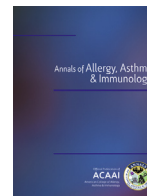




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Asthma and depression: the Cooper Center Longitudinal Study

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ABSTRACT

Background: Prior research suggests a possible association between asthma and depression.

Objectives: To examine the association between asthma and depressive symptoms, controlling for asthma medications, lung function, and overall health.

Methods: We conducted a cross-sectional study of 12,944 adults who completed physician-based preventive health examinations at the Cooper Clinic from 2000 to 2012. Information on medical histories, including asthma and depression, and medications were collected. Participants reported overall health status, completed spirometry testing, and underwent depression screening using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D). Dependent variables of current depressive symptoms (CES-D scores ≥ 10) and lifetime history of depression were separately modeled using logistic regression with independent variables, including demographics, spirometry, asthma controller medications, and patient-reported health status.

Results: The sample was predominantly white and well educated. The prevalence of asthma was 9.0%. Asthma was associated with an odds ratio (OR) of 1.41 (95% CI, 1.16–1.70; $P < .001$) of current depressive symptoms based on CES-D score. Asthma was also associated with lifetime history of depression (OR, 1.66; 95% CI, 1.40–1.95; $P < .001$). Neither lung function nor asthma controller medications were significantly associated with depression.

Conclusion: Asthma was associated with increased prevalence of current depressive symptoms and lifetime depression in a large sample of relatively healthy adults. These findings suggest that the increased likelihood of depression among patients with asthma does not appear to be exclusively related to severe or poorly controlled asthma. People with asthma, regardless of severity, may benefit from depression screening in clinical settings.

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Introduction

Asthma and depression each affect an estimated 8% to 12% of the population and cause significant morbidity and mortality.^{1–3} Both illnesses are challenging to treat. People with both depression and asthma have increased asthma-related emergency department visits, physician visits, days with asthma symptoms,⁴ mortality and morbidity, health-related work disability, and costs to employers due to lost work days⁵ and decreased work performance compared with those with asthma but without depression. Hakola et al⁶ observed that, compared with their healthy counterparts, employees with

asthma and depression had a 4.5 times higher risk of work disability. All of these factors contribute to substantial economic costs to both the patient and society.⁶

Several epidemiologic studies^{2,7–12} have reported an association between asthma and depression. World Healthy Survey data revealed significant associations between asthma and depression in 35 of 54 countries. However, the odds ratios (ORs) ranged widely across regions, from a nonsignificant 0.5 in Senegal to a high of 18.4 in Comoros.⁷ Global health care disparities and differences in disease reporting might explain the variation in reported associations in this report.^{2,7–9,13–16} The World Healthy Survey data did not include the United States, and the limited data on the association between asthma and depression in US populations have relied on patient self-reports of asthma and depression.

Single-country studies that assessed asthma and depression, using methods other than self-report, have focused on young

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people, not a broad age range of adults, and have revealed mixed results.^{17–19} Lev-Tzion et al¹⁷ evaluated 195,903 Israeli men who underwent military service eligibility evaluations and found that people with asthma were more likely to have mood and anxiety disorders than those without (OR, 1.31; 95% CI, 1.19–1.46). During recruitment, asthma was diagnosed based on medical record history of previous diagnosis or history of wheezing with those with positive responses then receiving assessment by a pulmonologist that included history, physical examination, and spirometry. A depression diagnosis was based on previous medical history and psychiatric screening and evaluation. Hayatbakhsh et al¹⁸ assessed 2,443 Australian young adults (ages 18–24 years) for psychiatric disorders and found that both self-reported asthma and asthma medication use were significantly associated with lifetime major depressive disorder (MDD) ($P < .001$), but reduced lung function (forced expiratory volume in 1 second [FEV₁]) was only significantly associated with increased depression among males.¹⁸ Finally, Goodwin et al³⁶ found in an asthma cohort (N = 2,193) in Western Australia that severe, but not mild, asthma at 5 years of age significantly increased the likelihood of mental health problems presenting later in youth (ages 5–17 years).

Smaller cohort studies (N < 743) of adults that assessed lung function, asthma severity, asthma control, and quality of life also had mixed results. Most studies found significant associations between depression and increased asthma severity, depression and poor asthma control, or depression and decreased quality of life in people with asthma.^{13,20–24} These cohorts, which included primarily moderate to severe asthma, attribute asthma disease burden to the associated increased rates of depression.^{13,20–25} Conversely, Goodwin et al²⁶ examined adults (N = 4,181) using the Composite International Diagnostic Interview and did not find an association between either severe asthma or nonsevere asthma and depression.²⁶ Thus, the association between asthma severity and depression remains unclear.

The current report describes patients who underwent fee-for-service preventive medical evaluations in the Cooper Center Longitudinal Study (CCLS) to examine depression and asthma in a US sample of mostly healthy people from across the adult age spectrum. To our knowledge, this is the first large sampling of US adults with asthma to explore the prevalence of depression in people in generally good physical health and with relatively high socioeconomic status. The previous population surveys largely relied on relatively subjective measures, such as self-report of asthma. The current study goes beyond patient self-reports to include physician-verified asthma diagnosis, objective measures of lung function and asthma medication use, and a standardized, well-validated depression assessment. In addition, the report minimizes confounding factors, such as physical disability, poor access to health care, and low household income, that may affect the association between an asthma diagnosis and depression.

Methods

The CCLS is a prospective study of patients who have completed a fee-for-service preventive medical examination at the Cooper Clinic in Dallas, Texas.²⁷ These individuals were self-referred or referred by their corporation for elective examinations. The current study population (n = 12,944 adults) was derived from those individuals whose examination data included the key study variables of spirometry, asthma history, and depression symptom screening at the Cooper Clinic from 2000 to 2012. During physician assessment, demographic information, including age, body mass index, educational level, and smoking status, was collected. Self-identified race was collected on participants. Medical history and medication information were obtained. Each participant signed an informed consent that allowed for the use of their data in research.

Overall, approximately 95% of clinic patients consent to the use of their data for research. Those who do not consent do so for individual reasons and not because of systematic exclusions. According to clinic policy, no data are obtained on nonconsenters. The informed consent, the CCLS, and data security procedures are reviewed and approved annually by The Cooper Institute's Institutional Review Board. All data were deidentified before analysis.

Assessments

Depression

Participants completed the 10-item CES-D to quantify current depressive symptom severity. The self-reported CES-D scores assess depressed affect, somatic retardation, and positive affect, generating a total severity score of 0 to 30. The CES-D has high reliability and validity in detecting symptoms of depression.²⁸ On the basis of previously published studies, we defined current clinically significant depressive symptoms as CES-D scores of 10 or higher.²⁸ Lifetime history of depression was assessed using the question, "Please indicate whether you have ever had a significant problem with any of the symptoms or conditions listed below" with depression as one choice.

Asthma

Asthma was screened for using "Please indicate whether you have ever had a significant problem with any of the symptoms or conditions listed below" with asthma as one choice. A physician reviewed participant responses to determine an asthma diagnosis in each participant. Current asthma medications were also recorded.

Lung function

Spirometry data, including FEV₁ and force vital capacity (FVC) using a Collins 421 Survey spirometer, were collected. On the basis of prior studies and guidelines, we defined current obstruction as FEV₁/FVC less than 0.7.²⁹

Health status

Self-reported overall health status was assessed using "How do you rate your overall health?" with choices of poor, fair, good, and excellent provided. This instrument was designed for clinical screening at the Cooper Clinic.

Statistical Analysis

We used CES-D scores of 10 or higher or less than 10 as the dependent variable and a history of asthma as the independent variable. After examining unadjusted associations between asthma and depression using logistic regression, we constructed a logistic regression model with covariates, including sex (male or female), race (white or nonwhite), educational level (high school or less or some college or above), age (<50 or ≥50 years), medical history (hypertension, myocardial infarction, stroke, cancer, or diabetes mellitus), self-reported health rating (poor or fair or good or excellent), smoking status (never or former smoker or current smoker), alcohol consumption status (nondrinker or drinker), body mass index (normal to overweight or obese), current inhaled corticosteroid (ICS) use (yes or no), current ICS plus long-acting β -agonist (LABA) use (yes or no), and FEV₁/FVC (<70 or ≥70). Variables were dichotomized to assist in constructing clinically relevant ORs. A similar analysis was conducted using history of depression rather than CES-D scores as the dependent variable. SPSS statistical software, version 20 (SAS Institute Inc, Cary, North Carolina), was used for the statistical analyses, including the summary statistics analyzed using χ^2 tests (Table 1).

Table 1

Participant characteristics divided by presence of asthma (N = 12,944)

Characteristic	No. (%) of patients	
	Asthma (n = 1,169)	No asthma (n = 11,175)
White	1,100 (94.1)	11,177 (94.9)
Started college and above ^a	970 (83.0)	9,473 (80.5)
Male	774 (66.2)	8,057 (68.4)
Age ≥50 years ^a	550 (47.0)	5,985 (50.8)
Hypertension ^a	263 (22.5)	2,318 (19.7)
Diabetes mellitus ^a	41 (3.5)	284 (2.4)
Myocardial infarction	10 (0.9)	114 (1.0)
Stroke	7 (0.6)	61 (0.5)
Cancer	105 (9.0)	1,108 (9.4)
Current alcohol consumption	924 (79.0)	9,501 (80.7)
Current smoker ^a	119 (10.2)	1,482 (12.6)
ICS ^b	63 (5.4)	15 (0.1)
ICS plus LABA ^b	86 (7.4)	23 (0.2)
Poor or fair health ^b	292 (25.0)	2,163 (18.4)
Good or excellent health ^b	877 (75.0)	9,612 (81.6)
BMI ≥30 ^b	300 (25.7)	2,554 (21.7)
FEV ₁ /FVC <70 ^b	175 (15.0)	618 (5.2)

Abbreviations: BMI, body mass index; FEV₁/FVC, forced expiratory volume in 1 second/forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; OR, odds ratio.

^a $P < .05$.

^b $P < .005$.

Results

Participant characteristics are detailed in Table 1. The sample was predominantly white and had high levels of formal education. The prevalence of asthma was 9.0%. Asthma patients more often listed ICS ($P < .001$) and LABA plus ICS or ICS ($P < .001$) prescriptions and demonstrated obstructive lung function (FEV₁/FVC < 70%) on spirometry tests ($P < .001$). People with asthma were younger ($P < .001$) and less likely to be current smokers ($P = .02$) than those

without asthma. Comorbid conditions of hypertension ($P = .002$), diabetes ($P = .004$), or obesity ($P < .001$) occurred more often in those with asthma. Good or excellent health status was reported in 75% of people with asthma and 81% of those without asthma ($P < .001$).

Unadjusted analyses revealed that asthma associated with increased current depressive symptoms (OR, 1.60; 95% CI, 1.35–1.90; $P < .001$) and an increased lifetime history of depression (OR, 1.73; 95% CI, 1.49–2.01). After controlling for multiple covariates, asthma was associated with an increased risk of clinically significant current depressive symptoms as defined by the CES-D (OR, 1.41; 95% CI, 1.16–1.70; $P < .001$). Figure 1 highlights the primary analysis results for the association between CES-D scores and asthma. Asthma was associated with an increased risk of lifetime depression (OR, 1.66; 95% CI, 1.40–1.95) after multivariate adjustment. Figure 2 details results for the association between lifetime history of depression and asthma.

To evaluate whether this association was also seen in those with mild asthma, a sensitivity analysis was performed that excluded participants with an FEV₁/FVC less than 70% and/or with use of LABA plus ICS or ICS. This sample size of this subgroup was 12,016. In this subgroup with less severe asthma, there was also a significantly increased risk of current depressive symptoms (OR, 1.35; 95% CI, 1.10–1.67; $P = .004$) and lifetime depression (OR, 1.77; 95% CI, 1.49–2.11; $P < .001$).

Discussion

In this group of adults with good access to health care, who were not seeking short-term medical treatment, asthma was associated with a 41% increased odds of current depressive symptoms and a 66% greater likelihood of lifetime depression than those without asthma after controlling for demographic characteristics, spirometry, and asthma medications. The results remained significant

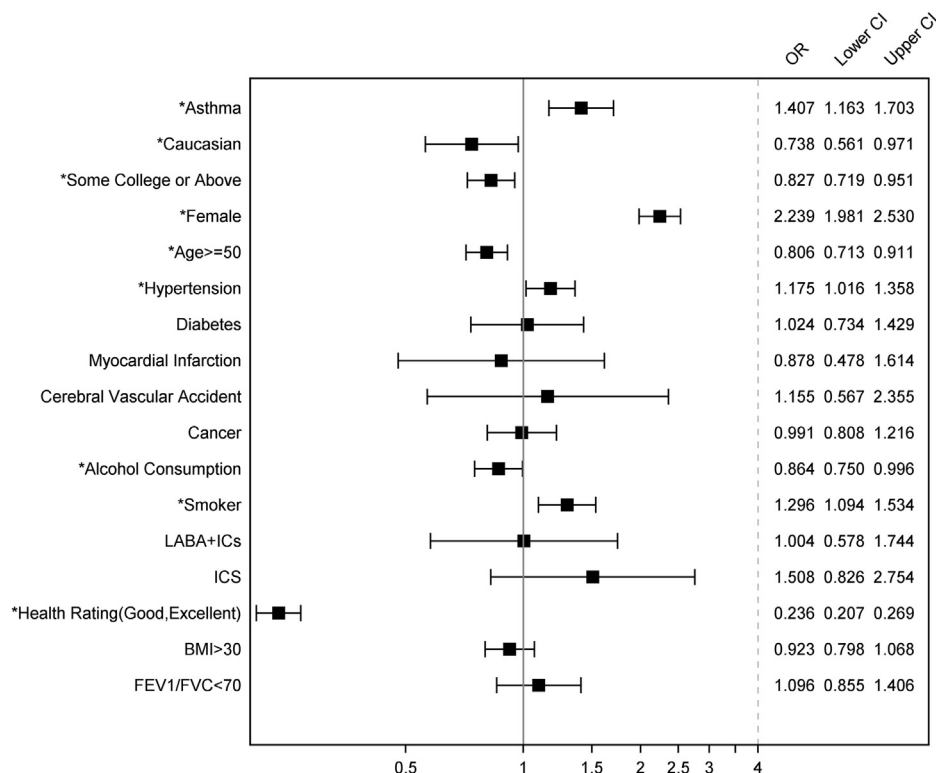


Figure 1. Logistic regression model of Center for Epidemiological Studies Depression Scale (CES-D) score. * $P < .05$. Nagelkerke $R^2 = 0.119$. BMI, body mass index; FEV₁/FVC, forced expiratory volume in 1 second/forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; OR, odds ratio.

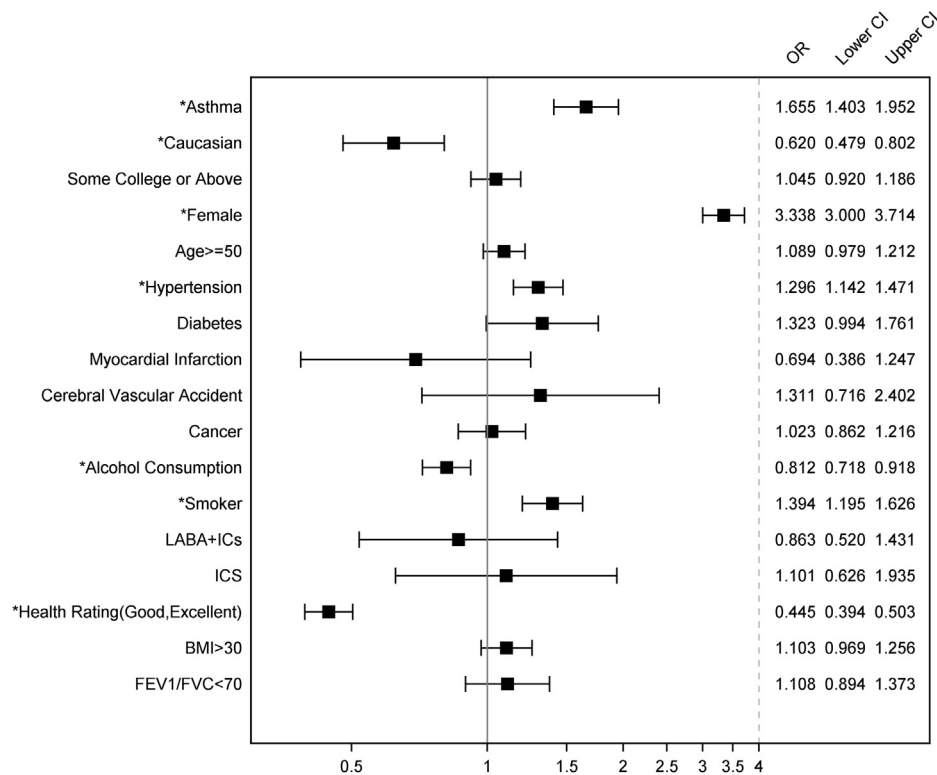


Figure 2. Logistic regression model of personal history of depression. * $P < .05$. Nagelkerke $R^2 = 0.110$. BMI, body mass index; FEV₁/FVC, forced expiratory volume in 1 second/forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; OR, odds ratio.

after excluding participants with FEV₁/FVC less than 70 and those taking LABA plus ICS or ICS. Low frequencies of controller medications (ICS = 5%, ICS plus LABA = 7%) and obstructive spirometry (FEV₁/FVC < 0.70 = 15%) suggest that most patients in the asthma group had relatively mild asthma. Prior studies suggest that poor asthma control is a risk factor for depressive symptoms, depression, and decreased quality of life.^{30,31} Thus, poor asthma control may confound previously reported asthma and depression associations studies that rely on self-reported depressive symptoms.^{13,20–25} The current findings suggest that associations between asthma and depression in prior reports are not likely fully explained by factors such as low income and poor access to health care of asthma-related disease burden. Using a generally healthy, mild asthmatic cohort and controlling for patient-reported health status, our findings suggest that depression in asthma patients may not be largely due to disability or distress related to having a severe medical illness.

If the association between asthma and depression cannot be in large part explained by disease burden, then other etiologic factors must be considered. Increasing evidence supports possible shared immunologic, endocrine, and peripheral nervous system dysfunction in depression and asthma.^{32–38} In humans, proinflammatory cytokine treatment has been long known to be associated with depressive symptoms.^{32,39} Similarly, many asthma phenotypes demonstrate increased proinflammatory states at baseline, with noxious stimuli, and during exacerbations.^{40,41} Hypothalamic-pituitary-adrenal (HPA) axis dysregulation occurs in MDD- and stress-based depression animal models.^{33,34} Systemic and inhaled glucocorticoids asthma may directly modulate the HPA axis, and genetic abnormalities of the HPA axis have been associated with steroid-resistant asthma.^{35,36} Studies suggest that leptin, a circulating adipocytokine with some receptors in the lungs and elevated by glucocorticoid increases associated with HPA hyperactivity, such as in depression,^{42,43} may contribute to the pathogenesis of both asthma and depression. Common genetic factors could also explain

the association between asthma and depression. A study of monozygotic (N = 1,337) and dizygotic Finnish twins (N = 2,506) reported that 64% of the association between atopic illnesses and depressive symptoms was explained by shared familial vulnerability and additive genetic influences.⁴⁴ However, the specific genes that might link asthma and depression have not been established. A study examining housekeeping genes in asthma patients with and without depression and controls found that the gene for cyclophilin A (*PPIA*) distinguished asthma from controls but showed less ability to distinguish depression status within asthma.⁴⁵ Abnormalities of central and autonomic nervous systems have been described in both asthma and depression.³⁷ For example, Flinders Sensitive Line rats, genetically engineered for an increased cholinergic response, demonstrate depressive symptoms in response to stress.⁴⁶ Moreover, cholinergic hyperresponsiveness predisposes the rats to allergen-induced bronchoconstriction and airway inflammation.⁴⁷ Ritz et al.^{48,49} found that the ability of emotional stimuli to induce airway constriction in people with asthma depended on functioning cholinergic pathways due mainly to vagal excitation, rather than greater cholinergic sensitivity of the airways, with depressive disorders speculated as a consequence of this association, particularly in female children with nonatopic asthma.⁵⁰

The study has strengths and limitations. Because of the limitations of the information in the data set, as well as the generally mild severity of asthma, we were not able to compare associations between asthma and depression in those with intermittent, mild persistent, moderate persistent, and severe persistent asthma. However, a secondary analysis that excluded those with FEV₁/FVC less than 70% and/or with use of LABA plus ICS or ICS yielded similar findings as the analysis of the entire sample. The limited racial and socioeconomic data, as well as male predominance, may reduce the generalizability. However, homogeneity of the population may provide increased internal validity to the results and provided an opportunity to assess the association between asthma and depression in adults with a broad age range, who were in generally

good health, had relatively mild asthma, and had good access to health care. Another limitation is that without airway hyper-responsiveness testing, we cannot rule out the possibility of inappropriate asthma diagnoses. However, the generally healthy nature of our cohort, an asthma diagnosis based on physician reviewed data, and model inclusion of asthma medications and spirometry reduce this possibility. Finally, the cross-sectional nature of the data does not allow a determination of cause and effect.

In a generally healthy cohort, asthma is associated with an increased prevalence of current and lifetime depressive symptoms. These results should encourage more extensive depression screening in people with asthma. In addition, further research should be conducted to illuminate the underlying mechanism that links asthma and depression.

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