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Avoid exclusion of studies in synthesis of dose–response data using a novel one-stage approach

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Dose–response meta-analysis

Summarize results from multiple studies on the relation between a quantitive exposure (e.g. diet or physical activity) and the occurrence of a health outcome (e.g. cancer or mortality)

Research questions

- What is the shape of the association between the quantitative exposure and the outcome?
- What are the exposure values associated with the best or worst outcome?
- How heterogenous are the individual dose–response curves?

Aggregated data

id	exposure category	dose	cases	n	OR (95% CI)
1	[-0.00336,3.5)	2.43	42	2260	1 (ref)
1	[3.5,7.01]	5.21	102	6136	0.89 (0.62, 1.28)
2	[-2.39,2.73)	1.70	39	651	1 (ref)
2	[2.73,7.83)	5.14	164	3962	0.68 (0.47, 0.97)
2	[7.83,12.9]	8.78	26	387	1.13 (0.68, 1.89)
3	[-2.14,1.64)	0.78	11	224	1 (ref)
3	[1.64,5.41)	3.89	99	2639	0.75 (0.4, 1.43)

Common practice in statistical analysis

Two-stage analysis:

1. Define and estimate a common dose-response model in each $i-$th study: $\mathbf{y}_i = \mathbf{X}\boldsymbol{\beta_i} + \boldsymbol{\varepsilon_i}$
2. Combine study-specific $\boldsymbol{\beta_i}$ using meta-analysis.

To investigate non-linear functions, studies with less than 3 exposure categories are excluded.

Aims

- Develop a one-stage method to avoid exlcusion of studies.
- Describe the new methodology and compare with a two-stage analysis.
- Implement the one-stage approach in most common statistical software.

One stage approach

A one-stage model for meta-analysis of aggregated dose-response data can be written in the general form of a linear mixed model

$$\mathbf{y}_i = \mathbf{X}_i\beta + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i \quad (1)$$

$\mathbf{y}_i$ vector of non-referent log RRs in the i-th study $\mathbf{X}_i$ contains the assigned doses (and/or transformations)

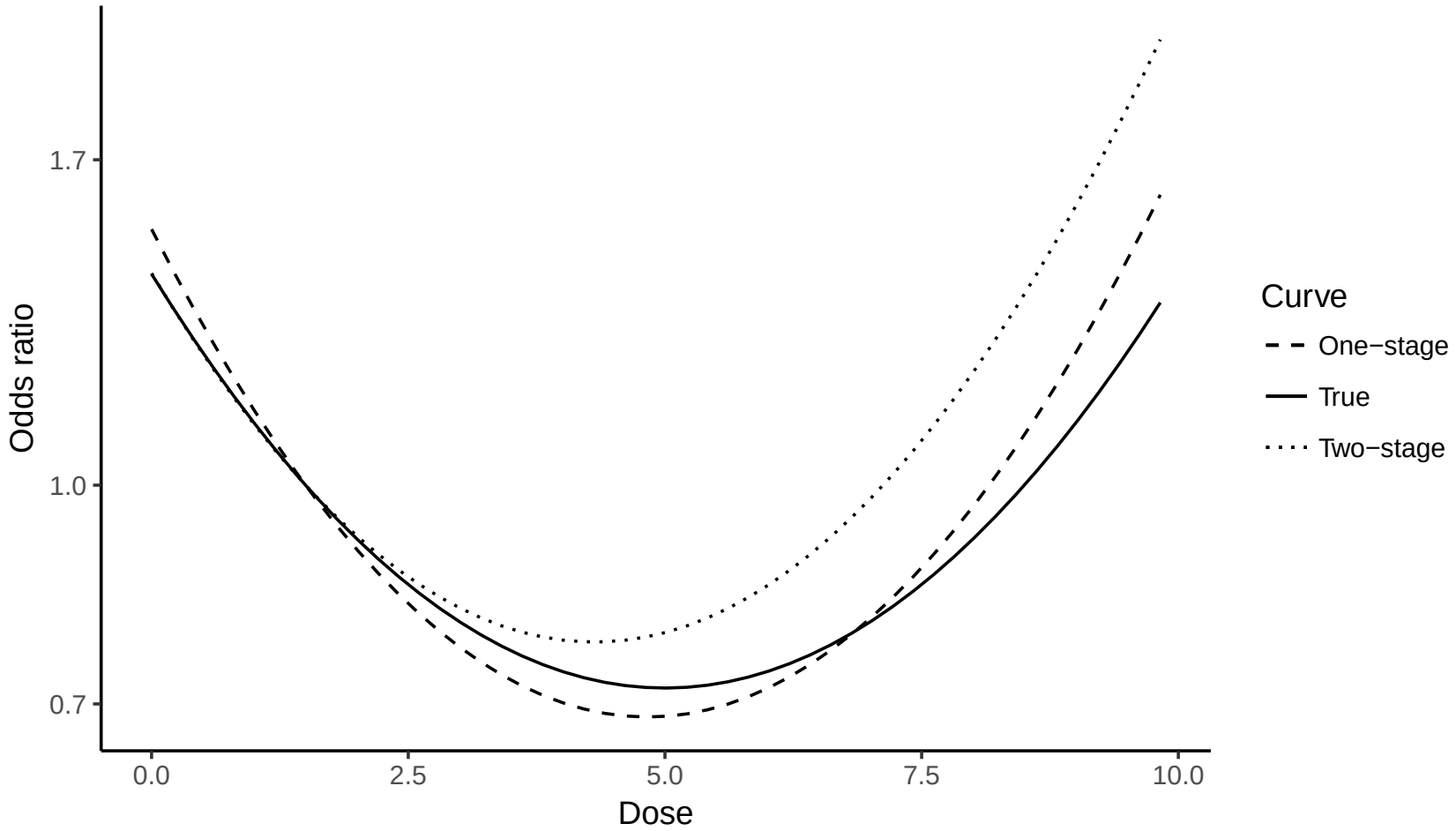
- Model without intercept
- $\mathrm{Cov}(\boldsymbol{\varepsilon}_i) = \boldsymbol{\Sigma}_i$ can be approximated

Main features

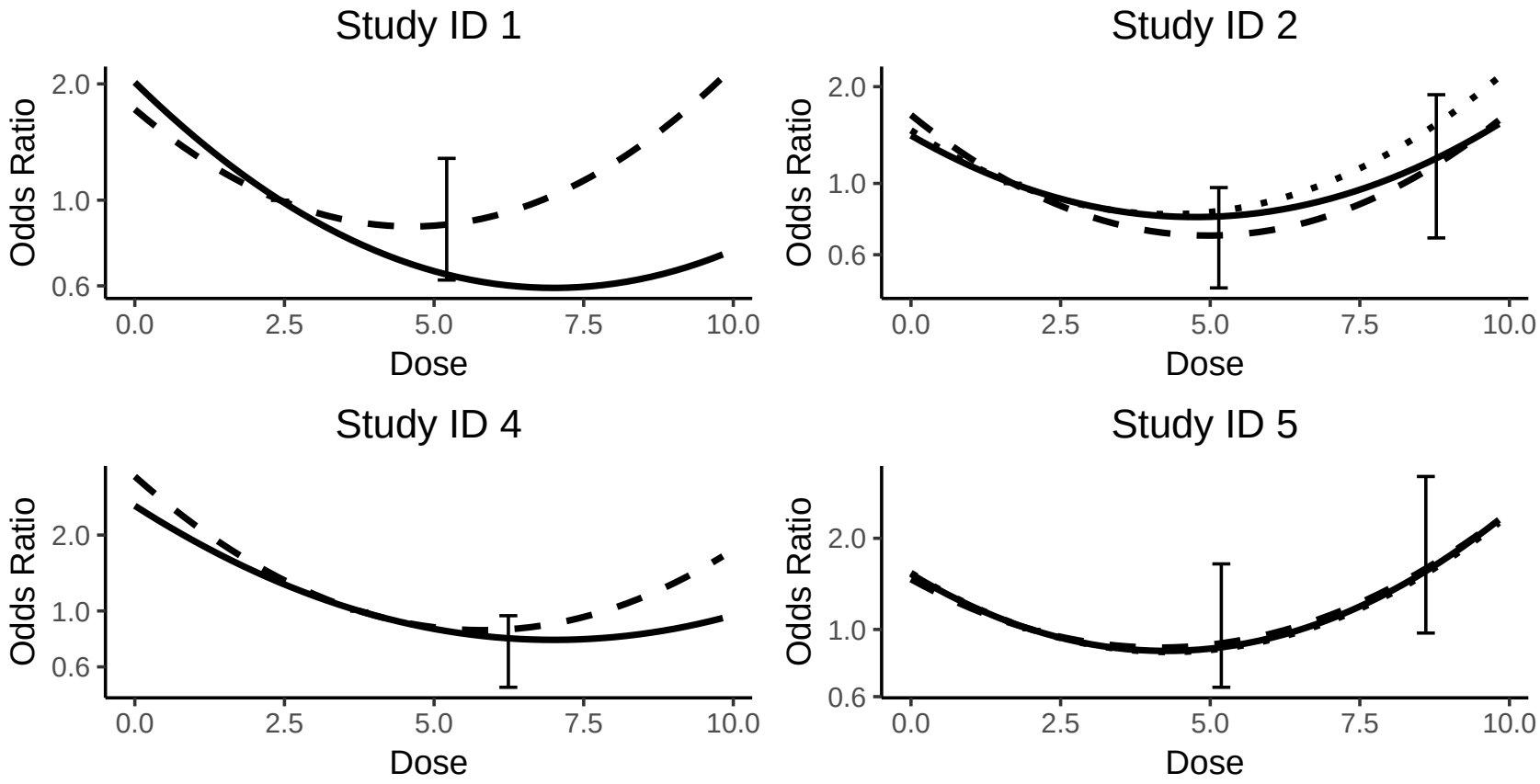
The mixed-models theory offers a good framework for several specific aspects

- inferential procedures (test if is there any dose-response association)
- predictions (predict the mean and individual curves)
- model comparison (which model best fits the data?)
- goodness-of-fit assessment (is there any evidence of lack of fit?)

Comparison


Odds ratio
1.7
1.0
0.7
0.0
2.5
5.0
7.5
10.0
Dose
Curve
One−stage
True
Two−stage

BLUP


Study ID 1
Study ID 2
Study ID 4
Study ID 5
Odds Ratio
2.0
1.0
0.6
0.0
2.5
5.0
7.5
10.0
Dose
Curve One−stage True Two−stage

Conclusions

- We introduced a one-stage approach for dose–response meta-analysis.
- It avoides exclusion of valuable data.
- It facilitates many aspects of a dose–response mete-analysis
- We have implented in the `dosresmeta` **R** package and in the `drmeta` Stata command.

References

- Greenland S, Longnecker MP (1992). Methods for trend estimation from summarized dose– response data, with applications to meta-analysis. American Journal of Epidemiology, 135(11): 1301–1309.
- Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D (2012). Meta–analysis for linear and nonlinear dose–response relations: examples, an evaluation of approximations, and software. American journal of epidemiology, 175(1):66–73.
- Crippa A, Orsini N (2016). Multivariate dose–response meta-analysis: the dosresmeta R package. Journal of Statistical Software, Code Snippets, 72(1), 1-15. doi:10.18637/jss.v072.c01
- Discacciati A, Crippa A, Orsini N (2015). Goodness of fit tools for dose–response meta-analysis of binary outcomes. Research synthesis methods.