Alternative weighting schemes in the random-effects model to reduce the impact of publication bias

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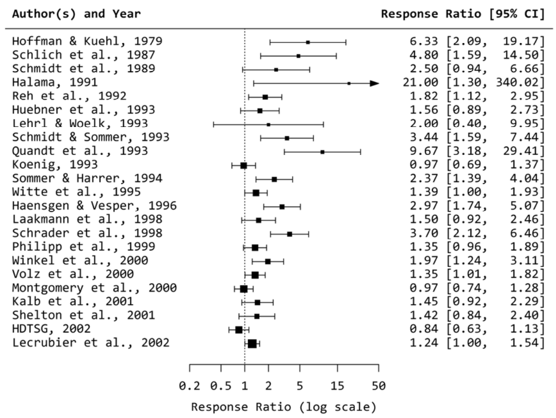
Standard RE Model

- $y_i = \mu + u_i + \epsilon_i$
  - $u_i \sim N(0, \tau^2)$
  - $\epsilon_i \sim N(0, v_i)$
- model fitting:
  - estimate τ^2 (DL, ML, REML, EB/PM, …)
  - $w_i = 1/(v_i + \hat{\tau}^2)$
  - $\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i}$ with $SE[\hat{\mu}] = \sqrt{\frac{1}{\sum w_i}}$
  - 95% CI for μ: $\hat{\mu} \pm 1.96\, SE[\hat{\mu}]$

Example: St. John's Wort for Depression

- based on Linde et al. (2005)
- 23* placebo-controlled trials that examined the clinical effects of *Hypericum* extract in adults with depression
- outcome measure: response ratio (RR)
- analysis with log-transformed RRs

* one study with no events excluded



Example: St. John's Wort for Depression

- standard RE model results:
  - $\hat{\tau}^2_{DL} = 0.14$ ($I^2 = 73.9\%$)
  - Q(22) = 84.42, p < .0001
  - $\hat{\mu} = 0.56$ ($SE = 0.10$)
  - back-transformed: 1.75 (95% CI: 1.43 to 2.12)
  - 95% CR/PI: 0.81 to 3.74

Critique of the RE Model

- as $\tau^2 \to \infty$, $\hat{\mu}$ approaches $\sum y_i / k$
- "so small studies are getting too much weight"
- under the RE model, $\hat{\mu}$ is the UMVUE of μ, so from that perspective, weights are 'correct'
- (actually, since τ^2 is estimated, $\hat{\mu}$ is only an approximation to the UMVUE)

RE Model with Arbitrary Weights

- but we can still fit a RE model using weights that deemphasize smaller studies
- $y_i \sim N(\mu, v_i + \tau^2)$
- then for any arbitrary fixed weights w_i:
  - $\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i}$ is still an unbiased estimate of μ
  - $SE[\hat{\mu}] = \sqrt{\frac{\sum w_i^2 (v_i + \tau^2)}{(\sum w_i)^2}}$
- a sensible choice for the weights: $w_i = 1/v_i$
- some loss of efficiency, but often not much

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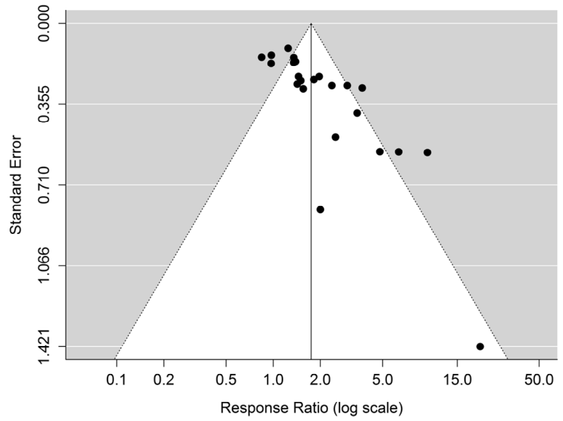
  - back-transformed: 1.75 (95% CI: 1.43 to 2.12)
- RE model with $w_i = 1/v_i$ weights:
  - $\hat{\tau}^2_{DL} = 0.14\ (I^2 = 73.9\%)$
  - $\hat{\mu} = 0.34\ (SE = 0.12)$
  - back-transformed: 1.40 (95% CI: 1.12 to 1.77)

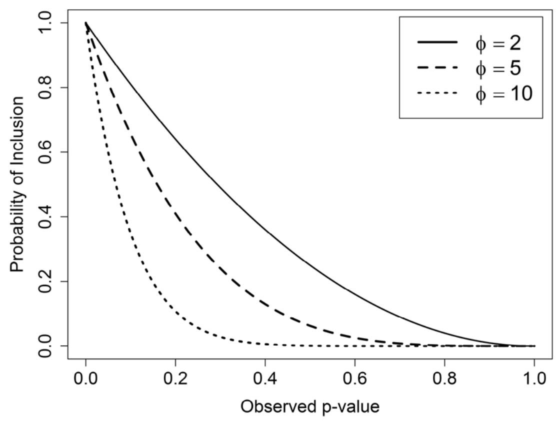


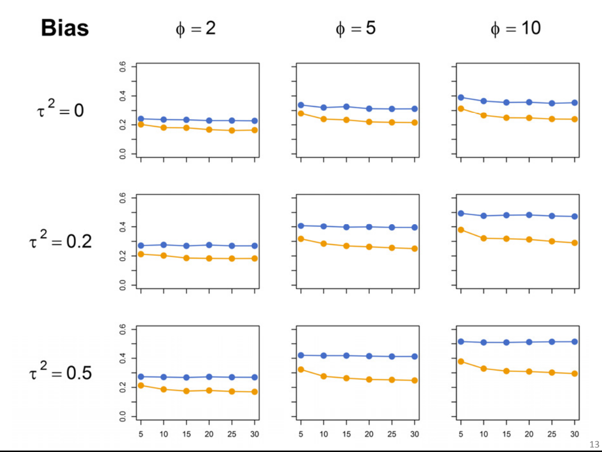
Publication Bias

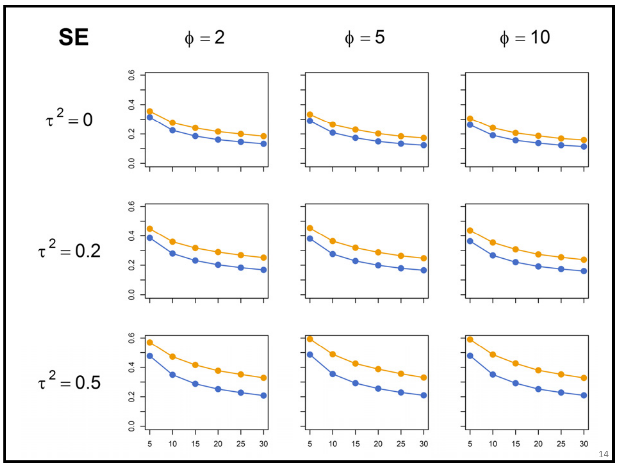
- assume probability of inclusion in meta-analysis is an inverse function of the p-value
- then smaller studies will tend to be included only if they greatly overestimate the effect
- using the standard RE model weights will then lead to more bias
- using $1/v_i$ weights counteracts this

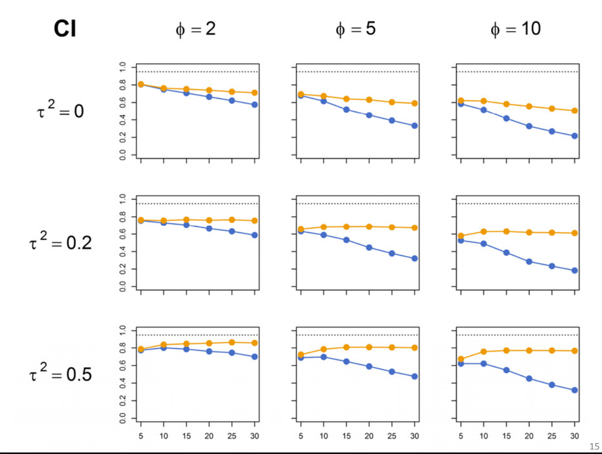
Simulation Study

- simulated data under the RE model with different degrees of publication bias
  - $\mu = 0.5$
  - $\tau^2 = 0, 0.2, 0.5$
  - $k = 5, 10, 15, 20, 25, 30$
  - $\phi = 2, 5, 10$ (severity of publication bias)
- examined bias, SE, and CI coverage
  - RE model with $w_i = 1/(v_i + \hat{\tau}^2)$:
  - RE model with $w_i = 1/v_i$:



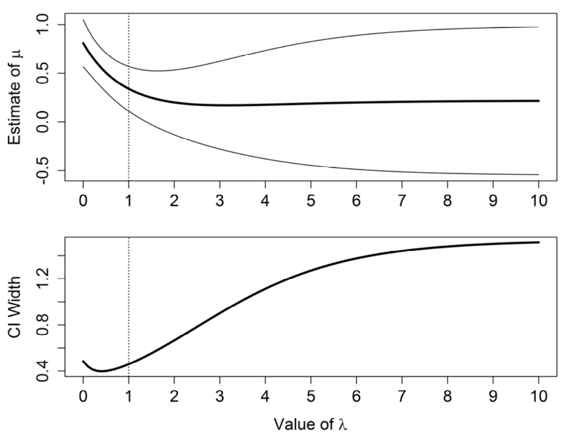






Bias-Variance Tradeoff

- using only the large(r) studies decreases bias, but increases variance (bias-variance tradeoff)
- let $w_i = 1/v_i^\lambda$: examine $\hat{\mu}$ as a function of λ
  - $\lambda = 0$: $\hat{\mu}$ with $w_i = 1$
  - $\lambda = ½$: $\hat{\mu}$ with $w_i = 1/\sqrt{v_i} = 1/se_i$
  - $\lambda = 1$: $\hat{\mu}$ with $w_i = 1/v_i$
  - for some $\lambda \in [0,1]$: $\hat{\mu}$ with $w_i = 1/(v_i + \hat{\tau}^2)$
  - as $\lambda \to \infty$, $\hat{\mu}$ converges to y_i of the study with the smallest v_i



Henmi & Copas (2010)

- describe the same idea of estimating μ using $w_i = 1/v_i$ weights to reduce bias
- way to get CI for μ is a wee bit complicated

Henmi & Copas (2010)

The conditional distribution of Q given R [...] is a little complicated, but it is well approximated by the gamma distribution with mean

$$(n-1)+\tau^2(W_1-W_2)+\tau^4\{(1+\tau^2W_2)^{-2}R^2-(1+\tau^2W_2)^{-1}\}(W_3-W_2^2)$$

and variance

$$\begin{aligned}&2(n-1)+4\tau^2(W_1-W_2)+2\tau^4(W_1W_2-2W_3+W_2^2)\\&\quad+4\tau^4\{(1+\tau^2W_2)^{-2}R^2-(1+\tau^2W_2)^{-1}\}(W_3-W_2^2)\\&\quad+4\tau^6\{(1+\tau^2W_2)^{-2}R^2-(1+\tau^2W_2)^{-1}\}(W_4-2W_2W_3+W_2^3)\\&\quad+2\tau^8\{(1+\tau^2W_2)^{-2}-2(1+\tau^2W_2)^{-3}R^2\}(W_3-W_2^2)^2.\end{aligned}$$

$$\begin{aligned}\mathrm{Var}(Q|R)&=2\mathrm{tr}\{(\boldsymbol{\mu}_1\boldsymbol{\mu}_1^{\mathrm{T}}+\Sigma_1)^2\}-2\{\mathrm{tr}(\boldsymbol{\mu}_1\boldsymbol{\mu}_1^{\mathrm{T}})\}^2\\&=2\mathrm{tr}\{(E_{-1}W^{1/2})A(E_{-1}W^{1/2})^{\mathrm{T}}(E_{-1}W^{1/2})A(E_{-1}W^{1/2})^{\mathrm{T}}\}\\&\quad-2[\mathrm{tr}\{(E_{-1}W^{1/2})B(E_{-1}W^{1/2})^{\mathrm{T}}\}]^2\\&=2\mathrm{tr}\{A(E_{-1}W^{1/2})^{\mathrm{T}}(E_{-1}W^{1/2})A\}-2\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}A(E_{-1}W^{1/2})^{\mathrm{T}}(E_{-1}W^{1/2})AW^{1/2}\boldsymbol{e}_1\\&\quad-2(\mathrm{tr}B-\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}BW^{1/2}\boldsymbol{e}_1)^2\\&=2\mathrm{tr}\{(E_{-1}W^{1/2})A^2(E_{-1}W^{1/2})^{\mathrm{T}}\}-2\mathrm{tr}\{(E_{-1}W^{1/2})AW^{1/2}\boldsymbol{e}_1\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}A(E_{-1}W^{1/2})^{\mathrm{T}}\}\\&\quad-2(\mathrm{tr}B-\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}BW^{1/2}\boldsymbol{e}_1)^2\\&=2\mathrm{tr}(A^2)-2\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}A^2W^{1/2}\boldsymbol{e}_1-2\mathrm{tr}(AW^{1/2}\boldsymbol{e}_1\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}A)\\&\quad+2\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}AW^{1/2}\boldsymbol{e}_1\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}AW^{1/2}\boldsymbol{e}_1-2(\mathrm{tr}B-\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}BW^{1/2}\boldsymbol{e}_1)^2\\&=2\mathrm{tr}(A^2)-4\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}A^2W^{1/2}\boldsymbol{e}_1+2(\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}A^2W^{1/2}\boldsymbol{e}_1)^2-2(\mathrm{tr}B-\boldsymbol{e}_1^{\mathrm{T}}W^{1/2}BW^{1/2}\boldsymbol{e}_1)^2\\&=2(n-1)+4\tau^2(W_1-W_2)+2\tau^4(W_1W_2-2W_3+W_2^2)\\&\quad+4\tau^4\{(1+\tau^2W_2)^{-2}R^2-(1+\tau^2W_2)^{-1}\}(W_3-W_2^2)\\&\quad+4\tau^6\{(1+\tau^2W_2)^{-2}R^2-(1+\tau^2W_2)^{-1}\}(W_4-2W_2W_3+W_2^3)\\&\quad+2\tau^8\{(1+\tau^2W_2)^{-2}-2(1+\tau^2W_2)^{-3}R^2\}(W_3-W_2^2)^2,\end{aligned}$$

$$A=I_n+\tau^2W-\tau^4\{(1+\tau^2W_2)^{-1}-(1+\tau^2W_2)^{-2}R^2\}W^{3/2}\boldsymbol{e}_1\boldsymbol{e}_1^{\mathrm{T}}W^{3/2},$$

$$B=\tau^4(1+\tau^2W_2)^{-2}R^2W^{3/2}\boldsymbol{e}_1\boldsymbol{e}_1^{\mathrm{T}}W^{3/2}$$

Henmi & Copas (2010)

- comparison:

Method	$\hat{\mu}$	$\exp(\hat{\mu})$	**95% CI**
RE with $w_i = 1/(v_i + \hat{\tau}^2)$	0.56	1.75	1.43 to 2.12
RE with $w_i = 1/v_i$	0.34	1.40	1.12 to 1.77
Henmi & Copas (2010)	0.34	1.40	1.09 to 1.80

Estimation of τ^2

- τ^2 estimator also implies certain weights:
  - HE: $w_i = 1$
  - DL: $w_i = 1/v_i$
  - ML, REML, EB/PM: $w_i = 1/(v_i + \hat{\tau}^2)$
- general method-of-moments estimator (DerSimonian & Kacker, 2007):
  - HE and DL are special cases
  - can work with any weights

Conclusions

- fitting RE model with $w_i = 1/v_i$ (or other weights) is no problem
- can be used to avoid giving “undue” weight to small studies
- decreases bias if there is publication bias

References

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- Henmi, M., & Copas, J. B. (2010). Confidence intervals for random effects meta-analysis and robustness to publication bias. *Statistics in Medicine, 29(29), 2969-2983.*
- Linde, K., Berner, M., Egger, M., & Mulrow, C. (2005). St John's wort for depression: Meta-analysis of randomised controlled trials. *British Journal of Psychiatry, 186, 99-107.*