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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

bronchodilators (see SUISSA [1], p. 393, table 1, column 3). Comparison of table 1 in our study [2] and table 1 in SUISSA [1] shows that drug use was more irregular in the Saskatchewan database with low use of the recommended bronchodilators. In spite of this, S. Suissa′s own results using "very first regular exposure identified after diagnosis" in his "conventional intention-to-treat approach" still indicated a significant association between ICS use and mortality, rate ratio 0.75 (0.62–0.90). Furthermore, S. Suissa ignores that our study used two designs, a cohort approach for the main analysis and a nested case-control approach to explore a dose-response relationship, with both methods indicating an association with ICS. The latter design has been described previously by SUISSA [5] as one that simplifies the cohort analysis when exposures vary over time and leads to valid estimates with negligible loss in precision.

Finally, SUISSA [1] used a time-dependent exposure approach and obtained results, which suggested that inhaled corticosteroids were not better than bronchodilators at reducing the risk of death in chronic obstructive pulmonary disease patients. We are not surprised that the benefit of inhaled corticosteroids could not be established with the treatment switching approach. This methodology is known to be valid only if the reason for the switch to inhaled corticosteroids is unrelated to the patient′s subsequent risk of death [6]. In our setting, the switch to inhaled corticosteroids was unlikely to be independent of mortality risk. Clinical experience suggests inhaled corticosteroids would be prescribed to sicker patients who were no longer responsive to bronchodilator therapy alone.

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From the author:

V.A. Kiri and colleagues bring up three points regarding my recent paper on bias from unaccounted immortal time in observational studies of inhaled corticosteroids and mortality in chronic obstructive pulmonary disease (COPD) [1]. Indeed, unlike my previous paper on misclassified (not "unaccounted" as stated by the authors) immortal time [2], the nature of the unaccounted immortal time bias presented in the current paper [1] is more insidious and I welcome this opportunity to clarify these points.

First, V.A. Kiri and colleagues note that, in their study, the 317 patients receiving fluticasone and salmeterol (F+S: the exposed group) had a duration of 74 days between the first and third prescriptions, compared with 87 days for the 3,620 patients receiving short-acting bronchodilators (SABA: the reference group). The fact that the study used a 180-day period from the date of the first of these three prescriptions before starting to count the deaths implies two periods of immortal time. The first is the span between the first and third prescriptions, which can be addressed by using the date of the third prescription as cohort entry. The second is the time between the third prescription and day 180. This period differs between the two groups, with a mean of 106 days for the F+S group and 93 days for the SABA reference group. This difference implies that a patient who dies 100 days after their third prescription will not be considered if they were in the F+S exposed group but will be counted if in the SABA reference group. To avoid such inconsistencies from differential classification and the resulting immortal time bias, the rule is straightforward: if regular use is defined by three prescriptions, simply use the date of the third prescription to define cohort entry.

The stepped care approach to COPD treatment, while appropriate, may lead to an inappropriate hierarchical definition of exposure, which results in the problem of "unaccounted immortal time bias". To understand this principle, consider patient A diagnosed with COPD in 1995 who for the first time receives three prescriptions for a SABA within 6 months in 1996, subsequently receives for the first time three prescriptions for F+S in 1999 and dies in 2001. Under the hierarchical approach, this patient is included only in the F+S exposed group. The fact that the patient survived for 3 yrs after the reference SABA is never considered under this approach. This is incorrect because the identical patient B also diagnosed with COPD in 1995, who receives for the first time three prescriptions for a SABA within 6 months in 1996 but dies in 1997 is included in the SABA group. Thus, patient A, who as patient B would have contributed to the SABA reference group had they died before receiving F+S, was not counted because they survived. Here again, the rule is straightforward: the design and analysis must use all time accumulated after any of the exposure criteria are met. Moreover, the use of a nested case-control approach within an incorrectly defined cohort will only produce incorrect results.

Finally, we agree that patients switched to inhaled corticosteroids (ICS) (who should be the majority of patients on ICS because of the stepped care approach) are probably the sicker patients. Therefore, we would expect that the crude mortality rate of such patients on ICS to be higher than the rate for those on bronchodilators alone, *i.e.* confounding by indication. Surprisingly, the reverse was observed in the study of SORIANO *et al.* [3]. The crude 1-yr mortality rate of the F+S group was 3.8% compared with 11.6% for the SABA group. This anomalous absence of confounding by indication is simply due to the fact that the SABA group (3,620 patients) excluded a large number of patients (up to 1,045) with 1 yr of immortality, who survived to receive F+S. As a result, the rate of death in the SABA group is overestimated because its calculation is based on the person-yrs of the 3,620 patients only (the group where all the deaths occurred) instead of all 4,665 patients (that includes the 1,045 where no death could have occurred). In fact, this denominator is much larger because it should also include the contribution of immortal SABA time from patients subsequently put on ICS other than fluticasone, who were excluded from this study.