Medical Statistics (MATH38071) Solutions to Exercise Sheet 10

(Meta-analysis)

1. The table below summarizes the outcome of three trials comparing dietary advice given by a dietician with that given by a practice nurse for patients for with high blood cholesterol. The treatment effect for each trial ($\hat{\theta}_i$, i = 1,2,3) is the difference in mean cholesterol between the dietician advice group and nurse group. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate of the *i*th study.

Study	*Reduction in blood cholesterol,* $\hat{\theta}_i$	$Var\left[\hat{\theta}_i\right]$
O'Donoghue(1993)	0.34	0.0289
Ahmed (2001)	0.18	0.0729
Cohen (2003)	0.27	0.0676

(i) Compute the minimum variance estimate of the overall treatment effect, $\hat{\theta}_{MV}$, and determine its 95% confidence interval stating any assumptions you make.

Solution

	Reduction in cholesterol		*Solution*	
Study	$\hat{\theta}_i$	$Var\left[\hat{\theta}_i\right]$	$w_i = 1/Var\left[\hat{\theta}_i\right]$	$w_i\hat{\theta}_i$
O'Donoghue(1993)	0.34	0.0289	*34.60*	*11.76*
Ahmed (2001)	0.18	0.0729	*13.72*	*2.47*
Cohen (2003)	0.27	0.0676	*14.79*	*3.99*
		Σ	*63.11*	*18.23*

The minimum variance estimate $\hat{\theta}_{MV} = \dfrac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i} = \dfrac{18.23}{63.11} = 0.2888$

$$Var\left[\hat{\theta}_{MV}\right] = \frac{1}{\sum_i^k w_i} = \frac{1}{63.11} = 0.0158$$

$$SE\left[\hat{\theta}_{MV}\right] = \sqrt{0.0158} = 0.1258$$

Assuming $\hat{\theta}_{MV}$ is normally distributed the 95% C.I. is 0.289±1.96 $SE\left[\hat{\theta}_{MV}\right]$, which gives the 95% C.I. to be from 0.042 to 0.536.

(ii) By calculating the p-value, test the hypothesis $H_0: \theta = 0$ vs $H_1: \theta \neq 0$ using a 5% significance level.

(iii) .

Solution

$$T = \hat{\theta}_{MV} \big/ SE\left[\hat{\theta}_{MV}\right] = \frac{0.2888}{0.1258} = 2.2957$$

Assuming normality $p-value = 2\times\left(1-\Phi\left(|T|\right)\right) = 2\times\left(1-\Phi\left(2.2957\right)\right) \cong 2\times\left(1-0.9859\right) = 0.0282$ from tables.

Using a 5% significance level one can reject the null hypothesis $H_0: \theta = 0$

(iv) What do you conclude from the meta-analysis?

Solution

There is evidence from the meta-analysis dietary advice given by a dietician is more effective than dietary advice given by a doctor as the dietician advice gives a reduction of 0.29 (95% C.I. 0.042 to 0.536,p=0.282)

2. The table below summarizes the outcome for three trials of a new drug compared to the standard drug for patients with heart failure giving the survival after two years follow-up.

	New			***Standard***		
Study	**Died**	***Alive***	***N***	**Died**	***Alive***	***N***
A	33	214	247	45	201	246
B	6	61	67	12	58	70
C	5	44	49	7	41	48

(i) From the data in the table estimate the odds ratio of death (OR) and $\log_e[OR]$ for each trial for *New* compared to *Standard* drug treatment.

(ii) From the data in the table estimate the variance and standard error of $\log_e\left[OR\right]$ for each trial.

(iii) Calculate the 95% confidence interval of the odds ratio (OR) for each trial.

Solution

The question specifies calculate the odds ratio of death comparing New against Standard treatment . The table below summarizes the results. If you have calculated based on survival, change the sign of the log odds ratio and take the reciprocal for the odd ratio, and reverses the limits of confidence intervals.

Study	***OR of death***	***θ_i= ln(OR)***	***Var [ln(OR)]***	***SE [Log(OR)]***	***Confidence Interval of OR 95%***			***W_i***	***$W_i\theta_i$***
A	0.689	-0.373	0.06217	0.249346	0.423	to	1.123	16.084	-5.997
B	0.475	-0.744	0.28363	0.532574	0.167	to	1.350	3.526	-2.622
C	0.666	-0.407	0.38997	0.62448	0.196	to	2.263	2.564	-1.044
			Σ					22.174	-9.662

(iv) Determine the minimum variance estimate of the pooled log odds ratio.

Solution

$\log\left[\hat{OR}\right]=\hat{\theta}_{MV}=\frac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i}=\frac{-9.662}{22.174}=-0.436$. Hence pool odds ratio $\exp(-0.436)=0.647$

(v) Determine the variance of the minimum variance estimate of the pooled log odds ratio.

Solution $\hat{Var}\left[\log\hat{OR}\right]=\frac{1}{22.174}=0.045098$.

(vi) From (iv) and (v) calculate the pooled odds ratio and its 95% confidence interval.

Solution $SE\left[\log\hat{OR}\right]=\sqrt{\hat{Var}\left[\log\hat{OR}\right]}=0.212$

Assuming normality of the 95% c.i. of the odds ratio is

$\exp\left[\log_e\hat{OR}\pm1.96\times\hat{SE}\left[\log_e\hat{OR}\right]\right]=\exp[-0.436\pm1.96\times0.212]$

Hence the 95% confidence interval of the pooled odds ratio of death is 0.427 to 0.981. If you have calculated the odds ratio of survival, the confidence interval is 1.020 to 2.344.

(vii) Using the estimate from (iv) and the standard error obtained from (v) test the hypothesis

$H_0: OR=1 \text{ vs } H_1: OR\neq1$

Solution The test of H_o: OR=1 vs H_o: OR≠1 is equivalent to the test H_o: $\log_e$ OR=0 vs H_o: $\log_e$ OR≠0

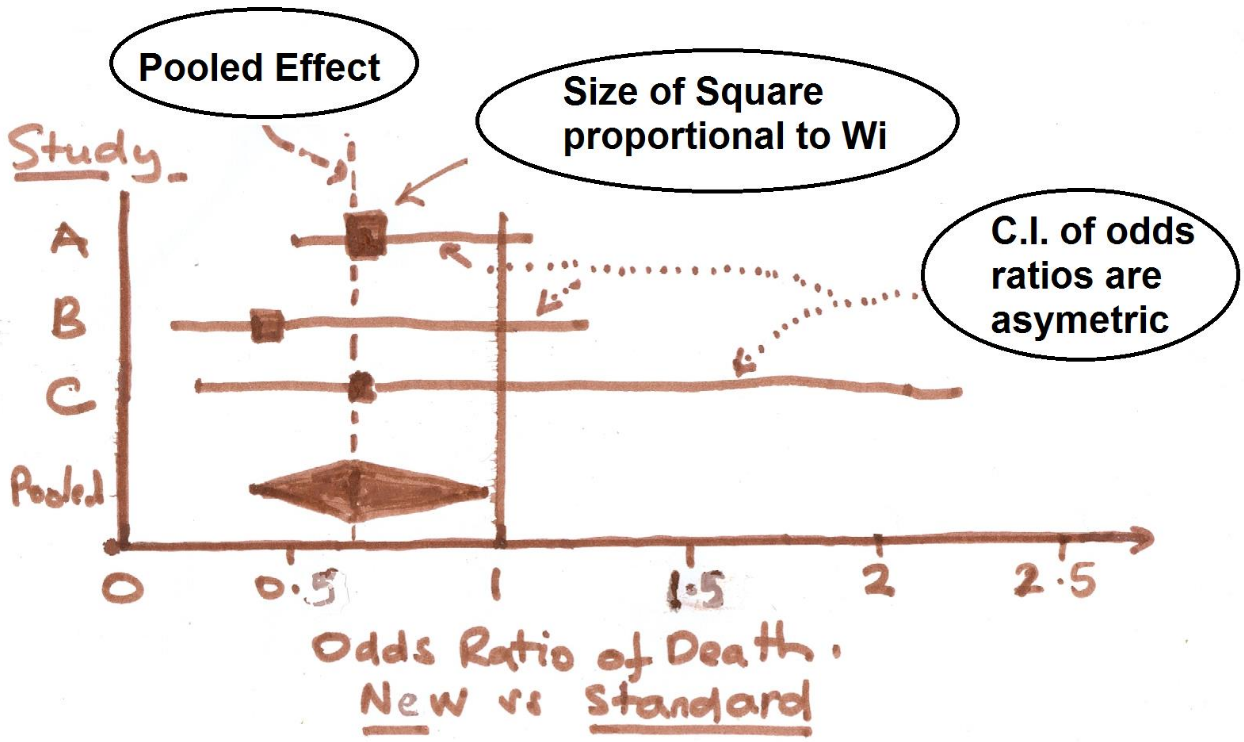
$z=\frac{\log_e OR}{SE[\log_e OR]}=\frac{-0.436}{0.212}=-2.057$. Since |z| >1.96 one would reject the hypothesis at a 5% level.

Alternative from tables $p=(1-\Phi(|z|))\times2=(1-\Phi(2.057))\times2=(1-0.9803)\times2=0.039$.

Hence the null hypothesis H_o: OR=1 would be rejected.

(viii) Using the results of (i), (iii), (v) and (vi) sketch a forest plot of the odds ratio for your meta-analysis.

Solution

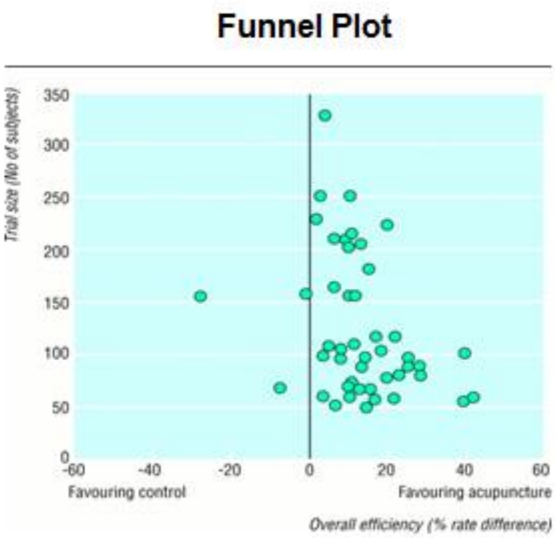


(ix) Briefly comment on the results of the meta-analysis as compared to the results for individual trials.

Solution The results of the meta-analysis suggest that the new treatment increased survival as the odds ratio of death by two years is less than 1 being 0.647 (95% c.i. 0.427 to 0.981,p=0.039). By considering the 95% c.i. of the individual trials, none showed a statistically significant benefit of the new drug on survival.

3. Briefly comment on the funnel plot showing the results of a meta-analysis of 49 published trials considering the effectiveness of acupuncture for the treatment of Stroke.

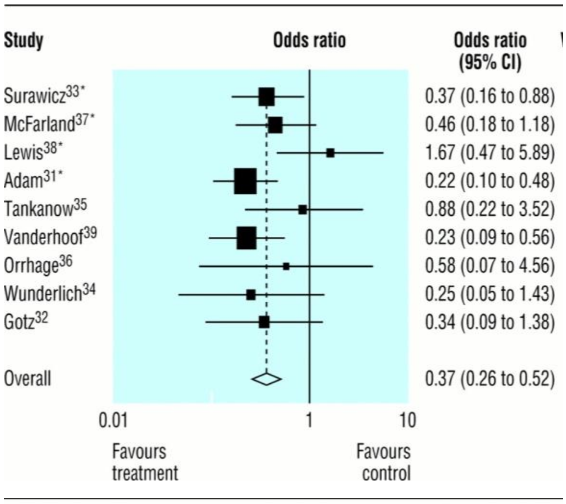
http://www.bmj.com/cgi/content/full/319/7203/160

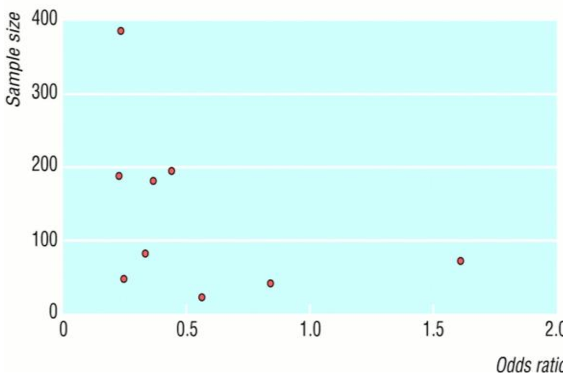


Solution

The funnel plot shows strong evidence of publication bias. It would seem to suggest that there may be small studies showing a negative effect of acupuncture treatment , that is favour control, that are not getting published.

4. The forest and funnel plots below illustrates a meta-analysis of trials evaluating the efficacy of probiotics in prevention of diarrhoea associated with taking antibiotics. The trials estimate the odds ratio of diarrhoea after taking a probiotics dietary supplement compared to placebo. By examining the two figures consider whether there is evidence of publication bias.





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Solution

The funnel plot does appear to show an incomplete funnel, which might suggest publication bias, but it should be noted that the number of studies is small, and so one would not expect to see a "perfect" funnel. But this is not the whole story. If we examine the forest plot, the treatment effect of probiotic compared to control, one can see that the two studies with greatest weight (Adams & Vanderhoof) shows the greatest reduction in diarrhoea probiotic compared to control. The asymmetry in the funnel plot is therefore not consistent with smaller studies with a small effect not being published or found by the systematic review. From the forest plot it can be seen that the odd ratio for probiotic as compared to control is 0.37 (95% c.i. 0.26 to 0.52). Hence based on this meta-analysis it would suggest that probiotics may be effective.