Development of disability in chronic obstructive pulmonary disease: beyond lung function

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ABSTRACT

Background COPD is a major cause of disability, but little is known about how disability develops in this condition.
Methods The authors analysed data from the Function, Living, Outcomes and Work (FLOW) Study which enrolled 1202 Kaiser Permanente Northern California members with COPD at baseline and re-evaluated 1051 subjects at 2-year follow-up. The authors tested the specific hypothesis that the development of specific non-respiratory impairments (abnormal body composition and muscle strength) and functional limitations (decreased lower extremity function, poor balance, mobility-related dyspnoea, reduced exercise performance and decreased cognitive function) will determine the risk of disability in COPD, after controlling for respiratory impairment (FEV_1 and oxygen saturation). The Valued Life Activities Scale was used to assess disability in terms of a broad range of daily activities. The primary disability outcome measure was defined as an increase in the proportion of activities that cannot be performed of 3.3% or greater from baseline to 2-year follow-up (the estimated minimal important difference). Multivariable logistic regression was used for analysis.
Results Respiratory impairment measures were related to an increased prospective risk of disability (multivariate OR 1.75; 95% CI 1.26 to 2.44 for 1 litre decrement of FEV_1 and OR 1.57 per 5% decrement in oxygen saturation; 95% CI 1.13 to 2.18). Non-respiratory impairment (body composition and lower extremity muscle strength) and functional limitations (lower extremity function, exercise performance, and mobility-related dyspnoea) were all associated with an increased longitudinal risk of disability after controlling for respiratory impairment (p<0.05 in all cases). Non-respiratory impairment and functional limitations were predictive of prospective disability, above-and-beyond sociodemographic characteristics, smoking status and respiratory impairment (area under the receiver operating characteristic curve increased from 0.65 to 0.75; p<0.001).
Conclusions Development of non-respiratory impairment and functional limitations, which reflect the systemic nature of COPD, appear to be critical determinants of disablement. Prevention and treatment of disability require a comprehensive approach to the COPD patient.

INTRODUCTION

The recent Institute of Medicine report on comparative effectiveness research identified studies of functional limitations and disability as a priority research area.[1] The report ranked research on disability as the third most important priority area, with nearly one-fifth of research topics falling within this category. Chronic obstructive pulmonary disease (COPD), because it is one of the top five causes of disability among middle-aged US adults, is a key condition for such disability research.[2 3] We have previously shown that adults with COPD have a 10-fold higher risk of disability than members of the general population.[4] Moreover, COPD is associated with greater disability than other chronic health conditions, such as diabetes or heart disease.[4] COPD is also associated with reduced ability to perform basic self-care tasks necessary for survival and activities necessary for living independently.[5–10] Although prior research indicates that COPD-related disability is a substantive problem, very little is known about how the disease progresses to disability.

To study the progression to COPD-related disability, we have adapted a specific conceptual disablement model proposed by Verbrugge and Jette.[11] In this model, the central pathway begins with the impact of disease pathology, which includes specific biochemical or physiological alterations, on impairments. Impairments are specific structural or functional alterations of organ systems, such as reduced pulmonary function, that lead to functional limitation, which are decrements of basic physical or mental actions (eg, mobility, strength, and central cognitive and emotional functions). Functional limitation in turn leads to disability, which is difficulty in performing activities or roles that are normal for one's age and sex. These range from activities of daily living, which are necessary for survival, to discretionary activities that make life meaningful, such as socialising and recreation.

Based on this disablement model, we tested a specific theory of how disability develops in COPD. We reasoned that respiratory impairment alone was unlikely to explain most of the disability risk. We hypothesised that, for a given level of respiratory impairment, the development of specific non-respiratory impairments (abnormal body composition and muscle strength) and functional limitations (decreased lower extremity function, poor balance, mobility-related dyspnoea, reduced exercise performance and decreased cognitive function) will determine the risk of disability in COPD.

METHODS

Recruitment and follow-up of the cohort

The Function, Living, Outcomes and Work (FLOW) study of COPD is an ongoing prospective cohort study of adult members of an integrated healthcare

delivery system with a physician's diagnosis of COPD. Recruitment methods have been previously reported in detail.[12–15] We recruited a population-based cohort of 1202 Kaiser Permanente Medical Care Program (KPMCP) members who were recently treated for COPD using a validated algorithm based both on healthcare utilisation and pharmacy dispensing for COPD.[16] A diagnosis of COPD was confirmed, based on interviews and spirometry, using Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. At baseline assessment, we conducted structured telephone interviews that ascertained sociodemographic characteristics, COPD clinical history, health status and disability.[12–14] Research clinic visits included spirometry and other physical assessments.

Approximately 2 years later, we conducted follow-up telephone interviews that ascertained COPD status and disability. Of the 1202 subjects interviewed at baseline, 40 subjects subsequently died before follow-up interview. We completed interview follow-up in 1051 subjects, which reflects an 87% completion rate (90% among subjects who were still alive). 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.

Baseline characteristics
Personal characteristics were assessed by structured telephone interview. These included sociodemographic characteristics such as age, sex, educational attainment and income, which were measured as previously described.[12–15] Cigarette smoking was assessed using questions developed for the National Health Interview Survey.[17]

Respiratory impairment
To assess respiratory impairment, we conducted spirometry according to American Thoracic Society (ATS) Guidelines.[18] [19] We used the EasyOne Frontline spirometer (ndd Medical Technologies, Chelmsford, Massachusetts, USA), which is known for its reliability, accuracy and durability.[20] [21] The Easyone spirometer has been used by large scale multicenter international epidemiologic studies of COPD.[21] [22] Baseline oxygen saturation was measured at rest in the seated position using the Nellcor N-180 (Covidien-Nellcor, Boulder, Colorado, USA).

Non-respiratory impairment assessment: body composition and muscle strength
We assessed bioelectrical impedance as a measure of body composition using the Quantum II Bioelectrical Body Composition Analyser (RJL Systems, Clinton Township, Michigan, USA). To calculate lean and fat mass, we used established sex-specific regression equations.[23] Based on our previous work, we chose the lean-to-fat ratio as a key measure of body composition.[24]

The ratio was calculated by dividing lean mass by fat mass. The lean-to-fat ratio is advantageous because it is independent of body size and avoids the collinearity between lean and fat mass. Moreover, the ratio is more closely related to functional limitation than lean mass or fat mass alone.[23] [25]

Isometric skeletal muscle strength was evaluated following standard manual muscle testing procedures.[26] A hand-held dynamometer was used to improve the objectivity of the force estimates (MicroFet2 dynamometer; Saemmons Preston, Bolingbrook, Illinois, USA).[26] The examiners were trained in manual muscle testing by the same experienced physical therapist. Each of the examiners practiced testing control subjects

until there was agreement between the raters 90% of the time within five pounds of force.

Knee extensor (quadriceps), hip extensor and hip abductor (ie, gluteus medius) strength were measured because these muscles are considered critical for standing and walking. In addition, previous work has also suggested the importance of quadriceps weakness as a predictor of reduced maximal exercise performance in COPD.[27–30] In the upper extremity, power grip, precision grip and elbow flexion strength were measured because these muscles are important for performing many daily activities. We have previously described these methods in detail.[13]

Assessment of functional limitations
The central distinction between functional limitation and disability can be illustrated by the difference between 'action' and 'activity'.[11] Specifically, functional limitation indicates decreased capacity or capability, whereas disability refers to activity in a social or role-based context. For example, measurement of distance walked in 6 min (Six Minute Walk Test) reflects functional limitation; difficulty walking to perform errands comprises disability.

We assessed functional limitations, which are decrements in basic physical or mental actions, using a multifaceted physical assessment. Lower extremity function was measured using the validated Short Physical Performance Battery (SPPB) which includes tests of standing balance, gait speed and chair stand.[31–33] A summary performance score integrates the three performance measures, ranging from 0 to 12. Previous work indicates that the battery has excellent inter-observer reliability, test-retest reliability and predictive validity.[31–33]

We also measured balance with the functional reach test. This test measures how far a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position, without losing balance.[34] The functional reach test has excellent test–retest reliability and validity.[34–37]

Submaximal exercise performance was measured using the Six Minute Walk Test, which has been widely used in studies of COPD.[38] [39] We measured submaximal rather than maximal exercise performance because most daily activities are likely to require sustained submaximal exertion, rather than maximal exercise levels. We used a standardised flat, straight course of 30 m in accordance with American Thoracic Society (ATS) Guidelines.[40]

Mobility-related dyspnoea, which is the extent of mobility limitation due to breathlessness, was measured by the British Medical Research Council (MRC) dyspnoea scale.[41] Used for many years, this scale has five items that assess the degree of dyspnoea during basic mobility tasks, ranging from dyspnoea with strenuous exercise (grade 1) to inability to leave the house due to dyspnoea (grade 5). The MRC dyspnoea scale has been used extensively; its construct validity is supported by correlation with health-related quality of life, exercise performance and ability to perform activities of daily living.[42–44]

Cognitive function was measured using the Mini-Mental State Examination, which is the leading screening test for cognitive impairment in North America.[45] The 11-item instrument assesses orientation, recall ability, short-term memory and arithmetic ability.[46] It evaluates most of the main domains of cognitive status and has been extensively validated.[45–50] We used the recommended cut-point score of <24 points to indicate cognitive impairment.[51]

Study outcome: measurement of COPD-related disability
We conceptualise disability as the impact of COPD on a broad range of daily activities. These activities include those that are

necessary for survival, but also social, spiritual, and recreational activities. To measure disability, as this comprehensive construct, we used the Valued Life Activities scale which was originally developed for arthritis and subsequently adapted for use in asthma and COPD.[52–55] The scale measures difficulty with functioning in 22 distinct activity domains, ranging from self-care to social and recreational pursuits. For each activity domain, subjects rate the amount of difficulty that they have because of their breathing problems on a scale from 0 to 10 (0=no difficulty, 10=unable to perform the activity). Based on subject responses, the proportion of activities that they cannot perform is calculated as the principle measure of COPD-related disability. The proportion has a theoretical range from 0 to 1.0 (or 0 to 100% in percentage terms).

The disability scale was administered at baseline and follow-up telephone interviews and change scores were calculated. We used the method of Wywrich et al to estimate the 'minimal important difference' in score, based on the SE of measurement (SEM).[56 57] The SEM is calculated as the SD of a score multiplied by the square root of 1 minus the reliability coefficient.[56] Using this method, we estimated that the minimal important difference is an absolute increase in the proportion of activities that cannot be performed of 3.3% from baseline to 2-year follow-up assessments. Based on the continuous disability score, we defined the primary measure of prospective disability—a dichotomous study outcome—as a score increase of at least 3.3% from baseline. We also defined a secondary disability outcome as the development of any new activity domain that cannot be performed due to COPD among subjects who had reported no baseline disability.

Statistical analysis

Statistical analysis was conducted using SAS software, version 9.1 (SAS Institute, Inc.) and STATA 10. Bivariate analysis was conducted with the t-test for continuous variables and χ^2 test for dichotomous variables. A 2-tailed p value of <0.05 was used to indicate statistical significance.

Multivariable logistic regression analysis was used to evaluate the impact of respiratory impairment (FEV_1 and oxygen saturation) on the prospective risk of disability after controlling for potential confounding variables. Confounders were selected a priori based on our prior work examining the sociodemographic and personal factors that are related to physical activity and disability: age, sex, race, height, educational attainment, household income and smoking status.[4 58 59] The analysis was repeated for the primary disability outcome (a longitudinal increase of 3.3% or more in the percentage of activities that cannot be performed) and the secondary disability outcome (development of one or more new activity domains that cannot be performed, among subjects with no baseline disability).

We used multivariable logistic regression analysis to examine the impact of each non-respiratory impairment and functional limitation on the prospective risk of disability from baseline to 2-year follow-up assessment. Because the non-respiratory impairment and functional limitation tests (eg, Short Physical Performance Battery) yield continuous variables, we defined non-respiratory impairment/functional limitation as the lowest quartile of performance on an a priori basis. The exception is cognitive impairment, which has a well-established cut-point (<24 points) on the Mini-Mental State Examination.[51]

To examine the impact of non-respiratory impairment/functional limitations on the prospective risk of disability, we compared three nested logistic regression models. Model 1 included baseline sociodemographic and personal characteristics (age, sex, race, educational attainment, household income and

Table 1 Baseline characteristics among adults with COPD by follow-up status

	Cohort (n=1051)	No follow-up (n=151)	p-Value
Age (mean years, SD)	58.3 (6.2)	57.6 (6.4)	0.19
Female sex (n, %)	620 (59%)	71 (47%)	0.006
Race (white, non-hispanic)	725 (69%)	87 (58%)	0.006
Educational attainment (n, %)			
High school or less	300 (29%)	51 (34%)	0.03
Some college	453 (43%)	72 (48%)	
College degree+	298 (28%)	28 (19%)	
Household income (n, %)*			
Low income (<$20K)	103 (9.8%)	26 (17%)	0.064
Medium income ($20−80K)	614 (58%)	85 (56%)	
High income (>$80K)	247 (24%)	29 (19%)	
Smoking history (n, %)			
Past smoker	571 (54%)	73 (48%)	0.032
Current smoker	330 (31%)	63 (42%)	
Never smoker	150 (14%)	15 (10%)	
Forced expiratory volume in 1 s	1.80 (0.77)	1.77 (0.81)	0.67

Proportions are column %.
Forced expiratory volume in 1 s per cent was 63% in both groups. The proportion of subjects who were GOLD Stage II or higher was similar in both groups (61%).
*A minority of all subjects (8%) declined to report their income.

smoking history). Model 2 included the same variables plus respiratory impairment measures (FEV_1 and oxygen saturation). Model 3 included all previous variables plus non-respiratory impairment (body composition and skeletal muscle strength) and functional limitations (lower extremity function, balance, submaximal exercise performance, dyspnoea on exertion, and cognitive impairment). The c-statistic was used to quantify the area under the receiver operating characteristic (ROC) curve, which represents the predictive or discriminatory capacity of each model. The method of Delong and colleagues was used to statistically compare the area under each ROC curve.[60] The incremental contribution of respiratory impairment to the longitudinal prediction of disability was determined by comparing model 2 to model 1; the incremental impact of non-respiratory impairment/functional limitation was derived from comparing model 3 to model 2.

To evaluate a more severe spectrum of COPD, we repeated the ROC analysis re-defining COPD as an FEV_1/FVC ratio <0.70 and $FEV_1 < 80\%$ predicted (ie, GOLD stage II or greater; consistent with the Burden of Lung Disease (BOLD) Study strategy).[22] This sensitivity analysis focused on subjects with more severe disease.

RESULTS

Baseline characteristics

Completion of the 2-year follow-up assessment was high (87%). As shown in table 1, the cohort completing follow-up was somewhat more likely to be female, white non-hispanic, better educated, higher income and past (as opposed to current) smoker. There were no differences in age or lung function (FEV_1) by follow-up status.

Respiratory impairment and the prospective risk of disability

At baseline, 26% of subjects indicated disability (one or more activity domains that they were unable to perform). The proportion of activities that they could not perform ranged from 0% to 68%. In the entire cohort, 110 subjects with COPD developed the primary disability outcome measure (10.5%; 95% CI 8.7 to 12.5%). Among subjects without baseline disability, a slightly lower proportion developed the secondary disability outcome (n=66; 8.5%; 95% CI 6.6 to 10.7%).

Table 2 Respiratory impairment and prospective risk of disability in COPD

Respiratory impairment measure	Prospective disability measure*	
	Primary Increase in proportion of activities unable to perform (n=1051)	**Secondary** Development of ≥1 activity unable to perform in those with no baseline disability (n=777)
Forced expiratory volume in 1 s		
Base model†	1.95 (1.41 to 2.70) p<0.0001	1.95 (1.28 to 2.98) p=0.002
Base model + covariates†	1.75 (1.26 to 2.44) p=0.0009	1.81 (1.17 to 2.80) p=0.007
Baseline oxygen saturation		
Base model	1.70 (1.23 to 2.34) p=0.0012	1.45 (1.00 to 2.12) p=0.053
Base model + covariates	1.57 (1.13 to 2.18) p=0.008	1.33 (0.90 to 2.0) p=0.16

*Incident disability was based on two measures. Primary disability outcome = an increase in the proportion of activities that subject is unable to perform from wave 1 to wave 2. A significant increase was defined as that exceeding 1 SE of measurement (see Methods). Secondary outcome was development of at least one new activity that subject is unable to perform among subcohort who had no disability at baseline.
†Results are from logistic regression analysis and are presented as ORs (95% CIs). ORs are expressed for a 1 l decrement of FEV_1 and 5% decrement of oxygen saturation. Baseline model used the following predictor variables: respiratory impairment measure plus age, sex, race, and height. Covariates (potential confounders) = race, educational attainment, household income, and smoking status.

Respiratory impairment measures were related to the development of COPD-related disability. Greater lung function impairment, as evidenced by lower FEV_1, was associated with a greater longitudinal risk of the primary disability outcome after controlling for covariates (OR 1.75 per 1 l decrement; 95% CI 1.26 to 2.44) (table 2). Lower oxygen saturation was also related to a greater risk of developing disability (OR 1.57 per 5% decrement; 95% CI 1.13 to 2.18). Analysis of the secondary disability outcome revealed similar effect estimates for FEV_1; the estimates were slightly lower for oxygen saturation (table 2).

Non-respiratory impairment/functional limitations and the prospective risk of disability

Both non-respiratory impairment domains were individually associated with a greater prospective risk of disability after controlling for respiratory impairment and other covariates (table 3). Decreased lower extremity muscle strength, as evidenced by strength of the quadriceps, hip flexors and hip abductors, was associated with a higher risk of developing disability (OR 1.93; 95% CI 1.22 to 3.05, OR 1.64; 95% CI 1.03 to 2.59, and OR 1.80; 95% CI 1.15 to 2.84, respectively). Abnormal body composition, as measured by low lean-to-fat ratio, was also related to a greater risk of COPD-related disability (OR 1.80; 95% CI 1.08 to 3.02). Analysis of the secondary disability outcome measure revealed similar results for muscle strength (albeit with wider CIs from the smaller sample size in this analysis); body composition was not statistically related to the secondary disability outcome.

Many of the functional limitation domains were associated with a higher longitudinal risk of disability, after controlling for respiratory impairment. Poor lower extremity functioning (OR 2.57; 95% CI 1.65 to 4.01) and exercise performance (OR 2.93; 95% CI 1.90 to 4.53) were related to a greater risk of COPD-related disability. Mobility-related dyspnoea was also related to greater disability risk (OR 2.93; 95% CI 1.80 to 4.75). Analysis of the secondary disability outcome revealed similar results, except that poorer balance was additionally associated with a higher risk of disability (OR 2.22; 95% CI 1.27 to 3.88).

Non-respiratory impairment/functional limitations increased the prospective risk of disability after taking respiratory impairment and other personal characteristics into account. Addition of respiratory impairment measures (FEV_1 and oxygen saturation) to the base logistic regression model including baseline sociodemographic and personal characteristics increased the area under the ROC curve from 0.65 to 0.69 (p=0.029) (table 4, figure 1A). When non-respiratory impairment/functional limitations were added to the model, the area under the ROC curve increased further to 0.75 (p=0.003). The results were highly similar for a sensitivity analysis of the cohort with more severe COPD (GOLD Stage II or higher) (table 4, figure 1B). The results were also highly similar for the secondary disability outcome (results were 0.67, 0.70 and 0.78, respectively).

DISCUSSION

Prospective development of disability was a common occurrence in our cohort of younger adults with COPD during the 2-year follow-up period (approximately 1 in 10 subjects). Although respiratory impairment increased the longitudinal risk of disability, the development of non-respiratory impairment and functional limitations in body systems remote from the lung had a greater impact on disablement. Muscle strength, lower

Table 3 Non-respiratory impairment/functional limitations and the prospective risk of COPD-related disability

Predictor variable*	Prospective disability measure	
	Primary outcome† Increase in proportion of activities unable to perform (n=1051)	**Secondary outcome†** Development of ≥1 activity unable to perform in those with no baseline disability (n=777)
Non-respiratory impairment*		
Body composition	1.80 (1.08 to 3.02) p=0.025	1.42 (0.71 to 2.82) p=0.32
Muscle strength		
Quadriceps	1.93 (1.22 to 3.05) p=0.0052	1.83 (0.98 to 3.40) p=0.057
Hip flexors	1.64 (1.03 to 2.59) p=0.036	1.83 (0.98 to 3.33) p=0.052
Hip abductors	1.80 (1.15 to 2.84) p=0.011	2.22 (1.21 to 4.05) p=0.01
Elbow flexors	1.51 (0.93 to 2.45) p=0.093	1.69 (0.89 to 3.20) P=0.11
Grip	0.86 (0.51 to 1.47) p=0.59	0.57 (0.26 to 1.28) p=0.18
Pinch	0.67 (0.39 to 1.15) p=0.15	0.64 (0.31 to 1.30) p=0.22
Functional limitations*		
Lower extremity functioning	2.57 (1.65 to 4.01) p<0.0001	3.20 (1.76 to 5.81) p<0.0001
Balance	1.41 (0.90 to 2.21) p=0.14	2.18 (1.23 to 3.86) p=0.008
Exercise performance	2.93 (1.90 to 4.53) p<0.0001	4.01 (2.23 to 7.20) p<0.0001
Mobility-related dyspnoea	2.93 (1.80 to 4.75) p<0.0001	4.55 (2.22 to 9.30) p<0.0001
Cognitive dysfunction	1.34 (0.62 to 2.90) p=0.46	1.53 (0.51 to 4.57) p=0.44

*For each non-respiratory impairment/functional limitation, poor function was defined as the lowest quartile of the distribution (except cognitive impairment which used a standard cut-point of 24 points on the Mini-Mental Status Examination). Measurements = body composition (lean/fat ratio from bioelectrical impedance), muscle strength testing (dynamometry), lower extremity functioning (Short Physical Performance Battery), balance (Functional Reach Test), exercise performance (Six Minute Walk Test), and dyspnoea (Modified MRC Dyspnoea Scale).
†Individual multivariable logistic regression analyses controlling for age, sex, race, height, educational attainment, household income, smoking status, and respiratory impairment (FEV_1 and oxygen saturation). All results are ORs (95% CIs) with accompanying p values.

Table 4 Relative contribution of respiratory impairment and non-respiratory impairment/functional limitations to prospective risk of COPD-related disability

COPD severity measure	Area under the receiver operating characteristic curve (95% CI)	
	Entire cohort (n = 1051)	GOLD Stage II or greater
Model 1: sociodemographic and personal characteristics	0.65 (0.59 to 0.70)	0.66 (0.60 to 0.72)
Model 2: sociodemographic characteristics + respiratory impairment	0.69 (0.63 to 0.74)	0.70 (0.65 to 0.76)
Model 3: sociodemographic characteristics + respiratory impairment + non-respiratory impairment/functional limitations	0.75 (0.70 to 0.80)	0.78 (0.72 to 0.84)
Overall comparison	p<0.001	p<0.001
Comparison of model 2 vs model 1	p=0.029	p=0.064
Comparison of model 3 vs model 2	p=0.003	p=0.0017

Area under the ROC curve derived from three multivariable logistic regression models using primary disability outcome. Baseline model included age, sex, race, height, educational attainment, household income, and smoking history. Second model included all baseline factors plus respiratory impairment indicators (FEV_1 and baseline resting oxygen saturation). Third model includes all previous variables plus non-respiratory impairment (muscle strength, body composition) and functional limitations (lower extremity function, balance, submaximal exercise performance, mobility-related dyspnoea, and cognitive impairment).

extremity function, exercise performance and mobility-related dyspnoea were potent risk factors for disability, even after taking lung function impairment into account. These results require a paradigm shift in COPD: the assessment and treatment of airway obstruction, which have been the cornerstones of treatment, will not be sufficient to prevent the development of COPD-related disability.

Although cross-sectional studies have found a high prevalence of activity restriction in COPD, longitudinal estimates of disablement are rare.[4–10] The SUPPORT study reported that more than half of adults hospitalised for COPD exacerbation subsequently had diminished ability to perform activities of daily living.[10] In addition, most studies of COPD-related disability have focused on a restricted range of daily activities, such as activities of daily living which are necessary for survival.[4–10] Other studies are limited by small sample size and focus on severe COPD.[4–10] Consequently, our adds important new information by prospectively elucidating the development of disability using a broad measure of daily activities in a cohort with a wide range of disease severity.

Our study advances the field because it systematically evaluated the impact of extra-pulmonary impairment and functional limitations on the prospective risk of disability in COPD, after accounting for respiratory impairment. Other studies have individually found that lung function, muscle strength or exercise capacity are related to performance of daily activities.[30 61–66] But none of these studies evaluated disability of a broad range of daily activities, comprehensively evaluated a functional limitations and ascertained prospective disability endpoints. Consequently, our work builds on these previous studies and establishes that non-respiratory impairment and physical functional limitations are the main drivers of the disablement process in COPD.

Our study has several limitations. There is some possibility of misclassification of COPD, although we performed rigorous steps to avoid it. The inclusion criteria required a physician diagnosis of COPD, healthcare utilisation for COPD, and dispending of COPD medications, which was designed to increase the accuracy of case ascertainment. We also previously demonstrated the validity of our approach using medical record review.[16] Nonetheless, we acknowledge this potential limitation.

Although we had excellent cohort retention (90% of living subjects were re-interviewed), it is possible that selection bias could have been introduced by losses to follow-up by death or

other factors. For example, there were some differences in sociodemographic characteristics by follow-up status. There were no differences in age or lung function, but the retained cohort had
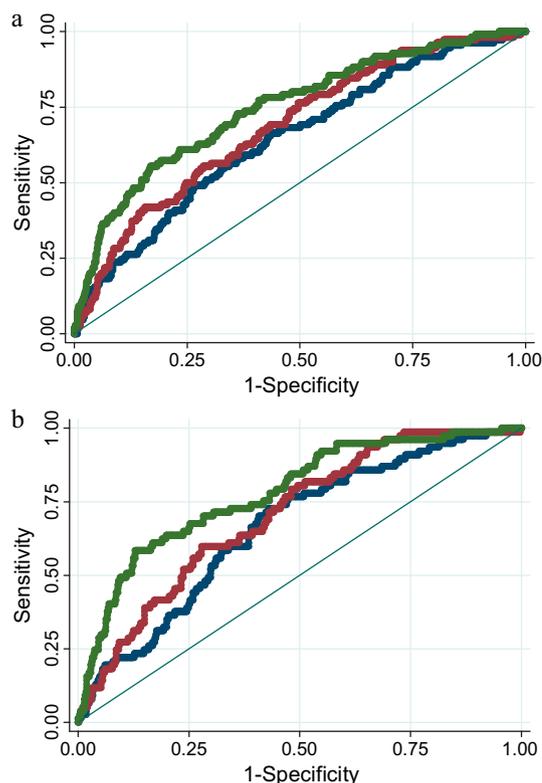
Figure 1 Non-respiratory impairment/functional limitations increase the risk of incident disability in COPD. Receiver operating characteristic curves for the prospective risk of incident disability defined as an increase in the proportion of activities that the subject is unable to perform. Blue curve is for sociodemographic characteristics and smoking status (age, sex, race, height, educational attainment, household income, smoking status). Red line also includes respiratory impairment (FEV_1 and oxygen saturation). Green line includes all previous variables plus non-respiratory impairment (muscle strength, body composition) and functional limitations (lower extremity function, balance, exercise performance, mobility-related dyspnoea, and cognitive impairment). Each curve was statistically different from the others (p<0.001). Figure 1A depicts the entire cohort. Figure 1B depicts the cohort with COPD GOLD Stage II or greater (more severe COPD).

somewhat higher socioeconomic status. Because lower social class is associated with a greater risk of poor health status and disability, our results likely underestimate the development of COPD-related disability. To the extent that functional limitations are greater in the group without follow-up, the analysis would also underestimate the impact of functional limitations on the risk of disability. Consequently, any bias introduced would be conservative.

Because our goal is ultimately disability prevention, we intentionally recruited younger subjects with COPD (aged 45–65 years). As a result, this age range may limit conclusions about elderly persons with COPD. Moreover, our patients were all insured with access to healthcare services. Our results may not fully apply to persons who are not receiving treatment for COPD. The demographic and socioeconomic characteristics of Northern California Kaiser Permanente members, however, are similar to those of the regional population.[67] There is also no evidence of systematic inclusion or exclusion of healthy persons into the KP system.[68] Overall, KPMCP members are likely similar to the general US population.

By elucidating the pathway to COPD-related disability, our goal is to provide a scientific basis for the screening and prevention of COPD-related disability. Although measurement of lung function, which is a cornerstone of clinical practice guidelines, predicts disability, it does not by itself fully characterise disability risk. Development of non-respiratory impairment and functional limitations, which reflect the systemic nature of COPD, are critical determinants of disablement. Consequently, medical management may need to be complemented by comprehensive rehabilitative strategies aimed at the diverse extra-pulmonary manifestations of COPD to prevent disability and restore of function.

Competing interests MDE completed this study while he was a full time member of the University of California San Francisco. Currently, he is a full time employee of Genentech, Inc. and continues to have a faculty position at University of California San Francisco. He has no financial interest in the topic of this manuscript. No other authors have declared a competing interest.

Ethics approval This study was conducted with the approval of the UCSF, KPNC.

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