Reply from the authors

Editor—I would like to thank Dr Bahlool for his interest in our recent publication,¹ and the opportunity to respond to his comments.

Firstly, the L’Abbe plot is useful as an adjunct to assess heterogeneity in meta-analysis; but I agree with Sharp and colleagues² that the L’Abbe plot should only be used as a visual means to identify outlying trials and not be used in conjunction with a regression analysis. L’Abbe plots can be misleading only if a regression line is plotted on the graph to identify or define regions in which treatment is or is not effective because the results will be affected by regression towards the mean.³ I agree with Dr Bahlool that imbalance in baseline characteristics between the control and treatment groups can affect the visual appearance of a L’Abbe plot and, for the same reason, also the results of a randomized controlled trial and meta-regression of a meta-analysis.

Secondly, in our recent study on interactions between severity of illness and effectiveness of corticosteroids in sepsis,¹ two outlying trials with excessive mortality in the control group used the APACHE II model and one outlying trial used SAPS II score. Both APACHE II and SAPS II prognostic models are well validated by many studies, and in most studies, including one from our own centre, they reported a lower observed mortality than predicted by these prognostic models with a standardized mortality ratio usually <1.³ Furthermore, the whole point of using a pooled calibration plot is not to compare between studies (or study centres) but to compare the mortality rates of the control and treatment groups within each study, in which only one prognostic model is used for both the control and treatment groups and should not preferentially increase the mortality of the control group but not the treatment group. Regardless of the precise mechanisms of the excessive mortality in the control group, I believe that if excessive mortality rate is observed in the control group of a trial, we must consider the external validity of this trial before we pool its results with other studies in a meta-analysis and meta-regression. However, this technique is not suitable to assess the interactions between severity of illness and effectiveness of an intervention in a clustered randomized controlled trial. In this type of trial, patients in the control group will be recruited from a centre that is completely different from patients in the intervention group from another centre. In this scenario, different calibration of a prognostic model between different study centres, in which either control or intervention is assigned to, in a clustered randomized controlled trial is important in determining the results in a pooled calibration plot.

Thirdly, I agree with Dr Bahlool that publication bias is important in a meta-analysis. Traditionally, sample size is considered as the main source of publication bias, with a tendency for many journals to publish small positive studies. Funnel plot, trim and fill, and fail-safe N methods have been used to assess the potential effect of publication bias on the summary estimate of many meta-analyses. Our analysis suggested that studies with a positive result can be due to excessive mortality in the control group and not just due to a small sample size. In this regard, excessive mortality in the control group leading to a positive effect of an intervention may represent another possible reason for ‘publication bias’ and should be considered. We suggest that a pooled calibration plot can be useful as an adjunct to assess this hidden ‘publication bias’ which would not be apparent in funnel plot, trim and fill, and fail-safe N methods; at least, this method should be conducted as a sensitivity analysis when meta-regression analysis is conducted to assess the interactions between severity of illness and effectiveness of an intervention.

Conflict of interest

None declared.

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Smokeless tobacco and cardiovascular risk in non-Caucasian patients

Editor—We report the findings of a recent audit that we carried out into the documentation by anaesthetists at our institution of the use of non-smoking tobacco in non-Caucasian patients. We believe that it highlights a knowledge gap among anaesthetists that would be valuable to share. A recent meta-analysis showed that the use of non-smoking tobacco is associated with an increased cardiovascular risk, specifically of fatal myocardial infarction and stroke.¹ The use of non-smoking tobacco products is widespread among South Asian communities in the UK.² We believe that anaesthetists should routinely enquire about the use of non-smoking tobacco in patient populations where its use is prevalent during the preoperative assessment. The results of this enquiry should be documented on the anaesthetic chart.

In our small audit of 39 non-Caucasian patients presenting for surgery, we found that 33% (13 patients) regularly used non-smoking tobacco products. In no case was this fact documented on the anaesthetic chart by the anaesthetist who saw the patient before operation. We believe that this demonstrates a knowledge gap among the anaesthetists who saw these patients, which may well be prevalent. The most
common varieties of smokeless tobacco used by our audited patients are known colloquially as *zarda* and *paan masalla*.

In our opinion, awareness that non-smoking tobacco use results in an increased cardiovascular risk and that its use is widespread among some non-Caucasian ethnic groups is not commonly appreciated by anaesthetists. We therefore wish to raise the profile of this issue.

**Conflict of Interest**
None declared.

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**Fluoroderma after exposure to sevoflurane**

Editor—Sevoflurane is currently used as an inhaled anaesthetic agent with few adverse drug reactions. Skin reaction after general anaesthesia is uncommon. We report a case of fluoroderma after exposure to sevoflurane.

A 56-yr-old man developed ulcerated, erythematous, painful nodules on his neck, face, arms, and hands 8 h after surgery for right retinal detachment (Fig. 1). Perioperatively, he received propofol, remifentanil, paracetamol, tramadol, and ketoprofen, and anaesthesia was maintained with sevoflurane 1.1% for 2 h. He had a history of exposure to sevoflurane anaesthesia 3 yr previously (1 h with alveolar concentration at 1.3%). Skin biopsy revealed epidermal hyperplasia with infiltrates of dermal neutrophils without leucocytes and vasculitis (Fig. 1c). Tissue culture was negative for microorganisms. Protein electrophoresis was normal.

Sevoflurane \([\text{CH}_2\text{F}–\text{O–CH(Cl)}_2]\) is metabolized (5–8%) into fluoride ions by oxidative defluorination by the cytochrome P450 system, resulting in high serum concentrations of inorganic fluoride with prolonged anaesthesia at higher concentrations.¹⁻³ The patient’s serum fluoride level was 182 μmol litre⁻¹ (normal level, <50 μmol litre⁻¹). A diagnosis of fluoroderma was made. Review of the

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**Fig 1** (a) Erythematous nodules on the face. (b) Ulcerated erythematous nodules on the dorsal aspect of the hands. (c) Skin biopsy: epidermal hyperplasia with infiltrates of dermal neutrophils, without leucocytes and vasculitis.