Meta-analysis: basic principles and methods

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Contents

Systematic reviews

It all starts here . . .

Briefly, from Alma's lecture:

- Define question, population, outcome, exposure, study design(s)
- Define search strategy
- Perform search
- Extract data (Alternatively: contact authors and collate individual data)

- Display and summarize findings: *meta-analysis*

Systematic reviews

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- Define question, population, outcome, exposure, study design(s)
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- Display and summarize findings: *meta-analysis*

Meta-analysis

Meta-analysis is a 'two-stage' approach:

1. study specific estimates of effect, $\hat{\beta}_s$, and precision, $\widehat{se(\hat{\beta}_s)}$,

No.	**Study**	$\hat{\beta}_s$	$\widehat{se(\hat{\beta}_s)}$
1	MRC NSHD (UK)	0.093	0.113
2	HBCS I (Helsinki)	0.103	0.077
3	PSWG (Gothenburg)	0.201	0.142
...	...		
S			

2. Overall summary

Meta-analysis

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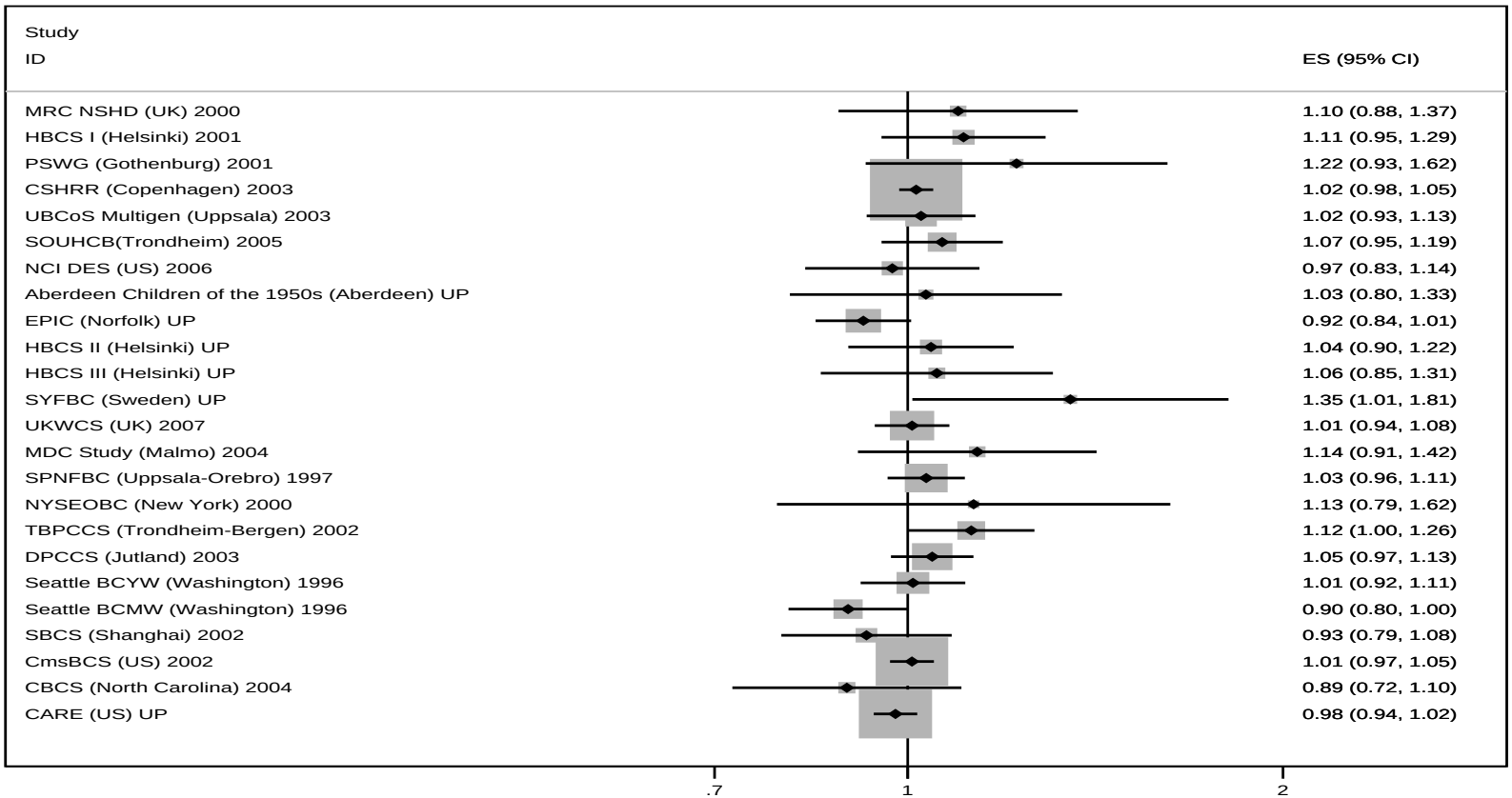
S			

2. examination of heterogeneity
3. Overall summary

An example

Birth weight and breast cancer incidence

Forest plot of rate relative risks (ES) and 95% confidence intervals



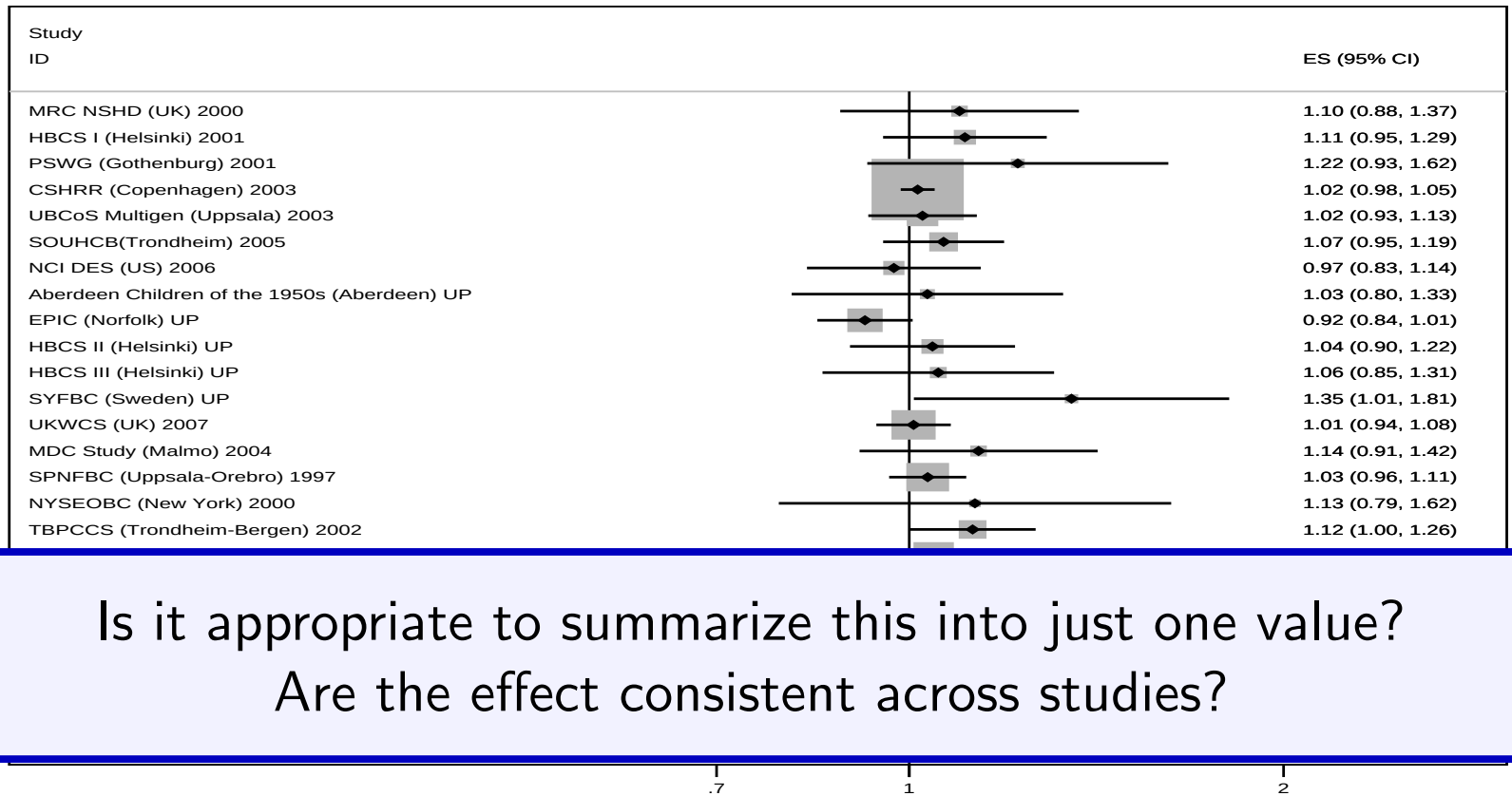
Box represents precision

Sorted by publication year

An example

Birth weight and breast cancer incidence

Forest plot of rate relative risks (ES) and 95% confidence intervals



Is it appropriate to summarize this into just one value?
Are the effect consistent across studies?

Assessing heterogeneity

1. Cochran's Q statistic:

$$Q = \sum w_s(\hat{\beta}_s - \overline{\beta})^2$$

where $w_s = 1/\widehat{\text{se}(\hat{\beta}_s)}$, and $\hat{\overline{\beta}}$ is a weighted mean of the $\hat{\beta}_s$.

Used to test whether all studies are evaluating the same effect, but has low power

2. Higgins and Thompson's I^2:

$$I^2 = (Q - df)/Q \times 100$$

the proportion of total variability explained by heterogeneity

Values $< 25\%$ re thought to be 'low' ...

Assessing heterogeneity

1. Cochran's Q statistic:

$$Q = \sum w_s(\hat{\beta}_s - \overline{\beta})^2$$

where $w_s = 1/\widehat{\text{se}(\hat{\beta}_s)}$, and $\hat{\overline{\beta}}$ is a weighted mean of the $\hat{\beta}_s$.

Used to test whether all studies are evaluating the same effect, but has low power

2. Higgins and Thompson's I^2:

$$I^2 = (Q - df)/Q \times 100$$

In the example: $Q = 28.99$(df=23) p=0.18, I^2=20.7%

Pooling effects

Two main ways to summarize (or pool) the separate study effects:

Fixed effects model

Assume each study measures the same effect:

$$\hat{\beta}_s = \beta + e_s$$

where β: true common effect; e_s: sampling error with variance σ_e^2

Pooling effects

Two main ways to summarize (or pool) the separate study effects:

Fixed effects model

Assume each study measures the same effect:

$$\hat{\beta}_s = \beta + e_s$$

where β: true common effect; e_s: sampling error with variance σ_e^2

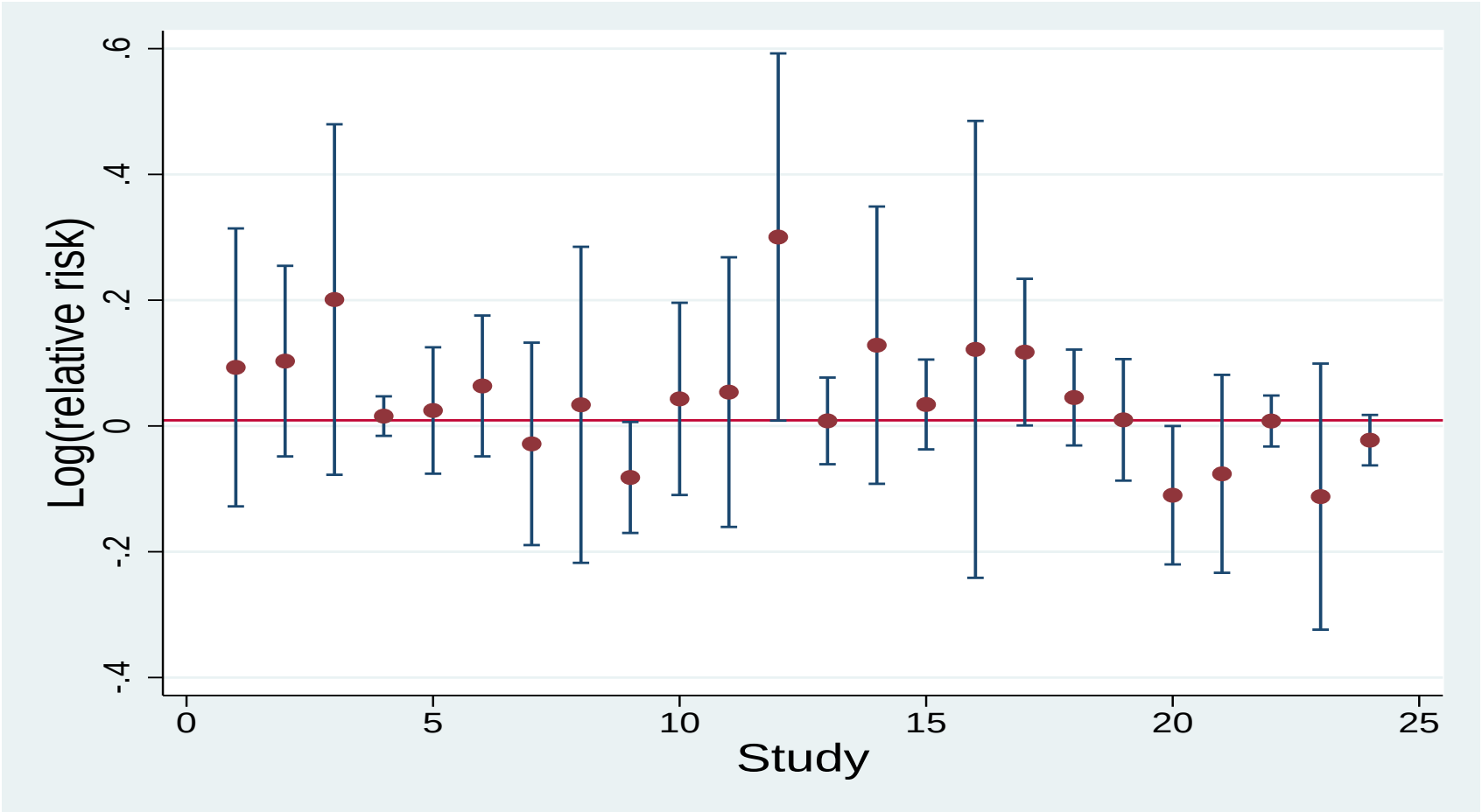
Random effects model

Assume the true effects in each study differs according to some distribution:

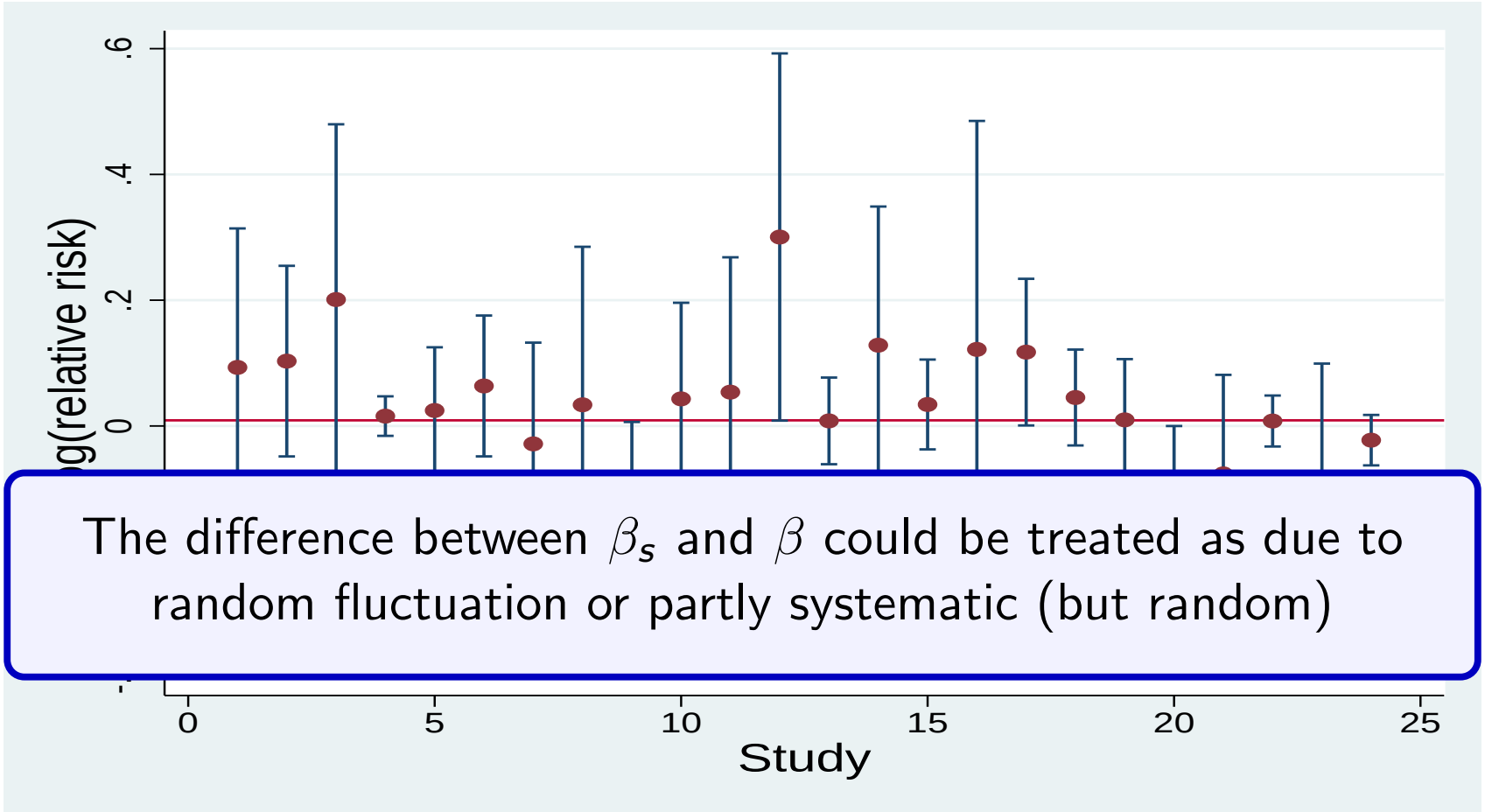
$$\hat{\beta}_s = \beta + u_s + \epsilon_s$$

u_s: rv with mean 0 and variance τ^2; $\beta_s = \beta + u_s$;
ϵ_s: within study random error with variance σ_ϵ^2

What the models imply



What the models imply



The difference between β_s and β could be treated as due to random fluctuation or partly systematic (but random)

Estimation by fixed effect meta-analysis

Estimation via weighted average of the separate estimated study effects:

$$\overline{\beta}_{FE} = \frac{\sum_s w_s \hat{\beta}_s}{\sum_s w_s}$$

With a choice of weights:

a) inverse of the variance of the study effect estimate:

$$w_s = \frac{1}{\widehat{se(\hat{\beta}_s)}^2}$$

b) Mantel-Haenszel weights (for ORs)

c) Peto's weights (for ORs)

Estimation by random effects meta-analysis

Estimation via weighted average of the separate estimated study effects:

$$\overline{\beta}_{\text{RE}} == \frac{\sum_s w_s \hat{\beta}_s}{\sum_s w_s}$$

where weights are:

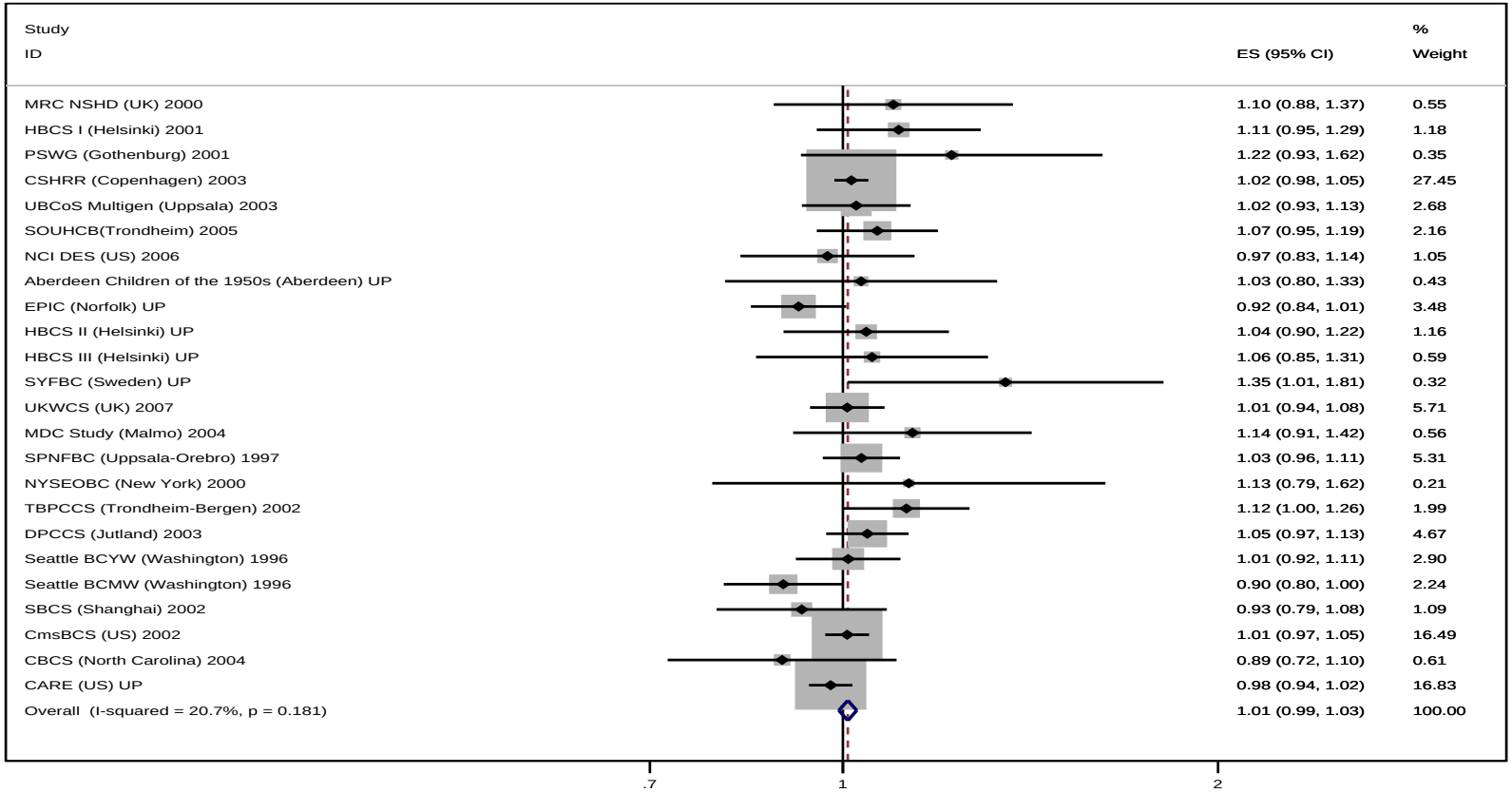
$$w_s = \frac{1}{\widehat{\text{se}(\hat{\beta}_s)}^2 + \hat{\tau}^2}$$

and τ^2 is estimated from the Q statistic

(DerSimonian and Laird method)

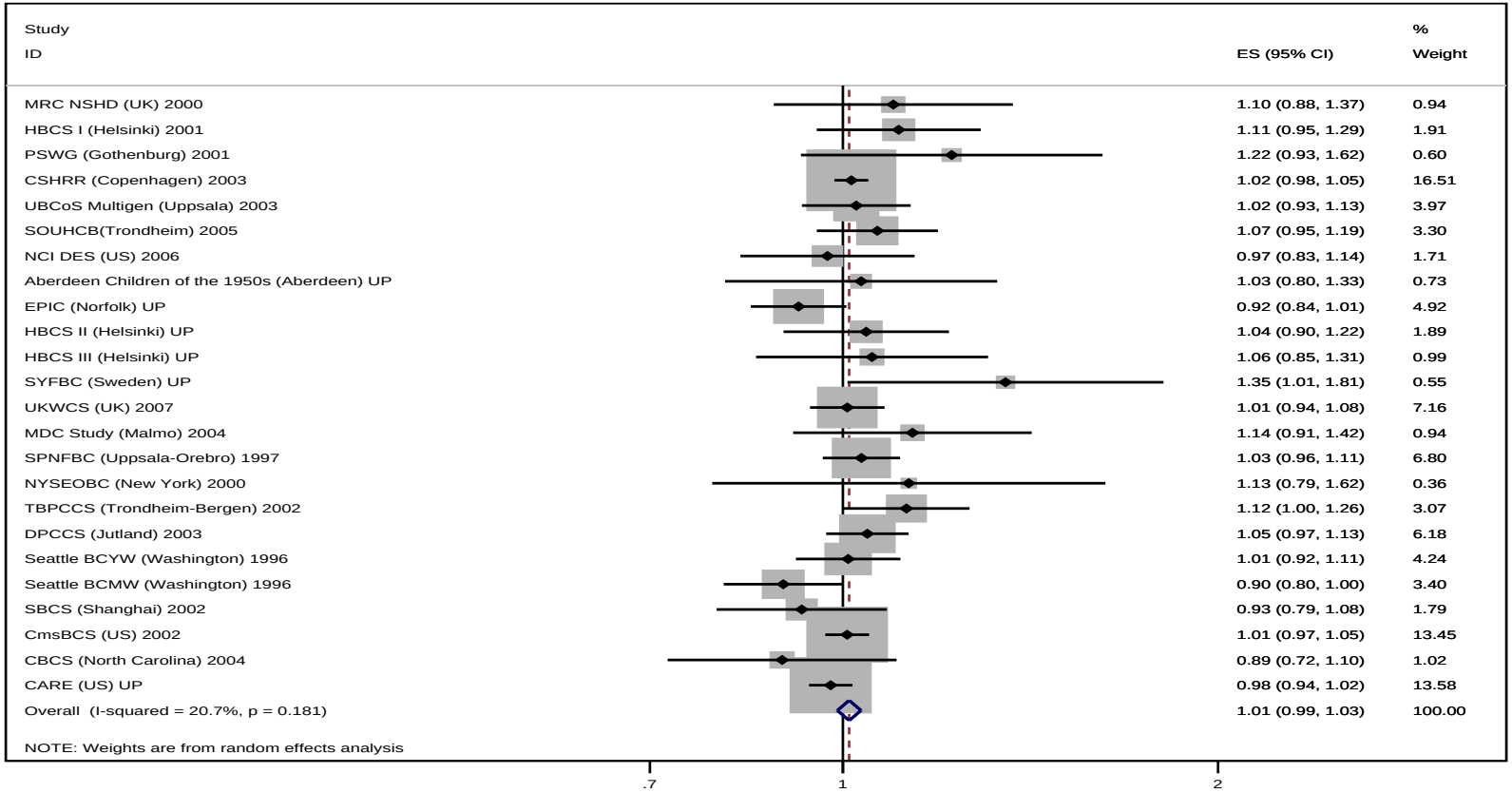
The example revisited

Fixed effect meta-analysis



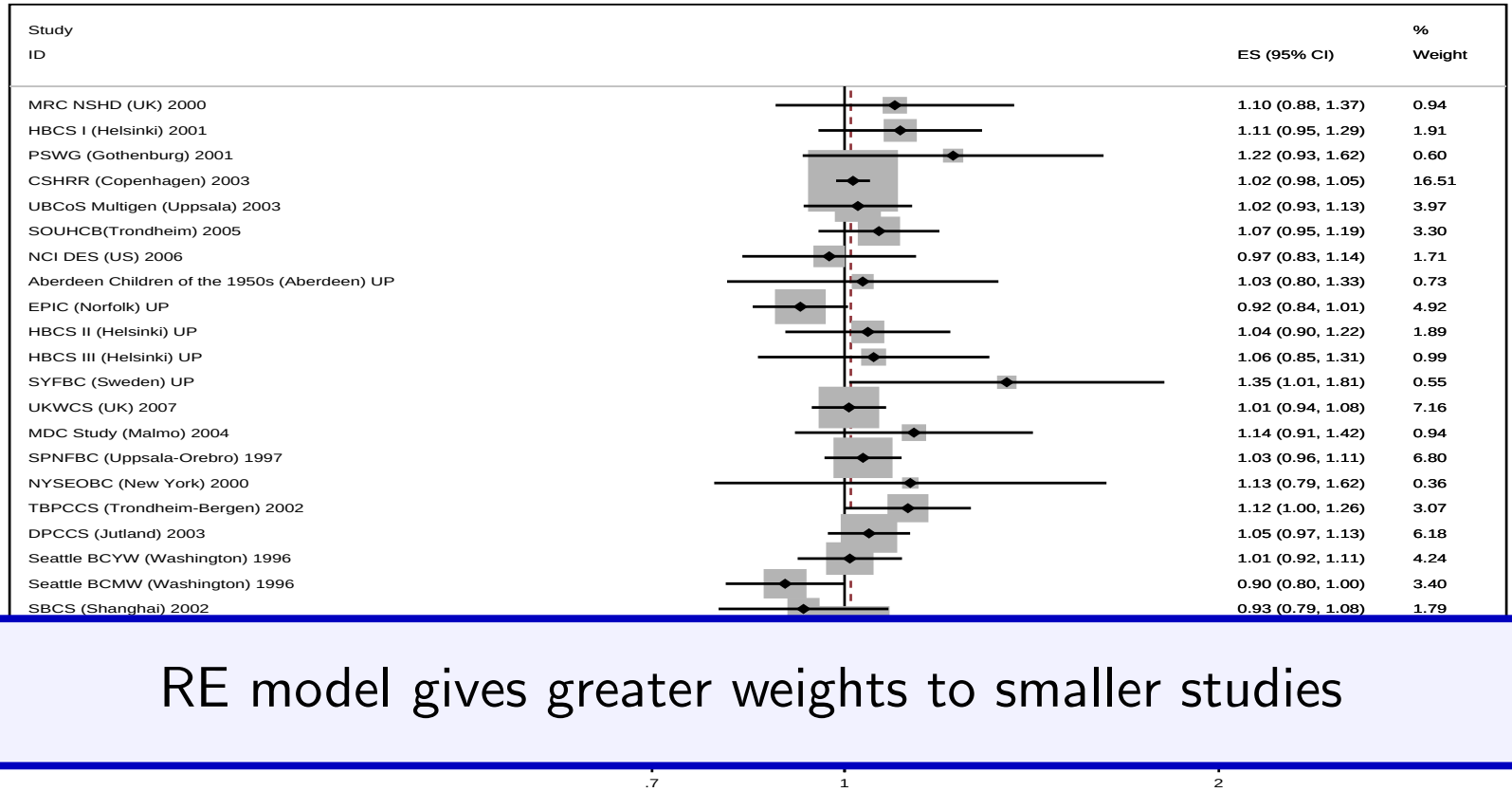
The example revisited

Random effect meta-analysis



The example revisited

Random effect meta-analysis



RE model gives greater weights to smaller studies

How to do it in Stata

'Risk of Bias'

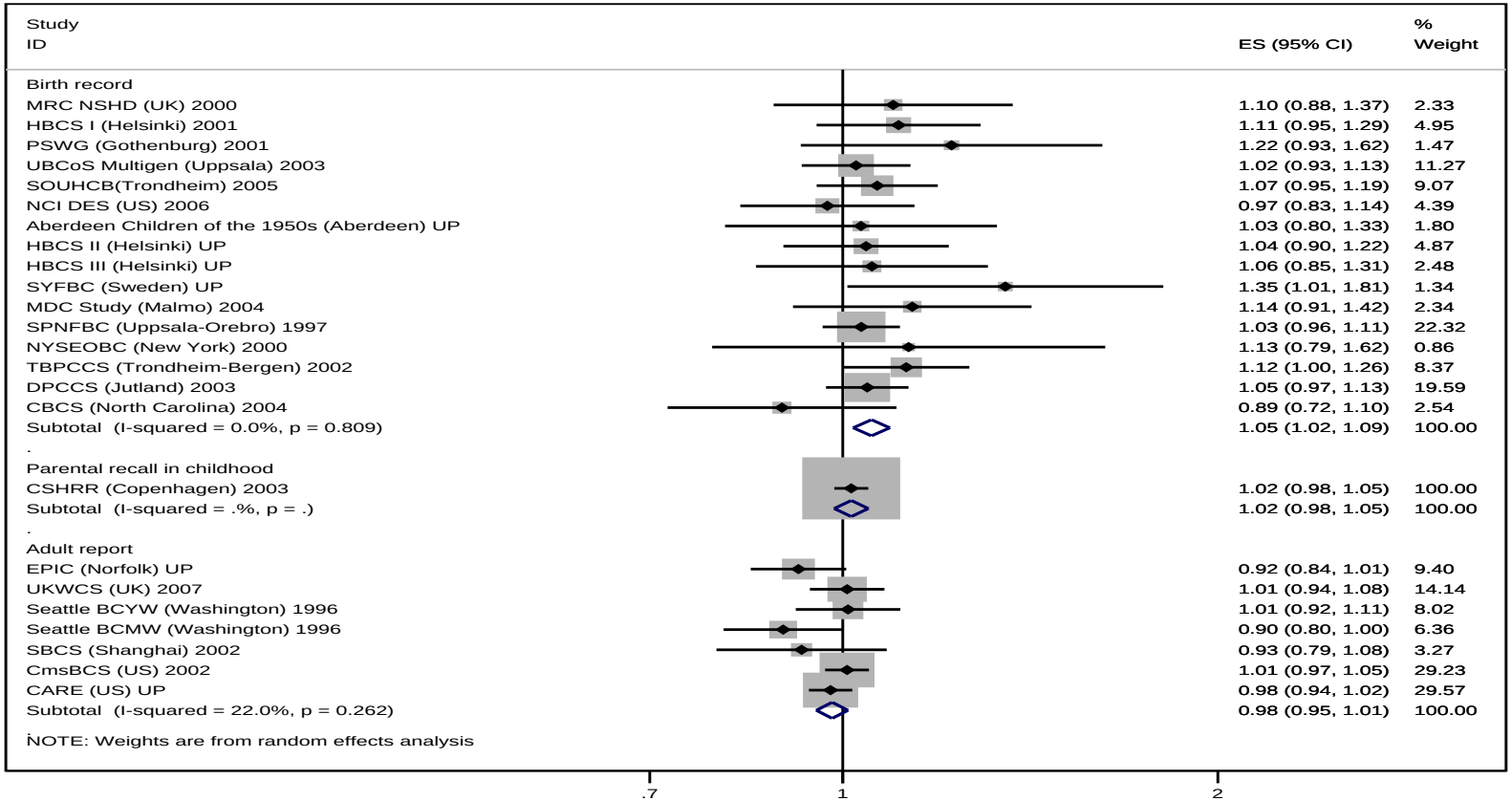
Summary estimate may be affected by bias because:

1. varying quality of the data:
   - outcome (*e.g.* via incomplete follow-up)
   - exposure (*e.g.* varying definitions)
2. publication bias:
   - studies with significant effects are more likely to be published
   - non-English language papers may not be fully represented
3. unmeasured confounding:
   - relevant for meta-analysis of observational studies

...

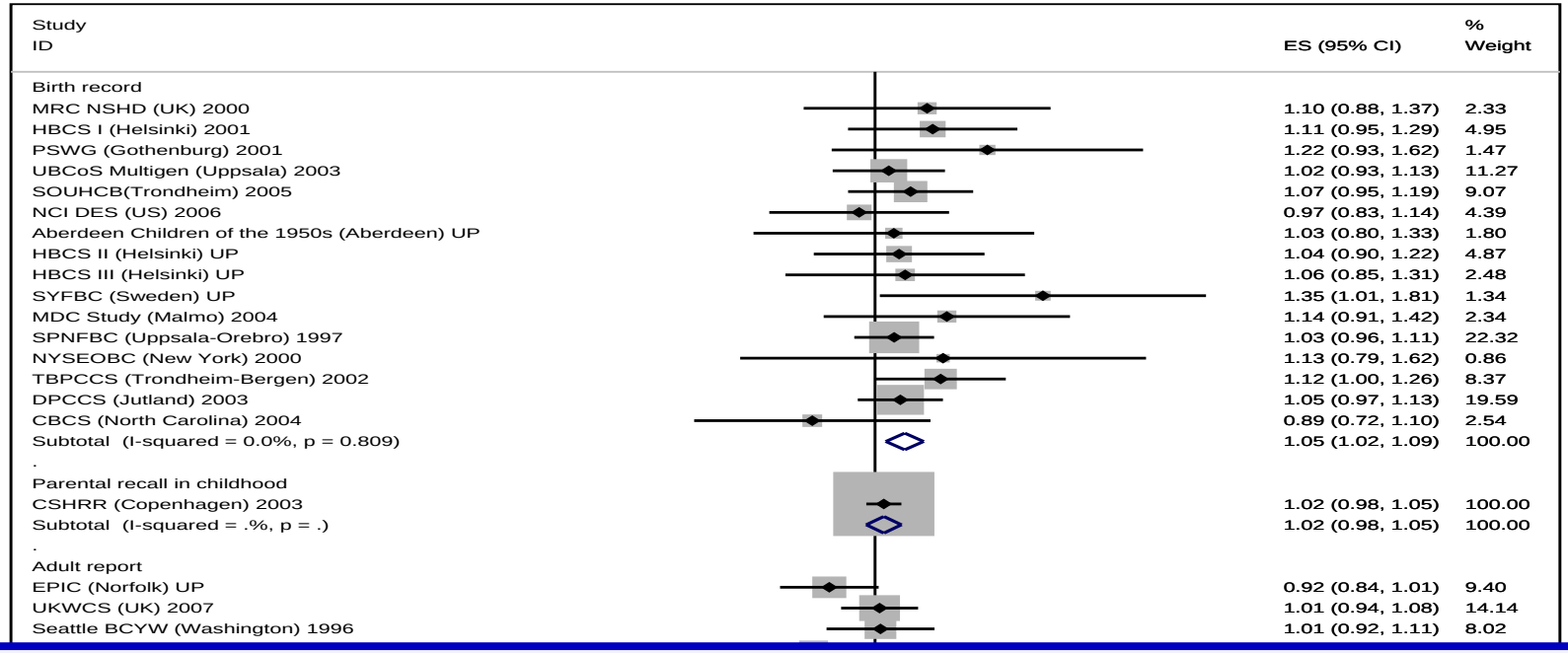
1 - Quality of the data

Stratifying by source of exposure data



1 - Quality of the data

Stratifying by source of exposure data

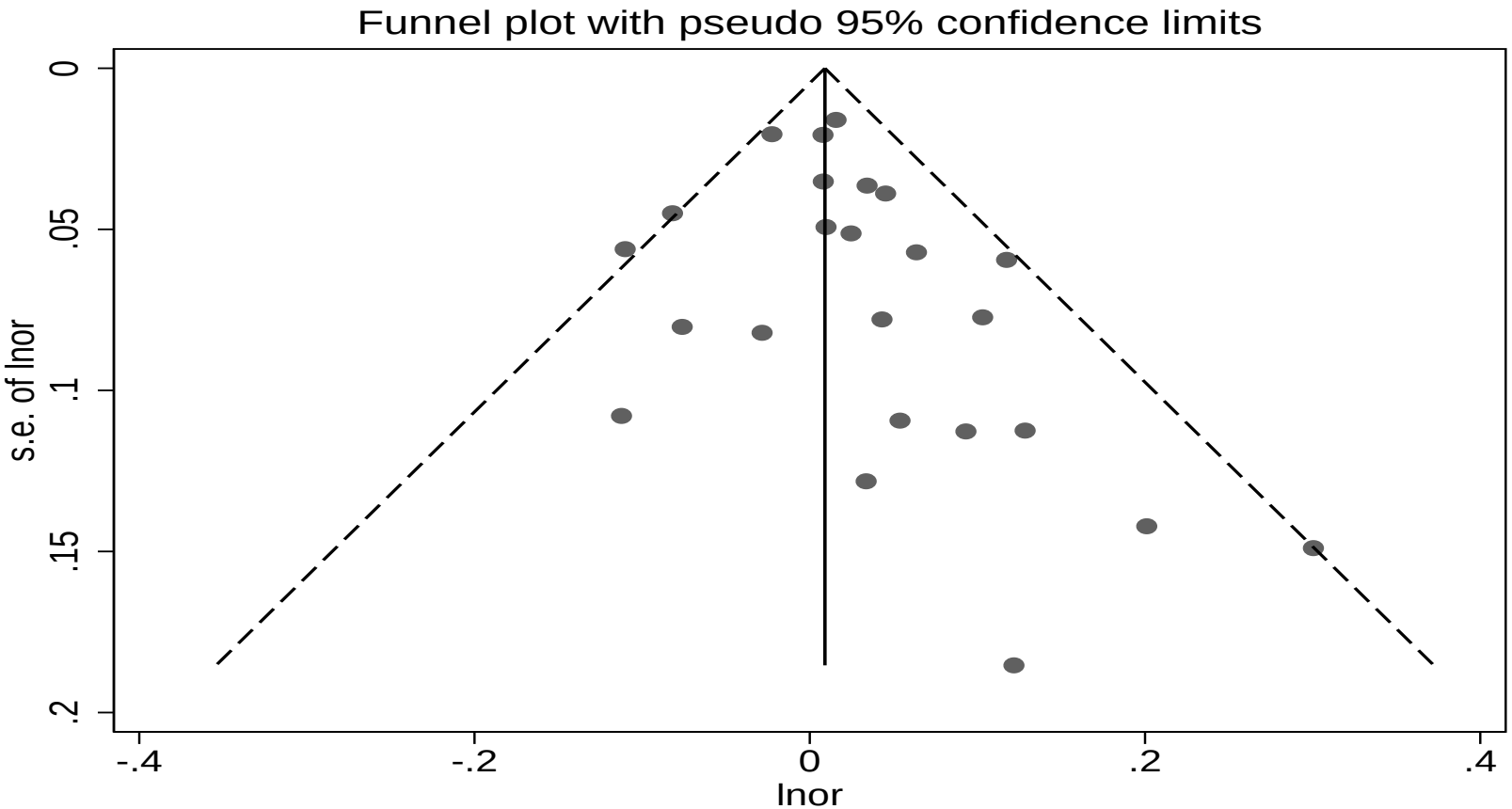


Greater homogeneity within first sub-group ("Birth records")
but not the last ("self-report")

2 - Publication bias

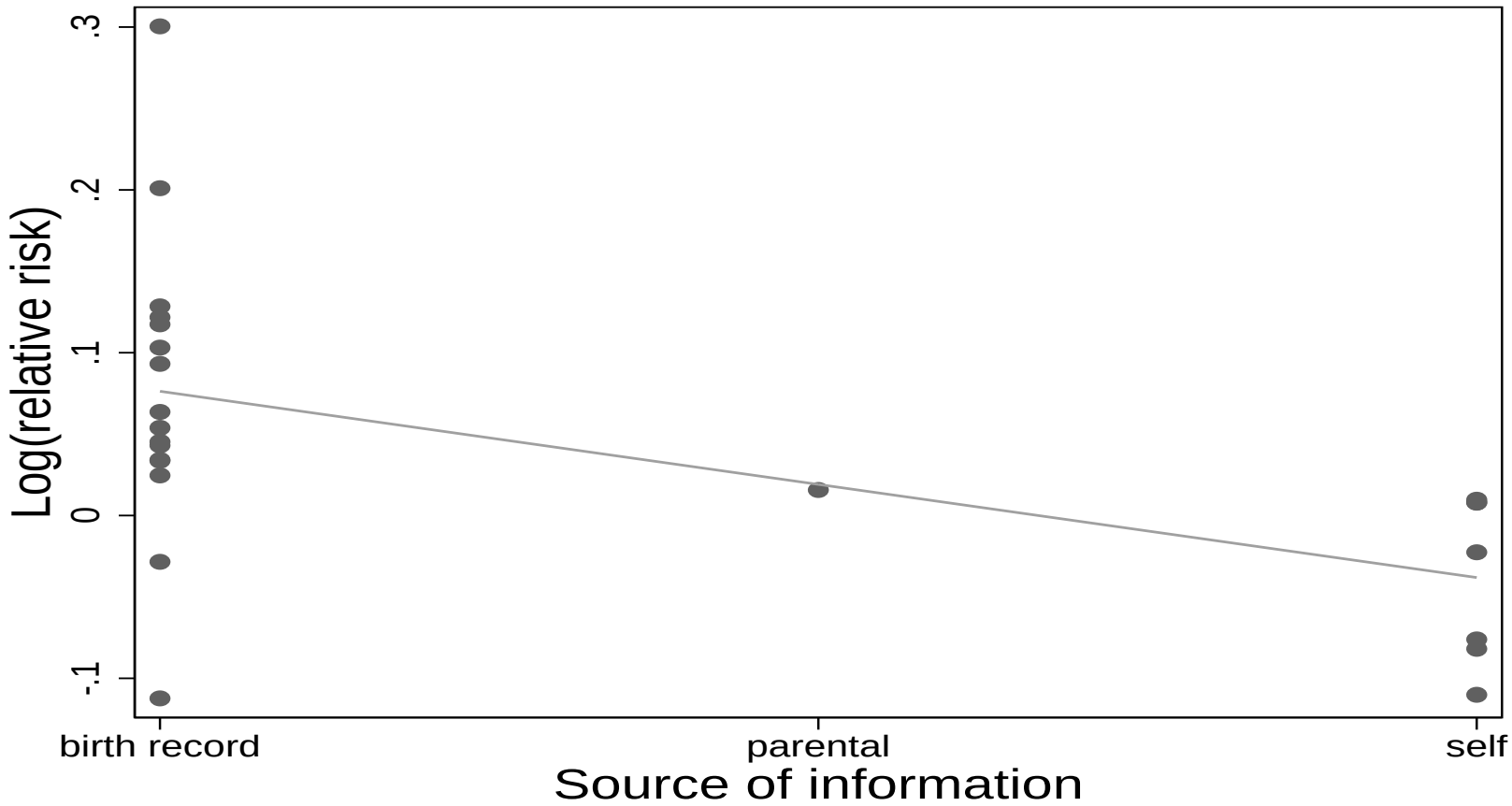
Funnel plots

Studies with low precision will show a wide variation in effects while studies with high precision will show much less variation,



Meta-regression

Combining results from multiple studies with regression, accounting for differences in precision:



Fixed or random effects?

- We should remember that this is a model fitting exercise
- The pooled summary represents:
  1. Fixed effect model: the common effect shared by all studies,
  2. Random effects model: is the *average* of the study specific effects.
- In general random effects pooled estimates are more appropriate
- If little variation across studies the choice is not crucial
- In most settings, investigation of sources of heterogeneity should be the focus

References

1. Egger M, Davey Smith G, Altman DG. Systematic Reviews in Health Care: Meta-Analysis in Context. BMJ Books: London, 2000.
2. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7:177188.
3. Higgins JP *et al.* Measuring inconsistency in meta-analysis. BMJ 2003; 327:557-560
4. Sutton AJ, Higgins JP. Recent developments in meta-analysis. Stat Med. 2008, 27: 625-650
5. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for Meta-Analysis in Medical Research. Wiley: London, 2000.
6. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Statistics in Medicine 1999; 18:26932708.

Meta Analysis in Stata

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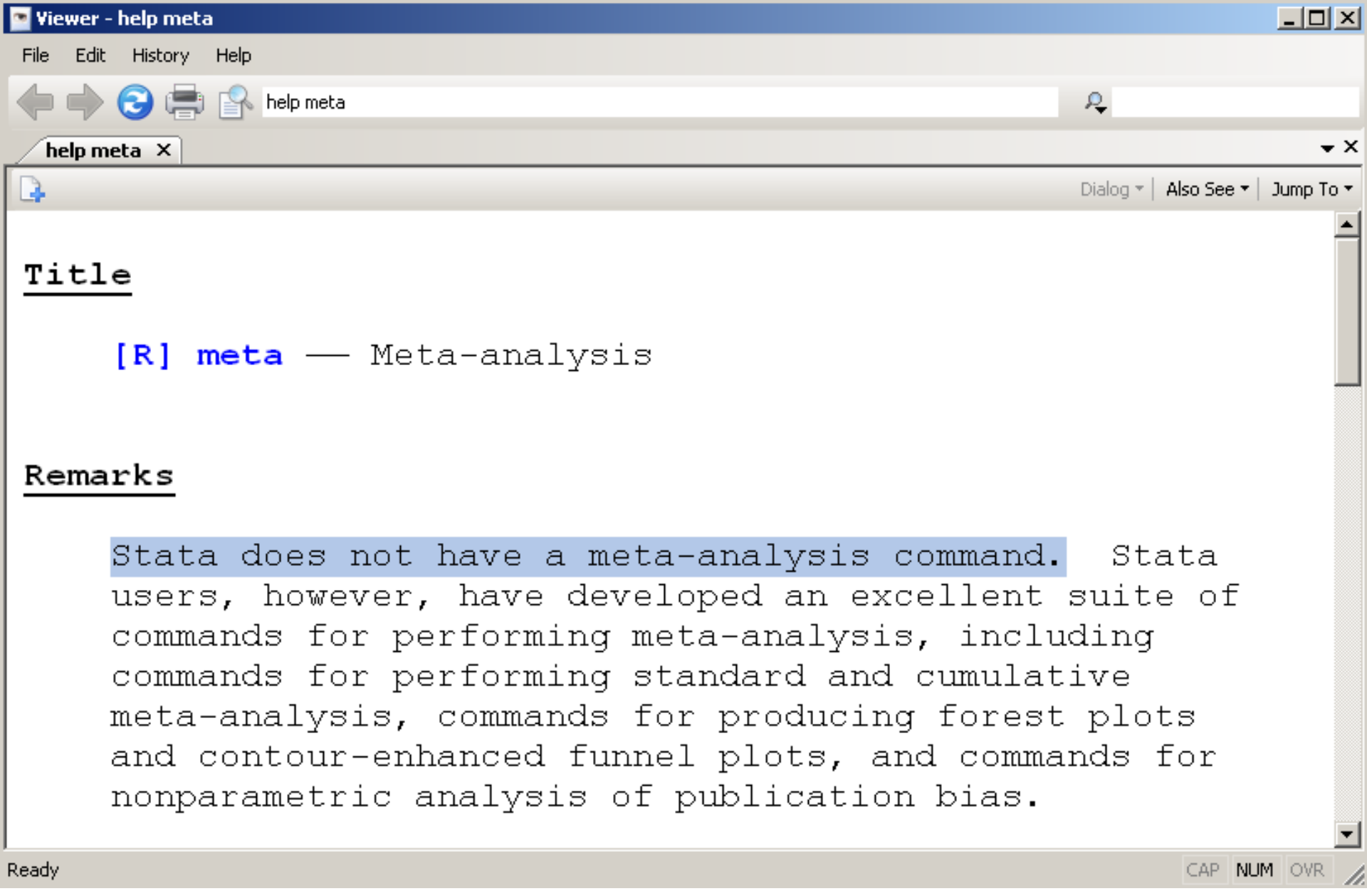
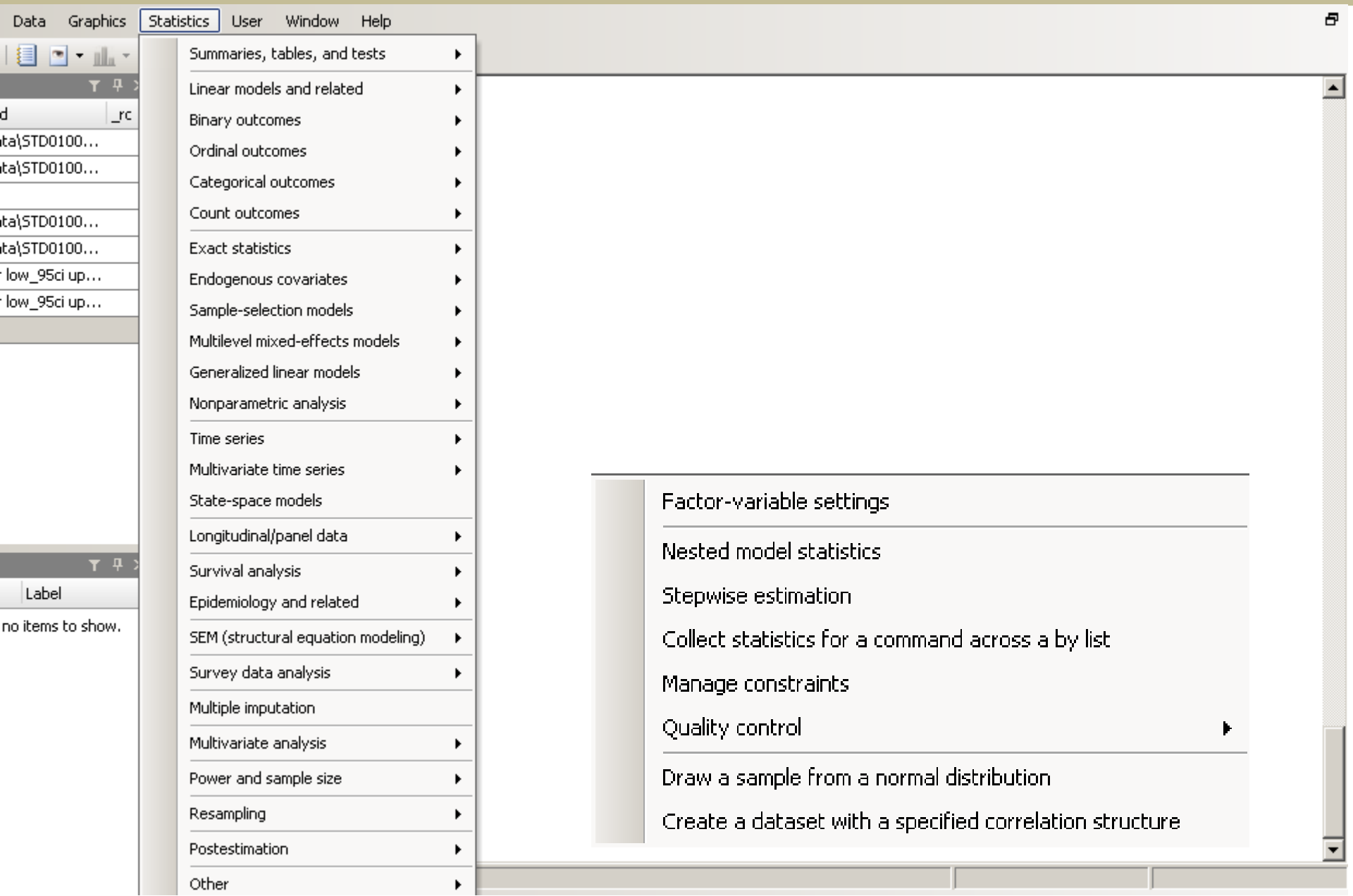
Outline

- Getting started in Stata
- FE & RE models with data in different formats using **metan** (GUI & syntax)
- Forest plots
- Investigating small study effects using **metafunnel** and **metabias**
- Investigating heterogeneity with meta-regression using **metareg**

Getting Started



Getting Started



Getting Started

```
. metan
unrecognized command:  metan
r(199);

. meta
unrecognized command:  meta
r(199);

. metafunnel
unrecognized command:  metafunnel
r(199);

. metabias
unrecognized command:  metabias
r(199);
```

Getting Started

Dialog | Also See | Jump To

Title

[R] meta — Meta-analysis

Remarks

Stata does not have a meta-analysis command. Stata users, however, have developed an excellent suite of commands for performing meta-analysis, including commands for performing standard and cumulative meta-analysis, commands for producing forest plots and contour-enhanced funnel plots, and commands for nonparametric analysis of publication bias.

Ready CAP NUM OVR

Getting Started

Install commands from Boston College SSC

Takes just a few seconds

```
. ssc install metaaggr.pkg , replace
checking metaaggr consistency and verifying not already installed.
installing into c:\ado\plus\...
installation complete.

. which metan
c:\ado\plus\m\metan.ado
*! 3.04 21Sep2010
```

Repeat for **metareg**, **metafunnel**, **metabias**, etc.

The Data

	trial	year	epubdate	type	ldl	trialsize	events	event_rate
1	LRC-CPPT	1984	20jan1984	Primary	4.55	3806	342	.0898581
2	4S	1994	19nov1994	Secondary	4.05	4444	1053	.2369487
3	WOSCOPS	1995	16nov1995	Primary	4.4	6595	422	.0639879
4	CARE	1996	03oct1996	Secondary	3	4159	486	.116855
5	AF/Tex-CAPS	1998	27may1998	Primary	3.45	6605	152	.0230129
6	LIPID	1998	05nov1998	Secondary	3.4	9014	1272	.1411138
7	Post-CABG	2000	11jul2000	Secondary	2.95	1351	155	.1147298
8	MIRACL	2001	04apr2001	Secondary	2.55	3086	324	.1049903
9	GREACE	2002	15jan2002	Secondary	3.45	1600	130	.08125
10	LIPS	2002	26jun2002	Secondary	2.95	1677	102	.0608229
11	HPS	2002	06jul2002	Secondary	2.8	20536	2110	.1027464
12	PROSPER	2002	23nov2002	Both	3.15	5804	881	.1517919
13	ALLHAT	2002	01dec2002	Both	3.1	10355	801	.0773539
14	ASCOT	2003	05apr2003	Primary	2.8	10305	254	.0246482
15	ALERT	2003	03jun2003	Both	3.6	2102	174	.0827783
16	PROVE-IT	2004	08apr2004	Secondary	2.05	4162	323	.0776069
17	CARDS	2004	21aug2004	Secondary	2.45	2838	128	.0451022
18	A TO Z	2004	15sep2004	Secondary	2.05	4497	652	.1449855
19	TNT	2005	07apr2005	Secondary	2.3	10001	982	.0981902

The Data – counts (2x2 tables)

	trial	pe_int	nope_int	pe_con	nope_con
1	LRC-CPPT	155	1751	187	1713
2	4S	431	1790	622	1601
3	WOSCOPS	174	3128	248	3045
4	CARE	212	1869	274	1804
5	AF/Tex-CAPS	57	3247	95	3206
6	LIPID	557	3955	715	3787
7	Post-CABG	69	607	86	589
8	MIRACL	155	1383	169	1379
9	GREACE	41	759	89	711
10	LIPS	42	802	60	773
11	HPS	898	9371	1212	9055
12	PROSPER	408	2483	473	2440
13	ALLHAT	380	4790	421	4764
14	ASCOT	100	5068	154	4983
15	ALERT	70	980	104	948
16	PROVE-IT	149	1914	174	1925
17	CARDS	51	1377	77	1333
18	A TO Z	309	1956	343	1889
19	TNT	434	4561	548	4458

pe_int =
number with PE in intervention group

nope_int =
number without PE in intervention group

pe_con =
number with PE in control group

nope_con =
number without PE in control group

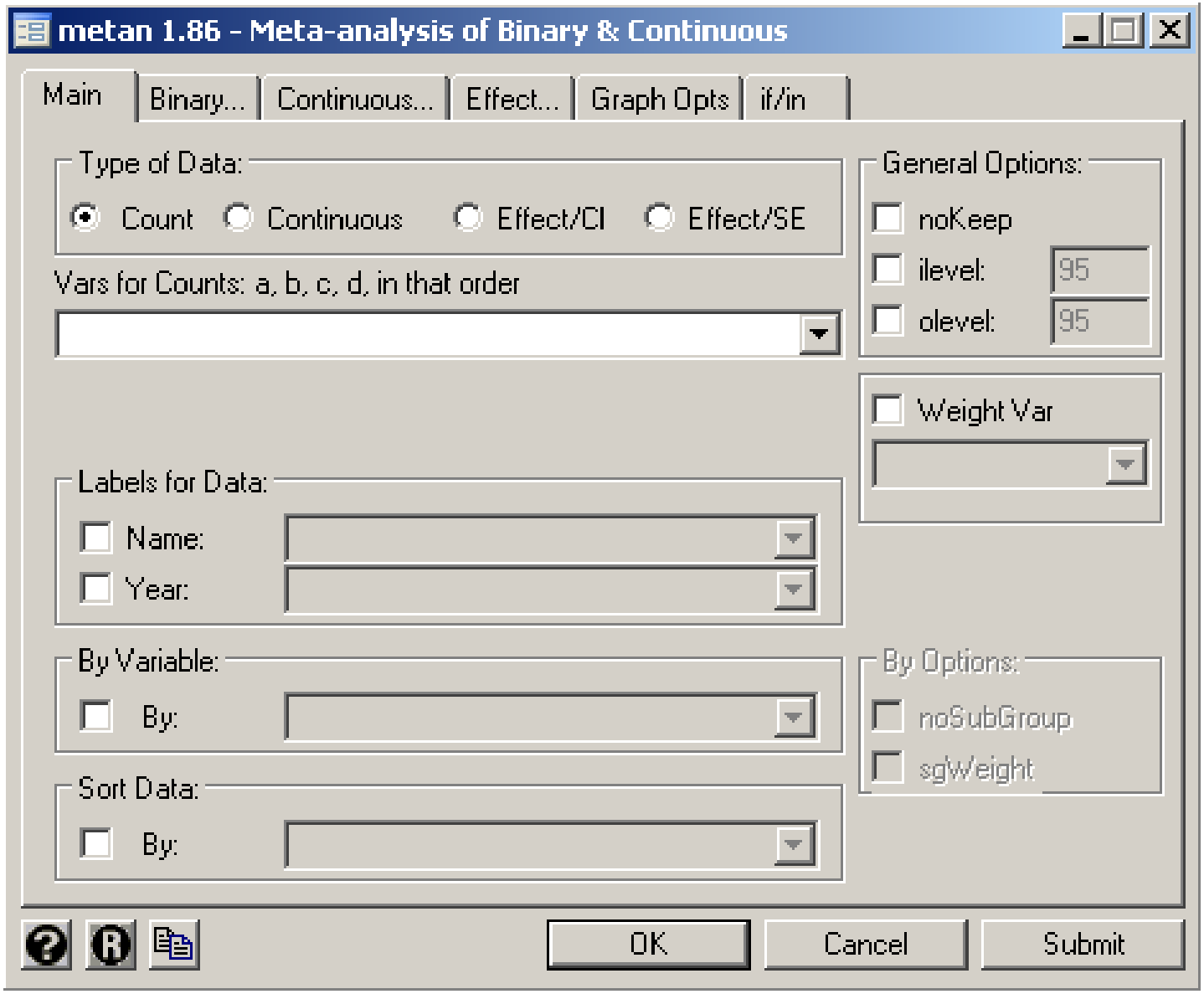
The Data – effect & CI

	trial	rr	low_95ci	up_95ci	log_rr	log_low	log_up
1	LRC-CPPT	0.826	0.674	1.012	-0.191	-0.394	0.012
2	4S	0.694	0.623	0.773	-0.366	-0.474	-0.258
3	WOSCOPS	0.700	0.580	0.844	-0.357	-0.545	-0.169
4	CARE	0.773	0.653	0.915	-0.258	-0.427	-0.089
5	AF/Tex-CAPS	0.599	0.433	0.830	-0.512	-0.837	-0.187
6	LIPID	0.777	0.701	0.861	-0.252	-0.355	-0.149
7	Post-CABG	0.801	0.595	1.080	-0.222	-0.520	0.077
8	MIRACL	0.923	0.751	1.135	-0.080	-0.286	0.126
9	GREACE	0.461	0.322	0.658	-0.775	-1.132	-0.418
10	LIPS	0.691	0.471	1.013	-0.370	-0.752	0.013
11	HPS	0.741	0.683	0.804	-0.300	-0.382	-0.218
12	PROSPER	0.869	0.769	0.982	-0.140	-0.262	-0.018
13	ALLHAT	0.905	0.792	1.034	-0.100	-0.233	0.034
14	ASCOT	0.645	0.503	0.828	-0.438	-0.687	-0.189
15	ALERT	0.674	0.504	0.902	-0.394	-0.685	-0.103
16	PROVE-IT	0.871	0.706	1.075	-0.138	-0.348	0.072
17	CARDS	0.654	0.463	0.924	-0.425	-0.771	-0.079
18	A TO Z	0.888	0.770	1.023	-0.119	-0.261	0.023
19	TNT	0.794	0.704	0.895	-0.231	-0.351	-0.111

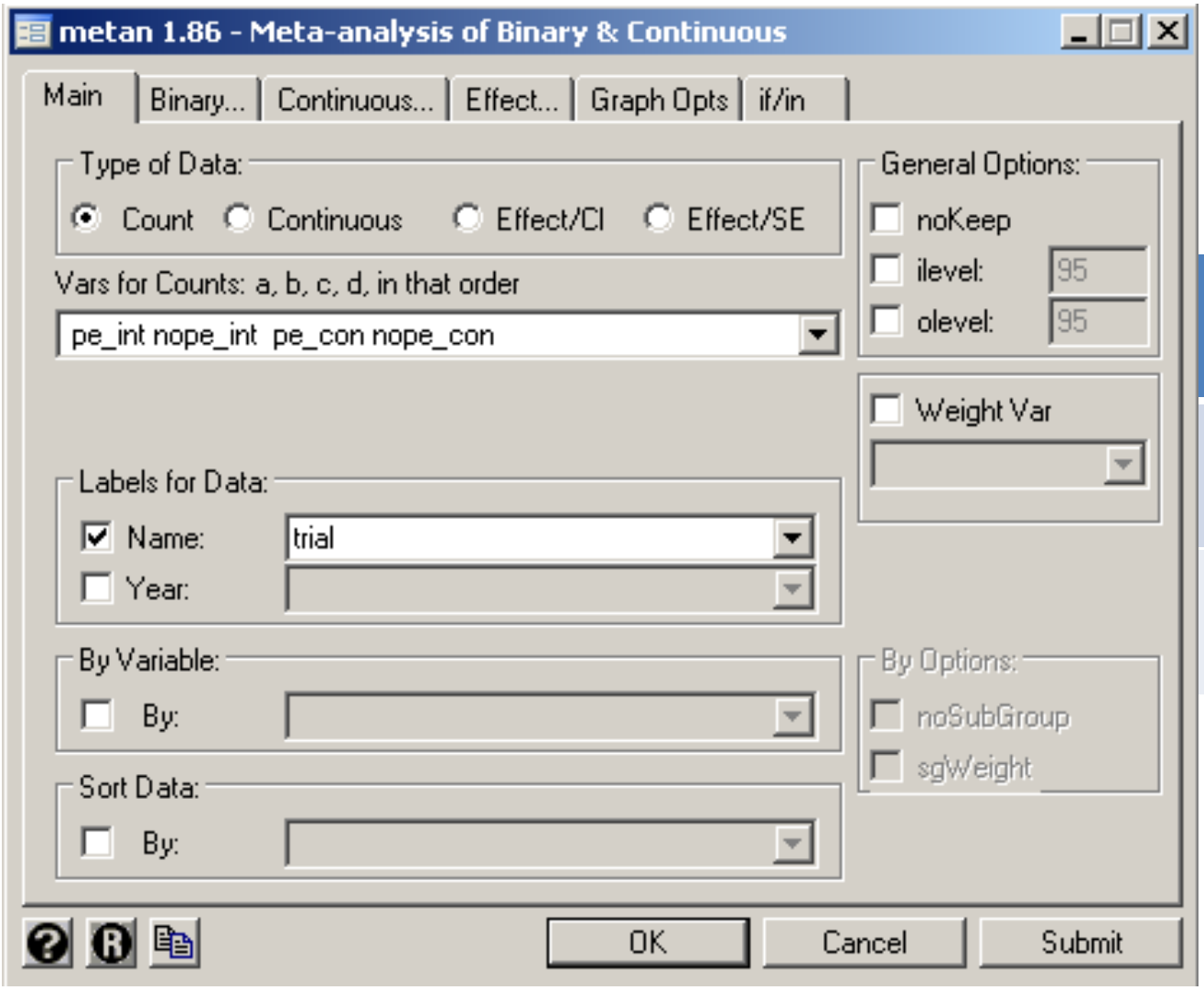
The Data – estimate & SE

	trial	log_rr	se_logrr
1	LRC-CPPT	-0.191	0.104
2	4S	-0.366	0.055
3	WOSCOPS	-0.357	0.096
4	CARE	-0.258	0.086
5	AF/Tex-CAPS	-0.512	0.166
6	LIPID	-0.252	0.052
7	Post-CABG	-0.222	0.152
8	MIRACL	-0.080	0.105
9	GREACE	-0.775	0.182
10	LIPS	-0.370	0.195
11	HPS	-0.300	0.042
12	PROSPER	-0.140	0.062
13	ALLHAT	-0.100	0.068
14	ASCOT	-0.438	0.127
15	ALERT	-0.394	0.148
16	PROVE-IT	-0.138	0.107
17	CARDS	-0.425	0.177
18	A TO Z	-0.119	0.073
19	TNT	-0.231	0.061

Graphical User Interface: db metan



db metan – count data (2x2 tables)



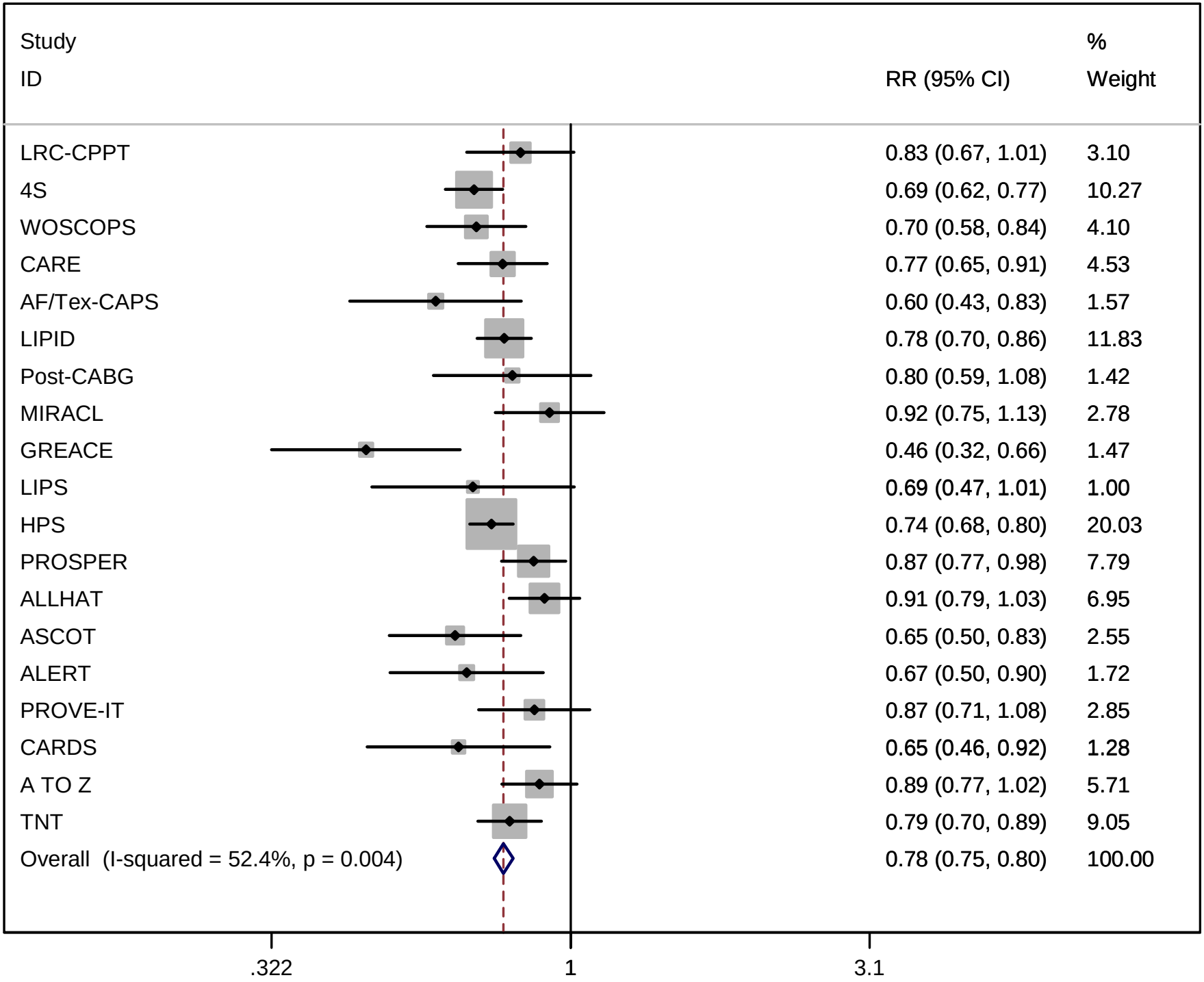
	Yes	No
Int.	a	b
Con.	c	d

```
. metan pe_int nope_int  pe_con nope_con, label(namevar=trial) fixed rr
```

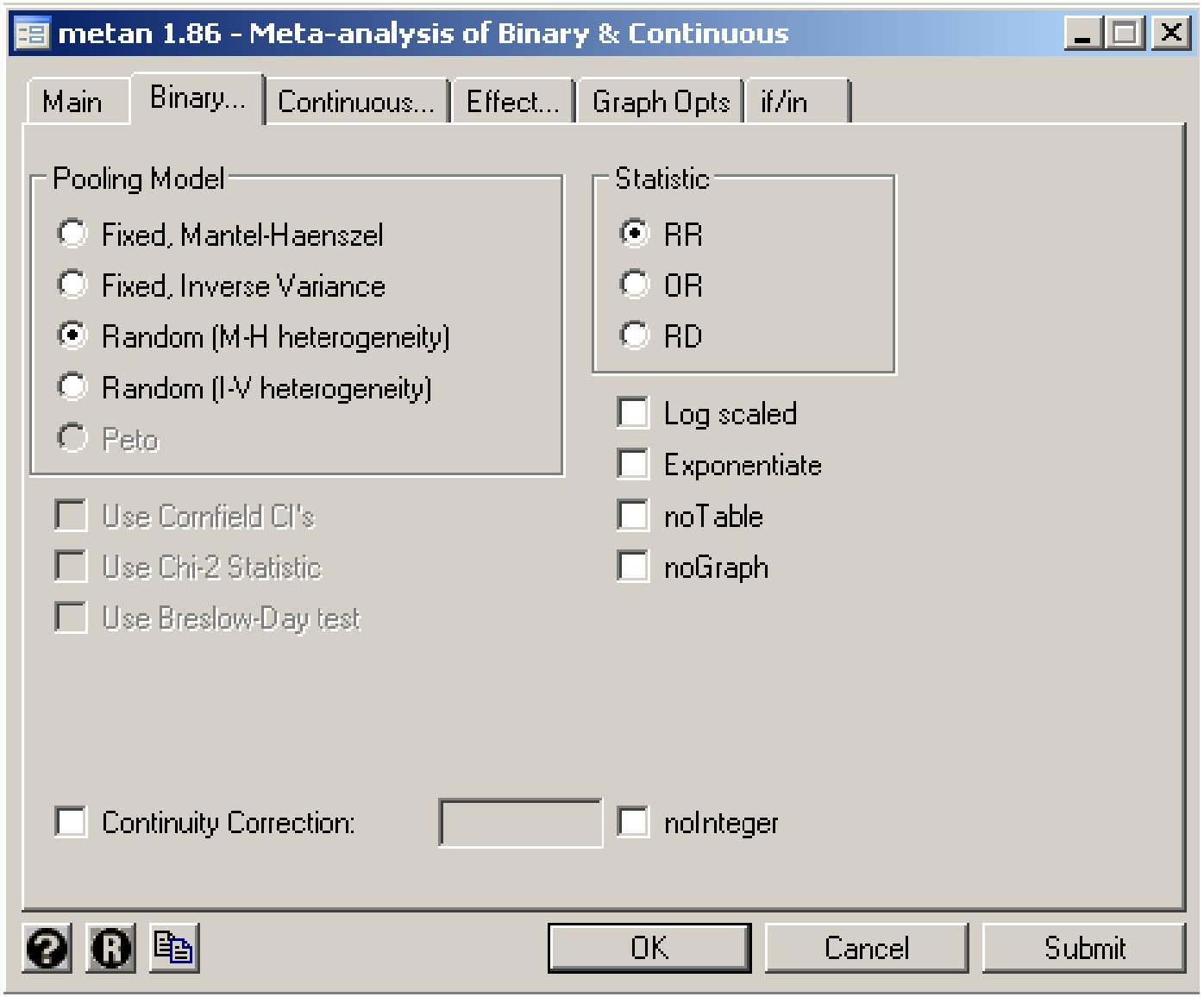
Study	RR	[95% Conf.	Interval]	% Weight
LRC-CPPT	0.826	0.674	1.012	3.10
4S	0.694	0.623	0.773	10.27
WOSCOPS	0.700	0.580	0.844	4.10
CARE	0.773	0.653	0.915	4.53
AF/Tex-CAPS	0.599	0.433	0.830	1.57
LIPID	0.777	0.701	0.861	11.83
Post-CABG	0.801	0.595	1.080	1.42
MIRACL	0.923	0.751	1.135	2.78
GREACE	0.461	0.322	0.658	1.47
LIPS	0.691	0.471	1.013	1.00
HPS	0.741	0.683	0.804	20.03
PROSPER	0.869	0.769	0.982	7.79
ALLHAT	0.905	0.792	1.034	6.95
ASCOT	0.645	0.503	0.828	2.55
ALERT	0.674	0.504	0.902	1.72
PROVE-IT	0.871	0.706	1.075	2.85
CARDS	0.654	0.463	0.924	1.28
A TO Z	0.888	0.770	1.023	5.71
TNT	0.794	0.704	0.895	9.05
M-H pooled RR	0.775	0.748	0.804	100.00

```
Heterogeneity chi-squared =  37.83 (d.f. = 18) p = 0.004
I-squared (variation in RR attributable to heterogeneity) =  52.4%

Test of RR=1 : z=  13.91 p = 0.000
```


Study
ID
RR (95% CI)
%
Weight
LRC-CPPT
0.83 (0.67, 1.01)
3.10
4S
0.69 (0.62, 0.77)
10.27
WOSCOPS
0.70 (0.58, 0.84)
4.10
CARE
0.77 (0.65, 0.91)
4.53
AF/Tex-CAPS
0.60 (0.43, 0.83)
1.57
LIPID
0.78 (0.70, 0.86)
11.83
Post-CABG
0.80 (0.59, 1.08)
1.42
MIRACL
0.92 (0.75, 1.13)
2.78
GREACE
0.46 (0.32, 0.66)
1.47
LIPS
0.69 (0.47, 1.01)
1.00
HPS
0.74 (0.68, 0.80)
20.03
PROSPER
0.87 (0.77, 0.98)
7.79
ALLHAT
0.91 (0.79, 1.03)
6.95
ASCOT
0.65 (0.50, 0.83)
2.55
ALERT
0.67 (0.50, 0.90)
1.72
PROVE-IT
0.87 (0.71, 1.08)
2.85
CARDS
0.65 (0.46, 0.92)
1.28
A TO Z
0.89 (0.77, 1.02)
5.71
TNT
0.79 (0.70, 0.89)
9.05
Overall (I-squared = 52.4%, p = 0.004)
0.78 (0.75, 0.80)
100.00
.322
1
3.1

random effects – count data



```
. metan pe_int nope_int  pe_con nope_con, label(namevar=trial) random rr
```

Study	RR	[95% Conf.	Interval]	% Weight
LRC-CPPT	0.826	0.674	1.012	4.81
4S	0.694	0.623	0.773	8.39
WOSCOPS	0.700	0.580	0.844	5.27
CARE	0.773	0.653	0.915	5.90
AF/Tex-CAPS	0.599	0.433	0.830	2.50
LIPID	0.777	0.701	0.861	8.62
Post-CABG	0.801	0.595	1.080	2.85
MIRACL	0.923	0.751	1.135	4.72
GREACE	0.461	0.322	0.658	2.15
LIPS	0.691	0.471	1.013	1.91
HPS	0.741	0.683	0.804	9.57
PROSPER	0.869	0.769	0.982	7.75
ALLHAT	0.905	0.792	1.034	7.27
ASCOT	0.645	0.503	0.828	3.71
ALERT	0.674	0.504	0.902	2.96
PROVE-IT	0.871	0.706	1.075	4.62
CARDS	0.654	0.463	0.924	2.26
A TO Z	0.888	0.770	1.023	6.90
TNT	0.794	0.704	0.895	7.86
D+L pooled RR	0.772	0.728	0.818	100.00

```
Heterogeneity chi-squared =  37.83 (d.f. = 18) p = 0.004
I-squared (variation in RR attributable to heterogeneity) =  52.4%
Estimate of between-study variance Tau-squared =  0.0073

Test of RR=1 : z=   8.79 p = 0.000
```

fixed v random

	trial	fix_wt	rand_wt
1	LRC-CPPT	3.1	4.8
2	4S	10.3	8.4
3	WOSCOPS	4.1	5.3
4	CARE	4.5	5.9
5	AF/Tex-CAPS	1.6	2.5
6	LIPID	11.8	8.6
7	Post-CABG	1.4	2.9
8	MIRACL	2.8	4.7
9	GREACE	1.5	2.1
10	LIPS	1.0	1.9
11	HPS	20.0	9.6
12	PROSPER	7.8	7.8
13	ALLHAT	6.9	7.3
14	ASCOT	2.6	3.7
15	ALERT	1.7	3.0
16	PROVE-IT	2.9	4.6
17	CARDS	1.3	2.3
18	A TO Z	5.7	6.9
19	TNT	9.0	7.9

Fixed (M-H pooled RR)

0.775 95% CI(0.748, 0.804)

Random (D-L pooled RR)

0.772 95% CI(0.728, 0.818)

Heterogeneity chi-squared

37.83 (18df) p = 0.004

I-squared = 52.4%

Demo of Stata Syntax