Extending Network Meta - Analysis to include Non - Randomized Evidence: Results of a scoping review

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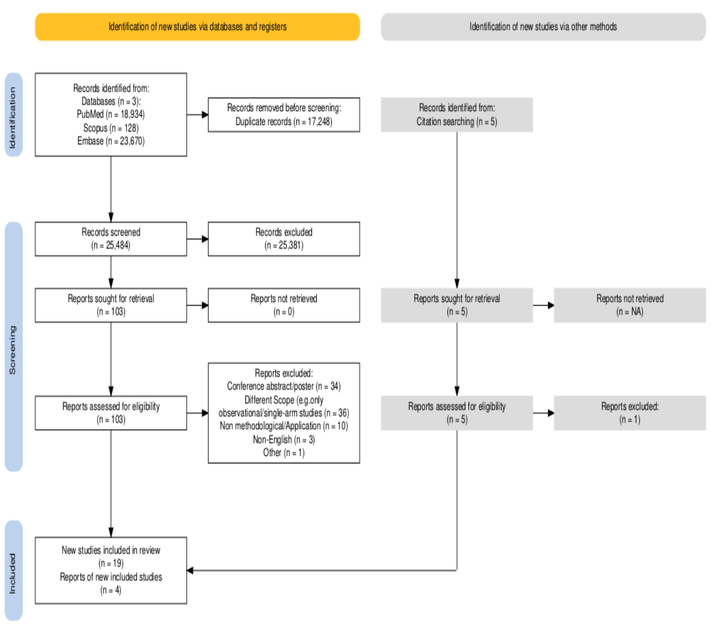
Background

Randomized clinical trials (RCTs) are considered the gold standard for evaluating the efficacy and safety of interventions and the synthesis of RCTs through meta-analysis (MA) is considered the strongest method for examining intervention effects. However, randomized evidence (RE) often suffer from low external validity, short follow-up time and limited feasibility. Non-randomized evidence (NRE), such as cohort studies and registries, can provide valuable insights as they may better reflect real-world conditions. We conducted a scoping review to identify the statistical methods used to combine RE and NRE within the MA or NMA frameworks.

Flowchart

We searched Embase, PubMed, and Scopus up until June 2024. The following PRISMA flowchart summarizes the selection of studies for our review.



Systematic Review finding

Of the 23 included studies, 17 were methodological papers focused on the integration of RE and NRE information in MA and NMA, while the remaining 6 were reviews of methods addressing the same topic. . Among these 17 methodological studies:

- 11 (64.7%) focused on combining RE and NRE in standard MA
- 5 (29.4%) in NMA alone and
- 1 (5.9%) addressed both approaches

The majority - 15 studies (88.2%) - adopted a Bayesian framework. Regarding data types:

- 13 studies (76.4%) synthesized only aggregated data (AgD)
- 2 (11.8%) required individual participant data (IPD) and
- 2 (11.8%) incorporated both IPD and AgD

Random-effects NMA model

- Within-study model

$$y_{i,jk} \sim Normal(\theta_{i,jk}, s^2_{i,jk})$$

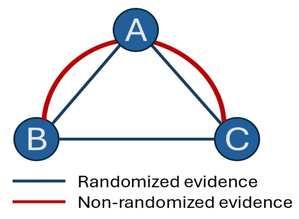
- Between-study model

$$\theta_{i,jk} \sim Normal(\mu_{jk}, \tau^2)$$

- Key assumptions:

✓Exchangeability: Differences in observed effects are due to random variation or sampling error.

✓Consistency: The direct and indirect evidence for a treatment comparison should agree.



Identified methods

➜ Naive data synthesis

All evidence (RCTs and NRE) is treated equally, without adjustment.

$$y_{i,jk} \sim Normal(\theta_{i,jk}, s^2_{i,jk})$$

! No distinction between RCT and NRE, risk of bias (RoB) or design are not accounted for.

➜ Design-adjusted analysis

Down-weights NRE by inflating their variance using a design-specific weight.

$$y_{i,jk} \sim Normal(\theta_{i,jk}, \frac{s^2_{i,jk}}{w_i})$$

Typically, $w_{RCT} = 1, w_{NRE} < 1$

Can be set to fixed values or random variables.
✓ Accounts for uncertainty in NRE
$\mathcal{X}$ Subjective specification of down-weighting

➜ Using NRE as prior information

- **Predictive prior with down-weighted variance**

This approach constructs a predictive distribution from NRE estimates and incorporates it a prior for μ_{jk}, but downweights it by inflating the variance using a factor w_{jk}

$$\mu_{jk} \sim Normal(\widehat{\mu}^{NRE}_{jk} + \beta_{jk}, \frac{\widehat{V}^{NRE}_{jk}}{w_{jk}})$$

- If $\beta_{jk} = 0 \quad and \quad w_{jk} = 1$ full trust in NRE
- If $w_{jk} \ll 1$, NRE evidence is heavily downweighted.

✓ Handles uncertainty and possible bias
$\mathcal{X}$ Requires specification of prior parameters and less useful with few NRS

- **Power Prior**

This method down-weights the contribution of NRE by raising its likelihood contribution to a power between $a_i \in [0, 1]$

$$L(\mu|NRE) = \prod_{i=1}^{k} [L(\mu|NRE_i)]^{a_i}$$

✓ Flexible
$\mathcal{X}$ Choosing a_i values can be subjective

➜ Three-level hierarchical model

First level, (within study differences)

$$y_{i,jk} \sim Normal(\theta_{i,jk}, s^2_{i,jk})$$

Second level, (between study differences)

$$\theta_{i,jk} \sim Normal(\mu^{design}_{jk}, \tau^2)$$

Third level, (between design differences)

$$\mu^{design}_{jk} \sim Normal(\mu_{jk}, \tau^2_{design})$$

✓ Accounts for design-specific effects and heterogeneity
$\mathcal{X}$ More complex, requires sufficient data per design

References

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