Example name	Vitamin E by Dose
Effect size	Risk difference
Analysis type	Subgroups analysis, Regression
Level	Advanced

Synopsis

This analysis includes 19 studies where patients were randomized to receive either daily dose of either Vitamin E or a placebo. Outcome was the proportion of patients dying in each group. The analysis focused on the risk difference, i.e. the absolute difference in risk of death.

The mean risk difference across all studies was close to zero. However, there was substantial dispersion in the risk difference, and we ran several analyses to see whether or not the impact of Vitamin E was related to the dose.

We use this example to show

- How to interpret a basic analysis using Risk Difference
- How to understand the heterogeneity statistics
- How to perform a subgroups analysis
- How a regression analysis corresponds to a subgroups analysis
- How to perform a regression analysis using a categorical predictor
- How to perform a regression analysis using a continuous predictor
- How to perform a regression analysis to test for a curvilinear relationship

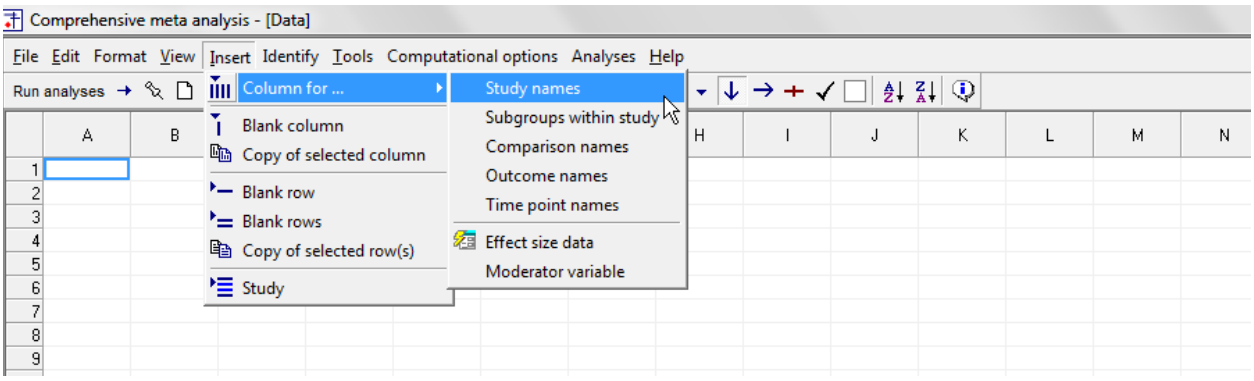
To open a CMA file > Download and Save file | Start CMA | Open file from within CMA

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

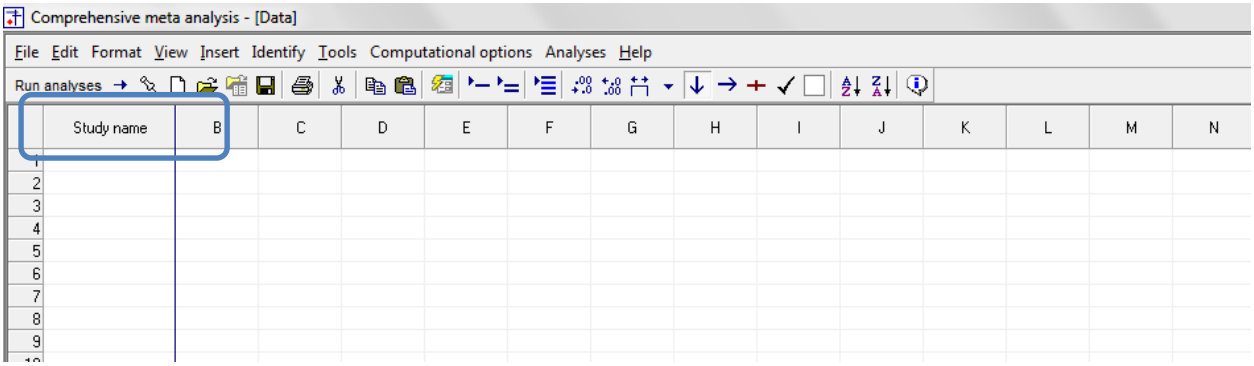
Download this PDF
Download data in Excel
Download trial of CMA

Start the program

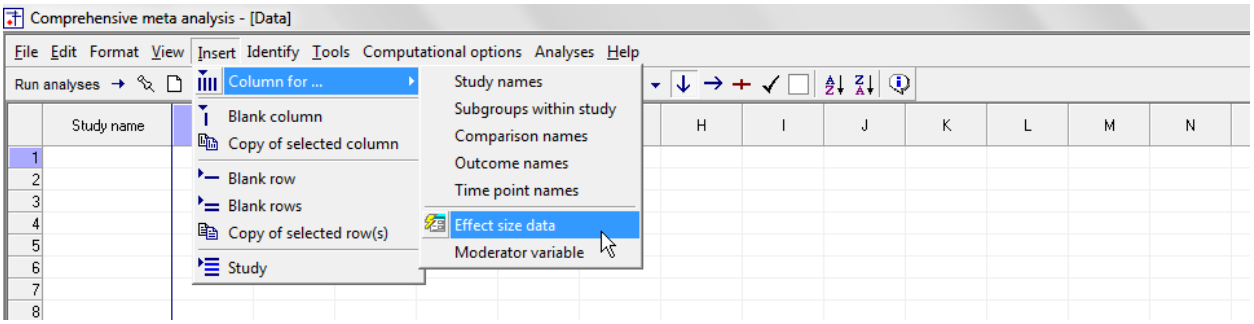
- Select the option [Start a blank spreadsheet]
- Click [Ok]
- Click Insert > Column for > Study names



The screen should look like this

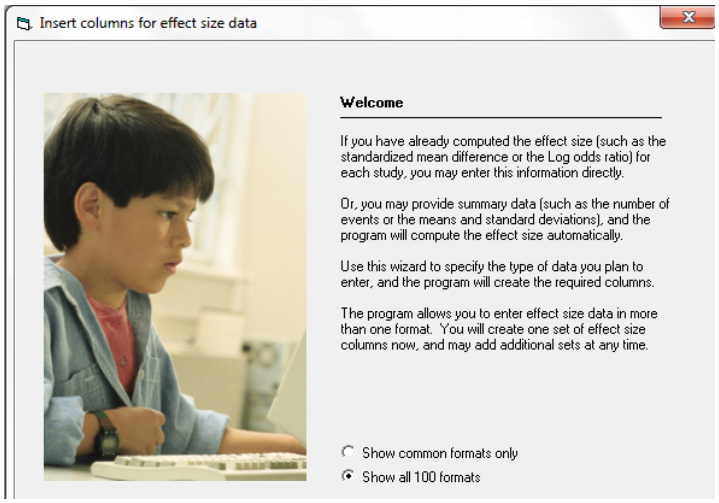


Click Insert > Column for > Effect size data

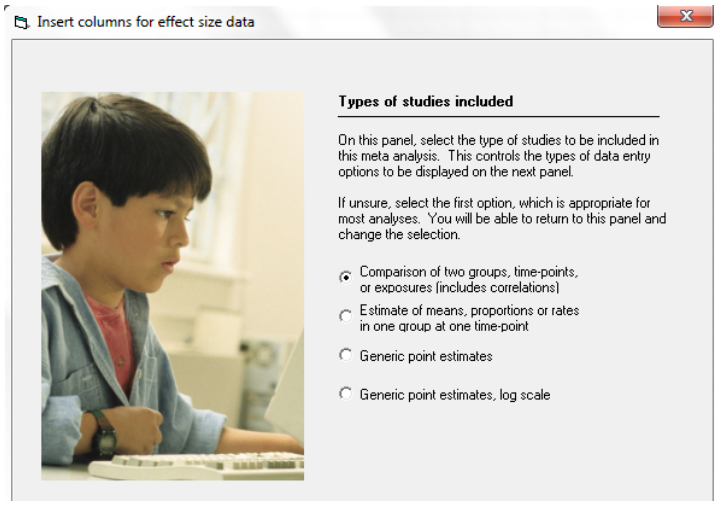


The program displays this wizard

Select [Show all 100 formats]
Click [Next]

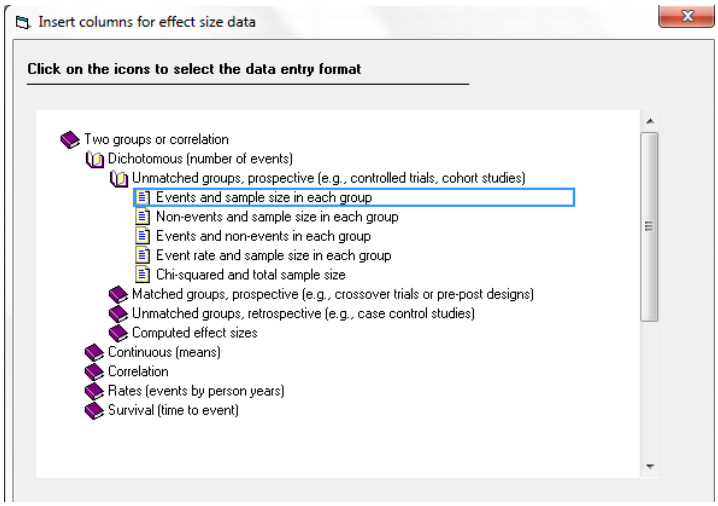


Select [Comparison of two groups…]
Click [Next]



Drill down to

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

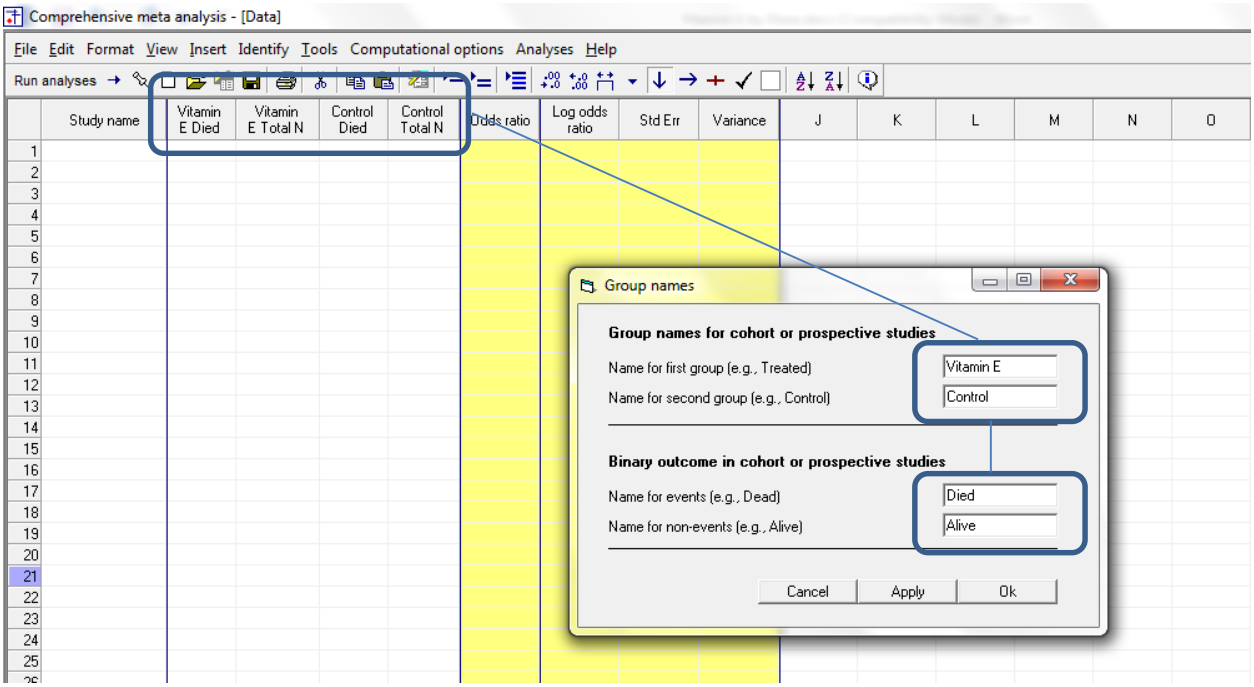


The program displays this wizard

Enter the following labels into the wizard

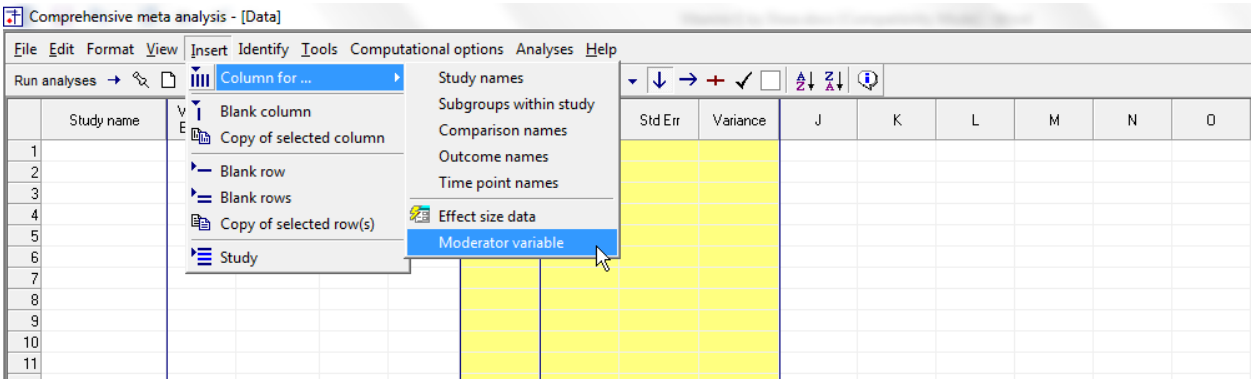
- First group > Vitamin E
- Second group > Control
- Name for events > Died
- Name for non-events > Alive

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

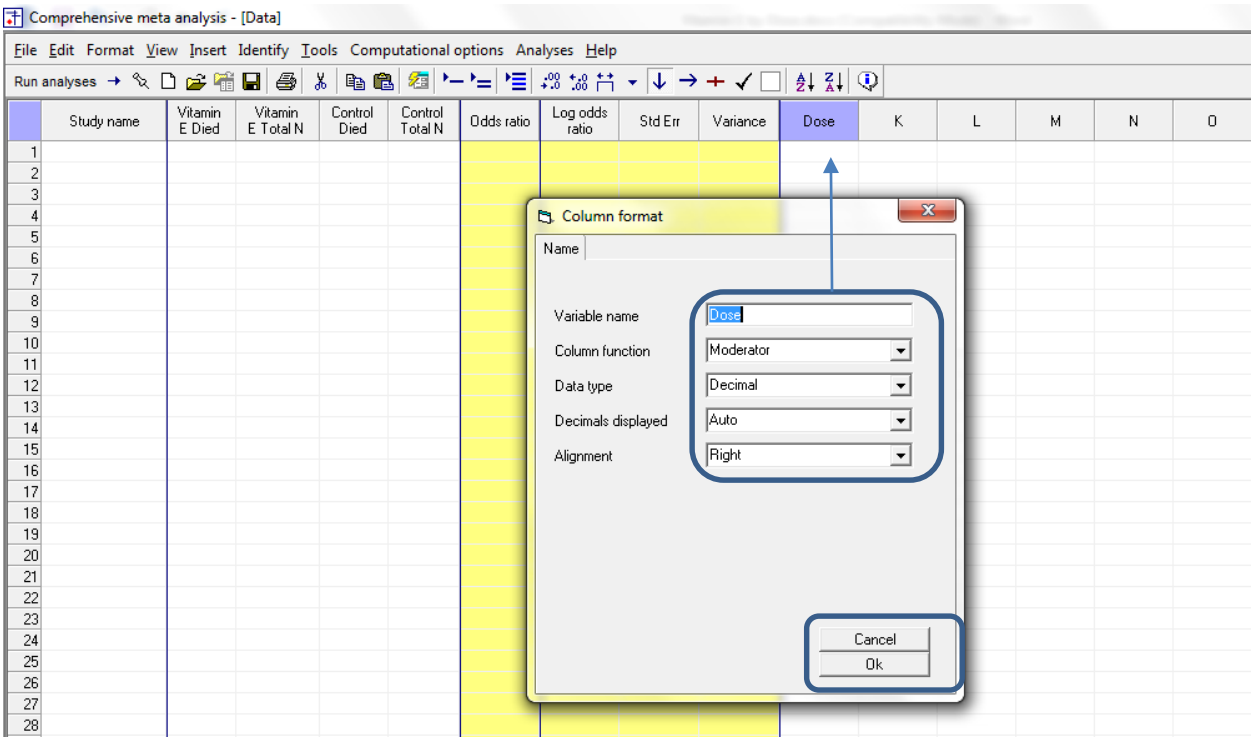


We need to add a column for the moderator, Dose

Click Insert > Column for > Moderator variable



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

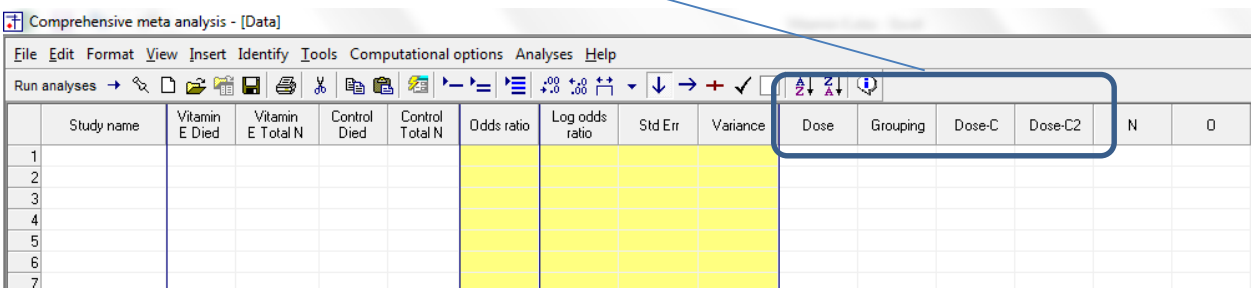


- Insert a column for > Moderator > Categorical with the name Grouping. This will be used to code the dose as Low or High.

- Insert a column for > Moderator > Decimal with the name Dose-C. This will be used to code the dose, centered (to have a mean of zero).

- Insert a column for > Moderator > Decimal with the name Dose-C2. This will be used to code the Dose-C squared.

The screen should look like this

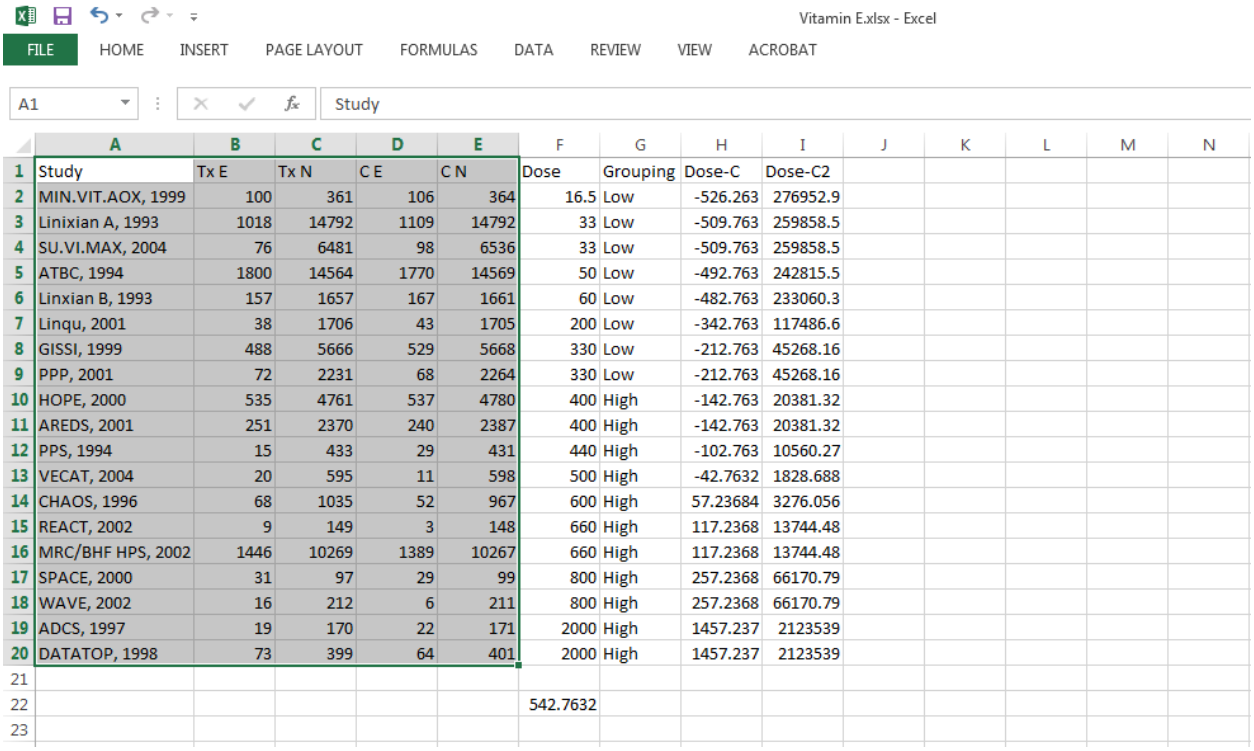


There are three options at this point

- Enter the data directly into CMA
- – or – Open the CMA data file
- – or – Copy the data from Excel

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

- Switch to Excel and open the file "Vitamin E.xls"
- Highlight the rows and columns as shown (Columns A to E only), and press CTRL-C to copy to clipboard



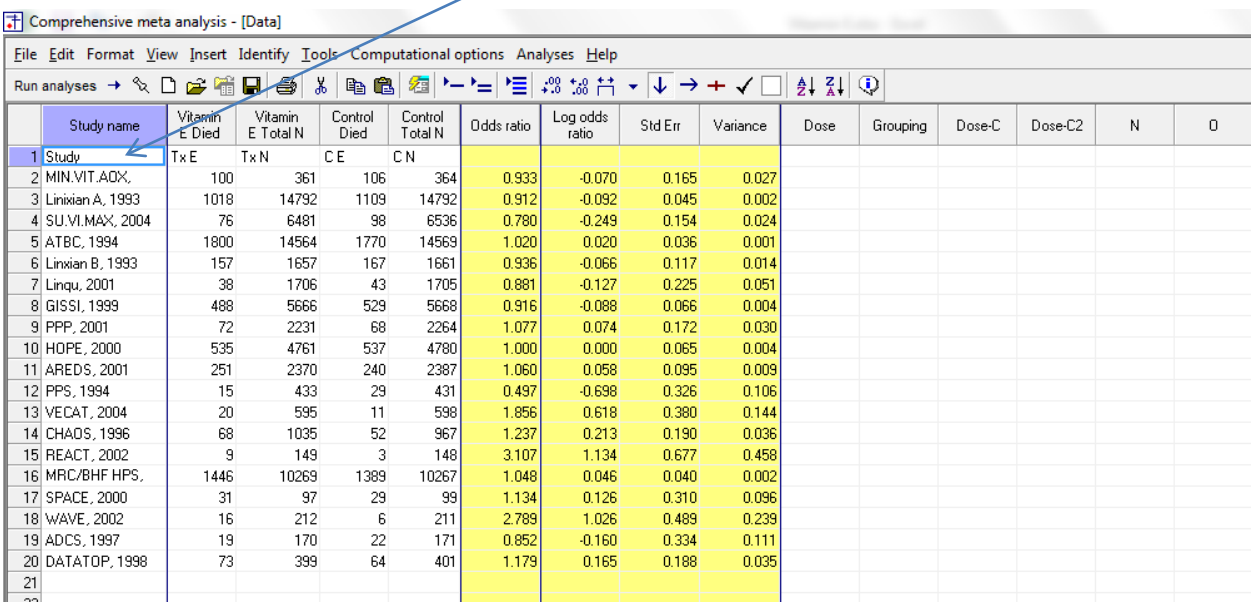
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Study	Tx E	Tx N	C E	C N	Dose	Grouping	Dose-C	Dose-C2					
2	MIN.VIT.AOX, 1999	100	361	106	364	16.5	Low	-526.263	276952.9					
3	Linixian A, 1993	1018	14792	1109	14792	33	Low	-509.763	259858.5					
4	SU.VI.MAX, 2004	76	6481	98	6536	33	Low	-509.763	259858.5					
5	ATBC, 1994	1800	14564	1770	14569	50	Low	-492.763	242815.5					
6	Linxian B, 1993	157	1657	167	1661	60	Low	-482.763	233060.3					
7	Linqu, 2001	38	1706	43	1705	200	Low	-342.763	117486.6					
8	GISSI, 1999	488	5666	529	5668	330	Low	-212.763	45268.16					
9	PPP, 2001	72	2231	68	2264	330	Low	-212.763	45268.16					
10	HOPE, 2000	535	4761	537	4780	400	High	-142.763	20381.32					
11	AREDS, 2001	251	2370	240	2387	400	High	-142.763	20381.32					
12	PPS, 1994	15	433	29	431	440	High	-102.763	10560.27					
13	VECAT, 2004	20	595	11	598	500	High	-42.7632	1828.688					
14	CHAOS, 1996	68	1035	52	967	600	High	57.23684	3276.056					
15	REACT, 2002	9	149	3	148	660	High	117.2368	13744.48					
16	MRC/BHF HPS, 2002	1446	10269	1389	10267	660	High	117.2368	13744.48					
17	SPACE, 2000	31	97	29	99	800	High	257.2368	66170.79					
18	WAVE, 2002	16	212	6	211	800	High	257.2368	66170.79					
19	ADCS, 1997	19	170	22	171	2000	High	1457.237	2123539					
20	DATATOP, 1998	73	399	64	401	2000	High	1457.237	2123539					
21														
22						542.7632								
23														

Column	Name	Description
F	Dose	The Average dose is 542.7632
G	Grouping	"Low" if dose is under 350 "High" if dose exceeds 350
H	Centered dose	Dose minus 542.7632 For Row 2 16.5 − 542.7632 = −526.263
I	(Centered Dose)Squared	For Row 2 $(-526.263)^2$ = 276952.9

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

Click here

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



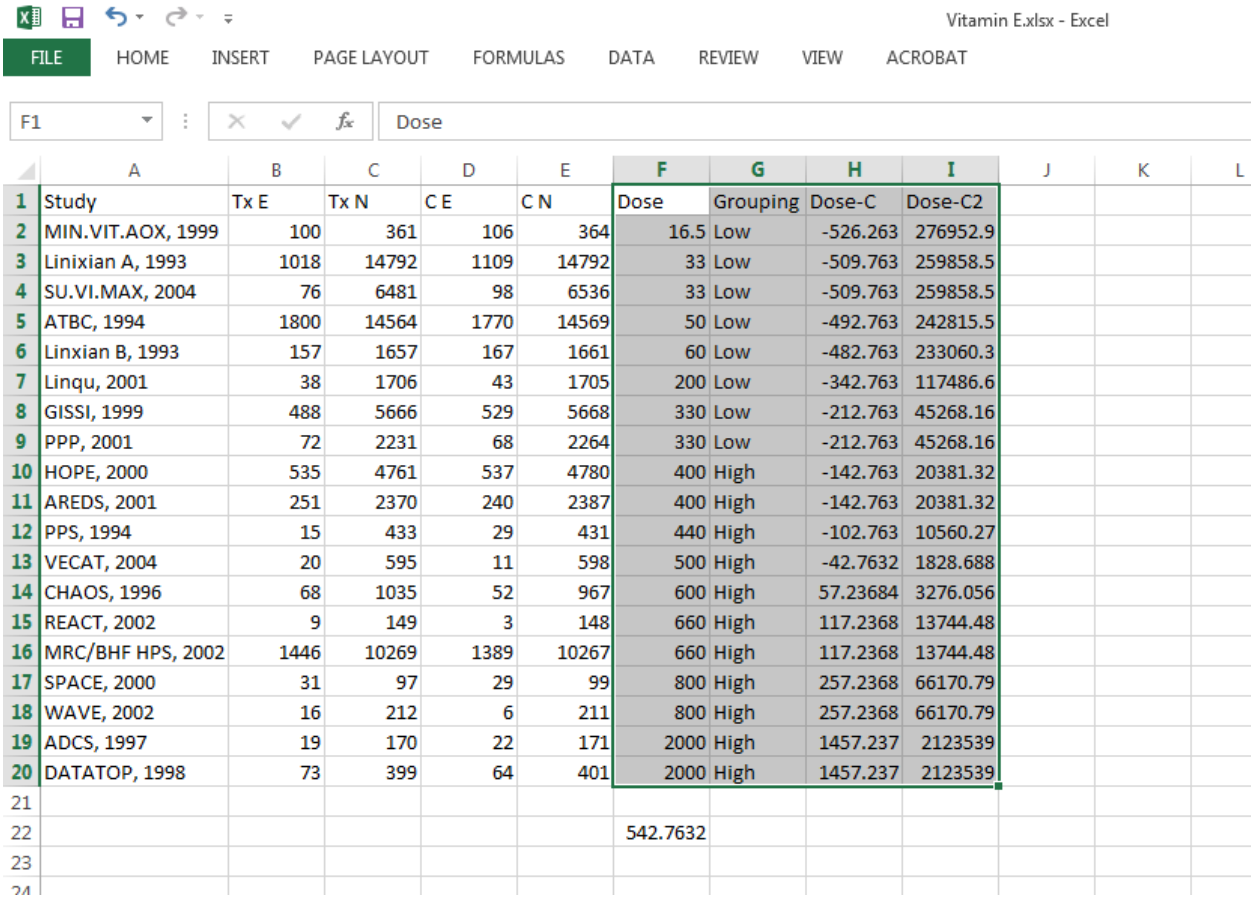
Comprehensive meta analysis - [Data]

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses

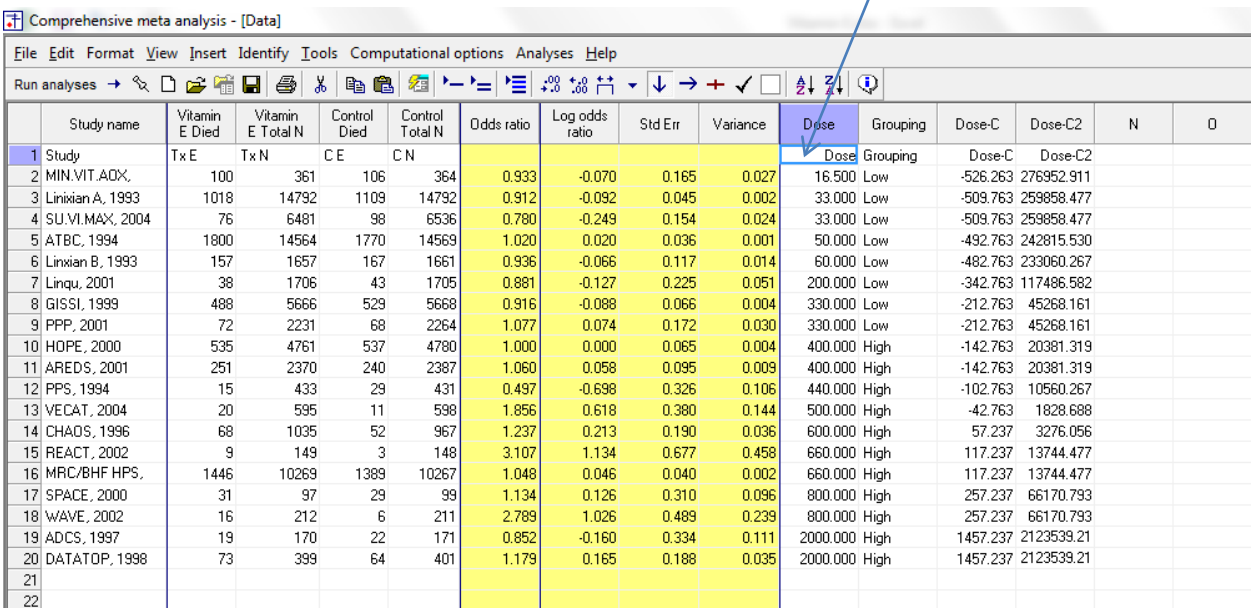
	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	N	O
1	Study	T x E	T x N	C E	C N										
2	MIN.VIT.AOX,	100	361	106	364	0.933	-0.070	0.165	0.027						
3	Linixian A, 1993	1018	14792	1109	14792	0.912	-0.092	0.045	0.002						
4	SU.VI.MAX, 2004	76	6481	98	6536	0.780	-0.249	0.154	0.024						
5	ATBC, 1994	1800	14564	1770	14569	1.020	0.020	0.036	0.001						
6	Linxian B, 1993	157	1657	167	1661	0.936	-0.066	0.117	0.014						
7	Linqu, 2001	38	1706	43	1705	0.881	-0.127	0.225	0.051						
8	GISSI, 1999	488	5666	529	5668	0.916	-0.088	0.066	0.004						
9	PPP, 2001	72	2231	68	2264	1.077	0.074	0.172	0.030						
10	HOPE, 2000	535	4761	537	4780	1.000	0.000	0.065	0.004						
11	AREDS, 2001	251	2370	240	2387	1.060	0.058	0.095	0.009						
12	PPS, 1994	15	433	29	431	0.497	-0.698	0.326	0.106						
13	VECAT, 2004	20	595	11	598	1.856	0.618	0.380	0.144						
14	CHAOS, 1996	68	1035	52	967	1.237	0.213	0.190	0.036						
15	REACT, 2002	9	149	3	148	3.107	1.134	0.677	0.458						
16	MRC/BHF HPS,	1446	10269	1389	10267	1.048	0.046	0.040	0.002						
17	SPACE, 2000	31	97	29	99	1.134	0.126	0.310	0.096						
18	WAVE, 2002	16	212	6	211	2.789	1.026	0.489	0.239						
19	ADCS, 1997	19	170	22	171	0.852	-0.160	0.334	0.111						
20	DATATOP, 1998	73	399	64	401	1.179	0.165	0.188	0.035						
21															

- Switch to Excel
- Highlight the columns for Dose, Grouping,Dose-C, and Dose-C2 as shown
- Click [CTRL-C]



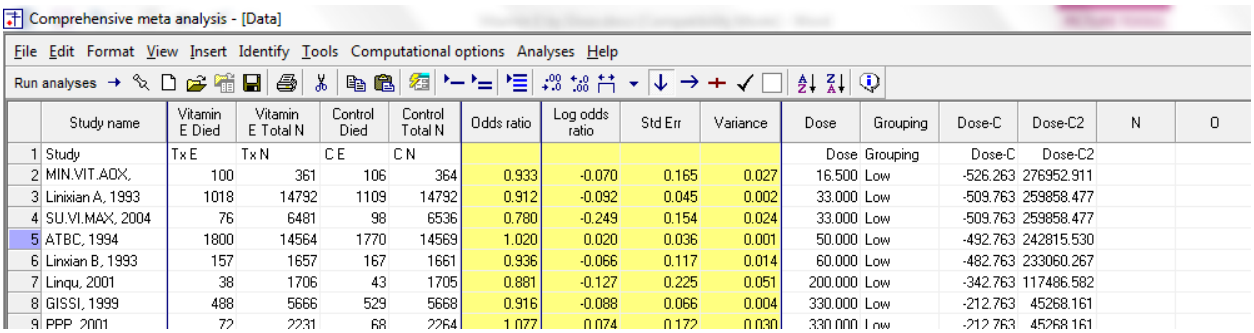
	A	B	C	D	E	F	G	H	I	J	K	L
1	Study	Tx E	Tx N	C E	C N	Dose	Grouping	Dose-C	Dose-C2			
2	MIN.VIT.AOX, 1999	100	361	106	364	16.5	Low	-526.263	276952.9			
3	Linixian A, 1993	1018	14792	1109	14792	33	Low	-509.763	259858.5			
4	SU.VI.MAX, 2004	76	6481	98	6536	33	Low	-509.763	259858.5			
5	ATBC, 1994	1800	14564	1770	14569	50	Low	-492.763	242815.5			
6	Linxian B, 1993	157	1657	167	1661	60	Low	-482.763	233060.3			
7	Linqu, 2001	38	1706	43	1705	200	Low	-342.763	117486.6			
8	GISSI, 1999	488	5666	529	5668	330	Low	-212.763	45268.16			
9	PPP, 2001	72	2231	68	2264	330	Low	-212.763	45268.16			
10	HOPE, 2000	535	4761	537	4780	400	High	-142.763	20381.32			
11	AREDS, 2001	251	2370	240	2387	400	High	-142.763	20381.32			
12	PPS, 1994	15	433	29	431	440	High	-102.763	10560.27			
13	VECAT, 2004	20	595	11	598	500	High	-42.7632	1828.688			
14	CHAOS, 1996	68	1035	52	967	600	High	57.23684	3276.056			
15	REACT, 2002	9	149	3	148	660	High	117.2368	13744.48			
16	MRC/BHF HPS, 2002	1446	10269	1389	10267	660	High	117.2368	13744.48			
17	SPACE, 2000	31	97	29	99	800	High	257.2368	66170.79			
18	WAVE, 2002	16	212	6	211	800	High	257.2368	66170.79			
19	ADCS, 1997	19	170	22	171	2000	High	1457.237	2123539			
20	DATATOP, 1998	73	399	64	401	2000	High	1457.237	2123539			
21												
22						542.7632						
23												

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



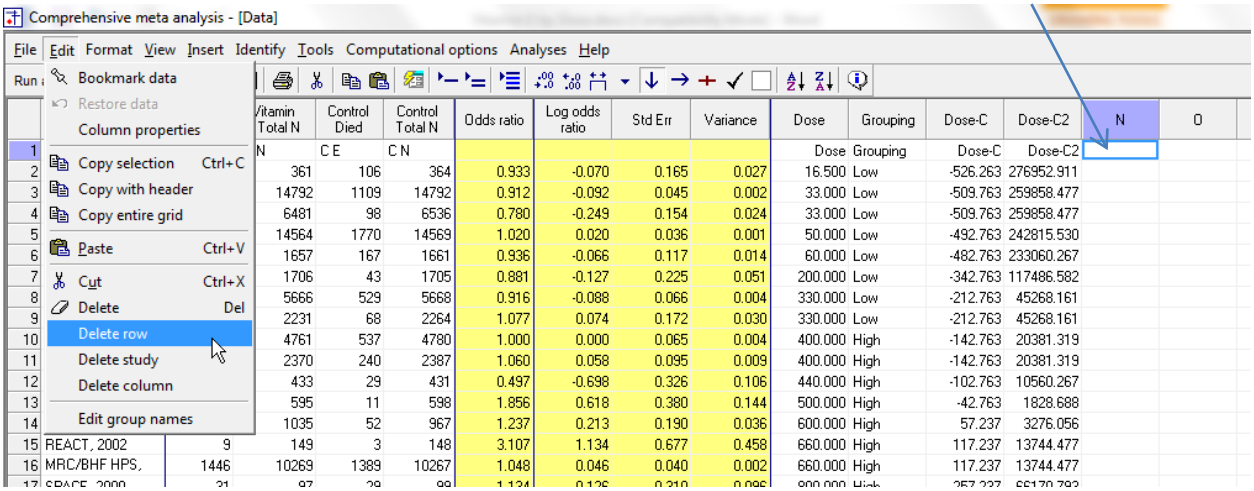
	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	N	O
1	Study	T x E	T x N	C E	C N					Dose	Grouping	Dose-C	Dose-C2		
2	MIN.VIT.AOX,	100	361	106	364	0.933	-0.070	0.165	0.027	16.500	Low	-526.263	276952.911		
3	Linixian A, 1993	1018	14792	1109	14792	0.912	-0.092	0.045	0.002	33.000	Low	-509.763	259858.477		
4	SU.VI.MAX, 2004	76	6481	98	6536	0.780	-0.249	0.154	0.024	33.000	Low	-509.763	259858.477		
5	ATBC, 1994	1800	14564	1770	14569	1.020	0.020	0.036	0.001	50.000	Low	-492.763	242815.530		
6	Linxian B, 1993	157	1657	167	1661	0.936	-0.066	0.117	0.014	60.000	Low	-482.763	233060.267		
7	Linqu, 2001	38	1706	43	1705	0.881	-0.127	0.225	0.051	200.000	Low	-342.763	117486.582		
8	GISSI, 1999	488	5666	529	5668	0.916	-0.088	0.066	0.004	330.000	Low	-212.763	45268.161		
9	PPP, 2001	72	2231	68	2264	1.077	0.074	0.172	0.030	330.000	Low	-212.763	45268.161		
10	HOPE, 2000	535	4761	537	4780	1.000	0.000	0.065	0.004	400.000	High	-142.763	20381.319		
11	AREDS, 2001	251	2370	240	2387	1.060	0.058	0.095	0.009	400.000	High	-142.763	20381.319		
12	PPS, 1994	15	433	29	431	0.497	-0.698	0.326	0.106	440.000	High	-102.763	10560.267		
13	VECAT, 2004	20	595	11	598	1.856	0.618	0.380	0.144	500.000	High	-42.763	1828.688		
14	CHAOS, 1996	68	1035	52	967	1.237	0.213	0.190	0.036	600.000	High	57.237	3276.056		
15	REACT, 2002	9	149	3	148	3.107	1.134	0.677	0.458	660.000	High	117.237	13744.477		
16	MRC/BHF HPS,	1446	10269	1389	10267	1.048	0.046	0.040	0.002	660.000	High	117.237	13744.477		
17	SPACE, 2000	31	97	29	99	1.134	0.126	0.310	0.096	800.000	High	257.237	66170.793		
18	WAVE, 2002	16	212	6	211	2.789	1.026	0.489	0.239	800.000	High	257.237	66170.793		
19	ADCS, 1997	19	170	22	171	0.852	-0.160	0.334	0.111	2000.000	High	1457.237	2123539.21		
20	DATATOP, 1998	73	399	64	401	1.179	0.165	0.188	0.035	2000.000	High	1457.237	2123539.21		
21															
22															

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



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	N	O
1	Study	T x E	T x N	C E	C N					Dose	Grouping	Dose-C	Dose-C2		
2	MIN.VIT.AOX,	100	361	106	364	0.933	-0.070	0.165	0.027	16.500	Low	-526.263	276952.911		
3	Linxian A, 1993	1018	14792	1109	14792	0.912	-0.092	0.045	0.002	33.000	Low	-509.763	259858.477		
4	SU.VI.MAX, 2004	76	6481	98	6536	0.780	-0.249	0.154	0.024	33.000	Low	-509.763	259858.477		
5	ATBC, 1994	1800	14564	1770	14569	1.020	0.020	0.036	0.001	50.000	Low	-492.763	242815.530		
6	Linxian B, 1993	157	1657	167	1661	0.936	-0.066	0.117	0.014	60.000	Low	-482.763	233060.267		
7	Linqu, 2001	38	1706	43	1705	0.881	-0.127	0.225	0.051	200.000	Low	-342.763	117486.582		
8	GISSI, 1999	488	5666	529	5668	0.916	-0.088	0.066	0.004	330.000	Low	-212.763	45268.161		
9	PPP, 2001	72	2231	68	2264	1.077	0.074	0.172	0.030	330.000	Low	-212.763	45268.161		

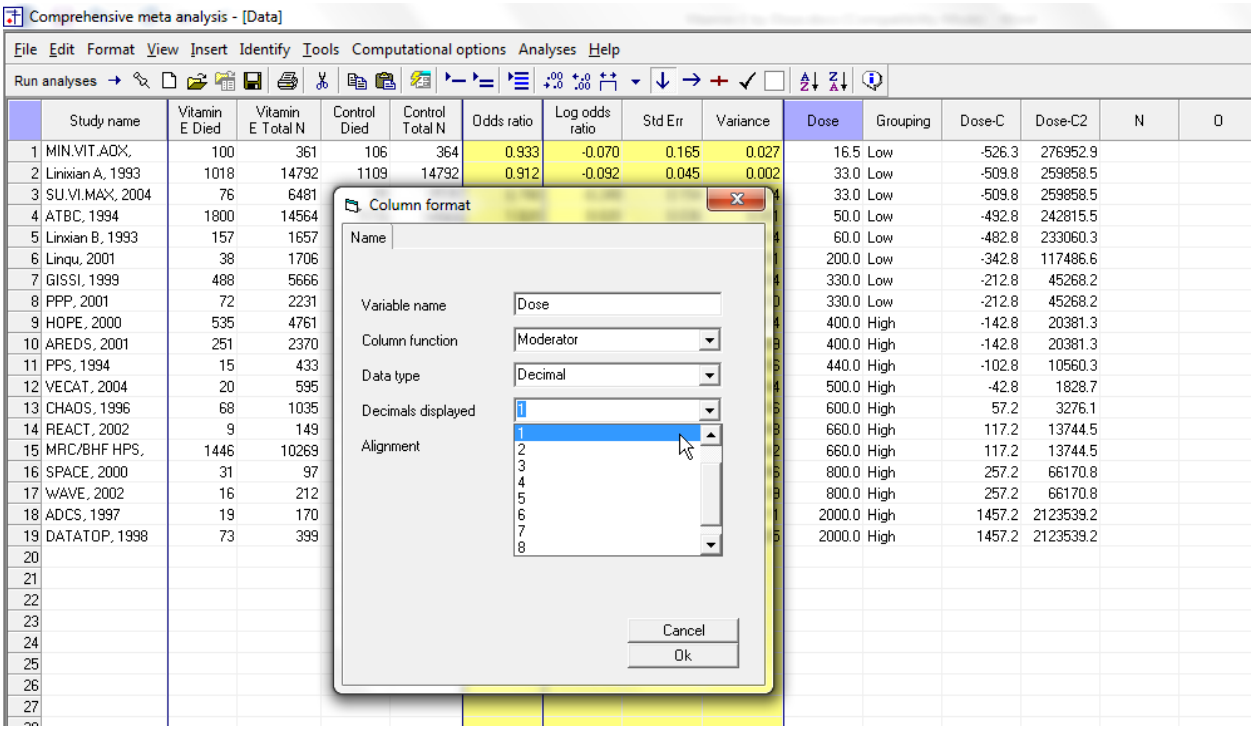
- Click anywhere in Row 1
- Select Edit > Delete row, and confirm



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	N	O
1			N	C E	C N					Dose	Grouping	Dose-C	Dose-C2		
2			361	106	364	0.933	-0.070	0.165	0.027	16.500	Low	-526.263	276952.911		
3			14792	1109	14792	0.912	-0.092	0.045	0.002	33.000	Low	-509.763	259858.477		
4			6481	98	6536	0.780	-0.249	0.154	0.024	33.000	Low	-509.763	259858.477		
5			14564	1770	14569	1.020	0.020	0.036	0.001	50.000	Low	-492.763	242815.530		
6			1657	167	1661	0.936	-0.066	0.117	0.014	60.000	Low	-482.763	233060.267		
7			1706	43	1705	0.881	-0.127	0.225	0.051	200.000	Low	-342.763	117486.582		
8			5666	529	5668	0.916	-0.088	0.066	0.004	330.000	Low	-212.763	45268.161		
9			2231	68	2264	1.077	0.074	0.172	0.030	330.000	Low	-212.763	45268.161		
10			4761	537	4780	1.000	0.000	0.065	0.004	400.000	High	-142.763	20381.319		
11			2370	240	2387	1.060	0.058	0.095	0.009	400.000	High	-142.763	20381.319		
12			433	29	431	0.497	-0.698	0.326	0.106	440.000	High	-102.763	10560.267		
13			595	11	598	1.856	0.618	0.380	0.144	500.000	High	-42.763	1828.688		
14			1035	52	967	1.237	0.213	0.190	0.036	600.000	High	57.237	3276.056		
15	REACT, 2002	9	149	3	148	3.107	1.134	0.677	0.458	660.000	High	117.237	13744.477		
16	MRC/BHF HPS,	1446	10269	1389	10267	1.048	0.046	0.040	0.002	660.000	High	117.237	13744.477		

- Double-click the Header cell for Dose and set the number of decimals displayed to 1
- Double-click the Header cell for Dose-C and set the number of decimals displayed to 1
- Double-click the Header cell for Dose-C2 and set the number of decimals displayed to 1

The screen should look like this



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	N	O
1	MIN.VIT.AOX,	100	361	106	364	0.933	-0.070	0.165	0.027	16.5	Low	-526.3	276952.9		
2	Linxian A, 1993	1018	14792	1109	14792	0.912	-0.092	0.045	0.002	33.0	Low	-509.8	259858.5		
3	SU.VI.MAX, 2004	76	6481							33.0	Low	-509.8	259858.5		
4	ATBC, 1994	1800	14564							50.0	Low	-492.8	242815.5		
5	Linxian B, 1993	157	1657							60.0	Low	-482.8	233060.3		
6	Linqu, 2001	38	1706							200.0	Low	-342.8	117486.6		
7	GISSI, 1999	488	5666							330.0	Low	-212.8	45268.2		
8	PPP, 2001	72	2231							330.0	Low	-212.8	45268.2		
9	HOPE, 2000	535	4761							400.0	High	-142.8	20381.3		
10	AREDS, 2001	251	2370							400.0	High	-142.8	20381.3		
11	PPS, 1994	15	433							440.0	High	-102.8	10560.3		
12	VECAT, 2004	20	595							500.0	High	-42.8	1828.7		
13	CHAOS, 1996	68	1035							600.0	High	57.2	3276.1		
14	REACT, 2002	9	149							660.0	High	117.2	13744.5		
15	MRC/BHF HPS,	1446	10269							660.0	High	117.2	13744.5		
16	SPACE, 2000	31	97							800.0	High	257.2	66170.8		
17	WAVE, 2002	16	212							800.0	High	257.2	66170.8		
18	ADCS, 1997	19	170							2000.0	High	1457.2	2123539.2		
19	DATATOP, 1998	73	399							2000.0	High	1457.2	2123539.2		
20															
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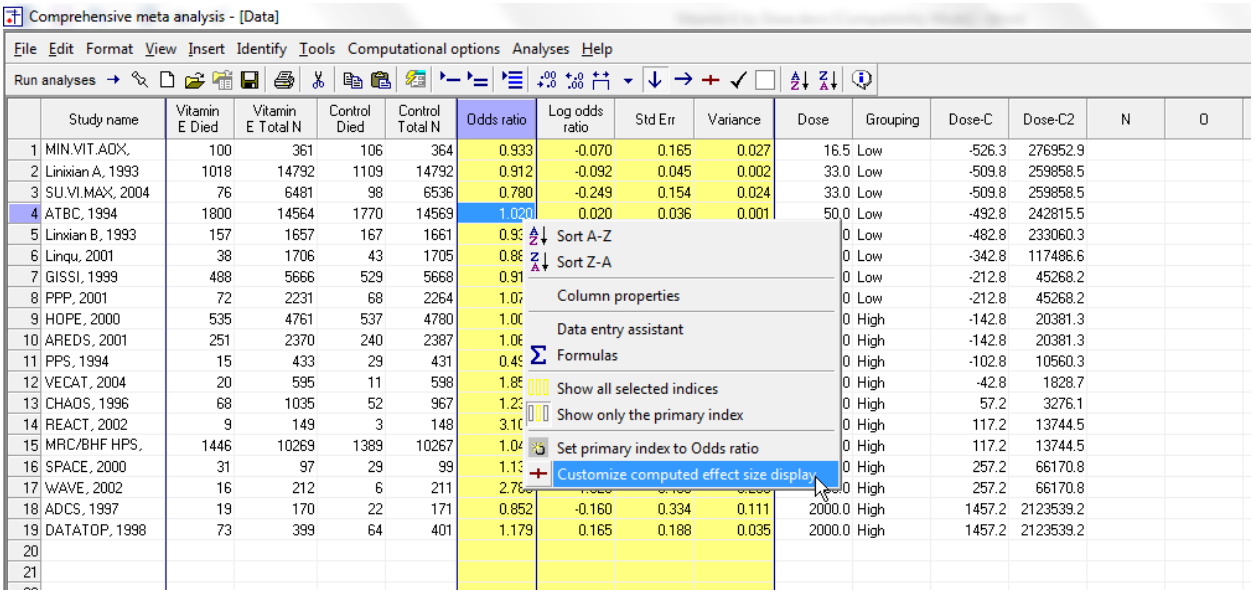
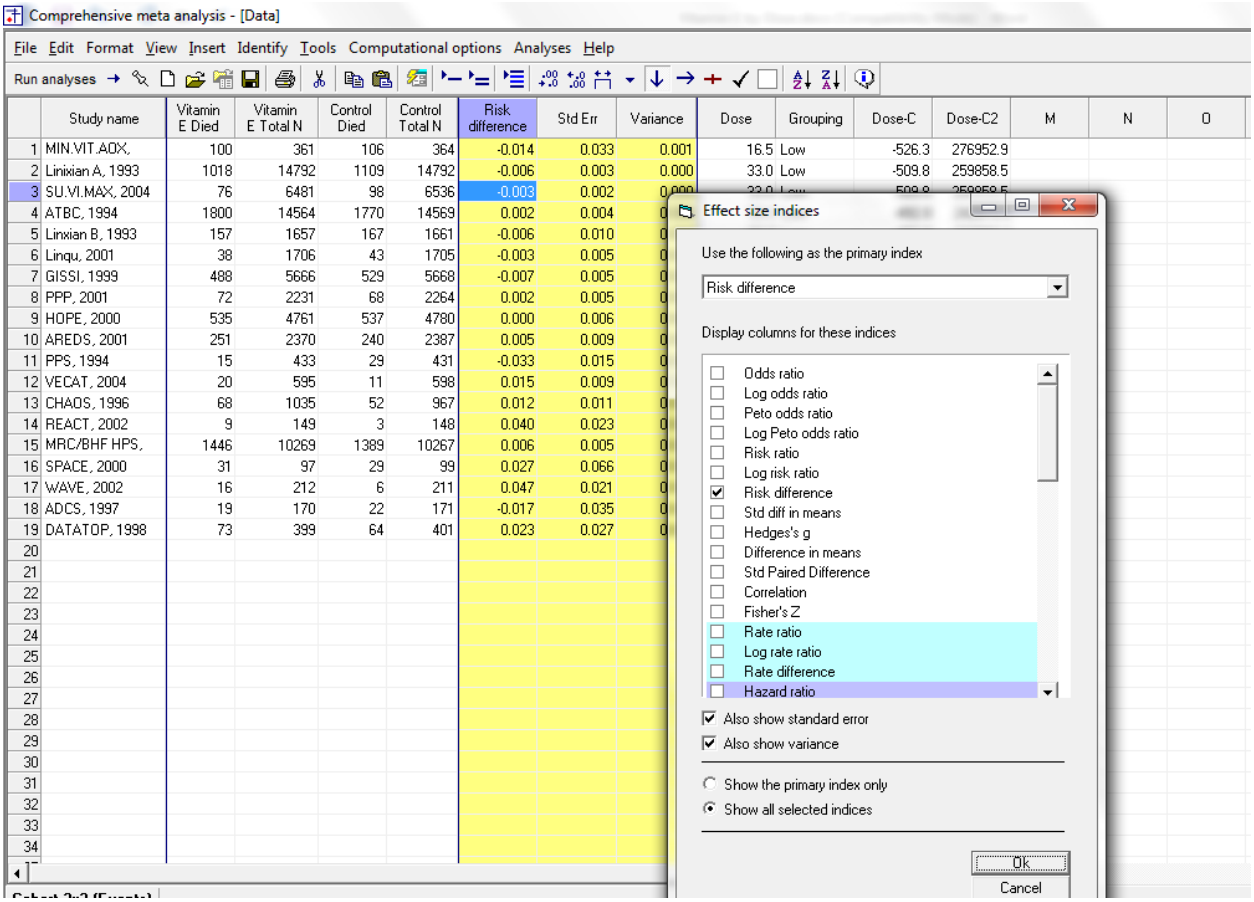
By default, the program is displaying the odds ratio as the effect size

We want to switch to the risk difference (RD)



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Odds ratio	Log odds ratio	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	N	O
1	MIN.VIT.AOX,	100	361	106	364	0.933	-0.070	0.165	0.027	16.5	Low	-526.3	276952.9		
2	Linixian A, 1993	1018	14792	1109	14792	0.912	-0.092	0.045	0.002	33.0	Low	-509.8	259858.5		
3	SU.VI.MAX, 2004	76	6481	98	6536	0.780	-0.249	0.154	0.024	33.0	Low	-509.8	259858.5		
4	ATBC, 1994	1800	14564	1770	14569	1.020	0.020	0.036	0.001	50.0	Low	-492.8	242815.5		
5	Linxian B, 1993	157	1657	167	1661	0.93				0	Low	-482.8	233060.3		
6	Linqu, 2001	38	1706	43	1705	0.88				0	Low	-342.8	117486.6		
7	GISSI, 1999	488	5666	529	5668	0.91				0	Low	-212.8	45268.2		
8	PPP, 2001	72	2231	68	2264	1.07				0	Low	-212.8	45268.2		
9	HOPE, 2000	535	4761	537	4780	1.00				0	High	-142.8	20381.3		
10	AREDS, 2001	251	2370	240	2387	1.06				0	High	-142.8	20381.3		
11	PPS, 1994	15	433	29	431	0.49				0	High	-102.8	10560.3		
12	VECAT, 2004	20	595	11	598	1.85				0	High	-42.8	1828.7		
13	CHAOS, 1996	68	1035	52	967	1.23				0	High	57.2	3276.1		
14	REACT, 2002	9	149	3	148	3.10				0	High	117.2	13744.5		
15	MRC/BHF HPS,	1446	10269	1389	10267	1.04				0	High	117.2	13744.5		
16	SPACE, 2000	31	97	29	99	1.13				0	High	257.2	66170.8		
17	WAVE, 2002	16	212	6	211	2.78				0	High	257.2	66170.8		
18	ADCS, 1997	19	170	22	171	0.852	-0.160	0.334	0.111	2000.0	High	1457.2	2123539.2		
19	DATATOP, 1998	73	399	64	401	1.179	0.165	0.188	0.035	2000.0	High	1457.2	2123539.2		
20															
21															

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



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Risk difference	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	M	N	O
1	MIN.VIT.AOX,	100	361	106	364	-0.014	0.033	0.001	16.5	Low	-526.3	276952.9			
2	Linxian A, 1993	1018	14792	1109	14792	-0.006	0.003	0.000	33.0	Low	-509.8	259858.5			
3	SU.VI.MAX, 2004	76	6481	98	6536	-0.003	0.002	0.000							
4	ATBC, 1994	1800	14564	1770	14569	0.002	0.004	0.000							
5	Linxian B, 1993	157	1657	167	1661	-0.006	0.010	0.000							
6	Linqu, 2001	38	1706	43	1705	-0.003	0.005	0.000							
7	GISSI, 1999	488	5666	529	5668	-0.007	0.005	0.000							
8	PPP, 2001	72	2231	68	2264	0.002	0.005	0.000							
9	HOPE, 2000	535	4761	537	4780	0.000	0.006	0.000							
10	AREDS, 2001	251	2370	240	2387	0.005	0.009	0.000							
11	PPS, 1994	15	433	29	431	-0.033	0.015	0.000							
12	VECAT, 2004	20	595	11	598	0.015	0.009	0.000							
13	CHAOS, 1996	68	1035	52	967	0.012	0.011	0.000							
14	REACT, 2002	9	149	3	148	0.040	0.023	0.000							
15	MRC/BHF HPS,	1446	10269	1389	10267	0.006	0.005	0.000							
16	SPACE, 2000	31	97	29	99	0.027	0.066	0.000							
17	WAVE, 2002	16	212	6	211	0.047	0.021	0.000							
18	ADCS, 1997	19	170	22	171	-0.017	0.035	0.000							
19	DATATOP, 1998	73	399	64	401	0.023	0.027	0.000							
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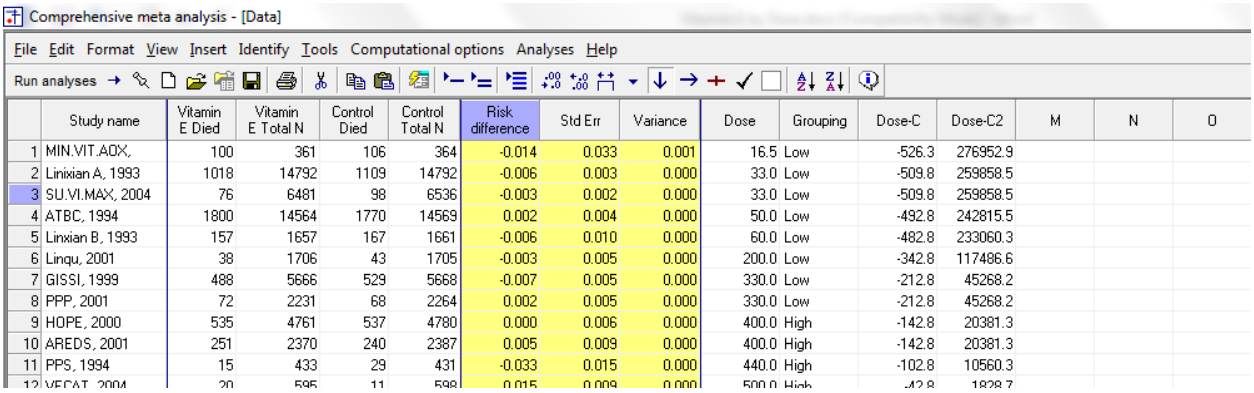
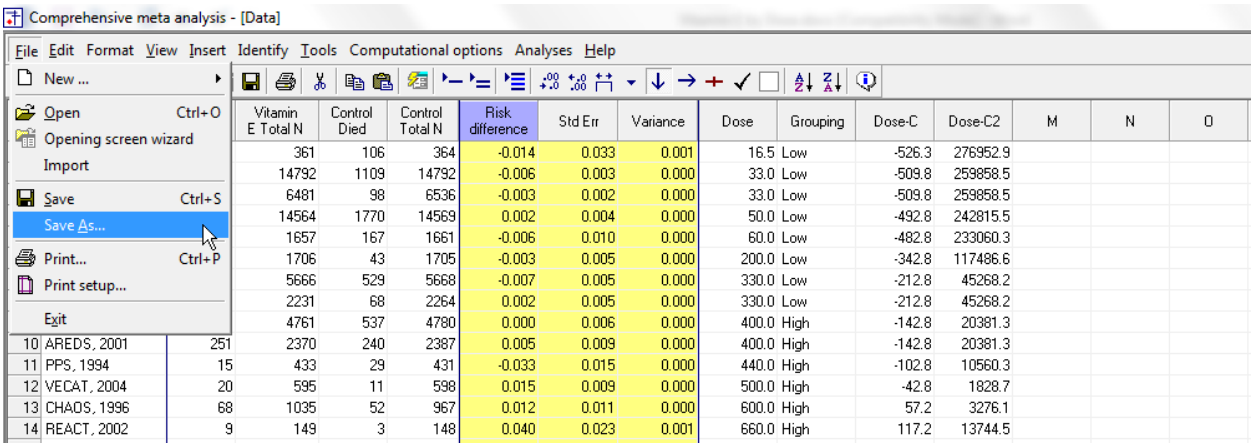
- Tick Risk difference
- Select Risk difference in the drop-down box in the wizard
- De-select Odds ratio
- De-select log odds ratio
- Click Ok

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



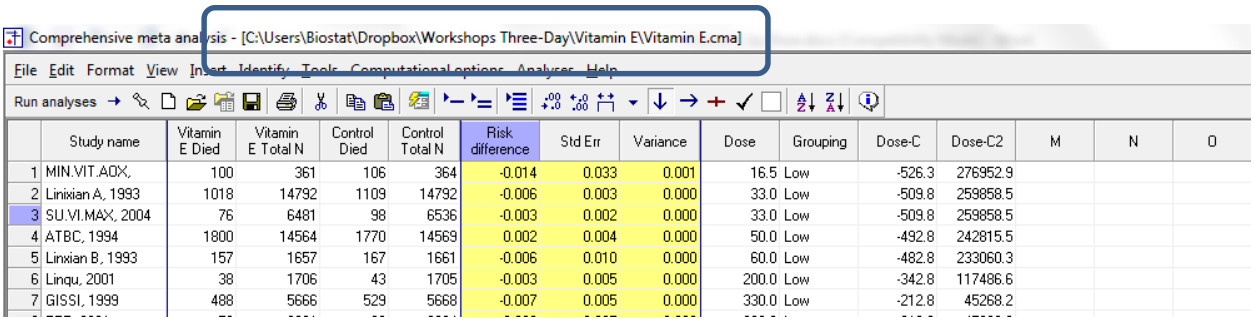
	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Risk difference	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	M	N	O
1	MIN.VIT.AOX,	100	361	106	364	-0.014	0.033	0.001	16.5	Low	-526.3	276952.9			
2	Linxian A, 1993	1018	14792	1109	14792	-0.006	0.003	0.000	33.0	Low	-509.8	259858.5			
3	SU.VI.MAX, 2004	76	6481	98	6536	-0.003	0.002	0.000	33.0	Low	-509.8	259858.5			
4	ATBC, 1994	1800	14564	1770	14569	0.002	0.004	0.000	50.0	Low	-492.8	242815.5			
5	Linxian B, 1993	157	1657	167	1661	-0.006	0.010	0.000	60.0	Low	-482.8	233060.3			
6	Linqu, 2001	38	1706	43	1705	-0.003	0.005	0.000	200.0	Low	-342.8	117486.6			
7	GISSI, 1999	488	5666	529	5668	-0.007	0.005	0.000	330.0	Low	-212.8	45268.2			
8	PPP, 2001	72	2231	68	2264	0.002	0.005	0.000	330.0	Low	-212.8	45268.2			
9	HOPE, 2000	535	4761	537	4780	0.000	0.006	0.000	400.0	High	-142.8	20381.3			
10	AREDS, 2001	251	2370	240	2387	0.005	0.009	0.000	400.0	High	-142.8	20381.3			
11	PPS, 1994	15	433	29	431	-0.033	0.015	0.000	440.0	High	-102.8	10560.3			

Click File > Save As and save the file



Note that the file name is now in the header.

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

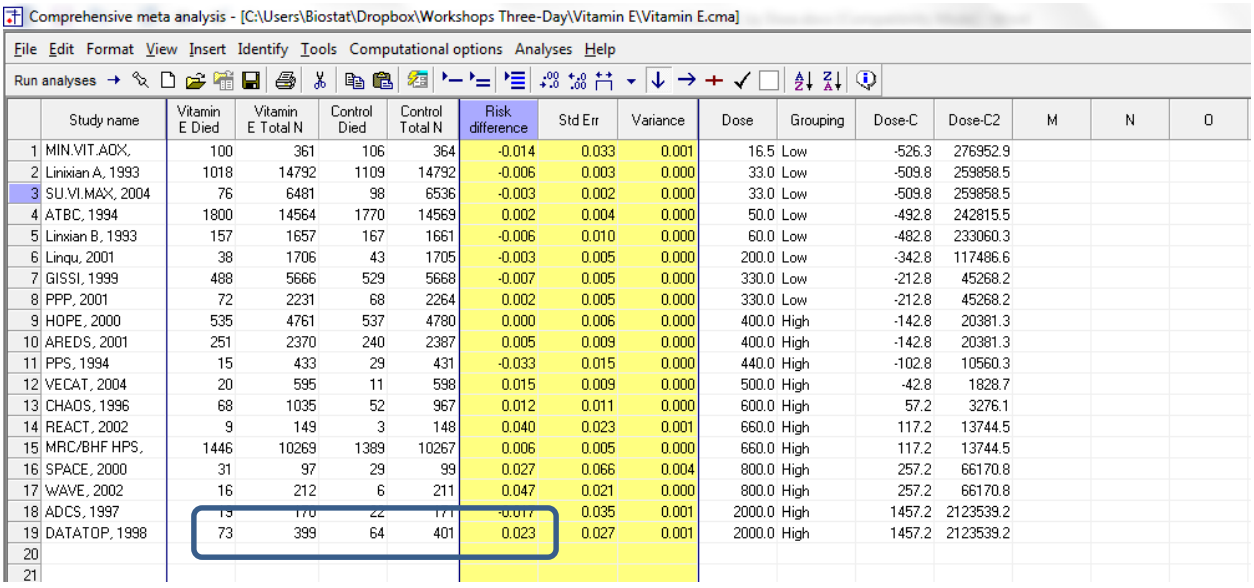


By convention we've put the treated group (Vitamin E) in the first two columns and the control (placebo) in the second two columns. Also by convention, we've defined "Event" as the presence of the outcome (Death).

When we follow these conventions, and the outcome is a bad event (as it is here) if the treated group does worse than the control, the risk difference will be greater than 0.

Therefore, in the present case, a risk difference greater than 0 indicates that Vitamin E was associated with an increased risk of death.

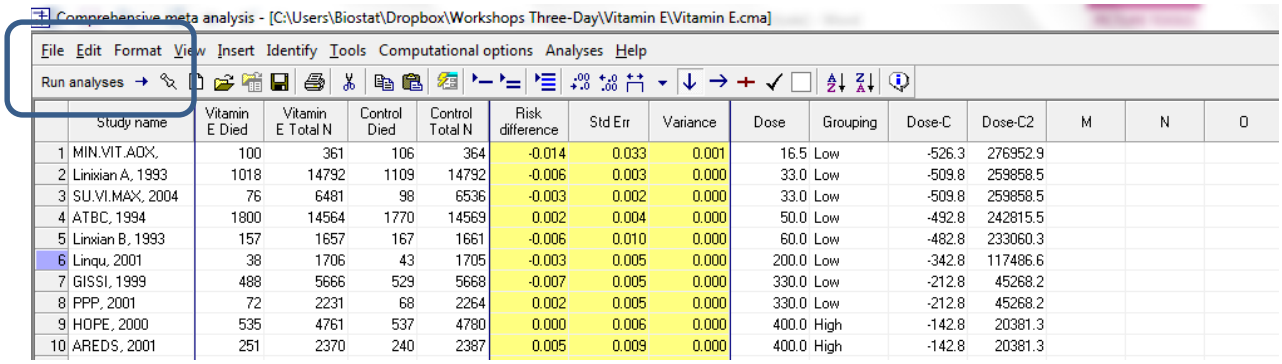
It's always a good idea to check at least one study and make sure that we have the direction right. For this purpose we'll use the last study (DATATOP), where the risk difference is relatively large, and the distinction between groups should be clear.



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Risk difference	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	M	N	O
1	MIN.VIT.AOX,	100	361	106	364	-0.014	0.033	0.001	16.5	Low	-526.3	276952.9			
2	Linxian A, 1993	1018	14792	1109	14792	-0.006	0.003	0.000	33.0	Low	-509.8	259858.5			
3	SU.VI.MAX, 2004	76	6481	98	6536	-0.003	0.002	0.000	33.0	Low	-509.8	259858.5			
4	ATBC, 1994	1800	14564	1770	14569	0.002	0.004	0.000	50.0	Low	-492.8	242815.5			
5	Linxian B, 1993	157	1657	167	1661	-0.006	0.010	0.000	60.0	Low	-482.8	233060.3			
6	Linqu, 2001	38	1706	43	1705	-0.003	0.005	0.000	200.0	Low	-342.8	117486.6			
7	GISSI, 1999	488	5666	529	5668	-0.007	0.005	0.000	330.0	Low	-212.8	45268.2			
8	PPP, 2001	72	2231	68	2264	0.002	0.005	0.000	330.0	Low	-212.8	45268.2			
9	HOPE, 2000	535	4761	537	4780	0.000	0.006	0.000	400.0	High	-142.8	20381.3			
10	AREDS, 2001	251	2370	240	2387	0.005	0.009	0.000	400.0	High	-142.8	20381.3			
11	PPS, 1994	15	433	29	431	-0.033	0.015	0.000	440.0	High	-102.8	10560.3			
12	VECAT, 2004	20	595	11	598	0.015	0.009	0.000	500.0	High	-42.8	1828.7			
13	CHAOS, 1996	68	1035	52	967	0.012	0.011	0.000	600.0	High	57.2	3276.1			
14	REACT, 2002	9	149	3	148	0.040	0.023	0.001	660.0	High	117.2	13744.5			
15	MRC/BHF HPS,	1446	10269	1389	10267	0.006	0.005	0.000	660.0	High	117.2	13744.5			
16	SPACE, 2000	31	97	29	99	0.027	0.066	0.004	800.0	High	257.2	66170.8			
17	WAVE, 2002	16	212	6	211	0.047	0.021	0.000	800.0	High	257.2	66170.8			
18	ADCS, 1997	13	170	22	171	-0.017	0.035	0.001	2000.0	High	1457.2	2123539.2			
19	DATATOP, 1998	73	399	64	401	0.023	0.027	0.001	2000.0	High	1457.2	2123539.2			
20															
21															

Both groups have approximately the same number of patients (about 400) but the number of deaths is higher in the Vitamin-E group than in the control group (73 vs. 64). The risk difference is positive (+0.023), which means that the Vitamin-E group had a higher mortality risk.

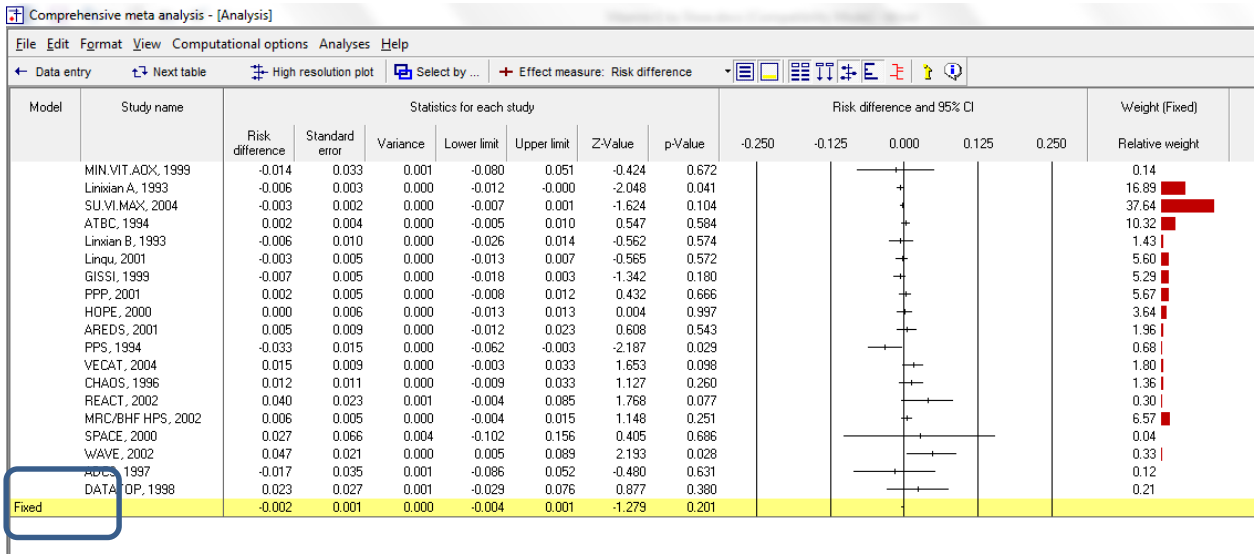
- To run the analysis, click [Run analysis]



	Study name	Vitamin E Died	Vitamin E Total N	Control Died	Control Total N	Risk difference	Std Err	Variance	Dose	Grouping	Dose-C	Dose-C2	M	N	O
1	MIN.VIT.AOX,	100	361	106	364	-0.014	0.033	0.001	16.5	Low	-526.3	276952.9			
2	Linixian A, 1993	1018	14792	1109	14792	-0.006	0.003	0.000	33.0	Low	-509.8	259858.5			
3	SU.VI.MAX, 2004	76	6481	98	6536	-0.003	0.002	0.000	33.0	Low	-509.8	259858.5			
4	ATBC, 1994	1800	14564	1770	14569	0.002	0.004	0.000	50.0	Low	-492.8	242815.5			
5	Linxian B, 1993	157	1657	167	1661	-0.006	0.010	0.000	60.0	Low	-482.8	233060.3			
6	Linqu, 2001	38	1706	43	1705	-0.003	0.005	0.000	200.0	Low	-342.8	117486.6			
7	GISSI, 1999	488	5666	529	5668	-0.007	0.005	0.000	330.0	Low	-212.8	45268.2			
8	PPP, 2001	72	2231	68	2264	0.002	0.005	0.000	330.0	Low	-212.8	45268.2			
9	HOPE, 2000	535	4761	537	4780	0.000	0.006	0.000	400.0	High	-142.8	20381.3			
10	AREDS, 2001	251	2370	240	2387	0.005	0.009	0.000	400.0	High	-142.8	20381.3			

This is the basic analysis screen

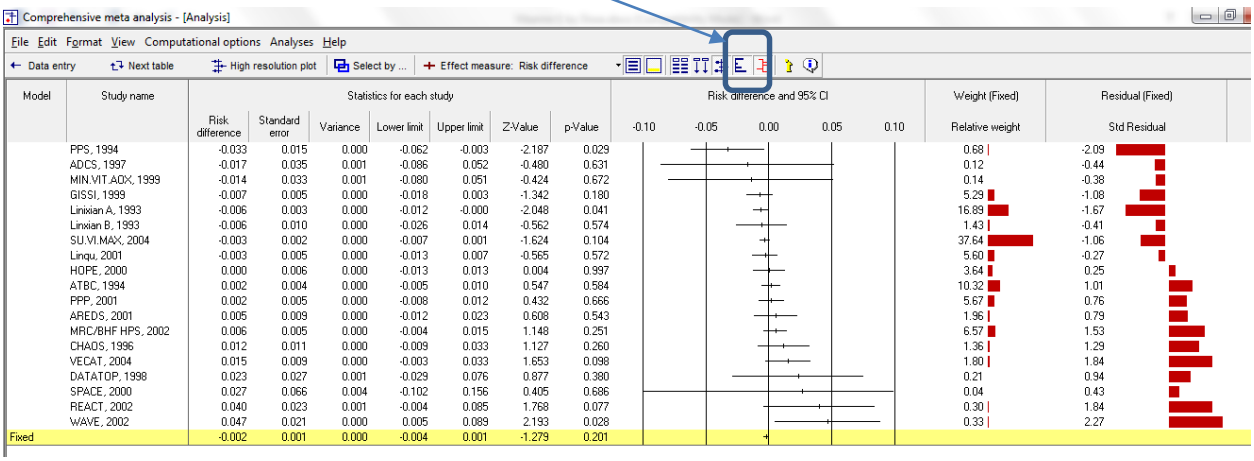
Initially, the program displays the fixed-effect analysis. This is indicated by the tab at the bottom and the label in the plot.



Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight
	MIN.VIT.AOX, 1999	-0.014	0.033	0.001	-0.080	0.051	-0.424	0.672	0.14
	Linxian A, 1993	-0.006	0.003	0.000	-0.012	-0.000	-2.048	0.041	16.89
	SU.VI.MAX, 2004	-0.003	0.002	0.000	-0.007	0.001	-1.624	0.104	37.64
	ATBC, 1994	0.002	0.004	0.000	-0.005	0.010	0.547	0.584	10.32
	Linxian B, 1993	-0.006	0.010	0.000	-0.026	0.014	-0.562	0.574	1.43
	Linqu, 2001	-0.003	0.005	0.000	-0.013	0.007	-0.565	0.572	5.60
	GISSI, 1999	-0.007	0.005	0.000	-0.018	0.003	-1.342	0.180	5.29
	PPP, 2001	0.002	0.005	0.000	-0.008	0.012	0.432	0.666	5.67
	HOPE, 2000	0.000	0.006	0.000	-0.013	0.013	0.004	0.997	3.64
	AREDS, 2001	0.005	0.009	0.000	-0.012	0.023	0.608	0.543	1.96
	PPS, 1994	-0.033	0.015	0.000	-0.062	-0.003	-2.187	0.029	0.68
	VECAT, 2004	0.015	0.009	0.000	-0.003	0.033	1.653	0.098	1.80
	CHAOS, 1996	0.012	0.011	0.000	-0.009	0.033	1.127	0.260	1.36
	REACT, 2002	0.040	0.023	0.001	-0.004	0.085	1.768	0.077	0.30
	MRC/BHF HPS, 2002	0.006	0.005	0.000	-0.004	0.015	1.148	0.251	6.57
	SPACE, 2000	0.027	0.066	0.004	-0.102	0.156	0.405	0.686	0.04
	WAVE, 2002	0.047	0.021	0.000	0.005	0.089	2.193	0.028	0.33
	ABC, 1997	-0.017	0.035	0.001	-0.086	0.052	-0.480	0.631	0.12
	DATA-TOP, 1998	0.023	0.027	0.001	-0.029	0.076	0.877	0.380	0.21
Fixed		-0.002	0.001	0.000	-0.004	0.001	-1.279	0.201	

To get a better sense of the dispersion

- Right-click on the forest plot
- Click Customized and set the scale to .1
- Right-click on the Risk Difference column and Sort Low-High
- Click the tool to display residuals



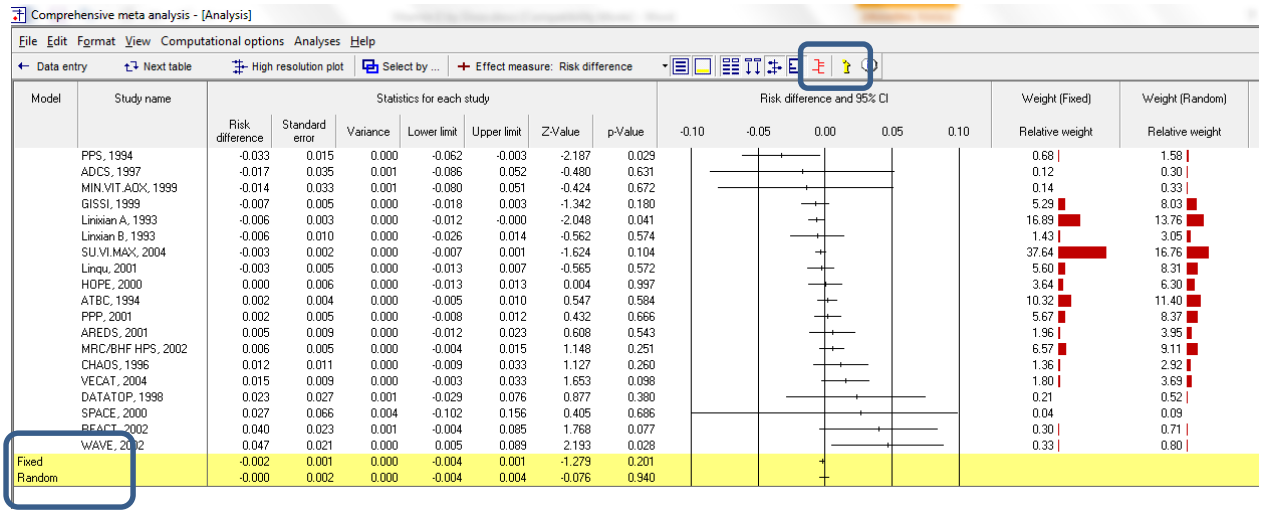
It seems that about half the effects are less than zero (favors control) while half are greater than zero (favors Vitamin E).

The effects seem to vary. There is little (if any) overlap between the confidence interval of the first studies and the last. While the confidence interval for most studies overlap the mean effect, some barely do so. This suggests that the impact of Vitamin E may vary from study to study. We'll see the corresponding statistics momentarily.

We are not going to use the fixed-effect model, but if we were, we would interpret the results as follows.

The pooled effect is -0.002 which means that the persons in the control group were less likely to die. Specifically, if we assigned 1,000 people to Vitamin E and 1,000 people to control, we would expect to see 2 more deaths in the Vitamin E group as compared with the control group. The confidence interval is -0.004 to +0.001, which includes 0.000. Therefore, we cannot rule out the null hypothesis that the risk of death is identical in the two groups. Similarly, the Z-value for a test of the null is -1.279 with p=0.201.

- Click [Both models]
- Turn off the display of residuals



Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	PPS, 1994	-0.033	0.015	0.000	-0.062	-0.003	-2.187	0.029	0.68	1.58
	ADCS, 1997	-0.017	0.035	0.001	-0.086	0.052	-0.480	0.631	0.12	0.30
	MIN.VIT.AOX, 1999	-0.014	0.033	0.001	-0.080	0.051	-0.424	0.672	0.14	0.33
	GISSI, 1999	-0.007	0.005	0.000	-0.018	0.003	-1.342	0.180	5.29	8.03
	Linxian A, 1993	-0.006	0.003	0.000	-0.012	-0.000	-2.048	0.041	16.89	13.76
	Linxian B, 1993	-0.006	0.010	0.000	-0.026	0.014	-0.562	0.574	1.43	3.05
	SU.VI.MAX, 2004	-0.003	0.002	0.000	-0.007	0.001	-1.624	0.104	37.64	16.76
	Linqu, 2001	-0.003	0.005	0.000	-0.013	0.007	-0.565	0.572	5.60	8.31
	HOPE, 2000	0.000	0.006	0.000	-0.013	0.013	0.004	0.997	3.64	6.30
	ATBC, 1994	0.002	0.004	0.000	-0.005	0.010	0.547	0.584	10.32	11.40
	PPP, 2001	0.002	0.005	0.000	-0.008	0.012	0.432	0.666	5.67	8.37
	AREDS, 2001	0.005	0.009	0.000	-0.012	0.023	0.608	0.543	1.96	3.95
	MRC/BHF HPS, 2002	0.006	0.005	0.000	-0.004	0.015	1.148	0.251	6.57	9.11
	CHAOS, 1996	0.012	0.011	0.000	-0.009	0.033	1.127	0.260	1.36	2.92
	VECAT, 2004	0.015	0.009	0.000	-0.003	0.033	1.653	0.098	1.80	3.69
	DATATOP, 1998	0.023	0.027	0.001	-0.029	0.076	0.877	0.380	0.21	0.52
	SPACE, 2000	0.027	0.066	0.004	-0.102	0.156	0.405	0.686	0.04	0.09
	REACT, 2002	0.040	0.023	0.001	-0.004	0.085	1.768	0.077	0.30	0.71
	WAVE, 2002	0.047	0.021	0.000	0.005	0.089	2.193	0.028	0.33	0.80
Fixed		-0.002	0.001	0.000	-0.004	0.001	-1.279	0.201		
Random		-0.000	0.002	0.000	-0.004	0.004	-0.076	0.940		

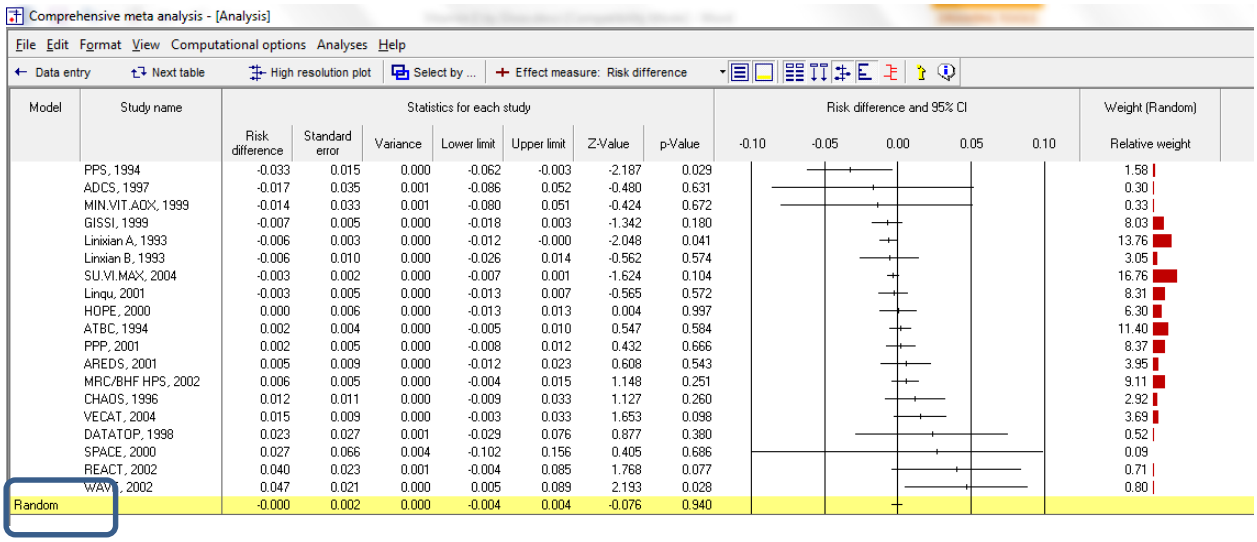
Under the fixed-effect model the pooled effect size is -0.002, while under the random-effects model the pooled effect size is -0.000.

- 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 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.



Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Random) Relative weight
	PPS, 1994	-0.033	0.015	0.000	-0.062	-0.003	-2.187	0.029	1.58
	ADCS, 1997	-0.017	0.035	0.001	-0.086	0.052	-0.480	0.631	0.30
	MIN.VIT.AOX, 1999	-0.014	0.033	0.001	-0.080	0.051	-0.424	0.672	0.33
	GISSI, 1999	-0.007	0.005	0.000	-0.018	0.003	-1.342	0.180	8.03
	Linxian A, 1993	-0.006	0.003	0.000	-0.012	-0.000	-2.048	0.041	13.76
	Linxian B, 1993	-0.006	0.010	0.000	-0.026	0.014	-0.562	0.574	3.05
	SU.VI.MAX, 2004	-0.003	0.002	0.000	-0.007	0.001	-1.624	0.104	16.76
	Linqu, 2001	-0.003	0.005	0.000	-0.013	0.007	-0.565	0.572	8.31
	HOPE, 2000	0.000	0.006	0.000	-0.013	0.013	0.004	0.997	6.30
	ATBC, 1994	0.002	0.004	0.000	-0.005	0.010	0.547	0.584	11.40
	PPP, 2001	0.002	0.005	0.000	-0.008	0.012	0.432	0.666	8.37
	AREDS, 2001	0.005	0.009	0.000	-0.012	0.023	0.608	0.543	3.95
	MRC/BHF HPS, 2002	0.006	0.005	0.000	-0.004	0.015	1.148	0.251	9.11
	CHAOS, 1996	0.012	0.011	0.000	-0.009	0.033	1.127	0.260	2.92
	VECAT, 2004	0.015	0.009	0.000	-0.003	0.033	1.653	0.098	3.69
	DATATOP, 1998	0.023	0.027	0.001	-0.029	0.076	0.877	0.380	0.52
	SPACE, 2000	0.027	0.066	0.004	-0.102	0.156	0.405	0.686	0.09
	REACT, 2002	0.040	0.023	0.001	-0.004	0.085	1.768	0.077	0.71
	WAV[illegible], 2002	0.047	0.021	0.000	0.005	0.089	2.193	0.028	0.80
Random		-0.000	0.002	0.000	-0.004	0.004	-0.076	0.940	

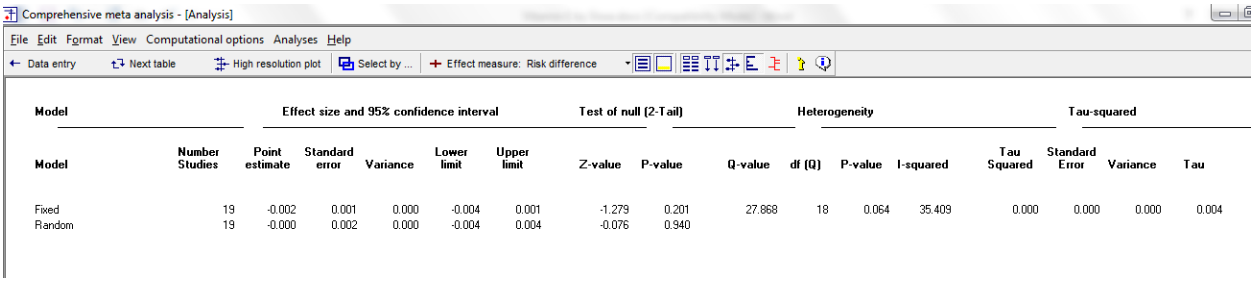
A quick view of the plot suggests the following

- About half the effects are less than zero (favors control) while half are greater than zero (favors Vitamin E).
- The summary effect is -0.000 with a CI of -0.004 to +0.004. Thus, the mean effect is essentially zero.
- The summary effect has a Z-value -0.076 a *p*-value of < 0.940. Thus we cannot reject the null hypotheses that the true risk ratio is 1.0.

Thus, it's clear that there's no evidence that the mean risk of death is different in one group than the other, when averaged over the universe of relevant studies.

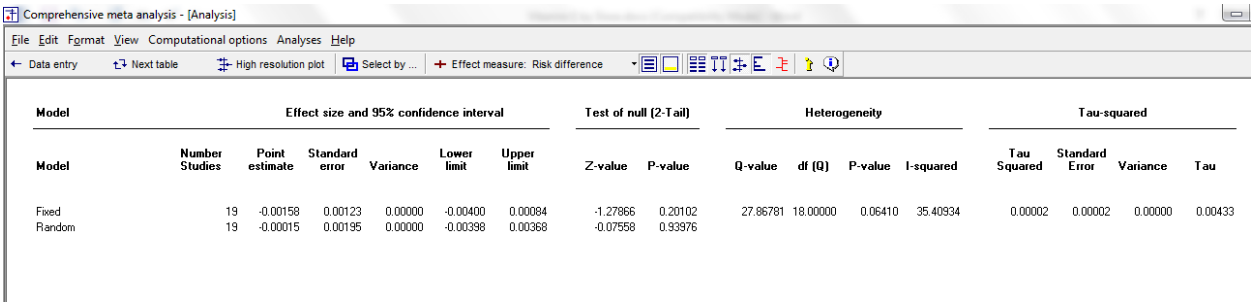
What about the variance in effect size? The observed effect sizes vary from -0.033 to +0.047 (thee additional deaths per 1,000 people in the control group to 5 additional deaths per 1,000 people in the Vitamin E group). What proportion of this variance reflects differences in true effect sizes (rather than sampling error)?

Click Next table



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	19	-0.002	0.001	0.000	-0.004	0.001	-1.279	0.201	27.868	18	0.064	35.409	0.000	0.000	0.000	0.004
Random	19	-0.000	0.002	0.000	-0.004	0.004	-0.076	0.940								

Because the numbers are so small, click Format > Increase decimals two times



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	19	-0.00158	0.00123	0.00000	-0.00400	0.00084	-1.27866	0.20102	27.86781	18.00000	0.06410	35.40934	0.00002	0.00002	0.00000	0.00433
Random	19	-0.00015	0.00195	0.00000	-0.00398	0.00368	-0.07558	0.93976								

Under the null hypothesis that the difference between groups is identical for all studies, the expected value of *Q* is equal to the degrees of freedom (number of studies minus 1), which is 18. The observed value of *Q* is 27.86781. This exceeds the expected value by enough that it is statistically significant, with p=0.06410 (by convention, the criterion alpha for this test is 0.10 rather than 0.05 since the test typically has low power).

How much variance is there?

I^2 is 35.40, which tells us that about 35% of the variance in observed effects reflects variance in true effects, while the balance (65%) reflects sampling error.

T^2, the variance of true effect sizes is 0.00002 while *T*, the standard deviation of true effect sizes is 0.00433.

We can use this to get a sense of the dispersion by using the spreadsheet as shown here.

- Open the spreadsheet [Prediction Intervals.xls]
- Select the tab for [Means]
- In CMA select Risk Difference as the index
- Copy the A|B|C|D values as shown from CMA to Excel

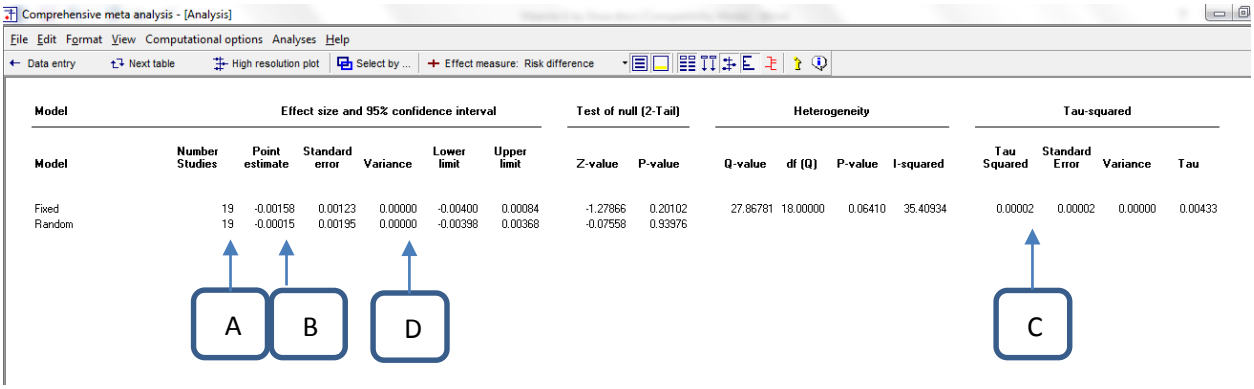
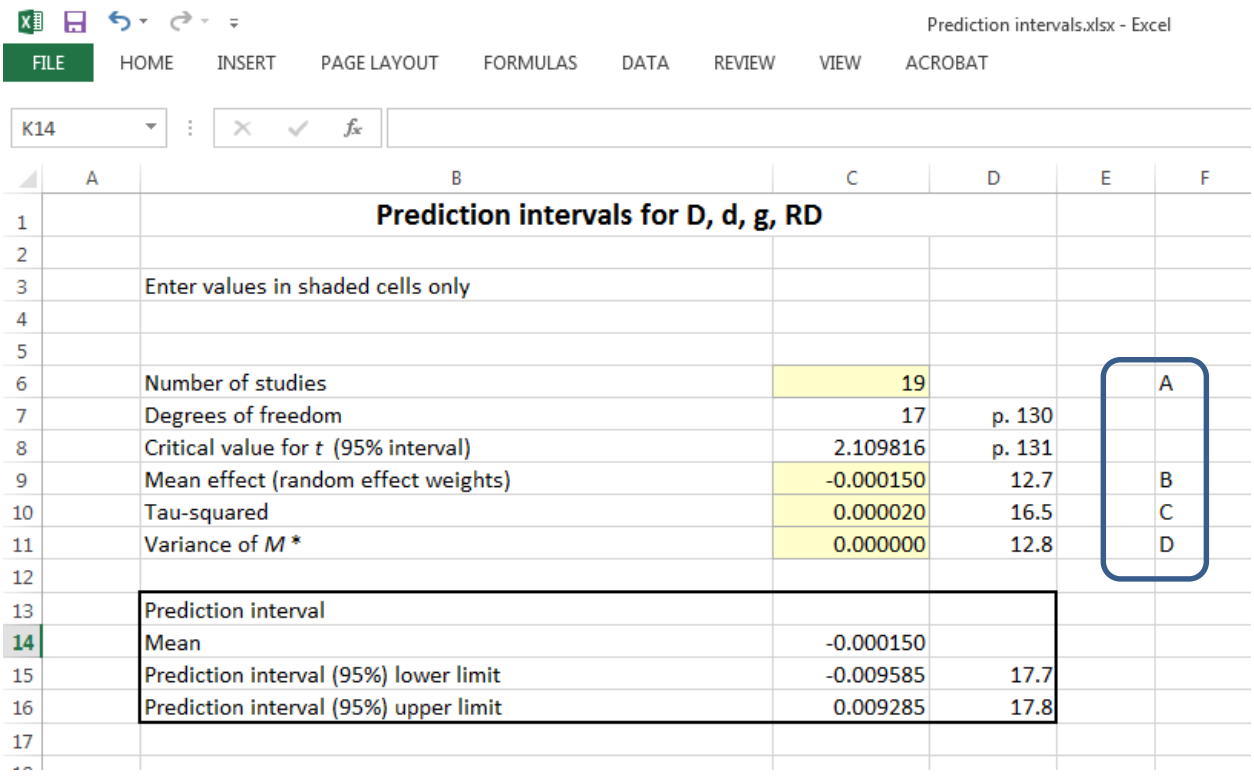


Figure 1



The confidence interval is −0.00398 to +0.00368 (We can read the CI from Figure 1 because the index here is the raw difference). In Excel, we see the prediction interval is −0.00959 to +0.00929.

The true effect size varies from study to study. The mean effect size probably falls in the range of −0.00398 to +0.00368. The true effect size for any single study will usually fall in the range of −0.00959 to +0.00929.

Thus, even if we assume that the mean effect is actually zero, the more important point is that the effect size in any single study may differ substantially from zero. If we assume that the effects are normally distributed, then the data suggest that in some studies Vitamin E could reduce the risk of death by 1 in 100, while in others it could increase the risk of death by 1 in 100.

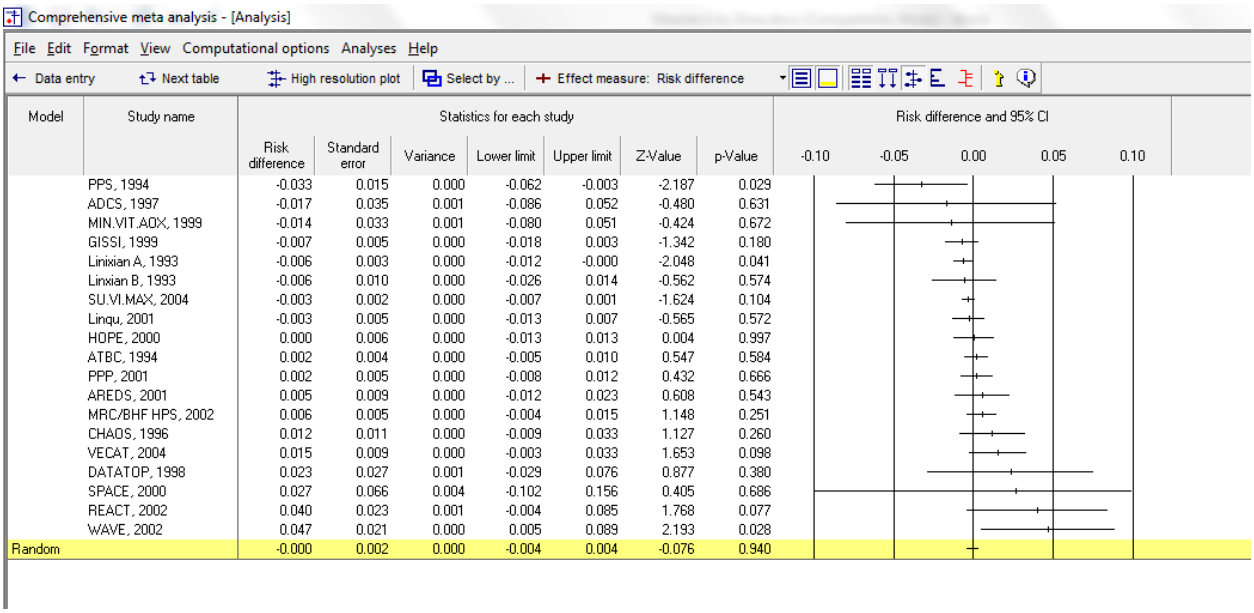
The next step is to try and explain some of this variance. Where is Vitamin E helpful, and where is it harmful?

The researchers hypothesized that Vitamin E in higher doses would be harmful. We can perform two kinds of analyses to test this hypothesis.

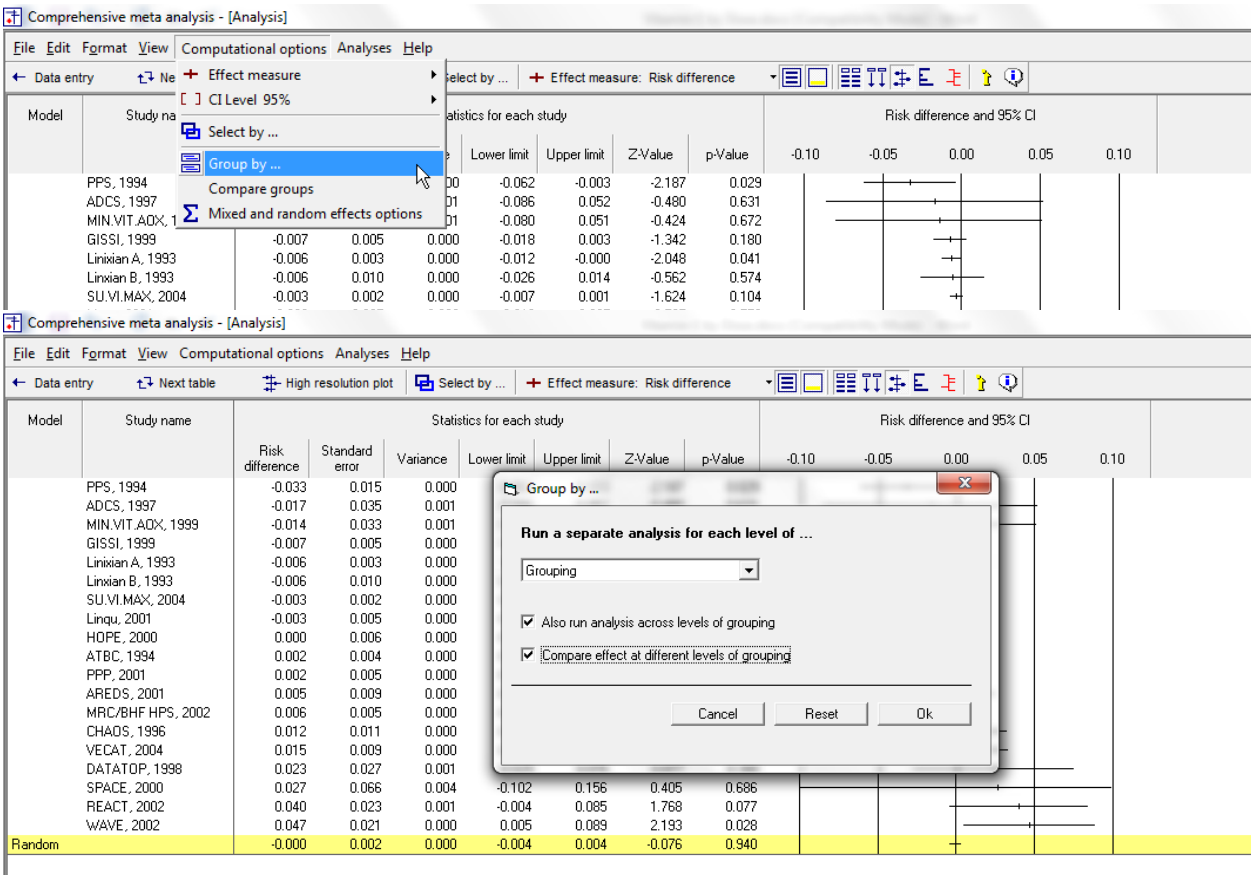
- We can treat dose as a dichotomy (high vs. low) and compare the risk difference by this grouping.
- Or, we can treat dose as a continuous variable and assess the relationship between dose and risk difference.

We'll do both.

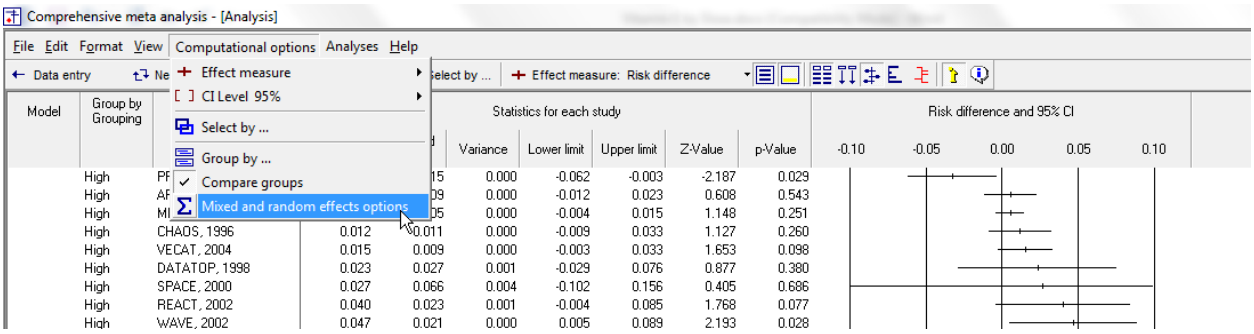
Subgroups analysis

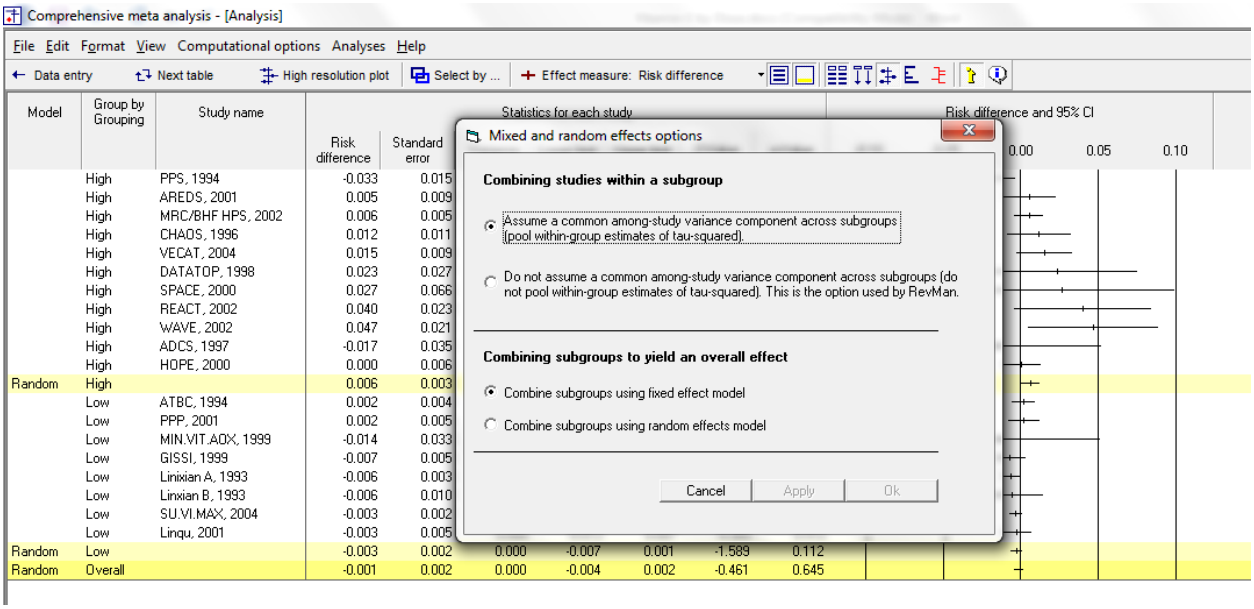


Click Computational options > Group by > Grouping



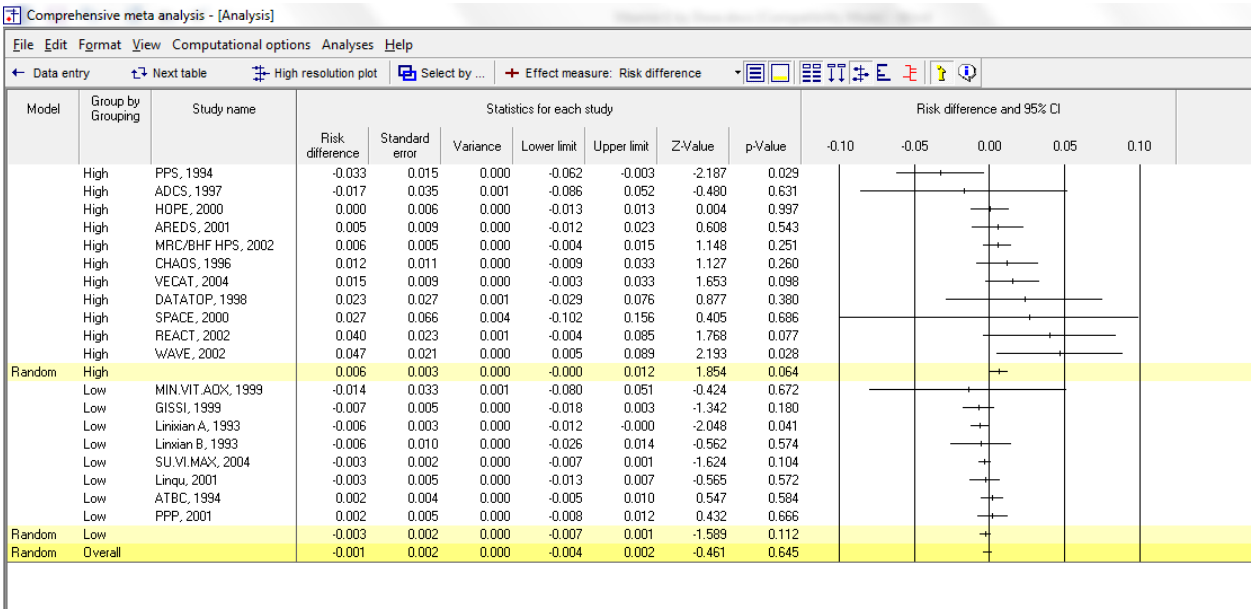
Click Computational options > Mixed and random effects options
Select the first option button in both sections





Right-click on Risk Difference and sort from low to high

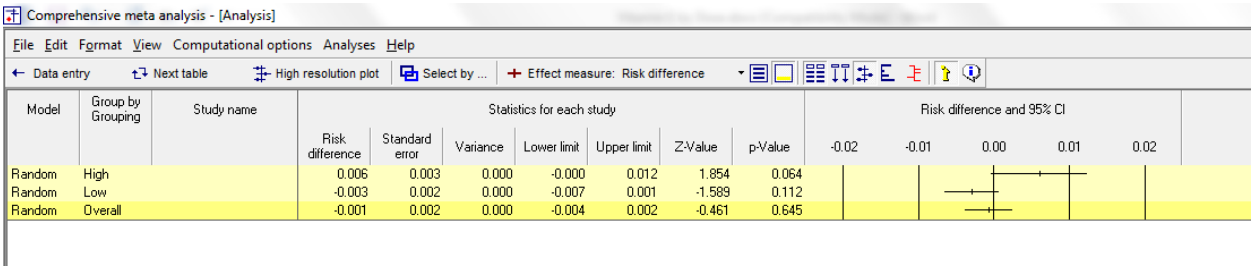
The screen should look like this



Model	Group by Grouping	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	High	PPS, 1994	-0.033	0.015	0.000	-0.062	-0.003	-2.187	0.029
	High	ADCS, 1997	-0.017	0.035	0.001	-0.086	0.052	-0.480	0.631
	High	HOPE, 2000	0.000	0.006	0.000	-0.013	0.013	0.004	0.997
	High	AREDS, 2001	0.005	0.009	0.000	-0.012	0.023	0.608	0.543
	High	MRC/BHF HPS, 2002	0.006	0.005	0.000	-0.004	0.015	1.148	0.251
	High	CHAOS, 1996	0.012	0.011	0.000	-0.009	0.033	1.127	0.260
	High	VECAT, 2004	0.015	0.009	0.000	-0.003	0.033	1.653	0.098
	High	DATATOP, 1998	0.023	0.027	0.001	-0.029	0.076	0.877	0.380
	High	SPACE, 2000	0.027	0.066	0.004	-0.102	0.156	0.405	0.686
	High	REACT, 2002	0.040	0.023	0.001	-0.004	0.085	1.768	0.077
	High	WAVE, 2002	0.047	0.021	0.000	0.005	0.089	2.193	0.028
Random	High		0.006	0.003	0.000	-0.000	0.012	1.854	0.064
	Low	MIN.VIT.AOX, 1999	-0.014	0.033	0.001	-0.080	0.051	-0.424	0.672
	Low	GISSI, 1999	-0.007	0.005	0.000	-0.018	0.003	-1.342	0.180
	Low	Linxian A, 1993	-0.006	0.003	0.000	-0.012	-0.000	-2.048	0.041
	Low	Linxian B, 1993	-0.006	0.010	0.000	-0.026	0.014	-0.562	0.574
	Low	SU.VI.MAX, 2004	-0.003	0.002	0.000	-0.007	0.001	-1.624	0.104
	Low	Linqu, 2001	-0.003	0.005	0.000	-0.013	0.007	-0.565	0.572
	Low	ATBC, 1994	0.002	0.004	0.000	-0.005	0.010	0.547	0.584
	Low	PPP, 2001	0.002	0.005	0.000	-0.008	0.012	0.432	0.666
Random	Low		-0.003	0.002	0.000	-0.007	0.001	-1.589	0.112
Random	Overall		-0.001	0.002	0.000	-0.004	0.002	-0.461	0.645

The studies at the top (high dose) tend to fall on the right-hand side of zero, indicating that Vitamin E was associated with increased risk of death. The studies at the bottom (low dose) tend to fall on the left-hand side of zero or at zero, indicating that (if anything) Vitamin E is associated with decreased risk of death.

To get a better sense of the difference we can hide the individual studies and expand the scale



Model	Group by Grouping	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Random	High		0.006	0.003	0.000	-0.000	0.012	1.854	0.064
Random	Low		-0.003	0.002	0.000	-0.007	0.001	-1.589	0.112
Random	Overall		-0.001	0.002	0.000	-0.004	0.002	-0.461	0.645

For the high-dose studies the mean effect is .006. This means that Vitamin E is associated with 6 *additional* deaths per 1,000 people. The confidence interval is -0.000 to 0.012 (At one extreme, Vitamin E could be associated with 0 additional deaths per 1,000 people. At the other extreme it could be associated with 12 *additional* deaths per 1,000 people). The test of the null (that the risk of death is the same for high-dose Vitamin E vs. Control) yields a Z-value of 1.854 and a *p*-value is 0.064.

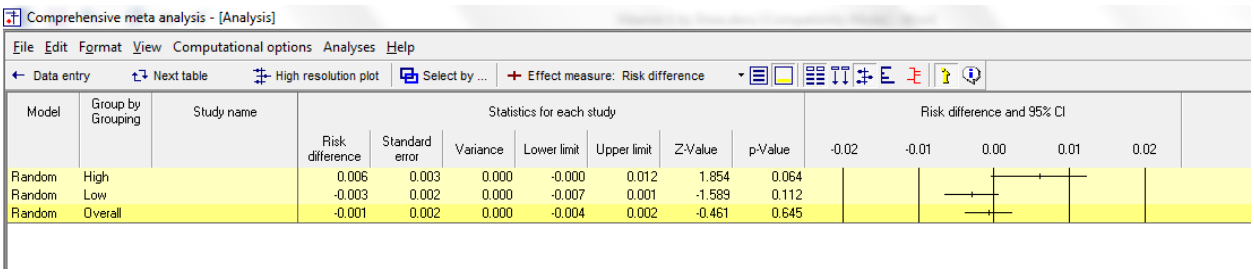
For the low-dose studies the mean effect is -.003. This means that Vitamin E is associated with 3 *fewer* deaths per 1,000 people. The confidence interval is -0.007 to 0.001 (At one extreme Vitamin E could be associated with 7 *fewer* deaths per 1,000 people. At the other extreme, Vitamin E could be associated

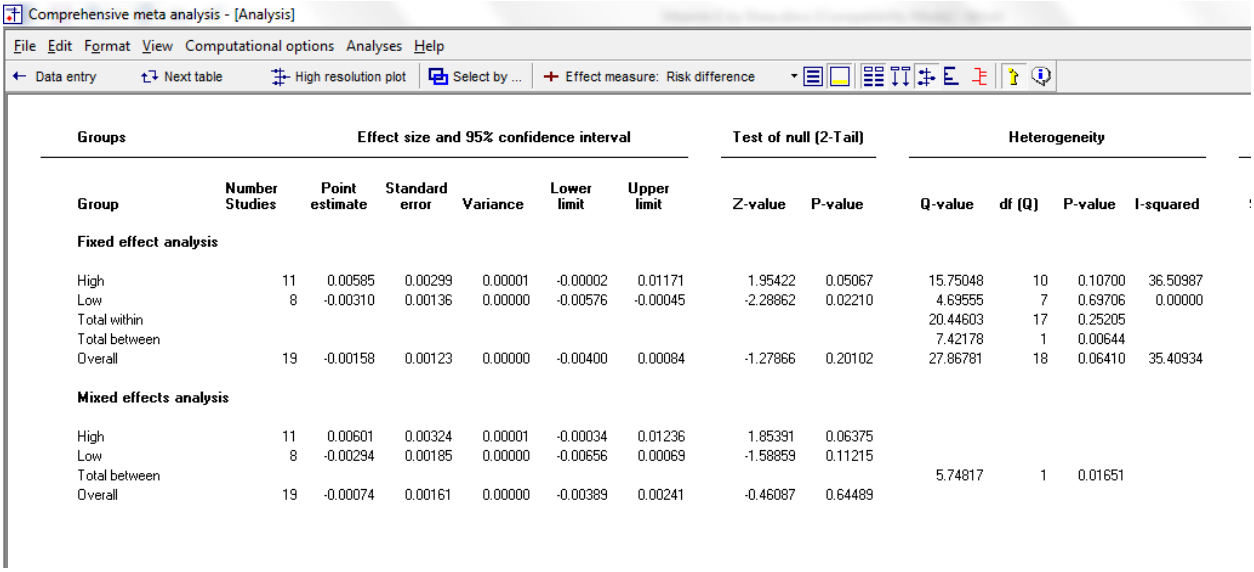
with 1 additional death per 1,000 people. The test of the null (that the risk of death is the same for low-dose Vitamin E vs. Control) yields a Z-value of -1.589 and a *p*-value is 0.112.

If we use the conventional criterion of 0.05, neither the risk associated with high-dose Vitamin E nor the protective effect associated with low-dose vitamin E is significantly different from zero.

However, the confidence intervals make it clear that the mean effect for high dose is either zero or harmful, while the mean effect for low dose is either zero or protective.

The next thing we want to do is compare the effect size in the two subgroups. This plot shows almost no overlap between the two confidence intervals, so we'd expect the difference between subgroups to be statistically significant.





The test to compare subgroups is a test of 0.00601 vs. -0.00294. The relevant statistic is on the line marked "Total between". The *Q*-value is 5.74817 with 1 degree of freedom and p=0.01651. We reject the null that the effect size (the impact of Vitamin E) is the same for Low-dose studies and High-dose studies. The data show that as we move from the low dose studies to the high dose studies, the risk difference shifts toward a higher risk for Vitamin E.

Goodness of fit test

The line marked “Total within” at the top tests the hypothesis that the variance within-subgroups is zero. In other words, a significant *p*-value tells us that some variance remains unexplained. In this case *Q* is 20.44 with df=17 and p=0.25. The data are consistent with the null hypothesis that all the low-dose studies share a common effect size, and the high-dose studies share a common effect size.

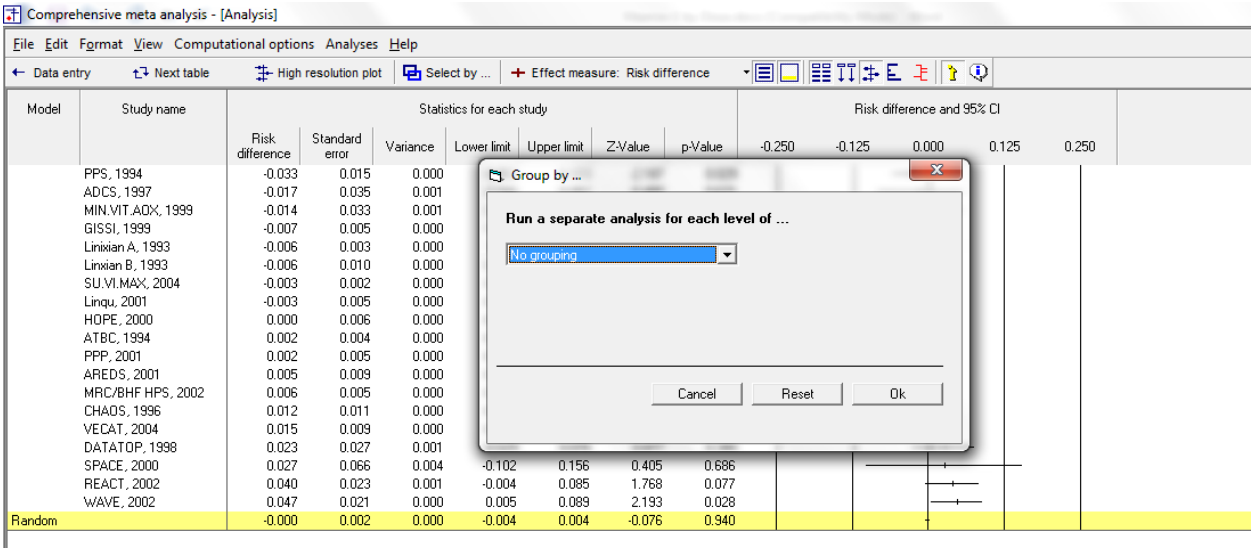
Next, we’ll shift to regression

First, we’ll repeat the identical analysis (High vs. Low) using regression rather than subgroups, to show that the two approaches yield the identical result.

Then we’ll use regression to assess the relationship between dosage (as a continuous variable) and risk difference, an analysis that is not possible using subgroups.

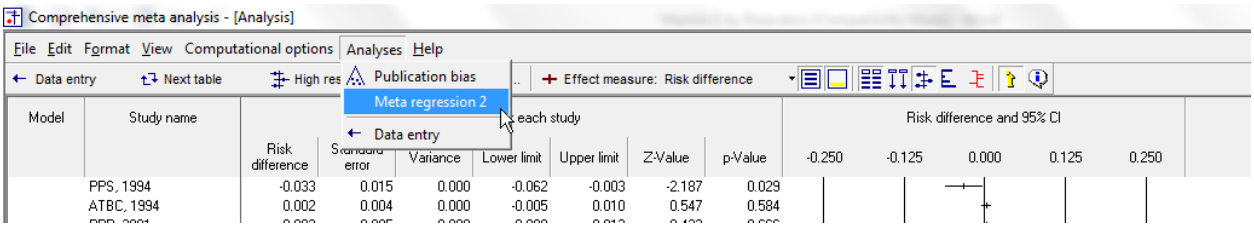
Before moving to regression we need to turn grouping off.

Click Computational options > Group by > Reset



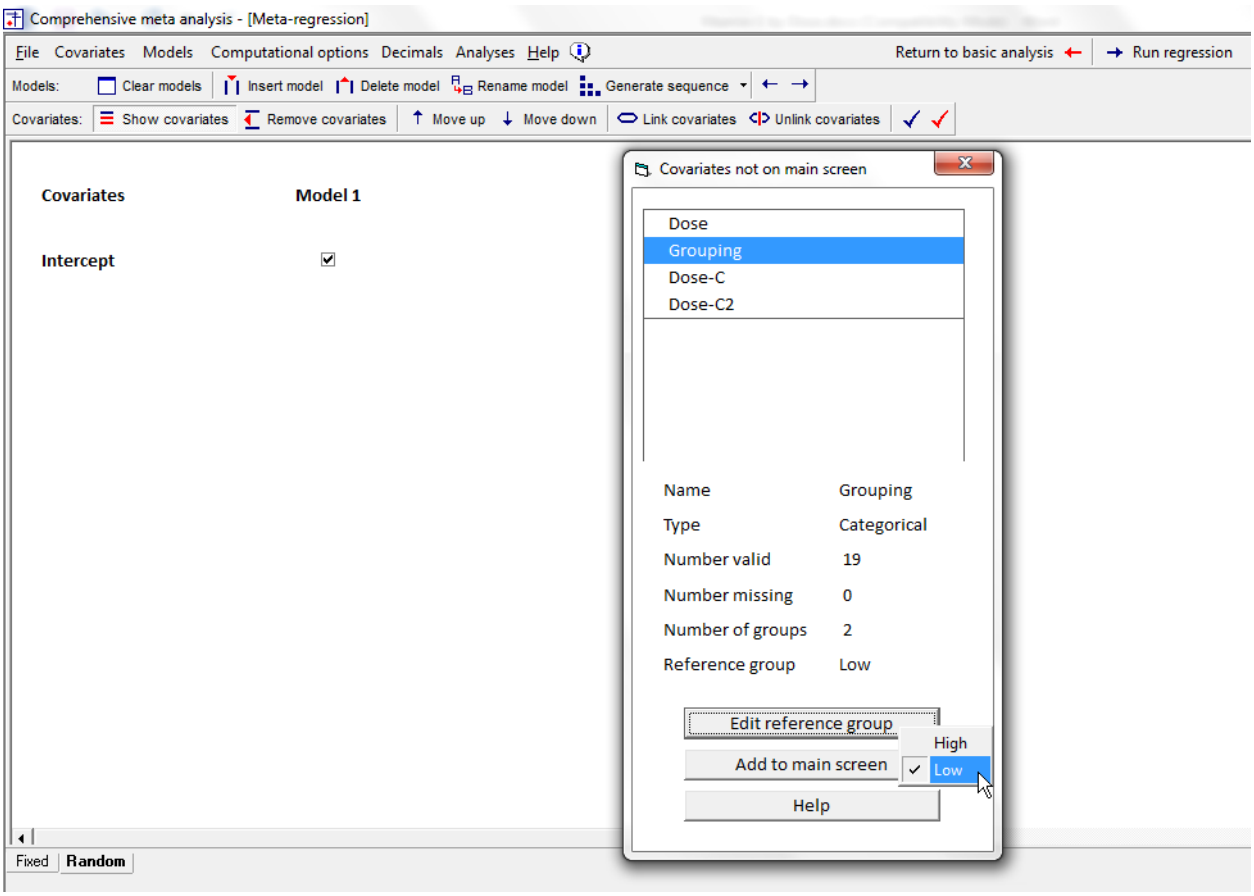
Click Analysis > Meta regression 2

[If you don't see this option, you may be using Version 2 of the program]

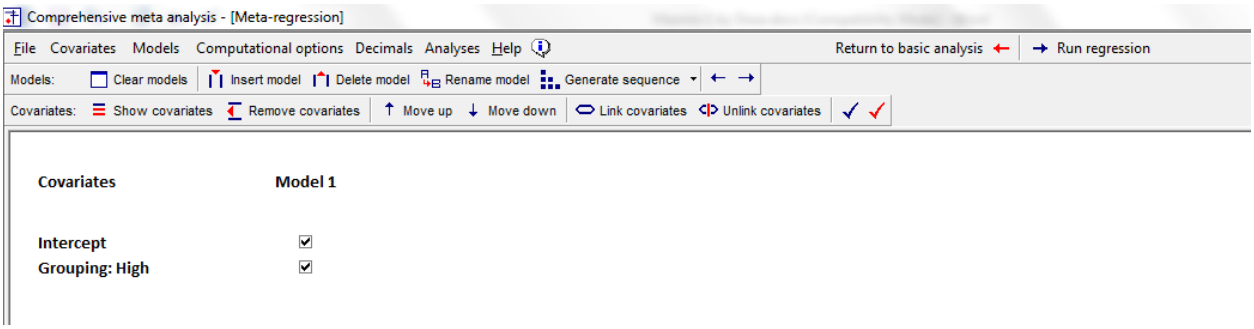


The program displays this screen

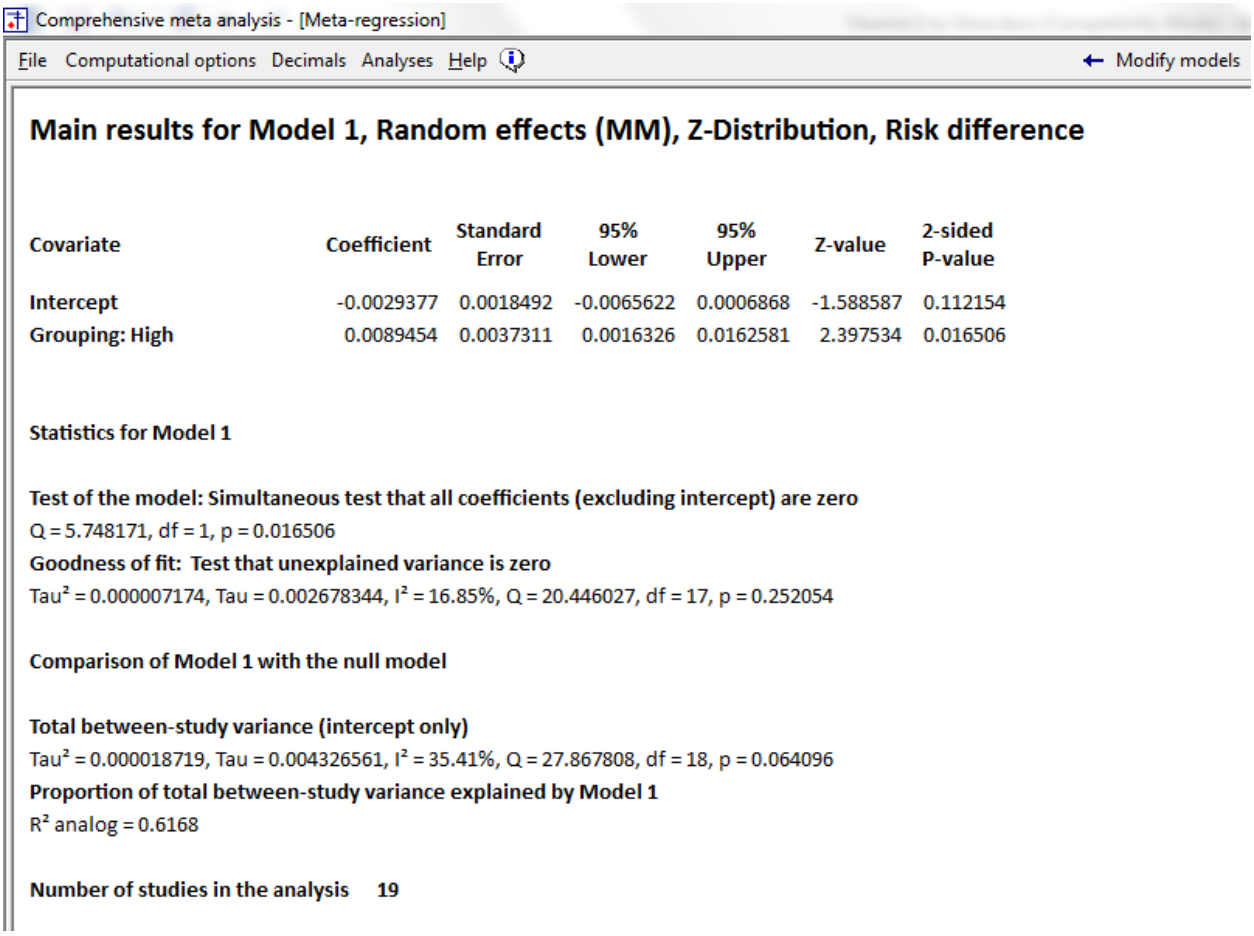
- Click Grouping
- Click Edit reference group > Low
- Click Add to model
- Tick the box for grouping



The screen should look like this



- Click Run Analysis
- Click Decimals and adjust as needed
- The screen should look like this



In the section Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero displays a *Q*-value of 5.7482, df=1, p=0.0165. This tests the null hypothesis that the mean effect size is identical in the two subgroups, and the *Q*-value and *p*-value are identical to the numbers we saw in the subgroups analysis.

Goodness of fit test

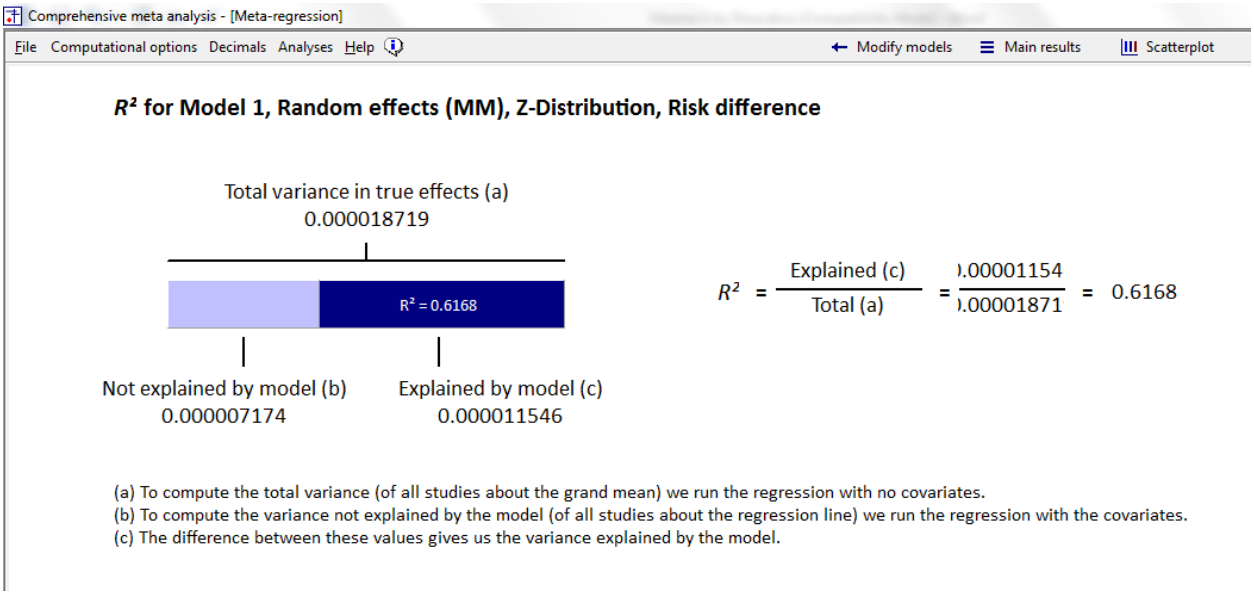
This tests the hypothesis that the variance within-subgroups is zero. In other words, a significant *p*-value tells us that some variance remains unexplained. In this case *Q* is 20.44 with *df*=17 and *p*=0.25. The data are consistent with the null hypothesis that all the low-dose studies share a common effect size, and the high-dose studies share a common effect size. Again, these are the same numbers we saw earlier.

The R^2 analog is 0.62. This tells us that 62% of the variance in true effects (the variance of all studies about the grand mean) can be explained by subgroup membership. Put another way, if we compute the variance of all true effects about the grand mean, and then we compute the variance of all true effects about their subgroup means, the second value will be only 38% as large as the first.

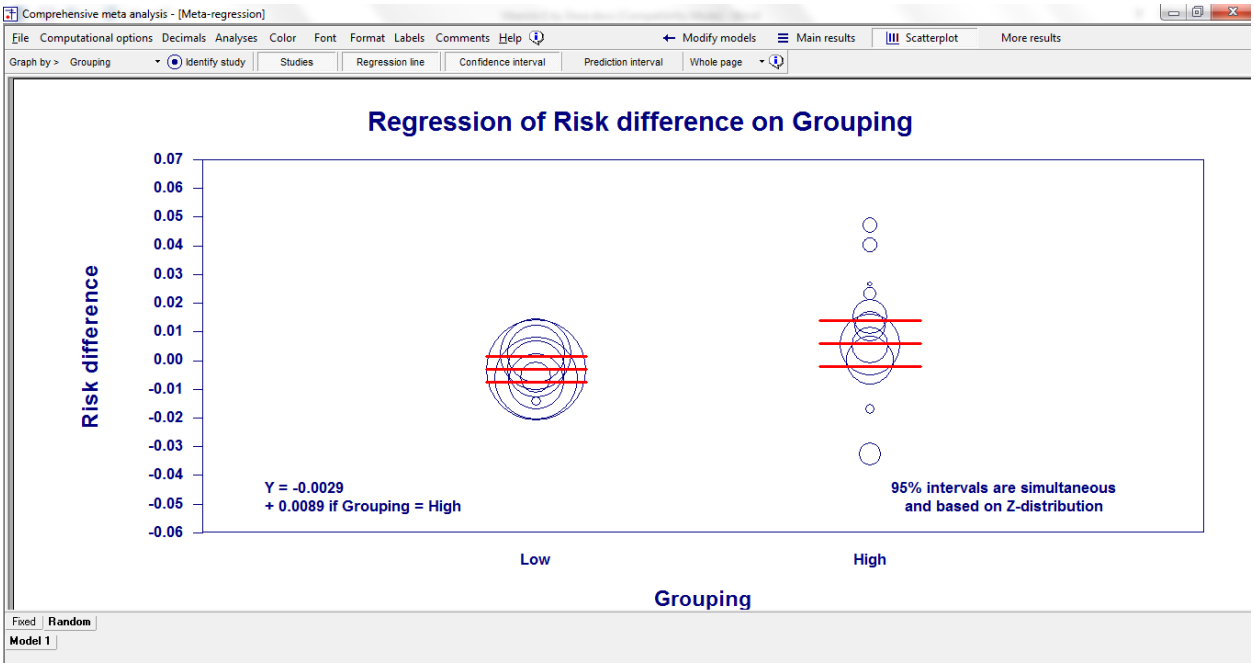
We can see where this number comes from.

- The value of T^2 computed within subgroups is 0.000007174
- The value of T^2 computed across all studies is 0.000018719
- The ratio within/total is 0.3824, which means that 38% of the variance remains unexplained
- R^2, the proportion explained by subgroup membership, is then (1 minus 0.3824, or) 0.6168.

Or, click More results > R2 Graphic



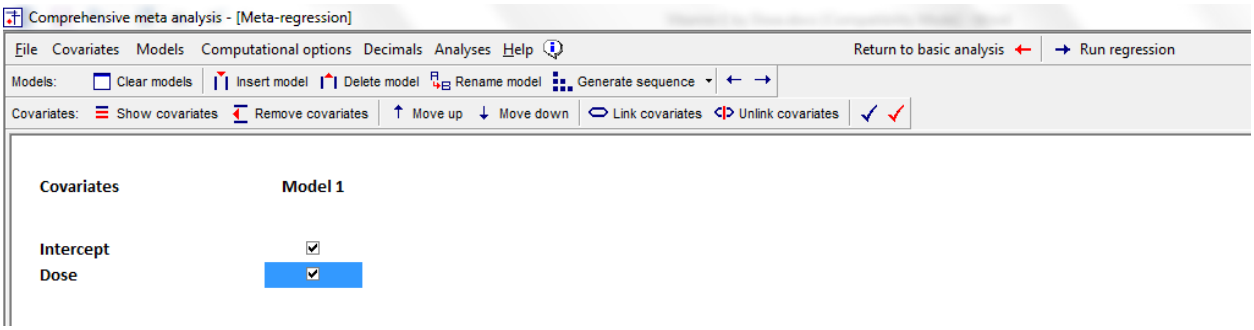
Click Scatterplot to get a visual sense of the effects, grouped by subgroup

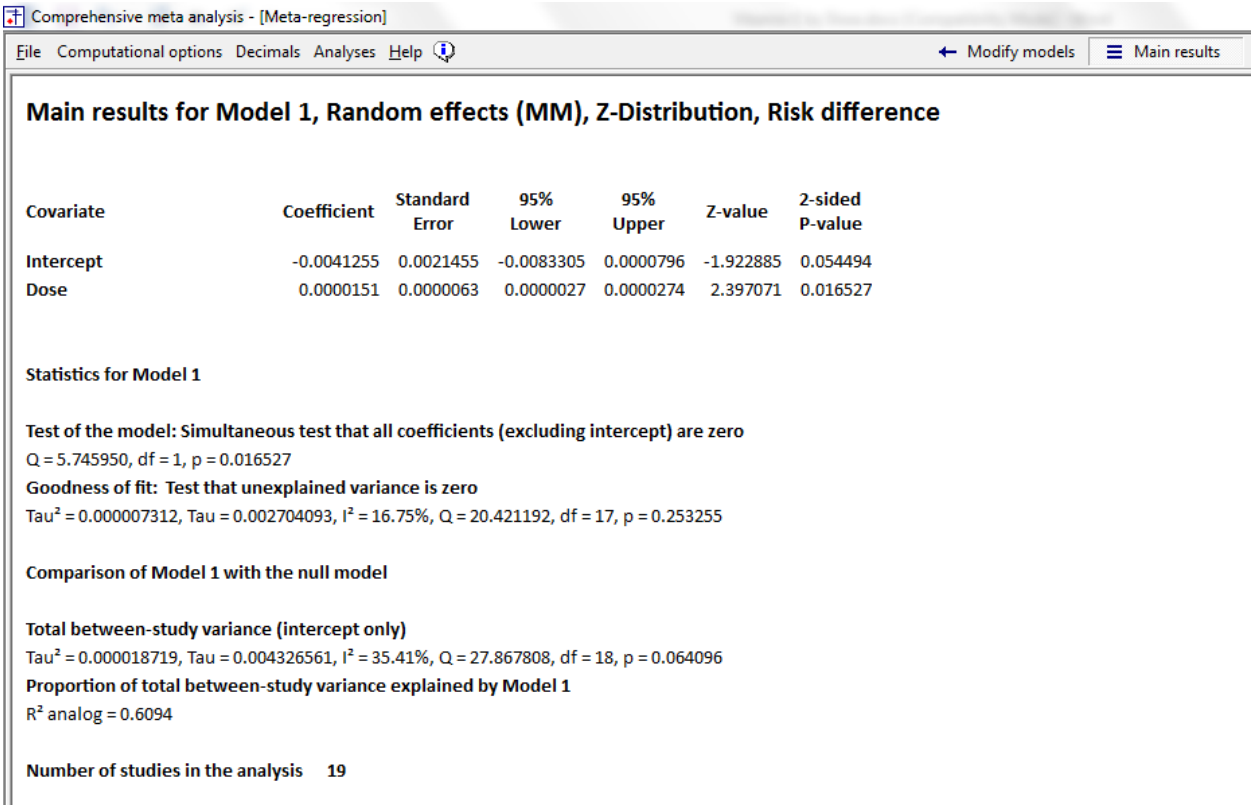


We started with a regression that classified dose as simply “High” or “Low” to show the correspondence between subgroups analysis and regression.

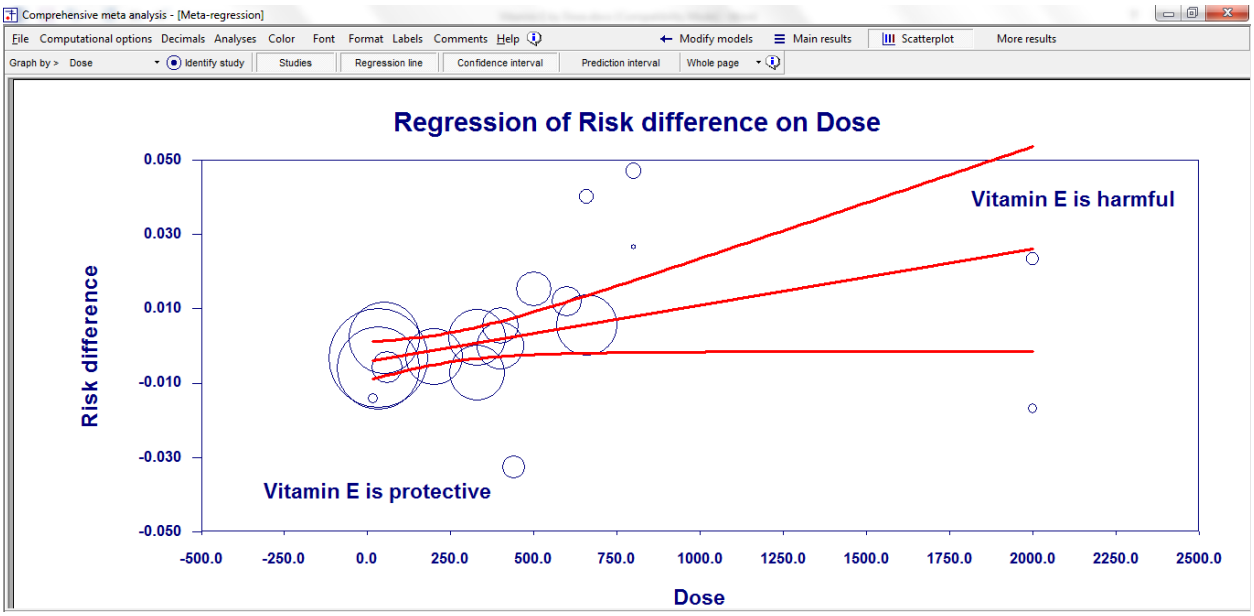
This analysis (like the subgroups analysis) treats all doses below 350 as one type and all doses above 350 as a second type. By contrast, if we treat dose as a continuous variable we can work with the actual dose. This will allow us to see, for example, if there is a linear relationship between dose and risk difference that is partially attentuated when we dichotomize the studies. Or, if there is a non-linear relationship, such that (for example) Vitamin E poses no risk at most doses but a substantial risk once the dose exceeds some thereshhold.

- Highlight Grouping and click Remove Covariates
- If needed, click Show covariates
- Click Dose and click Add to model
- Tick the box for Dose
- Click Run analysis





Click Scatterplot to see this plot


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 > Dose
Identify study
Studies
Regression line
Confidence interval
Prediction interval
Whole page
Regression of Risk difference on Dose
Vitamin E is harmful
Vitamin E is protective
Risk difference
0.050
0.030
0.010
-0.010
-0.030
-0.050
-500.0
-250.0
0.0
250.0
500.0
750.0
1000.0
1250.0
1500.0
1750.0
2000.0
2250.0
2500.0
Dose

In the section Statistics for Model 1

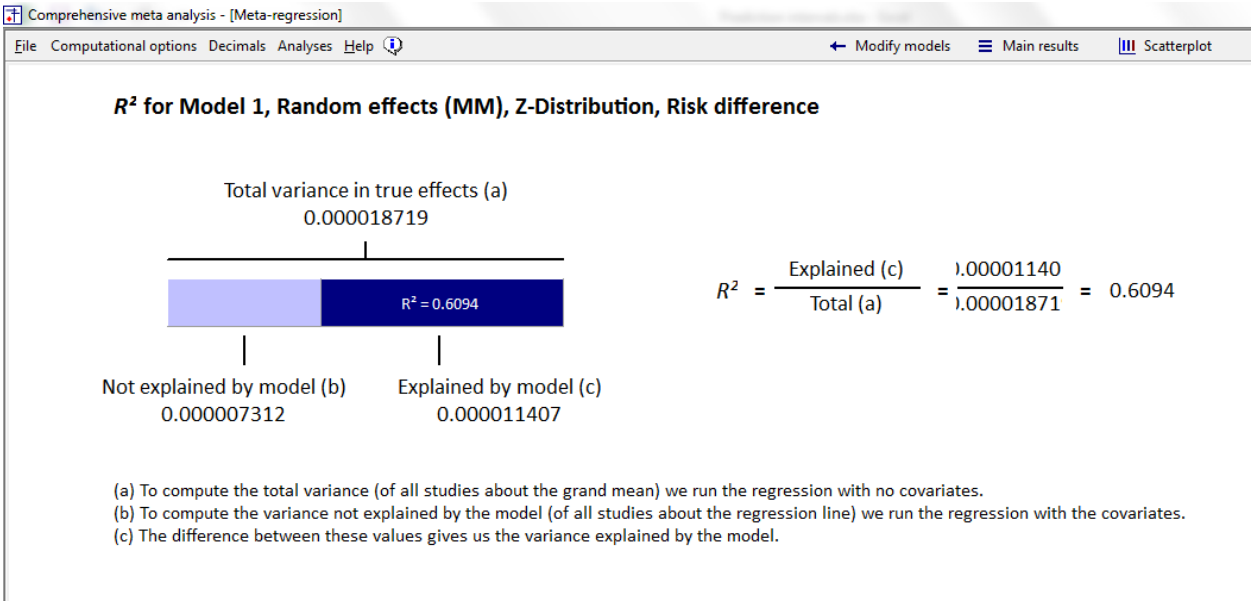
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero displays a *Q*-value of 5.745950, df=1, p=0.016527. This tests the null hypothesis that the mean effect size is identical at all values of dose, or that the regression line is horizontal. The *p*-value is statistically significant – the regression line moves up, which means that as the dose increases Vitamin E is more likely to be harmful

Goodness of fit test

This tests the hypothesis that the variance about the regression line is zero. In other words, a significant *p*-value tells us that some variance remains unexplained. In this case *Q* is 20.4211 with *df*=17 and *p*=0.2532. The data are consistent with the null hypothesis that all studies at any given dose share a common true effect size, and that all variation of observed effects from the regression line is due to sampling error.

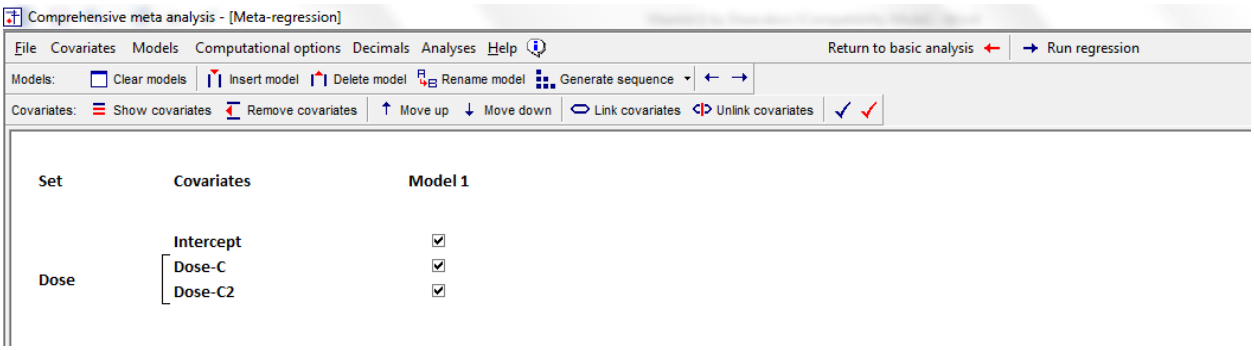
The R^2 analog is 0.6094. This tells us that 60.94% of the variance in true effects (the variance of all studies about the grand mean) can be explained by subgroup membership. Put another way, if we compute the variance of all true effects about the grand mean, and then we compute the variance of all true effects about their subgroup means, the second value will be only 39% as large as the first.

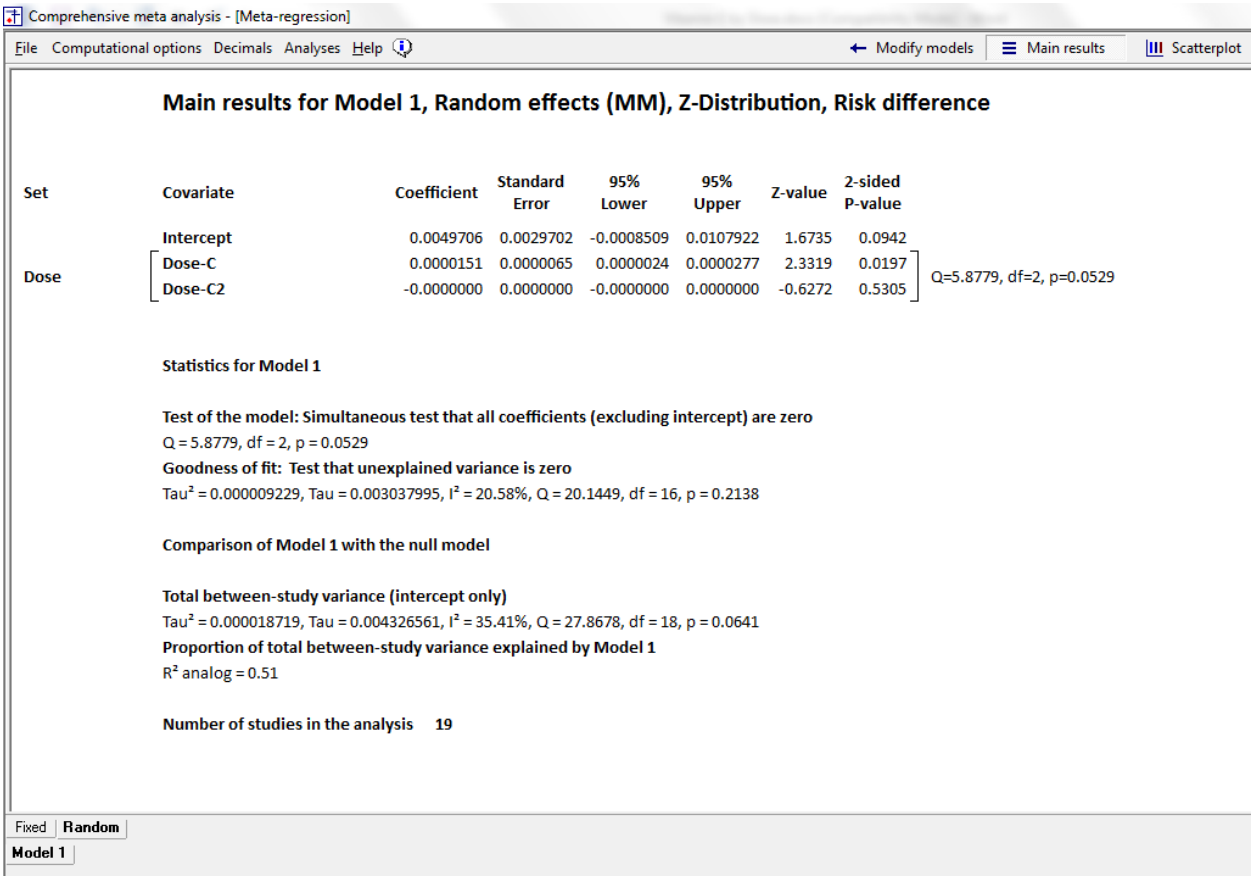
We can see where this number comes from. Click More results > R^2 graphic



We note that the statistics for Dose are nearly identical to the statistics for Grouping. The fact that the two sets of statistics are close suggests that we get as good prediction with the dichotomous grouping as we do by using Dose. The fact that the two sets of statistics are so close to each other is simply a coincidence. We displayed these statistics to additional decimal places to show that they are not identical.

Finally, we can run an analysis to see if there is a curvilinear relationship between dose and risk difference. For this analysis we use Dose-C and Dose-C^2





The test of the model is a test that Dose-C plus Dose-C2 explain some of the variance. Since Dose-C2 really adds nothing to Dose, the inclusion of Dose-C2 in the model simply dilutes the effect, and the *p*-value for the model is 0.0529

If we look at the *p*-value for each covariate, we see that the unique impact of Dose-C has a *p*-value of 0.0197 while the unique impact of Dose-C2 has a *p*-value of 0.5305.

Summary

The analysis included nineteen studies, each of which compared patients who were randomly assigned to either a daily dose of Vitamin E or a placebo. The dose of Vitamin E varied from 16.5 to 2,000 – the

highest dose was 120 times the lowest one. The outcome was mortality, and the effect size was the risk difference.

Is Vitamin E related to risk of death?

The mean risk difference across all studies is near zero. However, there is substantial variation in the risk difference, and we performed a series of analyses to see if this variation was related to dose.

We classified the studies as either Low Dose (under 350) of High Dose (over 350). The the mean risk difference in the low-dose studies is -0.00294 (Vitamin E is protective). By contrast, the mean risk difference in the High Dose studies is 0.00601 (Vitamin E is harmful). The difference between the two is statistically significant (Q= 5.74817, df=1, p=0.01651) which tells us that as we move from the low dose studies to the high dose studies, the risk difference shifts toward a higher risk for Vitamin E.

If we use the conventional criterion of 0.05, neither the risk associated with high-dose Vitamin E nor the protective effect associated with low-dose vitamin E is significantly different from zero. However, the confidence intervals make it clear that the mean effect for high dose is either zero or harmful, while the mean effect for low dose is either zero or protective.

We used regression to assess the relationship between dose (as a continuous variable) and the impact of Vitamin E. The predictive utility of dose was about the same whether we used actual dose or the dichotomous subgroups.

We also used regression to test for a curvilinear relationship between dose and effect size, but found no evidence of a curvilinear relationship. This could be because the analysis included only a few small studies at very high doses.

Note that a subgroups analysis or a regression analysis in meta-analysis must be treated as observational, even if each study employed random assignment to condition. While each study may have assigned patients at random to Placebo or Vitamin E, studies were not randomly assigned to a specific dose of Vitamin E.

It's *possible* that the high doses of Vitamin were associated with increased risk of death because the of the drug. But it's also possible that the studies which employed the higher doses happened to enroll patients who were different in some ways from the patients in the low-dose studies, and it's this factor which is responsible for the harmful effect that we see in the high-dose studies.

Put another way, we choose to call some studies "Low Dose" or "High Dose" but it's possible that these studies would be more appropriately labeled (to pick a completely random example) "Low-Dose Younger patients" and "High-Dose Older patients". We may think it's the dose that matters, but it's actually the fact that younger patients are better able to metabolize the Vitamin (regardless of dose).

If we have enough studies and we know what all the relevant variables are, we may be able to control for potential confounds as a way of partially (no pun intended) addressing this issue.