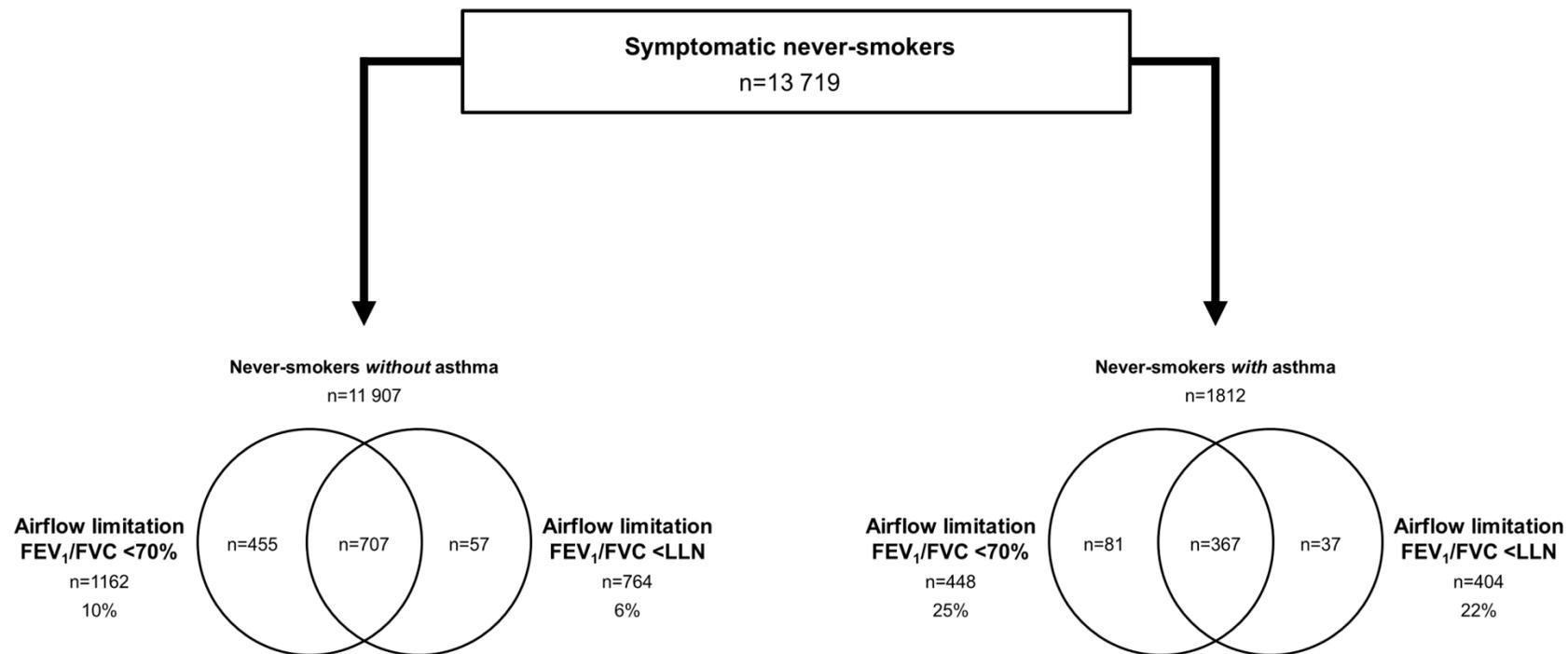


## **Online Data Repository**

### **Majority of never-smokers with airflow limitation do not have asthma. The Copenhagen General Population Study**

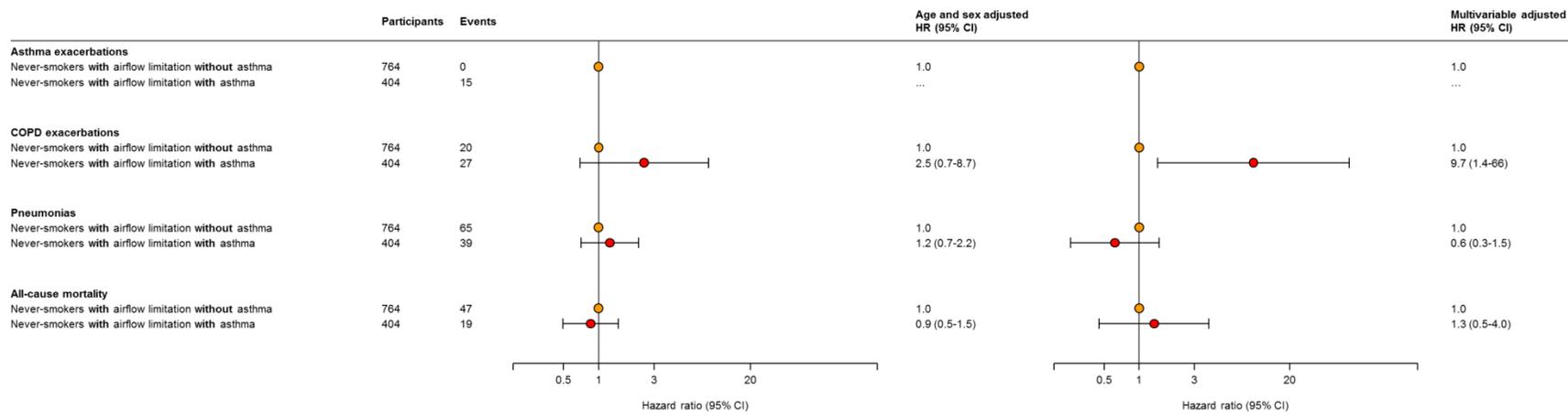
Yunus Çolak, MD; Shoaib Afzal, MD, PhD; Børge G. Nordestgaard, MD, DMSc; and Peter Lange,  
MD, DMSc



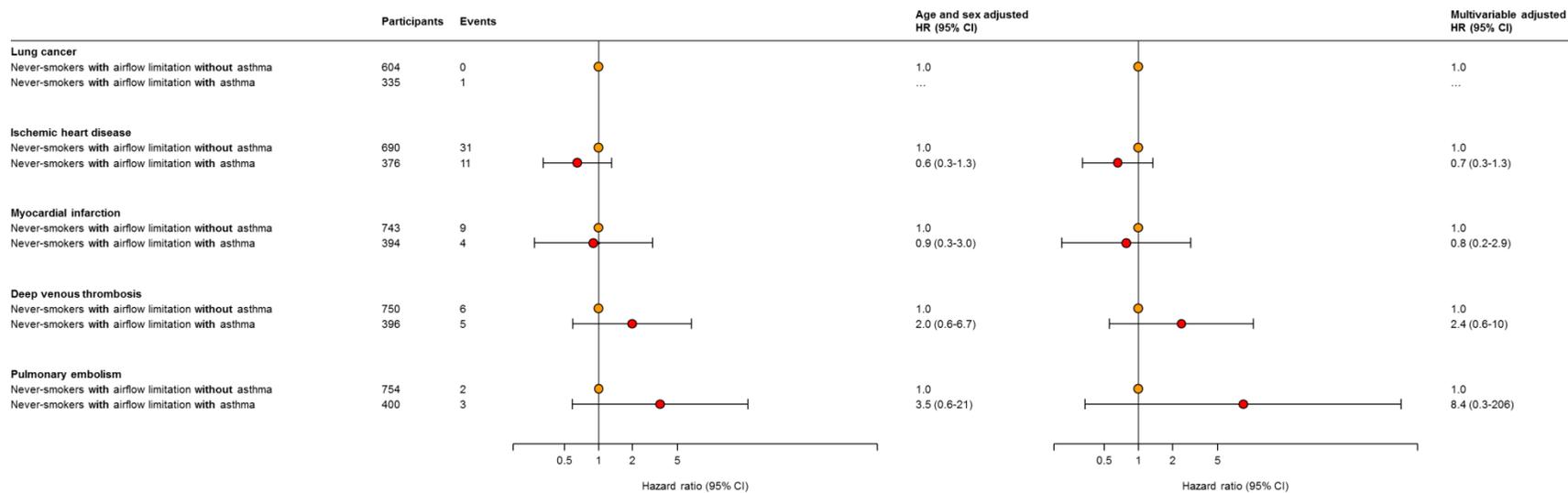
**Figure S1. Study population according to different criteria of airflow limitation.**

$FEV_1$  = forced expiratory volume in 1 second; FVC = forced vital capacity; LLN = lower limit of normal.

### Risk of complications



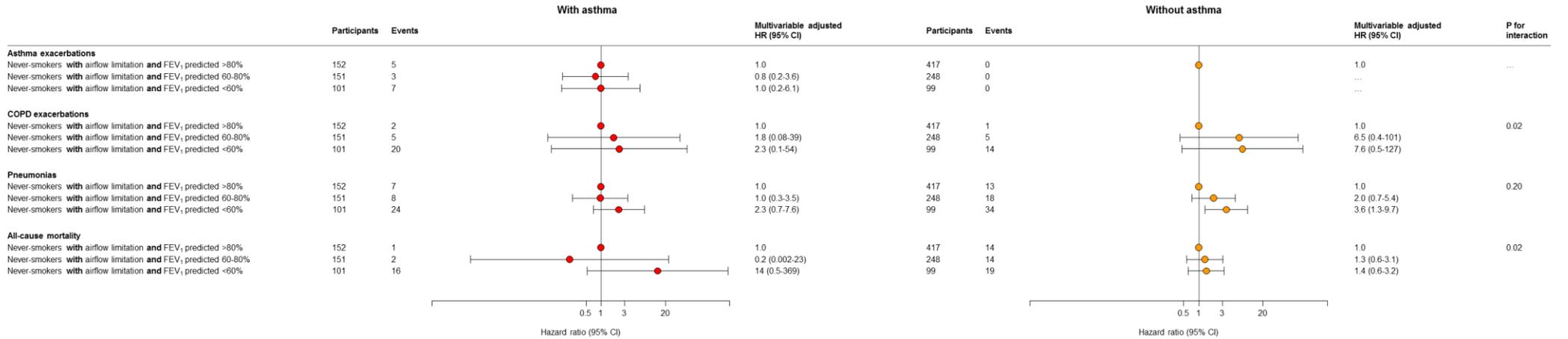
### Risk of comorbidities



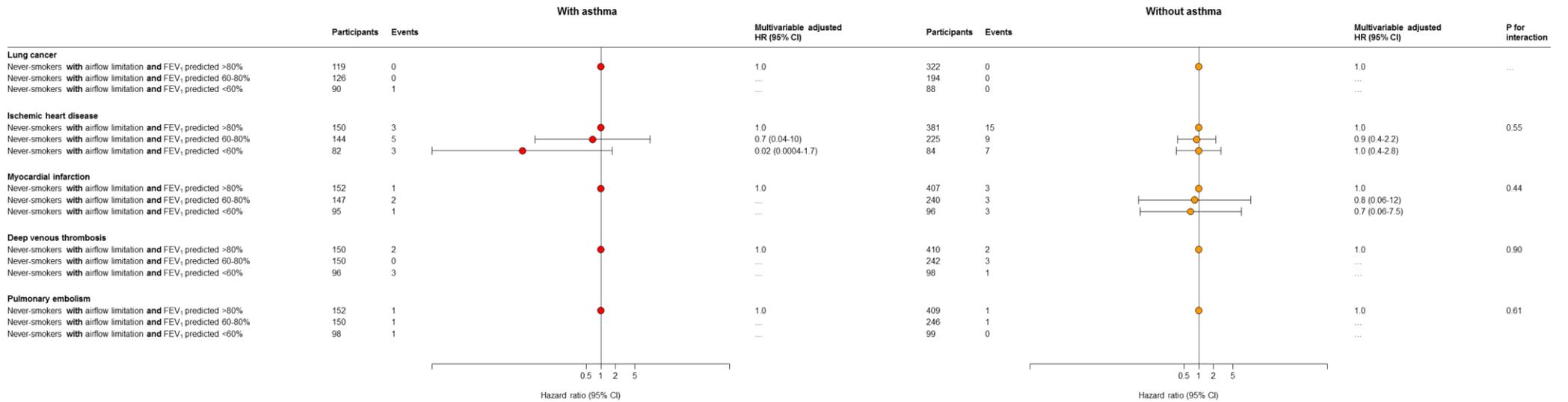
**Figure S2. Risk of complications and comorbidities according to presence and absence of asthma in never-smokers with airflow limitation.** Airflow limitation was defined according to FEV<sub>1</sub>/FVC < LLN. Models on risk of exacerbations and pneumonias were multivariable adjusted for age, sex, body mass index, familial predisposition for asthma, allergy, childhood asthma, hay fever, or eczema, use of respiratory medication, occupational exposure to dust and/or fumes, daily exposure to passive smoking, leisure time physical activity, education, and annual household income. Models on risk of ischemic heart disease, myocardial infarction, deep venous thrombosis, and pulmonary embolism were multivariable adjusted for age, sex, body mass index, leisure time physical activity, education, annual household income, alcohol consumption, systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medication, and presence of diabetes. Model on risk of all-cause mortality was multivariable adjusted for all of the above-mentioned potential confounders. Number of individuals for lung cancer differs slightly due to availability of data. Numbers of individuals for the other comorbidities differ slightly due to exclusion of participants with the outcome at baseline.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = hazard ratio; LLN = lower limit of normal.

**Risk of complications**

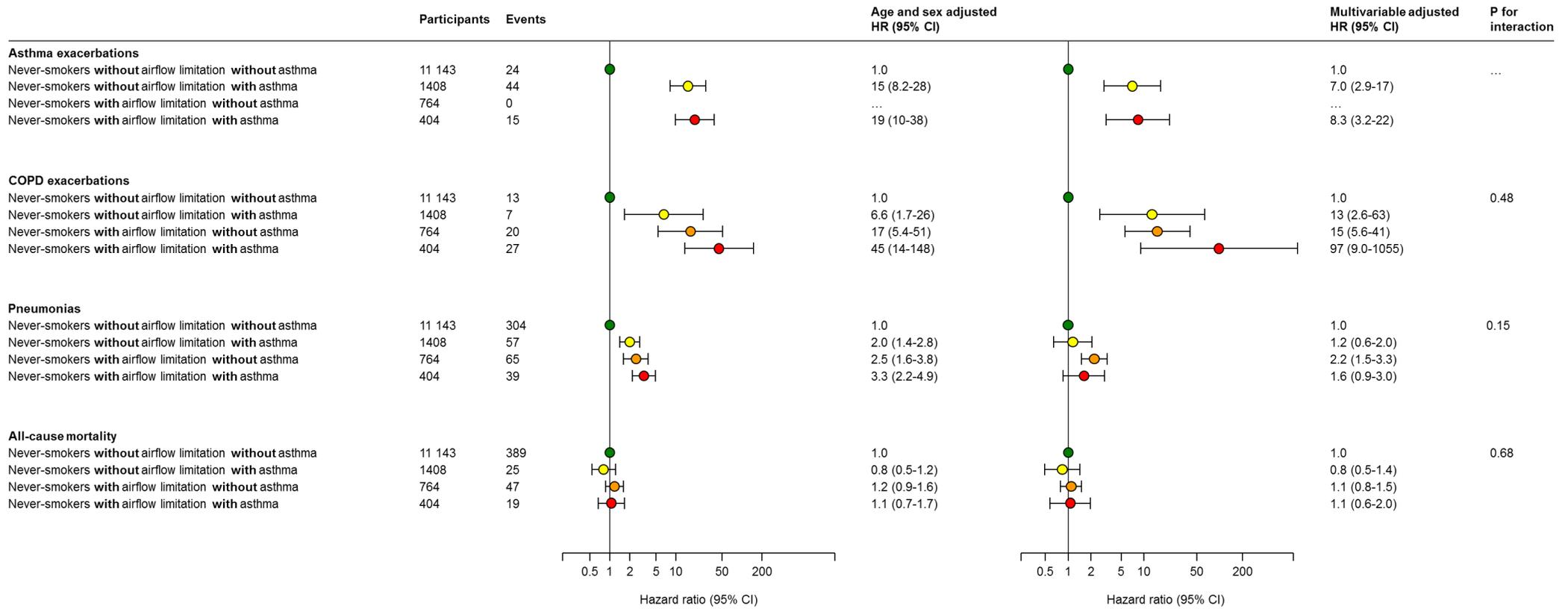


**Risk of comorbidities**

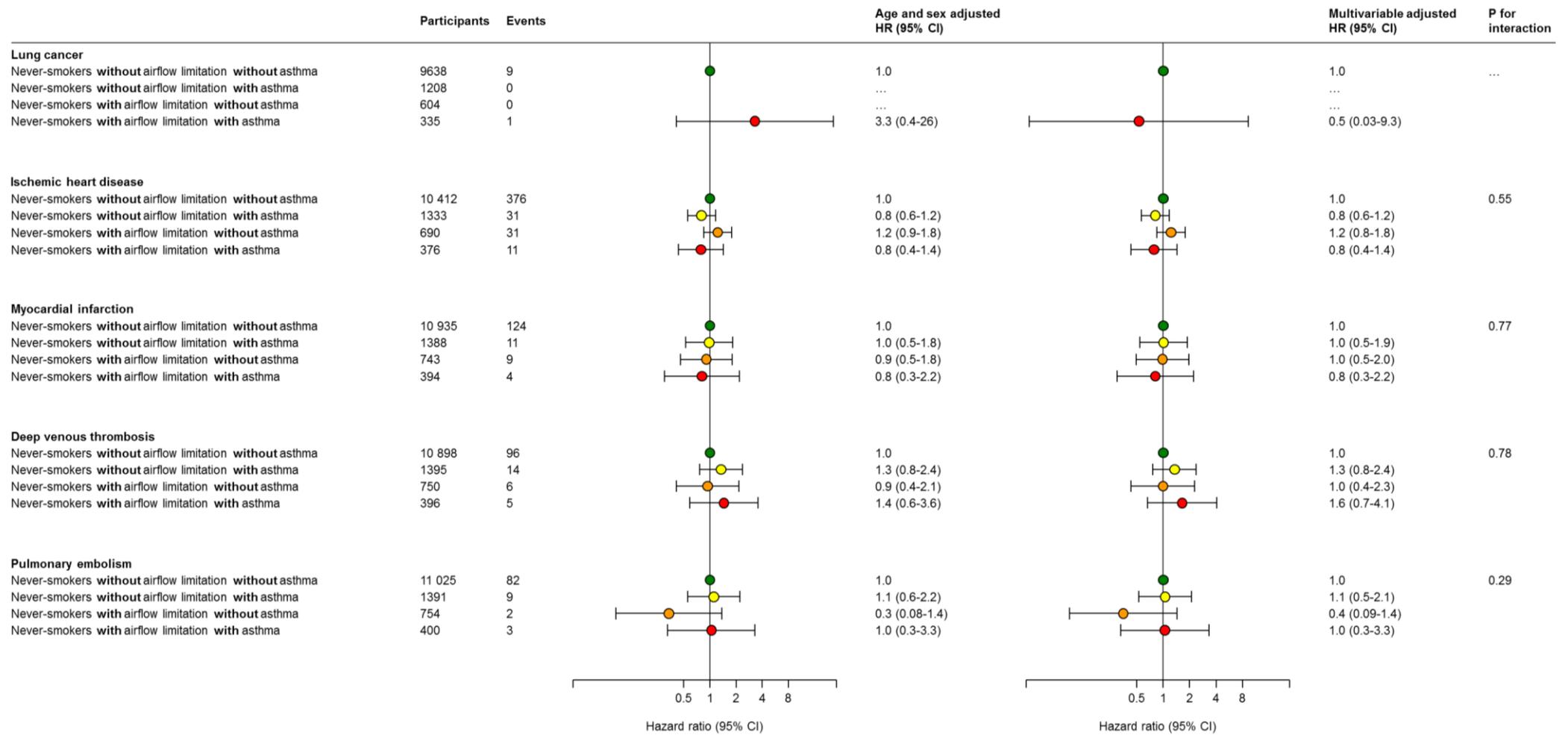


**Figure S3. Risk of complications and comorbidities according to severity of airflow limitation and presence and absence of asthma in never-smokers with airflow limitation.** Airflow limitation was defined according to FEV<sub>1</sub>/FVC <LLN. Models on risk of exacerbations and pneumonias were multivariable adjusted for age, sex, body mass index, familial predisposition for asthma, allergy, childhood asthma, hay fever, or eczema, use of respiratory medication, occupational exposure to dust and/or fumes, daily exposure to passive smoking, leisure time physical activity, education, and annual household income. Models on risk of ischemic heart disease, myocardial infarction, deep venous thrombosis, and pulmonary embolism were multivariable adjusted for age, sex, body mass index, leisure time physical activity, education, annual household income, alcohol consumption, systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medication, and presence of diabetes. Model on risk of all-cause mortality was multivariable adjusted for all of the above-mentioned potential confounders. P for interaction of FEV<sub>1</sub> % of predicted and asthma was assessed using the Wald test. Number of individuals for lung cancer differs slightly due to availability of data. Numbers of individuals for the other comorbidities differ slightly due to exclusion of participants with the outcome at baseline.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = hazard ratio; LLN = lower limit of normal.



**Figure S4. Risk of complications according to presence of airflow limitation and asthma in never-smokers.** Airflow limitation was defined according to  $FEV_1/FVC < LLN$ . Models on risk of exacerbations and pneumonias were multivariable adjusted for age, sex, body mass index, familial predisposition for asthma, allergy, childhood asthma, hay fever, or eczema, use of respiratory medication, occupational exposure to dust and/or fumes, daily exposure to passive smoking, leisure time physical activity, education, and annual household income. Model on risk of all-cause mortality was additionally multivariable adjusted for alcohol consumption, systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medication, and presence of diabetes. P for interaction of airflow limitation and asthma was assessed using the Wald test. CI = confidence interval; COPD = chronic obstructive pulmonary disease;  $FEV_1$  = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = hazard ratio; LLN = lower limit of normal.



**Figure S5. Risk of comorbidities according to presence of airflow limitation and asthma in never-smokers.** Airflow limitation was defined according to  $FEV_1/FVC < LLN$ . Model on risk of lung cancer was multivariable adjusted for age, sex, body mass index, familial predisposition for asthma, allergy, childhood asthma, hay fever, or eczema, use of respiratory medication, occupational exposure to dust and/or fumes, daily exposure to passive smoking, leisure time physical activity, education, and annual household income. Models on risk of ischemic heart disease, myocardial infarction, deep venous thrombosis, and pulmonary embolism were multivariable adjusted for age, sex, body mass index, leisure time physical activity, education, annual household income, alcohol consumption, systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medication, and presence of diabetes. P for interaction of airflow limitation and asthma was assessed using the Wald test. Number of individuals for lung cancer differs slightly due to availability of data. Numbers of individuals for the other comorbidities differ slightly due to exclusion of participants with the outcome at baseline. CI = confidence interval;  $FEV_1$  = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = hazard ratio; LLN = lower limit of normal.

**Table S1** Risk factors for airflow limitation defined as FEV<sub>1</sub>/FVC<LLN in never-smokers with and without asthma

Risk factors	Never-smokers with asthma n=2304		Never-smokers without asthma n=36 798	
	Age and sex adjusted ORs (95% CI)	Multivariable adjusted ORs (95% CI)	Age and sex adjusted ORs (95% CI)	Multivariable adjusted ORs (95% CI)
BMI (kg/m <sup>2</sup> )	0.94 (0.91-0.96)*	0.94 (0.91-0.96)*	0.95 (0.94-0.96)*	0.95 (0.94-0.96)*
Familial predisposition for asthma	0.98 (0.79-1.22)	0.99 (0.79-1.23)	1.27 (1.13-1.42)*	1.30 (1.15-1.46)*
Asthma, hay fever, or eczema in childhood	1.43 (1.15-1.77)*	1.00 (0.77-1.30)	1.17 (1.02-1.34)†	1.15 (1.00-1.33)
Low leisure time physical activity‡	1.21 (0.81-1.81)	1.29 (0.85-1.96)	1.27 (1.05-1.53)†	1.44 (1.19-1.74)*
Low education§	0.77 (0.58-1.01)	0.90 (0.66-1.23)	0.88 (0.78-0.99)†	0.91 (0.80-1.03)
Low annual household income	1.01 (0.73-1.40)	1.13 (0.80-1.61)	1.14 (1.00-1.31)	1.23 (1.06-1.41)†
Occupational exposure to dust and/or fumes	0.81 (0.58-1.13)	0.92 (0.65-1.32)	0.93 (0.78-1.11)	1.02 (0.85-1.24)
Daily exposure to passive smoking	0.84 (0.64-1.10)	0.91 (0.69-1.22)	0.83 (0.73-0.95)*	0.88 (0.77-1.00)
Allergy	0.95 (0.72-1.24)	0.76 (0.57-1.02)	1.00 (0.90-1.11)	0.93 (0.83-1.04)
Duration of asthma (years)	1.02 (1.01-1.02)*	1.02 (1.01-1.03)*	NA	NA
C-reactive protein (mg/L)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.00 (0.99-1.01)	1.01 (1.00-1.02)
Fibrinogen (µmol/L)	1.00 (0.96-1.05)	1.01 (0.96-1.06)	0.96 (0.95-0.98)*	0.97 (0.95-1.00)†
Leukocytes (x 10 <sup>9</sup> /L)	1.06 (1.00-1.12)	0.90 (0.77-1.05)	0.99 (0.97-1.02)	0.97 (0.93-1.01)
Neutrophils (x 10 <sup>9</sup> /L)	1.08 (1.01-1.16)†	1.23 (1.02-1.48)†	1.01 (0.98-1.03)	1.05 (0.99-1.11)
Eosinophils (0.10 x 10 <sup>9</sup> /L)	1.14 (1.08-1.20)*	1.15 (1.08-1.22)*	1.04 (1.01-1.07)†	1.05 (1.02-1.08)†
Immunoglobulin-E** (10 IU/mL)	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

The multivariable adjusted models included all of the potential risk factors listed in the table. However, since measurement of immunoglobulin-E was only available in a subgroup, it was not included. Immunoglobulin-E was only included in its own multivariable adjusted model. Risk factors included in the models were dichotomous except BMI, duration of asthma, and inflammatory biomarkers that were continuous.

\*p<0.001.

†p<0.05.

‡Low leisure time physical activity was none or light activity <2 h/week versus light activity ≥2 h/week or heavy activity ≥2 or regular exercises per week.

§Low education was <10 years versus ≥10 years of school attendance.

||Low annual household income was <200 000 Danish kroner versus ≥200 000 Danish kroner.

\*\*Not available for all individuals.

BMI = body mass index; CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; ORs = odds ratios; LLN = lower limit of normal; NA = not applicable.