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Point-wise averaging approach in dose-response meta-analysis of aggregated data

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Dose–response meta–analysis

Summarize results from multiple studies on the relation between a quantitive exposure and the occurrence of a health outcome

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

gday	dose	case	control	n	rr	lb	ub
Ref.	0	165	172	337	1.00	1.00	1.00
<2.5	2	74	93	167	0.80	0.51	1.27
2.5-9.3	6	90	96	186	1.16	0.73	1.85
>9.3	11	122	90	212	1.57	0.99	2.51

Two-stage approach

First stage:

Estimate a common dose–response model in each study $(i = 1, \ldots, K)$

$$\mathbf{y}_i = \mathbf{X}_i \beta_i + \varepsilon_i \tag{1}$$

with $\mathbf{y}_i$ vector of non-referent log relative risks

Second stage:

Combine study–specific regression coefficients $\hat{\beta}_i$, $\mathrm{Var}\left(\hat{\beta}_i\right)$

$$\bar{\beta} = \frac{\sum_{i=1}^{K} \mathbf{W}_i \hat{\beta}_i}{\sum_{i=1}^{K} \mathbf{W}_i} \tag{2}$$

with $\mathbf{W}_i = \left(Var\left(\hat{\beta}_i\right) + \mathbf{\Psi}\right)^{-1}$

Results are presented as pooled relative risks for selected dose levels x^*

$$\log \widehat{RR} = \mathbf{X}^* \bar{\beta} \tag{3}$$

General limitations:

- The dose–response model needs to be the same across studies: Poor fit in some of the study-specific dose-response analyses
- Pooling of $\hat{\beta}_i$ discards the initial exposure range: Predictions may be affected by extrapolation

Aims

To propose a point-wise averaging approach to take into account differential curves and exposure distributions

Specific aims:

- To introduce more flexibility in the dose-response analysis
- To allow each study to contribute to the overall curve based on the observed exposure distribution

Point-wise averaging approach

Intially proposed for IPD meta-analysis, it consists of the following steps:

1. Estimation of study-specific dose–response curves
2. Study-specific predictions
3. Combining study-specific predictions by meta-analysis

Estimation of study-specific curves

$$\mathbf{y}_i = f_i\left(\mathbf{x}_i; \beta_i\right) + \varepsilon_i \tag{4}$$

f_i can differ across studies

Fractional polynomials of order 2

$$\mathbf{y}_i = \beta_{i1}\mathbf{x}_i^{p_{i1}} + \beta_{i2}\mathbf{x}_i^{p_{i2}} + \varepsilon_i \tag{5}$$

with $\mathbf{x}_i^0 = \log\left(\mathbf{x_i}\right)$

Select (p_{i1}, p_{i2}) in the set of values $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ which minimize the AIC

Estimation of study-specific curves (2)

Restricted cubic splines with 3 knots

$$\mathbf{y}_i = \beta_{i1} f_{i1}(\mathbf{x}_i) + \beta_{i2} f_{i2}(\mathbf{x}_i) + \varepsilon \tag{6}$$

$$f_{i1} = \mathbf{x}_i$$

$$f_{i2} = \frac{(\mathbf{x}_i - k_{i1})_+^3 - \frac{k_{i3}-k_{i1}}{k_{i3}-k_{i2}}(\mathbf{x}_i - k_{i2})_+^3 + \frac{k_{i2}-k_{i1}}{k_{i3}-k_{i2}}(\mathbf{x}_i - k_{i3})_+^3}{(k_{i3} - k_{i1})^2} \tag{7}$$

Study specific knots location

Prediction and pooling

Limit prediction to study-specific range: $\mathbf{x}^* \in \text{range}(\mathbf{x_i})$

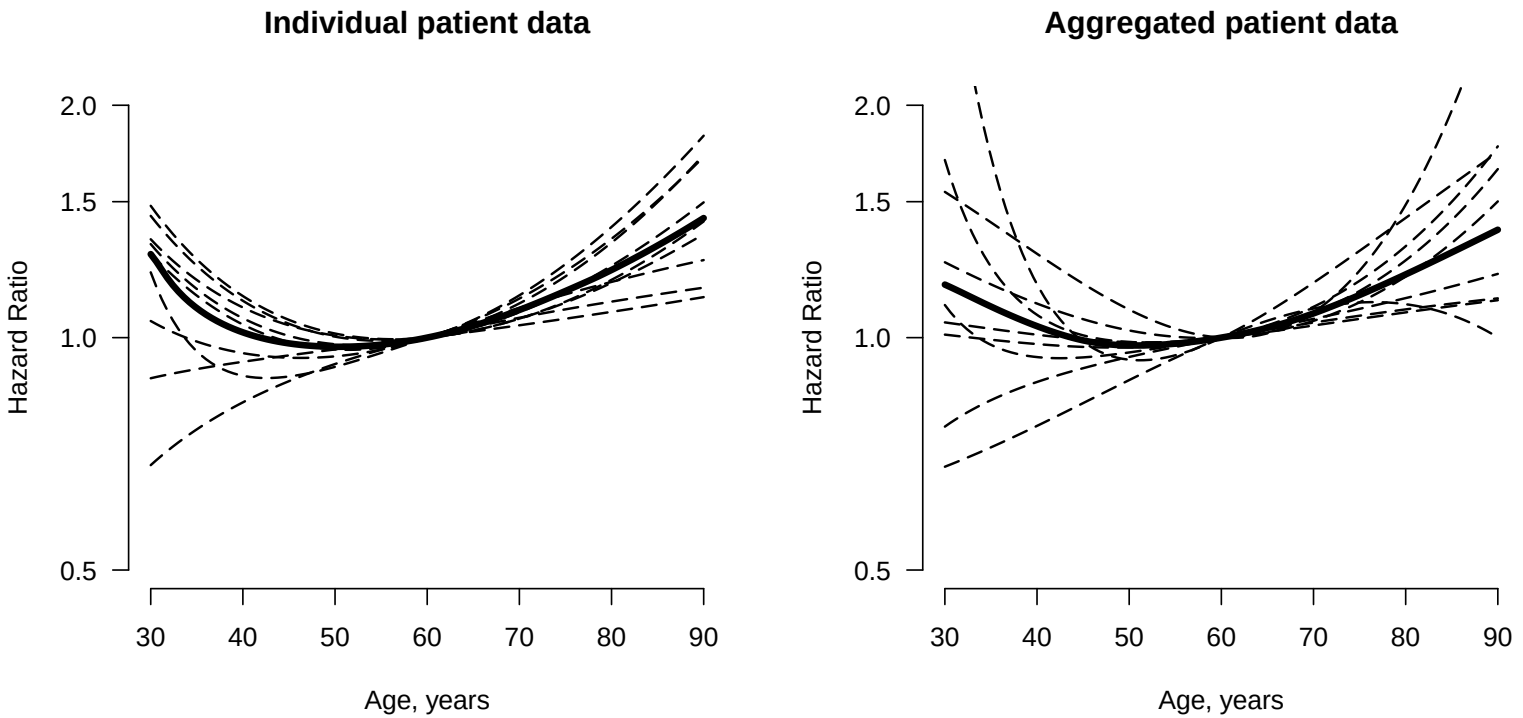
$$\begin{aligned} \mathbf{log}\,\widehat{\boldsymbol{RR}}_i &= \mathbf{X}^*\beta_i \\ \text{Var}\left(\mathbf{log}\,\widehat{\boldsymbol{RR}}_i\right) &= \text{diag}\left(\mathbf{X}^{*\top}\text{Var}\left(\beta_i\right)\mathbf{X}^*\right) \end{aligned} \tag{8}$$

Pool the study-specific effects (log RR)

$$\log \bar{RR}|x^* = \frac{\sum_{i=1}^{K} W_i \log \widehat{RR}_i I(x^* \in \text{range}(\mathbf{x_i}))}{\sum_{i=1}^{K} W_i I(x^* \in \text{range}(\mathbf{x_i}))} \tag{9}$$

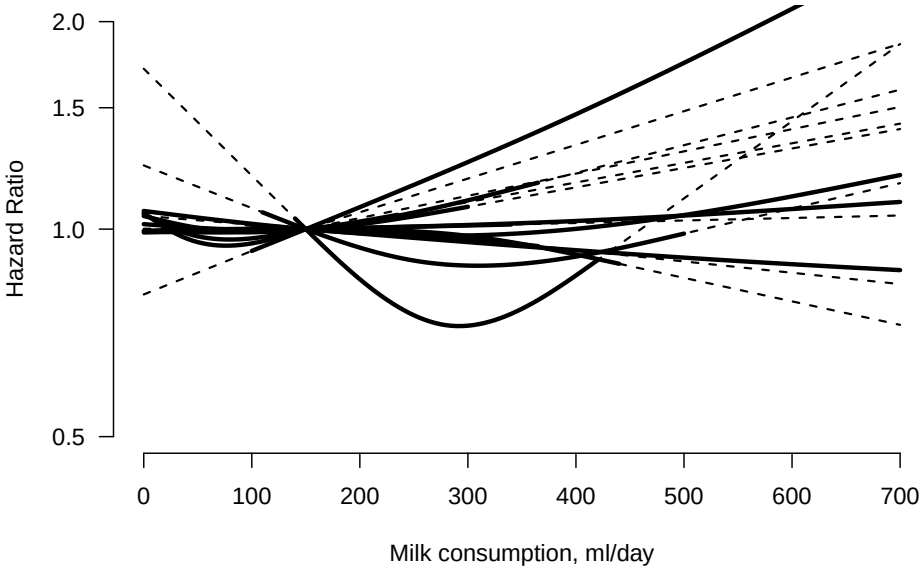
Comparison with IPD meta-analysis

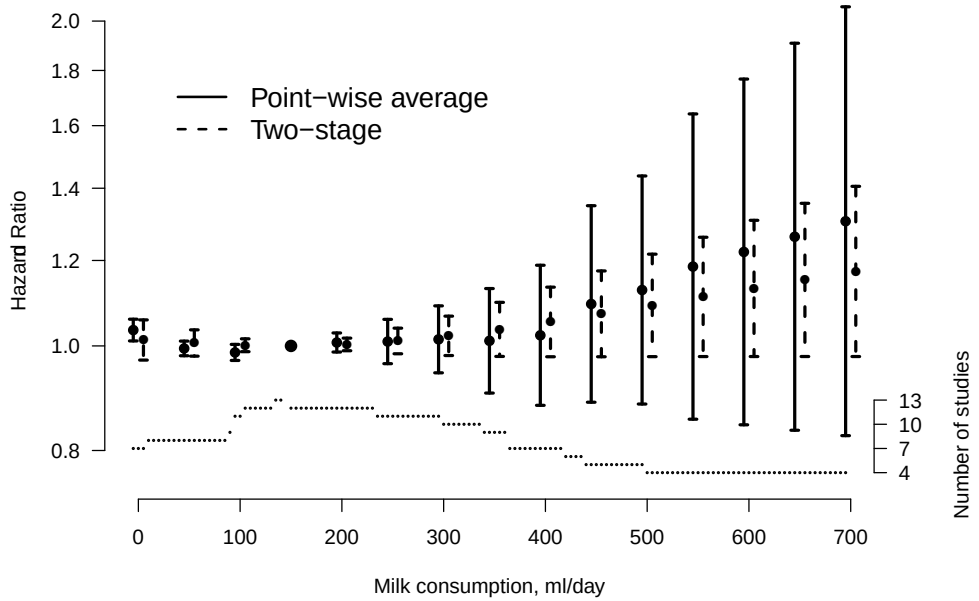
Based on breast cancer patients in the SEER program (`http://seer.cancer.gov/`)



Comparison with two-stage meta-analysis

Re-analysis of a dose-response meta-analysis between milk and mortality





Conclusions

- A point-wise averaging approach can properly address differential dose–response curves and exposure distribution, and limit the impact of extrapolation
- Results can be presented graphically for a grid of exposure values
- Differences with a two-stage approach may depend upon exposure distributions and strategies used in the dose–response analysis

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