School of Medicine

ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

Comparing multiple treatments 2: statistical methods for network meta-analysis

Georgia Salanti

University of Ioannina Medical School
Department of Hygiene and Epidemiology
Greece

Julian Higgins

MRC Biostatistics Unit, Cambridge, UK
Centre for Reviews and Dissemination, University of York, UK

Acknowledgements: Dimitris Mavridis, Andrea Cipriani, Jo McKenzie and many clinicians

Health Technology Assessment 2010; Vol. 14: No. 28

The safety and effectiveness of different methods of earwax removal: a systematic review and economic evaluation

AJ Clegg, E Loveman, E Gospodarevskaya,
P Harris, A Bird, J Bryant, DA Scott,
P Davidson, P Little and R Coppin

Results: Twenty-six clinical trials conducted in primary care (14 studies), secondary care (8 studies) or other care settings (4 studies), met the inclusion criteria for the review – 22 RCTs and 4 CCTs. The range of interventions included 16 different softeners, with or without irrigation, and in various different comparisons. Participants, outcomes, timing of intervention, follow-up and methodological quality varied between studies. On measures of wax clearance Cerumol, sodium bicarbonate, olive oil and water are all more effective than no treatment; triethanolamine polypeptide (TP) is better than olive oil; wet irrigation is better than dry irrigation; sodium bicarbonate drops followed by irrigation by nurse is more effective than sodium bicarbonate drops followed by self-irrigation; softening with TP and self-irrigation is more effective than self-irrigation only; and endoscopic de-waxing is better than microscopic de-waxing. AEs appeared to be minor and of limited extent. Resuts of the

4 Fluoride modalities for preventing dental carries: series of pairwise meta-analyses

Treatment comparison		Studies
Placebo	Toothpaste	69
	Gel	13
	Rinse	31
	Varnish	3
Toothpaste	Rinse	6
Toothpaste	Varnish	1
Gel	Rinse	1
Gel	Varnish	*?*

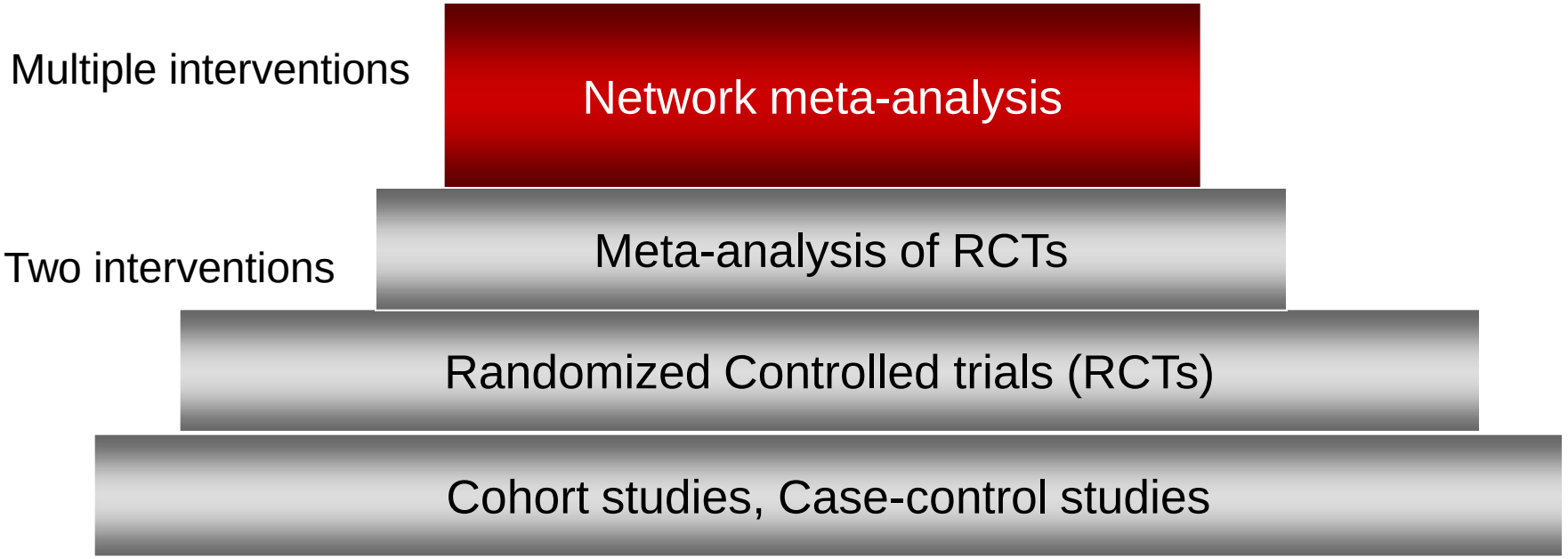
Multiple treatments and series of meta-analyses

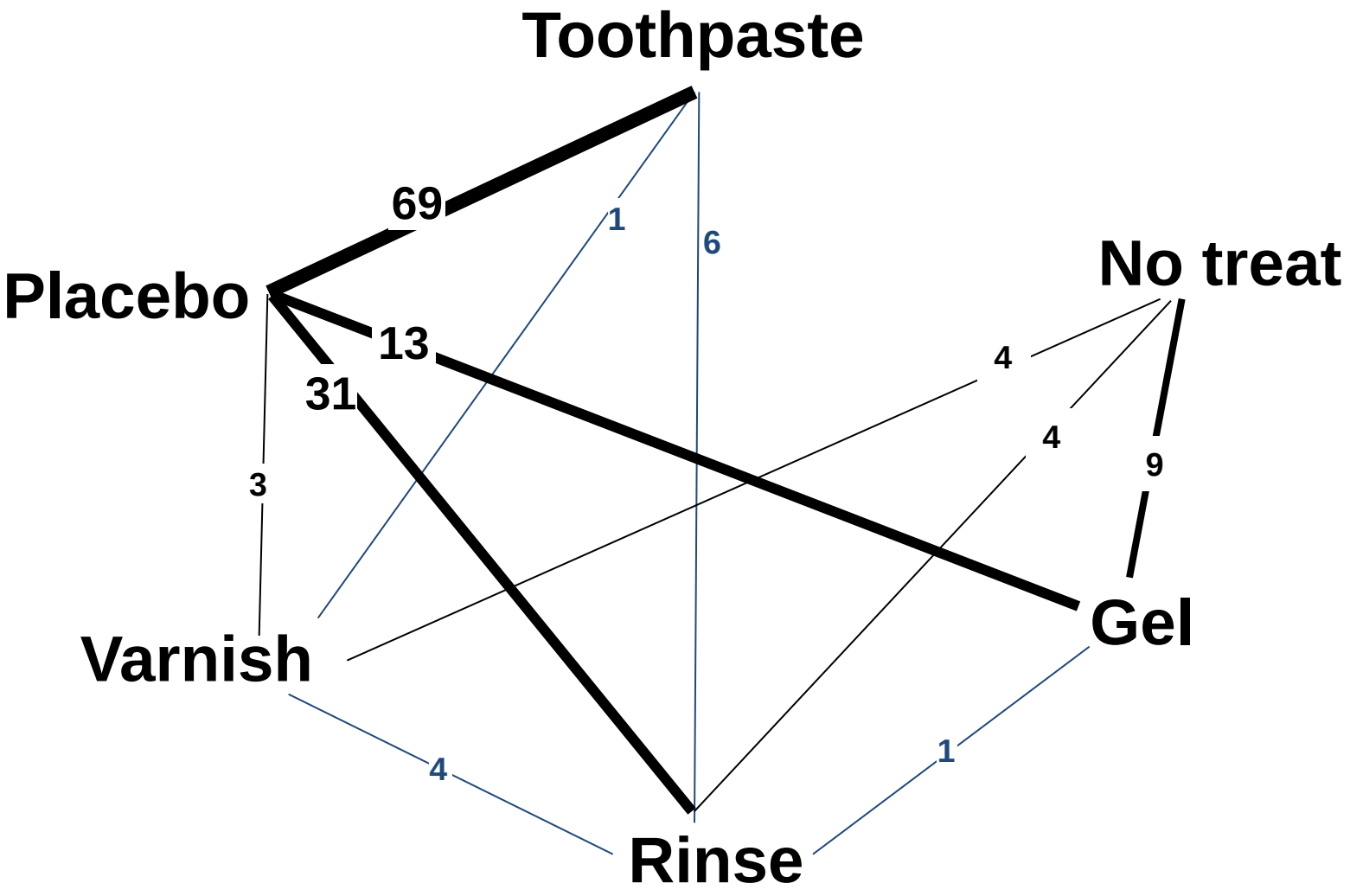
With pairwise meta-analyses we cannot answer the following questions:

- Which fluoride modality is the best?
- What is the ranking of fluoride treatments according to effectiveness?
- Which is better: Gel or Varnish (0 studies)

A new methodological framework

Other names:
Multiple treatments meta-analysis,
Mixed treatment comparisons




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

Aims of the workshop

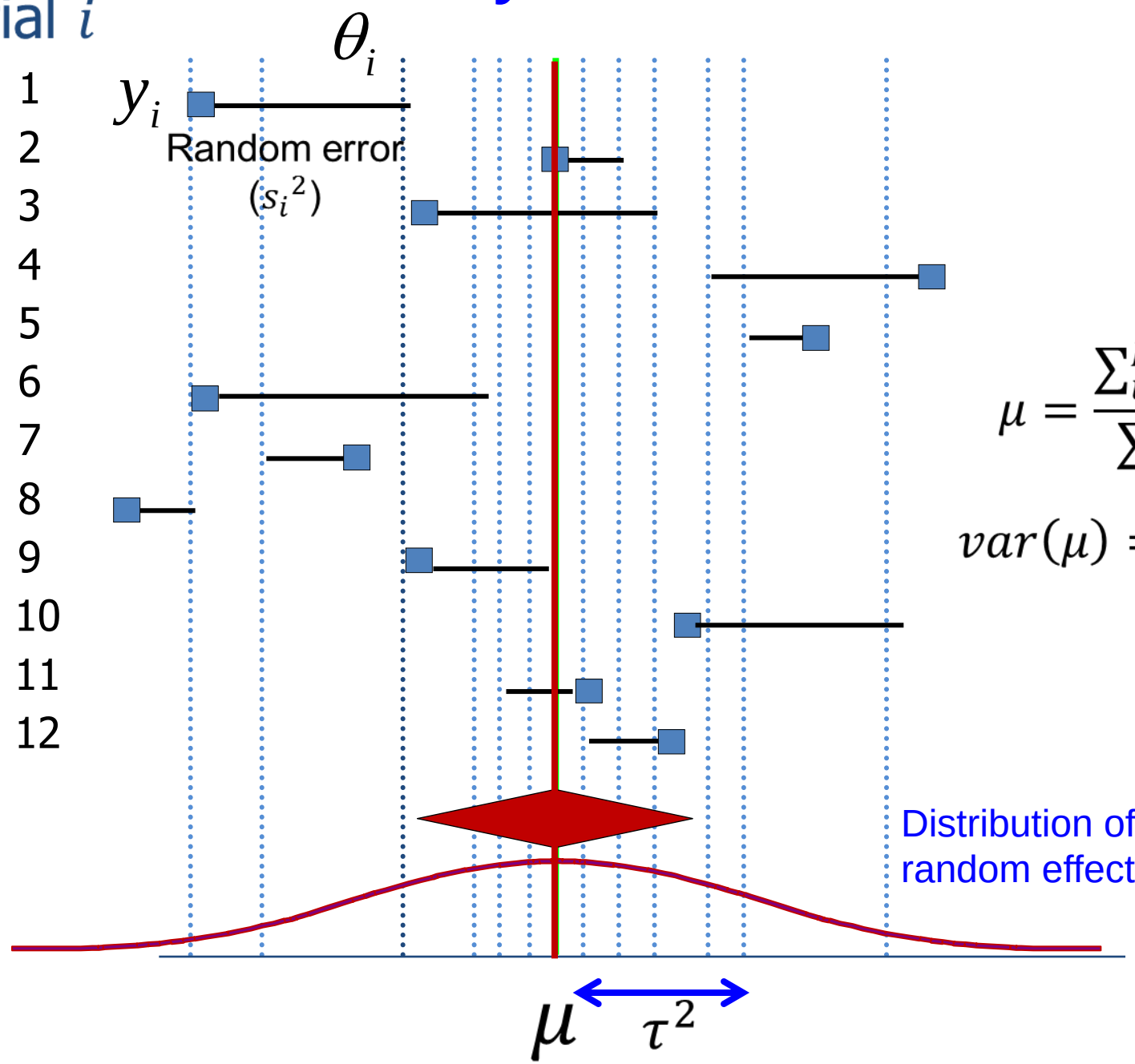
- To explain **indirect** and **mixed** comparison of interventions
  - Assumptions
  - Statistical methods
- To understand the statistical models for **network meta-analysis**
- To discuss presentation of results from network meta-analysis
- To understand inconsistency models

Pairwise meta-analysis

Treatment Comparison		Studies
Placebo	Toothpaste	69

Outcome: Mean difference y_i with variance ${s_i}^2$

Meta-analysis: Random effects



$$\mu = \frac{\sum_{i=1}^{N} y_i w_i}{\sum_{i=1}^{N} w_i}$$

$$var(\mu) = \frac{1}{\sum_{i=1}^{N} w_i}$$

Meta-analysis as a linear model

without covariates and with heteroscedasticity

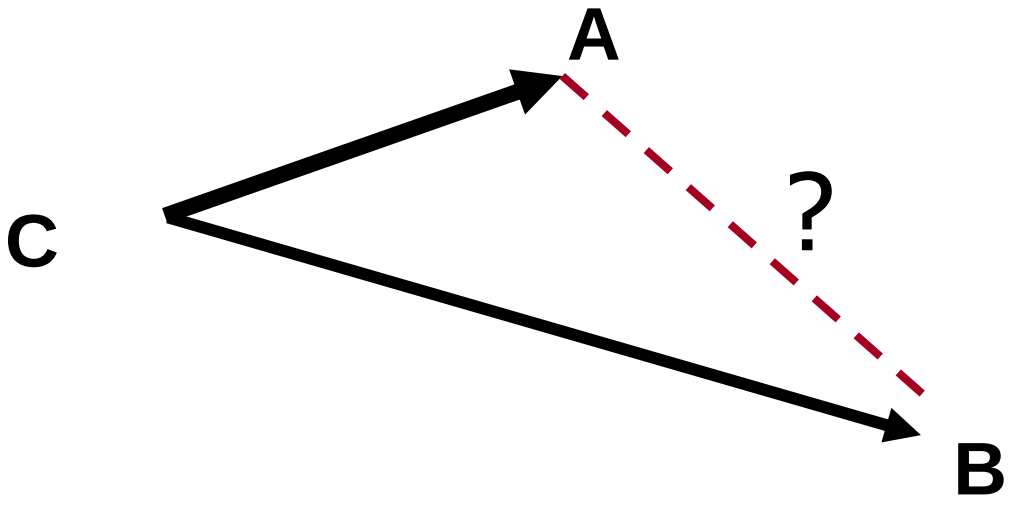
- $y_i = \mu + \delta_i + \varepsilon_i$
- $\varepsilon_i \sim N(0, s_i^2)$ Within study variance
- $\delta_i \sim N(0, \tau^2)$ Between studies variance

As a hierarchical model

- $y_i \sim N(\theta_i, s_i^2)$
- $\theta_i \sim N(\mu, \tau^2)$

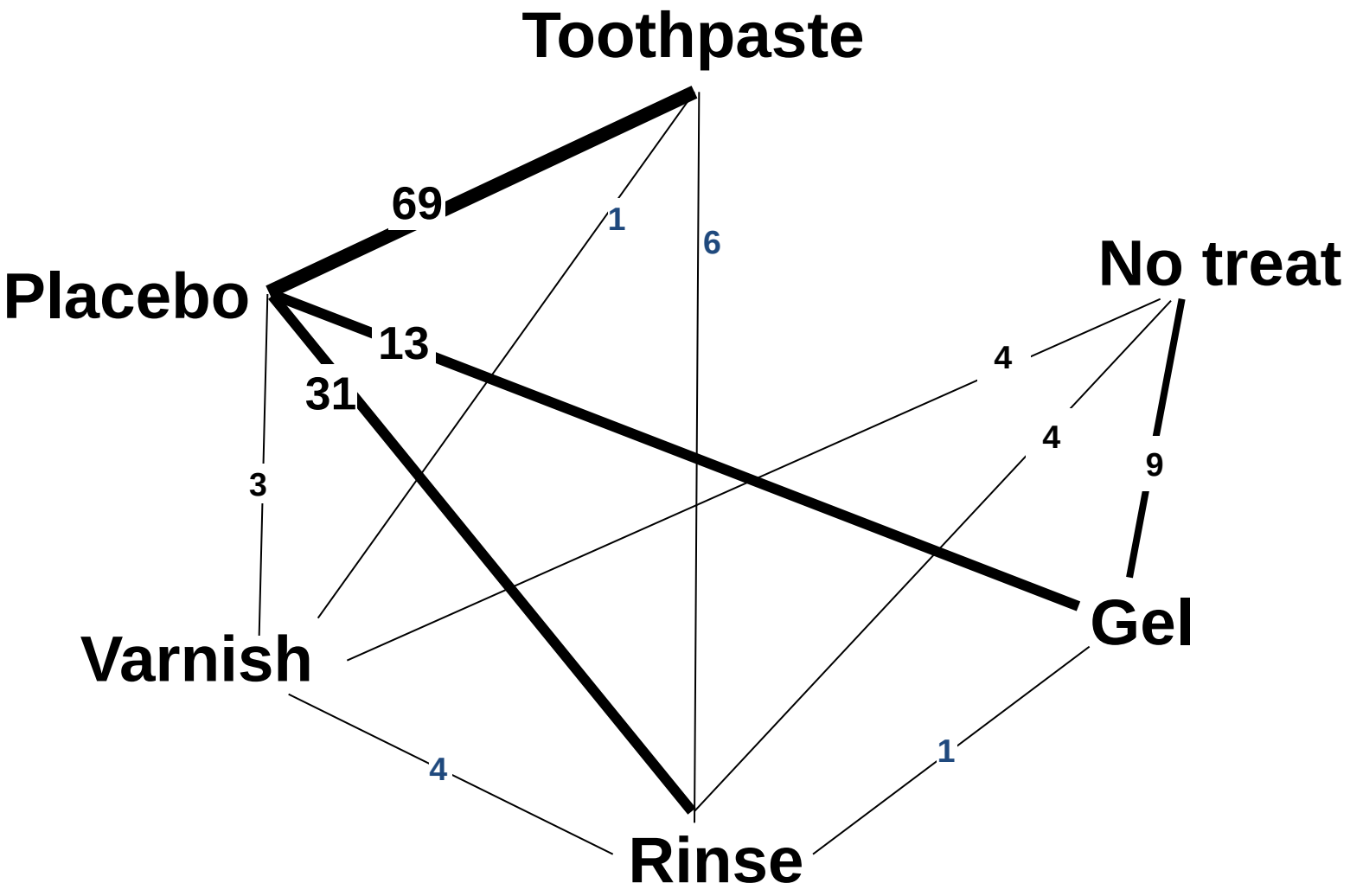
Indirect comparison

- We can obtain an *indirect* estimate for A vs B from RCTs comparing A vs C and B vs C:

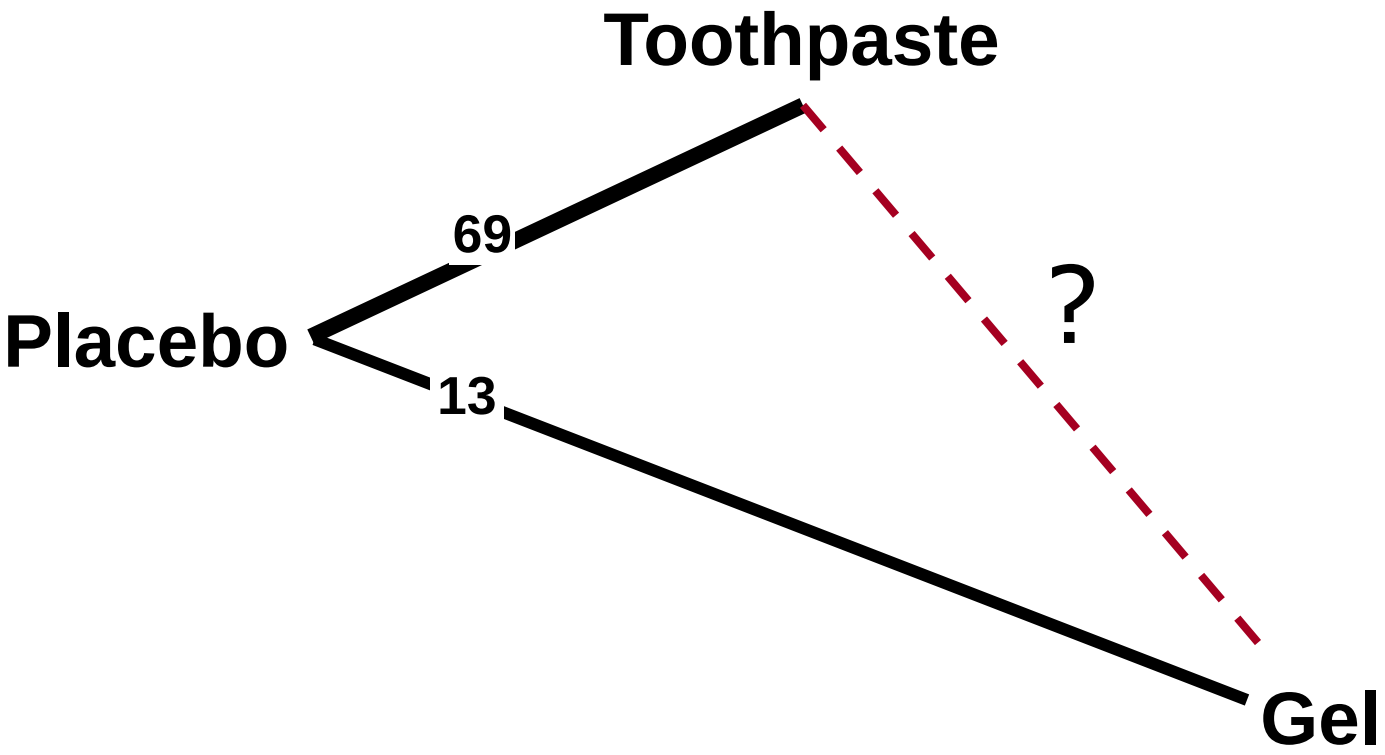


$$SMD_{AB} = SMD_{AC} - SMD_{BC}$$

$$Var(SMD_{AB}) = Var(SMD_{AC}) + Var(SMD_{BC})$$


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

Example



Comparison	MD	CIs
Placebo vs Toothpaste	-0.34	(-0.41, -0.28)
Placebo vs Gel	-0.19	(-0.30, -0.10)

How to compare Gel to Toothpaste?

Estimate indirect MD and a 95% CI

Exercise

Indirect MD_{GvsT} = $MD_{PvsT} - MD_{PvsG}$

Indirect MD_{GvsT} = –0.34 – (–0.19)= –0.15

Variance Indirect MD_{GvsT} = Variance MD_{PvsT} + Variance MD_{PvsG}

Variance MD_{PvsT} = ((high CI – low CI)/3.92)^2

Variance MD_{PvsT}= ((–0.28 – (–0.41))/3.92)^2 = 0.0011

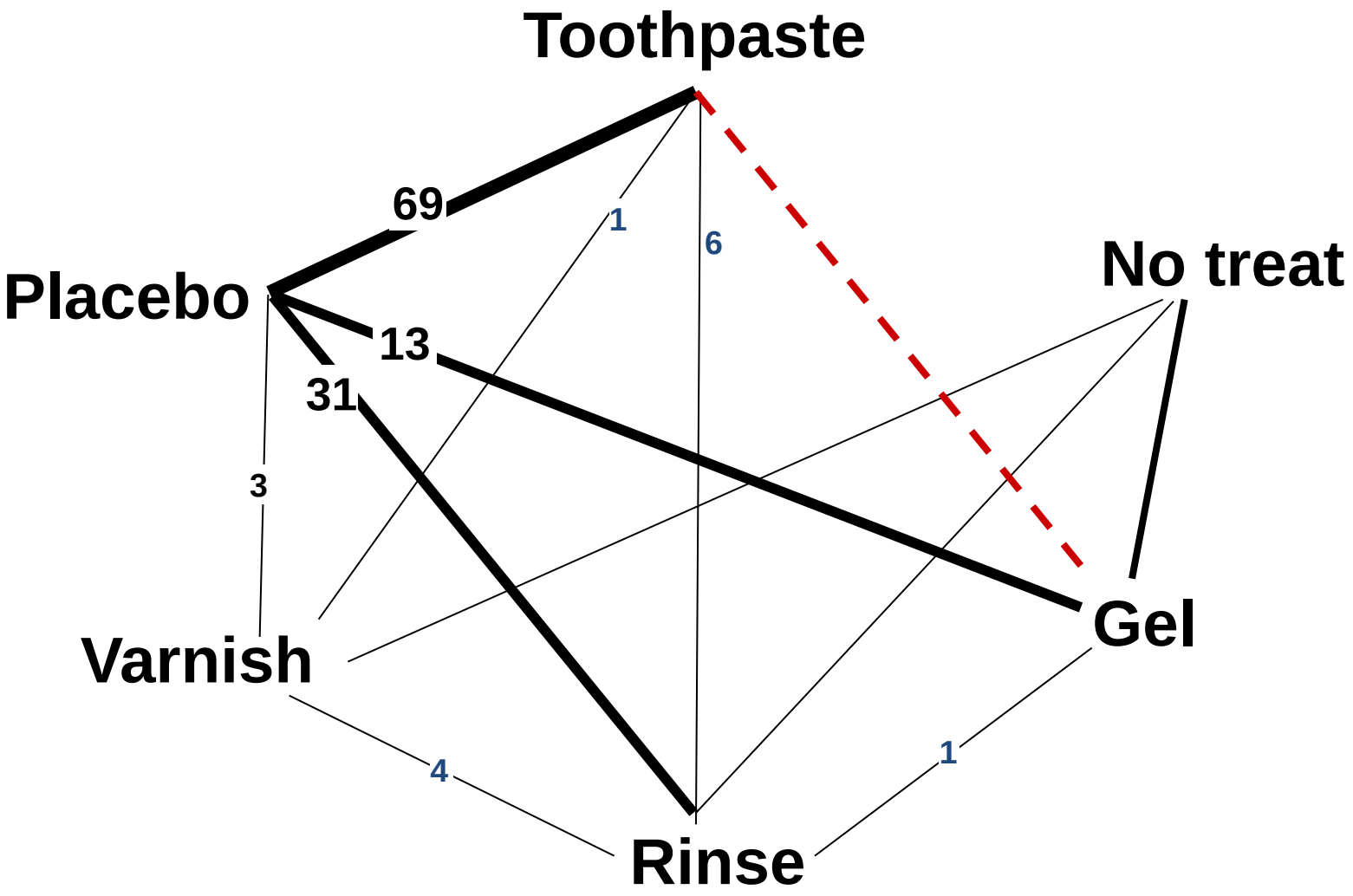
Variance MD_{GvsT}= ((–0.10 – (–0.30))/3.92)^2 = 0.0026

Variance Indirect MD_{GvsT} = 0.0011 + 0.0026 = 0.0037

SE Indirect MD_{GvsT} = sqrt(0.0037) = 0.061

95% CI for Indirect MD_{GvsT} = (–0.15 – 1.96×0.061, -0.15 + 1.96×0.061)

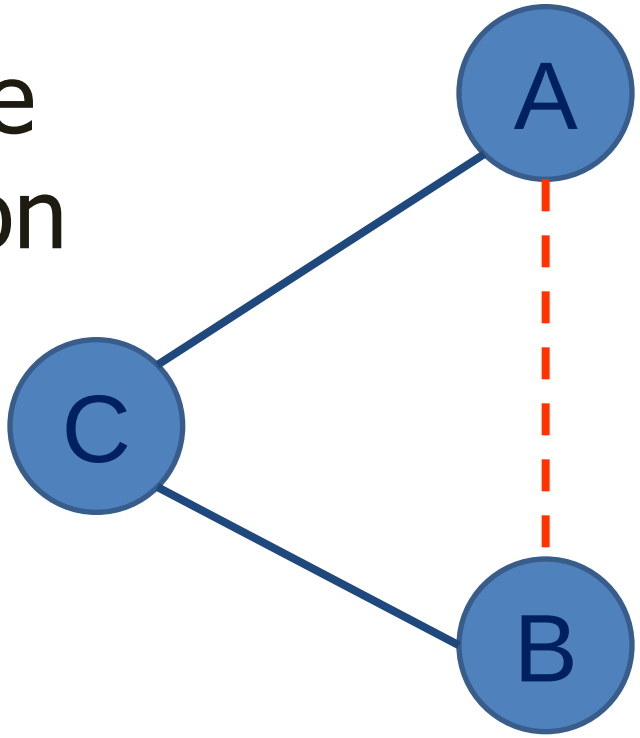
95% CI for Indirect MD_{GvsT} = (–0.27, –0.03)



Indirect SMD Gel vs Toothpaste: -0.15 (0.0037)

Transitivity

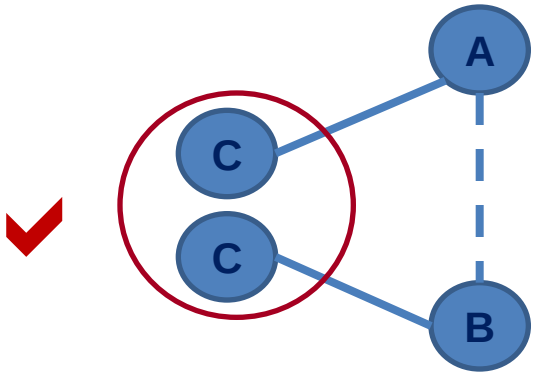
Untestable assumption

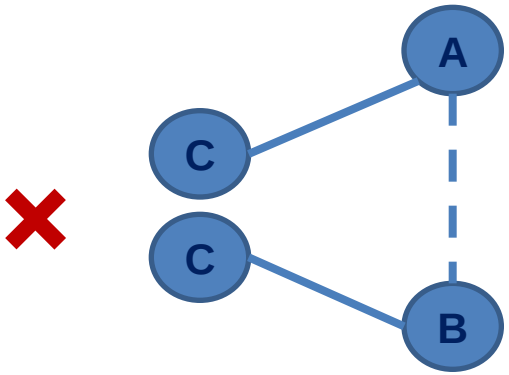


The anchor treatment C is 'transitive'

....but you can evaluate clinically and epidemiologically its plausibility

Transitivity means that…

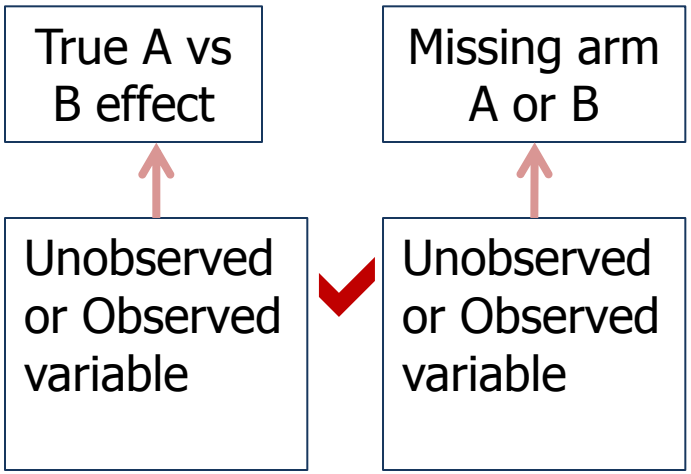


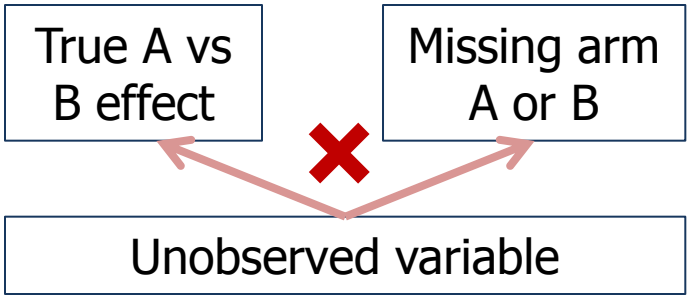


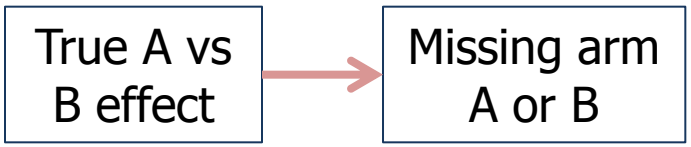
Treatment C is similar when it appears in A vs C and B vs C trials

Plausible when C is placebo vs an intrarticular or a per os treatment?

Transitivity means that…



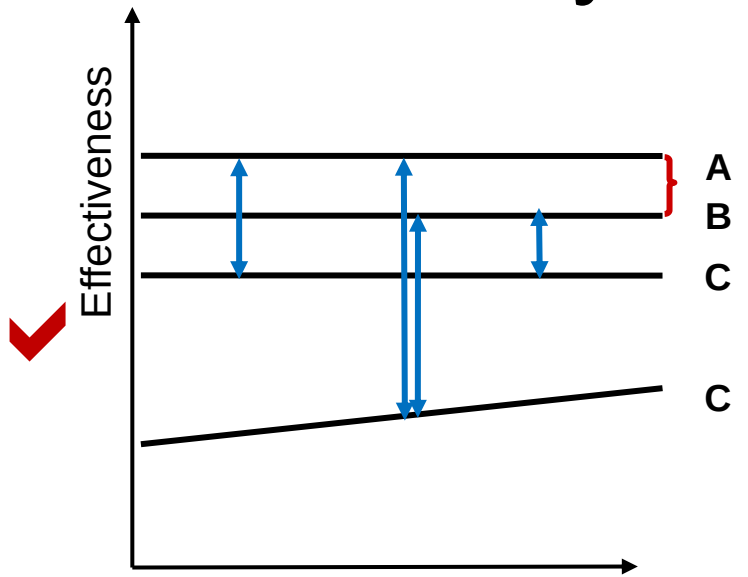




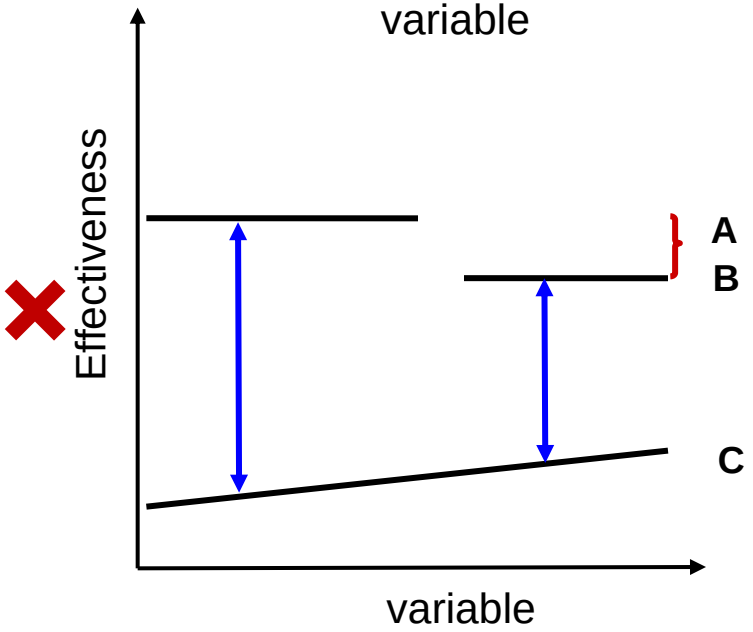
The 'missing' treatment in each trial (e.g. treatment A in B vs C trials) is missing at random

The choice of comparator is often chosen to make the active treatment 'look effective'

Transitivity means that…

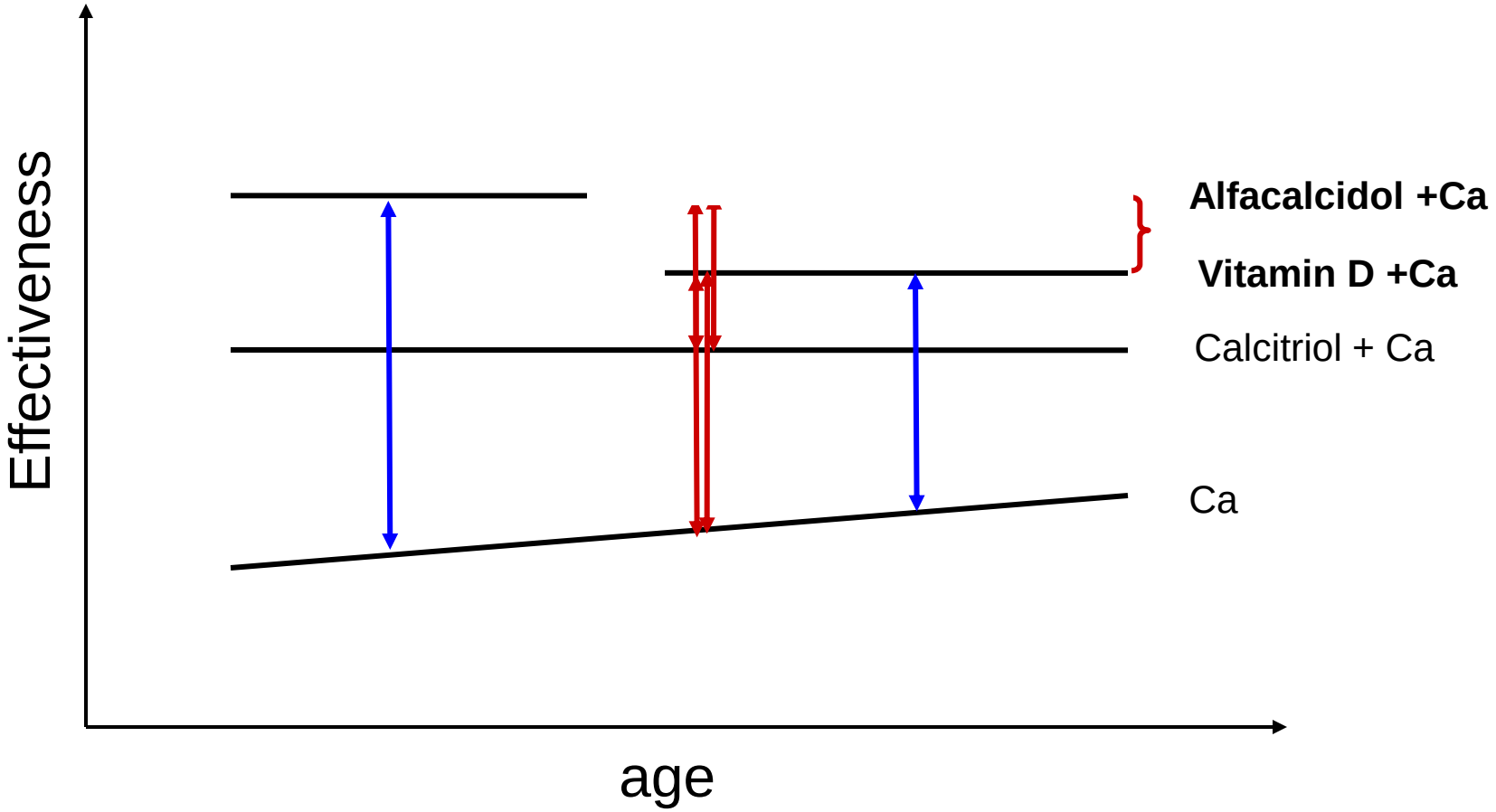


AC and BC trials do not differ with respect to the distribution of effect modifiers



Difficult to defend when you have older and newer treatments, and variables are often unobserved

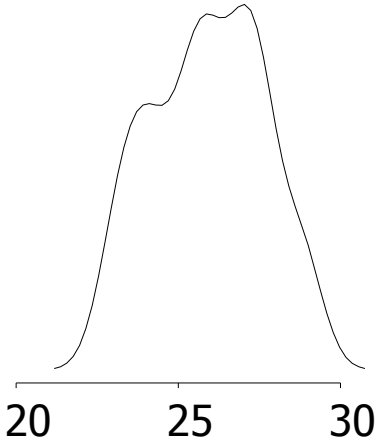
Confounding by trial characteristics



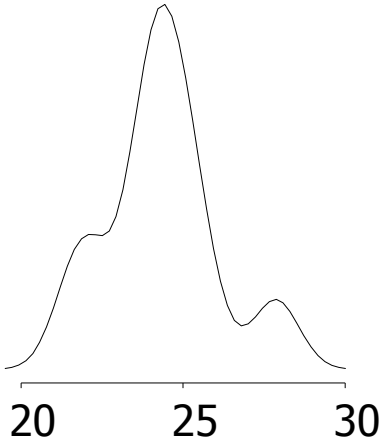
Calcif Tissue 2005 *Richy et al*

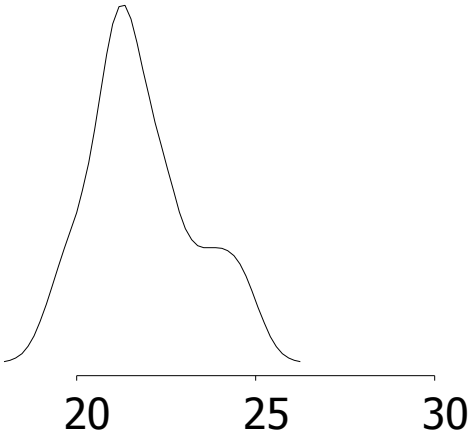
Distribution of mean dose of the active intervention in ten studies

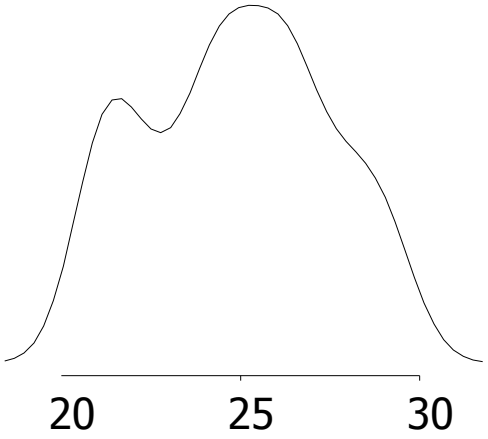
Placebo vs A

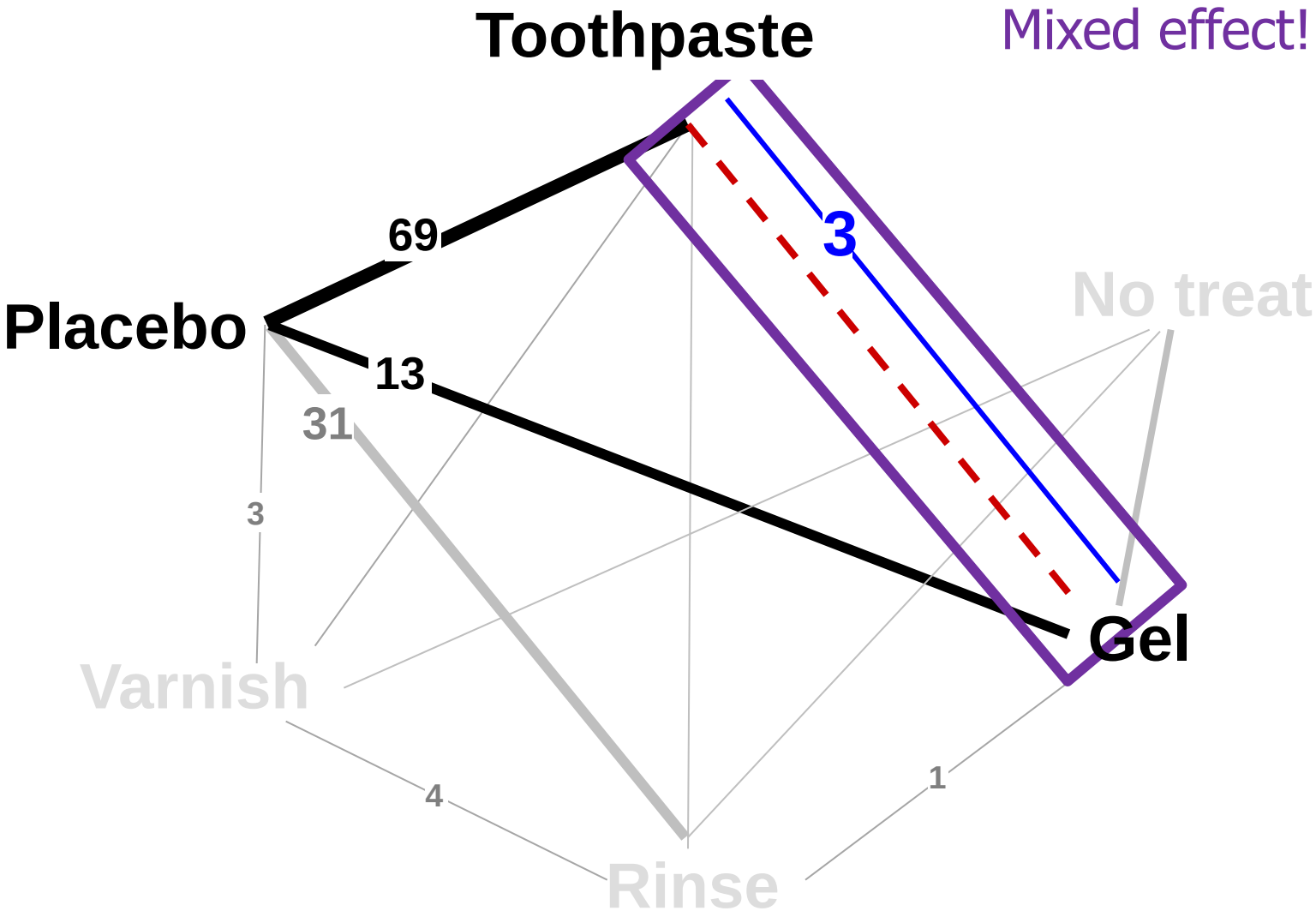


Placebo vs B









Indirect SMD Gel vs Toothpaste: -0.15 (0.0037)

Mixed comparison

- Summarize direct and indirect effect size into a single mixed effect

$$\text{Mixed SMD} = \frac{\frac{\text{SMD}_{\text{Direct}}}{\text{var}(\text{SMD}_{\text{Direct}})} + \frac{\text{SMD}_{\text{Indirect}}}{\text{var}(\text{SMD}_{\text{Indirect}})}}{\frac{1}{\text{var}(\text{SMD}_{\text{Direct}})} + \frac{1}{\text{var}(\text{SMD}_{\text{Indirect}})}}$$

$$\text{var}(\text{Mixed SMD}) = \frac{1}{\frac{1}{\text{var}(\text{SMD}_{\text{Direct}})} + \frac{1}{\text{var}(\text{SMD}_{\text{Indirect}})}}$$

Mixed comparison

Indirect SMD_{GvsT} = - 0.15

Var(Indirect SMD_{GvsT})= 0.004

Direct SMD_{GvsT} = 0.04

Var(Direct SMD_{GvsT} = 0.011

Mixed SMD_{GvsT} = -0.10

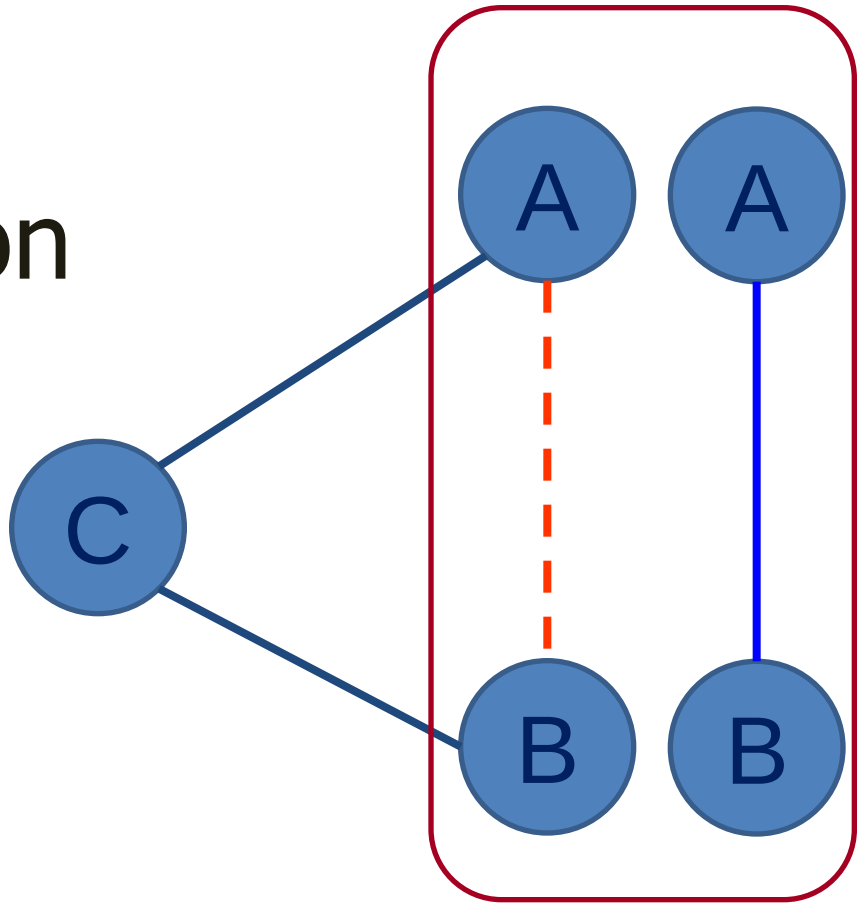
Var(Direct SMD_{GvsT} = 0.003

We gain precision!

You can do this with any measure... lnOR, lnRR, RD, mean difference, HR, Peto's lnOR etc…

Consistency

Testable assumption



Direct and indirect evidence are in agreement

If all three A, B and C are transitive then the loop is consistent

How much inconsistency?

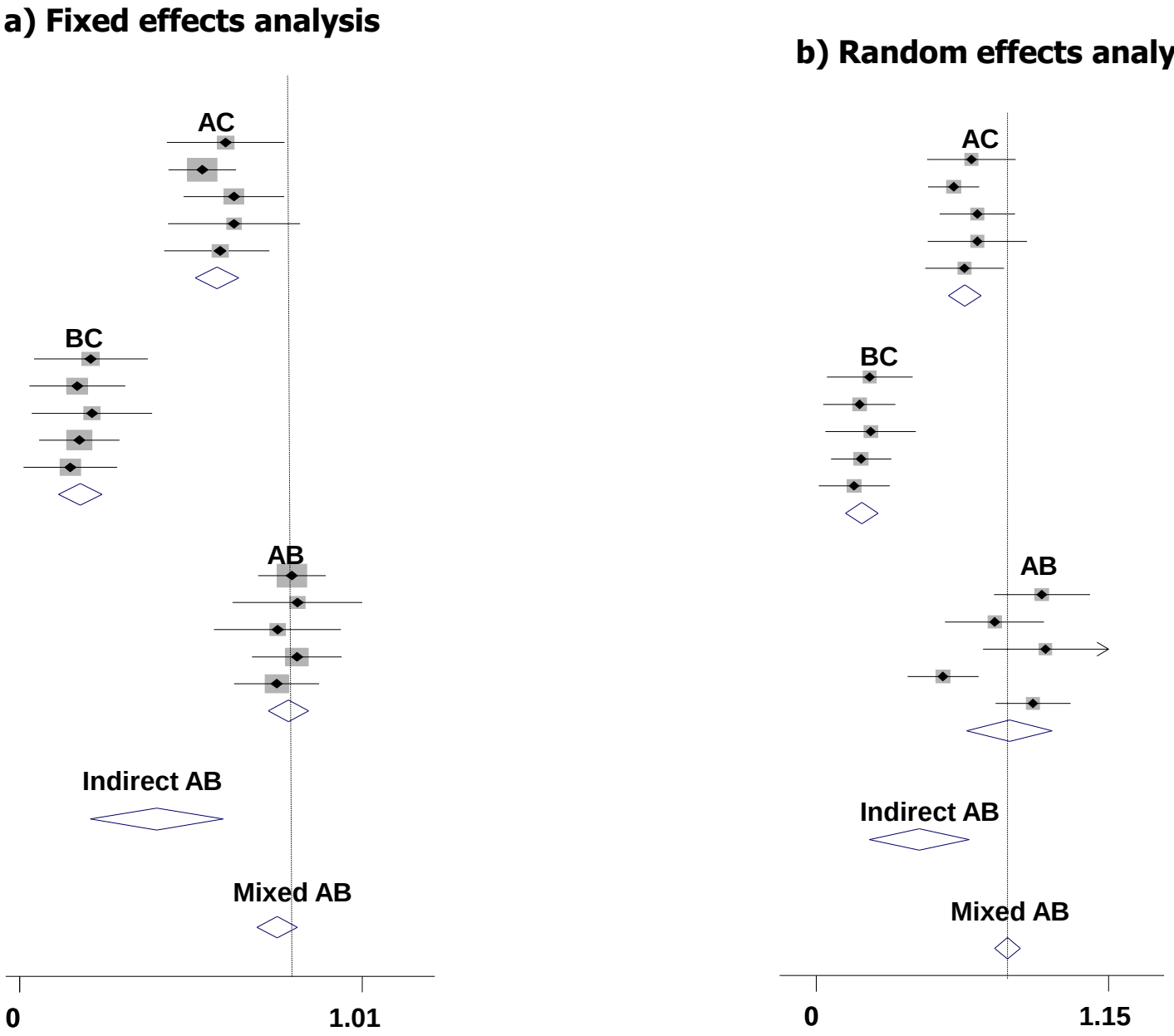
Indirect SMD_{GvsT} = - 0.15 (-0.27, -0.26)

Direct SMD_{GvsT} = 0.04 (-0.17, 0.25)

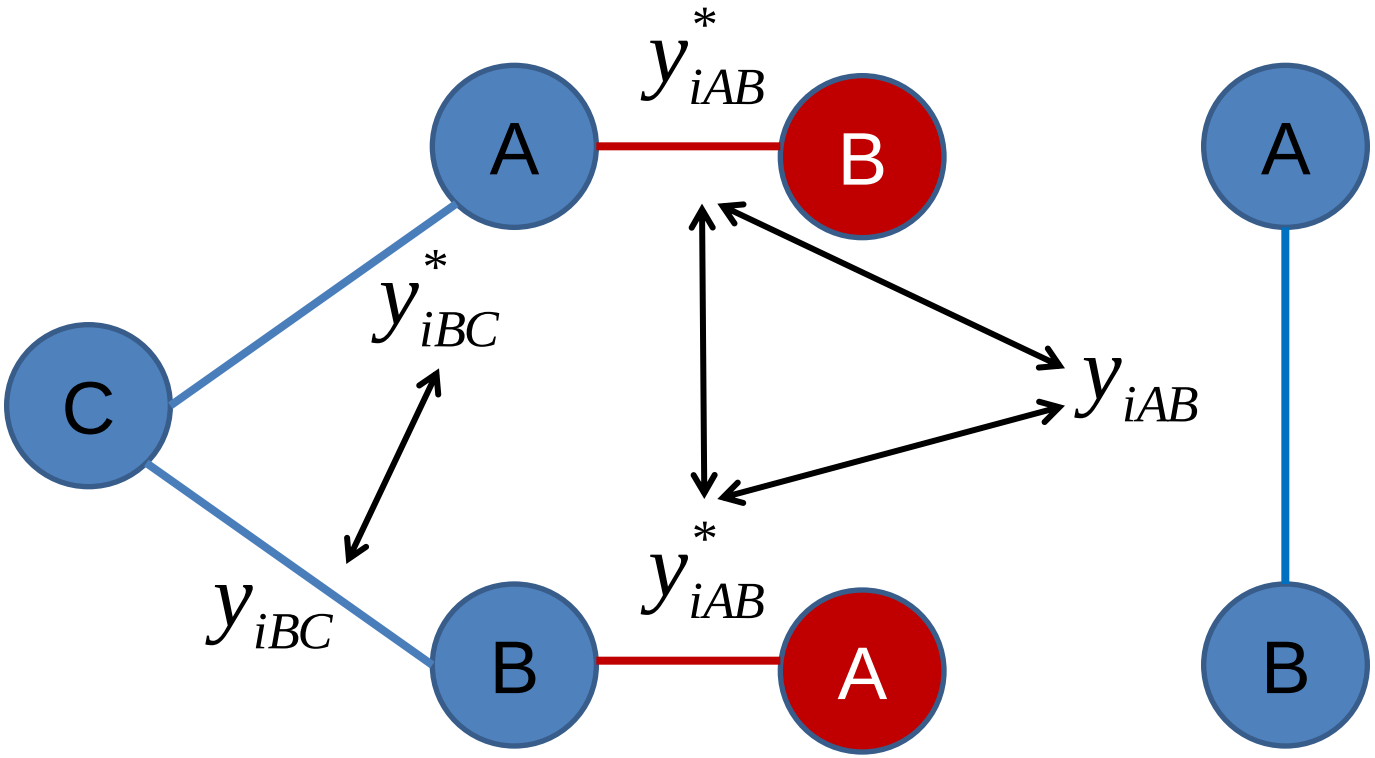
Inconsistency factor = 0.19 (-0.05, 0.43)

Is it important?

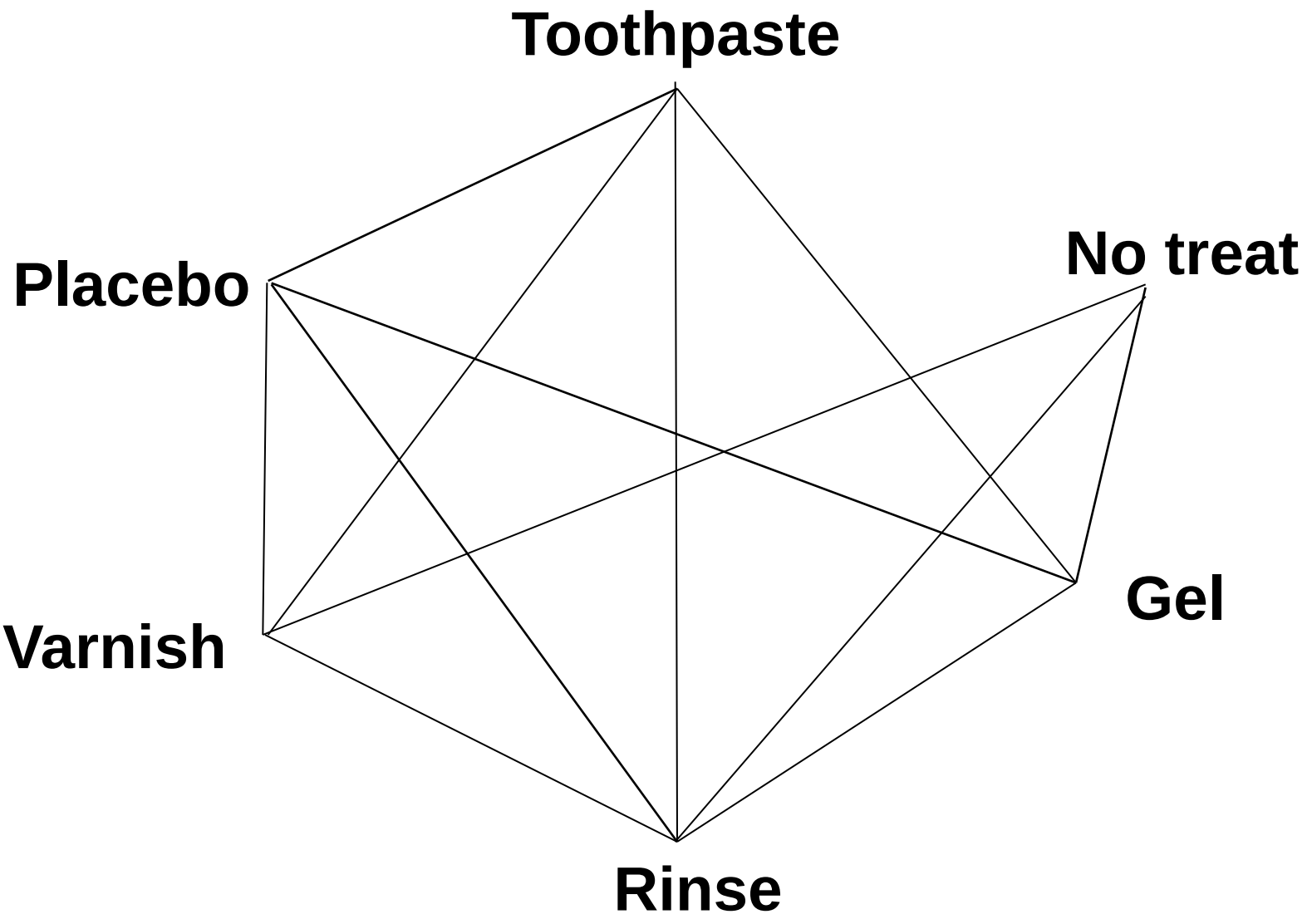
Consistency and heterogeneity



Heterogeneity, transitivity, consistency and exchangeability



Observed and unobserved estimates do not differ beyond what can be explained by heterogeneity



Extend the idea of mixed effect sizes in the entire network

Practical exercise

- Rank the interventions for workshop sleepiness, based on point estimates of effect, using indirect comparisons

Trial	Intervention 1	Sleepy score	Intervention 2	Sleepy score
Salanti 2005	Espresso coffee	9	Instant coffee	12
Higgins 1999	Espresso coffee	8	Breakfast tea	10
Clarke 1995	Earl Grey tea	14	Breakfast tea	9
Deeks 1998	Instant coffee	20	Hot chocolate	23
Schmid 2012	Cola	8	Lemonade	12
Kirkham 2010	Espresso coffee	5	Hot chocolate	10

Cook your own network meta-analysis

- Meta-analysis is a weighted regression with no covariates
- MTM is a weighted regression with dummy variables for the treatments
- So, you can fit it in standard software

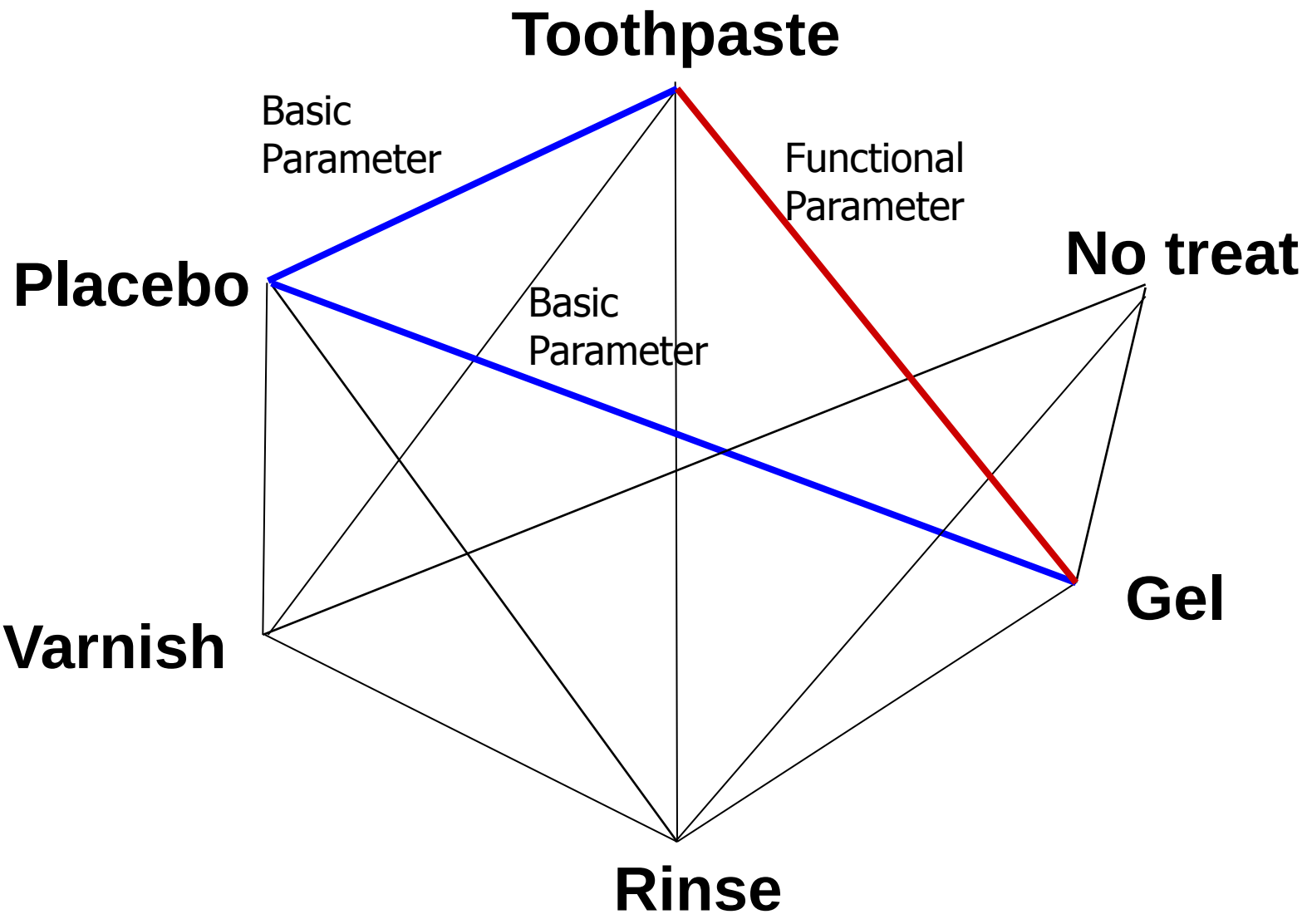
Network and meta-regression

- Meta-regression using the treatments as ‘covariates’ and without intercept
- With 3 treatments and AC, AB, BC studies, chose C as *reference,* so *AC and BC are basic parameters*

$$y_i = \beta_1 V_{i1} + \beta_1 V_{i2} + \delta_\iota + \varepsilon_\iota$$

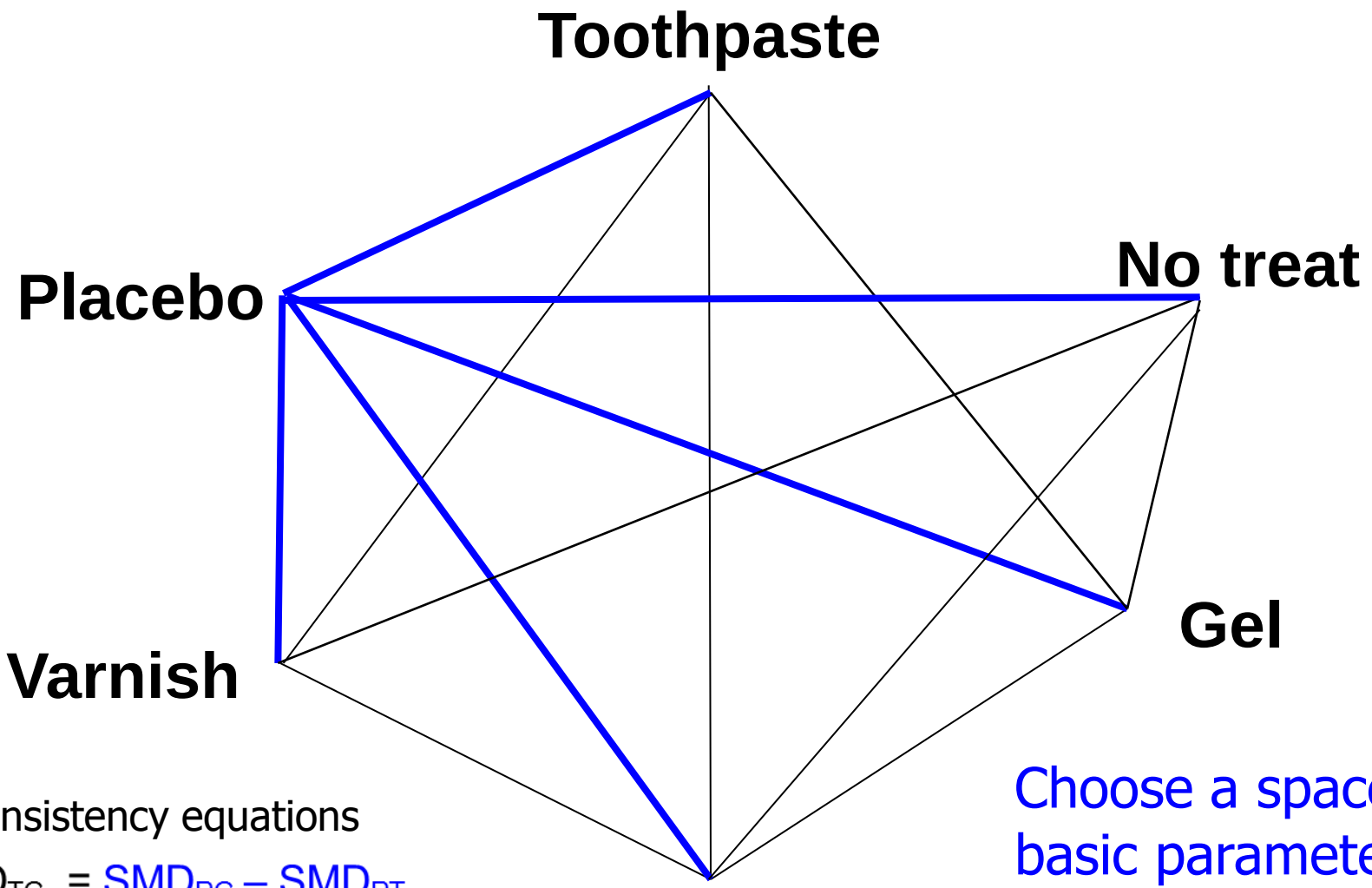
$$y_i = \mu_{AC} \mathrm{I}_{iAC} + \mu_{BC} \mathrm{I}_{iBC} + \delta_\iota + \varepsilon_\iota$$

- The AC studies have (1,0), the BC studies (0,1) [*basic*]
- AB studies have (1,-1) [*functional*] because *AB=AC-BC*



$$SMD_{TG} = SMD_{PG} - SMD_{PT}$$

Consistency equation



Consistency equations

$SMD_{TG} = SMD_{PG} - SMD_{PT}$
$SMD_{TR} = SMD_{PR} - SMD_{PT}$
$SMD_{TV} = SMD_{PV} - SMD_{PT}$
$SMD_{RG} = SMD_{PG} - SMD_{PR}$

⋮

Choose a space of basic parameters

How many basic parameters?

$$y_i = \mu^{PT} T_i + \mu^{PG} G_i + \mu^{PR} R_i + \mu^{PV} V_i + \mu^{PN} N_i$$

Use as ‘covariates’

No. studies	Placebo	Toothpaste	Gel	Rinse	Varnish	NoTreatment
69	-1	1		0	0	0
13	-1	0	1	0	0	0
31	-1	0	0	1	0	0
3	-1	0	0	0	1	0
4	0	0	0	-1	0	1
4	0	0	0	0	-1	1
9	0	0	-1	0	0	1
4	0	0	0	-1	1	0
6	0	-1	0	1	0	0

Network meta-analysis as meta-regression

- **We build the consistency equations into the design matrix**
- This minimizes the number of parameters and allows us to gain precision
- If we don’t, then it is a simple subgroup meta-analysis

$$y_i = \mu^{PT} T_i + \mu^{PG} G_i + \mu^{PR} R_i + \mu^{PV} V_i + \mu^{PN} N_i$$

$$\boldsymbol{y} = (\underbrace{\mu^{PT}, \mu^{PG}, \mu^{PR}, \mu^{PV}, \mu^{PN}}) \times X + \boldsymbol{\delta}$$

Matrix of all observations

Vector of summary effects

Design matrix

Random effects matrix

$$\mathbf{y} \sim N(\boldsymbol{\mu} X, diag(v_i))$$

Variances matrix (for the observed SMD)

$$\boldsymbol{\delta} \sim N(\mathbf{0}, diag(\tau^2))$$

We assume equal heterogeneities for all comparisons

Example

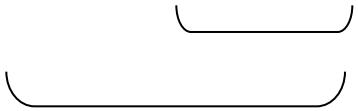
SMD compared to Placebo (RE model)

$$\boldsymbol{y} = (\mu^{PT}, \mu^{PG}, \mu^{PR}, \mu^{PV}, \mu^{PN}) \times X + \boldsymbol{\delta}$$

Regression coefficients μ	SMD(SE)
Toothpaste	
Gel	
Rinse	
Varnish	
No Treatment	

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_{iBC}

y_{iAC}

- The random effects ($\theta_{iBC,}\ \theta_{iAC}$) 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*

~~$\mathbf{y} \sim N(\boldsymbol{\mu}X, diag(v_i))$~~

$\mathbf{y} \sim N(\boldsymbol{\mu}X, S)$

~~$\boldsymbol{\delta} \sim N(\mathbf{0}, diag(\tau^2))$~~

$\boldsymbol{\delta} \sim N(\mathbf{0}, \Delta)$

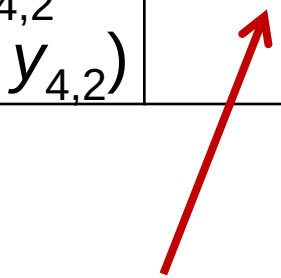
Hypothetical example

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

...as multivariate meta-analysis

Study	No. arms	#	Data	**Outcome**
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	$y_{4,1}$, $v_{4,1}$ $y_{4,2}$, $v_{4,2}$ $\text{cov}(y_{4,1}, y_{4,2})$	AB AC



correlated

Multivariate meta-analysis

- Studies typically report many outcomes
  - E.g. pain and function in treatments for osteoarthritis
  - Stroke and MI in antihypertensives
- **Multivariate meta-analysis** allows a joint synthesis of the multiple end points
- It is a multivariate extension of the meta-analysis
- Correlation is separated into two components, *within-study* and *between study* correlation

Advantages of Multivariate Meta-Analysis

- Describe the multivariate relationship between end points
- Obtain joint confidence regions-account for multiple comparisons
- The pooled estimates have better statistical properties with smaller mean-square error and standard error
- Address outcome selection bias
- See [Stat Med 2011 Jackson et all] for a review

Data: n studies with 2 outcomes

Pain Function

Study 1: $y_{11}, y_{12}, \begin{pmatrix} s_{11}^2 & S_{112} \\ S_{112} & s_{12}^2 \end{pmatrix}$

Study i: $y_{i1}, y_{i2}, \begin{pmatrix} s_{i1}^2 & S_{i12} \\ S_{i12} & s_{i2}^2 \end{pmatrix}$ $\quad S_{i12} = \rho_i s_{i1} s_{i2}$

Study n: $y_{n1}, y_{n2}, \begin{pmatrix} s_{n1}^2 & S_{n12} \\ S_{n12} & s_{n2}^2 \end{pmatrix}$

Random-effects multivariate meta-analysis (two outcomes)

The within-study model

$$\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} \Big| \begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix}, \begin{pmatrix} \sigma_{i1}^2 & \rho_i s_{i1} s_{i2} \\ \rho_i s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix} \right)$$

The between-study model

$$\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \tau_1^2 & \rho_\tau \tau_1 \tau_2 \\ \rho_\tau \tau_1 \tau_2 & \tau_2^2 \end{pmatrix} \right)$$

Marginal model

$$\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \rho_i s_{i1} s_{i2 i2} + \rho_\tau \tau_1 \tau_2 \\ \rho_i s_{i1} s_{i2 i2} + \rho_\tau \tau_1 \tau_2 & s_{i2}^2 + \tau_2^2 \end{pmatrix} \right)$$

Random effects multivariate meta-analysis (*p* outcomes)

- $\boldsymbol{y}_i = \boldsymbol{\mu} + \boldsymbol{\delta}_i + \boldsymbol{e}_i$
- $\boldsymbol{\delta}_i \sim MVN(0, \boldsymbol{\Delta})$
- $\boldsymbol{e}_i \sim MVN(0, \boldsymbol{S}_i)$
- $$\boldsymbol{\Delta} = \begin{pmatrix} \boldsymbol{\tau}_1^2 & \cdots & \boldsymbol{\rho}_{\boldsymbol{\tau}_{1,p}} \boldsymbol{\tau}_1 \boldsymbol{\tau}_p \\ \vdots & \ddots & \vdots \\ \boldsymbol{\rho}_{\boldsymbol{\tau}_{1,p}} \boldsymbol{\tau}_1 \boldsymbol{\tau}_p & \cdots & \boldsymbol{\tau}_p^2 \end{pmatrix}$$

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

Meta-regression

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

Study	No. arms	#	Data	Contrast
i=1	$T_1=2$	1	$y_{1,1}, v_{1,1}$	PT
i=2	$T_2=2$	1	$y_{2,1}, v_{2,1}$	PR
i=3	$T_3=2$	1	$y_{3,1}, v_{3,1}$	TR
i=4	$T_4=3$	2	$y_{4,1}, v_{4,1}$ $y_{4,2}, v_{4,2}$ $\text{cov}(y_{4,1}, y_{4,2})$	PT PR

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

Take into account correlation in observations

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

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	$y_{4,1}, v_{4,1}$ $y_{4,2}, v_{4,2}$ $\text{cov}(y_{4,1}, y_{4,2})$	AB AC

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

Take into account correlation in random effects

$$\begin{pmatrix} \delta_{1,1} \\ \delta_{2,1} \\ \delta_{3,1} \\ \delta_{4,1} \\ \delta_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau^2_{AB} & 0 & 0 & 0 & 0 \\ 0 & \tau^2_{AC} & 0 & 0 & 0 \\ 0 & 0 & \tau^2_{BC} & 0 & 0 \\ 0 & 0 & 0 & \tau^2_{AB} & \text{cov}(\delta_{4,1}, \delta_{4,2}) \\ 0 & 0 & 0 & \text{cov}(\delta_{4,1}, \delta_{4,2}) & \tau^2_{AC} \end{pmatrix} \right)$$

$= f(\tau_{PT}, \tau_{PR})$

How to fit network meta-analysis?

- R mvmeta,metasem
- STATA using metareg
- STATA mvmeta
- To my knowledge none of these macros models properly the matrix Δ
- There is a new version of STATA mvmeta suitable for network meta-analysis

Review of statistical methodology in [Statistical Methods in Medical Research 2008 Salanti et al]

Why use Bayesian statistics for network meta-analysis?

- 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

- Network meta-analysis with two-arm trials only

  Easy in frequentist meta-regression

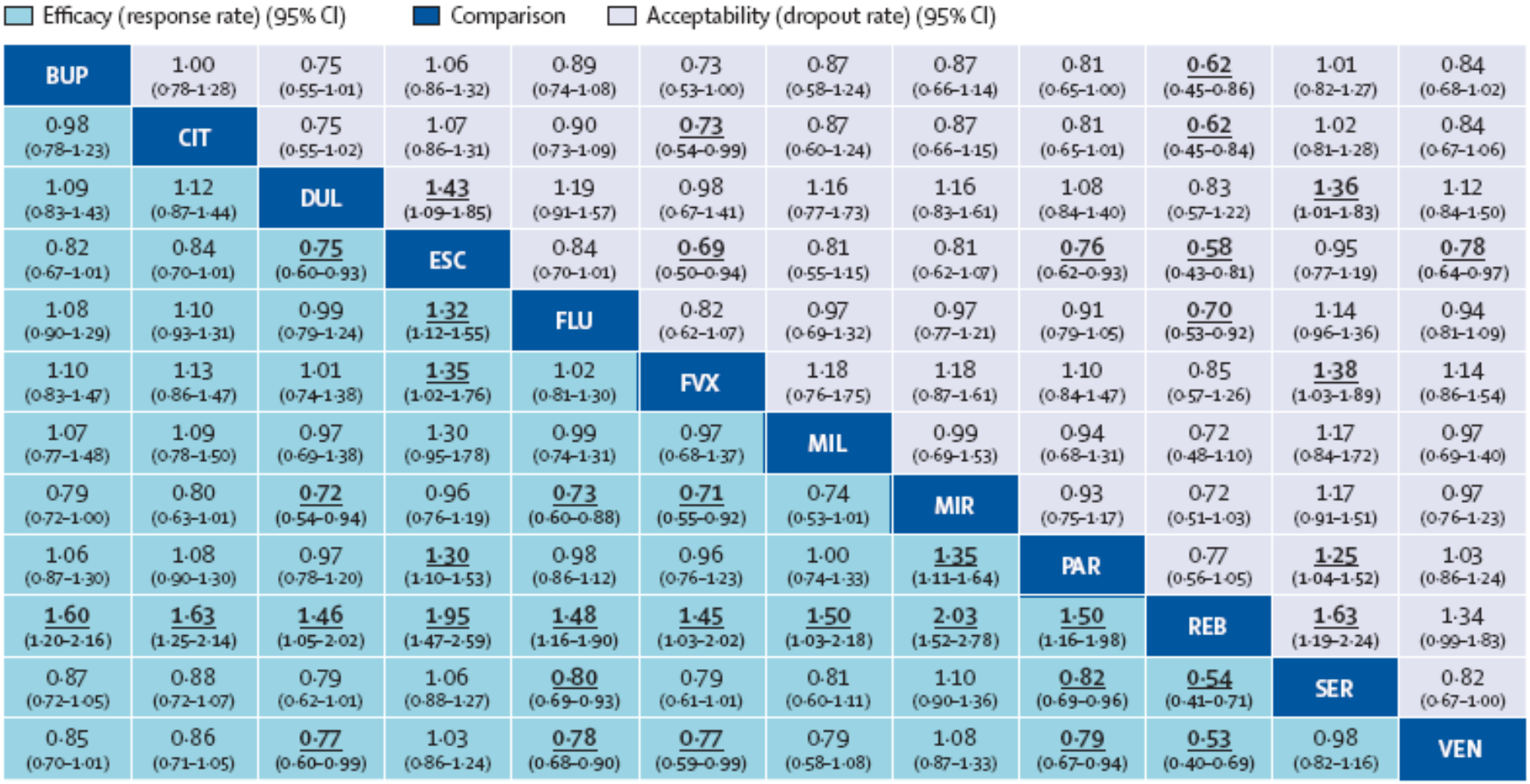
Network models in both settings are equivalent but it is convenient to think of
- In frequentist as **regression models**
- In Bayesian as **hierarchical models**

Arm-specific data versus effect sizes

- If the arm-specific data are available use them instead of effect sizes
  - Mean, SD, n per arm instead of SMD, SE(SMD)
  - Events *r* out of *n* per arm instead of *lnOR, SE(lnOR)*
- Model the arm-responses
- Parameterize to get the effect sizes
- Arm-based approaches typically have ‘better fit’ than those based on effect sizes

Presenting results from network meta-analysis

- With many treatments judgments based on pairwise effect sizes are difficult to make
- Example: Antidepressants

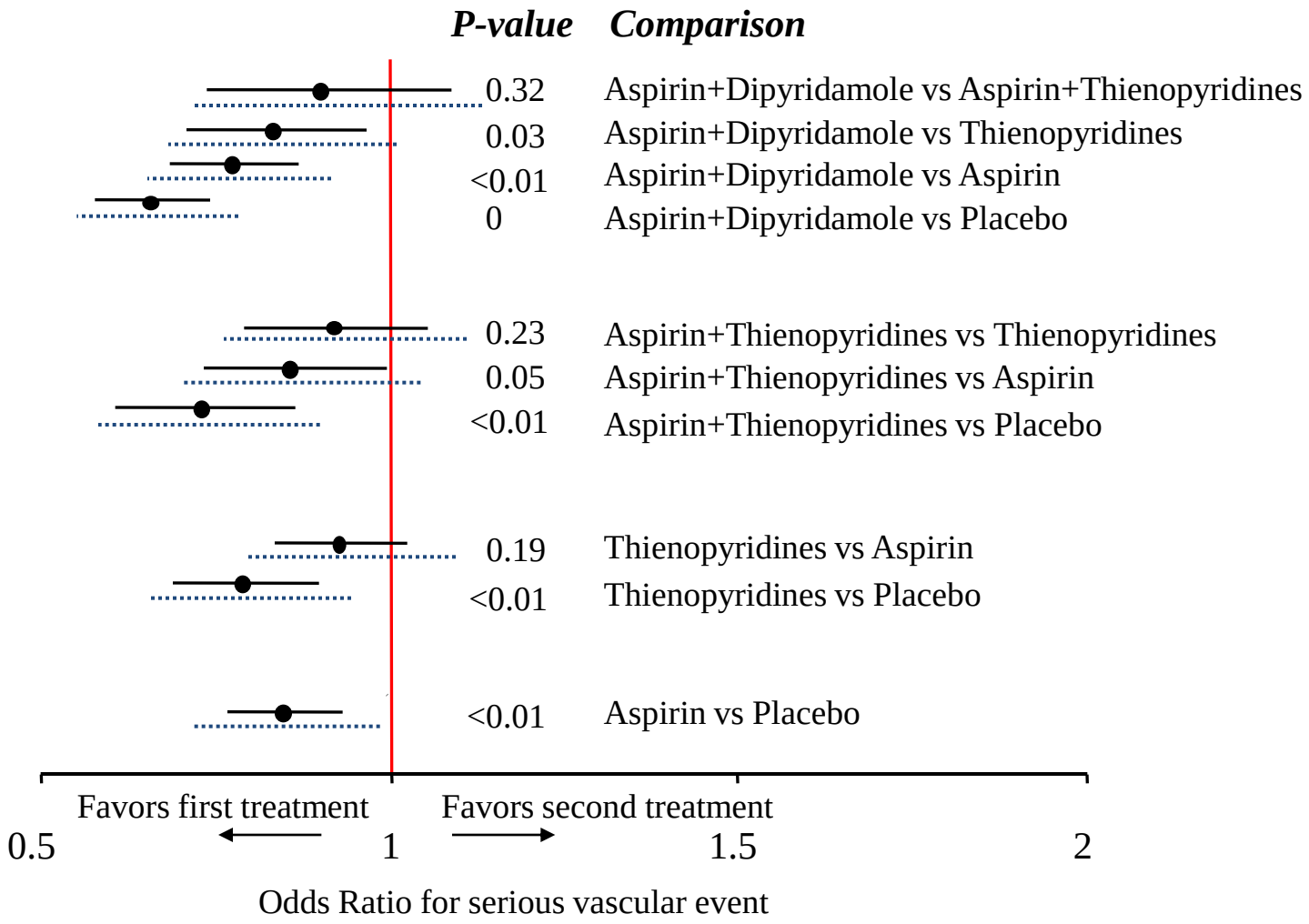


OR>1 means the treatment in top-left is better

Ranking measures from network meta-analysis

- With many treatments judgments based on pairwise effect sizes are difficult to make
- Example: Antidepressants
- Example: Antiplatelet regimens for serious vascular events

Serious vascular events with antiplatelet regimens



Probabilities

- Estimate for each treatment ***the probability of being the best***
- This is straightforward within a Bayesian framework
  - In each MCMC cycle rank the treatments
  - Run 1,000 000 cycles
  - (#J=1)/ 1,000 000 is the probability that J is the best treatment

12 new generation antidepressants

paroxetine — reboxetine

duloxetine — mirtazapine

escitalopram — fluvoxamine

milnacipran — citalopram

sertraline — venlafaxine

bupropion — fluoxetine

milnacipran — paroxetine

sertraline ..... duloxetine

bupropion — escitalopram

fluvoxamine — milnacipran

paroxetine	0%
sertraline	7%
citalopram	0%
escitalopram	26%
fluoxetine	0%
fluvoxamine	0%
milnacipran	1%
venlafaxine	11%
reboxetine	0%
bupropion	0%
mirtazapine	54%
duloxetine	0%

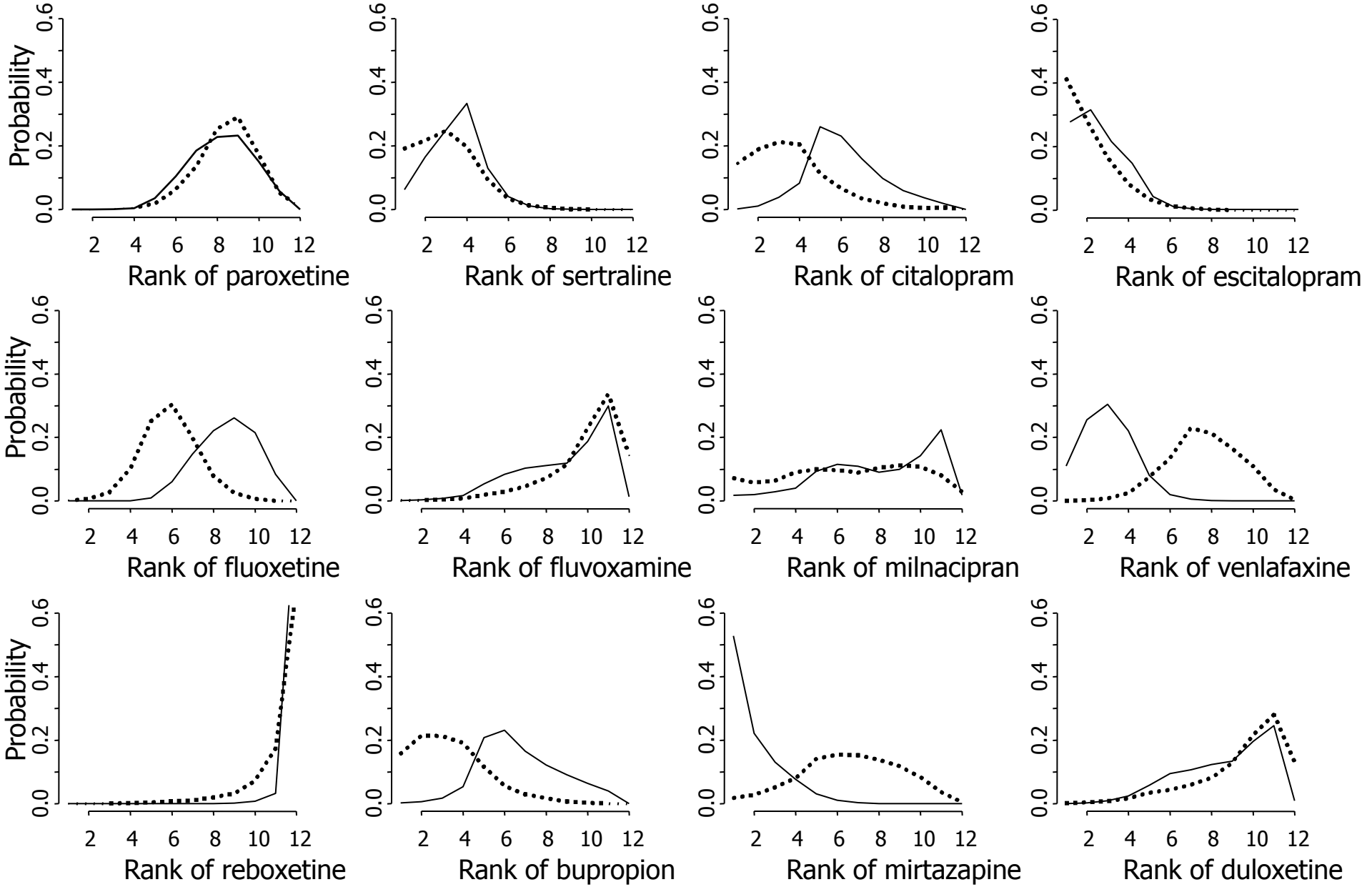
Probability of being the best

The probability of being the best does not convey the spread of the rank probabilities....

% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00

% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00
j=2	0.25	0.25	0.50	0.00
j=3	0.25	0.25	0.25	0.25
j=4	0.25	0	0	0.75

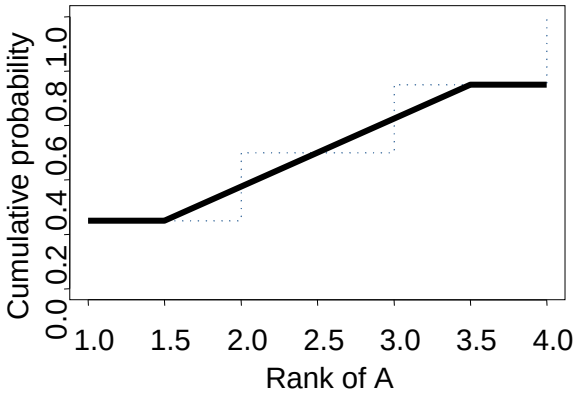
i the treatment
j the rank

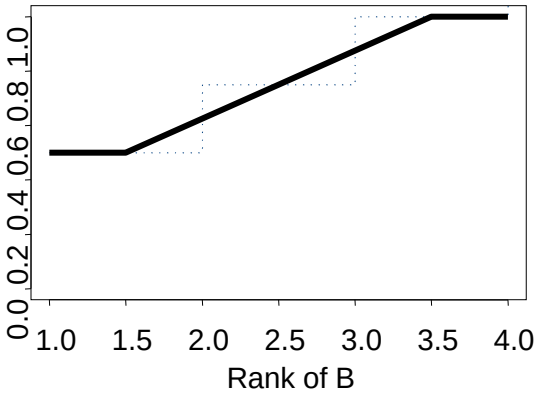


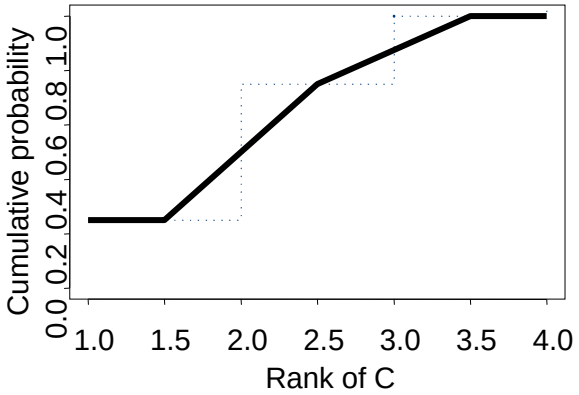
Ranking for efficacy (solid line) and acceptability (dotted line). Ranking: probability of being the best treatment, of being the second best, the third best and so on, among the 12 comparisons).

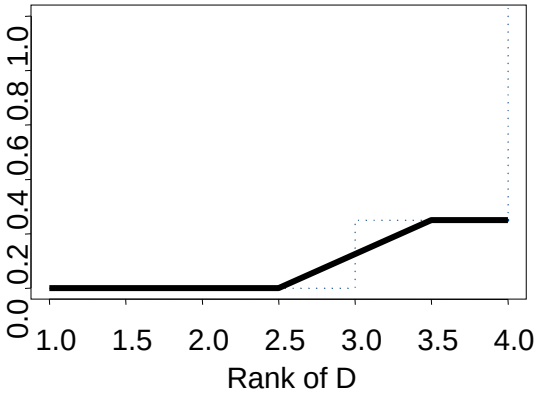
% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00
j=2	0.50	0.75	0.75	0.00
j=3	0.75	1.00	1.00	0.25
j=4	1.00	1.00	1.00	1.00

i the treatment
j the rank





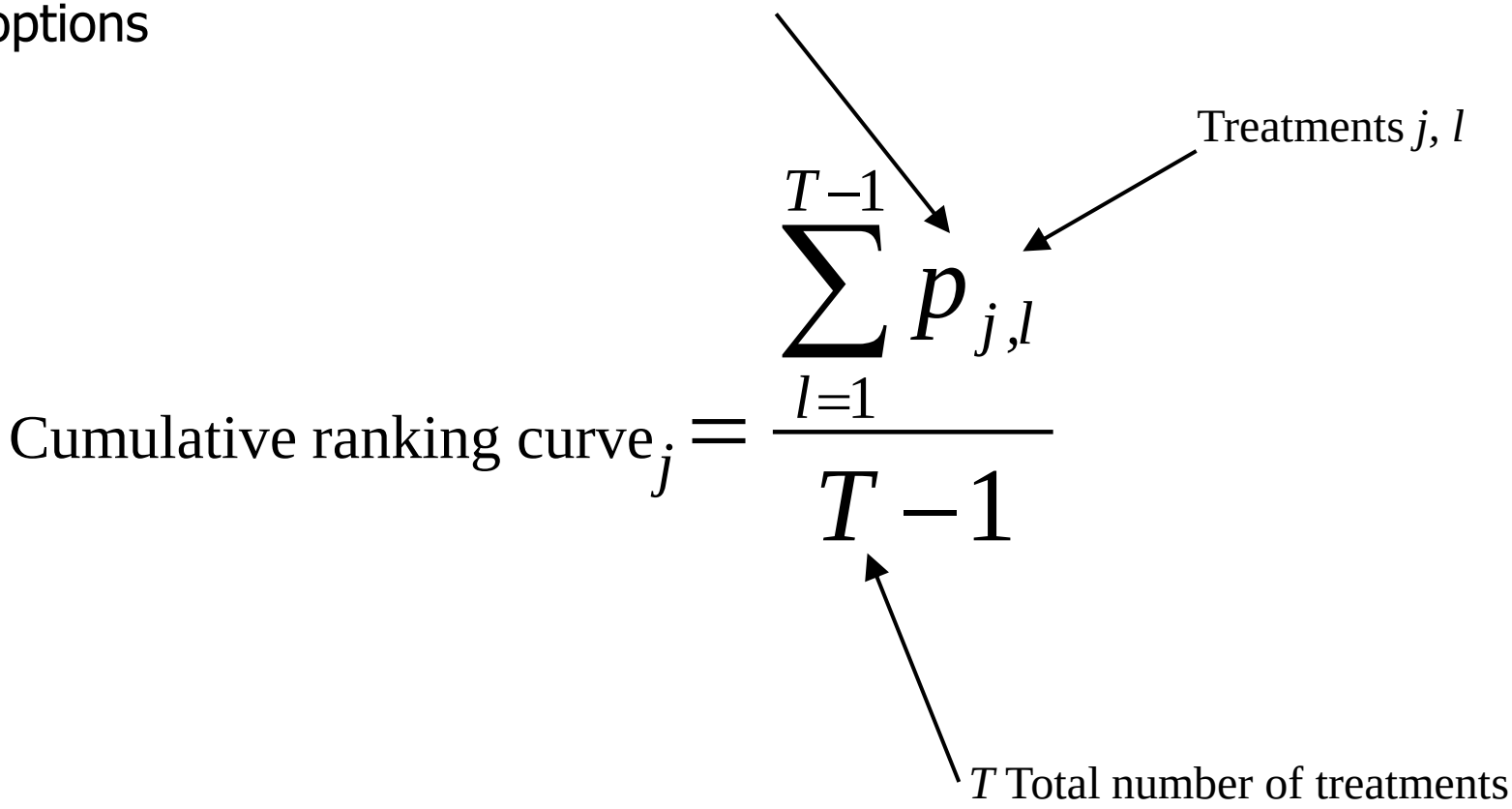




The areas under the cumulative curves for the four treatments of the example above are
A=0.5
B=0.75
C=0.67
D=0.08

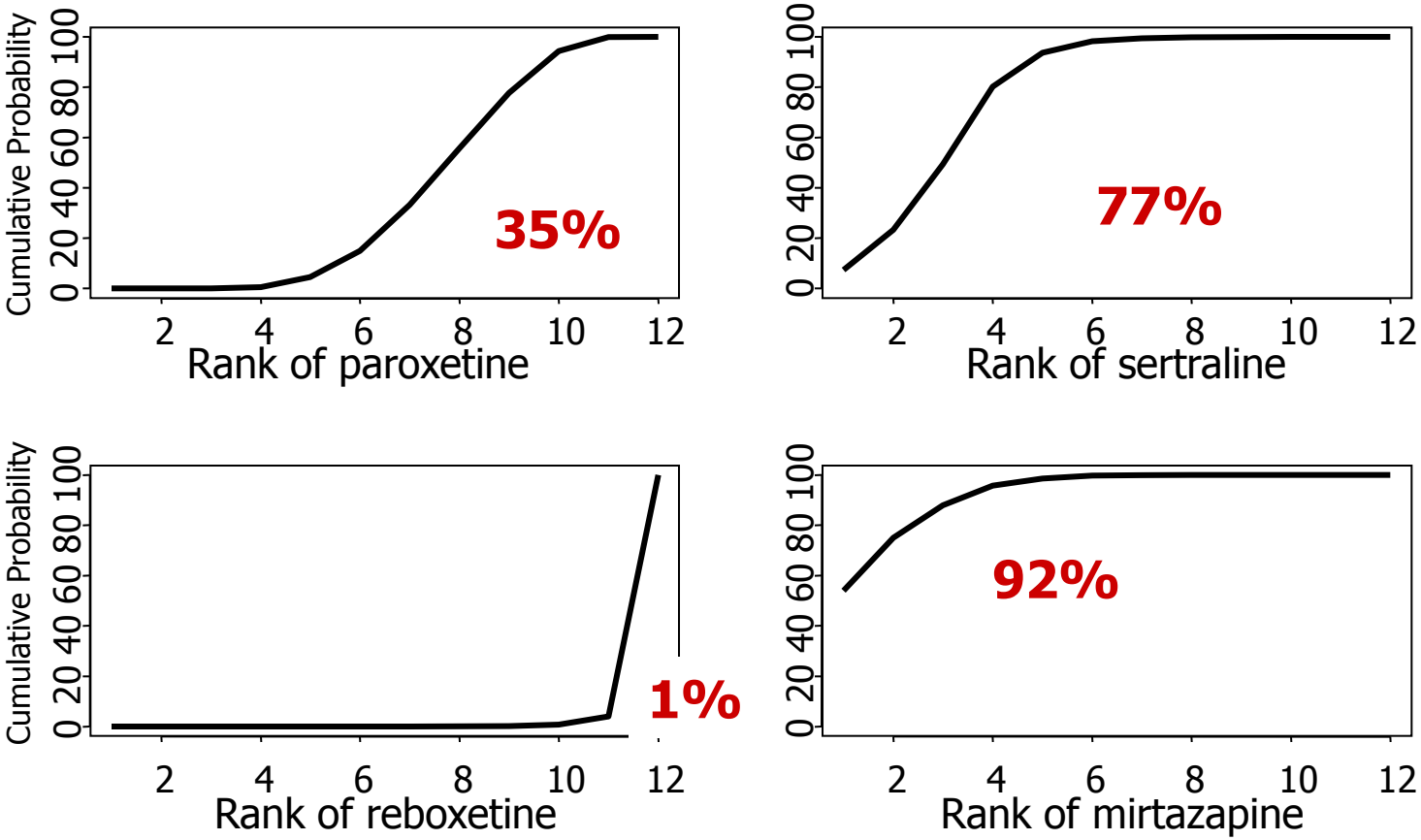
Surface under the cumulative ranking curve

Use posterior probabilities for each treatment to be among the *n* -best options

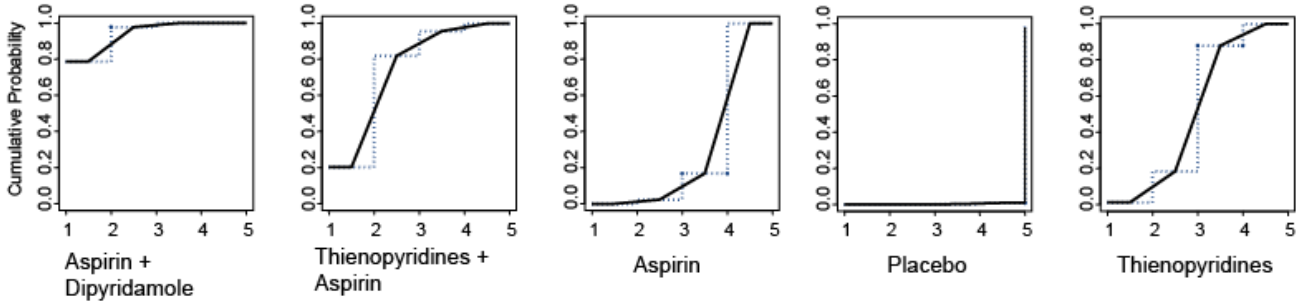


[J Clin Epidemiol. 2010 Salanti et al]

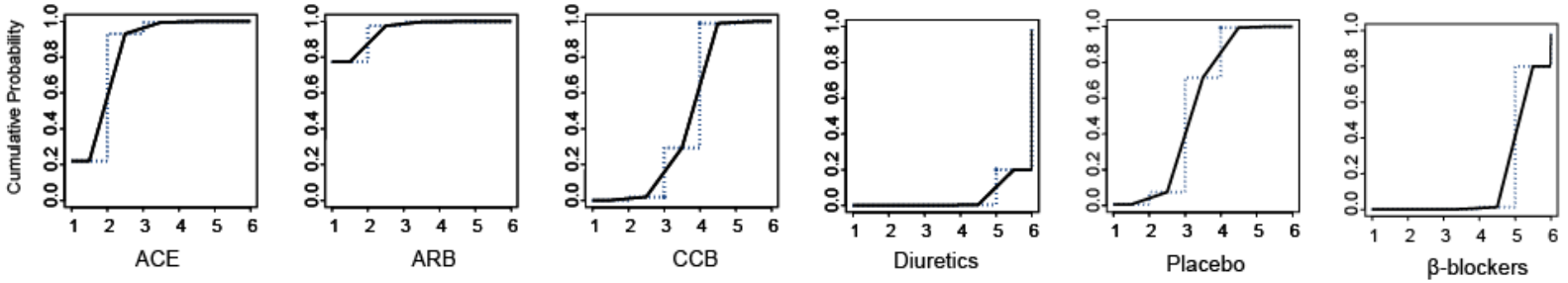
Surface under the cumulative ranking curve



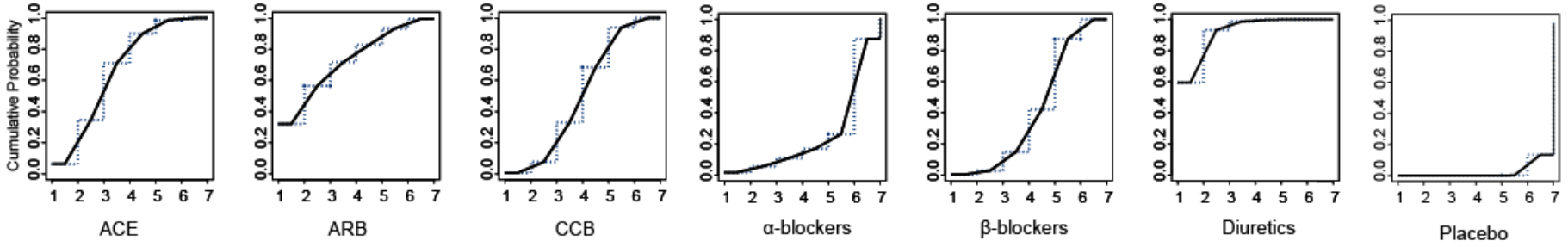
Serious vascular events with antiplatelet regimens



Incident diabetes with antihypertensive drugs



Serious cardiovascular event with antihypertensive drugs



Warning: measures based on probabilities are attractive, but can be unstable and should be presented along with the effect sizes!

INCONSISTENCY

Validity of network meta-analysis

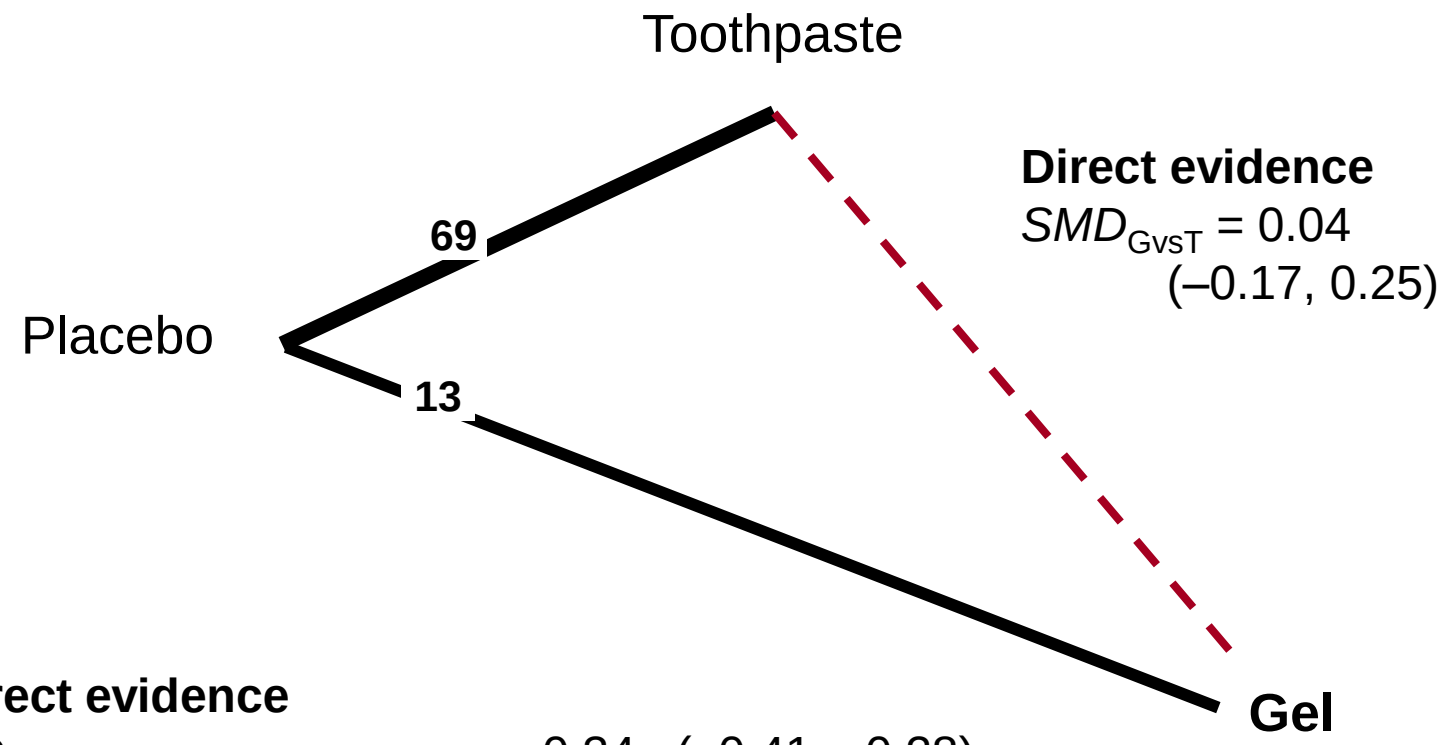
- The validity of a network meta-analysis depends on transitivity of effect size parameters:
- For any pair A and B,

typical (or mean) advantage of A over B =

advantage of A over C − advantage of B over C

- In a simple indirect comparison, we cannot test this assumption empirically.
- In a network meta-analysis, we sometimes can.
- We call this looking at *inconsistency*.

Example: a simple loop of treatments



Indirect evidence

SMD_{PvsT} = –0.34 (–0.41, –0.28)

SMD_{PvsG} = –0.19 (–0.30, –0.10)

Indirect comparison

SMD_{GvsT_ind} = –0.15 (–0.27, –0.03)

How much inconsistency?

- From before,
- Difference between direct and indirect estimates is

  $0.04 - (-0.15) = 0.19$

- and we add the variances (since the sources of evidence are independent):

  Var(difference between direct and indirect)

  $= 0.004 + 0.011 = 0.015$

  – *Inconsistency factor* = 0.19 (–0.05, 0.43)

What is inconsistency?

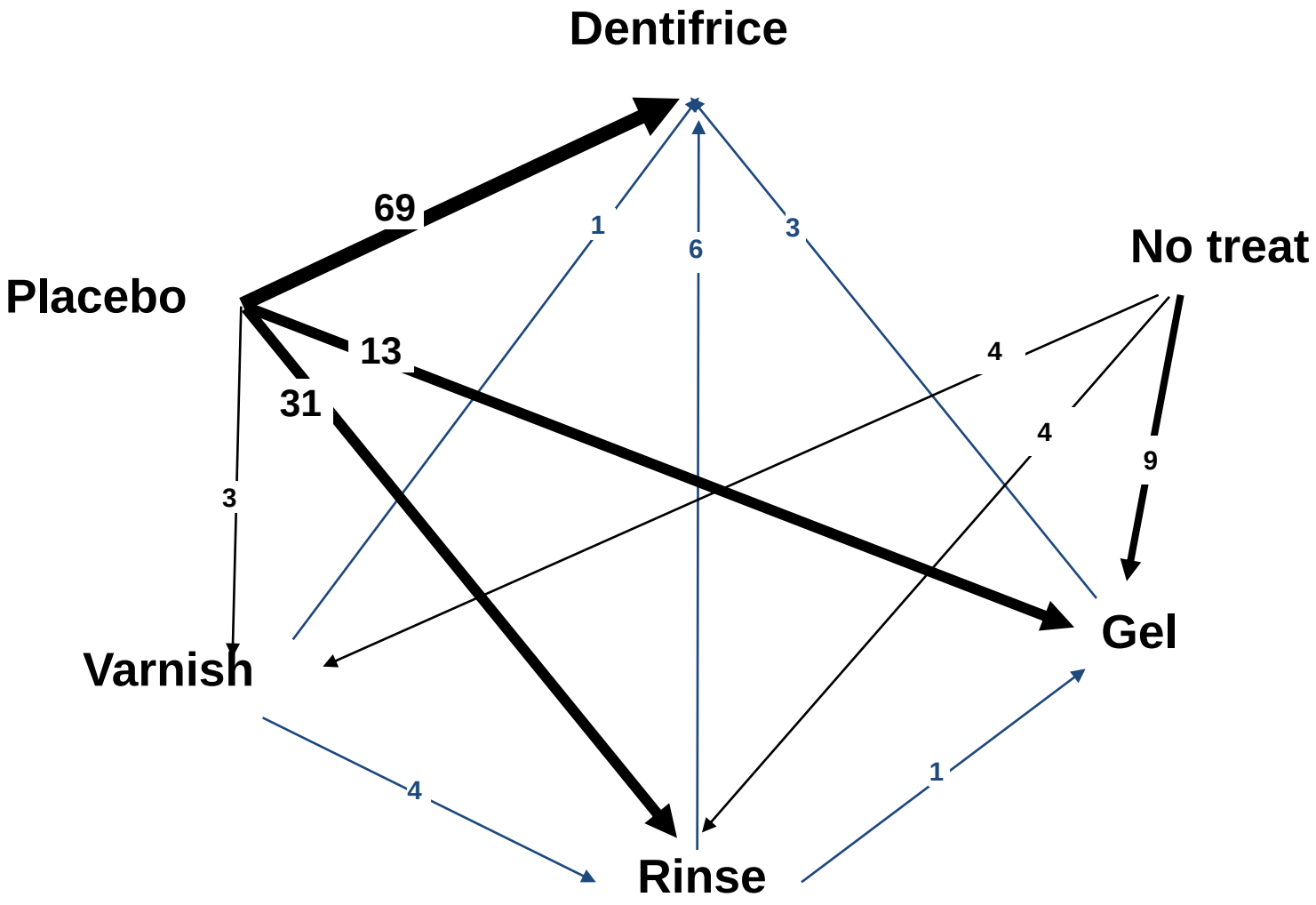
- *Consistency* = The data fit together according to the laws of transitivity

- i.e.
  - for each pair of interventions A and B, all sources of evidence about A vs B agree with each other
    - (this means direct evidence (if available) and different routes to indirect evidence)

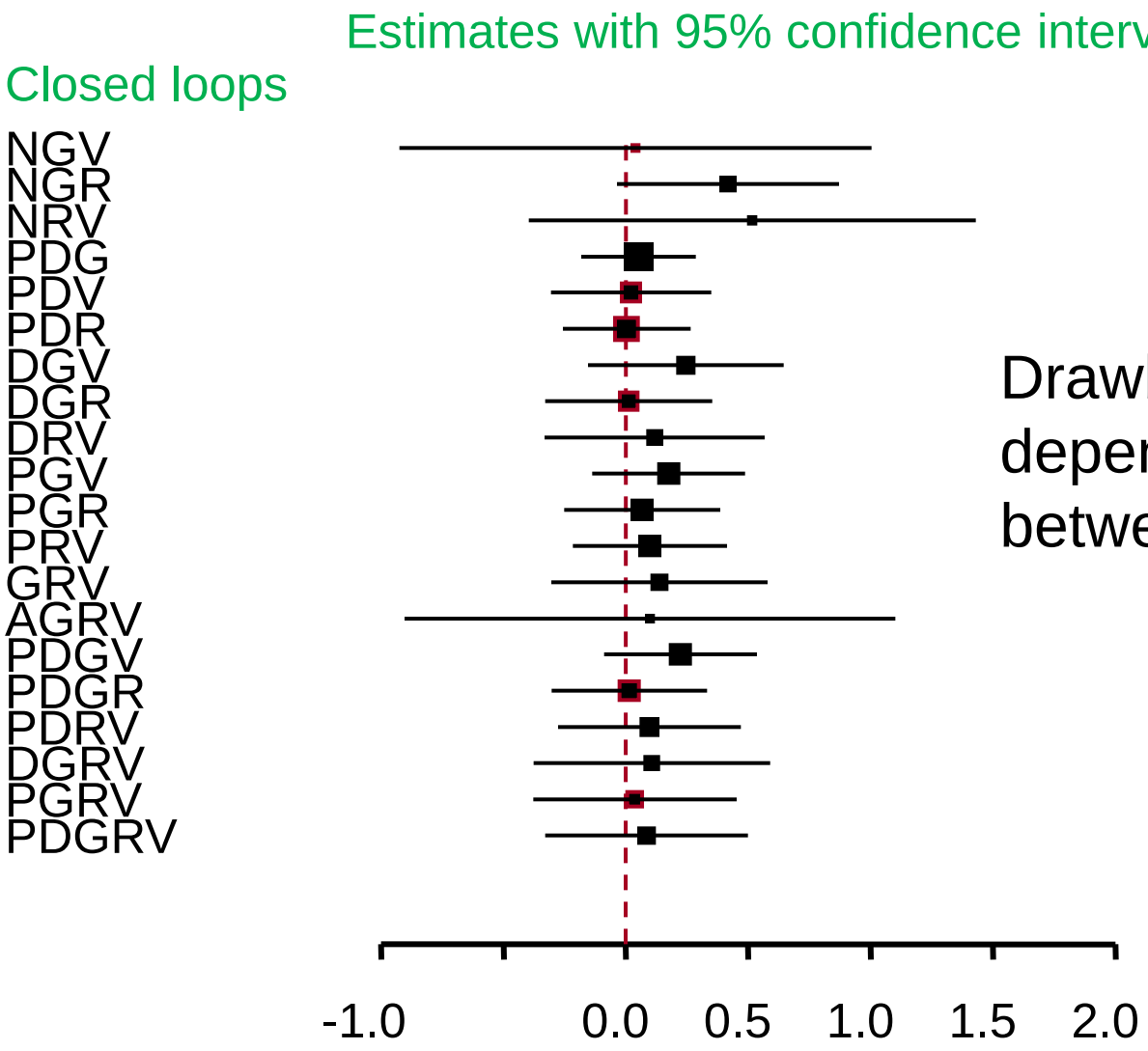
- *Inconsistency* = Lack of consistency

- Only *closed loops* can tell us about (in)consistency

Example: fluoride treatments



Evaluation of consistency within closed loops



Drawback: dependence between loops

R routine in www.mtm.uoi.gr/howotodoanmtm.html

[Clin Epidemiol 2009, Salanti et al]

Are networks typically inconsistent?

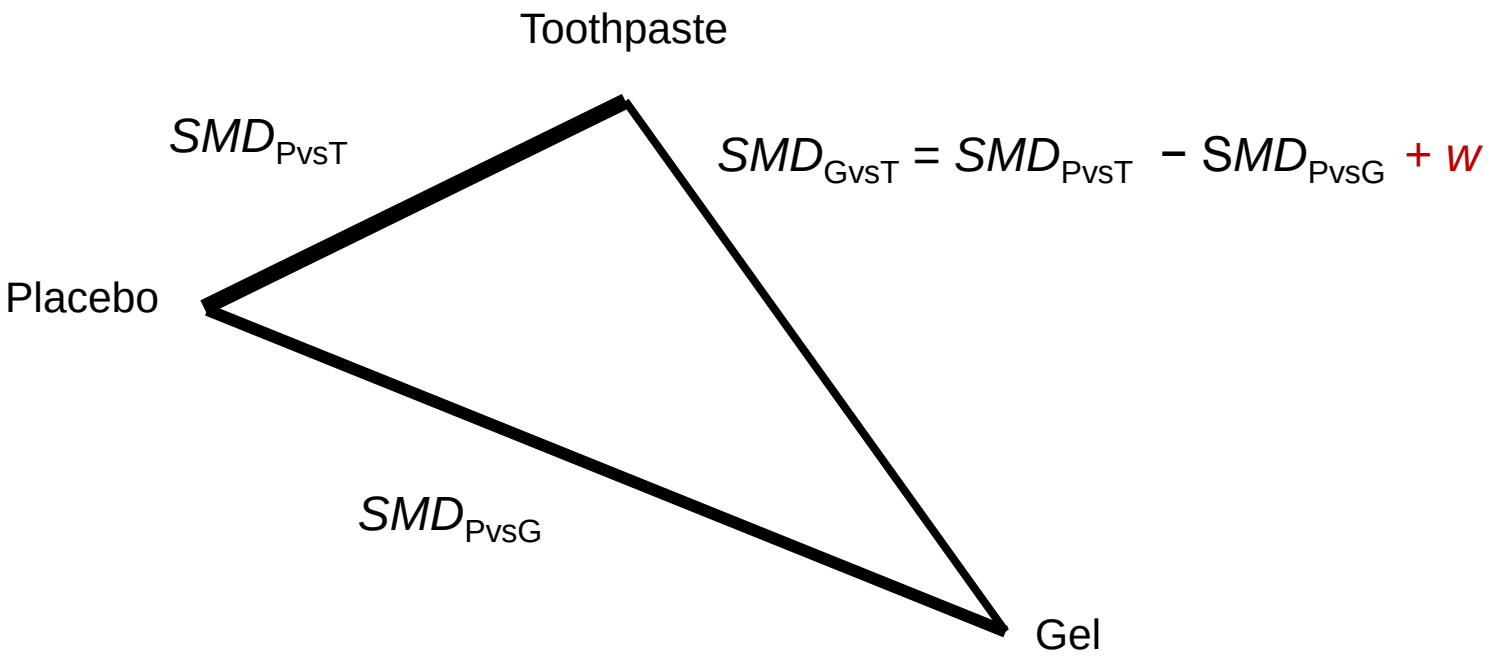
- There is empirical evidence
- Early study (Glenny HTA 2005) found 3/44 triangles inconsistent
- Recent extension (Song BMJ 2011) found 16/112
  - [but looked at triangular networks only]

- Georgia and colleagues are collecting all published network meta-analyses with binary data that involve at least 4 treatments
  - so far 44 networks, 505 loops

Approaches for exploring inconsistency

- Examine each closed loop separately (as above)
- Use a network meta-analysis model that allows for inconsistency
  - [e.g. Stat Med 2002 Lumley; JASA 2005 Lu & Ades]
- In a Bayesian framework:
  - node splitting
    - [Stat Med 2010 Dias et al]
  - compare DICs for consistency models and inconsistency models

Inconsistency models: introduction



Model for consistency

Modelled log odds ratios (basic parameters μ_{AB} and μ_{AC}); δ_i is the heterogeneity random effect			
Design	*A*	*B*	*C*
AB	*ref*	$\mu_{AB} + \delta_i$	
AC	*ref*		$\mu_{AC} + \delta_i$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$

Model for inconsistency

Modelled log odds ratios (basic parameters μ_{AB} and μ_{AC}); δ_i is the heterogeneity random effect			
Design	*A*	*B*	*C*
AB	*ref*	$\mu_{AB} + \delta_i$	
AC	*ref*		$\mu_{AC} + \delta_i$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i + w$

Model for consistency with a three-arm trial

Modelled log odds ratios (basic parameters μ_{AB} and μ_{AC}); δ_i is the heterogeneity random effect			
Design	*A*	*B*	*C*
ABC	*ref*	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$
AB	*ref*	$\mu_{AB} + \delta_i$	
AC	*ref*		$\mu_{AC} + \delta_i$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$

Lu and Ades model for inconsistency with a three-arm trial

Modelled log odds ratios (basic parameters μ_{AB} and μ_{AC}); δ_i is the heterogeneity random effect			
Design	*A*	*B*	*C*
ABC	*ref*	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$
AB	*ref*	$\mu_{AB} + \delta_i$	
AC	*ref*		$\mu_{AC} + \delta_i + w$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$

Issues with the Lu and Ades model

- In the presence of multi-arm trials, the Lu and Ades inconsistency model is not uniquely defined
- Problems arise because multi-arm trials *must* be consistent, so a network with multi-arm trials will have a mixture of consistent and inconsistent loops

This is a different Lu and Ades model

Modelled log odds ratios (basic parameters μ_{AB} and μ_{AC}); δ_i is the heterogeneity random effect			
Design	*A*	*B*	*C*
ABC	*ref*	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$
AB	*ref*	$\mu_{AB} + \delta_i + w$	
AC	*ref*		$\mu_{AC} + \delta_i$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$

Issues with the Lu and Ades model

- In the presence of multi-arm trials, the Lu and Ades inconsistency model is not uniquely defined
- Problems arise because multi-arm trials *must* be consistent, so a network with multi-arm trials will have a mixture of consistent and inconsistent loops
- A model that is completely general is one that allows for all types of inconsistency
  - inconsistency within loops made up of different trials
  - inconsistency between two-arm and three-arm trials
  - and beyond...
- Such a model has been termed a design-by-treatment interaction model

Design-by-treatment interaction model

Modelled log odds ratios (basic parameters μ_{AB} and μ_{AC}); δ_i is the heterogeneity random effect			
Design	*A*	*B*	*C*
ABC	*ref*	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$
AB	*ref*	$\mu_{AB} + \delta_i + w_{AB}$	
AC	*ref*		$\mu_{AC} + \delta_i + w_{AC}$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i + w_{BC}$

[Higgins et al, 2012], [White et al, 2012]

Modelling the *w* parameters

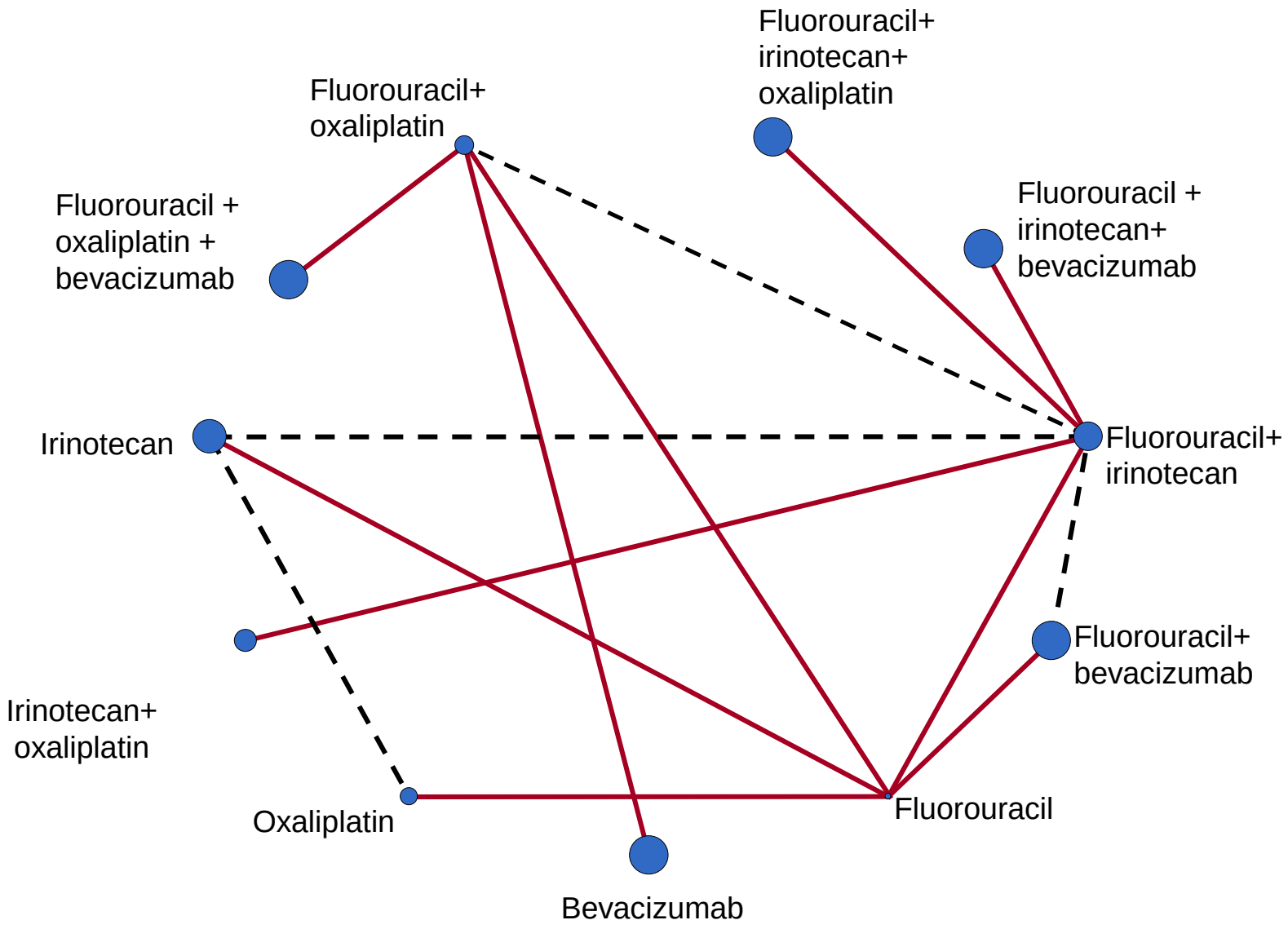
- When we have several inconsistency (*w*) parameters, we could let them have a random-effects distribution across comparisons

$$w_j \sim N(0,\sigma^2)$$

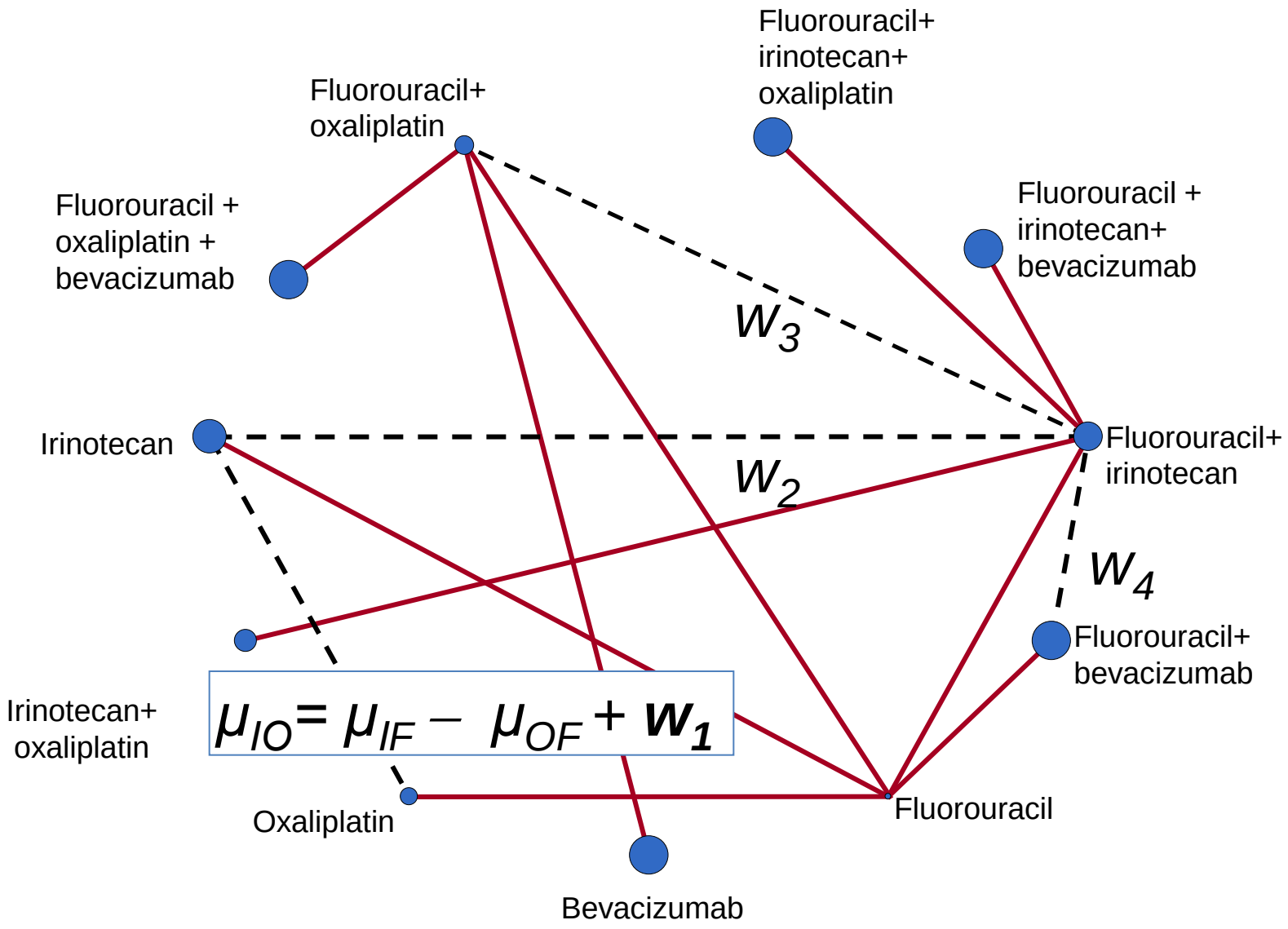
- Comparing σ^2 with τ^2 *(heterogeneity)* allows us to assess the magnitude of the inconsistency

- I prefer to use fixed effects for the *w* parameters
  - can interpret them individually
  - and it's easier to fit the model using Stata

Example: Survival with 11 chemotherapy regimens in colorectal cancer



Lu and Ades model for colorectal cancer



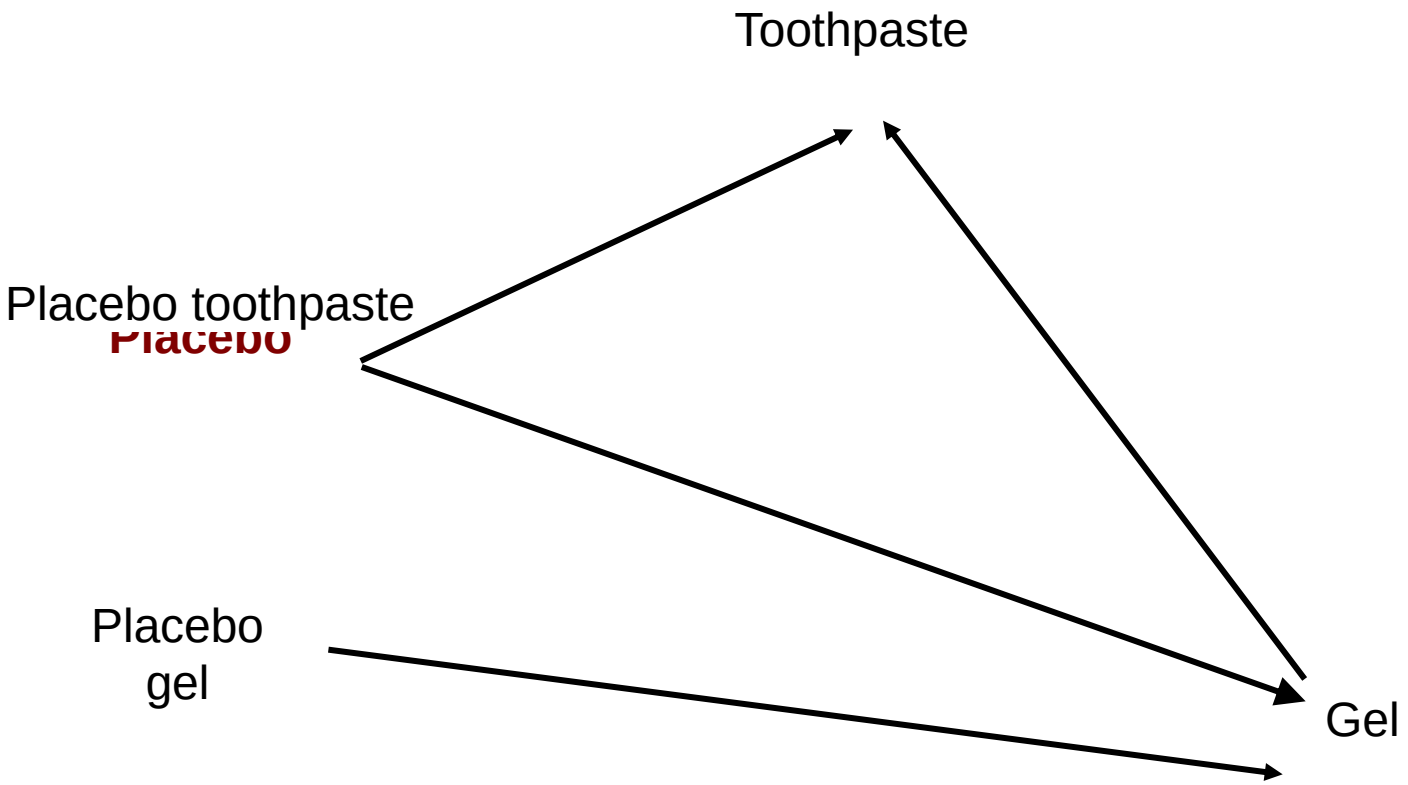
Results: colorectal cancer network

- $w_1 = -0.08$, $w_2 = -0.07$, $w_3 = -0.06$, $w_4 = -0.03$
  - No loop is remarkably inconsistent
- $\sigma^2 = 0.11$ (SD 0.04), $\tau^2 = 0.19$ (SD 0.18)
- $P(\sigma^2 > \tau^2) = 0.41$
  - No important changes in posterior HRs or fit

What if we find inconsistency?

- Tricky!
- Might consider
  - omitting interventions
  - splitting intervention nodes in the network
  - presenting results from the inconsistency model
  - presenting a variety of separate direct, indirect and mixed comparisons

Splitting intervention nodes

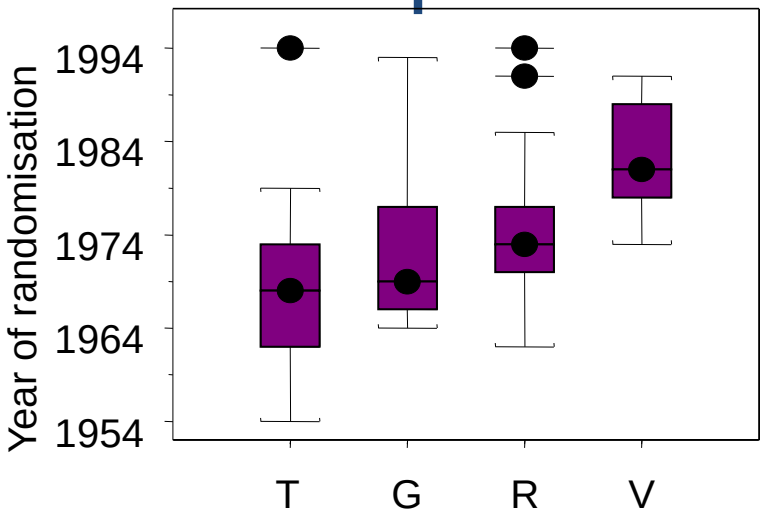


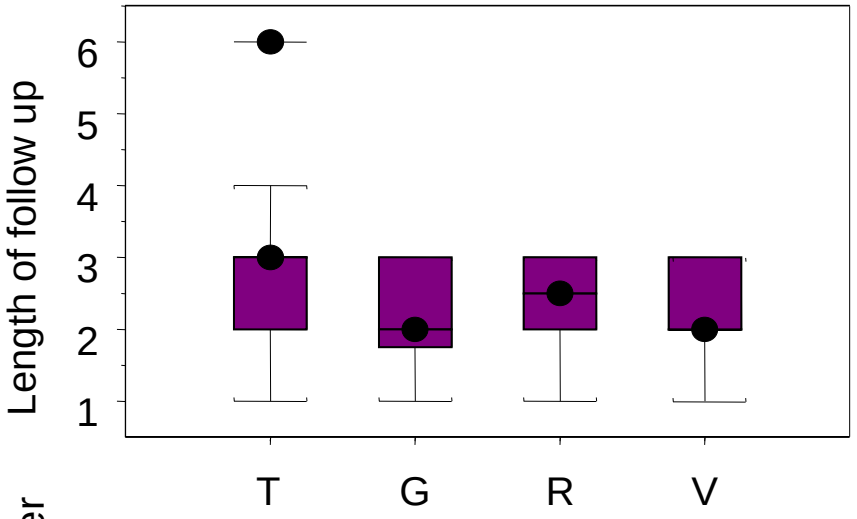
A BIT MORE

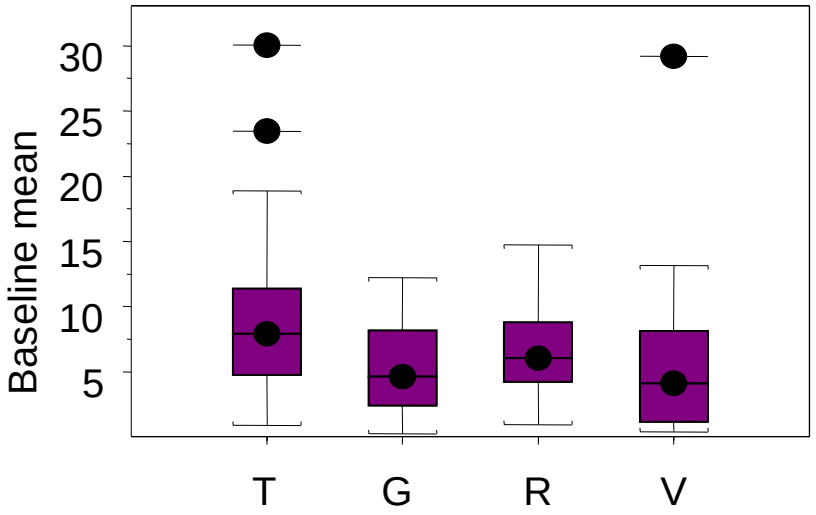
Comparison of assumptions (random effects models)

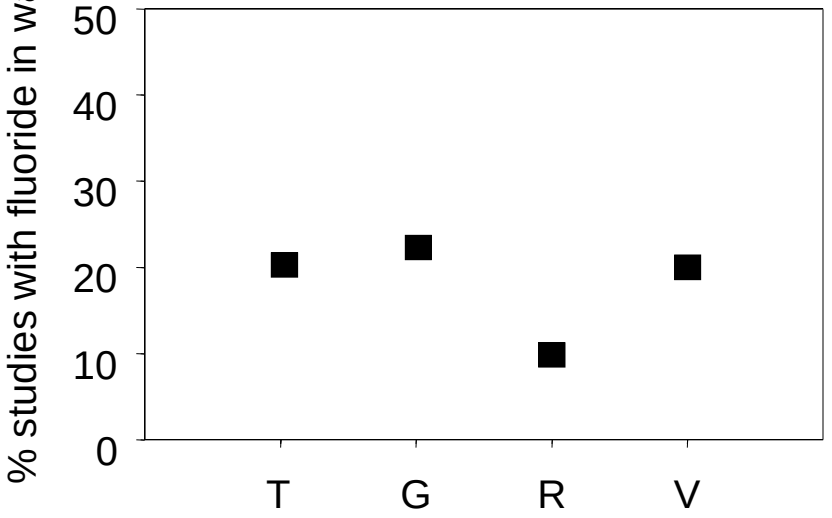
Meta-analysis	Network meta-analysis
Similarity of participants, interventions and outcomes	Similarity of participants, outcomes; 'random selection' of interventions
Appropriate modelling of study data (within-study variances often assumed known, uncorrelated with effects)	Appropriate modelling of study data (within-study variances often assumed known, uncorrelated with effects)
Normal distribution for random effects	Normal distribution for random effects
Possibly covariates to explain heterogeneity	Possibly covariates to explain heterogeneity and/or inconsistency
	Possibly assumptions about different τ values for different comparisons
	Possibly extra parameters to allow for inconsistency across comparisons

Fluorides: characteristics of placebo-controlled trials

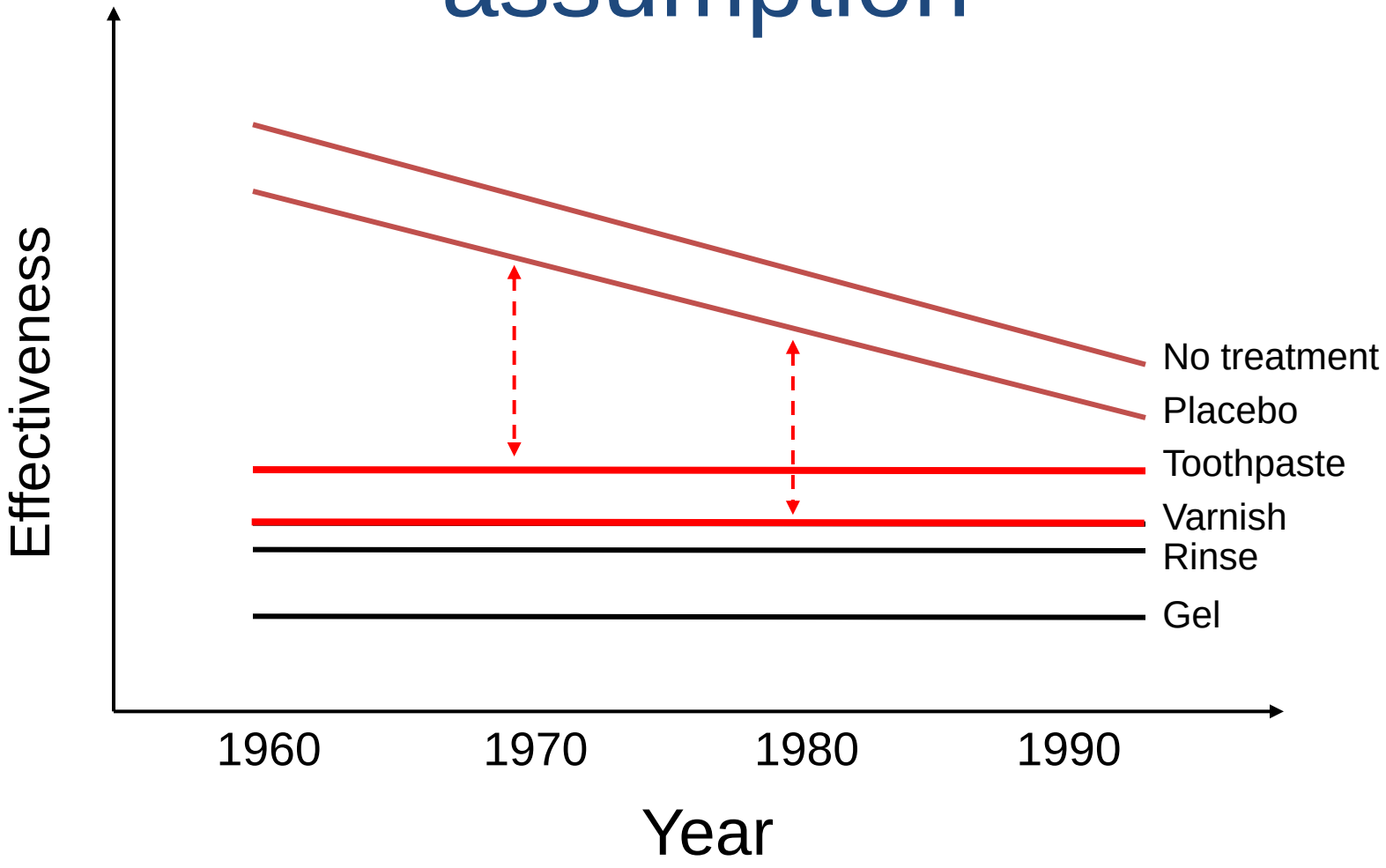








Hypothetical situation, which would violate the consistency assumption



Network meta-regression

Fluoride	No adjustment		Year of randomisation		Baseline mean caries level	
	Mean SMD	P(best)	Mean SMD adjusted to 1994 values	P(best)	Mean SMD adjusted to zero	P(best)
No treatment	reference		reference		reference	
Placebo	–0.22 (–0.34, –0.09)	0%	–0.23 (–0.36, –0.11)	0%	–0.17 (–0.29, –0.05)	0%
Toothpaste	–0.54 (–0.67, –0.40)	57%	–0.43 (–0.59, –0.26)	37%	–0.35 (–0.49, –0.20)	25%
Gel	–0.45 (–0.58, –0.34)	4%	–0.36 (–0.50, –0.21)	4%	–0.34 (–0.47, –0.22)	30%
Rinse	–0.50 (–0.63, –0.37)	14%	–0.41 (–0.56, –0.25)	16%	–0.35 (–0.49, –0.21)	24%
Varnish	–0.50 (–0.65, –0.34)	25%	–0.42 (–0.59, –0.26)	42%	–0.32 (–0.48, –0.17)	20%

[JCE 2009 Salanti et al]

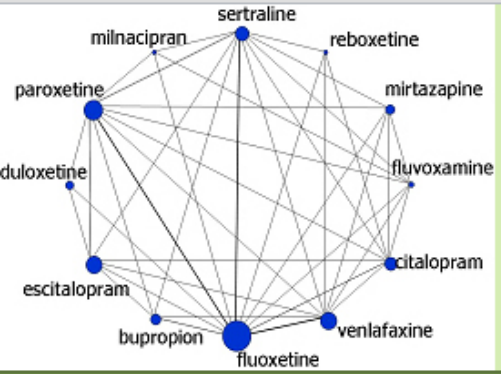
See also [Stat Med 2009 Cooper et al], [Stat Med 2006 Nixon et al]

Hands on

www.mtm.uoi.gr

www.mtm.uoi.gr

Αλληλογραφία :: IN... | Gmail: Email from G... | Greek-Movies - Ελλ... | PubMed home | E-Radio Greece - Th... | Βιβλιοθήκη Πανεπισ... | Facebook | Georgia ... | RS



Multiple-Treatments Meta-Analysis

A Framework for Evaluating and Ranking Multiple Healthcare Technologies

September 14, 2011

- HOME
- TUTORIAL
- HOW TO DO AN MTM
- IMMA ERC starting Grant
- RESEARCH
- Material from Publications
- Meta-analysis methods and tools
- CONTACT US

Multiple-Treatments Meta-analysis (MTM)

Meta-analysis is the statistical technique used to synthesize evidence from experiments addressing the same research question. It is often used to combine data from clinical trials regarding the relative effectiveness of two interventions in order, for example, to infer about whether antihypertensives A and B are equally effective in lowering blood pressure.
The main drawback of the current state of the art is that meta-analysis focuses on comparing only two alternatives. However, clinicians and patients need to know the relative ranking of a set of alternative options and not only whether option A is better than B.
The statistical methodology applied to synthesize information over a network of comparisons involving all alternative treatment options for the same condition is called Multiple-Treatments Meta-Analysis.

This site provides

- an introduction to statistical and methodological issues related to MTM
- links to training material
- support to statisticians with the analysis of networks of interventions

Hands on

- www.mtm.uoi.gr
- Go to ‘how to do an MTM’ tab
- Use R routine `mtmnetwork.plot` to plot a network
- In STATA, use `metan` for network meta-analysis
- Use the R routine `MTcoherence.fun` to plot inconsistency in all closed loops
- In WinBUGS: read the description of models (e.g. www.mtm.uoi.gr/3.binarymodeldescription.pdf) download the data and the WinBUGS code
- Use the R routine `sucraplot.fun` to get rankograms and SUCRA

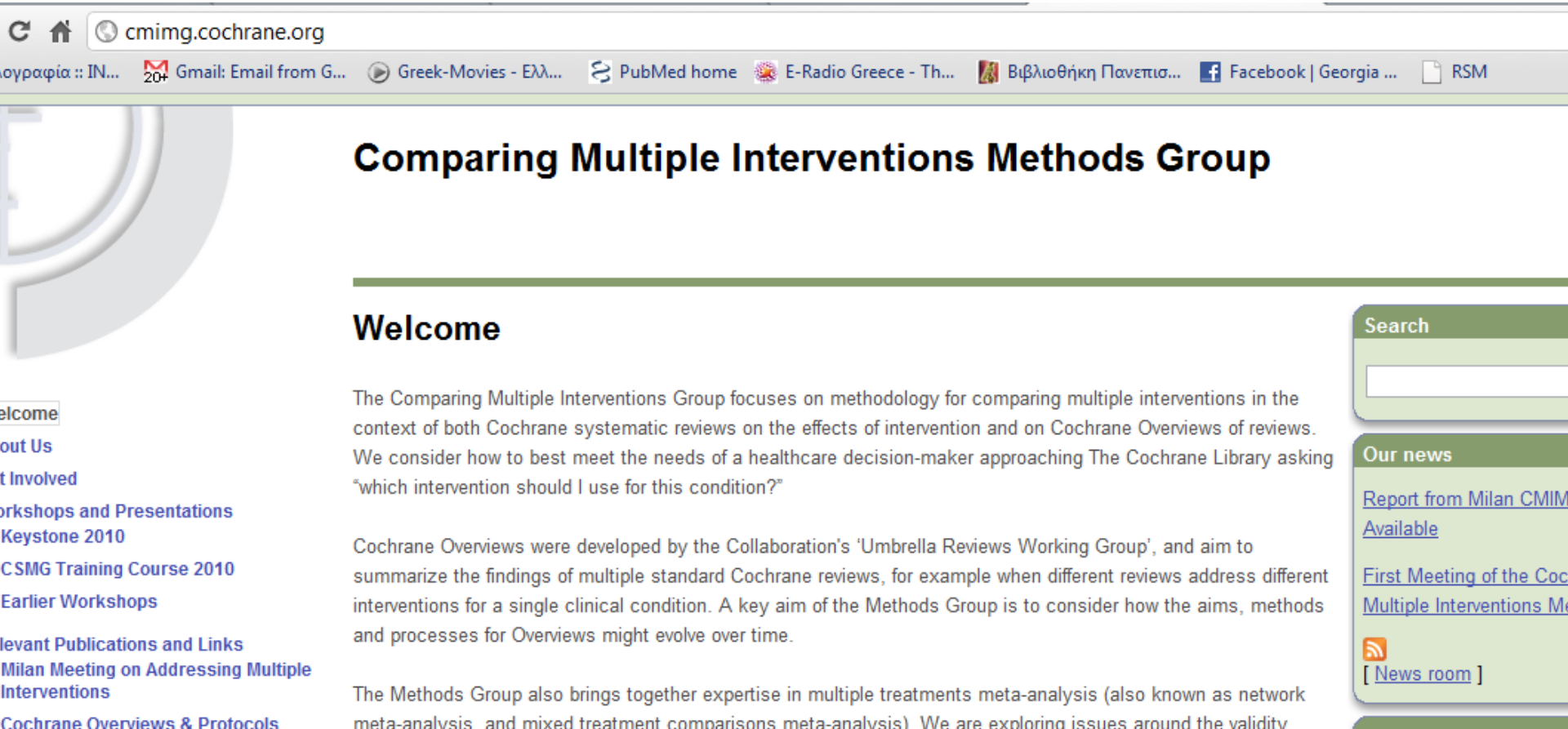
Research Synthesis Methods

The official journal of the Society for Research Synthesis Methodology
http://www.srsm.org/

A special issue for Network Meta-analysis published in 2012

The Cochrane Collaboration

A new methods group has been recently established to support reviews that aim to compare multiple interventions cmimg.cochrane.org



List of publications on methodological issues

Bucher HC, Guyatt GH, Griffith LE, Walter SD. 1997. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 50:683-691.

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.

Cooper NJ, Sutton AJ, Ades AE, Paisley S, Jones DR. 2007. Use of evidence in economic decision models: practical issues and methodological challenges. Health Economics 16:1277-1286.

Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. 2009. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. Statistics in Medicine 28:1861-1881.

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

Higgins JP, Whitehead A. 1996. Borrowing strength from external trials in a meta-analysis. Statistics in Medicine 15:2733-2749.

Salanti G, Ades AE, Ioannidis JP Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2010 Aug 3.

Salanti G, Dias S, Welton NJ, Ades AE et al Evaluating novel agent effects in multiple-treatments meta-regression. Stat Med. 2010 Oct 15;29(23):2369-83.

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

Salanti G, Kavvoura FK, Ioannidis JP. 2008b. Exploring the geometry of treatment networks. Ann Intern Med 148:544-553.

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.

Welton NJ, Cooper NJ, Ades AE, Lu G, Sutton AJ. 2008. Mixed treatment comparison with multiple outcomes reported inconsistently across trials: Evaluation of antivirals for treatment of influenza A and B. Statistics in Medicine 29:5620-5639.

Thank you!
Questions?