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## Author's response

We thank Dr Miller and colleagues for their valuable comments<sup>1</sup> on our recent article. Our findings<sup>2</sup> suggested a gender difference in susceptibility to the lung damaging effects of cigarette smoking. Female gender was associated with lung function reduction and more severe disease in COPD subjects with early-onset of disease or low smoking exposure. Interaction analysis also suggested that the effect of smoking on lung function might be different by gender.

Miller and colleagues question the use of lung function measurements expressed as per cent of predicted values, suggesting that this approach may introduce a gender bias. They argue that our prediction equations automatically make low results for women appear worse than equivalently low results for men.

FEV<sub>1</sub> expressed as per cent of predicted values was used as the outcome in several analyses in our article. As we pointed out in the discussion section of the article, we are fully aware that per cent of predicted values represent a potential limitation of the study. In the analyses of our article, we calculated predicted FEV<sub>1</sub> using Gulsvik reference equations.<sup>3</sup> As mentioned in the article, we repeated our analyses using prediction equations from Johannessen *et al*<sup>4</sup> and found that the main results were the same when changing the reference equations. To further verify our findings, we have now analysed our data using the equations of Stanojevic *et al*,<sup>5</sup> as suggested by Miller and colleagues. All of our main findings were still valid.

In addition, we have estimated lower limit of normal (LLN, 5th centile) as 1.645 SDs below predicted to check for inherent gender bias in our study population across age groups. The point made by Miller and colleagues is important and their example showed that LLN in per cent predicted was lower for women than for men. To examine this issue further, we used four different reference equations (Gulsvik 2001,<sup>3</sup> Johannessen 2006,<sup>4</sup> Stanojevic 2008,<sup>5</sup> Quanjer 1993<sup>6</sup>) and calculated LLN in per cent of predicted FEV<sub>1</sub> across age groups (40–50, 50–60, 60–70, >70) for men and women separately. As Miller points out, LLN in per cent of predicted FEV<sub>1</sub> declines with age. However, with the exception of men older than 70 years using Johannessen reference values and women older than 70 years using Quanjer values, LLN exceeded 80% predicted

for both genders across all age groups. Furthermore, an inherent gender bias is unlikely to explain the results in a population with our age and height distribution. If anything, the gender bias seemed to be towards men, in that men had slightly lower per cent predicted LLN than women—except when we used the Quanjer equations, where women had the lowest per cent predicted LLN.

In conclusion, both the rerun of our main analyses with alternative reference values and the additional estimations of LLN by gender suggest that our results are unlikely to be dependent on the use of FEV<sub>1</sub> in per cent predicted. We agree with Miller and colleagues that LLN in per cent of predicted FEV<sub>1</sub> clearly declines with age, and that there may be a gender bias depending on the reference equations used. To avoid results that are dependent on a specific set of reference values, alternative reference values should be applied to test the robustness of the initial results.

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Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;**16**:5–40.

## Utility of cytopathology in diagnosis and molecular testing of lung cancer

We read with interest the editorial by Booton *et al*<sup>1</sup> on advances in the treatment and diagnosis of non-small cell lung cancer. Recently published best practice guidelines for pathology recommend the provision of as precise a diagnosis as possible, with optimisation of specimen use.<sup>2</sup> We advocate the utility of cytopathology in this regard and share our experience of the diagnostic potential and the range of ancillary tests possible on respiratory-related cytology specimens.

During a 20-month period (1 September 2009 to 30 April 2011), 227 patients were diagnosed with lung cancer at our centre, 162 of whom (264 samples) had malignant cytology from a range of exfoliative (bronchial brushings, washings and lavages; pleural fluid) and fine needle aspiration samples, the latter encompassing transbronchial and transoesophageal ultrasound guided fine needle aspiration of mediastinal lymph nodes and lung. Patients had one to four samples each. Morphological diagnosis of keratinising squamous cell carcinoma could be made with confidence without the need for immunocytochemistry, and in experienced hands, cytological appearances of small cell carcinoma are also characteristic. Subtyping of other carcinomas was undertaken by means of immunocytochemistry performed on agar cell blocks, material permitting (table 1).

A morphological diagnosis of non-small cell carcinoma not otherwise specified, due to insufficient material for immunotyping, may still be clinically useful depending on other clinical and staging information. If required, extra material can be requested for further subtyping.

Epidermal growth factor receptor mutation testing was requested in 36 cases, with mutations identified in six patients. Three tests failed due to insufficient DNA. In some cases where testing was not possible due to insufficient sample, direct communication with the treating clinician was undertaken to request more material, for example, pleural fluid. Testing for ALK-EML4 fusion was performed in one case.

The strategic use and triage of cytological material enable the maximum diagnostic and therapeutic information to be obtained. This may entail using all of the material in a sample for ancillary tests without producing traditional diagnostic slides, when the diagnosis has already been established in preceding samples. Close collaboration with