technische universität dortmund
Mathematical Statistics and Applications in Industry

The consequences of neglected confounding and interactions in mixed-effects meta-regression: An illustrative example

Recent Advances in Meta-Analysis: Methods and Software

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Introduction

- Interactions reflecting effect moderators are often neglected in meta-regression
- often due to the limited number of available studies
- but still: we may end up with biased estimates and draw wrong conclusions when important moderators and interactions are not included

$\rightarrow$ Today we analyse an example which illustrates this problem

Content of today

- Method: the mixed-effects meta-regression model
- Introduction to an example of a meta-regression on acute heart failure
- Analysis of the example with different versions of the model
- Brief simulation on subsamples of the example
- Suggestions and outlook

The mixed effects meta regression model

$$y_i = \beta_0 + x_{i1}\beta_1 + ... + x_{ip}\beta_p + u_i + e_i, i = 1, ..., k$$

with:

- y_i, function of the effect measure of study $i = 1, ..., k$
- x_{ij}, moderator j in study i, for $j = 1, ..., p$
- β_j, coefficient of moderator j,
- $u_i \sim \mathcal{N}(0, \tau^2)$, between study heterogeneity
- $e_i \sim \mathcal{N}(0, \sigma_i^2)$, sampling error within study i

Estimation of the model parameters

- $\hat{\boldsymbol{\beta}} =$ weighted least squares estimator (WLS) for $\boldsymbol{\beta}$ with a consistent estimate $\hat{\tau}^2$ for τ^2 (we use REML).
- t-type confidence intervals for β_j:

$$\left[\hat{\beta}_j \mp t_{(k-m-1),(1-\frac{\alpha}{2})}\sqrt{\hat{\boldsymbol{\Sigma}}_{jj}}\right]$$

  with $t_{(k-m-1),(1-\frac{\alpha}{2})}$ being the $(1-\frac{\alpha}{2})$-quantile of the $t_{(k-m-1)}$-distribution and $\hat{\boldsymbol{\Sigma}}_{jj}$ the estimated variance of β_j.
- we estimate $\hat{\boldsymbol{\Sigma}}_{jj}$ with the Knapp-Hartung (2003) method

A meta regression on Acute Heart Failure by Kimmoun et. al (2021)

- research synthesis included 285 studies on acute heart failure (204 report 1-year mortality)
- studies published between 1998 and 2017
- outcome measures were 30-day and 1-year readmission rates and mortality
- study characteristics like median year of recruitment, average age of the patients and therapy effects were reported
- major finding: statistically significant decline of 1-year mortality over calendar time
- but: average age of patients decreased over calendar time as well (1.56 years every 10 years)

$\rightarrow$ is the observed time trend confounded by the average age or is there an interaction between those variables?

Meta-regression analysis with a univariable model

$$y_i = \beta_0 + \beta_{year} x_{i,year} + u_i + e_i \quad (y_i \text{ logit transformed 1-year mortality})$$

Figure: Model from the analysis by Kimmoun et al. (2021): Meta-regression model of median year of recruitment for the one-year mortality.

$$\hat{\beta}_{year} = -0.015 \text{ (95\%-CI: [-0.0263, -0.0042])}$$

Meta-regression analysis with a two variable model

$$y_i = \beta_0 + \beta_{year} x_{i,year} + \beta_{age} x_{i,age} + u_i + e_i$$

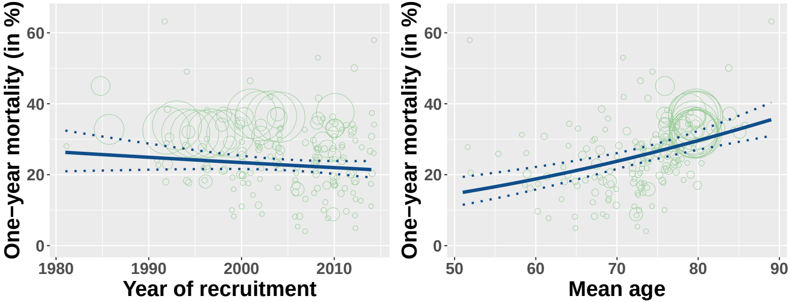

Figure: Trends of year of recruitment (left) and average age (right) on the one-year mortality in a mixed-effects meta-regression model with these two moderators.

$\hat{\beta}_{year} = -0.0081$, 95%-CI: $[-0.0200, 0.0038]$; $\hat{\beta}_{age} = 0.0299$, 95%-CI: $[0.0178, 0.0420]$

Meta-regression analysis with interaction

$$y_i = \beta_0 + \beta_{year} x_{i,year} + \beta_{age} x_{i,age} + \beta_{int} x_{i,year} x_{i,age} + u_i + e_i \quad \text{(moderators centered)}$$

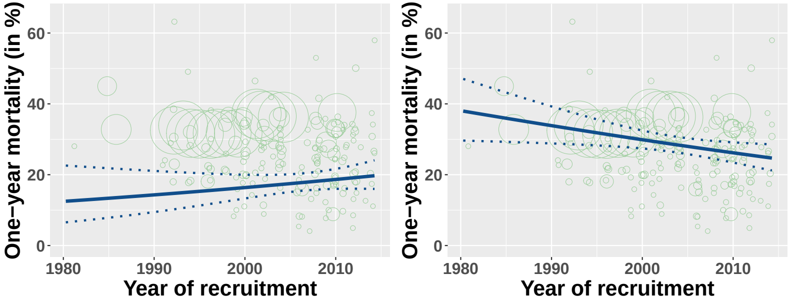

Figure: Trends of year of recruitment for an average age of 60.5 (left) and 79.5 (right) years in a mixed-effects meta-regression model with two moderators and their interaction.

$\hat{\beta}_{year} = -0.0066$, 95%-CI: $[-0.0185, 0.0052]$; $\hat{\beta}_{age} = 0.0333$, 95%-CI: $[0.0208, 0.0457]$;
$\hat{\beta}_{int} = -0.0018$, 95%-CI: $[-0.0035, -0.0001]$

Comparison of the results

Table: Parameter estimates and corresponding 95%-CIs for all three models.

model	$\hat{\beta}_{year}$	$\hat{\beta}_{age}$	$\hat{\beta}_{int}$
univariable	-0.0150, [-0.0263, -0.0042]	-	-
two variables	-0.0081, [-0.0200, 0.0038]	0.0299, [0.0178, 0.0420]	-
interaction	-0.0066, [-0.0185, 0.0052]	0.0333, [0.0208, 0.0457]	-0.0018, [-0.0035, -0.0001]

Analysis on subsamples

- a lot more (204) studies were available than common in meta-analysis
- would we draw the same conclusions if less studies were available?

$\rightarrow$ we draw subsamples of size 30 and fit the models for them:

Table: Rejection rates (at confidence level 0.95) and median interval lengths for 1000 subsamples of size 30 for each model, respectively.

	moderator/model	univariable	two variables	interaction
Rejection rate	β_{year}	0.124	0.036	0.052
	β_{age}	-	0.524	0.586
	β_{int}	-	-	0.125
Interval length	β_{year}	0.063	0.061	0.063
	β_{age}	-	0.063	0.068
	β_{int}	-	-	0.010

Suggestions

- Kimmoun et al. (2021) showed significant decline in 1-year mortality over calendar time
  - fitting a model with both moderators revealed that the time trend was confounded by the average age
  - including an interaction to the model showed that there is a significant time trend which depends on the average age

→ Which model should we believe?

- has to be considered by experts if confounding or interactions are plausible
- we suggest to always include interaction terms, when they are plausible
- generally considering possible confounding variables and interactions may generally improve insights into the underlying data, even when few studies are available

Limitations

- The analysis is based on one study. Extensive systematic reviews or simulations are necessary to generalize the suggestions.
- Much more studies were included than common in meta analysis.
- Knapp-Hartung estimator was originally proposed for models with a single covariate. What about other variance estimators for models with interactions?
  $\rightarrow$ more on that in the next talk by Markus Pauly

Literature

Kimmoun, A., Takagi, K., Gall, E., Ishihara, S., Hammoum, P., El Bèze, N., Bourgeois, A., Chassard, G., Pegorer-Sfes, H., Gayat, E., Solal, A. C., Hollinger, A., Merkling, T., Mebazaa, A., & METAHF Team (2021). Temporal trends in mortality and readmission after acute heart failure: a systematic review and meta-regression in the past four decades. *European journal of heart failure, 23(3)*, 420–431.

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