The Association Between Depression, Lung Function, and Health-Related Quality of Life Among Adults With Cystic Fibrosis*

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Background: More than 40% of people born with cystic fibrosis (CF) now reach adulthood. Greater attention is being focused on improving their health-related quality of life (HRQoL). While markers of disease severity such as lung function are only modestly associated with HRQoL, in other chronic illnesses depression is an important correlate. The objective of this study was to evaluate the relationships among lung function (i.e., FEV$_1$ percent predicted), depressive symptoms, and HRQoL among adults with CF.

Methods: Seventy-six adults with CF completed a mail-based survey. The Beck Depression Inventory and the Cystic Fibrosis Questionnaire were used to assess depressive symptoms and HRQoL, respectively. Values for FEV$_1$ percent predicted were abstracted from the medical record.

Results: Thirty percent of participants screened positive for depressive symptoms. Depressive symptoms and lung function were inversely correlated (rho $= -0.25$; $p < .05$). Correlations between depressive symptoms and HRQoL were maintained after stratifying by lung function. In the absence of depressive symptoms, those patients with good lung function (i.e., FEV$_1$, $> 70$% predicted) reported better physical HRQoL than those with poor lung function. Participants with both depressive symptoms and poor lung function reported significantly worse HRQoL on all domains than participants without depressive symptoms regardless of lung function status.

Conclusions: Depressive symptoms are prevalent among adults with CF and are associated with poorer HRQoL even after controlling for lung function. These results suggest that screening for and treating depression is important and may potentially improve HRQoL among patients with CF.

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Key words: adults; cystic fibrosis; depression; health-related quality of life; lung function; psychosocial; pulmonary function test

Abbreviations: BDI = Beck Depression Inventory; CF = cystic fibrosis; CFQ = Cystic Fibrosis Questionnaire; HRQoL = health-related quality of life

Advances in the diagnosis and treatment of cystic fibrosis (CF) have led to a substantial increase in survival rates with a growing percentage of individuals with CF surviving into adulthood. In 2005, the median survival age for individuals with CF in the United States was 36.5 years, and $> 40$% of patients were $\geq 18$ years. With increased survival, more
research and clinical attention is turning toward evaluating and improving the health-related quality of life (HRQoL) of adults with CF. Little is known about the factors that contribute to HRQoL in CF patients. Indicators of disease severity (eg, lung function, body mass index, exercise performance, and pulmonary exacerbations) are only modestly related to HRQoL scores, indicating that additional factors are important. Staab et al found that treatment burden (ie, the number of hours per day spent in therapy), health perceptions, and coping style explained a significant amount of variance in HRQoL beyond disease severity. However, little is known about the role other factors such as depression may play.

Previous studies have suggested that depressive symptoms are common in adults with CF. One study found that 46% of adults screened positive for depressive symptoms, with 12% having symptoms in the moderate-to-severe range. Another study found that while mean scores were within normal limits, 12% of adults with CF scored outside the normal range on a battery of depression and anxiety measures. Although there is no standardized definition for depression, in the 2005 CF patient registry, 16% of adults were noted to have depressive symptoms. The extent to which depressive symptoms contribute to HRQoL in adults with CF is not known. A substantial body of literature across other chronic illnesses, including asthma, COPD, congestive heart failure, epilepsy, and diabetes, has suggested that depressive symptoms are associated with HRQoL and even predict HRQoL even independent of disease severity. Treating depression can improve depressive symptoms, health-related functioning, and HRQoL. Thus, the objective of this study was to evaluate the relationships among disease severity (ie, lung function), depressive symptoms, and HRQoL in adults with CF. We hypothesized that the presence of depressive symptoms would be associated with significantly worse HRQoL even after controlling for disease severity.

**Materials and Methods**

This was a cross-sectional study that was conducted from April 2002 to November 2003. Adults ≥ 18 years of age were eligible to be included if they had a confirmed diagnosis of CF, had been seen in the clinic previously, and were scheduled for an outpatient appointment. A recruiter telephoned the patient, explained the study, assessed eligibility, and obtained verbal consent to mail the study materials. Participants completed the questionnaires at home and mailed back the consent form and questionnaires. If the questionnaire was not returned, the recruiter telephoned to remind them to do so and to answer questions. If the questionnaires were still not returned, study materials were mailed once more, with no additional phone contact. Participants were compensated for their participation with a payment of $20. The study protocol was approved by the Western Institutional Review Board.

Lung function results (ie, FEV1 percent predicted) obtained closest to the date of survey completion were abstracted from the participants' medical record. Forty-five percent of participants had undergone a lung function test within ± 4 weeks of completing the survey, and almost all participants (97%) had undergone the test within ± 6 months. An FEV1 of ≥ 70% predicted indicated mild illness, an FEV1 of ≥ 40 to 69% predicted indicated moderate illness, and an FEV1 of < 40% predicted severe illness. FEV1 percent predicted has been shown to be a predictor of 2-year and 5-year survival.

Depressive symptoms were assessed using the Beck Depression Inventory (BDI). The BDI is one of the most widely accepted clinical instruments for assessing severity of depression. Scores can range from 0 to 63, with higher scores indicating greater depressive symptomatology. Scores of 0 to 9 are considered to be asymptomatic, with scores of 10 to 18 and 19+, respectively, indicating mild and moderate-to-severe levels of depressive symptoms. Participants with scores in the moderate-to-severe range, suggesting clinically significant levels of depressive symptoms, were called by the first author and were offered assistance to obtain further assessment and treatment.

HRQoL was assessed using the Cystic Fibrosis Questionnaire (CFQ) teen/adult version. The measure consists of the following 12 subscales: physical (eg, ability to perform physical activities); role (eg, work/school limitations); vitality (eg, tired/energetic); emotional state (eg, sad/lonely); social/marginalization (eg, “have to stay home more than wanted”); body image (eg, perception of physical appearance); eating disturbance (eg, “force self to eat”); treatment burden (eg, ease of incorporating regimen into life); perception of health (eg, “lead a normal life”); weight (“trouble gaining weight”); respiratory (eg, wheezing/coughing); and digestion (eg, gas/diarrhea). Scores range from 0 to 100, with higher scores indicating better HRQoL. All subscales have been shown to have adequate internal consistency and test-retest reliability, and have demonstrated good convergent and predictive validity.

Descriptive statistics employed means (SD), medians, and proportions. All CFQ subscales were negatively skewed with a high proportion of participants scoring at the upper limit. Because no transformation normalized the distributions, non-parametric statistics were used. Spearman rho was used to test the associations among depressive symptoms, lung function, and HRQoL. To examine whether disease severity was an effect modifier of the relationship between depressive symptoms and HRQoL, we stratified by FEV1 percent predicted severity categories. Similarly, we stratified by the presence or absence of depressive symptoms to examine whether it modified the relationship between lung function and HRQoL. To further test for the effect modification of lung function and depressive symptoms on HRQoL, we divided participants into the following four groups: group 1, good lung function (FEV1 ≥ 70% predicted)/low depression (BDI score, < 10); group 2, good lung function/high depression (BDI score, ≥ 10); group 3, poor lung function (FEV1 < 70% predicted)/low depression; and group 4, poor lung function/high depression. The Kruskal-Wallis test with Bonferroni correction (due to multiple comparisons) was employed for the initial bivariate analyses. Post hoc exploratory analyses were conducted to examine group differences using the Mann-Whitney U test. Results were reanalyzed using different cut points for lung function (median score) and other published recommendations for BDI cut points as well as removing somatic complaint items. The results were the same regardless of the
Participants

Demographic characteristics are presented in Table 1. FEV\textsubscript{1} ranged from 21% to 116% predicted, with a mean of 62.8% predicted (SD, 24.6% predicted); the majority of participants (62%) had an FEV\textsubscript{1} of < 70% predicted. Eighty-seven percent of participants were pancreatic insufficient, and CF-related diabetes was diagnosed in 26%. No participant had undergone a lung transplant. Based on chart review, 12 participants (15.8%) were currently being treated for depression; 11 participants were receiving therapy with antidepressants, and 1 participant was receiving counseling.

Depressive Symptoms

Thirty percent of participants screened positive for clinically significant levels of depressive symptoms (ie, BDI score ≥ 10); 15 participants (19.7%) scored in the mild range (BDI score, 10 to 18), while 8 participants (10.5%) had moderate-to-severe levels of depressive symptoms (BDI score ≥ 19). Four of the 12 participants being treated for depression had BDI scores < 10; 1 person receiving treatment had a BDI score ≥ 19. Depressive symptoms and FEV\textsubscript{1} percent predicted were inversely correlated (rho = -0.25; p < 0.05), with higher depressive symptoms being associated with poorer lung function. Participants with poor lung function (ie, FEV\textsubscript{1} < 70% predicted) had three times the odds (95% confidence interval, 1.0 to 9.2) of a positive screen for depressive symptoms (BDI score ≥ 10) than those with better lung function. (38% vs 17%, respectively; p = 0.05).

**FEV\textsubscript{1} Percent Predicted, Depressive Symptoms, and HRQoL**

All CFQ subscales were inversely correlated with depression scores (rho = −0.23 to −0.74). That is, higher depressive symptoms were associated with poorer HRQoL (Table 2). After stratifying by FEV\textsubscript{1} percent predicted, the association between depressive symptoms and CFQ subscales was maintained regardless of lung function status. Similarly, all CFQ subscales were positively correlated with FEV\textsubscript{1} percent predicted scores (rho = 0.32 to 0.57), except for the emotional state and digestion subscales, which were not significantly correlated. That is, better lung function was associated with better HRQoL. Interestingly, when participants were stratified by the presence or absence of depressive symptoms, the association between HRQoL and lung function was unchanged for patients with high levels of depressive symptoms. For participants without depressive symptoms, only the physical, health perceptions, and weight CFQ subscales were significantly correlated with lung function, as is shown in Table 2.

To further evaluate the relationship between lung function, depressive symptoms, and HRQoL, we conducted exploratory analyses by dividing participants into the following four groups: group 1, good lung function (FEV\textsubscript{1} ≥ 70% predicted)/low depression (BDI score < 10; n = 24); group 2, good lung function/high depression (n = 5); group 3, poor lung function/low depression (n = 29); and group 4, poor lung function/high depression (n = 18). The Kruskal-Wallis test with Bonferroni correction (p = 0.05; per 12 comparisons, p = 0.004) showed statistically significant group differences for all but the weight subscale. We were specifically interested in the post hoc comparison of groups 1 vs 3, 1 vs 4, and 3 vs 4. Group 2 was not included in the post hoc analyses because it included only five participants. The physical subscale was the only statistically significant difference between groups 1 and 3 (Mann-
Whitney U test = 233.0; p < 0.05) [Fig 1]. Thus, in the absence of depressive symptoms, poor lung function had relatively little association with HRQoL compared with good lung function, except in physical functioning. Surprisingly, there was no statistical difference in scores on the respiratory subscale
(Mann-Whitney U test = 276.0; p = 0.20). In contrast, participants with both poor lung function and depressive symptoms (group 4) had significantly poorer HRQoL on all subscales relative to the participants in group 1 (p < 0.01). Similar results were found when comparing participants with poor lung function with and without depressive symptoms (groups 3 and 4). Those participants with depressive symptoms had statistically significantly lower HRQoL scores on all CFQ subscales than those participants without depressive symptoms (p < 0.01) [Fig 1].

**Discussion**

Consistent with previous studies, our study found that depressive symptoms are common among adults with CF, with 30% of participants exhibiting signs of depressive symptoms and 11% of participants screening positive for moderate-to-severe levels of depression. Only 13% of those participants who screened positively for moderate-to-severe levels of depressive symptoms were currently receiving treatment, suggesting that depression may be under-diagnosed and untreated in this population. Although individuals with poor lung function were three times as likely to exhibit depressive symptoms, overall, most of the persons in our sample who were in poor physical health were not depressed.

Fewer depressive symptoms and higher lung function were associated with better HRQoL, with the association between depressive symptoms and HRQoL remaining even after controlling for disease severity. Similarly, in the absence of depressive symptoms, those with good lung function reported better physical HRQoL than those with poor lung function; however, this relationship was not as strong for the other CFQ subscales. In contrast, participants with both depressive symptoms and poor lung function reported significantly worse HRQoL than participants without depressive symptoms, regardless of their lung function status. These results suggest that poor lung function alone does not necessarily lead to poorer HRQoL. Within individuals with poor lung function, however, the presence of depressive symptoms is associated with a dramatically lower HRQoL across all domains, suggesting a synergistic effect between depressive symptoms and lung function.

Our findings of poorer HRQoL in depressed participants have been reported in cross-sectional and prospective studies of patients with other chronic illnesses. Although as yet there are no CF-specific data, in patients with other chronic illnesses, depression is a risk factor for poor adherence to therapy, increased mortality, increased health-care utilization, and increased health-care costs. While the assessment and treatment of depression is in itself important, depressive symptoms appear to serve as an important prognostic indicator and therefore should be considered an important component of medical care. Research is needed to evaluate whether depression is also associated with these poorer health outcomes in persons with CF.

Pharmacotherapy and psychotherapy are effective treatments, particular when used in combination, for treating depression in the general population. Further, depression therapies are safe and effective in reducing depressive symptoms in chronically ill patients. Some studies have found that treating depression in patients with chronic illnesses results in reduced morbidity and mortality, but others have not shown that treating depression influences health outcomes. However, nonresponse to depression treatment may be a risk factor for mortality. Studies are needed to evaluate the effect of treating depressive symptoms in CF patients. Some side effects of pharmacotherapy may be particularly contraindicated or beneficial for patients with CF, such as the loss of appetite and anorexia or weight gain that can accompany the use of some antidepressants. Until CF-specific data are available, decisions about the type of depression therapy should take into consideration potential drug interactions, tolerability of therapy, and patient preferences.

Approximately 85% of patients with CF in the United States are treated at centers accredited by the Cystic Fibrosis Foundation. Medical data from these patients are included in the national Cystic Fibrosis Foundation Patient Registry, which includes a single check-box variable to indicate the presence or absence of depression without providing a standardized definition. To date, there has been no guidance provided to centers regarding whether, when, or how to assess for depression or which member of the health-care team is responsible for making the diagnosis, and this has resulted in great variability across CF centers in the proportion of patients classified as being depressed. This study indicates the need to systematically and effectively screen for depression, since it would increase the identification of patients who may benefit from treatment. There are several brief, validated depression screening measures (eg, BDI, Centers for Epidemiologic Studies Depression Scale, and the Hospital Anxiety and Depression Scale) that can be integrated into standard practice. Recently, an international effort has been coordinated through North American CF and European CF conferences to...
increase depression screening by developing a standardized assessment protocol, using the Hospital Anxiety and Depression Scale, with the results entered into the patient registry. Together, these data will enhance our understanding of not only the prevalence of depressive symptoms, but also the influence of depression on CF morbidity and mortality.

Our participants had mean HRQoL scores that were similar to those found in other studies using the CFQ. Similarly, correlations between FEV1 percent predicted scores and CFQ subscales were of comparable or larger magnitude than those found in previous CF research, suggesting that our sample is reasonably representative of adults with CF. However, there are several limitations to this study. Data on lung function obtained from medical charts differed from the date of survey completion by >1 month for 55% of the sample. Thus, the stronger relationship between depression and HRQoL could be due to the temporal relationship between the measures. To address this concern, all analyses were rerun stratifying for those persons who had undergone pulmonary function testing within 4 weeks of completing the survey or >4 weeks after completing the survey. Both groups showed similar patterns of results (data not shown), suggesting that the timing of the assessments was not a significant confounder of our results. Nevertheless, a concurrent assessment of all variables of interest is needed to fully address these concerns.

Our participants represented 57% of eligible patients from a single CF center. We were unable to assess whether nonparticipants differed from participants in terms of the variables of interest. Because study attrition is higher among depressed patients, our prevalence estimates for depression may be conservative. The cross-sectional nature of this study limits our conclusions; the assessment of psychosocial factors over time would allow inferences about the causal relationships among lung function, depression, and HRQoL. For example, does a decrease in lung function lead to increased depression or does depression precede a loss of lung function and HRQoL? Additionally, although the BDI is one of the most widely used and rigorously validated methods of assessing depressive symptoms in other illnesses including diabetes and HIV, its use has not been validated in a CF population. Thus, the use of conventional cut points may result in some misclassification of depression. Similarly, some researchers have suggested that somatic items be excluded from the measure for more reliable results in chronic illness patients. We analyzed our data using multiple cut points and without the somatic items, and found equivalent results. We chose to use a BDI score ≥ 10 because scores < 10 are indicative of no or minimal depression. Prior research in patients with other chronic illnesses has suggested that even minimal symptoms of depression in absence of a formal diagnosis may have prognostic value, and our data suggest that this may be true for adults with CF. Research in persons with CF is needed to confirm the validity of the cut points in this population. Moreover, we did not determine which participants qualified for a diagnosis of major depression; this is an important next step. Finally, we only measured one marker of CF disease severity; additional studies incorporating other measures (eg, number of exacerbations and nutritional status) are needed.

Our results suggest that depressive symptoms are prevalent among adults with CF and are significantly associated with impairments in HRQoL, even after controlling for disease severity. Our data are consistent with the growing body of studies in the literature that have suggested that depression is a significant risk factor for poor health outcomes among individuals with chronic illnesses. Because depression is treatable, our results suggest that periodic screening is appropriate and may potentially improve the HRQoL for persons with CF.

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