

Example name	Diastolic BP
Effect size	Mean difference
Analysis type	Basic
Level	Basic

### Synopsis

This analysis includes five studies where persons who donated a kidney were compared with persons in a control group. Outcome was the Diastolic Blood Pressure. Effect size was the difference in mean Diastolic Blood Pressure.

We use this example to show

- How to enter data for means in two independent groups
- How to get a sense of the weight assigned to each study
- How weights are affected by the statistical model
- How to interpret statistics for effect size
- How to interpret statistics for heterogeneity

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[Download CMA file for computers that use a period to indicate decimals](#)

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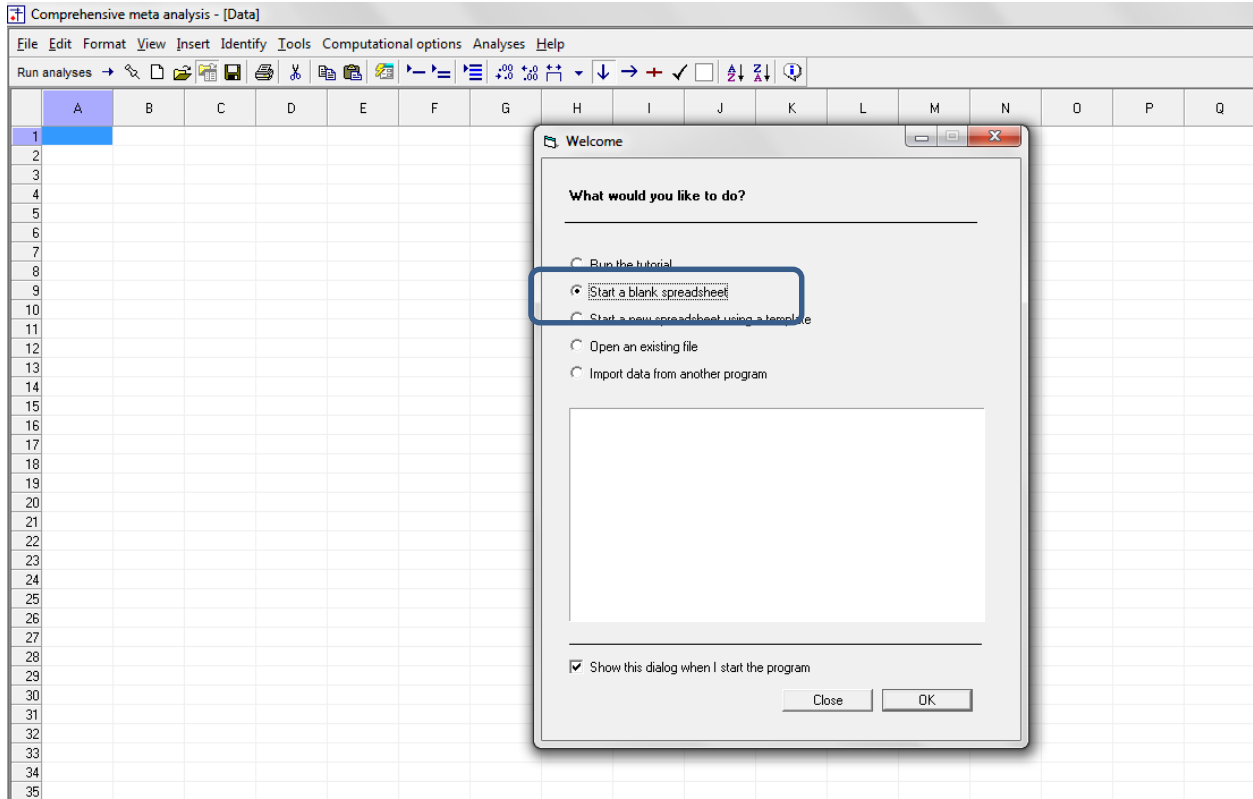
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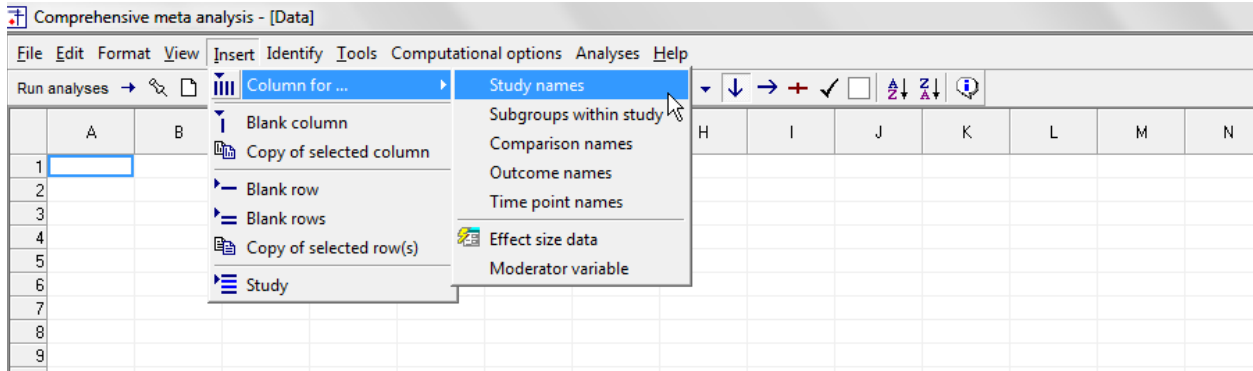
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Start the program

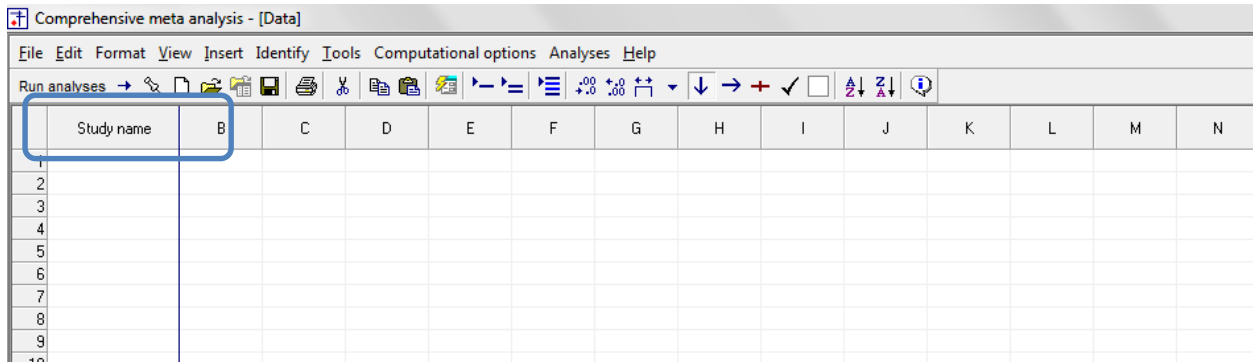
- Select the option [Start a blank spreadsheet]
- Click [OK]



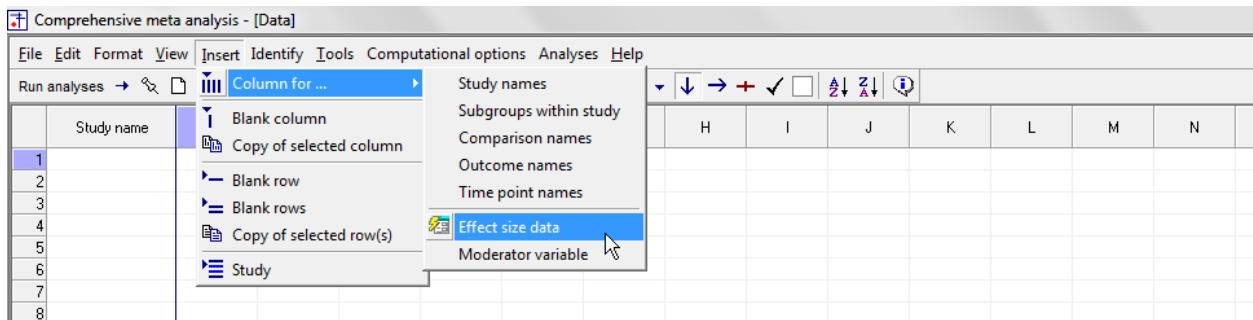
Click Insert > Column for > Study names



The screen should look like this

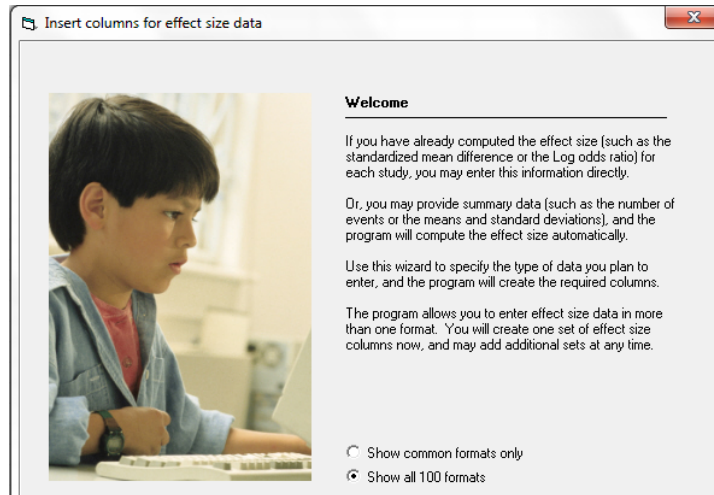


Click Insert > Column for > Effect size data

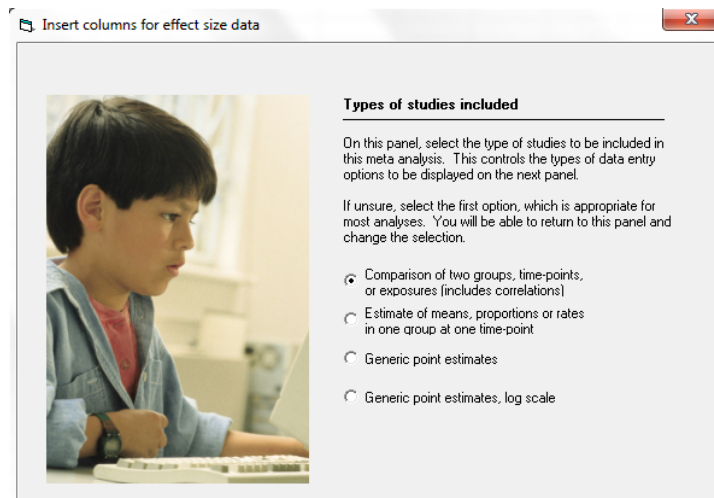


The program displays this wizard

Select [Show all 100 formats]  
Click [Next]

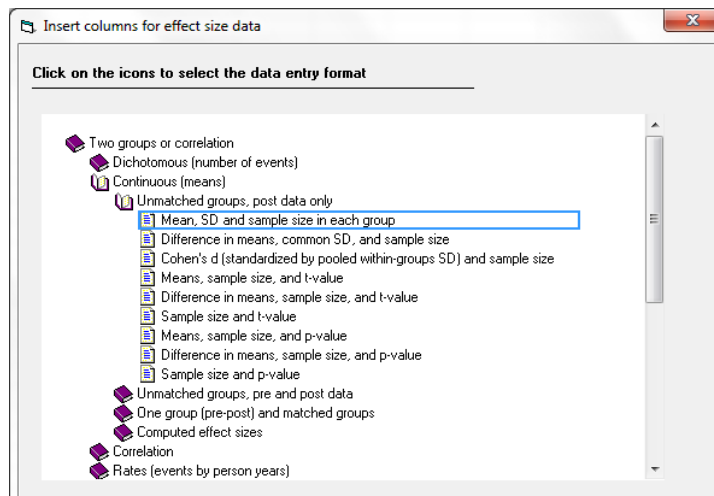


Select [Comparison of two groups...]  
Click [Next]



Drill down to

Continuous (means)  
Unmatched groups, post-data only  
Mean, SD and sample size in each group

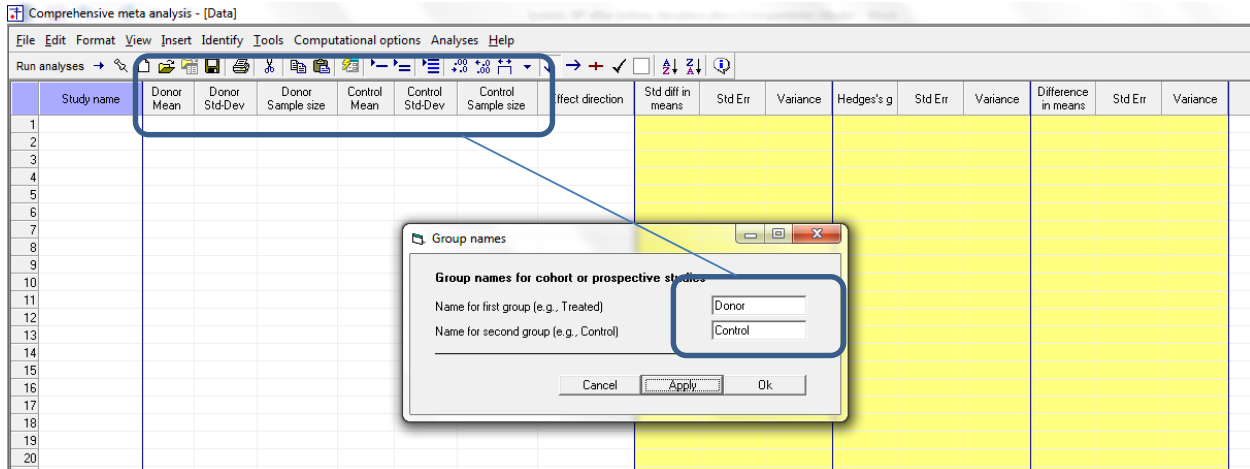


The program displays this wizard

Enter the following labels into the wizard

- First group > Donor
- Second group > Control

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

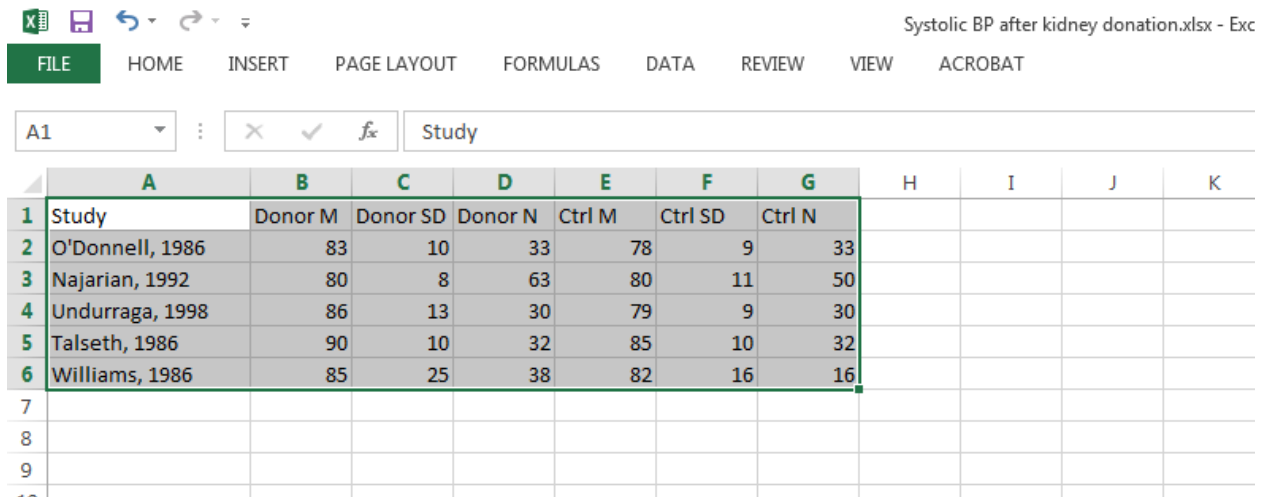


There are three options at this point

- Enter the data directly into CMA
- – or – Open the CMA data file “Diastolic BP after kidney donation.cma”
- – or – Copy the data from Excel “Diastolic BP after kidney donation.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 G), and press CTRL-C to copy to clipboard



Systolic BP after kidney donation.xlsx - Exc

	A	B	C	D	E	F	G	H	I	J	K
1	Study	Donor M	Donor SD	Donor N	Ctrl M	Ctrl SD	Ctrl N				
2	O'Donnell, 1986	83	10	33	78	9	33				
3	Najarian, 1992	80	8	63	80	11	50				
4	Undurraga, 1998	86	13	30	79	9	30				
5	Talseth, 1986	90	10	32	85	10	32				
6	Williams, 1986	85	25	38	82	16	16				
7											
8											
9											
10											

- 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	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Std diff in means	Std Err	Variance	Hedges's g	Std E
1 Study	Donor M	Donor SD	Donor N	Ctrl M	Ctrl SD	Ctrl N						
2 O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33						
3 Najarian, 1992	80.000	8.000	63	80.000	11.000	50						
4 Undurraga, 1998	86.000	13.000	30	79.000	9.000	30						
5 Talseth, 1986	90.000	10.000	32	85.000	10.000	32						
6 Williams, 1986	85.000	25.000	38	82.000	16.000	16						

After checking that the data has been copied correctly, we can delete Row 1

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

Click here

Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run: [Icons]

1	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Std diff in means	Std Err	Variance	Hedges's g	Std Err	Variance
or SD	Donor N	Ctrl M	Ctrl SD	Ctrl N								
2 10.000	33	78.000	9.000	33								
3 8.000	63	80.000	11.000	50								
4 13.000	30	79.000	9.000	30								
5 10.000	32	85.000	10.000	32								
6 25.000	38	82.000	16.000	16								

Context menu for Row 1:

- Restore data
- Column properties
- Copy selection Ctrl+C
- Copy with header
- Copy entire grid
- Paste Ctrl+V
- Cut Ctrl+X
- Delete Del
- Delete row**
- Delete study
- Delete column
- Edit group names

We need to enter a value for “Effect Direction”

Enter “Auto” for each study

Click here

Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Std diff in means	Std Err	Variance	Hedges's g	Std Err	Variance	Difference in means	Std Err	Variance	F
1 O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	Auto	0.526	0.250	0.063	0.519	0.247	0.061	5.000	2.342	5.485	
2 Najarian, 1992	80.000	8.000	63	80.000	11.000	50	Auto	0.000	0.189	0.036	0.000	0.188	0.035	0.000	1.788	3.199	
3 Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	Auto	0.626	0.264	0.070	0.618	0.261	0.068	7.000	2.887	8.333	
4 Talseth, 1986	90.000	10.000	32	85.000	10.000	32	Auto	0.500	0.254	0.064	0.494	0.251	0.063	5.000	2.500	6.250	
5 Williams, 1986	85.000	25.000	38	82.000	16.000	16	Auto	0.132	0.298	0.089	0.130	0.294	0.086	3.000	6.786	46.056	

The program displays three effect sizes –  $d$ ,  $g$ , and raw mean difference

- We want to hide the indices  $d$  and  $g$
- We want to set the raw mean difference as the primary index

Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Std diff in means	Std Err	Variance	Hedges's g	Std Err	Variance
1 O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	Auto	0.526	0.250	0.063	0.519	0.247	0.061
2 Najarian, 1992	80.000	8.000	63	80.000	11.000	50	Auto	0.000	0.189	0.036	0.000	0.188	0.035
3 Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	Auto					0.261	0.068
4 Talseth, 1986	90.000	10.000	32	85.000	10.000	32	Auto					0.251	0.063
5 Williams, 1986	85.000	25.000	38	82.000	16.000	16	Auto					0.294	0.086

- Right-click in any yellow column
- Click “Customize computed effect size display”



In the wizard,

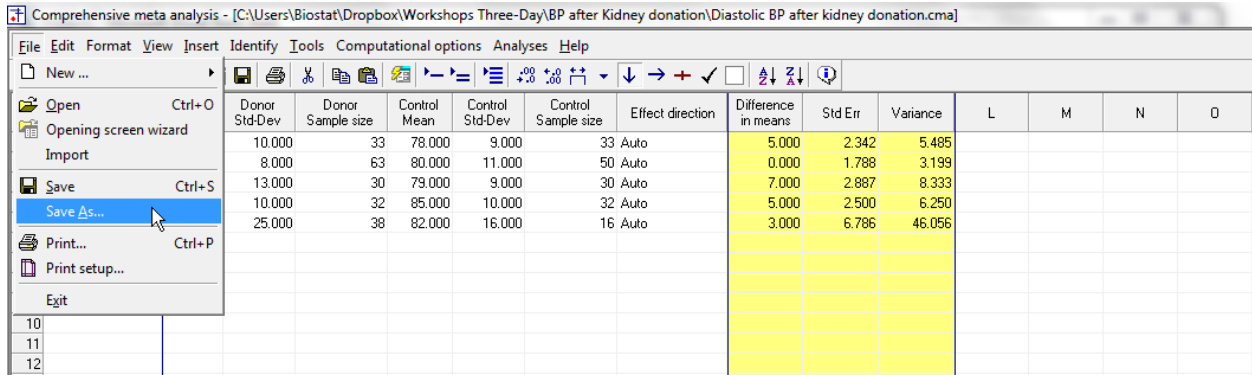
- Select “Difference in means” in the drop-down box
- Un-check “Std diff in means”
- Un-check “Hedges’s g”

Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Std Err	Variance	Difference in means
1 O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	0.247	0.061	5.0
2 Najarian, 1992	80.000	8.000	63	80.000	11.000	50	0.188	0.035	0.0
3 Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	0.261	0.068	7.0
4 Talseth, 1986	90.000	10.000	32	85.000	10.000	32	0.251	0.063	5.0
5 Williams, 1986	85.000	25.000	38	82.000	16.000	16	0.294	0.086	3.0

The screen should look like this

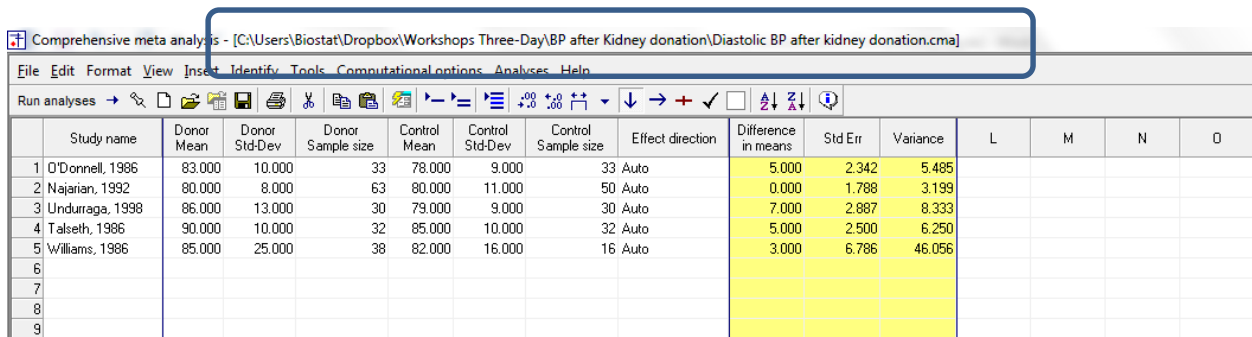
Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Difference in means	Std Err	Variance	L	M	N	O
1 O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	Auto	5.000	2.342	5.485				
2 Najarian, 1992	80.000	8.000	63	80.000	11.000	50	Auto	0.000	1.788	3.199				
3 Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	Auto	7.000	2.887	8.333				
4 Talseth, 1986	90.000	10.000	32	85.000	10.000	32	Auto	5.000	2.500	6.250				
5 Williams, 1986	85.000	25.000	38	82.000	16.000	16	Auto	3.000	6.786	46.056				

Click File > Save As and save the file



Note that the file name is now in the header.

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



There are two options for computing the variance of the mean difference. We can pool the estimates from the two groups, or keep them separate. We will pool them.

Click Computational options > Variance for mean difference

Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Difference in means	Std Err	Variance	L	M	N	O
1 O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	Auto	5.000	2.342	5.485				
2 Najarian, 1992	80.000	8.000	63	80.000	11.000	50	Auto	0.000	1.788	3.199				
3 Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	Auto	7.000	2.887	8.333				
4 Talseth, 1986	90.000	10.000	32	85.000	10.000	32	Auto	5.000	2.500	6.250				
5 Williams, 1986	85.000	25.000	38	82.000	16.000	16	Auto	3.000	6.786	46.056				

- Check the option “Assume a common variance”
- Click Ok

Options for computing treatment effects

**Variance for raw mean difference in independent groups**

When a study includes data for two independent groups, the user may elect to enter the SD for each of the groups separately. In this case the program can pool the variance in the two groups (option 1) or not pool them (option 2).

This option affects the variance (and weights) used in an analysis of raw mean differences. It has no impact on analyses of standardized mean differences.

Assume a common variance

Do not assume a common variance (Revman, STATA)

Cancel Apply Ok

By convention we've put the Experimental group (Donor) in the first columns and the control group in the next two columns.

The program will compute the mean difference as Experimental minus Control. Thus, a positive difference means that the donors had a higher BP.

(The column labeled Direction allows you to control this process. "Auto" means that the program will assign a "+" if the first group was higher and a "-" if the second group was higher.

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 first study (O'Donnell). The mean BP was 83 for Donor and 78 for Control. The Difference in means is positive (+5.000) which means that the donor group had a higher mean.

Comprehensive meta analysis - [C:\Users\Biostat\Dropbox\Workshops Three-Day\BP after Kidney donation\Diastolic BP after kidney donation.cma]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses → [Icons]

	Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Difference in means	Std Err	Variance	L	M	N	O
1	O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	Auto	5.000	2.342	5.485				
2	Najarian, 1992	80.000	8.000	63	80.000	11.000	50	Auto	0.000	1.788	3.199				
3	Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	Auto	7.000	2.887	8.333				
4	Talseth, 1986	90.000	10.000	32	85.000	10.000	32	Auto	5.000	2.500	6.250				
5	Williams, 1986	85.000	25.000	38	82.000	16.000	16	Auto	3.000	6.786	46.056				
6															
7															
8															
9															

- To run the analysis, click [Run analysis]

Comprehensive meta analysis - [C:\Users\Biostat\Dropbox\Workshops Three-Day\BP after Kidney donation\Diastolic BP after kidney donation.cma]

File Edit Format View Insert Identify Tools Computational options Analyses Help

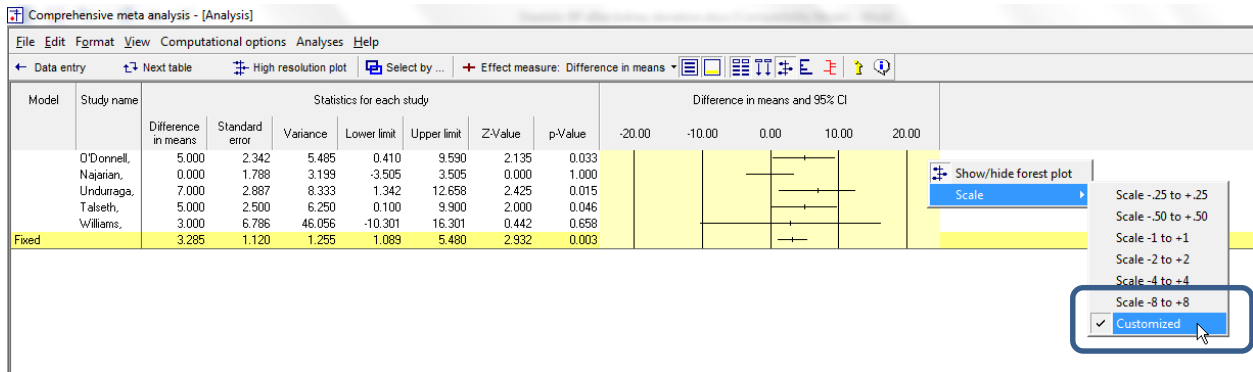
Run analyses → [Icons]

	Study name	Donor Mean	Donor Std-Dev	Donor Sample size	Control Mean	Control Std-Dev	Control Sample size	Effect direction	Difference in means	Std Err	Variance	L	M	N	O
1	O'Donnell, 1986	83.000	10.000	33	78.000	9.000	33	Auto	5.000	2.342	5.485				
2	Najarian, 1992	80.000	8.000	63	80.000	11.000	50	Auto	0.000	1.788	3.199				
3	Undurraga, 1998	86.000	13.000	30	79.000	9.000	30	Auto	7.000	2.887	8.333				
4	Talseth, 1986	90.000	10.000	32	85.000	10.000	32	Auto	5.000	2.500	6.250				
5	Williams, 1986	85.000	25.000	38	82.000	16.000	16	Auto	3.000	6.786	46.056				
6															
7															
8															
9															

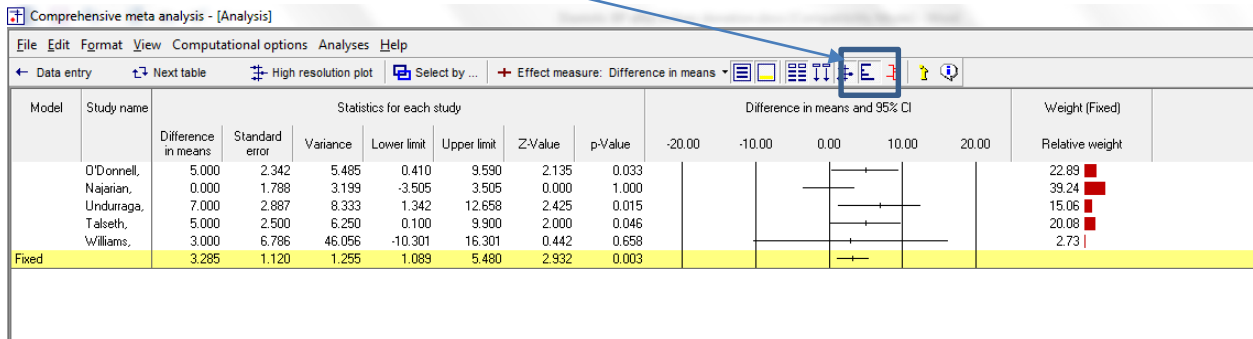
This is the basic analysis screen

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

Right-click on the forest plot > Customized > Set the scale to 20



Click the tool to show weights



Virtually all studies have mean differences over 0.0, which means that the donor group had a higher diastolic BP than the control.

The effects seem to be reasonably consistent. The confidence interval for most studies overlaps the mean effect size.

The pooled effect is 3.285, which means that the mean diastolic BP in the donor group was about 3 points higher than the control.

Click [Both models]

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

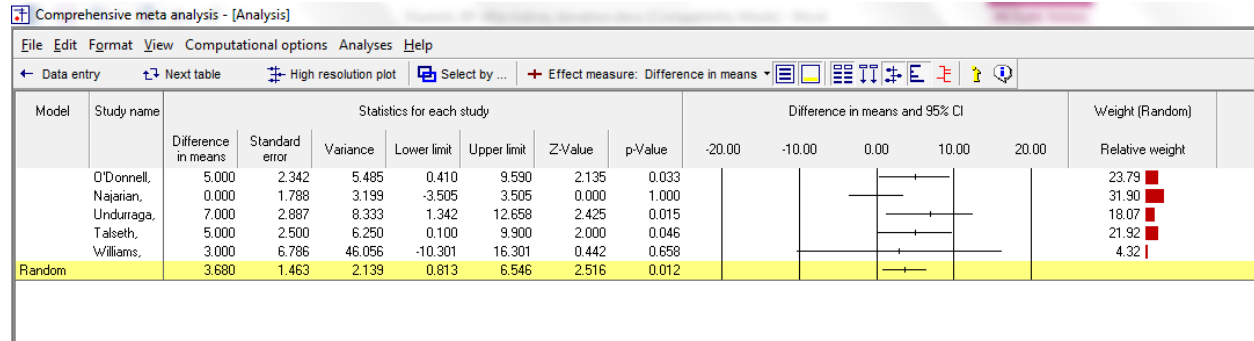
Model	Study name	Statistics for each study							Difference in means and 95% CI					Weight (Fixed)		Weight (Random)	
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	-20.00	-10.00	0.00	10.00	20.00	Relative weight	Relative weight		
	O'Donnell	5.000	2.342	5.485	0.410	9.590	2.135	0.033							22.89	23.79	
	Najarian	0.000	1.788	3.199	-3.505	3.505	0.000	1.000							39.24	31.90	
	Undurraga	7.000	2.887	8.333	1.342	12.658	2.425	0.015							15.06	18.07	
	Williams	5.000	2.500	6.250	0.100	9.900	2.000	0.046							20.08	21.92	
	Williams	3.000	6.786	46.056	-10.301	16.301	0.442	0.658							2.73	4.32	
Fixed		3.285	1.120	1.255	1.089	5.480	2.932	0.003									
Random		3.680	1.463	2.139	0.813	6.546	2.516	0.012									

Under the fixed-effect model the pooled mean difference is 3.285, while under the random-effects model the pooled mean difference is 3.680.

- The fixed-effect model would be appropriate if all the studies were virtual replicates of each other. This is not the case, which is not the case here since the study populations varied in numerous (if unknown) ways.
- The random-effects model would be appropriate if the studies vary in ways that may impact the effect size. 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

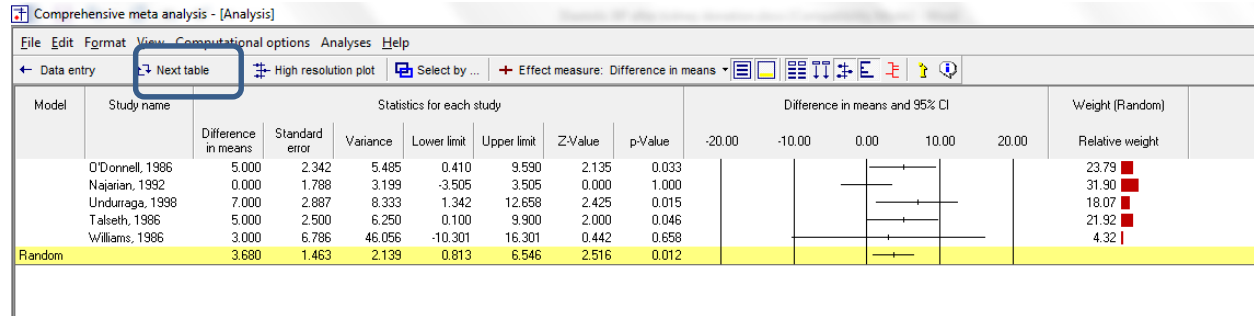
- The BP was always as high or higher in the donor group than the control
- The observed effects are pretty consistent, in that the confidence intervals for all studies but one overlap the mean effect size.
- The summary effect is 3.680 with a CI of 0.813 to 6.546.
- The summary effect has a Z-value 2.516 a  $p$ -value of 0.012. Thus we can reject the null hypotheses that the true mean difference is 0.0.
- At the same time, the magnitude of mean difference is relatively modest

The confidence interval tells us that the mean effect size falls in range of 0.813 to 6.546. It tells us nothing about how widely the true effect size varies from study to study. This is an important clinical issue since we need to distinguish between various possibilities, such as

- a) The mean BP is consistently about 3 points higher in the donor group
- b) The donor group sometimes has a mean BP 0 points higher, sometimes 3 points higher, sometimes 6 or more points higher

To address this we need not only the mean difference but also the standard deviation of the differences. For this we turn to the next screen.

Click Next Table



The program displays this screen

Model	Effect size and 95% confidence 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		5	3.285	1.120	1.255	1.089	5.480	2.932	0.003	6.039	4	0.196	33.759	3.506	7.474	55.866	1.872
Random		5	3.680	1.463	2.139	0.813	6.546	2.516	0.012								

The section labeled “Effect size and 95% confidence interval and the section labled “Test of null” address the mean effect size and the null hypothesis that the mean difference is zero. These are the same statistics we saw on the previous screen. The mean difference is 3.680 (0.813 to 6.546), the Z-value for a test of the null is 2.516 and the p-value for a test of the null is 0.012.

The section labeled Heterogeneity shows a test of the null hypothesis that the true effect size is identical in all five studies and that 100% of the variation in the observed effects is due to sampling error. Put another way, if every one of the studies had an infinite sample size (so that we knew the true effect size in that study exactly) the observed effects would all be identical to each other.

To test this hypothesis we compute Q, which is basically a weighted sum of squares (we compute the difference of every effect size from the mean effect size, square that difference, assign larger weights to more precise studies, and then sum these weighted values). If the null hypothesis is true (that all the variation in effects is due to sampling error), the expected value of Q is equal to the number of studies minus 1 (here, 5 minus 1 equals 4).

The observed Q value is 6.039. This is more than we would expect if the null is true (4.0), but not so large as to be statistically significant. If the null is true we would expect to see a Q value this high about one time in 5 ( $p = 0.196$ ). So, we do not reject the null. We have no evidence that the true effect size varies from study to study.

While we cannot conclude that the effect size actually varies, we can still describe how much variation we actually see. There are several statistics that relate to this.



$I^2$  is 33.759. This tells us that about 33% of the variance that we see in the forest plot reflects difference in the true effect sizes, while the other 66% reflects sampling error. Put another way, if we were able to plot the true effects rather than the observed effects, the data points would align more closely than they do now. The variance would decline by 66%.

Importantly,  $I^2$  is a proportion – it tells us what proportion of the observed variance is real (if our estimates are correct) but does not tell us how much variance there is. And that is what we need if we want to consider the clinical implications of the variance. The actual amount of dispersion is addressed by  $T^2$  and  $T$ , which are displayed at the right-hand side of the screen.

- $T^2$  (shown as 3.506) is the estimate of variance in true effect sizes.
- $T$  (shown 1.872) is the estimate of the standard deviation in true effect sizes.

We can use the spreadsheet [Prediction intervals] to get a sense of how the true effects are distributed. Copy the values A, B, C, D from this screen to the spreadsheet.

Model	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity			Tau-squared				
	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	5	3.285	1.120	1.255	1.089	5.480	2.932	0.003	6.039	4	0.196	33.759	3.506	7.474	55.866	1.872
Random	5	3.680	1.463	2.139	0.813	6.546	2.516	0.012								

	A	B	C	D	E	F	G	H
1	<b>Prediction intervals for D, d, g, RD</b>							
2								
3	Enter values in shaded cells only							
4								
5								
6	Number of studies		5			A		
7	Degrees of freedom		3	p. 130				
8	Critical value for t (95% interval)		3.182446	p. 131				
9	Mean effect (random effect weights)		3.680000	12.7		B		
10	Tau-squared		3.506000	16.5		C		
11	Variance of M *		2.139000	12.8		D		
12								
13	Prediction interval							
14	Mean		3.680000					
15	Prediction interval (95%) lower limit		-3.881241	17.7				
16	Prediction interval (95%) upper limit		11.241241	17.8				

The confidence interval is  $-0.813$  to  $-6.546$ . The prediction interval is  $-3.881$  to  $11.241$ .

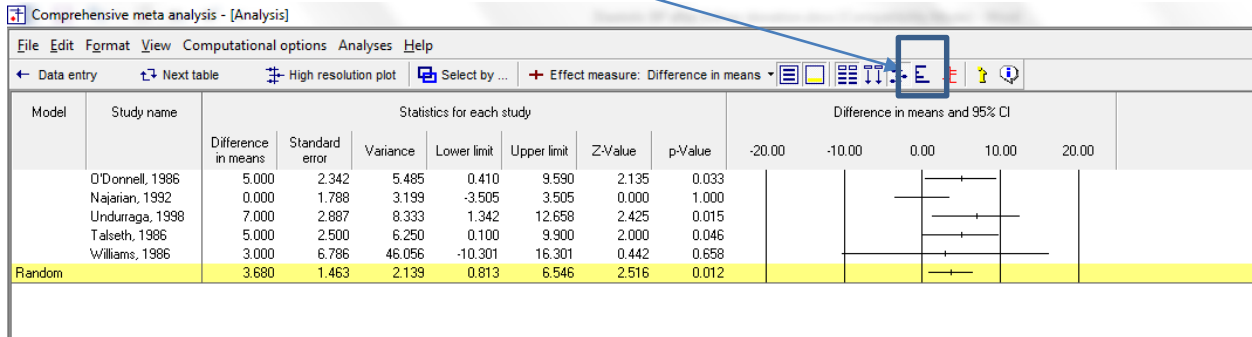
The true effect size varies from study to study. The mean effect size probably falls in the range of  $-0.813$  to  $-6.546$ . The true effect size for any single study will usually fall in the range of  $-3.881$  to  $11.241$ . Thus, while the true effect will be positive in most studies, it will be negative (higher for the control group) in some studies.

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.

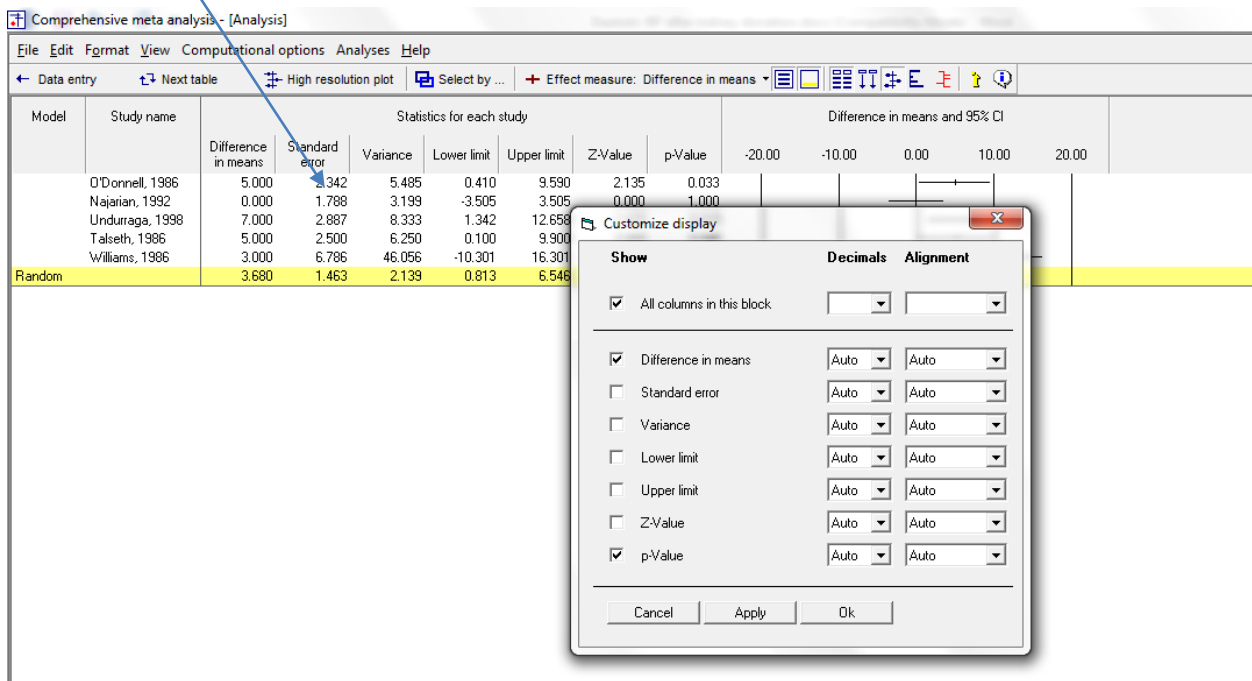
Click Next table

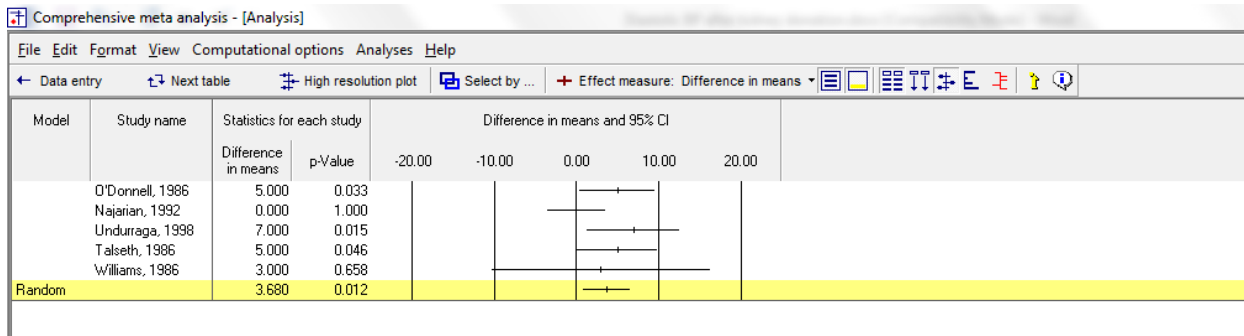
We want to create a high-resolution plot

Click here to hide the column of weights

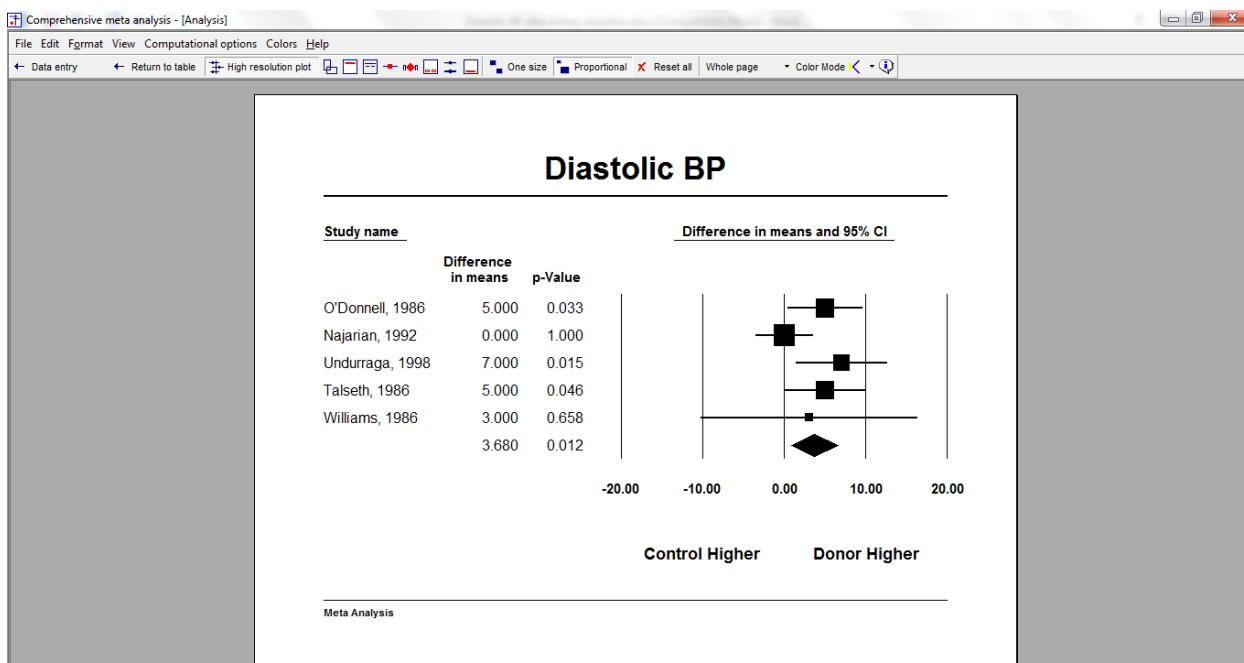


Right-click here and hide some of the statistics columns





- Select “Random” rather than “Both” on the bottom tab
- Click Hi-Resolution plot
- Adjust the columns widths



## Summary

This analysis includes five studies where persons who donated a kidney were compared with persons in a control group. Outcome was the Diastolic Blood Pressure. Effect size was the difference in mean Diastolic Blood Pressure.

### Is kidney donation related to Diastolic blood pressure?

The pooled difference in means is 3.680, which means that the diastolic BP for persons who donated a kidney was (on average) 3.680 units higher than the diastolic BP for persons who did not donate a kidney.

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 mean difference is 0.813 to 6.546, which tell us that the mean difference in the universe of studies could fall anywhere in this range. This range does not include a difference of zero, which tells us that the true difference is probably not zero.

Similarly, the Z-value for testing the null hypothesis (that the mean difference is zero) is 2.516, with a corresponding  $p$ -value is 0.012. We can reject the null that mean diastolic BP is the same in both groups, and conclude that the mean diastolic BP is higher in the donor 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 6.039 with 4 degrees of freedom, and the corresponding  $p$ -value is 0.196. Thus, the observed dispersion is more than the expected value but still within the range that can be attributed to chance. Therefore, we cannot reject the null hypothesis that the effect size is the same in all studies.

While we cannot reject the hypothesis that the true effect size is the same in all studies, our best estimate based on the data is that there is some variance in true effects. This is quantified by the following statistics.

The  $I^2$  statistic tells us what proportion of the observed variance reflects differences in true effect sizes rather than sampling error.  $I^2$  is 33.759. This tells us that if we could plot the true effects rather than the observed effects, the variance in the new plot would be about 34% as large as the variance in the current plot. Or, the variance would shrink by about 66%.

$T^2$  is the variance of true effect sizes (in log units). Here,  $T^2$  is 3.506.  $T$  is the standard deviation of true effects (in log units). Here,  $T$  is 1.872.