Identifying clinical trial characteristics influencing intervention effect estimates is crucial. Trials with such characteristics may lead to underestimating or overestimating true intervention effects. To assess risk of bias in randomized trials, the Cochrane Collaboration has developed a tool based on theoretical as well as empirical considerations regarding the impact of risk factors for bias.\textsuperscript{1} Empirical evidence comes from meta-epidemiology. This approach involves use of a collection of meta-analyses to compare intervention effect estimates among trials with and without a particular characteristic. More recently, meta-meta-epidemiology, which combines data from several meta-epidemiological studies, has been developed.\textsuperscript{2,3} In this issue of the journal, Chaimani \textit{et al.}\textsuperscript{4} propose network meta-epidemiology as an interesting new approach: meta-epidemiology in the framework of networks of trials, thus exploiting the assumption that the impact of risk factors is similar within networks.

Table 1 compares the methodological features of each approach. Each approach has pros and cons related to differences in data sources and assessment of risk factors. Meta-meta-epidemiology involves larger and probably more representative collections of meta-analyses than meta-epidemiology or network meta-epidemiology. In meta-epidemiology, an important restriction is that informative meta-analyses must include at least one trial with and one without the risk factor of interest. Moreover, a minimum number of trials per meta-analysis may be required, depending on how heterogeneity is modelled and whether multivariable analyses are undertaken. In network meta-epidemiology,
Table 1 Features of meta-epidemiology, meta-meta-epidemiology and network meta-epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Meta-epidemiology</th>
<th>Meta-meta-epidemiology</th>
<th>Network meta-epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data sources</strong></td>
<td>A collection of MAs of randomized trials</td>
<td>A collection of meta-epidemiological studies, combined into a harmonized dataset without overlap between MAs</td>
<td>Networks of randomized trials</td>
</tr>
<tr>
<td><strong>Restrictions</strong></td>
<td>Informative MAs must include at least one trial with and without the risk factor of interest</td>
<td>The different meta-epidemiological studies investigate various sets of risk factors, potentially assessed with different methods</td>
<td>Eligible networks must include more trials than interventions</td>
</tr>
<tr>
<td><strong>Assessment of trial-level risk factors</strong></td>
<td>Re-assessment from individual trial reports OR reliance on assessment from each selected MA</td>
<td>Assessment from each meta-epidemiological study</td>
<td>Re-assessment from individual trial reports OR reliance on assessment from each selected network MA</td>
</tr>
<tr>
<td><strong>Assumption regarding direction of bias</strong></td>
<td>In active–inactive comparisons, a risk factor is expected not to favour the inactive comparator</td>
<td>In star-shaped networks, a risk factor is expected not to favour the common comparator</td>
<td>In networks with closed loops, an assumption regarding direction of bias is needed</td>
</tr>
<tr>
<td><strong>Estimation of the impact of risk factors on intervention effect estimates</strong></td>
<td>Effect estimates are compared between trials with and without the risk factor within each MA; the mean impact of the risk factor is estimated across all MAs</td>
<td>Effect estimates are compared between trials with and without the risk factor within each network; the mean impact of the risk factor is estimated across all networks</td>
<td></td>
</tr>
<tr>
<td><strong>Assumption regarding exchangeability of the impact of risk factors on intervention effect estimates</strong></td>
<td>Between trials within MAs; Between MAs</td>
<td>Between trials within networks; Between networks</td>
<td></td>
</tr>
</tbody>
</table>

MAs, meta-analyses.
all meta-analyses included in the networks contribute to the analyses but eligible networks must include more trials than interventions. Because meta-meta-epidemiology combines data from pre-existing meta-epidemiological studies, some practical difficulties could occur: overlapping meta-analyses and trials must be identified and characteristics could have been assessed by different methods in the studies and may even be unavailable for some of the studies pooled. As an example, in the BRANDO meta-meta-epidemiological study combining data from 7 meta-epidemiological studies, of the 234 included meta-analyses (1973 trials) only 85 (664 trials) had data for comparing intervention effect estimates between single-centre and multicentre trials.

Other main differences between the three approaches lie in the statistical modelling. In meta-epidemiology, intervention effect estimates are basically compared among trials with and without the risk factor within each meta-analysis; the mean impact of the risk factor is then estimated across all meta-analyses. In network meta-analyses intervention effect estimates are basically compared among all trials of the network with and without the risk factor within each trial network, the impact of a risk factor being assumed identical for all meta-analyses in a network. The mean impact of this factor is then estimated across all networks. Assuming that the impact of a risk factor is identical for all meta-analyses in a network may be debatable when networks include active–inactive and active–active comparisons, pharmacological and non-pharmacological interventions or older and recent trials.

These three approaches have not been compared. In their sample of networks, Chaimani et al. did not find evidence that inadequate or unclear sequence generation, allocation concealment or double-blinding led to exaggerated effect estimates. These findings differ from that of the BRANDO meta-meta-epidemiological study. As suggested by the authors, these results may be explained by low power because of the inclusion of few trials with risk factors. Other explanations may be meta-confounding or differential impact of risk factors across meta-analyses included in networks. Researchers should also be aware of the improvement of methodological quality and reporting of trials with time. We could not exclude that future meta-epidemiological studies, including more recent trials, will no longer find any evidence of the impact of some important risk factors infrequently present in trials. However, Chaimani et al. found evidence that trial variance was strongly associated with intervention effect estimates. This finding is in line with our recent meta-epidemiological study, which showed that treatment effect estimates differed within meta-analyses, with stronger effects seen in small to moderately sized trials than in the largest trials.

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References