CORRESPONDENCE

Passive smoking and asthma death

To the Editors:

In 1998 during a flight from Athens (Greece) to San Francisco (CA, USA), A.M. Hanson, an asthmatic doctor aged 52 yrs, died due to an asthmatic reaction to second-hand cigarette smoke. In 2004, the US Supreme Court ruled that Olympic Airways was to pay the widow of A.M. Hanson US$1.4 million. This successful lawsuit by a passenger against an airline over smoking was unprecedented, and smoking on aeroplanes has become rare since the tragic incident occurred [1, 2]. A similar sudden death occurred in 1999, when Monica C., a 35-yr-old asthmatic, died from an acute asthma attack while working in the Paribas Bank in Milan (Italy). Asthma death was confirmed at autopsy. Monica C. had been hired by the bank under a programme providing tax incentives to employers who hire staff with physical handicaps, in this case severe asthma. She had complained for several months about the deleterious effects of second-hand cigarette smoke in her workplace and had requested several times to be moved to a smokefree office. In 2006, after a long and inconclusive lawsuit, in which the present authors were the plaintiff’s expert witnesses, the bank offered a monetary settlement to the victim’s family (husband and son), who accepted the settlement and suspended any legal action [3].

While asthmatics are advised to avoid passive smoking [4], there is no firm evidence to suggest that second-hand smoke may trigger an asthma attack. However, these two cases suggest that second-hand smoke can indeed trigger fatal attacks of asthma and that asthmatics should always be guaranteed a smokefree environment.

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STATEMENT OF INTEREST
None declared.

REFERENCES

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Exacerbations and intent-to-treat analyses in randomised trials

To the Editors:

The recent paper by Keene et al. [1] that reviews different approaches for the analysis of exacerbation rates is valuable because of the central role of exacerbations in evaluating the benefits of drugs in chronic obstructive pulmonary disease (COPD) trials [1]. The authors present reanalyses of the TRISTAN (Trial of Inhaled Steroids and Long-acting β₂-agonists) and ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) trial data, which have been previously identified as incorrectly analysed because of the absence of consideration for between-subject variability in exacerbation rates [2]. With the proper reanalyses, their conclusions from these trials remain the same; namely that inhaled corticosteroids (ICSs) with or without long-acting β₂-agonists reduce the frequency of exacerbations in patients with COPD. While the data reanalyses per se are appropriate, it is important to remember that two major imperfections in the study design of these trials could have led to flawed data and thus biased results.

First, the TRISTAN and ISOLDE trials did not follow patients until the end of the study, only until the patients discontinued the study drug, so that any exacerbation data beyond that point were missing. Consequently, the fundamental intent-to-treat analysis was not achievable. Keene et al. [1] correctly note that the Poisson methods do not account for the fact that
patients who withdraw early are more likely to have frequent exacerbations. However, they insinuate that the negative binomial method accounts for this fact. This is incorrect: the negative binomial approach only analyses the data available in the study and does not extrapolate or impute the uncollected missing data on exacerbations after patients discontinue the study drug. Exacerbation rates after discontinuation of study drug are much higher, which can introduce bias [3, 4]. The magnitude of this bias is illustrated by the ICS trials on mortality, where the trials with incomplete follow-up found a significant (p=0.04) 27% reduction in mortality with ICS compared with placebo [5, 6], while the TORCH (Towards a Revolution in COPD Health) trial with complete follow-up and, thus, a proper intent-to-treat analysis, found a nonsignificant (p=0.53) 6% increase in mortality with fluticasone alone compared with placebo [7]. Differences were also shown for exacerbations [8].

Secondly, the TRISTAN and ISOLDE trials imposed the discontinuation of ICSs prior to randomisation, which may affect the exacerbation rates. The mixture of patients who discontinue ICS with patients who initiate ICS or placebo will produce a convoluted effect of ICS [4]. Such analyses should thus be stratified by prior use of ICS.

Finally, the negative binomial distribution depends not only on a Poisson distribution for exacerbations in each patient, but also on a gamma distribution for the exacerbations between patients. In all examples, this second assumption appears to lead to higher estimates of exacerbation rates, lower estimates of rate ratios and lower p-values. Such comparative analyses of the Optimal trial data report wide differences between methods, even after accounting for patient variability, such as p-values of 0.21 versus 0.06 [8]. Further statistical work will be needed to verify the validity of these assumptions.

In all, while refinements in the statistical analysis of exacerbations are important, they become futile if the trials are not properly designed. The TRISTAN and ISOLDE trials had two major design flaws that violate fundamental principles of randomised trial methodology and that cannot simply be corrected with data analysis. Therefore, it is inappropriate to draw any conclusions regarding the effectiveness of inhaled corticosteroids on chronic obstructive pulmonary disease exacerbations from these reanalyses.

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STATEMENT OF INTEREST
A statement of interest for S. Suissa can be found at www.erj.ersjournals.com/misc/statements.shtml

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Asymptomatic airway hyperresponsiveness: what does it mean?

To the Editors:

I read with interest the study by Van den Nieuwenhof et al. [1], which appeared in a recent issue of the European Respiratory Journal. The study’s conclusion is certainly of interest: screening for asymptomatic airway hyperresponsiveness (AHR) in adolescents does not identify subjects at risk of developing asthma, whilst the presence of allergy is a risk factor for asthma. However, the observations leading to this statement should be interpreted with caution.

I agree with the authors that AHR may be variable. It can improve significantly at adolescence, the period associated with the highest incidence of asthma remission. The situation seems different in adults, however.

In some subjects, AHR may reflect a previous “insult” to the airways, either of infectious, toxic or allergic origin, or it could be the consequence of past airway inflammatory responses and associated structural changes, with persistence of the latter. In other subjects, however, AHR could reflect an ongoing