Meta-analyses based on previous meta-analyses

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#MedStatGoe

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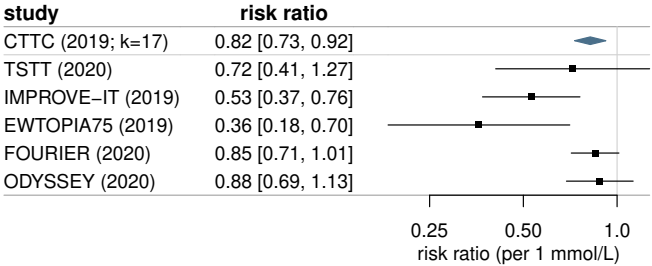
The problem

Puzzling meta-analysis data

- the problem:
  meta-analysis (without study-level data)
  included in subsequent meta-analysis
- “classical” meta-analysis models not applicable
- can estimates / models / external data
  be adapted for coherent inference?

The problem

Motivating example: LDL cholesterol lowering / major vascular events



- Gencer *et al.* (2020)[1] presented (random-effects) meta-analysis of 6 studies
- "CTTC" estimate: a (common-effect) meta-analysis of 17 studies
- CTTC's study-level data *not* available

[1] B. Gencer, N. A. Marston, K. Im, *et al.* Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *The Lancet*, **396**(10263):1637–1643, 2020.

The problem

Summary estimates without source data

- **why** missing study-level information:
  - IPD analyses (IPD data not published, study summaries not considered relevant)
  - secondary endpoints
  - . . . ?
- normally would require detailed data from *all* (here: $5 + 17$) studies
- how to **perform** / **approximate** “gold standard” full **analysis** ?

Modelling

Recap: the normal-normal (random-effects) model

- the meta-analysis **data** set:
  - effect estimates $y_i \quad (i = 1, \ldots, k)$
  - standard errors s_i (assumed known)
- model / **likelihood**:

$$\begin{aligned} y_i|\theta_i &\sim \text{Normal}(\theta_i, s_i^2) \\ \theta_i|\mu, \tau &\sim \text{Normal}(\mu, \tau^2) \end{aligned}$$

or (marginally):

$$y_i|\mu, \tau \sim \text{Normal}(\mu, s_i^2 + \tau^2)$$

- **parameters**:
  - overall mean μ
  - heterogeneity τ
  - study-specific means θ_i
- (common-effect model: $\tau = 0$)

Modelling

CE vs. RE models; Study-specific effects vs. overall mean effect

1. need to harmonize
   - **common-effect** estimate, and
   - **random-effects** model

2. need to consider differing **targets** of estimates:
   - studies: $y_i \rightarrow \theta_i$
   - meta-analyses: $\hat{\mu} \rightarrow \mu$

   and treat data accordingly

Reconciling CE estimates and RE models

Adjusting CE standard errors

- inconsistency when assuming common effect (homogeneity, $\tau = 0$) initial analysis and random effects (heterogeneity, $\tau \geq 0$) for subsequent update
- CE estimators may be overconfident
  (underestimated uncertainty due to neglected heterogeneity)

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Reconciling CE estimates and RE models

Adjusting CE standard errors

- inconsistency when assuming common effect (homogeneity, $\tau = 0$) initial analysis and random effects (heterogeneity, $\tau \geq 0$) for subsequent update
- CE estimators may be overconfident
  (underestimated uncertainty due to neglected heterogeneity)

- **Henmi & Copas** [2] considered RE standard errors for the CE point estimator
- approach may be used to **inflate CE standard error**
  to correspond to RE model (and given $\hat{\tau}$):

$$\text{SE}_{\text{RE}} \;=\; \text{SE}_{\text{CE}} \times \sqrt{1 + \tau^2 \, \frac{\sum_i s_i^{-4}}{\sum_i s_i^{-2}}}$$

(requires known standard errors (s_i) or approximation based on sample sizes (n_i))

[2] M. Henmi and J. B. Copas. Confidence intervals for random effects meta-analysis and robustness to publication bias. *Statistics in Medicine*, **29**(29):2969–2983, 2010. https://doi.org/10.1002/sim.4029

Joint modeling of (study-level and overall) estimates

Adapting common MA models: frequentist

- a frequentist approach
  - adapt **location-scale model** [3]
    allowing for heterogeneity covariates:

    meta-analysis ($\hat{\mu}$) estimates μ *without* heterogeneity
    $(\hat{\mu}|\mu, \tau, s_{\hat{\mu}} \sim \text{Normal}(\mu, s_{\hat{\mu}}^2 + 0 \times \tau^2))$,

    study (y_i) estimates μ *with* heterogeneity
    $(y_i|\mu, \tau, s_i \sim \text{Normal}(\mu, s_i^2 + 1 \times \tau^2))$

  - need to specify (0/1) covariates
    to distinguish "regular" studies and MA estimates
  - (remaining: issue of two heterogeneity parameters / estimates,
    initial and subsequent meta-analyses)

[3] W. Viechtbauer and J. A. López-López. Location-scale models for meta-analysis. *Research Synthesis Methods*, **13**(6):697–715, 2022. https://doi.org/10.1002/jrsm.1562

Joint modeling of (study-level and overall) estimates

Adapting common MA models: Bayesian

- a Bayesian approach
  - consider as **sequential updating**:
    posterior (μ, τ) from previous meta-analysis
    serves as prior for analysis of additional studies
  - need to translate meta-analytic estimate (of μ and possibly τ)
    into an (approximate) prior
  - τ prior may also be specified as weakly informative / non-informative [4]

[4] C. Röver. Bayesian random-effects meta-analysis using the `bayesmeta` R package. *Journal of Statistical Software*, **93**(6):1–51, 2020. `https://doi.org/10.18637/jss.v093.i06`

Example application

Gencer example: CE adjustment

- CTTC study's (CE-) estimate: RR 0.82 [0.73, 0.92]
  (log-RR $\pm$ s.e.: -0.20 ± 0.059)
- study-specific standard errors not provided, but: sample sizes (n_i) known
- heterogeneity information from (new) 5 *Gencer* studies: $\hat{\tau}_{\text{DL}} = 0.22$

	τ	log-RR SE	RR
CTTC original	0.00	0.059	0.82 [0.73, 0.92]

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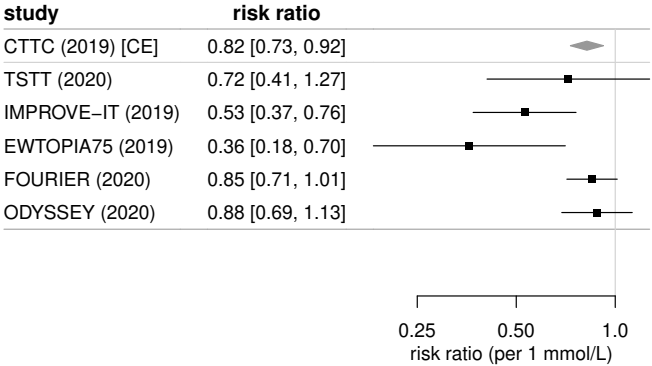
$\hat{\tau}$ from 5 *Gencer* studies	0.22	$0.059 \times 1.68 = 0.099$	0.82 [0.68, 1.00]

Example application

Gencer example: meta-analysis



Example application

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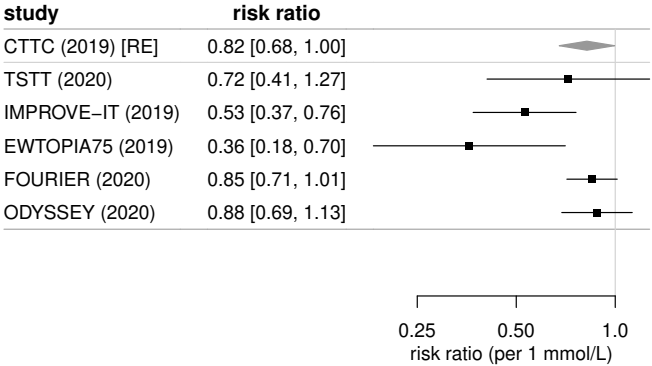
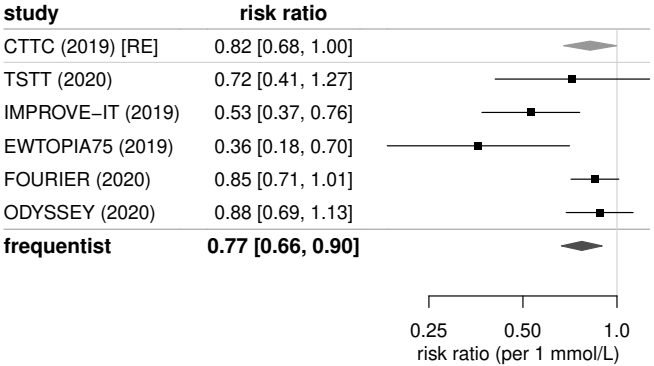


- adjust (CE) standard error

Example application

Gencer example: meta-analysis

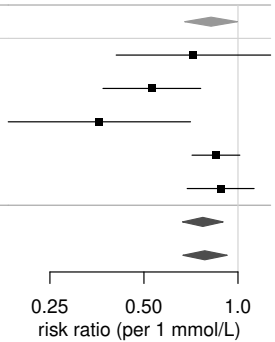


- adjust (CE) standard error
- frequentist estimate (location-scale model)

Example application

Gencer example: meta-analysis

study	risk ratio
CTTC (2019) [RE]	0.82 [0.68, 1.00]
TSTT (2020)	0.72 [0.41, 1.27]
IMPROVE–IT (2019)	0.53 [0.37, 0.76]
EWTOPIA75 (2019)	0.36 [0.18, 0.70]
FOURIER (2020)	0.85 [0.71, 1.01]
ODYSSEY (2020)	0.88 [0.69, 1.13]
frequentist	**0.77 [0.66, 0.90]**
Bayesian	**0.78 [0.67, 0.92]**



- adjust (CE) standard error
- frequentist estimate (location-scale model)
- Bayesian estimate (informative μ prior)

Extracting information from published data

Issues

- CE-to-RE conversion requires
  - heterogeneity estimate
    - from original study:
      quoted, from Q-test, I^2, from related publications (e.g., [5])
    - from available data only
    - possibly pooled from both sources
    - ...
  - standard errors (s_i)
    - approximate based on sample sizes (or event counts, ...)
    - assume equal standard errors
- separate heterogeneity estimation from two sources
  - possible inconsistency
  - effectively “stratified” by source

[5] C. Baigent, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *The Lancet*, **366**(9493):1267–1278, 2005.

Using MA estimates within the “classical” RE model

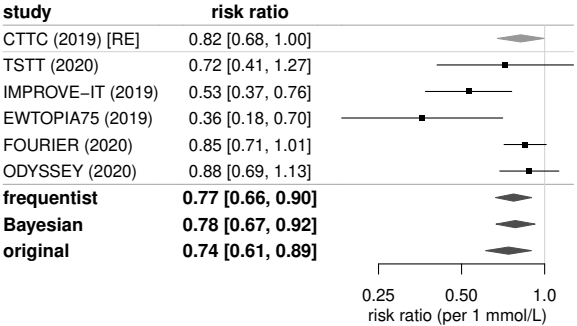
Problems

- use of a MA estimate ($\hat{\mu}$) and standard error ($s_{\hat{\mu}}$)
  in place of study estimates (y_i, s_i) leads to assumption violation
- compare assumed and actual variances (*conditional* on τ):

- common-effect estimate
  - assumed: $\text{Var}(\hat{\mu}|\tau) = s_{\hat{\mu}}^2 + \tau^2$
  - actual: $\text{Var}(\hat{\mu}|\tau) = s_{\hat{\mu}}^2 + \tau^2 \frac{\sum_i s_i^{-4}}{\sum_i s_i^{-2}}$

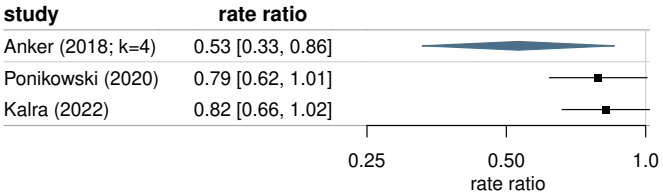
  (over- / underestimation of precision)
- random-effects estimate
  - assumed: $\text{Var}(\hat{\mu}|\tau) = s_{\hat{\mu}}^2 + \tau^2$
  - actual: $\text{Var}(\hat{\mu}|\tau) = s_{\hat{\mu}}^2$

  (greater precision than stated:
  conservative, suboptimal)



A trickier example

Intravenous iron meta-analysis



- Graham *et al.* (2023)[6] presented (random-effects) meta-analysis of 4 studies
- *Anker (2018)* estimate: a random-effects meta-analysis
- unclear whether Anker's $\hat{\tau} > 0$, $\hat{\tau}$ from studies 1–3 and 2–3 is $= 0$
  (without standard error adjustment or heterogeneity may lead to CE analysis)

[6] F. J. Graham, P. Pellicori, P. R. Kalra, I. Ford, D. Bruzzese, and J. G. F. Cleland. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *European Journal of Heart Failure*, **25**(4):528–537, 2023.

Conclusions

- need to consider different targeted parameters (study-specific effect θ_i vs. overall mean effect μ)
- CE estimates and RE models may be reconciled
- with some detective work, limited data may still be used
- with comprehensive reporting [7, 8] guesswork would be unnecessary
- not an issue in case of a common-effect model
- more complex solutions conceivable
- how to extend to a Student-*t* (HKSJ) approach?

[7] M. J. Page, D. Moher, P. M. Bossuyt, *et al.* PRISMA 2020 explanation and elaboration: updated guidance for reporting systematic reviews. *BMJ*, **372**:n160, 2021. https://doi.org/10.1136/bmj.n160

[8] L. A. Stewart, M. Clarke, M. Rovers, R. D. Riley, M. Simmonds, G. Stewart, J. F. Tierney. Preferred reporting items for a systematic review and meta-analysis of individual participant data: The PRISMA-IPD statement. *Journal of the American Medical Association*, **313**(16):1657–1665, 2015. https://doi.org/10.1001/jama.2015.3656

+++ additional slides +++

Examples

1: Gencer *et al.* (2020)

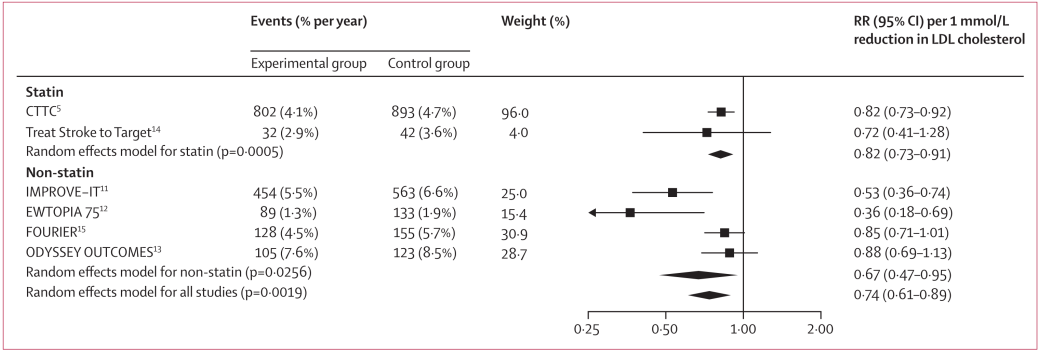


Figure 1: **Effect of LDL cholesterol lowering on the risk of major vascular events with statin and non-statin treatment in older patients**

- B. Gencer, N. A. Marston, K. Im, *et al.* Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *The Lancet*, **396**(10263):1637–1643, 2020. `https://doi.org/10.1016/S0140-6736(20)32332-1`
- "CTTC" study itself was a (common-effect, MH) meta-analysis including 17 studies

Examples

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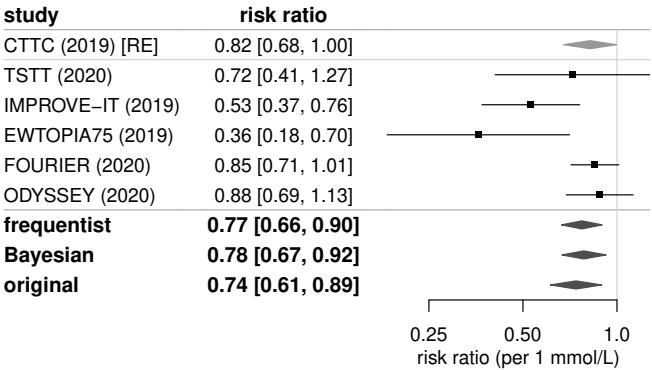
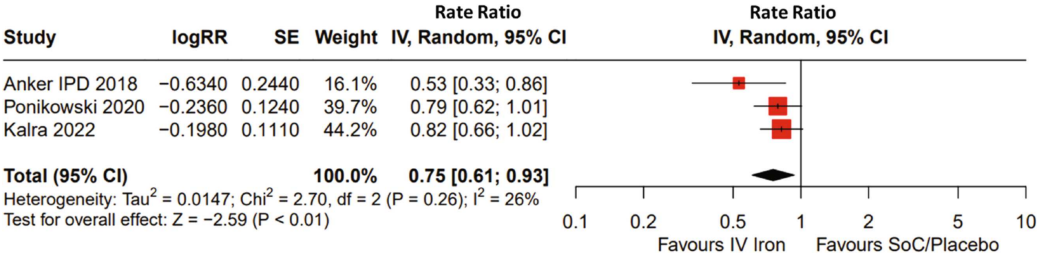


- original estimate in comparison to re-analyses
- standard errors (log-RR μ): 0.076 / 0.082 / 0.097
  $\rightarrow$ precision gain (despite inflated CTTC estimate)

Examples

2: Graham *et al.* (2023)



- F. J. Graham, P. Pellicori, P. R. Kalra, I. Ford, D. Bruzzese, and J. G. F. Cleland. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *European Journal of Heart Failure*, **25**(4):528–537, 2023. https://doi.org/10.1002/ejhf.2810
- Anker (2018) study was a meta-analysis including $k = 4$ studies

Converting CE to RE standard errors

Using Henmi / Copas approach

- **standard error** of a **common-effect estimate**:

$$\mathrm{SE}_0^{\mathrm{c}} = \sqrt{\frac{1}{\sum_i w_i}},$$

where $w_i = \frac{1}{s_i^2}$ are the (common-effect) inverse-variance (IV) weights.

- Henmi & Copas (2010)[9]: same **point estimate** may be used within **RE model**. **Standard error** then is larger, with

$$\mathrm{SE}_\tau^{\mathrm{c}} = \sqrt{\frac{\tau^2 \sum_i w_i^2 + \sum_i w_i}{\left(\sum_i w_i\right)^2}} = \mathrm{SE}_0^{\mathrm{c}} \sqrt{1 + \tau^2 \frac{\sum_i w_i^2}{\sum_i w_i}}$$

Inflation factor may be computed / approximated based on τ and w_i

[9] M. Henmi and J. B. Copas. Confidence intervals for random effects meta-analysis and robustness to publication bias. *Statistics in Medicine*, **29**(29):2969–2983, 2010. https://doi.org/10.1002/sim.4029

Reverse engineering

approximating IV weights w_i

- (common-effect) IV weights $w_i = \frac{1}{s_i^2}$ are rarely known
- assume: $s_i = \frac{\sigma_u}{\sqrt{n_i}}$ for constant *unit information standard deviation (UISD)* σ_u and known sample sizes n_i
- UISD may be derived from SE_0^c and total sample size ($N = \sum_i n_i$): $\sigma_u = \sqrt{N}\, SE_0^c$
- IV weights result as $w_i = \frac{n_i}{\sigma_u^2}$
- in case n_i are unknown, but studies are assumed to be equal-sized ($n_i = \frac{N}{k}$), IV weights result as $w_i = \frac{k}{SE_0^c}$

Reverse engineering

Heterogeneity (τ) estimates

- in case a heterogeneity (τ) estimate is not provided, it may be derived / approximated based on Q-statistic / p-value or I^2
- or other related evidence may be utilized:
  (earlier/related publications, estimate from additional studies, ...)
- heterogeneity estimates from study subsets may be pooled (e.g., based on their d.f.)

Example application

R code

```
library("metafor")

# specify effect sizes:
es <- escalc( ... )

# frequentist analysis (location-scale model):
rma01 <- rma.uni(es,
                 scale=c(0,1,1,1,1,1), link="identity",
                 control=list(optimizer="nloptr"))

# Bayesian analyis (informative effect prior):
library("bayesmeta")
bma01 <- bayesmeta(es[-1,],
                   mu.prior.mean = es$yi[1],
                   mu.prior.sd   = sqrt(es$vi[1]))
```