ON-LINE ONLY SUPPLEMENT:

FURTHER METHODOLOGICAL DETAILS AND RESULTS

METHODS

Overview

The Function, Living, Outcomes, and Work (FLOW) study is an ongoing cohort study of patients with chronic obstructive pulmonary disease (COPD).[1,2] The cohort was recruited from the membership of Kaiser Permanente (KP), the nation's largest non-profit managed-care organization. In Northern California, KP provides the full spectrum of primary to tertiary care to approximately 3.1 million members. KP's share of the Northern California population ranges from 25 to 30%.[3] With the exception of the extremes of income distribution, the demographic characteristics of KP members have been shown to be similar to the overall Northern California population.[4]

Subject Eligibility

FLOW investigators identified all adult KP members, living within a 30-mile radius of our research clinic in Oakland, CA, who were recently treated for COPD. The age range was restricted to 40-65 years because an important focus of the FLOW study is examining the long-term prevention of COPD-associated disability. First, FLOW investigators identified all patients, using KP computerized databases, who met both of two criteria for COPD: (1) health-care

utilization (having ≥1 ambulatory visits, ED visits, or hospitalizations over the prior 12 months with a principal ICD-9 diagnosis code for COPD (chronic bronchitis [491], emphysema [492], or COPD [496]) and (2) medication prescription (having ≥2 prescriptions for a COPD-related medication during a 12-month window beginning 6 months before the index utilization date and ending 6 months after index date). Second, a diagnosis of COPD was confirmed, based on interviews and spirometry, using Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[5] This algorithm was previously validated using medical record review.[6]

Recruitment

A total of 4,770 patients with COPD were identified on screening criteria, of which 1,398 declined to participate, 783 could not be reached, and 306 died before they could be recruited into the study. Of 2,283 recruited COPD subjects, 1,212 completed both structured telephone interviews and research clinic visits. Ten potential COPD subjects were excluded because they did not meet the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD based on interviews and spirometry,[5] yielding a COPD cohort of 1202 subjects.

Demographic information was available for interviewed subjects from their structured telephone interviews and non-interviewed subjects from Kaiser computerized databases. Compared to subjects who were eligible but not interviewed, interviewed subjects were slightly older (by 0.7 years on average), more likely to be female (59% vs. 51%), and more likely to be white (69% vs. 56%). In terms of race-ethnicity, the two largest minority subgroups were slightly over-represented among those who completed interviews: (African American 14% vs. 11%, Latino 9% vs. 4%). Most of the differences in race were driven by limitations inherent in the Kaiser computerized databases: the prevalence of unknown race was much higher among

those who did not complete interviews (17% vs. 0.3%) because race was often unknown prior to interviews but was assessed at the time of interviews.

Compared to subjects who completed interviews but not the clinic visit, clinic visit attendees were similar in age (mean difference 0.3 years), gender (58% vs. 55% female), and race-ethnicity (67% vs. 61% white). We were highly successful recruiting persons of African American or Latino background for the research clinic visit (17% completed vs. 11% not completed and 9% vs. 5%, respectively).

The study was approved both by the University of California, San Francisco Committee on Human Research and the Kaiser Foundation Research Institute's institutional review board and all participants provided written informed consent.

Development of the COPD Helplessness Index

Items for the COPD Helplessness Index (CHI) were adapted closely from the Arthritis Helplessness Index, a previously validated 15-item measure for arthritis.[7] This adaptation was accomplished by, in each item, replacing the words "arthritis" or "pain" with the words "breathing problems." For example, the Arthritis Helplessness Index asks respondents to use a Likert scale to rate agreement or disagreement with the statement, "Managing my arthritis is largely my own responsibility." In the COPD Helplessness Index, we asked subject to rate agreement with the statement, "Managing my breathing problems is largely my own responsibility." This approach is consistent with that used for earlier adaptations leading to the Perceived Control of Asthma Questionnaire.[8] It should be noted that "learned helplessness" and "perceived control" are closely related constructs. The arthritis and asthma disease-specific

measures of helplessness/perceived control have proved useful by multiple investigators in understanding the relationship between psychosocial factors and physical health, as well as in the prediction of poor clinical course for both rheumatologic diseases[9-18] and asthma.[19-26] As with these other scales, the items in the CHI address perceived responsibility for disease management, perceived ability to cope with and control COPD, and sense of futility or fatalism related to COPD. The specific questions that were tested for the CHI are shown in Table 2.

Item Administration and CHI Score Calculation

Individuals were asked in structured telephone interviews to rate each item using a 0 to 4 point Likert format by selecting one of the following response categories: "strongly agree," "agree," "neutral / neither agree nor disagree," "disagree," or "strongly disagree." The CHI is scored by summing responses to each item after reversing the scores for items 1, 2, 4, 5, 8, 9, 13, and 15. The CHI takes approximately 3-5 minutes to administer by telephone. Although we did not test for administration via written questionnaire, this approach may be possible, especially given that the Arthritis Helplessness Index, on which the CHI is based, was originally validated based on administration via written questionnaire.[7]

Measurements for Testing Concurrent and Predictive Validity

Overview

Subjects underwent structured telephone interviews followed by research clinic visits, at which time lung function and other physiological measures were made. Interviews ascertained sociodemographic characteristics, smoking status, depressive and anxiety symptoms, and health-related quality-of life (HRQL) measurements, as described below. Each of these measures was used to test the validity of the CHI.

Measurement of General and Disease-Specific Health-Related Quality of Life

Physical HRQL as reflective of generic (not disease-specific) health status was measured using the Short-Form (SF)-12 Physical Component Summary (PCS) score.[27] The SF-12 PCS is derived from the Medical Outcomes Study SF-36 instrument and has been validated in the general population and among adults with COPD.[28,29] Higher scores reflect more favorable generic HRQL.

Respiratory-specific HRQL was assessed using the validated revised Airways Questionnaire 20 (AQ20-R).[30-32] The AQ-20 is a 20-item instrument that has been shown to be comparable in performance to the longer St. George Respiratory Questionnaire in terms of measuring HRQL in patients with COPD; the AQ20-R is further refined from the AQ-20 to take into account activities no longer performed due to illness.[30-32] Lower scores reflect more favorable HRQL.

Depression and Anxiety Assessment

Depressive symptoms were obtained using the 15-item short-form Geriatric Depression Scale (GDS). The GDS was developed to minimize the problem of overlap between symptoms of a physical illness, such as COPD, and the somatic symptoms considered indicative of depression.[33] The GDS has been validated in non-geriatric populations generally, as well as specifically in younger adults with obstructive lung disease.[34-37] GDS scores can range from 0 to 15.

Anxiety was assessed using the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), which is intended for outpatient usage.[38,39] This is a self-assessment scale used to detect states of depression and anxiety in patients in the hospital outpatient setting. For the total HADS, individuals complete 14 questions, equally divided between symptoms of anxiety and depression, each with a four-point scale of potential answers. These answers result in two separate scores (ranging from 0 to 21) on an anxiety and a depressive subscale. However, in the FLOW study, only the anxiety subscale of the HADS was assessed because the GDS was felt to be a well-validated measure of depressive symptoms in obstructive lung disease.[36-37]

COPD Severity Assessment

COPD severity was assessed with the BODE Index, a commonly used multidimensional score which is predictive of death in COPD.[40] Specifically, it includes: body-mass index or BMI, [B]: airflow obstruction as measured by forced expiratory volume in 1 second (FEV_1), [O];

dyspnea [D], as assessed by the Modified Medical Research Council (MMRC) dyspnea scale; and exercise capacity [E], measured by the Six Minute Walk Test. The BODE Index has a possible range of 0 to 10 points. Dyspnea, FEV_1 and the Six Minute Walk Test each contribute between 0 and 3 points, while BMI contributes a maximum of 1 point (for BMI≤21 indicative of loss of body mass). Greater BODE scores indicate more severe COPD.

To determine FEV_1 ,we conducted spirometry according to American Thoracic Society (ATS) guidelines,[41] using the EasyOne™ Frontline spirometer (Medical Technologies, Chelmsford, MA). To calculate FEV_1 as a percentage of predicted (FEV_1% predicted), we used predictive equations derived from National Health and Nutrition Examination Survey (NHANES) III.[42] Although we did not administer bronchodilators prior to spirometry, 90% of subjects had taken their own short-acting bronchodilator within 4 hours of spirometry or had taken a long-acting bronchodilator earlier in the same day.

To measure the Six Minute Walk Test, we used a standardized protocol in accordance with ATS guidelines: a flat, straight course of 30 meters and uniform phrases to encourage effort.[43] Subjects who routinely used home oxygen or who had a resting oxygen saturation <90% were supplied with supplemental oxygen by nasal cannula during the test. The primary outcome was the total distance walked in 6 minutes.

Predictive Validity Outcome: COPD-Related Emergency Health-Care Utilization

To examine the impact of helplessness on COPD health outcomes, we used emergency health-care utilization for COPD as a proxy measure of acute COPD exacerbation. Although there is no uniformly-accepted definition of an acute exacerbation of COPD [43], hospitalization or

ED visit for COPD is often used for research purposes.[45,46] Thus, we used KP computerized databases to determine COPD-related hospitalizations and emergency department (ED) visits between the completion of subject's research clinic visit and June 30, 2008, which corresponded to the last available utilization date. COPD-related hospitalization was defined as 1 or more hospitalizations with primary discharge diagnosis (ICD-9) code for COPD (chronic bronchitis [491], emphysema [492], or COPD [496]). COPD-related ED visit was defined as 1 or more ED visits with such an ICD-9 code for COPD. The median duration of follow-up was 2.1 years (25^{th} – 75^{th} inter-quartile range: 1.7 – 2.6 years).

Statistical Analysis

All analyses used Stata/SE version 9.2 (College Station, TX).

Internal Consistency and Factor Analysis

We evaluated the internal consistency of the CHI by computing Cronbach's α and conducting a principal components analysis to examine factor loading on the generated eigen values.[47]

Concurrent Validity

A critical test of the validity of a scale is to determine whether that scale is related to other theoretically relevant constructs.[48,49] To test the concurrent validity of the CHI in this

manner, we examined the cross-sectional association of the index with each HRQL, psychological, and COPD severity (BODE) measurement described above. To provide evidence of the strength and statistical significance of each association, we used Pearson product-moment correlations. To take into account potential confounding, we also performed additional analyses in which we retested each measure's relationship to the CHI using multivariable linear regression. Here we developed separate multivariable linear regression models, each with the CHI as the dependent variable but with a different HRQL, psychological, or COPD severity measure as an independent variable. For all of these models, we also included, as independent variables, age, gender, race-ethnicity (non-Latino White vs. other), marital status, education (college graduate vs. not college graduate), and smoking status (defined as current, former or never smoker).

Predictive Validity

To examine the predictive validity of the CHI, we evaluated the longitudinal association between baseline helplessness and incident COPD exacerbations defined as subsequent occurrence of either a COPD-related ED visit or hospitalization. Specifically, we used multivariable Cox proportional hazards models to assess the prospective association of the CHI with such utilization outcomes, taking variable follow-up time into account. Person-time was censored for death (not associated with a COPD-related hospitalization or ED visit), termination of KP membership (because utilization records would not be available after such termination), and end of study. Ultimately, 19 patients were censored at the time of death and 77 patients at the time of termination of KP membership.

In one set of analyses, we adjusted for both smoking status and the potentially confounding sociodemographic factors of age, gender, race-ethnicity, marital status, and education. In a second set of analyses, we also adjusted for the BODE Index as a measure of COPD severity. Finally, because we anticipated that helplessness may be differentially associated with adverse COPD outcomes depending on the level of COPD severity, we repeated the second analysis after dichotomizing subjects into either low or high COPD severity based on the median BODE Index values of the cohort. That is, we conducted analyses in which we adjusted for the BODE Index, sociodemographic factors and smoking status separately in (1) the subgroup of patients with lower COPD severity and (2) the subgroup with higher COPD severity (based on BODE score). Because there is no generally-accepted consensus as to what threshold of the BODE Index represents "severe COPD," we chose an *a priori* cut-point from our own cohort, as indicated above, defining relatively less severe COPD as a BODE Index ≤ the cohort median and more severe COPD as a BODE Index > cohort median.

Inclusion Psychosocial Covariates in Multivariable Analysis

Learned helplessness theorists have posited that psychosocial factors such as depression may be caused, at least in part, by helplessness,[50,51] and it has been shown empirically that, in non-COPD populations, helplessness not only correlates with concurrent depression but also predicts the subsequent onset of depression.[52,53] Thus, because psychosocial factors are thought to be on the same causal pathway as helplessness, they may be mediators rather than confounders in the relationship between helplessness and adverse COPD outcomes. If so, the inclusion of both the CHI and psychosocial factors in multivariate analyses would bias our results towards the

null. Additionally, because of problems of collinearity between the CHI and psychosocial factors, the simultaneous inclusion of both the CHI and such factors may be statistically inappropriate. Nonetheless, to evaluate the potentially independent roles of helplessness and psychosocial factors, we constructed two multivariable linear regression models in which we did include, as predictor variables, the CHI, depressive symptoms, anxiety symptoms, and the BODE Index along with the aforementioned sociodemographic factors and tobacco history and used the HRQL measures (SF-12 PCS and AQ-20R) as the dependent, outcome variables.

Statistical Model Verification

Proportional hazards assumptions for Cox proportional hazard models were verified by obtaining scaled Schoenfeld residuals ($p>0.1$ for all variables in the model). Additionally, we assessed the reliability of our Cox proportional hazard models by computing bootstrap estimates using bias-corrected 95% confidence intervals (calculated using 1000 re-sampled data sets).[54] That is, we used a bootstrap procedure as a nonparametric method to allow us to estimate confidence intervals without making the same assumptions about sampling distributions used by standard Cox models; the bootstrap procedure re-sampled our data set, with replacement, 1000 times. For all results presented, this bootstrap method yielded highly similar results to that of standard Cox modeling. Therefore, only the results from standard multivariate Cox modeling are presented.

SUPPLEMENTAL RESULTS

Concurrent Validity

To take into account potential confounding, we also performed additional analyses in which we retested each HRQL, psychosocial, or COPD severity measure's relationship to the CHI using multivariable linear regression and controlling for sociodemographic factors and smoking status. In this analysis, presented in **Table E1**, each HRQL, psychosocial and COPD severity measure was associated with the CHI in the expected direction ($p<0.001$ for all).

Inclusion Psychosocial Covariates in Multivariable Analysis

To evaluate the potentially independent roles of helplessness and psychosocial factors, we constructed two multivariable linear regression models in which we included, as predictor variables, the CHI, depressive symptoms, anxiety symptoms, and the BODE Index along with the sociodemographic factors and tobacco history and used the HRQL measures (SF-12 PCS and AQ-20R) as the dependent, outcome variables. In this analysis, presented in **Table E2**, the CHI continued to be associated with both HRQL measures, in the expected directions, even after controlling for the BODE Index, depressive symptoms, and anxiety symptoms ($p<0.001$ for the association with both HRQL measures).

Table E1. Multivariable analysis of concurrent validity: Association of HRQL, Psychological, and COPD severity factors with the COPD Helplessness Index

Factors Associated with CHI	Cross-Sectional Change in COPD Helplessness Index per Standard Deviation Increment in Listed Factor	
	Coefficient (95 % CI)	p value
HRQL & Psychological Factors		
Overall Physical HRQL (SF-12 PCS) †	-2.7 (-3.1 to -2.3)	<0.001
Respiratory-Specific HRQL (AQ20-R) ‡	3.7 (3.3 to 4.0)	<0.001
Depression Scale (GDS) ‡	3.8 (3.4 to 4.1)	<0.001
Anxiety Scale (anxiety portion of HADS) ‡	2.6 (2.3 to 3.0)	<0.001
COPD Severity		
BODE Index ‡	2.3 (1.9 to 2.7)	<0.001
Selected BODE components:		
FEV_1% predicted †	-1.0 (-1.4 to -0.6)	<0.001
MMRC Dyspnea Scale ‡	2.9 (2.6 to 3.3)	<0.001
6 Minute Walk Test †	-1.7 (-2.1 to -1.3)	<0.001

All multivariate analyses included, as independent (predictor) variables, age, gender, race-ethnicity, marital status, education, and smoking status. Each model also included, as an independent variable, **one** of the HRQL, psychosocial or COPD severity factor listed above. All models included the CHI as the dependent (outcome) variable.

* All changes in CHI are expressed per standard deviation increment in listed factor. For example, in cross-sectional analysis, a one standard deviation **increase** in the SF-12 PCS was associated with a 2.7 point **decline** in the CHI.

† Higher SF-12 PCS scores, higher FEV_1% predicted, and higher distance walked on the 6 Minute Walk Test represent **better** health status.

‡ Higher scores on the AQ20-R, GDS, HADS, BODE Index, and MMRC Dyspnea Scale represent **worse** health status. Note that FEV_1 and the 6 Minute Walk Test are reverse scored for the summary BODE Index.

Table E2. Association of Health-Related Quality of Life (HRQL) with Psychological Factors and COPD Severity

Independent Predictors of HRQL	Respiratory-Specific HRQL (AQ20-R)* Δ in score per unit change of independent predictor		Overall Physical HRQL (SF-12 PCS)* Δ in score per unit change of independent predictor	
	Δ (95 % CI)	p value	Δ (95 % CI)	p value
Age†	**-0.6 (-0.8 to -0.5)**	**<0.001**	0.03 (-0.4 to 0.5)	0.89
Female gender	0.4 (-0.2 to 0.8)	0.06	**-1.1 (-2.2 to -0.05)**	**0.04**
Married or Cohabitating	**0.5 (0.1 to 0.9)**	**0.01**	-0.01 (-1.1 to 1.1)	0.99
College Graduate	**-0.6 (-1.0 to -0.1)**	**0.01**	**1.9 (0.7 to 3.2)**	**0.002**
White non-Latino	-0.4 (-0.8 to 0.02)	0.06	-0.5 (-1.6 to 0.5)	0.33
Tobacco Status				
Never smoker	1.0 [Reference]	N/A	1.0 [Reference]	N/A
Former smoker	-0.4 (-1.0 to 0.2)	0.16	0.4 (-1.2 to 2.0)	0.59
Current smoker	**-1.0 (-1.6 to -0.4)**	**0.001**	1.0 (-0.7 to 2.7)	0.24
BODE Index ‡	**1.5 (1.3 to 1.7)**	**<0.001**	**-4.4 (-5.0 to -3.8)**	**<0.001**
Depression Scale ‡	**0.7 (0.5 – 1.0)**	**<0.001**	**-2.7 (-3.4 to -1.9)**	**<0.001**
Anxiety Scale ‡	**0.6 (0.3 to 0.8)**	**<0.001**	0.4 (-0.3 to 1.1)	0.25
COPD Helplessness Index ‡	**1.2 (0.9 to 1.4)**	**<0.001**	**-1.7 (-2.3 to -1.1)**	**<0.001**

Two separate multivariable linear regression analyses simultaneously include **all** covariates listed above as predictors of either [1] Respiratory-Specific HRQL (AQ20-R) or [2] Overall Physical HRQL (SF-12 PCS).

* Higher AQ20-R scores represent **worse** health status. Higher SF-12 PCS scores represent **better** health status.

† Coefficient (Δ) expressed per 5 year increment in age.

‡ Coefficients (Δ) are expressed per 1 standard deviation increment in BODE Index (a measure of COPD severity), geriatric depression scale, anxiety portion of the HAD scale, and COPD Helplessness Index. Increments in all of these scales represent **worse** health status.

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