

Network meta-analysis: statistical methods in a network

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Statistical methods to fit NMA

- You don't need to understand every single technical detail in order to fit NMA!
- But a certain degree of understanding is important
- NMA can be fitted as
 - a) meta-regression
 - b) multivariate meta-analysis
 - c) hierarchical model in a Bayesian setting
- Inconsistency can be evaluated in the full network

Steps to undertake in network meta-analysis

- Plot the network
- Select $T-1$ basic parameters (=comparisons) [*T the number of treatments*]
- Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons
- Employ the consistency equations to calculate all pairwise treatment effects

**Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus
(Review)**

Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM



This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library*
2009, Issue 3

<http://www.thecochranelibrary.com>

ABSTRACT

Background

It is unclear whether patients with type 2 diabetes who have poor glycaemic control despite maximal oral hypoglycaemic agents (OHAs) should be commenced on insulin as monotherapy, or insulin combined with oral hypoglycaemic agents (insulin-OHA combination therapy).

Objectives

To assess the effects of insulin monotherapy versus insulin-OHA combinations therapy.

Search strategy

Eligible studies were identified by searching MEDLINE, EMBASE, and *The Cochrane Library*.

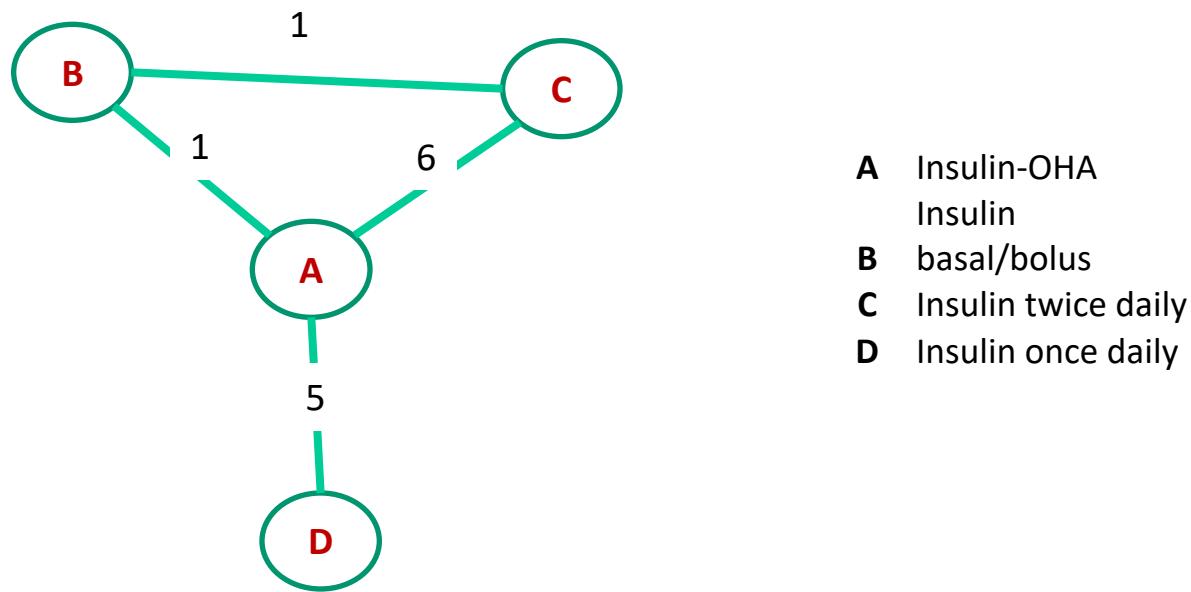
Selection criteria

Randomised controlled trials (RCTs) with 2 months minimum follow-up duration comparing insulin monotherapy (all schemes) with insulin-OHA combination therapy.

Data collection and analysis

Data extraction and assessment of study quality were undertaken by three reviewers in pairs.

Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus



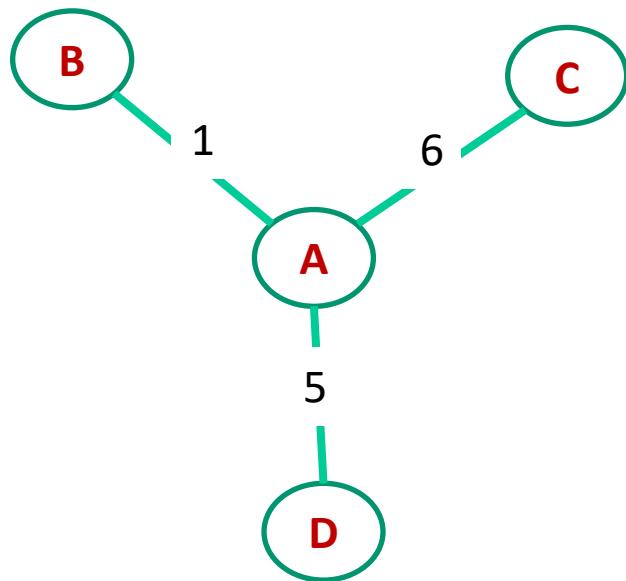
Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus

glycosylated haemoglobin

Study (name)	id	TREAT1	TREAT2	y1	sd1	n1	y2	sd2	n2	comp
Bastyr 1999	6	A	B	-1.21	1.21	135	-1.4	1.46	149	AB
Wolffenbuttel 1996	8	A	C	-2.52	1.17	33	-2.9	1.21	34	AC
Fvnyi 1997	9	A	C	-2.23	1.18	141	-1.4	1.11	145	AC
Yki-Jrvinen 1999	10	A	C	-2.1	1.4	23	-2	1.5	24	AC
Chow 1995	11	A	C	-1.4	1.22	27	-2.16	1.74	26	AC
Lotz 1988	12	A	C	-0.75	1.73	8	-1.72	1.6	8	AC
Wolffenbuttel 1991	13	A	C	-2.42	1.31	25	-3.1	1.26	22	AC
Sun 1995	1	A	D	-5.5	4.82	12	-3	3.53	11	AD
Riddle 1998	2	A	D	-2.2	1	72	-2.1	1	73	AD
Riddle 1992	3	A	D	-1.3	0.33	11	-0.8	0.63	10	AD
Shank 1995	4	A	D	-1.8	1.92	9	-0.7	1.74	9	AD
Du 2001	5	A	D	-1.7	1.57	45	-1.3	1.55	45	AD

Steps to undertake in network meta-analysis

Example



- *Plot the network*
- **Select T-1 basic parameters (=comparisons)**
- Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons
- Employ the consistency equations to calculate all pairwise treatment effects

Select basic parameters

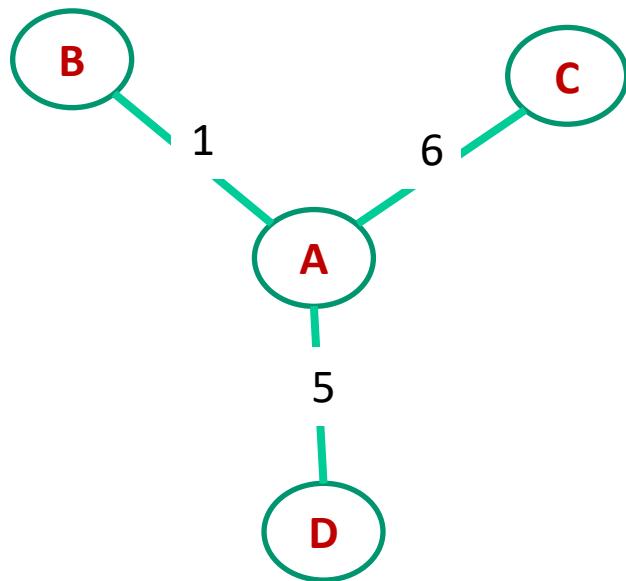
Select a number of comparisons equal with the number of treatments minus one that are independant and connected (see later)

For convenience: use all comparisons versus a common comparison

The results are insensitive to the choice of basic parameters

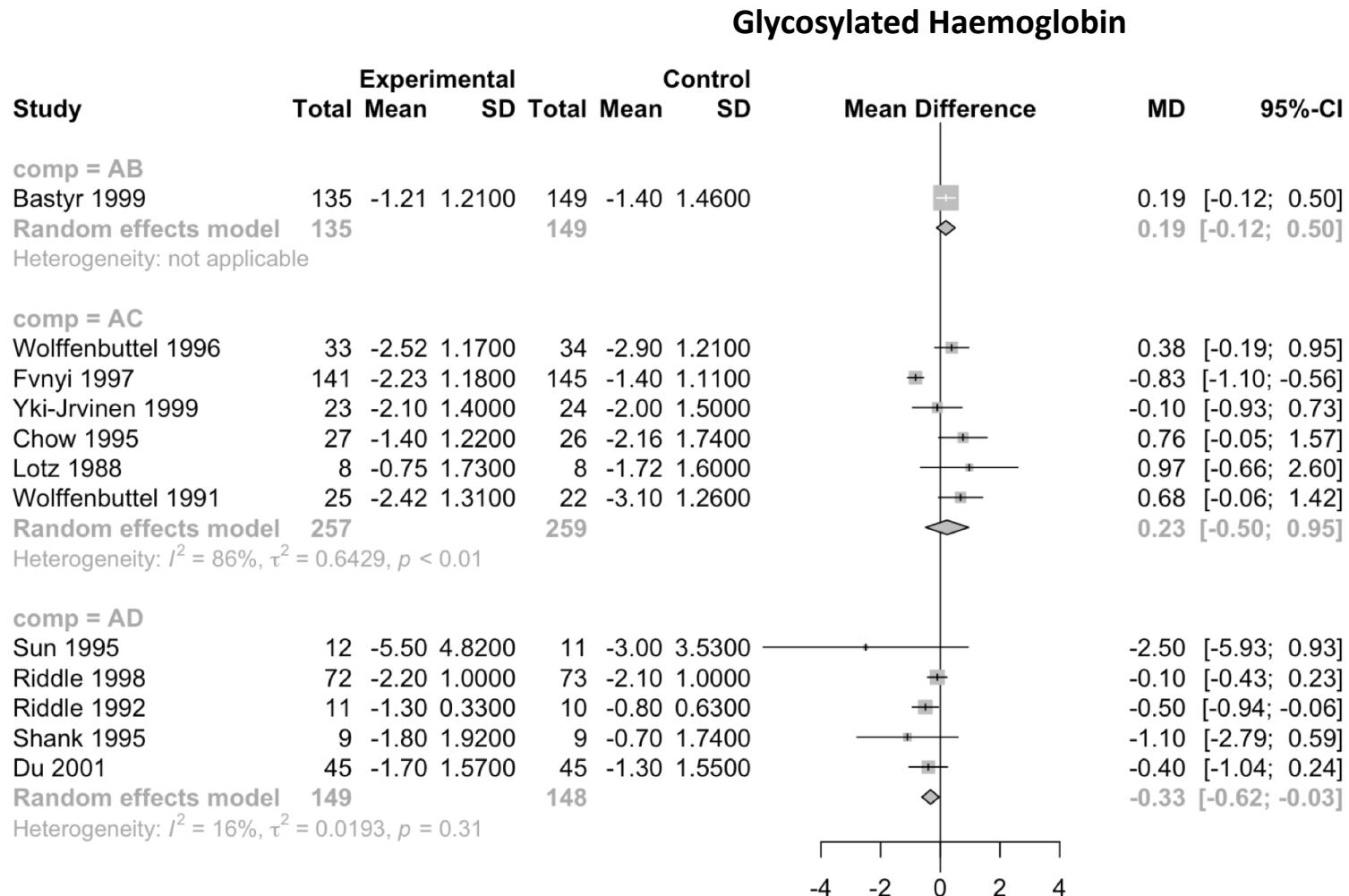
Steps to undertake in network meta-analysis

Example



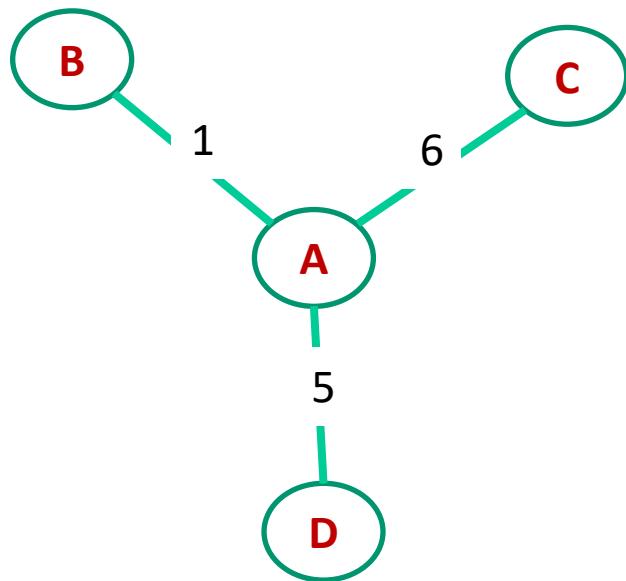
- *Plot the network*
- *Select $T-1$ basic parameters (=comparisons)*
- **Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons**
- Employ the consistency equations to calculate all pairwise treatment effects

Run subgroup analyses to estimate summary effects for each one of the B basic comparisons



Steps to undertake in network meta-analysis

Example



- *Plot the network*
- *Select $T-1$ basic parameters (=comparisons)*
- *Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons*
- **Employ the consistency equations to calculate all pairwise treatment effects**

Employ the consistency equations to calculate all pairwise treatment effects

Consistency equations: the equations that link all the comparisons!

With T treatments we have

- $T \times (T-1)/2$ possible treatment comparisons
- $T-1$ basic comparisons
- We need $T \times (T-1)/2 - (T-1)$ consistency equations

With 4 treatments A, B, C, D (as in the example) we have

- 6 possible treatment comparisons: AB, AC, AD, BC, BD, CD
- 3 basic comparisons: AB, AC, AD
- We need to write 3 consistency equations

Employ the consistency equations to calculate all pairwise treatment effects

- 6 possible treatment comparisons: AB, AC, AD, BC, BD, CD
- 3 basic comparisons: AB, AC, AD Estimated from the subgroup analysis

$$\mu_{AB}: 0.19 (-0.12, 0.50)$$

$$\mu_{AC}: 0.23 (-0.50, 0.95)$$

$$\mu_{AD}: -0.33 (-0.62, -0.03)$$

- We need to write 3 consistency equations

$$\mu_{BC} = \mu_{AC} - \mu_{AB} = 0.04$$

$$\mu_{BD} = \mu_{AD} - \mu_{AB} = -0.52$$

$$\mu_{CD} = \mu_{AD} - \mu_{AC} = -0.56$$

We cut some corners...

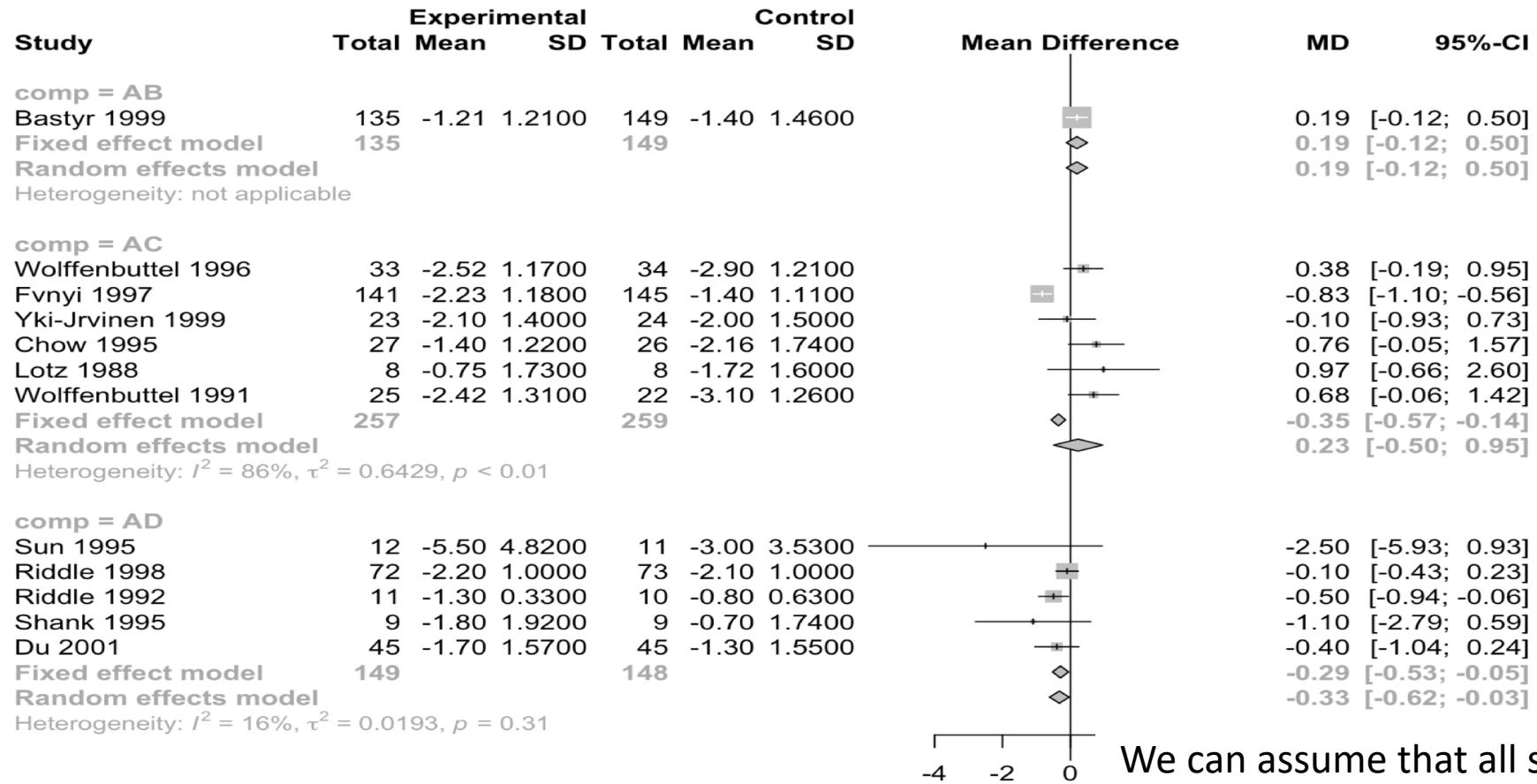
Random effects meta-analyses are more plausible in many clinical areas

(in the example we used fixed effects for simplicity)

Estimation of the heterogeneity parameter is an issue in random effects

- You need a few studies to estimate the heterogeneity variance properly...

Estimation of heterogeneity



Results for subgroups (random effects model):

	k	MD	95%-CI	Q	tau^2	I^2
comp = AB	1	0.1900	[-0.1208; 0.5008]	0.00	--	--
comp = AC	6	0.2273	[-0.4954; 0.9500]	36.42	0.6429	86.3%
comp = AD	5	-0.3260	[-0.6171; -0.0349]	4.78	0.0193	16.3%

We can assume that all studies have the same heterogeneity irrespectively of the comparison

Run subgroup analyses to estimate summary effects for each one of the B basic comparisons using the same heterogeneity

Results for subgroups (random effects model) equal heterogeneities

	k	MD	95%-CI	Q	tau^2	I^2
comp = AB	1	0.1900	[-1.0270; 1.4070]	0.00	--	--
comp = AC	6	0.1887	[-0.3876; 0.7651]	36.42	0.3604	86.3%
comp = AD	5	-0.4858	[-1.1642; 0.1927]	4.78	0.3604	16.3%

Results for subgroups (random effects model) different heterogeneities

	k	MD	95%-CI	Q	tau^2	I^2
comp = AB	1	0.1900	[-0.1208; 0.5008]	0.00	--	--
comp = AC	6	0.2273	[-0.4954; 0.9500]	36.42	0.6429	86.3%
comp = AD	5	-0.3260	[-0.6171; -0.0349]	4.78	0.0193	16.3%

Then the indirect treatment effects are:

$$\mu_{BC} = \mu_{AC} - \mu_{AB} = 0$$

$$\mu_{BD} = \mu_{AD} - \mu_{AB} = -0.68$$

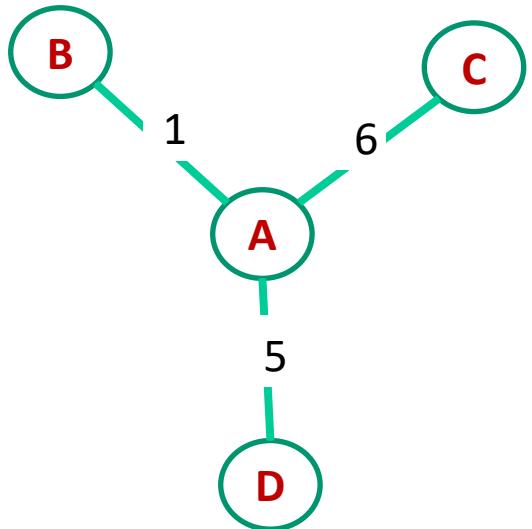
$$\mu_{CD} = \mu_{AD} - \mu_{AC} = -0.68$$

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \mu_{AD} \mathbf{AD} + \mu_{AB} \mathbf{AB} + \mu_{AC} \mathbf{AC}$$

μ_{AD} : the direct estimate AD
 μ_{AB} : the direct estimate AB
 μ_{AC} : the direct estimate AC

$\mu_{AB} - \mu_{AD}$: the indirect estimate DB
 $\mu_{AC} - \mu_{AD}$: the indirect estimate DC
 $\mu_{AC} - \mu_{AB}$: the indirect estimate BC



Author	comp	AB	AC	AD
Bastyr 1999	AB	1	0	0
Wolffenbuttel 1996	AC	0	1	0
Fvnyi 1997	AC	0	1	0
Yki-Jrvinen 1999	AC	0	1	0
Chow 1995	AC	0	1	0
Lotz 1988	AC	0	1	0
Wolffenbuttel 1991	AC	0	1	0
Sun 1995	AD	0	0	1
Riddle 1998	AD	0	0	1
Riddle 1992	AD	0	0	1
Shank 1995	AD	0	0	1
Du 2001	AD	0	0	1

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \alpha + \beta_1 AB + \beta_2 AC$$

α : the direct estimate AD μ_{AD}

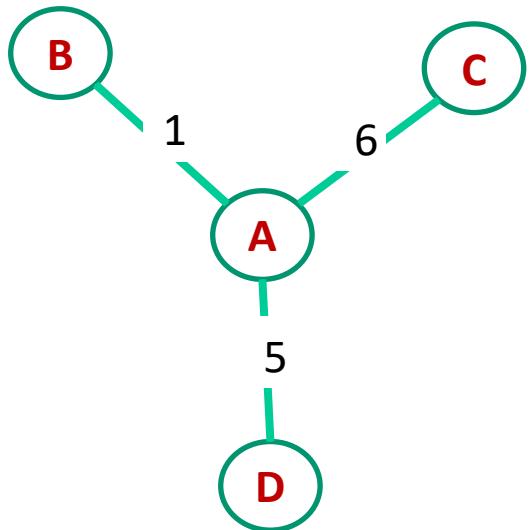
$\alpha + \beta_1$: the direct estimate AB μ_{AB}

$\alpha + \beta_2$: the direct estimate AC μ_{AC}

β_1 : the indirect estimate DB

β_2 : the indirect estimate DC

$\beta_2 - \beta_1$: the indirect estimate BC



Author	comp	AB	AC	AD
Bastyr 1999	AB	1	0	1
Wolffenbuttel 1996	AC	0	1	1
Fvnyi 1997	AC	0	1	1
Yki-Jrvinen 1999	AC	0	1	1
Chow 1995	AC	0	1	1
Lotz 1988	AC	0	1	1
Wolffenbuttel 1991	AC	0	1	1
Sun 1995	AD	0	0	1
Riddle 1998	AD	0	0	1
Riddle 1992	AD	0	0	1
Shank 1995	AD	0	0	1
Du 2001	AD	0	0	1

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \alpha + \beta_1 AB + \beta_2 AC$$

`metareg(HBStarmeta, ~AB+AC)` assumes equal heterogeneities

Model Results:

		estimate	se	zval	pval	ci.lb	ci.ub
Intrcpt	α	-0.4858	0.3461	-1.4033	0.1605	-1.1642	0.1927
AB	β_1	0.6758	0.7109	0.9506	0.3418	-0.7176	2.0691
AC	β_2	0.6745	0.4542	1.4850	0.1375	-0.2157	1.5647

Remember:

α : the direct estimate AD

β_1 : the indirect estimate DB

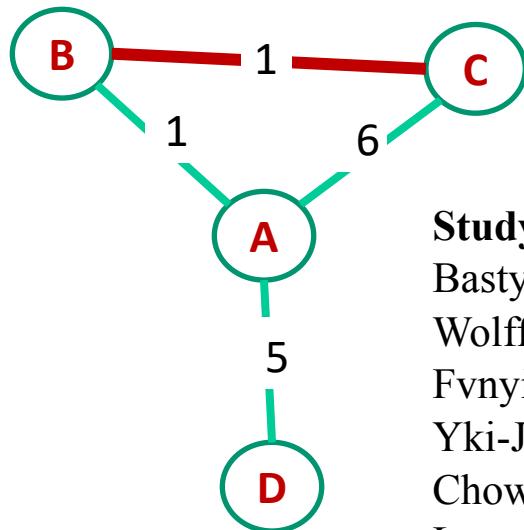
$\alpha + \beta_1$: the direct estimate AB

β_2 : the indirect estimate DC

$\alpha + \beta_2$: the direct estimate AC

$\beta_2 - \beta_1$: the indirect estimate BC

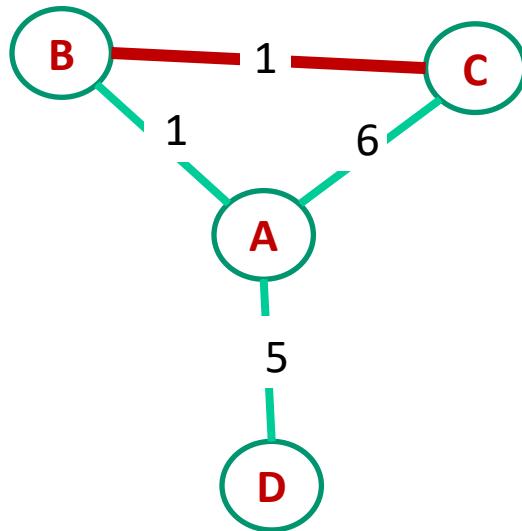
Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus



Study (name)	T1	T2	y1	sd1	n1	y2	sd2	n2 comp
Bastyr 1999	A	B	-1.21	1.21	135	-1.4	1.46	149 AB
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Du 2001	A	D	-1.7	1.57	45	-1.3	1.55	45 AD
Yki-Jrvinen 1992	B	C	-1.6	1.6	30	-1.8	1.6	29 BC

What is difficult with it?

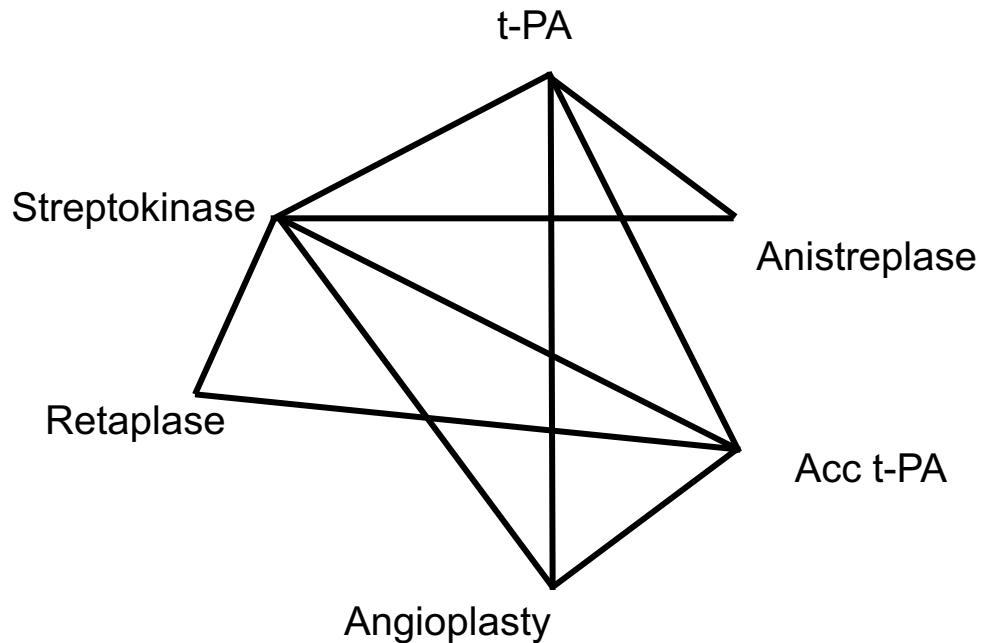
- The way that data informs you about the basic parameters
- The way the consistency equations enter the model



That differentiates the 3 approaches meta-regression vs multivariate meta-analysis vs hierarchical Bayesian model

- Plot the network – **easy!**
- Select B basic parameters (=comparisons) – **relatively easy**
- Run subgroup analyses or **meta-regressions** to estimate summary effects for each one of the B basic comparisons
 - The way that data informs you about the basic parameters in the presence of a BC comparison (not basic parameter)
 - Multi-arm studies
- Employ the consistency equations to calculate all pairwise treatment effects – **easy although tedious process!**

Select basic parameters



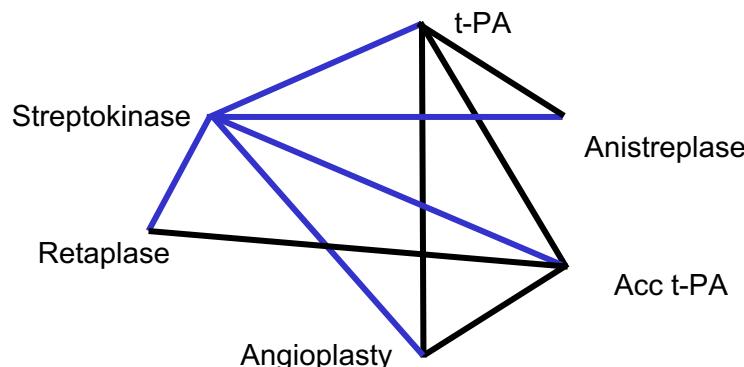
Treatments for MI and mortality Lumley Stat Med 2002

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$y_i = \mu_{tPA-S} tPA_i + \mu_{Anist-S} Anist_i + \mu_{AcctPA-S} AcctPA_i + \mu_{Ang-S} Ang_i + \mu_{Ret-S} Ret_i + \delta_i + e_i$$

Use as 'covariates'

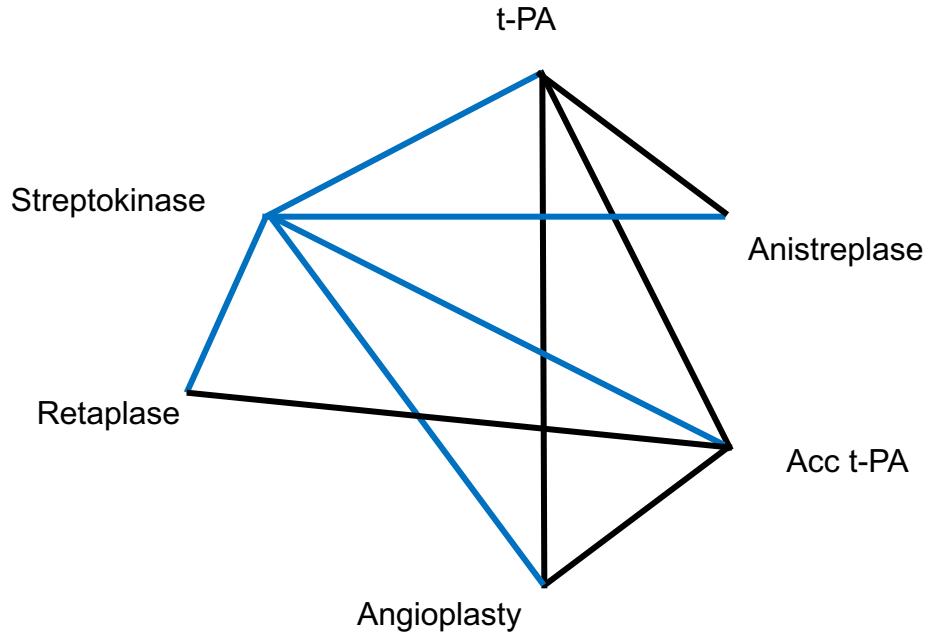
No. studies	Streptokinase	t-PA	Anistreplase	Acc t-PA	Angioplasty	Reteplase
3	Ref	1	0	0	0	0
1	Ref	0	1	0	0	0
1	Ref	0	0	1	0	0
3	Ref	0	0	0	1	0
1	Ref	0	0	0	0	1



We have ignored some studies

Employ the consistency equations to calculate all pairwise treatment effects

6 treatments, 15 possible comparisons, 5 basic comparisons, 10 consistency equations



10 consistency equations

$$\mu_{tPA \text{ vs } Anistr} = \mu_{Str \text{ vs } Anistr} - \mu_{Str \text{ vs } tPA}$$

$$\mu_{tPA \text{ vs } Reta} = \mu_{Str \text{ vs } Reta} - \mu_{Str \text{ vs } tPA}$$

.....

Design matrix

- The consistency equations are built into the design matrix
- This minimizes the number of parameters and allows us to gain precision

$$\mathbf{y} = \mathbf{X}\boldsymbol{\mu} + \boldsymbol{\delta} + \mathbf{e}$$

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

$$\mathbf{e} \sim N(\mathbf{0}, \text{diag}\{v_i\})$$

$$\mathbf{X} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \quad \boldsymbol{\mu} = \begin{pmatrix} \mu_{tPA-S} \\ \mu_{Anist-S} \\ \mu_{AcctPA-S} \\ \mu_{Ang-S} \\ \mu_{Ret-S} \end{pmatrix}$$

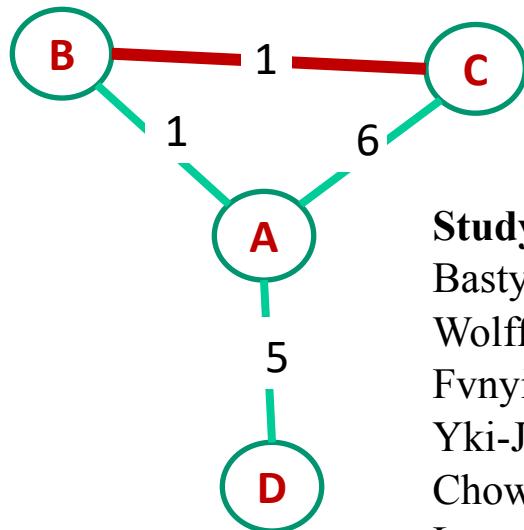
Estimate summary effects for each one of the B basic comparisons: technicalities

- In a star-shaped network – easy!
 - Think about the assumptions in heterogeneity
- What if we don't have a star-shaped network? How do non-basic comparisons enter the model?
 - Meta-regression
 - Multivariate meta-analysis
 - Hierarchical model

Implementing network meta-analyses with closed loops

- **Subgroup analyses** won't work
 - The consistency equations aren't built in
 - Although we can do this with flexible software that allows us to force the consistency equations to hold
 - e.g. WinBUGS in a Bayesian framework= this is the hierarchical model!
- **Meta-regression** can be used
 - CAUTION! Covariates need to be coded cleverly
 - Works only if every study has exactly two intervention arms
- **Multivariate meta-analysis** is preferable
 - It allows us to include studies with three or more arms

Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus



Study (name)	T1	T2	y1	sd1	n1	y2	sd2	n2 comp
Bastyr 1999	A	B	-1.21	1.21	135	-1.4	1.46	149 AB
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Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \alpha + \beta_1 AB + \beta_2 AC$$

α : the direct estimate AD μ_{AD}

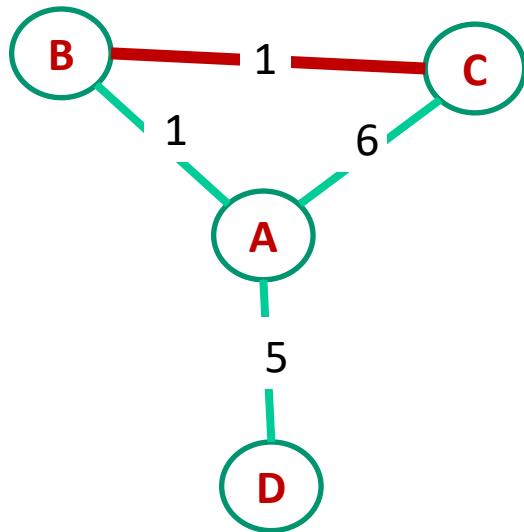
$\alpha + \beta_1$: the direct estimate AB μ_{AB}

$\alpha + \beta_2$: the direct estimate AC μ_{AC}

β_1 : the indirect estimate DB

β_2 : the indirect estimate DC

$\beta_2 - \beta_1$: the indirect estimate BC



Because
 $BC = AC - AB$

Author	comp	AB	AC	AD
Bastyr 1999	AB	1	0	0
Wolffenbuttel 1996	AC	0	1	0
Fvnyi 1997	AC	0	1	0
Yki-Jrvinen 1999	AC	0	1	0
Chow 1995	AC	0	1	0
Lotz 1988	AC	0	1	0
Wolffenbuttel 1991	AC	0	1	0
Sun 1995	AD	0	0	1
Riddle 1998	AD	0	0	1
Riddle 1992	AD	0	0	1
Shank 1995	AD	0	0	1
Du 2001	AD	0	0	1
Yki-Jrvinen 1992	BC	-1	1	0

Results from meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \alpha + \beta_1 AB + \beta_2 AC$$

α : the direct estimate AD μ_{AD}

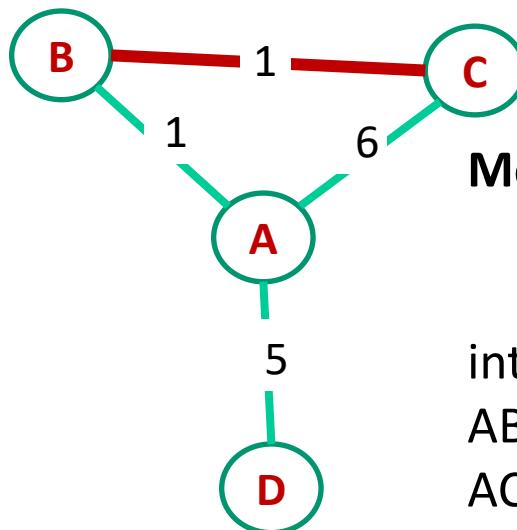
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Model Results:

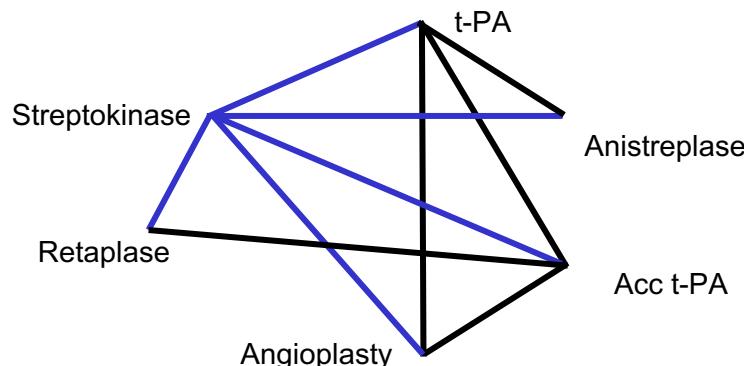
	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.4107	0.3246	-1.2654	0.2057	-1.0469	0.2254
AB	0.3663	0.5234	0.6999	0.4840	-0.6595	1.3921
AC	0.6506	0.4495	1.4474	0.1478	-0.2304	1.5317

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$y_i = \mu_{tPA-S} tPA_i + \mu_{Anist-S} Anist_i + \mu_{AcctPA-S} AcctPA_i + \mu_{Ang-S} Ang_i + \mu_{Ret-S} Ret_i + \delta_i + e_i$$

Use as 'covariates'

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



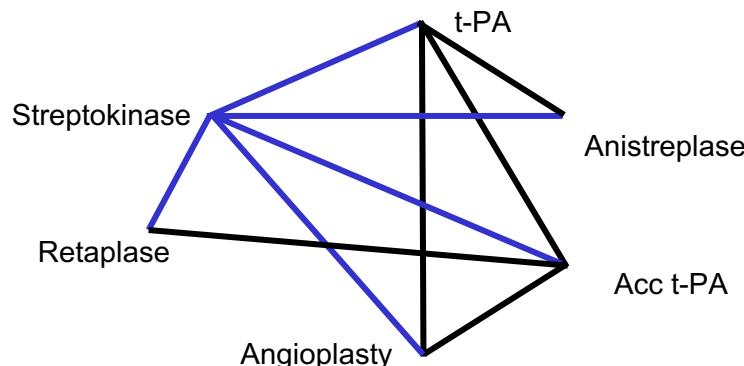
We have ignored some studies

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$y_i = \mu_{tPA-S} tPA_i + \mu_{Anist-S} Anist_i + \mu_{AcctPA-S} AcctPA_i + \mu_{Ang-S} Ang_i + \mu_{Ret-S} Ret_i + \delta_i + e_i$$

Use as 'covariates'

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



All studies are now included

Design matrix

The consistency equations are built into the design matrix

This minimizes the number of parameters and allows us to gain precision

$$\mathbf{y} = \mathbf{X}\boldsymbol{\mu} + \boldsymbol{\delta} + \mathbf{e}$$

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

$$\mathbf{e} \sim N(\mathbf{0}, \text{diag}\{\nu_i\})$$

$$X = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ -1 & 1 & 0 & 0 & 0 \\ -1 & 0 & 0 & 1 & 0 \\ -1 & 0 & 0 & 1 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 0 & 1 \\ 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$
$$\boldsymbol{\mu} = \begin{pmatrix} \mu_{tPA-S} \\ \mu_{Anist-S} \\ \mu_{AcctPA-S} \\ \mu_{Ang-S} \\ \mu_{Ret-S} \end{pmatrix}$$

Results from meta-regression

Treatments for MI versus Streptokinase

<i>Regression coefficients</i>	$\mu \ln OR$ (SE)
$\mu_{Str \text{ vs tPA}}$	-0.02 (0.03)
$\mu_{Str \text{ vs Anistr}}$	-0.00 (0.03)
$\mu_{Str \text{ vs Accelerated t-PA}}$	-0.15 (0.05)
$\mu_{Str \text{ vs Angioplasty}}$	-0.43 (0.20)
$\mu_{Str \text{ vs Reta}}$	-0.11 (0.06)

We obtain other comparisons by computing linear combinations of these, taking into account their variance-covariance matrix

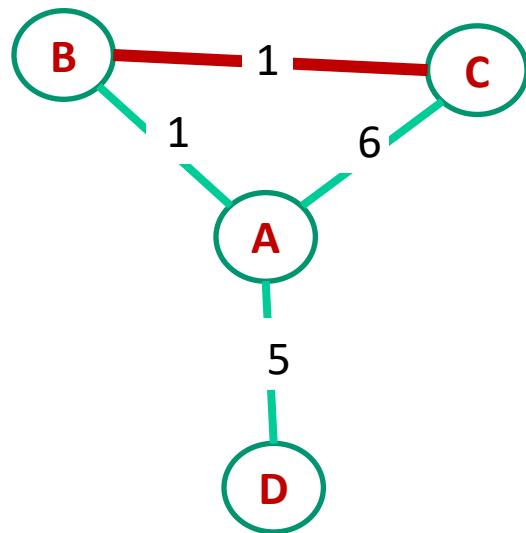
10 consistency equations

$$\mu_{tPA \text{ vs Anistr}} = \mu_{Str \text{ vs Anistr}} - \mu_{Str \text{ vs tPA}}$$

$$\mu_{tPA \text{ vs Reta}} = \mu_{Str \text{ vs Reta}} - \mu_{Str \text{ vs tPA}}$$

.....

Run multivariate meta-analysis to estimate summary effects for each one of the B basic comparisons



- Each basic parameter can be seen as a different ‘outcome’
- We have 3 ‘outcomes’: AB, AC, AD
- A study comparing BC does not provide information on any outcome
- We impute an A arm!
 - Using minimum information
 - This is what is implemented in Stata

But what about studies that don't have any of these basic parameters?

- Studies that don't include the basic parameters require a little 'trick'
- In the current example, this means the study that does not have treatment A

Study (name)	TREAT1	TREAT2	m1	sd1	n1	m2	sd2	n2	comp
Yki-Jrvinen 1992	B	C	-1.6	1.6	30	-1.8	1.6	29	BC

- We recode this as

Study (name)	TREAT1	TREAT2	m1	sd1	n1	m2	sd2	n2	comp
Yki-Jrvinen 1992	A	B	0	500	0.01	-1.6	1.6	30	AB
Yki-Jrvinen 1992	A	C	0	500	0.01	-1.8	1.6	29	AC

- 
- This is a tiny arm for intervention A (0.01 people)
 - It looks odd! But it works, and is safe. It's called *data augmentation*

Impute an A arm for the BC comparison

Study (name)	TREAT									comp
	TREAT1	2	y1	sd1	n1	y2	sd2	n2		
Bastyr 1999	A	B	-1.21	1.21	135	-1.4	1.46	149		AB
Wolffenbuttel 1996	A	C	-2.52	1.17	33	-2.9	1.21	34		AC
Fvnyi 1997	A	C	-2.23	1.18	141	-1.4	1.11	145		AC
Yki-Jrvinen 1999	A	C	-2.1	1.4	23	-2	1.5	24		AC
Chow 1995	A	C	-1.4	1.22	27	-2.16	1.74	26		AC
Lotz 1988	A	C	-0.75	1.73	8	-1.72	1.6	8		AC
Wolffenbuttel 1991	A	C	-2.42	1.31	25	-3.1	1.26	22		AC
Sun 1995	A	D	-5.5	4.82	12	-3	3.53	11		AD
Riddle 1998	A	D	-2.2	1	72	-2.1	1	73		AD
Riddle 1992	A	D	-1.3	0.33	11	-0.8	0.63	10		AD
Shank 1995	A	D	-1.8	1.92	9	-0.7	1.74	9		AD
Du 2001	A	D	-1.7	1.57	45	-1.3	1.55	45		AD
Yki-Jrvinen 1992	B	C	-1.6	1.6	30	-1.8	1.6	29		BC

Impute an A arm for the BC comparison

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Yki-Jrvinen 1999	A	C	-2.1	1.4	23	-2	1.5	24	AC	
Chow 1995	A	C	-1.4	1.22	27	-2.16	1.74	26	AC	
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Wolffenbuttel 1991	A	C	-2.42	1.31	25	-3.1	1.26	22	AC	
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Yki-Jrvinen 1992	A	C	0	500	0.01	-1.8	1.6	29	AC	
Yki-Jrvinen 1992	B	C	-1.6	1.6	30	-1.8	1.6	29	BC	

Impute an A arm for the BC comparison

Study (name)	TREAT									comp
	TREAT1	2	y1	sd1	n1	y2	sd2	n2		
Bastyr 1999	A	B	-1.21	1.21	135	-1.4	1.46	149	AB	
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Yki-Jrvinen 1992	A	C	0	500	0.01	-1.8	1.6	29	AC	

Then estimate the basic parameters!... But.....

You cannot simply do pairwise meta-analyses as in star network to estimate the basic parameters....

Complication: multi-arm studies

- When a study has more than 2 arms, it contributes 2 or more comparisons
- This complication occurs not only when we ‘impute’ an arm, but also when the study has multiple arms
- Such data are correlated and we need to employ more sophisticated statistical methodology: **multivariate meta-analysis** (mvmeta)

Yki-Jrvinen 1992	A	B	0	500	0.01	-1.6	1.6	30	AB
Yki-Jrvinen 1992	A	C	0	500	0.01	-1.8	1.6	29	AC

$$MD_i = \mu_{AB} \times AB_i + \mu_{AC} \times AC_i + \mu_{AD} \times AD_i + \delta_i + e_i$$

$$\begin{aligned}\delta_i &\sim MVN(0, \Delta^2) \\ e_i &\sim MVN(0, V)\end{aligned}$$

The residuals e and the random effects δ are correlated for the last two observations

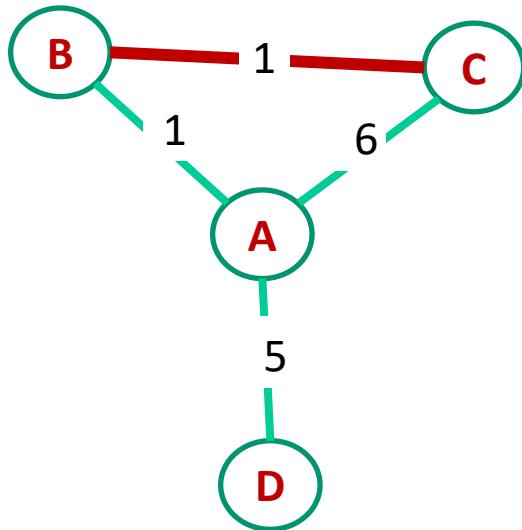
Multivariate meta-analysis

- *Multivariate* means we are interested in multiple *effect sizes* (or dependent variables) at the same time
- Not the same as using multiple *predictors* (or covariates) in a regression

Multiple variables on the **right** of the regression equation
= **multiple regression** (or multi-variable regression)

Multiple variables on the **left** of the regression equation
= **multivariate analysis**

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}	AD
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

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

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}	AD
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

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

V

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

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
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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

Meta-regression

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

Δ

$$\begin{pmatrix} \delta_{1,1} \\ \delta_{2,1} \\ \delta_{3,1} \\ \delta_{4,1} \\ \delta_{4,2} \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau^2 & 0 & 0 & 0 & 0 \\ 0 & \tau^2 & 0 & 0 & 0 \\ 0 & 0 & \tau^2 & 0 & 0 \\ 0 & 0 & 0 & \tau^2 & \kappa \\ 0 & 0 & 0 & \kappa & \tau^2 \end{pmatrix} \right)$$

How to fit such a model?

- The challenge lies in the estimation of matrix Δ
- The covariance of two random effects is a function of the heterogeneities. Taking the variance on a consistency equation results:

$$\text{second moments } \text{Cov}(\delta_{iAC}, \delta_{iBC}) = (\tau_{AB}^2 - \tau_{AC}^2 - \tau_{BC}^2)/2$$

often we assume equal $\tau \Rightarrow \text{Cov}(\delta_{iAC}, \delta_{iBC}) = \tau^2/2$

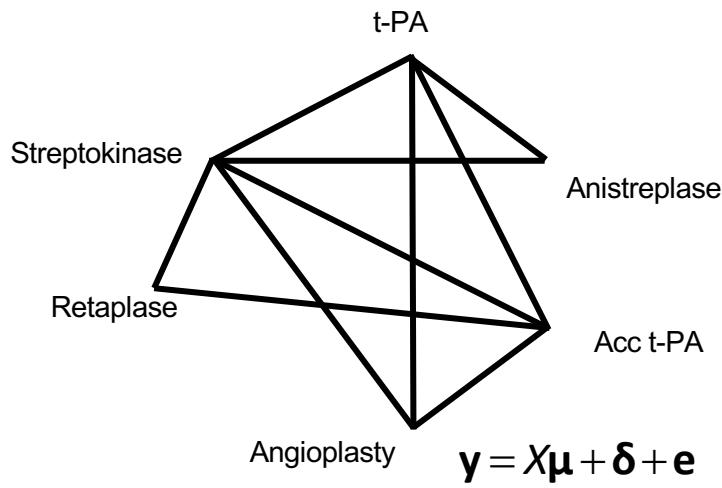
Simplified var-covariance matrix

The matrix Δ is easier to estimate

$$\Delta = \begin{bmatrix} \tau^2 & 0 & 0 & 0 \\ 0 & \ddots & 0 & 0 \\ 0 & 0 & \tau^2 & \tau/2 \\ 0 & 0 & \tau/2 & \tau^2 \end{bmatrix}$$

A general multivariate meta-analysis would not model the data properly, not even in this simpler case

Design matrix



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

$$\mathbf{e} \sim \mathbf{N}(\mathbf{0}, V)$$

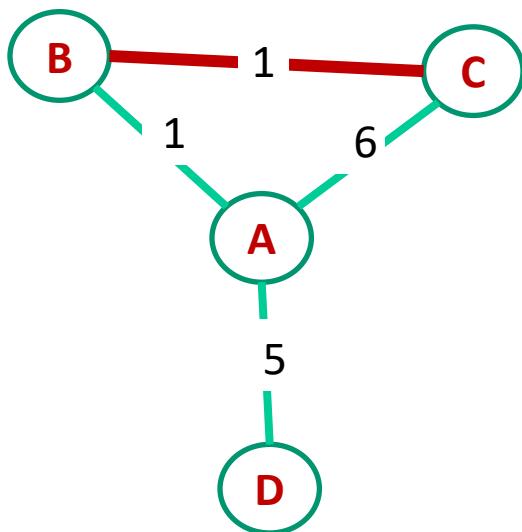
$$\boldsymbol{\delta} \sim \mathbf{N}(\mathbf{0}, \text{diag}\{\tau^2\})$$

$$\mathbf{e} \sim \mathbf{N}(\mathbf{0}, \text{diag}\{v_i\})$$

$$X = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ -1 & 1 & 0 & 0 & 0 \\ -1 & 0 & 0 & 1 & 0 \\ -1 & 0 & 0 & 1 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 0 & 1 \\ 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

$$\boldsymbol{\mu} = \begin{pmatrix} \mu_{tPA-S} \\ \mu_{Anist-S} \\ \mu_{AccPA-S} \\ \mu_{Ang-S} \\ \mu_{Ret-S} \end{pmatrix}$$

Hierarchical model to estimate each one of the B basic comparisons



- Do a meta-analysis in every comparison for which data is available
- The meta-analysis of the *non-basic* comparison (μ_{CD}) is estimated under the constraint that

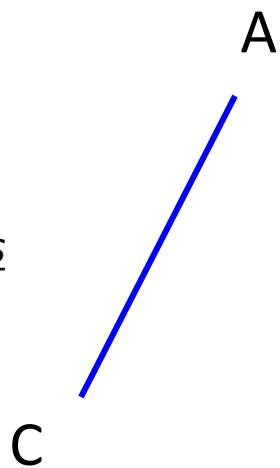
$$\mu_{BC} = \mu_{AC} - \mu_{AB}$$

Distributions of the observations

$$y_{iAC} \sim N(\theta_{iAC}, \sigma_i^2)$$

Distributions of the random effects

$$\theta_{iAC} \sim N(\mu_{AC}, \tau^2)$$



Measurement model (Likelihood)

$$y_{iAC} \sim N(\theta_{iAC}, v_i)$$

$$y_{iBC} \sim N(\theta_{iBC}, v_i)$$

$$y_{iAB} \sim N(\theta_{iAB}, v_i)$$

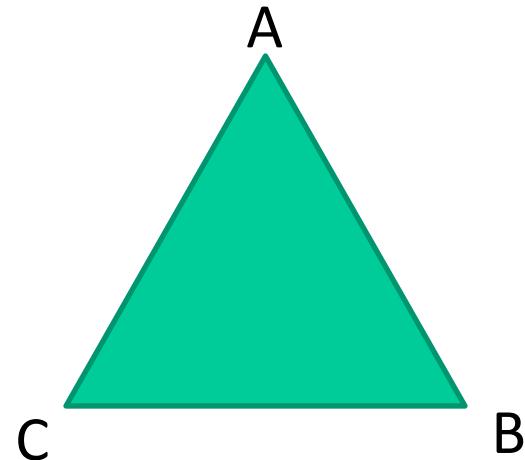
Structural model

$$\theta_{iAC} \sim N(\mu_{AC}, \tau_{AC}^2)$$

$$\theta_{iBC} \sim N(\mu_{BC}, \tau_{BC}^2)$$

$$\theta_{iAB} \sim N(\mu_{AB}, \tau_{AB}^2)$$

$$\mu_{AB} = \mu_{AC} - \mu_{BC}$$



Measurement model (Likelihood)

$$y_{iAC} \sim N(\theta_{iAC}, v_i)$$

$$(y_{iAC}, y_{iBC}) \sim MVN((\theta_{iAC}, \theta_{iBC}), S)$$

$$y_{iBC} \sim N(\theta_{iBC}, v_i)$$

S is the **variance-covariance matrix**

$$y_{iAB} \sim N(\theta_{iAB}, v_i)$$

estimated from the data

Structural model

$$\theta_{iAC} \sim N(\mu_{AC}, \tau_{AC}^2)$$

$$(\theta_{iAC}, \theta_{iBC}) \sim MVN((\mu_{AC}, \mu_{BC}), \Delta)$$

$$\theta_{iBC} \sim N(\mu_{BC}, \tau_{BC}^2)$$

Δ is the variance-covariance matrix

$$\theta_{iAB} \sim N(\mu_{AB}, \tau_{AB}^2)$$

of the random effects (unknown)

$$\mu_{AB} = \mu_{AC} - \mu_{BC}$$

Correlated observations

$$(y_{iAC}, y_{iBC}) \sim MVN((\theta_{iAC}, \theta_{iBC}), S_i)$$

S_i is the **variance-covariance matrix**
estimated from the data

$$S_i = \begin{pmatrix} v_{i1} & c_i \\ c_i & v_{i2} \end{pmatrix}$$

*c depends on the measure y_i
e.g. When we observe mean difference
 $Cov(y_{iAC}, y_{iBC}) = var_C$*

Correlated random effects

$$(\theta_{iAC}, \theta_{iBC}) \sim MVN((\mu_{AC}, \mu_{BC}), \Delta)$$

Δ is the variance-covariance matrix

of the random effects which is unknown

$$\Delta = \begin{pmatrix} \tau_{AC}^2 & c = f(\tau_{AC}, \tau_{BC}) \\ c = f(\tau_{AC}, \tau_{BC}) & \tau_{BC}^2 \end{pmatrix}$$

$$\Rightarrow \Delta = \begin{pmatrix} \tau^2 & \tau^2 / 2 \\ \tau^2 / 2 & \tau^2 \end{pmatrix}$$

[Stat Med. 1996 Higgins JP, Whitehead A.]

Correlated random effects

$$(\theta_{iAC}, \theta_{iBC}) \sim MVN((\mu_{AC}, \mu_{BC}), \Delta)$$

In practice we break MVN into two normal distributions,
one conditional on the other

$$\theta_{iAC} \sim N(\mu_{AC}, \tau^2)$$

$$\theta_{iBC} | \theta_{iAC} \sim N(\mu_{BC} + (\theta_{iAC} - \mu_{AC})/2, 3\tau^2/4)$$

If you want to assume different heterogeneities per comparison you need to decompose Δ matrix
[Biostatistics 2009 Lu & Ades]

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 $\ln OR$, $SE(\ln OR)$
- Model the arm-responses
- Parameterize to get the effect sizes
- Arm-based approaches typically have ‘better fit’ than those based on effect sizes

	No. studies	Control	Sclerotherapy	Beta-blockers
Treatments for first bleeding in cirrhosis	17	r_C/n_C	r_S/n_S	
	7	r_C/n_C		r_S/n_S
	2	r_C/n_C	r_S/n_S	r_S/n_S

Higgins & Whitehead
1996, Stat Med

$$r_{iC} \sim B(p_{iC}, n_{iC})$$

$$\text{Logit}(p_{iC}) = u_i$$

$$\theta_{iCS} \sim N(\mu_{CS}, \tau^2)$$

$$r_{iS} \sim B(p_{iS}, n_{iS})$$

$$\text{Logit}(p_{iS}) = u_i + \theta_{iCS}$$

$$\theta_{iCB} \sim N(\mu_{CB}, \tau^2)$$

$$r_{iB} \sim B(p_{iB}, n_{iB})$$

$$\text{Logit}(p_{iB}) = u_i + \theta_{iCB}$$

In the two 3-arms trials we only substitute

$$(\theta_{iCS}, \theta_{iCB}) \sim MVN((\mu_{CS}, \mu_{CB}), \Delta)$$

$$\mu_{SB} = \mu_{CB} - \mu_{CS}$$

Implementation

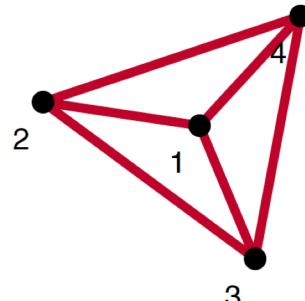
- Bayesian approach
 - WinBUGS/ OpenBUGS
 - GeMTC / BUGS / JAGS (van Valkenhoef et al., 2012)
- Frequentist approach: Multivariate Meta-Analysis
 - Stata: network (White, 2015) network_graphs (Chaimani, 2015)
 - SAS (Jones et al., 2011; Piepho, 2014)
 - R package netmeta (Rücker et al., 2017)
 - Overview to R packages (Neupane et al., 2014)

Method used in R netmeta

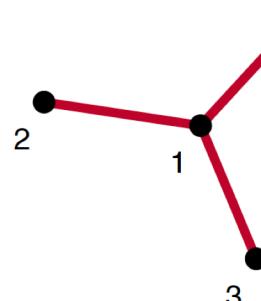
Based on electrical network methodology

- Similar to (multivariate) meta-regression (with dummy covariates, design matrix)
- Adjustment for multi-arm studies is done by reducing the weights of all comparisons (Rücker, 2012; Rücker and Schwarzer, 2014)

Given a four-arm study with six comparisons,



we may cut off three of six comparisons:



or reduce all weights by 1/2 (on average):

