



Sex-related differences in respiratory symptoms: results from the BOLD Study

To the Editor:

For both males and females, the pathway to diagnosis and treatment of lung disease often begins with the reporting of respiratory symptoms to their physician. Males and females with impaired lung function may experience the same symptoms but perceive and/or report them differently.

Physiological research on dyspnoea has provided some information on how sex differences in lung and airway size can influence the experience of dyspnoea during exercise [1]; however, there is still a knowledge gap with regard to sex-related differences in other respiratory symptoms, including cough and sputum production.

The objective of this analysis was to address this knowledge-gap with regard to respiratory symptoms in males and females with normal and impaired lung function using data from the international population-based Burden of Obstructive Lung Disease (BOLD) study [2].

The design and rationale for the BOLD initiative and preliminary prevalence data have been published elsewhere [2].

Representative population random sampling plans were used for the recruitment of participants for all study sites. As of June 2011, 20 sites (in 18 countries) had completed data collection and are included in this analysis: Guangzhou (China), Adana (Turkey), Salzburg (Austria), Cape Town (South Africa), Reykjavik (Iceland), Hannover (Germany), Krakow (Poland), Bergen (Norway), Vancouver (Canada), Lexington (USA), Manila (Philippines), Sydney (Australia), London (UK), Uppsala (Sweden), Mumbai (India), Pune (India), Lisbon (Portugal), Maastricht (The Netherlands), Nampicuan/Talugtug (Philippines) and Tartu (Estonia).

13 757 participants with acceptable post-bronchodilator spirometry were included in the analyses. The study recorded questionnaire data on respiratory symptoms, health status, and exposure to risk factors for chronic obstructive pulmonary disease (COPD).

We defined airflow limitation consistent with COPD as the ratio of post-bronchodilator forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) below the lower limit of normal (LLN), and used FEV₁ to further grade the disease: FEV₁ <80% predicted serving as the threshold for COPD II and an FEV₁ <50% pred serving as the threshold for COPD III or higher. The third US National Health and Nutrition Examination Survey (NHANES) reference equations [3] were used to calculate predicted values. Following the traditional practice of considering irreversible airflow limitation to be COPD, the COPD diagnosis was strictly based on the post-bronchodilator lung function criteria without requiring documented exposure to a known causative agent. A normal lung function was defined as a post-bronchodilator FEV₁/FVC ratio \geq LLN and FVC \geq 80%. A restrictive lung function pattern was defined when the FEV₁/FVC ratio was \geq LLN and FVC was <80% pred. Presence of self-reported cough was assessed using the following question: "Do you usually cough when you don't have a cold?" Self-reported phlegm was based on the answer to the following question: "Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold?" Self-reported wheezing and its intensity were recorded based on the answers to the following questions: "Have you had wheezing or whistling in your chest at any time in the last 12 months?" and, if appropriate, "In the last 12 months, have you had this wheezing or whistling only when you have a cold?" For this analysis wheeze was defined by an answer of "yes" to the first question and "no" to the second question. Presence and severity of self-reported dyspnoea was recorded according to the modified Medical Research Council (mMRC) dyspnoea scale (0–4). Severe dyspnoea was defined as mMRC grade 3–4.

Logistic regression was used for evaluation of sex-differences and all results were adjusted for smoking status (current, ex- or never-smoker), age, body mass index, comorbidities (using binary indicators for heart disease, hypertension, stroke, diabetes, and lung cancer), and site.

Any respiratory symptoms (dyspnoea, cough, phlegm or wheeze) were significantly more often reported by females than males with normal lung function (50% *versus* 43%; $p < 0.001$) and restrictive lung function

pattern (55% *versus* 43%; $p < 0.001$). In contrast, no significant difference in reported respiratory symptoms was seen in COPD III–IV (88% *versus* 91%; $p = 0.996$).

Overall, female sex was associated with increased odds for reported dyspnoea (OR 1.74, 95% CI 1.59–1.90; $p < 0.0001$) and reported cough (OR 1.26, 95% CI 1.16–1.38; $p < 0.0001$), but not for reported wheeze (OR 1.05, 95% CI 0.96–1.15; $p = 0.270$). In contrast, female sex was associated with decreased odds for reported phlegm (OR 0.91, 95% CI 0.84–0.99; $p < 0.042$). Odds ratios of cough, wheeze, dyspnoea, and phlegm by lung function are shown in figure 1. While females, when compared to males, had increased odds for dyspnoea in all lung function categories, increased odds for cough were only seen in normal and restrictive lung function. In contrast, decreased odds for phlegm were observed in normal lung function and COPD.

Our results indicate that for the same degree of lung function impairment females tend to report more dyspnoea and cough, but less phlegm/sputum production than males.

This is in accordance with results from the Confronting COPD International Survey, which showed that despite lower pack-years of smoking females were more likely to report severe dyspnoea than males, with similar cough and less sputum [4]. There is evidence that, compared with males, females with COPD report more functional dyspnoea for the same degree of airflow limitation [5].

A relationship exists between the sensation of dyspnoea and respiratory muscle strength. As males can generate greater maximal inspiratory and expiratory pressures than females [6], this could probably explain why female subjects with COPD are more dyspnoeic than males. In addition to this, natural anatomical differences in the size of the lungs, airways and respiratory musculature account for a relatively reduced maximum ventilatory reserve (capacity) in females [7].

Neurobiological studies have demonstrated that females have a higher intrinsic sensitivity to noxious somatic sensations, including dyspnoea [8]. Finally, females are held to an expectation of beauty and youthfulness, whereas males are expected to be physically strong and robust. These expectations may be disrupted by COPD [9]; however, these expectations may influence the perception and expression of respiratory symptoms in males and females. Thus, males might be less likely to describe themselves as breathless than females, and females might be less likely to report sputum or phlegm production. Physicians need to recognise that although a female may not report sputum or phlegm production and a male may not report dyspnoea, a diagnosis of COPD should still be considered.

The power of this study was limited in very severe airflow limitation due to relatively small numbers of participants. Taking into consideration that recognition of the term “COPD” is still poor in many of our participating sites we collapsed the reported diagnoses of COPD, emphysema and chronic bronchitis when presenting reported diagnoses. For the analyses, however, COPD was strictly defined by a post-bronchodilator airflow limitation ($FEV_1/FVC < LLN$) regardless of any reported diagnosis or risk factor.

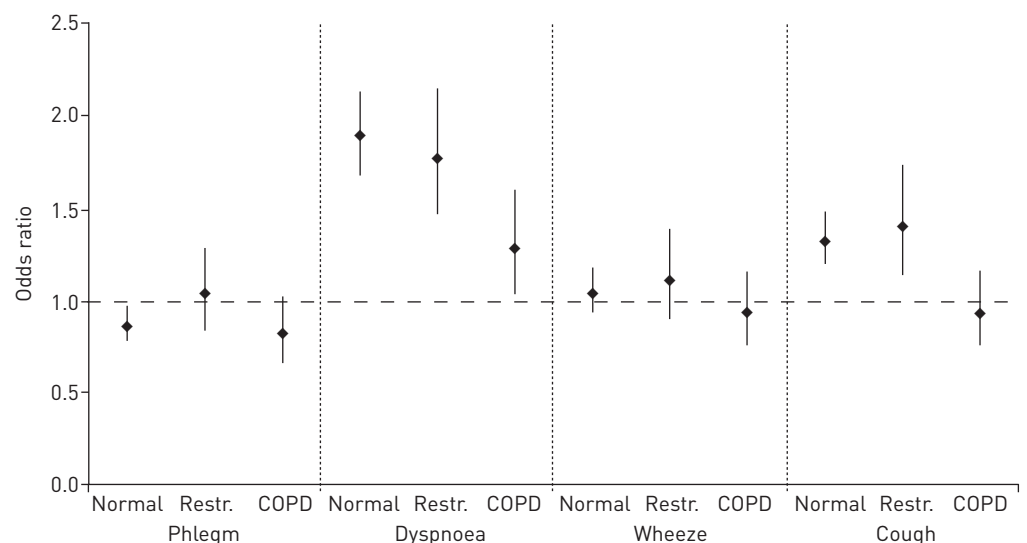


FIGURE 1 Odds ratios of respiratory symptoms in females (compared to males) by lung function. Odds ratios are adjusted for smoking-status, age, body mass index, comorbidities, and site. Normal: normal lung function; Restr.: restrictive lung function pattern; COPD: chronic obstructive lung disease.

We conclude that for the same degree of lung function impairment females tend to report more (severe) dyspnoea and cough, but less phlegm. Knowledge of this difference in reporting symptoms is important as symptoms often are the first step to a diagnosis of underlying airway disease.



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For the same degree of lung function impairment females tend to report more (severe) dyspnoea and cough, but less phlegm <http://ow.ly/mp2CF>

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Do we need bacteriological confirmation of cure in uncomplicated tuberculosis?

To the Editor:

Using data from English tuberculosis (TB) services, we investigate whether European guidelines recommending high levels of culture confirmation of pulmonary tuberculosis (PTB) cases and proof of bacteriological cure are achievable or needed.

The European Centre for Disease Prevention and Control (ECDC) recommends that 80% of pulmonary cases should be culture-confirmed [1]. In England, the Chief Medical Officer's action plan for TB [2], aims