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# Mood disorders in adult asthma phenotypes

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**ABSTRACT**

*Objective:* Studies show high comorbidity of mood disorders in asthma. As asthma is a highly heterogeneous disease with different phenotypes it can be expected that there is a difference in this association with different asthma phenotypes. The aim of our cross-sectional study was to assess the association of specific asthma phenotypes with anxiety and/or depression and their impact on asthma control. *Methods:* A cross-sectional study in 201 consecutive adult outpatients with asthma (≥18 years of age) was conducted. Each patient underwent physical examination, detailed medical history, Hospital Anxiety and Depression Scale, Asthma Control Questionnaire, Asthma Control Test, together with measurements of lung function and fraction of exhaled nitric oxide. Phenotypes were assessed using cluster analysis, and a multivariate analysis was used to identify associations of mood disorders with different phenotypes. *Results:* Five asthma phenotypes were identified: allergic (AA, 43.8%), aspirin-exacerbated respiratory disease (AERD, 21.9%), late-onset (LOA, 18.9%), obesity-associated (OAA, 10.0%), and respiratory infections associated asthma (RIAA, 5.5%). A multivariate analysis showed a significant association of anxiety with LOA and comorbid hypertension (LOA, odds ratio (OR) = 2.12; hypertension, OR = 2.37, $p = 0.012$), and depression with AA, RIAA, hypertension, and ACQ score (AA, OR = 6.07; RIAA, OR = 4.73; hypertension, OR = 5.67; ACQ, OR = 1.87; $p < 0.001$). Comorbid anxiety/depression was associated with AA, LOA, RIAA, hypertension, and ACQ score (AA, OR = 10.15; LOA, OR = 2.98; RIAA, OR = 6.29; hypertension, OR = 5.15; ACQ, OR = 1.90; $p < 0.001$. *Conclusion:* Mood disorders were significantly associated with AA, LOA, and infection-associated asthma, together with comorbid hypertension and the level of asthma control.

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Anxiety; asthma phenotypes; asthma control; comorbidities; depression; respiratory illness

## Introduction

Asthma is a very heterogeneous disease, a syndrome defined as a collection of different overlapping phenotypes [1] described by demographic, epidemiologic, clinical, physiological, morphologic, and biochemical characteristics, as well as the distinct response to different treatments [2]. Limited knowledge about asthma phenotypes is possibly the biggest obstacle in understanding the underlying pathophysiology (endotypes), (epi)genetics, improvement in treatment, and prognosis [3–5]. Studies show that despite the available and effective drugs, up to 40% of patients show poor or suboptimal (>50%) control of their asthma [6, 7] with comorbidities (e.g., psychological disturbances), adherence to treatment and physician's advice, being the key factors contributing to poor control [7, 8]. Patients with asthma have an increased risk for mood disorders like anxiety and depression [8–11], causing poorer asthma control, poorer quality of life, as well as functional disability, greater utilization of healthcare services, significantly more visits to general practitioner/emergency medical services, and more frequent hospitalizations than patients without mood disorders [8–13]. Identification of asthma phenotype/endotype became relevant for the determination and implementation of specific therapy (precision/personalized medicine) to achieve better asthma control, and disease outcomes [5, 8, 14]. There is evidence that different asthma phenotypes with clinical and morbidity differences are associated with higher prevalence of mood disorders [15, 16]. Our hypothesis was that different asthma phenotypes could be specifically associated with mood disorders (anxiety/depression), so the aim of our cross-sectional study was to assess the association of specific asthma phenotypes with anxiety and/or depression and their impact on asthma control.

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## Patients and methods

### Subjects

This was a cross-sectional study conducted at the single site (tertiary hospital pulmonology outpatient clinic) in successive outpatients with asthma (both sexes, aged ≥18 years) at a routine visit. Participants were eligible if they had a physician's diagnosed asthma set by a pulmonologist in accordance with Global Initiative for Asthma (GINA) [8] at least a year before the start of the study. All patients were skin-prick tested by our group in the past as a part of the routine diagnostic process for asthma using standardized allergen extracts and according to the standardized procedure (EAACI guidelines) [17], and were at the time of the visit on their regular asthma treatment. Patients with a physician's diagnosed comorbidities such as sinonasal polyposis, chronic rhinosinusitis, diabetes, or cardiovascular diseases were not excluded. Patients with chronic respiratory diseases other than asthma (e.g., COPD, TBC, sarcoidosis, carcinoma, etc.), as well as pregnant and lactating women, were not eligible. The study protocol and documents were assessed and approved by the Institutional Review Board/Ethics Committee (IRB/EC). The study was conducted according to the latest version of the Declaration of Helsinki, all relevant international and national laws and regulations and according to Good Clinical Practice (GCP) guidelines. All participants signed a written informed consent before any study procedure was started.

### Study workup and methods

All physicians (pulmonologists) involved in the recruitment of patients and data acquisition were previously informed in detail about the study protocol and trained specifically in all procedures before the start of the study. Each patient underwent a physical examination and detailed medical history. Structured questionnaire was used to collect data about: age, gender, smoking, atopic status, socioeconomic status (marital status, level of education, employment), data on residence (urban/suburban), family history of asthma, provoking factors (e.g., non-steroidal anti-inflammatory drugs, irritants, respiratory infections) and exposure to allergens (dust mites, molds, pets) and/or tobacco smoke, occurrence and duration of illness, exacerbations, utilization of healthcare resources (physician's visits, emergency department visits, number of hospitalizations), history of earlier mental disorders and comorbid diseases, drug use, and diurnal and nocturnal symptoms as indicators of asthma control (cough, sticky mucus production, tachypnea, wheezing, chest tightness, waking up because of asthma). Physical activity, possible inability to perform daily school or work obligations, and adherence to regular medication and physician's advice were also noted. Body height (BH) and body weight (BW) were measured, and body mass index (BMI) was calculated (BW in kg divided with squared BH in meters) with obesity defined as BMI $>30$ kgm$^{-2}$. Three self-assessment questionnaires were used to assess anxiety/depression and asthma control: Hospital Anxiety and Depression Scale (HADS), Asthma Control Questionnaire (ACQ), and Asthma Control Test (ACT). 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 [18, 19].

HADS was used to measure anxiety and depression symptoms [20]. 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). Values of 0–7 for each of the scales indicated no anxiety and depression, and ≥8 indicated anxiety and depression [21].

ACQ is a simple questionnaire to measure the adequacy of asthma control and change in asthma control occurring either spontaneously or as a result of treatment [22]. It has 7 items with a 1-week recall, assessing symptoms (5 items-self-administered), rescue bronchodilator use (1 item-self-administered), and forced expiratory volume in 1 second expressed as % predicted ($FEV_1$%, 1 item) completed by clinical staff. Scaling of items is done on a 7-point scale (0 = no impairment, 6 = maximum impairment for symptoms and rescue use; and 7 categories for $FEV_1$%) with scores ranging between 0 (totally controlled) and 6 (severely uncontrolled).

ACT is a patient self-administered tool for identifying patients with poorly controlled asthma [23]. It has 5 items, with 4-week recall (on symptoms and daily functioning), assessing the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. Each item is evaluated on a 5-point scale (for symptoms and activities: 1 = all the time to 5 = not at all; for asthma control rating: 1 = not controlled at all to 5 = completely controlled) with scores ranging from 5 (poor control of asthma) to 25 (complete control of asthma). An ACT score >19 indicates well-controlled asthma.

Lung function was assessed using spirometry on a computerized pneumotach (Pneumoscreen, Jäger, Germany) according to ATS/ERS guidelines [24]. Spirometry was repeated until three acceptable and repeatable attempts were recorded. The best attempt was used to assess forced vital capacity (FVC), forced expiratory volume in 1 st second ($FEV_1$), peak expiratory flow

(PEF), and $FEV_1$/FVC ratio (Tiffeneau index). Values were expressed as a % predicted according to Quanjer et al. [25]. Bronchodilator test was done with repeated spirometry 20 minutes after inhalation of 400 µg of salbutamol; a positive test being an improvement of $FEV_1$ of ≥12% and ≥200 ml.

To assess eosinophilic inflammation, a fraction of exhaled nitric oxide (FeNO) was measured using a Hyp'Air FeNO measuring system (Medisoft, Sorinnes, Belgium) during a single-breath exhalation according to the ATS/ERS recommendations at a flow rate of 50 mL/second [26]. It was considered positive if the result was ≥25 ppb and highly positive if ≥50 ppb.

Identification and definition of asthma phenotypes was made according to the definition of phenotype as an observable characteristic of a patient with no direct relationship to disease process [27–29]. Cluster analysis was conducted using a number of variables selected on the basis of mechanisms and clinical findings critical for the expression of a particular phenotype (sex, age, age of onset, symptoms, lung function, allergy to aeroallergens, FeNO, family history, smoking habit, disease control, comorbidities). Patients were sorted out using the approach published by Haldar et al. [30]. In brief, cluster analysis was conducted as a two-step approach. At first, a hierarchical cluster analysis using Ward's method with squared Euclidean distances and a dendrogram for an estimation of the number of likely clusters was conducted. Cuts were made at points of large change between successive fusion levels (at a linkage distance of 2500) and used to define likely cluster boundaries. This pre-specified the number of clusters for a *k*-means cluster analysis used as the principal clustering technique. To ensure repeatability and stability, *k*-means algorithm was repeated within subpopulations of a dataset. Five main phenotypes were identified and defined by their main features as allergic asthma (allergy to aeroallergens, positive FeNO, positive asthma family history, early onset), aspirin-exacerbated respiratory disease (non-steroid anti-inflammatory drug sensitivity, positive FeNO, sinonasal polyposis), late-onset asthma (late onset, female, non-allergic, negative family history), obesity-associated asthma (obesity, late onset, female), respiratory infections associated asthma (triggered by respiratory infections, negative FeNO, non-allergic, chronic rhinosinusitis).

### Data analysis

Data analyses were done using STATISTICA version 12 (StatSoft, Inc., OK, USA) and MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). The minimal sample size ($n = 150$) was calculated based on the hypothesis of the expected $R^2$ of 0.20 for the model, with 30 independent variables, and statistical power of 90% with alpha = 0.05. To describe quantitative variables, mean with standard deviation or median with interquartile range (IQR) was used depending on the type of distribution. The normality of distribution was tested using Kolmogorov–Smirnov test. Nominal variables were described as absolute and relative (%) frequencies. Cluster analysis was used to sort patients into phenotype groups. Differences between groups for nominal variables were tested using $\chi^2$-test or Fisher's exact test and for quantitative variables using analysis of variance (ANOVA) or Kruskal–Wallis ANOVA depending on the type of distribution with Bonferroni correction for multiple comparisons. Multivariate stepwise logistic regression analysis was used to define significant associations of anxiety/depression with specific asthma phenotypes with results expressed as ORs and 95% confidence intervals (CIs) and area under the curve (AUC) with 95% CIs for the model. All tests were two-sided with $p < 0.05$ considered as statistically significant for all tests.

## Results

### Study population

Of 201 recruited patients, the majority were women ($n = 137$, 68.2%) of a median age of 47 years (IQR 32–56), equally with urban (55.7%) and suburban (44.3%) residence, mostly low- and middle-level education (90.5% high school or lower), more than half (61.7%) not employed (26.4% retired and 13.4% students), and half of them married (50.3%). Five phenotypes of asthma were identified—allergic asthma (AA, 88 respondents – 43.8%), aspirin-exacerbated respiratory disease (AERD, 44 respondents – 21.9%), late-onset asthma (LOA, 38 respondents – 18.9%), obesity-associated asthma (OAA, 20 respondents – 10.0%), and respiratory infections associated asthma (RIAA, 11 respondents – 5.5%). Characteristics of patients according to phenotypes are presented in Table 1.

A significant difference regarding median age of different phenotypes was found, with patients with RIAA being the youngest and the ones with LOA being the oldest as expected ($p < 0.001$). No difference in sex distribution between phenotypes was found ($p = 0.150$, Table 1). Patients were mostly obese (>50%, Table 1) with the highest BMI, as expected, in OAA patients (33.46 kg $m^{-2}$) and lowest (25.02 kg $m^{-2}$) in RIAA patients ($p < 0.001$). There were no significant differences found between phenotypes regarding smoking habit, residence, education level, and marital status ($p > 0.100$ for all, Table 1) but a significant

**Table 1.** Patients characteristics according to phenotype ($N = 201$).

| Parameters | Asthma phenotype | | | | | *p*-value |
|---|---|---|---|---|---|---|
| | Allergic ($n = 88$) | Aspirin-associated ($n = 44$) | Late-onset ($n = 38$) | Obesity-associated ($n = 20$) | Respiratory infections associated (n = 11) | |
| Age, years[a] | 38 (26–51) | 47 (42–56.5) | 55 (49–61) | 50 (30.5–52.5) | 32 (27–60) | <0.001[c] |
| Women[b] | 55 (62.5) | 36 (81.8) | 25 (65.8) | 12 (60) | 9 (81.8) | 0.150[d] |
| Body Mass Index, kg $m^{-2}$[e] | 25.38 (4.36) | 27.59 (5.71) | 27.27 (3.90) | 33.46 (4.28) | 25.02 (3.45) | <0.001[f] |
| Obesity[b] | | | | | | |
| non-obese | 43 (48.9) | 15 (34.1) | 11 (29.0) | 0 (0) | 6 (54.6) | <0.001[d] |
| obese | 45 (51.1) | 29 (65.9) | 27 (71.0) | 20 (100) | 5 (45.4) | |
| Smokers[b] | 50 (56.8) | 29 (65.9) | 23 (60.5) | 8 (40) | 5 (45.5) | 0.333[d] |
| Pack-years[a] | 5.3 (2.5–12) | 14 (4.6–22.5) | 15 (9.5–28) | 4 (1.8–23.8) | 12.6 (1.5–15) | 0.122[c] |
| Urban residence[b] | 48 (54.6) | 24 (54.6) | 25 (65.8) | 10 (50.0) | 5 (45.5) | 0.668[d] |
| Education level[b] | | | | | | |
| Low | 16 (18.2) | 11 (25.0) | 10 (26.3) | 4 (20.0) | 1 (9.1) | 0.655[d] |
| Mid | 65 (73.9) | 26 (59.1) | 25 (65.8) | 15 (75.0) | 9 (81.8) | |
| High | 7 (7.9) | 7 (15.9) | 3 (7.9) | 1 (5.0) | 1 (9.1) | |
| Employed[b] | 30 (34.1) | 20 (45.5) | 16 (42.1) | 3 (15.0) | 8 (72.7) | 0.018[d] |
| Married[b] | 51 (58.0) | 18 (40.9) | 15 (39.5) | 11 (55.0) | 6 (54.5) | 0.227[d] |
| Time from dg.[b] | | | | | | |
| 1–2 years | 26 (29.6) | 11 (25.0) | 9 (23.7) | 6 (30.0) | 3 (27.3) | 0.850[d] |
| 2–5 years | 9 (10.2) | 6 (13.6) | 6 (15.8) | 4 (20.0) | 3 (27.3) | |
| >5 years | 53 (60.2) | 27 (61.4) | 23 (60.5) | 10 (50.0) | 5 (45.5) | |
| Age of onset[b] | | | | | | |
| <12 years | 32 (36.4) | 8 (18.2) | 0 (0) | 2 (10.0) | 4 (36.4) | <0.001[d] |
| 12–18 years | 9 (10.2) | 5 (11.4) | 0 (0) | 2 (10.0) | 1 (9.1) | |
| 19–30 years | 25 (28.4) | 7 (15.9) | 0 (0) | 6 (30.0) | 4 (36.4) | |
| >30 years | 22 (25.0) | 24 (54.6) | 38 (100) | 10 (50.0) | 2 (18.2) | |
| $FEV_1$%[e] | 98.1 (20.8) | 87.9 (25.0) | 95.4 (23.8) | 99.4 (23.9) | 94.5 (14.3) | 0.150[f] |
| FeNO[b] | | | | | | |
| <25 ppb | 50 (56.8) | 29 (65.9) | 29 (76.3) | 13 (65.0) | 10 (90.9) | 0.237[d] |
| 25–50 ppb | 23 (26.1) | 11 (25.0) | 6 (15.8) | 6 (30.0) | 1 (9.1) | |
| >50 ppb | 15 (17.1) | 4 (9.1) | 3 (7.9) | 1 (5.0) | 0 (0) | |
| ACQ[a] | 0.86 (0.29–2.00) | 1.57 (0.71–2.36) | 1.29 (0.71–2.29) | 0.60 (0.21–1.50) | 2.00 (0.29–2.43) | 0.023[c] |
| ACT[a] | 22 (19–25) | 20 (18–22.5) | 21 (19–24) | 22 (19–25) | 19 (15–24) | 0.100[c] |
| Level of control[b] | | | | | | |
| Well | 27 (30.7) | 5 (11.4) | 8 (21.1) | 8 (40.0) | 2 (18.2) | 0.071[d] |
| Partly | 35 (39.8) | 22 (50.0) | 20 (52.6) | 4 (20.0) | 3 (27.3) | |
| Uncontrolled | 26 (29.6) | 17 (38.6) | 10 (26.3) | 8 (40.0) | 6 (54.5) | |
| Asthma attacks | | | | | | |
| 2×/year | 54 (61.4) | 25 (56.8) | 25 (65.8) | 11 (55.0) | 6 (54.5) | 0.838[d] |
| 2–10×/year | 21 (23.9) | 12 (27.3) | 11 (29.0) | 7 (35.0) | 4 (36.4) | |
| >10×/year | 13 (14.8) | 7 (15.9) | 2 (5.3) | 2 (10.0) | 1 (9.1) | |
| Unscheduled physician's visits during last month[b] | 56 (63.6) | 20 (45.5) | 22 (57.9) | 6 (30.0) | 6 (54.5) | 0.051[d] |
| Hospitalizations due to asthma[b] | 14 (15.9) | 9 (20.4) | 9 (23.7) | 3 (15.0) | 0 (0) | 0.424[d] |
| Symptoms[b] | | | | | | |
| Cough | 40 (45.5) | 13 (29.6) | 15 (39.5) | 9 (45.0) | 5 (45.5) | 0.498[d] |
| Dyspnea | 56 (63.6) | 33 (75.0) | 27 (71.1) | 10 (50.0) | 8 (72.7) | 0.314[d] |
| Tight chest | 34 (38.6) | 23 (52.3) | 17 (44.7) | 9 (45.0) | 5 (45.5) | 0.686[d] |
| Sticky mucus | 23 (26.1) | 12 (27.3) | 12 (31.6) | 7 (35.0) | 4 (36.4) | 0.882[d] |
| Waking up | 36 (40.9) | 25 (56.8) | 17 (44.7) | 7 (35.0) | 4 (36.4) | 0.381[d] |
| Adherence[b] | | | | | | |
| No | 15 (17.2) | 6 (13.6) | 6 (15.8) | 2 (10.0) | 3 (27.3) | 0.667[d] |
| Partial | 21 (23.9) | 14 (31.8) | 15 (39.5) | 5 (25.0) | 2 (18.2) | |
| Family history of asthma[b] | | | | | | |
| Yes | 36 (40.9) | 18 (40.9) | 6 (15.8) | 7 (35.0) | 3 (27.3) | 0.075[d] |

(*Continued on next page*)

**Table 1.** Continued

| Parameters | Asthma phenotype | | | | | *p*-value |
|---|---|---|---|---|---|---|
| | Allergic ($n = 88$) | Aspirin-associated ($n = 44$) | Late-onset ($n = 38$) | Obesity-associated ($n = 20$) | Respiratory infections associated (n = 11) | |
| Comorbidities[b] | | | | | | |
| Diabetes | 1 (1.1) | 7 (15.9) | 0 (0) | 2 (10.0) | 0 (0) | 0.002[d] |
| Hypertension | 17 (19.3) | 15 (34.1) | 12 (31.6) | 10 (50.0) | 3 (27.3) | 0.060[d] |
| GERD | 5 (5.7) | 5 (11.4) | 3 (7.9) | 2 (10.0) | 0 (0) | 0.652[d] |
| SNP | 5 (5.7) | 10 (22.7) | 3 (7.9) | 1 (5.0) | 1 (9.1) | 0.032[d] |
| CRS | 20 (22.7) | 16 (36.4) | 10 (26.3) | 8 (40.0) | 6 (54.5) | 0.332[d] |
| Previously treated for mental disorders[b] | | | | | | |
| Yes | 8 (9.1) | 4 (9.1) | 8 (21.1) | 1 (5.0) | 0 (0) | 0.150[d] |
| HADS anxiety[a] | 6.0 (2.5–9.0) | 5.0 (2.5–10.0) | 6.5 (5.0–10.0) | 6.0 (3.5–8.5) | 8.0 (4.0–14.0) | 0.469[c] |
| ≥8[b] | 26 (29.6) | 14 (31.8) | 14 (36.8) | 5 (25.0) | 5 (45.5) | 0.732[d] |
| HADS depression[a] | 4.0 (1.0–6.0) | 4.0 (1.5–8.0) | 4.0 (2.0–7.0) | 3.0 (2.0–8.0) | 3.0 (1.0–6.0) | 0.709[c] |
| ≥8[b] | 12 (13.6) | 10 (22.7) | 4 (10.5) | 5 (25.0) | 0 (0) | 0.190[d] |

Obesity was defined as a BMI >30 kg $m^{-2}$. Abbreviations: $FEV_1$%, forced expiratory volume in 1 second; FeNO, fraction of exhaled nitric oxide; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; GERD, gastroesophageal reflux disease; SNP, sinonasal polyposis; CRS, chronic rhinosinusitis; HADS, Hospital Anxiety and Depression Scale.
[a]Presented as median (interquartile range).
[b]Presented as number of respondents (%).
[c]Kruskal—Wallis ANOVA.
[d]$\chi^2$-test.
[e]Presented as mean (standard deviation).
[f]Analysis of variance (ANOVA).

difference was found for employment status ($p = 0.018$, Table 1).

There was no difference in distribution of the duration of asthma ($p = 0.850$) with the majority of patients having asthma for more than 5 years (Table 1). As expected, a significant difference was found for the age of onset of asthma ($p < 0.001$, Table 1). Patients with AERD had the worst lung function although the difference did not reach significance ($p = 0.150$), and FeNO values were highest in AA ($p = 0.237$, Table 1).

A significant difference was found for the level of control of asthma using ACQ ($p = 0.023$) but not with ACT ($p = 0.100$). Lowest level of control and highest ratio of uncontrolled and partially controlled patients were found in RIAA and AERD, respectively (Table 1). Other markers of asthma control (asthma attacks, hospitalizations due to asthma during the previous year, symptoms and unscheduled visits to a physician during the previous month) were not significantly different between phenotypes ($p > 0.05$ for all, Table 1), although the number of patients with unscheduled visits to a physician during the previous month almost reached significance ($p = 0.051$), being the highest in patients with AA and LOA and not following the pattern seen with ACQ and ACT.

High self-reported non-adherence was found (>40%) but without significant difference between phenotypes ($p = 0.667$). Positive family history of asthma was, as expected, most common in AA and AERD (40.9%, Table 1).

Besides anxiety/depression present in 69 (34.3%) patients, chronic rhinosinusitis was the most common comorbid disease in 60 (29.9%) patients, followed by hypertension in 57 (28.4%), and sinonasal polyposis in 20 patients (10%). The presence of comorbidities showed a significant difference for diabetes ($p = 0.002$) and sinonasal polyposis ($p = 0.032$) and marginal difference for hypertension ($p = 0.060$) between phenotypes (Table 1). Diabetes and sinonasal polyposis were the most common in AERD, and hypertension in OAA patients. Gastroesophageal reflux disease and chronic rhinosinusitis were not significantly different between phenotypes ($p = 0.652$, $p = 0.332$, respectively).

### *Main outcome*

Twenty-one (10.4%) patients were previously treated for a mental disorder with no significant difference between different phenotypes ($p = 0.150$, Table 1). According to the HADS questionnaire, 64 (31.8%) of them had anxiety, 31 (15.4%) depression, with comorbid anxiety and depression present in 26 (12.9%) patients. No significant differences for the presence of anxiety and depression or HADS scores for anxiety and depression between different phenotypes were found ($p > 0.190$ for all four, Table 1).

Logistic regression analysis depicted LOA phenotype and hypertension as significant predictors for HADS anxiety (LOA, OR = 2.12, 95% CI 1.11–4.07; hypertension, OR = 2.37, 95% CI 1.17–4.81; AUC, OR = 0.676, 95% CI 0.607–0.740, $p = 0.012$ for the model, Figure 1). On the other hand, AA and RIAA phenotypes together with hypertension and ACQ score were depicted as significant

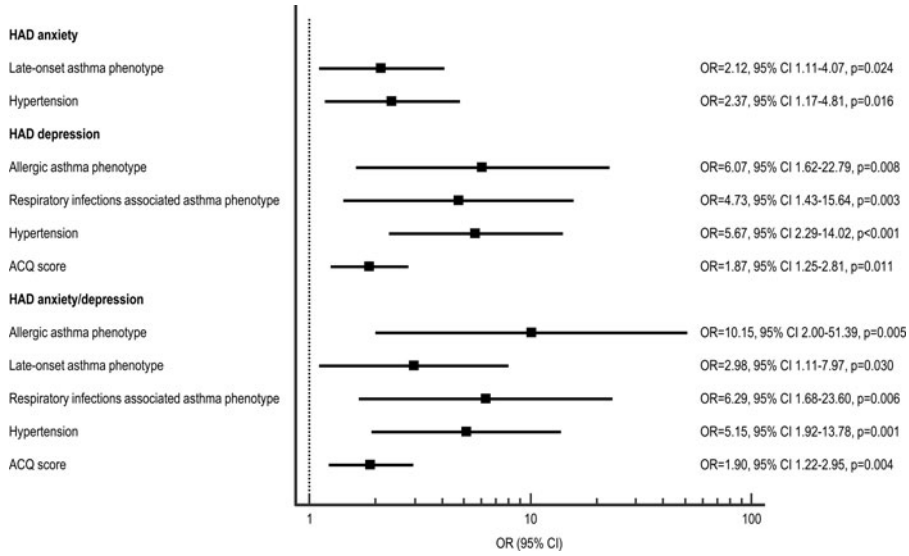


**Figure 1.** Forest plot of significant predictors for HADS anxiety, HADS depression and comorbid HADS anxiety/depression; OR – odds ratio, CI – confidence interval.

predictors for HADS depression (AA, OR = 6.07, 95% CI 1.62–22.79; RIAA, OR = 4.73, 95% CI 1.43–15.64; hypertension, OR = 5.67, 95% CI 2.29–14.02; ACQ, OR = 1.87, 95% CI 1.25–2.81; AUC = 0.804, 95% CI 0.742–0.857, $p < 0.001$ for the model, Figure 1). Comorbid HADS anxiety/depression was associated with AA, LOA, and RIAA phenotypes together with hypertension and ACQ score as significant predictors (AA, OR = 10.15, 95% CI 2.00–51.39; LOA, OR = 2.98, 95% CI 1.11–7.97; RIAA, OR = 6.29, 95% CI 1.68–23.60; hypertension, OR = 5.15, 95% CI 1.92–13.78; ACQ, OR = 1.90, 95% CI 1.22–2.95; AUC = 0.818, 95% CI 0.757–0.869, $p < 0.001$ for the model, Figure 1).

When comparing comorbid diseases for the prevalence of anxiety or depression, no significant difference for anxiety ($p = 0.392$), but a significant difference for depression ($p = 0.006$) was found, with the highest prevalence in diabetes and lowest in sinonasal polyposis (Figure 2).

## Discussion

Using cluster analysis we have identified 5 specific asthma phenotypes in our population: AA, AERD, LOA, OAA, and RIAA. Most of these phenotypes are commonly known from previous studies and are probably the best defined ones in asthma; AA, AERD, LOA, and OAA, all with general characteristics in accordance with already published data [1, 3, 8, 27–29]. Our study also corroborated high comorbid prevalence of HADS anxiety and depression in patients with asthma [10, 13]. It is important to understand the associations of comorbidities with asthma because they can complicate treatment pattern, influence adherence, deteriorate disease control, and increase prevalence of adverse effects, stress and mood disorders, such as anxiety and depression [8].

The main result of our study involves an association of mood disorders (anxiety/depression), as an important comorbidity, with specific asthma phenotypes identified in our adult outpatient population with asthma. To our knowledge, this is one of the few studies dealing with anxiety/depression in different asthma phenotypes [15, 16] and the first one showing an association of HADS anxiety and depression with specific asthma phenotypes (AA, LOA, and RIAA). The importance of these findings lies in the fact that each asthma phenotype has its own pattern of clinical characteristics and might have a specific subsequent treatment, additionally complicated by the presence of comorbidities. A complexity of this relation is more evident when analyzing our data, where HADS scores and the prevalence of mood disorders were evenly distributed between asthma phenotypes using univariate analysis. However, this was unveiled in a multivariate analysis confounded together with hypertension and the level of asthma control.

Multivariate analyses showed a complex association; anxiety was associated with LOA phenotype and hypertension, and depression was associated with AA and RIAA phenotypes, hypertension, and ACQ score. Comorbid presence of anxiety/depression was associated with AA, LOA, and RIAA phenotypes, hypertension, and ACQ score. AA in adolescents has already been prospectively associated with the development of mood disorders later in life [11]. LOA is mostly non-allergic and associated with female gender, smoking, and lower socioeconomic status [31], features seen also in our study. Female gender in this age group is associated with change in hormonal status and higher risk for mood disorders

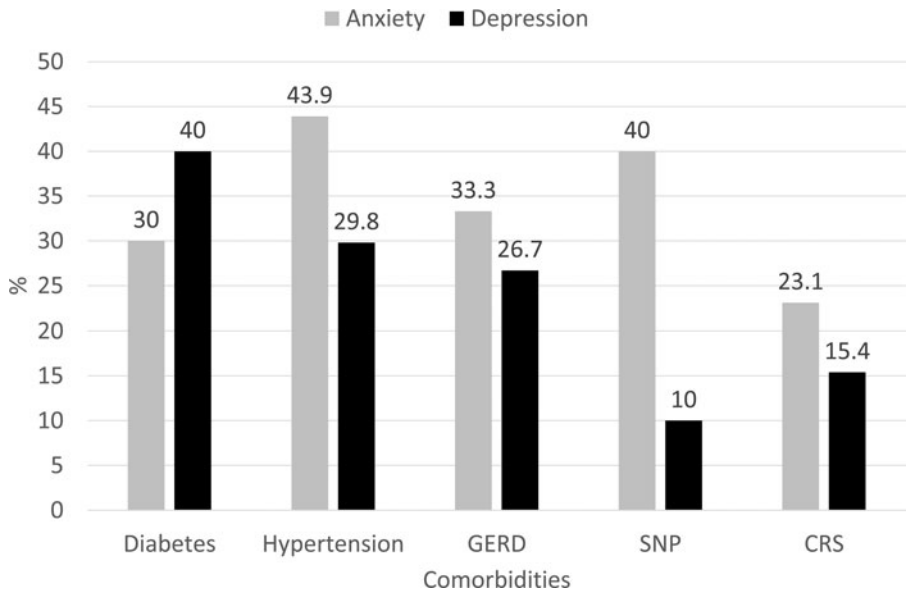


**Figure 2.** Prevalence of anxiety and depression in adult asthmatic patients according to physician's diagnosed comorbidities; GERD – gastroesophageal reflux disease, SNP – sinonasal polyposis, CRS – chronic rhinosinusitis.

[32–34]. Higher risk for mood disorders is also associated with smoking habit [35] and lower socioeconomic status [36]. RIAA phenotype is mostly non-allergic, with frequent respiratory infections, supporting prolonged nonspecific airways hyperreactivity, inducing changes related to disease chronicity, such as conditioning and plasticity [37]. Association of mood disorders with hypertension was published previously and confirmed in recent studies, showing a higher risk of having anxiety/depression with hypertension than in the general population [38, 39], with mood disorders also influencing treatment response and utilization of healthcare resources in these patients [40]. Our data regarding the association with asthma control are in line with the data of Favreau et al. who recently showed that mood disorders were prospectively associated with asthma control, quality of life, and utilization of healthcare resources [12].

Slavich and Irwin [41] in their comprehensive review discuss many layers of scientific evidence (basic, experimental, epidemiologic, and interventional) supporting the theory that connects societal stress, systemic inflammation (neurohumoral and inflammatory network), chronic inflammatory diseases, anxiety and depression, effects of anti-inflammatory treatment on depression, and association with comorbid chronic inflammatory disorders like asthma. Severe asthma has many of these underlying features. In support of this, de Carvalho-Pinto et al. [15] in their study showed very high overall prevalence of anxiety (>85%) and depression (>40%) in severe asthma phenotypes. On the other hand, they have not analyzed the difference between different severity phenotypes [15]. Possible asthma neurophenotypes have been suggested by Rosenkranz et al. based on functional MRI data in asthmatic patients [42]. Although with a high comorbid prevalence in asthma, it seems that anxiety and depression follow different patterns of association with disease characteristics [10]. This was also supported by a recent study investigating genetic polymorphism for serotonin transporter (5-HTT), brain-derived neurotrophic factor (BDNF), and neuropeptide S receptor 1 (NPSR1) in patients with asthma [43]. The difference in the pattern of comorbidities between different phenotypes including mood disorders suggests different major endotypes behind specific asthma phenotypes [44–47].

Our study also showed a significantly different level of asthma control in different phenotypes. Regarding the control of asthma, ACQ showed better discriminatory power (compared to ACT) between phenotypes with the lowest level of control in RIAA. Better discriminatory power of ACQ probably comes from combining lung function with symptoms and better recollection of symptoms (previous week compared to previous 4 weeks for ACT). These differences between ACQ and ACT are still not fully understood [48, 49] but suggest that asthma phenotypes can probably influence performance of these two instruments.

There are certain limitations to our study, such as the limited number of patients in some of the identified phenotypes, thus limiting the statistical power to detect smaller differences between groups as statistically significant. Although we recruited more patients than the calculated sample size, the study by design was not stratified for different asthma phenotypes, thus producing an uneven distribution. On the other hand, this approach

provided quite the realistic representation of different phenotypes in an adult asthmatic population. Compared to a longitudinal study, our cross-sectional study could not discover temporal associations of mood disorders with, for example, changes in asthma severity and control. This should be further explored in future studies. Also, apart from FeNO we have not measured other inflammatory markers (like blood eosinophils, eosinophil cationic protein, C-reactive protein), so a part of discussion is based on phenotype characteristics from other previously published studies. We have not actively searched for comorbidities other than mood disorders, but used the data from the physician's diagnosis. Also, as we compared many variables between different phenotypes, some of the comparisons although being significantly different could probably be trivial or without clinical relevance. Despite these limitations, we have identified five asthma phenotypes commonly present in adult patients with asthma, and using multivariate analyses, we showed the complexity of associations between asthma phenotypes, comorbidities, and asthma control.

## Conclusions

It is well known that mood disorders, especially anxiety and depression, are highly frequent in asthmatics, but little is known about the association of mood disorders with specific asthma phenotypes. We have determined five well-known asthma phenotypes in our adult patients with asthma. AA, LOA, and infection-associated asthma have been significantly associated with mood disorders, together with comorbid hypertension and the level of asthma control. This can have a significant effect on management and treatment of asthma in these specific phenotypes in adult patients.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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