A Look Into The Methods: Merits and Limits of Meta-analysis

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Disclosures

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What Is A Meta-analysis?

A statistical technique to quantitatively synthesize summary data from several related studies

<table>
<thead>
<tr>
<th>Advantages</th>
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<tr>
<td>❑ Combining studies “increases” sample size, precision</td>
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<tr>
<td>❑ Power to uncover <strong>trends</strong> across studies</td>
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<table>
<thead>
<tr>
<th>Disadvantages</th>
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<tr>
<td>❑ Limited to published summary data</td>
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<tr>
<td>❑ Inappropriate pooling and summary of heterogenous studies</td>
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<tr>
<td>❑ Only suggests association, does not prove a hypothesis</td>
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Meta-analyses Increasing Exponentially

PubMed search of the word “meta-analysis” returned 154727 hits Jan 9, 2019

Meta-analysis have gained popularity as an easy tool to help synthesize data Jan 9, 2019
Two Types of Statistical Models Used

One Fixed Effect
- One fixed treatment effect across all studies
- Not appropriate when studies are culled from literature review

Random Effects
- Effects change from study to study
- Reflects different study designs, populations, and treatments
- Focus is on an overall treatment effect
Random Effects Meta-analysis: Assumptions Matter

- Treatment effects follow a bell-shaped curve, also called a Gaussian or normal curve.

- Unfortunately, this assumption is **frequently violated** in meta-analyses.

- Example: for Katsanos et al. (2018) two-year data, reject sample log-relative risks are normal ($p=0.028$).
Katsanos et al. Two-year Data: Data vs. Assumptions

- Katsanos et al. meta analysis uses free “meta” software package set to defaults
- Assumes normality of treatment effects; doubtful based on plot & p=0.028
- Also uses method that underestimates between-study variability dating to 1980’s
- Intervals and p-values too small!
- Using correct tool changes results
Re-analysis of Two- and Five-year Data

Two-year data
- Normal model overall  RR = 1.72 (1.12,2.73),  p=0.02
- Non-normal model    RR = 1.73 (0.87,3.59),  p=0.14

Five-year data
- Normal model overall  RR = 1.82 (0.92,3.61),  p=0.09
- Non-normal model    RR = 1.82 (0.51,6.59),  p=0.36

Re-analysis shows no significant difference for one-, two-, & five-year follow-up.

Trend persists, but urgency diminishes.
Meta-analysis can show association, not causation. That’s what RCTs are for.
Association is NOT Causation

Risk Difference vs. PTX Exposure

\[ \text{Exposure}_i = \text{Dose}_i (\pi \times D_{i} \times \text{Length}_i) \times \text{Time}_i \]

Risk Difference vs. Hypertension

\[ \text{Exposure}_i = \text{Hypertension}_i \times \text{Time}_i \]

1. Katsanos K, et al., J Am Heart Assoc 2018;7:e011245. DOI: 10.1161/JAHA.118.011245
Association is NOT Causation

Risk Difference vs. PTX Exposure

\[ \text{Exposure}_i = \text{Dose}_i (\pi \times D_i \times \text{Length}_i) \times \text{Time}_i \]

Risk Difference vs. # Letters in Study Title

\[ \text{Exposure}_i = \# \text{Letters}_i \times \text{Time}_i \]

Study Name | # Letters
---|---
FAIR | 4
LEVANT II | 9
BATTLE | 6
IN.PACT SFA | 11
THUNDER | 7
ISAR-PEBIS | 10

1. Katsanos K, et al., J Am Heart Assoc 2018;7:e011245. DOI: 10.1161/JAHA.118.011245
Conclusions

- Understand and check assumptions going into model. Use tools *appropriately*.

- Results change using correct methodology!

- Meta-analysis simply averages study-effects; suggests *associations* to examine more carefully with patient-level data or new randomized trial.

- In presentations to follow, patient-level analyses will give much clearer understanding of paclitaxel and mortality.
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