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CORRESPONDENCE

Ireland needs healthier airways and lungs: the evidence (INHALE)

To the Editor:

We would like to congratulate the European Respiratory Society on the publication of the *European Lung White Book*. Here, on the western periphery of Europe, we have felt that our Irish Health Service is not fully aware of the importance of lung diseases and the resources necessary to deal with them. Accordingly, we have recently published a report entitled "Ireland needs healthier airways and lungs: the evidence", which has been circulated with the latest issue of the *Irish Medical Journal*. This report describes morbidity, mortality and treatment data for all types of lung disease in children and adults, involving both primary care and the hospital service. We chose a national publication in order to target planners in our health service and the Irish Thoracic Society supported the launch of the document.

Our work uncovered some disturbing facts. In Ireland, deaths from respiratory disease equal those from coronary artery disease and exceed those due to nonrespiratory cancer. Ireland has the highest death rate from respiratory disease in western Europe; death rates are over twice the EU average and nearly twice the European average. In Europe, only Kyrgyzstan, Kazakhstan and Turkmenistan have higher death rates from respiratory disease. The relative burden of respiratory disease in Ireland is rising, as that of heart disease decreases. The total direct medical cost for respiratory disease in Ireland was €388.7 million in 2001.

We invite readers of the *European Respiratory Journal* and members of the European Respiratory Society to read our document, which is available for free download in pdf format at www.imj.ie or www.imo.ie. We believe that our document complements the contents of the *European Lung White Book* (available at www.ersnet.org) and presents the statistics relating to lung disease in a more detailed national context for Ireland. By highlighting the scope of the problems in this large-volume, but politically unfashionable area, we hope that more effort and resources will be directed to policies and services that will improve standards of care for patients with pulmonary disease.

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Exhaled breath condensate: a space odessey, where no one has gone before…

To the Editor:

We read with great interest the editorial of RAHMAN [1] on the reproducibility of oxidative stress biomarkers in breath condensate. As a consequence, we would like to share some of our thoughts, as ultimately, we all may want to walk on planet Mars. However, this does not mean that we are already able to lift off, as many methodological problems first need to be properly addressed. Similarly, exhaled breath condensate (EBC) is an interesting noninvasive technique to explore inflammatory lung diseases, where no one has gone before… Many methodological issues are still waiting to be solved, as recently reviewed [2]. Indeed, the development of EBC is currently hampered by many conflicting reports on biomarker reproducibility. As clearly stated, one of the main obstacles consists of current analytical problems, due to limitations of sensitivity and specificity of the assays used to date [3].

However, the statement that "now with the use of EcoScreen, collection of EBC is being standardised in many leading laboratories" may be misleading, as it suggests that "this would no longer be a confounding factor contributing to the variations in biomarkers in EBC" [1]. We want to clearly point out that the EBC collection method still remains a possible confounding factor and an important source of biomarker variability, because standardisation involves applying more than one identical collection technique. To our knowledge, there is no scientific evidence that the EcoScreen condenser would be the most valid technique to collect EBC for the measurement of inflammatory mediators in condensate. In fact, the key issue is not the reproducibility of a certain biomarker, but the reproducibility of a certain biomarker for a certain condenser system [2]. We compared the influence of different inner condenser coatings on the detection of human albumin and 8-isoprostane in EBC [4]. Our data show a much greater efficiency of condenser systems with a borosilicate glass or silicone coating, compared with the EcoScreen or condensers with aluminium, polypropylene and teflon coating. This implicates that the EcoScreen may not be the most valid apparatus, at least not for some biomarkers.

Although the need for clear-cut methodological recommendations is incontestable, one has to recognise that we are not yet able to give such recommendations. Further research on the reproducibility of biomarkers with different condenser systems is urgently needed.

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References

1. Rahman I. Reproducibility of oxidative stress biomarkers in breath condensate: are they reliable? *Eur Respir J* 2004; 23: 183–184.
2. Rosias PPR, Dompeling E, Hendriks HJE, Heijnens JWCM, Donckerwolcke RAMG, Jöbsis Q. Exhaled breath condensate in children: pearls and pitfalls. *Pediatr Allergy Immunol* 2004; 15: 4–19.
3. Van Hoydonck PGA, Wuyts WA, Vanaudenaerde BM, Schouten EG, Dupont LJ, Temme EHM. Quantitative analysis of 8-isoprostane and hydrogen peroxide in exhaled breath condensate. *Eur Respir J* 2004; 23: 189–192.
4. Rosias PPR, Vernooy JHJ, Dentener MA, *et al.* The inner coating of condenser systems influences the detection of human albumin in exhaled breath condensate. *Eur Respir J* 2003; 22: Suppl. 45, 280s.

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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References

1. Rahman I. Reproducibility of oxidative stress biomarkers in breath condensate: are they reliable? *Eur Respir J* 2004; 23: 183–184.
2. Rosias PPR, Vernooy JHJ, Dentener MA, *et al.* The inner coating of condenser systems influences the detection of human albumin in exhaled breath condensate. *Eur Respir J* 2003; 22: Suppl. 45, 280s.

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