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.

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.

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

- Compute or specify effect sizes; (see `meta esize` and `meta set`).
- Summarize meta-analysis data;(see `meta summarize` `meta forestplot`).
- Perform meta-regression to address heterogeneity; (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
```

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

`meta` offers three basic models to compute the global effect: (formulas here) We will use random-effects models because they are popular and because they can be easily understood in the framework of multilevel regression.

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 can use meta summarize to estimate the global effect.

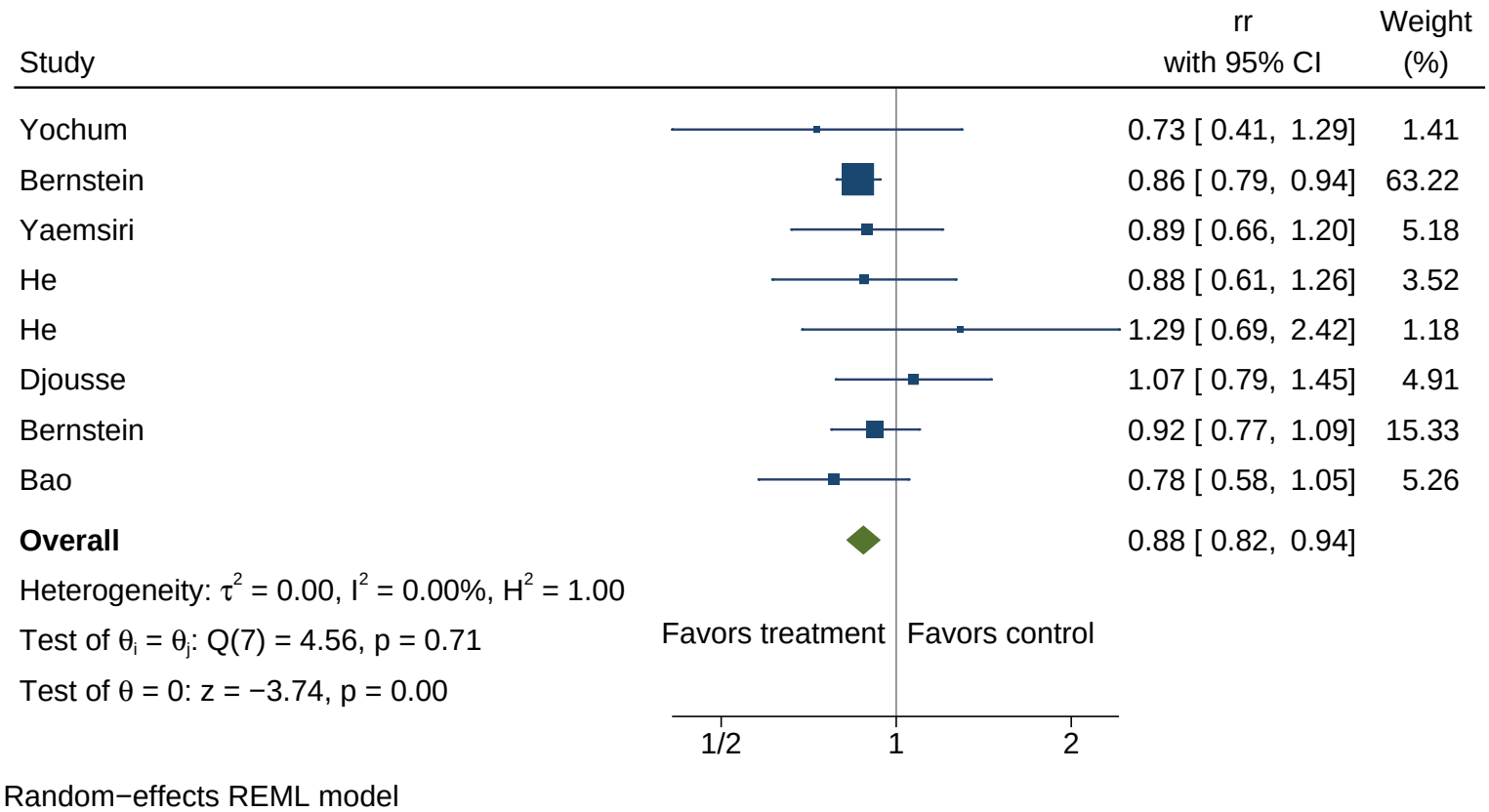
```
. meta summarize, eform(rr) nometashow
```

```
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
```

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



Sensitivity analysis

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

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

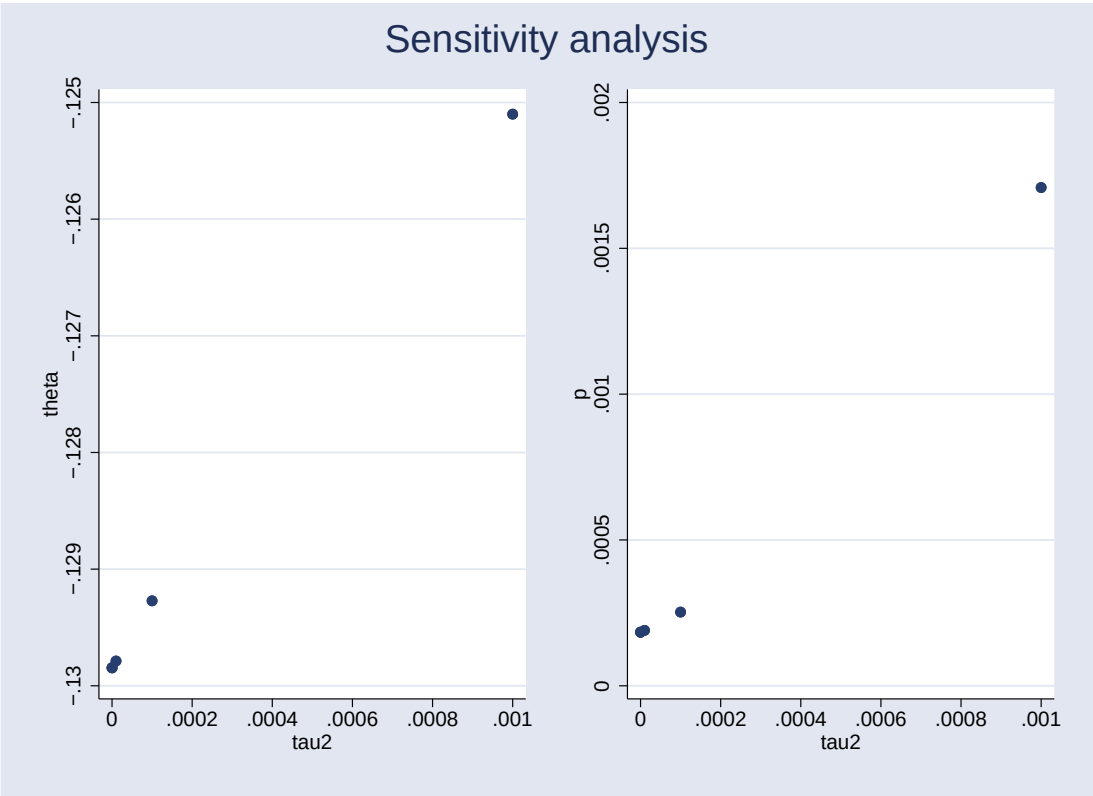
Study	Effect Size	[95% Conf.	Interval]	% Weight
Yochum	-0.315	-0.888	0.258	1.41
Bernstein	-0.151	-0.236	-0.065	63.22
Yaemsiri	-0.117	-0.415	0.182	5.18
He	-0.128	-0.491	0.235	3.52
He	0.255	-0.373	0.882	1.18
Djousse	0.068	-0.239	0.375	4.91
Bernstein	-0.083	-0.257	0.090	15.33
Bao	-0.248	-0.545	0.048	5.26
theta	-0.125	-0.203	-0.047	

```
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 1e-3

. frame create sens tau2 theta 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.   frame post sens (`r(tau2)´) (`r(theta)´) (`r(p)´)
  4. }

(Output omitted)

. frame sens: scatter theta  tau2, name(theta, replace)

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

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



Heterogeneity: subgroup analysis

We want to see if 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 forest, subgroup()`

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

Study	rr	[95% Conf.	Interval]	% Weight
Group: 1				
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: 2				
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)

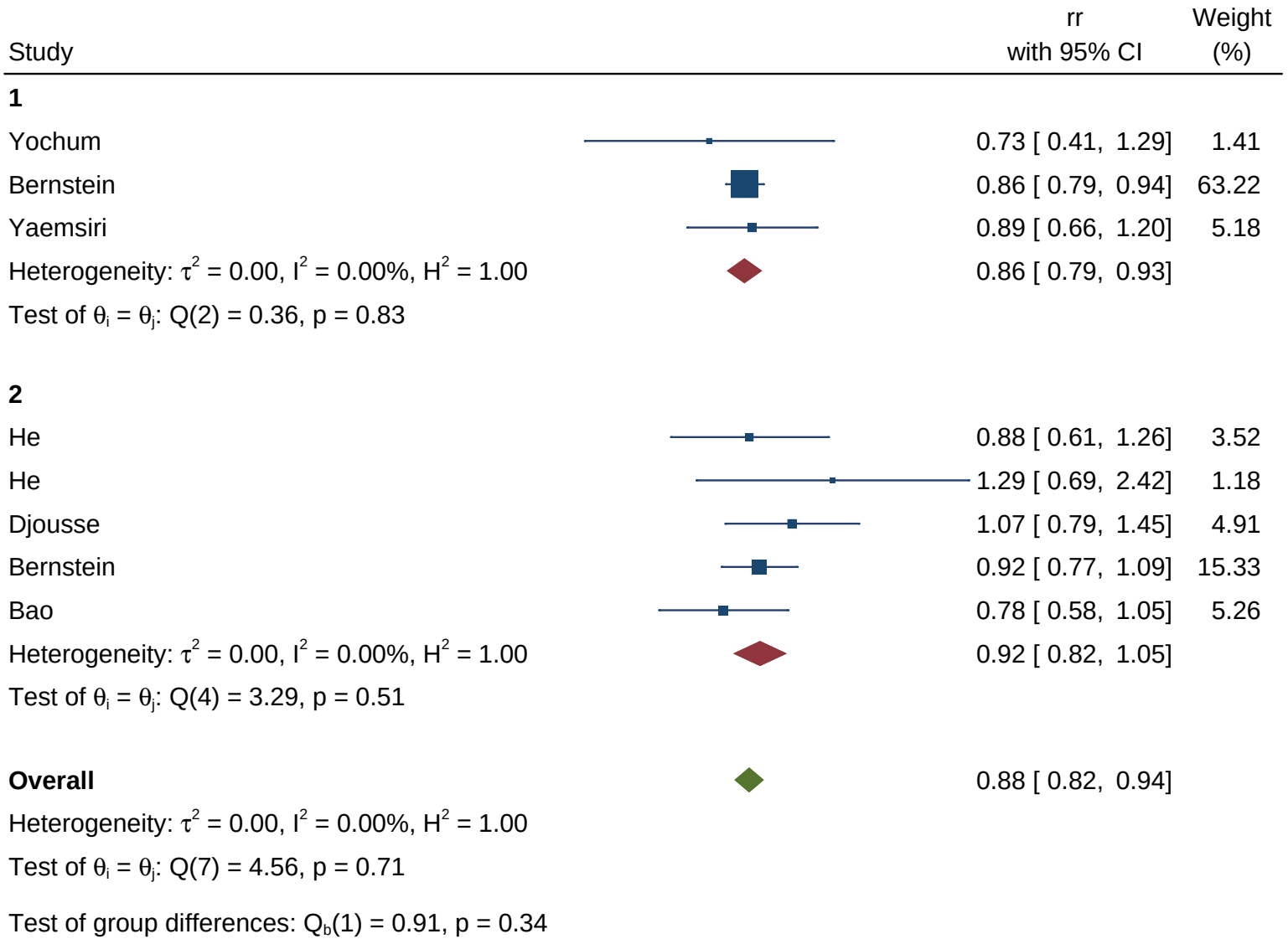
Heterogeneity summary

Group	df	Q	P > Q	tau2	% I2	H2
1	2	0.36	0.833	0.000	0.00	1.00
2	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) nometashow
```



In many cases researchers might want do account for covariates in the model.

Quizilvash et al. (1998) [2] performed a meta analysis on the effect of tacrine 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.

[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)

. 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
```

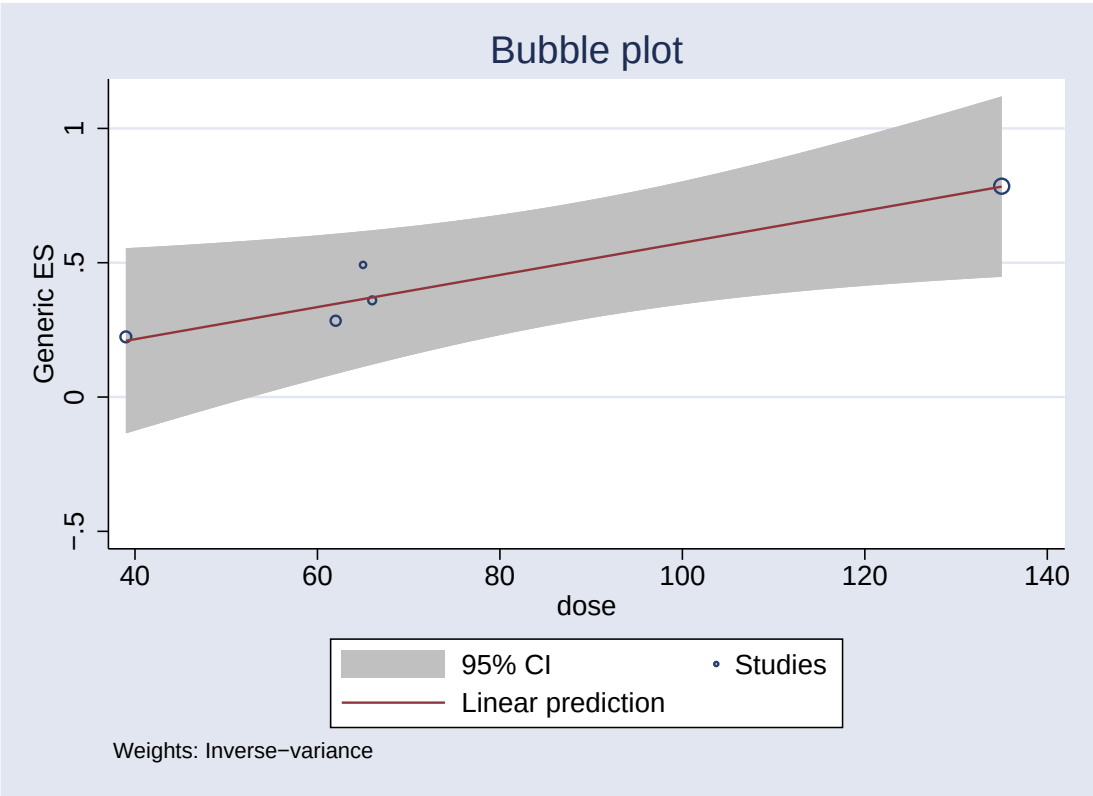
_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose	.0059788	.0027602	2.17	0.030	.0005689	.0113886
_cons	-.0237839	.2676855	-0.09	0.929	-.5484379	.5008701

```
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.

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

Example: Gruber et al. (2013). [4]
From the abstract: "Current guidelines recommend the use of Escherichia coli (EC) or thermotolerant ("fecal") coliforms (FC) as indicators of fecal contamination in drinking water. Despite their broad use as measures of water quality, there remains limited evidence for an association between EC or FC and diarrheal illness: a previous review found no evidence for a link between diarrhea and these indicators in household drinking water."

" We conducted a systematic review and meta-analysis to update the results of the previous review with newly available evidence, to explore differences between EC and FC indicators, and to assess the quality of available evidence"

[4] J. Gruber et al, Coliform Bacteria as Indicators of Diarrheal Risk in Household Drinking Water: Systematic Review and Meta- Analysis; PlosOne, Vol 9 issue 9, September 2013.

```
. use coliforms, clear
. list study n1 N1 n0 N0
```

	study	n1	N1	n0	N0
1.	Lang 2000	42	690	27	579
2.	Sorensen 1993	27	226	40	455
3.	Salina 1994	60	206	41	213
4.	Burling 1989	6	29	3	29
5.	Jason 1997	29	281	12	280
6.	Gamel 1993	8	82	1	130
7.	Koffman 1998	18	80	2	29
8.	Helyer 1998	16	52	5	62

We use `meta esize` to set up our data.

```
. gen m1 = N1 - n1

. gen m0 = N0 - n0

. 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
```

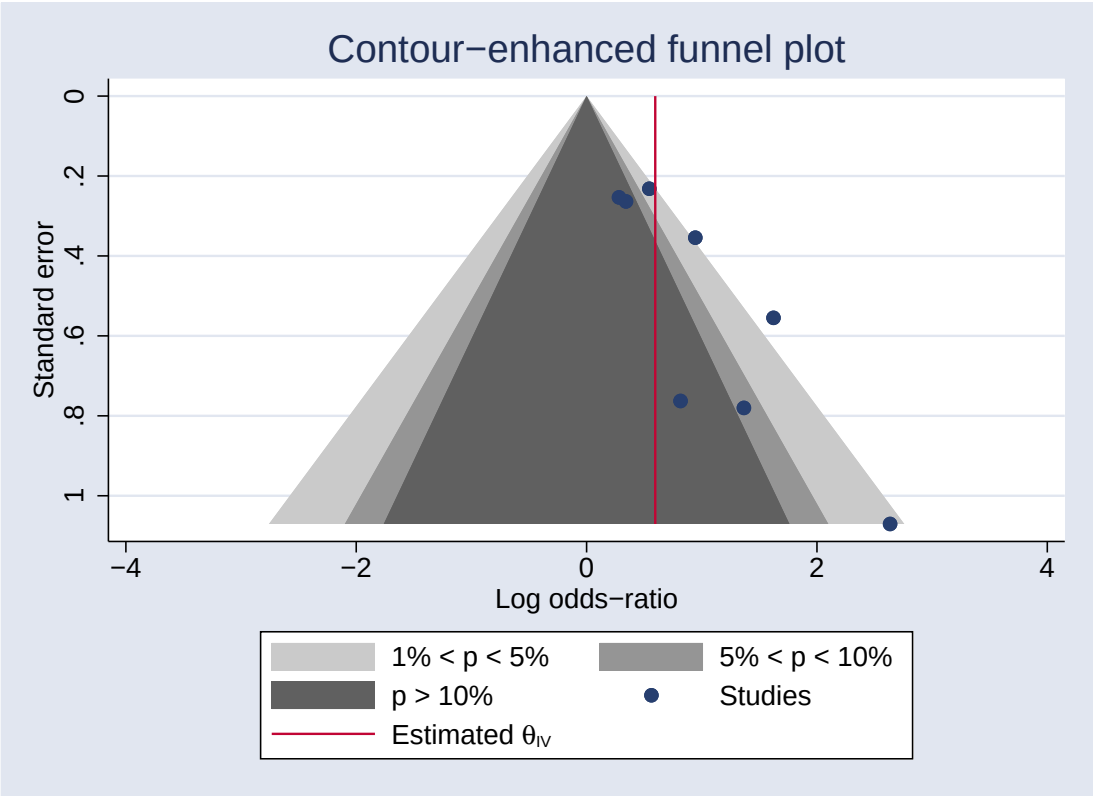
```
. meta summarize, nometashow
```

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

Study	Log Odds-Ratio	[95% Conf.	Interval]	% Weight
Lang 2000	0.281	-0.215	0.778	21.81
Sorensen 1993	0.342	-0.175	0.859	20.97
Salina 1994	0.545	0.090	0.999	23.70
Burling 1989	0.816	-0.679	2.311	4.41
Jason 1997	0.944	0.250	1.638	14.87
Gamel 1993	2.635	0.537	4.734	2.36
Koffman 1998	1.366	-0.163	2.895	4.24
Helyer 1998	1.623	0.535	2.710	7.64
theta	0.683	0.351	1.014	

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

```
. meta funnelplot, contours(1 5 10) nometashow
```



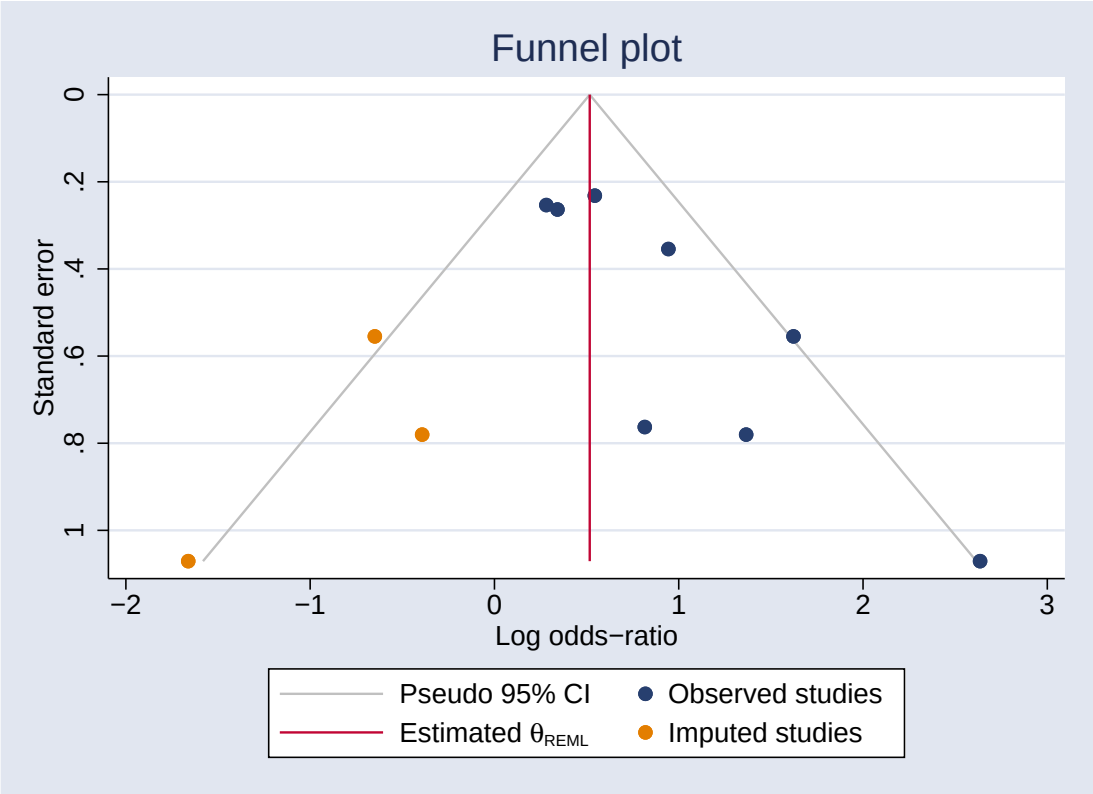
We perform Harbor's regression-based test.

```
. 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
```

`meta trimfill` allows us to explore the possible impact of publication bias.

```
. meta trimfill, funnel

  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	Log Odds-Ratio	[95% Conf.	Interval]
Observed	0.683	0.351	1.014
Observed + Imputed	0.517	0.124	0.910



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