Example name BCG

Effect sizeRisk ratioAnalysis typeSubgroups analysis, RegressionLevelAdvanced

Synopsis

This analysis includes studies where patients were randomized to receive either a vaccine or a placebo Outcome was the proportion of patients each group who developed TB. The analysis focused on the risk ratio.

There was substantial dispersion in the risk ratio. The researchers looked to see if this was related to the study's latitude (a surrogate for the vaccine's potency and for the natural immunity in the population) and several other variables.

We use this example to show

- How to interpret a basic analysis using Risk Ratio
- How to understand the heterogeneity statistics
- How to perform a subgroups analysis
- How a regression analysis corresponds to a subgroups analysis
- How to perform a regression analysis using a categorical predictor
- How to perform a regression analysis using a continuous predictor

To open a CMA file > Download and Save file | Start CMA | Open file from within CMA

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QUICK START

- 1) On the data-entry screen
 - a) Create a column for study name
 - b) Create a set of columns for the effect size
 - c) Identify one or more columns as "Moderators" and set the subtype to either "Integer", "Decimal", or "Categorical
 - d) Enter the data
- 2) On the main analysis screen
 - a) Optionally, select the effect size index
 - b) Optionally, select the studies to be included in the regression
 - c) Optionally, specify how to work with studies that included multiple subgroups, outcomes, timepoint, or comparisons.
 - d) Click Analyses > Meta-regression 2
- 3) On the regression screen define the regression
 - a) Select the covariates to be included in the model
 - b) Optionally, define "Sets" of covariates
 - c) Optionally, define multiple models
 - d) Optionally, select statistical options
 - e) Run the analysis
- 4) On the regression screen navigate the results
 - a) Click "Fixed" or "Random" to select the model
 - b) Click the model name (when several models have been created)
 - c) Use the toolbar to move between the main analysis screen, the scatterplot, diagnostics, increments, model comparisons, and other screens
- 5) On the regression screen save the analysis
- 6) On the regression screen export the results

STEP 1: ENTER THE DATA

Insert column for study names

Click Insert > Column for > Study names

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Figure 1

The program creates a column labeled "Study name"

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Insert columns for effect size data

Click Insert > Column for > Effect size data

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		Figure	3						

The program opens a wizard that allows you to specify the kind of summary data you will enter

- Select <Show all 100 formats>
- Click <Next>

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Figure 4

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- Select the top option button
- Click <Next>

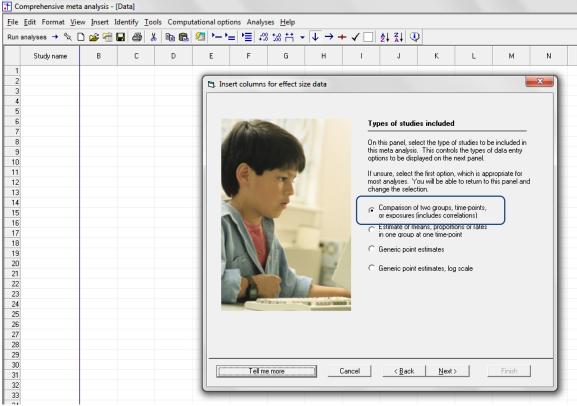


Figure 5

On this screen, drill down to

- Dichotomous (number of events)
- Unmatched groups, prospective (e.g., controlled trials, cohort studies)
- Events and sample size in each group [H]

Then, click <Finish>

Note that we will be entering events and sample size (N) for each group. Some of the texts that use the BCG example report events and non-events rather than events and N.

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27 Click 'Finish' to create the columns	
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Figure 6	

The program creates columns as shown here. It also opens a wizard that allows you to label the columns.

- Enter Vaccine/Control as names for the two groups
- Enter TB/Ok as names for the two outcomes

Then, click Ok

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The program applies the labels as shown here [K].

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Insert columns for moderators (covariates)

Next, we need to create columns for the moderator variables.

• Click Insert > Column for > Moderator variable

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Figure 9

The program opens a wizard

- Set the variable name to "Latitude"
- Set the column function to Moderator
- Set the data type to Integer

Then, click OK

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Click Insert > Column for > Moderator variable

- Set the variable name to "Year"
- Set the column function to Moderator
- Set the data type to Integer

(This is the year the study was performed, not the year of publication)

Then, click OK

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	Figure 11

Click Insert > Column for > Moderator variable

- Set the variable name to "Allocation"
- Set the column function to Moderator
- Set the data type to Categorical
- •

This moderator tracks the mechanism utilized to assign people to be vaccinated (or not). The possibilities are random, alternate, and systematic.

Then, click [Ok]

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Figure 12

Click Insert > Column for > Moderator variable

- Set the variable name to "Climate"
- Set the column function to Moderator
- Set the data type to Categorical

This moderator tracks the climate. The possibilities are Cold and Hot.

Then, click [OK]

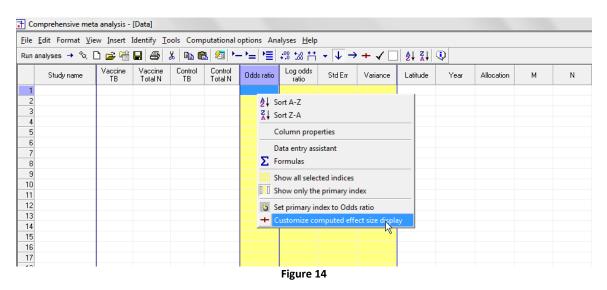
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Customize the screen

The program initially displays the odds ratio. Since we want to work with the log risk ratio we need to customize the display. (We will use the log risk ratio rather than the risk ratio since the computations are easier to understand in log units).

- Right-click in any yellow column
- Click <Customize computed effect size display> [A]



The program displays this wizard

- Tick the box for Risk ratio
- Tick the box for Log risk ratio

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31								Ok		
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Figure 15

To keep things simple we can set Log risk ratio as the default effect size, and also hide the odds ratio

- In the drop-down box, select Log risk ratio as the primary index
- Un-check the box for odds ratio
- Un-check the box for log odds ratio

Then click [Ok]

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Figure 16

The screen now looks like this

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Enter the data

You can enter the data manually, or copy and paste from Excel [™] or another source (see appendix)

Note that you enter data into the white columns. The program automatically computes the values in the yellow columns.

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2	TB Prevention trial, 1980	505	88391	499	88391	1.012	0.012	0.063	0.004	13	1968	Random	Hot		
3	Comstock et al, 1974	186	50634	141	27338	0.712	-0.339	0.111	0.012	18	1949	Systematic	Hot		
4	Vandiviere et al, 1973	8	2545	10	629	0.198	-1.621	0.472	0.223	19	1965	Random	Hot		
5	Coetzee & Berjak, 1968	29	7499	45	7277	0.625	-0.469	0.238	0.056	27	1965	Random	Hot		
6	Comstock and Webster, 1969	5	2498	3	2341	1.562	0.446	0.730	0.533	33	1947	Systematic	Hot		
7	Comstock et al, 1976	27	16913	29	17854		-0.017	0.267	0.071	33		-,	Hot		
	Rosenthal et al, 1960	3	231	11	220	0.260	-1.348	0.644	0.415	42	1937	Random	Cold		
	Rosenthal et al, 1961	17	1716	65	1665		-1.371	0.270	0.073	42		Systematic	Cold		
10	Aronson, 1948	4	123	11	139	0.411	-0.889	0.571	0.326	44	1935	Random	Cold		
11	Stein & Aronson, 1953	180	1541	372	1451	0.456	-0.786	0.083	0.007	44	1935	Alternate	Cold		
12	Hart & Sutherland, 1977	62	13598	248	12867	0.237	-1.442	0.141	0.020	52	1950	Random	Cold		
	Ferguson & Simes, 1949	6	306	29	303	0.205	-1.585	0.441	0.195	55	1933	Random	Cold		
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STEP 2: RUN THE BASIC META-ANALYSIS

To run the analysis, click <Run Analysis>

	Identify <u>I</u> o	ols Compu	utational o	ptions An	nalyses <u>H</u> elp									
lun analyses 🔸 🏷 🗋 🚅 🖷		6 🖻 🛍	/ 2010	•= • <u></u> →	Run analy	ses ↓ →	+ 🗸 🗌		Q					
Study name	Vaccine TB	Vaccine Total N	Control TB	Control Total N	Risk ratio	Log risk ratio	Std Err	Variance	Latitude	Year	Allocation	Climate	N	0
1 Frimodt-Moller et al, 1973	33	5069	47	5808	0.804	-0.218	0.226	0.051	13	1950	Alternate	Hot		
2 TB Prevention trial, 1980	505	88391	499	88391	1.012	0.012	0.063	0.004	13	1968	Random	Hot		
3 Comstock et al, 1974	186	50634	141	27338	0.712	-0.339	0.111	0.012	18	1949	Systematic	Hot		
4 Vandiviere et al, 1973	8	2545	10	629	0.198	-1.621	0.472	0.223	19		Random	Hot		
5 Coetzee & Berjak, 1968	29	7499	45	7277	0.625	-0.469	0.238	0.056	27	1965	Random	Hot		
6 Comstock and Webster, 1969	5	2498	3	2341	1.562	0.446	0.730	0.533	33	1947	Systematic	Hot		
7 Comstock et al, 1976	27	16913	29	17854	0.983	-0.017	0.267	0.071	33	1950	Systematic	Hot		
8 Rosenthal et al, 1960	3	231	11	220	0.260	-1.348	0.644	0.415	42	1937	Random	Cold		
9 Rosenthal et al, 1961	17	1716	65	1665		-1.371	0.270	0.073	42		Systematic	Cold		
10 Aronson, 1948	4	123	11	139	0.411	-0.889	0.571	0.326	44	1935	Random	Cold		
11 Stein & Aronson, 1953	180	1541	372	1451	0.456	-0.786	0.083	0.007	44	1935	Alternate	Cold		
12 Hart & Sutherland, 1977	62	13598	248	12867	0.237	-1.442	0.141	0.020	52		Random	Cold		
13 Ferguson & Simes, 1949	6	306	29	303	0.205	-1.585	0.441	0.195	55	1933	Random	Cold		
14														
15														
16														
17														

Figure 19

The main analysis screen

The program displays the main analysis screen.

The program shows the current effect size, which is "Log risk ratio". If you want to switch to another effect size, click on "Log risk ratio".

The next few pages outline the main analysis in *CMA*. However, this is optional. You can use the menu Analysis > Meta-regression 2 to proceed immediately to the regression module.

The initial meta-analysis

At the top, we have selected [Log risk ratio] as the effect size.

At the bottom the <Fixed> tab is selected, so the program is displaying the results for a fixed-effect analysis.

Model Study name User issue is training for each study Variance Log risk Variance Variance		ntry t7 Next table	- High resolu	ition plot	Select by .	🕂 🕂 Effe	ct measure: I	Log risk ratio	- =		ïī‡E ∔	🖓 🖞			
Primodi-Moller et al, 1973 -0.2175 0.2263 0.0512 -0.6611 0.2260 -0.9613 0.3364 TB Prevention trial, 1980 0.0120 0.02629 0.00611 0.2260 -0.9613 0.3364 Comstock et al, 1974 -0.3394 0.01120 0.0529 0.00040 -0.1114 0.1353 0.0839 0.4844 Vandwiere et al, 1974 -0.3394 0.1114 0.0122 -0.25465 -0.6913 -3.4460 0.0002 - + + Vandwiere et al, 1973 -1.6209 0.4722 0.22465 -0.69533 -3.4323 0.0002 +	Model	Study name			Statis	tics for each s	study				Log ri	sk ratio and S	95% CI		
Frimodt-Moler et al, 1973 -0.2175 0.2263 0.0512 -0.6611 0.2260 -0.9613 0.3364 TB Prevention trial, 1980 0.0120 0.0629 0.0040 -0.1114 0.01353 0.1889 0.8494 Comstock et al, 1974 -0.3394 0.1114 0.0127 -0.2120 -3.0460 0.0023 Vandrviere et al, 1973 -1.6209 0.4722 0.2230 -2.5465 -0.6953 -3.4323 0.0006 Coextock, and Webster, 1969 0.4459 0.2376 0.0524 -0.6953 -3.4323 0.0006 Comstock, and Webster, 1969 0.4459 0.2376 0.0564 -0.9950 -0.0038 -1.3760 0.0482 Comstock, and Webster, 1969 0.4459 0.7277 0.5325 -0.9943 1.8762 0.6111 0.5612 Comstock, et al, 1976 -0.0173 0.2672 0.0714 -0.5044 -0.9483 Rosenthal et al, 1960 -1.3481 0.6445 0.4154 -2.6113 -0.0484 -0.9493 Avonson, 1948 -0.8983 0.5706 0.3256 -2.0077 0.2290 -1.5564					Variance	Lower limit	Upper limit	Z-Value	p-Value	-4.00	-2.00	0.00	2.00	4.00	
Comstock et al, 1974 -0.3394 0.1114 0.0124 -0.5577 -0.1210 -3.0460 0.0023 Vandiviere et al, 1973 -1.6209 0.4722 0.2230 -2.5465 -0.6953 -3.4323 0.0006 Coetse & Berjak, 1986 0.4654 0.2376 0.0564 -0.3950 -0.0038 Comstock and Webster, 1969 0.4459 0.2376 0.5255 -0.9843 1.3760 0.0482 Comstock and Webster, 1969 0.4459 0.7237 0.5255 -0.9843 1.6762 0.6111 0.5412 Comstock et al, 1976 -0.0173 0.2572 0.0714 -0.5410 0.5064 0.9483 Rosenthal et al, 1960 -1.3481 0.6445 0.4154 -2.6113 -0.0648 0.9483 Anonson, 1948 -0.8833 0.5706 0.3256 -2.0977 0.2200 -1.5586 -1.191 Stein & Aronson, 1948 -0.8833 0.05706 -0.2230 -1.5586 0.0000 ++ Hat & Sutherland, 1977 -1.4416 0.0194 -0.6232 -3.4593 0.0000 ++ Hat & Sutherland, 1977		Frimodt-Moller et al, 1973			0.0512	-0.6611	0.2260	-0.9613	0.3364	- I		-++	- I.	- I.	
Vandiviere et al, 1973 -1.6209 0.4722 0.2230 -2.5465 -0.6953 -3.4323 0.0006 Coetzee & Berjak, 1968 -0.4654 0.2376 0.0564 -0.0380 -1.9760 0.0482 Comstock and Webster, 1969 0.4459 0.2737 0.5525 -0.9843 1.8762 0.01482 Comstock and Webster, 1969 -0.0173 0.2672 0.0714 -0.5410 0.5064 -0.0648 0.9483 Rosenthal et al, 1960 -1.3481 0.6445 0.4154 -2.0917 0.0365		TB Prevention trial, 1980	0.0120		0.0040							÷			
Coetzee & Berjak, 1968 -0.4694 0.2376 0.0564 -0.9350 -0.0038 -1.9760 0.0492 Constock and Webster, 1969 0.4459 0.7297 0.5325 -0.9343 1.9762 0.6111 0.5412 Constock and Webster, 1976 -0.0173 0.2672 0.0174 -0.5614 -0.0648 0.3483 Rosenthal et al, 1950 -1.3411 0.6445 0.4154 -2.6113 -0.0649 -2.9317 0.0355 Rosenthal et al, 1950 -1.3713 0.2702 0.0717 0.2260 -1.5566 0.1191 Aronson, 1348 -0.8983 0.0706												+			
Constock and Webster, 1963 0.4459 0.7327 0.5325 -0.9843 1.8762 0.6111 0.5412 Constock and Webster, 1963 -0.0173 0.2672 0.0714 -0.5410 0.0648 0.9483 Rosenthal et al, 1960 -1.3481 0.6445 0.4154 -2.6113 -0.0848 0.9483 Rosenthal et al, 1961 -1.3731 0.2702 0.0730 -1.9010 -0.8447 0.0000 Anonson, 1948 -0.8893 0.2756 -0.077 0.22901 0.0355 - Stein & Aronson, 1948 -0.8931 0.0069 -0.9440 -0.6232 -9.4559 0.0000 ++ Hat & Sutherland, 1977 -1.4416 0.1415 0.0200 -1.1718 -1.1643 -10.1908 0.0000 ++ Ferguon & Sime, 1949 -1.5854 0.0143 0.0003 ++ -												-			
Comstock et al. 1976 -0.0173 0.2672 0.0714 -0.5410 0.5064 -0.0648 0.9483 Rosenthal et al. 1960 -1.3481 0.6445 0.4154 -2.6113 -0.00849 -2.0917 0.0385 Rosenthal et al. 1961 -1.3713 0.2702 0.0730 -1.9010 -0.8417 -5.0747 0.0000 Aronson, 1948 -0.8893 0.5706 0.3256 -2.0077 0.2290 -1.5586 0.1191 Stein & Aronson, 1953 -0.7661 0.0831 0.0069 -0.9490 -0.6232 -9.4599 0.0000 + Hat & Sutheland, 1977 -1.416 0.11946 -1.1643 -10.1908 0.0000 + Forguon & Simes, 1949 -1.5554 0.7208 -3.5941 0.0003 +															
Rosenthal et al, 1960 -1.3481 0.6445 0.4154 -2.6113 -0.0849 -2.0917 0.0365 Rosenthal et al, 1951 -1.3713 0.2702 0.730 -1.9010 -0.04417 -5.0747 0.0000 Aronson, 1948 -0.8893 0.5706 0.2256 -2.0077 0.2290 -1.5568 0.1191 Stein & Aronson, 1953 -0.7061 0.0831 0.0069 -0.4490 -0.6522 -9.4593 0.0000 ++ Hat & Sutherland, 1977 -1.4416 0.1415 0.0200 -1.7188 -1.1633 -10.1998 0.0000 ++ Ferguench Simes, 1949 -1.5554 0.01208 -3.5941 0.0033 ++															
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Aronson, 1948 -0.8893 0.5706 0.3256 -2.0077 0.2290 -1.5586 0.1191 Stein & Aronson, 1953 -0.7861 0.0893 0.0669 -0.9490 -0.6232 -9.4599 0.0000 + Hart & Sutheland, 1977 -1.416 0.1415 0.0200 -1.7188 -1.1643 10.1908 0.0000 + Faguson & Simes, 1949 -1.5854 0.4110 1.946 -2.4500 -0.7208 -3.5941 0.0003 +															
Stein & Aronson, 1953 -0.7961 0.0063 -0.9490 -0.6232 -3.4599 0.0000 ++ Hat & Sutherland, 1977 -1.4416 0.1415 0.0200 -1.7188 -1.1643 -10.1906 0.0000 ++ Ferguson & Sime, 1949 -1.5854 0.0210 -1.7188 -1.1643 -0.1906 0.0000 ++															
Hart & Sutherland, 1977 - 1.4416 0.1415 0.0200 -1.7188 -1.1643 -10.1908 0.0000 Ferguson & Sines, 1949 -1.5854 0.4411 0.1946 -2.4500 -0.7208 -3.5941 0.0003												<u> </u>			
Ferguson & Simes, 1949 -1.5854 0.4411 0.1946 -2.4500 -0.7208 -3.5941 0.0003												- I			
												_			
	Fived	r eiguseir a sinies, 1345										+			

Click the tab for <Random>. The program displays results for a random-effects analysis.

 Data ent 	try t⊒ Next table	High resol	ution plot	Select by	+ Effe	ct measure: I	Log risk ratio	• 🗉		II 🕸 E 🛛	11 🔍			
Model	Study name			Statis	tics for each	study				Logi	isk ratio and 9	15% CI		
		Log risk ratio	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	-4.00	·2.00	0.00	2.00	4.00	
	Frimodt-Moller et al, 1973	-0.2175	0.2263	0.0512	-0.6611	0.2260	-0.9613	0.3364			-++-			
	TB Prevention trial, 1980	0.0120	0.0629	0.0040	-0.1114	0.1353	0.1899	0.8494			+			
	Comstock et al, 1974	-0.3394	0.1114	0.0124	-0.5577	-0.1210	-3.0460	0.0023			+			
	Vandiviere et al, 1973	-1.6209	0.4722	0.2230	-2.5465	-0.6953	-3.4323	0.0006		-+	-			
	Coetzee & Berjak, 1968	-0.4694	0.2376	0.0564	-0.9350	-0.0038	-1.9760	0.0482						
	Comstock and Webster, 1969	0.4459	0.7297	0.5325	-0.9843	1.8762	0.6111	0.5412						
	Comstock et al, 1976	-0.0173	0.2672	0.0714	-0.5410	0.5064	-0.0648	0.9483						
	Rosenthal et al, 1960	-1.3481	0.6445	0.4154	-2.6113	-0.0849	-2.0917	0.0365		-+-+				
	Rosenthal et al, 1961	-1.3713	0.2702	0.0730	-1.9010	-0.8417	-5.0747	0.0000			-			
	Aronson, 1948	-0.8893	0.5706	0.3256	-2.0077	0.2290	-1.5586	0.1191		- I	+			
	Stein & Aronson, 1953	-0.7861	0.0831	0.0069	-0.9490	-0.6232	-9.4599	0.0000			+			
	Hart & Sutherland, 1977	-1.4416	0.1415	0.0200	-1.7188	-1.1643	-10.1908	0.0000		-+				
	Ferguson & Simes, 1949	-1.5854	0.4411	0.1946	-2.4500	-0.7208	-3.5941	0.0003		-+	-			
Random		-0.7141	0.1787	0.0319	-1.0644	-0.3638	-3.9952	0.0001						

Fixed Random Both models
Basic stats Une study removed Cumulative analysis Calculations

Display moderator variables

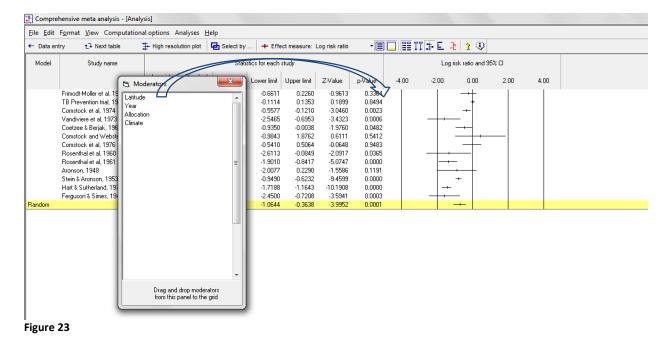
Next, we want to display the moderator variables on the plot. Note that this is optional, and has no effect on the regression.

ile <u>E</u> dit	Format View Computationa	loptions Ana	ilyses <u>H</u> el	р										
- Data en	· _ · · ·	L. L	on plot	Select by	+ Effe	ct measure:	Log risk ratio	- =		E II 3	E E	🖓 🖞		
Model	Meta-analysis sta High resolution			Statistics	for each	study					Log risk	ratio and 9	5% CI	
	Columns		Moder		limit	Upper limit	Z-Value	p-Value	-4.00)	-2.00	0.00	2.00	4.00
	Frimodt-ł Rows			ide basic stats	.6611	0.2260 0.1353	-0.9613 0.1899	0.3364 0.8494			· ·	-+		
	Comstoc Comstoc		The second se	ide forest plot	.5577	-0.1210	-3.0460	0.0023				+		
	Vandiviere et al, 1973 Coetzee & Beriak, 1968			ide counts	.5465 9350	-0.6953 -0.0038	-3.4323 -1.9760	0.0006		-	+	.		
	Comstock and Webster, 1969	-0.4694 0.4459		ide weights ide residuals	.9843	1.8762	0.6111	0.5412			-			
	Comstock et al, 1976 Rosenthal et al, 1960	-0.0173 -1.3481	0.6445	0.4154	5410 -2.6113	0.5064	-0.0648 -2.0917	0.9483 0.0365		_				
	Rosenthal et al, 1961	-1.3713	0.2702	0.0730	-1.9010		-5.0747	0.0000						
	Aronson, 1948	-0.8893	0.5706	0.3256	·2.0077	0.2290	-1.5586	0.1191				-		
	Stein & Aronson, 1953	-0.7861	0.0831	0.0069	-0.9490	-0.6232	-9.4599	0.0000			+			
	Hart & Sutherland, 1977	-1.4416	0.1415	0.0200	-1.7188		-10.1908	0.0000			-			
andom	Ferguson & Simes, 1949	-1.5854 -0.7141	0.4411	0.1946	-2.4500 -1.0644	-0.7208 -0.3638	-3.5941 -3.9952	0.0003				_		

Click View > Columns > Moderators

The program displays a list of all variables that had been defined as moderators on the data-entry screen.

Drag and drop each of these onto the main screen, to the right of the "p-value" column [G].



The screen should now look like this.

Since the data had been sorted by latitude on the data-entry screen, the program initially displays the studies in that sequence. It appears that the effect size is minor (near 1.0) toward the top (for studies near the equator) and larger (as extreme as 0.20) toward the bottom (for studies in colder climates).

Comprehensive meta analysis - [Analysis] <u>File Edit</u> Format <u>View</u> Computational options Analyses <u>H</u>elp 📜 High resolution plot • 🗏 🛄 🏥 🏗 🏦 🖡 🖡 🔍 Data entry t⊒ Next table + Effect measure: Log risk ratio Model Study name Statistics for each study Allocation Climate Log risk ratio and 95% Cl . Latitude Year Log risk ratio Standard -2.00 0.00 Variance Lower limit Upper limit Z-Value p-Value -4.00 2.00 4.00 error Frimodt-Moller et al, 1973 TB Prevention trial, 1980 Comstock et al, 1974 0.2263 0.0629 0.1114 1950 Alternate 1968 Random 1949 Systematic 1965 Random -0.2175 0.0120 0.0512 -0.6611 0.2260 -0.9613 0.336 13 Но ÷ł. -0.1114 0.1353 0.1899 0.8494 0.0040 13 18 Hot Hot 0.0124 -0.3394 -0.1210Vandiviere et al. 1973 -1.62090.4722 0.2230 -2.5465 -0.6953 -3.4323 0.0008 Hol 19 27 33 42 42 44 44 52 55 Coetzee & Berjak, 1975 Coetzee & Berjak, 1968 Comstock and Webster, 1969 Comstock et al, 1976 0.4722 0.2376 0.7297 0.2672 0.6445 1965 Random 1965 Random 1947 Systematic 1950 Systematic 1937 Random -0.4694 0.0564 -0.9350 -0.0038 -1.9760 0.0483 Hol -0.9350 -0.9843 -0.5410 -2.6113 -1.9760 0.6111 -0.0648 -2.0917 0.0482 0.5412 0.9483 0.0365 0.4459 0.5325 1.8762 0.5064 Hot Hot Rosenthal et al, 1960 -1.3481 0.4154 -0.0849Cold Rosenthal et al, 1961 Aronson, 1948 Stein & Aronson, 1953 Hart & Sutherland, 1977 0.0730 0.3256 0.0069 0.0200 -1.9010 -2.0077 -0.9490 -1.7188 -5.0747 -1.5586 -9.4599 -10.1908 -3.5941 1941 Systematic 1935 Random 1935 Alternate 1950 Random Cold Cold Cold Cold Cold -1.3713 0.2702 -0.8417 0.0000 -0.8893 -0.7861 -1.4416 0.2290 -0.6232 -1.1643 0.0000 0.1191 0.0000 0.0000 0.0831 1933 Random Ferguson & Simes, 1949 -1.58540.4411 0.1946 -2.4500 -0.72080.0003 0 7141 0.178 0.0319 0.3638 0.001

You can right-click on any column and sort by that column.

Display statistics

Click <Next table> to display the statistics shown here.

Using random-effects weights [J], the summary log risk ratio is -0.7141. The Z-value is -3.995 with a corresponding *p*-value of 0.0001. Thus, we can reject the null hypothesis that log risk ratio is 0.0 (or that the risk ratio is 1.0). If we assume that the studies are valid and that random assignment was carried out properly, we can conclude that, on the average, the vaccine does prevent TB.

At the same time, there is also a substantial amount of dispersion in the effect size. Tau-squared [K] is 0.3088 and Tau is 0.5557. To get a general sense of the true dispersion we can assume that the true effects are balanced about the random-effects estimate of the mean effect, and that some 95% of all true effects fall within 1.96 *T* of this mean. Then (in log units) most true effects fall in the range of -1.8032 to +0.3750. This corresponds to risk ratios of approximately 0.16 (a strongly protective effect) to 1.46 (a harmful effect).

It would be very important to understand the reason for this dispersion, and for this purpose we turn to meta-regression

	at <u>V</u> iew Computational		· - ·													
Data entry	tl Next table	High resolu	tion plot 🛛 🔁	Select by	+ Effect me	easure: Log ris	k ratio 🔹		∏≇⊑ ₹	()						
Model		I	ffect size ar	d 95% confid	ence interv	al	Test of nu	ll (2-Tail)		Hetero	geneity			T au-sc	quared	
Model	Number Studies	Point estimat		Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	l-squared	Tau Squared	Standard Error	Variance	Tau
Fixed Random	1	3 -0.43 3 -0.71			-0.5097 -1.0644	-0.3509 -0.3638	-10.6247 -3.9952	0.0000	152.2330	12.0000	0.0000	92.1173	0.3088	0.2299	0.0528	0.5557

STEP 3: RUN THE META-REGRESSION

At this point we proceed to the meta-regression.

On the analysis screen, select Analysis > Meta-regression 2

<u>F</u> ile <u>E</u> dit	Format View Computationa	I options A	nalyses <u>H</u> elp														
🔶 Data en	try t_7 Next table		Publication		🕂 🕂 Effe	ct measure:	Log risk ratio	- 🔳		ī ≇ E ∶	🖓 🖞 🗍						
Model	Study name	×	 Meta regress Meta regress 		tics for each :	study			Latitude	Year	Allocation	Climate		Log	risk ratio and 9	5% CI	
		Log risk ratio	Data entry	L}	Lower limit	Upper limit	Z-Value	p-Value					-4.00	-2.00	0.00	2.00	4.00
	Frimodt-Moller et al, 1973	-0.2175	0.2263	0.0512	-0.6611	0.2260	-0.9613	0.3364	13	1950	Alternate	Hot			-++		
	TB Prevention trial, 1980	0.0120	0.0629	0.0040	-0.1114	0.1353	0.1899	0.8494	13	1968	Random	Hot			+		
	Comstock et al, 1974	-0.3394	0.1114	0.0124	-0.5577	-0.1210	-3.0460	0.0023	18	1949	Systematic	Hot			+		
	Vandiviere et al, 1973	-1.6209	0.4722	0.2230	-2.5465	-0.6953	-3.4323	0.0006	19	1965	Random	Hot		-+	_		
	Coetzee & Berjak, 1968	-0.4694	0.2376	0.0564	-0.9350	-0.0038	-1.9760	0.0482	27	1965	Random	Hot					
	Comstock and Webster, 1969	0.4459	0.7297	0.5325	-0.9843	1.8762	0.6111	0.5412	33	1947	Systematic	Hot					
	Comstock et al, 1976	-0.0173	0.2672	0.0714	-0.5410	0.5064	-0.0648	0.9483	33	1950	Systematic	Hot			-		
	Rosenthal et al, 1960	-1.3481	0.6445	0.4154	·2.6113	-0.0849	-2.0917	0.0365	42	1937	Random	Cold		-+			
	Rosenthal et al, 1961	-1.3713	0.2702	0.0730	-1.9010	-0.8417	-5.0747	0.0000	42	1941	Systematic	Cold		+	-		
	Aronson, 1948	-0.8893	0.5706	0.3256	·2.0077	0.2290	-1.5586	0.1191	44	1935	Random	Cold					
	Stein & Aronson, 1953	-0.7861	0.0831	0.0069	-0.9490	-0.6232	-9.4599	0.0000	44	1935	Alternate	Cold			+		
	Hart & Sutherland, 1977	-1.4416	0.1415	0.0200	-1.7188	-1.1643	-10.1908	0.0000	52	1950	Random	Cold		→-			
	Ferguson & Simes, 1949	-1.5854	0.4411	0.1946	-2.4500	-0.7208	-3.5941	0.0003	55	1933	Random	Cold		-+	-		
Random		-0.7141	0.1787	0.0319	-1.0644	-0.3638	-3.9952	0.0001									

The Interactive Wizard

The program displays the screen shown in Figure 27.

The interactive wizard will walk you through all the steps in running the regression. To display or hide the wizard use the Help menu.

👬 Comprehensive meta a	analysis - [Form1]	
	ls Computational options Decimals Ana	
Models: Clear mode	els 👖 Insert model 📫 Delete model 🖏 F	tenam Tutorial
Covariates: E Show cov	variates 🧧 Remove covariates 🕇 Move up) 🕹 Technical support 👘 Variates 🖌 🗸
		About Comprehesive Meta Analysis
Covariates	Model 1	
Intercept		
		Interactive guide for main screen
		Video Next>
•		m
Fixed Bandom		

Figure 27

Add covariates to the model

When you initially open the regression module the program displays the following

- The main screen
- A list of available covariates

Covariates Models	Computational options Decimals An	alyses <u>H</u> elp	→ Run regression	
dels: Clear models	s 👖 Insert model 📫 Delete model 🖧	Rename model 👬 Generate sequence 🔹 ← \rightarrow 🕀		
		p ↓ Move down ◯ Link covariates <> Unlink covariates	11	
			·	
		🔄, Covariates not in models	×	
Covariates	Model 1			
		Latitude		
Intercept	v	Year		
		Allocation		
		Climate		
		Name Latitude		
		Type Integer		
		Number valid 13		
		Number missing 0		
		Add to model		

Figure 28

Move the covariates from the wizard onto the main screen.

Add variables in the sequence shown here (allocation, year, latitude) to recreate the example that we use in this text.

- Click "Allocation" on the wizard and then click [Add to model]
- Click "Year" on the wizard and then click [Add to model]
- Click "Latitude" on the wizard and then click [Add to model]

The model is shown in Figure 29

Note that "Allocation" is displayed as two lines, which are linked by a bracket. Since allocation is a categorical variable the program automatically creates and dummy variables to represent allocation. See next chapter for a full discussion.

Tick the check-boxes for all covariates

Covariates N	Iodels Computational options De	cimals Analyses <u>H</u> elp	→ Run regression
ls: 📃 Clea	r models 👖 Insert model 📫 Delete	model 🖏 Rename model 🚺 Generate sequence 👻 🔶 –	• 🕀
riates: 🔳 Shov	v covariates 🧧 Remove covariates	↑ Move up 🗼 Move down 🗢 Link covariates <> Unlin	ık covariates 🖌 🖌
Set	Covariates	Model 1	
	Intercept		
	Allocation: Alternate		
Allocation	Allocation: Systematic	V	
	Year		
	Latitude		

Figure 29

The covariates are controlled by the "Covariates" toolbar

- [Show covariates] shows or hides the wizard
- [Remove covariates] allows you to remove a covariate from the main screen
- [Move up] and [Move down] allow you to edit the sequence of covariates
- The blue and red checks allow you to add (or remove) checks from a series of check-boxes

Create a "Set" of covariates (optional)

In regression there are times when we use several covariates to capture a concept. For example

- If we have a categorical covariate with m values, we use (*m* − 1) covariates to represent this variable in the analysis.
- If we want to assess the relationship between duration of treatment and effect we might include powers of duration such as duration, duration², and duration³ as predictors.
- We may have a series of covariates, such as income and education that, together, are taken to represent the impact of socio-economic status.
- We may have a series of covariates such as dose and duration that, taken together, are intended to represent the intensity of a treatment
- We may have two covariates and also the interaction between, where the three together represent their influence on outcome.

For this example we'll assume that we have an additional covariate, called Latititude2, which is Latitude squared. We want to create a set that incorporates Latitude and Latitude2, and call that set "Latitude Set".

Move Latitude into the model Move Latitude2 into the model

🕂 Comprehensive meta an	nalysis - [Form1]			
Eile Covariates Models	Computational options Decima	als Analyses <u>H</u> elp		→ Run regression
Models: Clear model	is 👖 Insert model 📫 Delete mod	el 📮 Rename model 🔹 Generate sequ	ence $\bullet \leftrightarrow \bigcirc$	
Covariates: E Show cova	riates 🧧 Remove covariates 🕇	Move up ↓ Move down ◯ ⊂ Link cove	riates 🗘 Unlink covariates 🖌 🗸	
Covariates	Model 1			
Intercept				
Latitude	\checkmark			
Latitude2	\checkmark			

To create a set covariates

- Ensure that the covariates intended for the set are sequential in the list
- Highlight these covariates [B]

🕂 Comprehensive meta ana	alysis - [Form1]		
<u>File</u> Covariates Models	Computational options De	imals Analyses <u>H</u> elp	→ Run regression
Models: Clear models	s 👖 Insert model 📫 Delete	model 🖏 Rename model 🚺 Generate sequence 👻 🔸	$\rightarrow \mathbb{Q}$
Covariates: E Show covar	iates 🧧 Remove covariates	↑ Move up ↓ Move down ◯ ⊂ Link covariates <	Unlink covariates 🖌 🗸
Covariates	Model 1		
Intercept	V		
Latitude	⊻		
Latitude2	✓		
		ß	
Figure 30			
© www.Meta-	Analysis.com	BCG	— 30 —

To create the set

- Click [Link Covariates]
- Enter the name Latitude Set and click Ok

👬 Comprehensive meta an	alysis - [Form1]			
<u>File</u> Covariates Models	Computational options Decimals Ana	lyses <u>H</u> elp	→ Ru	n regression
Models: Clear models	s 👖 Insert model 📫 Delete model 🖡	Rename model Generate sequence 🔹	← → 🔃	
Covariates: E Show covar	riates 🧧 Remove covariates 🕇 Move up	→ Move down C Link covariates	🗘 Unlink covariates 🖌 🖌	
Covariates	Model 1		3 Grouping	1
Intercept			Specify name for this grouping	
Latitude	✓		specify name for this grouping	
Latitude2	✓		Latitude Set	
			Ok	
Figure 31				

🕂 Comprehensive met	ta analysis - [Form1]		
<u>F</u> ile Covariates Mo	dels Computational opti	ions Decimals Analyses <u>H</u> elp	→ Run regression
Models: Clear n	nodels 👖 Insert model 👔	🕇 Delete model 🚦 Rename model	Generate sequence $\bullet \leftrightarrow \to \overline{\mathbb{Q}}$
Covariates: E Show	covariates 🧧 Remove cov	rariates │ ↑ Move up ↓ Move down	🗢 Link covariates < 🗘 Unlink covariates 🗸 🗸
Models: □ Clear models ↑ I Delete model ♀ Rename model ♀ Generate sequence ← → ♀ Covariates: Ξ Show covariates ↑ Move up ↓ Move down ◯ Link covariates ✓ ✓ Set Covariates Model 1 Intercept ☑ Latitude Set Latitude ☑ Latitude2 ☑			
Set	Covariates	Model 1	
	Intercept 🗹 Latitude \checkmark		
Latitude Cat	Latitude		
Latitude Set	Covariates Model 1		
Intercept Latitude Set			
Figure 32			

The program has now created a set called "Latitude Set" which includes the two covariates. When you run the regression the program will display statistics for this set.

To remove a set

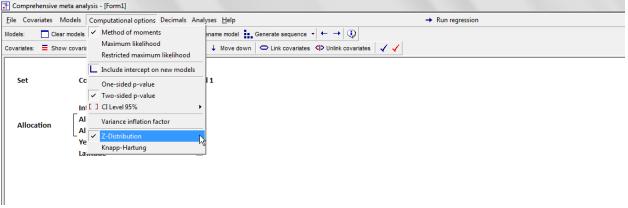
- Highlight the set's name
- Click Unlink Covariates

Comprehensive meta analysis - [Form1]
 Eile Covariates Models Computational options Decimals Analyses Help
 Models:
 Clear models
 There model
 Generate sequence
 Covariates
 Set
 Covariates
 Model 1
 Intercept
 Latitude
 Latitude
 Latitude
 Latitude
 Z

Set statistical options

The program allows you to specify various options for the computations

Click Computational options to display this menu





Edit any of the settings, including

- Set the method for estimating T^2
- Use a one-tailed or two-tailed test for *p*-values
- Set the confidence level
- Display the variance inflation factor
- Use the Z distribution or the Knapp-Hartung adjustment for p-values and confidence intervals

Run the regression

To run the regression, simply click "Run regression" on the toolbar [A]

```
Comprehensive meta analysis - [Form1]
 <u>File</u> Covariates Models Computational options Decimals Analyses <u>H</u>elp
                                                                                                                        → Run regression
Models: 🔲 Clear models 👔 Insert model 📫 Delete model 🖏 Rename model 🛄 Generate sequence 👻 🔶 🔍
Covariates: \Xi Show covariates 🤾 Remove covariates ↑ Move up \downarrow Move down 🗢 Link covariates 🗘 Unlink covariates 🗸 🗸
    Set
                     Covariates
                                                   Model 1
                                                      •
                     Intercept
                    Allocation: Alternate
                                                      •
    Allocation
                    Allocation: Systematic
                                                      •
                                                      •
                     Year
                                                      •
                     Latitude
```

STEP 4: NAVIGATE THE RESULTS

Main results screen

After you run the regression

- Click [Main Results] [A]
- Click the desired prediction model [B]
- Click "Fixed" or "Random" at the bottom to select the statistical model.

	nal options Decimals Analyses <u>H</u>	elp						 Modify models 	Main results	III Scatterplot	
	Main results for Model 1, Random effects (MM), Z-Distribution										
Set	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value				
	Intercept	-29.2359	45.7992	-119.0007	60.5289	-0.6383	0.5232				
	Allocation: Alternate	0.4855	0.4809	-0.4570	1.4279	1.0096	0.3127	o 4 5 400 1/ 0 0 4 500			
Allocation	Allocation: Systematic	0.4574	0.3778	-0.2831	1.1978	1.2106	0.2260	Q=1.5492, df=2, p=0.4609			
	Year	0.0148	0.0232	-0.0306	0.0603	0.6394	0.5225				
	Latitude	-0.0190	0.0159	-0.0503	0.0122	-1.1924	0.2331				
	Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero Q = 13.1742, df = 4, p = 0.0105 Goodness of fit: Test that unexplained variance is zero Tau-sq = 0.1194, SE = 0.1061, I-sq = 66.69%, Q = 24.0144, df = 8, p = 0.0023										
	Comparison of Model 1 with the null model										
	Total between-study varia Tau-sq = 0.3088, SE = 0.2299 Proportion of total betwee R-sq analog = 61.33%	, I-sq = 92.12%, Q	= 152.2330,		0.0000						
	Number of studies in the analysis 13										



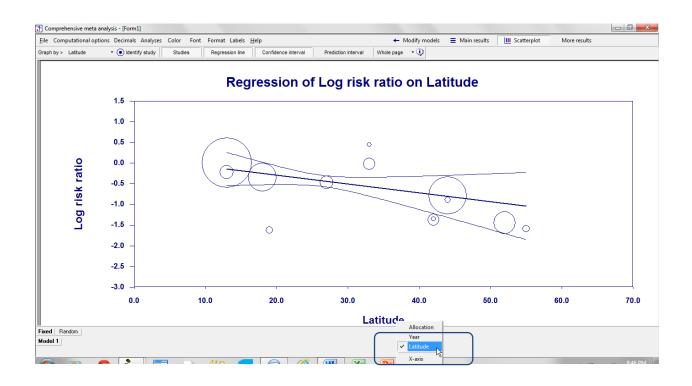
e Computation	al options Decimals Analyses <u>H</u>	lelp						 Modify models 	Main results	III Scatterplot	
	Main results for M	odel 1, Fixed	effect,	Z-Distrib	ution	н					
et	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value				
	Intercept	-45.9381	31.3109	-107.3063	15.4301	-1.4672	0.1423				
Allocation	Allocation: Alternate	0.6320	0.3023	0.0395	1.2245	2.0905	0.0366				
liocation	Allocation: Systematic	0.3062	0.2591	-0.2016	0.8140	1.1819	0.2372	Q=6.3651, df=2, p=0.0415			
	Year	0.0235	0.0159	-0.0076	0.0545	1.4795	0.1390				
	Latitude	-0.0213	0.0084	-0.0378	-0.0048	-2.5260	0.0115				
	Analysis of variance										
		Q	df	р							
	Model	128.2186	4.0000	0.0000							
	Residual	24.0144	8.0000	0.0023							
	Total	152.2330	12.0000	0.0000							
	Number of studies in the a	inalysis 13									
ed Random											

Figure 35

Plot

To display the plot

- Click [Scatterplot] on the menu bar to navigate to the plot [A]
- Select "Fixed" or "Random" on the tab [B]
- Select the model (if more than one model had been defined) [C]
- To specify the variable for the X-axis, right-click on the X-axis label [D]



Other screens

To navigate to other tables of results, click "More" and then select any of the following

The following provide additional information about the analysis for the predictive model that is selected at the bottom left of the screen

- R-squared graphic
- Covariance
- Correlation
- Diagnostics

The following provide information about the data included in (or excluded from) the analysis

- All studies
- Valid studies

The following provide statistics for and/or compare different models

- Increments
- Models summary
- Compare models (detailed)
- Compare models (p-value)

🕂 Comprehensi	ive meta analysis - [Form1]																		_	0 X
Eile Computat	tional options Decimals Analyse	s <u>H</u> elp								🔶 Modif	y ma	odels 🔳	Main resu	lts	l	II Scatterp	olot		More results	
	Increments for Mo	del 1, Ran	dom efi	fects (MN	и),	Z-Distril	oution												Main results Scatterplot R-squared graphic	
	· · · · · · · · · · · · · · · · · · ·						Model (a) Goodness of fit (b)				Change from prior (c)(d) Test			st of change (c)				_	Covariance Correlation Diagnostics All studies	
Set	Covariate	Tau-Sq	R-Sq	Q	df	P-value	Q	df	P-value	Tau-S	q	R-Sq	Q	df	f P	-value			Valid studies	
Allocation	Intercept Allocation: Alternate Allocation: Systematic Year Latitude This page tabulates statisti The first row is a model wil As such, this table address (a) Simultaneous test that (b) Test that with all covari (c) Change from the prior r (d) The row-to-row increas	cs from a seri th one covaria es the impact all coefficient ates up to and ow to the curr	te, the sec of each cor s up to and l including rent row (i.	ond row is a variate wher l including th the current i e., due to th	2 3 4 mod p PRIC row i is con	OR covariat rrent row a n the mode variate)	tes are held con re zero el, the residual	10 9 8 nd so nstar	0.0000 0.0004 0.0023 0 on. nt. or is zero	0.08 0.17 -0.42 -0.01	03 47	0.00% 0.00% 56.31% 5.02%	0.243 1.243 8.428 1.421	0	1 1 1 1	0.6218 0.2649 0.0037 0.2331				
Fixed Random Model 1	n																			

STEP 4: SAVE THE ANALYSIS

Once you've created a meta-regression you can save it using

- File > Save regression file as ...
- This will save the regression template with an extension of .cmr.

ie covariates mos	dels Computational options D	ecimals Analyses	<u>H</u> elp				→ Run regression			
Page size and man	gins Insert model ^ Deleti	e model 🚦 🖥 Renam	e model 🛛 Ger	erate sequence	• ← →	0				
Print Return to basic and	alysis	Remove covariates 🕇 Move up 🗼 Move down 🗢 Link covariates < D Unlink covariates 🗸 🗸								
 Open regression fi Save regression file Save regression file 	ile e ates	Intercept	+ Allocation:	+ Allocation:	+ Year	+ Latitude				
C:\test.cmr	ept	\checkmark				v				
	Allocation: Alternate		•	•		•				
Allocation	Allocation: Systematic			\checkmark		•				
	Year					•				
	Latitude					v				

The .cmr file save the instructions for the analysis, NOT the data. By analogy, programs such as SPSS[™], SAS[™], and stata[™] allow you to save a set of commands in one file and the data in another file. The commands can then be applied to any data file that has the same variables.

The .cmr file saves the following

- The list of covariates
- The list of models
- The check-boxes for each model
- The sets
- The model names

In another session you can return to the regression module and click

• File > Open file

to open this file, and re-run the analysis. This can be with the same dataset as you had used before, or with another dataset. For example, you may return to the data-entry screen and add new studies, or you may return to the main analysis screen and edit the filters, or you may be working with an entirely different data set that has the same variables as the first one. When you open a cmr file the program simply recreates the main MR screen as though you had entered it manually.

The MR file does *not* save the statistical settings that were in place when the file was created. These include the method employed to estimate T^2 , the use of Z or Knapp-Hartung, the confidence level, the choice of a one-sided or two-sided test.

Step 5: Export the results

The program offers two options for exporting the results of any analysis.

- Export the results to Excel. Then, you can perform additional computations within Excel, and/or format the results and copy them as a table to other programs
- Copy the results to the clipboard as a picture. Then, paste this picture into Word or any other program.

The example here is for the main analysis screen.

The screen looks like this

ile Computationa	l options Decimals Analyses <u>H</u> e	elp						 Modify models 	Main results	III Scatterplot						
 Modify models 									_							
		del 1, Rand	om effe	rts (MM	7-Dis	tributio	n									
Save results as E		act 1, Runa	onnene		,, 2 013	cinsucio										
	Excel file and open															
	clipboard as picture		Standard	95%	95%		2-sided									
Set	Covariate	Coefficient	Error	Lower	Upper	Z-value	P-value									
	Intercept	-29.2359	45.7992	-119.0007	60.5289	-0.64	0.5232459									
	Allocation: Alternate	0.4855	0.4809	-0.4570	1.4279		0.3126919									
Allocation	Allocation: Systematic	0.4574	0.3778	-0.2831	1.1978	1.21	0.2260301	Q=1.55, df=2, p=0.460877	74							
	Year	0.0148	0.0232	-0.0306	0.0603	0.64	0.5225461	-								
	Latitude	-0.0190	0.0159	-0.0503	0.0122	-1.19	0.2330983									
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero Q = 13.17, df = 4, p = 0.0104551 Goodness of fit: Test that unexplained variance is zero Tau-sq = 0.1194, SE = 0.1061, I-sq = 66.69%, Q = 24.01, df = 8, p = 0.0022791																
	Comparison of Model 1 wit	h the null mode	odel													
	Total between-study variance (intercept only)															
	Tau-sq = 0.3088, SE = 0.2299, I-sq = 92.12%, Q = 152.23, df = 12, p = 0.0000000															
	Proportion of total betwee	n-study variance	explained	by Model 1												
	R-sq analog = 61.33%															
	Number of studies in the ar	nalysis 13														
ixed Random																

- Click File > Export results to Excel and open
- Provide a name for the Excel file

	L) - (2 -		Farmulas	Data Daviau			Compatibility I	Mode] - Micro	soft Excel					
File	Home	Insert Page Layout		Data Review		Acrobat							Σ AutoSu	
		Calibri	т 11 т А́ А́	= =	»» 📑	Wrap Text	General	Ψ.	≤ ₿				Fill -	^m * 27
Paste		B I U -	🛛 - 🛛 🗞 - 🗛 -	E E E	建建 🔤	Merge & Center	\$ - %	• •.0 .00 •.• 00.		Format Cell	Insert Dele	te Format	Q Clear ▼	Sort &
Ť	Clipboard	For For	nt G		Alignment		Num	ber G	-	is Table * Styles * tyles	Cell	s	Z Clear	Filter * Editing
	A1	▼ (-							
	A	В	D	Н	1	J	К	L	N	S	Т	U	V	w
1			Main results	for Model 1, R	andom effec	ts (MM), Z-Dis	tribution						-	
2														
5		Set	Covariate	Coefficient	Standard	95%	95%	Z-value	2-sided					
6					Error	Lower	Upper		P-value	Set				
7			Intercept	-29.2359	45.7992	-119.0007	60.5289	-0.6383	0.5232					
8			Allocation: A	0.4855	0.4809	-0.457	1.4279	1.0096	0.3127	Q=1.55, df=2,	p=0.4608774			
9			Allocation: S	0.4574	0.3778	-0.2831	1.1978	1.2106	0.226	Q=1.55, df=2,	p=0.4608774			
10			Year	0.0148	0.0232	-0.0306	0.0603	0.6394	0.5225					
11			Latitude	-0.019	0.0159	-0.0503	0.0122	-1.1924	0.2331					
11														
41														
42			Statistics for	Model 1										
43														
44			Test of the m	odel: Simulta	neous test th	at all coefficie	nts (excludin	g intercept) a	are zero					
45			Q = 13.17, df =	= 4, p = 0.01045	551									
47			Goodness of	fit: Test that u	unexplained	ariance is zero)							
48			Tau-sq = 0.11	94, SE = 0.1061	, I-sq = 66.699	%, Q = 24.01, df	= 8, p = 0.002	22791						
51														
52			Comparison of	of Model 1 wit	th the null mo	odel								
53														
54				n-study variar										
.55						%, Q = 152.23, d		000000						
57					n-study varia	nce explained	by Model 1							
158			R-sq analog =	61.33%										
61														

Part 5: Understanding the results

MAIN RESULTS

FIXED-EFFECT ANALYSIS

To navigate to this screen

Run the analysis [A]

🕂 Compr	ehensive meta analysis - [Form1]		
Eile Cov	variates Models Computational options De	ecimals Analyses <u>H</u> elp	→ Run regression
Models:	Clear models 👖 Insert model 📫 Delete	e model 📮 Rename model	Generate sequence $\bullet \leftrightarrow \downarrow \bigcirc$
Covariates	: E Show covariates 🧲 Remove covariates	↑ Move up 👃 Move down	🗢 Link covariates 🗘 Unlink covariates 🗸 🗸
Set	Covariates	Model 1	
	Intercept	v	
	Allocation: Alternate		
	Allocation: Systematic		
	Year		
	Latitude		

The toolbar changes as shown here

- Click "Main results"
- Click on the predictive model
- Click "Fixed"

Set Covariate Coefficie Set Standard Standar	ile Computation	al options Decimals Analyses <u>H</u>	lelp						 Modify models 	Main results	III Scatterplot	
Set Covariate Covernee Error Lower Upper 2-Value P-value Allocation: Intercept -45.9381 31.3109 -107.3063 15.4301 -1.4672 0.1423 Allocation: Allocation: Systematic 0.6320 0.0395 1.2424 2.0905 0.0366 Year 0.0235 0.0259 -0.2016 0.8140 1.1819 0.2372 0 Year 0.0235 0.0084 -0.0378 0.0048 -2.5260 0.0115 Analysis of variance Q df p -		Main results for M	odel 1, Fixed	l effect, i	Z-Distrib	ution						
Allocation: Allocation: Systematic 0.3023 0.0395 1.245 2.0905 0.0366 Allocation: Q=6.3651, df=2, p=0.0415 Year 0.0235 0.0159 -0.0076 0.0545 1.4795 0.1390 Latitude -0.0213 0.0084 -0.0378 -0.0048 -2.5260 0.0115 Analysis of variance Q df p	Set	Covariate	Coefficient				Z-value					
Allocation: Allocation: 0.3062 0.2591 -0.2016 0.8140 1.1819 0.2372 Q=6.3651, df=2, p=0.0415 Year 0.0235 0.0159 -0.0076 0.0545 1.4795 0.1390 Latitude -0.0213 0.0084 -0.0378 -0.0048 -2.5260 0.0115 Analysis of variance Q df p		Intercept	-45.9381	31.3109	-107.3063	15.4301	-1.4672	0.1423				
Allocation: Systematic 0.3062 0.2591 -0.2016 0.8140 1.1819 0.2372 Year 0.0235 0.0159 -0.0076 0.0545 1.4795 0.1390 Latitude -0.0213 0.0084 -0.0378 -0.0048 -2.5260 0.0115 Analysis of variance Q df p - - - - Model 128.2186 4.000 0.0000 - - - - - Residual 24.0144 8.0000 0.0000 - - - - - Number of studies in the analysis 13 13 -	Allocation	Allocation: Alternate	0.6320	0.3023	0.0395	1.2245	2.0905	0.0366	0-6 2651 df-2 p-0.0415			
Latitude -0.0213 0.0084 -0.0378 -0.048 -2.5260 0.0115 Analysis of variance Q df p - <t< td=""><td>Anocation</td><td>Allocation: Systematic</td><td>0.3062</td><td>0.2591</td><td>-0.2016</td><td>0.8140</td><td>1.1819</td><td>0.2372</td><td>Q=0.5051, u1=2, p=0.0415</td><td></td><td></td><td></td></t<>	Anocation	Allocation: Systematic	0.3062	0.2591	-0.2016	0.8140	1.1819	0.2372	Q=0.5051, u1=2, p=0.0415			
Q df p Model 128.2186 4.000 0.0000 Residual 24.0144 8.000 0.0023 Total 152.2330 12.000 0.0000					-0.0076	0.0545	1.4795	0.1390				
Q df p Model 128.2186 4.000 0.0000 Residual 24.0144 8.000 0.0023 Total 152.2330 12.0000 0.0000		Latitude	-0.0213	0.0084	-0.0378	-0.0048	-2.5260	0.0115				
Model 128.2186 4.0000 0.0000 Residual 24.0144 8.0000 0.0023 Total 152.2330 12.0000 0.0000 Number of studies in the analysis 13		Analysis of variance										
Residual 24.0144 8.000 0.0023 Total 152.2330 12.0000 0.0000 Number of studies in the analysis 13			Q	df	р							
Total 152.2330 12.0000 0.0000 Number of studies in the analysis 13		Model	128.2186	4.0000	0.0000							
Number of studies in the analysis 13		Residual	24.0144	8.0000	0.0023							
		Total	152.2330	12.0000	0.0000							
		Number of studies in the a	analysis 13									
												_



Analysis of variance

In this section the total WSS is partitioned into its component parts -

- The WSS *explained* by the covariates (the model)
- The WSS *not explained* by the covariates (the residual).

Model

This is the test that the predictive model explains *any* of the variance in effect size. Put another way, it asks if the dispersion of effects about the regression line smaller when the regression line is based on the covariates rather than based solely on the grand mean. Here, Q = 128.2186 with df = 4 and p < 0.0001, so we conclude that the predictive model explains (at least) some of the variance in effect size.

Residual

This is the test that the data are consistent with the model's assumption of a common effect size for all studies with the same predicted value. The *Q* value is 24.0144 with df = 8 and p = 0.0023. We conclude that the data are not consistent with the assumptions of the fixed-effect model.

Total

This is the test that the variance for the full set of studies (with no predictors) is zero. The *Q*-value is 152.2330 with df = 12 and p < 0.0001.

Impact of individual covariates

The test of the model is an omnibus test for the full set of covariates. It tells us that the set as a whole is related to effect size. By contrast, the table at the top addresses the impact of each covariate. *In this table, the impact of each covariate is reported with all of the other covariates partialled* out (or held constant).

Since the effect size is the risk ratio, all analyses are carried out in log metric and all coefficients are in the log metric. In this example, virtually all predicted effects are less than zero, so 0 is no effect, -1 is a large effect, and -2 is a very large effect. In this example, therefore, a negative coefficients means that as the covariate gets larger the vaccine is more effective. (The reverse would be true if the predicted values were all positive).

The coefficient for Year is 0.0235, which means that for every increase of one year the log risk ratio will increase by 0.0235 (the vaccine became less effective over time). The corresponding *p*-value is 0.1390.

The coefficient for latitude [I]is -0.0213, which means that for every increase of one unit (degree) in latitude the log risk ratio will decrease by 0.0213 (vaccine is more effective at greater latitudes). The coefficient plus/minus 1.96 times the standard error (0.0084) yields the 95% confidence interval for the coefficient, which is -0.0378 to -0.0048. The coefficient divided by its standard error yields a Z value of -2.526, and the corresponding *p*-value of 0.0115. Thus, when year and allocation method are held constant, the relationship between latitude and effect size is statistically significant.

Impact of a set of covariates

The model includes two covariates that have been identified as a set. These are Alternate allocation and Systematic allocation. The test of the set tells us if allocation is related to effect size. In this case Q = 6.3651 with df = 2 and p = 0.0412, and so there is evidence that effect size is related to allocation type. For a more specific analysis we can look at each line within the set, and see that Alternate allocation has a coefficient of 0.6320 (the vaccine is less effective in studies that employed alternate allocation) and a p-value of 0.0366. However, as discussed in the chapter on caveats, this finding is almost certainly due to a confound with other factors.

Summary

The total Q of each effect size about the grand mean can be partitioned into its component parts – the Q due to the variation in effect size that can be explained by the covariates, and the part that cannot.

- Model. The *Q*-value for the model is 128.2186 with *df* = 4 and *p* < 0.0001, which tells us that effect size is related to at least one of the covariates.
- Residual. The *Q*-value for the residual is 24.0144 with df = 8 and p = 0.0023, which tells us that the assumptions of the fixed-effect model have been violated.
- Total. The *Q*-value for the total is 152.23 with *df* = 12 and *p* < 0.0001, which tells us that that effect sizes vary when we ignore subgroups and work with deviations of all studies from the grand mean.

Impact of individual covariates

The test of the model is an omnibus test for the full set of covariates. It tells us that at least one of the covariates is related to effect size. By contrast, the table at the top addresses the impact of each covariate. *In this table, the impact of each covariate is reported with all of the other covariates partialled out (or held constant)*.

The p-values tell us if there is evidence that the covariate is related to effect size when the other covariates are held constant.

- The *p*-value for allocation is 0.0415. Specifically, with other covariates held constant alternate allocation is associated with a smaller effect size (but see the chapter on caveats).
- The *p*-value for year is 0.1390, with the studies that fall further from the equator showing more impact of the vaccine.
- The *p*-value for latitude is 0.0115, with the studies that fall further from the equator showing more impact of the vaccine.

RANDOM-EFFECTS ANALYSIS

To navigate to this screen

Run the analysis

ve meta analysis - [Form1]		
Models Computational options De	cimals Analyses <u>H</u> elp	→ Run regression
Clear models 👖 Insert model 📫 Delete	model 👢 Rename model 🚺 Gen	erate sequence $ \leftarrow \rightarrow $
Show covariates 🧧 Remove covariates	↑ Move up \downarrow Move down ⊂	Link covariates 🗘 Unlink covariates 🗸 🗸
Covariates	Model 1	
Intercept		
Allocation: Alternate		
Allocation: Systematic	\checkmark	
Year	\checkmark	
Latitude	\checkmark	
	Models Computational options De Clear models in Insert model in Delete Show covariates remove covariates Covariates Intercept Allocation: Alternate Allocation: Systematic Year	Models Computational options Decimals Analyses Help Clear models Image:

The toolbar changes as shown here

- Click "Main results"
- Click on the predictive model
- Click "Random"

ile Computatio	nal options Decimals Analyses <u>H</u>	lelp						 Modify models 	Main results	III Scatterplot	More			
	Main results for Model 1, Random effects (MM), Z-Distribution													
Set	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value							
	Intercept	-29.2359	45.7992	-119.0007	60.5289	-0.6383	0.5232							
	Allocation: Alternate	0.4855	0.4809	-0.4570	1.4279	1.0096	0.3127	Q=1.5492, df=2, p=0.4609						
Allocation	Allocation: Systematic	0.4574	0.3778	-0.2831	1.1978	1.2106	0.2260	Q=1.3452, u1=2, p=0.4009						
	Year	0.0148	0.0232	-0.0306	0.0603	0.6394	0.5225							
	Latitude	-0.0190	0.0159	-0.0503	0.0122	-1.1924	0.2331							
	Statistics for Model 1													
	Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero													
	Q = 13.1742, df = 4, p = 0.0105													
	Goodness of fit: Test that unexplained variance is zero													
	Tau-sq = 0.1194, SE = 0.1061, I-sq = 66.69%, Q = 24.0144, df = 8, p = 0.0023													
	Comparison of Model 1 wi	th the null mode	I											
	Total between-study varia	nce (intercept on	ly)											
	Tau-sq = 0.3088, SE = 0.2299	9, I-sq = 92.12%, Q	= 152.2330,	df = 12, p =	0.0000									
	Proportion of total betwee	Proportion of total between-study variance explained by Model 1												
	R-sq analog = 61.33%													
	Number of studies in the a	inalysis 13												

Test of the model

Is effect size related to the covariates?

The test of the model is a simultaneous test that all covariates (except the intercept) are zero. The *Q*-value is 13.1742 with df = 4 and p = 0.0105. We reject the null and conclude that at least one of the covariates is related to effect size.

Goodness of fit

Is there any unexplained variance in the true effect sizes?

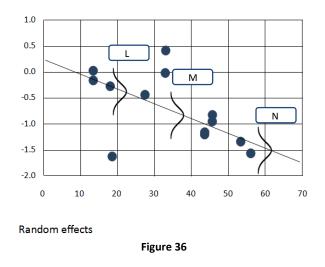
Immediately above, we saw that the covariates improve our ability to predict that study's effect. But does this information enable us to completely predict that study's effect – do all studies with the same values on all covariates share a common effect size? Or is there variance in true effects among studies with the same predicted value?

The *Q* statistic, based on the deviation of each study from its predicted value, is 24.0144, with 8 *df* and the corresponding *p*-value is 0.0023. This tells us that the true effect size varies from study to study, even for studies that are identical on all covariates. Put another way, the model is incomplete – knowing a study's allocation type, year, and latitude does not allow us to completely predict its effect size.

How much variance is there?

The program shows that T^2 , the variance of true effect sizes at any point on the regression line, is 0.1194. It follows that the *T*, the standard deviation of true effect sizes at any point on the regression line is 0.3455. We can use this to get a sense of how closely the true effects at any point on the regression line are (or are not) clustered together.

In Figure 26 we've plotted all 13 studies, the regression line, and a series of normal curves about the regression line. Each normal curve has a height of 1.96 *T* and is centered about some point on the regression line. If the true effects are normally distributed with standard deviation *T*, then 95% of studies with that predicted value will have a true effect size within the range of the normal curve.



What proportion of the observed variance is true variance?

The variance that cannot be explained by the covariates includes within-study variance (essentially error) and between-study variance (that can be potentially explained by additional study-level covariates). The l^2 statistic is 66.69%, which tells us that 67% of the remaining variance falls into the latter group.

Impact of individual covariates

The test of the model is an omnibus test for the full set of covariates. It tells us that at least one of the covariates is related to effect size. By contrast, the table at the top addresses the impact of each covariate. *In this table, the impact of each covariate is reported with all of the other covariates partialled* out (or held constant).

Since the effect size is the risk ratio, all analyses are carried out in log metric and all coefficients are in the log metric. In this example, virtually all predicted effects are less than zero, so 0 is no effect, -1 is a © www.Meta-Analysis.com BCG - 49 - large effect, and -2 is a very large effect. In this example, therefore, a negative coefficients means that as the covariate gets larger the vaccine is more effective. (The reverse would be true if the predicted values were all positive).

The model includes two covariates that have been identified as a set. These are Alternate allocation and Systematic allocation [G]. The test of the set tells us if allocation is related to effect size. In this case Q = 1.5402 with df = 2 and p = 0.46, and so there is no evidence that effect size is related to allocation type.

The coefficient for Year [H] is 0.0148, which means that for every increase of one year the log risk ratio will increase by 0.0148 (the vaccine became less effective over time). The corresponding *p*-value is 0.5225.

The coefficient for latitude [I] is -0.0190, which means that for every increase of one unit (degree) in latitude the log risk ratio will decrease by 0.0190 (vaccine is more effective at greater latitudes). The coefficient plus/minus 1.96 times the standard error (0.0159) yields the 95% confidence interval for the coefficient, which is -0.0503 to 0.0122. The coefficient divided by its standard error yields a Z value of -1.1924, and the corresponding *p*-value of 0.23. Thus, when year and allocation method are held constant, the relationship between latitude and effect size not is statistically significant.

In this example none of the individual covariates has a *p*-value less than 0.05. Since the model as a whole is statistically significant, the fact that no covariate is statistically significant probably reflects the fact that some of the covariates are correlated with each other. For example, latitude or year might be statistically significant if entered into the equation alone. However, if the two are correlated with each other and compete for the same variance, neither meets the threshold for statistical significance.

Comparison of Model 1 with the null model

The intent of this display is to report how much variance there is initially (without covariates), and how much variance remains (with covariates). Then, by comparing the two, we can report that the covariates explained some proportion of the initial variance.

Total between-study variance (intercept only)

To get the initial amount of variance we run a regression with no covariates and compute T^2 . Here, T^2 is 0.3088, which is the variance of all studies about the grand mean.

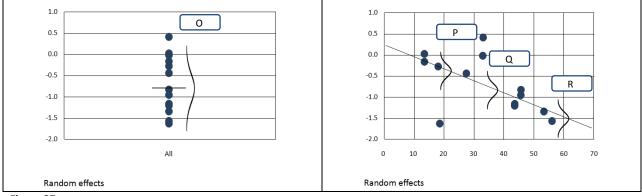
Proportion of variance explained

To get the final amount of variance we run a regression with the covariates and compute T^2 . This value, reported above as 0.1194, is the variance of studies about their predicted value.

If the initial T^2 is 0.3088 and the remaining T^2 is 0.1194, the difference (0.1894) is the T^2 explained by the model. Then we can compute R^2 , the proportion explained by the model, as 0.6133.

The proportion of variance explained is called R^2 . To compute R^2 we follow the logic in the preceding paragraph. We compute T^2 with no covariates [J] to provide the value at left. We already have T^2 with covariates [E] to provide the value at right. Then R^2 is computed as (0.3088 - 0.1194)/(0.3088 = 0.6133).

We can show this graphically. At left, the normal curve reflects the unexplained variance in effects when the predicted value for each study is the grand mean. At right, the normal curves represent the unexplained variance in effects when the predicted value for each study is based on the regression line. The variance at the right is less than the variance at the left, which tells us that by using these covariates we can reduce the unexplained variance – or (equivalently) explain some of the variance.





Summary

- The *Q*-Model is 18.85 with *df* = 1 and *p* < 0.0001. This tells us that effect size is related to latitude.
- The *Q*-value for goodness of fit is 30.73 with df = 12 and p = 0.0012. This tells us that the effect size varies, even within studies at the same latitude.
- The *Q*-total is 152.23 with *df* = 12 and *p* < 0.0001. This tells us that effect sizes vary when we ignore latitude and work with deviations of all studies from the grand mean.
- The *observed* variance in effect sizes is partly due to real differences and partly due to withinstudy sampling error. When there are no covariates [D] the *I*² value is 92%, which tells us that 92% of the observed variance is real, and may potentially be explained by covariates. When we use these covariates [J] the *I*² value is 66.69%, which tells us that 66.69% of the remaining variance is real, and may potentially be explained by additional covariates.
- The between-study variance is estimated at 0.1194 at any given point on the regression line based on these covariates, as compared to 0.3088 for the regression line based on the grand mean. This corresponds to an *R*² of 61.33%, meaning that some 61% of the true variance in effects can be explained by the covariates.