



✦ Estimation and Adjustment of Bias in Randomised Evidence Using Mixed Treatment Comparison Meta-analysis

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Overview

- Bias models in pairwise meta-analysis
 - Motivation
 - Limitations
- Adjusting for Bias in Mixed Treatment Comparisons Meta-analysis (MTC)
 - Fluoride dataset
 - Probability of bias model
- Results and Conclusions

Motivation

- Trial characteristics such as **inadequate allocation concealment** are associated with bias.
- Estimate bias and adjust for it
- True treatment effect
 - Unbiased studies $\rightarrow \delta_{AB}$
 - Biased studies $\rightarrow \delta_{AB} + \beta$
 - Assume $\beta \sim \text{Normal}(b, \kappa)$
- Where does information on β come from?

✦ Bias Models: info on β from...

- External sources
 - Guess
 - Formal elicitation (Turner *et al* JRSS A, 2009)
 - Evidence-based: compare biased and unbiased evidence to inform β
(Welton *et al* JRSS A, 2009)
- **Internal sources**
 - Evidence-based
 - Estimate bias *within* same set of trials and adjust

Mixed Treatment Comparisons

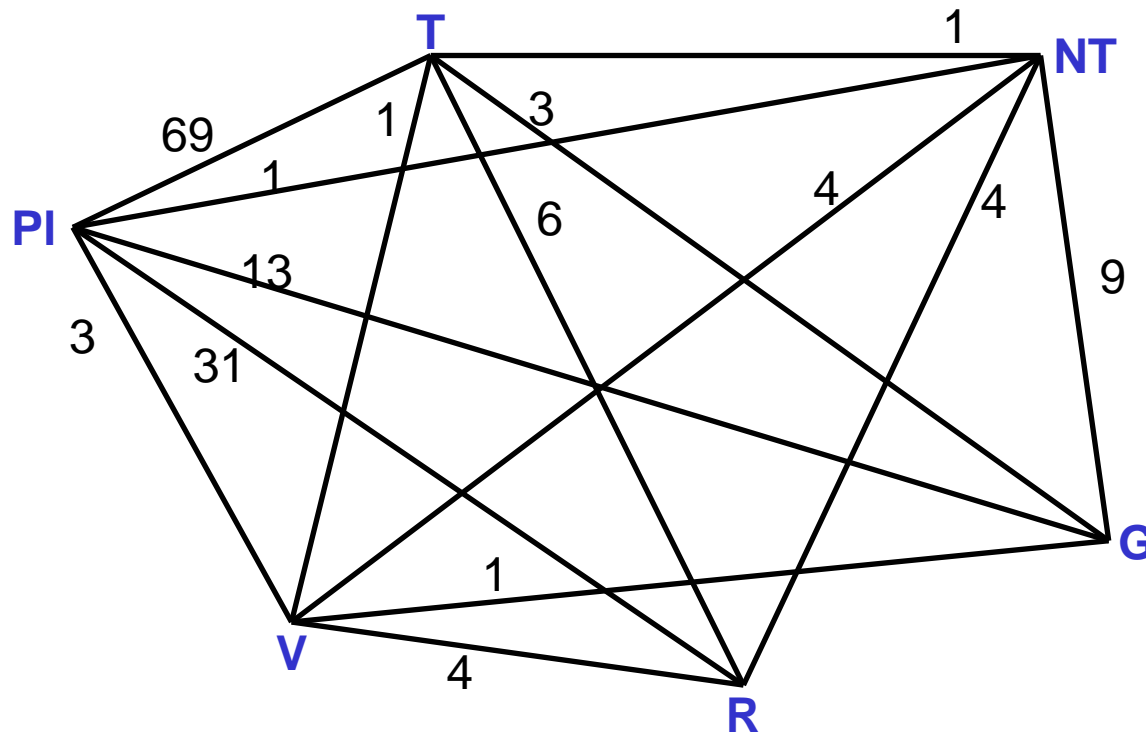
- A network of trials comparing different interventions for a condition
 - Direct and indirect evidence available on treatment effects
- Because of the network structure, there is enough information to estimate and adjust for bias within the network
- No need to rely on exchangeability assumption between meta-analyses in different fields

🌿 Example: The Fluoride Data

- 6 different interventions for preventing dental caries in children and adolescents
 1. **No Treatment**
 2. **Placebo**
 3. Fluoride in **T**oothpaste
 4. Fluoride in **R**inse
 5. Fluoride in **G**el
 6. Fluoride in **V**arnish
- From 6 Cochrane Reviews*

} **Active Treatments**

🔥 Network and Number of trials



- 130 trials
 - eight 3-arm trials
 - one 4-arm trial
- 150 pairwise comparisons

🌿 Introduction to MTC

- 6 treatments: 1, 2, 3, ..., 6
- Take Treatment 1 as the **reference** treatment
- Treatment effects d_{1k} of all other treatments relative to treat 1 are the **basic** parameters
- Given them priors: $d_{1,2}, d_{1,3}, \dots, d_{1,6} \sim N(0, 100^2)$
- The remaining contrasts are **functional** parameters **CONSISTENCY assumption**

$$\begin{aligned} d_{2,3} &= d_{1,3} - d_{1,2} & d_{2,4} &= d_{1,4} - d_{1,2} \quad \dots \\ \dots \quad d_{4,6} &= d_{1,6} - d_{1,4} & d_{5,6} &= d_{1,6} - d_{1,5} \end{aligned}$$

🌿 Fluoride: Poisson MTC RE model

$$r_{ik} \sim \text{Poisson}(\lambda_{ik} E_{ik}) \quad i = 1, \dots, 130$$

λ_{ik} : rate at which events occur in arm k of trial i
 E_{ik} : Exposure time in person years

$$\theta_{ik} = \log(\lambda_{ik}) = \mu_i + \delta_{ik} I_{k \neq 1}$$

$$\delta_{ik} \sim N\left(\underbrace{d_{1,t_{ik}} - d_{1,t_{i1}}}_{\text{MTC consistency equations}}, \tau^2\right)$$

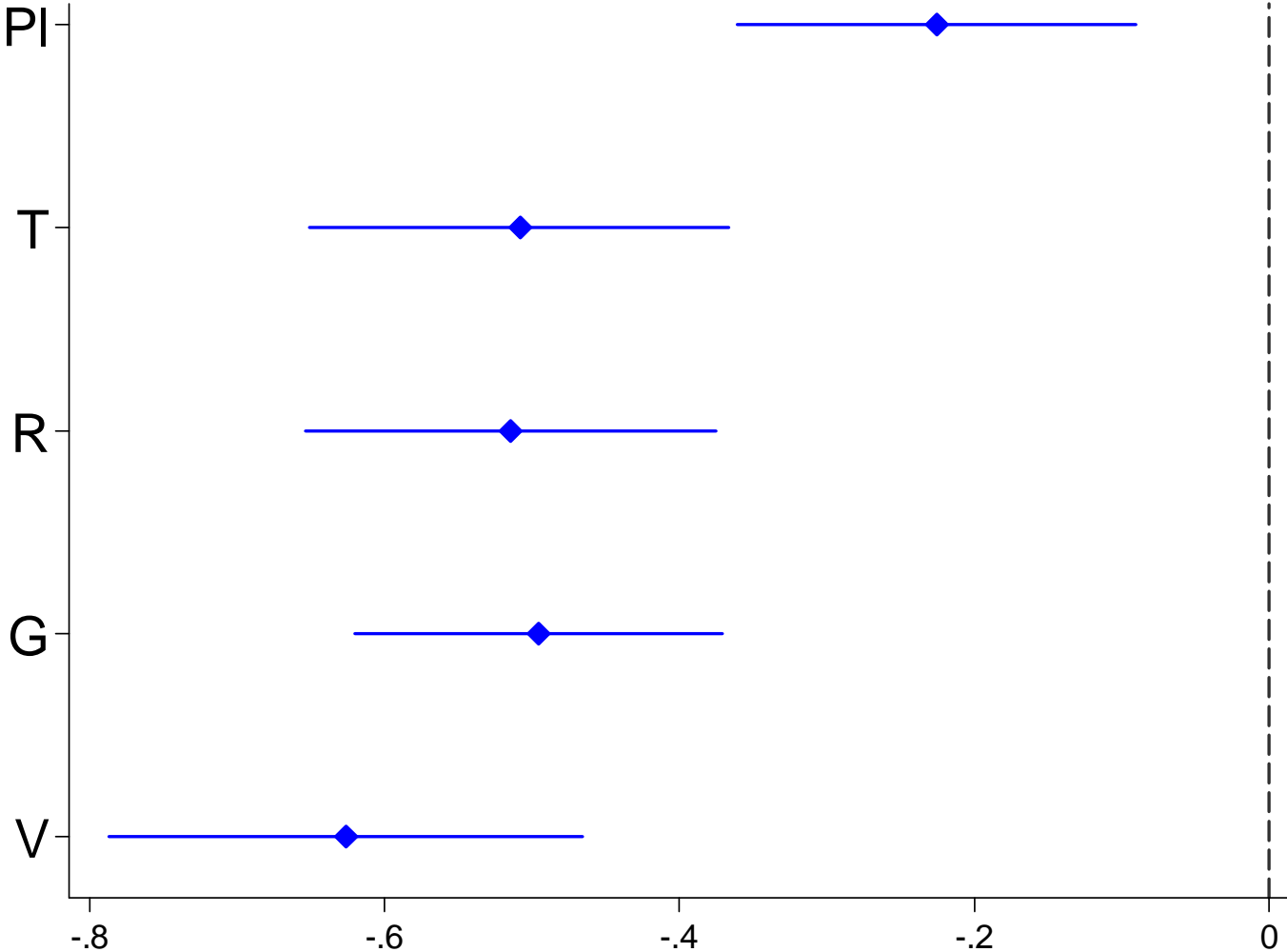
Priors

$$\tau \sim U(0, 10)$$

$$d_{1,j} \sim N(0, 100^2) \quad j = 2, \dots, 6$$

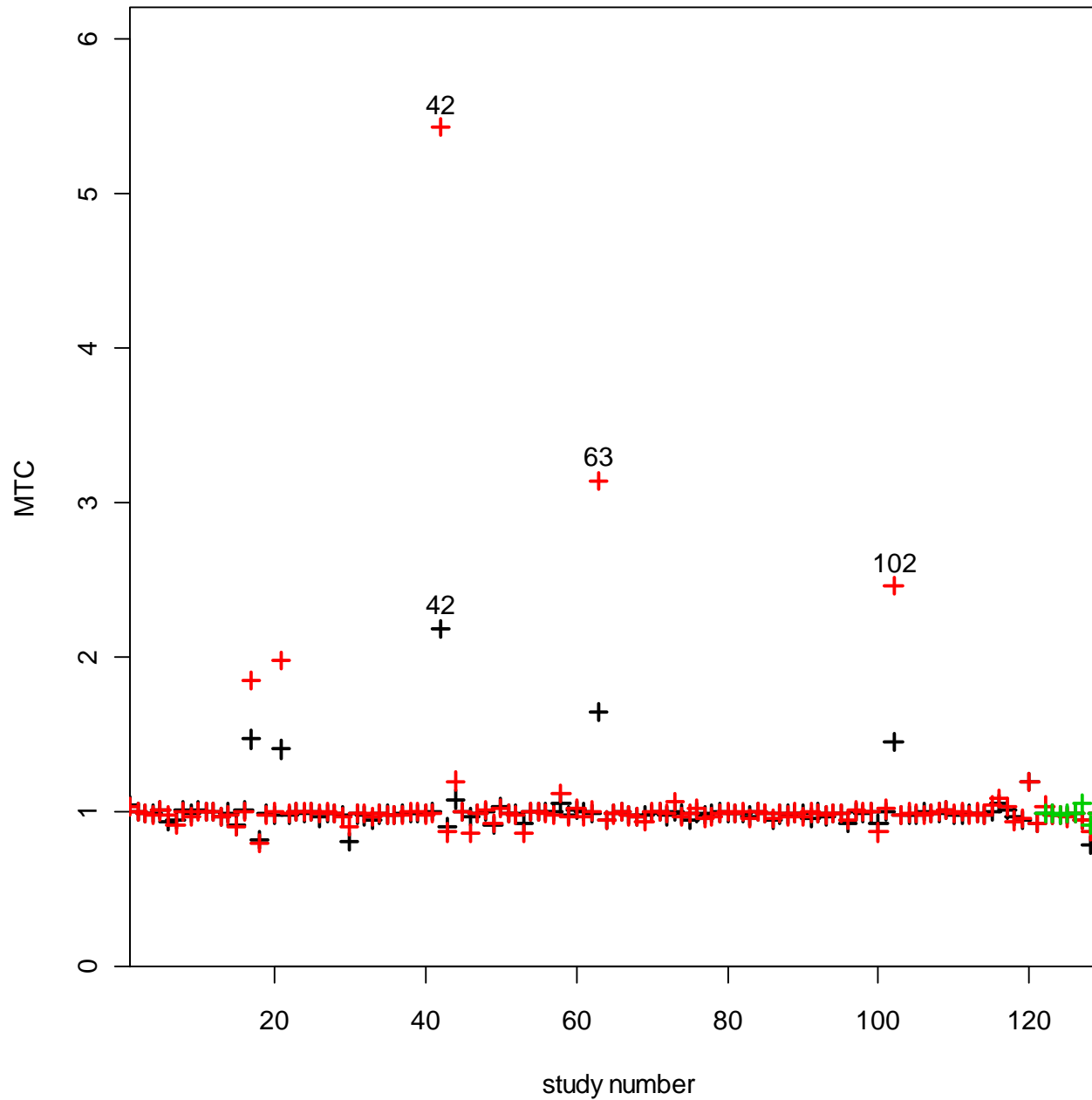
$$\mu_i \sim N(0, 100^2) \quad i = 1, \dots, 130$$

MTC results: LHR relative to No Treatment



Residual deviance is 278.6
(270 data points)

Posterior mean of residual deviances for each point



🌿 MTC RE model with bias

$$\theta_{ik} = \log(\lambda_{ik}) = \mu_i + (\delta_{ik} + \beta_{ik} X_i) I_{k \neq 1}$$

$$\beta_{ik} \sim N(b_i, \kappa)$$

$$X_i = \begin{cases} 1 & \text{if study at risk of bias} \\ 0 & \text{otherwise} \end{cases}$$

$$\delta_{ik} \sim N\left(\underbrace{d_{1,t_{ik}} - d_{1,t_{i1}}}_{\text{MTC consistency equations}}, \tau^2\right)$$

MTC consistency
equations

Priors

$$\tau \sim U(0, 10)$$

$$d_{1,k} \sim N(0, 100^2) \quad k = 2, \dots, 6$$

$$\mu_i \sim N(0, 100^2) \quad i = 1, \dots, 130$$

MTC Bias Model

- Assume non-zero mean bias, $b_i = b \neq 0$, in comparisons of NT or PI with Active treatments
- For Active-Active comparisons assume mean bias is zero
 - When assuming non-zero mean need to make assumptions on direction of bias
- Expect bias to increase size of treatment effect: $b < 0$

🌿 Fluoride: Risk of Bias indicators

- Allocation concealment
 - Best empirical evidence of bias
 - But... 98/130 studies 'unclear'
 - Only 11/130 studies 'adequate'
 - Some comparisons have no adequately concealed trials
- Other bias indicators available to inform risk of bias status
 - Used **“Any bias”** as a composite indicator of bias: 54/130 studies at risk of bias.

Probability of Bias Model

- Any study with **unclear** allocation concealment has a probability p of being at risk of bias
 - Adequately concealed trials are not at risk of bias
 - Inadequately concealed trials are at risk of bias
- No need to include other bias indicators
 - Use only allocation concealment
- Bias terms identifiable

✦ Probability of Bias Model

$$\theta_{ik} = \mu_i + (\delta_{ik} + \beta_{ik} X_i) I_{k \neq 1}$$

$$X_i = \begin{cases} 1 & \text{if allocation concealment is inadequate} \\ B_i & \text{if allocation concealment is unclear} \\ 0 & \text{if allocation concealment is adequate} \end{cases}$$

$$B_i \sim \text{Bernoulli}(p) \quad \text{and} \quad p \sim \text{Beta}(1,1)$$

Comparing Model Fit

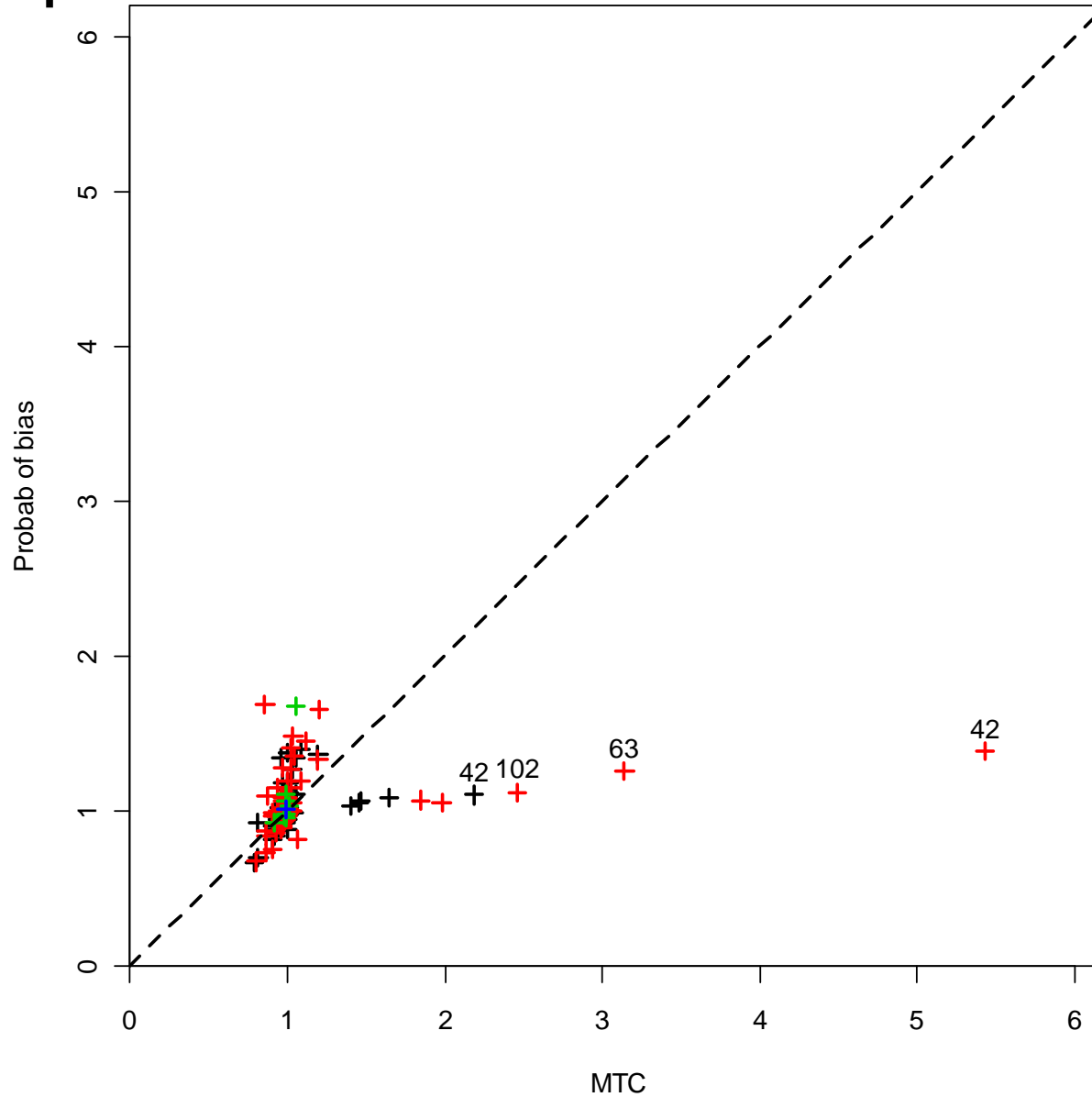
	ResDev*	pD	DIC	Between trial heterogeneity
MTC with no bias adjustment	278.6	259.3	537.9	0.22 (0.19, 0.26)

Bias adjustment

AnyBias	277.6	257.9	535.5	0.15 (0.12, 0.18)
Probability of bias	274.6	253.0	527.6	0.12 (0.10, 0.15)

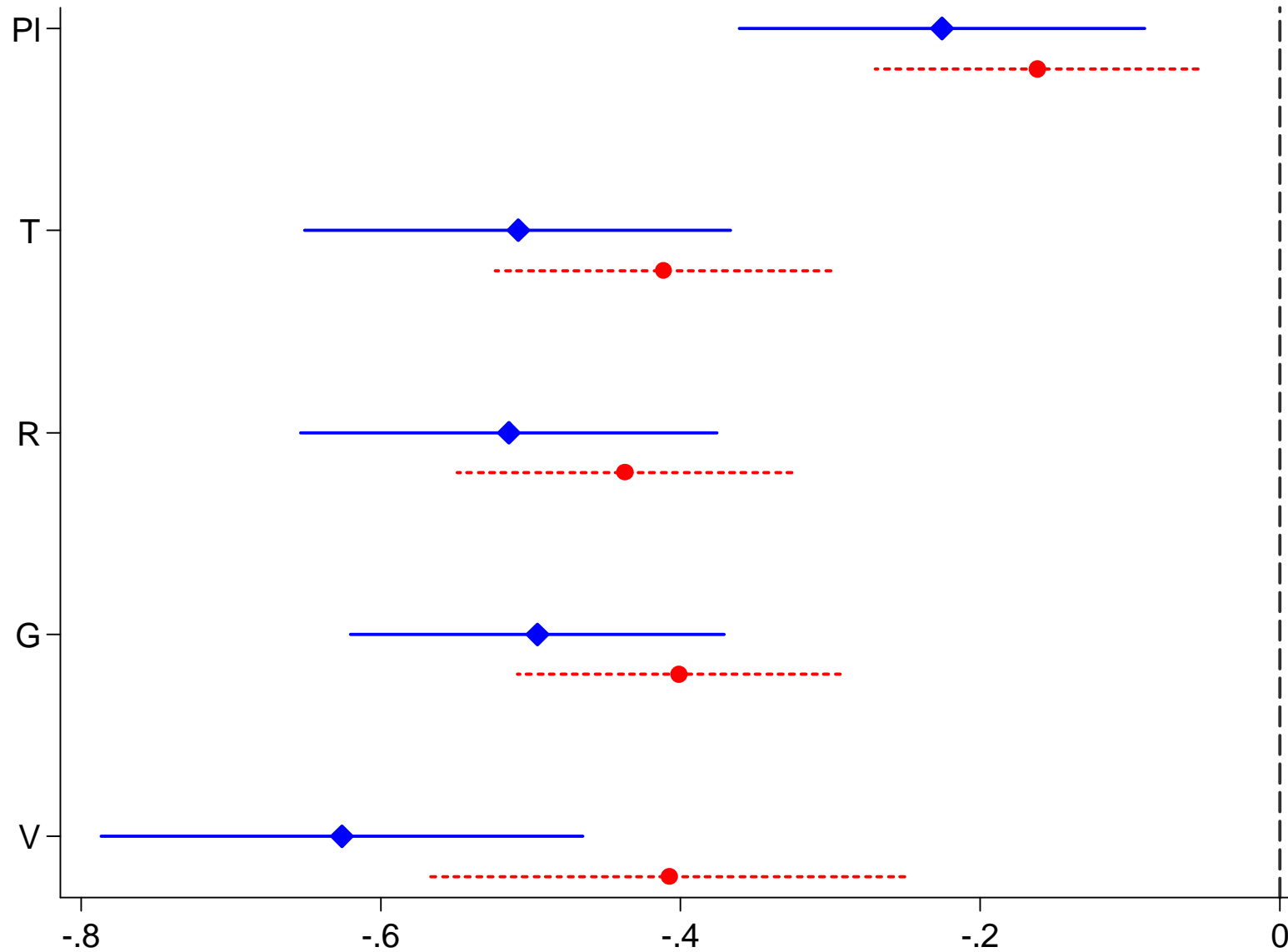
* Compare with 270 data points

Posterior mean of residual deviances for each point: MTC and Probab of bias models



Treatment effects relative to No Treatment (LHR)

Unadjusted MTC (solid) and Probability of Bias model (dashed)



✦ Results: Probability of Bias

- Bias
 - posterior mean = -0.19, CrI (-0.36, -0.02)
 - posterior sd = 0.40, CrI (0.29, 0.55)
- Trials with unclear allocation concealment are at risk of bias with probability p
 - Posterior mean of $p = 0.13$
- Model identified 5 trials (with unclear allocation concealment) as having a **high probability of bias**

Other findings

- Between trial heterogeneity in treatment effects reduced in bias-adjusted model
- Model with Active-Active bias was also fitted with similar results: Active-Active bias had posterior mean of zero
 - But assumptions on direction of bias not easy...

Conclusions

- Bias estimation and adjustment possible within MTC
 - because there is a degree of redundancy in the network
- Uses only internal evidence
- Assumption that study specific biases are exchangeable *within* the network
 - Weaker than required from using external evidence

References

- Our website: <http://bristol.ac.uk/cobm/research/mpes>
- Dias, S, Welton, NJ, Marinho, VCC, Salanti, G, Higgins, JPT, Ades, AE (2009) Estimation and adjustment of Bias in randomised evidence using Mixed Treatment Comparison Meta-analysis. Submitted to *Journal of the Royal Statistical Society A*.
- Schulz, KF, Chalmers, I, Hayes, RJ and Altman, DG (1995) Empirical Evidence of Bias. Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials. *JAMA*, **273**, 408-412.
- Turner, RM, Spiegelhalter, DJ, Smith, GCS and Thompson, SG (2009) Bias modelling in evidence synthesis. *Journal of the Royal Statistical Society A*, **172**, 21-47.
- Welton, NJ, Ades, AE, Carlin, J, Altman, D and Sterne, J (2009) Models for potentially biased evidence in meta-analysis using empirically based priors. *Journal of the Royal Statistical Society A*, **172**, 119-136.



Treatments						No of studies	Allocation concealment			Blinding			Including language
NT	P	T	R	G	V		adequate	unclear	inadequate	Double	Single	?	Any bias
						1	0	1	0	0	1	0	1
						4	1	3	0	3	1	0	1
						3	0	3	0	1	0	2	2
						1	0	1	0	1	0	0	0
						3	0	2	1	0	2	1	3
						9	0	5	4	0	6	3	9
						4	0	3	1	0	3	1	4
						61	8	46	7	61	0	0	17
						25	2	20	3	22	0	3	8
						9	0	6	3	9	0	0	3
						3	0	3	0	3	0	0	1
						1	0	1	0	1	0	0	0
						1	0	0	1	0	1	0	1
						4	0	3	1	2	2	0	3
						1	0	1	0	0	1	0	1
Total						130	11	98	21	103	17	10	54

The Fluoride Data

- Data

$i = 1, \dots, 130$ study index

$k = 1, 2, 3, \dots, 6$ treatment index

n_{ik} - number of subjects in trial i , treatment k

T_i – length of follow-up in trial i
(range 1-6 years)

r_{ik} - number of caries occurring in trial i ,
treatment k , during the trial follow-up period

RE Pairwise meta-analysis

$$\theta_{ik} = \begin{cases} \mu_i & \text{if } k = 1, \text{ i.e. control arm} \\ \mu_i + \delta_i & \text{if } k = 2, \text{ i.e. treatment arm} \end{cases}$$

Random effects

$$\delta_{ik} \sim N(d, \tau^2)$$

Priors

$$\tau \sim U(0, 10)$$

$$d \sim N(0, 100^2)$$

$$\mu_i \sim N(0, 100^2) \quad i = 1, \dots, n$$

But may believe that some studies are at high risk of bias...

RE pairwise meta-analysis with bias term

$$\theta_{ik} = \begin{cases} \mu_i & \text{if } k = 1, \text{ i.e. control arm} \\ \mu_i + \delta_i + \beta_i X_i & \text{if } k = 2, \text{ i.e. treatment arm} \end{cases}$$

$$\beta_i \sim N(b, \kappa)$$

$$X_i = \begin{cases} 1 & \text{if study at risk of bias} \\ 0 & \text{otherwise} \end{cases}$$

Bias term exchangeable between trials

Estimating and adjusting for bias

- In a single pairwise meta-analysis there will not be enough information on the extent of bias
- So need to assume the prior distribution of the bias is known to adjust treatment effects
- Use collection of pairwise MAs to build prior distribution for bias (meta-epidemiological studies)
 - Requires strong assumption of exchangeability of bias between MAs in different fields

Poisson MTC RE model

$$r_{ik} \sim \text{Poisson}(\lambda_{ik} E_{ik}) \quad \text{likelihood}$$

$$E_{ik} = n_{ik} T_i \quad \text{Exposure time in person years}$$

$$\theta_{ik} = \log(\lambda_{ik}) = \mu_i + \delta_{ik} I_{k \neq 1} \quad \text{model}$$

rate at which events occur in arm k of trial i

$$\delta_{ik} \sim N\left(\underbrace{d_{1,t_{ik}} - d_{1,t_{i1}}}_{\text{MTC consistency equations}}, \tau^2\right)$$

MTC consistency
equations

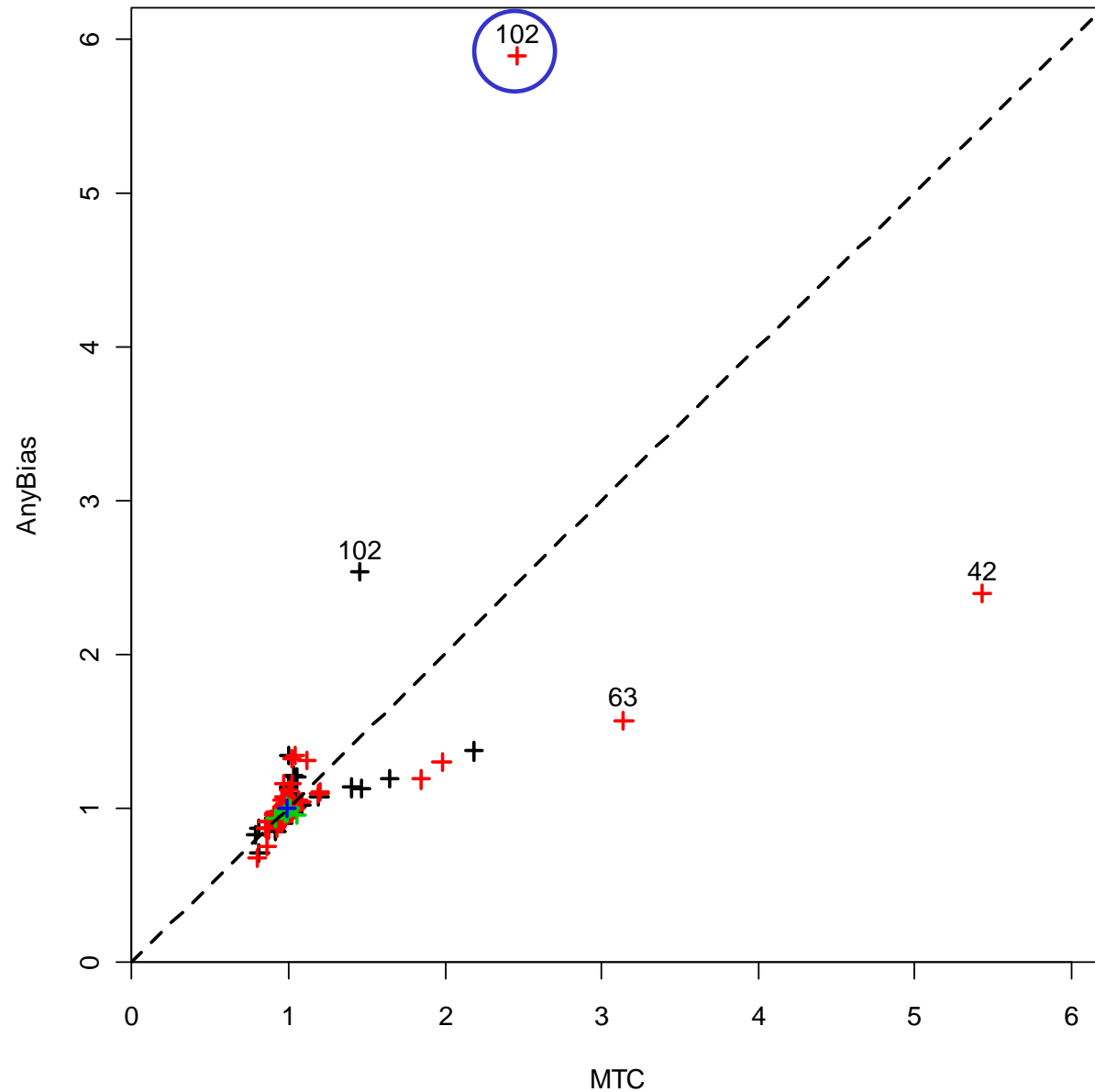
Priors

$$\tau \sim U(0,10)$$

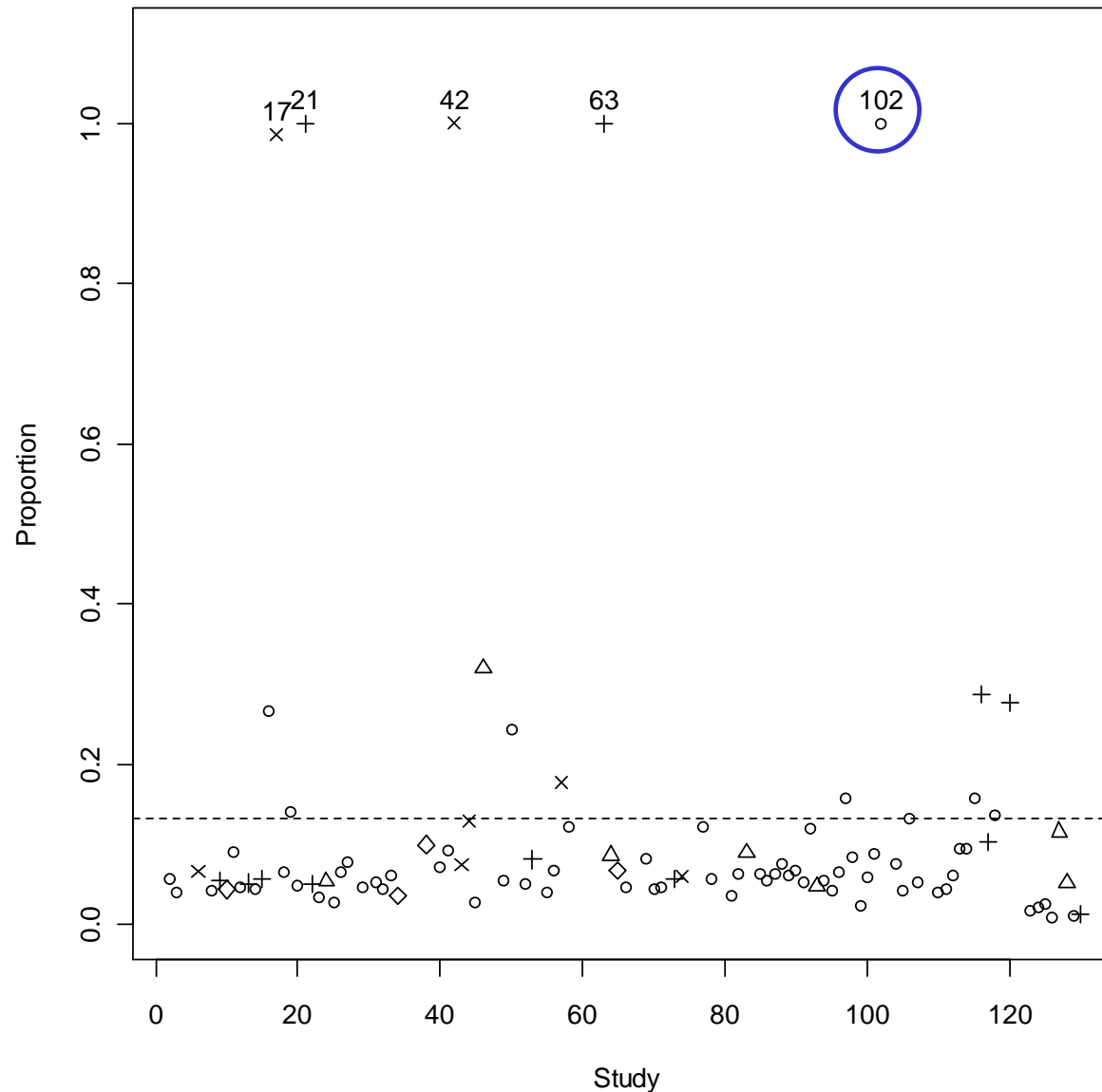
$$d_{1,k} \sim N(0,100^2) \quad k = 2, \dots, 6$$

$$\mu_i \sim N(0,100^2) \quad i = 1, \dots, 130$$

Posterior mean of residual deviances for each point: MTC and AnyBias models



Probability of bias for each study with unclear allocation concealment



- Unclear allocation concealment and no other bias indicators
- Has a high probability of being at risk of bias under this model

← Posterior mean of p