8th June 2021

Dear Michiel Tack

Thanks again for your interest in our study.

We would be pleased to engage in a scientific discussion on the interpretation of the MetaBLIND results.

However, we find that the issues you raise have been discussed in our paper[1], and, at greater length, in the accompanying publication *Ten questions to consider when interpreting results of a meta-epidemiological study: the MetaBLIND study as a case* [2]. Please find attached a copy of this paper.

In the accompanying paper we discuss in depth the following issues, among others:

- the sampling inherent in the meta-epidemiological approach (only areas where both blinded and non-blinded trials occur are included)

- the issues surrounding correct identification of experimental and control interventions

- risk of misclassification of trial blinding status, and the impact of differential vs. non-differential misclassification

- determinants of precision of the meta-epidemiological estimate, including variability between trials within meta-analyses. The degree of variability between trials within meta-analyses is reflected in the confidence interval around the overall estimate of the impact of blinding.

- the possibility of systematic differences, associated with trial effect estimates, between blinded and non-blinded trials within meta-analyses (i.e. confounding).

For further discussion on confounding and the interpretation of observational vs. experimental studies on the impact of blinding, please see also previous studies by the last author, including a systematic review of trials randomizing patients to blind ad non-blind sub-studies[3] and of trials with both blinded and non-blinded outcome assessors[4].

Kind regards,

Helene Moustgaard, MD, PhD

Asbjørn Hróbjartsson, Professor of evidence-based medicine

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[1] Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study | The BMJ

[2] Moustgaard, H. , Jones, H. E., Savović, J., Clayton, G. L., Sterne, J. A. C., Higgins, J. P. T., & Hróbjartsson, A. (2019). Ten questions to consider when interpreting results of a meta-epidemiological study: the MetaBLIND study as a case. Research Synthesis Methods. https://doi.org/10.1002/jrsm.1392

[3] Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies | International Journal of Epidemiology | Oxford Academic (oup.com)

[4] Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors | The BMJ