Measures of Association - Stratified Samples

1 Prospective Studies - Relative Risks

Here we summarize various means of combining relative risks from various studies/strata. Using the following notation for table i:

outcome/condition	Exposed	Unexposed	Total
Success	A_i	B_i	S_i
Failure	C_i	D_i	F_i
Total	E_i	U_i	N_i

Whenever possible, the weights will be given with respect to the actual association measure (relative risk) as well as the individual risk measures for the two groups.

Using this notation, the table specific relative risks can be written as follows:

$$RR_i = \frac{\frac{A_i}{E_i}}{\frac{B_i}{U_i}} = \frac{A_i U_i}{B_i E_i}$$

1.1 Combining Results from Clinical Trials (DerSimonian and Laird, 1986)

Without explicitly describing the full method for relative risks (they illustrate with differences in proportions, and give some detail to odds ratios), this is how their method would apply:

They (presumably) would use the log(Relative Risk) with the sample variance, as follows:

$$y_i = ln\left(\frac{A_i/E_i}{B_i/U_i}\right) \qquad s_i^2 = \frac{1-(A_i/E_i)}{A_i} + \frac{1-(B_i/U_i)}{B_i} \qquad w_i = \frac{1}{s_i^2}$$

From this, a Q statistic is obtained:

$$Q = \sum_i w_i (y_i - \overline{y}_w)^2 \qquad \overline{y}_w = \frac{\sum w_i y_i}{\sum w_i}$$

Their weighted least squares estimator of the mean effect is:

$$\mu_w = \frac{\sum w_i^* y_i}{\sum w_i^*} \qquad w_i^* = \frac{1}{s_i^2 + \Delta_w^2} \qquad \Delta_w^2 = max\left\{0, \frac{Q_w - (k-1)}{\sum w_i - \left(\frac{\sum w_i^2}{\sum w_i}\right)}\right\}$$

The asymptotic standard error of their estimator is:

$$SE(\mu_w) = \left(\sum w_i^*\right)^{-1/2}$$

This corresponds to the noniterative procedure with weights to reflect unequal variances.

1.2 Mantel-Haenszel Estimator - (Rothman and Greenland, 1998, p. 271)

$$\hat{RR}_{MH} = \frac{\sum_i \frac{A_i U_i}{N_i}}{\sum_i \frac{B_i E_i}{N_i}}$$

$$\hat{V}\left[ln\left(\hat{RR}_{MH}\right)\right] = \frac{\sum_i\left(\frac{S_iE_iU_i}{N_i^2} - \frac{A_iB_i}{N_i}\right)}{\left(\sum_i\frac{A_iU_i}{N_i}\right)\left(\sum_i\frac{B_iE_i}{N_i}\right)}$$

In terms of the table specific relative risks, this can be written:

$$\hat{RR}_{MH} = \sum_i \frac{\frac{E_iB_i}{N_i}\left(\frac{A_iU_i}{B_iE_i}\right)}{\sum_j\frac{E_jB_j}{N_j}} = \sum_i u_i^{MH}\hat{RR}_i$$

$$u_i^{MH} = \frac{\frac{E_iB_i}{N_i}}{\sum_j\frac{E_jB_j}{N_j}}$$

Note that the weight is proportional to the product of the fraction of exposed subjects in study times the count of successes among the unexposed.

In terms of the individual exposure group risks:

$$\hat{RR}_{MH} = \frac{\sum_i w_i^{MH}\left(\frac{A_i}{E_i}\right)}{\sum_i w_i^{MH}\left(\frac{B_i}{U_i}\right)}$$

$$w_i^{MH} = \frac{\frac{E_iU_i}{N_i}}{\sum_j\frac{E_jU_j}{N_j}}$$

Note that the weight is proportional to the product of the exposure group sizes divided by the total in the strata.

1.3 Standardized Mortality Ratio (Miettinen 1972)

$$\hat{RR}_{SMR} = \frac{\sum_i A_i}{\sum_i\frac{B_iE_i}{U_i}}$$

Assuming Poisson sampling (E_i and U_i are cumulative exposures): (**at least I found this somewhere**)

$$\hat{V}\left[ln\left(\hat{RR}_{SMR}\right)\right] = \frac{\sum_i\frac{E_i^2A_i}{S_i^2}}{\left(\sum_i\frac{E_iA_i}{S_i}\right)^2} + \frac{\sum_i\frac{E_i^2C_i}{F_i^2}}{\left(\sum_i\frac{E_iC_i}{F_i}\right)^2}$$

Assuming Binomial sampling (E_i and U_i are counts of individuals):

$$\hat{V}\left[ln\left(\hat{RR}_{SMR}\right)\right] = \frac{\sum_i\frac{A_iC_i}{E_i-1}}{\left(\sum_i A_i\right)^2} + \frac{\sum_i\frac{E_i^2B_iD_i}{U_i^2(U_i-1)}}{\left(\sum_i\frac{B_iE_i}{U_i}\right)^2}$$

In terms of the table specific relative risks, this can be written:

$$\hat{RR}_{SMR} = \sum_i \frac{\frac{E_iB_i}{U_i}\left(\frac{A_iU_i}{B_iE_i}\right)}{\sum_j\frac{E_jB_j}{U_j}} = \sum_i u_i^{SMR}\hat{RR}_i$$

$$u_i^{SMR} = \frac{\frac{E_iB_i}{U_i}}{\sum_j\frac{E_jB_j}{U_j}}$$

Note that the weight is proportional to the expected number of exposed successes assuming no association between exposure and outcome.

In terms of the individual exposure group risks:

$$\hat{RR}_{SMR} = \frac{\sum_i w_i^{SMR}\left(\frac{A_i}{E_i}\right)}{\sum_i w_i^{SMR}\left(\frac{B_i}{U_i}\right)}$$

$$w_i^{SMR} = \frac{E_i}{\sum_j E_j}$$

Note that the weight is proportional to the the number exposed in the strata.

1.4 Standardized Risk Ratio (Miettinen 1972)

$$\hat{RR}_{SRR} = \frac{\sum_i \frac{A_i U_i}{E_i}}{\sum_i \frac{U_i B_i}{U_i}} = \frac{\sum_i \frac{U_i A_i}{E_i}}{\sum_i B_i}$$

$$\hat{V}\left[ln\left(\hat{RR}_{SRR}\right)\right] = \frac{\frac{\sum_i \frac{S_i^2 A_i C_i}{E_i^2(E_i-1)}}{\left(\sum_i S_i\right)^2}}{\left(\frac{\sum_i \frac{S_i A_i}{E_i}}{\sum_i S_i}\right)^2} + \frac{\frac{\sum_i \frac{S_i^2 B_i D_i}{U_i^2(U_i-1)}}{\left(\sum_i S_i\right)^2}}{\left(\frac{\sum_i \frac{S_i B_i}{U_i}}{\sum_i S_i}\right)^2}$$

In terms of the table specific relative risks, this can be written:

$$\hat{RR}_{SRR} = \sum_i \frac{B_i\left(\frac{A_i U_i}{B_i E_i}\right)}{\sum_j B_j} = \sum_i u_i^{SRR}\hat{RR}_i$$

$$u_i^{SRR} = \frac{B_i}{\sum_j B_j}$$

Note that the weight is proportional to the observed number of unexposed successes.

In terms of the individual exposure group risks:

$$\hat{RR}_{SRR} = \frac{\sum_i w_i^{SRR}\left(\frac{A_i}{E_i}\right)}{\sum_i w_i^{SRR}\left(\frac{B_i}{U_i}\right)}$$

$$w_i^{SRR} = \frac{U_i}{\sum_j U_j}$$

Note that the weight is proportional to the the number unexposed in the strata.

2 Retrospective Studies - Odds Ratios

Here we summarize various means of combining odds ratios from various studies/strata. Using the following notation for table i:

outcome/condition	Exposed	Unexposed	Total
Success (Case)	A_i	B_i	S_i
Failure (Control)	C_i	D_i	F_i
Total	E_i	U_i	N_i

Whenever possible, the weights will be given with respect to the actual association measure (odds ratio) as well as the individual risk measures for the two groups.

Using this notation, the table specific relative risks can be written as follows:

$$OR_i = \frac{\frac{A_i}{C_i}}{\frac{B_i}{D_i}} = \frac{A_i D_i}{B_i C_i}$$

2.1 Combining Results from Clinical Trials (DerSimonian and Laird, 1986)

For the odds ratio, DerSimonian and Laird combine the individual odds ratios as follows:

They use the log(odds ratio) with the sample variance, as follows:

$$y_i = ln\left(\frac{A_i D_i}{B_i C_i}\right) \qquad s_i^2 = \frac{E_i}{A_i C_i} + \frac{U_i}{B_i D_i} \qquad w_i = \frac{1}{s_i^2}$$

From this, a Q statistic is obtained:

$$Q = \sum_i w_i (y_i - \overline{y}_w)^2 \qquad \overline{y}_w = \frac{\sum w_i y_i}{\sum w_i}$$

Their weighted least squares estimator of the mean effect is:

$$\mu_w = \frac{\sum w_i^* y_i}{\sum w_i^*} \qquad w_i^* = \frac{1}{s_i^2 + \Delta_w^2} \qquad \Delta_w^2 = max\left\{0, \frac{Q_w - (k-1)}{\sum w_i - \left(\frac{\sum w_i^2}{\sum w_i}\right)}\right\}$$

The asymptotic standard error of their estimator is:

$$SE(\mu_w) = \left(\sum w_i^*\right)^{-1/2}$$

This corresponds to the noniterative procedure with weights to reflect unequal variances.

2.2 Mantel-Haenszel Estimator - (Mantel and Haenszel, 1959)

$$\hat{OR}_{MH} = \frac{\sum_i \frac{A_i D_i}{N_i}}{\sum_i \frac{B_i C_i}{N_i}}$$

Two estimators of the variance are as follow:

Hauck's method (1979):

$$\hat{V}\left[ln\left(\hat{OR}_{MH}\right)\right] = \frac{\left(\frac{B_i}{U_i}\right)\left(\frac{C_i}{E_i}\right)}{\frac{1}{U_i} + \frac{1}{E_i}}$$

Robins, Greeenland, and Breslow method (1986):

$$\hat{V}\left[ln\left(\hat{OR}_{MH}\right)\right] = \frac{\sum_i \left(\frac{A_i D_i}{N_i}\right)\left(\frac{A_i + D_i}{N_i}\right)}{2\left[\sum_i \frac{A_i D_i}{N_i}\right]^2} + \frac{\sum_i \left[\left(\frac{A_i D_i}{N_i}\right)\left(\frac{B_i + C_i}{N_i}\right) + \left(\frac{B_i C_i}{N_i}\right)\left(\frac{A_i + D_i}{N_i}\right)\right]}{2\left[\sum_i \frac{A_i D_i}{N_i}\right]\left[\sum_i \frac{B_i C_i}{N_i}\right]} + \frac{\sum_i \left(\frac{B_i C_i}{N_i}\right)\left(\frac{B_i + C_i}{N_i}\right)}{2\left[\sum_i \frac{B_i C_i}{N_i}\right]^2}$$

In terms of the table specific odds ratios, this can be written:

$$\hat{OR}_{MH} = \sum_i \frac{\frac{B_i C_i}{N_i}\left(\frac{A_i D_i}{B_i C_i}\right)}{\sum_j \frac{B_j C_j}{N_j}} = \sum_i u_i^{MH} \hat{OR}_i$$

$$u_i^{MH} = \frac{\frac{B_i C_i}{N_i}}{\sum_j \frac{B_j C_j}{N_j}}$$

Note that the weight is proportional to the product of the unexposed successes and exposed failures divided by the overall sample size.

In terms of the individual outcome group odds:

$$\hat{OR}_{MH} = \frac{\sum_i w_i^{MH} \left(\frac{A_i}{B_i}\right)}{\sum_i w_i^{MH} \left(\frac{C_i}{D_i}\right)}$$

$$w_i^{MH} = \frac{\frac{B_i D_i}{N_i}}{\sum_j \frac{B_j D_j}{N_j}}$$

Note that the weight is proportional to the product of the numbers of unexposed successes (cases) and failures (controls) divided by the total in the strata.

2.3 Standardized Mortality Ratio (Miettinen 1972)

$$\hat{OR}_{SMR} = \frac{\sum_i A_i}{\sum_i \frac{B_i C_i}{D_i}}$$

Assuming Binomial sampling (S_i and F_i are counts of individuals):

$$\hat{V}\left[ln\left(\hat{OR}_{SMR}\right)\right] = \frac{1}{\sum_i A_i} + \frac{\sum_i \left[\left(\frac{B_i C_i}{D_i}\right)^2 \left(\frac{1}{B_i} + \frac{1}{C_i} + \frac{1}{D_i}\right)\right]}{\left[\sum_i \frac{B_i C_i}{D_i}\right]^2}$$

In terms of the table specific odds ratios, this can be written:

$$\hat{OR}_{SMR} = \sum_i \frac{\frac{B_i C_i}{D_i}\left(\frac{A_i D_i}{B_i C_i}\right)}{\sum_j \frac{B_j C_j}{D_j}} = \sum_i u_i^{SMR} \hat{OR}_i$$

$$u_i^{SMR} = \frac{\frac{B_i C_i}{D_i}}{\sum_j \frac{B_j C_j}{D_j}}$$

Note that the weight is the expected number of exposed cases under the hypothesis of no association.

In terms of the individual outcome group odds:

$$\hat{OR}_{SMR} = \frac{\sum_i w_i^{SMR} \left(\frac{A_i}{B_i}\right)}{\sum_i w_i^{SMR} \left(\frac{C_i}{D_i}\right)}$$

$$w_i^{SMR} = \frac{B_i}{\sum_j B_j}$$

Note that the weight is proportional to the number of the cases (Successes) that were not exposed.

2.4 Standardized Risk Ratio (Miettinen 1972)

$$\hat{OR}_{SRR} = \frac{\sum_i B_i}{\sum_i \frac{A_i D_i}{C_i}}$$

$$\hat{V}\left[ln\left(\hat{OR}_{SRR}\right)\right] = \frac{1}{\sum_i B_i} + \frac{\sum_i \left[\left(\frac{A_i D_i}{C_i}\right)^2 \left(\frac{1}{A_i} + \frac{1}{C_i} + \frac{1}{D_i}\right)\right]}{\left[\sum_i \frac{A_i D_i}{C_i}\right]^2}$$

In terms of the table specific (inverse) odds ratios, this can be written:

$$\hat{OR}_{SRR} = \sum_i \frac{\left(\frac{A_i D_i}{C_i}\right)\left(\frac{A_i D_i}{B_i C_i}\right)}{\sum_j \frac{A_i D_i}{C_i}} = \sum_i u_i^{SRR} \hat{OR}_i^{-1}$$

$$u_i^{SRR} = \frac{\frac{A_i D_i}{C_i}}{\sum_j \frac{A_j D_j}{C_j}}$$

Note that the weight (of the inverse odds ratio) is proportional to the expected number of cases in the unexposed group under the hypothesis of no assocoaion.

In terms of the individual (inverse) exposure group risks:

$$\hat{OR}_{SRR} = \frac{\sum_i w_i^{SRR}\left(\frac{B_i}{C_i}\right)}{\sum_i w_i^{SRR}\left(\frac{D_i}{C_i}\right)}$$

$$w_i^{SRR} = \frac{A_i}{\sum_j A_j}$$

Note that the weight is proportional to number of exposed cases.