

Example name Cannon | High Dose vs. Standard Dose Statins

Effect size Risk ratio
Analysis type Basic
Level Basic

Synopsis

This analysis includes four studies where patients were randomized to receive either a standard dose or a high dose of statins. Outcome was the proportion of patients with a cardiovascular event or death in each group.

Cannon, C. P., Steinberg, B. A., Murphy, S. A., Mega, J. L., & Braunwald, E. (2006). Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*, 48(3), 438-445.

We use this example to show

- How to enter data from 2x2 tables
- How get a sense of the weight assigned to each study
- How to perform a sensitivity analysis
- How to choose between fixed-effect and random-effects models
- How to interpret statistics for effect size
- How to interpret statistics for heterogeneity

The data for this exercise are located at

www.Common-Mistakes-in-Meta-Analysis.com

Navigate to the folder for the Canon analysis and download the following

- This PDF
- The data for this analysis in an Excel format
- The data for this analysis in CMA format

To download a trial of CMA go to

www.Meta-Analysis.com

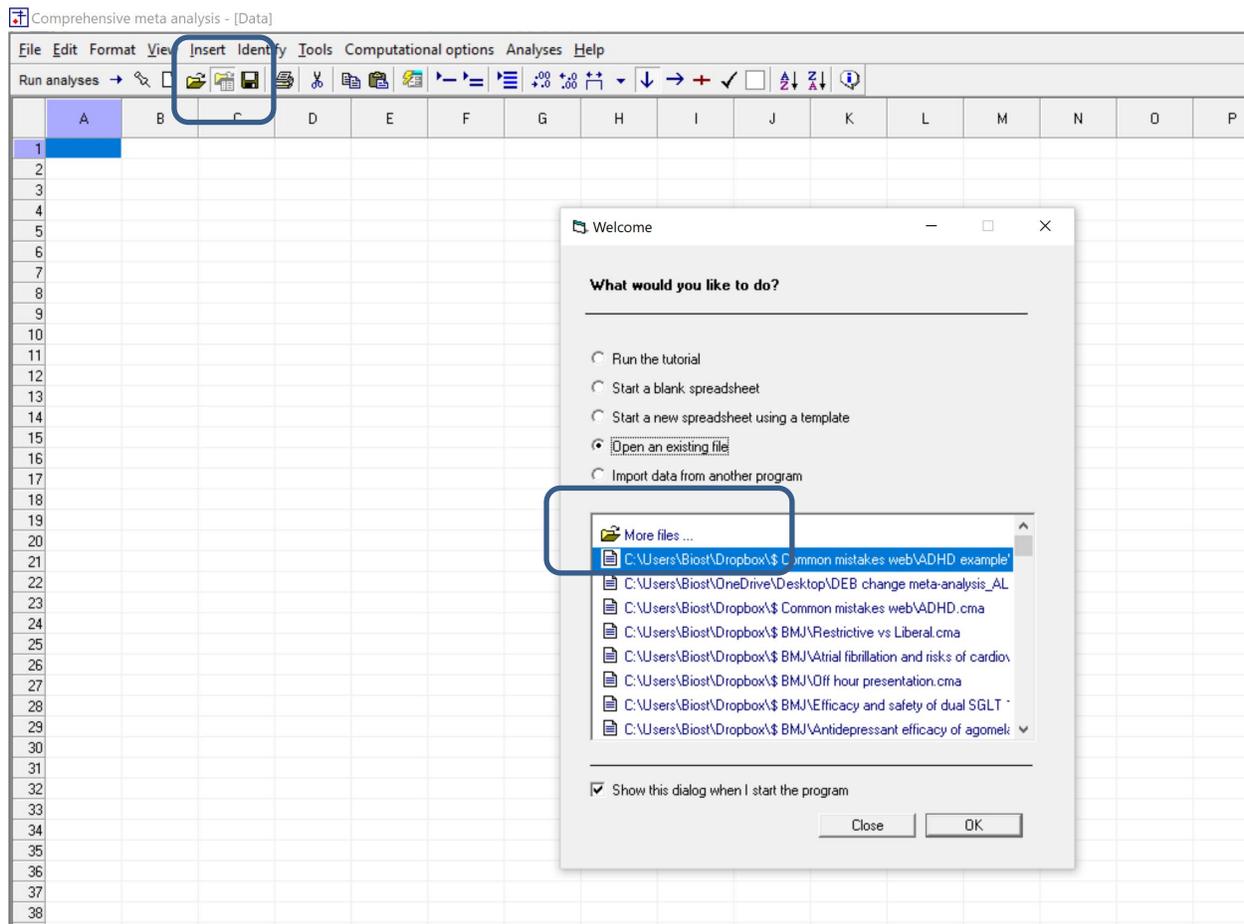
To open a CMA file > Open file from within CMA

You cannot open the file by clicking on it

If you would like to start with a blank file and enter the data, proceed with the next page

If you would like to simply open the file with the Cannon data, proceed with this page

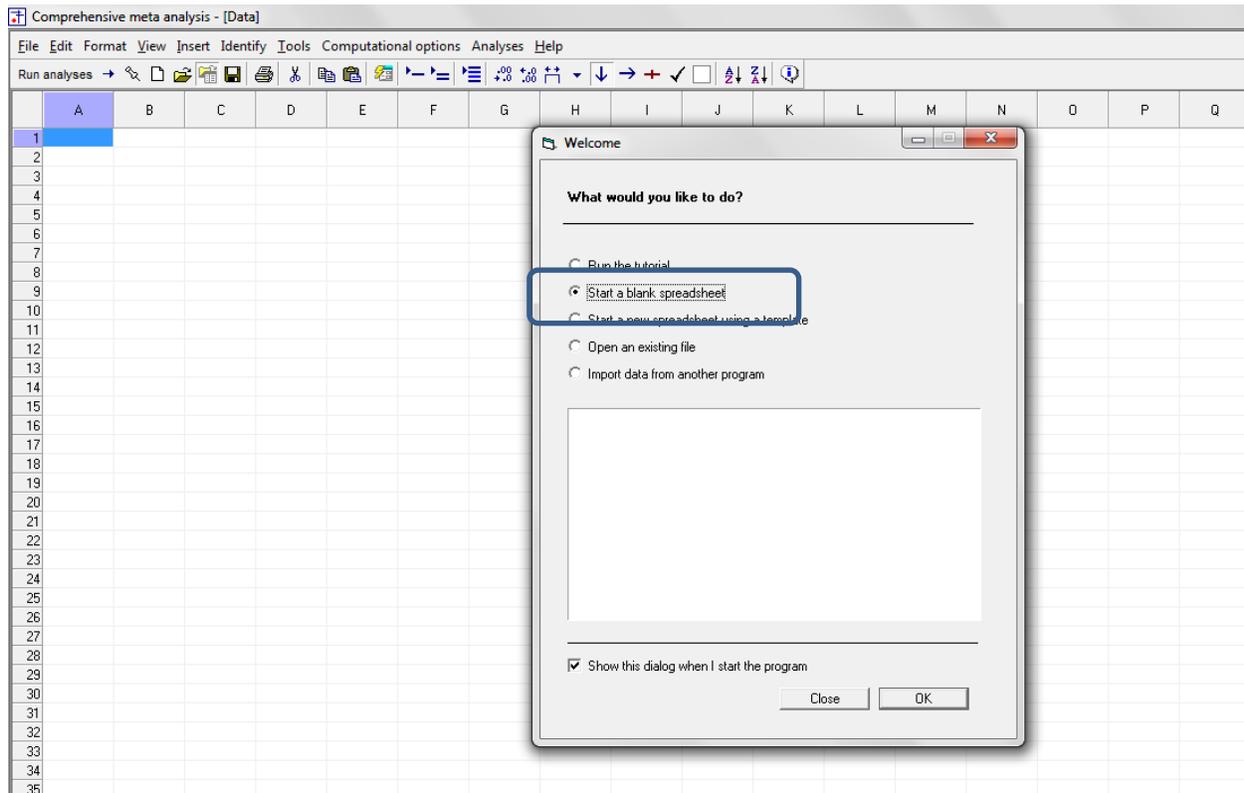
- Start the CMA program
- Click the icon for the Opening Wizard
- Click More Files
- Locate the file Cannon.CMA
- Proceed with the analysis on Page 21



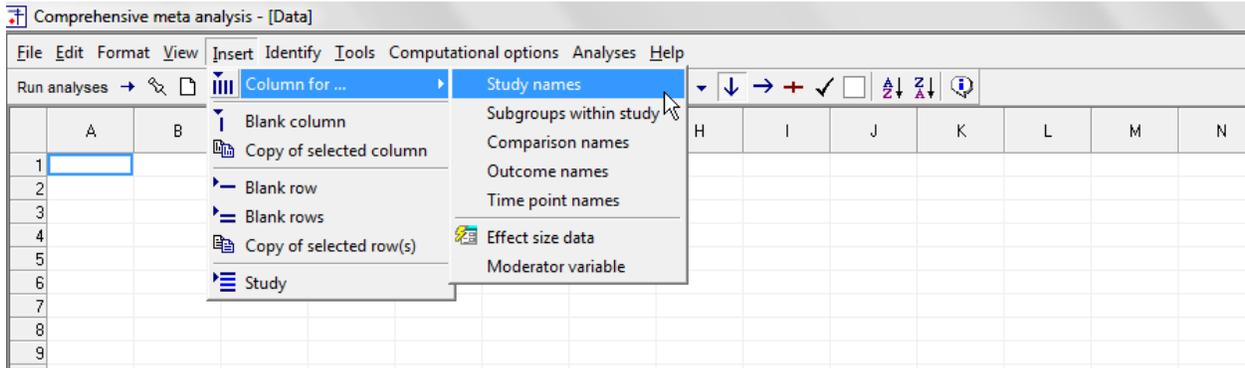
To create a new file from scratch, start here.

Start the program

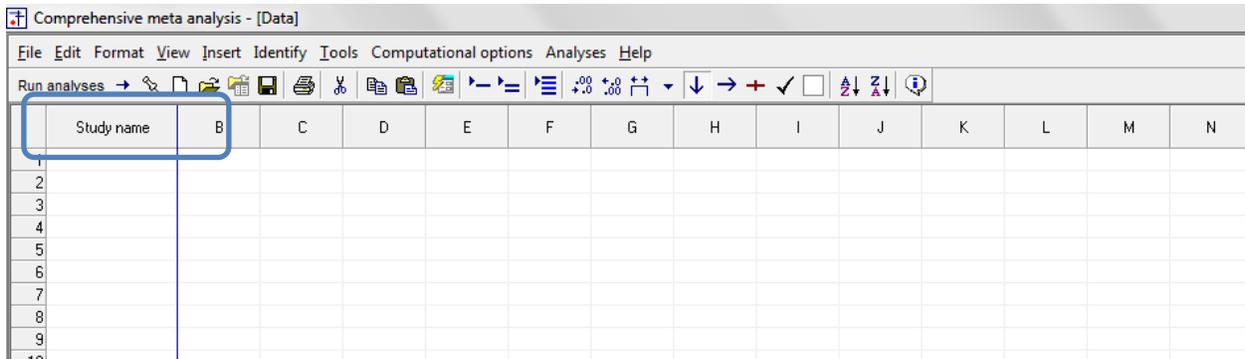
- Select the option [Start a blank spreadsheet]
- Click [Ok]



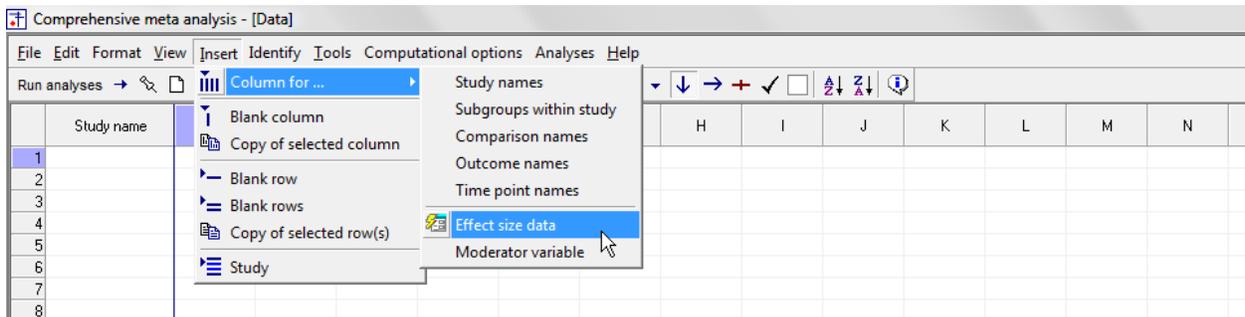
Click Insert > Column for > Study names



The screen should look like this

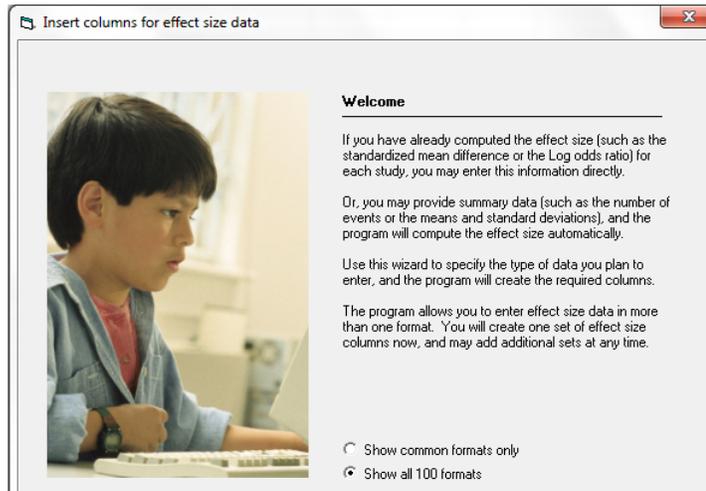


Click Insert > Column for > Effect size data

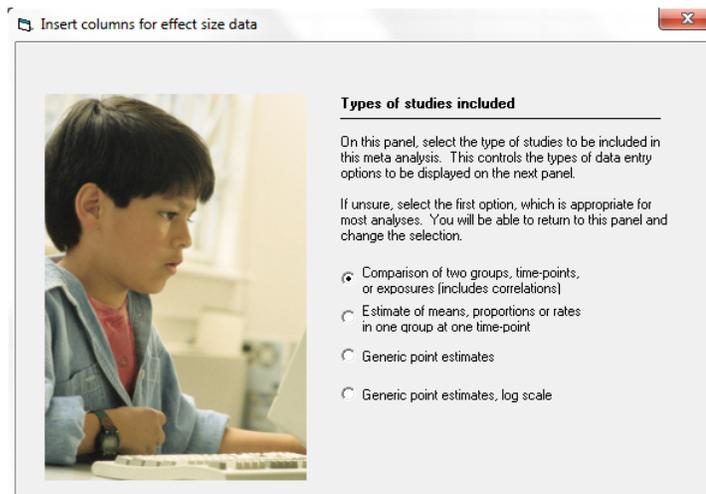


The program displays this wizard

Select [Show all 100 formats]
Click [Next]

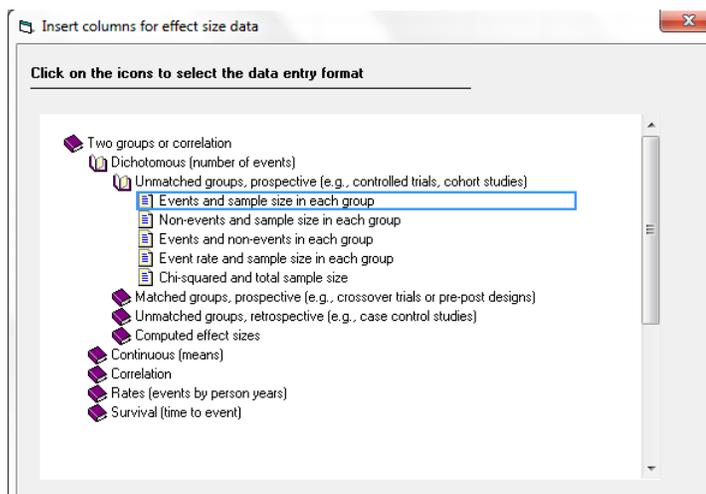


Select [Comparison of two groups...]
Click [Next]



Drill down to

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



The program displays this wizard

Enter the following labels into the wizard

- First group > High
- Second group > Standard
- Name for events > Event
- Name for non-events > Ok

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

The screenshot shows a software window titled "Comprehensive meta analysis - [C:\Users\Biotat\Dropbox\Workshops Three-Day\Cannon\cannon.cma]". The window contains a menu bar (File, Edit, Format, View, Insert, Identify, Tools, Computational options, Analyses, Help) and a toolbar. Below the toolbar is a data grid with the following columns: Study name, High Event, High Total N, Standard Event, Standard Total N, Risk ratio, Log risk ratio, Std Err, Variance, J, K, L, M, N, O. The first four rows of data are highlighted in yellow. A blue box highlights the first four columns of the grid. Overlaid on the grid is a "Group names" dialog box. The dialog box has two sections: "Group names for cohort or prospective studies" and "Binary outcome in cohort or prospective studies". The first section has two input fields: "Name for first group (e.g., Treated)" with the value "High" and "Name for second group (e.g., Control)" with the value "Standard". The second section has two input fields: "Name for events (e.g., Dead)" with the value "Event" and "Name for non-events (e.g., Alive)" with the value "Ok". The dialog box has "Cancel", "Apply", and "Ok" buttons at the bottom.

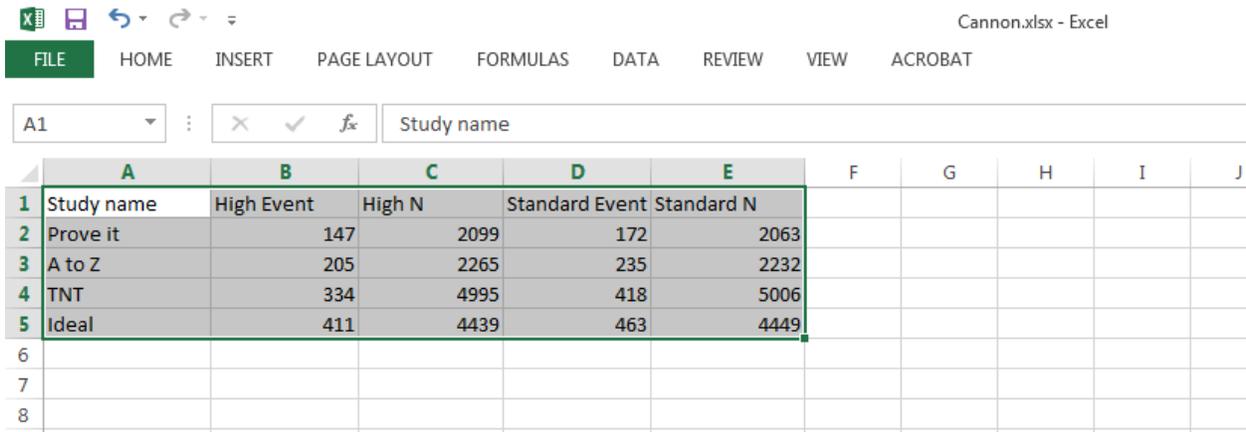
Study name	High Event	High Total N	Standard Event	Standard Total N	Risk ratio	Log risk ratio	Std Err	Variance	J	K	L	M	N	O
1 Prove it	147	2090	172	2066	0.840	-0.174	0.108	0.012						
2 A to Z	205	2265	235	2232	0.860	-0.151	0.091	0.008						
3 TNT	334	4995	418	5006	0.801	-0.222	0.071	0.005						
4 Ideal	411	4439	463	4449	0.890	-0.117	0.064	0.004						
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There are two options at this point

- Enter the data directly into CMA
- Copy the data from Excel [Cannon.xls]

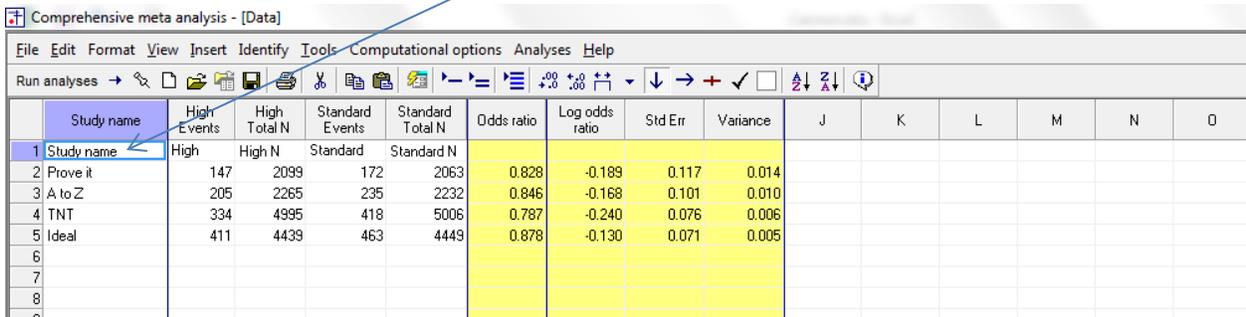
Here, we'll show how to copy the data from Excel

- Switch to Excel and open the file
- Highlight the rows and columns as shown (Columns A to E only), 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

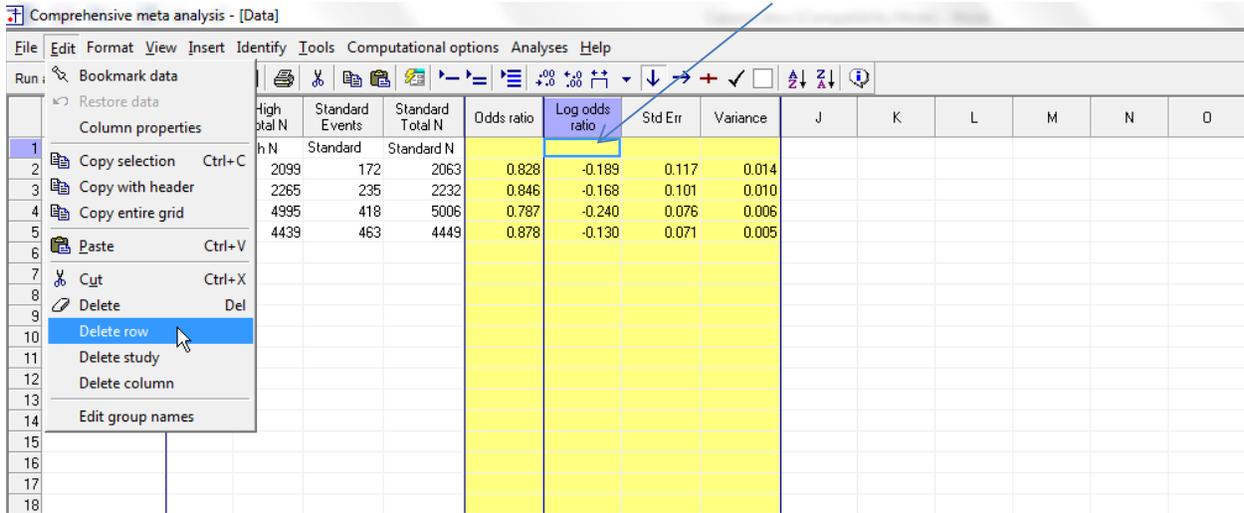
Click here



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

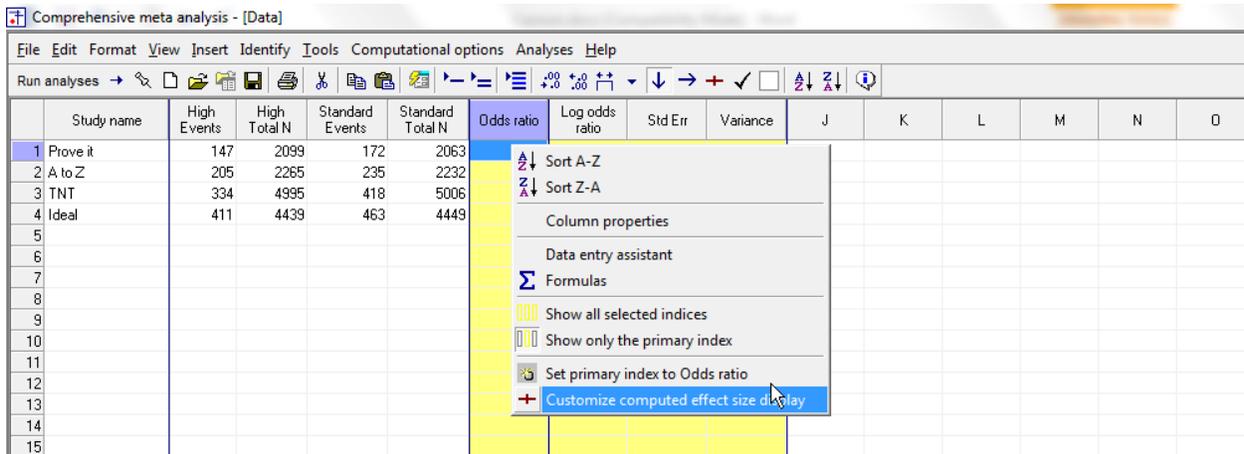
- Click anywhere in Row 1
- Select Edit > Delete row, and confirm

Click here



By default, the program is displaying the odds ratio as the effect size. We want to switch to the risk ratio

- Right-click on any of the yellow columns
- Click Customize computed effect size display



- Tick Risk ratio
- Tick Log risk ratio
- Select Risk Ratio in the drop-down box in the wizard
- De-select Odds ratio
- De-select log odds ratio
- Click Ok

Effect size indices

Use the following as the primary index

Risk 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

Study name	High Events	High Total N	Standard Events	Standard Total N	Odds ratio	Log odds ratio
1 Prove it	147	2099	172	2063	0.828	-0.189
2 A to Z	205	2265	235	2232	0.846	-0.168
3 TNT	334	4995	418	5006	0.787	-0.240
4 Ideal	411	4439	463	4449	0.878	-0.130

The program now display the risk ratio rather than the odds ratio

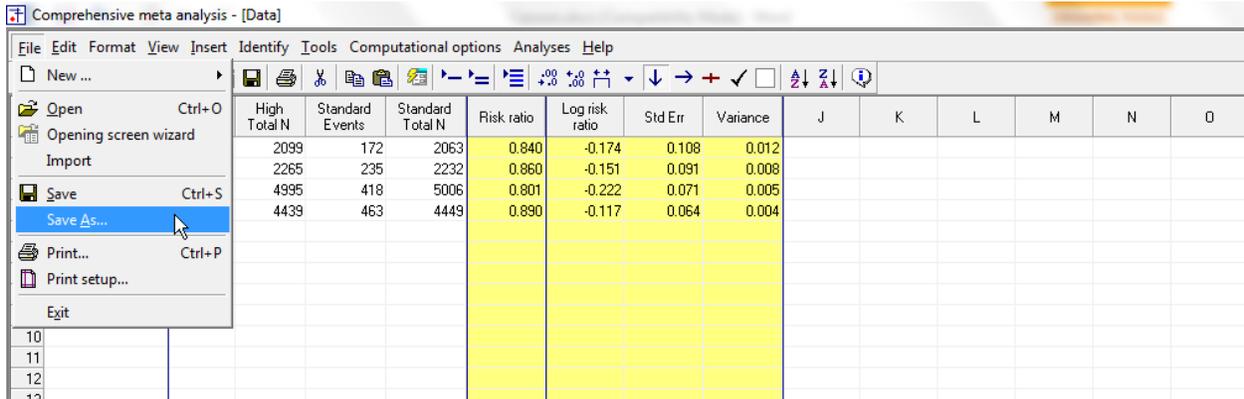
Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses →

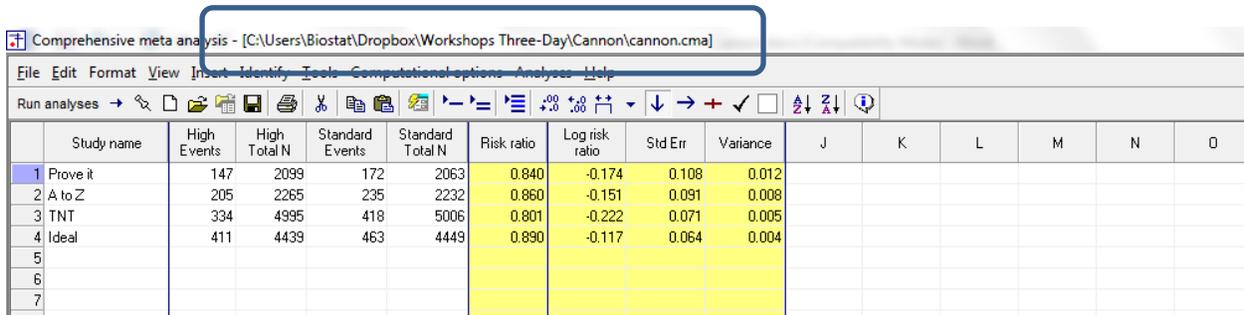
Study name	High Events	High Total N	Standard Events	Standard Total N	Risk ratio	Log risk ratio	Std Err	Variance
1 Prove it	147	2099	172	2063	0.840	-0.174	0.108	0.012
2 A to Z	205	2265	235	2232	0.860	-0.151	0.091	0.008
3 TNT	334	4995	418	5006	0.801	-0.222	0.071	0.005
4 Ideal	411	4439	463	4449	0.890	-0.117	0.064	0.004

Click File > Save As and save the file



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



By convention we've put the treated group (High) in the first two columns and the control (Standard) in the second two columns. Also by convention, we've defined "Event" as the presence of the outcome (Dead).

When we follow these conventions, and the outcome is a bad event (as it is here) if the treated group does better than the control, the risk ratio will be less than 1.

Therefore, in the present case, a risk ratio less than 1 indicates that High-Dose was associated with a decreased risk of a coronary event.

It's always a good idea to check at least one study and make sure that we have the direction right. For this purpose we'll use the third study (TNT).

Study name	High Events	High Total N	Standard Events	Standard Total N	Risk ratio	Log risk ratio	Std Err	Variance	J	K	L	M	N	O
1 Prove it	147	2099	172	2063	0.840	-0.174	0.108	0.012						
2 A to Z	205	2265	235	2232	0.860	-0.151	0.091	0.008						
3 TNT	334	4995	418	5006	0.801	-0.222	0.071	0.005						
4 Ideal	411	4439	463	4449	0.890	-0.117	0.064	0.004						

Both groups have approximately the same number of patients (about 5,000) but the number of events is lower in the High-dose group than in the Standard-Dose group (334 vs. 418). The risk ratio is less than 1 (0.801), which means that patients treated with High-Dose were less likely to die.

- To run the analysis, click [Run analysis]

Study name	High Events	High Total N	Standard Events	Standard Total N	Risk ratio	Log risk ratio	Std Err	Variance	J	K	L	M	N	O
1 Prove it	147	2099	172	2063	0.840	-0.174	0.108	0.012						
2 A to Z	205	2265	235	2232	0.860	-0.151	0.091	0.008						
3 TNT	334	4995	418	5006	0.801	-0.222	0.071	0.005						
4 Ideal	411	4439	463	4449	0.890	-0.117	0.064	0.004						

This is the basic analysis screen

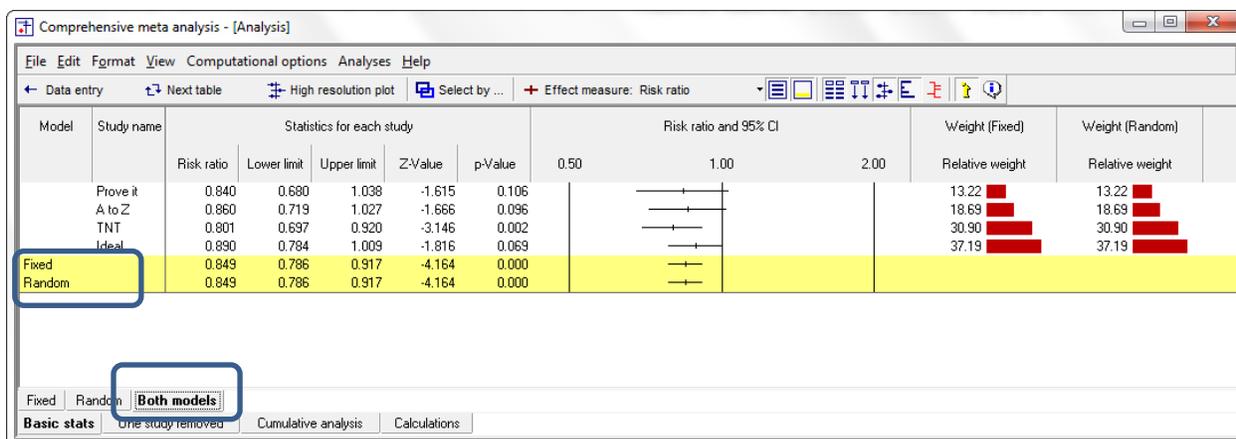
Initially, the program displays the fixed-effect analysis. This is indicated by the tab at the bottom and the label in the plot.



All four studies have risk ratios in the range of 0.80 to 0.90. Only one (TNT) is statistically significant. The effects seem to be reasonably consistent. The confidence interval for every study overlaps the mean.

Click [Both models]

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



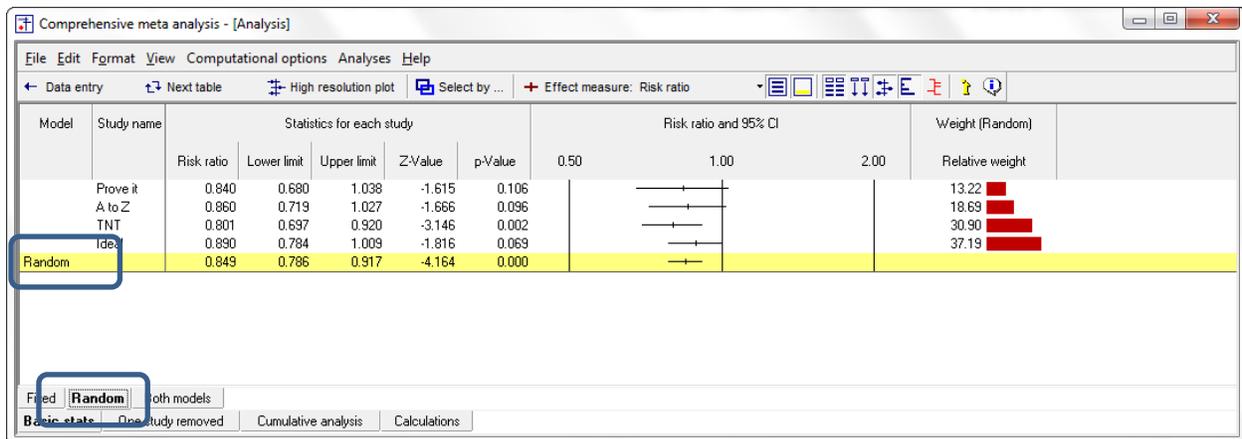
Under the fixed-effect model the pooled effect size is 0.849 with a confidence interval of 0.786 to 0.917. Under the random-effects model the pooled effect size is 0.849 with a confidence interval of 0.786 to 0.917.

- The fixed-effect model would be appropriate if all the studies were virtual replicates of each other, which may or may not be the case here. They may have patients varied in some ways.
- The random-effects model is appropriate because the studies may vary in ways that could impact the effect size.

While the two models yield identical results, 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

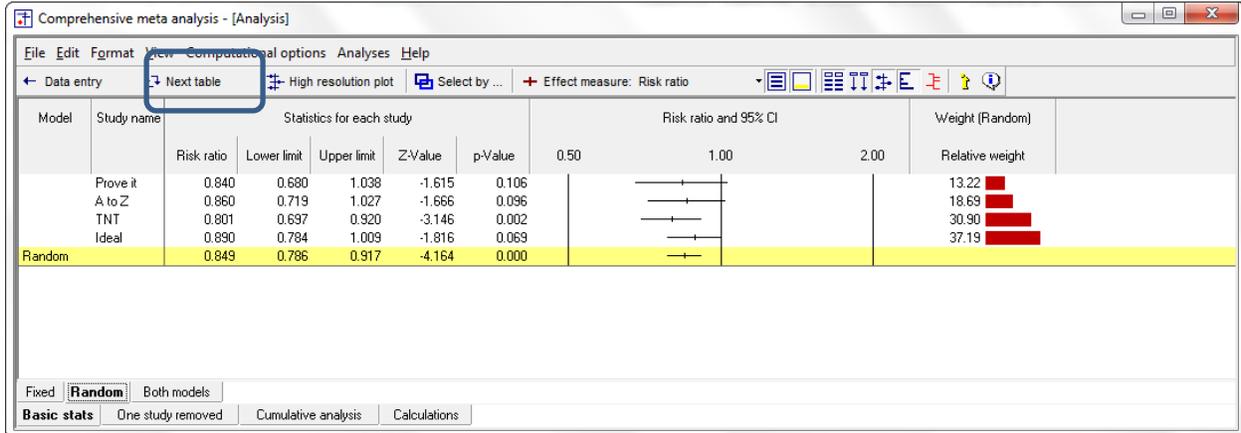
The plot now displays the random-effects analysis alone.



A quick view of the plot suggests the following

- Most of the studies show an advantage for the high-dose group, but only one is statistically significant
- The observed effects are pretty consistent
- The summary effect is 0.849 with a confidence interval of 0.786 to 0.917.
- The summary effect has a Z-value -4.164 a p -value of < 0.001 . We reject the null hypotheses that the true mean risk ratio is 1.0, and conclude that the risk of an event is lower in the high-dose group.

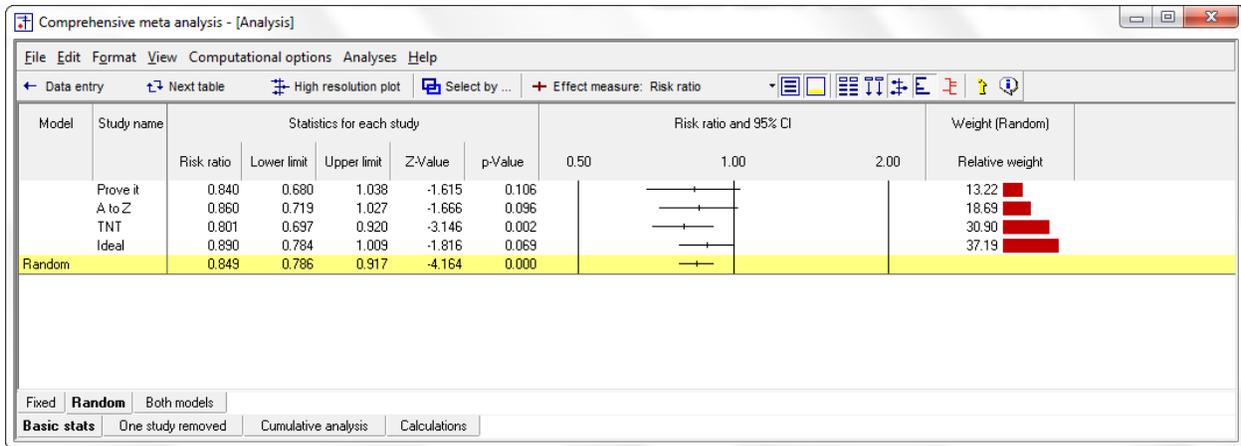
Click [Next table]



Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity			Tau-squared				
	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	4	0.849	0.786	0.917	-4.164	0.000	1.242	3	0.743	0.000	0.000	0.005	0.000	0.000
Random	4	0.849	0.786	0.917	-4.164	0.000								

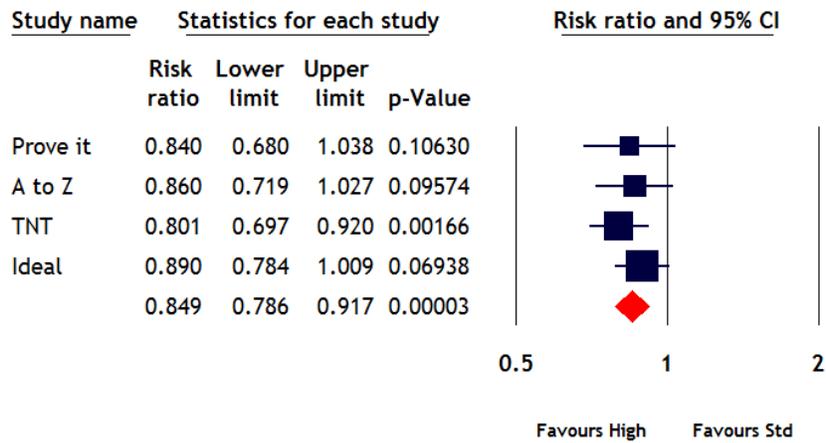
The statistics at the left duplicate those we saw on the prior screen.

- The summary effect is 0.849 with a confidence interval of 0.786 to 0.917.
- The summary effect has a Z-value -4.164 a p -value of < 0.001 . We reject the null hypotheses that the true mean risk ratio is 1.0, and conclude that the risk of death is lower in the high-dose group.
- The statistics at the upper right relate to the dispersion of effect sizes across studies. The Q -value is 1.242 with $df = 3$. 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).
- If all studies actually shared the same true effect size, the expected value of Q would be equal to df (which is 3). Here, Q is less than this value, and so there is no evidence of variance in true effects.
- I^2 is the proportion of the observed variance that reflects differences in true effects rather than sampling error. Since the variance in true effects is zero, I^2 must be zero.
- T^2 is the estimate of the between-study variance in true effects. T is the estimate of the between-study standard deviation in true effects. Since the variance in true effects is zero, both of these values must be zero. These value are both in log units.
- Click [Next table] to return to this screen



Click Hi-Resolution plot

Impact of Statin Dose on CV Events



Random-effects meta-analysis

High dose vs. standard dose of statins

Overview

The analysis included four studies, each of which compared patients who were randomly assigned to either a standard dose or a high dose of statins. The outcome was mortality or cardiovascular event, and the effect size was the risk ratio. The results of this analysis will be generalized to comparable studies, and so the random-effects model was employed for the analysis.

Is statin dose related to risk of a cardiovascular event?

The mean risk ratio is 0.849, which means that being assigned to a high dose rather than a standard dose of statins resulted in a 15% lower risk of a cardiovascular event. The confidence interval for the risk ratio is 0.786 to 0.917, which tells us that the mean risk ratio in the universe of comparable 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 -4.164 , with a corresponding p -value of < 0.001 . We can reject the null hypothesis that the risk of a cardiovascular event is the same in both groups, and conclude that the risk is lower in the high-dose group.

How much does the effect size vary across studies?

The Q -statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. If all studies shared the same effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). The Q -value is 1.242 with 3 degrees of freedom. Thus, the observed dispersion is actually less than we would expect by chance. It follows that there is no evidence that the true effect size varies from study to study. The I^2 statistic is 0%, which tells us that none of the variance in observed effects reflects variance in true effects – all of it is due to sampling error. The variance of true effects in log units (T^2) is 0.000, and the standard deviation of true effects in log units (T) is 0.000 [G].

The between-study variance is estimated as zero. While this is probably an underestimate, since the impact of this treatment almost certainly varies by population, we will assume that the variation in effects is minor. If this assumption is correct, the impact of the treatment for all comparable populations falls close to the mean effect size.