Meta-analysis of continuous outcomes: using pseudo IPD created from aggregate data to adjust for baseline imbalance and assess treatment-by-baseline modification

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Background

- We consider studies of aggregate continuous outcome data measured at baseline (pre-treatment) and follow-up (post-treatment)
- Aim: estimate the **summary (average) effect** by fixed (common)-effect or random effects analyses
- Meta-analysis can be performed using
  1. aggregate data (AD), e.g., mean difference of treatment effect and its standard error
  2. individual participant/patient data (IPD)
     Data confidentiality - GDRP

Illustrating example

- Meta-analysis of IPD of Wang *et al., 2005.* and re-analysed by Riley *et. al., 2013*
- Comparing active antihypertensive drugs against placebo/no treatment on systolic blood pressure (SBP)

Measurements of SBP (mmHg) at baseline and follow-up of 10 studies (28 851 participants)

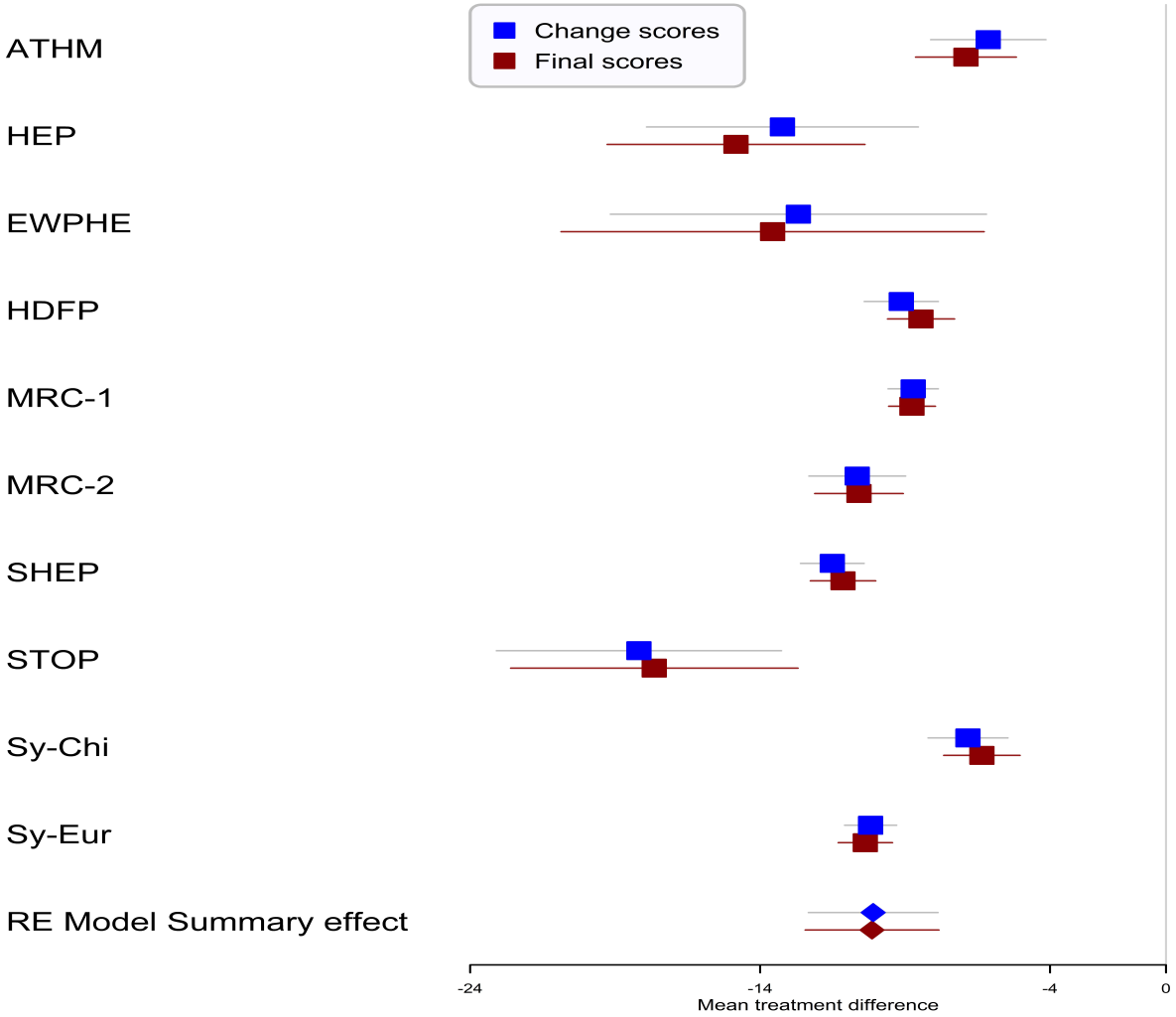
1. *Baseline balanced dataset*
2. *Baseline imbalanced dataset*

Systolic blood pressure levels pre and post-treatment

	Number of subjects		**SBP baseline (mmHg)**		**SBP final (mmHg)**		**Correlation (SBP_B, SBP_F)**	
			Treatment	Control	Treatment	Control		
ID	Treatment	Control	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Treatment	Control
1	750	780	152.28 (15.25)	153.05 (15.73)	132.85 (16.72)	139.75 (17.85)	0.265	0.284
2	150	199	189.94 (16.15)	191.55 (17.64)	165.06 (20.03)	179.89 (22.15)	0.335	0.331
⋮				⋮				
10	2398	2297	173.75 (9.86)	173.94 (10.07)	154.87 (16.31)	165.24 (16.33)	0.319	0.431

How to synthesize these data?

Systolic blood pressure levels - standard meta-analysis results on final and change scores



Issues with standard meta-analysis of AD

- **Follow-up scores analysis**: ignores baseline values
  What happens in case of baseline imbalance?

- **Change scores [Follow-up - baseline] analysis**: not possible to study treatment-by-baseline interaction
  (patients with higher baseline values will benefit more)

Research problem

How can we obtain ***unbiased and precise treatment effect estimates*** *possibly investigating an interaction between the baseline value and the effect?*

Notation for IPD and AD meta-analysis

- i: study (1,...,m)
- j: patient (1,...,n)
- k: treatment group $(1, 2)$
- Y_{Bijk}: Outcome at baseline (pre-treatment)
- Y_{Fijk}: Outcome at follow-up (post-treatment)
- X_{ij}: Treatment group; X_{ij}=1 for treated participants, 0 for control

AD: per study and treatment arm, mean baseline $\bar{Y}_{Bijk}$ and mean post-treatment $\bar{Y}_{Fijk}$, their standard deviations s_{Bijk}, s_{Fijk} and $r_{ijk} = cor(Y_{Bijk}, Y_{Fijk})$.

What if IPD are available?
ANCOVA: stratified study model

$$Y_{Fij} = \beta_{0i} + (\beta_1 + b_{1i})X_{ij} + \beta_{2i}(Y_{Bij} - \bar{Y}_{Bi}) + \epsilon_{ij}$$

- β_{0i}: mean outcome in the control in study i
- β_1: summary (average) treatment effect
- β_{2i}: study-specific adjustment term for baseline
- b_{1i}: study-specific treatment difference

$$b_{1i} \sim N(0, \tau^2)$$
$$\epsilon_{ij} \sim N(0, \sigma^2_{ik})$$

What if IPD are available?
ANCOVA: random study model

$$Y_{Fij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})X_{ij} + (\beta_2 + b_{2i})(Y_{Bij} - \bar{Y}_{Bi}) + \epsilon_{ij},$$

$$where \begin{bmatrix} b_{0i} \\ b_{1i} \\ b_{2i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau_0^2 & \tau_{01} & \tau_{02} \\ \tau_{01} & \tau_1^2 & \tau_{12} \\ \tau_{02} & \tau_{12} & \tau_2^2 \end{bmatrix} \right)$$

- b_{0i}: random intercept per study
- b_{2i}: random baseline adjustment term

What if IPD are available? ANCOVA including treatment-by-baseline interaction: stratified study model

$$Y_{Fij} = \beta_{0i} + (\beta_1 + b_{1i})X_{ij} + \beta_{2i}(Y_{Bij} - \bar{Y}_{Bi}) + (\beta_3 + b_{3i})[(Y_{Bij} - \bar{Y}_{Bi})X_{ij}] + \epsilon_{ij}$$

- β_3: mean increase in treatment effect for one-unit increase in baseline values
- b_{3i}: random term allowing for between-studies heterogeneity in the treatment-baseline interaction

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ANCOVA including treatment-by-baseline interaction: random study model

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Different options of within-study residual variance models

1. *All variances different (study- and arm-specific):* $\boldsymbol{\epsilon_{ij}} \sim N(0, \sigma^2_{ik})$
2. *Study-specific variances:* $\sigma^2_{ik} = \sigma^2_{i.}$
3. *One variance for control and one variance for treated group* $\sigma^2_{ij} = \sigma^2_{.k}$
4. *One overall variance* $\sigma^2_{ij} = \sigma^2$

What to do if we *only* have aggregate data?

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A new idea: generate pseudo IPD using the aggregate data

General principle of pseudo IPD

- Papadimitropoulou *et al., 2018* [1] proposed a method to create pseudo IPD for a single continuous outcome
- We extended this method for outcomes reported at baseline and at follow-up:
  Aggregate/summary observed mean and SD of baseline and follow-up measurements, and the correlation of the baseline and follow-up value in each group
- These are the appropriate **sufficient statistics** for ANCOVA 

Any dataset with exactly these sample means, SDs, and correlations will yield ***identical results to the true IPD***

Construction of pseudo IPD - Algorithm

For each group in each study:

1. Generate two samples, from a certain distribution, e.g., a standard normal distribution.

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3. Scale the observations from Step [1] such that theirs means are exactly $\bar{Y}_B$, $\bar{Y}_F$ and their standard deviations, respectively.
4. Apply linear mixed models whose **likelihood** depend on the data only through the **sufficient statistics**.

Meta-analysis results of *summary treatment effect* using the pseudo IPD approach, compared to two-stage true IPD and standard AD

			pseudo IPD meta-analysis	**true IPD meta-analysis**	**AD meta-analysis**
			ANCOVA	ANCOVA model results as described in Riley *et al.*, *2013* [2]	Change scores
Dataset	Model	Results	$\sigma_{i.}^2$	$\sigma_{i.}^2$	
Hypertension (balanced)	Stratified study (Eq. 1)	Estimate	-10.166	-10.167	-10.096
		SE	0.931	0.934	0.986
		95%CI	(-12.271, -8.060)	(-12.281, -8.053)	(-12.327, -7.865)
	Random study (Eq. 2)	Estimate	-10.460		
		SE	0.986		
		95%CI	(-12.393, -8.526)		
Hypertension (imbalanced)	Stratified study (Eq. 1)	Estimate	-14.555	-14.554	-10.096
		SE	1.659	1.658	0.986
		95%CI	(-18.308, -10.802)	(-18.304, -10.804)	(-12.327, -7.865)
	Random study (Eq. 2)	Estimate	-14.435		
		SE	1.651		
		95%CI	(-18.132, -10.737)		

Meta-analysis results of *interaction* of baseline with treatment using the pseudo IPD approach, compared to two-stage true IPD and standard AD

			pseudo IPD meta-analysis	**true IPD meta-analysis**	**AD meta-analysis**
			ANCOVA: using final values adjusting for baseline including the interaction between baseline and treatment	ANCOVA model results as described in Riley *et al., 2013* [2]	Meta-regression
Dataset	Model	Results	$\sigma^2_{i.}$	$\sigma^2_{i.}$	Using $\bar{Y}_{BTi}$
Hypertension (balanced)	Stratified study (Eq. 3)	Estimate	-0.087	-0.090	-0.159
		SE	0.038	0.033	0.050
		95% CI	(-0.162, -0.012)	(-0.155, -0.025)	(-0.275, -0.044)
	Random study (Eq. 4)	Estimate	-0.091		
		SE	0.040		
		95% CI	(-0.190, 0.007)		
Hypertension (imbalanced)	Stratified study (Eq. 3)	Estimate	-0.092	-0.090	0.195
		SE	0.039	0.033	0.113
		95% CI	(-0.170, -0.015)	(-0.155, -0.025)	(-0.066, 0.455)
	Random study (Eq. 4)	Pooled effect	-0.091		
		SE	0.040		
		95% CI	(-0.190, 0.007)		

Conclusions

- In the **balanced case**, pseudo IPD ANCOVA, two-stage ANCOVA, AD change scores produce very **similar** treatment effect estimates
- Extended ANCOVA with interaction showed treatment effect slightly larger in patients with higher baseline SPB values
- In **imbalanced case**, AD change scores produce **biased results** compared to pseudo IPD ANCOVA
- Summary interaction estimate from meta-regression is in the **opposite** direction of pseudo and true IPD ANCOVA

General conclusions

- Framework to generate pseudo baseline and follow-up IPD from AD for meta-analysis of continuous outcomes
- Subsequently analyze pseudo IPD using ANCOVA approach - more **efficient** estimates than follow-up and change score approaches

Important general aspects

1. *Immediate solution to the difficulty of gaining access to original IPD*
2. *Robust estimation of the treatment-by-baseline interaction where AD methods suffer from ecological bias and low power issues*

Thank you for your attention :)

Questions?


Papadimitropoulou, K., Stijnen, T., Dekkers, O. M., and le Cessie, S.
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