Suggested answers to exercise: Practical Meta-Analysis using CMA Version 2

1. *Start CMA2.* Exactly how to do this depends on the system you are using.

2. *Enter these into CMA as follows: click "Insert", "Column" "Study names". Type in the study names. Click "Insert", "Column", "Effect size data". Click "Next", "Comparison of two groups" "Next", "Dichotomous, Unmatched groups.", "Events and sample size in each group", "Finish". Enter the data. Put in the group names, "Metoclopramide" and "Placebo", and the names for events and not events, "Significant pain relief" and "No significant pain relief". Now type the data into the columns. The odds ratios, log odds ratios and standard error should appear.* You should see:

Study name	Metoclopramide Significant pain relief	Metoclopramide Total N	Placebo-B Significant pain relief	Placebo-B Total N	Odds ratio	Log odds ratio	Std Err
Tfelt-Hansen (1980)	19	40	18	47	1.458	0.377	0.436
Tek (1990)	16	24	5	26	8.400	2.128	0.660
Coppola (1995)	12	24	7	24	2.429	0.887	0.607

3. *Click "Run analyses". What do you get?* You should see:

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-value	p-value
	Tfelt-Hansen (1980)	1.458	0.620	3.427	0.864	0.388
	Tek (1990)	8.400	2.306	30.603	3.226	0.001
	Coppola (1995)	2.429	0.739	7.9797	1.462	0.144
Fixed		2.469	1.340	4.551	2.896	0.004

There is also a simple line forest plot.

4. *Now click "Next table". What additional information do you have?* We get a random effects estimate in addition to the fixed effect estimate we had in Question 3. We also get the heterogeneity test and the I^2 statistic.

5. *What kind of analysis would you use here, fixed effects or random effects? Does it make a difference?* The chi-squared heterogeneity test gives P = 0.086. This is not significant by the conventional standard of <0.05, but it is by the more relaxed standard of <0.10 often advocated for this low-powered test. In this case the fixed and random effects point estimates are similar, though the random effects confidence interval is much wider. Personally, I would choose the fixed model here unless I had some other reason for thinking that the studies are not all estimating the same treatment effect, but many people (including referees and examiners) would disagree with me. It was the random effects estimate which was reported in the original paper.

6. *Try "High resolution plot". What do you think?* I don't like it much. It doesn't label the treatments, despite making you type the names in earlier. You can type them in yourself. There is a toolbar icon for doing this, a square with two little bars at the bottom. It doesn't label the combined estimate, which is the fixed effects estimate. You can get the random effects estimate on the plot, but it is tricky.

7. *Go back to the table view. At the bottom of the screen there are three buttons labelled "Fixed", "Random", and "Both models". Try clicking each of them. What happens?* You get the fixed effects estimate, the random effects estimate, and both model estimates on the table. *Stay with "Both models". Try the high resolution plot again. What has changed?* The fixed effects estimate is now labelled. *Now try clicking "Computational options". This gives us the same three options: "Fixed", "Random", and "Both models". Try clicking each. What happens?* Now we get the random effects estimate or both estimates, as well as the labelling of the fixed effect estimate.

8. *In the table view, try changing the "Effect measure". There are three different odds ratios. How does choosing each of them effect the tests and estimates?* (See overleaf for output tables.) Each version gives slightly different estimates for the effect, its confidence interval, and the heterogeneity. Note that for the default odds ratio and the Mantel Haenszel odds ratio the random effect estimate appears the same, but it is not if we take more decimal places. ("Format", "Increase decimals", will do this.) *How does changing to relative risk affect the tests and estimates?* The point estimates are smaller. It is usually the case that risk ratios are closer to one than are the corresponding odds ratios. The P values for the point estimates are larger, though the difference is small. There is slightly more heterogeneity on the odds ratio scale than on the risk ratio scale. I don't think that this is a consistent thing, it depends on the data set, as do the P values. As for odds ratios, the different versions of the risk ratios give slightly estimates and tests. *How about risk difference?* The point estimate is now quite different. Being the difference between two proportions, it has to lie between +1 and −1 and the no difference value is zero, not one. There are two extra columns, for standard error and variance of the effect size. The standard error would be meaningless for risk ratio and for odds ratio, because the standard error is calculated for the log of the ratio, not the ratio itself. The variance is just the square of the standard error. The P values and heterogeneity are also different. As with odds ratios and risk ratios, the different versions of the risk difference give slightly estimates and tests.

9. *What might influence the choice of estimate for the effect?* Risk ratios are more easy to understand than odds ratios. We might have to use odds ratios where the individual trial estimates have been adjusted using logistic regression. I think that I would prefer risk ratios where I could estimate them. However, where risks are high, they are forced to be close to one, which makes them difficult to interpret and so they don't work well when the risks vary a lot between studies. Risk differences are also easy to interpret if the risks on a treatment are all similar, not if they vary much. Odds ratios should work for any dichotomous outcome data, but are more difficult to interpret intuitively.

Output tables for Question 8

Odds ratio:

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	3	2.469	1.339	4.551	2.896	0.004	4.906	2	0.086	59.230	0.458	0.780	0.608	0.677
Random	3	2.837	1.048	7.680	2.052	0.040								

MH Odds ratio:

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	3	2.510	1.387	4.542	3.040	0.002	4.908	2	0.086	59.253	0.458	0.780	0.608	0.677
Random	3	2.837	1.048	7.683	2.052	0.040								

Peto Odds ratio:

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	3	2.497	1.396	4.464	3.086	0.002	4.647	2	0.098	56.959	0.364	0.643	0.413	0.604
Random	3	2.704	1.094	6.687	2.154	0.031								

Risk ratio:

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	3	1.634	1.133	2.357	2.629	0.009	4.346	2	0.114	53.980	0.140	0.262	0.069	0.374
Random	3	1.802	1.016	3.205	2.006	0.045								

MH risk ratio:

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	3	1.734	1.207	2.491	2.979	0.003	4.447	2	0.108	55.022	0.146	0.268	0.072	0.382
Random	3	1.806	1.008	3.233	1.988	0.047								

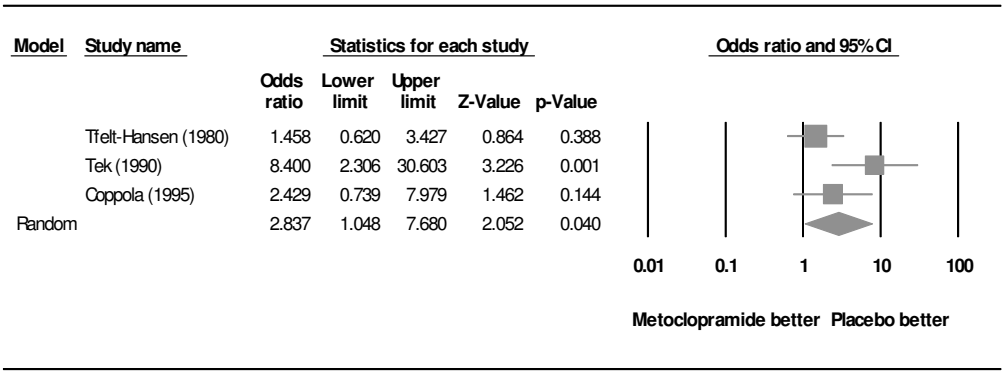
Risk difference:

Model		Effect size and 95% interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	3	0.243	0.070	0.005	0.107	0.379	3.493	0.000	5.601	2 0.061	64.292	0.027	0.042	0.002	0.163	0.243
Random	3	0.254	0.118	0.014	0.023	0.485	2.154	0.031								

MH risk difference:

Model		Effect size and 95% interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	3	0.226	0.070	0.005	0.089	0.363	3.232	0.001	5.661	2	0.059	64.668	0.027	0.042	0.002	0.165
Random	3	0.254	0.118	0.014	0.022	0.486	2.143	0.032								

10. *Try to capture the high resolution plot in Windows by clicking and CRTL-C, then clicking CRTL-V in a Word document. Does it work?* No, it doesn't. *Try a right-click. Does that work?* Yes, we have an option "Copy to clipboard as WMF" (Windows Meta-File). *Try "File", "Export to Word." Notice that this creates a new Word document. You can then copy this into anything in the usual Windows way.* I have done this here:



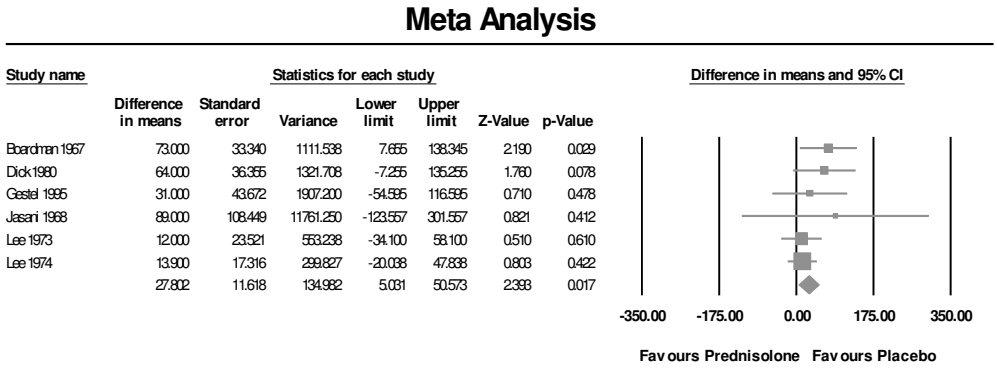
11. *Enter the data in CMA and carry out a meta-analysis.* The P value for heterogeneity is 0.10. We could use a random effects model, as the original authors did, giving a combined odds ratio estimate 1.023 (95% CI 0.717 to 1.460, P = 0.9).

12. *Compare this to the analysis published in the BMJ. Do you get the same answer? If you didn't, how does yours differ?* They got a random effects estimate odds ratio = 1.03 (95% CI 0.71 to 1.48). It is not quite the same. If you choose "Computational options" and "Effect measures", there are three different odds ratios but none are the same as the estimate in the *BMJ*. The authors of the paper do not say which method they used, but they do say that they used CMA.

13. *Enter the data by extracting them from the Word file. This time, after you choose "Compare two groups" you will need to choose "Continuous (Means)", "Unmatched groups, post data only" and "Mean, SD, and sample size in each group". This creates columns for all these, plus an extra column labelled "Effect direction". In Word, highlight the table columns, excluding the heading rows. Click CTRL-C. Highlight the first cell of the CMA spreadsheet and click CTRL-V.* It is easy if the data table is in the right format. You can also enter data column by column if it is not.

14. *Carry out a meta-analysis.* The fixed effects combined estimate for the standardised difference in mean grip strength, prednisolone minus placebo, is 0.372 standard deviations (95% CI 0.097 to 0.647 standard deviations, P = 0.008. There is no evidence of heterogeneity (chi-squared = 2.427, d.f. = 5, P = 0.8, I^2 = 0.000).

15. *Try changing the "Effect measure" from "Standardised difference in means" to "Difference in means". What happens?* The combined estimate is now 27.802 mm Hg (95% CI = 5.031 to 50.573 mm Hg, P = 0.017). The surprising thing is that the significance P value has changed, more than doubled. This is because for the standardised estimate each trial is standardised by its own standard deviation. Neither is more correct than the other, we should decide which we want before we do the analysis and stick to it. *Adjust the scale of the forest plot using "Format". (Hint: you will need to insert your own "Customized scale").* You can adjust the scale on the forest plot. You have to do this in the table view, as the menu box in the high-resolution view doesn't allow a wide enough scale for this data set. Set the number you enter to be big enough to accommodate your plot. I don't like arrows much, so I picked 350. I also put the treatment labels in.

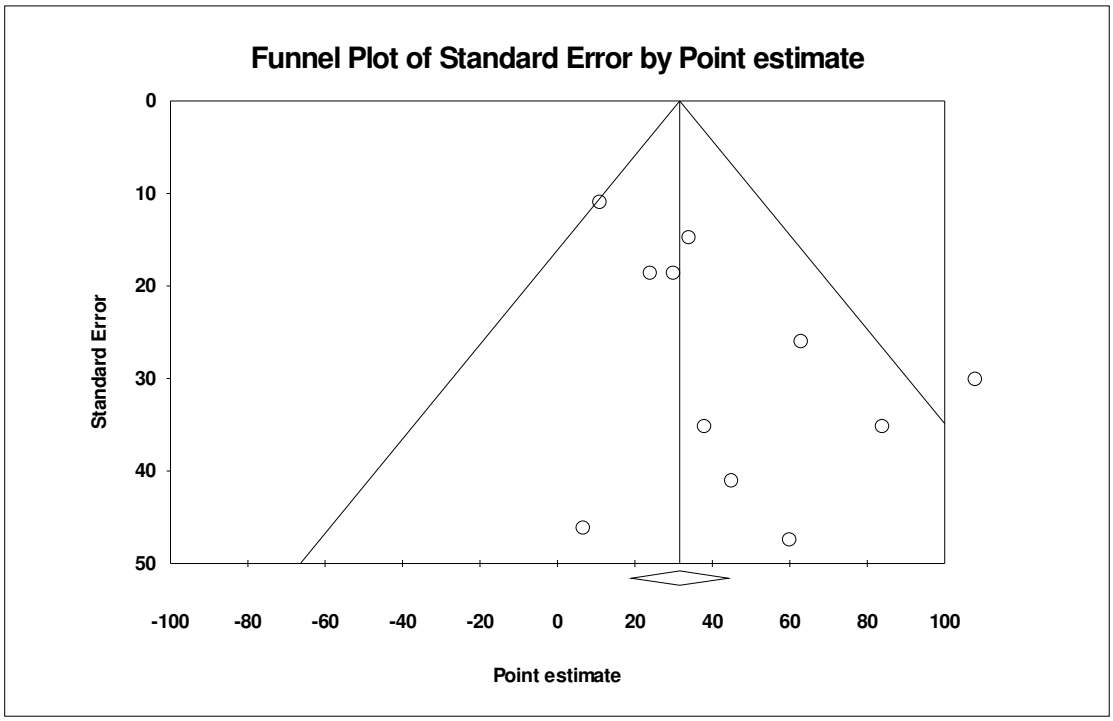


16. *Why is there no difference between the results of the fixed effects analysis and the random effects analysis? (I think this is wrong. Why might it be wrong?)* The I^2 statistic is zero. This means that the estimated variance between studies for the random effects is zero. This does not change the study weights from those used in the fixed effects estimate. So why is it wrong? A fixed effects estimate ***assumes*** that there is no variance between the studies; they all have the same treatment difference apart from the random variation expressed in their individual standard errors calculated within the

study. A random effects estimate assumes that there is a variance between the studies, which it estimates. That variance between studies is ***only an estimate***, it has error. That error should be allowed for in the confidence interval for the treatment effect estimate, but it isn't, because for this study they are identical for fixed and random effects. (That question was ***really*** hard, by the way!)

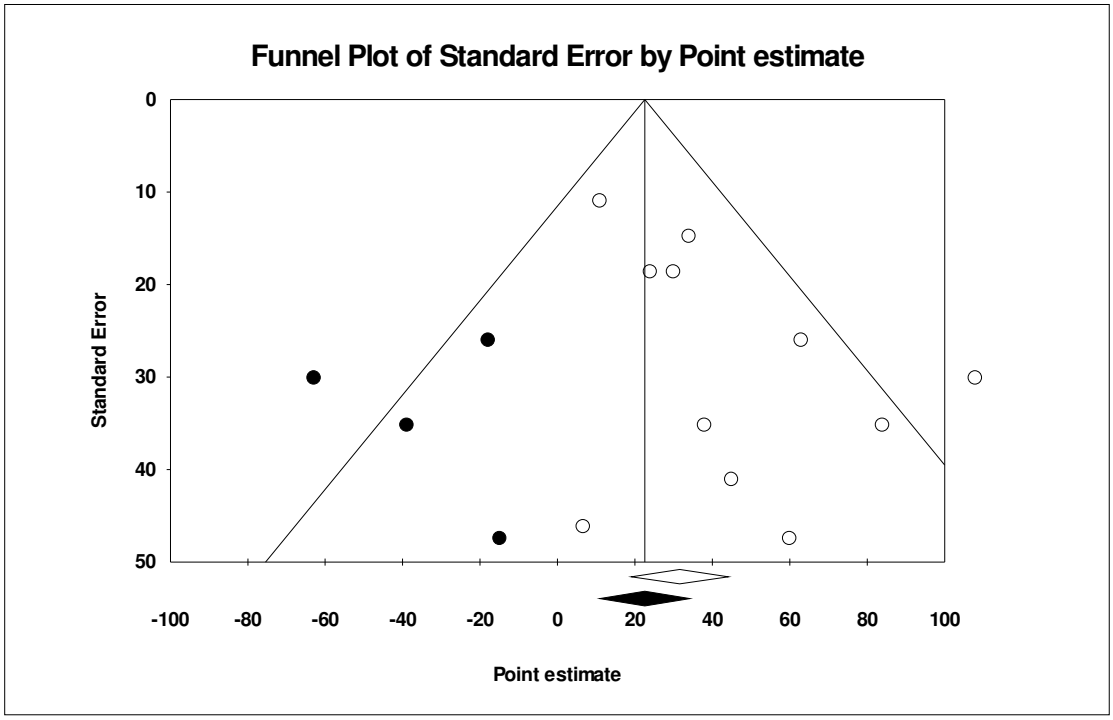
17. *Enter the data in CMA and carry out a meta-analysis. (Hint: try "Generic point estimates" and "Computed effect sizes". You will need to put "0.95" in "Confidence level".) What is your estimate of the effect of passive smoking on birthweight?* I think we could argue for either a fixed or random effects analysis here. I opted for fixed effects and got a difference in mean birthweight, passive non-smokers minus passive smokers, = 31.610 g (95% CI 19.049 to 44.172g, P = 0.000). We should round this up, differences of a thousandth of a gramme in mean birthweight could not possibly be meaningful, and it is conventional not to quote the P-value as zero, so we get difference in mean birthweight, passive non-smokers minus passive smokers, = 32 g (95% CI 19 to 44g, P < 0.001).

18. *Is there any evidence of publication bias? (Hint: try "Analyses", "Publication bias" and then try "Table" and "Next table".)* The Begg and Mazumdar test gives P = 0.27576, rounding, P = 0.3, no evidence of publication bias. The Eggar test gives P = 0.03944, or P = 0.04, which is significant and so does give evidence of publication bias. Although I think the Eggar test is flawed, I do think that there is publication bias, as the funnel plot suggests:



There appear to be missing studies on the left compared to the right.

19. *What is the effect on the estimate of using the trim and fill method? (Hint: try "Plot observed . . .".)* If we plot observed and imputed studies, we get this:



CMA has invented some studies on the left and reduced the size of the estimate a little. Because it is the nature of publication bias that these are small studies which have a small impact on the estimate, it does not make a lot of difference here.

20 *Try storing this data file using "File", clearing the memory, and bringing the file back. You need enter data only once*. Go back to "Data entry", click "File", "Save As", enter a file name. You can clear the memory by "File", "New", "Blank file". You can load a CMA data file by "File", "Open".

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