NETWORK META-ANALYSIS
Outline

- Background
- Indirect Comparisons
- Networks
- Heterogeneity
- Exchangeability
- Consistency
- Models
- Ranking
Clinicians, patients, and health-policy makers need to decide which treatment is “best” and want to use relevant evidence. Often use meta-analysis to synthesize studies of two treatments. Many questions involve multiple treatments. Examples:

- Behavioral and pharmacological treatments for smoking cessation
- SSRIs for treatment of depression
- Oral and intravenous treatments for knee osteoarthritis

Unfortunately, robustly designed RCTs that simultaneously compare all interventions of interest are almost never available. Different meta-analyses compare different treatment pairs.
New drugs are often compared with placebo or standard care, but not against each other, in trials aimed to contribute toward obtaining approval for drug licensing.

Commercial disincentive to compare new treatment with active control.

*Indirect treatment comparisons* provide useful evidence.

*Network meta-analysis* extends standard pairwise meta-analysis by including multiple pairwise comparisons across a range of interventions.

Incorporates both *direct* and *indirect* evidence.
Example: Antidepressants

## Example: Antidepressants

### Source data. New-generation antidepressants for major depression, dropouts

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<th>fluoxetine r</th>
<th>bupropion r</th>
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<th>duloxetine r</th>
<th>escitalopram r</th>
<th>fluvoxamine r</th>
<th>milnacipram r</th>
<th>mirtazapine r</th>
<th>paroxetine r</th>
<th>reboxetine r</th>
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<td>Bennie, 1995</td>
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</tbody>
</table>

Source: For complete dataset see Cipriani et al., 2009; r refers to dropouts; n refers to number of patients.

Treatments Without Direct Comparison

OR(B vs M) = 0.79 (0.72, 1)

Lancet 2009 Cipriani, Fukurawa, Salanti et al
Fluoxetine vs Milnacipran (response to treatment)
Meta-analysis: 1.15 (0.72, 1.85)
MTM: 0.97 (0.69, 1.32)
## Ranking Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy (response rate) (95% CI)</th>
<th>Comparison</th>
<th>Acceptability (dropout rate) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP</td>
<td>0.98 (0.78-1.23)</td>
<td></td>
<td>0.84 (0.68-1.02)</td>
</tr>
<tr>
<td>CIT</td>
<td>0.75 (0.55-1.02)</td>
<td></td>
<td>0.77 (0.45-0.86)</td>
</tr>
<tr>
<td>DUL</td>
<td>1.43 (1.09-1.85)</td>
<td></td>
<td>1.36 (1.01-1.83)</td>
</tr>
<tr>
<td>ESC</td>
<td>0.75 (0.60-0.93)</td>
<td></td>
<td>0.78 (0.64-0.97)</td>
</tr>
<tr>
<td>FLU</td>
<td>1.32 (1.12-1.55)</td>
<td></td>
<td>1.14 (0.81-1.09)</td>
</tr>
<tr>
<td>FVX</td>
<td>1.35 (1.02-1.76)</td>
<td></td>
<td>1.14 (0.86-1.54)</td>
</tr>
<tr>
<td>MIL</td>
<td>0.97 (0.68-1.37)</td>
<td></td>
<td>0.97 (0.69-1.40)</td>
</tr>
<tr>
<td>MIR</td>
<td>0.97 (0.68-1.37)</td>
<td></td>
<td>0.97 (0.76-1.23)</td>
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<tr>
<td>PAR</td>
<td>1.35 (1.11-1.64)</td>
<td></td>
<td>1.03 (0.86-1.24)</td>
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<tr>
<td>REB</td>
<td>1.60 (1.20-2.16)</td>
<td></td>
<td>1.34 (0.99-1.83)</td>
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<tr>
<td>SER</td>
<td>0.88 (0.62-1.01)</td>
<td></td>
<td>0.82 (0.67-1.00)</td>
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</tbody>
</table>

**OR > 1 means the treatment in top-left is better**
Network Meta-Analysis

- Combine direct + indirect estimates of multiple treatment effects
- Internally consistent set of estimates that respects randomization
- Estimate effect of each intervention relative to every other whether or not there is direct comparison in studies
- Calculate probability that each treatment is most effective
- Compared to conventional pair-wise meta-analysis:
  - Greater precision in summary estimates
  - Ranking of treatments according to effectiveness or safety
## Indirect Comparisons

<table>
<thead>
<tr>
<th>Trial</th>
<th>1</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

- Want to compare A vs. B
  - Direct evidence from trials 1, 2 and 7
  - Indirect evidence from trials 3, 4, 5, 6 and 7

- Combining all “A” arms and comparing with all “B” arms destroys randomization

- Use indirect evidence of A vs. C and B vs. C comparisons as additional evidence to preserve randomization and within-study comparison
Naive indirect comparison

- Invalid because study effect differences not acknowledged.
Indirect comparison

Two studies A vs C and B vs C

Want to compare A vs B
Indirect comparison

\[ A - B = (A - C) - (B - C) \]

Can do this through common comparator C (under certain conditions)
Indirect comparison

$$A - B = (A - C) - (B - C)$$
Indirect comparison

\[
\begin{array}{ccc}
A & \rightarrow & B \\
\downarrow & & \downarrow \\
-10 & & -8 \\
\end{array}
\]

C

?
Indirect comparison

\[-10 - (-8) = -2\]

A \[\rightarrow\] C \[\rightarrow\] B
Indirect comparison

\[ d_{BC} = d_{AC} - d_{AB} \]

Indirect comparison

Trial 1
- B
- A (Placebo)

Trial 2
- C
- A (Placebo)

Trial 3
- D
- C

Relative tx effect

Delta y

Indirect estimate of D vs. B

Indirect estimate of C vs. B

Indirect estimate of D vs. A

B vs. A
- B
- A

C vs. A
- C
- A

D vs. C
Consistency

Little difference between direct and indirect estimates
Inconsistency

Big difference between direct and indirect estimates
A total of $k(k-1)/2$ contrasts

Consistent Closed Loop Network

Diagram showing a network with nodes A, B, and C connected by trials 1, 2, and 3. The diagram includes bar charts for trials 1, 2, and 3, with comparisons between B, A (Placebo), C, A (Placebo), C, and B. It also shows a comparison of delta y vs. A with indirect and direct estimates of C vs. B.
Inconsistent Closed Loop Network
# Inconsistent Network

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of trials</th>
<th>Log odds ratio (SE)</th>
<th>Odds ratio (95% CI)</th>
<th>I²%</th>
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</thead>
<tbody>
<tr>
<td>Placebo controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Risperidone vs placebo</td>
<td>3</td>
<td>−0.909 (0.218)</td>
<td>0.40 (0.26, 0.62)</td>
<td>37%</td>
</tr>
<tr>
<td>Haloperidol vs placebo</td>
<td>9</td>
<td>−1.707 (0.318)</td>
<td>0.18 (0.10, 0.34)</td>
<td>11%</td>
</tr>
<tr>
<td>Risperidone vs haloperidol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct comparison</td>
<td>10</td>
<td>−0.262 (0.142)</td>
<td>0.77 (0.58, 1.02)</td>
<td>14%</td>
</tr>
<tr>
<td>Adjusted indirect comparison</td>
<td>3/9</td>
<td>0.798 (0.386)</td>
<td>2.22 (1.04, 4.72)</td>
<td></td>
</tr>
<tr>
<td>Combination of direct and indirect estimates</td>
<td>10+(3/9)</td>
<td>0.207 (0.527)</td>
<td>1.23 (0.44, 3.45)</td>
<td>85%</td>
</tr>
</tbody>
</table>

NB Random-effects model was used in meta-analyses of trials and for the combination of the direct and indirect estimates. Odds ratio = EXP(log odds ratio).

CI: confidence interval; SE: standard error

Source: Song F. What is indirect comparison? What is series 2009
Inconsistent Network

![Odds ratio diagram](image)

- Treatment 1 vs treatment 2
  - Risperidone vs placebo
  - Haloperidol vs placebo
- Risperidone vs haloperidol
- Adjusted indirect estimate
- Direct estimate
- Combination of direct and indirect

CI = confidence interval

Source: Song F. What is indirect comparison? What is series 2009
Need for a network

Trial 1

A

B

C

D

Trial 3

y

B

A (Placebo)

D

C

Relative tx effect

Tx effect

B vs. A

D vs. C

delta y

Vs. A

Unknown indirect estimate of D vs. B

Unknown estimate of C vs. A

?
Mixed Treatment Comparisons

- Network of direct and indirect evidence contributing to contrast estimates.
- AB studies provide direct evidence for $d_{AB}$
- Other studies provide indirect evidence for this contrast.
How Do We Choose Treatments?

- Relevance depends on research question and analysis plan
- Requires collaboration among methods and subject matter experts
- Rankings may be affected by inclusion criteria
- Consider including placebo, older and legacy treatments
- Lump or split?
  - Different treatments within class
  - Different doses within treatment
  - Different comparison groups
- Size of network, comparability, heterogeneity, precision
Basic Assumptions

• **Exchangeability** of Treatment Effects Between Studies

  Needed for valid combining of estimates

• **Exchangeability** of Treatment Comparisons Between Studies

  Needed for valid indirect comparison estimates

• **Consistency**: Direct and indirect estimates give same answer

  Needed for valid mixed treatment comparison estimates
Heterogeneity

- Extent to which *true* treatment effect varies with different populations/patient characteristics, treatment characteristics (such as dose or duration) or study characteristics.

- Known as *interaction* or *effect modification*

- Caused by variation in (un)measured effect-modifiers of relative treatment effect.
Heterogeneity across studies
Prognostic Factors and Effect Modifiers

Effect modifiers
Patient or study characteristics that influence the treatment effect.

Prognostic factors
Patient or study characteristics that influence the outcomes in the intervention and placebo arm to the same extent.
Heterogeneity and Inconsistency

- **Heterogeneity** occurs within direct treatment comparisons
  - Effect modification (treatment effects vary by study characteristics)

- **Inconsistency** occurs across different treatment comparisons
  - Interaction with study design (e.g. 3-arm vs. 2-arm) or within loops of treatments
  - Consistency can be checked by model extensions when direct and indirect evidence is available
Heterogeneity in a network

Without heterogeneity

Severe/Moderate 70:30
Severe/Moderate 70:30
Severe/Moderate 70:30
Pooled effect

Valid indirect estimate of C vs. B

Similar distribution of effect modifiers between AB and AC studies

0  treatment effect B vs. A

0  treatment effect C vs. A

With heterogeneity

Severe/Moderate 70:30
Severe/Moderate 50:50
Severe/Moderate 70:30
Pooled effect

Valid indirect estimate of C vs. B

Similar distribution of effect modifiers between AB and AC studies

0  treatment effect B vs. A

0  treatment effect C vs. A
Exchangeability

- Treatment C is similar when it appears in AC and BC studies. 
  *What if* C is standard care and A and B are different generations of drugs

- AC and BC trials have similar distribution of effect modifiers. 
  *What if* AC studies have higher proportion of very ill patients than BC studies

- Participants could be randomized to any of treatments A, B, C.  
  *What if* C can only be given to certain types of patients

- ‘Missing’ treatment in each trial is missing (completely) at random

Two Placebos in One Network

Figure 1. Network of different placebo comparisons.

A. Differential placebo effects model. B. Nondifferential combined placebo effects model. Combined placebo = all 4 placebo groups (oral, topical, IA, and oral plus topical) are combined into a single group. Circle size reflects number of participants, and the line width reflects number of direct comparisons. No connecting line between 2 circles indicates that there was no direct comparison between the 2 treatments. COX = cyclooxygenase; IA = intra-articular; NSAID = nonsteroidal anti-inflammatory drug.

(Un)biased indirect treatment comparison

Unbiased indirect comparison

Biased indirect comparison

Disease severity modifies AB and AC effect

Transitivity assumption holds

Transitivity assumption fails

$$d_{BC}^{\text{indirect}} = d_{AC}^{\text{direct}} - d_{AB}^{\text{direct}}$$

AB, AC have different distribution of effect modifiers

BC estimate affected by confounding bias from differences in effect modifiers across comparisons

Consistency in MTC

\[ d_{BC}^{\text{direct}} = d_{BC}^{\text{indirect}} = d_{AC}^{\text{direct}} - d_{AB}^{\text{direct}} \]

\[ d_{AC}^{\text{direct}} = d_{AC}^{\text{indirect}} = d_{AB}^{\text{direct}} + d_{BC}^{\text{direct}} \]

\[ d_{AB}^{\text{direct}} = d_{AB}^{\text{indirect}} = d_{AC}^{\text{direct}} - d_{BC}^{\text{direct}} \]

No inconsistency, no bias

Inconsistency in MTC

\[ d_{BC}^{\text{direct}} \neq d_{BC}^{\text{indirect}} = d_{AC}^{\text{direct}} - d_{AB}^{\text{direct}} \]

- Severe: Moderate
- Moderate: Moderate
- Biased: Moderate

\[ d_{AC}^{\text{direct}} \neq d_{AC}^{\text{indirect}} = d_{AB}^{\text{direct}} + d_{BC}^{\text{direct}} \]

- Moderate: Biased
- Severe: Moderate

\[ d_{AB}^{\text{direct}} \neq d_{AB}^{\text{indirect}} = d_{AC}^{\text{direct}} - d_{BC}^{\text{direct}} \]

- Moderate: Biased
- Severe: Moderate

**BC:** unbiased indirect estimate is different from direct estimate. Inconsistency does not result in biased BC estimates. (Only variation in BC estimates, in similar fashion as heterogeneity in pairwise meta-analysis)

**AC:** Biased indirect estimate because effect modifiers different for AB and BC. Biased indirect estimate is different from direct AC. Inconsistency in network results in biased AC estimate

**AB:** Biased indirect estimate because effect modifiers different for AC and BC. Biased indirect estimate is different from direct AB. Inconsistency in network results in biased AB estimate

Inconsistency in MTC

\[ d_{BC}^{direct} \neq d_{BC}^{indirect} = d_{AC}^{direct} - d_{AB}^{direct} \]

- Severe
- Biased
- Mild
- Moderate

\[ d_{AC}^{direct} \neq d_{AC}^{indirect} = d_{AB}^{direct} + d_{BC}^{direct} \]

- Mild
- Biased
- Moderate
- Severe

\[ d_{AB}^{direct} \neq d_{AB}^{indirect} = d_{AC}^{direct} - d_{BC}^{direct} \]

- Moderate
- Biased
- Mild
- Severe

Inconsistency, all estimates biased

Biased network meta-analysis

**Without heterogeneity**

- Severe/Moderate 30:70
- Severe/Moderate 30:70
- Severe/Moderate 30:70

**Without heterogeneity**

BIASED indirect estimate of C vs. B

Imbalance in distribution of effect modifiers between AB and AC studies

**With heterogeneity**

- Severe/Moderate 30:70
- Severe/Moderate 50:50
- Severe/Moderate 30:70

**With heterogeneity**

BIASED indirect estimate of C vs. B

Imbalance in distribution of effect modifiers between AB and AC studies

- Severe/Moderate 70:30
- Severe/Moderate 70:30
- Severe/Moderate 70:30

- Severe/Moderate 70:30
- Severe/Moderate 50:50
- Severe/Moderate 70:30

*School of Public Health*
Indirect comparison with Effect Modifier Imbalance

- Disease severity is effect modifier
- Valid indirect comparisons for moderate and severe disease
- Invalid indirect comparison for overall population – distribution of severity differs for AB and AC studies
‘Trial 1: Porsche versus Golf’

Porsche - Golf = 2s

‘Trial 2: Volvo versus Golf’

Volvo - Golf = 8s

→ Volvo versus Porsche: 8-2=6s (Indirect comparison)

Is a Volvo faster than a Porsche?

No, biased indirect estimate due to imbalance in treatment effect modifier (snow) across comparisons
Trials of HAART regimes for HIV

A: 2 NRTIs
B: 2 NRTIs + PI
C: 2 NRTIs + NNRTI

- Indirect B vs C evidence inconsistent with direct evidence from B vs C trials

Conclusion: Indirect Comparisons unreliable for complex interventions like HAART
Trials of HAART regimes for HIV

A: 2 NRTIs
B: 2 NRTIs + PI
C: 2 NRTIs + NNRTI

- BUT the NRTIs in A vs B trials were DIFFERENT from NRTIs in B vs C trials
- When comparison restricted to trials with SAME NRTI regimes, inconsistency no longer statistically significant
Indirect Comparison: No Adjusting for Covariate

Adjusting for Imbalance with Meta-regression

- Treatment effects depend on the value of effect modifier
Biased Indirect Treatment Comparison

**Graph:**
- **Vertical Axis:** log(OR)
- **Horizontal Axis:** Covariate
- **AC studies:** Red dots and lines
- **AB studies:** Blue dots and lines

The graph illustrates a comparison of AC and AB studies, showing how the log odds ratio (OR) varies with the covariate.
Correcting Bias Using IPD
Adjustment with IPD and AD

Assumption that impact of covariate is the same for AB (Aggregated data) and AC (IPD) studies;

Exchangeable slopes assumption is an alternative

MODELS
Basic and Functional Parameters

- Three treatments with treatment A as reference
- Relative treatment effects (log odds ratios) of B, C relative to A are the **basic** parameters

\[ \Delta_{AB}, \Delta_{AC} \]

- Remaining contrasts are **functional** parameters

\[ \Delta_{BC} = \Delta_{AC} - \Delta_{AB} \]

- Basic parameters determine functional parameters
- Functional parameters inform indirectly about basic parameters
- Could also model treatment arms rather than contrasts
Basic and Functional Parameters

$k$ treatments

$k(k-1)/2$ contrasts

$k-1$ basic parameters: $d_{AB}, d_{AC}$

(Priors needed for these in Bayesian model)

Functional parameter: $d_{BC}$

(to relate data back to basic parameters)

Consistency relation: $d_{BC} = d_{AC} - d_{AB}$

Direct comparison

Indirect comparison
Expressing Network by Meta-Regression

<table>
<thead>
<tr>
<th>Contrast</th>
<th>X1</th>
<th>X2</th>
</tr>
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<tbody>
<tr>
<td>AC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>BC</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AB</td>
<td>1</td>
<td>-1</td>
</tr>
</tbody>
</table>

\[
\begin{pmatrix}
 y_{1,AB} \\
 y_{2,AC} \\
 y_{3,BC}
\end{pmatrix}
= \begin{pmatrix}
 1 & 0 \\
 0 & 1 \\
-1 & 1
\end{pmatrix}
\begin{pmatrix}
 \mu_{AB} \\
 \mu_{AC}
\end{pmatrix}
+ \begin{pmatrix}
 \beta_1 \\
 \beta_2 \\
 \beta_3
\end{pmatrix}
+ \begin{pmatrix}
 \epsilon_1 \\
 \epsilon_2 \\
 \epsilon_3
\end{pmatrix}
\]

Observed Fixed Random Error
Multi-Arm Trials

\[
\begin{pmatrix}
  y_{1,AB} \\
  y_{2,AC} \\
  y_{3,BC} \\
  y_{4,AB} \\
  y_{4,AC}
\end{pmatrix} =
\begin{pmatrix}
  1 & 0 \\
  0 & 1 \\
  -1 & 1 \\
  1 & 0 \\
  0 & 1
\end{pmatrix}
\begin{pmatrix}
  \mu_{AB} \\
  \mu_{AC}
\end{pmatrix} +
\begin{pmatrix}
  \beta_{1,1} \\
  \beta_{2,1} \\
  \beta_{3,1} \\
  \beta_{4,1} \\
  \beta_{4,2}
\end{pmatrix} +
\begin{pmatrix}
  \varepsilon_{1,1} \\
  \varepsilon_{2,1} \\
  \varepsilon_{3,1} \\
  \varepsilon_{4,1} \\
  \varepsilon_{4,2}
\end{pmatrix}
\]

\(y_{4,AB}\) and \(y_{4,AC}\) are correlated

Random effects \(b\) and observed error \(e\) are correlated

\(\varepsilon \sim N(0,V)\)

\(\beta \sim N(0,T)\)

\(Y \sim N(X\mu, T+V)\)
Multi-Arm Trials

\[
\begin{pmatrix}
  y_{1,AB} \\
  y_{2,AC} \\
  y_{3,BC} \\
  y_{4,AB} \\
  y_{4,AC}
\end{pmatrix}
= 
\begin{pmatrix}
  1 & 0 \\
  0 & 1 \\
  -1 & 1 \\
  1 & 0 \\
  0 & 1
\end{pmatrix}
\begin{pmatrix}
  \mu_{AB} \\
  \mu_{AC}
\end{pmatrix}
+ 
\begin{pmatrix}
  \beta_{1,1} \\
  \beta_{2,1} \\
  \beta_{3,1} \\
  \beta_{4,1} \\
  \beta_{4,2}
\end{pmatrix}
+ 
\begin{pmatrix}
  \varepsilon_{1,1} \\
  \varepsilon_{2,1} \\
  \varepsilon_{3,1} \\
  \varepsilon_{4,1} \\
  \varepsilon_{4,2}
\end{pmatrix}
\]

\[
\begin{pmatrix}
  \varepsilon_{1,1} \\
  \varepsilon_{2,1} \\
  \varepsilon_{3,1} \\
  \varepsilon_{4,1} \\
  \varepsilon_{4,2}
\end{pmatrix}
\sim \mathcal{N}
\begin{pmatrix}
  0 \\
  0 \\
  0 \\
  0 \\
  0
\end{pmatrix},
\begin{pmatrix}
  v_{1,1} & 0 & 0 & 0 & 0 \\
  0 & v_{2,1} & 0 & 0 & 0 \\
  0 & 0 & v_{3,1} & 0 & 0 \\
  0 & 0 & 0 & v_{4,1} & c_{4,14,2} \\
  0 & 0 & 0 & c_{4,14,2} & v_{4,2}
\end{pmatrix}
\]

\[
\begin{pmatrix}
  \beta_{1,1} \\
  \beta_{2,1} \\
  \beta_{3,1} \\
  \beta_{4,1} \\
  \beta_{4,2}
\end{pmatrix}
\sim \mathcal{N}
\begin{pmatrix}
  0 \\
  0 \\
  0 \\
  0 \\
  0
\end{pmatrix},
\begin{pmatrix}
  \tau_{AB}^2 & 0 & 0 & 0 & 0 \\
  0 & \tau_{AC}^2 & 0 & 0 & 0 \\
  0 & 0 & \tau_{BC}^2 & 0 & 0 \\
  0 & 0 & 0 & \text{cov}(\beta_{4,1}, \beta_{4,2}) & \tau_{AB}^2 \\
  0 & 0 & 0 & \text{cov}(\beta_{4,1}, \beta_{4,2}) & \tau_{AC}^2
\end{pmatrix}
\]

Correlations in observed values

Correlation in random effects

Correlations of random effects are ½ if equivariant effects

Fit using mixed models
Modeling by Arms: Single AB study

\[ \theta_k = \begin{cases} 
\mu & k = A \\
\mu + d & k = B 
\end{cases} \]
Equal (Fixed) Effects model

\[ \theta_{jk} = \begin{cases} 
\mu_j & k = A \\
\mu_j + d & k = B 
\end{cases} \]
Random Effects Model

\[ \theta_{jk} = \begin{cases} 
\mu_j & k = A \\
\mu_j + \delta_j & k = B 
\end{cases} \]

\[ \delta_j \sim \text{Normal}(d, \sigma_{\delta}^2) \]
Arm-based FE & RE NMA Models

Fixed effects

\[
\theta_{jk} = \begin{cases} 
\mu_{jb} & \text{if } k = b \\
\mu_{jb} + d_{bk} = \mu_{jb} + d_Ak - d_Ab & \text{if } k \text{ 'after' } b
\end{cases}
\]

\[d_{AA} = 0\]

Random effects

\[
\theta_{jk} = \begin{cases} 
\mu_{jb} & \text{if } k = b \\
\mu_{jb} + \delta_{jbk} & \text{if } k \text{ 'after' } b
\end{cases}
\]

\[\delta_{jbk} \sim Normal(d_{bk}, \sigma_\delta^2) = Normal(d_{Ak} - d_{Ab}, \sigma_\delta^2)\]

\[d_{AA} = 0\]
MA and NMA Models

Fixed effects meta-analysis

\[
\begin{align*}
\theta_{jk} &= \begin{cases} 
\mu_j & k = A \\
\mu_j + d_j & k = B
\end{cases} \\
\delta_j &\sim N(d, \sigma^2)
\end{align*}
\]

Fixed effects network meta-analysis

\[
\begin{align*}
\theta_{jk} &= \begin{cases} 
\mu_{jb} & k = A \\
\mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & k 'after' b
\end{cases} \\
b = A, B, C, ... \text{ if } k = b
\end{align*}
\]

\[
d_{AA} = 0
\]

Random effects meta-analysis

\[
\begin{align*}
\theta_{jk} &= \begin{cases} 
\mu_j & k = A \\
\mu_j + \delta_j & k = B
\end{cases} \\
\delta_j &\sim N(d, \sigma^2)
\end{align*}
\]

Random effects network meta-analysis

\[
\begin{align*}
\theta_{jk} &= \begin{cases} 
\mu_{jb} & k = A \\
\mu_{jb} + \delta_{jbk} & k 'after' b
\end{cases} \\
b = A, B, C, ... \text{ if } k = b
\end{align*}
\]

\[
\begin{align*}
\delta_{jbk} &\sim N(d_{bk}, \sigma^2) = N(d_{Ak} - d_{Ab}, \sigma^2) \\
d_{AA} = 0
\end{align*}
\]
Models for Binary Outcomes

\[ r_{jk} \sim \text{binomial}\left(n_{jk}, p_{jk}\right) \]

\[
\logit(p_{jk}) = \begin{cases} 
\mu_{jb} & \text{if } k = b \\
\mu_{jb} + \delta_{jbk} & \text{if } k \text{'after' } b
\end{cases}
\]

\[
\delta_{jbk} \sim N(d_{bk}, \sigma^2) = N(d_{Ak} - d_{Ab}, \sigma^2)
\]

\[ d_{AA} = 0 \]
NMA model for IPD and AD

**IPD**

\[ y_{ijk} \sim Bernoulli(p_{ijk}) \]

\[
\logit(p_{ijk}) = \begin{cases} 
\mu_{jb} + \beta_{0j} x_{ij} 
& \text{if } k = b \\
\mu_{jb} + \beta_{0j} x_{ij} + \delta_{jbk} + (\gamma_{Ak} - \gamma_{Ab}) x_{ij} 
& \text{if } k \text{ 'alphabetically after' } b 
\end{cases}
\]

**AgD**

\[ r_{jk} \sim \text{binomial}(q_{jk}, n_{jk}) \]

\[
\logit(q_{jk}) = \begin{cases} 
\lambda_{jb} 
& \text{if } k = b \\
\lambda_{jb} + \delta_{jbk} + (\gamma_{Ak} - \gamma_{Ab}) m_j 
& \text{if } k \text{ 'alphabetically after' } b 
\end{cases}
\]

\[ \delta_{jbk} \sim N(d_{bk}, \tau^2) = N(d_{Ak} - d_{Ab}, \tau^2) \]

\[ d_{AA} = 0, \gamma_{AA} = 0 \]

Source: Janssen JP. Network meta-analysis of individual and aggregate level data. Research Synthesis Methods 2012 (in press)
Analysis of inconsistency

- Bucher method

- Inconsistency models / Independent means models

- Network models with inconsistency factors

- Edge splitting
Bucher Method for Testing Inconsistency

Suppose we have AB, AC, BC direct evidence

Indirect estimate
\[ \hat{d}_{BC}^{\text{indirect}} = \hat{d}_{AC}^{\text{direct}} - \hat{d}_{AB}^{\text{direct}} \]

Measure of inconsistency:
\[ \hat{\omega}_{BC} = \hat{d}_{BC}^{\text{indirect}} - \hat{d}_{BC}^{\text{direct}} \]

Approximate test (normal distribution):
\[ z_{BC} = \frac{\hat{\omega}_{BC}}{\sqrt{V(\hat{\omega}_{BC})}} \]

with variance
\[ V(\hat{\omega}_{BC}) = V(d_{BC}^{\text{direct}}) + V(d_{AC}^{\text{direct}}) + V(d_{AB}^{\text{direct}}) \]

Cannot include 3-arm trials


Probabilistic interpretation of the findings

Software

- Specialized meta-analysis software cannot handle multivariate models
- Facilities in standard packages for weighted least squares regression and maximum likelihood but requires fix-ups
- Stata has a suite of meta-analysis programs including MVMETA for fitting multivariate normal models
- BUGS and STAN can fit arbitrary Bayes models
- R package metafor
- Open Meta-Analyst (from our shop) provides GUI over metafor
Summary

- Network meta-analysis extends traditional meta-analysis
- Includes multiple different pairwise comparisons across a range of different interventions to allow for multiple treatment comparisons including direct and indirect effects
- Networks can be analyzed with regression models relying on consistency relations
- Individual patient level data will improve the validity of a network meta-analysis
Caveats

- Randomization does not hold across trials
- Risk of imbalance in (unmeasured) effect-modifiers across comparisons which causes heterogeneity and inconsistency
- Imbalance in effect-modifiers across comparisons gives biased indirect estimates and invalid mixed estimates
- Inconsistency in a closed loop network can be investigated by comparing direct with indirect estimates
- Extension of network meta-analysis models with treatment-by-covariate interactions can help explore heterogeneity and improve consistency
Thank You