Example name	Caffeine by subgroups
Effect size	Risk ratio
Analysis type	Subgroups analysis, Meta-Regression
Level	Intermediate

Synopsis

This analysis includes 25 studies where patients were randomized to receive either analgesic alone or analgesic plus caffeine. Outcome was the proportion of patients who reported a "good" level of pain relief. The effect size was the risk ratio.

For the 25 studies there was clear evidence that patients treated with caffeine were about 10% more likely to report success as compared with the control group. However, there was substantial dispersion in the effect size. The true effect size probably ranges from a risk ratio of 1.02 to 1.22. We ran additional analyses to see if this variation could be explained by various factors.

We used subgroup analyses to compare the effect size in studies –

- That employed a low dose, moderate dose, or high dose of caffeine
- Where the basic analgesic was Ibuprofen vs. studies where it was Paracetamol
- Where the pain was from headache vs. studies where the pain was from surgery

We use this example to show

- How to enter data from 2x2 tables
- How to perform a basic analysis
- How to interpret statistics for heterogeneity
- How to estimate the dispersion in true effects
- How to compare the effect size in different subgroups using subgroup analysis
- How to compare the effect size in different subgroups using meta-regression

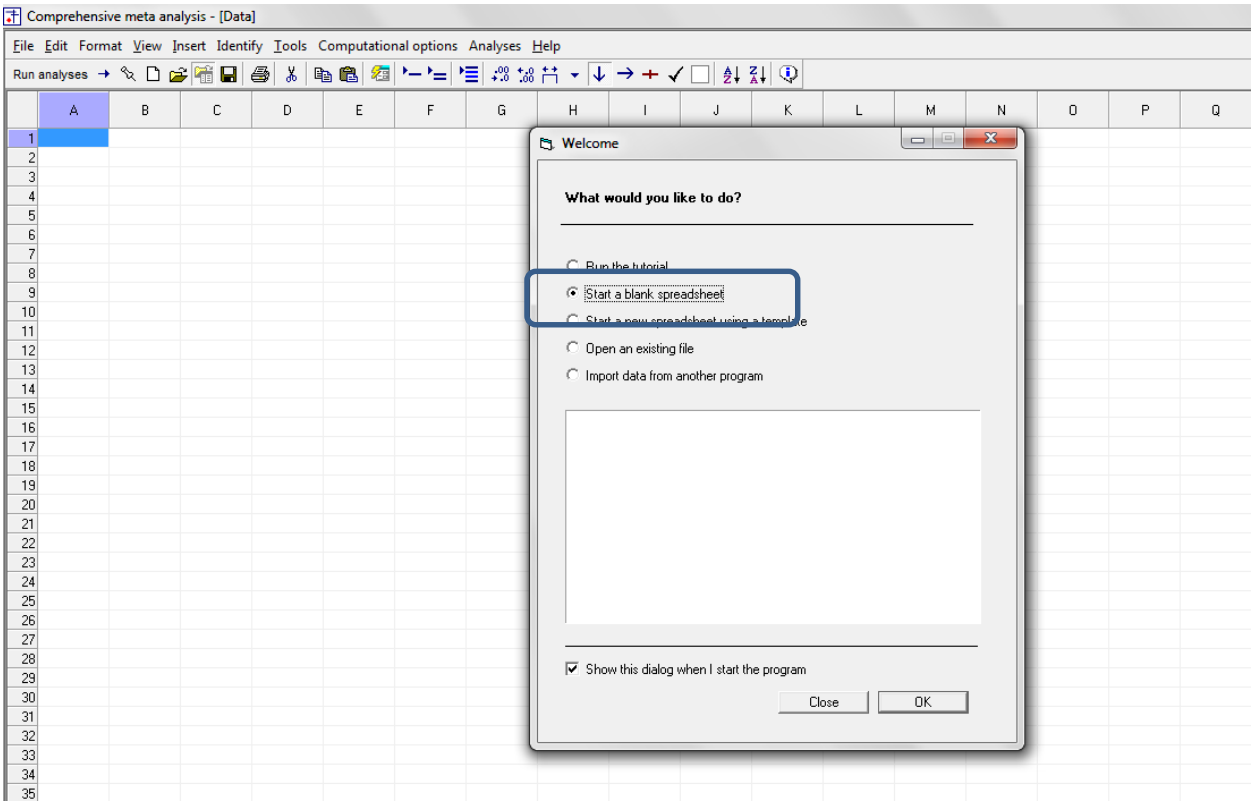
To open a CMA file > Download and Save file | Start CMA | Open file from within CMA

Download CMA file for computers that use a period to indicate decimals
Download CMA file for computers that use a comma to indicate decimals

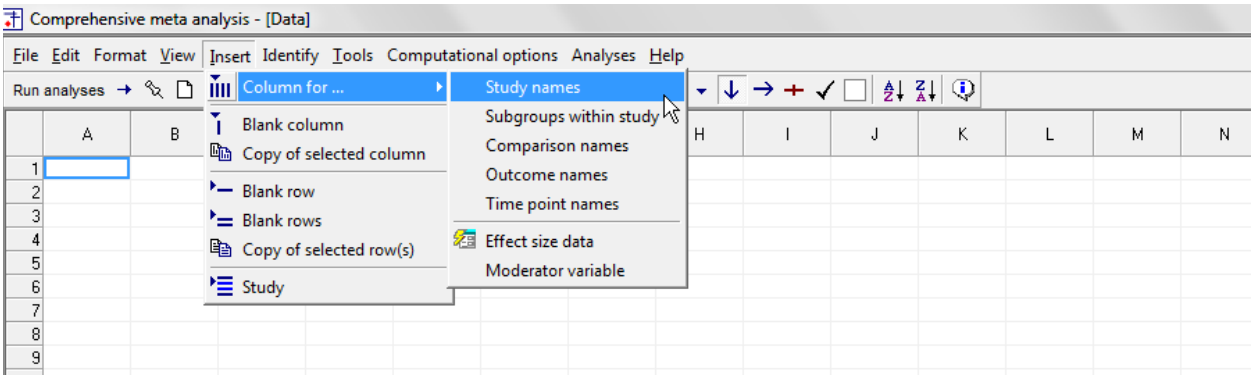
Download this PDF
Download data in Excel
Download trial of CMA

Start the program

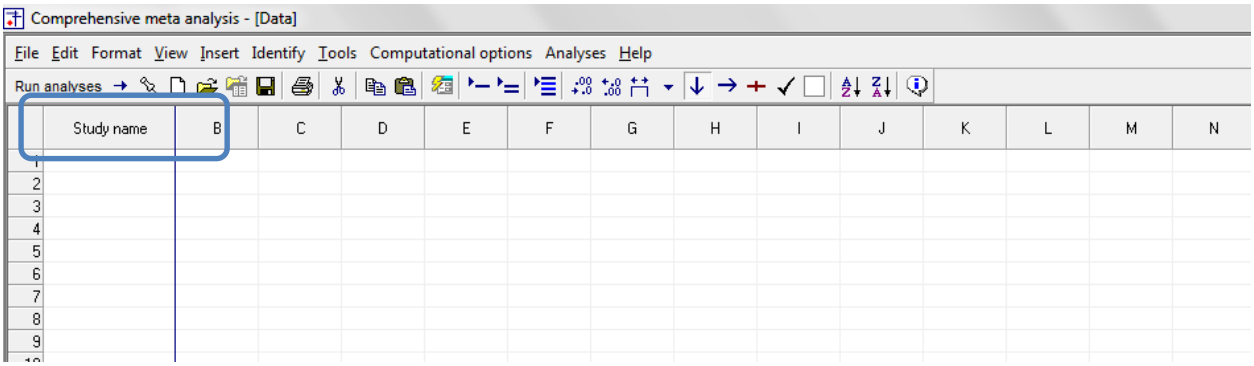
- Select the option [Start a blank spreadsheet]
- Click [Ok]



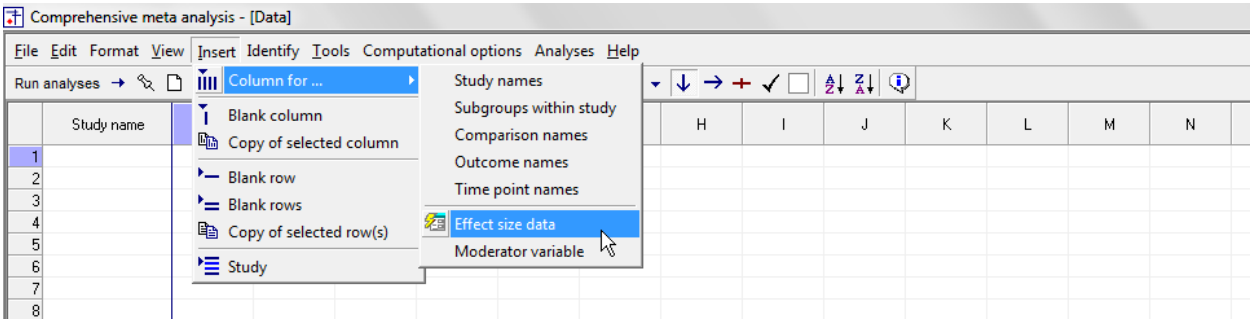
Click Insert > Column for > Study names



The screen should look like this

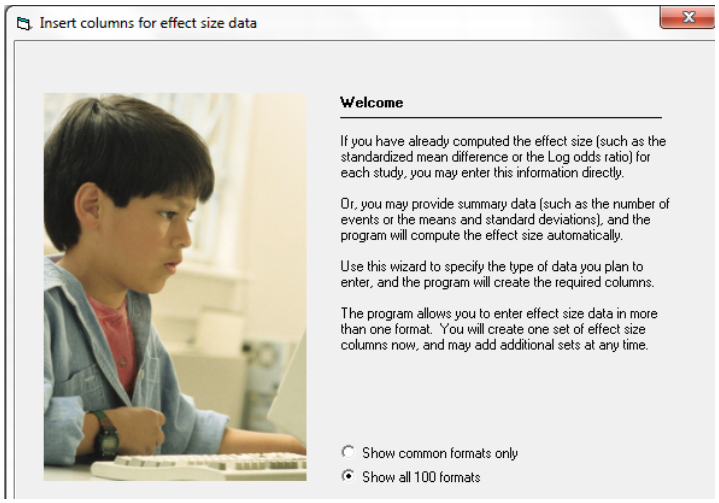


Click Insert > Column for > Effect size data

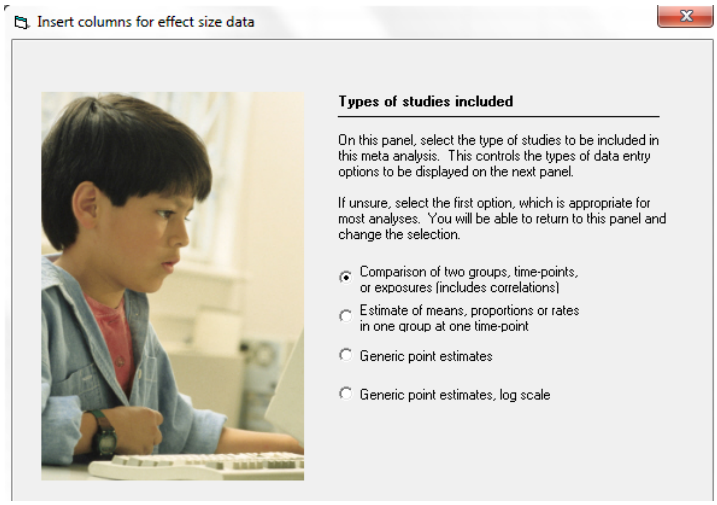


The program displays this wizard

Select [Show all 100 formats]
Click [Next]

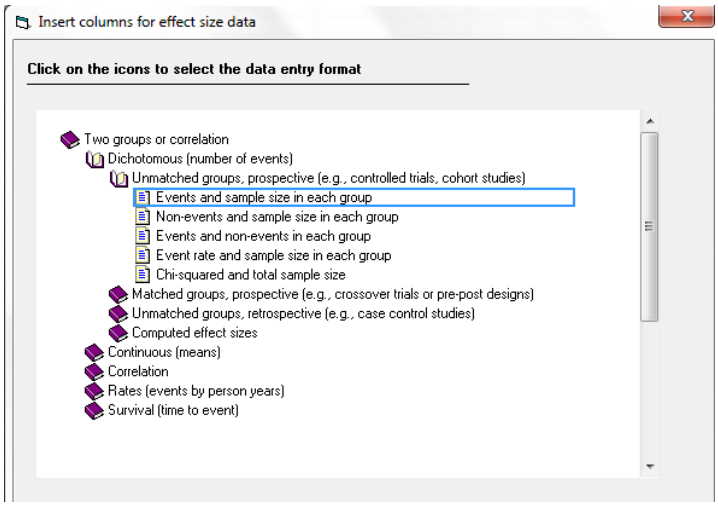


Select [Comparison of two groups…]
Click [Next]



Drill down to

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

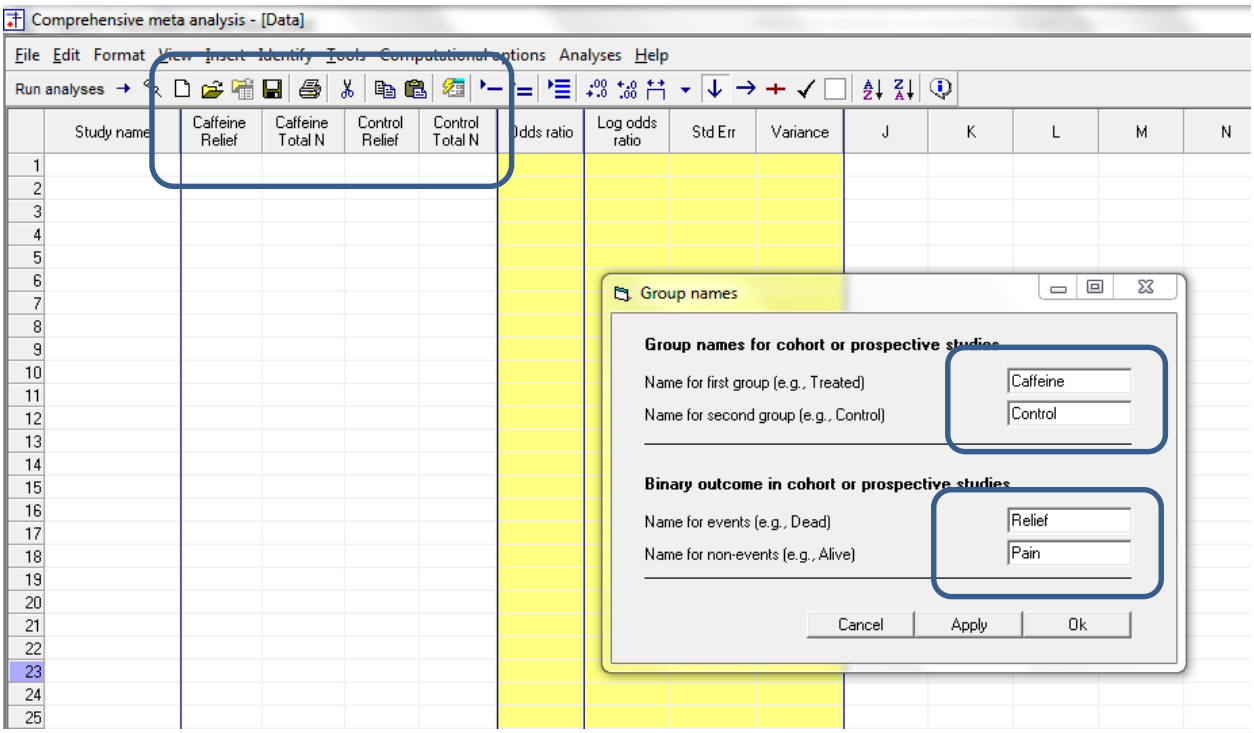


The program displays this wizard

Enter the following labels into the wizard

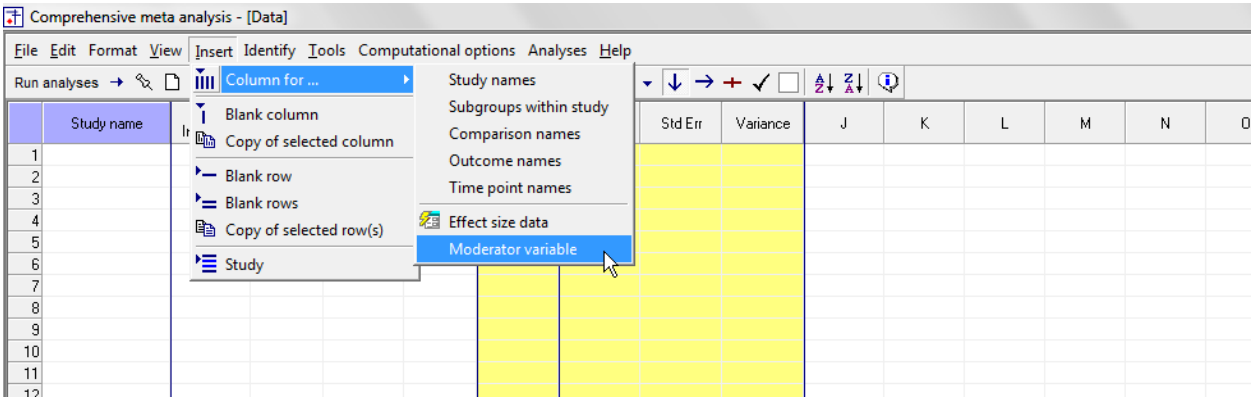
- First group > Caffeine
- Second group > Control
- Name for events > Relief
- Name for non-events > Pain

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

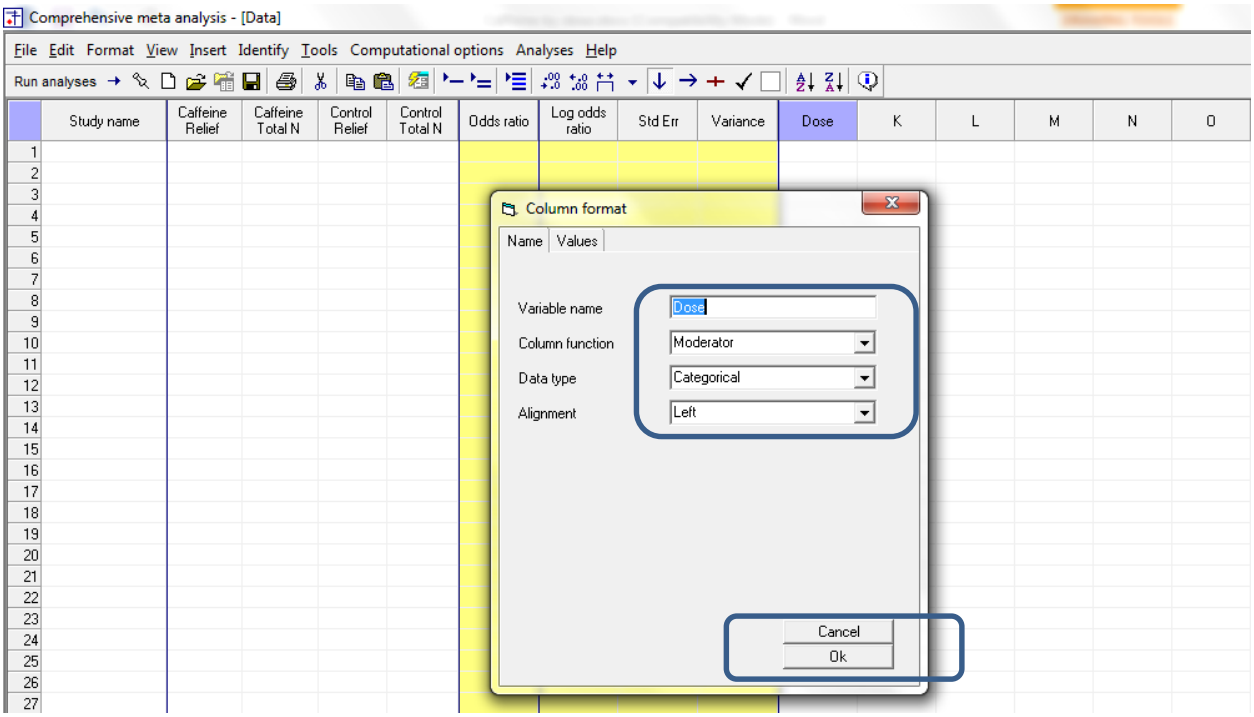


We need to add a column for the moderator, Dose

Click Insert > Column for > Moderator variable



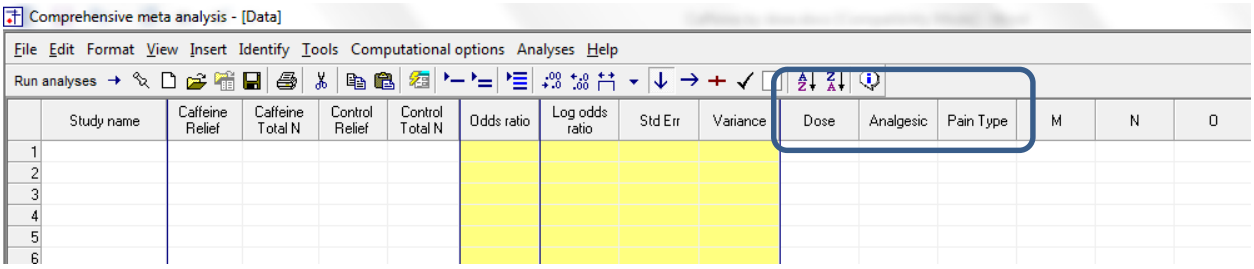
- Name the moderator > Dose
- Set the data type to Categorical
- Click Ok



- Insert a column for > Moderator > Categorical with the name Analgesic. This will be used to code the type of medication (e.g. ibuprofen)

- Insert a column for > Moderator > Categorical with the name Pain Type. This will be used to code the type of pain (e.g. post-surgical)

The screen should look like this

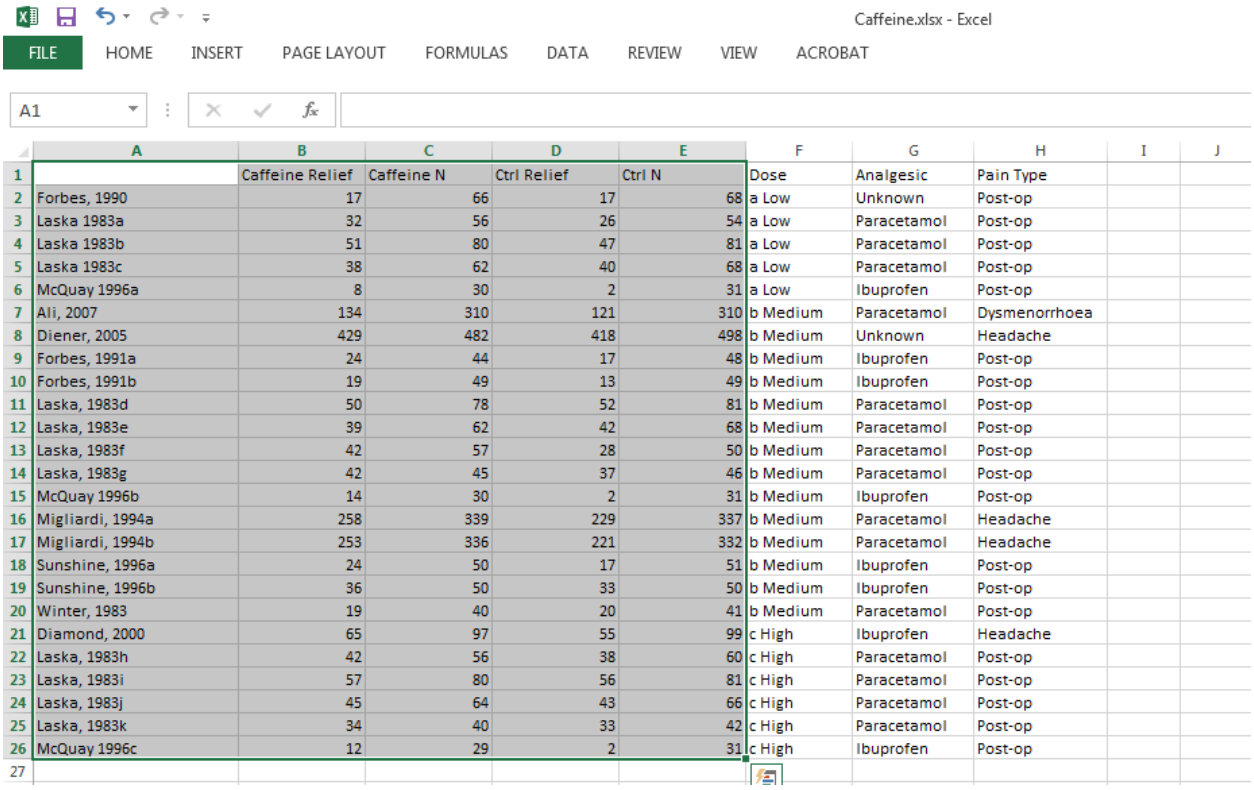


There are three options at this point

- Enter the data directly into CMA
- – or – Open the CMA data file “Caffeine.cma”
- – or – Copy the data from Excel“Caffeine.xls”

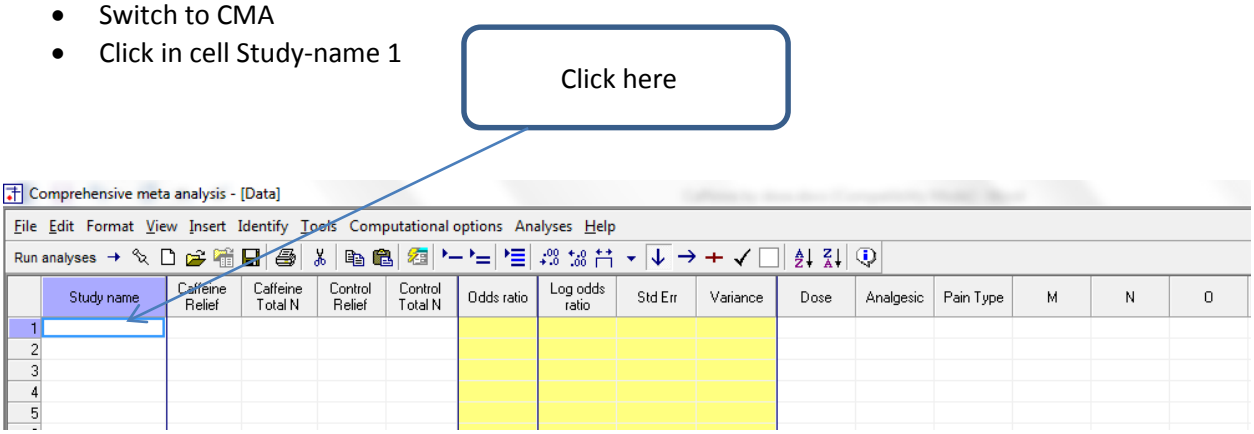
Here, we’ll show how to copy the data from Excel

- 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



	A	B	C	D	E	F	G	H	I	J
1		Caffeine Relief	Caffeine N	Ctrl Relief	Ctrl N	Dose	Analgesic	Pain Type		
2	Forbes, 1990	17	66	17	68	a Low	Unknown	Post-op		
3	Laska 1983a	32	56	26	54	a Low	Paracetamol	Post-op		
4	Laska 1983b	51	80	47	81	a Low	Paracetamol	Post-op		
5	Laska 1983c	38	62	40	68	a Low	Paracetamol	Post-op		
6	McQuay 1996a	8	30	2	31	a Low	Ibuprofen	Post-op		
7	Ali, 2007	134	310	121	310	b Medium	Paracetamol	Dysmenorrhoea		
8	Diener, 2005	429	482	418	498	b Medium	Unknown	Headache		
9	Forbes, 1991a	24	44	17	48	b Medium	Ibuprofen	Post-op		
10	Forbes, 1991b	19	49	13	49	b Medium	Ibuprofen	Post-op		
11	Laska, 1983d	50	78	52	81	b Medium	Paracetamol	Post-op		
12	Laska, 1983e	39	62	42	68	b Medium	Paracetamol	Post-op		
13	Laska, 1983f	42	57	28	50	b Medium	Paracetamol	Post-op		
14	Laska, 1983g	42	45	37	46	b Medium	Paracetamol	Post-op		
15	McQuay 1996b	14	30	2	31	b Medium	Ibuprofen	Post-op		
16	Migliardi, 1994a	258	339	229	337	b Medium	Paracetamol	Headache		
17	Migliardi, 1994b	253	336	221	332	b Medium	Paracetamol	Headache		
18	Sunshine, 1996a	24	50	17	51	b Medium	Ibuprofen	Post-op		
19	Sunshine, 1996b	36	50	33	50	b Medium	Ibuprofen	Post-op		
20	Winter, 1983	19	40	20	41	b Medium	Paracetamol	Post-op		
21	Diamond, 2000	65	97	55	99	c High	Ibuprofen	Headache		
22	Laska, 1983h	42	56	38	60	c High	Paracetamol	Post-op		
23	Laska, 1983i	57	80	56	81	c High	Paracetamol	Post-op		
24	Laska, 1983j	45	64	43	66	c High	Paracetamol	Post-op		
25	Laska, 1983k	34	40	33	42	c High	Paracetamol	Post-op		
26	McQuay 1996c	12	29	2	31	c High	Ibuprofen	Post-op		
27										

- Switch to CMA
- Click in cell Study-name 1



- Press [CTRL-V] to paste the data
- The screen should look like this

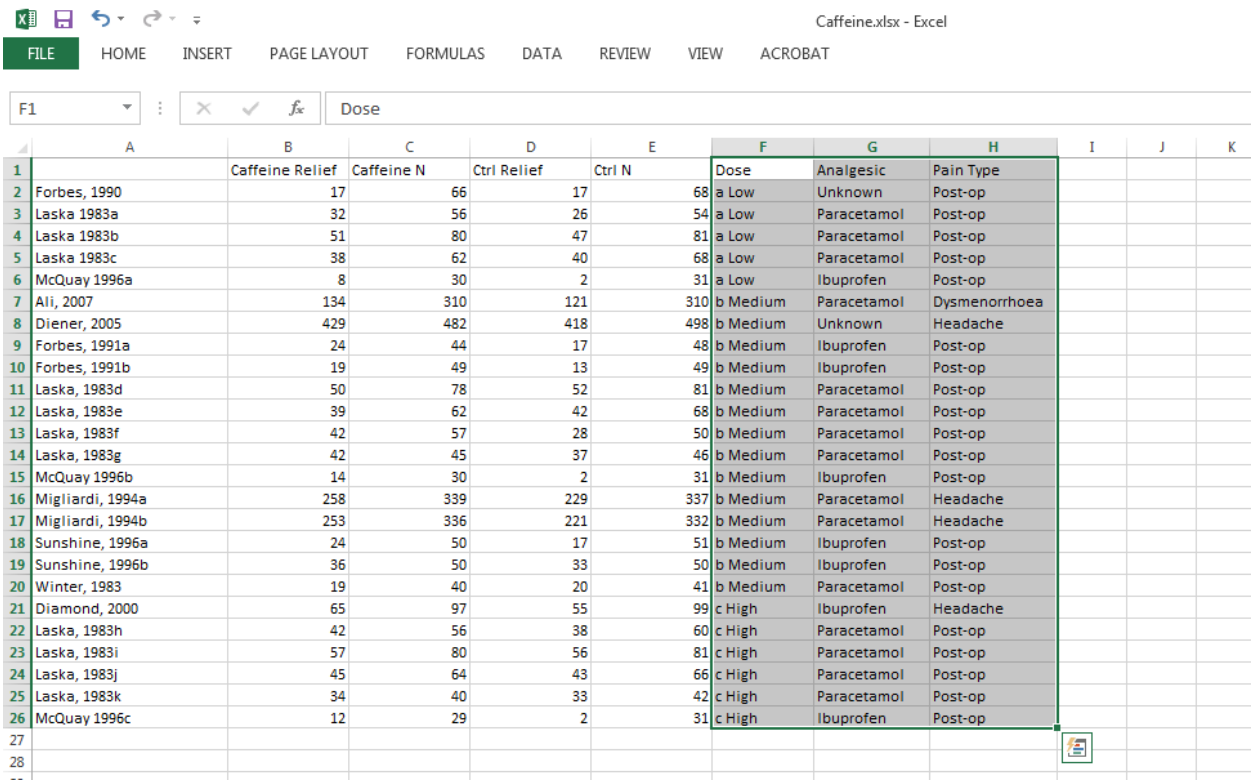
Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses

	Study name	Caffeine Relief	Caffeine Total N	Control Relief	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Analgesic	Pain Type	M	N	O
1		Caffeine	Caffeine N	Ctrl Relief	Ctrl N										
2	Forbes, 1990	17	66	17	68	1.041	0.040	0.397	0.158						
3	Laska 1983a	32	56	26	54	1.436	0.362	0.384	0.147						
4	Laska 1983b	51	80	47	81	1.272	0.241	0.324	0.105						
5	Laska 1983c	38	62	40	68	1.108	0.103	0.359	0.129						
6	McQuay 1996a	8	30	2	31	5.273	1.663	0.840	0.705						
7	Ali, 2007	134	310	121	310	1.189	0.173	0.163	0.027						
8	Diener, 2005	429	482	418	498	1.549	0.438	0.190	0.036						
9	Forbes, 1991a	24	44	17	48	2.188	0.783	0.427	0.183						
10	Forbes, 1991b	19	49	13	49	1.754	0.562	0.437	0.191						
11	Laska, 1983d	50	78	52	81	0.996	-0.004	0.331	0.109						
12	Laska, 1983e	39	62	42	68	1.050	0.048	0.362	0.131						
13	Laska, 1983f	42	57	28	50	2.200	0.788	0.414	0.172						
14	Laska, 1983g	42	45	37	46	3.405	1.225	0.704	0.495						
15	McQuay 1996b	14	30	2	31	12.688	2.541	0.818	0.668						
16	Migliardi, 1994a	258	339	229	337	1.502	0.407	0.173	0.030						
17	Migliardi, 1994b	253	336	221	332	1.531	0.426	0.172	0.030						
18	Sunshine, 1996a	24	50	17	51	1.846	0.613	0.410	0.168						
19	Sunshine, 1996b	36	50	33	50	1.325	0.281	0.434	0.188						
20	Winter, 1983	19	40	20	41	0.950	-0.051	0.445	0.198						
21	Diamond, 2000	65	97	55	99	1.625	0.486	0.296	0.088						
22	Laska, 1983h	42	56	38	60	1.737	0.552	0.409	0.167						
23	Laska, 1983i	57	80	56	81	1.106	0.101	0.345	0.119						
24	Laska, 1983j	45	64	43	66	1.267	0.237	0.376	0.142						
25	Laska, 1983k	34	40	33	42	1.545	0.435	0.581	0.337						
26	McQuay 1996c	12	29	2	31	10.235	2.326	0.823	0.677						
27															

- Switch to Excel
- Highlight the columns for Dose, Analgesic, and Pain Type as shown and click [CTRL-C]



	A	B	C	D	E	F	G	H
1		Caffeine Relief	Caffeine N	Ctrl Relief	Ctrl N	Dose	Analgesic	Pain Type
2	Forbes, 1990	17	66	17	68	a Low	Unknown	Post-op
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6	McQuay 1996a	8	30	2	31	a Low	Ibuprofen	Post-op
7	Ali, 2007	134	310	121	310	b Medium	Paracetamol	Dysmenorrhoea
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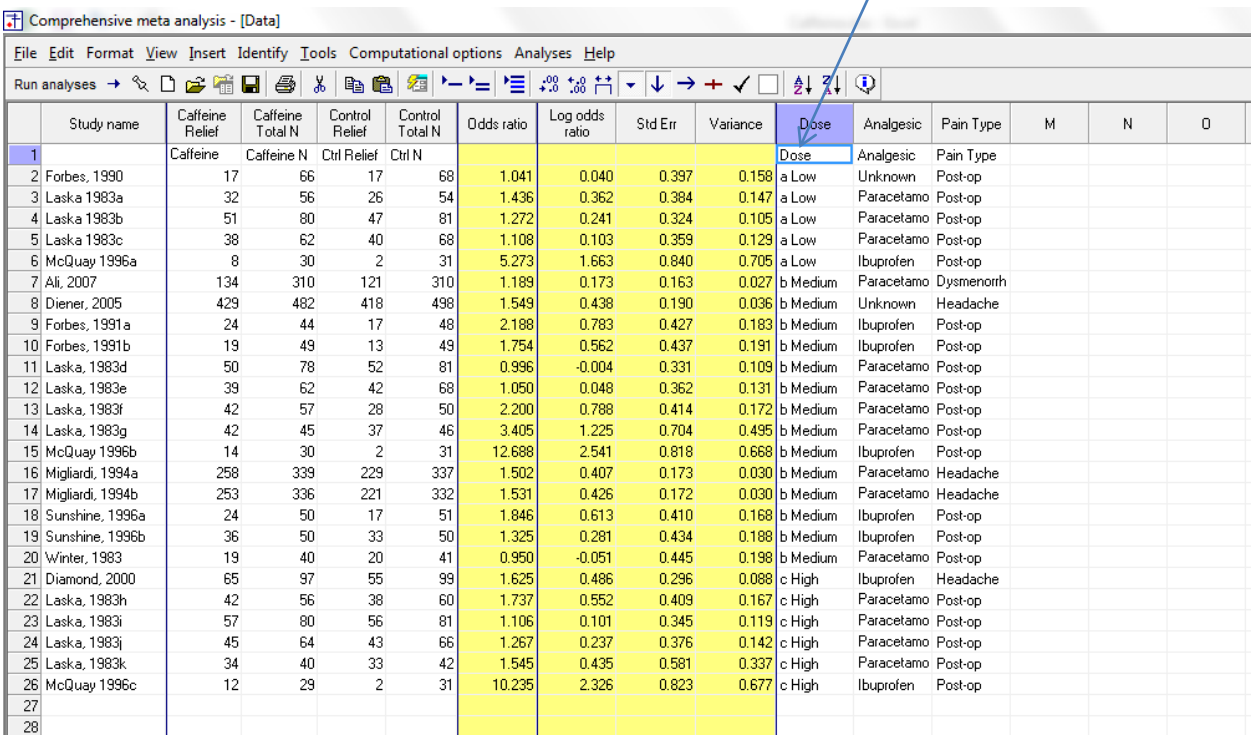
9	Forbes, 1991a	24	44	17	48	b Medium	Ibuprofen	Post-op
10	Forbes, 1991b	19	49	13	49	b Medium	Ibuprofen	Post-op
11	Laska, 1983d	50	78	52	81	b Medium	Paracetamol	Post-op
12	Laska, 1983e	39	62	42	68	b Medium	Paracetamol	Post-op
13	Laska, 1983f	42	57	28	50	b Medium	Paracetamol	Post-op
14	Laska, 1983g	42	45	37	46	b Medium	Paracetamol	Post-op
15	McQuay 1996b	14	30	2	31	b Medium	Ibuprofen	Post-op
16	Migliardi, 1994a	258	339	229	337	b Medium	Paracetamol	Headache
17	Migliardi, 1994b	253	336	221	332	b Medium	Paracetamol	Headache
18	Sunshine, 1996a	24	50	17	51	b Medium	Ibuprofen	Post-op
19	Sunshine, 1996b	36	50	33	50	b Medium	Ibuprofen	Post-op
20	Winter, 1983	19	40	20	41	b Medium	Paracetamol	Post-op
21	Diamond, 2000	65	97	55	99	c High	Ibuprofen	Headache
22	Laska, 1983h	42	56	38	60	c High	Paracetamol	Post-op
23	Laska, 1983i	57	80	56	81	c High	Paracetamol	Post-op
24	Laska, 1983j	45	64	43	66	c High	Paracetamol	Post-op
25	Laska, 1983k	34	40	33	42	c High	Paracetamol	Post-op
26	McQuay 1996c	12	29	2	31	c High	Ibuprofen	Post-op
27								
28								

- Switch to CMA
- Click the cell Dose – 1
- Press CTRL-V to paste the data



	Study name	Caffeine Relief	Caffeine Total N	Control Relief	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Analgesic	Pain Type	M	N	O
1		Caffeine	Caffeine N	Ctrl Relief	Ctrl N					Dose	Analgesic	Pain Type			
2	Forbes, 1990	17	66	17	68	1.041	0.040	0.397	0.158	a Low	Unknown	Post-op			
3	Laska 1983a	32	56	26	54	1.436	0.362	0.384	0.147	a Low	Paracetamo	Post-op			
4	Laska 1983b	51	80	47	81	1.272	0.241	0.324	0.105	a Low	Paracetamo	Post-op			
5	Laska 1983c	38	62	40	68	1.108	0.103	0.359	0.129	a Low	Paracetamo	Post-op			
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10	Forbes, 1991b	19	49	13	49	1.754	0.562	0.437	0.191	b Medium	Ibuprofen	Post-op			
11	Laska, 1983d	50	78	52	81	0.996	-0.004	0.331	0.109	b Medium	Paracetamo	Post-op			
12	Laska, 1983e	39	62	42	68	1.050	0.048	0.362	0.131	b Medium	Paracetamo	Post-op			
13	Laska, 1983f	42	57	28	50	2.200	0.788	0.414	0.172	b Medium	Paracetamo	Post-op			
14	Laska, 1983g	42	45	37	46	3.405	1.225	0.704	0.495	b Medium	Paracetamo	Post-op			
15	McQuay 1996b	14	30	2	31	12.688	2.541	0.818	0.668	b Medium	Ibuprofen	Post-op			
16	Migliardi, 1994a	258	339	229	337	1.502	0.407	0.173	0.030	b Medium	Paracetamo	Headache			
17	Migliardi, 1994b	253	336	221	332	1.531	0.426	0.172	0.030	b Medium	Paracetamo	Headache			
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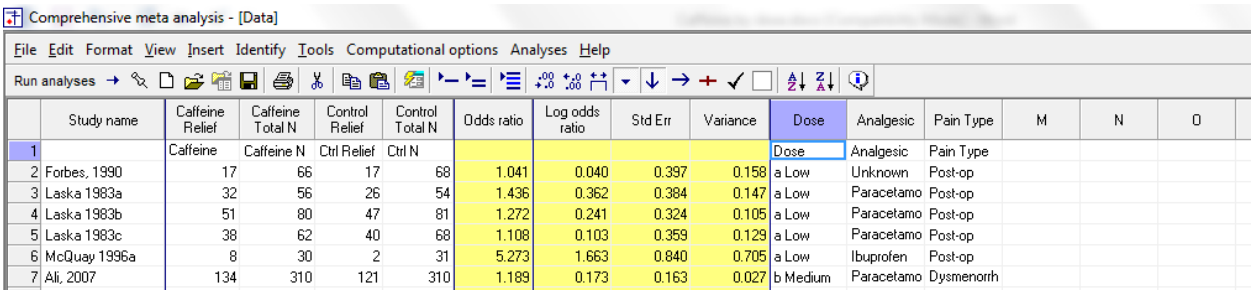
24	Laska, 1983j	45	64	43	66	1.267	0.237	0.376	0.142	c High	Paracetamo	Post-op			
25	Laska, 1983k	34	40	33	42	1.545	0.435	0.581	0.337	c High	Paracetamo	Post-op			
26	McQuay 1996c	12	29	2	31	10.235	2.326	0.823	0.677	c High	Ibuprofen	Post-op			
27															
28															

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



	Study name	Caffeine Relief	Caffeine Total N	Control Relief	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Analgesic	Pain Type	M	N	O
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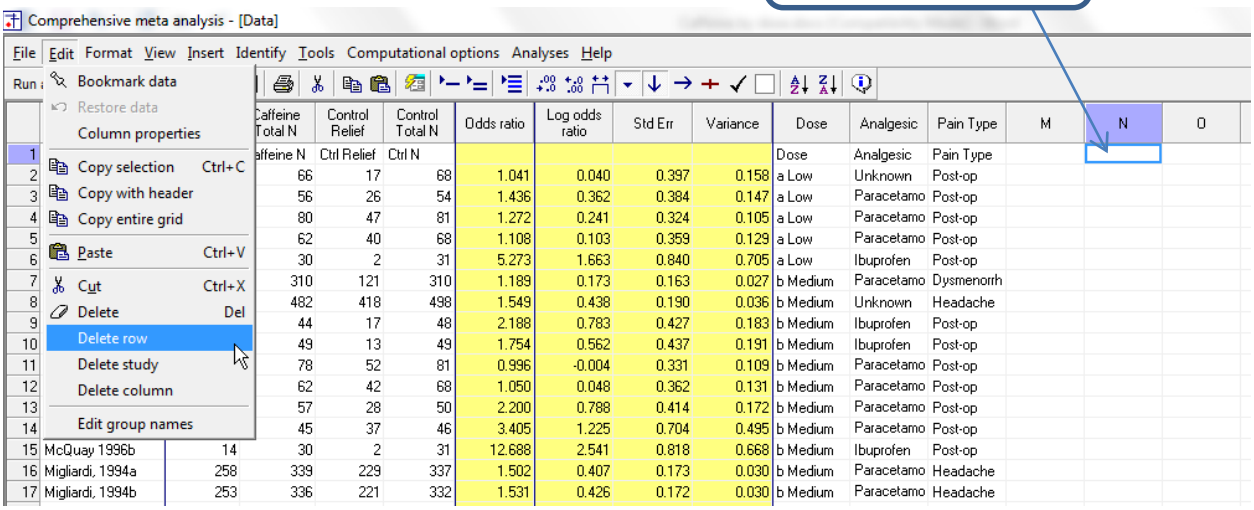
7	Ali, 2007	134	310	121	310	1.189	0.173	0.163	0.027	b Medium	Paracetamo	Dysmenorrh			

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



	Study name	Caffeine Relief	Caffeine Total N	Control Relief	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Analgesic	Pain Type	M	N	O
1			affeine N	Ctrl Relief	Ctrl N					Dose	Analgesic	Pain Type			
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6			30	2	31	5.273	1.663	0.840	0.705	a Low	Ibuprofen	Post-op			
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11			78	52	81	0.996	-0.004	0.331	0.109	b Medium	Paracetamo	Post-op			
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13			57	28	50	2.200	0.788	0.414	0.172	b Medium	Paracetamo	Post-op			
14			45	37	46	3.405	1.225	0.704	0.495	b Medium	Paracetamo	Post-op			
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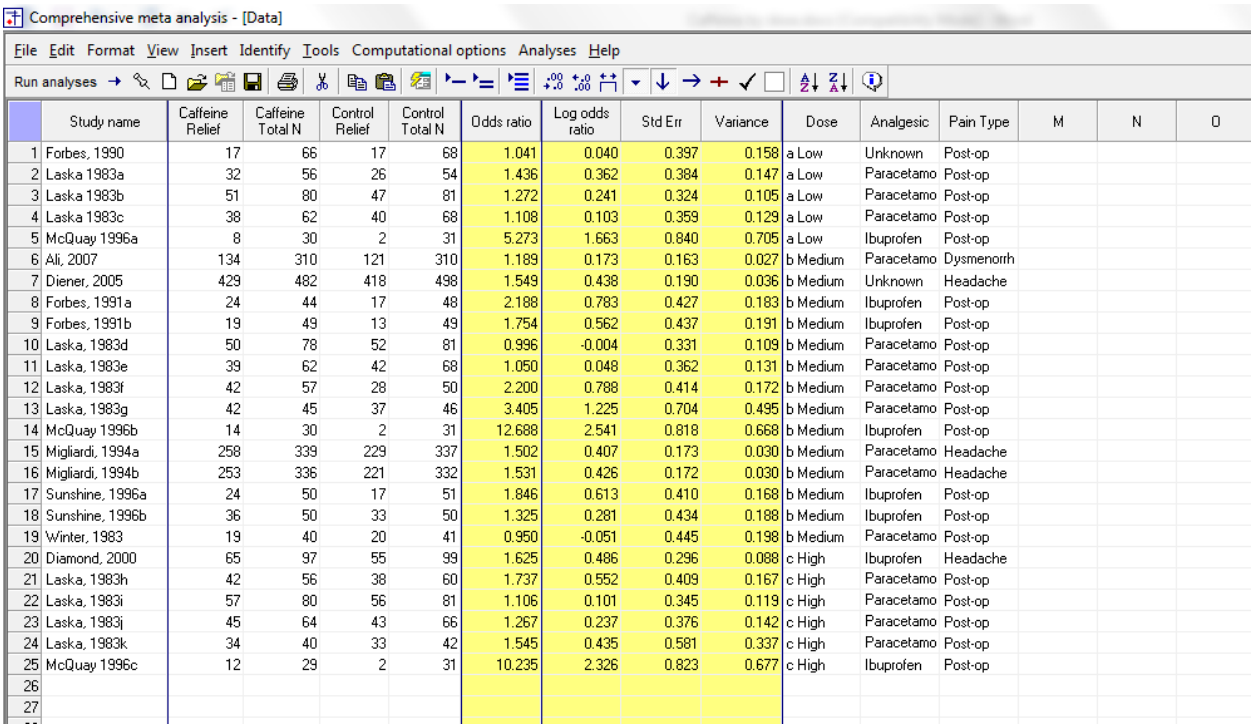
The screen should look like this



	Study name	Caffeine Relief	Caffeine Total N	Control Relief	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Analgesic	Pain Type	M	N	O
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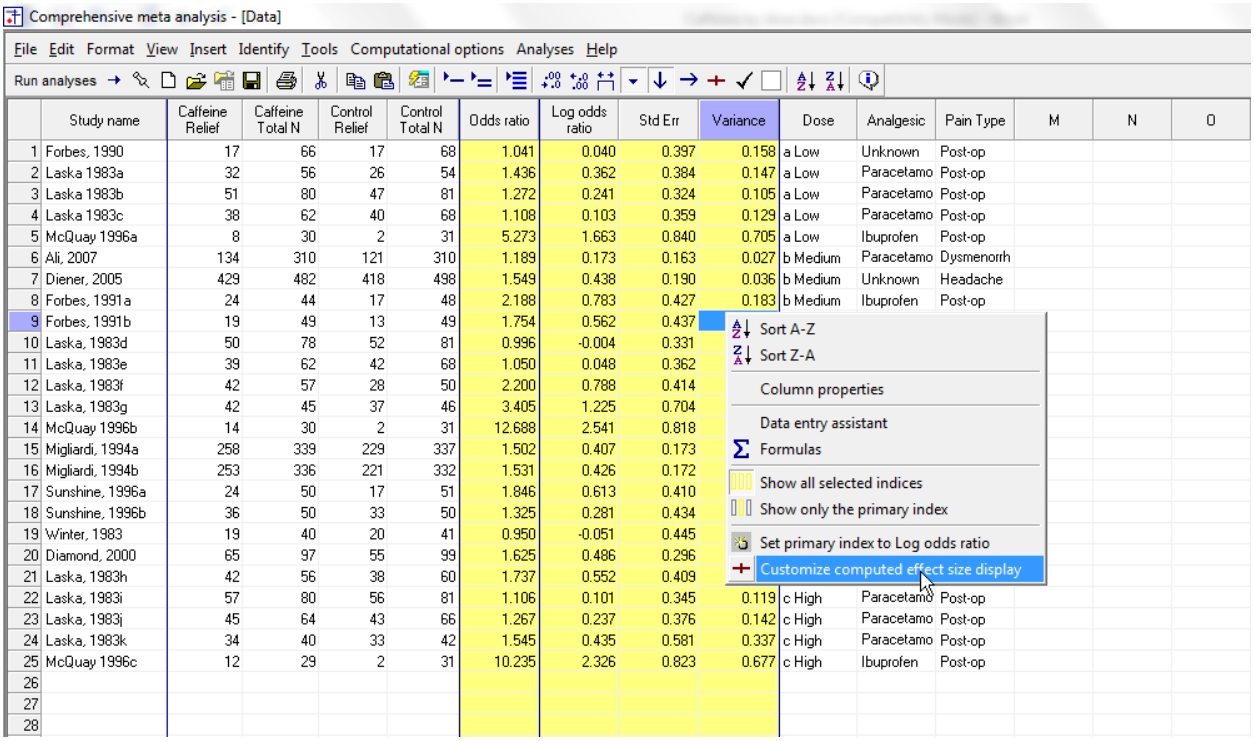
2	Laska 1983a	32	56	26	54	1.436	0.362	0.384	0.147	a Low	Paracetamo	Post-op			
3	Laska 1983b	51	80	47	81	1.272	0.241	0.324	0.105	a Low	Paracetamo	Post-op			
4	Laska 1983c	38	62	40	68	1.108	0.103	0.359	0.129	a Low	Paracetamo	Post-op			
5	McQuay 1996a	8	30	2	31	5.273	1.663	0.840	0.705	a Low	Ibuprofen	Post-op			
6	Ali, 2007	134	310	121	310	1.189	0.173	0.163	0.027	b Medium	Paracetamo	Dysmenorrh			
7	Diener, 2005	429	482	418	498	1.549	0.438	0.190	0.036	b Medium	Unknown	Headache			
8	Forbes, 1991a	24	44	17	48	2.188	0.783	0.427	0.183	b Medium	Ibuprofen	Post-op			
9	Forbes, 1991b	19	49	13	49	1.754	0.562	0.437	0.191	b Medium	Ibuprofen	Post-op			
10	Laska, 1983d	50	78	52	81	0.996	-0.004	0.331	0.109	b Medium	Paracetamo	Post-op			
11	Laska, 1983e	39	62	42	68	1.050	0.048	0.362	0.131	b Medium	Paracetamo	Post-op			
12	Laska, 1983f	42	57	28	50	2.200	0.788	0.414	0.172	b Medium	Paracetamo	Post-op			
13	Laska, 1983g	42	45	37	46	3.405	1.225	0.704	0.495	b Medium	Paracetamo	Post-op			
14	McQuay 1996b	14	30	2	31	12.688	2.541	0.818	0.668	b Medium	Ibuprofen	Post-op			
15	Migliardi, 1994a	258	339	229	337	1.502	0.407	0.173	0.030	b Medium	Paracetamo	Headache			
16	Migliardi, 1994b	253	336	221	332	1.531	0.426	0.172	0.030	b Medium	Paracetamo	Headache			
17	Sunshine, 1996a	24	50	17	51	1.846	0.613	0.410	0.168	b Medium	Ibuprofen	Post-op			
18	Sunshine, 1996b	36	50	33	50	1.325	0.281	0.434	0.188	b Medium	Ibuprofen	Post-op			
19	Winter, 1983	19	40	20	41	0.950	-0.051	0.445	0.198	b Medium	Paracetamo	Post-op			
20	Diamond, 2000	65	97	55	99	1.625	0.486	0.296	0.088	c High	Ibuprofen	Headache			
21	Laska, 1983h	42	56	38	60	1.737	0.552	0.409	0.167	c High	Paracetamo	Post-op			
22	Laska, 1983i	57	80	56	81	1.106	0.101	0.345	0.119	c High	Paracetamo	Post-op			
23	Laska, 1983j	45	64	43	66	1.267	0.237	0.376	0.142	c High	Paracetamo	Post-op			
24	Laska, 1983k	34	40	33	42	1.545	0.435	0.581	0.337	c High	Paracetamo	Post-op			
25	McQuay 1996c	12	29	2	31	10.235	2.326	0.823	0.677	c High	Ibuprofen	Post-op			
26															
27															

By default, the program is displaying the odds ratio as the effect size

We want to switch to the risk ratio



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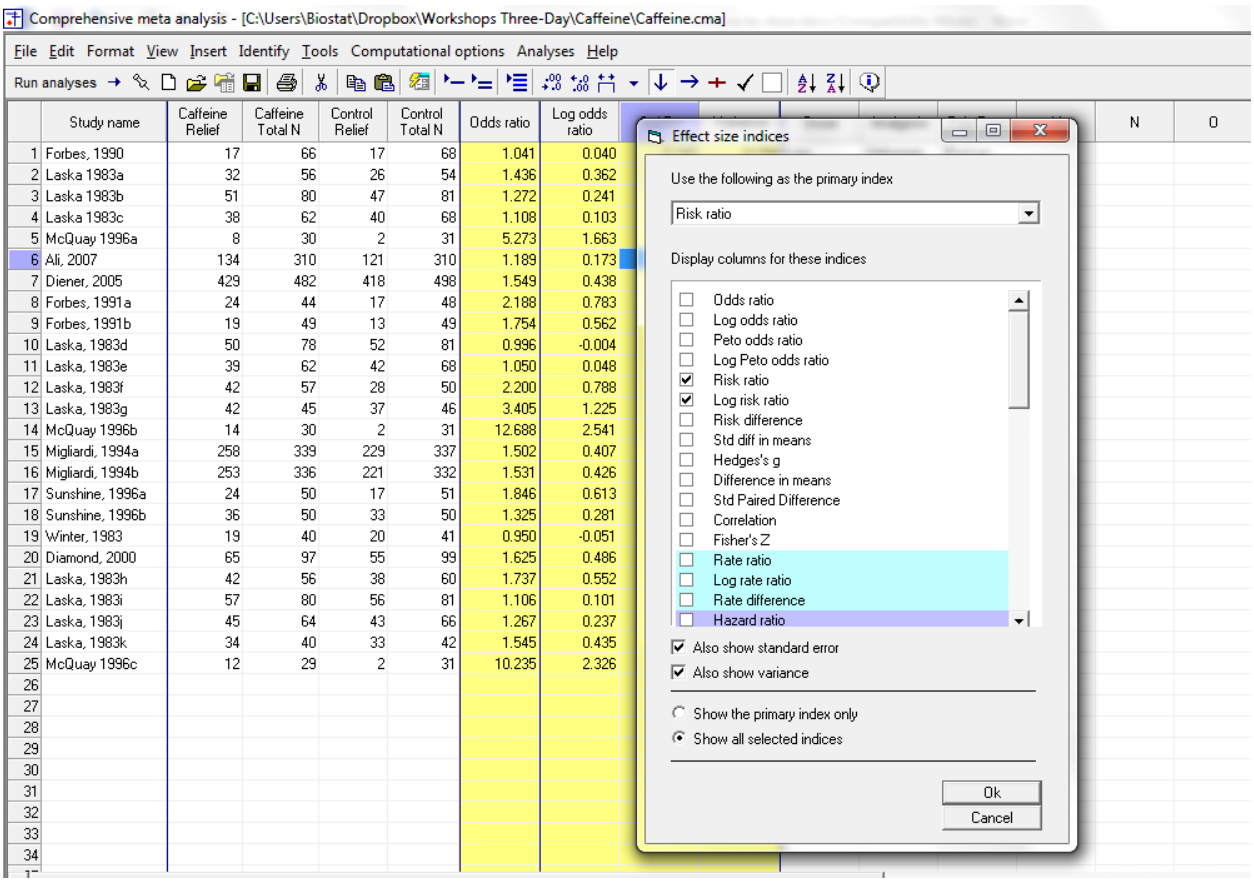
26															
27															
28															

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



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9	Forbes, 1991b	19	49	13	49	1.754	0.562
10	Laska, 1983d	50	78	52	81	0.996	-0.004
11	Laska, 1983e	39	62	42	68	1.050	0.048
12	Laska, 1983f	42	57	28	50	2.200	0.788
13	Laska, 1983g	42	45	37	46	3.405	1.225
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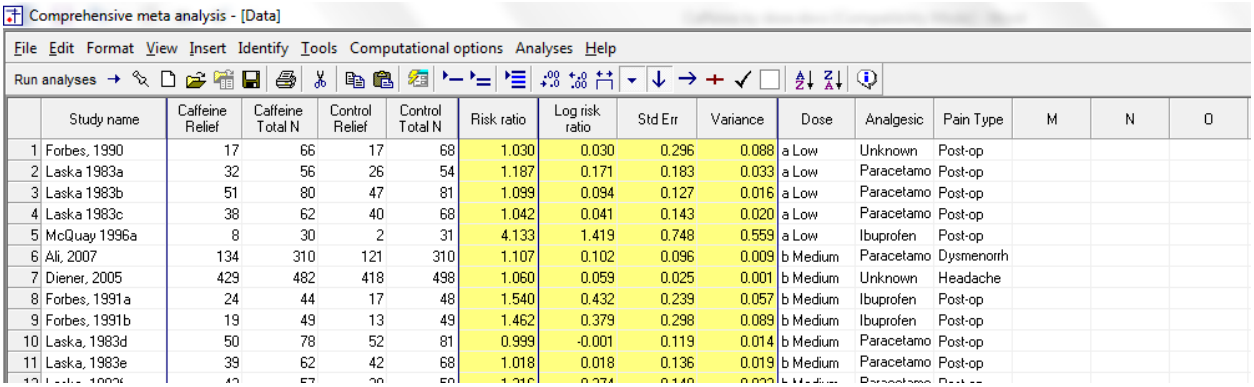
19	Winter, 1983	19	40	20	41	0.950	-0.051
20	Diamond, 2000	65	97	55	99	1.625	0.486
21	Laska, 1983h	42	56	38	60	1.737	0.552
22	Laska, 1983i	57	80	56	81	1.106	0.101
23	Laska, 1983j	45	64	43	66	1.267	0.237
24	Laska, 1983k	34	40	33	42	1.545	0.435
25	McQuay 1996c	12	29	2	31	10.235	2.326

- 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

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



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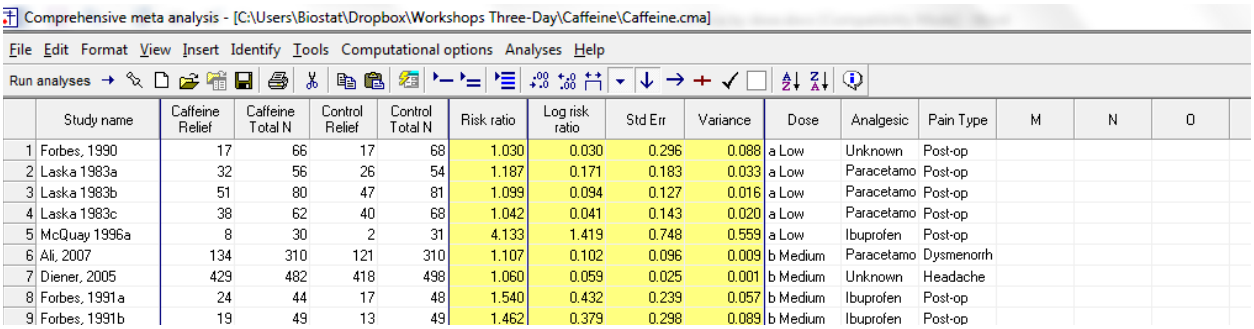
2	Laska 1983a	32	56	26	54	1.187	0.171	0.183	0.033	a Low	Paracetamo	Post-op			
3	Laska 1983b	51	80	47	81	1.099	0.094	0.127	0.016	a Low	Paracetamo	Post-op			
4	Laska 1983c	38	62	40	68	1.042	0.041	0.143	0.020	a Low	Paracetamo	Post-op			
5	McQuay 1996a	8	30	2	31	4.133	1.419	0.748	0.559	a Low	Ibuprofen	Post-op			
6	Ali, 2007	134	310	121	310	1.107	0.102	0.096	0.009	b Medium	Paracetamo	Dysmenorrh			
7	Diener, 2005	429	482	418	498	1.060	0.059	0.025	0.001	b Medium	Unknown	Headache			
8	Forbes, 1991a	24	44	17	48	1.540	0.432	0.239	0.057	b Medium	Ibuprofen	Post-op			
9	Forbes, 1991b	19	49	13	49	1.462	0.379	0.298	0.089	b Medium	Ibuprofen	Post-op			
10	Laska, 1983d	50	78	52	81	0.999	-0.001	0.119	0.014	b Medium	Paracetamo	Post-op			
11	Laska, 1983e	39	62	42	68	1.018	0.018	0.136	0.019	b Medium	Paracetamo	Post-op			

Click File > Save As and save the file



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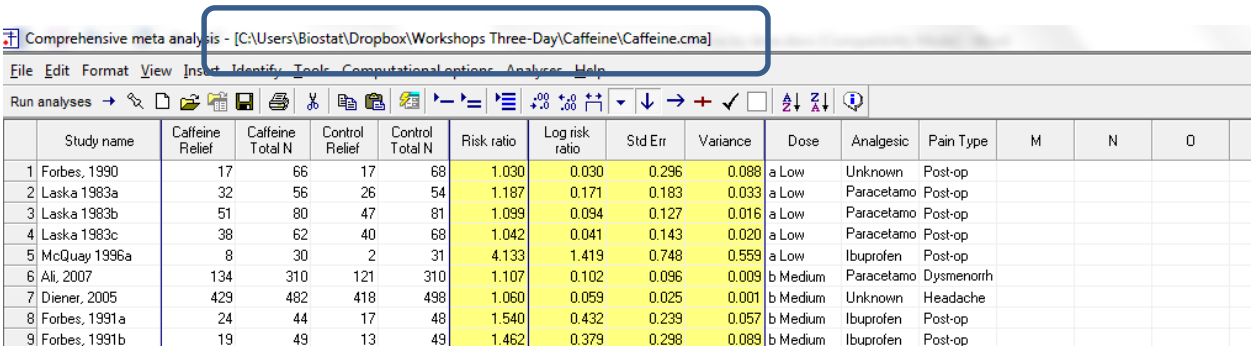
Note that the file name is now in the header.

- [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



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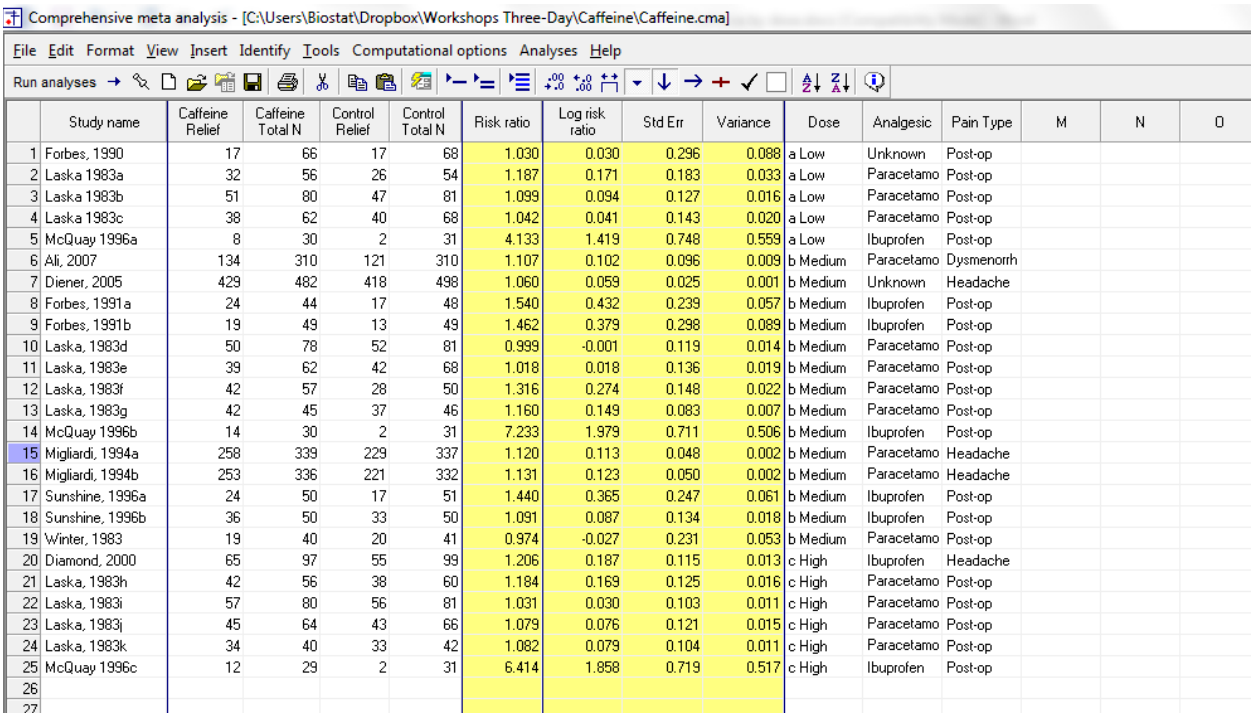
By convention we've put the treated group (caffeine plus analgesic) in the first two columns and the control (analgesic alone) in the second two columns. Also by convention, we've defined "Event" as the presence of the outcome (relief).

When we follow these conventions, and if the treated group does better than the control, then

- If the "event" is a bad outcome (such as relapse), the risk ratio will be less than 1.
- If the "event" is a good outcome (such as relief), the risk ratio will be greater than 1.

Therefore, in the present case, a risk ratio greater than 1 indicates that patients treated with caffeine were more likely to get relief.

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 last study (McQauy), where the risk ratio is very high, and the distinction between groups should be clear.



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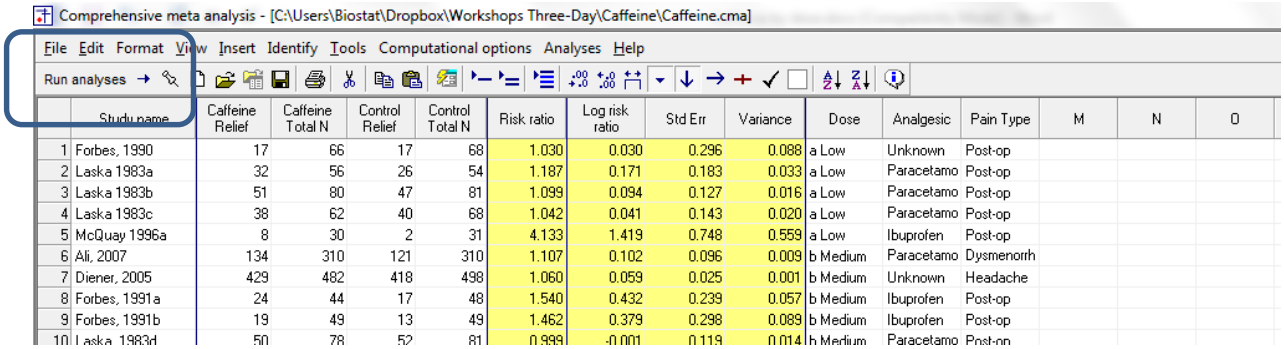
18	Sunshine, 1996b	36	50	33	50	1.091	0.087	0.134	0.018	b Medium	Ibuprofen	Post-op			
19	Winter, 1983	19	40	20	41	0.974	-0.027	0.231	0.053	b Medium	Paracetamo	Post-op			
20	Diamond, 2000	65	97	55	99	1.206	0.187	0.115	0.013	c High	Ibuprofen	Headache			
21	Laska, 1983h	42	56	38	60	1.184	0.169	0.125	0.016	c High	Paracetamo	Post-op			
22	Laska, 1983i	57	80	56	81	1.031	0.030	0.103	0.011	c High	Paracetamo	Post-op			
23	Laska, 1983j	45	64	43	66	1.079	0.076	0.121	0.015	c High	Paracetamo	Post-op			
24	Laska, 1983k	34	40	33	42	1.082	0.079	0.104	0.011	c High	Paracetamo	Post-op			
25	McQuay 1996c	12	29	2	31	6.414	1.858	0.719	0.517	c High	Ibuprofen	Post-op			
26															
27															

For the caffeine group, more than half the patients (12/29) improved. For the control group, less than 10% (2/31) improved. Clearly, the treated group did better, and the risk ratio (6.414) is greater than one. This tells us that we are interpreting the direction of the effect size properly.

- To run the analysis, click [Run analysis]



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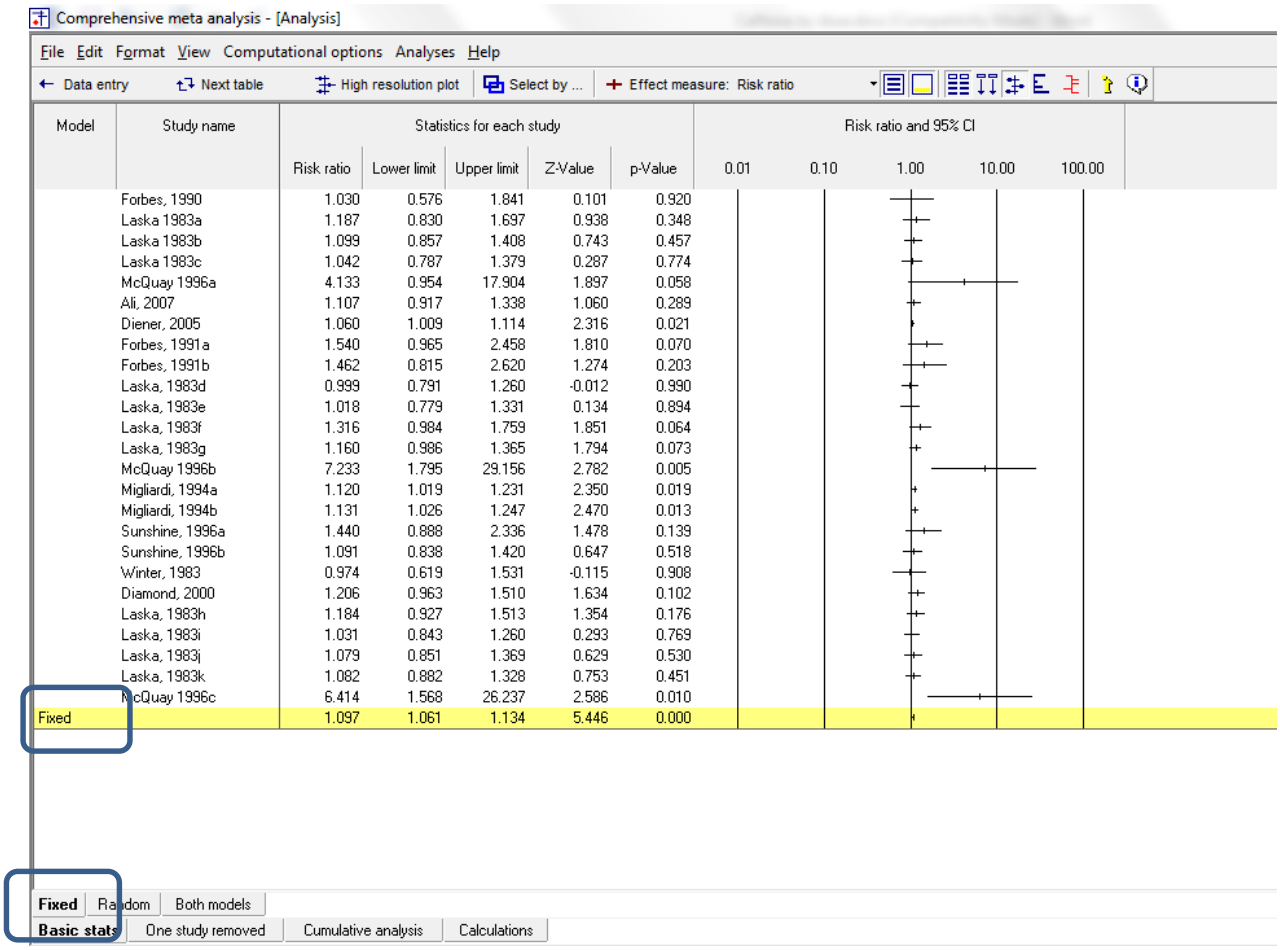
10	Laska 1983d	50	78	52	81	0.999	-0.001	0.119	0.014	b Medium	Paracetamo	Post-op			

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.



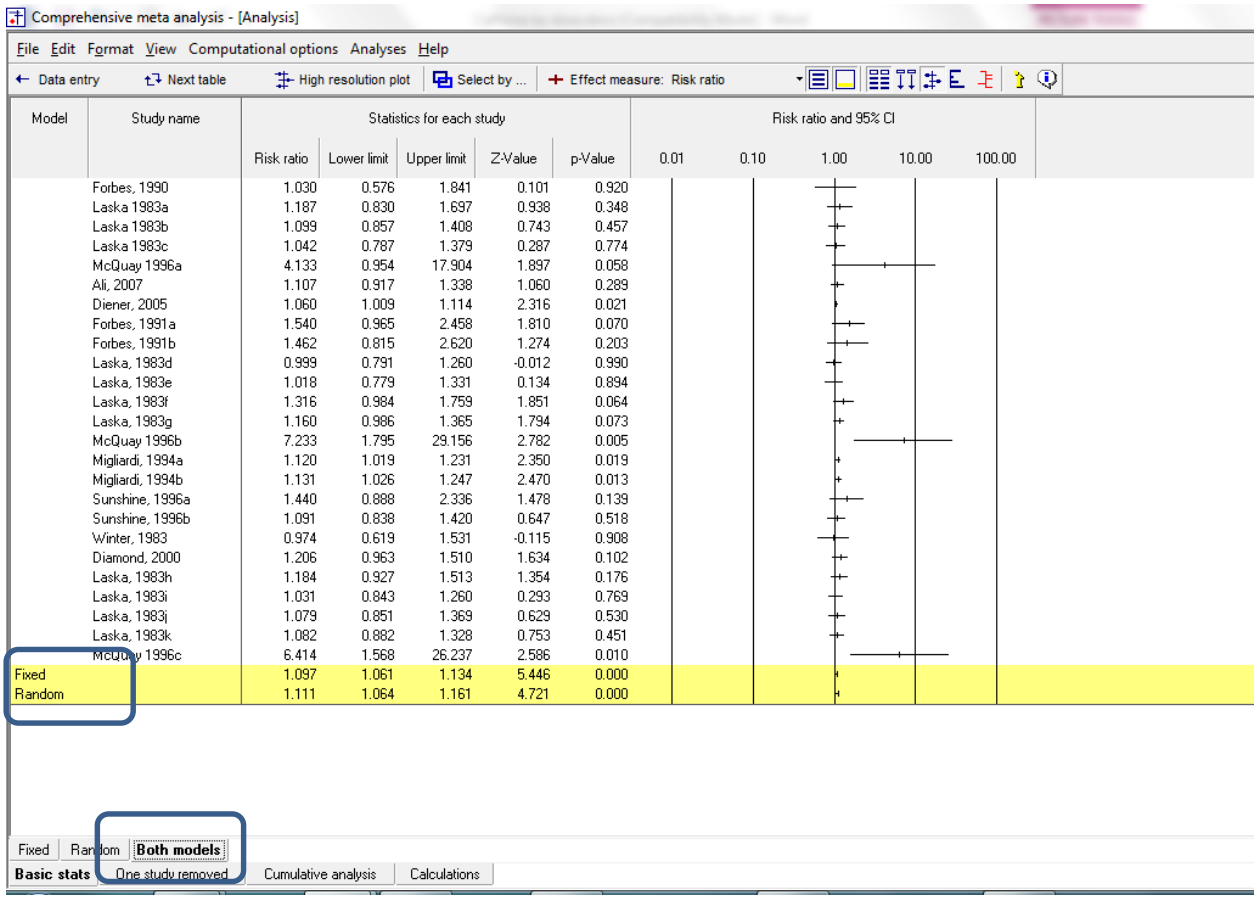
Virtually all studies have risk ratios over 1.0, which means that the caffeine group (analgesic plus caffeine) did better than the control (analgesic alone), but the effect is statistically significant in only a few of the studies.

The effects seem to be reasonably consistent. Aside from three exceptions, all of the studies have effect sizes that line up in a fairly narrow range.

The pooled effect is 1.097, which means that the addition of caffeine increases the chance of relief by about 10%. This is a modest increase but statistically significant ($p < 0.001$).

Click [Both models]

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



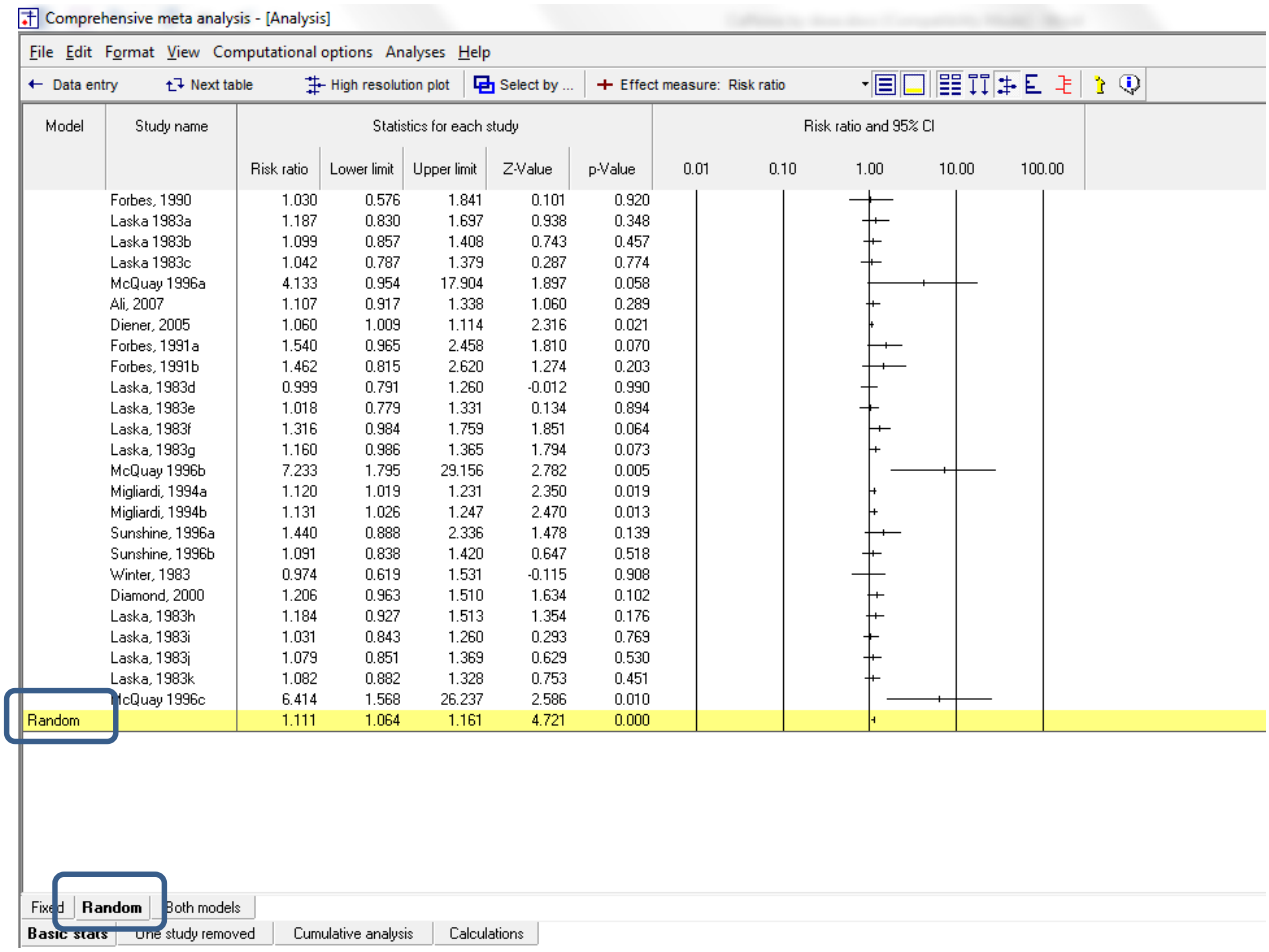
Under the fixed-effect model the pooled effect size is 1.097, while under the random-effects model the pooled effect size is 1.111. While the two models yield very similar results, the random-effects model is a better fit for the way the studies were sampled, and therefore that is the model we will use in the analysis.

- The fixed-effect model would be appropriate if all the studies were virtual replicates of each other, which is not the case here. The dose varied, the analgesic varied, the patients varied.

- The random-effects model would be appropriate if the studies vary in ways that may impact the effect size (such as those mentioned immediately above). Therefore, we will use the random-effects model.

- 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 suggest an advantage for caffeine
- The observed effects are pretty consistent, with three exceptions.
- The summary effect is 1.111 with a CI of 1.064 to 1.161. Thus, the mean effect is small (only about a 10% increase in response as compared with the control).
- The summary effect has a Z-value 4.721 a *p*-value of < 0.001. Thus we can reject the null hypotheses that the true risk ratio is 1.0.

Click [Next table]

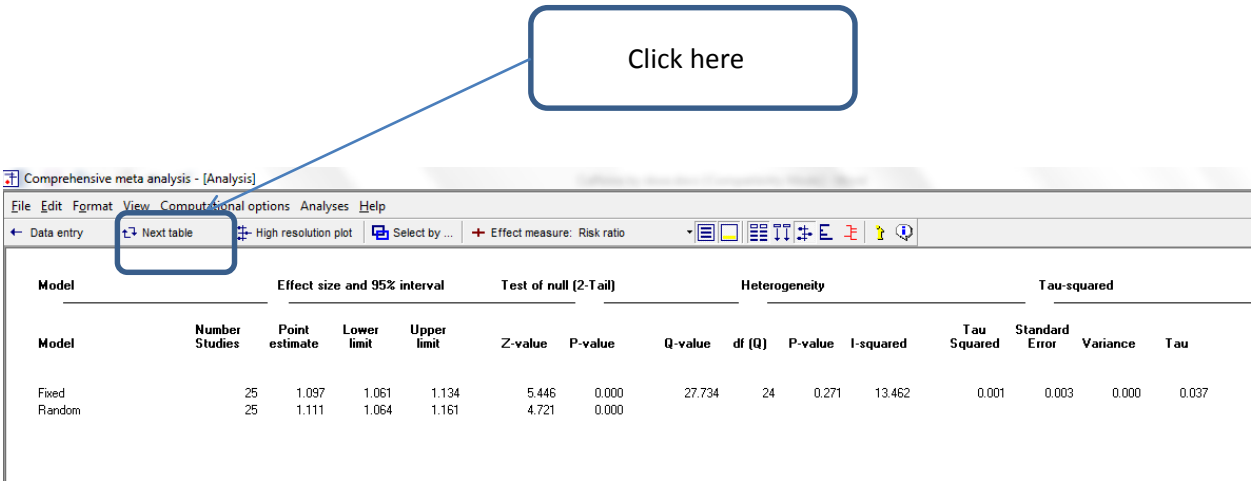


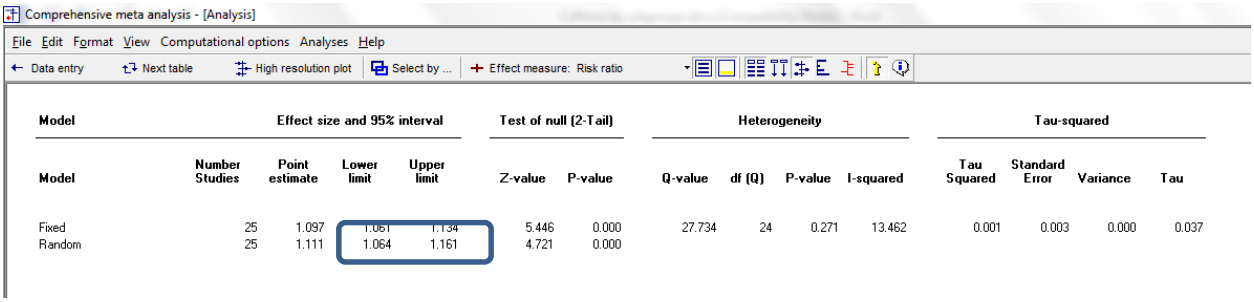
Figure 1

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

- Under the random-effects model the risk ratio is 1.111 with a 95% confidence interval of 1.064 to 1.161. The test of the null (that the true risk ratio is 1.0) yields a Z-value of 4.721 and a corresponding p-value of < 0.001.
- The statistics at the upper right relate to the dispersion of effect sizes across studies.
- The Q-value is 27.7234 with df=24 and p=0.271. *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 24). Here, Q is greater than that value, and so there is some evidence of variance in true effects. However, this excess variance falls within the range that could be attributed to random sampling error in effect sizes (not statistically significant).
- While the heterogeneity is not statistically significant, we will still use the random-effects model, since this matches the sampling frame for the studies.
- T^2 is the estimate of the between-study variance in true effects. This estimate is 0.001. *T* is the estimate of the between-study standard deviation in true effects. This estimate is 0.037. These value are both in log units.
- I^2 reflects the proportion of true variance to observed variance. This is 13.46, which tells us that only about 13% of the observed variance in effects is real. Put another way, if we were looking at a plot of the true effects rather than the observed effects, the variance in effects would be decreased by (1 minus .13) some 87%.
- Click [Next table] to return to this screen

Under the random-effects model the risk ratio is 1.111 with a 95% confidence interval of 1.064 to 1.161. This tells is that the mean true effect probably falls in the range of 1.064 to 1.161. However, since the true risk ratio varies from study to study, we might also want to know how widely the true risk ratios vary from the mean. This is the role of the prediction interval. We can use the spreadsheet [Prediction intervals] as follows.

Since we have select Risk ratio as the effect size, some of the statistics in this table are presented in risk ratio units. To compute the prediction interval we'll need to see statistics in log units.



Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	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	25	1.097	1.061	1.134	5.446	0.000	27.734	24	0.271	13.462	0.001	0.003	0.000	0.037
Random	25	1.111	1.064	1.161	4.721	0.000								

- Open the spreadsheet [Prediction Intervals.xls]
- Select the tab for [Ratios]
- In CMA select Log risk ratio as the index
- Select Format > Increase decimals
- Copy the A|B|C|D values as shown from CMA to Excel

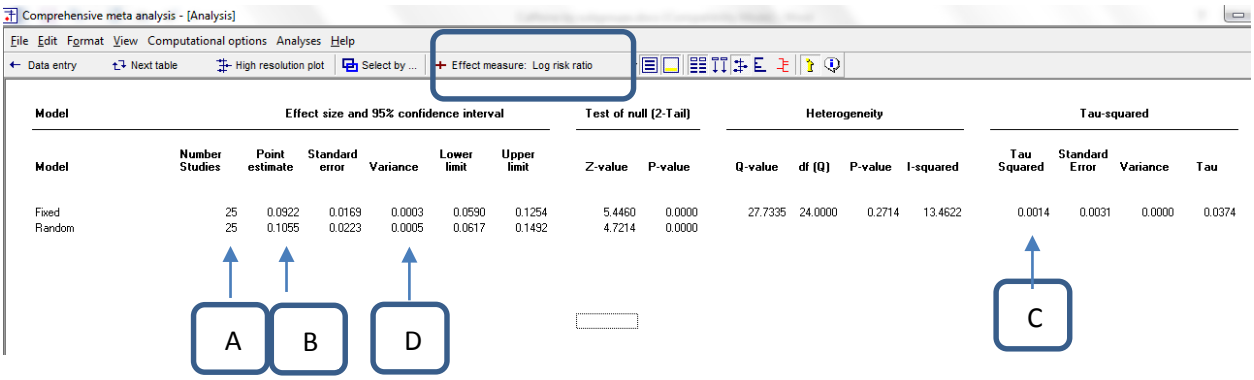
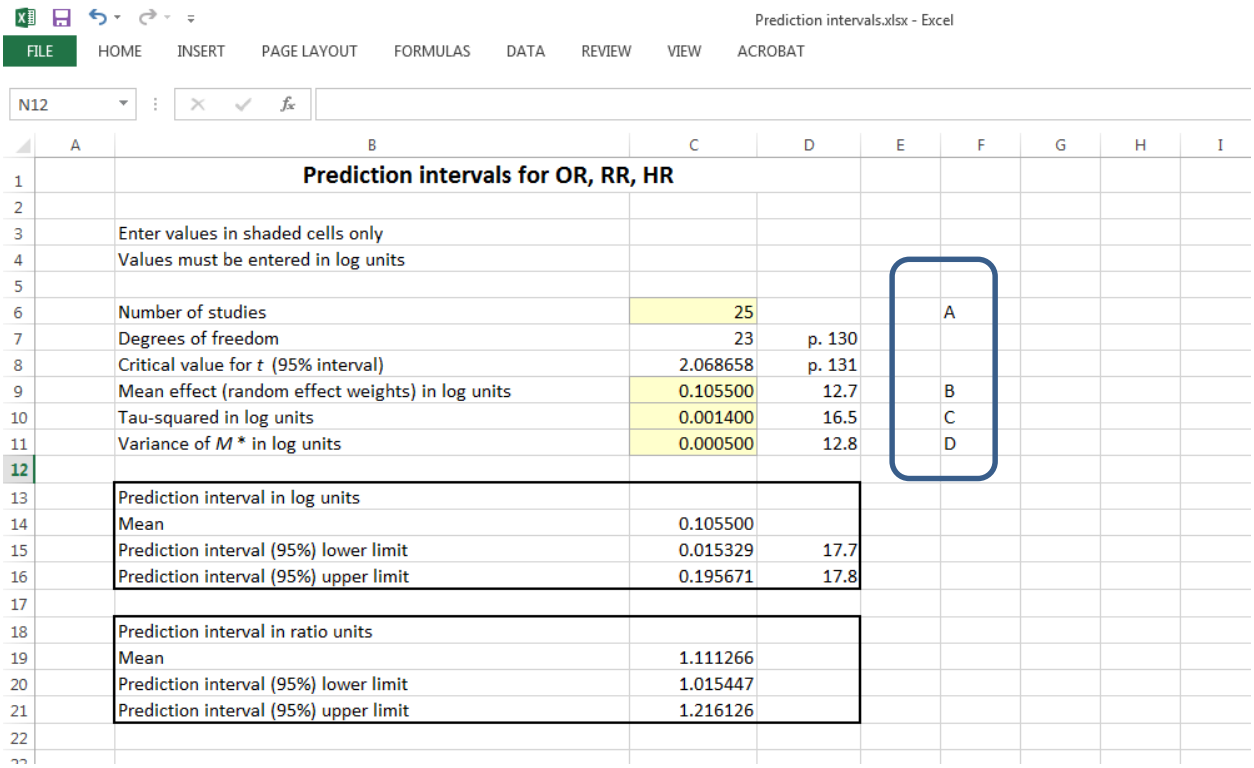


Figure 2



The confidence interval is 1.064 to 1.161 (we read this from Figure 1 which shows the risk ratios rather than the log values). The prediction interval (from Excel) is 1.015 to 1.216.

The true risk ratio varies from study to study. The mean risk ratio probably falls in the range of 1.064 to 1.161. The true effect size for any single study will usually fall in the range of 1.015 to 1.216.

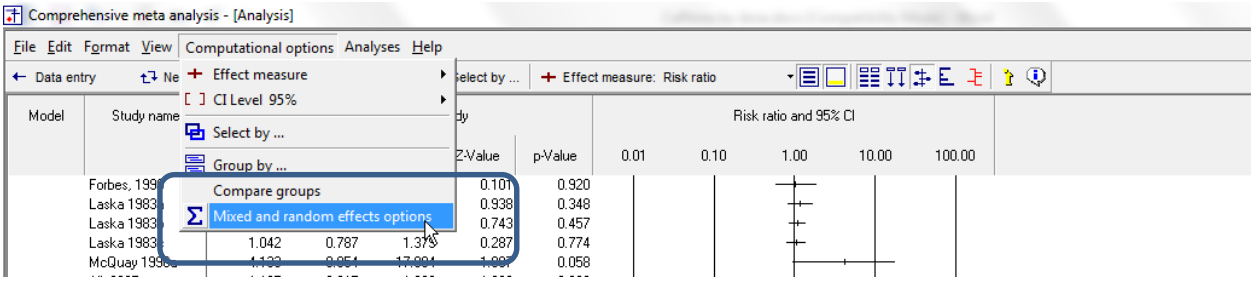
In 95% of all possible meta-analyses, the true mean will fall in the range indicated by the CI. In 95% of all meta-analyses, 95% of all studies will fall inside the range indicated by the PI. This assumes that the true effect sizes are normally distributed.

To this point we've established that caffeine is effective, but the effect is rather small. However, we know that the dose of caffeine varied among studies. We're going to group by dose (low, moderate, or high) and see if the effect size was related to dose.

When we're dividing the studies into 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.

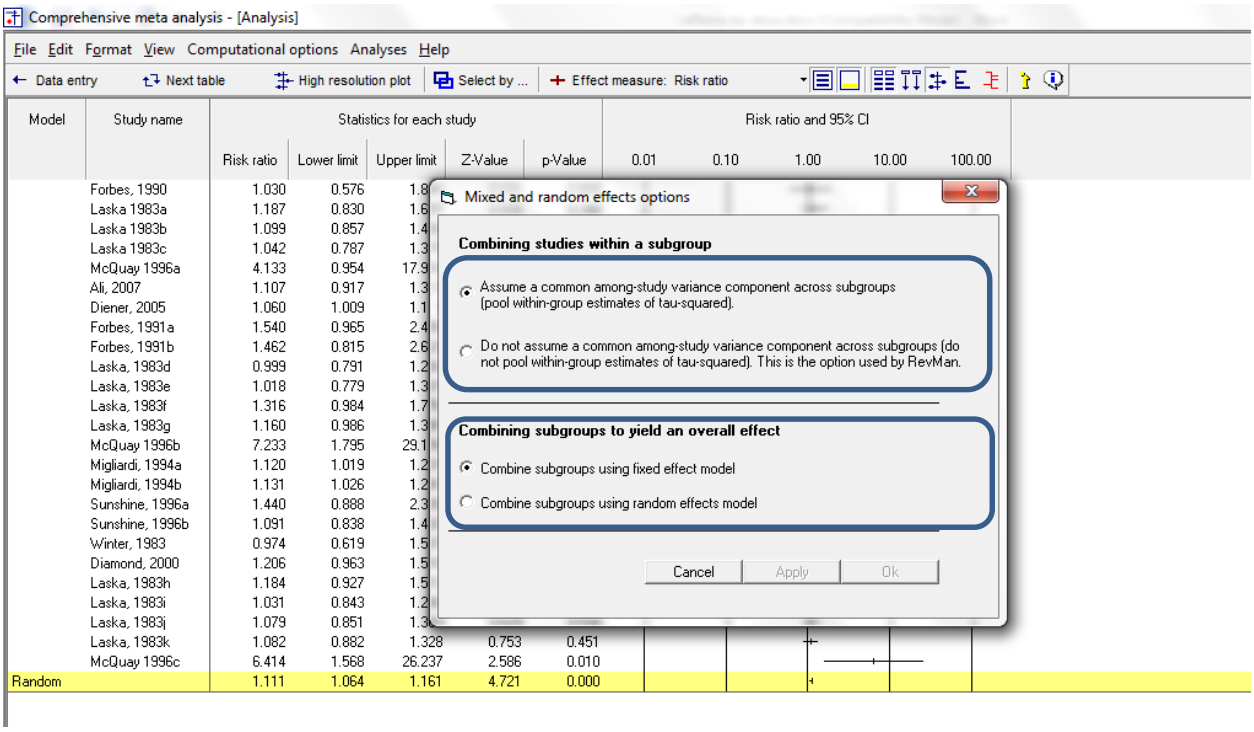
Our plan is to pool the estimates. To select that option

Click Computational options > Mixed and random effects options



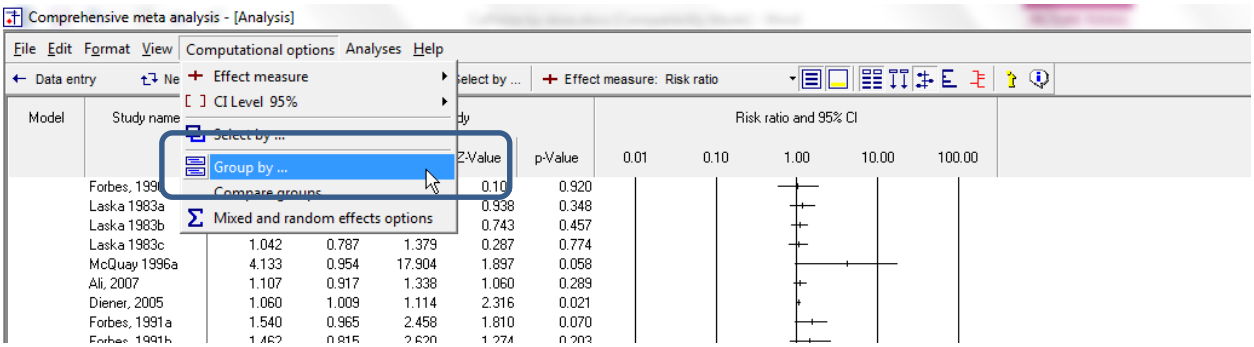
The program displays this wizard

- 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"

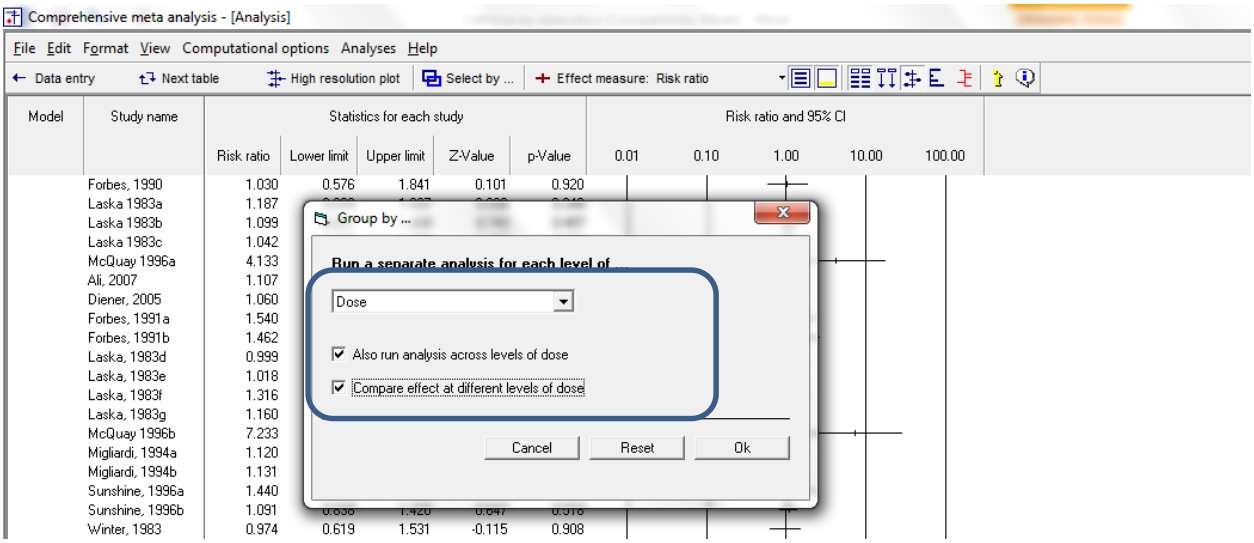

Comprehensive meta analysis - [Analysis]
File Edit Format View Computational options Analyses Help
Data entry
Next table
High resolution plot
Select by ...
Effect measure: Risk ratio
Model
Study name
Statistics for each study
Risk ratio
Lower limit
Upper limit
Z-Value
p-Value
Risk ratio and 95% CI
0.01
0.10
1.00
10.00
100.00
Forbes, 1990 1.030 0.576
Laska 1983a 1.187 0.830
Laska 1983b 1.099 0.857
Laska 1983c 1.042 0.787
McQuay 1996a 4.133 0.954
Ali, 2007 1.107 0.917
Diener, 2005 1.060 1.009
Forbes, 1991a 1.540 0.965
Forbes, 1991b 1.462 0.815
Laska, 1983d 0.999 0.791
Laska, 1983e 1.018 0.779
Laska, 1983f 1.316 0.984
Laska, 1983g 1.160 0.986
McQuay 1996b 7.233 1.795
Migliardi, 1994a 1.120 1.019
Migliardi, 1994b 1.131 1.026
Sunshine, 1996a 1.440 0.888
Sunshine, 1996b 1.091 0.838
Winter, 1983 0.974 0.619
Diamond, 2000 1.206 0.963
Laska, 1983h 1.184 0.927
Laska, 1983i 1.031 0.843
Laska, 1983j 1.079 0.851
Laska, 1983k 1.082 0.882 1.328 0.753 0.451
McQuay 1996c 6.414 1.568 26.237 2.586 0.010
Random 1.111 1.064 1.161 4.721 0.000
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.

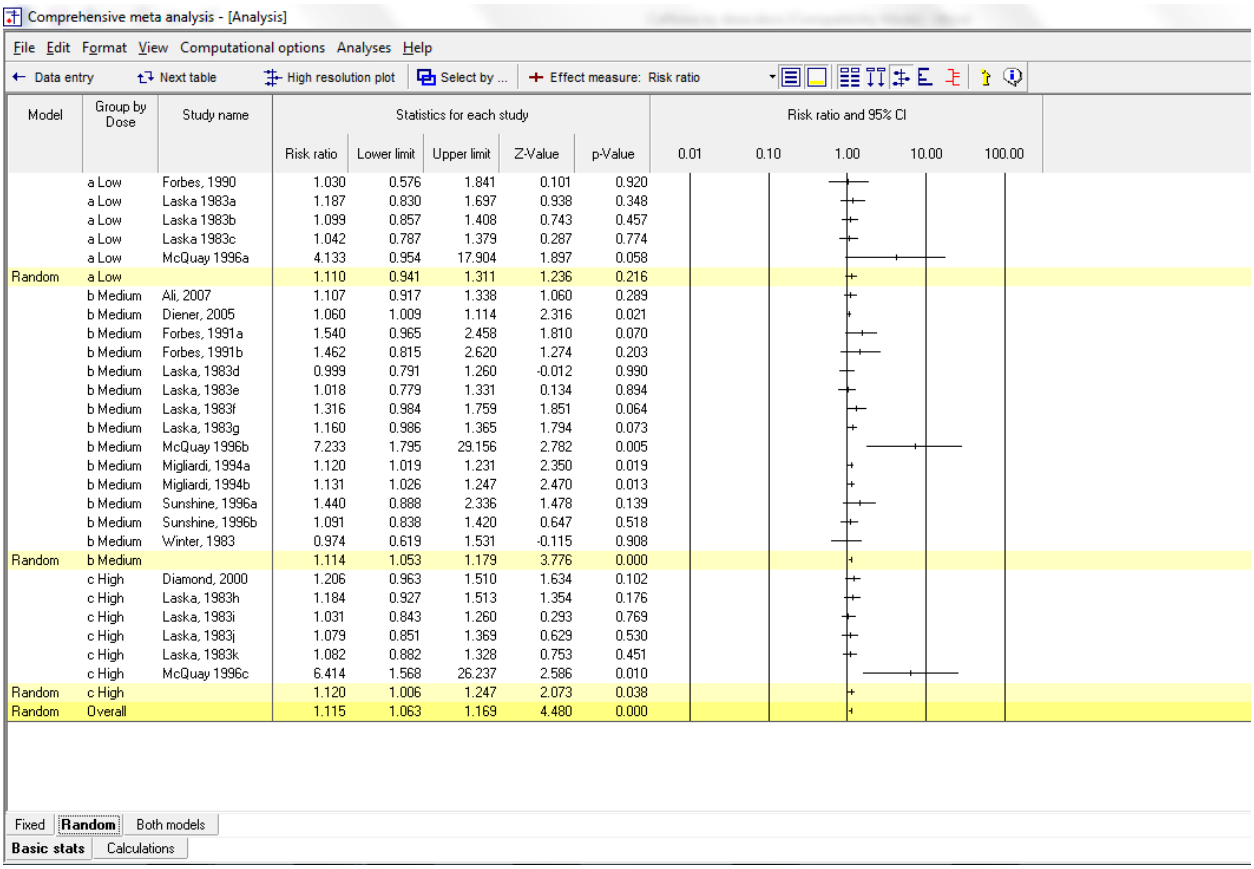
Click Computational options > Group by



- Select Dose
- Check the two boxes
- Click Ok



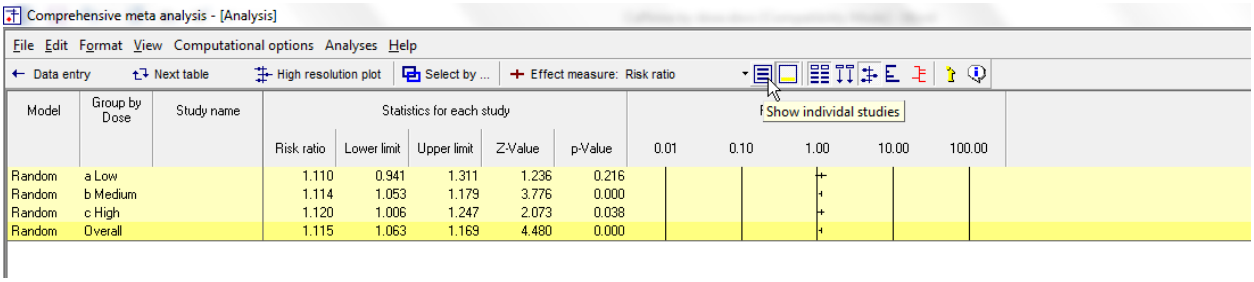
The screen should look like this



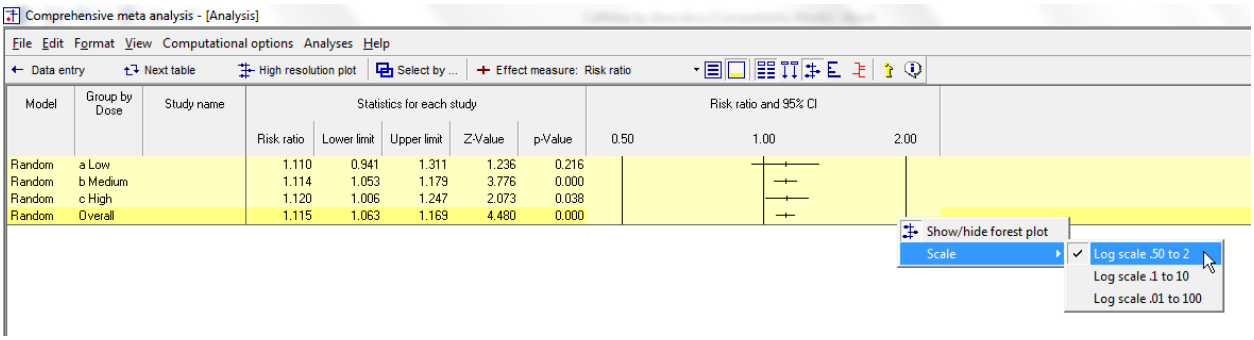
Model	Group by Dose	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	a Low	Forbes, 1990	1.030	0.576	1.841	0.101	0.920
	a Low	Laska 1983a	1.187	0.830	1.697	0.938	0.348
	a Low	Laska 1983b	1.099	0.857	1.408	0.743	0.457
	a Low	Laska 1983c	1.042	0.787	1.379	0.287	0.774
	a Low	McQuay 1996a	4.133	0.954	17.904	1.897	0.058
Random	a Low		1.110	0.941	1.311	1.236	0.216
	b Medium	Ali, 2007	1.107	0.917	1.338	1.060	0.289
	b Medium	Diener, 2005	1.060	1.009	1.114	2.316	0.021
	b Medium	Forbes, 1991a	1.540	0.965	2.458	1.810	0.070
	b Medium	Forbes, 1991b	1.462	0.815	2.620	1.274	0.203
	b Medium	Laska, 1983d	0.999	0.791	1.260	-0.012	0.990
	b Medium	Laska, 1983e	1.018	0.779	1.331	0.134	0.894
	b Medium	Laska, 1983f	1.316	0.984	1.759	1.851	0.064
	b Medium	Laska, 1983g	1.160	0.986	1.365	1.794	0.073
	b Medium	McQuay 1996b	7.233	1.795	29.156	2.782	0.005
	b Medium	Migliardi, 1994a	1.120	1.019	1.231	2.350	0.019
	b Medium	Migliardi, 1994b	1.131	1.026	1.247	2.470	0.013
	b Medium	Sunshine, 1996a	1.440	0.888	2.336	1.478	0.139
	b Medium	Sunshine, 1996b	1.091	0.838	1.420	0.647	0.518
	b Medium	Winter, 1983	0.974	0.619	1.531	-0.115	0.908
Random	b Medium		1.114	1.053	1.179	3.776	0.000
	c High	Diamond, 2000	1.206	0.963	1.510	1.634	0.102
	c High	Laska, 1983h	1.184	0.927	1.513	1.354	0.176
	c High	Laska, 1983i	1.031	0.843	1.260	0.293	0.769
	c High	Laska, 1983j	1.079	0.851	1.369	0.629	0.530
	c High	Laska, 1983k	1.082	0.882	1.328	0.753	0.451
	c High	McQuay 1996c	6.414	1.568	26.237	2.586	0.010
Random	c High		1.120	1.006	1.247	2.073	0.038
Random	Overall		1.115	1.063	1.169	4.480	0.000

For the low, medium, and high-dose studies the mean risk ratio is 1.110, 1.114, and 1.120, respectively. Therefore, there's no evidence that the impact varies by dose.

Click the “Show individual studies” button. This will hide all of the individual studies and display the summary effects only as shown here.



Right-click on the forest plot and change the scale to 0.50 to 2



With the pooled effects clarified in this way, we can see clearly that the summary effect size is virtually identical in all three dose groups.

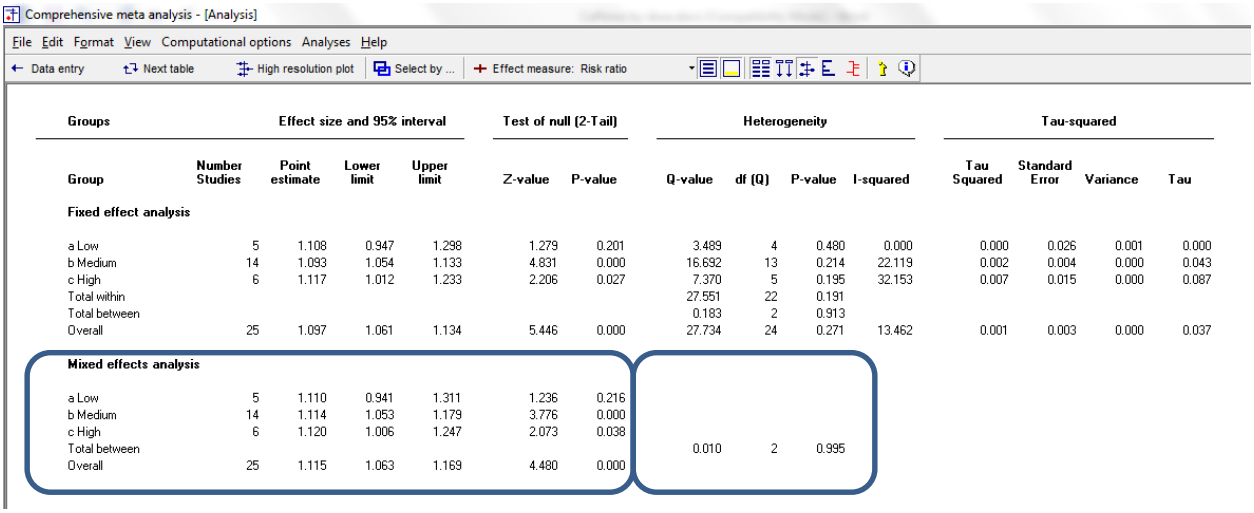
Note that the effect is statistically significant for the medium and high doses, but not for the low dose. However, it would be a serious mistake to conclude that the effect varies by dose. Clearly, the effect is essentially identical for all three doses. What distinguishes the low dose group from the others is not that the effect is smaller, but only that the estimate of the effect size is less precise. (And in this example that’s solely because there are only four studies in the low-dose group).

It is fair to say that we have evidence of the effect in two groups only. It is not correct to say that the effect in the low dose group is smaller unless the test that compares the effects shows a statistically significant effect of dose (which it will not in this case).

Toggle the “All studies button” to display the studies again.

Given what we've seen, it's clear that there the test to compare doses will not be statistically significant, but we'll proceed to show the test.

Click Next table



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														
a Low	5	1.108	0.947	1.298	1.279	0.201	3.489	4	0.480	0.000	0.000	0.026	0.001	0.000
b Medium	14	1.093	1.054	1.133	4.831	0.000	16.692	13	0.214	22.119	0.002	0.004	0.000	0.043
c High	6	1.117	1.012	1.233	2.206	0.027	7.370	5	0.195	32.153	0.007	0.015	0.000	0.087
Total within							27.551	22	0.191					
Total between							0.183	2	0.913					
Overall	25	1.097	1.061	1.134	5.446	0.000	27.734	24	0.271	13.462	0.001	0.003	0.000	0.037
Mixed effects analysis														
a Low	5	1.110	0.941	1.311	1.236	0.216								
b Medium	14	1.114	1.053	1.179	3.776	0.000								
c High	6	1.120	1.006	1.247	2.073	0.038								
Total between							0.010	2	0.995					
Overall	25	1.115	1.063	1.169	4.480	0.000								

This screen displays two sets of statistics

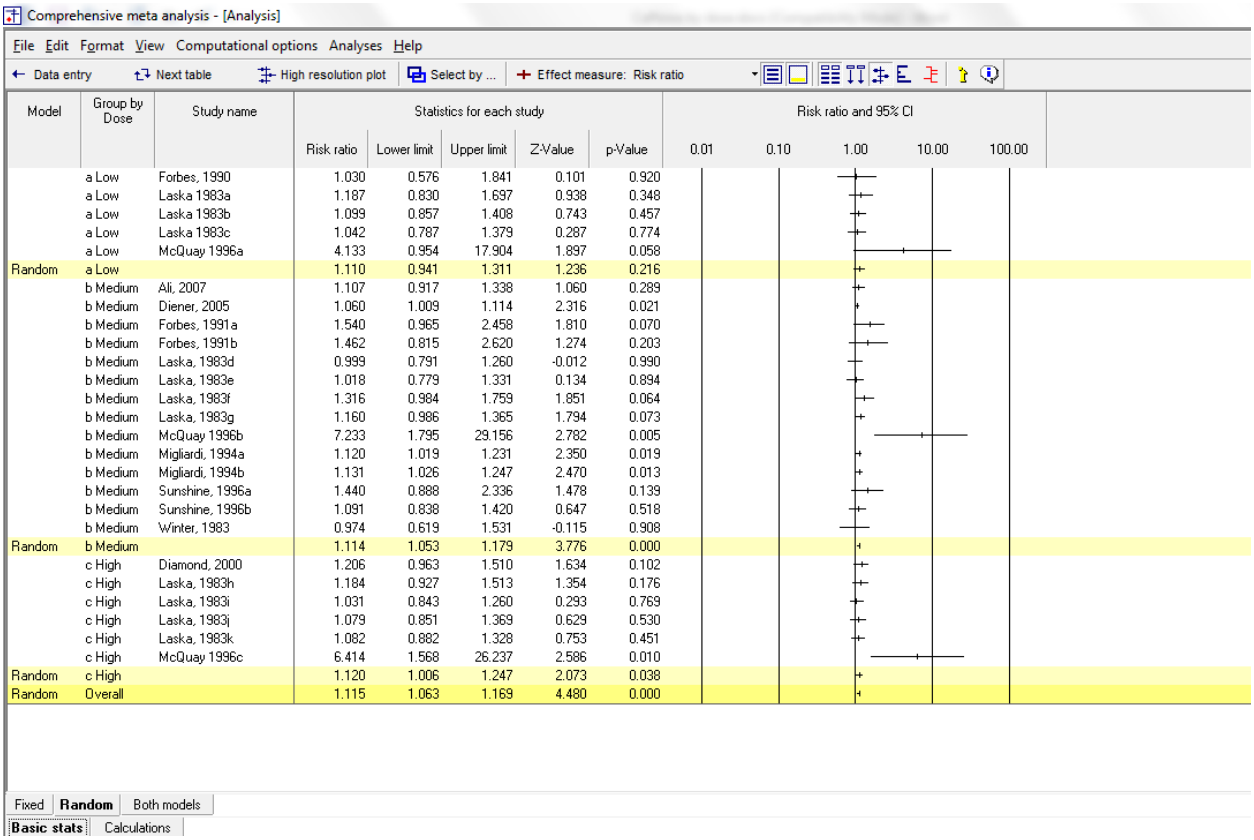
The table labeled "Fixed-effect analysis" uses fixed-effect weights within subgroups. The table labeled "Mixed-effects analysis" uses random-effects weights within subgroups. This is the table we will use.

As we saw on the prior screen, the risk ratio within the three subgroups is 1.110, 1.114, and 1.117. The effect is not statistically significant in the low-dose group (p=0.216) but is statistically significant in the other two (p< 0.001, p=0.038). However, this does not suggest that the effect is smaller in the first group (clearly, the effect size in the sample is virtually identical in all three groups).

To test the hypothesis that the effect size varies by dose we look to the line labeled "Total between". The Q-value is 0.010 with 2 df, and the corresponding p-value is 0.995.

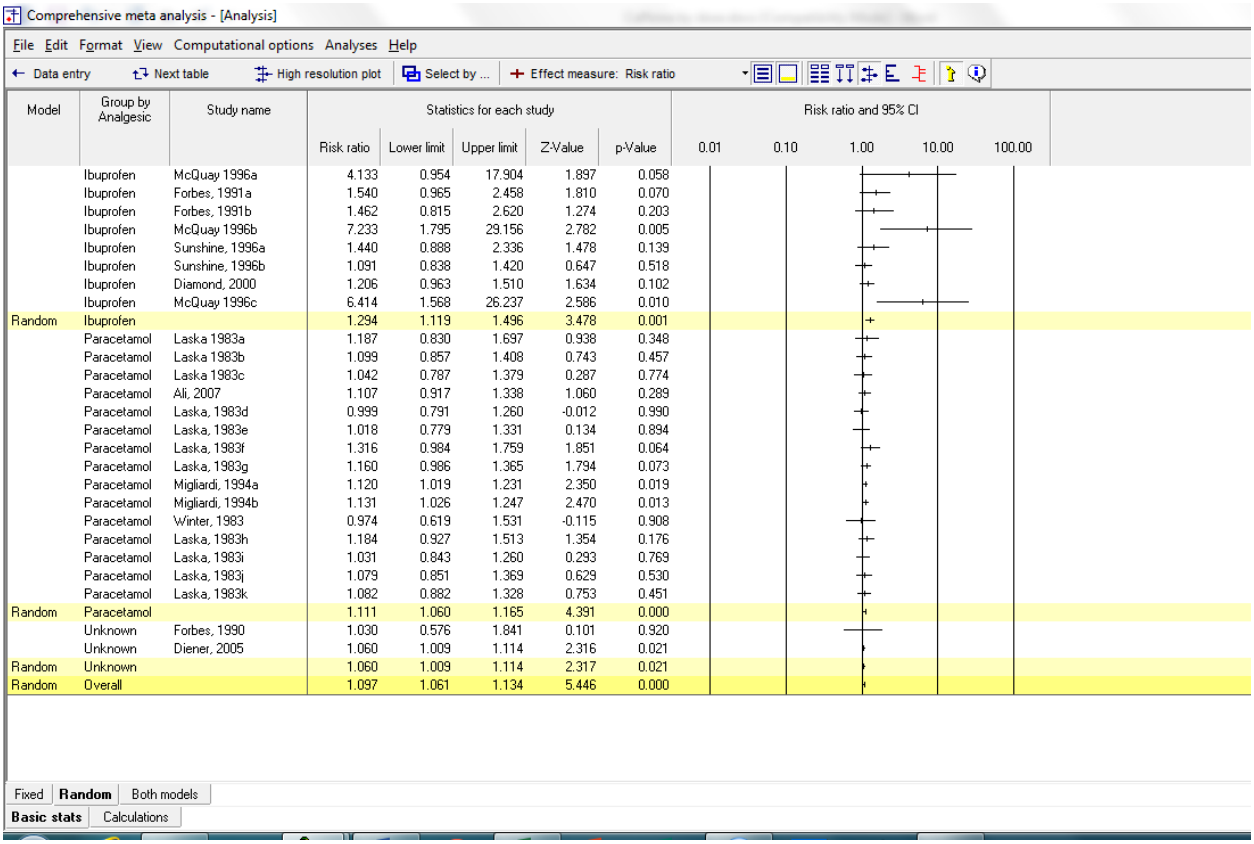
Click Next table to return to this screen.

Re-set the scale to 0.01 to 100



Above, we ran an analysis to see if the effect size varied by dose. Now, we'll run an analysis to see if the effect size varies by the type of analgesic.

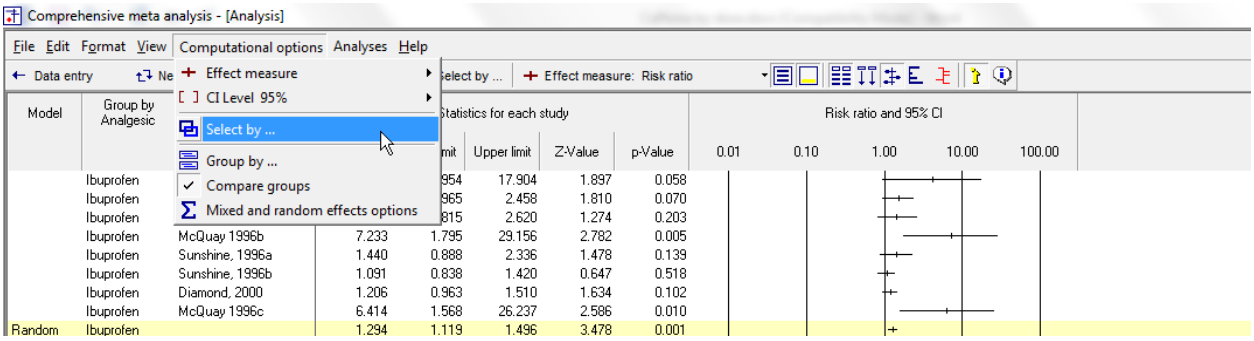
Click Computational options > Group by > Analgesic

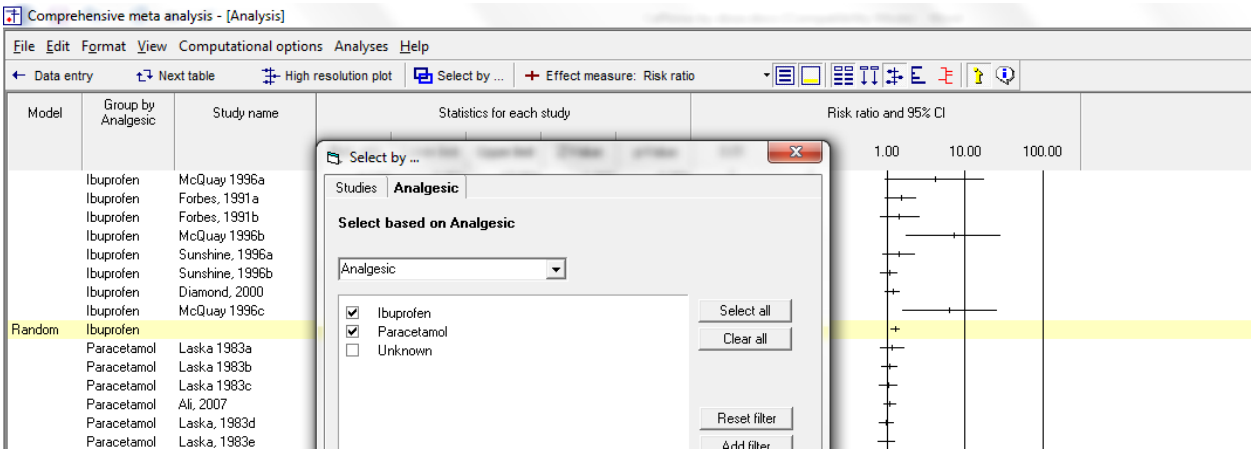


We see that there are a number of studies that used Ibuprofen or Paracetamol, but only a few that are classified as "Unknown". Let's limit the analysis to those the first two groups.

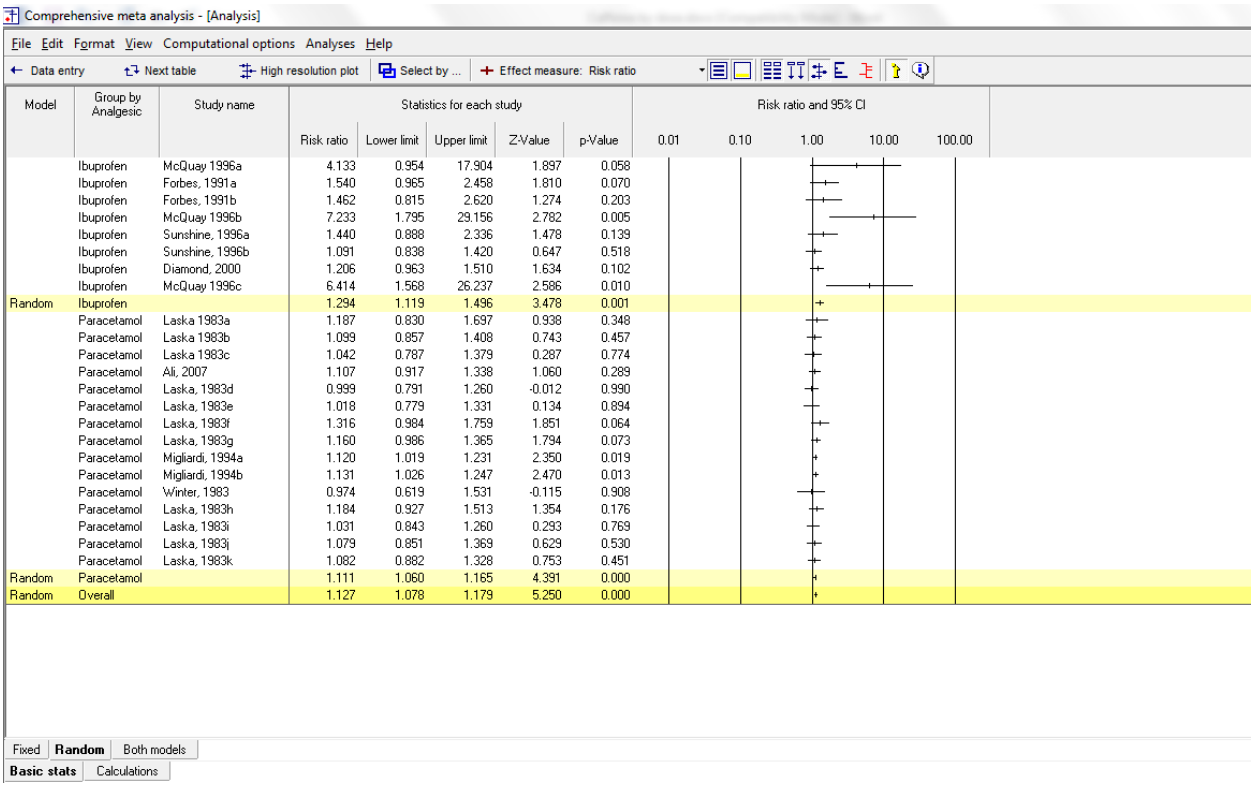
Click Computational options > Select by > Analgesic

- Select Ibupfrofen and Paracetamol
- De-select “Unknown”
- Click Ok

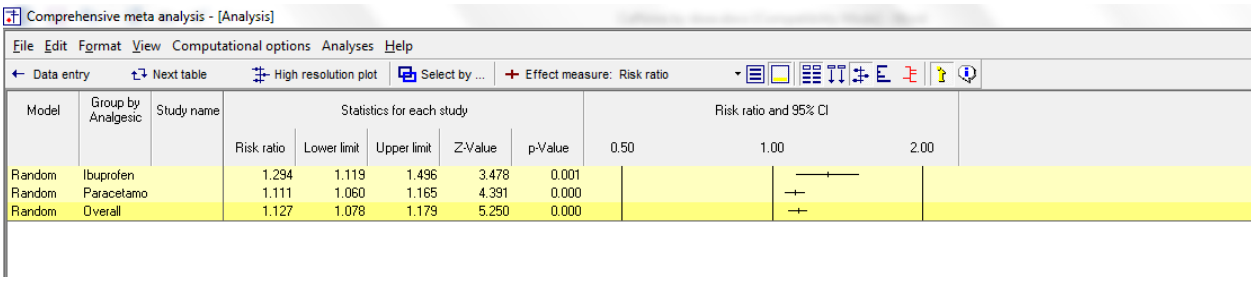




The screen should look like this

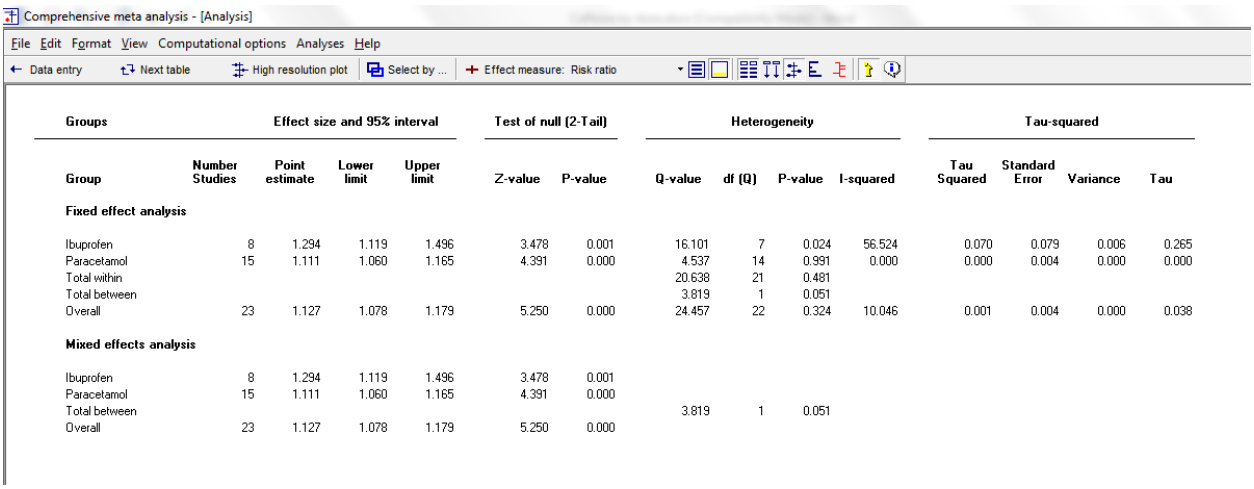


Hide the individual studies and change the scale



For studies that used ibuprofen, caffeine increased the response rate by 29%. For studies that used Paracetemol, caffeine increased the response rate by 11%. Thus, the difference in this sample is substantial.

However, there's a lot of overlap in the confidence intervals and it's not clear whether or not this difference is statistically significant. To compare the two effects, click Next table.



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														
Ibuprofen	8	1.294	1.119	1.496	3.478	0.001	16.101	7	0.024	56.524	0.070	0.079	0.006	0.265
Paracetamol	15	1.111	1.060	1.165	4.391	0.000	4.537	14	0.991	0.000	0.000	0.004	0.000	0.000
Total within							20.638	21	0.481					
Total between							3.819	1	0.051					
Overall	23	1.127	1.078	1.179	5.250	0.000	24.457	22	0.324	10.046	0.001	0.004	0.000	0.038
Mixed effects analysis														
Ibuprofen	8	1.294	1.119	1.496	3.478	0.001								
Paracetamol	15	1.111	1.060	1.165	4.391	0.000								
Total between							3.819	1	0.051					
Overall	23	1.127	1.078	1.179	5.250	0.000								

As before, we're working with the section labeled "Mixed effects analysis" and the relevant line is the one labelled "Total between". The Q-value is 3.819 with 1 df, and the corresponding p-value is 0.051.

People have different ways of reacting to a p-value this close to 0.05. I would conclude that caffeine does have more of an impact for patients being treated with ibuprofen than for patients being treated with paracetamol.

Perhaps more to the point, this suggests that the overall effect size reported earlier (that caffeine increases the response rate by 11%) is really not that relevant to clinical practice. Rather, the utility of caffeine depends on the analgesic. For patients being treated with paracetamol, caffeine had a small impact. For patients being treated with ibuprofen, caffeine had a larger impact.

As always, the difference between groups is observational, not causal. It's possible that caffeine works better with ibuprofen. But it's also possible that the studies which used ibuprofen differed in some ways from the studies that used paracetamol and that it's this factor that was responsible (at least in part) for the difference in effect sizes.

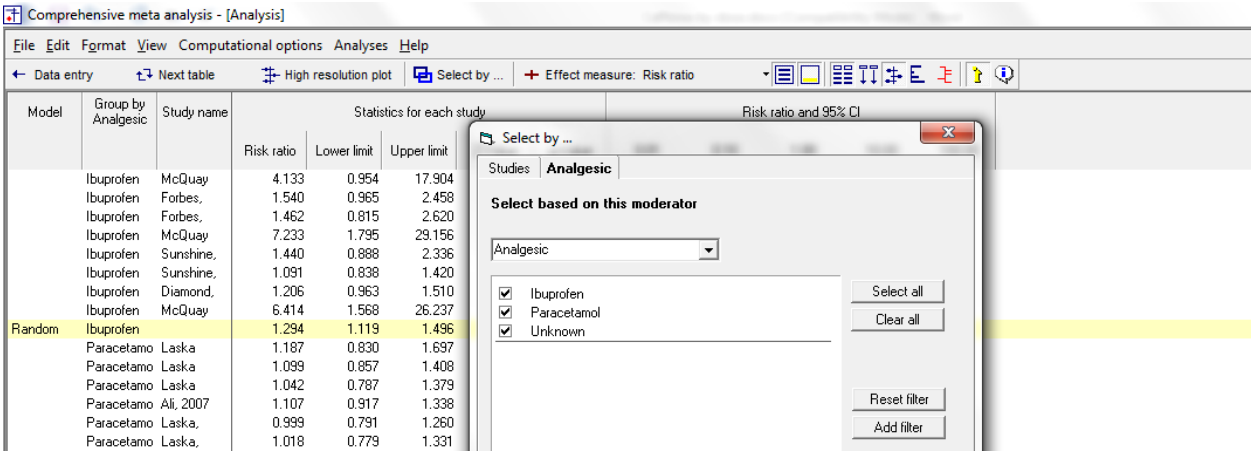
It's worth noting that the higher response rate for the ibuprofen studies seems to be driven (at least in part) by three studies. If there was something unique about these studies that led to the higher response rate, then the difference between subgroups might be due to this factor, and not to the analgesic.

This is always a concern when we compare subgroups. While the allocation to caffeine vs control is based on random assignment, the "allocation" to one subgroup vs. another is observational. While we are referring to the subgroups as "Ibuprofen" vs. "Paracetamol", it's possible that they should be called "Ibuprofen young sample" vs. "Paracetamol older sample", and that caffeine works better with younger patients. (The age part of this example is purely hypothetical).

The studies were also coded for the nature of the pain, and we want to see if the effect size varies by this factor.

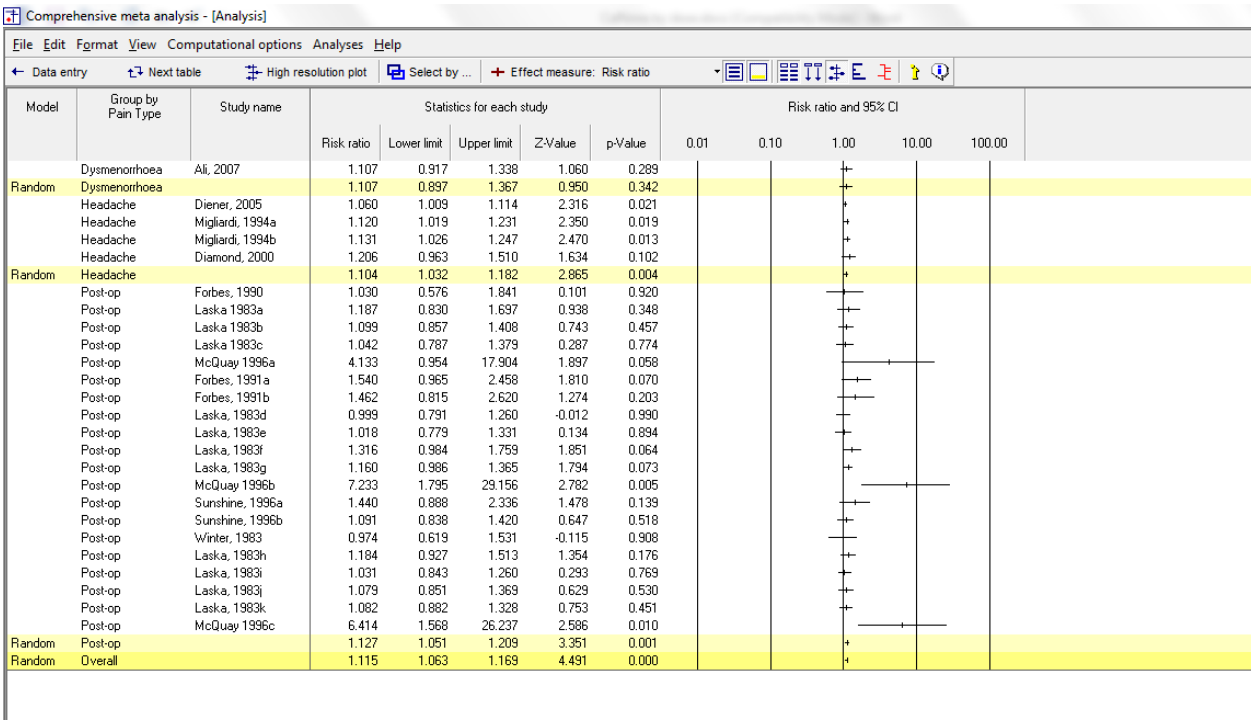
First, we need to remove the current filter.

Click Computation options > Select by and tick all the options



Group by Pain type

Select Computational options > Group by > Pain type



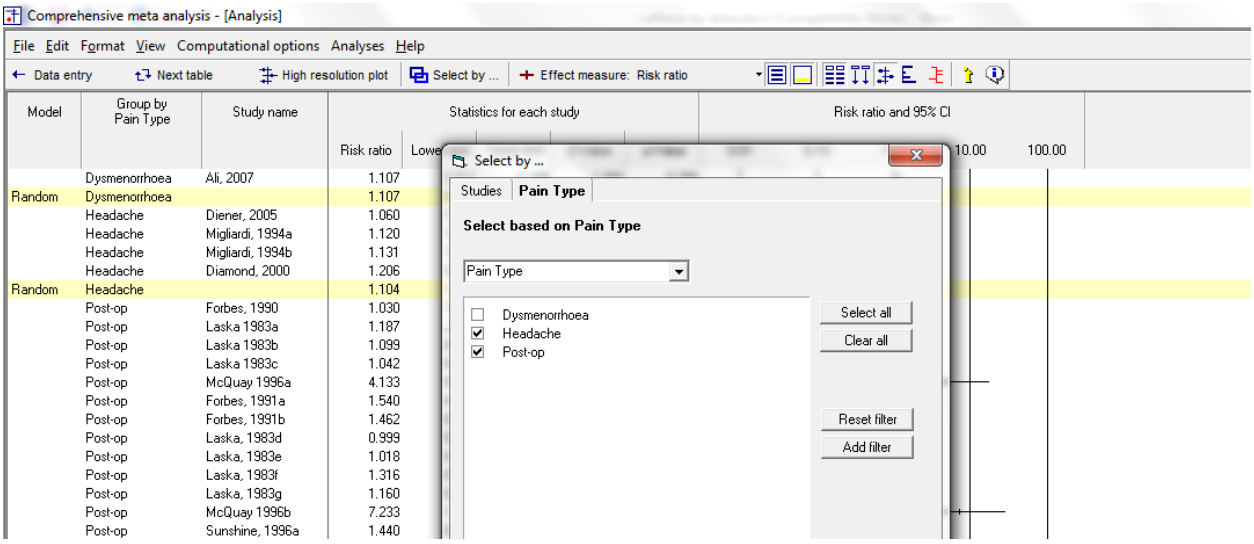
Model	Group by Pain Type	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	Dysmenorrhoea	Ali, 2007	1.107	0.917	1.338	1.060	0.289
Random	Dysmenorrhoea		1.107	0.897	1.367	0.950	0.342
	Headache	Diener, 2005	1.060	1.009	1.114	2.316	0.021
	Headache	Migliardi, 1994a	1.120	1.019	1.231	2.350	0.019
	Headache	Migliardi, 1994b	1.131	1.026	1.247	2.470	0.013
	Headache	Diamond, 2000	1.206	0.963	1.510	1.634	0.102
Random	Headache		1.104	1.032	1.182	2.865	0.004
	Post-op	Forbes, 1990	1.030	0.576	1.841	0.101	0.920
	Post-op	Laska 1983a	1.187	0.830	1.697	0.938	0.348
	Post-op	Laska 1983b	1.099	0.857	1.408	0.743	0.457
	Post-op	Laska 1983c	1.042	0.787	1.379	0.287	0.774
	Post-op	McQuay 1996a	4.133	0.954	17.904	1.897	0.058
	Post-op	Forbes, 1991a	1.540	0.965	2.458	1.810	0.070
	Post-op	Forbes, 1991b	1.462	0.815	2.620	1.274	0.203
	Post-op	Laska, 1983d	0.999	0.791	1.260	-0.012	0.990
	Post-op	Laska, 1983e	1.018	0.779	1.331	0.134	0.894
	Post-op	Laska, 1983f	1.316	0.984	1.759	1.851	0.064
	Post-op	Laska, 1983g	1.160	0.986	1.365	1.794	0.073
	Post-op	McQuay 1996b	7.233	1.795	29.156	2.782	0.005
	Post-op	Sunshine, 1996a	1.440	0.888	2.336	1.478	0.139
	Post-op	Sunshine, 1996b	1.091	0.838	1.420	0.647	0.518
	Post-op	Winter, 1983	0.974	0.619	1.531	-0.115	0.908
	Post-op	Laska, 1983h	1.184	0.927	1.513	1.354	0.176
	Post-op	Laska, 1983i	1.031	0.843	1.260	0.293	0.769
	Post-op	Laska, 1983j	1.079	0.851	1.369	0.629	0.530
	Post-op	Laska, 1983k	1.082	0.882	1.328	0.753	0.451
	Post-op	McQuay 1996c	6.414	1.568	26.237	2.586	0.010
Random	Post-op		1.127	1.051	1.209	3.351	0.001
Random	Overall		1.115	1.063	1.169	4.491	0.000

Risk ratio and 95% CI: 0.01 0.10 1.00 10.00 100.00

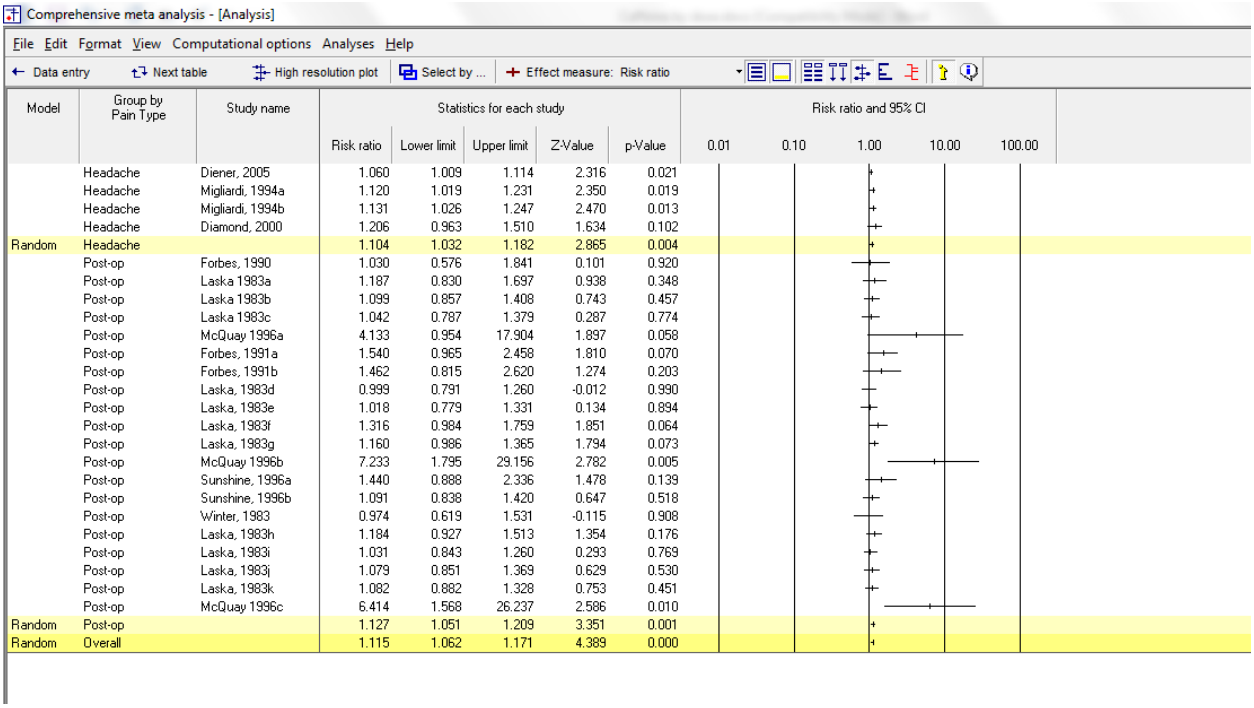
It seems that we have only one study where the pain type is Dysmenorrheea, and so let's remove that from this analysis

Click Computational options > Select by > Pain type

Select Headache and Post-op



Group by Pain type



Model	Group by Pain Type	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	Headache	Diener, 2005	1.060	1.009	1.114	2.316	0.021
	Headache	Migliardi, 1994a	1.120	1.019	1.231	2.350	0.019
	Headache	Migliardi, 1994b	1.131	1.026	1.247	2.470	0.013
	Headache	Diamond, 2000	1.206	0.963	1.510	1.634	0.102
Random	Headache		1.104	1.032	1.182	2.865	0.004
	Post-op	Forbes, 1990	1.030	0.576	1.841	0.101	0.920
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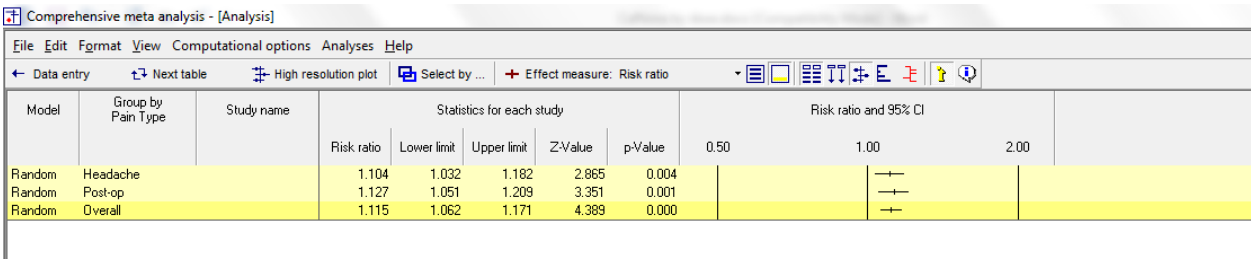
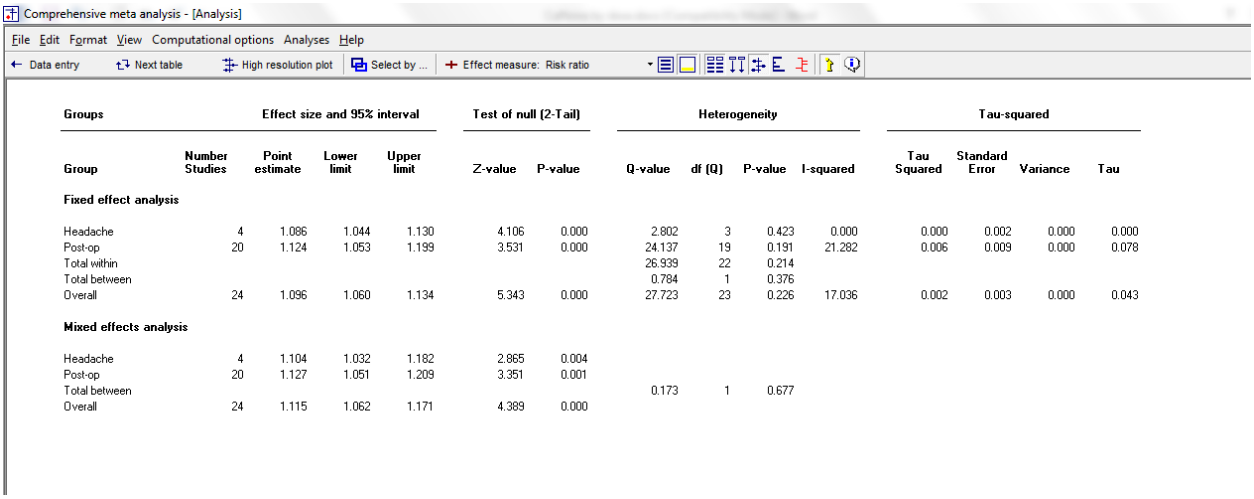
	Post-op	Laska, 1983k	1.082	0.882	1.328	0.753	0.451
	Post-op	McQuay 1996c	6.414	1.568	26.237	2.586	0.010
Random	Post-op		1.127	1.051	1.209	3.351	0.001
Random	Overall		1.115	1.062	1.171	4.389	0.000

Hide the individual studies and expand the scale



The effect size seems to be almost identical for the two types of pain

Click Next table



The risk ratio is 1.104 for Headache, and 1.127 for Post-op. The line total-between shows the Q-value that compares these two effects sizes. The Q-value is 0.173 with 1 df and p=0.677.

There's no evidence that the impact of caffeine differs by pain type.

Above, we found evidence that caffeine had a stronger effect for patients on ibuprofen than for patients on parecetamol.

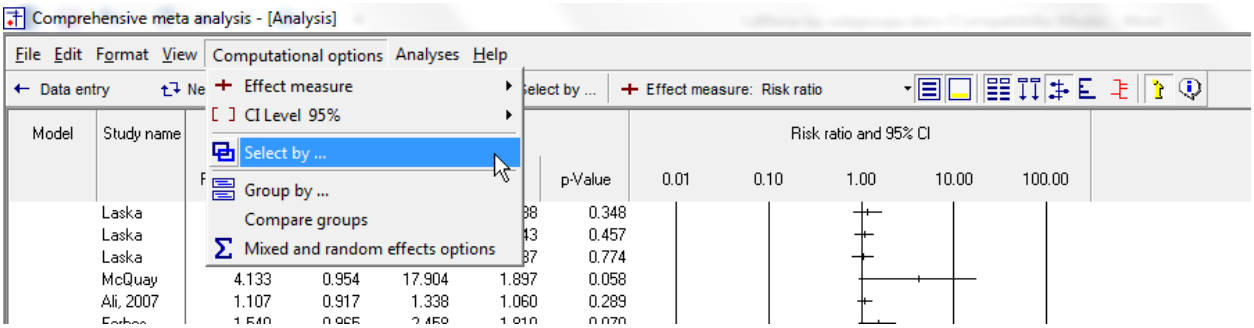
It would be helpful to know if this relationship could be explained by a confound with type of pain, or with dose. For example, if the patients taking ibuprofen were more likely to have had a higher dose of caffeine, this could explain the larger effect for these patients. In the present case this seems unlikely, since we found essentially no effect for dose. However, for completeness we will proceed with a meta-regression.

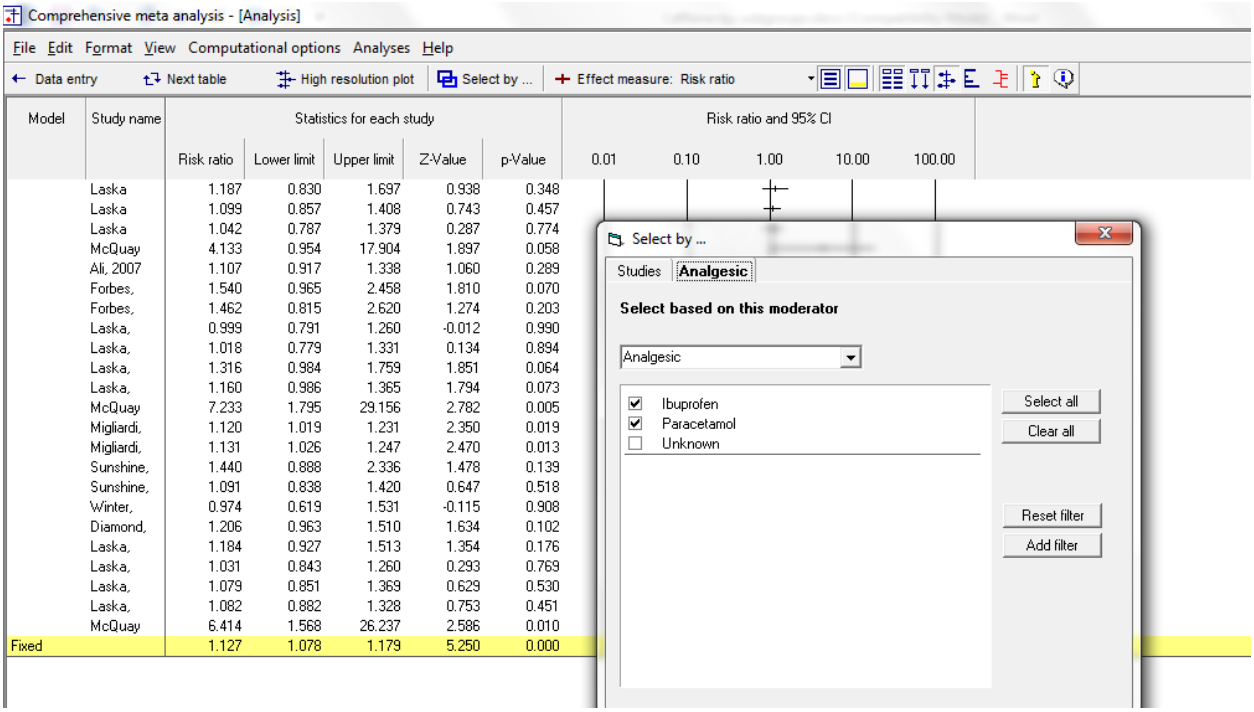
As before, we will limit the analysis to studies that used ibuprofen or paracetamol. We will do this for all the regressions, to ensure that all are based on the same set of studies.

To select only the desired studies

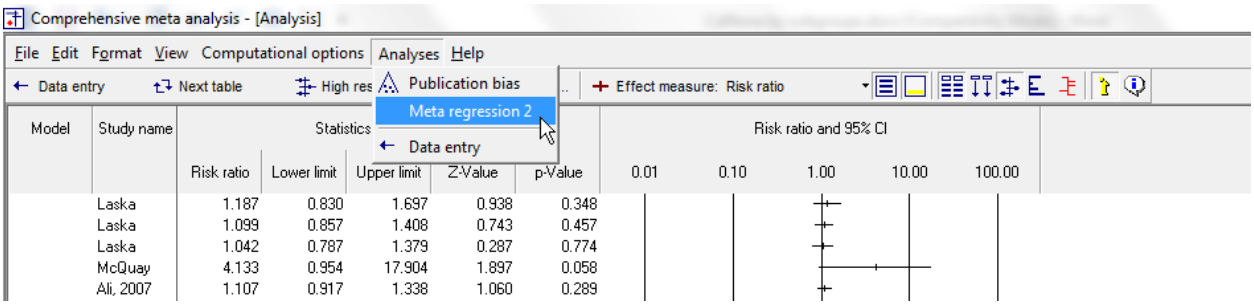
On the main analysis screen (before proceeding to the regression)

- Click Computational options > Select by
- Select Analgesic
- Select Ibuprofen and Paracetamol
- De-select Unknown
- Click Ok

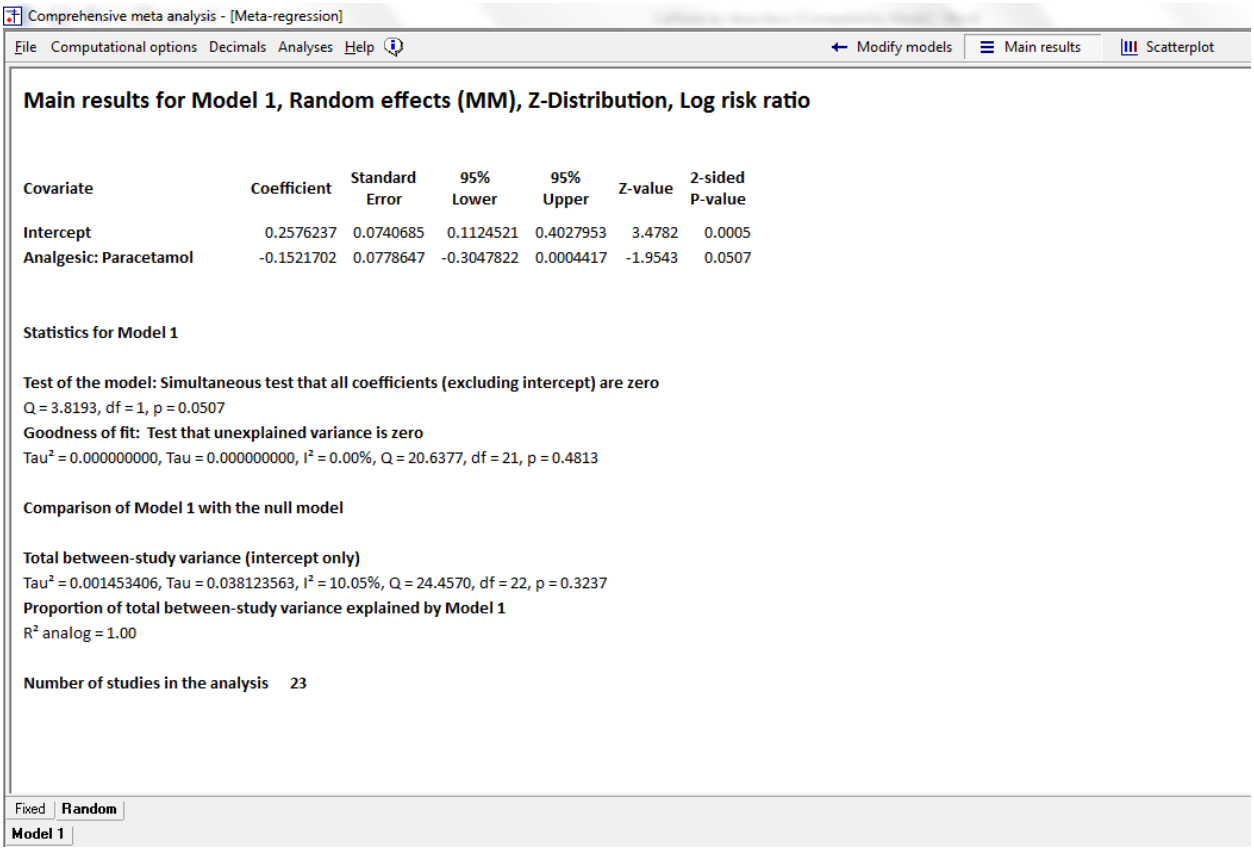




Click Analyses > Meta-regression 2

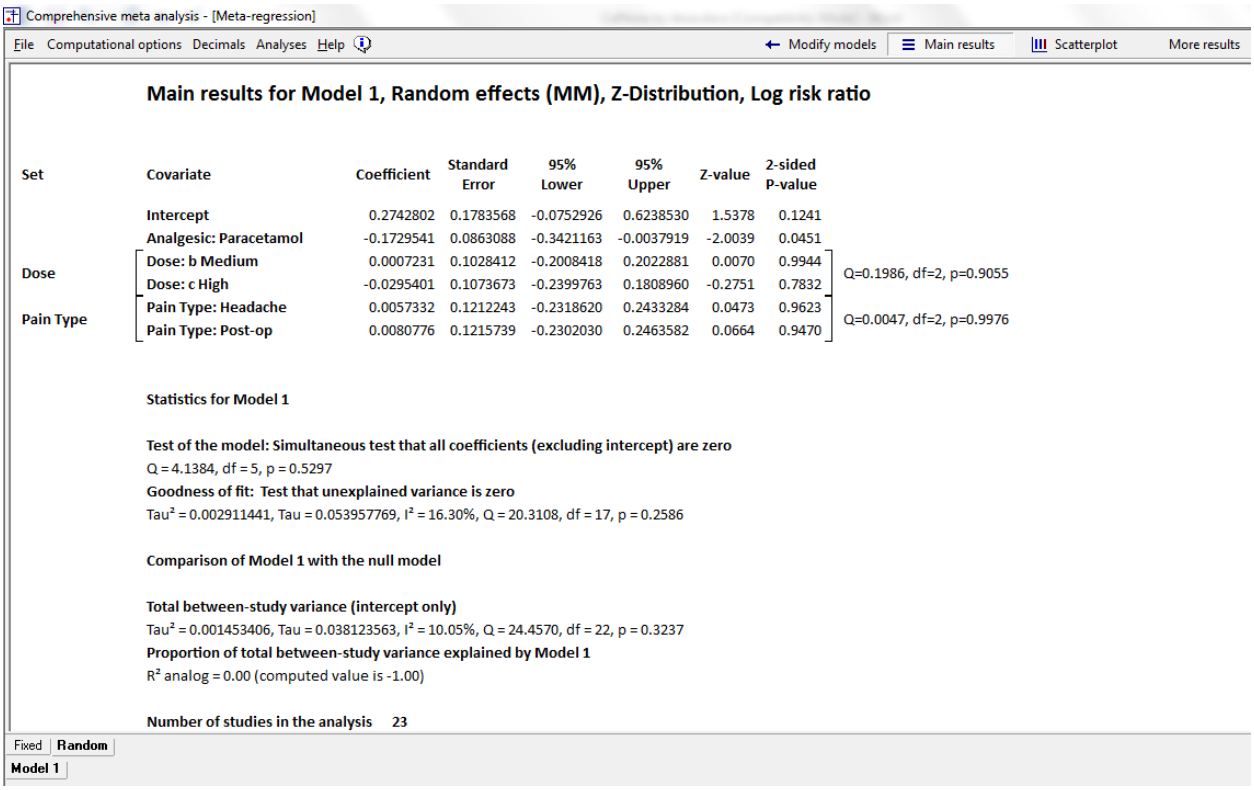


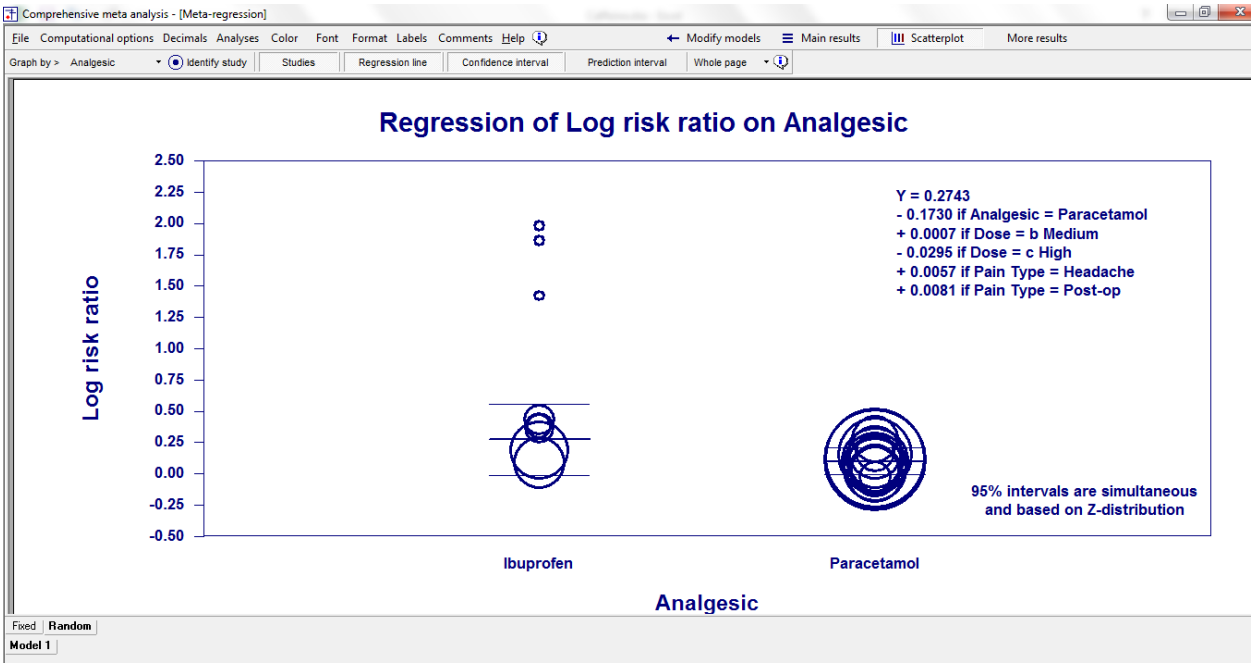
First, we run the regression using only Analgesic as the covariate. The Q-value for the analgesic is 3.8193 with p= 0.0507, precisely the same values we saw in the subgroups analysis.



Now, we add Dose and Pain Type as covariates in addition to the analgesic. With these covariates in the model, the line for "Analgesic" tests the impact of this covariate controlling for the other covariates. The p-value is now 0.0451. As expected, since the other covariates had no relation to effect size, including them in the model made no real difference. The p-value for analgesic is essentially unchanged.

This tells us that the relationship between analgesic type and effect size is not due to a confound with these other two covariates. Unfortunately, it's still possible that it's due to a confound with some other (unknown) covariates (possibly some unique aspect of the three outlier studies in the ibuprofen group).




Comprehensive meta analysis - [Meta-regression]
File Computational options Decimals Analyses Color Font Format Labels Comments Help
Modify models
Main results
Scatterplot
More results
Graph by > Analgesic
Identify study
Studies
Regression line
Confidence interval
Prediction interval
Whole page
Regression of Log risk ratio on Analgesic
Log risk ratio
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
Y = 0.2743
- 0.1730 if Analgesic = Paracetamol
+ 0.0007 if Dose = b Medium
- 0.0295 if Dose = c High
+ 0.0057 if Pain Type = Headache
+ 0.0081 if Pain Type = Post-op
95% intervals are simultaneous and based on Z-distribution
Ibuprofen
Paracetamol
Analgesic
Fixed
Random
Model 1

Summary

This analysis includes 25 studies where patients were randomized to receive either analgesic alone or analgesic plus caffeine. Outcome was the proportion of patients who reported a "good" level of pain relief. The effect size was the risk ratio.

Does caffeine affect the likelihood of a good response?

The mean risk ratio is 1.111, which means that caffeine increased the likelihood of a good response by about 11%.

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 1.064 to 1.161, which tells us that the mean 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 4.721, with a corresponding *p*-value is < 0.001. We can reject the null hypothesis that caffeine has no effect on response, and conclude that the risk of death is lower in the high-dose group.

Does the effect size vary across studies?

The *observed* effect size varies somewhat from study to study, but a certain amount of variation is expected due to sampling error. We need to determine if the observed variation falls within the range that can be attributed to sampling error (in which case there is no evidence of variation in true effects), or if it exceeds that range.

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 27.73 with 24 degrees of freedom and a p-value of 0.271. Since the observed variance falls within the range that can be attributed to sampling error, we cannot reject the null that the true effect size is the same in all studies. At the same time, since the observed variance does exceed the expected value, we can report statistics for the estimate of dispersion in true effects.

The I^2 statistic tells us what proportion of the observed variance reflects differences in true effect sizes rather than sampling error. Here, I^2 is 13.642%.

T^2 is the variance of true effect sizes (in log units). Here, T^2 is 0.001. *T* is the standard deviation of true effects (in log units). Here, *T* is 0.037.

Does the effect size vary by subgroup?

While the mean effect size across all studies is modest (a risk ratio of 1.111), it's possible that the mean risk ratio varies by subgroup.

We used subgroup analyses to compare the effect size in studies that employed a low dose, moderate dose, or high dose of caffeine. The mean risk ratio in these three groups was 1.11, 1.11, and 1.12, respectively. The *Q*-value for the difference is 0.010with 2 *df* and $p = 0.995$. Thus, there was no evidence that the risk ratio varied as a function of caffeine dose.

We used subgroup analyses to compare the effect size in studies where patients were being treated for headache vs. studies were being treated for post-surgical pain. The mean risk ratio in these two groups was 1.10, 1.13, respectively. The *Q*-value for the difference is 0.173 with 1 *df* and $p = 0.877$. Thus, there was no evidence that the risk ratio varied as a function of the pain type.

We used subgroup analyses to compare the effect size in studies where the analgesic was Ibuprofen vs. studies where the analgesic was Paracetamol. The mean risk ratio in these two groups was 1.29, 1.11, respectively. The *Q*-value for the difference is 3.819 with 1 *df* and $p = 0.051$. Thus, there is evidence that the caffeine had more of an impact in the Ibuprofen studies than it did in the Paracetamol studies.

We used regression to see if this relationship could be explained by a confound with other moderators. The relationship between effect size and drug type remained even after we controlled for caffeine dose and for pain-type. Nevertheless, we cannot rule out the possibility that the selection of drug was related to other factors, and that these factors were responsible for the fact that caffeine was more effective in one subgroup than the other.