Statistical considerations in indirect comparisons and network meta-analysis

Said Business School, Oxford, UK

March 18-19, 2013

THE COCHRANE COLLABORATION®

Handout S6-L

Introduction

Tianjing Li

Acknowledgements

- Georgia Salanti

Outline

- Fixed and random-effects meta-regression
- Some pitfalls and software options
- Indirect comparisons using meta-regression
- Network meta-analysis using meta-regression
- Example

Fixed-effect Versus Random-effects

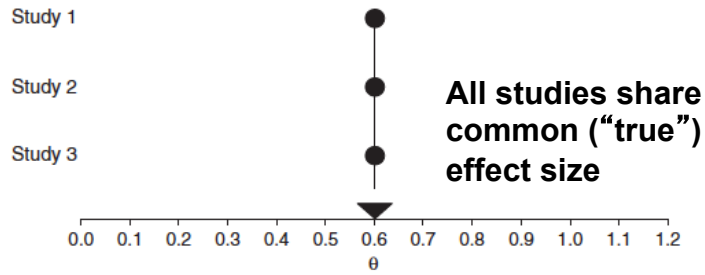
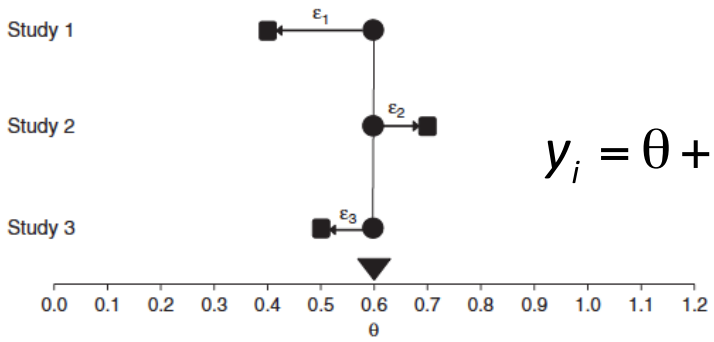


Figure 11.1 Fixed-effect model – true effects.



$$y_i = \theta + e_i$$

Figure 11.2 Fixed-effect model – true effects and sampling error.

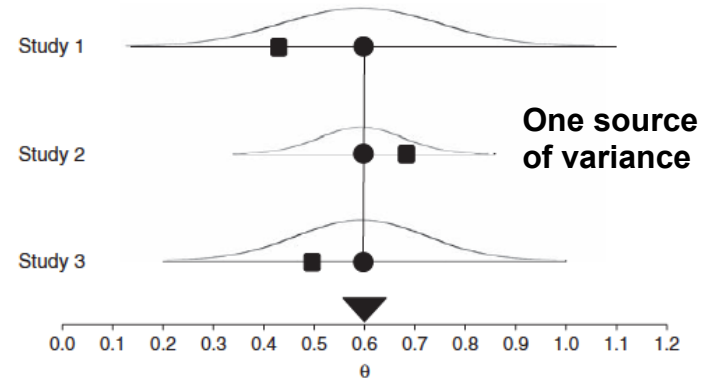


Figure 11.3 Fixed-effect model – distribution of sampling error.

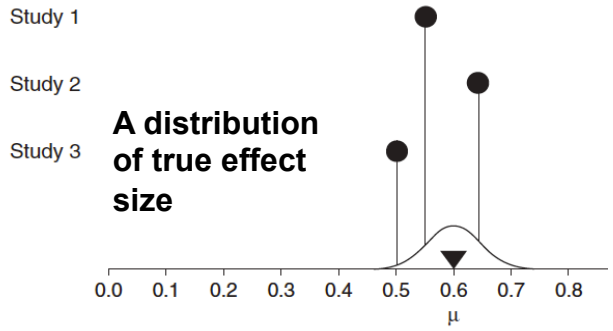
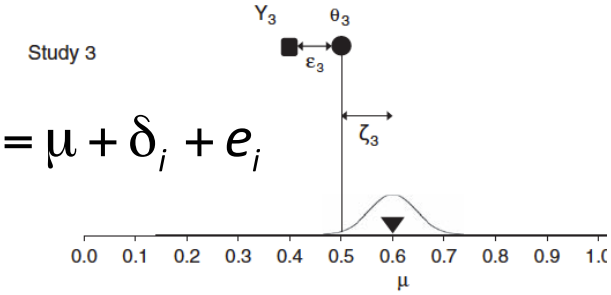


Figure 12.2 Random-effects model – true effects.



$$y_i = \mu + \delta_i + e_i$$

Figure 12.3 Random-effects model – true and observed effect in one study.

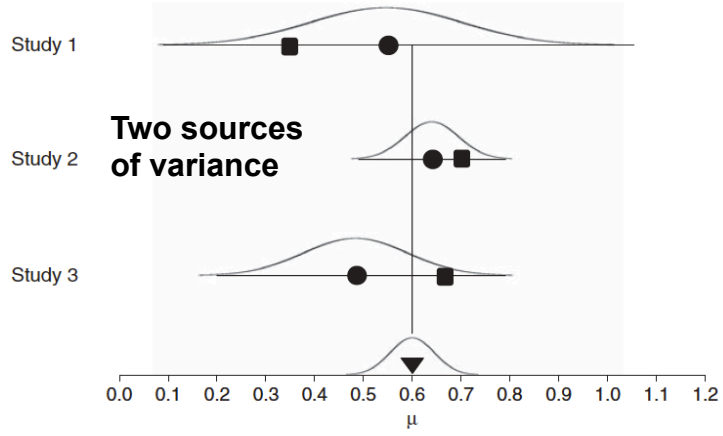


Figure 12.4 Random-effects model – between-study and within-study variance.

Meta-analysis as a multilevel model (hierarchical model) and a linear model

- Fixed-effect model

$$y_i \sim N(\theta, v_i)$$

$$y_i = \theta + e_i$$

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

Meta-analysis as a multilevel model (hierarchical model) and a linear model

- Fixed-effect model

$$y_i \sim N(\theta, v_i)$$

$$y_i = \theta + e_i$$

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

- Random-effects model

$$y_i \mid \theta_i \sim N(\theta_i, v_i)$$

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

$$y_i = \mu + \delta_i + e_i$$

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

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

Meta-regression models

- Models earlier generalize naturally to a regression framework

- Fixed-effect model

$$y_i \sim N\left(\theta + \sum_j \beta_j x_{ij}, v_i\right) \qquad y_i = \theta + \sum_j \beta_j x_{ij} + e_i$$

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

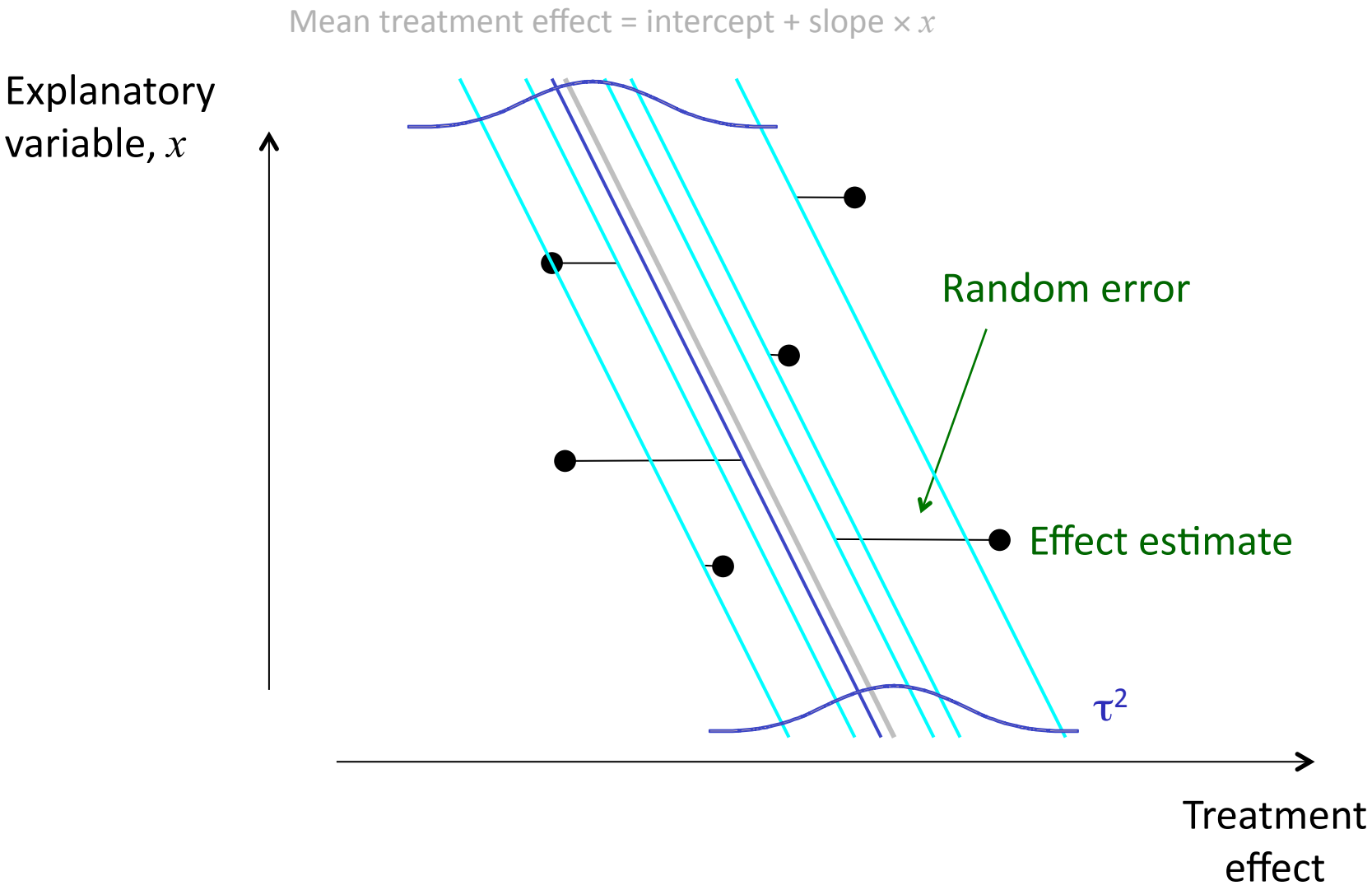
- Random-effects model

$$y_i \mid \theta_i \sim N\left(\theta_i + \sum_j \beta_j x_{ij}, v_i\right) \qquad y_i = \mu + \delta_i + \sum_j \beta_j x_{ij} + e_i$$

$$\theta_i \sim N(\mu, \tau^2) \qquad \delta_i \sim N(0, \tau^2)$$

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

Random-effects meta-regression



Fixed-effect meta-regression

- "In general, it is an unwarranted assumption that all the heterogeneity is explained by the covariate, and the between-trial variance should be included as well, corresponding to a "random-effects" analysis."

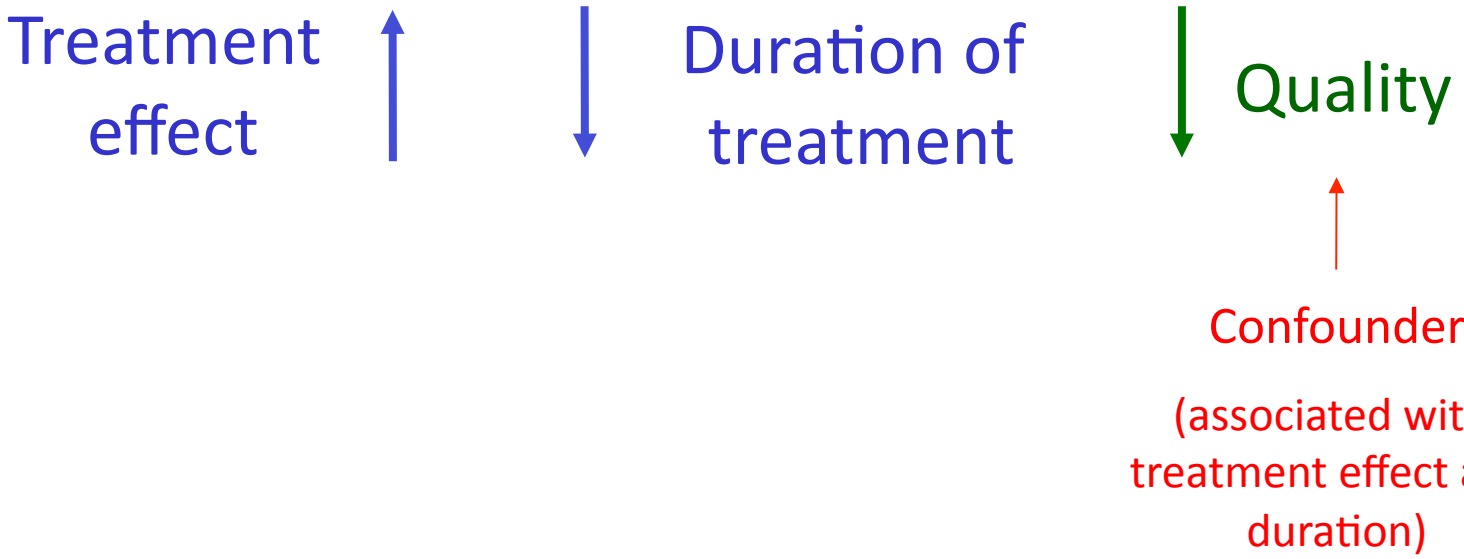
  (Thompson 2001 *Systematic Reviews in Health Care* Ch. 9)

- Fixed-effect meta-regression has a high false-positive rate when there is heterogeneity

- **"Fixed-effect meta-regression should not be used"**
  (Higgins and Thompson 2004 *Statistics in Medicine*)

Common pitfall: confounding

- Meta-regression looks at observational relationships
  - even if the studies are randomized controlled trials
- A relationship may not be causal
- Confounding (due to co-linearity) is common



Common pitfall: confounding

- Meta-regression looks at observational relationships
  - even if the studies are randomized controlled trials

- In indirect comparisons, confounding equates to lack of transitivity

Common pitfall: lack of power

- Unfortunately most meta-analyses do not have many studies
- Meta-regression typically has low power to detect relationships
- Model diagnostics / adequacy difficult to assess

Software for meta-regression

Stata

- **`metareg`** : random-effects meta-regression
- **`vwls`** : fixed-effect meta-regression

WinBUGS

- A natural extention to the model

SAS

- See van Houwelingen et al (2002)

Comprehensive Meta-analysis

- Single covariate only in CMA 2; multiple in next version

RevMan

- Not available

Indirect comparison using meta-regression

Trial	Comparison	Dummy code
1	B vs A	0
2	B vs A	0
3	C vs A	1
4	C vs A	1
5	C vs A	1

Indirect comparison using meta-regression

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Meta-regression on these data will produce

- Intercept:

Indirect comparison using meta-regression

Trial	Comparison	Dummy code
1	B vs A	0
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Meta-regression on these data will produce

- Intercept: B vs A
- Slope:

Indirect comparison using meta-regression

Trial	Comparison	Dummy code
1	B vs A	0
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Meta-regression on these data will produce

- Intercept: B vs A

- Slope: (C vs A) – (B vs A) = C vs B

… in more detail

Trial	Comparison	Intercept	Dummy code
1	B vs A	1	0
2	B vs A	1	0
3	C vs A	1	1
4	C vs A	1	1
5	C vs A	1	1

Meta-regression on these data will produce

- Intercept: B vs A
- Slope: (C vs A) – (B vs A) = C vs B

Adding the other comparison

Trial	Comparison	Intercept	Dummy code 1	Dummy code 2
1	B vs A	1	0	0
2	B vs A	1	0	0
3	C vs A	1	1	0
4	C vs A	1	1	0
5	C vs A	1	1	0
6	B vs C	1	0	1
7	B vs C	1	0	1

*In fact it's an 'inconsistency model'

Meta-regression on these data will produce

- Intercept: B vs A
- Slope 1: (C vs A) – (B vs A) = C vs B
- Slope 2: (B vs C) – (B vs A) = A vs C
- But this does NOT impose our consistency equation*

For mixed comparisons and network MA: Alternative coding: drop the intercept

Trial	Comparison	Dummy code 1	Dummy code 2
1	B vs A	1	0
2	B vs A	1	0
3	C vs A	0	1
4	C vs A	0	1
5	C vs A	0	1
6	C vs B	–1	1
7	C vs B	–1	1

A is used as the reference.

Meta-regression on these data will produce

- B vs A: Slope 1
- C vs A: Slope 2
- C vs B: Slope 2 – Slope 1

General coding algorithm

- Choose a reference treatment (let's say A)
- Create a dummy variable for all treatments other than A (*k* = B, C, …)
- Code dummy *k* as
  - 1 if treatment *k* is the non-reference arm in that trial
  - −1 if treatment *k* is the reference arm in that trial
  - 0 otherwise
- Omit the intercept in the meta-regression

- The dummy variables correspond to basic parameters
- Other comparisons computed from these: functional parameters

Coding and meta-regression

- With 3 treatments and AC, AB, BC studies, chose A as *reference,* so *AB and AC are basic parameters*

$$y_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \delta_i + e_i$$

$$y_i = \mu_{AB} I_{iAB} + \mu_{AC} I_{iAC} + \delta_i + e_i$$

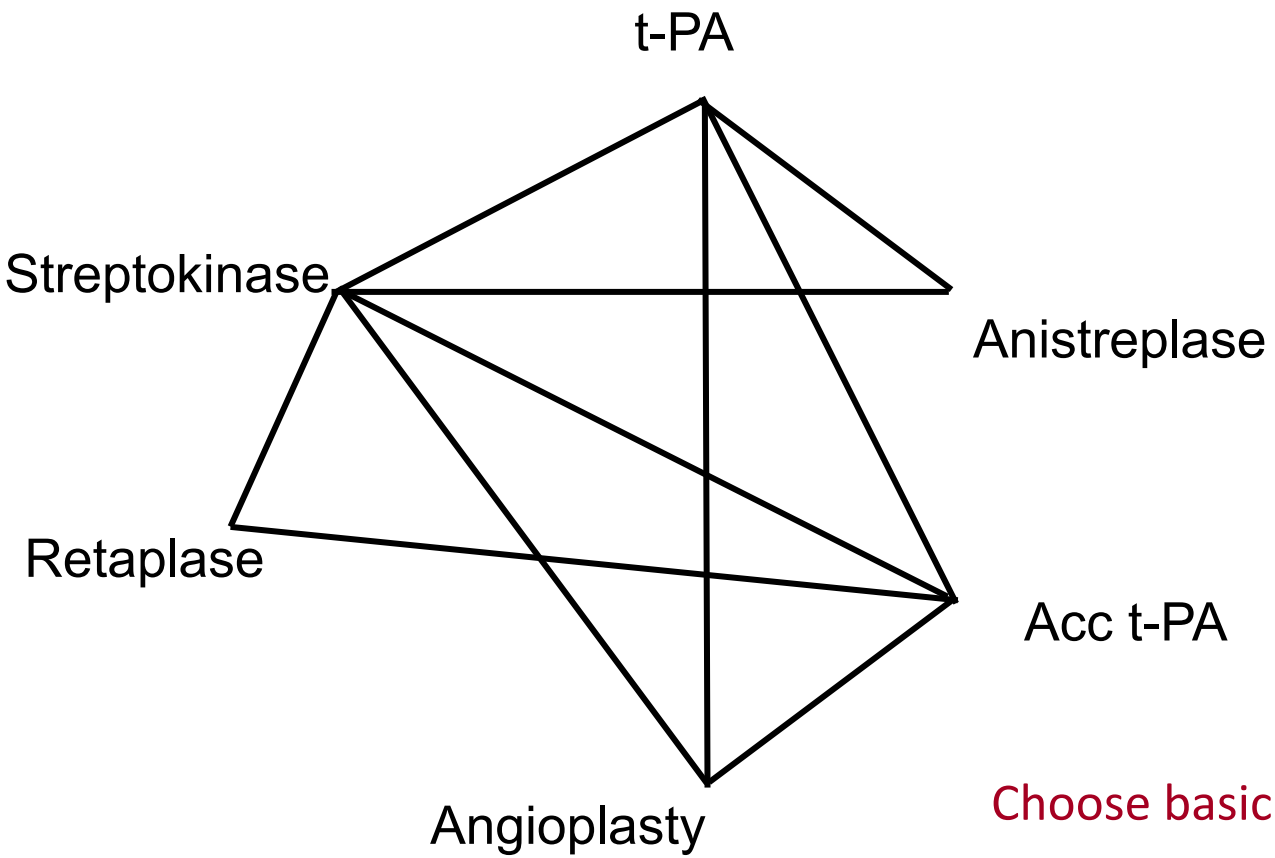
- The AB studies have (1,0), the AC studies (0,1) [*basic*]
- BC studies have (1,-1) [*functional*] if coded as *B–C [=(B–A)–(C–A)]*
- BC studies have (-1,1) [*functional*] if coded as *C–B [=(C–A)–(B–A)]*

- *So it helps to have a convention: e.g. Code BC as C–B ('bigger' – 'smaller' letter)*

Limitations

- To use standard meta-regression software (e.g. metareg)
  - cannot deal with trials with more than two treatments
  - must assume the same heterogeneity variance for every comparison
  - cannot rank treatments easily

Example: treatments for MI



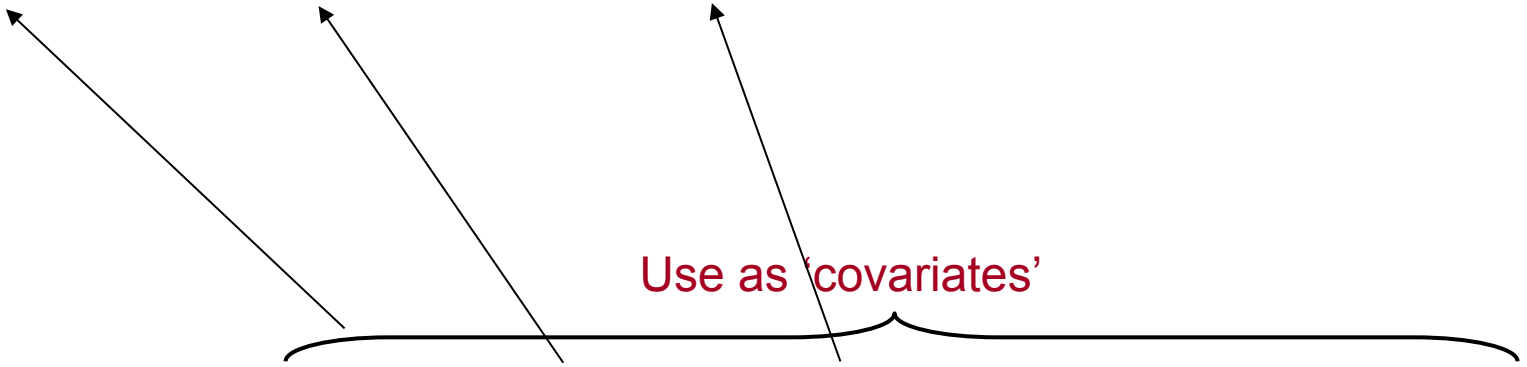
Choose basic parameters

Write all other contrasts as linear functions of the basic parameters to build the design matrix

Lumley 2002

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

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



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

Design matrix

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

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

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

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

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

Results: treatments for MI

Regression coefficients, μ	Log OR (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)

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

Summary

- Meta-regression examines the relationship between treatment effects and one or more study-level characteristics
- Meta-analysis is a meta-regression with no covariates
- Network meta-analysis is a meta-regression with dummy variables for the treatments
- Standard meta-regression cannot deal with trials with more than two treatments
- Standard meta-regression assumes the same heterogeneity variance for every comparison

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