



## Research Article

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# Uncontrolled Asthma is Associated with Comorbid Stress and Somatoform Symptoms

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## Abstract

**Background:** Anxiety and depression are recognized comorbidities that may limit control of asthma. The purpose of this study is to identify the associations between perceived stress, somatization, and perceived asthma control in patients with asthma.

**Methods:** The present study included 100 adult outpatients who were treated at the Tulane Asthma Center for asthma-related symptoms between March 2018 and November 2018. Patients were asked to complete a 3-item demographics form, an Asthma Control Test (ACT), Patient Health Questionnaire 15 (PHQ-15), and a Perceived Stress Scale (PSS).

**Results:** Using validated scoring for Asthma Control Tests, we classified patients as well controlled (ACT score greater than or equal to 20) and not controlled (ACT score less than or equal to 19). Using SPSS software, chi-squared analysis indicated a significant association between PSS and ACT scores, PHQ-15 and ACT scores, and PSS and PHQ-15 scores. The analysis demonstrated a significant inverse relationship between PHQ-15 and ACT scores, and also between PSS and ACT scores, and a significant direct relationship between PSS and PHQ-15 scores. A statistically significant relative risk was found among moderate-to-high scores on PHQ-15, uncontrolled and moderate-to-high PSS scores, and uncontrolled asthma. A slight increase in relative risk in uncontrolled asthma was found in patients less than or equal to 50 years of age as compared to those older than 50, and the relative risk of uncontrolled asthma was similar in women as compared to men.

**Conclusion:** The results of this study indicate an association between perceived stress, somatization, and uncontrolled asthma. These findings suggest the need to develop effective interventions in patients with asthma and comorbid stress and somatization.

## Background

Asthma is a heterogeneous chronic airway disease impacting over 25 million adults in the United States, with annual direct and indirect costs of approximately \$56 billion dollars [1]. The pathogenesis of asthma is characterized by recurrent inflammation and repeated exacerbations over time that can be attributed to a wide variety of causes, commonly including environmental antigens, viruses, some medications, aspirin, and poor air quality [2-5]. Asthma is often present in patients with various comorbidities. The most frequently reported of these include rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders, and psychopathologies [6-10]. The presence of psychopathologies has been shown to increase the likelihood of poorly controlled asthma, either by affecting the diagnosis or assessment of control, influencing asthma phenotypes, or affecting the efficacy or adherence to therapy [11].

Numerous studies have documented poor asthma control and worse outcomes in patients with clinical depression and anxiety [12-16]. The Global Initiative for Asthma (GINA 2020) highlights anxiety and depression as being associated with worse asthma control and suggests clinicians help patients distinguish between anxiety and asthma symptoms. GINA

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also suggests that clinicians address anxiety and depression in order to achieve symptom control in the majority of their patients [17]. Studies stress the importance of identifying these comorbidities in patients with asthma, as they can negatively affect asthma control if left untreated [18,19].

Chronic stress has been shown to manifest allergic diseases in susceptible individuals as well as complicate control of existing allergic diseases [20]. In one study, patients with anxiety and atopy were shown to have positive skin prick tests (SPTs) for antigens they previously tested negative for [21]. In addition, chronic stress has been shown to alter beta-adrenergic and glucocorticoid receptors gene expression, to change cytokine regulation, and to increase cortisol levels. Many of these same cytokines are often derived from mast cells, which have been shown to be involved in the pathogenesis of asthma [22]. All of these changes may impact development of asthma and allergy flairs, eventually altering therapy response [23,24].

The prevalence of somatization is estimated to be 5-7% of the general population and is an important topic due to its impact on healthcare utilization [25]. One well validated and commonly used tool to measure somatization is the PHQ 15 [26-28]. One study of 2091 primary care clinic patients found comorbid depression, anxiety, and somatization in roughly 50% of patients [29]. According to a study of 1456 patients, those with higher somatization scores had around twice the annual health care costs and around twice the outpatient and inpatient visits compared to those without somatization [30]. Additionally, a survey of 212 asthma patients found that those with anxiety, depressive, and somatoform disorders were at increased risk of asthma related emergency room visits [31].

The purpose of this study was to identify the associations between perceived stress, somatization, and perceived asthma control in patients with asthma. The patient centered and guideline-driven approach used in this study attempts to identify these associations among patients with asthma in an outpatient asthma center.

## Subjects and Methods

Study participants were adult patients with a diagnosis of moderate to severe asthma who were receiving guideline driven outpatient care by a trained allergist and pulmonologist at the Tulane Asthma Center from May 2018 to December 2018. In total, there were 100 participants (76% Female) with a mean age of 53.4 (SD  $\pm$  14) and mean time with asthma of 26.1 years (SD  $\pm$  2.1). All participants provided verbal informed consent prior to participation. Participants were then instructed to complete the following four self-administered questionnaires:

**Demographic Data:** A brief 3-question questionnaire including sex, age, and time since asthma diagnosis in years.

**Asthma Control Test (ACT):** Five questions, each scored on a 5-point Likert-type scale (ranging from 1-5), with a total score ranging from 5 (poor asthma control) to 25 (well controlled asthma). The questions measure self-perception of asthma's effect on activities of daily living, frequency of shortness of breath and other asthma symptoms, use of res-

cue medications, and overall perception of asthma control during the previous 4 weeks.

**Perceived Stress Scale (PSS):** Ten questions, each scored on a 5-point Likert-type scale (ranging from 0-4), with a total score ranging from 0 (low stress) to 40 (high stress). The questions measure self-perception of frequency and severity of stressful events within one's life for the past 4 weeks. Questions include "How often have you been upset because something happened unexpectedly?", "How often have you felt that you were unable to control important things in your life?", "How often have you felt nervous and stressed?", "How often have you felt confident about your ability to handle your personal problems?", "How often have you felt that things were going your way?", "How often have you found that you could not cope with all the things that you had to do?", "How often have you been able to control irritations in your life?", "How often have you felt that you were on top of things?", "How often have you been angered because of things that were outside of your control?", and "How often have you felt difficulties were piling up so high that you could not overcome them?" [32].

**Patient Health Questionnaire (PHQ-15):** Fifteen questions, each scored on a 3-point Likert-type scale (ranging from 0-2), with a total score ranging from 0 (Minimal level of Somatic Symptom Severity) to 30 (High level of Somatic Symptom Severity). The questions measure self-perception of the prevalence and frequency of physical symptoms commonly associated with somatization. Symptoms included: stomach pain, back pain, extremity pain, menstrual cramps, headaches, chest pain, dizziness, fainting spells, heart racing, shortness of breath, pain/problems with sexual intercourse, constipation/loose bowels/diarrhea, nausea/gas/indigestion, low energy, and trouble sleeping [26-28].

The institutional review board at Tulane University approved the use of PSS, PHQ-15, and ACT surveys in clinical practice.

## Statistical Analysis

All raw data from original paper questionnaires was entered into Excel and verified by two research assistants to check for transcribing errors. Overall, summative scores for individual ACT, PSS, and PHQ-15 questionnaires were calculated. Scores were then placed in stratified categories based on accepted validated guidelines. Categorical variables were then analyzed using Chi-Square, Spearman's Rho Correlation Coefficient, and relative risk using SPSS. Statistical significance was determined based on a p-value < 0.05 or the values of a 95% confidence interval entirely being greater than one.

## Results

**Table 1** describes the 100 participants. The majority of the patients were women (76%). The median age of the patients was 55 (range: 18-87). The vast majority of patients (76%) had a diagnosis of asthma greater than 5 years.

**Table 2** assesses relative risk of uncontrolled asthma based on the clinical data elucidated in this study. Of the 100 patients in the study, 60 had uncontrolled asthma (ACT less than

**Table 1:** General demographic information for patients in this study.

Sex			Age	Time with Asthma		
Male	Female	Prefer Not to Answer	Median: 55	Greater Than 5 years	LessThan/Equal to 5 Years	Unanswered
21	76	3	Range: 18-87	76	22	2

**Table 2:** Relative risk of uncontrolled asthma based on demographics, stress scores, and somatization.

	Sex		Age (Years)		Time with Asthma (Years)		PHQ-15 Score Category		PSS Score Category	
	Male	Female	> 50	< or = 50	> 5	< or = 5	Mod to High	Low	Mod to High	Low
<b>Uncontrolled</b>	12	46	33	27	44	16	44	16	44	16
<b>Controlled</b>	9	30	29	11	31	9	13	27	20	20
Relative Risk of U/C Asthma	If Female: 1.06 (95% CI: 0.70-1.60)		If Age < or = 50: 1.34 (95% CI: 0.98-1.82)		If time w/ asthma > 5: 1.09 (95% CI: 0.77-1.55)		If Mod-High Score: 2.75 (95% CI: 1.62-4.68)		If Mod-High Score: 1.78 (95% CI: 1.12-2.83)	

**Table 3:** Relative Risk of individual PHQ-15 symptom prevalence per ACT score category.

Somatic Symptom	Total# w/ Symptom	# w/ Uncontrolled ACT Score	# 24w/ Controlled ACT Score	Relative Risk of U/C Asthma
Stomach pain	49	36	13	2.00 (95% CI: 1.17-3.40)
Back pain	71	47	24	1.69 (99% CI: 1.07-2.67)
Arm/Leg/Joint Pain	72	48	24	1.78 (95% CI : 1.13-2.79)
Menstrual Pain	13	6	7	0.76 (95% CI: 0.42-1.37)
Headaches	64	44	20	1.78 (95% CI: 1.12-2.83)
Chest pain	49	42	7	4.62 (95% CI: 2.26-9.44)
Dizziness	40	34	6	3.78 (95% CI: 1.75-8.16)
Fainting	15	12	3	2.20 (95% CI: 0.78-6.23)
Heart pounding	46	35	11	2.25 (95% CI: 1.27-3.98)
Shortness of Breath	79	57	22	3.23 (95% CI: 2.20-4.74)
Pain with Sex	14	10	4	1.51 (95% CI: 0.64-3.59)
Constipation	46	33	13	1.77 (95% CI: 1.04-3.01)
Nausea/Gas	62	45	17	2.27 (95% CI: 1.41-3.65)
Tiredness / Low Energy	81	56	25	2.60 (95% CI: 1.77-3.82)
Trouble Sleeping	68	50	18	2.68 (95% CI: 1.70-4.23)

or equal to 19) and 40 had controlled asthma (ACT greater than or equal to 20). The relative risk of uncontrolled asthma was similar in women as compared to men (RR = 1.06; 95% confidence interval 0.70 to 1.60). There was a slight increase in relative risk in uncontrolled asthma in patients less than or equal to 50 years of age as compared to those older than 50; however this was not statistically significant (RR = 1.34; 95% confidence interval 0.98-1.82). Time since diagnosis of asthma had no association on asthma control (RR = 1.09; 95% confidence interval 0.77-1.55). A moderate to high score on the PHQ-15 questionnaire had a higher relative risk of uncontrolled asthma as compared to participants with a minimal to low score (RR = 2.75; 95% CI, 1.62-4.68). A moderate to high score on the PSS questionnaire had higher relative risk of uncontrolled asthma as compared to participants with a low score (RR = 1.78; 95% CI, 1.12-2.83). Both of these validated

questionnaire findings are statistically significant.

**Table 3** delves further into the association of individual PHQ-15 symptoms and asthma control. Twelve of the fifteen symptoms in the PHQ-15 questionnaire showed an increased relative risk of uncontrolled asthma. These include stomach pain, back pain, arm/leg/joint pain, headaches, chest pain, dizziness, heart pounding, shortness of breath, constipation, nausea/gas/indigestion, tired/low energy, and trouble sleeping. The symptoms that were not statistically significantly associated were menstrual pain, fainting, and pain with sex. Relative risk of uncontrolled asthma for each of these symptoms can be found in **Table 3**.

**Table 4** further elucidates associations between ACT scores, PSS scores, and PHQ-15 scores. A significant association between ACT and PSS was observed ( $\chi^2(2) = 6.62$ ,

**Table 4:** Associations of ACT, PSS, and PHQ-15 score categories: Raw data, Chi Square Analysis, Likelihood Ratio, and Spearman's Rho.

		ACT		PSS	
		Controlled	Uncontrolled	High-Mod	Low
PSS	High-Mod	20	44		
	Low	20	16		
PHQ-15	High- Med	13	44	44	13
	Low-Min	27	16	20	33
ACT v.PSS		Pearsons Chi-Square: 6.616; df = 2. Likelihood Ratio: 6.787; df = 2. Spearman's Rho = 0.26. N valid cases = 100			
ACT v.PHQ-15		Pearsons Chi-Square: 26.294; df = 3. Likelihood Ratio: 29.152; df = 3. Spearman's Rho = 0.502. N valid cases = 100			
PSS v.PHQ-15		Pearsons Chi-Square: 26.492; df = 6. Likelihood Ratio: 29.388; df = 6. Spearman's Rho = 0.47. N valid cases = 100			

$p < 0.05$ ; Spearman's Rho = 0.26). A significant association between ACT and PHQ-15 was observed ( $\chi^2(3) = 26.29$ ,  $p < 0.001$ ; Spearman's Rho = -0.502). A significant association between PSS and PHQ-15 was observed ( $\chi^2(6) = 26.49$ ,  $p < 0.001$ ; Spearman's Rho = 0.47).

## Discussion

This study shows that a clinically significant association exists between uncontrolled asthma, perceived stress, and psychosomatic symptoms. Significant relationships were found between ACT and PSS scores, ACT and PHQ-15 scores, and PSS and PHQ-15 scores. The increased relative risk of uncontrolled asthma among participants with a moderate-to-high PSS score seen in this study reveals an association between increased anxiety and poorer outcomes for asthma patients. In regard to asthma control and somatization, patients showed an increased relative risk of uncontrolled asthma with both a cumulative moderate-to-high score on the PHQ-15 questionnaire and with high scores on a multitude of the individual PHQ-15 questions. The significant association between PSS and PHQ-15 scores is also notable.

Although previous studies have shown a relationship between female gender and more severe asthma symptoms, [29,30] this study was unable to identify a significant association between gender and asthma. Specifically, female gender lacked a statistically significant increase in relative risk of uncontrolled asthma (RR: 1.06 [95% CI: 0.70-1.60]). Furthermore, neither age nor time since diagnosis had a statistically significant effect on asthma control in this study.

In light of the findings of both this study and prior research, it is clear that patient care teams need to assess for stress and psychosomatic symptoms in patients with asthma in order to properly address these conditions with personalized care. Some previous studies have approached interventions such as meditation, yoga, and breathing exercises. These studies did show improvement in overall quality of life without change in lung function [31,33]. A yoga breathing intervention study, involving twenty-minute sessions twice a day over three months, showed improvement in both quality of life and FEV1 [34]. Meditations have also been shown to

improve lung function in patients with asthma [35]. To further clarify the effects of breathing and relaxation interventions, future prospective studies need to focus on lung physiology, inflammation, stress assessment, presence of somatization symptoms, and asthma control.

A number of limitations exist for this six-month study. This study does not include any clinical data, pulmonary physiology data, or inflammation data, as it focused on the assessment of asthma control and validated questionnaires for stress and somatization. Assessment of asthma control, stress, and somatic symptoms are subjective measures. This study included one fall allergy season, and only included patients in the Greater New Orleans area. In addition, this study did not collect information on whether ethnicity and socioeconomic class may affect somatic symptom severity [36-38].

## Conclusion

This study shows a significant association between uncontrolled asthma, higher levels of perceived stress, and an increased incidence of somatic symptoms among patients with asthma. These results reinforce the need for assessment of stress and somatic symptoms in asthma patients, and reveal new research opportunities aimed at analyzing the possible benefits of stress and psychosomatic symptom management treatments in improving asthma control. Future prospective studies would benefit from investigating how these symptoms change with effective interventions.

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