Model selection in dose-response meta-analysis of summarized data

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Outline

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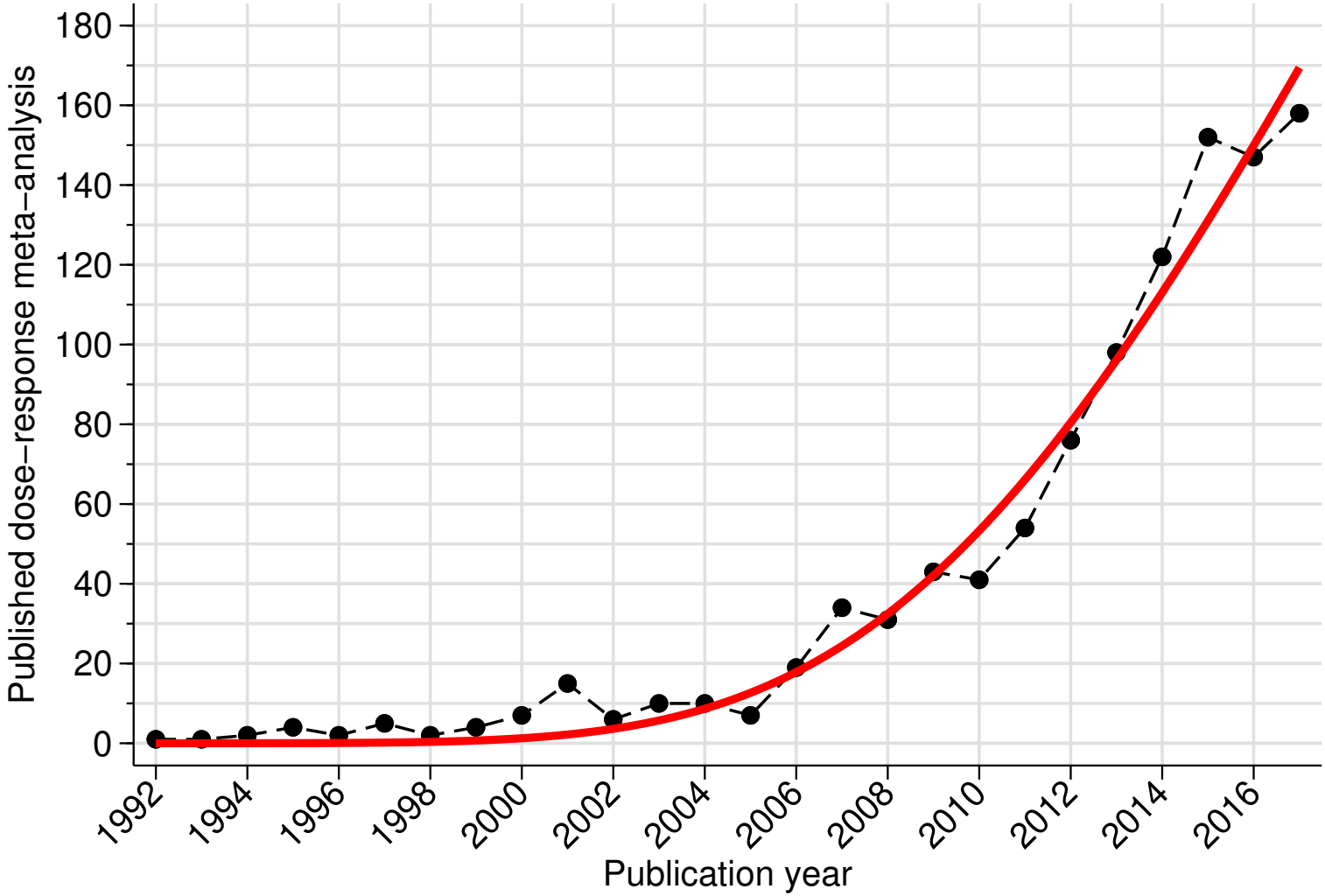
- Aim
- Simulation study
- Results
- Summary

Background

- A dose-response analysis describes the changes of a response across levels of a quantitative factor. The quantitative factor could be an administered drug or an exposure.

- A meta-analysis of dose-response (exposure-disease) relations aims at identifying the trend underlying multiple studies trying to answer the same research question.

Increasing number of dose-response meta-analyses



Data source: Web of Science

Current applications

- Potassium intake in relation to blood pressure levels in adult population
- Antipsychotic drugs in relation to symptoms in acute schizophrenia patients

Example of summarized data from 5 studies

id	md	semd	dose	n	sd
1	0.0	0.0	2.7	500	30.3
1	0.9	1.9	7.6	500	29.7
2	0.0	0.0	2.1	334	27.9
2	-2.9	2.3	4.4	333	29.3
2	4.9	2.3	8.8	333	30.0
3	0.0	0.0	2.6	500	30.5
3	4.1	1.9	7.5	500	30.9
4	0.0	0.0	2.7	500	30.1
4	1.5	2.0	7.6	500	31.8
5	0.0	0.0	2.0	334	31.9
5	2.6	2.4	4.3	333	30.5
5	2.9	2.4	8.4	333	29.4

Linear Mixed Model

A one-stage approach for meta-analysis of summarized dose-response data has been proposed in the general framework of linear mixed model (*Stat Meth Med Res*, 2019).

$$\hat{\boldsymbol{\gamma}}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i$$

$\hat{\boldsymbol{\gamma}}_i$ is the vector of empirical constrasts (mean differences) estimated in the i-th study

$\boldsymbol{X}_i$ is the design matrix for the fixed-effects $\boldsymbol{\beta}$

It is implemented in the **drmeta** command (Type **ssc install drmeta**).

Random effects and residual error term

$\mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Psi})$

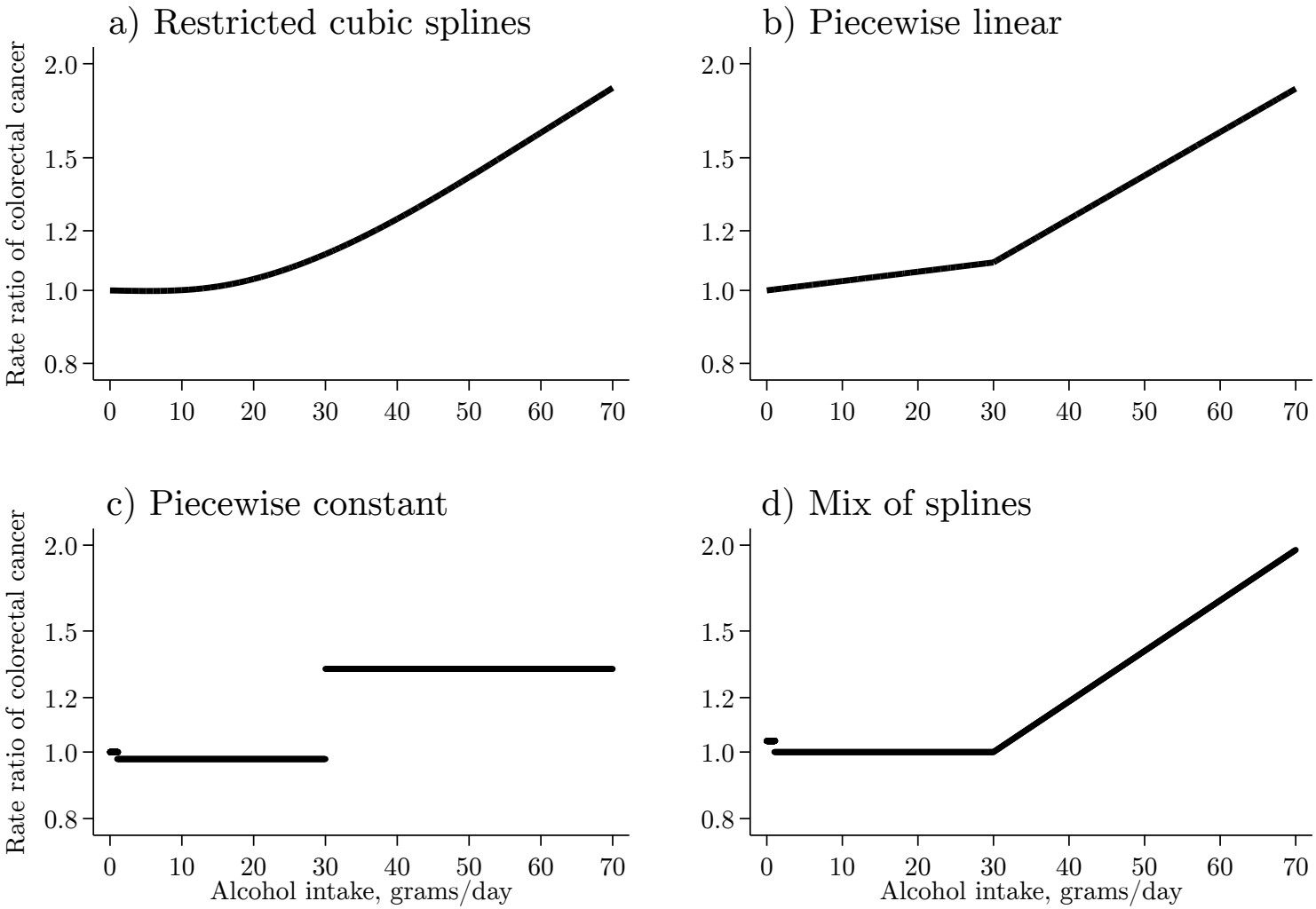
The random-effects $\mathbf{b}_i$ represent study-specific deviations from the population average dose-response coefficients $\boldsymbol{\beta}$.

$\boldsymbol{Z}_i$ is the analogous design matrix for the random-effects.

The residual error term $\boldsymbol{\epsilon}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{S}_i)$, whose variance matrix $\mathbf{S}_i$ is assumed known.

$\mathbf{S}_i$ can be either given or approximated using available summarized data (*BMC Med Res Meth*, 2016).

Splines according to the research question *Am J Epi, 2012*



Aim

- Explore the ability of the Akaike Information Criterion (AIC) to suggest the correct functional relationship using linear mixed models for meta-analysis of summarized dose-response data.

Sketch of the Monte-Carlo simulation

- Generate multiple individual data according to a certain dose-response relationship
- Create a table of summarized data upon categorization of the dose
- Fit a linear mixed-effects model on the summarized data using alternative dose-response functions
- Tag the dose-response functions associated with lowest AIC
- Repeat the steps above a large number of times
- Examine the frequency of correctly identified dose-response relationships

Design matrix

Since the $\hat{\gamma}_i$ is a set of response contrasts relative to the baseline dose x_{i0}, $\boldsymbol{X}_i$ needs to be constructed in a similar way by centering the p transformations of the dose levels to the corresponding values in x_{i0}.

Let consider, for example, a transformation g; the generic j-th row of $\boldsymbol{X}_i$ would be defined as $g(x_{ij}) - g(x_{i0})$.

As a consequence $\boldsymbol{X}_i$ does not contain the intercept term ($\hat{\gamma}_i = 0$ for $x = x_{i0}$).

Random effects and residual error term

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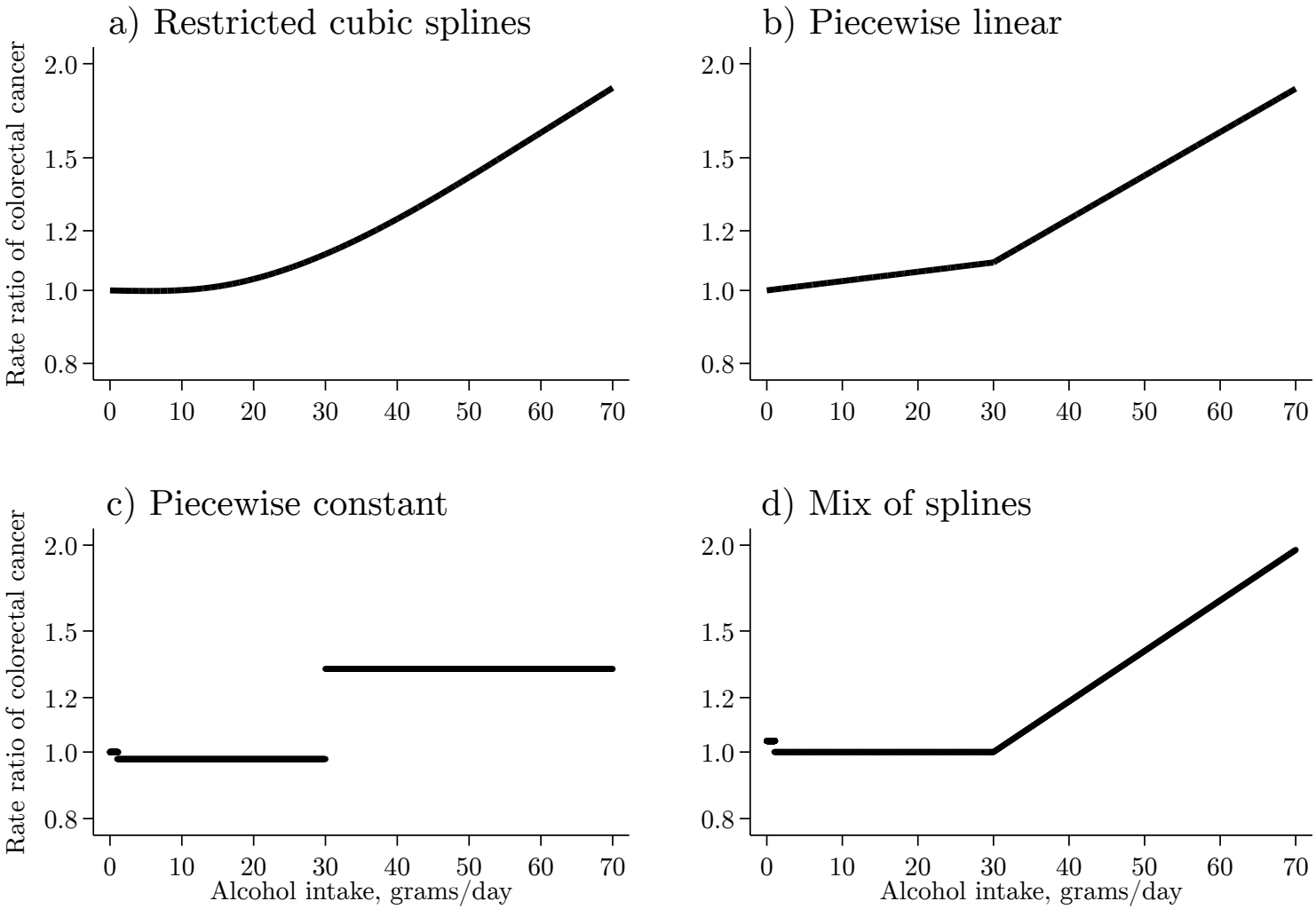
Regression splines (cubic) are very popular (*AJE*, 2012)



The point is

- dose-response meta-analysis are likely to be published in top journals and highly influential
- given the limited number of data points, can you really trust the results of selected models?
- what are the chances of misleading conclusions/artefacts?

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Simulating individual data for a single study

Random values X drawn from a χ^2 distribution with 5 degrees of freedom

Random values Y drawn according the the following functions

Linear function S_l

$$Y = \beta_0 + \beta_1 x + \epsilon$$

Quadratic function S_q

$$Y = \beta_0 + \beta_1 x + \beta_2 x^2 + \epsilon$$

with $\epsilon \sim N(0, 30)$.

Mechanism generating data

Common-effect. Regression coefficients are fixed constant across studies

$$E(Y|x) = 10 + 0.5x$$

$$E(Y|x) = 10 + 0.5x - 0.5x^2$$

Random-effects. Regression coefficients $(\beta_1, \beta_2)^T$ across studies are vectors randomly drawn from a multivariate normal with specified means and var/covariance structures

$$\beta_1 \sim N(0.5, .1)$$

$$\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0.5 \\ -0.5 \end{pmatrix}, \begin{pmatrix} 0.1 & 0.05 \\ 0.05 & 0.1 \end{pmatrix} \right)$$

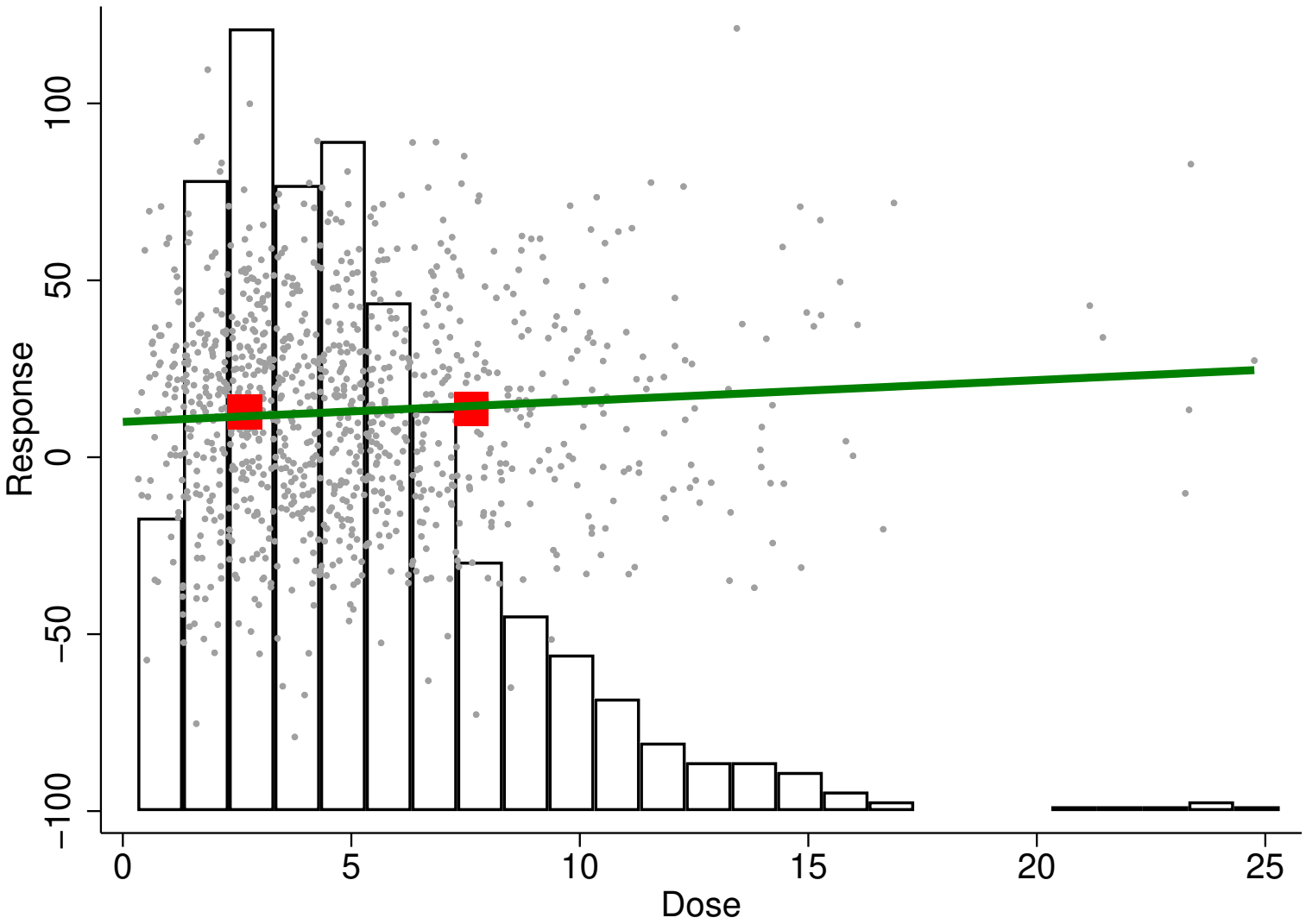
Create a table of summarized data

Quantiles. Dose is categorized into quantiles (2, 3). Mean dose within each quantile is assigned to each dose interval.

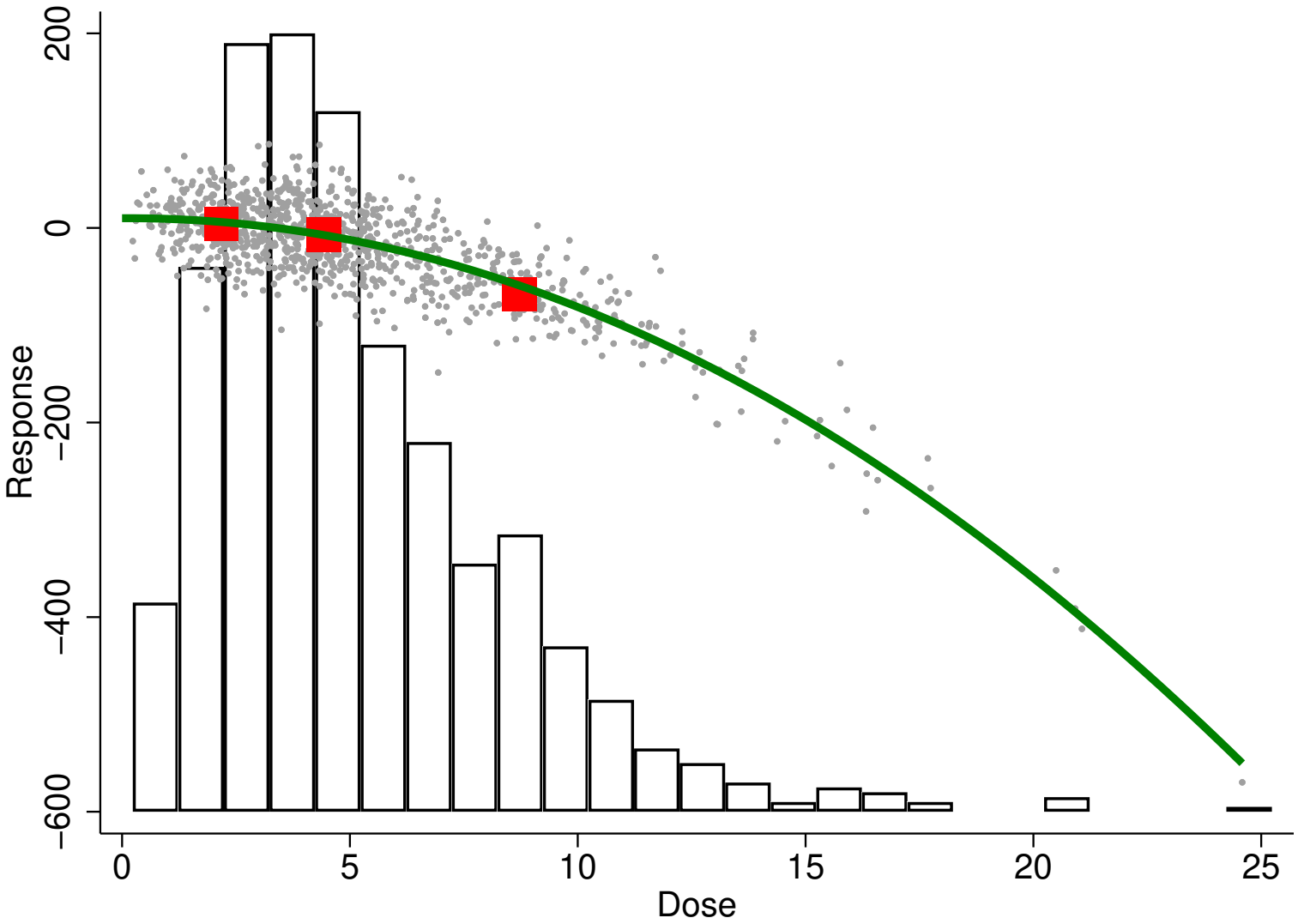
Measure of effect. Differences in mean responses (std errors) comparing each dose interval relative to the baseline dose using a linear regression model.

Additional basic information. Sample size and sample standard deviation of the response for each dose interval.

A single simulated study from $E(Y|x) = 10 + 0.5x$



A single simulated study from $E(Y|x) = 10 + 0.5x - 0.5x^2$



Estimation

We consider estimation methods based on maximum likelihood (ML). The log-likelihood for the linear mixed model is defined as

$$\ell(\boldsymbol{\beta}, \boldsymbol{\xi}) = -\frac{1}{2} n \log(2\pi) - \frac{1}{2} \sum_{i=1}^{k} \log |\boldsymbol{\Sigma}_i(\boldsymbol{\xi})| +$$
$$- \frac{1}{2} \sum_{i=1}^{k} \left[(\hat{\boldsymbol{\gamma}}_i - \mathbf{X}_i \boldsymbol{\beta})^\top \boldsymbol{\Sigma}_i(\boldsymbol{\xi})^{-1} (\hat{\boldsymbol{\gamma}}_i - \mathbf{X}_i \boldsymbol{\beta}) \right]$$

where $n = \sum_{i=1}^{k} n_i$ and $\boldsymbol{\xi}$ is the vector of the variance components in $\boldsymbol{\Psi}$ to be estimated.

Number of studies included in the simulated dose-response meta-analysis is $k = 10$.

Candidate Models

Linear function M_l

$$\hat{\gamma}_{ij} = (\beta_1 + b_{1i})(x_{ij} - x_{i0}) + \epsilon_{ij}$$

Restricted cubic spline function M_s

$$\hat{\gamma}_{ij} = (\beta_1 + b_{1i})[g_1(x_{ij}) - g_1(x_{i0})] + (\beta_2 + b_{2i})[g_2(x_{ij}) - g_2(x_{i0})] + \epsilon_{ij}$$

with three knots (k_1, k_2, k_3) at fixed percentiles (10th, 50th, 90th) of the dose is defined only in terms of $p = 2$ regression coefficients (*AJE*, 2012). The two splines are

$$g_1(x_{ij}) = x_{ij}$$

$$g_2(x_{ij}) = \frac{(x_{ij} - k_1)_+^3 - \frac{k_3 - k_1}{k_3 - k_2}(x_{ij} - k_2)_+^3 + \frac{k_2 - k_1}{k_3 - k_2}(x_{ij} - k_3)_+^3}{(k_3 - k_1)^2}$$

Definition of Akaike Information Criteria

$$\text{AIC} = -2\ell(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\xi}}) + 2(p + q)$$

$\ell(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\xi}})$ maximized log-likelihood using ML method

p number of fixed effects ($M_l = 1$; $M_s = 2$)

q number of variance/covariance components ($M_l = 1$; $M_s = 3$)

Performance measures

Proportion of simulated dose-response meta-analysis for which the minimum AIC corresponds to the true data-generating mechanism.

If data are generated under S_l (linear)

$$P_l = \frac{\sum[min\{AIC_l, AIC_s\} = AIC_l]}{n_{sim}}$$

If data are generated under S_q (quadratic)

$$P_s = \frac{\sum[min\{AIC_l, AIC_s\} = AIC_s]}{n_{sim}}$$

$n_{sim} = 1,000$

AIC_l and AIC_s correspond to the candidate models M_l and M_s, respectively.

Results I: True dose-response shape is linear (S_l)

Table: Proportion (P_l) of correctly identified linear (S_l) dose-response relationships according to different categorizations of the dose and data generating mechanism.

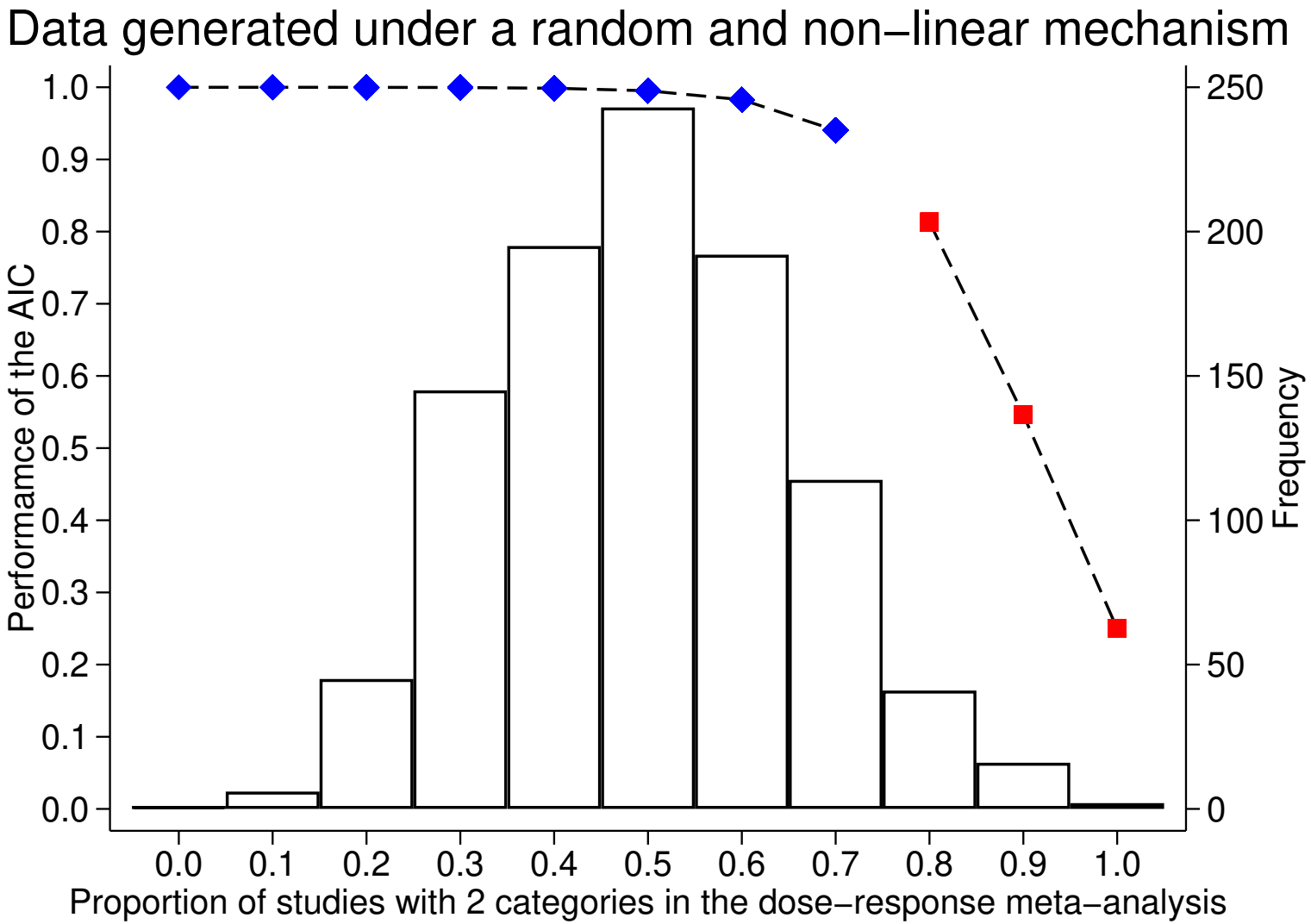
	Common-effect	**Random-effects**
2 Doses	0.99	0.98
Mix 2/3 Doses	0.98	0.97

Results II: True dose-response shape is quadratic (S_q)

Table: Proportion (P_s) of correctly identified non-linear (S_q) dose-response relationships according to different categorizations of the dose and data generating mechanism.

	Common-effect	**Random-effects**
2 Doses	0.03	0.26
Mix 2/3 Doses	0.99	0.97

How many studies with just two doses?



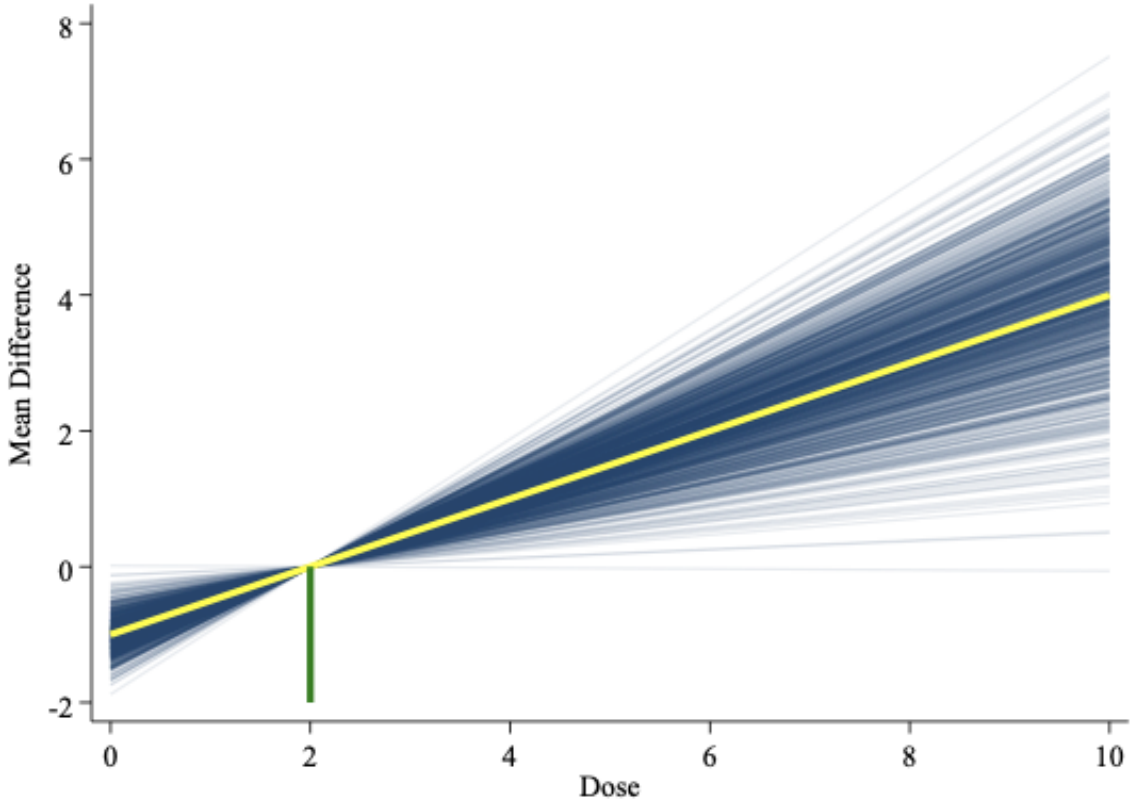
What about increasing from $k = 10$ to $k = 30$ the number of studies included in each dose-response meta-analysis?

Table: Proportion (P_s) of correctly identified non-linear (S_q) dose-response relationships according to different categorizations of the dose and data generating mechanism.

	Common-effect	**Random-effects**
2 Doses	0.12	0.13
Mix 2/3 Doses	1.00	1.00

Are 1,000 predicted dose-response models of type M_I estimating the right shape under S_I?

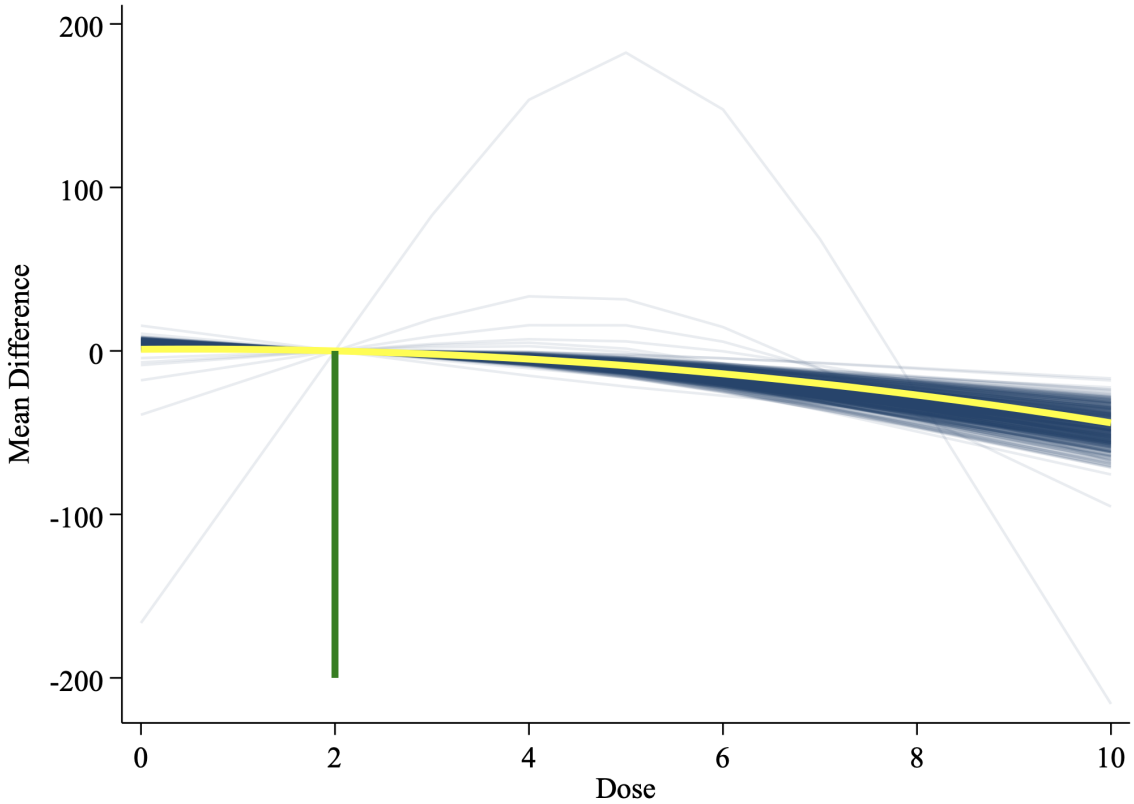
$$E(Y|X = x) - E(Y|X = 2) = 0.5(X - 2)$$



Settings: Random-effects mechanism, truly linear, mix of 2/3 doses.

Are 1,000 predicted dose-response models of type M_s estimating the right shape under S_q?

$$E(Y|X = x) - E(Y|X = 2) = 0.5(X - 2) - 0.5(X - 2^2)$$



Settings: Random-effects mechanism, truly quadratic, mix of 2/3 doses.

Summary

- We evaluated the performance of the AIC based on linear mixed models (ML method) suitable for summarized data in realistic Monte-Carlo simulations.
- If the dose-response relationship underlying multiple studies is linear, the AIC is very good in suggesting linearity even when all studies categorize the dose into two quantiles.
- If the dose-response relationship underlying multiple studies is non-linear (quadratic), the AIC is very bad in suggesting non-linearity when all studies categorize the dose into two quantiles.
- In such a case, a mix of studies categorizing the dose into either 2 or 3 quantiles increased substantially the performance of the AIC.
- Model selection was not sensitive to the data-generating mechanism (common-effect, random-effects) of the individual studies.

References

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