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IPD-MA of RCTs: One-stage or two-stage?

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Which one is more common?

2011

General strategies used for estimating treatment effect in 26 IPD-MA of binary outcomes published in 2011.		
Two-stage method	6	(31%)
One-stage method	19	(69%)

Ref: Thomas D et al (2014). Systematic review of methods for individual patient data meta- analysis with binary outcomes. *BMC Medical Research Methodology*, *14*, 79.

Which one is more common?

1999-2001

General strategies used for estimating treatment effect in 44 IPD-MA published during 1999-2001.		
Two-stage method	28	(64%)
One-stage method	6	(14%)
Both methods	8	(18%)
Unclear	1	(2%)
Not performed	1	(2%)

Ref: Simmonds MC et al. (2005). Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clinical Trials*, *2*(3), 209–217.

Empirical comparisons

Pooled treatment effects

	Relative risk	95% CI	Amount of Heterogeneity
Two-stage fixed	0.90	0.83 to 0.96	NA
One-stage fixed	0.90	0.83 to 0.97	NA
Two-stage random	0.87	0.78 to 0.97	0.011 (se 0.016)
One-stage random	0.90	0.83 to 0.97	0 (se 0.000)

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Empirical comparisons

ELSEVIER

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Journal of Clinical Epidemiology

A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners

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Abstract

Objective: Treatments may be more effective in some patients than others, and individual participant data (IPD) meta-analysis of randomized trials provides perhaps the best method of investigating treatment-covariate interactions. Various methods are used; we provide a comprehensive critique and develop guidance on method selection.

Study Design and Setting: We searched MEDLINE to identify all frequentist methods and appraised them for simplicity, risk of bias, and power. IPD data sets were reanalyzed.

Results: Four methodological categories were identified: PWT: pooling of within-trial covariate interactions; OSM: ''one-stage'' model with a treatment-covariate interaction term; TDCS: testing for difference between covariate subgroups in their pooled treatment effects; and CWA: combining PWT with meta-regression. Distinguishing across- and within-trial information is important, as the former may be subject to ecological bias. A strategy is proposed for method selection in different circumstances; PWT or CWA are natural first steps. The OSM method allows for more complex analyses; TDCS should be avoided. Our reanalysis shows that different methods can lead to substantively different findings.

Conclusion: The choice of method for investigating interactions in IPD meta-analysis is driven mainly by whether across-trial information is considered for inclusion, a decision, which depends on balancing possible improvement in power with an increased risk of bias.

Keywords: Meta-analysis; IPD; RCT; Interaction; Subgroup; Methodology

Empirical comparisons

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PLOS ONE

Statistical Analysis of Individual Participant Data Meta-Analyses: A Comparison of Methods and Recommendations for Practice

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Abstract

Background: Individual participant data (IPD) meta-analyses that obtain ''raw'' data from studies rather than summary data typically adopt a ''two-stage'' approach to analysis whereby IPD within trials generate summary measures, which are combined using standard meta-analytical methods. Recently, a range of ''one-stage'' approaches which combine all individual participant data in a single meta-analysis have been suggested as providing a more powerful and flexible approach. However, they are more complex to implement and require statistical support. This study uses a dataset to compare ''two-stage'' and ''one-stage'' models of varying complexity, to ascertain whether results obtained from the approaches differ in a clinically meaningful way.

Methods and Findings: We included data from 24 randomised controlled trials, evaluating antiplatelet agents, for the prevention of pre-eclampsia in pregnancy. We performed two-stage and one-stage IPD meta-analyses to estimate overall treatment effect and to explore potential treatment interactions whereby particular types of women and their babies might benefit differentially from receiving antiplatelets. Two-stage and one-stage approaches gave similar results, showing a benefit of using anti-platelets (Relative risk 0.90, 95% CI 0.84 to 0.97). Neither approach suggested that any particular type of women benefited more or less from antiplatelets. There were no material differences in results between different types of one-stage model.

Conclusions: For these data, two-stage and one-stage approaches to analysis produce similar results. Although one-stage models offer a flexible environment for exploring model structure and are useful where across study patterns relating to types of participant, intervention and outcome mask similar relationships within trials, the additional insights provided by their usage may not outweigh the costs of statistical support for routine application in syntheses of randomised controlled trials. Researchers considering undertaking an IPD meta-analysis should not necessarily be deterred by a perceived need for sophisticated statistical methods when combining information from large randomised trials.

Empirical comparisons

Treatment-covariate interaction

		Two-stage		One-stage	
Subgroup	**Category**	**Relative risk (95% CI)**	**Interaction p value**	**Relative risk (95% CI)**	**Interaction coefficient (standard error) p value**
First pregnancy with/without high risk factor	with	0.90 (0.76 to 1.08)	0.71	0.88 (0.66 to 1.09)	0.03 (0.13) p = 0.81
	without	0.87 (0.75 to 1.02)		1.16 (1.00 to 1.31)	
Second pregnancy with/without high risk factor	with	0.89 (0.81 to 0.99)	0.56	0.88 (0.78 to 0.98)	−0.08 (0.17) p = 0.62
	without	0.98 (0.73 to 1.33)		0.95 (0.63 to 1.27)	
Second pregnancy with/without History of hypertension	Yes	0.86 (0.77 to 0.97)	0.25	0.88 (0.49 to 1.25)	−0.07 (0.10) p = 0.46
	No	0.96 (0.82 to 1.12)		0.94 (0.53 to 1.35)	
Renal disease	Yes	0.63 (0.38 to 1.06)	0.23	0.60 (0.35 to 1.04)	−0.43 (0.31) p = 0.17
	No	0.90 (0.82 to 0.96)		0.90 (0.82 to 0.98)	
Diabetes	Yes	0.63 (0.38 to 1.06)	0.26	0.71 (0.35 to 1.06)	−0.21 (0.19) p = 0.27
	No	0.90 (0.82 to 0.96)		090 (0.81 to 0.98)	
Hypertension	Yes	0.97 (0.84 to 1.12)	0.28	0.97 (0.82 to 1.15)	0.10 (0.10) p = 0.32
	No	0.88 (0.81 to 0.96)		0.89 (0.82 to 0.96)	
Previous small for gestational age infant	Yes	1.05 (0.86 to 1.28)		1.05 (0.80 to 1.36)	
	No	0.85 (0.73 to 0.98)	0.27	0.85 (0.69 to 1.05)	0.25 (0.14) p = 0.07
	No previous infant	0.89 (0.79 to 0.99)		0.85 (0.75 to 1.32)	

The two-stage model with fixed-effect replicating the analysis of [29]. One-stage models were consistent whether treatment effects were fixed or random.
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Empirical comparisons

Treatment-covariate interaction

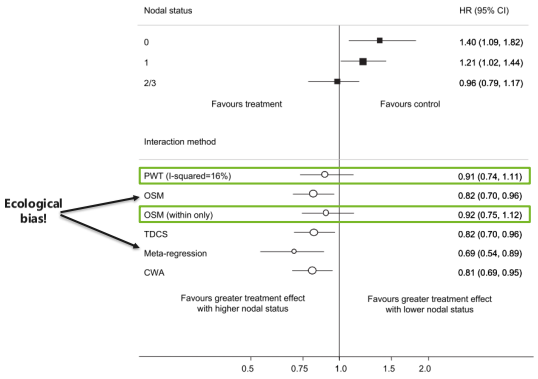

Fig. 4. Treatment effect by nodal status: PORT data set. Independently pooled results for each nodal stage subgroup, and covariate interaction estimates from each of the methods under discussion.

One-stage versus two-stage IPD-MA

Advantages two-stage IPD-MA

- Least complicated approach
- Conservative: does not borrow information across trials when estimating study-specific associations
- Does not require IPD sets to be combined
  => may avoid confidentiality issues

Empirical comparisons

Treatment-covariate interaction

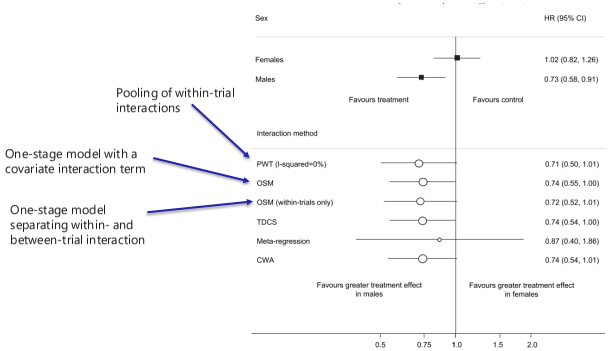

Fig. 2. Treatment effect by sex: sarcoma data set. Independently pooled results for male and female subgroups, and covariate interaction estimates from each of the methods under discussion.

One-stage versus two-stage IPD-MA

One-stage and two-stage meta-analysis models

- Often yield similar estimates of treatment effects
- May lead to equivalent results when the interest lies in estimating a summary treatment effect

One-stage versus two-stage IPD-MA

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Statistics in Medicine

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Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ

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One-stage versus two-stage IPD-MA

Key reasons why they may differ pt 2

- Choice of fixed-effect or random effects
- Different estimation method for τ^2
- Derivation of confidence intervals
- Accounting for correlation amongst parameters
- Ecological bias for treatment covariate interactions

One-stage versus two-stage IPD-MA

Disadvantages two-stage IPD-MA

- Prone to bias
  - Few studies or few participants (or events) per study
  - Failure to fully account for follow-up times
  - Failure to account for the time between recurrent events
  - When some important covariates have not been measured in all studies
  - Danger of ecological bias when investigating patient-level interactions on the aggregate level
- Lack of power
  - Detecting nonlinear associations
  - Detecting treatment-covariate interactions

One-stage versus two-stage IPD-MA

Key reasons why they may differ pt 1

- Exact versus approximate likelihoods
- Use of alternative weighting schemes in two-stage MA
- Clustering and choice of specification for the intercept
- Choice of specification for any adjustment terms
- Choice of specification for the residual variances

One-stage versus two-stage IPD-MA

Recommendations

- Implement two-stage IPD-MA
  - To explore the available data
  - To present intermediate results
  - To avoid ecological bias
  - To identify key challenges when designing a one-stage IPD-MA
- Implement one-stage IPD-MA
  - To adopt more appropriate likelihood functions
  - To avoid small-sample bias
  - To define more complex associations
  - To simplify unnecessary assumptions

One-stage versus two-stage IPD-MA

An overview

Method	Computational and statistical complexity	Potential problems
Two-stage subgroup analysis	***Low:*** Requires only standard meta-analysis techniques and interaction tests. Available in several meta-analysis packages (eg. Cochrane Review Manager which requires pre-processing of IPD analyses within trials and SHARRP). Possible in most statistical packages (e.g. R, Stata).	***High:*** Limited statistical power. Potential for aggregation bias if trials lack data in some subgroup categories.
Two-stage, combining within-trial regression coefficients [9], [19]	***Moderate:*** Requires regression models estimating treatment effect and treatment-covariate interaction in each trial, and meta-analysis. Possible in statistical packages with regression and meta-analysis facilities (R, Stata).	***Low:*** Intermediate statistical power. Eliminates potential aggregation bias.
Simple one-stage regression [8]	***Moderate to high:*** Requires some experience in fitting regression models. Possible in R, Stata, SAS or equivalent.	***Moderate:*** Maximal statistical power. Potential for aggregation bias.
Complex one-stage regression (e.g. separating within- and across-trial information [7], [9]	***High:*** Requires expertise in fitting mixed-effect regression models and programming ability in R, Stata, SAS or equivalent. May require specialist software such as WinBUGS. Statistical support is recommended.	***Low:*** Intermediate to high statistical power. Eliminates aggregation bias if only within-trials information considered.

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Extension to time-to-event data

REVIEW | Open Access

Individual participant data meta-analysis of intervention studies with time-to-event outcomes: A review of the methodology and an applied example

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