After I submitted my comment on their article (which eventually became my published letter), the authors replied (also replying to Jesper M Kivelä from the University of Helsinki, who also wrote expressing concern), largely dismissing my concerns, particularly with their statement: "We can certainly argue back and forth for a long time about which model is best. However, our decision was made a priori and repeating the analysis with a different model will be a data driven approach that opens the door for biased personal believes*[sic]* and data dredging."

Safi U. Khan 1, Di Zhao 2, Erin D. Michos 2, M. Hassan Murad 3 • 1. West Virginia University, USA; 2. Johns Hopkins School of Medicine, USA; 3. Mayo Clinic, USA • 10 September 2019

The Choice of Meta-Analytic Model- Setting the Goals of the Analyses

We thank Drs. Kivelä and Mayer for their comments regarding the choice of meta-analytic model in estimating effects of salt reduction on all-cause mortality. Dr. Kivelä suggests using a Bayesian random effects (RE) model, yielding a 65% probability of mortality benefit with low salt diet. Dr. Mayer believes that a conservative RE model without Hartung-Knapp (HK) adjustment should have been considered.

Bayesian approaches in meta-analysis offer some advantages, such as the ability to include external evidence (from other data or from expert's opinion), ability to adjust for bias (from outside sources) and overall model flexibility. Bayesian approaches are helpful in dealing with missing data and a limited number of studies (1). However, the Bayesian framework requires some strong assumptions; the most controversial of which is identifying reliable prior distributions. Different priors can yield inconsistent results. In this scenario, what constitutes a reasonable prior for salt reduction on all-cause mortality is unsettled.

In terms of the HK adjustment, this method assumes that variances are derived from small samples and constructs confidence limits based on the t distribution. Thus, KH adjustments should usually generate conservative (wider) confidence intervals (CIs). The CIs reduce towards fixed effects model results when results are more homogenous (2). It is thought to be more appropriate for meta-analyses with a small number of studies, binary outcomes and high degree of heterogeneity (3, 4).

Knowing that we were dealing with substantial clinical and methodological heterogeneity, small number of studies and binary outcomes, we set a priori the RE Paule-Mandel (PM) model with HK adjustments when number of trials were <10. We can certainly argue back and forth for a long time about which model is best. However, our decision was made a priori and repeating the analysis with a different model will be a data driven approach that opens the door for biased personal believes and data dredging. There is no gold standard and no single preferred approach (5). In the original paper, we noted the moderate certainty for the estimated effects, and we acknowledge that different results provided by different models can limit the certainty in the evidence.

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To which I responded (this content is not in my published letter but is viewable in the comments to the article):

Martin Mayer • Innovations and Evidence-Based Medicine Development, EBSCO Health; Triad Hospitalist Group, Cone Health • 17 September 2019

Sticking with a hammer when you find out you are working with a screw is not the best choice – The analytic tool should be appropriate for the data.

I thank Dr. Khan and colleagues for responding. However, with respect, their response does not address my concern; rather, their response seems to construct a "straw man" that acts as a "red herring".

They note I believe a "RE [random effects] model without Hartung-Knapp (HK) adjustment should have been considered" for the analysis in question (salt reduction in patients without hypertension for the outcome of all-cause mortality). They are correct about this. However, it seems they missed or misunderstood the concepts in my original letter. The HK adjustment has several advantages and should be considered accordingly in meta-analyses.[1,2] However, it is – like anything else – a tool, and people must use tools appropriately, even if their original belief about the "best" tool turns out to be incorrect.[1,2] As noted in my original letter, the HK adjustment typically yields more conservative estimates (i.e., wider confidence intervals). However, for the analysis in question, it does exactly the opposite. This effect is so pronounced that Dr. Khan and colleagues' analysis (with a Paule-Mandle RE estimator and the HK adjustment) yields a narrower confidence interval than the fixed-effects (FE) analysis in the Cochrane review.[3,4] Although I noted this originally, it bears repeating, because this simple observation makes my point: The fact that the same data analyzed with a FE model would yield a wider confidence interval than a RE model lacks even face validity, and I explain why this is likely occurring in my original letter.

Rather than engaging with the concerns in my letter, Dr. Khan and colleagues seem to disregard the importance of ensuring model specifications are appropriate for the data at hand; instead, they suggest this "opens the door for biased personal believes[sic] and data dredging". Although presumably inadvertent, this constructs a "straw man" that acts as a "red herring". It is clear in my original letter I am not calling for an "anything goes" framework; what I am calling for, however, is avoidance of inappropriately stringent adherence to a priori specifications when it becomes clear that those specifications are inappropriate for the data at hand. If you tell everyone you are going to use a hammer because you anticipate needing to drive in nails and later find out you actually have one or more screws that need to be put in place, using the hammer for the screws because that was what you told people you would use is imprudent.

References

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As can be seen in the published letters, two editors from *Annals of Internal Medicine* also weighed in with a letter, noting my concerns were correct and also recommending alternative analyses. The authors thereafter conducted such analyses and corrected their article.