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A likelihood-based sensitivity analysis for publication bias in meta-analysis

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The paper

- discusses the statistical difficulties of publication bias, essentially a problem of non-random sampling
- suggests a sensitivity analysis based on a sample selection model

1. Introduction
2. Example — a classic meta-analysis debacle (§2)
3. Selection models for publication bias (§2-4)
4. Example revisited (§5.1)
5. Discussion (§5.3 and 6)

The three stages of meta analysis:

- Literature search and systematic review of relevant studies
- Statistical summary of each study
  - Study estimates $\hat{\theta}_i$
  - Within-study variances σ_i^2
- Combining summary statistics into an overall inference
  - fixed effects model

$$\hat{\theta}_i \sim N(\theta, \sigma_i^2)$$

  - MLE $= \tilde{\theta} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}, \quad w_i = \frac{1}{\sigma_i^2}$
  - $\text{Var}\{\tilde{\theta}\} = \frac{1}{\sum w_i}$

Example: Yusuf *et al.* (1993)

Meta-analysis of 15 clinical trials on the effectiveness of intravenous magnesium in acute myocardial infarction

$$\theta = \log \frac{\mathrm{P}(\text{death} \mid \text{treatment})}{\mathrm{P}(\text{death} \mid \text{control})}$$

$$\text{Relative risk} = \exp\{\tilde{\theta}\} = .58(.46, .73)$$

$$\text{P-value} \approx 2 \times 10^{-6}$$

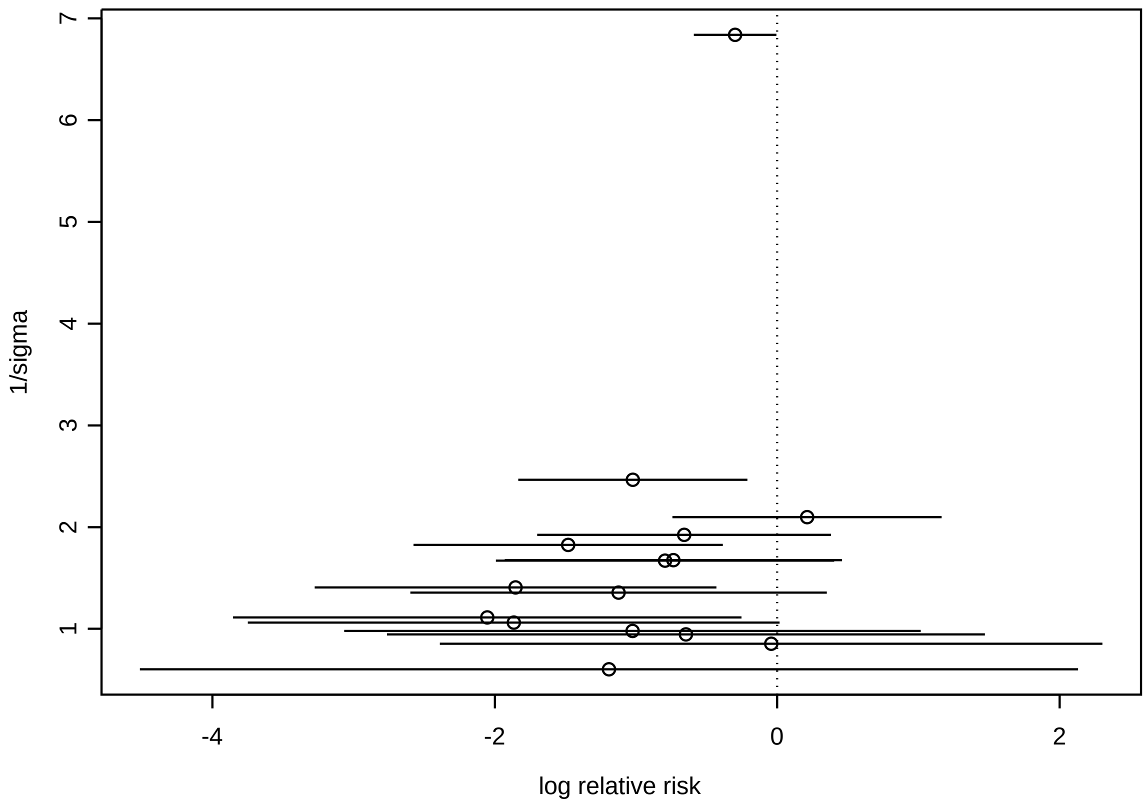
Published conclusion: "magnesium is an effective, safe, simple and inexpensive intervention that should be introduced into clinical practice without delay"

But then .....

ISIS-4 (1995), a very large multi-centre randomized clinical trial, reported mortality rates

- 2216/29011 (magnesium)
- 2103/29039 (control)
- Relative risk $= 1.06(0.99, 1.13)$
- P-value ≈ 0.09

Conclusion: there is **no significant difference**, magnesium may in fact be harmful.



Funnel plot for magnesium studies

To appear in a meta analysis a study has to be

- written up
- submitted
- accepted for publication
- found by the reviewer

Conjecture

Studies reporting a significant result are more likely to survive this selection process

⇒ the meta analysis will be biased

Selection model for publication bias

- There is a population of studies $(\hat{\theta}, \sigma^2)$ from which the n observed studies are a (non-random) selection
- The probability that a study is selected may depend on its t-statistic $y = \hat{\theta}/\sigma$

$$\Rightarrow \mathrm{P}(\text{selected} \mid \text{study with } \hat{\theta}, \sigma^2) = a(y)$$

for some function $a(y)$

Examples

$a(y) = 1$ (no bias)

$$a(y) = \begin{cases} 1 & \text{if} \quad y \leq k \\ 0 & \text{if} \quad y > k \end{cases} \quad \text{(negative bias)}$$

Under the null hypothesis $H_0 : \theta = 0$, for each study

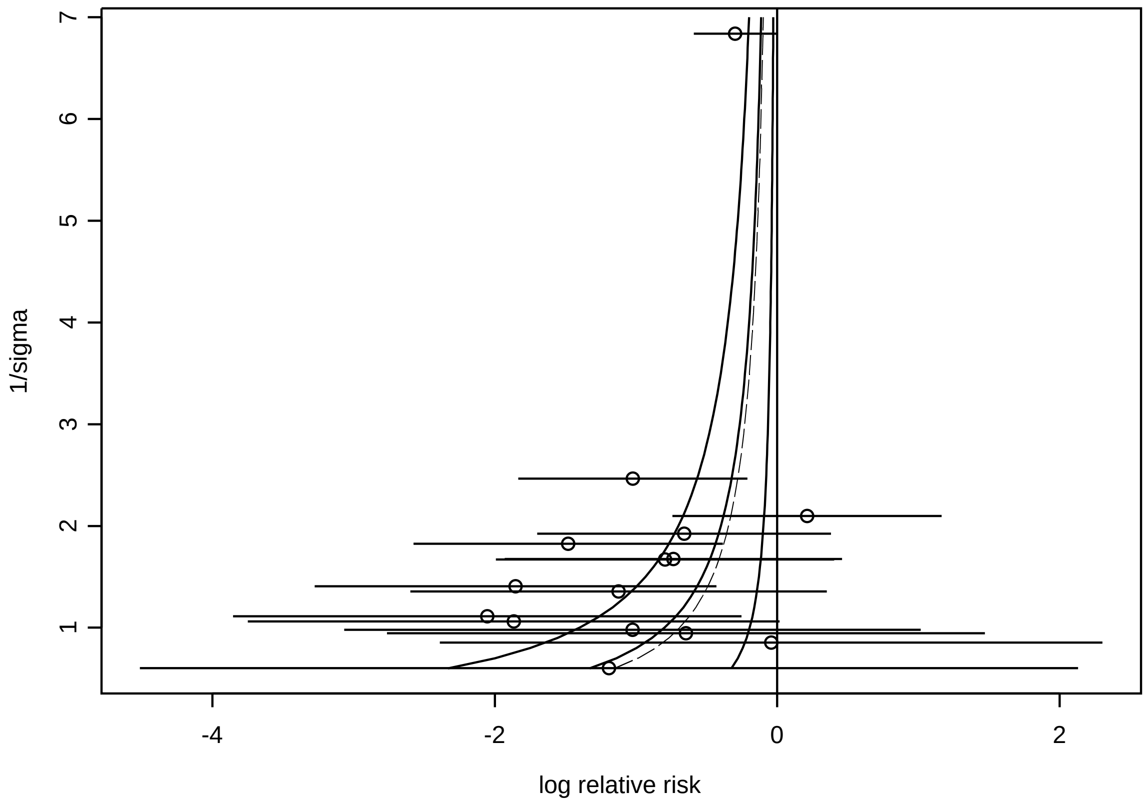
$$y = \frac{\hat{\theta}}{\sigma} \sim N(0,1)$$

Then under H_0

$$\begin{aligned} P(\text{selection}) &= p = \int a(y)\phi(y)dy \\ \mathrm{E}(y|\text{selection}) &= \mu = \frac{\int y a(y)\phi(y)dy}{p} \end{aligned}$$

So under H_0

$$\mathrm{E}(\hat{\theta}|\text{study selected}) = \mu\sigma$$



$\mathrm{E}(\hat{\theta}|\text{study selected}, \theta = 0)$ for different values of μ

Probit random effects selection model

$$\begin{aligned} \hat{\theta}|\sigma &\sim N(\theta, \sigma^2 + \tau^2) \\ P(\text{select}|\hat{\theta}, \sigma) &= \Phi(\alpha + \beta\hat{\theta}/\sigma) \end{aligned}$$

Then the paper shows that

- $p \approx \left(\frac{1}{n} \sum \left[\Phi \left\{ \frac{\alpha+\beta\theta/\sigma_i}{\{1+\beta^2(1+\tau^2/\sigma_i^2)\}^{\frac{1}{2}}} \right\} \right]^{-1} \right)^{-1}$
- Log likelihood is

$$L = -\frac{1}{2} \sum \log(\tau^2 + \sigma_i^2) - \frac{1}{2} \sum \frac{(\hat{\theta}_i - \theta)^2}{\tau^2 + \sigma_i^2}$$

$$+ \sum \log \Phi(\alpha + \beta\hat{\theta}_i/\sigma_i) - \sum \log \Phi \left\{ \frac{\alpha + \beta\theta/\sigma_i}{\{1 + \beta^2(1 + \tau^2/\sigma_i^2)\}^{\frac{1}{2}}} \right\}$$

Statistical difficulty: *the available data (funnel plot) usually gives very little information about the value of p (the overall proportion of studies which are selected).*

Sensitivity analysis. Fix the value of p and find the corresponding maximum likelihood estimates of the other parameters. Then

- Plot the confidence interval for θ against p.
- Superimpose the fitted values $\mathrm{E}(\hat{\theta}|\mathrm{select}, \sigma, p)$ on the funnel plot for a selection of values of p

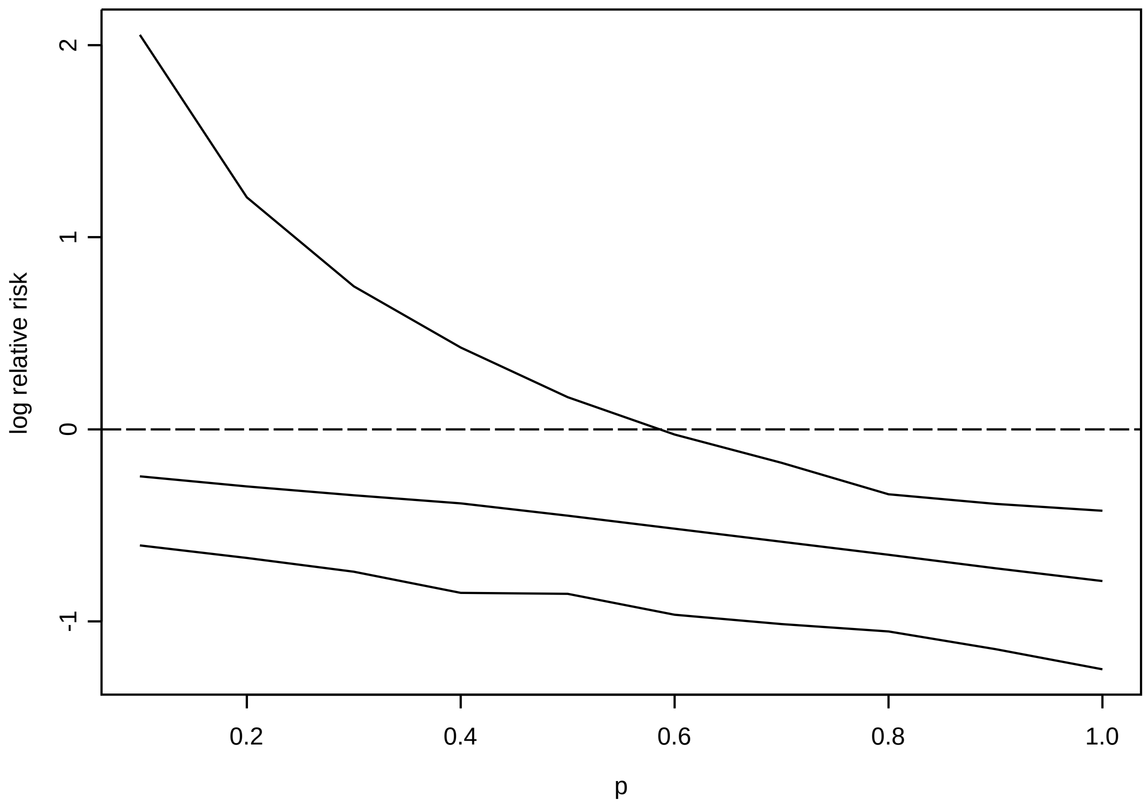
Sensitivity analysis

For any given value of p we can get

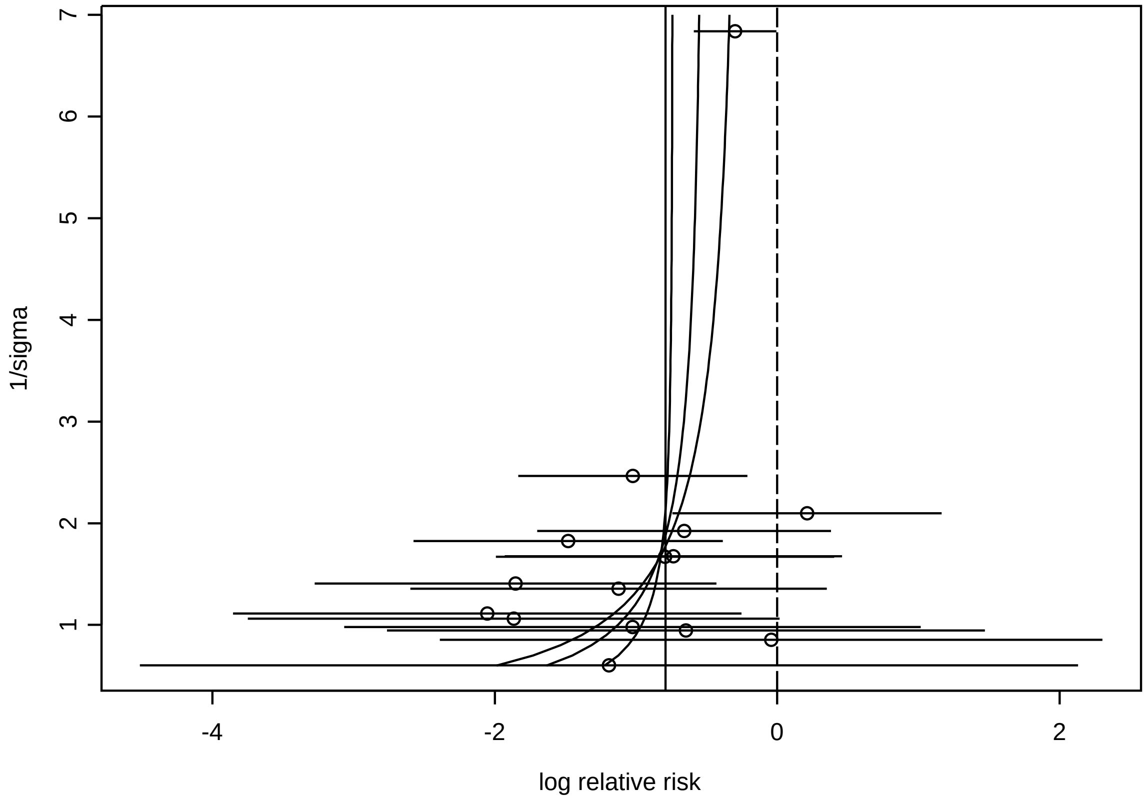
- MLE $\hat{\theta}_p$
- Confidence limits $\{\hat{\theta}_p^{(L)}, \hat{\theta}_p^{(U)}\}$ based on $2\{\max L_p - L_p(\theta)\} \sim \chi_1^2$
- Fitted values: estimate of $\mathrm{E}(\hat{\theta}|\text{select}, \sigma, p) =$

$$\theta + \beta\sigma \frac{1 + \tau^2/\sigma^2}{\sqrt{1 + \beta^2(1 + \tau^2/\sigma^2)}} \lambda\left(\frac{\alpha + \beta\theta/\sigma}{\sqrt{1 + \beta^2(1 + \tau^2/\sigma^2)}}\right)$$

($\lambda =$ Mills ratio ϕ/Φ)



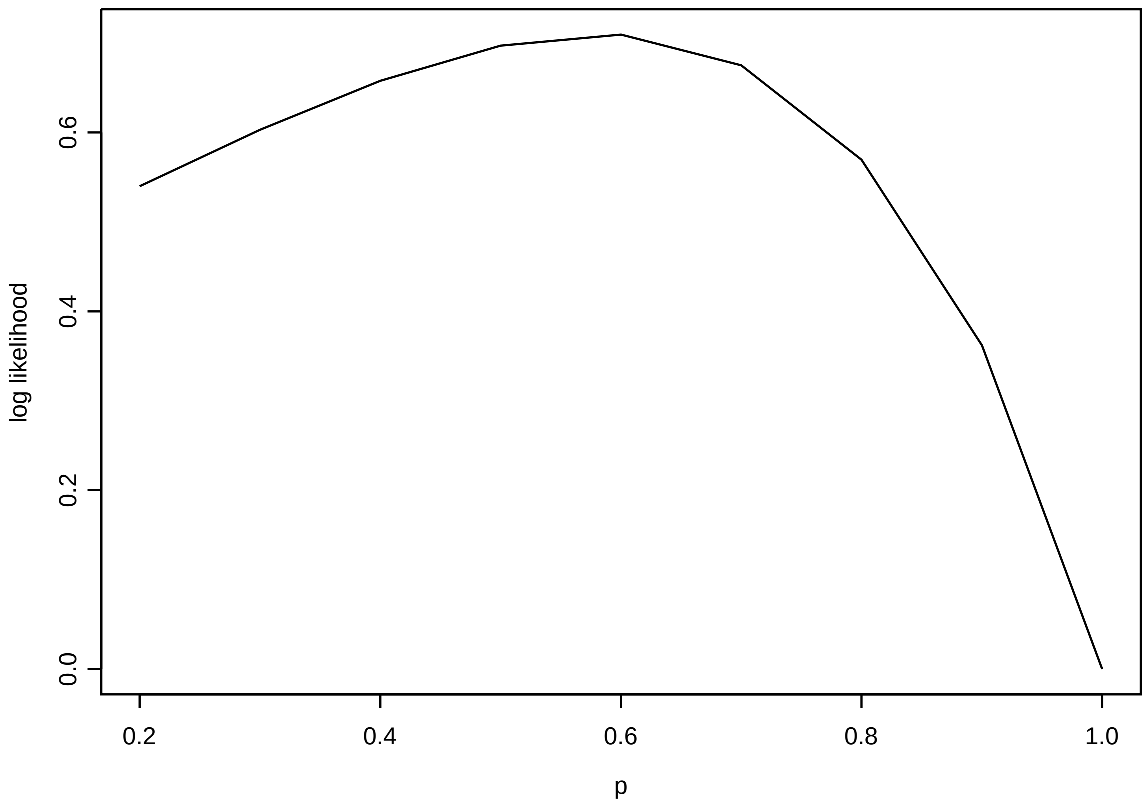
Estimates and confidence intervals for the magnesium meta-analysis



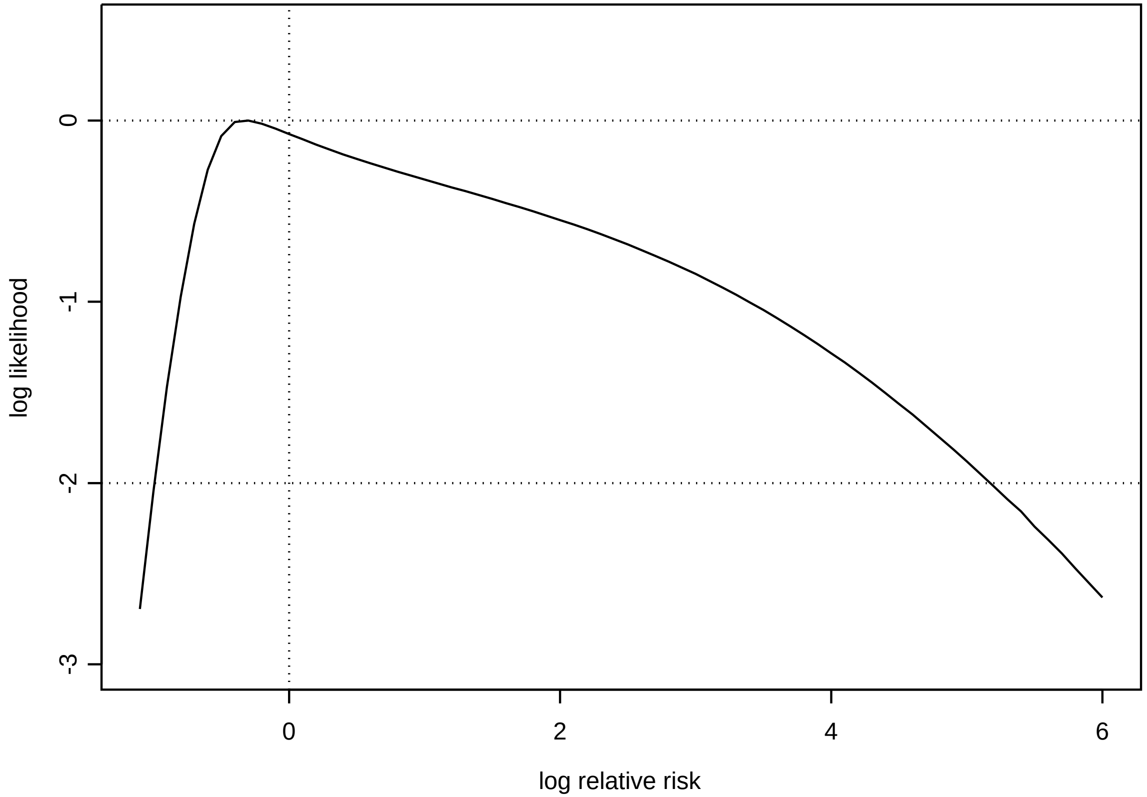
Funnel plot and fitted values for $p = 1, 0.9, 0.5, 0.1$

Discussion — sensitivity analysis versus bias correction

- why don't we estimate all the parameters and hence find the MLE of p?
- why don't we use one of the selection models in the literature to find the MLE of θ?



Likelihood for p for the second example in the paper



Application of Preston et al. (2004) to the magnesium meta-analysis: the profile likelihood for θ

General comments

- many meta analyses suffer from publication bias, but this is almost always ignored
- publication bias usually means that the treatment effect is exaggerated
- it is impossible to adjust for publication bias unless we make un-testable assumptions
- ‘selection by significance’ $\Rightarrow a(y)$
- the sensitivity analysis conditions on an interpretable parameter
- sensitivity analyses tend to be more robust to modelling assumptions than bias correction methods

In the magnesium example

- standard meta-analysis gives a strongly significant (and strongly misleading) result
- there is evidence of a ‘small study effect’: smaller studies tend to give stronger treatment effects than the one reasonably larger study
- the selection model explains the funnel plot trend (e.g. fitted values of θ when $p = 0.5$ all lie within the individual confidence intervals)
- the treatment effect is no longer significant if $p < 0.6$
- the sensitivity analysis suggests that the evidence remains significant provided there are less than about 9 missing studies, but at a much more modest level of significance

References

ISIS-4 Collaborative Group (1995) A randomized factorial trial assessing early oral captopril, oral mononitrate and intravenous magnesium sulphate in 58,050 patients with suspected myocardial infarction. *Lancet*, **345**, 669-685.

Preston, C., Ashby, D. and Smyth, R. (2004) Adjusting for publication bias: modelling the selection process. *J. Evaluation in Clinical Practice*, **10**, 313-322.

Yusuf S, Koon T, Woods K (1993) Intravenuos magnesium in acute myocardial infarction: an effective, safe, simple and inexpensive intervention. *Circulation*, **87**, 2043-2046.