Meta analysis and the curse of publication bias

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

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An early example of a controlled trial in the treatment of juvenile offenders:

Klein *et al. (J Consult. Clin. Psychol. 1977,* **3***, 469-474)*

	success	failure	%
structured counselling	34	12	74
control	29	27	52

$$\hat{\theta} = \pm\sqrt{\chi^2/n} = 0.227$$

$$\hat{\theta} \sim N(\theta, \sigma^2) \;\;,\;\; \sigma^2 = 1/n = 1/102$$

$$t = \hat{\theta}/\sigma = 2.29 \;\;,\;\; P = \Phi(-2.27) < 5\%$$

Conclusion : new treatment is effective in reducing recidivism

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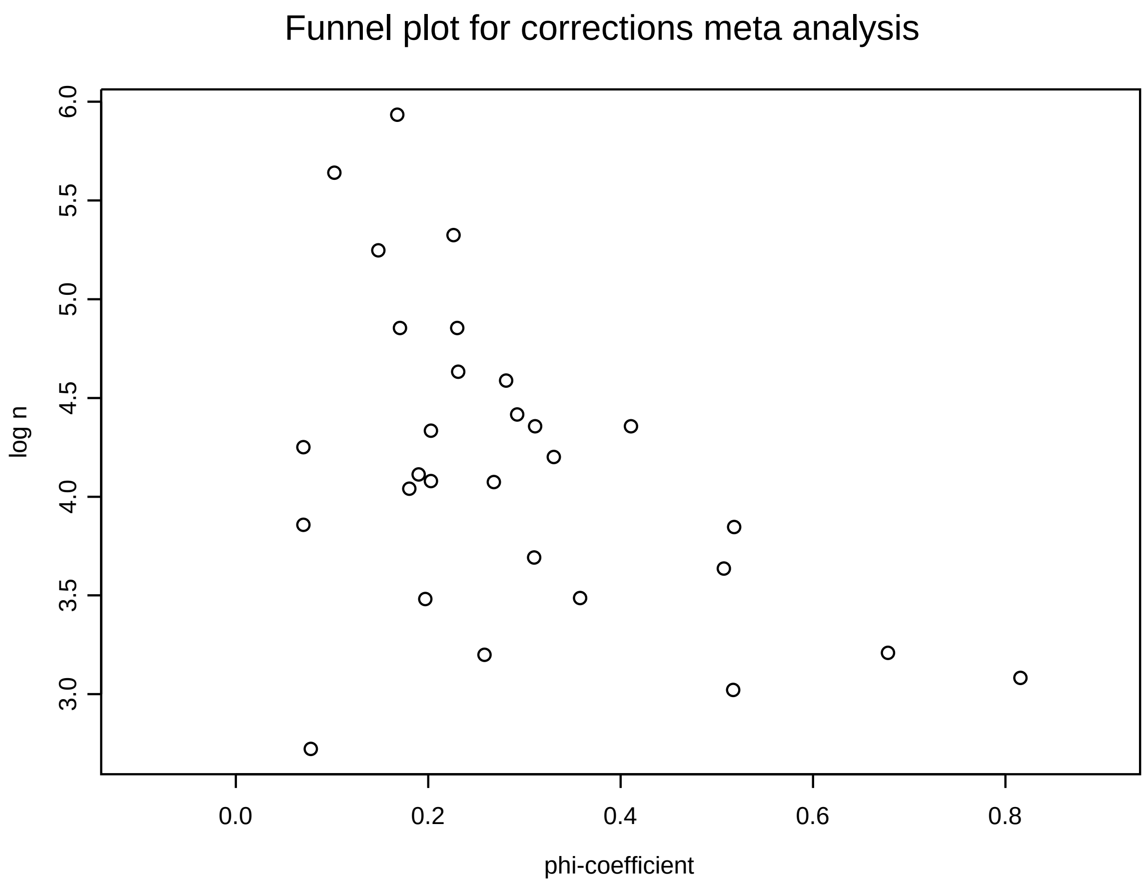
One of the first systematic reviews of corrections studies:

Andrews *et al. (Criminology, 1990,* **28**, *369-429)*



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Corrections meta analysis:

k studies with data $(\hat{\theta}_i, \sigma_i)$ for $i = 1, 2, \cdots, k$

Conventional (fixed effects) meta analysis estimate is

$$\hat{\hat{\theta}} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}\ , \ \text{Var}(\hat{\hat{\theta}}) = \frac{1}{\sum w_i}\ , \ w_i = \frac{1}{\sigma_i^2}$$

$$k = 29\ , \ \hat{\hat{\theta}} = 0.225\ , \ SD = 0.0198$$

cf. the Klein study: $\hat{\theta} = 0.227\ , \ SD = 0.0990$

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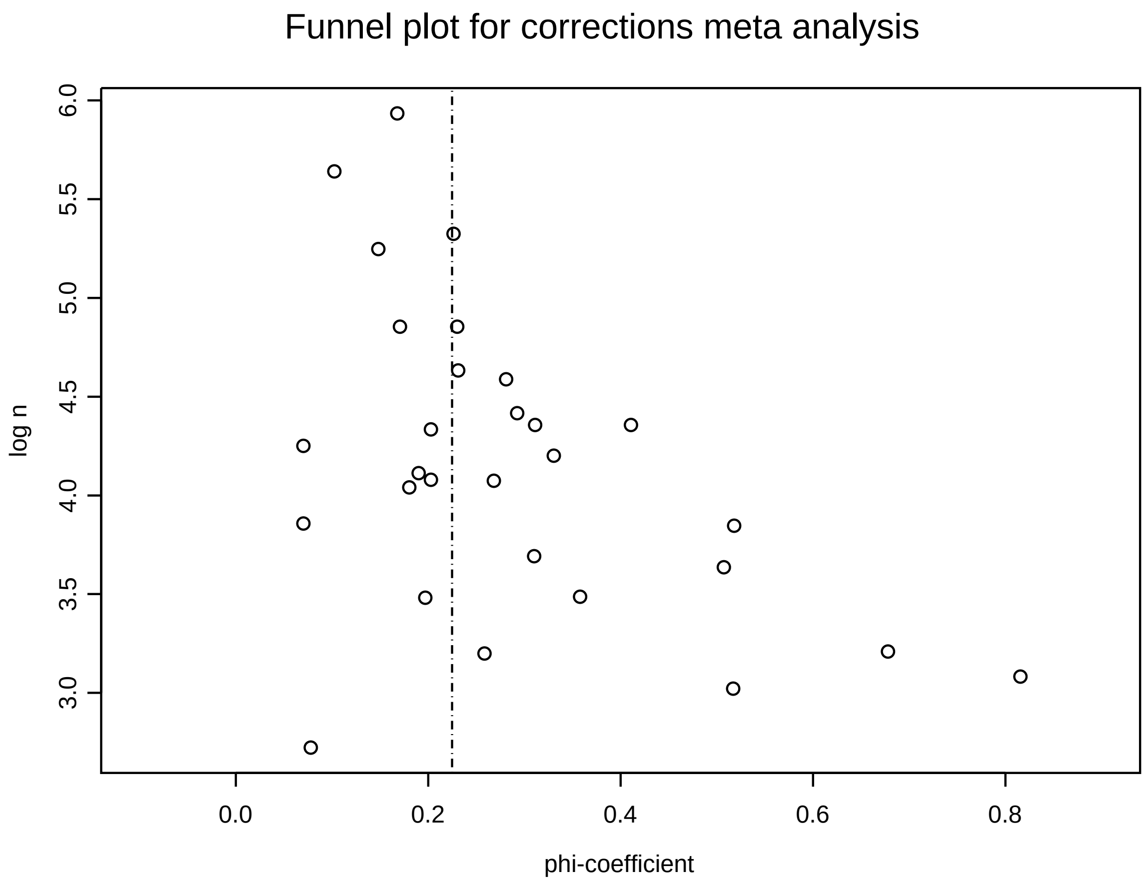
Funnel plot for corrections meta analysis
log n
6.0
5.5
5.0
4.5
4.0
3.5
3.0
0.0
0.2
0.4
0.6
0.8
phi-coefficient

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Second example:

What is the effect of passive smoking on the risk of lung cancer?

Meta analysis of 37 case-control studies quoted by *SCOTH* (Hackshaw *et al., BMJ 1997,* **315***, 980-988*)

$$\hat{\hat{\theta}} = \text{estimated log relative risk} = 0.184\ ,\ SD = 0.037$$

$$\Rightarrow \text{risk increase} \in (12\%, 30\%)$$

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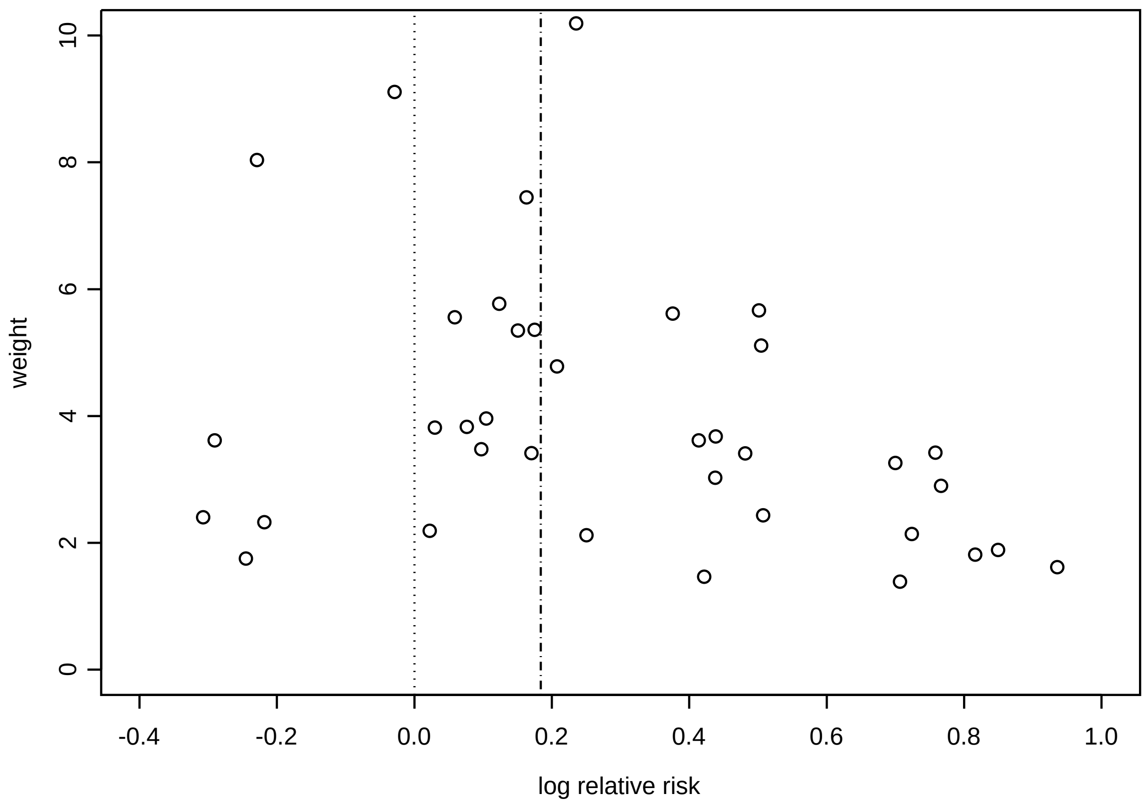
Funnel plot for smoking meta analysis



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Third example:

Yusuf *et al.* (1993)

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

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

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

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

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

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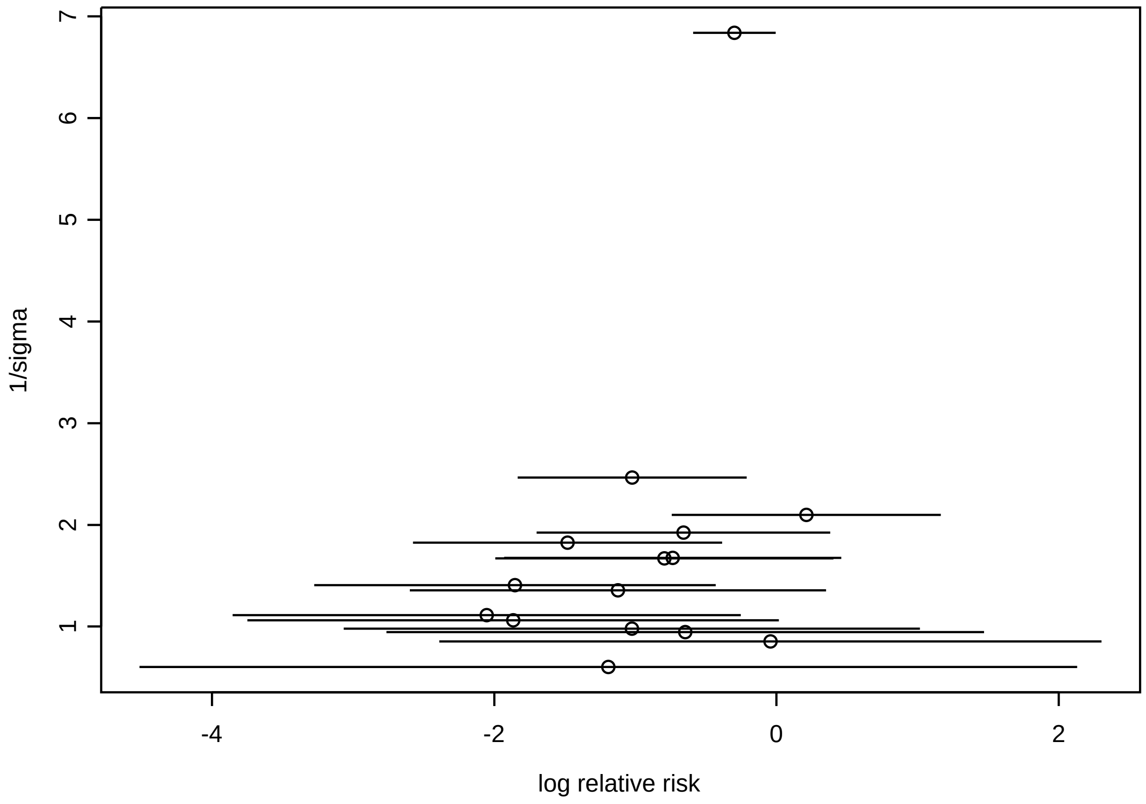
This was soon contradicted by ISIS-4 (1995), a very large multi-centre randomized clinical trial which gave mortality rates

- 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



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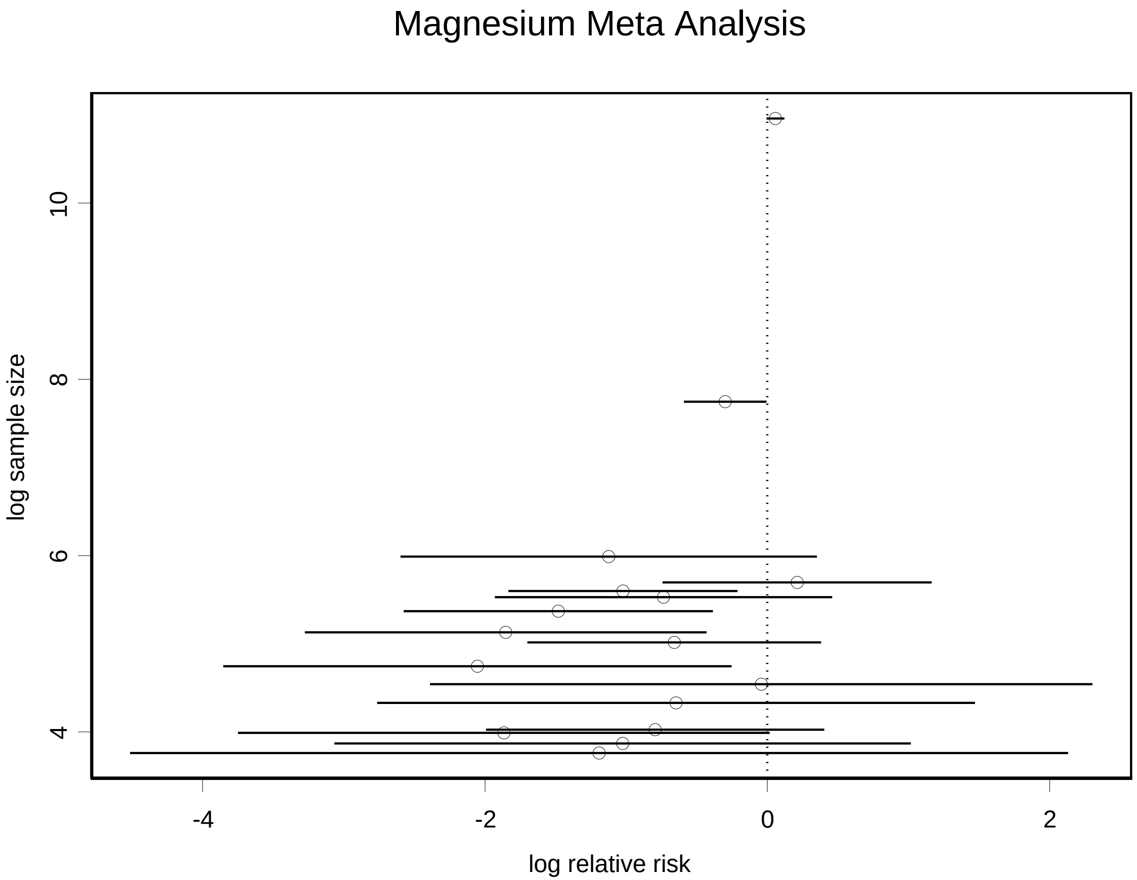
Magnesium Meta Analysis
log sample size
10
8
6
4
-4
-2
0
2
log relative risk

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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

$\Rightarrow$ the meta analysis will be biased

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Probit selection model

$$
\begin{aligned}
\hat{\theta}|\sigma &\sim N(\theta, \sigma^2) \\
P(\text{select}|\hat{\theta}, \sigma) &= \Phi(\alpha + \beta\hat{\theta}/\sigma) \\
P(\text{select}|\sigma) &= \Phi\left\{\frac{\alpha + \beta\theta/\sigma}{(1+\beta^2)^{\frac{1}{2}}}\right\} \\
P(\sigma|\text{selection}) &= \frac{P(\text{select}|\sigma)P(\sigma)}{P(\text{select})} \\
P(\sigma) &= \frac{P(\text{select})P(\sigma|\text{select})}{P(\text{select}|\sigma)} \\
\int P(\sigma)d\sigma &= P(\text{select})\int \frac{1}{P(\text{select}|\sigma)} P(\sigma|\text{select})d\sigma
\end{aligned}
$$

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$$
\begin{aligned}
P(\textsf{select}) &= \left[\mathsf{E}_\sigma\{P(\textsf{select}|\sigma)^{-1}|\textsf{select}\}\right]^{-1} \\
&\approx \left(\frac{1}{n}\sum\left[\Phi\left\{\frac{\alpha+\beta\theta/\sigma_i}{(1+\beta^2)^{\frac{1}{2}}}\right\}\right]^{-1}\right)^{-1} \\
&= p(\alpha,\beta,\theta)
\end{aligned}
$$

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Log likelihood function is

$$L(\alpha,\beta,\theta) = -\frac{1}{2}\sum\frac{(\hat{\theta}_i-\theta)^2}{\sigma_i^2}$$

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

For a sensitivity analysis we can fix

$$p(\alpha,\beta,\theta) = p$$

and find the conditional likelihood function over the two parameters (β,θ)

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Sensitivity analysis

For any given value of p we can get the MLE $\hat{\theta}_p$ and the associated confidence limits $\{\theta_p^{(L)}, \theta_p^{(U)}\}$

Then

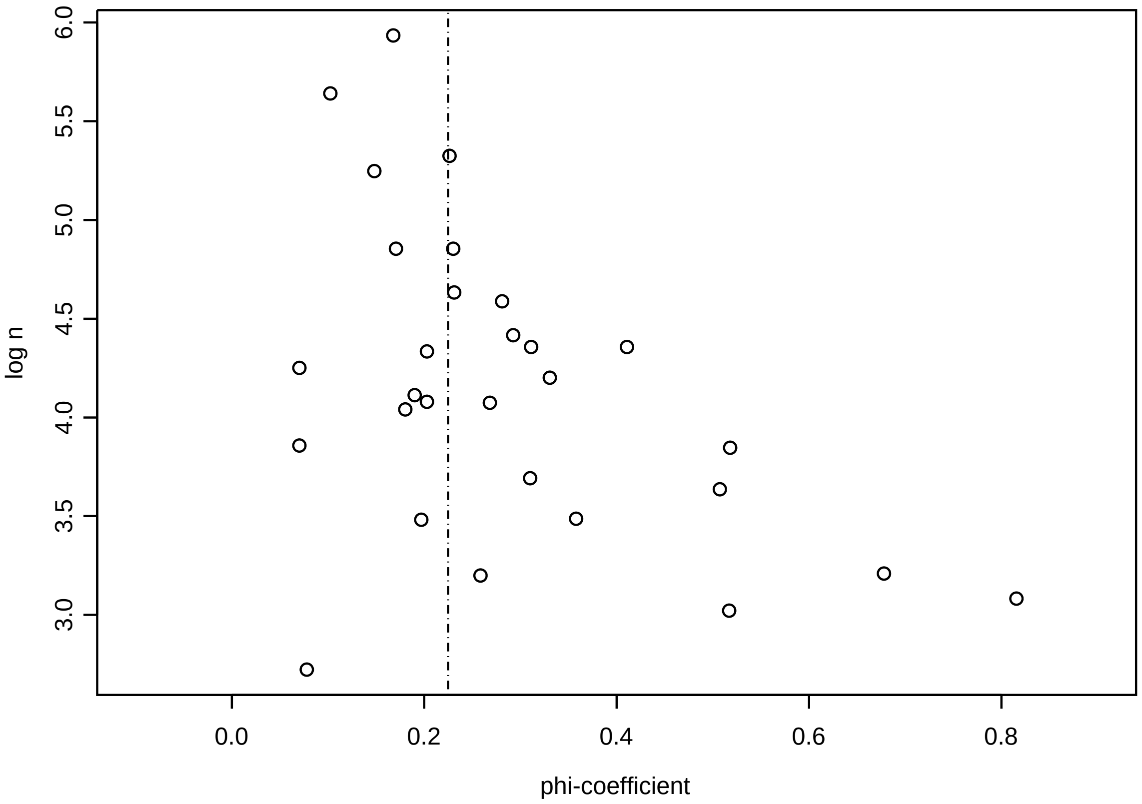
- $p = 1 \Rightarrow$ standard analysis (no bias)
- $p < 1 \Rightarrow$ allowing for selection bias

As p decreases from 1 we are adjusting for increasing bias

Note

In practice we find that the profile likelihood for p is surprisingly flat (and non-robust), so it is virtually impossible to estimate p (i.e. to estimate the number of unpublished studies).

Funnel plot for corrections meta analysis



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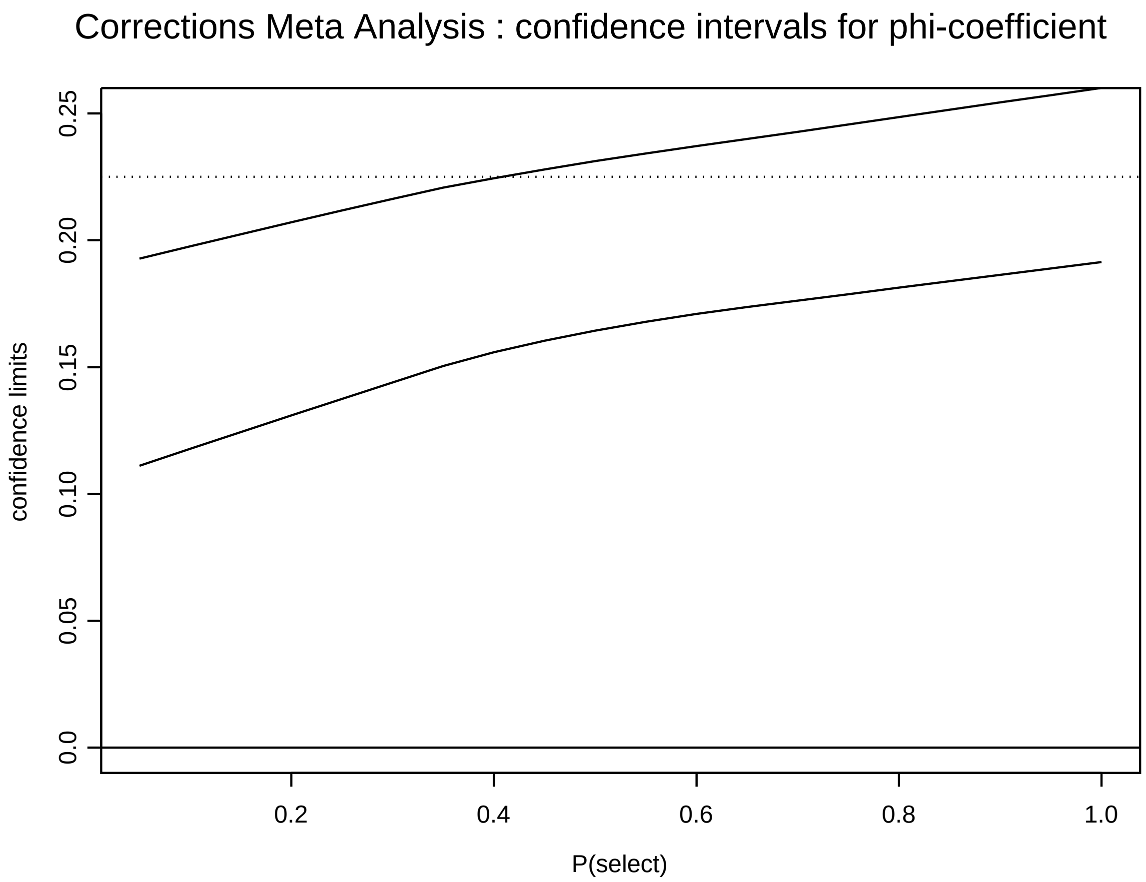
Corrections Meta Analysis : confidence intervals for phi-coefficient
0.0
0.05
0.10
0.15
0.20
0.25
confidence limits
0.2
0.4
0.6
0.8
1.0
P(select)

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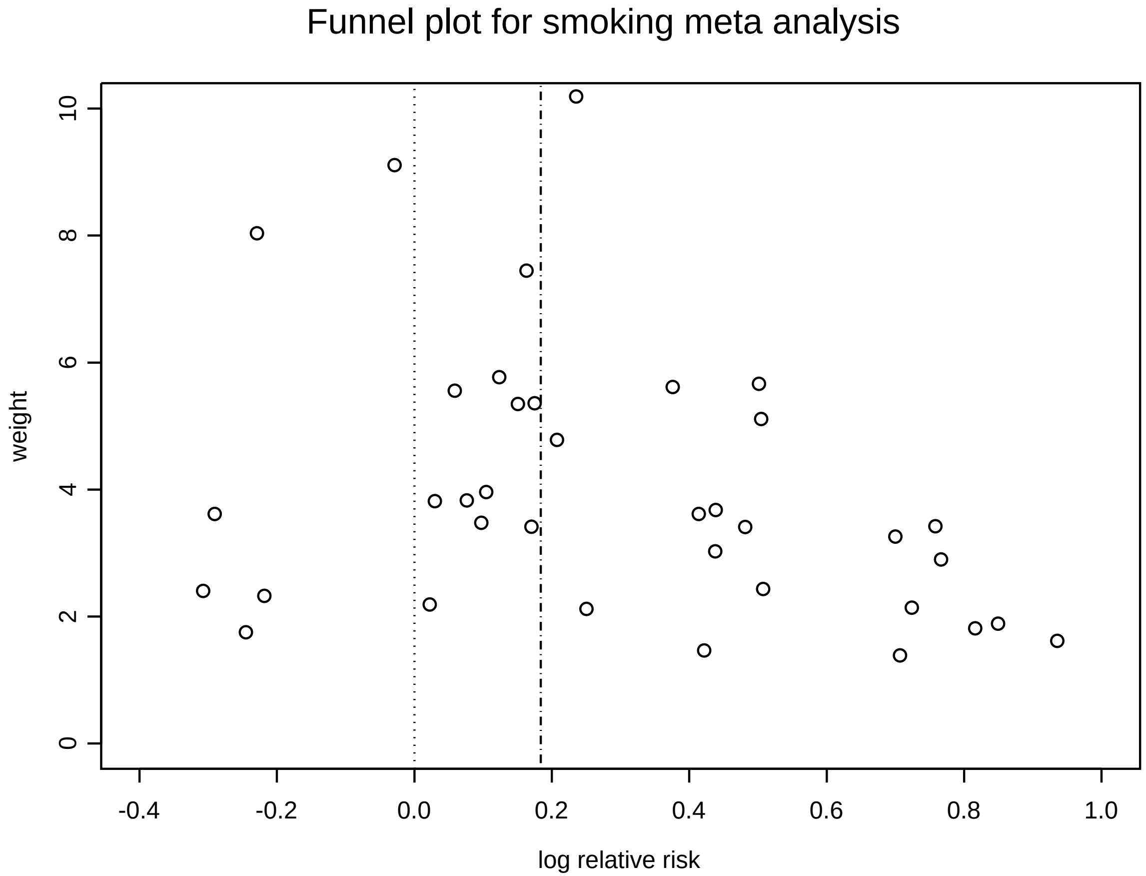
Funnel plot for smoking meta analysis
weight
log relative risk
0
2
4
6
8
10
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0

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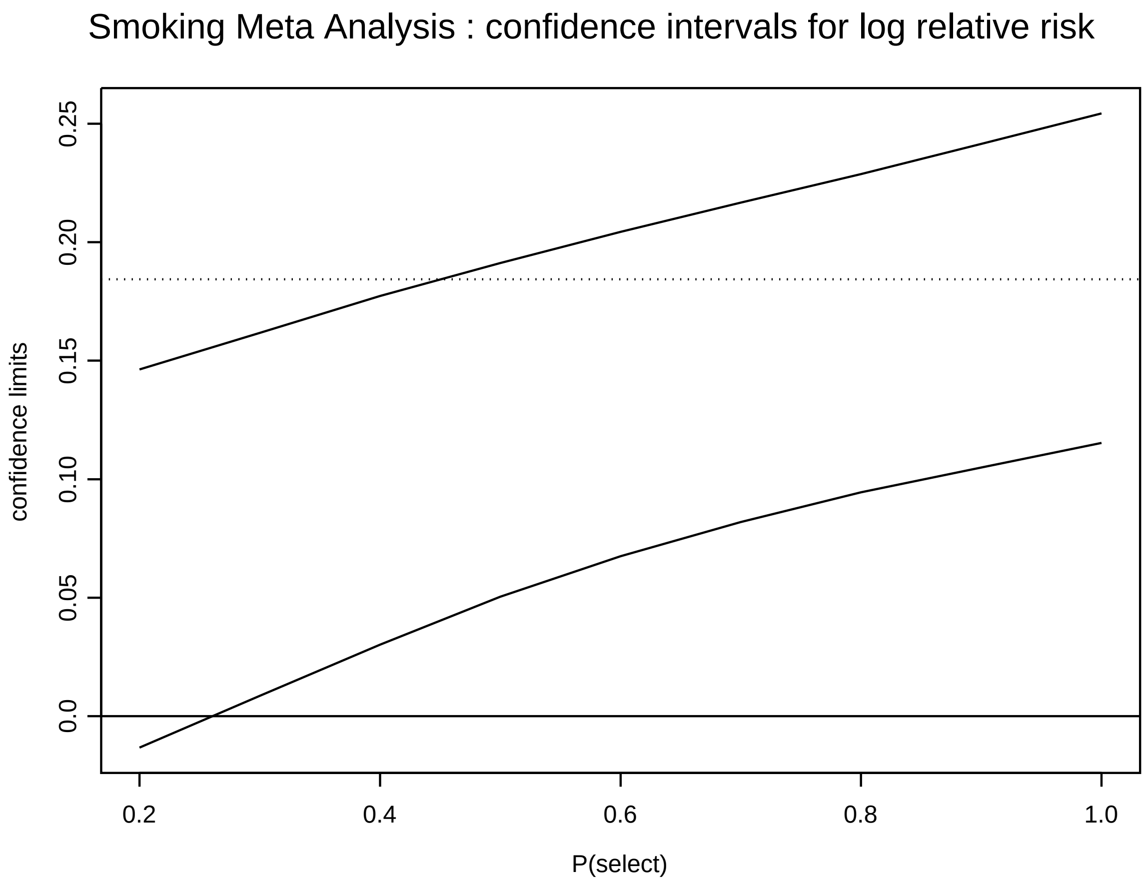
Smoking Meta Analysis : confidence intervals for log relative risk
confidence limits
0.0
0.05
0.10
0.15
0.20
0.25
0.2
0.4
0.6
0.8
1.0
P(select)

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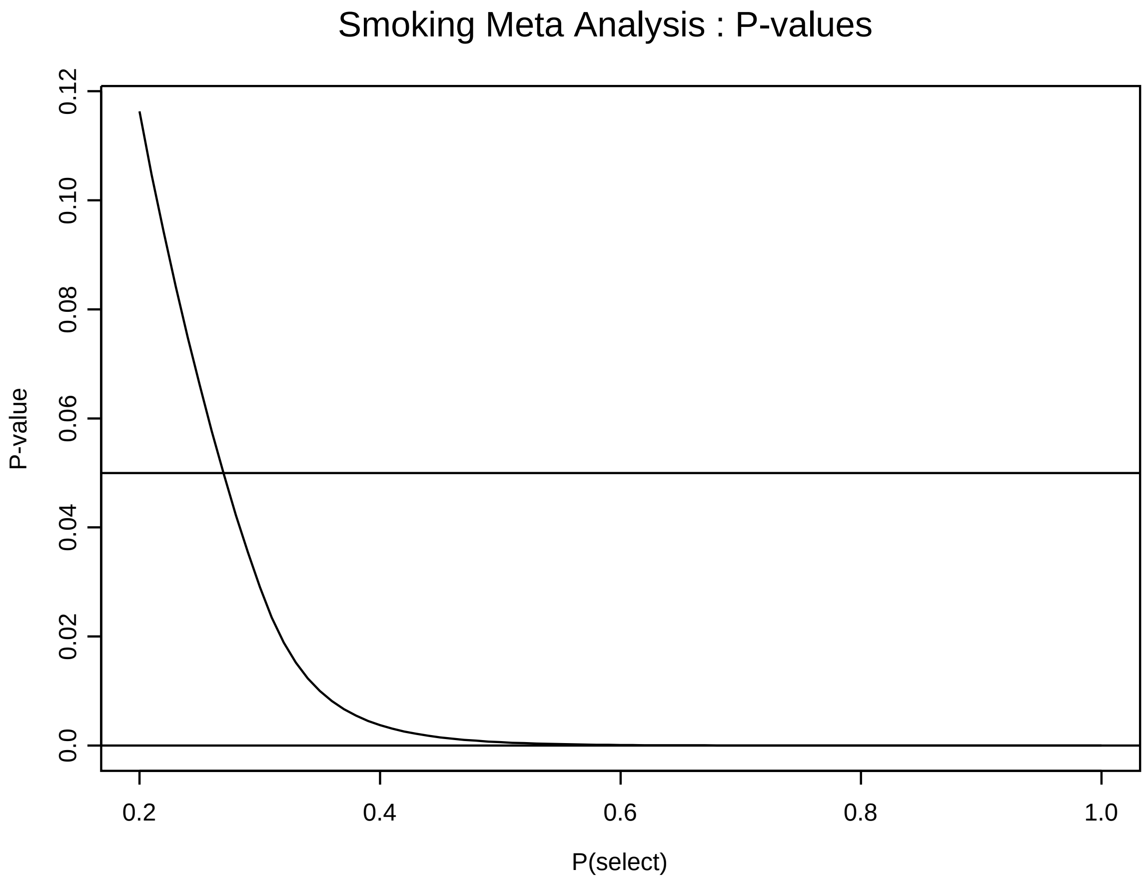

Conclusion: risk may be overestimated, but still significant unless there are more than about 75 ”unpublished” studies

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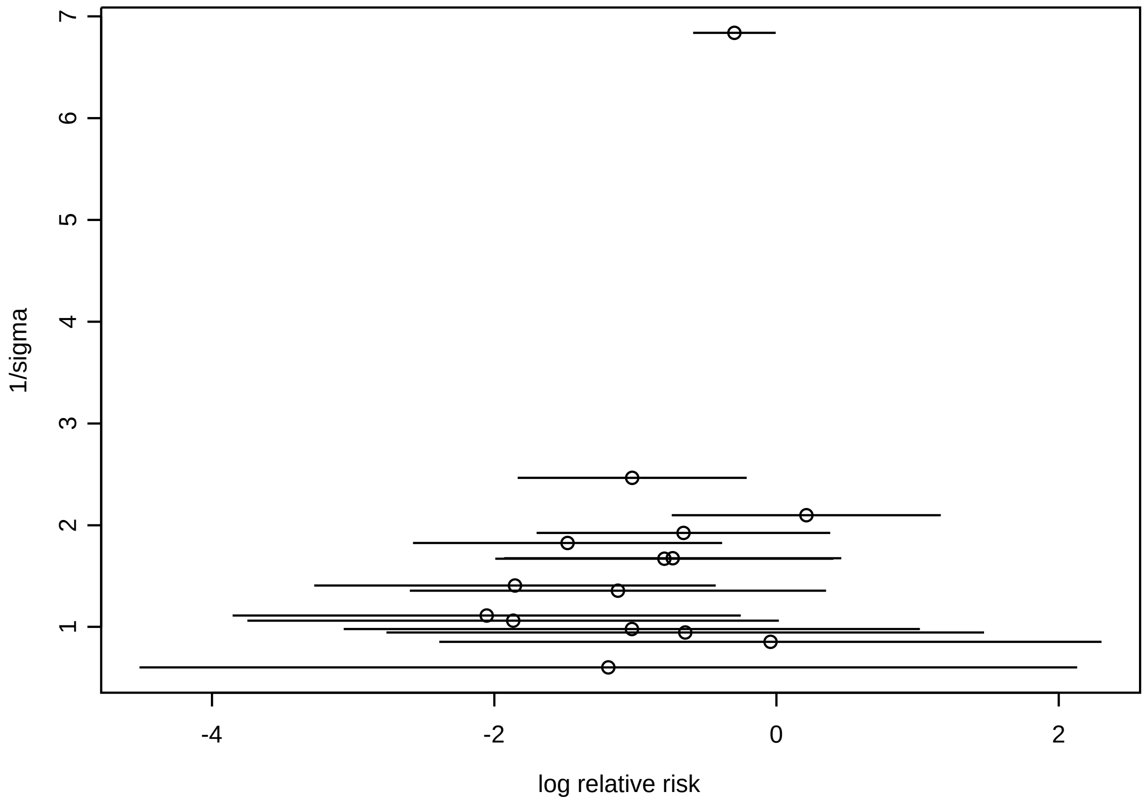
Funnel plot for magnesium studies



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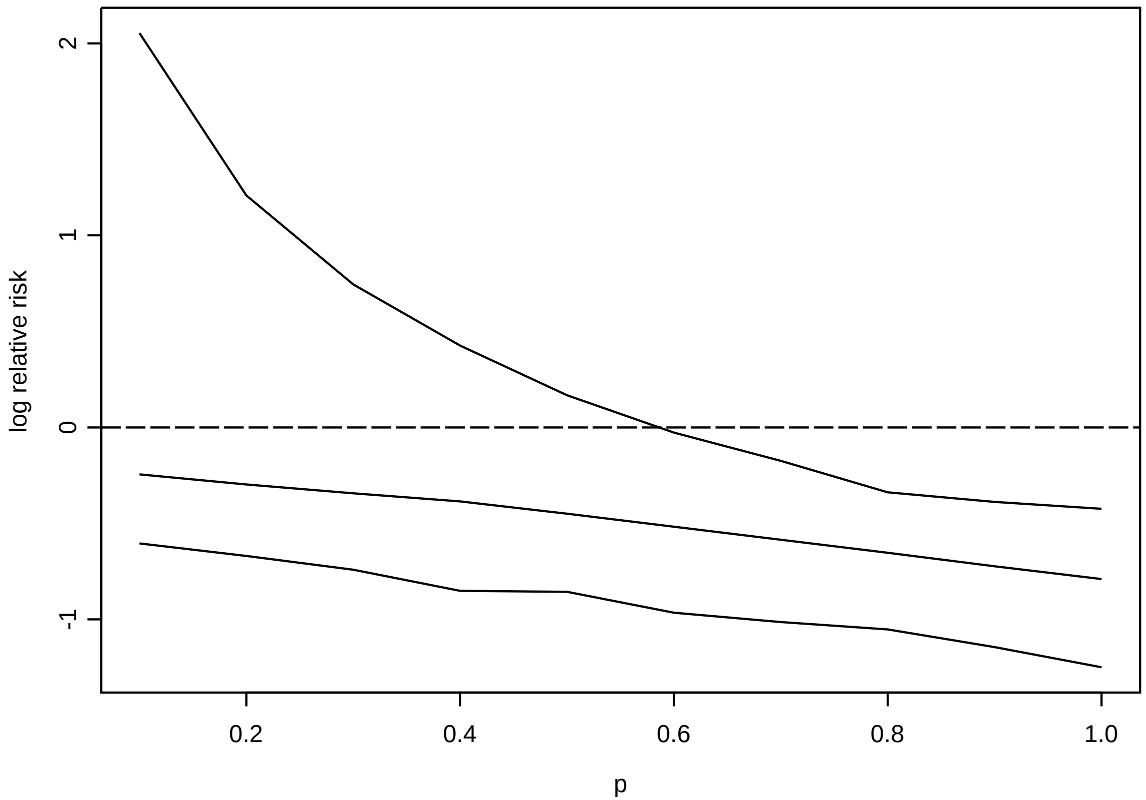

confidence intervals for magnesium studies

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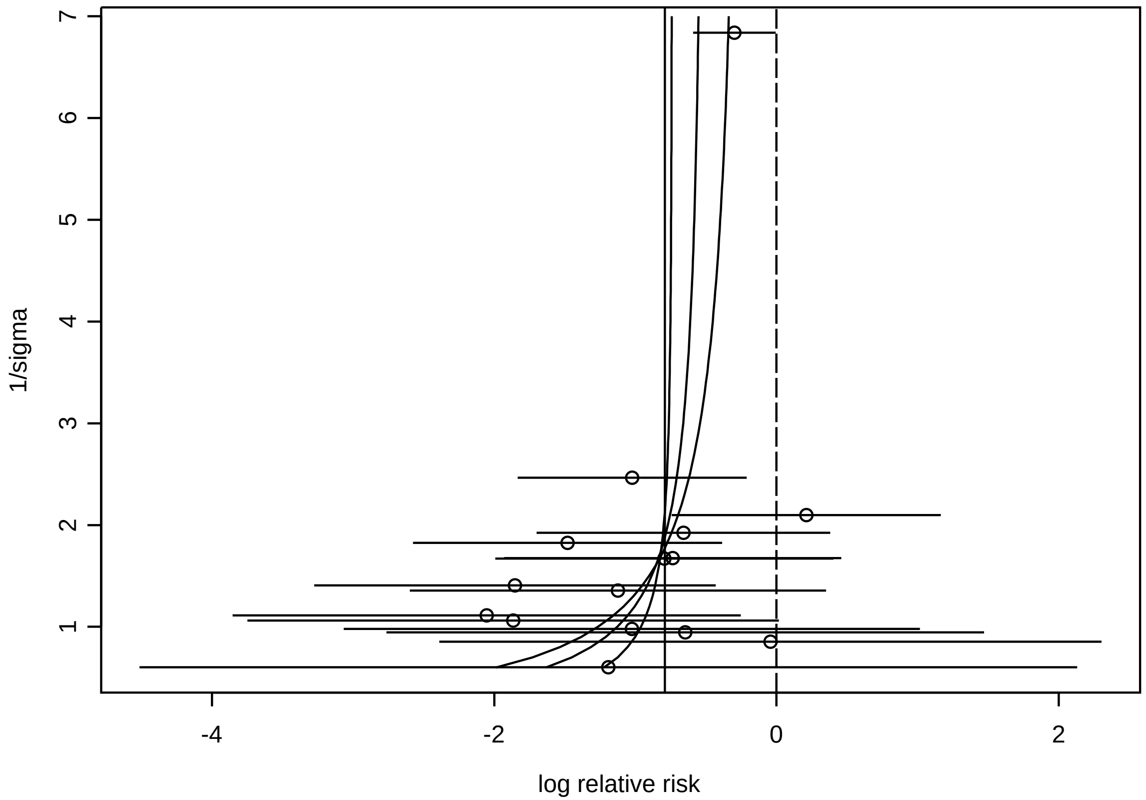

MLE's of E$(\hat{\theta}|$select$, p)$ for $p = 1, 0.9, 0.5, 0.1$

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General comments

- many meta analyses suffer from publication bias, but this is almost always ignored
- publication bias usually means that treatment effects are exaggerated and that significance is exaggerated
- skewness in the funnel plot is a tell-tale sign of publication bias — 40% of all meta analyses show this?
- it is impossible to adjust for publication bias unless we make some unverifiable assumptions about the selection mechanism
- eg the ‘selection by significance’ approach of Copas (*Applied Stats*, 2013)
- There is no fully convincing way of correcting for publication bias — sensitivity analysis and not bias correction in the usual sense

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- Fixed effects meta analysis may be OK, but usually we use random effects models by adding a random effects term to the likelihood

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References

Andrews DA *et al.* (1990). Does correctional treatment work?: a clinically relevant and psychologically informed meta-analysis. *Criminology*, **28**, 369-429.

Copas JB (1999) What works?: selectivity models and meta-analysis. *J Roy Stats Soc, A*, **162**, 95-109.

Copas JB and Shi JQ (2000) Reanalysis of epidemiological evidence on lung cancer and passive smoking. *British Medical Journal*, **7232**, 417-418.

Copas JB (2013) A likelihood-based sensitivity analysis for publication bias in meta-analysis. *Applied Stats*, bf 62. 47-66.

Hackshaw, AK *et al.* (1997) The accumulated evidence on lung cancer and environmental tobacco smoke. *British Medical Journal*, **315**, 980-8.

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.

Thompson, S and Pockock, SJ (1991) Can meta analysis be trusted? *Brit Med J*, **303**, 1499-1503.

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

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