Long-term Predictors of Anxiety and Depression in Adult Patients with Asthma

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Long-term predictors of anxiety and depression in adult patients with asthma

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Summary
Background It is well established that anxiety and depression are associated with asthma, but there is limited evidence about the persistence of anxiety/depression in asthma. The aim of our study was to assess the long-term predictors of anxiety and depression in adult asthmatic patients.
Methods A total of 90 adult asthma patients (63 women, age 18–50 years) with different levels of disease control (28 uncontrolled and 34 partially controlled) were assessed at baseline and at follow-up after 7 years for anxiety, depression and asthma control. The same work-up on both occasions included: demographics, living conditions, medical history (e.g. comorbidities, adherence and exacerbations), Hospital Anxiety and Depression Scale (HADS), Asthma Quality of Life Questionnaire (AQLQ), disease control and lung function. Persistence was defined as the HADS scores for anxiety and depression present at baseline and follow-up.
Results The HADS results at follow-up visit showed 36 (40%) asthma patients with anxiety and 13 (14%) with depression, with the persistence of anxiety in 17 (19%) and of depression in 7 (8%) patients. Significant predictors of anxiety at follow-up were HADS and AQLQ results at baseline and several parameters of asthma control at follow-up (area under the curve AUC 0.917, 95% confidence interval CI 0.829–0.969, $p < 0.001$) and for depression AQLQ mood disorder domain, asthma control and lung function (AUC 0.947, 95% CI 0.870–0.986, $p < 0.001$).
Conclusion Anxiety and depression persist over years in some patients with asthma. The association between mood disorders and asthma suggests potential mutual treatability.

Keywords Asthma · Mood disorders · Disease control · Health related quality of life · Long term effects

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Introduction

Asthma is one of the most prevalent chronic diseases worldwide, representing a significant global health problem [1]. The incidence of asthma is highest in childhood (incidence up to 80% up to the age of 15 years) and lasts in most patients until adulthood. The latest prevalence estimates for Croatia are between 3–10% depending on the age group and region [2, 3], although in developed countries the prevalence in children can reach >30% [4]. Asthma is still underdiagnosed and inadequately controlled despite effective treatment being available [5]. This is further heightened by the fact that uncontrolled asthma markedly impairs the quality of life of patients and increases the costs of treatment [6]. Asthma is first in the group of the "Holy seven" diseases that are

considered to be psychosomatic with significantly more prevalent mood disorders, such as anxiety and depression in this population [7–9]. Also, it seems that anxiety and depression act as independent comorbid factors in asthma morbidity [10–12]. Our group has previously published data showing a high prevalence of anxiety (44.5%) and depression (24.5%) present in adult patients with asthma, which is significantly associated with the level of lung function for both mood disorders, but with a different pattern of healthcare resource utilization [13]. Although a link between asthma and mood disorders is a common knowledge and both have been recognized as usual comorbidities in asthma [1], little is still known about possible underlying pathogenetic mechanisms connecting these mood disorders with asthma and even less about the long-term predictors of these disorders in patients with asthma [12, 14]. Our hypothesis was that there is a long-lasting association of mood disorders with asthma in vulnerable patients associated with individual and disease characteristics. Consequently, the aim of our study was to assess the long-term predictors of anxiety and depression in adult asthmatic patients.

Patients and methods

Study design

This study is a follow-up of a cross-sectional study in which adult patients with asthma were assessed for asthma signs and symptoms, level of asthma control, utilization of healthcare resources, lung function, current level and adherence to treatment and anxiety and depression according to the Hospital Anxiety and Depression Scale (HADS) during their regular outpatient visits at our tertiary care pulmonology department [13]. The study protocol together with this extension was approved by the Institutional Review Board and Medical Faculty Ethics Committee. All participants signed written informed consent before any procedure.

The patients from the initial study were recalled for a follow-up visit after 7 years. Out of the initial 200, 90 patients were willing to come for a follow-up visit (both sexes, 25–57 years of age) and were reassessed using the same diagnostic routine as during the baseline visit (7 years previously). They all had a physician diagnosed asthma at least 1 year before the baseline visit (8 years at the follow-up visit). At the time of both visits they were all on their regular anti-inflammatory treatment, symptomatic medications or a combination thereof. The regular wash-out before both visits regarding short or long-acting bronchodilators was carried out as for lung function measurement. Exclusion criteria were: other respiratory diseases, such as chronic obstructive pulmonary disease (COPD), emphysema or any significant lung disease other than asthma, patients with other significant disorders, such as diabetes, autoimmune and systemic diseases, cancer and other serious illnesses, patients with alcohol or drugs abuse and pregnant and lactating women. Study outcomes were defined as HADS anxiety and depression at follow-up visit and persistence of HADS anxiety and depression at follow-up visit. Persistence of anxiety or depression was defined as having a HADS score indicating anxiety or depression at baseline and at the follow-up visit. Simultaneous presence of anxiety and depression was not used as an outcome in this study because of the small number of patients with this outcome.

Patients were given three questionnaires:

1. Q score Questionnaire,
2. Asthma Quality of Life Questionnaire (AQLQ) and
3. Hospital Anxiety and Depression Scale (HADS).

These questionnaires were chosen by the expert panel for the baseline visit (>10 years ago) and they were then used for a follow-up visit to preserve the consistency of the study methodology. All three questionnaires were adapted for local language following modified principles adapted from Beaton et al., involving a forward-backward translation technique, a pilot study, and a refinement process via an expert panel [15].

The Q score Questionnaire is used to estimate the severity of asthma symptoms over a period of the past 7 days [16]. It is a short, patient focused morbidity index, consisting of four questions in relation to the past week and the result is expressed as a summed score ranging from 0–8. A lower total score indicates a greater control of asthma symptoms with a score ≤4 indicating good control and >4 indicating poor control of asthma symptoms.

The AQLQ was used to measure the health-related quality of life (HRQoL) over a period of the past 4 weeks in patients with asthma [17, 18]. The questionnaire is a self-assessment tool of 20 questions, which include physical and emotional impact of asthma by measuring the impact of asthma in four subscales: breathlessness, social dysfunction, mood disorder and concern for health. Answers are scored according to the Likert scale from 0–4 (0 = not at all, 1 = slight, 2 = moderate, 3 = difficult, 4 = very difficult). The result is expressed as total and as 4 subscale scores ranging from 0–10 (10 indicating significant deterioration).

The HADS was used to measure anxiety and depression symptoms [19]. It consists of 14 claims, of which 7 are related to anxiety and 7 to depression, each receiving a score of 0–3 (total score 0–21). The values 0–7 for each of the scales indicate no anxiety and depression, and ≥8 indicates anxiety and depression [20].

Patient history at both visits was recorded using the same structured questionnaire with questions about demographics, smoking habits, socioeconomic status, frequency and severity of asthma symptoms, adherence to treatment and physician advice (e.g. acute

asthma plan and non-pharmacological measures), exacerbation and utilization of healthcare during the past year. Vitals signs, body height and body mass were measured, body mass index (BMI) was calculated (as body mass in kg divided by body height in m^2) and a physical examination was performed.

Lung function was measured using computerized pneumotach (Pneumoscreen, Jäger, Höchberg, Germany) in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [21]. Spirometry was repeated three times and the best of three acceptable attempts was recorded. From the best attempt forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF) and FEV_1/FVC (Tiffeneau index) were recorded and expressed as absolute values and as % predicted according to Quanjer et al. [22]. A bronchodilation test was carried out with repeated spirometry 20 min after inhalation of 400 µg salbutamol; a positive test result being an improvement of FEV_1 ≥12% and ≥200 ml.

Data analyses

Data analyses and presentation of data were done using STATISTICA version 12 (StatSoft, Tulsa, OK) and MedCalc Statistical Software version 15.8 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2016). Categorical variables are presented as numbers and proportions (%). Quantitative variables are presented as mean and standard deviations (SD) and tested for the normality of distribution using Kolmogorov-Smirnov test. Differences between subgroups for categorical variables were evaluated using the χ^2-test. Differences for quantitative variables were evaluated using Student's t-test or Mann-Whitney U-test depending on the distribution. Significant associations for each of the outcomes (anxiety and depression at control visit and their persistence) were assessed using generalized linear/non-linear models and expressed as area under the curve (AUC) and 95% confidence intervals (95% CI) and as odds ratio (OR) with 95% CI for each of the predictors. The analysis was done using anxiety and depression at follow-up visit (HAD score ≥ 8) and their persistence as dependent variables, and patients characteristics, socioeconomic variables, measures of asthma control, HRQoL, adherence and utilization of healthcare as independent variables. As the current status of disease control and HRQoL can be associated with the presence of mood disorders, both baseline and follow-up characteristics were used in multivariable models to define all independent associations. Independent variables were used for the specific model if their univariate association with the dependent variable was at a level of $p < 0.10$. Each multivariate model was produced using a step-wise approach. Variance inflation factor was used to assess collinearity. The AUC statistics were derived from the models using automated procedure from the statistical software. All tests were two-tailed and $p < 0.05$ was used as statistically significant for all analyses.

Results

A total of 90 asthmatics having the whole dataset from both baseline and follow-up visits were included in this analysis with an average age at follow-up visit (mean ± SD) 45.6 ± 11.5 years, 70% (n=63) women and 47% (n=42) with rural residence. These patients (n = 90) were not significantly different compared to patients who did not show up for a follow-up visit (n = 110) regarding their baseline characteristics as to demographics (e.g. age and sex), presence of asthma signs and symptoms, level of asthma control, utilization of healthcare resources, lung function, current level and adherence to treatment and anxiety and depression ($p > 0.10$ for all, Table 1). Characteristics of patients regarding demographics, smoking habit, social status, asthma characteristics and lung function, adherence, HRQoL, HADS anxiety and depression at follow-up visit are presented in Table 2. Most of the patients were non-smokers (79%), completed secondary education (73%), and were unemployed (59%) at follow-up visit. Of the patients one third had a physician diagnosed asthma for less than 10 years and one in six (17%) had an asthma attack almost every month showing poor asthma control. In half of the patients exacerbations lasted for more than 2 days (52%) but most of the patients (84%) were not hospitalized because of asthma and in most cases (63%) had not visited their doctor or emergency department because of asthma showing a low level of healthcare utilization despite symptoms of asthma. Average (±SD) HADS anxiety and depression scores were 7.7 (4.7) and 5.1 (4.2) and 36 (40%) of the asthma patients had anxiety and 13 (14%) depression with persistence of anxiety present in 17 (19%) and depression in 7 (8%) asthmatic patients at follow-up visit.

Patients with anxiety at follow-up had significantly more depression (33% vs. 2%, $p < 0.001$). Although patients with anxiety had more frequent exacerbations (25% vs. 11%, $p = 0.206$), longer lasting exacerbations (61% vs. 46%, $p = 0.168$), unplanned visits (47% vs. 30%, $p = 0.090$), morning or persistent cough (50% vs. 32%, $p = 0.077$), partial adherence to physicians advice (14% vs. 4%, $p = 0.077$), and higher AQLQ scores for breathlessness (4.4 ± 3.8 vs. 3.3 ± 2.2, $p = 0.100$) and social dysfunction (4.7 ± 2.4 vs. 4.0 ± 2.5, $p = 0.161$), these differences did not reach significance.

Patients with depression at follow-up had significantly more anxiety (92% vs. 31%, $p < 0.001$), more frequently had morning or persistent cough (77% vs. 33%, $p = 0.004$), and were less breathless (46% vs. 82%, $p = 0.010$). They had marginally greater BMI (30.48 ± 6.14 vs. 27.50 ± 5.14 kgm^{-2}, $p = 0.064$) and marginally more frequent hospitalizations due to asthma (31% vs. 12%, $p = 0.119$).

Table 1 Baseline characteristics of patients according to willingness to come for a follow-up visit *(N* = 200)

Characteristic	Follow-up		
	Yes (*n* = 90)	No (*n* = 110)	*p*-value
Age (years), mean ± SD	38.4 ± 11.5	36.8 ± 10.9	0.315
Sex, women (%)	65 (72.2)	66 (60.0)	0.206
Residence, rural (%)	42 (46.7)	50 (45.6)	0.959
Smokers (%)	19 (21.1)	23 (20.9)	0.899
Exacerbation frequency			
1–2 times/year	45 (50.0)	58 (52.7)	0.902
2–10 times/year	31 (34.4)	37 (33.6)	
Almost every month	14 (15.6)	15 (13.6)	
Hospitalizations due to asthma (%)			
No	72 (80.0)	95 (86.4)	0.457
1×	7 (7.8)	5 (4.5)	
More times	11 (12.2)	10 (9.1)	
Unplanned visits[a]	35 (38.9)	40 (36.4)	0.884
Frequent symptoms during last month (%)			
Morning or persistent cough	36 (40.0)	40 (36.4)	0.598
Breathlessness	55 (61.1)	61 (55.5)	0.420
Chest tightness	45 (50.0)	54 (49.1)	0.898
Sticky mucus	30 (33.3)	34 (30.9)	0.715
Nocturnal wakening due to asthma	27 (30.0)	34 (30.9)	0.890
Adherence to drugs (%)			
No	7 (7.8)	8 (7.3)	0.709
Partial	35 (38.9)	37 (33.6)	
Yes	48 (53.3)	65 (59.1)	
HADS Anxiety (%)	7.4 ± 4.5	7.4 ± 5.1	0.937
HADS Depression (%)	5.4 ± 4.3	5.1 ± 4.2	0.626
Asthma control (%)			
No	16 (17.8)	26 (23.6)	0.479
Yes/partial	74 (82.2)	88 (76.4)	
Lung function, mean ± SD			
FVC (% predicted)	107.8 ± 18.0	105.8 ± 17.1	0.413
FEV_1 (% predicted)	99.1 ± 23.2	100.0 ± 22.7	0.786
FEV_1/FVC (% predicted)	94.0 ± 12.7	96.3 ± 13.2	0.217
PEF (% predicted)	98.3 ± 28.9	95.8 ± 25.7	0.651
AQLQ, mean ± SD			
Breathlessness	3.7 ± 3.0	4.2 ± 3.2	0.302
Social dysfunction	4.3 ± 2.5	4.4 ± 2.4	0.775
Mood disorder	2.7 ± 2.7	2.8 ± 2.7	0.746
Concern for health	2.8 ± 2.4	3.2 ± 2.6	0.252
Total score	3.5 ± 2.8	3.8 ± 3.0	0.479

Data are presented as mean ± SD or as number of observations and percentage (%)
SD standard deviation, *NA* not applicable, *HADS* Hospital Anxiety and Depression Scale, *FVC* forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *PEF* peak expiratory flow, *AQLQ* Asthma Quality of Life Questionnaire
[a]Unplanned visit to a general practitioner or emergency department due to asthma during the month preceding the visit

Anxiety at follow-up was significantly associated with residence, smoking habit, level of anxiety and depression at baseline, scores of 3 domains (breathlessness, mood disorder and concern for health) and total score of AQLQ at baseline, adherence to physician's advice at follow-up, nocturnal wakening due to asthma at follow-up, use of bronchodilators at follow-up, level of asthma control at follow-up with an AUC 0.917 (95% CI 0.829–0.969, $p < 0.001$, multivariable regression analysis; Fig. 1). Persistence of anxiety was significantly associated with the level of anxiety and depression, and breathlessness domain of AQLQ at baseline, and unplanned visits to a general practitioner or emergency department due to asthma during the month preceding the follow-up visit with an

Table 2 Characteristics of patients at follow-up visit according to the presence of anxiety and depression at follow-up visit (*N* = 90)

Characteristic	All	HADS anxiety			HADS depression		
	(*N* = 90)	Yes (*n* = 36)	No (*n* = 54)	*p*-value	Yes (*n* = 13)	No (*n* = 77)	*p*-value
Age (years), mean ± SD	45.6 ± 11.5	47.0 ± 11.4	44.7 ± 11.6	0.360	47.2 ± 11.6	45.4 ± 11.6	0.609
Sex, women (%)	63 (70.0)	25 (69.4)	38 (70.4)	0.925	8 (61.5)	55 (71.4)	0.472
Body mass index (kgm^{-2}), mean ± SD	27.93 ± 5.36	28.24 ± 5.70	27.73 ± 5.17	0.662	30.48 ± 6.14	27.50 ± 5.14	0.064
Residence, rural (%)	42 (46.7)	15 (41.7)	27 (50.0)	0.438	4 (30.8)	38 (49.4)	0.214
Smokers (%)	19 (21.1)	9 (25.0)	10 (18.5)	0.406	1 (7.7)	18 (23.4)	0.200
Education (%)							
Primary	24 (26.7)	12 (33.3)	12 (22.2)	0.228	4 (30.8)	20 (26.0)	0.935
Secondary	59 (65.6)	23 (63.9)	36 (66.7)		8 (61.5)	51 (66.2)	
Higher	7 (7.8)	1 (2.8)	6 (11.1)		1 (7.7)	6 (7.8)	
Unemployed (%)	53 (58.9%)	22 (61.1)	31 (57.4)	0.726	9 (69.2)	44 (57.1)	0.413
Duration of asthma (%)							
<10 years	28 (31.1)	11 (30.6)	17 (31.5)	0.945	2 (15.4)	26 (33.8)	0.412
Exacerbation frequency							
1–2 times/year	44 (48.9)	15 (41.7)	29 (53.7)	0.206	6 (46.2)	38 (49.4)	0.300
2–10 times/year	31 (34.4)	12 (33.3)	19 (35.2)		3 (23.1)	28 (36.4)	
Almost every month	15 (16.7)	9 (25.0)	6 (11.1)		4 (30.8)	11 (14.3)	
Duration of exacerbations (%)							
1–2 days	43 (47.8)	14 (38.9)	29 (53.7)	0.168	6 (46.2)	37 (48.1)	0.899
>2 days	47 (52.2)	22 (61.1)	25 (46.3)		7 (53.8)	40 (51.9)	
Hospitalizations due to asthma (%)							
No	69 (83.5)	27 (75.0)	42 (77.8)	0.884	9 (69.2)	60 (77.9)	0.119
1×	8 (6.0)	3 (8.3)	5 (9.3)		0 (0)	8 (10.4)	
More times	13 (10.5)	6 (16.7)	7 (12.9)		4 (30.8)	9 (11.7)	
Unplanned visits[a]	33 (36.7)	17 (47.2)	16 (29.6)	0.090	6 (46.2)	27 (35.1)	0.443
Frequent symptoms during last month (%)							
Morning or persistent cough	35 (38.9)	18 (50.0)	17 (31.5)	0.077	10 (76.9)	25 (32.5)	0.004
Breathlessness	69 (76.7)	28 (77.8)	41 (75.9)	0.839	6 (46.2)	63 (81.8)	0.010
Chest tightness	50 (55.6)	18 (50.0)	32 (59.3)	0.386	7 (53.9)	43 (55.8)	0.893
Sticky mucus	33 (36.7)	16 (44.4)	17 (31.5)	0.211	5 (38.5)	28 (36.4)	0.885
Nocturnal wakening due to asthma	37 (41.1)	17 (47.2)	20 (37.0)	0.336	6 (46.2)	31 (40.3)	0.765
Adherence to drugs (%)							
No	6 (6.7)	4 (11.1)	2 (3.7)	0.355	1 (7.7)	5 (6.5)	0.894
Partial	37 (41.1)	15 (41.7)	22 (40.7)		6 (45.2)	31 (40.3)	
Yes	47 (52.2)	17 (47.2)	30 (55.6)		6 (45.2)	41 (53.3)	
Adherence to physician's advice (%)							
Always	83 (92.2)	31 (86.1)	52 (96.3)	0.077	11 (84.6)	72 (93.5)	0.268
Sometimes	7 (7.8)	5 (13.9)	2 (3.7)		2 (15.4)	5 (6.5)	
HADS Anxiety (%)	36 (40.0)	NA	NA	–	12 (92.3)	24 (31.2)	<0.001
HADS Depression (%)	13 (14.4)	12 (33.3)	1 (1.9)	<0.001	NA	NA	–
Asthma control (%)							
No	28 (31.1)	12 (33.3)	16 (29.6)	0.495	4 (30.8)	24 (31.2)	0.794
Partial	34 (37.8)	11 (30.6)	23 (42.6)		4 (30.8)	30 (39.0)	
Complete	28 (31.1)	13 (36.1)	15 (27.8)		5 (38.5)	23 (29.9)	
Lung function, mean ± SD							
FVC (% predicted)	108.0 ± 18.1	109.0 ± 17.8	107.3 ± 18.4	0.665	109.2 ± 14.6	107.8 ± 18.7	0.807
FEV_1 (% predicted)	99.0 ± 23.4	98.4 ± 23.1	99.4 ± 23.8	0.855	99.2 ± 23.9	99.0 ± 23.5	0.970
FEV_1/FVC (% predicted)	93.7 ± 12.8	91.6 ± 11.8	95.1 ± 13.3	0.204	92.9 ± 12.9	93.9 ± 12.8	0.804
PEF (% predicted)	93.5 ± 22.5	94.4 ± 21.2	92.9 ± 23.4	0.761	102.8 ± 23.4	91.9 ± 22.0	0.104

Table 2 (Continued)

Characteristic	All	HADS anxiety			HADS depression		
	(*N* = 90)	Yes (*n* = 36)	No (*n* = 54)	*p*-value	Yes (*n* = 13)	No (*n* = 77)	*p*-value
AQLQ, mean ± SD							
Breathlessness	3.7 ± 3.0	4.4 ± 3.8	3.3 ± 2.2	0.100	4.0 ± 2.2	3.7 ± 3.1	0.779
Social dysfunction	4.3 ± 2.5	4.7 ± 2.4	4.0 ± 2.5	0.161	4.5 ± 2.0	4.2 ± 2.5	0.751
Mood disorder	2.7 ± 2.6	3.0 ± 2.7	2.5 ± 2.6	0.408	3.2 ± 2.6	2.6 ± 2.6	0.426
Concern for health	2.8 ± 2.3	3.0 ± 2.4	2.7 ± 2.3	0.608	2.9 ± 2.7	2.8 ± 2.3	0.860
Total score	3.5 ± 2.7	3.8 ± 2.9	3.3 ± 2.6	0.453	4.3 ± 2.8	3.4 ± 2.7	0.282

Data are presented as mean ± SD or as number of observations and percentage (%)
SD Standard deviation, *NA* Not applicable, *HADS* Hospital Anxiety and Depression Scale, *FVC* Forced vital capacity, FEV_1 Forced expiratory volume in 1 s, *PEF* Peak expiratory flow, *AQLQ* Asthma Quality of Life Questionnaire
[a]Unplanned visit to a general practitioner or emergency department due to asthma during the month preceding the visit

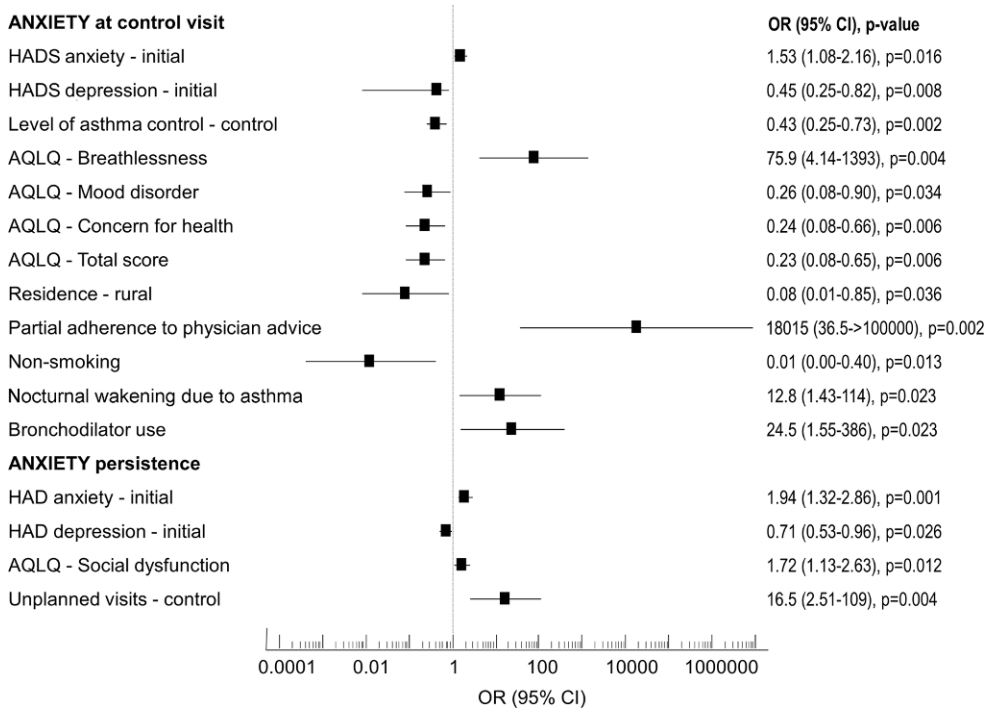

Fig. 1 Factors significantly associated (OR and 95% CI) with anxiety at follow-up visit and with persistence of anxiety in adults with asthma (*n* = 90). *HADS* Hospital Anxiety and Depression Scale, *AQLQ* Asthma Quality of Life Questionnaire; *X-axis* is represented in a log scale, *squares* represent the odds ratios (OR) and the *bars* represent the 95% confidence intervals (95% CIs)

AUC 0.918 (95% CI 0.841–965, $p < 0.001$, multivariable regression analysis; Fig. 1).

Depression at follow-up was significantly associated with mood disorder domain of AQLQ at baseline, PEF and level of asthma control at follow-up with an AUC 0.947 (95% CI 0.870–0.986, $p < 0.001$, multivariable regression analysis; Fig. 2). 'Persistence' of depression was significantly associated with breathlessness domain of AQLQ at baseline, adherence to physician's advice and duration of exacerbations at follow-up, with an AUC 0.973 (95% CI 0.915–0.996, $p < 0.001$, multivariable regression analysis; Fig. 2).

Discussion

The main result of our study is that significant predictors of long-term anxiety and depression were identified from the set of usual variables defining asthma control and HRQoL. Anxiety showed a different pattern than depression, both for the presence and persistence of anxiety at follow-up, independently associated with baseline levels of anxiety, depression and HRQoL, even when controlled for the current level of asthma control. Depression on the other hand was independently associated with baseline HRQoL, but not with anxiety. The predictions were for both anxiety and depression of a relatively high precision (>55% variance explained and with AUC > 0.91 for all outcomes). The results of our study also have important practical implications for the treatment of asthma patients. They show that in patients with poor asthma control and low HRQoL physicians should ask the patient about the symptoms of anxiety/depression or use a simple tool like HADS and not only try to change or adjust asthma treatment strategy. Our study showed that there is a long-term association of asthma and anxiety/depression with negative health outcomes, so diagnosing mood dis-

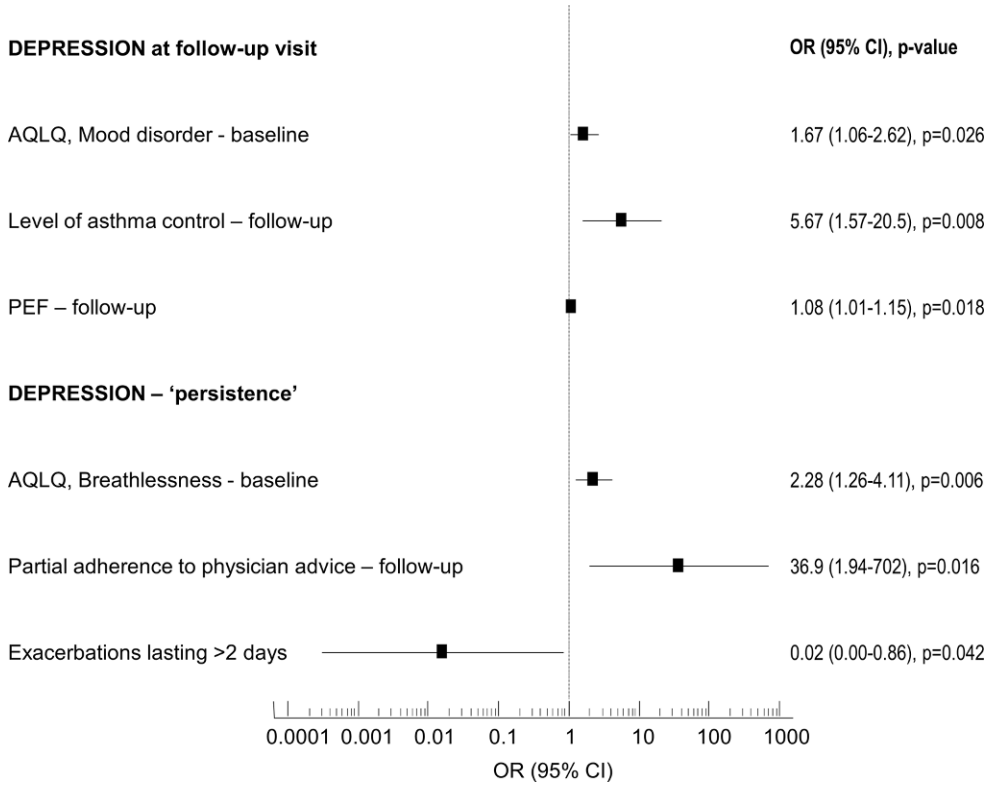

Fig. 2 Factors significantly associated (OR and 95% CI) with depression at follow-up visit and with persistence of depression in adults with asthma ($n = 90$). *AQLQ* Asthma Quality of Life Questionnaire, *PEF* peak expiratory flow (% predicted); *X-axis* is represented in a log scale, *squares* represent the odds ratios (OR) and the *bars* represent the 95% confidence intervals (95% CIs)

orders would allow an intervention. The systematic review [23] about the psychological interventions in adults with asthma and the newest study by Stoop et al. [24] suggest that education and simple psychological interventions like relaxation techniques and biofeedback or a stepped care approach could produce significant positive healthcare outcomes.

The results of our study corroborate the persistence or recurrence of anxiety and depression already shown in cohort studies following adolescents with asthma to young adulthood [12, 14]. Data on the causality of this association show dual results. Favreau et al. showed that asthma morbidity measures like the level of control, HRQoL and utilization of healthcare were predicted during the 4-year follow-up by the presence of panic disorder/anxiety at baseline [25]. On the other hand Chen et al. showed that asthma can be a significant risk factor for the development of mood disorders in later life [26], so although there is enough evidence showing a significant comorbid association between asthma and anxiety/depression [27, 28] the nature of this association, causality and pathophysiology behind it is still not clear. This can also mean that there is a mutual causality between asthma and mood disorders suggesting possible mutual treatability, enhancing the need for early identification of a mood disorder in an asthmatic patient.

Our results also corroborated the already know fact that anxiety and depression show different pathways of association with asthma [11], by identifying different independent associations for the occurrence and persistence of these mood disorders in adult patients with asthma after 7 years of follow-up. Persistence of anxiety in asthma was associated with initial HADS results for both anxiety and depression but with opposite effects, AQLQ social dysfunction domain and unplanned visits to a physician or emergency department due to asthma. Persistence of depression was on the other hand significantly associated with AQLQ breathlessness domain, partial adherence to physician's advice and duration of exacerbations.

Low level of direct evidence about causality between asthma and anxiety/depression prompted researchers to try to disentangle this association using indirect evidence as it was done by Slavich and Irwin [29] using comprehensive evidence linking depression and asthma and systemic inflammation. As higher morbidity and low adherence to treatment in asthma is closely associated with uncontrolled underlying inflammation, the associations that we found for both anxiety and depression, could be based on this common pathophysiological mechanism, although this is very much speculative as we have not measured markers of inflammation in our patients. On the other hand, possible mechanisms of associations could be based on neural mechanism and different neurophenotypes in asthma, such as individual differences in sensitivity to visceral signals, the influence of expectation and emotion on symptom perception, and changes related to disease chronicity, such as conditioning and plasticity [30, 31].

A recently published study [32] added to existing evidence of the significant burden of comorbid mental illness in asthma showing increased length of hos-

pitalization, cost, and decreased likelihood of routine disposition in asthmatics with mental illness. These and an abundance of other published data so far, highlight the need for integrated care, both in diagnosing and treating mental illness in patients with asthma. Although mental disorders are mentioned in guidelines for the management of asthma, the level of evidence D attached to both diagnosing and treating anxiety and depression in asthmatic patients is a consequence of the low number of studies with high quality evidence published so far [1]. Based on the prevalence and impact estimates it is an appropriate time for a scientific community to produce high quality evidence both supporting active case finding and proper treatment strategies for mental disorders in patients with asthma.

Obviously, there are limitations to our study that have to be taken into account when interpreting the results. Although anxiety and depression had a high prevalence in our sample of adults with asthma and the estimates of outcomes were quite precise, the relatively small sample size limits the conclusions that could be drawn. Also, although the sample at follow-up was comparable to the initial study, a significant number of patients from that study were lost to follow-up (55%) but they were not included into this analysis. Also, we had no objective data about anxiety/depression and/or asthma during the 7-year interval between the two visits. Because of these facts, we have to interpret the results of our study with caution, as persistence could actually mean a new episode of anxiety or depression in the same patient. Nevertheless, the results of our study confirmed previously known facts about anxiety/depression in patients with asthma, which makes our data more credible, corroborating the need for further high quality research in this area.

Conclusion

Anxiety and depression persist over years in some patients with asthma, and are associated with HRQoL, morbidity of asthma and disease control. The association between mood disorders and asthma suggest potential mutual treatability.

Compliance with ethical guidelines

Conflict of interest M. Labor, S. Labor, I. Jurić, V. Fijačko, S. Popović Grle, and D. Plavec declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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