The funnel plot appears asymmetric, and there is evidence of bias using the Egger (weighted regression) method (P for bias 0·007) but not using the Begg (rank correlation method). This is compatible with a greater statistical power of the regression test, as discussed in Chapter 11. The horizontal line in the funnel plot indicates the fixed-effects summary estimate (using inverse-variance weighting), while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies.

Meta-regression

If evidence is found of heterogeneity in the effect of treatment between studies, then meta-regression can be used to analyse associations between treatment effect and study characteristics. Meta-regression can be done in Stata by using the **metareg** command.[19]

Example 3: trials of BCG vaccine against tuberculosis

The following table is based on a meta-analysis by Colditz *et al.*[20] which examined the efficacy of BCG vaccine against tuberculosis.

Table 18.3

Trial	Trial name	Authors	Start year	Latitude*	Intervention group		Control group	
					TB cases	Total	TB cases	Total
1	Canada	Ferguson & Simes	1933	55	6	306	29	303
2	Northern USA	Aronson	1935	52	4	123	11	139
3	Northern USA	Stein & Aronson	1935	52	180	1541	372	1451
4	Chicago	Rosenthal *et al.*	1937	42	17	1716	65	1665
5	Chicago	Rosenthal *et al.*	1941	42	3	231	11	220
6	Georgia (School)	Comstock & Webster	1947	33	5	2498	3	2341
7	Puerto Rico	Comstock *et al.*	1949	18	186	50 634	141	27 338
8	UK	Hart & Sutherland	1950	53	62	13 598	248	12 867
9	Madanapalle	Frimont-Moller *et al.*	1950	13	33	5069	47	5808
10	Georgia (Community)	Comstock *et al.*	1950	33	27	16 913	29	17 854
11	Haiti	Vandeviere *et al.*	1965	18	8	2545	10	629
12	South Africa	Coetzee & Berjak	1965	27	29	7499	45	7277
13	Madras	TB prevention trial	1968	13	505	88 391	499	88 391

* Expressed in degrees from equator.

The data were saved in Stata dataset **bcgtrial.dta**.

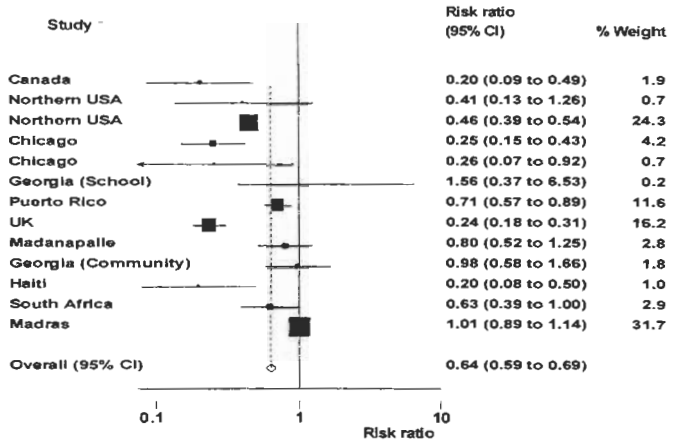
```
describe
```

```
Contains data from bcgtrial.dta
  obs:            13
 vars:             9
 size:           754 (99.9% of memory free)
-------------------------------------------------------------------------------
              storage  display    value
variable name   type   format     label      variable label
-------------------------------------------------------------------------------
trial           byte   %8.0g
trialnam        str19  %19s
authors         str19  %19s
startyr         int    %8.0g
latitude        byte   %8.0g
cases1          int    %8.0g
tot1            long   %12.0g
cases0          int    %8.0g
tot0            long   %12.0g
-------------------------------------------------------------------------------
Sorted by: trial
```

Scientists had been aware of discordance between the results of these trials since the 1950s. The clear heterogeneity in the protective effect of BCG between trials can be seen in the forest plot (we analyse this study using risk ratios):

```
gen h1=tot1-cases1
gen h0=tot0-cases0

metan cases1 h1 cases0 h0, xlab(.1,1,10)
label(namevar=trialnam)
```



To use the **metareg** command, we need to derive the treatment effect estimate (in this case log risk ratio) and its standard error, for each study.

```
generate logrr=log((cases1/tot1)/(cases0/tot0))
generate  selogrr=sqrt((1/cases1)-(1/tot1)+(1/cases0)-
(1/tot0))
```

In their meta-analysis, Colditz *et al.* noted the strong evidence for heterogeneity between studies, and concluded that a random-effects meta-analysis was appropriate:

```
meta logrr selogrr, eform
Meta-analysis (exponential form)
```

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	0.650	0.601	0.704	-10.625	0.000	13
Random	0.490	0.345	0.695	-3.995	0.000	

```
Test for heterogeneity: Q= 152.233 on 12 degrees of
freedom (p= 0.000)
Moment-based estimate of between studies variance =
0.309
```


(The different weight of studies under the fixed and random effects assumption is discussed in Chapter 2).

The authors then examined possible explanations for the clear differences in the effect of BCG between studies. The earlier studies may have produced different results than later ones. The latitude at which the studies were conducted may also be associated with the effect of BCG. As discussed by Fine,[21] the possibility that BCG might provide greater protection at higher latitudes was first recognised by Palmer and Long,[22] who suggested that this trend might result from exposure to certain environmental mycobacteria, more common in warmer regions, which impart protection against tuberculosis.

To use **metareg**, we provide a list of variables, the first of which is the treatment effect (here, the log risk ratio) and the rest of which are (one or more) study characteristics (covariates) hypothesized to be associated with the treatment effect. In addition, the standard error or variance of the treatment effect must be provided, using the **wsse** (within-study standard error) or **wsvar** (within-study variance) option. It is also possible to specify the method for estimating the between-study variance: here we use the default; restricted maximum-likelihood (reml). To look for an association with start year and latitude:

```
metareg logrr startyr latitude, wsse(selogrr)

Iteration 1: tau^2 = 0
Iteration 2: tau^2 = .02189942
:
:
Iteration 9: tau^2 = .1361904
Iteration 10: tau^2 = .13635174

Meta-analysis regression          No of studies =  13
                                  tau^2 method    reml
                                  tau^2 estimate = .1364

Successive values of tau^2 differ by less than 10^-4 :con-
vergence achieved
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
startyr	-.004966	.0162811	-0.305	0.760	-.0368763	.0269444
latitude	-.0270477	.0118195	-2.288	0.022	-.0502135	-.0038819
_cons	9.890987	32.02516	0.309	0.757	-52.87717	72.65914

The regression coefficients are the estimated increase in the log risk ratio per unit increase in the covariate. So in the example the log risk ratio is estimated to decrease by 0·027 per unit increase in the latitude at which the study is conducted. The estimated between-study variance has been reduced from 0·31 (see output from the **meta** command) to 0·14. While there is strong evidence for an association between latitude and the effect of BCG, there is no evidence for an association with the year the study started. The estimated treatment effect given particular values of the covariates may be derived from the regression equation. For example, for a trial beginning in 1950, at latitude 50°, the estimated log risk ratio is given by:

$$\text{Log risk ratio} = 9{\cdot}891 - 0{\cdot}00497 \times 1950 - 0{\cdot}0270 \times 50 = -1{\cdot}1505$$

which corresponds to a risk ratio of $\exp(-1{\cdot}1505) = 0{\cdot}316$

The use of meta-regression in explaining heterogeneity and identifying sources of bias in meta-analysis is discussed further in Chapters 8–11.

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