Multiple-Treatments **M**eta-**A**nalysis

A framework for evaluating and ranking multiple health technologies

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How to do it?

Short reminder of the method

Meta-analysis and meta-regression

MTM models using meta-regression

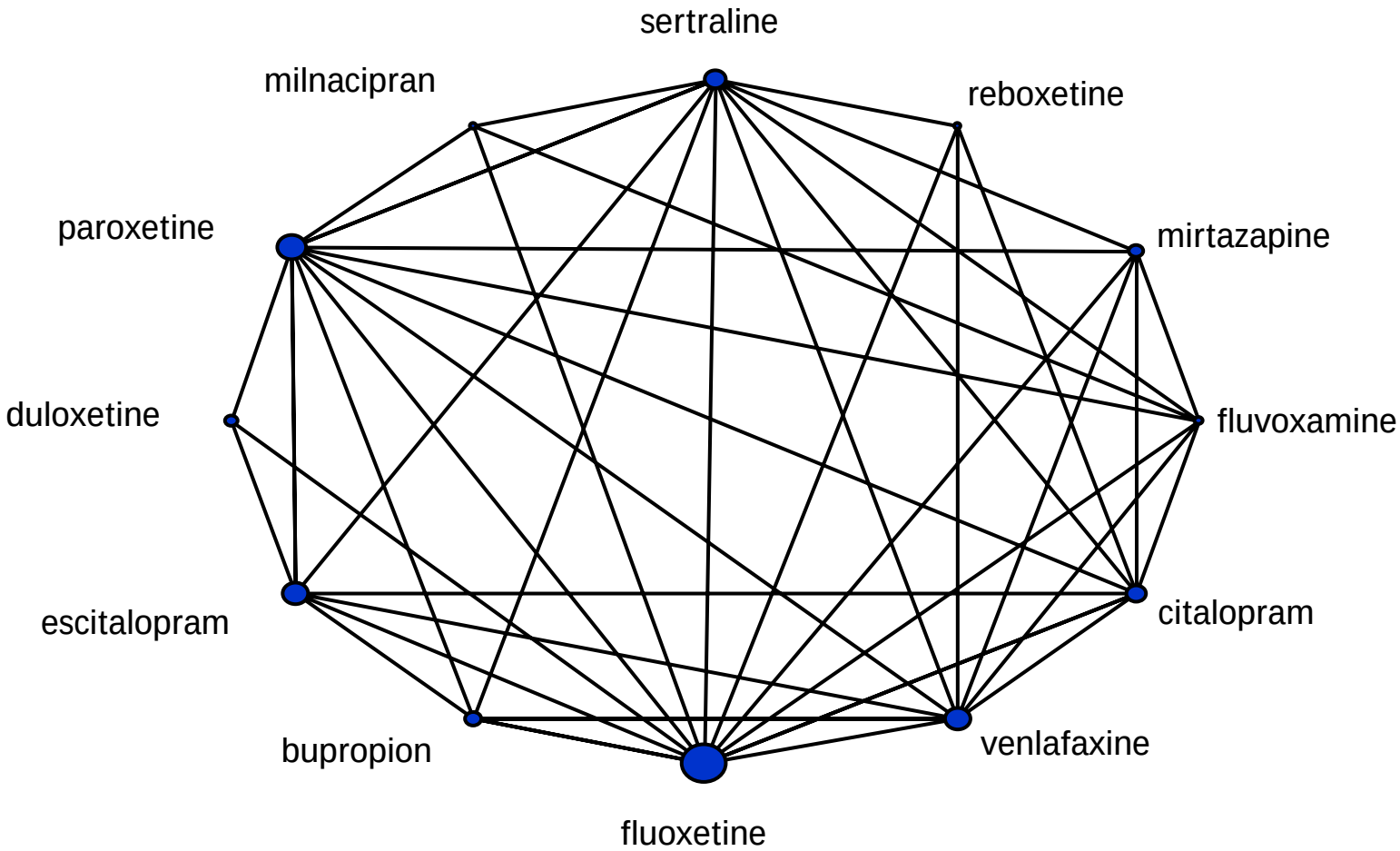
Bayesian MTM

Advanced models

(Inconsistency models, MTM meta-regression)

Maths Warning!

Network of experimental comparisons



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

Network of experimental comparisons

Indirect estimation

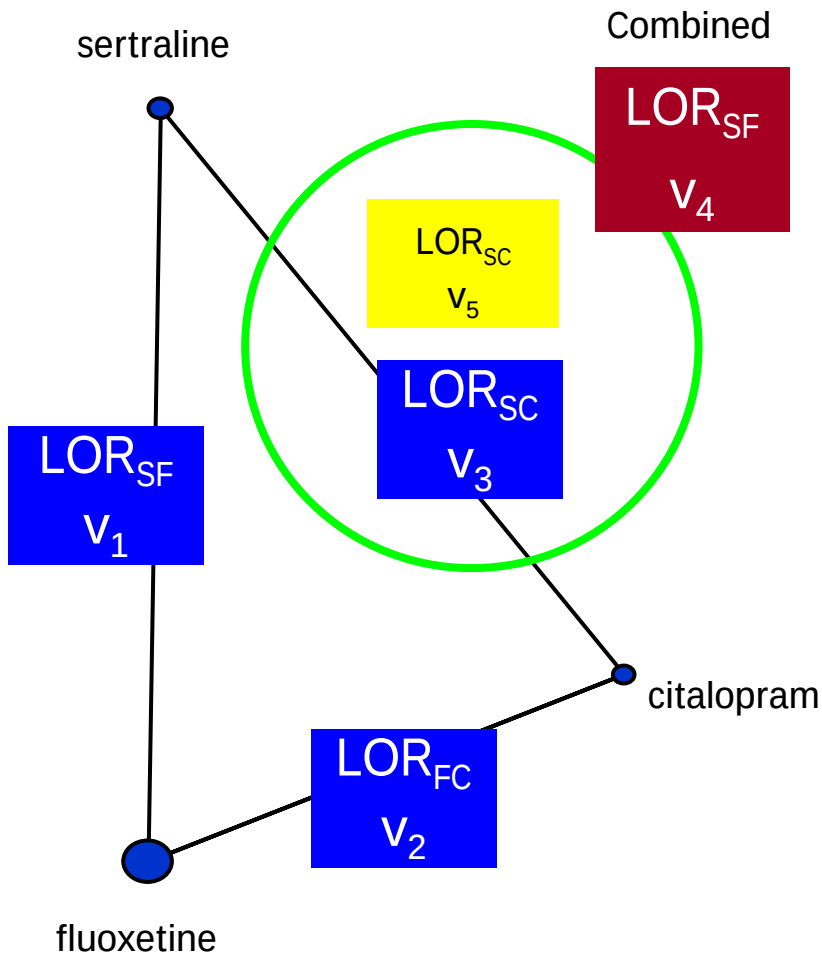
$LOR_{SC} = LOR_{SF} + LOR_{FC}$

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

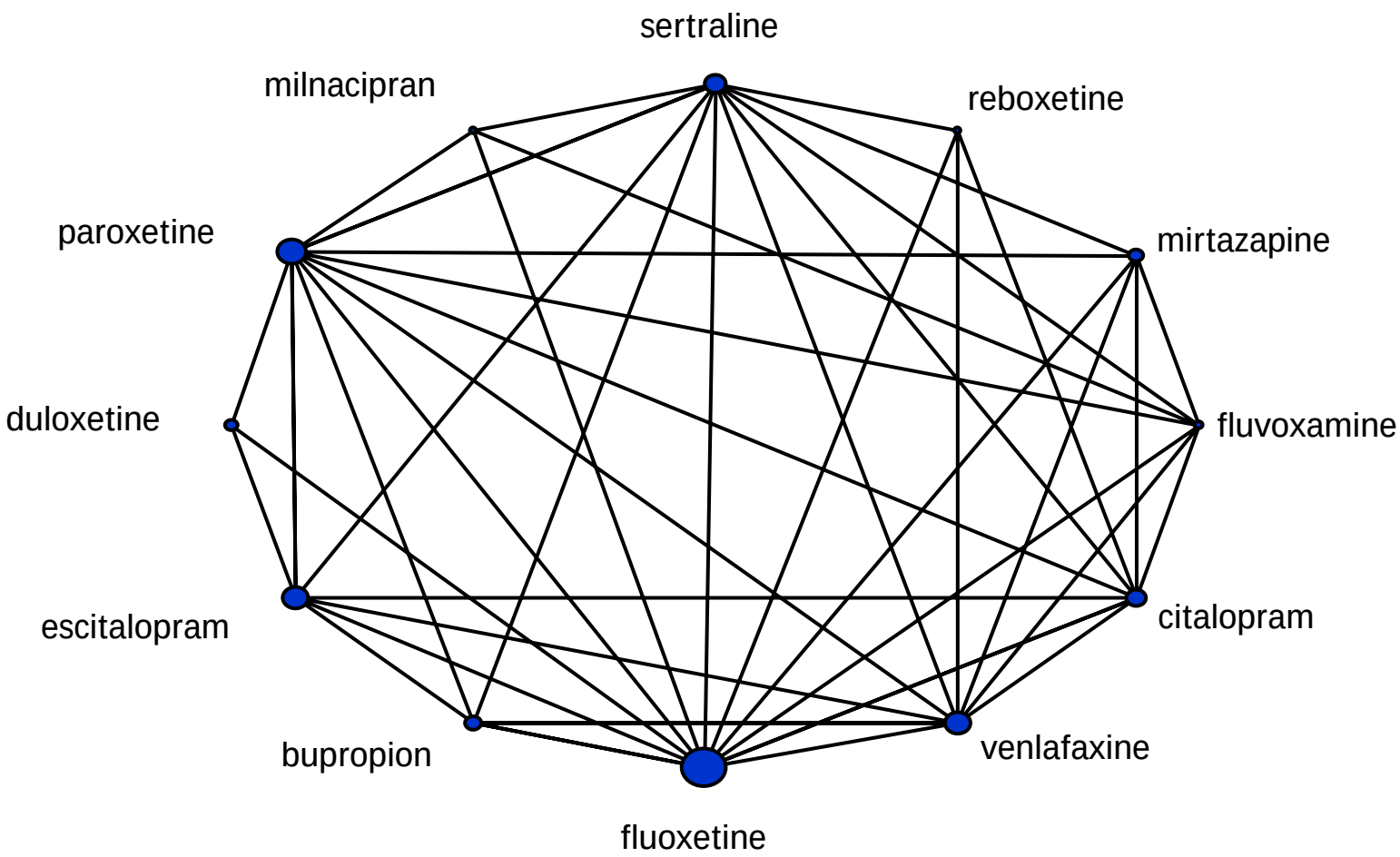
Combine the direct estimate with the indirect estimate using IV methods

Get a combined ***LOR!***

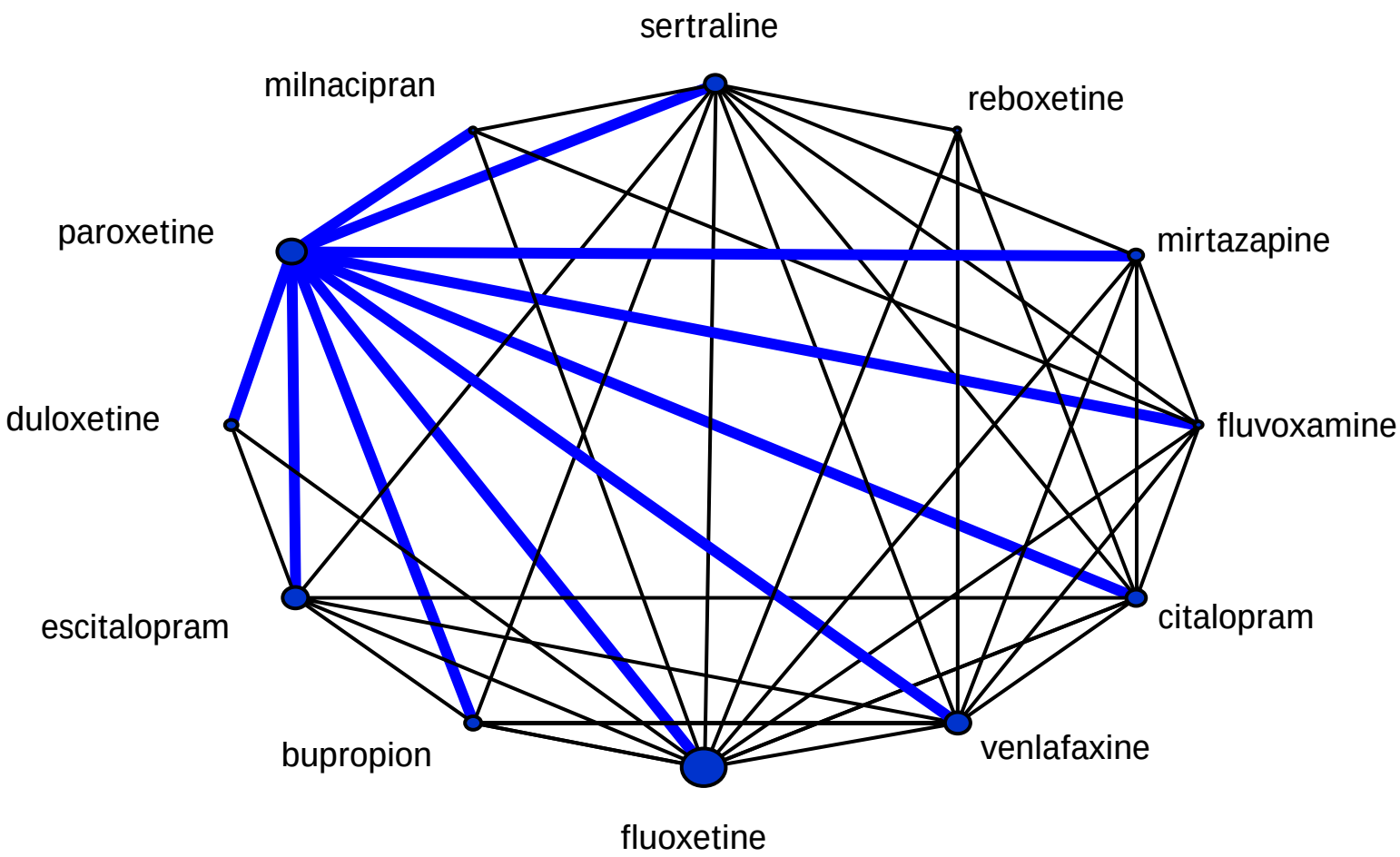
v4<v3



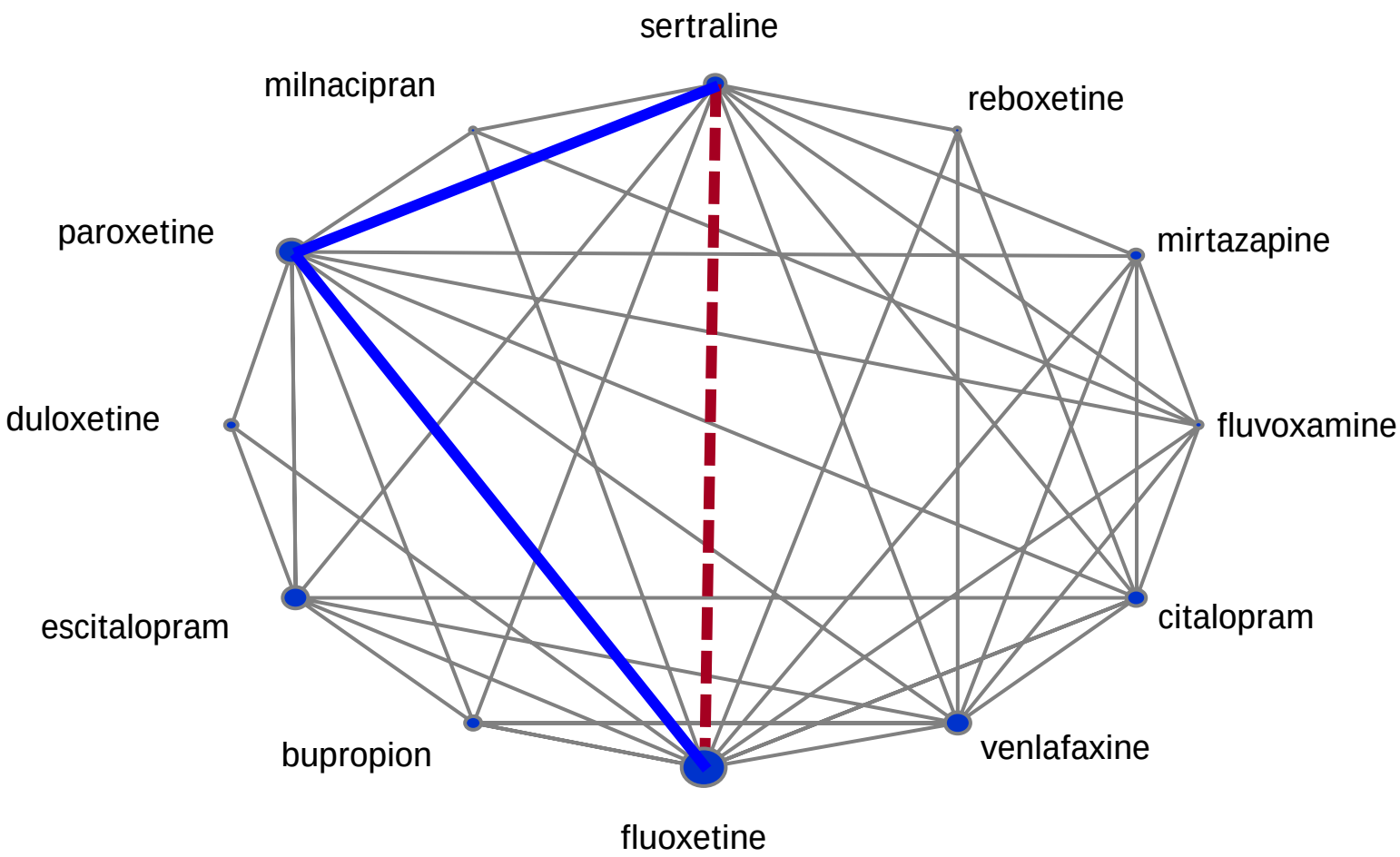
Expand the idea in the entire network!



Choose basic parameters



All other contrasts are functional!



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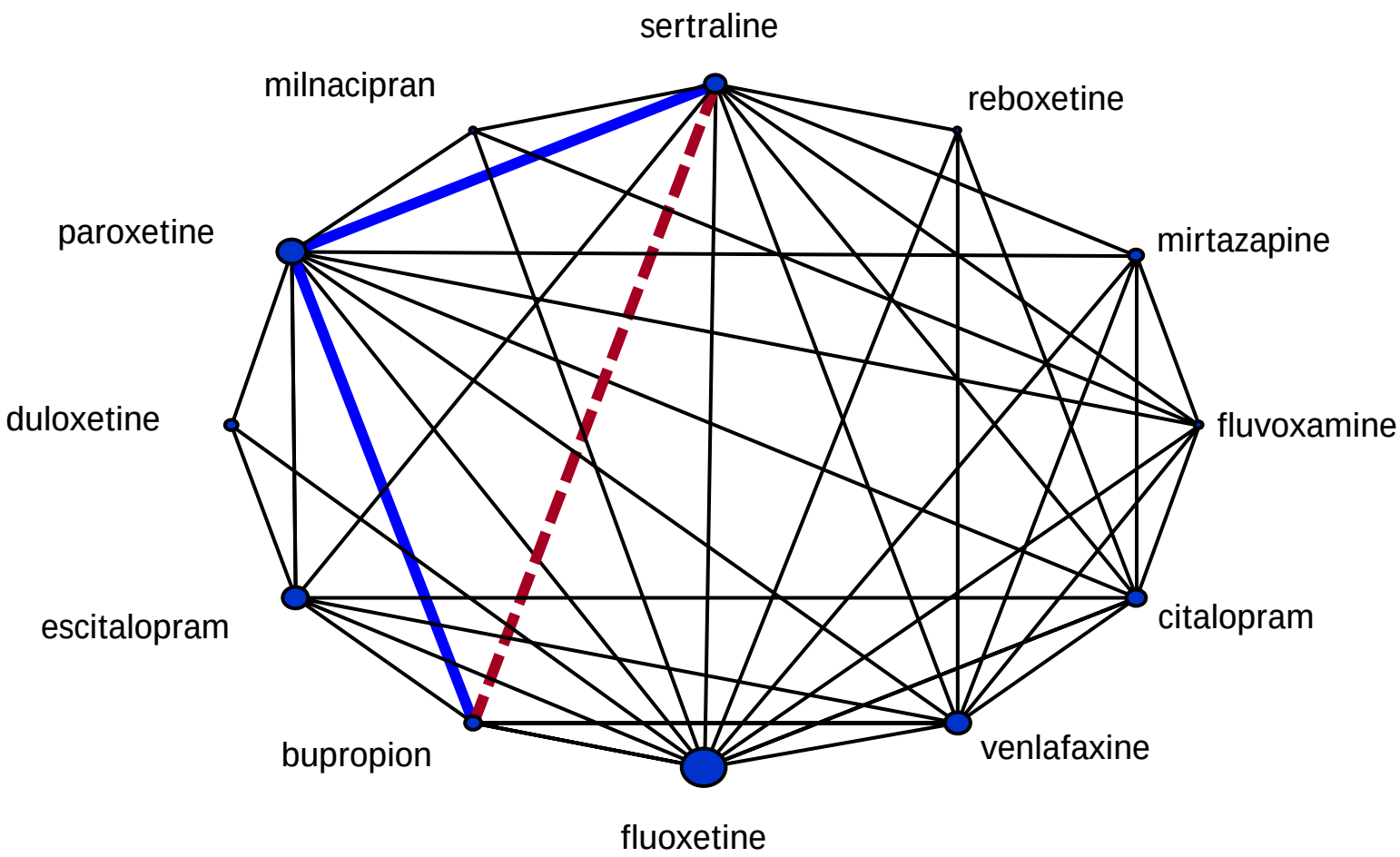

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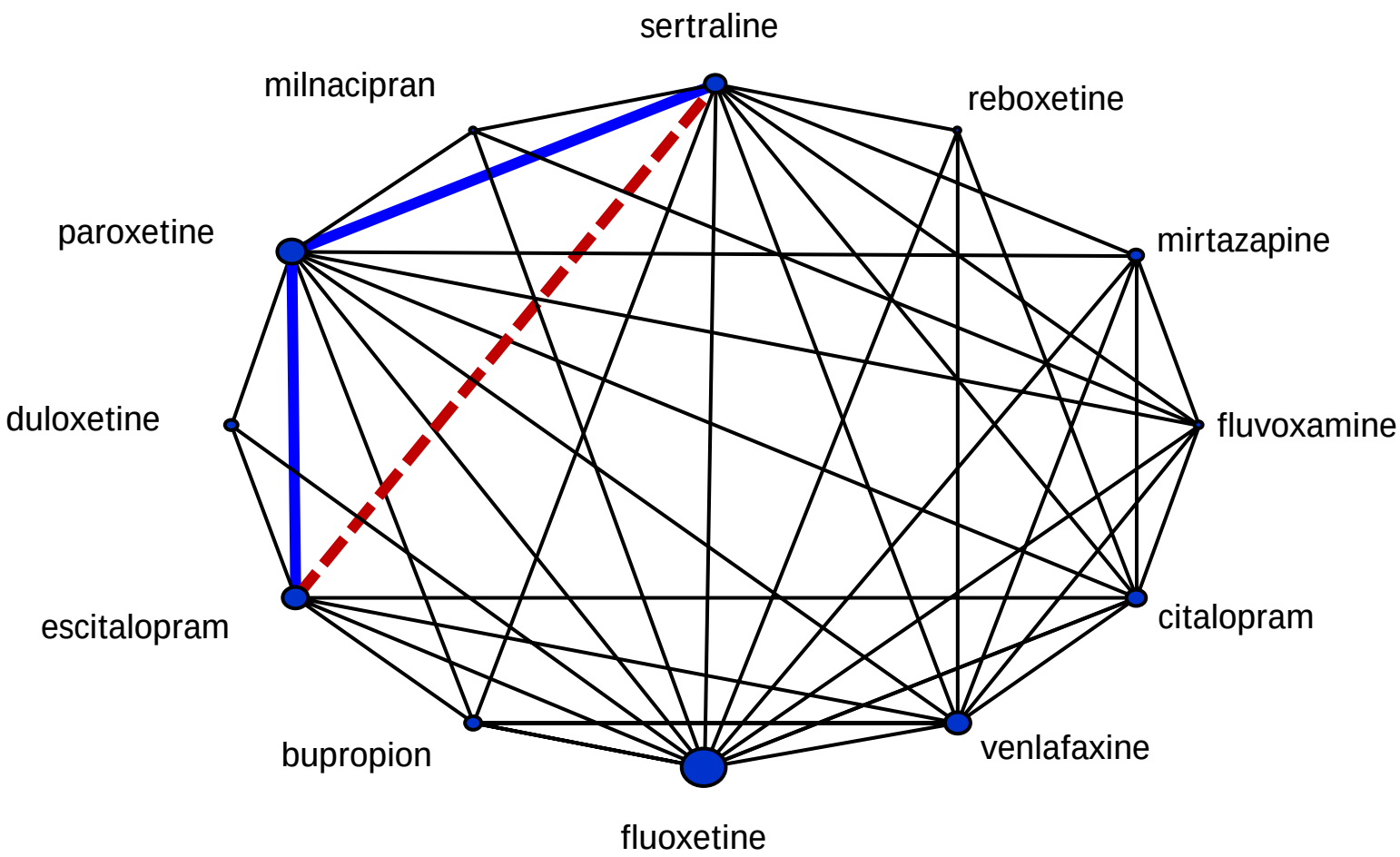

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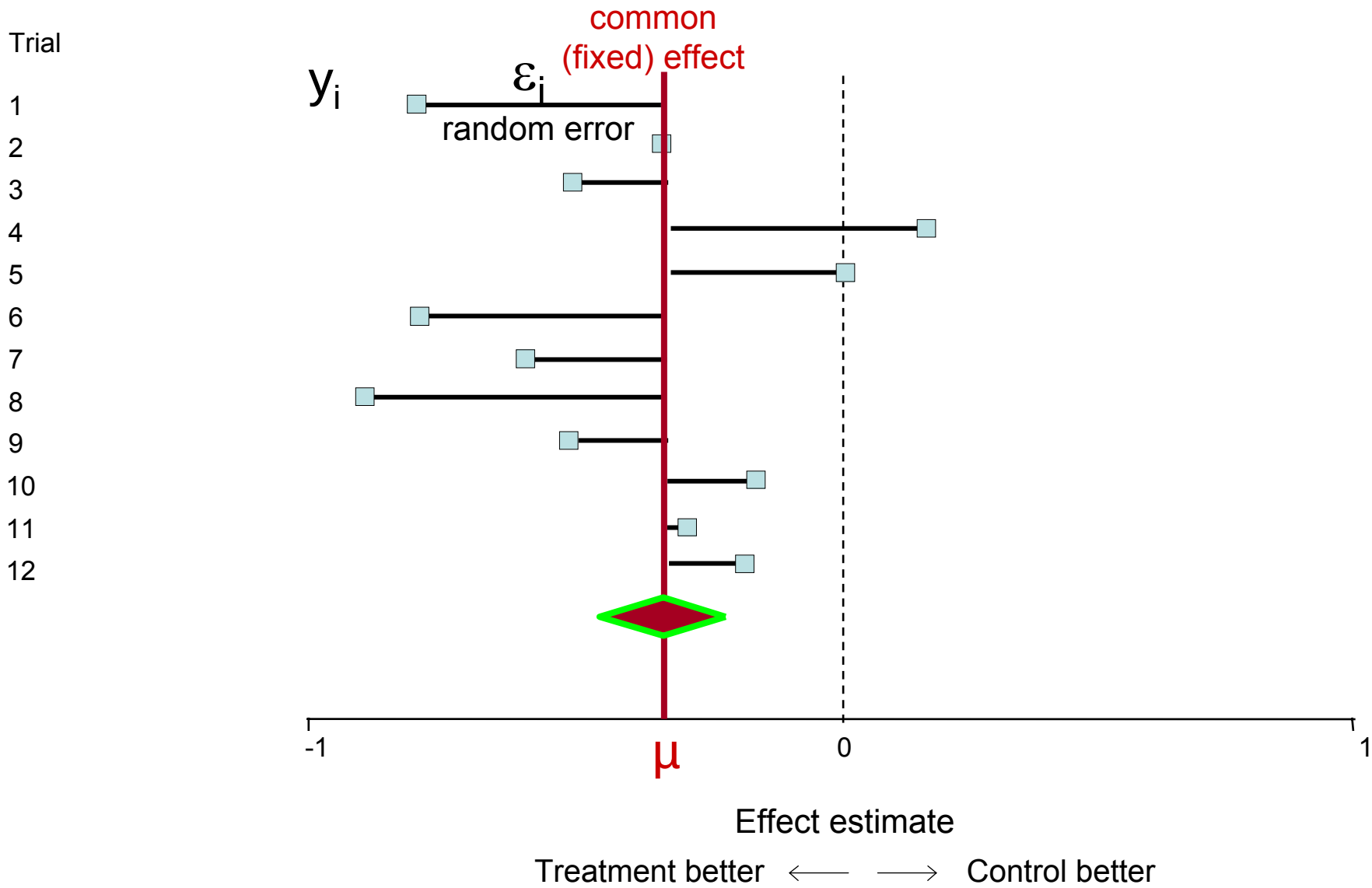
Fixed effect meta-analysis



FE meta-analysis

It is just a weighted regression!

$\mathbf{Y_i}$ the observation in each study

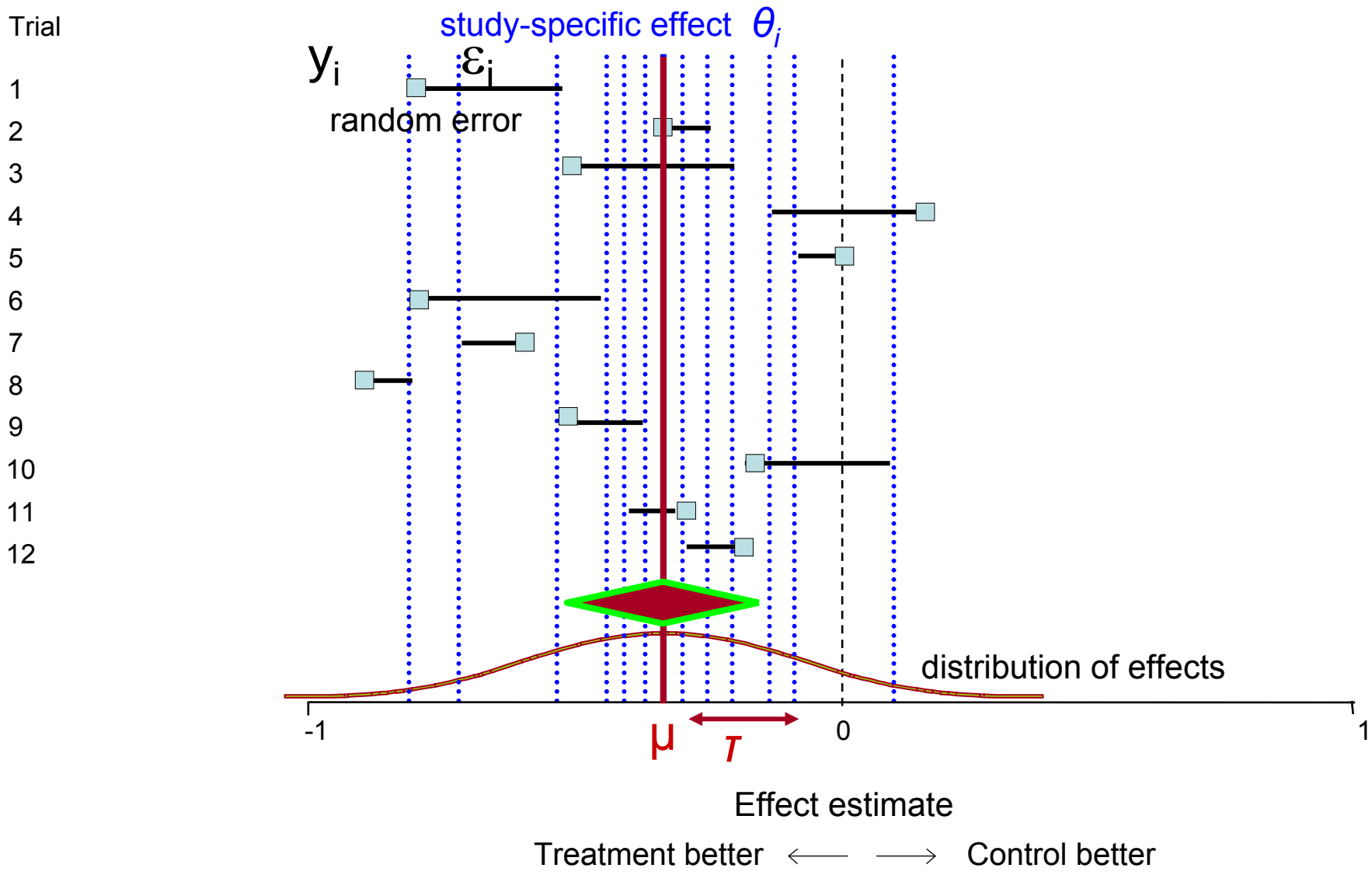
$\mathbf{v_i}$ the variance of each estimate

$$\mathbf{y_i = \mu + e_i} \text{ with weights } \mathbf{w_i = 1/v_i}$$

$$e_i \sim N(0, v_i)$$

The mean of the diamond

Random effects meta-analysis



RE meta-analysis

It is just a weighted regression plus a random effects term!

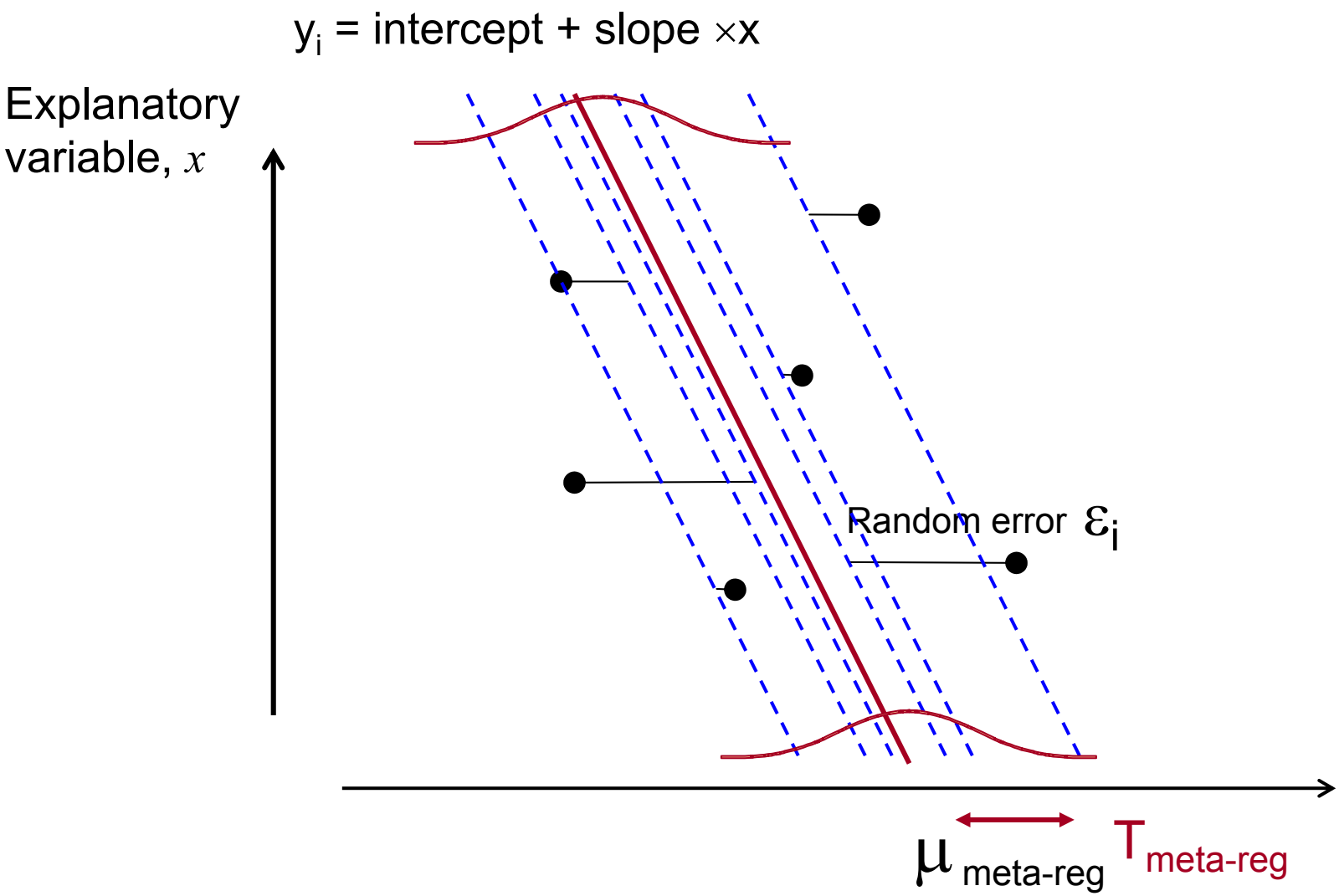
$$\mathbf{y_i = \mu + u_i + e_i} \text{ with weights } \mathbf{w_i = 1/v_i}$$

$$e_i \sim N(0, v_i)$$

The random effects $\mathbf{u_i \sim N(0, \tau^2)}$

The heterogeneity

Random effects meta-regression



RE meta-regression

We add a variable!

$$\mathbf{y_i = \mu + u_i + \beta \times duration + e_i}$$

with weights $\mathbf{w_i = 1/v_i}$

$$e_i \sim N(0, v_i)$$

$$u_i \sim N(0, \tau^2)$$

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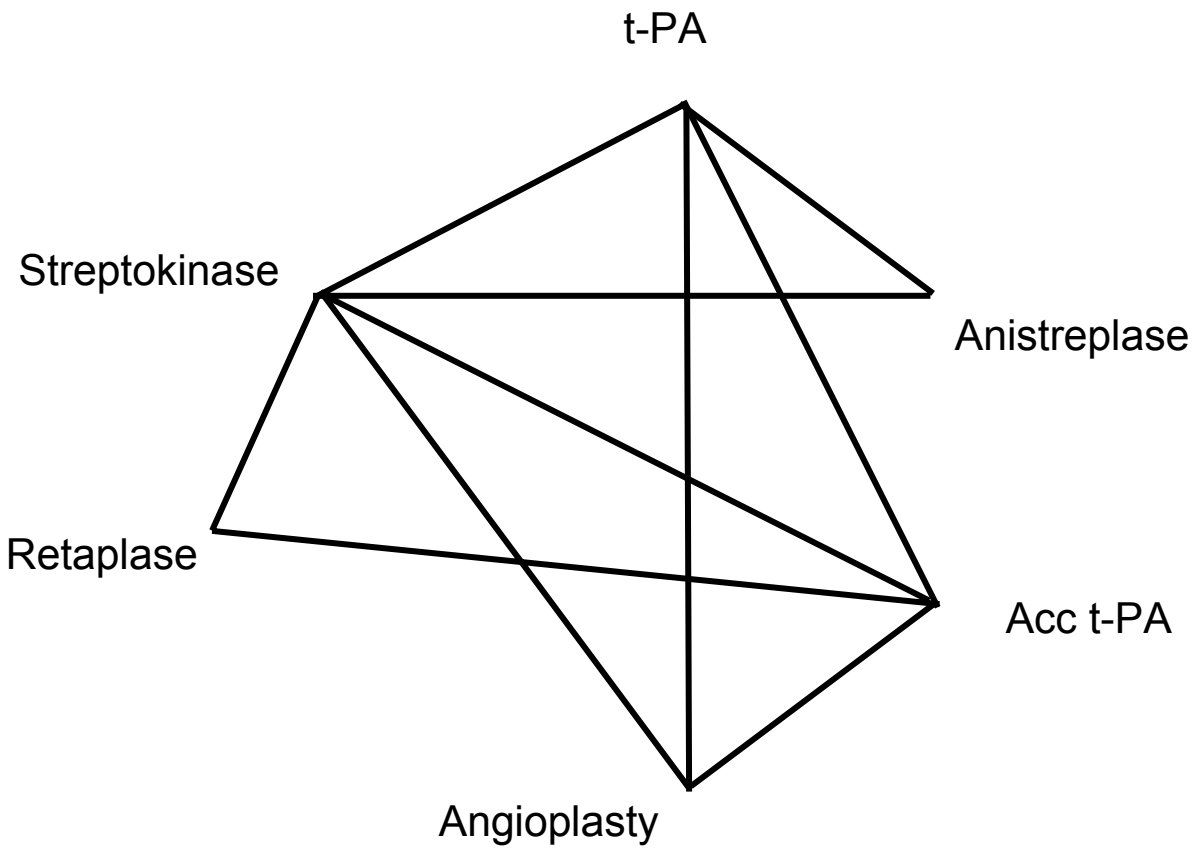
Meta-regression

- 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 + μ^B Anistreplase$_i$ + μ^C Accelerated t-PA$_i$ + μ^D Angioplasty$_i$ + μ^E Reteplase$_i$

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

Matrix of all observations

Vector of LogOR

Design matrix

Random effects matrix

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

Variance-covariance matrix (for the observed LOR)

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

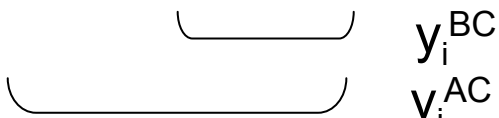
LOR compared to Streptokinase (RE model)

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

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



- 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*

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

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

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

Take into account correlation in observations

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

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i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
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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

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

Take into account correlation in random effects

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

How to fit such a model?

- MLwiN
- SAS, R
- STATA using metan

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Why use Bayesian statistics for meta-analysis?

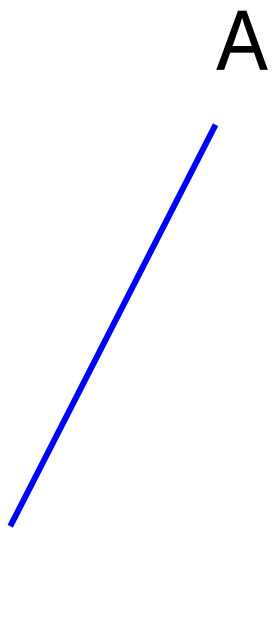
- **Natural approach for accumulating data**
- **Repeated updating of meta-analyses fine**: posterior should always reflect latest beliefs
- **People naturally think as Bayesians:** they have degrees of belief about the effects of treatment, which change when they see new data
- Probability statements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

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

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

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

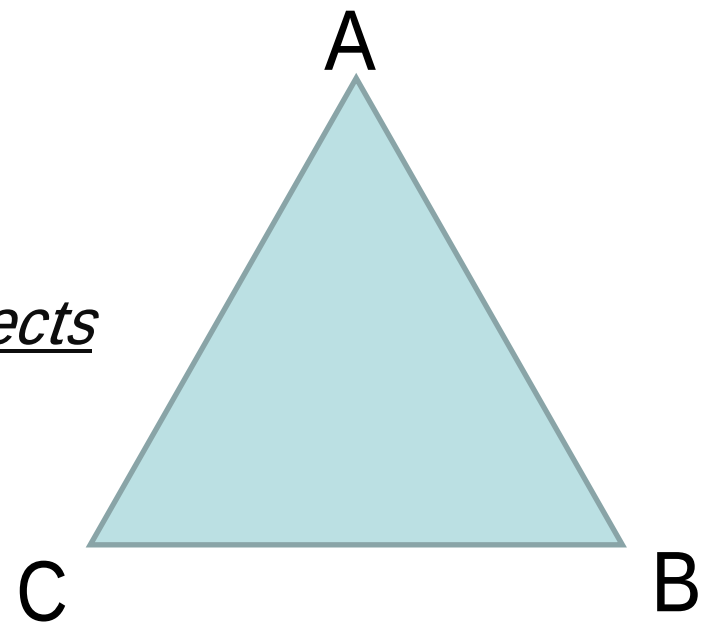
$y_i^{AB} \sim N(\theta_i^{AB}, se_i^2)$

Distributions of the random effects

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

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

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



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

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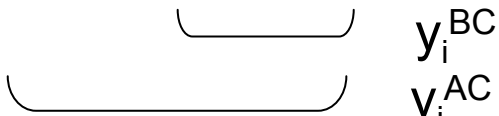
- A B C



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

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

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

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

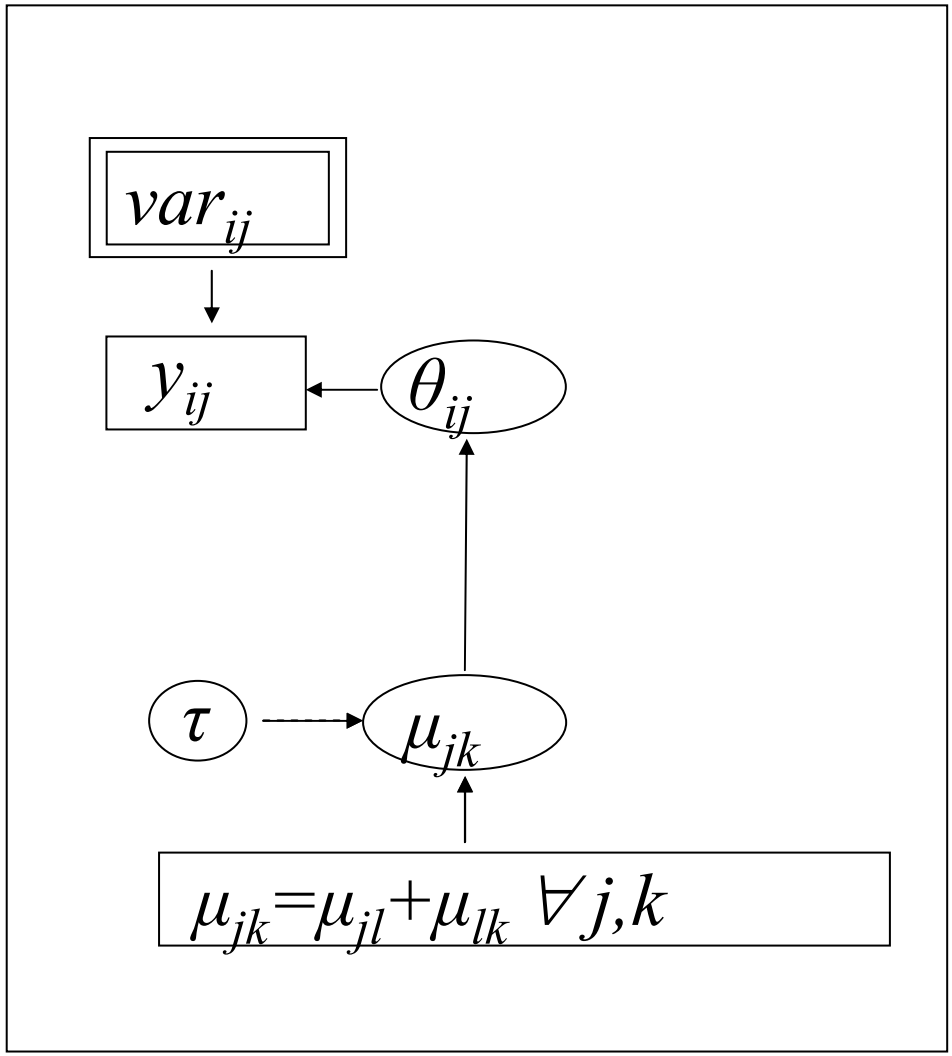
$$\Sigma = \begin{pmatrix} \tau_{AC}^{\ 2} & c \\ c & \tau_{BC}^{\ 2} \end{pmatrix}$$

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_t 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

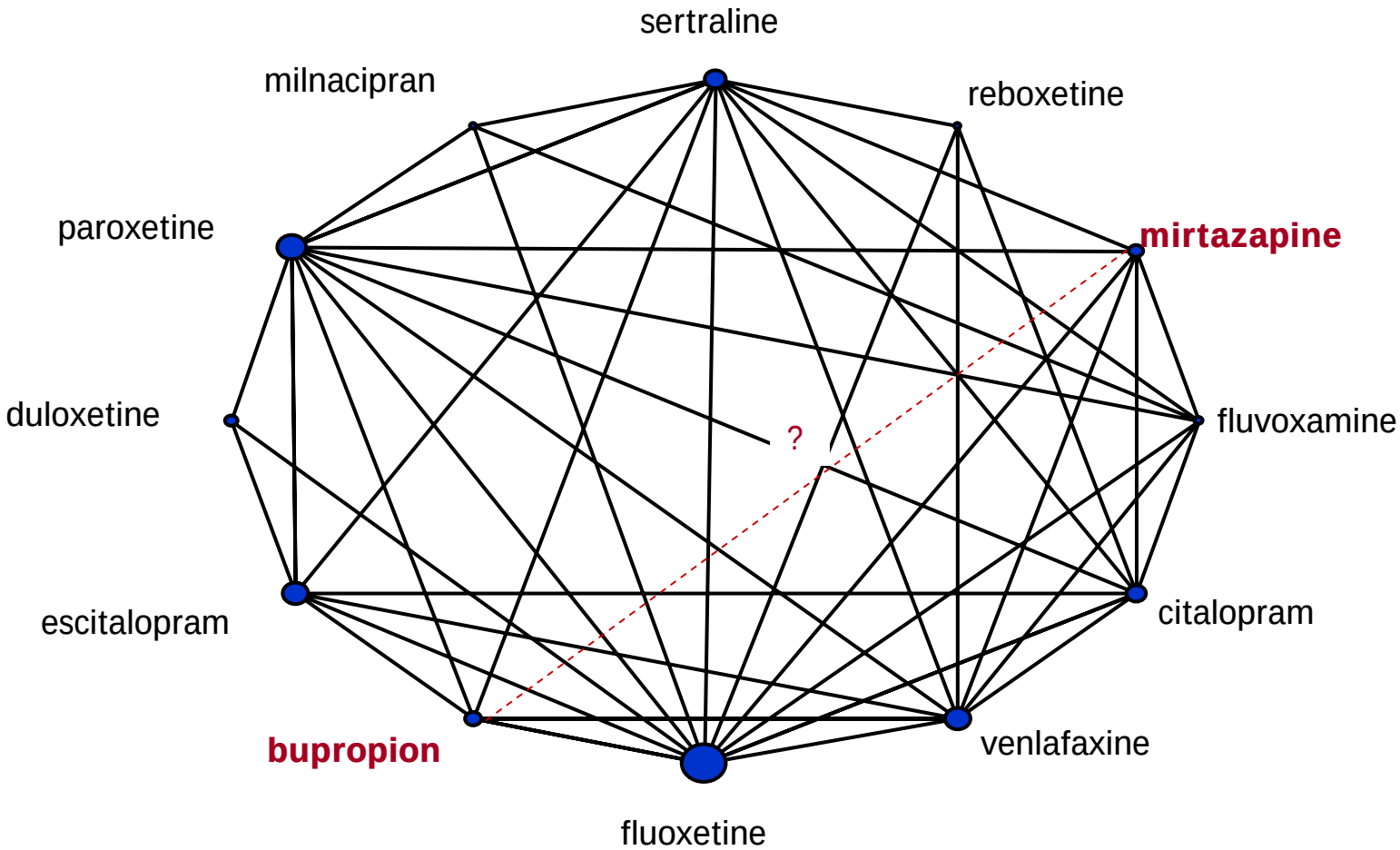
```
precision<-1/pow(sd,2)
sd~dnorm(0,1)I(0,)}
```

Priors

Salanti G, Higgins JP, Ades AE, Ioannidis JP: ***Evaluation of networks of randomized trials.*** *Stat Methods Med Res 2008,* ***17:*** *279-301.*

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



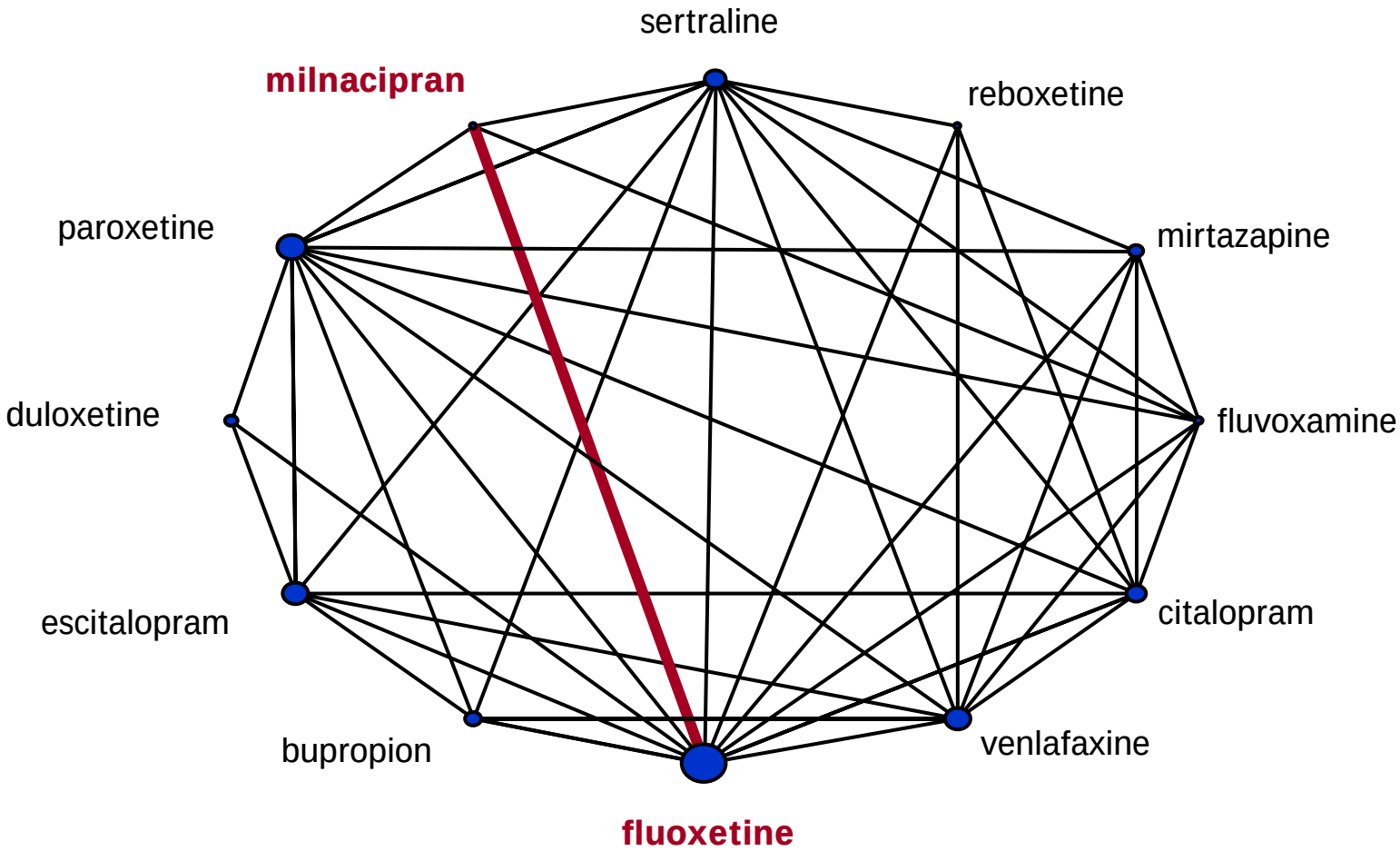
OR(B vs M)= 0.79 (0.72, 1)

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

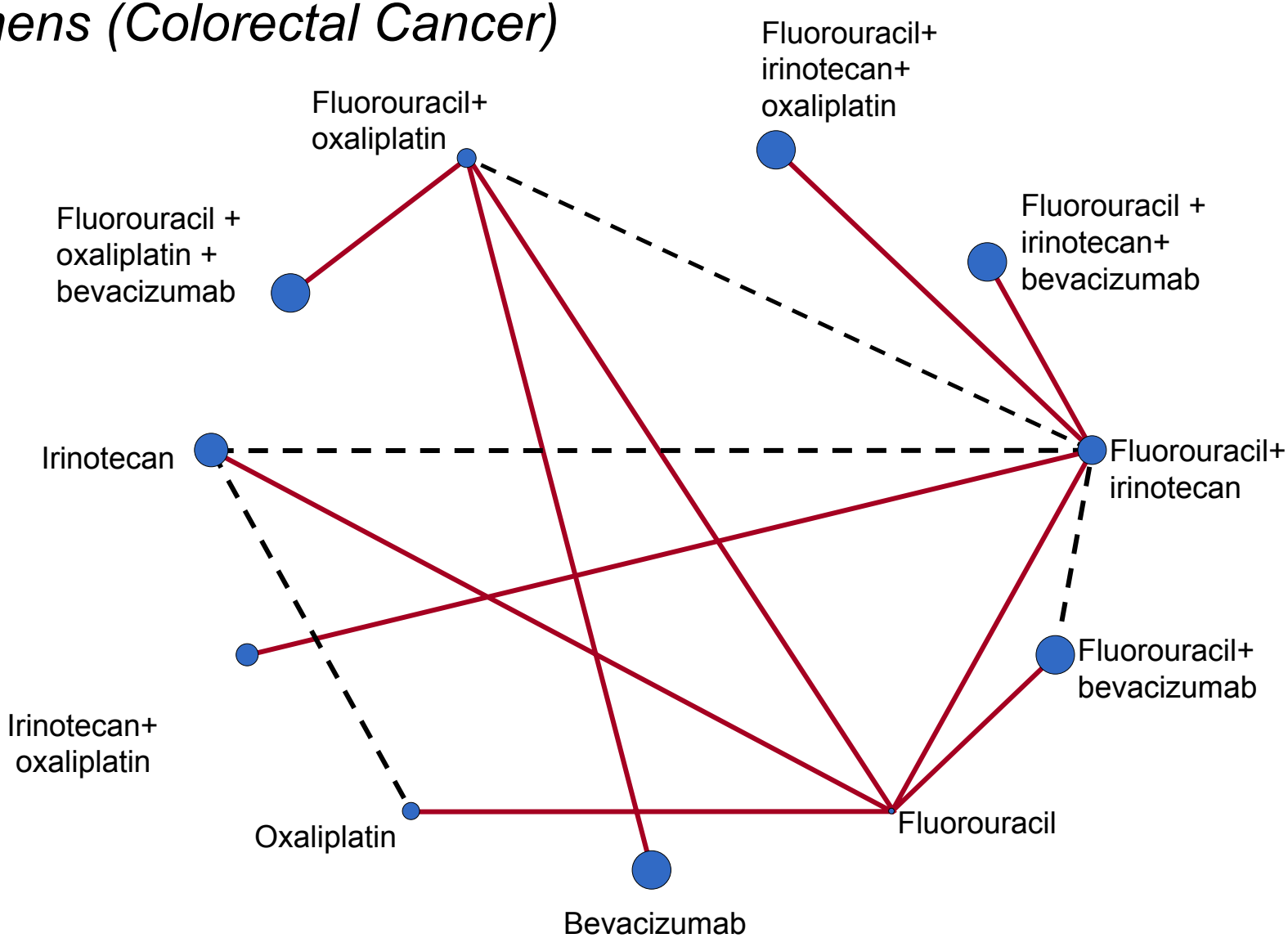
- Only 2 studies: $LOR_{BS} = -0.77$ (– 7.74, 6.23)
- All studies: $LOR_{BS} = -0.18$ (– 1.22, 0.82)

We gained precision

Inconsistency models

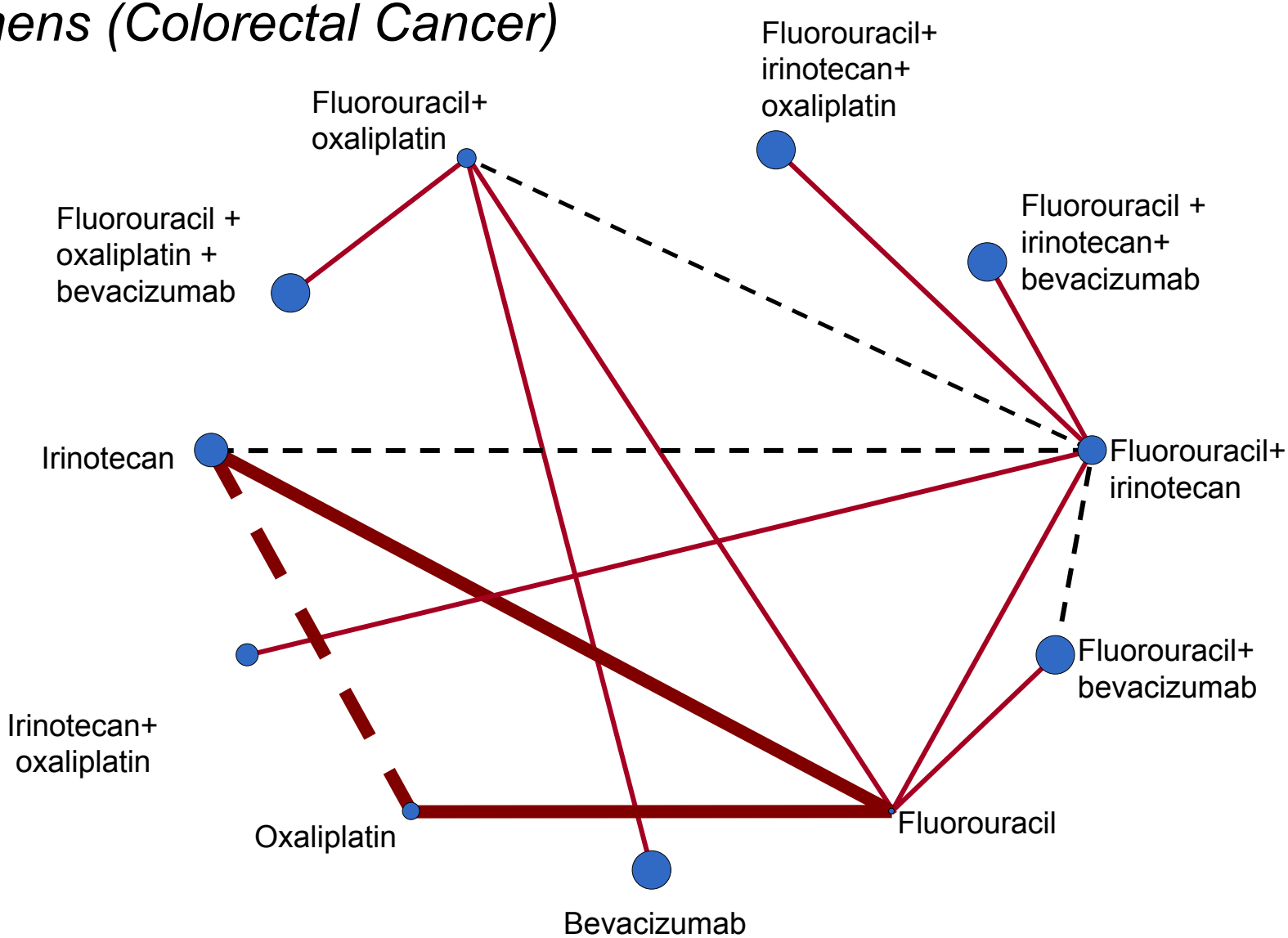
- Separate basic and functional parameters
- Add an inconsistency term at each consistency equation
- Estimate the extend of inconsistency

Survival with chemotherapy regimens (Colorectal Cancer)



Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP: ***Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis.*** *Lancet Oncol 2007,* ***8:*** *898-911.*

Survival with chemotherapy regimens (Colorectal Cancer)



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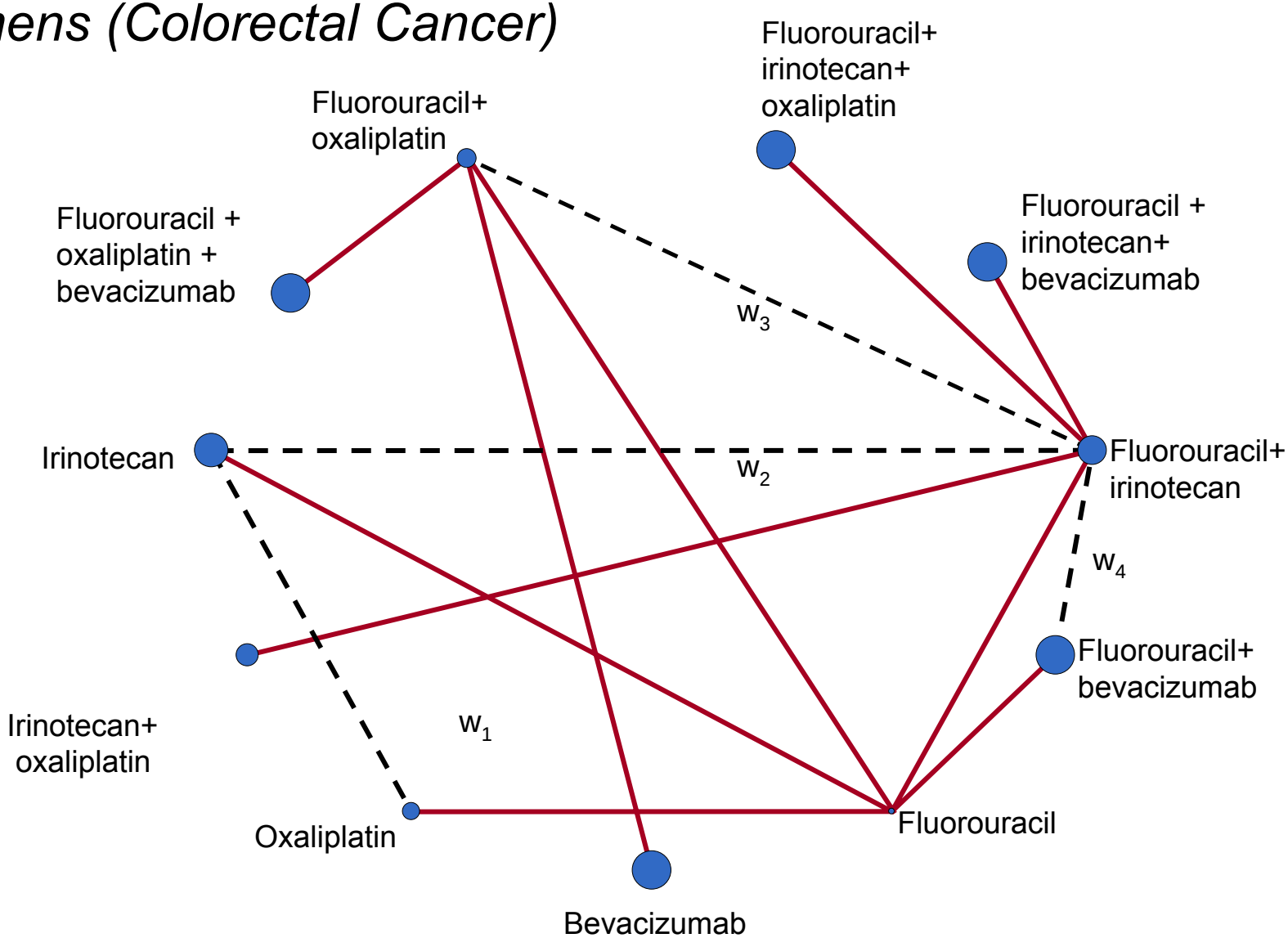


Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP: ***Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis.*** *Lancet Oncol 2007,* ***8:*** *898-911.*

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*($\sigma^2 > \tau^2$)

Lu & Ades JASA 2005

Results

- $w_1 = -0.08$, $w_2 = -0.07$, $w_3 = -0.06$, $w_1 = -0.03$
  - No loop is remarkably inconsistent
- $\sigma^2 = 0.11(0.04)$, $\tau^2 = 0.19(0.18)$
  - $P(\sigma^2 > \tau^2) = 0.61$
- 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

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

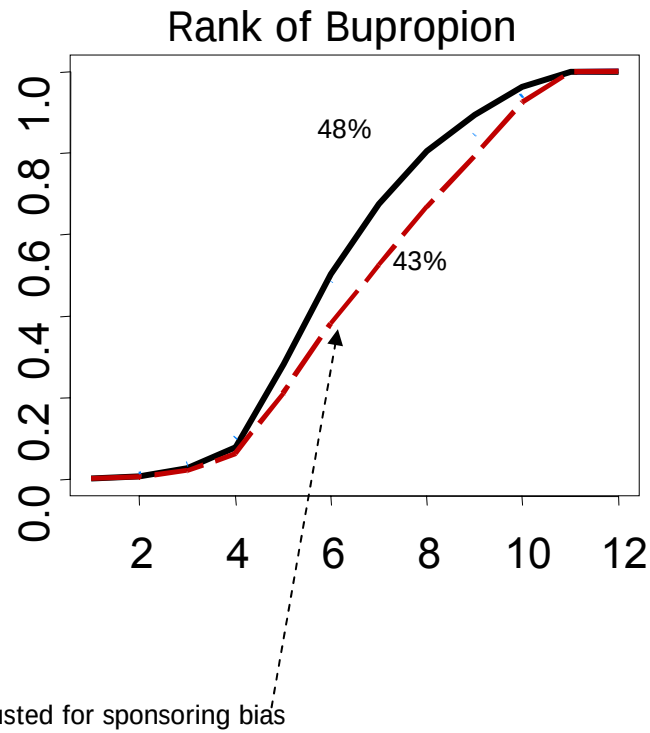
Bias adjusted estimate $\theta_i^{AB} = \mu_i^{AB} + \beta_i I^{AB}$

coefficient

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

Random effects in the effect of the covariate

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



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

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