Comparing Two Person-Time Rates (PersonTime2)

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FORMULAE AND EXAMPLE FOR A SINGLE TABLE WITH PERSON-TIME DENOMINATOR

For a single person-time table comparing exposed and nonexposed, the notation is depicted in Table 15-10. Estimates of the incidence rate ratio (IRR), the incidence rate difference (IRD), their confidence intervals, and test for interaction are presented. Approximate confidence interval methods are provided but it is important to note that there are better confidence interval methods when the data are sparse.

Table 15-10. Notation for comparing exposed and nonexposed with person-time denominators.

	Exposed	Nonexposed	
Cases	a	b	m_1
Person-time	n_1	n_0	n

Estimated incidence rate in the exposed = $I\hat{R}_e = a / n_1$

Estimated incidence rate in the nonexposed = $I\hat{R}_n = b / n_0$

Incidence Rate Ratio

Point estimate:

$$I\hat{R}R = \frac{I\hat{R}_e}{I\hat{R}_u}$$

Variance estimate:

$$V\hat{a}r(\ln I\hat{R}R) \approx \frac{1}{a} + \frac{1}{b}$$

Confidence interval:

$$\mathrm{I\hat{R}R}\exp\left[\pm Z_{1-\alpha/2}\sqrt{V\hat{a}r(\ln I\hat{R}R)}\right]$$

Incidence Rate Difference

Point estimate:

$$I\hat{R}D = I\hat{R}_e - I\hat{R}_u$$

Variance estimate:

$$V\hat{a}r(I\hat{R}D) \approx \frac{a}{n_1^2} + \frac{b}{n_0^2}$$

Confidence interval:

$$I\hat{R}D \pm Z_{1-\alpha/2}\sqrt{V\hat{a}r(I\hat{R}D)}$$

A statistical test based on the normal approximation for the binomial for a single 2x2 table with person-time denominators would be:

$$Z = \frac{a - n_1 m_1 / n}{\sqrt{\frac{m_1 n_1 n_0}{n^2}}}$$

To work through an example of the calculations on a single table, the person-time data from Chapter 14 will be used and is presented in Table 15-11.

Table 15-11. Example data 3: Single table for analyzing person-time data.

	Placebo	Treated	
Recurrence	21	9	30
Pt-wks	182	359	541

The **incidence rate** *estimates* are:

Incidence rate in placebo group = 21/182 = 11.538 cases per 100 patient-weeks

Incidence rate in the treatment group = 9/359 = 2.507 cases per 100 patient-weeks

The **incidence rate ratio** point estimate, variance estimate, and 95% confidence interval are as follows:

IRR=11.538 per 100 pt-wks / 2.507 per 100 pt-wks = 4.60256

The variance of the incidence rate ratio =

$$\frac{1}{21} + \frac{1}{9} = .15873$$

95% confidence interval =

$$4.60256\exp\left[\pm 1.96\sqrt{.15873}\right] = 4.60256\exp\left[\pm .78088\right]$$
(2.108, 10.049)

The interpretation would be that the placebo group had a rate of recurrence 4.6 times greater than the treatment group. We would be 95% confident that truth is somewhere between 2.1 and 10.0.

The **incidence rate difference** is calculated as:

IRD=11.538 per 100 pt-wks **-** 2.507 per 100 pt-wks = 9.031 per 100 pt-weeks

The variance =

$$\frac{21}{182^2}+\frac{9}{359^2}=.000704$$

95% confidence interval =

$$.09031 \pm 1.96\sqrt{.000704}=.09031 \pm .05200$$

(.03831 per pt-week, .14231 per pt-week)

or

(3.8 per 100 pt-weeks, 14.2 per 100 pt-wks)

The interpretation would be that patients randomized to the placebo group had an absolute rate of recurrence of 9.0 per 100 patient-weeks greater than those randomized to the treatment group. We are 95% confident that the true difference or excess is between 3.8 and 14.2 per 100 patient-weeks.

To assess whether there is a statistically significant association between recurrence and treatment, the z-value would be calculated as:

$$Z=\frac{21-182\times 30/541}{\sqrt{\dfrac{30\times 182\times 359}{541^2}}}=4.21855$$

which has a p-value <.001. The conclusion would be that there was a statistically significant association between recurrence and treatment group.

Formulae and Example for Stratified Person-Time Data

For stratified person-time data, the same calculations shown above for the "crude" table can be used for stratum-specific estimates. The notation is modified for stratified person-time data similar to that for stratified count data, where the subscript *i* is added to denote estimates from stratum *i* (see. Table 15-12).

Table 15-12. Notation for stratified person-time data.

	Exposed	Nonexposed	
Cases	a_i	b_i	m_{1i}
Person-time	n_{1i}	n_{0i}	n_i

Two different approaches for estimating the adjusted incidence rate ratio and one approach for the estimating the adjusted incidence rate difference is provided. In addition, tests for interaction are described.

Directly Adjusted Incidence Rate Ratio

Point estimate:

$$\hat{IRR}_{Direct} = \exp\left[\frac{\sum_{i=1}^{s} w_i \ln(\hat{IRR}_i)}{\sum_{i=1}^{s} w_i}\right]$$

where

$$\hat{IRR}_i = \frac{\frac{a_i}{n_{1i}}}{\frac{b_i}{n_{0i}}}$$

and

$$w_i = \frac{a_i b_i}{m_{1i}}$$

Confidence interval based on the Taylor series approach:

$$\hat{IRR}_{Direct} \exp\left(\pm \frac{Z_{1-\alpha/2}}{\sqrt{\sum_{i=1}^{s} w_i}}\right)$$

Mantel-Haenszel Adjusted Incidence Rate Ratio

Point estimate:

$$\hat{IRR}_{MH} = \frac{\sum_{i=1}^{s} \frac{a_i n_{oi}}{n_i}}{\sum_{i=1}^{s} \frac{b_i n_{1i}}{n_i}}$$

Confidence interval based on the method by Robins, Greenland, and Breslow:

$$\hat{IRR}_{MH} \exp\left(\pm Z_{1-\alpha/2} \mathrm{SE}\left[\ln \hat{IRR}_{\mathrm{MH}}\right]\right)$$

where

$$\mathrm{SE}\left[\ln I\hat{R}R_{\mathrm{MH}}\right] = \sqrt{\frac{\sum_{i=1}^{s}\left(m_{1i}n_{1i}n_{0i}\right)/n_i^2}{\left[\sum_{i=1}^{s}\frac{a_i n_{0i}}{n_i}\right]\left[\sum_{i=1}^{s}\frac{b_i n_{1i}}{n_i}\right]}}$$

Directly Adjusted Incidence Rate Difference

The directly adjusted incidence rate difference (IRD) using inverse variance weights derived from binomial variance estimates is calculated as

$$I\hat{R}D_{Direct} = \frac{\sum_{i=1}^{s} w_i I\hat{R}D_i}{\sum_{i=1}^{s} w_i}$$

where

$$w_i = \frac{1}{\frac{a_i}{n_{1i}^2} + \frac{b_i}{n_{0i}^2}}$$

and

$$I\hat{R}D_i = \frac{a_i}{n_{1i}} - \frac{b_i}{n_{0i}}$$

Confidence interval based on Taylor series approach:

$$I\hat{R}D_{Direct} \pm \frac{Z_{1-\alpha/2}}{\sqrt{\sum_{i=1}^{s} w_i}}$$

Tests for Interaction for the Incidence Rate Ratio and Incidence Rate Difference

The tests for interaction presented here are generally referred to as the "Breslow-Day test of homogeneity" and are based on a chi square test.

The test for interaction for the incidence rate ratio is:

$$\chi_{s-1}^2 = \sum_{i=1}^{s} \frac{\left[\ln\left(I\hat{R}R_i\right) - \ln\left(I\hat{R}R_{Direct}\right)\right]^2}{V\hat{a}r\left[\ln(I\hat{R}R_i)\right]}$$

where the Var[ln(IRR_i)] = 1/w_i from the direct IRR point estimate calculation.

The test for interaction for the incidence rate difference is

$$\chi^2_{s-1} = \sum_{i=1}^{s} \frac{\left[I\hat{R}D_i - I\hat{R}D_{Direct}\right]^2}{V\hat{a}r(I\hat{R}D_i)}$$

where the Var(IRD_i) = 1/w_i from the direct IRD point estimate calculation.

Summary Statistical Test of Association

An extension to the single table statistic for stratified tables is:

$$Z = \frac{\sum_{i=1}^{s} a_i - \sum_{i=1}^{s} n_{1i} m_{1i} / n_i}{\sqrt{\sum_{i=1}^{s} \frac{m_{1i} n_{1i} n_{0i}}{n_i^{\ 2}}}}$$

An example of stratified person-time data are shown in Table 15-13. The calculations of the adjusted incidence rate ratios and rate difference are provided below.

Table 15-13. Example data 3: Stratified person-time data.

Male

	Placebo	Treated	
Recurrence	10	4	14
Pt-wks	53	245	298

Female

	Placebo	Treated	
Recurrence	11	5	16
Pt-wks	129	114	243

To calculate the **directly adjusted incidence rate ratio**, Table 15-14 is completed.

Table 15-14. Calculations for computing directly adjusted incidence rate ratio

Stratum	IRRi	ln(IRR_i)	w_i	w_i ln(IRR_i)
1	11.557	2.44726	2.85714	6.99216
2	1.944	0.66484	3.43750	2.28539
Sum			6.29464	9.27755

The calculated point estimate is:

$$I\hat{R}R_{Direct} = \exp\left[\frac{9.27755}{6.29464}\right] = 4.36615$$

The 95% confidence interval is:

$$4.36615\exp\left(\pm\frac{1.96}{\sqrt{6.29464}}\right)=4.36615\exp(\pm.78122)$$

(1.99903, 9.53626)

The conclusion would be that those receiving the placebo had a rate of recurrence 4.4 times greater than the treatment group. However, we need to assure there is no interaction using the **test for interaction for the incidence rate ratio**. First, you will need to calculate the natural log of the IRR_{direct} value, and remember that the variance = $1/w_i$:

$$\chi^2_{s-1}=\frac{[2.44726-1.47388]^2}{.35000}+\frac{[.66484-1.47388]^2}{.29091}$$
$$\chi^2_{s-1}=2.70705+2.24999=4.95704$$

This chi square value has a p-value of .026, which would indicate that there is statistically significant effect modification. It appears that the relationship between treatment groups and recurrence of disease is much stronger in males (IRR_m=11.6) than females (IRR_f=1.9).

To calculate the **Mantel-Haenzsel adjusted incidence rate ratio** (IRR_{MH}), Table 15-15 is completed.

Table 15-15. Calculations for computing the Mantel-Haenszel Incidence rate ratio

Stratum	$A_i n_{0i}/n_i$	$b_i n_{1i}/n_i$	$(m_{1i}n_{1i}n_{0i})/n_i^2$
1	8.22148	.71141	2.04709
2	5.16049	2.65432	3.98476
Sum	13.38197	3.36573	6.03185

The point estimate is

$$I\hat{R}R_{MH}=\frac{13.38197}{3.36573}=3.97595$$

To calculate the 95% confidence interval we will first calculate the standard error of the estimate:

$$SE\left[\ln I\hat{R}R_{MH}\right]=\sqrt{\frac{6.03185}{13.38197*3.36573}}=.36595$$

The 95% confidence interval is calculated as:

$$3.97595\exp(\pm1.96[.36595])=3.97595\exp(\pm.71726)$$
(1.94061, 8.14516)

The above show the calculations for the IRR_{MH}, however, because there is a statistically significant interaction (as described for the calculations for the IRR_{direct}), an adjusted value should not be presented.

Calculation of the **directly adjusted incidence rate difference** and its 95% confidence interval is as follows, starting with Table 15-16.

Table 15-16. Calculations for computing the direct adjusted incidence rate difference

Stratum	IRD_i	w_i	$w_i\ IRD_i$
1	.17235	275.73849	47.52353

2	.04141	956.24991	39.59831
Sum		1231.98840	87.12184

The point estimate is:

$$I\hat{R}D_{Direct} = \frac{87.12184}{1231.9884} = .07072$$

or 7.1 cases per 100 patient days, and the 95% confidence interval is:

$$.07072 \pm \frac{1.96}{\sqrt{1231.9884}} = .07072 \pm .05584$$

(.01488, .12656) or, per 100 patient days, (1.5, 12.7)

The **test for interaction for incidence rate difference** would be:

$$\chi^2_{s-1} = \frac{[0.17235 - .07072]^2}{.00363} + \frac{[0.04141 - .07072]^2}{.00105} =$$

$$\chi^2_{s-1} = 2.84536 + .81817 = 3.66353$$

The chi square value of 3.66353 with one degree of freedom would have a p-value of .055, which would *not* be statistically significant. The next step would be to determine whether mother's education confounds the sex-anemia relationship. The adjusted incidence rate difference was 7.1 cases per 100 patient days and the crude value was 9.0 cases per 100 patient days. Because there is a 26% difference between the crude and adjusted values, the adjusted value should be used.

The **summary statistical test** which could be used if it had been decided that there was no statistically significant interaction would be calculated as shown in Table 15-17.

Table 15-17. Calculations for computing the summary statistic

Stratum	**a_i**	**$n_{1i}m_{1i}/n_i$**	**$n_{1i}m_{1i}n_{0i}/ n_i^2$**
1	10	2.48993	2.04709
2	11	8.49383	3.98476
Sum	21	10.98376	6.03185

$$Z = \frac{21 - 10.98376}{\sqrt{6.03185}} = 4.07830$$

which has a p-value of <.001. The interpretation would be, if there is no interaction, that there is a statistically significant association between recurrence and treatment group controlling for the sex of the individual.

Table 15-18. Notation used in Chapter 15

$\hat{R}_e$	Estimated risk in the exposed group
$\hat{R}_u$	Estimated risk in the *un*exposed group
$\hat{R}R$	Estimated risk ratio

ln	Natural log
Exp	Exponentiate, or *e* to the power
$\hat{Var}$	Estimated variance
$\hat{RD}$	Estimated risk difference
$\hat{OR}$	Estimated Odds ratio
$\hat{PR}$	Estimated prevalence ratio; only difference between the risk and prevalence ratio is that the former is based on risk and the latter on prevalence
$\hat{PD}$	Estimate of the prevalence difference
$P\hat{OR}$	Estimate of the prevalence odds ratio
I	Subscript *i*, represents the ith stratum
$\sum_{i=1}^{s}$	Summation; add or sum across strata starting with stratum no. 1 through *s* strata; if there are 2 strata then *s* = 2
S	Subscript *s*, the number of strata
w_i	Weight for the *i*th stratum
Direct	Subscript for directly adjusted values
MH	Subscript for Mantel-Haenszel adjusted values
SE	Standard error
χ^2_{s-1}	Chi square value with *s*-1 degrees of freedom
$I\hat{R}R$	Estimate of the incidence rate ratio
$IR\hat{D}$	Estimate of the incidence rate difference

SUMMARY

This chapter provides the formulae and examples of how to calculate adjusted epidemiologic parameters with their confidence interval and tests for interaction. The notation used in this chapter is summarized in Table 15-18.