Session V: Network Meta-Analysis

James Carpenter¹, Ulrike Krahn²,³, Gerta Rucker⁴, Guido Schwarzer⁴

¹London School of Hygiene and Tropical Medicine & MRC Clinical Trials Unit, London, UK
²Institute of Medical Biostatistics, Epidemiology and Informatics, Mainz, Germany
³Institute of Medical Informatics, Biometry and Epidemiology, Duisburg-Essen, Germany
⁴Institute for Medical Biometry and Statistics, Freiburg, Germany

ulrike.krahn@uk-essen.de

IBC Short Course
Florence, 6 July 2014

Overview Introduction Model and Estimating Decomposition of Q Locating Inconsistency Flow of evidence Summary

Plan of the Session

At the end of this session the aim is that you should understand

- the background for network meta-analysis;
- the principal model and underlying assumptions;
- how to assess heterogeneity/inconsistency;
- how to assess the evidence flow.

The objectives are that you are able to:
- carry out a network meta-analysis;
- report and visualize results;
- interpret the results taking diagnostic measures and graphics into account.

Background: Evidence based healthcare decisions

Classical meta-analysis
- comparison between two treatments

Network meta-analysis/ Multiple-treatments comparison/ Mixed-treatment comparison
- comparison between a set of treatments

National Institute for Health and Care Excellence (NICE)

"has a preference for data from head-to-head RCTs [...]"
"[...] evidence from mixed treatment analyses may be presented if it is considered to add information [...]"
"If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used [...]"

(see NICE: Guide to the methods of technology appraisal, 2008 and NICE Decision Support Unit, Series of Technical Support Documents)
Illustrative example: Network meta-analysis in diabetes

HbA1c change in patients with type II diabetes and a baseline therapy of sulfonylurea (by Senn et al., 2013)

10 treatments
26 RCTs: 25 two-armed, 1 three-armed
28 assessed pairwise comparisons
15 different designs
(defined by compared treatments, e.g. plac:acar, plac:acar:metf)

15 observed / 45 possible edges

Adjusted indirect comparison

\[ \hat{\theta}_{\text{ind}} = \hat{\theta}_{\text{dir}} - \hat{\theta}_{\text{dir}:\text{plac}} \]
\[ \hat{V}_{\text{ind}} = \hat{V}_{\text{dir}} + \hat{V}_{\text{dir}:\text{plac}} \]

\[ \hat{\theta}_{\text{nma}} = \frac{\hat{\theta}_{\text{dir}}}{\sqrt{\frac{1}{\hat{V}_{\text{dir}}} + \frac{1}{\hat{V}_{\text{ind}}}}} \]
\[ \hat{V}_{\text{nma}} = \frac{1}{\frac{1}{\hat{V}_{\text{dir}}} + \frac{1}{\hat{V}_{\text{ind}}}} \]

Assumption

- of transitivity
  - an indirect comparison validly estimates an unobserved head-to-head comparison
  - cannot be tested statistically, but can be evaluated conceptually and contextually

- of consistency
  - extension of transitivity: direct and indirect estimates are in agreement
  - can be tested statistically

(see Salanti, 2012)
Different models and estimation methods...

- Bayesian approaches (using WinBUGS, see e.g. Dias et al. 2011, Lu & Ades 2004 or R package gemtc)
- Frequentist approaches
  - using two-way linear mixed models with main effects for treatment and trial (Piepho et al. 2012, SAS)
  - using multivariate meta-regression (White et al. 2012, R package mvmeta)
  - two approaches using generalized least squares (Krahn et al. 2013, Rücker 2012) leading to identical estimates (Rücker 2014) implemented in R package netmeta:

<table>
<thead>
<tr>
<th>a) reducing dimensions</th>
<th>b) reducing weights</th>
</tr>
</thead>
</table>
  | each study with p treatments | p – 1 comparisons to a reference treatment with corresponding SEs all \( \frac{p(p-1)}{2} \) pairwise comparisons with adjusted SEs

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Two-stage fixed effects model fitting

1. Aggregation per study design \( d \) by multivariate meta-analysis methods

\[
\hat{\theta}^{\text{dir}} := V_d^{\text{dir}} \sum_{s \in S_d} V_s^{-1} Y_s, \quad V_d^{\text{dir}} := \text{Cov}(\hat{\theta}_d^{\text{dir}}) = \left( \sum_{s \in S_d} V_s^{-1} \right)^{-1}
\]

2. Model fitting

\[
\hat{\theta}^{\text{dir}} = (\hat{\theta}_1^{\text{dir}}, \ldots, \hat{\theta}_D^{\text{dir}})' = X_\delta \theta^{\text{nma}} + \epsilon_a
\]

with \( E(\epsilon_a) = 0 \) and \( \text{Cov}(\epsilon_a) =: V_a = \text{diag}(V_1^{\text{dir}}, \ldots, V_D^{\text{dir}}) \)

Example:

\[
\hat{\theta}^{\text{dir}} = \begin{pmatrix} \hat{\theta}_1^{\text{dir}} \\ \hat{\theta}_2^{\text{dir}} \\ \hat{\theta}_3^{\text{dir}} \\ \hat{\theta}_4^{\text{dir}} \end{pmatrix}, \quad X_d = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \end{pmatrix}, \quad \theta^{\text{nma}} = \begin{pmatrix} \theta^{\text{nma}}_{AB} \\ \theta^{\text{nma}}_{AC} \end{pmatrix}, \quad V_a = \text{diag}(V_1^{\text{dir}}, \ldots, V_4^{\text{dir}})
\]

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Fixed effects model

\[
Y = X\theta^{\text{nma}} + \epsilon
\]

with \( E(\epsilon) = 0 \) and \( \text{Cov}(\epsilon) =: V = \text{diag}(V_1^{\text{dir}}, \ldots, V_k^{\text{dir}}) \)

Example:

3 treatments, independent studies \( s = 1, \ldots, 4 \), designs \( d = AB, AC, BC \)

\[
Y = \begin{pmatrix} Y_{1,AB} \\ Y_{2,AB} \\ Y_{3,AC} \\ Y_{4,BC} \end{pmatrix}, \quad X = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ -1 & 1 \end{pmatrix}, \quad \theta^{\text{nma}} = \begin{pmatrix} \theta^{\text{nma}}_{AB} \\ \theta^{\text{nma}}_{AC} \end{pmatrix}, \quad V = \text{diag}(V_{1,AB}, \ldots, V_{4,BC})
\]

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--- | --- | --- | --- | --- | --- | ---

Two-stage fixed effects model

1. Aggregation per study design \( d \) by multivariate meta-analysis methods

\[
\hat{\theta}_d^{\text{dir}} := V_d^{\text{dir}} \sum_{s \in S_d} V_s^{-1} Y_s, \quad V_d^{\text{dir}} := \text{Cov}(\hat{\theta}_d^{\text{dir}}) = \left( \sum_{s \in S_d} V_s^{-1} \right)^{-1}
\]

2. Model fitting

\[
\hat{\theta}^{\text{dir}} = (\hat{\theta}_1^{\text{dir}}, \ldots, \hat{\theta}_D^{\text{dir}})' = X_\delta \theta^{\text{nma}} + \epsilon_a
\]

with \( E(\epsilon_a) = 0 \) and \( \text{Cov}(\epsilon_a) =: V_a = \text{diag}(V_1^{\text{dir}}, \ldots, V_D^{\text{dir}}) \)

Example:

with one further study of design \( ABC \) with treatment effect estimates \( \hat{\theta}_\text{AB}^{\text{dir}}, \hat{\theta}_\text{AC}^{\text{dir}}, \hat{\theta}_\text{ABC}^{\text{dir}}, \) and covariance matrix \( V_{\text{ABC}}^{\text{dir}} \)

\[
\hat{\theta}^{\text{dir}} = \begin{pmatrix} \hat{\theta}_\text{AB}^{\text{dir}} \\ \hat{\theta}_\text{AC}^{\text{dir}} \\ \hat{\theta}_\text{ABC}^{\text{dir}} \end{pmatrix}, \quad X_a = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \end{pmatrix}, \quad \theta^{\text{nma}} = \begin{pmatrix} \theta^{\text{nma}}_{\text{AB}} \\ \theta^{\text{nma}}_{\text{AC}} \end{pmatrix}, \quad V_a = \text{diag}(V_{\text{AB}}^{\text{dir}}, \ldots, V_{\text{ABC}}^{\text{dir}})
\]

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--- | --- | --- | --- | --- | --- | ---
# R package netmeta

> # 1. Install R package netmeta
> install.packages("netmeta")
> # 2. Load R package netmeta
> library(netmeta)
> # 3. Load data set Senn2013
> data(Senn2013)
> # 4. Print data set
> Senn2013

<table>
<thead>
<tr>
<th>TE</th>
<th>seTE</th>
<th>treat1</th>
<th>treat2</th>
<th>studlab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.90</td>
<td>metf</td>
<td>plac</td>
<td>DeFronzo1995</td>
</tr>
<tr>
<td>2</td>
<td>-0.82</td>
<td>metf</td>
<td>plac</td>
<td>Lewin2007</td>
</tr>
<tr>
<td>3</td>
<td>-0.20</td>
<td>metf</td>
<td>acar</td>
<td>Willms1999</td>
</tr>
<tr>
<td>4</td>
<td>-1.34</td>
<td>rosi</td>
<td>plac</td>
<td>Davidson2007</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>-1.20</td>
<td>metf</td>
<td>plac</td>
<td>Willms1999</td>
</tr>
<tr>
<td>28</td>
<td>-1.00</td>
<td>acar</td>
<td>plac</td>
<td>Willms1999</td>
</tr>
</tbody>
</table>

## R package netmeta: Object netmeta

> # Fixed effects model (default)
> # The netmeta function generates an object of class
> # netmeta with corresponding functions print, summary,
> # forest, netgraph, netheat, decomp.design, and netmeasures
> > nma <- netmeta(TE, seTE, treat1, treat2, studlab,
> + data=Senn2013, sm="MD", reference="plac")

Warning messages:
1: In netmeta(TE, seTE, treat1, treat2, studlab, data = Senn2013, sm = "MD", reference = "plac")
1: Treatments within a comparison have been re-sorted in increasing order.

## R package netmeta: Network graph

> netgraph(nma, seq=c("plac", "benf", "migl", "acar", "sulf",
> "metf", "rosi", "piog", "sita", "vild"))

Original data (with adjusted standard errors for multi-arm studies):

<table>
<thead>
<tr>
<th>treat1</th>
<th>treat2</th>
<th>TE</th>
<th>seTE</th>
<th>seTE.adj</th>
<th>narms</th>
<th>multiarm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defronzo1995</td>
<td>metf</td>
<td>plac</td>
<td>-1.90</td>
<td>0.14</td>
<td>0.14</td>
<td>2</td>
</tr>
<tr>
<td>Lewin2007</td>
<td>metf</td>
<td>plac</td>
<td>-0.82</td>
<td>0.10</td>
<td>0.10</td>
<td>2</td>
</tr>
<tr>
<td>Willms1999</td>
<td>acar</td>
<td>metf</td>
<td>0.20</td>
<td>0.36</td>
<td>0.39</td>
<td>3</td>
</tr>
<tr>
<td>Davidson2007</td>
<td>plac</td>
<td>rosi</td>
<td>1.34</td>
<td>0.14</td>
<td>0.14</td>
<td>2</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Willms1999</td>
<td>metf</td>
<td>plac</td>
<td>-1.20</td>
<td>0.38</td>
<td>0.41</td>
<td>3</td>
</tr>
<tr>
<td>Willms1999</td>
<td>acar</td>
<td>plac</td>
<td>-1.00</td>
<td>0.47</td>
<td>0.82</td>
<td>3</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**R package netmeta: Estimating treatment effects**

**Number of treatment arms (by study):**

<table>
<thead>
<tr>
<th>Study</th>
<th>narms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alex1998</td>
<td>2</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Willms1999</td>
<td>3</td>
</tr>
<tr>
<td>Woffenbutter1999</td>
<td>2</td>
</tr>
<tr>
<td>Yang2003</td>
<td>2</td>
</tr>
<tr>
<td>Zhu2003</td>
<td>2</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Data utilised in network meta-analysis (fixed effect model):**

<table>
<thead>
<tr>
<th>treat1</th>
<th>treat2</th>
<th>MD</th>
<th>95%-CI</th>
<th>Q</th>
<th>leverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeFronzo1995</td>
<td>metf</td>
<td>plac</td>
<td>-1.11</td>
<td>[-1.23; -1.00]</td>
<td>30.89</td>
</tr>
<tr>
<td>Lewin2007</td>
<td>metf</td>
<td>plac</td>
<td>-1.11</td>
<td>[-1.23; -1.00]</td>
<td>8.79</td>
</tr>
<tr>
<td>Willms1999</td>
<td>acar</td>
<td>metf</td>
<td>0.29</td>
<td>[0.06; 0.51]</td>
<td>0.05</td>
</tr>
<tr>
<td>Davidson2007</td>
<td>plac</td>
<td>rosi</td>
<td>1.20</td>
<td>[1.11; 1.30]</td>
<td>0.93</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Willms1999</td>
<td>metf</td>
<td>plac</td>
<td>-0.83</td>
<td>[-1.04; -0.61]</td>
<td>0.04</td>
</tr>
<tr>
<td>Willms1999</td>
<td>acar</td>
<td>plac</td>
<td>-0.83</td>
<td>[-1.04; -0.61]</td>
<td>0.04</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

> # Q: each comparison’s contribution to the heterogeneity statistic $Q_{total}$
> # leverage: small leverage means that the precision of a contrast benefits largely from the indirect inference; a leverage of 1 means that there is no gain at all

**Without a specification of argument reference.group in function netmeta matrices of the TE estimates, lower and upper 95%-confidence limits for all possible contrasts are shown, e.g.**

**Fixed effect model**

Treatment estimate (sm='MD', reference.group='plac'):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MD</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>acar</td>
<td>-0.83</td>
<td>[-1.04; -0.61]</td>
</tr>
<tr>
<td>benf</td>
<td>-0.91</td>
<td>[-1.15; -0.66]</td>
</tr>
<tr>
<td>metf</td>
<td>-1.11</td>
<td>[-1.23; -1.00]</td>
</tr>
<tr>
<td>migl</td>
<td>-0.94</td>
<td>[-1.19; -0.70]</td>
</tr>
<tr>
<td>piog</td>
<td>-1.07</td>
<td>[-1.22; -0.92]</td>
</tr>
<tr>
<td>plac</td>
<td>0.00</td>
<td>[0.00; 0.00]</td>
</tr>
<tr>
<td>rosi</td>
<td>-1.20</td>
<td>[-1.30; -1.11]</td>
</tr>
<tr>
<td>sita</td>
<td>-0.57</td>
<td>[-0.82; -0.32]</td>
</tr>
<tr>
<td>sulf</td>
<td>-0.44</td>
<td>[-0.62; -0.26]</td>
</tr>
<tr>
<td>vild</td>
<td>-0.70</td>
<td>[-0.95; -0.45]</td>
</tr>
</tbody>
</table>

> acar benf metf migl piog plac...
Generalization to a random effects model

\[ Y = Xθ + b + ϵ \] \text{with} \quad \text{Cov}(Y) =: V = V + V_{het}(τ)

Estimation of \( τ^2 \) e.g. by a generalized DerSimonian-Laird method with the assumptions:

- \( τ^2 \) is the same for all designs/comparisons
- random effects of multi-arm studies have correlation \( 1/2 \)

Example: studies of design AB, AC, BC, and ABC

\[
V = \begin{bmatrix}
\text{Var}(Y_{AB}) & 0 & 0 & 0 & 0 \\
0 & \text{Var}(Y_{AC}) & 0 & 0 & 0 \\
0 & 0 & \text{Var}(Y_{BC}) & 0 & 0 \\
0 & 0 & 0 & \text{Var}(Y_{AB,BC}) & \text{Cov}(Y_{AB,BC}, Y_{AC,BC}) \\
1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 1/2 \\
0 & 0 & 0 & 1/2 & 1
\end{bmatrix} + τ^2 \begin{bmatrix}
1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 1/2 \\
0 & 0 & 0 & 1 & 1/2 \end{bmatrix}
\]

R package netmeta: Estimating treatment effects

> # In order to explicitly conduct a random effects model
> nma_re <- netmeta(TE, seTE, treat1, treat2, studlab, +
> data=Senn2013, sm="MD", reference="plac", +
> comb.random=TRUE)

Warning messages:
1: In netmeta(TE, seTE, treat1, treat2, studlab, data = Senn2013, sm = "MD", : Treatments within a comparison have been re-sorted in increasing order.

Note: Even though object nma has been generated without argument comb.random all necessary information on the random effects network meta-analysis is also part of object nma.

R package netmeta: Forest plot

> forest(nma,xlab="HbA1c mean difference", xlim=c(-1.5,1.5))
### Decomposition of Q in pairwaise comparisons

\[ Q_{nma} = Q_{within} + Q_{inc} \]

- **Q\(^{within}\)**: Heterogeneity within pairwise comparisons OR within designs
- **Q\(^{inc}\)**: Inconsistency/Heterogeneity between pairwise comparisons OR between designs

### R package netmeta: Forest plot

```r
> forest(nma_re,xlab="HbA1c mean difference")
```

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Random Effects Model</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>acar</td>
<td></td>
<td>-0.84</td>
<td>[-1.32; -0.36]</td>
</tr>
<tr>
<td>benf</td>
<td></td>
<td>-0.73</td>
<td>[-1.29; -0.17]</td>
</tr>
<tr>
<td>metf</td>
<td></td>
<td>-1.13</td>
<td>[-1.43; -0.82]</td>
</tr>
<tr>
<td>migl</td>
<td></td>
<td>-0.95</td>
<td>[-1.40; -0.50]</td>
</tr>
<tr>
<td>piog</td>
<td></td>
<td>0.11</td>
<td>[-1.56; -0.70]</td>
</tr>
<tr>
<td>plac</td>
<td></td>
<td>-0.70</td>
<td>[-1.39; -0.01]</td>
</tr>
<tr>
<td>rosi</td>
<td></td>
<td>0.00</td>
<td>[-1.48; -0.98]</td>
</tr>
<tr>
<td>sita</td>
<td></td>
<td>-0.57</td>
<td>[-1.26; 0.12]</td>
</tr>
<tr>
<td>sulf</td>
<td></td>
<td>-0.42</td>
<td>[-0.89; 0.06]</td>
</tr>
<tr>
<td>vild</td>
<td></td>
<td>0.00</td>
<td>[-1.26; 0.12]</td>
</tr>
</tbody>
</table>

### Decomposition of Q\(^{nma}\) in pairwise comparisons

```r
> #Heterogeneity of the whole network
> round(nma$Q, 1)
97

> #Heterogeneity within pairwise comparisons
> round(nma$Q.heterogeneity, 1)
74.5

> #Heterogeneity between pairwise comparisons
> round(nma$Q.inconsistency, 1)
22.5
```
Decomposition of $Q^nma$ in design components

> decomp.design(nma)

Q statistics to assess homogeneity / consistency

<table>
<thead>
<tr>
<th></th>
<th>Q</th>
<th>df</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole network</td>
<td>96.99</td>
<td>18</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Within designs</td>
<td>74.46</td>
<td>11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Between designs</td>
<td>22.53</td>
<td>7</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Locating inconsistency: The net heat plot

> netheat(nma)

Generalized Cochran’s $Q$ for design inconsistency

$$Q^{inc} := \sum_d Q^{inc}_d$$

$$Q^{inc}_d := (\hat{\theta}^{dir}_d - X_d \hat{\theta}^{nma})' V^{-1}_d (\hat{\theta}^{dir}_d - X_d \hat{\theta}^{nma})$$

($\chi^2$ distributed with $\sum_d (a_d - 1) - (n - 1)$ degrees of freedom

$n$: number of treatments, $a_d$: number of arms in design $d$)

Network meta-analysis example in diabetes:

$$Q^{inc} = 0.04 + 0.00 + 0.20 + \ldots = 22.53$$

with $df = 16 - 9 = 7$ (p value: 0.002)
Detaching of single designs

1. Model fitting that allows for a deviating effect in one design $d$
2. Recalculation of the $Q$ statistic
   \[ Q_{d'}^\text{inc} = \sum_d Q_{d'}^\text{inc}(d) \]
3. Investigation of the change in inconsistency for each summand
   \[ Q_{d'}^\text{inc} - Q_{d'}^\text{inc}(d) \]

Visualization $\forall d = 1, \ldots, D$ in the nma heat plot:

- $Q_{d'}^\text{inc} > Q_{d'}^\text{inc}(d)$ increase after detaching/
  inconsistent evidence
- $Q_{d'}^\text{inc} < Q_{d'}^\text{inc}(d)$ decrease after detaching/
  supporting evidence

\[ Q^\text{inc} = 0.04 + 0.00 + 0.20 + \cdots = 22.53 \text{ with } df_{Q^\text{inc}} = 16 - 9 = 7 \text{ (p value: 0.002)} \]

Net heat plot in the diabetes example

\[ Q^\text{inc} = 0.04 + 0.00 + 0.20 + \cdots = 22.53 \text{ with } df_{Q^\text{inc}} = 16 - 9 = 7 \text{ (p value: 0.002)} \]
Net heat plot in the diabetes example

\[
Q_{inc} = 0.04 + 0.00 + 0.20 + \cdots = 22.53 \text{ with } df_{Q_{inc}} = 16 - 9 = 7 \text{ (p value: 0.002)}
\]

\[
Q_{inc}(\text{metf:SUal}) = 0.48 + 0.00 + 0.23 + \cdots = 7.52
\]

\[
Q_{diff,\text{metf:SUal}} = (-0.46, 0.00, -0.03, \ldots)
\]

Contributions of direct estimates

\[
\hat{\theta}_{dir} = X_a\hat{\theta}^{nma} + \epsilon_a
\]

\[
X_a\hat{\theta}^{nma} = H\hat{\theta}_{dir}
\]

\[
H := X_a(X_a'V_{a}^{-1}X_a)^{-1}X_a'V_{a}^{-1}
\]
Contributions of direct estimates

Direct Estimate

* three-armed study

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Net heat plot in the diabetes example

* three-armed study

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Net heat plot in the diabetes example

In the case of only two-arm studies:

1. Direct evidence proportion
   
   \[ w_{tu}^{\text{dir}} := \frac{\text{var}(\hat{\theta}_{tu})}{\text{var}(\hat{\theta}_{tu}^{\text{dir}})} = h_{tu,tu} \]

2. Mean path length (short is nice)
   
   \[ \eta_{tu} = \sum_d h_{tu,d} \]

3. Minimal parallelism (large is nice)
   
   \[ \pi_{tu} = \frac{1}{\max_d h_{tu,d}} \]

(where \( h_{i,j} \) is one element of \( H \). In the case of multi-arm studies, \( \tilde{H} \) with design specific net flows is used instead; see König et al., 2013)

Characterizing measures in the diabetes example

```r
> m <- netmeasures(nma)
> # Direct evidence proportion
> m$proportion[order(m$proportion)]
```

... sulf:vild acar:metf metf:rosi piog:rosi plac:piog rosish:ulf ... 0.0000 0.1025 0.1750 0.1995 0.3578 0.4106 plac:rosi plac:benf plac:migl plac:sita plac:vild 0.8317 1.0000 1.0000 1.0000 1.0000
Characterizing measures in the diabetes example

> # Mean path length
> m$meanpath[order(m$meanpath)]

plac:benf ... sita:sulf sulf:vild  
1.0000 3.1383 3.1383

> # Minimal parallelism
> m$minpar[order(m$minpar)]

plac:benf ... plac:sulf rosi:sulf  
1.0000 2.2156 2.3054

Summary

Network meta-analysis

- Estimating the effects of all pairwise treatment comparisons in a trial network
- Indirect evidence is taken into account
  - Assumption of consistency
- Issues known from classical meta-analysis when evaluating the validity of results (e.g. heterogeneity, limited power for assessing heterogeneity, selection bias, extent to which results rest on a few studies)
- R package `netmeta` provides some methods: effect estimating, decomposition of a generalized Q statistic, net heat plot, measures for characterizing the evidence flow

References