

Meta-analysis using Stata

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Overview

- What is meta-analysis?
- Set up our data
- Summarize meta-analysis data
- Perform meta-regression
- Investigate small-study effects (publication bias)

Meta-analysis

- Meta-analysis is a statistical technique for combining the results from several similar studies.
- The goal is to provide a single estimate of the effect of interest.
- If results vary widely across studies, the goal is then to understand the inconsistencies in the results.
- One potential issue is that the results from published literature may not necessarily reflect the results from all the relevant research that has been conducted.

Impactful application

- Several studies were performed between 1959 and 1988 to determine the effectiveness of streptokinase in preventing death after a heart attack.
- Some studies did not find a statistically significant effect, but others did.
- Lau et al. (1992) performed meta-analysis on the odds ratio and noted that the overall effect size was statistically significant beginning in 1977; thus, more lives could have been potentially saved.

Applications in different fields

Although meta-analysis originated in the medical field, it has been useful in many fields:

- Winfree et al. (2009) performed meta-analysis to determine the impact of human disruption on the abundance of bees and the number of species within a region.
- Fan and Chen (2001) performed meta-analysis to examine the relationship between parental involvement and the academic achievement of their children.
- Longhi, Nijkamp, and Poot (2005) performed meta-analysis to assess the effect of immigration on wages.

Effect size

The effect size measures the effect of interest, such as the magnitude of group differences or the strength of a relationship between two variables. This might be

- the standardized mean difference for comparing a continuous outcome across two groups,
- the odds ratio or risk ratio for comparing a binary outcome across two groups,
- the correlation between two variables, or
- a regression coefficient.

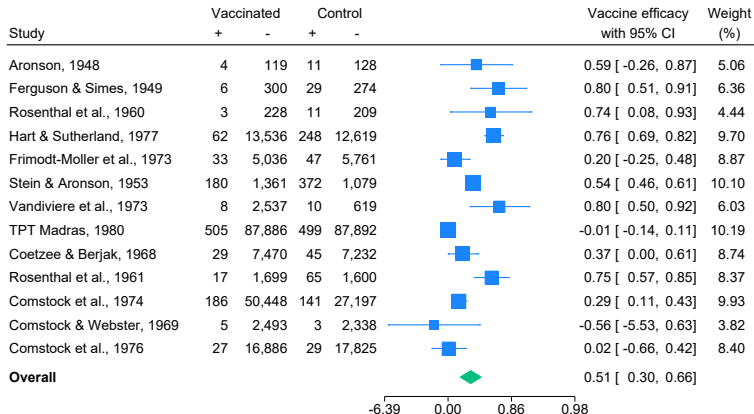
Estimate of vaccine efficacy

Suppose that a clinical trial was performed and researchers found that the Bacillus Calmette–Guérin (BCG) vaccine reduced the risk of contracting tuberculosis by 51%.

Estimate of vaccine efficacy

Suppose that a second clinical trial was performed and researchers found that the BCG vaccine reduced the risk of contracting tuberculosis by 11%.

Estimates of vaccine efficacy



Random-effects REML model

Meta-analysis goals

- Our goal is to report a single estimate of the vaccine efficacy.
 - We assume that the effect sizes are independent across studies.
- If we observe substantial variation across the studies, we instead focus on trying to explain this variation, possibly with study-level covariates.
- For example, perhaps the location of the studies might help explain the differences we see.

Meta-analysis models

K independent studies; each reports

- an estimate, $\hat{\theta}_j$, of the true (unknown) effect size θ_j ; and
- an estimate, $\hat{\sigma}_j$, of its standard error

$$\hat{\theta}_j = \theta_j + \epsilon_j$$

for $j = 1, 2, \dots, K$, where $\epsilon_j \sim \mathcal{N}(0, \hat{\sigma}_j^2)$.

- We treat the estimated values of the variances, $\hat{\sigma}_j^2$, as known.
- We assume that each study has estimated the variance with enough accuracy to treat it as known.

Meta-analysis models

K independent studies; each reports

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- an estimate, $\hat{\sigma}_j$, of its standard error

$$\hat{\theta}_j = \theta_j + \epsilon_j$$

for $j = 1, 2, \dots, K$, where $\epsilon_j \sim \mathcal{N}(0, \hat{\sigma}_j^2)$.

Model	Assumption	Target of inference
Common-effect	$\theta_1 = \theta_2 = \dots = \theta_K$	Common value θ
Fixed-effects	θ_j fixed	$\theta = \text{weighted average}(\theta_j)$
Random-effects	$\theta_j = \{\theta + \mu_j\} \sim \mathcal{N}(\theta, \tau^2)$	$\theta = \mathbb{E}(\theta_j)$

Random-effects meta-analysis model

K independent studies; each reports

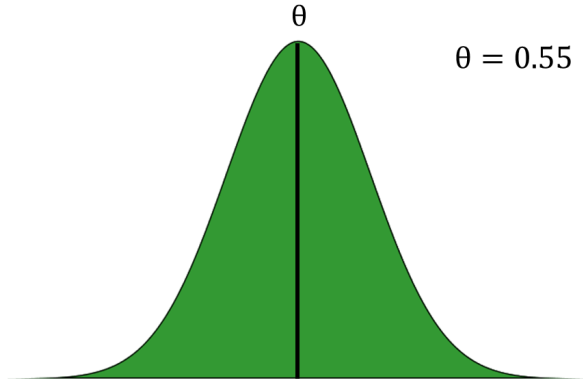
- an estimate, $\hat{\theta}_j$, of the true (unknown) effect size θ_j ; and
- an estimate, $\hat{\sigma}_j$, of its standard error

$$\hat{\theta}_j = \theta_j + \epsilon_j = \theta + u_j + \epsilon_j$$

for $j = 1, 2, \dots, K$, where $\epsilon_j \sim \mathcal{N}(0, \hat{\sigma}_j^2)$ and $u_j \sim \mathcal{N}(0, \tau^2)$.

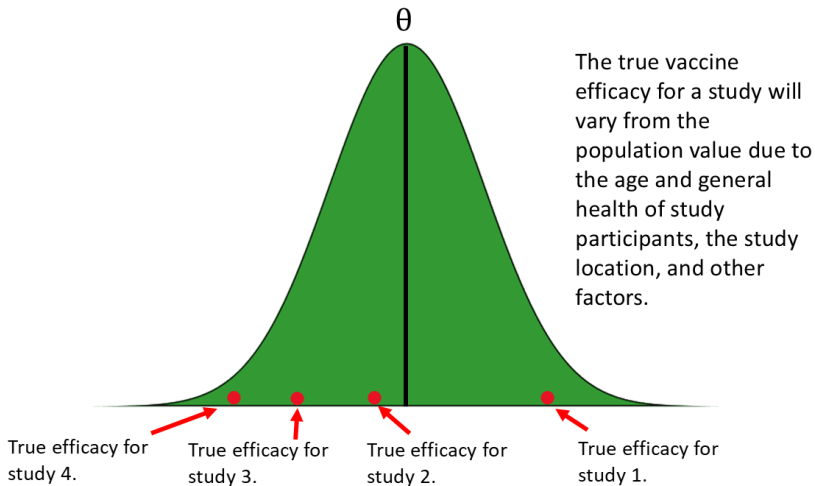
- The ϵ_j 's are the sampling errors, and the u_j 's are the random effects.
- The estimate of the overall effect size is the mean of the distribution of effect sizes, $\theta_{pop} = \mathbb{E}(\theta_j)$.

True vaccine efficacy in the population

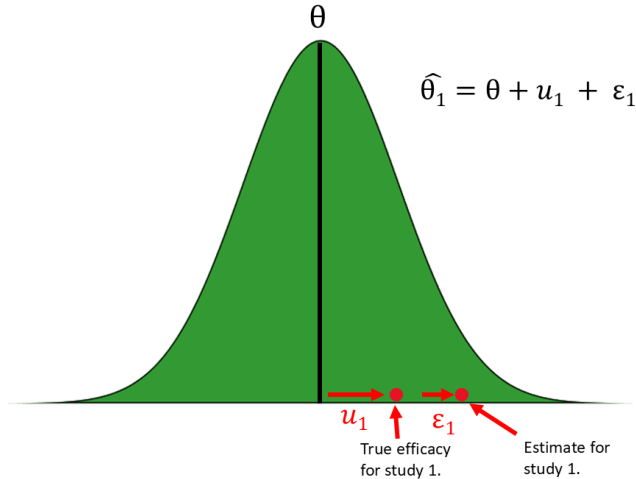


Suppose that the vaccine efficacy is 55%.

Underlying values for each study



Estimate of the vaccine efficacy for study 1



Random-effects meta-analysis

- For each study, we have an estimate of the vaccine efficacy, $\hat{\theta}_j$, and an estimate, $\hat{\sigma}_j$, of its standard error.
- The overall estimate of the vaccine efficacy is a weighted average of the study-specific estimates

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

where $w_j = \frac{1}{\hat{\sigma}_j^2 + \hat{\tau}^2}$ and $\hat{\tau}^2$ is the variance of the random effects.

Declare meta-analysis data

BCG vaccine efficacy data

```
. use bcgefficacy
(Efficacy of BCG vaccine against tuberculosis)
. describe
```

Contains data from bcgefficacy.dta

```
Observations:      13      Efficacy of BCG vaccine against tuberculosis
Variables:         12      10 Sep 2025 23:27
                        (_dta has notes)
```

Variable name	Storage type	Display format	Value label	Variable label
trial	byte	%9.0g		Trial number
trialloc	str14	%14s		Trial location
author	str21	%21s		Author
year	int	%9.0g		Publication year
npost	int	%9.0g		Number of TB positive cases in treated group
nnegt	long	%9.0g		Number of TB negative cases in treated group
npsc	int	%9.0g		Number of TB positive cases in control group
nnegc	long	%9.0g		Number of TB negative cases in control group
latitude	byte	%9.0g		Absolute latitude of the study location (in degrees)
alloc	byte	%10.0g	alloc	Method of treatment allocation
studylbl	str27	%27s		Study label
latitude_c	double	%10.0g		Mean-centered latitude

Sorted by: trial

Meta-analysis data

```
. list trial npost nnegt nposc nnegc latitude
```

	trial	npost	nnegt	nposc	nnegc	latitude
1.	1	4	119	11	128	44
2.	2	6	300	29	274	55
3.	3	3	228	11	209	42
4.	4	62	13536	248	12619	52
5.	5	33	5036	47	5761	13
6.	6	180	1361	372	1079	44
7.	7	8	2537	10	619	19
8.	8	505	87886	499	87892	13
9.	9	29	7470	45	7232	27
10.	10	17	1699	65	1600	42
11.	11	186	50448	141	27197	18
12.	12	5	2493	3	2338	33
13.	13	27	16886	29	17825	33

Two-group comparison of binary data

When comparing a binary outcome across two groups, studies typically report the cell counts for the following table:

Group	Success	Failure	Sample size
Treatment	n_{11}	n_{12}	$n_1 = n_{11} + n_{12}$
Control	n_{21}	n_{22}	$n_2 = n_{21} + n_{22}$

Declare meta-analysis data

- Compute effect sizes for two-group comparison of binary outcomes

```
meta esize n11 n12 n21 n22 [ , model esize(effect)  
zerocells(spec) ]
```

model: random, common, or fixed

effect: log odds-ratio, log risk-ratio, risk difference, Peto's log odds-ratio

- Precomputed effect sizes

```
meta set esize se [ , model ]
```

```
meta set esize ciupper cilower [ , model ]
```

Effect sizes

- We need to work in the metric that is closest to being normally distributed. For example, we can work with the log odds-ratio or the log risk-ratio.
- Odds ratios and risk ratios typically have skewed distributions, but their logs are asymptotically normally distributed.
- When using `meta set`, it is assumed that you are specifying the effect size in the metric closest to normality.

Declare meta-analysis data

```
. meta esize npost nnegt nposc nnegc, esize(lnrratio) studylabel(study1bl)
Meta-analysis setting information
Study information
  No. of studies: 13
  Study label: study1bl
  Study size: _meta_studysize
  Summary data: npost nnegt nposc nnegc
  Effect size
    Type: lnrratio
    Label: Log risk-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
```

Summarize meta-analysis data

Summary of meta-analysis data

```
. meta summarize, rr nometashow
```

Meta-analysis summary
Random-effects model
Method: REML

Number of studies = 13
Heterogeneity:
tau2 = 0.3132
I2 (%) = 92.22
H2 = 12.86

Study	Risk ratio	[95% conf. interval]		% weight
Aronson, 1948	0.411	0.134	1.257	5.06
Ferguson & Simes, 1949	0.205	0.086	0.486	6.36
Rosenthal et al., 1960	0.260	0.073	0.919	4.44
Hart & Sutherland, 1977	0.237	0.179	0.312	9.70
Frimodt-Moller et al., 1973	0.804	0.516	1.254	8.87
Stein & Aronson, 1953	0.456	0.387	0.536	10.10
Vandiviere et al., 1973	0.198	0.078	0.499	6.03
TPT Madras, 1980	1.012	0.895	1.145	10.19
Coetzee & Berjak, 1968	0.625	0.393	0.996	8.74
Rosenthal et al., 1961	0.254	0.149	0.431	8.37
Comstock et al., 1974	0.712	0.573	0.886	9.93
Comstock & Webster, 1969	1.562	0.374	6.528	3.82
Comstock et al., 1976	0.983	0.582	1.659	8.40
exp(theta)	0.489	0.344	0.696	

Test of theta = 0: z = -3.97

Test of homogeneity: Q = chi2(12) = 152.23

Prob > |z| = 0.0001

Prob > Q = 0.0000

I^2 statistic

The following rough guidelines are provided by Higgins et al. (2003).

- Small heterogeneity $I^2 = 25\%$
- Medium heterogeneity $I^2 = 50\%$
- Large heterogeneity $I^2 = 75\%$

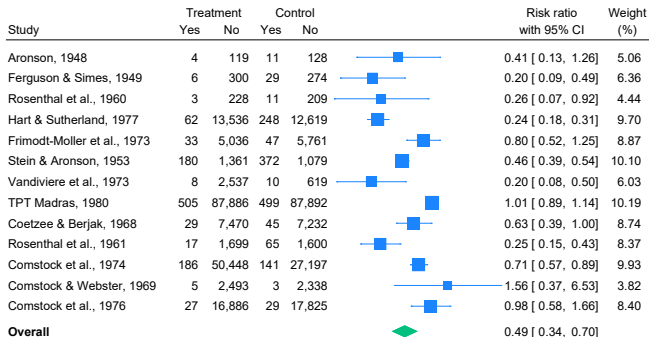
Quantifying heterogeneity



$$I^2 = \frac{\text{Between-study heterogeneity}}{\text{Sampling error (within-study heterogeneity)} + \text{Between-study heterogeneity}} \times 100\%$$

Forest plot

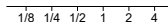
```
. meta forestplot, rr
```



Heterogeneity: $\tau^2 = 0.31$, $I^2 = 92.22\%$, $H^2 = 12.86$

Test of $\theta_1 = \theta_0$: $Q(12) = 152.23$, $p = 0.00$

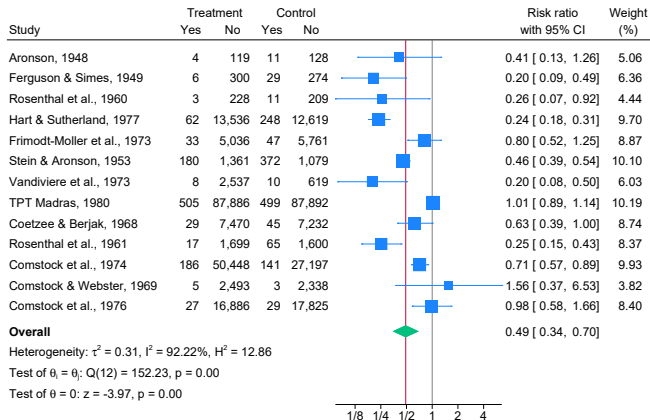
Test of $\theta = 0$: $z = -3.97$, $p = 0.00$



Random-effects REML model

Forest plot with reference lines

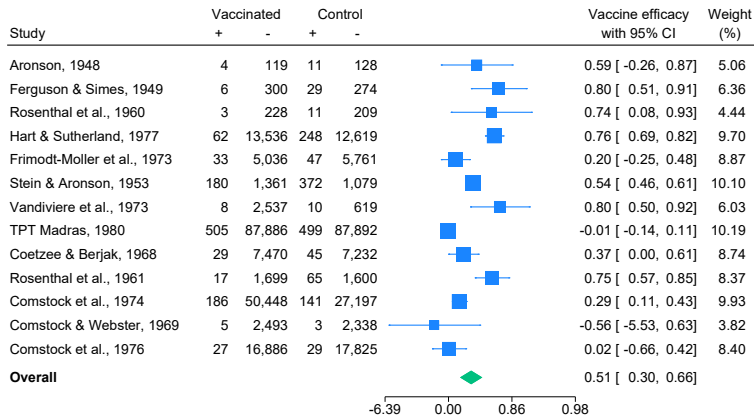
```
. meta forestplot, rr esrefline nullrefline
```



Random-effects REML model

Reporting efficacies

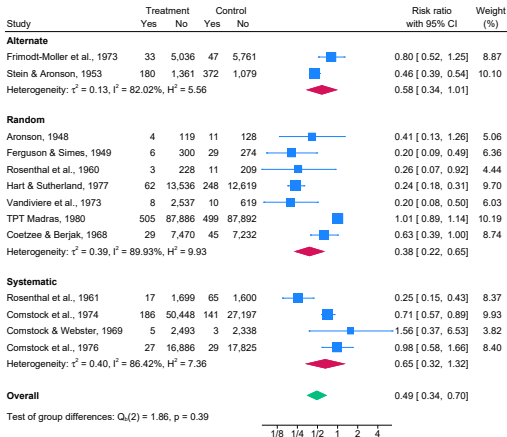
```
. meta forestplot, transform(Vaccine efficacy: efficacy) columnopts(_data1,
supertitle(Vaccinated)) columnopts(_a _c, title(+)) columnopts(_b _d, title(-))
```



Random-effects REML model

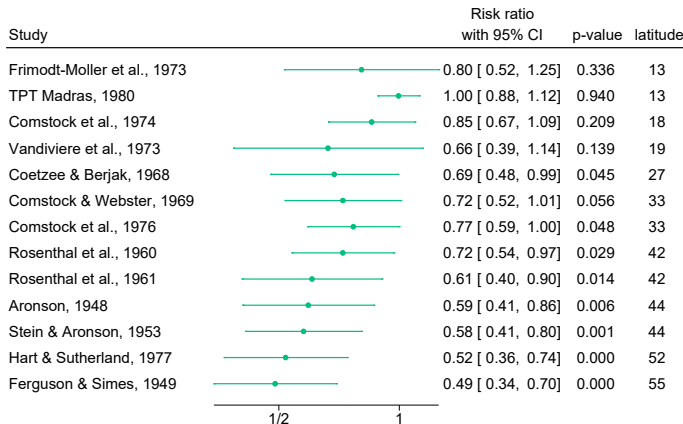
Subgroup meta-analysis

```
. meta forestplot, rr subgroup(alloc)
```



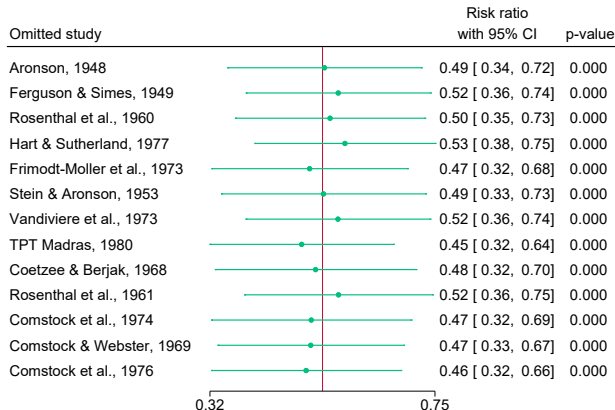
Cumulative meta-analysis

```
. meta forestplot, rr cumulative(latitude)
```



Leave-one-out meta-analysis

```
. meta forestplot, leaveoneout rr
```



Random-effects REML model

Perform meta-regression

Random-effects meta-regression

- Random-effects model

$$\hat{\theta}_j = \theta_j + \epsilon_j = \theta + u_j + \epsilon_j$$

- Random-effects meta-regression

$$\hat{\theta}_j = x_j\beta + u_j + \epsilon_j$$

for $j = 1, 2, \dots, K$, where $\epsilon_j \sim \mathcal{N}(0, \hat{\sigma}_j^2)$ and $u_j \sim \mathcal{N}(0, \tau^2)$.

- A portion of the between-study heterogeneity is explained by the moderators.
- The unexplained portion is referred to as residual heterogeneity.

Meta-regression

```
. meta regress latitude_c
```

Effect-size label: Log risk-ratio

Effect size: `_meta_es`

Std. err.: `_meta_se`

Random-effects meta-regression

Method: REML

Number of obs = 13

Residual heterogeneity:

tau2 = .07635

I2 (%) = 68.39

H2 = 3.16

R-squared (%) = 75.63

Wald chi2(1) = 16.36

Prob > chi2 = 0.0001

<code>_meta_es</code>	Coefficient	Std. err.	z	P> z	[95% conf. interval]	
latitude_c	-.0291017	.0071953	-4.04	0.000	-.0432043	-.0149991
_cons	-.7223204	.1076535	-6.71	0.000	-.9333174	-.5113234

Test of residual homogeneity: $Q_{res} = \chi^2(11) = 30.73$ Prob > $Q_{res} = 0.0012$

Predictions of the effect size

- What is the predicted risk ratio for Thailand? Nepal? Ukraine?
- We can obtain the mean latitude with `summarize latitude`.
- Then we subtract the mean (33.46) from the latitude of the locations of interest.
- Thailand: latitude 15; centered latitude -18.5
- Nepal: latitude 28; centered latitude -5.5
- Ukraine: latitude 50; centered latitude 16.5

Predictions of the log risk-ratio

```
. margins, at(latitude_c = (-18.5 -5.5 16.5))
```

Adjusted predictions

Number of obs = 13

Expression: Fitted values; fixed portion (xb), predict(fitted fixedonly)

1._at: latitude_c = -18.5

2._at: latitude_c = -5.5

3._at: latitude_c = 16.5

	Delta-method		z	P> z	[95% conf. interval]	
	Margin	std. err.				
_at						
1	-.1839386	.1586092	-1.16	0.246	-.4948069	.1269297
2	-.562261	.1091839	-5.15	0.000	-.7762574	-.3482645
3	-1.202499	.1714274	-7.01	0.000	-1.53849	-.8665072

Predictions of the risk ratio

```
. margins, at(latitude_c = (-18.5 -5.5 16.5)) expression(exp(predict(xb)))
```

Adjusted predictions

Number of obs = 13

Expression: exp(predict(xb))

1._at: latitude_c = -18.5

2._at: latitude_c = -5.5

3._at: latitude_c = 16.5

	Delta-method		z	P> z	[95% conf. interval]	
	Margin	std. err.				
_at						
1	.8319869	.1319608	6.30	0.000	.5733486	1.090625
2	.569919	.062226	9.16	0.000	.4479584	.6918797
3	.3004425	.0515041	5.83	0.000	.1994964	.4013887

Predictions of the risk ratio

- The predicted risk ratio is 0.3 for locations with a centered latitude of 16.5.
- We expect the vaccine to reduce the risk of tuberculosis by 70% when administered in regions with a centered latitude of 16.5.
- However, for regions with a centered latitude of -18.5 , such as Thailand, we expect the vaccine to reduce the risk only by roughly 17%.

Investigate small-study effects

Small-study effects

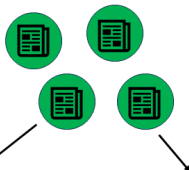
- Small-study effects are present when smaller studies report results that are systematically different from those reported by larger studies.
- Small-study effects may be present because of publication bias.
- Publication bias refers to cases in which the decision to publish a study depends on the statistical significance of its results.
- We will assess whether small-study effects are present; if they are, we will assess the impact on the overall effect size.

Missing studies

Observed studies



Studies not included in the MA



Random subset

↓
We'll obtain valid conclusions, but with wider CIs and less powerful tests

Systematically different
(e.g., when smaller studies with nonsignificant findings are suppressed from publication)

↓
Our meta-analytic results will be biased, and decisions based on them will be invalid

Tools for exploring small-study effects

- Funnel plots
 - Create a scatterplot of the study-specific effect sizes against measures of study precision.
- Tests for small-study effects
 - Regression-based and nonparametric rank correlation tests.
- Trim-and-fill analysis
 - Assess the impact of publication bias on the results of the meta-analysis.

Nonsteroidal anti-inflammatory drug data

Moore et al. (1998) performed meta-analysis with the following data:

```
. webuse nsaids
(Effectiveness of nonsteroidal anti-inflammatory drugs)
. describe
```

Contains data from <https://www.stata-press.com/data/r19/nsaids.dta>

```
Observations:      37      Effectiveness of nonsteroidal anti-inflammatory drugs
Variables:         5      24 Apr 2024 17:09
                        (_dta has notes)
```

Variable name	Storage type	Display format	Value label	Variable label
study	byte	%8.0g		Study ID
nstreat	byte	%8.0g		Number of successes in the treatment arm
nftreat	byte	%9.0g		Number of failures in the treatment arm
nscontrol	byte	%8.0g		Number of successes in the control arm
nfcontrol	byte	%9.0g		Number of failures in the control arm

Sorted by:

Declare meta-analysis data

```
. meta esize nstreat nftreat nscontrol nfcontrol
Meta-analysis setting information
Study information
  No. of studies: 37
  Study label: Generic
  Study size: _meta_studysize
  Summary data: nstreat nftreat nscontrol nfcontrol
  Effect size
    Type: lnoratio
    Label: Log odds-ratio
    Variable: _meta_es
  Zero-cells adj.: 0.5, only0
  Precision
    Std. err.: _meta_se
    CI: [_meta_cil, _meta_ciu]
    CI level: 95%
Model and method
  Model: Random effects
  Method: REML
```

Summary of meta-analysis data

```
. meta summarize, or
```

```
    Effect-size label: Log odds-ratio
```

```
    Effect size: _meta_es
```

```
    Std. err.: _meta_se
```

```
Meta-analysis summary
```

```
Random-effects model
```

```
Method: REML
```

```
Number of studies =      37
```

```
Heterogeneity:
```

```
    tau2 =    0.4880
```

```
    I2 (%) =    69.23
```

```
    H2 =      3.25
```

Study	Odds ratio	[95% conf. interval]		% weight
Study 1	6.571	2.109	20.479	2.67
Study 2	1.467	0.881	2.443	3.96
Study 3	4.351	2.371	7.983	3.77
Study 4	5.577	2.265	13.733	3.15
Study 5	13.000	2.074	81.479	1.61
(output omitted)				
Study 34	5.289	2.648	10.564	3.59
Study 35	4.457	1.311	15.158	2.51
Study 36	21.000	1.777	248.103	1.06
Study 37	5.688	1.510	21.424	2.33
exp(theta)	3.752	2.805	5.018	

```
Test of theta = 0: z = 8.91
```

```
Test of homogeneity: Q = chi2(36) = 113.35
```

```
Prob > |z| = 0.0000
```

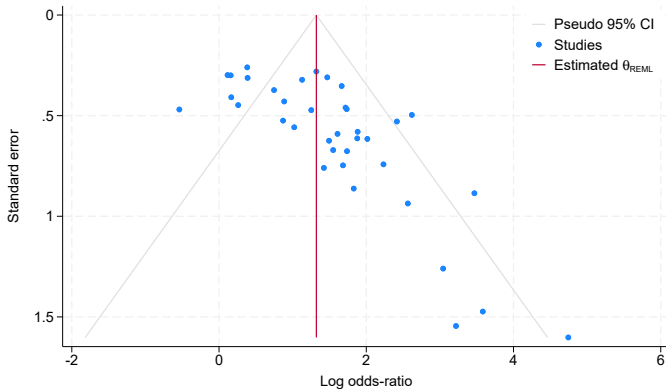
```
Prob > Q = 0.0000
```

Heterogeneity and small-study effects

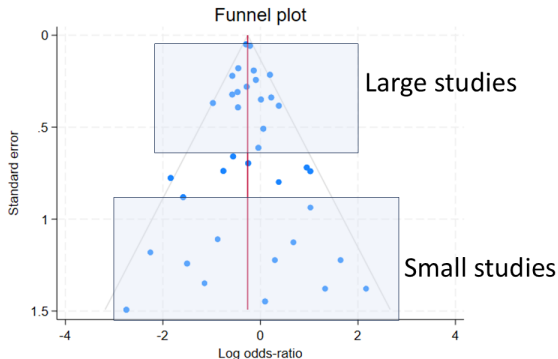
- There is substantial between-study heterogeneity ($I^2 = 69.23$), which should be addressed before we explore the presence of publication bias.
- For example, if we had a categorical variable that explained the heterogeneity, we would explore the presence of publication bias separately for each category.
- However, for the purpose of illustration, we will explore the presence of publication bias without having explained the between-study heterogeneity.

Funnel plot

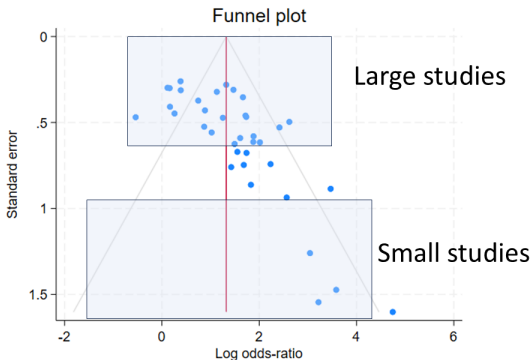
```
. meta funnelplot, random
```



Funnel plot with no evidence of small-study effects

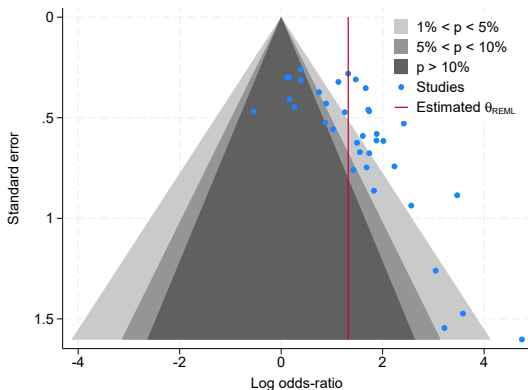


Funnel plot with evidence of small-study effects



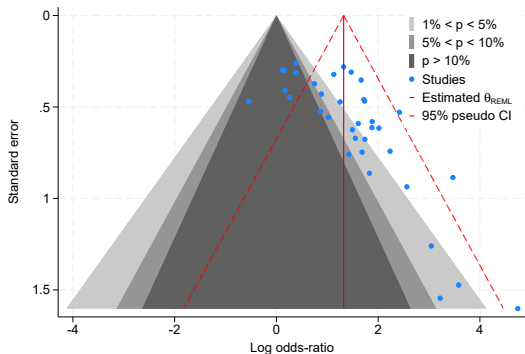
Contour-enhanced funnel plot

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



Contour-enhanced funnel plot with pseudo 95% CI

```
. meta funnelplot, random contours(1 5 10)  
  
> addplot(function theta-1.96*x || function theta+1.96*x)
```



Test for small-study effects

```
. 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 =          3.03
      SE of beta1 =      0.741
              z =        4.09
      Prob > |z| =      0.0000
```

Trim-and-fill analysis

```
. meta trimfill, or
    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

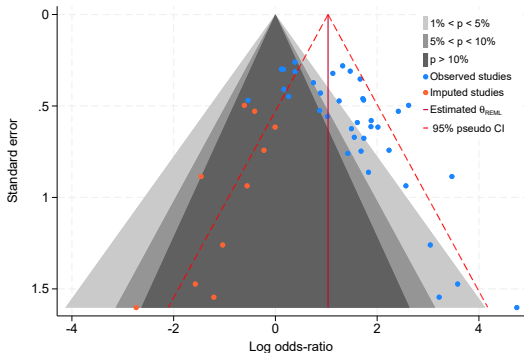
Iteration                                Number of studies =      47
  Model: Random-effects                    observed =      37
  Method: REML                            imputed =      10

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

Studies	Odds ratio	[95% conf. interval]	
Observed	3.752	2.805	5.018
Observed + Imputed	2.815	2.067	3.832

Contour-enhanced funnel plot with imputed studies

```
. meta trimfill, or funnel(contours(1 5 10))  
  
> addplot(function imptheta-1.96*x || function imptheta+1.96*x)
```



Conclusion

How effective are NSAIDS for pain reduction?

- Our meta-analysis suggests that the odds of pain reduction are 3.75 times greater when taking an NSAID as opposed to a placebo.
- However, because there is substantial heterogeneity, it would not be wise to synthesize the results from these studies with a single estimate.
- We found evidence of publication bias, but in our applied work, we should address heterogeneity before exploring the presence of publication bias.

Support for other data types

- With `meta esize`, you can also compute effect sizes for
 - a two-group comparison of continuous outcomes,
 - one-sample binary data (proportions), and
 - estimating a correlation.
- With `meta set` you can declare your data to be meta-analysis data by specifying precomputed effect sizes. For example, you might be working with regression coefficients or log odds-ratios.

Beyond standard meta-analysis

- I have multiple effect sizes reported for each study. How can I obtain the estimate of the overall effect size for each outcome, taking their dependence into account?
 - Perform multivariate meta-regression with `meta mvregress`.
- What is the overall effect size when accounting for the hierarchical structure of the effect sizes? And what level of heterogeneity is present at different levels of hierarchy?
 - Perform multilevel mixed-effects meta-regression with `meta meregress`.

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