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Title Pulmonary function, symptoms, and quality of life in cystic fibrosis: a cross-sectional analysis of the InSPIRe:CF trial

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Pulmonary function, symptoms, and quality of life in cystic fibrosis: a cross-sectional analysis of the InSPIRe:CF trial

By

Natalia Smirnova, M.D., University of North Carolina – Chapel Hill, 2017

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An abstract of
A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research
2024

Abstract

Pulmonary function, symptoms, and quality of life in cystic fibrosis:
a cross-sectional analysis of the InSPIRe:CF trial

By
Natalia Smirnova

Background: People living with cystic fibrosis (CF) experience a high symptom burden. Due to the changing landscape of CF in the era of modulator therapy, we sought to examine the epidemiology of symptoms and the association between pulmonary function, symptoms, and quality of life.

Methods: Using baseline data from a trial of specialist palliative care in adults with CF, we conducted a cross-sectional study on symptom prevalence and distress. We then examined association between pulmonary function and quality of life (measured with the Functional Assessment of Chronic Illness Therapy Total Score), as well as between individual symptoms and quality of life.

Results: Among 262 participants, median age was 33, and 78% were on modulator therapy. The most common symptoms were lack of energy (n = 194, 74%) and cough (190, 73%), whereas the most distressing were difficulty sleeping (range 0-4, mean 2.19, SD 1.15) and pain (mean 2.04, SD 1.1). In an unadjusted model, we observed a non-significant trend toward lower quality of life with worse pulmonary obstruction—compared to participants with mild obstruction, those with moderate obstruction had quality of life score 7.46 points lower (95% CI -15.03 to 0.10) and those with severe obstruction had a score 9.98 points lower (95% CI -21.76 to 1.80). However, this association was no longer statistically significant in the adjusted model, which may reflect confounding due to sex, age, BMI, and modulator therapy. The symptoms that impaired quality of life the most were extrapulmonary: lack of energy (average quality of life score -29.8, 95% CI -36.8 to -22.8), feeling sad (-29.8, 95% CI -35.6 to -23.9) and worrying (-28.7, 95% CI -34.9 to -22.5).

Conclusions: There was no statistically significant association between pulmonary function and quality of life. The symptoms that were associated with the lowest quality of life were extrapulmonary. CF clinicians may consider screening for common symptoms that affect quality of life the most (lack of energy, worrying, difficulty sleeping, feeling irritable, pain, and shortness of breath). These symptoms may identify people living with CF who are most at risk for a decreased quality of life and may benefit from additional support.

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Table of Contents

Introduction

Cystic fibrosis (CF) is a genetic disease affecting more than 160,000 individuals worldwide.[1] People living with CF often report a high symptom burden comprised of physical (e.g., cough, dyspnea), psychosocial (e.g., depression, anxiety) and existential (e.g., fear of dying) symptoms.[2-5] Advances in CF care such as highly effective modulator therapy, improved airway clearance therapies, nutritional support, and lung transplantation are projected to add decades to the lives of people with CF, with a median predicted survival of 56 years.[6,7] Given these increases in life expectancy, people living with CF may experience a longer duration of CF-related symptoms,[8] as well as extrapulmonary complications of aging, such as CF-related diabetes, obesity, osteoporosis, and cancer. [9-11] These complications may cause extrapulmonary symptoms and render traditional pulmonary- and gastrointestinal-focused strategies for managing CF symptoms inadequate.

Since people with CF are now living with an impaired quality of life for longer than ever and have more extrapulmonary symptoms as they age, it is crucial to examine the CF symptom experience in the era of highly effective modulator therapy. Identifying factors that are associated with a decreased quality of life will help identify people with CF who may benefit from additional screening and support. Focusing on feasibly ascertainable factors that CF clinicians already check for during clinic visits, such as pulmonary function tests and symptoms, may help improve quality of life in this patient population without worsening clinician time constrains and patients' treatment burden.

The extent to which pulmonary function tests (PFTs) such as forced expiratory volume in one second (FEV1) are associated with subjective, patient-centered outcomes such as quality of life in CF remains poorly understood, with prior studies demonstrating conflicting results regarding the association between FEV1 and quality of life.[12,13] Prior studies examining the association between FEV1 and quality of life had substantial limitations in that they were conducted at a single center,[12,13] included small participant numbers,[13] or were conducted in the setting of a CF exacerbation.[14-16] However, FEV1 is typically measured at every clinic visit and is used to guide decisions that affect patients' quality of life such as CF treatments, clinical trial enrollment, and transplant referral.[17,18] Additionally, while highly effective modulator therapy improves lung function,[19] CF has many non-pulmonary manifestations such as pancreatitis, pain, and constipation that may worsen quality of life independently from lung function.[20]

Symptoms may be an additional, patient-centered way to identify people living with CF with a decreased quality of life. Prior studies examining the epidemiology of symptoms are limited and were conducted prior to the widespread use of modulator therapy.[2,21] Additionally, while previous studies have found associations between a few symptoms (depression, anxiety, and pain) and decreased quality of life, the impact of a variety of symptoms on quality of life in CF remains unknown.[22,23]

Basic symptom screening in CF clinics is recommended by the Cystic Fibrosis Foundation (CFF),[24] yet CF clinicians report not having enough time or resources to address their patients' symptoms in clinic.[25] Therefore, understanding which symptoms are most prevalent, most distressing, and most strongly associated with quality of life may help streamline the symptom

screening process and help identify individuals who may need more intensive follow-up or those who would benefit from additional support to improve their quality of life.

In this study, we sought to examine the CF disease experience in the era of modulator therapy by (1) describing symptom prevalence and associated distress, (2) assessing the association between pulmonary function and quality of life, and (3) assessing the association between individual symptoms and quality of life using data from a multi-center trial of specialist palliative care in adults with CF.[26] The findings of this study will leverage existing CF clinic resources to help identify individuals who need may more intensive follow-up, those at greater risk for poor long-term outcomes, or those who would benefit from additional support or interventions to improve their quality of life, in order to improve the whole-person experience of living with CF.

Methods

Study overview

We evaluated baseline data from the "Integrating specialist palliative care to improve care and reduce suffering: cystic fibrosis" (InSPIRe:CF), a five-site randomized clinical trial comparing usual care provided by a CF clinic team versus usual care plus outpatient longitudinal specialist palliative care.[26] The study was approved by Emory University Institutional Review Board (STUDY00000071), which served as the coordinating IRB for all U.S. sites, and the UnityHealth Toronto Research Ethics Board (ISRCTN53323164).

Study population

Adults age ≥18 years with CF were eligible if they had: ≥2 CF-related hospitalizations in the past year and/or ≥1 moderate or severe symptom captured by the Integrated Palliative Outcomes

Scale (IPOS).[27] Participants were recruited from CF clinics at five academic medical centers in North America: Emory University (Atlanta, Georgia, USA), University of North Carolina at Chapel Hill (Chapel Hill, North Carolina, USA), University of California San Diego (San Diego, California, USA), University of Alabama at Birmingham (Birmingham, Alabama, USA), and St. Michael's Hospital (Toronto, Ontario, Canada). Exclusion criteria included CF transmembrane conductance regulator-related disorder, lack of reliable telephone or internet access, pregnancy, active suicidal ideation, lack of decision-making capacity, receipt of specialist palliative care in the 12 prior to enrollment months, or intent to transfer primary CF care elsewhere in the next year. In addition, adults with CF who received a lung transplant were excluded because post-transplant care is often centered in transplant clinics rather than CF care centers. Additional details regarding recruitment and enrollment have been published previously.[26]

Primary exposures by aim

The primary exposure for aims 1 and 3 was symptoms assessed with the Memorial Symptoms Assessment Scale–CF (MSAS-CF).[2] The MSAS-CF comprises 22 symptoms that participants were asked to endorse ("yes" or "no"). If a symptom was present, participants rated the symptom in terms of frequency (from 1 "rarely" to 4 "almost constantly"), severity (from 1 "slight" to 4 "very severe"), and associated distress (from 0 "not at all" to 4 "very much"). Since this analysis focuses on practical ways to improve symptom screening in CF, we selected the most prevalent symptoms, using a natural prevalence cut point of 30% or above, resulting in 14 symptoms included in the analysis. We compared symptom prevalence and distress, as prior studies have suggested that the presence of a symptom does not always correlate with distress.[21]

The primary exposure for aim 2 was airflow obstruction (categorized as FEV1 >70=mild, 40-70=moderate, or <40=severe obstruction), obtained from spirometry results from chart review. The highest FEV1 in the 12 months prior to enrollment was selected to avoid capturing transiently lower FEV1 values during pulmonary exacerbations.

Primary outcome

The primary outcome for aims 2 and 3 was quality of life, measured with the Functional Assessment of Chronic Illness Therapy (FACIT-Pal) Total Score Outcome Index (0-184 score, higher score indicating better quality of life). FACIT-Pal comprises 46 items that evaluate overall quality of life.[28] It contains the following subscales: physical, social, emotional, functional, and a palliative subscale measuring factors particularly salient to individuals living with serious illness, such as symptoms, relationships (e.g., being a burden to family), existential issues (e.g., having "made peace" with others), and decision-making and communication abilities.[28] Although the minimal clinically important difference (MCID) for the FACIT-Pal is unknown, prior literature suggests that MCIDs for total Functional Assessment of Cancer Therapy (FACT) scores, including the FACIT-Pal, are 4% to 6% of a measure's overall score.[29] A midrange change of 5% (9 points) was therefore considered to be meaningful.

Covariates

Additional demographic and clinical information obtained from chart review and questionnaires included age, sex, race, ethnicity, body mass index (BMI), use of highly effective modulator therapy, financial security, and education. Medical comorbidities (CF-related diabetes, depression, and anxiety) were obtained from chart review using *International Statistical Classification of Diseases (ICD)-10* codes.

Statistical analysis

Descriptive statistics were reported for baseline demographic and clinical characteristics for study participants.

In aim 1, proportions of participants reporting each of the 14 most prevalent symptoms on the MSAS-CF were reported as percentages. In addition, we calculated the mean and standard deviation for symptom distress scores.

In aim 2, we assessed associations between demographic and clinical characteristics with airflow obstruction using Kruskal-Wallis tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Linear regression was used to examine the association between airflow obstruction and quality of life, with adjustment for highly effective modulator therapy, BMI, sex, and age, as these variables have been found to be independently associated with both FEV1 and Quality of life.[19,30-32] We performed sensitivity analyses to determine the robustness of results if we analyzed FEV1 as a continuous variable.

In aim 3, linear regression models were used to examine the association between the presence of each individual symptom and quality of life. Adjusted model one included highly effective modulator therapy and age, whereas adjusted model two included highly effective modulator therapy, age, pulmonary function (FEV1) and BMI. We performed subgroup analyses examining the association between the presence of each individual symptom and quality of life stratified by the presence or absence of depression, anxiety, and modulator use.

A 2-sided P-value < 0.05 was considered statistically significant for aim 2. For aim 3, as we considered 14 symptoms, we used Bonferroni correction for multiple comparisons and established an adjusted 2-sided alpha of $p < 0.004$. All analyses were performed using SAS 9.4.

Results

Of 1,731 potential participants, 321 were eligible, 536 were not contacted and 874 were excluded (Figure 1). Three additional participants were randomized but withdrew prior to completing the baseline visit and questionnaires. Among the 262 participants with complete baseline visit information and included in this analysis, median age was 33 (IQR 26-44), median FEV1 was 70% predicted (IQR 47-87%), 78% were on modulator therapy and the mean FACIT-Pal quality of life score was 130 (SD 29).

Comorbid diagnoses of anxiety (42%) and depression (39%) were common (see Table 1 for full baseline characteristics). Participants with a depression diagnosis had significantly lower quality of life scores (mean FACIT-Pal score 121, standard deviation 29) than those without depression (mean 135, SD 27), p-value <0.001. Participants with an anxiety diagnosis had significantly lower quality of life scores (mean 120, standard deviation 27) than those without anxiety (mean 137, SD 28), p-value <0.001. There was a strong positive association between depression and anxiety ICD diagnoses (Phi coefficient 0.60).

Aim 1

The most common symptoms included lack of energy (n = 194, 74%) and cough (190, 73%). The most distressing symptoms were difficulty sleeping (mean 2.19, SD 1.15) and pain (mean 2.04, SD 1.1) (Figure 2).

Aim 2

Compared to participants with moderate/severe obstruction, those with mild obstruction were younger (median 31 years vs. 37), had a higher BMI (median 23 vs. 22 kg/m^2), were less often

on home oxygen (0% vs. 5%), and less often referred for lung transplant (0% vs. 4%) (all p-values <0.05, Table 2).

Overall, the median quality of life score was 130 (IQR 109-151). Reduced quality of life was associated with the presence of financial insecurity (median 96 vs 133), lack of college education (122 vs 135), lack of modulator therapy use (121 vs 135), depression (119 vs 135) and anxiety (119 vs 140) (all p-values <0.05, Table 3).

The median quality of life score was higher in those with mild obstruction (135, IQR 110-156) compared to moderate (125, IQR 109-146) and severe obstruction (120, IQR 106-136) (p = 0.03). In an unadjusted model, we observed a non-significant trend toward lower quality of life with increased obstruction—compared to participants with mild obstruction, those with moderate obstruction had quality of life score 7.46 points lower (95% CI -15.03 to 0.10) and those with severe obstruction had a score 9.98 points lower (95% CI -21.76 to 1.80). In a multivariable model adjusted for age, sex, modulator therapy and BMI, participants with moderate obstruction had a quality of life score 4.69 points lower (95% CI -12.05 to 3.51, p = 0.28) and those with severe obstruction had a score 6.52 points lower (95% CI -18.60 to 5.56, p = 0.28), compared to participants with mild obstruction (Table 4). In a sensitivity analysis with FEV1 as a continuous variable, for every percent increase in FEV1, there was a 0.18 (95% CI 0.04 to 0.33, p = 0.01) increase in quality of life score. This association was not statistically significant after adjusting for age, sex, modulator therapy and BMI.

Aim 3

The symptoms that were associated with the lowest quality of life were extrapulmonary: lack of energy, feeling sad, worrying, feeling irritable, and pain. In an unadjusted model, participants who lacked energy had quality of life scores that were 31.10 points lower on average (95% CI -38.19 to -24.01) than those who did not lack energy. Participants who reported feeling sad had mean quality of life scores that were 30.67 lower (95% CI -36.61 to -24.72), and those who reported worrying had quality of life scores that were 28.63 lower (95% CI -34.93 to -22.32) compared to participants who did not report these symptoms. All symptoms except for sinus discharge and diarrhea were associated with a decreased quality of life score. These associations were both statistically significant and clinically significant, as the differences were larger than the MCID for the FACIT-Pal quality of life scale (9 points). These associations remained statistically and clinically significant in the adjusted models (Table 5). In a stratified analysis, there were no statistically significant differences in the strength of the association between symptoms and quality of life among participants on or off modulator therapy, those with and without a depression diagnosis, and those with or without an anxiety diagnosis (Tables 6, 7, and 8).

When comparing symptom prevalence and the association of symptoms and quality of life, the most prevalent symptoms that were also associated with the largest decrease in quality of life scores included lack of energy, worrying, shortness of breath, difficulty sleeping, and feeling irritable. Pain, while less prevalent, was also strongly associated with a worse quality of life (Table 9).

Discussion

In this sample of 262 adults with CF, we found an association between reduced pulmonary obstruction and reduced quality of life. However, this association was no longer statistically significant in the adjusted model, which may reflect confounding due to sex, age, BMI, and highly effective modulator therapy.

The symptoms that caused the most distress (difficulty sleeping, pain, lack of energy, and difficulty concentrating) and the highest impairment in quality of life (lack of energy, feeling sad, and worrying) were all extrapulmonary. The participants in this sample had a substantial symptom burden, consistent with previous studies of adults with CF.[2,3,33] The symptoms that caused the most distress and the greatest impairment in quality of life were neither pulmonary-, gastrointestinal-, nor nutrition-related. These findings may reflect changes in the impact of symptoms on quality of life in this patient population in the era of highly effective modulator therapy. There are several potential explanations for this change. Given the historical focus on CF as a pulmonary and gastrointestinal disease, perhaps people living with CF expect to experience these symptoms and are therefore not as bothered by them. While pulmonary symptoms have improved on modulator therapy, other symptoms (pain, fatigue, irritability, worrying) may not have improved as much.[19,34] The relief of pulmonary symptoms may therefore have unmasked the presence of other bothersome symptoms that are associated with a decreased quality of life.

Since people living with CF get most of their medical care from pulmonary clinicians, the findings of this study highlight the importance of looking beyond pulmonary function and

symptoms and in CF clinic. Pulmonary clinical training may not provide sufficient skills to address the extrapulmonary symptoms that impair quality of life in CF, and time for symptom screening and management in CF clinic is limited.[25,35] However, prioritizing screening for six common symptoms that impair quality of life the most (lack of energy, worrying, feeling sad, feeling irritable, pain, and shortness of breath) may allow CF clinicians to be more efficient in performing basic symptom screening in CF clinic. Additionally, the fact that the most prevalent symptoms that were strongly associated with decreased quality of life were psychosocial (lack of energy, feeling sad, worrying, and feeling irritable) suggests that psychosocial support may be of particular benefit to improve quality of life in this patient population. Notably, most of these symptoms (except for pain) would be addressed by depression and anxiety screening. These findings are consistent with the CFF and the European Cystic Fibrosis Society (ECFS) guidelines recommending annual depression and anxiety screening for people living with CF, and the integration of mental health clinicians into CF clinics.[5]

While previous studies examined the association between depression, anxiety and pain with quality of life in CF,[22,23] to our knowledge this study is the first to analyze the relationship between a broad range of symptoms and quality of life in this patient population. Overall, we found a strong association between 12 common CF symptoms and decreased quality of life. These associations remained statistically significant after adjusting for modulator therapy use and age. While many quality of life instruments, including the FACIT-Pal, include physical and emotional symptoms, the fact that certain symptoms had a much stronger association with quality of life than others provides valuable information about prioritizing screening for these symptoms in CF clinic.

The strengths of this study include a multi-center design and a large sample of participants recruited from diverse CF clinics. Based on the 2022 CFF patient registry, the median age of the population in our study is approximately 11 years older than the general CF population (33 to 21.9). This makes our work even more relevant, as the CF population is getting older in the era of modulator therapy, with an increased life expectancy.[11] Using a single measurement of FEV1, rather than looking at other pulmonary function tests or FEV1 over time, is a limitation, although FEV1 is the most used pulmonary function test to capture disease progression and evaluate therapeutic efficacy.[17] The use of the MSAS-CF scale, as was done in previous studies of symptom prevalence and distress in CF, allows for direct comparisons with previous literature on this subject.[2,21] Although not specifically validated in CF, the FACIT-Pal is one of the most widely utilized quality of life instruments in palliative care trials across different disease states.[28] Focusing on the 14 most prevalent symptoms instead of all 22 symptoms in the MSAS-CF may have caused us to overlook some less prevalent symptoms that are strongly associated with quality of life. However, the purpose of this study was to identify common, distressing symptoms in CF clinic. Selecting participants with a high symptom burden allowed us to examine various symptoms and their association with quality of life. There is variability in how depression and anxiety ICD-10 codes are recorded in the chart, leading to either over- or -under-diagnosis of these comorbidities based on chart review alone. However, a stratified analysis of participants with and without depression and anxiety comorbidities did not show statistically significant differences in the association between symptoms and quality of life in our study. The cross-sectional nature of this analysis limits our ability to examine causation. Since quality of life is a composite measure, one challenge in quality of life research is the overlap

between different dimensions of quality of life (including symptoms) and quality of life itself. Nonetheless, the fact that certain symptoms were much more strongly associated with quality of life than others may help clinicians decide which symptoms to prioritize screening for. One additional limitation was the focus on individual symptoms, which limits our ability to assess the synergistic impact of multiple symptoms on quality of life. Future analyses are needed to explore the association between symptom clusters (two or more concurrent symptoms that are stable over time and are linked by an underlying mechanism[36]) and quality of life.

In this study of people living with CF with a heavy symptom burden despite high modulator therapy use, we sought to identify easily ascertainable factors that impair quality of life to help CF clinicians identify patients at risk for decreased quality of life without worsening clinic time constraints. Focusing on pulmonary function and symptoms, as has been routinely done in CF clinical practice, may cause clinicians to overlook other factors that affect quality of life. Based on our findings, screening for prevalent symptoms that affect quality of life the most (lack of energy, worrying, feeling sad, feeling irritable, and shortness of breath) and a less common symptom that is also strongly associated with decreased quality of life (pain) could help identify people living with CF who are most at risk for a decreased quality of life and may benefit from additional support. Advancing our understanding of patient-centered markers of quality of life is the first step to help identify novel interventions to improve quality of life in this patient population, so that adults with CF who are now living longer in the era of highly effective modulator therapy can also live better.

Figure 1. CONSORT diagram.

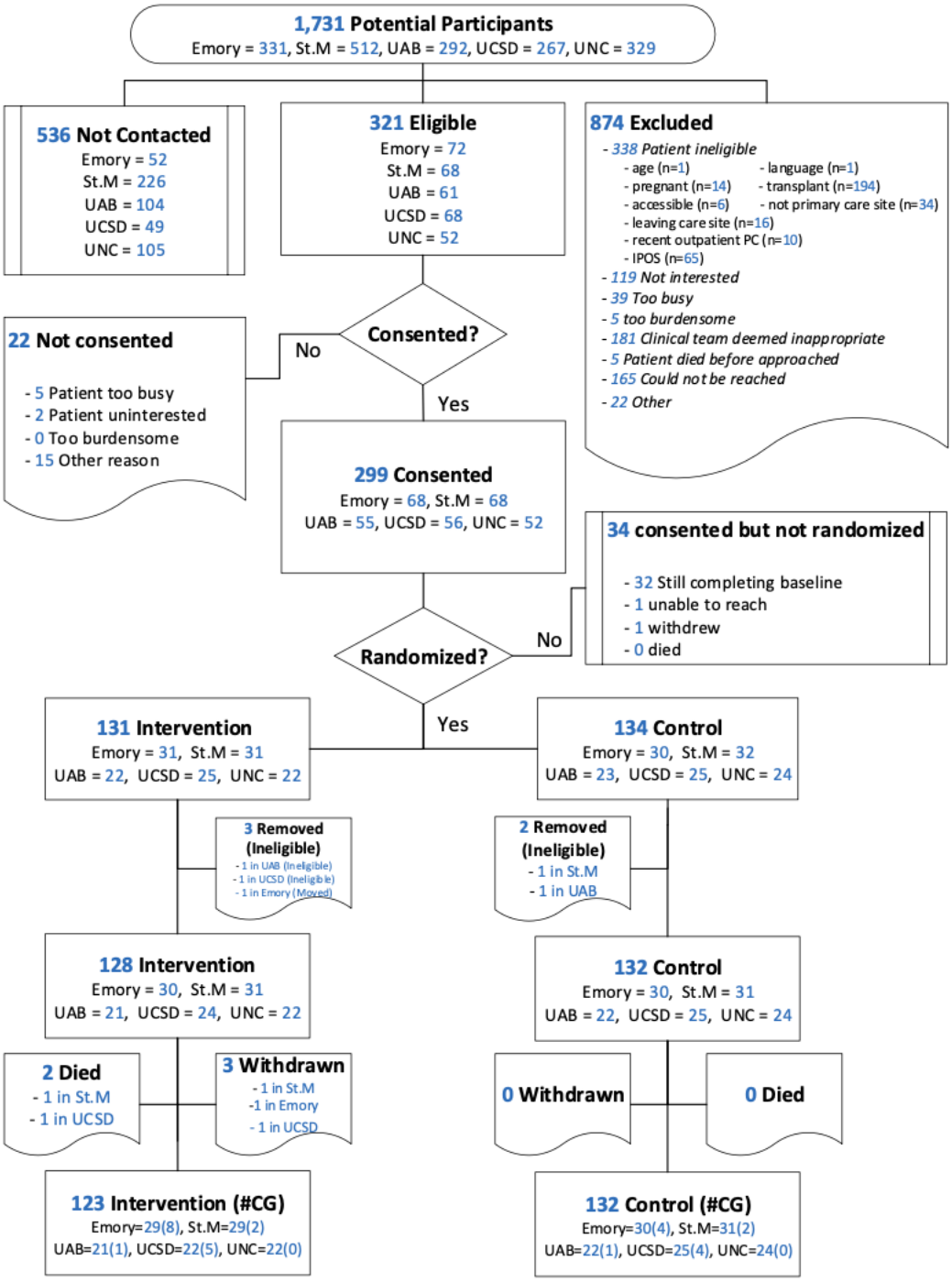
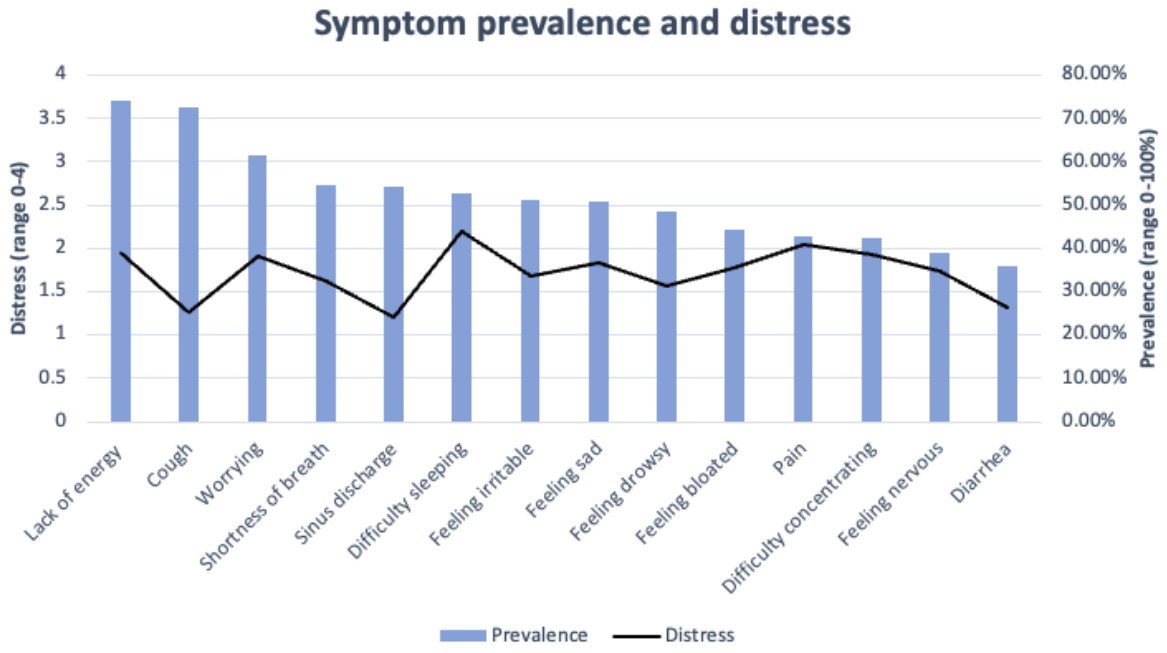


Table 1. Baseline characteristics of participants

Participant Characteristics	**n (%)** **N=262**
Age, years, Median (IQR)	33 (26-43)
Male sex (n, %)	110 (42%)
White Race (n, %)	235 (90%)
Latinx Ethnicity (n, %)	15 (6%)
Financial insecurity (n, %)	18 (7%)
College education (n, %)	155 (59%)
FEV1, % predicted, Median (IQR)	70 (47-87)
Body Mass Index (BMI), kg/m2, Median (IQR)	23.4 (21.2-27.0)
On highly effective modulator therapy (n, %)	205 (78%)
Home oxygen use	13 (5%)
Referral to lung transplant clinic	9 (3%)
CF-related diabetes	100 (38%)
Depression	102 (39%)
Anxiety	109 (42%)
Quality of life (Functional Assessment of Chronic Illness Therapy-Palliative Care Score), Mean (SD)	130 (29)

Abbreviations: IQR, interquartile range

Figure 2. Symptom prevalence and distress among adults with CF.



Symptoms were measured using the Memorial Symptom Assessment Scale-Cystic fibrosis (MSAS-CF) scale. Mean symptom distress scores are represented by a line, with scores (range 0-4) displayed on the left y-axis. Symptom prevalence is represented by vertical bars, with proportions (range 0-100%) displayed on the right y-axis.

Table 2. Baseline characteristics of participants by degree of obstruction

Participant Characteristics	**Mild obstruction n = 146**	**Moderate obstruction n = 89**	**Severe obstruction n = 27**	**Total N=262**	**p-value for difference between mild obstruction and moderate/severe obstruction**
Demographics					
Age, years, Median (IQR)	31 (25-37)	37 (27-44)	41 (34-50)	33 (26-43)	<0.01*
Male sex (n, %)	66 (46%)	34 (38%)	10 (37%)	110 (42%)	0.24
White Race (n, %)	134 (92%)	79 (89%)	22 (81%)	235 (90%)	0.21
Latinx Ethnicity (n, %)	8 (6%)	6 (7%)	1 (4%)	15 (6%)	0.85
Financial insecurity (n, %)	9 (7%)	6 (7%)	3 (11%)	18 (7%)	0.61
College education (n, %)	89 (61%)	55 (62%)	11 (41%)	155 (59%)	0.46
Clinical characteristics					
FEV1, % predicted, Median (IQR)	88 (79-101)	53 (46-62)	35 (31-37)	70 (47-87)	<0.01*
Body Mass Index (BMI), kg/m2, Median (IQR)	24.4 (21.9-27.3)	22.7 (20.7-25.5)	22.0(19.7-24.3)	23.4 (21.2-27.0)	0.01*
On highly effective modulator therapy (n, %)	115 (79%)	69 (78%)	21 (78%)	205 (78%)	0.82
Home oxygen use	0	6 (7%)	7 (26%)	13 (5%)	<0.01*
Referral to lung transplant clinic	0	4 (5%)	5 (24%)	9 (3%)	<0.01*
CF-related diabetes	55 (38%)	35 (39%)	10 (38%)	100 (38%)	0.81
Depression	54 (37%)	37 (42%)	11 (41%)	102 (39%)	0.47
Anxiety	63 (43%)	36 (40%)	10 (37%)	109 (42%)	0.57

Abbreviations: IQR, interquartile range

Mild obstruction FEV1 >70%, moderate obstruction FEV1 40-70%, severe obstruction FEV1 <40%

An asterisk (*) in the data table indicates a p value <0.05

** Kruskal-Wallis tests for continuous variables, chi-square and Fisher's exact tests for categorical comparisons

Table 3. Differences in Functional Assessment of Chronic Illness Therapy (FACIT-Pal) quality of life score by patient characteristics among adults with cystic fibrosis

Participant Characteristics	**Quality of life score (median, IQR)**	**P-value for differences in quality of life score****
Total cohort	130 (109-151)	
Pulmonary obstruction		
Mild (FEV1 >70%)	135 (110-156)	
Moderate (FEV1 40-70%)	125 (109-146)	
Severe (FEV1 <40%)	120 (106-136)	0.03
Demographic		
Younger (<50th percentile)	135 (113-156)	0.05
Older (>50th percentile)	126 (107-146)	
Male sex	134 (113-152)	0.29
Female sex	128 (108-150)	
White Race	132 (109-152)	0.26
Non-White race	119 (110-141)	
Latinx Ethnicity	151 (129-159)	0.03*
Non-Latinx Ethnicity	128 (108-150)	
Financial insecurity	96 (80-115)	<0.01*
Financial security	133 (113-152)	
College education	135 (113-155)	0.04*
No college education	122 (104-147)	
Clinical		
Body Mass Index (BMI) <18.5	119 (113-123)	0.15
BMI >=18.5	132 (110-151)	
On highly effective modulator therapy	135 (110-154)	0.08*
Not on highly effective modulator therapy	121 (107-135)	
Referral to lung transplant clinic	123 (84-138)	0.19
Not referred to lung transplant clinic	132 (110-152)	
Depression	119 (103-140)	<0.01*
No depression	135 (115-157)	
Anxiety	119 (102-138)	<0.01*
No anxiety	140 (116-158)	

Abbreviations: IQR, interquartile range

FACIT-Pal quality of life score: range 0-184, higher values indicate better quality of life

* Indicates a p value <0.05

** Kruskal-Wallis test used

Table 4. Multivariate linear regression model of forced expiratory volume in one second (FEV1) and quality of life among adults with cystic fibrosis

Obstruction	**Linear regression coefficient, unadjusted model**	**Linear regression coefficient, adjusted model 1**	**Linear regression coefficient, adjusted model 2**
Mild (FEV1 >70%)	Reference	Reference	Reference
Moderate (FEV1 40-70%)	-7.46 (95% CI -15.03 to 0.10)	-4.57 (95% CI -12.32 to 3.17)	-4.72 (95% CI -12.39 to 2.95)
Severe (FEV1 <40%)	- 9.98 (95% CI -21.76 to 1.80)	-5.25 (95% CI -17.36 to 6.87)	-5.59 (95% CI -17.60 to 6.40)
FEV1 as a continuous variable	0.18 (95% CI 0.04 to 0.33)*	0.11 (95% CI -0.04 to 0.26)	0.11 (-0.04 to 0.26)

An asterisk (*) in the data table indicates a p value <0.05
Adjusted model 1 included the following covariates: age, BMI, and sex
Adjusted model 2 included the following covariates: age, BMI, sex, and highly effective modulator therapy

Table 5. Multivariate linear regression model of individual symptoms and quality of life among adults with cystic fibrosis

Symptom	Linear regression coefficient, unadjusted model	95% CI	Linear regression coefficient, adjusted model 1*	95% CI	p-value	Linear regression coefficient, adjusted model 2**	95% CI	p-value
Lack of energy	-31.10	-38.19, -24.01	-29.79	-36.83, -22.75	<.0001	-29.81	-35.65, -23.96	<.0001
Feeling sad	-30.67	-36.61, -24.72	-29.75	-35.64, -23.87	<.0001	-29.38	-36.40, -22.36	<.0001
Worrying	-28.63	-34.93, -22.32	-28.70	-34.86, -22.54	<.0001	-29.21	-35.32, -23.10	<.0001
Feeling irritable	-26.81	-33.03, -20.59	-25.89	-32.03, -19.75	<.0001	-25.27	-31.43, -19.11	<.0001
Pain	-25.86	-32.21, -19.50	-24.12	-30.42, -17.82	<.0001	-24.45	-31.14, -17.76	<.0001
Shortness of breath	-24.73	-31.11, -18.35	-24.47	-30.83, -18.12	<.0001	-24.25	-30.57, -17.93	<.0001
Feeling nervous	-20.94	-27.68, -14.20	-20.64	-27.11, -14.16	<.0001	-21.85	-28.42, -15.28	<.0001
Difficulty sleeping	-21.86	-28.37, -15.35	-21.29	-27.89, -14.70	<.0001	-21.27	-27.67, -14.87	<.0001
Difficulty concentrating	-17.73	-24.51, -10.96	-13.77	-21.45, -6.10	<.0001	-18.57	-25.16, -11.98	<.0001
Feeling drowsy	-19.05	-25.68, -12.41	-18.15	-24.80, -11.49	<.0001	-17.45	-24.08, -10.81	<.0001
Cough	-15.68	-23.34, -8.02	-17.34	-24.03, -10.65	0.0005	-13.08	-19.89, -6.27	0.0002
Feeling bloated	-12.45	-19.35, -5.54	-11.84	-18.62, -5.06	0.0007	-12.43	-20.33, -4.53	0.0022
Sinus discharge	-7.31	-14.31, -0.31	-5.20	-12.21, 1.81	0.145	-6.76	-13.97, 0.44	0.0658
Diarrhea	-6.15	-13.43, 1.13	-5.13	-12.30, 2.03	0.1597	-5.21	-12.16, 1.74	0.1412

Symptoms: the 14 most prevalent symptoms on the Memorial Symptoms Assessment Scale–Cystic Fibrosis were selected.

Quality of life: the Functional Assessment of Chronic Illness Therapy (FACIT-Pal) was used to determine the quality of life score (range 0-184, higher score indicates better quality of life, minimal clinically important difference 9). Linear regression was used to calculate the difference in FACIT-PAL quality of life scores. The referent group is participants who did not experience the symptom. A p-value was considered statistically significant if it was lower than the adjusted alpha of 0.0036, using the Bonferroni correction.

The results are ordered by the strength of association between each symptom and quality of life using the adjusted model.

* Adjusted model 1 includes modulator therapy and age.

* Adjusted model 2 includes modulator therapy, age, forced expiratory volume in the first second (FEV1) and BMI

Table 6. Association between the 14 most prevalent symptoms on the Memorial Symptoms Assessment Scale–Cystic Fibrosis scale and quality of life, stratified by modulator therapy use.

	On modulator therapy (n=205)			Not on modulator therapy (n=57)		
		Linear regression coefficient, unadjusted model	95% confidence interval		Linear regression coefficient, unadjusted model	95% confidence interval
Lack of energy	-30.23	-38.00	-22.45	-25.72	-39.17	-12.26
Feeling sad	-31.33	-37.92	-24.74	-20.70	-43.00	1.59
Worrying	-28.37	-35.36	-21.37	-31.37	-48.50	-14.23
Feeling irritable	-28.20	-35.04	-21.35	-26.68	-41.22	-12.14
Pain	-25.49	-32.73	-18.25	-4.35	-19.95	11.24
Shortness of breath	-24.51	-31.67	-17.35	-18.62	-33.15	-4.09
Feeling nervous	-22.93	-30.44	-15.42	-15.89	-30.56	-1.23
Difficulty sleeping	-21.88	-29.15	-14.60	-17.33	-32.43	-2.24
Difficulty concentrating	-17.35	-25.03	-9.68	-19.61	-33.74	-5.48
Feeling drowsy	-18.93	-26.39	-11.47	-24.84	-38.81	-10.87
Cough	-13.30	-21.60	-5.01	0.80	-14.69	16.30
Feeling bloated	-9.62	-17.48	-1.76	-23.49	-37.24	-9.74
Sinus discharge	-7.02	-14.85	0.81	-16.23	-30.67	-1.79
Diarrhea	-7.80	-15.98	0.38	-12.02	-26.88	2.83

Linear regression was used to calculate the difference in mean quality of life scores.
The referent group is participants who did not experience the symptom

Table 7. Association between the 14 most prevalent symptoms on the Memorial Symptoms Assessment Scale–Cystic Fibrosis scale and quality of life, stratified by depression comorbidity.

Symptom	Depression (n= 102)		No depression (n=160)		
	Linear regression coefficient, unadjusted model	95% Confidence Interval	Linear regression coefficient, unadjusted model	95% Confidence Interval	
Cough	-20.69	-32.15	-9.24	-9.37	-19.06	0.31
Shortness of breath	-23.20	-33.09	-13.30	-22.83	-30.65	-15.01
Lack of energy	-28.66	-40.67	-16.66	-27.83	-36.25	-19.41
Worrying	-26.54	-36.46	-16.62	-27.93	-35.47	-20.39
Sinus discharge	-2.82	-13.68	8.05	-5.49	-14.27	3.28
Feeling irritable	-21.22	-31.20	-11.23	-26.19	-33.72	-18.66
Feeling drowsy	-9.83	-20.47	0.81	-21.48	-29.54	-13.42
Difficulty sleeping	-18.68	-29.05	-8.32	-19.05	-27.19	-10.92
Feeling sad	-21.94	-32.03	-11.84	-31.33	-38.41	-24.25
Feeling bloated	-14.56	-24.98	-4.14	-8.07	-16.63	0.48
Diarrhea	-0.39	-11.24	10.45	-6.33	-15.44	2.79
Pain	-19.17	-29.17	-9.17	-25.71	-33.67	-17.75
Feeling nervous	-16.13	-26.32	-5.93	-21.47	-29.96	-12.99
Difficulty concentrating	-8.16	-19.14	2.82	-20.75	-29.13	-12.38

Linear regression was used to calculate the difference in mean quality of life scores.
The referent group is participants who did not experience the symptom

Table 8. Association between the 14 most prevalent symptoms on the Memorial Symptoms Assessment Scale–Cystic Fibrosis scale and quality of life, stratified by anxiety comorbidity.

Symptom	Anxiety (n = 109)		No anxiety (n = 153)		
	Linear regression coefficient, unadjusted model	95% Confidence Interval	Linear regression coefficient, unadjusted model	95% Confidence Interval	
Cough	-19.35	-30.43	-8.28	-10.05	-19.95	-0.15
Shortness of breath	-20.74	-30.27	-11.21	-23.91	-32.02	-15.80
Lack of energy	-26.99	-37.93	-16.05	-29.54	-38.24	-20.85
Worrying	-25.57	-34.96	-16.18	-28.33	-36.20	-20.45
Sinus discharge	-5.44	-15.67	4.80	-2.50	-11.59	6.59
Feeling irritable	-20.67	-30.32	-11.02	-25.56	-33.54	-17.58
Feeling drowsy	-11.43	-21.46	-1.41	-19.49	-28.00	-10.98
Difficulty sleeping	-18.66	-28.14	-9.17	-20.12	-28.52	-11.72
Feeling sad	-22.17	-31.57	-12.76	-31.53	-38.90	-24.16
Feeling bloated	-15.45	-25.36	-5.55	-7.02	-16.02	1.98
Diarrhea	-2.91	-13.30	7.48	-5.04	-14.37	4.29
Pain	-21.47	-30.73	-12.21	-23.48	-31.95	-15.01
Feeling nervous	-19.38	-28.68	-10.08	-18.02	-27.45	-8.59
Difficulty concentrating	-12.26	-22.11	-2.40	-16.72	-25.98	-7.45

Linear regression was used to calculate the difference in mean quality of life scores.
The referent group is participants who did not experience the symptom

Table 9. Symptom prevalence and association with quality of life

High association between symptom and quality of life	Low association between symptom and quality of life

Higher prevalence	Lack of energy Worrying Feeling sad Feeling irritable Shortness of breath	Cough Sinus discharge
Lower Prevalence	Pain	Feeling drowsy Feeling bloated Diarrhea

Higher prevalence was defined as more than 50% of study participants experiencing a symptom.

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