Relative Efficiency of Using Summary Statistics and Individual Participant-level Data in Meta-Analysis

(Din)Ding-Geng Chen, Ph.D.

Wallace H. Kuralt Distinguished Professor, School of Social Work
Professor, Department of Biostatistics, Gillings School of Global Public Health
University of North Carolina, Chapel Hill, USA
DST-NRF-SAMRC SARChI Chair Professor in Biostatistics
Department of Statistics, University of Pretoria

Joint Work with Dungang Liu (UCincinnati), Xiaoyi Min (Georgia State University) and Heping Zhang (Yale University)

Outline

Data to Models in Meta-Analysis(MA)

MA-IPD: Meta-Analysis with Individual Participant-level Data

IPD	Study $k = 1, \cdots, K$				
1	$(Y, X)_{11}$	$\cdots$	$(Y, X)_{k1}$	$\cdots$	$(Y, X)_{K1}$
$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\iddots$	$\vdots$
i	$(Y, X)_{i1}$	$\cdots$	$(Y, X)_{ki}$	$\cdots$	$(Y, X)_{Ki}$
$\vdots$	$\vdots$	$\iddots$	$\vdots$	$\ddots$	$\vdots$
n_k	$(Y, X)_{n_1 1}$	$\cdots$	$(Y, X)_{k n_k}$	$\cdots$	$(Y, X)_{K n_K}$

MA-SS:Meta-Analysis with Summary Statistics

MLE	$\left(\hat{\beta}, se(\hat{\beta})\right)_1$	$\cdots$	$\left(\hat{\beta}, se(\hat{\beta})\right)_k$	$\cdots$	$\left(\hat{\beta}, se(\hat{\beta})\right)_K$
Continuous	$(\bar{X}, S^2)_1$	$\cdots$	$(\bar{X}, S^2)_k$	$\cdots$	$(\bar{X}, S^2)_K$
Binary	$(n, x)_1$	$\cdots$	$(n, x)_k$	$\cdots$	$(n, x)_K$

8 Randomized Clinical Trials on Amlodipine

To evaluate the efficacy in improving work capacity in patients with angina. The work capacity is defined as the (log-)ratio of exercise time after the intervention to the time at baseline.

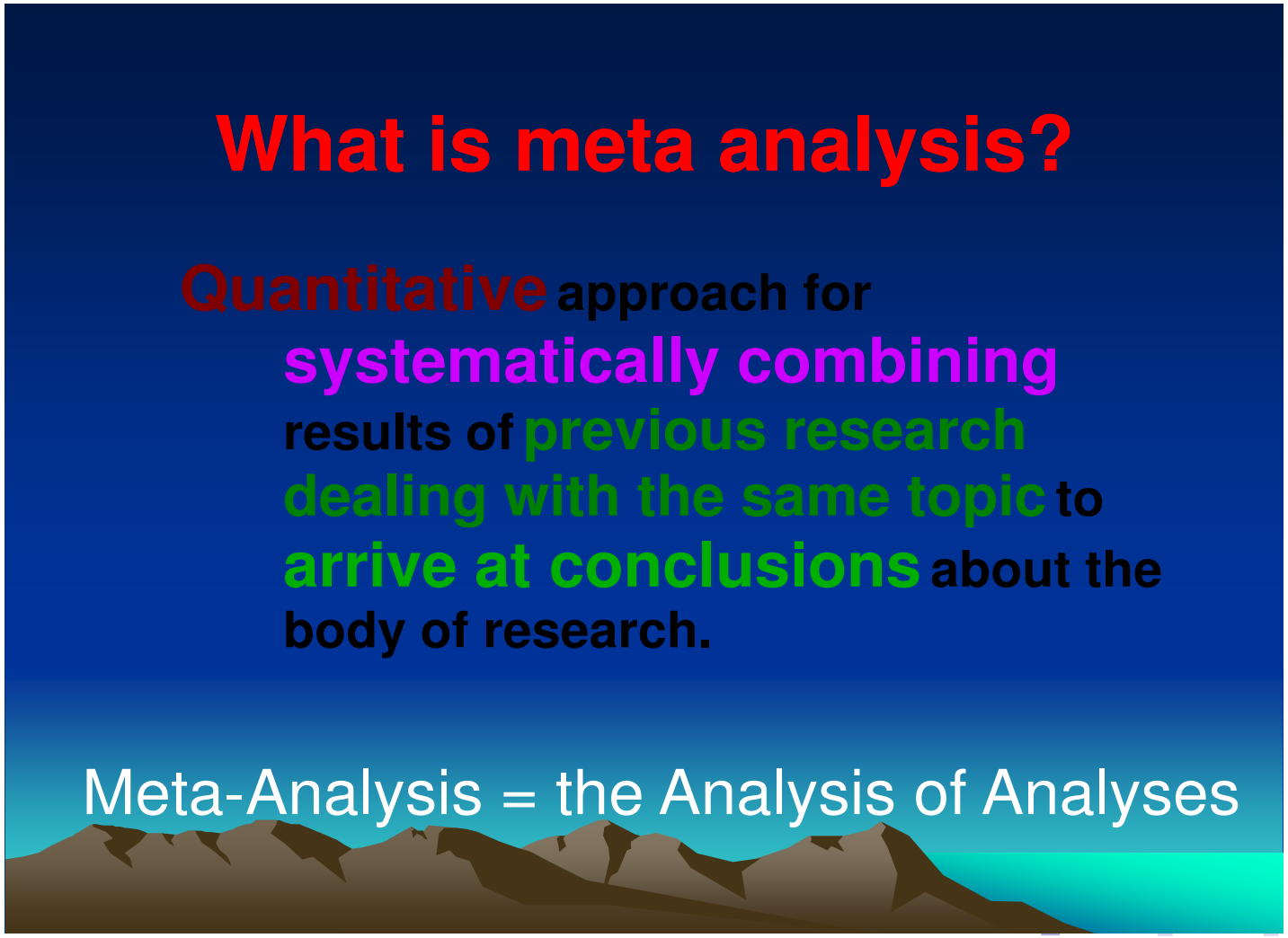
	Intervention			Control		
Studies	n	mean	var	n	mean	var
154	46	0.2316	0.2254	48	-0.0027	0.0007
156	30	0.2811	0.1441	26	0.0270	0.1139
157	75	0.1894	0.1981	72	0.0443	0.4972
162	12	0.0930	0.1389	12	0.2277	0.0488
163	32	0.1622	0.0961	34	0.0056	0.0955
166	31	0.1837	0.1246	31	0.0943	0.1734
303	27	0.6612	0.7060	27	-0.0057	0.9891
306	46	0.1366	0.1211	47	-0.0057	0.1291

13 Studies on Efficacy of BCG to Prevent TB

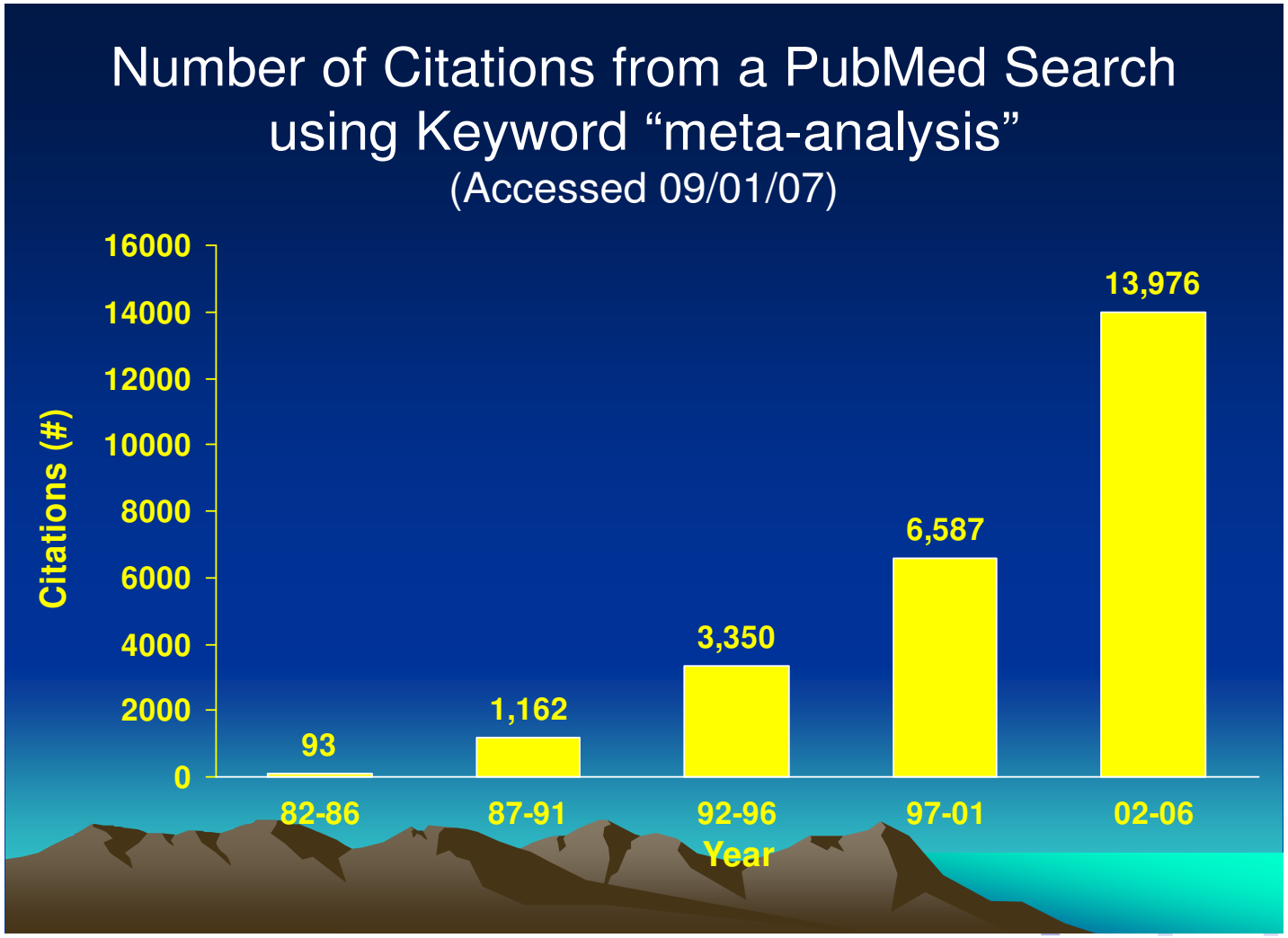
To assess Bacillus Calmette-Guerin (BCG) vaccine to prevent tuberculosis from meta-search with total 357,347 patients.

Studies		BCG		Control		Moderator
Study Author	year	TB+	TB-	TB+	TB-	ablat
Aronson	1948	4	119	11	128	44
Ferguson & Simes	1949	6	300	29	274	55
Rosenthal et al	1960	3	228	11	209	42
Hart & Sutherland	1977	62	13536	248	12619	52
Frimodt-Moller et al	1973	33	5036	47	5761	13
Stein & Aronson	1953	180	1361	372	1079	44
Vandiviere et al	1973	8	2537	10	619	19
TPT Madras	1980	505	87886	499	87892	13
Coetzee & Berjak	1968	29	7470	45	7232	27
Rosenthal et al	1961	17	1699	65	1600	42
Comstock et al	1974	186	50448	141	27197	18
Comstock & Webster	1969	5	2493	3	2338	33
Comstock et al	1976	27	16886	29	17825	33

What is MA


What is meta analysis?
Quantitative approach for systematically combining results of previous research dealing with the same topic to arrive at conclusions about the body of research.
Meta-Analysis = the Analysis of Analyses

Popularity of MA



Study Hypothesis and Effect Size (ES)

- Study hypothesis:

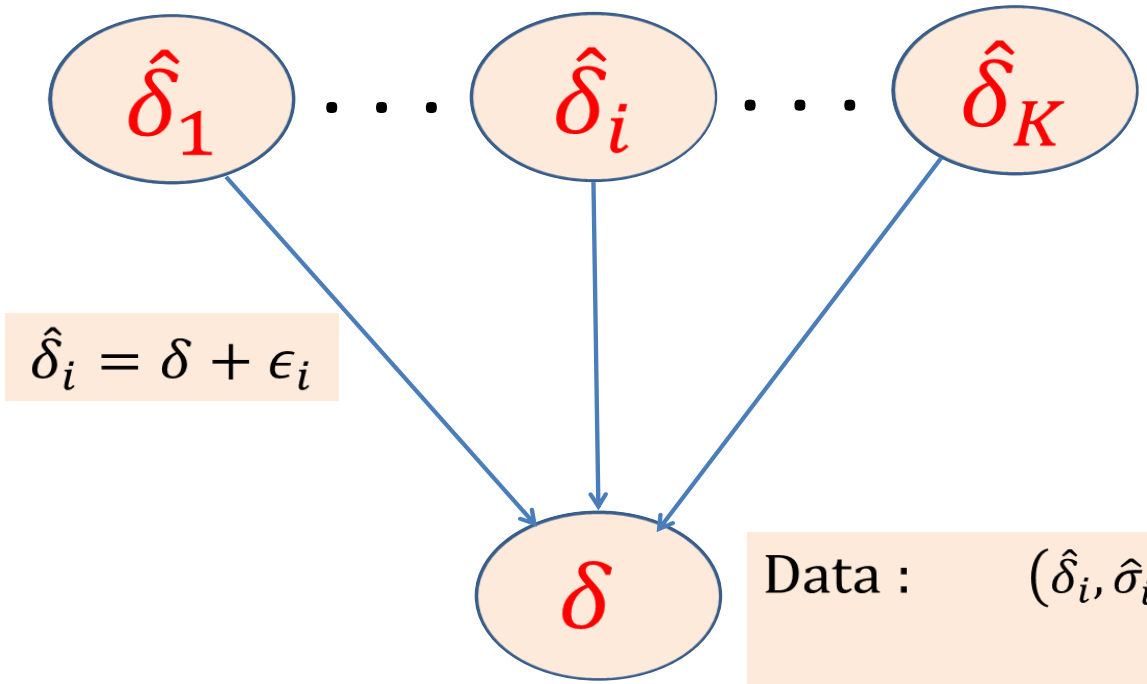
$$H_0 : \text{New is not different from Control}$$
$$H_a : \text{New is better than Control}$$

- Define treatment ES by δ, H_0 and H_a above become:

$$H_0 : \delta = 0 \quad vs. \quad H_a : \delta > 0$$

- In MA for $i = 1, \cdots, K$ studies with known $(\hat{\delta}_i, \hat{\sigma}_i^2)$, **two methods to get the overall ES estimate:**

Fixed-Effects Meta-Analysis (FE-MA)



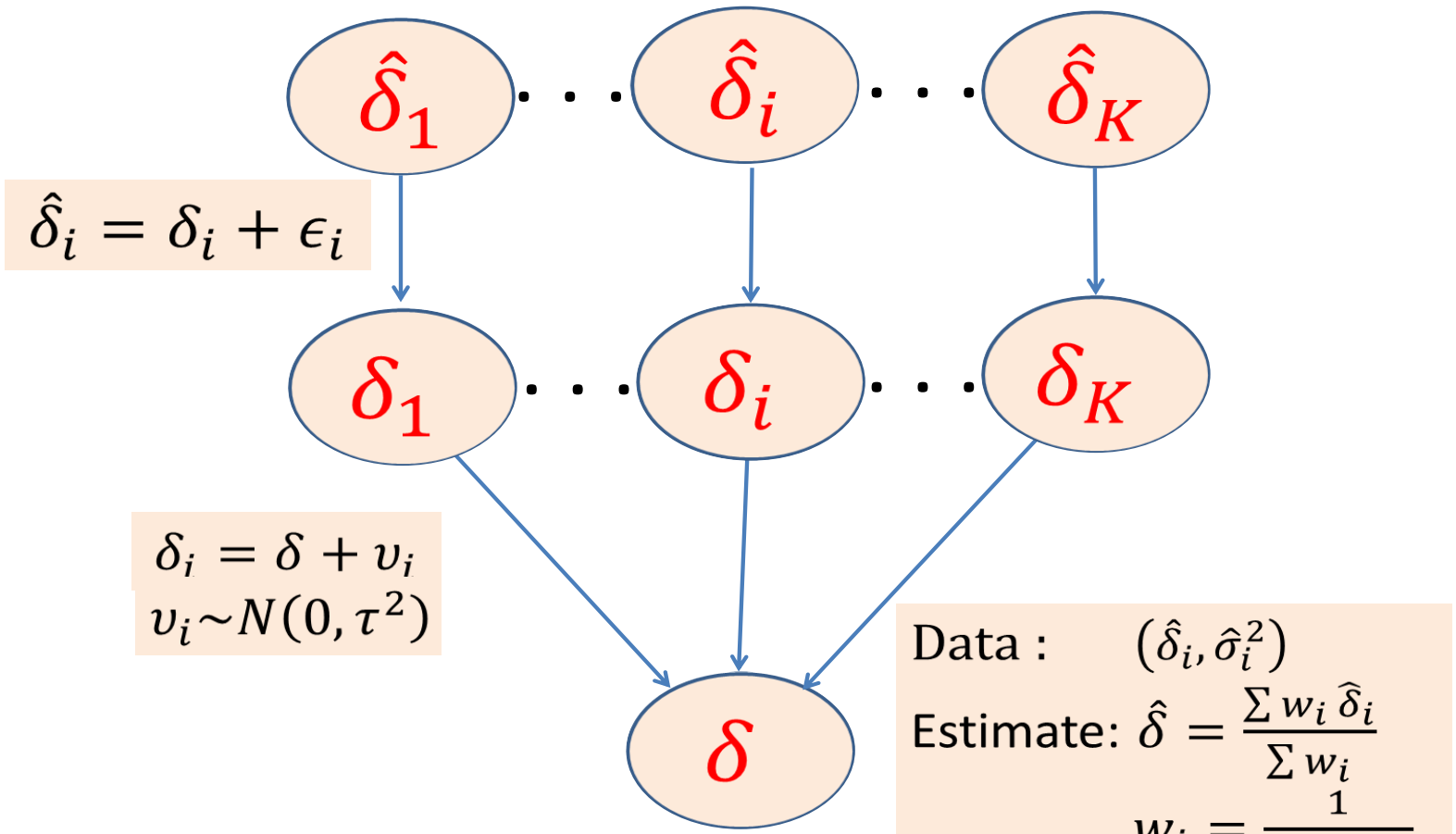
$$\hat{\delta}_i = \delta + \epsilon_i$$

Data : $(\hat{\delta}_i, \hat{\sigma}_i^2)$

Estimate: $\hat{\delta} = \frac{\sum w_i \hat{\delta}_i}{\sum w_i}$

$w_i = 1/\hat{\sigma}_i^2$

Random-Effects Meta-Analysis (RE-MA)



DerSimonian-Laird $\hat{\tau}^2$ Estimator for Heterogeneity

- Method of Moments, no iterative search algorithms,as:

$$\hat{\tau}^2 = \frac{Q - (K-1)}{U}$$

if $Q > K-1$, otherwise, $\hat{\tau}^2 = 0$
where $Q = \sum_{i=1}^{K} w_i(\hat{\delta}_i - \hat{\delta})^2$ and $U = \sum_{i=1}^{K} w_i - \frac{\sum_{i=1}^{K} w_i^2}{\sum_{i=1}^{K} w_i}$

- Q-statistic is used to test the statistical significance of heterogeneity across studies, i.e. between-study variation.

R Package *metafor* Among Many Others

- Functions for all FE-MA and RE-MA
- Meta-regression to include (study-level) moderators
- Various plot functions (forest, funnel, etc.)
- Functions for
  - assessing the model fit,
  - obtaining case diagnostics,
  - testing of publication bias

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Bacillus Calmette-Guerin (BCG) Vaccine Data

- 13 clinical trials to assess the impact of BCG vaccine in the prevention of tuberculosis (TB)
- Commonly used as example to quantify the efficacy of the BCG vaccine against tuberculosis
- The heterogeneity was explained partially by geographical latitude with meta-regression

```
# Step 1: Calculate the ES using "escalc"
> dat=escalc(measure="RR",ai=tpos,bi=tneg,ci=cpos,di=cneg)
```

trial	tpos	tneg	cpos	cneg	ablat	yi	vi
1	4	119	11	128	44	-0.8893	0.32558
2	6	300	29	274	55	-1.5854	0.19458
3	3	228	11	209	42	-1.3481	0.41537
4	62	13536	248	12619	52	-1.4416	0.02001
5	33	5036	47	5761	13	-0.2175	0.05121
6	180	1361	372	1079	44	-0.7861	0.00691
7	8	2537	10	619	19	-1.6209	0.22302
8	505	87886	499	87892	13	0.0120	0.00396
9	29	7470	45	7232	27	-0.4694	0.05643
10	17	1699	65	1600	42	-1.3713	0.07302
11	186	50448	141	27197	18	-0.3394	0.01241
12	5	2493	3	2338	33	0.4459	0.53251
13	27	16886	29	17825	33	-0.0173	0.07140

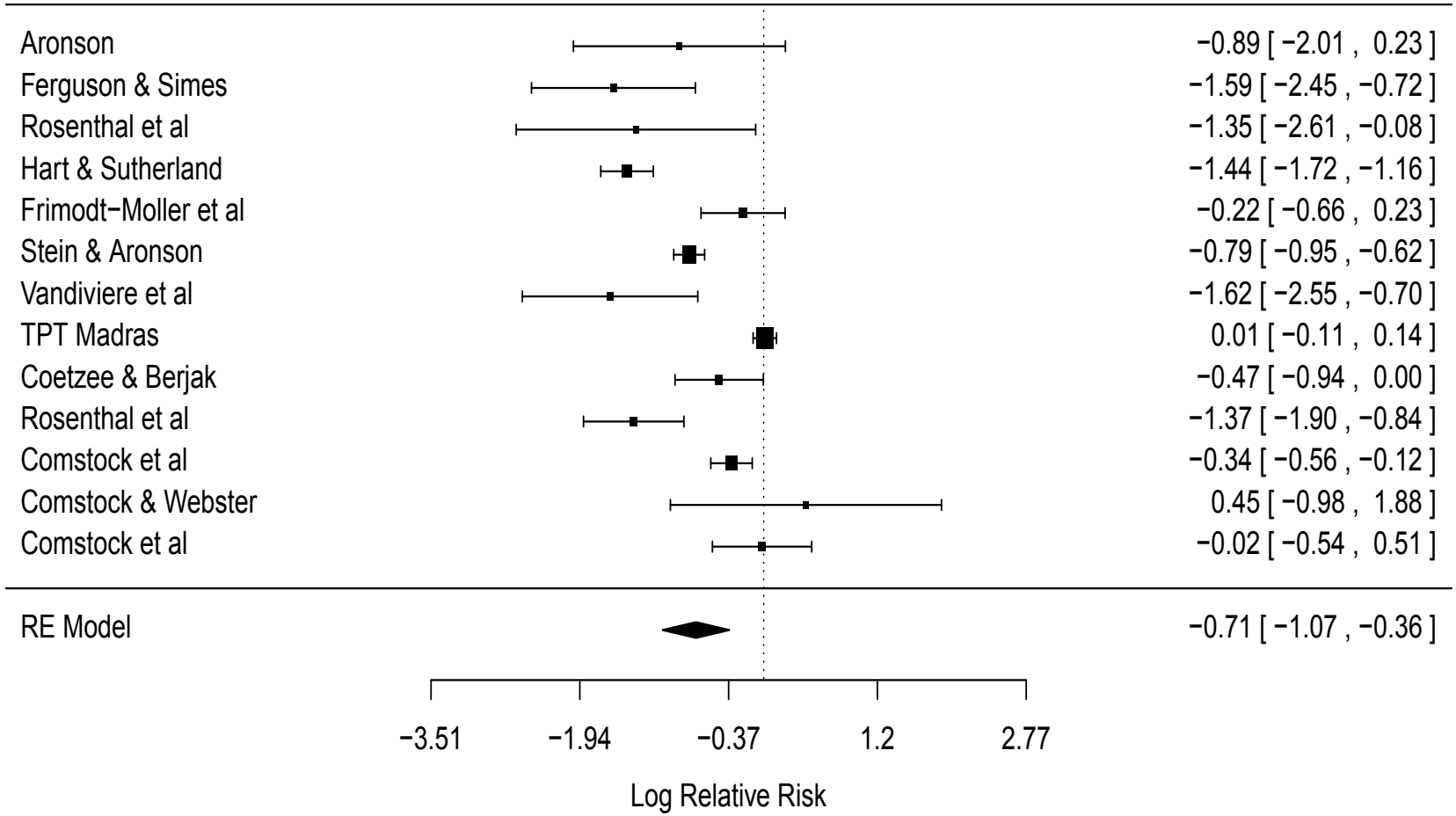
```
# Step 2: Call `rma' to fit the BCG data
> meta.RE = rma(yi, vi, data = dat)


Random-Effects Model (k = 13; tau^2 estimator: REML)

tau^2(estimate of heterogeneity): 0.3132(SE=0.1664)
tau (sqrt of the estimate of total heterogeneity): 0.5597
I^2 (% of total variability due to heterogeneity): 92.22%

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

Model Results:
estimate       se     zval     pval    ci.lb    ci.ub
 -0.7145   0.1798  -3.9744   <.0001  -1.0669  -0.3622 ***
```


Aronson
Ferguson & Simes
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Stein & Aronson
Vandiviere et al
TPT Madras
Coetzee & Berjak
Rosenthal et al
Comstock et al
Comstock & Webster
Comstock et al
RE Model
−0.89 [−2.01 , 0.23]
−1.59 [−2.45 , −0.72]
−1.35 [−2.61 , −0.08]
−1.44 [−1.72 , −1.16]
−0.22 [−0.66 , 0.23]
−0.79 [−0.95 , −0.62]
−1.62 [−2.55 , −0.70]
0.01 [−0.11 , 0.14]
−0.47 [−0.94 , 0.00]
−1.37 [−1.90 , −0.84]
−0.34 [−0.56 , −0.12]
0.45 [−0.98 , 1.88]
−0.02 [−0.54 , 0.51]
−0.71 [−1.07 , −0.36]
−3.51
−1.94
−0.37
1.2
2.77
Log Relative Risk

Result

- Overall ES from a RE-MA is statistically significant (estimate= -0.7145 and p-value < 0.0001)
- The estimated total amount of heterogeneity $\hat{\tau}^2$ is 0.3132(SE $= 0.1664$)
- The percentage of total variability due to heterogeneity is $\hat{I}^2 = 92.22\%$
- *Test for Heterogeneity* is statistically significant since $\hat{Q} = 152.233$ with $df = 12$ and p-value $< .0001$
- Need to explain the extra-heterogeneity from other covariates, and hence the meta-regression

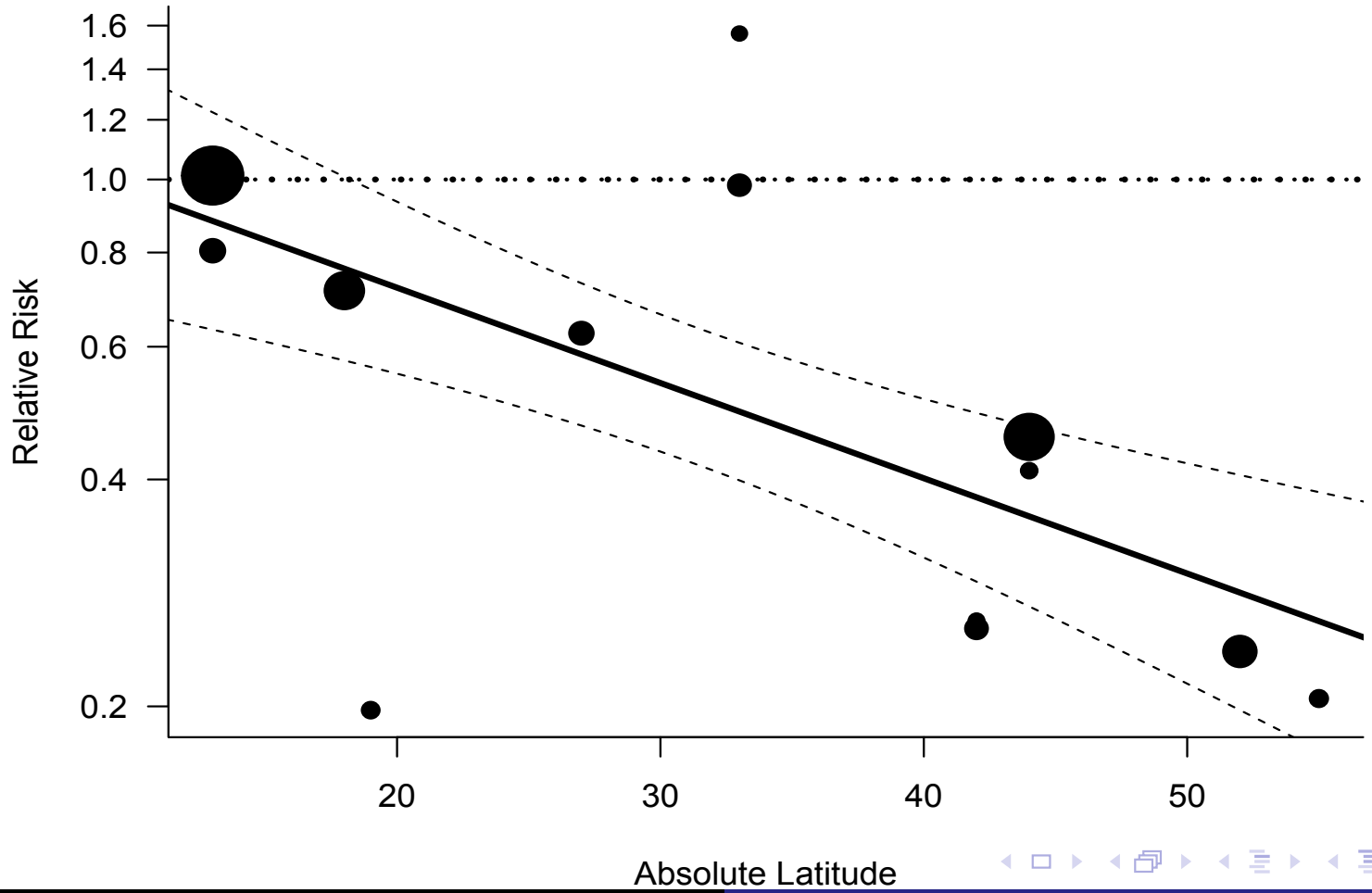
```
> metaReg.ablat = rma(yi, vi, mods = ~ablat, data = dat)


Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2(estimate of residual amount of heterogeneity):0.076(S

Test for Residual Heterogeneity:
QE(df = 11) = 30.7331, p-val = 0.0012


Model Results:
        estimate     se    zval   pval   ci.lb  ci.ub
intrcpt   0.2515 0.2491  1.0095 0.3127 -0.2368  0.7397
ablat    -0.0291 0.0072 -4.0444 <.0001 -0.0432 -0.0150 ***
```

Meta-Regression Summary-cont.

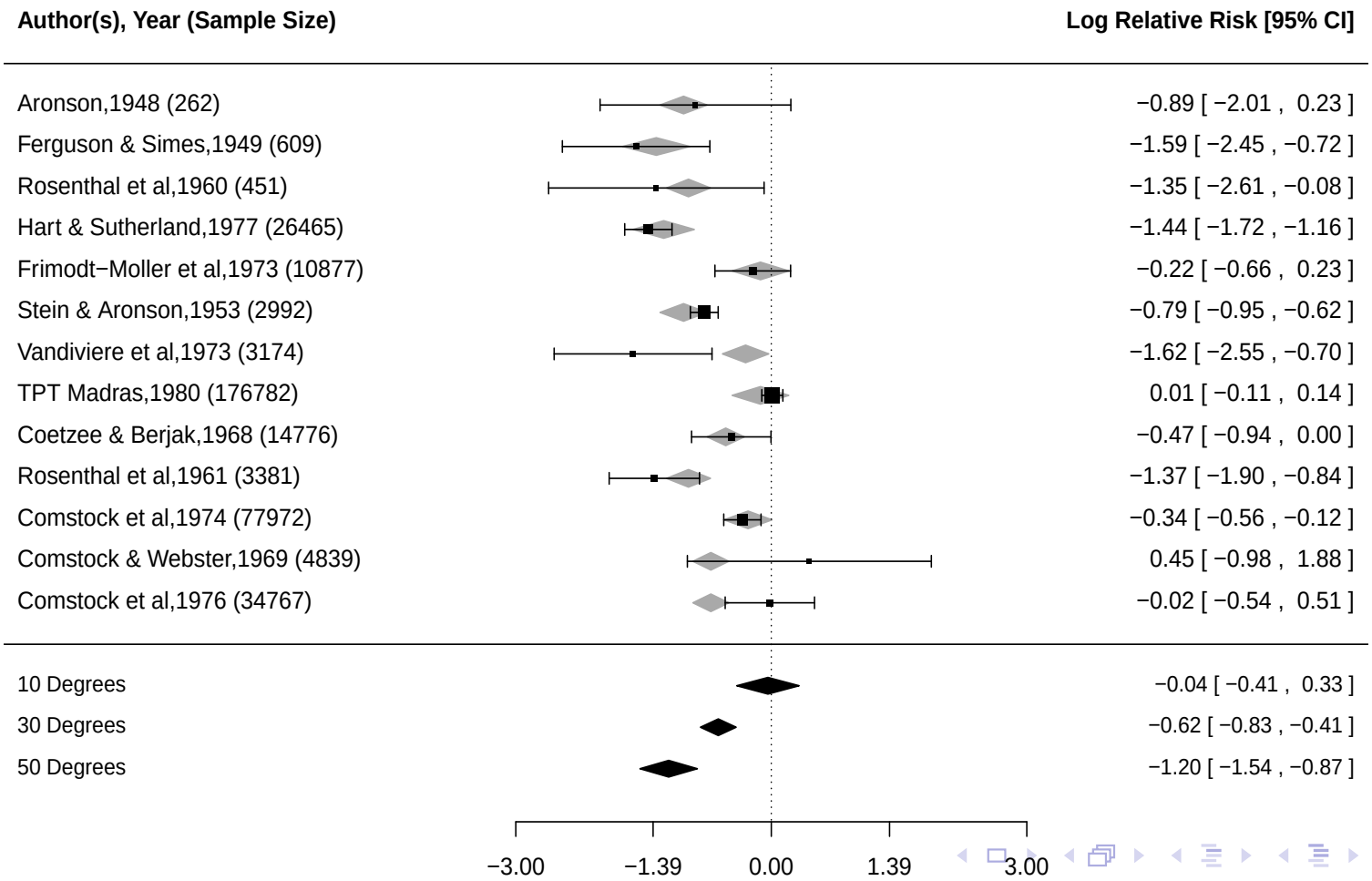
- With only `ablat`, the estimated residual heterogeneity $\hat{\tau}^2$ dropped to 0.0764 from 0.3132
- Moderator *ablat* accounts for (0.3132-0.0764)/0.3132 = 75.6% of the total amount of heterogeneity
- The absolute latitude is significantly related to the effectiveness of the BCG vaccine in preventing TB as quantified in the estimated meta-regression:

$$log(RR) = 0.2515 - 0.0291 \times ablat \qquad (1)$$

Meta-Regression Using "ablat"



ForestPlot After Meta-Reg



Data to Models in Meta-Analysis(MA)

MA-IPD: Meta-Analysis with Individual Participant-level Data

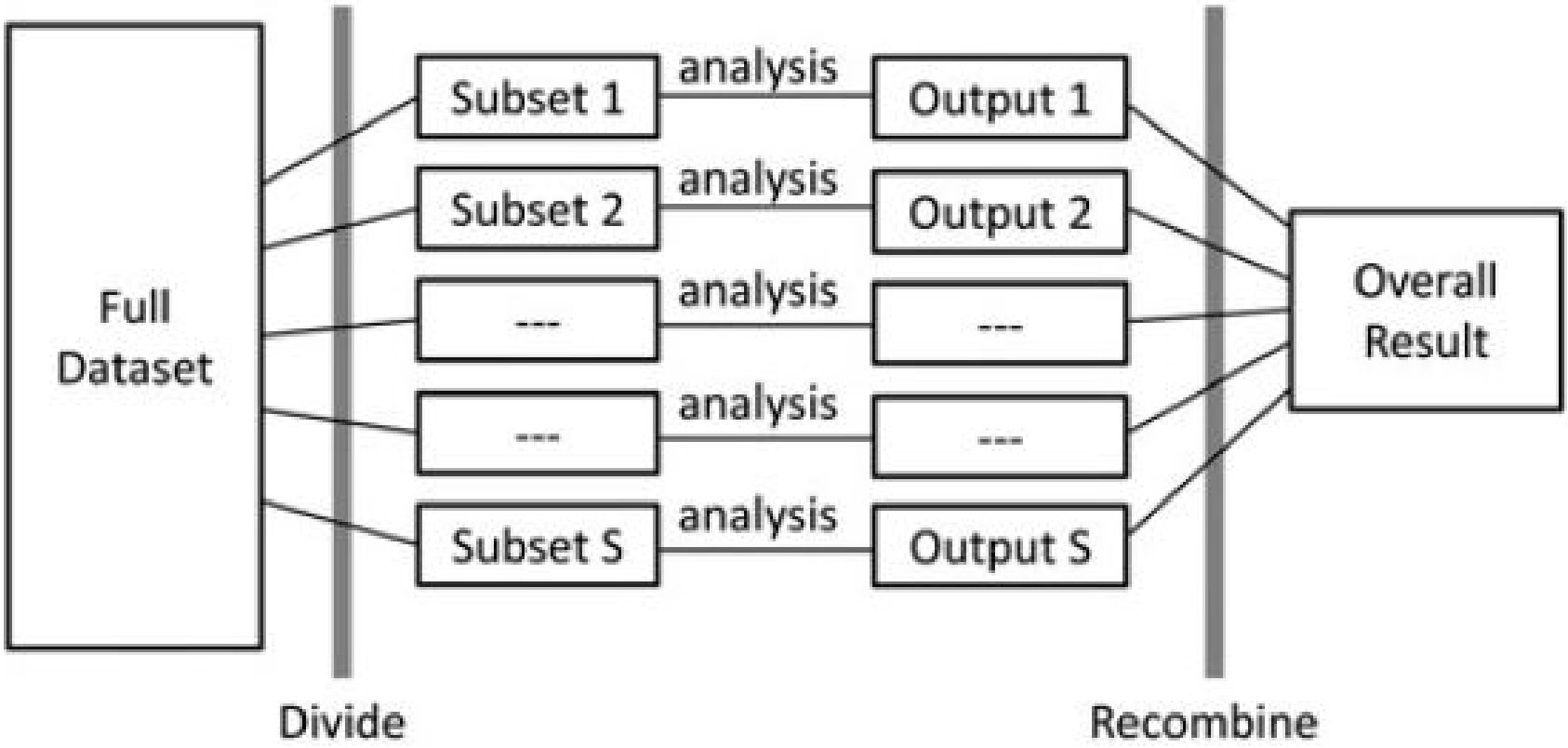
IPD	Study $k = 1, \cdots, K$				
1	$(Y,X)_{11}$	$\cdots$	$(Y,X)_{k1}$	$\cdots$	$(Y,X)_{K1}$
$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\iddots$	$\vdots$
i	$(Y,X)_{i1}$	$\cdots$	$(Y,X)_{ki}$	$\cdots$	$(Y,X)_{Ki}$
$\vdots$	$\vdots$	$\iddots$	$\vdots$	$\ddots$	$\vdots$
n_k	$(Y,X)_{n_1 1}$	$\cdots$	$(Y,X)_{kn_k}$	$\cdots$	$(Y,X)_{Kn_K}$

MA-SS:Meta-Analysis with Summary Statistics

MLE	$\left(\hat{\beta}, se(\hat{\beta})\right)_1$	$\cdots$	$\left(\hat{\beta}, se(\hat{\beta})\right)_k$	$\cdots$	$\left(\hat{\beta}, se(\hat{\beta})\right)_K$
Continuous	$(\bar{X}, S^2)_1$	$\cdots$	$(\bar{X}, S^2)_k$	$\cdots$	$(\bar{X}, S^2)_K$
Binary	$(n,x)_1$	$\cdots$	$(n,x)_k$	$\cdots$	$(n,x)_K$

Meta-Analysis in Big Data Era

Lee, J.Y., Brown, J,J. and Ryan, L.M. The American Statistician (2017)



MA-IPD vs. MA-SS

1. MA-IPD: Statistical Multi-Level Modeling
   - Pros: "Golden standard" in statistics to integrate all the information
   - Cons: Access to the IPD: **We Usually Do Not Have it**! In Big Data: **We Usually Can Not Run the Analysis**!
2. MA-SS: MA-FE and MA-RE models
   - Pros: Easy to access and analyze the SS data
   - Cons: Concerns to loss some statistical properties!

Fundamental Questions

- **Any efficiency gain from MA-IPD to MA-SS?**
- **Any efficiency loss from MA-SS to MA-IPD?**

Partial Answer: No Efficiency Loss in TrT/Cont Comparison

1. Olkin and Sampson (Biometrics 1998):
   For treatment vs. control comparison with continuous outcome, MA-SS is equivalent to MA-IPD if no study-by-treatment interactions and variances are constant across trials
2. Mathew and Nordstrom(Biometrics 1999):
   This equivalence holds even if the error variances are different across trials

Partial Answer: No Efficiency Loss Asymptotically for FE-MA

1. Whitehead (2002) Ch 5: Two approaches are generally similar even not identical
2. Lin and Zeng (Biometrika 2010): No asymptotic efficiency gain for MA-IPD to MA-SS in MA-FE
3. Chen and Peace (2013,Ch8): More simulations and real data analysis
4. Liu, Liu and Xie (JASA 2015): Confidence distribution approach for heterogenous studies

MA-RE Model: Unresolved Question

1. Random-Effects MA: The most commonly used MA model
2. "Technically More Challenging": Is this asymptotic equivalence still true for MA-RE?
3. Answer: Yes for almost all commonly used likelihood inference settings
4. Will Show:
   - Theoretically, i.e. some mathematics equations
   - Numerically, i.e. simulation studies

Data and Model in IPD

1. IPD data: $(Y_{ki}, X_{ki}), i = 1, \cdots, n_k$ for k-th study $(k = 1, \ldots, K)$
2. A general mixed-effects model:
   - Level 2: The random-effects $\beta_k \mid \beta \sim N(\beta, \tau^2)$
   - Level 1: Given β_k and η_k (nuisance parameter vector) in the kth study, the IPD $(Y_{ki}, X_{ki}) \sim f_k(Y_{ki}, X_{ki}; \beta_k, \eta_k)$ (i.e. for continuous, categorical, survival and longitudinal data, etc.).
3. Simple regression model:

$$Y_{ki} = \alpha_k + \beta_k^T X_{ki} + \epsilon_{ki}, \quad \epsilon_{ki} \sim N(0, \sigma_k^2),$$

MA with Summary Statistics

1. MA-SS collects MLE $\hat{\beta}_k$, $\hat{\eta}_k$ and their estimated variances:

$$\ell_k(\beta_k, \eta_k) = \log L_k(\beta_k, \eta_k) = \sum_{i=1}^{n_k} \log f_k(Y_{ki}, X_{ki}; \beta_k, \eta_k).$$

2. Random-effects MA model:

$$\hat{\beta}_k | \beta_k \sim N\left(\beta_k, \widehat{var}\left(\hat{\beta}_k\right)\right), \ \beta_k \sim N(\beta, \tau^2)$$

3. MA-SS estimator:

$$\hat{\beta}_{SS} = \frac{\sum_{k=1}^{K} w_k \hat{\beta}_k}{\sum_{k=1}^{K} w_k}, \quad \widehat{var}(\hat{\beta}_{SS}) = \frac{1}{\sum_{k=1}^{K} w_k}$$

where $w_k = \frac{1}{\widehat{\text{var}}(\hat{\beta}_k) + \hat{\tau}^2}$ and $\hat{\tau}^2$ is a consistent estimator of τ^2

MA-IPD: Likelihood Function

1. Both random:

$$\begin{aligned} \beta_k &\sim N(\beta, \tau^2) \\ \eta_k &\sim N(\eta, \phi^2), k = 1, \ldots, K \end{aligned}$$

2. Log-likelihood function for kth study:

$$\begin{aligned} \ell_k(\beta, \eta) &= \log L_k(\beta, \eta) \\ &= \log \int_{-\infty}^{\infty} L_k(\beta_k, \eta_k) \exp\left(\frac{\beta_k - \beta}{2\tau^2}\right) \exp\left(\frac{\eta_k - \eta}{2\phi^2}\right) d\beta_k d\eta_k \end{aligned}$$

3. Overall log-likelihood function: $\ell(\beta, \eta) = \sum_{k=1}^{K} \ell_k(\beta, \eta)$ which can be approximated by the logarithm of a normal density function, i.e. Laplace Approximation Theory.

Laplace Approximation Theory

1. Expand each $\ell_k(\beta_k, \eta_k)$ around its MLE:

$$\begin{aligned}\ell_k(\beta_k, \eta_k) &= \ell_k(\hat{\beta}_k, \hat{\eta}_k) \\ &\quad -\frac{1}{2}\begin{pmatrix}\beta_k - \hat{\beta}_k \\ \eta_k - \hat{\eta}_k\end{pmatrix}^T \begin{pmatrix}\mathcal{I}_{k,\beta_k\beta_k} & \mathcal{I}_{k,\beta_k\eta_k} \\ \mathcal{I}_{k,\eta_k\beta_k} & \mathcal{I}_{k,\eta_k\eta_k}\end{pmatrix}^{-1}_{|\hat{\beta}_k,\hat{\eta}_k} \begin{pmatrix}\beta_k - \hat{\beta}_k \\ \eta_k - \hat{\eta}_k\end{pmatrix} \\ &\quad +o_p(||\beta_k - \hat{\beta}_k||^2)\end{aligned}$$

2. Plug it into $\ell_k(\beta, \eta)$ and Integrate Out:

$$\ell_k(\beta, \eta) = \begin{pmatrix}\beta - \hat{\beta}_k \\ \eta - \hat{\eta}_k\end{pmatrix}^T \left\{\begin{pmatrix}\mathcal{I}_{k,\beta_k\beta_k} & \mathcal{I}_{k,\beta_k\eta_k} \\ \mathcal{I}_{k,\eta_k\beta_k} & \mathcal{I}_{k,\eta_k\eta_k}\end{pmatrix}^{-1} + \begin{pmatrix}\tau^2 & 0 \\ 0 & \phi^2\end{pmatrix}\right\}^{-1} \begin{pmatrix}\beta - \hat{\beta}_k \\ \eta - \hat{\eta}_k\end{pmatrix}$$

3. Maximizing the overall log-likelihood function:
$\ell(\beta, \eta) = \sum_{k=1}^{K} \ell_k(\beta, \eta)$

Estimation from MA-IPD

1. MA-IPD estimator:

$$\hat{\beta}_{IPD} = \left\{ \sum_{k=1}^{K} \mathcal{M}_k(\hat{\beta}_k, \hat{\eta}_k, \tilde{\tau}^2, \tilde{\phi}^2)^{-1} \right\}^{-1} \left[\sum_{k=1}^{K} \mathcal{M}_k(\hat{\beta}_k, \hat{\eta}_k, \tilde{\tau}^2, \tilde{\phi}^2)^{-1} \begin{pmatrix} \hat{\beta}_k \\ \hat{\eta}_k \end{pmatrix} \right]_{[\beta}$$

where

$$\mathcal{M}_k(\beta_k, \eta_k, \tau^2, \phi^2) = \begin{pmatrix} \mathcal{I}_{k,\beta_k\beta_k} & \mathcal{I}_{k,\beta_k\eta_k} \\ \mathcal{I}_{k,\eta_k\beta_k} & \mathcal{I}_{k,\eta_k\eta_k} \end{pmatrix}^{-1} + \begin{pmatrix} \tau^2 & 0 \\ 0 & \phi^2 \end{pmatrix},$$

2. MA-IPD variance estimator:

$$\widehat{\text{var}}\left(\hat{\beta}_{IPD}\right) = \left\{ \sum_{k=1}^{K} \mathcal{M}_k(\hat{\beta}_k, \hat{\eta}_k, \tilde{\tau}^2, \tilde{\phi}^2)^{-1} \right\}^{-1}_{[\beta,\beta]}$$

Asymptotic Efficiency

1. For any finite and fixed K and n_k $(k = 1, \ldots, K)$

$$\widehat{\text{var}}\left(\hat{\beta}_{IPD}\right) \leq \widehat{\text{var}}\left(\hat{\beta}_{SS}\right)$$

2. As n_k and $K \to \infty$

$$\widehat{\text{var}}\left(\hat{\beta}_{SS}\right) \Big/ \widehat{\text{var}}\left(\hat{\beta}_{IPD}\right) \to 1$$

3. Conclusion:
   $\hat{\beta}_{IPD}$ has no efficiency gain over $\hat{\beta}_{SS}$ asymptotically

Data Generation for Continuous Data

Simulate K studies and each study with n individuals:

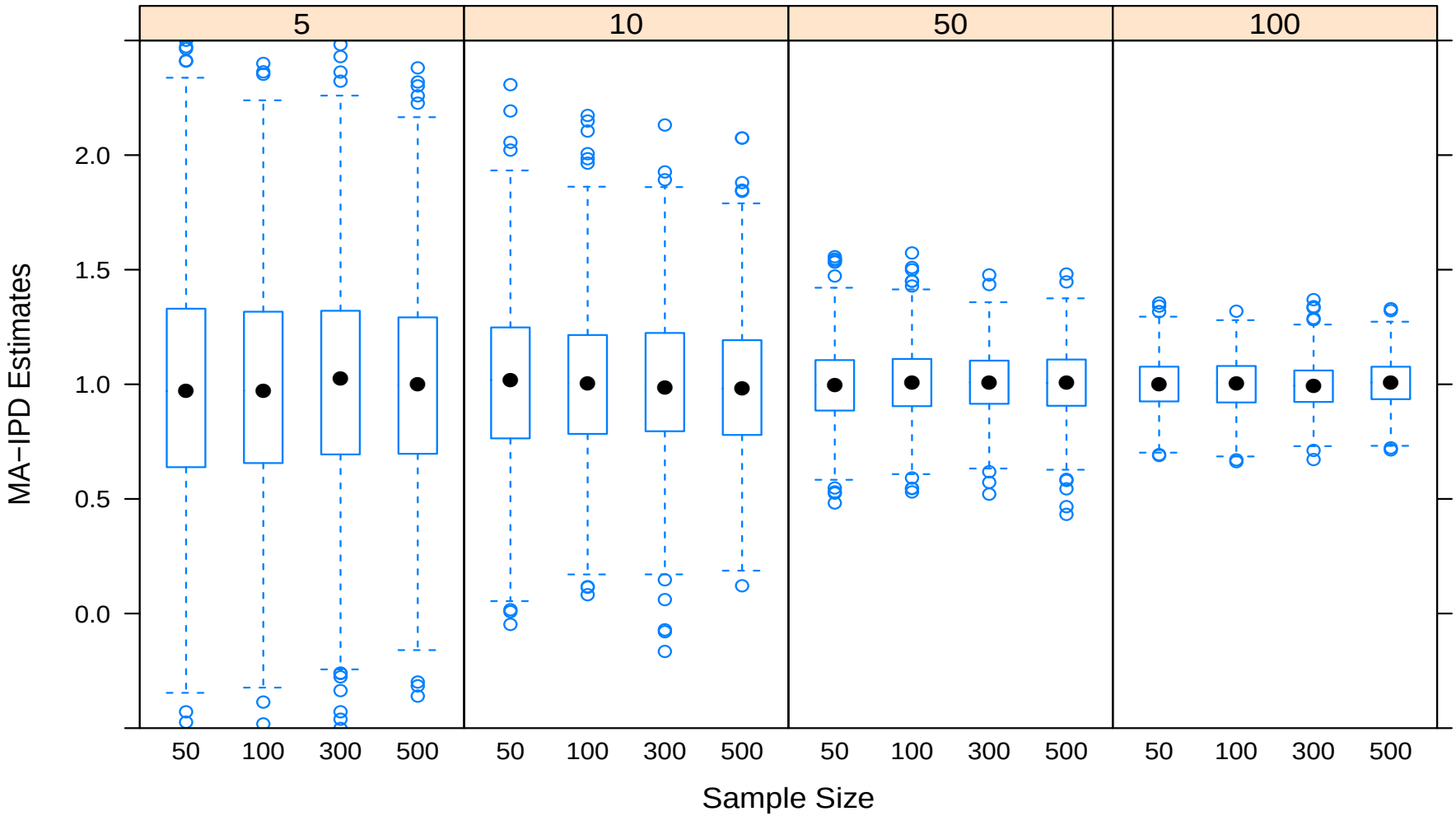
1. Parameters: $\alpha_k \sim N(\alpha, \sigma_\alpha^2)$ and $\beta_k \sim N(\beta, \tau^2)$
2. Treatment Assignment X_{ki}: Random binomial with $p = 0.5$ for treatment and control
3. Data y_{ki}: Random normal with

$$y_{ki} = \alpha_k + \beta_k X_{ki} + \epsilon_{ki}$$

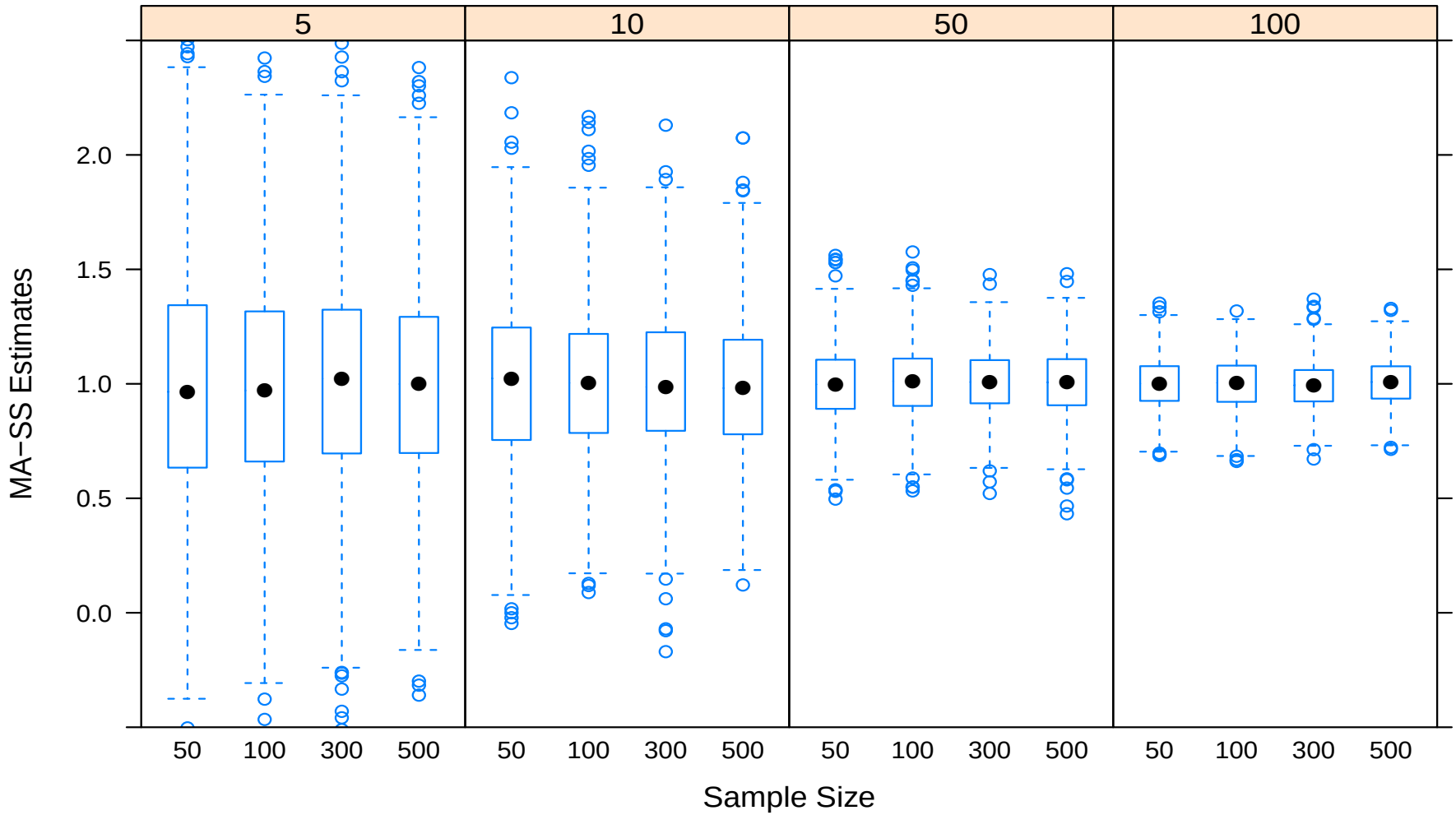
Estimation with MA-IPD and MA-SS

1. MA-IPD: Linear mixed-effects model using *lmer* in R package *lme4*
2. MA-SS: Meta-analysis using *rma* in R package *metafor*
3. Number of Simulations:
   1,000 for each specifications of
   $K = 5, 10, 50, 100$ and $n = 50, 100, 300, 500$.
4. True Parameters: $\alpha = \beta = 1$ and $\sigma_\alpha = \tau = 0.5$

Estimated Treatment Effect ($\beta = 1$) from MA-IPD



Estimated Treatment Effect ($\beta = 1$) from MA-SS



Simulation Results for Continuous Outcome

		MA-IPD				MA-SS			
K	N	Est.	SE	ESE	CP	Est.	SE	ESE	CP
5	50	0.995	0.518	0.442	0.868	0.996	0.521	0.441	0.861
5	100	0.989	0.481	0.404	0.844	0.989	0.482	0.404	0.844
5	300	1.012	0.497	0.387	0.830	1.012	0.497	0.387	0.830
5	500	1.000	0.445	0.377	0.853	1.000	0.445	0.377	0.854
10	50	1.009	0.357	0.332	0.898	1.009	0.358	0.331	0.898
10	100	1.005	0.330	0.311	0.919	1.006	0.330	0.311	0.917
10	300	1.002	0.329	0.298	0.900	1.002	0.329	0.298	0.897
10	500	0.989	0.304	0.301	0.908	0.989	0.304	0.301	0.907
50	50	0.998	0.168	0.162	0.944	0.998	0.167	0.162	0.944
50	100	1.008	0.155	0.149	0.938	1.007	0.155	0.149	0.938
50	300	1.006	0.141	0.143	0.952	1.006	0.141	0.143	0.952
50	500	1.003	0.145	0.142	0.947	1.003	0.145	0.142	0.947
100	50	1.001	0.115	0.114	0.945	1.001	0.115	0.114	0.945
100	100	1.000	0.111	0.107	0.940	1.000	0.111	0.107	0.942
100	300	0.992	0.099	0.102	0.950	0.992	0.100	0.102	0.950
100	500	1.004	0.102	0.101	0.948	1.004	0.102	0.101	0.948

Relative Efficiency Between MA-IPD and MA-SS

	K			
n	5	10	50	100
50	0.955	0.997	0.998	0.999
100	1	1	1	1
300	1	1	1	1
500	1	1	1	1

Data Generation for Categorical Data

Simulate K studies and each study with n individuals:

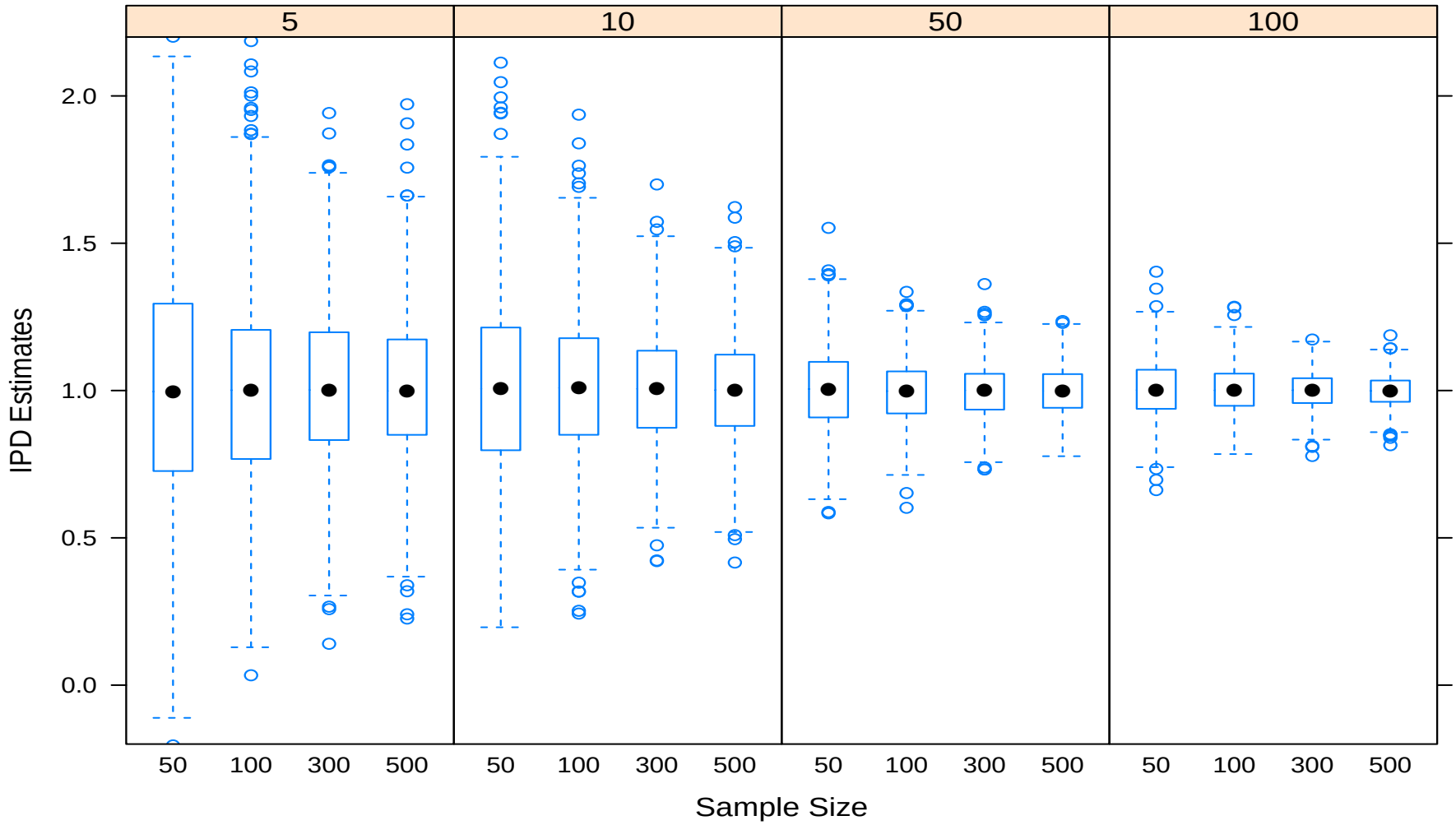
1. Parameters: $\alpha_k \sim N(\alpha, \sigma_\alpha^2)$ and $\beta_k \sim N(\beta, \tau^2)$
2. Treatment Assignment X_{ki}: Random binomial with $p = 0.5$ for treatment and control
3. Data y_{ki}: Random binomial with

$$p_{ki} = \frac{exp(\alpha_k + \beta_k X_{ki})}{1 + exp(\alpha_k + \beta_k X_{ki})}$$

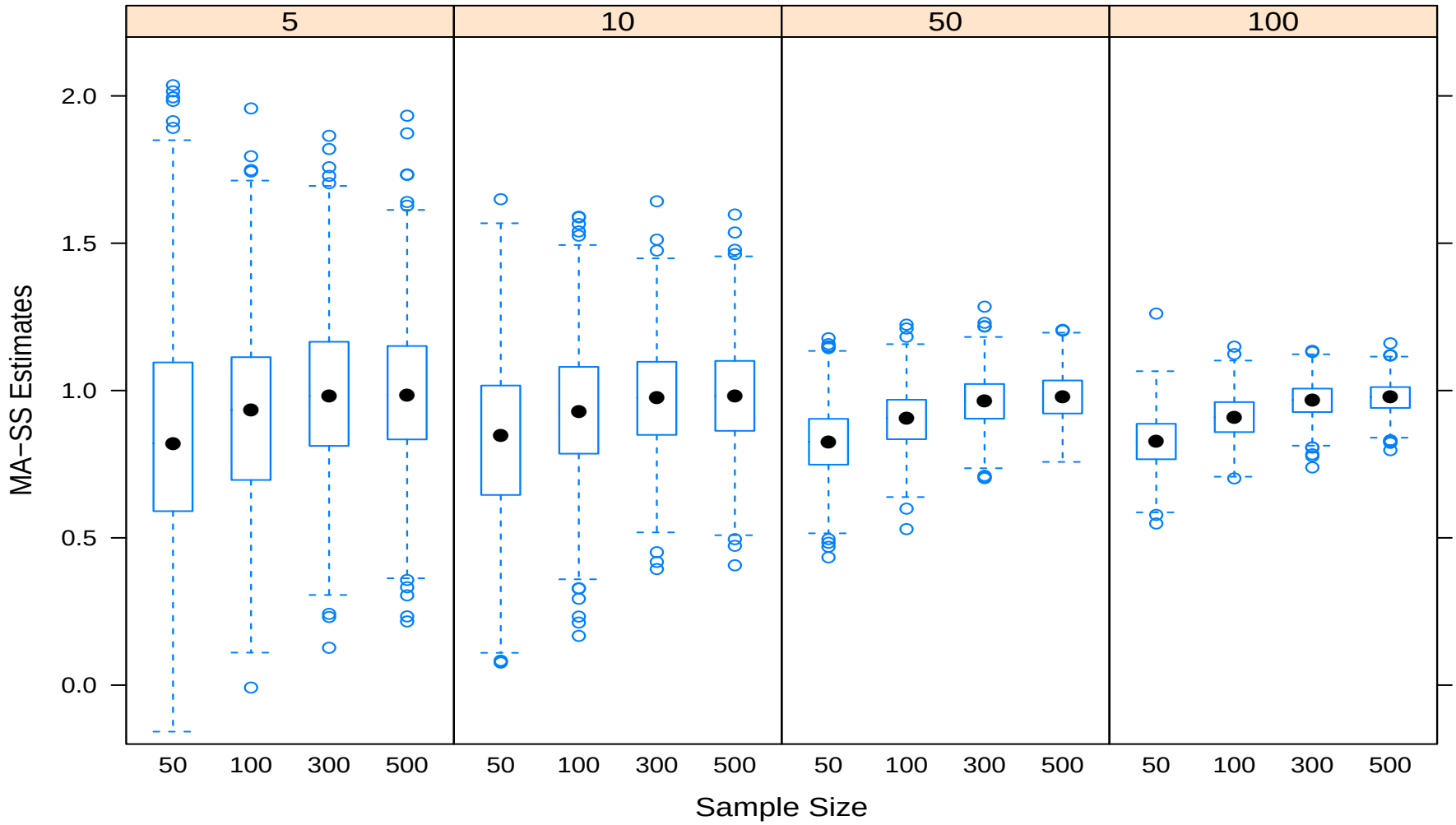
Estimation with MA-IPD and MA-SS

1. MA-IPD: Generalized linear mixed-effects model using *glmer* in R package *lme4*
2. MA-SS: Meta-analysis using *rma* in R package *metafor*
3. Number of Simulations:
   1,000 for each specifications of
   $K = 5, 10, 50, 100$ and $n = 50, 100, 300, 500$.
4. True Parameters: $\alpha = \beta = 1$ and $\sigma_\alpha = \tau = 0.5$

Estimated Treatment Effect ($\beta = 1$) from MA-IPD



Estimated Treatment Effect ($\beta = 1$) from MA-SS



Relative Efficiency Between MA-SS to MA-IPD

	K			
n	5	10	50	100
50	1.064	1.060	1.058	1.057
100	1.035	1.032	1.028	1.025
300	1.008	1.005	1.005	1.004
500	1.004	1.003	1.002	1.001

- To reduce mortality after myocardial infarction
- 22 CTs with total 20,290 patients

Table: Data from 22 CT Centers to be "Re-Structured" for MA-IPD

	Control		Treated			Control		Treated	
Center	Death	Total	Death	Total	Center	Death	Total	Death	Total
1	3	39	3	38	12	47	266	45	263
2	14	116	7	114	13	16	293	9	291
3	11	93	5	69	14	45	883	57	858
4	127	1520	102	1533	15	31	147	25	154
5	27	365	28	355	16	38	213	33	207
6	6	52	4	59	17	12	122	28	251
7	152	939	98	945	18	6	154	8	151
8	48	471	60	632	19	3	134	6	174
9	37	282	25	278	20	40	218	32	209
10	188	1921	138	1916	21	43	364	27	391
11	52	583	64	873	22	39	674	22	680

- MA-IPD: $\hat{\beta}_{IPD}$ = -0.247 (log odds-ratio) with SE=0.057(p<0.001)
- MA-SS: $\hat{\beta}_{SS}$ = -0.250 with SE=0.058($p < 0.001$)
- **MA-SS is virtually efficient without the knowledge of nuisance parameters α_k's even if the two random-effects α_k's and β_k's are correlated**

Table: Summary Statistics Used in MA-SS

Center	$\hat{\beta}_k$	$\widehat{\text{var}}(\hat{\beta}_k \mid \beta_k)$	Center	$\hat{\beta}_k$	$\widehat{\text{var}}(\hat{\beta}_k \mid \beta_k)$
1	0.028	0.723	12	-0.039	0.053
2	-0.741	0.233	13	-0.593	0.181
3	-0.541	0.319	14	0.282	0.042
4	-0.246	0.019	15	-0.321	0.089
5	0.069	0.079	16	-0.135	0.068
6	-0.584	0.457	17	0.141	0.133
7	-0.512	0.019	18	0.322	0.305
8	-0.079	0.042	19	0.444	0.514
9	-0.424	0.075	20	-0.218	0.068
10	-0.335	0.014	21	-0.591	0.066
11	-0.213	0.038	22	-0.608	0.074

1. In MA-RE, MA-SS has no efficiency loss asymptotically
   - Theoretical justification and simulation demonstrations
   - There are efficiency loss for small sample size and small number of studies
2. Research:
   - MA-IPD and MA-SS are asymptotically equivalent, but there are more to be done.
   - Multivariate MAs and Longitudinal MAs
   - Network meta-analysis, especially for Comparative Effectiveness Research.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