

Online supplement

**Absolute Value of Lung Function (FEV₁ or FVC) Explains the Sex Difference in
Breathlessness in the General Population**

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Table S1. Comparison between patients who were excluded or included in the analysis

Characteristic	Excluded N = 1,618		Included N = 3,250
	Measurements, N (% of total)	Values	Values
Women, n (%)	1,618 (100)	843 (52)	1,673 (51)
Age	1, 618 (100)	53.4 ± 7.3	54.0 ± 7.0
mMRC breathlessness score, n (%)	1, 618 (100)		
0		1,337 (83)	2,575 (79)
1		205 (13)	546 (17)
2		62 (4)	117 (4)
3-4		14 (0.9)	12 (0)
FEV ₁ , L	694 (43)	3.3 ± 0.8	3.2 ± 0.8
FVC, L	675 (42)	4.2 ± 1.0	4.0 ± 0.96
FEV ₁ /FVC	675 (42)	0.79 ± 0.06	0.78 ± 0.06
Body mass index (kg/m ²)	981 (61)	26.7 ± 8.1	26.7 ± 4.6
Pack-years smoking, median (IQR)	1,348 (83)	0 (0 to 21.3)	3.9 (0 to 24.3)
Current smoker, n (%)	1,607 (99)	337 (21)	581 (18)
Ever-smoker, n (%)	1,618 (100)	889 (55)	1,446 (44)
Occupational exposure, n (%)	1,577 (97)	644 (41)	1,516 (40)
Exercise (hours per week), n (%)	1,412 (87)		
≥ 2		555 (39)	1,451 (45)
0.5 to 1		471 (33)	803 (25)
None		386 (27)	996 (31)
Asthma	1,609 (99)	236 (15)	419 (13)
CAL (FEV ₁ /FVC < LLN)	675 (42)	30 (4)	160 (5)
Chronic bronchitis	1,183 (73)	120 (10)	308 (9)
IHD	1,091 (65)	35 (3)	69 (2)
Severe respiratory infection < age five	1,365 (84)	127 (9)	314 (10)
History of cancer	1,505 (93)	95 (6)	177 (5)
History of depression	1,504 (93)	204 (14)	469 (14)

Data are compared between people in ECRHS III who had complete data on study variables were included in the analysis (N = 3,250) and people who were excluded due to missing data on any study variable (N = 1, 618).

Table S2. Activity-related breathlessness stratified by absolute FEV₁ and sex

Quintile of absolute FEV ₁	Prevalence of mMRC ≥ 1	
	Men	Women
1.0 to 2.4 L	25 (42)	216 (37)
2.5 to 2.8 L	30 (28)	126 (23)
2.9 to 3.2 L	53 (20)	80 (20)
3.3 to 3.7 L	65 (13)	24 (17)
3.8 to 5.9 L	55 (8)	1 (8)
Overall (non-stratified)	228 (14)	444 (27)

The sex disparity in the prevalence of activity-related breathlessness (27% in women vs. 14% in men overall) was largely reduced within each stratum of absolute FEV₁. Data presented as N (%) for each stratum of sex and increasing absolute FEV₁.

Abbreviations: FEV₁ = forced expiratory volume in one second; mMRC = Modified Medical Research Council Breathlessness Scale.

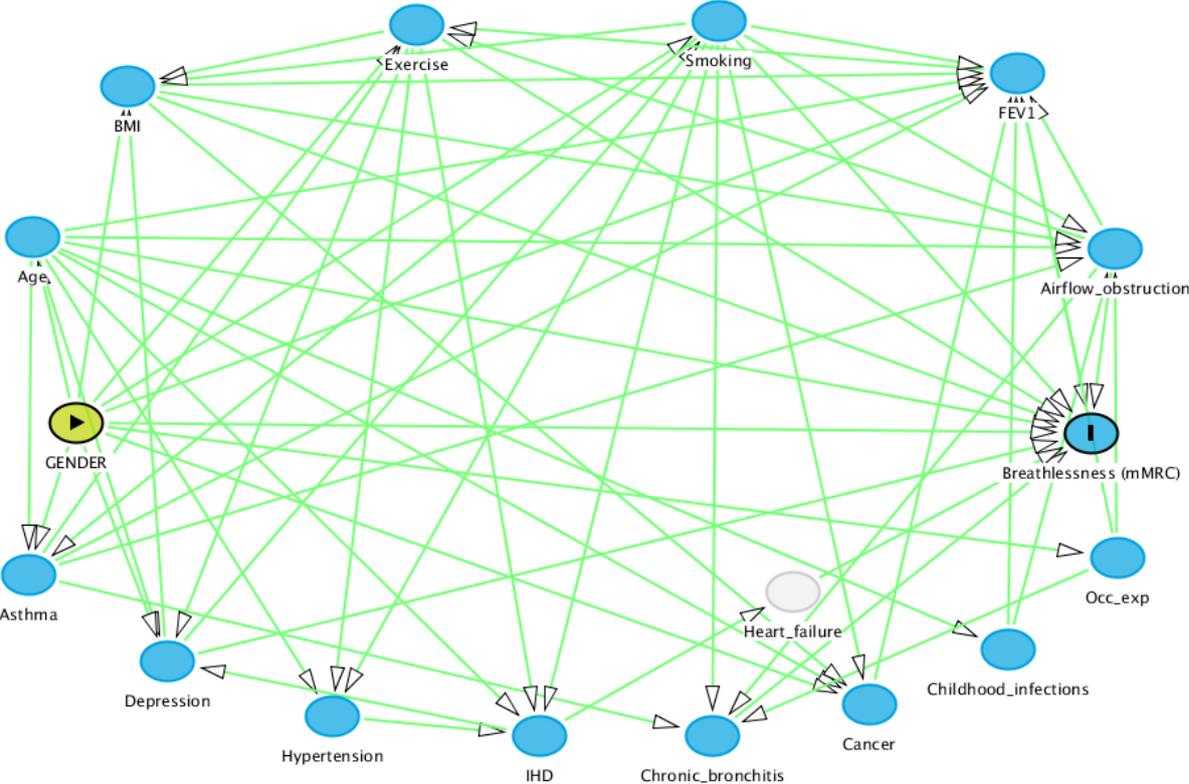
Table S3. Absolute FVC and sex difference in activity-related breathlessness

Model	Model without FVC		Model with FVC		Percent of the sex variance in breathlessness explained by absolute FVC
	OR women vs. men (95% CI)	Percent explained by sex	OR women vs. men (95% CI)	Percent explained by sex	
Crude	2.21 (1.71 to 2.72)	4.8	0.95 (0.71 to 1.26)	0	100
Risk factors	2.52 (2.01 to 3.11)	5.2	1.30 (0.92 to 1.84)	0.1	98
Diseases	2.28 (1.90 to 2.77)	4.7	1.02 (0.77 to 1.35)	0	100
Physiology	2.56 (2.07 to 3.16)	5.2	1.31 (0.88 to 1.95)	0	100
Final	2.63 (2.12 to 3.25)	5.1	1.50 (1.00 to 2.27)	0.3	94

The odds ratio (OR) of more severe activity-related breathlessness in women compared to men, in models without and with absolute FVC. Analyses are crude and adjusted for: risk factors (pack-years of smoking, exercise, occupational exposure, lung infection before age five, and hypertension); diseases (asthma, chronic bronchitis, CAL, depression, IHD, and history of cancer); and physiology (age, BMI, and CAL). The final model controlled for age, BMI, chronic bronchitis, CAL, pack-years smoking, exercise, IHD, history of depression, and history of cancer. Estimated using ordinal logistic regression clustering on country with 3,305 participants in all models. R^2 is the variance in mMRC scores explained by sex for each model.

Abbreviations: BMI = body mass index; CAL = chronic airflow limitation; CI = confidence interval; FVC = forced vital capacity; IHD = ischemic heart disease; mMRC = Modified Medical Research Council Dyspnoea Scale; R^2 = McKelvey & Zavoina's R^2 (explained variance).

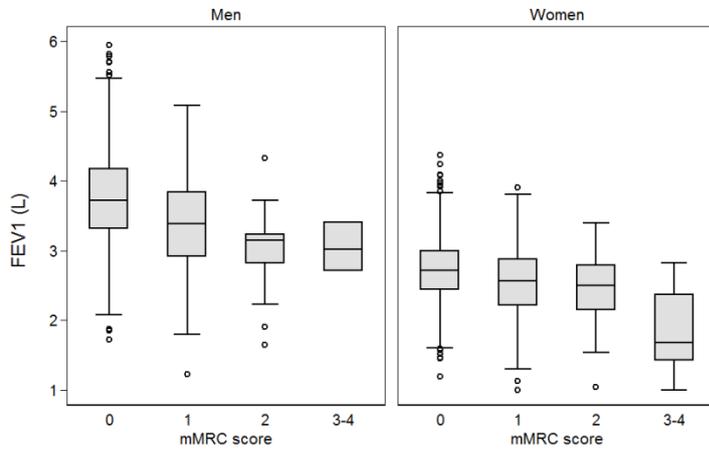
Figure S1. Directed acyclical graph of proposed associations between study variables



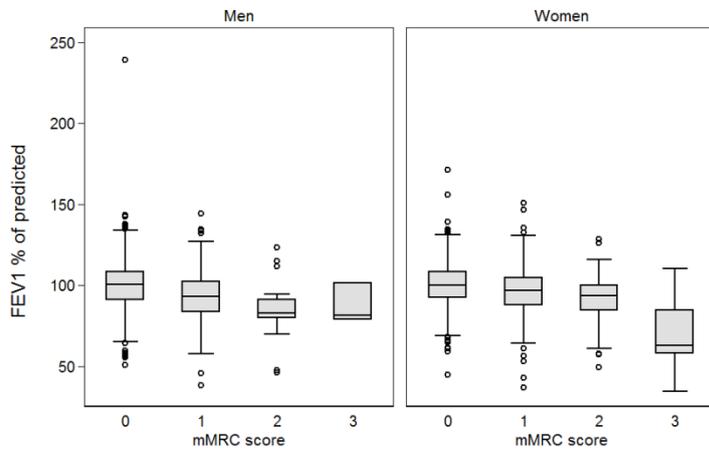
Directed acyclical graph of the relation between sex, potential confounding variables and activity-related breathlessness, created using the software DAGitty (www.DAGitty.net). The graph was based on the breathlessness literature and discussion between all co-authors, and was used to visualize and explore the assumed relations between variables, evaluate and refine the model using testable assumptions (generated based on the model), and to generate a sufficient set of covariates to include in the final model.

Figure S2. FEV₁ per level of activity-related breathlessness in men and women

A)



B)



The A) absolute forced expiratory volume in one second (FEV₁); and B) FEV₁ in percent of predicted, per level of increasing activity-related breathlessness measured on the modified Medical Research Council (mMRC) scale in 1,577 men and 1,673 women in the general population aged 38 to 67 years.

Figure S3. Forced vital capacity (FVC) per level of activity-related breathlessness in 1,577 men and 1,673 women aged 38 to 67 years in the general population

