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Epidemiology and Big Data (INFOMEBD)

Outline of this presentation

- Principles of IPD meta-analysis
- Performing subgroup analysis

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Principles of IPD meta-analysis

Data structure IPD meta-analysis

Example of individual participant data from 10 hypertension trials that assess effect of treatment versus placebo on systolic blood pressure

Study ID	Patient ID	Age (years)	Sex (1=male, 0=female)	Treatment group (1=treatment, 0=control)	Systolic blood pressure before treatment (mm Hg)	Systolic blood pressure after treatment (mm Hg)
1	1	46	1	1	137	111
1	2	35	1	0	143	133
...	...	...	...	...	...	...
1	1520	62	0	0	209	219
2	1	55	0	1	170	155
2	2	38	1	1	144	139
...	...	...	...	...	...	...
2	368	44	1	0	153	129
3	1	51	1	1	186	166
3	2	39	0	1	201	144
...	...	...	...	...	...	...
3	671	54	0	0	166	141
...	...	...	...	...	...	...
10	1	71	0	1	149	128
10	2	59	1	0	168	169
...	...	...	...	...	...	...
10	978	63	0	1	174	128

Dotted line indicates where non-displayed rows of data occur.

Hypothetical data based on Wang et al.[27]

Key feature IPD

- IPD collected in different studies with likely differences in protocol, population, study features, interventions, outcomes

- Analysing the IPD as if from a single trial ignores these differences. Consequences:
  - differences in pooled estimates
  - differences in precision
  - no insight in heterogeneity of results between studies

Main approaches in IPD meta-analysis

first analyze the studies separately then all together

- Take clustering of data into account through:
  - two stage approach
  - one stage approach

- Two stage: analyze each study separately and then combine results using traditional meta-analytical approaches

- One stage: analyze the individual data of all studies combined with a single model, but take clustering into account

2-stage IPD meta-analysis: Principles

- Stage 1: Estimate the effect estimate of interest and its precision (standard error) in each trial like odds ratio, relative risk, hazard ratio, mean difference
- Stage 2: calculate pooled (weighted) effect estimate across studies using traditional methods (fixed or random effects model)
- Statistical output looks similar to aggregate data meta-analysis
- Display individual results and summary measure in forest plot

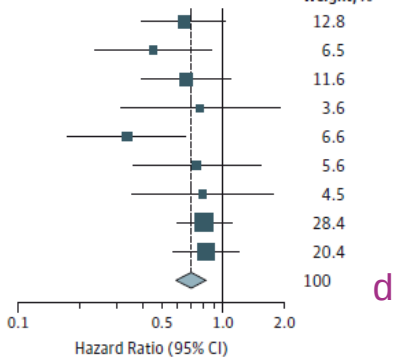
Simmonds et al. Meta-Analysis of individual patient data from Randomized Trials: A review of methods used in practice. Clinical Trials 2005:2;209-17.

2 stage IPD meta-analysis

Figure 2. Random Effects Meta-analyses Comparing Mindfulness-Based Cognitive Therapy (MBCT) With Other Variables

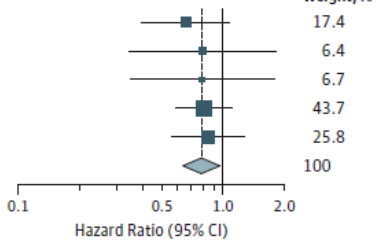
A MBCT vs no MBCT

Study	Hazard Ratio (95% CI)	Weight, %
Teasdale et al,[7] 2000	0.64 (0.40-1.03)	12.8
Ma and Teasdale,[6] 2004	0.45 (0.23-0.88)	6.5
Kuyken et al,[13] 2008	0.66 (0.40-1.08)	11.6
Bondolfi et al,[15] 2010	0.77 (0.31-1.90)	3.6
Godfrin and van Heeringen,[17] 2010	0.34 (0.17-0.66)	6.6
Segal et al,[18] 2010	0.74 (0.36-1.52)	5.6
Huijbers et al,[19] 2015	0.80 (0.36-1.78)	4.5
Kuyken et al,[21] 2015	0.81 (0.59-1.10)	28.4
Williams et al,[23] 2014	0.82 (0.57-1.20)	20.4
Overall (I^2 = 1.7%, P = .42)	0.69 (0.58-0.82)	100



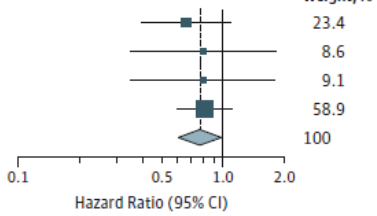
B MBCT vs any active treatment

Study	Hazard Ratio (95% CI)	Weight, %
Kuyken et al,[13] 2008	0.66 (0.40-1.08)	17.4
Segal et al,[18] 2010	0.80 (0.35-1.82)	6.4
Huijbers et al,[19] 2015	0.80 (0.36-1.78)	6.7
Kuyken et al,[21] 2015	0.81 (0.59-1.11)	43.7
Williams et al,[23] 2014	0.85 (0.56-1.28)	25.8
Overall (I^2 = 0.0%, P = .96)	0.79 (0.64-0.97)	100



C MBCT vs antidepressants

Study	Hazard Ratio (95% CI)	Weight, %
Kuyken et al,[13] 2008	0.66 (0.40-1.08)	23.4
Segal et al,[18] 2010	0.80 (0.35-1.82)	8.6
Huijbers et al,[19] 2015	0.80 (0.36-1.78)	9.1
Kuyken et al,[21] 2015	0.81 (0.59-1.11)	58.9
Overall (I^2 = 0.0%, P = .92)	0.77 (0.60-0.98)	100



Forest plot of 2-stage meta-analysis of aggregate data on hazard ratio scale comparing (A) risk of relapse of depression in participants receiving MBCT with participants not receiving MBCT; (B) risk of relapse of depression in participants receiving MBCT with participants receiving an alternative active therapy; and (C) risk of relapse of depression in participants receiving MBCT with participants receiving antidepressant medication. Weights are from random effects analyses.

shows results of individual studies with ratio for each study

diamond showing results over all studies

IPD allows all to calculate all measures in standardized way before including all studies

2-stage IPD meta-analysis

- Benefits:
  - intuitive and straightforward approach
  - apply standard approaches for meta-analysis
  - similar measures, output & presentation
  - through forest plots: insight in heterogeneity
  - combination of IPD and AD technically straightforward
- Limitations:
  - potential for bias with few studies and/or few events per study
  - less flexible & power when examining patient- and study-level modifiers
  - survival data & prediction data

analyzing separately can cause bias

1-stage IPD meta-analysis: Principles

- Single regression model taking clustering within studies into account
- Various names: multilevel models, hierarchical models, mixed effects models

including random effects again

- Can explore simultaneously impact of trial and patient characteristics on treatment effect
- Requires greater statistical expertise
- Output will look different
- Results as in original studies:
  - RD, RR, OR, mean difference

directly measuring effect measures of interest while taking clustering into account

1- vs. 2-stage IPD meta-analysis

simpler statistics

- 2-stage more common, but 1-stage increasing
- 1- and 2-stage frequently give similar results
- 1-stage can provide greater flexibility and power when examining interactions and non-linear relationships with outcomes
- Sometimes 2-stage can be biased when having few and/or small studies

because it doesn't take the weight or number of participants into account?

- 1-stage more complex and more choices during modelling
- 2-stage analysis a useful addition to 1-stage and vice versa

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IPD Review Benefits: Subgroup Analysis

Variation in treatment effect (single trial)

- Trials typically focus on the average effect
- Clinical intuition/experience: some patients benefit more than average
- Does the intervention effect vary by subgroups?
- Such variation is known as interaction by statisticians and as effect modification by epidemiologists

Variation in treatment effects (across studies)

- Many potential factors may cause variation in the effect
- Two main types of factors:
  - Patient factors: factors measured at patient level, values differ between patients
  - Study factors: factors measured at study level, same value for patients within studies, different between studies e.g. blinding might create a different odd ratio than non-blinded study

- Patient factors: disease stage, presence of comorbid condition, age, gender
- Study factors: design features, region in the World, different dose or administration

AD meta-analysis: meta-regression

- The outcome variable is the effect estimate (like mean difference, log odds ratio or log risk ratio)
- The explanatory variables (covariates) are characteristics of studies that might influence the size of intervention effect

- Y = int ⟶ overall pooling, 1 pooled estimate
- Y = int +b1*X1
  - b1=change in effect measure from one category to another or 1 unit change in continuous covariate
  - test for b1=0 is test for significance of covariate

regression coefficient

AD meta-analysis: study-level covariate

- Study-level covariate: works well because we can add these study characteristics to the model
  - Y = int ⟶ overall pooling, 1 pooled estimate
  - Y = int +b1*non-blinding
    (1=non-blinded, 0=blinded)

AD meta-analysis: summary measure of patient-level covariate

more difficutls

- because of Summary measure of patient-level covariate:
  - Y = int ⟶ overall pooling, 1 pooled estimate
  - Y = int +b1*%males

  Or
  - Y = int +b1*mean_age

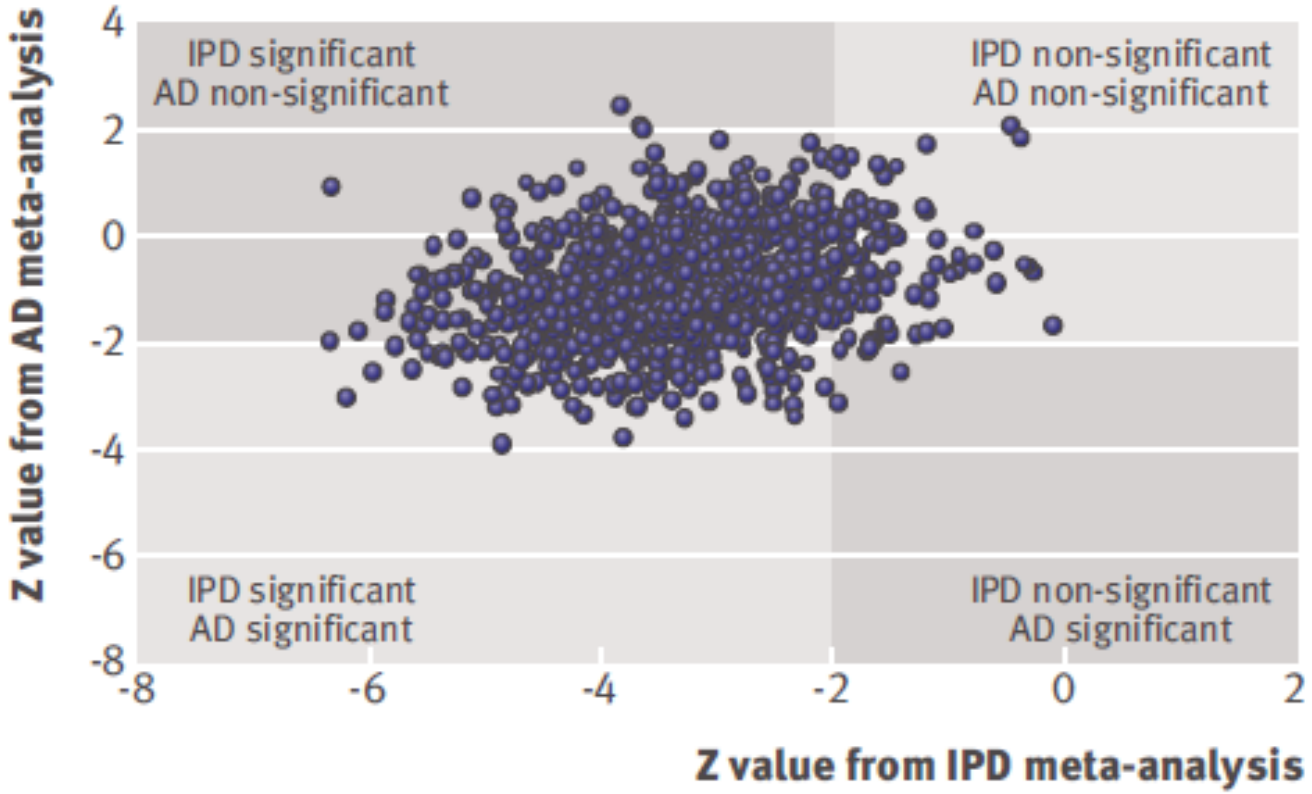
  e.g. examine impact of mean age across studies on effect

- Investigate whether the effect measure (e.g. OR) varies with the % male or mean age across studies
- Indirect way: loose power & result may be invalid

IPD vs AD review: power subgroup analysis

each dot one meta analysis with primary study

Minute 13 Video 2



Power:

IPD 91%

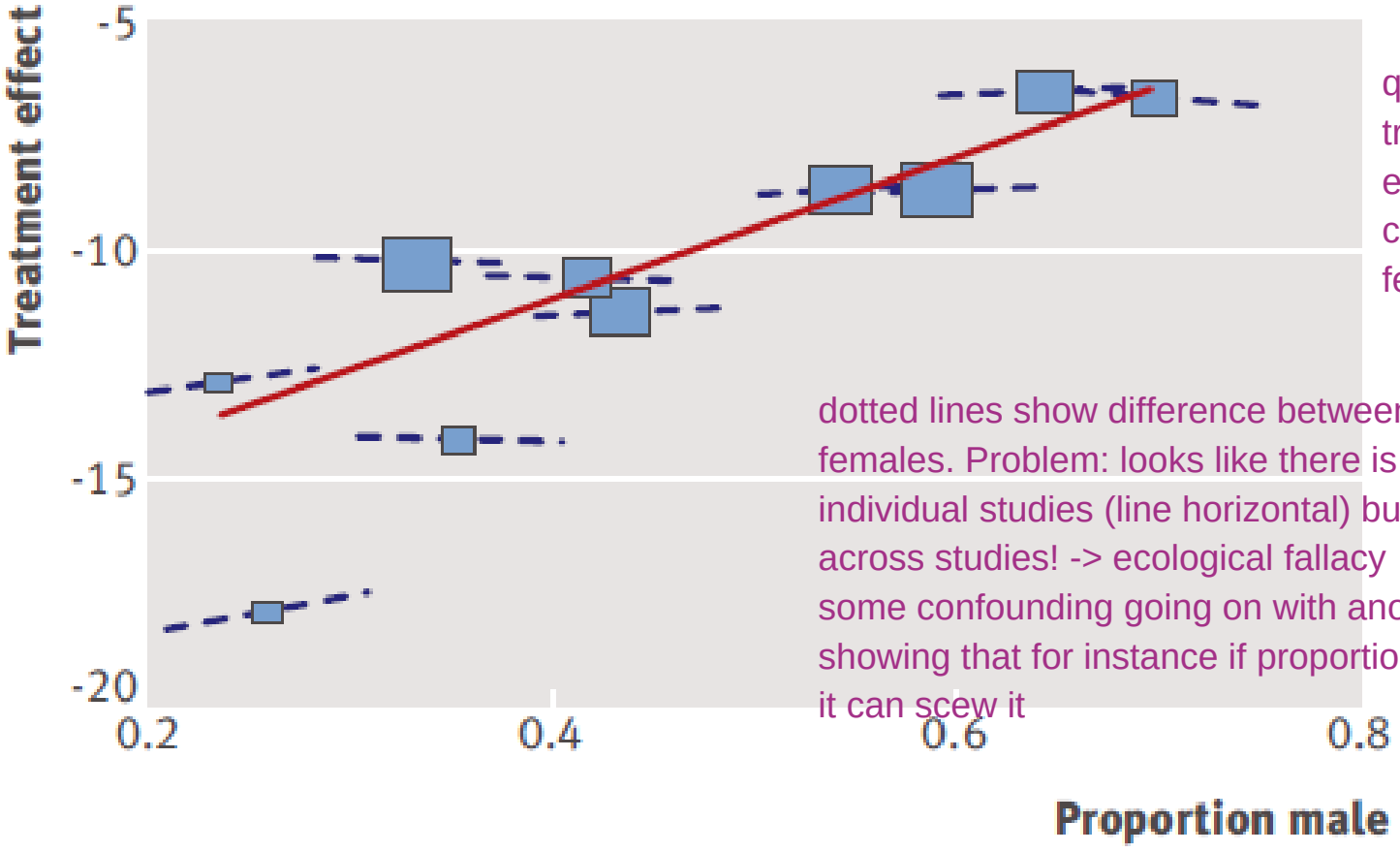
AD 15%

91% of the analysis will pick up the effect

Fig 2 | Comparison of the power of meta-analyses to detect a differential treatment effect across two groups of patients when individual participant data (IPD) or aggregate data (AD) are used. Adapted from Lambert et al[19]

Ecological fallacy / Simpson's paradox

each rectangle = one single study



question: is the treatment more efficient in men compared to females?

dotted lines show difference between males and females. Problem: looks like there is no issue with the individual studies (line horizontal) but there is an effect across studies! -> ecological fallacy
some confounding going on with another factor showing that for instance if proportion of males is high it can scew it

Fig 3 |An example of ecological bias within an aggregate data meta-analysis

Careful modelling of subgroups

always consider when to include across trial information

RESEARCH METHODS AND REPORTING

Cite this as: *BMJ* 2017;356:j573
http://dx.doi.org/10.1136/bmj.j573

Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach?

David J Fisher,[1] James R Carpenter,[1,2] Tim P Morris,[1] Suzanne C Freeman,[1] Jayne F Tierney[1]

Research Article

Statistics in Medicine

Received: 14 April 2016, Accepted: 28 October 2016 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.7171

One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information

Hairui Hua,[a] Danielle L. Burke,[b] Michael J. Crowther,[c,d] Joie Ensor,[b] Catrin Tudur Smith[e] and Richard D. Riley[b*†]

Benefits of subgroup analyses in IPD

- Analyze subgroups at the individual level across all studies (if measured)
- Greater power by analyzing subgroups at the level of the patient
- Flexible modelling of continuous covariates
- Analyze subgroups in a consistent way
- Examine combination of factors

  two way interactions

  effect of age different in males/females
- Possibility to adjust for imbalance in important prognostic factors between subgroups

  extending the IPD data

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Summary

Summary

- Hierarchical nature (clustering) of data within a IPD meta-analysis needs to be taken into account
- Two-stage and one-stage approaches each having their pros and cons, but can also complement each other
- IPD meta-analysis offer greater flexibility, validity and power to examine subgroup effects (interactions between treatment and patient-level covariates). Still need sufficient data!
- Benefits of IPD even greater when developing and validating multivariable prediction models (more later this week)
- IPD no cure for poorly designed studies