Effects of Depressive Symptoms on Health-Related Quality of Life in Asthma Patients

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OBJECTIVE: To assess the effects of depressive symptoms on asthma patients' reports of functional status and health-related quality of life.

DESIGN: Cross-sectional study.

SETTING: Primary care internal medicine practice at a tertiary care center in New York City.

PATIENTS: We studied 230 outpatients between the ages of 18 and 62 years with moderate asthma.

MEASUREMENTS AND MAIN RESULTS: Patients were interviewed in person in English or Spanish with two health-related quality-of-life measures, the disease-specific Asthma Quality of Life Questionnaire (AQLQ) (possible score range, 1 to 7; higher scores reflect better function) and the generic Medical Outcomes Study SF-36 (general population mean is 50 for both the Physical Component Summary [PCS] score and Mental Component Summary [MCS] score). Patients also completed a screen for depressive symptoms, the Geriatric Depression Scale (GDS), and a global question regarding current disease activity. Stepwise multivariate analyses were conducted with the AQLQ and SF-36 scores as the dependent variables and depressive symptoms, comorbidity, asthma, and demographic characteristics as independent variables. The mean age of patients was $41 \pm \text{SD } 11$ years and 83% were women. The mean GDS score was $11 \pm \text{SD } 8$ (possible range, 0 to 30; higher scores reflect more depressive symptoms), and a large percentage of patients, 45%, scored above the threshold considered positive for depression screening. Compared with patients with a negative screen for depressive symptoms, patients with a positive screen had worse composite AQLQ scores ($3.9 \pm \text{SD } 1.3$ vs $2.8 \pm \text{SD } 0.8$, $P < .0001$) and worse PCS scores ($40 \pm \text{SD } 11$ vs $34 \pm \text{SD } 8$, $P < .0001$) and worse MCS scores ($48 \pm \text{SD } 11$ vs $32 \pm \text{SD } 10$, $P < .0001$) scores. In stepwise analyses, current asthma activity and GDS scores had the greatest effects on patient-reported health-related quality of life, accounting for 36% and 11% of the variance, respectively, for the composite AQLQ, and 11% and 38% of the variance, respectively, for the MCS in multivariate analyses.

CONCLUSIONS: Nearly half of asthma patients in this study had a positive screen for depressive symptoms. Asthma patients with more depressive symptoms reported worse health-related quality of life than asthma patients with similar disease activity but fewer depressive symptoms. Given the new emphasis on functional status and health-related quality of

life measured by disease-specific and general health scales, we conclude that psychological status indicators should also be considered when patient-derived measures are used to assess outcomes in asthma.

KEY WORDS: asthma; depressive symptoms; quality of life; global measure.

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Patients with asthma who also have depression report more respiratory symptoms and have worse asthma outcomes.¹⁻⁹ According to the Medical Outcomes Study, depression and chronic diseases have additive adverse effects on patient functional status and well-being.^{10,11}

The nature of the association between asthma and depression is controversial and complex—some investigators propose common physiologic etiologies, while others propose that depression develops in reaction to asthma.^{2,4,6-8,12-14} Despite the unclear association, patients with asthma and depression have worse outcomes as measured by traditional means, such as mortality and the need for more therapy.²⁻⁵

Currently, new outcome measures are becoming important in assessing asthma care. These outcomes focus on patient-reported functional status and health-related quality of life obtained from disease-specific and general health scales.¹⁵⁻²⁰ According to the National Heart, Lung and Blood Institute's Expert Panel on Asthma as well as other sources, addressing quality of life concerns should be a routine part of outcome assessment for asthma patients.^{15,17,19,21} However, self-reports that depend on interpretation of physical sensations are influenced by psychological factors, such as depression.^{12,22} Thus, it is important to consider patients' psychological status when interpreting self-reports, especially if this information is then used to compare patients or populations.^{12,22}

The objective of this study was to assess the effects of depressive symptoms on asthma patients' reports of health-related quality of life measured by the disease-specific Asthma Quality of Life Questionnaire (AQLQ) and the general health Medical Outcome Study SF-36.

METHODS

Patients were identified from the computerized appointment logs at the Cornell Internal Medicine Associates, a primary care internal medicine practice in New York City. All patients scheduled for an outpatient appointment with their physician, either housestaff or full-time faculty, between October 1995 and October 1997 were screened. Patients were eligible for this study if they were between the ages of 18 and 62 years and had moder-

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ate asthma as defined by the 1991 National Heart, Lung and Blood Institute's Expert Panel on Asthma.²³ We chose a younger adult group because we were interested in measuring as broad a spectrum of functional status as possible, including employment and fulfilling diverse family responsibilities. According to the 1991 Expert Panel criteria, patients in the treated state have moderate asthma if they require medications daily, but do not require high doses of corticosteroids daily. Patients were recruited for this study if daily medications had been prescribed for them (data obtained from chart review) and if patients stated they took their medications daily. Patients were excluded if they had other pulmonary diseases, had severe comorbidity, were not fluent in English or Spanish, or could not provide informed consent because of cognitive impairment, as determined by their physicians. Patients were approached during their outpatient visits and informed of the study. If they agreed to participate, they were enrolled and interviewed in person at that time.

Interviews were conducted by one of the authors (CAM) and 2 research assistants trained by the author to ensure uniformity in interviewing and in responding to any questions from patients. Interviews were conducted jointly by CAM and research assistants as part of the training process. Joint interviews were also done for spot checks throughout the study to reinforce interviewing techniques. In these instances, 1 interviewer (CAM or a research assistant) would conduct the interview while the other 2 interviewers observed. These interviews were followed by discussions regarding what responses were recorded and what clarifications were offered. No formal interrater reliability analyses were conducted. Patients did not receive monetary reimbursement for their participation. Institutional review board approval was obtained for this study.

During the interview, patients were asked a series of demographic questions including educational level and household income. Annual household income per number of household members was calculated from the estimated total household income divided by the total number of people living in the household (including children and unemployed adults). Questions about asthma included duration of disease, symptom characteristics, estimated resource utilization (hospitalizations, emergency department visits, and urgent office visits for asthma) during the prior 3 months and use of a home nebulizer and home peak flow meter.

Patients were also asked to rate their current asthma activity with the global question, "How active is your asthma now?" with possible responses of "extremely active," "very active," "moderately active," "mildly active," or "not active." The use of global ratings of disease activity has been advocated in health-related quality-of-life research for a variety of reasons.^{24,25} For example, patients' global ratings reflect a composite of unique patient-specific conditions, which, although not precisely delineated, still provide valuable measures of health-related quality of life.²⁵ Although used predominantly in longitudinal studies, glo-

bal assessments have been used cross-sectionally in several asthma studies. For example, in a recent study to develop an asthma severity index (defined as the number and intensity of exacerbations), response to a single global question was the best predictor of asthma severity among a series of items, including respiratory comorbidity, asthma precipitants, spirometry measures, and psychological factors.²⁶ For our study, the global assessment was used as a measure of current asthma activity, not as a measure of long-term asthma severity.

We also compared responses to the global question with medication use and frequency of exacerbations. Patients were asked what asthma medications they were currently taking; this information was compared with prescribed medications recorded on patients' charts. Frequency of exacerbations was obtained from response to the question, "How often do you have a flare?" with possible responses of "every day," "several times a week," "every week," "a few times a month," "once a month," or "once every few months." Patients were also given the questionnaires described below.

The AQLQ, developed by Juniper et al, is a disease-specific scale composed of 32 questions with Likert-like response formats.²⁷ The questions are grouped into 4 domains measuring symptoms, activity limitations, emotional responses, and reactions to environmental stimuli. Scores for each domain, as well as a total composite score, can range from 1 to 7 with higher scores indicating better condition. The AQLQ has been extensively tested for validity, reliability, and responsiveness, has been shown to be sensitive to a wide spectrum of disease activity, and is one of the most widely used health-related quality-of-life scales in asthma research.^{20,27-32}

The Medical Outcomes Study SF-36 is a general health scale that has been used widely in cross-sectional and longitudinal studies.³³ The SF-36 is composed of 36 questions grouped into 8 domains. In addition, Physical Component Summary (PCS) and Mental Component Summary (MCS) scores can be calculated, which are transformed scores based on a mean score of 50 for each in the general population.³⁴ The SF-36 has been shown to be valid in asthma patients.^{20,35-37}

The Geriatric Depression Scale (GDS) is a well-established, valid, and reliable screening instrument for depression.³⁸ It is composed of 30 brief questions with yes/no response formats. Scores can range from 0 to 30 (higher scores reflect more depressive symptoms); a score of 11 yielded an 84% sensitivity and 95% specificity for a diagnosis of depression; a more stringent cutoff score of 14 yielded 80% sensitivity and 100% specificity for depression.³⁸ The major advantage of the GDS over other depression scales is that it was specifically designed to measure psychological symptoms of depression and does not include somatic symptoms. This is important in our study because respiratory symptoms have been shown to confound depressive somatic symptoms in patients with and patients without respiratory diseases.^{1,12,13,22,39} Although

to our knowledge no studies have been done comparing the performance of different depression scales in patients with asthma, it has been shown in patients with other chronic diseases that instruments that include somatic symptoms can result in overreporting of depressive symptoms.^{40–42} Thus, measuring psychological symptoms with the GDS provided the discriminative properties required for our study without confounding from somatic respiratory symptoms.

Other important considerations for our study were that the GDS has been formally tested in younger patients and in patients with chronic diseases.⁴³ For example, 1 study compared the performance of a variety of instruments in younger patients (aged 45 to 60 years) and older patients (aged 66 to 87 years) followed in family practice clinics and community settings. Among the various scales, the GDS was found to be one of the best predictors of major depression in the younger group.⁴³ In other studies, the GDS was also tested in physically ill patients already classified as depressed or not depressed on the basis of comprehensive clinical review. These studies showed the GDS was effective in differentiating depressed patients and not depressed patients with arthritis and with mild to moderate dementia.⁴³

The Charlson comorbidity index (CCI) is a weighted scale originally designed to evaluate the longitudinal risk of mortality attributed to comorbid disease.⁴⁴ In our study, patients were asked about major comorbid diseases using a standardized questionnaire. A CCI score was then calculated on the basis of assigned weights for different diseases. Scores on the CCI are usually reported from 0 (no comorbidity) to >4 (significant comorbidity).

In addition to patients' reports of comorbidity, physician-assigned *International Classification of Diseases, Ninth Revision (ICD-9)*, codes for other diagnoses, including depression, were also recorded from patients' computerized charts. No formal questioning of physicians or review of office charts was done to ascertain the presence of depressive symptoms.

All questionnaires were administered during in-person interviews in either English or Spanish. Instruments that were not already available in Spanish were translated and back-translated according to standard techniques as part of this study.⁴⁵ Specifically, we selected 4 individuals (2 were research assistants) who were ethnically and culturally similar to patients in this study to first translate the questionnaires from English to Spanish, then back-translate from Spanish to English, and finally translate the questionnaires again to Spanish. Through discussion and consensus, these individuals made adjustments throughout the translation process to address issues of content and cultural appropriateness for our patients. Testing all translated questionnaires for validity and reliability in our patients was beyond the scope of this project. We also assessed the Spanish versions of the AQLQ and the SF-36 for cultural appropriateness in our sample through a similar process.

Data Analyses

Means and standard deviations were calculated for all continuous variables, such as AQLQ, PCS, MCS, and GDS scores. Frequencies were calculated for all ordinal and nominal variables, and comparisons of frequencies were done with the χ^2 test. Pearson product-moment correlation coefficients were calculated between pairs of continuous variables, Spearman rank-order coefficients were calculated between pairs where at least one variable was ordinal and the other was ordinal or continuous, and ϕ coefficients were calculated between pairs of nominal variables.^{46–48} Comparison of mean AQLQ, PCS, MCS, and GDS scores for 2 samples were done with the t test; and for 3 samples or more, using analysis of variance. Independent variables were assessed for covariability by calculating correlation coefficients. Simple linear regression equations were then calculated with AQLQ, PCS, and MCS as the dependent variables and current asthma activity, GDS score, comorbidity, age, gender, race, marital status, education, work status, household income, recent resource utilization, use of a peak flow meter, and use of a home nebulizer as independent variables. Multivariate regression models were then generated for each dependent variable using several methods. First, percentages of variance explained (R^2) from simple linear regression models were ranked from highest to lowest. Variables that were statistically significant at the $P \leq .05$ level in simple linear regression were then sequentially added to the multivariate model according to their R^2 values. For covariables with correlation coefficients of 0.2 or greater, the covariable with the highest R^2 was selected for further analysis. Variables that remained statistically significant at the $P \leq .05$ level in each multivariate model were retained to be included in the next model.^{47–49} Through this method, independent variables were included in a stepwise fashion to generate the final models. In addition, other methods to generate multivariate regression equations were also used, such as incorporating demographic and comorbidity variables first. We did not use the principal components method for reducing the number of variables, however, because we wanted to measure the effect of individual variables. Multivariate models were developed using PROC GLM in SAS. All statistical analyses were done using the Statistical Analysis System (SAS Institute, Cary, NC).

RESULTS

A total of 1,174 patients were screened for this study; of these, 588 patients were ineligible because of age over 62 years or mild asthma. Of the remaining 586 eligible patients, 21% were excluded because of other pulmonary disease or severe comorbidity, and another 21% were excluded because they did not come for their scheduled physician visits. Approximately 18% of patients were excluded for other reasons, such as not being fluent in En-

glish or Spanish. Only 5 patients (1%) refused to participate because of lack of time to complete the interview. In total, 230 patients (39% of those eligible) were enrolled. Of these, 45% were followed primarily by full-time faculty and 55% were followed by housestaff under the supervision of the same full-time faculty. Interviewing time was about 30 minutes, with the GDS requiring approximately 4 to 5 minutes to complete.

Patients excluded because of comorbidity (21%) tended to be older than enrolled patients. The 39% of patients excluded for other reasons, such as not coming for scheduled physician visits or not being fluent in English or Spanish, were similar to enrolled patients in age, gender, and spectrum of medications. We contacted by telephone a random sample of patients who did not come for their scheduled physician visits to find out about the status of their asthma and why they had not come. Some patients stated they forgot their appointments, some stated their asthma was not currently active and therefore they

did not need to see their physician, and others stated their asthma was too active for them to go outside into the hot, humid weather or the cold weather.

Demographic and asthma characteristics for enrolled patients are listed in Tables 1 and 2. The mean age was 41 years with a range of 18 to 62 years. Although 42% of the patients were Latino (mostly Puerto Rican and Dominican), only 8% preferred to have the interviews in Spanish. The mean duration of asthma was 20 years with a range of 1 to 58 years. Most patients required more than 1 medication daily. Almost all patients reported taking inhaled β -agonists daily, and 77% of patients reported taking inhaled corticosteroids daily. Few patients were using leukotriene inhibitors, which first became available toward the end of the enrollment period. Although 27% of patients owned a home peak flow meter, only 7% used it

Table 1. Demographic Characteristics (N = 230)

Characteristic	Value
Mean age $\pm$ SD, y	41 $\pm$ 11
Women, %	83
Race, %	
White	21
African American	30
Latino	42
Other	7
Marital status, %	
Married	28
Separated/divorced	27
Widowed	5
Never married	40
Education, %	
Finished college	30
Some college	27
Finished high school	17
Some high school	18
No high school	8
Work status, %	
Working/student	48
Unemployed	14
Temporary leave	11
Homemaker	25
Retired	2
Type of insurance, %	
HMO	41
Private	3
Medicare	8
Medicaid	45
Self-pay	3
Annual household income per person, %	
$\leq$ \$5,000	22
$>$ \$5,000, $\leq$ \$12,000	37
$>$ \$12,000, $\leq$ \$20,000	17
$>$ \$20,000, $\leq$ \$40,000	18
$>$ \$40,000	6

Table 2. Asthma Characteristics and Comorbidity

Characteristic	Value
Duration of asthma (mean $\pm$ SD), y	20 $\pm$ 14
Medications used daily, %*	
Inhaled β -agonists	94
Inhaled corticosteroids	77
Methylxanthines	14
Cromolyn sodium/nedocromil	7
Oral β -agonists	6
Anticholinergics	2
Leukotriene inhibitors	1
Own home peak flow meter, %	27
Use home peak flow meter daily, %	7
Own home nebulizer, %	13
Ever prescribed course of oral corticosteroids, %	57
Resource utilization for asthma during prior 3 mo, %†	
Hospitalized	5
Emergency department visits	28
Urgent care visit at internist's office	31
Frequency of flares, %	
Every day	10
Several times a week	17
Every week	6
A few times a month	29
Once a month	11
Once every few months	27
Disease activity at time of enrollment, %	
Extremely active	5
Very active	20
Moderately active	33
Mildly active	31
Not active	11
Charlson comorbidity score, %	
1	72
2	18
3	9
$\geq$ 4	1

*Most patients were taking more than 1 asthma medication.

†Patients cited are in more than 1 utilization category.

daily. Approximately one third of patients reported emergency department visits or urgent care visits with their physicians for asthma in the prior 3 months, with 5% being hospitalized for asthma during this period. By definition, all patients scored at least 1 on the CCI (for asthma); however, only 28% of patients had additional diagnoses as measured by the CCI. Approximately 67% of patients reported flares a few times a month or less often, while approximately 33% reported flares every week or more often. Patients did not appear to have difficulty understanding the global question of current asthma activity as noted by their ease in answering the question and their infrequent requests for clarification during the interviews. Over 60% of patients considered their current asthma to be mildly or moderately active, and 25% considered it to be very or extremely active. Patients' ratings of disease activity were associated with frequency of flares ($r = .37$, $P = .0001$); that is, patients rating their asthma as more active also tended to have more frequent flares. In addition, patients rating asthma as extremely, very, or moderately active were also more likely to be using oral β -agonists or oral methylxanthines in addition to inhaled medications than were patients who rated their asthma as mildly or not active ($P = .03$).

The mean GDS score was $11 \pm \text{SD } 8$. Using the stipulated cutoff score of ≥ 11 , 45% of patients had a positive screen for depression based on the GDS. Using a more stringent cutoff of ≥ 14 , 32% of patients had a positive screen for depression. Of patients with a positive screen for depression, 29% reported a diagnosis of depression, and physicians diagnosed depression by ICD-9 code in 21%.

There were no significant differences in the frequency of depressive symptoms based on gender or marital status; however, the prevalence of depressive symptoms was higher in older patients, nonwhite patients, and those with less education. The prevalence of depressive symptoms was also higher in patients who were not working, in those with Medicaid insurance, and in those with comorbidity. Finally, there was a trend of increasing depressive symptoms and decreasing household income.

The SF-36 component summary scores and the composite AQLQ scores (transformed to range from 0 to 100) according to depressive symptoms are in Figure 1. In addition, patients who had a positive screen for depression scored markedly worse on all domains for both scales compared with patients who had a negative screen for depression ($P < .001$ for all comparisons).

In order to develop multivariate models for health-related quality of life, we first assessed bivariate relations between patient, asthma, and depressive symptoms (independent variables) and AQLQ, PCS, and MCS scores (dependent variables), shown in Table 3. Patients with more depressive symptoms and patients with medical comorbidity had worse AQLQ scores than patients with fewer depressive symptoms. There was a trend for older patients and women to have worse AQLQ scores. White patients had better AQLQ scores, with no differences in

FIGURE 1. Medical Outcomes Study SF-36 and Asthma Quality of Life Questionnaire (AQLQ) scores according to depressive symptoms measured by the Geriatric Depression Scale. SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores are based on a mean score of 50 in the general population. The composite AQLQ score is transformed to range from 0 (worst score) to 100 (best score) according to the following equation: $((\text{Raw Score} - \text{Minimum Possible Score}) / \text{Possible Score Range}) \times 100$. For both the SF-36 and the AQLQ, higher scores reflect better condition.

scores between African-American and Latino patients. Patients who were divorced or separated scored worse on the AQLQ than patients who were married, widowed, or never married. Nonworking patients, those with Medicaid insurance, those with less education, and patients with lower income per household member had markedly worse AQLQ scores. Patients who had been in the emergency department or had urgent care visits with their physicians in the prior 3 months for asthma scored markedly worse on the AQLQ. A similar trend was observed for patients hospitalized versus those not hospitalized for asthma in the prior 3 months ($2.8 \pm \text{SD } 1.0$ vs $3.4 \pm \text{SD } 1.2$). Patients who used peak flow meters and those with home nebulizers also scored worse on the AQLQ, possibly reflecting the use of these devices only by sicker patients. Similar relations were observed for the SF-36 scores, especially the PCS.

Associations among independent variables were assessed before conducting multivariate analyses. Household income had the greatest associations with most other sociodemographic variables: for example, r values of .34, .44, .57, and .62 for race, education, work status, and insurance type, respectively. Emergency department visits had the greatest associations with other resource utilization variables, but resource utilization variables were weakly associated with peak flow meter and nebulizer use.

Table 4 shows results of simple linear regression with AQLQ, PCS, and MCS as the dependent variables. Variance explained, P values, and estimates with standard errors are listed for each covariable. The order of addition of covariables into the multivariate regression models was governed by percentage of variance explained by covari-

Table 3. Mean Composite Asthma Quality of Life Questionnaire Scores and Mean SF-36 Component Summary Scores According to Various Patient and Asthma Characteristics*

Characteristic	Mean $\pm$ SD Composite AQLQ	P	Mean $\pm$ SD PCS	P	Mean $\pm$ SD MCS	P
Geriatric Depression Scale score						
≥ 11 (positive screen for depressive symptoms)	2.8 $\pm$ 0.8	.0001	34 $\pm$ 8	.0001	32 $\pm$ 10	.0001
<11 (negative screen for depressive symptoms)	3.9 $\pm$ 1.3		40 $\pm$ 11		48 $\pm$ 11	
Charlson Comorbidity Index score						
No comorbidity	3.6 $\pm$ 1.2	.0001	39 $\pm$ 11	.0001	43 $\pm$ 13	.0001
Some comorbidity	2.9 $\pm$ 1.0		32 $\pm$ 8		34 $\pm$ 13	
Demographic variables						
Age <41 y	3.6 $\pm$ 1.3	.04	40 $\pm$ 10	.0001	42 $\pm$ 13	NS
Age ≥ 41 y	3.3 $\pm$ 1.1		34 $\pm$ 10		40 $\pm$ 14	
Men	3.8 $\pm$ 1.3	.02	40 $\pm$ 10	NS	43 $\pm$ 12	NS
Women	3.3 $\pm$ 1.2		37 $\pm$ 11		40 $\pm$ 14	
White	4.3 $\pm$ 1.1	.0001	45 $\pm$ 10	.0001	44 $\pm$ 13	NS
Not white	3.2 $\pm$ 1.1		35 $\pm$ 10		40 $\pm$ 14	
Not divorced	3.6 $\pm$ 1.3	.0001	38 $\pm$ 11	.002	42 $\pm$ 13	.01
Divorced	2.9 $\pm$ 0.9		34 $\pm$ 10		37 $\pm$ 13	
Some college	3.6 $\pm$ 1.3	.001	40 $\pm$ 12	.0001	43 $\pm$ 13	.03
No college	3.1 $\pm$ 1.0		34 $\pm$ 8		39 $\pm$ 13	
Working	3.9 $\pm$ 1.3	.0001	42 $\pm$ 11	.0001	44 $\pm$ 13	.002
Not working	3.0 $\pm$ 0.9		32 $\pm$ 8		38 $\pm$ 13	
Annual income per household member						
$\leq \$5,000$	2.7 $\pm$ 0.9	.0001	30 $\pm$ 7	.0001	37 $\pm$ 12	.05
>\$5,000, $\leq \$20,000$	3.5 $\pm$ 1.2		37 $\pm$ 10		43 $\pm$ 14	
>\$20,000	4.1 $\pm$ 1.3		44 $\pm$ 10		42 $\pm$ 13	
Medicaid insurance	3.1 $\pm$ 1.0	.0002	33 $\pm$ 8	.0001	38 $\pm$ 13	.003
Other than Medicaid	3.8 $\pm$ 1.3		41 $\pm$ 11		44 $\pm$ 13	
Resource utilization for asthma during prior 3 mo						
Hospitalized	2.8 $\pm$ 1.0	NS	35 $\pm$ 11	NS	34 $\pm$ 11	NS
Not hospitalized	3.4 $\pm$ 1.2		37 $\pm$ 11		41 $\pm$ 14	
Emergency department visits	2.8 $\pm$ 1.0	.0001	34 $\pm$ 9	.004	37 $\pm$ 11	.006
No emergency department visits	3.6 $\pm$ 1.2		38 $\pm$ 11		42 $\pm$ 14	
Urgent care visits	2.9 $\pm$ 1.2	.0001	34 $\pm$ 10	.005	37 $\pm$ 13	.009
No urgent care visits	3.6 $\pm$ 1.2		38 $\pm$ 11		42 $\pm$ 14	
Uses peak flow meter	2.8 $\pm$ 1.0	.04	34 $\pm$ 9	NS	39 $\pm$ 12	NS
Does not use peak flow meter	3.4 $\pm$ 1.2		37 $\pm$ 11		41 $\pm$ 14	
Uses nebulizer	2.8 $\pm$ 1.1	.002	33 $\pm$ 10	.03	40 $\pm$ 14	NS
Does not use nebulizer	3.5 $\pm$ 1.2		38 $\pm$ 11		41 $\pm$ 13	

*AQLQ indicates Asthma Quality of Life Questionnaire score; PCS, Physical Component Summary score; MCS, Mental Component Summary score; NS, not significant.

ables that had P values of $\leq .05$ (described in the "Data Analyses" section above). Table 5 shows 6 models constructed by stepwise addition of covariables along with the resulting variance explained and P values. Each successive model incorporated another category of independent covariables, specifically asthma activity, depressive symptoms, sociodemographic status, comorbidity, resource utilization, and the use of a home nebulizer. Asthma activity and depressive symptoms were added first because in simple linear regression for the AQLQ they explained the largest part of the variance and had P values of .0001 (seen in Table 4). Based on correlation matrices, household income was associated with most sociodemographic covariables, and emergency department use was associated with other resource utilization covariables; therefore, these 2 covariables were subsequently added to the model. Current disease activity in model 1, as expected, explained more of the variance for the AQLQ ($R^2 = 0.36$) than for the PCS ($R^2 = 0.17$) and the MCS ($R^2 = 0.11$). In model 2, incorporating depressive symptoms explained more of the variance for all equations, with a 0.11 increase in the AQLQ, a 0.08 increase in the PCS, and a marked 0.38 increase in the MCS. In models 3 through 6 for the AQLQ, household income explained most of the additional 0.05 variance, while comorbidity, emergency department use, and use of a nebulizer were not significant. The AQLQ has a short range, but at every observed point in the range the standard deviation was low and the variances were equal. Therefore, use of a linear fit for estimating correlation and association is acceptable.

Alternative models were also constructed with the addition of age and sociodemographic variables before disease activity and depressive symptoms. Disease activity and depressive symptoms accounted for a greater part of

the variance than any of the sociodemographic variables and explained variance over and above that explained by all sociodemographic variables. For example, with age, gender, comorbidity, and emergency department use together initially in the model, the R^2 for the AQLQ was .16. When disease activity was added to this model, R^2 increased to 0.42; and when GDS score was then added, R^2 increased to 0.50. It should be noted, however, that age and comorbidity were no longer statistically significant in the model ($P > .05$), while disease activity ($P = .0001$), emergency department use ($P = .008$), and GDS score ($P = .0001$) remained statistically significant. With PCS as the dependent variable, disease activity, GDS, and age remained statistically significant ($P < .0001$ for all), but comorbidity did not ($P = .07$). With MCS as the dependent variable, age, gender, comorbidity, and emergency department use together initially generated an R^2 of 0.12. When disease activity was added, R^2 increased to 0.18; and when GDS was then added, R^2 increased to 0.52.

DISCUSSION

The results of this study showed that after adjusting for current disease activity, depressive symptoms had an important role in patient-derived functional status and health-related quality of life measured by the AQLQ and the MCS score of the SF-36. These effects were found with a global patient measure of disease activity and the 30-item GDS. Our study is the first large study to document the additive effects of asthma activity level and depressive symptoms on patients' reports of overall health-related quality of life.

Several prior large studies have assessed the impact of depressive symptoms on reports of respiratory symp-

Table 4. Indices from Simple Linear Regression for All Covariables*

Covariable	AQLQ			PCS			MCS		
	R^2	P	Estimate $\pm$ SE	R^2	P	Estimate $\pm$ SE	R^2	P	Estimate $\pm$ SE
Asthma activity	.36	.0001	0.654 $\pm$ 0.058	.17	.0001	3.864 $\pm$ 0.573	.11	.0001	3.996 $\pm$ 0.757
GDS score	.23	.0001	-0.075 $\pm$ 0.009	.16	.0001	-0.537 $\pm$ 0.083	.47	.0001	-1.190 $\pm$ 0.084
Household income	.18	.0001	0.443 $\pm$ 0.070	.26	.0001	4.464 $\pm$ 0.554	.02	.0519	1.586 $\pm$ 0.811
Race	.14	.0001	1.102 $\pm$ 0.184	.14	.0001	9.860 $\pm$ 1.588	.01	.1002	3.599 $\pm$ 2.181
Working status	.13	.0001	0.892 $\pm$ 0.150	.21	.0001	9.565 $\pm$ 1.244	.04	.0017	5.546 $\pm$ 1.745
Emergency dept use	.08	.0001	-0.778 $\pm$ 0.171	.04	.0039	-4.435 $\pm$ 1.522	.03	.0057	-5.430 $\pm$ 1.947
Marital status	.07	.0001	-0.710 $\pm$ 0.175	.04	.0018	-4.870 $\pm$ 1.539	.03	.0125	-4.991 $\pm$ 1.982
Education	.07	.0001	-0.216 $\pm$ 0.050	.10	.0001	-2.140 $\pm$ 0.431	.02	.0309	-1.245 $\pm$ 0.573
Insurance	.07	.0001	0.681 $\pm$ 0.173	.14	.0001	7.890 $\pm$ 1.419	.04	.0041	5.475 $\pm$ 1.886
Urgent office visit	.06	.0001	-0.657 $\pm$ 0.169	.03	.0049	-4.218 $\pm$ 1.485	.03	.0086	-5.038 $\pm$ 1.901
Comorbidity	.05	.0008	-0.390 $\pm$ 0.114	.07	.0001	-4.130 $\pm$ 0.978	.08	.0001	-5.630 $\pm$ 1.243
Use nebulizer	.04	.0017	-0.744 $\pm$ 0.234	.02	.0307	-4.460 $\pm$ 2.051	.001	.6192	-1.317 $\pm$ 2.646
Gender	.03	.0119	-0.531 $\pm$ 0.209	.01	.0658	-3.378 $\pm$ 1.827	.01	.2437	-2.741 $\pm$ 2.345
Age	.02	.0256	-0.170 $\pm$ 0.008	.10	.0001	-0.313 $\pm$ 0.063	.003	.4345	-0.066 $\pm$ 0.084
Use peak flow	.02	.0417	-0.662 $\pm$ 0.323	.01	.2730	-3.097 $\pm$ 2.819	.002	.5568	-2.123 $\pm$ 3.608
Hospitalized	.01	.0926	-0.608 $\pm$ 0.360	.003	.3976	-2.655 $\pm$ 3.133	.01	.0854	-6.881 $\pm$ 3.983

*AQLQ indicates Asthma Quality of Life Questionnaire score; PCS, Physical Component Summary score; MCS, Mental Component Summary score; GDS, Geriatric Depression Scale.

Table 5. Multivariate Linear Regression for the Asthma Quality of Life Questionnaire and SF-36 Summary Scores*

Model	Variables	AQLQ		PCS		MCS	
		R ²	P	R ²	P	R ²	P
1	Asthma activity	.36	.0001	.17	.0001	.11	.0001
2	Asthma activity		.0001		.0001		.0013
		.47		.25		.49	
	GDS score		.0001		.0001		.0001
3	Asthma activity		.0001		.0001		.0003
	GDS score	.51	.0001	.40	.0007	.55	.0001
	Household income		.0002		.0001		.0082
4	Asthma activity		.0001		.0001		.0003
	GDS score		.0001		.0024		.0001
		.51		.41		.58	
	Household income		.0003		.0001		.0020
	Comorbidity		.4510		.1499		.0006
5	Asthma activity		.0001		.0001		.0014
	GDS score		.0001		.0007		.0001
		.52		.40		.58	
	Household income		.0002		.0001		.0068
	Emergency dept visits		.0663		.9218		.0443
6	Asthma activity		.0001		.0001		.0002
	GDS score		.0001		.0005		.0001
		.52		.41		.55	
	Household income		.0002		.0001		.0088
	Use nebulizer		.0704		.1914		.3276

*AQLQ indicates Asthma Quality of Life Questionnaire score; PCS, Physical Component Summary score; MCS, Mental Component Summary score.

toms by individuals with and without pulmonary diagnoses. In a study by Dales et al., 600 "healthy" individuals were surveyed regarding 5 main categories of respiratory symptoms, such as breathlessness and wheezing.²² Their results showed individuals with more depressive symptoms reported more respiratory symptoms in all categories. In another study by Janson and colleagues with over 700 individuals, there was also a strong association between more depressive symptoms and worse reported respiratory status.¹² The studies of Dales and Janson are important because they highlight the powerful influence of psychological status on self-reported respiratory status. Both studies concluded that psychological status should be considered and measured when individuals are asked to report respiratory symptoms. Neither of these studies, however, assessed asthma and the joint effect of asthma and depressive symptoms on patient-reported well-being.

In contrast, Yellowlees et al. considered the combination of psychological status and severe asthma.^{1,13,39} In a series of studies, these researchers found high rates (33%–40%) of psychiatrically diagnosed anxiety and depression in small groups of patients who had near-fatal attacks of asthma.¹ They also found that patients with psychiatric diagnoses reported more respiratory symptoms and worse quality of life than patients without psychiatric diagnoses.

The rate of depressive symptoms found in our study is notable, with 45% of patients enrolled from our primary care practice scoring over the threshold considered positive for depression screening according to the GDS. The

GDS, originally developed for older patients but shown to be valid in younger patients, was specifically chosen for this study because it is not subject to the confounding effects of somatic complaints, which as shown above, are important when considering respiratory symptoms. Although the GDS is an excellent screen for depressive symptoms, it does not provide a diagnosis of major depression, which requires fulfillment of psychiatric criteria. In our study, physicians' diagnoses of depression were obtained by searching for appropriate ICD-9 codes in computerized charts. Using this method to establish a diagnosis of depression, we found that although not many patients had an ICD-9 code for major depression, 45% had a positive screen for depressive symptoms when a GDS cutoff score of 11 was used, and 32% had a positive screen when a cutoff score of 14 was used. This is similar to other studies that have shown that many primary care patients screening positive for depressive symptoms do not fulfill criteria for major depression, but rather have a milder affective syndrome.⁵⁰

The prevalence of depressive symptoms in primary care practices has also been reported by other researchers. For example, in a study of over 1,900 family practice patients screened for depressive symptoms with the Center for Epidemiological Studies Depression Scale, the prevalence of all depressive disorders was found to be approximately 22%.⁵¹ In another study of 119 high utilizers of primary care, 45% of patients evaluated by a psychiatrist were found to have depressive symptoms requiring

antidepressant therapy.⁵² According to several recent reports, including a recent consensus report, depression may be underreported by design by physicians for a variety of reasons as well as underdiagnosed in general medical practice.⁵³⁻⁵⁶ Because we neither confirmed a diagnosis of depression in our patients by comprehensive clinical criteria, nor discussed the presence of depressive symptoms with their physicians, we are not able to conclude what the actual prevalence of depression was in our patients. However, patients who had high GDS scores were encouraged to speak to their physicians about their depressive symptoms. In addition, physicians were made aware of the high prevalence of depressive symptoms in this sample during presentation of group results.

Several studies have also compared depressive symptoms in asthma patients to those in control patients with and without pulmonary disease. For example, one study found higher rates of depressive symptoms in asthma patients compared with healthy controls and another study found higher rates of depressive symptoms in hospitalized asthma patients compared with hospitalized patients with other pulmonary diagnoses.^{14,57} The precise nature of the relation between asthma and depressive symptoms is not known. Some researchers propose the same physiologic etiology, such as impaired voluntary activation of the diaphragm in depressed asthma patients,⁶ or a cholinergic imbalance that links depression and smooth muscle bronchoconstriction.³ Some researchers have found correlations between more depressive symptoms and worse forced expiratory volume in 1 second (FEV₁) and forced vital capacity,^{8,14} while other researchers have found no correlation between depressive symptoms and FEV₁ or bronchial hyperresponsiveness to methacholine challenge.¹² Other researchers view depression either as independently coexisting with asthma or as being due to the drugs used to treat asthma.^{2,4,7} Alternatively, it is also possible that in some patients, asthma reduces quality of life (for example, when patients avoid desired activities that precipitate symptoms), which in turn causes or contributes to depression.^{2,4,7} Because of the cross-sectional design of this study, directionality or a causal relation between asthma and depressive symptoms cannot be concluded from our results.

There are several limitations to this study. First, recruitment was limited to patients who came for scheduled physician visits and did not have severe comorbidity. Health-related quality of life and depressive symptoms may be different in these patients compared with enrolled patients. Also, although this study included patients from diverse sociodemographic groups, it is not possible to generalize these findings to all sociodemographic groups. Second, measures of current asthma activity were obtained from self-report. Performance-based measures, such as peak flow meter measurements, might have provided a more standardized approach to rate asthma activity among patients. Third, the GDS was originally designed to be a self-administered questionnaire. In our

study, the GDS was administered during in-person interviews, which may have affected the way certain patients responded. Also, while the GDS has been tested in younger individuals, to our knowledge it has not been tested in individuals as young as some in our study. Fourth, although the GDS is an excellent screen for depression, we did not formally diagnose depression as part of this study. Finally, we did not measure other psychological states, especially anxiety, which have been reported to occur along with depressive symptoms in asthma patients.

The results of this study showed that asthma patients with more depressive symptoms had worse functional status and worse health-related quality of life than asthma patients with similar disease activity but fewer depressive symptoms. Whether this is due to depressed patients being more likely to report worse respiratory status or an intrinsic underlying relation between depression and asthma is not known. However, given the current emphasis on functional status and health-related quality of life measured by disease-specific and general health scales, we conclude that psychological status indicators should be considered when patient-derived measures are used to assess outcomes in patients with asthma.

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REFERENCES

1. Yellowlees PM, Ruffin RE. Psychological defenses and coping styles in patients following a life-threatening attack of asthma. *Chest*. 1989;95:1298-303.
2. Thompson WL, Thompson TL. Treating depression in asthmatic patients. *Psychosomatics*. 1984;25:809-12.
3. Miller BD. Depression and asthma: a potentially lethal mixture. *J Allergy Clin Immunol*. 1987;80:481-6.
4. Rubin NJ. Severe asthma and depression. *Arch Fam Med*. 1993;2:433-40.
5. Struck RC, Mrazek DA, Fuhrmann GSW, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. *JAMA*. 1985;254:1193-8.
6. Allen GM, Hickie I, Gandevia SC, McKenzie DK. Impaired voluntary drive to breathe: a possible link between depression and unexplained ventilatory failure in asthmatic patients. *Thorax*. 1994;49:881-4.
7. Alt HL. Psychiatric aspects of asthma. *Chest*. 1992;101:S415-S417.
8. Belloch A, Perpina M, Paredes T, Gimenez A, Compte L, Banos R. Bronchial asthma and personality dimensions: a multifaceted association. *J Asthma*. 1994;31:161-70.
9. Rushford N, Tiller JW, Pain MCF. Perception of natural fluctuations in peak flow in asthma: clinical severity and psychological correlates. *J Asthma*. 1998;35:251-9.
10. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA*. 1989;262:914-9.
11. Stewart AL, Greenfield S, Hays RD, et al. Functional status and

- well-being of patients with chronic conditions: results from the Medical Outcomes Study. *JAMA*. 1989;262:907-13.
12. Janson C, Bjornsson E, Jerker H, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med*. 1994;149:930-4.
 13. Yellowlees PM, Kalucy RS. Psychobiological aspects of asthma and the consequent research implications. *Chest*. 1990;97:628-34.
 14. Lyketsos GC, Karabetsos A, Jordanoglou J, Liokis T, Armagianidis A, Lyketsos CG. Personality characteristics and dysthymic states in bronchial asthma. *Psychother Psychosom*. 1984;41:177-85.
 15. Bukstein DA. Practical approach to the use of outcomes in asthma. *Immun Allergy Clin North Am*. 1996;16:859-91.
 16. Rose R, Weiss KB. An overview of outcomes measurement in asthma care. *Immun Allergy Clin North Am*. 1996;16:841-58.
 17. Richards JM, Hemstreet MP. Measures of life quality, role performance and functional status in asthma research. *Am J Respir Crit Care Med*. 1994;149:S31-S39.
 18. Player R, Richards J, Kohler CL, Woodby LL, Brooks CM, Bailey WC. Scale for assessing functional impairment in adults with asthma. *J Asthma*. 1994;31:437-44.
 19. Blaiss MS. Outcomes analysis in asthma. *JAMA*. 1997;278:1874-80.
 20. Van der Molen T, Postma DS, Schreurs JM, Bosveid HEP, Sears MR, Meyboom de Jong B. Discriminative aspects of two generic and two asthma-specific instruments: relation with symptoms, bronchodilator use and lung function in patients with mild asthma. *Qual Life Res*. 1997;6:353-61.
 21. Guidelines for the Diagnosis and the Management of Asthma Expert Panel Report II. Bethesda, Md: National Asthma Education and Prevention Program; April 1997. NIH publication no 97-4051.
 22. Dales RE, Spitzer WO, Schechter MT, Suissa S. The influence of psychological status on respiratory symptom reporting. *Am Rev Respir Dis*. 1989;139:1459-63.
 23. National Heart, Lung and Blood Institute. Guidelines for the Diagnosis and Management of Asthma. *J Allergy Clin Immunol*. 1991;88:435.
 24. Guyatt GH, King DR, Feeny DH, Stubbings D, Goldstein RS. Generic and specific measurement of health-related quality of life in a clinical trial of respiratory rehabilitation. *J Clin Epidemiol*. 1999;52:187-92.
 25. Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. *JAMA*. 1994;272:619-26.
 26. Kucera CM, Greenberger PA, Yarnold PR, Choy AC, Levenson T. An attempted prospective testing of an asthma severity index and a quality of life survey for 1 year in ambulatory patients with asthma. *Allergy Asthma Proc*. 1999;20:29-38.
 27. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992;47:76-83.
 28. Malo JL, Boulet LP, Dewitte JD, et al. Quality of life of subjects with occupational asthma. *J Allergy Clin Immunol*. 1993;91:1121-7.
 29. Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. *Am J Respir Crit Care Med*. 1995;151:66-70.
 30. Rowe BH, Oxman AD. Performance of an asthma quality of life questionnaire in an outpatient setting. *Am Rev Respir Dis*. 1993;148:675-81.
 31. Rutten-van Molken MPMH, Custers F, van Doorslaer EKA, et al. Comparison of performance of four instruments in evaluating the effects of salmeterol on asthma quality of life. *Eur Respir J*. 1995;8:888-98.
 32. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial. *Ann Intern Med*. 1999;130:487-95.
 33. Stewart AL, Hays RD, Ware JE. The MOS Short-form General Health Survey: reliability and validity in a patient population. *Med Care*. 1988;26:724-32.
 34. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care*. 1995;33:AS264-AS2779.
 35. Bousquet J, Knani J, Dhivert H, et al. Quality of life in asthma: internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med*. 1994;149:371-5.
 36. Mahajan P, Okamoto LJ, Schaberg A, Kellerman D, Schoenwetter WF. Impact of fluticasone propionate powder on health-related quality of life in patients with moderate asthma. *J Asthma*. 1997;34:227-34.
 37. Noonan M, Chervinsky P, Busse WW, et al. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med*. 1995;152:1467-73.
 38. Yesavage JA, Brink TL. Development and validation of a geriatric depression screening scale: a preliminary report. *Psychiatr Res*. 1983;17:37-49.
 39. Yellowlees PM, Haynes S, Potts N, Ruffin RE. Psychiatric morbidity in patients with life threatening asthma: initial report of a controlled study. *Med J Aust*. 1988;149:246-9.
 40. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-71.
 41. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *J Appl Psychol Meas*. 1977;1:385-401.
 42. Callahan LF, Kaplan MR, Pincus T. The Beck Depression Inventory, Center for Epidemiological Studies Depression Scale (CES-D), and General Well-Being Schedule Depression subscale in rheumatoid arthritis. *Arthritis Care Res*. 1991;4:3-11.
 43. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol*. 1986;5:165-73.
 44. Charlson ME, Pompei P, Ales KI, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-83.
 45. Aaronson NK, Acquadro C, Alonso J, et al. International quality of life assessment (IQOLA) project. *Qual Life Res*. 1992;1:349-51.
 46. Lang TA, Secic M. How to Report Statistics in Medicine. Philadelphia, Pa: American College of Physicians/BMJ Publishing Group; 1997.
 47. Armitage P, Berry G. Statistical Methods in Medical Research, 3rd ed. Oxford, UK: Blackwell Science Ltd; 1994.
 48. Tukey JW. Exploratory Data Analysis. Reading, Mass: Addison-Wesley; 1977.
 49. Draper NR, Smith H. Applied Regression Analysis. 2nd ed. New York, NY: Wiley; 1981.
 50. Coulehan JL, Schulberg HC, Block MA, Janosky JE, Arena VC. Depressive symptomatology and medical co-morbidity in a primary care clinic. *Int J Psychiatry Med*. 1990;20:335-47.
 51. Coyne JC, Fechner-Bates S, Schwenk TL. Prevalence, nature, and comorbidity of depressive disorders in primary care. *Gen Hosp Psychiatry*. 1994;16:267-76.
 52. Katon W, von Korff M, Lin E, Bush T, Ormel J. Adequacy and duration of antidepressant treatment in primary care. *Med Care*. 1992;30:67-76.
 53. Bell JR. Underdiagnosis of depression in primary care: by accident or design? *JAMA*. 1997;277:1433.
 54. Simon GE, Goldberg D, Tiemens BG, Ustun TB. Outcomes of recognized and unrecognized depression in an international primary care study. *Gen Hosp Psychiatry*. 1999;21:97-105.
 55. Goldman LS, Nielsen NH, Champion HC. Awareness, diagnosis, and treatment of depression. *J Gen Intern Med*. 1999;14:569-80.
 56. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA*. 1997;277:333-40.
 57. Fitzpatrick MF, Engleman H, Whyte KF, Deary IJ, Shapiro CM, Douglas NJ. Morbidity in nocturnal asthma: sleep quality and daytime cognitive performance. *Thorax*. 1991;46:569-73.