LECTURE 5:
Using IPD meta-analysis to identify effect modifiers (treatment-covariate interactions)

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Aims

- **Motivation: Importance of stratified medicine**
- What do we mean by **interactions**
  - One-step and two-step approaches
- Differences from meta-regression of summary data
  - Threat of **ecological bias** & how to remove it
- Illustrated examples

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Part 1:

Rationale

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Stratified medicine

- Increasing interest in *stratified medicine* ... also known as *individualised* or *personalised* or *precision* medicine
- We want to tailor treatment to individuals, or to groups (strata) of similar individuals
- To do this, we need to identify individual-level factors (covariates) that *modify* treatment response
- Essentially, what factors cause some patients to respond better to treatment than others?

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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*
  - or an intervention ("targeted agent") may be developed *specifically for an identifiable subgroup*

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Stratified medicine

- Statistically, this means we want to quantify how particular covariates interact with the treatment effect
  - treatment-covariate interactions
  - also known as subgroup effects; effect modifiers
- Individual studies usually have *low power* to detect them, as studies are powered on the overall treatment effect
- By combining studies, meta-analysis thus offers an opportunity to increase power to detect true treatment-covariate interactions
  - and hence, which patients truly benefit and which do not

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Low power to detect interactions in a single study

Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives

Health Technology Assessment 2001; Vol. 5: No. 33

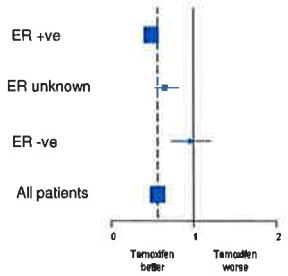
Methodology

ST Brookes
E Whitley
TJ Peters
PA Mulheran
M Egger
G Davey Smith

as the overall treatment effect. However, power was considerably reduced for smaller interactions, which are much more likely in practice. The inflation factor required to increase the sample size to enable detection of the interaction with the same power as the overall effect varied with the size of the interaction. For an interaction of the same magnitude as the overall effect, the inflation factor was 4, and this increased dramatically to ≥ 100 for more subtle interactions of < 20% of the overall effect.

Example: Estrogen receptor in breast cancer

- Tamoxifen is only given to patients who are ER positive, as an IPD meta-analysis found ...



Part 2:

Estimation of interactions: Two-stage approach

A two-stage approach

- So how do we estimate treatment-covariate interactions in an IPD meta-analysis?
- Interested in testing for a difference in treatment effect between two (or more) participant subgroups

N.B. Inappropriate to just look at subgroups separately ... must *test* for interaction before concluding that one subgroup is better than another!

(see e.g. Altman and Bland, 2003)

- Consider an example with a continuous outcome:
  - 10 trials in hypertension (high blood pressure)
  - Outcome is systolic blood pressure (SBP)

Continuous data IPD

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

Can see that treatment effects, baseline factors and prognostic variables are available *per individual*

(note data are truncated for each study, as actually hundreds of patients)

A two-stage approach

(a) Overall treatment effect – i.e. NOT the interaction (yet!)

Step 1: Estimate the treatment effect and its variance in each IPD study using an appropriate method, such as analysis of covariance

Step 2: Take the effect estimates for each study, and pool them in a standard random-effects meta-analysis

- Pooled treatment effect (across all individuals)
  = -9.84 (95% CI: -11.13 to -8.56)
- So hypertension treatment is significantly effective in reducing systolic blood pressure by, on average, 9.84 mm Hg more than control.

Example: meta-analysis of 10 hypertension trials

Stata code:

```
. use "Practical 1\SBP.dta", clear
. label variable trialdummy "Study ID"
. ipdmetan, study(trialdummy) re
      forestplot(xlabel(-20(5)0) effect(Mean difference)
      xtitle(Mean difference (treatment - control)) nonull
      range(-35 0) astext(40))
      : regress sbpl treat sbpi
```

Load dataset

Label the trial ID variable

Example: meta-analysis of 10 hypertension trials

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      xtitle(Mean difference (treatment - control)) nonull
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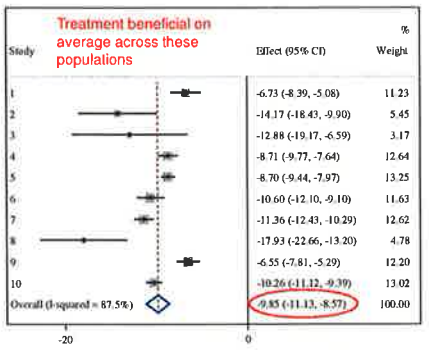
      : regress sbpl treat sbpi
```

Load dataset

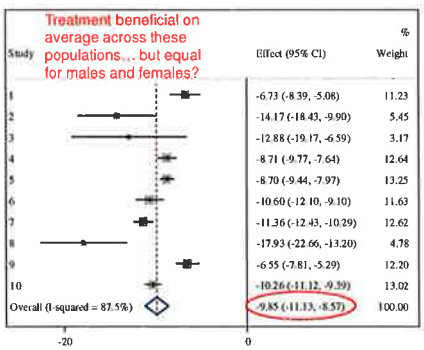
Label the trial ID variable

Aesthetic options; ignore for now

Example: meta-analysis of 10 hypertension trials



Example: meta-analysis of 10 hypertension trials



A two-stage approach

(b) Now let's do an interaction!

Effect of sex on the treatment effect

- Let 1 = males, and 0 = females

Step 1: Estimate the interaction between sex covariate and treatment effect, and its variance, in each IPD study separately using an appropriate method, such as analysis of covariance

Step 2: Take the interaction estimates for each study, and combine them in a usual fixed-effect of random-effects meta-analysis

A two-stage approach

(b) Interaction: effect of sex on the treatment effect

- *sex* = 1 for males, and 0 for females;
- *treat* = 1 for treatment, and 0 for control
- Let *i* = study, and *j* = patient

Change in control response for males

Treatment effect for females

STEP 1: $$SBP_{ij} = \phi_i + \beta_{1_i} SBP_{0ij} + \beta_{2i} sex_{ij} + \theta_i treat_{ij} + \gamma_i (sex_{ij} \times treat_{ij}) + \varepsilon_{ij} \qquad \varepsilon_{ij} \sim N(0, \sigma_i^2)$$

Change in response for a 1-unit increase in SBP_0

Control response for females with SBP_0 = 0 in study *i*

treatment-sex interaction

Residual error

$\hat{\gamma}_i$ = Estimated change in treatment effect for males compared to females for study *i*

A two-stage approach

(b) Interaction: effect of sex on the treatment effect

- *sex* = 1 for males, and 0 for females;
- *treat* = 1 for treatment, and 0 for control
- Let *i* = study, and *j* = patient

STEP 2: Fixed effect or random effects meta-analysis

e.g. fixed-effect meta-analysis

$$\hat{\gamma}_i = \gamma_W + \varepsilon_i \qquad \varepsilon_i \sim N(0, \mathrm{var}(\hat{\gamma}_i))$$

$\hat{\gamma}_W$ = *Summary estimate of the difference within (W) studies in the treatment effect for males compared to females*

A two-stage approach

Stata code:

```
. use "Practical 1\SBP.dta", clear
. label variable trialdummy "Study ID"
. ipdmetan, study(trialdummy) re interaction
      forestplot(effect(mean diff.)
      xtitle("Sex*treatment interaction"
      "(Difference in mean difference, males - females)")
      range(-35 22) astext(40))
      : regress sbpl treat##sex sbpi
```

Load dataset

Label the trial ID variable

A two-stage approach

Stata code:

```
. use "Practical 1\SBP.dta", clear
. label variable trialdummy "Study ID"
. ipdmetan, study(trialdummy) re interaction
      forestplot(effect(mean diff.)
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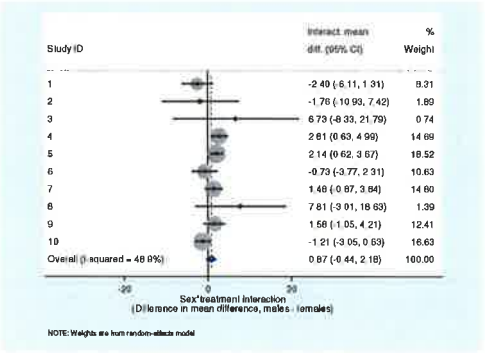
      range(-35 22) astext(40))
      : regress sbpl treat##sex sbpi
```

Load dataset

Label the trial ID variable

Aesthetic options; ignore for now

Can display results on a forest plot again



Part 3:

Estimation of interactions: why is IPD meta-analysis better than meta-regression of aggregate data?

If IPD are not available …

- Hope that study authors report the treatment-covariate interactions ….
  - If they do, then we can easily combine them in the second stage of the two-stage approach
  - For a binary subgroup covariate, e.g. sex, we can easily recreate the interaction if the treatment effect is given for males and females separately
  - Unfortunately, treatment-covariate interactions (or the means to recreate them) are rarely available from study publications
- If some studies provide IPD, and some non-IPD studies provide treatment-covariate interactions then:

(1) Estimate the treatment-covariate interactions in the IPD studies

(2) Combine all available interaction estimates (i.e. from IPD studies and non-IPD studies) in a standard fixed-effect or random-effects meta-analysis

If IPD are not available …

- Often one can only do a meta-regression without IPD

i.e. regress the study (i) treatment effect estimates (θ_i) against average patient-level covariates

$$\hat{\theta}_i = \alpha_i + \gamma_A(\text{proportion male})_i + u_i + \varepsilon_i \qquad \varepsilon_i \sim N(0, \mathrm{V}(\hat{\theta}_i)) \qquad u_i \sim N(0, \tau^2)$$

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i.e. regress the study (i) treatment effect estimates (θ_i) against average patient-level covariates

$$\hat{\theta}_i = \alpha_i + \gamma_A(\text{proportion male})_i + u_i + \varepsilon_i \qquad \varepsilon_i \sim N(0, \mathrm{V}(\hat{\theta}_i)) \qquad u_i \sim N(0, \tau^2)$$

Called the 'across-study interaction'.

Tells us how much the overall treatment effect differs with proportion male across studies (e.g. in a study with only males compared to in a study with only females)

- crucially, this is in general *different* to the 'within-study interaction' obtained by analysing the IPD (see later)

(e.g. Riley et al., 2008; Fisher et al., 2011)

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Within-study vs Between-study interactions

Within-study interaction (usually only from IPD)

- Describes effect of covariates on treatment effectiveness at the patient level
- Therefore, results tailored to individual patients
- e.g. the treatment effect for *a male* compared to *a female* is …
- Explains within-study variability (residual error)

Across-study interaction

- Describes how *average* covariate in a study is associated with the *overall* treatment effect
- Results relate only to the study (population) level
- e.g. In a population with a proportion of 70% males, the predicted average treatment effect is …
- or, more abstractly: the treatment effect in an all-male population compared to an all-female population is …
- Explains between-study variability

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Within-study versus between-study interactions

- Within-study effects meaningful to individual patient
- But usually not obtainable if IPD not available
- Across-study effects meaningful at the population level
- Available when mean covariate is available for each study
- Simulation studies show that in *ideal* conditions across-study interactions will reflect within-study interactions ('unbiased') for *continuous* outcomes, but not necessarily for binary or time-to-event (survival) outcomes
- However, empirical data suggests that in general the two do not correlate well. Also across-study effects have low power, & prone to ecological bias & confounding across studies: Interpret with caution!
- e.g. studies with high proportion male may also have a higher dose of treatment; thus trend in treatment effect due to dose of drug and not proportion male

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Recent open-access paper: Empirical comparison of across vs within

thebmj

Research Methods & Reporting

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

Article | Related content | Metrics | Responses | Peer review

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Example 1: Application to hypertension data

- How does being male modify treatment effect on SBP?
- Within-study effect
- γ_W = 0.87 (-0.44 to 2.18)

if for a female, the treatment reduces SBP by 20 mmHg more than placebo

then for a male, the treatment reduces SBP by 19.13 mmHg more than placebo

Non-significant

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Example 1: Application to hypertension data

- How does being male modify treatment effect on SBP?

Within-study effect	Across-study effect
γ_W = 0.87 (-0.44 to 2.18)	γ_A = 15.3 (8.10 to 22.6)
if for a female, the treatment reduces SBP by 20 mmHg more than placebo	if an all-female study has an average treatment effect that reduces SBP by 20 mmHg
then for a male, the treatment reduces SBP by 19.13 mmHg more than placebo	then an all-male study has an average treatment effect that reduces SBP by 4.7 mmHg
Non-significant	Significant

VERY DIFFERENT CONCLUSIONS, DUE TO ECOLOGICAL BIAS / CONFOUNDING

Example 1: Application to hypertension data

Stata code

Within-trials effect (we've seen this already a few slides back)

```
ipdmetan, study(trialdummy) re interaction
     : regress sbpl treat##sex sbpi
```


Example 1: Application to hypertension data

- How does being male modify treatment effect on SBP?

Within-study effect	Across-study effect
?	γ_A = 15.3 (8.10 to 22.6)
NO IPD	if an all-female study has an average treatment effect that reduces SBP by 20 mmHg
	then an all-male study has an average treatment effect that reduces SBP by 4.7 mmHg
	Significant

Example 1: Application to hypertension data

Stata code

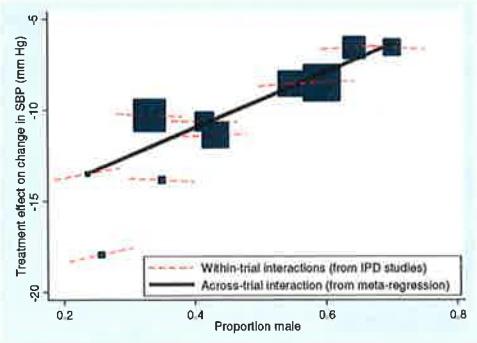
Within-trials effect (we've seen this already a few slides back)

```
. ipdmetan, study(trialdummy) re interaction
     : regress sbpl treat##sex sbpi
```

Across-trials effect: we will artificially create an aggregate dataset to simulate "no IPD"

```
. ipdmetan, study(trial) saving(noIPD) lcols(sex)
     nooverall nograph : regress sbpl treat sbpi
. use noIPD, clear
. metareg _ES sex, wsse(_seES)
```


Example 1: graphical illustration of "ecological bias"



Stata code to produce plot on previous slide (1)

```
// Save study-level treatment effects and sex ratios
. ipdmetan, study(trial) saving(noIPD, replace) lcols(sex)
      nooverall nograph : regress sbpl treat sbpi

// Save within-trial interaction slopes
. ipdmetan, study(trial) saving(slopes, replace) interaction
      nooverall nograph : regress sbpl treat##sex sbpi

// Load and merge our new datasets
. use noIPD, clear
. rename (_ES _seES) (eff se_eff)
. merge 1:1 _STUDY using slopes

// Generate meta-regression prediction line
. metareg eff sex, wsse(se_eff)
. predict xb
```

Stata code to produce plot on previous slide (2)

```
// Generate co-ordinates of red dashed lines
. gen ylci = eff - _ES*.05
. gen yuci = eff + _ES*.05
. gen xlci = sex - .05
. gen xuci = sex + .05

// Create macro containing commands
// to create red dash lines
. qui count
. forvalues i = 1/`r(N)' {
    local lineplot `"`lineplot' || scatteri `=ylci[`i']'
    `=xlci[`i']' `=yuci[`i']' `=xuci[`i']', c(l) ms(i)
    lc(red) lp(dash) lw(thin)"'
}
```


Stata code to produce plot on previous slide (3)

```
// Finally, create the plot
. twoway scatter eff sex [aw=1/se_eff^2],
    msymbol(square) msize(small)
    || line xb sex, lc(black) lw(thick) `lineplot'
    ||, ytitle(Treatment effect on change in SBP (mm Hg))
    xtitle(Proportion male)
    xlabel(.2(.2).8, format("%3.1f"))
    legend(order(3 "Within-trial interactions (from IPD
    studies)" 2 "Across-trial interaction (from meta-
    regression)") cols(1) ring(0) position(4) nobox)
```

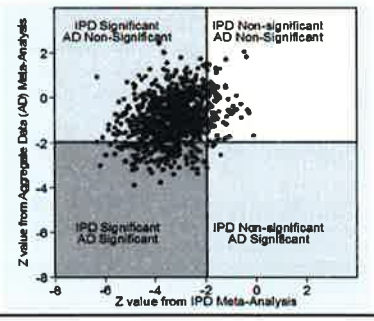

Example 2: Increased power to detect true covariate interactions (Lambert et al., 2002)

- 1000 meta-analyses simulated, each with 5 trials and treatment effective for high risk patients but ineffective for low risk patients.
- Each meta-analysis analysed first using IPD, and then using meta-regression; treatment-covariate interactions estimated in both cases
- The % of 1000 meta-analyses that detect this (true) treatment-covariate interaction with statistical significance gives the power.
- They found that the % is usually far higher when using IPD than when using meta-regression
- BUT the authors failed to separate within- and across-trials effects in their IPD interaction (see one-stage section), meaning that their comparison was within + across vs across only, NOT within vs across!!
- Inadvertently demonstrates the pitfalls of interaction analysis

Example 2: graphical illustration

IPD approach (within + across) has a power of 90.8%

Meta-regression approach (across only) has a power of 10.8%



Example 3: Effect of elevated panel reactive antibodies on the effectiveness of anti-lymphocyte antibody induction (Berlin et al., 2002)

- Meta-analysis of five randomised trials of anti-lymphocyte antibody induction therapy vs control for renal transplant patients
- Odds ratio < 1 (log OR < 0) indicates that odds of treatment failure are smaller in research arm than in control arm
- Interaction: Interested in *difference* in treatment effect (ratio of odds ratios) between patients with elevated antibodies compared to non-elevated
- A meta-regression is used to examine the across-trials interaction:

  estimated difference in the treatment effect (log odds ratio) between a trial with only elevated patients compared to a trial with only non-elevated patients = -0.01 ($p = 0.68$)

- Did the authors need IPD to obtain this result?
- Is there evidence that the treatment effect is different for elevated and non-elevated patients?

- Meta-analysis of five randomised trials of anti-lymphocyte antibody induction therapy vs control for renal transplant patients
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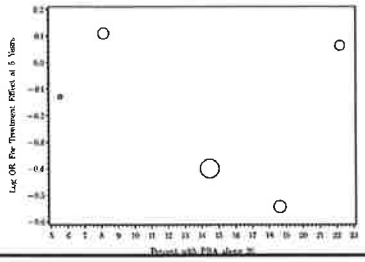
Example 3: Effect of elevated panel reactive antibodies on the effectiveness of anti-lymphocyte antibody induction (Berlin et al., 2002)

- IPD was not required to obtain this result
- Simply did a meta-regression of: logOR = alpha + beta*%elevated
- 'beta' provides the across-trial interaction (meta-regression slope)
- 'beta' = 0.01 (p = 0.68) … only 5 studies, so very little power:



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Example 3: Effect of elevated panel reactive antibodies on the effectiveness of anti-lymphocyte antibody induction (Berlin et al., 2002)

- The reviewers also estimate the pooled within-study interaction

  estimated difference in the treatment effect (log odds ratio) between elevated and non-elevated patients is = - 1.33 (p = 0.01)

- Did the authors need IPD to obtain this result?
- Is there evidence of a difference in treatment effect between elevated and non-elevated patients?
- Suggest potential reasons why there is a substantial difference between within-study & across-study interactions

Example 3: Effect of elevated panel reactive antibodies on the effectiveness of anti-lymphocyte antibody induction (Berlin et al., 2002)

- Now IPD is required – to fit a model at the patient-level
- Obtained within-study interactions via one-stage model

Variable	Unadjusted models*			Adjusted models*		
	Coefficient	Standard error	p-value	Coefficient	Standard error	p-value
Prior transplant	−0.2104	0.7428	0.78	0.5395	0.8739	0.54
Number of donor–recipient HLA-DR mismatches			0.23 (2 d.f.)			0.31 (2 d.f.)
No mismatches (reference)	—	—	—	—	—	—
1 mismatch	−0.6767	0.4521	0.13	−0.4959	0.4616	0.28
2 mismatches	−0.7872	0.5054	0.12	−0.7503	0.5176	0.14
Black race (versus all others)	−0.0630	0.4956	0.90	−0.0239	0.5171	0.96
PRA ≥20 per cent	−1.2315	0.5050	0.015	−1.2785	0.5360	0.01
Diabetes	−0.2333	0.4267	0.58	−0.2600	0.4469	0.42

Why do within-trial and across-trial interactions differ?

- Low power (5 studies = 5 data points!) in meta-regression
- Possibility for "ecological bias" (see scatter plot)
- More power at patient-level (628 patients; 89 elevated), so more chance of detecting effect if true

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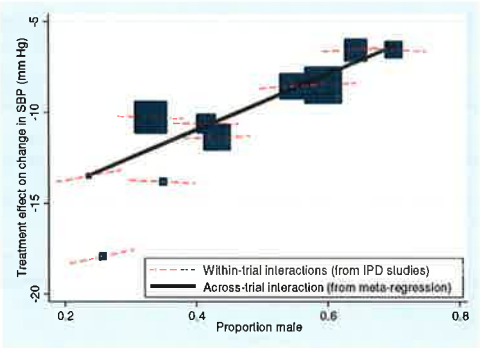
Graphical illustration of "ecological bias" (again!)



Part 4:

Estimation of interactions: One-stage approach

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A one-stage approach

- A one-stage IPD meta-analysis approach can also be used
  - The IPD from all trials are analysed simultaneously
  - Clustering of patients within trials needs to be accounted for
- Quicker and obtain multiple summary estimates together
- Usually obtains similar estimates to two-stage approach

However …

- Analysis of interactions requires *careful separation* of within-study & across-study effects (Riley et al., 2008; Fisher et al., 2011)
- One-stage approach allows modelling of both within-study *and* between-study variability … so must separate them out to avoid *ecological bias*

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One-stage meta-analysis with patient-level covariate

As before, but now include patient-level covariate (z_{ij})

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

(W = within-study interaction)

within-study interaction

One-stage meta-analysis with patient-level covariate

As before, but now include patient-level covariate (z_{ij})

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

(W = within-study interaction)

within-study interaction

Centering z_{ij} (e.g. age of patient *j* in study *i*) about the mean covariate value $\bar{z}_i$ (e.g. mean age) in each study ensures the within-study interaction separated from between-study interaction

In other words, it ensures γ_W explains only patient-level variation in treatment response (not study-level)

One-stage meta-analysis with patient-level covariate

As before, but now include patient-level covariate (z_{ij})

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

(W = within-study interaction)

within-study interaction

$$\theta_i = \alpha + \gamma_A \bar{z}_i + u_i \qquad u_i \sim N(0, \tau^2)$$

Across-trials interaction (= meta-regression result = trial-level association of the treatment effect estimates & covariate means)

Unexplained between-study variance

One-stage meta-analysis with patient-level covariate: Stata code (example)

```
. use "Practical 1\SBP.dta", clear

. bysort trial : egen meansex = mean(sex)
. gen diffsex = sex - meansex

. mixed sbpl i.trial##(c.sbpi i.sex)
        i.treat##(c.meansex c.diffsex)
        || trial: treat, nocons
```

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

$$\theta_i = \alpha + \gamma_A \bar{z}_i + u_i \qquad u_i \sim N(0, \tau^2)$$

One-stage meta-analysis with patient-level covariate: Stata code

```
. use "Practical 1\SBP.dta", clear

. bysort trial : egen meansex = mean(sex)
. gen diffsex = sex - meansex

. mixed sbpl i.trial##(c.sbpi i.sex)
        i.treat##(c.meansex c.diffsex)
        || trial: treat, nocons
```

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

$$\theta_i = \alpha + \gamma_A \bar{z}_i + u_i \qquad u_i \sim N(0, \tau^2)$$

One-stage meta-analysis with patient-level covariate: Stata code

```
. use "Practical 1\SBP.dta", clear

. bysort trial : egen meansex = mean(sex)
. gen diffsex = sex - meansex

. mixed sbpl i.trial##(c.sbpi i.sex)
        i.treat##(c.meansex c.diffsex)
        || trial: treat, nocons
```

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

$$\theta_i = \alpha + \gamma_A \bar{z}_i + u_i \qquad u_i \sim N(0, \tau^2)$$

One-stage meta-analysis with patient-level covariate: Stata code

```
. use "Practical 1\SBP.dta", clear

. bysort trial : egen meansex = mean(sex)
. gen diffsex = sex - meansex

. mixed sbpl i.trial##(c.sbpi i.sex)
      i.treat##(c.meansex c.diffsex)
      || trial: treat, nocons
```

$$SBP_{ij} = \varphi_i + \beta_{1i} SBP_{0ij} + \beta_{2i} z_{ij} + \theta_i \text{treat}_{ij} + \gamma_W \text{treat}_{ij}(z_{ij} - \bar{z}_i) + \varepsilon_{ij}$$

$$\theta_i = \alpha + \gamma_A \bar{z}_i + u_i \qquad u_i \sim N(0, \tau^2)$$

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One-stage method

Can even extend further to include:

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One-stage method

Can even extend further to include:

- multiple patient-level covariates (e.g. age, sex) — Within-study relationships (IPD model)

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One-stage method

Can even extend further to include:

- multiple patient-level covariates (e.g. age, sex) — Within-study relationships (IPD model)
- multiple study-level covariates (e.g. USA vs Europe) or aggregated patient-level covariates (e.g. mean age, proportion male) — Across-study relationships (IPD & AD models)

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One-stage method

Can even extend further to include:

- multiple patient-level covariates (e.g. age, sex) — Within-study relationships (IPD model)
- multiple study-level covariates (e.g. USA vs Europe) or aggregated patient-level covariates (e.g. mean age, proportion male) — Across-study relationships (IPD & AD models)

- **Non-linear trends, complex interactions, …**
- **Non-IPD studies can again be included using dummy variables, & help estimate across-study interactions but not usually within-study interactions**

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One-stage versus two-stage for interactions

One-stage:

- All parameters estimated together; automatically accounts for correlation between parameters
- Facilitates non-linear trends and associations
- Complex model specification, potentially multiple random effects, risk of non-convergence
  - ALSO: must account for study-level clustering (e.g. with study identifier)
  - …and must remove ecological bias
- Perhaps best for deriving a prognostic / risk prediction model

Two-stage:

- Less complex than one-stage, and may be easier to fit
  - Model fitting within each study can be automated, e.g. with `ipdmetan`
- Can easily display results in a forest plot
- Automatically accounts for study-level clustering, and avoids ecological bias
- BUT Ignores correlation between interaction estimate and other parameter estimates within each study
- Difficult to combine non-linear interactions

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Other outcome data types

- So far focused on continuous outcomes
- But same approaches used for binary and time-to-event
- e.g. two-stage approach

  logistic model in each study for a binary outcome

$$\ln(p_{ij}/(1-p_{ij})) = \phi_i + \beta_{1_i} SBP_{0ij} + \beta_{2i} sex_{ij} + \theta_i treat_{ij} + \gamma_i (sex_{ij} \times treat_{ij})$$

  Cox model in each study for time-to-event outcome

$$h(t)_{ij} = h_{0ij}(t)\exp(\beta_{1_i} SBP_{0ij} + \beta_{2i} sex_{ij} + \theta_i treat_{ij} + \gamma_i (sex_{ij} \times treat_{ij}))$$

Then in the second stage meta-analyse the $\hat{\gamma}_i$

Other outcome data types

- So far focused on continuous outcomes
- But same approaches used for binary and time-to-event
- e.g. one-stage approach
  - logistic model for a binary outcome
  - Cox model (or flexible parametric model) for time-to-event (survival) outcome
  - In all cases, centre patient-level covariate to separate within-trial & across-trial interactions and avoid ecological bias

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Cox model example

- 5 trials of epilepsy treatment A versus treatment B
- HR values < 1 favour treatment A
- One-stage IPD meta-analysis using Cox model
- Is age a treatment effect-modifier?
  - what is the change in treatment effect (log HR) for a 1-unit increase in age?

ORIGINAL ANALYSIS (does not separate out within and across-trial interactions):

$$\hat{\gamma} = -0.011 \quad 95\%\,CI: (-0.015, -0.007)$$

CORRECT ANALYSIS (does separate them out):

$$\hat{\gamma}_A = -0.013 \quad 95\%\,CI: (-0.023, -0.003)$$

$$\hat{\gamma}_W = -0.007 \quad 95\%\,CI: (-0.019, 0.05)$$

Discuss!

Example: A common (but flawed) way of presenting survival data interactions

- Often seen in the literature
  - due to apparently simple presentation
  - furthermore, does not require iterative modelling
- Uses neither a one-stage nor a two-stage model in the sense we have been using the terms
  - but if anything, is closer to a two-stage model
- Results in within- and across-trials effects being combined, with no possibility of separating them
  - therefore, results are often over-precise (false-positive)
- Again, shows importance of separating the two

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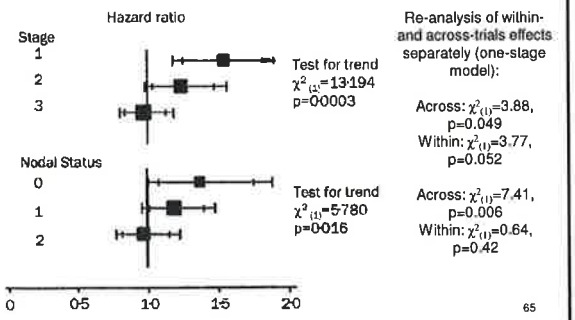
Example of a "flawed" plot

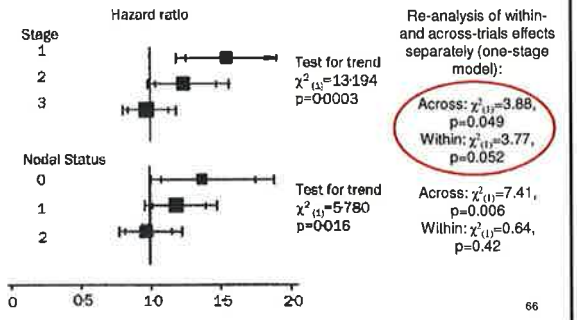
Taken from:
PORT Meta-analysis Trialists Group, Lancet 1998



65

Example of a "flawed" plot

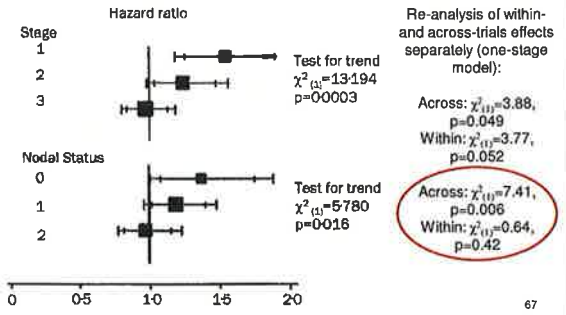
Taken from:
PORT Meta-analysis Trialists Group, Lancet 1998



66

Example of a "flawed" plot

Taken from:
PORT Meta-analysis Trialists Group, Lancet 1998

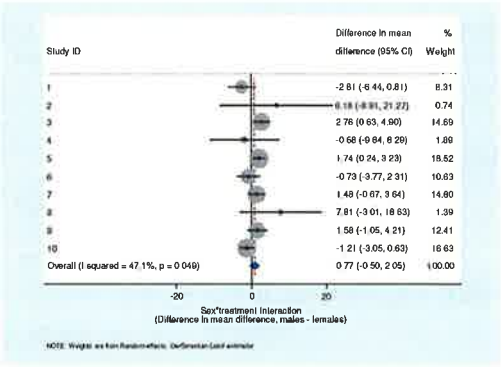


Re-analysis of within- and across-trials effects separately (one-stage model):

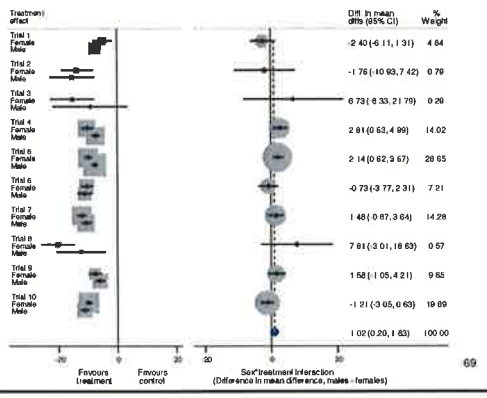
Across: $\chi^2_{(1)}$=3.88, p=0.049
Within: $\chi^2_{(1)}$=3.77, p=0.052

Across: $\chi^2_{(1)}$=7.41, p=0.006
Within: $\chi^2_{(1)}$=0.64, p=0.42

Our recommended alternative (1)



Our recommended alternative (2)



Conclusion

- Stratified medicine a high priority for research funders
- Meta-analysis of within-trial interactions (using IPD) is fundamental to maximising power to detect true subgroups where treatment is more (or less) beneficial than others
- Two-stage & one-stage approaches available for identifying interactions with treatment effect
- Usually provide similar results
- Crucial to avoid ecological bias
- Empirical data (Fisher et al. BMJ 2017) suggests many analyses do not currently do this
- Work is ongoing on this areal

References

- Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003; 326: 219.
- Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: conduct, rationale and reporting. BMJ 2010; 340: c221
- Berlin JA, et al. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med* 2002;21(3):371-87
- Lambert PC, et al. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. *J Clin Epidemiol* 2002;55(1):86-94.
- Turner RM, Omar RZ, Yang M, Goldstein H, Thompson SG: A multilevel model framework for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2000, **19**: 3417-3432.
- Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. J Research Synthesis Methods 2010
- Riley RD, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. *Stat Med* 2008; **27**: 1870-93
- Simmonds MC, Higgins JP. Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. Stat Med 2007; 26: 2982-2999.
- Fisher DJ, et al. 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. *J Clin Epidemiol* 2011; 64: 949-967.
- Fisher DJ. Two-stage individual participant data meta-analysis and generalized forest plots. *Stata Journal* 2015; 15: 369-396
- Fisher DJ, et al. Meta-analytical methods to identify who benefits most from treatments: daft, deluded or deft approach? *BMJ* 2017; 356: j573.

Our recommended alternative (2): Stata code

```
cap graph drop _all
use "Practicals (DF versions)\Practical 1 - two-stage IPD meta-analysis\SBP", clear

label define trial_ 1 "Trial 1" 2 "Trial 2" 3 "Trial 3" 4 "Trial 4" 5 "Trial 5" ///
      6 "Trial 6" 7 "Trial 7" 8 "Trial 8" 9 "Trial 9" 10 "Trial 10"
label values trialdummy trial_

label define sex_ 0 "Female" 1 "Male"
label values sex sex_

// Subgroup plot
ipdover, over(sex) over(trial) nosubgroup nooverall nogr saving(recommend, replace) :
regress sbpl treat sbpl

preserve
      use recommend, clear

      // extra three obs at bottom for pooled interaction
      local oldN = _N
      set obs `=`oldN' + 3'
      replace _USE = 6 if _n > `oldN'

      label var _LABELS ""Treatment" "effect""
      forestplot, effect(Mean diffs) nowt nostats astext(15) range(-30 20) boxsca(75)
          favours("Favours" "treatment" # "Favours" "control", fp(10)) name(plot1)
          savedims(A)
restore
```



```
// Interaction plot
ipdmetan, study(trial) saving(slopes2, replace) interaction nograph
      : regress sbpl treat##sex sbpi

preserve
      use slopes2, clear

      // extra obs to match spacing with plot of subgroup effects
      local oldN = _N
      gen byte expand1 = 4*(_USE==1)    // 3 new obs per interaction
      expand expand1
      gen byte newobs1 = (_n > `oldN')

      local oldN = _N
      gen byte expand2 = 2*(_USE==5)    // 1 new obs per pooled interaction
      expand expand2
      gen byte newobs2 = (_n > `oldN')

      local oldN = _N
      set obs `=`oldN' + 1'
      replace _USE = 0 if _n > `oldN'   // 1 new obs right at the top (first trial title)
      replace newobs1 = 0 if _n > `oldN'
      replace newobs2 = 0 if _n > `oldN'

      sort _USE _STUDY newobs1 newobs2
      replace _USE=6 if newobs1 | newobs2
      replace _LABELS="" if newobs1 | newobs2
      replace _ES=. if newobs1 | newobs2
      replace _seES=. if newobs1 | newobs2
      drop expand1 expand2

      // forestplot, hr lcols(counts_treat counts_control) interaction
      forestplot, interaction effect(Diff. in mean diffs) nonames name(plot2) usedims(A) ///
          xtitle("Sex*treatment interaction"  "(Difference in mean difference, males - females)")
restore
```

PRACTICAL 3: Estimation of interactions

Please follow the instructions in the Stata do file labelled Practical 3

Learning objectives:

- Gain experience of estimating treatment-covariate interactions in a one-stage and two-stage IPD meta-analysis.
- Recognise how meta-regression may give very different results to an IPD meta-analysis.
- Gain experience of centring patient-level covariates for examining treatment-covariate interactions in a one-stage IPD meta-analysis.
- Interpret Stata output from meta-regression and IPD meta-analysis models.

LECTURE 6: Multivariate meta-analysis using IPD

Summary:

A multivariate meta-analysis allows the joint synthesis of correlated estimates from multiple effects of interest, such as multiple outcomes (e.g. the treatment effect for systolic and diastolic blood pressure) and multiple time-points. The multivariate approach uses the correlation to 'borrow strength' and gain more information; by doing so it may improve efficiency over separate univariate syntheses, may reduce selective outcome reporting biases, and enables joint inferences across the multiple effects outcomes. A common issue is that within-study correlations needed to fit the multivariate model are unknown from published reports. However, provision of IPD allows them to be calculated directly. In this lecture we describe the rationale, theory and estimation of multivariate meta-analysis models, and explain how to derive within-study correlations using IPD. We then provide illustrated applications of multivariate meta-analysis for multiple outcomes, partially and fully adjusted risk factors results, and multiple treatment comparisons (network meta-analysis), amongst others.

Learning objectives:

- Understand the rationale for multivariate meta-analysis, and why IPD substantially helps apply the method
- Appreciate the specification and estimation of a multivariate meta-analysis model
- Understand the meaning of within-study and between-study correlation
- Understand how to use IPD to derive within-study correlations
- Appreciate the concept of 'borrowing of strength' and how this may lead to multivariate meta-analysis giving different conclusions to univariate meta-analysis
- Recognise the broad application of multivariate meta-analysis, especially for multiple outcomes and multiple treatments (network meta-analysis)
- Understand why a multivariate meta-analysis is essential when deriving joint inferences across multiple correlated effects

Key references:

1. Jackson D, Riley RD, White IR. Multivariate meta-analysis: potential and promise. Stat Med 2011; 30: 2481-2498.

2. Becker BJ. Multivariate Meta-analysis. In: Tinsley HEA, Brown S, editors. Handbook of Applied Multivariate Statistics and Mathematical Modeling San Diego: Academic Press; 2000. p. 499-525.

3. Berkey CS, et al. Meta-analysis of multiple outcomes by regression with random effects. Stat Med 1998;17(22):2537-50.

4. Riley RD, et al. (2007) An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes. Statistics in Medicine, 26, 78-97.

5. Riley RD, et al. Multivariate meta-analysis using individual participant data. Res Synth Method. 2015;6 157-74.

6. Riley RD, et al. (2009) Multivariate meta-analysis: the effect of ignoring within-study correlation. JRSS-A 172: 789-811

7. Van Houwelingen HC, et al. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21(4):589-624.

LECTURE 6:
Multivariate meta-analysis using IPD

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ACKNOWLEDGEMENTS: Ian White, Dan Jackson

Objectives

To understand:
- multivariate meta-analysis models
- key advantages over univariate meta-analysis
- within-study & between-study correlations
- why IPD is crucial

Consider key applications, including ...
- multiple outcomes
- longitudinal data
- network meta-analysis

(widen IPD application beyond trials)

Practical: gain experience of estimating within-study correlations and using 'mvmeta' & 'network' in Stata

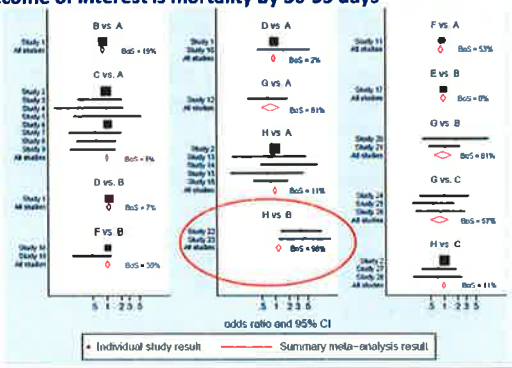
Motivation

'Good clinical data are expensive and hard to come by. We want to extract maximum information from available data ... many clinical studies have more than one outcome variable; these variables are seldom independent and so each must carry some information about the others.

If we can use this information, we should.'

Martin Bland (2011)

e.g: Network meta-analysis of 28 trials to compare eight thrombolytic treatments after acute myocardial infarction: outcome of interest is mortality by 30-35 days



Part 1:

Rationale & model specification

Recap: two-stage IPD meta-analysis

- **Stage 1**: Use IPD from *i*th study to obtain:
  Y_i : the estimate of effect
  S_i : its standard error
- **Stage 2**: Apply...

Fixed-effect model: $Y_i \sim N(\mu, S_i^2)$
- assumes each study has the same true effect, μ
- we are interested in estimating this effect

Recap: two-stage IPD meta-analysis

- **Stage 1**: Use IPD from *i*th study to obtain:
  Y_i : the estimate of effect
  S_i : its standard error
- **Stage 2**: Apply...

Random-effects model: $Y_i \sim N(\mu_i, S_i^2)$ where $\mu_i \sim N(\mu, \tau^2)$

or $Y_i \sim N(\mu, S_i^2+\tau^2)$

- each study now has their own true effect, μ_i
- we are interested in the mean effect μ
  - » and the between-studies SD τ (heterogeneity)
  - » and possibly the (predictive distribution of) study-specific effects μ_i
- estimate μ, τ by method of moments or REML

Multiple effects of interest

- The two-stage IPD meta-analysis methods outlined on Day 1 allow the traditional approaches routinely used, for example within Cochrane
- I call these 'univariate' meta-analysis methods
  - in the second-stage, they focus on combining a single effect measure of interest across studies
- But in systematic reviews we are often interested in:
  - multiple treatment groups
  - multiple time-points
  - multiple outcomes, etc

e.g. In 75 reviews by the Cochrane Pregnancy & Childbirth Group, the median no. of meta-analyses per review was 52 (min = 5; max = 409) (Riley et al., 2011)

Example A: Multiple outcomes

Q: Does hypertension treatment improve outcome?

- 10 randomised trials available (30,000 patients)
- each compare hypertension treatment to control
- all provide their IPD

Multiple ***correlated*** outcomes of interest, including:

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Time to cardiovascular disease
- Time to stroke

Illustration of the IPD available

Trial	Patient	SBP initial	SBP final	treat	placebo	follow-up	Stroke
1	1	190	185	1	0	58	1
1	2	175	172	1	0	69	0
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	0
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	0
3	4	168	161	0	1	61	0

etc

Effect estimates derived from the IPD

	Number of patients		ANCOVA[b] treatment effect outcomes 1 and 2		Cox regression treatment effect outcomes 3 and 4	
			SBP	DBP	CVD	Stroke
Trial name[a]	Control	Treatment	Mean difference (var)	Mean difference (var)	log(HR) (var)	log(HR) (var)
ATMH	750	780	−6.66 (0.72)	−2.99 (0.27)	−0.09 (0.17)	−1.91 (1.17)
HEP	199	150	−14.17 (4.73)	−7.87 (1.44)	0.06 (0.13)	−0.15 (0.17)
EWPHE	82	90	−12.88 (10.31)	−6.01 (1.77)	−0.17 (0.20)	0.75 (0.35)
HDFP	2371	2427	−8.71 (0.30)	−5.11 (0.10)	−0.24 (0.03)	−0.29 (0.07)
MRC-1	3445	3546	−8.70 (0.14)	−4.64 (0.05)	−0.18 (0.03)	−0.41 (0.11)
MRC-2	1337	1314	−10.60 (0.58)	−5.56 (0.18)	−0.23 (0.02)	−0.20 (0.03)
SHEP	2371	2365	−11.36 (0.30)	−3.98 (0.075)	−0.32 (0.02)	−0.45 (0.02)
STOP	131	137	−17.93 (5.82)	−6.54 (1.31)	−1.87 (1.17)	0.32 (0.83)
Sy-Chi	1139	1252	−6.55 (0.41)	−2.08 (0.11)	−0.33 (0.09)	−0.48 (0.04)
Sy-Eur	2297	2398	−10.26 (0.20)	−3.49 (0.04)	−0.26 (0.03)	−0.55 (0.03)

Research questions we might ask:

(1) Is the treatment more effective than control for each outcome?

(2) What is the probability that the treatment reduces BP and reduces risk of stroke more than control?

(3) What is the probability that, in a new population, the treatment will reduce BP and risk of stroke by a clinically relevant amount?

The last two questions require JOINT inferences

Example B: Partially & Fully adjusted results

Q: Is fibrinogen an independent risk factor for coronary disease? (Fibrinogen Studies Collaboration, 2009)

- 31 observational studies available with IPD
- However, available set of confounders differs in each

- Partially (P) adjusted results available in all 31 studies (adjusted for basic factors like age and smoking)

- Fully (F) adjusted results also available in 14 of these studies (adjusted for basic factors plus others like alcohol)

NB: P and F results likely to be correlated

The 17 studies with just P results derived from IPD

Table III. The estimates $\tilde{\beta}_1^P$ of the log hazards ratio of the effect of fibrinogen level and their within-cohort standard errors, for the 17 fibrinogen cohorts that do not provide full details of X_2.

Cohort	$\tilde{\beta}_1^P$	σ_2
15	0.438	0.342
16	0.484	0.115
17	0.154	0.120
18	0.660	0.252
19	0.290	0.083
20	0.333	0.117
21	0.122	0.147
22	0.666	0.349
23	0.219	0.053
24	0.354	0.126
25	0.553	0.148
26	0.338	0.087
27	0.439	0.083
28	0.215	0.045
29	0.304	0.278
30	0.429	0.108
31	1.190	0.499

The 14 studies with both P and F results derived from IPD

Table II. The estimates $\tilde{\beta}_1^F$ and $\tilde{\beta}_1^P$ of the log hazards ratio of the effect of fibrinogen level, their within-cohort standard errors and correlations, for complete-case analyses of the 14 fibrinogen cohorts that provide the necessary details of X_2

Cohort	$\tilde{\beta}_1^F$	σ_1	$\tilde{\beta}_1^P$	σ_2	ρ_b	ρ_a	ρ_m
1	−0.353	0.381	−0.188	0.387	0.861	0.984	0.970
2	0.334	0.088	0.425	0.085	0.971	0.981	0.961
3	0.309	0.132	0.394	0.129	0.963	0.978	0.962
4	0.324	0.198	0.435	0.191	0.963	0.988	0.976
5	0.400	0.296	0.543	0.272	0.961	0.999†	0.980
6	0.149	0.104	0.151	0.103	0.988	0.999†	0.994
7	0.262	0.120	0.327	0.117	0.974	0.996	0.982
8	0.436	0.310	0.541	0.312	0.945	0.957	0.974
9	0.337	0.113	0.451	0.108	0.965	0.998	0.976
10	0.474	0.143	0.609	0.137	0.952	0.999†	0.982
11	0.110	0.086	0.159	0.085	0.985	0.984	0.985
12	0.413	0.065	0.532	0.064	0.963	0.982	0.970
13	0.213	0.078	0.262	0.077	0.964	0.976	0.969
14	0.062	0.175	0.129	0.170	0.962	0.989	0.976

Correlations marked † were estimated to be more than unity, and hence have been truncated at 0.999.

How do we analyse multiple effects?

OPTION 1: Two-stage IPD meta-analysis done separately (univariate meta-analysis) for each effect

- Simple, allows traditional methods & software
- BUT ignores correlation

OPTION 2: Two-stage IPD meta-analysis with a multivariate model to analyse all effects jointly & account for their correlation

- Utilises correlation, may gain more information
- BUT more complex … are they necessary?

(NB From now onwards we focus on two-stage IPD multivariate meta-analysis; one-stage is also possible especially for multiple continuous outcomes)

STATISTICS IN MEDICINE
Statist. Med. 2002; 21:589–624 (DOI: 10.1002/sim.1040)

TUTORIAL IN BIOSTATISTICS

Advanced methods in meta-analysis: multivariate approach and meta-regression

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SUMMARY

This tutorial on advanced statistical methods for meta-analysis can be seen as a sequel to the recent Tutorial in Biostatistics on meta-analysis by Normand, which focused on elementary methods. Within the framework of the general linear mixed model using approximate likelihood, we discuss methods to analyse univariate as well as bivariate treatment effects in meta-analyses as well as meta-regression methods. Several extensions of the models are discussed, like exact likelihood, non-normal mixtures and multiple endpoints. We end with a discussion about the use of Bayesian methods in meta-analysis. All methods are illustrated by a meta-analysis concerning the efficacy of BCG vaccine against tuberculosis. All analyses that use approximate likelihood can be carried out by standard software. We demonstrate how the models can be fitted using SAS Proc Mixed. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS: meta-analysis; meta-regression; multivariate random effects models

Research Article

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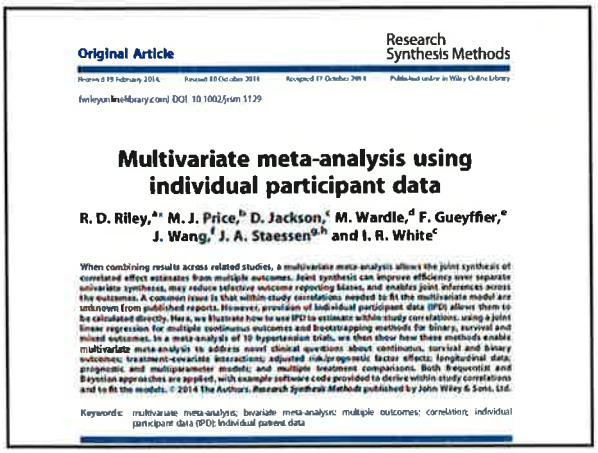
Multivariate meta-analysis: Potential and promise

Dan Jackson,[a*†] Richard Riley[b] and Ian R. White[a]

The multivariate random effects model is a generalization of the standard univariate model. Multivariate meta-analysis is becoming more commonly used and the techniques and related computer software, although continually under development, are now in place. In order to raise awareness of the multivariate methods, and discuss their advantages and disadvantages, we organized a one day 'Multivariate meta-analysis' event at the Royal Statistical Society. In addition to disseminating the most recent developments, we also received an abundance of comments, concerns, insights, critiques and encouragement. This article provides a balanced account of the day's discussions. By giving others the opportunity to respond to our assessment, we hope to ensure that the various view points and opinions are aired before multivariate meta-analysis simply becomes another widely used *de facto* method without any proper consideration of it by the medical statistics community. We describe the areas of application that multivariate meta-analysis has found, the methods available, the difficulties typically encountered and the arguments for and against the multivariate methods, using four representative but contrasting examples. We conclude that the multivariate methods can be useful, and in particular can provide estimates with better statistical properties, but also that these benefits come at the price of making more assumptions which do not result in better inference in every case. Although there is evidence that multivariate meta-analysis has considerable potential, it must be even more carefully applied than its univariate counterpart in practice. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: multivariate meta-analysis; random effects models; statistical software



Original Article

Research Synthesis Methods

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Multivariate meta-analysis using individual participant data

R. D. Riley,[a]* M. J. Price,[b] D. Jackson,[c] M. Wardle,[d] F. Gueyffier,[e] J. Wang,[f] J. A. Staessen[g,h] and I. R. White[c]

When combining results across related studies, a multivariate meta-analysis allows the joint synthesis of correlated effect estimates from multiple outcomes. Joint synthesis can improve efficiency over separate univariate syntheses, may reduce selective outcome reporting biases, and enables joint inferences across the outcomes. A common issue is that within-study correlations needed to fit the multivariate model are unknown from published reports. However, provision of individual participant data (IPD) allows them to be calculated directly. Here, we illustrate how to use IPD to estimate within-study correlations, using a joint linear regression for multiple continuous outcomes and bootstrapping methods for binary, survival and mixed outcomes. In a meta-analysis of 10 hypertension trials, we then show how these methods enable multivariate meta-analysis to address novel clinical questions about continuous, survival and binary outcomes; treatment-covariate interactions; adjusted risk/prognostic factor effects; longitudinal data; prognostic and multiparameter models; and multiple treatment comparisons. Both frequentist and Bayesian approaches are applied, with example software code provided to derive within-study correlations and to fit the models. © 2014 The Authors. Research Synthesis Methods published by John Wiley & Sons, Ltd.

Keywords: multivariate meta-analysis; bivariate meta-analysis; multiple outcomes; correlation; individual participant data (IPD); individual patient data

Two-stage IPD multivariate meta-analysis: what model do we need in the second stage?

- Consider there are 2 outcomes (j=1,2)
- Two univariate random-effects models are written:

Outcome 1: $Y_{i1} \sim N(\mu_{i1}, S_{i1}^2)$ where $\mu_{i1} \sim N(\mu_1, \tau_1^2)$
Outcome 2: $Y_{i2} \sim N(\mu_{i2}, S_{i2}^2)$ where $\mu_{i2} \sim N(\mu_2, \tau_2^2)$

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Outcome 2: $Y_{i2} \sim N(\mu_{i2}, S_{i2}^2)$ where $\mu_{i2} \sim N(\mu_2, \tau_2^2)$

Same as:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix}, \mathbf{S}_i\right) \qquad \mathbf{S}_i = \begin{pmatrix} S_{i1}^2 & 0 \\ 0 & S_{i2}^2 \end{pmatrix}$$

$$\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \boldsymbol{\Sigma}\right) \qquad \boldsymbol{\Sigma} = \begin{pmatrix} \tau_1^2 & 0 \\ 0 & \tau_2^2 \end{pmatrix}$$

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Two-stage IPD multivariate meta-analysis: what model do we need in the second stage?

A bivariate model can be written as:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix}, \mathbf{S}_i\right) \qquad \mathbf{S}_i = \begin{pmatrix} S_{i1}^2 & \lambda_i \\ \lambda_i & S_{i2}^2 \end{pmatrix}$$

$$\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \boldsymbol{\Sigma}\right) \qquad \boldsymbol{\Sigma} = \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix}$$

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$$\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \boldsymbol{\Sigma}\right) \qquad \boldsymbol{\Sigma} = \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix}$$

Within-study covariance (assumed known from IPD)

Within-study correlation = $\rho_{W_i} = \lambda_i / s_{i1} s_{i2}$

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Two-stage IPD multivariate meta-analysis: what model do we need in the second stage?

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$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix}, \mathbf{S}_i\right) \qquad \mathbf{S}_i = \begin{pmatrix} S_{i1}^2 & \lambda_i \\ \lambda_i & S_{i2}^2 \end{pmatrix}$$

$$\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \boldsymbol{\Sigma}\right) \qquad \boldsymbol{\Sigma} = \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix}$$

Between-study covariance (to be estimated)

Between-study correlation = $\rho_B = \tau_{12} / \tau_1 \tau_2$

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Bivariate random-effects meta-analysis

Rewritten as a marginal model...

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \mathbf{S}_i + \boldsymbol{\Sigma} \right)$$

$$\mathbf{S}_i = \begin{pmatrix} s_{i1}^2 & \lambda_i \\ \lambda_i & s_{i2}^2 \end{pmatrix}$$

$$\boldsymbol{\Sigma} = \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix}$$

Two types of correlation

Within-study correlation (ρ_{W_i}):

- Arises when same patients contribute to both outcomes

e.g.

an individual's time to disease recurrence (DFS) is correlated with their time to death (OS)

↓

log hazard ratio estimate for DFS (Y_{i1}) is correlated with log hazard ratio estimate for OS (Y_{i2})

- In some situations ρ_{W_i} may be zero

e.g. Sensitivity and specificity estimates within a test accuracy study are obtained from distinct sets of patients

Bivariate random-effects meta-analysis

Between-study correlation (ρ_B):

- Arises when underlying effect sizes for each effect are correlated across studies

e.g. (1)

cancer studies with a high underlying hazard ratio for OS often have a high underlying hazard ratio for DFS *(positive correlation)*

e.g. (2)

test accuracy studies with a high underlying sensitivity often have a low underlying specificity, due to changes in threshold level across studies *(negative correlation)*

Multivariate meta-analysis: general model specification for *p* outcomes

- **Model**: $Y_i \sim N(\mu, S_i + \Sigma)$

Where

Y_i – vector of effect estimates (*p*-dimensional for studies with all outcomes, but < p if some outcomes missing)

μ – vector of mean (treatment) effects for the outcomes (p-dimensional)

S_i – within-study variance-covariance matrix of Y_i (assumed known)

Σ – between-study variance-covariance matrix (to be estimated – usually unstructured, but can be simplified to aid estimation, especially when p large)

- Total variance = within + between

(e.g. p = 2)

$$\text{var}\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} = \begin{pmatrix} s_{i1}^2 & \rho_{Wi12} s_{i1} s_{i2} \\ \rho_{Wi12} s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix} + \begin{pmatrix} \tau_1^2 & \rho_{Bi2} \tau_1 \tau_2 \\ \rho_{Bi2} \tau_1 \tau_2 & \tau_2^2 \end{pmatrix}$$

Two-stage IPD multivariate meta-analysis: what data do we need for the first stage?

- **Use IPD from *i*th study to obtain:**

Y_{i1}, Y_{i2}, ... : effect estimates for 1st, 2nd, ... outcomes

S_{i1}, S_{i2}, ... : their standard errors

We did this yesterday, for example using a linear, logistic or Cox regression

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we also need the within-study correlation of each pair of Ys in each study (e.g. ρ_{Wi12} between Y_{i1} and Y_{i2}; ρ_{Wi13} between Y_{i1} and Y_{i3} , *etc)*

Two-stage IPD multivariate meta-analysis: what data do we need for the first stage?

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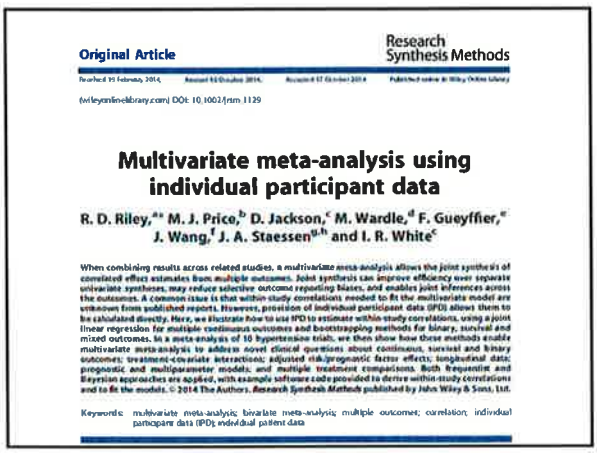
- In matrix notation, we need $Y_i = (Y_{i1}, Y_{i2}, \ldots)'$ and also the "within-study" var-cov matrix of Y_i

written as $S_i = \begin{pmatrix} S_{i1}^2 & \rho_{WI12}S_{i1}S_{i2} & \cdots \\ \rho_{WI12}S_{i1}S_{i2} & S_{i2}^2 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} = \text{var}\begin{pmatrix} Y_{i1} \\ Y_{i2} \\ \vdots \end{pmatrix}$

NB: not all effects needed for every study (see later)

Part 2:

How to use IPD to derive within-study correlations



Original Article — Research Synthesis Methods

(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1129

Multivariate meta-analysis using individual participant data

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When combining results across related studies, a multivariate meta-analysis allows the joint synthesis of correlated effect estimates from multiple outcomes. Joint synthesis can improve efficiency over separate univariate syntheses, may reduce selective outcome reporting biases, and enables joint inferences across the outcomes. A common issue is that within-study correlations needed to fit the multivariate model are unknown from published reports. However, provision of individual participant data (IPD) allows them to be calculated directly. Here, we illustrate how to use IPD to estimate within-study correlations, using a joint linear regression for multiple continuous outcomes and bootstrapping methods for binary, survival and mixed outcomes. In a meta-analysis of 10 hypertension trials, we then show how these methods enable multivariate meta-analysis to address novel clinical questions about continuous, survival and binary outcomes; treatment-covariate interactions; adjusted risk/prognostic factor effects; longitudinal data; prognostic and multiparameter models; and multiple treatment comparisons. Both frequentist and Bayesian approaches are applied, with example software code provided to derive within-study correlations and to fit the models. © 2014 The Authors. *Research Synthesis Methods* published by John Wiley & Sons, Ltd.

Keywords: multivariate meta-analysis; bivariate meta-analysis; multiple outcomes; correlation; individual participant data (IPD); individual patient data

Using IPD to estimate within-study correlations

- Within-study correlations needed to fit the model
- But rarely available without IPD
- IPD allows them to be estimated in each study
  - this is a major advantage of having IPD
- Consider here two key approaches for estimating within-study correlation:
  (i) Jointly fit two linear regression models ('seemingly unrelated regression')
  (ii) Bootstrapping

(i) Joint linear regressions

- Two continuous (blood pressure) outcomes per subject
- Consider them like a repeated measures model
- Account for the correlation between patient values
  i.e. allow for correlated residuals
- In each trial separately fit two regressions jointly to IPD:

(i) Joint linear regressions

- Two continuous (blood pressure) outcomes per subject
- Consider them like a repeated measures model
- Account for the correlation between patient values
  i.e. allow for correlated residuals
- In each trial separately fit two regressions jointly to IPD:

$$\text{Final SBP}_{ij} = \alpha_{1i} + \beta_{1i} * \text{BaselineSBP}_{ij} + \theta_{1i} * \text{Treat}_{ij} + e_{ij1}$$
$$\text{Final DBP}_{ij} = \alpha_{2i} + \beta_{2i} * \text{BaselineDBP}_{ij} + \theta_{2i} * \text{Treat}_{ij} + e_{ij2}$$

$$e_{ij1} \sim N(0, \sigma_{i1}^2) \quad e_{ij2} \sim N(0, \sigma_{i2}^2) \quad cov(e_{ij1}, e_{ij2}) = \sigma_{i12}$$

- `sureg (sbpl = sbpi treat) (dbpl = dbpi treat), corr`
- Leads to treatment effect estimates $\hat{\theta}_{1i}$ & $\hat{\theta}_{2i}$ (= Y_{1i} & Y_{2i})
- Inverse of Fisher's Information matrix gives their variances **and** within-study correlation (see practical)

(ii) Non-parametric bootstrapping

- Joint regressions most suitable for continuous outcomes
- A more general option is to use **bootstrapping**
- Bootstrapping takes the IPD for each study and:
  - creates a bootstrap sample by randomly selecting one patient with replacement, then randomly selecting a second patient with replacement, and so on until the same sample size is obtained as in the original study
  - repeats this process *b* times, so that *b* bootstrap samples are obtained.
  - then, to each outcome separately, the relevant model is fitted to obtain the effect estimates of interest (e.g. linear model outcome 1, Cox model outcome 2, etc)
  - this produces *b* values of Y_{i1} , Y_{i2} , Y_{i3} , *etc*
  - **for each pair, their observed correlation gives ρ_{wl}**

Bootstrapping example: SBP and DBP

In each study separately:

1. Sample patients with replacement from the IPD until same study size is achieved
2. Fit an ANCOVA model to estimate treatment effect on SBP
3. Fit an ANCOVA model to estimate treatment effect on DBP
4. Repeat steps 1 to 3 1000 times
5. *Estimate the correlation between the 1000 SBP & 1000 DBP effect estimates … this is your within-study correlation*

Suitable for mixed outcomes:

e.g. a logHR from Cox regression in step 2
a mean difference from a linear regression in step 3

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Bootstrapping example: SBP and DBP

```
* Define a program 'myprog' where we run an ANCOVA for SBP and then
DBP. Each time we save the treatment effect estimates
capture program drop myprog
prog def myprog, rclass
regress sbpl sbpi treat
return scalar sbptreat = _b[treat]
regress dbpl dbpi treat
return scalar dbptreat = _b[treat]
end

* We then apply the bootstrap to our data 1000 times and run our
program, saving the treatment effect estimates for SBP and DBP each
time
bootstrap b_treat_sbp=r(sbptreat) b_treat_dbp=r(dbptreat), ///
saving(boot, replace) rep(1000) seed(231): myprog

* Thus we now have a big dataset of 1000 estimates for each of SBP
and DBP. If we work out their correlation it is our within-study
correlation
use boot, clear
corr b_treat_dbp b_treat_sbp
```

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Within-study correlations derived by bootstrapping for hypertension trials

Trial	SBP, DBP	SBP, CVD	SBP, Stroke	DBP, CVD	DBP, Stroke	CVD, Stroke
1	0.79	0.01	-0.01	-0.02	-0.02	0.16
2	0.5	0.11	0.1	0.09	0.1	0.64
3	0.59	-0.21	-0.05	-0.04	-0.04	0.1
4	0.77	0.09	0.02	0.13	0.04	0.52
5	0.64	0.04	0.04	0.04	0.04	0.42
6	0.5	0	0.03	-0.02	0	0.62
7	0.48	-0.01	-0.02	-0.03	-0.03	0.69
8	0.59	-0.02	-0.07	-0.03	0	0.35
9	0.45	0.11	0.08	0.03	0.03	0.78
10	0.48	0.05	0.04	0.04	0.05	0.62

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Within-study correlations between P and F results derived from bootstrapping using the IPD in fibrinogen example

Table II. The estimates $\hat{\beta}_1^F$ and $\hat{\beta}_1^P$ of the log hazards ratio of the effect of fibrinogen level, their within-cohort standard errors and correlations, for complete-case analyses of the 14 fibrinogen cohorts that provide the necessary details of X_2.

Cohort	$\hat{\beta}_1^F$	σ_1	$\hat{\beta}_1^P$	σ_2	ρ_b	ρ_a	ρ_m
1	−0.353	0.381	−0.188	0.387	0.861	0.984	0.970
2	0.334	0.088	0.425	0.085	0.971	0.981	0.961
3	0.309	0.132	0.394	0.129	0.963	0.978	0.962
4	0.324	0.198	0.435	0.191	0.963	0.988	0.976
5	0.400	0.296	0.543	0.272	0.961	0.999†	0.980
6	0.149	0.104	0.151	0.103	0.988	0.999†	0.994
7	0.262	0.120	0.327	0.117	0.974	0.996	0.982
8	0.436	0.310	0.541	0.312	0.945	0.957	0.974
9	0.337	0.113	0.451	0.108	0.965	0.998	0.976
10	0.474	0.143	0.609	0.137	0.952	0.999†	0.982
11	0.110	0.086	0.159	0.085	0.985	0.984	0.985
12	0.413	0.065	0.532	0.064	0.963	0.982	0.970
13	0.213	0.078	0.262	0.077	0.964	0.976	0.969
14	0.062	0.175	0.129	0.170	0.965	0.989	0.976

Correlations marked † were estimated to be more than unity, and hence have been truncated at 0.999.

Part 3:

Estimating the multivariate meta-analysis model

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Two-stage IPD multivariate meta-analysis: how do we estimate the multivariate model in the second stage?

- Maximum likelihood - but produces downwardly biased tau estimates with small numbers of studies
- Restricted maximum likelihood (the most common choice) – unbiased, iterative procedure
- Method of moments (Jackson et al)
  - non-iterative, non-parametric
  - extremely fast even with a large number of outcomes
- Handles missing effects in some studies **under a missing at random assumption**
- Software sometimes uses data augmentation to do this; e.g. missing estimates given a 0 with variance of 1000000; all associated within-study covariances set to 0

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The Stata Journal (2009)
9, Number 1, pp. 40–56

Multivariate random-effects meta-analysis

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Abstract. Multivariate meta-analysis combines estimates of several related parameters over several studies. These parameters can, for example, refer to multiple outcomes or comparisons between more than two groups. A new Stata command, **mvmeta**, performs maximum likelihood, restricted maximum likelihood, or method-of-moments estimation of random-effects multivariate meta-analysis models. A utility command, **mvmeta make**, facilitates the preparation of summary datasets from more detailed data. The commands are illustrated with data from the Fibrinogen Studies Collaboration, a meta-analysis of observational studies, to estimate the shape of the association between a quantitative exposure and disease events by grouping the quantitative exposure into several categories.

Keywords: st0156, mvmeta, mvmeta make, mvmeta_d, meta-analysis, multivariate meta-analysis, individual participant data, observational studies

- 'mvmeta' module in Stata fits ML, REML, MM

net install mvmeta, from(http://www.mrc-bsu.cam.ac.uk/IW_Stata/meta/)

- R package also available (also called 'mvmeta')
- SAS Proc Mixed for ML and REML

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Frequentist estimation issues

- By default, frequentist estimation methods ignore uncertainty in the estimate of the between studies var-cov matrix Σ
- In the 'mvmeta' module in Stata, the standard errors of the pooled estimates, $\hat{\mu}_j$, are therefore inflated to account for this (based on observed Fishers information matrix)
- Can be turned off by the 'nounc' option
- Jackson and Riley (2012) also propose a scaling factor, H, for inflating the standard errors of $\hat{\mu}_j$ (and so confidence intervals for μ_j) following a multivariate meta-analysis
- Extends the univariate approach of Hartung & Knapp

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Frequentist estimation issues

- **Cholesky decomposition** of the between-studies var-cov matrix Σ is needed to ensure it is estimated as positive semi-definite
- Ensures all eigenvalues of Σ are non negative
- Between-study correlations are often poorly estimated at +1 or -1 (Riley et al., 2007)
- Often very little information in the likelihood to estimate between-study correlations precisely
- Most prevalent issue for outcome pairs where:
  - number of studies with both is few (<5)
  - within-study variances are large relative to between-studies variances

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Bayesian estimation

- **Bayesian approach has potential advantages:**
  - can account for all parameter uncertainty
  - incorporate external evidence through prior distribution
  - allows direct probability statements
  - naturally allows predictive inferences
- For more details see Appendix 1

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Model estimation: key references

- Jackson D, Riley RD, White IR. Multivariate meta-analysis: potential and promise. *Stat Med* 2011; **30**: 2481-2498
- Jackson D et al. A matrix-based method of moments for fitting the multivariate random effects model for meta-analysis and meta-regression. *Biom J* 2013; **55**: 231-245.
- Jackson D et al. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med* 2010; **29**: 1282-1297.
- White IR. Multivariate meta-analysis. *The STATA Journal* 2009; **9**: 40-56.
- Van Houwelingen HC, et al. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002; **21**: 589-624.
- Chen H, Manning AK, Dupuis J. A method of moments estimator for random effect multivariate meta-Analysis. *Biometrics* 2012.
- Ma Y, Mazumdar M. Multivariate meta-analysis: a robust approach based on the theory of U-statistic. *Stat Med* 2011; **30**: 2911-2929.
- Nam IS, et al. Multivariate meta-analysis. *Stat Med* 2003; **22**: 2309-2333.
- Wei Y, Higgins JP. Bayesian multivariate meta-analysis with multiple outcomes. *Stat Med* 2013; **32**: 2911-2934.
- Bujkiewicz S, Thompson JR, Sutton AJ, et al. Multivariate meta-analysis of mixed outcomes: a Bayesian approach. *Stat Med* 2013. 32(22):3926-43
- Jackson D, Riley RD. A refined method for multivariate meta-analysis and meta-regression. *Stat Med* 2014.33(4):541-54
- Riley RD, et al. Bivariate random-effects meta-analysis and the estimation of between-study correlation. *BMC Med Res Methodol* 2007; **7**: 3.

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Part 4:

Advantages and applications

'In the realm of research synthesis ... the consequences of accounting for (modeling) dependence or ignoring it are not well understood'

Becker et al., 2000

In the last 15 years, we have made progress on this front...

Advantage 1: Borrowing strength

- Multivariate meta-analysis allows the ***borrowing of strength*** across effects in regard their **pooled estimates**
- e.g. the synthesis of outcome 1 utilises (via correlation) the available data for outcome 2, and vice-versa
- Particularly useful given some studies that only provide a subset of the effects of interest (e.g. outcome 1 is missing)

Advantage 1: Borrowing strength

- Borrowing of strength does *not* occur when:
  - zero within-study & between-study correlation
  - all studies provide all effects and there is no difference in the within-study covariance matrices (Riley et al., 2007)
- Otherwise, with complete data or data missing at random the borrowing strength gives pooled estimates with:
  - smaller mean-square errors
  - smaller standard errors, on average

  compared to univariate meta-analysis
- The larger the differences in the within-study covariance matrices, the larger the borrowing of strength
- Occurs for complete data and, especially, missing data

STATISTICS IN MEDICINE
Statist. Med. 2007; 26:78–97
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An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes

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SUMMARY

Often multiple outcomes are of interest in each study identified by a systematic review, and in this situation a separate univariate meta-analysis is usually applied to synthesize the evidence for each outcome independently; an alternative approach is a single multivariate meta-analysis model that utilizes any correlation between outcomes and obtains all the pooled estimates jointly. Surprisingly, multivariate meta-analysis is rarely considered in practice, so in this paper we illustrate the benefits and limitations of the approach to provide helpful insight for practitioners.

Example: Partially & Fully adjusted results

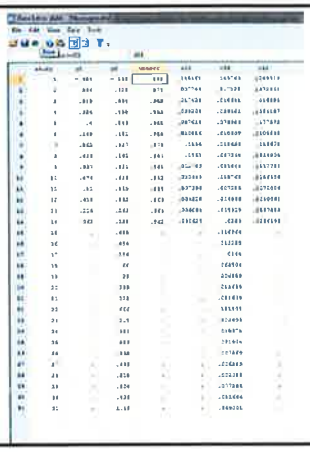
Q: Is fibrinogen an independent risk factor for coronary disease? (Fibrinogen Studies Collaboration, 2009)

- 31 observational studies available with IPD
- However, available set of confounders differs in each
- Partially (P) adjusted results available in all 31 studies
- Fully (F) adjusted results also available in 14 of these studies
- Bivariate IPD meta-analysis of P and F results needed to:
  - derive within-study correlations using IPD
  - account for correlation of P & F results in multivariate model
  - allow F to borrow strength from P

    ... especially in the 17 studies missing F

Bivariate IPD meta-analysis of P and F

Stata data:



Bivariate IPD meta-analysis of P and F
Stata code and output:

```
. mvmeta y v,
Note: using method reml
Note: using variables y1 y2
Note: 31 observations on 2 variables
Note: variance-covariance matrix is unstructured

Initial:        log likelihood =  30.466482
(rescale)       log likelihood =  30.466482
Iteration 1:    log likelihood =  30.523635

Multivariate meta-analysis
Variance-covariance matrix = unstructured
Method = reml                                   Number of dimensions      =     2
Restricted log likelihood = 31.169651           Number of observations    =    31

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Overall_mean |
          y1 |   .2713415   .0266242    10.19   0.000     .2191591    .3235238
          y2 |   .3466436   .0300262    11.54   0.000     .2877933    .4054938
------------------------------------------------------------------------------

Estimated between-studies SDs and correlation matrix:
             SD          y1          y2
y1    .07388893           1           .
y2    .10608829           1           1
```

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Results

Model	Fully adjusted logHR $\hat{\mu}_1$ (s.e.)	$\hat{\tau}_1$	Partially adjusted logHR $\hat{\mu}_2$ (s.e.)	$\hat{\tau}_2$	$\hat{\rho}_B$
Univariate	0.273 **(0.039)**	0.075	0.342 (0.029)	0.096	-
Bivariate	0.271 **(0.027)**	0.074	0.347 (0.030)	0.106	1

- Bivariate analysis gives a more precise fully adjusted result

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Results

Model	Fully adjusted logHR $\hat{\mu}_1$ (s.e.)	$\hat{\tau}_1$	Partially adjusted logHR $\hat{\mu}_2$ (s.e.)	$\hat{\tau}_2$	$\hat{\rho}_B$
Univariate	0.273 **(0.039)**	0.075	0.342 (0.029)	0.096	-
Bivariate	0.271 **(0.027)**	0.074	0.347 (0.030)	0.106	1

- Bivariate analysis gives a more precise fully adjusted result (though less precise partially adjusted result)
- **How to best quantify this borrowing of strength?**

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A new BoS statistic
(Jackson et al., Stat Meth Med Res, in-press)

- We proposed BoS, a new statistic to quantify the Borrowing of Strength in multivariate meta-analysis
- BoS gives the percentage contribution of the related outcome data (e.g. outcome 2) toward the summary result for the pooled effect of interest (e.g. outcome 1)

  e.g. BoS = 0%: no information borrowed from outcome 2

  e.g. BoS = 95%: nearly all information borrowed from outcome 2
- If we fix the τ estimates in univariate and multivariate, then **BoS is the % reduction in the variance of the pooled estimate when using multivariate rather than univariate**
- Derivation of BoS uses the % study weights for multi-parameter models I showed in Lecture 4

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BoS & Weights in Fibrinogen example

- Use *"wt"* option in *"mvmeta"*
- In fibrinogen example:

BoS = 53% for the fully adjusted pooled estimate

(53% of the information toward the summary fully adjusted result was obtained from the partially adjusted data)

BoS = 1.9% for the partially adjusted result

(even though precision was reduced due to increased tau estimate, there is still some information gained)

- Can provide BoS and study weights on a forest plot

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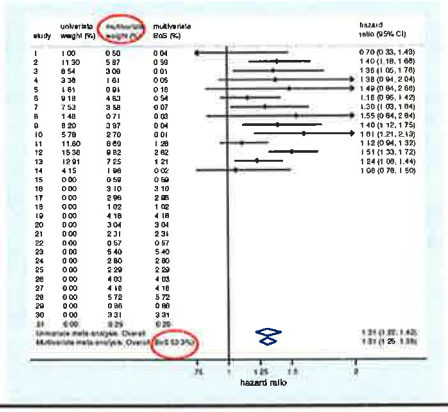
Forest plot of multivariate 'fully adjusted' result



Advantage 2: Reduce impact of non-ignorable missing data (outcome reporting bias)

- Borrowing of strength very important given non-ignorable missing data

e.g. only 1 of the 2 effects are reported when neither are significant or positive (outcome reporting bias)

- Univariate meta-analysis will give biased results here
- Multivariate meta-analysis can reduce the bias (and mean-square error) by *borrowing strength*
- *Thus reduce impact of outcome reporting bias*

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Hypothetical example

- 2 studies and 2 outcomes of interest, with
  Outcome 1: Y_{11} = ? and Y_{21} = 1
  Outcome 2: Y_{12} = -1 and Y_{22} = 1
- Let between-study variances = 1 for both outcomes
- Let within-study variances = 1 for Y_{21}, Y_{12}, and Y_{22}
- Let within-study and between-study correlation = 0.5
- **Let us focus on the pooled estimate for outcome 1**

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Hypothetical example

- 2 studies and 2 outcomes of interest, with
  Outcome 1: Y_{11} = ? and Y_{21} = 1
  Outcome 2: Y_{12} = -1 and Y_{22} = 1
- **Univariate analysis gives pooled estimate = Y_{21} = 1 for outcome 1**

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Hypothetical example

- 2 studies and 2 outcomes of interest, with
  Outcome 1: Y_{11} = ? and Y_{21} = 1
  Outcome 2: Y_{12} = -1 and Y_{22} = 1
- **Univariate analysis gives pooled estimate = Y_{21} = 1 for outcome 1**
- Riley et al. (2009) shows that the maximum likelihood solution for the bivariate pooled estimate for outcome 1 is:

$$\hat{\mu}_1 = Y_{21} - \frac{(Y_{22}-Y_{12})(S_{21}S_{22}\rho_{W_2}+\tau_1\tau_2\rho_B)}{2\tau_{22}^2+S_{12}^2+S_{22}^2} = 1-\frac{(1-(-1))*(0.5+0.5)}{4} = 0.5$$

- **The bivariate analysis utilises the correlation to reduce the pooled estimate from 1 to 0.5**

Q: What would have been the answer had the correlations = 1 ?

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Example : p53

Tandon et al. (2010) assess the prognostic association of mutant p53 for OS & DFS in patients with head & neck cancer

For cancers at the Oropharynx site, they extracted hazard ratios for:

3 studies reporting OS alone
3 studies reporting both OS and DFS

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p53 data

Study	Log hazard ratio (mutant vs. normal p53 gene)			
	Overall survival		Disease-free survival	
	Y_1	S_1	Y_2	S_2
1	-0.18	0.56	-0.58	0.56
2	0.79	0.24		
3	0.21	0.66		
4	-0.63	0.29	-1.02	0.39
5	1.01	0.48		
6	-0.64	0.40	-0.69	0.40

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Example: p53

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For cancers at the Oropharynx site, they extracted hazard ratios for:

3 studies reporting OS alone

3 studies reporting both OS and DFS

For DFS:

A univariate meta-analysis gives:

a pooled hazard ratio estimate of 0.45 (p=0.001)

A bivariate meta-analysis gives:

a pooled hazard ratio estimate of 0.73 (p=0.39)

... very different conclusions!

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Advantage 3: Joint confidence or prediction intervals

- Multivariate meta-analysis of IPD allows us to describe the relationship between the multiple effects
- Allows joint confidence or prediction intervals to be obtained, that properly account for correlation

95% Confidence region – area where we are 95% confident that the true pair of average (pooled) effects lie

95% Prediction region – area where we are 95% confident that the true pair of effects *in a single new study* will lie

(see Higgins et al., 2009, JRSS-A)

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Example: Is hypertension treatment effective?

- Recall: 10 hypertension trials with IPD
- 4 outcomes: SBP, DBP, Stroke and CVD

First stage:

- IPD used in each trial to derive effect estimates and variances for each outcome
- And within-study correlation of effect estimates for each pair of outcomes

Second stage:

- Fit a 4-outcome multivariate meta-analysis model
  - accounts for all correlations & outcomes jointly

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Is hypertension treatment effective?

Outcome	Effect type	Average treatment effect	95% CI	τ
SBP	Mean difference	-10.22	-12.14 to -8.30	2.73
DBP	Mean difference	-4.63	-5.67 to -3.60	1.51
CVD	Hazard ratio	0.79	0.69 to 0.91	0.05
Stroke	Hazard ratio	0.73	0.61 to 0.87	0.14

Hypertension treatment is effective on average across the trials, for all four outcomes

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Joint probabilistic inferences

- What is the probability that, when applied to a single population, the treatment will reduce ***both*** SBP and DBP by at least 5mmHg more than control?

- Consider 95% prediction regions derived following the multivariate meta-analysis (Riley et al. 2014)

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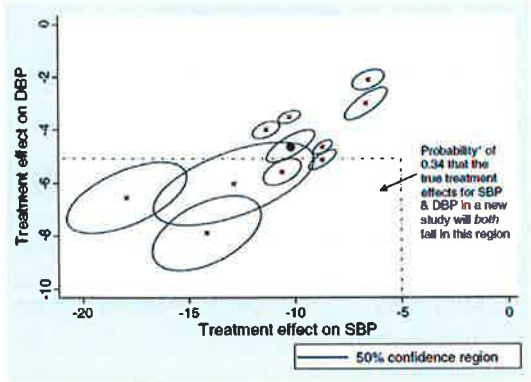
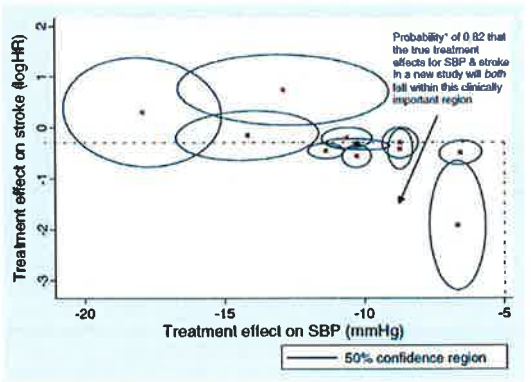


* As estimated following a Bayesian multivariate model

Joint probabilistic inferences

- What is the probability that, when applied to a single population, treatment will reduce SBP by >5mmHg and reduce risk of stroke by >20%?



* As estimated following a Bayesian multivariate model

Advantage 4: Longitudinal data & other novel applications

- Multivariate meta-analysis using IPD can handle correlated effects at multiple time-points in each study

i.e. a multivariate meta-analysis of longitudinal data (repeated measures over time)

- Jones et al. discuss one-stage and two-stage approaches
- Produces pooled estimates for all time-points jointly
  - for which borrowing of strength will apply
  - especially important given missing time-points
- A detailed discussion of two-stage approaches is given in Appendix 2; recall an example was given in Lecture 3

CLINICAL TRIALS ARTICLE

Clinical Trials 2009; 6: 16–27

Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials

Ashley P Jones[a], Richard D Riley[b], Paula R Williamson[a] and Anne Whitehead[c]

Background In clinical trials following individuals over a period of time, the same assessment may be made at a number of time points during the course of the trial. Our review of current practice for handling longitudinal data in Cochrane systematic reviews shows that the most frequently used approach is to ignore the correlation between repeated observations and to conduct separate meta-analyses at each of a number of time points.

Purpose The purpose of this paper is to show the link between repeated measurement models used with aggregate data and those used when individual patient data (IPD) are available, and provide guidance on the methods that practitioners might use for aggregate data meta-analyses, depending on the type of data available.

Methods We discuss models for the meta-analysis of longitudinal continuous outcome data when IPD are available. In these models time is included either as a

Other potential applications

Many other novel areas benefit from a multivariate meta-analysis, such as:

- Sensitivity and specificity in test accuracy studies
- Multiple thresholds in meta-analysis of diagnostic test and prognostic factor studies
- Survival probabilities at multiple time-points
- Calibration and discrimination performance of a clinical prediction model
- Categorised & continuous risk factor trends/associations (see Greenland and Longnecker, 1992)

The multivariate approach will be increasingly popular!

Advantage 5: functions of pooled estimates

- Functions of the effects may be of interest

e.g. (1): hypothesis test of $m_1 = m_2 = 0$

e.g. (2): multiple treatment comparison
m_1 = treatment effect of A versus placebo
m_2 = treatment effect of B versus placebo

Then: $m_1 - m_2$ = treatment effect of A versus B

Advantage 5: functions of pooled estimates

- Functions of the effects may be of interest

$\text{Var}(m_1 - m_2) = \text{Var}(m_1) + \text{Var}(m_2) - 2\text{cov}(m_1, m_2)$

- Clearly must account for correlation
- Univariate meta-analysis would assume $\text{cov}(m_1, m_2) = 0$; may lead to wrong conclusions

Network meta-analysis

- Multivariate meta-analysis of IPD can be used to fit a network meta-analysis of multiple treatments (White et al, 2012)
- Network meta-analysis analyses all treatment contrasts in same model (A vs B, A vs C, B vs C) and accounts for their correlation
- Comparison of A vs B 'borrows' indirect information from studies only reporting B vs C, or A vs C etc
- Can be undertaken in a one-stage IPD model, but here I focus on the two-stage IPD approach

Network meta-analysis

A two-stage IPD network meta-analysis is:

- First stage: Use IPD to derive estimates and variances for each treatment contrast in each trial; also the within-study correlations for each pair of treatment contrasts


```
. network setup r n, studyvar(study) trtvar(treat)
Treatments used
   A (reference):                A
   B:                            B
   C:                            C
   D:                            D
   E:                            E
   F:                            F
   G:                            G
   H:                            H

Measure                          Log odds ratio

Studies
   ID variable:                  study
   Number used:                  28
   IDs with zero cells:          [none]
   IDs with augmented reference arm:  17 18 19 20 21 22 23 24 25 26 27 28
   - observations added:         0.001
   - mean in augmented observations:  study-specific mean

Network information
   Components:                   1 (connected)
   Df. for inconsistency:        8
   Df. for heterogeneity:        35

Current data
   Data format:                  augmented
   Design variable:              _design
   Estimate variables:           _y*
   Variance variables:           _S*
   Command to list the data:     list study _y* _S*, nod noobs(_design)
```

Stata has a package to prepare the data for a network meta-analysis.

This is an example with binary data
- See practical

Network meta-analysis

A two-stage IPD network meta-analysis is:

- Second stage: Fit a multivariate model with one treatment contrast omitted.

NB: The omitted treatment contrast can be specified in terms of the included treatment contrasts; if you include ALL contrasts the model is over-parameterised.

```
network meta consistency, wt
```

e.g. Consider 2 treatments are of interest & placebo:

- In the first stage we use the IPD to derive
  Y_{i1} : the effect estimate of A versus placebo
  Y_{i2} : the effect estimate of B versus placebo

from each trial, plus their within-study variances & correlation

- In the second stage, we fit:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix}, \mathbf{S}_i\right) \qquad \mathbf{S}_i = \begin{pmatrix} S_{i1}^2 & \lambda_i \\ \lambda_i & S_{i2}^2 \end{pmatrix}$$

$$\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Sigma\right) \qquad \Sigma = \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix}$$

μ_1 = treatment effect of A versus placebo
μ_2 = treatment effect of B versus placebo
Then $\mu_1 - \mu_2$ = treatment effect of A versus B

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Borrowing strength in network meta-analysis

- Previous example assumed all trials had 3 groups (for the 2 treatments and placebo)

- However, key advantage of using a network meta-analysis is when there are different sets of treatment contrasts available in each trial
  (e.g. trial 1: A, B & C; trial 2: A & C; trial 3: B & C)

- If we assume treatment groups are missing at random, the multivariate (network) meta-analysis model will
  - Borrow strength from correlations, as shown in previous multiple outcomes examples

& crucially

- Borrow strength from indirect evidence by assuming consistency (coherence, transitivity)

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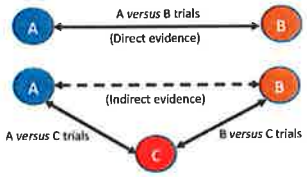
The consistency assumption



- Assumes consistency:

Treatment effect of A versus B
= (treatment effect of A versus C) – (treatment effect of B versus C)

- Always holds within a single randomised trial of A, B and C
- Under a **missing at random** assumption, it will also hold (on average) across trials that only compare a subset of treatments.
- Thus, the benefit of A versus B can be inferred from the indirect evidence from trials of A versus C and from trials of B versus C.

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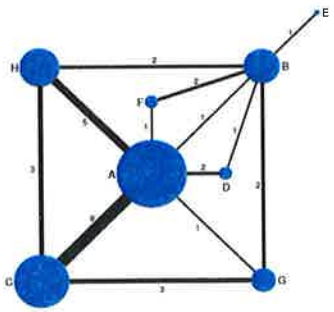
e.g: Network meta-analysis of 28 trials to compare eight thrombolytic treatments after acute myocardial infarction: outcome of interest is mortality by 30-35 days.

- For brevity we refer to these treatments as **A to H**.
- As there are eight treatments, there are 28 comparisons of interest overall; however, only 13 of these comparisons are directly reported in at least one trial.
- Maximum number of trials providing direct evidence for a particular comparison is only eight.
- By invoking the consistency assumption above, all eight treatments can be evaluated in a network meta-analysis of all 28 trials, thus allowing thousands more patients and hundreds more events to be retained toward each contrast.

e.g: Network meta-analysis of 28 trials to compare eight thrombolytic treatments after acute myocardial infarction: outcome of interest is mortality by 30-35 days



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Network meta-analysis example
Stata code and output

```
. network meta consistency, wt
Command is: mvmeta _y _S , bscovariance(exch 0.5) longparm suppress(uv mm) wt
> vars(_y_B _y_C _y_D _y_E _y_F _y_G _y_H)
Note: using method reml
Note: using variables _y_B _y_C _y_D _y_E _y_F _y_G _y_H
Note: 28 observations on 7 variables
Note: variance-covariance matrix is proportional to .5*I(7)+.5*J(7,7,1)
```

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Network meta-analysis example: Stata code and output (Treatment A is the reference)

		Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_y_B	_cons	-.1612882	.0464011	-3.48	0.001	-.2522326	-.0703438
_y_C	_cons	.002128	.0324348	0.07	0.948	-.061443	.065699
_y_D	_cons	-.0438161	.048854	-0.90	0.370	-.1395682	.0519359
_y_E	_cons	-.1556532	.0803957	-1.94	0.053	-.3134259	.0017195
_y_F	_cons	-.113092	.0619172	-1.83	0.068	-.2343574	.0081334
_y_G	_cons	-.1972319	.2215621	-0.89	0.373	-.6314857	.2370219
_y_H	_cons	.0143583	.0403238	0.36	0.722	-.0646749	.0933915

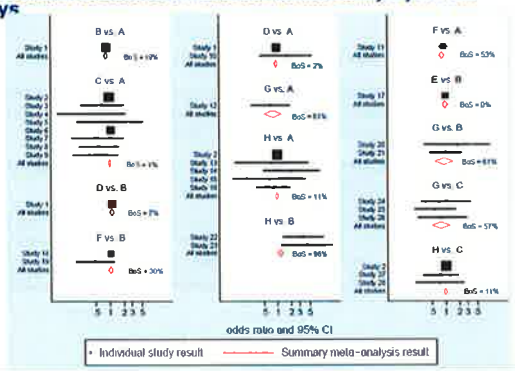
Network meta-analysis example Stata code and output

Estimated between-studies SDs and correlation matrix:

	SD	_y_B	_y_C	_y_D	_y_E	_y_F
_y_B	.01520341	1	.	.	.	.
_y_C	.01520341	.5	1	.	.	.
_y_D	.01520341	.5	.5	1	.	.
_y_E	.01520341	.5	.5	.5	1	.
_y_F	.01520341	.5	.5	.5	.5	1
_y_G	.01520341	.5	.5	.5	.5	.5
_y_H	.01520341	.5	.5	.5	.5	.5

	_y_G	_y_H
_y_B	.	.
_y_C	.	.
_y_D	.	.
_y_E	.	.
_y_F	.	.
_y_G	1	.
_y_H	.5	1

e.g: Network meta-analysis of 28 trials to compare eight thrombolytic treatments after acute myocardial infarction: outcome of interest is mortality by 30-35 days



Inconsistency

- **Inconsistency is when direct & indirect evidence disagree.**
- Inconsistency may arise due to chance, bias in the direct or indirect comparison, or heterogeneity.
- Bias in the available evidence, e.g. due to publication bias, may invalidate missing at random assumption.
- Heterogeneity is important when there are key differences in trials with direct evidence and those with indirect evidence, e.g. in terms of their case-mix variation, follow-up length, etc.
- Example: If there is an important interaction between a patient-level covariate and treatment effect, and the distribution of the covariate changes across trials with and without direct evidence, then the consistency assumption is unlikely to hold.

Inconsistency

- The consistency assumption can be examined for each treatment comparison where there is direct and indirect evidence (sometimes referred to a closed loop within the network plot).
- Does treatment effect (direct) = treatment effect (indirect)?
- Often low power to detect inconsistency.
- No strong evidence of inconsistency in the thrombolytic example.
- Excellent overviews for further reading are:

Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33(5):641-56.

Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29(7-8):932-44.

Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013;42(1):332-45.

Software

- 'network' in Stata is highly recommended (White, 2015)

White IR. Network meta-analysis. The Stata Journal 2015;15:951-85.

- Fits network meta-analysis models using the multivariate framework.
- Often restrictions enforced to facilitate estimation and assumptions: e.g. $\tau_1 = \tau_2$, and $\rho_B = 0.5$.
- Uses data augmentation to deal with missing and different treatment contrasts in each study.
- Can examine inconsistency
- See practical 4.

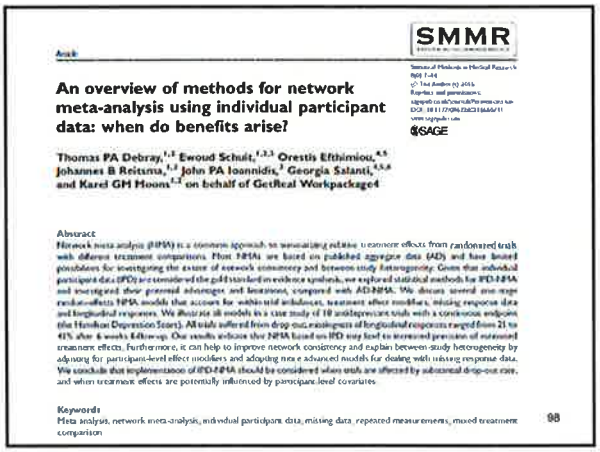
Benefits of IPD for network meta-analysis

Key advantage is to improve consistency by:

- Reducing heterogeneity, e.g. by adjusting for patient-level covariates, including interactions, and standardising outcome definition and follow-up length,
- Reducing bias concerns, e.g by adjusting for confounders.

Plus other generic benefits of IPD, such as:

- Standardise analysis methods for each trials,
- Derive aggregate data directly,
- Handle missing outcomes and covariate data appropriately (see Debray guest lecture),
- Handle repeated measures (longitudinal data) properly, etc.



SMMR

An overview of methods for network meta-analysis using individual participant data: when do benefits arise?

Thomas PA Debray,[1,2] Ewoud Schuit,[1,2,3] Orestis Efthimiou,[4,5] Johannes B Reitsma,[1,2] John PA Ioannidis,[3] Georgia Salanti,[4,5,6] and Karel GM Moons[1,2] on behalf of GetReal Workpackage4

SAGE

Abstract

Keywords

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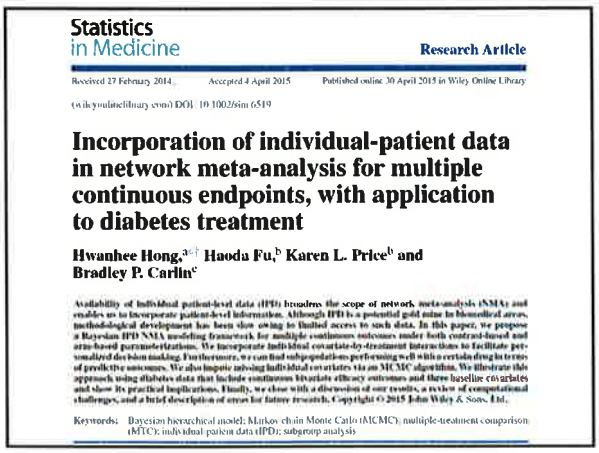

Statistics in Medicine

Research Article

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(wileyonlinelibrary.com) DOI: 10.1002/sim.6519

Incorporation of individual-patient data in network meta-analysis for multiple continuous endpoints, with application to diabetes treatment

Hwanhee Hong,[a*†] Haoda Fu,[b] Karen L. Price[b] and Bradley P. Carlin[c]

Keywords: Bayesian hierarchical model; Markov chain Monte Carlo (MCMC); multiple-treatment comparison (MTC); individual patient data (IPD); subgroup analysis

Part 5:

Limitations of multivariate meta-analysis

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Limitations

Despite the advantages, there are some limitations & disadvantages to be aware of (Jackson et al., 2011)

- Estimation of between-study correlations can be difficult, especially with only few studies.
- Dealing with missing within-study correlations in non-IPD studies (See Bujkiewicz et al, 2013; Wei and Higgins, 2013).
- Is the between-studies multivariate normal assumption correct? It assumes a linear relationship between effects but is this justified? (copula approaches are an alternative).
- Borrowing weakness? Do we want a well reported outcome to 'borrow' information from a selectively reported outcome?
- Is the missing at random (consistency) assumption justified?

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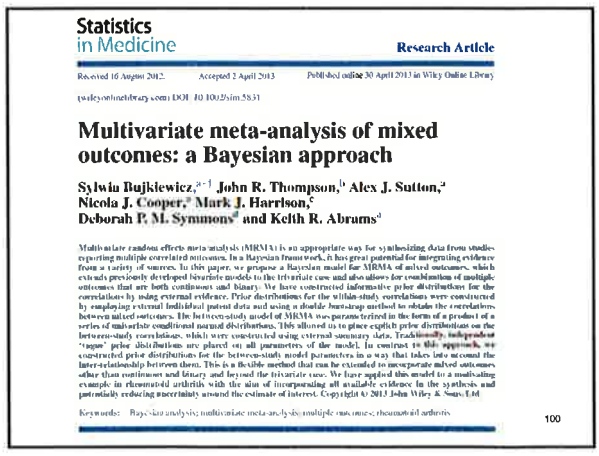

Statistics in Medicine

Research Article

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Multivariate meta-analysis of mixed outcomes: a Bayesian approach

Sylwia Bujkiewicz,[a*†] John R. Thompson,[b] Alex J. Sutton,[a] Nicola J. Cooper,[a] Mark J. Harrison,[c] Deborah P. M. Symmons[d] and Keith R. Abrams[a]

Keywords: Bayesian analysis; multivariate meta-analysis; multiple outcomes; rheumatoid arthritis

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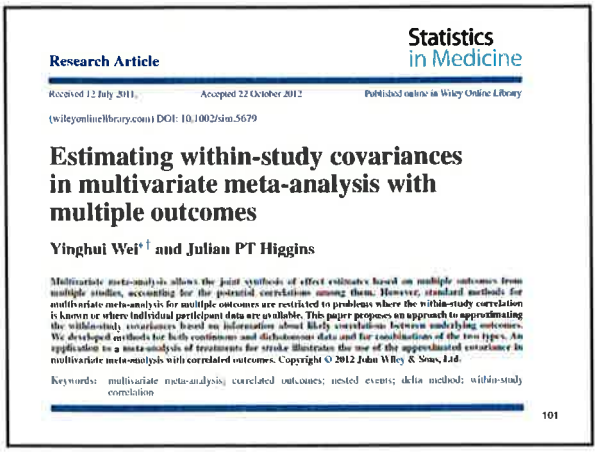

Research Article

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Estimating within-study covariances in multivariate meta-analysis with multiple outcomes

Yinghui Wei*† and Julian PT Higgins

Multivariate meta-analysis allows the joint synthesis of effect estimates based on multiple outcomes from multiple studies, accounting for the potential correlations among them. However, standard methods for multivariate meta-analysis for multiple outcomes are restricted to problems where the within-study correlation is known or where individual participant data are available. This paper proposes an approach to approximating the within-study covariances based on information about likely correlations between underlying outcomes. We developed methods for both continuous and dichotomous data and for combinations of the two types. An application to a meta-analysis of treatments for stroke illustrates the use of the approximated covariance in multivariate meta-analysis with correlated outcomes. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: multivariate meta-analysis; correlated outcomes; nested events; delta method; within-study correlation

Conclusions

'Good clinical data are expensive and hard to come by. We want to extract maximum information from available data ... many clinical studies have more than one outcome variable; these variables are seldom independent and so each must carry some information about the others. *If we can use this information, we should.*'

Martin Bland (2011)

- **Multivariate & network meta-analysis achieves this**
  - Jointly synthesises all effects & accounts for their correlation
  - Correlation allows the borrowing of strength; IPD often critical for obtaining within-study correlations
  - Improved statistical properties compared to separate univariate analyses (under assumptions)
  - Coherent framework to compare multiple treatments

THANK YOU **e-mail: r.riley@keele.ac.uk**

Selected References:

Jackson D, Riley RD, White IR. Multivariate meta-analysis: potential and promise. *Stat Med* 2011; 30: 2481-2498.
Becker BJ. Multivariate Meta-analysis. In: Tinsley HEA, Brown S, editors. Handbook of Applied Multivariate Statistics and Mathematical Modeling San Diego: Academic Press; 2000. p. 499-525.
Berkey CS, et al. Meta-analysis of multiple outcomes by regression with random effects. Stat Med 1998;17(22):2537-50.
Raudenbush SW, et al. Modeling multivariate effect sizes. Psychological Bulletin 1988;103(1):111-120.
Riley RD, et al. (2007) An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes. *Statistics in Medicine*, 26, 78-97.
Riley RD, et al. Multivariate meta-analysis using individual participant data. Res Synth Method. 2015;6 157-74.
Riley RD, et al. (2009) Multivariate meta-analysis: the effect of ignoring within-study correlation. JRSS-A 172: 789-811
Van Houwelingen HC, et al. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21(4):589-624.

Selected References:

Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. Bmj 2005;331(7521):897-900
Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. J Am Stat Assoc 2006;101(474):447-59.
White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Method 2012;3: :111-25.
Higgins JPT, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Method 2012;3:98-110.
Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9(7):e99682.
Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:58.
Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23(20):3105-24.
Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8(10):e76654.

Appendix 1: Bayesian estimation

- Bayesian approach has potential advantages:
  - can account for all parameter uncertainty
  - incorporate external evidence through prior distribution
  - allows direct probability statements
  - naturally allows predictive inferences
- Specification of (vague) prior distributions for the between-study var-cov matrix, S, is non-trivial when there are >2 outcomes (Wei and Higgins, 2013)
- Need to ensure it is positive semi-definite
- Conjugate prior for S is the inverse Wishart prior
- Choosing values for its parameters is difficult
- Not vague (generalises gamma distribution, known to be informative as prior for 'tau' in univariate meta-analysis)

Bayesian estimation

- Wei and Higgins (2013) suggest separation priors
- That is, place priors on the between-study standard deviations and correlations separately
- More flexible and intuitive. Consider 2 options
  - Cholesky decomposition
  - Spherical decomposition
- Give similar findings (in our experience)

e.g. in the bivariate setting, separation enables priors of:

$$\mu_1 \sim N(0,1000000) \qquad \mu_2 \sim N(0,1000000)$$
$$\tau_1 \sim N(0,1)I(0,) \qquad \tau_2 \sim N(0,1)I(0,)$$
$$\rho_{B(1,2)} \sim \text{Uniform}(-1,1)$$

Bayesian estimation

- With few studies, the prior distributions for the taus & the between-study correlation are still potentially informative

e.g. Uniform (-1,1) or Uniform (0,1) for $\rho_{B(1,2)}$?

- Burke et al, 2016 show that U(-1,1) is highly informative, & that use of a sensible prior is preferred
- Similarly, sensible prior needs for each τ
- At very least, sensitivity analysis to the choice of prior distributions is recommended
- Bujkiewicz et al. also suggest using a product-normal specification ... express multivariate model as a series of conditional univariate normal distributions.

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Appendix 2: Two-stage IPD meta-analysis of longitudinal data

- Jones et al. show that time can either be modelled:

Approach (i): As a factor

- a set of distinct time-points is identified and each is treated as an 'outcome' in your multivariate analysis

STAGE ONE: In each study, use the IPD to fit a standard repeated measures model (with time as a factor) to account for multiple records per individual (correlated residuals) and post-estimation obtain the (treatment) effect estimates at each time-point, with their variances and within-study correlations.

STAGE TWO: Fit a multivariate meta-analysis to combine the correlated effect estimates across studies (e.g. 3 time-points = a trivariate meta-analysis).

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Two-stage IPD meta-analysis of longitudinal data

- Jones et al. show that time can either be modelled:

Approach (ii): As continuous - option 1

e.g a linear trend is fitted in each study followed by a bivariate meta-analysis of intercepts & slopes (or differences in intercepts & slopes when comparing two treatment groups)

STAGE ONE: Use the IPD to fit a standard repeated measures model with time treated as a continuous variable (rather than a factor) to obtain a linear trend (or the difference in a linear trend if comparing two groups)

STAGE TWO: Use a bivariate meta-analysis to pool the (differences in) intercepts and (differences in) slopes.

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Two-stage IPD meta-analysis of longitudinal data

- Jones et al. show that time can either be modelled:

Approach (ii): As continuous - option 1

e.g a linear trend is fitted in each study followed by a bivariate meta-analysis of intercepts & slopes (or differences in intercepts & slopes when comparing two treatment groups)

Major disadvantage:

This process can only handle studies that give 2 or more time-points, as otherwise a slope cannot be estimated.

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Two-stage IPD meta-analysis of longitudinal data

- Jones et al. show that time can either be modelled:

Approach (iii): As continuous - option 2

Time is treated as a factor in each study followed by a multivariate meta-regression that fits a linear trend through the multiple correlated study estimates

(allows studies with only one time-point)

STAGE ONE: In each study, use the IPD to fit a standard repeated measures model (with time as a factor) to account for multiple records per individual (correlated residuals) and post-estimation obtain the (treatment) effect estimates at each time-point with variances & within-study correlations.

STAGE TWO: Use a multivariate meta-regression to fit a line through the multiple, correlated study estimates.

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Example: Meta-analysis of 5 trials of Alzheimer's Disease

Outcome = mini-mental state examination (MMSE; a measure cognitive function) at 6 time-points

- Jones et al. fit fixed effect multivariate models

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Example: Meta-analysis of 5 trials of Alzheimer's Disease

Outcome = mini-mental state examination (MMSE; a measure cognitive function) at 6 time-points

- Jones et al. fit fixed effect multivariate models

Approach (i): When time treated as a factor

Time (months)	SUMMARY TREATMENT EFFECT (S.E.) Using correct within-study correlations (from IPD)	Assuming within-study correlations are zero
1	0.30 (0.47)	0.43 (0.54)
2	-0.47 (0.59)	-0.84 (0.97)
4	0.33 (0.47)	0.75 (0.57)
6	0.19 (0.48)	0.31 (0.50)
9	0.34 (0.52)	0.69 (0.63)
12	-0.03 (0.55)	0.29 (0.66)

BoS is very clear: large gain in precision and big change in estimates.

Example: Meta-analysis of 5 trials of Alzheimer's Disease

Outcome = mini-mental state examination (MMSE; a measure cognitive function) at 6 time-points

- Jones et al. fit fixed effect multivariate models

Approach (iii): When time treated as a factor in the first stage, and then continuous in the multivariate meta-regression

Time (months)	SUMMARY TREATMENT EFFECT (S.E.) Using correct within-study correlations (from IPD)	Assuming within-study correlations are zero
Intercept	0.37 (0.52)	0.38 (0.46)
slope	-0.005 (0.036)	0.017 (0.067)
1	0.37 (0.52)	0.40 (0.40)
2	0.37 (0.52)	0.41 (0.35)
4	0.36 (0.52)	0.45 (0.28)
6	0.35 (0.53)	0.48 (0.26)
9	0.33 (0.56)	0.53 (0.34)
12	0.32 (0.61)	0.58 (0.50)

A meta-regression ignoring correlation gives an intercept that is too precise & a slope in wrong direction ... leads to pooled estimates that are too large & too precise

PRACTICAL 4: Multivariate and network meta-analysis

Please follow the instructions in the Stata do files labelled Practical 4a, 4b and 4c

Practical 4(a): Derivation of within-study correlations using IPD of a single trial.

Practical 4(b): Application of multivariate meta-analysis models to bivariate situations.

Practical 4(c): Application of multivariate models to four outcomes and network meta-analysis.

Learning objectives:

- Gain experience of using IPD to estimate within-study correlations using joint regressions and bootstrapping, for multiple outcomes and partially & fully adjusted effects.
- Apply multivariate models using the 'mvmeta' module.
- Experience the gain in information (borrowing of strength) by using multivariate meta-analysis rather than separate univariate meta-analyses.
- Understand how to derive study weights and BoS statistics following a multivariate meta-analysis.
- Interpret Stata output following a multivariate and network meta-analysis.
- Gain experience of using the 'network' module for analysing IPD from multiple studies with multiple treatment groups and binary outcomes.
- Gain experience of deriving forest plots and network graphs to display results from multivariate and network meta-analysis.
- Gain experience of examining inconsistency.

Multiple Imputation in Individual Participant Data Meta-Analysis

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Aims

At the end of the lecture, you should be able to:

- Understand why missing data is important
- Distinguish between different types of missing data
- Formulate major challenges of missing data in IPD-MA
- Understand the concepts of multiple imputation
- Impute missing data in a single dataset
- Impute missing data in IPD-MA

Missing Data

Common examples in primary studies

- Self-reported outcomes (e.g. Quality of Life)
- Laboratory measurements
- Biomarkers that are difficult to measure
- Characteristics not of primary interest
- Dropout due to treatment toxicity or non-effectiveness

Missing Data

This talk focuses on imputation of missing covariates

Example (diagnosis of deep vein thrombosis):

PID	dvt	sex	age	malign	par	ddimdich	durat
9464	0	1	15.7900	0	0	<NA>	<NA>
1869	0	1	16.0000	0	1	<NA>	10.000000
5912	0	0	16.0000	<NA>	1	1	<NA>
8414	0	0	16.0000	0	0	0	7.210618
1029	0	0	16.8137	1	0	0	<NA>
8493	0	1	17.0000	0	0	1	9.809352

Types of Missing Data

Missing completely at random (MCAR): The probability of missingness depends *only* on the overall probability of being missing.

Examples

- Questionnaire of a subject is accidentally lost.
- Blood pressure measurements may be missing due to breakdown of automatic sphygmomanometer.

Types of Missing Data

Missing at random (MAR): the probability of missingness *may* depend on observed information, including any design factors.

Example

- Imaging tests have not been performed for some of the non-diseased subjects

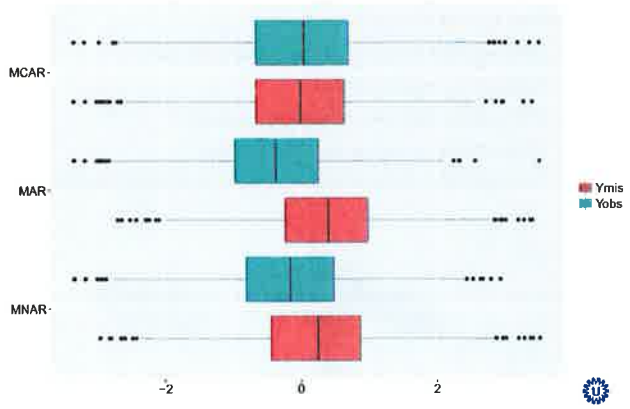
Types of Missing Data

Missing not at random (MNAR): the probability of missingness depends on unobserved information or on the status of the missing value

Examples

- People with high blood pressure may be more likely to miss clinic appointments because they have headaches
- A typical study-level example of MNAR is publication bias!

Types of Missing Data



Dealing with missing data

Multiple imputation

Aim: To create and analyze multiple complete datasets, representing *plausible* versions of the original incomplete dataset

Reasons to use multiple imputation

- To improve precision in MCAR problems
- To avoid bias in MAR and MNAR problems
- To separate the missing data problem from data analysis

Multiple imputation

Main characteristics

- Imputations are based on probabilistic models derived from the observed data
- Variability in imputed values are caused only because of the uncertainty about what value to impute
- Two approaches: joint modeling versus fully conditional specification

Multiple imputation - example

Original dataset

PID	dvt	sex	age	malign	par	ddimdich	durat
9464	0	1	15.7900	0	0	<NA>	NA
1869	0	1	16.0000	0	1	<NA>	10.000000
5912	0	0	16.0000	<NA>	1	1	NA
8414	0	0	16.0000	0	0	0	7.210618
1029	0	0	16.8137	1	0	0	NA
8493	0	1	17.0000	0	0	1	9.809352

Imputed dataset 1

PID	dvt	sex	age	malign	par	ddimdich	durat
9464	0	1	15.7900	0	0	1	7.000000
1869	0	1	16.0000	0	1	0	10.000000
5912	0	0	16.0000	0	1	1	7.000000
8414	0	0	16.0000	0	0	0	7.210618
1029	0	0	16.8137	1	0	0	10.000000
8493	0	1	17.0000	0	0	1	9.809352

Multiple imputation - example

Imputed dataset 2

PID	dvt	sex	age	malign	par	ddimdich	durat
9464	0	1	15.7900	0	0	0	1.000000
1869	0	1	16.0000	0	1	0	10.000000
5912	0	0	16.0000	0	1	1	2.000000
8414	0	0	16.0000	0	0	0	7.210618
1029	0	0	16.8137	1	0	0	7.000000
8493	0	1	17.0000	0	0	1	9.809352

Imputed dataset 3

PID	dvt	sex	age	malign	par	ddimdich	durat
9464	0	1	15.7900	0	0	0	4.000000
1869	0	1	16.0000	0	1	0	10.000000
5912	0	0	16.0000	0	0	1	61.000000
8414	0	0	16.0000	0	0	0	7.210618
1029	0	0	16.8137	0	0	0	59.000000
8493	0	1	17.0000	0	0	1	9.809352

Joint Modeling

1. Specify a multivariate distribution for all data
2. Estimate the parameters of the multivariate distribution using the observed data
3. Draw imputations directly from (the conditional densities of) this distribution

This approach has several desirable theoretical properties, but may be difficult to implement when there is a mixture of complex data types (e.g. non-Normally distributed data).

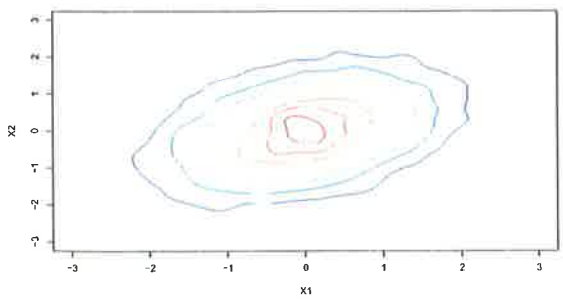
Fully Conditional Specification

Imputations are created by drawing from iterated conditional models.

1. Specify a conditional distribution for each covariate with missing values (e.g. by specifying a regression model for each covariate with missing values)
2. Replace missing (or previously imputed) values using the relevant conditional density
3. Update the parameters of each conditional distribution
4. Step 2-3 are iterated using Markov Chain Monte Carlo sampling to ensure that the conditional densities converge towards their (posterior) joint distribution.

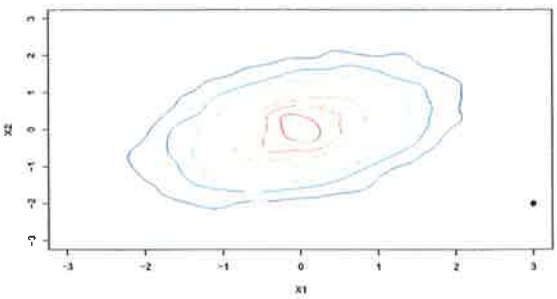
This cycle is repeated numerous times to generate multiple imputed data sets

Fully Conditional Specification



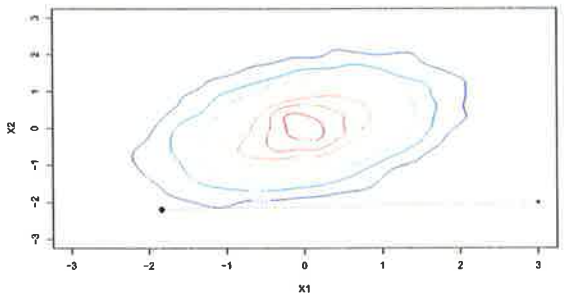
Suppose we have a dataset where for one individual X1=<NA> and X2=<NA>. The observed distribution of X1 and X2 is given above.

Fully Conditional Specification



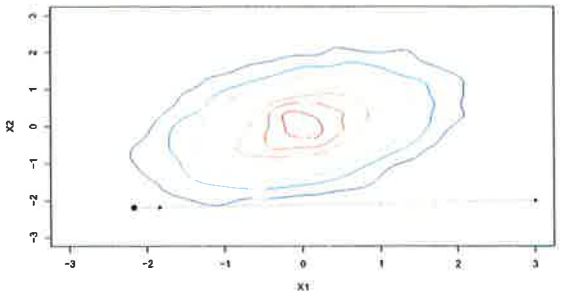
Step 1: Start with a random guess, for instance, X1=3 and X2=-2.

Fully Conditional Specification



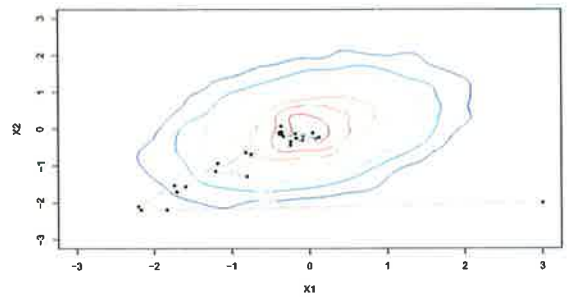
Step 2: Update X1 using a conditional model that involves the initial guess for X2. Update X2 using a conditional model that involves the updated value for X1.

Fully Conditional Specification



Keep updating X1 and X2 using most recent values. It may take some iterations before imputed values of X1 and X2 are plausible and no longer depend on the initial "guess".

Fully Conditional Specification



Finanlly, after several iterations, we end up in the posterior distribution of X1 and X2. Try this yourself at http://www.mas.ncl.ac.uk/ ndjw1/teaching/sim/gibbs/gibbs.html

Fully Conditional Specification

Key issues

- Specification of conditional densities (imputation model)
- Specification of Data Analysis Model
- Congeniality between analysis and imputation model
- Combining estimates from imputed datasets

Congeniality

The imputation model should *minimally* allow for the same complexities as the analysis model.

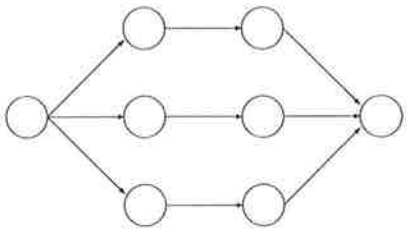
- Interactions
- Transformed versions of a variable
- Heteroscedasticity
- Time-to-event information
- Between-study heterogeneity
  More on this later!
- ...

Congeniality

Strategies to improve/ensure congeniality

- Generate new variables for interactions, data transformations etc. and treat them as "just another variable" in the imputation model (JAV)
- Adopt *passive imputation* to maintain consistency among different transformations of the same data
- Adopt advanced methods for imputing variables with non-linear trends (e.g. broken-stick)

Combining estimates from imputed datasets



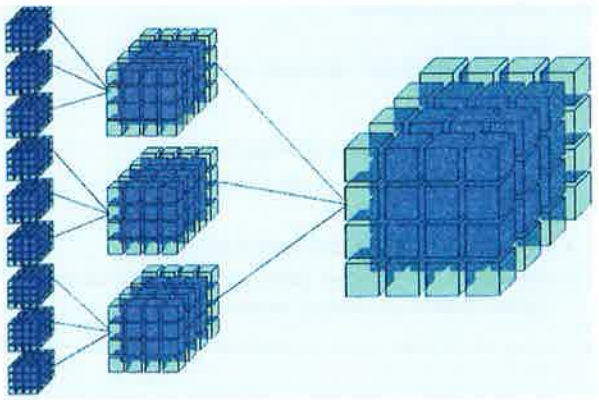
Incomplete data Imputed data Analysis results Pooled results

Rubin's rules

The last step is to pool the D parameter estimates into one estimate, and to estimate its variance. The total variance is a combination of:

- Conventional sampling variance (within-imputation variance)
- Extra variance caused by the missing data (between-imputation variance)
- Extra simulation variance caused by the fact that pooled estimates are based on a finite set of imputed data sets

The larger D gets, the smaller the effect of simulation error on the total variance.



Three types of missing data in IPD-MA

- Partially missing data
- Systematically missing data
- Entire studie(s) missing
- Combination of above issues

Partially missing data

Variable(s) partially missing in one or more studies
Similar to missing data in primary studies

PID	studyid	dvt	sex	age	malign	par	ddimdich	durat
67	1	0	0	18.00000	0	0	0	7
142	1	0	0	18.00000	<NA>	0	<NA>	2
451	1	0	0	18.93973	0	0	0	1
154	1	0	0	19.00000	0	0	<NA>	15
1028	2	0	0	16.81370	<NA>	0	0	NA
1394	2	1	0	17.05479	0	0	1	14
1118	2	0	1	18.14795	0	0	0	NA
1031	2	0	0	18.18356	0	0	0	21
1868	3	0	1	16.00000	0	1	<NA>	NA
1927	3	0	0	19.00000	0	0	1	2
1870	3	0	1	20.00000	0	0	1	7
1859	3	0	0	21.00000	0	0	<NA>	1

Systematically missing data

Variable(s) completely missing in one or more studies
e.g. due to budget constraints, lack of medical equipment, inconsistent variable definitions, use of alternative tests, ...

PID	studyid	dvt	sex	age	malign	par	ddimdich	durat
67	1	0	0	18.00000	0	0	0	7
102	1	0	0	18.00000	0	0	0	2
451	1	0	0	18.93973	0	0	0	1
54	1	0	0	19.00000	0	0	0	15
1029	2	0	0	16.81370	0	0	0	NA
1393	2	1	0	17.05479	0	0	1	NA
1118	2	0	1	18.14795	0	0	0	NA
1030	2	0	0	18.18356	0	0	0	NA
1869	3	0	1	16.00000	0	1	<NA>	10
1927	3	0	0	19.00000	0	0	<NA>	2
1870	3	0	1	20.00000	0	0	<NA>	7
1859	3	0	0	21.00000	0	0	<NA>	1

Imputing missing data in IPD-MA

Main issue

IPD-MA are naturally affected by clustering. This may lead to:

- Differences in patient spectrum across studies
- Differences in predictive associations across studies
- Differences in missing data patterns across studies

Imputation that ignores clustering leads to underestimation of the magnitude of clustering and hence underestimated standard errors, even if the analysis does allow for clustering

→ Imputation models should account for clustering

Imputing missing data in IPD-MA

Methodological challenges

- Imputation that allows for the clustering through fixed effects overestimates the magnitude of the clustering and hence overestimates standard errors
- Identifiability problems in the presence of systematically missing variables
- Conditional distributions of covariates are likely to be heteroscedastic and cannot be described by GLMM

Congeniality of imputation and analysis models cannot be ensured, even when fully accounting for clustering

Imputing missing data in IPD-MA

Imputation Strategy

- Within-study imputation
- Stratified imputation
- Hierarchical imputation

Imputation Paradigm

- Fully Conditional Specification (FCS)
- Joint Modeling (JM)

Data Analysis Strategy

- Two-stage meta-analysis
- One-stage meta-analysis

Several combinations are possible!

Within-study imputation

Impute each study dataset separately using traditional methods

Pros:

- No need for advanced software packages
- Preserves heterogeneity across data sources

Cons:

- Unfeasible for small studies with many missings
- Unfeasible when there are systematically missing variables (unless datasets or variables are entirely omitted)

Stratified imputation

Stack all data sources and include study ID as a dummy variable in the imputation model

Pros:

- No need for advanced software packages
- Allows for heterogeneity in prevalence of missing predictor

Cons:

- Ignores heterogeneity in predictive associations across studies
- Unfeasible when there are systematically missing variables

Hierarchical imputation

Adopt mixed effect models to impute missing values

Pros:

- Cutting edge technology
- Allows to preserve heterogeneity across data sources

Cons:

- Cutting edge technology
- Requires careful modeling to ensure congeniality (compatibility) between imputation and analysis model
- Convergence may be problematic

JM or FCS?

FCS methods possibly less likely to yield biased imputations because they allow for more flexibility. However...

- Theoretical background of FCS is not well understood (as compared to JM)
- Estimation of conditional densities is computationally more demanding (than the estimation of a joint distribution)
- Performance differences between JM and FCS often (relatively) small

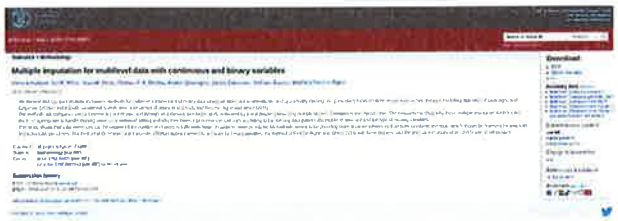
Simulation study

Evaluation of cutting-edge methods for imputing sporadically and/or systematically missing data in IPD-MA

- (Extension of) within-study imputation
  - Fully conditional specification: `FCS-2stage` (estimation using REML and MM)
- Hierarchical imputation
  - Fully conditional specification: `FCS-GLM`
  - Joint modeling: `JM-JOMO`

Ref: Audigier V, White IR, Jolani S, Debray TPA, Quartagno M, Carpenter JR, et al. Multiple imputation for multilevel data with continuous and binary variables. 2017. Available from: `https://arxiv.org/abs/1702.00971`

Simulation study



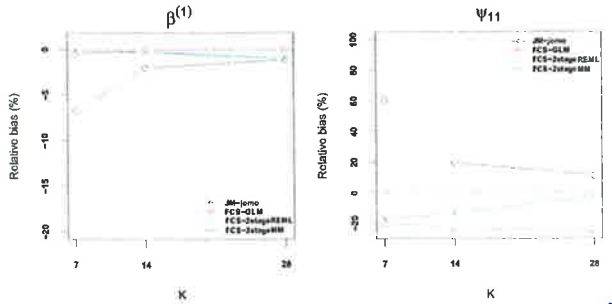
Simulation study

Simulation parameters

- IPD-MA with 4 variables
  - x_1 continuous variable
  - x_2 binary variable
  - x_3 continuous variable, used to generate missing data
  - y outcome (continuous or binary)
- Presence of heterogeneity
  - in covariate distributions
  - in predictive associations
- Presence of missing data
  - Sporadically missing data (MCAR and MAR)
  - Systematically missing data (MCAR)

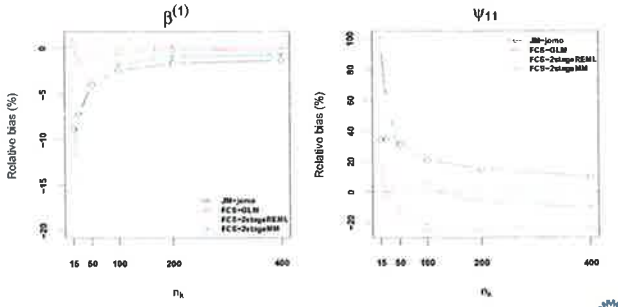
Simulation study

Robustness to the number of studies



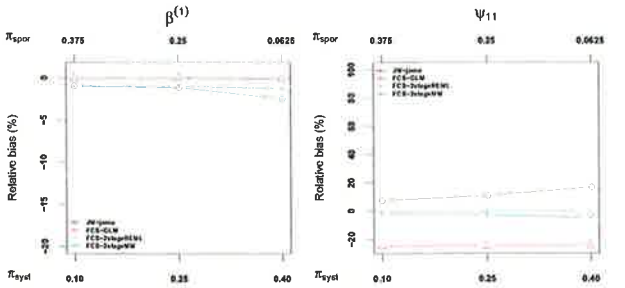
Simulation study

Robustness to the study size



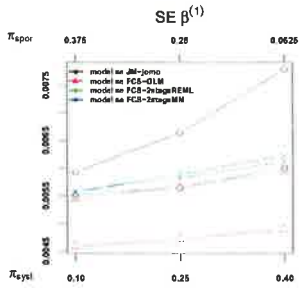
Simulation study

Robustness to the proportion of systematically missing values



Simulation study

Robustness to the proportion of systematically missing values: model versus empirical standard errors



Dashed lines indicate the empirical SE

Key findings

Ad-hoc methods

- Bias and poor coverage for `FCS-noclust` (ignore clustering), `FCS-fixclust` (stratified imputation), and `JM-pan` (simplified version of `JM-jomo`)
- Should be avoided in IPD-MA

JM-jomo

- Prone to bias when few individuals and/or studies
- (Over-)conservative w.r.t. heterogeneity
- Recommended when the number of incomplete binary variables and #studies is large

Key findings

FCS-2stage

- Prone to bias when imputing binary covariates in small studies
- Low precision (due to stratification)
- Very fast
- To be avoided when avoided when studies are small, or when the proportion of sporadically missing values is large

FCS-glm

- Low bias for imputation of continuous variables
- Under-estimation of precision and heterogeneity
- Computationally intensive!
- Advantageous when clusters are small

One-stage or two-stage meta-analysis?

Should one-stage IPD-MA be preferred when adopting hierarchical imputation, and vice versa?

Work in progress!

Software

- R
  - mice (Van Buuren *et al.*, 2011)
  - jomo (Quartagno *et al.*, 2015)
  - pan (Schafer, 2016)
  - areglmpute (HMisc package from Frank Harrell)
  - mi (Su *et al.*, 2011)
  - VIM (Templ *et al.*, 2011)
- SAS
  - PROC MI
  - PROC MIANALYZE
  - IVEware
- Stata
  - Ice (Royston, 2005)
  - MI

Recommendations

- Evaluate the extent of missing data
- Compare patients with complete data to patients with missing data to the justifiability of complete case analysis
- When pursuing multiple imputation
  - think carefully about which variables to include and how (ensure **congeniality**)
  - adopt within-study imputation if lack of time or expertise
  - adopt hierarchical imputation if in presence of partially & systematically missing data
  - think carefully about MA and RR ordering when performing a two-stage meta-analysis
  - Evaluate the impact of modeling choices and simplifications through sensitivity analyses

Background Literature

Relevant books

Imputation in single IPD

Key papers

- Erler NS et al. Dealing with Missing Covariates in Epidemiologic Studies: A Comparison between Multiple Imputation and a Full Bayesian Approach. Stat Med 2016.
- Meng X-L. Multiple-Imputation Inferences with Uncongenial Sources of Input. Statistical Science 1994.
- Schafer JL. Multiple Imputation: A Primer. Stat Meth Med Res 1999.
- Sterne JAC et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009.
- van Buuren S et al. Fully conditional specification in multivariate imputation. Journal of Statistical Computation and Simulation 2006.
- van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Meth Med Res 2007.
- White IR, Royston P. Imputing Missing Covariate Values for the Cox Model. Stat Med 2009.

Imputation in multiple IPDs

Key papers

- Audigier V et al. Comparison of multiple imputation methods for multilevel mixed data. In preparation.
- Burgess S et al. Combining multiple imputation and meta-analysis with individual participant data. Stat Med 2013.
- Debray T & Jolani S, et al. Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. Stat Med 2015.
- Debray T et al. Dealing with missing data in Individual Participant Data Meta-Analysis. In preparation.
- Quartagno M, Carpenter JR. Multiple Imputation for IPD Meta-Analysis: Allowing for Heterogeneity and Studies with Missing Covariates. Stat Med 2015.
- Resche-Rigon M et al. Multiple imputation for handling systematically missing confounders in meta-analysis of individual participant data. Stat Med 2013.
- Resche-Rigon M and White I. Multiple imputation by chained equations for systematically and sporadically missing multilevel data. SMMR 2016.

REFERENCE LIST

Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: conduct, rationale and reporting. BMJ 2010; 340: c221

Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341(8842):418-22.

Oxman AD, Clarke MJ, Stewart LA. From science to practice. Meta-analyses using individual patient data are needed. JAMA 1995; 274 (10):845-6.

Stewart LA, Clarke MJ, on behalf of the Cochrane Working Party Group on Meta-analysis using Individual Patient Data. Practical methodology of meta-analyses (overviews) using updated individual patient data. Statistics in Medicine 1995; 14: 2057-2079.

Vale CL, Rydzewska LHM, Rovers MM, Emberson JR, Gueyffier F, Stewart LA. Uptake of systematic reviews and meta-analyses based on individual participant data in clinical practice guidelines: descriptive study. BMJ 2015; 350:h1088.

Stewart LA, Tierney JF. To IPD or Not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Evaluation & the Health Professions 2002; 25: 76-97.

Stewart L, Tierney J, Burdett S. Do systematic reviews based on individual patient data offer a means of circumventing biases associated with trial publications? In: Rothstein H, Sutton A, Borenstein M, editors. Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments. Chichester: John Wiley & Sons. 2005; pp. 261-286

Simmonds MC, Higgins JPT, Stewart LA, Tierney JF, Clarke MJ, et al. Meta-analysis of individual patient data from randomised trials -a review of methods used in practice. Clinical Trials 2005; 2: 209-217.

Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J.R.Statist.Soc.A 2009; 172(1):137-159.

Riley RD, Higgins JPT, Deeks JJ. Interpretation of random-effects meta-analyses. BMJ 2011; 342:d549.

Debray TPA, et al. Get real in individual participant data (IPD) meta-analysis: a review of the methodology. Research Synthesis Methods 2015; 6(4):293-309.

Simmonds M, Stewart G, Stewart L. A decade of individual participant data meta-analyses: a review of current practice. Contemporary Clinical Trial 2015; 45:76-83.

Thomas D, Radji S, Benedetti A. Systematic review of methods for individual patient data meta-analysis with binary outcomes. BMC Med Res Method 2014; 14:79.

Tierney JF, et al. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. PLOS Med 2015; 12(7):e1001855.

Tudur Smith C, Williamson PR, Marson AG. An overview of methods and empirical comparison of aggregate data and individual patient data results for investigating heterogeneity in meta-analysis of time-to-event outcomes. J Eval Clin Pract 2004; 11(5):468-478.

Stewart, GB, et al. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. PLoS One 2012; **7**(10): p. e46042.

Tudur Smith C, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. Cochrane Database of Systematic Reviews 2016; 9 MR000007. [Epub ahead of print].

Statistical methods for a meta-analysis of IPD

Higgins JP, Whitehead A, Turner RM, Omar RZ, Thompson SG: Meta-analysis of continuous outcome data from individual patients. Stat Med 2001; 20: 2219-4.

Turner RM, Omar RZ, Yang M, Goldstein H, Thompson SG: A multilevel model framework for meta-analysis of clinical trials with binary outcomes. Stat Med 2000, **19**: 3417-3432.

Tudur-Smith C, Williamson PR, Marson AG: Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes. Stat Med 2005, **24**: 1307-1319.

Riley RD, Kauser I, Bland M, Wang J, Gueyffier F, Thijs L, Deeks JJ. Meta-analysis of continuous outcomes according to baseline imbalance and availability of individual participant data. Stat Med 2013; 32(16):2747-66. doi: 10.1002/sim.5726

Crowther MJ, Riley RD, Staessen JA, Wang J, Gueyffier F, Lambert PC. Individual patient data meta-analysis of survival data using Poisson regression models. BMC MedResMeth 2012; 12:34.

Abo-Zaid G, et al. Individual participant data meta-analyses should not ignore clustering. Journal of Clinical Epidemiology 2013; 66:865-873.

Riley RD, Kauser I, Bland M, Thijs L, Staessen JA, Wang J, Gueyffier F, Deeks JJ. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual patient data. Statistics in Medicine 2013; 32:2747-2766.

Thompson S, et al. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. Int J Epidemiol 2010; 39:1345-1359.

Jones AP, Riley RD, Williamson PR, Whitehead A. Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. Clinical Trials 2009; 6:16-27.

Ensor J, Burke DL, Snell KIE, Hemming K, Riley RD. Simulation-based power calculations for planning a two-stage individual participant data meta-analysis: with application to randomised trials with a continuous outcome. *Submitted.*

Meta-analysis combining IPD and AD

Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. Research Synthesis Methods 2010; 1 (1): 2-19.

Riley RD, et al. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. J Clin Epidemiol 2007, **60:**431-439.

Riley RD, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. Stat Med 2008; **27**: 1870-93.

One-stage versus two-stage

Olkin I, Sampson A. Comparison of meta-analysis versus analysis of variance of individual patient data. Biometrics 1998; 54 (1):317-322.

Mathew T, Nordstrom K. On the equivalence of meta-analysis using literature and using individual patient data. Biometrics 1999; 55(4):1221-1223.

Mathew T, Nordstrom K. Comparison of one-step and two-step meta-analysis models using individual patient data. Biometrical Journal 2010; 52(2):271-287.

Debray TPA, Moons KGM, Abo-Zaid GMA, Koffijberg H, Riley RD. Individual Participant Data Meta-Analysis for a Binary Outcome: One-Stage or Two-Stage? PLoS ONE 2013; 8(4): e60650.

Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. Journal of Clinical Epidemiology 2008; 61:41-51.

Tudur-Smith C, Williamson PR. A comparison of methods for fixed-effect meta-analyses of individual patient data with time-to-event outcomes. Clinical Trials 2007; 4:621-630.

Bowden J, Tierney JF, Simmonds M, Copas AJ, Higgins JPT. Individual patient data meta-analysis of time-to-event outcomes: one-stage versus two-stage approaches for estimating the hazard ratio under a random-effects model. Research Synthesis Methods 2011; 2:150-162.

Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med, 2017; 36(5):855-875 doi: 10.1002/sim.7141.

Accounting for uncertainty in between-study heterogeneity

Cornell JE, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Annals of Internal Medicine 2014; 160:267-270.

Hartung J, Knapp G. On tests of the overall treatment effect in meta-analysis with normally distributed responses. Statistics in Medicine 2001; 20:1771-1782.

Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Statistics in Medicine 2003; 22:2693-2710.

IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random-effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Method. 2014; 14:25.

Bias and Reporting of IPD meta-analyses

Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. BMJ 2012; 344: d7762.

Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 342:d4002.

Riley RD. Commentary: Like it and lump it? Meta-analysis using individual participant data. Int J Epidemiol 2010; 39(5):1359-1361.

Stewart L, Tierney J, Burdett S. Do Systematic Reviews Based on Individual Patient Data Offer a Means of Circumventing Biases Associated with Trial Publications? In: Rothstein HR, Sutton AJ, Borenstein M, editors. *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*. Chichester, UK.: John Wiley & Sons, Ltd., 2006.

Clarke MJ, Stewart LA. Obtaining data from randomised controlled trials: how much do we need for reliable and informative meta-analyses? In: Chalmers I, Altman DG, editors. *Systematic reviews*. London: BMJ Publishing, 1995:37-47.

Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. Jama. 2015; 313:1657-1665.

Riley RD, Ensor J, Jackson D, Burke DL. Deriving percentage study weights in multi-parameter meta-analysis models: with application to meta-regression, network meta-analysis and one-stage individual participant data models. Stat Meth Med Res, 2017; doi: 10.1177/0962280216688033. [Epub ahead of print].

Estimation of effect modifiers (interactions)

Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003; 326: 219.

Berlin JA, et al. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med 2002; 21(3):371-387.

Lambert PC, et al. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. J Clin Epidemiol 2002; 55 (1):86-94.

Hua H, Burke DL, Crowther MJ, Ensor J, Tudur-Smith C, Riley RD. 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. Stat Med, 2017; 36(5):772-789.

Simmonds MC, Higgins JP. Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. Stat Med 2007; 26: 2982-2999.

Fisher, DJ, et al. 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. J Clin Epidemiol 2011; 64(9): 949-967.

Schmid CH, Stark PC, Berlin JA, Landais P, Lau J. Meta-regression detected associations between heterogeneous treatment effects and study-level, but not patient-level, factors. J Clin Epidemiol 2004; 57:683-697.

Huang Y, et al. Comparing the overall result and interaction in aggregate data meta-analysis and individual patient data meta-analysis. Sys Rev Meta-Analysis 2016; 95 (14):1-7.

Multivariate meta-analysis using IPD

Jackson D, Riley RD, White IR. Multivariate meta-analysis: potential and promise. Stat Med 2011; 30: 2481-2498.

Becker BJ. Multivariate Meta-analysis. In: Tinsley HEA, Brown S, editors. Handbook of Applied Multivariate Statistics and Mathematical Modelling San Diego: Academic Press; 2000. p. 499-525.

Berkey CS, et al. Meta-analysis of multiple outcomes by regression with random effects. Stat Med 1998; 17(22):2537-50.

Raudenbush SW, et al. Modelling multivariate effect sizes. Psychological Bulletin 1988; 103 (1): 111-120.

Riley RD, et al. An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes. Statistics in Medicine 2007; 26:78-97.

Riley RD, et al. Multivariate meta-analysis using individual participant data. Res Synth Method. 2015; 6 157-74.

Riley RD, et al. Multivariate meta-analysis: the effect of ignoring within-study correlation. JRSS-A 2009; 172: 789-811.

Van Houwelingen HC, et al. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002; 21(4):589-624.

White IR. Multivariate random-effects meta-analysis. The Stata Journal 2009; 9(1):40-56.

Jackson D et al. A matrix-based method of moments for fitting the multivariate random effects model for meta-analysis and meta-regression. Biometric Journal 2013; 55: 231-245.

Jackson D et al. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. Stat Med 2010; 29: 1282-1297.

Chen H, Manning AK, Dupuis J. A method of moments estimator for random effect multivariate meta-analysis. Biometrics 2012; 68(4):1278-84.

Ma Y, Mazumdar M. Multivariate meta-analysis: a robust approach based on the theory of U-statistic. Stat Med 2011; 30: 2911-2929.

Nam IS, et al. Multivariate meta-analysis. Stat Med 2003; 22: 2309-2333.

Wei Y, Higgins JP. Bayesian multivariate meta-analysis with multiple outcomes. Stat Med 2013; 32: 2911-2934.

Bujkiewicz S, Thompson JR, Sutton AJ, et al. Multivariate meta-analysis of mixed outcomes: a Bayesian approach. Stat Med 2013. 32(22):3926-43.

Jackson D, Riley RD. A refined method for multivariate meta-analysis and meta-regression. Statistics in Medicine 2014.33(4):541-54.

Riley RD, et al. Bivariate random-effects meta-analysis and the estimation of between-study correlation. BMC Med Res Methodology 2007; **7**:3.

Jackson D, White IR, Price M, Copas J, Riley RD. Borrowing of strength and study weights in multivariate and network meta-analysis. Stat Meth Med Res 2015; pii: 0962280215611702. [Epub ahead of print].

Debray TPA, et al. An overview of methods for network meta-analysis using individual participant data: when do benefits arise? Stat Methods Med Res. 2016; pii: 0962280216660741. [Epub ahead of print].

IPD meta-analysis for prognosis and prediction

Abo-Zaid G et al. IPD meta-analysis of prognostic factor studies: state of the art? BMC Med Res 2012; 12:56.

Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. J Natl Cancer Inst 2005; 97(14):1043-55.

Trivella M, et al. Microvessel density as a prognostic factor in non-small-cell lung carcinoma: a meta-analysis of individual patient data. Lancet Oncology. 2007(6): 488-499.

Maas AI, et al. Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. J Neurotrauma 2007; 24(2):232-238.

Riley RD, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. PLoS Med 2013; 10(2): e1001380.

Sauerbrei W, et al. Evidence-based assessment and application of prognostic markers: the long way from single studies to meta-analysis. Communications in Statistics 2006; 35:1333-1342.

Riley RD, Elia EG, Malin G, Hemming K, Price MP. Multivariate meta-analysis of prognostic factor studies with multiple cut-points and/or methods of measurement. Statistics in Medicine 2015; 34:2481-2496.

Debray TP, Moons KG, Ahmed I, Koffijberg H, Riley RD: A framework for developing, implementing, and evaluating clinical prediction models in an individual participant data meta-analysis. Stat Med 2013, 32(18):3158-80.

Royston P, Parmar MKB, Sylvester R: Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. Stat Med 2004, 23:907-926.

Steyerberg EW: Clinical prediction models: a practical approach to development, validation, and updating. New York: Springer; 2009.

Royston P, Moons KGM, Altman DG, Vergouwe Y: Prognosis and prognostic research: developing a prognostic model. BMJ 2009, 338:b604 (1373-1377).

Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S, Riley RD, Hemingway H, Altman DG: Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS Med 2013, 10(2):e1001381.

Ahmed I, Debray TP, Moons KG, Riley RD. Developing and validating risk prediction models in an individual participant data meta-analysis. BMC Med Res Methodol. 2014;14:3.

Altman DG, Vergouwe Y, Royston P, Moons KGM: Prognosis and prognostic research: validating a prognostic model. BMJ 2009, 338:b605.

Harrell FE: Regression modeling strategies, with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.

Snell KIE, et al. Multivariate meta-analysis of individual participant data helped externally validate the performance and implementation of a prediction model. Journal of Clinical Epidemiology 2016; 69: 40-50.

Debray TPA, Riley RD, Rovers MM, Reitsma JB, Moons KGM, Cochrane IPD Meta-analysis Methods Group. Individual participant data (IPD) meta-analyses of diagnostic and prognostic modelling studies: guidance on their use. PLOS Med 2015; 12(10):e1001886.

Pennells L, et al. Assessing risk prediction models using individual participant data from multiple studies. Am J Epidemiol 2014; 179(5):621-632.

Missing data in IPD meta-analysis

Jolani S, Debray TPA, Koffijberg H, va Buuren S, Moons KGM. Multiple imputation of systematically missing predictors in an individual participant data meta-analysis: a generalised approach using MICE. Stat Med 2015; 34(11):1841-1863.

Resche-Rigon M, White IR, Bartlett JW, Peters SA, Thompson SG. Multiple imputation for handling systematically missing confounders in meta-analysis of individual participant data. Stat Med 2013; 32(28):4890-4905.

Burgess S, White IR, Resche-Rigon M, Wood AM. Combining multiple imputation and meta-analysis with individual participant data. Stat Med 2013; 32:4499-4514.

Koopman L, et al. Comparison of methods of handling missing data in individual patient data meta-analyses: an empirical example on antibiotics in children with acute otitis media. Am J Epidemiol 2008; 167(5):540-545.

Quartagno M, Carpenter JR. Multiple imputation for IPD meta-analysis: allowing for heterogeneity and studies with missing covariate. Stat Med 2016; 35(17):2938-54.

NOTES