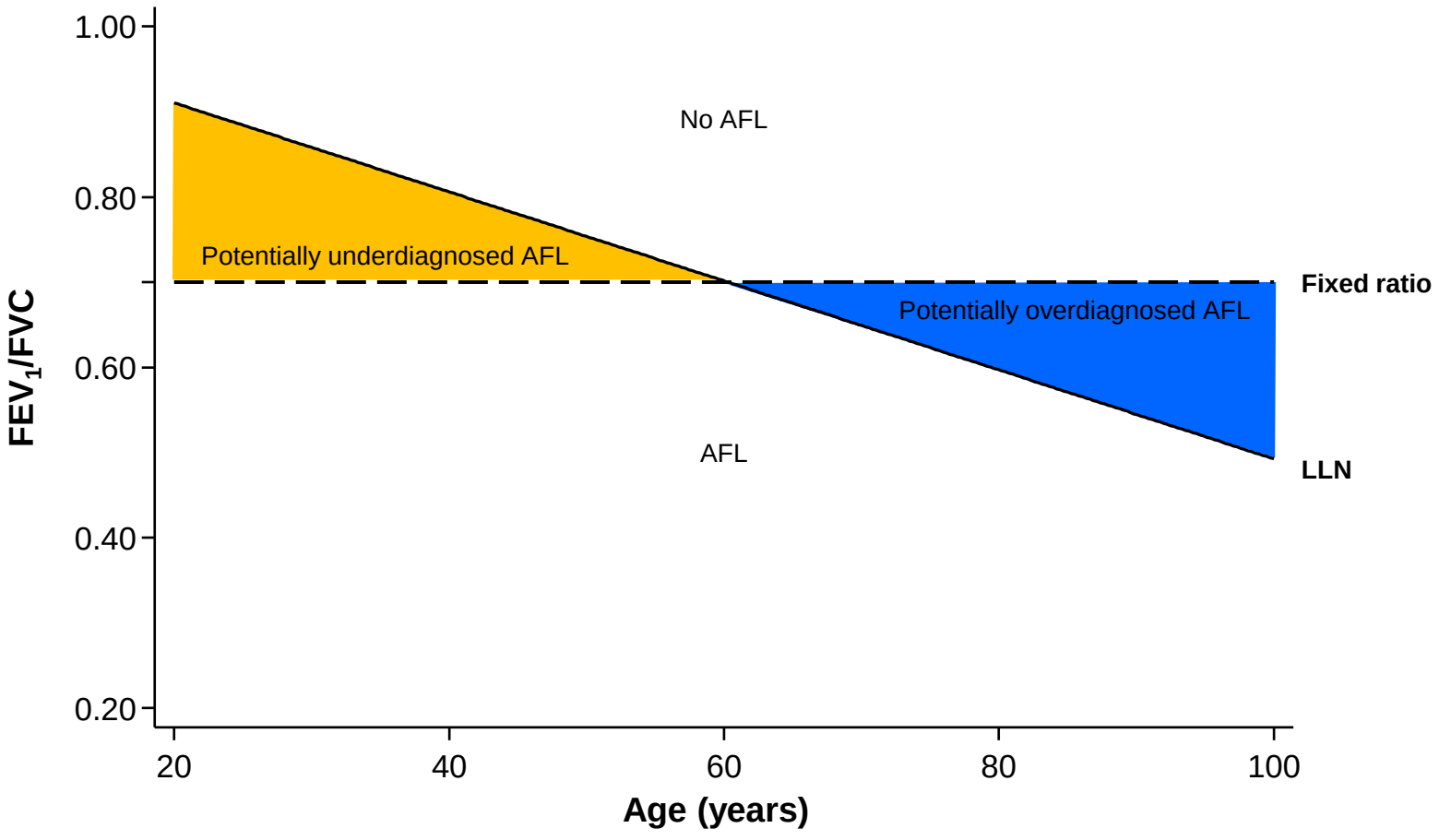
Figure 4. Competing risk analyses for pneumonia and heart failure and Kaplan-Meier analysis for all-cause mortality in individuals with potentially underdiagnosed airflow limitation.

All risk estimates were age and sex adjusted. Risk estimates for pneumonia and heart failure acquired from competing risk analyses using the methods proposed by Fine and Gray with the competing event being all-cause mortality. Risk estimates for all-cause mortality acquired from Cox proportional hazard models. Note that risk for pneumonia was assessed using single failure-time analysis and not multiple failure-time analysis. P-values obtained from Wald test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN) and potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN. CI = confidence interval. HR = hazard ratio. SHR = subhazard ratio.

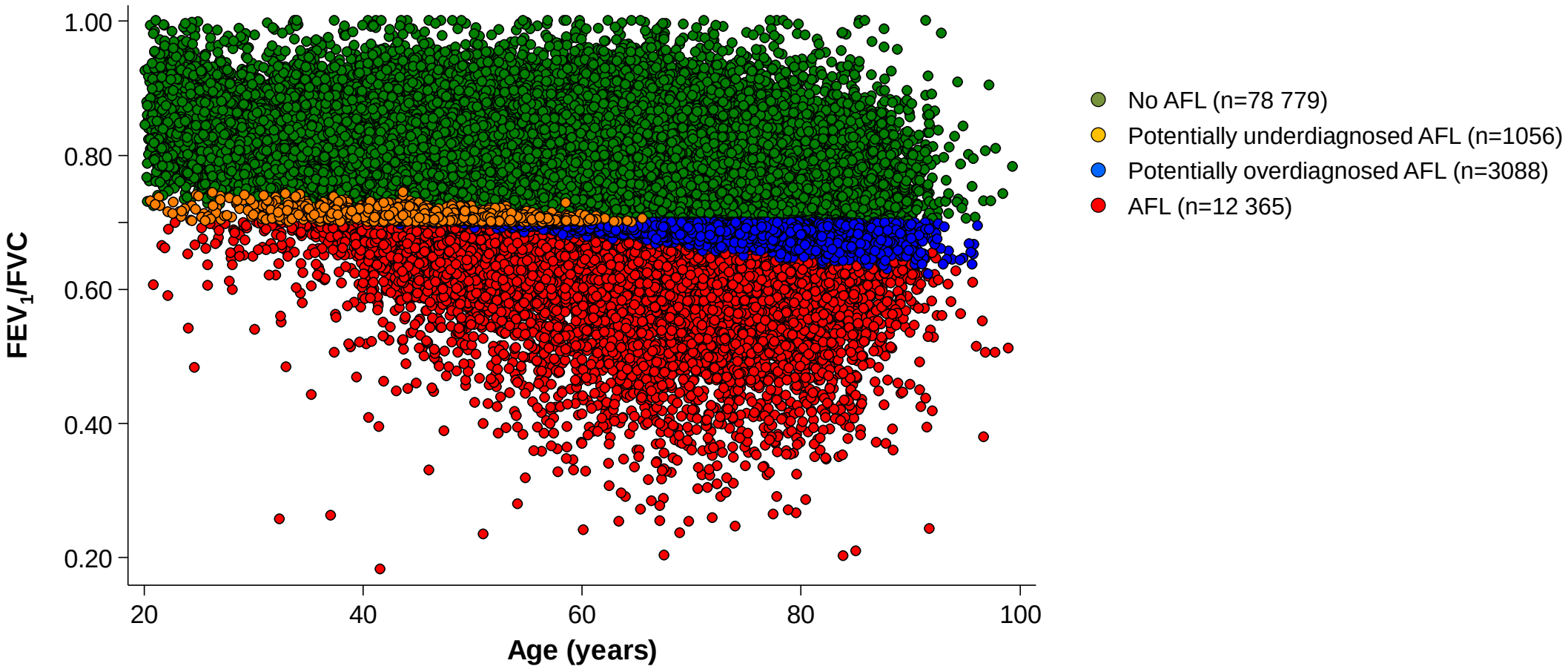
Figure 5. Area-proportional Venn diagrams of pneumonia, heart failure, and all-cause mortality in individuals with potentially underdiagnosed airflow limitation.

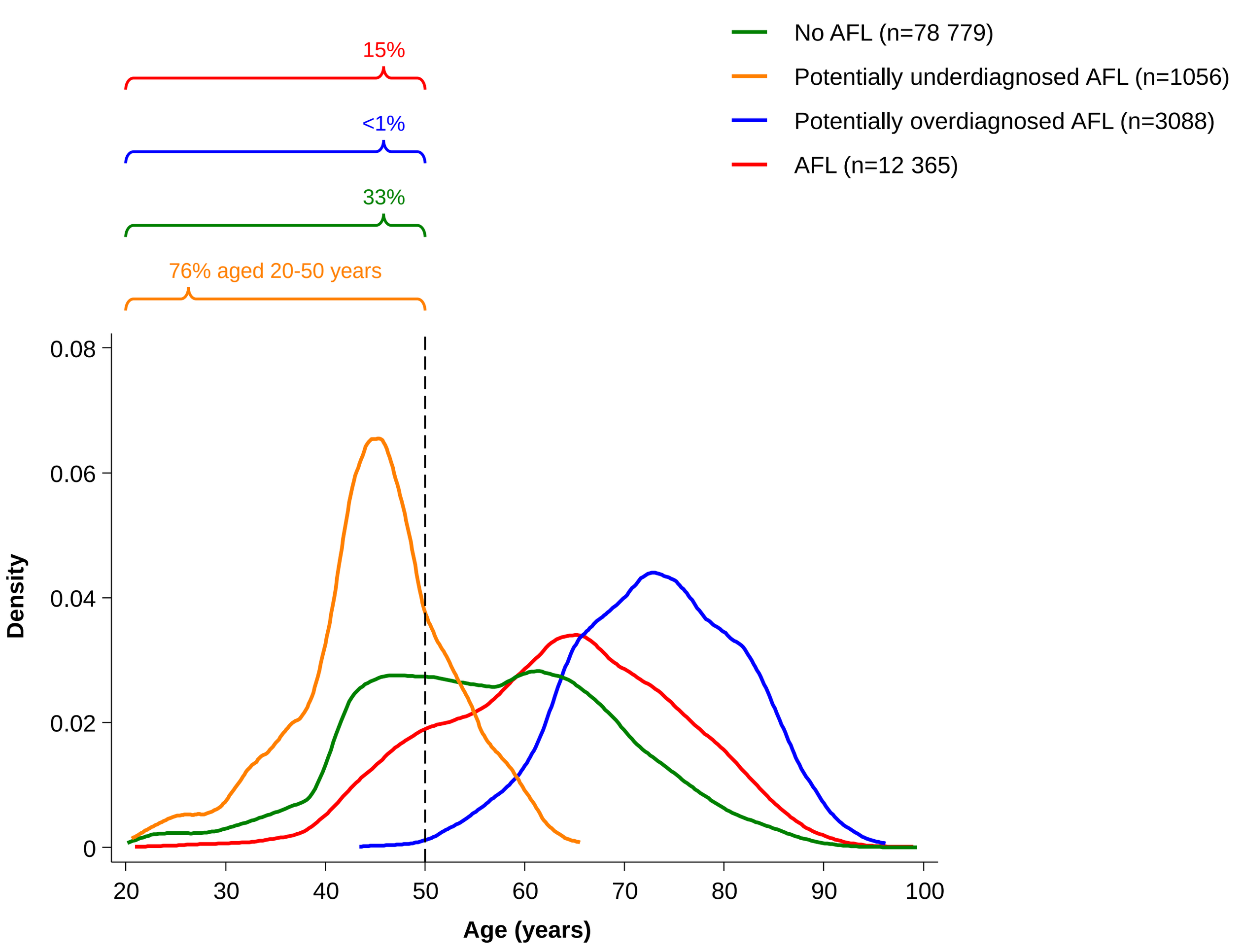
Potentially underdiagnosed airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC <lower limit of normal (LLN).

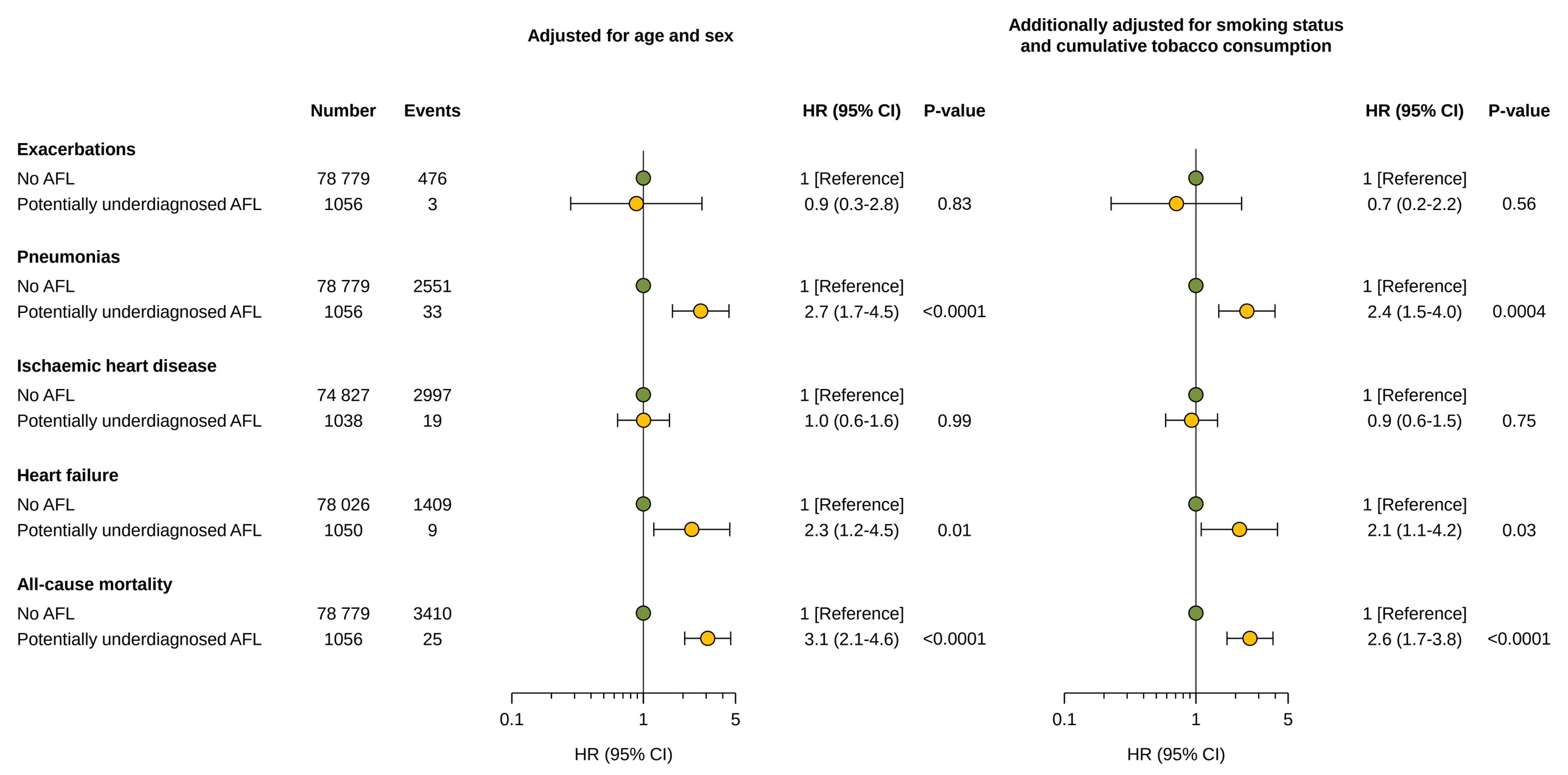
A


1.00
0.80
0.60
0.40
0.20
FEV1/FVC
No AFL
Potentially underdiagnosed AFL
Potentially overdiagnosed AFL
AFL
Fixed ratio
LLN
20
40
60
80
100
Age (years)

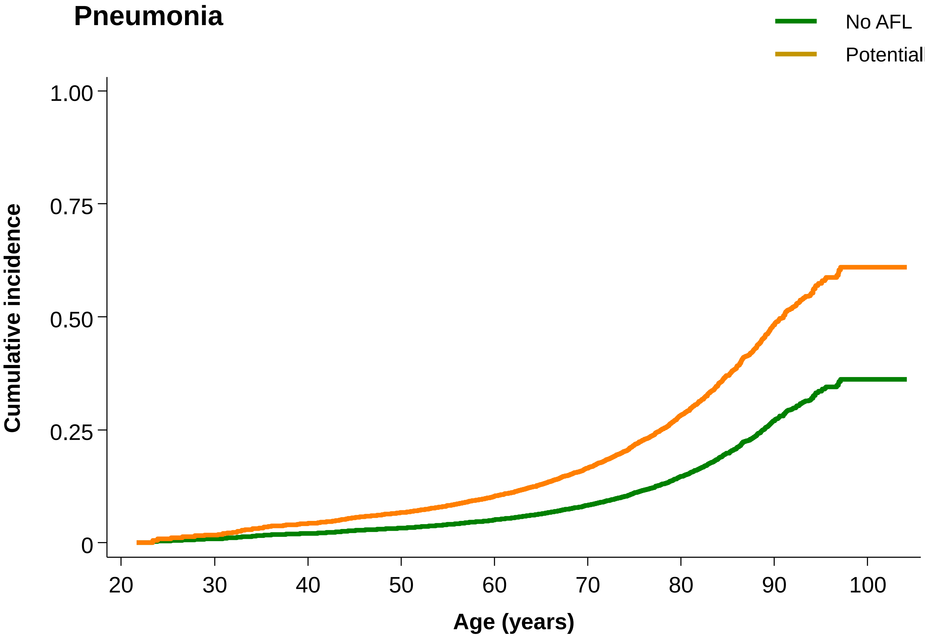
B


1.00
0.80
0.60
0.40
0.20
FEV1/FVC
20
40
60
80
100
Age (years)
No AFL (n=78 779)
Potentially underdiagnosed AFL (n=1056)
Potentially overdiagnosed AFL (n=3088)
AFL (n=12 365)


No AFL (n=78 779)
Potentially underdiagnosed AFL (n=1056)
Potentially overdiagnosed AFL (n=3088)
AFL (n=12 365)
15%
<1%
33%
76% aged 20-50 years
0.08
0.06
0.04
0.02
0
Density
20
30
40
50
60
70
80
90
100
Age (years)

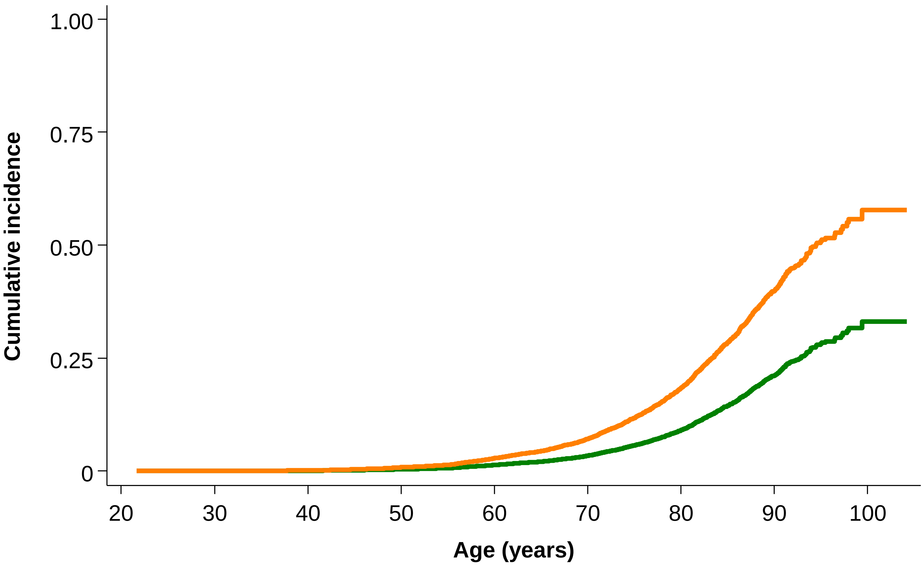

Adjusted for age and sex
Additionally adjusted for smoking status and cumulative tobacco consumption
Number
Events
HR (95% CI)
P-value
HR (95% CI)
P-value
Exacerbations
No AFL 78 779 476 1 [Reference] 1 [Reference]
Potentially underdiagnosed AFL 1056 3 0.9 (0.3-2.8) 0.83 0.7 (0.2-2.2) 0.56
Pneumonias
No AFL 78 779 2551 1 [Reference] 1 [Reference]
Potentially underdiagnosed AFL 1056 33 2.7 (1.7-4.5) <0.0001 2.4 (1.5-4.0) 0.0004
Ischaemic heart disease
No AFL 74 827 2997 1 [Reference] 1 [Reference]
Potentially underdiagnosed AFL 1038 19 1.0 (0.6-1.6) 0.99 0.9 (0.6-1.5) 0.75
Heart failure
No AFL 78 026 1409 1 [Reference] 1 [Reference]
Potentially underdiagnosed AFL 1050 9 2.3 (1.2-4.5) 0.01 2.1 (1.1-4.2) 0.03
All-cause mortality
No AFL 78 779 3410 1 [Reference] 1 [Reference]
Potentially underdiagnosed AFL 1056 25 3.1 (2.1-4.6) <0.0001 2.6 (1.7-3.8) <0.0001
0.1
1
5
HR (95% CI)
0.1
1
5
HR (95% CI)

Pneumonia



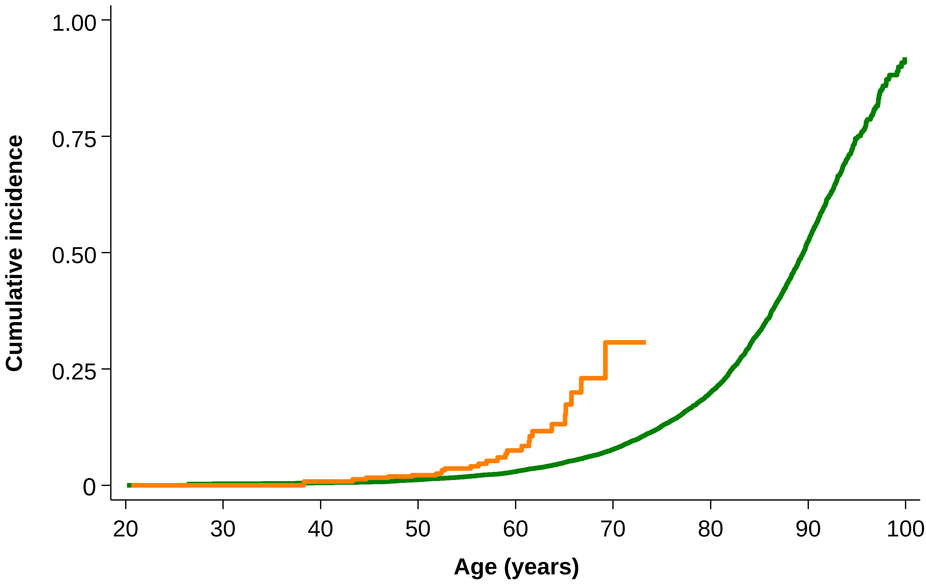
	Number	Events	SHR (95% CI)	P-value
No AFL	78 779	1877	1 [Reference]	
Potentially underdiagnosed AFL	1056	21	2.1 (1.3-3.2)	0.001

Heart failure



	Number	Events	SHR (95% CI)	P-value
No AFL	78 026	1409	1 [Reference]	
Potentially underdiagnosed AFL	1050	9	2.1 (1.1-4.2)	0.02

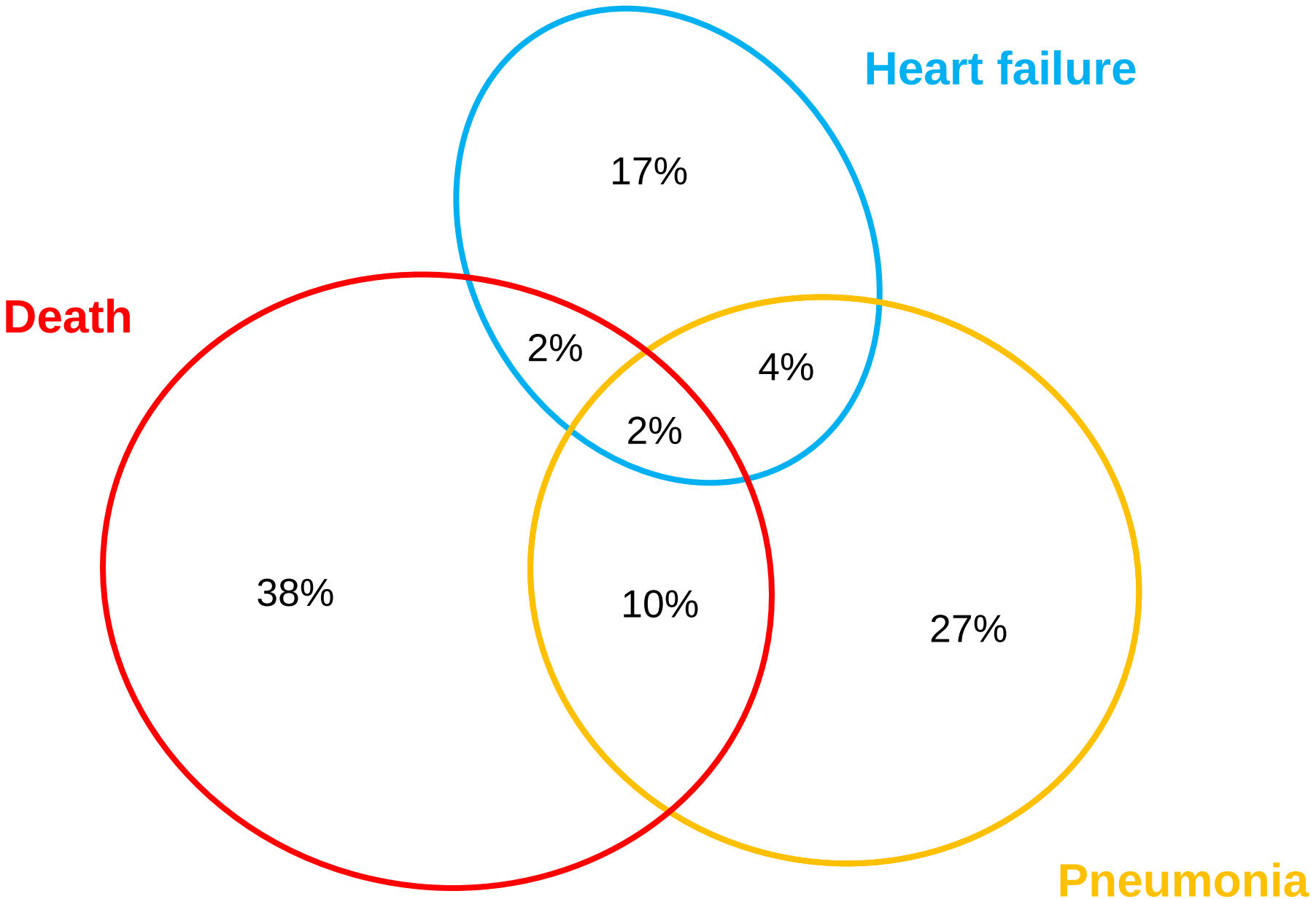
All-cause mortality



	Number	Events	HR (95% CI)	P-value
No AFL	78 779	3410	1 [Reference]	
Potentially underdiagnosed AFL	1056	25	3.1 (2.1-4.6)	<0.0001

Potentially underdiagnosed AFL

n=1056



Supplement

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_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 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 ≥ 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_1. 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^2). 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
Use of airway medication – no. (%)	3246 (4)	2154 (17)	83 (8)	<0.0001	<0.0001	224 (7)	<0.0001	<0.0001
Asthma – no. (%)	4157 (5)	2026 (16)	130 (12)	<0.0001	0.001	203 (7)	0.002	<0.0001
Allergy – no. (%)	22 016 (28)	3468 (28)	365 (35)	<0.0001	<0.0001	672 (22)	<0.0001	<0.0001
Symptoms								
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
Degree of airflow limitation								
FEV_1 % predicted ≥80 – no. (%)	71 763 (91)	6151 (50)	841 (80)	<0.0001	<0.0001	2292 (74)	<0.0001	<0.0001
FEV_1 % predicted 50-79 – no. (%)	6907 (9)	5167 (42)	212 (20)	<0.0001	<0.0001	777 (25)	<0.0001	<0.0001
FEV_1 % predicted 30-49 – no. (%)	98 (<1)	923 (7)	3 (<1)	0.15	<0.0001	19 (<1)	<0.0001	<0.0001
FEV_1 % predicted <30 – no. (%)	11 (<1)	124 (1)	0 (0)	0.70	0.001	0 (0)	0.51	<0.0001
Levels of inflammatory biomarkers								
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 10^9/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 10^9/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 10^9/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
Number of acute bronchitis or pneumonia episodes in the last 10 years								
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
Number of visits to the GPs office in the last 12 months								
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 χ^2 test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/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^2)	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_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/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
Body mass index – kg/m^2	26 (23-29)	25 (23-28)	25 (22-27)	<0.0001	0.0002	25 (23-28)	<0.0001	0.35
Familial predisposition for asthma – no. (%)	13 433 (17)	2696 (22)	275 (26)	<0.0001	0.001	437 (14)	<0.0001	<0.0001
Childhood asthma, hay fever, or eczema – no. (%)	10 714 (14)	1801 (15)	234 (22)	<0.0001	<0.0001	256 (8)	<0.0001	<0.0001
Occupational exposure to dust/fumes – no. (%)	7615 (10)	1816 (15)	114 (11)	0.22	0.001	269 (9)	0.08	<0.0001
Daily exposure to passive smoking – no. (%)	14 232 (18)	2175 (18)	242 (23)	<0.0001	<0.0001	336 (11)	<0.0001	<0.0001
Poor socioeconomic status – no. (%)	5102 (6)	1560 (13)	23 (2)	<0.0001	<0.0001	530 (17)	<0.0001	<0.0001
Alcohol – g/week	96 (48-180)	108 (48-204)	72 (30-144)	<0.0001	<0.0001	108 (48-192)	<0.0001	0.68
Diabetes – no. (%)	3156 (4)	661 (5)	14 (1)	<0.0001	<0.0001	182 (6)	<0.0001	0.23
Systolic blood pressure – mmHg	139 (125-154)	142 (129-158)	130 (120-142)	<0.0001	<0.0001	149 (135-162)	<0.0001	<0.0001
Diastolic blood pressure – mmHg	84 (76-91)	84 (76-91)	82 (75-89)	<0.0001	<0.0001	83 (76-90)	0.02	0.03
Physical inactivity – no. (%)	4695 (6)	1052 (9)	80 (8)	0.03	0.30	177 (6)	0.60	<0.0001
Use of cholesterol lowering medication – no. (%)	8516 (11)	2029 (16)	35 (3)	<0.0001	<0.0001	672 (22)	<0.0001	<0.0001
Plasma cholesterol – mmol/L	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
Plasma triglycerides – mmol/L	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 χ^2 test. No airflow limitation (AFL) was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN.

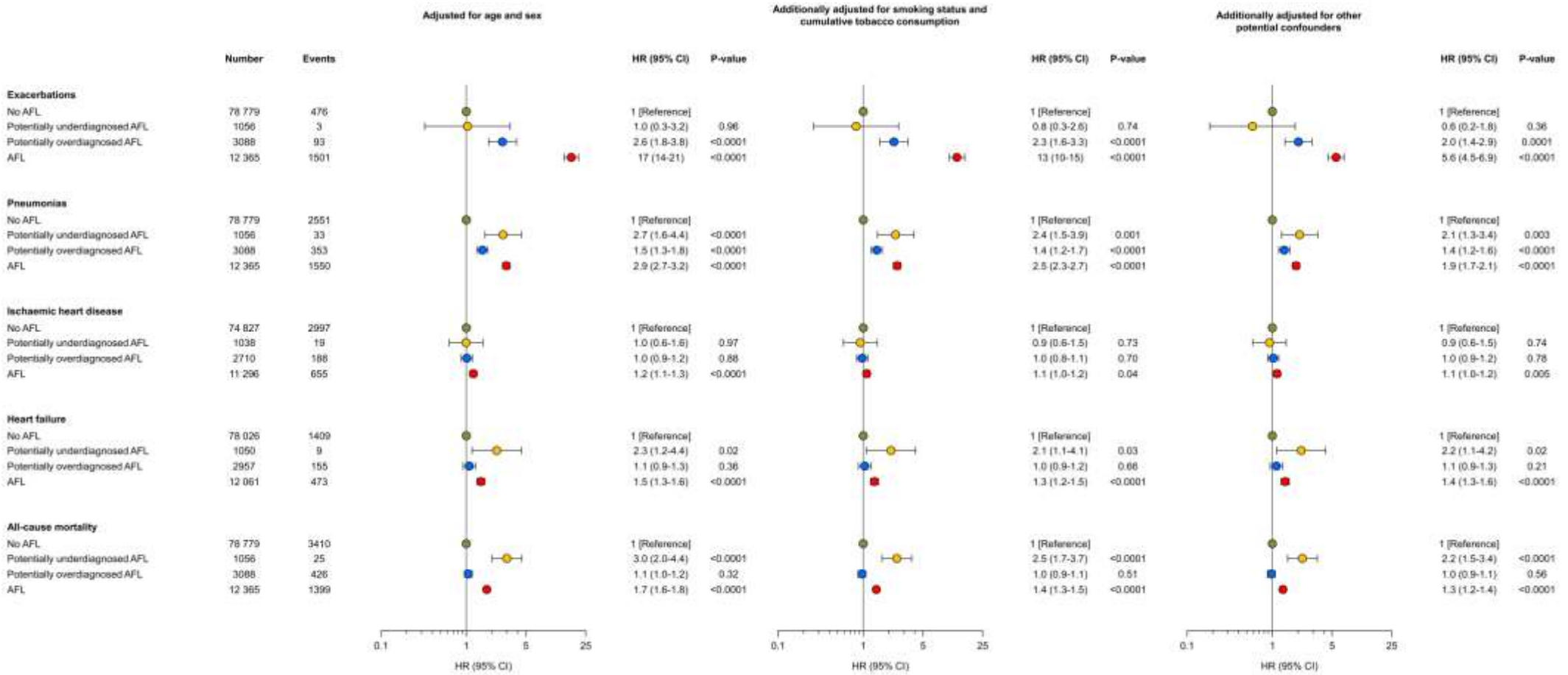


Figure S1. Prognosis according to different criteria for airflow limitation with adjustment for other potential confounders. Risk of exacerbations and pneumonias was assessed using multiple failure-time analysis; otherwise, a single failure-time analysis was used. P-values obtained from Wald test. Other 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) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN. CI = confidence interval. HR = hazard ratio.

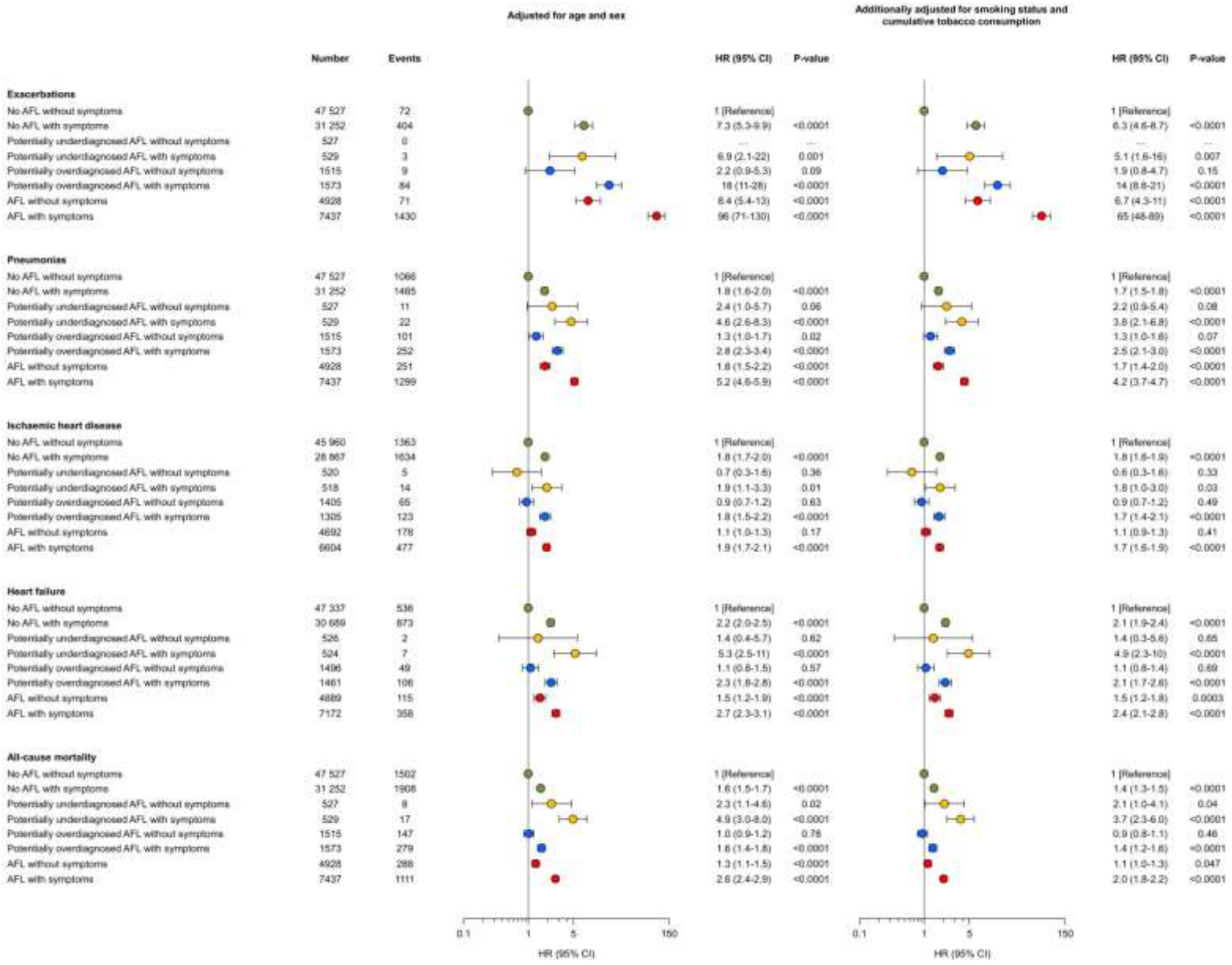


Figure S2. Prognosis according to different criteria for airflow limitation and presence of symptoms. Risk of exacerbations and pneumonias was assessed using multiple failure-time analysis; otherwise, a single failure-time analysis was used. P-values obtained from Wald test. Presence of symptoms was 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) ≥0.70 and FEV_1/FVC ≥lower limit of normal (LLN), potentially underdiagnosed AFL was defined as FEV_1/FVC ≥0.70 and FEV_1/FVC <LLN, potentially overdiagnosed AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC ≥LLN, and AFL was defined as FEV_1/FVC <0.70 and FEV_1/FVC <LLN. CI = confidence interval. HR = hazard ratio.

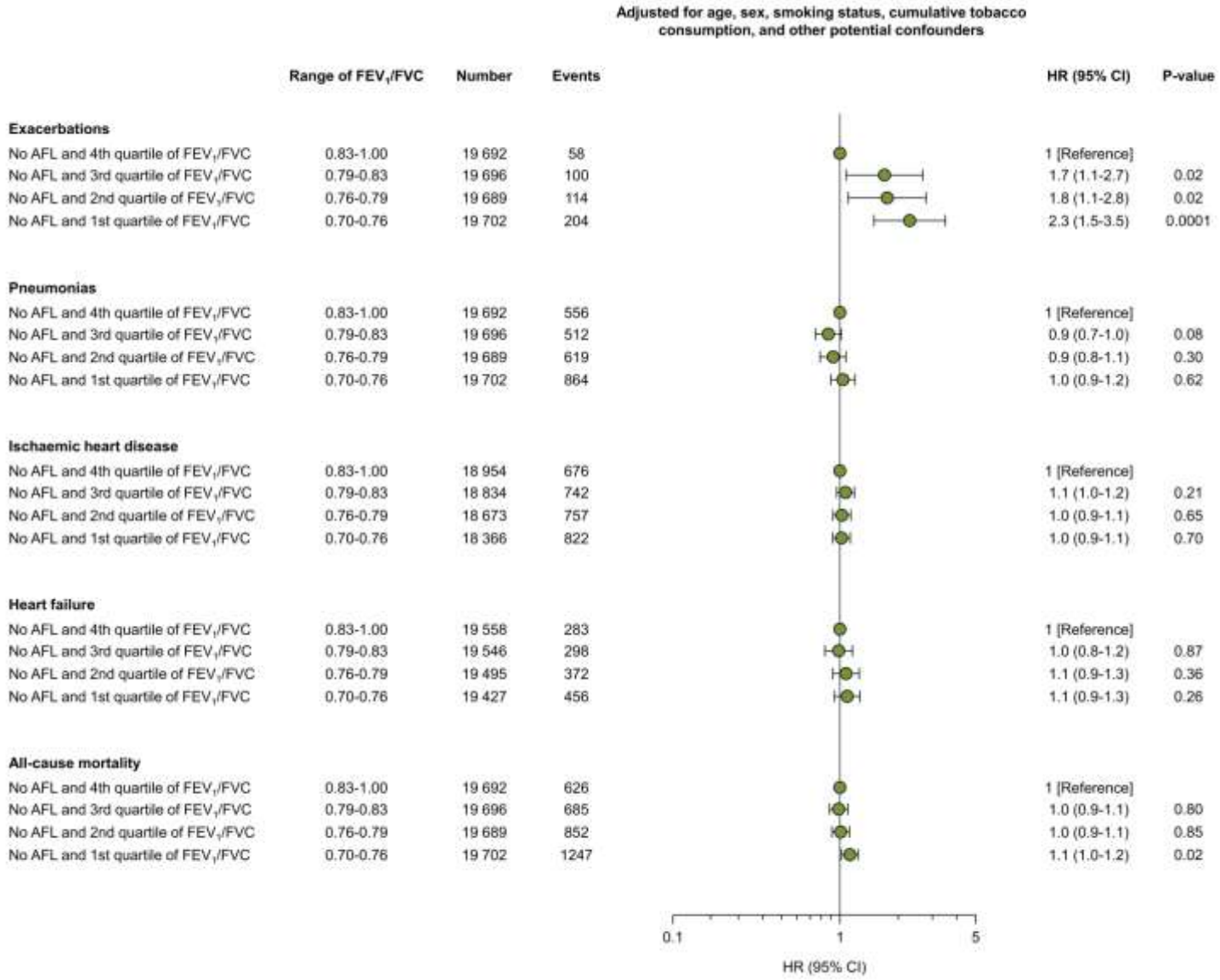


Figure S3. Prognosis of individuals without airflow limitation according to quartiles of FEV_1/FVC. Risk of exacerbations and pneumonias was assessed using multiple failure-time analysis; otherwise, a single failure-time analysis was used. P-values obtained from Wald test. Other potential confounders 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_1)/forced vital capacity (FVC) $\geq$0.70 and $FEV_1/FVC \geq$lower limit of normal (LLN). CI = confidence interval. HR = hazard ratio.