www.jpeds.com • THE JOURNAL OF PEDIATRICS

Caregiver Burden Due to Pulmonary Exacerbations in Patients with Cystic Fibrosis

Ellison Suthoff, MBA[1], Jochen G. Mainz, MD[2,3], Desmond W. Cox, MD[4], Teja Thorat, MPH, MSC[1], Daniel H. Grossoehme, DMin, MS[5,6], Moshe Fridman, PhD[7], Gregory S. Sawicki, MD, MPH[8], and Margaret Rosenfeld, MD, MPH[9]

Objective To describe the poorly understood burden of pulmonary exacerbations experienced by primary caregivers of children (aged 2-17 years) with cystic fibrosis (CF), who frequently require prolonged hospitalizations for treatment of pulmonary exacerbations with intravenous (IV) antibiotics.

Study design In this prospective observational study, 88 caregivers in Germany, Ireland, the United Kingdom, and the US completed a survey during pulmonary exacerbation–related hospitalizations (T1) and after return to a "well state" of health (T2). The impact of pulmonary exacerbations on caregiver-reported productivity, mental/physical health, and social/family/emotional functioning was quantified.

Results Primary caregivers of children with CF reported significantly increased burden during pulmonary exacerbations, as measured by the 12-item Short-Form Health Survey mental health component and the Work Productivity and Activity Impairment: Specific Health Problem absenteeism, presenteeism, work productivity loss, and activity impairment component scores. Compared to the "well state," during pulmonary exacerbations-related hospitalization caregivers reported lower physical health scores on the Child Health Questionnaire–Parent Form 28. Quality-of-life scores on the Caregiver Quality of Life Cystic Fibrosis scale and total support score on the Multidimensional Scale of Perceived Social Support did not differ significantly between T1 and T2. More caregivers reported a negative impact on family/social/emotional functioning during pulmonary exacerbations than during the "well state."

Conclusions Pulmonary exacerbations necessitating hospitalization impose a significant burden on primary caregivers of children with CF. Preventing pulmonary exacerbations may substantially reduce this burden. *(J Pediatr 2019;215:164-71)*.

Patients with cystic fibrosis (CF) experience recurrent pulmonary exacerbations and episodic worsening of health characterized by increased cough and sputum production, dyspnea, acute decline in lung function, and weight loss.[1] Pulmonary exacerbations are associated with adverse outcomes, including long-term loss of lung function, decreased health-related quality of life, and increased risk of lung transplantation and death,[2-4] and often require hospitalization and treatment with intravenous (IV) antibiotics.[5]

Given the multiorgan presentation of CF and the associated symptomatic burden and complexity of treatment regimens, children with CF rely on parental caregivers for management of CF treatment regimens and facilitation of health care engagement. There is currently a lack of understanding of the overall burden of this chronic disease on caregivers of children with CF, with only a few published studies using CF-specific instruments.[6,7] In addition, there is a paucity of quantitative information on changes to the burden experienced by caregivers during a pulmonary exacerbation.

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CHQ-PF28	Child Health Questionnaire–Parent Form 28
CQOLCF	Caregiver Quality of Life Cystic Fibrosis
IV	Intravenous
MCID	Minimal clinically important difference
MSPSS	Multidimensional Scale of Perceived Social Support
ppFEV$_1$	Percent predicted forced expiratory volume in 1 second
SF-12	12-item Short-Form Health Survey
WPAI:SHP	Work Productivity and Activity Impairment: Specific Health Problem

From [1]Vertex Pharmaceuticals Incorporated, Boston, MA; [2]Department of Pediatrics, Pediatric Pulmonology, Jena University Hospital, Jena, Germany; [3]Pediatric Pulmonology and Cystic Fibrosis, Brandenburg Medical School, University Hospital, Brandenburg, Germany; [4]Respiratory Department, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland; [5]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; [6]Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [7]AMF Consulting, Los Angeles, CA; [8]Division of Pulmonary Medicine, Boston Children's Hospital, Boston, MA; and [9]Division of Pulmonary and Sleep Medicine, Seattle Children's Hospital, Seattle, WA

Funding and conflict of interest information is available at www.jpeds.com.

Portions of this study were presented as a poster at the North American Cystic Fibrosis Conference annual meeting, November 2-4, 2017, Indianapolis, Indiana; the Academy of Managed Care Pharmacy annual meeting, April 23-26, 2018, Boston, Massachusetts; and the European Conference on Rare Diseases & Orphan Products, May 10-12, 2018, Vienna, Austria.

https://doi.org/10.1016/j.jpeds.2019.08.038

The objective of this study was to quantify the mental/physical health, social/emotional, and productivity burden experienced by primary caregivers of children with CF during a pulmonary exacerbation event necessitating hospitalization and treatment with IV antibiotics, compared with a period of "well state" following recovery from a pulmonary exacerbation.

Methods

This investigation was a prospective observational international cohort study of primary caregivers of children with CF conducted at 10 sites in 4 countries—Germany (3 sites), Ireland (1 site), United Kingdom (3 sites), and the US (3 sites)—from August 2015 to November 2016. The study consisted of a self-reported survey (5 validated instruments and additional questions) at 2 time points: the first (T1) during hospitalization for a pulmonary exacerbation and the second (T2) at a time point ≥4 weeks after completion of IV antibiotics and following caregiver-reported return of the child to a "well state" of health for ≥1 week. Surveys were administered on paper in Germany, Ireland, and the United Kingdom and electronically in the US. All study sites had ethics review approval, and informed consent was obtained from all participants.

Primary caregivers were defined as individuals who self-identified as the primary person caring for the child with CF; they had to be aged ≥19 years. Only 1 primary caregiver per patient was enrolled. Caregivers were recruited to the study during the child's hospitalization for a pulmonary exacerbations and consented to participate in surveys at T1 and T2. Eligible children had a confirmed diagnosis of CF and were aged 2-17 years. The children were required to be hospitalized for a minimum of 1 night due to a pulmonary exacerbation and to have initiated IV antibiotic treatment in the hospital with completion of treatment in either the hospital or at home.

The study excluded primary caregivers with a diagnosis of CF or who were unable to read and write in English (Ireland/United Kingdom/US) or German (Germany), as well as those who were unable or unwilling to provide informed consent. The study also excluded primary caregivers of children with CF treated with cystic fibrosis transmembrane conductance regulator (CFTR) modulators (ivacaftor or lumacaftor/ivacaftor) at the time of recruitment (owing to a significant reduction in the number of pulmonary exacerbation events observed in trials for CFTR modulators), those with a child with CF treated prophylactically with IV antibiotics for prevention of pulmonary exacerbations in the 3 months before recruitment, and those with a child with CF who had previously undergone lung transplantation. Primary caregivers of children with CF experiencing a pulmonary exacerbation necessitating hospitalization for the first time were also excluded, because it was hypothesized that the first hospitalized pulmonary exacerbation event may impose a greater burden on the caregivers than subsequent events.

Demographic and clinical characteristics of children with CF were collected by surveying their caregivers at the time of pulmonary exacerbation–related hospitalization (T1). Clinical percent predicted forced expiratory volume in 1 second ($ppFEV_1$) was extracted from medical records. When clinical FEV_1 was recorded only in liters, Global Lung Function Initiative reference equations were applied to convert to $ppFEV_1$.[8]

Validated Instruments

Five validated self-report instruments were administered at T1 and T2. A description of each instrument and the instrument's scoring scheme follows, with further details on instrument subscales provided in **Table I**.

The 12-Item Short Form Survey (SF-12) is a generic instrument that assesses general health status; it measures both mental and physical health components over the previous 4 weeks, with each component including 4 subdomains (**Table I**).[9] The SF-12 is scored from 0 to 100, with higher scores indicating better health status.

The Work Productivity and Activity Impairment: Specific Health Problem V2.0 (WPAI:SHP) questionnaire can be adapted by investigators to focus on a specific health problem (in this case, CF) by inserting the specific health problem's name throughout the survey as instructed by survey publishers; thus, it can be applied to caregivers of patients with CF following adaptation.[10] WPAI:SHP generates percentages to quantify absenteeism, presenteeism, work productivity loss, and activity impairment associated with caring for a child with CF, using a recall time of the past 7 days. Absenteeism is defined as the percentage of additional hours missed from work; presenteeism, as the percentage of additional productivity loss while at work; work productivity loss, as the percentage of usual productivity lost due to both absenteeism and presenteeism; and activity impairment, as the percentage of additional impairment in daily activities due to caregiving activities for a child with CF. Absenteeism, presenteeism, and work productivity loss data were collected only from primary caregivers who were employed, and activity impairment data were collected from all participants. The instrument is scored from 0% to 100%, with lower scores representing lower impact.

The Caregiver Quality of Life Cystic Fibrosis (CQOLCF) scale is a disease-specific instrument for caregivers of patients with CF, focusing on physical, emotional, family, and social functioning over the past 7 days from the time of administration.[11] The instrument is scored from 0 to 140, with lower scores indicating better functioning of caregivers of children with CF.

The Multidimensional Scale of Perceived Social Support (MSPSS) is a generic instrument that assesses perceived social support offered by family, friends, or a significant other and quantifies the adequacy of that support.[12] The MSPSS is scored from 1 to 7, with higher scores representing a perception of greater support from social networks.[13]

The Child Health Questionnaire–Parent Form 28 (CHQ-PF28) is a generic instrument that assesses a child's physical

Table I. Scoring elements and scoring of validated instruments

Instrument	Scoring elements		Scoring	Recall period
SF-12	• Mental health-related domains ○ Vitality ○ Social functioning ○ Role limitation ○ Mental health perception	• Physical health-related domains ○ Physical functioning ○ Role limitation ○ Bodily pain ○ General health	0-100 (higher scores indicate better health status)	4 weeks
WPAI:SHP	• Work productivity loss ○ Absenteeism ○ Presenteeism • Activity impairment		0%-100% (lower scores indicate reduced impairment)	7 days
CQOLCF	• Total		0-140 (lower scores indicate better health status)	7 days
MSPSS	• Total support ○ Family support ○ Friend support ○ Significant other support		1-7 (higher scores indicate greater availability of support)	0 days (same day)
CHQ-PF28	• Child-specific components ○ Physical health component ○ Psychosocial health component	• Parent/family-specific scores ○ Parental impact–emotional score ○ Parental impact–time ○ Family activities ○ Family cohesion	0-100 (higher scores indicate better health status and family functioning)	4 weeks

and psychological well-being from the perspective of a parent/guardian (child-specific components). It evaluates the effect of the child's health on the caregiver (eg, the impact of worry/concern and limitation of time available for personal needs) and the effect of the child's physical and emotional well-being on family functioning (parent/family-specific scores), using a recall period of 4 weeks.[14] The CHQ-PF28 is scored from 0 to 100, with higher scores indicating that the caregiver perceives the child's well-being and family functioning as being in a better state.

Additional Questions

Additional questions were posed to caregivers to capture information about caregiver burden related to the complexities of caring for a child with CF. A 9-member panel consisting of 5 caregivers of children with CF, 3 adult patients with CF, and 1 spouse of a patient with CF was consulted in developing these questions. The complete list of questions is presented in the **Appendix** (available at www.jpeds.com). Broadly, the additional questions examined caregiver burden related to employment and work life; social, emotional, and family life; treatment and caregiving responsibilities; personal finances; and direct/indirect economic burden. Recall periods for these additional questions ranged from 2 weeks to 12 months.

Statistical Analyses

Data were summarized using descriptive statistics. Values were compared between T1 and T2 using paired t tests for continuous variables and the McNemar test for binary variables. All statistical tests were 2-sided. Only paired responses at T1 and T2 were used to make comparisons between the 2 time points. P values were not adjusted for multiple testing and results were considered statistically significant at $P < .05$. Summary statistics, paired t tests, and McNemar tests were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

A total of 88 self-identified primary caregivers of children with CF participated in this study at T1 (during hospitalization due to a pulmonary exacerbation; Germany, n = 11; Ireland, n = 7; United Kingdom, n = 14; US, n = 56). Subsequently, 82 of the 88 primary caregivers (93%) completed the survey at T2 (during the caregiver-reported "well state" of their child with CF; Germany, n = 11; Ireland, n = 6; United Kingdom, n = 13; US, n = 52). The mean (SD) number of days between T1 and T2 survey completion was 60.8 (31.5) (range, 25-195 days).

Characteristics of primary caregivers, characteristics of children with CF, and details of CF-related care and pulmonary exacerbation-related hospitalizations are presented in **Table II**. Most caregivers were female (85%), and the caregivers' mean (SD) age at T1 was 40.8 (8.4) years. Most caregivers (77%) were cohabitating with partners (married, 68%; living with partner, 9%), and 15% of caregivers were divorced, 6% were single, and 2% were widowed.

The mean (SD) age of children at T1 was 11.9 (3.9) years, with 56% aged 2-12 years and 44% aged 13-17 years; 59% were female. The mean (SD) number of pulmonary exacerbations requiring IV antibiotics during the preceding 2 years was 2.5 (2.8).

Validated Instruments

Primary caregivers of children with CF reported a significantly increased burden during pulmonary exacerbations from a number of instruments (**Figure 1**). The SF-12 mental health composite score showed that caregivers'

Table II. Characteristics of primary caregivers of children with CF and children with CF, and details of CF-related care and pulmonary exacerbations-related hospitalization

Characteristics	Values
Primary caregivers of children with CF (N = 88)	
Age, y, mean (SD; range)	40.8 (8.4; 26.0-68.0)
Female sex, n (%)	74 (85)
Race/ethnicity, n (%)	
Caucasian	67 (92)
African American	2 (3)
Hispanic	2 (3)
Asian or Pacific Islander	1 (1)
Other	1 (1)
Education level, n (%)[*]	
High school or less/general educational development diploma	34 (39)
Vocational school	8 (9)
Some college	17 (20)
College degree	23 (27)
Postcollege degree	4 (5)
Marital status, n (%)[*]	
Single	5 (6)
Living with a partner	8 (9)
Married	59 (68)
Divorced/separated	13 (15)
Widowed	2 (2)
Number of children, mean (SD; range)	2 (1; 1-6)
Number of children with CF, mean (SD; range)	1 (1; 1-3)
Employment status, n (%)[*]	
Employed full-time	28 (33)
Employed part-time	18 (21)
Unable to work due to child's CF	9 (10)
Unemployed	30 (35)
Self-employed	1 (1)
Caregiver self-reported depression, n (%)	21 (24)
Physician visits for caregiver in the past 12 months, mean (SD; range)	2.3 (2.9; 0.0-12.0)
Children with CF (N = 88)	
Age, y, mean (SD; range)	11.9 (3.9; 2.8-17.9)
2-12 years, n (%)	49 (56)
13-17 years, n (%)	39 (44)
Female sex, n (%)	51 (59)
F508del homozygous, n (%)	58 (67)
Number of pulmonary exacerbations experienced in last 2 y, mean (SD; range)[†]	2.5 (2.8; 0.0-12.0)
Number of courses of IV antibiotics in the past 12 mo, mean (SD; range)	2.3 (2.3; 0.0-15.0)
Number of visits to CF physician in past 12 mo, mean (SD; range)	6.9 (4.6; 0.0-20.0)
ppFEV$_1$, mean (SD; range)	
T1	74.2 (19.6; 26.0-105.8)
T2[‡]	83.9 (19.7; 36.0-124.0)
Number of caregiver-reported comorbidities, n (%)[§]	
0	15 (17)
1	19 (22)
2	16 (18)
≥3	38 (43)
Details of CF-related care and pulmonary exacerbation-related hospitalization	
Distance to CF clinic, miles, mean (SD; range)	67.4 (133.0; 1.2-900)
Distance to CF urgent care, miles, mean (SD; range)	21.2 (28.1; 0-170)
Distance to emergency department/hospital, miles, mean (SD; range)	45.2 (111.8; 1.0-900)
Hospitalization for this pulmonary exacerbations, n (%)	
Planned	39 (44)
Unplanned	49 (56)
Hospital length of stay, d, mean (SD; range)	11.3 (6.3; 2.0-43.0)
Location of IV antibiotic-treatment completion, n (%)[¶]	
Hospital	50 (62)
Home	30 (38)
Days of IV antibiotic treatment at home, mean (SD; range)	10.0 (3.7; 1.0-21.0)

With the exception of age, genotype information, and ppFEV$_1$, all children's characteristics in this table were provided by caregivers.

[*] Missing data: education level (n = 86), marital status (n = 87), employment status (n = 86).

[†] Excluding current pulmonary exacerbations.

[‡] ppFEV$_1$ values from children of 82 caregivers who completed the survey at T2.

[§] Comorbidities included in the survey: pancreatic insufficiency (60%), anxiety (27%), gastroesophageal reflux disease (27%), asthma (24%), CF-related diabetes (19%), nasal polyps (19%), bronchiectasis (15%), liver damage (11%), hemoptysis (5%), and other (20%).

[¶] Location of IV antibiotic-treatment completion (n = 80). Data for location of IV antibiotic treatment completion are missing in 8 children.

mental health was significantly affected by pulmonary exacerbation-related hospitalization events; the mean (SD) score was 39.8 (10.9) at T1 vs 42.5 (10.4) at T2 ($P < .001$). SF-12 physical health composite scores did not change between T1 and T2 ($P = .326$; Figure 1).

Caregivers reported a significant increase in burden due to caring for a child with CF in the previous 7 days in the absenteeism (mean [SD] increase, 30.1% [28.8%]; $P < .001$) and presenteeism (22.2% [34.6%]; $P = .003$) components of the WPAI:SHP questionnaire at T1 vs T2, leading to a mean (SD) work productivity loss of 32.8% (37.8%) ($P < .001$) among employed caregivers. The mean (SD) increase in activity impairment across all caregivers at T1 vs T2 was 23.6% (37.3%) ($P < .001$; Figure 1). Employed caregivers reported an increase in missed hours at work, with a mean (SD) of 16.7 (14.7) missed hours per week at T1 vs 3.5 (6.7) at T2 ($P < .001$). Caregiver-reported quality of life, as measured by the CQOLCF scale, did not change significantly between T1 and T2 (Figure 1). Primary caregivers reported that social support, as measured by the MSPSS, was high regardless of the child's health status; however, family support was significantly increased at T1 relative to T2 (Figure 1).

Caregiver-assessed physical health of the child with CF as measured using the CHQ-PF28 was significantly lower at T1 vs T2 (Figure 1). The psychosocial health of children with CF as assessed by caregivers did not change significantly between T1 and T2. As measured by CHQ-PF28 parent/family-specific scales, caregivers reported a

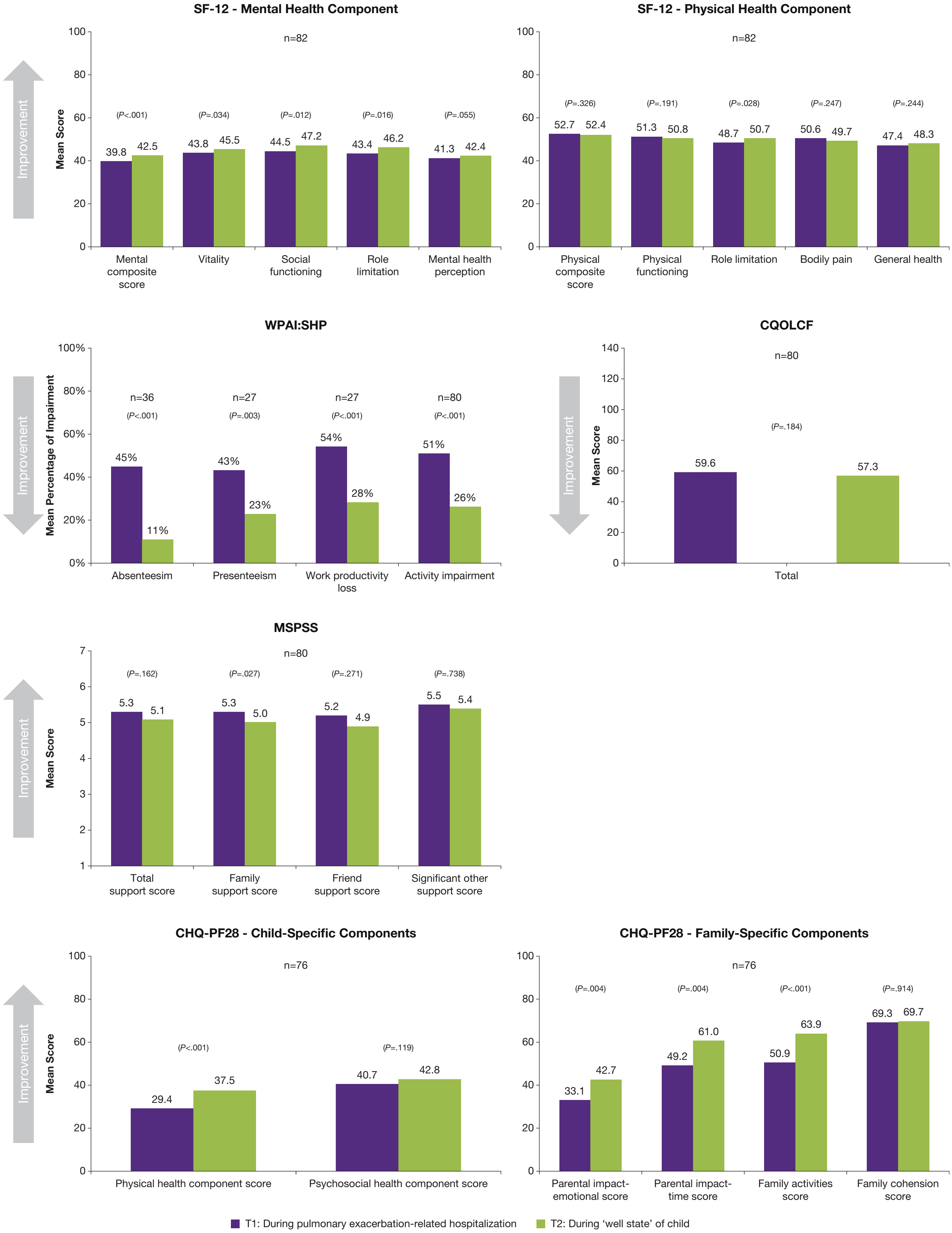

Figure 1. Results of validated instruments. The direction of the arrow indicates whether ascending or descending scores represent a positive change.

significantly greater impact on emotional worry/concern, greater limitation in time available for personal needs due to the child's physical health and emotional well-being, and greater interruption in family activities at T1 vs T2. Caregivers reported no change in the family's ability to get along with one another between the 2 time points.

Additional Questions

Based on data collected at T1, the majority of caregivers reported reducing or ceasing employment due to their child's CF, including 61% who reported changing from full-time to part-time work or reduced hours and 61% reporting cessation of employment altogether due to their child's CF (non-mutually exclusive categories). Overall, 75% of caregivers reported ever reducing working hours or quitting their jobs due to their child's CF. A total of 61% of caregivers altered their career path or career choice, and 36% felt afraid of losing their job because of their child's CF (**Figure 2**, available at www.jpeds.com).

Caregivers reported a high burden of their child's CF on social, emotional, and family life at both time points, although the proportion reporting a burden was significantly greater at T1. The proportion of caregivers reporting that their ability to look after other children in their care was affected by their child with CF was 85% at T1 vs 47% at T2 ($P < .001$); a similar pattern was reported in caregivers' ability to look after other family members at T1 compared with T2 (69% vs 48%; $P = .002$). The proportion of caregivers reporting an impact of CF on participation in social activities was higher at T1 compared with T2 (79% vs 58%; $P < .001$); similarly, a higher proportion of caregivers reported an impact on planning family outings and travel at T1 compared with T2 (79% vs 63%; $P = .018$). In addition, caregivers reported a significant decrease in their ability to spend quality time with partners during their child's pulmonary exacerbation–related hospitalization at T1 compared with T2 (88% vs 68%; $P = .001$), as well as a more significant burden related to their ability to take care of their own heath during T1 (77% vs 62%; $P = .004$) (**Figure 2**).

Caregivers reported similar combined direct and indirect hours per day spent caring for the child with CF (including activities such as managing nonmedication treatment, driving to the hospital/clinic, speaking with the clinician, and managing appointments) at T1 and T2 (mean [SD], 6.1 [7.3] hours vs 4.7 [5.8] hours; $P = .132$) (**Figure 2**).

Pulmonary exacerbations were associated with a significant increase in both paid and unpaid assistance from friends and family as well as from childcare and health care providers. The total mean (SD) hours of assistance in the previous 2 weeks across categories was 25.1 (69.2) at T1 vs 6.1 (16.7) at T2 ($P = .023$), with the majority of those hours composed of unpaid assistance from family members (mean [SD], 20.1 [53.7] at T1 vs 3.7 [12.4] at T2; $P = .010$) (**Figure 2**).

Respondents in the US were asked to quantify the estimated out-of-pocket costs associated with their child's CF during the previous year. Mean (SD) estimated costs were USD 2126 (4747) (median, USD 525; range, USD 0-28 400), and the main estimated contributors to mean cost were professional childcare (mean, USD 818), out-of-pocket costs for CF medications (mean, USD 627), and travel to the clinic (mean, USD 303).

Discussion

The negative impact of pulmonary exacerbations on physical health and quality of life in both adults and children with CF have been studied previously.[2-4] However, there remains limited understanding of the wide-ranging psychological and social impacts of pulmonary exacerbations in children with CF on their primary caregivers. This study specifically evaluated the family/social/emotional burden of pulmonary exacerbations on caregivers of children with CF. We found that the burden on a primary caregiver is substantially higher during a pulmonary exacerbation-related hospitalization than in a "well state" of health. This increase in burden during a pulmonary exacerbation–related hospitalization compared with the existing burden associated with caring for a child with CF demonstrates that the impact of pulmonary exacerbations events is considerable for caregivers.

Our results are generally consistent with the few previous studies of caregiver burden in CF. The burden of care during "well state" in our cohort is similar to that recently reported by Fitzgerald et al[6] in an Irish cohort. Similarly, the vocational impact of CF on caregivers, collected from adolescents and their parents at 19 Italian CF referral centers, was substantial .[15]

The findings of this study are also similar to those of studies assessing caregiver burden in other chronic illnesses. Although the studies used different instruments to assess caregiver burden, substantial levels of burden were reported among those caring for children with general chronic diseases,[16] hemophilia,[17] cerebral palsy,[18] autism,[19] feeding/swallowing problems,[20] and cancer,[21] as well as among those caring for adults with Parkinson disease[22] and various types of cancer.[23-25] In addition, the levels of burden reported using the WPAI:SHP questionnaire in our study during the "well state" are similar in magnitude to those reported in studies using WPAI:SHP among caregivers of children with uncontrolled asthma[26] and among caregivers of adults with poststroke spasticity,[27] with schizophrenia,[28] and undergoing cancer treatment.[29] The 2- to 4-fold increase in WPAI:SHP scores in our study during a pulmonary exacerbation–related hospitalization relative to the "well state" suggest that this markedly increased burden is meaningful.

The minimal clinically important difference (MCID) for a patient-reported outcome indicates the smallest change that a patient would identify as meaningful. The MCID for the

SF-12 has been established in other disease states; the values range from at the low end 3 points in the mental component composite score in Parkinson disease[30] to at the high end 13 points in the physical component composite score for pain after spinal surgery.[31] Although an MCID for patients with CF or their caregivers has not been determined, this study reported a difference of 3.2 points between T1 and T2 for the SF-12 mental health composite score, which could indicate a meaningful change. Moreover, MCIDs for the other validated instruments in this study (WPAI:SHP, CQOLCF, MSPSS, SF-12, and CHQ-PF28) have not been determined in CF. Therefore, future studies aimed at evaluating the MCID for these validated health-related quality of life instruments in patients with CF would be of value.

Some of the validated instruments (eg, the CHQ-PF28 and SF-12) have reference values for the US population that are useful for benchmarking CF caregivers' reported values.[14,32] The CHQ-PF28 and SF-12 have an established mean reference value of 50 with a SD of 10 for the US population.[14,30,32] Caregivers in this study reported lower scores for the CHQ-PF28 physical and psychosocial health of their children with CF at both time points relative to the US population. Furthermore, compared with parents of school-age children with chronic conditions such as asthma, headaches, and hearing problems, in this study, caregivers of children with CF reported lower scores on the CHQ-PF28 physical and psychosocial health components for their children, and for parental impact–emotional score, parental impact–time, and family activities scales during the "well state". However, the results for family cohesion were similar for caregivers of children with CF and parents of school-age children with other chronic conditions.[14] The caregivers of children with CF in this study reported a lower SF-12 mental health composite score at both time points relative to the US population. These findings suggest that the burden on caregivers in CF, although markedly increased during pulmonary exacerbations, may also be substantial during the "well state".

In addition, caregivers reported a substantial impact on many aspects of their lives, including career, family life, social activities, and level of emotional burden. The impact on caregivers' careers is pronounced; a majority of participants (mostly mothers) reported changing jobs or altering their career choice because of their child's CF, and one-third of caregivers reported a fear of losing their job. During pulmonary exacerbation–related hospitalization, and compared with the "well state," almost twice as many caregivers reported that their ability to care for their other children and family members was reduced. Hours of unpaid assistance from family, friends, and neighbors increased markedly, and direct and indirect hours of care (including hours spent managing the medication of their child with CF) also were increased during a pulmonary exacerbation-related hospitalization.

This study has several strengths, including its examination of burden with a variety of instruments both during and after a pulmonary exacerbation. The sample size is reasonable for a longitudinal study in a relatively rare disease such as CF, and the results come directly from primary caregivers. Despite these strengths, however, the study has several limitations. It evaluates the burden only on the primary caregiver, and not on any other members of the family. Consequently, the results do not address the burden experienced by the entire family unit. The primary caregivers composing the study population were overwhelmingly female (85%); although this may reflect a real-world division of sex in the role of caregiver, caution should be exercised when applying the results of the study, and its implications, to male caregivers, who may have different employment and caregiving patterns. We also did not enroll participants on CFTR modulator therapy, so our results are not generalizable to this population. It will be important to evaluate the burden of pulmonary exacerbations on caregivers of patients with CF who are prescribed highly effective modulators in the future. The recall periods for the validated instruments and additional questions that composed the study were between 0 days and 4 weeks, which might affect the validity of the results due to recall bias. Because this study included a sample of medical centers and may have included a particularly engaged population of caregivers willing to complete the surveys, the results might not be generalizable to the wider population. Furthermore, the intent of this study was to identify the domains of increased caregiver burden during periods of hospitalization using validated and other questionnaires, and thus we did not perform multivariable modeling to adjust for disease severity or other potential confounding factors. Finally, differences may exist across patient and caregiver populations and insurance groups and socioeconomic status; however, the limited sample size did not allow for stratified analyses by different subgroups. Stratified analyses of caregivers by countries (European cohort of this study) and by insurance type in the US cohort (commercial/Medicaid) reported similar trends in results.[33,34]

In conclusion, we found that during pulmonary exacerbation–related hospitalization of a child with CF, primary caregivers report significant work productivity loss and social activity impairment and lower mental health status. They also report increased limitations in family functioning, reduced physical health status of the child with CF in their care, and high level of support from family and social networks. Preventing pulmonary exacerbations in children with CF may substantially reduce the burden on their primary caregivers. ■

We thank Gauri Dixit, PhD, for editorial coordination and support. G.D. is an employee of Vertex Pharmaceuticals Incorporated, United States and may own stock or stock options in that company. We thank Michael L. Friedman, MA, of Excerpta Medica, for writing and editorial support in the preparation of this manuscript, which was funded by Vertex Pharmaceuticals Incorporated. We also thank the caregivers and their families who participated in the study, which could not have been conducted without their involvement.

Submitted for publication Apr 4, 2019; last revision received Jul 10, 2019; accepted Aug 20, 2019.

Reprint requests: Margaret Rosenfeld, MD, MPH, Division of Pulmonary and Sleep Medicine, Seattle Children's Hospital, OC.7.720, 4800 Sand Point Way NE, Seattle, WA 98105. E-mail: margaret.rosenfeld@seattlechildrens.org

References

1. Rosenfeld M, Emerson J, Williams-Warren J, Pepe M, Smith A, Montgomery AB, et al. Defining a pulmonary exacerbation in cystic fibrosis. J Pediatr 2001;139:359-65.
2. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002;121:64-72.
3. Orenstein DM, Pattishall EN, Nixon PA, Ross EA, Kaplan RM. Quality of well-being before and after antibiotic treatment of pulmonary exacerbation in patients with cystic fibrosis. Chest 1990;98:1081-4.
4. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. Health Qual Life Outcomes 2016;14:63.
5. de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. Thorax 2011;66:680-5.
6. Fitzgerald C, George S, Somerville R, Linnane B, Fitzpatrick P. Caregiver burden of parents of young children with cystic fibrosis. J Cyst Fibros 2018;17:125-31.
7. Driscoll KA, Montag-Leifling K, Acton JD, Modi AC. Relations between depressive and anxious symptoms and quality of life in caregivers of children with cystic fibrosis. Pediatr Pulmonol 2009;44:784-92.
8. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324-43.
9. Kosinski M, Ware JE, Turner-Bowker DM, Gandek B. User's manual for the SF-12v2 health survey: With a supplement documenting the SF-12® health survey. Lincoln (RI): QualityMetric Incorporated; 2007.
10. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353-65.
11. Boling W, Macrina DM, Clancy JP. The Caregiver Quality of Life Cystic Fibrosis (CQOLCF) scale: modification and validation of an instrument to measure quality of life in cystic fibrosis family caregivers. Qual Life Res 2003;12:1119-26.
12. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 1988;52:30-41.
13. Yildiz E, Aşti T. Determine the relationship between perceived social support and depression level of patients with diabetic foot. J Diabetes Metab Disord 2015;14:59.
14. Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. J Epidemiol Community Health 2005;59:75-82.
15. Neri L, Lucidi V, Catastini P, Colombo C, LINFA Study Group. Caregiver burden and vocational participation among parents of adolescents with CF. Pediatr Pulmonol 2016;51:243-52.
16. Khanna AK, Prabhakaran A, Patel P, Ganjiwale JD, Nimbalkar SM. Social, psychological and financial burden on caregivers of children with chronic illness: a cross-sectional study. Indian J Pediatr 2015;82:1006-11.
17. Wisniewski T, Petrilla AA, DeKoeven M, Lee WC, Cooper DL, Holot N, et al. PSY45 Characteristics of caregivers and their experience associated with congenital hemophilia of inhibitor patients. Value Health 2011;14:A67.
18. Bella G, Turolla R, Spadary R. The assistance impact on the stress and burden in mothers of children with cerebral palsy. Physiotherapy (United Kingdom) 2011;97(Suppl 1):eS1263-4.
19. Becerra TA, Massolo ML, Yau VM, Owen-Smith AA, Lynch FL, Crawford PM, et al. A survey of parents with children on the autism spectrum: experience with services and treatments. Perm J 2017;21:16-1009.
20. Lefton-Greif MA, Okelo SO, Wright JM, Collaco JM, McGrath-Morrow SA, Eakin MN. Impact of children's feeding/swallowing problems: validation of a new caregiver instrument. Dysphagia 2014;29:671-7.
21. Santos S, Crespo C, Canavarro MC. Caregiver burden and parents' adaptation in pediatric oncology settings: the mediating role of family cohesion. Psychooncology 2014;23:12-3.
22. Neri VC, Muratori CT, Ferreira PP, Sandin P, Licassali G, Gomes SB, et al. Psychosocial evaluation in caregivers of patients with Parkinson's disease: analysis of a cohort of Rio de Janeiro/Brazil. Mov Disord 2017;32(suppl 2):173.
23. Rha SY, Park Y, Song SK, Lee CE, Lee J. Caregiving burden and health-promoting behaviors among the family caregivers of cancer patients. Eur J Oncol Nurs 2015;19:174-81.
24. Turkoglu N, Kilic D. Effects of care burdens of caregivers of cancer patients on their quality of life. Asian Pac J Cancer Prev 2012;13:4141-5.
25. Jassem J, Gilloteau I, Penrod JR, Goren A. Quantifying the humanistic burden of caregiving for patients with lung cancer in Europe. J Thorac Oncol 2013;8:S157-8.
26. Dean BB, Calimlim BC, Sacco P, Aguilar D, Maykut R, Tinkelman D. Uncontrolled asthma: assessing quality of life and productivity of children and their caregivers using a cross-sectional internet-based survey. Health Qual Life Outcomes 2010;8:96.
27. Ganapathy V, Graham GD, DiBonaventura MD, Gillard PJ, Goren A, Zorowitz RD. Caregiver burden, productivity loss, and indirect costs associated with caring for patients with poststroke spasticity. Clin Interv Aging 2015;10:1793-802.
28. Gupta S, Isherwood G, Jones K, Van Impe K. Productivity loss and resource utilization, and associated indirect and direct costs in individuals providing care for adults with schizophrenia in the EU5. Clinicoecon Outcomes Res 2015;7:593-602.
29. Kamal KM, Covvey JR, Dashputre A, Ghosh S, Shah S, Bhosle M, et al. A systematic review of the effect of cancer treatment on work productivity of patients and caregivers. J Manag Care Spec Pharm 2017;23:136-62.
30. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol 2010;67:64-70.
31. Parker SL, Mendenhall SK, Shau D, Adogwa O, Cheng JS, Anderson WN, et al. Determination of minimum clinically important difference in pain, disability, and quality of life after extension of fusion for adjacent-segment disease. J Neurosurg Spine 2012;16:61-7.
32. Hullmann SE, Ryan JL, Ramsey RR, Chaney JM, Mullins LL. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). Arthritis Care Res (Hoboken) 2011;63(suppl 11):S420-30.
33. Thorat T, Suthoff E, Mainz JG, Cox DW, Fridman M, Desai M. Caregiver burden due to pulmonary exacerbations (PEx) in cystic fibrosis (CF): a survey of caregivers of paediatric patients with CF in the UK, Ireland, and Germany. Orphanet J Rare Dis 2018;13(suppl 2):167.
34. Suthoff E, Rosenfeld M, Thorat T, Grossoehme D, Fridman M, Sawicki G. Caregiver burden due to pulmonary exacerbations in cystic fibrosis: a survey of caregivers of publicly and commercially insured children with cystic fibrosis in the United States [abstract]. J Manag Care Spec Pharm 2018;24(suppl 4A):S46.

Funding and Conflicts of Interest Disclosure

Sponsored by Vertex Pharmaceuticals Incorporated, which was involved in study design; the collection, analysis, and interpretation of data; and the decision to submit the manuscript for publication. E.S. is a former employee of Vertex Pharmaceuticals Incorporated and may own stock in that company. J.M. reports receiving compensation from Vertex Pharmaceuticals Incorporated for lectures and advisory boards, and reports receiving an investigator-initiated study grant, all outside of the submitted study. T.T. is an employee of Vertex Pharmaceuticals Incorporated, and may own stock or stock options in that company. M.F. reports receiving compensation as a consultant to Vertex Pharmaceuticals Incorporated. G.S. is an employee of Boston Children's Hospital, which received funding from Vertex Pharmaceuticals Incorporated for the submitted study, and reports receiving compensation from Vertex Pharmaceuticals Incorporated for advisory boards. M.R. is an employee of Seattle Children's, which received funding from Vertex Pharmaceuticals Incorporated for the submitted study. D.C. and D.G. report no conflicts of interest.

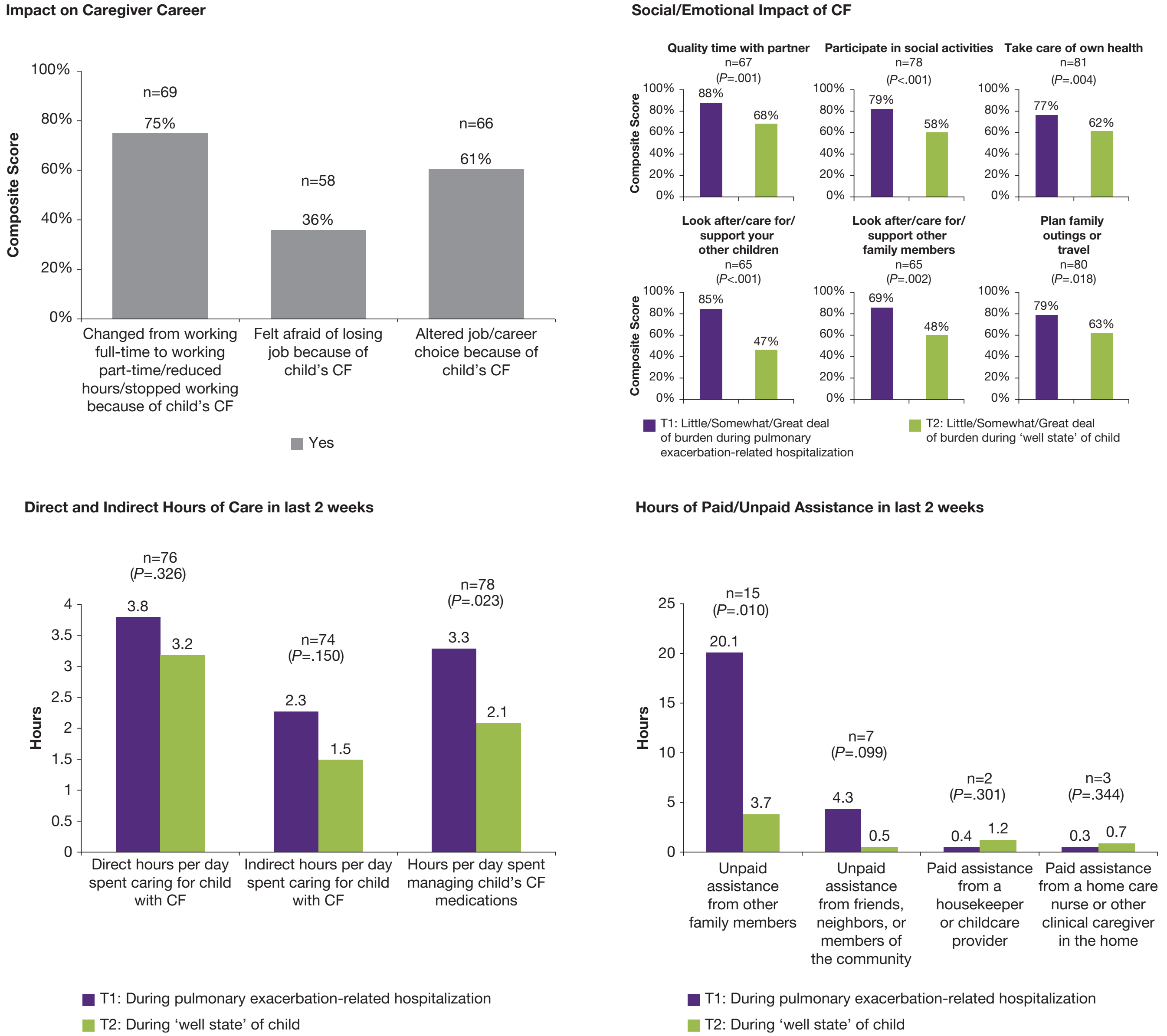

Figure 2. Categories for impact on caregiver career are not mutually exclusive. Social/emotional impact of CF at T1 and T2 is depicted by combining the categories of little/somewhat/great deal of burden, and excluding the category of no burden.