A Bayesian Hierarchical Model Estimating CACE in Meta-Analysis of Randomized Clinical Trials with Noncompliance

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Outline

- Introduction to CACE and MA
- Motivating example: MA of epidural analgesia trials
- Bayesian hierarchical models to estimate CACE in MA
- Case study results
- Simulation
- Discussion

Background

- Randomized Clinical Trials
- Noncompliance – common, information bias

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- Randomized Clinical Trials
- Noncompliance – common, information bias

- Solutions?
  - Intent-to-treat (ITT) analysis
  - Per-protocol analysis, as-treated analysis

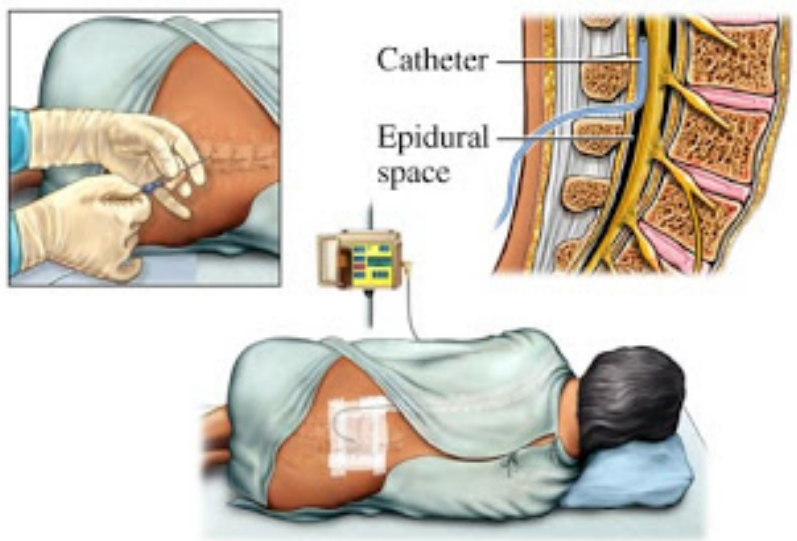
Background

Solutions: Principal stratification (Frangakis & Rubin, 2002)

- Causal effect estimands are defined within "principal strata" (latent compliance classes)
- Complier average causal effect (CACE) – causal estimates of an intervention in the subgroup that *complies* with its assigned treatment
- Single study

Case Study: Epidural Analgesia Trials

- A meta-analysis of epidural analgesia in labor on the outcome of cesarean section (Bannister-Tyrrell et al. 2015).



- Randomization group (R): 1=Epidural analgesia, 0=No/other analgesia in labor
- Actual received treatment (T): 1=Epidural analgesia, 0=No/other analgesia in labor
- Outcome (O): cesarean section (1=Yes, 0=No)

Epidural Analgesia Trials

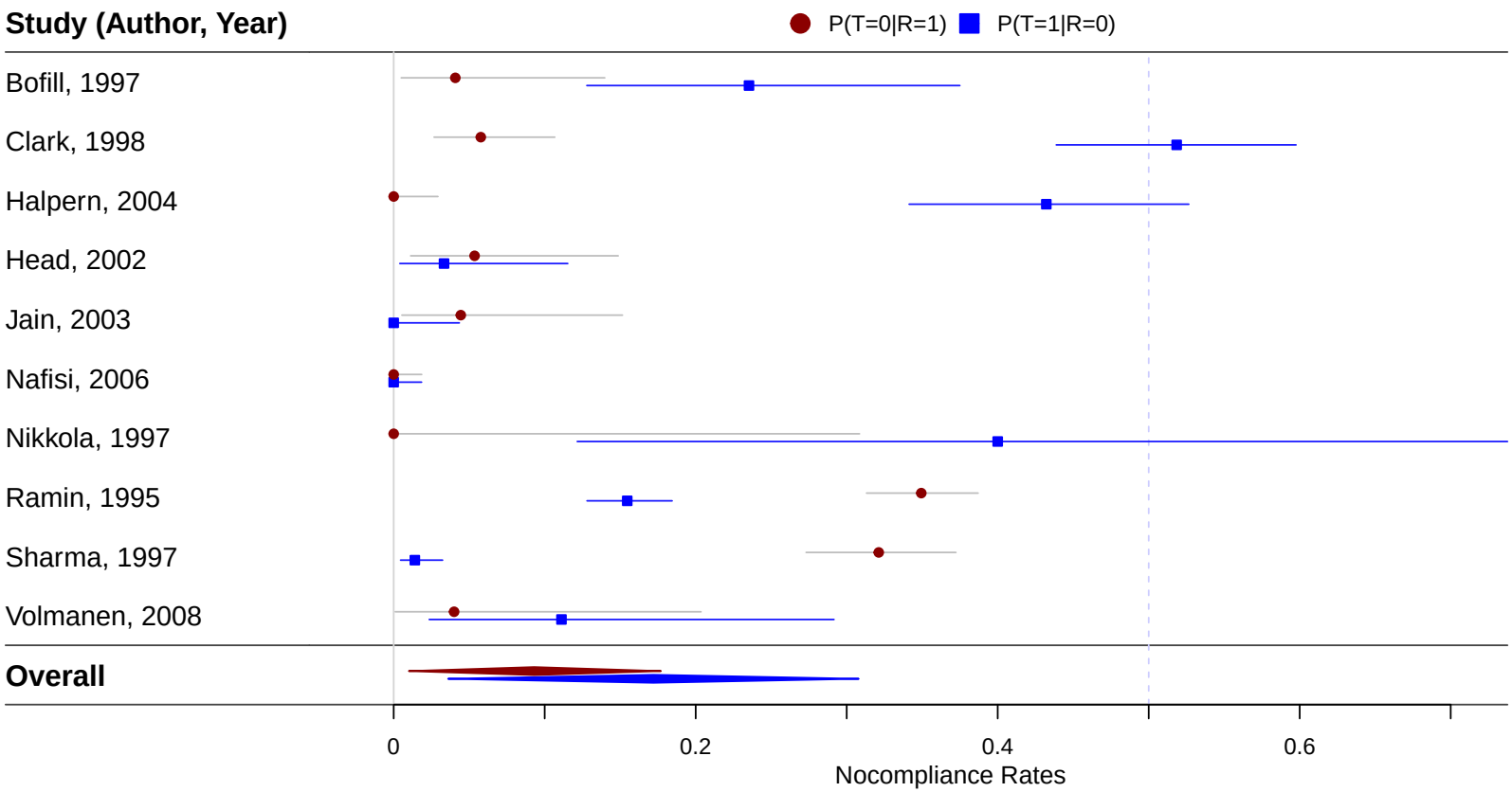


Figure: Forest plot of study-specific noncompliance rates in studies of epidural analgesia.

Objectives

The existing meta-regression methods:

- Fixed study-level covariates ✓
- Noncompliance – post-randomization random variable ✗

Objective:

- To estimate the causal effect in *meta-analysis* accounting for noncompliance
- To account for inherent heterogeneity in noncompliance and event rates
- To propose Bayesian hierarchical models
- To deal with ordinal or binary outcomes

Notation

I two-armed randomized trials. For trial $i \in \{1, ..., I\}$:

- N_i – randomly assigned to the control/placebo N_{i0}, treatment N_{i1}
- $\boldsymbol{R}_i$, $\{R_{ij}\} = r \in \{0, 1\}$, randomized group
- $\boldsymbol{T}_i^{\mathbf{r}}$, $\{T_{ij}^r\} = t \in \{0, 1\}$, *potential* actual treatment received
- $\boldsymbol{Y}_i^{\mathbf{r,t}}$, $\{Y_{ij}^{r,t}\} = y \in \{1, \ldots, O\}$, *potential* ordinal outcome status
- Y_{ij}, T_{ij} observed response and received treatment variables
- N_{irto}, observed counts

Assumptions

Similar as listed in Angrist et al (1996):

- A1. Stable unit treatment value assumption (SUTVA): The outcome for a subject is unaffected by the assignment of treatments to other subjects.
- A2. Random assignment to randomization groups
- A3. Exclusion restriction: the randomization assignment affects responses only through its effect on treatment received. Therefore, for always-takers and never-takers, the distribution of outcomes does not depend on randomization group.
- A4. Nonzero average causal effect of randomization on treatment: $E[T_{ij}^1 - T_{ij}^0] \neq 0$.
- A5. Monotonicity ($P[T_{ij}^1 \geq T_{ij}^0] = 1$), no subject necessarily receives the treatment opposite to the randomized assignment, under assignment to both active treatment and control. This assumption rules out the existence of defiers.

Latent Compliance Classes

Latent compliance classes:

$$C_{ij} = \begin{cases} 0, & \text{never-taker, if } (T_{ij}^0, T_{ij}^1) = (0,0) \\ 1, & \text{complier, if } (T_{ij}^0, T_{ij}^1) = (0,1) \\ 2, & \text{always-taker, if } (T_{ij}^0, T_{ij}^1) = (1,1) \\ 3, & \text{defier, if } (T_{ij}^0, T_{ij}^1) = (1,0). \end{cases}$$

Table: The relations between observed groups and latent classes

R_{ij}	T_{ij}	C_{ij}
0	0	0(never-taker) or 1(complier)
0	1	2(always-taker) or 3(defier)
1	0	0(never-taker) or 3(defier)
1	1	1(complier) or 2(always-taker)

Latent Compliance Classes

Latent compliance classes:

$$C_{ij} = \begin{cases} 0, & \text{never-taker, if } (T_{ij}^0, T_{ij}^1) = (0,0) \\ 1, & \text{complier, if } (T_{ij}^0, T_{ij}^1) = (0,1) \\ 2, & \text{always-taker, if } (T_{ij}^0, T_{ij}^1) = (1,1) \end{cases}$$

~~$C_{ij} = 3$, defier, if $(T_{ij}^0, T_{ij}^1) = (1,0)$.~~

Table: Observed groups, latent compliance classes and outcome probabilities of trial i

R_{ij}	T_{ij}	C_{ij}	Count $Y_{ij} = o \in \{1, \ldots, O\}$
0	0	0 (never-taker) or 1 (complier)	N_{i00o}
0	1	2 (always-taker) ~~or 3 (defier)~~	N_{i01o}
1	0	0 (never-taker) ~~or 3 (defier)~~	N_{i10o}
1	1	1 (complier) or 2 (always-taker)	N_{i11o}

Notation (cont.)

Extending the notation in Cheng (2009) and Baker (2011)

Latent classes probabilities:

- π_{ia} (being an always-taker)
- π_{in} (being a never-taker)
- $\pi_{ic} = 1 - \pi_{ia} - \pi_{in}$ (being a complier)

Outcome probabilities:

- u_{io} (complier in treatment)
- v_{io} (complier in control)
- s_{io} (never-taker)
- b_{io} (always-taker), where $\sum_{o=1}^{O} u_{io} = \sum_{o=1}^{O} v_{io} = \sum_{o=1}^{O} s_{io} = \sum_{o=1}^{O} b_{io} = 1$

CACE

CACE (Complier Average Causal Effect):

$$\theta_i^{\text{CACE}} = E(Y_{ij}^1 - Y_{ij}^0 | C_{ij} = 1)$$

- For binary outcomes, $o \in \{0, 1\}$, $\theta_i^{\text{CACE}} = u_{i1} - v_{i1}$.
- The overall causal effect from the meta-analysis $\theta^{\text{CACE}} = E(\theta_i^{\text{CACE}})$, taking the expectation over all I trials.

Case Study: Epidural Analgesia Trials

Table: Data in 10 RCTs of epidural analgesia in labor

Study (Author, Year)	Allocated control				Allocated epidural			
	Received control		Received epidural		Received control		Received epidural	
	Cesarean – N_{i000}	+ N_{i001}	Cesarean – N_{i010}	+ N_{i011}	Cesarean – N_{i100}	+ N_{i101}	Cesarean – N_{i110}	+ N_{i111}
Bofill, 1997	37	2	11	1	2	0	42	5
Clark, 1998	72	6	68	16	7	2	134	13
Halpern, 2004	62	5	44	7	0	0	112	12
Head, 2002	51	7	2	0	3	0	43	10
Jain, 2003	72	11	0	0	0	2	36	7
Nafisi, 2006	179	19	0	0	0	0	173	24
Nirkola, 1997	6	0	4	0	0	0	10	0
Ramin, 1995	546	17	95	8	230	0	393	39
Sharma, 1997	336	16	5	0	114	1	231	12
Volmanen, 2008	23	1	3	0	1	0	23	1

N_{irto}: observed count $\{j : R_{ij} = r, T_{ij} = t\}, o \in \{0, 1\}$.

Estimation for a Single Trial i

Study (Author, Year)	Allocated control				Allocated epidural			
	Received control		Received epidural		Received control		Received epidural	
	Cesarean – N_{000}	+ N_{001}	Cesarean – N_{010}	+ N_{011}	Cesarean – N_{100}	+ N_{101}	Cesarean – N_{110}	+ N_{111}
Clark, 1998	72	6	68	16	7	2	134	13

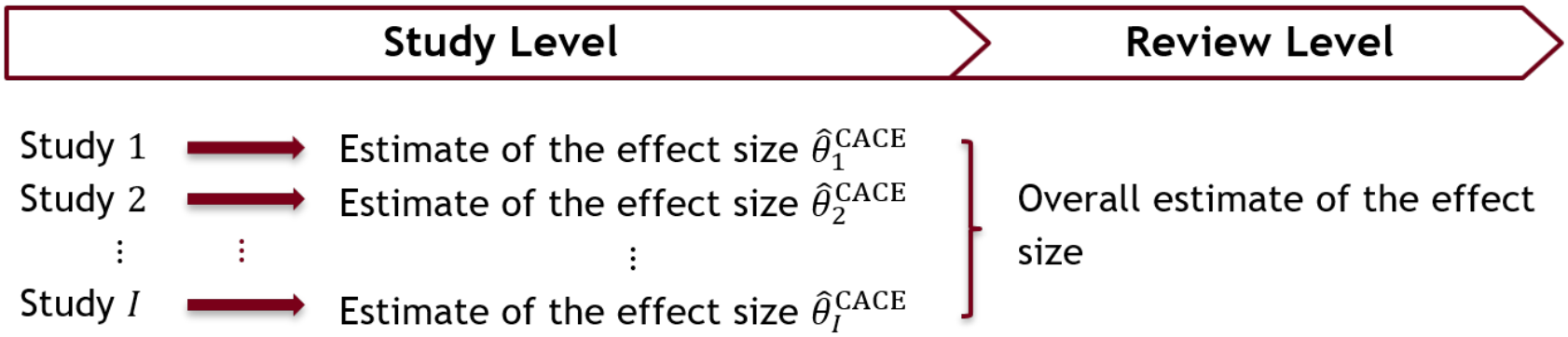
N_{rto}: observed count $\{j : R_j = r, T_j = t\}$, $o \in \{0, 1\}$.

- Parameters: $\boldsymbol{\beta} = (\pi_a, \pi_n, s_1, b_1, u_1, v_1)$

$$L(\boldsymbol{\beta}) \propto [\{\pi_c(1 - v_1) + \pi_n(1 - s_1)\}]^{N_{000}} \{(\pi_c v_1 + \pi_n s_1)\}^{N_{001}} \{\pi_a(1 - b_1)\}^{N_{010}} \{\pi_a b_1\}^{N_{011}} \{\pi_n(1 - s_1)\}^{N_{100}} \{\pi_n s_1\}^{n_{101}} [\{(\pi_c(1 - u_1) + \pi_a(1 - b_1)\}]^{N_{110}} \{(\pi_c u_1 + \pi_a b_1)\}^{N_{111}}$$

- CACE: $\theta^{\text{CACE}} = u_1 - v_1$
- Posterior CACE with 95% CI: -0.022 $(-0.122, 0.079)$
- ITT Risk Difference (RD): -0.040 $(-0.110, 0.031)$

Two-step Approach



$$\hat{\theta}_i^{\text{CACE}} \sim N(\theta_i, \sigma_i^2),\ \theta_i \sim N(\mu, \tau^2)$$

- *Meta-analysis* accounting for noncompliance ✓
- Incomplete noncompliance information ✗

Random Effects Models

Table: Observed data and probabilities in the i^{th} trial

Observed	Probabilities
N_{i000}	$(1-\lambda_i)\{\pi_{ic}(1-v_{i1})+\pi_{in}(1-s_{i1})\}$
N_{i001}	$(1-\lambda_i)(\pi_{ic}v_{i1}+\pi_{in}s_{i1})$
N_{i010}	$(1-\lambda_i)\pi_{ia}(1-b_{i1})$
N_{i011}	$(1-\lambda_i)\pi_{ia}b_{i1}$
N_{i100}	$\lambda_i\pi_{in}(1-s_{i1})$
N_{i101}	$\lambda_i\pi_{in}s_{i1}$
N_{i110}	$\lambda_i\{\pi_{ic}(1-u_{i1})+\pi_{ia}(1-b_{i1})\}$
N_{i111}	$\lambda_i(\pi_{ic}u_{i1}+\pi_{ia}b_{i1})$

where $\lambda_i = \mathrm{P}(R_{ij}=1)$, usually known in practice.

$$L_i(\boldsymbol{\beta}_i) = [(1-\lambda_i)\{\pi_{ic}(1-v_{i1})+\pi_{in}(1-s_{i1})\}]^{N_{i000}}\{(1-\lambda_i)(\pi_{ic}v_{i1}+\pi_{in}s_{i1})\}^{N_{i001}}$$
$$\{(1-\lambda_i)\pi_{ia}(1-b_{i1})\}^{N_{i010}}\{(1-\lambda_i)\pi_{ia}b_{i1}\}^{N_{i011}}\{\lambda_i\pi_{in}(1-s_{i1})\}^{N_{i100}}$$
$$\{\lambda_i\pi_{in}s_{i1}\}^{n_{i101}}[\lambda_i\{\pi_{ic}(1-u_{i1})+\pi_{ia}(1-b_{i1})\}]^{N_{i110}}\{\lambda_i(\pi_{ic}u_{i1}+\pi_{ia}b_{i1})\}^{N_{i111}}$$

Random Effects Models

- Parameters: $\boldsymbol{\beta}_i = (\pi_{ia}, \pi_{in}, s_{i1}, b_{i1}, u_{i1}, v_{i1})$
- $\pi_{in} = \frac{exp(n_i)}{1+exp(n_i)+exp(a_i)}$, $\pi_{ia} = \frac{exp(a_i)}{1+exp(n_i)+exp(a_i)}$, $\pi_{ic} = \frac{1}{1+exp(n_i)+exp(a_i)}$
- To allow for potential heterogeneity in parameters:

$n_i = \alpha_n + \delta_{in}, a_i = \alpha_a + \delta_{ia}.$

$(\delta_{in}, \delta_{ia})^T \sim N(\mathbf{0}, \boldsymbol{\Sigma}_{ps}), \boldsymbol{\Sigma}_{ps} = \begin{pmatrix} \sigma_n^2 & \rho\sigma_n\sigma_a \\ \rho\sigma_n\sigma_a & \sigma_a^2 \end{pmatrix}.$

$g(s_{i1}) = \alpha_s + \delta_{is}, \ g(b_{i1}) = \alpha_b + \delta_{ib},$

$g(u_{i1}) = \alpha_u + \delta_{iu}, \ g(v_{i1}) = \alpha_v + \delta_{iv}$

$\delta_{is} \sim N(0, \sigma_s^2), \delta_{ib} \sim N(0, \sigma_b^2), \delta_{iu} \sim N(0, \sigma_u^2), \delta_{iv} \sim N(0, \sigma_v^2)$

Parameter of Interest

- $\theta^{\text{CACE}} = \text{E}(\theta_i^{\text{CACE}}) = \text{E}(u_{i1}) - \text{E}(v_{i1}) =$

  $\int_{-\infty}^{+\infty} g^{-1}(\alpha_u + t)\sigma_u^{-1}\phi(\frac{t}{\sigma_u})dt - \int_{-\infty}^{+\infty} g^{-1}(\alpha_v + t)\sigma_v^{-1}\phi(\frac{t}{\sigma_v})dt.$

- For probit link, $\text{E}(u_{i1}) = \Phi(\frac{\alpha_u}{\sqrt{1+\sigma_u^2}})$ and $\text{E}(v_{i1}) = \Phi(\frac{\alpha_v}{\sqrt{1+\sigma_v^2}})$

Model Implementation

- Likelihood: $\mathcal{L}(\boldsymbol{\beta}) = \prod_i L_i(\boldsymbol{\beta}_i)$
- Parameters: $\boldsymbol{\beta}_i = (\pi_{ia}, \pi_{in}, s_{i1}, b_{i1}, u_{i1}, v_{i1})$, distributions $f(\boldsymbol{\beta_i}|\boldsymbol{\beta_0}, \boldsymbol{\Sigma_0})$
- $\boldsymbol{\beta_0}$: the vector of mean hyper-parameters $(\alpha_n, \alpha_a, \alpha_s, \alpha_b, \alpha_u, \alpha_v)$
- $\boldsymbol{\Sigma_0}$: the covariance matrix of hyper-parameters $\boldsymbol{\Sigma}_{ps}$, σ_s^2, σ_b^2, σ_u^2 and σ_v^2
- Prior distributions: $f(\boldsymbol{\beta_0})$ and $f(\boldsymbol{\Sigma_0})$
- The joint posterior distribution: $\prod_i L_i(\boldsymbol{\beta}_i) f(\boldsymbol{\beta}_i|\boldsymbol{\beta_0}, \boldsymbol{\Sigma_0}) f(\boldsymbol{\beta_0}) f(\boldsymbol{\Sigma_0})$

Model Selection

Table: Selection of random effects using a forward selection procedure for RCTs of epidural analgesia in labor

*DIC: deviance information criterion

Random effects models	DIC	DIC improvement	p_D
Model **I** (None)	**917.4**	N/A	6.0
Model IIa (δ_{is})	896.8	20.6	21.3
Model IIb (δ_{ib})	918.3	-0.9	16.1
Model IIc (δ_{iu})	915.0	2.4	12.4
Model IId (δ_{iv})	907.4	10.0	14.1
Model IIe (δ_{in})	577.1	340.3	13.6
Model **IIf** (δ_{ia})	**537.2**	**380.2**	15.7
Model IIIa (δ_{ia}, δ_{is})	514.9	22.3	29.3
Model IIIb (δ_{ia}, δ_{ib})	538.6	-1.4	19.5
Model IIIc (δ_{ia}, δ_{iu})	531.9	5.3	21.1
Model IIId (δ_{ia}, δ_{iv})	526.3	10.9	22.9
Model **IIIe** (δ_{ia}, δ_{in})	**265.7**	**271.5**	21.4
Model **IVa** ($\delta_{ia}, \delta_{in}, \delta_{is}$)	**246.5**	**25.0**	27.3
Model IVb ($\delta_{ia}, \delta_{in}, \delta_{ib}$)	266.5	5.0	24.9
Model IVc ($\delta_{ia}, \delta_{in}, \delta_{iu}$)	262.1	9.4	28.2
Model IVd ($\delta_{ia}, \delta_{in}, \delta_{iv}$)	267.1	4.4	29.3
Model IVe ($\delta_{ia}, \delta_{in}, \rho$)	265.7	5.8	22.1
Model Va ($\delta_{ia}, \delta_{in}, \delta_{is}, \rho$)	246.2	0.3	27.6
Model Vb ($\delta_{ia}, \delta_{in}, \delta_{is}, \delta_{ib}$)	247.2	-0.7	30.7
Model Vc ($\delta_{ia}, \delta_{in}, \delta_{is}, \delta_{iu}$)	242.9	3.6	34.0
Model Vd ($\delta_{ia}, \delta_{in}, \delta_{is}, \delta_{iv}$)	253.0	-6.5	34.4

Parameter Estimates

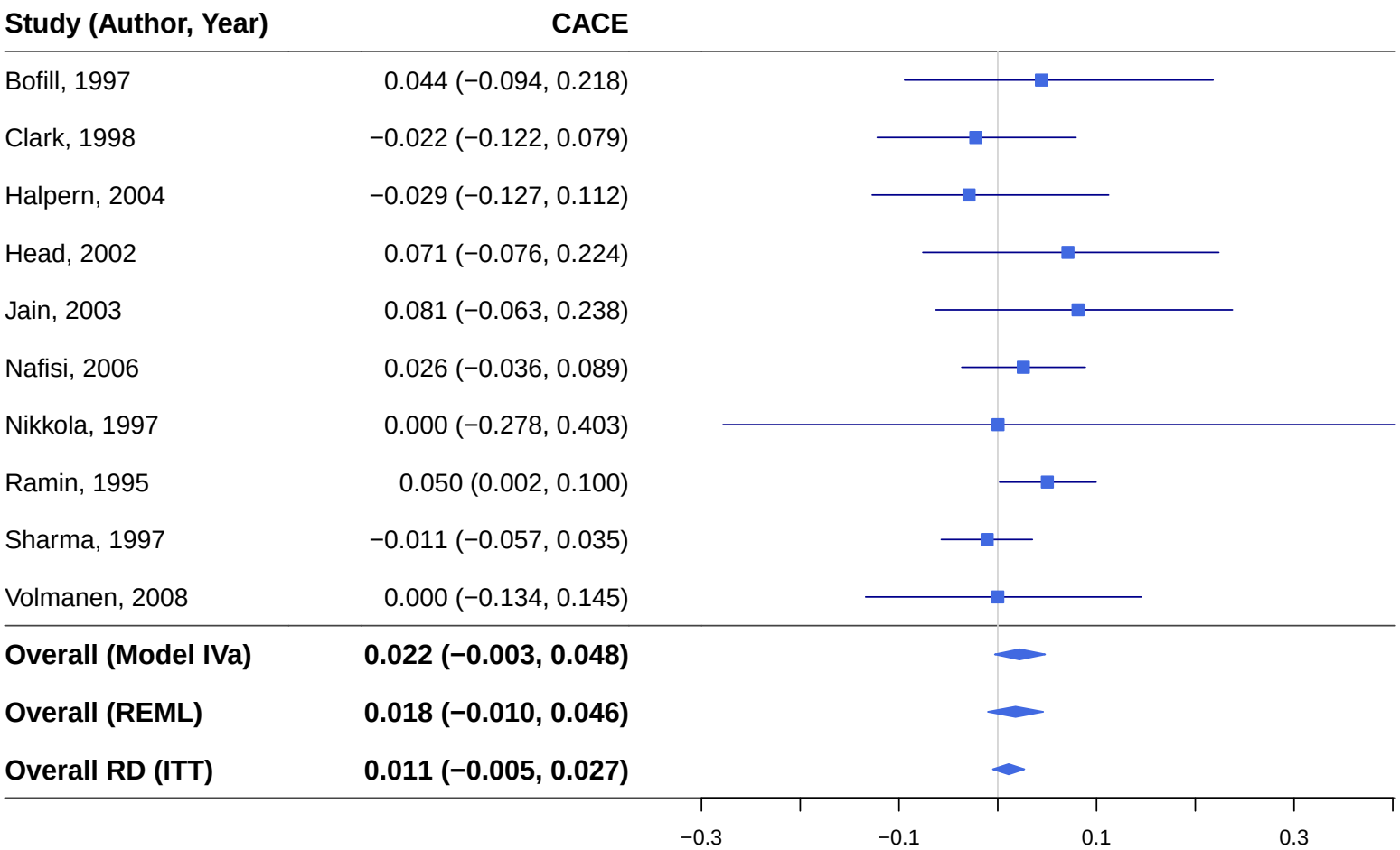


Figure: Forest plot of CACE of epidural analgesia in labor on caesarean section.

Conclusions

- The first meta-analysis of RCTs estimating CACE accounting for noncompliance.
- Case study – allowing for appropriate # of random effects improves the goodness of fit of models.
- Simulation studies

Zhou, J., Hodges, J.S., Suri, M.F.K., and Chu, H. “A Bayesian Hierarchical Model Estimating CACE in Meta-analysis of Randomized Clinical Trials with Noncompliance." *Biometrics*. 2019. DOI: 10.1111/biom.13028.

Future work

- Extensions – Incomplete noncompliance information
- CACE analysis extensions: relaxing key assumptions, other types of outcomes
- Extending to network meta-analysis

Zhou, J., Hodges, J.S., and Chu, H. “A Bayesian Hierarchical CACE Model Accounting for Incomplete Noncompliance in Meta-analysis." 2019. Under review by *JASA*.

Thank you!

Back-up Slides

Epidural Analgesia Trials

Obtained from Bannister-Tyrrell et al. 2015:

		No of cesareans/total in group					
		Allocated epidural			Allocated control		
Author	Year	Received epidural	No epidural	Total	Received epidural	No epidural	Total
Bofill	1997	5/47	0/2	5/49	1/12	2/39	3/51
Clark	1998	13/147	2/9	15/156	16/84	6/78	22/162
Dickinson	2002	—/356	—/137	85/493	—/306	—/193	71/499
Evron	2008	—/—	—/—	19/148	0/0	4/44	4/44
El Kerdawy	2010	—/—	—/—	4/15	—/—	—/—	3/15
Gambling	1998	29/400	10/216	39/616	—/159	—/448	34/607
Grandjean	1979	—/—	—/—	0/30	—/—	—/—	1/60
Halpern	2004	12/124	0/0	12/124	7/51	5/67	12/118
Head	2002	10/53	0/3	10/56	0/2	7/58	7/60
Hogg	2000	—/—	—/—	7/53	—/—	—/—	6/52
Howell	2001	—/123	—/61	13/184	—/52	—/133	16/185
Jain	2003	7/43	2/2	9/45	0/0	11/83	11/83
Long	2003	—/—	—/—	1/30	—/—	—/—	6/50
Loughnan	2000	—/257	—/47	36/304	—/175	—/135	40/310
Lucas	2001	—/321	—/51	63/372	—/—	—/—	62/366
Muir	1996	—/—	—/—	3/28	—/11	—/11	2/22
Muir	2000	—/—	—/—	11/97	—/18	—/70	9/88
Nafisi	2006	24/197	0/0	24/197	0/0	19/198	19/198
Nikkola	1997	0/10	0/0	0/10	0/4	0/6	0/10
Philipsen	1989	—/—	—/—	10/57	—/—	—/—	6/54
Ramin	1995	39/432	2/232	41/664	8/103	17/563	25/666
Sharma	1997	12/243	1/115	13/358	0/5	16/352	16/357
Sharma	2002	15/214	1/12	16/226	—/14	—/219	20/233
Shifman	2007	—/—	—/—	15/60	—/—	—/—	18/50
Thalme	1974	—/—	—/—	6/14	—/—	—/—	4/14
Thorp	1993	—/—	—/—	12/48	—/—	—/—	1/45
Volmanen	2008	1/24	0/1	1/25	0/3	1/24	1/27
Total		2,991	888	4,459	999	2,721	4,426

Notation (added.)

I two-armed randomized trials. For the i^{th} trial:

- $T_{ij} = *$ if the actual treatment is not recorded
- $\boldsymbol{M}_i$, $\{M_{ij}\} = m \in \{0, 1\}$, actual treatment received status missing indicator
- N_{irto}, observed counts

Model Implementation

- Computation: JAGS, “rjags" package in R
- Estimations: posterior means with 95% credible intervals
- Priors: proper but diffuse priors

$$\alpha_n, \alpha_a \sim N(0, 2.5^2)$$

$$\alpha_s, \alpha_b, \alpha_u, \alpha_v \sim N(0, 2^2)$$

$$\sigma_n^{-2}, \sigma_a^{-2}, \sigma_s^{-2}, \sigma_b^{-2}, \sigma_u^{-2}, \sigma_v^{-2} \sim Gamma(2, 2)$$

$$\mathbf{\Sigma}_{ps}^{-1} \sim Wishart(I, 3)$$

Simulation settings

- Focus on random effects $(\delta_{iz1}, \delta_{iu})$.
- Each simulation: 20 meta-studies, each with 350 observations. 1:1 allocation ($\lambda_i = 0.5$) of being randomized to the treatment group.
- True values:
  $(\alpha_{z1}, \alpha_{z2}, \alpha_s, \alpha_b, \alpha_u, \alpha_v) = (-0.4, -0.6, 0.5, -0.5, -0.5, 0.5)$,
  giving true $\pi_{in} = 0.302$, $\pi_{ia} = 0.247$, $\pi_{ic} = 0.451$ and
  $\theta_i^{\text{CACE}} = -0.383$
  $Var(\delta_{iz1}, \delta_{iu}, \delta_{iv}) = 0.5^2$
- Fit models with up to three random effects.

Simulation results

Table: The estimated probability of selecting a candidate model as the final model using DIC* based on 2000 simulated datasets

True Random Effects Model	Selected Random Effects Model							
	None	δ_{iz1}	δ_{iu}	δ_{iv}	$\delta_{iz1}, \delta_{iu}$	$\delta_{iz1}, \delta_{iv}$	δ_{iu}, δ_{iv}	$\delta_{iz1}, \delta_{iu}, \delta_{iv}$
None	**950.5**	16	18.5	14.5	0	0.5	0	0
δ_{iz1}	0	**962.5**	0	0	18.5	19	0	0
δ_{iu}	0	0	**966.5**	0	12.5	0	20	1
$\delta_{iz1}, \delta_{iu}$	0	0	0	0	**982.5**	0	0	17.5

NOTE: The numbers have been multiplied by 1,000 for presentation. *DIC: deviance information criterion.

Simulation results

Table: Performance of estimates and credible intervals for θ^{CACE} for each model, based on 2000 simulated datasets

True Random Effects Model		Selected Random Effects Model							
		None	δ_{iz1}	δ_{iu}	δ_{iv}	$\delta_{iz1}, \delta_{iu}$	$\delta_{iz1}, \delta_{iv}$	δ_{iu}, δ_{iv}	$\delta_{iz1}, \delta_{iu}, \delta_{iv}$
None	Mean	**-0.383**	-0.383	-0.373	-0.374	-0.372	-0.374	-0.363	-0.363
	Bias	**0.000**	0.000	0.010	0.009	0.011	0.009	0.020	0.020
	95% CIL*	**0.100**	0.099	0.171	0.171	0.170	0.172	0.220	0.221
	95% CICp**	**0.947**	0.948	0.999	0.999	0.999	0.999	1.000	1.000
δ_{iz1}	Mean	-0.383	**-0.382**	-0.372	-0.374	-0.372	-0.373	-0.364	-0.363
	Bias	0.000	**0.001**	0.011	0.009	0.011	0.010	0.019	0.020
	95% CIL	0.101	**0.098**	0.172	0.173	0.170	0.175	0.222	0.223
	95% CICp	0.946	**0.947**	0.998	0.999	0.998	0.999	1.000	1.000
δ_{iu}	Mean	-0.365	-0.364	**-0.356**	-0.355	-0.355	-0.355	-0.346	-0.346
	Bias	-0.001	0.000	**0.008**	0.009	0.009	0.009	0.018	0.018
	95% CIL	0.100	0.099	**0.204**	0.171	0.204	0.172	0.247	0.248
	95% CICp	0.755	0.759	**0.986**	0.944	0.986	0.946	0.995	0.996
$\delta_{iz1}, \delta_{iu}$	Mean	-0.365	-0.365	-0.357	-0.356	**-0.356**	-0.355	-0.348	-0.347
	Bias	-0.001	-0.001	0.008	0.008	**0.008**	0.009	0.016	0.017
	95% CIL	0.101	0.099	0.205	0.173	**0.204**	0.175	0.249	0.250
	95% CICp	0.763	0.753	0.986	0.951	**0.987**	0.951	0.997	0.996

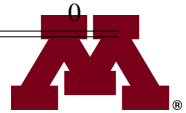
*95% CIL: 95% equal-tail credible interval length. **95% CICp: 95% credible interval coverage probability.

Case Study: Epidural Analgesia Trials

Reorganize the data as follows:

Author, Year	Complete data								Missing compliance data			
	Allocated control				Allocated epidural				Allocated control		Allocated epidural	
	Received Control		Received epidural		Received Control		Received epidural					
	Cesarean – N_{i000}	+ N_{i001}	Cesarean – N_{i010}	+ N_{i011}	Cesarean – N_{i100}	+ N_{i101}	Cesarean – N_{i110}	+ N_{i111}	Cesarean – N_{i0*0}	+ N_{i0*1}	Cesarean – N_{i1*0}	+ N_{i1*1}
Bofill, 1997 *	37	2	11	1	2	0	42	5	0	0	0	0
Clark, 1998 *	72	6	68	16	7	2	134	13	0	0	0	0
Dickinson, 2002	0	0	0	0	0	0	0	0	428	71	408	85
Evron, 2008	40	4	0	0	0	0	0	0	0	0	129	19
El Kerdawy, 2010	0	0	0	0	0	0	0	0	12	3	11	4
Gambling, 1998	0	0	0	0	206	10	371	29	573	34	0	0
Grandjean, 1979	0	0	0	0	0	0	0	0	59	1	30	0
Halpern, 2004 *	62	5	44	7	0	0	112	12	0	0	0	0
Head, 2002 *	51	7	2	0	3	0	43	10	0	0	0	0
Hogg, 2000	0	0	0	0	0	0	0	0	46	6	46	7
Howell, 2001	0	0	0	0	0	0	0	0	169	16	171	13
Jain, 2003 *	72	11	0	0	0	2	36	7	0	0	0	0
Long, 2003	0	0	0	0	0	0	0	0	44	6	29	1
Loughnan, 2000	0	0	0	0	0	0	0	0	270	40	268	36
Lucas, 2001	0	0	0	0	0	0	0	0	304	62	309	63
Muir, 1996	0	0	0	0	0	0	0	0	20	2	25	3
Muir, 2000	0	0	0	0	0	0	0	0	79	9	86	11
Nafisi, 2006 *	179	19	0	0	0	0	173	24	0	0	0	0
Nikkola, 1997 *	6	0	4	0	0	0	10	0	0	0	0	0
Philipsen, 1989	0	0	0	0	0	0	0	0	48	6	47	10
Ramin, 1995 *	546	17	95	8	230	2	393	39	0	0	0	0
Sharma, 1997 *	336	16	5	0	114	1	231	12	0	0	0	0
Sharma, 2002	0	0	0	0	11	1	199	15	213	20	0	0
Shifman, 2007	0	0	0	0	0	0	0	0	32	18	45	15
Thalme, 1974	0	0	0	0	0	0	0	0	10	4	8	6
Thorp, 1993	0	0	0	0	0	0	0	0	44	1	36	12
Volmanen, 2008 *	23	1	3	0	1	0	23	1	0	0	0	0

The * indicates that the corresponding study has complete data on compliance status.

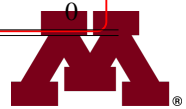


Case Study: Epidural Analgesia Trials

Reorganize the data as follows:

Author, Year	Complete data								Missing compliance data			
	Allocated control				Allocated epidural				Allocated control		Allocated epidural	
	Received Control		Received epidural		Received Control		Received epidural					
	Cesarean – N_{i000}	+ N_{i001}	Cesarean – N_{i010}	+ N_{i011}	Cesarean – N_{i100}	+ N_{i101}	Cesarean – N_{i110}	+ N_{i111}	Cesarean – N_{i0*0}	+ N_{i0*1}	Cesarean – N_{i1*0}	+ N_{i1*1}
Bofill, 1997 *	37	2	11	1	2	0	42	5	0	0	0	0
Clark, 1998 *	72	6	68	16	7	2	134	13	0	0	0	0
Dickinson, 2002	0	0	0	0	0	0	0	0	428	71	408	85
Evron, 2008	40	4	0	0	0	0	0	0	0	0	129	19
El Kerdawy, 2010	0	0	0	0	0	0	0	0	12	3	11	4
Gambling, 1998	0	0	0	0	206	10	371	29	573	34	0	0
Grandjean, 1979	0	0	0	0	0	0	0	0	59	1	30	0
Halpern, 2004 *	62	5	44	7	0	0	112	12	0	0	0	0
Head, 2002 *	51	7	2	0	3	0	43	10	0	0	0	0
Hogg, 2000	0	0	0	0	0	0	0	0	46	6	46	7
Howell, 2001	0	0	0	0	0	0	0	0	169	16	171	13
Jain, 2003 *	72	11	0	0	0	2	36	7	0	0	0	0
Long, 2003	0	0	0	0	0	0	0	0	44	6	29	1
Loughnan, 2000	0	0	0	0	0	0	0	0	270	40	268	36
Lucas, 2001	0	0	0	0	0	0	0	0	304	62	309	63
Muir, 1996	0	0	0	0	0	0	0	0	20	2	25	3
Muir, 2000	0	0	0	0	0	0	0	0	79	9	86	11
Nafisi, 2006 *	179	19	0	0	0	0	173	24	0	0	0	0
Nikkola, 1997 *	6	0	4	0	0	0	10	0	0	0	0	0
Philipsen, 1989	0	0	0	0	0	0	0	0	48	6	47	10
Ramin, 1995 *	546	17	95	8	230	2	393	39	0	0	0	0
Sharma, 1997 *	336	16	5	0	114	1	231	12	0	0	0	0
Sharma, 2002	0	0	0	0	11	1	199	15	213	20	0	0
Shifman, 2007	0	0	0	0	0	0	0	0	32	18	45	15
Thalme, 1974	0	0	0	0	0	0	0	0	10	4	8	6
Thorp, 1993	0	0	0	0	0	0	0	0	44	1	36	12
Volmanen, 2008 *	23	1	3	0	1	0	23	1	0	0	0	0

The * indicates that the corresponding study has complete data on compliance status.



Typical Data Display

Table: Typical data for study i with missing actual treatment received status in randomization group $r \in \{0, 1\}$

Treatment received	Outcome 1	...	O
0	N_{ir01}	...	N_{ir0O}
	P_{ir01}	...	P_{ir0O}
1	N_{ir11}	...	N_{ir1O}
	P_{ir11}	...	P_{ir1O}
* (Missing)	N_{ir*1}	...	N_{ir*O}
	$P_{ir01} + P_{ir11}$	...	$P_{ir0O} + P_{ir1O}$

In each cell, the first row: the observed count;
second row: the corresponding probability.

Likelihood

Table: Typical data for study i in randomization group $r \in \{0, 1\}$

Treatment received	Outcome 1	...	O
0	N_{ir01}	...	N_{ir0O}
	P_{ir01}	...	P_{ir0O}
1	N_{ir11}	...	N_{ir1O}
	P_{ir11}	...	P_{ir1O}
* (Missing)	N_{ir*1}	...	N_{ir*O}
	$P_{ir01} + P_{ir11}$	...	$P_{ir0O} + P_{ir1O}$

$$L_i(\boldsymbol{\beta}_i) = \prod_j \prod_o P_{i00o}^{(1-R_{ij})(1-T_{ij})(1-M_{ij})I(Y_{ij}=o)} P_{i01o}^{(1-R_{ij})T_{ij}(1-M_{ij})I(Y_{ij}=o)}$$

$$P_{i10o}^{R_{ij}(1-T_{ij})(1-M_{ij})I(Y_{ij}=o)} P_{i11o}^{R_{ij}T_{ij}(1-M_{ij})I(Y_{ij}=o)}$$

$$(P_{i00o} + P_{i01o})^{(1-R_{ij})M_{ij}I(Y_{ij}=o)} (P_{i10o} + P_{i11o})^{R_{ij}M_{ij}I(Y_{ij}=o)}$$

Model Selection

Table: Selecting random effects using a forward selection procedure for the epidural analgesia in labor meta-analysis

*DIC: deviance information criterion

Random effects models	DIC	DIC improvement	p_D
Model **I** (None)	**1409.0**	N/A	6.8
Model IIa (δ_{is})	1225.2	183.8	36.1
Model IIb (δ_{ib})	1258.5	150.5	33.2
Model IIc (δ_{iu})	1325.9	83.1	25.6
Model IId (δ_{iv})	1321.4	87.6	27.0
Model IIe (δ_{in})	992.5	416.5	89.6
Model **IIf** (δ_{ia})	**814.2**	**594.8**	26.2
Model IIIa (δ_{ia}, δ_{is})	748.3	65.9	45.0
Model IIIb (δ_{ia}, δ_{ib})	781.8	32.4	37.0
Model IIIc (δ_{ia}, δ_{iu})	790.9	23.3	37.6
Model IIId (δ_{ia}, δ_{iv})	804.6	9.6	39.2
Model **IIIe** (δ_{in}, δ_{ia})	**508.2**	**306.2**	33.3
Model **IVa** ($\delta_{in}, \delta_{ia}, \delta_{is}$)	**464.3**	**43.9**	46.2
Model IVb ($\delta_{in}, \delta_{ia}, \delta_{ib}$)	490.7	17.5	41.6
Model IVc ($\delta_{in}, \delta_{ia}, \delta_{iu}$)	494.3	13.9	47.7
Model IVd ($\delta_{in}, \delta_{ia}, \delta_{iv}$)	514.4	-6.2	49.1
Model IVe ($\delta_{in}, \delta_{ia}, \rho$)	507.8	0.4	34.0
Model Va ($\delta_{in}, \delta_{ia}, \delta_{is}, \rho$)	465.4	-1.1	46.9
Model Vb ($\delta_{in}, \delta_{ia}, \delta_{is}, \delta_{ib}$)	465.1	-0.7	49.9
Model **Vc** ($\delta_{in}, \delta_{ia}, \delta_{is}, \delta_{iu}$)	**457.7**	**6.7**	59.9
Model Vd ($\delta_{in}, \delta_{ia}, \delta_{is}, \delta_{iv}$)	478.0	-13.7	60.3
Model VIa ($\delta_{in}, \delta_{ia}, \delta_{is}, \delta_{iu}, \delta_{ib}$)	457.1	0.6	62.9
Model VIb ($\delta_{in}, \delta_{ia}, \delta_{is}, \delta_{iu}, \delta_{iv}$)	465.9	-8.2	70.2

Parameter Estimates

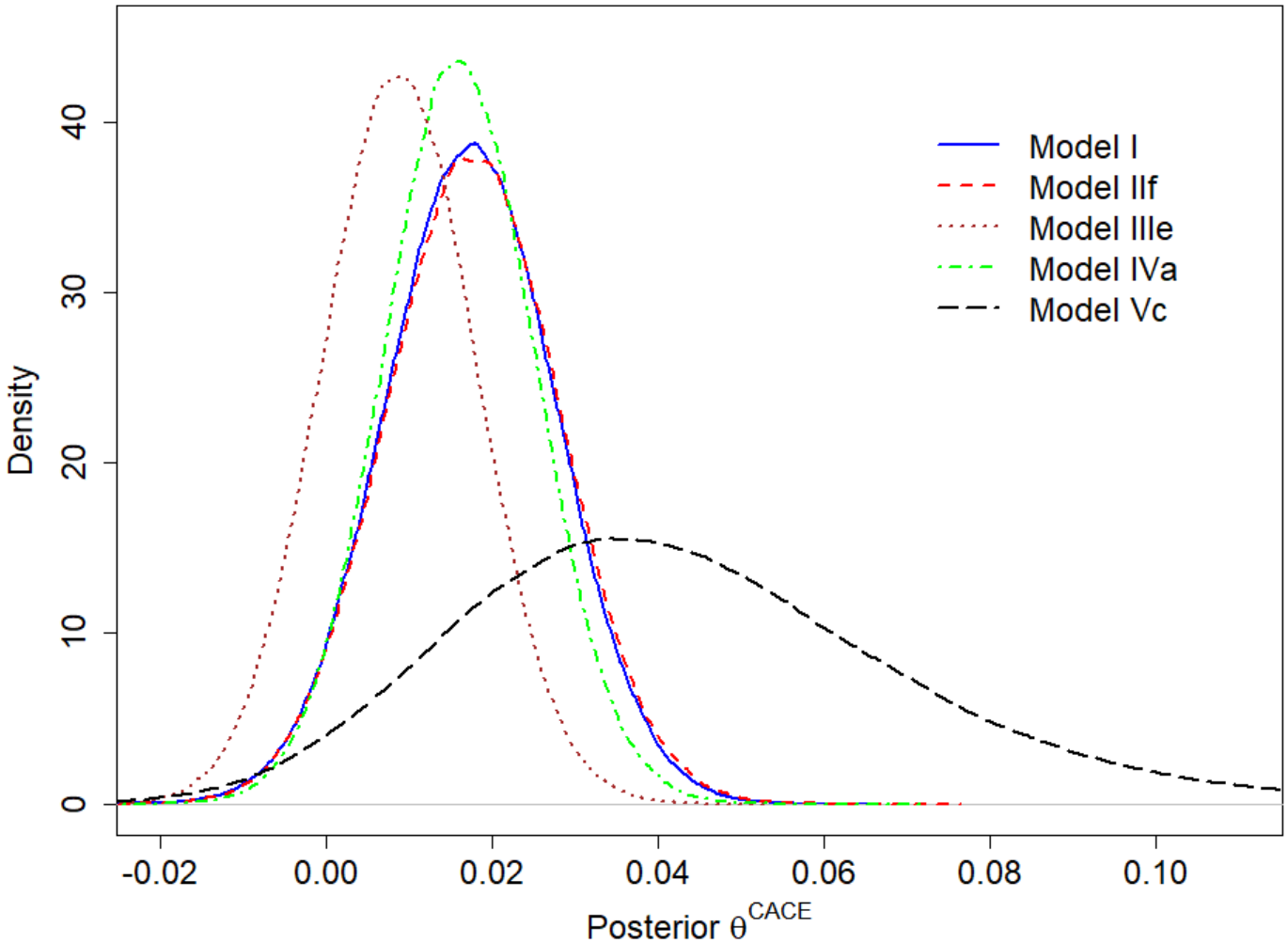


Figure: Posterior distributions of θ^{CACE} of epidural analgesia in labor on cesarean section.

Parameter Estimates

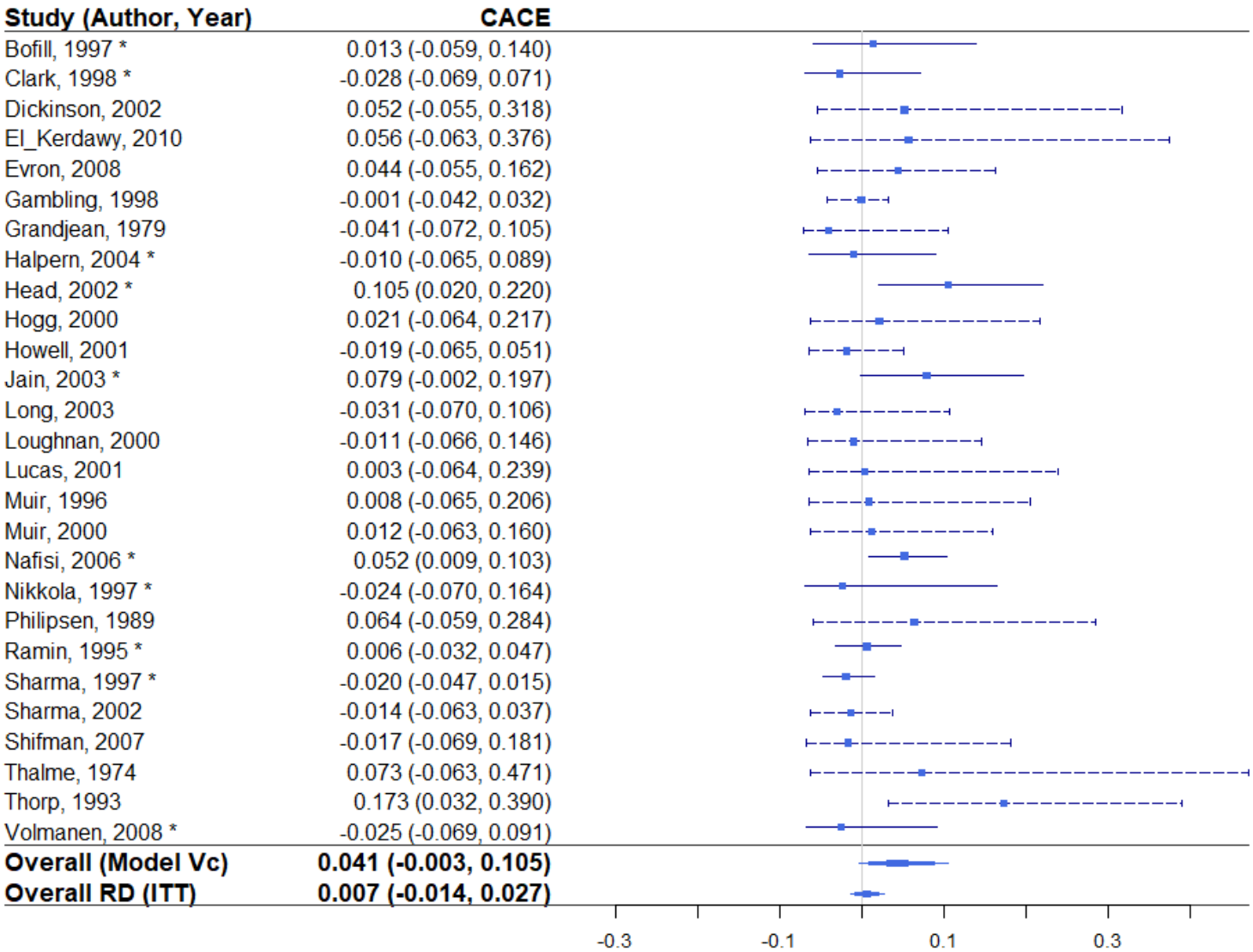


Figure: Forest plot of θ^{CACE} of epidural analgesia in labor on cesarean section.

Discussion

- All 27 epidural analgesia trials are included in the CACE meta-analysis.
- May introduce more heterogeneity into the meta-analysis and may affect the CACE estimate.
- Sensitivity analysis and simulations under different missingness mechanisms

Zhou, J., Hodges, J.S., and Chu, H. “A Bayesian Hierarchical CACE Model Accounting for Incomplete Noncompliance in Meta-analysis." 2019. Under review by *JASA*.

Future work

- CACE analysis extensions: relaxing key assumptions, other types of outcomes
- Extending to network meta-analysis