HW7

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1 Endocrinology

A study of raloxifene and incidence of fractures was conducted among women with evidence of osteoporosis. The women were initially divided into two groups: those with and those without pre-existing fractures. The women were then randomized to raloxifene or placebo and followed for 3 years to determine the incidence of new vertebral fractures, with the results shown in Table 13.51.

No pre-existing fractures Pre-existing fractures

	New fractures	No new fractures	Total		New fractures	No new fractures	Total
Raloxifene	34	1466	1500	Raloxifene	103	597	700
Placebo	68	1432	1500	Placebo	170	630	800
Total	102	2898	3000	Total	273	1227	1500

Table 13.51 Comparison of fracture incidence between raloxifene- and placebo-treated women

1.1 13.85 Among those with no pre-existing fractures, test whether raloxifene affects the incidence of new fractures.

This is a prospective study, we can use risk difference(RD), risk ratio(RR) or odds ratio(OR) to test

$$H_0 : p_1 = p_2 \qquad H_1 : p_1 \neq p_2$$

where p_1 and p_2 are the probabilities of developing new fractures of raloxifene- and placebo-treated groups.

RD: Since $n_1\hat{p}_1\hat{q}_1 = 33.22933$ and $n_2\hat{p}_2\hat{q}_2 = 64.91733$, we have

$$\hat{p}_1 - \hat{p}_2 \dot{\sim} N\left(p_1 - p_2, \frac{p_1q_1}{n_1} + \frac{p_2q_2}{n_2}\right)$$
$$\overset{H_0}{\sim} N\left(0, \frac{p_1q_1}{n_1} + \frac{p_2q_2}{n_2}\right)$$

By estimating the variance with $\frac{\hat{p}_1\hat{q}_1}{n_1} + \frac{\hat{p}_2\hat{q}_2}{n_2}$, we have s

$$\frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\frac{\hat{p}_1\hat{q}_1}{n_1} + \frac{\hat{p}_2\hat{q}_2}{n_2}}} \overset{H_0}{\sim} N(0,1)$$

```
No_pre_existing <- matrix(c(34,1466,68,1432),2,2)
n1 <- 1500
n2 <- 1500

p1_hat <- 34 / 1500
p2_hat <- 68 / 1500

Z <- (p1_hat - p2_hat) / sqrt(p1_hat * (1 - p1_hat) / n1 + p2_hat * (1 - p2_hat) / n2)
cat('The p-value is ',2*(1 - pnorm(abs(Z))))
```

```
## The p-value is  0.0005992547
```

Since p-value< 0.05, with $\alpha = 0.05$ we reject H_0.

1.2 13.86 Among those with no pre-existing fractures, compute the relative risk of new fractures among those randomized to raloxifene vs. placebo, along with its associated 95% CI.

$\because$

$$
\begin{aligned}
Var(\ln \hat{p}_1) &\approx \frac{1}{\hat{p}_1^2} Var(\hat{p}_1) \\
&= \frac{1}{\hat{p}_1^2} \frac{\hat{p}_1 \hat{q}_1}{n_1} \\
&= \frac{\hat{q}_1}{n_1 \hat{p}_1} \\
Var(\ln \hat{p}_2) &\approx \frac{1}{\hat{p}_2^2} Var(\hat{p}_2) \\
&= \frac{1}{\hat{p}_2^2} \frac{\hat{p}_2 \hat{q}_2}{n_2} \\
&= \frac{\hat{q}_2}{n_2 \hat{p}_2} \\
Var(\ln \hat{RR}) &= Var\left(\ln \frac{\hat{p}_1}{\hat{p}_2}\right) \\
&= Var(\ln \hat{p}_1) + Var(\ln \hat{p}_2) \\
&= \frac{\hat{q}_1}{n_1 \hat{p}_1} + \frac{\hat{q}_2}{n_2 \hat{p}_2}
\end{aligned}
$$

$\therefore$ the approximated 95% CI for $\ln \hat{RR}$ is given by

$$
\left(\ln \hat{RR} - z_{1-\frac{\alpha}{2}} \sqrt{\frac{\hat{q}_1}{n_1 \hat{p}_1} + \frac{\hat{q}_2}{n_2 \hat{p}_2}}, \ln \hat{RR} + z_{1-\frac{\alpha}{2}} \sqrt{\frac{\hat{q}_1}{n_1 \hat{p}_1} + \frac{\hat{q}_2}{n_2 \hat{p}_2}} \right)
$$

```
RR_hat <- p1_hat / p2_hat
var_ln_RR_hat <- (1 - p1_hat) / p1_hat / n1 + (1 - p2_hat) / p2_hat / n2
cat('The estimated relative risk is ',RR_hat,'\n',
    'The approximated 95% confidence interval is (',
    RR_hat*exp(-qnorm(0.975)*sqrt(var_ln_RR_hat)),
    ',',RR_hat*exp(qnorm(0.975)*sqrt(var_ln_RR_hat)),')')
```

```
## The estimated relative risk is  0.5
##  The approximated 95% confidence interval is ( 0.333353 , 0.7499558 )
```

1.3 13.87 Test the association of study agent with new fractures combining both groups of those with and without preexisting fractures.

```
O <- 34 + 103
E <- 1500 * 102 / 3000 + 700 * 273 / 1500
```

```
V <- 1500 * 1500 * 102 * 2898 / (3000^2 * (3000-1) ) +
    700 * 800 * 273 * 1227 / (1500^2 * (1500-1) )
X2_MH <- (abs(O - E) - 0.5)^2 / V
cat('The p-value is ', 1- pchisq(X2_MH,1))
```

```
## The p-value is  4.985801e-06
```

80.2586654 Since p-value< 0.05, with $\alpha = 0.05$ we reject H_0.

1.4 13.88 Combining both groups, compute the standardized RR for raloxifene vs. placebo and new fractures. (Hint: Use the total population as the standard.)

```
SRR <- (3000 * 34 / 1500 + 1500 * 103 / 700) / (3000 + 1500) /
    ((3000 * 68 / 1500 + 1500 * 170 / 800) / (3000 + 1500))
```

The standardized RR for raloxifene vs. placebo and new fractures is 0.6348857.

1.5 13.89 Is pre-existing fracture a confounder in these data?

We use Chi-Square Test for Homogeneity of ORs over Different Strata (Woolf Method) to test

$$H_0 : OR_1 = OR_2 \qquad H_1 : OR_1 \neq OR_2$$

The test statistic is given by

$$X^2_{HOM} = \sum_{i=1}^{2} w_i (\ln \hat{OR} - \overline{\ln OR})^2$$

where

$$w_i = \frac{1}{\frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}}$$

$$\overline{\ln OR} = \frac{\sum_{i=1}^{2} w_i \ln \hat{OR}}{\sum_{i=1}^{2} w_i}$$

```
OR1_hat <- 34 / 1500 * (1 - 68 / 1500) /
    (68 / 1500 * (1 - 34 / 1500))
OR2_hat <- 103 / 700 * (1 - 170 / 800) /
    (170 / 800 * (1 - 103 / 700))
w1 <- 1 / (1/34+1/1466+1/68+1/1432)
w2 <- 1 / (1/103+1/597+1/170+1/630)
weighted_lnOR <- (w1 * log(OR1_hat) + w2 * log(OR2_hat)) / (w1 + w2)
X2_HOM <- w1 * (log(OR1_hat) - weighted_lnOR)^2 + w2 * (log(OR2_hat) - weighted_lnOR)^2
cat('The p-value is ', 1 - pchisq(X2_HOM,1))
```

```
## The p-value is  0.2883395
```

Since p-value is bigger than $\alpha = 0.05$, we cannot reject H_0, i.e., pre-existing fracture is not a confounder in these data.

2 Cardiovascular Disease

A study was performed relating baldness pattern to MI (heart attack) among men in the Atherosclerosis Risk in Communities (ARIC) study [49]. Baldness pattern and prevalent MI were determined at the same examination during the period 1996−1998. Baldness was categorized into 5 categories (none/frontal/mild vertex/ moderate vertex/severe vertex). For this example, we focus on the comparison of severe vertex baldness to no baldness. The data in Table 13.55 were reported by age group.

Age group	Baldness	MI	No MI	Total
	Severe vertex	49	280	329
$\leq$ 60 years	None	71	639	710
	Total	120	919	1039
	Severe vertex	131	656	787
$>$ 60 years	None	144	782	926
	Total	275	1438	1713

Table 13.55 Association between severe vertex baldness and MI in the ARIC study

2.1 13.98 What type of study was this?

Cross-sectional study.

2.2 13.99 What is the estimated OR for MI comparing men with severe vertex baldness vs. no baldness after controlling for age?

```
OR <- (49 * 639 / 1039 + 131 * 782 / 1713) / (280 * 71 / 1039 + 656 * 144 / 1713)
```

The Mantel-Haenszel estimated OR for MI comparing men with severe vertex baldness vs. no baldness after controlling for age is 1.2108163.

2.3 13.100 Is there a significant association between MI and severe vertex baldness after controlling for age? Please report a two-tailed p-value.

```
O <- 49 + 131
E <- 120 * 329 / 1039 + 275 * 787 / 1713
V <- 120 * 919 * 329 * 710 / (1039^2 * (1039-1)) + 275 * 1438 * 787 * 926 / (1713^2 * (1713-1))
X2_MH <- (abs(O - E) - 0.5)^2 / V
cat('The p-value is ', 1- pchisq(X2_MH,1))
```

```
## The p-value is  0.0908176
```

80.3556916 Since the p-value is bigger than $\alpha = 0.05$, we cannot reject H_0, i.e., there is no significant association between MI and severe vertex baldness after controlling for age.

2.4 13.101 What is the OR between MI and severe vertex baldness in (i) men ≤ 60 and (ii) men > 60? If these are the true ORs, is age an effect modifier of the association between baldness and MI? Why or why not?

```
OR1_hat <- 49 * 639 / 280 / 71
OR2_hat <- 131 * 782 / 656 / 144
w1 <- 1 / (1/49+1/639+1/280+1/71)
w2 <- 1 / (1/131+1/782+1/656+1/144)
weighted_lnOR <- (w1 * log(OR1_hat) + w2 * log(OR2_hat)) / (w1 + w2)
X2_HOM <- w1 * (log(OR1_hat) - weighted_lnOR)^2 + w2 * (log(OR2_hat) - weighted_lnOR)^2
cat('The p-value is ', 1 - pchisq(X2_HOM,1))
```

```
## The p-value is  0.1180697
```

$\hat{OR}_1 = 1.575$, $\hat{OR}_2 = 1.0844555$. Since the p-value is bigger than $\alpha = 0.05$, we cannot reject H_0, i.e., age is not an effect modifier of the association between baldness and MI.