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

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ABSTRACT

Activity-related breathlessness is twice as common among women as men in the general population and is associated with adverse health outcomes. We tested whether this sex difference is explained by the lower absolute FEV₁ or FVC in women.

This was a cross-sectional analysis of 3,250 people (51% women) aged 38–67 years across 13 countries in the population-based third European Community Respiratory Health Survey. Activity-related breathlessness was measured using the modified Medical Research Council (mMRC) scale. Associations with mMRC were analyzed using ordered logistic regression clustering on center, adjusting for post-bronchodilator spirometry, body mass index, pack-years smoking, cardio-pulmonary diseases, depression, and level of exercise.

Activity-related breathlessness (mMRC ≥ 1) was twice as common in women (27%) as in men (14%); odds ratio (OR) 2.21 ([95% confidence interval] 1.79–2.72). The sex difference was not reduced when controlling for FEV₁% predicted (OR 2.33) but disappeared when controlling for absolute FEV₁ (OR 0.89; 0.69–1.14). Absolute FEV₁ explained 98–100% of the sex difference adjusting for confounders. The effect was similar within men and women; using FVC instead of FEV₁; and in healthy never-smokers.

The markedly more severe activity-related breathlessness among women in the general population is explained by their smaller spirometric lung volumes.

INTRODUCTION

Breathlessness related to daily activities is common, affecting 15 – 45% of middle-aged and older people in the community.[1-3] More severe disability due to activity-related breathlessness measured on the modified Medical Research Council (mMRC) scale [4] is associated with worse health status [1, 5] and increased mortality.[6, 7]

Women report significantly higher prevalence and severity of activity-related breathlessness than men, with odds about twice that of men for each level of breathlessness both in patients with chronic obstructive pulmonary disease (COPD) [8-10] and in the general population.[1, 2, 11-13]

The more severe activity-related breathlessness in women is not explained by age, body mass index (BMI), smoking, socio-economic status, heart disease, chronic airflow limitation (CAL), or by lung function impairment.[1-3, 9, 11, 13, 14] However, recent laboratory data indicate that women have a lower maximal ventilatory capacity and more ventilatory constraints during exercise.[15, 16] Furthermore, for a given level of physical activity, women have higher respiratory drive, use more of their maximal ventilatory capacity, and are more breathless than men.[15-17] The sex disparity was attenuated when controlling for differences in absolute lung volume in the laboratory [15-17] and in patients with severe COPD and emphysema.[10] Taken together, this suggests revisiting the relation between dyspnea, sex and lung function.

No population study has evaluated the association between absolute spirometric lung volumes and the sex difference in breathlessness. Most previous studies have included relative lung function, most often forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC) expressed as percentage of the predicted normal when investigating the link between sex and breathlessness.[1-3, 9, 11, 13, 14] Laboratory studies were small, did not evaluate the interplay of multiple factors, or the importance of the suggested mechanisms for breathlessness related to activities of daily life.[15-17] As lower spirometric lung volume might be associated with smoking and increased morbidity, analysis in healthy never-smokers would be informative on a possible causal relation between lung volumes and activity-related breathlessness.

We aimed to test the hypothesis that the sex difference in activity-related breathlessness is mediated through the lower absolute spirometric lung volume (FEV₁ or FVC) in women due to their on average smaller lungs, airways, and respiratory musculature.

MATERIAL AND METHODS

Study design and population

This was a cross-sectional analysis of the third multicenter European Community Respiratory Health Survey (ECRHS III). The ECRHS has been detailed elsewhere.[18] ECRHS III was a population-based study of people aged 38 to 67 years at 27 centers across 12 European countries and Australia between 2010 and 2014.[19] The present analysis included people in

the random population sample with data on the mMRC breathlessness scale.[4, 20] Exclusion criterion was disability to walk for other reason than cardiopulmonary disease.

Measurements

All participants had their height, weight, and post-bronchodilator spirometry measured at the local study centers and completed written questionnaires on smoking habits, respiratory symptoms, exercise habits, and comorbidities.

The outcome severity of activity-related breathlessness was measured using a mMRC scale[20] as breathlessness during strenuous exercise (grade 0); when hurrying on the level or up slight hill (grade 1); when walking on the level (grade 2); when walking for a few minutes (grade 3) and at rest or during minimal activity (grade 4). Grade 3 and 4 were merged due to low numbers.

Post-bronchodilator dynamic spirometry was performed using EasyOne spirometer by certified technicians according to ATS/ERS standards.[21] Absolute and relative lung volume was defined as spirometric FEV₁ and FVC in liters and percent of predicted, respectively. Predicted values were estimated using the global lung function initiative reference values.[22] Chronic airflow limitation (CAL) was defined as FEV₁/FVC below the 5th percentile (lower limit of normal) of the reference population.[21] Exercise was reported as weekly hours of physical activity that led to sweating. Pack-years of smoking was calculated as: [mean number of cigarettes per day] x [years smoking] divided by 20. Occupational exposure was defined as work-related exposure to vapors, gas, dust or fumes. Diagnoses included chronic

bronchitis, self-reported asthma, ischemic heart disease (IHD), hypertension, history of cancer and depression.

Ethical considerations

Informed consent was obtained from each participant prior to inclusion in the ECRHS III. Each study center obtained approval to the study from their regional committees of medical research ethics according to national legislations.

Statistical analyses

Stratified analysis and ordered logistic regression were used to explore associations with the mMRC. The variance in mMRC scores explained by sex was measured using McKelvey & Zavoina's R^2 as the difference in variance explained by the model with sex compared to the model without sex.[23] The measure of primary interest was the reduction in the variance explained by sex by adding the FEV₁ or FVC as absolute volume and percent of predicted to the model, respectively.

Potential confounders of the association between lung function and mMRC score for the final model were selected using a directed acyclical graph (DAG) of the relations between study variables (Figure S1 in the online supplement).[24] The DAG was based on the literature and input from co-authors.[25] We also evaluated pre-specified models adjusting for diseases (asthma, chronic bronchitis, CAL, IHD, history of cancer and depression), risk factors (pack-years of smoking, exercise, occupational exposure, lung infection before age five, and

hypertension), and physiologic variables (age, BMI, and CAL). The functional form of continuous covariates was investigated using splines. All models accounted for clustering within countries using robust variance estimation.[26] The analysis included complete cases only. No data were imputed. Associations were expressed as odds ratios (OR) with 95% confidence intervals (CI). The sex OR of 2.0 is interpreted as, for each level of mMRC, the odds of having a higher mMRC score is twice as high in women as in men. The proportional odds assumption of ordinal logistic regression was evaluated by repeating the analyses using a partial proportional odds model, with similar findings. Findings were also similar when analyzing mMRC dichotomously (≥ 1 vs 0) using logistic regression.

Analyses were performed in the total study population; women and men separately; and in healthy never-smokers, defined as never-smokers without CAL, self-reported chronic bronchitis, IHD, history of cancer or depression. Statistical analyses were performed with Stata version 12.1 (StataCorp LP; College Station, TX, USA).

RESULTS

Participants

A total of 3,250 participants (51% women) were included in the analysis. Included and excluded patients had similar characteristics (Table S1 in the online supplement). The included participants' mean age of was $54 \pm$ [standard deviation] 7.0 years (Table 1). Compared with men, women had lower mean absolute FEV₁ (2.7 vs. 3.7 liter) but similar

FEV₁ percent of predicted, slightly lower BMI, less smoking exposure, but more asthma and previous depression (Table 1).

Sex difference of breathlessness

Activity-related breathlessness (mMRC \geq 1) was twice as common in women (27%) as in men (14%; Table 1); unadjusted odds ratio (OR) 2.21 (95% CI, 1.79 to 2.72) for more severe breathlessness. The sex difference was not reduced when controlling for age, BMI, chronic bronchitis, CAL, pack-years smoking, exercise, IHD, and a history of depression; OR 2.63 (95% CI, 2.12 to 3.25) in the final model (Table 2).

Predictors of breathlessness

In the final model, independent predictors of increased activity-related breathlessness were lower FEV₁ (absolute or relative value), higher BMI, less exercise, chronic bronchitis (strong association), IHD, and history of depression (Table 3). Smoking and CAL predicted breathlessness only when not adjusting for absolute FEV₁. The estimates for predictors were similar in men and women except that women had weaker associations for exercise and IHD, and stronger for chronic bronchitis (Table 3).

Both a lower absolute and relative FEV₁ were associated with more severe activity-related breathlessness (Figure S2 in the online supplement). As shown in Figure 1, the associations remained when adjusting for possible confounders and were similar in men and women

(Table 2) for both the absolute FEV₁ ($p = 0.69$ for interaction) and percent of predicted ($p = 0.49$ for interaction).

Spirometric lung volume and sex difference in breathlessness

Adjusting for FEV₁ percent of predicted did not reduce the sex difference in activity-related breathlessness, OR 2.66 (95% CI, 2.13 to 3.34).

In contrast, the sex difference disappeared when adjusting for absolute FEV₁, OR 0.89 (95% CI, 0.69 to 1.14). This was consistent with stratified analysis (Table S2 in the online supplement). Differences in absolute FEV₁ explained 98-100% of the difference (variance) in activity-related breathlessness between men and women (Figure 2), which was consistent when controlling for age, BMI, smoking, exercise level, diseases, and other risk factors (Table 3). Findings were similar when analyzing FVC instead of FEV₁ (Figure S3 and Table S3 in the online supplement) which is also shown in Figure 2.

The absolute FEV₁ was closely correlated to height ($r = 0.72$). In a sensitivity analysis adding height to the final model, the association for FEV₁ remained unchanged (OR 0.42 vs. OR 0.48 in Table 3) but the association for height became non-significant (OR 1.02; 95% CI, 1.00 to 1.04; $p = 0.065$). Compared with height, absolute FEV₁ was a stronger predictor and explained more of the sex difference in breathlessness (98% vs 55%). Findings were consistent when including weight instead of BMI and when not adjusting for level of exercise in the final model.

Healthy never-smokers

Findings were consistent in healthy never-smokers (n = 971 [30%]; 455 men and 516 women). The more severe adjusted activity-related breathlessness in women (OR 2.69; 95% CI, 1.94 to 3.73) was not reduced by FEV₁ percent of predicted (OR 2.71; 95% CI, 1.96 to 3.76) but by absolute FEV₁ (OR 1.65; 95% CI, 1.07 to 2.53; P = 0.039 for change). The absolute FEV₁ explained 96% of the sex difference in activity-related breathlessness among healthy never-smokers.

DISCUSSION

Main findings

In a middle-aged general population, 1) women reported about twice as much activity-related breathlessness as men; 2) the sex difference was eliminated when accounting for the absolute FEV₁ or FVC, whereas it was not reduced when controlling for the level of lung function impairment (percent of predicted); 3) the association between lower spirometric lung volumes and increased breathlessness was similar across men and women and in healthy never-smokers.

Sex difference in activity-related breathlessness

The finding of increased activity-related breathlessness in women is in line with previous population-based studies,[1-3, 14] including from five Latin American cities [1] and the

Burden of Obstructive Lung Disease (BOLD) study of 15 countries, and thus seems to have high validity globally.[2, 11]

The sex disparity increased from OR 2.21 to 2.63 when controlling for potential confounders which was also seen in the BOLD study.[2] This likely reflects that several determinants of more severe breathlessness such as overweight and IHD, were less common in women than men. No factor except absolute spirometric lung volumes was found to decrease the sex difference in the final model, which was also unchanged in previous studies adjusting for education level and socioeconomic status.[2, 3, 14]

That absolute FEV₁ and FVC explained the sex difference in activity-related breathlessness is consistent with a study of selected patients with severe emphysema.[10] The effect of absolute spirometric lung volume was robust across models controlling for potential confounders.

The impact of absolute spirometric lung volume was not mainly related to sex differences in body size. Although height and absolute FEV₁ were closely correlated, height explained less of the sex difference (55% vs. 98%) and did not predict breathlessness independent of the absolute FEV₁.

The association between lower spirometric lung volumes and increased breathlessness was not explained by concurrent lung volume impairment, as most participants had normal lung function and findings were similar in healthy never-smokers.

Mechanisms

The present findings are consistent with recent laboratory data that women have smaller absolute lung volumes and experience more dyspnea for a given absolute work rate, ventilation, or metabolic requirement during laboratory based cardiopulmonary exercise testing in young and older subjects.[15-17, 27] In addition to having smaller lungs, women have narrower airways than men even when matched on lung size (dysanapsis).[12, 28, 29] Narrower airways could contribute to the increased exertional breathlessness in women, likely mediated, at least partly, through reduced ventilatory capacity.[30] In the laboratory, the sex difference in breathlessness disappears when ventilation is expressed as a percentage of maximal voluntary ventilation or when accounting for the reduced exercise capacity in women.[15-17, 27] In other words, women breathe at a higher percentage of their ventilatory capacity, resulting in increased resistive work of breathing and increased neural ventilatory drive [31] for any given work rate or minute ventilation and therefore experience more breathlessness.[17, 32]

Implications

This study extends previous laboratory data and supports that absolute spirometric lung volume has an important impact on the severity of breathlessness related to daily activities, and that it explains the difference in severity between men and women in the general

population. This highlights the importance of evaluating both the relative and the absolute lung volume in research and clinical practice. By just focusing on the relative values we may miss associations of which the causal pathway includes the absolute lung volume. Relative lung volume reflects the level of lung volume *impairment* compared to the predicted normal, and might reflect an active disease process (such as COPD) that influence the trajectory of absolute lung volume over time, as well as systemic consequences of the disease, health status, and mortality.[33] The functional impact of a given impairment however depends on the person's baseline absolute lung volume which reflects the remaining ventilatory capacity. Importantly, smaller absolute spirometric lung volume was associated with more severe activity-related breathlessness both overall and within each sex; men with smaller lungs had more severe breathlessness than men with larger lungs, with the same seen among women.

Among women in the present study, a FEV₁ of 50% of predicted corresponds to an average FEV₁ of some 1.34 liters, whereas the mean FEV₁ in men with the same level of lung function impairment is 1.84 liters – a difference of 500ml or 37% higher compared with women.

Although matched on relative lung volume, men and women can therefore have markedly different absolute lung volume or ventilatory capacity, which may explain the sex disparity in breathlessness seen in previous clinical studies matching on the FEV₁ in percent of predicted.[8-11] An important implication for future clinical studies is that matching on relative lung volume puts women at a disadvantage in relation to breathlessness due to their average lower absolute lung volume. This sex bias can be overcome by accounting for absolute lung volume.

Clinically and in studies, absolute lung volumes are rarely analyzed or reported and its importance in breathlessness has been largely overlooked. We propose that in both research and clinical care, relative and absolute spirometric lung volumes provide complimentary information on the lung volume impairment and remaining ventilatory reserve.

Strengths and limitations

This was an international, multicenter study that included a large general population sample with standardized assessments across 13 countries.[21] The analyses accounted for variability between study centers and potential confounders including BMI, detailed smoking exposure, the presence of cardiopulmonary disease and risk factors. Sensitivity analyses showed consistent results supporting the validity of the findings. Both FEV₁ and FVC were analysed as they may contribute complimentary information on airway size and respiratory mechanics which influence exertional breathlessness.

Some potential limitations deserve mentioning. First we excluded subjects with missing study data. However, the representativeness of the sample for the general population is supported by that their characteristics were similar to those of the excluded people and were similar to in previous population-based studies.[1, 2] A previous analysis found no major effect of missing data in ECRHS on analyses of symptoms.[34] The findings pertain to people aged 38-67 years. Secondly, we lacked data on standardized exercise tests. Exercise tests have limited feasibility in large population-based studies. The mMRC is a discriminative and valid measure that performs similar to other instruments of activity-related breathlessness.[4, 35, 36] It is strongly related to health status,[1, 4, 5] mortality,[6, 7] and is commonly used, enabling comparisons between studies.[1, 2, 4] Finally, we have not measured static lung

volumes, diffusion capacity or cardiopulmonary exercise capacity, which should be evaluated to provide more detailed information concerning both the nature and implication of reduced spirometric lung volumes.

Relation to prevailing hypotheses

This study does not support the prevailing view that women report more activity-related breathlessness for a given lung function impairment compared to men mainly because of hormonal, affective, or sociocultural reasons.[11, 12, 37, 38] Breathlessness is a complex experience that consists of qualitatively distinct sensations that arise through interplay of biochemical, mechanical, neurobiological, affective, and sociocultural factors.[35] This is reflected in our final model where only 22.8% of the mMRC variance was explained in the population. However, accounting for differences in absolute lung volume eliminated the difference in activity-related breathlessness between men and women. Women have been found to select more unpleasant descriptors of breathlessness at peak exercise which might be due to women breathing closer to their maximum ventilatory capacity.[27] In the same study, The intensity of breathlessness was similar in men and women when expressing ventilation in percent of the individual's maximum ventilation.[27] The importance of the ventilatory capacity rather than sex for exertional breathlessness is also supported by laboratory findings that men and women experience a similar increase in the intensity and unpleasantness of breathlessness for a similar change in ventilatory motor drive.[16]

New hypothesis

The present findings support that the functional impact of a given lung volume impairment depends on the underlying absolute lung volume.[11, 39] We further hypothesize that people with smaller absolute lung volumes are at increased risk of developing significant activity-related breathlessness in relation to different disease processes or noxious exposures such as smoking, which needs to be validated in longitudinal studies.

Conclusion

The markedly more severe activity-related breathlessness in women was explained by differences in absolute FEV₁ or FVC in the general population. The association between lower lung volumes and increased breathlessness was similar in men, women, and among healthy never-smokers. This highlights the importance of both relative and absolute values of lung function to evaluate the level of lung impairment and remaining ventilatory reserve.

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TABLES

Table 1. Characteristics of 3,250 people in the general population

Characteristic	Women N = 1,673 (51%)	Men N = 1,577 (49%)	All N = 3,250
Age	53.7 ± 7.0	54.2 ± 7.0	54.0 ± 7.0
mMRC breathlessness score			
0	1,226 (73)	1,349 (86)	2,575 (79)
1	343 (21)	203 (13)	546 (17)
2	95 (6)	22 (1)	117 (4)
3-4	9 (1)	3 (0)	12 (0)
FEV ₁ , L	2.67 ± 0.46	3.68 ± 0.66	3.16 ± 0.76
FEV ₁ , % of predicted	98.8 ± 13.8	98.5 ± 14.5	98.7 ± 14.1
FVC, L	3.39 ± 0.56	4.74 ± 0.80	4.04 ± 0.96
FVC, % of predicted	99.6 ± 12.9	99.2 ± 13.5	99.4 ± 13.2
FEV ₁ /FVC	0.79 ± 0.06	0.78 ± 0.06	0.78 ± 0.06
Body mass index (kg/m ²)	26.3 ± 5.0	27.2 ± 4.1	26.7 ± 4.6
< 18.5	18 (1)	5 (0)	23 (1)
18.5 to < 25	770 (46)	480 (30)	1,250 (38)
25 to 30	554 (33)	775 (49)	1,329 (41)
> 30	331 (20)	317 (20)	648 (20)
Pack-years smoking, median (IQR)	1.3 (0 to 19.2)	7.0 (0 to 30.5)	3.9 (0 to 24.3)
Current smoker	283 (17)	398 (19)	581 (18)
Never-smoker	801 (48)	645 (41)	1,446 (44)
Occupational exposure	569 (34)	947 (60)	1,516 (40)

Exercise (hours per week)			
≥ 2	688 (41)	763 (48)	1,451 (45)
0.5 to 1	437 (26)	366 (23)	803 (25)
None	548 (33)	448 (28)	996 (31)
Asthma	248 (15)	171 (11)	419 (13)
CAL (FEV ₁ /FVC < LLN)	73 (4)	87 (6)	160 (5)
Chronic bronchitis	148 (9)	160 (10)	308 (9)
IHD	24 (1)	45 (3)	69 (2)
Severe respiratory infection < age five	168 (10)	146 (9)	314 (10)
History of cancer	95 (6)	82 (5)	177 (5)
History of depression	301 (18)	168 (11)	469 (14)

Data presented as mean \pm standard deviation or count (percent) unless otherwise defined.

Percentages may not sum to 100 due to rounding.

Abbreviations: BMI = body mass index; CAL = chronic airflow limitation; FEV₁ = forced expiratory volume in one second after bronchodilation; FVC = forced vital capacity after bronchodilation; IHD = ischemic heart disease; IQR = interquartile range; LLN = lower limit of normal.

Table 2. Absolute FEV₁ and sex-related difference in breathlessness

Model	Without absolute FEV ₁		With absolute FEV ₁		Percent of the sex variance in breathlessness explained by absolute FEV ₁
	OR women vs. men (95% CI)	Variance explained by sex	OR women vs. men (95% CI)	Variance explained by sex	
Crude	2.21 (1.79 to 2.72)	4.8	0.89 (0.69 to 1.14)	0	100
Risk factors	2.52 (2.01 to 3.11)	5.2	1.18 (0.88 to 1.59)	0.1	98
Diseases	2.28 (1.90 to 2.77)	4.7	0.99 (0.78 to 1.26)	0	100
Physiology	2.56 (2.07 to 3.16)	5.2	1.13 (0.79 to 1.61)	0	100
Final	2.63 (2.12 to 3.25)	5.1	1.29 (0.89 to 1.88)	0.1	98

Sex difference in breathlessness expressed as odds ratios (OR) of more severe breathlessness for women compared with men in models with or without the absolute value of FEV₁ (n = 3,250 participants). The sex estimates were 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, IHD, and history of cancer and depression); and physiology (age, BMI, and CAL). The final model was controlled for age, BMI, chronic bronchitis, CAL, pack-years smoking, exercise, IHD, and history of depression. Analysis performed using ordinal logistic regression clustering on country with 3,250

participants in all models. The variance in mMRC scores explained by sex was measured as the difference in variance explained by the model with sex compared to the model without sex, using McKelvey & Zavoina's R^2 .

Abbreviations: BMI = body mass index; CI = confidence interval; FEV₁ = forced expiratory volume in one second; IHD = ischemic heart disease.

Table 3. Final model of absolute FEV₁ and sex difference in breathlessness in 3,250 people in the general population

Variable	Overall N = 3,250		Women N = 1,673		Men N = 1,577	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds ratio	95% CI
Women vs. men	1.29	0.89 to 1.87	-		-	
FEV ₁ (per L)	0.48	0.33 to 0.69	0.48	0.33 to 0.69	0.48	0.30 to 0.75
Age (per y)	0.99	0.97 to 1.01	0.99	0.98 to 1.01	0.98	0.95 to 1.02
BMI (per 1 kg/m ²)	1.10	1.07 to 1.13	1.10	1.07 to 1.13	1.11	1.06 to 1.16
Exercise ≥ 2 h per week	<i>Ref</i>		<i>Ref</i>		<i>Ref</i>	
Exercise 0.5 to 1 h per week	1.53	1.20 to 1.96	1.24	0.92 to 1.69	2.31	1.71 to 3.11
No exercise	2.17	1.66 to 2.84	1.77	1.25 to 2.50	3.16	2.20 to 4.55
Smoking (per pack-year)	1.00	1.00 to 1.01	1.00	0.99 to 1.01	1.01	1.00 to 1.01
CAL (FEV ₁ /FVC < LLN)	1.40	0.83 to 2.37	1.44	0.87 to 2.36	1.33	0.63 to 2.82
Chronic bronchitis	2.22	1.71 to 2.89	2.68	1.94 to 3.70	1.65	1.02 to 2.68
IHD	1.60	1.01 to 2.52	1.34	0.67 to 2.69	2.01	1.13 to 3.56
History of depression	1.37	1.10 to 1.71	1.53	1.17 to 2.00	1.03	0.64 to 1.66

Adjusted associations with the severity of exercise-related breathlessness on the modified Medical Research Council Dyspnea (mMRC) scale overall and in men and women separately, estimated using ordered logistic regression clustering over 24 centers. The model explained 22.8% of the variation in mMRC scores.

Abbreviations: BMI = body mass index; CI = confidence interval; CAL = chronic airflow limitation; FEV₁ = forced expiratory volume in one second; IHD = ischemic heart disease; pack-year = [mean cigarettes per day/20] x [number of years of smoking]; LLN = lower limit of normal.

FIGURE LEGENDS

Figure 1. Adjusted association between absolute and relative FEV₁ and activity-related breathlessness. Lower forced expiratory volume in one second (FEV₁) was associated with more severe activity-related breathlessness in the general population (n = 3,250) for A) the absolute FEV₁, and B) the relative FEV₁ in percent of predicted. Higher quintiles of FEV₁ imply higher FEV₁ values. Odds ratios are compared with the lowest quintile of FEV₁ (quintile 1), and are adjusted for age, body mass index, hours of exercise per week, pack-years of smoking, chronic bronchitis, chronic airflow limitation, ischemic heart disease, and history of depression. The adjusted association with mMRC was similar between men and women both for absolute FEV₁ (p = 0.69 for interaction) and FEV₁ in percent of predicted (p = 0.49 for interaction).

Figure 2. Percent of the sex difference in activity-related breathlessness explained by FEV₁ and FVC expressed in absolute volume and percent of predicted. Percent of the sex difference in activity-related breathlessness explained by FEV₁ and FVC expressed in absolute volume and percent of predicted in the general population (n=3,250). Sex difference was measured as the variance in the modified Medical Research Council (mMRC) breathlessness score explained by sex in ordinal logistic regression adjusted for age, BMI, chronic bronchitis, chronic airflow limitation, pack-years smoking, exercise, IHD, and a history of depression. The sex disparity disappeared when adjusting for differences in the absolute FEV₁ or FVC between men and women. In contrast, the sex difference was not reduced when adjusting for FEV₁ or FVC in percent of predicted.