Reply to "The effect of smoking on exacerbation risk in eosinophilic patients with chronic obstructive pulmonary disease"

We thank the authors for raising these comments and would like to explain the rationale behind our chosen strategy of analyses.

Our previous work on risk factors of frequent COPD exacerbations confirms the authors' statement that a recent history of exacerbations is the strongest risk predictor of future exacerbations.[1] This strong association is probably caused by factors, mostly unknown, that are consistently present and influencing the degree of airway inflammation.[2] One of these factors may be increased migration of eosinophils from the circulation to the airways.[3] Little is known about the long-term course of eosinophilic airway inflammation in COPD, but some patients may have persistent eosinophilic inflammation, whereas in others eosinophilic inflammation may be intermittently present. This theory is supported by our unpublished work analysing the stability of blood eosinophil counts over time in patients diagnosed with COPD from the Optimum Patient Care Research Database (OPCRD; http://optimumpatientcare.org/), in which we find a within-patient correlation coefficient of 0.56.

We agree with the authors that it is important to correct for baseline differences in exacerbation rates between study arms when studying effectiveness of specific interventions to achieve comparison groups that are similar in exacerbation risk at the start. By doing so, a potential change in exacerbation rate from baseline to outcome year caused by the intervention will be the focus of the outcome analyses.

However, the aim of our observational study, like similar studies[4], was to evaluate the association between blood eosinophil counts and exacerbation risk of patients with COPD. Patients with persistent eosinophilic inflammation are likely to have increased rates of exacerbations over both the baseline and the outcome year due to the same underlying mechanism. These persistent effects would be dampened by additional adjustment for the baseline exacerbation rate, which would change the focus towards a change in exacerbation rate from baseline to outcome period. In our opinion, the baseline exacerbation rate does not fulfil the definition of a real confounder, i.e. an extraneous factor that is associated with the exposure under study (eosinophils) and also predictive of disease occurrence (exacerbations)[5] but instead is an intermediate factor on the pathway from persistent recruitment of eosinophils to exacerbations. The suggested adjustment could thus be defined as an overadjustment in the context of intermediate variables, which would bias the results towards the null.[6]

Indeed, the rate ratio of the association in ex-smokers is reduced from 1.32 to 1.18 (95% confidence interval; 1.04-1.34) when the analyses were additionally adjusted for the number of baseline exacerbations, which nonetheless is still significant, suggesting that some of the effect is caused by varying eosinophil levels.

The authors also suggest that a so-called “healthy smoker effect” may have biased the association between blood eosinophil count and exacerbation rate, namely, the tendency of people who tolerate cigarettes to continue smoking, whereas those who experience serious health problems tend to quit.[7] We cannot fully rule this out, but there is no reason to assume that this tendency would be very different between patients with and without high blood eosinophil counts, unless the health problems are related to these counts. Moreover, 43% of all patients were still smoking, as were 39% of patients with frequent exacerbations in the baseline year, illustrating that smoking cessation can be very difficult for patients with COPD.

We acknowledge the authors’ concern regarding the potential for selection bias; however, a full blood count is a common blood test to check a person’s general health or to screen for conditions such as anaemia, which will limit the amount of eosinophil group misclassification due to the presence of unknown acute co-existing inflammatory illness. Additional adjustment for comorbidities did not relevantly influence the results.

Finally, we would like to emphasise that further research is needed to shed more light on our observations.

Marjan Kerkhof, Elizabeth V.Hilllyer and David B. Price on behalf of all authors.

References

1. Kerkhof M, Freeman D, Jones R, Chisholm A, Price DB. Predicting frequent COPD exacerbations using primary care data. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2439-2450.
2. Brightling CE. Chronic obstructive pulmonary disease phenotypes, biomarkers, and prognostic indicators. *Allergy and asthma proceedings.* 2016;37(6):432-438.
3. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med.* 2011;184(6):662-671.
4. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med.* 2016;193(9):965-974.
5. Rothman KJG, S; Lash, T.L. *Modern Epidemiology.* Philadelphia, USA: Lippincott Williams & Wilkins; 2008.
6. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology (Cambridge, Mass).* 2009;20(4):488-495.
7. Bednarek M, Gorecka D, Wielgomas J, et al. Smokers with airway obstruction are more likely to quit smoking. *Thorax.* 2006;61(10):869-873.

Maximum 800 words, up to 8 references. Deadline for submission: 10 October 2017