An introduction to meta-analysis in Stata

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Outline

- Systematic reviews and meta-analysis
- History
- Meta-analysis in Stata – the **`metan`** and **`metacum`** commands
- Bias in meta-analysis, and Stata commands to investigate bias

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 Deaths	Streptokinase group Total	Control group Deaths	Control group 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

Fixed (common) effect meta-analysis

- Summary (pooled) $\log(OR_F) = \dfrac{\sum w_i \times \log OR_i}{\sum w_i}$
- 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.

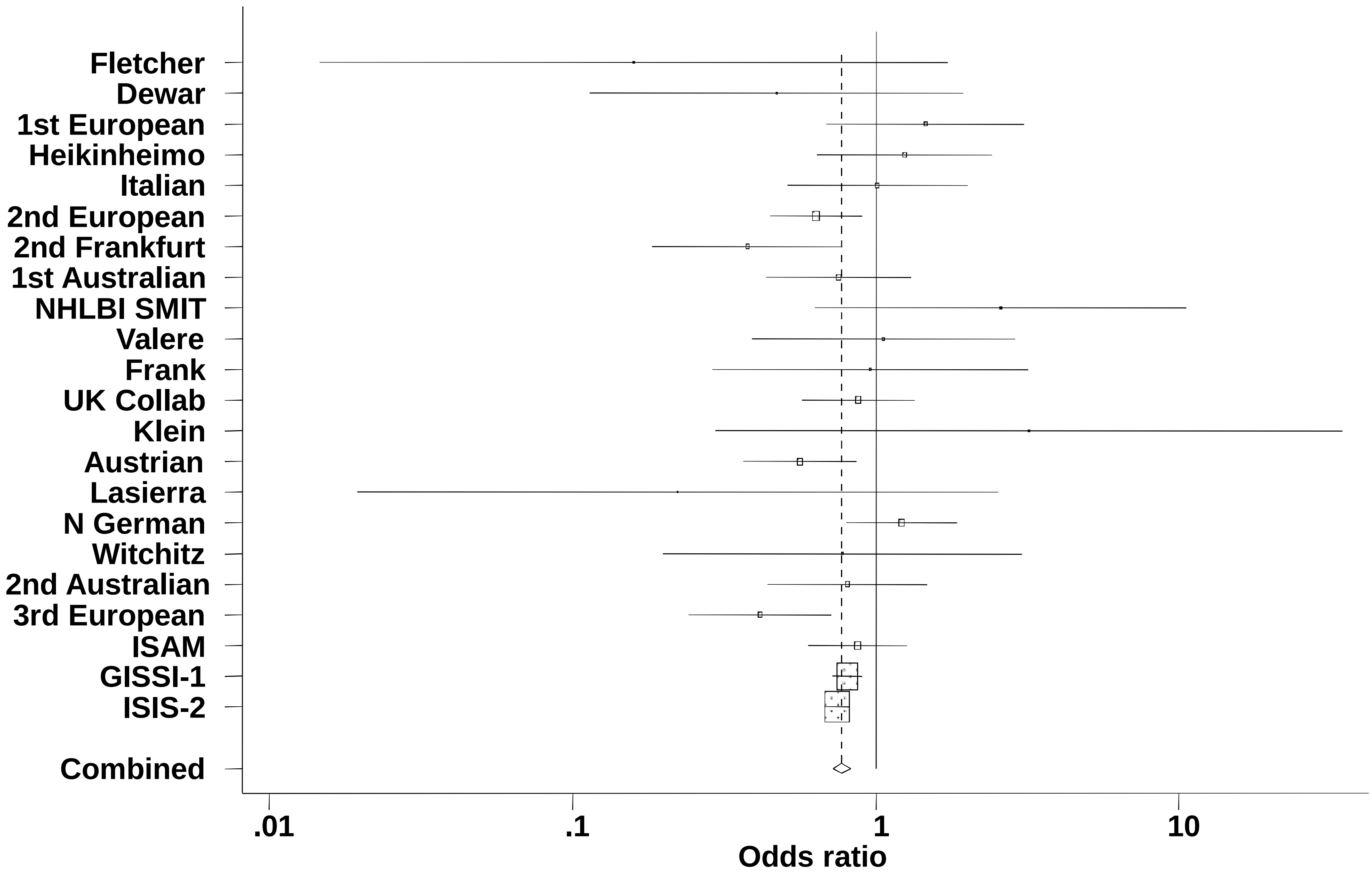
The `meta` command (Sharp and Sterne)

- 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)
```



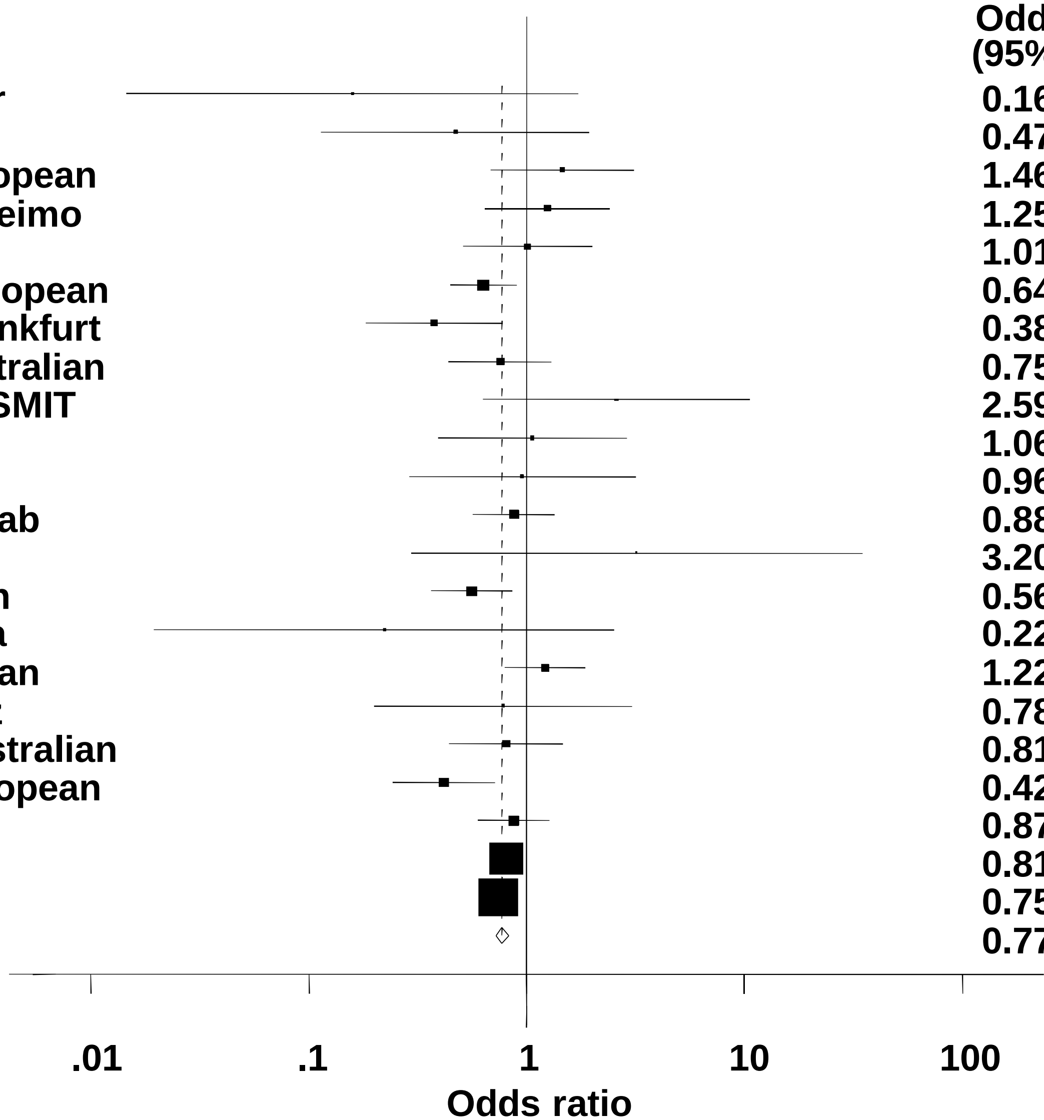
Meanwhile, in Oxford…..

- 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

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
  - Mean differences and standardized mean differences
- Forest plots included text showing effects and weights
- Generally a more comprehensive command…
- Updated a number of times, but documentation of new features became patchy and not all users accessed the correct version

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



Study	Odds ratio (95% CI)	% Weight
Fletcher	0.16 (0.01, 1.73)	0.2
Dewar	0.47 (0.11, 1.94)	0.3
1st European	1.46 (0.69, 3.10)	0.5
Heikinheimo	1.25 (0.64, 2.42)	0.8
Italian	1.01 (0.51, 2.01)	0.8
2nd European	0.64 (0.45, 0.90)	3.8
2nd Frankfurt	0.38 (0.18, 0.78)	1.2
1st Australian	0.75 (0.44, 1.31)	1.4
NHLBI SMIT	2.59 (0.63, 10.60)	0.1
Valere	1.06 (0.39, 2.88)	0.4
Frank	0.96 (0.29, 3.19)	0.3
UK Collab	0.88 (0.57, 1.35)	2.1
Klein	3.20 (0.30, 34.59)	0.0
Austrian	0.56 (0.36, 0.87)	2.7
Lasierra	0.22 (0.02, 2.53)	0.1
N German	1.22 (0.80, 1.85)	1.9
Witchitz	0.78 (0.20, 3.04)	0.2
2nd Australian	0.81 (0.44, 1.48)	1.1
3rd European	0.42 (0.24, 0.72)	2.0
ISAM	0.87 (0.60, 1.27)	2.8
GISSI-1	0.81 (0.72, 0.90)	32.5
ISIS-2	0.75 (0.68, 0.82)	44.8
Overall	0.77 (0.72, 0.83)	100.0

Version 9/10 update

- The original authors of the Stata meta-analysis commands never got to grips with the new and improved Stata graphics that were introduced in Version 8
- Luckily, Ross Harris took on the job brilliantly (with help from Vince Wiggins)
- A request from Vince to edit a collection of Stata Journal articles about meta-analysis prompted us to update and fully document the commands
- The authors of the original `metan` command were happy to collaborate on a new Stata Journal article

```
. metan cases1 h1 cases0 h0, lcols(trialnam)
```

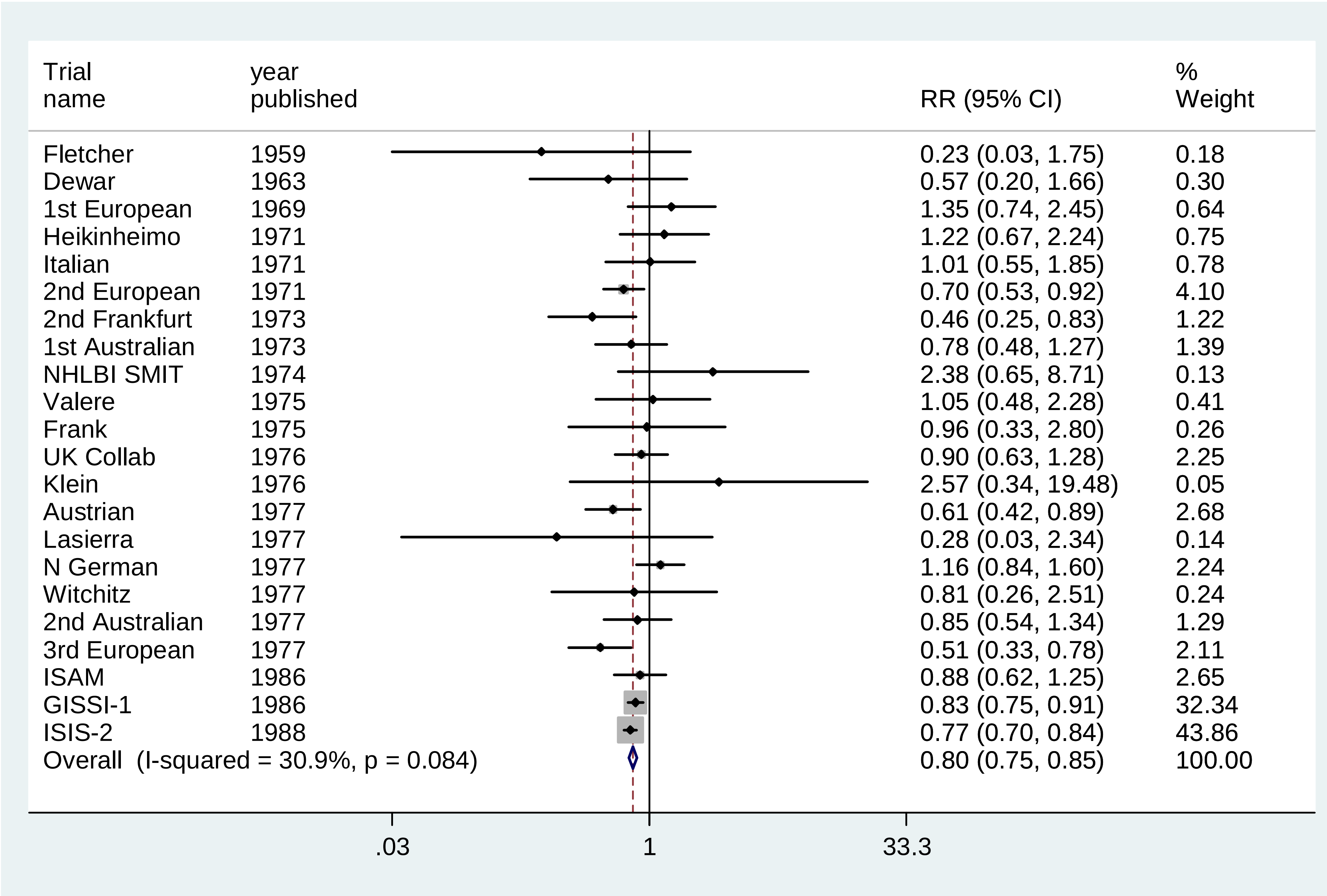
Study	RR	[95% Conf.	Interval]	% Weight
Fletcher	0.229	0.030	1.750	0.18
Dewar	0.571	0.196	1.665	0.30
1st European	1.349	0.743	2.451	0.64
Heikinheimo	1.223	0.669	2.237	0.75
Italian	1.011	0.551	1.853	0.78
2nd European	0.703	0.534	0.925	4.10
2nd Frankfurt	0.457	0.252	0.828	1.22
1st Australian	0.779	0.478	1.268	1.39
NHLBI SMIT	2.377	0.649	8.709	0.13
Valere	1.048	0.481	2.282	0.41
Frank	0.964	0.332	2.801	0.26
UK Collab	0.896	0.626	1.281	2.25
Klein	2.571	0.339	19.481	0.05
Austrian	0.608	0.417	0.886	2.68
Lasierra	0.282	0.034	2.340	0.14
N German	1.161	0.840	1.604	2.24
Witchitz	0.813	0.263	2.506	0.24
2nd Australian	0.850	0.537	1.345	1.29
3rd European	0.510	0.333	0.780	2.11
ISAM	0.880	0.619	1.250	2.65
GISSI-1	0.827	0.749	0.914	32.34
ISIS-2	0.769	0.704	0.839	43.86
M-H pooled RR	0.799	0.755	0.845	100.00

Heterogeneity chi-squared = 30.41 (d.f. = 21) p = 0.084

I-squared (variation in RR attributable to heterogeneity) = 30.9%

Test of RR=1 : z= 7.75 p = 0.000

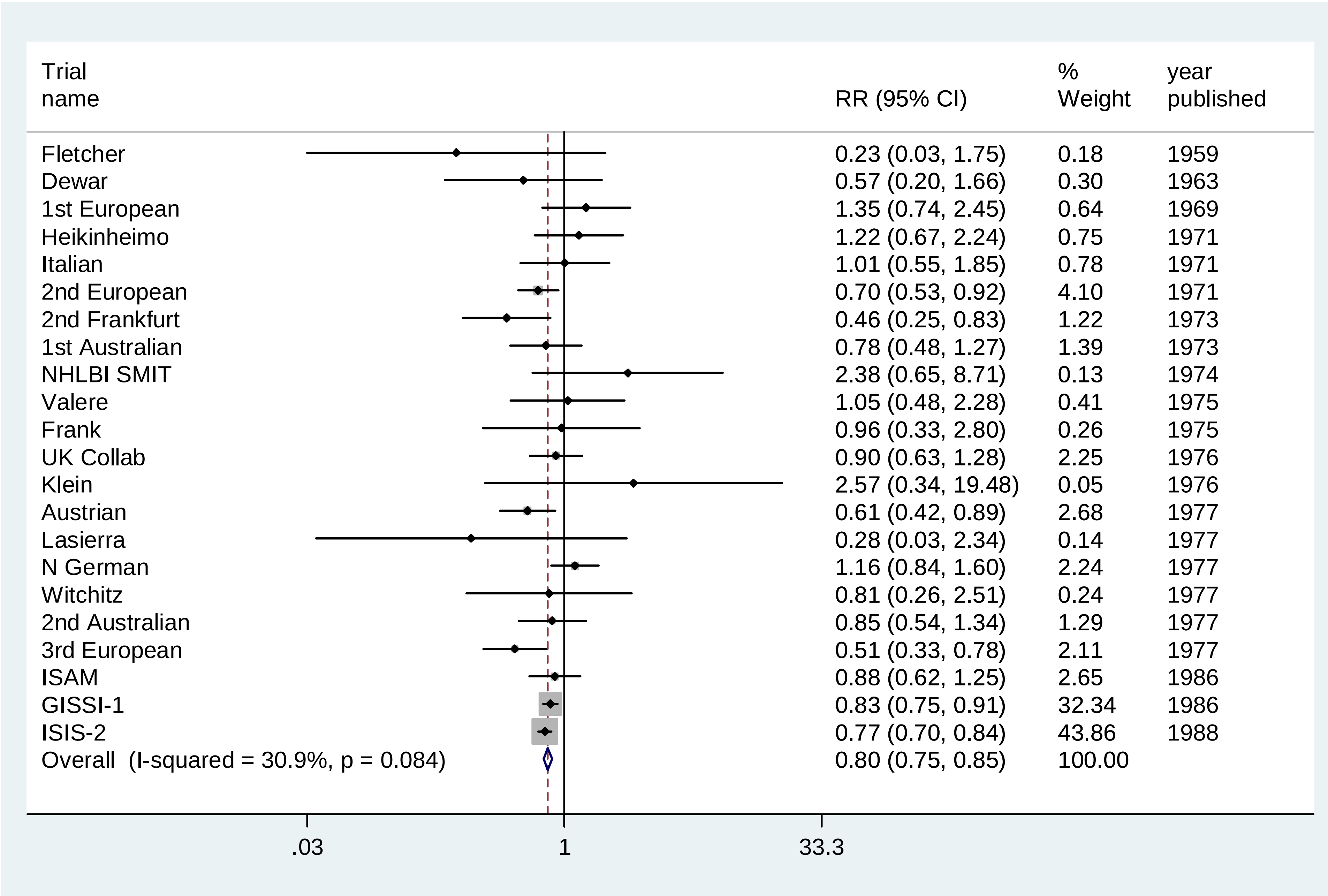
```
. metan cases1 h1 cases0 h0, aspect(0.6) ///
 lcols(trialnam year) boxsca(40) textsize(110) astext(60)
```



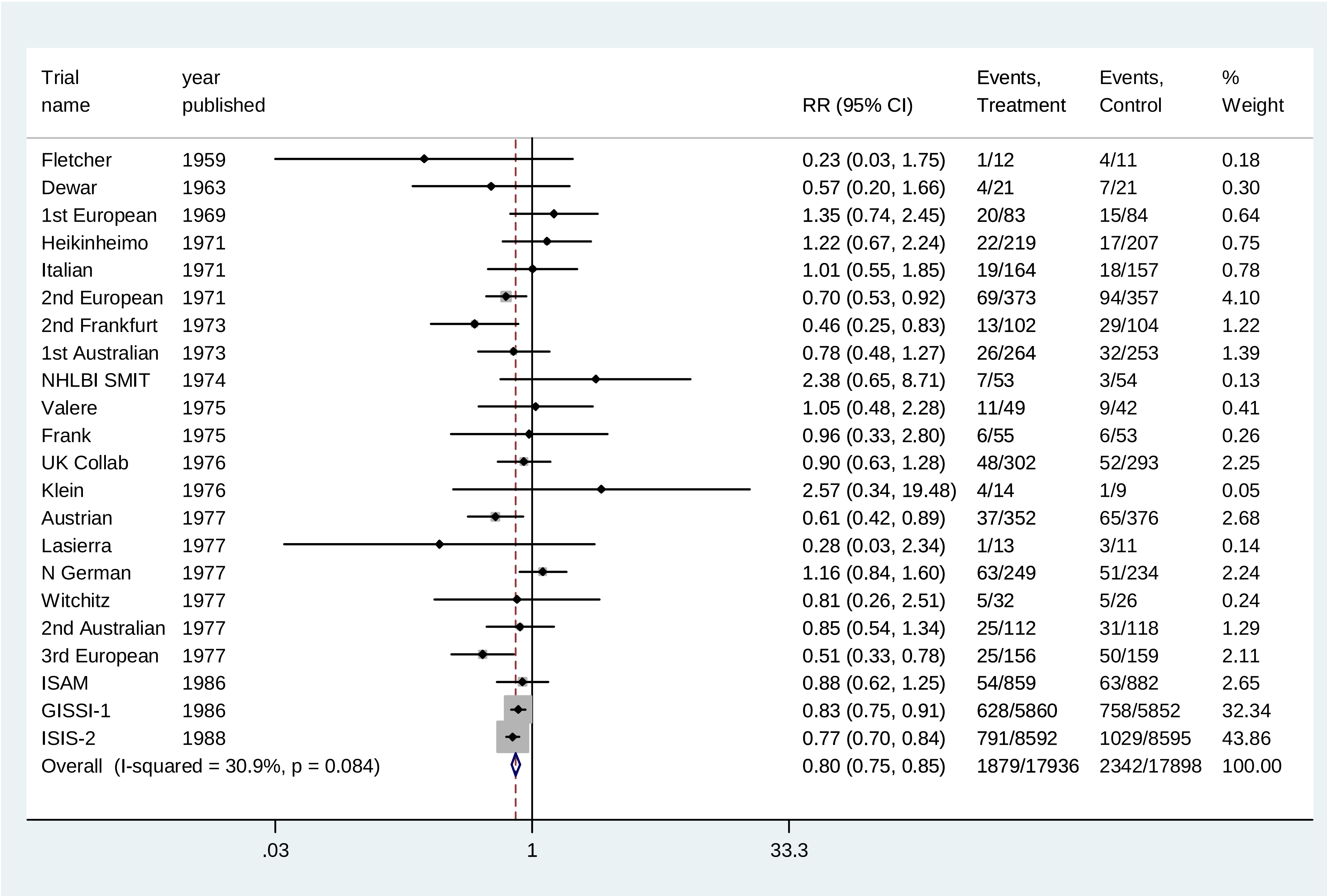
My favourite `metan` features

- Ability to add columns of text to the left and right of the forest plot, with control of the proportion of the plot used by text columns
- **`by()`** option, with flexibility as to whether meta-analyses are conducted within and/or across subgroups
- Ability to include both fixed- and random-effects meta-analyses on the same plot

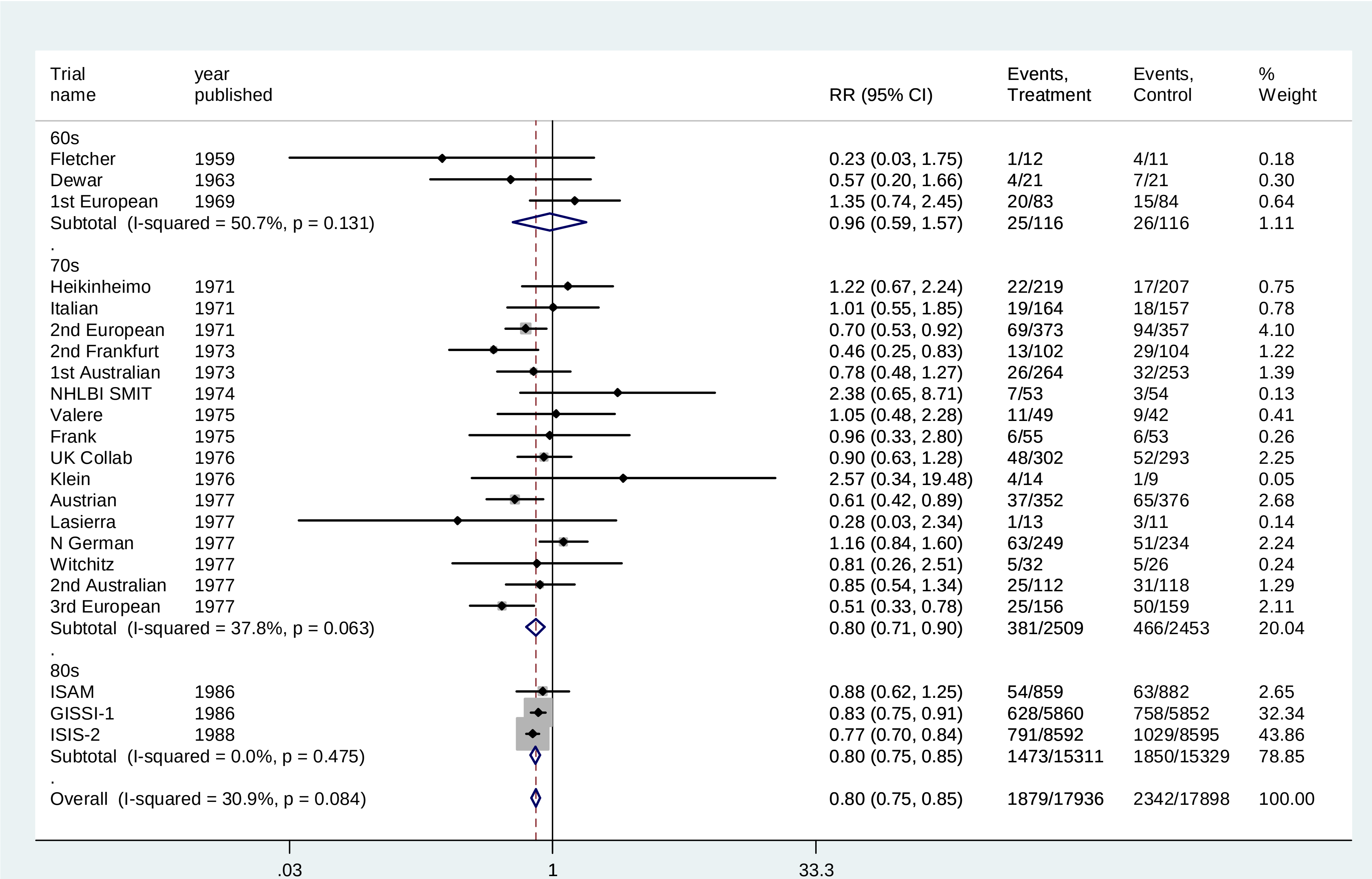
```
. metan cases1 h1 cases0 h0, aspect(0.6) lcols(trialnam) ///
rcols(year) boxsca(40) textsize(110) astext(60)
```



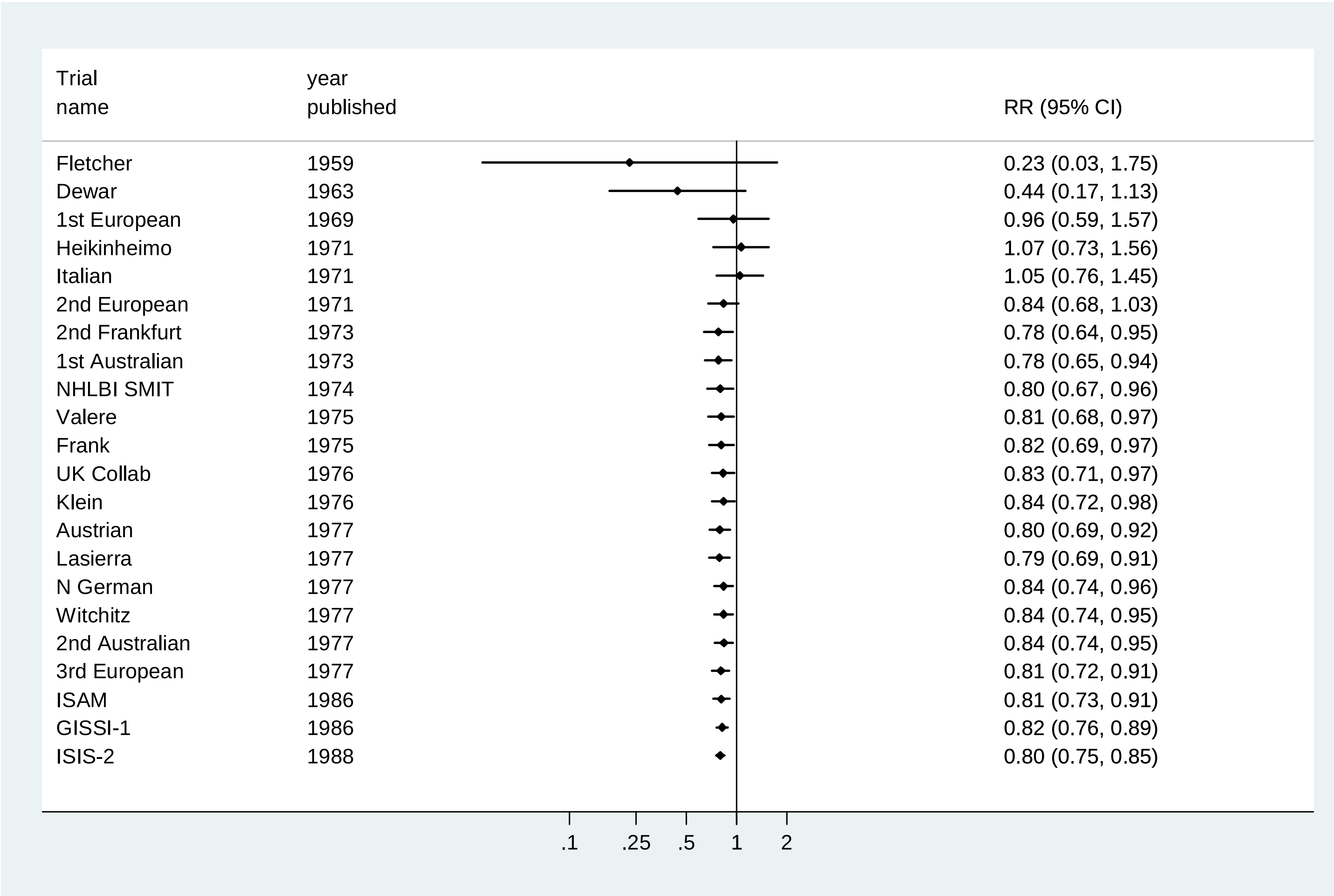
```
. metan cases1 h1 cases0 h0, aspect(0.6) counts ///
lcols(trialnam year) boxsca(50) textsize(130) astext(60)
```



```
. metan cases1 h1 cases0 h0, aspect(0.6) lcols(trialnam year)
counts boxsca(50) textsize(110) astext(60) by(decade)
```



```
. metacum cases1 h1 cases0 h0, aspect(0.6) lcols(trialnam
year) fixed astext(60) xlab(0.1,0.2,5,0.5,1,2)
```



Random-effects meta-analysis

- We assume the *true* treatment effect in each study is randomly, normally distributed between studies, with variance t^2
- Estimate the between-study variance t^2, and use this to modify the weights
  - The usual estimate of t^2 is the DerSimonian and Laird estimate

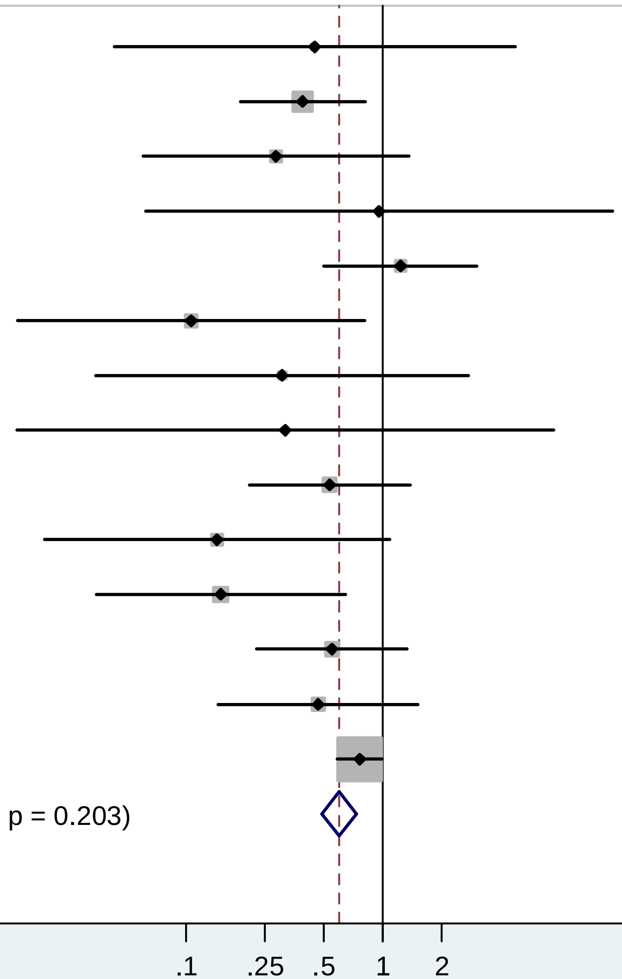
$$\log \mathrm{OR}_R = \frac{\sum_{i=1}^{k} w_i^* \log \mathrm{OR}_i}{\sum_{i=1}^{k} w_i^*} \quad \text{where} \quad w_i^* = \frac{1}{v_i + \hat{t}^2}$$

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

Magnesium after myocardial infarction

(fixed-effect meta-analysis excluding ISIS-4)

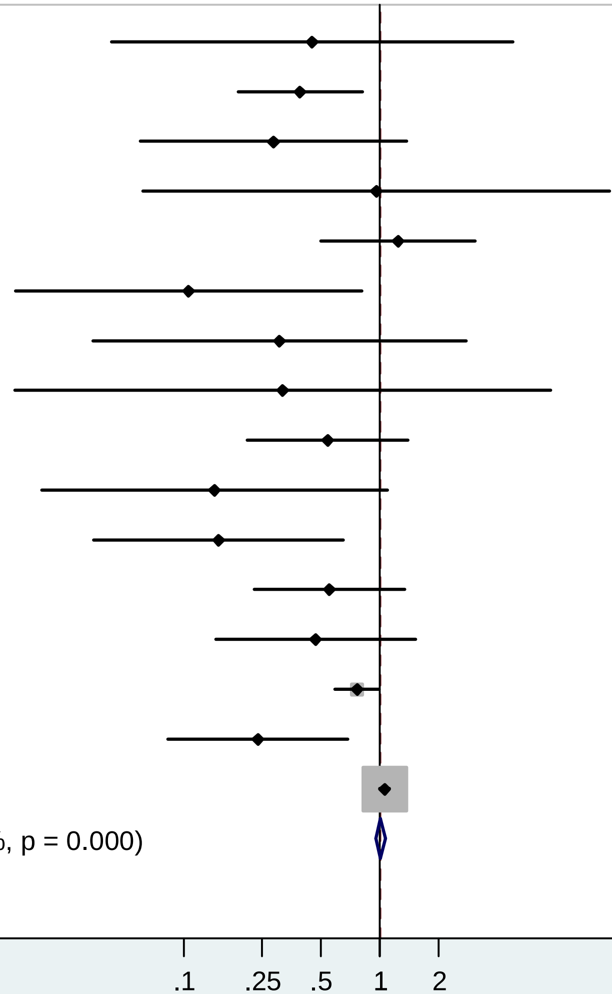
Trial name	Year of publication	RR (95% CI)	Events, Treatment	Events, Control	% Weight
Morton	1984	0.45 (0.04, 4.76)	1/40	2/36	0.94
Rasmussen	1986	0.39 (0.19, 0.81)	9/135	23/135	10.32
Smith	1986	0.29 (0.06, 1.36)	2/200	7/200	3.14
Abraham	1987	0.96 (0.06, 14.87)	1/48	1/46	0.46
Feldstedt	1988	1.23 (0.50, 3.04)	10/150	8/148	3.61
Schechter	1989	0.11 (0.01, 0.81)	1/59	9/56	4.14
Ceremuzynski	1989	0.31 (0.03, 2.74)	1/25	3/23	1.40
Bertschat	1989	0.32 (0.01, 7.42)	0/22	1/21	0.69
Singh	1990	0.54 (0.21, 1.38)	6/76	11/75	4.97
Pereira	1990	0.14 (0.02, 1.08)	1/27	7/27	3.14
Schechter 1	1991	0.15 (0.03, 0.65)	2/89	12/80	5.67
Golf	1991	0.55 (0.23, 1.33)	5/23	13/33	4.79
Thogersen	1991	0.47 (0.14, 1.52)	4/130	8/122	3.70
LIMIT-2	1992	0.76 (0.59, 0.99)	90/1159	118/1157	53.00
Overall (I-squared = 23.1%, p = 0.203)		0.60 (0.49, 0.74)	133/2183	223/2159	100.00



Magnesium after myocardial infarction

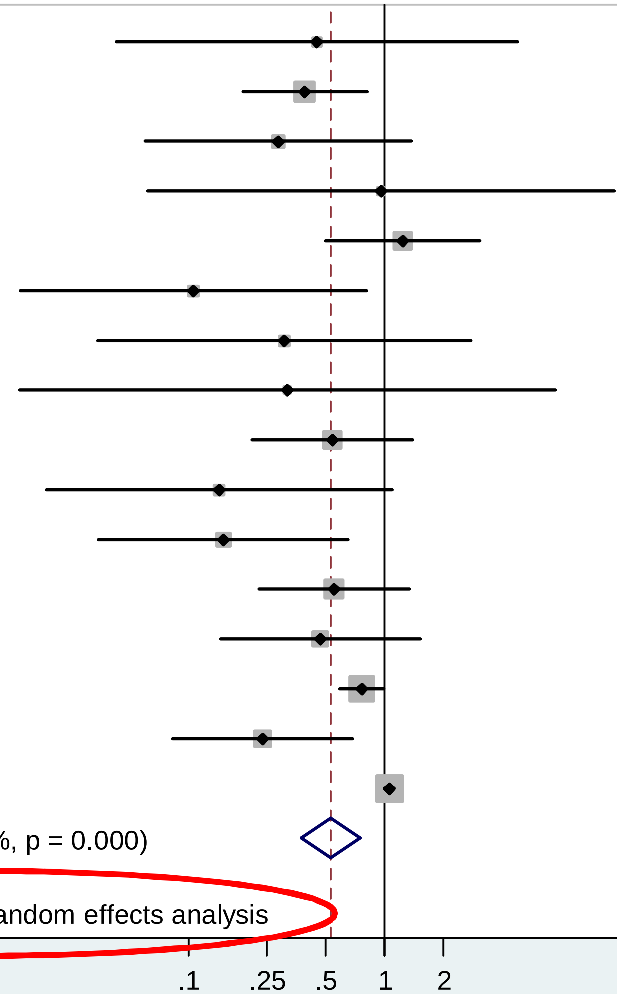
(fixed-effect meta-analysis including ISIS-4)

Trial name	Year of publication	RR (95% CI)	Events, Treatment	Events, Control	% Weight
Morton	1984	0.45 (0.04, 4.76)	1/40	2/36	0.09
Rasmussen	1986	0.39 (0.19, 0.81)	9/135	23/135	0.98
Smith	1986	0.29 (0.06, 1.36)	2/200	7/200	0.30
Abraham	1987	0.96 (0.06, 14.87)	1/48	1/46	0.04
Feldstedt	1988	1.23 (0.50, 3.04)	10/150	8/148	0.34
Schechter	1989	0.11 (0.01, 0.81)	1/59	9/56	0.39
Ceremuzynski	1989	0.31 (0.03, 2.74)	1/25	3/23	0.13
Bertschat	1989	0.32 (0.01, 7.42)	0/22	1/21	0.07
Singh	1990	0.54 (0.21, 1.38)	6/76	11/75	0.47
Pereira	1990	0.14 (0.02, 1.08)	1/27	7/27	0.30
Schechter 1	1991	0.15 (0.03, 0.65)	2/89	12/80	0.54
Golf	1991	0.55 (0.23, 1.33)	5/23	13/33	0.46
Thogersen	1991	0.47 (0.14, 1.52)	4/130	8/122	0.35
LIMIT-2	1992	0.76 (0.59, 0.99)	90/1159	118/1157	5.04
Schechter 2	1995	0.24 (0.08, 0.68)	4/107	17/108	0.72
ISIS-4	1995	1.05 (1.00, 1.12)	2216/29011	2103/2903	89.76
Overall (I-squared = 66.8%, p = 0.000)		1.01 (0.95, 1.06)	2353/31301	2343/31306	100.00



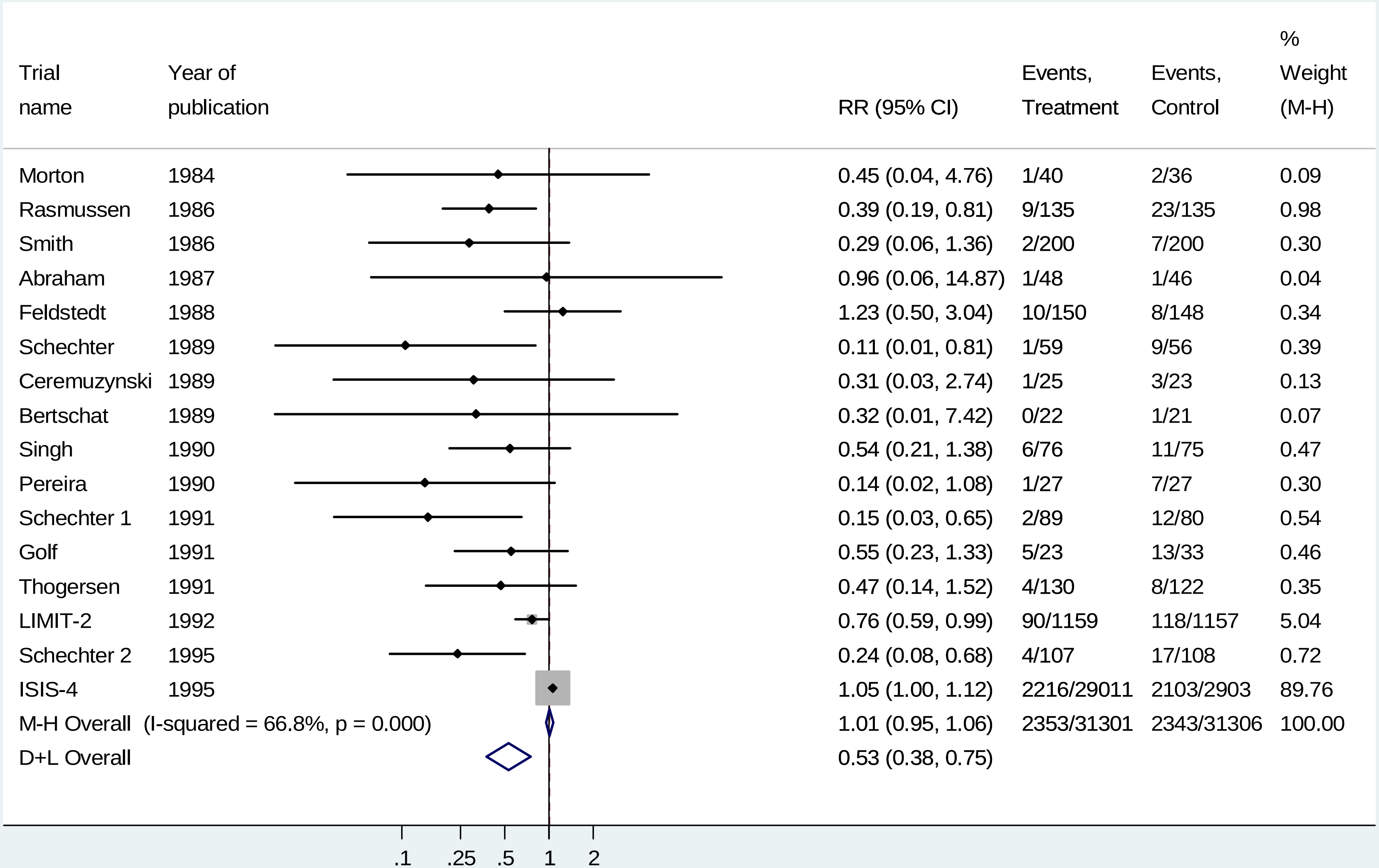
```
metan deaths1 h1 deaths0 h0, aspect(0.6) boxsca(50) ///
 lcols(trialnam year) counts textsize(150) astext(60) ///
 xlab(0.1,0.25,0.5,1,2) random
```

Trial name	Year of publication	RR (95% CI)	Events, Treatment	Events, Control	% Weight
Morton	1984	0.45 (0.04, 4.76)	1/40	2/36	1.92
Rasmussen	1986	0.39 (0.19, 0.81)	9/135	23/135	9.89
Smith	1986	0.29 (0.06, 1.36)	2/200	7/200	3.85
Abraham	1987	0.96 (0.06, 14.87)	1/48	1/46	1.46
Feldstedt	1988	1.23 (0.50, 3.04)	10/150	8/148	8.05
Schechter	1989	0.11 (0.01, 0.81)	1/59	9/56	2.49
Ceremuzynski	1989	0.31 (0.03, 2.74)	1/25	3/23	2.18
Bertschat	1989	0.32 (0.01, 7.42)	0/22	1/21	1.13
Singh	1990	0.54 (0.21, 1.38)	6/76	11/75	7.67
Pereira	1990	0.14 (0.02, 1.08)	1/27	7/27	2.50
Schechter 1	1991	0.15 (0.03, 0.65)	2/89	12/80	4.24
Golf	1991	0.55 (0.23, 1.33)	5/23	13/33	8.23
Thogersen	1991	0.47 (0.14, 1.52)	4/130	8/122	5.83
LIMIT-2	1992	0.76 (0.59, 0.99)	90/1159	118/1157	16.16
Schechter 2	1995	0.24 (0.08, 0.68)	4/107	17/108	6.69
ISIS-4	1995	1.05 (1.00, 1.12)	2216/29011	2103/2903	17.72
Overall (I-squared = 66.8%, p = 0.000)		0.53 (0.38, 0.75)	2353/31301	2343/31306	100.00



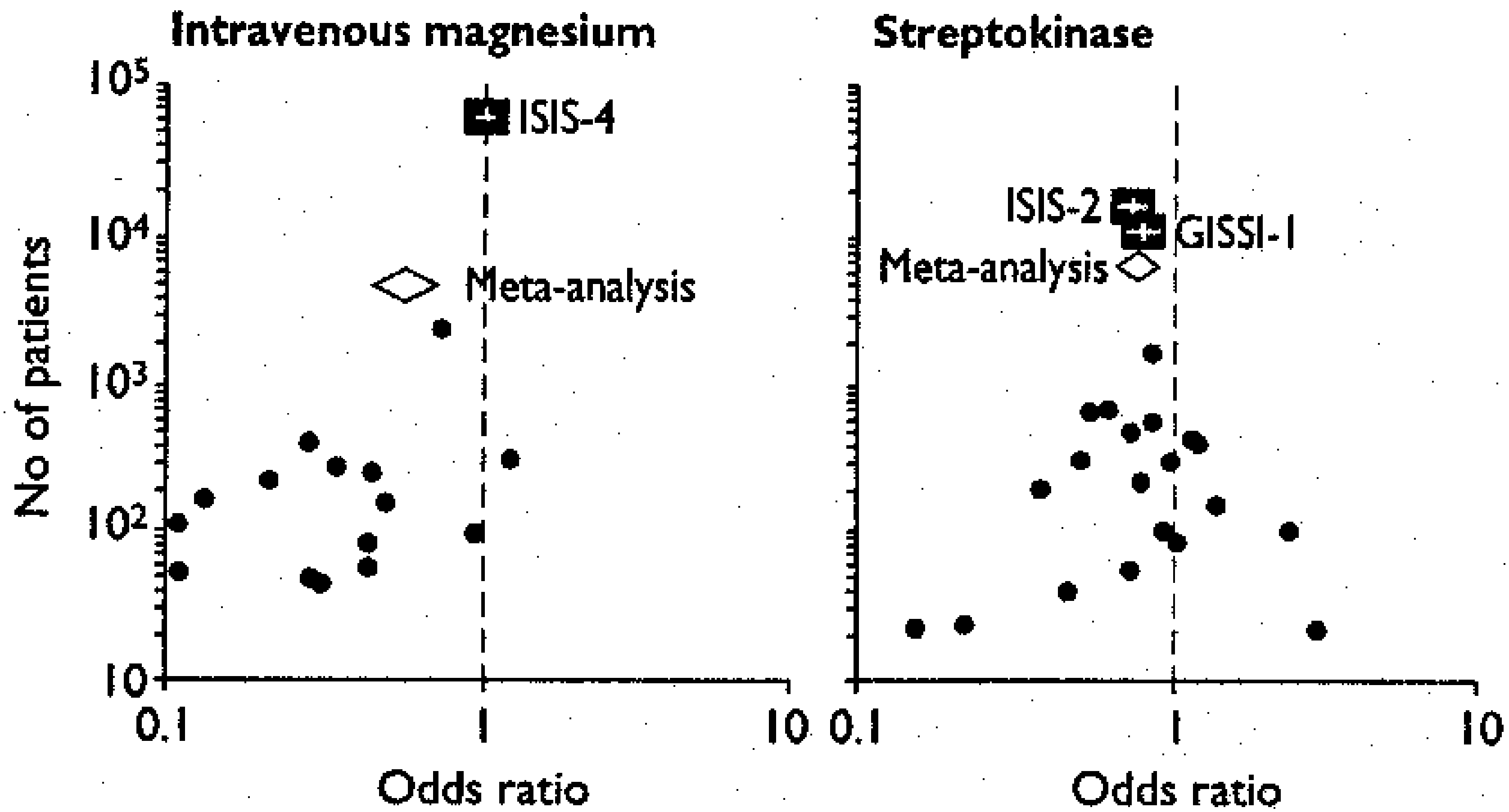
NOTE: Weights are from random effects analysis

```
metan deaths1 h1 deaths0 h0, aspect(0.6) boxsca(50) ///
 lcols(trialnam year) counts textsize(150) astext(60) ///
 xlab(0.1,0.25,0.5,1,2) second(random)
```

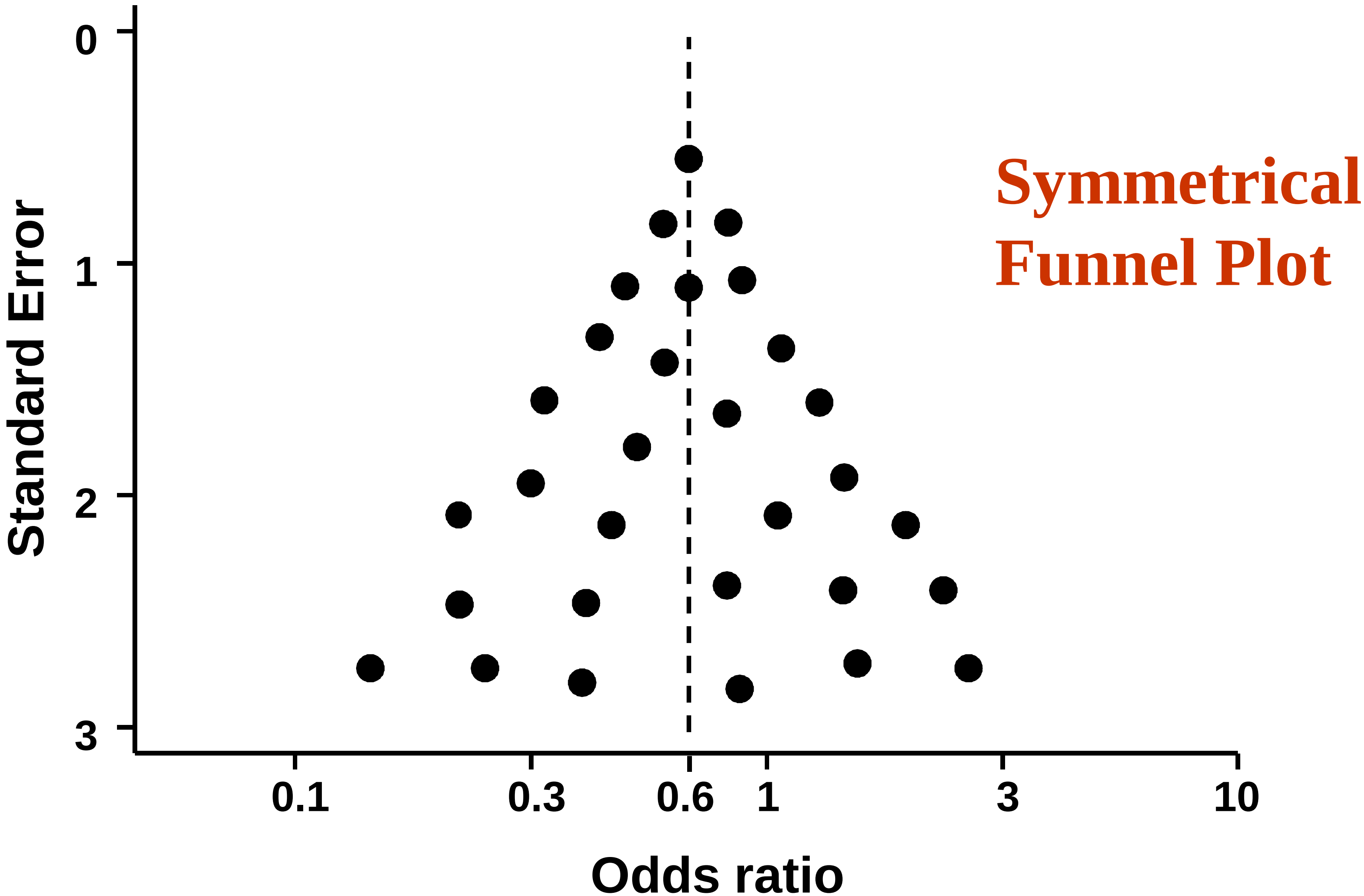


Funnel plots from Egger & Davey Smith (BMJ 1995)

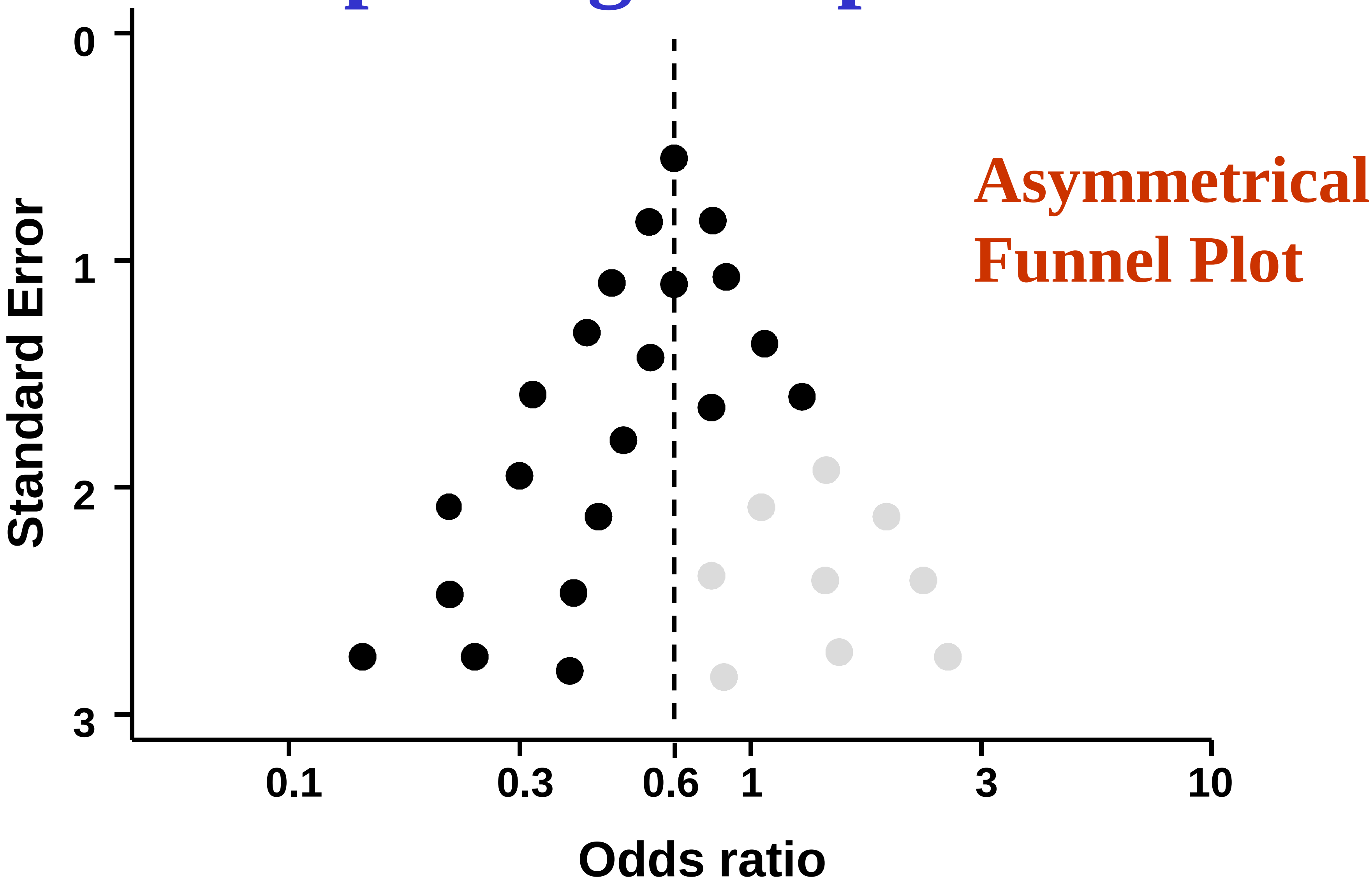
Funnel plots for meta-analyses refuted and confirmed by subsequent mega trials: intravenous magnesium (left) and streptokinase (right) in acute myocardial infarction.



No bias

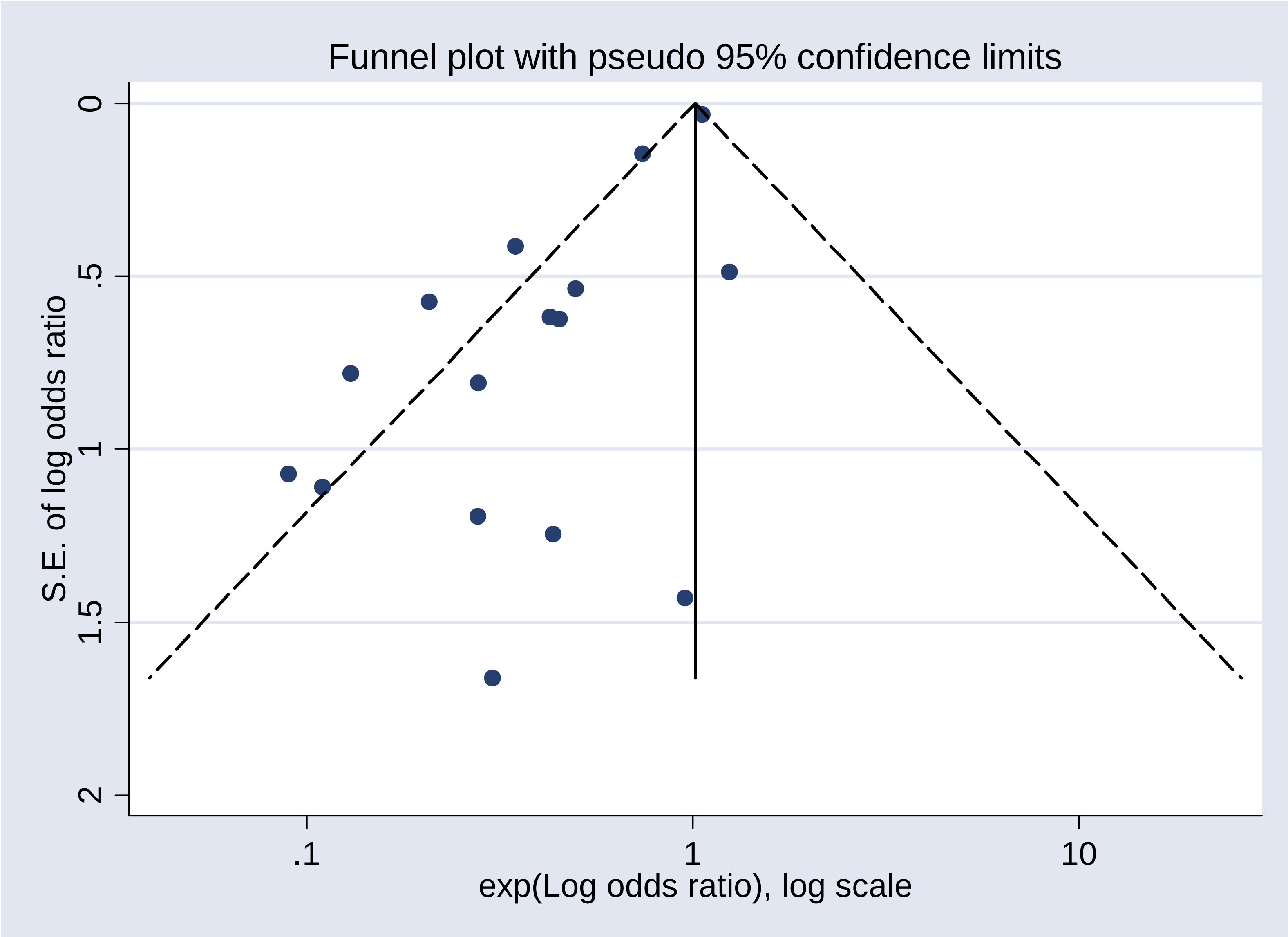

Symmetrical
Funnel Plot
Standard Error
0
1
2
3
0.1
0.3
0.6
1
3
10
Odds ratio

Reporting bias present

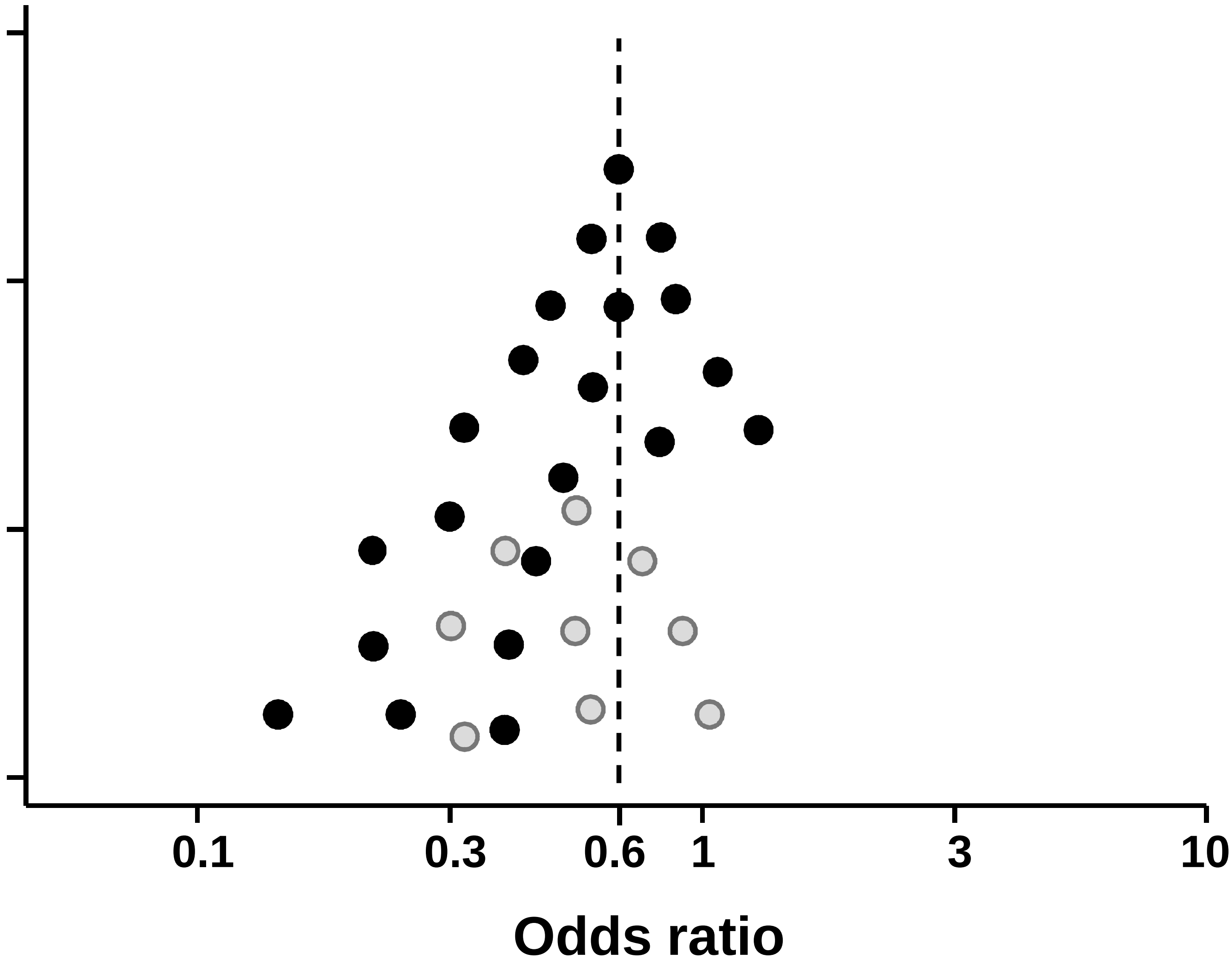


`metafunnel` (Sterne & Harbord 2004)

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



Bias because of poor quality of small trials



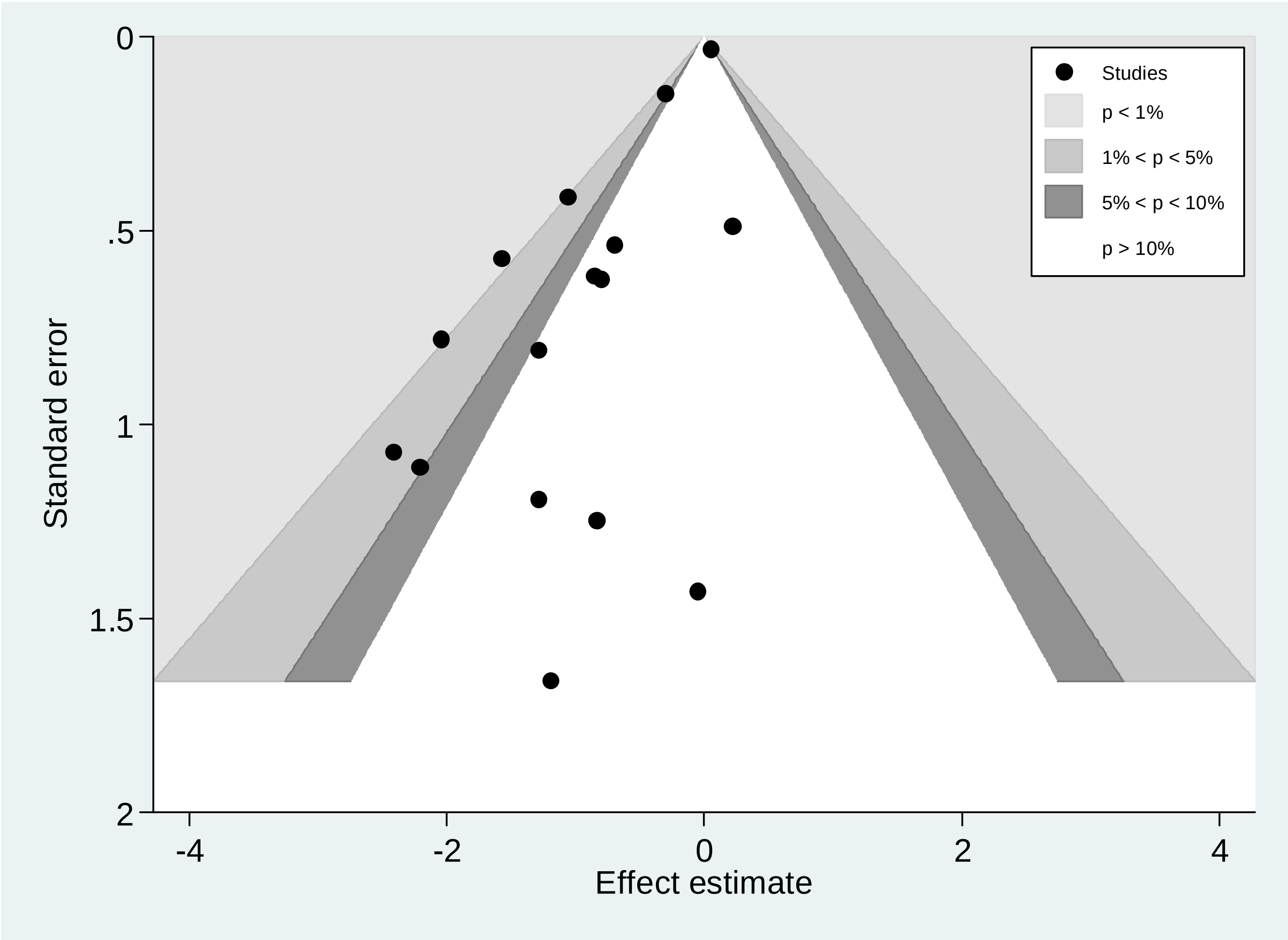
Small study effect

- 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

Contour-enhanced funnel plots (Palmer 2008)

```
confunnel logor selogor, shadedcontours
```



Statistical tests for funnel plot asymmetry – the `metabias` command

- Original command by Steichen (1997) implemented tests by Begg & Mazumdar (*Biometrics* 1994) and Egger et al. (*BMJ* 1997).
  - The paper by Egger et al. has now been cited 3000 times
- Subsequent methodological work showed that there are statistical problems with these tests, and alternatives have been proposed

`metabias` (Steichen 1997, Harbord 2008)

Excluding ISIS-4:

```
. metabias deaths1 h1 deaths0 h0 if trial<16, harbord

Harbord's modified test for small-study effects:
Regress Z/sqrt(V) on sqrt(V) where Z is efficient score and V is score variance

Number of studies =  15                         Root MSE      =   1.033
Z/sqrt(V) |      Coef.   Std. Err.    t    P>|t|   [95% Conf. Interval]
----------+-----------------------------------------------------------
  sqrt(V) |  -.1975284   .1837316  -1.08   0.302  -.5944565    .1993997
     bias |  -1.207083   .4372929  -2.76   0.016  -2.151796   -.2623686

Test of H0: no small-study effects          P = 0.016
```

Fundamental difference between meta-analyses of RCTs and observational studies

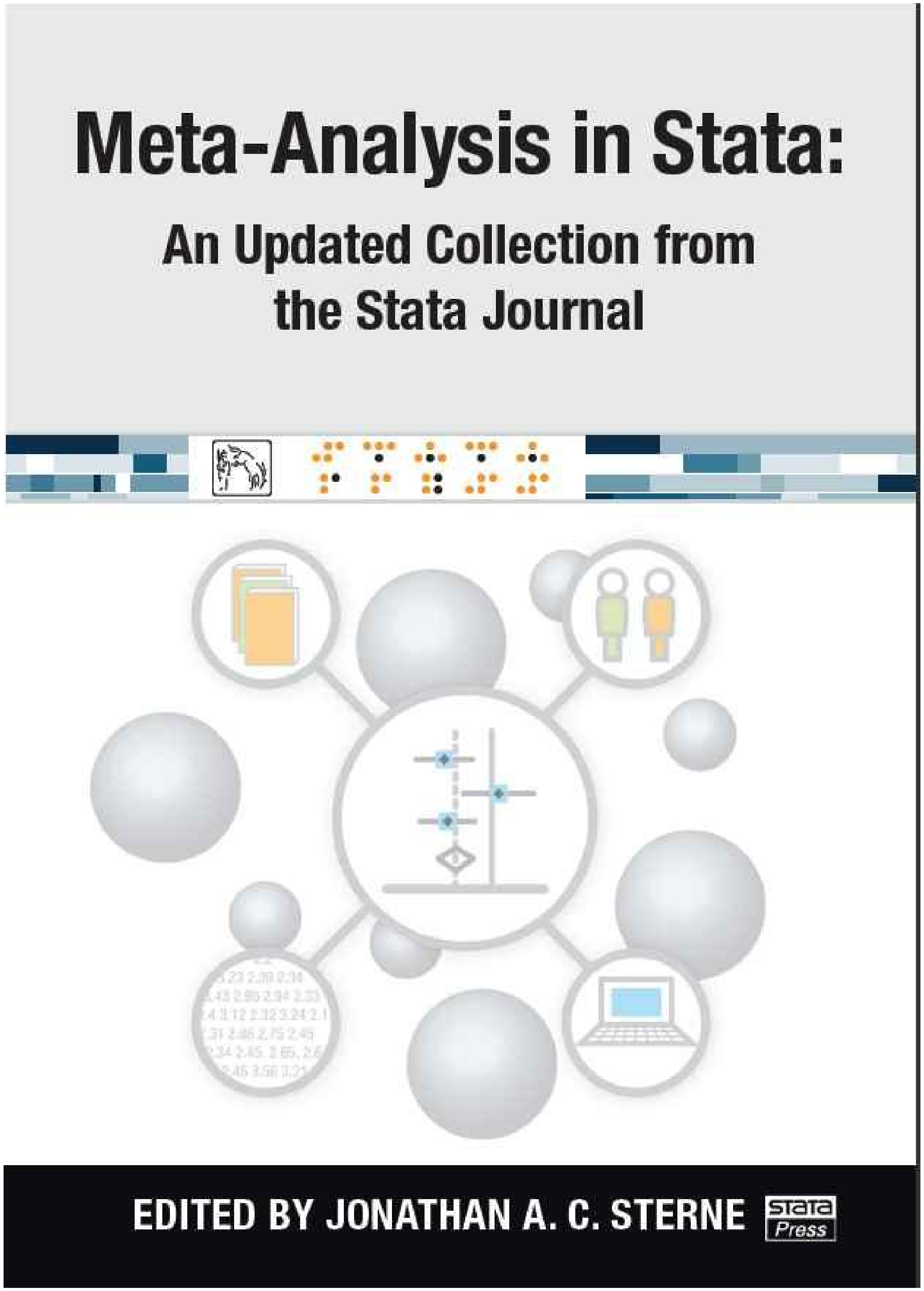
- In meta-analysis of observational studies confounding, residual confounding and bias:
  - May introduce heterogeneity
  - May lead to misleading (albeit very precise) estimates

Meta-analyses of results from observational studies

- For binary exposures, we can **use standard methods for meta-analysis** (e.g. meta-analyse the log OR and its standard error from each study)
  - Need to specify a minimum set of confounders for which we will consider a result to be "adjusted"
  - Need to consider criteria for results to be considered at low risk of bias
- For numerical or ordered categorical exposures (e.g. studies of diet and cancer), by deriving **dose-response estimates of association**
  - The `glst` command can be used for this

The future – a view from 2004

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



1. Meta-analysis in Stata: **`metan`**, **`metacum`**, and **`metap`**
2. Meta-regression: the **`metareg`** command
3. Investigating bias in meta-analysis: **`metafunnel`**, **`confunnel`**, **`metabias`**, and **`metatrim`**
4. Advanced methods: **`metandi`**, **`glst`**, **`metamiss`**, and **`mvmeta`**

Thanks to…

- Ross Harris

  - Doug Altman
  - Mike Bradburn
  - Jon Deeks
  - Matthias Egger
  - Roger Harbord
  - Stephen Sharp
  - Tom Steichen