Individual Participant Data Meta-Analysis Projects:

Rationale, Concepts and Pitfalls

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Objectives

To understand:

(1) rationale & key steps

(2) statistical methods

(3) precision medicine & notable examples

(4) notes of caution

PART 1:

Rationale & Key Steps

Meta-analysis

The statistical analysis that usually follows a systematic review, to combine the quantitative results from studies identified

Derivation:

μετα: ‘after’, ‘above’, ‘transcending’

Definition:

‘the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings‘

Glass (1976)

Meta-analysis using aggregate data

- Traditional meta-analysis uses **aggregate data**
- Obtainable from publications or study authors
- Meta-analysis of RCTs usually requires from each study:

an estimate of the treatment effect

e.g. odds ratio, relative risk, hazard ratio etc

& the standard error of this estimate

e.g. standard error of log hazard ratio

Meta-analysis using aggregate data

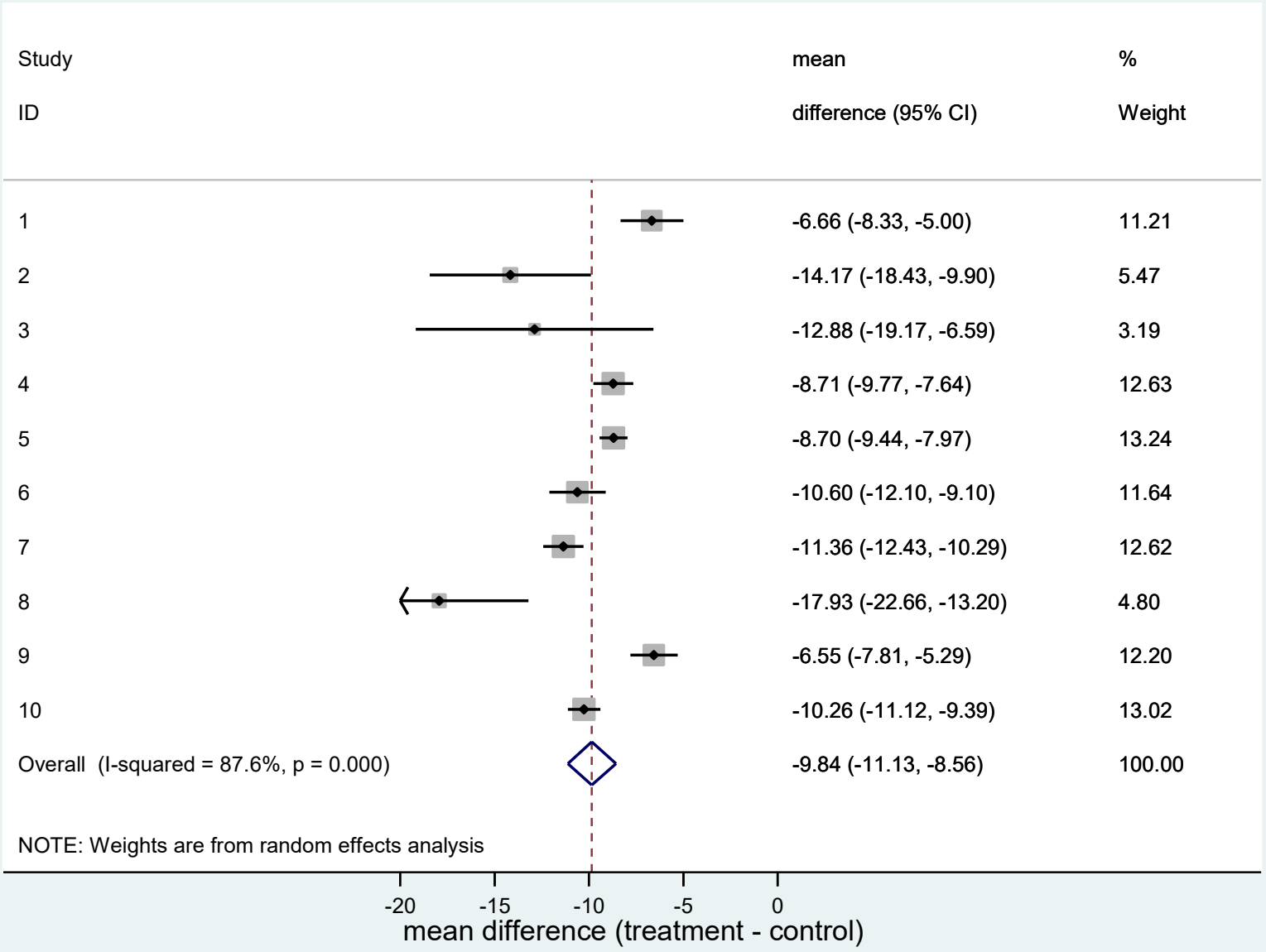
Advantages:

- Quick (in theory at least, if studies are well reported)
- Cheap

- Meta-analysis methods well established:
  such as inverse-variance, Mantel-Hansel,
  fixed-effect, random-effects ,…

- Software suitable for non-statisticians (e.g. RevMan)
- Leads to forest plots, nice visual summaries, …

Example: meta-analysis of 10 hypertension trials



Meta-analysis using aggregate data

Disadvantages:

- Reliant on reporting of published articles
- Often face poor reporting (e.g. p-values rather than estimates)
- **Not in control of the statistical analysis method used**
  - Inconsistency in choice of effect (hazard ratio, odds ratio, etc.)
  - Inconsistent or no adjustment for prognostic factors
  - Complexities ignored (e.g. clustering, non-proportional hazards, non-linear relationships) etc
- Vulnerable to publication bias: studies with significant results more likely to be published (or reported well) than non-significant studies
- Vulnerable to **outcome reporting bias** – studies report only those outcomes that were significant or most interesting

Meta-analysis using aggregate data

Disadvantages:

- Going beyond original analyses is very hard (often impossible), e.g. couldn't examine proportional hazards, develop a prediction model, etc
- **Aggregate data collapses participant-level information**
  - Observe study-level summaries, such as mean age, proportion male, overall treatment effect

  Loses power to explain participant-level variation

  - Cannot adjust for prognostic factors
  - Cannot identify subgroup results, treatment-covariate interactions (effect modifiers), etc.

    i.e. can't examine whether some patients do better than others

Call for IPD meta-analysis

IPD: Individual Patient Data , Individual Participant Data

(the latter is now being adopted, as more inclusive)

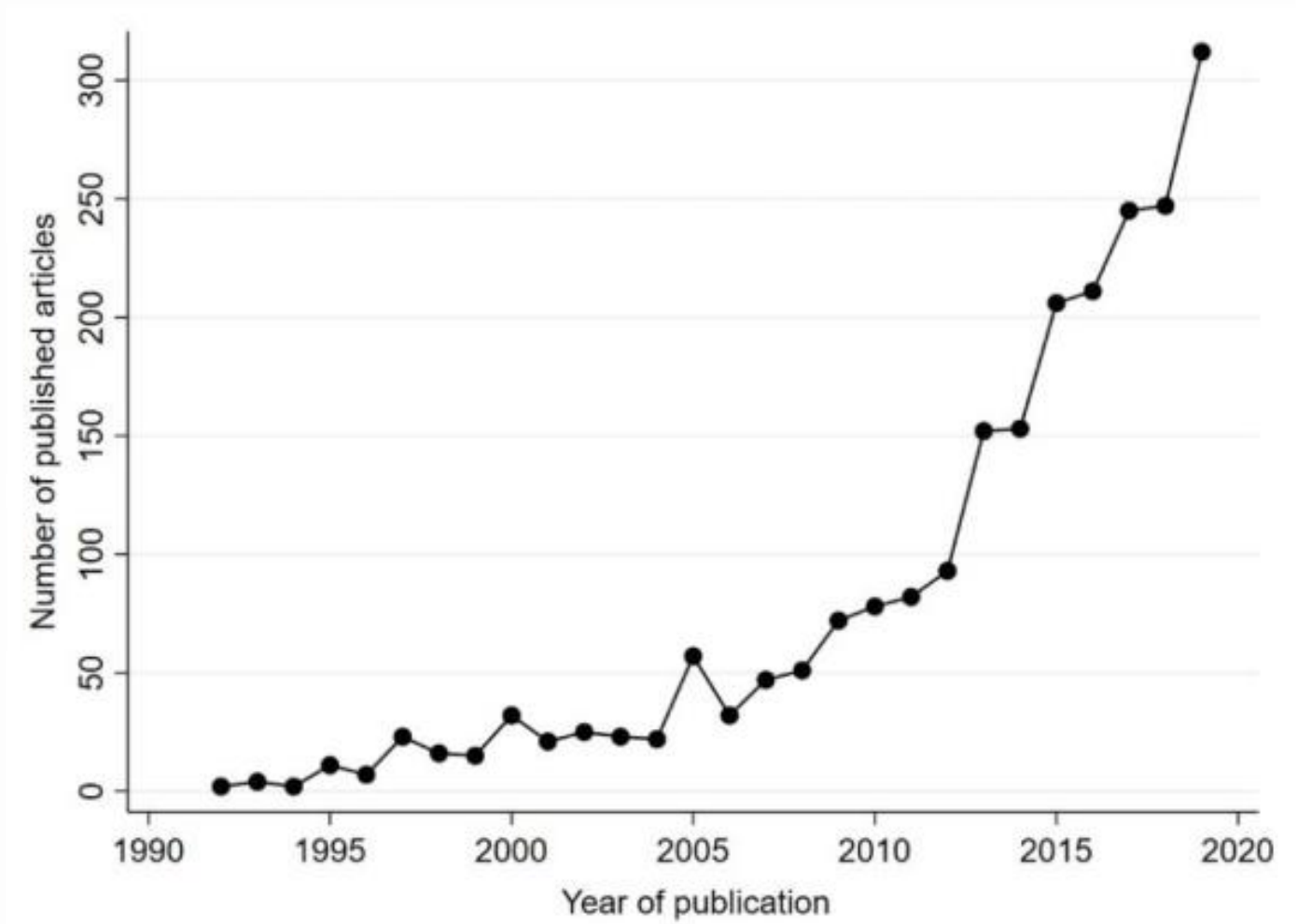
- The original, raw individual-level data from the primary studies identified by the review
- The original source material, from which aggregate data are derived

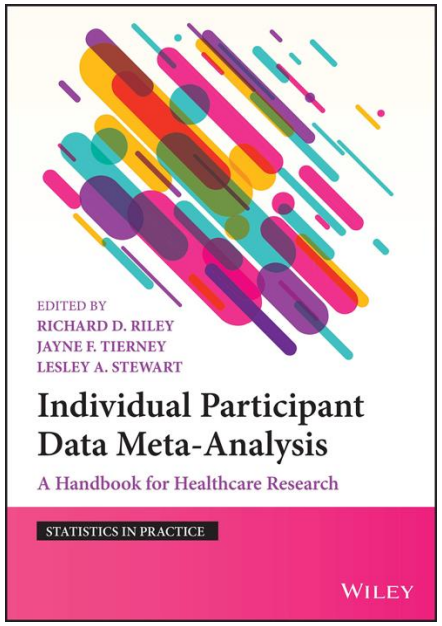
IPD meta-analysis:

The synthesis (in a statistical model) of the IPD from multiple studies for the purpose of summarising the evidence

- Increasingly relevant with the advent of 'stratified medicine' – the tailoring of treatment decisions for individual patients

Number of IPD meta-analysis articles over time (Riley, Tierney, Stewart. 2021)





Example: IPD from multiple trials, merged into a single dataset ready for meta-analysis

Trial ID	Participant ID	Treatment group, 1 = treatment 0 = control	Age (years)	SBP before treatment (mmHg)	SBP at 1 year (mmHg)
1	1	1	46	137	111
1	2	1	35	143	133
(other rows for trial 1 omitted for brevity)					
1	1454	0	62	209	219
2	1	0	55	170	155
2	2	1	38	144	139
(other rows for trial 2 omitted for brevity)					
2	337	1	44	153	129
(rows for trials 3 to 9 omitted for brevity)					
10	1	0	71	149	128
10	2	1	59	168	169
(other rows for trial 10 omitted for brevity)					
10	4695	0	63	174	128

Example: IPD from multiple cancer prognosis studies merged ready for meta-analysis

		Marker levels				Adjustment factors			Survival & disease status		
study	Patient	TH	LDH	MYCN	…	Age	Stage	…	Time of recurrence	Final survival time	Final disease status
1	1	Pos	200	5		3 yrs	1		-	150 days	ALIVE
1	2	Neg	350	3		2 yrs	4		330 days	390 days	DEAD
1	3	Neg	120	1		2 yrs	3		230 days	250 days	ALIVE with disease
2	1	Neg	320	1		6 yrs	4		27 days	48 days	DEAD
…	…	…	…	…		…	…		…	…	…

Meta-analysis using IPD

Potential advantages:

- Use consistent inclusion and exclusion criteria across studies, and if appropriate reinstate individuals into the analysis who were originally excluded

- Observe and account for missing data at the individual-level

- Verify results presented in the original study publications (assuming IPD provided can be matched to that IPD used in the original analyses)

Meta-analysis using IPD

- Inform risk of bias assessments: for example, regarding randomisation process and whether groups were balanced at baseline

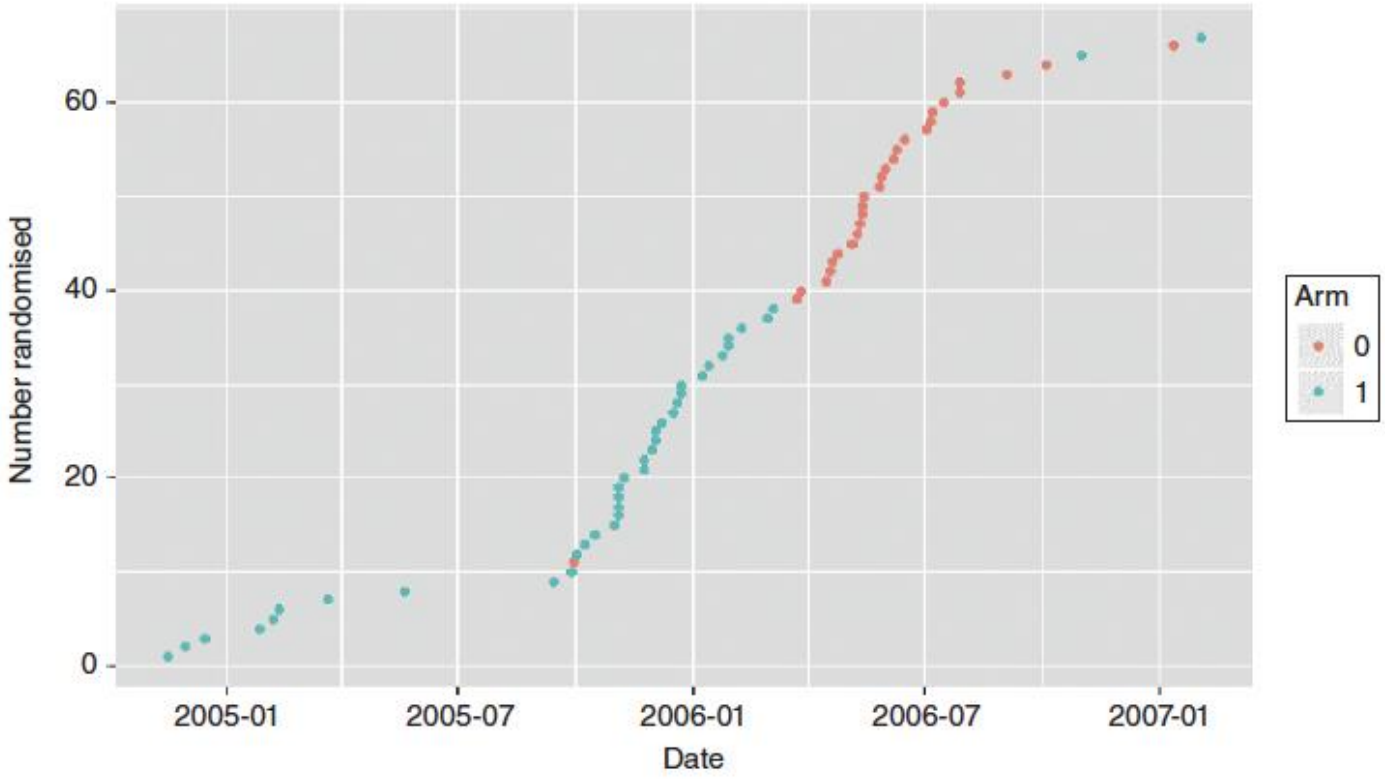
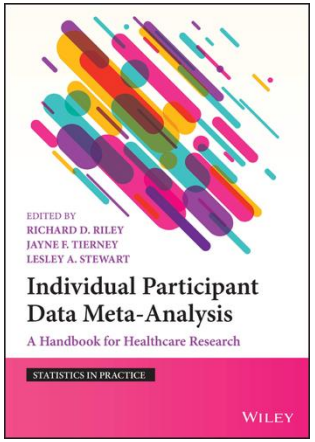


Figure 4.9 Date (shown by year-month) participants were allocated to treatment and control in a trial excluded from an IPD meta-analysis, because participants in one group ('arm 1') were generally recruited earlier than those in the other group ('arm 0'). *Source:* Lesley Stewart.



Meta-analysis using IPD

Potential advantages:

- Use up-to-date follow-up information
  - potentially longer than that used in the original study publications
- Identify studies which contain the same or overlapping sets of participants
- Calculate and incorporate results for those missing or poorly reported outcomes and summary statistics across published studies
  - may reduce the problem of selective within-study reporting (e.g. of outcomes)
- Calculate and incorporate results for unpublished studies
  - may thus reduce the problem of publication bias

Meta-analysis using IPD

Potential advantages:

- Standardise the strategy of statistical analysis across studies
  - e.g. the analysis method, how continuous variables are analysed
  - use more appropriate/advanced methods than primary studies where necessary

- Assess model assumptions in each study
  - e.g. proportional hazards in Cox regression model

- Produce estimates adjusted for prognostic factors
  - may increase power, reduce heterogeneity & allows conditional treatment effects

Meta-analysis using IPD

Potential advantages:

- Obtain meta-analysis results for specific subgroups of participants, and assess differential (treatment) effects across individuals
  - this facilitates individualised or stratified medicine

- Examine and compare accuracy of tests at multiple thresholds

- Generate and validate prognostic/prediction models (risk scores), and examine multiple individual-level factors in combination
  - e.g. multiple biomarkers and genetic factors, and their interaction

- Account for the correlation between multiple endpoints
  - a meta-analysis of longitudinal data where each participant provides results at multiple time-points

Data sharing

We are in an era where data sharing is becoming expected

BMJ 2015;350:h599 doi: 10.1136/bmj.h599 (P

norm."[1] The IOM joins many other organizations, including drug companies,[2 3] the European Medicines Agency,[4] the National Institutes of Health,[5] and the Bill and Melinda Gates Foundation,[6] in making clear that study reporting and data sharing in medical research are imperative and the questions ahead are how, not whether.

Why data sharing should be the expected norm

The Institute of Medicine takes a step in the right direction but we should move even faster

Harlan M Krumholz *professor of medicine*

[1]Section of Cardiovascular Medicine and Robert Wood Johnson Foundation Clinical Scholars Program, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06510, USA; [2] Department of Health Policy and Management, Yale School of Public Health, New Haven; [3]Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven

Do I need IPD for meta-analysis?

Decision process for IPD approach:

- What is the research question?
- Has a previous review been done before to answer this question?
- What aggregate data are required to answer the question?
- Are such aggregate data available in the majority of studies?
- If not, will availability of IPD allow them to be calculated?
- How much IPD can I realistically obtain? Is it of sufficient power?
- How long will it take to obtain it?
- Do I have the resources for obtaining, collating, checking and managing large sets of IPD?
- Do I have statistical expertise and software to analyse the IPD?

Aided by: collaborating groups, different disciplines working together, leaders in the field being involved – & of course funding

Do I need IPD for meta-analysis?

Decision depends on many issues, such as:

- The research question:
  - interested in overall treatment effect
  - interested in conditional effects
  - interested in subgroups
  - identifying non-linear trends
  - developing risk prediction models

more nuance, more need for IPD

- Whether IPD would **improve quality** (e.g. improve risk of bias assessments, better adhere to inclusion/exclusion criteria, examine modelling assumptions, include more outcomes, standardise variables)
- The **current analysis methods** within primary studies (are they appropriate? Do they provide the estimands of interest?)
- The **current reporting standards** within primary studies (is the aggregate data required for meta-analysis available?)

Planning an IPD meta-analysis project?

- Set-up tasks include:
  - developing a project scope
  - establishing the central research team and advisory group
  - seeking in principle agreement to collaborate from study investigators
  - identifying other sources of IPD
  - developing data-sharing agreements
  - applying for research funding
  - applying for ethical approval or exemption.

- The central research team should include members with experience of successfully completing an IPD meta-analysis project, advanced statistical knowledge, experience in managing and coding IPD, and strong communication skills.

- Specify proposed inclusion and exclusion criteria in terms of the PICOS (Population, Intervention, Comparator, Outcomes, Study design)

Examining risk of bias

- Assessment of risk of bias for each study and its IPD is a continual process:

  - initially based on information from publications or protocols

  - supplemented by information provided by study investigators

  - refined or updated once IPD have been received, checked and cleaned.

- Some risk of bias concerns may be alleviated by actually having the IPD

  e.g. inclusion of participants originally excluded by the trial investigators

- Conversely, some risk of bias concerns may only become apparent from checking the IPD

  e.g. noticeable baseline imbalance indicative of flawed randomization

Meta-analysis & reporting

- After IPD obtained, checked, harmonized & (ideally) merged, statistical methods for IPD meta-analysis needed for a quantitative synthesis.

- These use either a two-stage or a one-stage approach to produce summary results (e.g. about treatment effect).

- Sensitivity analyses needed (e.g. excluding trials not at low risk of bias, inclusion of aggregate data from non-IPD trials, small-study effects)

- Reporting and dissemination activity should be planned from the outset, with a broad range of potential stakeholders in mind, including patients and policy-makers.

- PRISMA-IPD, and its associated checklist and flow diagram, provide a framework to help authors describe essential elements of IPD meta-analysis design, conduct and findings in their journal article.

PART 2

Key statistical approaches to meta-analysis

Two-stage IPD approach

- Let us focus on obtaining pooled effect estimates
- The most common method is a two-stage approach:

STEP 1: Perform a regression analysis of the IPD to obtain effect estimate in each study separately

(e.g. mean difference, odds ratio, or hazard ratio)

STEP 2: Pool these in a fixed effect or random effects model

Two-stage IPD approach

- Thus we mirror traditional meta-analysis approach
- But rather than extract aggregate data from published articles, we now analyse the IPD separately in each study to obtain it ourselves

- **Two-stage approach:**

  STEP 1: reduce the IPD to aggregate data in each study

  STEP 2: pool aggregate data using standard meta-analysis methods

- Stata module *ipdmetan* (Fisher, 2014)
  - does all this for you

Step 1

- For each IPD study separately, reduce the IPD to AD

  This requires a statistical analysis of the IPD in each study (*i*) separately. Choice of model depends on outcome type:

Continuous outcomes (e.g. blood pressure in hypertension)

- Linear regression

Binary outcomes (e.g. risk of adverse outcome in pregnancy)

- Logistic regression

Time-to-event outcomes (e.g. mortality rates in cancer)

- Cox regression

Produces an effect estimate ($\hat{\theta}_i$) and its variance ($\mathrm{V}(\hat{\theta}_i)$)

Step 2

- Choose and apply a meta-analysis model, akin to those used in a traditional meta-analysis of aggregate data

- A common-effect meta-analysis model can be written as:

$$\hat{\theta}_i \sim N(\theta, \mathrm{V}(\hat{\theta}_i))$$

- A random-effects meta-analysis model can be written as:

$$\hat{\theta}_i \sim N(\theta_i, \mathrm{V}(\hat{\theta}_i))$$

$$\theta_i \sim N(\theta, \tau^2)$$

Applied example: hypertension

- Wang et al. (2005) performed a quantitative overview of trials in hypertension to investigate hypertension treatments and their lowering of systolic blood pressure (SBP).

- They selected randomised controlled trials that tested active anti-hypertensive drugs against placebo or no treatment

- IPD was sought from trials in the INdividual Data ANalysis of Anti-hypertensive intervention trials (INDANA) data set or at the Studies Coordinating Centre in Leuven (Belgium)

- Ten trials were ultimately included, and these provided IPD for a total of 28581 patients.

Applied example: hypertension

- An IPD meta-analysis of the 10 trials is important to summarise the effect of anti-hypertensive drugs on SBP

- Specifically

  (i) to examine the distribution of treatment effects across the trials in order to estimate the average effect (that is, how much anti-hypertensive drugs reduce SBP compared to control on average across the trial populations)

  (ii) to quantify the amount of between-trial variation in the effect of anti-hypertension drugs

  (iii) identify effect modifiers: patient-level factors that modify (interact with) treatment effect

Sample of the data …

Study	Patient	SBP initial	SBP final	treat	placebo	age	sex
1	1	190	185	1	0	58	1
1	2	175	172	1	0	69	1
1	3	184	185	0	1	39	0
1	4	192	182	0	1	45	1
2	1	201	199	1	0	51	0
2	2	169	154	1	0	42	1
2	3	171	170	0	1	50	1
2	4	179	168	0	1	67	0
3	1	197	167	1	0	83	1
3	2	189	171	1	0	78	0
3	3	184	188	0	1	55	1
3	4	168	161	0	1	61	0

Two-stage analysis

- The treatment and control groups are well balanced in SBP in each trial at baseline, and this was true for other patient characteristics.

STEP 1: ANCOVA in each trial, to obtain mean difference in SBP at follow-up after adjusting for baseline

(ANCOVA = analysis of covariance;

just a linear regression adjusting for baseline SBP)

Stage 1 aggregate data

- Aggregate data for the 10 hypertension trials

Trial ID	Number of participants		Mean age (years)		Mean SBP before treatment (mmHg)		Mean SBP at 1 year (mmHg)		Treatment effect on SBP at 1 year adjusted for baseline (treatment minus control)
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Estimate (variance)
1	750	704	42.36	42.17	153.05	153.88	139.75	132.54	-6.53 (0.75)
2	199	138	69.57	69.71	191.55	188.30	179.89	164.67	-13.81 (4.95)
(rows for trials 3 to 9 omitted for brevity)									
10	2297	2398	70.21	70.26	173.94	173.75	165.24	154.87	-10.26 (0.20)

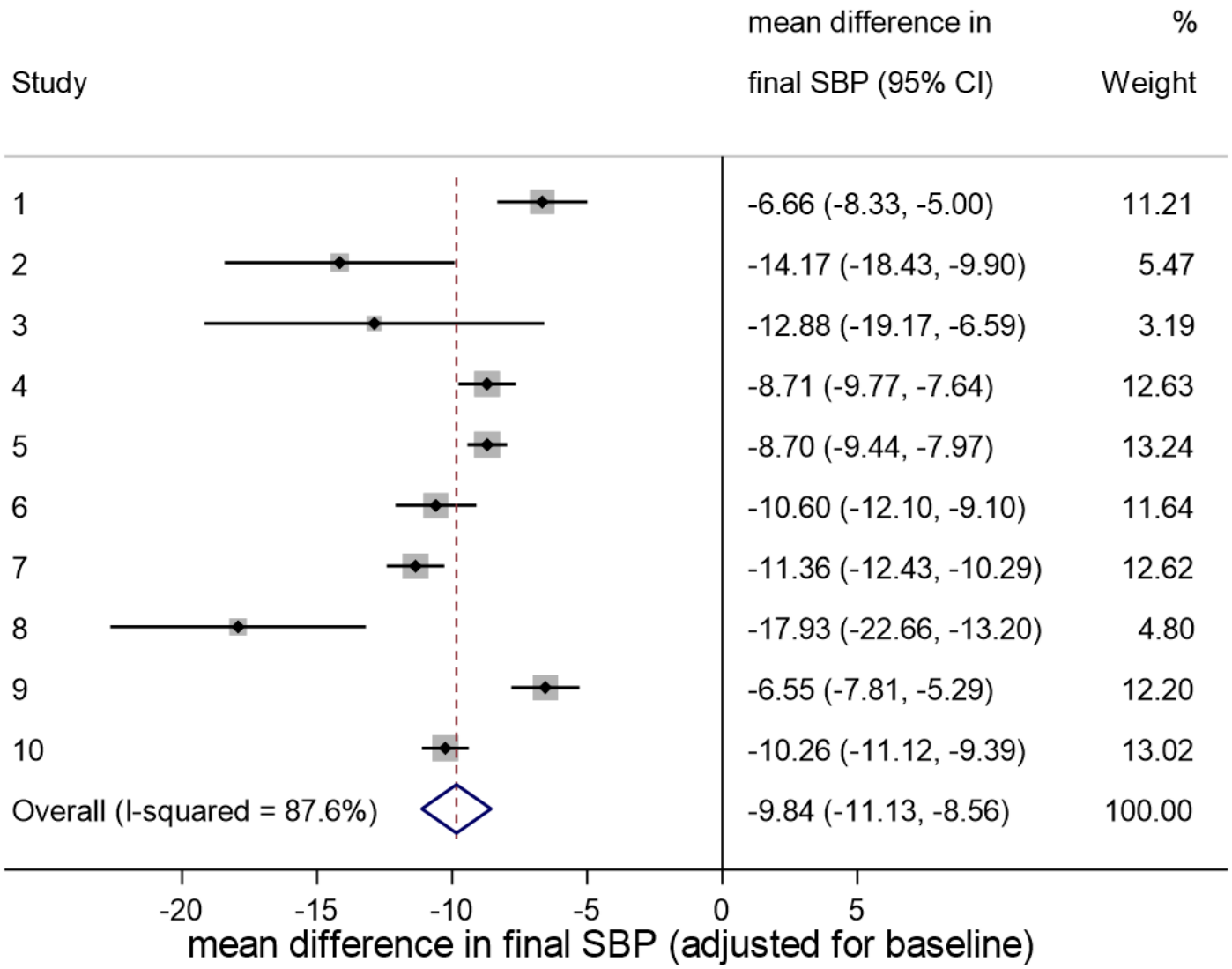
Two-stage analysis

- The treatment and control groups are well balanced in SBP in each trial at baseline, and this was true for other patient characteristics.

STEP 1: ANCOVA in each trial, to obtain mean difference in SBP at follow-up after adjusting for baseline

STEP 2: Random-effects meta-analysis of the treatment effect estimates (e.g. estimated using DerSimonian and Laird approach)

Results



$\hat{\tau}^2 = 3.09$

Reminder: IPD may not be needed…

- Perhaps all trials:
  - used ANCOVA
  - reported the treatment effect estimate
  - reported its 95% confidence interval

- If we are only interested in summarising the overall treatment effect, the IPD is giving us nothing new

  (other things being equal, like length of follow-up, number of included patients, etc)

- Advantages of having IPD begin to arise when studies do not report the results, outcomes, subgroups of interest; use inconsistent analysis methods; etc …. (see later)

One-stage IPD meta-analysis

- An alternative approach is a one-stage meta-analysis
- This analyses all the IPD from all studies *simultaneously*
- Must account for the clustering of patients within studies

  e.g. use a separate intercept per study
- Basically a multi-level (mixed effects) regression model & stratify nuisance terms (e.g. intercepts) by study
- Usually one-stage and two-stage approaches give very similar results (if same estimation method used)
- Key exception is when events are rare, then the one-stage approach is preferred to model the exact likelihood directly

DOI: 10.1002/jrsm.1661

RESEARCH IN BRIEF

Research Synthesis Methods WILEY

Two-stage or not two-stage? That is the question for IPD meta-analysis projects

Richard D. Riley[1] | Joie Ensor[1] | Miriam Hattle[1,2] | Katerina Papadimitropoulou[3] | Tim P. Morris[4]

Example 1: hypertension revisited

- 10 hypertension trials (>>200 patient per trials),
- Continuous outcome of SBP

Approach	Estimation method	Summary mean difference (95% CI)	$\hat{\tau}^2$
Two-stage	REML	-10.17 (-12.27 to -8.07)	7.10
One-stage	REML	-10.16 (-12.27 to -8.06)	7.13
Two-stage	ML	-10.10 (-12.03 to -8.16)	5.84
One-stage	ML (no centering)	-10.03 (-11.83 to -8.23)	4.94
One-stage	ML (centering)	-10.09 (-12.03 to -8.17)	5.87

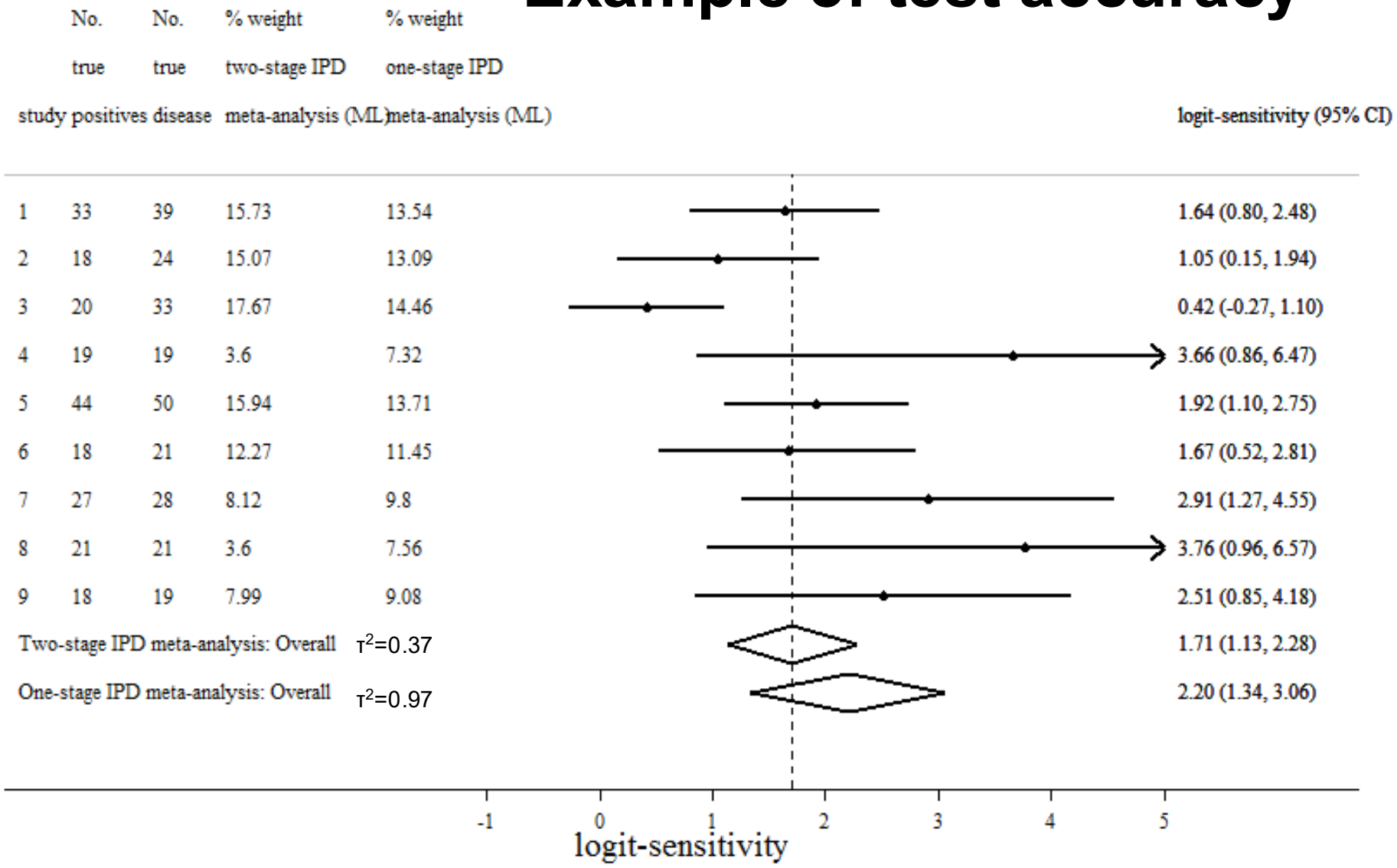
Example 2: trials with zero events

- Simmonds et al. combine IPD from 7 trials examining the effect of hormone replacement therapy (HRT) on the incidence of heart disease.
- zero and few events in all studies – must use the one-stage approach here

	Number of women		Number of cardiovascular disease events	
Study	Control	Treatment	Control	Treatment
1	174	701	0	5
2	14	15	1	0
3	16	15	0	1
4	20	20	1	1
5	26	29	0	1
6	84	84	3	1
7	66	68	0	3

Approach	$\boldsymbol{OR}\ (95\%\ \boldsymbol{CI})$
One-stage (ML, with centering)	1.91 (0.50 to 7.28)
Two-stage (ML, continuity corrections)	1.31 (0.44 to 3.93)

Example 3: test accuracy



Stijnen T, Hamza TH, Özdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med* 2010;29:3046-67.

Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol* 2008;61(1):41-51.

PART 3

Individualised prediction

& other notable examples of IPD meta-analysis

"I never make predictions and I never will"

Paul Gascoigne

Stratified medicine

- Increasing interest in *personalised* or *precision* or *stratified* medicine

- We want to tailor treatment to individuals, or to groups of similar individuals

- To do this, we need **individual patient data (IPD)** to identify individual-level factors (covariates) that *modify* treatment response

- Essentially, what factors cause some patients to respond better to treatment than others?

Stratified medicine

- For commissioners of healthcare

  - stratified medicine offers the potential to ***maximise treatment related benefit*** and ***reduce treatment related harm***

- For developers of new interventions

  - stratification may offer the opportunity to rescue a treatment which fails to show overall benefit in unselected patients, but that might have ***worthwhile benefit in an identifiable subgroup***

Stratified medicine

• Statistically, this means we want to examine & estimate so-called treatment-covariate interactions

- *i.e. quantify how particular covariates interact with treatment effect*

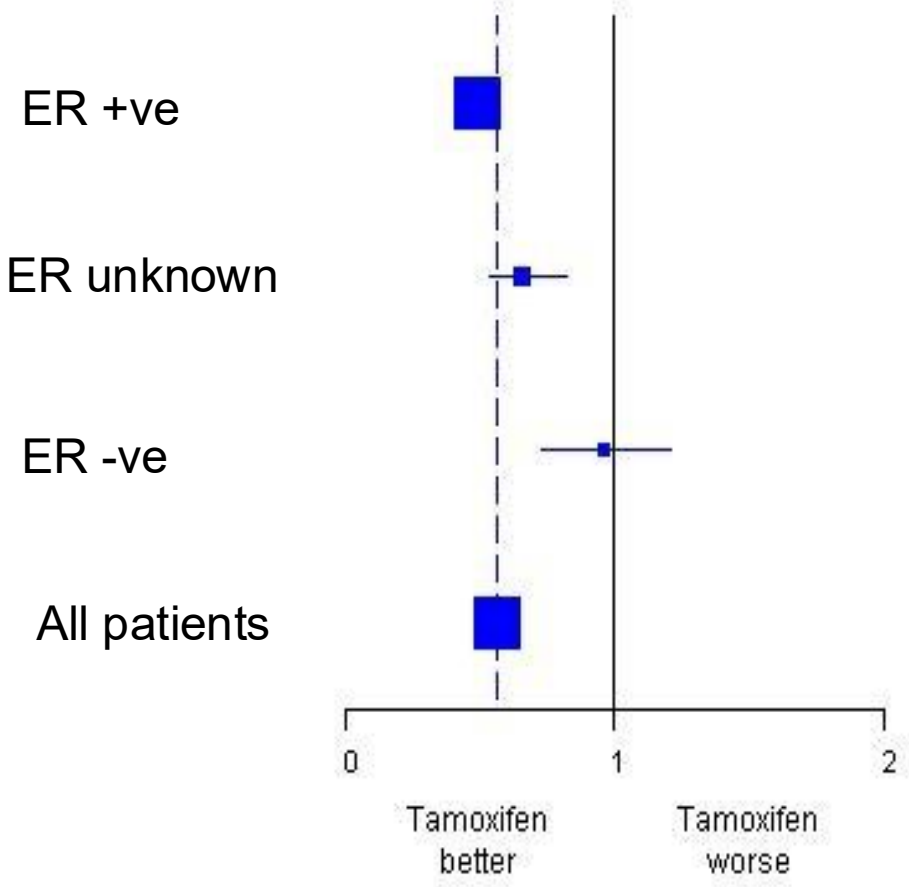
• Also known as subgroup effects & effect modifiers

• Individual studies usually have *low power* to detect them, as they are powered on the overall treatment effect (the average across all individuals)

• By combining studies, meta-analysis thus offers an opportunity to increase power to detect true treatment-covariate interactions

Example: Estrogen receptor in breast cancer

• Tamoxifen is only given to patients who are ER positive, as an individual patient data meta-analysis found …



Statistical methods to identify effect modifiers

Two-stage approach

- Estimate within-study interactions in each study separately
- Combine using standard meta-analysis methods

One-stage approach

- Fit a regression model (with random effects) stratified by study, and including treatment, covariate, & interaction terms
- Careful: Including a single interaction between treatment and a covariate AMALGAMATES within-study & across-study interactions
- Separate them by centering covariate by its mean …

Riley RD et al. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: Statistical recommendations for conduct and planning.

Stat Med 2020: 39; 2115-2137

Understanding effect modifiers in meta-analysis

Assess within-study interaction (subgroups) using IPD

- Effect of individual covariates on treatment effectiveness
- Results tailored to individual patient
- e.g. the treatment effect for males compared to females is …
- Explains within-study variability (at the patient-level)

Understanding effect modifiers in meta-analysis

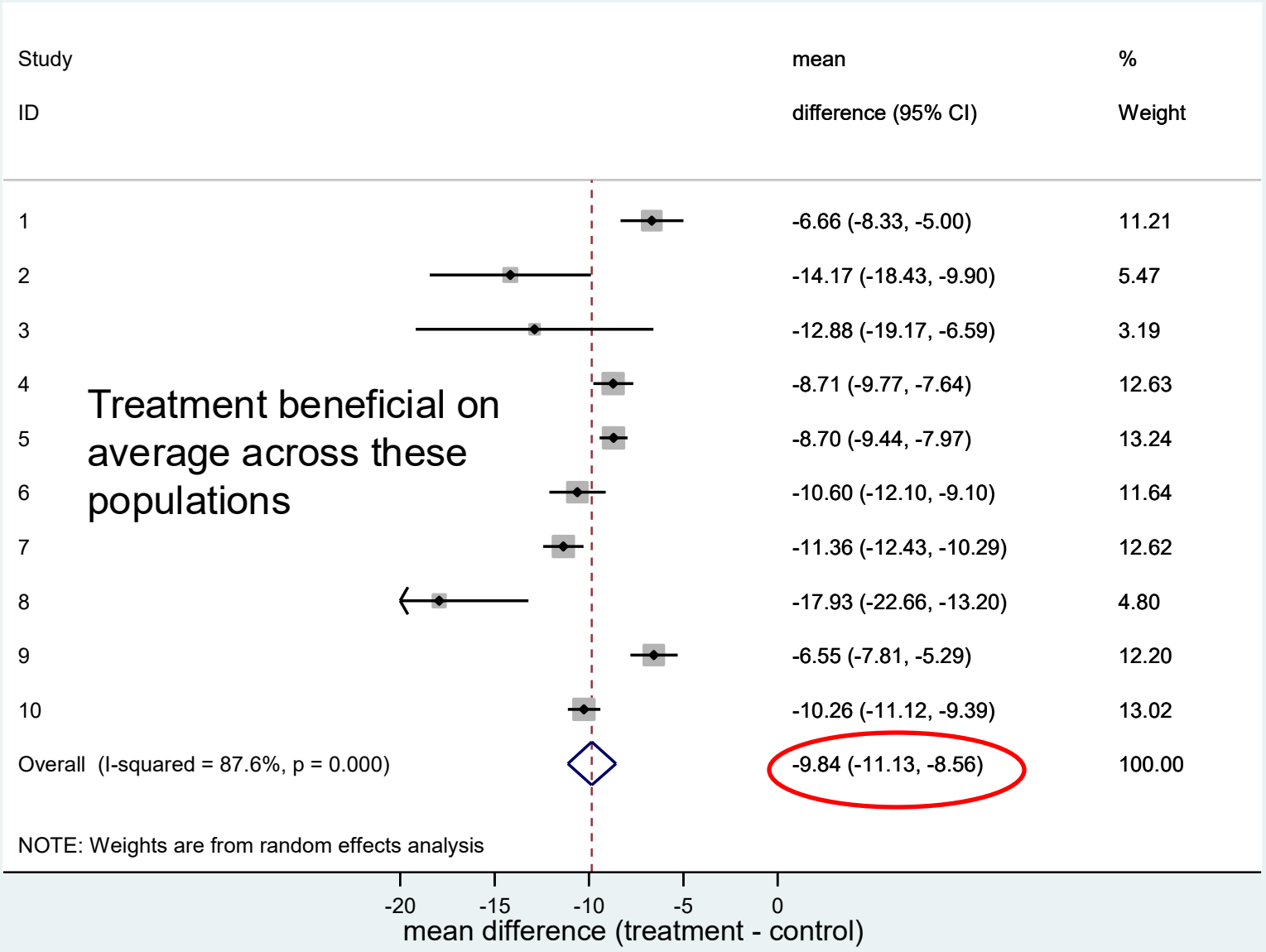
Assess within-study interaction (subgroups) using IPD

- Effect of individual covariates on treatment effectiveness
- Results tailored to individual patient
- e.g. the treatment effect for males compared to females is …
- Explains within-study variability (at the patient-level)

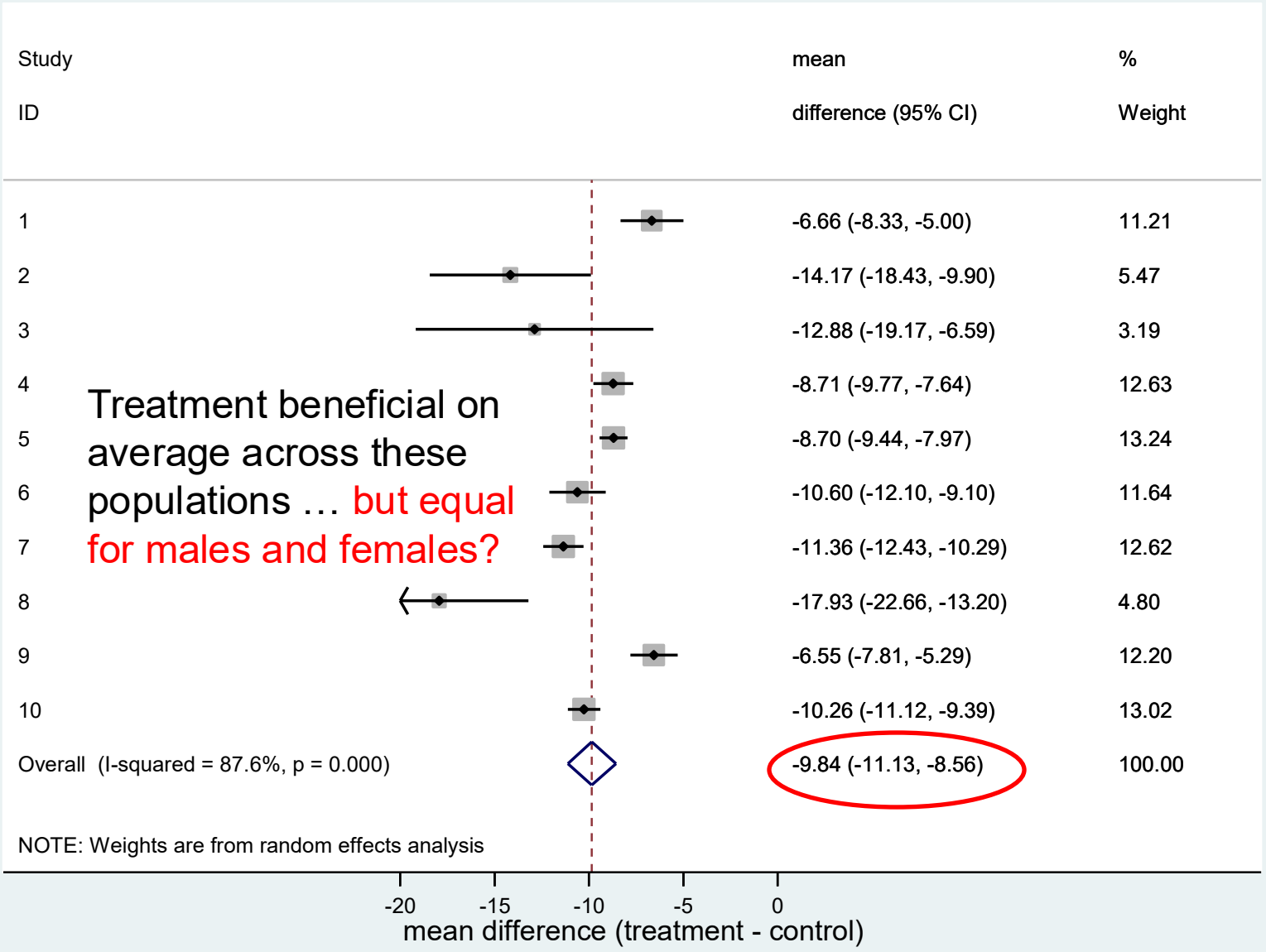
But meta-analysts often consider the across-study interaction

- How mean patient-level covariate in a study is associated with the mean treatment effect
- Meta-regression: How does the treatment effect change across studies as the proportion of males changes across studies?
- Explains between-study variability BUT may not reflect patient-level relationship due to ecological bias or confounding

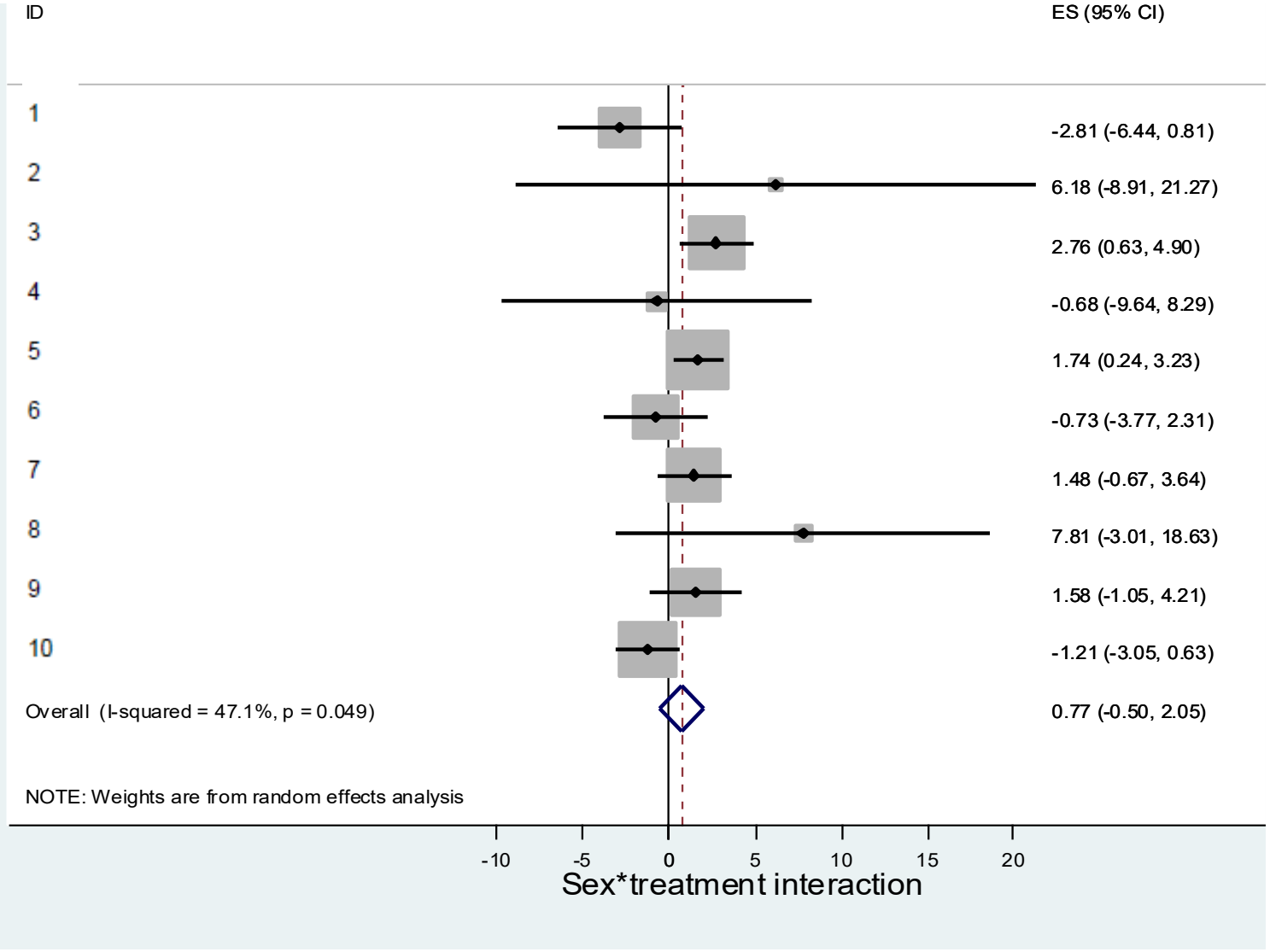
Example: meta-analysis of 10 hypertension trials



Example: meta-analysis of 10 hypertension trials



Two-stage approach: Obtain and pool the difference in treatment effect for males compared to females (within-study interactions)



Example: meta-analysis of 10 hypertension trials

- How does being male modify treatment effect on SBP?
- Within-study effect
- γ_w = 0.77 (-0.5 to 2.05)

if for females the treatment
reduces SBP by 20 mmHg
more than placebo

then for males the treatment
reduces SBP by 19.23 mmHg
more than placebo

non-significant

Example: meta-analysis of 10 hypertension trials

- How does being male modify treatment effect on SBP?

Within-study effect	Across-study effect
γ_W = 0.77 (-0.5 to 2.05)	γ_A = 15.02 (8.98 to 21.1)
if for females the treatment reduces SBP by 20 mmHg more than placebo	if female studies have an underlying treatment effect that reduces SBP by 20 mmHg
then for males the treatment reduces SBP by 19.23 mmHg more than placebo	then male studies have an underlying treatment effect that reduces SBP by 4.98 mmHg
non-significant	significant

DIFFERENT CONCLUSIONS, DUE TO AGGREGATION BIAS / CONFOUNDING

Example: meta-analysis of 10 hypertension trials

- How does being male modify treatment effect on SBP?
- Within-study effect

?

NO IPD

Across-study effect

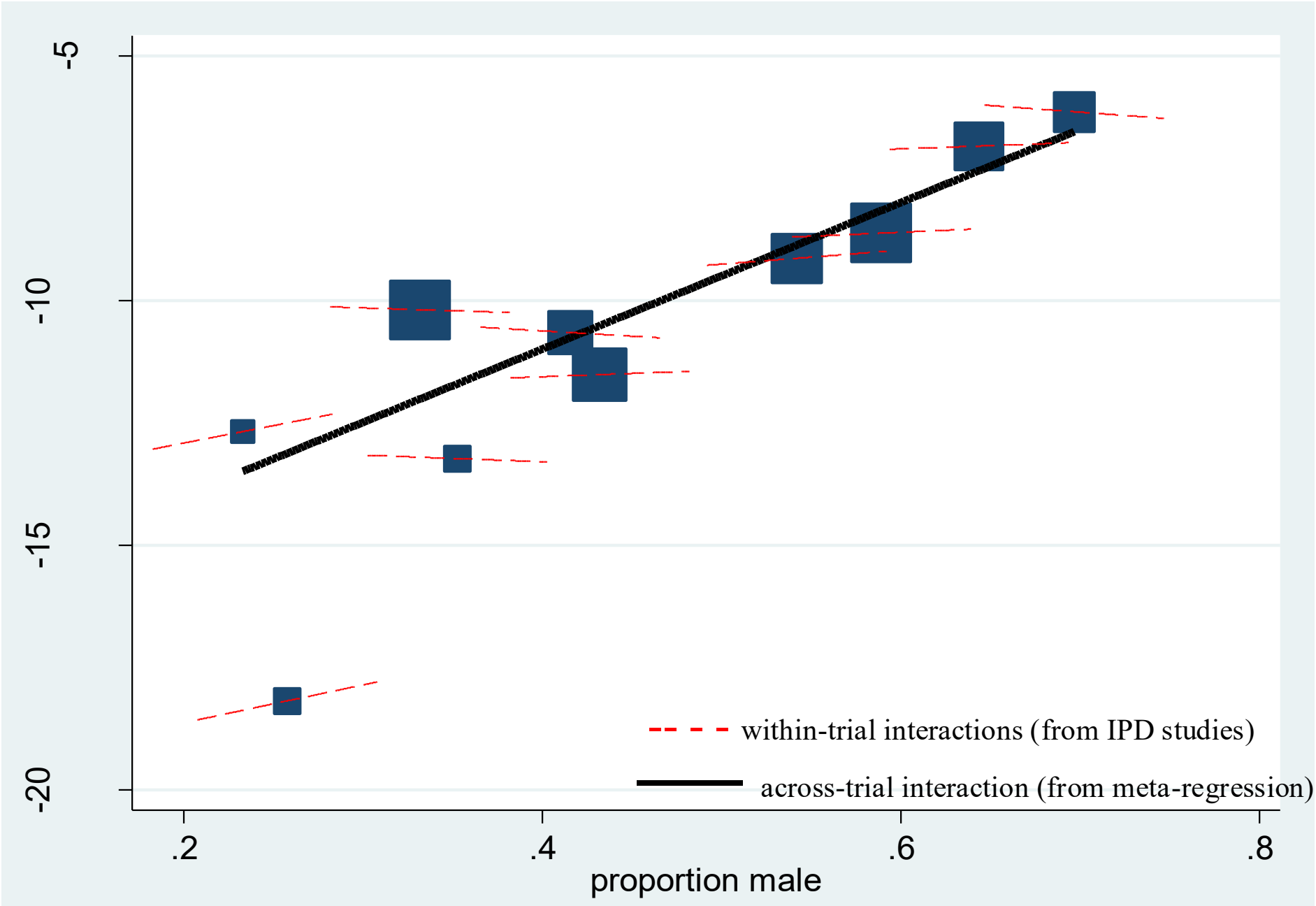
γ_A = 15.02 (8.98 to 21.1)

if female studies have an underlying treatment effect that reduces SBP by 20 mmHg

then male studies have an underlying treatment effect that reduces SBP by 4.98 mmHg

significant

Example: graphical illustration



“I have never, and will not, start predicting the future… I don’t do predictions ever.”

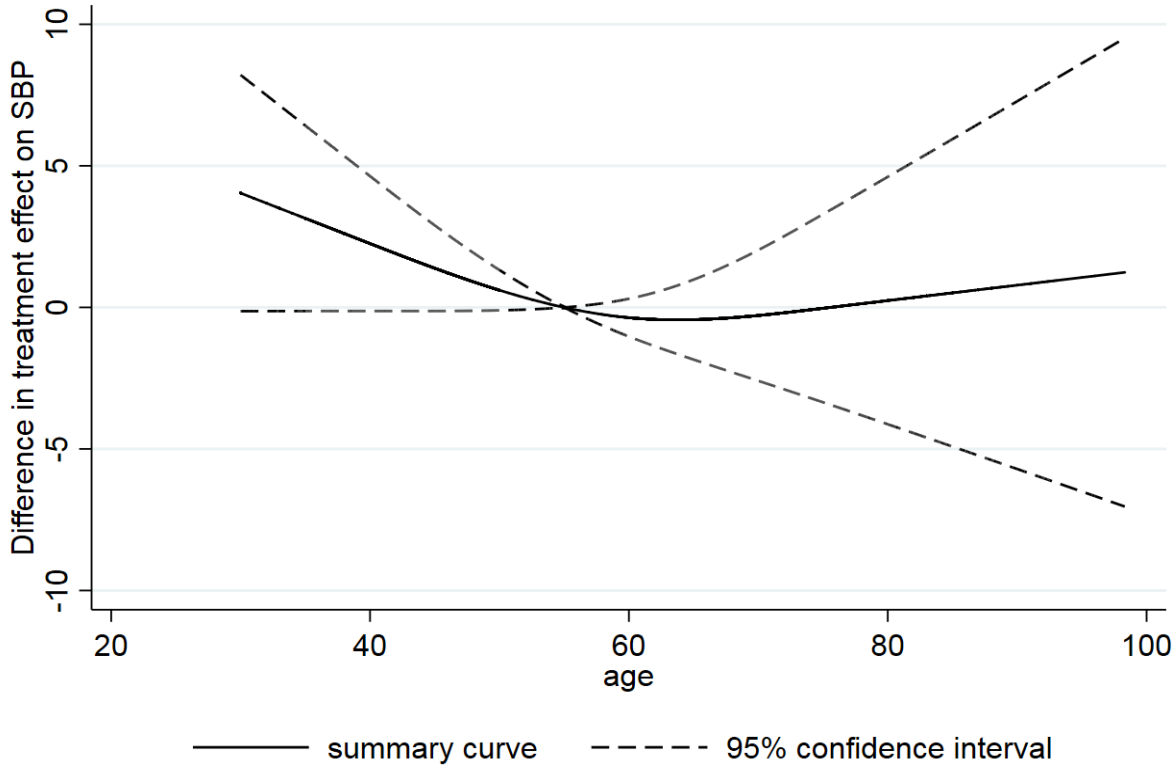
Andrea Leadsom (MP), 5th December 2018

(a few hours later)

“I am a very strong arch Brexiteer, I genuinely believe that we have a bright future ahead of us when we leave the EU”

Non-linear relationships

- Wang et al., and then Riley et al., use IPD from 10 randomized trials to examine whether the effect of anti-hypertensive treatment differs according to age.
- IPD allows non-linear interaction to be examined - compared to those aged 55, younger patients benefit less than older benefits



Wang JG, Staessen JA, Franklin SS, et al. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. Hypertension 2005;45(5):907-13

Riley RD, Debray TPA, Fisher D, et al. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: Statistical recommendations for conduct and planning. Stat Med 2020;39(15):2115-37

A related field: IPD meta-analysis for risk prediction models

External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges

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Access to big datasets from e-health records and individual participant data (IPD) meta-analysis is signalling a new advent of external validation studies for clinical prediction models. In this article, the authors illustrate novel opportunities for external validation in big, combined datasets, while drawing attention to methodological challenges and reporting issues.

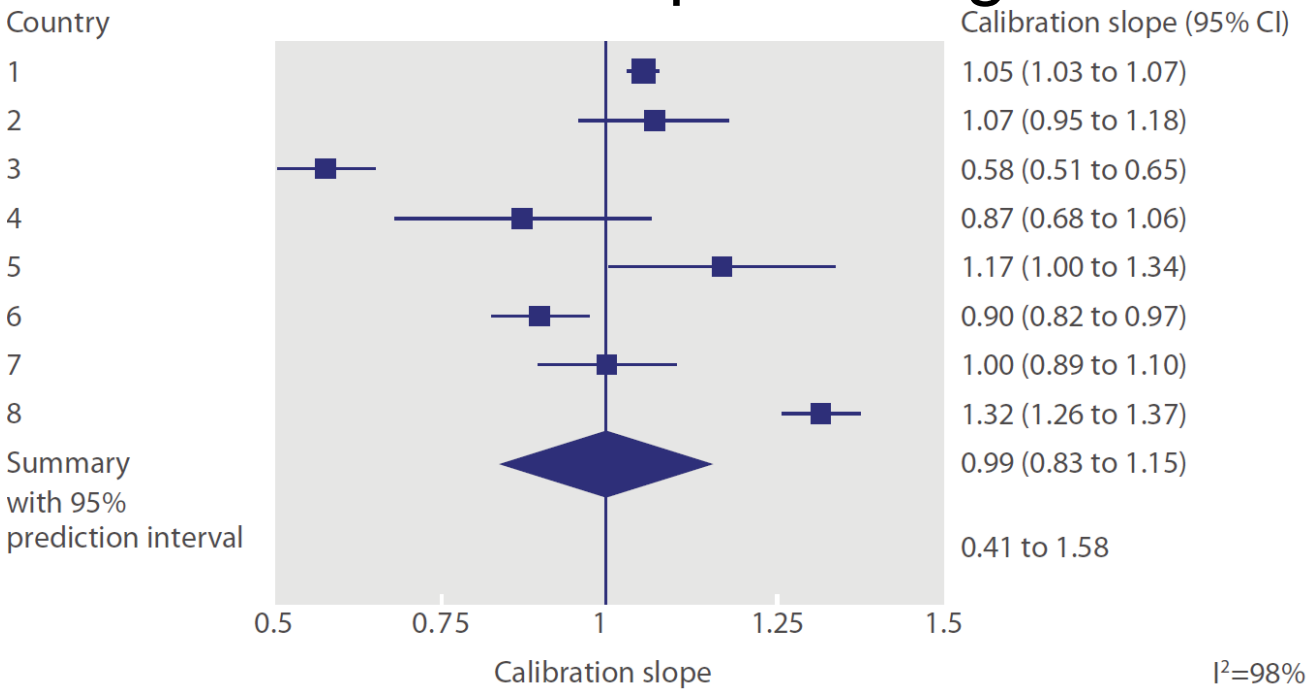
hazard ratios). Well known examples are the Framingham risk score and QRISK2,[4 5] which estimate the 10 year risk of developing cardiovascular disease; the Nottingham prognostic index, which predicts the five year survival probability of a woman with newly diagnosed breast cancer;[6 7] and the Wells score for predicting the presence of a pulmonary embolism.[8 9]

In 2009, *The BMJ* published a series of four articles to guide those undertaking prediction model research,[2 10-12] and further recommendations were made in the 2013 PROGRESS series.[3 13-15] These articles all emphasised three fundamental components of prediction model research: model development, external validation, and impact evaluation.

External validation in multiple settings

OPTION 1:

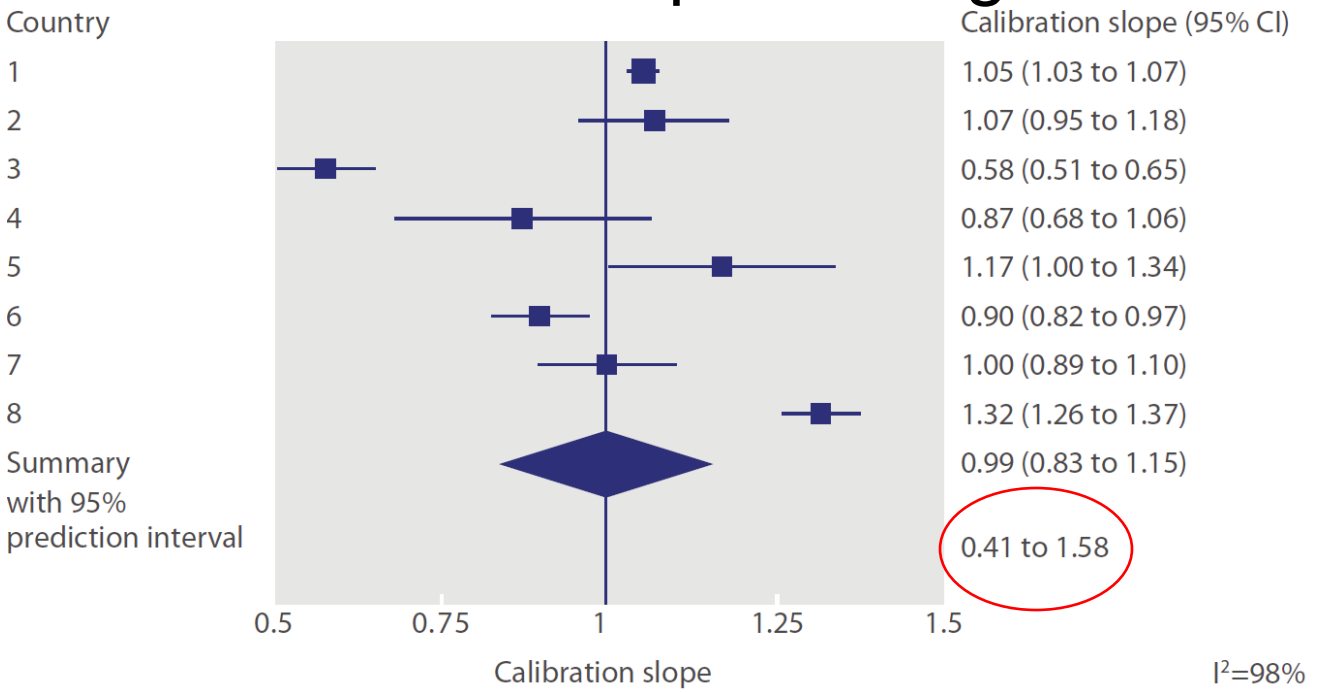
No recalibration



External validation in multiple settings

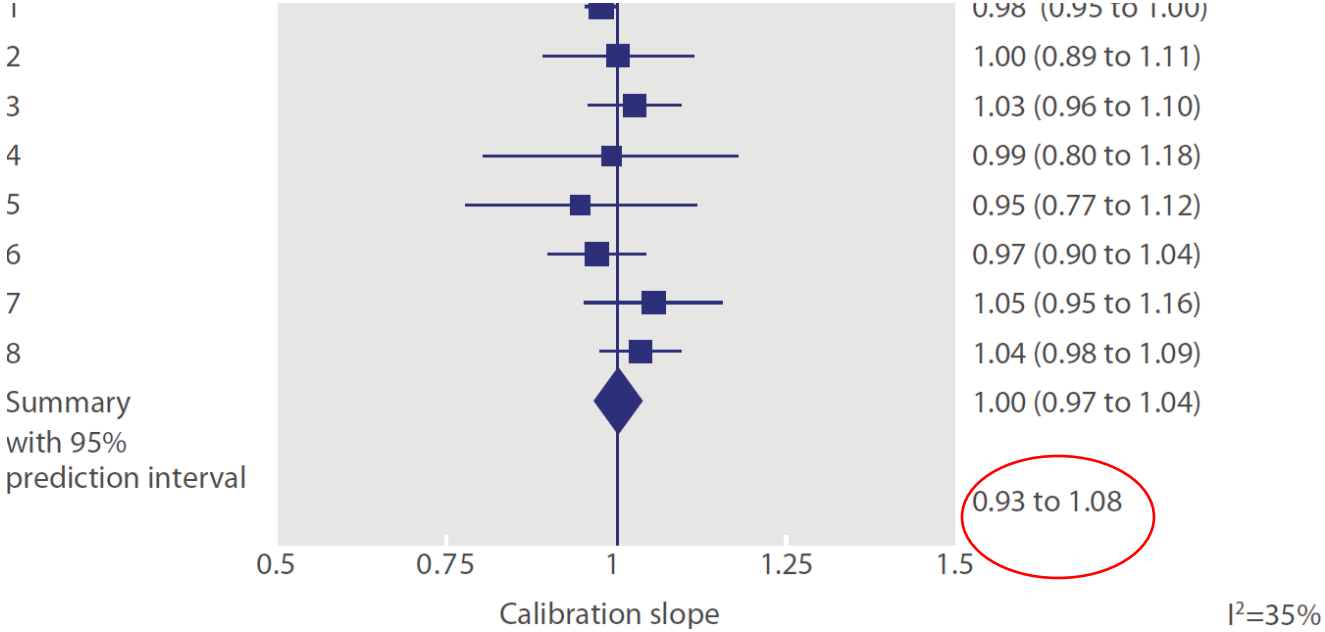
OPTION 1:

No recalibration



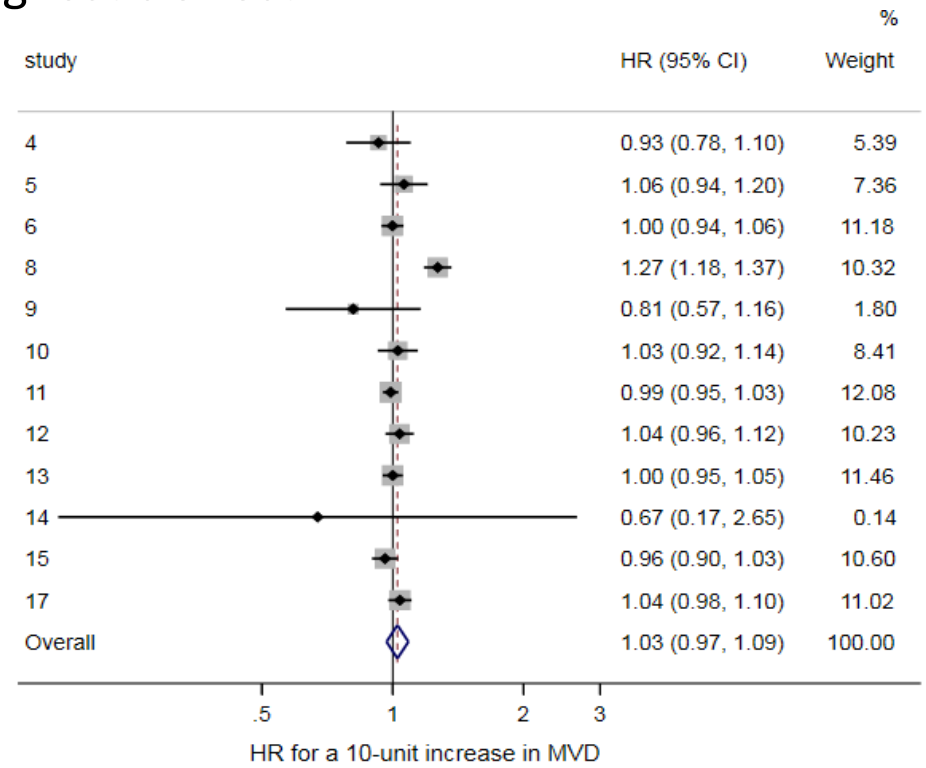
OPTION 2:

Recalibration of the baseline hazard



Added Prognostic Value

- IPD meta-analysis of IPD from 17 published and unpublished studies, involving a total of 3200 participants in non-small-cell lung carcinoma
- Is microvessel density (MVD) a prognostic factor for death?
- IPD enabled results by measurement method (here, all vessels method), adjustment for age and stage of disease, & analysis of continuous scale
- **Results:** contradict an earlier meta-analysis using published aggregate data that concluded MVD was a prognostic effect



Trivella M, Pezzella F, Pastorino U, et al. Microvessel density as a prognostic factor in non-small-cell lung carcinoma: a meta-analysis of individual patient data. *Lancet Oncology* 2007;8(6):488-99

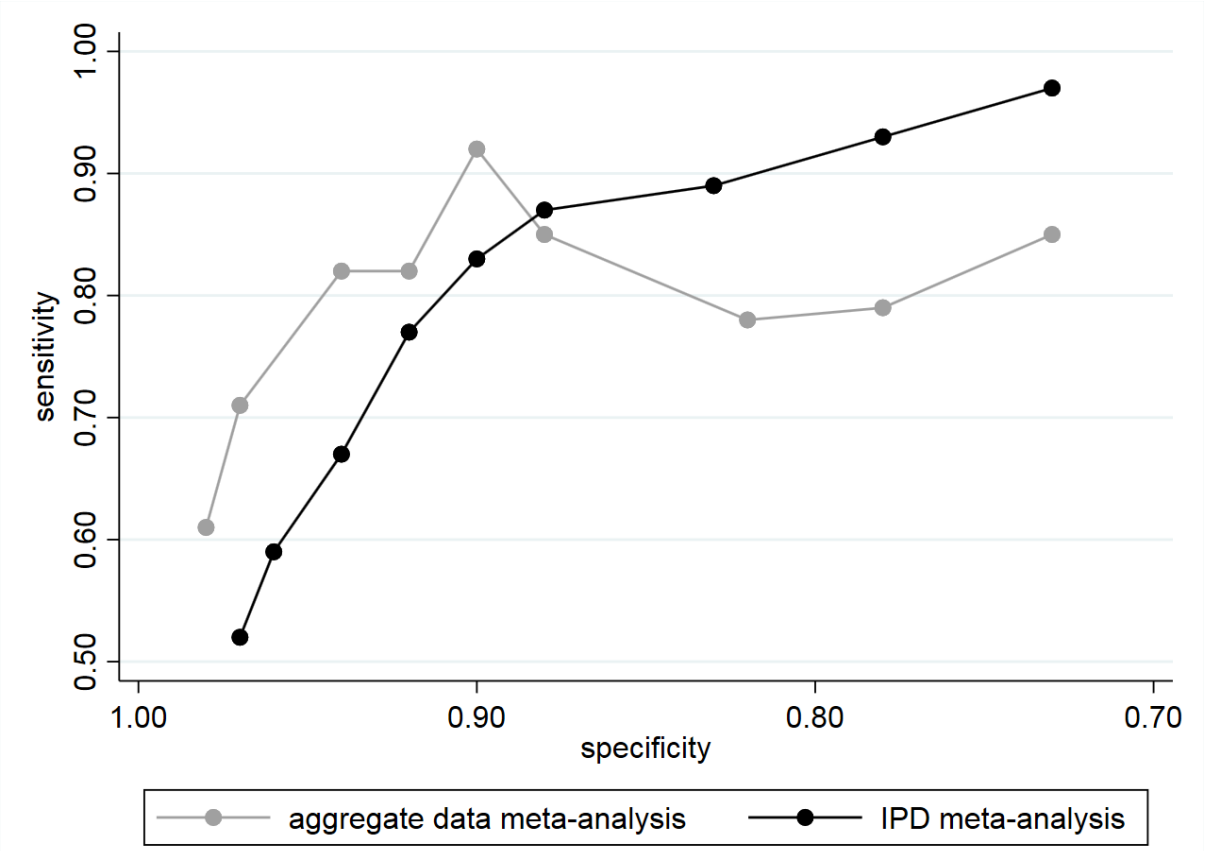
Test accuracy at multiple thresholds

- For continuous tests, different studies (selectively) report results at different thresholds
- This leads to different studies per threshold
- IPD allows any threshold to be examined in all studies and a proper ROC curve to be constructed

Figure based on:

Levis B,, et al. Selective Cutoff Reporting in Studies of Diagnostic Test Accuracy: A Comparison of Conventional and Individual-Patient-Data Meta-Analyses of the Patient Health Questionnaire-9 Depression Screening Tool. *Am J Epidemiol* 2017;185(10):954-64

The points shown correspond to PHQ-9 threshold values of 7 to 15, from right to left.



PART 4:

Are IPD meta-analyses

always the 'gold-standard'?

Is IPD meta-analysis really the gold-standard?

- 'Gold-standard' often used to describe the IPD approach
- Many reasons why IPD is potentially preferable

- Yet little consideration of potential biases in IPD meta-analyses

- For example, biases may act in:
  - the identification of relevant studies,
  - the decision about which studies to seek IPD from,
  - the amount of IPD obtained from studies,
  - the type of studies that agree to provide their IPD

“We have to reduce our expectations of England and we have the players to do it”

Steve McLaren

Evidence synthesis using IPD

Possible disadvantages:

- Costly (data managers, advanced statistics, specialised techniques, travel to see collaborators)
- Time-consuming (e.g. to obtain, collate, manage IPD)

  "checking, validation and standardisation of all datasets took nearly two years" (Trivella et al. Lancet Oncol 2007; 8: 488–99)

- Inconsistent variables, data coding, measurement methods, etc used from study to study (heterogeneity still likely!)

- Does not solve a study being poor quality (high risk of bias)
- More advanced statistical methods required
- Dealing with missing patient-level data

Collecting IPD can be painful!

BMJ

BMJ 2013;347:f6927 doi: 10.1136/bmj.f6927 (Published 2 December 2013)

VIEWS & REVIEWS

OPEN DATA CAMPAIGN

Why did it take 19 months to retrieve clinical trial data from a non-profit organisation?

Asbjørn Hróbjartsson *The Nordic Cochrane Centre, Copenhagen, Denmark*

For just one of the trials:

The emails we received during the prolonged exchange were all friendly, and the individuals involved were helpful and understood the need for data sharing, but they were hampered by inflexible, formalistic, and slow bureaucratic procedures. Since our first inquiry we communicated with four people, sent 25 emails, filled in four data use agreement forms, and waited one year and seven months.

Organisations finalising a data sharing agreement

Summary

- IPD meta-analysis involves obtaining and synthesising the raw patient-level data from each study
- May be costly, time-consuming and painful to obtain IPD from study authors … but has many potential advantages

- Increasingly needed in era of data sharing & stratified medicine
- Allows us to go beyond overall treatment effects, and examine subgroups & treatment-covariate interactions

  (more generally IPD allows individualised prediction)

- Meta-analysis involves a two-stage or one-stage approach
- Two-stage approach often easiest
- Don't automatically assume a published IPD meta-analysis is the gold-standard: many issues may still exist

NEW WEBSITE www.ipdma.co.uk

INDIVIDUAL PARTICIPANT DATA (IPD) META-ANALYSIS

Home | What, why & when? | Guidance & methods | Our book | Software | Videos | Courses & resources

Promoting good practice in IPD meta-analysis projects

- entry-level information & guidance
- important steps & principles
- key articles & references
- videos of seminars & new developments
- statistical software code & information
- training courses & resources

NEW TEXTBOOK

Individual Participant Data Meta-Analysis:
A Handbook for Healthcare research

- Comprehensive introduction to IPD meta-analysis projects
- 18 chapters & over 500 pages, written and edited by researchers with substantial experience in the field
- Key concepts and practical guidance for each stage of an IPD meta-analysis project, alongside examples & learning points.
- Intended for a broad audience
- Covers trials, diagnosis, prognosis & prediction