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To cite this article: Martín Bedolla-Barajas, Jaime Morales-Romero, Juan Carlos Fonseca-López, Norma Angélica Pulido-Guillén, Désirée Larenas-Linnemann & Dante Daniel Hernández-Colín (2020): Anxiety and depression in adult patients with asthma: the role of asthma control, obesity and allergic sensitization, Journal of Asthma, DOI: [10.1080/02770903.2020.1759087](https://doi.org/10.1080/02770903.2020.1759087)

To link to this article: <https://doi.org/10.1080/02770903.2020.1759087>



Accepted author version posted online: 21 Apr 2020.
Published online: 02 May 2020.



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Anxiety and depression in adult patients with asthma: the role of asthma control, obesity and allergic sensitization

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ABSTRACT

Objective: To determine the frequency of anxiety and depression in adult patients with asthma and to identify factors associated with them.

Methods: This cross-sectional study included 164 consecutively recruited patients with asthma aged ≥ 18 years. Participants were clinically assessed and the mental state was analyzed through of the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI-II); the Asthma Control Test (ACT) was measured, and allergic sensitization and respiratory function were also evaluated. Binary logistic regression models to identify the factors related to anxiety or depression were carried out. Complementary, 95% confidence intervals (CI) were estimated.

Results: Anxiety was present in 54.3% of patients (95% CI: 46.6%–61.7%) while depression was found in 50.6% (95% CI: 43.0%–58.2%). Depression increased the odds of anxiety in patients with asthma (OR: 26.00, $p < 0.0001$), whereas an ACT score ≥ 20 points and allergic asthma were associated with a lower odds than the reference group (OR: 0.29; $p = 0.007$ and OR: 0.29; $p = 0.024$, respectively). Depression was associated with anxiety and obesity (OR: 25.33, $p < 0.0001$ and OR: 3.66; $p = 0.014$, respectively).

Conclusions: Overall, more than half of all asthmatic patients suffer from anxiety and depression. Well-controlled asthma and allergic sensitization decreased the likelihood of anxiety, while depression was associated with both obesity and anxiety.

ARTICLE HISTORY

Received 16 September 2019
Revised 30 March 2020
Accepted 18 April 2020

KEYWORDS

Asthma; adult;
anxiety; depression

Introduction

Recently, The Global Asthma Report highlighted that asthma is a major disease burden, which has been linked to more premature deaths and lower quality of life; in the same report, it is noted that worldwide almost 340 million people have asthma (1). In Mexico, the prevalence of asthma in the adult population is 5% (2). Like in other regions of the world, in our country asthma prevalence has been growing; when comparing the prevalence of asthma in late adolescence in two different periods of time, the frequency rose from 7.8% to 12.7% in a period of only seven years (3).

According to the World Health Survey (WHS) the prevalence of asthma-related depression and anxiety

can reach values higher than 50% and up to 80%, respectively (4). Nonetheless, these values can vary greatly in developing countries owing to social, cultural, and economic inequalities (5–7).

These mental disorders have been associated with poor asthma control and lower treatment adherence and quality of life (8–10) although obesity (11–13), allergic sensitization (14,15), and the sex of individuals (16), also plays an important role in this association.

On the other hand, several studies have shown that the presence of anxiety or depression in asthma is associated with lower quality of life and lower productivity. In Canada, patients with asthma combined with psychological disorders generate higher costs compared to those with asthma alone, in amounts similar to those seen in those with cardiovascular

disease or diabetes (17). In terms of quality of life, the presence of anxiety or depression in asthma is one factor more that notoriously deteriorates it (18).

Current asthma management guidelines recommend avoiding factors that increase the risk of exacerbations (19,20). Studies that evaluate the relationship between asthma with depression or anxiety in Latin America are scarce; therefore the main goal of our study was to determine the prevalence of anxiety and depression in adults with asthma receiving medical attention in a teaching hospital in Mexico. A second objective was to test the hypothesis that there exists an association between these mental disorders and obesity, sex, allergic sensitization, and asthma control and severity.

Methods

Study design and patients

In this cross-sectional study we analyzed the data of 164 patients with newly diagnosed asthma aged ≥ 18 years who were consecutively recruited from an allergology department of a teaching hospital. Patients were recruited between October 2014 and January 2016.

We excluded patients who were pregnant or breastfeeding at the time of the study or who had a clinical background of diabetes mellitus, arterial hypertension, rheumatoid arthritis, hives, kidney disease, neoplasia, systemic steroids usage within the previous month, exacerbated asthma in the previous month or death of a family member 6 months prior to the study. Data about alcohol consumption, tobacco usage, and comorbid diseases such as allergic rhinitis, atopic dermatitis or food allergy were also recorded.

The diagnosis of asthma was established if two or more of the following symptoms were present: wheezing, cough (especially if paroxysmal and nocturnal), chest tightness or dyspnea (19,20), along with the presence of reversible airflow obstruction on spirometry after the administration of a short acting bronchodilator.

Asthmatic patients were classified as allergic if they had a positive skin-prick test result for one or more of the aeroallergens included in the panel used.

The Asthma Control Test (ACT) was used to determine the level of asthma control. Controlled asthma was defined as a score ≥ 20 points whereas uncontrolled asthma as a score < 20 points (21). Each of the ACT items were read to the patients by a physician and their answers were recorded. Afterwards, the final score was calculated.

The frequency of asthma-related hospitalizations ≥ 1 in the previous year was used as a marker of asthma severity.

The body mass index (BMI) was obtained by dividing the patients' weight in kg by their height in meters squared. A BMI of 18.5 to 25 kg/m² was defined as normal weight, >25 to < 30 kg/m² as overweight, and ≥ 30 kg/m² as obesity.

Psychological evaluation

Depression and anxiety were assessed using the Beck Depression Inventory-II (BDI-II) and the Beck Anxiety Inventory (BAI), respectively, in their Spanish versions (22,23). They consist of 21 items and the final score is obtained by adding up the values assigned to each item. A diagnosis of anxiety or depression was made when the final score was >13 points. These instruments were applied as self-administered questionnaires in a private area, separate from the rest of the patients, and special care was taken to avoid response bias. At the same time, each of the patients was ascertained the information would be kept confidential.

Pulmonary function tests

Pulmonary function tests (PFT's) were performed on a MasterScreen® PFT system (Jaeger®, Care Fusion, Baesweiler, Germany). Patients were instructed not to use short acting or long acting bronchodilators for at least 8 and 12 h prior to testing respectively. PFT's were performed during the morning with patients in a sitting position and their noses occluded with a clip, the tests were stopped once three maneuvers which met the acceptability and repeatability criteria were obtained or a maximum of eight attempts had been made.

Airflow obstruction reversibility was assessed by repeating the PFT's 15 min after the administration of a dose of Salbutamol (400 mcg) delivered via a metered-dose-inhaler attached to a spacer. The presence of reversibility was defined as a Forced Expiratory Volume (FEV1) increase $\geq 12\%$ and ≥ 200 ml (24).

Skin-prick test

As previously mentioned, asthmatic patients were classified as allergic if they had a positive skin-prick test result for one or more of the aeroallergens included in a panel consisting of 40 different non-standardized glycerinated allergen extracts in a 1:20 weight/volume concentration (Allergomex, Mexico) which included pollens coming from weeds, grasses and trees, indoor

allergens (dust mites, cockroach mix, feather mix, dog and cat epithelia). All tests were performed and interpreted following international standards by the same allergologist (25).

Procedure

Outpatient patients were included. Initially, a complete medical history was taken of each participant; if it was compatible with asthma, then on the same day or any other following day, respiratory function tests (pre and post bronchodilator forced spirometry) were carried out. If the findings were compatible with a reversible, obstructive pattern, at that time, inventories of anxiety, depression, and the asthma control test, respectively, were applied. Finally, when the patient's condition was adequate, skin testing was carried out.

Statistical analysis

Data analysis was conducted using IBM SPSS 20.0 for Windows (IBM Co., Armonk, NY, USA). According to their distribution continuous variables were compared using Student's *t* tests or Mann-Whitney *U* tests and qualitative variables were compared using Chi-square tests or Fisher's exact tests as appropriate. We used binary logistic regression models to identify the factors related to anxiety or depression. The independent covariates used in these models were sex, ACT score ≥ 20 , BMI category, and allergic asthma. The strength of association between variables was calculated using odd ratios (OR) and 95% confidence intervals (CI), the level of alpha was 0.05.

Ethics

Approval to conduct the study was obtained from the research ethics committee. All patients included in the study signed a written consent and those in which anxiety or depression were detected were referred to a psychologist. None of the selected patients received any incentive to participate in the study.

Results

A total of 164 patients with asthma were included, 131/164 (80%) of them were women. The mean age was 39.0 ± 14.0 years. The prevalence of anxiety was 89/164 (54.3%; 95% CI: 46.6%–61.7%).

The mean age did not differ significantly between the anxiety and non-anxiety groups ($p=0.127$), Table 1. However, there was a significant higher

number of women in the group with anxiety ($p=0.002$). In both groups allergic rhinitis was the most frequent comorbid disease with no significant difference between them ($p=0.065$). In comparison with the group of anxious patients, the non-anxious group had a better asthma control ($p<0.05$). Respiratory function tests did not show a significant difference between the anxiety and non-anxiety groups. Finally, the proportion of patients with depression was higher among those with anxiety (80% vs 16%, $p<0.0001$).

The prevalence of depression was 83/164 (50.6%; 95% CI: 43.0%–58.2%). Table 2 shows that the proportion of women ($p=0.009$) as well as the mean BMI ($p=0.012$) was significantly higher in the group of patients with depression. However, when patients were classified according to their nutritional status no difference was seen between the depression and non-depression groups ($p=0.208$). In both groups the most frequent comorbid atopic disease was allergic rhinitis. In comparison to patients without depression patients with asthma and depression had a significantly lower level of asthma control ($p<0.05$) although respiratory function tests did not differ between them. Finally, the frequency of anxiety was significantly higher in the group of patients with depression ($p<0.0001$).

Table 3 shows the factors associated with anxiety in patients with asthma. Among these factors depression was the most important (OR: 26.00, $p<0.0001$) whereas an ACT score ≥ 20 diminished this risk by approximately 70% (OR: 0.29; $p=0.007$); allergic asthma also diminished the risk by an equal extent (OR: 0.29; $p=0.024$). Regarding the factors associated to depression we found that, besides anxiety, (OR: 25.33, $p<0.0001$) obesity was an independent risk factor associated with depression in patients with asthma (OR: 3.66; $p=0.014$) Table 4.

Discussion

Our study found a high prevalence of anxiety and depression (>50%) in patients with asthma. It also shows that patients with controlled asthma and allergic sensitization have a lower risk of anxiety whereas depression was associated with obesity and anxiety.

The association between anxiety or depression and poorly controlled asthma could be the result of diverse mechanisms such as unhealthy lifestyle or lack of self-care, a diminished ability of patients to accurately describe their symptoms to their treating physician, or

Table 1. Clinical characteristics of patients in the anxiety and non-anxiety groups.

	Anxiety		<i>p</i>
	Yes <i>n</i> = 89	No <i>n</i> = 75	
Age, years, mean $\pm$ SD	40.6 $\pm$ 14.5	37.2 $\pm$ 13.4	0.127
Female, <i>n</i> (%)	79 (88.8)	52 (69.3)	0.002
Current smokers, <i>n</i> (%)	5 (5.6)	5 (6.7)	0.780
Current drinkers, <i>n</i> (%)	14 (15.7)	19 (25.3)	0.126
BMI, Kg/m ² , mean $\pm$ SD	29.6 $\pm$ 6.7	28.8 $\pm$ 4.8	0.348
BMI, <i>n</i> (%)			0.935
Normal	26 (29.2)	20 (26.7)	
Overweight	26 (29.2)	23 (30.7)	
Obesity	37 (41.6)	32 (42.7)	
Comorbid atopic diseases, <i>n</i> (%)			
Allergic rhinitis	64 (71.9)	63 (84.0)	0.065
Food allergy	12 (13.5)	13 (17.3)	0.494
Atopic dermatitis	6 (6.7)	4 (5.3)	0.756
ACT			
Mean $\pm$ SD	15.0 $\pm$ 4.9	17.3 $\pm$ 5.4	0.004
Median (P ₂₅ -P ₇₅)	15 (11 to 18)	18 (14 to 22)	0.004
Minimum-Maximum	6 to 24	5 to 25	
≥ 20 , <i>n</i> (%)	19 (21.3)	33 (44.0)	0.002
Pulmonary function, % of predicted			
Pre-bronchodilator, mean $\pm$ SD			
FVC	88.2 $\pm$ 14.7	90.8 $\pm$ 20.6	0.348
FEV ₁	72.3 $\pm$ 16.3	75.3 $\pm$ 20.4	0.307
FEV ₁ /FVC	67.8 $\pm$ 10.4	68.6 $\pm$ 10.2	0.618
Post-bronchodilator, mean $\pm$ SD			
FVC	95.8 $\pm$ 18.2	98.4 $\pm$ 17.6	0.361
FEV ₁	86.8 $\pm$ 16.3	87.9 $\pm$ 20.4	0.690
FEV ₁ /FVC	73.5 $\pm$ 9.2	74.6 $\pm$ 9.7	0.480
Allergic asthma, <i>n</i> (%)	69 (77.5)	63 (84.0)	0.297
Hospitalizations in the previous year, <i>n</i> (%)	30 (33.7)	21 (28.0)	0.431
Depression, <i>n</i> (%)	71 (79.8)	12 (16.0)	<0.0001

p values were obtained using Student's *t* tests, Chi square tests, Fisher's exact tests or Mann-Whitney U tests as appropriate.

SD: Standard deviation.

BMI: Body mass index.

ACT: Asthma control test.

FVC: Forced vital capacity.

FEV₁: Forced expiratory volume in 1 s.

through the direct effects these disorders have on the immune and autonomic nervous systems (8).

In this study the patients with anxiety had a lower level of asthma control compared to the non-anxious group. However, due to the characteristics of our study design we couldn't establish the direction of the relationship between anxiety and the level of asthma control. Nonetheless, a bidirectional association, i.e., patients with asthma and anxiety are more likely to perceive their symptoms as being more severe and conversely patients whose asthma is poorly controlled have an increased risk of anxiety due to the fear of having an exacerbation, between these variables was recently documented in another study (9). The high proportion of patients whose asthma wasn't under control seen in our study could be attributed, at least in part, to the characteristics of our population since it was comprised of first-time patients and many of them were newly diagnosed and hadn't received proper education about their disease, also some patients didn't have healthcare access and had to buy their treatment themselves resulting in lower treatment adherence.

An interesting finding of our study is that allergic asthma was associated with a lower risk of anxiety. To the best of our knowledge we are not aware of studies that have reported similar results, although the role of allergy on anxiety has been previously described (14,15).

Similar to the direction of the association between asthma control and anxiety explained above, a bidirectional relationship between obesity and depression has also been reported as possible (11,12). It has been observed that anxiety and depression in the presence of obesity can increase the risk of developing asthma (13). This risk also increases with age as patients with asthma who are overweight and ≥ 65 years have a higher risk of depression (26). In Italy, patients with asthma and depression had a higher BMI in comparison to patients who did not suffer from depression (27). Conversely, the first Israel National Health Survey failed to show an association between obesity and depression in patients with asthma (28). In Latin America the prevalence of obesity and overweight has increased significantly in recent years. Consequently,

Table 2. Clinical characteristics of patients in the depression and non-depression groups.

	Depression		<i>p</i>
	Yes <i>n</i> = 83	No <i>n</i> = 81	
Age, years, mean $\pm$ SD	40.3 $\pm$ 13.7	37.8 $\pm$ 14.3	0.253
Female, <i>n</i> (%)	73 (88.0)	58 (71.6)	0.009
Current smokers, <i>n</i> (%)	4 (4.8)	6 (7.4)	0.532
Current drinkers, <i>n</i> (%)	16 (19.3)	17 (21.0)	0.785
BMI, Kg/m ² , mean $\pm$ SD	30.4 $\pm$ 6.5	28.1 $\pm$ 5.0	0.012
BMI, <i>n</i> (%)			0.208
Normal	19 (22.9)	27 (33.3)	
Overweight	24 (28.9)	25 (30.9)	
Obesity	40 (48.2)	29 (35.8)	
Comorbid atopic disease, <i>n</i> (%)			
Allergic rhinitis	64 (77.1)	63 (77.8)	0.918
Food allergy	13 (15.7)	12 (14.8)	0.880
Atopic dermatitis	7 (8.4)	3 (3.7)	0.329
ACT			
Mean $\pm$ SD	15.2 $\pm$ 4.9	16.8 $\pm$ 5.5	0.045
Median (P ₂₅ -P ₇₅)	15 (12 to 20)	17 (13 to 22)	0.039
Minimum-Maximum	6 to 24	5 to 25	
≥ 20 , <i>n</i> (%)	21 (25.3)	31 (38.3)	0.074
Pulmonary function, % of predicted			
Pre-Bronchodilator, mean $\pm$ SD			
FVC	88.7 $\pm$ 15.0	90.1 $\pm$ 20.1	0.602
FEV ₁	72.8 $\pm$ 16.3	74.6 $\pm$ 20.2	0.534
FEV ₁ /FVC	67.9 $\pm$ 10.2	68.4 $\pm$ 10.4	0.715
Post-Bronchodilator, mean $\pm$ SD			
FVC	96.9 $\pm$ 16.2	97.2 $\pm$ 19.6	0.918
FEV ₁	87.3 $\pm$ 16.5	87.3 $\pm$ 20.1	0.918
FEV ₁ /FVC	74.0 $\pm$ 9.0	74.0 $\pm$ 10.0	0.998
Allergic asthma, <i>n</i> (%)	69 (83.1)	63 (77.8)	0.387
Hospitalizations in the previous year, <i>n</i> (%)	25 (30.1)	26 (32.1)	0.784
Anxiety, <i>n</i> (%)	71 (85.5)	18 (22.2)	<0.0001

p values were obtained using Student's *t* tests, Chi square tests, Fisher's exact tests or Mann-Whitney *U* tests as appropriate.

SD: Standard deviation.

BMI: Body mass index.

ACT: Asthma control test.

FVC: Forced vital capacity.

FEV₁: Forced expiratory volume in 1 s.

Table 3. Factors associated with anxiety in adult asthmatic patients.

	Non-adjusted model			Adjusted model		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Depression						
No	1			1		
Yes	32.71	12.03–88.91	< 0.0001	26.00	10.61–63.72	< 0.0001
Sex						
Female	1					
Male	0.44	0.14–1.31	0.140	–	–	0.121
ACT ≥ 20						
No	1			1		
Yes	0.26	0.10–0.67	0.006	0.29	0.12–0.71	0.007
BMI						
Normal	1					
Overweight	0.51	0.16–1.60	0.510	–	–	0.989
Obesity	0.29	0.10–0.90	0.033	–	–	0.066
Allergic asthma						
No	1			1		
Yes	0.27	0.08–0.86	0.027	0.29	0.10–0.85	0.024

OR were obtained using binary logistic regression. All variables were dichotomous except for age which was continuous.

95% CI: 95% Confidence interval.

GINA: Global Initiative for Asthma.

ACT: Asthma control test.

BMI: Body mass index.

an increase in the number of patients with depression is expected to occur, especially if asthma is present as a comorbid disease. Therefore, therapeutic

interventions directed not only to achieve asthma control but also weight loss could lead to a decrease in the frequency of depression in patients with asthma.

Table 4. Factors associated with depression in adult asthmatic patients.

	Non-adjusted model			Adjusted model		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Anxiety						
No	1			1		
Yes	28.67	11.18–73.52	< 0.0001	25.33	10.58–60.62	< 0.0001
Sex						
Female	1					
Male	0.59	0.19–1.76	0.341	–	–	0.404
ACT $\geq$ 20						
No	1					
Yes	1.40	0.54–3.63	0.484	–	–	0.531
BMI						
Normal	1			1		
Overweight	1.91	0.64–5.68	0.246	1.96	0.68–5.68	0.214
Obesity	3.51	1.23–9.98	0.019	3.66	1.30–10.29	0.014
Allergic asthma						
No	1					
Yes	2.49	0.90–6.92	0.080	–	–	0.085

OR were obtained using binary logistic regression. All variables were dichotomous except for age which was continuous.

95% CI: 95% Confidence interval.

GINA: Global Initiative for Asthma.

ACT: Asthma control test.

BMI: Body mass index.

In Latin America, there are few research studies on obesity and depression in patients with asthma, thus our study provides valuable information about this population by showing that patients with asthma and obesity have an increased risk of suffering depression by up to 4 times.

Interestingly, the variables: asthma control, allergic sensitization, and sex were not associated with depression. From an epidemiological perspective, depressive disorders occur more frequently in women. This trend starts at adolescence and the highest levels of incidence are reached at the age of 20–40 years (16). It is likely that sex-specific immune mechanisms, which are subject to hormonal and genetic influences, underlie the differences seen in the frequency of mood disorders between men and women (29). In our study women had a higher risk of depression in the univariate model but this difference was not significant; therefore, the variable sex was not included in the final multivariate model, which might be explained because depression is a disorder that occurs primarily during reproductive years (16) and the mean age of the women in the population we studied was in the fifth decade.

If the relationship between asthma control and depression is bidirectional, then depression could modify the degree of severity with which symptoms are perceived by patients and consequently alter the level of asthma control, while poorly controlled asthma could lead to depression (10). With respect to allergic asthma and depression, it has been proposed that these two variables are positively related to each other. Similarly, a study conducted in patients with

allergic rhinitis found that the severity of depressive symptoms increased during pollen season (30). We have previously reported that allergic sensitization wasn't associated with depression, but was the chronic course of the disease that did it (31).

With regard to the lack of association between the severity of asthma with depression and anxiety could be explained by the way in which the severity of the disease was defined. Asthma-related hospitalizations is a subrogated variable as an indirect measure of the severity of the disease, so it is possible that no association has been found where it actually exists (type II error in the hypothesis testing).

Worldwide, diverse instruments have been used to assess anxiety and depression in patients with asthma; in this study a large number of patients with these disorders were identified using the BAI and BDI-II. However, there are studies whose results differ importantly from ours. Also, diverse multicentric studies that have followed the same methodology have yielded different results on the prevalence of depression and anxiety (4,32).

Factors such as the instruments used, cultural and socioeconomic differences, and the presence of comorbidity (5–7) can have an important impact on the observed prevalence of these disorders. Thus, in order to prevent the impact of confounding variables we decided to exclude pregnant or breastfeeding women and patients with a background of chronic-degenerative diseases, recent systemic steroids usage, exacerbated asthma in the previous month or loss of a family member. It's likely that the high frequency of anxiety and depression seen in this study could be

partially explained because the population was comprised of first-time patients and many of them did not have an adequate level of asthma control as it has been shown that patients experience improvement of these mental disorders after receiving guideline-directed medical therapy (33).

The limitations of this study include that the diagnosis of anxiety and depression were made through the use of the BAI and BDI-II and not by a psychiatrist. Nonetheless, the BAI and BDI-II are tools that have previously demonstrated their ability to detect patients with these conditions. We also didn't assess the history of depression and anxiety episodes that occurred >2 weeks and >1 month, respectively, prior to the application of these instruments. Another limitation is that because of the cross-sectional nature of this study we couldn't establish temporal relationships between the clinical course of asthma with anxiety and depression. On the other hand, our results should be interpreted in the light of the setting where our research was carried out; it is a university hospital, which attends a population that does not have regular social medical care. In this study, although sex was not associated with anxiety or depression, it should be noted that women predominated in the sample which could have modified the results; however, it is known that in Mexico, women often request health services more frequently than men, so the sample is a reflection of this. Another limitation is also noteworthy: patients could not be categorized by the severity of asthma according to the need for treatment; since they were newly diagnosed asthma patients (first visit to our clinic), most of them used only short-acting bronchodilators as the only therapy. Finally, diagnosis such as diabetes, hypertension, rheumatoid arthritis, urticaria, kidney disease, or neoplasia were established by means of a medical interview and weren't confirmed by diagnostic tests.

Some of the strengths of this study are that the included patients were consecutively recruited, thus reducing the risk of selection bias. The cross-sectional association design is ideal for identifying prevalence and also allows exploring non-causal associations between variables. Beck Depression Inventory-II (BDI-II) and the Beck Anxiety Inventory (BAI) are two instruments validated in the Mexican population. In the pulmonary function tests, equipment, procedures, and reference values valid worldwide were used. In the skin-prick test were performed and interpreted following international standards. Multivariate analysis using binary logistic regression is the appropriate technique to find associations between variables in

cross-sectional designs. Also, the impact of confounding variables related to anxiety and depression was minimized by the exclusion criteria, and the multivariate analysis allowed us to perform covariate adjustment.

In summary, a large number of patients with asthma suffer from anxiety and depression, and according to the hypothesis, adequate asthma control and an allergic asthma phenotype were among the most important factors that were associated with a lower risk of anxiety, whereas depression conferred a higher risk. The most important factors related to depression were anxiety and obesity.

Conflict of interests

The authors report no conflicts of interest.

Author contributions

Martín Bedolla-Barajas conceived the study design, oversaw its conduct, did the statistical analysis, and wrote the first draft of the article; Jaime Morales-Romero did the statistical analysis, and wrote the first draft of the article; Désirée Larenas-Linnemann commented on study results and wrote the first draft of the article, Norma Angélica Pulido-Guillén, contributed elements of the study design, collected patient information, and helped write and revise the article; Juan Carlos Fonseca-López, and Dante Daniel Hernández-Cólin, helped conduct the study, collect and interpret the data.

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