Chapter 11
Meta-Regression

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11.1 Basic Theory

11.1.1 The Classical Meta-Regression Method

Suppose $\hat{\theta}_j$ is the effect estimated in the *jth* study, then under the fixed-effect model,

$$\hat{\theta}_j \sim N(\mu, \sigma_j^2)$$

The fixed-effect model assumes all the studies are from the same population so there is no heterogeneity between these studies (Thompson and Higgins 2002). Now let's consider the random-effect model:

$$\hat{\theta}_j \sim N(\theta_j, \sigma_j^2); \theta_j \sim N(\mu, \tau^2)$$

The heterogeneity term τ^2 is generated under the assumption that the difference between the overall population parameter (μ) and the study population characteristics modified effect (e.g. difference in mean age) is distributed normally with a common variance (Thompson and Sharp 1999). The regression model is then

$$\hat{\theta}_j = \mu + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \ldots + \beta_i \cdot x_i + b_j + \varepsilon_j$$

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Here x represents the study-level characteristics and ε_j represents the random error with the variance of σ_j^2 and b the non-random error with the variance of τ^2, both of which share the expectation (mean) of zero. Because all the characteristics (independent variables) are mean or median based on the study-level, each study is independent from another, and these variables are independent from each other. To take account of the variance of error information into the meta-regression, the weighted least square method can be used to get the parameter estimations.

A problem with fixed-effect meta-regression is that most studies are heterogeneous and thus there is overdispersion of the data compared to the model that random-effect meta-regression tries to address (Harbord and Higgins 2008). However, it should be pointed out that with increasing heterogeneity of studies, the random-effect weights become more equal and the regression therefore becomes more and more unweighted and this tends to lead to continued overdispersion with this model as well (Doi et al. 2015). As expected, when variables are added (or dropped) within the regression model, the total weighted variance (Q) will change, while the within study variance (σ_j^2) is known to us and keeps the same. This will result in the change of the between study variance (τ^2) so that when it reduces, this means that the variable can explain part of the heterogeneity and when it increases, this means adding the variable will make the fitting of the model poorer and the variable should not be added and of course is not the source of heterogeneity. The proportion of heterogeneity explained by the added variables is then

$$R^2 = [(\tau_0^2 - \tau_{model}^2) \big/ \tau_0^2, 0]$$

The equation implies that when the heterogeneity is reduced then the $\tau_{model}^2 \leq \tau_0^2$, and when heterogeneity increased that $\tau_{model}^2 > \tau_0^2$, with the proportion tending towards zero (Thompson and Higgins 2009). Here the proportion is actually the same as the R square of the generic regression and is then indexed as R squared.

$$R^2 = \frac{\tau_0^2 - \tau_{model}^2}{\tau_0^2} = 1 - \frac{SS_{res}}{SS_{total}} = \frac{SS_{model}}{SS_{total}}$$

Here τ_0^2 is the heterogeneity when we did not add any variables into the regression and obviously, the result of this model is the pooled effect estimate of the population parameter μ(the constant term).

$$\hat{\theta}_j = \mu + b_j + \varepsilon_j$$

11.1.2 The Robust Error Meta-Regression Method

The classical meta-regression model is based on the random-effect meta-analytic model while this model has the limitation we noted previously. An alternative solution is to use the generic regression with the robust (Huber-Eicker-White-sandwich) error variances to account for the underestimated variance in such analyses under the regression model (Hedges et al. 2010). These standard errors are usually bigger than the ordinary least squares (OLS) standard errors when effect sizes further from the mean are more variable. Weights applied to this model are fixed-effect weights and overdispersion is avoided through use of robust standard errors.

11.2 Application in MetaXL/STATA

11.2.1 The Meta-Regression Dataset

The IHDChol example uses 28 randomized trials of serum cholesterol reduction (by various interventions), and the risk of ischaemic heart disease (IHD) events observed. Both fatal IHD and non-fatal myocardial infarction were included as IHD events, and the analysis is based on the 28 trials reported by Law et al. (Law et al. 1994). In these trials, cholesterol had been reduced by a variety of means, namely dietary intervention, drugs, and, in one case, surgery. The meta-regression looks at if increased benefit in terms of IHD risk reduction is associated with greater reduction in serum cholesterol, in order to lend support to the efficacy of cholesterol reduction and to predict the expected IHD risk reduction consequent upon a specified decrease in serum cholesterol (Table 11.1).

11.2.2 The Robust Error Meta-Regression in STATA

We may first use the inverse-variance weights with the following command to conduct a generic meta-analysis. The reason we use the inverse-variance weights is that with the robust standard errors it mimics the IVhet model (Doi et al. 2015) of meta-analysis which is a robust error fixed-effect model and results can then be compared against the latter. The pooled OR under the IVhet model is 0.83 (95%CI: 0.72, 0.95) and the relative heterogeneity (I^2) is 45.7% and the between-study variance (τ^2) is 0.0188.

Table 11.1 Comparisons on the IDH events of various interventions

Study name	N1	Cases1	Non-cases1	N2	Cases2	Non-cases2	Chol_reduc
T1	5331	173	5158	5296	210	5086	0.55
T2	244	54	190	253	85	168	0.68
T3	350	54	296	367	75	292	0.85
T4	2222	676	1546	2789	936	1853	0.55
T5	145	42	103	284	69	215	0.59
T6	279	73	206	276	101	175	0.84
T7	1906	157	1749	1900	193	1707	0.65
T8	71	6	65	72	11	61	0.85
T9	1149	36	1113	1129	42	1087	0.49
T10	88	2	86	30	2	28	0.68
T11	2051	56	1995	2030	84	1946	0.69
T12	94	1	93	94	5	89	1.35
T13	4541	131	4410	4516	121	4395	0.7
T14	424	52	372	422	65	357	0.87
T15	199	45	154	194	52	142	0.95
T16	229	61	168	229	81	148	1.13
T17	221	37	184	237	24	213	0.31
T18	28	8	20	52	11	41	0.61
T19	130	47	83	134	50	84	0.57
T20	421	82	339	417	125	292	1.43
T21	6582	62	6520	1663	20	1643	1.08
T22	94	2	92	52	0	52	1.48
T23	23	1	22	29	0	29	0.56
T24	60	3	57	30	5	25	1.06
T25	1018	132	886	1015	144	871	0.26
T26	311	35	276	317	24	293	0.76
T27	79	3	76	78	4	74	0.54
T28	76	7	69	79	19	60	0.68

```
. admetan cases1 noncases1 cases2 noncases2, or ivhet summaryonly

Studies included: 28
Participants included: 52350

Meta-analysis pooling of Odds Ratios
using Doi's IVHet model
based on DerSimonian-Laird estimate of tau²
```

	Odds Ratio	[95% Conf.	Interval]	% Weight
Overall effect	0.825	0.719	0.946	100.00

```
Test of overall effect = 1:  z =  -2.750  p = 0.006

Heterogeneity Measures
```

	Value	df	p-value
Mantel-Haenszel Q	49.69	27	0.005
I² (%)	45.7%		
Modified H²	0.840		
tau²	0.0294		

From the results, we can see that there is moderate heterogeneity ($I^2 = 45.7\%$, $tau^2 = 0.0294$) between studies. The total variance based on Mantel-Haenszel estimates is 49.69.

Using a robust error meta-regression without covariates, we can reproduce these results as follows:

```
.  regress _ES [aw=1/(_seES^2)], vce(robust) eform(expb)
(sum of wgt is   8.8607e+02)

Linear regression                               Number of obs     =         28
                                                F(0, 27)          =       0.00
                                                Prob > F          =          .
                                                R-squared         =     0.0000
                                                Root MSE          =     .24116
```

_ES	expb	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
_cons	.8245754	.0329994	-4.82	0.000	.7595715	.8951422

We may further investigate whether the amount of cholesterol reduction is associated with the lnORs across studies by the robust error meta-regression analysis with inverse-variance weights and where _ES and _seES are the effect size and standard error of the effect size respectively.

```
. regress _ES chol_reduc [aw=1/(_seES^2)], vce(robust) eform(expb)
(sum of wgt is   8.8607e+02)

Linear regression                               Number of obs     =         28
                                                F(1, 26)          =      30.23
                                                Prob > F          =     0.0000
                                                R-squared         =     0.2380
                                                Root MSE          =     .21453

------------------------------------------------------------------------------
             |               Robust
         _ES |       expb   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  chol_reduc |   .6217327   .0537374    -5.50   0.000     .5205299    .7426115
       _cons |   1.128355   .0764952     1.78   0.087     .9815813    1.297077
------------------------------------------------------------------------------
```

The meta-regression analysis suggests there is significant association between amount of cholesterol reduction and lnORs ($p < 0.001$) and each unit reduction in cholesterol will lead to a 38% reduction of the odds (OR = 0.62, 95%CI: 0.52, 0.74). The proportion of between-study variance explained by cholesterol reduction was 23.8% ($R^2 = \frac{mss}{mss+rss}$, see below). Here mss indicate the model sum of square (SS_{model}) while rss is the residual sum of squares (SS_{res}). The *ereturn list* command allows us to see the total variance when the *chol_reduc* variable was added into the model. The *e(r2_a)* gives the adjusted R^2 (20.9%).

```
. ereturn lis

scalars:
                  e(N) =  28
               e(df_m) =  1
               e(df_r) =  26
                  e(F) =  30.23358785102188
                 e(r2) =  .2379548957201425
               e(rmse) =  .2145287950676138
                e(mss) =  .3736444210308938
                e(rss) =  1.196587701742218
               e(r2_a) =  .2086454686324557
                 e(ll) =  4.407949273183275
               e(ll_0) =  .6034558100779854
               e(rank) =  2
```

We may observe that the total variance also reduced ($F_{model} = 30.23$). And we can use the total variance to calculate the I^2 statistic

$$I^2_{model} = \frac{F_{model} - (df\_r)}{F_{model}} = \frac{30.23 - 26}{30.23} = 13.99\%$$

To depict this relationship we can create a *twoway* plot as follows:

twoway (scatter _ES chol_reduc [w = 1/(_seES^2)], msymbol(oh)) (lfit _ES chol_reduc [w = 1/(_seES^2)], yline(–0.193) ytitle("Effect size (interval scale)"))

Figure 11.1 presents the regression plot between amount of cholesterol reduction and lnORs. The figure may help us to explain the reason for the reduction on total variance. The dash line is the pooled lnOR by IVhet method [ln(0.825) = –0.193] without adding the chol_reduc variable and the solid line is the linear prediction for

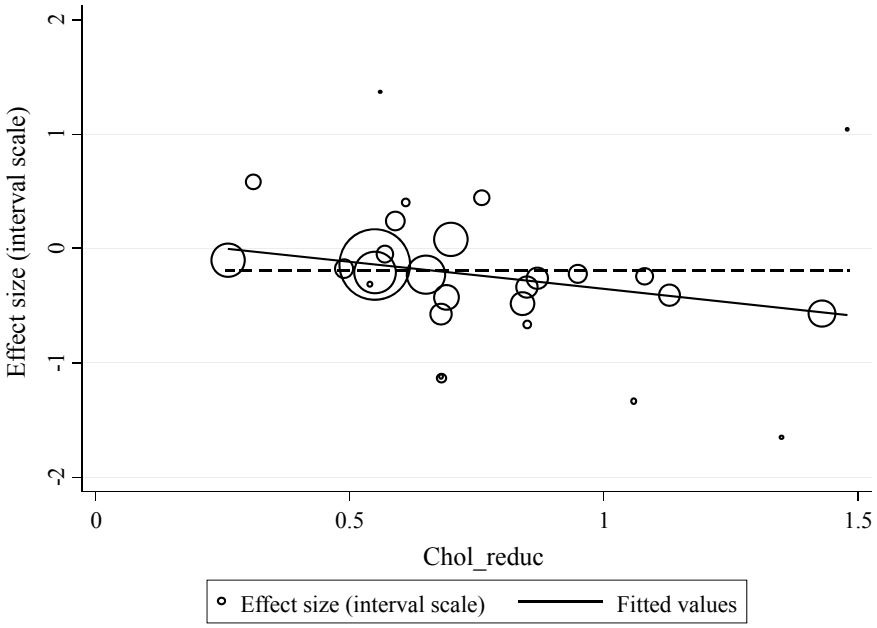


Fig. 11.1 The regression plot between amount of cholesterol reduction and lnORs

cholesterol reduction and lnORs. As we known, the total variance is the sum weighted distance for the observed value to the predicted value ($Q = \sum w_j \cdot \left(\theta - \hat{\theta}\right)^2$). Obviously, the sum weighted distance for the observed value to the dash line is different to the linear prediction and the latter shows better fitting.

As we add the chol_reduc variable into the regression model, the risk of IHD is comparable when the cholesterol reduction is zero (OR = 1.13, 95%CI: 0.98, 1.30).

The meta-regression may also be done using the classic random-effect meta-regression method using the *metareg* command. We then obtain the following results where _seES is the standard error for the effect size (_ES) in each study from the *admetan* command described earlier:

```
. metareg _ES chol_reduc, wsse( _seES ) eform graph mm

Meta-regression                                         Number of obs  =      28
Method of moments estimate of between-study variance    tau2           =  .01647
% residual variation due to heterogeneity               I-squared_res  =  31.34%
Proportion of between-study variance explained          Adj R-squared  =  43.97%
With Knapp-Hartung modification
```

_ES	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
chol_reduc	.5941587	.113809	-2.72	0.012	.4007817	.8808399
_cons	1.172955	.1707306	1.10	0.283	.8696468	1.582049

The point estimates are similar but in this instance the confidence intervals are slightly different given the Knapp-Hartung modification (Knapp and Hartung 2003).

11.2.3 Meta-Regression in MetaXL

The MetaXL add-in program in Excel also provide solutions for meta-analysis and it allows us to generate data for meta-regression. The MARegresData function in MetaXL allows the creation of a regression dataset that can be directly pasted in Stata and used to run meta-regression analyses under this framework. The dataset appears in a table under the Meta-Regression data tab that will show in the MAInputTable output pop-up window when a MARegresData function is linked to the MAInput-Table function. The MARegresData function creates all the necessary variables and weights required for the analysis.

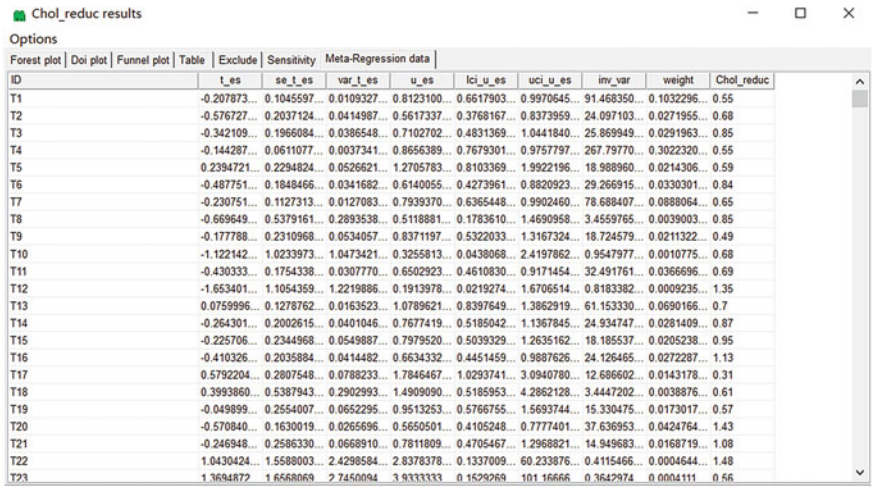
The regression dataset table consists of nine fixed columns that describe each study's characteristics, and any number of user-defined columns that describe each study's moderator variables. The fixed columns are defined in the table below (Table 11.2).

Please note that the regression is performed on the transformed variables: the transformed effect size called "t_es" as well as a weight under the model of interest called "weight". (The un-transformed variables u_es and its CI are there only for the convenience of the user, useful when back-transformed outputs are cumbersome to obtain, such as with the double arcsine transformation for prevalence). The variable t_es is the outcome variable and this is regressed against the user-defined moderator variables in the dataset.

We open the IHDCholMetaRegres example module and use the MAInputTable and the MARegresData function preparing the meta-regression data by MetaXL. We then see the meta-regression data is presented in the table (Fig. 11.2).

Table 11.2 Definition of variables for meta-regression in cholesterol reduction example

Variable name	Contents
ID	Study name
t_es	Transformed effect size
se_t_es	Standard error of the transformed effect size
var_t_es	Variance of the transformed effect size
u_es	Un-transformed effect size (i.e. natural scale)
lci_u_es	Lower CI of the un-transformed effect size
uci_u_es	Higher CI of the un-transformed effect size
inv_var	Inverse of the variance of the transformed effect size
weight	Weight of the study in the meta-analysis (normalized weights that sum to 1)


Chol_reduc results

Options

Forest plot | Doi plot | Funnel plot | Table | Exclude | Sensitivity | Meta-Regression data

ID	t_es	se_t_es	var_t_es	u_es	lci_u_es	uci_u_es	inv_var	weight	Chol_reduc
T1	-0.207873...	0.1045597...	0.0109327...	0.8123100...	0.6617903...	0.9970645...	91.468350...	0.1032296...	0.55
T2	-0.576727...	0.2037124...	0.0414987...	0.5617337...	0.3768167...	0.8373959...	24.097103...	0.0271955...	0.68
T3	-0.342109...	0.1966084...	0.0386548...	0.7102702...	0.4831369...	1.0441840...	25.869949...	0.0291963...	0.85
T4	-0.144287...	0.0611077...	0.0037341...	0.8656389...	0.7679301...	0.9757797...	267.79770...	0.3022320...	0.55
T5	0.2394721...	0.2294824...	0.0526621...	1.2705783...	0.8103369...	1.9922196...	18.988960...	0.0214306...	0.59
T6	-0.487751...	0.1848466...	0.0341682...	0.6140055...	0.4273961...	0.8820923...	29.266915...	0.0330301...	0.84
T7	-0.230751...	0.1127313...	0.0127083...	0.7939370...	0.6365448...	0.9902460...	78.688407...	0.0888064...	0.65
T8	-0.669649...	0.5379161...	0.2893538...	0.5118881...	0.1783610...	1.4690958...	3.4559765...	0.0039003...	0.85
T9	-0.177788...	0.2310968...	0.0534057...	0.8371197...	0.5322033...	1.3167324...	18.724579...	0.0211322...	0.49
T10	-1.122142...	1.0233973...	1.0473421...	0.3255813...	0.0438068...	2.4197862...	0.9547977...	0.0010775...	0.68
T11	-0.430333...	0.1754338...	0.0307770...	0.6502923...	0.4610830...	0.9171454...	32.491761...	0.0366696...	0.69
T12	-1.653401...	1.1054359...	1.2219886...	0.1913978...	0.0219274...	1.6706514...	0.8183382...	0.0009235...	1.35
T13	0.0759996...	0.1278762...	0.0163523...	1.0789621...	0.8397649...	1.3862919...	61.153330...	0.0690166...	0.7
T14	-0.264301...	0.2002615...	0.0401046...	0.7677419...	0.5185042...	1.1367845...	24.934747...	0.0281409...	0.87
T15	-0.225706...	0.2344968...	0.0549887...	0.7979520...	0.5039329...	1.2635162...	18.185537...	0.0205238...	0.95
T16	-0.410326...	0.2035884...	0.0414482...	0.6634332...	0.4451459...	0.9887626...	24.126465...	0.0272287...	1.13
T17	0.5792204...	0.2807548...	0.0788233...	1.7846467...	1.0293741...	3.0940780...	12.686602...	0.0143178...	0.31
T18	0.3993860...	0.5387943...	0.2902993...	1.4909090...	0.5185953...	4.2862128...	3.4447202...	0.0038876...	0.61
T19	-0.049899...	0.2554007...	0.0652295...	0.9513253...	0.5766755...	1.5693744...	15.330475...	0.0173017...	0.57
T20	-0.570840...	0.1630019...	0.0265696...	0.5650501...	0.4105248...	0.7777401...	37.636953...	0.0424764...	1.43
T21	-0.246948...	0.2586330...	0.0668910...	0.7811809...	0.4705467...	1.2968821...	14.949683...	0.0168719...	1.08
T22	1.0430424...	1.5588003...	2.4298584...	2.8378378...	0.1337009...	60.233876...	0.4115466...	0.0004644...	1.48
T23	1.3694872...	1.6568069...	2.7450094...	3.9333333...	0.1529269...	101.16666...	0.3642974...	0.0004111...	0.56

Fig. 11.2 The output sheet for meta-regression data prepared for meta-regression

Right-click on the "Meta-regression data" table in the results window and click copy. Then we paste the data into Stata software and run the robust meta-regression.

```
. regress t_es chol_reduc[aw=weight], vce(robust) eform(expb)
(sum of wgt is   1.0000e+00)

Linear regression                               Number of obs     =         28
                                                F(1, 26)          =      30.23
                                                Prob > F          =     0.0000
                                                R-squared         =     0.2380
                                                Root MSE          =     .21453

------------------------------------------------------------------------------
             |               Robust
        t_es |       expb   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  chol_reduc |   .6217327   .0537374    -5.50   0.000      .52053     .7426115
       _cons |   1.128355   .0764952     1.78   0.087     .9815813     1.297077
------------------------------------------------------------------------------
```

11.3 Meta-Regression for Categorical Variables

In the above example we illustrated meta-regression for continues variable, there comes to the question that when the variable is discontinuous how to conduct the meta-regression? Let's use the same dataset to simulate a categorical variable by categorizing the cholesterol reduction into three levels (<0.5, 0.5 ~ 0.99, 1 ~ 1.5) and assign 0, 1, 2 to these three dummy variables.

recode chol_reduc (min/0.499 = 0) (0.5/0.999999 = 1) (1/max = 2), gen(chol_grp)

Now we get the dataset as show in the following figure (Fig. 11.3).

Again, we run the meta-regression analysis with indicator variable for group to allow a categorical robust meta-regression.

Data Editor (Edit) - [Untitled]

File Edit View Data Tools

var10[34]

	studyname	n1	cases1	noncases1	n2	cases2	noncases2	chol
1	T1	5331	173	5158	5296	210	5086	1
2	T2	244	54	190	253	85	168	1
3	T3	350	54	296	367	75	292	1
4	T4	2222	676	1546	2789	936	1853	1
5	T5	145	42	103	284	69	215	1
6	T6	279	73	206	276	101	175	1
7	T7	1906	157	1749	1900	193	1707	1
8	T8	71	6	65	72	11	61	1
9	T9	1149	36	1113	1129	42	1087	0
10	T10	88	2	86	30	2	28	1
11	T11	2051	56	1995	2030	84	1946	1
12	T12	94	1	93	94	5	89	2
13	T13	4541	131	4410	4516	121	4395	1
14	T14	424	52	372	422	65	357	1
15	T15	199	45	154	194	52	142	1
16	T16	229	61	168	229	81	148	2
17	T17	221	37	184	237	24	213	0
18	T18	28	8	20	52	11	41	1
19	T19	130	47	83	134	50	84	1
20	T20	421	82	339	417	125	292	2
21	T21	6582	62	6520	1663	20	1643	2

Length: 3 Vars: 8 Order: Dataset Obs: 28

Fig. 11.3 Simulated categorical variable for meta-regression

```
. regress t_es i.chol_grp[aw=weight], vce(robust) eform(expb)
(sum of wgt is   1.0000e+00)

Linear regression                               Number of obs     =         28
                                                F(2, 25)          =       8.32
                                                Prob > F          =     0.0017
                                                R-squared         =     0.1863
                                                Root MSE          =     .22606
```

t_es	expb	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
chol_grp						
1	.8534954	.1004852	-1.35	0.191	.6697221	1.087696
2	.6335032	.0836576	-3.46	0.002	.4826499	.8315061
_cons	.9763426	.1075545	-0.22	0.830	.778161	1.224997

We may observe that when using the categorical variable, the proportion of between-study variance explained is much less than the continues one (18.6% versus 23.8%). The constant takes the value of the zero category (reference group).

11.4 Multivariable Meta-Regression

Both classical meta-regression method and the robust error meta-regression method allow us to achieve multivariable meta-regression just like the multivariable regression in individual-level data (Thompson and Higgins 2009). Sometimes multivariable meta-regression is necessary because single covariate generally is only able to explain part of the between-study heterogeneity. In our above example, we know that cholesterol reduction can explain 23.8% of the between-study heterogeneity but not 100%. This means there is still a lot of between-study heterogeneity due to other covariates, which may be the mean age, the region, the mean body mass index and so forth. To address this, we may just add these variables into the meta-regression model. For example, suppose we have another covariate of age in the above example, we may then put both cholesterol and age into the model.

It is notable that more covariates mean we need more studies (one study is a data point) to ensure the statistical power of meta-regression. Then, when we put covariates into the meta-regression model, we should first ensure a sufficient number of studies and note that for every covariate added we need at least 10 additional studies. Therefore, two covariates need at least 20 studies to be present. When the total number of studies is less than 10, it is not appropriate to employ a meta-regression analysis and the subgroup analysis may be employed as an alternative solution to detect the source of heterogeneity. Similarly, when the total number of studies is less than 20, we may only use 1 covariate to fit the meta-regression.

Some characteristics cannot be treated as a covariate for meta-regression, for example, the sample size. This is because sample size in each study is highly correlated with the standard errors of effect estimates. When entered into the meta-regression model, it will break the assumption of orthogonality and make the regression model invalid (Dobson and Barnett 2008).

It might be noted that subgroup analysis is a special case of meta-regression of categorical variables. The difference is that subgroup analysis can only deal with one variable each time and does not have a relative comparison to the reference group within the analysis. The advantage of subgroup analysis to meta-regression is that it does not have the restriction regarding the minimum number of studies. It is notable that for subgroup analysis the interaction test of the potential difference of the effects among sub groups is generally underpowered when there are 3 or more sub groups.

11.5 Summary

In this chapter, we give a detailed introduction to the meta-regression method, including the basic theories, the step-by-step application for meta-regression in Stata and MetaXL as well as the multivariable meta-regression. We suggest that readers read this chapter with Chap. 13 which introduces dose-response meta-analysis, as this may help readers acquire a deeper understanding of both meta-regression and dose-response meta-analysis.

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