Advances in Medical Sciences 64 (2019) 303–308

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Clinical importance of sex differences in dyspnea and its sex related determinants in asthma and COPD patients

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ARTICLE INFO

Keywords:
Asthma
COPD
Dyspnea sex determinants

ABSTRACT

Purpose: There is an increasing amount of data regarding the influence of sex on dyspnea perception, however, the influence of sex has not been included in clinical guidelines for asthma and chronic obstructive pulmonary disease (COPD).

Materials and methods: The study included 123 clinically stable subjects. Seventy five patients had COPD, of which 70.6% were men and 29.4% were women. Forty-eight subjects had asthma, comprised of 45.8% and 54.2%, men and women, respectively. Dyspnea was assessed with the use of modified Medical Research Council (mMRC) Visual Analogue Scale VAS, and BORG scale. All patients underwent spirometry with a broncho-reversibility test.

Results: There were no differences in age for neither asthma patients, 56.5 ± 11.6 and 55.0 ± 12.7 (p = 0.5) for males and females, nor for COPD patients, 66.8 ± 9.0 and 66.8 ± 7.7 (p = 0.7) for males and females, respectively. Asthmatic females had more dyspnea than males when assessed with VAS, 1.85 ± 2.24 and 3.84 ± 2.80 (p = 0.01), for males and females, respectively. When assessed with BORGpre 6-MWT, dyspnea results were 0.86 ± 1.83 and 2.43 ± 2.31 (p = 0.005), for males and females, respectively. In the whole group, apart from FEV_1 (for mMRC, VAS, BORGpre) and BMI (BORGpost) the severity of dyspnea was related to female sex when assessed with mMRC (OR = 2.83; 95%CI: 1.25–6.42) and VAS (OR = 2.17; 95%CI:1.00–4.73).

Conclusions: Although more apparent in asthma, it was revealed for the first time, that sex has a strong influence on the magnitude of dyspnea perception, both in asthma and COPD. Therefore, sex related dyspnea sensation should probably be included in clinical assessment and patient treatment.

1. Introduction

1.1. Dyspnea assessment

Dyspnea is a common clinical symptom frequently described as air hunger, or the perception of increased work of breathing. When present in respiratory tract diseases, dyspnea is accepted as an increased mortality risk factor [1]. Two of the widely used single dimensional tools for dyspnea assessment are the Visual Analogue Scale (VAS) [2], which assesses dyspnea as Sensory–perceptual experience, and the Modified British Medical Research Council (mMRC) scale used to measure the limitation of daily activities [3].

1.2. Dyspnea in asthma and COPD

In both, asthma and Chronic Obstructive Pulmonary Disease (COPD), dyspnea is the most frequent and clinically relevant symptom. Dyspnea plays a central role during diagnosis and in determining the severity of each disease [4,5]. In asthma, dyspnea is described as paroxysmal [4], whereas in COPD, as chronic activity limitation [5].

Although Global Initiative for Asthma - GINA guidelines [4] describe different patient subpopulations such as pregnancy, perimenstrual asthma, elderly people, smokers or obese patients, there is no data concerning sex-related differences in dyspnea character and severity. In GINA guidelines, the only sex-related data describes females as more likely for acute hospital admission, but it is still not possible to tell why females are more prone to hospitalization [4,6].

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https://doi.org/10.1016/j.advms.2019.03.003
Received 13 December 2018; Accepted 20 March 2019
Available online 03 April 2019

In COPD, exertional dyspnea is caused mainly by pulmonary hyperinflation and/or hypoxemia, which are reported to be the most important causes of exercise limitation [5,7]. However, even in severe cases, dyspnea may not be present [8]. One of the most dangerous periods in the natural course of COPD is during COPD exacerbations where dyspnea plays a key role [9]. In COPD, dyspnea is the most important factor responsible for a patient's search for medical help [5,10], as well as one of three key symptoms, which warrants the possibility to diagnose COPD exacerbation [5,11]. In COPD, the most commonly accepted method of dyspnea measurement is the mMRC questionnaire, which is used for differentiating between GOLD A&B or C&D categories in patients with a similar number of COPD exacerbations [3,5]. Severe persistent dyspnea in the course of COPD is accepted as a major palliative treatment goal [12]. Dyspnea also plays an important role in the assessment of COPD related patients' death risk. One of the most commonly used survival calculators is the BODE-index, in which 3 out of 10 possible points are dependent on dyspnea as assessed by the mMRC scale [13]. Another widely accepted COPD death risk calculator is the DOSE index which helps to define COPD related death risk in a General Practitioner's population setting [14]. In the DOSE index, mMRC may account for 3 out of 8 possible points, which indicates, that the dyspnea sensation may be considered as one of the most important COPD mortality risk factors [14].

1.3. The role of sex in dyspnea sensation

According to current GINA and GOLD guidelines [4,5], and according to the American Thoracic Society (ATS) dyspnea dedicated guidelines [1], there is lack of data concerning sex-related dyspnea determinants. However, according to the most recent literature on COPD, there are substantial sex-related differences in COPD symptoms perception amongst patients [15]. Similarly, in asthma, it was reported that females have more dyspnea and poorer quality of life than males [16]. Taking into account the fact that dyspnea plays a central role in asthma and COPD diagnosis and treatment, and has a strong impact on patients' prognosis, we aimed to assess sex-related differences in dyspnea determinants in asthma and COPD patients.

2. Material and methods

2.1. Material

The study group included 123 subjects, 75 men (60.9%) and 48 women (39.1%). Patients were recruited from the Department of Pneumonology in Katowice (Poland) and its outpatient clinic to participate in the study based on the following criteria: older than 18 years of age, prior asthma diagnosis at least 6 months ago based on GINA guidelines, well-controlled disease (20–25/25 points in asthma control test) [17], and on at least a 3 STEP treatment level [4]. Furthermore, COPD patients who were older than 18 years of age, had a COPD diagnosis established for at least 6 months [5] and had at least II stage bronchial obstruction, were found suitable and recruited to participate in the study. Before inclusion in the study, all patients read and signed an informed consent form to participate in the study. Table 1 shows the differences between distributions of anthropometric and lung function variables in men and women. Compared with women, men were older, had higher BMI, worse predicted lung function status and smoked more than women.

2.1.1. Ethical issues

The study has been approved by the Ethics Committee of the Medical University of Silesia, Poland (approval number: KNW/0022/KB1/54/15).

All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments.

2.2. Methods

2.2.1. Patients assessment

Patients were evaluated using the mMRC, VAS and BORG scales. All of the study subjects underwent a spirometry test according to the new ATS/ ERS standardization guidelines [18]. All tests met the acceptability and repeatability criteria set out in the guidelines. All patients performed a 6-minute walk test (6-MWT) that met the Polish guidelines' acceptance requirements for the 6-MWT methodology [19]. Taking into account probable sex related differences in exercise capacity, both heart rate and oxygen saturation were measured before, during and after the performance of the exercise test. Formula "predicted 6MWT = 361 – (age in yrs x 4) + (height in cm x 2) + (HR max /HR max % pred x 3) – (weight in kg x 1.5) – 30 (if females)" was used for the calculation of percentage of reference value (%rv) of distance in the 6-MWT calculated for each study participant [20].

2.2.2. Statistical analysis

Data analysis included quantitative and qualitative variables. Distribution of all quantitative variables was shown by arithmetic mean values, standard deviations and ranges, and was not normal (result of Shapiro-Wilk test). Distribution of qualitative variables was shown by absolute and relative frequencies of the values. Between-group differences in the distribution of quantitative variables were assessed using the nonparametric Kruskal-Wallis test, and in the case of qualitative variables, the chi^2 test was used. Interpretation of the statistical significance of the differences examined in the simple analyses was based on the criterion $p < 0.05$. Results of univariate analyses were verified by means of a multivariable logistic regression providing logistic odds ratios and their 95% confidence intervals. Four separate models of mMRC, VAS, BORGpre, BORGpost were used with dependent variables expressing dyspnea levels. Each model included the same set of independent variables checked for multicollinearity by analysis of correlation. Statistical inference regarding multivariate analysis was based on the criterion $p < 0.1$. All data analyses were performed using SAS statistical package.

3. Results

3.1. Asthma and COPD in men and women

COPD was diagnosed in 75 subjects (60.9%), including 53 men (70.6%) and 22 women (29.4%). Asthma was diagnosed in 48 subjects (39.1%), including 22 men (45.8%) and 26 women (54.2%). Distribution of sex differed between the two diagnostic groups ($p = 0.005$).

3.2. Anthropometric and lung function parameters in men and women

Table 2 shows the anthropometric and lung function status of the examined men and women according to two diagnostic categories. In general, between-sex differences were more apparent in asthma subjects. In this subgroup, women, as compared with men, had smaller BMI, better predicted lung function and had a lesser smoking burden, but covered a similar distance in the 6-MWT. However, in terms of age, basic lung function indices in men and women were similar. In the COPD subgroup, women had larger FVC% reference value and smoked less, but airflow (FEV_1) was similar in both sex-defined categories.

3.3. Dyspnea in asthma and COPD according to single variable analysis

Symptoms of dyspnea were assessed using four scales: mMRC, VAS, BORGpre and BORGpost 6-MWT. Many subjects presented low scores of dyspnea: mMRC < 2 in 45.9% of men and in 41.6% of women, VAS < 3 in 43.8% of men and in 35.4% of women, BORGpre < 3 in 68.9% of men and in 61.9% of women, and BORGpost < 3 in 26.3% of

Table 1
Anthropometric and lung function variables in men and women.

Variable	Men		Women		p value*
	X ± SD	Range	X ± SD	Range	
Age (years)	63.7 ± 10.9	31-83	60.4 ± 12.2	22-81	0.09
BMI (kg/m^2)	29.7 ± 6.5	16.7-48.3	27.9 ± 7.1	16.3-49.3	0.06
FVC (l)	2.77 ± 0.64	1.54-4.74	2.08 ± 0.64	0.42-3.62	< 0.0001
FVC (%rv)	68.2 ± 15.0	39.7-112.8	78.7 ± 19.5	16.7-120.0	0.0005
FEV_1 (l)	1.54 ± 0.54	0.48-2.92	1.25 ± 0.47	0.32-2.38	0.003
FEV_1 (%rv)	48.7 ± 14.7	18.7-76.4	54.2 ± 14.7	15.0-76.8	0.06
FEV_1/FVC (%)	55.8 ± 15.8	26.1-90.2	60.9 ± 15.2	33.0-99.1	0.01
$SatO_2$ (%)	92.4 ± 3.9	83-98	93.4 ± 4.5	75-99	0.01
6-MWT distance (m)	357 ± 102	93-531	347 ± 112	90-600	0.6
6-MWT distance (%rv)	68.0 ± 19.3	18.3-97.3	68.2 ± 20.8	18.1-100.9	0.8
Smoking (pack years)	31.1 ± 23.1	0-110	15.9 ± 18.6	0-90	< 0.0001

BMI - body mass index; FVC - forced vital capacity; FEV_1 - forced expiratory volume in 1 s; $SatO_2$ - Oxygen saturation; 6-MWT - distance measured in a 6-Minute-Walk-Test.
* result of the Kruskal-Wallis test.

men and in 29.7% of women.

In terms of the frequency analysis (chi^2 test: results not shown), in the asthma subgroup, men and women did not differ in terms of the distribution of mMRC, VAS and BORGpost scores. However, women had higher scores of BORGpre than men, although the difference was not statistically significant (p = 0.07). In the COPD subgroup, the distribution of dyspnea scores did not differ statistically significantly between men and women, although there was a tendency towards lower scores in women than in men (p = 0.06).

Table 3 shows mean values and the range of dyspnea scores in men and women, according to two diagnostic categories. In the asthma subgroup, women presented larger scores and the men-women difference was statistically significant for the assessment according to VAS and BORGpre scales. In the COPD subgroup, men as compared with women had lower dyspnea mMRC and VAS scores and higher scores of dyspnea measured by BORGpre and BORGpost scales, and the last difference was statistically significant.

3.4. Dyspnea in asthma and COPD according to multivariate analysis

Results of the simple analysis were verified by multivariate analysis (GLM-SAS) with dyspnea intensity as the dependent variable (four independent models). The following variables were considered as explanatory variables: age, BMI, FEV_1 (%rv), $SatO_2$, distance (%rv), diagnosis (asthma/COPD), smoking category and sex. The choice of independent variables resulted from earlier analyses of correlation between candidates for explanatory variables. As a result, and in order to control collinearity, only FEV_1 (%rv), but not FVC, was included in the model, and the distance covered in a 6-MWT was not entered (correlation with BMI: p = 0.02, FEV_1%rv: p < 0.0001, $SatO_2$: p = 0.001, smoking status: p = 0.02). Moreover, because of the statistically significant correlation between pack-years and age (p < 0.0001) or FEV_1 (p < 0.0001), smoking burden in the model was expressed as a categorical variable: non-smokers (men: 18.8%, women: 8.8%), ex-smokers (men: 65.1%, women: 45.1%), non-smokers (men:16.1%, women: 45.1%). The effect of sex on the severity of dyspnea after adjustment for diagnostic category and confounding variables is shown in Table 4.

In the whole group, apart from FEV_1 (for mMRC, VAS, BORGpre) and BMI (BORGpost) the severity of dyspnea was related to female sex when assessed with mMRC (OR = 2.83; 95%CI: 1.25–6.42) and VAS (OR = 2.17; 95%CI:1.00–4.73).

In all subjects (both diseases), the severity of dyspnea, as measured according to mMRC scale, was related to sex in a marginally statistically significant way – women presented higher scores after adjustment for diagnostic category and other important variables including airflow, smoking status, oxygen saturation, age and BMI. Multivariate analyses restricted to data from asthma subjects showed that the effect of sex was marginally statistically significant on dyspnea severity measured by mMRC scale (p = 0.06). On the other hand, respective analyses in a subset of data from COPD subjects showed a statistically significant effect of sex only on the dependent BORGpost variable (p = 0.04) and

Table 2
Anthropometric and lung function variables in men and women, according to two diagnostic categories.

Variable	Asthma			COPD		
	Men X ± SD (Range)	Women X ± SD (Range)	p value*	Men X ± SD (Range)	Women X ± SD (Range)	p value*
Age (years)	56.5 ± 11.6 (31-76)	55.0 ± 12.7 (22-73)	0.5	66.8 ± 9.0 (39-83)	66.8 ± 7.7 (56-81)	0.7
BMI (kg/m^2)	32.3 ± 6.0 (21.5-47.8)	27.9 ± 8.6) (16.3-49.3	0.01	28.5 ± 6.5 (16.7-48.3)	27.9 ± 5.0 (22.2-39.1)	0.6
FVC (l)	2.84 ± 0.63 (1.76-3.73)	2.20 ± 0.73 (0.42 = 3.62)	0.006	2.74 ± 0.65 (1.54-4.74)	1.94 ± 0.51 (1.09-3.11)	< 0.0001
FVC (%rv)	63.7 ± 13.1 (39.7-86.5)	74.6 ± 19.7 (16.7-108.0)	0.01	69.6 ± 15.4 (42.2-112.8)	83.3 ± 18.8 (40.3-120.1)	0.002
FEV_1 (l)	1.85 ± 0.64 (0.96-2.90)	1.42 ± 0.53 (0.32-2.38)	0.05	1.43 ± 0.47 (0.48-2.92)	1.05 ± 0.29 (0.7-1.68)	0.0006
FEV_1 (%rv)	52.46 ± 16.40 (25.2-74.7)	55.93 ± 14.9 (15.0-75.9)	0.4	47.4 ± 14.1 (18.7-76.4)	52.2 ± 14.6 (29.5-76.8)	0.3
$SatO_2$ (%)	94.0 ± 3.9 (83-98)	94.8 ± 2.9 (82-99)	0.3	91.8 ± 3.8 (84-98)	91.6 ± 5.0 (75-98)	0.8
6MWT (m)	392 ± 101 (120-531)	367 ± 105 (90-600)	0.2	341 ± 100 (93-494)	317 ± 117 (90-472)	0.5
6MWT (%rv)	73.6 ± 18.0 (24.1-96.4)	70.0 ± 18.1 (18.7-100.6)	0.4	65.5 ± 19.56 (18.3-97.3)	65.5 ± 24.7 (18.1-100.9)	0.8
Smoking (pack-years)	22.4 ± 20.3 (0-65)	5.5 ± 7.5 (0-25)	< 0.001	34.7 ± 23.4 (0-110)	28.1 ± 20.4 (0-90)	0.07

BMI - body mass index; FVC - forced vital capacity; FEV_1 - forced expiratory volume in 1 s; $SatO_2$ - Oxygen saturation; 6-MWT - distance measured in a 6-Minute-Walk-Test.
* result of the Kruskal-Wallis test.

Table 3
Intensity of dyspnea as assessed using four scales in men and women.

Dyspnea Scale	Asthma			COPD		
	Men X ± SD (Range)	Women X ± SD (Range)	p value*	Men X ± SD (Range)	Women X ± SD (Range)	p value*
mMRC	1.22 ± 1.37 (0-4)	1.80 ± 1.44 (0-4)	0.1	2.23 ± 1.33 (0-4)	2.63 ± 1.43 (0-4)	0.2
VAS	1.85 ± 2.24 (0-9)	3.84 ± 2.80 (0-10)	0.01	3.82 ± 2.59 (0-9)	4.04 ± 2.90 (0-8)	0.7
BORGpre	0.86 ± 1.83 (0-7)	2.43 ± 2.31 (0-7)	0.005	2.00 ± 2.35 (0-9)	1.73-2.53 (0-7)	0.5
BORGpost	4.00 ± 3.16 (0-10)	4.86 ± 2.29 (0-10)	0.1	4.82 ± 2.62 (0-10)	2.86 ± 2.61 (0-7)	0.02

mMRC - modified Medical Research Council scale; VAS - Visual Analogue Scale; BORGpre – assessment with BORG scale before the 6-Minute-Walk-Test; BORGpost - assessment with BORG scale after participation in the 6-Minute-Walk-Test.
* result of the Kruskal-Wallis test.

not on other presentations of dyspnea.

4. Discussion

4.1. General findings

According to our best knowledge, our report is the first one to report that the female sex in both asthma and COPD patients is strongly related with the increasing severity of dyspnea sensation when assessed with the use of mMRC or VAS scales. The strength of this impact was found comparable or even stronger than the FEV_1, which for years has a well-established role both in asthma and COPD guidelines [4,5]. The results of our study reveal that females are more prone to the presence of dyspnea when compared to males. It is important to underline that in our study we have assessed dyspnea sensation in three different aspects (single dimension assessed by VAS) [2], as possible daily activities limitation (mMRC) [3] and in the aspect of exercise induced dyspnea assessed by the old, but still valid, BORG scale [21] which was assessed both pre and post 6-MWT. The strength of sex influence on dyspnea sensation was stronger than in case of FEV_1, which was partially in line with recent findings by Crisafulli et al. [22] who reported that dyspnea had a stronger impact on exercise capacity than FEV_1. Currently, official GINA and GOLD guidelines do not focus on possible sex related differences in the clinical presentation of asthmatic and COPD patients [4,5]. However, with growing evidence for sex related differences in the magnitude of dyspnea perception and well confirmed dyspnea prognostic value [13,14] it seems likely, that future asthma and COPD guidelines will address both sexes in an independent way regarding dyspnea sensation and its influence on disease severity or control. Sex discrepancies in dyspnea sensation should be considered in clinic, as a sex-related approach could improve management of obstructive lung diseases. The subjective dyspnea sensation presented by patients cannot be underestimated. More severe dyspnea felt by women may be a factor affecting more frequent use of rescue medication, more frequent hospitalizations and outpatient appointments. Uncontrolled dyspnea may lead to decreased quality of life, anxiety and depression.

4.2. Dyspnea in asthmatic patients

We have shown in the asthmatic population, known for rapid asthma attacks which are usually secondary to sudden bronchial obstruction episodes but may frequently be enriched by an emotional affective sensation [4], that assessed females had stronger baseline dyspnea severity than males (Table 3). However, this was not confirmed when assessed by the post 6-MWT BORG scale assessment. Nevertheless, taking into account the paroxysmal dyspnea character in asthmatic patients, which frequently may be characterized as exercise induced bronchoconstriction [23], we have to underline that asthmatic females had significantly better lung function and smaller tobacco burden. However, females were not keen to walk faster during the 6-MWT; both when assessed in meters and when assessed as patient predicted value (Table 2) [19]. Taking into account that there were no age or FEV_1 % predicted differences between both sexes (Table 2), this might be explained by the fact that females walked slower than possible to avoid the potential risk of an exercise-induced bronchospasm and therefore dyspnea attack. A potential explanation could be due to different resistance to perceived dyspnea in both sexes. Although assessed on an older population, our results are partially in line with Guldberg-Møller et al. [24] who revealed that the female sex and smoking are related with the presence of asthma-like symptoms, whereas in our study, only the female sex proved to have influence on dyspnea perception.

4.3. Dyspnea in COPD patients

In the COPD population, the magnitude of dyspnea related daily life limitations (mMRC) is one of the most important in terms of prognosis [13]. Females were found to have less exercise induced dyspnea, which was somewhat surprising, but possible to explain by better lung function when assessed by FVC, and marginally better when assessed by

Table 4
Effect of sex on the severity of dyspnea – results of multivariate analyses in all patients.

Independent Variable	Dependent Variable			
	mMRC OR* (95% CI)	VAS OR (95% CI)	BORGpre OR (95% CI)	BORGpost OR (95% CI)
Age (years)	0.99 (0.95-1.02) p = 0.6	0.99 (0.96-1.03) p = 0.8	0.96 (0.92-1.00) p = 0.09	0.98 (0.94-1.02) p = 0.4
BMI	0.95 (0.90-1.00) p = 0.09	1.01 (0.96-1.07) p = 0.5	0.96 (0.91-1.02) p = 0.2	**0.94 (0.89-0.99) p = 0.03**
FEV_1 (%rv)	**1.02 (1.00-1.05) p = 0.03**	**1.03 (1.00-1.05) p = 0.02**	**1.03 (1.00-1.06) p = 0.03**	1.02 (0.99-1.05) p = 0.1
$SatO_2$	1.04 (0.93-1.16) p = 0.4	1.05 (0.95-1.16) p = 0.3	0.92 (0.82-1.03) p = 0.1	1.01 (0.90-1.14) p = 0.7
Asthma/COPD	0.36 (0.13-1.01) p = 0.05	0.61 (0.22-1.62) p = 0.3	1.29 (0.44-3.74) p = 0.6	1.26 (0.44-3.63) p = 0.6
Smoking Status	0.89 (0.31-2.56) p = 0.8	0.87 (0.31-2.43) p = 0.8	0.98 (0.32-2.97) p = 0.9	**3.89 (1.23-12.26) p = 0.02**
Sex – female	**2.83 (1.25-6.42) p = 0.01**	**2.17 (1.00-4.73) p = 0.04**	1.47 (0.63-3.44) p = 0.3	0.51 (0.21-1.22) p = 0.1

BMI - body mass index; FEV_1 - forced expiratory volume in 1 s; $SatO_2$ - Oxygen saturation; COPD - chronic obstructive pulmonary disease.
* Odds Ratio (95% Confidence Interval); p values of regression coefficients. Bolded font was used for statistically significant findings.

FEV_1, as well as taking into account a significantly smaller nicotine burden (Tables 2 and 3). It has to be underlined that the differences in FEV_1 predicted value in men and women were small, and not statistically significant when expressed in %rv. However, the mean FEV_1 value for men was placed on the level of severe, whereas in the case of women on the level of moderate obstruction [5]. Taking into account the mean value of mMRC ≥ 2 both in men and women (Table 3), and the fact that > 50% males and females have had mMRC ≥ 2 was important in clinical means. Based on current 2019 GOLD guidelines [5], the above observation is not that vital in terms of treatment. However, when looking at previous GOLD guidelines (2018 and former) and current Polish Respiratory Society COPD guidelines, the change from severe to moderate obstruction at ≥ 2 mMRC points would change the COPD classification from B to D; resulting in a different level of disease related treatment and prognosis [25]. Moreover, the borderline of predicted FEV_1- placed at 50%, differentiates between 1 or 2 points collected in BODE index which is accepted as a relevant predictive tool [13]. Although in our population a similar number of patients were classified as ≥ 2 mMRC points, it has to be remembered that our population differed slightly according to lung function and strongly according to smoking burden. Therefore, it may be speculated that in case of FEV_1 matched men and women, females would have received more BODE points and therefore would have higher mortality risk [13]. The results of our work confirm earlier reports about the significance of the patient's sex as an independent factor influencing dyspnea in obstructive diseases [26,27]. In both assessed subgroups, despite the better lung function determined by FEV_1%, women showed a greater intensity of dyspnea on the BORG scale. One of the potential factors that may affect this may be the smaller lung capacity in liters in the female population versus male. One of the possible explanations of another factor that could influence the results of our work is the relatively lower strength of the respiratory muscles in women, which can influence their dyspnea sensation [28].

4.4. Study limitations

We considered our results as innovative and clinically meaningful, however there are some study limitations with should be addressed.

First of all, at the time of data analysis, we found that there was a probable patient selection bias, which resulted in better lung function (according to reference value) in females than in males. This was probably caused by larger smoking burden in our males, both in asthma and COPD population. In our study, included females presented a smaller amount of pack-years in both asthma and COPD subgroups (Table 2). This is especially important when taking into account that it is accepted that females are more sensitive to tobacco smoke and even lower exposure may lead to greater lung impairment in this group of patients [29–32]. However, taking into account that smoking likelihood in general is decreasing, males are still more prone to smoking. Accordingly, the difference between the smoking likelihood of males and females is still meaningful [33,34]. Taking this into account, possible prospective matching of included patients according to their smoking burden expressed by pack-years would result in falsification of a real life scenario and in poorer possibility of implementing our results into clinics. On the other hand, it must be remembered that smoking females are more prone to lung function decline than smoking males [35].

Another possible limitation is no control for upper airway complaints during the stage of patient recruiting. Taking into account the definition of United Airways Disease (UAD), that upper and lower airways are connected to each other anatomically and immunologically, they should therefore be treated as one single organ. This hypothesis proposes that some types of upper and lower airway diseases are different manifestations of one medical condition [36]. Uraguchi et al. [37] established that eosinophilic chronic rhinosinusitis patients had more peripheral airway obstruction than patients with non-eosinophilic chronic rhinosinusitis and needed to be monitored more carefully. However, to the best of our knowledge, there is no research reporting the influence on basic lung function and perception of dyspnea in these patients. Moreover, according to our study protocol, all patients - both with asthma and COPD, had to be clinically stable, and therefore upper airway problems should not be considered as important in terms of obtained results.

The probably last study limitation is the potential influence of the menstrual cycle's secondary hormonal changes that may influence the magnitude of dyspnea sensations. This can partially explain the larger dyspnea sensation in younger asthmatic females [38,39]. This should be addressed in future studies from which females who reported perimenstrual symptoms should be excluded.

5. Conclusions

According to our best knowledge, it was found, probably for the first time, that in patients with asthma and COPD, women are much more susceptible to dyspnea than men. It seems that sex related dyspnea perception differences should be considered clinically relevant in clinical management of patients with asthma and COPD.

Conflict of interest

The authors declare no conflict of interests.

Financial disclosure

The research was performed as a part of Silesian Medical University (Poland) grant number: KNW-1-173/K/8/K.

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