Statistical considerations in indirect comparisons and network meta-analysis

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Handout S8-L

Problems introduced by multi-arm trials: full network meta-analysis

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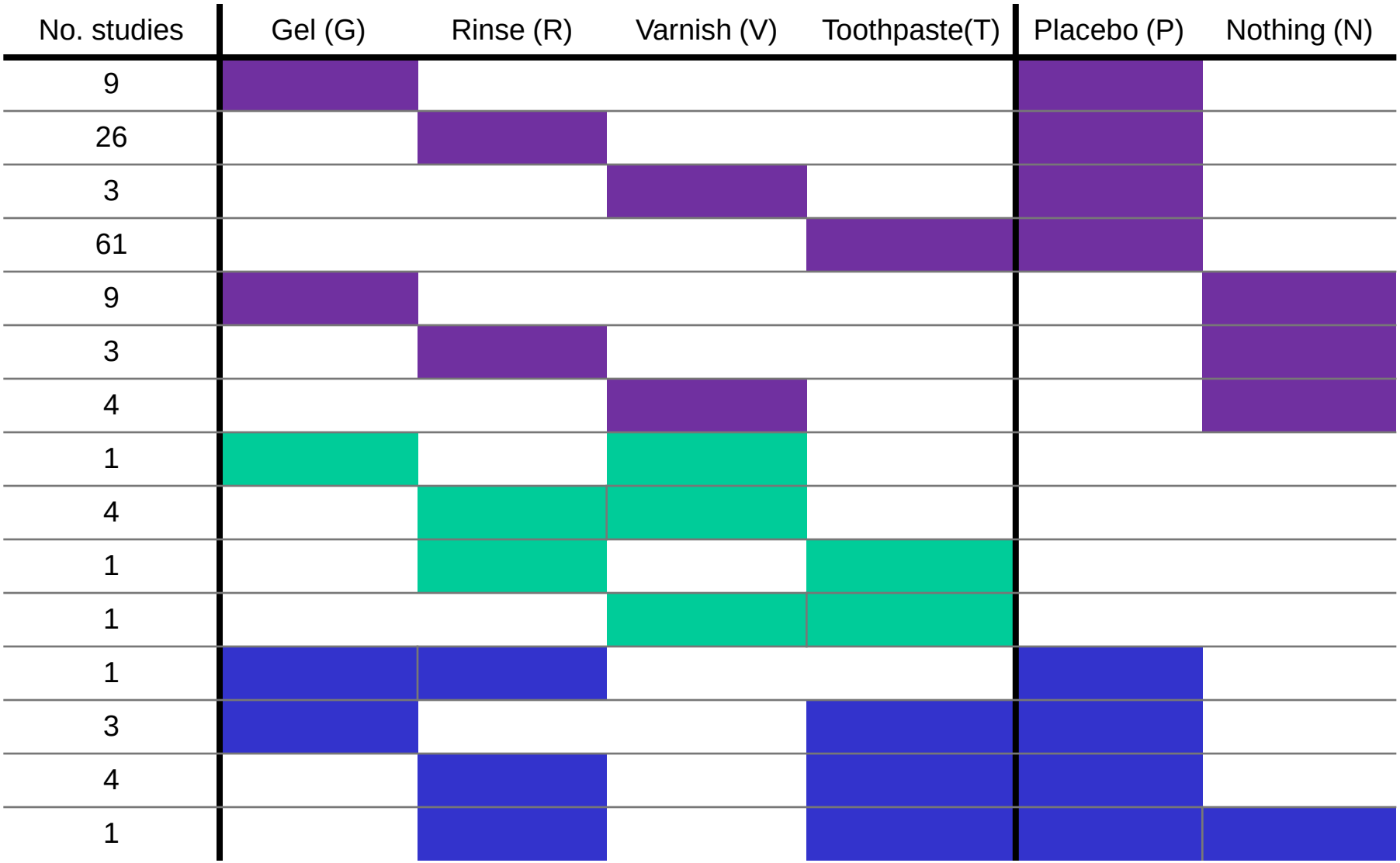
Fluoride data



Salanti *et al*, 2009

Network meta-analysis

- Simultaneous comparison of multiple treatments in a single analysis
- y_i: the relative effect (SMD here) between the treatments compared in study i with variance v_i
  - We define a set of 'basic' parameters and specify the rest as 'functional' parameters

$$\mu_{PN}, \mu_{PT}, \mu_{PR}, \mu_{PV}, \mu_{PG}$$

$$y_i = \mu_{AB} + \delta_i + \varepsilon_i$$

$$\mu_{AB} = \mu_{PB} - \mu_{PA}$$

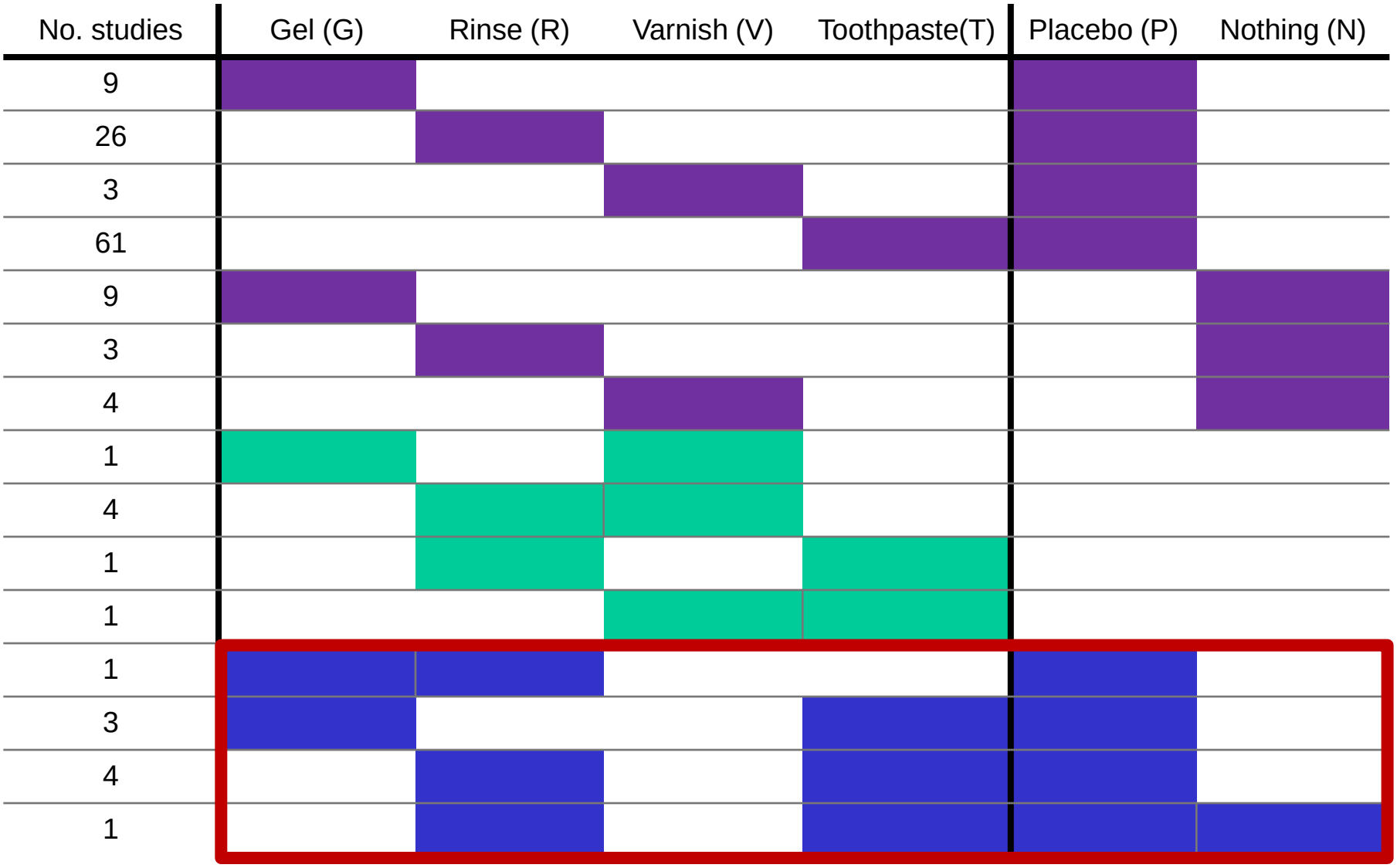
$$A, B = N, T, R, V, G$$

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

$$\varepsilon_i \sim N(0, v_i) \xrightarrow{\text{estimates}} s_i^2$$

Assumptions in *every* meta-analysis: y_i s are independent

Fluoride data



Salanti *et al*, 2009

Multi-arm studies: a significant "problem"?

- Chan et al examined a representative sample of 519 randomized trials (those published in December 2000, and listed in PubMed)

Number of arms	All trials (n = 519)	Parallel group trials (n = 381)
2	379 (73%)	286 (75%)
3	85 (16%)	60 (16%)
4	37 (7%)	25 (7%)
> 4	18 (3%)	12 (3%)

- Approximately a quarter of randomized trials have multiple arms

Chan *et al*, 2005

Multi-arm studies

- They introduce ‘dependent’ observations
  - y_i are not independent when they refer to the same study
  - From an A, B, P study we need to extract two y_is: AP and BP
- We need to model them properly using multivariate methods!

Multivariate methods

- Simultaneous (joint) analysis of more than one variable
- Why: because they are correlated!
  - Example: systolic (S) and diastolic (D) blood pressure
- Univariate fixed effects:

$$y_{i,S} \sim N(\mu_S, \sigma^2_{i,S})$$
$$y_{i,D} \sim N(\mu_D, \sigma^2_{i,D})$$

$$\rightarrow \begin{pmatrix} y_{i,S} \\ y_{i,D} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_S \\ \mu_D \end{pmatrix}, \begin{pmatrix} \sigma^2_{i,S} & 0 \\ 0 & \sigma^2_{i,D} \end{pmatrix} \right)$$

- Multivariate fixed:

$$\begin{pmatrix} y_{i,S} \\ y_{i,D} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_S \\ \mu_D \end{pmatrix}, \begin{pmatrix} \sigma^2_{i,S} & \mathrm{cov}_y \\ \mathrm{cov}_y & \sigma^2_{i,D} \end{pmatrix} \right)$$

Multivariate methods FE

- Multivariate fixed effects:

$$\begin{pmatrix} y_{i,S} \\ y_{i,D} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_S \\ \mu_D \end{pmatrix}, \begin{pmatrix} \sigma^2_{i,S} & cov_y \\ cov_y & \sigma^2_{i,D} \end{pmatrix} \right)$$

Within study covariance

- Multivariate fixed effects (equivalent):

$$\begin{pmatrix} y_{i,S} \\ y_{i,D} \end{pmatrix} = \left(\begin{pmatrix} \mu_S \\ \mu_D \end{pmatrix} + \begin{pmatrix} \varepsilon_{i,S} \\ \varepsilon_{i,D} \end{pmatrix} \right)$$

$$\begin{pmatrix} \varepsilon_{i,S} \\ \varepsilon_{i,D} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{i,S} & cov_y \\ cov_y & \sigma^2_{i,D} \end{pmatrix} \right)$$

Multivariate methods RE

- Multivariate random effects:

$$\begin{pmatrix} y_{i,S} \\ y_{i,D} \end{pmatrix} = \left(\begin{pmatrix} \mu_S \\ \mu_D \end{pmatrix} + \begin{pmatrix} \delta_{i,S} \\ \delta_{i,D} \end{pmatrix} + \begin{pmatrix} \varepsilon_{i,S} \\ \varepsilon_{i,D} \end{pmatrix} \right)$$

$$\begin{pmatrix} \varepsilon_{i,S} \\ \varepsilon_{i,D} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{i,S} & cov_y \\ cov_y & \sigma^2_{i,D} \end{pmatrix} \right)$$

Within study
covariance

$$\begin{pmatrix} \delta_{i,S} \\ \delta_{i,D} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_S{}^2 & cov_\delta \\ cov_\delta & \tau_D{}^2 \end{pmatrix} \right)$$

Between studies
covariance

Network meta-analysis: Simple example

Study	No. arms	No. effects	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

Let us choose basic parameters to represent AB and AC

$$y_{1,1} = \mu_{AB} + \delta_{1,1} + \varepsilon_{1,1}$$

$$y_{2,1} = \mu_{AC} + \delta_{2,1} + \varepsilon_{2,1}$$

$$y_{3,1} = \mu_{AC} - \mu_{AB} + \delta_{3,1} + \varepsilon_{3,1}$$

$$\varepsilon_{1,1} \sim N(0, v_{1,1})$$

$$\delta_{1,1} \sim N(0, \tau_{AB}^2)$$

Network meta-analysis: Simple example

Study	No. arms	No. effects	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

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

$$\begin{pmatrix} \delta_{1,1} \\ \delta_{2,1} \\ \delta_{3,1} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_{AB}^2 & 0 & 0 \\ 0 & \tau_{AC}^2 & 0 \\ 0 & 0 & \tau_{BC}^2 \end{pmatrix} \right)$$

$$y_{1,1} = \mu_{AB} + \delta_{1,1} + \varepsilon_{1,1}$$

$$y_{2,1} = \mu_{AC} + \delta_{2,1} + \varepsilon_{2,1}$$

$$y_{3,1} = \mu_{AC} - \mu_{AB} + \delta_{3,1} + \varepsilon_{3,1}$$

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

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

$$\boldsymbol{\varepsilon} \sim N(0, \mathrm{diag}(v_{i,j}))$$

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

Network meta-analysis: Simple example

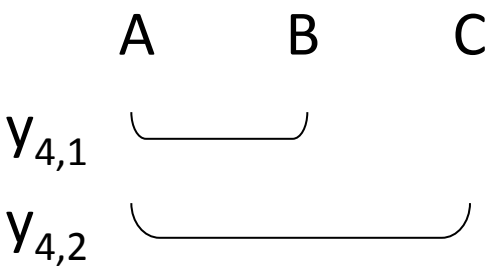
Study	No. arms	No. effects	Data	Contrast
i=1	$T_1=2$	1	$y_{1,1}, v_{1,1}$	AB
i=2	$T_2=2$	1	$y_{2,1}, v_{2,1}$	AC
i=3	$T_3=2$	1	$y_{3,1}, v_{3,1}$	BC
i=4	$T_4=3$	2	$y_{4,1}, v_{4,1}$ $y_{4,2}, v_{4,2}$	AB AC

These two estimates are correlated

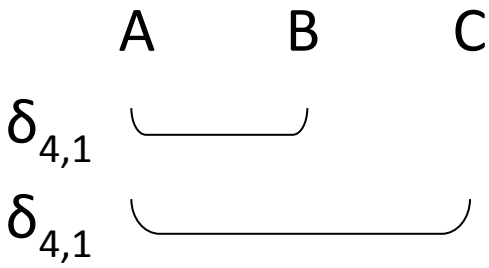
$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_{1,1} \\ \delta_{2,1} \\ \delta_{3,1} \\ \delta_{4,1} \\ \delta_{4,2}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

Multi-arm studies

- If we model treatment effect estimates, these are correlated if they include the same treatment



- In random-effects network meta-analyses, treatment effect parameters may be correlated when they come from the same study



Simple example

Study	No. arms	No. effects	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

So we introduce their covariance

Study	No. arms	No. effects	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

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

Multivariate meta-regression approach

The within-study variance-covariance matrix

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

Study	No. arms	No. effects	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

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

Multivariate meta-regression approach

The between-studies variance-covariance matrix

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

Network meta-analysis and multivariate approaches

- We can look at network meta-analysis as either a multivariate meta-regression or a multivariate meta-analysis
- Multivariate meta-regression (what we had so far):
  - extends the meta-regression approach we saw earlier to allow for multi-arm trials
  - dummy 1, -1 and 0 codes for treatments (with a reference in mind)
  - assumes a common heterogeneity variance
  - Involves the covariances in the random errors and random effects
- Multivariate meta-analysis:
  - no covariates required
  - requires a common reference arm for every study
    - a problem that is surmountable using *data augmentation* (see later)

Study	No. arms	No. effects	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	$T_3=3$	2	$y_{3,1}, v_{3,1}$ $y_{3,2}, v_{3,2}$ $\text{cov}(y_{3,1}, y_{3,2})$	AB AC
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

Multivariate meta-analysis approach

$$y_{1,1}=\mu_{AB}+\delta_{1,1}+\varepsilon_{1,1}$$

$$y_{2,1}=\mu_{AC}+\delta_{2,1}+\varepsilon_{2,1}$$

$$\begin{pmatrix} y_{3,1} \\ y_{3,2} \end{pmatrix} = \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_{3,1} \\ \delta_{3,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{3,1} \\ \varepsilon_{3,2} \end{pmatrix}$$

$$\begin{pmatrix} y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_{4,1} \\ \delta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

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

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

We can write

$$\begin{pmatrix} y_{1,1} \\ . \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ . & . \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_{1,1} \\ . \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ . \end{pmatrix}$$

$$\begin{pmatrix} y_{2,1} \\ . \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ . & . \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_{2,1} \\ . \end{pmatrix} + \begin{pmatrix} \varepsilon_{2,1} \\ . \end{pmatrix}$$

$$\begin{pmatrix} y_{3,1} \\ . \end{pmatrix} = \begin{pmatrix} -1 & 1 \\ . & . \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_{3,1} \\ . \end{pmatrix} + \begin{pmatrix} \varepsilon_{3,1} \\ . \end{pmatrix}$$

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

Multivariate meta-analysis

as

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

Multivariate meta-regression

$$\mathbf{y = X\mu + \delta + \varepsilon}$$

Assumption of consistency

- **Multivariate meta-regression:** The consistency equations are explicitly written in the design matrix X
- **Multivariate meta-analysis:** The consistency assumption is implicit when we 'impute' the 'missing' arm
  - Transitivity: "the missing arm is missing at random"

WITHIN-STUDY CORRELATION
WITHIN-STUDY COVARIANCE

Estimating within-study covariance (1)

- The covariance $\mathbf{cov}_y$ between two estimates from the same study (sharing a common treatment group) is simply the variance of the data in the shared arm
- E.g. for odds ratios,

$$\log \mathrm{OR}_{AB} = \log \frac{r_{Bi} f_{Ai}}{f_{Bi} r_{Ai}} = \mathrm{logit}\left(p_{Bi}\right) - \mathrm{logit}\left(p_{Ai}\right)$$

$$\mathrm{var}\left(\log \mathrm{OR}_{ABi}\right) = \frac{1}{r_{Ai}} + \frac{1}{f_{Ai}} + \frac{1}{r_{Bi}} + \frac{1}{f_{Bi}} = \mathrm{var}\left(\mathrm{logit}\left(p_{Ai}\right)\right) + \mathrm{var}\left(\mathrm{logit}\left(p_{Bi}\right)\right)$$

$$\log \mathrm{OR}_{ACi} = \log \frac{r_{Ci} f_{Ai}}{f_{Ci} r_{Ai}}$$

$$\mathrm{var}\left(\log \mathrm{OR}_{ACi}\right) = \frac{1}{r_{Ai}} + \frac{1}{f_{Ai}} + \frac{1}{r_{Ci}} + \frac{1}{f_{Ci}}$$

$$\mathrm{cov}\left(\log OR_{ABi}, \log OR_{ACi}\right) = \mathrm{var}\left(\mathrm{logit}\left(p_{Ai}\right)\right) = \frac{1}{r_{Ai}} + \frac{1}{f_{Ai}}$$

Estimating within-study covariance (2)

- The covariance between two estimates from the same study (sharing a common treatment group) is simply the variance of the data in the shared arm
- e.g. for continuous data,

$$\mathrm{cov}\left(MD_{ABi}, MD_{ACi}\right) = \frac{SD_{Ai}^2}{n_{Ai}}$$

$$\mathrm{cov}\left(SMD_{ABi}, SMD_{ACi}\right) \approx \frac{1}{n_{Ai}}$$

Estimating within-study covariance (3)

- We usually need to estimate the within-study covariance ourselves
  - e.g. using simple 'for' loops in Stata (see practical later)
- Within study covariances are irrelevant when we model the arm-level data directly
  - When we have arm-level data, e.g. number of successes and failures per arm, and we model them using the binomial likelihood
  - But if we are faced with data that can't readily be modelled at the arm level (perhaps due to the study design) then we might be modelling y's and v's
  - Then we need to account for within-study correlation

BETWEEN-STUDY CORRELATION
BETWEEN-STUDY COVARIANCE

Specifying between-study covariance

- A particular challenge is **the estimation** of between-studies variance-covariance matrix
- The covariance of two random effects is a function of the heterogeneities
- Within a multi-arm study, we must have true effects satisfying the consistency equations implying that deviations satisfy $\delta_{i,BC}=\delta_{i,AC}-\delta_{i,AB}$

- so $$\tau^2_{BC}=\text{var}\left(\delta_{i,BC}\right)=\text{var}\left(\delta_{i,AC}\right)+\text{var}\left(\delta_{i,AB}\right)-2\text{cov}\left(\delta_{i,AC},\delta_{i,AB}\right)$$
$$=\tau^2_{AC}+\tau^2_{AB}-2\text{cov}\left(\delta_{i,AC},\delta_{i,AB}\right)$$

- and therefore $$\text{cov}\left(\delta_{i,AC},\delta_{i,AB}\right)=\frac{\tau^2_{AC}+\tau^2_{AB}-\tau^2_{BC}}{2}$$

A common assumption about heterogeneity

- In network meta-analysis we very often assume the same heterogeneity variance for every comparison

$$\mathrm{cov}\left(\delta_{i,AC},\delta_{i,AB,}\right)=\frac{\tau^2+\tau^2-\tau^2}{2}=\frac{\tau^2}{2}$$

- In the running example, this gives the between-studies covariance matrix

$$\begin{pmatrix} \tau^2 & 0 & 0 & 0 & 0 \\ 0 & \tau^2 & 0 & 0 & 0 \\ 0 & 0 & \tau^2 & 0 & 0 \\ 0 & 0 & 0 & \tau^2 & \frac{\tau^2}{2} \\ 0 & 0 & 0 & \frac{\tau^2}{2} & \tau^2 \end{pmatrix}$$

A common assumption about heterogeneity

- This assumption makes estimation easier
- It is also particularly valuable when there are comparisons in the network with only one contributing study
  - in which case the between-study variance can't be estimated without an assumption such as this

IMPLEMENTATION: STATA

Multivariate meta-analysis approach

- Either the multivariate approach or the multivariate meta-regression approach can be used
- We'll use the former
- We assume all studies include treatment A
- When some trials don't include arm A, we "augment" the observed data
  - we create an arm A with a very small amount of data
  - e.g. 0.01 individuals with 10% success
- What does this do?
  - Enables us to use the estimation method in mvmeta
  - Adding a near-empty arm A to a trial B vs C yields
    - treatment effects B vs A and C vs A with very large standard errors
    - large covariance – so that the data still convey the evidence about B vs C

Heterogeneity variance-covariance matrix

- This can be ‘structured’
  - e.g. setting all heterogeneity variances equal, as discussed earlier
- or ‘unstructured’
  - estimates a heterogeneity variance for each treatment comparison
  - requires at least two studies for each comparison

Example: smoking data – raw

study	design	dA	nA	dB	nB	dC	nC	dD	nD
1	ACD	9	140	.	.	23	140	10	138
2	BCD	.	.	11	78	12	85	29	170
3	AB	79	702	77	694	.	.	.	.
4	AB	18	671	21	535	.	.	.	.
5	AB	8	116	19	146	.	.	.	.
6	AC	75	731	.	.	363	714	.	.
7	AC	2	106	.	.	9	205	.	.
..									
20	AD	0	20	.	.	.	.	9	20
21	BC	.	.	20	49	16	43	.	.
22	BD	.	.	7	66	.	.	32	127
23	CD	.	.	.	.	12	76	20	74
24	CD	.	.	.	.	9	55	3	26

Smoking data – augmenting arm A

study	design	dA	nA	dB	nB	dC	nC	dD	nD
1	ACD	9	140	.	.	23	140	10	138
2	BCD	.001	.01	11	78	12	85	29	170
3	AB	79	702	77	694	.	.	.	.
4	AB	18	671	21	535	.	.	.	.
5	AB	8	116	19	146	.	.	.	.
6	AC	75	731	.	.	363	714	.	.
7	AC	2	106	.	.	9	205	.	.
..									
20	AD	0	20	.	.	.	.	9	20
21	BC	.001	.01	20	49	16	43	.	.
22	BD	.001	.01	7	66	.	.	32	127
23	CD	.001	.01	.	.	12	76	20	74
24	CD	.001	.01	.	.	9	55	3	26

Smoking data – handling zero cells

study	design	dA	nA	dB	nB	dC	nC	dD	nD
1	ACD	9	140	.	.	23	140	10	138
2	BCD	.001	.01	11	78	12	85	29	170
3	AB	79	702	77	694	.	.	.	.
4	AB	18	671	21	535	.	.	.	.
5	AB	8	116	19	146	.	.	.	.
6	AC	75	731	.	.	363	714	.	.
7	AC	2	106	.	.	9	205	.	.
..									
20	AD	0.5	21	.	.	.	.	9.5	21
21	BC	.001	.01	20	49	16	43	.	.
22	BD	.001	.01	7	66	.	.	32	127
23	CD	.001	.01	.	.	12	76	20	74
24	CD	.001	.01	.	.	9	55	3	26

Smoking data – treatment effects

study	design	yB	yC	yD	SBB	SBC	SBD	SCC	SCD	SDD
1	ACD	.	1.1	.13	.	.	.	.17	.12	.23
2	BCD	.39	.39	.62	1111	1111	1111	1111	1111	1111
3	AB	-.016	.	.	.029	.	.	.	.	.
4	AB	.39	.	.	.11	.	.	.	.	.
5	AB	.7	.	.	.19	.	.	.	.	.
6	AC	.	2.2	.	.	.	.	.02	.	.
7	AC	.	.87	.	.	.	.	.63	.	.
..										
20	AD	.	.	3.5	.	.	.	.	.	2.2
21	BC	1.8	1.7	.	1111	1111	.	1111	.	.
22	BD	.066	.	1.1	1111	.	1111	.	.	1111
23	CD	.	.52	1.2	.	.	.	1111	1111	1111
24	CD	.	.57	.16	.	.	.	1111	1111	1111

Actually 1111.24 1111.11 1111.49

Smoking data – consistency model

```
. mvmeta y S
Note: using method reml
Note: using variables yB yC yD
Note: 24 observations on 3 variables
Variance-covariance matrix: unstructured

initial:       log likelihood = -160.17951
rescale:       log likelihood = -100.23937
rescale eq:    log likelihood = -92.544656
Iteration 0:   log likelihood = -92.544656
Iteration 1:   log likelihood = -92.513256  (not concave)
Iteration 2:   log likelihood = -92.425625
...
```

Smoking data – consistency model

```
Multivariate meta-analysis
Variance-covariance matrix = unstructured
Method = reml                                Number of dimensions    =      3
Restricted log likelihood = -91.5034         Number of observations  =     24
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Overall_mean |
          yB |   .3326131    .304882     1.09   0.275    -.2649446    .9301709
          yC |   .6810119    .218974     3.11   0.002     .2518307    1.110193
          yD |   .8357448   .3664473     2.28   0.023     .1175213    1.553968
------------------------------------------------------------------------------

Estimated between-studies SDs and correlation ma
             SD          yB          yC          yD
yB   .31410631           1           .           .
yC   .74977714   .93628482           1           .
yD   .72246328   .85580592   .61958179           1
```

Unstructured heterogeneity matrix: estimable because each contrast (AB, BC…) occurred in >1 trial

Summary

- When we have multi-arm studies, we need to move to a multivariate meta-analysis framework
- Each study may contribute two or more treatment effects
- Effect estimates are correlated (within the study)
  - not a problem if we model the arms rather than the effect estimates, e.g. using (random-effects) logistic regression
- mvmeta lets us do network meta-analysis using multivariate methods
  - in the practicals, we'll use a data augmentation procedure, and pick one of the treatments to be a reference

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