Comparison of meta-analysis methods for synthesizing heterogeneous studies

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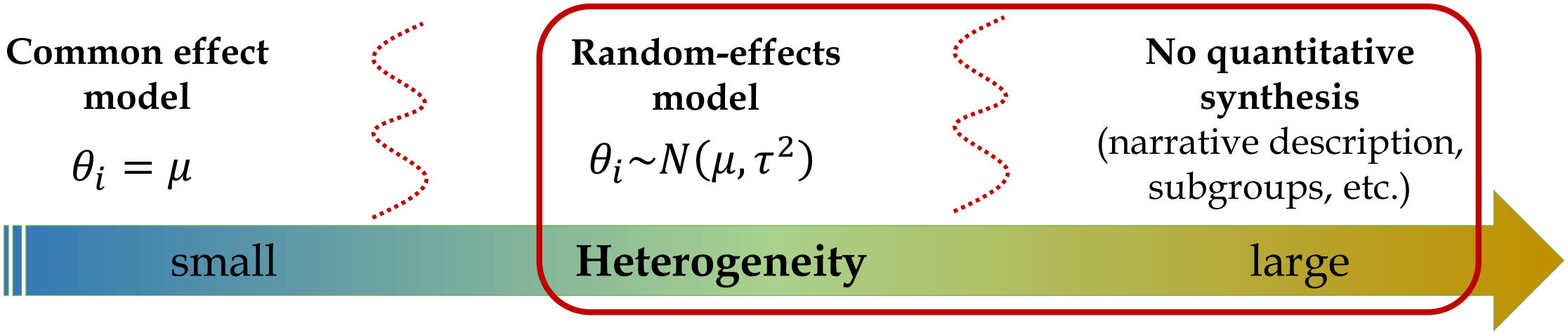
Introduction

- Meta-analysis generally requires that studies are sufficiently homogeneous to be synthesized
- In the presence of heterogeneity, a random effects model is usually considered more appropriate
- "meta-analyses of very diverse studies can be misleading"
- "the presence of heterogeneity affects the extent to which generalizable conclusions can be formed"

Cochrane Handbook



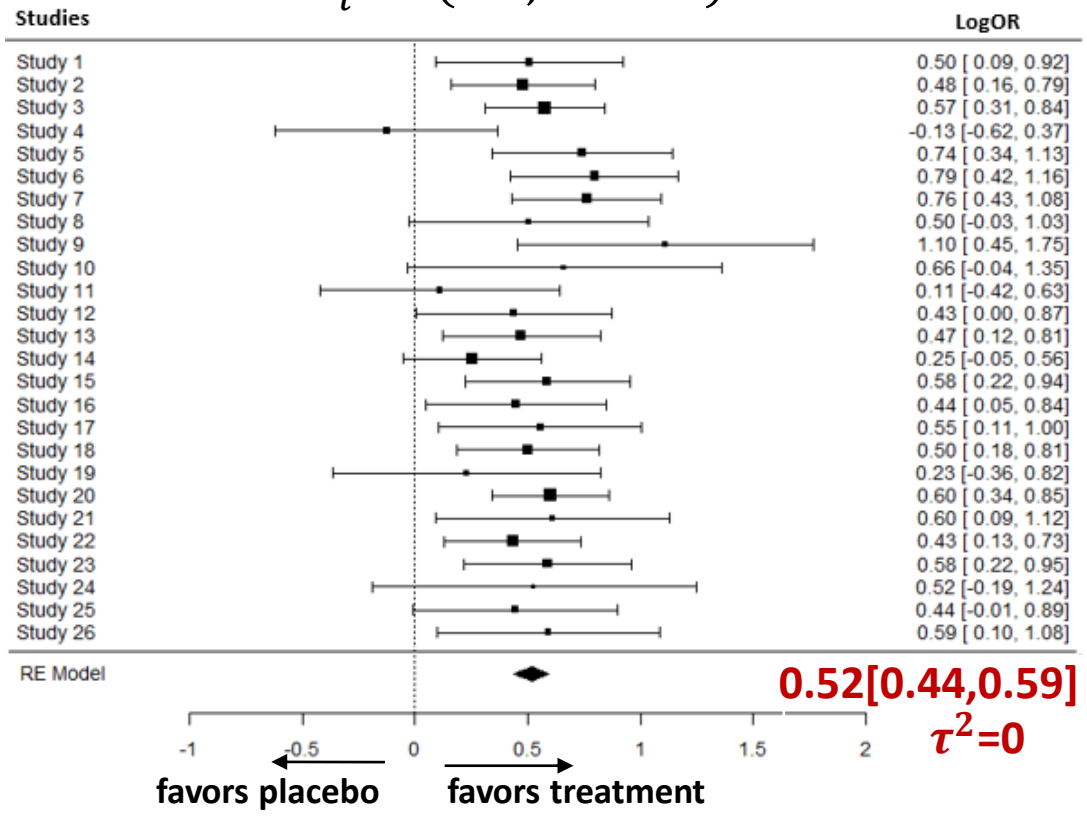
- collection of meta-analyses combining RCTs with observational studies: τ^2=369, 419, 1152!

*Cheurfa et al. **Syst Rev** 2024*

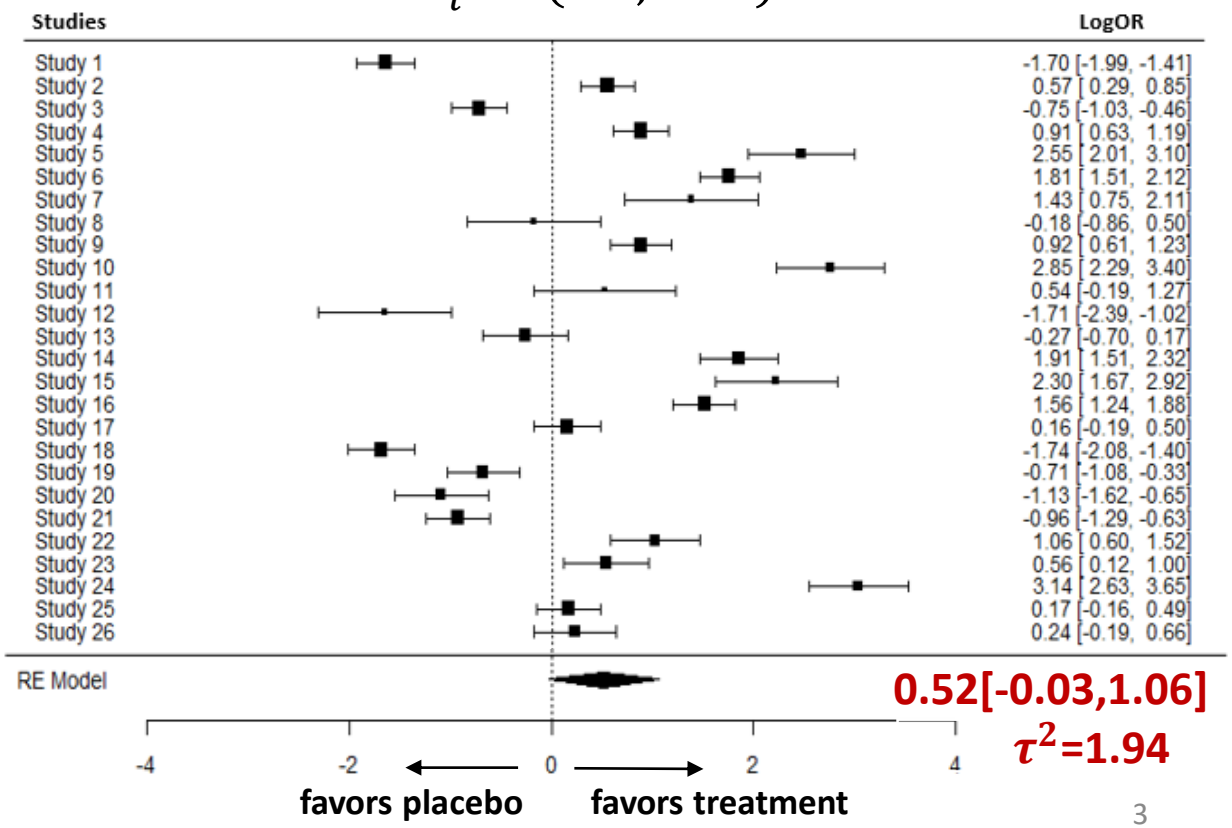
Common practice in published meta-analyses

- A tendency in the literature to ignore the extent of variation of study results and to focus on the estimated summary effect
- e.g. several meta-epidemiological studies comparing results from observational studies and RCTs

$\theta_i \sim N(0.5, 0.0001)$



$\theta_i \sim N(0.5, 2.63)$

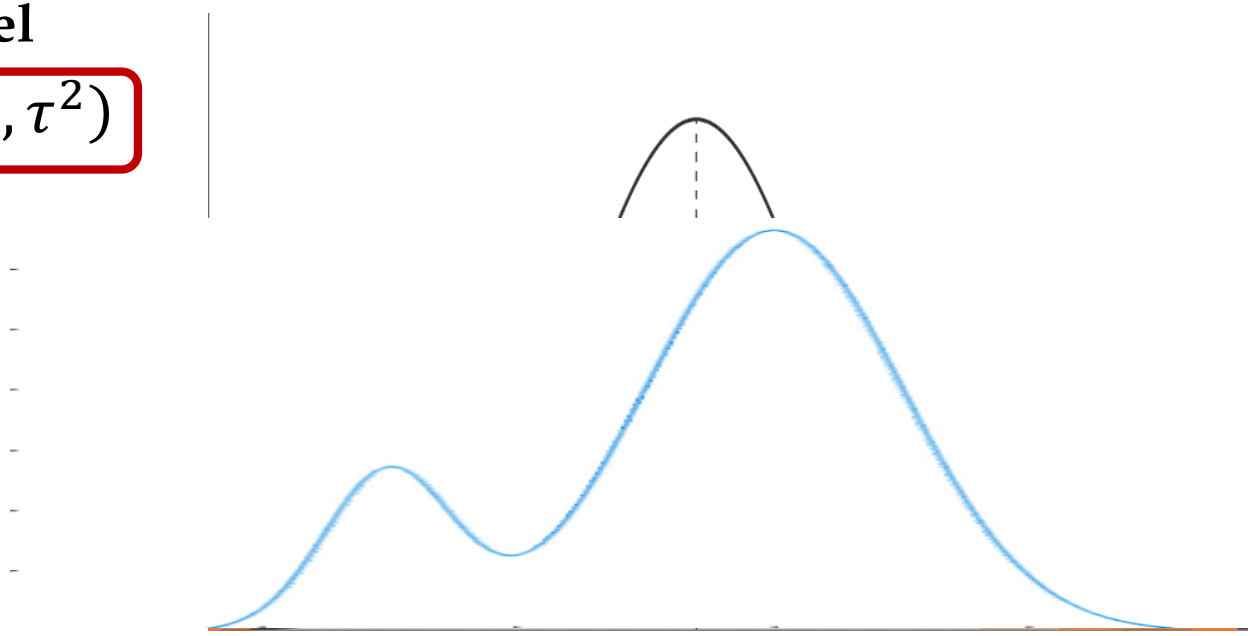


Conventional random effects meta-analysis

Random-effects model

$$\theta_i \sim N(\mu, \tau^2)$$

- outlying studies
- effect modifiers
  - known and observed
  - unknown or unobserved



- A systematic review to identify alternative flexible meta-analysis models that relax the between study normality assumption
- A simulation study to investigate and compare their performance under the presence of substantial heterogeneity for normal and non-normal data

Results of systematic review

16 eligible articles suggesting 14 alternative between-study distributions:

1. long-tail and skewed extensions
2. mixture of distributions
3. models using based on Dirichlet Process priors

- most in Bayesian framework
- most provided code and few accompanied by an R package

Identified alternative random effects models
long-tail and skewed distributions (1)

- **t-distribution model** $\theta_i \sim t(\mu, \omega, \nu)$
  - with $\tau^2 = \frac{\nu}{(\nu-2)}\omega^2$
  - more weight in the tails – outliers less influential
  - *metaplus* package in R

ω: scale parameter
ν: degrees of freedom
(determining the weight of the tails)
ξ: location parameter
γ: shape parameter
(determining the level of skewness)

- **skew-normal model** $\theta_i \sim SN(\xi, \omega, \gamma)$
  - with $\mu = \xi + \omega b\delta$, $\tau^2 = \omega^2[1 - (b\delta)^2$, $b = \sqrt{\frac{2}{\pi}}$, $\delta = \frac{\gamma}{\sqrt{1+\gamma^2}}$
  - *flexmeta* package in R

Identified alternative random effects models
long-tail and skewed distributions (2)

- **skew-t model** $\theta_i \sim ST(\xi, \omega, \nu, \gamma)$
  - with $\mu = \xi + \omega b_\nu \delta$, $\tau^2 = \omega^2 \left[\frac{\nu}{\nu-2} - (b_\nu\, \delta)^2\right]$,

    $b_\nu = \frac{\sqrt{\nu}\Gamma\left(\frac{\nu-1}{2}\right)}{\sqrt{\pi}\Gamma\left(\frac{\nu}{2}\right)}$, $\Gamma(\nu) = (\nu-1)!$

  - *flexmeta* package in R
  - bivariate extensions (assuming correlation of treatment effect and baseline risk or DTA meta-analysis) *Lee & Thompson* ***Stat Med*** *2008, Negeri et al.* ***Biom J*** *2020*

ω: scale parameter
ν: degrees of freedom
(determining the weight of the tails)
ξ: location parameter
γ: shape parameter
(determining the level of skewness)

- **other skewed distributions**
  - asymmetric Subbotin II $\theta_i \sim AS2(\xi, \omega, \nu, \gamma)$
    sharper skewness and excess kurtosis for very small ν
  - Jones–Faddy $\theta_i \sim JF(\xi, \omega, \gamma, d)$ – equivalent to a t-distribution with $\gamma + d$ dof
  - sinh-arcsinh $\theta_i \sim SAS(\xi, \omega, \gamma, d)$
    allows for both symmetric and skewed shapes as well as heavy or light tail-weight
  - *flexmeta* package in R

Identified alternative random effects models
mixture of distributions (1)

- when the data come from sub-populations or several outliers are present

- **common-mean mixture model** $\theta_i \sim w_1 N(\mu, \tau_1^2) + w_2 N(\mu, \tau_2^2)$
  - for outlier detection
  - weights propotional to the number of studies
  - summary effect is estimated including all studies but with outliers being down-weighted due to the larger variance assumed for their class
  - if $\tau_1^2 \approx \tau_2^2$, suggests the absence of outliers
  - extension for covariates
  - *metaplus* package in R

w: the weight in the mixture

Identified alternative random effects models
mixture of distributions (2)

- **mixture of bivariate normal distributions**

$$\begin{pmatrix}\theta_{i1}\\ \theta_{i2}\end{pmatrix} \sim w_1 N\left(\begin{pmatrix}\mu_{11}\\ \mu_{12}\end{pmatrix}\begin{matrix}\mu_{11}\\ \mu_{12}\end{matrix}, \Sigma_1\right)\begin{pmatrix}\mu_{11}\\ \mu_{12}\end{pmatrix}, \Sigma_1\Big) + \cdots + \; w_k N\left(\begin{pmatrix}\mu_{k1}\\ \mu_{k2}\end{pmatrix}\begin{matrix}\mu_{k1}\\ \mu_{k2}\end{matrix}, \Sigma_k\right)\begin{pmatrix}\mu_{k1}\\ \mu_{k2}\end{pmatrix}, \Sigma_k\Big)$$

  - DTA meta-analyses
  - to identify latent subgroups of studies and estimate sensitivity and specificity for each subgroup
  - *CAMAN* and *mada* R packages
  - extension for covariates predicting the latent subgroup classification

- **mixture of multivariate normal distributions**
  - longitudinal data

- **random-intercept mixture of regressions**
  - meta-analysis with multiple outcome reports nested within studies

k: number of mixture components (subgroups)
$w_k > 0$: the weight in the mixture

Identified alternative random effects models

Dirichlet process (DP) prior mixture models

- to identify the potential underlying clustering of the data (e.g. relevant subgroups of studies)

$$\theta_i \sim F$$
$$F \sim DP(\alpha, F_0)$$
$$F_0 \sim N(\mu_b, \tau_b^2)$$

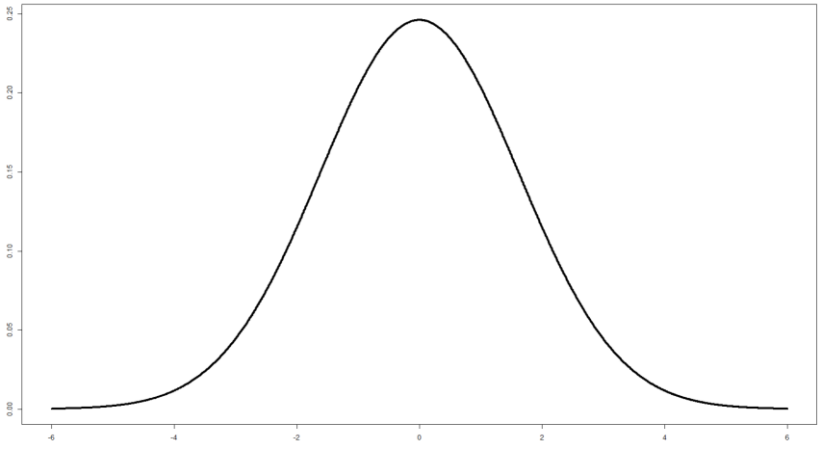
  - with α the concentration parameter that measures the variability of F around F_0 (high values suggest that F is 'close' to F_0)
  - F_0 is the base distribution that controls the mean of the process
  - a truncation that allows obtaining a plausible approximation to F is usually applied (e.g. the number of studies)
  - assumption of a discrete (mixture of points) or a continuous distribution (mixture of distributions)
  - conditional DP for small number of studies: conditional distribution for F given that the posterior median of F is μ_b
  - *bspmma, DPpackage* R packages

Models compared in the simulation

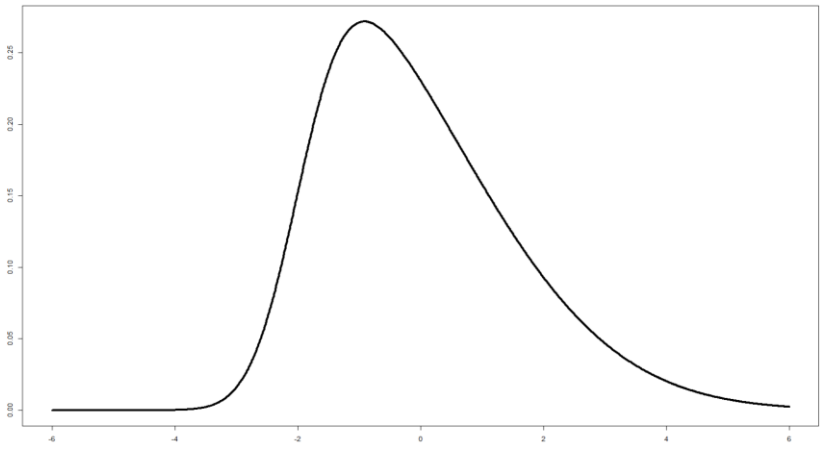
	Framework fitted	Within-study distribution	Between-study distribution	Prior distributions
1	Bayesian	Binomial	Normal	$\tau \sim HN(0,1)$
2	Bayesian	Binomial	Normal	$\tau \sim U(0,10)$
3	Frequentist	Normal	Normal	-
4	Bayesian	Binomial	t-distribution	$\omega \sim U(0,20)$
5	Frequentist	Normal	t-distribution	-
6	Bayesian	Binomial	Skew Normal	$\omega \sim U(0,20)$
7	Frequentist	Normal	Mixture of 2 normal distributions with common mean	-
8	Bayesian	Binomial	DP mixture of points	$\tau \sim HN(0,1)$, $\alpha \sim U(0.3,5)$
9	Bayesian	Binomial	DP mixture of points	$\tau \sim HN(0,1)$, $\alpha \sim U(0.3,10)$
10	Bayesian	Binomial	DP mixture of points	$\tau \sim U(0,10)$, $\alpha \sim U(0.3,5)$
11	Bayesian	Binomial	DP mixture of points	$\tau \sim U(0,10)$,$\alpha \sim \Gamma(1,1)$

Data generating process

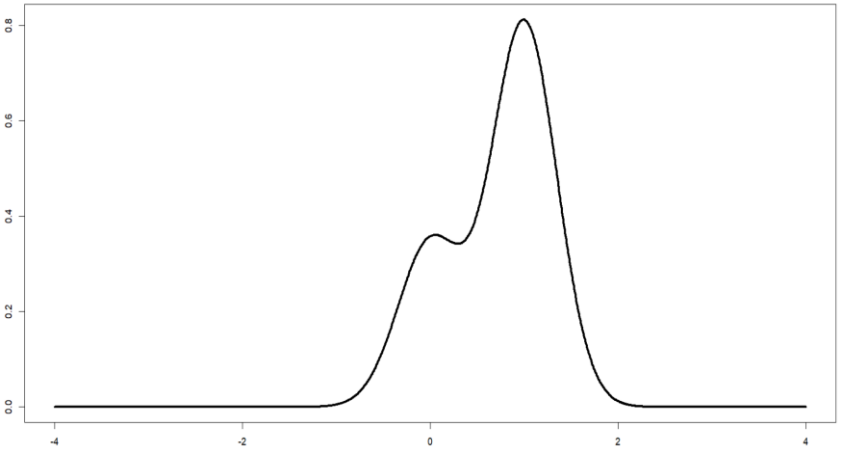
Shape of the true distributions



Normal



Skew normal



Mixture of two normal distributions

22 scenarios varying

- the number of studies $n = 14,26$
- the true mean treatment effect $\mu = 0,0.5$ or $\mu_1 = 0$ and $\mu_2 = 1$ (for the mixture scenarios)
- the heterogeneity, $\tau^2 = 0.12, 2.63$

For each scenario we generated 1000 datasets

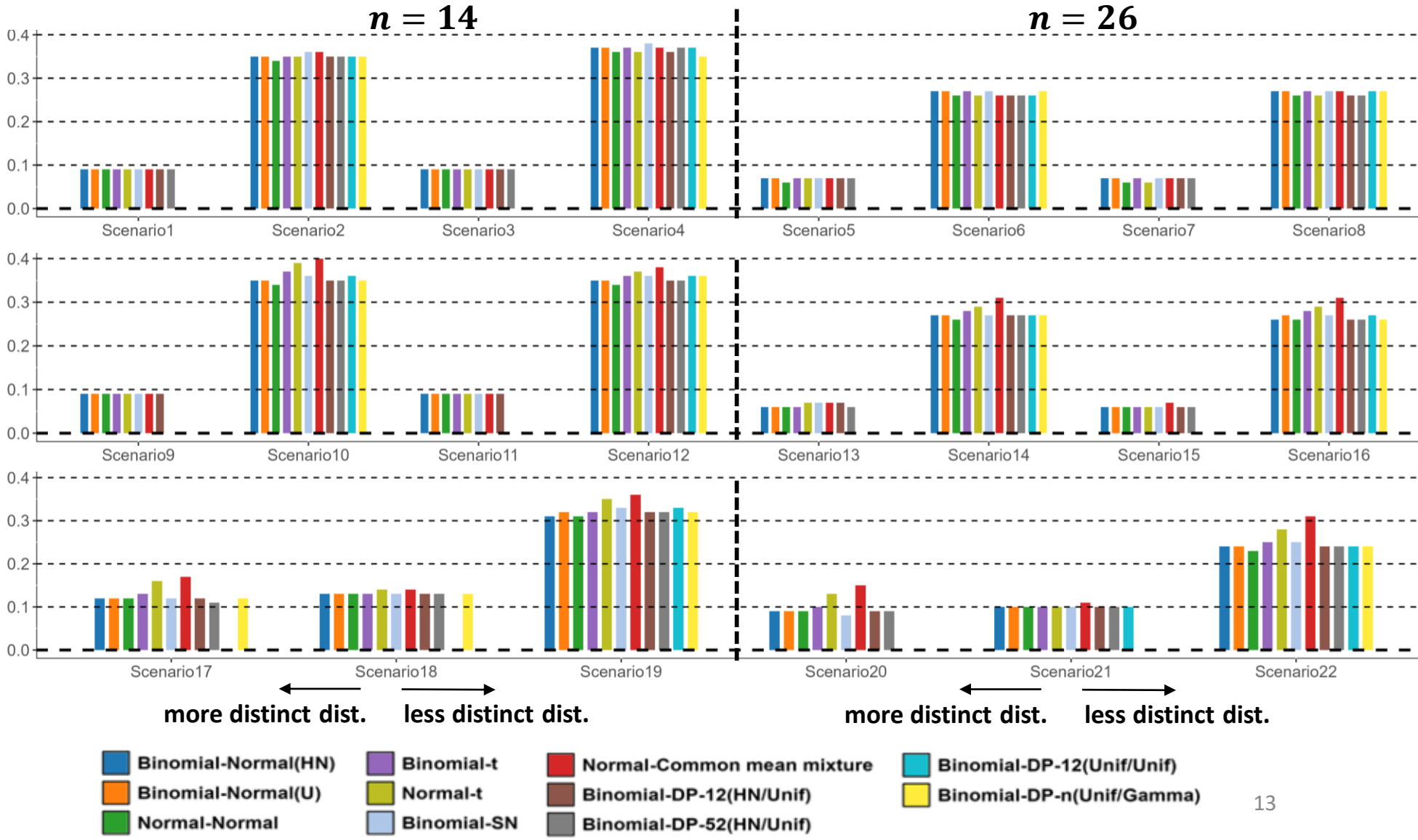
Simulation results

Average bias for the mean treatment effect (μ)

- **normal true dist.**
- sc. 1, 3, 5, 7: $\tau^2 = 0.12$
- sc. 2, 4, 6, 8: $\tau^2 = 2.63$
- sc. 1, 2, 5, 6: $\mu = 0$
- sc. 3, 4, 7, 8: $\mu = 0.5$

- **skew-normal true dist.**
- sc. 9, 11, 13, 15: $\tau^2 = 0.12$
- sc. 10, 12, 14, 16: $\tau^2 = 2.63$
- sc. 9, 10, 13, 14: $\mu = 0$
- sc. 11, 12, 15, 16: $\mu = 0.5$

- **normal mixture true dist.**
- $\mu_1 = 0, \mu_2 = 1$
- $\tau_1^2 = 0.12$
- sc. 17, 20: $\tau_2^2 = 0.005$
- sc. 18, 21:$\tau_2^2 = 0.12$
- sc. 19, 22:$\tau_2^2 = 2.63$



Simulation results

Average bias for the heterogeneity (τ^2)

- **normal true dist.**
- sc. 1, 3, 5, 7: $\tau^2 = 0.12$
- sc. 2, 4, 6, 8: $\tau^2 = 2.63$
- sc. 1, 2, 5, 6: $\mu = 0$
- sc. 3, 4, 7, 8: $\mu = 0.5$

- **skew-normal true dist.**
- sc. 9, 11, 13, 15: $\tau^2 = 0.12$
- sc. 10, 12, 14, 16: $\tau^2 = 2.63$
- sc. 9, 10, 13, 14: $\mu = 0$
- sc. 11, 12, 15, 16: $\mu = 0.5$

- **normal mixture true dist.**
- $\mu_1 = 0, \mu_2 = 1$
- $\tau_1^2 = 0.12$
- sc. 17, 20: $\tau_2^2 = 0.005$
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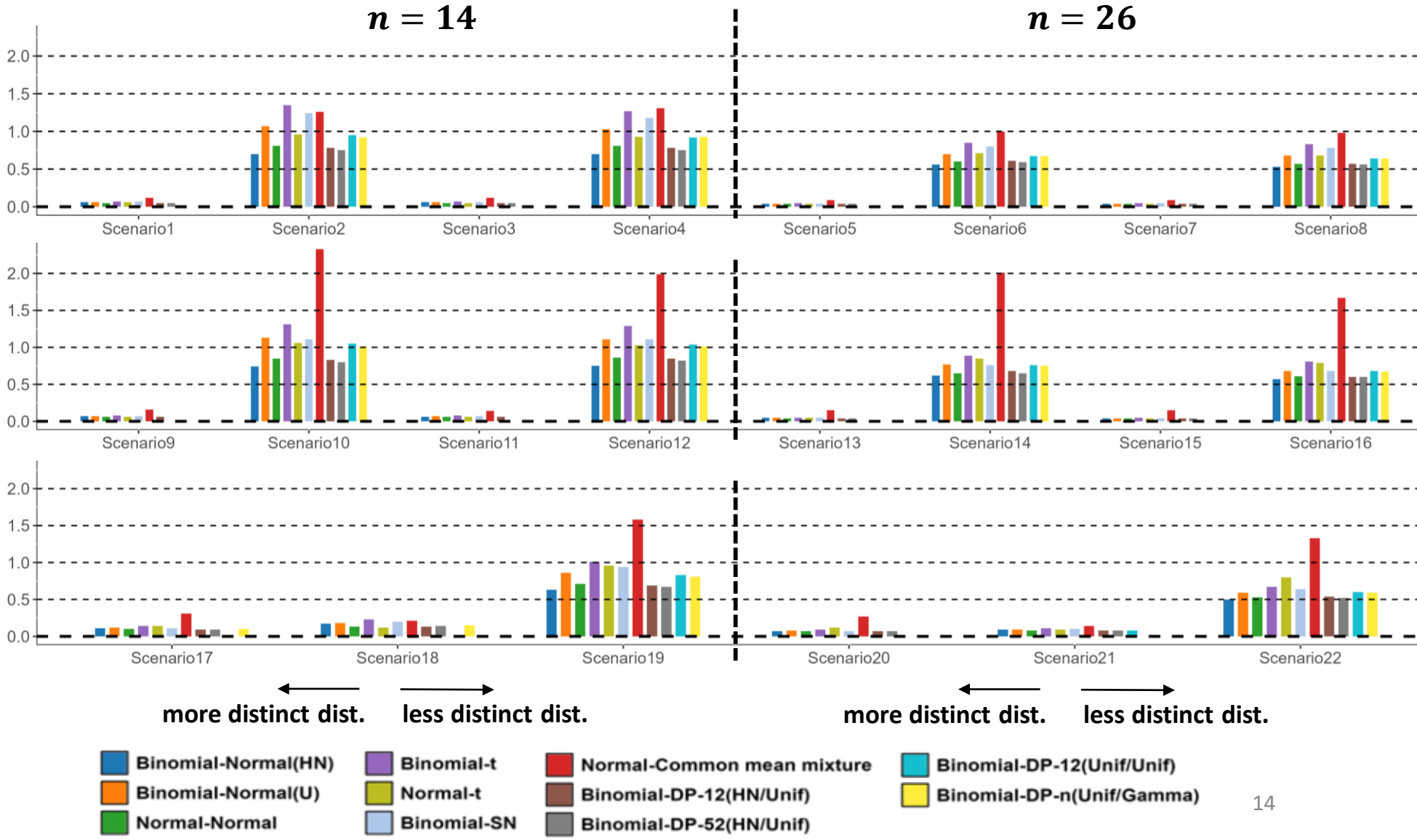


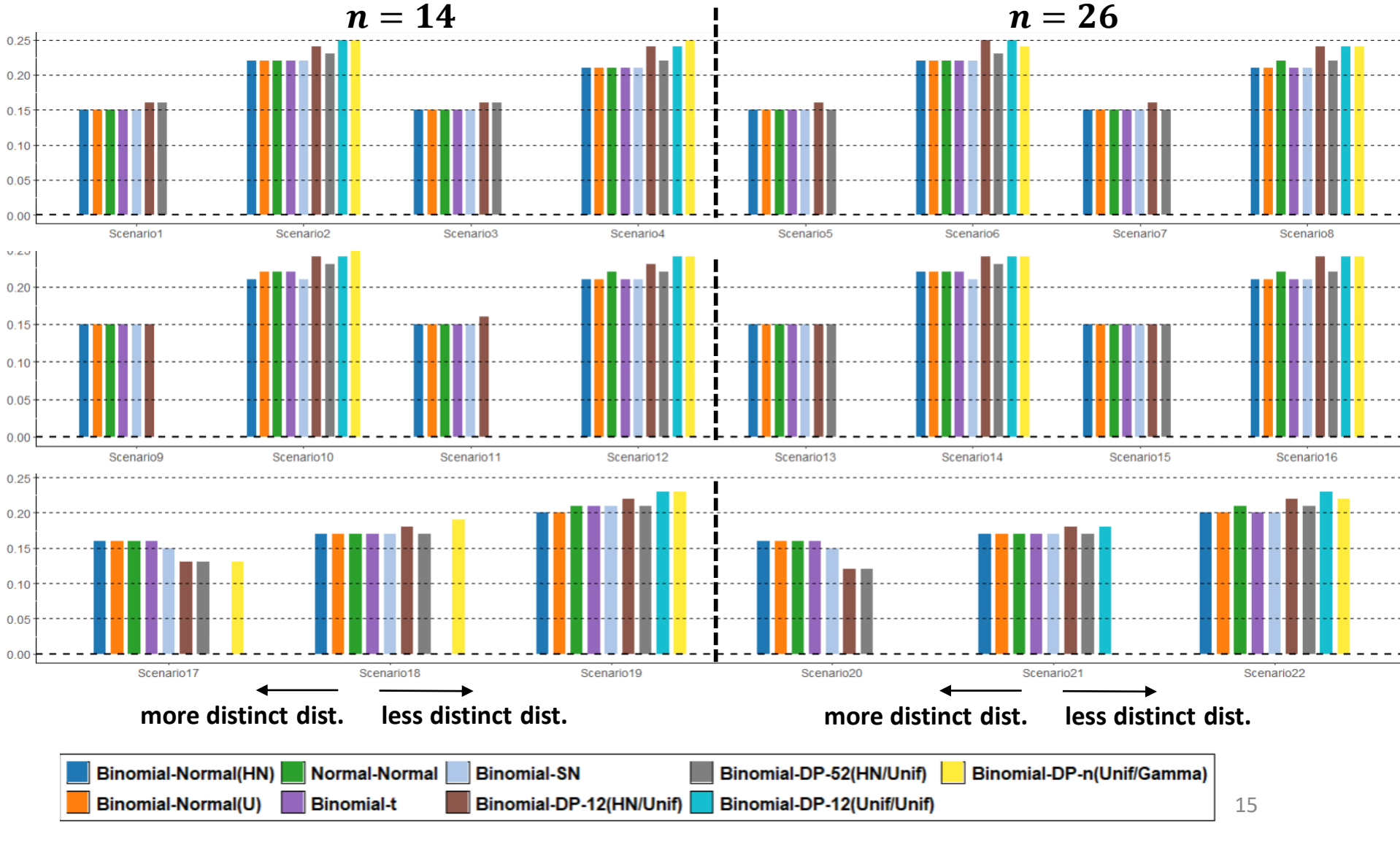
Simulation results

Average bias for the study-specific effects (θ_i)

- **normal true dist.**
- sc. 1, 3, 5, 7: $\tau^2 = 0.12$
- sc. 2, 4, 6, 8: $\tau^2 = 2.63$
- sc. 1, 2, 5, 6: $\mu = 0$
- sc. 3, 4, 7, 8: $\mu = 0.5$

- **skew-normal true dist.**
- sc. 9, 11, 13, 15: $\tau^2 = 0.12$
- sc. 10, 12, 14, 16: $\tau^2 = 2.63$
- sc. 9, 10, 13, 14: $\mu = 0$
- sc. 11, 12, 15, 16: $\mu = 0.5$

- **normal mixture true dist.**
- $\mu_1 = 0, \mu_2 = 1$
- $\tau_1^2 = 0.12$
- sc. 17, 20: $\tau_2^2 = 0.005$
- sc. 18, 21:$\tau_2^2 = 0.12$
- sc. 19, 22:$\tau_2^2 = 2.63$



Simulation results

Coverage probability and mean square error

Mean square error

- For scenarios with large heterogeneity
  - normal-normal and binomial-DP models – generally smaller MSE for the mean treatment effect estimate
  - binomial-normal(HN) – the smallest MSE for the heterogeneity estimate followed by the binomial-DP(HN) and the normal-normal models

Coverage probability

- For scenarios with large heterogeneity
  - normal and skew-normal scenarios with 26 studies: normal models – best coverage of the mean treatment effect
  - mixture scenarios: binomial-DP models best coverage overall of the mean treatment effect followed by the binomial-normal models
  - choice of prior more important than the choice of the model for heterogeneity

Discussion

- When substantial heterogeneity among studies is suspected or outlying studies are present, focusing on the mean treatment effect may lead to spurious conclusions

- Average bias of both the mean treatment effect and the heterogeneity is substantial in presence of high heterogeneity regardless of the model used

- These results are in agreement with smaller simulations studies when they found the alternative models mostly beneficial in terms of precision and model fit

- In meta-analyses where the distribution of the data seems multimodal, mixture models may result in more accurate estimates of the study-specific effects and should be considered

- Semi-parametric models (e.g. DP models) may assist identifying homogeneous subgroups of studies when potential effect modifiers are unobserved

Limitations

- Using scenarios with more studies might have improved the performance of some models
- We used a fixed skewness parameter that might have not resulted in many highly skewed datasets to properly assess the performance of the skew-normal model
- We did not compare all the identified models in our simulation
- We only used the normal distribution as base distribution in the DP models

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