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Symptoms of anxiety and depression in patients with persistent asthma: agreement between HADS and EQ-5D

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Title

Symptoms of anxiety and depression in patients with persistent asthma: agreement between HADS and EQ-5D

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Abstract

Objectives: Anxiety and depression are relevant comorbidities in asthma, but, in Portugal and Spain, data on this topic are scarce**.** We assessed, in patients with asthma, the frequency of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) and the European Quality of Life Five Dimension Questionnaire (EQ-5D); the level of agreement between these questionnaires, and the factors associated with these symptoms.

Methods: This is a secondary analysis of the INSPIRERS studies. A total of 614 adolescents and adults with persistent asthma (32.6±16.9y, 64.7% female) were recruited from 30 primary care centres and 32 allergy, pulmonology and pediatric clinics. Demographic and clinical characteristics, HADS and EQ-5D were collected. A score ≥8 on HADS-A/HADS-D or a positive answer to EQ-5D item 5 indicated the presence of these symptoms. Agreement was determined by Cohen's kappa. Two multivariable logistic regressions were built.

Results: According to HADS, 36% of the participants had symptoms of anxiety and 12% of depression. According to EQ-5D, 36% of the participants had anxiety/depression. The agreement between questionnaires in identifying anxiety/depression was moderate (k=0.55, 95%CI 0.48-0.62). Late asthma diagnosis, comorbidities and female gender were predictors of anxiety/depression, while better asthma control, health-related quality of life and perception of health were associated with lower odds for anxiety/depression.

Conclusion: At least 1/3 of the patients with persistent asthma experience symptoms of anxiety/depression, showing the relevance of screening these disorders in patients with asthma. Our results support the complementary use of these questionnaires.

Strengths and limitations of this study

- This study is a secondary analysis of a multicentric study that recruited both adults and adolescents with asthma from primary and secondary care.
- A comprehensive set of individual-level characteristics was analysed, which allowed us to explore the impact of sociodemographic factors and cofactors such as quality of life and asthma control on the presence of anxiety/depression symptoms.
- A possible source of bias was the recruitment strategy based on convenience sampling.
- The frequency of distressing symptoms and the relationships with associated factors could not be established overtime.

Word count: 3094

Key Words: Asthma; Anxiety Disorders; Anxiety Disorders/epidemiology; Depression Disorder; Depressive Disorder/epidemiology; Surveys and Questionnaires; Portugal/epidemiology; Spain/epidemiology.

Introduction

Asthma affects approximately 300 million people worldwide [1]. In Portugal, asthma affects 695 000 Portuguese, with a general prevalence of 6.8% [2]. In Spain, asthma affects more than three million people, with an estimated prevalence of 5% in adults [3]. Asthma is primarily related to chronic inflammation of the lower respiratory tract, variable airflow obstruction, and bronchial hyperresponsiveness [4]. Yet, this disease is often accompanied by multiple associated comorbidities, such as chronic rhinosinusitis, nasal polyposis, allergic rhinitis, gastroesophageal reflux disease, obstructive sleep apnea syndrome [5], and also anxiety and depression.

In two systematic reviews, the average of the reported prevalence of any anxiety disorder among patients with asthma was 24% [6] and 34% [7]. Regarding depression, a pragmatic literature review found that 1% to 45% of patients with asthma suffer from depression or depressive symptoms [8]. In severe asthma, a study reported an average prevalence of 27% for emotional distress (mainly due to anxiety and depression) [9]. Currently, most studies about emotional distress focus essentially on adult patients with more severe asthma [10]. There is a lack of data regarding other asthma sub-groups, namely adolescents and those with mild or moderate persistent asthma.

Anxiety and depression are associated with significantly lower quality of life, poor asthma control, higher frequency of exacerbations and increased use of healthcare resources [11]. Moreover, anxiety is associated with greater perceived dyspnea intensity and may shape the quality and intensity of this symptom at a given respiratory load [12]. However, it is still uncertain whether other factors can affect the patient's psychological state. It is important to have a more sophisticated understanding of the interplay between emotional distress and asthma [13].

Despite these negative impacts, anxiety and depression in patients with asthma is not routinely assessed during clinical visits and thus there is a lack of information about its real-world frequency. One of the most used tools for psychological screening is the Hospital Anxiety and Depression Scale (HADS). HADS is a self-report questionnaire designed to screen anxiety and depression symptoms [14] and it was already used in adolescents and adults with asthma in previous studies [15, 16]. However, this scale has 14 items and although it takes around 5 minutes to complete [17], it is not always feasible to administer in a busy clinic setting [18, 19]. European Quality of Life Five Dimension Questionnaire (EQ-5D) is a generic measure of health status that provides a simple descriptive profile and a single index value that can be used for the clinical and economic evaluation of healthcare [20], but also emotional distress screening [21]. Currently, EQ-5D is being widely used in a variety of conditions, where asthma is integrated [22]. Some studies compared HADS and EQ-5D in patients with other diseases and showed that EQ-5D can be responsive to different degrees of HADS-assessed distress [23]. Yet, there is no published data comparing HADS and EQ-5D in patients with asthma.

With the present study, we aimed to assess i) the frequency of symptoms of anxiety and depression in patients with asthma as assessed by HADS and EQ-5D questionnaires; ii) the level of agreement between the two questionnaires and iii) the factors associated with the presence of these symptoms

Methods

Patient and public involvement

No patient involved

Study design

Data from the baseline face-to-face visit from 5 prospective observational studies of the INSPIRERS project were analysed [24]. This project addresses the topic of adherence to asthma inhalers among adolescents and adults with persistent asthma. Convenience samples were recruited between November 2017 and October 2020 at 32 allergy, pulmonology and paediatric secondary care outpatient clinics (30 from Portugal and 2 from Spain) and 30 primary care centres from Portugal. The studies were approved by the ethics committees of all participating centres. Eligible patients were approached by physicians during medical visits. Adult patients signed a consent form. Adolescents signed an assent form, and a parental consent form was also obtained. The studies had similar inclusion criteria and methods. The study is reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [25].

Patients

Patients were included in the analysis if they had a previous medical diagnosis of persistent asthma, were at least 13 years old (13–17 years adolescents; ≥18 years adults) and had an active prescription for an inhaled controller medication for asthma. All inhaled controller treatments were allowed, and there was no change in any prescribed medication regarding the participation in these studies. Patients were excluded if they had a diagnosis of a chronic lung disease other than asthma or a diagnosis of another significant chronic condition with possible interference with the study aims.

Data collection

During the baseline face-to-face visit, data were collected from both physicians and patients. Physicians answered a questionnaire including the Global Initiative for Asthma (GINA) assessment of symptom control [25], the asthma treatment plan and comorbidities.

Information about the healthcare setting (primary, secondary) was obtained based on the centre where patients were recruited.

Demographic data (age, gender, educational level, marital status and current occupation) and clinical data (weight, height, smoking habits, and age of asthma diagnosis) were collected from patients. Asthma control was also assessed using the Control of Allergic Rhinitis and Asthma Test (CARAT). CARAT is a self-report questionnaire with a total score (CARAT-T) calculated by summing up the score of each of the 10 questions, resulting in a range of 0–30 points. A score >24 indicates good disease control [26].

The Portuguese version of the Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of symptoms of anxiety and depression [27]. HADS contains 14 items related to the past week, 7 of which assess anxiety symptoms (HADS-A) and the other 7 depression symptoms (HADS-D). HADS-A and HADS-D are scored separately. The item response scale varies between 0 and 3 points, with total scores ranging from 0 (minimum symptomatic load) up to 21 (maximum symptomatic load) for HADS-A and HADS-D. A score ≥8 on HADS-A or HADS-D was considered as the presence of symptoms of anxiety or depression, respectively [28].

The European Quality of Life Five Dimension Questionnaire (EQ-5D) three-level version was filled in by the patients to assess their overall quality of life. The item 5 “Anxiety and Depression” could be a useful tool in screening for anxiety and depressive symptoms in hospital and community settings [29]. Therefore, this item, with its 3 response options (“I am not anxious or depressed”, “I am moderately anxious or depressed”, “I am extremely anxious or depressed”) was additionally used to assess the presence of these symptoms [30]. Patients were considered to have anxiety/depression when answering “I am moderately anxious or depressed” or “I am extremely anxious or depressed”. The EQ-5D summary index score was

calculated to characterize the sample. It ranges from less than 0 (where 0 is a health state equivalent to death) to 1 (perfect health) [31]. The EQ-5D VAS was also used to assess patients' perception of their general health (from 0 'the worst health you can imagine' to 100 'the best health you can imagine').

Statistical Analyses

Descriptive statistics were used to characterize the sociodemographic variables, clinical characteristics, the HADS score and EQ-5D responses. Absolute and relative frequencies were used to characterize the categorical variables. Means and standard deviations or medians and interquartile ranges were used, according to data distribution, to characterize the numerical variables.

To determine the agreement between HADS and EQ-5D questionnaires for the presence of symptoms of anxiety/depression, the percentage of agreement and weighted Cohen's kappa were used. Cohen's kappa values were interpreted as follows: <0, no agreement; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial and 0.81–1.0, almost perfect agreement [32].

To explore associations between variables related to the presence of symptoms of anxiety and depression, patients with and without symptoms of anxiety and depression were compared using independent t-tests for normally distributed data, Mann-Whitney U tests for non-normally distributed continuous data and ordinal data, and Chi-square tests for categorical data. In the case of Chi-square tests, when a statistically significant difference was found for a categorical variable with more than two categories, chi-square multiple comparison tests with Bonferroni correction were performed to explore which categories differed from each other. The variables that were statistically different ($p<0.05$) between the two groups were selected to further explore their relationship with the presence of anxiety

and depression and to adjust for possible confounders in two stepwise multivariable logistic regression models. The dependent variable in each multivariable logistic regression was the presence of symptoms of anxiety or depression based on HADS (0 = absent, 1 = present). The overall models were evaluated using the goodness-of-fit tests and Nagelkerke's R-square and the final model was selected based on the best combination of these results. The level of significance considered was 0.05. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient's Characteristics

A total of 614 participants with asthma (mean age 32.6 ± 16.9 years) were included in this study. There were 447 (72.8%) adults and 397 (64.7%) females. Forty percent of the participants had completed primary school (n=244), 47.4% were employed (n=289) and 65.1% were prescribed only 1 inhaler (n=396). According to the GINA assessment of symptom control, 296 (48.7%) patients had well controlled asthma. Table 1 shows the socio-demographic and clinical characteristics of the study participants.

TABLE 1. Socio-demographic and clinical characteristics of the participants (n=614).

Characteristics	
Age (years) M ± SD[a]	32.6 ± 16.9
Age group n (%)	
Adolescent	167 (27.2)
Adult	447 (72.8)
Gender n (%)	
Female	397 (64.7)
Male	217 (35.3)
Educational level n (%)[b]	
No education completed	4 (0.7)
Primary school	244 (40.4)
High school	177 (29.3)

Qualification above high school (but not university)	23 (3.8)
University	156 (25.4)
Other	1 (0.2)
Marital status n (%)[c]	
Single	348 (56.7)
Married/Living as a couple	223 (36.3)
Separated/divorced	33 (5.4)
Widowed	9 (1.5)
Current occupation n (%)[d]	
Employed	289 (47.1)
Student	235 (38.3)
Unemployed	41 (6.7)
Retired	36 (5.9)
Other	9 (1.5)
BMI Kg/m2, M ± SD[e]	24.7 (5.3)
Smoking Status n (%)[d]	
Never smoker	457 (74.4)
Ex-smoker	106 (17.3)
Current smoker	47 (7.7)
Setting	
Secondary care	475 (77.4)
Primary care	139 (22.6)
Age of asthma diagnosis (years) M ± SD[f]	16.2 ± 14.8
Number of prescribed inhalers n (%)[g]	
1	396 (64.5)
2	193 (31.4)
≥3	19 (3.1)
GINA assessment symptom control n (%)[g]	
Well controlled	296 (48.2)
Partly controlled	188 (30.6)
Uncontrolled	124 (20.2)
Number of physician-reported comorbidities Median (P25-P75)	1 [0-2]
CARAT-T Median (P25-P75)	21 [16-25]
CARAT-T Classification	
Controlled n (%)	156 (25.4)
Uncontrolled n (%)	458 (74.6)
EQ-5D-3L Median (P25-P75)	
Total	0.91 [0.81-1.0]
VAS	80.0 [70.0-90.0]

M = Mean; SD= Standard Deviation; BMI=body mass index; GINA = Global Initiative for Asthma; P25= 25th percentile; P75= 75th percentile; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D-3L= European Quality of Life Five Dimension Questionnaire-three-level version; VAS= Visual analogue scale.

[a] 8 missing values. [b] 9 missing values.[c] missing value. [d] 4 missing values.[e] 28 missing values. [f] 22 missing values.[g] 6 missing values.

Symptoms of anxiety and depression

According to HADS, 221 (36.0%) participants had symptoms of anxiety, 73 (11.9%) had symptoms of depression, 59 (9.6%) both symptoms and 235 (38.3%) participants had symptoms of anxiety or depression. Both anxiety (41.4% vs 21.6%) and depression (14.1% vs 6%) symptoms were more frequent in adults than adolescents. According to EQ-5D, 223 (36.3%) participants had anxiety or depression problems, 32.6% were moderately anxious or depressed and 3.7% extremely anxious or depressed. The agreement between these two questionnaires was moderate for anxiety (k=0.54 (95%CI 0.47-0.61)); sufficient for depression (k=0.23 (95%CI 0.17-0.30)) and moderate for anxiety/depression (k=0.55 (95% CI 0.48-0.62)).

Predictors of anxiety and depression

In the multivariable logistic regression (Table 2), being an adolescent (OR 0.43, 95% CI 0.27-0.68), having a better asthma control (CARAT-T score) (OR 0.98, 95% CI 0.94-1.00) and a perception of better health (OR 0.97, 95% CI 0.95-0.98) were significantly associated with lower odds for the presence of anxiety symptoms. In contrast, being a female was significantly associated with a higher odd for the presence of anxiety symptoms (OR 1.75, 95% CI 1.56-2.64). Having better health-related quality of life (OR 0.97, 95%CI 0.95-0.99) and perception of better health (OR 0.97, 95% CI 0.96-0.99) were associated with a lower odd for the presence of depression. While asthma diagnosis at a later age (OR 1.03, 95% CI 1.01-1.05) and the presence of a higher number of comorbidities (OR 1.31, 95% CI 1.05-1.64) were associated with an increase in the likelihood of exhibiting symptoms of depression. The univariate analyses are presented in Supplementary Table 1.

Table 2 – Multivariable logistic regression analyses to explain anxiety and depression.

	Anxiety adjusted OR (95% CI)*	Depression adjusted OR (95% CI)**
Age group		
Adolescent	0.43 (0.27-0.68)	-
Adult	Reference	-
Gender		
Female	1.75 (1.56-2.64)	-
Male	Reference	-
Age of asthma diagnosis	-	1.03 (1.01-1.05)
Number of physician-reported comorbidities	1.17 (0.99-1.37)	1.31 (1.05-1.64)
CARAT T	0.98 (0.94-1.00)	-
Quality of life (EQ-5D total)	-	0.97 (0.95-0.99)
Perception of better health (EQ-5D VAS)	0.97 (0.95-0.98)	0.97 (0.96-0.99)
R^2	22%	23%
Hosmer-Lemeshow test - p-value	.435	.449

OR = Odds ratio; CI = Confidence interval; BMI = body mass index; CARAT-T = Control of Allergic Rhinitis and Asthma Test total score; EQ-5D = European Quality of Life Five Dimension Questionnaire; VAS= Visual analogue scale.
*Age, current occupation, setting, age of asthma diagnosis, GINA assessment of symptom control and quality of life (EQ-5D total) were also tested but not included in the final adjusted model.
**Age, age group, educational level, marital status, current occupation, BMI, GINA assessment of symptom control and CARAT T were also tested but not included in the final adjusted model.

Discussion

This study showed that more than 1/3 of participants with asthma experienced symptoms of anxiety and/or depression. Asthma diagnosis at a later age, presence of comorbidities and female gender were predictors of anxiety/depression, while better asthma control, health-related quality of life and perception of better health were factors associated with lower odds for anxiety/depression. In this study, the agreement between HADS and EQ-5D questionnaires in identifying anxiety and depression was sufficient to moderate.

According to HADS and EQ-5D questionnaires, more than 1/3 of the patients with persistent asthma experience symptoms of anxiety/depression (38.3% and 36.3% respectively). Therefore, the percentages of participants with one of these symptoms detected by HADS and EQ-5D were similar. With HADS, it was possible to detect the

percentages of patients with persistent asthma that had only symptoms of anxiety (36.0%) or had only symptoms of depression (11.9%). The proportions found in the present study were similar to the ones found among patients with asthma in previous reviews [7, 8], analysing studies that included only, or mostly, adults with asthma. A study from the UK found similar frequencies of anxiety and depression using HADS, although a slightly higher cut-off has been used (HADS-A/HADS-D≥10) [33]. We found a lower frequency for depression as compared with a study in patients with severe asthma, where 25% reported depression [34]. This difference might be explained by the role of poorer physical functioning on symptoms of depression [35]. Patients with severe asthma experience more physical disability. Other studies reported that patients with severe asthma have more often emotional distress as compared to patients with mild-moderate asthma [36, 37].

This study includes both adolescents and adults with persistent asthma, which is rarely found in previous articles. However, anxiety and depression were only assessed at one time point. Analysing emotional distress in the long run could be important as suggested in previous cohort studies that followed adolescents with asthma to young adulthood, showing that there was a persistence or recurrence of anxiety and depression in adulthood [38, 39]. In our study, adults with persistent asthma presented an increased frequency of anxiety/depression symptoms (vs adolescents), which is in accordance with a population-based study that reported that having asthma and older age were independent risk factors for the presence of anxiety disorders, in participants above the age of 15 years [40]. Therefore, emotional distress seems to be associated with age differences in patients with persistent asthma.

Age at asthma onset has emerged as a critical factor in distinguishing the phenotypes of asthma [41]. Adult-onset asthma differs from asthma that first occurs in childhood since it usually is less well controlled, is associated with a faster decline in lung function and with more comorbidities [42, 43]. Moreover, worse asthma control and the presence of more comorbidities might be associated with an increased risk of emotional distress [44]. These results contribute to explaining our finding that asthma diagnosis at a later age and number of physician-reported comorbidities were associated with a higher frequency of depression. Female patients were more likely to have anxiety symptoms. This was previously observed in other studies in asthma but also other respiratory diseases, such as COPD. Possibly these gender differences are more than a specificity of respiratory diseases, but a reflection of the known gender differences in the general population [45, 46].

In our study, the perception of better health was associated with a lower odd for the presence of anxiety symptoms. In a previous study with patients with chronic obstructive pulmonary disease (COPD), the perceived severity of COPD symptoms was predictive of depression and anxiety [47]. These findings are in line with our study, although coming from a different disease. The close correlation between asthma control, quality of life, anxiety, and depression has been also confirmed in other studies [48, 49]. Consequently, in patients with poor asthma control, physicians should ask about the symptoms of anxiety/depression or screen it using simple tools like EQ-5D or HADS before making adjustments on asthma treatment strategy [16].

EQ-5D questionnaire is a common generic tool used to evaluate health interventions. This questionnaire could be useful in clinical practice [50]. The EQ-5D anxiety or depression domain had a greater agreement with the HADS score in identifying cases with both

symptoms, as expected, than in identifying anxiety or depressive symptoms. In general, the percentages of patients with anxiety/depression detected by HADS and EQ-5D were similar. Furthermore, it is expected that remarkably less time consumption is needed for the EQ-5D item 5 assessment compared with HADS [17, 51]. Therefore, EQ-5D score appears to have value as a screening tool for anxiety or depression in patients with asthma. In a previous study, this questionnaire also seemed to be reasonably valid and moderately responsive in patients with anxiety disorders [52]. This could be important in clinical practice because a generic health instrument like the EQ-5D, with few and quick questions, could be used to easily raise awareness of a possible emotional distress in patients with asthma. A limitation of EQ-5D is that anxiety and depression are two separate emotional disorders and their combination in a single item in this questionnaire could lead to inconsistencies in responses [53]. Nevertheless, EQ-5D could be used as a first screening questionnaire and, in patients reporting anxiety or depression symptoms, a more specific questionnaire, such as HADS, could be used to better characterize their symptoms. Actually, emotional distress screening is very important in clinical practice because physicians can use targeted interventions to improve patients' symptoms. Studies about psychological interventions in adults with asthma suggest that education and simple psychological interventions namely relaxation techniques and biofeedback or a stepped care approach could produce significant positive healthcare outcomes [54, 55].

This study has some strengths that should be acknowledged: it is a multicentric study that recruited both adults and adolescents with asthma from primary and secondary care. A comprehensive set of individual-level characteristics was collected and analysed, which allowed us to explore the impact of a range of sociodemographic factors, health literacy and cofactors such as quality of life and asthma control. Therefore, includes a sample from

different health care contexts and with different clinical presentations, contributing to the robustness of these findings.

Nevertheless, it also has some limitations. A possible source of bias was the recruitment strategy of using a convenience sampling. Future studies using other sampling strategies could be important to generalise the results of our study. A control group of healthy individuals with similar socio-demographic characteristics should also be included in further research to increase the validity of these findings. In the absence of a control group it would have been useful to compare anxiety/depression frequencies with normative data from Portugal and Spain, but we did not find it neither for HADS nor EQ-5D. Moreover, the impact of the presence of specific comorbidities, such as rhinitis, which is closely associated both with asthma and anxiety/depression, was not assessed [56]. Another limitation of the present study is related to its cross-sectional nature. The frequency of distressing symptoms and the relationships with associated factors could not be established along the progression of the disease. Also, patients were not recruited at the same time point, as recruitment in the Inspirers studies occurred across 4 different years (from 2017 to 2020), and the last 15% of the sample was recruited during COVID-19 pandemic. Longitudinal studies following a cohort of patients with asthma would address these issues and identify other predictors of symptoms of anxiety and depression.

This study shows that more than 30% of the patients with persistent asthma experience symptoms of anxiety/depression, which supports the relevance of emotional distress screening in patients with asthma. The study also showed that for screening purposes, it is possible to use either EQ-5D and HADS questionnaires.

a. Contributorship statement

All authors contributed to the selection of bibliography, revision and final approval of the manuscript. AMP, RA, MAC, RAlmeida, JAF and CJ were responsible for study conception and design; RA, AMP, RAlmeida, MAC, CCL, CL, JC, CR, CV, DAA, DP, MFM, MJV, CLozoya, NS, FC, LTB, RF, PMS, TMF, RC, ES, DB, CG, MJC, SS, MLM, AM, CN, CVieira, RP, AA, JVM, BR, LM, RM, MC, BV, DSC, SF, PM, MAA, ARM, JAF and CJ participated in the data collection; CJ and AMP performed the data analysis and MSC prepared the first draft. All authors contributed to the interpretation of data, to the critical revision of the manuscript for important intellectual content.

b. Competing interests

None

c. Funding

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d. Data sharing statement

The data sets generated during and/or analysed during the current study are not publicly available.

Ethics approval

The studies were approved by the ethics committees of all participating centres. For example, the study was approved by the Ethics Committee of Centro Hospitalar de S. João—EPE (protocol code 258-17 and date of approval: 5th of January 2018).

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Supplementary table 1 – Univariate analyses to explain anxiety and depression symptoms.

	Anxiety crude OR (95% CI)	Depression crude OR (95% CI)
Age	1.02 (1.01-1.03)	1.05 (1.03-1.06)
Age group		
Adolescent	0.39 (0.26-0.59)	0.39 (0.19-0.78)
Adult	Reference	Reference
Gender		
Females	2.44 (1.68-3.53)	1.64 (0.95-2.85)
Males	Reference	Reference
Educational level		
No education completed/Primary school	0.99 (0.71-1.39)	1.67 (1.01-2.74)
High school/Qualification above high school (but not university)/University/Other	Reference	Reference
Marital status		
Single/ Separated/Divorced/Widowed	0.72 (0.52-1.02)	0.45 (0.27-0.74)
Married/Living as a couple	Reference	Reference
Current occupation		
Employed/Student/Other	0.55 (0.35-0.87)	0.25 (0.14-0.43)
Unemployed/Retired	Reference	Reference
BMI	1.03 (0.99-1.06)	1.08 (1.04-1.13)
Smoking status		
Non-smokers	0.56 (0.31-1.02)	0.92 (0.37-2.24)
Smokers	Reference	Reference
Setting		
Primary care	1.60 (1.09-2.35)	1.04 (0.58-1.86)
Secondary care	Reference	Reference
Age of asthma diagnosis	1.02 (1.01-1.03)	1.04 (1.03-1.06)
Number of physician-reported comorbidities	1.32 (1.14-1.53)	1.55 (1.29-1.87)
Number of prescribed inhalers	1.29 (0.97-1.71)	1.29 (0.87-1.91)
GINA assessment symptom control		
Well controlled	0.61 (0.44-0.85)	0.51 (0.30-0.85)
Partly controlled/Uncontrolled	Reference	Reference
CARAT T	0.93 (0.91-0.96)	0.91 (0.88-0.95)
Quality of life (EQ-5D total)	0.94 (0.92-0.95)	0.94 (0.93-0.96)
Perception of better health (EQ-5D VAS)	0.96 (0.95-0.97)	0.96 (0.95-0.97)

OR = Odds ratio; CI= Confidence interval; BMI=body mass index; GINA = Global Initiative for Asthma; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D= European Quality of Life Five Dimension Questionnaire.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12 11-12 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Title

Symptoms of anxiety and depression in patients with persistent asthma: a cross-sectional analysis of the INSPIRERS studies

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Abstract

Objectives: Anxiety and depression are relevant comorbidities in asthma, but, in Portugal and Spain, data on this topic are scarce**.** We assessed, in patients with asthma, the frequency of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) and the European Quality of Life Five Dimension Questionnaire (EQ-5D); the level of agreement between these questionnaires, and the factors associated with these symptoms.

Methods: This is a secondary analysis of the INSPIRERS studies. A total of 614 adolescents and adults with persistent asthma (32.6±16.9y, 64.7% female) were recruited from 30 primary care centres and 32 allergy, pulmonology and pediatric clinics. Demographic and clinical characteristics, HADS and EQ-5D were collected. A score ≥8 on HADS-A/HADS-D or a positive answer to EQ-5D item 5 indicated the presence of these symptoms. Agreement was determined by Cohen's kappa. Two multivariable logistic regressions were built.

Results: According to HADS, 36% of the participants had symptoms of anxiety and 12% of depression. According to EQ-5D, 36% of the participants had anxiety/depression. The agreement between questionnaires in identifying anxiety/depression was moderate (k=0.55, 95%CI 0.48-0.62). Late asthma diagnosis, comorbidities and female gender were predictors of anxiety/depression, while better asthma control, health-related quality of life and perception of health were associated with lower odds for anxiety/depression.

Conclusion: At least 1/3 of the patients with persistent asthma experience symptoms of anxiety/depression, showing the relevance of screening these disorders in patients with asthma. EQ-5D and HADS questionnaires showed a moderate agreement in the identification of anxiety/depression symptoms. The identified associated factors need to be further investigated in long-term studies.

Strengths and limitations of this study

- This study is a secondary analysis of a multicentric study that recruited both adults and adolescents with asthma from primary and secondary care.
- A comprehensive set of individual-level characteristics was analysed, which allowed us to explore the impact of sociodemographic factors and cofactors such as quality of life and asthma control on the presence of anxiety/depression symptoms.
- A possible source of bias was the recruitment strategy based on convenience sampling.
- The frequency of distressing symptoms and the relationships with associated factors could not be established overtime.

Word count: 3661

Key Words: Asthma; Anxiety Disorders; Depression Disorder; Surveys and Questionnaires.

Introduction

Asthma affects approximately 300 million people worldwide [1]. In Portugal, asthma affects 695 000 Portuguese, with a general prevalence of 6.8% [2]. In Spain, asthma affects more than three million people, with an estimated prevalence of 5% in adults [3]. Asthma is primarily related to chronic inflammation of the lower respiratory tract, variable airflow obstruction, and bronchial hyperresponsiveness [4]. Yet, this disease is often accompanied by multiple associated comorbidities, such as chronic rhinosinusitis, nasal polyposis, allergic rhinitis, gastroesophageal reflux disease, obstructive sleep apnea syndrome [5], and also anxiety and depression [6].

In two systematic reviews, the average of the reported prevalence of any anxiety disorder among patients with asthma was 24% [7] and 34% [8]. Regarding depression, a pragmatic literature review found that 1% to 45% of patients with asthma suffer from depression or depressive symptoms [9]. In severe asthma, a study reported an average prevalence of 27% for emotional distress (mainly due to anxiety and depression) [10]. Currently, most studies about emotional distress focus essentially on adult patients with more severe asthma [11]. There is a lack of data regarding other asthma sub-groups, namely adolescents and those with mild or moderate persistent asthma.

Anxiety and depression are associated with significantly lower quality of life, poor asthma control, higher frequency of exacerbations and increased use of healthcare resources [12]. Moreover, anxiety is associated with greater perceived dyspnea intensity and may shape the quality and intensity of this symptom at a given respiratory load [13]. However, it is still uncertain whether other factors can affect the patient's psychological state. It is important to have a more sophisticated understanding of the interplay between emotional distress and asthma [14].

Despite these negative impacts, anxiety and depression in patients with asthma is not routinely assessed during clinical visits and thus there is a lack of information about its real-world frequency. One of the most used tools for psychological screening is the Hospital Anxiety and Depression Scale (HADS). HADS is a self-report questionnaire designed to screen anxiety and depression symptoms [15] and it was already used in adolescents and adults with asthma in previous studies [16, 17]. However, this scale has 14 items and although it takes around 5 minutes to complete [18], it is not always feasible to administer in a busy clinic setting [19, 20]. European Quality of Life Five Dimension Questionnaire (EQ-5D) is a generic measure of health status that provides a simple descriptive profile and a single index value that can be used for the clinical and economic evaluation of healthcare [21], but also emotional distress screening [22]. Currently, EQ-5D is being widely used in a variety of conditions, where asthma is integrated [23]. Some studies compared HADS and EQ-5D in patients with other diseases and showed that EQ-5D can be responsive to different degrees of HADS-assessed distress [24]. Yet, there is no published data comparing HADS and EQ-5D in patients with asthma.

With the present study, we aimed to assess i) the frequency of symptoms of anxiety and depression in patients with asthma as assessed by HADS and EQ-5D questionnaires; ii) the level of agreement between the two questionnaires and iii) the factors associated with the presence of these symptoms

Methods

Patient and public involvement

No patient involved

Study design

Data from the baseline face-to-face visit from 5 prospective observational studies of the INSPIRERS project were analysed [25]. This project addresses the topic of adherence to asthma inhalers among adolescents and adults with persistent asthma. Convenience samples were recruited between November 2017 and October 2020 at 32 allergy, pulmonology and paediatric secondary care outpatient clinics (30 from Portugal and 2 from Spain) and 30 primary care centres from Portugal. The studies were approved by the ethics committees of all participating centres. Eligible patients were approached by physicians during medical visits. Adult patients signed a consent form. Adolescents signed an assent form, and a parental consent form was also obtained. The studies had similar inclusion criteria and methods. The study is reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [26].

Patients

Patients were included in the analysis if they had a previous medical diagnosis of persistent asthma, were at least 13 years old (13–17 years adolescents; ≥18 years adults) and had an active prescription for an inhaled controller medication for asthma. All inhaled controller treatments were allowed, and there was no change in any prescribed medication regarding the participation in these studies. Patients were excluded if they had a diagnosis of a chronic lung disease other than asthma or a diagnosis of another significant chronic condition with possible interference with the study aims.

Data collection

During the baseline face-to-face visit, data were collected from both physicians and patients in an attempt to improve the quality of the information obtained. Physicians

answered a questionnaire including the asthma treatment plan and comorbidities. Information about the healthcare setting (primary, secondary) was obtained based on the centre where patients were recruited.

Demographic data (age, gender, educational level, marital status and current occupation) and clinical data (weight, height, smoking habits, and age of asthma diagnosis) were collected from patients.

Two asthma control questionnaires were used to gather the perspectives of the physician and the patient. Physicians answered the Global Initiative for Asthma (GINA) assessment of symptom control [26], which is recommended to be use at every opportunity in adolescents and adults. Patients answered the Control of Allergic Rhinitis and Asthma Test (CARAT). CARAT is a self-report questionnaire with a total score (CARAT-T) calculated by summing up the score of each of the 10 questions, resulting in a range of 0–30 points. A score >24 indicates good disease control [27]. This questionnaire has been widely used in clinical practice and in scientific research, being translated/culturally adapted in >27 languages and used in >15 different countries [28].

The Portuguese version of the Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of symptoms of anxiety and depression [29]. HADS contains 14 items related to the past week, 7 of which assess anxiety symptoms (HADS-A) and the other 7 depression symptoms (HADS-D). HADS-A and HADS-D are scored separately. The item response scale varies between 0 and 3 points, with total scores ranging from 0 (minimum symptomatic load) up to 21 (maximum symptomatic load) for HADS-A and HADS-D. A score ≥8 on HADS-A or HADS-D was considered as the presence of symptoms of anxiety or depression, respectively [30].

The European Quality of Life Five Dimension Questionnaire (EQ-5D) three-level version was filled in by the patients to assess their overall quality of life. The item 5 “Anxiety and Depression” could be a useful tool in screening for anxiety and depressive symptoms in hospital and community settings [31]. Therefore, this item, with its 3 response options (“I am not anxious or depressed”, “I am moderately anxious or depressed”, “I am extremely anxious or depressed”) was additionally used to assess the presence of these symptoms [32]. Patients were considered to have anxiety/depression when answering “I am moderately anxious or depressed” or “I am extremely anxious or depressed”. The EQ-5D summary index score was calculated to characterize the sample. It ranges from less than 0 (where 0 is a health state equivalent to death) to 1 (perfect health) [33]. The EQ-5D VAS was also used to assess patients’ perception of their general health (from 0 ‘the worst health you can imagine’ to 100 ‘the best health you can imagine’).

Statistical Analyses

Descriptive statistics were used to characterize the sociodemographic variables, clinical characteristics, the HADS score and EQ-5D responses. Absolute and relative frequencies were used to characterize the categorical variables. Means and standard deviations or medians and interquartile ranges were used, according to data distribution, to characterize the numerical variables.

To determine the agreement between HADS and EQ-5D questionnaires for the presence of symptoms of anxiety/depression, the percentage of agreement and weighted Cohen’s kappa were used. Cohen’s kappa values were interpreted as follows: <0, no agreement; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial and 0.81–1.0, almost perfect agreement [34].

To explore associations between variables related to the presence of symptoms of anxiety and depression, patients with and without symptoms of anxiety and depression were compared using independent t-tests for normally distributed data, Mann-Whitney U tests for non-normally distributed continuous data and ordinal data, and Chi-square tests for categorical data. In the case of Chi-square tests, when a statistically significant difference was found for a categorical variable with more than two categories, chi-square multiple comparison tests with Bonferroni correction were performed to explore which categories differed from each other. The variables that were statistically different ($p<0.05$) between the two groups were selected to further explore their relationship with the presence of anxiety and depression and to adjust for possible confounders in two stepwise multivariable logistic regression models. The dependent variable in each multivariable logistic regression was the presence of symptoms of anxiety or depression based on HADS (0 = absent, 1 = present). The overall models were evaluated using the goodness-of-fit tests and Nagelkerke's R-square and the final model was selected based on the best combination of these results. The level of significance considered was 0.05. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient's Characteristics

A total of 614 participants with asthma (mean age 32.6 ± 16.9 years) were included in this study. There were 447 (72.8%) adults and 397 (64.7%) females. Forty percent of the participants had completed primary school (n=244), 47.4% were employed (n=289) and 65.1% were prescribed only 1 inhaler (n=396). According to the GINA assessment of symptom

control, 296 (48.7%) patients had well controlled asthma. Table 1 shows the socio-demographic and clinical characteristics of the study participants.

TABLE 1. Socio-demographic and clinical characteristics of the participants (n=614).

Characteristics	
Age (years) M ± SD[a]	32.6 ± 16.9
Age group n (%)	
Adolescent	167 (27.2)
Adult	447 (72.8)
Gender n (%)	
Female	397 (64.7)
Male	217 (35.3)
Educational level n (%)[b]	
No education completed	4 (0.7)
Primary school	244 (40.4)
High school	177 (29.3)
Qualification above high school (but not university)	23 (3.8)
University	156 (25.4)
Other	1 (0.2)
Marital status n (%)[c]	
Single	348 (56.7)
Married/Living as a couple	223 (36.3)
Separated/divorced	33 (5.4)
Widowed	9 (1.5)
Current occupation n (%)[d]	
Employed	289 (47.1)
Student	235 (38.3)
Unemployed	41 (6.7)
Retired	36 (5.9)
Other	9 (1.5)
BMI Kg/m2, M ± SD[e]	24.7 (5.3)
Smoking Status n (%)[d]	
Never smoker	457 (74.4)
Ex-smoker	106 (17.3)
Current smoker	47 (7.7)
Setting	
Secondary care	475 (77.4)
Primary care	139 (22.6)
Age of asthma diagnosis (years) M ± SD[f]	16.2 ± 14.8
Number of prescribed inhalers n (%)[g]	

1	396 (64.5)
2	193 (31.4)
≥3	19 (3.1)
GINA assessment symptom control n (%)[g]	
Well controlled	296 (48.2)
Partly controlled	188 (30.6)
Uncontrolled	124 (20.2)
Number of physician-reported comorbidities Median (P25-P75)	1 [0-2]
CARAT-T Median (P25-P75)	21 [16-25]
CARAT-T Classification	
Controlled n (%)	156 (25.4)
Uncontrolled n (%)	458 (74.6)
EQ-5D-3L Median (P25-P75)	
Total	0.91 [0.81-1.0]
VAS	80.0 [70.0-90.0]

M = Mean; SD= Standard Deviation; BMI=body mass index; GINA = Global Initiative for Asthma; P25= 25th percentile; P75= 75th percentile; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D-3L= European Quality of Life Five Dimension Questionnaire-three-level version; VAS= Visual analogue scale.

[a] 8 missing values. [b] 9 missing values.[c] missing value. [d] 4 missing values.[e] 28 missing values. [f] 22 missing values.[g] 6 missing values.

Symptoms of anxiety and depression

According to HADS, 221 (36.0%) participants had symptoms of anxiety, 73 (11.9%) had symptoms of depression, 59 (9.6%) both symptoms and 235 (38.3%) participants had symptoms of anxiety or depression. Both anxiety (41.4% vs 21.6%) and depression (14.1% vs 6%) symptoms were more frequent in adults than adolescents. According to EQ-5D, 223 (36.3%) participants had anxiety or depression problems, 32.6% were moderately anxious or depressed and 3.7% extremely anxious or depressed. The agreement between these two questionnaires was moderate for anxiety (k=0.54 (95%CI 0.47-0.61)); fair for depression (k=0.23 (95%CI 0.17-0.30)) and moderate for anxiety/depression (k=0.55 (95% CI 0.48-0.62)).

Predictors of anxiety and depression

In the multivariable logistic regression (Table 2), being an adolescent (OR 0.43, 95% CI 0.27-0.68), having a better asthma control (CARAT-T score) (OR 0.98, 95% CI 0.94-1.00) and a perception of better health (OR 0.97, 95% CI 0.95-0.98) were significantly associated with

lower odds for the presence of anxiety symptoms. In contrast, being a female was significantly associated with a higher odd for the presence of anxiety symptoms (OR 1.75, 95% CI 1.56-2.64). Having better health-related quality of life (OR 0.97, 95%CI 0.95-0.99) and perception of better health (OR 0.97, 95% CI 0.96-0.99) were associated with a lower odd for the presence of depression. While asthma diagnosis at a later age (OR 1.03, 95% CI 1.01-1.05) and the presence of a higher number of comorbidities (OR 1.31, 95% CI 1.05-1.64) were associated with an increase in the likelihood of exhibiting symptoms of depression. The univariate analyses are presented in Supplementary Table 1.

Table 2 – Multivariable logistic regression analyses to explain anxiety and depression.

	Anxiety adjusted OR (95% CI)*	**Depression** adjusted OR (95% CI)**
Age group		
Adolescent	0.43 (0.27-0.68)	-
Adult	Reference	-
Gender		
Female	1.75 (1.56-2.64)	-
Male	Reference	-
Age of asthma diagnosis	-	1.03 (1.01-1.05)
Number of physician-reported comorbidities	1.17 (0.99-1.37)	1.31 (1.05-1.64)
CARAT T	0.98 (0.94-1.00)	-
Quality of life (EQ-5D total)	-	0.97 (0.95-0.99)
Perception of better health (EQ-5D VAS)	0.97 (0.95-0.98)	0.97 (0.96-0.99)
R^2	22%	23%
Hosmer-Lemeshow test - p-value	.435	.449

OR = Odds ratio; CI = Confidence interval; BMI = body mass index; CARAT-T = Control of Allergic Rhinitis and Asthma Test total score; EQ-5D = European Quality of Life Five Dimension Questionnaire; VAS= Visual analogue scale.

*Age, current occupation, setting, age of asthma diagnosis, GINA assessment of symptom control and quality of life (EQ-5D total) were also tested but not included in the final adjusted model.

**Age, age group, educational level, marital status, current occupation, BMI, GINA assessment of symptom control and CARAT T were also tested but not included in the final adjusted model.

Discussion

This study showed that more than 1/3 of participants with asthma experienced symptoms of anxiety and/or depression. Asthma diagnosis at a later age, presence of comorbidities and female gender were predictors of anxiety/depression, while better asthma control, health-related quality of life and perception of better health were factors associated with lower odds for anxiety/depression. In this study, the agreement between HADS and EQ-5D questionnaires in identifying anxiety and depression was sufficient to moderate.

According to HADS and EQ-5D questionnaires, more than 1/3 of the patients with persistent asthma experience symptoms of anxiety/depression (38.3% and 36.3% respectively). Therefore, the percentages of participants with one of these symptoms detected by HADS and EQ-5D were similar. With HADS, it was possible to detect the percentages of patients with persistent asthma that had only symptoms of anxiety (36.0%) or had only symptoms of depression (11.9%). The proportions found in the present study were similar to the ones found among patients with asthma in previous reviews [8, 9], analysing studies that included only, or mostly, adults with asthma. A study from the UK found similar frequencies of anxiety and depression using HADS, although a slightly higher cut-off has been used (HADS-A/HADS-D≥10) [35]. We found a lower frequency for depression as compared with a study in patients with severe asthma, where 25% reported depression [36]. This difference might be explained by the role of poorer physical functioning on symptoms of depression [37]. Patients with severe asthma experience more physical disability. Other studies reported that patients with severe asthma have more often emotional distress as compared to patients with mild-moderate asthma [38, 39].

This study includes both adolescents and adults with persistent asthma, which is rarely found in previous articles. However, anxiety and depression were only assessed at one time point. Analysing emotional distress in the long run could be important as suggested in previous cohort studies that followed adolescents with asthma to young adulthood, showing that there was a persistence or recurrence of anxiety and depression in adulthood [40, 41]. In our study, adults with persistent asthma presented an increased frequency of anxiety/depression symptoms (vs adolescents), which is in accordance with a population-based study that reported that having asthma and older age were independent risk factors for the presence of anxiety disorders, in participants above the age of 15 years [42]. Therefore, emotional distress seems to be associated with age differences in patients with persistent asthma.

Age at asthma onset has emerged as a critical factor in distinguishing the phenotypes of asthma [43]. Adult-onset asthma differs from asthma that first occurs in childhood since it usually is less well controlled, is associated with a faster decline in lung function and with more comorbidities [44, 45]. Moreover, worse asthma control and the presence of more comorbidities might be associated with an increased risk of emotional distress [46]. These results contribute to explaining our finding that asthma diagnosis at a later age and number of physician-reported comorbidities were associated with a higher frequency of depression. Female patients were more likely to have anxiety symptoms. This was previously observed in other studies in asthma but also other respiratory diseases, such as COPD. Possibly these gender differences are more than a specificity of respiratory diseases, but a reflection of the known gender differences in the general population [47, 48].

In our study, the perception of better health was associated with a lower odd for the presence of anxiety symptoms. In a previous study with patients with chronic obstructive pulmonary disease (COPD), the perceived severity of COPD symptoms was predictive of depression and anxiety [49]. These findings are in line with our study, although coming from a different disease. The close correlation between asthma control, quality of life, anxiety, and depression has been also confirmed in other studies [50, 51]. Consequently, in patients with poor asthma control, physicians should ask about the symptoms of anxiety/depression or screen it using simple tools like EQ-5D or HADS before making adjustments on asthma treatment strategy [17].

EQ-5D questionnaire could be useful in clinical practice [52]. The EQ-5D anxiety or depression domain had a greater agreement with the HADS score in identifying cases with both symptoms, as expected, than in identifying anxiety or depressive symptoms. In general, the percentages of patients with anxiety/depression detected by HADS and EQ-5D were similar. Furthermore, it is expected that remarkably less time consumption is needed for the EQ-5D item 5 assessment compared with HADS [18, 53]. Therefore, EQ-5D score appears to have value as a screening tool for anxiety or depression in patients with asthma. In a previous study, this questionnaire also seemed to be reasonably valid and moderately responsive in patients with anxiety disorders [54]. This could be important in clinical practice because a generic health instrument like the EQ-5D, with few and quick questions, could be used to easily raise awareness of a possible emotional distress in patients with asthma. A limitation of EQ-5D is that anxiety and depression are two separate emotional disorders and their combination in a single item in this questionnaire could lead to inconsistencies in responses [55]. Nevertheless, EQ-5D could be used as a first screening questionnaire and, in patients reporting anxiety or depression symptoms, a more specific questionnaire, such as HADS,

could be used to better characterize their symptoms. Actually, emotional distress screening is very important in clinical practice because physicians can use targeted interventions to improve patients' symptoms [56]. Studies about psychological interventions in adults with asthma suggest that education and simple psychological interventions namely relaxation techniques and biofeedback or a stepped care approach could produce significant positive healthcare outcomes [57, 58].

This study has some strengths that should be acknowledged: it is a multicentric study that recruited both adults and adolescents with asthma from primary and secondary care. A comprehensive set of individual-level characteristics was collected and analysed, which allowed us to explore the impact of a range of sociodemographic factors, health literacy and cofactors such as quality of life and asthma control. Therefore, includes a sample from different health care contexts and with different clinical presentations, contributing to the robustness of these findings.

Nevertheless, it also has some limitations. A possible source of bias was the recruitment strategy of using a convenience sampling. Future studies using other sampling strategies could be important to generalise the results of our study. A control group of healthy individuals with similar socio-demographic characteristics should also be included in further research to increase the validity of these findings. In the absence of a control group it would have been useful to compare anxiety/depression frequencies with normative data from Portugal and Spain, but we did not find it neither for HADS nor EQ-5D. Moreover, the impact of the presence of specific comorbidities, such as rhinitis, which is closely associated both with asthma and anxiety/depression, was not assessed [59]. Another limitation of the present study is related to its cross-sectional nature. The frequency of distressing symptoms and the

relationships with associated factors could not be established along the progression of the disease. Also, patients were not recruited at the same time point, as recruitment in the Inspirers studies occurred across 4 different years (from 2017 to 2020), and the last 15% of the sample was recruited during COVID-19 pandemic. Longitudinal studies following a cohort of patients with asthma would address these issues and identify other predictors of symptoms of anxiety and depression.

This study shows that more than 30% of the patients with persistent asthma experience symptoms of anxiety/depression, which supports the relevance of emotional distress screening in patients with asthma. EQ-5D and HADS questionnaires showed a moderate agreement in the identification of anxiety/depression symptoms. Late asthma diagnosis, presence of comorbidities and female gender were positively associated with the presence of emotional distress, while better asthma control, health-related quality of life and perception of better health presented a negative association. These factors need to be further investigated in future long-term studies.

a. Contributorship statement

All authors contributed to the selection of bibliography, revision and final approval of the manuscript. AMP, RA, MAC, RAlmeida, JAF and CJ were responsible for study conception and design; RA, AMP, RAlmeida, MAC, CCL, CL, JC, CR, CV, DAA, DP, MFM, MJV, CLozoya, NS, FC, LTB, RF, PMS, TMF, RC, ES, DB, CG, MJC, SS, MLM, AM, CN, CVieira, RP, AA, JVM, BR, LM, RM, MC, BV, DSC, SF, PM, MAA, ARM, JAF and CJ participated in the data collection; CJ and AMP performed the data analysis and MSC prepared the first draft. All authors contributed to the interpretation of data, to the critical revision of the manuscript for important intellectual content.

b. Competing interests

None

c. Funding

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d. Data sharing statement

The data sets generated during and/or analysed during the current study are not publicly available.

Ethics approval

The studies were approved by the ethics committees of all participating centres. For example, the study was approved by the Ethics Committee of Centro Hospitalar de S. João—EPE (protocol code 258-17 and date of approval: 5th of January 2018).

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Supplementary table 1 – Univariate analyses to explain anxiety and depression symptoms.

	Anxiety crude OR (95% CI)	Depression crude OR (95% CI)
Age	1.02 (1.01-1.03)	1.05 (1.03-1.06)
Age group		
Adolescent	0.39 (0.26-0.59)	0.39 (0.19-0.78)
Adult	Reference	Reference
Gender		
Females	2.44 (1.68-3.53)	1.64 (0.95-2.85)
Males	Reference	Reference
Educational level		
No education completed/Primary school	0.99 (0.71-1.39)	1.67 (1.01-2.74)
High school/Qualification above high school (but not university)/University/Other	Reference	Reference
Marital status		
Single/ Separated/Divorced/Widowed	0.72 (0.52-1.02)	0.45 (0.27-0.74)
Married/Living as a couple	Reference	Reference
Current occupation		
Employed/Student/Other	0.55 (0.35-0.87)	0.25 (0.14-0.43)
Unemployed/Retired	Reference	Reference
BMI	1.03 (0.99-1.06)	1.08 (1.04-1.13)
Smoking status		
Non-smokers	0.56 (0.31-1.02)	0.92 (0.37-2.24)
Smokers	Reference	Reference
Setting		
Primary care	1.60 (1.09-2.35)	1.04 (0.58-1.86)
Secondary care	Reference	Reference
Age of asthma diagnosis	1.02 (1.01-1.03)	1.04 (1.03-1.06)
Number of physician-reported comorbidities	1.32 (1.14-1.53)	1.55 (1.29-1.87)
Number of prescribed inhalers	1.29 (0.97-1.71)	1.29 (0.87-1.91)
GINA assessment symptom control		
Well controlled	0.61 (0.44-0.85)	0.51 (0.30-0.85)
Partly controlled/Uncontrolled	Reference	Reference
CARAT T	0.93 (0.91-0.96)	0.91 (0.88-0.95)
Quality of life (EQ-5D total)	0.94 (0.92-0.95)	0.94 (0.93-0.96)
Perception of better health (EQ-5D VAS)	0.96 (0.95-0.97)	0.96 (0.95-0.97)

OR = Odds ratio; CI= Confidence interval; BMI=body mass index; GINA = Global Initiative for Asthma; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D= European Quality of Life Five Dimension Questionnaire.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12 11-12 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.