Random-effects meta-analysis via generalized linear mixed models (GLMMs) for few studies

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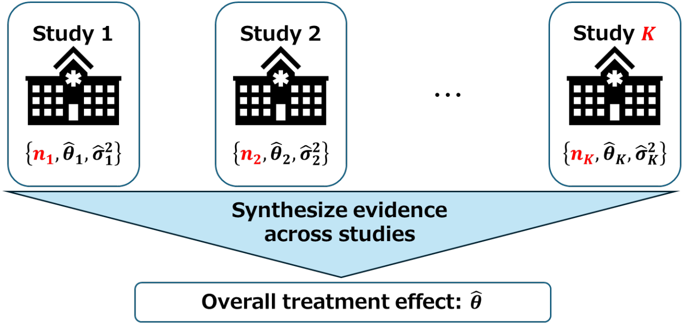
Aim of this talk



- Small-sample issues in meta-analysis:
  - Few studies (K is small)
  - GLMM meta-analysis often suffers from bias when K is small

Aim

Provide a small-sample correction for GLMM meta-analysis using only aggregate data.

Meta-analyses often include few studies

- Most meta-analyses include very few studies.
- Small-sample correction is essential in practice.

Table: Number of studies in empirical meta-analyses [Davey et al., 2011]

	All	50%	75%	90%	99%	Max
All meta-analyses	22,453	**3**	6	**10**	28	294
Binary outcomes	14,886	**3**	6	**10**	28	294
Continuous outcomes	6,672	**3**	5	**8**	24	98
Binary & continuous	895	**4**	7	**12**	46	133

- About 90% of meta-analyses include 10 studies or fewer.
  $\Rightarrow$ Inference usually occurs under small K.

Existing small-sample corrections

✓ Several small-sample corrections have been proposed:
- Profile likelihood + Bartlett correction [Noma, 2011]
- Exact confidence intervals [Michael et al., 2019]

✓ These methods improve coverage when K is small.

✗ All rely on the Normal–Normal model and its strong assumptions.

Normal–Normal model assumptions [Jackson et al., 2018]

(A1) Unbiased study-level estimates: $E[\hat{\theta}_k \mid V_k] = \theta_k$.

(A2) Known within-study variance: $\mathrm{Var}(\hat{\theta}_k \mid V_k) = \sigma_k^2$.

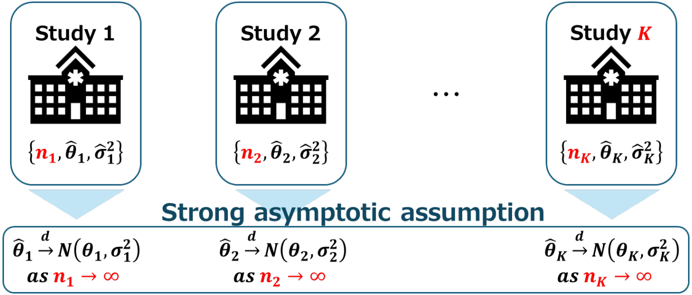
(A3) Within-study normality: $\hat{\theta}_k \mid \theta_k \sim N(\theta_k, \sigma_k^2)$.

(A4) Between-study normality: $\theta_k = \theta_0 + V_k,\ V_k \sim N(0, \tau^2)$.

Are assumptions (A1)–(A3) really reasonable?

✓ (A1)–(A3) require asymptotic normality of study estimates.

✗ Asymptotic normality requires large n_k in every study.

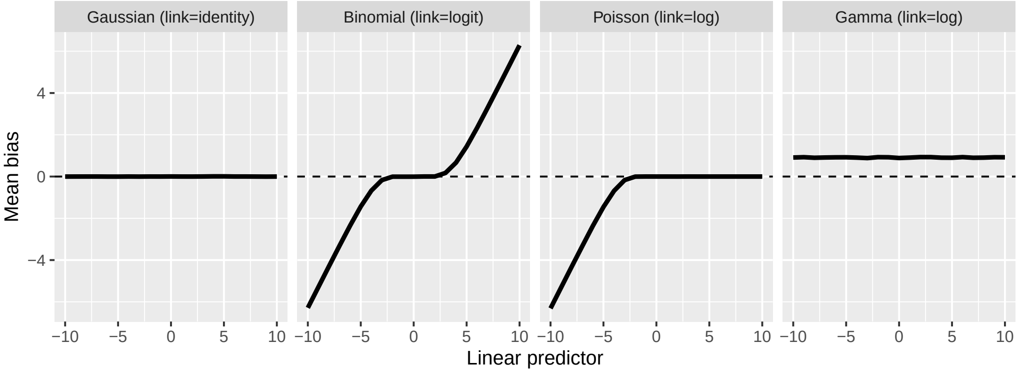


But in real meta-analyses, n_k is fixed

Small studies are often included, so (A1)–(A3) may fail.

Bias from nonlinear transformations

- ✗ Nonlinear transformations cause bias when n_k is small.
- ✗ Assumption (A1) fails: $E[\hat{\theta}_k \mid V_k] \neq \theta_k$.
- ✗ Bias remains even when $K \to \infty$.



Small-sample correction is necessary under GLMM meta-analysis.

Extension of random-effects meta-analysis to GLMM

- Individual outcomes Y_{ki} are not observed in practice in meta-analysis.
- Study k model:

$$\mu_k = E(Y_{ki} \mid V_k), \quad \theta_k = g(\mu_k) = \boldsymbol{x}_k^\top \boldsymbol{\beta} + V_k.$$

- $\boldsymbol{x}_k$ is a study-level covariate (not individual-level).

Individual-data likelihood (not available in practice)

$$L_{ki}(\boldsymbol{\beta}, \tau^2; y_{ki} \mid v_k) \propto \exp\left[\frac{y_{ki}(\boldsymbol{x}_k^\top \boldsymbol{\beta} + v_k) - b(\boldsymbol{x}_k^\top \boldsymbol{\beta} + v_k)}{a(\varphi_k)}\right]$$

- Between-study random effects:

$$V_k \overset{\text{i.i.d.}}{\sim} f_V(\cdot; \tau^2), \quad E(V_k) = 0, \; \mathrm{Var}(V_k) = \tau^2.$$

Sufficiency of aggregate data

- The study mean $\bar{y}_k = \frac{1}{n_k}\sum_{i=1}^{n_k} y_{ki}$ is a sufficient statistic for $(\boldsymbol{\beta}, \tau^2)$.
- ✓ All information on $(\boldsymbol{\beta}, \tau^2)$ is contained in $\{n_k, \bar{y}_k, \boldsymbol{x}_k\}$.
- Individual data are unnecessary to form the likelihood.

Likelihood for study k (aggregate-data only)

$$L_k(\boldsymbol{\beta}, \tau^2) \propto \int \exp\left[\frac{n_k\{\bar{y}_k(\boldsymbol{x}_k^\top\boldsymbol{\beta} + v_k) - b(\boldsymbol{x}_k^\top\boldsymbol{\beta} + v_k)\}}{a(\varphi_k)}\right] f_V(v_k; \tau^2)\, dv_k.$$

Maximum likelihood estimator

$$(\hat{\boldsymbol{\beta}}, \hat{\tau}^2) = \underset{(\boldsymbol{\beta}, \tau^2)}{\arg\max} \log L(\boldsymbol{\beta}, \tau^2), \quad L = \prod_{k=1}^{K} L_k.$$

Confidence interval from aggregate-data likelihood

Profile likelihood ratio statistic for β_ℓ

Let β_ℓ be the parameter of interest. The profile likelihood ratio statistic is

$$T(\beta_\ell^0) = -2\{\log L(\hat{\boldsymbol{\beta}}(\beta_\ell^0), \tilde{\tau}^2(\beta_\ell^0)) - \log L(\hat{\boldsymbol{\beta}}, \hat{\tau}^2)\} \xrightarrow{d} \chi_1^2 \quad (K \to \infty)$$

where $\hat{\boldsymbol{\beta}}(\beta_\ell^0)$ and $\tilde{\tau}^2(\beta_\ell^0)$ are constrained MLEs under the constraint $\beta_\ell = \beta_\ell^0$.

- ✓ Aggregate-data likelihood allows full MLE and CI without individual data.
- ✗ The χ^2 approximation requires large K.
- ✗ Meta-analyses often have only $K \leq 10$.

  $\Rightarrow$ Small-sample correction with respect to K is essential.

Classical Bartlett correction

Bartlett correction [Lawley, 1956]

Bartlett correction modifies the test statistic T as follows:

$$T_{BC}(\beta_\ell^0) = \frac{T(\beta_\ell^0)}{1 + 2C_{BC}(\beta_\ell^0)}, \quad C_{BC} = \frac{1}{2K}\left\{ l_2^{-2}\left(\tfrac{1}{4}l_4 - l_{31} + l_{22}\right) - l_2^{-3}\left(\tfrac{5}{12}l_3^2 - 2l_3 l_{21} + 2l_{21}^2\right)\right\}$$

$$l_r = E\left[\frac{\partial^r l}{\partial \beta_\ell^r}\right], \quad l_{rs} = \frac{\partial^s l_r}{\partial \beta_\ell^s}, \quad l(\beta_\ell) = \sum_{k=1}^{K} \log L_k(\hat{\boldsymbol{\beta}}(\beta_\ell), \tilde{\tau}^2), \quad r = 1,2,3,4, \quad s = 1,2,$$

where all expectations and derivatives are evaluated under $\beta_\ell = \beta_\ell^0$.

- ✓ Improves convergence from $O(K^{-1})$ to $O(K^{-2})$.
- ✗ Requires 3rd- and 4th-order derivatives of the profile likelihood.
  $\rightarrow$ Derivatives depend on link functions, exponential-family forms, and random effects, making analytical computation very difficult.

Contribution: simplified Bartlett correction (SBC)

- Approximate $C_{BC}(\beta_\ell^0)$ by the normal–normal correction term [Noma, 2011]:

$$C_{SBC}(\beta_\ell^0) = \frac{\sum_{k=1}^{K}(\sigma_k^2+\tilde{\tau}^2)^{-3}}{\left\{\sum_{k=1}^{K}(\sigma_k^2+\tilde{\tau}^2)^{-1}\right\}\left\{\sum_{k=1}^{K}(\sigma_k^2+\tilde{\tau}^2)^{-2}\right\}} > 0.$$

- PLSBC statistic:

$$T_{SBC}(\beta_\ell^0) = \frac{T(\beta_\ell^0)}{1+2C_{SBC}(\beta_\ell^0)}.$$

Theorem (Approximation error of SBC)

Under Y_{ki} from an exponential family, $V_k \sim N(0,\tau^2)$, $n_k = na_k$, $\sum a_k = 1$, $a_k > 0$:

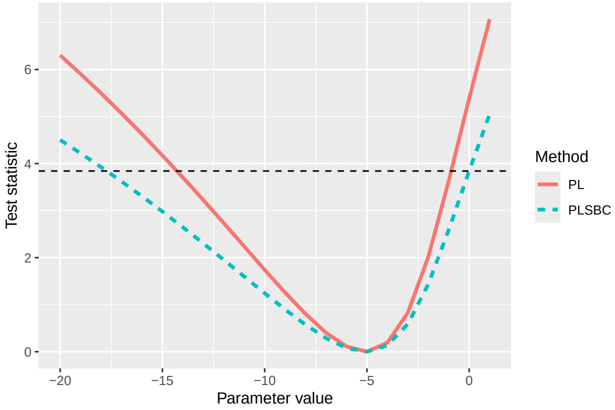
$$T_{SBC}(\beta_\ell^0) = T_{BC}(\beta_\ell^0) + O_p(n^{-1/2}) = \chi_1^2 + O_p(n^{-1/2} + K^{-2}).$$

✓ Approximation error is small: SBC retains second-order accuracy.

Real data example with 7 studies [Chu et al., 2020]

✓ SBC reduces $T(\beta_\ell)$ and widens the confidence interval.

$$\mathrm{CI}_{SBC} = \{\beta_\ell : T_{SBC}(\beta_\ell) \le q_{\chi_1^2,\alpha}\}.$$



✓ PLSBC is more conservative than PL, especially when K is small.

Simulation setup (main scenario)

- Methods compared:
  - **Normal–Normal (NN)**:
    - nDL: inverse-variance estimator [DerSimonian and Laird, 1986]
    - nPLBC: profile likelihood + Bartlett correction [Noma, 2011]
    - nMI: exact CI under NN model [Michael et al., 2019]
  - **GLMM**:
    - gPL: profile likelihood under GLMM
    - gPLSBC: PL + simplified Bartlett correction (proposed)
- Outcome types: normal, binomial, Poisson, gamma.
- Data-generating model:

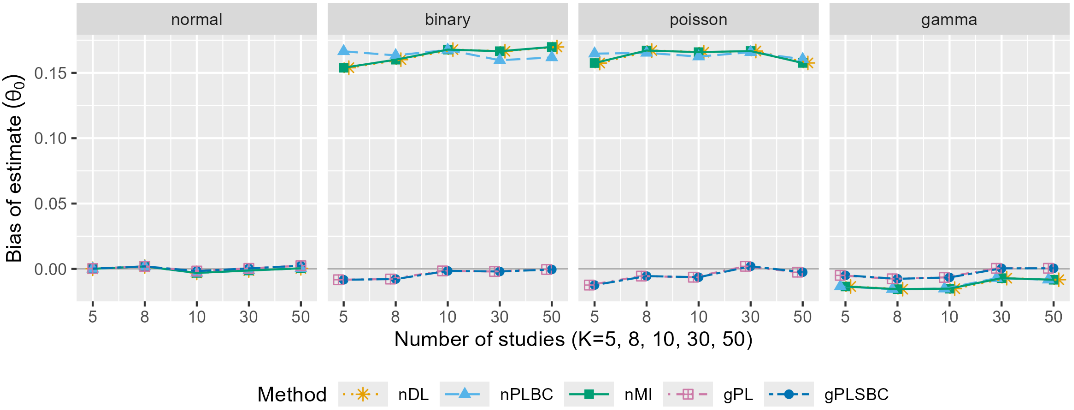
$$g(\mu_k) = \theta_0 + V_k, \quad V_k \sim N(0, \tau^2), \quad g(\cdot) : \text{link function.}$$

- Parameters:

$$\theta_0 = -2, \quad \tau^2 = 1, \quad K = 5, 8, 10, 30, 50, \quad n_k \sim \lfloor U(15, 150) \rfloor.$$

- Repetitions: 10,000 per setting.

Simulation results: mean bias of overall effect $\hat{\theta}_0$

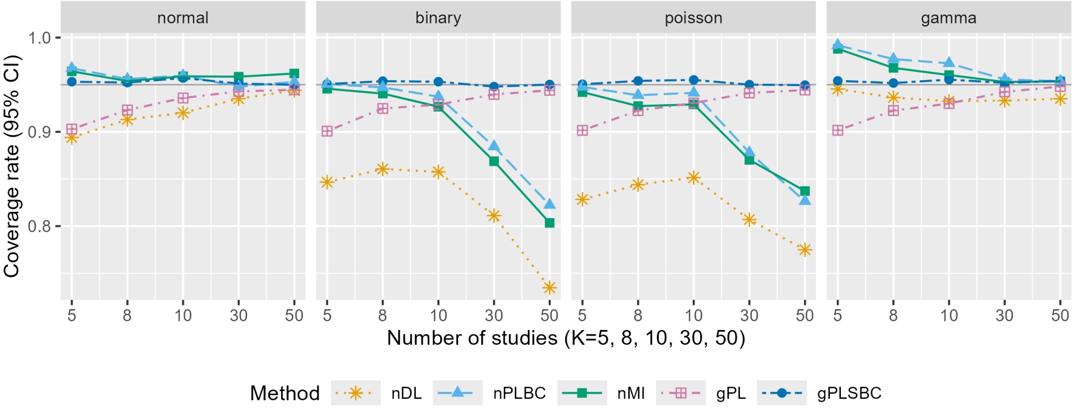


✓ GLMM methods (gPL, gPLSBC) remain consistent as $K \to \infty$.

✗ NN methods (nDL, nPLBC, nMI) show structural bias for non-normal outcomes.

$\Rightarrow$ Correct outcome modeling is essential for unbiased estimation.

Simulation results: coverage probability of nominal 95% CI



✓ gPLSBC maintains near-nominal coverage across all outcome types.

✗ NN methods (nDL, nPLBC, nMI) undercover for non-normal outcomes.

✗ gPL undercoveres when K is small.

$\Rightarrow$ Only gPLSBC is stable across both outcome types and small K.

Simulation summary

	Normal–Normal (nDL, nPLBC, nMI)	**GLMM** (gPL, gPLSBC)
Normal model correct	✓ Bias ≈ 0; coverage $\approx$ 95%	✓ Bias ≈ 0; coverage $\approx$ 95%
Non-normal outcomes (binomial, Poisson, gamma)	✗ Structural bias persists even for large K	✓ Correct model reduces structural bias
Coverage for small K (non-normal outcomes)	✗ nDL: undercoverage △ nPLBC/nMI: $\approx$ 95% when (A1)–(A3) hold; ✗ severely undercoverage when (A1) fails	✗ gPL: undercoverage ✓ gPLSBC: coverage $\approx 95\%$

Summary

- Meta-analyses often involve few studies.
- Normal–normal methods fail under non-normal outcomes.
- gPLSBC provides robust inference with near-nominal coverage even for small K.

For proofs, extended simulations, real-data analyses, and R packages, see:

arXiv:2508.08758

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