Lecture 5

# Network meta-analysis: statistical methods in a full network

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**Network meta-analysis**
*A project-based course using R*
Kea island, April 2018

## 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

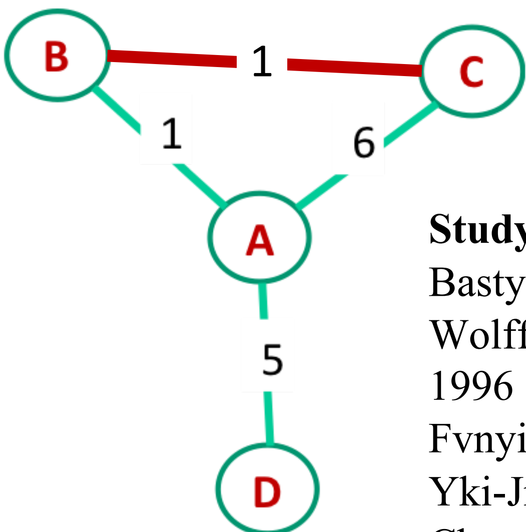
# Implementing network meta-analyses with closed loops

- **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 |
| 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 |
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| 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** |

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

$$MD_i = \alpha + \beta_1 \boldsymbol{AB} + \beta_2 \boldsymbol{AC}$$

$\alpha$: the direct estimate AD $\mu_{AD}$

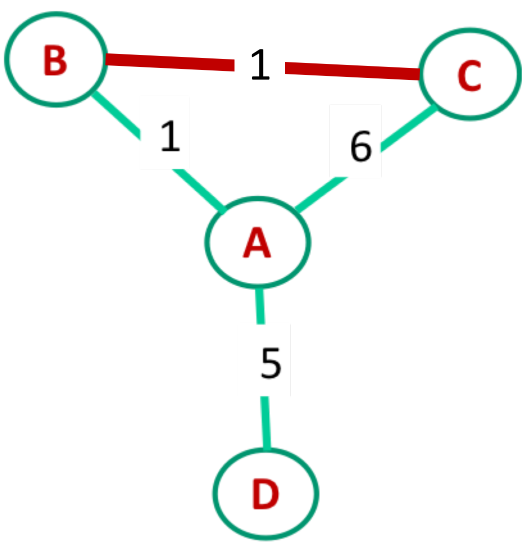
$\alpha + \beta_1$ : the direct estimate AB $\mu_{AB}$

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

$\beta_1$ : the indirect estimate DB

$\beta_2$ : the indirect estimate DC

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




Because
BC = AC – AB

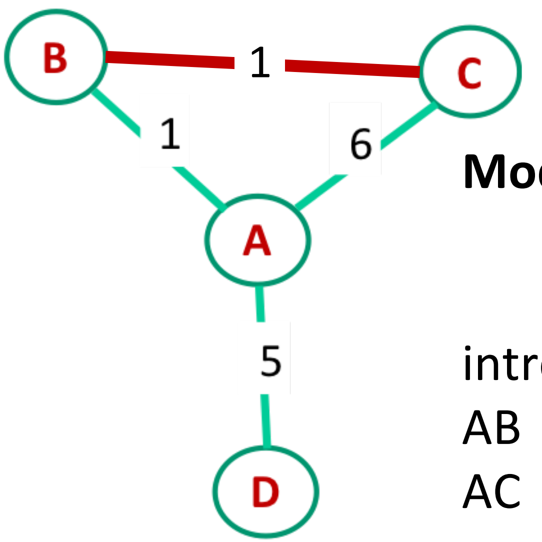
| Author | comp | AB | AC | AD |
|---|---|---|---|---|
| Bastyr 1999 | AB | 1 | 0 | 0 |
| Wolffenbuttel 1996 | AC | 0 | 1 | 0 |
| Fvnyi 1997 | AC | 0 | 1 | 0 |
| Yki-Jrvinen 1999 | AC | 0 | 1 | 0 |
| Chow 1995 | AC | 0 | 1 | 0 |
| Lotz 1988 | AC | 0 | 1 | 0 |
| Wolffenbuttel 1991 | AC | 0 | 1 | 0 |
| 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

$$MD_i = \alpha + \beta_1 \mathbf{AB} + \beta_2 \mathbf{AC}$$

α: the direct estimate AD $\mu_{AD}$
$\alpha+\beta_1$ : the direct estimate AB $\mu_{AB}$
$\alpha+\beta_2$ : the direct estimate AC $\mu_{AC}$

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




AB -0.1116 [-1.0390; 0.8158]
AC -0.2009 [-0.7374; 0.3355]
AD 0.4790 [-0.1807; 1.1387]

**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

$$y_i = \mu_{tPA-S}\text{tPA}_i + \mu_{Anist-S}\text{Anist}_i + \mu_{AcctPA-S}\text{AcctPA}_i + \mu_{Ang-S}\text{Ang}_i + \mu_{Ret-S}\text{Ret}_i + \delta_i + e_i$$

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** |
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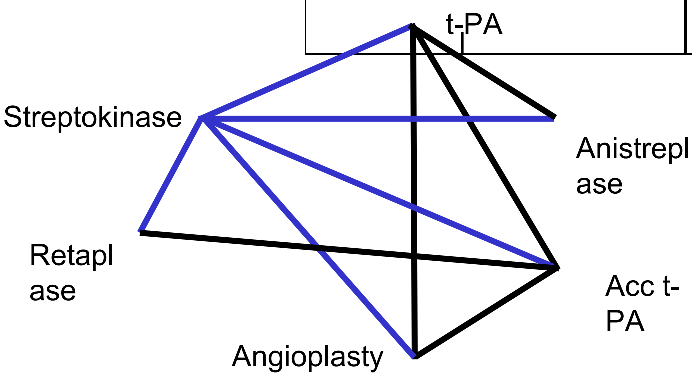


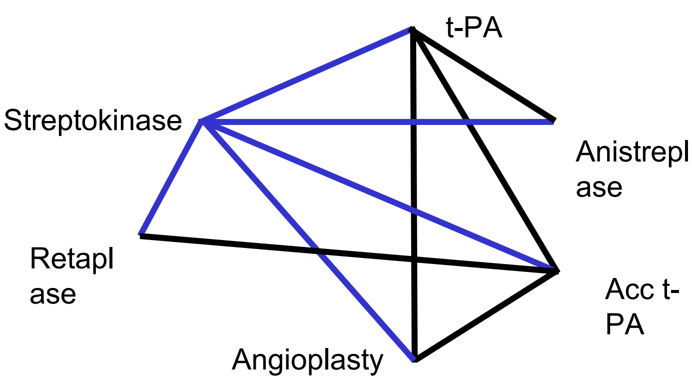

We have ignored some studies

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

$$y_i = \mu_{tPA-S}\text{tPA}_i + \mu_{Anist-S}\text{Anist}_i + \mu_{AcctPA-S}\text{AcctPA}_i + \mu_{Ang-S}\text{Ang}_i + \mu_{Ret-S}\text{Ret}_i + \delta_i + e_i$$

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** |
| 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

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

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

$$\mathbf{e} \sim N\left(\mathbf{0}, \mathrm{diag}\left\{v_i\right\}\right)$$

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

# Results from meta-regression

## Treatments for MI versus Streptokinase

| *Regression coefficients* | μ lnOR (SE) |
|---|---|
| $\mu_{\text{Str vs tPA}}$ | −0.02 (0.03) |
| $\mu_{\text{Str vs Anistr}}$ | −0.00 (0.03) |
| $\mu_{\text{Str vs Accelerated t-PA}}$ | −0.15 (0.05) |
| $\mu_{\text{Str vs Angioplasty}}$ | −0.43 (0.20) |
| $\mu_{\text{Str vs Reta}}$ | −0.11 (0.06) |

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

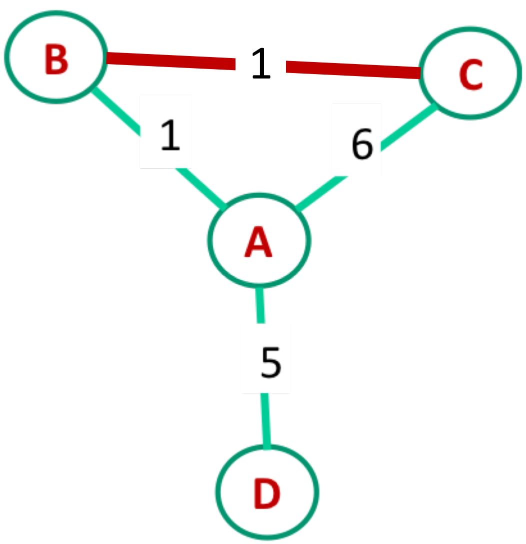
10 consistency equations

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

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

........

# Run meta-regression 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 | TREAT 2 | 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 1 | TREAT 2 | 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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| | | | | | | | | | |
| 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 1 | TREAT 2 | y1 | sd1 | n1 | y2 | sd2 | n2 | comp |
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| Bastyr 1999 | A | B | -1.21 | 1.21 | 135 | -1.4 | 1.46 | 149 | AB |
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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 |

$$MD_i = \mu_{AB} \times \mathbf{AB}_i + \mu_{AC} \times \mathbf{AC}_i + \mu_{AD} \times \mathbf{AD}_i + \delta_i + e_i$$

$$\delta_i \sim MVN(0, \Delta^2)$$
$$e_i \sim MVN(0, V)$$

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

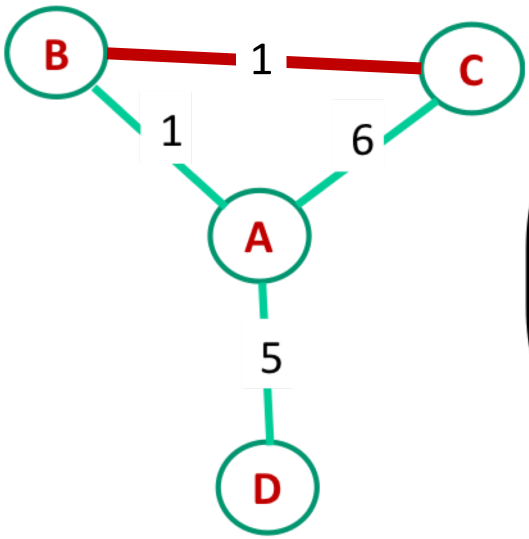
# Multivariate meta-analysis

- *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 | $y_{4,1}$, $v_{4,1}$<br>$y_{4,2}$, $v_{4,2}$<br>cov($y_{4,1}$, $y_{4,2}$) | AB<br>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 | $y_{4,1}$, $v_{4,1}$<br>$y_{4,2}$, $v_{4,2}$<br>cov($y_{4,1}$, $y_{4,2}$) | AB<br>AC |

Meta-regression

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

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

| 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 | $y_{3,1}$, $v_{3,1}$ | AD |
| i=4 | $T_4$=3 | 2 | $y_{4,1}$, $v_{4,1}$<br>$y_{4,2}$, $v_{4,2}$<br>cov($y_{4,1}$, $y_{4,2}$) | AB<br>AC |

**Meta-regression**

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

**Δ**

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

# How to fit such a model?

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

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

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

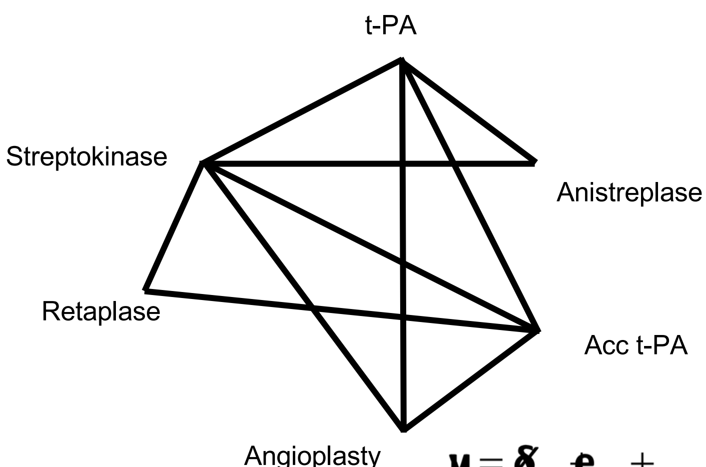
# Simplified var-covariance matrix

The matrix Δ is easier to estimate

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

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

# Design matrix



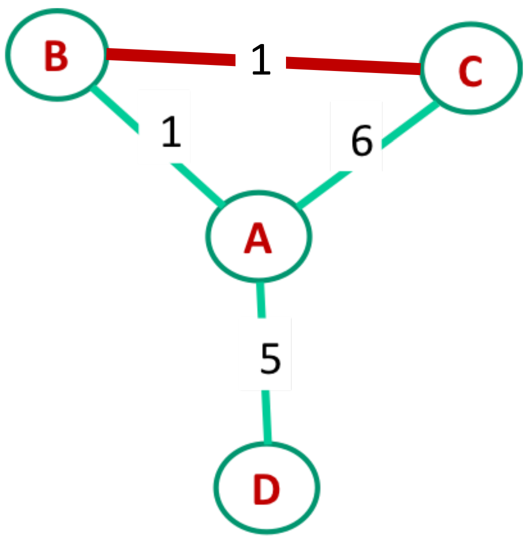

$$\boldsymbol{\mu} = X\boldsymbol{\delta} + \mathbf{e}$$

$$\boldsymbol{\delta} \sim \text{N}(0, \Delta)$$
$$\boldsymbol{e} \sim \text{N}(0, V)$$

$$\cancel{\boldsymbol{\delta} \sim N\left(\mathbf{0}, \text{diag}\left\{\tau^2\right\}\right)}$$
$$\cancel{\mathbf{e} \sim N\left(\mathbf{0}, \text{diag}\left\{v_i\right\}\right)}$$

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

# 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 ($\mu_{CD}$) is estimated under the constraint that

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

# 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)