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When patient-reported respiratory symptoms shed light on pathophysiology in adult asthma: a cross-sectional study

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While studies have demonstrated the impact of asthma symptoms on quality of life, very few studies have investigated the relationship between detailed asthma symptoms, as reported by the patient, and lung function and inflammation. A cross-sectional study was conducted on treated (ICS/LABA) adult (> 18 years) asthma patients recruited from the Liege University Hospital Asthma Clinic (Belgium) between 2018 and 2023 ($n = 505$). The intensity of asthma symptoms (dyspnea, wheezing, chest tightness, cough, and airway secretion) was measured using five-point Likert scales (5 expressing the greatest intensity). Multiple linear regression models including all independent variables were carried out to evaluate whether lung function and inflammatory parameters were independently associated with distinct symptoms. Cough associated with female gender ($p < 0.05$), smoking ($p < 0.01$), low FeNO ($p < 0.05$) and FEV1% pred. ($p < 0.05$), and high blood and sputum eosinophils ($p < 0.05$ for both). Airway secretion associated with smoking ($p < 0.05$). Chest tightness associated with young age ($p < 0.001$), female gender ($p < 0.05$) and low FEV1% pred. ($p < 0.01$). Dyspnea associated with female gender ($p < 0.001$), high BMI ($p < 0.05$), low FEV1% pred. ($p < 0.0001$) and high FEV1/FVC % ($p < 0.01$). Wheezing associated with young age ($p < 0.01$), high BMI ($p < 0.05$), smoking ($p < 0.01$), low FEV1% pred. ($p < 0.0001$) and high FEV1/FVC % ($p < 0.05$). Different respiratory symptoms are associated with distinct demographic, functional and inflammatory features paving the way for personalized therapeutic interventions.

Keywords Asthma, Symptoms, PROMs, Lung function, Inflammation

Asthma, a chronic respiratory disease, is a huge public health problem affecting approximatively 358 millions of people worldwide and around 8% of the population in Europe[1]. This pathology has important socio-economic impact[2]. The social incidence of the disease is reflected especially in an impaired health-related quality of life (HRQL), a loss of work productivity and a job loss[3,4]. The economic impact of asthma includes significant direct (e.g., medical, and non-medical costs associated with day-to-day care) and indirect (e.g., absenteeism from work and loss of productivity) costs[5,6].

The primary goal of asthma care is to reach an optimal control of the disease[7]. However, in Europe, the scientific literature reports 54% of asthmatics being not controlled[8,9]. The level of asthma control is expressed by the frequency and intensity of asthma symptoms, as well as their impact on daily activities over a period of 1 to 4 weeks[7,10]. While previous studies have demonstrated the impact of symptoms on HRQL[11,12], few studies have investigated the relationship between detailed asthma symptoms as reported by the patient and lung function and inflammation.

Knowing which symptom is related to either lung function parameters or inflammatory parameters is important in order to better understand the disease status. For instance, symptoms related to lung function and/or inflammation could have an impact on treatment choice. Indeed, the expression of a symptom linked to inflammation could lead to use a inhaled corticosteroids while the expression of another symptom linked to the impaired function could lead to the use of bronchodilators[13,14]. The appropriate treatment choice is a public

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health issue given the cost of asthma medications[15] and their potential harmful environmental effects when consumed inappropriately[16].

Therefore, the main objective of this study was to assess the relationship between five asthma symptoms, as reported by the patient, and lung function and inflammatory parameters in a population of treated adult asthmatics.

Methods

Study design, setting, and participants

A cross-sectional study was conducted on adult (≥ 18 years) asthma patients, receiving ICS/LABA, recruited from the Liege University Hospital Asthma Clinic (Belgium) between 2018 and 2023. Asthma diagnosis was based on the presence of typical asthma symptoms (wheezing, dyspnea, chest tightness, cough and airway secretion) associated with a 12% and 200 ml forced expiratory volume in 1 s (FEV1) reversibility after inhalation of 400 µg salbutamol, and/or a provocative concentration of methacholine causing a 20% drop in FEV1 ≤16 mg/ml when FEV1 ≥ 70% predicted[17]. Of the asthmatics who completed symptom scales, only those with complete data including sputum cell counts were included. The sample size was 505 participants (Fig. 1).

Studied variables

All the variables described below were collected as part of the patient routine examination.

Patient-reported asthma symptoms intensity scales (dependent variable)

The intensity level of the 5 classic asthma symptoms[17] including dyspnea (breathlessness), wheezing, chest tightness, cough, and sputum production were measured using five-point Likert scales (from 1 to 5), where the level 1 means that the symptom is not present, and level 5 expresses the greatest intensity of the symptom concerned.

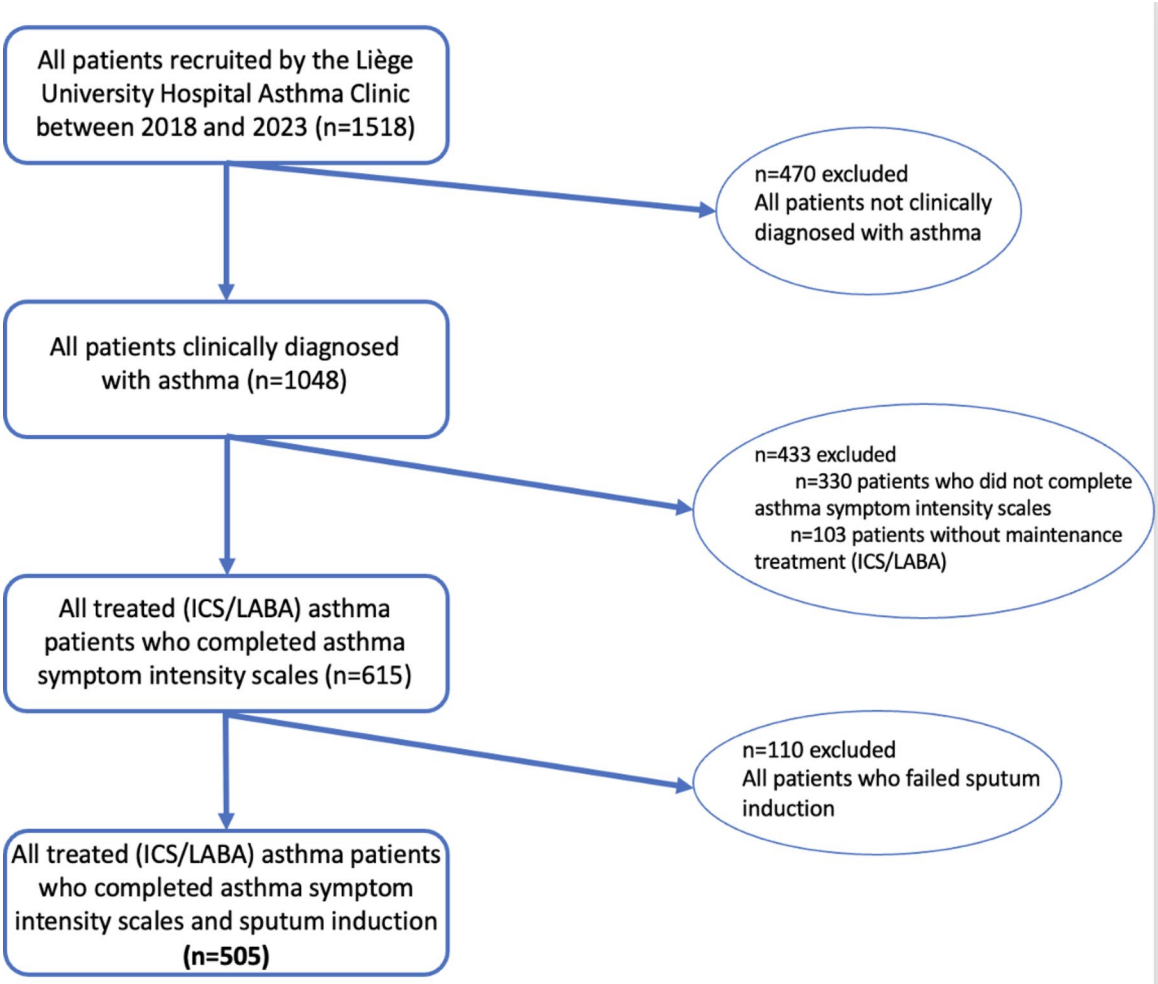

Fig. 1. Flow chart of the patient selection process.

Demographic and disease characteristics (independent variables)
Demographic characteristics were age, gender, BMI and smoking status. Smoking status was divided in three categories: never-smoker, ex-smoker (quit smoking at least 6 months previously) and current smokers. Disease characteristics were lung function and systemic and airway inflammation. Lung function testing was performed by spirometry (PFT spirostick, Geratherm, Germany), according to the ERS/ATS standard[18]. Inflammatory parameters included FeNO, sputum cell counts, blood cell counts, and systemic markers. FeNO was measured at a flow rate of 50 ml/s (NIOX; Aerocrine, Solna, Sweden) before spirometry. Sputum induction and processing were performed as previously described[19,20]. C-reactive protein (CRP), fibrinogen, (blood and sputum) eosinophils and neutrophils counts, and total serum IgE were determined by routine laboratory analysis at Liège University Hospital.

Statistical analysis

The normality of the distribution of the quantitative data was evaluated numerically by comparing mean and median and graphically by using a histogram and quantile-quantile plot. The Shapiro-Wilk test for normality was used to complete this assessment. Quantitative variables were summarized accordingly using median and interquartile range (P25–P75), while counts and percentages were calculated for qualitative variables.

The associations between quantitative variables and each symptom intensity scale were first determined using the Spearman correlation coefficient. To take into account the possibility of an important variable which could have not come out as significant because of confounding factors from univariate analyses, multiple linear regression models including all independent variables were carried out to evaluate how lung function and inflammatory parameters were independently associated with each patient-reported asthma symptoms[21].

All statistical analyses were performed using GraphPad Prism software (version 9.4.1) at a significance level of 0.05.

Ethics

This study was approved by the Liège University Hospital ethics committee. Signed informed consent was obtained from patients as soon as they entered the asthma clinic. They agreed to allow their clinical data and the health outcomes they reported in the routine setting to be used for research purpose. Moreover, all methods were performed in accordance with the relevant guidelines and regulations. More specifically, this study was conducted in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement", that are guidelines for reporting observational studies.

Results

Characteristics of the study population

The demographic characteristics of the study population are presented in Table 1. The majority of patient were female (58%) with a median age of 54 years. Non-smokers represented 50% of the population, while ex-smokers and smokers represented 29% and 21% respectively. The median BMI was 27, with an interquartile range from 23 to 30, i.e. 25% of our population was obese. Median FEV1% pred. was 83 and median FeNO was 22 ppb. Only 26% of the study population had well controlled asthma, as measured by an asthma control test (ACT) $\geq$ 20. Median (IQR) values of other lung function and inflammatory parameters are shown in Table 1.

Variables	Median (IQR)/percentage (*n*)
Age (years)	54 (40–63)
Gender (male)	42% (214)
Smoking status	
Non-smokers	50% (254)
Ex-smokers	29% (144)
Smokers	21% (107)
BMI (kg/m^2)	27 (23–30)
ICS dose* (µg/day)	1600 (1000–2000)
Asthma control test (ACT)	15 (11–20)
FEV1 (% predicted)	83 (69–95)
FEV1/FVC (%)	75 (68–81)
FeNO (ppb)	22 (13–40)
Sputum neutrophils (%)	67 (44–81)
Sputum eosinophils (%)	2 (0.4–6.3)
Blood neutrophils (10^3 1/µL)	4 (3.2–5.3)
Blood eosinophils (10^3 1/µL)	0.19 (0.11–0.32)
Fibrinogen (g/L)	3.3 (2.8–3.9)
CRP (mg/L)	2.1 (1–4.8)
Total IgE (KU/L)	109 (34–306)

Table 1. Patient characteristics ($n = 505$). *Equivalent beclomethasone.

In the study population, dyspnea was the symptom displaying the highest intensity with a mean (±SD) value of 3.68 (±1.1), followed by cough, chest tightness, wheezing and airway secretion with mean values of 3.10 (±1), 2.91 (±1.1), 2.68 (±1.1) and 2.61 (±1.2) respectively (Fig. 2). Figure 3 showed that the strongest correlations were found between dyspnea and chest tightness (rs = 0.55) and dyspnea and wheezing (rs = 0.53) while the lowest correlation was found between chest tightness and airway secretion (rs = 0.17).

Factors associated with cough intensity

Results of spearman correlation coefficient (univariate analysis) are given in Table 2. FeNO (rs: − 0.18), FEV1% pred. (rs: − 0.14), blood neutrophils (rs: 0.11), fibrinogen (rs: 0.12) and CRP (rs: 0.10) were significantly correlated to cough intensity. In multivariate analysis, gender, smoking status, FeNO, FEV1% pred., blood eosinophils and sputum eosinophils were significantly and independently associated with cough intensity (Table 3; Fig. 4). Female gender was associated with increased cough intensity ($p < 0.05$). Being a smoker in comparison to ex-smokers and never-smokers associated with increased cough intensity ($p < 0.01$ for both). FeNO decreased with increasing cough intensity ($p < 0.05$). FEV1% pred. decreased with increasing cough intensity ($p < 0.05$). Blood eosinophils and sputum eosinophils increased with increasing cough intensity ($p < 0.05$ for both).

Factors associated with airway secretion intensity

Results of spearman correlation coefficient (univariate analysis) are given in Table 2. Only blood eosinophils (rs: 0.14) were significantly correlated to airway secretion intensity. In multivariate analysis, smoking status was significantly and independently associated with airway secretion intensity (Table 3). Being a smoker in comparison to ex-smokers associated with increased airway secretion intensity ($p < 0.05$).

Factors associated with chest tightness intensity

Results of spearman correlation coefficient (univariate analysis) are given in Table 2. Only age (rs: − 0.15), FeNO (rs: − 0.13), FEV1% pred. (rs: − 0.14), were significantly correlated to chest tightness intensity. In multivariate analysis, age, gender and FEV1% pred were significantly and independently associated with chest tightness intensity (Table 3; Fig. 4). Age decreased with increasing chest tightness intensity ($p < 0.001$). Being a female

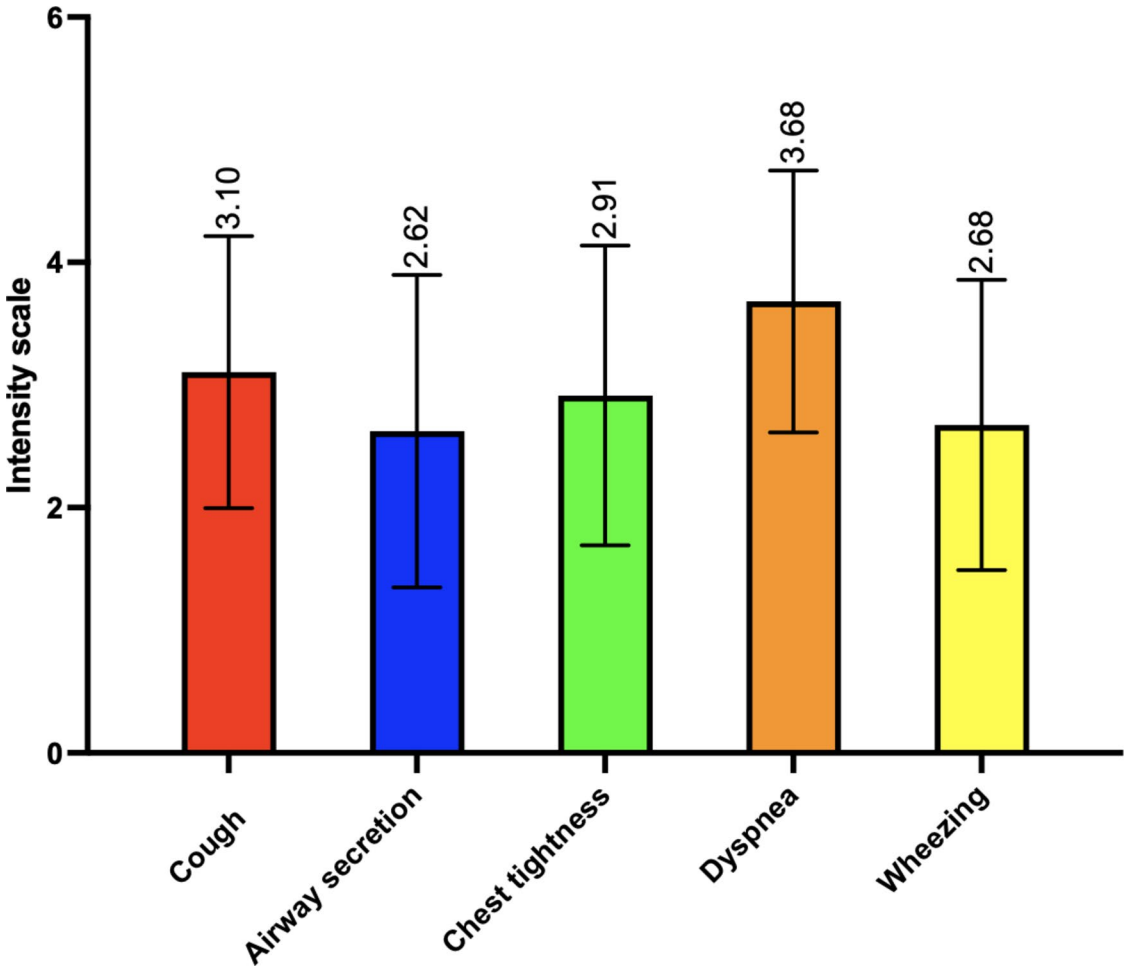

Fig. 2. Mean (SD) value of each patient-reported asthma symptom intensity scale ($n = 505$).

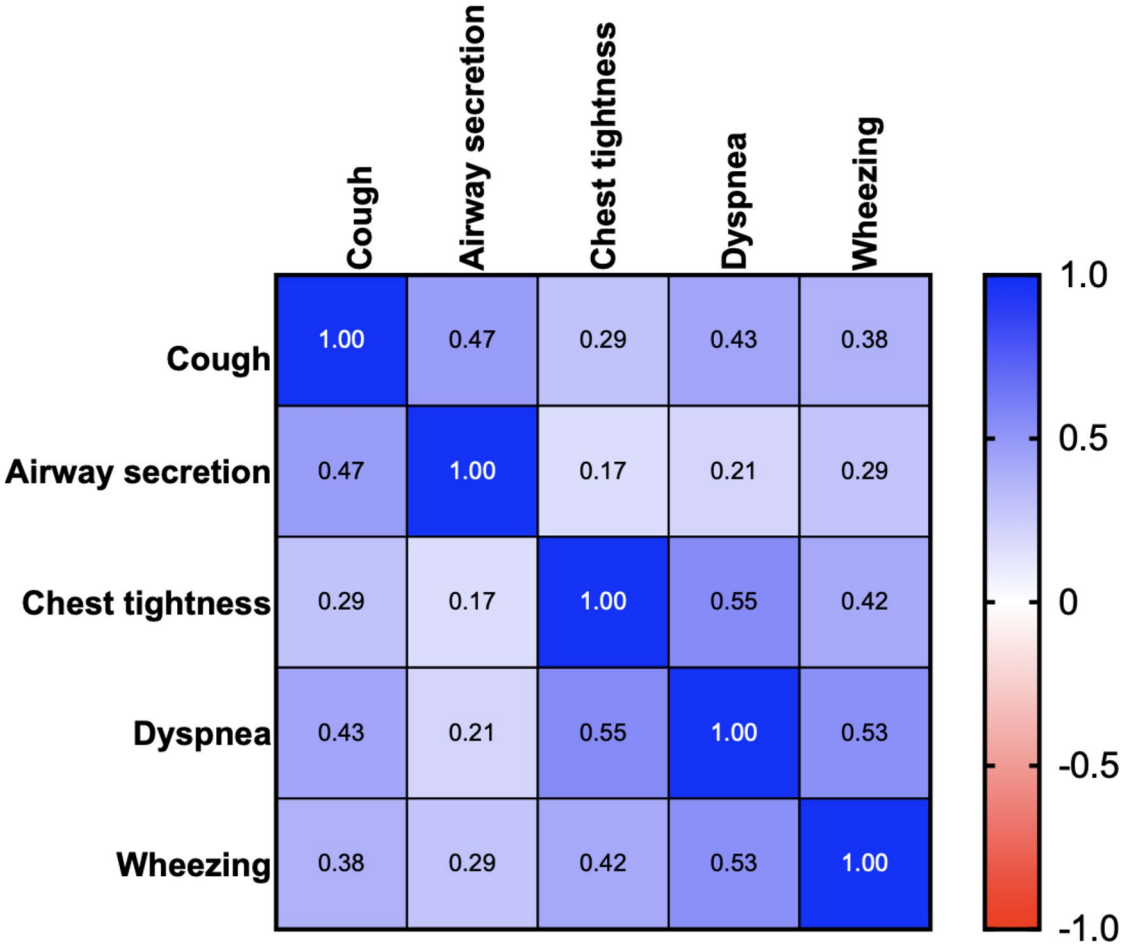

Fig. 3. Correlation matrix of the intensity of asthma symptoms reported by the patient ($n = 505$).

	Cough intensity		Airway Secretion intensity		Chest tightness intensity		Dyspnea intensity		Wheezing intensity	
	Coefficient correlation (rs)	*P*-value	Coefficient correlation (rs)	*P*-value	Coefficient correlation (rs)	*P*-value	Coefficient correlation (rs)	*P*-value	Coefficient correlation (rs)	*P*-value
Age (years)	0.080	0.0742	0.046	0.3028	− 0.15***	0.0007	0.00058	0.9896	− 0.12**	0.0095
BMI (kg/m^2)	0.046	0.3047	− 0.00089	0.9841	0.034	0.4437	0.17***	0.0001	0.14**	0.0022
FeNO (ppb)	− 0.18****	< 0.0001	− 0.074	0.0984	− 0.13**	0.0048	− 0.15***	0.0006	− 0.051	0.2564
FEV_1 (% pred.)	− 0.14**	0.0011	− 0.078	0.0819	− 0.14**	0.0019	− 0.26****	< 0.0001	− 0.26****	< 0.0001
FEV_1/FVC (%)	− 0.033	0.4579	− 0.015	0.7442	0.018	0.6883	− 0.019	0.6636	− 0.077	0.0820
Sputum neutrophils (10^3/g)	0.0054	0.9047	0.086	0.0575	− 0.027	0.5599	− 0.034	0.4491	− 0.042	0.3596
Sputum eosinophils (10^3/g)	− 0.0044	0.9229	0.071	0.1157	− 0.072	0.1150	− 0.11*	0.0115	0.047	0.2970
Sputum neutrophils (%)	0.041	0.3635	0.0058	0.8960	0.0032	0.9425	0.032	0.4788	− 0.085	0.0561
Sputum eosinophils (%)	− 0.0086	0.8474	0.038	0.3945	− 0.050	0.2644	− 0.071	0.1134	0.064	0.1516
Blood neutrophils (µL)	0.11*	0.0118	0.079	0.0778	0.059	0.1870	0.13**	0.0043	0.12**	0.0083
Blood eosinophils (µL)	0.079	0.0765	0.14**	0.0023	− 0.029	0.5192	− 0.021	0.6395	0.079	0.0762
Fibrinogen (g/L)	0.12**	0.0060	0.082	0.0680	0.024	0.5896	0.10*	0.0231	0.056	0.2191
CRP (mg/L)	0.10*	0.0245	0.079	0.0792	0.075	0.0958	0.18****	< 0.0001	0.12**	0.0074
Total IgE (KU/L)	− 0.085	0.0564	0.014	0.7588	− 0.023	0.6124	− 0.11*	0.0169	0.036	0.4218

Table 2. Univariate analysis: correlations between each asthma symptom and independent variables ($n = 505$). *Significant at the $p < 0.05$ level; **Significant at the $p < 0.01$ level; ***Significant at the $p < 0.001$ level; ****Significant at the $p < 0.0001$ level.

	Cough intensity		Airway secretion intensity		Chest tightness intensity		Dyspnea intensity		Wheezing intensity	
	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
Age (years)	0.004 (− 0.002; 0.011)	0.2250	0.0020 (− 0.005; 0.01)	0.6168	− 0.01364*** (− 0.02144; − 0.005828)	0.0007	− 0.001761 (− 0.008906; 0.005383)	0.6283	− 0.01076** (− 0.0181; − 0.0034)	0.0042
Gender (Male)	− 0.2329* (− 0.42; − 0.04)	0.0149	0.1633 (− 0.057; 0.38)	0.1468	− 0.2465* (− 0.4617;− 0.03139)	0.0248	− 0.3430*** (− 0.5399; − 0.1461)	0.0007	0.1203 (− 0.08203; 0.3226)	0.2433
BMI (kg/m^2)	0.007038 (− 0.01; 0.02)	0.4278	− 0.0009 (− 0.02; 0.01)	0.9338	0.01025 (− 0.009770; 0.03026)	0.3150	0.02311* (0.004796; 0.04143)	0.0135	0.02427* (0.0054; 0.043)	0.0116
Smoking status	− 0.4439** (− 0.71; − 0.17)	0.0013	− 0.3767* (− 0.69; − 0.05)	0.0202	0.006330 (− 0.3031; 0.3158)	0.9680	0.02477 (− 0.2584; 0.3080)	0.8636	− 0.2650 (− 0.5560; 0.02607)	0.0743
	− 0.3201** (− 0.56; − 0.07)	0.0098	− 0.2423 (− 0.5280; 0.04348	0.0964	− 0.1400 (− 0.4185; 0.1385)	0.3237	− 0.03248 (− 0.2873; 0.2224)	0.8023	− 0.4164** (− 0.6783; − 0.1545)	0.0019
Ex-smokers	− 0.4439** (− 0.71; − 0.17)	0.0013	− 0.3767* (− 0.69; − 0.05)	0.0202	0.006330 (− 0.3031; 0.3158)	0.9680	0.02477 (− 0.2584; 0.3080)	0.8636	− 0.2650 (− 0.5560; 0.02607)	0.0743
No smokers	− 0.3201** (− 0.56; − 0.07)	0.0098	− 0.2423 (− 0.5280; 0.04348	0.0964	− 0.1400 (− 0.4185; 0.1385)	0.3237	− 0.03248 (− 0.2873; 0.2224)	0.8023	− 0.4164** (− 0.6783; − 0.1545)	0.0019
FeNO (ppb)	− 0.003437* (− 0.006; − 0.0005)	0.0221	− 0.002470 (− 0.005936;0.0009960)	0.1621	− 1.264e5 (− 0.003390; 0.003365)	0.9941	− 0.002223 (− 0.005313; 0.0008683)	0.1583	0.001592 (− 0.001585; 0.004768)	0.3253
FEV_1 pre (%)	− 0.007188* (− 0.013; − 0.0005)	0.0337	− 0.003302 (− 0.01112; 0.004514)	0.4069	− 0.01289*** (− 0.02050; − 0.005270)	0.0010	− 0.02086**** (− 0.02783; − 0.01389)	< 0.0001	− 0.01908**** (− 0.0262; − 0.0119)	< 0.0001
FEV_1/FVC pre %	0.008646 (− 0.005; 0.022)	0.2214	0.004668 (− 0.01169; 0.02102)	0.5751	0.01117 (− 0.004763; 0.02711)	0.1690	0.02154** (0.006959; 0.03613)	0.0039	0.01517* (0.0001; 0.0301)	0.0473
Sputum neutrophils (%)	0.002941 (− 0.001; 0.007)	0.1836	0.0009930 (− 0.004123; 0.006109)	0.7031	− 2.841e5 (− 0.005014; 0.004957)	0.9911	− 0.001062 (− 0.005625; 0.003500)	0.6475	− 0.003504 (− 0.0081; 0.0011)	0.1427
Sputum eosinophils (%)	0.008295* (0.0001; 0.016)	0.0469	0.005766 (− 0.003876; 0.01541)	0.2406	− 0.001944 (− 0.01134; 0.007452)	0.6845	− 0.003377 (− 0.01198; 0.005222)	0.4407	0.001513 (− 0.0073; 0.010)	0.7367
Blood neutrophils (μL)	0.03824 (− 0.007; 0.083)	0.0978	0.03301 (− 0.02040; 0.08641)	0.2252	0.01628 (− 0.03576; 0.06832)	0.5390	0.03858 (− 0.009042; 0.08621)	0.1121	0.02843 (− 0.0205; 0.0773)	0.2542
Blood eosinophils (μL)	0.3031* (0.033; 0.57)	0.0276	0.1888 (− 0.1290; 0.5066)	0.2436	− 0.1410 (− 0.4506; 0.1687)	0.3715	0.1365 (− 0.1469; 0.4199)	0.3444	− 0.01594 (− 0.3072; 0.2753)	0.9144
Fibrinogen (g/L)	0.01782 (− 0.12; 0.15)	0.8051	0.02231(− 0.1449; 0.1895)	0.7933	0.01805 (− 0.1449; 0.1810)	0.8278	0.01899 (− 0.1301; 0.1681)	0.8025	0.04449 (− 0.1087; 0.1977)	0.5686
CRP (mg/L)	− 0.005146 (− 0.02; 0.009)	0.5024	0.009259 (− 0.008501; 0.02702)	0.3061	0.004638 (− 0.01267; 0.02194)	0.5987	0.002622 (− 0.01322; 0.01846)	0.7451	0.005134 (− 0.011; 0.021)	0.5357
Total IgE (KU/L)	− 5.963e−5 (− 0.001; 1.531e−5)	0.1186	5.960e6 (− 8.238e− 5; 9.430e− 5)	0.8946	− 3.143e5 (− 0.0001175; 5.465e−5)	0.4735	− 3.619e5 (− 0.0001150;4.258e−5)	0.3671	− 4.37e5 (− 0.0001; 4.059e−5)	0.3277

Table 3. Multivariate regression results for the five patient-reported asthma symptoms ($n = 505$). *Significant at the $p < 0.05$ level; **Significant at the $p < 0.01$ level; ***Significant at the $p < 0.001$ level; ****Significant at the $p < 0.0001$ level.

associated with increased chest tightness intensity ($p < 0.05$). FEV1% pred. decreased with increasing chest tightness intensity ($p < 0.001$).

Factors associated with dyspnea intensity

Results of spearman correlation coefficient (univariate analysis) are given in Table 2. Only BMI (rs: 0.17), FeNO (rs: − 0.15), FEV1% pred. (rs: − 0.26), sputum eosinophils (rs: − 0.11), blood neutrophils (rs: 0.13), fibrinogen (rs: 0.10), CRP (rs: 0.18) and total IgE (rs: − 0.11) were significantly correlated to dyspnea intensity. In multivariate analysis, gender, BMI, FEV1% pred. and FEV1/FVC % were significantly and independently associated with dyspnea intensity (Table 3; Fig. 4). Being a female associated with increased dyspnea intensity ($p < 0.001$). BMI increased with increasing dyspnea intensity ($p < 0.05$). FEV1% pred. decreased with increasing dyspnea intensity ($p < 0.0001$), while FEV1/FVC % increased with increasing dyspnea intensity ($p < 0.01$).

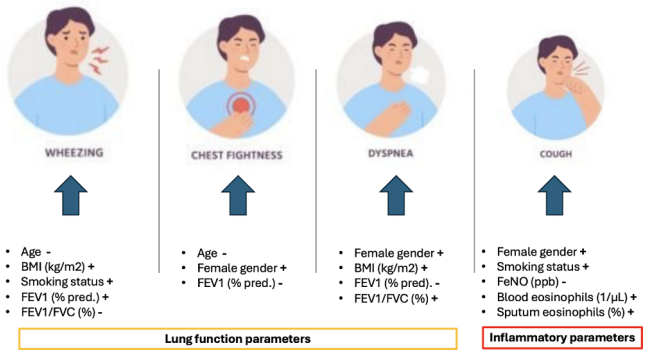

Fig. 4. Schematic representation of the relationship between demographics, functional, inflammatory features and asthma symptoms. +Corresponds to a positive association, while −corresponds to a negative association.

Factors associated with wheezing intensity

Results of spearman correlation coefficient (univariate analysis) are given in Table 2. Only age (rs: − 0.12), BMI (rs: 0.14), FEV1% pred. (rs: − 0.26), blood neutrophils (rs: 0.12) and CRP (rs: 0.12) were significantly correlated with wheezing intensity. In multivariate analysis, age, BMI, smoking status, FEV1% pred. and FEV1/FVC % were significantly and independently associated with wheezing intensity (Table 3; Fig. 4). Age decreased with increased wheezing intensity ($p < 0.01$). BMI increased with increasing wheezing intensity ($p < 0.05$). Being a smoker in comparison to never-smokers associated with increased wheezing intensity ($p < 0.01$). FEV1% pred. decreased with increasing wheezing intensity ($p < 0.0001$), while FEV1/FVC % increased with increasing wheezing intensity ($p < 0.05$).

Discussion

This study provides evidence that, in a large cohort of asthmatics treated with ICS/LABA, different respiratory symptoms are associated with specific demographic, functional and inflammatory features. While some associations were expected like smoking history with cough and airway secretion or BMI with dyspnea and wheezing, others such as the opposite relationship that sputum eosinophils and FeNO have with cough is an original finding.

The relationship between obesity and the symptoms of dyspnoea and wheezing on the one hand[22,23], and the one between smoking history and the symptoms of cough and airway secretion on the other hand are well documented, the latter supporting the concept of tobacco induced chronic bronchitis[24]. The inverse relationship between age and some symptoms intensity has important public health consequences as it would suggest that physicians have to be careful about the possibility of some kind underreporting in elderly asthmatics. This in line with a review conducted by Battaglia et al.[25] related to asthma in the elderly, where the authors showed that age-related cognitive decline contribute to an impairment of the perception of asthma symptoms. This would suggest asking physicians to use cognitive assessment tools to avoid negative consequences of an underestimated asthma in the elderly[26]. While females experiencing a greater dyspnea intensity than males has been largely demonstrated in the literature[27,28], the reasons of this difference is complex and controversial. A potential explanation shared by several authors is that anxiety and depression, traits more prevalent in women, are two recognized predictors of dyspnea[29,30]. Another valuable explanation might be the lower airway size associated with smaller lung volumes in females[31].

The expiratory flow rate measured by the FEV1 is the parameter that showed the strongest association with symptoms, being significantly related to all asthma symptoms except for the airway secretion. Interestingly, in the univariate analysis, the symptom of dyspnea was correlated with reduced FEV1 but not the FEV1/FVC ratio, often considered as the gold standard of airway obstruction. However, in the multivariate analysis, the ratio FEV1/FVC positively associated with the intensity of dyspnea which indicates that dyspnea was maximal when spirometry showed a restrictive pattern featuring a reduction in FVC that surpasses the reduction in FEV1. This is an original and somewhat unexpected finding. Of course, reduced FVC are likely to reflect increased residual volume as a consequence of air trapping caused by distal airway obstruction since total lung capacity is generally preserved in our cohorts of asthmatics[32]. Previous studies have highlighted the critical role of distal airway obstruction in lack of asthma control[33].

Airway inflammation has been considered of paramount importance in asthma and its understanding has driven much of the pharmacological progress in the disease. Here, eosinophilic trait, both at the systemic and the airway level, associates with cough intensity but not with other symptoms. This finding strengthens the role of eosinophils in generating the symptom of cough and is in keeping with the recognized existence of chronic eosinophilic bronchitis, a pathological entity that shares some clinical features with asthma but differs from the latter by the absence of dyspnea and bronchial hyperresponsiveness[34]. Surprisingly the multivariate model shows that FeNO levels were in fact inversely associated with cough intensity. This is the demonstration that molecular pathways leading to either eosinophilia or raised FeNO may actually impact disease expression in a very different manner, and it would suggest that elevated FeNO by itself might actually confer some protection to the patients against excessive cough. Since this association emerged after multivariate analysis including smoking

as an independent variable the relationship between low FeNO and high cough intensity cannot be accounted by the smoking habit, known to dramatically reduce FeNO levels[35,36]. A high FeNO level has traditionally been seen as detrimental in asthmatics. Indeed FeNO levels were found to correlate with sputum eosinophils[35,37] and high FeNO levels combined to high blood eosinophils in moderate to severe asthmatics is a risk factor for future exacerbation[38] and in particular for viral induced exacerbation[39]. However, other studies found that a low FeNO level was an independent factor associated with poor quality of life and, in particular, in the activity dimension[40]. Furthermore, a longitudinal study has shown that a rise in FeNO may increase the chance to achieve a good quality of life (AQLQ > 6) in asthmatics not treated with biologics[20]. Finally, patients receiving anti-IL-5 and anti-IL5(R) have not shown convincing fall in FeNO despite major clinical improvement[41,42]. Whether residual high FeNO without eosinophilia may accelerate lung function decline is a key issue that needs to be answered in long term studies although the recent SHAMAL study suggest it might be the case[43].

The results of this study may help the clinician better understand the disease based on the patient complains and therefore better choose a treatment according to the symptom reported by the patient. This is in line with the recent integration of the patient perspective, using patient-reported outcome measures, in chronic disease management as a way to refine personalized medicine[44,45]. The latter aims to help healthcare providers to individualized patient treatment based on biomarkers, genetics and demographic characteristics[44,45]. In patients receiving ICS/LABA as maintenance treatment, our study would suggest that an increase in perceived cough intensity could lead the patient to prioritize the use of inhaled corticosteroid therapy[13,14]. Conversely, due to their independent relationship with lung function parameters, an increase in the perceived intensity of dyspnea and/or wheezing could lead the patient to prioritize bronchodilating agents to improve airway flow rates[13,14]. As a result, disseminating asthma symptom scales in family practices could be a simple, quick and inexpensive way to better manage asthma patients in routine, where spirometry and FeNO measurement are rarely available[46,47].

In our real-life study, it appears that the majority of patients treated with ICS/LABA remain symptomatic with an ACT score below 20. The reasons for that are probably plural. First, a poor adherence is likely to contribute in some patients[48]. Second, some comorbidities like smoking and obesity may impair the response to ICS by generating respiratory symptoms not directly related to asthma itself[49]. Third there might also be true pharmacological resistance to ICS either because the disease was T2 low before starting ICS or because ICS was unable to fully control T2 high disease as demonstrated by the fact that 50% of patients still exhibit sputum eosinophil count of at least 2%.

Strengths and limitations of the study

One strength is the fact that it is one of the first real-life study to investigate the relationship between detailed asthma symptoms and lung function and inflammatory parameters. Another strength is the inclusion of asthma patients for whom the diagnosis has been made according to the recently published ERS guidelines on asthma diagnosis[50]. However, this study has some limitations. First, because of its cross-sectional design, the cause and effect of the demonstrated associations cannot be established. A prospective interventional study to see if change in management strategy according to symptoms could be efficient would be needed. Second, this study did not include patient occupation in the multivariate model, a factor which is known to have an impact on respiratory symptoms[51]. Third, data on comorbidities—such as rhinosinusitis or gastroesophageal reflux—would have been useful as it is known that they may influence asthma symptoms[52].

Conclusion

This study demonstrates that, in a large cohort of asthmatics treated with ICS/LABA, distinct patient-reported respiratory symptoms are associated with specific demographic, functional and inflammatory features. In particular, while dyspnea, wheezing and chest tightness are associated with impairment of spirometric indices, cough rather relates to eosinophilic inflammation. These findings pave the way for a new personalized medicine based on patient perspective, which could lead to a better management of asthma in primary care where spirometry and FeNO measurement are rarely available. To fully support a concept of symptoms-guided treatment a prospective longitudinal study would be warranted.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the privacy of certain patient data but are available from the corresponding author on reasonable request.

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Author contributions

GL, BP, RL, JB & FS contributed to the conception of the study. FS, & RL contributed to data acquisition. GL performed statistical analysis. GL, BP, FS, RL, EVG, BSP & JB drafted and critically revised the work. All authors gave final approval of the manuscript.

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Declarations

Competing interests

Outside of this submitted work, RL received unrestricted research grants from GSK, AstraZeneca, Novartis and Chiesi and lecture or adboard fees from GSK, AZ, Novartis and Sonafi. Outside of this submitted work, FS received lecture or adboard fees from Chiesi, AZ, GSK, and Novartis. Outside this submitted work, JB reports personal fees (member of advisory boards, consultations, honoraria for meeting lectures) from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach. Shareholder of KYomed Innov and MASK-air-SAS. The rest of the authors declare that they have no relevant conflicts of interest.

Ethics approval and consent to participate

The Study was approved by the CHU Liège ethics committee. Signed informed consent was obtained from patients as soon as they entered the asthma clinic of the CHU Liège. They agreed that their clinical data and the health outcomes they reported in the routine setting would be used for the purposes of research.

Additional information

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