Example nameStatins by genderEffect sizeRisk ratioAnalysis typeSubgroups within studyLevelIntermediateReferenceCheung Figure 6

Synopsis

The goal of this review was to assess the impact of statins on stroke and mortality, and to see if the impact differed by subgroups. The analysis that follows looks at the impact of statins on major coronary events.

This analysis includes seven studies where patients were randomized to receive either a statins or a placebo. Outcome was the proportion of patients in each group suffering a major coronary event, and the effect size was the risk ratio.

<u>Within each study</u> patients were classified as being male or female. We ran an analysis to see if the impact of statins was greater (or smaller) for males vs. females.

We use this example to show

- How to enter data for independent subgroups within studies
- How to use study as the unit of analysis
- How to use subgroup as the unit of analysis
- How to compare the effect in different subgroups

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

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Click Insert > Column for > Effect size data

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The program displays this wizard

Select [Show all 100 formats] Click [Next]



Drill down to

Click [Next]

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



Enter the following labels into the wizard

- First group > Statin
- Second group > Control
- Name for events > Event
- Name for non-events > Ok

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

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Every study will include data for two INDEPENDENT samples. That is, each person appears in one sample or the other, but not both.

The two samples are females and males. We will be using two rows for each study, and need a column that will identify the sample as non-smokers or smokers.

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Click Insert > Column for > Subgroups within study

The screen should look like this

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Rather than enter the data directly into CMA we will copy the data from Excel

- Switch to Excel and open the file "Statins by gender"
- Highlight the rows and columns as shown, and press CTRL-C to copy to clipboard

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2	AFCAPS	Female	7	499	13	498				
3	AFCAPS	Male	109	2805	170	2803				
4	ASCOT	Female	19	979	17	963				
5	ASCOT	Male	81	4189	137	4174				
6	CARE	Female	46	286	80	290				
7	CARE	Male	384	1795	469	1788				
8	FOUR S	Female	59	407	91	420				
9	FOUR S	Male	372	1814	531	1803				
10	LIPID	Female	90	756	104	760				
11	LIPID	Male	467	3756	611	3742				
12	PROSPER	Female	125	1495	137	1505				
13	PROSPER	Male	167	1396	219	1408				
14	WOSCOP	Male	174	3302	248	3293				
15										

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

Click here

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	Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio	Log odds ratio	Std Err	Variance	к	L	м	N
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24	AFCAPS	Female	7	499	13	498	0.531	-0.633	0.473	0.224				
3 /	AFCAPS	Male	109	2805	170	2803	0.626	-0.468	0.126	0.016				
4 /	ASCOT	Female	19	979	17	963	1.101	0.097	0.337	0.114				
5 /	ASCOT	Male	81	4189	137	4174	0.581	-0.543	0.142	0.020				
6 (CARE	Female	46	286	80	290	0.503	-0.687	0.208	0.043				
70	CARE	Male	384	1795	469	1788	0.765	-0.267	0.079	0.006				
8 F	FOUR S	Female	59	407	91	420	0.613	-0.489	0.184	0.034				
9 F	FOUR S	Male	372	1814	531	1803	0.618	-0.481	0.078	0.006				
10 L	JPID	Female	90	756	104	760	0.852	-0.160	0.154	0.024				
11 L	JPID	Male	467	3756	611	3742	0.728	-0.318	0.066	0.004				
12 F	PROSPER	Female	125	1495	137	1505	0.911	-0.093	0.129	0.017				
13 F	PROSPER	Male	167	1396	219	1408	0.738	-0.304	0.110	0.012				
14 \	WOSCOP	Male	174	3302	248	3293	0.683	-0.381	0.102	0.010				
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At this point we should check that the data has been copied correctly

The column that had been called "Tx E" is now "Statin Events". Similarly, all columns have the intended labels

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2	AFCAPS	Female	7	499	13	498	0.531	-0.633	0.473	0.224					
3	AFCAPS	Male	109	2805	170	2803	0.626	-0.468	0.126	0.016					
4	ASCOT	Female	19	979	17	963	1.101	0.097	0.337	0.114					
5	ASCOT	Male	81	4189	137	4174	0.581	-0.543	0.142	0.020					
6	CARE	Female	46	286	80	290	0.503	-0.687	0.208	0.043					
7	CARE	Male	384	1795	469	1788	0.765	-0.267	0.079	0.006					
8	FOUR S	Female	59	407	91	420	0.613	-0.489	0.184	0.034					
9	FOUR S	Male	372	1814	531	1803	0.618	-0.481	0.078	0.006					
10	LIPID	Female	90	756	104	760	0.852	-0.160	0.154	0.024					
11	LIPID	Male	467	3756	611	3742	0.728	-0.318	0.066	0.004					
12	PROSPER	Female	125	1495	137	1505	0.911	-0.093	0.129	0.017					
13	PROSPER	Male	167	1396	219	1408	0.738	-0.304	0.110	0.012					
14	WOSCOP	Male	174	3302	248	3293	0.683	-0.381	0.102	0.010					
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- Click anywhere in Row 1
- Select Edit > Delete row, and confirm

Click here

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3	ASCOT	Female	19	979	17	963	1.101	0.097	0.337	0.114					
4	ASCOT	Male	81	4189	137	4174	0.581	-0.543	0.142	0.020					
5	CARE	Female	46	286	80	290	0.503	-0.687	0.208	0.043					
6	CARE	Male	384	1795	469	1788	0.765	-0.267	0.079	0.006					
7	FOUR S	Female	59	407	91	420	0.613	-0.489	0.184	0.034					
8	FOUR S	Male	372	1814	531	1803	0.618	-0.481	0.078	0.006					
9	LIPID	Female	90	756	104	760	0.852	-0.160	0.154	0.024					
10	LIPID	Male	467	3756	611	3742	0.728	-0.318	0.066	0.004					
11	PROSPER	Female	125	1495	137	1505	0.911	-0.093	0.129	0.017					
12	PROSPER	Male	167	1396	219	1408	0.738	-0.304	0.110	0.012					
13	WOSCOP	Male	174	3302	248	3293	0.683	-0.381	0.102	0.010					
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Witness Trees

Click File > Save As and save the file

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Note that the file name is now in the header.

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

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- Click the Merge Rows icon
- The program will merge the study names for each study

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	Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio Log odds Std Err Variance K L M N O											
1	AECADO	Female	7	499	13	498	0 E21 0 E22 0 472 0 224											
2	AFLAFS	Male	109	2805	170	2803	[∄↓ Sort A-Z											
3	ASCOT	Female	19	979	17	963	1 🔏 Sort Z-A											
4	ASCOT	Male	81	4189	137	4174												
5	CARE	Female	46	286	80	290	Column properties											
6	CARE	Male	384	1795	469	1788	C Data entry assistant											
7		Female	59	407	91	420	C S Formulas											
8	roon 5	Male	372	1814	531	1803												
9		Female	90	756	104	760	C []] Show all selected indices											
10	LIFID	Male	467	3756	611	3742	C Show only the primary index											
11	DDOCDED	Female	125	1495	137	1505												
12	THOSELIT	Male	167	1396	219	1408	🕻 🖄 Set primary index to Odds ratio											
13	WOSCOP	Male	174	3302	248	3293	C + Customize compute effect size display											
14																		
15																		
16																		

Right-click on the yellow columns and click [Customize computed effect size display]

Add Risk ratio and Log risk ratio to the display and click Ok

🕂 Co	omprehensive met	a analysis - [C:\Use	rs\Biostat\I	Dropbox\W	orkshops T	hree-Day\S	tatins\Statin	s by gender.c	ma]
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	Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio	Log odds ratio	□ □ □ □ □ □
1 2 3	AFCAPS	Female Male Female	7 109 19	499 2805 979	13 170 17	498 2803 963	0.531 0.626 1.101	-0.633 -0.468 0.097	Use the following as the primary index
4	ASCOT	Male Female	81 46	4189 286	137	4174 290	0.581 0.503	-0.543 -0.687	Odds ratio
6	FOUR S	Male Female	384 59	1795	469	1788	0.765	-0.267 -0.489	Display columns for these indices
9 10	LIPID	Male Female Male	372 90 467	756	531 104 611	760	0.618 0.852 0.728	-0.481 -0.160 -0.318	Oug odds ratio Peto odds ratio
11 12	PROSPER	Female Male	125 167	1495 1396	137 219	1505 1408	0.911 0.738	-0.093 -0.304	Cog Peto odds ratio E Risk ratio ✓ Risk ratio Cog risk ratio
13 14 15 16 17	WUSCUP	Male	1/4	3302	248	3293	0.683	-0.381	Risk difference Std diff in means Hedges's g Difference in means
18 19 20									Star Paired Dimeterice Correlation Fisher's Z Rate ratio
21 22 23									Cog rate ratio Rate difference Hazard ratio
24 25 26									Also show standard error Also show variance
27 28 29									Show the primary index only Show all selected indices
30 31 32									
33 34									

- Right-click on Risk ratio
- Click [Set primary index to Risk ratio]
- Click File > Save

Comprenensive me	ta analysis - [c.(ose	is (biostat (i	Diopbox(orkshops h	ince-Day(5	tatins (Statin	s by genuer.	cinaj						
<u>F</u> ile <u>E</u> dit Format <u>V</u>	iew <u>I</u> nsert Identify	<u>T</u> ools C	omputatio	nal options	Analyses	<u>H</u> elp								
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Study name	Subgroup within study	Statin Events	Statin Total N	Placebo Events	Placebo Total N	Odds ratio	Log odds ratio	Std Err	Variance	Risk ra	atio Log risk ratio	Std Err	Variance	0
1 450400	Female	7	499	13	498	0.531	-0.633	0.473	0.224	0.	.537 -0.62	1 0.465	0.216	
2 AFCAFS	Male	109	2805	170	2803	0.626	-0.468	0.126	0.016	A	Sort A-7			
3 ACCOT	Female	19	979	17	963	1.101	0.097	0.337	0.114	27	+ 3011A-2			
4	Male	81	4189	137	4174	0.581	-0.543	0.142	0.020	Ā	(↓ Sort Z-A			
5 CARE	Female	46	286	80	290	0.503	-0.687	0.208	0.043		Column pro	perties		
6 CANE	Male	384	1795	469	1788	0.765	-0.267	0.079	0.006	-				-
7 COLID S	Female	59	407	91	420	0.613	-0.489	0.184	0.034		Data entry a	ssistant		
8 1001 3	Male	372	1814	531	1803	0.618	-0.481	0.078	0.006	Σ	Formulas			
9 LIPID	Female	90	756	104	760	0.852	-0.160	0.154	0.024		11. Channell and			_
10	Male	467	3756	611	3742	0.728	-0.318	0.066	0.004		Show all set	ected indices		
11 PROSPER	Female	125	1495	137	1505	0.911	-0.093	0.129	0.017		Show only t	he primary in	dex	
12	Male	167	1396	219	1408	0.738	-0.304	0.110	0.012		Set priman/	index to Risk	ratio	
13 WOSCOP	Male	174	3302	248	3293	0.683	-0.381	0.102	0.010		See printing			
14											- Customize	computed eff	ect size displa	1
15														
16														
17														
19														

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Click [Run analysis]

At this point we have the usual analysis, with a single set of studies. The two samples within each study are treated as two separate studies, since there is no overlap in the subjects.

This is the basic analysis screen, showing a fixed-effect analysis.

Lun		Computatio	onal options	Analyses	Help	C							
Data er	itry t∓ N	ext table	井 High re	solution plot	E Select	by I	Effect measure	e: Risk ratio	-]] # E	2 🛛 🕄	I
Model	Study name	Subgroup within study		Statis	stics for each s	study			Ria	Inctic and 95	% CI		Weight (Fixed)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Female	0.537	0.216	1.336	-1.337	0.181		-				0.32
	AFCAPS	Male	0.641	0.507	0.810	-3.717	0.000			-+-			4.86
	ASCOT	Female	1.099	0.575	2.102	0.286	0.775						0.64
	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000			-+-			3.64
	CARE	Female	0.583	0.422	0.806	-3.266	0.001						2.55
	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			19.26
	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008						3.02
	FOUR S	Male	0.696	0.620	0.781	-6.148	0.000			+			20.12
	LIPID	Female	0.870	0.668	1.132	-1.036	0.300			-+-			3.86
	LIPID	Male	0.761	0.681	0.851	-4.784	0.000		1	+			21.49
	PROSPER	Female	0.919	0.729	1.158	-0.719	0.472			-+			4.99
	PROSPER	Male	0.769	0.638	0.927	-2.748	0.006		1	+			7.64
	WDSCOP	Male	0.700	0.580	0.844	-3.729	0.000		1	+			7.60
xed			0.744	0.706	0.784	-11.198	0.000			4			

Click [Both models]

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

Data er	ntry t∓ N	ext table	🛨 High re	solution plot	E Select	by 🕇 E	Effect measure	Risk ratio	-]] ⊅ E	1 🕄		
Model	Study name	Subgroup within study		Statis	tics for each s	study			Ris	k ratio and 95%	i Cl		Weight (Fixed)	Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight	Relative weight
	AFCAPS	Female	0.537	0.216	1.336	-1.337	0.181		-				0.32	0.58
	AFCAPS	Male	0.641	0.507	0.810	-3.717	0.000			+			4.86	6.69
	ASCOT	Female	1.099	0.575	2.102	0.286	0.775			_ 			0.64	1.12
	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000			-+-			3.64	5.34
	CARE	Female	0.583	0.422	0.806	-3.266	0.001						2.55	3.98
	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			19.26	15.30
	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008						3.02	4.58
	FOUR S	Male	0.696	0.620	0.781	-6.148	0.000			+			20.12	15.59
	LIPID	Female	0.870	0.668	1.132	-1.036	0.300			-+			3.86	5.59
	LIPID	Male	0.761	0.681	0.851	-4.784	0.000			+			21.49	16.02
	PROSPER	Female	0.919	0.729	1.158	-0.719	0.472			-+			4.99	6.82
	PR0SPER	Male	0.769	0.638	0.927	-2.748	0.006			+			7.64	9.21
	WOS COP	Male	0.700	0.580	0.844	-3.729	0.000			+			7.60	9.18
ixed			0.744	0.706	0.784	-11.198	0.000			+				
andom			0.739	0.689	0.793	-8.468	0.000			+				

The random-effects model is a better fit for the way the studies were sampled, and therefore that is the model we will use in the analysis.

Statins by gender

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• Click Random on the tab at the bottom

The plot now displays the random-effects analysis alone.

ile <u>E</u> dit	F <u>o</u> rmat <u>V</u> iew	Computatio	onal options	Analyses	<u>H</u> elp								
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Model	Study name	Subgroup within study		Statis	stics for each s	study			Risł	k ratio and 95	% CI		Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Female	0.537	0.216	1.336	-1.337	0.181		- I -				0.58
	AFCAPS	Male	0.641	0.507	0.810	-3.717	0.000			+			6.69
	ASCOT	Female	1.099	0.575	2.102	0.286	0.775			_ _			1.12
	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000			+			5.34
	CARE	Female	0.583	0.422	0.806	-3.266	0.001						3.98 📕
	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			15.30
	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008			+			4.58
	FOUR S	Male	0.696	0.620	0.781	-6.148	0.000			+			15.59
	LIPID	Female	0.870	0.668	1.132	-1.036	0.300			+			5.59
	LIPID	Male	0.761	0.681	0.851	-4.784	0.000			+			16.02
	PROSPER	Female	0.919	0.729	1.158	-0.719	0.472			+			6.82
	PROSPER	Male	0.769	0.638	0.927	-2.748	0.006			+			9.21
	w JSCOP	Male	0.700	0.580	0.844	-3.729	0.000			+			9.18
andom			0.739	0.689	0.793	-8.468	0.000			+			

A quick view of the plot suggests the following

- All of the studies suggest an advantage for statins over placebo
- The observed effect sizes fall within a relatively narrow range.
- The summary effect is 0.7389 with a CI of 0.689 to 0.793. Thus, the mean effect is in the clinically important range.
- The summary effect has a Z-value –8.468 and a *p*-value of < 0.001. Thus we can reject the null hypotheses that the true risk ratio is 1.0.



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

- Under the random-effects model the summary effect is 0.739 with a CI of 0.689 to 0.793. Thus, the mean effect is in the clinically important range.
- The summary effect has a Z-value -8.468 and a *p*-value of < 0.001. Thus we can reject the null hypotheses that the true risk ratio is 1.0.
- The statistics at the upper right relate to the dispersion of effect sizes across studies.
- The Q-value is 17.775 with df=12 and p=0.123. Q reflects the distance of each study from the mean effect (weighted, squared, and summed over all studies). Q is always computed using FE weights (which is the reason it is displayed on the "Fixed" row, but applies to both FE and RE analyses.
- T² is the estimate of the between-study variance in true effects. This estimate (in log units) is 0.005. T is the estimate of the between-study standard deviation in true effects. This estimate (in log units) is 0.069.
- *I*² reflects the proportion of true variance to observed variance. *I*² is 32.488, which means that about 32% of the variance on observed effects reflects variance in true effects. The remaining 68% is attributed to sampling error, and would probably disappear if the sample sizes were large enough.
- Click [Next table] to return to this screen

In this analysis we want to focus on the treatment effect as a function of smoking. Specifically, we're going to run the analysis separately (a) for females and (b) for males.

When we're dividing the studies into two subgroups, the between-studies variance (T^2) must be computed within subgroups. However, we have two options. We can then pool the separate estimates, and use the pooled value for all subgroups. Or, we can use a separate estimate for each subgroup.

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

Click Computational options > Mixed and random effects options

🕂 Compre	hensive meta a	nalysis - [An	alysis]		_			-		-				
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Model	Study name	[] CI Leve	el 95%	,	- each :	shurlu			Bisk	ratio and 952	% CI		Weight (Bandom)	
	chailing frame	🔁 Select	by						11000				in organ (in an aonin)	
		블 Group	by		limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight	
	AFCAPS	Compa	are groups		.336	-1.337	0.181		-	·			0.58	
	ASCOT	D Mixed	and random ef	fects options	2.102	0.286	0.000						1.12	
	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000			+			5.34	
	CARE	Female	0.583	0.422	0.806	-3.266	0.001						3.98 📕	
	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			15.30	
	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008			+			4.58	
	5000.0		0.000	0.000	0.704	0.4.40	0.000				1		15 50	

The program displays this wizard

- At the top select the first option, to "Assume a common among-study variance"
- At the bottom select the first option, to "Combine subgroups using a fixed-effect model"

+ Compre	hensive meta a	nalysis - [Ana	alysis]							
<u>F</u> ile <u>E</u> dit	F <u>o</u> rmat <u>V</u> iew	Computatio	onal options Analyses	<u>H</u> elp						
← Data er	itry t⊒ Ne	ext table	- High resolution plot	E Select by	+ Effect measu	re: Risk ratio		11 # E	Q 1 🗄	
Model	Study name	Subgroup within study	Stati Risk ratio	stics for each study Upper limit Z-\	/alue p-Value	0.01	Risk ratio and 95%	CI	100.00	Weight (Random) Relative weight
	AFCAPS AFCAPS ASCOT ASCOT CARE CARE FOUR S FOUR S FOUR S LIPID LIPID PROSPER PROSPER	Female Male Female Female Male Female Male Female Female Male	0.537 0.641 1.039 0.583 0.866 0.669 0.669 0.666 0.669 0.666 0.670 0.761 0.761 0.759 0.759	d and random effe	ects options in a subgroup ong-study variance co rates of tau-squared), non among-study vari- stimates of tau-square	omponent across ance component d). This is the op	subgroups across ubgroups (do otion use by RevMan.			0.58 6.69 1.12 5.34 3.98 15.30 4.58 15.59 5.59 16.02 6.82 9.21
Random	WUSLUP	Male	0.700 0.739 © Co	mbine subgroups usi	ing fixed effect model ing random effects model Cancel	odel	Ok	J		3.18

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Statins by gender

Now, we can tell the program to run the analysis by subgroups.

Click Computational options > Group by

🕂 Compre	hensive meta a	nalysis - [An	alysis]					Sector Sec.				-		
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+ Data en	try 1구 Ne	+ Effect	measure	,	elect b	y + E	ffect measur	e: Risk ratio	-		11 3 E	🤹 🖞 🗐		
Model	Study name	[] CI Lev	el 95%	,	each st	udy			Risk	ratio and 95%	: Cl		Weight (Random)	
	ſ	P Select	by		East	J. Caluar	n) (nhun	0.01	0.10	1.00	10.00	100.00	Deletive weight	
		🚔 Group	by		limit	2-value	p-value	0.01	0.10	1.00	10.00	100.00	Relative weight	
	AFCAPS	Comp			1.336	J -1.337	0.181						0.58	
	AFCAPS	S).810	-3.717	0.000			+			6.69	
	ASCOT	2. Mixed	and random eff	ects options	2.102	0.286	0.775			_ 			1.12	
	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000						5.34	
	CARE	Female	0.583	0.422	0.806	-3.266	0.001						3.98	
	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			15.30	
	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008				- 1		4.58	
			0.000	0.000	0.704	~ • • •	0.000	I	1	I	I	I	45.50	

- Select Subgroup within study
- Check the two boxes
- Click Ok

🕂 Compre	hensive meta a	nalysis - [An	alysis]						-				
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Model	Study name	Subgroup within study		Stati	stics for each s	study			Ris	k ratio and 95%	(CI		Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
Random	AFCAPS AFCAPS ASCOT CARE CARE FOUR S FOUR S LIPID LIPID PROSPER PROSPER WOSCOP	Female Male Female Male Female Male Female Male Female Male Male Male	0.537 0.641 1.099 0.583 0.583 0.816 0.669 0.696 0.870 0.761 0.919 0.769 0.769 0.700 0.739	Rui Su V	oup by n a separate bgroup within Also run analy Compare effe	e analysis study isis across le ct at differen	for each lev	el of up within study roup within stud					0.58 6.69 1.12 5.34 3.98 15.30 4.58 15.59 5.59 16.02 6.82 9.21 9.18
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The screen should look like this

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Model	Group by Subgroup	Study name	Subgroup within study		Stati	stics for each	study			Risk ra	tio and 95%	CI		Weight (Pooled tau)
				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	Female Female Female Female Female	AFCAPS ASCOT CARE FOUR S LIPID	Female Female Female Female Female	0.537 1.099 0.583 0.669 0.870	0.216 0.575 0.422 0.497 0.668 0.720	1.336 2.102 0.806 0.901 1.132 1.150	-1.337 0.286 -3.266 -2.644 -1.036 0.710	0.181 0.775 0.001 0.008 0.300 0.472		-	+ + +			2.59 5.00 17.64 20.25 24.61
Random	Female	PRUSPER	remale	0.919	0.729	0.906	-0.719	0.472			+			29.90
Pandom	Male Male Male Male Male Male Male	AFCAPS ASCOT CARE FOUR S LIPID PROSPER WOSCOP	Male Male Male Male Male Male	0.641 0.589 0.816 0.696 0.761 0.769 0.700	0.507 0.449 0.725 0.620 0.681 0.638 0.580	0.810 0.773 0.918 0.781 0.851 0.927 0.844	-3.717 -3.822 -3.388 -6.148 -4.784 -2.748 -3.729	0.000 0.000 0.001 0.000 0.000 0.000 0.000		-	+ + + + + + + + + +			8.84 7.09 19.59 19.94 20.46 12.06 12.02
Bandom	Overall			0.727	0.670	0.766	-7.660	0.000			+			

For Females the mean effect size is a risk ratio of 0.781 with a confidence interval of 0.673 to 0.906, a Z-value of -3.270 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

For Males the mean effect size is a risk ratio of 0.727 with a confidence interval of 0.670 to 0.798, a Z-value of -7.680 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

For all samples together the mean effect size is a risk ratio of 0.739 with a confidence interval of 0.688 to 0.794, a Z-value of -8.306 and a corresponding p-value of < 0.001.

We want to know if the difference between the two effect sizes (0.781 vs. 0.727) is statistically significant, and we'll run a test for this.

To get a better sense of what we're testing, click the "All studies" button. This will hide all of the individual studies and display the summary effects only as shown here.

The test will compare the two mean effects relative to the precision of each effect. For two groups we can think of this as a Z-test for the ratio of the difference in means to the standard error of the difference.

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				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight	
Random	Female			0.781	0.673	0.906	-3.270	0.001			+				
Random	Male			0.727	0.670	0.788	-7.680	0.000			+				
Random	Overall			0.739	0.688	0.794	-8.306	0.000			+				

Expand the scale for detail

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				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.50	1.	00	2.00	Relative weight		
Random	Female			0.781	0.673	0.906	-3.270	0.001			at.		1		
Random	Male			0.727	0.670	0.788	-7.680	0.000		<u> </u>	-+	 Show/hide forest plot 			
Random	Overall			0.739	0.688	0.794	-8.306	0.000					🔸 🖌 Log scale .50 to	2	
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- Re-set the scale
- Toggle the "All studies button" to display the studies again.
- Click Next Table to see the results

The top section of the page (labeled Fixed-effect analysis) is for an analysis where we compute the summary effect in each group using FE weights, and then compare these values

The bottom section of the page (Mixed-effects analysis) is for an analysis where we compute the summary effect for each group using RE weights, and then compare these values.

We want to use the bottom section. The RE model is a better fit for the way the studies were sampled, and so this is the appropriate analysis.

Statins by gender

entry the Next t	able 🏪 H	ligh resolution	plot 🛛 🔁 S	elect by	+ Effect measur	re: Risk ratio	- 3		1≇E	£ 1 0				
Groups		Effect siz	e and 95%	interval	Test of nu	ıll (2-Tail)		Hetero	geneity			Tau-so	quared	
Group	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	l-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analy	vsis													
Female	6	0.787	0.689	0.898	-3.566	0.000	8.399	5	0.136	40.468	0.020	0.033	0.001	0.
Male	7	0.737	0.696	0.779	-10.653	0.000	8.570	6	0.199	29.988	0.003	0.005	0.000	0.0
Total within							16.969	11	0.109					
Total between							0.806	1	0.369					
Overall	13	0.744	0.706	0.784	-11.198	0.000	17.775	12	0.123	32.488	0.005	0.006	0.000	0.
Mixed effects and	lysis													
Female	6	0.781	0.673	0.906	-3.270	0.001								
Male	7	0.727	0.670	0.788	-7.680	0.000								
Total between							0.689	1	0.406					
Overall	13	0.739	0.688	0.794	-8.306	0.000		-						

Toward the left of the screen the program displays the same numbers we saw a moment ago.

For Females the mean effect size is a risk ratio of 0.781 with a confidence interval of 0.673 to 0.906, a Z-value of -3.270 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is clinically as well as statistically significant.

For Males the mean effect size is a risk ratio of 0.727 with a confidence interval of 0.670 to 0.788, a Z-value of -7.680 and a corresponding p-value of < 0.001. It's clear that the statins are more effective than placebo, and that the impact is chinically as well as statistically significant.

The test to compare the two effect sizes (0.781 vs. 0.727) yields a Q-value of 0.689 with 1 df and a corresponding p-value of 0.406.

Comprehensive meta ana	alysis - [Analysis]					The second second								
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Groups		Effect siz	e and 95%	interval	Test of nu	ıll (2-Tail)	\square	Hetero	geneity			Tau-so	quared	
Group	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	⊋-value	df (Q)	P-value	l-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect ana	lysis													
Female Male	6 7	0.787 0.737	0.689 0.696	0.898	-3.566 -10.653	0.000	8.399 8.570	5 6	0.136 0.199	40.468 29.988	0.020	0.033	0.001	0.142 0.051
Total within Total between							16.969 0.806	11 1	0.109 0.369					
Overall	13	0.744	0.706	0.784	-11.198	0.000	17.775	12	0.123	32.488	0.005	0.006	0.000	0.069
Mixed effects an	nalysis													
Female Male Total between	6 7	0.781 0.727	0.673 0.670	0.906 0.788	-3.270 -7.680	0.001 0.000	0 699	1	0.406					
Overall	13	0.739	0.688	0.794	-8.306	0.000	0.663	1	0.406					

Toward the right of the screen the program displays information about between-study heterogeneity. As was true for the single-group of studies, these statistics are based on FE weights and are therefore displayed in the top section, but they apply to the RE analysis as well.

For Females the variance in effects yields a Q-value of 8.399, with 5 df and p=0.136. Therefore, there is no evidence of dispersion in true effects among the studies that enrolled females.

For Males the variance in effects yields a Q-value of 8.570 with 6 df and p=0.199. Therefore, there is no evidence of dispersion in true effects among the studies that enrolled males

We can also perform an omnibus test by pooling the Q values and df across subgroups. The pooled Q is 16.969 with 11 df and p=0.109. The conventional level for significance of heterogeneity is 0.10, and this is very close to that level.

These tests are goodness-of-fit tests. They ask if the grouping (Females vs. Males) explains all of the variance in true effect sizes, or if some true variance remains, even within subgroups. Here (based on the p-value of 0.109), there is evidence of true variance within subgroups.

Note that the tests of homogeneity are displayed in the fixed-effect section, even though we're using the random-effects model within subgroups. This is because these tests always are always based on using within-study (fixed-effect) weights. That is, we pose the null (that T^2 is zero) and then see is the variance is consistent with the null.

Click Next table to return to this screen.

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Model	Group by Subgroup	Study name	Subgroup within study		Statis	stics for each s	study			Risk	ratio and 95%	CI		Weight (Pooled tau)
				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	Female	AFCAPS	Female	0.537	0.216	1.336	-1.337	0.181		<u> </u>				2.59
	Female	ASCOT	Female	1.099	0.575	2.102	0.286	0.775			_ -			5.00
	Female	CARE	Female	0.583	0.422	0.806	-3.266	0.001						17.64
	Female	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008						20.25
	Female	LIPID	Female	0.870	0.668	1.132	-1.036	0.300			+			24.61
	Female	PROSPER	Female	0.919	0.729	1.158	-0.719	0.472			+			29.90
Random	Female			0.781	0.673	0.906	-3.270	0.001			+			
	Male	AFCAPS	Male	0.641	0.507	0.810	-3.717	0.000			+			8.84
	Male	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000						7.09
	Male	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			19.59
	Male	FOUR S	Male	0.696	0.620	0.781	-6.148	0.000			+			19.94
	Male	LIPID	Male	0.761	0.681	0.851	-4.784	0.000			+			20.46
	Male	PROSPER	Male	0.769	0.638	0.927	-2.748	0.006			+			12.06
	Male	WOSCOP	Male	0.700	0.580	0.844	-3.729	0.000			+			12.02
Random	Male			0.727	0.670	0.788	-7.680	0.000			+			
Random	Overall			0.739	0.688	0.794	-8.306	0.000			+			

To this point, the analysis where each study provided data for two subgroups was identical to the analysis we would have performed if each row of data came from a different study.

This is true for the overall analysis, and it's true for the analysis where we compared the treatment effect for Females vs. the treatment effect for Males.

However, there is one additional option available in when we have subgroups within studies that is not available when each row of data comes from a different study. We have the option to take all the rows from each study and collapse them into a single row.

In the current example, we might decide that while the effect size is not identical for Females and for Males, the two effects are close enough that we want to combine the data. This might make sense, for example, if all studies had included both Females and Males, but some studies reported the data for each gender separately, while others reported the data only for the sample as a whole.

First, we need to turn off grouping. If we are going to collapse subgroups into a single group we obviously cannot group by gender.

Click Computational options > Group by > Reset

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Model	Study name	Subgroup within study		Stal	istics for each	study			Ris	k ratio and 95%	: CI		Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS AFCAPS	Female Male	0.537 0.641	GG	roup by		12		1.1	×			0.58
	ASCOT ASCOT CARE	Female Male Female	1.099 0.589 0.583	B	un a separat	e analysis I	for each lev	el of					1.12 5.34
	CARE FOUR S	Male Female	0.816 0.669	N	o grouping		•						15.30 4.58
	FOUR S LIPID	Male Female	0.696										15.59 5.59
	LIPID PROSPER PROSPER	Male Female Malo	0.761										6.82
	WOSCOP	Male	0.763				Cancel	Beset					9.18
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Model	Study name	Subgroup within study		Stati	stics for each s	study			Ris	< ratio and 95	% CI		Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Female	0.537	0.216	1.336	-1.337	0.181		<u> </u>				0.58
	AFCAPS	Male	0.641	0.507	0.810	-3.717	0.000			+			6.69
	ASCOT	Female	1.099	0.575	2.102	0.286	0.775			_ 			1.12
	ASCOT	Male	0.589	0.449	0.773	-3.822	0.000			+			5.34
	CARE	Female	0.583	0.422	0.806	-3.266	0.001						3.98
	CARE	Male	0.816	0.725	0.918	-3.388	0.001			+			15.30
	FOUR S	Female	0.669	0.497	0.901	-2.644	0.008						4.58
	FOUR S	Male	0.696	0.620	0.781	-6.148	0.000			+			15.59
	LIPID	Female	0.870	0.668	1.132	-1.036	0.300			-+-			5.59
	LIPID	Male	0.761	0.681	0.851	-4.784	0.000			+			16.02
	PROSPER	Female	0.919	0.729	1.158	-0.719	0.472			-+			6.82
	PROSPER	Male	0.769	0.638	0.927	-2.748	0.006			+			9.21
	WOSCOP	Male	0.700	0.580	0.844	-3.729	0.000			+			9.18
Random			0.739	0.689	0.793	-8.468	0.000			+			

- Right-click on the column "Subgroup within study"
- Click Select by Subgroup within study

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Model	Study name	Subgroup within study		Stati	stics for each s	tudy			Ris	sk ratio and 95%	% CI		Weight (Random)
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight
	AFCAPS	Female	0.537	0.216	1.336	-1.337	0.181		- 1				0.58
	AFCAPS	Male	0.641	0.507	0.810	-3.717	0.000						6.69
	ASCOT	Femal∈ ≜↓	Sort Lo-Hi b	v Subaroup	within study	0.286	0.775			_ 			1.12
	ASCOT	Male Z	C	. C		-3.822	0.000						5.34
	CARE	Female A+	SOIT HI-LO D	y subgroup	within study	-3.266	0.001						3.98
	CARE	Male 🕞	Select by Sul	baroup with	in study 🕟	-3.388	0.001			+			15.30
	FOUR S	Female .00	C		4	-2.644	0.008			-+-			4.58
	FOUR S	Male	Set decimais			-6.148	0.000			+			15.59
	LIPID	Female 📴	Align			• -1.036	0.300	1		-+-			5.59
	LIPID	Male	0.761	0.681	0.851	-4.784	0.000			+			16.02
	PROSPER	Female	0.919	0.729	1.158	-0.719	0.472			+			6.82

Comprehensive meta analysis - [Analysis]

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Model	Study name	Subgroup within study		Statis	for each study Risk ratio and 95% Cl		Weight (Random)		
			Risk ratio	Lower limit	perlimit Z3/alue n3/alue		100.00 Relative weight		
	AFCAPS AFCAPS ASCOT ASCOT CARE CARE FOUR S FOUR S LIPID	Female Male Female Male Female Male Female Female	0.537 0.641 1.099 0.589 0.583 0.816 0.669 0.669 0.696	0.216 0.507 0.575 0.449 0.422 0.725 0.497 0.620 0.668	Studies Subgroups Moderato	r ps Select all Clear all	0.58 6.63 1.12 5.34 3.98 15.30 4.58 15.55 5.55		
Random	LIPID PROSPER PROSPER WOSCOP	Male Female Male Male	0.761 0.919 0.769 0.700 0.739	0.680 0.681 0.729 0.638 0.580 0.689			9.18		
					 C Use subgroup within study as the 𝔅 Use study as the unit of analysis 	e unit of analysis			
Fived Ba	andom Both s	nodels				Cancel Apply Ok			

The two options here are "Use subgroup within study as the unit of analysis" and "Use study as the unit of analysis"

To this point we've been using the first option. Now, select the second option and click OK

Statins by gender

T Comprehensive meta analysis - [Analysis]														
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Model	Study name	Subgroup within study	Statistics for each study					Risk ratio and 95% Cl					Weight (Random)	
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight	
	AFCAPS	Combined	0.633	0.504	0.795	-3.935	0.000			+			7.05	
	ASCOT	Combined	0.645	0.503	0.828	-3.450	0.001			+			6.05 📕	
	CARE	Combined	0.782	0.700	0.874	-4.354	0.000			+			20.24	
	FOUR S	Combined	0.694	0.623	0.773	-6.650	0.000			+			20.83	
	LIPID	Combined	0.777	0.701	0.861	-4.804	0.000			+			21.97	
	PROSPER	Combined	0.826	0.714	0.956	-2.560	0.010			+			14.17	
	WOSCOP	Male	0.700	0.580	0.844	-3.729	0.000			+			9.70	
Random			0.740	0.693	0.790	-9.035	0.000			+				

Note the following

- We now have seven rows of data rather than thirteen
- The subgroup for most studies is listed as "Combined" since these studies had two subgroups, and the data displayed is for the two combined. The Subgroup for WOSCOP is listed as Male, since this study had a male subgroup only.
- The summary effect size is 0.740, which is very close to the one before (0.739). We wouldn't expect them to be identical
- The confidence interval is 0.694 to 0.790. Again, this is very close to the one before (0.689 to 0.793). The reason that the CI width is approximately the same in both versions of the analysis is that the two samples (Female and Male) are independent of each other. As long as we treat them as independent in both versions of the analysis, the two versions may have similar precision (but see note below).
- The same applies to the Z-value and p-value. These are -9.035 with p < 0.001 in the new analysis. They had been -8.468 with p < .001 in the earlier analysis.

Note

Because the two subgroups are independent of each other, either approach to the analysis is based on the same amount of information and may yield estimates with similar precision. However, there are other factors that affect the precision of the estimate as well and these may differ in the two versions of the analysis. In particular, the estimates may differ substantially if the two approaches yield substantially different estimates of T^2 .

This example focused on the case of independent subgroups within studies. This is very different from the case where the same sample provides data for more than one outcome, time-point, or comparison. In that case the samples are not independent and a very different analysis would be used.

Summary

This analysis includes seven studies where patients were randomized to receive either a statins or a placebo. Outcome was the proportion of patients in each group suffering a major coronary event, and the effect size was the risk ratio.

Within each study patients were classified as being females or males. We ran an analysis to see if the impact of statins was greater (or smaller) for either gender.

Do statins affect the risk of major cardiovascular events?

For this analysis we used subgroups within studies as the unit of analysis.

The mean risk ratio is 0.739, which means that statins decreased the risk of a major cardiovascular event by some 26%. The 95% confidence interval is 0.688 to 0.794. The Z-value for a test of the null (that statins have no impact on the event rate) is -8.306 with a corresponding p-value of < 0.001.

These studies were sampled from a universe of possible studies defined by certain inclusion/exclusion rules as outlined in the full paper. The confidence interval for the risk ratio is 0.688 to 0.794, which tell us that the <u>mean</u> risk ratio in the universe of studies could fall anywhere in this range. This range does not include a risk ratio of 1.0, which tells us that the mean risk ratio is probably not 1.0.

Similarly, the Z-value for testing the null hypothesis (that the mean risk ratio is 1.0) is -8.306, with a corresponding *p*-value is < 0.001. We can reject the null that the risk of a major cardiovascular event is the same in both groups, and conclude that the risk is lower in the statin group.

Does the effect size vary by subgroup?

The mean risk ratio for females is 0.781. The mean risk ratio for smokers is 0.727. The test of the difference in risk between the two subgroups of studies yields a Q-value of 0.689 with df = 1 and p=0.406. Thus, there is no evidence that the impact of statins varies by gender.