Mahidol University
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Section for Clinical Epidemiology and Biostatistics

Journal Club Presentation

Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies‡

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Wisdom of the Land

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Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies‡

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Outline of talks

- **Introduction**
- Concepts of heterogeneity and inconsistency
- Models for inconsistency
- Discussion and Conclusion

Introduction

- Compare multiple treatments
  -> More useful than pairwise comparisons alone
  -> Ranking of treatment interventions

- Network meta-analyses (NMA)
  -> Simultaneous analysis of both direct and indirect comparisons among multiple treatments across multiple studies

GleserandOlkin,1994;HigginsandWhitehead,1996;Lumley,2002; Lu and Ades, 2004; Caldwell et al., 2005; Lu and Ades, 2006; Salanti et al., 2008; Ioannidis, 2009)

- Component of NMA

-> Assessment of the different of comparable sources of evidence both substantively and statistically

- Simple indirect comparison will be confounded

-> If studies involving one of interested treatments are fundamentally different from the studies involving the other treatment

"Termed incoherence or inconsistency in the literature"

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Outline of talks

- Introduction
- **Concepts of heterogeneity and inconsistency**
- Models for inconsistency
- Discussion and Conclusion

Concepts of heterogeneity and inconsistency

- **Indirect comparisons**
- Heterogeneity
- Consistency
- Loop inconsistency
- Multi-arm trials
- Design inconsistency
- Design-by-treatment interaction

Indirect comparisons

Indirect comparison

- **Maintains** benefits of randomization within each trial

- Provided that the differences affect **only** prognosis of participants and not their response to treatment

Indirect comparisons

- Trial 1: Two-arm trial of 'B–A' comparison

  [$\hat{\delta}_1^{AB}$ = Estimated effect sizes of trial 1]

- Trial 2: Two-arm trial of 'C–B' comparison

  [$\hat{\delta}_2^{BC}$ = Estimated effect sizes of trial 2]

- Then, indirect comparison of 'C–A' as….

$$\hat{\delta}_{(\text{indirect})}^{AC} = \hat{\delta}_1^{AB} + \hat{\delta}_2^{BC}$$

Indirect comparisons

On assumption….

- B treatment as same in both trials
- When ‘B–A’ and ‘C–B’ are added together
  -> B effects **are cancelled out**
- Indirect comparison
  -> reflective of difference between A and C is not testable in absence of further information

Indirect comparisons

- Third trial of 'C–A' (yielding result $\hat{\delta}_3^{AC}$)

  -> Compare the indirect comparison with a direct comparison

- Network of 3 trials is consistent

  If underlying treatment effects are related as follows:

$$\delta_3^{AC} = \delta_1^{AB} + \delta_2^{BC}, \qquad (1)$$

δ_1^{AB}, δ_2^{BC} and δ_3^{AC} -> represent true effects underlying 3 studies

Indirect comparisons

Equation (1) -> very unlikely to hold for particular set of 3 trials because….

- In terms of heterogeneity:
  Within each treatment comparison, each individual study is **not fully representative** of all studies of that particular comparison

- In terms of inconsistency:
  Across treatment comparisons, there are important differences in types of studies contributing to comparisons

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Concepts of heterogeneity and inconsistency

- Indirect comparisons
- **Heterogeneity**
- Consistency
- Loop inconsistency
- Multi-arm trials
- Design inconsistency
- Design-by-treatment interaction

Heterogeneity

- Multiple studies of same research question have different values of estimated effect measurement.
- By holding treatment comparison constant and varying study index.

- Heterogeneity may be present for comparison 'B–A'

  if $\delta_i^{AB} \neq \delta_j^{AB}$ for some pair of studies i and j

Heterogeneity

- Heterogeneity has been **argued** to be inevitable in meta-analysis…

: 2 trials of same pairwise comparison **are unlikely** to have equal underlying treatment effects

-> Equality in equation 1 is questionable

[Particular instance of ‘C–A’ investigated in trial 3
is unlikely to represent all instances of ‘C–A’ comparisons]

Heterogeneity

- Random-effects model

  -> Common way to allow for heterogeneity

- Assumes that underlying effects in multiple studies of same comparison come from normal distribution

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Concepts of heterogeneity and inconsistency

- Indirect comparisons
- Heterogeneity
- **Consistency**
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Consistency

Consistency equation

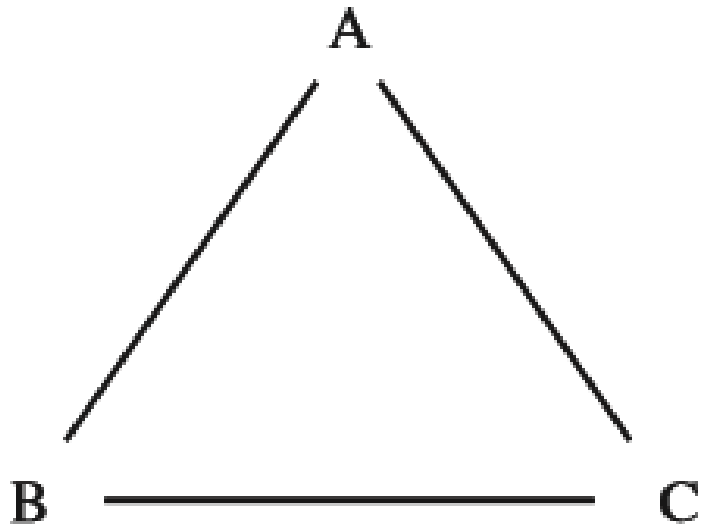
$$\delta^{AC} = \delta^{AB} + \delta^{BC}$$

- Show **desirable relationship** between direct and indirect sources of evidence for **single comparison**

Consistency

- Network with only two-arm trials

  Triangle of relationships with 3 (nontouching) solid edges



Consistency in 2 arm trials

- Each edge represents 1 or >2 arm trials comparing 2 treatments identified at either end of edge
- All 3 edges used same line style (solid line)
  -> There is no conflict (inconsistency)

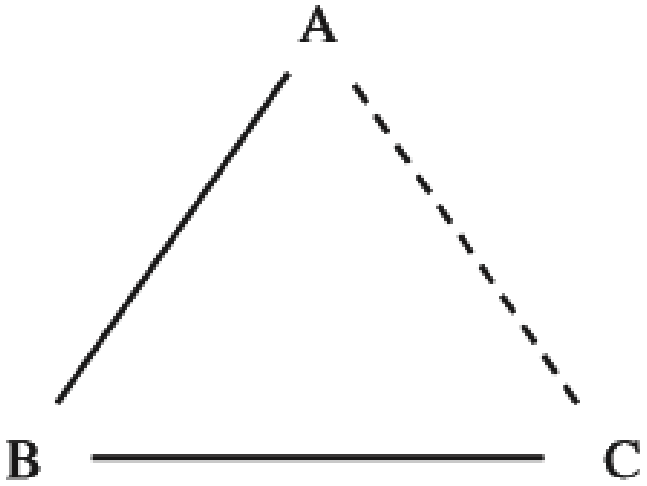
Concepts of heterogeneity and inconsistency

- Indirect comparisons
- Heterogeneity
- Consistency
- **Loop inconsistency**
- Multi-arm trials
- Design inconsistency
- Design-by-treatment interaction

Loop Consistency

Studies of different treatment comparisons
-> Different in ways that affect effect sizes

Drawing edges in different line styles



Evidence on direct comparison AC (dashed line) **conflicts with** evidence drawn via indirect comparison AB, BC (solid lines)

Loop inconsistency in 2 arm trials

Loop Consistency

- Occur only at least 3 separate sets of studies making different comparisons

  (For example, 'B–A', 'C–A' and 'C–B' studies)

Or

- When both indirect and direct estimates of effect size are available

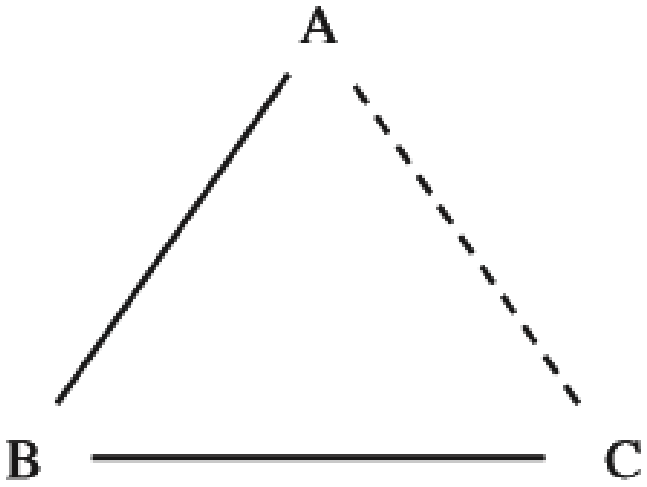
  (For example, when 'C–B' is measured both directly and via 'A' as indirect estimate)

Causes of Loop Consistency

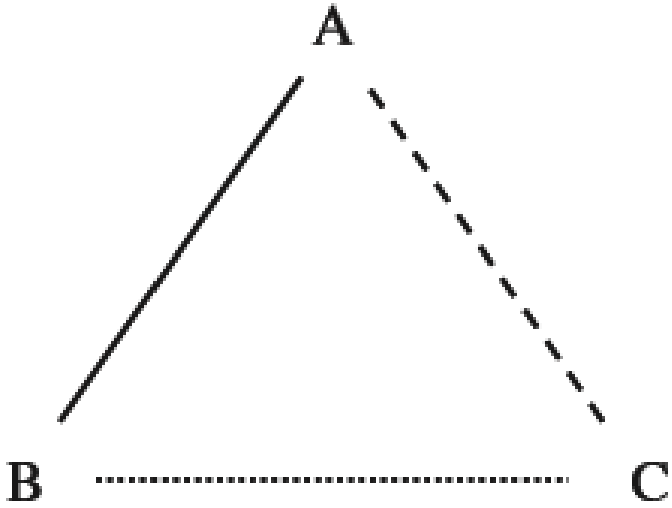
: Participants in head-to-head studies ‘C–A’ are **different** from studies ‘B–A’ and ‘C–B’ (Because they are contraindicated for treatment B)

: Versions of treatment B are different in studies ‘B–A’ and ‘C–B’ (Because of different doses) that are associated with magnitude of treatment effect -> Sum of ‘B–A’ and ‘C–B’ not equal to ‘C–A’

: Studies of different comparisons were different periods, different settings or different contexts (studies ‘C–B’ = recent but studies A = old historical standard)



Loop inconsistency in
2 arm trials



Loop inconsistency in
2 arm trials (Alternative)

- 3 edges could be drawn in 3 different line styles to indicate that different effect modifiers are associated with each edge in loop
- Difference cannot be tested statistically & have to be informed by expert judgement

Concepts of heterogeneity and inconsistency

- Indirect comparisons
- Heterogeneity
- Consistency
- Loop inconsistency
- **Multi-arm trials**
- Design inconsistency
- Design-by-treatment interaction

Multi-arm trials

- Studies with > 2 treatment arms
- Network of multi-arms trial may be **consistent**

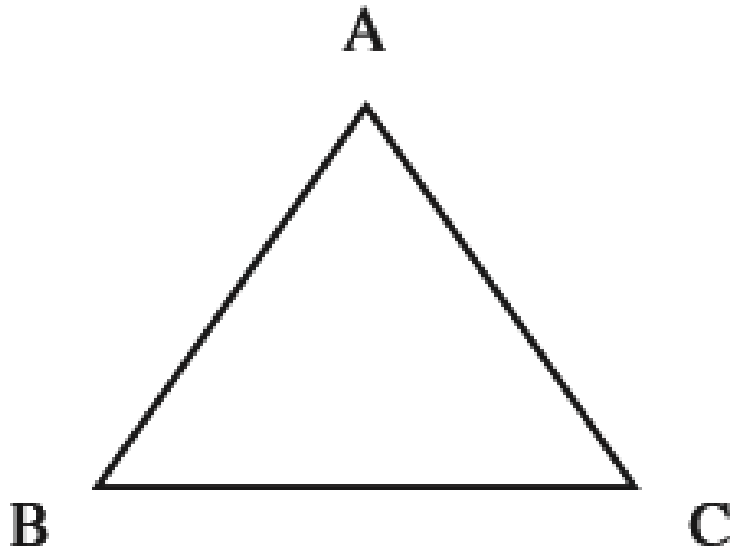
: By structurally (because all studies include all treatments) or…

: By observation (assumptions around equality of direct & various indirect comparisons hold across studies) or…

: Combination of both

Multi-arm trials

- Loop inconsistency cannot occur within multi-arm trial



Consistency is considered in 3 arms trials using closed (joined-up) polygon

Concepts of heterogeneity and inconsistency

- Indirect comparisons
- Heterogeneity
- Consistency
- Loop inconsistency
- Multi-arm trials
- **Design inconsistency**
- Design-by-treatment interaction

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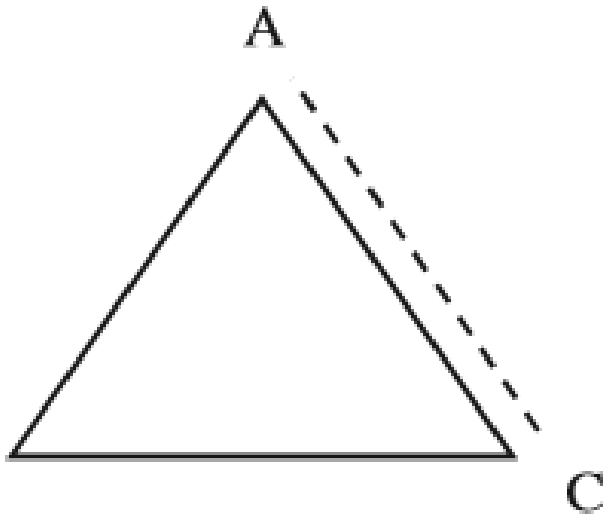
Design consistency

- 'Design' of a study = Set of treatments compared within study
- Design inconsistency = Differences in effect sizes between studies involving different sets of treatments
- Potential conflicts between study designs represented by different line styles



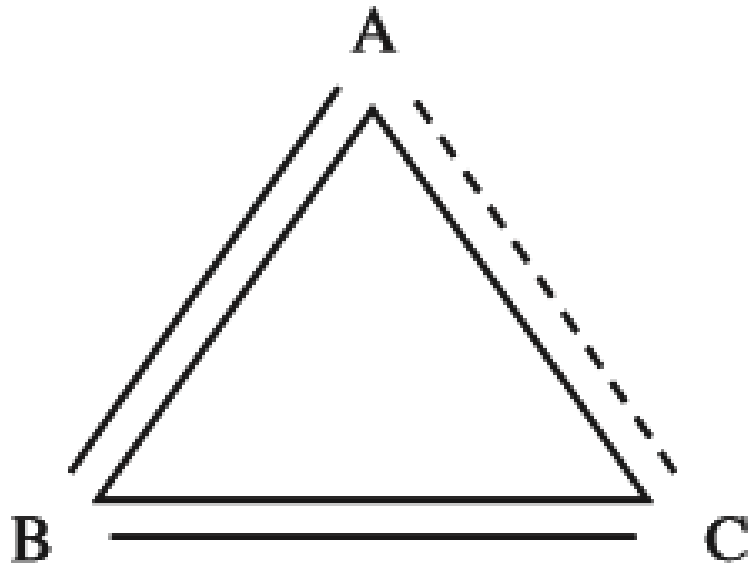
AC effect size in 3-arm trials (drawn as solid line) differs from 2-arm trials (drawn as dashed line)

Design consistency

When multi-arm trial is involved
: loop inconsistency in two-arm trials indicates design inconsistency

Because multi-arm trial must be internally consistent
-> difference between effect sizes from multi-arm trial

Design consistency

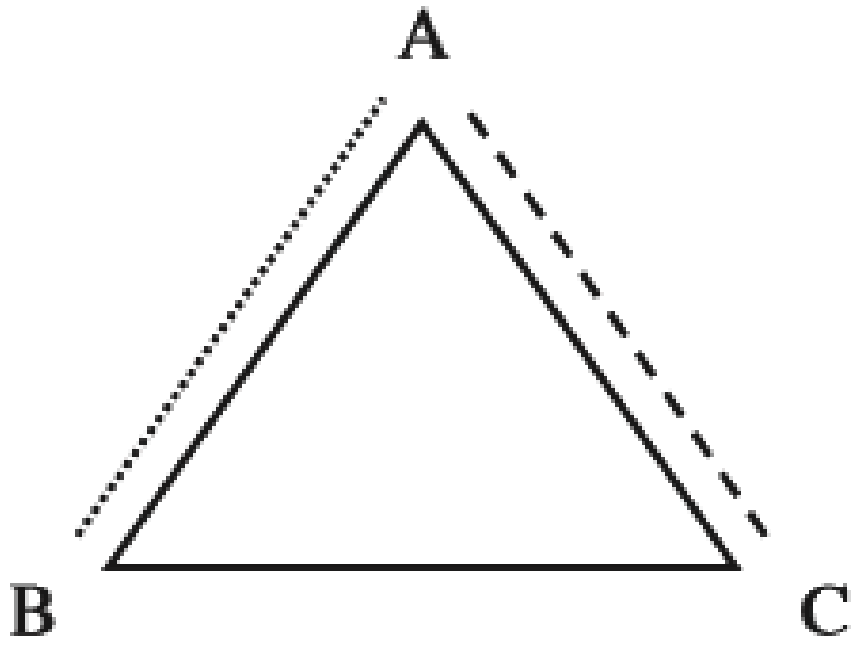


Design inconsistency and loop inconsistency

: Pairwise trials display loop inconsistency

whereas 3-arm trials conflicts with at least 1 pairwise trial reflecting design inconsistency

Design consistency

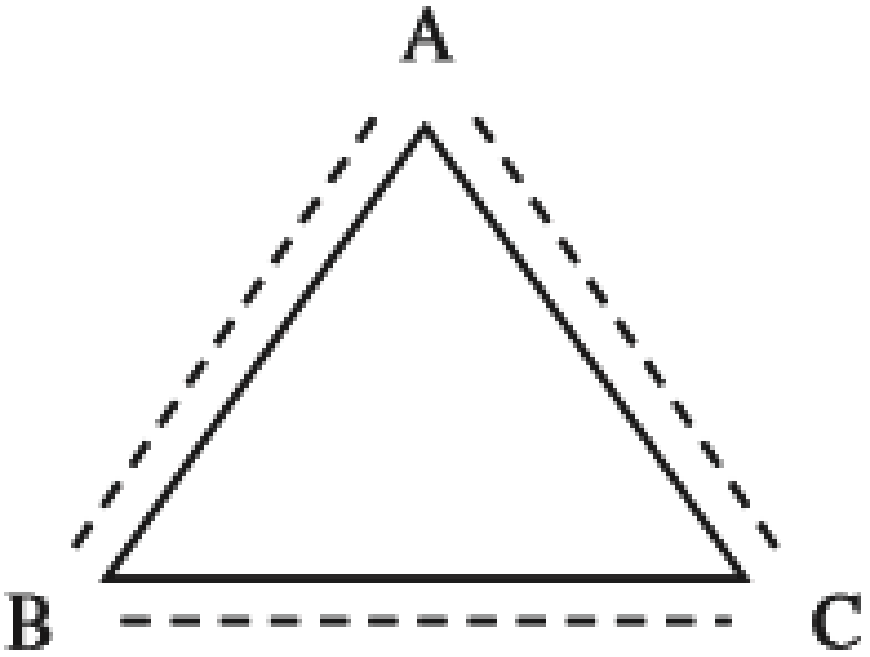


Design inconsistency with one 3-arm trial & two 2-arm trials

- Loop can be constructed by isolating BC comparison from 3-arm trial and comparing it with two-arm trials
- However, this ignores presence of consistent loop within 3-arm trials

-> unclear we should describe this network as displaying loop inconsistency

Design consistency



- Two-arm trials
  -> consistent among themselves, but effect sizes differ from those of multi-arm trial
- Does this display design inconsistency without loop inconsistency?

Design inconsistency without loop inconsistency?

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Concepts of heterogeneity and inconsistency

- Indirect comparisons
- Heterogeneity
- Consistency
- Loop inconsistency
- Multi-arm trials
- Design inconsistency
- **Design-by-treatment interaction**

Design-by-treatment interaction

- Loop inconsistency reflects important question of whether direct and indirect evidence agree with each other
- Design inconsistency reflects less substantive interest question; particular choice of treatments in study is associated with different effect sizes for particular contrasts

Presence of multi-arm trials, distinction between two types is difficult

Design-by-treatment interaction

- Meta-regression approach for design inconsistency
- Method describes by Lu and Ades for loop inconsistency
- We argue case for statistical model that encompasses both types of inconsistency
- This is a model that includes the full set of design-by-treatment interaction terms

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Outline of talks

- Introduction
- Concepts of heterogeneity and inconsistency
- **Models for inconsistency**
- Discussion and Conclusion

Models for inconsistency

- **Design-by-treatment interaction model**
- Lumley model
- The Lu–Ades model

Design-by-treatment interaction model

- Full model for design-by-treatment interaction

  J=A, B, ... index treatments

  d=1, ... index designs

  i=1, ... index studies

Consider parameter μ_{di}^{AJ} reflect treatment effect

compare treatment J with reference treatment A in study i

Model for treatment effect parameters: not necessary for treatment A to have been included in every study

$$\mu_{di}^{AJ} = \delta^{AJ} + \beta_{di}^{AJ} + \omega_{d}^{AJ},$$

$$\mu_{di}^{AJ} = \delta^{AJ} + \beta_{di}^{AJ} + \omega_{d}^{AJ},$$

- Where δ^{AJ} is fixed effect of treatment J relative to A

- β_{di}^{AJ} is study-by-treatment interaction term to reflect standard heterogeneity
  (variability in treatment effects for comparison AJ, within studies of design d)

- ω_{d}^{AJ} is design-by-treatment interaction term to reflect inconsistency (variability between designs)

$$\mu_{di}^{AJ} = \delta^{AJ} + \beta_{di}^{AJ} + \omega_{d}^{AJ},$$

- This model has largest number of degrees of freedom (d.f.) among models allowing for both loop and design inconsistency

- Inconsistency parameter ω_{d}^{AJ} describes perturbation in AJ comparison in specific study design D

Design-by-treatment interaction model

- Prefer fixed effects because…..

: Common distribution assumption in random-effects formulation is impossible

: Facilitates straightforward test of null hypothesis of consistency throughout network of comparisons

: Easier and less sensitive to reparameterization

: There are often too few inconsistency parameters for random-effects model to produce reliable inferences on random-effects variance parameter

Design-by-treatment interaction model

Disadvantage of fixed-effects approach

: Constraints are required on ω_d^{AJ} terms in order to avoid over-parameterization

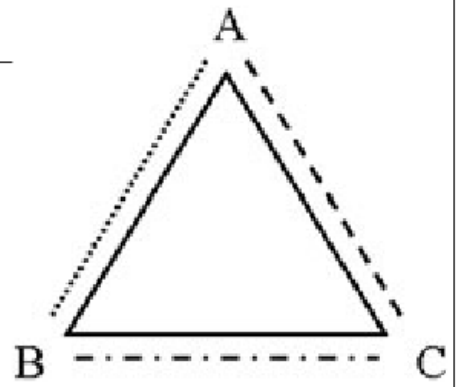
-> Interpretation of δ^{AJ} parameters is not straightforward depends on parameterization of model

Design-by-treatment interaction model

- Example, Network with 4 designs AB, AC, BC and ABC

Table 1. Design-by-treatment interaction model for three treatments (all possible designs). Heterogeneity terms have been omitted.

Design	A	B	C
ABC	Ref	δ^{AB}	δ^{AC}
AB	Ref	$\delta^{AB} + \omega_2^{AB}$	—
AC	Ref	—	$\delta^{AC} + \omega_3^{AC}$
BC	Ref	δ^{AB}	$\delta^{AC} + \omega_4^{AC}$



: This network has potential for 3 conflicts & has 3 d.f. for inconsistency

: Reflected 4 different line styles

Design-by-treatment interaction model

Three potential conflicts may be parameterized as follows:

- Difference in 'B–A' effects between AB and ABC studies ω_2^{AB}
- Difference in 'C–A' effects between AC and ABC studies ω_3^{AC}
- Difference in 'C–B' effects between BC and ABC studies which could be placed on either treatment B or C

(we adopt convention of placing it on last of such possibilities ω_4^{AC})

For example, following separates out parameter to represent loop inconsistency

: Loop inconsistency in two-arm trials, by contrasting direct evidence 'B–A' in AB studies with indirect evidence involving 'C–A' from AC studies and 'C–B' from BC studies

$$\omega^{(1)} = \left(\delta^{AB} + \omega_2^{AB}\right) - \left(\left[\delta^{AC} + \omega_3^{AC}\right] - \left[\left(\delta^{AC} + \omega_4^{AC}\right) - \delta^{AB}\right]\right) = \omega_2^{AB} - \omega_3^{AC} + \omega_4^{AC}$$

: Design inconsistency, by contrasting 'B–A' effects between AB and ABC studies

$$\omega^{(2)} = \omega_2^{AB}$$

: Design inconsistency, by contrasting 'C–A' effects between AC and ABC studies

$$\omega^{(3)} = \omega_3^{AC}$$

Models for inconsistency

- Design-by-treatment interaction model
- **Lumley model**
- The Lu–Ades model

Lumley model

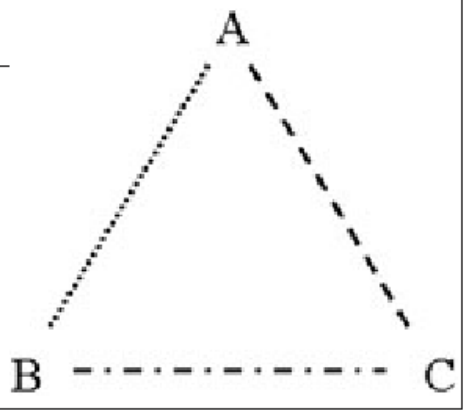
- Full design-by-treatment interaction model proposed by Lumley in 2002
- Inconsistency factors follow random-effects distribution
- **However,** model was constructed **only for two-arm trials**, & not extension to multi-arm trials

Lumley's model for simple network of 3 pairwise comparisons

Table 2. Lumley model for three treatments (applicable only to two-arm trials).

Design	A	B	C
AB	Ref	$\delta^{AB} + \omega_1$	—
AC	Ref	—	$\delta^{AC} + \omega_2$
BC	Ref	δ^{AB}	$\delta^{AC} + \omega_3$

Assumption for inconsistency factors: $\omega_d \sim N(0, \sigma_\omega^2)$



- Network of only pairwise studies

-> Inconsistency parameters viewed as being clearly to specific pairwise comparisons

- Design-by-treatment interaction model present only 1 inconsistency factor for data set

Models for inconsistency

- Design-by-treatment interaction model
- Lumley model
- **The Lu–Ades model**

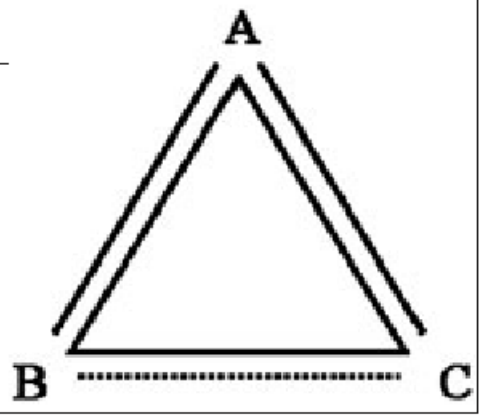
The Lu–Ades model

Described by Lu and Ades (2006)

- Motivated primarily by loop inconsistency
- One inconsistency parameter is added for each independent closed loop in evidence network
  (not including loops created only by multi-arm trials)

Table 3. Lu and Ades model for three treatments with order *A*, *B*, *C* (all possible designs).

Design	A	B	C
ABC	Ref	δ^{AB}	δ^{AC}
AB	Ref	δ^{AB}	—
AC	Ref	—	δ^{AC}
BC	Ref	δ^{AB}	$\delta^{AC}+\omega^{AC}$



The Lu–Ades model

- Not guarantee that all possible independent closed loops are identified
- Lu and Ades ensured that they include all closed loops

: by careful selection of modelled treatment contrasts from multi-arm trial

- For example

: There are AB, AC and ABC studies

: Ensured that BC contrast is among two modelled contrasts from ABC study

[because it forms closed loop with two-arm studies]

The Lu–Ades model

Contains subset of inconsistency parameters from design-by-treatment interaction model

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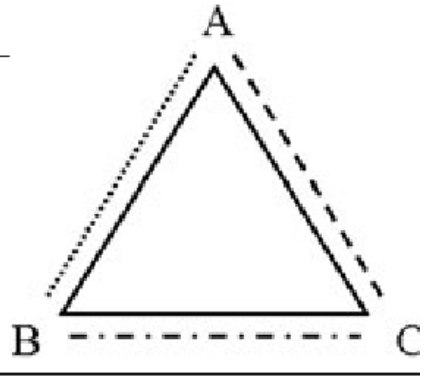

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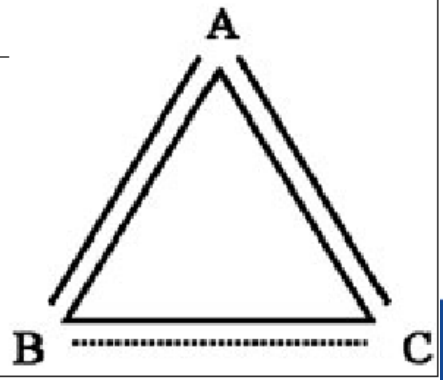

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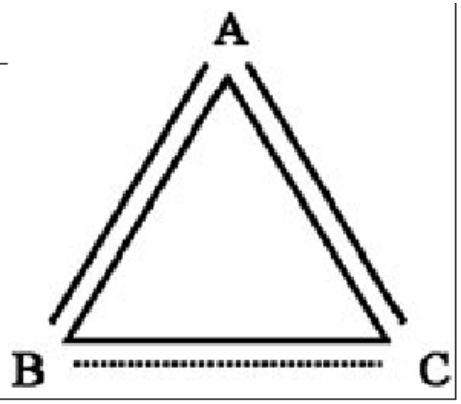

- Model assumptions in choice of treatment as follows:

: All studies containing treatment A are assumed to estimate same treatment effects

: All studies containing treatment B but not treatment A are assumed to estimate same treatment effects

: All studies containing treatment C but not treatment A or treatment B are assumed to estimate same treatment effects

Although basing on loop inconsistency model, but

- Lu and Ades model depends on choice of baseline treatment to which all other treatments are compared (treatment A)

Table 3. Lu and Ades model for three treatments with order *A*, *B*, *C* (all possible designs).

Design	A	B	C
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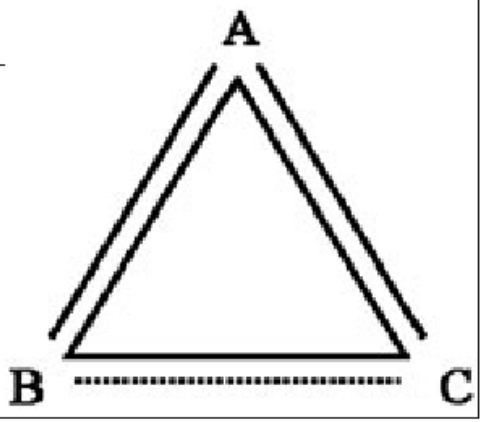
AB	Ref	δ^{AB}	—
AC	Ref	—	δ^{AC}
BC	Ref	δ^{AB}	$\delta^{AC}+\omega^{AC}$



Outline of talks

- Introduction
- Concepts of heterogeneity and inconsistency
- Models for inconsistency
- **Discussion**

Discussion and Conclusion

- Propose design-by-treatment interaction models to identify inconsistency in NMA
- Propose more complex methods for illustrating evidence networks in multi-arm studies
- Evidence inconsistency is impossible within multi-arm study

-> Loop inconsistency is difficult when there is mixture of two-arm and multi-arm studies

Discussion and Conclusion

Design-by-treatment approach

- Integrates idea of loop inconsistency with possibility of design inconsistency
- Only way to avoid arbitrary modelling constraints in NMA

- Design-by-treatment interaction models requires careful evaluation in practice

Discussion and Conclusion

Major concern about validity of NMA

: Possibility of loop inconsistency

: Attention to differences due to design
(choice of treatments included in studies)

: Presence or absence of other treatment arms in individual trials
: Complexity and loss in power in statistical tests involved
(differences across designs -> low likelihood of finding important conflicts)

Discussion and Conclusion

If inconsistency is identified in network

Q: What is the best strategy to proceed? -> **Remain unclear**

<u>Strategies for addressing inconsistency</u>

: Removing portions of evidence network

: Splitting nodes in network
(> 2 different treatments replace what was previously included as single treatment)

: Using study-level or individual-level covariates

: Seeking relevant inferences to presence of inconsistency

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Thank you for your comments