A Pointwise Approach to Dose-Response Meta-Analysis of Aggregated Data

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Abstract: In a two-stage dose-response meta-analysis a common functional relationship is applied to each study and an overall curve is obtained by combining study-specific dose-response coefficients. Possible limitations are: 1) a common dose-response model may have a poor fit in some of the studies; 2) combining dose-response coefficients discard information about study-specific exposure range. A pointwise approach for meta-analysis may overcome those limitations by combining predicted relative risks for a fine grid of exposure values based on potentially different dose-response models.

We described how to flexibly model the dose-response association in a single study using fractional polynomials and spline, and how to present the combined results from study-specific analyses.

The strategy is illustrated using aggregated data derived from the Surveillance, Epidemiology, and End Results program, with results compared to the corresponding analysis based on individual data.

Another example on milk consumption and all-cause mortality is used to show the advantages of the pointwise approach regarding flexibility in the dose-response analyses, limitations of extrapolations, and informativeness in presenting pooled results.

Application of the proposed strategy may improve dose-response meta-analysis of observational studies in case of particularly heterogeneous exposure distributions.

Keywords: Dose-response, Meta-analysis, Pointwise average, Flexible model.

INTRODUCTION

Dose-response meta-analysis is an increasingly popular statistical technique for combining and contrasting the association between a quantitative exposure on a health outcome. The number of quantitative reviews including an evaluation of the dose-response relation increased from 6 in 2002 to 158 in 2017. The traditional approach consists of a two-stage procedure in which the dose-response coefficients are estimated within each study (first stage) and then combined across studies using meta-analysis (second stage) [1, 2]. Alternatively, a one stage approach can be based on a single mixed-effect model for meta-analysis, which has been shown to be equivalent to the two-stage approach [3, 4].

Both approaches are flexible tools for modeling the dose-response relation under investigation. However, a feature of these models is that the same functional form (e.g. linear, quadratic) is assumed to equally apply to all the studies [5]. This may have important consequences if the estimated dose-response relation has a good fit for only a subset of the studies or if the dose-response model cannot be uniformly specified across studies. The former case may occur, for instance, in a fractional polynomial model where the same power terms are chosen for all the studies [6]. The latter, instead, could happen in a spline model where equally locating the knots across the studies may be difficult because the exposure may vary considerably across studies [7].

The pooled dose-response curve is typically presented in terms of predicted effects, here referred to as relative risks, for a range of exposure values. All the studies participate to the pooled predictions regardless of their observed exposure distribution. This may be have an impact in meta-analyses where part of the studies considered only a limited exposure range. The pooled relative risk for high exposure values will also be based on those extrapolations.

In 2011 Sauerbrei and Royston [8] proposed a flexible strategy to combine dose-response data for individual patient data (IPD) meta-analysis. The strategy consists of predicting the study-specific relative risks for selected exposure levels in each study using different dose-response models. The predicted relative risks are then combined pointwise by a weighted average to obtain a summary estimate of the dose-response relation. The described approach has

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E-ISSN: 1929-6029/18

the potential to overcome the aforementioned limitations: different dose-response models can be fitted within each study while predicted relative risks can be limited in each study to the observed exposure range and then combined.

Aim of this is paper is to evaluate whether and to what extent the pointwise approach can be used for meta-analysis of aggregated patient data (APD). In Section 2 we describe what are the steps of the pointwise analysis for dose-response meta-analysis. The methodology applied to either individual or aggregated patient data in the Surveillance, Epidemiology, and End Results (SEER) program is presented in Section 3. We also consider potential advantages as compared to the two-stage approach by analyzing aggregated data on the association between milk consumption and all-cause mortality. We conclude with the discussion and final remarks in Section 4.

METHODS

Aggregated dose-response data typically consist of a series of relative risks for a set of exposure comparisons. One category, generally the unexposed one, serves as referent [2]. We first present how to independently estimate the curves and predict relative risks in each study based on aggregated data using both fractional polynomial and spline models. The predicted relative risks are then combined pointwisely across studies by meta-analysis.

Estimation of Study-Specific Curves

Separately for each *i*-th study, *i* = 1, …, *I*, the dose-response model can be expressed as

$$\mathrm{E}\left[\boldsymbol{y_i}\middle|\boldsymbol{x_i}\right]=\sum_{j=1}^{p}\theta_{ij}f_{ij}(x_i)=\theta_{i1}f_{i1}(x_i)+\cdots+\theta_{ip}f_{ipi}(x_i) \quad (1)$$

where $\boldsymbol{y_i}$ and $\boldsymbol{x_i}$ are, respectively, the vectors of non-referent log relative risks and dose levels in the *i*-th study. The dose-response models are typically expressed as a linear combination of *p* transformations of the dose. Given the limited number of non-referent dose levels, $p < 3$ transformations are often adopted. The reported relative risks are not independent since they share a common reference group. Greenland and Longnecker described how to account for the correlations and efficiently estimate a trend from such aggregated data by using weighted least square estimation [9].

Several alternatives can be chosen to model the dose-response relation under investigation. Fractional polynomials and splines models are two common choices, since many curves can be estimated by using a limited number of dose transformations (p = 2).

A fractional polynomial model is defined as

$$\mathrm{E}\left[\boldsymbol{y_i}\middle|\boldsymbol{x_i}\right]=\theta_{i1}x_i^{pi1}+\theta_{i2}x_i^{pi2} \quad (2)$$

for each p_{i1} and p_{i2}, combination of predefined values {-2,-1, -0.5, 0, 0.5, 1, 2, 3}. The fractional polynomial with the lowest value of the Akaike's Information Criterion is generally chosen as the best in the predefined set of models [10].

Splines consist of piecewise polynomials jointly connected over sequentially intervals defined by knots. Restricted cubic splines, in particular, restrict the ends of the curve to be linear [11]. By using three knots (k_{i1},k_{i2},k_{i3}), two dose transformations are required in Equation 1

$$\begin{cases} f_{i1}(x_i)=x_i \\ f_{i2}(x_i)=\dfrac{(x_i-k_{i1})_+^3-\dfrac{k_{i3}-k_{i1}}{k_{i3}-k_{i2}}(x_i-k_{i2})_+^3+\dfrac{k_{i2}-k_{i1}}{k_{i3}-k_{i2}}(x_i-k_{i3})_+^3}{(k_{i3}-k_{i2})^2} \end{cases} \quad (3)$$

where the "+" notation ($u_+=u$ if $u_+>0$ and $u_+=0$ otherwise) has been used.

In both Equation 2 and 3 we used the subscript *i* for the power terms ***p*** and for the knots ***k*** to emphasize that they can vary across the study. For instance, the best fitting fractional polynomials may have a different combination of power terms in two studies, as well as different knots in a spline model. This is not possible in the two-stage approach since the $\boldsymbol{\theta}_i$ needs to refer to (exactly the) same dose transformations in order to be combined by meta-analysis.

Prediction of Study-Specific Log Relative Risks

Once the study-specific curves have been chosen, the predicted log relative risks, $\hat{\boldsymbol{y}}_i$, and the corresponding variances, $\hat{\boldsymbol{v}}_i$, can be calculated for a fine grid of exposure values $\tilde{\boldsymbol{x}}$ using a suitable value $\tilde{x}_0$ as referent,

$$\begin{aligned} \hat{\boldsymbol{y}}_i &= \mathrm{E}\left[\hat{\boldsymbol{y}}_i\middle|\tilde{\boldsymbol{x}}\right]=\sum_{j=1}^{p}\hat{\theta}_{ij}\left[f_{ij}(\tilde{\boldsymbol{x}})-f_{ij}(\tilde{x}_0)\right] \\ \hat{\boldsymbol{v}}_i &= \mathrm{Var}\left[\hat{\boldsymbol{y}}_i\middle|\tilde{\boldsymbol{x}}\right]=\left(f_{ij}(\tilde{\boldsymbol{x}})-f_{ij}(\tilde{x}_0)\right)^2\mathrm{Var}(\hat{\boldsymbol{\theta}}_{\mathrm{ij}}) \end{aligned} \quad (4)$$

with study-specific predictions that can be limited to the observed exposure range with the clear advantage of limiting the impact of extrapolation.

Averaging Dose-Response Predictions

A pointwise strategy derives a pooled curve by combining the study-specific predicted log relative risks instead of combining dose-response coefficients. Differently from the $\hat{\theta}_i$ that are specific to the chosen dose transformations, $\hat{y}_i$ refer to $\tilde{x}$ dose levels that are common for all the studies, and thus can be properly combined using standard methodology for meta-analysis.

Assuming a random-effects model, the pooled predicted log relative risks $\hat{\bar{y}}$ can be estimated as a pointwise weighted average

$$\hat{\bar{y}} = \sum_{i=1}^{I} \frac{\hat{y}_i w_i^T}{\sum_{i=1}^{I} w_i^T} \quad (5)$$

where the weights are defined as $w_i = \hat{v}_i + \tau^2$ with τ^2 being the between-studies heterogeneity [12].

The pooled dose-response curve can be graphically presented as a smooth function of the pooled relative risks for selected exposure values. Similarly, a variety of useful results from the meta-analytic models, such as τ^2 estimates, values of w_i and measures of heterogeneity, can also be presented pointwisely either in a graphical or tabular format.

RESULTS

We present two applications of the pointwise approach summarizing the relationships between 1) age and breast cancer survival, and 2) milk consumption and all-cause mortality.

Age and Breast Cancer Survival

The SEER program provides individual data about cancer statistics from several population-based registries in the United States (http://seer.cancer.gov), here treated as independent studies. We are interested in pooling the evidence regarding age as prognostic factor for breast cancer survival, using nine of the SEER registries (5719 cases and 75,249 participants).

Separately for each study we first derived aggregated data by categorizing age in five categories with 47, 57, 65, 73 years as cut-points (i.e. the 20th, 40th, 60th, and 80th percentiles of the overall age distribution). We thus modeled age by including 4 dummy variables using (57, 65] as reference category and adjusting for major confounding variables in 9 separate Cox models, one for each registry. More information about the data, variables considered, and selection criteria can be found in the article by Tai *et al*. [13]. A snapshot of the data obtained for the first two registries is presented in Table **1**.

We then used fractional polynomials as in Equation 2 to estimate the study-specific curves from the obtained aggregated data. The Akaike's Information Criterion was used to choose, separately in each study, the best fitting model. The corresponding analysis were also performed on individual patient data. The optimal set of power transformations based on APD and IPD are reported in Web Table **1**. In the following step we computed the predicted (log) hazard ratios for a fine grid of age values from 30 to 90 years, using 60 as

Table 1: Aggregated dose-response data for two registries of the Surveillance, Epidemiology, and End Results Program obtained by modeling age as categorical variable. The log hazard ratios (logHR) and corresponding standard error are calculated using the age category [57,65) as referent

Registry	Age Category	Median Age	Cases	N	logHR	se
San Francisco-Oakland	[57,65]	61	156	2341	ref	-
	[20,48]	42	261	2613	0.101	0.102
	[48,57]	52	171	2621	-0.005	0.111
	[65,73]	68	178	2587	0.073	0.110
	[73,101]	77	176	2528	0.161	0.110
Connecticut	[57,65]	61	139	1967	ref	-
	[20,48]	42	179	2028	-0.039	0.114
	[48,57]	52	125	2016	-0.114	0.123
	[65,73]	68	150	2179	-0.021	0.118
	[73,101]	77	173	2269	0.165	0.114

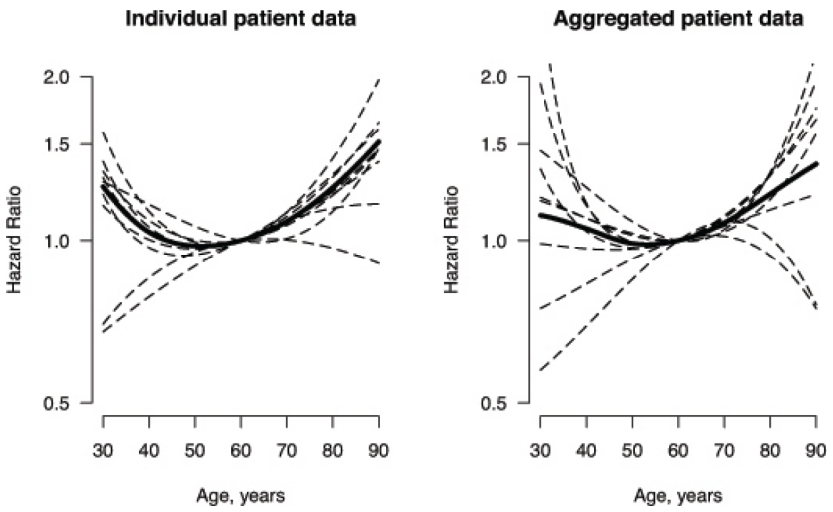

Figure 1: Graphical comparison between pointwise meta-analysis on the relation between age and relative hazard of breast cancer survival based on individual (left panel) and aggregated (right panel) patient data. The dashed lines represent study-specific best fractional polynomials of order two. The thick black lines represent the pooled dose-response associations. The predicted hazard ratios are presented on the log scale with 60 years serving as referent.

reference value (Equation 4). The predictions were then combined through random-effects meta-analysis.

A graphical comparison of the pooled hazard ratios from the two strategies is presented in Figure **1**. The study-specific curves based on APD predicted more heterogeneous hazard ratios at the extremes of the age distribution. The pooled dose-response curves, however, provided comparable findings, suggesting a U-shaped relation with a minimum at 50 years of age. The hazard ratios of breast cancer were 1.03 (95% CI 0.98, 1.09) at 40 years and 1.25 (95% CI 1.17, 1.32) at 80 years in the IPD analysis. The corresponding estimates were 1.05 (95% CI 0.96, 1.14) and 1.21 (95% CI 1.11, 1.32) in the APD analysis.

Milk and all-Cause Mortality

Let's consider a meta-analysis of APD between milk consumption (ml/day) and mortality based on 14 prospective studies including 70,743 deaths occurred among 367,505 participants [14].

The exposure range was considerably heterogeneous across studies. Table **2** shows how the assigned exposure scores for milk consumption differed in terms of number of values considered, range definition, and choice of referent.

In case of heterogeneous exposure distribution, choosing common knots is difficult. For instance, the 3 selected knots at the 10th, 50th, and 90th percentiles of the overall distribution (0, 149, and 500 ml/day) were in the exposure range of only 2 studies. As a consequence, problems in the estimation may occur (singularity in the design matrix) and/or fictitious non-linear curves may be observed in some of the study-specific analyses.

In the pointwise strategy, instead, knots location can be defined within the singles studies, for example selecting the minimum, median, and maximum of the assigned dose levels (Table **2**). This avoids problems in the estimation algorithm and has the potential of improving the fit in the individual analyses.

Table 2: Descriptive statistics of the assigned exposure scores for the 14 studies included in the dose-response meta-analysis on milk consumption (ml/day) and all-cause mortality

	Study													
Statistic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Referent	140	94	0	0	109	0	0	147	12	0	100	100	0	0
No. Categories	2	2	3	3	2	4	4	2	3	3	3	3	4	4
Min	140	94	0	0	109	0	0	147	12	0	100	100	0	0
Median	280	473	282	150	250	52	90	294	154	192	400	400	31	31
Max	420	1041	715	300	500	238	342	441	366	369	700	700	150	150

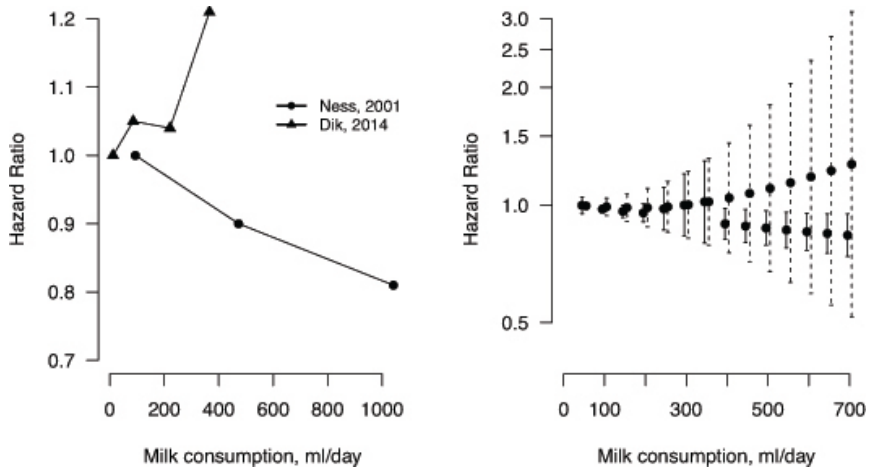

Figure 2: Comparison between pointwise (solid line) and two-stage approach (dashed line) based on two studies on the association between milk consumption and all-cause mortality (right panel). The observed data are represented in the spaghetti plot (left panel).

Estimation of pooled hazard ratios may also be cumbersome when pooling dose-response coefficients. Let us consider for example two of the studies included in the analysis, presented graphically in the left panel of Figure **2**. When the two exposure distributions were overlapping, saying milk consumption below 350 ml/day, the two approaches provided similar inference (right panel of Figure **2**). Above 350 ml/day the two-stage approach suggests an upward trend mainly driven by extrapolating the results of Dik 2014, whereas the pointwise approach indicates a downward trend based on the only study available (Ness, 2001).

We now analyze the dose-response associations arising from all the 14 included studies. In each study, we modeled milk consumption by using restricted cubic splines, where the knots were defined separately in each study. The advantage of the pointwise approach is to visualize and distinguish predicted hazard ratios based on observed data and model-based extrapolations (Figure **3**). Figure **4** plots the pooled hazard ratios and their corresponding confidence intervals comparing the two strategies. It is interesting to note the narrower confidence intervals for the two-stage approach's estimates in the upper tail of the exposure distribution (above 500 ml/day) where only 4 out of 14 (30%) studies were available. The pooled hazard ratio of all-cause mortality associated with 700 relative to 150 ml/day was 1.30 (95% CI 0.83, 2.06) for the pointwise, and 1.17 (95% CI 0.98 1.41) for the two-stage approach.

The pointwise approach allows the presentation of statistics from the meta-analytical models as a function of the exposure (Figure **5**). Estimates of the between-study heterogeneity, τ^2, were close to zero for milk consumption less than 300 ml/day and progressively increased for higher values (panel (a)). The weights

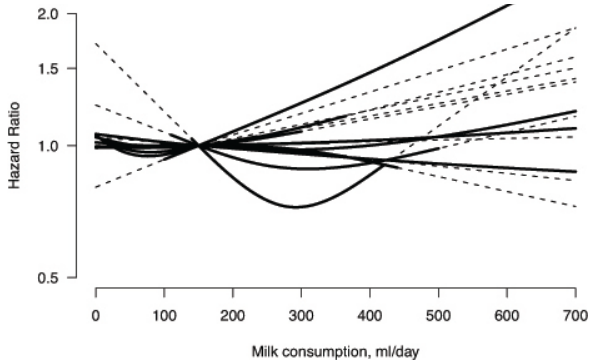

Figure 3: Study-specific curves on the association between milk consumption (ml/day) and all-cause mortality. Dashed lines correspond to extrapolation. The predicted hazard ratios are presented on the log scale with 150 ml/day serving as referent.

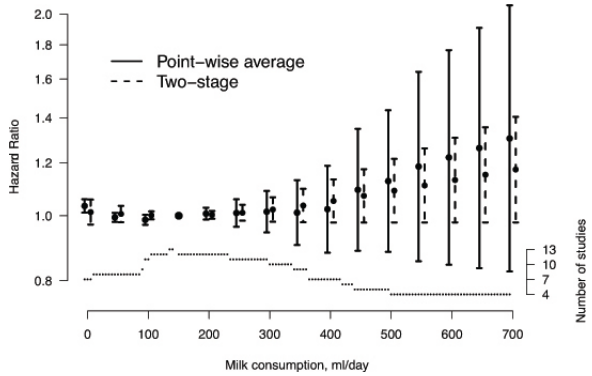

Figure 4: Comparison between pointwise and two-stage predicted hazard ratios of all-cause mortality for selected values of milk consumption. The step function at the bottom represents the number of studies participating to prediction in the pointwise meta-analysis. The predicted hazard ratios are presented on the log scale with 150 ml/day serving as referent.

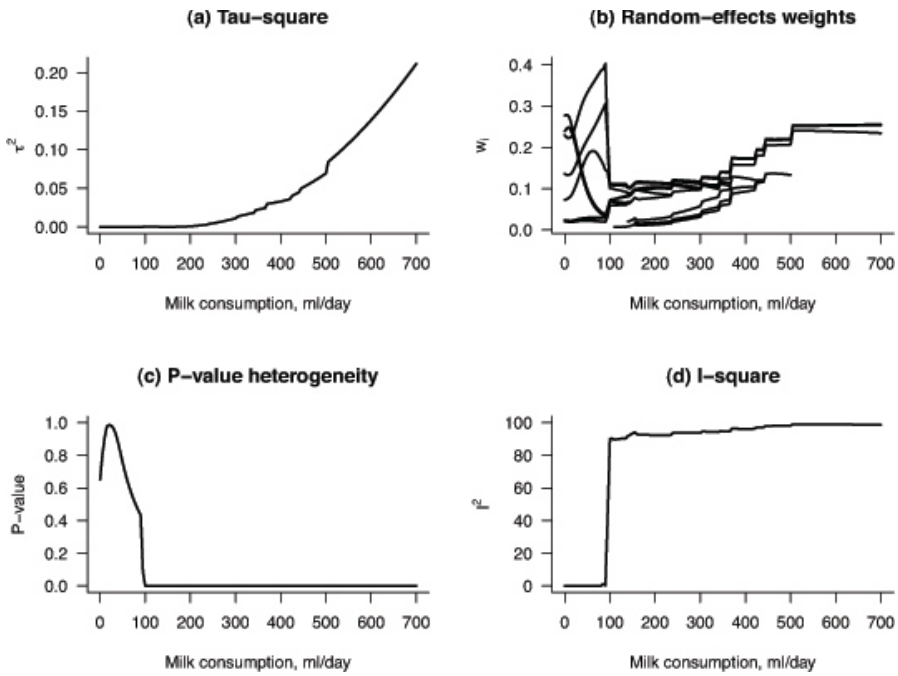

Figure 5: Pointwise results for the meta-analysis between milk and all-cause mortality: (**a**) estimates of between-study heterogeneity τ^2 , τ^2 (**b**) random-effects weights for the included studies, (**c**) *p*-value for the *Q* statistic, and (**d**) I^2 .I^2

used in the random-effects meta-analysis suggested a certain degree of homogeneity, with the exception for milk consumption of 100 ml/day, where two studies counted for the 70% of the total weight in the pooled hazard ratio (panel (b)).

Measures of heterogeneity can also be presented graphically. The *p*-value for the *Q* statistic is often used to test presence of statistical heterogeneity. The *Q* test detected significant heterogeneity for milk consumption greater than 100 ml/day (panel (c)). The I^2 confirmed a substantial degrees of heterogeneity for levels of milk consumption higher than 100 ml/day.

DISCUSSION

In this paper we presented a pointwise approach described for dose-response meta-analysis of aggregated data. The strategy consists in combining predicted relative risks arising from different study-specific dose-response models. We described how to flexibly model the dose-response associations using either fractional polynomials or restricted cubic splines. The pointwise approach allows a better fit of the data within each study and prevent overconfidence in the pooled estimates by taking into account the varying number of data points along the range of the exposure distribution.

Our empirical evaluation of the SEER program based on aggregated data provided very similar results to those based on individual data, which are often considered as the gold standard of systematic review [15]. Collecting and analyzing summarized data has several benefits in terms of reducing time, cost, and number of people involved in pooling the available evidence on a certain exposure-disease association [16]. An alternative explanation for the good agreement may be the fact that individual registries data were uniformly collected, organized, and documented [17]. Published studies, however, can be expected to be more heterogeneous in terms of study populations, available potential confounders, exposure, and outcome definitions [18]. Analysis of aggregated data is inevitably sensitive to how individual data have been summarized. An evaluation of the extent of the heterogeneity of the study-specific curves should be performed before presenting a pooled dose-response association [19]. In the practical examples we addressed this problem by both visually inspecting the individual curves and reporting measures of heterogeneity commonly used in quantitative reviews.

Although the aim of a dose-response meta-analysis is to estimate a curve that equally applies across the studies, forcing a common functional relationship may lower the fit of some individual analyses [5]. One of the advantage of the pointwise approach consists in the flexibility in the modeling individual curves. In a two-stage meta-analysis of non-linear relationships, for example, all the studies providing less than two non-

Table A1: Optimal set of power transformations for nine study on the association between age and hazard of survival for breast cancer

study	individual		aggregated	
	p1	p2	p1	p2
San Francisco-Oakland	-0.5	0.5	-0.5	-0.5
Connecticut	-1.0	3.0	-2.0	3.0
Metropolitan Detroit	-2.0	2.0	3.0	3.0
Hawaii	-2.0	3.0	3.0	3.0
Iowa	-1.0	3.0	-2.0	-2.0
New Mexico	0.5	1.0	3.0	3.0
Seattle (Puget Sound)	-1.0	3.0	3.0	3.0
Utah	1.0	3.0	3.0	3.0
Metropolitan Atlanta	3.0	3.0	3.0	3.0

referent exposure levels are excluded from the analysis. In the proposed approach, instead, this can be avoided by fitting a linear trend in those studies with just one non-referent exposure level.

Another important advantage of the pointwise strategy is in terms of pooling relative risks, taking into account the exposure range upon which they were estimated. In case of heterogeneous exposure distributions, as in the presented example on milk consumption and all-cause mortality, this feature may have important consequences when deriving the pooled curve. In particular, both point and interval predictions are affected, with the latter being generally narrower and prone to overconfident conclusions.

Finally, numerical and graphical presentation of the pooled results in the pointwise strategy is richer as compared to a two-stage approach. Results from the meta-analytic models can be examined pointwisely for a fine grid of selected exposure values.

CONCLUSION

In conclusion, application of the proposed strategy may improve dose-response meta-analysis of epidemiological studies, particularly in case of heterogeneous exposure distributions. The described methodology is fairly general so that intermediate steps can be adapted to handle specific issues at hand. R code to reproduce results from worked examples is available on GitHub.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

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Received on 16-04-2018 Accepted on 23-04-2018 Published on 08-05-2018

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