Selection models with monotone weight functions in meta analysis

Kaspar Rufibach

Division of Biostatistics
Institute for Social and Preventive Medicine
University of Zurich

Agenda

Publication bias

Publication bias:

- Threat to validity of meta analysis.
- Numerous tools to detect publication bias, see e.g. review by Sutton and Higgins (2008).

Goal: explicitly model selection bias, i.e.

- Explore selection mechanism.
- Visual display of (relative) weight function $\Rightarrow$ identify publication bias.
- Assess evidence against null hypothesis of no selection.

Assumptions

Basic assumption: Weight of a study only depends on standardized effect size or p-value.

Unlike Copas selection model: dependence on effect size estimate and corresponding standard error separately.

Rationale for p-value approach:

– Decisions in medical research often based on p-value only.

– "Making the selection function depending on the p-value only has the longest history in meta analysis." Hedges and Vevea (2005). Large amount of literature.

Model

Framework of weighted distributions or biased sampling.

Statistical literature somewhat underrepresented in meta analysis research.

Model:

- Y^*: effect size before selection, assumed normal with density $f(y|\theta,\sigma)$.
- w: non-negative weight function, depending on observed effect size y.

Weighted density of observed effect Y is:

$$g(y|\theta,\sigma) = \frac{f(y|\theta,\sigma)w(y)}{\int f(y|\theta,\sigma)w(y)\,\mathrm{d}y}.$$

Properties of g:

- w constant $\Rightarrow$ no selection.
- w non-constant: sampling distribution of Y differs from unselected effect size Y^*.
- Shape of w: way of describing selection bias.

Weight function proposed in this model

We estimate w in setup of Dear and Begg (1992):

- w assumed left-continuous step function,
- pooling of p-values in pairs.

For $p \in [0,1]$ w is defined as

$$w(p) = \begin{cases} w_j & \text{if } p_{2j-2} \geq p > p_{2j} \\ w_k & \begin{cases} p_{n-1} \geq p > 0 & \text{if } n \text{ odd} \\ p_n \geq p > 0 & \text{if } n \text{ even.} \end{cases} \end{cases}$$

$j = 1 + \lfloor i/2 \rfloor = 1, \ldots, k$: $k = \#$categories of p-values from pairing.

Setup likelihood.

Monotonicity of w

Assumption

Large values of $|Y^*|$ are more likely to be observed $\Rightarrow$ smaller p-values are more likely to be observed $\Rightarrow$ w as a function of p-value is non-increasing.

Monotonicity of w seems an a priori plausible assumption.

Givens et al. (1997): "A monotonicity constraint is much harder [than in their Bayesian framework] to put in place in the frequentist setting...".

Maximize likelihood under restriction that $w(p) \searrow$.

Monotonicity of w

Advantages besides plausibility of monotonicity in this context:

- All parametric weight functions so far proposed are non-increasing.
- Typically, #studies in meta analysis is small to moderate ⇒ regularization sensible.
- Restricting parameter space typically yields estimates with better performance, e.g. measured by MSE, if restriction applies.
- Unlike kernel estimators or penalized monotone estimator of Sun and Woodroofe (1997) shape-constraint estimators fully automatic ⇒ no choice of smoothing or penalty parameter.
- Main purpose of weight functions: exploratory and informal means to assess degree of publication bias.
- Many of these functions in Bayesian framework, see Sutton et al. (2000) or Silliman (1997).

Computational aspects

Log-likelihood ℓ in general not concave.

Maximization of ℓ for different w's:

- Parametric estimates: using R's function `optim`.
- Unconstrained estimate of Dear and Begg (1992): ad-hoc "coordinate-wise EM type algorithm", but works.
- Monotonicity restriction: Maximization via differential evolution algorithm:
  - unconstrained global maximization,
  - penalize violation of constraints with $-\infty$,
  - neither continuity nor differentiability of target function necessary,
  - implemented in R package **DEoptim** (Ardia and Mullen (2010)).

Implemented in **selectMeta** Rufibach (2011), available from CRAN.

Quantifying evidence against a constant w

If w is constant:

$$g(y|\theta,\eta) \quad = \quad f(y|\theta,\eta).$$

Conditional on the data, get a simulation-based p-value as follows:

1. Choose $T = \min w$ as test statistic.
2. Compute $\widehat{\theta}_0, \widehat{\sigma}_0^2, \widehat{w}_0, \widehat{T}_0 = \min \widehat{w}_0$ from p-value sample $p_1, \ldots, p_n$ in standard random effects model.
3. Draw samples $y_{j1}, \ldots, y_{jn} \sim N(\widehat{\theta}_0, \widehat{\eta}_0^2)$ from the null model, compute corresponding p-values, $\widehat{w}_j$, and $\widehat{T}^{(j)} = \min \widehat{w}_j$ for $j = 1, \ldots, M$.
4. Approximate p-value quantifying evidence against constant w:

$$p \quad = \quad \frac{1 + \#\{j \leq M \;:\; \widehat{T}_0 \leq \widehat{T}^{(j)}\}}{1 + M}.$$

`DearBeggMonotonePvalSelection` implements this in **selectMeta**.

Statistical inference on θ and σ^2

Conclusions:

- Publication bias suspected $\Rightarrow$ focus attention on possible causes of bias.
- Search for "missing" studies rather than using model to adjust $\widehat{\theta}$ and $\widehat{\sigma}^2$.
- See estimation of w as sensitivity analysis.
- Advocated in Hedges (1988), Dear and Begg (1992), Sutton et al. (2000).

However, reviewer was not satisfied.

Think more about the problem:

- Interested in finite-dimensional parameter (θ, σ^2).
- Nuisance parameter w infinite-dimensional.
- Simple setup of Dear and Begg (1992): dimension of w grows with n. Validity of p-value proposed in Hedges (1992) for $H_0 : w_2 = \ldots = w_k$ questionable.

Statistical inference on θ and σ^2

Proposal:

- Invoke theory by Murphy and van der Vaart (2000): inference for finite-dimensional parameter θ with infinite-dimensional nuisance parameter (σ^2, w).
- Our setup: only approximate (pooling of *p*-values).
- Assumption: class of nuisance parameter not "too large" (in terms of entropy). For monotone functions verified in Fan and Wong (2000).

Profiling out w yields χ^2 limiting distribution for θ.

Implemented in `DearBeggMonotoneCItheta` in **selectMeta**.

Environmental tobacco smoke data

Environmental tobacco smoke data, Hackshaw et al. (1997):

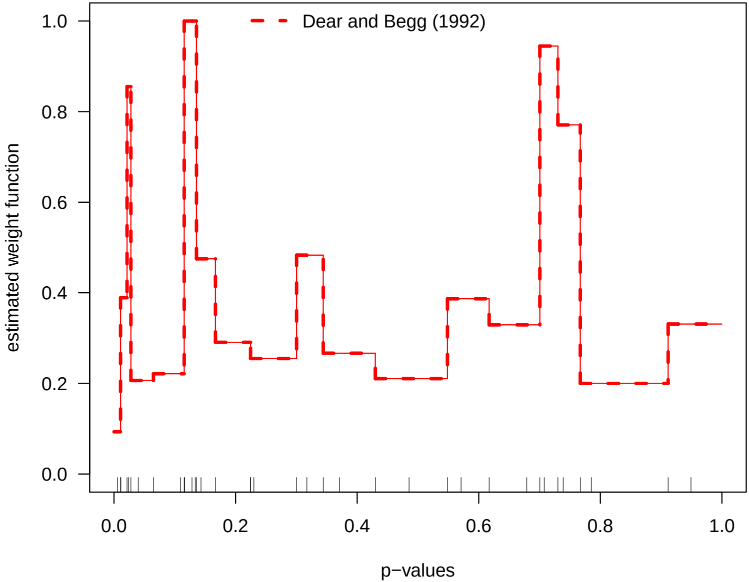
– Effect of environmental tobacco smoke on lung cancer in lifetime non-smokers, quantified via log-relative risk in 37 studies.

– Rothstein et al. (2005): 'Ongoing controversy whether this meta analysis suffers from publication bias."

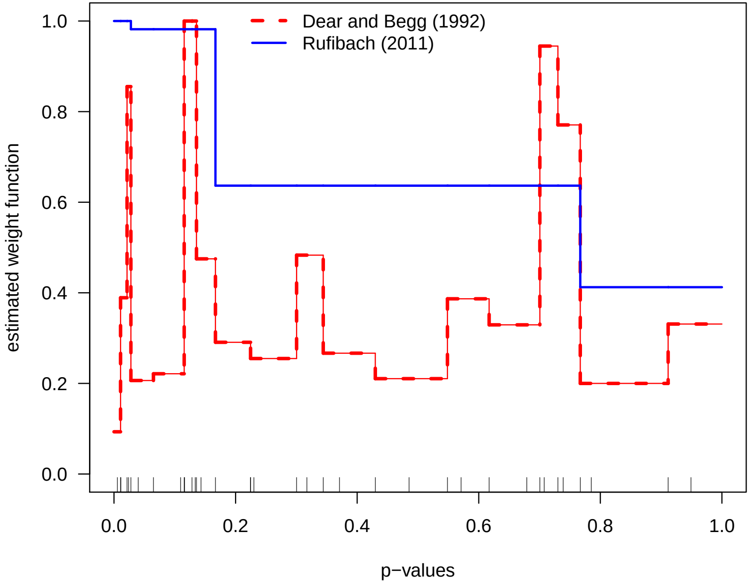
– Original publication: "failsafe N" analysis $\Rightarrow$ claimed absence of publication bias.

– Re-analysis by Copas and Shi (2000): "The possibility of publication bias cannot be ruled out altogether, and at least some publication bias is needed to explain the trend we found."

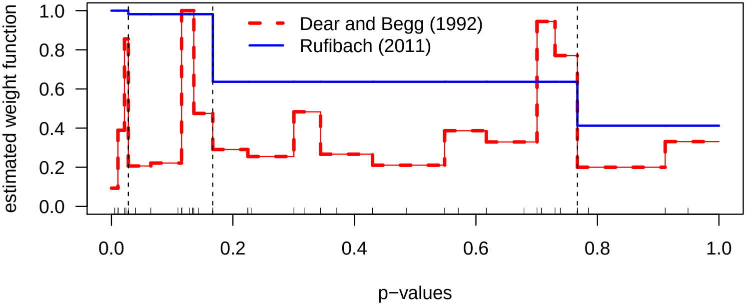
Environmental tobacco smoke data



Environmental tobacco smoke data

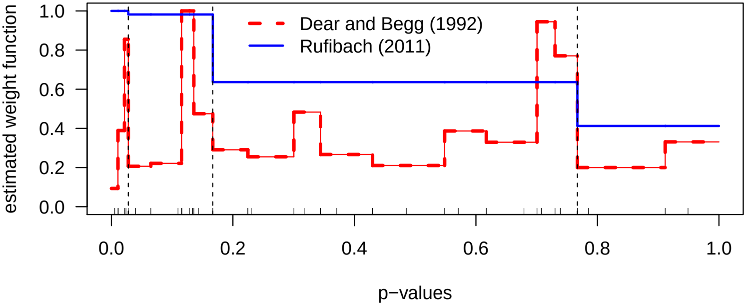


Environmental tobacco smoke data



- Unlike claimed in Dear and Begg (1992) publication bias not clear from their estimate.
- $p_{\text{tobacco}} = 0.13 \Rightarrow$ slight evidence against H_0 of no selection.
- Four distinct intervals: $[0, 0.03]$, $(0.03, 0.17]$, $(0.17, 0.77]$, $(0.77, 1.00]$ where w is constant.
- Sharp drops around "psychological barriers" 0.05 and 0.15.

Environmental tobacco smoke data



– Probability of selecting study with $p > 0.17$ only 64.8% compared to $p \leq 0.17$.

– Standard random effects model: $\widehat{\theta} = 0.21, [0.12, 0.31]$ and $\widehat{\sigma}^2 = 0.02$.

– Monotone selection model: $\widehat{\theta} = 0.17, [0.08, 0.26]$ and $\widehat{\sigma}^2 = 0.01$.

– Slight attenuation of effect, same conclusion.

Conclusions

- Propose to estimate monotone weight function in framework of Dear and Begg (1992).
- Provide algorithm, p-value to assess H_0 of no selection, adjusted estimates for θ and σ^2.
- R package available from CRAN: **selectMeta**.

Outlook

Future research plans:

- Implement estimation method of Sun and Woodroofe (1997). Adapt their theory to meta analysis.
- Analyze setup assuming monotonicity only: $\widehat{w}$ has to be a step function.
- Estimate w under other shape constraints, add smoothness.
- Make profile likelihood confidence interval for θ rigorous.

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Thank you for your attention.