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Addressing multiple treatments II: multiple-treatments meta-analysis basic methods

Maths Warning!

Πανεπιστήμιο Ιωαννίνων

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Why use Bayesian statistics for MTM?

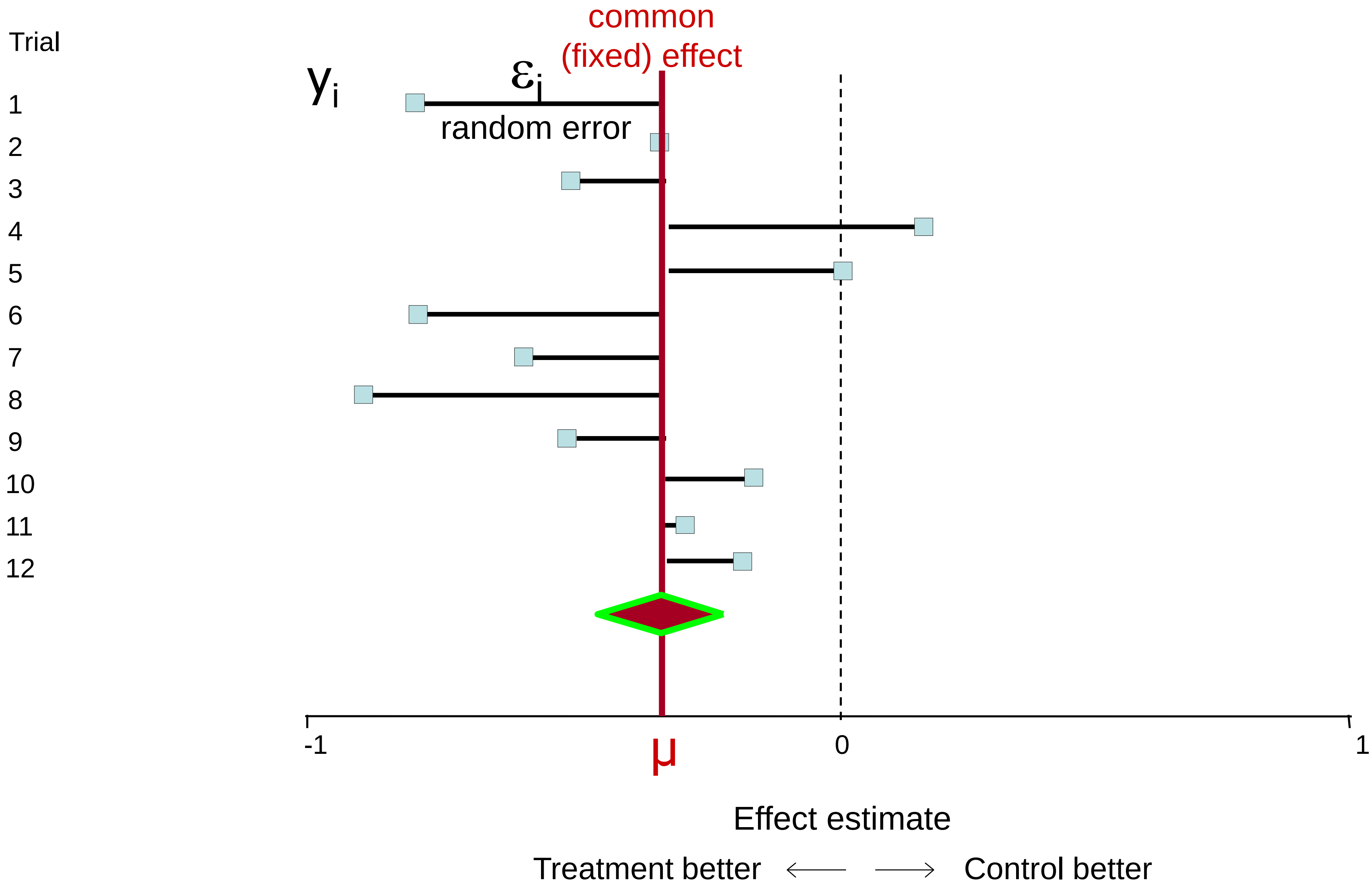
- Bayesian approach is **easier to account for correlations** induced by multi-arm trials
- Estimation of **predictive intervals** is straightforward
- Estimation of **ranking probabilities** is straightforward

- MTM with two-arm trials only (or ignoring the correlations)

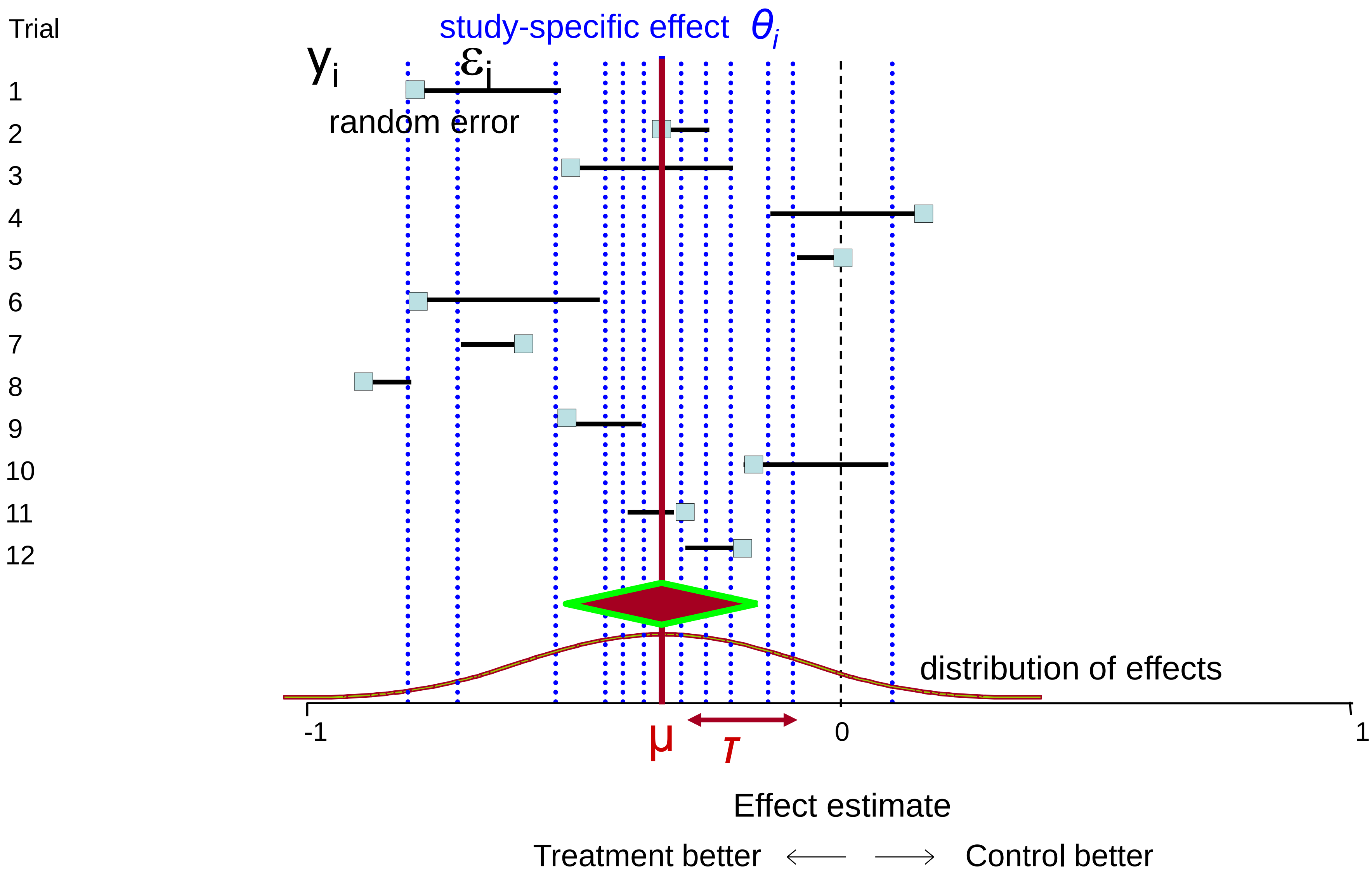
  Easy with frequentist meta-regression

  (come to the workshop tomorrow...)

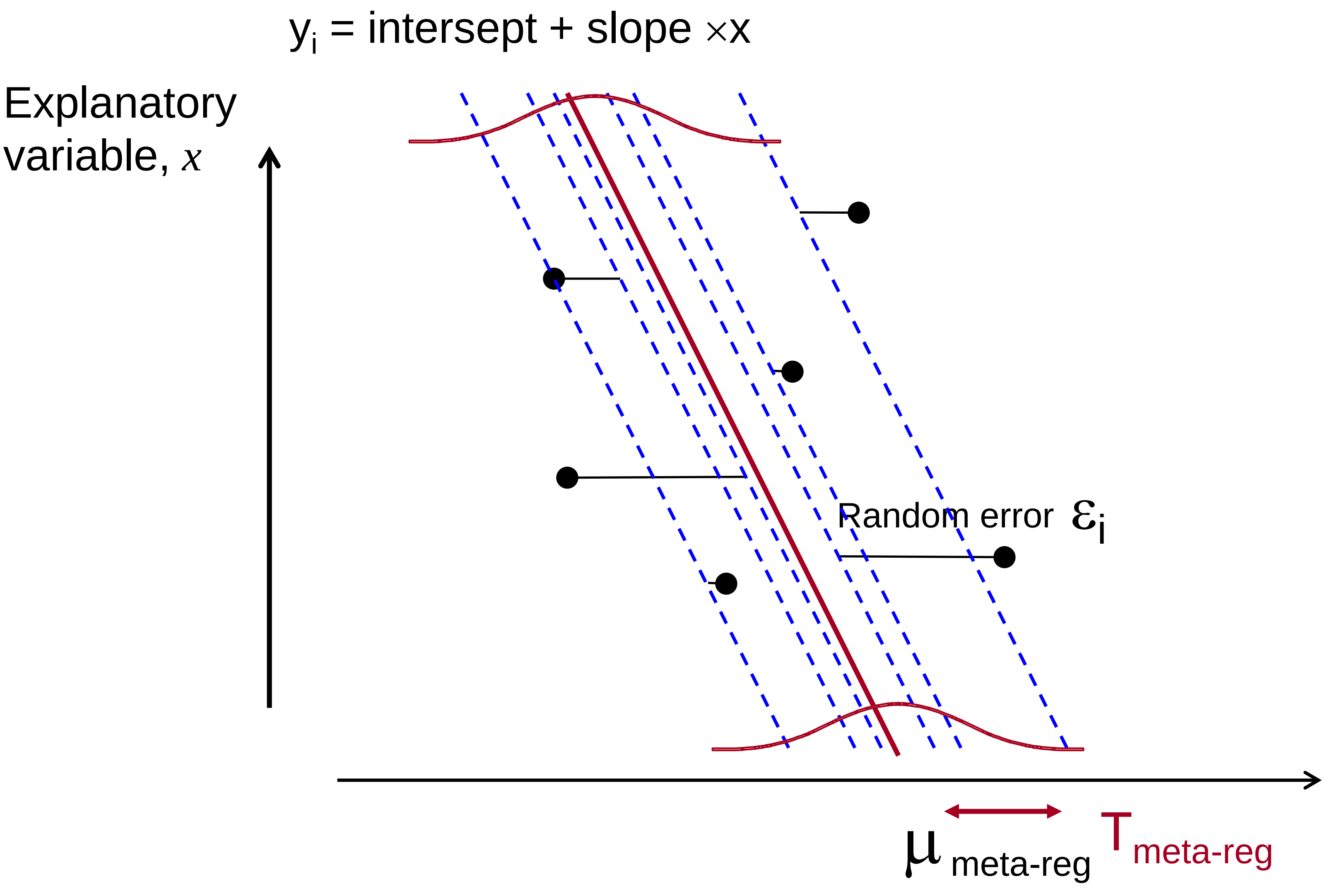
Fixed effect meta-analysis



Random effects meta-analysis



Random effects meta-regression



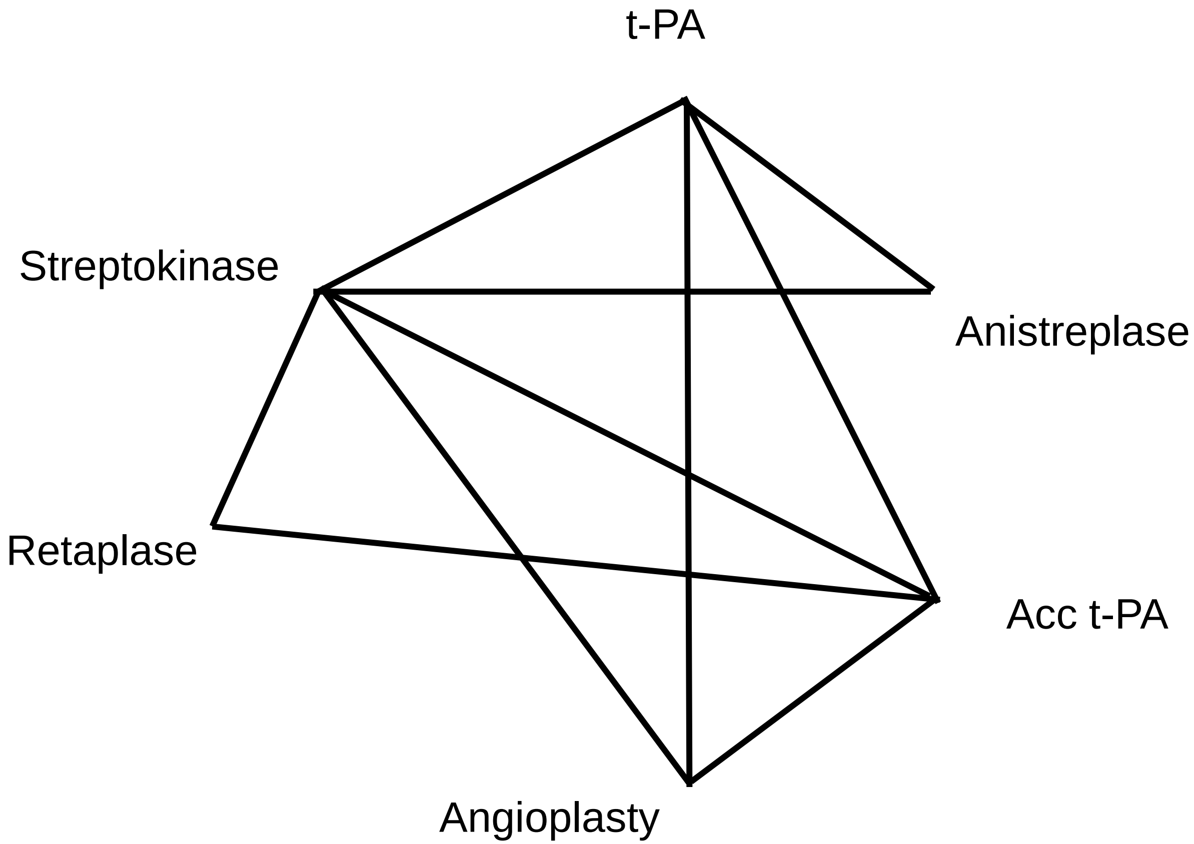
Meta-regression

- We observe y_i in each study (e.g. the log(OR))
- Meta-regression using the treatments as 'covariates'
- AC, AB, BC studies, chose C as *reference*

$$y_i = \mu^{AC} \times (Treat_i{=}A) + \mu^{BC} \times (Treat_i{=}B)$$

- The AC studies have (1,0), the BC studies (0,1) [*basic*]
- AB studies have (1,-1) [*functional*]
- Please use random effects only

Parametrisation of the network



Choose basic parameters

Write all other contrasts as linear functions of the basic parameters to build the design matrix

LOR for death in treatments for MI

LOR for death in treatments for MI

$y_i = \mu^A \text{ t-PA} + \mu^B \text{ Anistreplase}_i + \mu^C \text{ Accelerated t-PA}_i + \mu^D \text{ Angioplasty}_i + \mu^E \text{ Reteplase}_i$

Use as ‘covariates’

No. studies	Streptokinase	t-PA	Anistreplase	Acc t-PA	Angioplasty	Reteplase
3	-1	1	0	0	0	0
1	-1	0	1	0	0	0
1	-1	0	0	1	0	0
3	-1	0	0	0	1	0
1	-1	0	0	0	0	1
1		-1	1	0	0	0
2		-1	0	0	1	0
2		0	0	-1	1	0
2		0	0	-1	0	1

Lumley 2002, Stat Med

LOR for death in treatments for MI

$y_i = \mu^A$ t-PA $+ \mu^B$ Anistreplase$_i$ $+ \mu^C$ Accelerated t-PA$_i$ $+ \mu^D$ Angioplasty$_i$ $+ \mu^E$ Reteplase$_i$

$$Y = \underbrace{(\mu^A, \mu^B, \mu^C, \mu^D, \mu^E)}_{\text{Vector of LogOR}} \times X + \Delta$$

Matrix of all observations

Vector of LogOR

Design matrix

Random effects matrix

$$Y \sim N(\boldsymbol{\mu} X, V) \qquad \Delta \sim N(\mathbf{0}, diag(\tau^2))$$

Variance-covariance matrix (for the observed LOR)

LOR compared to Streptokinase (RE model)

$$Y = (\boxed{\mu^A, \mu^B, \mu^C, \mu^D, \mu^E}) \times X + \Delta$$

Treatment	LOR(SE)
t-PA	–0.02 (0.03)
Anistreplase	–0.00 (0.03)
Accelerated t-PA	– 0.15 (0.05)
Angioplasty	– 0.43 (0.20)
Reteplase	– 0.11 (0.06)

What’s the problem with multi-arm trials?

- We need to take into account the correlations between the estimates that come from the same study
- A B C

y_i^{BC}

y_i^{AC}

- The random effects (θ_i^{BC}, θ_i^{AC}) that refer to the same trial are correlated as well
- You have to built in *the correlation matrix for the observed effects*, **and** *the correlation matrix for the random effects*

$$Y \sim N(\boldsymbol{\mu} X, \boxed{V})$$

$$\Delta \sim N(\mathbf{0}, \boxed{diag(\tau^2)})$$

Hypothetical example

Study	No. arms	#	Data	Contrast
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	T_3=2	1	$y_{3,1}$, $v_{3,1}$	BC
i=4	T_4=3	2	$y_{4,1}$, $v_{4,1}$ $y_{4,2}$, $v_{4,2}$ cov($y_{4,1}$, $y_{4,2}$)	AB AC

Basic parameters: AB and AC

Study	No. arms	#	Data	Contrast
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	T_3=2	1	$y_{3,1}$, $v_{3,1}$	BC
i=4	T_4=3	2	$y_{4,1}$, $v_{4,1}$ $y_{4,2}$, $v_{4,2}$ cov($y_{4,1}$, $y_{4,2}$)	AB AC

Meta-regression

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Study	No. arms	#	Data	Contrast
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	T_3=2	1	$y_{3,1}$, $v_{3,1}$	BC
i=4	T_4=3	2	$y_{4,1}$, $v_{4,1}$ $y_{4,2}$, $v_{4,2}$ cov($y_{4,1}$, $y_{4,2}$)	AB AC

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \boxed{\begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}}$$

Take into account correlation in observations

$$\begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} v_{1,1} & 0 & 0 & 0 & 0 \\ 0 & v_{2,1} & 0 & 0 & 0 \\ 0 & 0 & v_{3,1} & 0 & 0 \\ 0 & 0 & 0 & v_{4,1} & \operatorname{cov}(y_{4,1}, y_{4,2}) \\ 0 & 0 & 0 & \operatorname{cov}(y_{4,1}, y_{4,2}) & v_{4,2} \end{pmatrix} \right)$$

Study	No. arms	#	Data	Contrast
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	T_3=2	1	$y_{3,1}$, $v_{3,1}$	BC
i=4	T_4=3	2	$y_{4,1}$, $v_{4,1}$ $y_{4,2}$, $v_{4,2}$ cov($y_{4,1}$, $y_{4,2}$)	AB AC

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \boxed{\begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix}} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Take into account correlation in random effects

$$\begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_{AB}^2 & 0 & 0 & 0 & 0 \\ 0 & \tau_{AC}^2 & 0 & 0 & 0 \\ 0 & 0 & \tau_{BC}^2 & 0 & 0 \\ 0 & 0 & 0 & \tau_{AB}^2 & \operatorname{cov}\left(\beta_{4,1}, \beta_{4,2}\right) \\ 0 & 0 & 0 & \operatorname{cov}\left(\beta_{4,1}, \beta_{4,2}\right) & \tau_{AC}^2 \end{pmatrix} \right)$$

How to fit such a model?

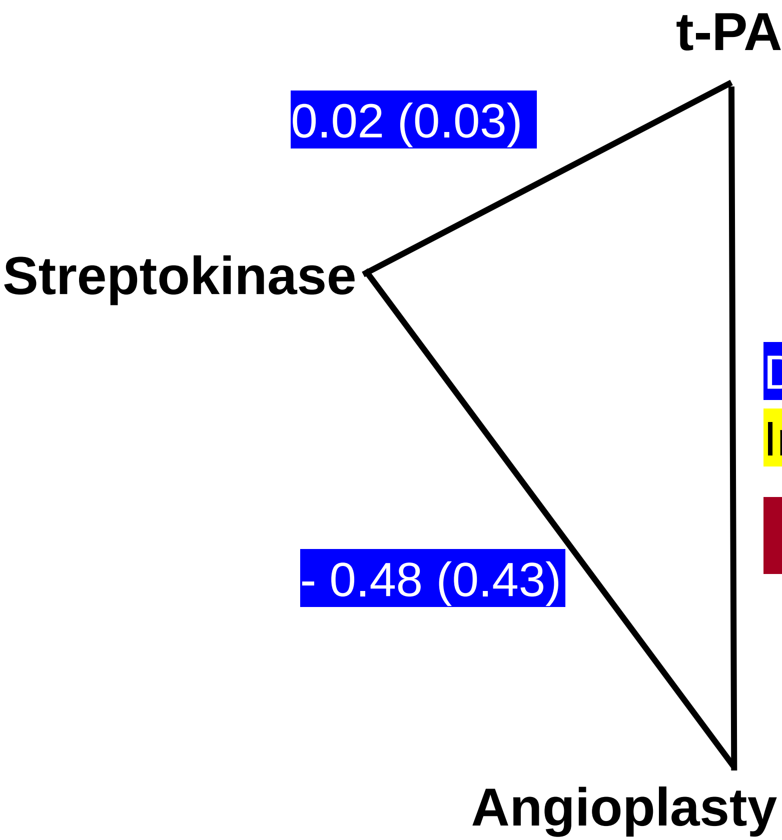
- MLwiN
- SAS, R
- STATA using metan

Review of statistical methodology in Salanti G, Higgins JP, Ades AE, Ioannidis JP. 2008. Evaluation of networks of randomized trials. Statistical Methods in Medical Research 17:279-301.

Inconsistency

LOR (SE) for MI

Calculate a difference between direct and indirect estimates



Direct t-PA vs Angioplasty= – 0.41 (0.36)

Indirect t-PA vs Angioplasty = – 0.46 (0.18)

Inconsistency Factor IF = 0.05

Inconsistency - Heterogeneity

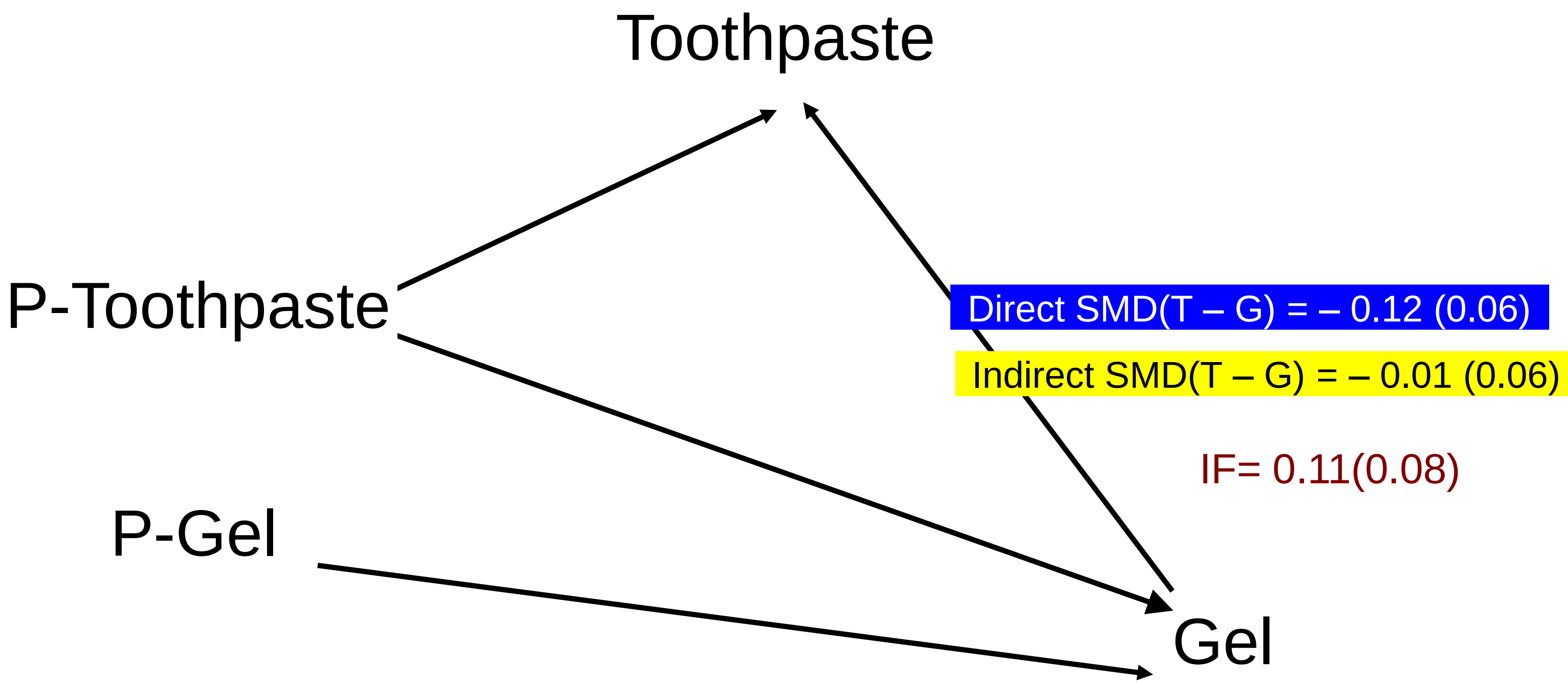
- *Heterogeneity:* ‘excessive’ discrepancy among study-specific effects
- *Inconsistency:* it is the excessive discrepancy among source-specific effects (direct and indirect)
- In 3 cases out of 44 there was an important discrepancy between direct/indirect effect.

Glenny et al ***HTA 2005***

What can cause inconsistency?

Inappropriate common comparator

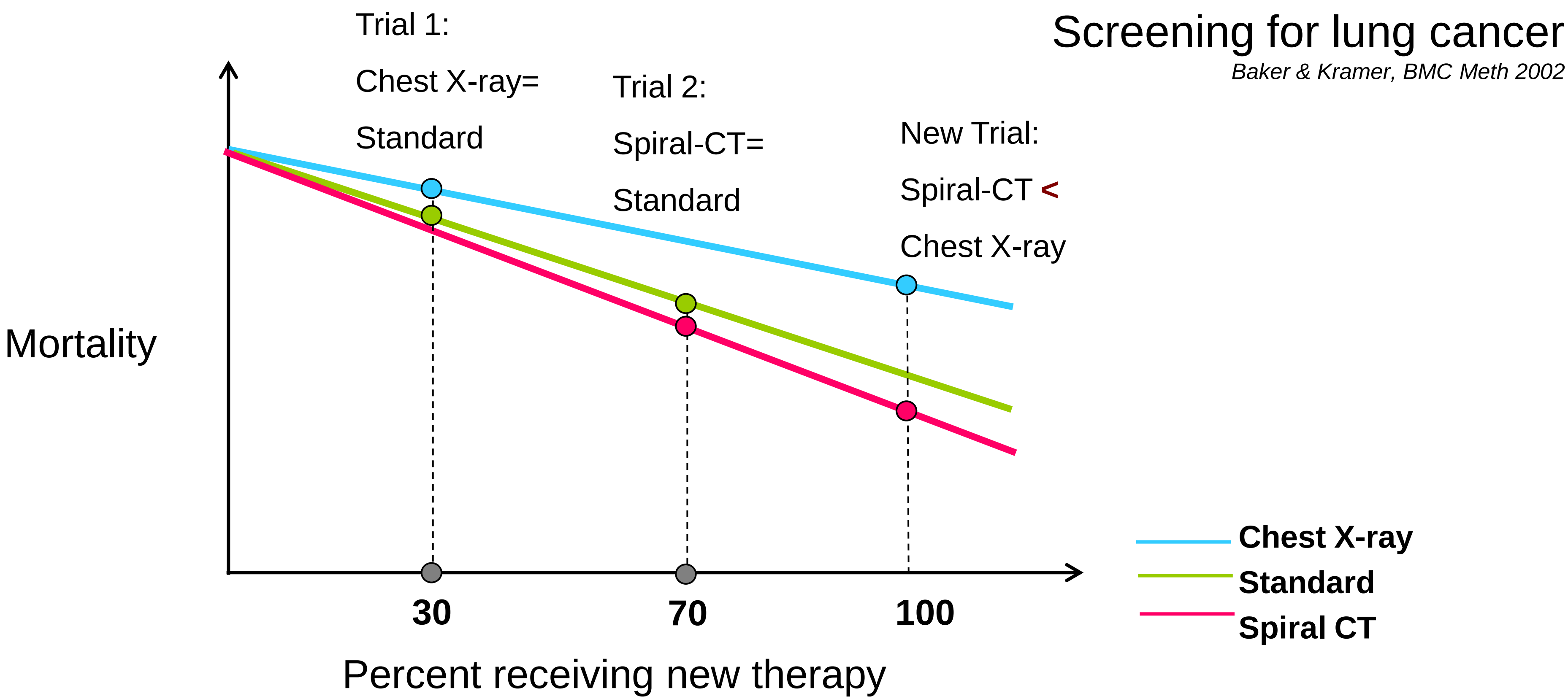
Compare Fluoride treatments in preventing dental caries



I cannot learn about Toothpaste versus Gel through Placebo!

What can cause inconsistency?

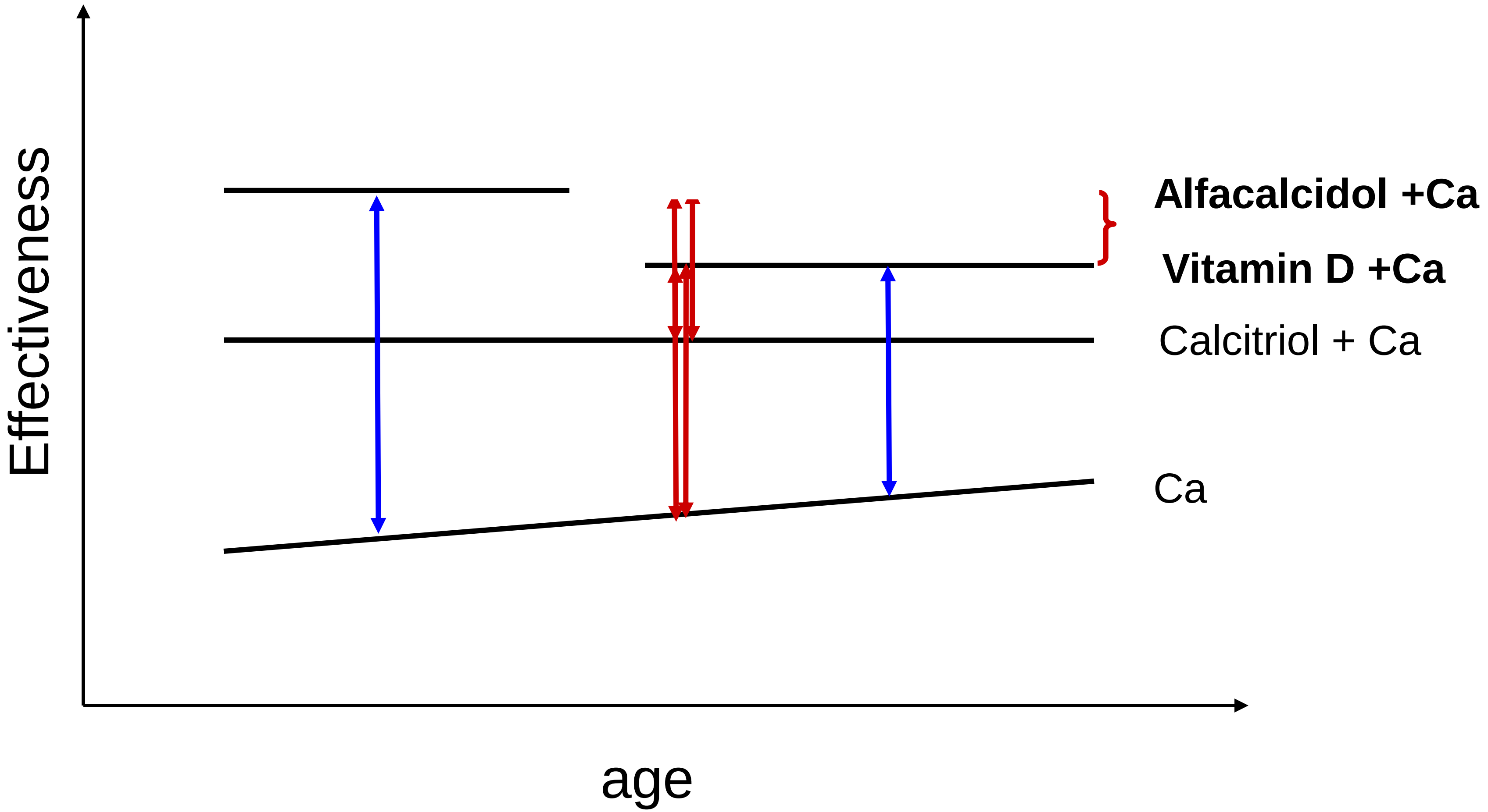
Confounding by trial characteristics



A new therapy (possibly unreported in the trials) decreases the mortality but in different rates for the three screening methods

What can cause inconsistency?

Confounding by trial characteristics



Different characteristics across comparisons may cause inconsistency

Assumptions of MTM

- There is **not confounding** by trial characteristics that are related to both the comparison being made and the magnitude of treatment difference
- The trials in two different comparisons are **exchangeable** (other than interventions being compared)
- Equivalent to the assumption ***'the unobserved treatment is missing at random'***
  - *Is this plausible?*
  - *Selection of the comparator is not often random!*

Inconsistency

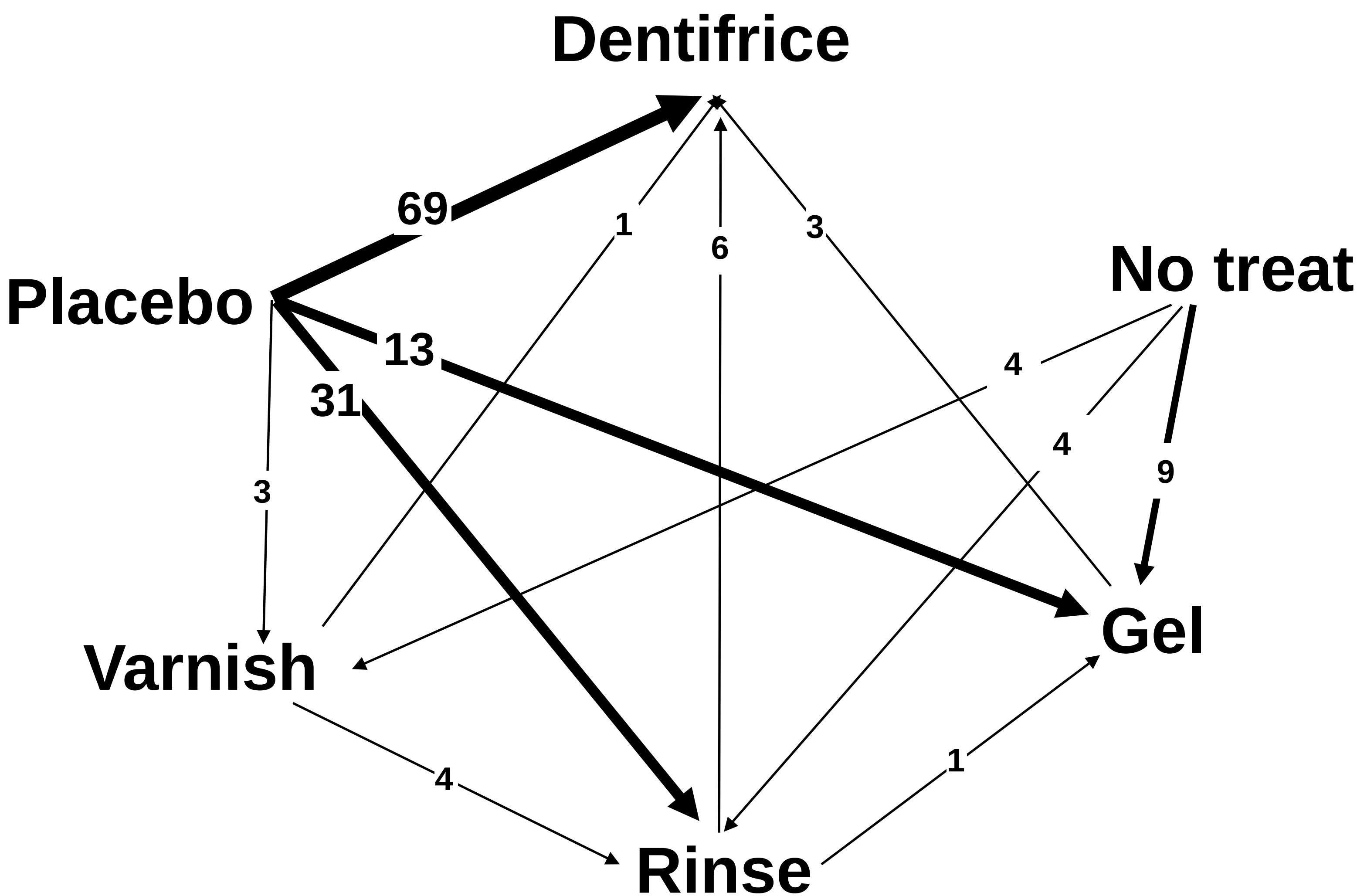
Detecting

- Check the distribution of important characteristics per treatment comparison
  - Usually unobserved….
  - Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM
- Get a taste by looking for inconsistency in closed loops
- Fit a model that relaxes consistency
  - Add an extra *‘random effect’ per loop (Lu & Ades JASA 2005*)

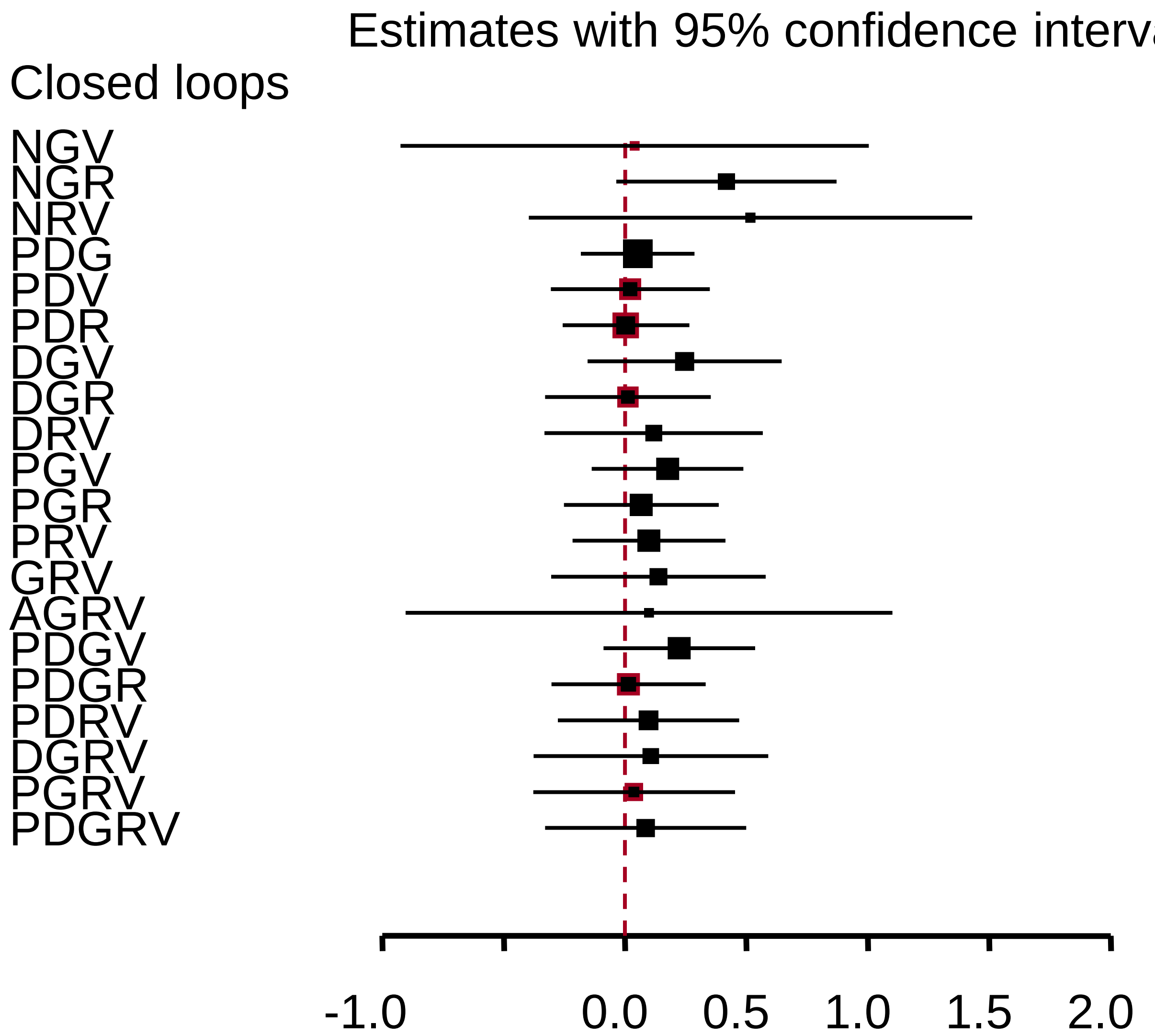
Compare the characteristics!

No. studies	T	G	R	V	P	Fup	Baseline	Year	Water F (yes/no)
69	■				■	2.6	11.8	1968	0.2
13		■			■	2.3	3.8	1973	0.2
30			■		■	2.4	5.9	1973	0.1
3				■	■	2.3	2.7	1983	0
3	■	■				2.7	NA	1968	0.66
6	■		■			2.8	14.7	1969	0
1	■			■		2	0.9	1978	0
1		■	■			1	NA	1977	0
1		■		■		3	7.4	1991	NA
4			■	■		2.5	7.6	1981	0.33

Salanti G, Marinho V, Higgins JP: **A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered.** *J Clin Epidemiol* 2009, **62:** 857-864.


Dentifrice
Placebo
No treat
Varnish
Gel
Rinse
69
13
31
3
1
6
3
4
4
9
4
1

Evaluation of concordance within closed loops



R routine in http://www.dhe.med.uoi.gr/software.htm

Salanti G, Marinho V, Higgins JP: **A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered.** *J Clin Epidemiol* 2009, **62:** 857-864.

More assumptions of MTM!

- *Appropriate modelling of data* (sampling distributions)
- *Normality* of true effects in a random-effects analysis
- *Comparability of studies*
  - exchangeability in all aspects other than particular treatment comparison being made
- *Equal heterogeneity variance in each comparison*
  - not strictly necessary

References

Caldwell DM, Ades AE, Higgins JP. 2005. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 331:897-900.
Caldwell DM, Gibb DM, Ades AE. 2007. Validity of indirect comparisons in meta-analysis. Lancet 369:270.
Caldwell DM, Welton NJ, Ades AE. 2010. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. J Clin Epidemiol.
Dias S, Welton N, Marinho V, Salanti G, Ades A. 2010. Estimation and adjustment of Bias in randomised evidence using Mixed Treatment Comparison Meta-analysis. Journal of the Royal Statistical Society (A) 173.
Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, Bradburn M, Eastwood AJ. 2005. Indirect comparisons of competing interventions. Health Technol Assess 9:1-iv
Salanti G, Higgins JP, Ades AE, Ioannidis JP. 2008. Evaluation of networks of randomized trials. Statistical Methods in Medical Research 17:279-301.
Salanti G, Marinho V, Higgins JP. 2009. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. Journal of Clinical Epidemiology 62:857-864.
Song F, Altman DG, Glenny AM, Deeks JJ. 2003. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 326:472.
Song F, Harvey I, Lilford R. 2008. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. Journal of Clinical Epidemiology 61:455-463.
Sutton A, Ades AE, Cooper N, Abrams K. 2008. Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics 26:753-767.