LETTER

Author's response

We thank Dr Miller and colleagues for their valuable comments[1] on our recent article. Our findings[2] 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_1 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_1 using Gulsvik reference equations.[3] As mentioned in the article, we repeated our analyses using prediction equations from Johannessen *et al*[4] 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*,[5] 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,[3] Johannessen 2006,[4] Stanojevic 2008,[5] Quanjer 1993[6]) and calculated LLN in per cent of predicted FEV_1 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_1 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_1 in per cent predicted. We agree with Miller and colleagues that LLN in per cent of predicted FEV_1 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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