Mixed Treatment Comparisons in Revision

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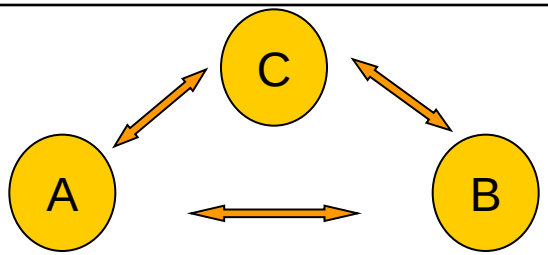
Direct and Indirect Evidence



- We want to compare treatments A and B.

Clinical trials comparing A and B — Direct Evidence to compare A and B

Clinical trials comparing A and C — Indirect Evidence to compare A and B

Clinical trials comparing B and C — Indirect Evidence to compare A and B

- In both cases we can use meta-analysis.

Should we use indirect evidence?

It is a controversial question. Today it seems consensus that indirect evidence should be used when:

- Direct evidence is not available.
  Example: comparisons of two active drugs are not as usual as placebo controlled trials.

- Direct evidence exist but is not enough to prove superiority of one treatment over another.

If indirect evidence provides evidence it seems improper to exclude them.

What is Mixed Treatment Comparison (MTC)?

- The MTC models were proposed by Lu and Ades (Statistics in Medicine, 2004).
- Also known as Network Meta-analysis.
- It is an extension of the traditional meta-analysis methodology that combines direct and indirect evidence.
- The structures are analogous to incomplete block designs (imagine if every trial included every treatment and some arms are missing at random).
- It is a Bayesian Model. Results can be obtained using the Winbugs Package. It is important to have a help from a person that knows about Bayesian statistics and modelling.

Motivation

The potential of the use of MTC methods in HTA has been recognized in various countries as demonstrated by increasing number of published studies.

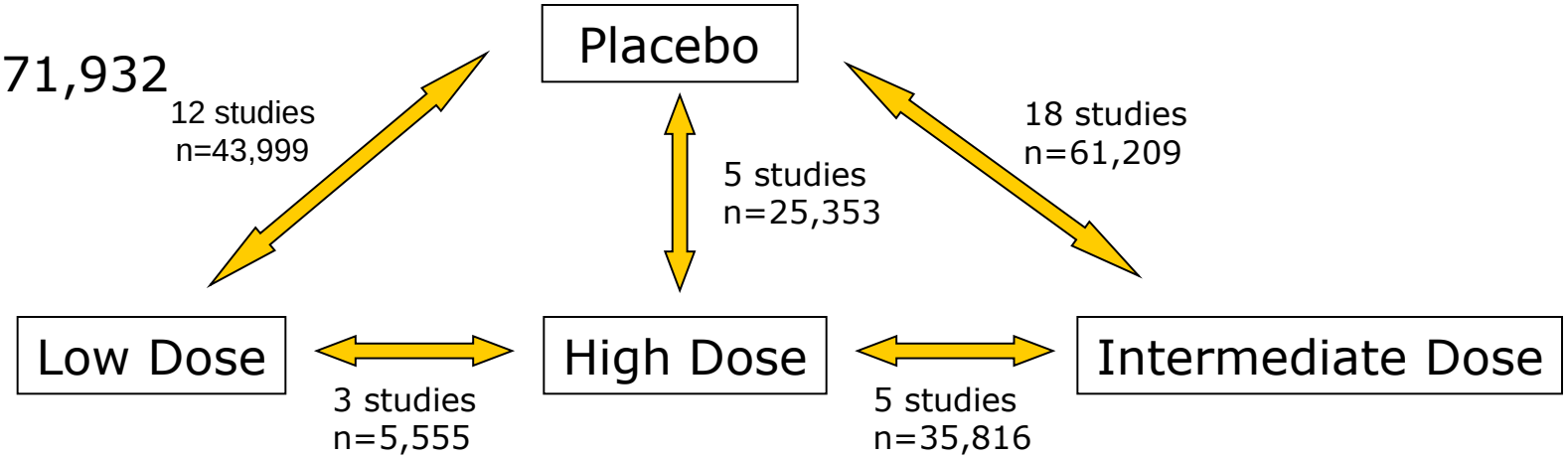
MTC methods were developed under the Bayesian statistical approach and have been presented mainly to a statistical methods audience.

Objective

To disseminate Bayesian MTC methods and assist researchers and decision-makers in understanding the key characteristics of this new methodology.

Case Study

- Data from clinical trials comparing 4 treatments: placebo, low, intermediate and high dose of statin.
- Systematic review conducted in Pubmed and Cochrane.
- Outcome: myocardial infarction.
- Effect size measure: Relative Risk.
- 43 studies
- n = 171,932



Model Assumptions

- Homogeneity: the same ideas as for standard meta-analysis.

  For example, the homogeneity among low x Placebo trial should be verified (Random x Fixed Effect Models).

- Similarity: the same ideas as for pairwise indirect analysis.

  For example, (Low x Placebo) and (High x Placebo) should be similar in clinical and methodological aspects since they estimate (Low x High).

- Consistency: key assumption for MTC.

  Direct evidence = Indirect evidence

Basic Ideas

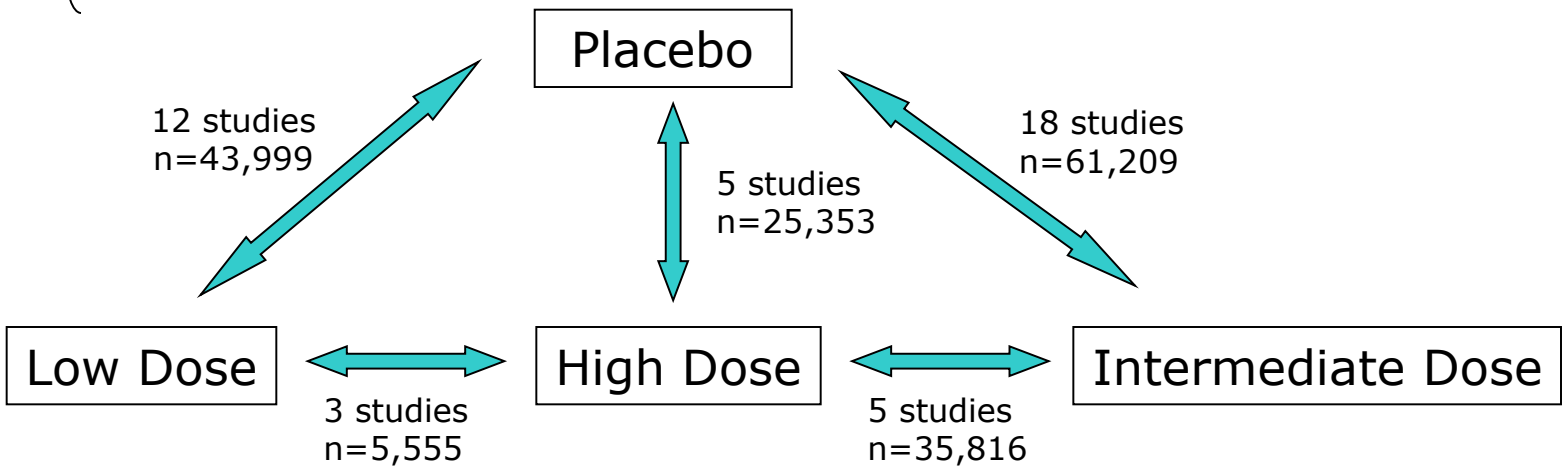
- MTC evaluates a single consistent summary for each pairwise comparison.

- The MTC point estimate is a weighted average between the direct estimate and the indirect estimate.

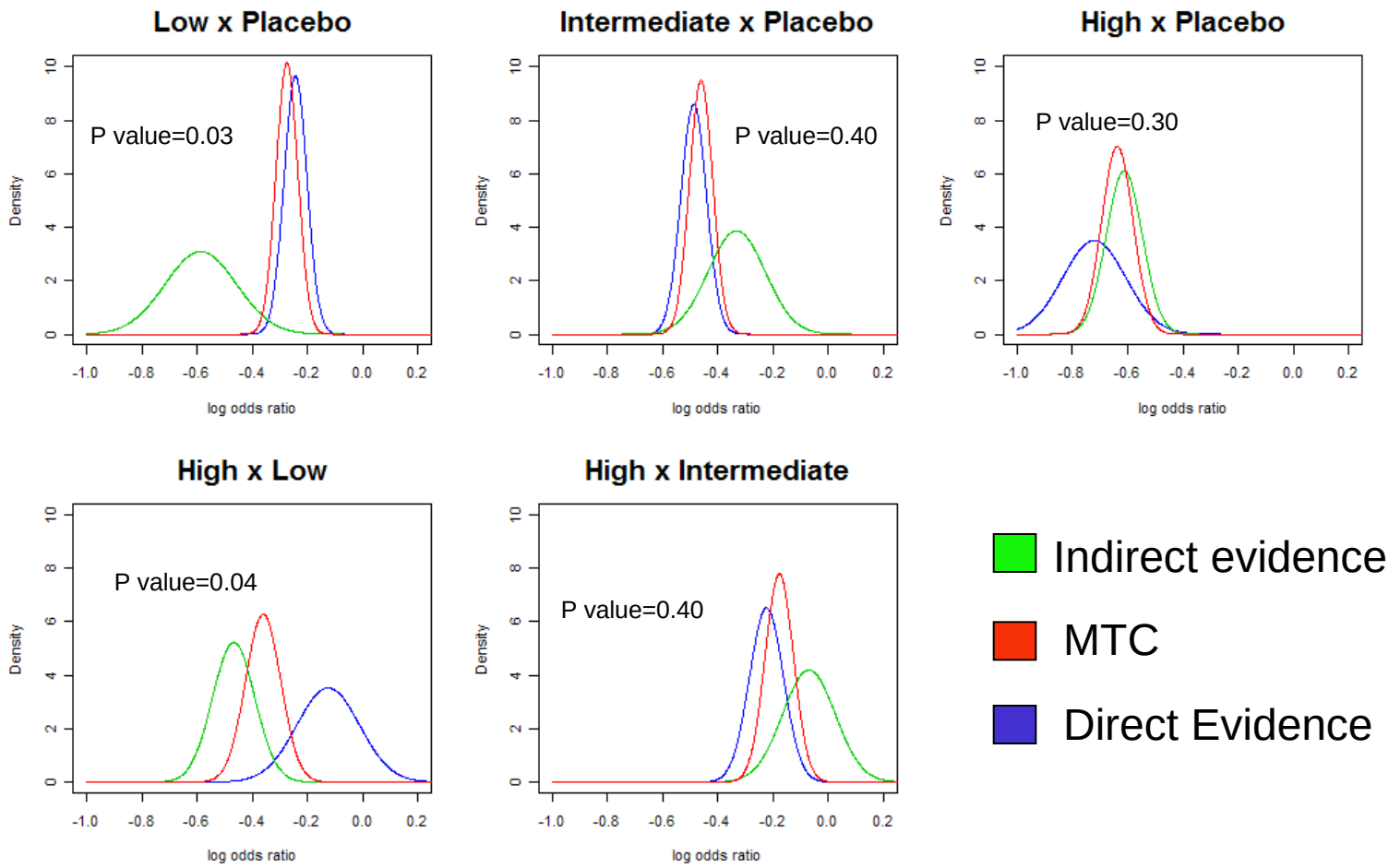
- The indirect evidence is a result from all network of evidences.

Example: High x Low Dose

- Direct: High x Low
- Indirect:
  - High x Placebo
    - Direct: High x Placebo
    - Indirect:
      - High x Low
      - Placebo x Low
    - Indirect:
      - High x Intermediate
      - Placebo x Intermediate
  - Low x Placebo ...



Consistency



Split node method: proposed by Dias et all (statistics in Medicine 2010).

Why we should care about consistency

- Because the MTC model will produce an estimate which is a weighted average between the direct estimate and the indirect estimate.

- If the two information are inconsistent this average has no meaning.

Results

The weight is proportional to the sample size.

Treatments	Sample Size	Relative Risk Direct Evidence	Relative Risk Indirect Evidence	Relative Risk MTC
Low X Placebo	n=43,999	0.79 (0.73, 0.85)	0.61 (0.48, 0.77)	0.77 (0.70, 0.84)
Intermediate X Placebo	n=61,209	0.64 (0.58, 0.69)	0.69 (0.58, 0.82)	0.65 (0.59, 0.71)
High X Placebo	n=25,353	0.50 (0.40, 0.62)	0.92 (0.77, 1.10)	0.86 (0.79, 0.93)
High X Intermediate	n=19,255	0.85 (0.78, 0.92)	0.92 (0.77, 1.10)	0.86 (0.79, 0.93)
High X Low	n=5,555	0.88 (0.70, 1.08)	0.67(0.59, 0.76)	0.72 (0.64, 0.82)
Intermediate X Low			0.83 (0.75, 0.93)	0.83 (0.75, 0.93)

Note: direct and indirect evidence was obtained through split node method.

Results

Considering the same sample size the weight for indirect evidence is smaller.

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Results

In the absence of inconsistency the precision of MTC results are usually higher

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Results

Using MTC we can calculate the probability that each treatment is best.

The estimates of those probabilities are shown in the table bellow.

Treatment	Placebo	Low Dose	Intermediate Dose	High Dose
Posterior probability	0	0.0001	0.0011	0.9988

Discussion

- When more than two treatments are being compared it is common that pairwise comparisons for all of them are not available.

- If we want to use all evidence available to compare two treatments, the indirect evidence should always be considered since it can add important information.

- The MTC model is a flexible model that combines direct and indirect evidence and it is a single model that explain all the network of evidence.

Discussion

- Consistency should be checked since it can mislead the results.

- MTC models can incorporate trials with more than two arms of treatments and study level covariates.

- Meta-analysis results are commonly used in cost effectiveness analysis and the posterior distributions obtained through Bayesian methodology are the natural inputs for those analyses.

Main References

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Thanks

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