

Dear Editor,

We read with interest “Incomparability of treatment groups is often blindly ignored in randomised controlled trials – a post hoc analysis of baseline characteristic tables” by Nguyen and Xie [1]. We would like to commend the authors on this interesting paper, and, in particular, for helpfully highlighting again the critical observation that randomisation leads to baseline comparability “in expectation – but not necessarily in realisation”.

We would, however, contest the characterisation that where reports of RCTs do not include details of how they assessed baseline imbalance that this was “blindly ignored”. Simply not reporting the details of the methods used does not mean that there were none; for example, in a phase 3 randomised trial it is common practice that the baseline comparability of groups is regularly assessed by a data monitoring committee examining summaries of the data as well as this being repeated by the trial team once recruitment is completed. The fact that the specific methods used are not reported may simply be a reflection of limitations in reporting and not the absence of any assessment.

In addition, as the authors note, it has long been recognised that applying standard significance testing approaches indiscriminately to baseline comparability is not helpful [2]. The method the authors propose for assessing comparability, routine calculation of SMDs, avoids some of the pitfalls of a significance testing approach. We note that the translation of differences onto a standardised scale may in fact make the assessment of importance of any observed imbalance more difficult to gauge for some variables when the original scale is intuitive and its prognostic influence is reasonably well understood (e.g. age or blood pressure). Furthermore, despite asserting that their approach should not be used as “a supreme measure”, the authors go on to apply it as a rule to the RCTs identified in their review. Such an approach does not acknowledge the nuances of different trials in terms of background clinical knowledge, population recruited and trial design, in particular randomisation method used (such as the use of minimisation). We note that not all imbalances are of equal prognostic importance both within and between trials. Therefore, the review findings should be interpreted cautiously. Further studies could usefully illustrate impact of differences between trials in greater depth.

Finally, whilst we agree simply partitioning variables a priori into important and non-important prognostic factors may be sub-optimal, consideration as to whether a baseline variable is likely to have an impact on any key outcome variables remains crucial. Inclusion of a variable in a baseline table does not necessarily imply that it is viewed as a “relatively important prognostic” variable. A variable may be important in describing the participants included in the trial (and perhaps their generalisability to a wider population) without there being any belief that the variable might be linked to any key outcome. In summary, the case of “blind ignorance” related to baseline imbalances in treatment groups within RCTs is not proven.

[1] Nguyen TL, Xie L. Incomparability of treatment groups is often blindly ignored in randomised controlled trials—a post hoc analysis of baseline characteristic tables. *Journal of Clinical Epidemiology*. 2020 Oct 17.

[2] Altman DG. Comparability of randomised groups. *Journal of the Royal Statistical Society: Series D (The Statistician)*. 1985 Mar;34(1):125-36.