

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

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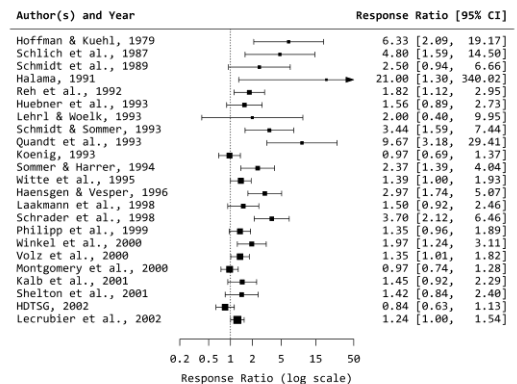
Standard RE Model

- $y_i = \mu + u_i + \epsilon_i$
 - $u_i \sim N(0, \tau^2)$
 - $\epsilon_i \sim N(0, v_i)$
- 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:
 - $\hat{\tau}_{DL}^2 = 0.14$ ($I^2 = 73.9\%$)
 - $Q(22) = 84.42$, $p < .0001$
 - $\hat{\mu} = 0.56$ ($SE = 0.10$)
 - 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 $\tau^2 \rightarrow \infty$, $\hat{\mu}$ 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

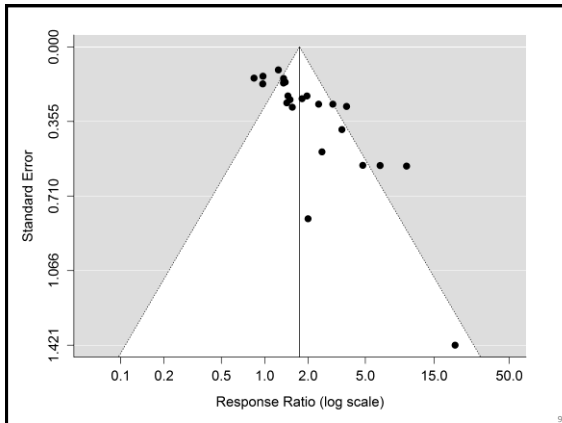
- but we can still fit a RE model using weights that deemphasize smaller studies
- $y_i \sim N(\mu, v_i + \tau^2)$
- then for any arbitrary fixed weights w_i :
 - $\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i}$ is still an unbiased estimate of μ
 - $SE[\hat{\mu}] = \sqrt{\frac{\sum w_i^2 (v_i + \tau^2)}{(\sum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

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

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Publication Bias

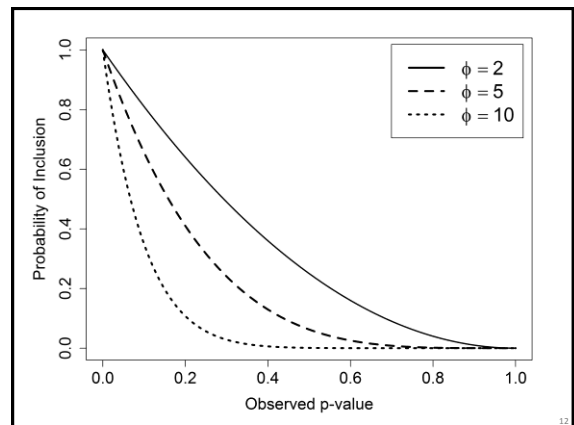
- assume probability of inclusion in meta-analysis is an inverse function of the p-value
- then smaller studies will tend to be included only if they greatly overestimate the effect
- using the standard RE model weights will then lead to more bias
- using $1/v_i$ weights counteracts this

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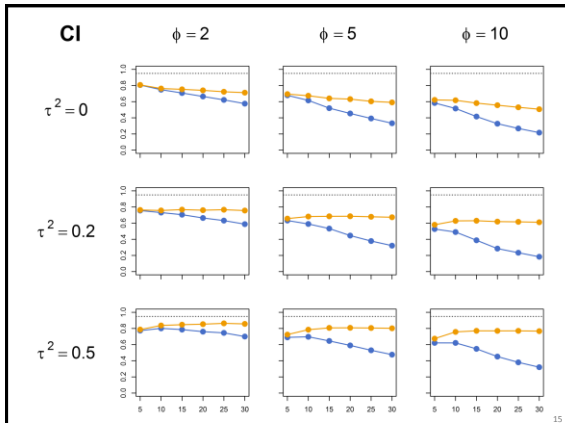
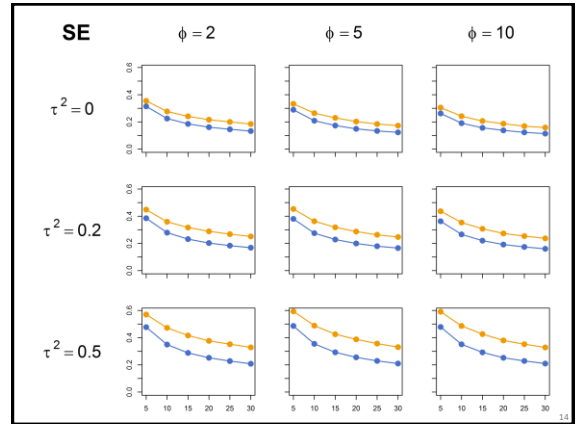
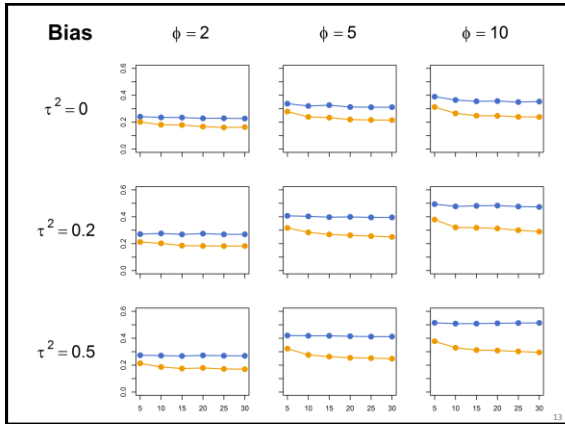
Simulation Study

- 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 $w_i = 1/v_i$: ●—●—●—●—●

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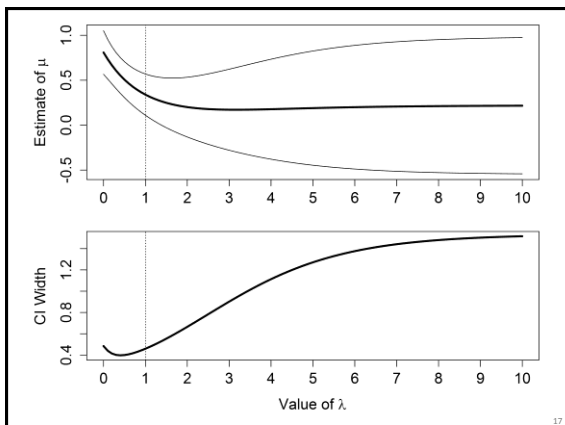
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Bias-Variance Tradeoff

- 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 $w_i = 1$
 - $\lambda = 1/2$: $\hat{\mu}$ 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 $\lambda \rightarrow \infty$, $\hat{\mu}$ converges to y_i of the study with the smallest v_i

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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

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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

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

and variance

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

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$$\begin{aligned} \text{Var}(Q|R) &= 2\text{tr}((\mu_1 \mu_1^T + \Sigma_1)^2) - 2[\text{tr}(\mu_1 \mu_1^T)]^2 \\ &= 2\text{tr}\{(E_{-1} W^{1/2}) A (E_{-1} W^{1/2})^T (E_{-1} W^{1/2}) A (E_{-1} W^{1/2})^T\} \\ &\quad - 2[\text{tr}\{(E_{-1} W^{1/2}) B (E_{-1} W^{1/2})^T\}]^2 \\ &= 2\text{tr}\{A (E_{-1} W^{1/2})^T (E_{-1} W^{1/2}) A\} - 2e_1^T W^{1/2} A (E_{-1} W^{1/2})^T (E_{-1} W^{1/2}) A W^{1/2} e_1 \\ &\quad - 2(\text{tr} B - e_1^T W^{1/2} B W^{1/2} e_1)^2 \\ &= 2\text{tr}\{(E_{-1} W^{1/2}) A^2 (E_{-1} W^{1/2})^T\} - 2\text{tr}\{(E_{-1} W^{1/2}) A W^{1/2} e_1 e_1^T W^{1/2} A (E_{-1} W^{1/2})^T\} \\ &\quad - 2(\text{tr} B - e_1^T W^{1/2} B W^{1/2} e_1)^2 \\ &= 2\text{tr}(A^2) - 2e_1^T W^{1/2} A^2 W^{1/2} e_1 - 2\text{tr}(A W^{1/2} e_1 e_1^T W^{1/2} A) \\ &\quad + 2e_1^T W^{1/2} A W^{1/2} e_1 e_1^T W^{1/2} A W^{1/2} e_1 - 2(\text{tr} B - e_1^T W^{1/2} B W^{1/2} e_1)^2 \\ &= 2\text{tr}(A^2) - 4e_1^T W^{1/2} A^2 W^{1/2} e_1 + 2(e_1^T W^{1/2} A^2 W^{1/2} e_1)^2 - 2(\text{tr} B - e_1^T W^{1/2} B W^{1/2} e_1)^2 \\ &= 2(n-1) + 4\tau^2(W_1 - W_2) + 2\tau^4(W_1 W_2 - 2W_3 + W_2^2) \\ &\quad + 4\tau^4\{(1 + \tau^2 W_2)^{-2} R^2 - (1 + \tau^2 W_2)^{-1}\}(W_3 - W_2^2) \\ &\quad + 4\tau^6\{(1 + \tau^2 W_2)^{-2} R^2 - (1 + \tau^2 W_2)^{-1}\}(W_4 - 2W_2 W_3 + W_2^3) \\ &\quad + 2\tau^8\{(1 + \tau^2 W_2)^{-2} - 2(1 + \tau^2 W_2)^{-3} R^2\}(W_3 - W_2^2)^2. \\ A &= I_n + \tau^2 W - \tau^4\{(1 + \tau^2 W_2)^{-1} - (1 + \tau^2 W_2)^{-2} R^2\} W^{3/2} e_1 e_1^T W^{3/2}, \\ B &= \tau^4(1 + \tau^2 W_2)^{-2} R^2 W^{3/2} e_1 e_1^T W^{3/2} \end{aligned}$$

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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

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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

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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

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References

- DerSimonian, R., & Kacker, R. (2007). Random-effects model for meta-analysis of clinical trials: An update. *Contemporary Clinical Trials, 28*(2), 105-114.
- 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.