Meta Analysis

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Acknowledgements

Stata has a long history of meta-analysis methods contributed by Stata researchers, e.g. Palmer and Sterne (2016). We want to express our deep gratitude to Jonathan Sterne, Roger Harbord,Tom Palmer, David Fisher, Ian White, Ross Harris, Thomas Steichen, Mike Bradburn, Doug Altman (1948–2018), Ben Dwamena, and many more for their invaluable contributions.Their previous and still ongoing work on meta-analysis in Stata influenced the design and development of the official meta suite.

Meta-analysis is a set of techniques for combining the results from several studies that address similar questions.
It has been used in many fields of research. Besides many areas of healthcare, it has been used in econometrics, psychology, education, criminology, ecology, veterinary sciences.

Often, different studies about the same topic present inconsistent or contradictory results.

Before meta-analysis, systematic reviews were narrative in nature.

Meta-analysis provides an objective statistical framework for the process of systematic reviewing.

Meta-Analysis aims to provide an overall effect if there is evidence of such.

In addition, it aims to explore heterogeneities among studies as well as evaluate the presence of publication bias.

Because our input data are estimates, subject to a certain error, it is important to perform sensitivity analysis, to see how sensitive our conclusions would be to variations on the parameters.

The `meta` suite of commands provides an environment to:

- Set up your data to be analyzed with meta-analysis techniques; (see `meta esize` and `meta set`).
- Summarize and visualize meta-analysis data;(see `meta summarize` `meta forestplot`).
- Perform meta-regression; (see `meta regress`).
- Explore small-study effects and publication bias; (see `meta funnelplot`, `meta bias`, and `meta trimfill`).

Example: Nut consumption and risk of stroke

Our first example is from Zhizhong et al, 2015 [1] From the abstract: " Nut consumption has been inconsistently associated with risk of stroke. Our aim was to carry out a meta-analysis of prospective studies to assess the relation between nut consumption and stroke"

[1] Z. Zhizhong et al; Nut consumption and risk of stroke Eur J Epidemiol (2015) 30:189–196

```
. use nuts_meta, clear
. list study year logrr se sex
```

	study	year	logrr	se	sex
1.	Yochum	2000	-.3147107	.2924136	Female
2.	Bernstein	2012	-.1508229	.0436611	Female
3.	Yaemsiri	2012	-.1165338	.1525122	Female
4.	He	2003	-.1278334	.1850565	Male
5.	He	2003	.2546422	.3201159	Male
6.	Djousse	2010	.0676587	.156676	Male
7.	Bernstein	2012	-.0833816	.0886604	Male
8.	Bao	2013	-.2484614	.1514103	Male

The original studies published the risk ratio of having a stroke for the treatment group versus the control group (treatment group is the group that consumed nuts).

Effect size

In Meta-Analysis, the term "effect size" is used to refer to our effect of interest. In our example, the effect size is the log risk-ratio. The effect size, depending on the study, can be a difference of means, a log odds-ratio, a log hazard ratio, etc.

Meta analysis uses the following basic theoretical framework:
We have K independent studies, each reporting an estimate $\hat{\theta}_j$ of the corresponding effect size θ_j and its standard error estimate σ_j.
We assume

$$\hat{\theta}_j = \theta_j + \varepsilon_j,$$

$$\varepsilon_j \sim N(0, \sigma_j^2)$$

The `meta` suite of commands offers three basic models to define and estimate the global effect: common-effect, fixed-effects and random-effects.
(Note: these are not the same concepts of fixed-effect or random-effects models used in econometrics)

Meta analysis models:

$$\hat{\theta}_j = \theta_j + \varepsilon_j,$$

$$\varepsilon_j \sim N(0, \sigma_j^2)$$

- The common-effect model assumes $\theta_1 = \theta_2 = \ldots = \theta_K$; it estimates the common value θ.
- The fixed-effects model assumes that θ_j are fixed values; it estimates a weighted average of those values.
- The random-effects model assumes that $\theta_j \sim N(\theta, \tau^2)$; it estimates θ, the expected value of θ_j.

In all cases, the population parameter is estimated as weighted average of the estimates from the individual studies:

$$\hat{\theta} = \frac{\sum_{j=1}^{K} w_j \hat{\theta}_j}{\sum_{j=1}^{K} w_j}$$

Depending on the model, there will be a different interpretation for this estimated value, and the formula will use different weights; Studies with smaller variance will have larger weights.

Our three models (common-effect, fixed-effects and random-effects) can be fit with `meta summarize`, using options `common()`, `fixed()`, and `random()`.

We'll mainly discuss random-effects meta-analysis models, which are currently the most frequently found in the literature.

`meta summarize` with the `random` option offers several estimation methods available in the literature (restricted maximum likelihood, maximum likelihod, empirical Bayes, DerSimonian-Laird, Sidik-Jonkman, Hedges, Hunter-Smidth).
The default method is restricted maximum likelihood.

The two commands available declare meta analysis data are `meta set` and `meta esize`. We use `meta set` when we have generic effect size (that is, for each group, we have effect size and standard errors or CI)

```
. meta set logrr se, studylabel(study) random

Meta-analysis setting information

 Study information
    No. of studies:  8
       Study label:  study
        Study size:  N/A

       Effect size
              Type:  Generic
             Label:  Effect Size
          Variable:  logrr

         Precision
         Std. Err.:  se
                CI:  [_meta_cil, _meta_ciu]
          CI level:  95%

  Model and method
             Model:  Random-effects
            Method:  REML
```

`meta set` generates the following system variables that will be used for subsequent analyses.

```
. describe _meta*
```

variable name	storage type	display format	value label	variable label
_meta_id	byte	%9.0g		Study ID
_meta_studyla~l	str9	%9s		Study label
_meta_es	float	%9.0g		Generic ES
_meta_se	float	%9.0g		Std. Err. for ES
_meta_cil	double	%10.0g		95% lower CI limit for ES
_meta_ciu	double	%10.0g		95% upper CI limit for ES

We use meta summarize to estimate the global effect.

```
. meta summarize, eform(rr) nometashow
```

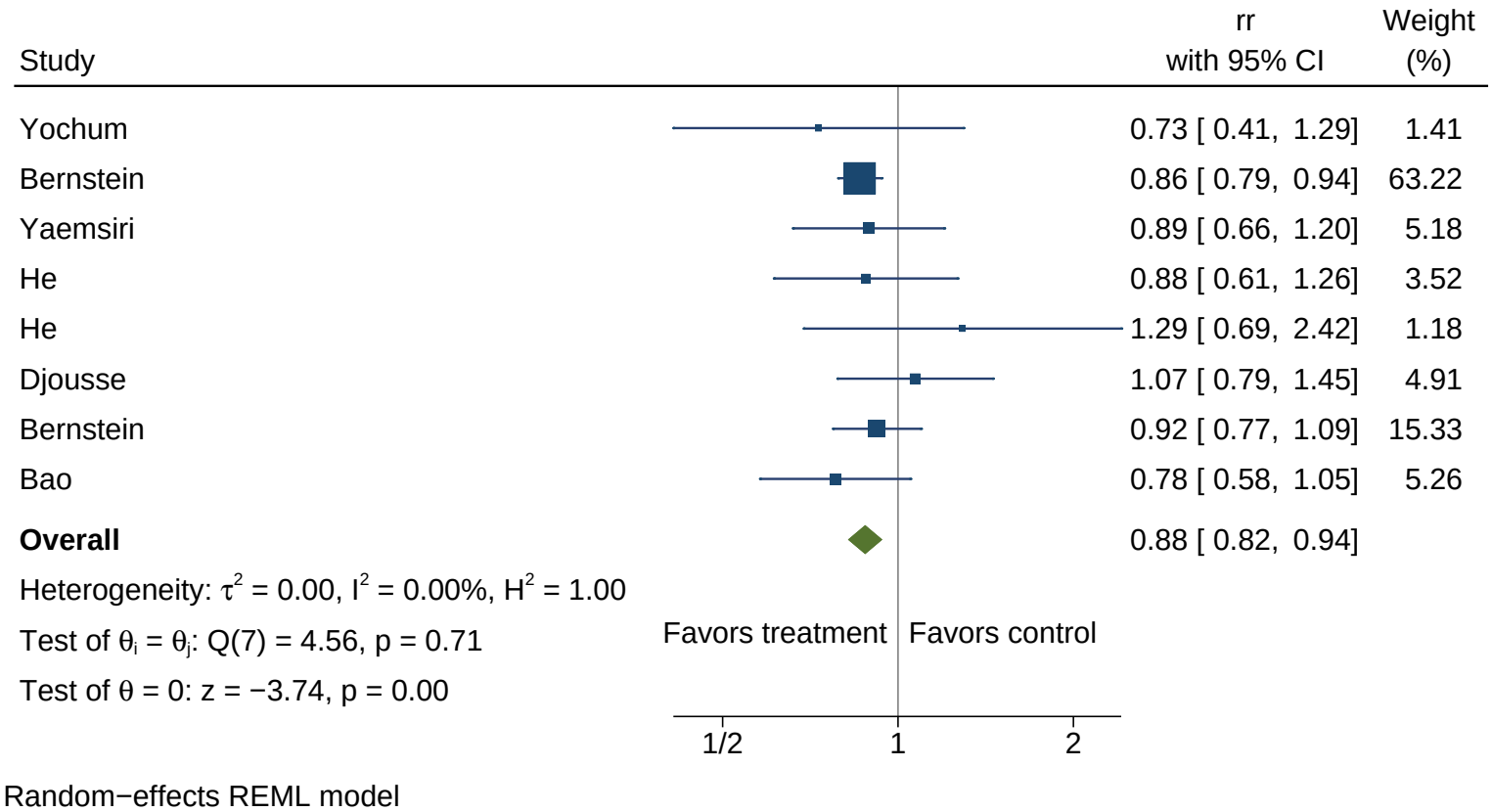
```
Meta-analysis summary                       Number of studies =      8
Random-effects model                        Heterogeneity:
Method: REML                                            tau2 =  0.0000
                                                     I2 (%) =    0.00
                                                         H2 =    1.00
```

Study	rr	[95% Conf.	Interval]	% Weight
Yochum	0.730	0.412	1.295	1.41
Bernstein	0.860	0.789	0.937	63.22
Yaemsiri	0.890	0.660	1.200	5.18
He	0.880	0.612	1.265	3.52
He	1.290	0.689	2.416	1.18
Djousse	1.070	0.787	1.455	4.91
Bernstein	0.920	0.773	1.095	15.33
Bao	0.780	0.580	1.049	5.26
exp(theta)	0.878	0.820	0.940	

```
Test of theta = 0: z = -3.74                Prob > |z| = 0.0002
Test of homogeneity: Q = chi2(7) = 4.56       Prob > Q = 0.7137
```

meta forestplot draws a forest plot for visualization.

```
. local opts nullrefline(favorsleft("Favors treatment") ///
>       favorsright("Favors control")) nometashow
. meta forest, eform(rr) `opts´
```



After `meta summarize`, we can display the returned results by writing `return list`. This is the estimate of our overall effect:

```
. display exp(r(theta))
.87823134
```

which is based on the following estimate of the between study variance:

```
. display r(tau2)
1.529e-07
```

Sensitivity analysis

How would our results be affected by variations in the between-group variance? Our variance is equal to 1.53e-7 what if it was .001?

```
. meta summarize, tau2(.001) eform  nometashow noheader
```

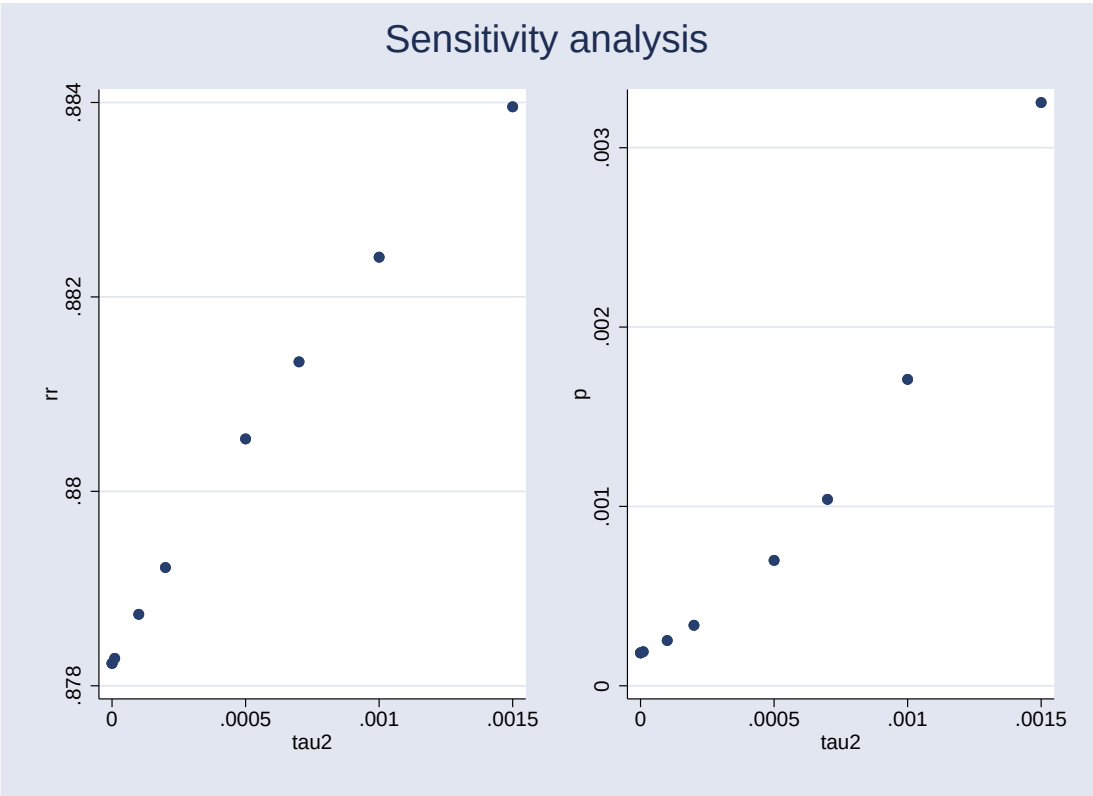
Study	exp(ES)	[95% Conf.	Interval]	% Weight
Yochum	0.730	0.412	1.295	1.41
Bernstein	0.860	0.789	0.937	63.22
Yaemsiri	0.890	0.660	1.200	5.18
He	0.880	0.612	1.265	3.52
He	1.290	0.689	2.416	1.18
Djousse	1.070	0.787	1.455	4.91
Bernstein	0.920	0.773	1.095	15.33
Bao	0.780	0.580	1.049	5.26
exp(theta)	0.882	0.816	0.954	

```
Test of theta = 0: z = -3.14                     Prob > |z| = 0.0017
Test of homogeneity: Q = chi2(7) = 4.56           Prob > Q = 0.7137
```

We can write a loop to understand how our global effect and its p-value are affected by the variance. Here we take advantage of the `frames` feature, which allows us to have several datasets in memory.

```
. local variances 1e-8 1.5e-7 1e-5 1e-4 2e-4 5e-4 7e-4 1e-3  1.5e-3

. frame create sens tau2 rr p

. frames dir
* default  8 x 12; nuts_meta.dta
* sens     0 x 3

Note: frames marked with * contain unsaved data

. foreach t2 of local variances{
  2.   meta summarize, tau2(`t2´)
  3.   local rr = exp(r(theta))
  4.   frame post sens (`r(tau2)´) (`rr´) (`r(p)´)
  5. }

(Output omitted)
. frame sens: scatter rr  tau2, name(rr, replace)

. frame sens: scatter p  tau2, name(p, replace)
```

The following plots show how the global effect estimate and its p-value would be affected by variations on the between-study variance estimate.



Heterogeneity: subgroup analysis

For our random-effects model, we have asumed:
$\hat{\theta}_j = \theta_j + \varepsilon_j$, $\varepsilon_j \sim N(0, \sigma_j^2)$ $\theta_j \sim N(\theta, \tau^2)$

An alternative possibility would be to have two values of θ, each corresponding to a different sex group.

We want to see if the effects differ by sex, and in that case, obtain an estimate of the global effect that accounts for those differences. We use `meta summarize, subgroup()` and `meta forestplot, subgroup()`

```
. meta summarize, subgroup(sex) eform(rr) nometashow noheader
```

Study	rr	[95% Conf.	Interval]	% Weight
Group: Female				
Yochum	0.730	0.412	1.295	1.41
Bernstein	0.860	0.789	0.937	63.22
Yaemsiri	0.890	0.660	1.200	5.18
exp(theta)	0.859	0.792	0.932	
Group: Male				
He	0.880	0.612	1.265	3.52
He	1.290	0.689	2.416	1.18
Djousse	1.070	0.787	1.455	4.91
Bernstein	0.920	0.773	1.095	15.33
Bao	0.780	0.580	1.049	5.26
exp(theta)	0.924	0.816	1.045	
Overall				
exp(theta)	0.878	0.820	0.940	

(output continues)

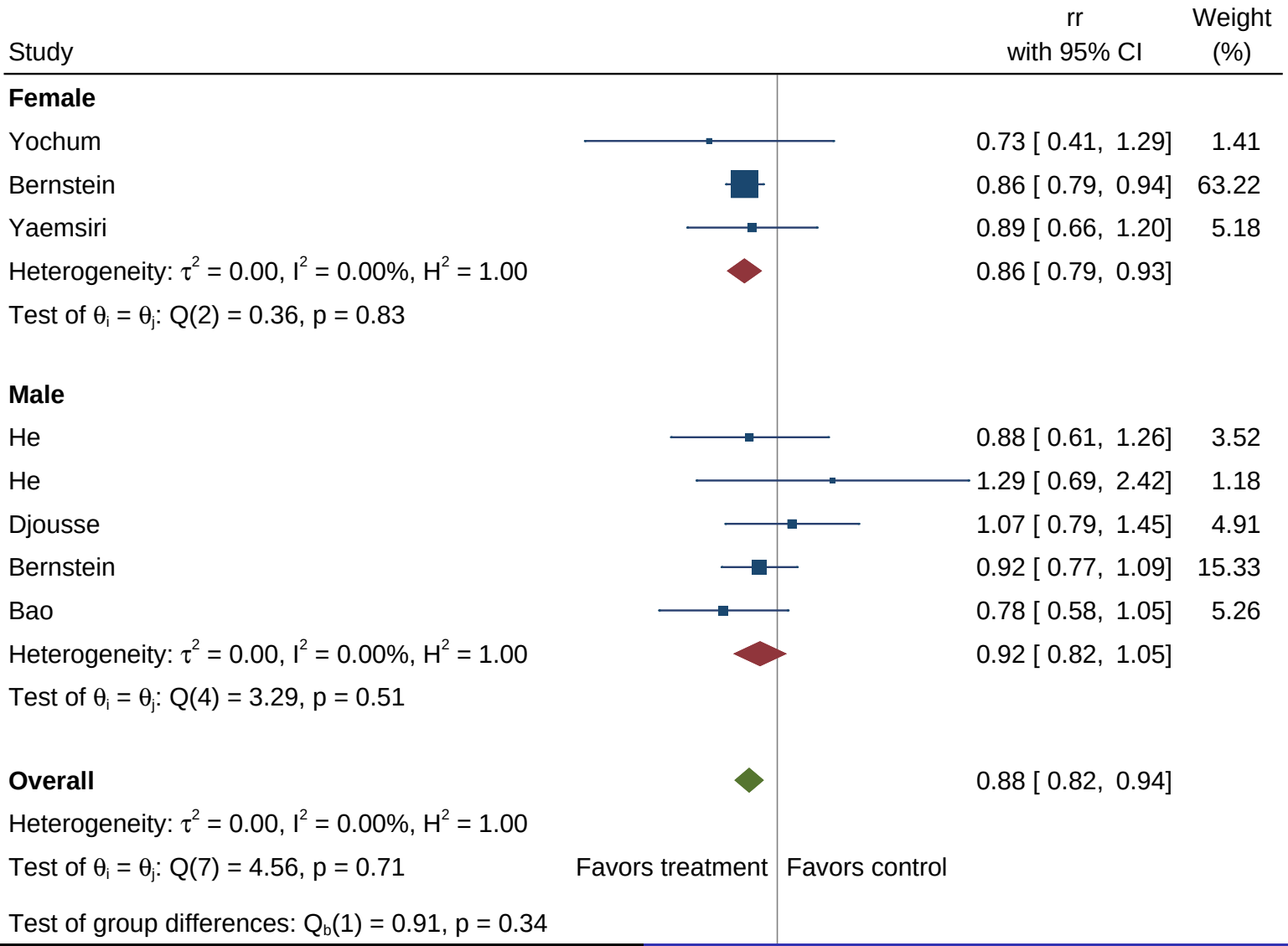
Heterogeneity summary

Group	df	Q	P > Q	tau2	% I2	H2
Female	2	0.36	0.833	0.000	0.00	1.00
Male	4	3.29	0.511	0.000	0.00	1.00
Overall	7	4.56	0.714	0.000	0.00	1.00

Test of group differences: Q_b = chi2(1) = 0.91 Prob > Q_b = 0.341

There is no evidence of difference of effect among sex groups.

```
. meta forest, subgroup(sex) eform(rr) `opts´
```



Heterogeneity: Meta regression

Another situation where heterogeneity is present is when $\theta_j = \mu + \beta * x_j$ For a covariate x.
In those cases, we can use `meta regress` to account for covariates in the model.

Example: Effect of tacrine on Alzheimer's disease

Quizilvash et al. (1998) [2] performed a meta analysis on the effect of the drug tacrine on CGIC (scale for Alzheimer's disease). Whitehead (2002) [3] studied the effect of the dose of tacrine on the log-odds ratio for being in a better category in the scale.

If the drug has the desired effect, we would expect that an increase in the dose (within a safe range) increases the effect.

[2] Quizilbash, N. Whitehead, A. Higgins, J. Wilcock, G., Schneider, L. and Farlow, M. on behalf of Dementia Trialist' Collaboration (1998). Cholinesterase inhibition for Alzheimer disease: a meta-analysis of tacrine trials. *Journal of the American Medical Assotiation*, 280, 1777-1782.

[3] Whitehead, A. Meta-Analysis of Controled Clinical Trials. Wiley, 2002.

Let's look at the data:

```
. use alzheimer, clear
. list
```

	study	effect	se	dose
1.	1	.284	.261	62
2.	2	.224	.242	39
3.	3	.36	.332	66
4.	4	.785	.174	135
5.	5	.492	.421	65

We use `meta set` to specify our meta-analysis characteristics,

```
. meta set effect se
(output omitted)
```

and `meta regress` to perform a meta regression.

```
. meta regress dose

  Effect-size label:  Effect Size
        Effect size:  effect
          Std. Err.:  se

Random-effects meta-regression                  Number of obs   =         5
Method: REML                                    Residual heterogeneity:
                                                           tau2 = 2.1e-07
                                                     I2 (%)     =    0.00
                                                     H2         =    1.00
                                                R-squared (%)   =  100.00
                                                Wald chi2(1)    =    4.69
                                                Prob > chi2     =  0.0303
```

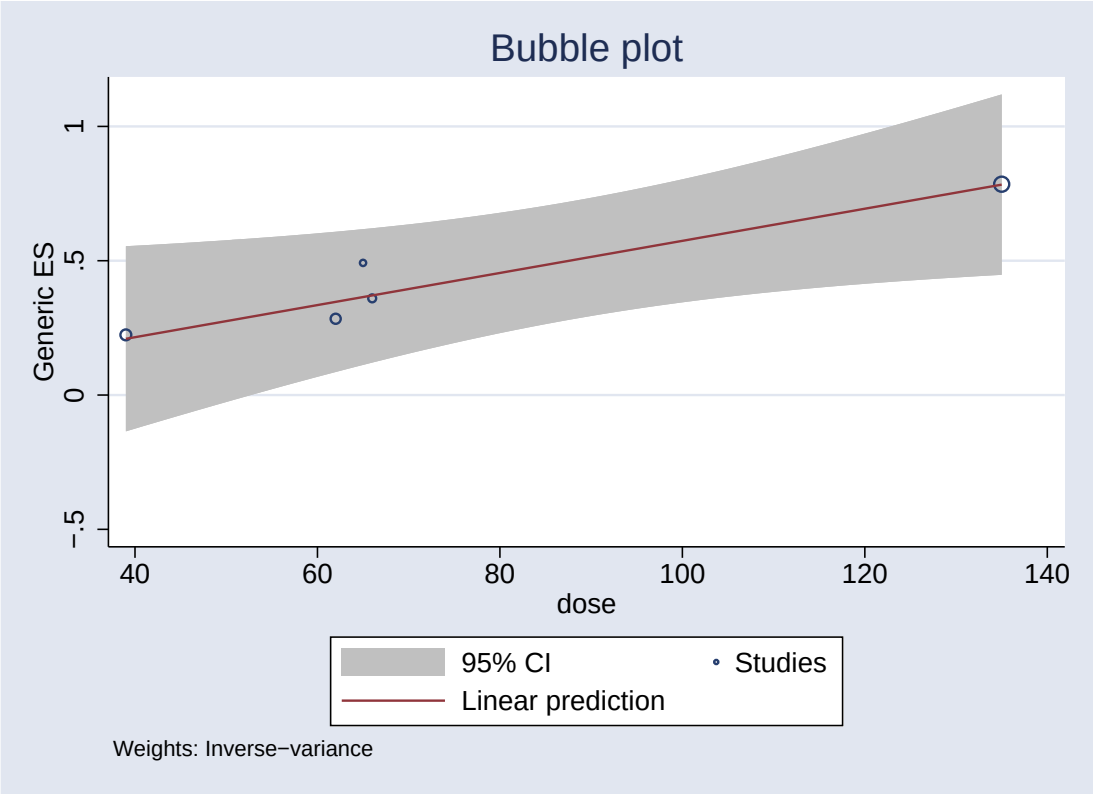
_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose	.0059788	.0027602	2.17	0.030	.0005689	.0113886
_cons	-.0237839	.2676855	-0.09	0.929	-.5484379	.5008701

```
Test of residual homogeneity: Q_res = chi2(3) =  0.15    Prob > Q_res = 0.9846
```

According to our meta-regression, log-odds ratio of being in a better category increases significantly with dose.
After `meta regress` we can use postestimation tools as `predict`, `margins`, `marginsplot`.

`estat bubbleplot` allows us visualize the regression and identify possible outliers or influencial points. The size of the bubbles are the inverses of the effect-size variances.

```
. estat bubbleplot
```



Publication bias/small-study effect

Publication bias occurs when the results of a research affect the decision of being published. Often it manifests in the presence of fewer non-significant smaller studies than non-significant larger studies.

Example: The effectiveness of workplace smoking cessation programmes. [4]

Smedslund et al. Performed a meta-analysis on the effective of workplace smoking cessation programs. We use a subset of their data.

[4] G Smedslund, K J Fisher, S M Boles, E Lichtenstein. The effectiveness of workplace smoking cessation programmes: a meta-analysis of recent studies. Tobacco Control 2004; 13:197

```
. use smoking, clear
. list study n1 m1 n0 m0
```

	study	n1	m1	n0	m0
1.	Lang 2000	42	648	27	552
2.	Sorensen 1993	27	199	40	415
3.	Salina 1994	60	146	41	172
4.	Burling 1989	6	23	3	26
5.	Jason 1997	29	252	12	268
6.	Gamel 1993	8	74	1	129
7.	Koffman 1998	18	62	2	27
8.	Helyer 1998	16	36	5	57

```
. describe n1 m1 n0 m0
```

variable name	storage type	display format	value label	variable label
n1	float	%9.0g		No. successes treatment
m1	float	%9.0g		No. failures treatment
n0	float	%9.0g		No. success control
m0	float	%9.0g		No. failures control

We use meta esize to set up our data.

```
. meta esize n1 m1 n0 m0, studylabel(study) random

Meta-analysis setting information

 Study information
    No. of studies:  8
       Study label:  study
        Study size:  _meta_studysize
      Summary data:  n1 m1 n0 m0

       Effect size
             Type:  lnoratio
            Label:  Log Odds-Ratio
         Variable:  _meta_es
  Zero-cells adj.:  None; no zero cells

        Precision
        Std. Err.:  _meta_se
               CI:  [_meta_cil, _meta_ciu]
         CI level:  95%

  Model and method
            Model:  Random-effects
           Method:  REML
```

Our effect sizes are log odds ratios, where our odds ratios are:

$$OR = \frac{\text{Odds of success for treatment group}}{\text{Odds of success for control group}}$$

Therefore, values of the OR larger than 1 would favor the treatment.

```
. meta summarize, nometashow eform(or)
```

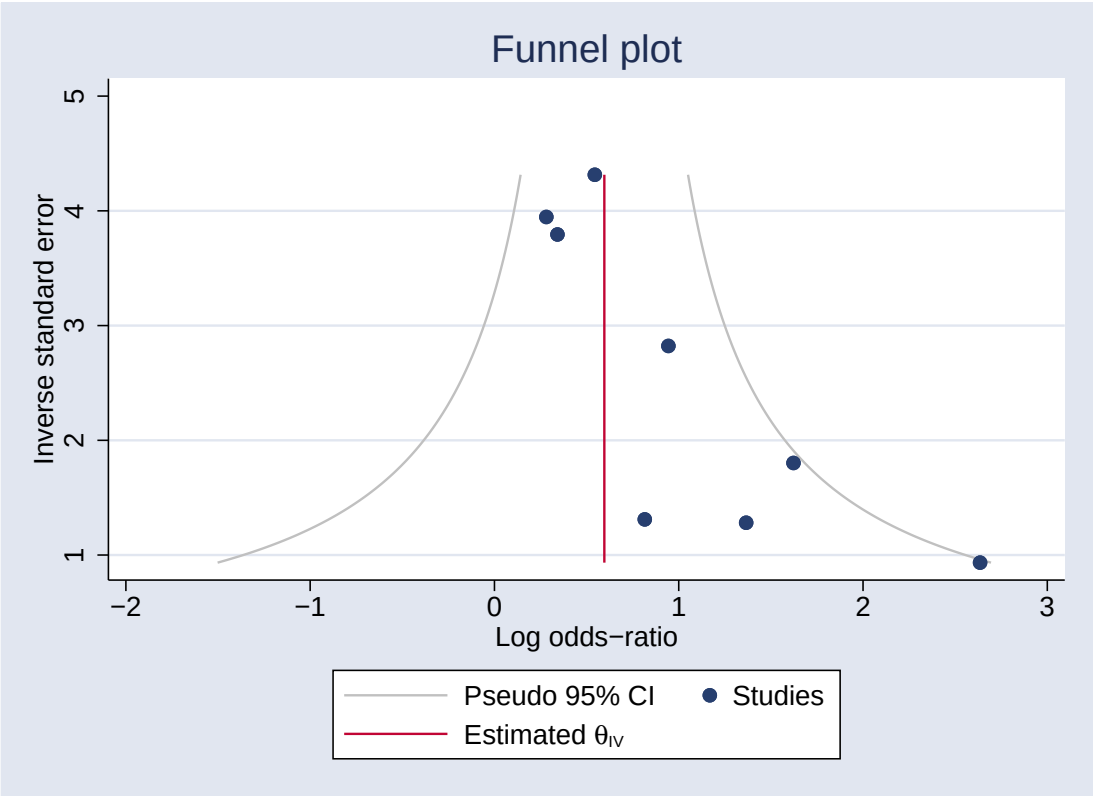
Meta-analysis summary — Number of studies = 8
Random-effects model — Heterogeneity:
Method: REML — tau2 = 0.0671
I2 (%) = 32.56
H2 = 1.48

Study	or	[95% Conf.	Interval]	% Weight
Lang 2000	1.325	0.806	2.177	21.81
Sorensen 1993	1.408	0.840	2.360	20.97
Salina 1994	1.724	1.095	2.715	23.70
Burling 1989	2.261	0.507	10.084	4.41
Jason 1997	2.570	1.283	5.147	14.87
Gamel 1993	13.946	1.710	113.704	2.36
Koffman 1998	3.919	0.849	18.085	4.24
Helyer 1998	5.067	1.708	15.031	7.64
exp(theta)	1.979	1.420	2.758	

Test of theta = 0: z = 4.03 — Prob > |z| = 0.0001
Test of homogeneity: Q = chi2(7) = 11.59 — Prob > Q = 0.1148

We create a funnel plot to explore the presence of small-study effects.

```
. meta funnelplot, metric(invse) nometashow
```



We perform Harbor's regression-based test. It is based on a meta-regression of the study effects and their precisions.

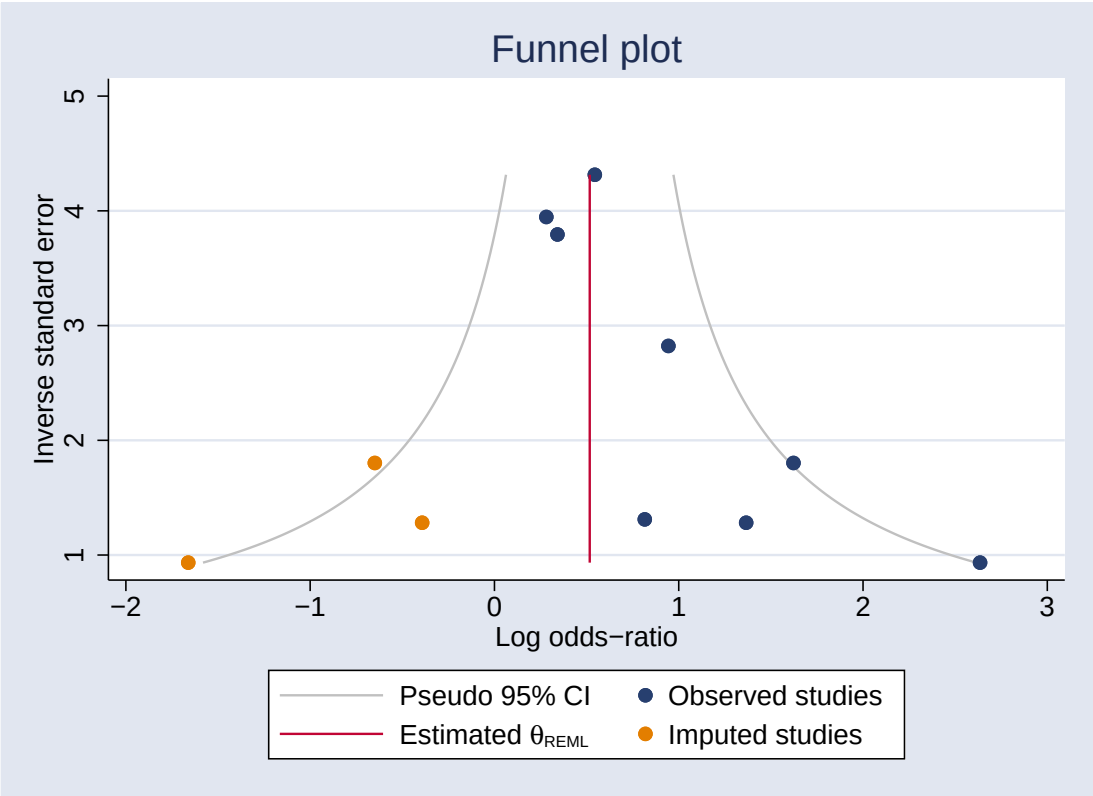
```
. meta bias,  harbord

  Effect-size label:  Log Odds-Ratio
        Effect size:  _meta_es
          Std. Err.:  _meta_se

Regression-based Harbord test for small-study effects
Random-effects model
Method: REML

H0: beta1 = 0; no small-study effects
            beta1 =      2.57
      SE of beta1 =     0.926
                z =      2.77
      Prob > |z| =    0.0055
```

We obtain a p-value 0.0055 for the coefficient β_1 , which indicates evidence of small-study effects.

`meta trimfill` allows us to explore the possible impact of publication bias. It uses an algorithm to impute the studies potentially missing because of publication bias.

```
. meta trimfill, eform(or) funnel(metric(invse))

  Effect-size label:  Log Odds-Ratio
        Effect size:  _meta_es
          Std. Err.:  _meta_se

Nonparametric trim-and-fill analysis of publication bias
Linear estimator, imputing on the left

Iteration                              Number of studies =     11
  Model: Random-effects                       observed =      8
 Method: REML                                 imputed =      3

Pooling
  Model: Random-effects
 Method: REML
```

Studies	or	[95% Conf.	Interval]
Observed	1.979	1.420	2.758
Observed + Imputed	1.677	1.132	2.484



This suggests that the effect reported in the reviewed literature might be larger than it would have been without publication bias.

Concluding remarks:

- Meta analysis provides objective tools to address and interpret an often contradictory or inconsistent body of literature.
- The Stata set of commands `meta` provides an unified environment to perform meta analysis estimation and assess possible issues on the data.
- Meta regression allows us to include information from covariates in the model.
- It is important to perform sensitivity analysis to understand how variations on the parameters would affect our results.
- Funnel plots and regression-based test allow us to asses the presence of publication bias.