

Example name	Avandia
Effect size	Peto odds ratio
Analysis type	Multiple outcomes from same subjects
Level	Advanced

### Synopsis

Avandia a drug for treating diabetes, but these analyses focused on side-effects. The analysis uses data from 42 studies where patients were randomized to receive Avandia or Placebo. Each study reports data for two outcomes – (a) Myocardial infarction and (b) Death from Cardiovascular causes. The effect size is the Peto odds ratio.

We use this example to show

- How to enter data for multiple outcomes within a study
- How to perform the analysis for one outcome at a time

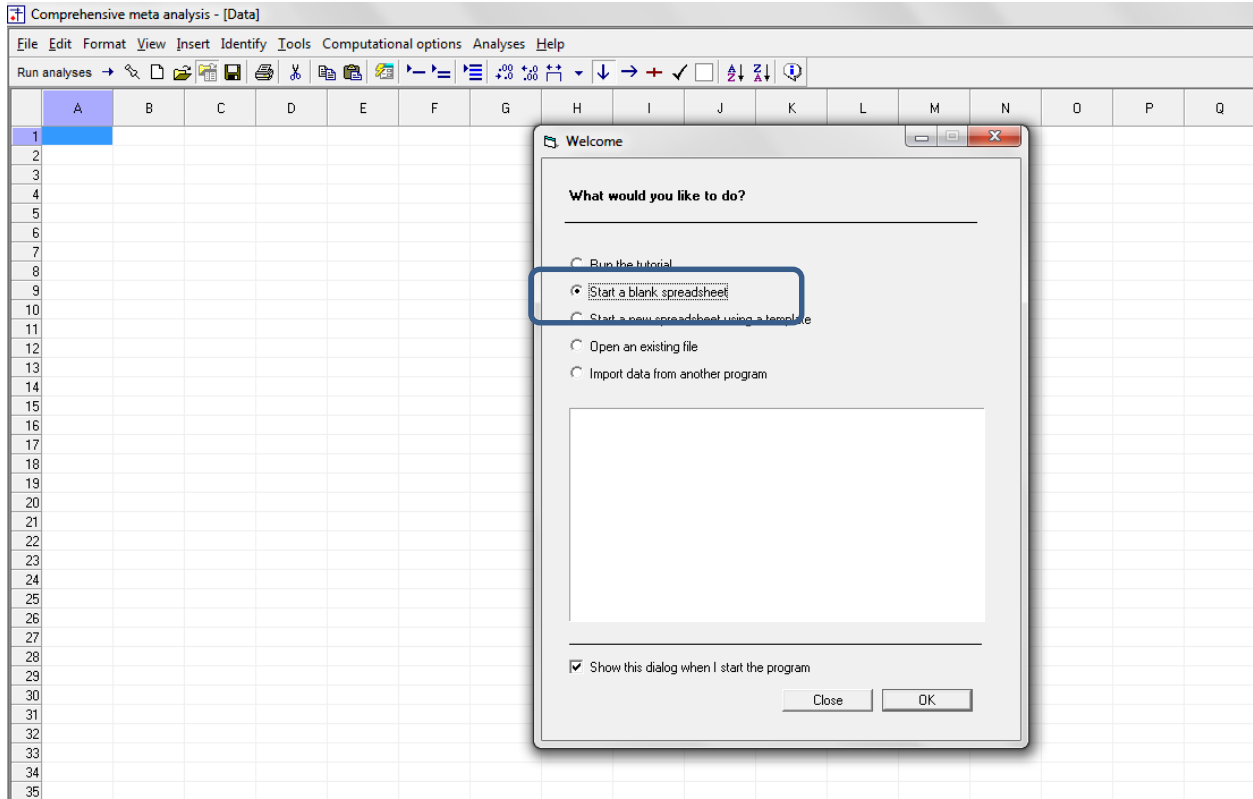
To open a CMA file > [Download and Save file](#) | [Start CMA](#) | [Open file from within CMA](#)

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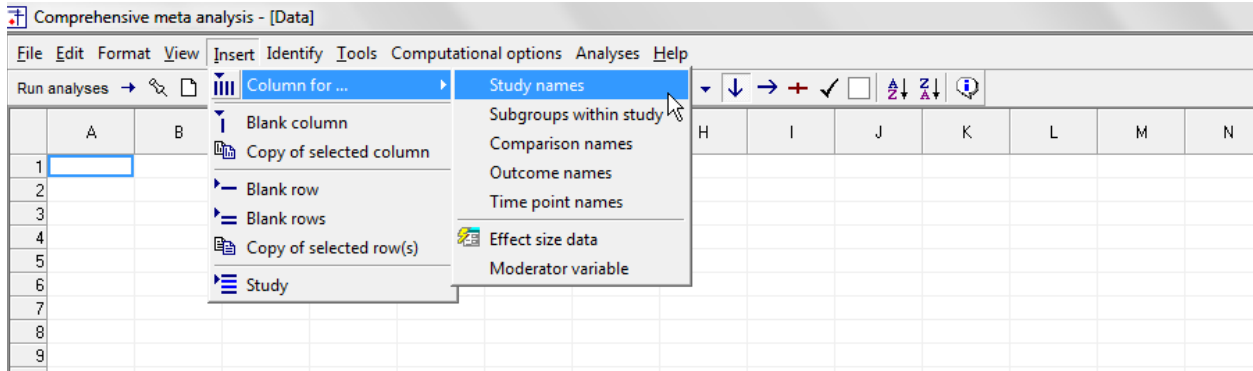
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Start the program

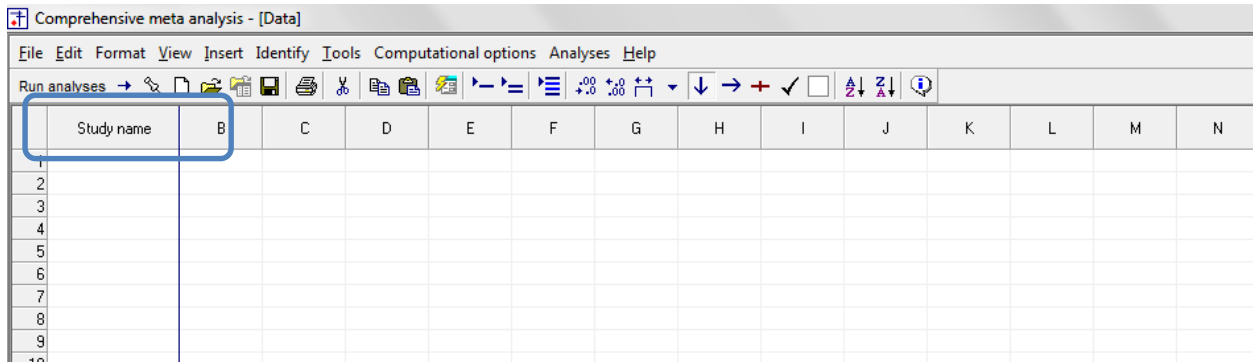
- Select the option [Start a blank spreadsheet]
- Click [OK]



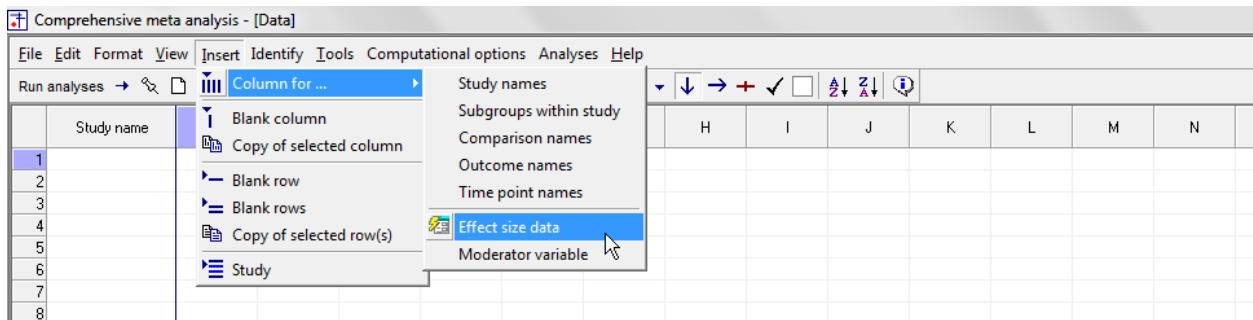
Click Insert > Column for > Study names



The screen should look like this

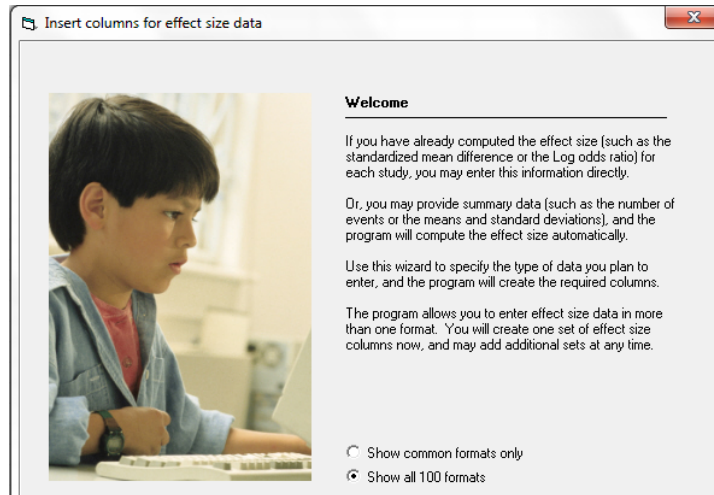


Click Insert > Column for > Effect size data

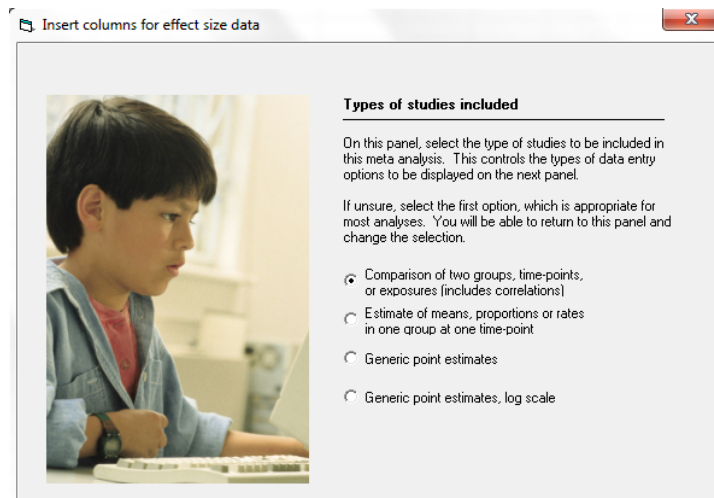


The program displays this wizard

Select [Show all 100 formats]  
Click [Next]

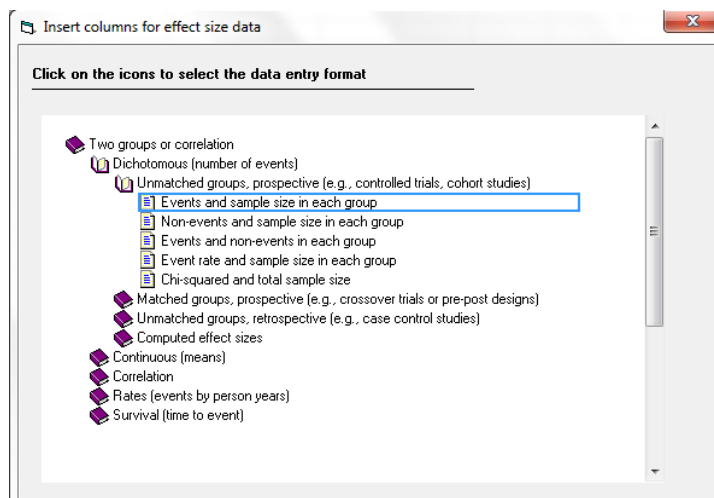


Select [Comparison of two groups...]  
Click [Next]



Drill down to

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



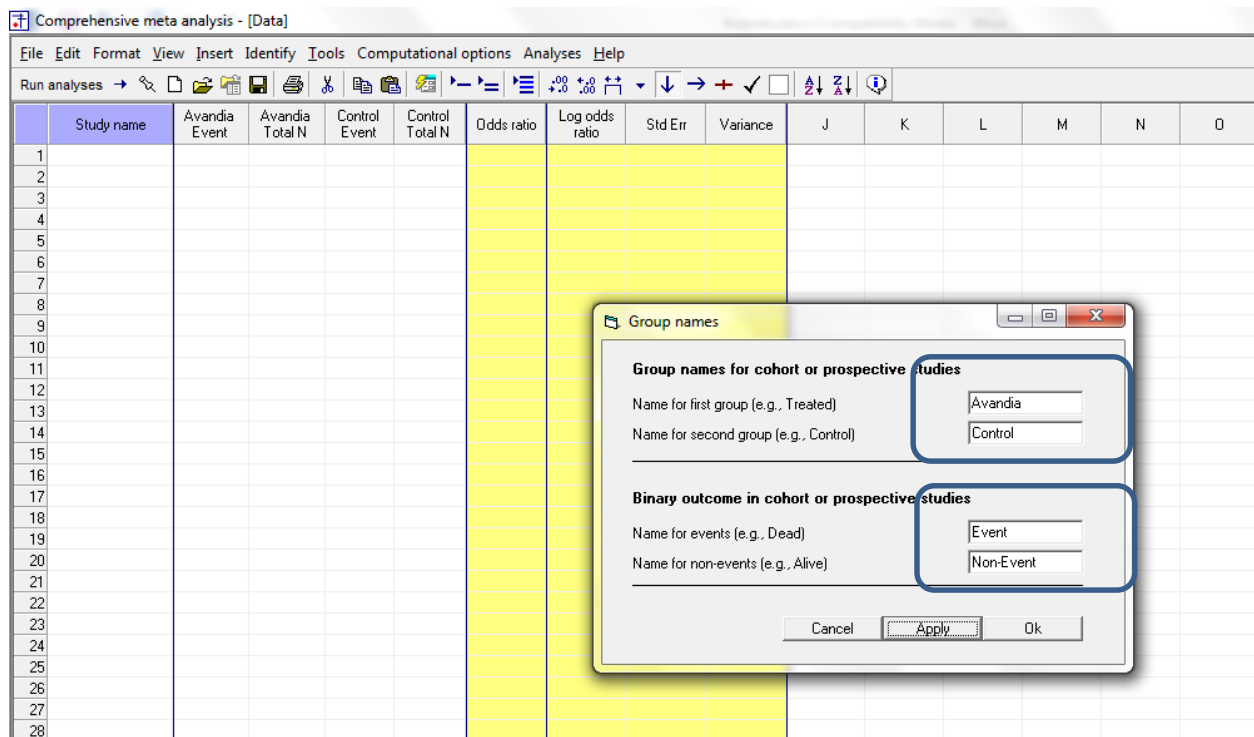
The program displays this wizard

Enter the following labels into the wizard

- First group > Avandia
- Second group > Control
- Events > Event
- Non-events > Non-event

(If all rows had the same outcome we would use “Dead” or “MI” as the label for Events. However, the event will vary (Dead or MI depending on the row) so we use the generic “Event” as the label here.

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

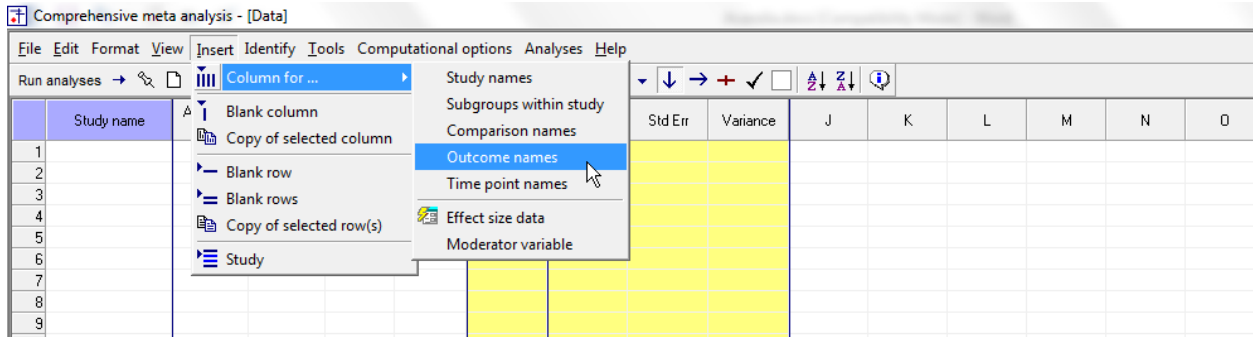


The screenshot shows a software window titled "Comprehensive meta analysis - [Data]". The window contains a menu bar (File, Edit, Format, View, Insert, Identify, Tools, Computational options, Analyses, Help) and a toolbar. Below the toolbar is a data grid with columns: Study name, Avandia Event, Avandia Total N, Control Event, Control Total N, Odds ratio, Log odds ratio, Std Err, Variance, J, K, L, M, N, O. The grid has rows numbered 1 to 28. A dialog box titled "Group names" is overlaid on the grid. 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 "Avandia" and "Name for second group (e.g., Control)" with the value "Control". 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 "Non-Event". The dialog box has "Cancel", "Apply", and "Ok" buttons at the bottom.

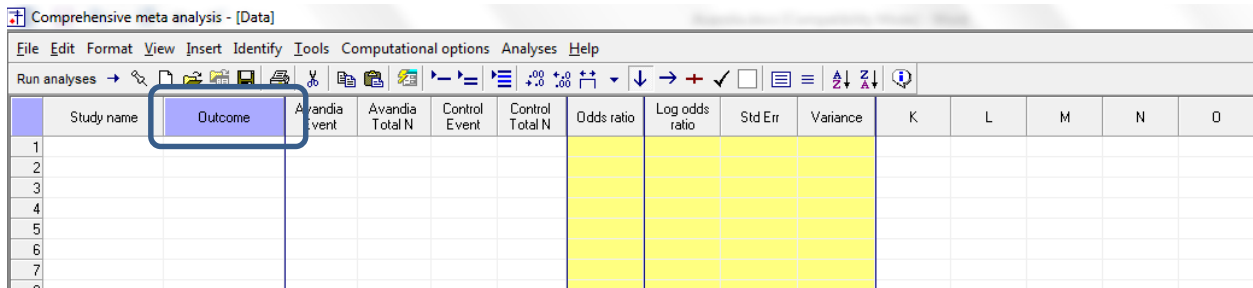
All studies will include data for two or more outcomes. These outcomes are based on THE SAME subjects.

The possible outcomes are MI and Death. We will be using multiple rows for each study, and need a column that will identify the outcome for each row.

Click Insert > Column for > Outcome names



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 “Avandia”
- Highlight all rows and columns as shown, and press CTRL-C to copy to clipboard

A1 : Study

	A	B	C	D	E	F	G	H
1	Study	Outcome	Avandia Events	Avandia N	CTRL Events	CTRL N		
2	49653/011	MI	2	357	0	176	1-Small	
3	49653/020	MI	2	391	1	207	1-Small	
4	49653/024	MI	1	774	1	185	1-Small	
5	49653/093	MI	0	213	1	109	1-Small	
6	49653/094	MI	1	232	0	116	1-Small	
7	100684	MI	0	43	1	47	1-Small	
8	49653/143	MI	1	121	0	124	1-Small	
9	49653/211	MI	5	110	2	114	1-Small	
10	49653/284	MI	1	382	0	384	1-Small	
11	712753/008	MI	1	284	0	135	1-Small	
12	AVM100264	MI	0	294	1	302	1-Small	
13	BRL 49653C/185	MI	2	563	0	142	1-Small	
14	BRL 49653/334	MI	2	278	1	279	1-Small	
15	BRL 49653/347	MI	2	418	0	212	1-Small	
16	49653/015	MI	2	395	1	198	1-Small	
17	49653/079	MI	1	203	1	106	1-Small	
18	49653/080	MI	1	104	2	99	1-Small	
19	49653/082	MI	2	212	0	107	1-Small	
20	49653/085	MI	3	138	1	139	1-Small	
21	49653/095	MI	0	196	0	96	1-Small	
22	49653/097	MI	0	122	1	120	1-Small	
23	49653/125	MI	0	175	1	173	1-Small	
24	49653/127	MI	1	56	0	58	1-Small	
25	49653/128	MI	1	39	0	38	1-Small	
26	49653/134	MI	0	561	2	276	1-Small	
27	49653/135	MI	2	116	3	111	1-Small	
28	49653/136	MI	1	148	0	143	1-Small	
29	49653/145	MI	1	231	0	242	1-Small	
30	49653/147	MI	1	89	0	88	1-Small	
31	49653/162	MI	1	168	0	172	1-Small	
32	49653/234	MI	0	116	0	61	1-Small	
33	49653/330	MI	1	1172	0	377	1-Small	
34	49653/331	MI	0	706	0	325	1-Small	
35	49653/137	MI	1	204	2	185	1-Small	
36	SB-712753/002	MI	1	288	0	280	1-Small	
37	SB-712753/003	MI	1	254	0	272	1-Small	
38	SB-712753/007	MI	1	314	0	154	1-Small	
39	SB-712753/009	MI	0	162	0	160	1-Small	
40	49653/132	MI	1	442	0	112	1-Small	
41	AVA100193	MI	1	394	0	124	1-Small	
42	DREAM	MI	15	2635	9	2634	3-DREAM	
43	ADOPT	MI	27	1456	41	2895	2-ADOPT	
44	49653/011	Dead	1	357	0	176	1-Small	
45	49653/020	Dead	0	391	0	207	1-Small	
46	49653/024	Dead	0	774	0	185	1-Small	
47	49653/093	Dead	0	213	0	109	1-Small	
48	49653/094	Dead	1	232	0	116	1-Small	
49	100684	Dead	0	43	0	47	1-Small	
50	49653/143	Dead	0	121	0	124	1-Small	



51	49653/211	Dead	3	110	2	114	1-Small
52	49653/284	Dead	0	382	0	384	1-Small
53	712753/008	Dead	0	284	0	135	1-Small
54	AVM100264	Dead	2	294	1	302	1-Small
55	BRL 49653C/185	Dead	0	563	0	142	1-Small
56	BRL 49653/334	Dead	0	278	1	279	1-Small
57	BRL 49653/347	Dead	0	418	0	212	1-Small
58	49653/015	Dead	2	395	0	198	1-Small
59	49653/079	Dead	1	203	1	106	1-Small
60	49653/080	Dead	0	104	0	99	1-Small
61	49653/082	Dead	1	212	0	107	1-Small
62	49653/085	Dead	1	138	0	139	1-Small
63	49653/095	Dead	1	196	0	96	1-Small
64	49653/097	Dead	0	122	0	120	1-Small
65	49653/125	Dead	0	175	0	173	1-Small
66	49653/127	Dead	0	56	0	58	1-Small
67	49653/128	Dead	0	39	0	38	1-Small
68	49653/134	Dead	1	561	0	276	1-Small
69	49653/135	Dead	2	116	1	111	1-Small
70	49653/136	Dead	2	148	0	143	1-Small
71	49653/145	Dead	1	231	0	242	1-Small
72	49653/147	Dead	0	89	0	88	1-Small
73	49653/162	Dead	1	168	0	172	1-Small
74	49653/234	Dead	0	116	0	61	1-Small
75	49653/330	Dead	1	1172	0	377	1-Small
76	49653/331	Dead	1	706	0	325	1-Small
77	49653/137	Dead	0	204	1	185	1-Small
78	SB-712753/002	Dead	1	288	0	280	1-Small
79	SB-712753/003	Dead	0	254	0	272	1-Small
80	SB-712753/007	Dead	0	314	0	154	1-Small
81	SB-712753/009	Dead	0	162	0	160	1-Small
82	49653/132	Dead	1	442	0	112	1-Small
83	AVA100193	Dead	1	394	0	124	1-Small
84	DREAM	Dead	12	2635	10	2634	3-DREAM
85	ADOPT	Dead	2	1456	5	2895	2-ADOPT

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

Click here

Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses → [Icons]

	Study name	Outcome	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1	Study	Outcome	Avandia	Avandia N	CTRL	CTRL N									
2	49653/011	MI	2	357	0	176	2.482	0.909	1.552	2.408					
3	49653/020	MI	2	391	1	207	1.059	0.057	1.228	1.507					
4	49653/024	MI	1	774	1	185	0.238	-1.435	1.417	2.007					
5	49653/093	MI	0	213	1	109	0.169	-1.775	1.637	2.681					
6	49653/094	MI	1	232	0	116	1.510	0.412	1.637	2.680					
7	100684	MI	0	43	1	47	0.356	-1.032	1.647	2.711					
8	49653/143	MI	1	121	0	124	3.100	1.131	1.638	2.683					
9	49653/211	MI	5	110	2	114	2.667	0.981	0.848	0.718					
10	49653/284	MI	1	382	0	384	3.024	1.106	1.635	2.672					
11	712753/008	MI	1	284	0	135	1.434	0.360	1.636	2.678					
12	AVM100264	MI	0	294	1	302	0.341	-1.075	1.635	2.673					
13	BRL 49653C/185	MI	2	563	0	142	1.289	0.238	1.552	2.409					
14	BRL 49653/334	MI	2	278	1	279	2.014	0.700	1.228	1.507					
15	BRL 49653/347	MI	2	418	0	212	2.551	0.936	1.551	2.407					
16	49653/015	MI	2	395	1	198	1.003	0.003	1.228	1.508					
17	49653/079	MI	1	203	1	106	0.520	-0.654	1.419	2.014					
18	49653/080	MI	1	104	2	99	0.471	-0.753	1.233	1.520					
19	49653/082	MI	2	212	0	107	2.553	0.937	1.554	2.414					
20	49653/085	MI	3	138	1	139	3.067	1.121	1.161	1.348					
21	49653/095	MI	0	196	0	96									
22	49653/097	MI	0	122	1	120	0.325	-1.123	1.638	2.683					
23	49653/125	MI	0	175	1	173	0.328	-1.116	1.637	2.678					
24	49653/127	MI	1	56	0	58	3.162	1.151	1.644	2.702					
25	49653/128	MI	1	39	0	38	3.000	1.099	1.649	2.719					
26	49653/134	MI	0	561	2	276	0.098	-2.325	1.551	2.405					
27	49653/135	MI	2	116	3	111	0.632	-0.460	0.923	0.951					
28	49653/136	MI	1	148	0	143	2.919	1.071	1.637	2.680					
29	49653/145	MI	1	231	0	242	3.156	1.149	1.636	2.675					
30	49653/147	MI	1	89	0	88	3.000	1.099	1.640	2.689					
31	49653/162	MI	1	168	0	172	3.090	1.128	1.637	2.678					
32	49653/234	MI	0	116	0	61									
33	49653/330	MI	1	1172	0	377	0.967	-0.034	1.634	2.670					

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

Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run: Bookmark data

Restore data

Column properties

1 Copy selection Ctrl+C

2 Copy with header

3 Copy entire grid

4 Paste Ctrl+V

5 Cut Ctrl+X

6 Delete Del

7 Delete row

8 Delete study

9 Delete column

10 Edit group names

	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1	2	357	0	176	2.482	0.909	1.552	2.408					
2	2	391	1	207	1.059	0.057	1.228	1.507					
3	1	774	1	185	0.238	-1.435	1.417	2.007					
4	0	213	1	109	0.169	-1.775	1.637	2.681					
5	1	232	0	116	1.510	0.412	1.637	2.680					
6	0	43	1	47	0.356	-1.032	1.647	2.711					
7	1	121	0	124	3.100	1.131	1.638	2.683					
8	5	110	2	114	2.667	0.981	0.848	0.718					
9	1	382	0	384	3.024	1.106	1.635	2.672					
10	1	284	0	135	1.434	0.360	1.636	2.678					
11	0	294	1	302	0.341	-1.075	1.635	2.673					
12	2	563	0	142	1.269	0.238	1.552	2.409					
13	2	278	1	279	2.014	0.700	1.228	1.507					
14	2	418	0	212	2.551	0.936	1.551	2.407					
15	BRL 49653/347	MI											
16	49653/0115	MI											

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	Outcome	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1	49653/011	MI	2	357	0	176	2.482	0.909	1.552	2.408					
2	49653/020	MI	2	391	1	207	1.059	0.057	1.228	1.507					
3	49653/024	MI	1	774	1	185	0.238	-1.435	1.417	2.007					
4	49653/093	MI	0	213	1	109	0.169	-1.775	1.637	2.681					
5	49653/094	MI	1	232	0	116	1.510	0.412	1.637	2.680					
6	100684	MI	0	43	1	47	0.356	-1.032	1.647	2.711					
7	49653/143	MI	1	121	0	124	3.100	1.131	1.638	2.683					
8	49653/211	MI	5	110	2	114	2.667	0.981	0.848	0.718					
9	49653/284	MI	1	382	0	384	3.024	1.106	1.635	2.672					
10	712753/008	MI	1	284	0	135	1.434	0.360	1.636	2.678					
11	AVM100264	MI	0	294	1	302	0.341	-1.075	1.635	2.673					
12	BRL 49653C/185	MI	2	563	0	142	1.269	0.238	1.552	2.409					
13	BRL 49653/334	MI	2	278	1	279	2.014	0.700	1.228	1.507					
14	BRL 49653/347	MI	2	418	0	212	2.551	0.936	1.551	2.407					

Click File > Save As and save the file

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

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

	Study name	Outcome	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1	49653/011	MI	2	357	0	176	2.482	0.909	1.552	2.408					
2	49653/020	MI	2	391	1	207	1.059	0.057	1.228	1.507					
3	49653/024	MI	1	774	1	185	0.238	-1.435	1.417	2.007					
4	49653/093	MI	0	213	1	109	0.169	-1.775	1.637	2.681					
5	49653/094	MI	1	232	0	116	1.510	0.412	1.637	2.680					
6	100684	MI	0	43	1	47	0.356	-1.032	1.647	2.711					
7	49653/143	MI	1	121	0	124	3.100	1.131	1.638	2.683					
8	49653/211	MI	5	110	2	114	2.667	0.981	0.848	0.718					
9	49653/284	MI	1	382	0	384	3.024	1.106	1.635	2.672					
10	712753/008	MI	1	284	0	135	1.434	0.360	1.636	2.678					
11	AVM100264	MI	0	294	1	302	0.341	-1.075	1.635	2.673					
12	BRL 49653C/185	MI	2	563	0	142	1.269	0.238	1.552	2.409					
13	BRL 49653/334	MI	2	278	1	279	2.014	0.700	1.228	1.507					
14	BRL 49653/347	MI	2	418	0	212	2.551	0.936	1.551	2.407					

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

Comprehensive meta analysis - [C:\Users\Biostat\Dropbox\Workshops Three-Day\Avandia\Avandia.cma]															
File Edit Format View Insert Identify Tools Computational options Analyses Help															
Run analyses →															
	Study name	Outcome	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1	49653/011	MI	2	357	0	176	2.482	0.909	1.552	2.408					
2	49653/020	MI	2	391	1	207	1.059	0.057	1.228	1.507					
3	49653/024	MI	1	774	1	185	0.238	-1.435	1.417	2.007					
4	49653/093	MI	0	213	1	109	0.169	-1.775	1.637	2.681					
5	49653/094	MI	1	232	0	116	1.510	0.412	1.637	2.680					
6	100684	MI	0	43	1	47	0.356	-1.032	1.647	2.711					
7	49653/143	MI	1	121	0	124	3.100	1.131	1.638	2.683					
8	49653/211	MI	5	110	2	114	2.667	0.981	0.848	0.718					
9	49653/284	MI	1	382	0	384	3.024	1.106	1.635	2.672					
10	712753/008	MI	1	284	0	135	1.434	0.360	1.636	2.678					
11	AVM100264	MI	0	294	1	302	0.341	-1.075	1.635	2.673					
12	BRL 49653C/185	MI	2	563	0	142	1.269	0.238	1.552	2.409					

- Click on the Header for the Study column
- Click Sort A-Z
- Click the Merge Rows icon

Comprehensive meta analysis - [CAUsers\Biostat\Dropbox\Workshops Three-Day\Avandia\Avandia.cma]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses → [Icons]

Stud	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1 49653/0	2	357	0	176	2.482	0.909	1.552	2.408					
2 49653/0	2	391	1	207	1.059	0.057	1.228	1.507					
3 49653/0	1	774	1	185	0.238	-1.435	1.417	2.007					
4 49653/093 MI	0	213	1	109	0.169	-1.775	1.637	2.681					
5 49653/094 MI	1	232	0	116	1.510	0.412	1.637	2.680					
6 100684 MI	0	43	1	47	0.356	-1.032	1.647	2.711					
7 49653/143 MI	1	121	0	124	3.100	1.131	1.638	2.683					
8 49653/211 MI	5	110	2	114	2.667	0.981	0.848	0.718					
9 49653/284 MI	1	382	0	384	3.024	1.106	1.635	2.672					
10 712753/008 MI	1	284	0	135	1.434	0.360	1.636	2.678					
11 AVM100264 MI	0	294	1	302	0.341	-1.075	1.635	2.673					

Comprehensive meta analysis - [CAUsers\Biostat\Dropbox\Workshops Three-Day\Avandia\Avandia.cma]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses → [Icons]

Study name	Outcome	Avandia Event	Avandia Total N	Control Event	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	K	L	M	N	O
1 100684	MI	0	43	1	47	0.356	-1.032	1.647	2.711					
2	Dead	0	43	0	47									
3	MI	2	357	0	176	2.482	0.909	1.552	2.408					
4	Dead	1	357	0	176	1.485	0.396	1.636	2.675					
5	MI	2	395	1	198	1.003	0.003	1.228	1.508					
6	Dead	2	395	0	198	2.522	0.925	1.552	2.408					
7	MI	2	391	1	207	1.059	0.057	1.228	1.507					
8	Dead	0	391	0	207									
9	MI	1	774	1	185	0.238	-1.435	1.417	2.007					
10	Dead	0	774	0	185									
11	MI	1	203	1	106	0.520	-0.654	1.419	2.014					
12	Dead	1	203	1	106	0.520	-0.654	1.419	2.014					
13	MI	1	104	2	99	0.471	-0.753	1.233	1.520					
14	Dead	0	104	0	99									

- To run the analysis, click [Run analysis]

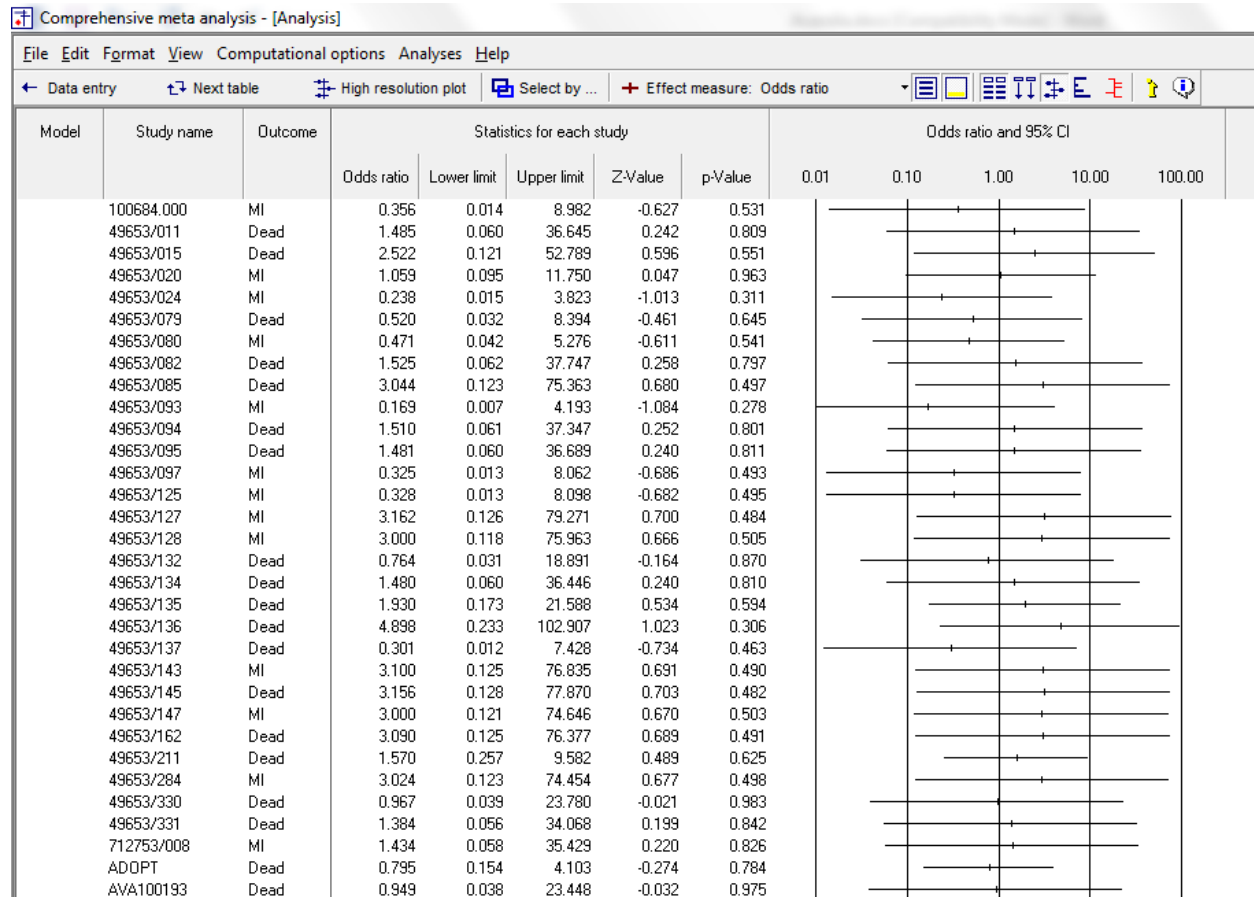
The issue we need to address when working with multiple outcomes is the fact that the outcomes are not independent of each other, and therefore do not contain independent information

If we compute an effect size for MI only, or for Death only, or for MI and Death separately, the effect size and its variance are valid. But, if we compute an effect size based on MI and Death, a variance that is based on the combined sample size (counting each subject twice) overstates the amount of information contained in the data, over-estimates the precision of the summary effect and under-estimates the variance.

We can see how this plays out in the analyses that follow.

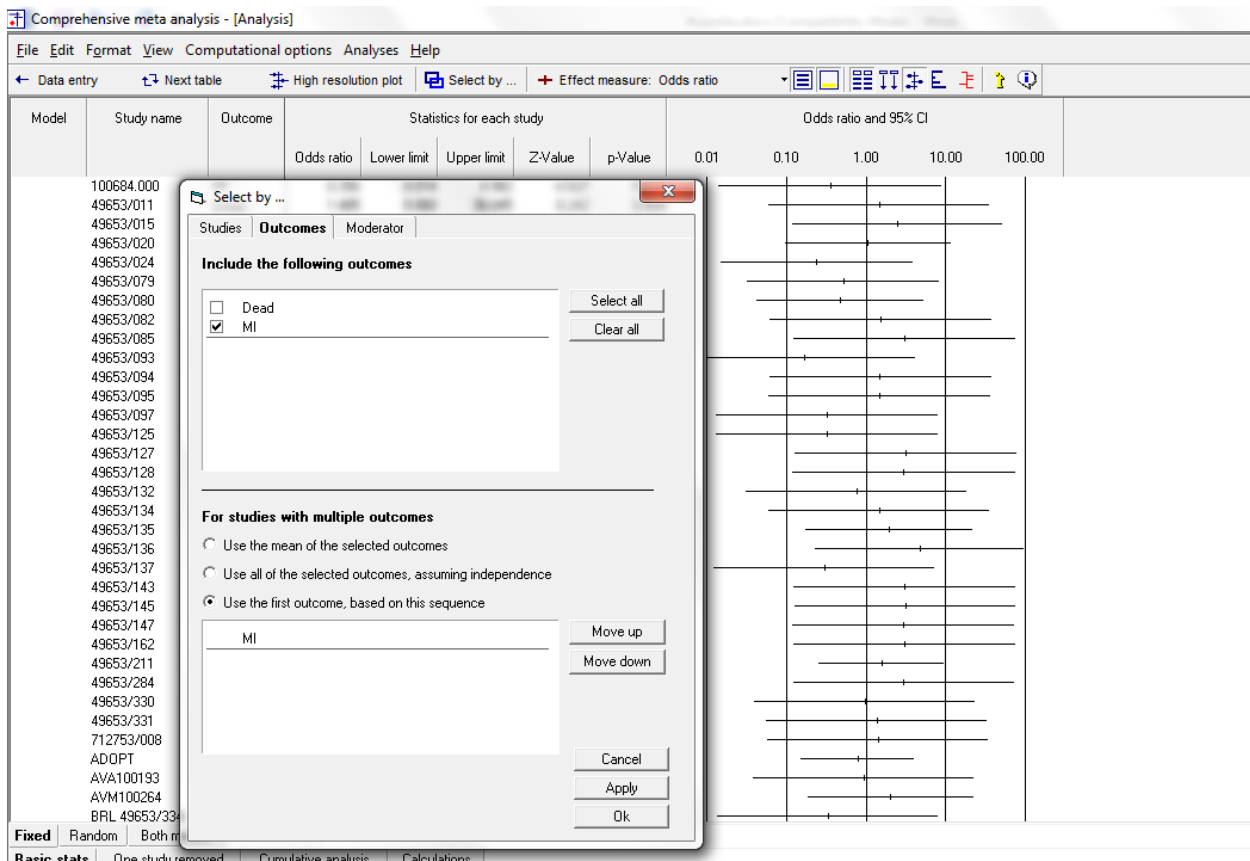
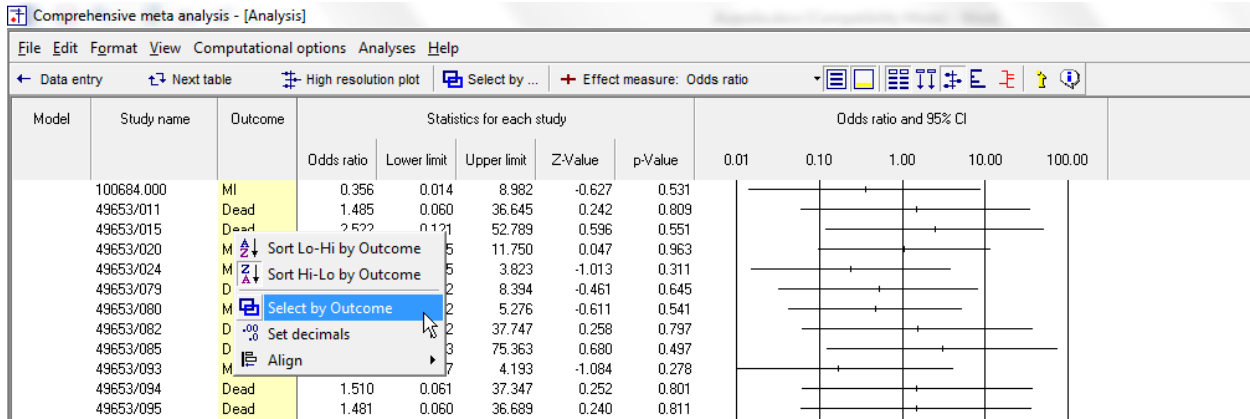
By default the program picks one outcome for each study. Since each study had a row for Death and a row for MI, the program would normally pick the first (Death) for each.

However, some studies have zero outcomes in both groups for Death. When this happens, the program will pick MI. Therefore, the initial screen looks like this. Each study is included only once, but the analysis includes MI for some studies and Death for others.



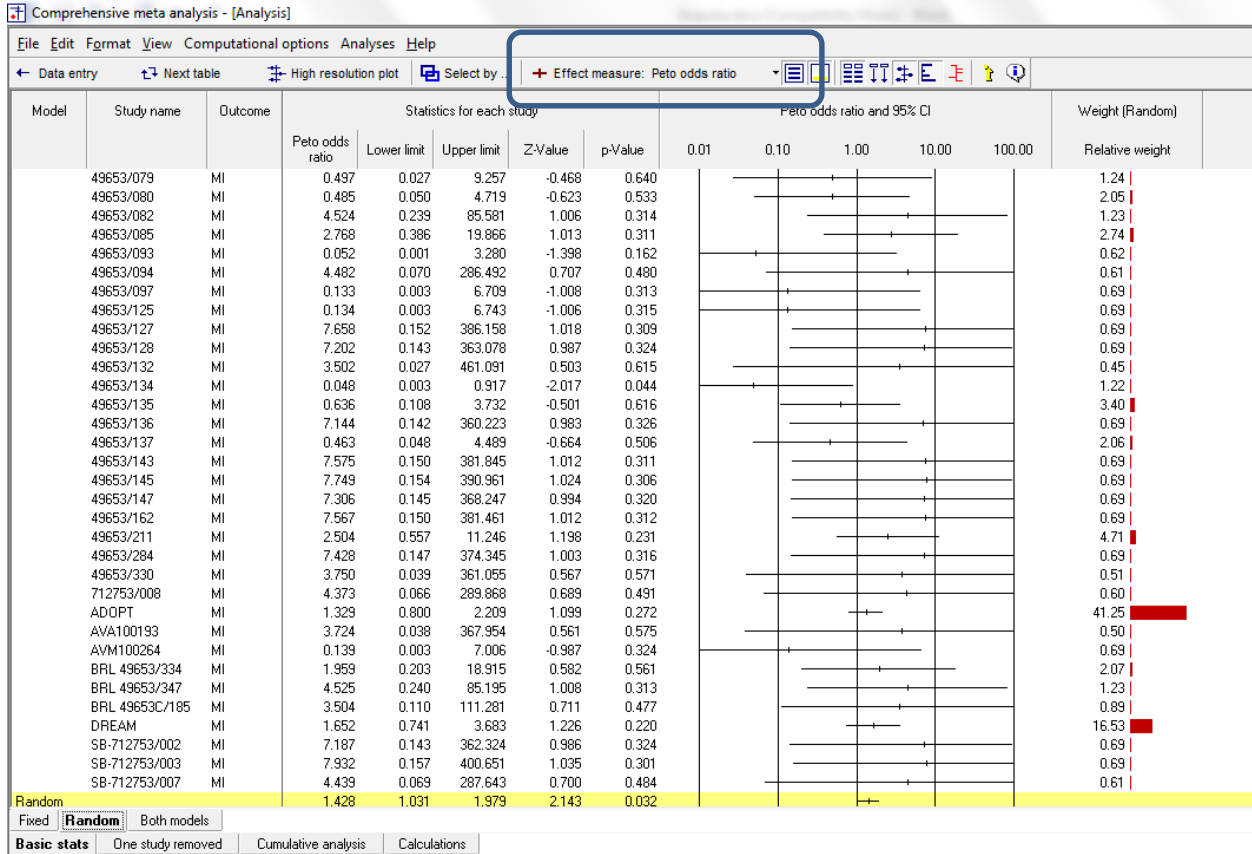
We can run an analysis for MI only (that is, selecting MI for studies that report an effect size for MI, and omitting studies that do not)

- Right-click on the Outcome column and click [Select by outcome]
- De-Select Death

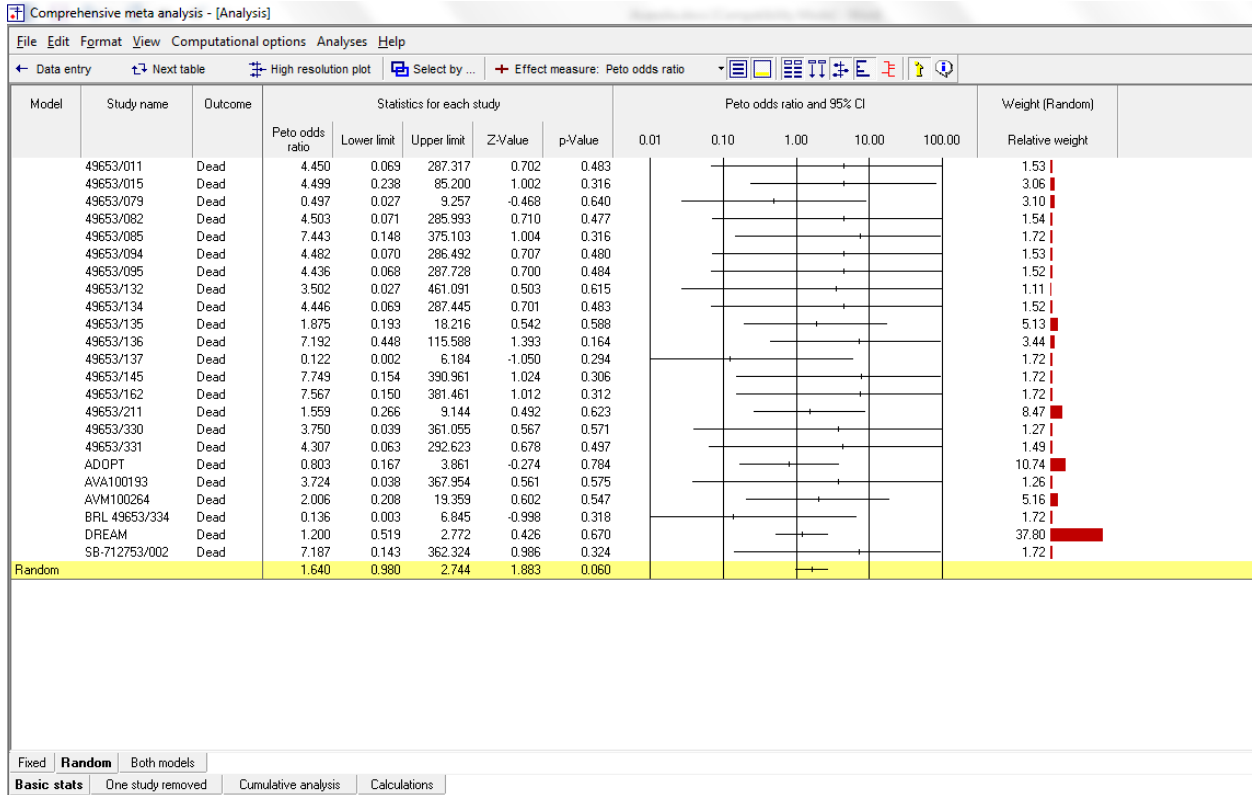




# Select Peto Odds ratio as the Index



- Right-click on Outcome
- Select Dead only



## Summary

This analysis uses data from 42 studies where patients were randomized to receive Avandia or Placebo. Avandia is used to treat diabetes, but these analyses focused on side-effects. Each study reports data for two outcomes – (a) Myocardial infarction and (b) Death from Cardiovascular causes. The effect size is the Peto odds ratio.

### **Is Avandia related to the risk of MI?**

The Peto odds ratio is 1.428 with a CI of 1.031 to 1.979. The Z-value for a test of the null is 2.143 with a corresponding p-value of 0.032.

### **Is Avandia related to the risk of Death?**

The Peto odds ratio is 1.640 with a CI of 0.980 to 2.744. The Z-value for a test of the null is 1.883 with a corresponding p-value of 0.060.