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From the author:

I would like to thank P. Rosias and coworkers for reading my editorial with great interest [1]. It is clear from their letter that they agreed with the limitations of collection and assay methodologies used, and the reproducibility of the oxidative biomarkers in exhaled breath condensate (EBC), particularly in smokers described in the editorial [1]. The question now arises as to whether home-made and/or commercial EcoScreen are valid for collection of EBC? This is an important question and certainly more research is needed to provide a clear-cut answer to a choice of assay method for a specific collection system. The home-made machine may vary from one laboratory to another but the EcoScreen condenser is at least being standardised and manufactured commercially and, therefore, will have constant degree of baseline limitations. It is understandable that oxidant biomarkers and proteins, such as albumin (which contains thiol groups), would be useful to collect EBC in an inert environment due to their high reactivity, whereas any metallic coating would be highly reactive with peroxides and thiol groups. ROISIAS *et al.* [3] have compared the influence of different inner condenser coating materials on the detection of human albumin but not for 8-isoprostane in EBC. Nevertheless, online (real-time) measurements of oxidative stress biomarkers may resolve this controversial issue.

In light of the discussion above on collection, storage, analysis and reproducibility of exhaled breath condensate biomarkers, it is highly welcome and timely that the European Respiratory Society/American thoracic Society Task Force "Exhaled Breath Condensate" is due to publish its methodological recommendations in the *European Respiratory Journal*.

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Inhaled steroids and mortality in COPD: bias from unaccounted immortal time

To the Editor:

In the March 2004 issue of the *European Respiratory Journal*, an article was published in which SUISSA [1] claimed to replicate the design of our previously published study [2] in a different cohort in Saskatchewan. Our study had suggested that inhaled corticosteroids (ICS) with or without long-acting β_2-agonists were associated with a reduction in all-cause mortality risk in chronic obstructive pulmonary disease (COPD) patients compared to short-acting bronchodilators alone. From his analysis in a different dataset, S. Suissa makes the categorical statement in the last line of the abstract that our published conclusion "is the result of bias from unaccounted immortal time in its cohort design and analysis". This statement, astonishingly, totally omits any consideration of differences between the results of the Saskatchewan database and the General Practice Research Database we used.

We are well aware of an earlier paper by SUISSA [3] on bias due to unaccounted immortal time, which clearly is irrelevant to our paper published in the *European Respiratory Journal* [2]. However, S. Suissa now postulates that the association we found was due to a further "subtle" type of unaccounted immortal time bias. Our study design specifically addressed the issue of immortal time bias as defined in analytical epidemiology [4].

First, patient follow-up time in the cohort design only started a day after the immortal period of 180 days from the start of therapy (see p. 820 and figs 1 and 4 in our paper [2]). S. Suissa suggests that because "regular treatment" was defined as at least three prescriptions of the relevant drug in the 180 days after the first prescription, cohort entry should be defined as the date of the third prescription and this has a significant impact in his analyses. The distinction may matter in the Saskatchewan database but in our study it was irrelevant as groups receiving ICS actually had shorter duration between first and third prescription than the control group (short-acting bronchodilators: 87.1 days; fluticasone: only 77.3 days; and fluticasone and salmeterol: 74.3 days). Thus, the theoretical distinction between the first and third prescription was without any relevance and seems difficult to justify. In our study, we also reported the number of prescriptions of the relevant drugs over the first 12 months after cohort entry, providing strong evidence that the initial pattern of prescribing in our groups was well maintained.

Secondly, we are unable to follow his reasoning on the "hierarchial" approach to treatment, which is implicit in the stepped care approach recommended in all major guidelines on COPD (and asthma) throughout the 1990s. Indeed, we are unaware of the circumstances that would lead to regular prescription of ICS in COPD without regular use of