Meta-analysis in Stata: history, progress and prospects

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Outline

- Systematic reviews and meta-analysis
- Meta-analysis in Stata
- Bias in meta-analysis
- Stata commands to investigate bias
- Present situation
- The Future……

Systematic reviews

- Systematic approach to minimize biases and random errors
- Always includes materials and methods section
- May include meta-analysis

Chalmers and Altman 1994

Meta-analysis

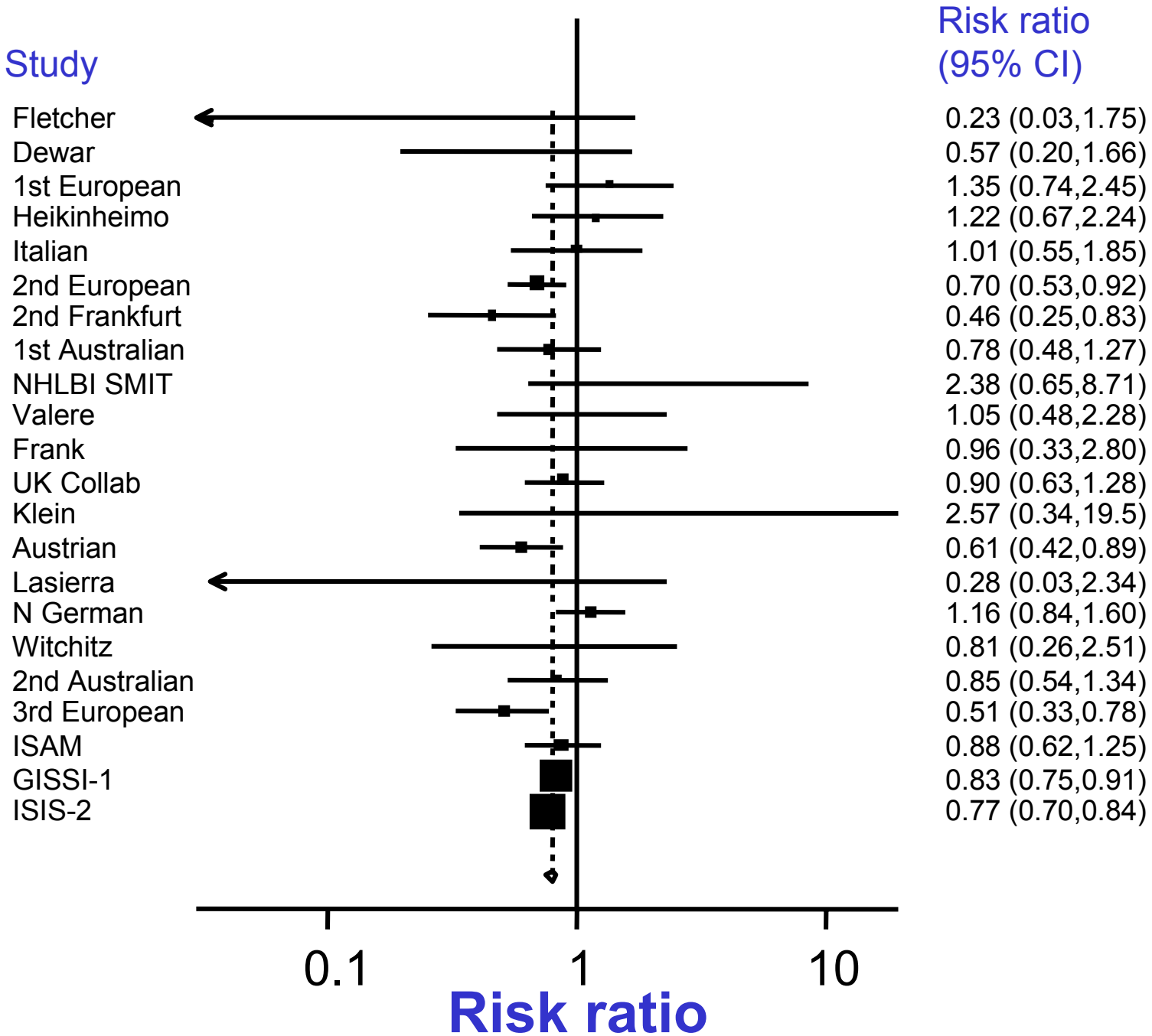
- A statistical analysis which combines the results of several independent studies considered by the analyst to be ‘combinable’

Huque 1988

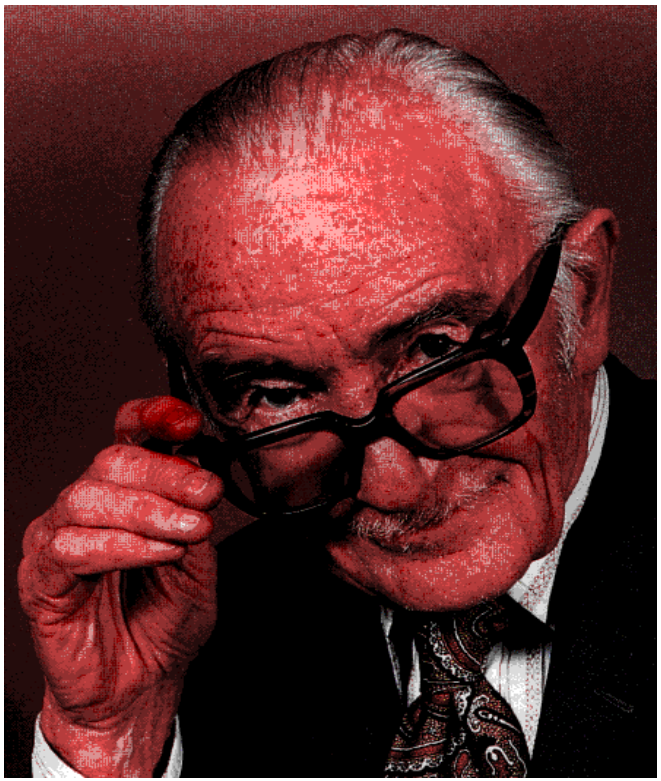
Streptokinase (thrombolytic therapy)

- Simple idea if we can dissolve the blood clot causing acute myocardial infarction then we can save lives
- However – possible serious side effects
- First trial - 1959

Trial	Trial name	Pub year	Streptokinase group		Control group	
			Deaths	Total	Deaths	Total
1	Fletcher	1959	1	12	4	11
2	Dewar	1963	4	21	7	21
3	1st European	1969	20	83	15	84
4	Heikinheimo	1971	22	219	17	207
5	Italian	1971	19	164	18	157
6	2nd European	1971	69	373	94	357
7	2nd Frankfurt	1973	13	102	29	104
8	1st Australian	1973	26	264	32	253
9	NHLBI SMIT	1974	7	53	3	54
10	Valere	1975	11	49	9	42
11	Frank	1975	6	55	6	53
12	UK Collaborative	1976	48	302	52	293
13	Klein	1976	4	14	1	9
14	Austrian	1977	37	352	65	376
15	Lasierra	1977	1	13	3	11
16	N German	1977	63	249	51	234
17	Witchitz	1977	5	32	5	26
18	2nd Australian	1977	25	112	31	118
19	3rd European	1977	25	156	50	159
20	ISAM	1986	54	859	63	882
21	GISSI-1	1986	628	5860	758	5852
22	ISIS-2	1988	791	8592	1029	8595


Study
Risk ratio
(95% CI)
Fletcher
Dewar
1st European
Heikinheimo
Italian
2nd European
2nd Frankfurt
1st Australian
NHLBI SMIT
Valere
Frank
UK Collab
Klein
Austrian
Lasierra
N German
Witchitz
2nd Australian
3rd European
ISAM
GISSI-1
ISIS-2
0.23 (0.03,1.75)
0.57 (0.20,1.66)
1.35 (0.74,2.45)
1.22 (0.67,2.24)
1.01 (0.55,1.85)
0.70 (0.53,0.92)
0.46 (0.25,0.83)
0.78 (0.48,1.27)
2.38 (0.65,8.71)
1.05 (0.48,2.28)
0.96 (0.33,2.80)
0.90 (0.63,1.28)
2.57 (0.34,19.5)
0.61 (0.42,0.89)
0.28 (0.03,2.34)
1.16 (0.84,1.60)
0.81 (0.26,2.51)
0.85 (0.54,1.34)
0.51 (0.33,0.78)
0.88 (0.62,1.25)
0.83 (0.75,0.91)
0.77 (0.70,0.84)
0.1
1
10
Risk ratio

Archie Cochrane (1979)



“ It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials ”

The Cochrane Collaboration

- "An international organization that aims to help people make well informed decisions about health care by preparing, maintaining and ensuring the accessibility of systematic reviews of the effects of health care interventions"
  - Ten principles: collaboration, building on the enthusiasm of individuals, avoiding duplication, minimizing bias, keeping up to date, striving for relevance, promoting access, ensuring quality, continuity, enabling wide participation
- To date, more than 3000 reviews or protocols for reviews have been published, and a database of more than 375,000 trials has been accumulated
- See www.cochrane.org

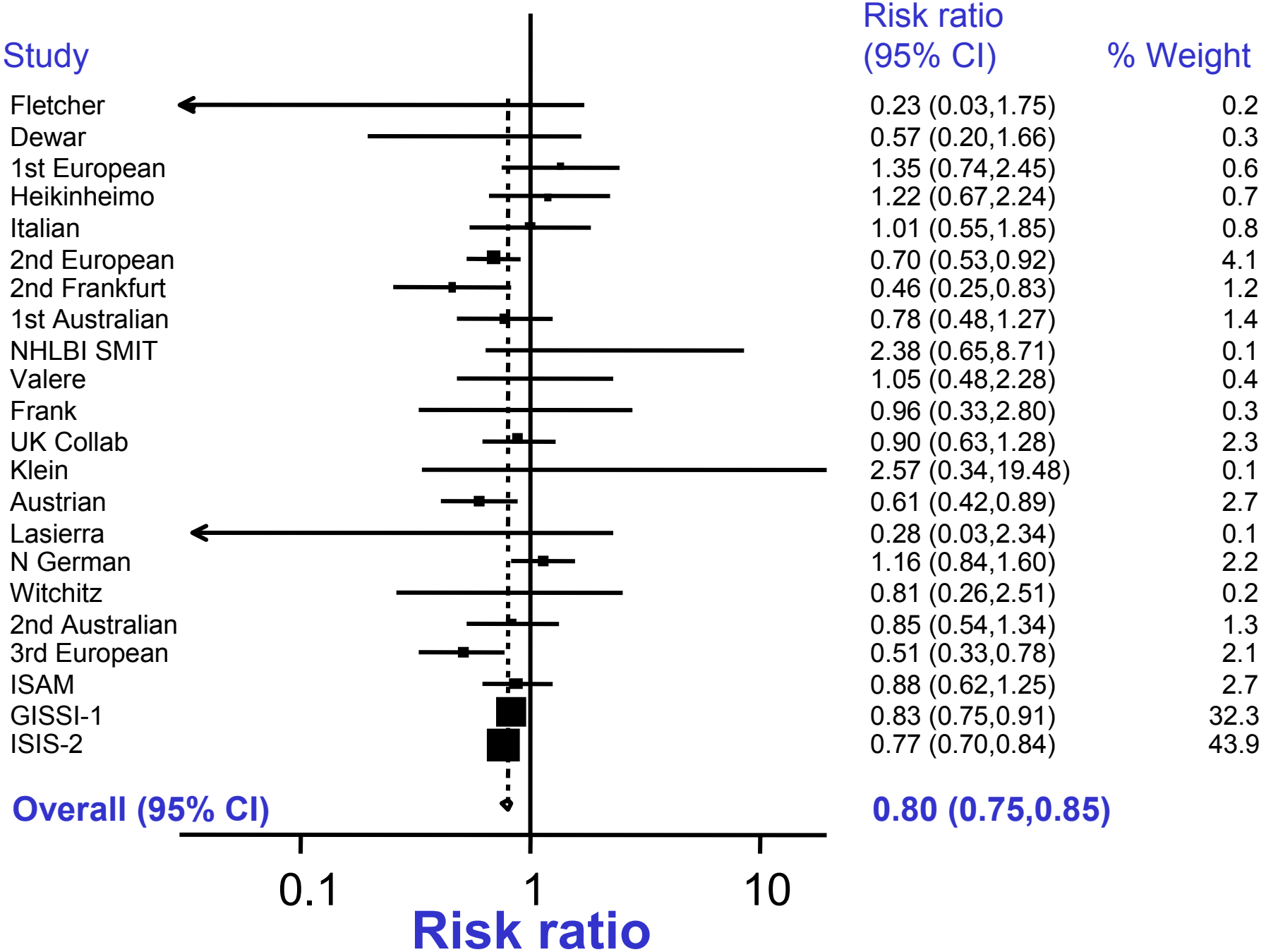
THE COCHRANE COLLABORATION®

Fixed (common) effect meta-analysis

- Summary (pooled) $\log(\mathrm{OR}_F) = \dfrac{\sum w_i \times \log \mathrm{OR}_i}{\sum w_i}$
- This assumes that the effect of diuretics is the same (Fixed) in each study
- Individuals are only compared with others in the same study
- It seems sensible to give more weight to the bigger studies

Fixed-effect meta-analysis (2)

- The choice of weight that minimises the variability of the summary log OR is $w_i = 1/v_i$, where is v_i is the variance (variance=s.e.^{2}) of the log odds ratio in study i
- The variance of the pooled log OR is $\dfrac{1}{\sum_{i=1}^{k} w_i}$
- This can be used to calculate confidence intervals, a z statistic and hence a P value for the pooled log odds ratio
- These are converted to an odds ratio with 95% C.I.


Study
Risk ratio (95% CI)
% Weight
Fletcher 0.23 (0.03,1.75) 0.2
Dewar 0.57 (0.20,1.66) 0.3
1st European 1.35 (0.74,2.45) 0.6
Heikinheimo 1.22 (0.67,2.24) 0.7
Italian 1.01 (0.55,1.85) 0.8
2nd European 0.70 (0.53,0.92) 4.1
2nd Frankfurt 0.46 (0.25,0.83) 1.2
1st Australian 0.78 (0.48,1.27) 1.4
NHLBI SMIT 2.38 (0.65,8.71) 0.1
Valere 1.05 (0.48,2.28) 0.4
Frank 0.96 (0.33,2.80) 0.3
UK Collab 0.90 (0.63,1.28) 2.3
Klein 2.57 (0.34,19.48) 0.1
Austrian 0.61 (0.42,0.89) 2.7
Lasierra 0.28 (0.03,2.34) 0.1
N German 1.16 (0.84,1.60) 2.2
Witchitz 0.81 (0.26,2.51) 0.2
2nd Australian 0.85 (0.54,1.34) 1.3
3rd European 0.51 (0.33,0.78) 2.1
ISAM 0.88 (0.62,1.25) 2.7
GISSI-1 0.83 (0.75,0.91) 32.3
ISIS-2 0.77 (0.70,0.84) 43.9
Overall (95% CI) 0.80 (0.75,0.85)
0.1
1
10
Risk ratio

Forest plots

- Boxes draw attention to the studies with the greatest weight
- Box area is proportional to the weight for the individual study
- The diamond (and broken vertical line) represents the overall summary estimate, with confidence interval given by its width
- Unbroken vertical line is at the null value (1)

Random-effects meta-analysis (1)

- We suppose the *true* treatment effect in each study is randomly, normally distributed between studies, with variance τ^2 ("tau-squared")
- Estimate the between-study variance τ^2, and use this to modify the weights used to calculate the summary estimate.
- The usual estimate of τ^2 is called the DerSimonian and Laird estimate.

Random-effects meta-analysis (2)

Random-effects estimate: $\log \mathrm{OR}_R = \dfrac{\sum_{i=1}^{k} w_i^* \log \mathrm{OR}_i}{\sum_{i=1}^{k} w_i^*}$

where $w_i^* = \dfrac{1}{v_i + \hat{\tau}^2}$

The variance of the random-effects summary OR is: $\dfrac{1}{\sum_{i=1}^{k} w_i^*}$

Back to 1996….

- Bill Clinton always in the news….
- In the UK, Labour look unbeatable….
- England's stars crash out of the European football championship….
- JS gets his first laptop

Stata 5 (1996)

- A revolutionary advance, based on the Windows environment!
- Host of new facilities, including……
- A new graphics programming command (**`gph`**)

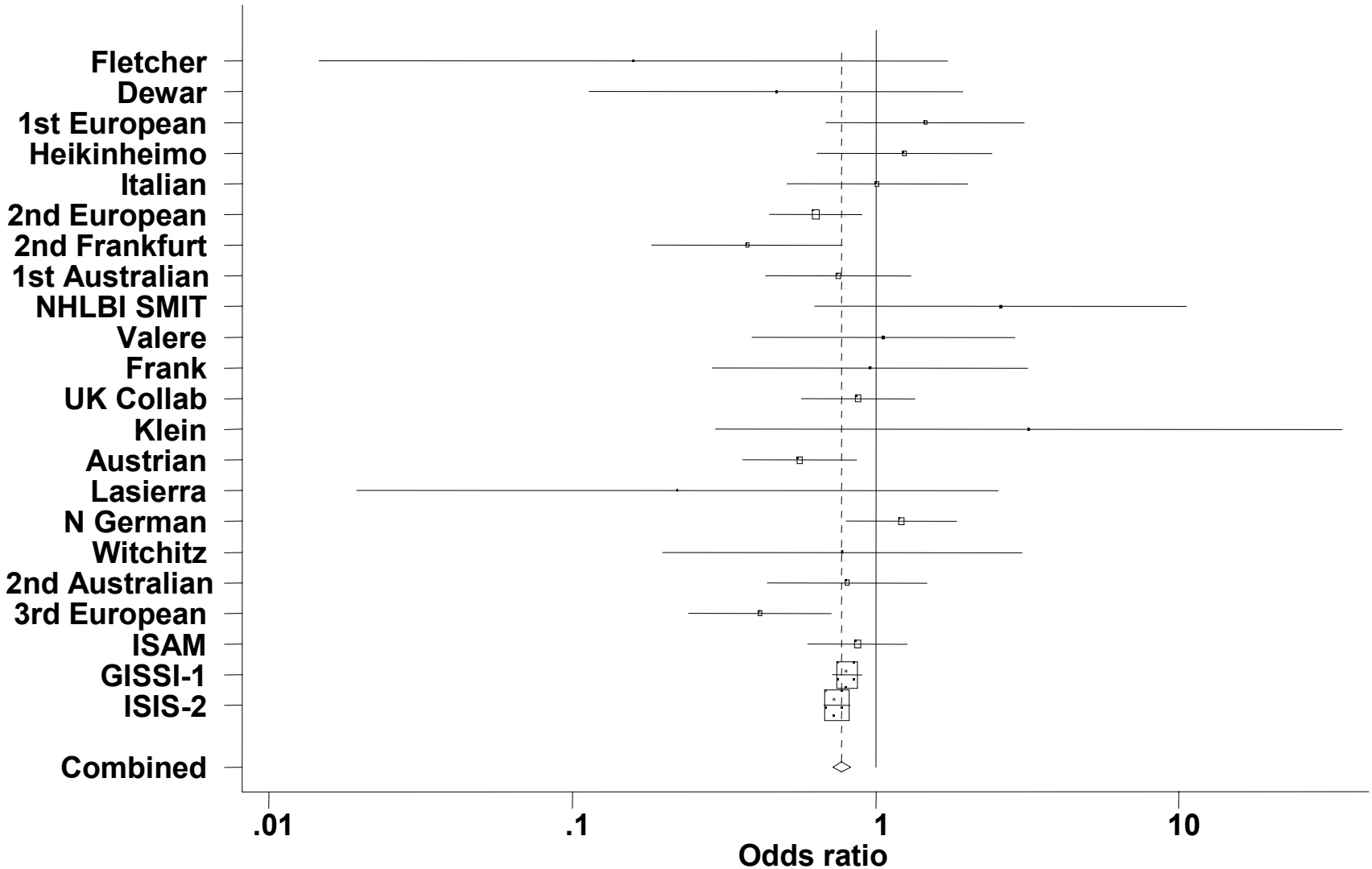
The `meta` command (Sharp and Sterne)

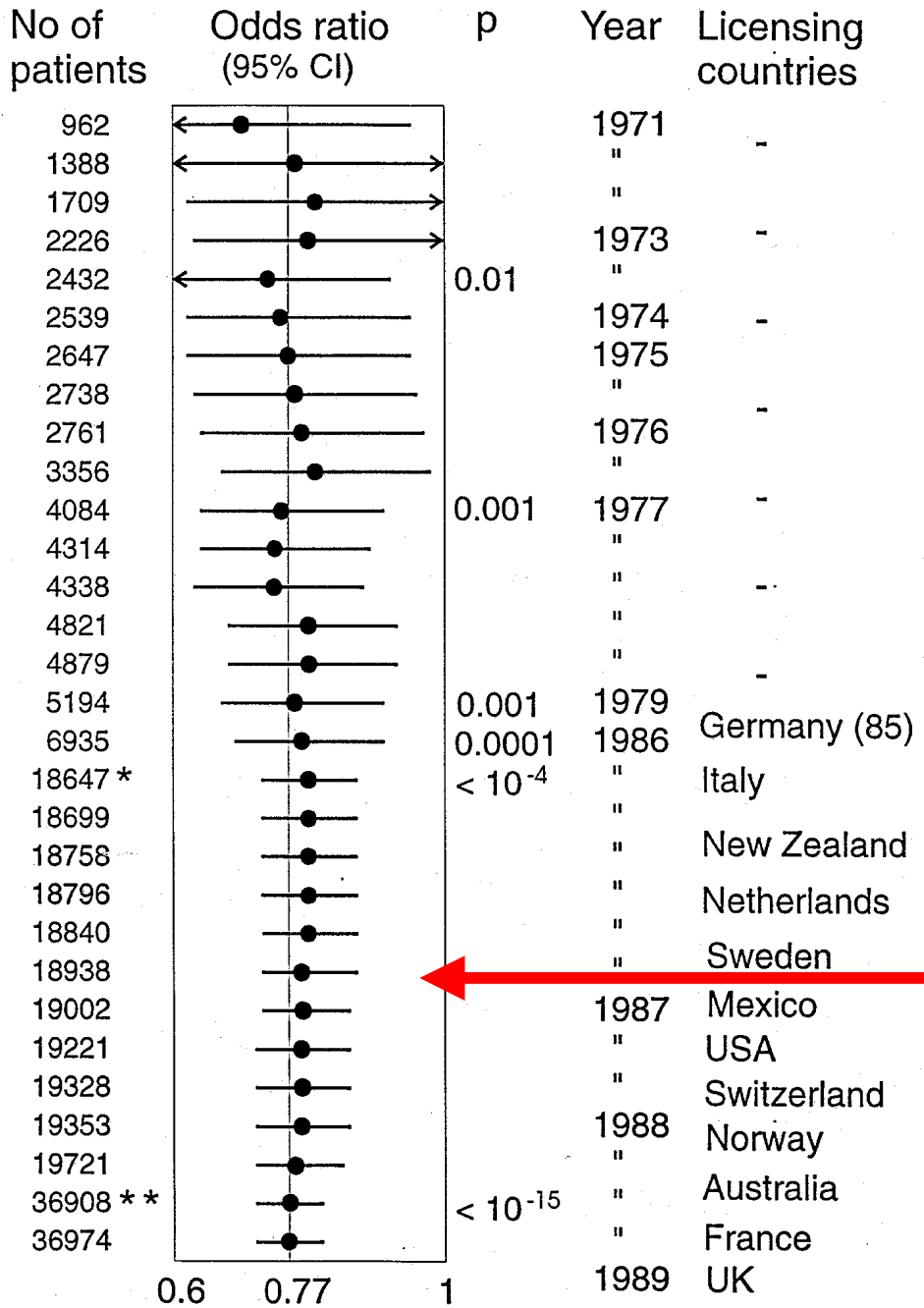
- Inverse-variance weighted fixed- and random-effects meta-analysis
- Forest plots, programmed using the **`gph`** command
- Published in the Stata Technical Bulletin, in 1997
- Syntax: **`meta logor selogor, options`**…

```
Meta-analysis (exponential form)
        |  Pooled      95% CI       Asymptotic       No. of
Method  |     Est   Lower   Upper z value  p value   studies
--------+-------------------------------------------------------
Fixed   |   0.774   0.725   0.826  -7.711    0.000     22
Random  |   0.782   0.693   0.884  -3.942    0.000

Test for heterogeneity: Q= 31.498 on 21 df (p= 0.066)
Moment-based estimate of variance =  0.017
```

```
meta logor selogor, graph(f) id(trialnam)
  eform xlab(0.01,0.1,1,10) cline xline(1)
  b2title(Odds ratio)
```





Thrombolytic therapy (streptokinase) in acute myocardial infarction: Cumulative meta-analysis

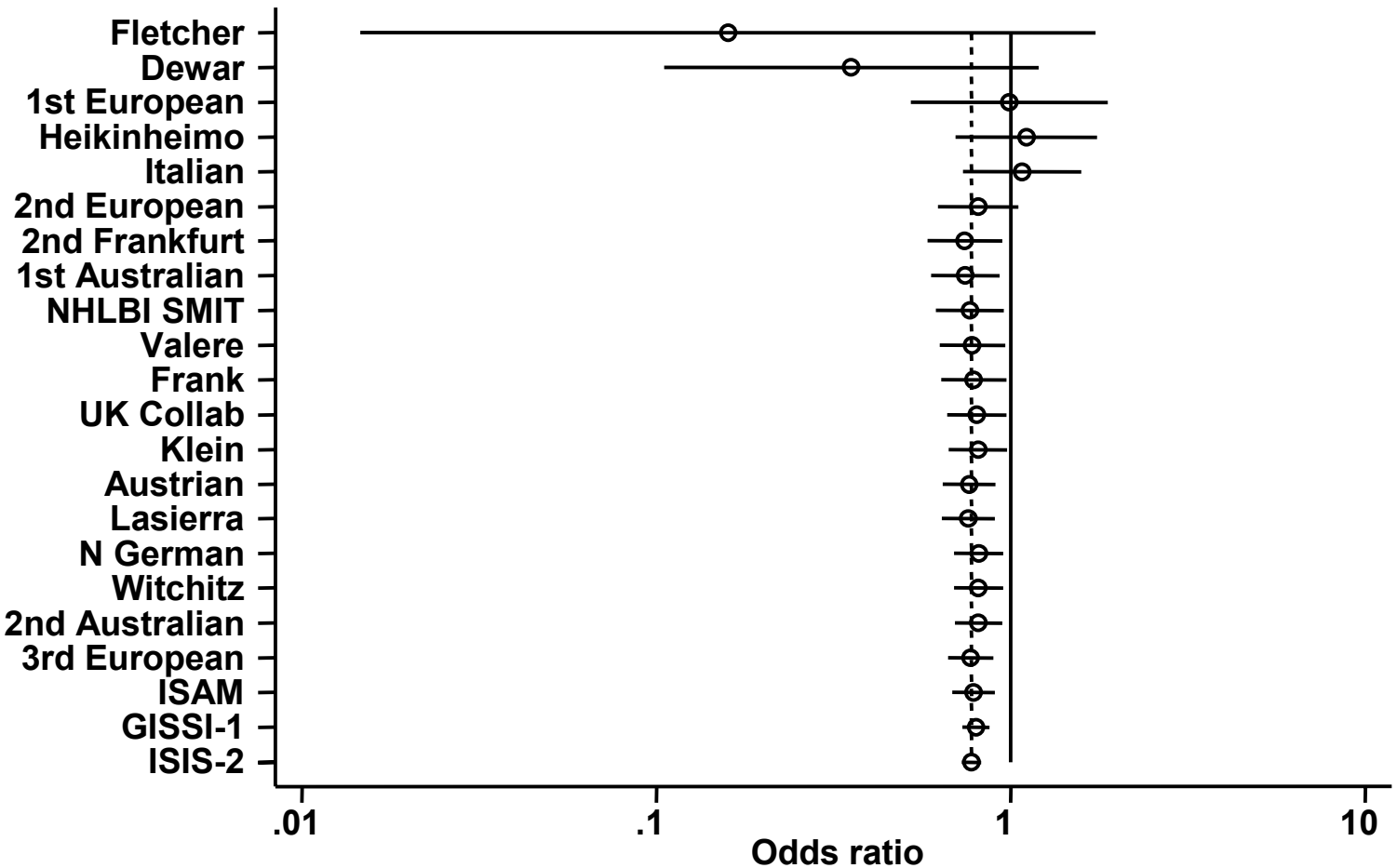
Oxford Textbook of Medicine 1987

"the clinical value of thrombolysis … remains uncertain"

* includes GISSI-1, ** ISIS-2

The `metacum` command (Sterne 1998)

```
metacum logor selogor, effect(f) graph
  id(trialnam) eform xlab(0.01,0.1,1,10)
  cline xline(1) b2title(Odds ratio)
```



Meanwhile, in Oxford…..

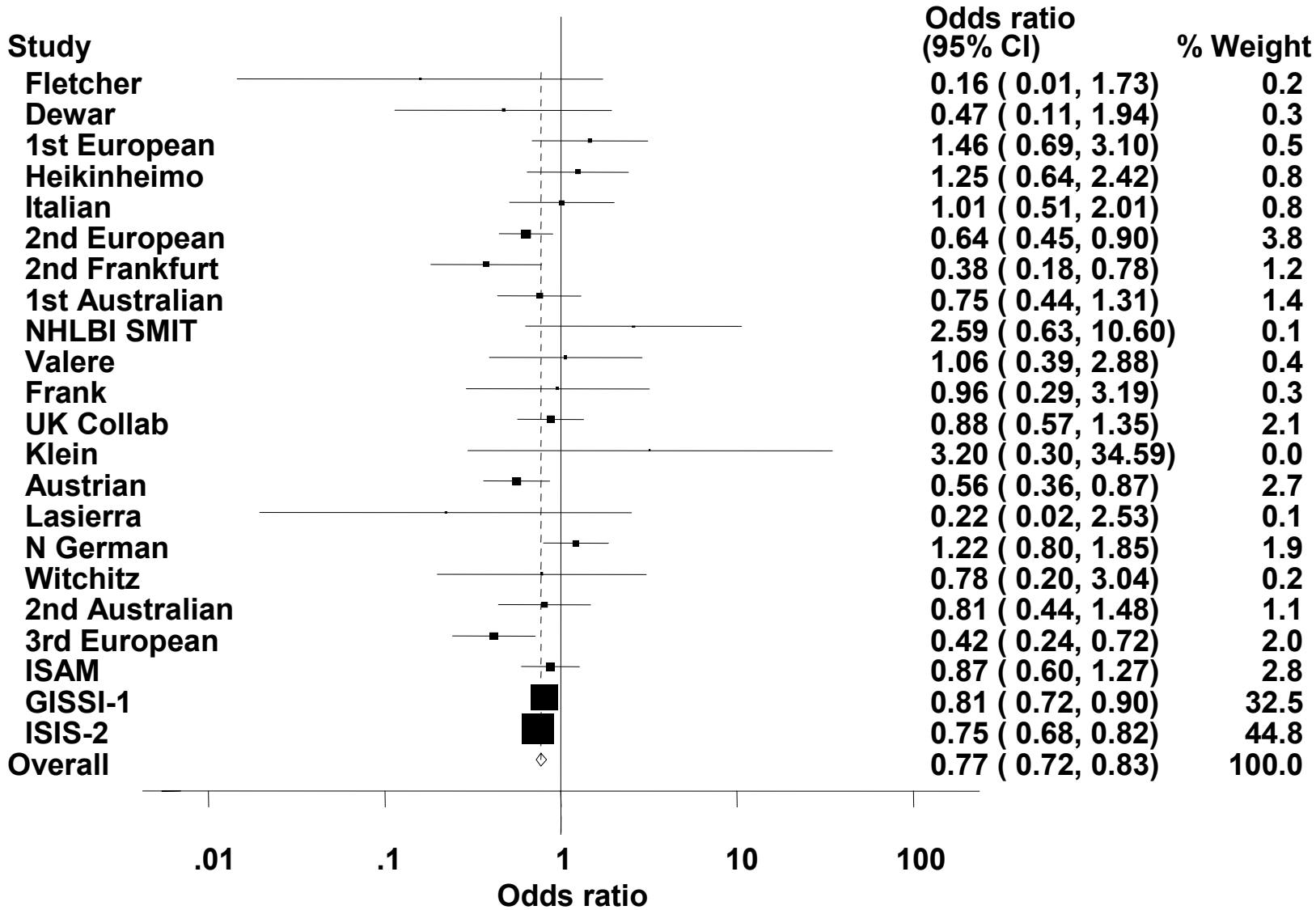
- Mike Bradburn, Jon Deeks and Douglas Altman actually knew something about meta-analysis…
- The Cochrane Collaboration was about to release a new version of its Review manager software, and some checking algorithms were needed
- Mike Bradburn presented a version of his meta command at the 1997 UK Stata Users' group

"When I found out you'd published your meta command, I sulked for quite a few months, before I could face finishing our command"

The `metan` command (Bradburn, Deeks and Altman 1998)

- Input based on the 2×2 table as well as on summary statistics (which are automatically calculated)
- Wide range of measures and methods
  - Mantel-Haenszel method and Peto method as well as inverse-variance weights
  - Risk ratio and risk difference as well as odds ratios
- Forest plots included text showing effects and weights
- Generally a more comprehensive command…

```
metan d1 h1 d0 h0, or label(namevar=trialnam)
  xlab(0.01,0.1,1,10,100)
```



This week I went through the mails I've received: there's approximately 200 in the six years I've kept. The users have grown; this year I have had 27 people write, some more than once (that's >1 a week). The typical mail either asks whether **`metan`** can do something or how to use it to analyse data. Early requests tended to be basic "where's the xtick option?" but others have required more time. There were a few bugs too, and so the feedback has helped make **`metan`** far better than it was in 1998. People have tended to be appreciative too - one mail this year thanked me for writing it, nothing else.

Supporting it is difficult at times: as I work for a cancer charity quite a lot of their time has gone into this. Maybe I shouldn't feel uneasy about that (most requests were from academia), but I do. In my new job I will likely not have the opportunity, save in my own time, to continue this.

Given that Stata has gained publicity and users on the back of these routines, it would probably be for the better that Stata's 1998(?) claim that "Stata should have a meta-analysis command [...] but does not" were carried into practice.

Meta-regression

- used to examine associations between study characteristics and treatment effects
  - e.g. difference in treatment effect estimates comparing studies that were and were not double-blind
  - Berkey *et al*. *Statistics in Medicine* 1995;**14**:395-411, Thompson & Sharp, Statistics in Medicine 1999;**18**:2693-708
  - Observational analyses!!

Assume the treatment effect (e.g. log OR) is related to one or more covariates:

$$\log \mathrm{OR}_i = \sum_j \beta_j x_j$$

Allow for a variance component τ^2, which accounts for unexplained heterogeneity between studies

The metareg command (Sharp 1998)

```
metareg logor studychars, wsse(selogor)
```

Summary statistics for each study

- Iterative estimation procedure:
  1. estimate τ^2
  2. use in a weighted regression to estimate the covariate effects
  3. new estimate of τ^2 and so on
- Still the only readily-available software?
- Recently adapted by Roger Harbord to use new Stata procedures to improve estimation of τ^2
- Replace existing command or release new one?

"I'd be delighted if someone else took responsibility for `metareg` – I still get a couple of requests for support every month and I have no interest in this any more…"

Meta-analysis is no panacea...

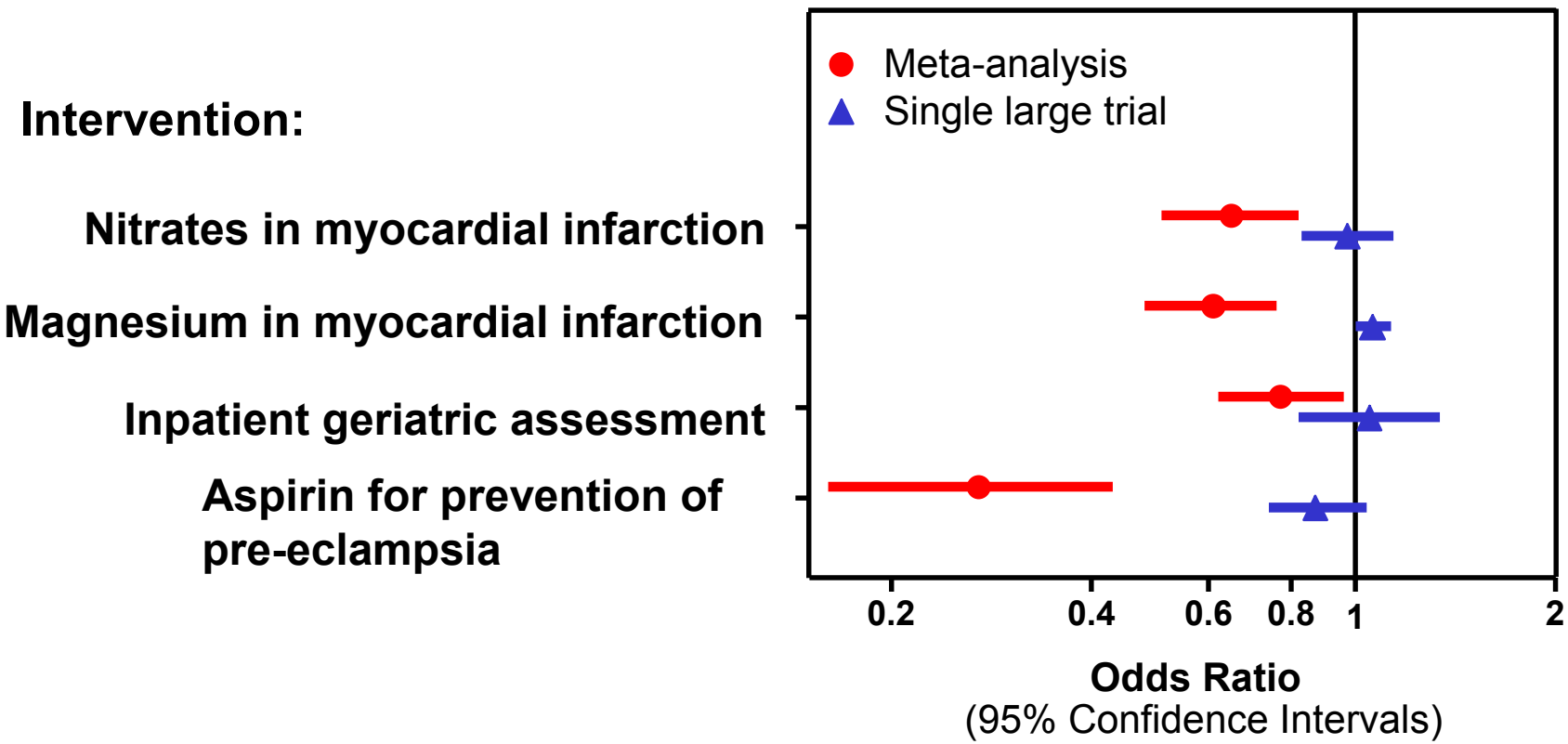
- Contrasting conclusions from
  - meta-analyses of the same issue
  - meta-analyses and single large trials

- **“Low molecular weight heparins seem to have a higher benefit to risk ratio than unfractionated heparin in preventing perioperative thrombosis”**

Leizorovicz A et al. *BMJ* 1992

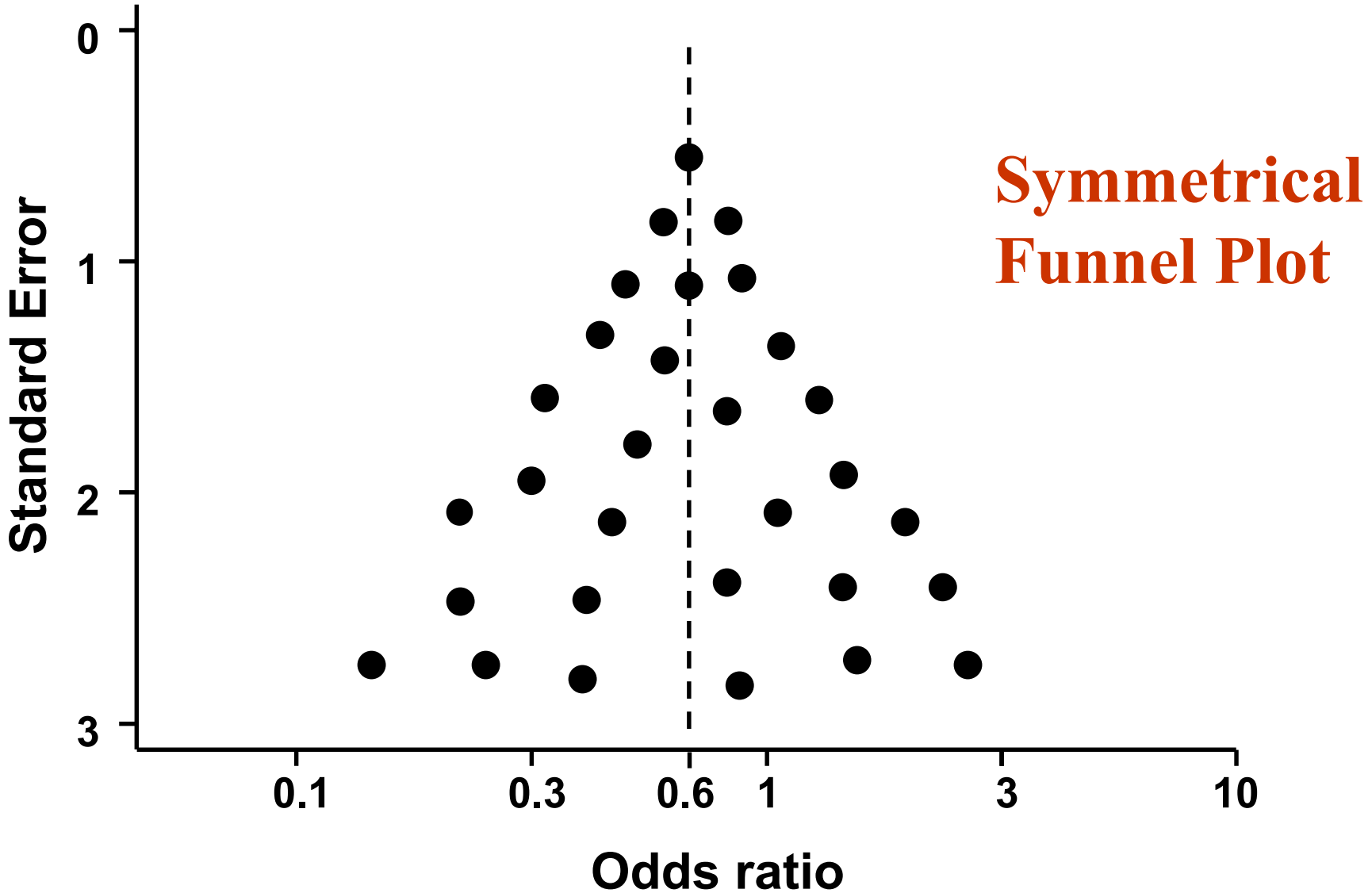
- **“There is no convincing evidence that in general surgery patients LMWHs, compared with standard heparin, generate a clinically important improvement in the benefit to risk ratio”**

Nurmohamed et al. *Lancet* 1992



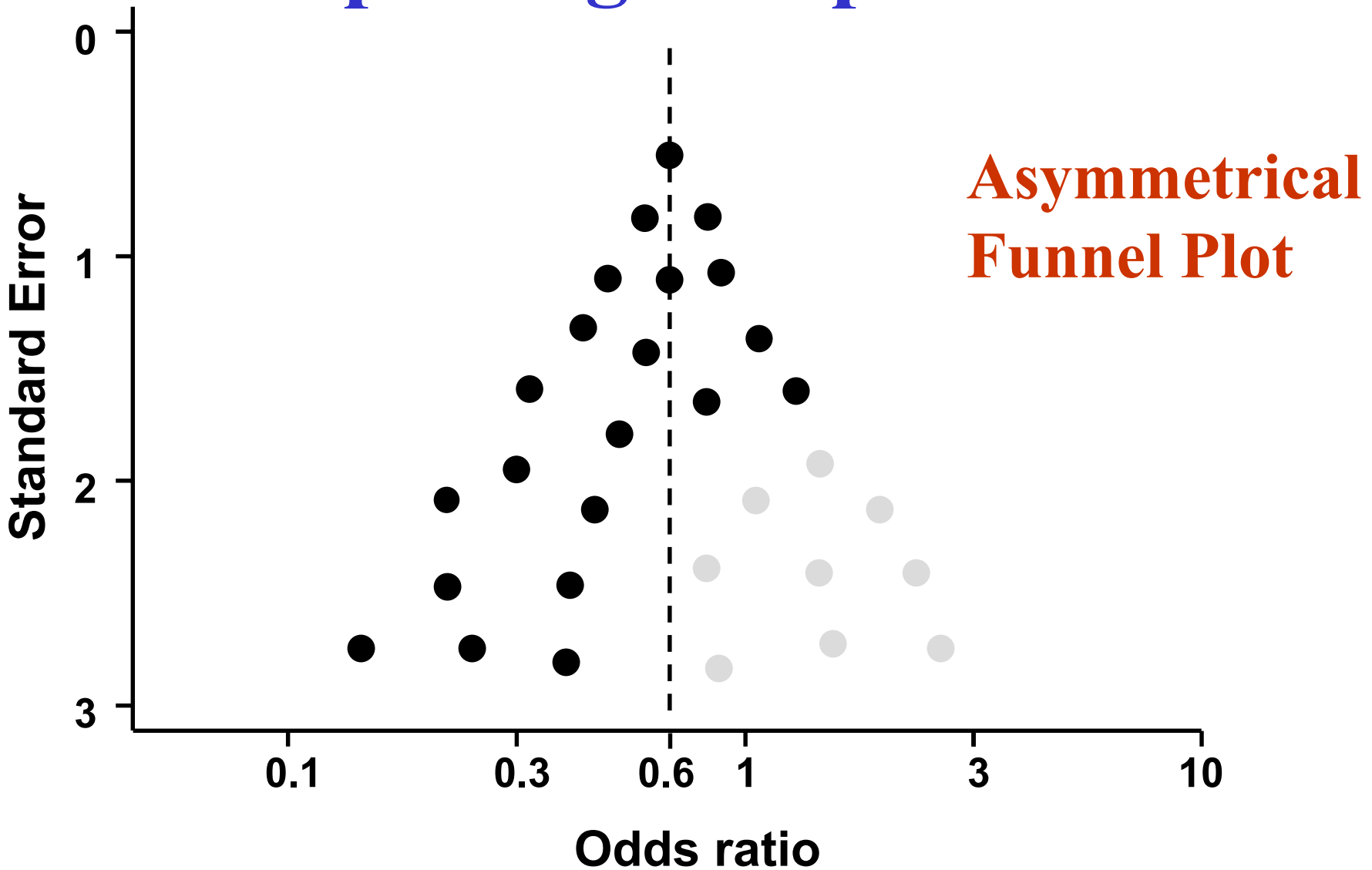
Egger et al. *BMJ* 1997

No bias



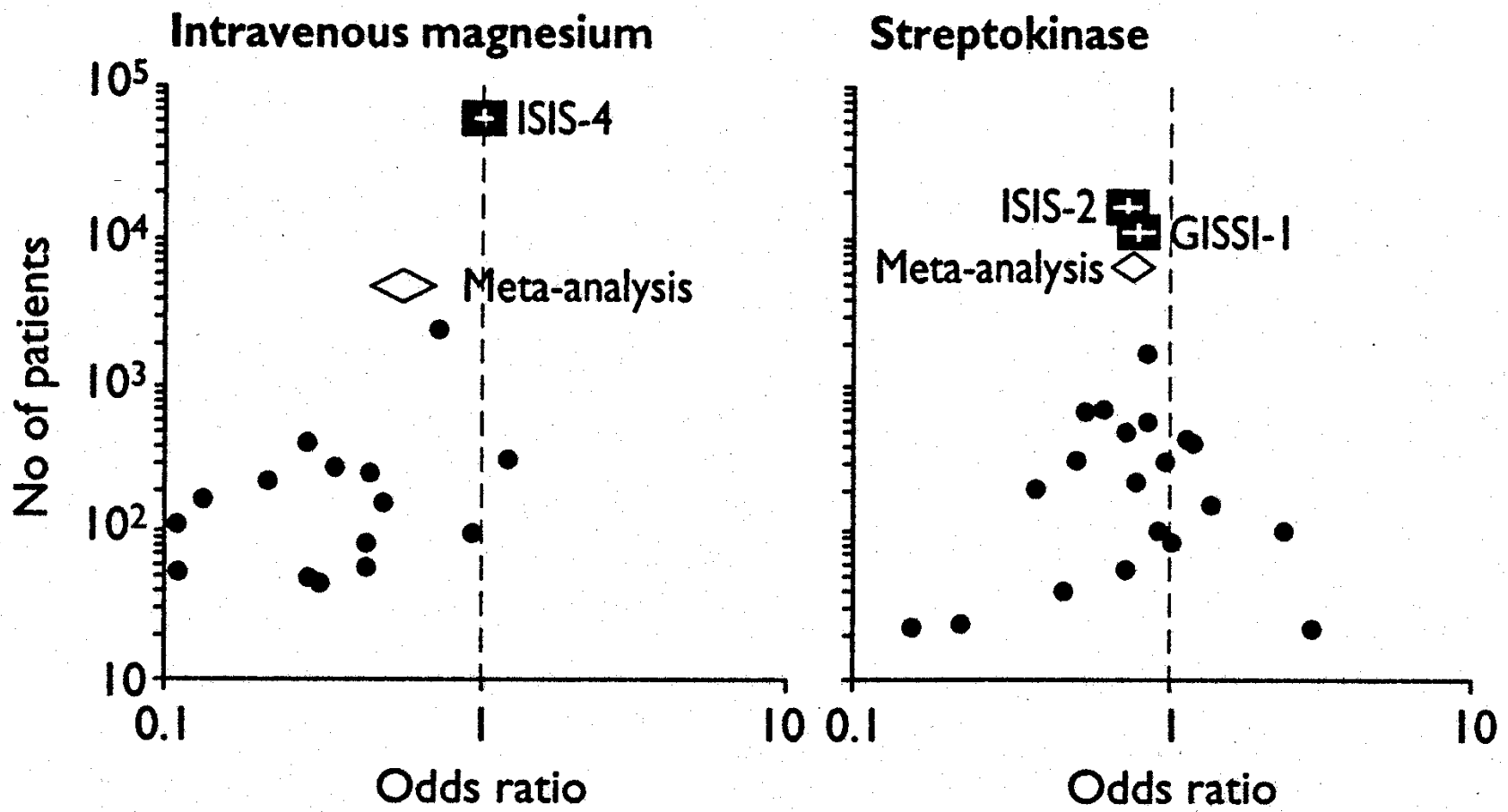
Symmetrical Funnel Plot

Reporting bias present



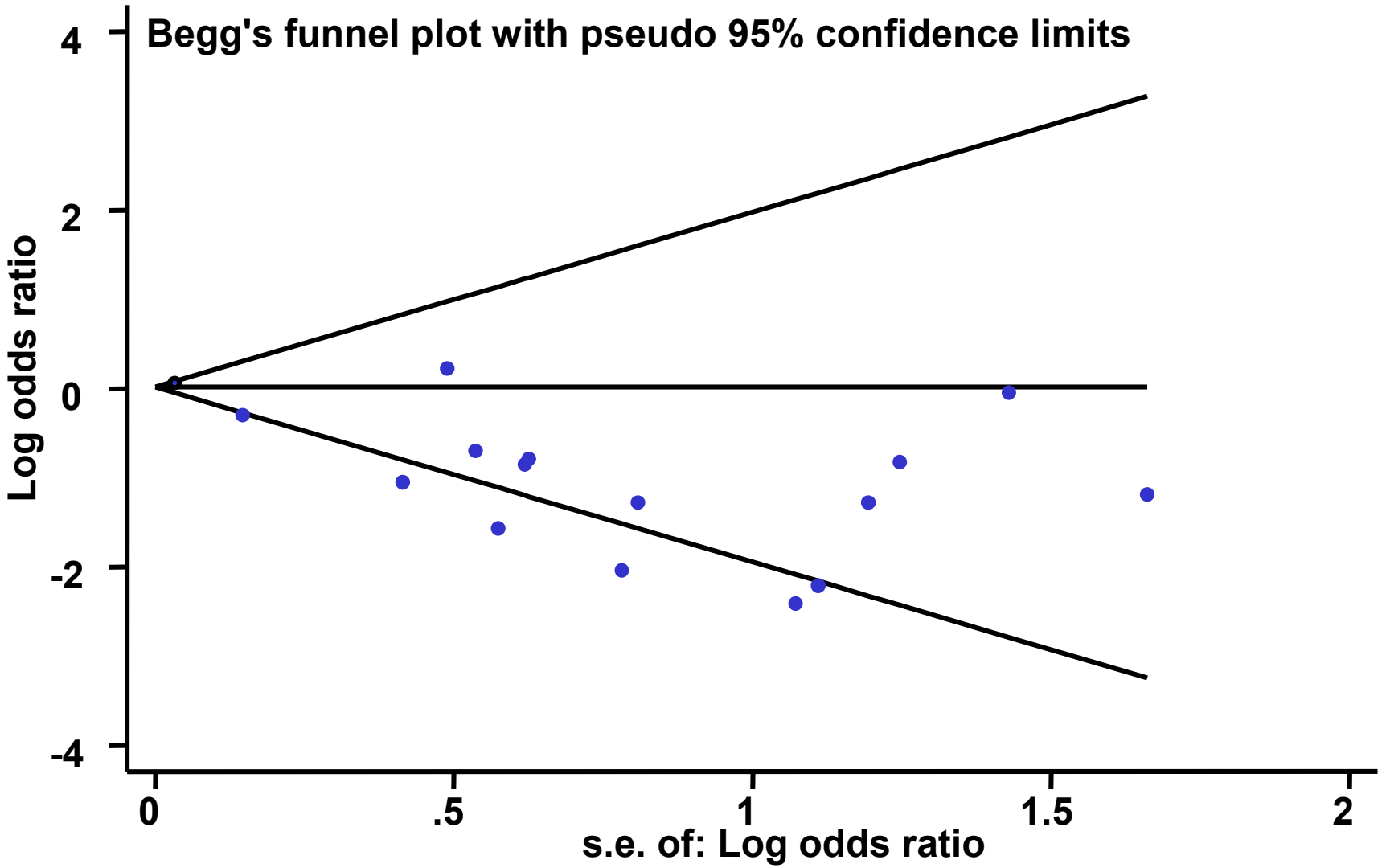
Funnel plots from Egger & Davey Smith (BMJ 1995)

Funnel plots for meta-analyses refuted and confirmed by subsequent mega trials: intravenous magnesium (left) and streptokinase (right) in acute myocardial infarction.

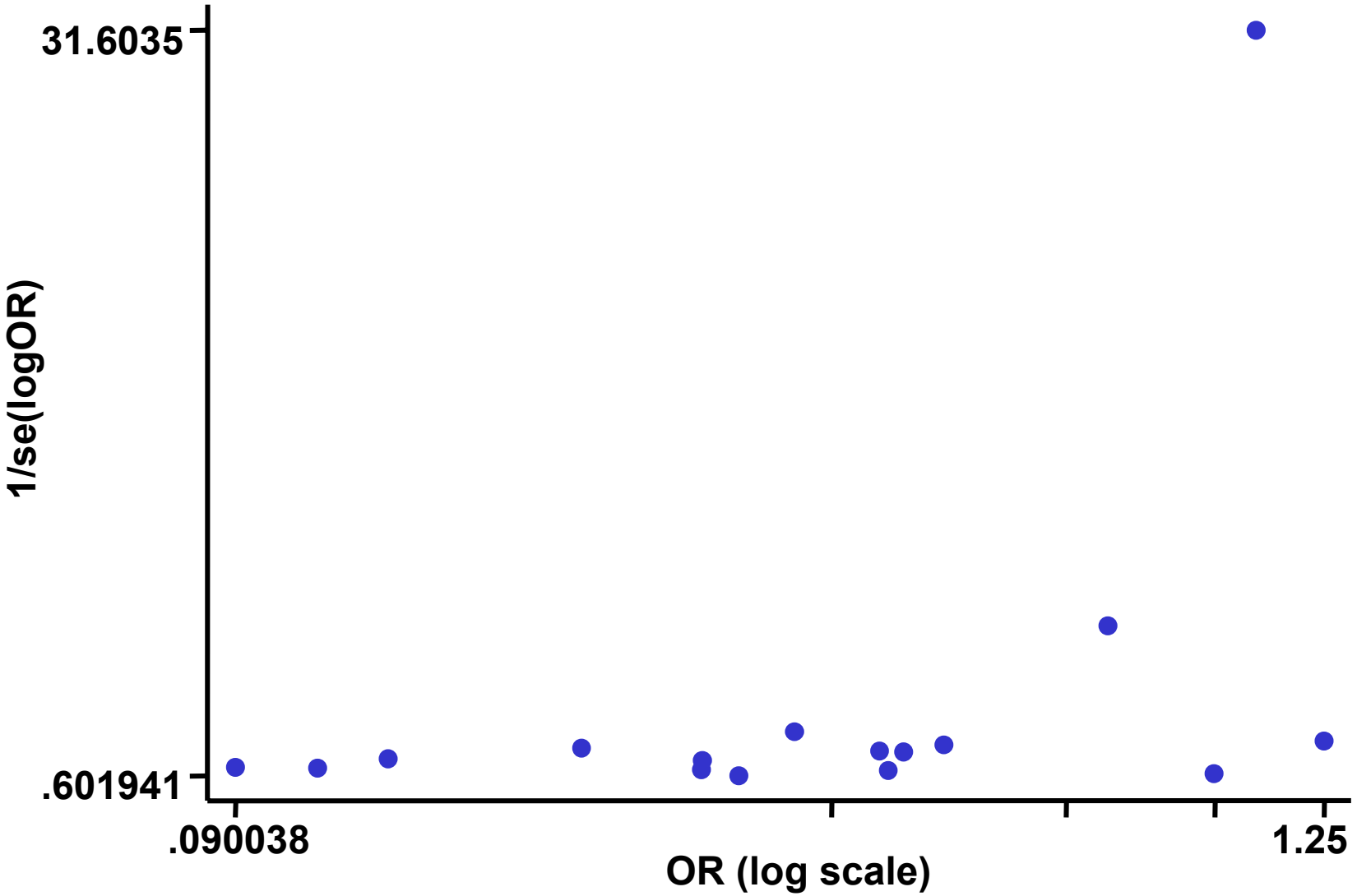


metabias (Steichen 1997)

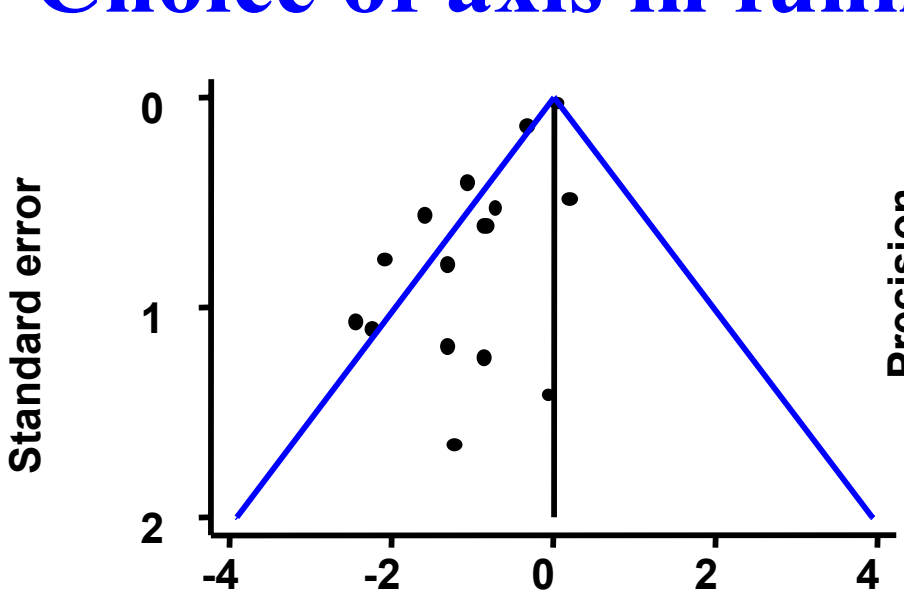
```
metabias logor selogor, gr(begg)
```

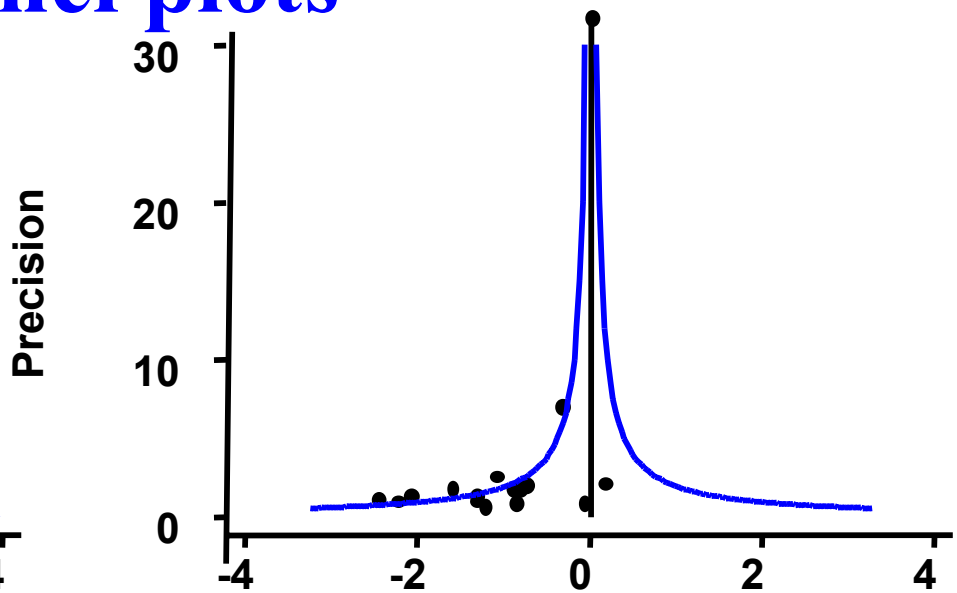


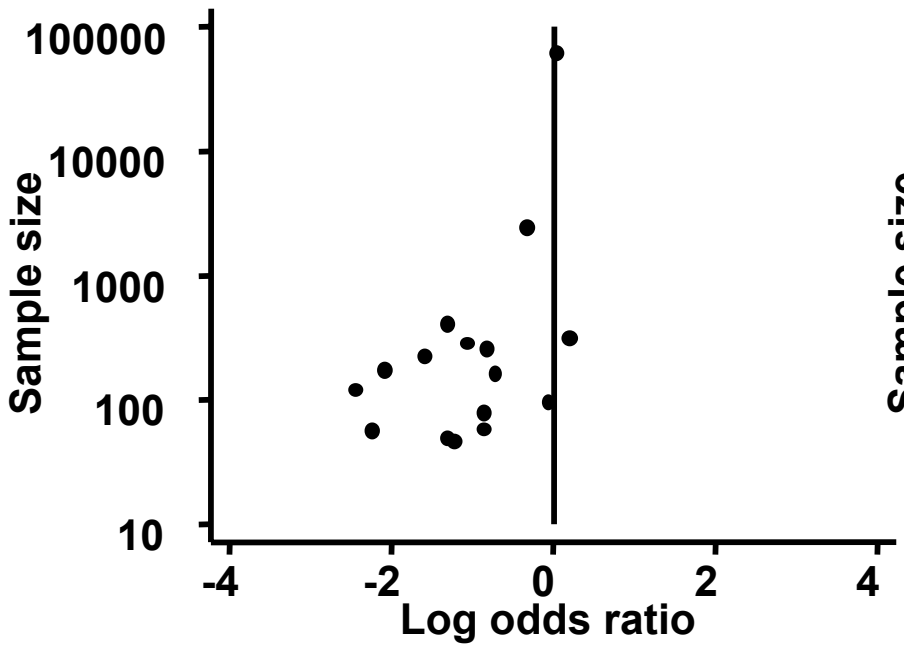
```
metan d1 h1 d0 h0, or
funnel
```

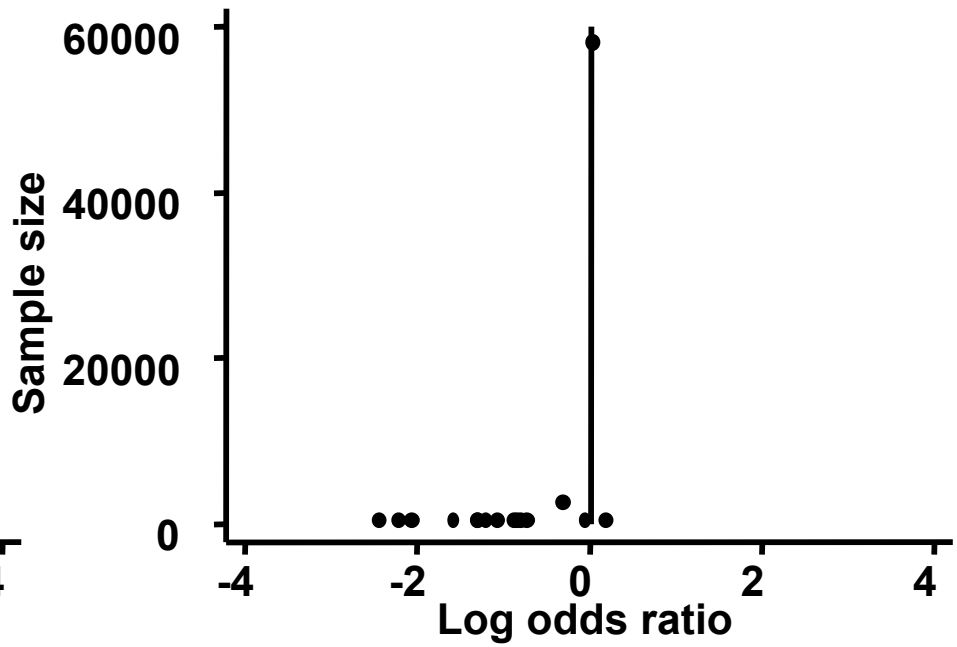


Choice of axis in funnel plots





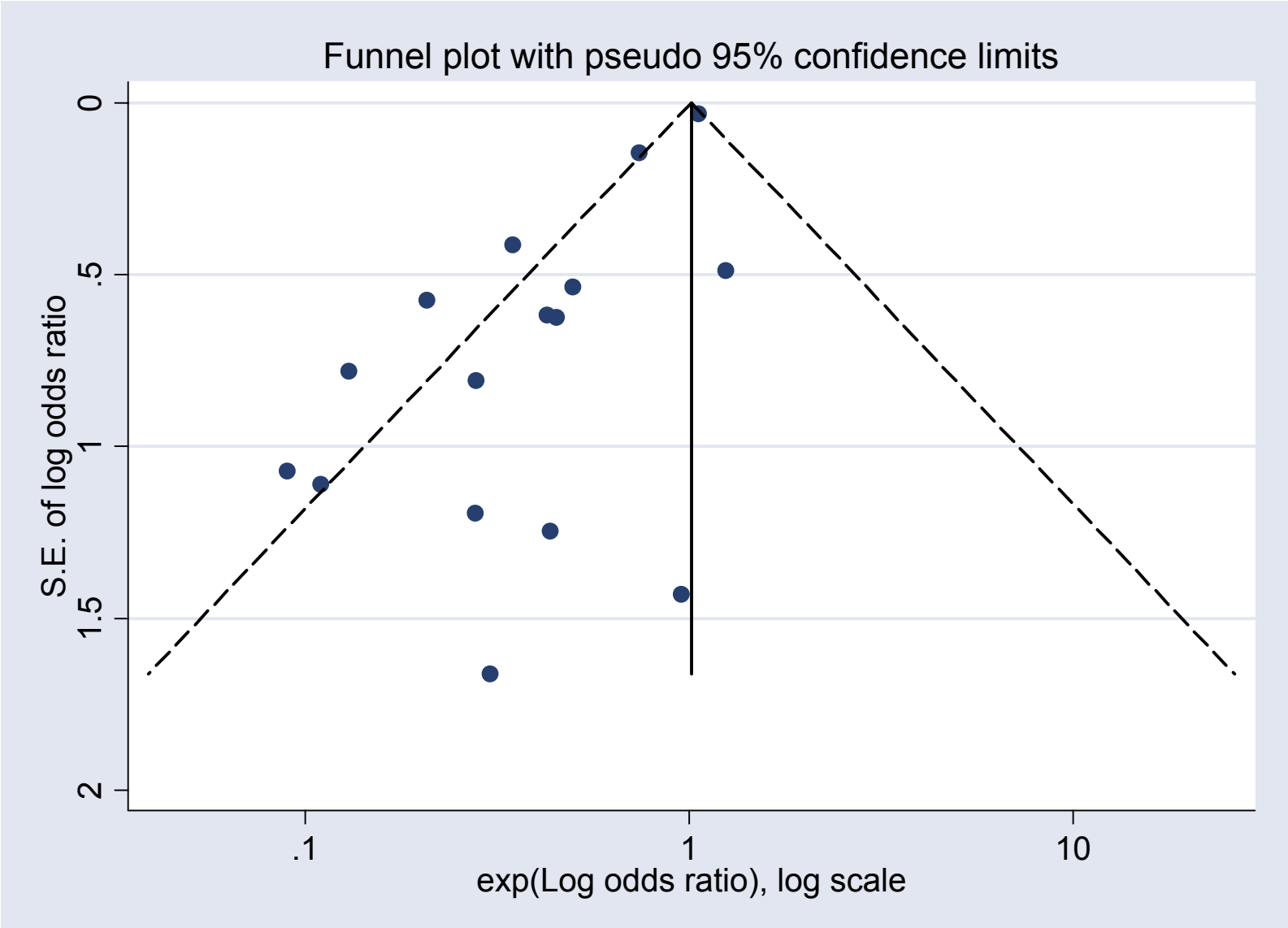




Journal of Clinical Epidemiology 2001; **54**: 1046-1055

`metafunnel` (Sterne & Harbord 2004)

```
metafunnel logor selogor, eform xlab(0.1 1 10)
```

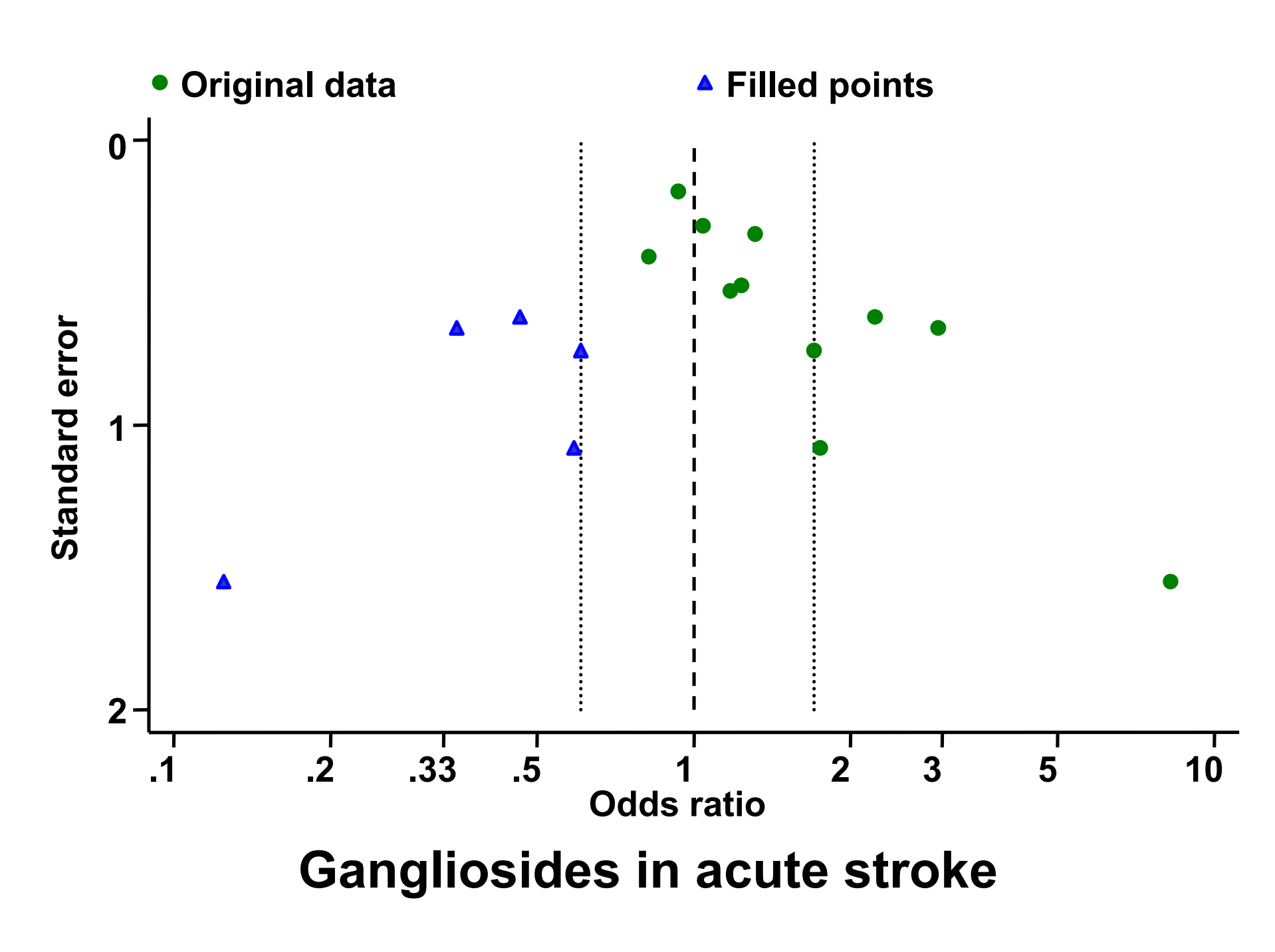


Selection models for publication bias

- detect publication bias, based on assuming that a study's results (e.g. the P value) affect its probability of publication
- Example: assume publication is certain if the study $P<0.05$. If $P>0.05$ then publication probability might be a constant (<1) or might decrease with decreasing treatment effect
- More complex models have been proposed, but may require much larger numbers of studies than available in typical meta-analyses
- The complexity of the methods, and the large number of studies needed, probably explain why selection models have not been widely used in practice

Trim and fill
(Duval & Tweedie 1999, 2000)

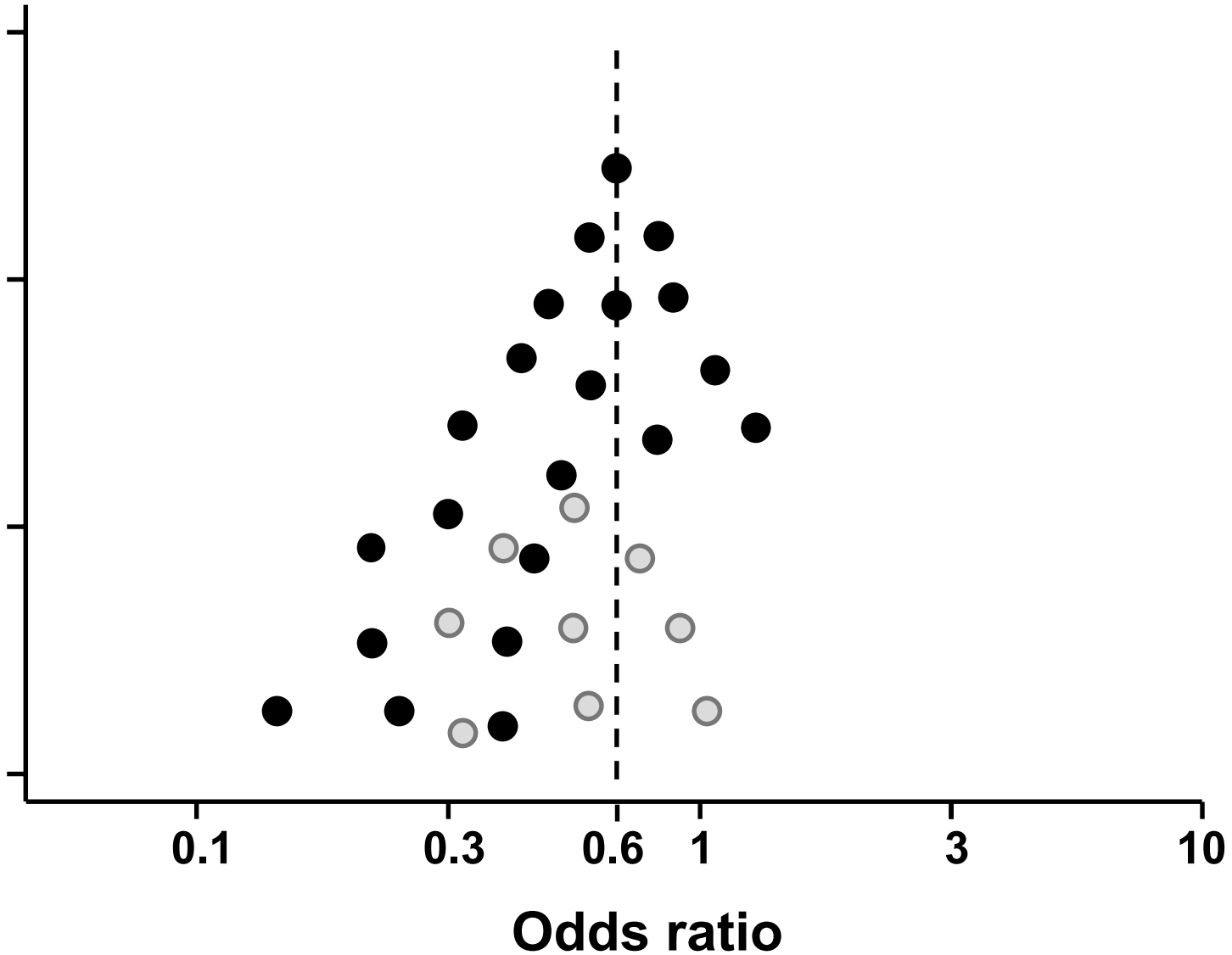
`metatrim` (Steichen 2000)


Original data
Filled points
0
1
2
Standard error
.1
.2
.33
.5
1
2
3
5
10
Odds ratio
Gangliosides in acute stroke

Selection models are unlikely to account (fully) for funnel plot asymmetry

- Statistically significant studies are more likely to produce multiple publications
- Large studies are more likely to be published whatever their results
- Poorer quality studies produce more extreme treatment effects, and are also more likely to be small
- The true treatment effect may differ according to study size:
  - Intensity of intervention
  - Differences in underlying risk

Bias because of poor quality of small trials



Small study effect

- a tendency for smaller trials in a meta-analysis to show greater treatment effects than the larger trials

Small study effects need not result from bias

Statistical tests for funnel plot asymmetry

- **Begg & Mazumdar (*Biometrics* 1994)** - Rank correlation test for association between treatment effect and its variance (standard error) in each study
- **Egger *et al.* (*BMJ* 1997)** - equivalent to a weighted regression of treatment effect on its standard error

Simulation analyses:

(i) low power unless there is severe bias & a large number of trials

(ii) regression more powerful than rank correlation method

(iii) problems in some circumstances

(*J Clin Epidemiol* 2000; **53:** 1119-1129)

Tests for funnel plot asymmetry for the magnesium trials (exc. ISIS-4)

```
. metabias logor selogor if trial<16
Tests for Publication Bias

Begg's Test
adj Kendall's Score (P-Q)      =     -3
      Std. Dev. of Score       =  20.21
       Number of Studies       =     15
                         z     =  -0.15
                  Pr > |z|     =  0.882
                         z     =   0.10 (continuity corrected)
                  Pr > |z|     =  0.921 (continuity corrected)

Egger's test
Std_Eff|      Coef   Std Err      t    P>|t|     95% Conf Int
-------+------------------------------------------------------
  slope|  -.15122   .167460    -0.90   0.383   -.51300   .21055
   bias|  -1.1924   .375174    -3.18   0.007   -2.0029 -.38191
```

Modified test for funnel plot asymmetry (Harbord): command under development

Other Stata meta-analysis commands

search meta

metap: Meta-analysis of p-values
A. Tobias

metainf: Assessing the influence of a single study in meta-analysis
A. Tobias

galbr: Assessing heterogeneity in meta-analysis: the Galbraith plot
A. Tobias

The present

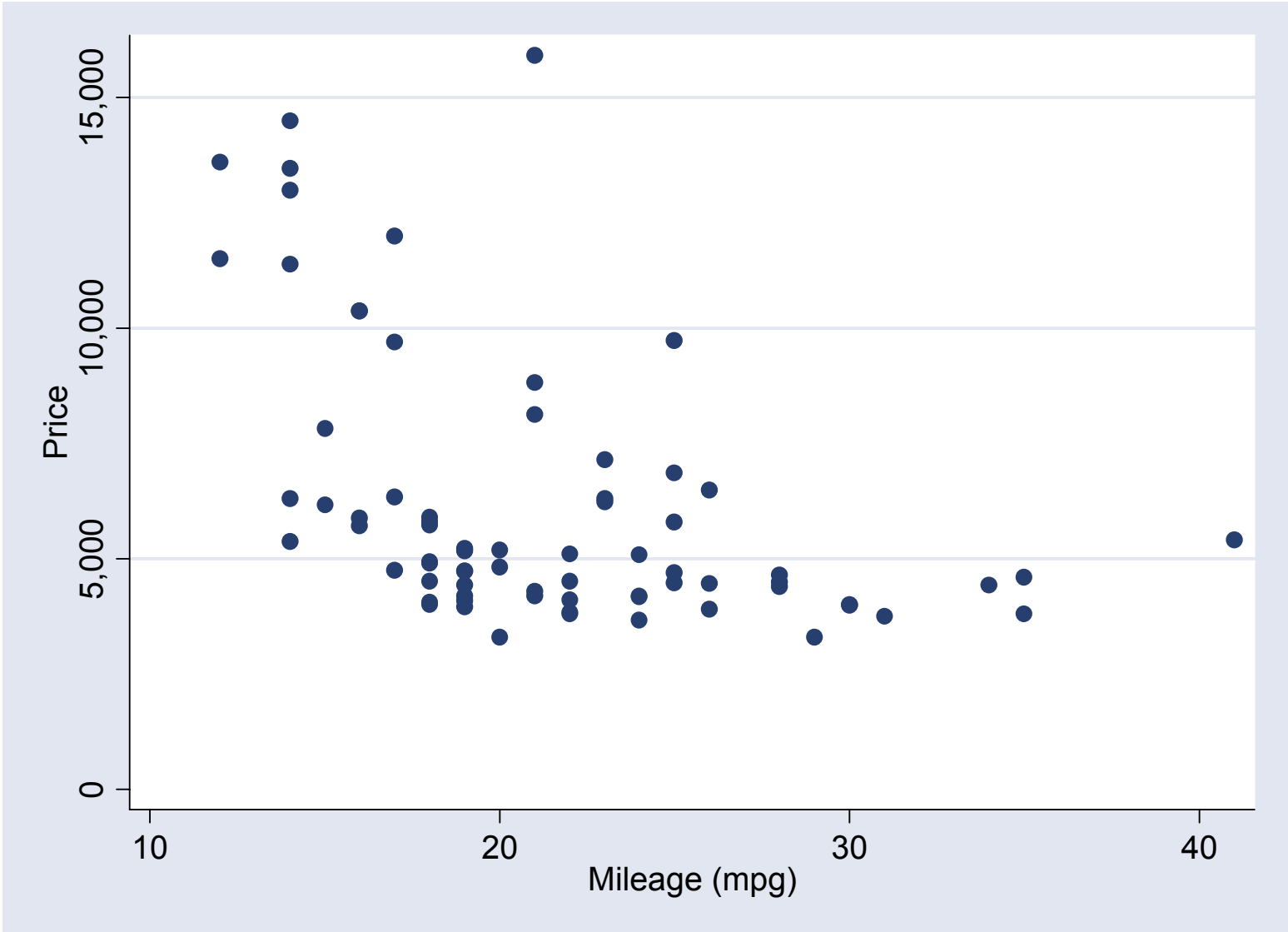
- Stata should have a meta-analysis command, but it does not….

Stata reference manual

- Mike Bradburn has recently left the Centre for Statistics in Medicine in Oxford
  - **`metan`** unlikely to be maintained?

- Very little benefit in maintaining **`metan`** and **`meta`** as separate commands
  - each should be able to display forest plots with no summary estimate

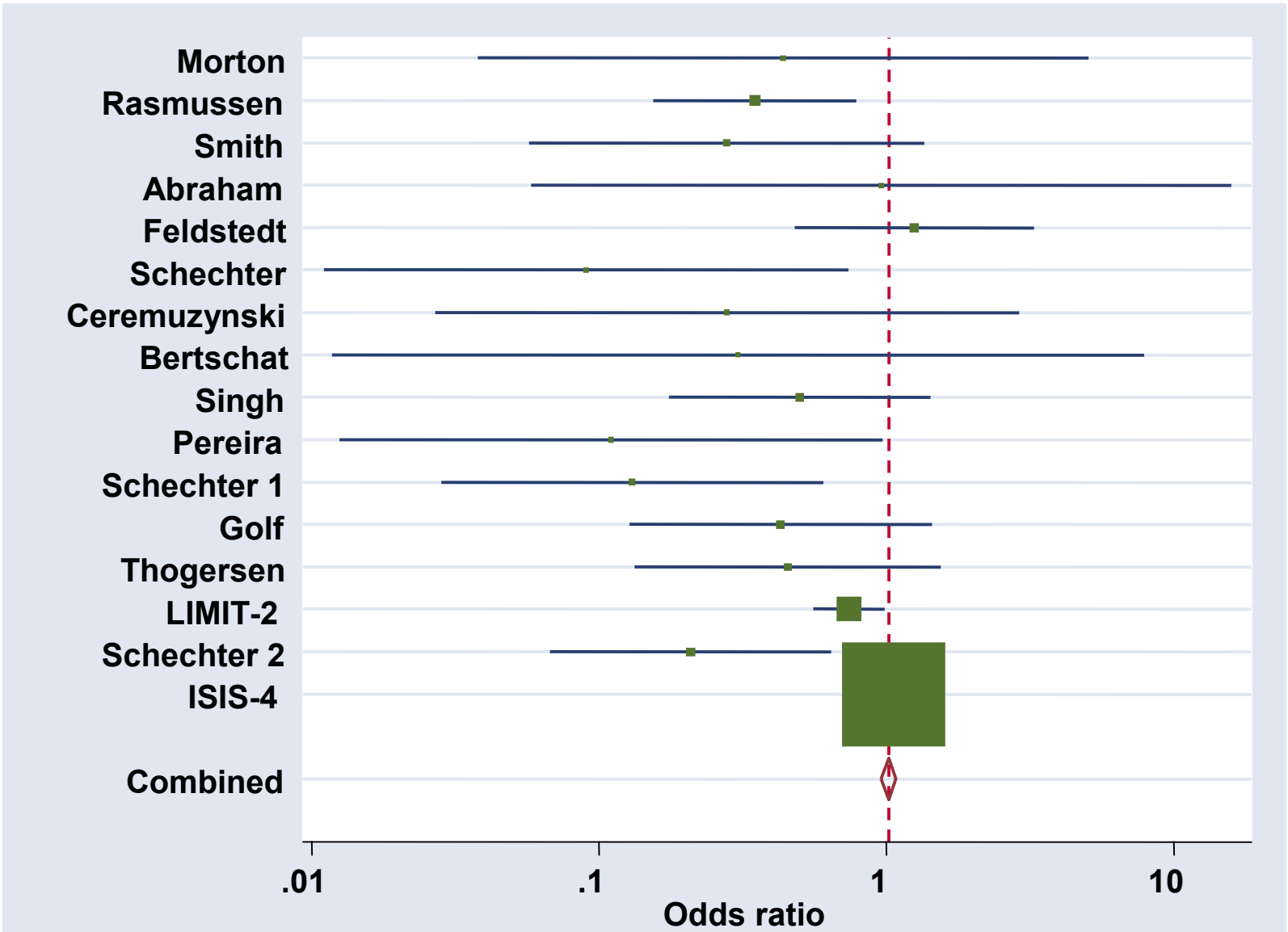
The obstacle



The future

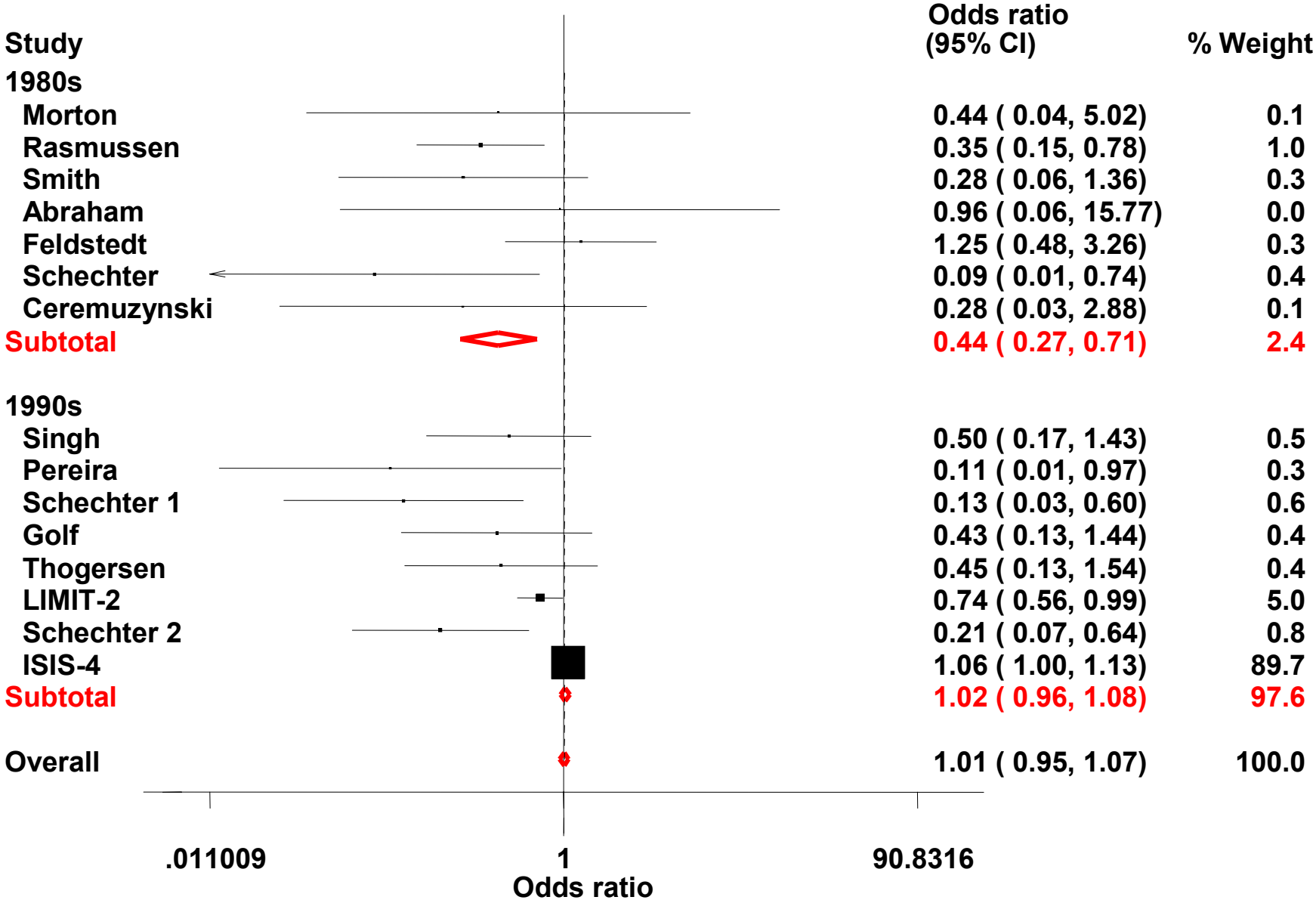
1. Update graphical displays to Stata 8
   - new talent is replacing tired old programmers bewildered by Stata 8 graphics
2. Unify existing commands into one or more official Stata commands
   - where these are stable and uncontroversial
3. New areas/commands

```
meta8 logor selogor, id(trialnam) eform
   graph(f) xlab(0.01 0.1 1 10)
```



Thanks to Aijing Shang and Roger Harbord…

```
metan dead1 alive1 dead0 alive0, or by(period)
   label(namevar=trialnam)
```



New developments

- Meta-analysis of diagnostic tests
  - Major area of expansion for the Cochrane Collaboration
  - Statistically, much more complex than meta-analysis of randomised controlled trials
  - First command (**`meta_lr`**) recently released by Aijing Shang
  - Formal synthesis of these studies requires bivariate methods accounting for the association between sensitivity and specificity (meta-analyse in ROC-space)
  - Obvious extensions to existing ROC methods in Stata
  - Opportunities to use **`gllamm`** and new mixed models procedures to be released in Stata 9?
- As always, developments will occur in areas that no-one predicts…

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