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Examining the relationship between depression and asthma exacerbations in a prospective follow-up study

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Abstract

Background—While depression has been linked with asthma in numerous studies, its relationship with asthma exacerbations, including emergency room (ER) visits and oral steroid (OS) use has not been well documented. The main aim is to investigate whether comorbid depression increases exacerbations among patients with asthma.

Method—The study included 568 participants with asthma, who were between 18-56 years old, were taking an inhaled corticosteroid, and participated in both baseline and follow-up surveys. Surveys and medical records from a large, integrated health system were collected as part of the Adherence Feedback for Improving Respiratory Medication Use trial (ClinicalTrials.gov: NCT00459368). Number of ER visits and OS prescription fills for asthma were calculated for 12-month periods before and after the follow-up survey. Depression was measured using a standardized two-item instrument on both surveys. Negative binomial regression and modified proportional hazards models were used in the analyses.

Results—Among patients with asthma, those who had depression (n=187; 32.9%) were at increased risk of having an asthma-related ER visit (adjusted relative risk (aRR): 1.96, 95% confidence interval (CI): 1.02 - 3.75), but not an OS fill (aRR: 0.98; 95%CI: 0.72-1.32). Participants with depression and asthma, who also received psychiatric treatment via antidepressant medication (n=126; 22.2%) or psychotherapy (n=39; 6.9%), were more likely to have an ER visit (medication hazard ratio (HR): 2.09, 95%CI: 1.35-3.25; psychotherapy HR: 2.07, 95%CI: 1.38-3.22).

Conclusion—This study suggests a temporal relationship between depression and asthma-related ER visits. Research and practice must further consider the importance of these comorbid conditions.

Keywords

asthma; depression; emergency care; oral steroid; mental health services

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INTRODUCTION

Depression and asthma are two of the most prevalent chronic diseases in the United States and around the world.(1-3) Depression is highly comorbid with most chronic general medical conditions such as diabetes, heart disease, and chronic pain, but the relationship between depression and asthma has not always been quite so clear.(4-8) While most recent research indicates that there is a strong positive association, other more dated studies did not support the connection between depression and asthma.(9-12) Currently, though, as most researchers agree that a relationship does exist, the focus has shifted to understanding the bi-directional causal nature, course, and clinical implications of comorbid depression and asthma.(8, 13)

Most recently, a large historical cohort and nested case control study demonstrated that depression was much more common among those with asthma, but there was not an observed relationship between depression and asthma severity or oral steroid use for asthma events.(14) In addition, some research supports the link between combined anxiety and depression and more frequent unplanned asthma treatment contacts (i.e., unplanned medical and emergency visits).(15) Several other smaller studies confirm the relationship between depression and asthma exacerbations, such that depression increases the occurrence of inpatient hospital visits, emergency room (ER) visits, and oral steroid (OS) use.(16-18) A particularly important limitation of studies to date, though, are that asthma exacerbations are rare events, and large samples are needed to study these phenomena in the context of depression.(19) In addition, most studies rely heavily on cross-sectional data to detect differences precluding the assessment of a temporal relationship.

Another potentially important factor to consider, treatment participation, has not been explored in this type of research to date. In this context, treatment participation includes using a prescribed inhaled corticosteroid (ICS) for asthma and/or receiving psychiatric treatment (e.g., antidepressant medication or psychotherapy) for depression. This may be especially important, as studies, including those by the study team, have demonstrated poor levels of adherence to these forms of treatment, which may increase symptom burden. (20-23) The study team has also shown that poor adherence to medication is linked with an increase in asthma exacerbations.(23)

Given the increasing importance of depression in treatment outcomes for general medical conditions, and its unclear relationship with asthma exacerbations, the current study aims to investigate this relationship using a large prospective follow-up study of patients with asthma. Specifically, this study seeks to examine whether comorbid depression and asthma in comparison to asthma alone leads to an increase in subsequent asthma exacerbations (OS fills and ER visits).

METHODS

Setting and Population

The sample and surveys for the current study were derived from a prospective cohort of patients with asthma from the Adherence Feedback for Improving Respiratory Medication Use (AFFIRM) trial (ClinicalTrials.gov: NCT00459368).(24) Participants were enrolled in a cluster-randomized clinical trial to improve adherence to inhaled corticosteroids, in which physicians were informed of adherence information via the electronic medical records (EMR). All participants were randomized to a control or treatment group along with their primary care physician. The AFFIRM trial was conducted within the Henry Ford Health System, which is a large integrated health care delivery system in southeast Michigan that includes a large medical group of providers and an affiliated health maintenance

organization (HMO). This combination allows nearly complete capture of all medication use and treatment utilization both within and outside the health system for all medical group patients who are members of the HMO (i.e., the study population).

To be eligible for the study, participants needed to fulfill the following criteria: 1) an electronic ICS prescription between January 2005 and April 2007, 2) age 18-56 years old at the time of study enrollment, 3) at least one visit to a primary care physician in the health system's medical group, 4) continuous enrollment for at least a year in the health system's affiliated health maintenance organization (HMO), 5) prescription drug insurance coverage, 6) at least one clinical encounter with a diagnosis of asthma (ICD9 493.xx), and 7) no earlier diagnosis of chronic obstructive pulmonary disease or congestive heart failure. The AFFIRM protocol was reviewed and approved by the Institutional Review Board at Henry Ford Hospital and was in accordance with its Health Insurance Portability and Accountability Act. Passive implied consent was obtained from all study participants in the form of a letter sent to all study individuals accompanied by the questionnaires. Individuals were informed in the letter that their return of the survey was considered to be consent to participate. More detailed information on the protocol, clinical trial, and intervention are published elsewhere.(24, 25)

Survey Administration and Responses

This study used baseline and follow-up questionnaires to assess demographic and behavioral risk and protective factors, including depression. The baseline and follow-up surveys were mailed to 1,787 eligible patients in May 2007 and August 2008, respectively. Second mailings were sent to non-respondents approximately 8 weeks after the initial mailing at each time point. Participants, who were at least 18 years old, were instructed to complete their own surveys. The overall level of participation among eligible participants was 56.3% (n=1,006) on the baseline survey and 46.6% (n=832) on the follow-up survey. A total sample of 568 adult individuals (18-56 years old) completed both surveys. Compared with respondents, survey non-responders were more often younger, male, and of non-white race-ethnicity.

Participants responded to questions on the survey that queried several factors, including on perceptions and beliefs about their asthma and treatment,(26, 27) asthma control (i.e., the Asthma Control Test [ACT] – QualityMetric Inc., Lincoln, Rhode Island),(28) social support/stressors,(29) perceived discrimination,(30) exposure to crime/violence,(31) health locus of control,(32-34) and depression.(35, 36) An ACT score ≤19 was considered to be uncontrolled asthma, whereas scores >19 were considered to be controlled asthma.(28) Depression was measured via the two-item depression case finding instrument by Whooley et al.,(35, 36) which was found to detect depression with similar test characteristics [sensitivity: 96%; specificity: 57%] as compared to several widely used depression assessment tools, including the Beck Depression Inventory [sensitivity: 89%; specificity: 64%].(35, 37) The two questions were, "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?" An affirmative answer to either question was considered a positive screen. Thus, this study seeks to measure depressive symptoms. Mentions of depression in relation to the study methods or results should be considered as such in this study.

Study Variables from Electronic Medical Records Data

Information on the age, race/ethnicity, and sex as well as the numbers of ER visits for asthma, OS fills, ICS fills, psychotherapy visits, and antidepressant medication fills were collected for each eligible patient. Race-ethnicity is typically recorded as a self-report

measure in the health system, but in some instances is assigned by health care personnel. In previous research, the study team has demonstrated a high concordance between self-reported race-ethnicity and race-ethnicity as recorded in the electronic medical record.(38) As previously reported,(20, 23) medication use and adherence was estimated using automated data from the health system's electronic prescription and claims databases. In short, the study team calculated a 'continuous, multiple-interval measure of medication adherence' (CMA) for the 3-month time period preceding the administration of the second survey.(23, 25) Episodes of treatment for depression (i.e., psychotherapy visits or antidepressant medication fills) were identified during the same time period. Asthma-related ER visits and OS medication fills were identified in the 12-month time period between the baseline and follow-up survey period and prospectively following the second survey.

Statistical Analysis

The primary plan for statistical analysis sought to investigate whether comorbid depression increases the risk for asthma exacerbations (OS fills and ER visits) among patients with this condition. The primary outcome variables, OS fills and ER visits, are often rare events, but are consistent with a standardized definition of asthma exacerbations according to the American Thoracic Society and European Respiratory Society and are recommended as outcome variables for research according to a recent working group from the National Institutes of Health.(23, 39, 40) In these analyses the baseline period (Time 1) was defined as the first survey assessment. The follow-up period (Time 2) includes the variables on the second survey, which was 15 months following the first survey. The predictor clinical variables were measured during a 12-month span between the first and second survey time points. All of these variables were used to predict ER visit and OS prescription fill outcomes for the 12-month period following the second survey.

Descriptive analysis was first performed on the main study variables and covariates. For the main analysis, negative binomial regression models were used to examine whether depression was prospectively associated with asthma-related ER visits and OS fills for asthma in the 12 months following the survey. Here, the study is focused on depression status at survey follow-up, since it is the most recent measurement to the capture of outcome data on asthma exacerbations. The baseline assessment allows adjustment for depression status prior to the intervention period of the clinical trial (i.e., baseline, time of the first survey). Two depression assessments also allow the study team to account for fluctuation in the experience of depression symptoms over time, since symptoms can be cyclical or more severe at times. This analysis adjusted for age, race-ethnicity, sex, study group assignment (i.e., treatment intervention vs. control for the intervention study), ACT score, ICS adherence, and prior history of an exacerbation of that type.

The remaining analyses were conducted to provide additional context to the discussion and are available in an online supplement. First, change in depression between survey time points was assessed by categorizing the responses as follows: no-no, yes-no, no-yes, yes-yes (for the baseline survey and follow-up survey, respectively). This dummy variable replaces the two separate depression variables in the first model, but similarly adjusts for all the same clinical, demographic, and behavioral factors.

Lastly, proportional hazards regression models were used, which allowed for recurring end points to examine the asthma exacerbations outcomes among patients with both depression and asthma. In other words, in contrast to standard survival analysis, these models allowed for multiple events (i.e., ER visits and OS fills) per person, thereby treating each person as a cluster. In addition to the covariates used in the other regression models, time-updated measures of antidepressant medication use and psychotherapy visits were included – both as

a proxy for depression severity as previous research has linked treatment utilization with depression severity.(41)

All of the analyses used an acceptable statistical significance level at $p \leq 0.05$. The analyses were performed using SAS version 9.2.(42)

RESULTS

Electronic medical record and prospective survey data were available for 568 adult participants in this study. The sample characteristics are shown in Table 1. Over 30% of the sample met criteria for depression at both the baseline (35.9%) and 15-month follow-up (32.9%) survey time points. Over one-fifth of the participants (22.2%) filled an antidepressant medication prescription in a 3-month window preceding the follow-up survey, and 6.9% had a psychotherapy visit during the same period. Also during that period, among participants the average adherence to ICS medications was 33.1%. Following the second survey, participants had an average of 0.13 ER visits per year (range 0-5) and an average of 1.14 OS fills per year (range 0-33). The bivariable relationships between the study variables of interest and the outcomes variables are reported in Table E1. Poor ACT control was associated with an increase in both ER visits and OS fills (p=0.047). In addition, females (p=0.031), African Americans (p=0.006), and history of OS fills (p<0.001) were associated with an increase in later OS fills, while history of ER visits was linked with an increase in later ER visits (p=0.010).

Table 2 shows the results of negative binomial regression models predicting ER visits and OS fills adjusting for age, race-ethnicity, sex, study group, ACT score, and ICS adherence. In both models, history of a prior asthma exacerbation predicted recurrent events. Depression reported on the last survey was associated with subsequent ER visits (p=0.015), but not OS fills (p=0.519). Depression, as reported a year earlier on the initial survey, was not prospectively associated with either ER visits or OS fills following the last survey. In these main analyses, we adjust for study group assignment, but do not stratify for this variable in a separate analysis, as we found that ‘study group’ was not associated with outcomes (see Table E1) in our sample (p>0.05 for ER visits and OS fills). This null relationship has been previously published by the study team.(24) Also, ‘study group’ was not associated with depression at follow-up, the main independent variable of interest.

Table E2 shows the relationship between depression and asthma exacerbations using an indicator variable for the combinations of patient-reported depression on the initial and second survey. The results from these models show that participants who appeared to develop depression during the baseline period (i.e., no-yes responses on the subsequent surveys) and those who reported depression at both time points (i.e., yes-yes responses), were significantly more likely to have a subsequent asthma-related ER visit as compared to individuals whose depression appeared to resolve or improve over the baseline period (i.e., yes-no responses) – hazard ratio (HR) 3.30 (p=0.035) and HR 3.04 (p=0.014), respectively. Again, history of ER visits for asthma was also an important predictor of future asthma-related ER visits for asthma (aRR: 2.78, 95%CI: 1.62-4.76). Change in depression over time was not significantly associated with OS use (p>0.05).

Finally, proportional hazards models showed that among individuals with both asthma and depression (i.e., as assessed on the last survey), receipt of either psychotherapy or antidepressant medication were both positively associated with the risk of future asthma-related ER visits – HR 2.09 (p<0.001) and 2.07 (p<0.001), respectively (Table E3). There was no statistically significant association with OS fills (p>0.05).

DISCUSSION

This is one of the first large prospective studies to show a temporal relationship between depression and future ER visits for asthma.(43, 44) These findings build upon, and are consistent with, prior studies that have demonstrated an association between depression and asthma exacerbations using cross-sectional designs or smaller sample sizes.(16-18) They are also consistent with research showing that depression is associated with an increase in the number asthma symptoms and asthma symptom burden, as well as overall health care utilization.(45, 46) This relationship between depression and asthma exacerbations existed even after controlling for important clinical, demographic, and behavioral factors, including asthma and depression treatment participation, history of prior events, and the level of asthma control.

It is also important to note that this study did not find an association between depression and OS fills. The relationship for adults is consistent with the findings of others.(14) This finding perhaps suggests that depression may be more influential on the severity of exacerbations for adults rather than on the overall rate of events. For example, the most severe cases of asthma may require care in the ER or inpatient hospital and may be affected more by depression. OS use is more common, but most often it can mitigate symptoms without more serious hospital care. In cases that require OS use only, depression appears not to be as impactful for adults.

Interestingly, individuals with depression at the time of the last survey and who received subsequent treatment for depression (i.e., psychotherapy and/or antidepressant medication) were more likely to have asthma-related ER visits as compared to those who did not receive these treatments. Research has shown that there is often a long lag-time between the onset of depressive symptoms and treatment participation, that individuals with more severe depression are more likely to seek services, and that depression severity is linked with the need to continue receiving treatment.(47-49) As such, these treatments were considered as a potential proxy for more severe depression. Thus, these findings support a potential dose-response relationship between the presence and severity of depression and the frequency of asthma-related ER visits.

A potential indirect mechanism relating depression to asthma outcomes, may be that the former results in poor adherence to asthma medication, which then precipitates poor asthma outcomes.(50) Nevertheless, this study demonstrates that depression is still associated with ER visits for asthma even after controlling for adherence to ICS medication, which is considered cornerstone therapy for controlling asthma.

One way to understand a direct relationship between asthma and depression is via exploring candidate pathways. Recent research suggests that individuals may be predisposed to asthma and major depressive disorder if they have dysregulation of the hypothalamic pituitary adrenal axis or other biological processes that are sensitive to stress and mental health problems, such as the immune and autonomic nervous systems.(51) Other theories suggest that exposure to adversity, the stress of having a chronic illness, or the effect of medications used to treat asthma may increase the likelihood of an individual experiencing comorbid asthma and depression.(51-53) In addition, there may be a link between the genetic susceptibility of both asthma and depression, as is suggested by research showing that caregivers of children with asthma are at greater risk of mental health problems.(54) Environmental factors, such as exposure to prolonged air pollution, have been implicated in the onset of pulmonary diseases and may also be linked with depressive-like symptoms.(55) While this finding suggest a link between depression and asthma-related ER visits for

patients, none of the above mechanisms were explored, and therefore, additional research will be needed to understand the contribution of these potential pathways.

While the findings from this research are intriguing they must be taken in the context of limitations. First, this study was conducted among patients in a clinical trial who receive health services from a large health system in one metropolitan area. While this may affect generalization, the rich set of available electronic medical records and claims data allowed the study team to track exposures and identify outcomes in great detail. Second, the depression case-finding measure that was used in this study did not provide an actual clinical depression diagnosis, but the test characteristics of this instrument have been shown to be consistent with several other depression measures among adults.(35) Moreover, a two-item depression case-finding instrument was more practicable given the large size of the current study. However, given competing demands in busy clinical settings, it is relevant that a simple two-item tool has predictive import for other disease co-morbidity besides depression. This suggests that clinicians may be able to use this and other abbreviated depression screening tools to identify both depression and risk of co-morbid complications, although additional validation of this and other instruments is needed among children and adolescents.(35, 36, 56-58) Third, medication fill records do not reveal whether participants actually took their medication. Nevertheless, as has been previously shown, the measures of adherence developed by the study team show predictive validity for disease-related complications.(19, 24, 59) Fourth, socioeconomic status and health risk behaviors such as smoking, BMI, and physical activity were not controlled for in the analyses. These factors are associated with depression, and may be considered in future research. Fifth, the reading level of eligible participants was not captured, but all measures used in this study were validated in previous studies of similar groups. Finally, the survey response rate was near 50%. As has been previously shown, respondents were more likely to be women, older in age, and white.(25) Because complete depression information on non-respondents is not available, it is unclear how these response rates influenced the overall findings.

Overall, this study demonstrated a consistent relationship between depression and asthma-related ER visits. Future research may seek to replicate these findings, but should also consider expanding the sample size further so as to examine rarer events such as asthma-related hospitalizations. Building upon these findings, it is critical that future research seek to examine possible biological and environmental factors that may cause comorbid depression and asthma. Detecting these factors may more appropriately direct treatment. Finally, these findings promote the integration of psychiatric screening into general medical practice, both for the early identification and treatment of depression, but also for mitigating complications from co-morbid conditions, such as asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations Used

AFFIRM	Adherence feedback for improving respiratory medication use
CMA	Continuous, multiple-interval measure of medication availability
ER	Emergency room
OS	Oral steroid
ICS	Inhaled corticosteroid
ACT	Asthma control test
EMR	Electronic medical records
HMO	Health maintenance organization

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Table 1

Characteristics of the study sample

	Total sample [n=568]
Age (in years) – mean ± SD	45.2 ± 9.2
Female sex – no. (%)	409 (72.0)
Race/Ethnicity	
Non-Hispanic, White – no. (%)	424 (74.7)
Non-Hispanic, Black/African American – no. (%)	144 (25.4)
Study Group (Treatment) – no. (%) *	272 (47.9)
Asthma Exacerbations **	
No. ER visits for asthma – mean ± SD	0.13 ± 0.46
No. oral corticosteroid fills – mean ± SD	1.14 ± 2.66
History of ER visits for asthma – mean ± SD	0.07 ±0.32
History of oral corticosteroid fills – mean ± SD	0.75 ± 1.30
Antidepressant Medication Prescription Fills – no. (%) †	126 (22.2)
Psychotherapy Visits – no. (%)‡	39 (6.9)
ACT controlled – no. (%)§	359 (64.5) [n=557]
ICS Adherence (%) – mean ± SD ‖	33.1 ± 39.3
Depression ¶	
Baseline (Time 1) – no. (%)	204 (35.9)
15-Month Follow-up (Time 2) – no. (%)	187 (32.9)

SD denotes standard deviation; no., number; ER, emergency room; ACT, asthma control test; ICS, inhaled corticosteroid.

*Represents individuals who participated in the Adherence Feedback for Improving Respiratory Medication Use (AFFIRM) trial by group (treatment versus control).

**Represents the number of asthma-related events in the 12-month window before (History) and after the date of the follow-up survey.

†Includes individuals with at least one antidepressant fill in a 3-month window corresponding to the follow-up survey.

‡Includes individuals with at least one psychotherapy visit in a 3-month window corresponding to the follow-up survey.

§Baseline ACT dichotomized such that scores ≤19 were considered uncontrolled asthma and scores >19 were considered controlled asthma.

‖Represents a 3-month measure of ICS use from the time of the follow-up survey.

¶Represents individuals who met criteria for depression, as measured using the Whooley 2-item case finding instrument. An answer of yes to either question is considered positive.

Table 2

Predictors of asthma exacerbations among individuals with asthma*

	ER Visits		OS Prescription Fills	
	RR (95% CI)	***p*-value**	**RR (95% CI)**	***p*-value**
History of ER visits †	2.79 (1.65, 4.71)	**<0.001**	-	-
History of OS fills ‡	-	-	1.45 (1.36, 1.55)	**<0.001**
Depression (follow-up) §	1.96 (1.02, 3.75)	**0.043**	0.98 (0.72, 1.32)	0.87
Depression (baseline) ‖	0.68 (0.38, 1.21)	0.19	1.20 (0.93, 1.56)	0.16

ER denotes emergency room; OS, oral steroid; RR, relative risk; CI, confidence interval

*Negative binomial regression models predict ER visits and OS fills separately in the 12-month period after the second survey administration point for individuals in the study age 18-56. All models adjusted for age (continuous), race/ethnicity, sex, study group (intervention vs. control), asthma control (good at 80% vs. poor at baseline), and 3-month CMA for ICS (continuous measure of medication adherence for inhaled corticosteroids at follow-up).

†Continuous number of ER visits for asthma in the 12-month period prior to the second survey administration point. This variable was not included in the analysis for OS Prescription Fills, as there was a null relationship found between the two variables.

‡Continuous number of OS fills for asthma in the 12-month period prior to the second survey administration point. This variable was not included in the analysis for ER visits, as there was a null relationship found between the two variables.

§Depression measured by answering ‘yes’ to either of the two-items on the Whooley et al. depression case finding instrument on the second, 12-month follow-up, survey.

‖Depression measured by answering ‘yes’ to either of the two-items on the Whooley et al. depression case finding instrument on the first, baseline, survey.