Relationship between the conflicts of interest and the results of meta-analyses of homoeopathy trials

Quentin Perrier ,[1] Agathe Coste,[1,2] Aminata Diallo,[1,2] Alicia Guigui,[1,2] Charles Khouri,[1,2] Matthieu Roustit[1,2]

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[1]University Grenoble Alpes, Inserm CIC1406, CHU Grenoble Alpes, Grenoble, France
[2]University Grenoble Alpes, HP2, Inserm U1300, Grenoble, France

Correspondence to:
Matthieu Roustit, Centre d'Investigation Clinique - Inserm CIC1406, Univ. Grenoble Alpes, CHU Grenoble Alpes, Grenoble, France; mroustit@chu-grenoble.fr

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In the absence of robust trials supporting the efficacy of homoeopathy, people who criticise or, on the contrary, defend homoeopathy, refer to meta-analyses whose results support their point of view. We hypothesised that the discrepant results of meta-analyses of homoeopathic medicines were related to potential conflicts of interest (COIs). Indeed, there is evidence suggesting that COI influences research outcomes.[1] While such association has recently been studied for various drugs and nutrition studies,[2 3] it remains unexplored for homoeopathy trials.

The objective of this study was, therefore, to assess whether COI was associated with the results of meta-analyses of homoeopathy trials.

We conducted a literature search until July 2022 on PubMed and Embase to identify meta-analyses of randomised controlled trials assessing the efficacy of homoeopathy. There was no restriction on the investigational product or its comparator. The study population thus included patients with various medical conditions, including both children and adults. We assessed the existence of potential COI, defined by at least one of the following criteria: affiliation of one or more author to an academic homoeopathy research or care facility, or to a homoeopathy industry; study sponsored or funded by homoeopathy industry; COI declared by the authors. We also assessed and classified spin in meta-analyses conclusions into three categories (misleading reporting, misleading interpretation and inappropriate extrapolation) as previously described.[4] Two reviewers assessed the quality of meta-analyses and the risk of bias based on the ROBIS tool.[5] Publication bias was assessed by the reporting of a funnel plot and its asymmetry, when applicable.

We further extracted all studies included in these meta-analyses, and assessed whether they reported a statistically significant result in favour of homoeopathy, and if the study was indexed in Medline. The proportion of articles not indexed was used as an indicator of grey literature.

All outcomes were re-expressed as OR, with their 95% CI. The meta-analysis was performed using a random effect model, with the presence or absence of conflict of interest as subgrouping variable. We further tested whether there was an association between COI and the risk of bias or the presence of spin (Fisher's exact test). Statistical analyses were performed using R (V.4.0.2) and the meta and metaphor packages. Details about the methods are provided as available on OSF (https://osf.io/nqw7r/) and in the preregistered protocol (CRD42020206242).

Twenty meta-analyses were included in the analysis (and list of references available at https://osf.io/nqw7r/). Among the 13 meta-analyses with COI, there was a significant efficacy of homoeopathy (OR=0.60 (95% CI 0.50 to 0.70)), while there was no efficacy for meta-analyses without COI (OR=0.96 (95% CI 0.75 to 1.23)) (p=0.002 for the subgroup difference) (figure 1). There was no significant difference according to the category of potential COI. Additional sensitivity analyses did not change the conclusion ().

We found no significant relationship between COI and the risk of bias or the presence of spin (, https://osf.io/nqw7r). Only three meta-analyses with COI and two without COI reported a funnel plot, all but one being asymmetric (assessed visually and, for four of them, through the Egger's test).

Overall, the meta-analyses included 183 different studies and 198 comparisons: 138 significantly favoured homoeopathy, 41 did not and 19 were not available. The median proportion of results in favour of homoeopathy was higher in meta-analyses with COI (82.5% vs 42.9%, p=0.036).

The sources used by meta-analyses for literature search are summarised in (https://osf.io/nqw7r). Fewer studies from journals indexed in Medline were included in meta-analyses with COI (42.2% vs 79.7%, p=0.027). In addition, 45% of studies published in journals not indexed in Medline had significant results in favour of homoeopathy, compared with 27% for studies published in journals indexed in Medline (p=0.015).

Our study suggests that in the presence of COI, meta-analyses of homoeopathy trials are more likely to have favourable results. This is consistent with recent research suggesting that systematic reviews with financial COI are associated with more positive outcomes.[2] Unlike the latter, however, we did not identify a significantly higher risk of bias in meta-analyses with COI. Similarly, the risk of spin was not significantly higher. However, these conclusions should be taken with caution given the small number of meta-analyses included in this study.

We rather hypothesise that the choice of studies included in the meta-analyses explains the results. Indeed, there were more statistically significant 'positive' studies included when a potential COI was identified. In addition, inclusion of trials from the grey literature was more likely in meta-analyses with COI. Yet, there was no obvious difference in sources used for literature search, which strengthens the hypothesis of selection bias.

This is consistent with the results of a recent study, which has shown substantial reporting bias in trials assessing homoeopathic treatments, with

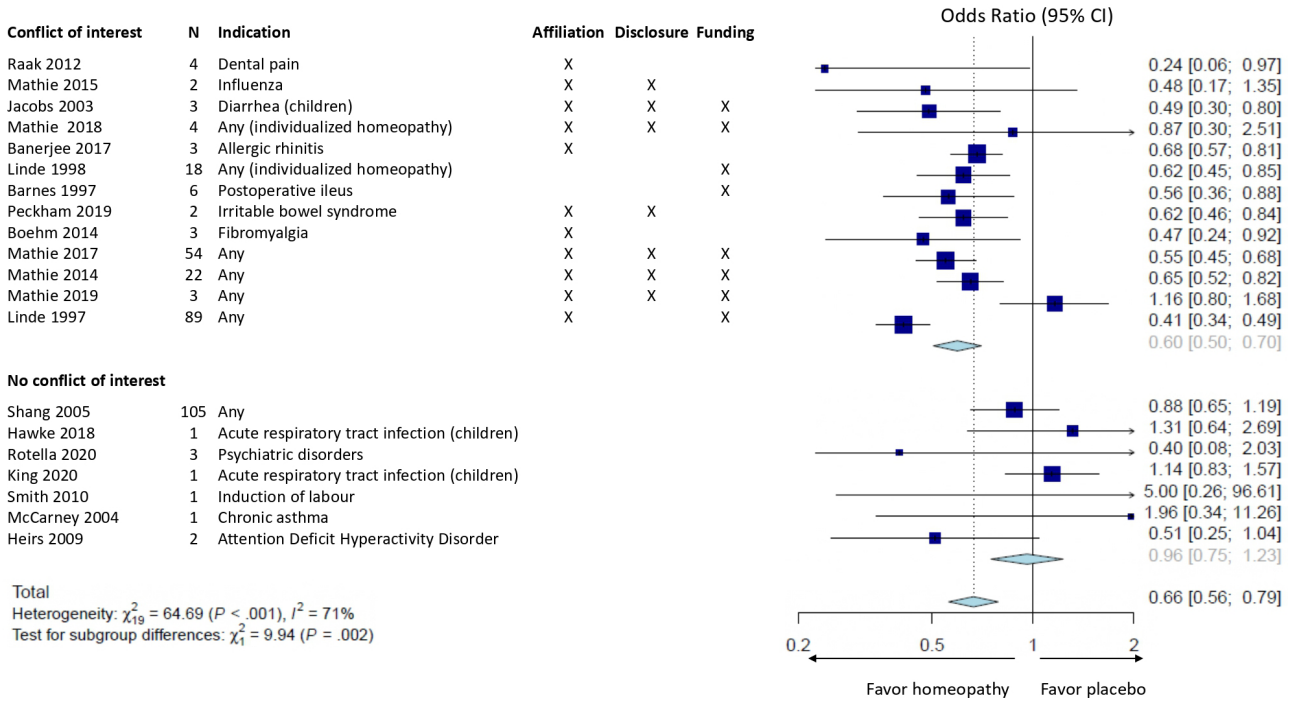

Figure 1 Forest plot for homoeopathy meta-analysis, according to the COI. N: number of studies included in meta-analysis. COI, conflict of interest.

a low proportion of registered protocols, and the absence of publication of many registered trials.[6] This selection bias may result from differences in the choice of inclusion/exclusion criteria and analytical models a posteriori, which can yield opposite results (known as 'Janus effect').[7] If our hypothesis was wrong, we should have observed an almost perfect overlap in trials included in meta-analyses with and without COI on the same indications. Yet, the overlap seemed limited, representing only 59 out of the 183 studies included in the 2 largest meta-analyses on any indication. However, a limitation of this study is that we cannot exclude differences between subgroups other than COI, due to different indications for example. Too few studies were available to conduct subgroup analyses by indication.

Similarly, we were not able to compare bias from funnel plots asymmetry. Indeed, only four studies reported asymmetric funnel plots (two with COI and two without COI), which is understandable for most of them given the very low number of included studies in the majority of meta-analyses: 15 out of 20 meta-analyses have included 6 studies or less. Only 1 meta-analysis including 19 studies did not perform a funnel plot.[8]

In conclusion, our study suggests that in the presence of COI, meta-analyses of homoeopathy trials conclude to more favourable results, which is likely due to selection bias of included studies.

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ORCID iD
Quentin Perrier http://orcid.org/0000-0002-7445-7922

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