Predictors of dyspnea prevalence: Results from the BOLD study

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ABSTRACT

Dyspnea is a cardinal symptom for cardiorespiratory diseases. No study has assessed worldwide variation in dyspnea prevalence or predictors of dyspnea.

We used cross-sectional data from population-based samples in 15 countries of the BOLD study to estimate prevalence of dyspnea in the full sample as well as in an a priori defined low-risk group (few risk factors or dyspnea-associated diseases). Dyspnea was defined by the modified Medical Research Council questions. We used ordered logistic regression analysis to study the association of dyspnea with site, sex, age, education, smoking habits, low/high BMI, self-reported disease, and spirometry results.

Of the 9,484 participants, 27% reported any dyspnea. In the low-risk subsample (N=4,329), 16% reported some dyspnea. In multivariate analyses, all covariates were correlated to dyspnea, but only 13% of dyspnea variation was explained. Women reported more dyspnea than men (odds ratio ≈ 2.1). When forced vital capacity (FVC) fell below 60% of predicted, dyspnea was much more likely.

There was considerable geographical variation in dyspnea, even when we adjusted for known risk factors and spirometry results. We were only able to explain 13% of dyspnea variation.
INTRODUCTION

The presence of dyspnea predicts long-term mortality (1) and characterizes high-prevalence diseases like congestive heart failure, ischemic heart disease, chronic obstructive pulmonary disease (COPD), and asthma. In 2004, ischemic heart disease, lower respiratory infections, and COPD together accounted for more than 14 million deaths worldwide (2). In COPD, chronic dyspnea is one of the strongest predictors of poor quality of life (3), an important predictor of exacerbation outcomes (4), and a marker of both disease severity and disability.

Dyspnea prevalence has varied greatly across studies (5-9) and countries (10, 11). Some might be due to differences in the distribution of known correlates of dyspnea such as age, sex, and smoking status (6, 8, 9, 11, 12). But differences might also reflect variation in how dyspnea was measured, the nature of the samples studied and the burden of chronic diseases that cause dyspnea. Various dyspnea scales have been proposed, but no consensus exists regarding which scale to choose and whether the standard approach of picking a rather arbitrary cut-off for defining dyspnea is appropriate. By reducing a graded scale, some information is inevitably lost.

Some population-based studies have reported a dyspnea prevalence of more than 20% (6, 7, 11, 13). A high-prevalence of cardiopulmonary diseases, life-style changes, obesity and subclinical medical conditions might have explained this dyspnea. To improve understanding of geographical variation in dyspnea and its correlates, large international studies using standardized methods are needed. The PLATINO study was a population-based study in São Paulo (Brazil), Santiago (Chile), Mexico City (Mexico), Montevideo (Uruguay), and Caracas (Venezuela)(14). They reported several correlates of dyspnea, including sex, FEV₁ % predicted, comorbidities, age, body mass index (BMI), race, education, quality of life and other respiratory symptoms that all predicted (any) dyspnea (11). Dyspnea was defined by a dichotomous cut-off using standardized questionnaires in Spanish and Portuguese in Latin American countries.

As the PLATINO study, the Burden of Obstructive Lung Diseases (BOLD) study was also designed to estimate the social and economic burden of COPD. In order to provide state-of-the-art estimates, population-based samples from American, European, Asian, African and Oceanic countries were recruited and investigated using standardized questionnaires and post-
bronchodilation spirometry (15). Dyspnea was evaluated by the five-level modified Medical Research Questionnaire (mMRC) (16), measuring the impact domain of activity-related dyspnea. The BOLD study applied identical methods across culturally and geographically diverse study sites, and thus provided a unique opportunity to assess correlates of dyspnea.

Our goal in this paper was to examine the prevalence and correlates of self-reported dyspnea across sites representing substantial geographic variation. Using BOLD data from 15 countries, and strictly standardized methods, we examined a variety of possible predictors. By using ordered logistic regression we were able to avoid dichotomizing a multi-level categorical variable. In addition we estimated the degree of dyspnea reporting in low-risk individuals by examining how dyspnea prevalence changed when subjects with risk factors for dyspnea, spirometric lung function impairment and self-reported dyspnea-causing conditions were excluded.

**METHODS**

**Study population:** The design of the BOLD study was prospectively described elsewhere (15). All sites aimed at recruiting population-based samples of at least 300 men and 300 women aged 40 years and older. Target populations were well-characterized administrative areas. The current analyses included participants from sites recruited as part of the initial phase of the BOLD study: Australia, Austria, Canada, China, Germany, Iceland, India, Norway, Philippines, Poland, South Africa, Sweden, Turkey, United Kingdom and the USA. Of the 11,048 respondents to the survey (individuals with both post-bronchodilator spirometry data and minimal questionnaire data), 10,441 (94.5%) also had acceptable lung function data and were potentially eligible to be included in the analyses. Site-specific sampling strategies and response rates are given in E-Table 1 of the online supplement. All participants signed informed consent forms, and the study protocol conformed to the Helsinki Declaration and was approved by local ethic committees at all sites.

**Data Collection:** The BOLD Study required cross-sectional surveys of population-based samples. Participants completed a face-to-face interview by trained and certified research assistants. Height, weight, and pre- and post-bronchodilator (BD) spirometry were measured. For this report we used questionnaire-derived data on smoking habits, education, occupational exposure, dyspnea as measured by the modified Medical Research Council (mMRC) questionnaire (16), attacks of dyspnea with wheezing; and the presence of selected...
medical conditions: heart disease, asthma, emphysema, current chronic bronchitis, COPD, tuberculosis, lung cancer, diabetes, lung surgery, and childhood hospitalizations for breathing problems. In non-English-speaking countries, standardized questionnaires were forward and backward translated. (15)

The mMRC dyspnea questions describe 5 grades of dyspnea: dyspnea only with strenuous exercise (grade 0, or normal); dyspnea when hurrying on the level or up a slight hill (grade 1); dyspnea when walking at own pace on the level (grade 2); dyspnea when walking 100 yards or a few minutes (grade 3) and dyspnea at rest (grade 4). (16) Subjects were assigned the highest dyspnea grade with a positive response. Subjects with inability to walk due to other reasons than dyspnea were excluded from further analyses, which left 9,484 individuals available for the current analyses. The exact wording of all BOLD mMRC questions are included in the online appendix.

Spirometry was measured by trained and certified technicians according to ATS standards (17) using a portable spirometer (EasyOne® from ndd Medizintechnik AG, Zürich, Switzerland). Post-BD spirometry was done 15 minutes after 200 mcg salbutamol had been administered through a spacer. All maneuvers were reviewed and quality graded at a central pulmonary function reading center. Predicted and lower limit of normal (LLN) values for the forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were calculated using the U.S. National Health and Nutrition Examination Survey (NHANES) III prediction equations from healthy Caucasians. (18)

For these analyses we defined a restrictive spirometry pattern as a post-BD FVC <LLN and FEV₁/FVC >LLN. Chronic airway obstruction was defined as post-BD FEV₁/FVC < LLN, whereas spirometric COPD was defined as post-BD FEV₁/FVC < LLN and FEV₁ % of predicted <LLN. Pre-bronchodilator obstruction was defined as FEV₁/FVC < LLN before administration of salbutamol. A body mass index (BMI) >30 kg/m² was defined as obesity, while a BMI <18.5 kg/m² was considered underweight according to WHO guidelines.

The dyspnea low-risk group: We defined a subsample in order to investigate the prevalence of dyspnea when subjects with abnormal spirometry or self-reported dyspnea-causing conditions were excluded. This low-risk sub-sample excluded participants with any of the following: self-reported heart disease, asthma, attacks of wheezing with dyspnea, emphysema, chronic
bronchitis, COPD, tuberculosis, lung cancer, pre- or post-BD airway obstruction, or a low FVC.

Statistical methods: We first investigated dyspnea prevalence in the cohort as a whole and in the dyspnea low-risk subset as well as the relationship between lung function and dyspnea. Thereafter we conducted multivariable ordered logistic regression to identify correlates of mMRC defined dyspnea. We used-Wald chi-square tests to assess statistical significance of individual variables in our models and used reductions in the Wald statistic as a measure of the amount of site-site variability that was explainable by other covariates. (19) All analyses ignored sampling weights and instead presented results as unweighted means and regression coefficients.

The outcome variable was the five-level categorical mMRC-variable. The regression coefficients from these models have the interpretation of ln(odds ratios). Specifically, for an increase of one unit in any given predictor variable, the model assumes that the natural log odds ratios, ln(OR)s, for (mMRC 1-4 vs mMRC 0), (mMRC 2-4 vs mMRC 0-1), (mMRC 3-4 vs mMRC 0-2) and (mMRC 4 vs mMRC 0-3) are identical. Thus a positive regression coefficient implies increased severity of dyspnea with increasing values of the corresponding predictor variable. For a binary indicator of a particular exposure, the regression coefficients therefore represent ln(odds ratios) for the exposed group relative to the reference (unexposed) group.

We tested several different models:

- Model 1 estimated the association of dyspnea with site and sex.
- Model 2 estimated the association of dyspnea with site, sex, age, smoking status, obesity, underweight, education, occupational exposure to dust, reported doctor-diagnosed or history of heart disease, hypertension, diabetes, tuberculosis, lung surgery and hospitalization for respiratory disease in childhood.
- Model 3 estimated the association of dyspnea with the factors in model 2, plus post-bronchodilation FEV1/FVC below LLN (a dichotomous variable, obstruction or not).
- Model 4 estimated the association of dyspnea with the factors in model 2, plus post-bronchodilator FVC in % percent of predicted (a continuous lung function variable).
• Model 5 estimated the association of dyspnea with the factors in model 2 plus both lung function parameters from models 3 and 4.

We also investigated interaction effects between site and sex, but these models are not reported in full. All analyses were done using Stata 10 for Windows (Stata Corp, College Station, TX).
RESULTS

About one-quarter of participants were obese and 45% were never-smokers (Table 1). A diagnosis of asthma was reported by 11%, but only 1-2% reported COPD, chronic bronchitis, or emphysema. The prevalence of the four dyspnea grades by site is shown in Figure 1, and exact prevalence and confidence intervals are given in E-Table 2 of the online supplement. Any dyspnea (grades 1-4) was reported more frequently by women than men (Table 2). These patterns persisted in the low-risk for dyspnea sample, which included 41% of the men and 40% of the women from the entire study population.

Figure 2 shows the unadjusted prevalence of mMRC 2-4 dyspnea in men and women by FVC % predicted and by FEV1/FVC % predicted, stratified by dyspnea risk. Lower FVC or lower FEV1/FVC ratio was associated with more dyspnea in both women and men, but for all levels of lung function there was more dyspnea in women. The same pattern was found in the low-risk subsample. Figure 3 shows a boxplot of FVC % predicted by mMRC grades. Consistent with the message of figure 2, we see a pattern of declining FVC with increasing level of dyspnea. Although this association was highly significant (1-way ANOVA F=134.8, p < 0.001), the distributions of FVC nonetheless exhibit considerable overlap across the dyspnea grades. E-figure 1 in the online supplement shows a boxplot of FEV1 % predicted by mMRC grades.

Results of multivariate models: In ordered logistic regression models, site was a highly significant predictor of dyspnea, even after adjustment for socio-demographic variables, comorbidities, and lung function (Table 3). Reductions in the Wald chi-square statistic for site can be used as a proxy for the amount of variability associated with site-site differences that are explainable by the other variables in the model. So for instance the socio-demographic and comorbidity variables appear to explain about 45% of the variability attributable to site, while %predicted FVC explains an additional 6-7% of site-site variability.

In virtually all of the models we examined, female gender; increasing age; less education; both obesity and underweight; both current and past smoking history; occupational dust exposure; reported diagnoses of hypertension, heart disease, diabetes, or tuberculosis; prior lung surgery; hospitalization for breathing problems as a child; and reduced FEV1/FVC and FVC were all associated with increased dyspnea. The distribution of these risk factors across
sites is shown in E-table 3 of the online supplement. We also assessed whether the impact of gender on dyspnea varied by site (data not shown), and observed statistically significant interactions (p<0.04) for models 3 and 5. No other interactions were assessed.

Figures 4 and 5 shows the odds ratios for mMRC grade 2-4 dyspnea when FVC % predicted and FEV₁/FVC % predicted were categorized as in Figure 2, and adjusted for the same covariates as in models 2-4. These adjusted analyses reinforce the visual impression from Figure 2.
DISCUSSION

We observed that dyspnea exhibited geographical variation beyond that which might be explained by known risk factors such as age, sex, education, smoking habits, comorbidities and spirometry results. But despite comprehensive information, only 13% of dyspnea variance was explained in these multivariate analyses.

Both in bivariate and multivariate analyses we observed a much higher risk of dyspnea when FVC % predicted and FEV₁/FVC % predicted fell below 60% and 70%, respectively. In addition, dyspnea was reported in nearly 1 in 6 study participants of the low-risk group for dyspnea. A change of lifestyle and issues regarding how to measure dyspnea across cultural and linguistic borders might explain some dyspnea variance, but more research is clearly needed on the heterogeneity of dyspnea.

The heterogeneity of dyspnea across sites remained highly significant in all our multivariate models, but adjustment for an increasing number of covariates clearly reduced this variation. The European Respiratory Health Survey (ECRHS) showed site variation in asthma-related dyspnea symptoms (10), but concluded that in multivariate analyses there was no significant site heterogeneity (20). The PLATINO study found significant effects of sex, age, education, FEV₁, comorbid diseases, wheeze, cough, phlegm and health-related quality of life on MRC-defined dyspnea (11). The current results from the BOLD study confirm that most of these predictors were present also in population-based samples worldwide. As in previous reports the odds of more dyspnea in women were about twice that of men. However, despite a large number of centers, the ECRHS emphasized asthmatic symptoms in young adults and did not include Asian, South-American or African countries. The PLATINO study consisted of 5 cities in one subcontinent. The BOLD study with its greater global spread may have greater ability to show true geographical variation.

We observed an accelerated increase in prevalence of dyspnea with decreasing FVC and FEV₁/FVC. Jakeways and colleagues observed similar patterns in a single site study, but did not adjust for potential confounders (7). The visual inspection of our data, although not formally tested, also appeared consistent with findings in studies where activity related dyspnea was elicited during cardiopulmonary exercise testing (21).
The association between FVC and dyspnea supports recent findings by Burney and Hooper who observed in data also from the BOLD Study that an association between FEV₁ and mortality disappeared after adjusting for FVC in subjects without known chronic respiratory diseases or symptoms (22). In patients with COPD or asthma, a low FEV₁ is an index of the severity of airway obstruction, while a low FVC is often due to hyperinflation (airtrapping) or obesity. Though closely related, these two mechanisms of pathology are not identical. It might be that the inclusion of FVC when assessing risk and symptoms of COPD could improve the performance of the suggested new classification of COPD (23). A low FVC may also be associated with poverty (24), and if this is the case, the origins may be developmental i.e. *in utero*.

Although we have found strong associations between dyspnea and several covariates, the coefficient of determination, or R² of our multivariate models indicated that we only were able to explain 13% of dyspnea variance. Several factors might account for this phenomenon. First, some dyspnea probably represents true unexplainable variation. Second, several factors were not measured, such as the individual level of stimuli sensitivity, level of physical activity, verified comorbidities, cardiovascular function and external variables such as air pollution and altitude. However, we did include information regarding key disease groups and lung function parameters. Third, the chosen measurement method for dyspnea (the mMRC) has some limitations. The mMRC measures the impact domain of activity-related dyspnea, but breathlessness with activity is not necessarily perceived as discomforting, and does not necessarily represent dyspnea (25). Furthermore the definition somehow assumes that this physical activity is a part of everyday life. However, both industrialized and developing countries are affected by a global epidemic of inactivity and obesity (26). If physical deconditioning is not to be regarded a disease, then one might hypothesize a baseline level of exercise-related breathlessness, explaining some of the 16% dyspnea observed in the *a priori* low-risk group. Fourth, we do now know whether the observed geographic variation represented site-site variation or variation by country. However, the BOLD study had a strong quality control program and used a translation-back-translation process for the questionnaires used in non-English speaking countries. Despite our careful attention to quality control, it is still possible that site differences may be the result of language and cultural differences in the understanding, recognition and expression of symptoms.
Two major strengths of the BOLD study are the population-based samples and the application of uniform, standardized methods with careful quality control. By using ordered logistic regression we have been able to include all information in the mMRC dyspnea scale instead of choosing some more or less arbitrary cut-point. This approach to statistical modeling might be challenging. Formal statistical testing indicated that these data do not meet the proportional odds assumption, though the significance of this test may in part reflect our very large sample size. Nonetheless we feel it is still a useful analysis that attempts to reflect the multilevel nature of the mMRC dyspnea score.

We observed a large number of participants with a restrictive spirometry pattern. This might reflect difficulties with reaching the true residual volume during a forced expiratory maneuver despite very careful attention to training and certification of technicians. But it might also reflect that we used a common reference equation for lung function variables rather than local reference values. However, it has been shown that it is not necessary to adjust the FEV₁/FVC-ratio with regards to ethnicity (27) and that such adjustments of the FVC in % of predicted might obscure associations between this variable and markers of a poor prognosis (28). Thus, our position has been that if we applied local reference equations or adjusted for ethnicity in global reference equations, we could risk obscuring associations between FVC and dyspnea.

One possible interpretation of our results might be that dyspnea is of limited usefulness as a marker of impaired health, since known risk factors and diseases explained only 13% of variance. On the other hand, dyspnea is a strong predictor of hard end-points (1, 29, 30), and the minor impact of adding spirometry information to our models underscore the inclusion of symptoms in clinical guidelines in respiratory medicine alongside pulmonary function data (23).

In conclusion, we have found significant variation in dyspnea-prevalence across 15 countries of the BOLD study. Consequently, the cross-cultural validity of research based on dyspnea as an outcome, needs to be reaffirmed. Furthermore, we found a marked increase in dyspnea prevalence as FVC fell below 60% of predicted. We observed considerable dyspnea reporting also in participants without obvious causes for breathlessness. The interpretation of exercise-related dyspnea should not be static, and dyspnea in this sub-group might be attributed to other causes than disease, for instance a modern, sedentary lifestyle. Finally, the key finding was that in a large epidemiological study, with comprehensive participant-derived
information and high-quality pulmonary function data, only a minor fraction of dyspnea variation could be explained.

**DEDICATION:**
This paper is dedicated to the memory of Michael Lebowitz, a superb pulmonary epidemiologist from Tucson, Arizona who collaborated with investigators in many countries.

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In the first phase of the study Dr R O Crapo and Dr R L Jensen (LDS Hospital, 10 Pulmonary Division, 325 8th Ave., Salt Lake City, Utah 84143-0001, USA.) were responsible for quality assurance of lung function; they and Dr Paul Enright (The University of Arizona, Tucson, AZ, USA) and Georg Harmoncourt (ndd Medizintechnik AG, Zurich, Switzerland) assisted with training lung function technicians.

REFERENCES


Tables:

Table 1: Prevalence and mean of study participant characteristics in 15 countries.  
N= 9,484.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>55.5 (11.1)</td>
</tr>
<tr>
<td>Male sex</td>
<td>49%</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.8 (5.2)</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30 kg/m²)</td>
<td>22%</td>
</tr>
<tr>
<td>Underweight (BMI&lt;18.5 kg/m²)</td>
<td>2%</td>
</tr>
<tr>
<td>Spirometry patterns</td>
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<tr>
<td>Spirometric COPD</td>
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</tr>
<tr>
<td>Post-BD Restriction</td>
<td>19%</td>
</tr>
<tr>
<td>Pre-BD obstruction</td>
<td>17%</td>
</tr>
<tr>
<td>Smoking status</td>
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<tr>
<td>Current</td>
<td>24%</td>
</tr>
<tr>
<td>Former</td>
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<tr>
<td>Never</td>
<td>45%</td>
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<tr>
<td>Education</td>
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</tr>
<tr>
<td>Primary/ Middle school</td>
<td>27%</td>
</tr>
<tr>
<td>High school/some college</td>
<td>48%</td>
</tr>
<tr>
<td>Four-year College/University</td>
<td>20%</td>
</tr>
<tr>
<td>Self-reported</td>
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<tr>
<td>Hypertension</td>
<td>28%</td>
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<td>Heart disease</td>
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<td>Diabetes</td>
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<td>Tuberculosis</td>
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<tr>
<td>Self-reported obstructive lung diseases</td>
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<td>Current chronic bronchitis</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Asthma</td>
<td>11%</td>
</tr>
<tr>
<td>Attacks of wheezing with dyspnea</td>
<td>9%</td>
</tr>
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</table>

Table 2 Prevalence (%) of mMRC dyspnea grades, stratified by health status and sex

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Low-risk</td>
<td>All</td>
<td>Low-risk</td>
</tr>
<tr>
<td>N</td>
<td>9484</td>
<td>4329</td>
<td>4640</td>
<td>2159</td>
</tr>
<tr>
<td>mMRC 0</td>
<td>73%</td>
<td>84%</td>
<td>80%</td>
<td>89%</td>
</tr>
<tr>
<td>mMRC 1</td>
<td>14%</td>
<td>12%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>mMRC 2</td>
<td>7%</td>
<td>3%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>mMRC 3</td>
<td>4%</td>
<td>1%</td>
<td>2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>mMRC 4</td>
<td>2%</td>
<td>0.3%</td>
<td>2%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Footnotes: The low-risk for dyspnea subgroup of study participants was defined as those without post-BD airflow restriction, spirometric COPD or pre-BD airflow obstruction, or self-reported heart disease, asthma, attacks of wheezing and dyspnea, emphysema, chronic bronchitis, COPD, tuberculosis or lung cancer.
Table 3: Odds ratios (95% confidence intervals) for variables predicting a higher category of dyspnea, using ordered logistic regression models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Number of participants in model</th>
<th>R² (pseudo, %)</th>
<th>Site, overall effect, Wald chi²</th>
<th>Female</th>
<th>Age, 10 year increase</th>
<th>Obesity</th>
<th>Underweight</th>
<th>High-school education</th>
<th>College or university education</th>
<th>Current smoker</th>
<th>Ex-smoker</th>
<th>Dust exposure at work</th>
<th>Heart disease</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Tuberculosis</th>
<th>Lung surgery</th>
<th>Childhood hospitalization for breathing problems</th>
<th>FEV1/FVC &lt; LLN</th>
<th>FVC % predicted, per 10% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>9,484</td>
<td>5.9%</td>
<td>748, p &lt; 0.001</td>
<td>1.78 (1.62 – 1.96)</td>
<td>1.22 (1.16 – 1.28)</td>
<td>2.00 (1.79 – 2.25)</td>
<td>1.84 (1.29 – 2.64)</td>
<td>0.74 (0.64 – 0.84)</td>
<td>0.57 (0.50 – 0.67)</td>
<td>1.99 (1.75 – 2.27)</td>
<td>1.36 (1.20 – 1.54)</td>
<td>1.44 (1.29 – 1.61)</td>
<td>2.39 (2.05 – 2.77)</td>
<td>1.33 (1.19 – 1.72)</td>
<td>1.43 (1.19 – 1.72)</td>
<td>1.66 (1.29 – 2.14)</td>
<td>4.05 (2.18 – 7.53)</td>
<td>1.54 (1.17 – 2.02)</td>
<td>2.33 (2.02 – 2.68)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>9,334</td>
<td>11.3%</td>
<td>414, p &lt; 0.001</td>
<td>2.13 (1.91 – 2.37)</td>
<td>1.17 (1.11 – 1.23)</td>
<td>2.10 (1.87 – 2.36)</td>
<td>0.75 (0.65 – 0.86)</td>
<td>0.59 (0.51 – 0.68)</td>
<td>1.75 (1.53 – 1.99)</td>
<td>1.75 (1.53 – 1.99)</td>
<td>1.27 (1.12 – 1.44)</td>
<td>1.42 (1.27 – 1.58)</td>
<td>2.38 (2.05 – 2.77)</td>
<td>1.34 (1.20 – 1.50)</td>
<td>1.27 (1.11 – 1.16)</td>
<td>1.51 (1.18 – 1.94)</td>
<td>3.47 (1.81 – 6.63)</td>
<td>1.45 (1.11 – 1.90)</td>
<td>0.77 (0.74 – 0.80)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>9,334</td>
<td>12.1%</td>
<td>416, p &lt; 0.001</td>
<td>2.11 (1.89 – 2.35)</td>
<td>1.24 (1.18 – 1.31)</td>
<td>1.83 (1.63 – 2.06)</td>
<td>1.61 (1.13 – 2.31)</td>
<td>0.75 (0.65 – 0.86)</td>
<td>0.59 (0.50 – 0.68)</td>
<td>1.94 (1.70 – 2.22)</td>
<td>1.37 (1.12 – 1.45)</td>
<td>1.46 (1.31 – 1.63)</td>
<td>2.25 (1.94 – 2.62)</td>
<td>1.26 (1.12 – 1.41)</td>
<td>1.37 (1.11 – 1.61)</td>
<td>1.65 (1.28 – 2.13)</td>
<td>3.40 (1.87 – 6.18)</td>
<td>1.49 (1.14 – 1.96)</td>
<td>0.78 (0.75 – 0.81)</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>9,334</td>
<td>12.6%</td>
<td>365, p &lt; 0.001</td>
<td>2.19 (1.96 – 2.44)</td>
<td>1.19 (1.13 – 1.25)</td>
<td>1.92 (1.71 – 2.15)</td>
<td>1.56 (1.09 – 2.22)</td>
<td>0.75 (0.65 – 0.86)</td>
<td>0.59 (0.50 – 0.68)</td>
<td>1.71 (1.49 – 1.96)</td>
<td>1.37 (1.06 – 1.96)</td>
<td>1.44 (1.29 – 1.61)</td>
<td>2.26 (1.94 – 2.63)</td>
<td>1.27 (1.13 – 1.42)</td>
<td>1.37 (1.13 – 1.66)</td>
<td>1.50 (1.17 – 1.92)</td>
<td>2.94 (1.58 – 5.48)</td>
<td>1.40 (1.07 – 1.84)</td>
<td>0.78 (0.75 – 0.81)</td>
<td></td>
</tr>
<tr>
<td>Model 5</td>
<td>9,334</td>
<td>13.4%</td>
<td>355, p &lt; 0.001</td>
<td>2.16 (1.94 – 2.42)</td>
<td>1.19 (1.13 – 1.25)</td>
<td>1.92 (1.71 – 2.15)</td>
<td>1.37 (0.96 – 1.96)</td>
<td>0.75 (0.66 – 0.87)</td>
<td>0.60 (0.52 – 0.70)</td>
<td>1.71 (1.49 – 1.96)</td>
<td>1.37 (1.06 – 1.96)</td>
<td>1.44 (1.29 – 1.61)</td>
<td>2.26 (1.94 – 2.63)</td>
<td>1.27 (1.13 – 1.42)</td>
<td>1.37 (1.13 – 1.66)</td>
<td>1.50 (1.17 – 1.92)</td>
<td>2.94 (1.58 – 5.48)</td>
<td>1.40 (1.07 – 1.84)</td>
<td>0.78 (0.75 – 0.81)</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: Missing values for models 2-4: weight - 113 subjects, education - 15 subjects, lung surgery - 1 subject, childhood breathing problems - 21 subjects. FEV1/FVC and FVC % predicted was measured post-bronchodilator.
Figures:

**Figure 1:** Prevalence of mMRC-defined dyspnea grades by site in 15 countries of the BOLD study.

**Figure 2:** Prevalence of mMRC grade 2 or higher dyspnea by FVC (% predicted) and FEV1/FVC (% predicted) in participants with a lower risk for dyspnea (stapled lines), and subjects with higher risk for dyspnea (solid lines).
lines), stratified by sex. See the text or footnotes of Table 2 for the definition the low-risk group and for number of participants.

**Figure 3:** Box-plot of FVC % predicted by mMRC dyspnea. The box represents the interquartile range (IQR), the line within the box is the median value and the whiskers shows values within 1.5 IQR of the adjacent quartile. Outliers are plotted.
Figure 4: Odds ratio (logistic regression) for mMRC 2 and higher dyspnea at different levels of FVC of % predicted. Adjusted for all covariates in table 3 except lung function variables. N=9,334.
**Figure 5:** Odds ratio (logistic regression) for mMRC 2 and higher dyspnea at different levels of FEV$_1$/FVC (% predicted, not absolute). Adjusted for all covariates in table 3 except lung function variables. N = 9,334.