

Methods for IPD meta-analysis

A methodological overview

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Meta-analysis

Summarizing published aggregate data (AD) is often challenged:

- Difficult to harmonize variable definitions
- Difficult to harmonize in- and exclusion criteria
- Difficult to combine studies with different follow-up times
- Difficult to adjust for study-specific biases
- Difficult to explore sources of between-study heterogeneity (e.g. due to treatment-covariate interactions)

Researchers therefore increasingly embark in an Individual Participant Data Meta-Analysis (IPD-MA). Methodological guidance is warranted!

A review of methodology for IPD-MA

- Search strategy
 - English articles in MedLine, EMBASE, selected set of journals
 - Addressing IPD-MA issues in intervention research
 - Statistical models
 - Simulation studies
 - Empirical comparisons
 - Didactic or Guidelines
- Results
 - 3360 unique records found eligible for screening
 - 153 studies included in this review

Two-stage IPD-MA

Analyze each dataset separately and summarize the results

- Advantages
 - Relatively simple to perform
 - Does not borrow information **across** studies when estimating effect sizes **within** a particular study
- Disadvantages
 - Poor power: non-linear associations & interactions
 - Problematic in small samples, different follow-up times, recurrent events

One-stage IPD-MA

Analyze all IPD in a single statistical model

- Advantages
 - Increased power due to borrowing of information **across** studies
 - Increased flexibility (e.g. interaction terms)
- Disadvantages
 - Requires substantial statistical expertise
 - Requires additional assumptions

The one-stage approach is typically considered as gold standard due to its increased flexibility

Investigation of heterogeneity in treatment effect

- Investigation of study-level characteristics
 - Account for risk of bias, study design, ...
 - Meta-regression, subgroup analysis
- Investigation of participant-level characteristics
 - Avoid ecological fallacy and improve power to detect effect modification
 - Disentangle study-level interaction from participant-level interaction
 - Danger for data dredging and overparameterization
 - Expert opinion
 - Publication of a study protocol (before undertaking the IPD-MA)

Combining IPD and AD

Avoid bias and increase statistical power

- Two-stage approaches
 - Reduce available IPD to AD and then perform an AD-MA
 - Risk of ecological bias in the presence of effect modification!
- One-stage approaches
 - Reconstruct IPD using 2 by 2 tables (information on covariates lost)
 - Hierarchical Related Regression (shared parameter models)

Network Meta-Analysis (mixed treatment comparisons)

- Summarize evidence from multiple treatment comparisons
 - Compare treatments for which no head-to-head trials exist
 - Rank treatments by efficacy or safety
- Concerns
 - Model assumptions
 - Model complexity
 - Network (in)consistency
- IPD access may help to resolve important concerns (cfr. talk C29)

Cross-design synthesis

Combine IPD from randomized and non-randomized studies

- Potential advantages
 - Increased sample size
 - Increased variability in inclusion criteria, follow-up information, undergone treatments, treatment patterns, the presence of co-morbidities and co-medication -> generalizability of research findings
- Challenges
 - Risk of bias & confounding
 - Harmonization between data sources
 - Transparency of synthesis methods

Missing data

- Two-stage imputation
 - Impute each data set separately to account for heterogeneity
 - Problematic when some important variables have not been measured within all studies
- One-stage imputation
 - Single model to impute all data
 - Requires advanced statistical expertise

Concluding remarks

- Access to IPD offers numerous advantages
- However ...
 - IPD is still prone to several forms of bias
 - IPD is no panacea against poorly designed and conducted primary research
 - Combining IPD from multiple studies requires additional efforts and statistical expertise

Resources

Tutorial

Research Synthesis Methods

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Get real in individual participant data (IPD) meta-analysis: a review of the methodology

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Individual participant data (IPD) meta-analysis is an increasingly used approach for synthesizing and investigating treatment effect estimates. Over the past few years, numerous methods for conducting an IPD meta-analysis (IPD-MA) have been proposed, often making different assumptions and modeling choices while addressing a similar research question. We conducted a literature review to provide an overview of methods for performing an IPD-MA using evidence from clinical trials or non-randomized studies when investigating treatment efficacy. With this review, we aim to assist researchers in choosing the appropriate methods and provide recommendations on their implementation when planning and conducting an IPD-MA. © 2015 The Authors. *Research Synthesis Methods* published by John Wiley & Sons, Ltd.



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