Example name   Statins by smoking

Effect size   Risk ratio
Analysis type   Subgroups within study
Level   Intermediate
Reference   Cheung et al, Figure 7

Synopsis

The goal of this review was to assess the impact of statins on stroke and mortality, and to see if the impact differed by subgroups. The analysis that follows looks at the impact of statins on major coronary events.

This analysis includes five studies where patients were randomized to receive either a statins or a placebo. Outcome was the proportion of patients in each group suffering a major coronary event, and the effect size was the risk ratio.

Within each study patients were classified as being smokers or non-smokers. We ran an analysis to see if the impact of statins was greater (or smaller) for smokers vs. non-smokers.

We use this example to show

- How to enter data for independent subgroups within studies
- How to use study as the unit of analysis
- How to use subgroup as the unit of analysis
- How to compare the treatment effect in different subgroups

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

Download CMA file for computers that use a period to indicate decimals
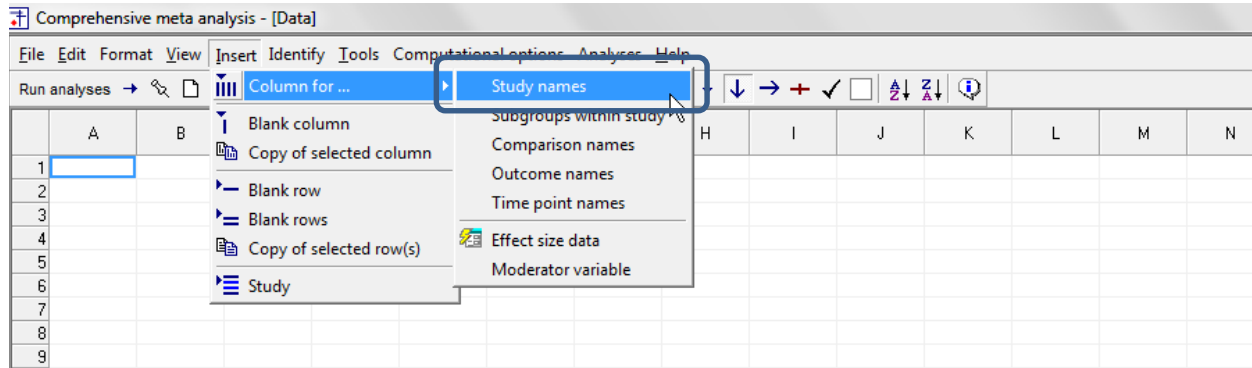Download CMA file for computers that use a comma to indicate decimals
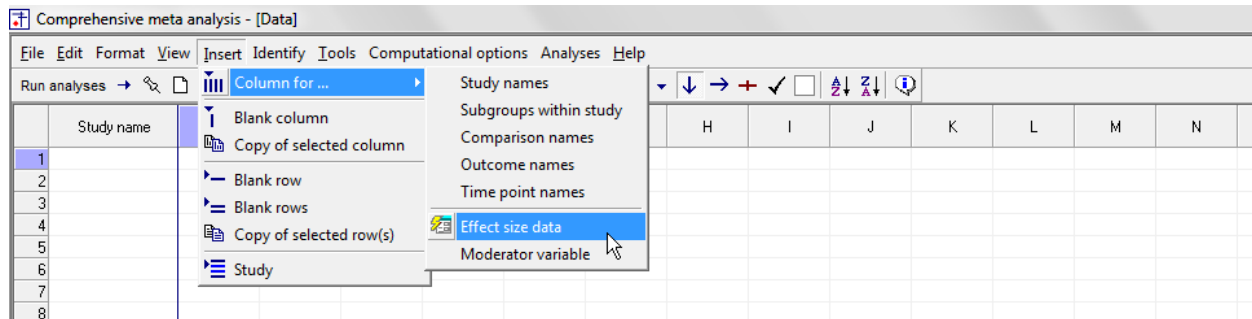
Download this PDF
Download data in Excel
Download trial of CMA

Start the program

- Select the option [Start a blank spreadsheet]
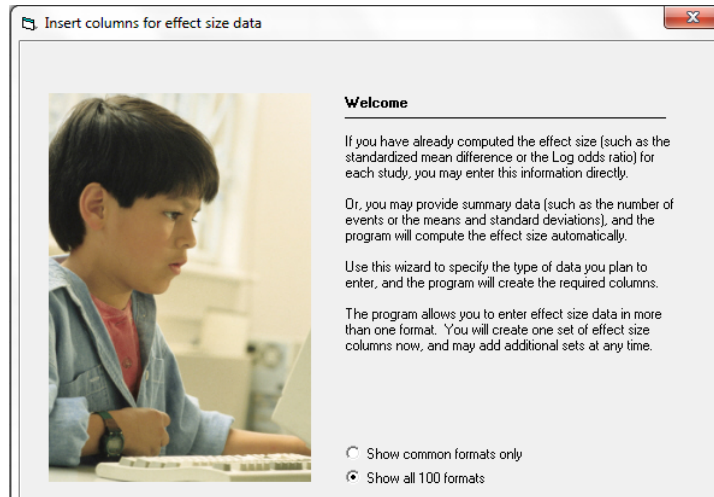- Click [Ok]
- Click Insert > Column for > Study names

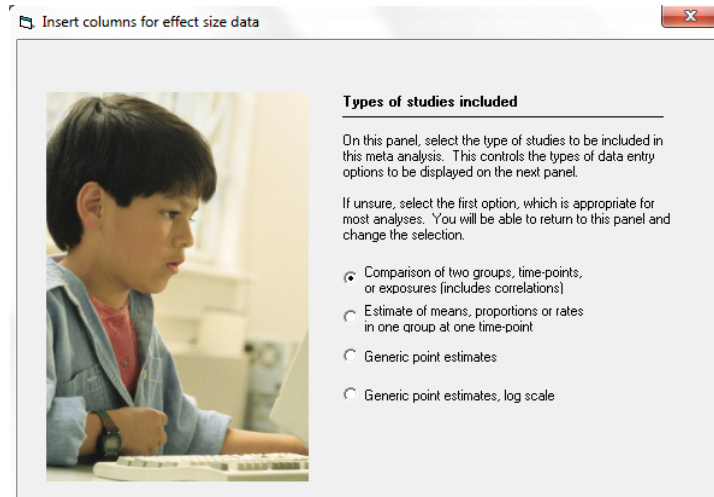Click Insert > Column for > Effect size data

The program displays this wizard
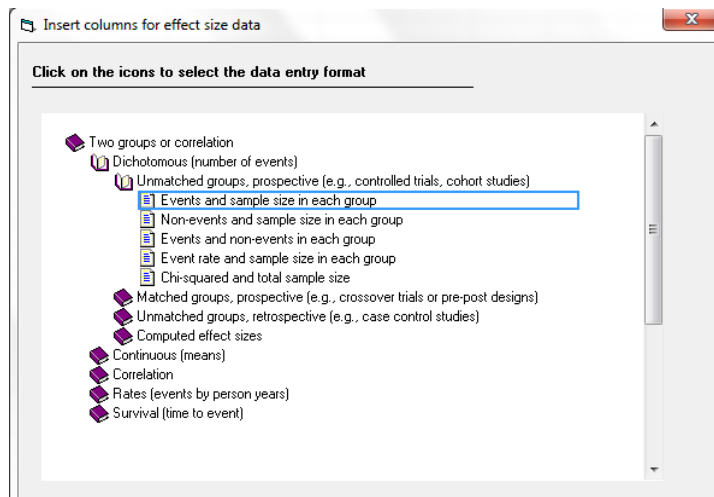
Select [Show all 100 formats]
Click [Next]

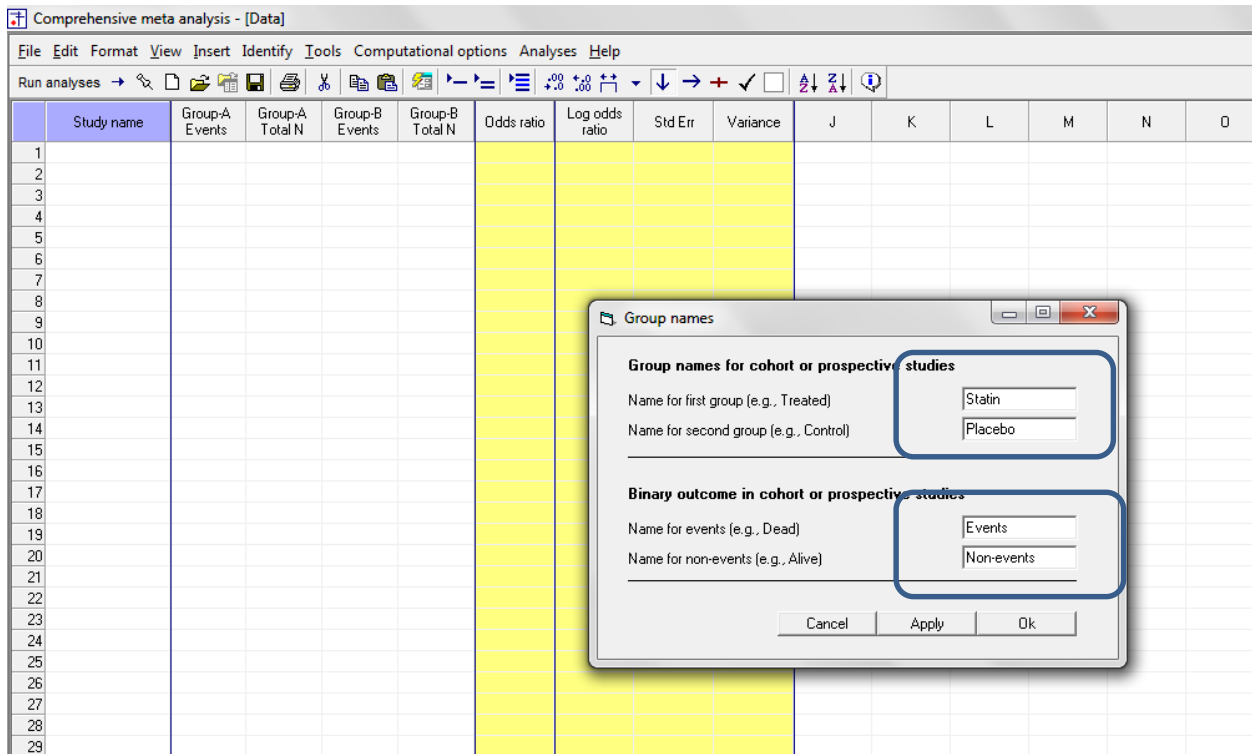Select [Comparison of two groups…]
Click [Next]

Drill down to

Dichotomous (number of events)
Unmatched groups, prospective …
Events and sample size in each group

Enter the following labels into the wizard

- First group > Statin
- Second group > Control
- Name for events > Event
- Name for non-events > Ok

Click [Ok] and the program will copy the names into the grid

The screen should look like this
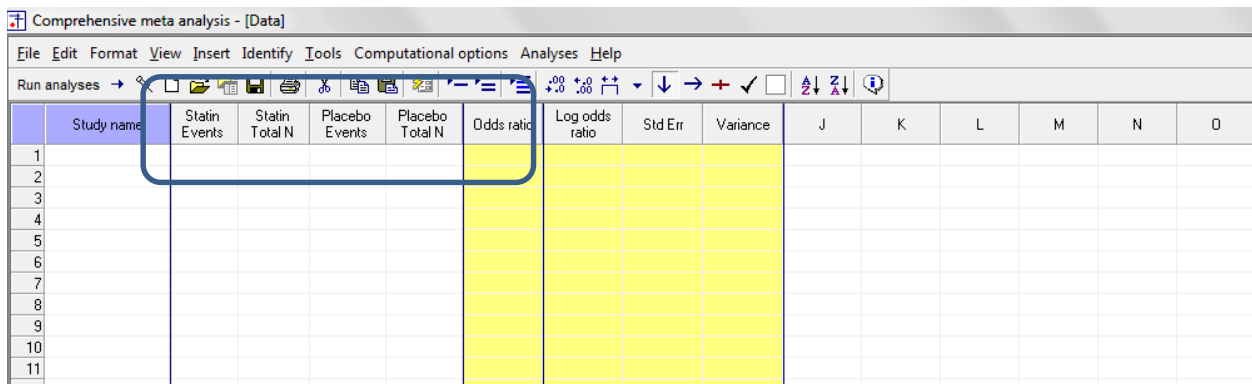
Every study will include data for two INDEPENDENT samples. That is, each person appears in one sample or the other, but not both.

The two samples are non-smokers and smokers. We will be using two rows for each study, and need a column that will identify the sample as non-smokers or smokers.

Click Insert > Column for > Subgroups within study
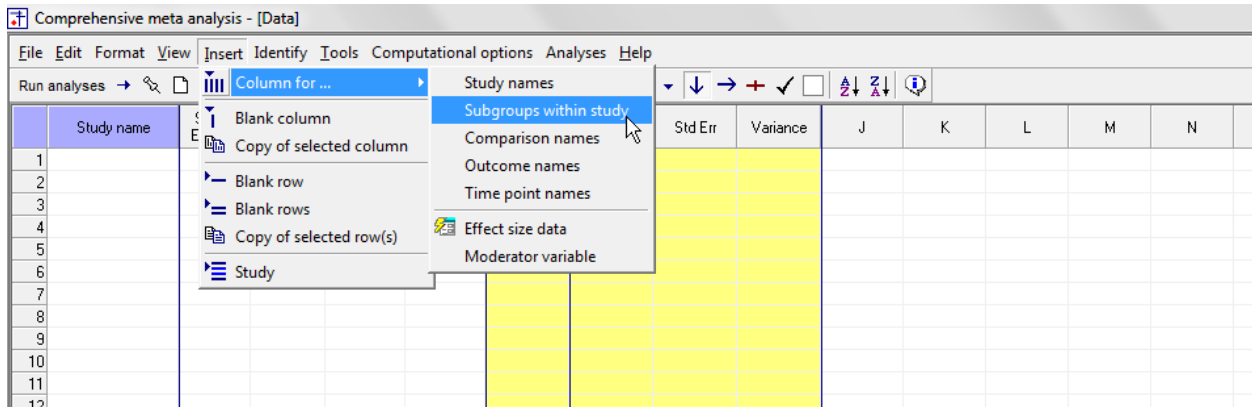
The screen should look like this
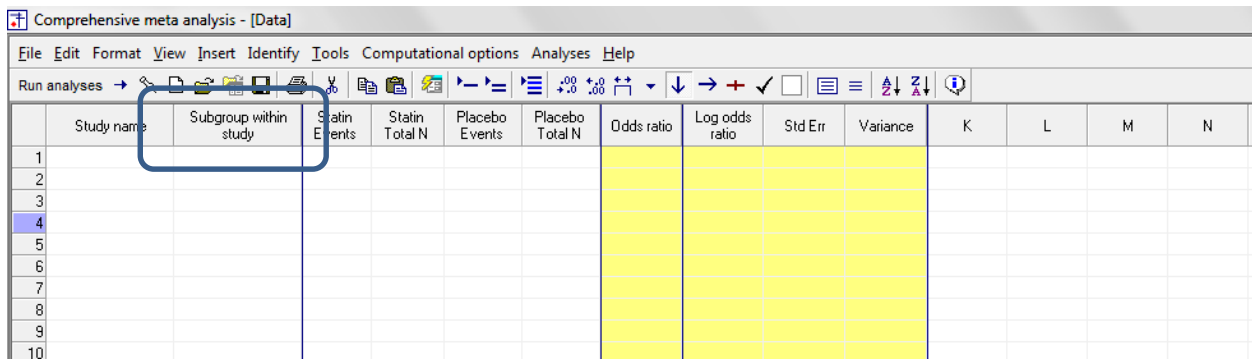
Rather than enter the data directly into CMA we will copy the data from Excel

- Switch to Excel and open the file "Statins by smoking"
- Highlight the rows and columns as shown, and press CTRL-C to copy to clipboard

- Switch to CMA
- Click in cell Study-name 1
- Press [CTRL-V] to paste the data
- The screen should look like this

Click here

At this point we should check that the data has been copied correctly

The column that had been called "Tx E" is now "Statin Events". Similarly, all columns have the intended labels

- Click anywhere in Row 1
- Select Edit > Delete row, and confirm

Click here

The screen should look like this

Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses →

	Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N
1	AFCAPS	Non-smoker	99	2875	147	2912	0.671	-0.399	0.133	0.018				
2	AFCAPS	Smoker	17	429	36	389	0.405	-0.905	0.303	0.092				
3	ASCOT	Non-smoker	65	3450	94	3481	0.692	-0.368	0.163	0.027				
4	ASCOT	Smoker	35	1718	60	1656	0.553	-0.592	0.216	0.046				
5	CARE	Non-smoker	349	1744	437	1744	0.748	-0.290	0.081	0.007				
6	CARE	Smoker	81	337	112	304	0.542	-0.612	0.174	0.030				
7	LIPID	Non-smoker	491	4126	623	4112	0.756	-0.279	0.065	0.004				
8	LIPID	Smoker	66	425	92	444	0.703	-0.352	0.178	0.032				
9	WOSCOP	Non-smoker	74	1832	104	1855	0.709	-0.344	0.156	0.024				
10	WOSCOP	Smoker	100	1445	144	1460	0.679	-0.386	0.136	0.018				
11														
12														
13														
14														
15														
16														
17														
18														

Click File > Save As and save the file

Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

New ...
Open   Ctrl+O
Opening screen wizard
Import
Save   Ctrl+S
Save As...
Print...   Ctrl+P
Print setup...
Exit

		Drug Total N	Control Infection	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	K	L	M	N	O	P
	4	31	1	28	4.000	1.386	1.151	1.324	Low						
	7	144	7	133	0.920	-0.084	0.549	0.301	Low						
	4	101	3	101	1.347	0.298	0.777	0.604	Low						
	2	54	2	43	0.788	-0.238	1.022	1.044	Low						
	5	104	8	106	0.619	-0.480	0.588	0.345	Low						
	5	83	7	84	0.705	-0.349	0.607	0.369	Low						
	8	281	13	276	0.593	-0.523	0.458	0.209	High						
	4	248	5	246	0.790	-0.236	0.677	0.458	High						
	1	59	4	56	0.224	-1.495	1.134	1.286	High						
10	Marr	9	147	12	148	0.739	-0.302	0.457	0.209	High					
11	Menichetti	3	201	9	204	0.328	-1.114	0.674	0.455	High					
12	Morgenstern	1	288	6	293	0.167	-1.792	1.083	1.174	High					
13	Winston	6	71	17	67	0.271	-1.304	0.511	0.261	High					
14															
15															
16															
17															
18															

Note that the file name is now in the header.

- [Save] will over-write the prior version of this file without warning
- [Save As…] will allow you to save the file with a new name

- Click the Merge Rows icon

- The program will merge the study names for each study

Right-click on the yellow columns and click [Customize computed effect size display]

Comprehensive meta analysis - [C:\Users\Biostat\Dropbox\Workshops Three-Day\Statins\Statins by smoking.cma]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses →

	Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1	AFCAPS	Non-smoker	99	2875	147	2912	0.671	-0.399	0.122	0.010					
2	AFCAPS	Smoker	17	429	36	389									
3	ASCOT	Non-smoker	65	3450	94	3481									
4	ASCOT	Smoker	35	1718	60	1656									
5	CARE	Non-smoker	349	1744	437	1744									
6	CARE	Smoker	81	337	112	304									
7	LIPID	Non-smoker	491	4126	623	4112									
8	LIPID	Smoker	66	425	92	444									
9	WOSCOP	Non-smoker	74	1832	104	1855									
10	WOSCOP	Smoker	100	1445	144	1460									
11															
12															
13															
14															

Sort A-Z
Sort Z-A
Column properties
Data entry assistant
Σ Formulas
Show all selected indices
Show only the primary index
Set primary index to Odds ratio
+ Customize computed effect size display

Add Risk ratio and Log risk ratio to the display and click Ok

Comprehensive meta analysis - [C:\Users\Biostat\Dropbox\Workshops Three-Day\Statins\Statins by smoking.cma]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses →

	Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio	Log odds ratio	O
1	AFCAPS	Non-smoker	99	2875	147	2912	0.671	-0.399	
2	AFCAPS	Smoker	17	429	36	389	0.405	-0.905	
3	ASCOT	Non-smoker	65	3450	94	3481	0.692	-0.368	
4	ASCOT	Smoker	35	1718	60	1656	0.553	-0.592	
5	CARE	Non-smoker	349	1744	437	1744	0.748	-0.290	
6	CARE	Smoker	81	337	112	304	0.542	-0.612	
7	LIPID	Non-smoker	491	4126	623	4112	0.756	-0.279	
8	LIPID	Smoker	66	425	92	444	0.703	-0.352	
9	WOSCOP	Non-smoker	74	1832	104	1855	0.709	-0.344	
10	WOSCOP	Smoker	100	1445	144	1460	0.679	-0.386	
11									
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32									
33									
34									

Effect size indices

Use the following as the primary index

[Odds ratio ▼]

Display columns for these indices

☑ Odds ratio
☑ Log odds ratio
☐ Peto odds ratio
☐ Log Peto odds ratio
☑ Risk ratio
☑ Log risk ratio
☐ Risk difference
☐ Std diff in means
☐ Hedges's g
☐ Difference in means
☐ Std Paired Difference
☐ Correlation
☐ Fisher's Z
☐ Rate ratio
☐ Log rate ratio
☐ Rate difference
☐ Hazard ratio

☑ Also show standard error
☑ Also show variance

○ Show the primary index only
● Show all selected indices

[Ok]
[Cancel]

- Right-click on Risk ratio
- Click [Set primary index to Risk ratio]
- Click File > Save

Click [Run analysis]

At this point we have the usual analysis, with a single set of studies. The two samples within each study are treated as two separate studies, since there is no overlap in the subjects.

This is the basic analysis screen, showing a fixed-effect analysis.

Model	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% CI	Weight (Fixed)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value		Relative weight
	AFCAPS	Non-smoker	0.682	0.531	0.875	-3.004	0.003		6.67
	AFCAPS	Smoker	0.428	0.245	0.750	-2.967	0.003		1.32
	ASCOT	Non-smoker	0.698	0.510	0.954	-2.257	0.024		4.25
	ASCOT	Smoker	0.562	0.373	0.848	-2.743	0.006		2.45
	CARE	Non-smoker	0.799	0.705	0.904	-3.552	0.000		26.97
	CARE	Smoker	0.652	0.513	0.830	-3.485	0.000		7.20
	LIPID	Non-smoker	0.785	0.704	0.877	-4.299	0.000		34.24
	LIPID	Smoker	0.749	0.563	0.998	-1.971	0.049		5.05
	WOSCOP	Non-smoker	0.720	0.539	0.964	-2.208	0.027		4.90
	WOSCOP	Smoker	0.702	0.549	0.896	-2.840	0.005		6.94
Fixed			0.744	0.698	0.794	-8.987	0.000		

Click [Both models]

The program displays results for both the fixed-effect and the random-effects analysis.

Model	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% CI	Weight (Fixed)	Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value		Relative weight	Relative weight
	AFCAPS	Non-smoker	0.682	0.531	0.875	-3.004	0.003		6.67	7.45
	AFCAPS	Smoker	0.428	0.245	0.750	-2.967	0.003		1.32	1.55
	ASCOT	Non-smoker	0.698	0.510	0.954	-2.257	0.024		4.25	4.85
	ASCOT	Smoker	0.562	0.373	0.848	-2.743	0.006		2.45	2.85
	CARE	Non-smoker	0.799	0.705	0.904	-3.552	0.000		26.97	25.53
	CARE	Smoker	0.652	0.513	0.830	-3.485	0.000		7.20	8.01
	LIPID	Non-smoker	0.785	0.704	0.877	-4.299	0.000		34.24	30.72
	LIPID	Smoker	0.749	0.563	0.998	-1.971	0.049		5.05	5.72
	WOSCOP	Non-smoker	0.720	0.539	0.964	-2.208	0.027		4.90	5.57
	WOSCOP	Smoker	0.702	0.549	0.896	-2.840	0.005		6.94	7.74
Fixed			0.744	0.698	0.794	-8.987	0.000			
Random			0.738	0.688	0.792	-8.470	0.000			

The random-effects model is a better fit for the way the studies were sampled, and therefore that is the model we will use in the analysis.

- Click Random on the tab at the bottom

The plot now displays the random-effects analysis alone.

Model	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% CI					Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Non-smoker	0.682	0.531	0.875	-3.004	0.003						7.45
	AFCAPS	Smoker	0.428	0.245	0.750	-2.967	0.003						1.55
	ASCOT	Non-smoker	0.698	0.510	0.954	-2.257	0.024						4.85
	ASCOT	Smoker	0.562	0.373	0.848	-2.743	0.006						2.85
	CARE	Non-smoker	0.799	0.705	0.904	-3.552	0.000						25.53
	CARE	Smoker	0.652	0.513	0.830	-3.485	0.000						8.01
	LIPID	Non-smoker	0.785	0.704	0.877	-4.299	0.000						30.72
	LIPID	Smoker	0.749	0.563	0.998	-1.971	0.049						5.72
	WOSCOP	Non-smoker	0.720	0.539	0.964	-2.208	0.027						5.57
	WOSCOP	Smoker	0.702	0.549	0.896	-2.840	0.005						7.74
Random			0.738	0.688	0.792	-8.470	0.000						

A quick view of the plot suggests the following

- All of the studies suggest an advantage for statins over placebo
- The observed effect sizes fall within a relatively narrow range.
- The summary effect is 0.738 with a CI of 0.688 to 0.792. Thus, the mean effect is in the clinically important range.
- The summary effect has a Z-value −8.470 and a *p*-value of < 0.001. Thus we can reject the null hypotheses that the true risk ratio is 1.0.

Click [Next table]

The statistics at the left duplicate those we saw on the prior screen.

- Under the random-effects model the summary effect is 0.738 with a CI of 0.688 to 0.792. Thus, the mean effect is in the clinically important range.
- The summary effect has a Z-value −8.470 and a *p*-value of < 0.001. Thus we can reject the null hypotheses that the true risk ratio is 1.0.
- The statistics at the upper right relate to the dispersion of effect sizes across studies.
- The Q-value is 9.747 with *df*=9 and p=0.371. *Q* reflects the distance of each study from the mean effect (weighted, squared, and summed over all studies). Q is always computed using FE weights (which is the reason it is displayed on the "Fixed" row, but applies to both FE and RE analyses.
- T^2 is the estimate of the between-study variance in true effects. This estimate (in log units) is 0.001. T is the estimate of the between-study standard deviation in true effects. This estimate (in log units) is 0.032.
- I^2 reflects the proportion of true variance to observed variance. I^2 is 7.661, which means that only about 8% of the variance on observed effects reflects variance in true effects. The remaining 92% is attributed to sampling error, and would probably disappear if the sample sizes were large enough.
- Click [Next table] to return to this screen

In this analysis we want to focus on the treatment effect as a function of smoking. Specifically, we're going to run the analysis separately (a) for non-smokers and (b) for smokers.

When we're dividing the studies into two subgroups, the between-studies variance (T^2) must be computed within subgroups. However, we have two options. We can then pool the separate estimates, and use the pooled value for all subgroups. Or, we can use a separate estimate for each subgroup.

Our plan at the moment is to pool the two estimates. To select that option

Click Computational options > Mixed and random effects options
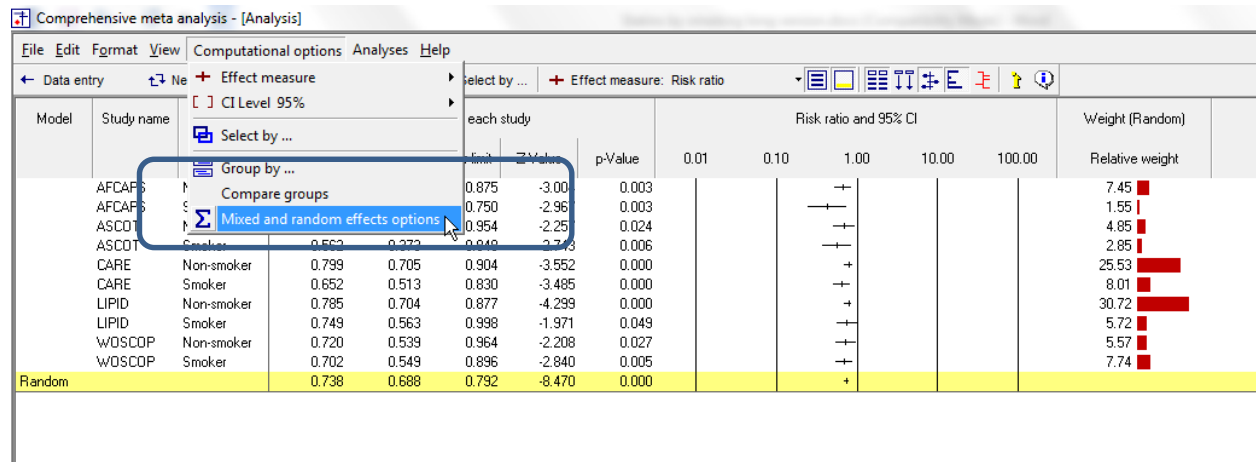
The program displays this wizard

- At the top select the first option, to "Assume a common among-study variance"
- At the bottom select the first option, to "Combine subgroups using a fixed-effect model"

Comprehensive meta analysis - [Analysis]

File   Edit   Format   View   Computational options   Analyses   Help

← Data entry   ↕ Next table   ⊡ High resolution plot   Select by ...   ✛ Effect measure: Risk ratio

Model	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% CI					Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Non-smoker	0.682	0.531									7.45
	AFCAPS	Smoker	0.428	0.245									1.55
	ASCOT	Non-smoker	0.698	0.510									4.85
	ASCOT	Smoker	0.562	0.373									2.85
	CARE	Non-smoker	0.799	0.705									25.53
	CARE	Smoker	0.652	0.513									8.01
	LIPID	Non-smoker	0.785	0.704									30.72
	LIPID	Smoker	0.749	0.563									5.72
	WOSCOP	Non-smoker	0.720	0.539									5.57
	WOSCOP	Smoker	0.702	0.549									7.74
Random			0.738	0.688									

Mixed and random effects options

Combining studies within a subgroup

○ Assume a common among-study variance component across subgroups (pool within-group estimates of tau-squared).

○ Do not assume a common among-study variance component across subgroups (do not pool within-group estimates of tau-squared). This is the option used by RevMan.

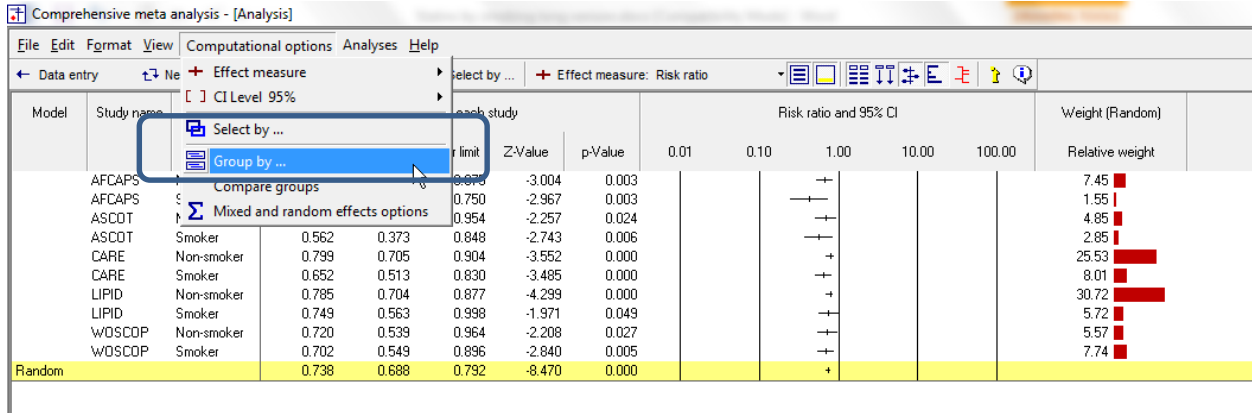Combining subgroups to yield an overall effect

⦿ Combine subgroups using fixed effect model

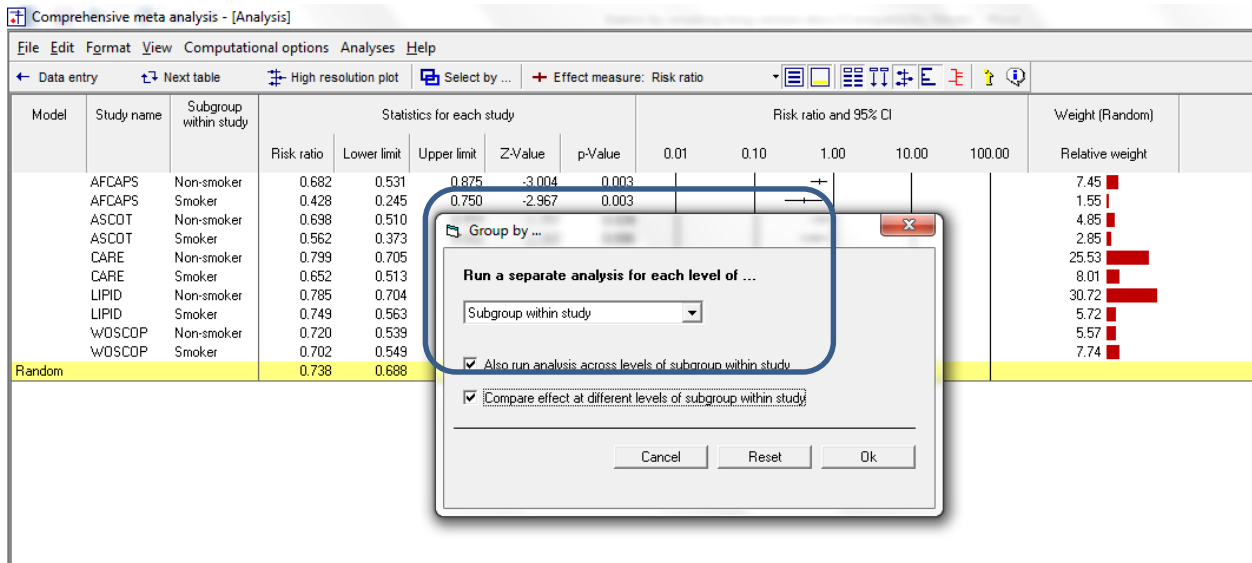○ Combine subgroups using random effects model

Cancel   Apply   Ok

Now, we can tell the program to run the analysis by subgroups.

Click Computational options > Group by

Comprehensive meta analysis - [Analysis]

File Edit Format View **Computational options** Analyses Help

← Data entry   ↵ Ne   **+ Effect measure** ▸   Select by ...   **+ Effect measure: Risk ratio**

[ ] CI Level 95% ▸

Select by ...

Group by ...

Compare groups

Σ Mixed and random effects options

Model	Study name		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS				0.875	-3.004	0.003						7.45
	AFCAPS	S			0.750	-2.967	0.003						1.55
	ASCOT	N			0.954	-2.257	0.024						4.85
	ASCOT	Smoker	0.562	0.373	0.848	-2.743	0.006						2.85
	CARE	Non-smoker	0.799	0.705	0.904	-3.552	0.000						25.53
	CARE	Smoker	0.652	0.513	0.830	-3.485	0.000						8.01
	LIPID	Non-smoker	0.785	0.704	0.877	-4.299	0.000						30.72
	LIPID	Smoker	0.749	0.563	0.998	-1.971	0.049						5.72
	WOSCOP	Non-smoker	0.720	0.539	0.964	-2.208	0.027						5.57
	WOSCOP	Smoker	0.702	0.549	0.896	-2.840	0.005						7.74
Random			0.738	0.688	0.792	-8.470	0.000						

- Select Subgroup within study
- Check the two boxes
- Click Ok

Comprehensive meta analysis - [Analysis]

File Edit Format View Computational options Analyses Help

← Data entry   ↵ Next table   High resolution plot   Select by ...   **+ Effect measure: Risk ratio**

Model	Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Non-smoker	0.682	0.531	0.875	-3.004	0.003						7.45
	AFCAPS	Smoker	0.428	0.245	0.750	-2.967	0.003						1.55
	ASCOT	Non-smoker	0.698	0.510									4.85
	ASCOT	Smoker	0.562	0.373									2.85
	CARE	Non-smoker	0.799	0.705									25.53
	CARE	Smoker	0.652	0.513									8.01
	LIPID	Non-smoker	0.785	0.704									30.72
	LIPID	Smoker	0.749	0.563									5.72
	WOSCOP	Non-smoker	0.720	0.539									5.57
	WOSCOP	Smoker	0.702	0.549									7.74
Random			0.738	0.688									

Group by ...

Run a separate analysis for each level of ...

Subgroup within study ▾

☑ Also run analysis across levels of subgroup within study

☑ Compare effect at different levels of subgroup within study

Cancel   Reset   Ok

The screen should look like this

Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% CI					Weight (Pooled tau)
				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	Non-smoker	AFCAPS	Non-smoker	0.682	0.531	0.875	-3.004	0.003						8.65
	Non-smoker	ASCOT	Non-smoker	0.698	0.510	0.954	-2.257	0.024						5.51
	Non-smoker	CARE	Non-smoker	0.799	0.705	0.904	-3.552	0.000						35.02
	Non-smoker	LIPID	Non-smoker	0.785	0.704	0.877	-4.299	0.000						44.45
	Non-smoker	WOSCOP	Non-smoker	0.720	0.539	0.964	-2.208	0.027						6.36
Random	Non-smoker			0.771	0.717	0.830	-6.939	0.000						
	Smoker	AFCAPS	Smoker	0.428	0.245	0.750	-2.967	0.003						5.76
	Smoker	ASCOT	Smoker	0.562	0.373	0.848	-2.743	0.006						10.68
	Smoker	CARE	Smoker	0.652	0.513	0.830	-3.485	0.000						31.34
	Smoker	LIPID	Smoker	0.749	0.563	0.998	-1.971	0.049						21.98
	Smoker	WOSCOP	Smoker	0.702	0.549	0.896	-2.840	0.005						30.23
Random	Smoker			0.661	0.577	0.756	-6.045	0.000						
Random	Overall			0.744	0.698	0.794	-8.987	0.000						

For non-smokers the mean effect size is a risk ratio of 0.771 with a confidence interval of 0.717 to 0.830, a Z-value of −6.939 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

For smokers the mean effect size is a risk ratio of 0.661 with a confidence interval of 0.577 to 0.756, a Z-value of −6.045 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

For all samples together the mean effect size is a risk ratio of 0.744 with a confidence interval of 0.698 to 0.794, a Z-value of −8.987 and a corresponding p-value of < 0.001.

We want to know if the difference between the two effect sizes (0.771 vs. 0.661) is statistically significant, and we'll run a test for this.

To get a better sense of what we're testing, click the "All studies" button. This will hide all of the individual studies and display the summary effects only as shown here.

The test will compare the two mean effects relative to the precision of each effect. For two groups we can think of this as a Z-test for the ratio of the difference in means to the standard error of the difference.

Expand the scale for detail

- Re-set the scale
- Toggle the "All studies button" to display the studies again.
- Click Next Table to see the results

The top section of the page (labeled Fixed-effect analysis) is for an analysis where we compute the summary effect in each group using FE weights, and then compare these values

The bottom section of the page (Mixed-effects analysis) is for an analysis where we compute the summary effect for each group using RE weights, and then compare these values.

We want to use the bottom section. The RE model is a better fit for the way the studies were sampled, and so this is the appropriate analysis.

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis														
Non-smoker	5	0.771	0.717	0.830	-6.939	0.000	1.944	4	0.746	0.000	0.000	0.006	0.000	0.000
Smoker	5	0.661	0.577	0.756	-6.045	0.000	3.878	4	0.423	0.000	0.000	0.018	0.000	0.000
Total within							5.822	8	0.667					
Total between							3.924	1	0.048					
Overall	10	0.744	0.698	0.794	-8.987	0.000	9.747	9	0.371	7.661	0.001	0.006	0.000	0.032
Mixed effects analysis														
Non-smoker	5	0.771	0.717	0.830	-6.939	0.000								
Smoker	5	0.661	0.577	0.756	-6.045	0.000								
Total between							3.924	1	0.048					
Overall	10	0.744	0.698	0.794	-8.987	0.000								

Toward the left of the screen the program displays the same numbers we saw a moment ago.

For non-smokers the mean effect size is a risk ratio of 0.771 with a confidence interval of 0.717 to 0.830, a Z-value of −6.939 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

For smokers the mean effect size is a risk ratio of 0.661 with a confidence interval of 0.577 to 0.756, a Z-value of −6.045 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

The test to compare the two effect sizes (0.771 vs. 0.661) yields a Q-value of 3.924 with 1 *df* and a corresponding p-value of 0.048.

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis														
Non-smoker	5	0.771	0.717	0.830	-6.939	0.000	1.944	4	0.746	0.000	0.000	0.006	0.000	0.000
Smoker	5	0.661	0.577	0.756	-6.045	0.000	3.878	4	0.423	0.000	0.000	0.018	0.000	0.000
Total within							5.822	8	0.667					
Total between							3.924	1	0.048					
Overall	10	0.744	0.698	0.794	-8.987	0.000	9.747	9	0.371	7.661	0.001	0.006	0.000	0.032
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Non-smoker	5	0.771	0.717	0.830	-6.939	0.000								
Smoker	5	0.661	0.577	0.756	-6.045	0.000								
Total between							3.924	1	0.048					
Overall	10	0.744	0.698	0.794	-8.987	0.000								

Toward the right of the screen the program displays information about between-study heterogeneity. As was true for the single-group of studies, these statistics are based on FE weights and are therefore displayed in the top section, but they apply to the RE analysis as well.

For non-smokers the variance in effects yields a Q-value of 1.944, which is less than the degrees of freedom. Therefore, there is no evidence of dispersion in true effects within the non-smoker studies, and T^2 is estimated at zero.

For smokers the variance in effects yields a Q-value of 3.878, which is less than the degrees of freedom. Therefore, there is no evidence of dispersion in true effects within the smoker studies, and T^2 is estimated at zero.

We can also perform an omnibus test by pooling the Q values and *df* across subgroups. The pooled Q is 5.833 which is less than the pooled *df*. Again, there is no evidence of dispersion in true effects.

These tests are goodness-of-fit tests. They ask if the grouping (smokers vs non-smokers) explains all of the variance in true effect sizes, or if some true variance remains, even within subgroups. Here, there is no evidence of true variance within subgroups.

Note that the tests of homogeneity are displayed in the fixed-effect section, even though we're using the random-effects model within subgroups. This is because these tests always are always based on using within-study (fixed-effect) weights. That is, we pose the null (that T^2 is zero) and then see is the variance is consistent with the null.

Click Next table to return to this screen.

Model	Group by Subgroup	Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
	Non-smoker	AFCAPS	Non-smoker	0.682	0.531	0.875	-3.004	0.003	8.65
	Non-smoker	ASCOT	Non-smoker	0.698	0.510	0.954	-2.257	0.024	5.51
	Non-smoker	CARE	Non-smoker	0.799	0.705	0.904	-3.552	0.000	35.02
	Non-smoker	LIPID	Non-smoker	0.785	0.704	0.877	-4.299	0.000	44.45
	Non-smoker	WOSCOP	Non-smoker	0.720	0.539	0.964	-2.208	0.027	6.36
Random	Non-smoker			0.771	0.717	0.830	-6.939	0.000	
	Smoker	AFCAPS	Smoker	0.428	0.245	0.750	-2.967	0.003	5.76
	Smoker	ASCOT	Smoker	0.562	0.373	0.848	-2.743	0.006	10.68
	Smoker	CARE	Smoker	0.652	0.513	0.830	-3.485	0.000	31.34
	Smoker	LIPID	Smoker	0.749	0.563	0.998	-1.971	0.049	21.98
	Smoker	WOSCOP	Smoker	0.702	0.549	0.896	-2.840	0.005	30.23
Random	Smoker			0.661	0.577	0.756	-6.045	0.000	
Random	Overall			0.744	0.698	0.794	-8.987	0.000	

To this point, the analysis where each study provided data for two subgroups was identical to the analysis we would have performed if each row of data came from a different study.

This is true for the overall analysis, and it's true for the analysis where we compared the treatment effect for smokers vs. the treatment effect for non-smokers.

However, there is one additional option available in when we have subgroups within studies that is not available when each row of data comes from a different study. We have the option to take all the rows from each study and collapse them into a single row.

In the current example, we might decide that while the effect size is different for smokers vs. non-smokers, the two effects are close enough that we want to combine the data. This might make sense, for example, if all studies had included both smokers and non-smokers, but some studies reported the data for smokers and non-smokers separately, while others reported the data only for the sample as a whole.
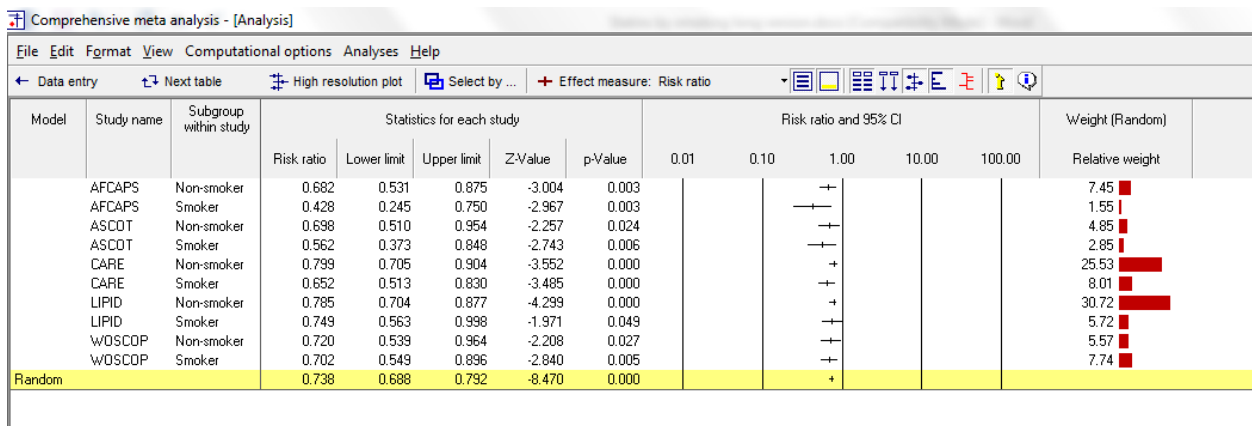
In the current example we probably would not want to collapse the data within studies, but we will proceed to show how this could be done.

First, we need to turn off grouping. If we are going to collapse smokers and non-smokers into a single group, we obviously cannot group by smoking status.

Click Computational options > Group by > Reset
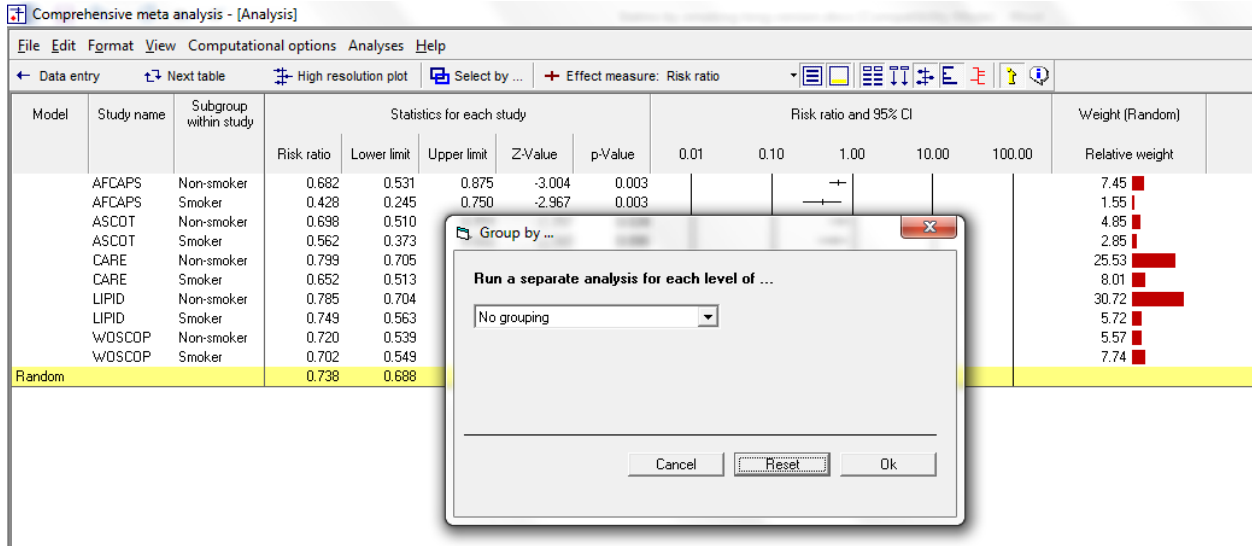
The screen should look like this

- Right-click on the column "Subgroup within study"
- Click Select by Subgroup within study

The two options here are "Use subgroup within study as the unit of analysis" and "Use study as the unit of analysis"

To this point we've been using the first option. Now, select the second option and click OK

Comprehensive meta analysis - [Analysis]

File   Edit   Format   View   Computational options   Analyses   Help

← Data entry   ↑↓ Next table   ‡ High resolution plot   🖰 Select by ...   ✛ Effect measure: Risk ratio

Model	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% CI					Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Combined	0.633	0.504	0.795	-3.935	0.000			⊶			9.37
	ASCOT	Combined	0.645	0.503	0.828	-3.450	0.001			⊶			7.93
	CARE	Combined	0.771	0.690	0.861	-4.617	0.000			+			32.79
	LIPID	Combined	0.780	0.704	0.864	-4.737	0.000			+			36.54
	WOSCOP	Combined	0.710	0.588	0.856	-3.580	0.000			⊶			13.36
Random			0.741	0.690	0.797	-8.146	0.000			+			

Note the following

- We now have five rows of data rather than 10
- The subgroup for each study is listed as "Combined" since every study had two subgroups
- The summary effect size is 0.741, which is very close to the one before (0.738). We wouldn't expect them to be identical
- The confidence interval is 0.690 to 0.797. Again, this is very close to the one before (0.688 to 0.792). The reason is that these samples are independent of each other. As long as we treat them as independent in both versions of the analysis, the two versions may have similar precision (but see the note below)
- The same applies to the Z-value and p-value. These are −8.146 with p < 0.001 in the new analysis. They had been −8.470 with p < .001 in the earlier analysis.

Note

Because the two subgroups are independent of each other, either approach to the analysis is based on the same amount of information and may yield estimates with similar precision. However, there are other factors that affect the precision of the estimate as well and these may differ in the two versions of the analysis. In particular, the estimates may differ substantially if the two approaches yield substantially different estimates of T^2.

This example focused on the case of independent subgroups within studies. This is very different from the case where the same sample provides data for more than one outcome, time-point, or comparison. In that case the samples are not independent and a very different analysis would be used.

Summary

This analysis includes five studies where patients were randomized to receive either a statins or a placebo. Outcome was the proportion of patients in each group suffering a major coronary event, and the effect size was the risk ratio.

Within each study patients were classified as being smokers or non-smokers. We ran an analysis to see if the impact of statins was greater (or smaller) for smokers vs. non-smokers.

Do statins affect the risk of major cardiovascular events?

For this analysis we used subgroups within studies as the unit of analysis.

The mean risk ratio is 0.738, which means that statins decreased the risk of a major cardiovascular event by some 26%. The 95% confidence interval is 0.688 to 0.792. The Z-value for a test of the null (that statins have no impact on the event rate) is −8.470 with a corresponding p-value of < 0.001.

These studies were sampled from a universe of possible studies defined by certain inclusion/exclusion rules as outlined in the full paper. The confidence interval for the risk ratio is 0.688 to 0.792, which tell us that the <u>mean</u> risk ratio in the universe of studies could fall anywhere in this range. This range does not include a risk ratio of 1.0, which tells us that the mean risk ratio is probably not 1.0.

Similarly, the *Z*-value for testing the null hypothesis (that the mean risk ratio is 1.0) is −8.470, with a corresponding *p*-value is < 0.001. We can reject the null that the risk of a major cardiovascular event is the same in both groups, and conclude that the risk is lower in the statin group.

Does the effect size vary by subgroup?

The mean risk ratio for non-smokers is 0.771. The mean risk ratio for smokers is 0.661. The test of the difference in risk between the two subgroups of studies yields a Q-value of 3.924 with *df* = 1 and p=0.048. Thus, statins have more of an effect for smokers (where they reduce the risk of an event by 34%) than they do for non-smokers (where they reduce the risk of an event by 23%).