Supporting Information of

Excess Relative Risk as an Effect Measure in Case-Control Studies of Rare Diseases

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S1 Exhibit. Optimal weighting systems and variance formulas for excess relative risk (ERR), population attributable fraction (PAF) and attributable fraction among the exposed population (AFE).

Let \( \hat{A} \) and \( \hat{B} \) denote the \( L \times 2 \) matrices, the \((s,e)\)-th elements of which being the sample proportions of subjects with \( S = s \) and \( E = e \) in the case \((\hat{a}_{s,e})\) and the control \((\hat{b}_{s,e})\) groups, respectively. Assuming that the cells counts are distributed according to two independent multinomial distributions (one for the cases and the other, the controls), the asymptotic variance-covariance matrices (of dimension, \( 2L \times 2L \)) are

\[
\text{Var} \hat{A} = \text{Var}(\text{vec} \hat{A}) = \frac{1}{n_1} \times \left[ \text{Diag}(\text{vec} \hat{A}) - (\text{vec} \hat{A})(\text{vec} \hat{A})' \right],
\]

\[
\text{Var} \hat{B} = \text{Var}(\text{vec} \hat{B}) = \frac{1}{n_2} \times \left[ \text{Diag}(\text{vec} \hat{B}) - (\text{vec} \hat{B})(\text{vec} \hat{B})' \right],
\]

and

\[
\text{Cov}(\hat{A}, \hat{B}) = 0,
\]

respectively.

Let \( \hat{\theta}, \hat{\psi}, \) and \( \hat{\phi} \) be \( L \times 1 \) vectors, with the \( s \)th element of which being

\[
\hat{\theta}_s = \left(\frac{a_{s,1} - a_{s,2}}{b_{s,1} - b_{s,2}}\right) \times \frac{b_{s,2}}{a_{s,2}},
\]

\[
\hat{\psi}_s = \left(\frac{a_{s,1} - a_{s,2}}{b_{s,1} - b_{s,2}}\right) \times b_{s,1},
\]

and

\[
\hat{\phi}_s = \left(\frac{a_{s,1} - a_{s,2}}{b_{s,1} - b_{s,2}}\right) \times \frac{b_{s,1}}{a_{s,1}},
\]

respectively. Their variance-covariance matrices can be obtained using the multivariate delta
method:

\[ \text{Var} \hat{\theta} = \left( \frac{\partial \hat{\theta}}{\partial \mathbf{A}} \right) (\text{Var} \; \hat{\mathbf{A}}) \left( \frac{\partial \hat{\theta}}{\partial \mathbf{B}} \right) (\text{Var} \; \hat{\mathbf{B}}), \]

\[ \text{Var} \hat{\psi} = \left( \frac{\partial \hat{\psi}}{\partial \mathbf{A}} \right) (\text{Var} \; \hat{\mathbf{A}}) \left( \frac{\partial \hat{\psi}}{\partial \mathbf{B}} \right) (\text{Var} \; \hat{\mathbf{B}}), \]

and

\[ \text{Var} \hat{\phi} = \left( \frac{\partial \hat{\phi}}{\partial \mathbf{A}} \right) (\text{Var} \; \hat{\mathbf{A}}) \left( \frac{\partial \hat{\phi}}{\partial \mathbf{B}} \right) (\text{Var} \; \hat{\mathbf{B}}), \]

respectively. Here the differentiation of a vector with respect to a matrix follows the convention:

\[ \frac{\partial \mathbf{y}}{\partial \mathbf{X}} = \frac{\partial \mathbf{y}^t}{\partial (\text{vec} \; \mathbf{X})} \]

and has a dimension of \( 2L \times L \).

Let \( \text{I}_\text{statement} \) be an indicator function with a value of 1, if the statement is true, and 0, if otherwise. For \( i \in \{1,...,L\} \), \( j \in \{1,2\} \), and \( k \in \{1,...,L\} \), the \((i + L \times j - L, k)\)-th elements of the derivative matrices are

\[
\left( \frac{I_{(i=k,j=1)}}{b_{k,1}} - \frac{I_{(i=k,j=2)}}{b_{k,2}} - \frac{I_{(j=2)} \times \hat{\theta}_k}{b_{r,2}} \right) \times \frac{b_{r,2}}{a_{r,2}} \quad \text{for} \quad \frac{\partial \hat{\theta}}{\partial \mathbf{A}},
\]

\[
\frac{I_{(j=2)} \times \hat{\theta}_k}{b_{r,2}} \left( \frac{I_{(i=k,j=1)}}{b_{k,1}^2} - \frac{I_{(i=k,j=2)}}{b_{k,2}^2} \right) \times \frac{b_{r,2}}{a_{r,2}} \quad \text{for} \quad \frac{\partial \hat{\theta}}{\partial \mathbf{B}},
\]

\[
\left( \frac{I_{(i=k,j=1)}}{b_{k,1}} - \frac{I_{(i=k,j=2)}}{b_{k,2}} \right) \times b_{r,1} \quad \text{for} \quad \frac{\partial \hat{\psi}}{\partial \mathbf{A}},
\]

\[
\frac{I_{(j=1)} \times \hat{\psi}_k}{b_{r,1}} \left( \frac{I_{(i=k,j=1)}}{b_{k,1}^2} - \frac{I_{(i=k,j=2)}}{b_{k,2}^2} \right) \times b_{r,1} \quad \text{for} \quad \frac{\partial \hat{\psi}}{\partial \mathbf{B}},
\]

\[
\left( \frac{I_{(i=k,j=1)}}{b_{k,1}} - \frac{I_{(i=k,j=2)}}{b_{k,2}} - \frac{I_{(j=1)} \times \hat{\phi}_k}{b_{r,1}} \right) \times \frac{b_{r,1}}{a_{r,1}} \quad \text{for} \quad \frac{\partial \hat{\phi}}{\partial \mathbf{A}},
\]

and
\[
\frac{I_{(j=1)} \times \hat{\phi}_k}{b_{i,1}} - \left( \frac{I_{(i=k,j=1)} \times a_{k,1}}{b_{k,1}^2} - \frac{I_{(i=k,j=2)} \times a_{k,2}}{b_{k,2}^2} \right) \times \frac{b_{n,1}}{a_{n,1}} \quad \text{for} \quad \frac{\partial \phi}{\partial B},
\]
respectively.

The estimates for ERR, PAF and AFE are

\[
\hat{\text{ERR}} = w^\prime \hat{\theta},
\]
\[
\hat{\text{PAF}} = u^\prime \hat{\psi},
\]
and

\[
\hat{\text{AFE}} = v^\prime \hat{\phi},
\]
respectively, with the weighting vectors subject to \( w^\prime 1 = u^\prime 1 = v^\prime 1 = 1 \), where \( 1 \) is the summing vector (a ‘1’ for each and every element). Using the extended Cauchy-Schwarz inequality (see Johnson RA, Wichern DW. Applied Multivariate Statistical Analysis. 3rd ed. New Jersey: Prentice-Hall International; 1992), the variances are

\[
\text{Var}(\hat{\text{ERR}}) = w^\prime \left( \text{Var} \, \hat{\theta} \right) w \geq \frac{1}{1^t \left( \text{Var} \, \hat{\theta} \right)^{-1} 1},
\]
\[
\text{Var}(\hat{\text{PAF}}) = u^\prime \left( \text{Var} \, \hat{\psi} \right) u \geq \frac{1}{1^t \left( \text{Var} \, \hat{\psi} \right)^{-1} 1},
\]
and

\[
\text{Var}(\hat{\text{AFE}}) = v^\prime \left( \text{Var} \, \hat{\phi} \right) v \geq \frac{1}{1^t \left( \text{Var} \, \hat{\phi} \right)^{-1} 1},
\]

with equalities if and only if

\[
w = \frac{\left( \text{Var} \, \hat{\theta} \right)^{-1} 1}{1^t \left( \text{Var} \, \hat{\theta} \right)^{-1} 1}, \quad u = \frac{\left( \text{Var} \, \hat{\psi} \right)^{-1} 1}{1^t \left( \text{Var} \, \hat{\psi} \right)^{-1} 1}, \quad \text{and} \quad v = \frac{\left( \text{Var} \, \hat{\phi} \right)^{-1} 1}{1^t \left( \text{Var} \, \hat{\phi} \right)^{-1} 1},
\]
respectively.