Multiple-**T**reatments **M**eta-Analysis

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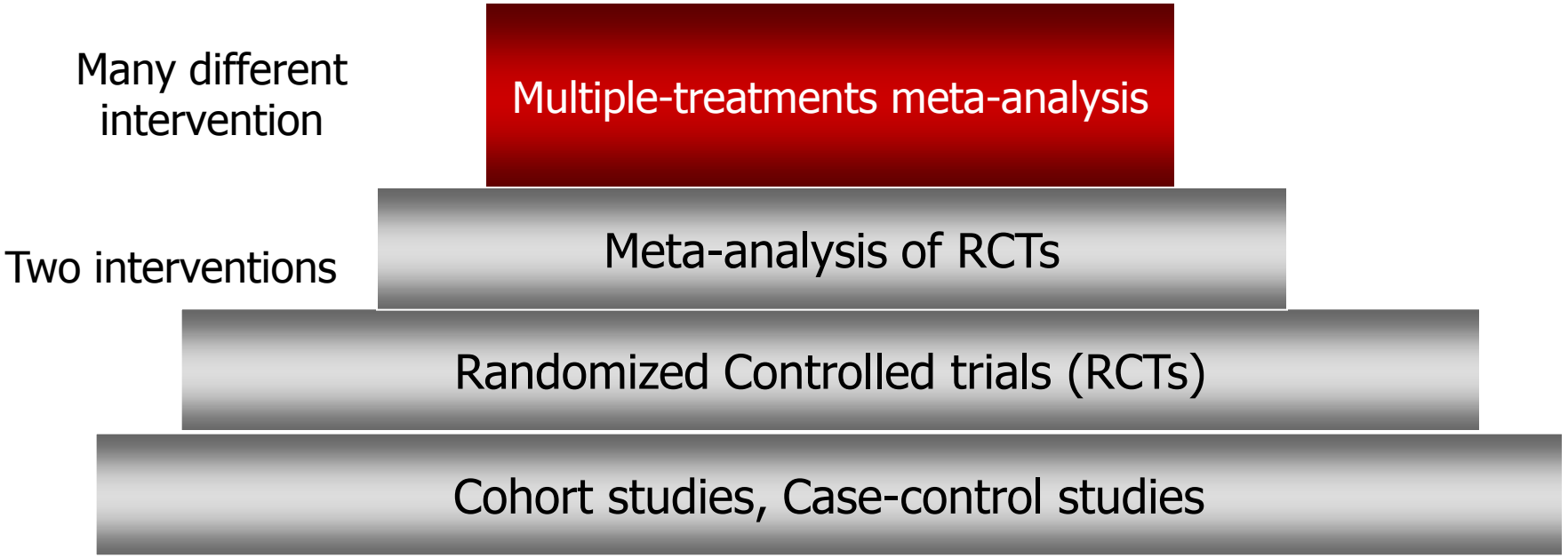
With thanks to Deborah Caldwell, Julian Higgins and Sofia Dias

Evidence Based Medicine

- Backbone: **meta-analysis**
- Rigorous statistical models
- Clinical practice guidelines
  - NICE, WHO, The Cochrane Collaboration, HuGENet



12 new generation antidepressants

19 **meta-analyses** published in the last two years

"Although **Mirtazapine** is likely to have a faster onset of action than **Sertraline and Paroxetine** no significant differences were observed..."

"...statistically significant differences in terms of efficacy .... between **Fluoxetine and Venlafaxine**, but the clinical meaning of these differences is uncertain..."

"...**meta-analysis** highlighted a trend in favour of **Sertraline** over other **Fluoxetine**"

"**Venlafaxine** tends to have a favorable trend in response rates compared with **duloxetine**"

Fluoxetine: 28€ Venlafaxine:111€ Sertaline: 76 €

How to do it?

Models within a Bayesian Framework

Advantages of the methods

Presentation of results

MTM using meta-regression In Workshop II

Assumption of consistency

Maths Warning!

Why use Bayesian statistics for meta-analysis?

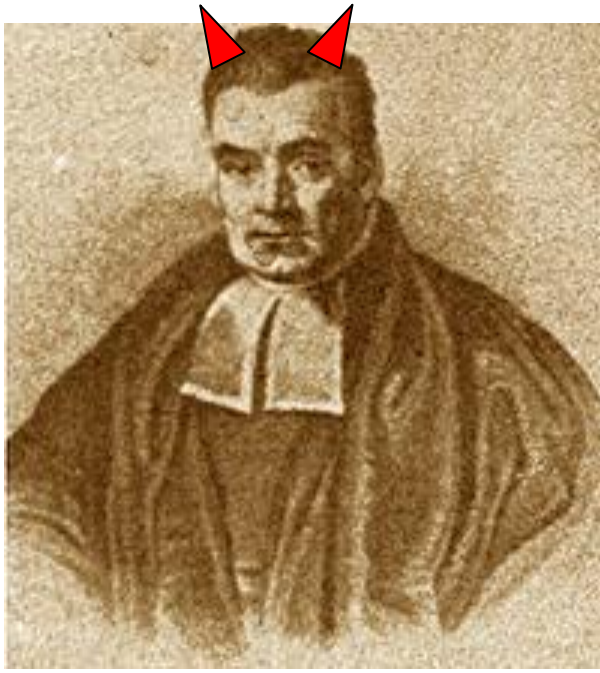
- **Natural approach for accumulating data**
- **Repeated updating of meta-analyses fine**: posterior should always reflect latest beliefs
- **People naturally think as Bayesians:** they have degrees of belief about the effects of treatment, which change when they see new data
- Probability statements about true effects of treatment easier to understand than confidence intervals and *p* -values

Why use Bayesian statistics for MTM?

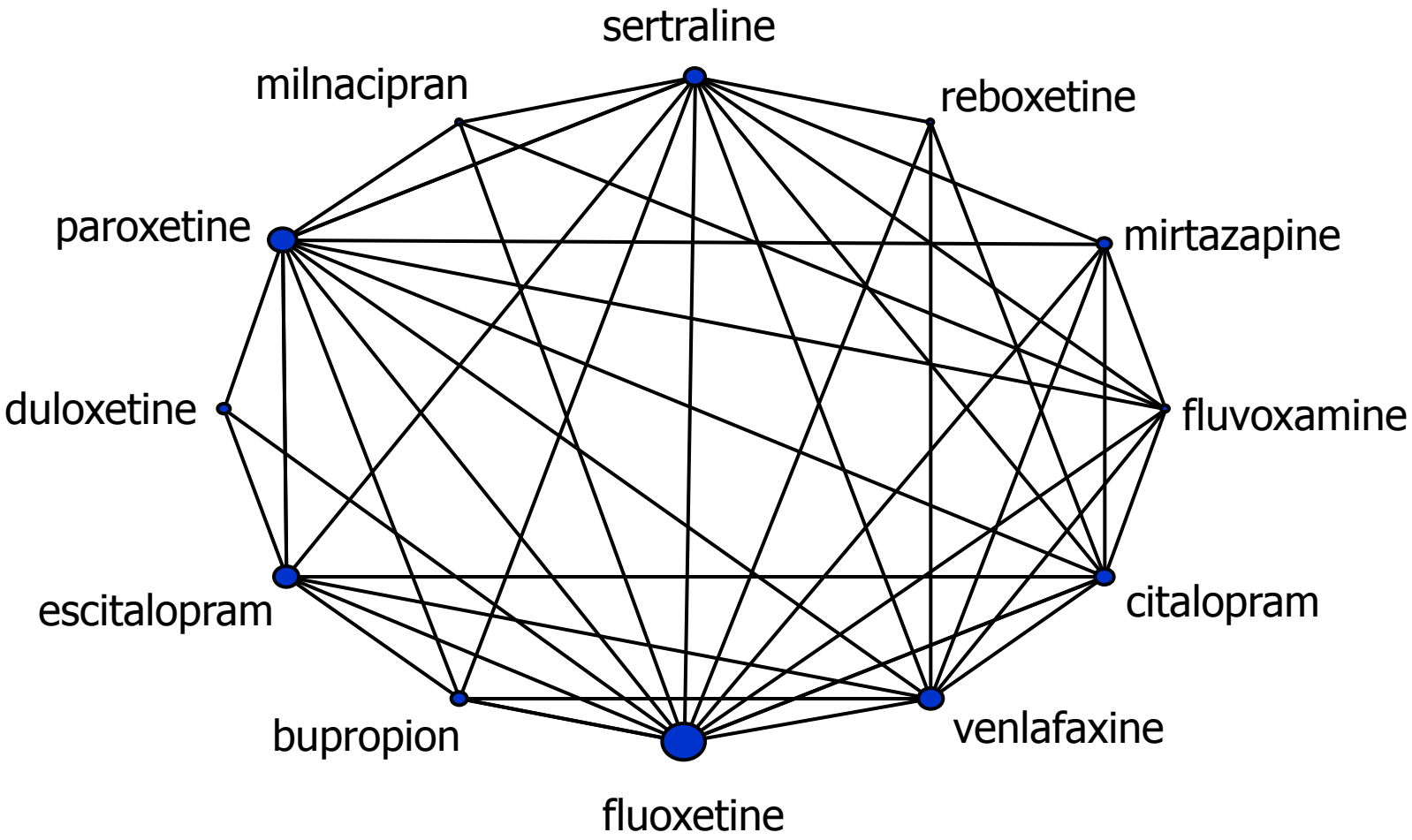
- Bayesian approach is **easier to account for correlations** induced by multi-arm trials
- Estimation of **predictive intervals** is straightforward
- Estimation of **ranking probabilities** is straightforward

- MTM with two-arm trials only

  Easy in frequentist meta-regression



Network of experimental comparisons



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

Network of experimental comparisons

Indirect estimation

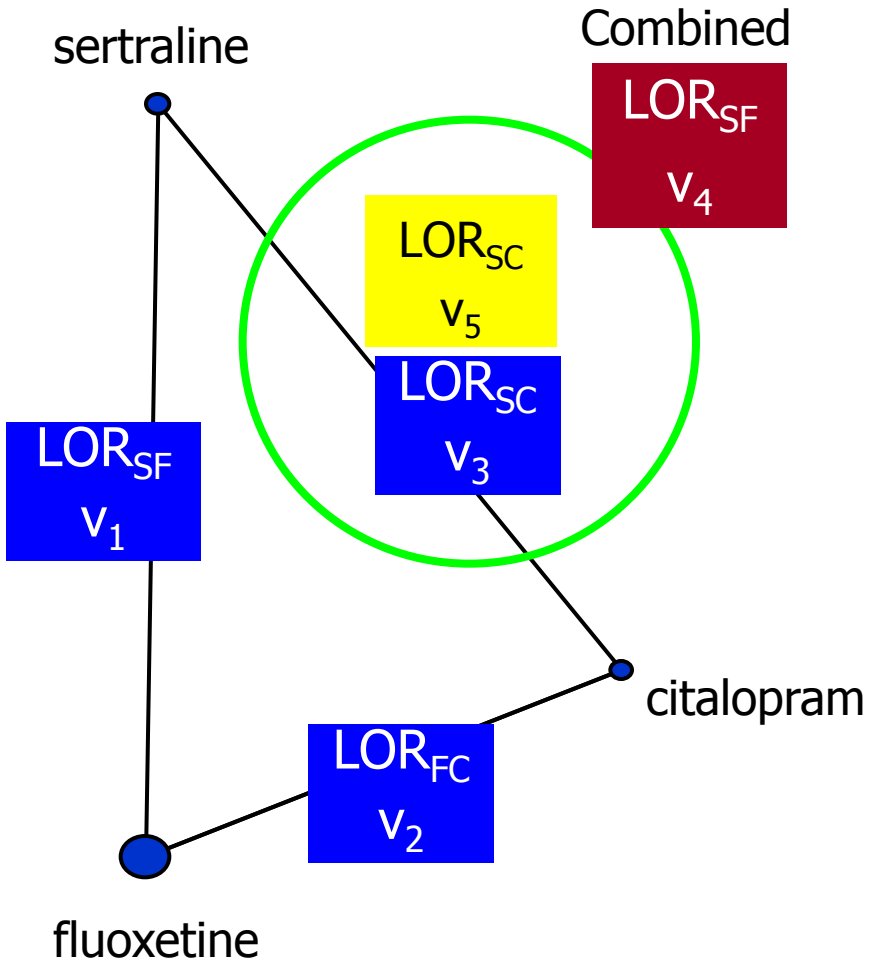
$LOR_{SC} = LOR_{SF} + LOR_{FC}$

$Var(LOR_{SC}) = v_5 = v_1 + v_2$

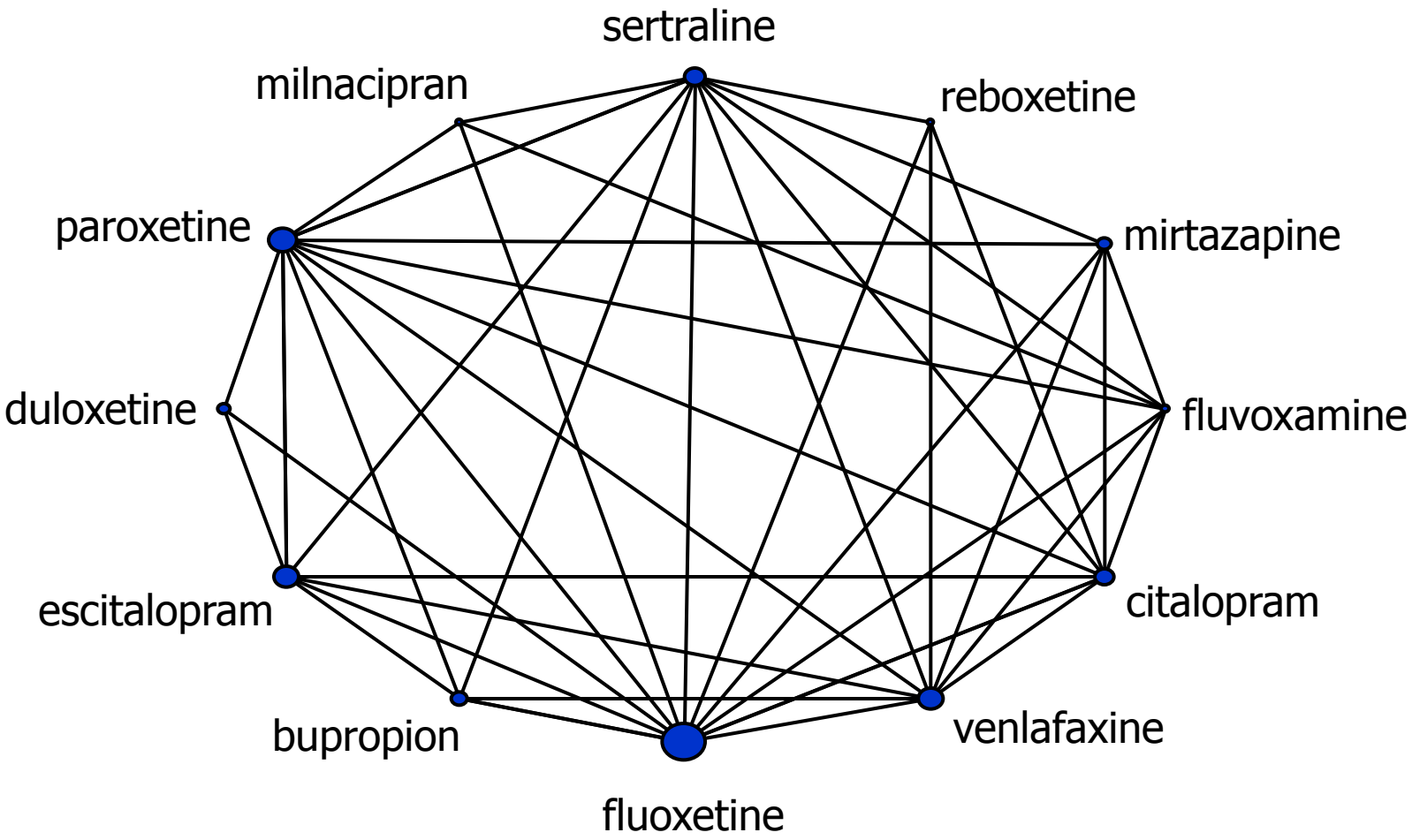
Combine the direct estimate with the indirect estimate using IV methods

Get a combined ***LOR!***

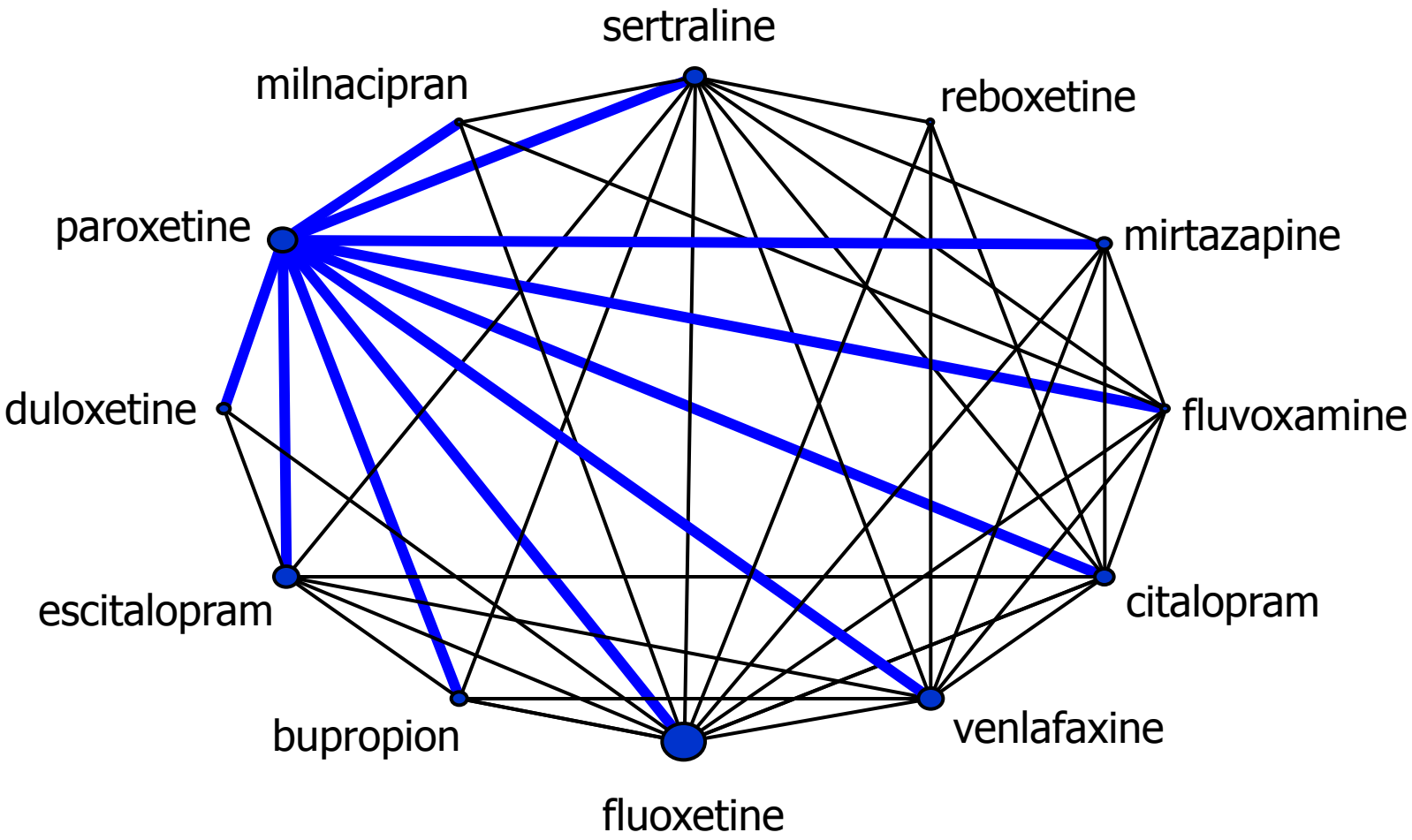
v4<v3



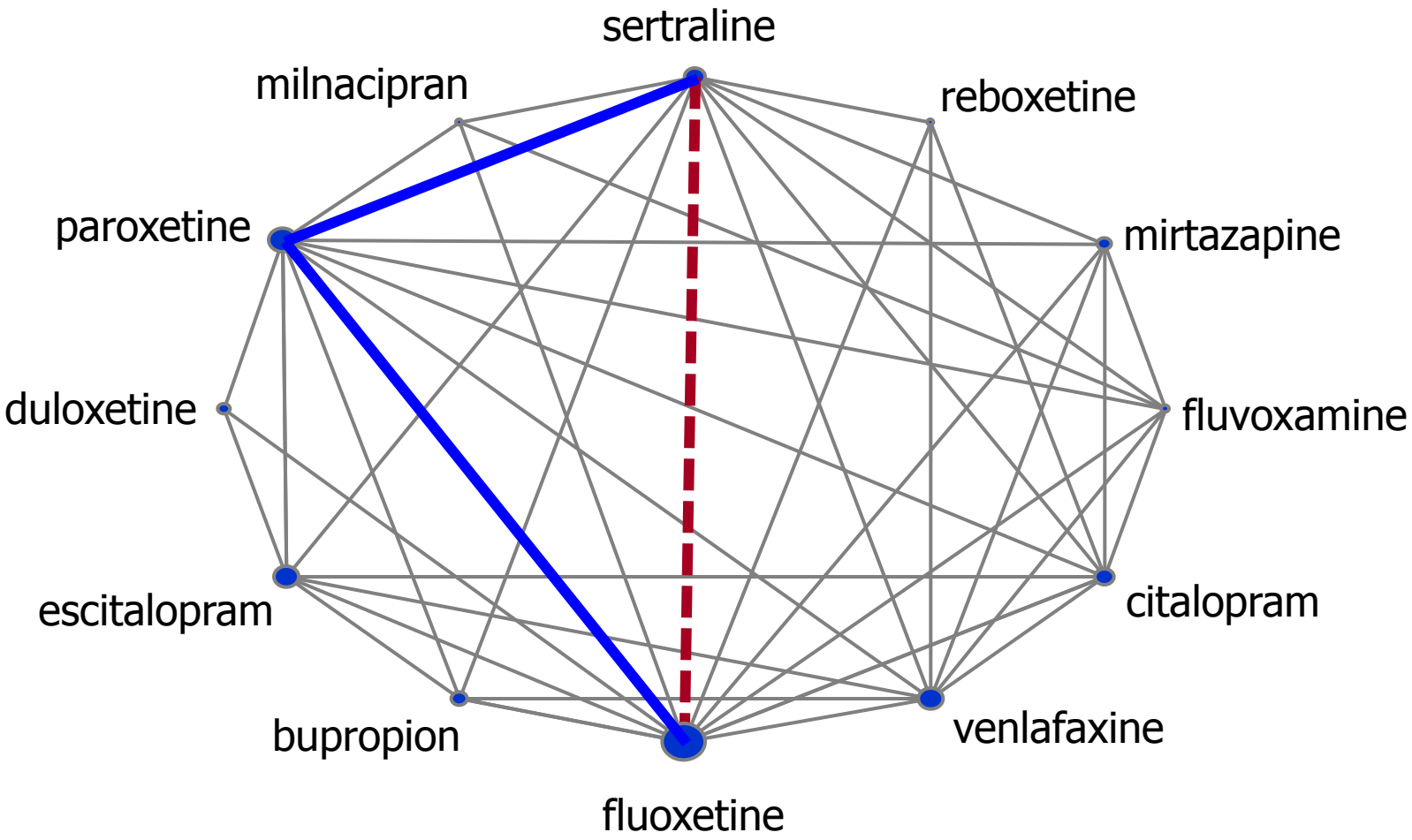
Expand the idea in the entire network!



Choose basic parameters



All other contrasts are functional!



Distributions of the observations

$y_i^{AC} \sim N(\theta_i^{AC}, se_i^2)$

Distributions of the random effects

$\theta_i^{AC} \sim N(\mu^{AC}, \tau^2)$

Distributions of the observations

$y_i^{AC} \sim N(\theta_i^{AC}, se_i^2)$

$y_i^{BC} \sim N(\theta_i^{BC}, se_i^2)$

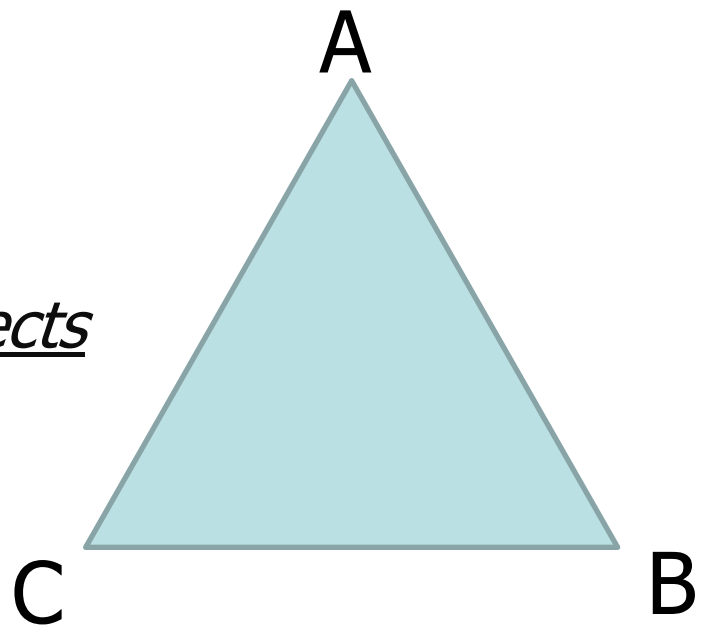
$y_i^{AB} \sim N(\theta_i^{AB}, se_i^2)$

Distributions of the random effects

$\theta_i^{AC} \sim N(\mu^{AC}, \tau^2)$

$\theta_i^{BC} \sim N(\mu^{BC}, \tau^2)$

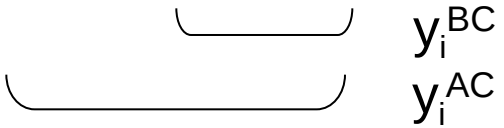
$\theta_i^{AB} \sim N(\mu^{AB}, \tau^2)$



$$\mu^{AB} = \mu^{AC} - \mu^{BC}$$

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



- 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*

Distributions of the observations

$y_i^{AC} \sim N(\theta_i^{AC}, se_i^2)$

$y_i^{BC} \sim N(\theta_i^{BC}, se_i^2)$

$y_i^{AB} \sim N(\theta_i^{AB}, se_i^2)$

$(y_i^{AC}, y_i^{BC}) \sim MVN((\theta_i^{AC}, \theta_i^{BC}), S)$

S is the variance-covariance matrix estimated from the data

Distributions of the random effects

$\theta_i^{AC} \sim N(\mu^{AC}, \tau^2)$

$\theta_i^{BC} \sim N(\mu^{BC}, \tau^2)$

$\theta_i^{AB} \sim N(\mu^{AB}, \tau^2)$

$(\theta_i^{AC}, \theta_i^{BC}) \sim MVN((\mu^{AC}, \mu^{BC}), \Sigma)$

Σ is the variance-covariance matrix of the random effects (involves $\tau^2/2$) which is unknown

$$\mu^{AB} = \mu^{AC} - \mu^{BC}$$

Correlated observations

$(y_i^{AC}, y_i^{BC}) \sim MVN((\theta_i^{AC}, \theta_i^{BC}), S)$

S is the variance-covariance matrix estimated from the data

$$S = \begin{pmatrix} var_1 & c \\ c & var_2 \end{pmatrix}$$

c depends on the measure y_i
e.g. When we observe mean difference
$Cov(y_i^{AC}, y_i^{BC}) = var_C$

Correlated random effects

$(\theta_i^{AC}, \theta_i^{BC}) \sim MVN((\mu^{AC}, \mu^{BC}), \Sigma)$

Σ is the variance-covariance matrix

of the random effects (involves $\tau^2/2$)

which is unknown

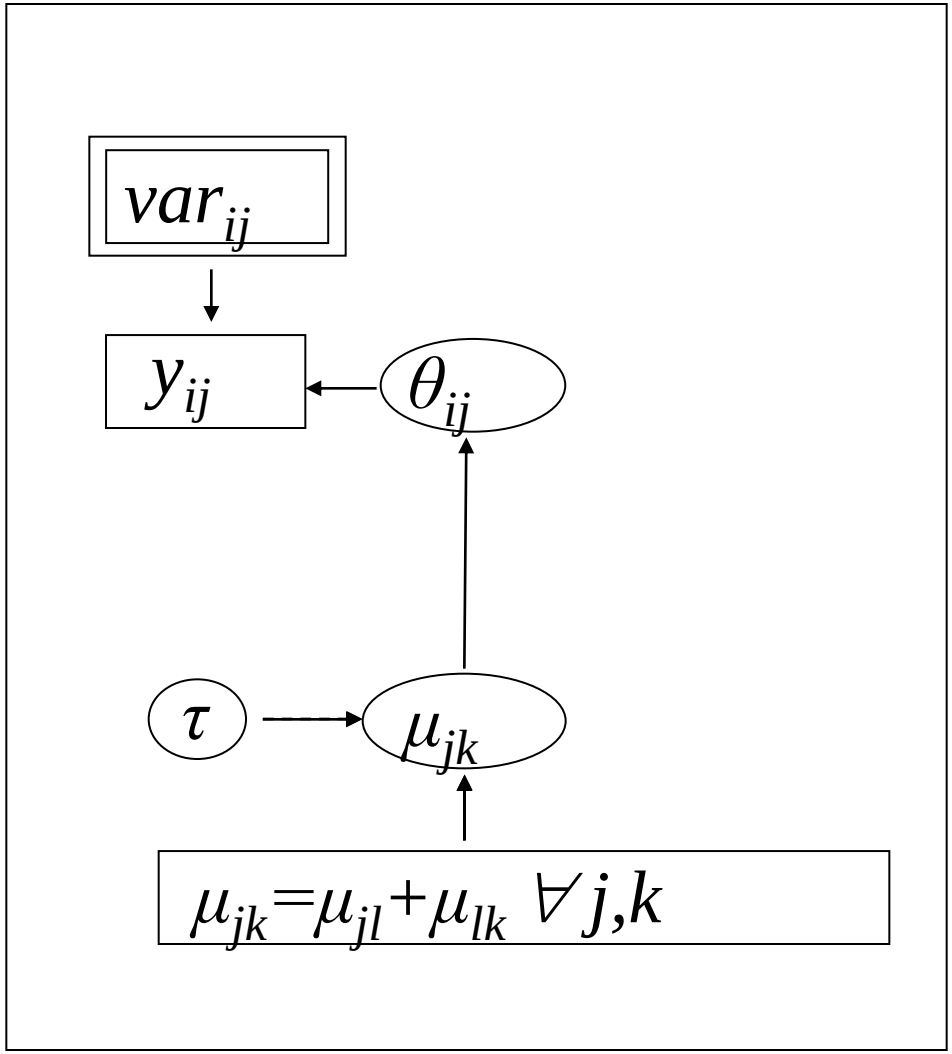
$$\Sigma = \begin{pmatrix} \tau_{AC}^{\ 2} & c \\ c & \tau_{BC}^{\ 2} \end{pmatrix}$$

c depends on τ^2

e.g. Assuming equal heterogeneities

Cov($\theta_i^{AC}, \theta_i^{BC}$ *)* $= \tau^2/2$

Borrowing strength from external trials in a meta-analysis. Higgins JP, Whitehead A. Stat Med. 1996 Dec 30;15(24):2733-49.



For each study arm j, k in study i
According to a baseline treatment l

Treatments for first bleeding in cirrhosis

No. studies	Control	Sclerotherapy	Beta-blockers
17	x^C/n^C	x^S/n^S	
7	x^C/n^C		x^B/n^B
2	x^C/n^C	x^S/ n^S	x^B/n^B

Higgins & Whitehead 1996, Stat Med

$$x_i^C \sim B(\pi_i^C, n_i^C) \qquad \text{Logit}(\pi_i^C)=u_i \qquad \theta_i^{CS} \sim N(\mu^{CS}, \tau^2)$$

$$x_i^S \sim B(\pi_i^S, n_i^S) \qquad \text{Logit}(\pi_i^S)=u_i+\theta_i^{CS} \qquad \theta_i^{CB} \sim N(\mu^{CB}, \tau^2)$$

$$x_i^B \sim B(\pi_i^B, n_i^B) \qquad \text{Logit}(\pi_i^B)=u_i+\theta_i^{CB}$$

In the two 3-arms trials we only substitute

$$(\theta_i^{CS}, \theta_i^{CB}) \sim MVN((\mu^{CS}, \mu^{CB}), \Sigma)$$

$$\mu^{SB} = \mu^{CB} - \mu^{CS}$$

l,j,k random treatments

y_i the outcome of experiment i

θ_i the random effect

$$\begin{pmatrix} y_{1,l_1,j_1} \\ y_{2,l_2,j_2} \\ \vdots \\ y_{N,l_N,j_N} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_{1,l_1,j_1} \\ \theta_{2,l_2,j_2} \\ \vdots \\ \theta_{N,l_N,j_N} \end{pmatrix}, S \right)$$

Likelihood

$$\begin{pmatrix} \theta_{1,l_1,j_1} \\ \theta_{2,l_2,j_2} \\ \vdots \\ \theta_{N,l_N,j_N} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{1,l_1,j_1} \\ \mu_{2,l_2,j_2} \\ \vdots \\ \mu_{N,l_N,j_N} \end{pmatrix}, \begin{bmatrix} \tau_1^2 & c & c & c \\ c & \tau_2^2 & c & c \\ \vdots & \vdots & \ddots & \vdots \\ c & c & c & \tau_N^2 \end{bmatrix} \right)$$

Random effects

$$\mu_{lj} = \mu_{lk} + \mu_{kj}$$

Coherence equations

Winbugs Code

Likelihood

```
model{
for(i in 1:NHtH){delta[i]~dnorm(mean[i],precision )}
delta[(NHtH+1):N]~dmnorm(mean[(NHtH+1):N],K[,])
for(i in 1:(N-NHtH)){for(j in 1:(N-NHtH)){
K[i,j]<-precision*H[i,j]}}
```

Random effects

```
for(i in 1:N){mean[i] <- d[t[i]] - d[b[i]] }
for (k in 1:NT)  {d[k] ~ dnorm(0,.0001) }
for (c in 1:(NT-1)) {  for (k in (c+1):NT)
{ mean[c,k] <- d[k] - d[c]
 OR[c,k] <- exp(mean[c,k] )}}
```

Coherence equations

```
precision<-1/pow(sd,2)
sd~dnorm(0,1)I(0,)}
```

Priors

How to do it?

Models within a Bayesian Framework

Advantages of the methods

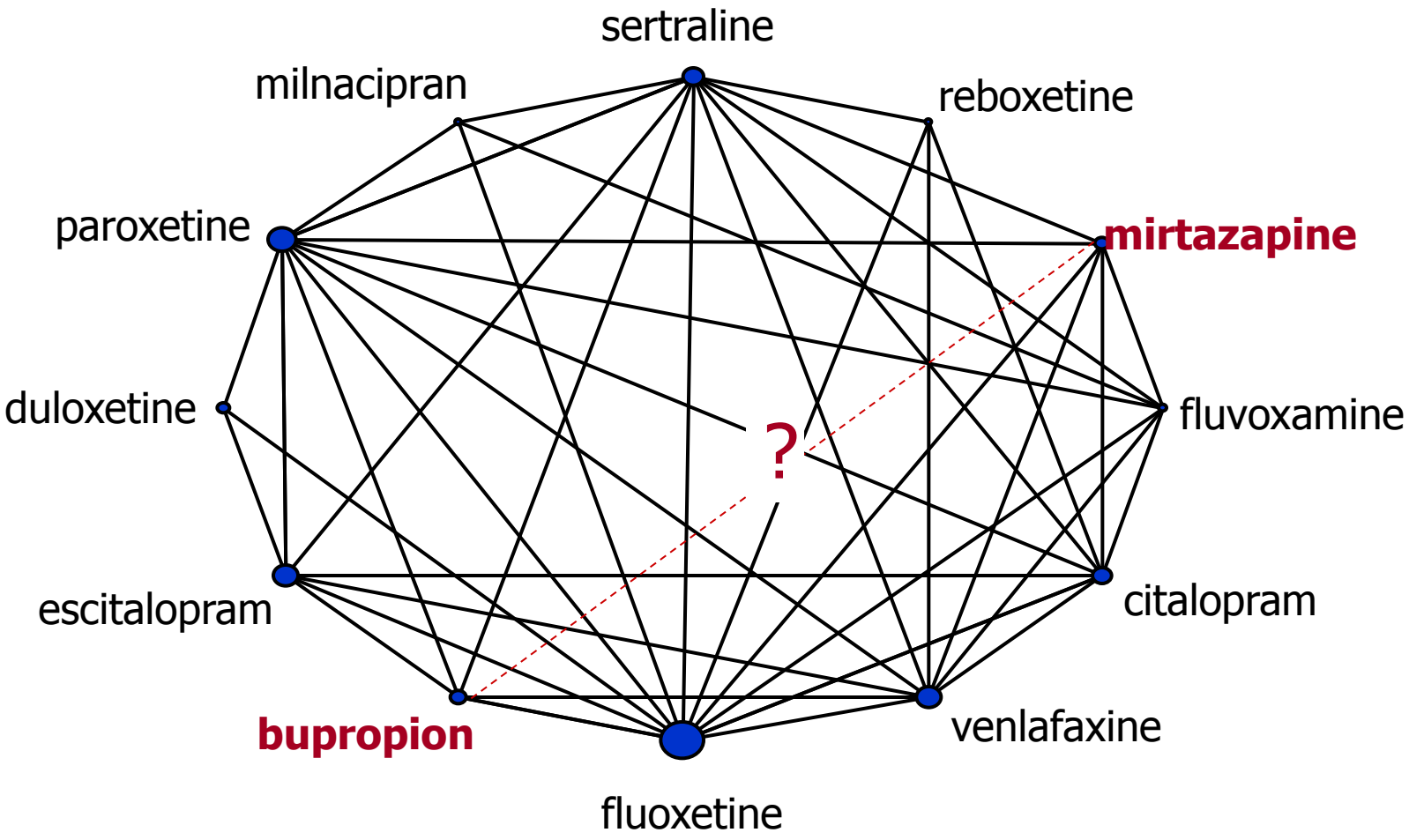
Presentation of results

Assumption of consistency

Maths Warning!

Advantages

- Ranking of many treatments for the same condition (see later)
- Comprehensive use of all available data (indirect evidence)
- Comparison of interventions which haven't been directly compared in any experiment



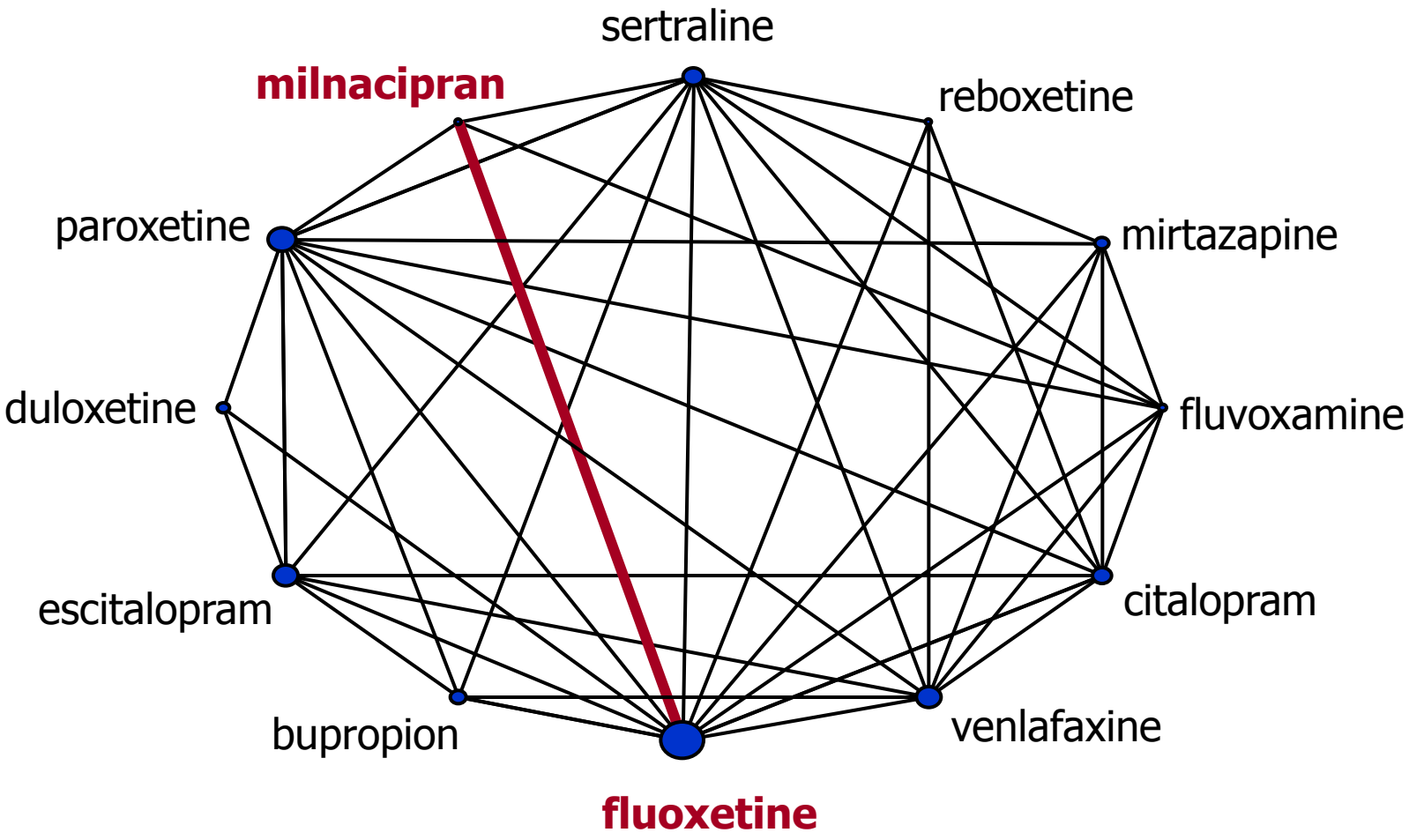
OR(B vs M)= 0.79 (0.72, 1)

Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

Advantages

- Ranking of many treatments for the same condition (see later)
- Comprehensive use of all available data (indirect evidence)
- Comparison of interventions which haven't been directly compared in any experiment
- Improved precision for each comparison

Network of experimental comparisons



Fluoxetine vs Milnacipran (response to treatment)
Meta-analysis: 1.15 (0.72, 1.85)
MTM: 0.97 **(0.69, 1.32)**

Treatments for first bleeding in cirrhosis

No. studies	Control	Sclerotherapy	Beta-blockers
17	x^C/n^C	x^S/n^S	
7	x^C/n^C		x^B/n^B
2	x^C/n^C	x^S/ n^S	x^B/n^B

Higgins & Whitehead 1996, Stat Med

- Only 2 studies: LOR $_{BS}$= – 0.77 (– 7.74, 6.23)
- All studies: LOR $_{BS}$= – 0.18 (– 1.22, 0.82)

We gained precision

Stat Med *1996 Higgins and Whitehead [the first MTM]*

How to do it?

Models within a Bayesian Framework

Advantages of the methods

Presentation of results

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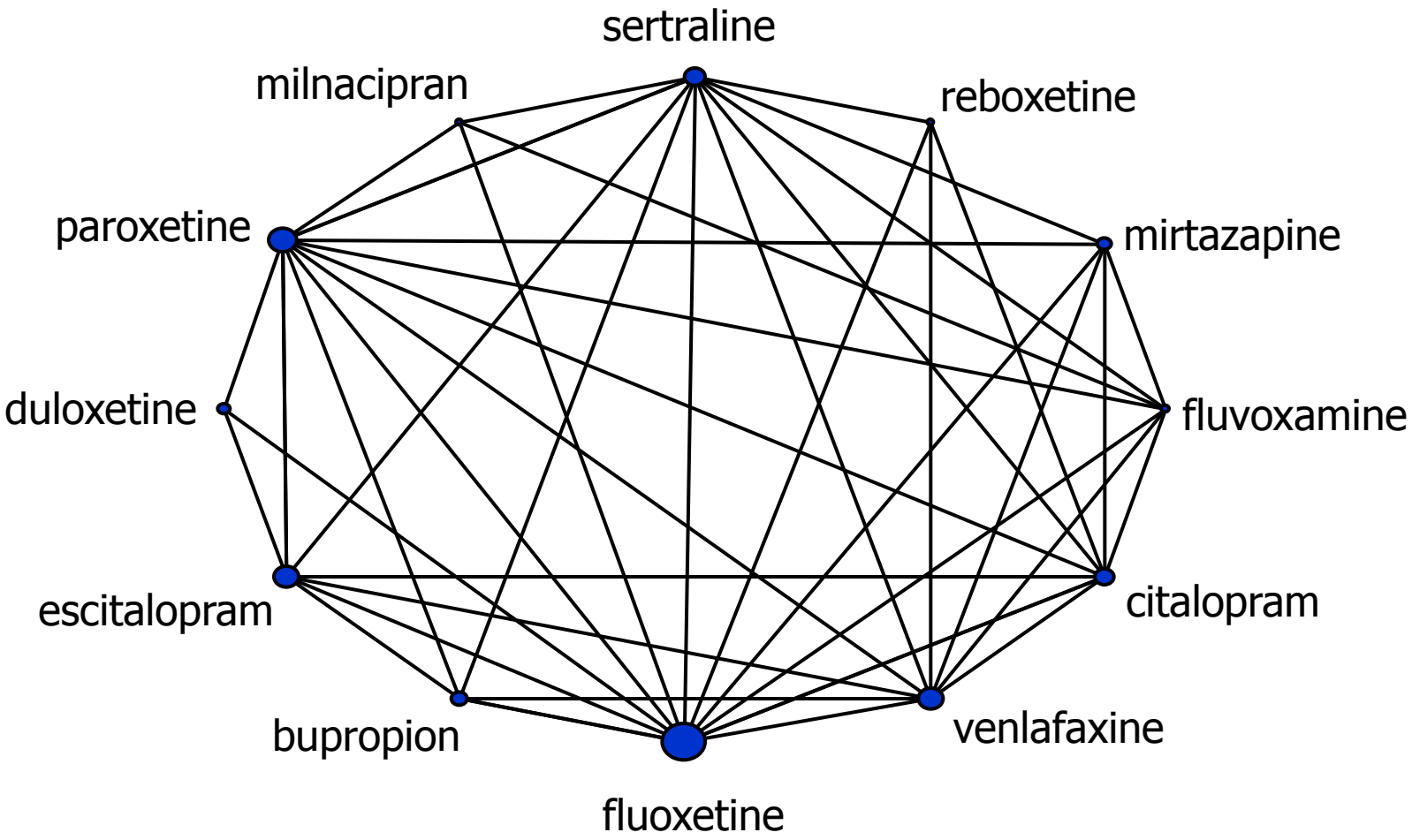
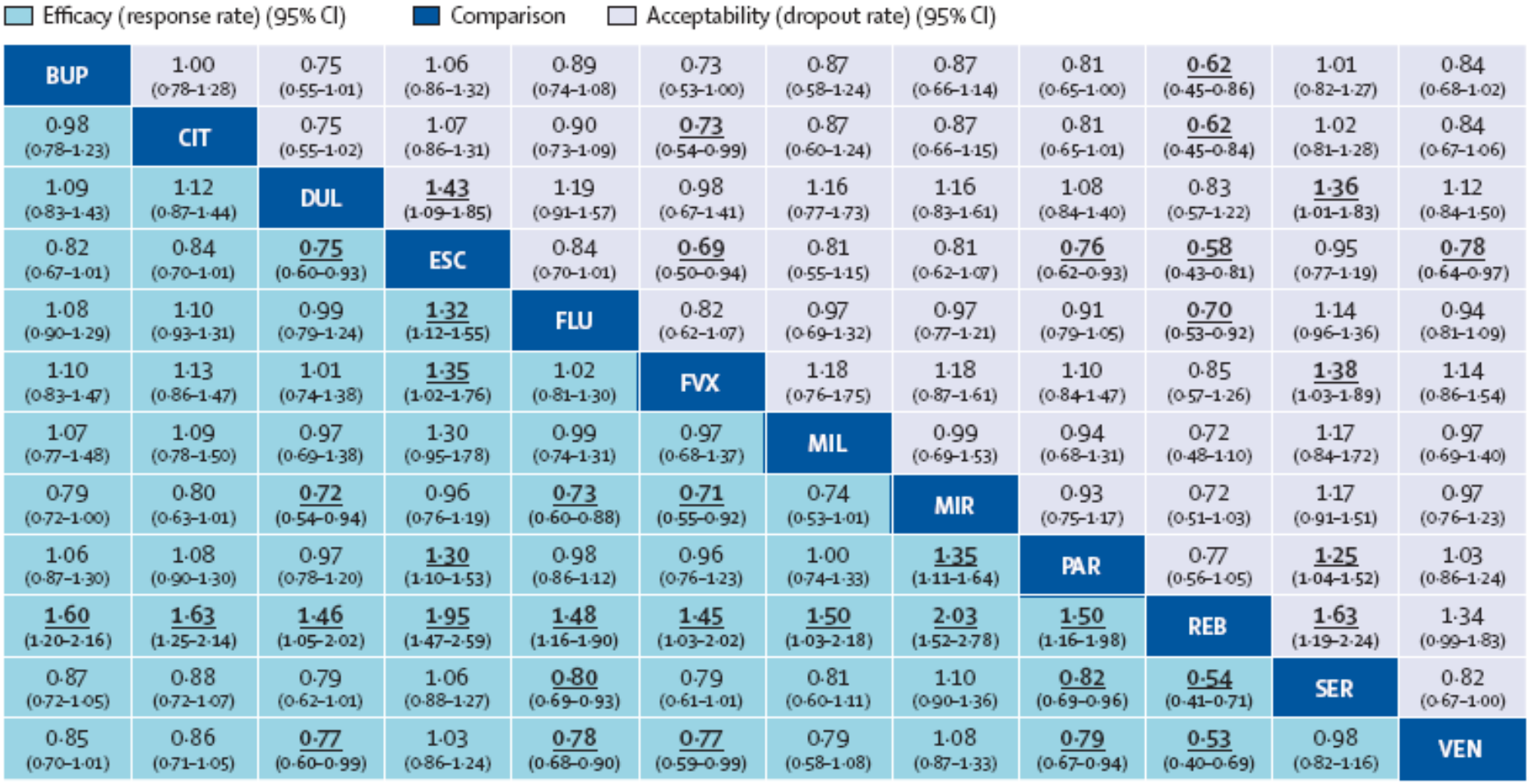
Ranking measures from MTM

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

Network of experimental comparisons



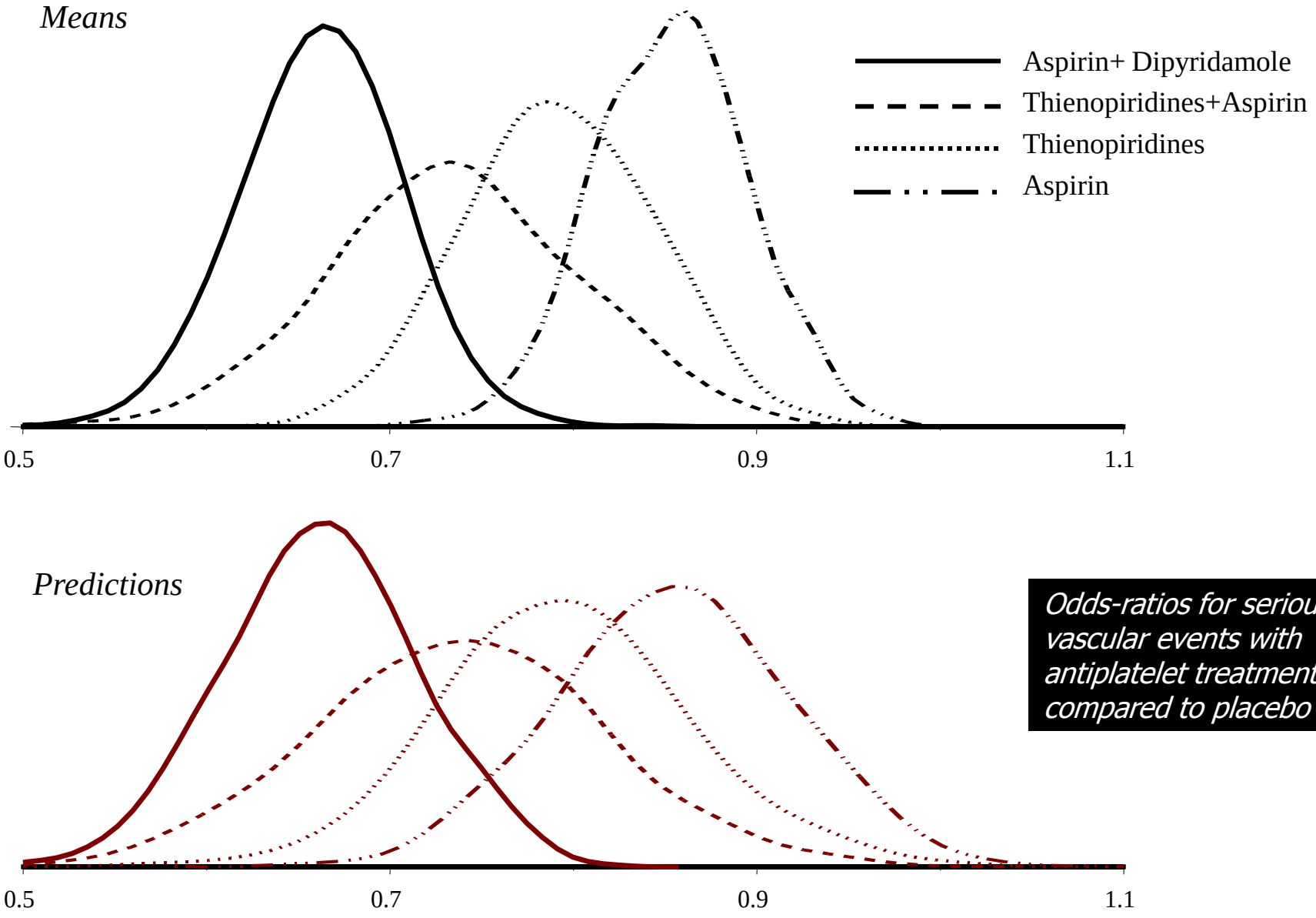
Lancet 2009 *Cipriani, Fukurawa, Salanti et al*



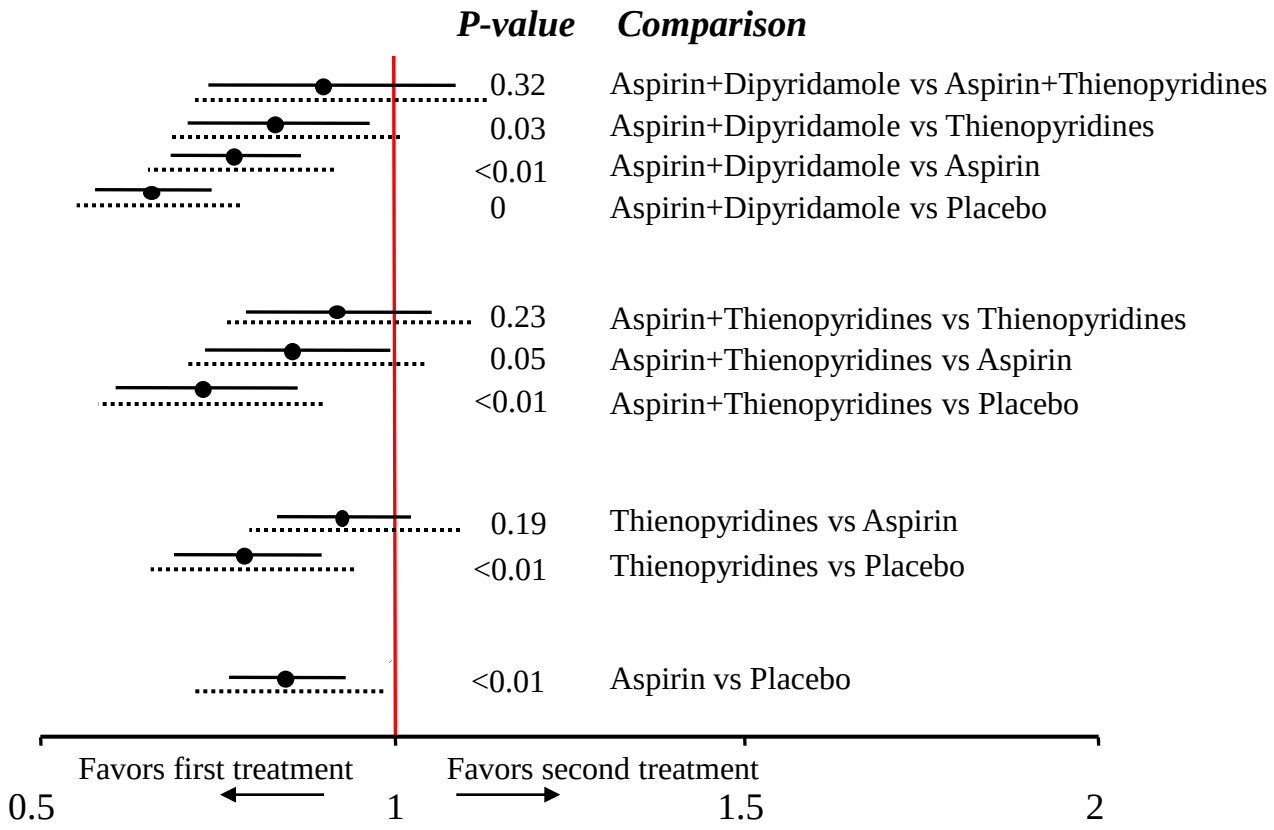
OR>1 means the treatment in top-left is better

Ranking measures from MTM

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


Means
Aspirin+ Dipyridamole
Thienopiridines+Aspirin
Thienopiridines
Aspirin
0.5
0.7
0.9
1.1
Predictions
0.5
0.7
0.9
1.1
Odds-ratios for serious vascular events with antiplatelet treatments compared to placebo
Odds ratios for severe vascular events compared to placebo

Serious vascular events with antiplatelet regimens



Odds Ratio for serious vascular event

J Clin Epidemiol. 2010 *Salanti, Ades, Ioannidis*

Probabilities

- Estimate for each treatment ***the probability to be 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
- But this does not convey the entire picture…

12 new generation antidepressants

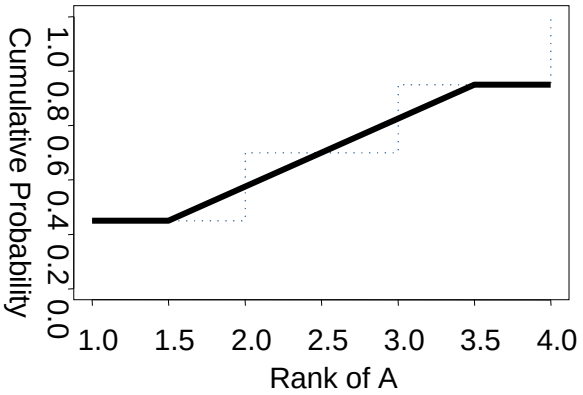
19 **meta-analyses** published in the last two years

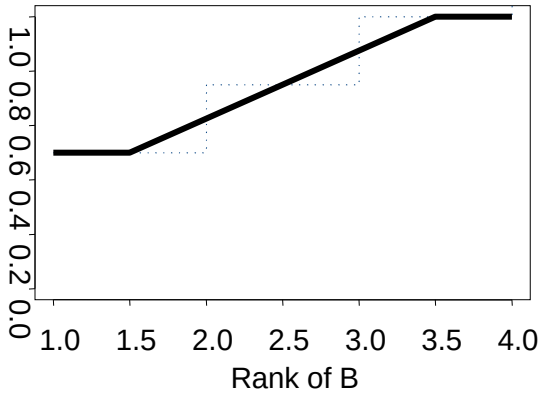
paroxetine	reboxetine
duloxetine	mirtazapine
escitalopram	fluvoxamine
milnacipran	citalopram
sertraline	venlafaxine
bupropion	fluoxetine
milnacipran	paroxetine
sertraline	duloxetine
bupropion	escitalopram
fluvoxamine	milnacipran

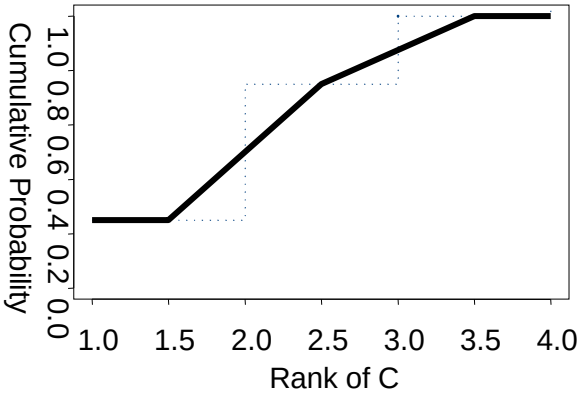
	Probability to be the best
paroxetine	0%
sertraline	7%
citalopram	0%
escitalopram	26%
fluoxetine	0%
fluvoxamine	0%
milnacipran	1%
venlafaxine	11%
reboxetine	0%
bupropion	0%
mirtazapine	54%
duloxetine	0%

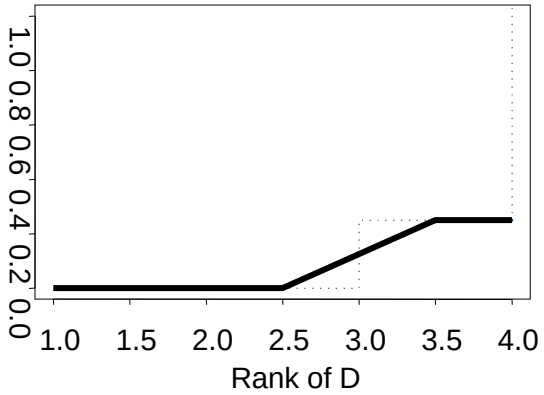
% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00
j=2	0.50	0.75	0.75	0.00
j=3	0.75	1.00	1.00	0.25
j=4	1.00	1.00	1.00	1.00

i the treatment
j the rank

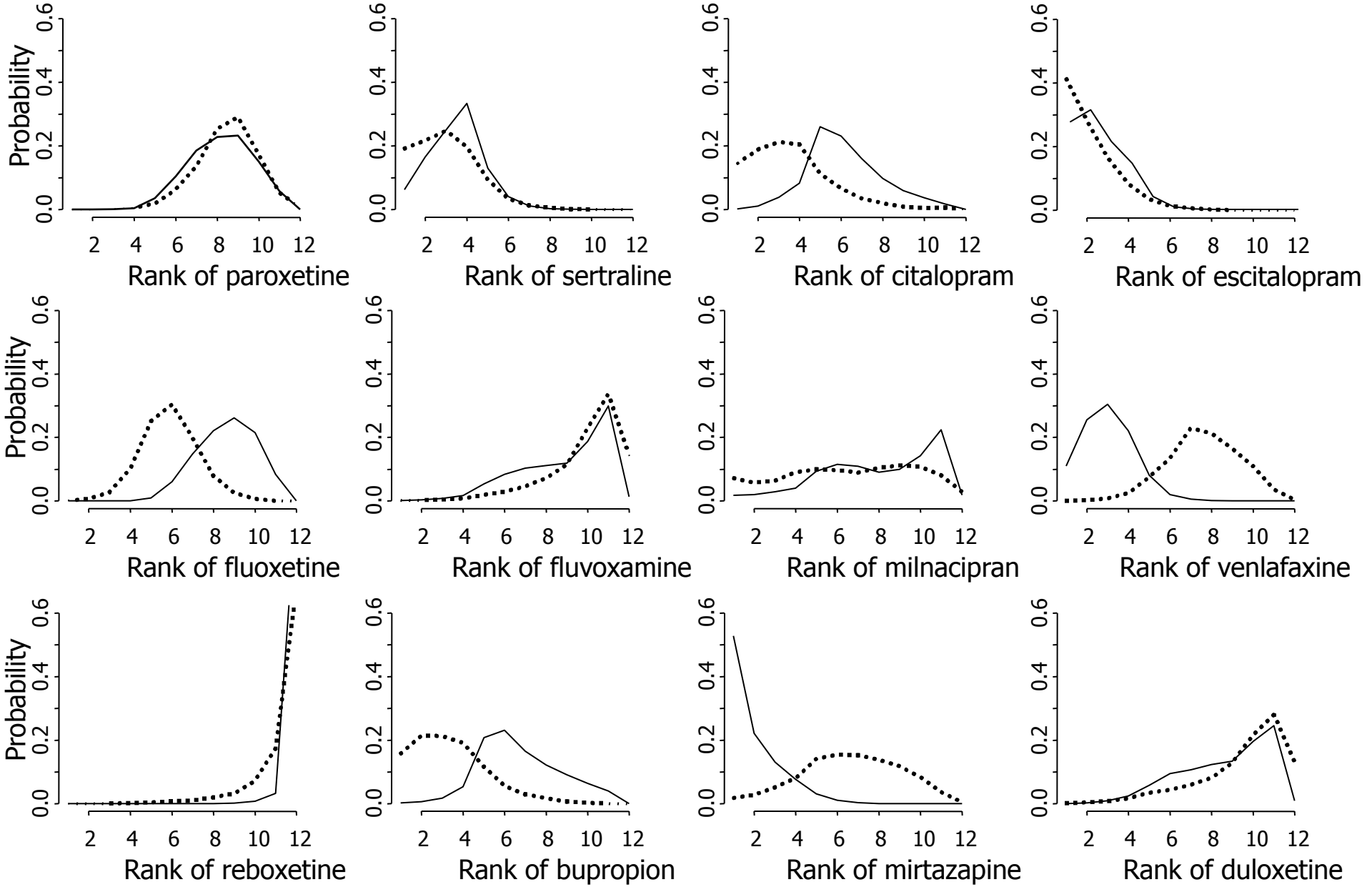








The areas under the cumulative curves for the four treatments of the example above are
A=0.5
B=0.75
C=0.67
D=0.08



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

Surface under the cumulative ranking curve

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

$$\text{Cumulative ranking curve}_j = \frac{\sum_{l=1}^{T-1} p_{j,l}}{T-1}$$

Treatments *j*, *l*

T Total number of treatments

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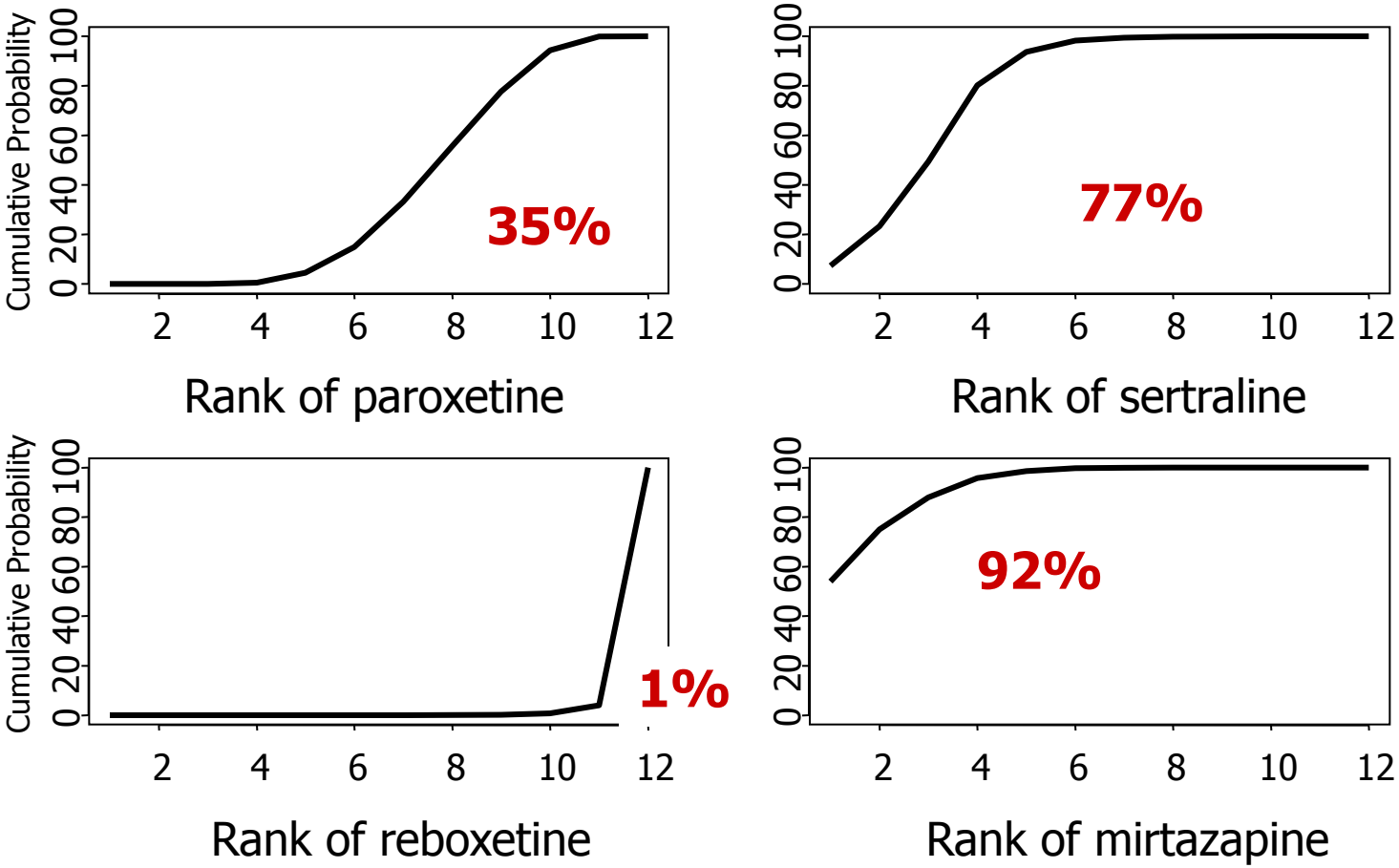
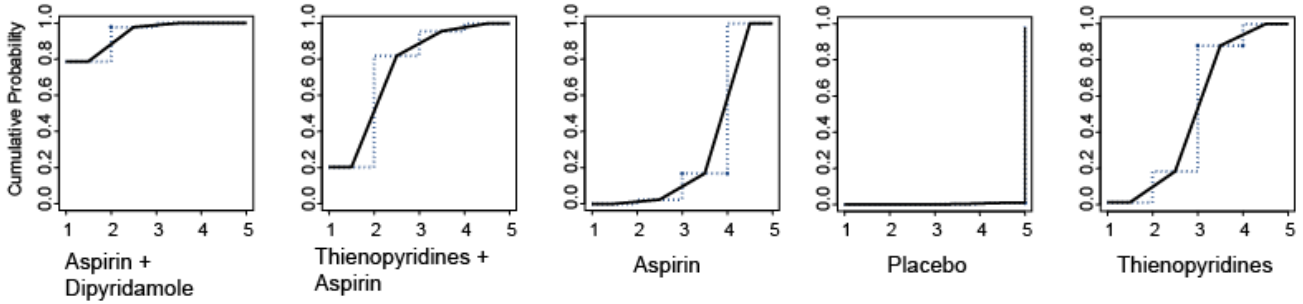
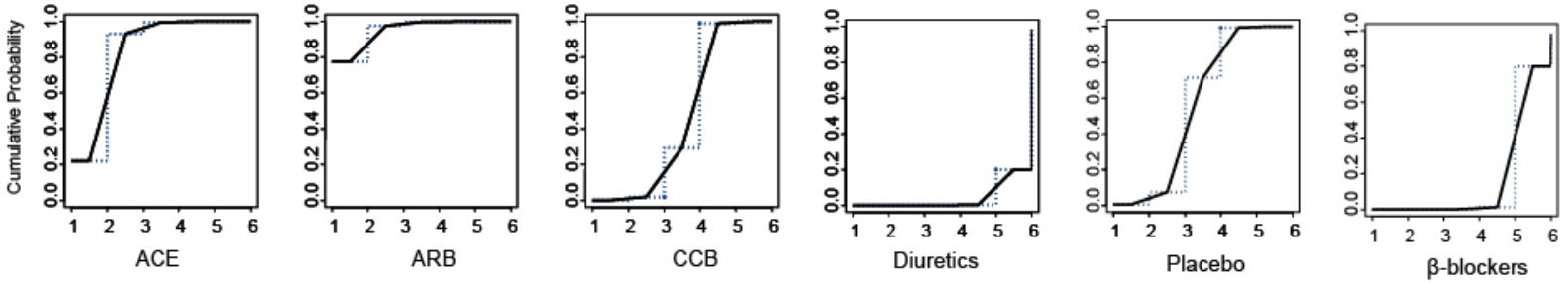
Surface under the cumulative ranking curve



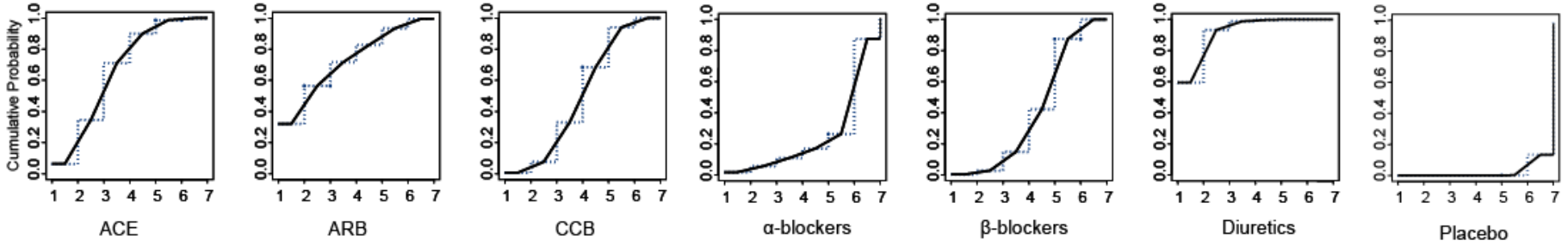
Serious vascular events with antiplatelet regimens



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!

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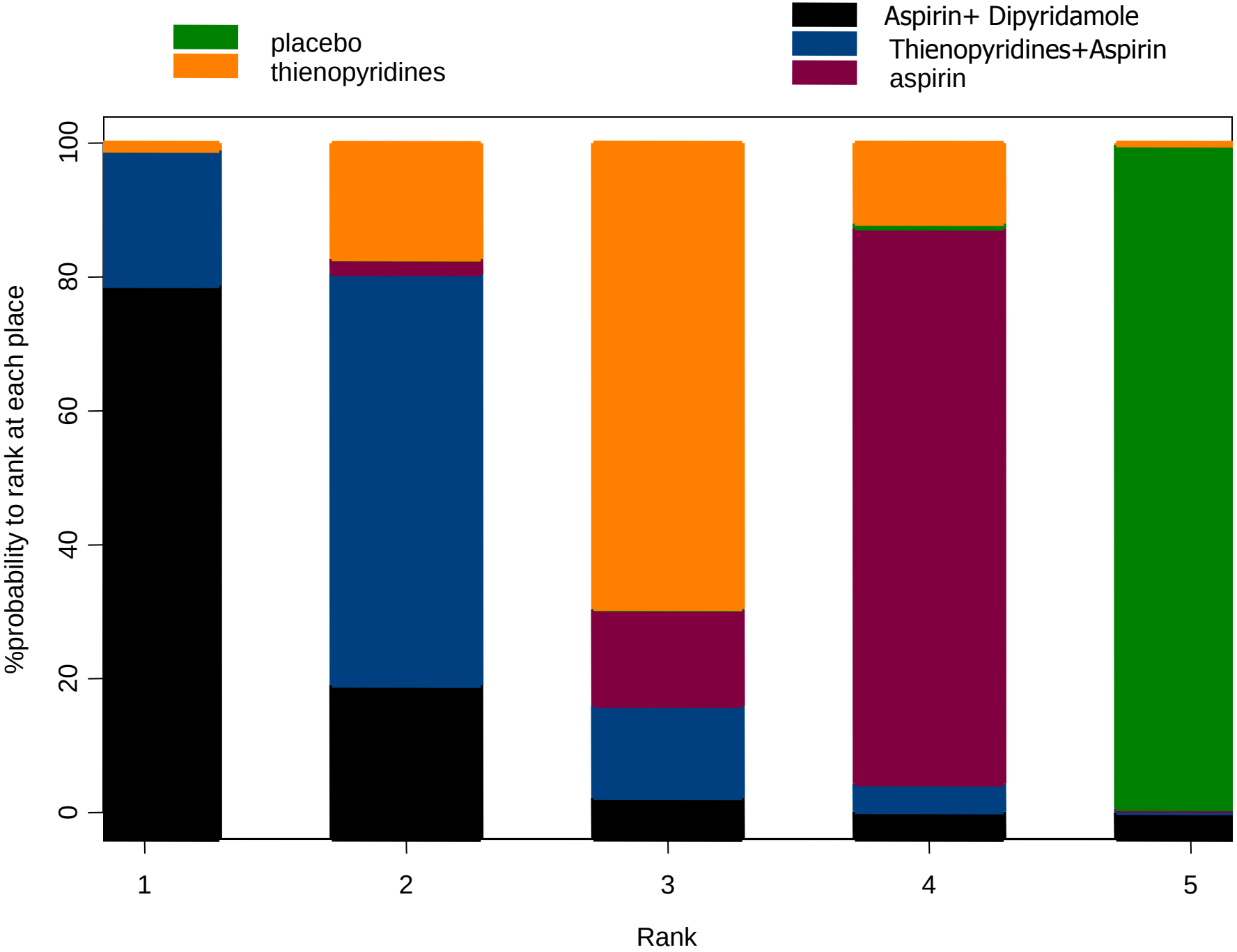

J Clin Epidemiol. 2010 *Salanti, Ades, Ioannidis*

How to do it?

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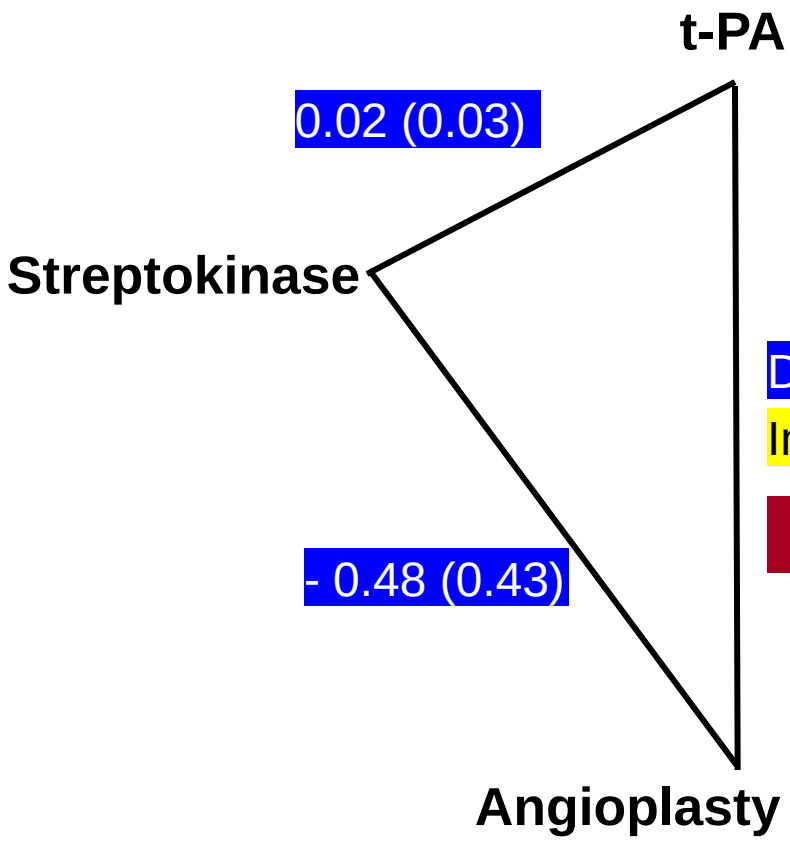
Maths Warning!

Inconsistency

LOR (SE) for MI

Calculate a difference between direct and indirect estimates



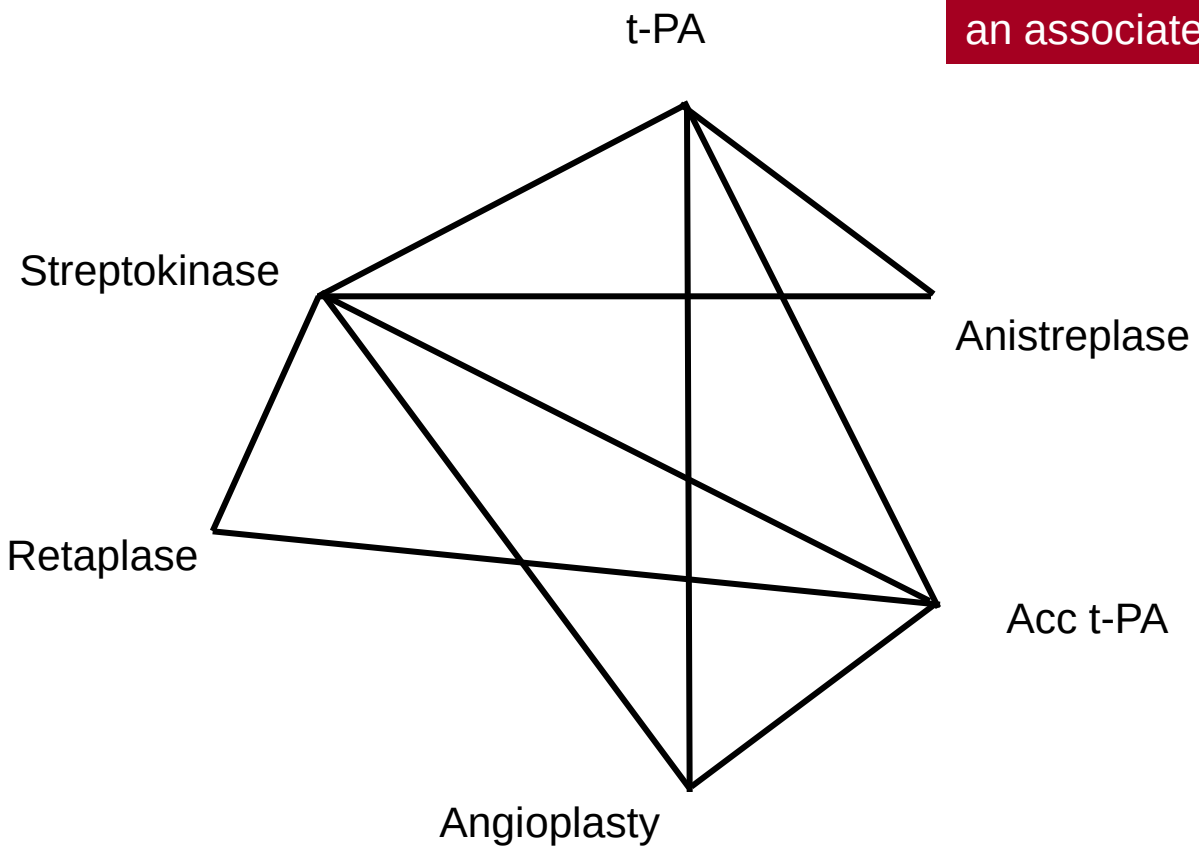
Direct t-PA vs Angioplasty= – 0.41 (0.36)

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

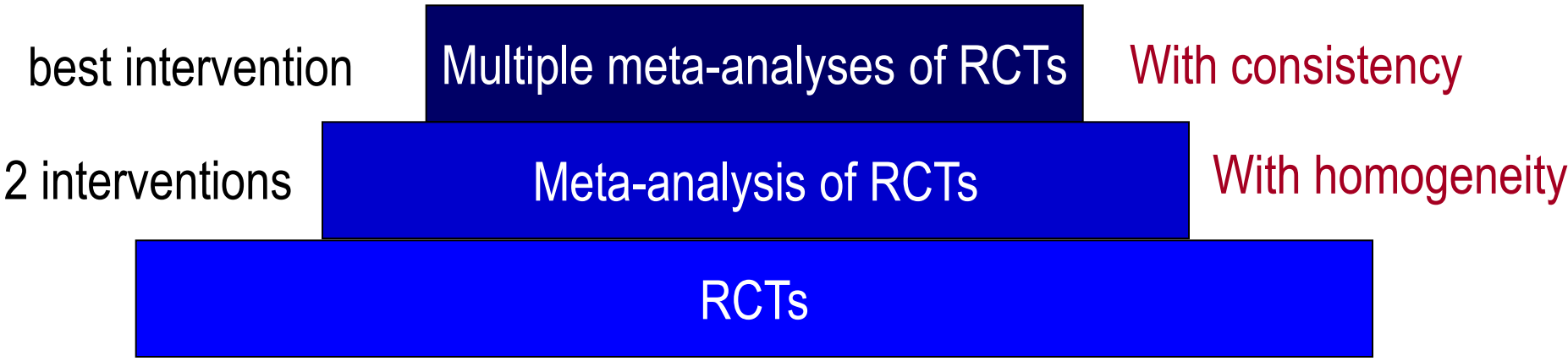
Inconsistency Factor IF = 0.05

Inconsistency

Calculate IF for all ‘triangles’ and an associated 95%CI



Inconsistency - Heterogeneity



- *Heterogeneity:* 'excessive' discrepancy among study-specific effects
- *Inconsistency:* it is the excessive discrepancy among source-specific effects (direct and indirect)

Inconsistency

Empirical Evidence

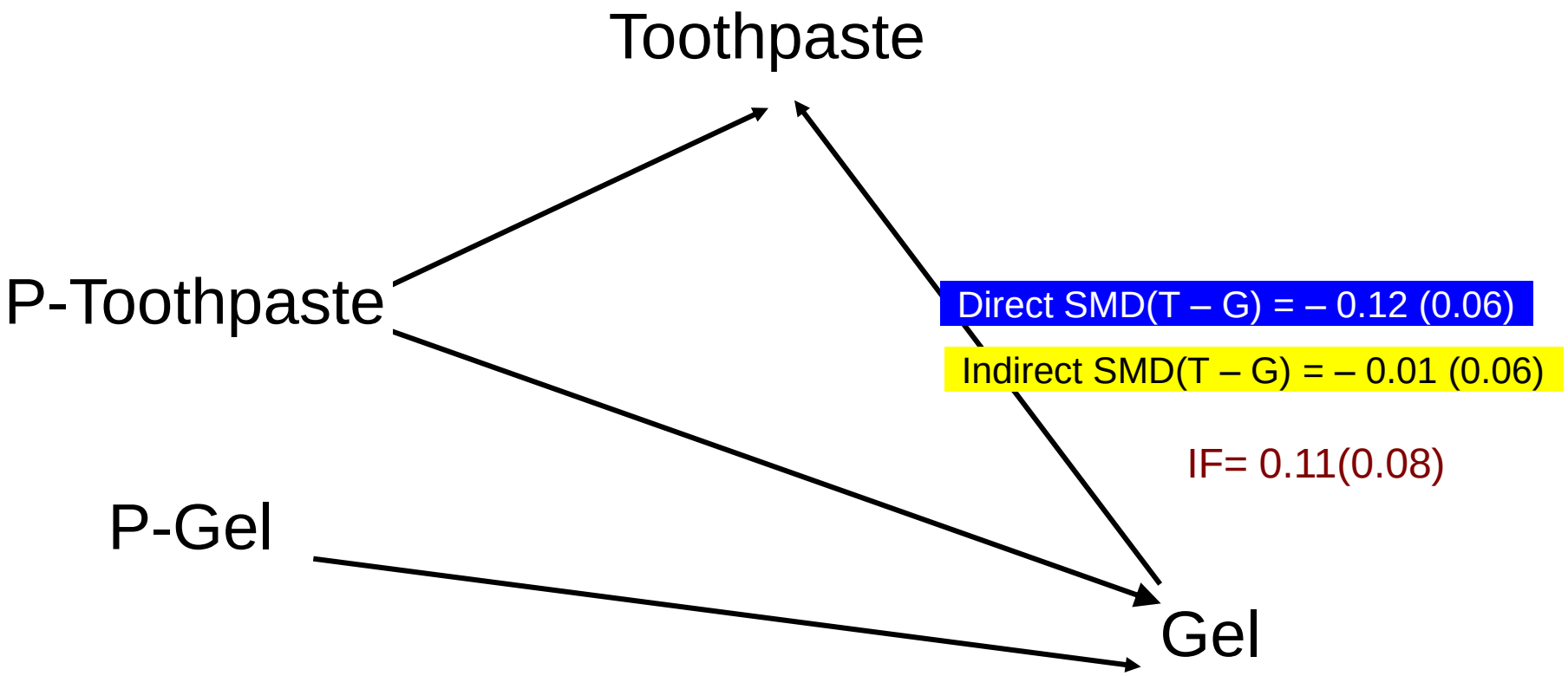
- In 3 cases out of 44 there was an important discrepancy between direct/indirect effect.
- Direction of the discrepancy is inconsistent

Glenny et al HTA 2005

What can cause inconsistency?

Inappropriate common comparator

Compare Fluoride treatments in preventing dental caries

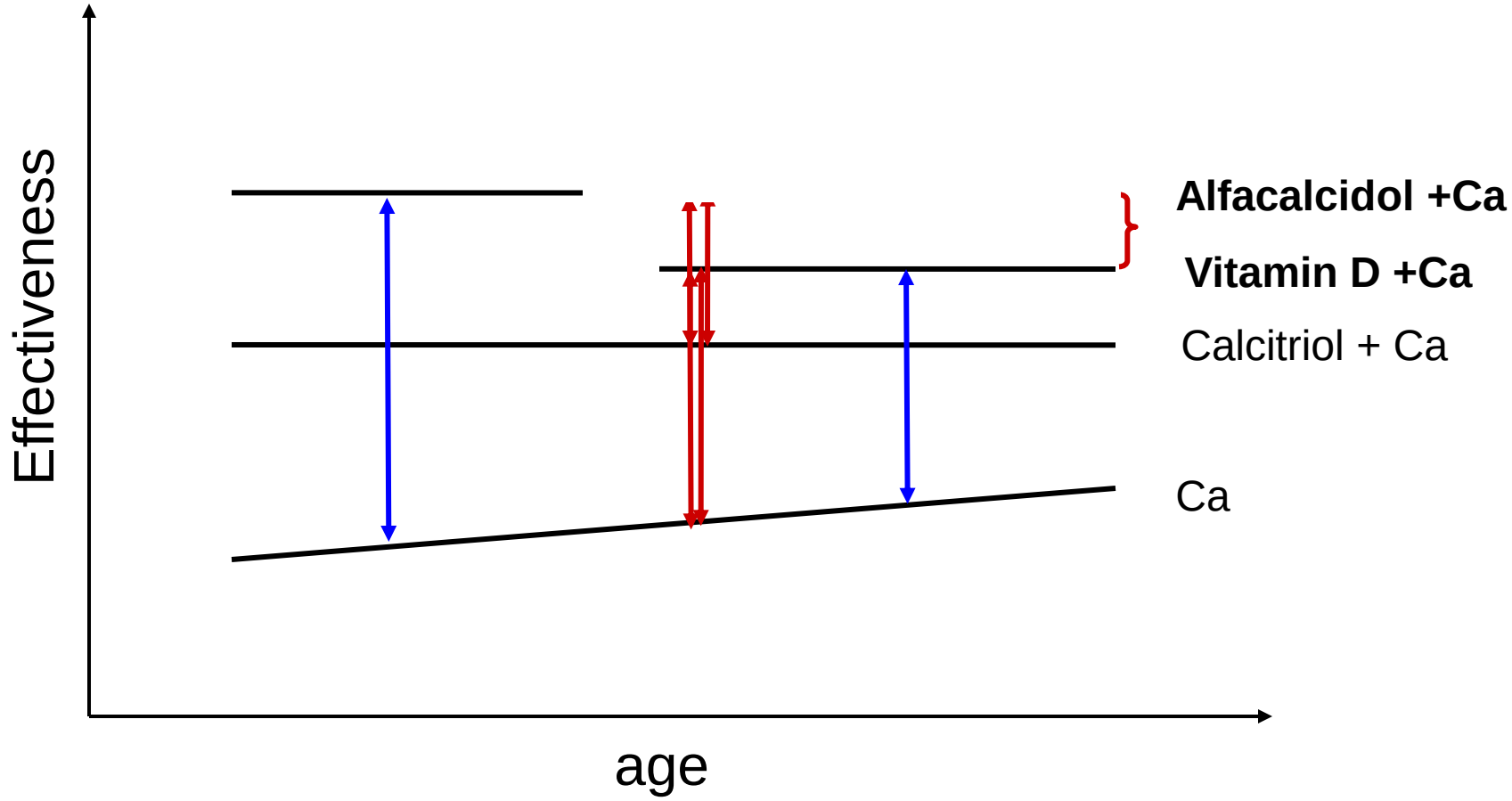


I cannot learn about Toothpaste versus Gel through Placebo!

J Clin Epidemiol. 2009 *Salanti, Marinho, Higgins*

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

- Consistency is an assumption for MTM
  - Untestable?
- 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

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

J Clin Epidemiol. 2009 *Salanti, Marinho, Higgins*

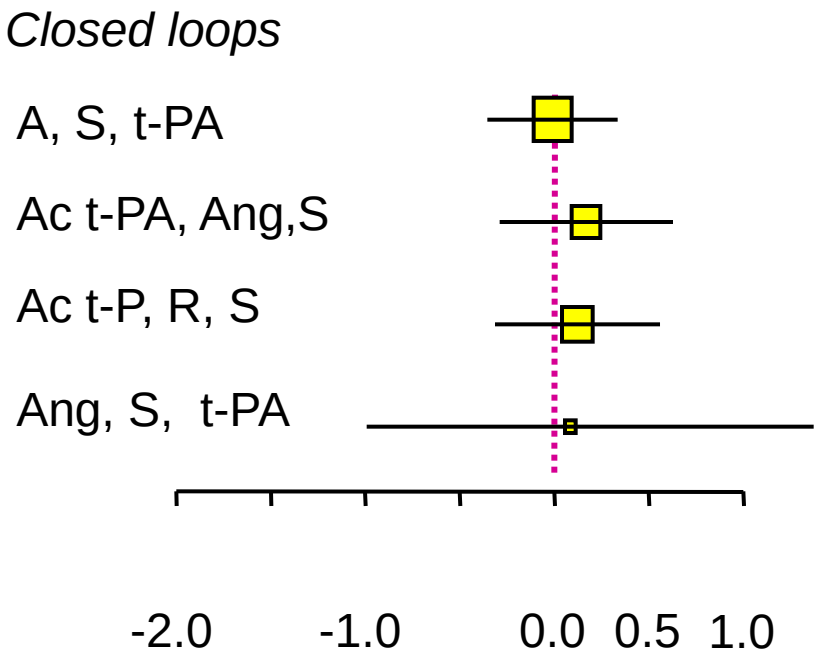
Inconsistency

Detecting

- Consistency is an assumption for MTM
  - Untestable?
- 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

Evaluation of consistency within closed loops

IF estimates with 95% confidence intervals



Warning!
this is not a formal test**!**

An R code can be found in http://www.dhe.med.uoi.gr/R%20routine.htm
*An example can be found in **J Clin Epidemiol.** 2009 Salanti, Marinho, Higgins*

Inconsistency

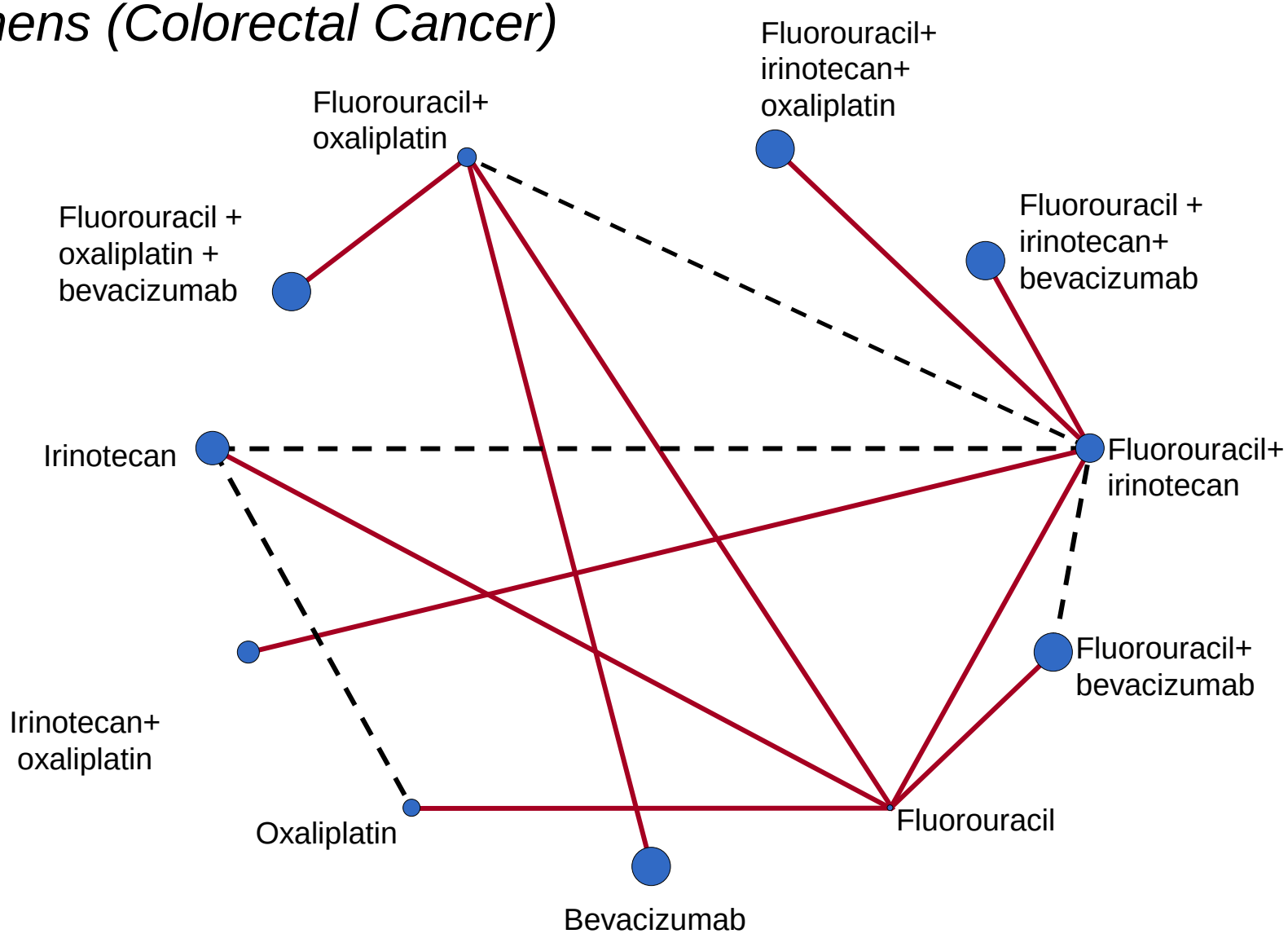
Detecting

- Consistency is an assumption for MTM
  - Untestable?
- 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 (**JASA 2005** Lu & Ades, **Stat Med 2010** Dias et al, **J Clin Epidemiol 2010** Caldwell et al*)

Inconsistency models

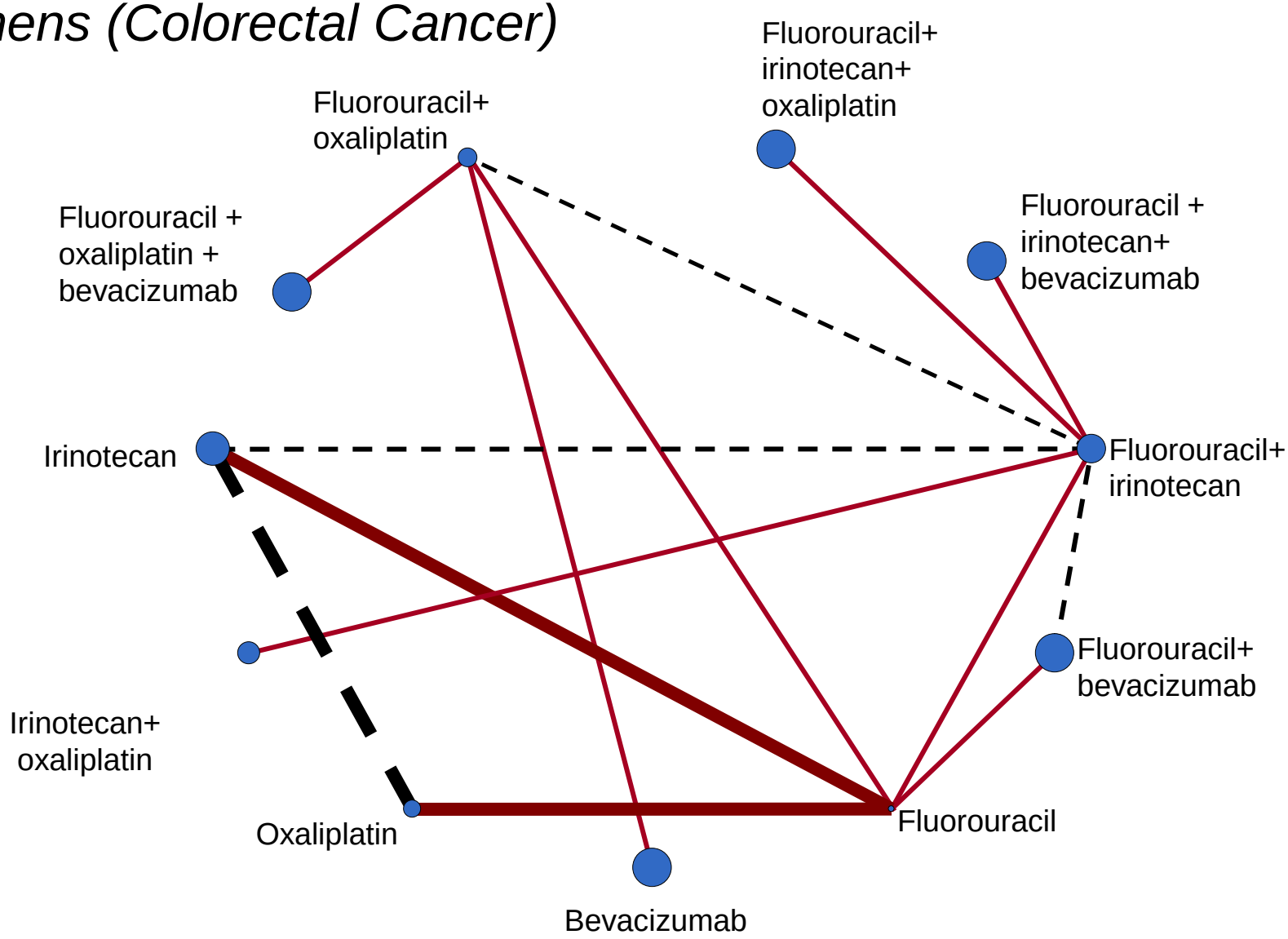
- Separate basic and functional parameters
- Add an inconsistency term at each consistency equation
- Estimate the extend of inconsistency

Survival with chemotherapy regimens (Colorectal Cancer)



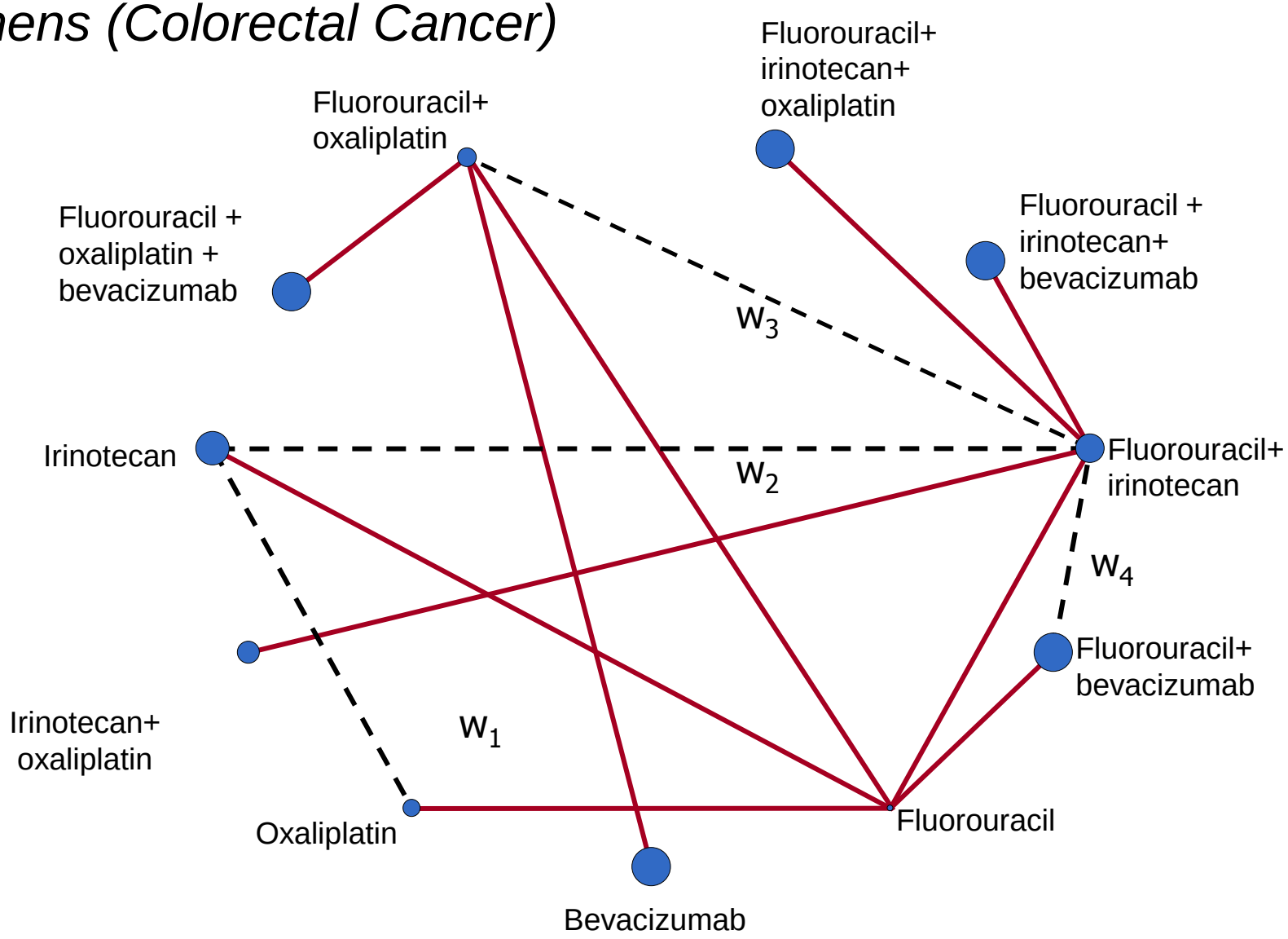
Lancet Oncol 2007 *Golfinopoulos V, Salanti G et al*

Survival with chemotherapy regimens (Colorectal Cancer)



Lancet Oncol 2007 *Golfinopoulos V, Salanti G et al*

Survival with chemotherapy regimens (Colorectal Cancer)



Lancet Oncol 2007 *Golfinopoulos V, Salanti G et al*

Inconsistency models

- $w_i \sim N(0,\sigma^2)$
- Look at the individual w values to locate any inconsistencies
- Compare σ^2 to τ^2 *(heterogeneity)*
  - $P(\sigma^2 > \tau^2)$

JASA 2006 *Lu & Ades*

Results

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

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

Model diagnostics

- D, pD, DIC
- Leverage plots

Estimate the fit of a model: Continuous data

$\theta_i, \tilde{\theta}_i$ The fitted values ($y_i \sim N(\theta_i, var_i)$) and their posterior mean

$$\tilde{D}_i = \frac{(y_i - \theta_i)^2}{var_i}$$

residual deviance

(estimated within WinBUGS at each iteration)

$\bar{D}_i$ Posterior mean of residual deviance for each data point (mean taken from M iterations)

Summarised by posterior mean in WinBUGS

$$D(\tilde{\theta}_i) = (y_i - \tilde{\theta}_i)^2 / var_i$$

Deviance at the posterior mean of the fitted values

$$pD = \sum pD_i = \sum \left[\bar{D}_i - D(\tilde{\theta}_i) \right]$$

Effective number of parameters

Posterior mean of residual deviance minus deviance at posterior mean

Estimate the fit of a model: Binary Data

$p_{i,k}, \tilde{p}_{i,k}$ The fitted probability values and their posterior mean

$$\tilde{D}_{i,k} = r\log\left(\frac{pn}{r}\right) + (n-r)\log\left(\frac{(1-p)n}{n-r}\right)$$

residual deviance

(estimated within WinBUGS at each iteration)

$\overline{D}_{i,k}$ Posterior mean of residual deviance for each data point (mean taken from M iterations)

Summarised by posterior mean in WinBUGS

$$D(\tilde{p}_{i,k}) = r\log\left(\frac{\tilde{p}n}{r}\right) + (n-r)\log\left(\frac{(1-\tilde{p})n}{n-r}\right)$$

Deviance at the posterior mean of the fitted values

$$pD = \sum pD_i = \sum\left[\bar{D}_i - D(\tilde{\theta}_i)\right]$$

Effective number of parameters

Posterior mean of residual deviance minus deviance at posterior mean

Estimate the fit of a model: Measures

For fit of the model to the data

$\overline{D} = \sum \overline{D}_i$ Should approximate the number of data points

Bad fitted observations

Plot $\sqrt{\left|\tilde{D}_i\right|}$ vs pD_i

Studies outside $x^2+y=3$ show poor fit

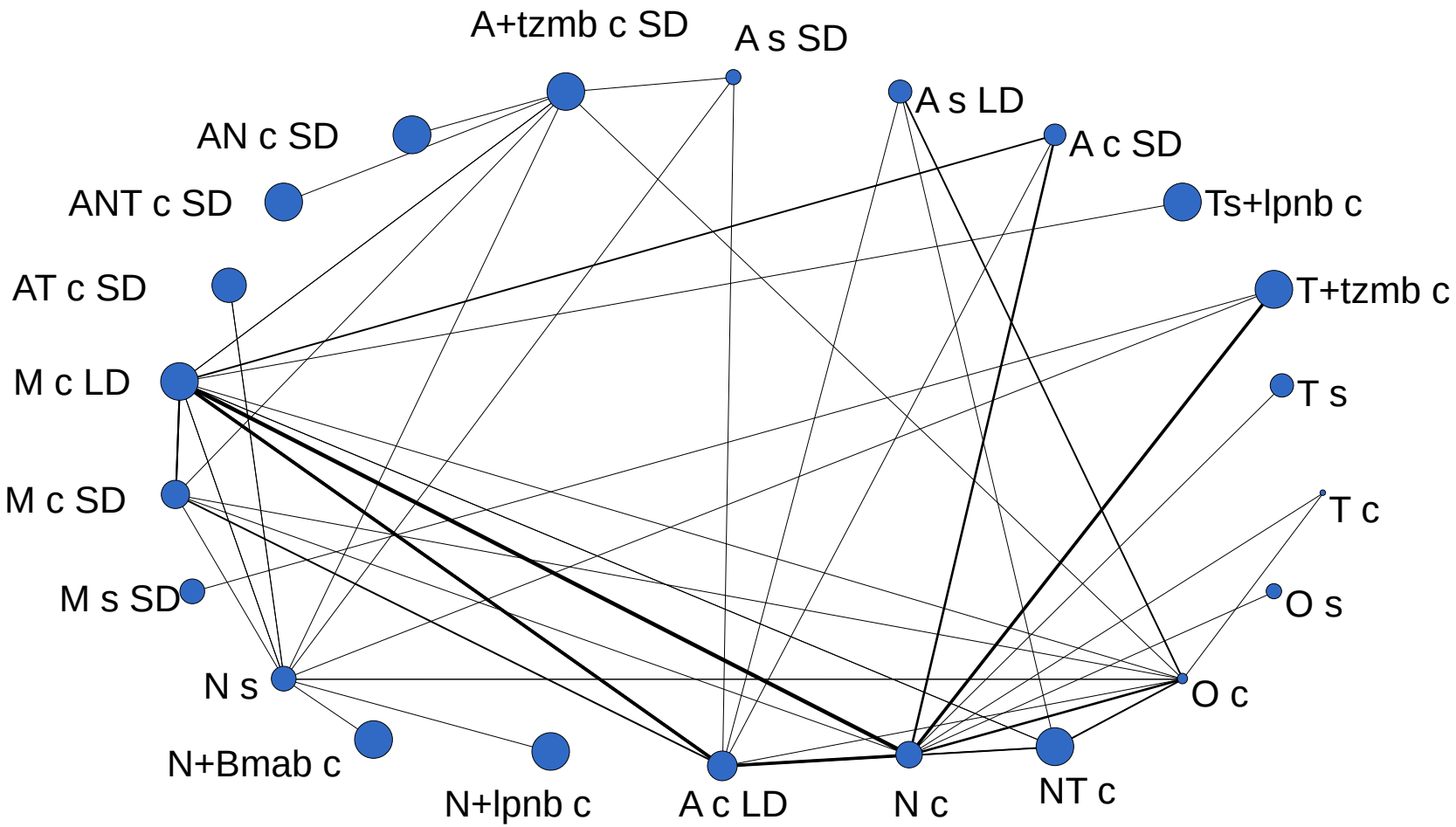
Compare models

$DIC = \overline{D} + pD$ Can be used to compare different models

JRSS (B) 2002 *Spiegelhalter et al*

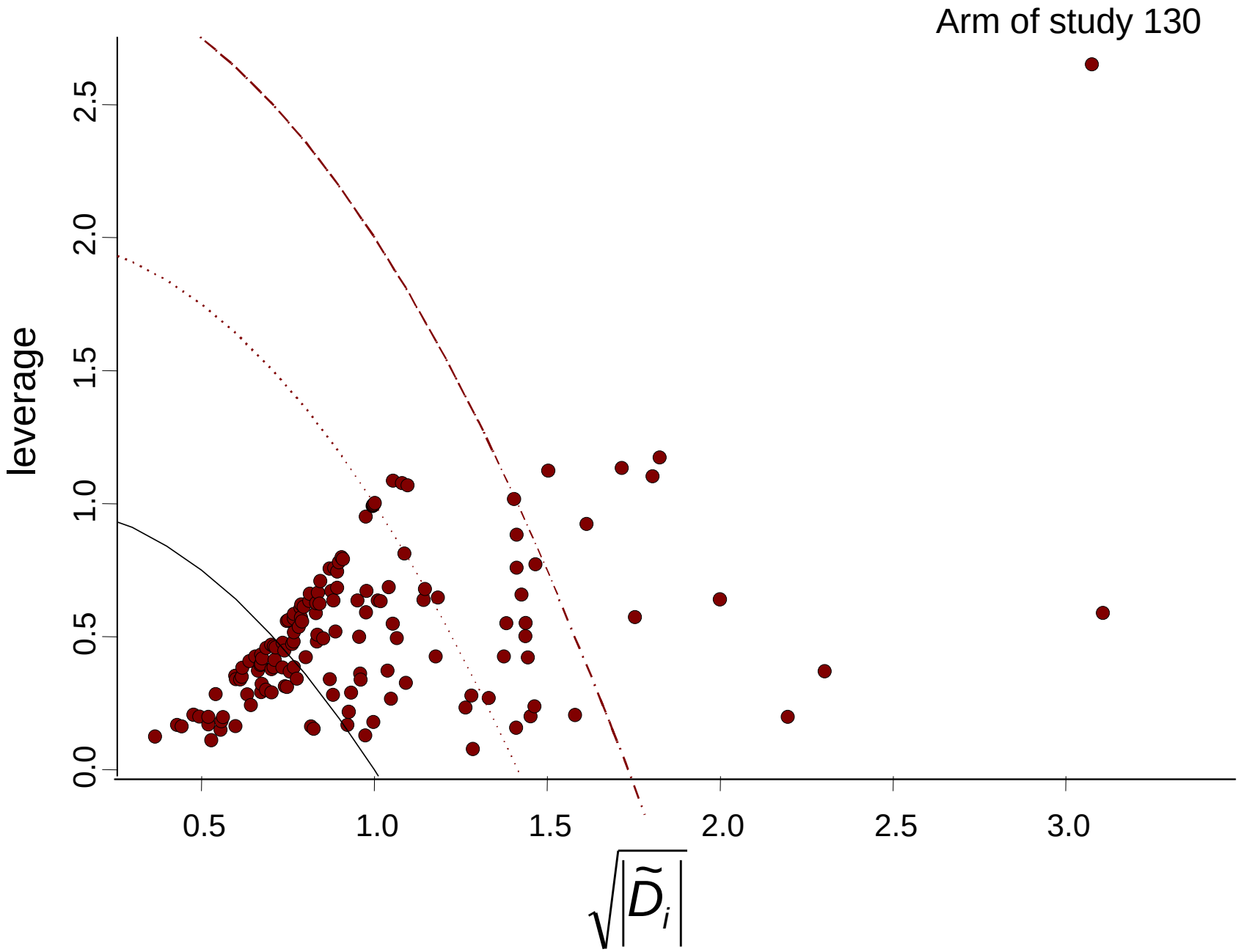
Example: Breast Cancer

Network of treatments for advanced breast cancer. AcLD = Low-dose anthracycline (combination regimen); **AcSD =** Standard-dose anthracycline (combination regimen); **AsLD =** Low-dose anthracycline (single agent); **AsSD =** Standard-dose anthracycline (single agent); **A+tzmbSD =** Standard-dose anthracycline + trastuzumab; **AN SD =** Standard-dose anthracycline + novel non-taxane agents; **ANT SD =** Standard-dose anthracycline + novel non-taxane agents + taxanes; **AT SD =** Standard-dose anthracycline + taxanes; **McLD =** Lowdose mitoxantrone (combination regimen); **McSD =** Standard-dose mitoxantrone (combination regimen); **MsSD =** Standard-dose mitoxantrone (single agent); **Nc =** Novel non-taxane agents (combination regimen); **Ns =** Novel non-taxane agents(single agent); **N+bmab =** Novel non-taxane agents + bevacizumab (single agent); **N+lpnb =** Novel non-taxane agents + lapatinib; **NT =** Novel non-taxane agents + taxanes; **Oc =** Old agents (combination regimen); **Os =** Old agents (single agent); **Tc =** Taxanes (combination regimen); **Ts =** Taxanes (single agent); **T+tzmb =** Taxanes + trastuzumab; **Ts+lpnb =** Taxanes + lapatinib



J Natl Cancer Inst 2008 *Mauri et al*

Example: Breast Cancer



Example: Breast Cancer

Model	$\overline{D}$	p_D	*DIC*	*Data Points*
Original Data	168.3	77.5	245	148
Without 130	166.4	68.6	235	147

Multiple-Treatments Meta-regression

Adjust for and quantify the effect of a covariate in each network

HOW: Multidimensional extensions of meta-regression

y_i^{AB} the outcome of experiment A vs B

Likelihood: $y_i^{AB} \sim N(\theta_i^{AB}, (var_i^{AB})^2)$

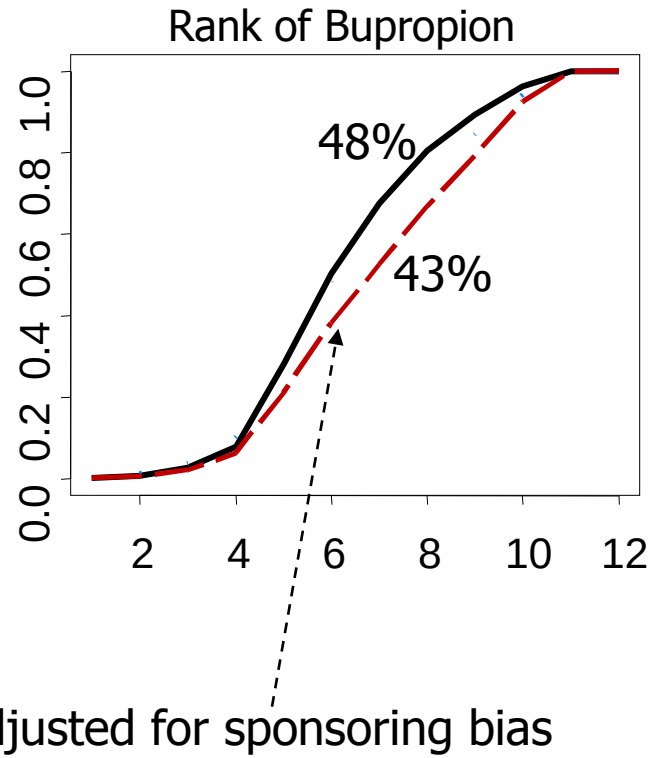
Bias adjusted estimate $\theta_i^{AB} = \mu_i^{AB} + \beta_i I^{AB}$

coefficient

Index, (0 or 1) depending on whether A is favored by bias compared to B

Random effects in the effect of the covariate

$$\beta_i \sim N(B, \tau_r^2)$$



Stat Med 2010 *Salanti et al*
JRSS 2010 *Dias et al*

Multiple-Treatments Meta-regression

- **Compared the models** (adjusted and unadjusted) and examine
  - Improvement in fit as measured by DIC
  - Changes in heterogeneity τ^2, τ_r^2
  - The distribution of the effect of the covariate (β)
- It is expected that MTMr has the same problems (low power, prone to bias) as regular meta-regression

List of publications on methodological issues

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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.

List of applied publications (from Cochrane-related authors…)

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Golfinopoulos V, Pentheroudakis G, Salanti G, Nearchou AD, Ioannidis JP, Pavlidis N. 2009. Comparative survival with diverse chemotherapy regimens for cancer of unknown primary site: multiple-treatments meta-analysis. Cancer Treat Rev 35:570-573.

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