Standard errors of probabilities, RR and RD estimations using a logistic MSM

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1) Introduction

The `ltmleMSM` function from the `ltmle` package estimates parameters of a working Marginal Structural Model (MSM). The MSM is a logistic regression from which OR estimates can be easily calculated using the exponential of the estimated coefficients.

Applying delta method, it is possible to estimate relative risks and risk diffenrences from the same logistic regression MSM.

In order to estimate the marginal interaction effect between two binary exposures A_1 and A_2, the following MSM is applied:

$$\text{logit} m_\beta(A_1, A_2) = \ln \frac{P\left(Y_{A_1,A_2} = 1\right)}{P\left(Y_{A_1,A_2} = 0\right)} = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 (A_1 \times A_2)$$

For given values $A_1 = a_1$ and $A_2 = a_2$, we note the predicted probability:

$$m_\beta(a_1, a_2) = \frac{\exp\left(\beta_0 + \beta_1 a_1 + \beta_2 a_2 + \beta_3 (a_1 \times a_2)\right)}{1 + \exp\left(\beta_0 + \beta_1 a_1 + \beta_2 a_2 + \beta_3 (a_1 \times a_2)\right)}$$

We also note:

$$e_{a_1,a_2} = \exp\left(-\beta_0 - \beta_1 a_1 - \beta_2 a_2 - \beta_3 (a_1 \times a_2)\right)$$

so that:

$$m_\beta(a_1, a_2) = \frac{1}{1 + e_{a_1,a_2}}$$

and

$$\begin{aligned}
P\left(Y_{A_1=0,A_2=0} = 1\right) &= m_\beta(0,0) = \frac{1}{1 + \exp(-\beta_0)} = \frac{1}{1 + e_{00}} \\
P\left(Y_{A_1=1,A_2=0} = 1\right) &= m_\beta(1,0) = \frac{1}{1 + \exp(-\beta_0 - \beta_1)} = \frac{1}{1 + e_{10}} \\
P\left(Y_{A_1=0,A_2=1} = 1\right) &= m_\beta(0,1) = \frac{1}{1 + \exp(-\beta_0 - \beta_2)} = \frac{1}{1 + e_{01}} \\
P\left(Y_{A_1=1,A_2=1} = 1\right) &= m_\beta(1,1) = \frac{1}{1 + \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3)} = \frac{1}{1 + e_{11}}
\end{aligned}$$

For a given function $f(\beta)$ of the $\beta = \{\beta_0, \beta_1, \beta_2, \beta_3\}$ coefficients such as $m_\beta(a_1, a_2)$, by Delta method, the variance of $f(\beta)$ can be calculed by:

$$var\left[f(\beta)\right] = \left(\frac{\partial f(\beta)}{\partial \beta}\right)^T var(\beta) \left(\frac{\partial f(\beta)}{\partial \beta}\right)$$

where $var(\beta)$ is a 4×4 covariance matrix, that can be estimated using the variance of the influence curve (`IC`) of the MSM coefficients given in the output values of the `ltmleMSM` function, divided by the sample size: `var(IC) / n`.

2) Standard errors of point estimates of the probabilities of interest

2.1) Standard error of $P\left(Y_{A_1=0,A_2=0} = 1\right) = m_\beta(0,0)$

$$m_\beta(0,0) = \frac{1}{1+e_{00}}, \text{ where } e_{00} = \exp(-\beta_0)$$

The partial derivative of $f(\beta) = m_\beta(0,0)$ with respect to β is:

$$\left(\frac{\partial m_\beta(0,0)}{\partial \beta}\right) = \frac{-\left(\frac{\partial e_{00}}{\partial \beta}\right)}{(1+e_{00})^2}$$

where $\left(\frac{\partial e_{00}}{\partial \beta_0}\right) = -e_{00}$ and $\left(\frac{\partial e_{00}}{\partial \beta_1}\right) = \left(\frac{\partial e_{00}}{\partial \beta_2}\right) = \left(\frac{\partial e_{00}}{\partial \beta_3}\right) = 0$.

$$\begin{aligned}\left(\frac{\partial m_\beta(0,0)}{\partial \beta_0}\right) &= \frac{-(-e_{00})}{(1+e_{00})^2} = \frac{1+e_{00}-1}{(1+e_{00})} \times \frac{1}{1+e_{00}} \\ &= [1-m_\beta(0,0)] \times m_\beta(0,0)\end{aligned}$$

$$\left(\frac{\partial m_\beta(0,0)}{\partial \beta}\right) = \begin{pmatrix} \left(\frac{\partial m_\beta(0,0)}{\partial \beta_0}\right) \\ \left(\frac{\partial m_\beta(0,0)}{\partial \beta_1}\right) \\ \left(\frac{\partial m_\beta(0,0)}{\partial \beta_2}\right) \\ \left(\frac{\partial m_\beta(0,0)}{\partial \beta_3}\right) \end{pmatrix} = \begin{pmatrix} [1-m_\beta(0,0)] \times m_\beta(0,0) \\ \frac{-0}{(1+e_{00})^2} \\ \frac{-0}{(1+e_{00})^2} \\ \frac{-0}{(1+e_{00})^2} \end{pmatrix} = \begin{pmatrix} [1-m_\beta(0,0)] \times m_\beta(0,0) \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

The variance of $m_\beta(0,0)$ can then be calculated by:

$$var\left(m_\beta(0,0)\right) = \begin{pmatrix} [1-m_\beta(0,0)] \times m_\beta(0,0) \\ 0 \\ 0 \\ 0 \end{pmatrix}^T \times \frac{var(IC)}{n} \times \begin{pmatrix} [1-m_\beta(0,0)] \times m_\beta(0,0) \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

2.2) Standard error of $P\left(Y_{A_1=1,A_2=0}=1\right)=m_\beta(1,0)$

$$m_\beta(1,0)=\frac{1}{1+e_{10}},\text{ where } e_{10}=\exp(-\beta_0-\beta_1)$$

The partial derivative of $f(\beta)=m_\beta(1,0)$ with respect to β is:

$$\left(\frac{\partial m_\beta(1,0)}{\partial\beta}\right)=\frac{-\left(\frac{\partial e_{10}}{\partial\beta}\right)}{(1+e_{10})^2}$$

where $\left(\frac{\partial e_{10}}{\partial\beta_0}\right)=\left(\frac{\partial e_{10}}{\partial\beta_1}\right)=-e_{10}$ and $\left(\frac{\partial e_{10}}{\partial\beta_2}\right)=\left(\frac{\partial e_{10}}{\partial\beta_3}\right)=0$.

$$\begin{aligned}\left(\frac{\partial m_\beta(1,0)}{\partial\beta_0}\right)=\left(\frac{\partial m_\beta(1,0)}{\partial\beta_1}\right)&=\frac{-(-e_{10})}{(1+e_{10})^2}=\frac{1+e_{10}-1}{(1+e_{10})}\times\frac{1}{1+e_{10}}\\&=[1-m_\beta(1,0)]\times m_\beta(1,0)\end{aligned}$$

$$\left(\frac{\partial m_\beta(1,0)}{\partial\beta}\right)=\begin{pmatrix}[1-m_\beta(1,0)]\times m_\beta(1,0)\\ [1-m_\beta(1,0)]\times m_\beta(1,0)\\ \frac{-0}{(1+e_{10})^2}\\ \frac{-0}{(1+e_{10})^2}\end{pmatrix}=\begin{pmatrix}[1-m_\beta(1,0)]\times m_\beta(1,0)\\ [1-m_\beta(1,0)]\times m_\beta(1,0)\\ 0\\ 0\end{pmatrix}$$

The variance of $m_\beta(1,0)$ can then be calculated by:

$$var\left(m_\beta(1,0)\right)=\begin{pmatrix}[1-m_\beta(1,0)]\times m_\beta(1,0)\\ [1-m_\beta(1,0)]\times m_\beta(1,0)\\ 0\\ 0\end{pmatrix}^T\times\frac{var(IC)}{n}\times\begin{pmatrix}[1-m_\beta(1,0)]\times m_\beta(1,0)\\ [1-m_\beta(1,0)]\times m_\beta(1,0)\\ 0\\ 0\end{pmatrix}$$

2.3) Standard error of $P\left(Y_{A_1=0,A_2=1}=1\right)=m_\beta(0,1)$

$$m_\beta(0,1)=\frac{1}{1+e_{01}}, \text{ where } e_{01}=\exp(-\beta_0-\beta_2)$$

The partial derivative of $f(\beta)=m_\beta(0,1)$ with respect to β is:

$$\left(\frac{\partial m_\beta(0,1)}{\partial\beta}\right)=\frac{-\left(\frac{\partial e_{01}}{\partial\beta}\right)}{(1+e_{01})^2}$$

where $\left(\frac{\partial e_{01}}{\partial\beta_0}\right)=\left(\frac{\partial e_{01}}{\partial\beta_2}\right)=-e_{01}$ and $\left(\frac{\partial e_{01}}{\partial\beta_1}\right)=\left(\frac{\partial e_{01}}{\partial\beta_3}\right)=0$.

$$\begin{aligned}\left(\frac{\partial m_\beta(0,1)}{\partial\beta_0}\right)=\left(\frac{\partial m_\beta(0,1)}{\partial\beta_2}\right)&=\frac{-(-e_{01})}{(1+e_{01})^2}=\frac{1+e_{01}-1}{(1+e_{01})}\times\frac{1}{1+e_{01}}\\&=[1-m_\beta(0,1)]\times m_\beta(0,1)\end{aligned}$$

$$\left(\frac{\partial m_\beta(0,1)}{\partial\beta}\right)=\begin{pmatrix}[1-m_\beta(0,1)]\times m_\beta(0,1)\\ \frac{-0}{(1+e_{01})^2}\\ [1-m_\beta(0,1)]\times m_\beta(0,1)\\ \frac{-0}{(1+e_{01})^2}\end{pmatrix}=\begin{pmatrix}[1-m_\beta(0,1)]\times m_\beta(0,1)\\ 0\\ [1-m_\beta(0,1)]\times m_\beta(0,1)\\ 0\end{pmatrix}$$

The variance of $m_\beta(0,1)$ can then be calculated by:

$$var\left(m_\beta(0,1)\right)=\begin{pmatrix}[1-m_\beta(0,1)]\times m_\beta(0,1)\\ 0\\ [1-m_\beta(0,1)]\times m_\beta(0,1)\\ 0\end{pmatrix}^T\times\frac{var(IC)}{n}\times\begin{pmatrix}[1-m_\beta(0,1)]\times m_\beta(0,1)\\ 0\\ [1-m_\beta(0,1)]\times m_\beta(0,1)\\ 0\end{pmatrix}$$

2.4) Standard error of $P\left(Y_{A_1=1,A_2=1}=1\right)=m_\beta(1,1)$

$$m_\beta(1,1)=\frac{1}{1+e_{11}},\text{ where } e_{11}=\exp(-\beta_0-\beta_1-\beta_2-\beta_3)$$

The partial derivative of $f(\beta)=m_\beta(1,1)$ with respect to β is:

$$\left(\frac{\partial m_\beta(1,1)}{\partial\beta}\right)=\frac{-\left(\frac{\partial e_{11}}{\partial\beta}\right)}{(1+e_{11})^2}$$

where $\left(\frac{\partial e_{11}}{\partial\beta_0}\right)=\left(\frac{\partial e_{11}}{\partial\beta_2}\right)=\left(\frac{\partial e_{11}}{\partial\beta_1}\right)=\left(\frac{\partial e_{11}}{\partial\beta_3}\right)=-e_{11}$.

$$\begin{aligned}\left(\frac{\partial m_\beta(1,1)}{\partial\beta_0}\right)=\left(\frac{\partial m_\beta(1,1)}{\partial\beta_1}\right)=\left(\frac{\partial m_\beta(1,1)}{\partial\beta_2}\right)=\left(\frac{\partial m_\beta(1,1)}{\partial\beta_3}\right)&=\frac{-(-e_{11})}{(1+e_{11})^2}=\frac{1+e_{11}-1}{(1+e_{11})}\times\frac{1}{1+e_{11}}\\&=[1-m_\beta(1,1)]\times m_\beta(1,1)\end{aligned}$$

$$\left(\frac{\partial m_\beta(1,1)}{\partial\beta}\right)=\begin{pmatrix}[1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\end{pmatrix}$$

The variance of $m_\beta(1,1)$ can then be calculated by:

$$var\left(m_\beta(1,1)\right)=\begin{pmatrix}[1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\end{pmatrix}^T\times\frac{var(IC)}{n}\times\begin{pmatrix}[1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\\ [1-m_\beta(1,1)]\times m_\beta(1,1)\end{pmatrix}$$

3) Standard errors of risk differences

3.1) Risk difference for the effect of A_1, setting $A_2 = 0$

$$RD_{A_1|A_2=0} = m_\beta(1,0) - m_\beta(0,0) = \frac{1}{1+e_{10}} - \frac{1}{1+e_{00}}$$

where $e_{00} = \exp(-\beta_0)$ and $e_{10} = \exp(-\beta_0 - \beta_1)$.

The partial derivative of the risk difference $m_\beta(1,0) - m_\beta(0,0)$ with respect to β is:

$$\frac{\partial}{\partial\beta}\left(m_\beta(1,0) - m_\beta(0,0)\right) = \frac{-\left(\frac{\partial e_{10}}{\partial\beta}\right)}{(1+e_{10})^2} - \frac{-\left(\frac{\partial e_{00}}{\partial\beta}\right)}{(1+e_{00})^2}$$

$$\begin{aligned}\frac{\partial}{\partial\beta_0}\left(m_\beta(1,0) - m_\beta(0,0)\right) &= \frac{-(-e_{10})}{(1+e_{10})^2} - \frac{-(-e_{00})}{(1+e_{00})^2} \\ &= [1 - m_\beta(1,0)] \times m_\beta(1,0) - [1 - m_\beta(0,0)] \times m_\beta(0,0)\end{aligned}$$

$$\frac{\partial}{\partial\beta_1}\left(m_\beta(1,0) - m_\beta(0,0)\right) = \frac{-(-e_{10})}{(1+e_{10})^2} - 0 = [1 - m_\beta(1,0)] \times m_\beta(1,0)$$

$$\text{and } \frac{\partial}{\partial\beta_2}\left(m_\beta(1,0) - m_\beta(0,0)\right) = \frac{\partial}{\partial\beta_3}\left(m_\beta(1,0) - m_\beta(0,0)\right) = 0$$

$$\frac{\partial}{\partial\beta}\left(m_\beta(1,0) - m_\beta(0,0)\right) = \begin{pmatrix} [1 - m_\beta(1,0)] \times m_\beta(1,0) - [1 - m_\beta(0,0)] \times m_\beta(0,0) \\ [1 - m_\beta(1,0)] \times m_\beta(1,0) \\ 0 \\ 0 \end{pmatrix} = \Delta$$

The variance of $RD_{A_1|A_2=0}$ can then be calculated by:

$$var\left(RD_{A_1|A_2=0}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

3.2) Risk difference for the effect of A_1, setting $A_2 = 1$

$$RD_{A_1|A_2=1} = m_\beta(1,1) - m_\beta(0,1) = \frac{1}{1+e_{11}} - \frac{1}{1+e_{01}}$$

where $e_{11} = \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3)$ and $e_{01} = \exp(-\beta_0 - \beta_2)$.

The partial derivative of the risk difference $m_\beta(1,1) - m_\beta(0,1)$ with respect to β is:

$$\frac{\partial}{\partial \beta}\left(m_\beta(1,1) - m_\beta(0,1)\right) = \frac{-\left(\frac{\partial e_{11}}{\partial \beta}\right)}{(1+e_{11})^2} - \frac{-\left(\frac{\partial e_{01}}{\partial \beta}\right)}{(1+e_{01})^2}$$

$$\begin{aligned}\frac{\partial}{\partial \beta_0}\left(m_\beta(1,1) - m_\beta(0,1)\right) &= \frac{-(-e_{11})}{(1+e_{11})^2} - \frac{-(-e_{01})}{(1+e_{01})^2} \\ &= [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(0,1)] \times m_\beta(0,1)\end{aligned}$$

$$\frac{\partial}{\partial \beta_1}\left(m_\beta(1,1) - m_\beta(0,1)\right) = \frac{-(-e_{11})}{(1+e_{11})^2} - 0 = [1 - m_\beta(1,1)] \times m_\beta(1,1)$$

$$\begin{aligned}\frac{\partial}{\partial \beta_2}\left(m_\beta(1,1) - m_\beta(0,1)\right) &= \frac{-(-e_{11})}{(1+e_{11})^2} - \frac{-(-e_{01})}{(1+e_{01})^2} \\ &= [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(0,1)] \times m_\beta(0,1)\end{aligned}$$

$$\frac{\partial}{\partial \beta_3}\left(m_\beta(1,1) - m_\beta(0,1)\right) = \frac{-(-e_{11})}{(1+e_{11})^2} - 0 = [1 - m_\beta(1,1)] \times m_\beta(1,1)$$

$$\frac{\partial}{\partial \beta}\left(m_\beta(1,1) - m_\beta(0,1)\right) = \begin{pmatrix} [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(0,1)] \times m_\beta(0,1) \\ [1 - m_\beta(1,1)] \times m_\beta(1,1) \\ [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(0,1)] \times m_\beta(0,1) \\ [1 - m_\beta(1,1)] \times m_\beta(1,1) \end{pmatrix} = \Delta$$

The variance of $RD_{A_1|A_2=1}$ can then be calculated by:

$$var\left(RD_{A_1|A_2=0}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

3.3) Risk difference for the effect of A_2, setting $A_1 = 0$

$$RD_{A_2|A_1=0} = m_\beta(0,1) - m_\beta(0,0) = \frac{1}{1+e_{01}} - \frac{1}{1+e_{00}}$$

where $e_{01} = \exp(-\beta_0 - \beta_2)$ and $e_{00} = \exp(-\beta_0)$.

The partial derivative of the risk difference $m_\beta(0,1) - m_\beta(0,0)$ with respect to β is:

$$\frac{\partial}{\partial\beta}\left(m_\beta(0,1) - m_\beta(0,0)\right) = \frac{-\left(\frac{\partial e_{01}}{\partial\beta}\right)}{(1+e_{01})^2} - \frac{-\left(\frac{\partial e_{00}}{\partial\beta}\right)}{(1+e_{00})^2}$$

$$\begin{aligned}\frac{\partial}{\partial\beta_0}\left(m_\beta(0,1) - m_\beta(0,0)\right) &= \frac{-(-e_{01})}{(1+e_{01})^2} - \frac{-(-e_{00})}{(1+e_{00})^2} \\ &= [1 - m_\beta(0,1)] \times m_\beta(0,1) - [1 - m_\beta(0,0)] \times m_\beta(0,0)\end{aligned}$$

$$\frac{\partial}{\partial\beta_1}\left(m_\beta(0,1) - m_\beta(0,0)\right) = 0$$

$$\begin{aligned}\frac{\partial}{\partial\beta_2}\left(m_\beta(0,1) - m_\beta(0,0)\right) &= \frac{-(-e_{01})}{(1+e_{01})^2} - 0 \\ &= [1 - m_\beta(0,1)] \times m_\beta(0,1)\end{aligned}$$

$$\frac{\partial}{\partial\beta_3}\left(m_\beta(0,1) - m_\beta(0,0)\right) = 0$$

$$\frac{\partial}{\partial\beta}\left(m_\beta(0,1) - m_\beta(0,0)\right) = \begin{pmatrix} [1 - m_\beta(0,1)] \times m_\beta(0,1) - [1 - m_\beta(0,0)] \times m_\beta(0,0) \\ 0 \\ [1 - m_\beta(0,1)] \times m_\beta(0,1) \\ 0 \end{pmatrix} = \Delta$$

The variance of $RD_{A_2|A_1=0}$ can then be calculated by:

$$var\left(RD_{A_2|A_1=0}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

3.4) Risk difference for the effect of A_2, setting $A_1 = 1$

$$RD_{A_2|A_1=1} = m_\beta(1,1) - m_\beta(1,0) = \frac{1}{1+e_{11}} - \frac{1}{1+e_{10}}$$

where $e_{11} = \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3)$ and $e_{10} = \exp(-\beta_0 - \beta_1)$.

The partial derivative of the risk difference $m_\beta(1,1) - m_\beta(1,0)$ with respect to β is:

$$\frac{\partial}{\partial\beta}\left(m_\beta(1,1) - m_\beta(1,0)\right) = \frac{-\left(\frac{\partial e_{11}}{\partial\beta}\right)}{(1+e_{11})^2} - \frac{-\left(\frac{\partial e_{10}}{\partial\beta}\right)}{(1+e_{10})^2}$$

$$\begin{aligned}\frac{\partial}{\partial\beta_0}\left(m_\beta(1,1) - m_\beta(1,0)\right) &= \frac{-(-e_{11})}{(1+e_{11})^2} - \frac{-(-e_{10})}{(1+e_{10})^2}\\ &= [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(1,0)] \times m_\beta(1,0)\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial\beta_1}\left(m_\beta(1,1) - m_\beta(1,0)\right) &= \frac{-(-e_{11})}{(1+e_{11})^2} - \frac{-(-e_{10})}{(1+e_{10})^2}\\ &= [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(1,0)] \times m_\beta(1,0)\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial\beta_2}\left(m_\beta(1,1) - m_\beta(1,0)\right) &= \frac{-(-e_{11})}{(1+e_{11})^2} - 0\\ &= [1 - m_\beta(1,1)] \times m_\beta(1,1)\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial\beta_3}\left(m_\beta(1,1) - m_\beta(1,0)\right) &= \frac{-(-e_{11})}{(1+e_{11})^2} - 0\\ &= [1 - m_\beta(1,1)] \times m_\beta(1,1)\end{aligned}$$

$$\frac{\partial}{\partial\beta}\left(m_\beta(1,1) - m_\beta(1,0)\right) = \begin{pmatrix}[1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(1,0)] \times m_\beta(1,0)\\ [1 - m_\beta(1,1)] \times m_\beta(1,1) - [1 - m_\beta(1,0)] \times m_\beta(1,0)\\ [1 - m_\beta(1,1)] \times m_\beta(1,1)\\ [1 - m_\beta(1,1)] \times m_\beta(1,1)\end{pmatrix} = \Delta$$

The variance of $RD_{A_2|A_1=1}$ can then be calculated by:

$$var\left(RD_{A_2|A_1=1}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

4) Standard errors of relative risks

4.1) Relative risk for the effect of A_1, setting $A_2 = 0$

Applying a log transformation of the relative risk,

$$\log RR_{A_1|A_2=0} = \log \frac{m_\beta(1,0)}{m_\beta(0,0)} = \log m_\beta(1,0) - \log m_\beta(0,0)$$

and the variance of $\log RR$ is:

$$var(\log RR) = \left(\frac{\partial \log RR}{\partial \beta}\right)^T \times var(\beta) \times \left(\frac{\partial \log RR}{\partial \beta}\right)$$

With $m_\beta = \frac{1}{1+e}$, we have: $(\log m_\beta)' = \frac{m'_\beta}{m_\beta} = \frac{-e'}{(1+e)^2} \times (1+e) = \frac{-e'}{1+e}$
where $e_{00} = \exp(-\beta_0)$ and $e_{10} = \exp(-\beta_0 - \beta_1)$.

$$\begin{aligned}\frac{\partial \log RR_{A_1|A_2=0}}{\partial \beta_0} &= \frac{-(-e_{10})}{1+e_{10}} - \frac{-(-e_{00})}{1+e_{00}} \\ &= \frac{1+e_{10}-1}{1+e_{10}} - \frac{1+e_{00}-1}{1+e_{00}} \\ &= [1 - m_\beta(1,0)] - [1 - m_\beta(0,0)] = m_\beta(0,0) - m_\beta(1,0)\end{aligned}$$

$$\begin{aligned}\frac{\partial \log RR_{A_1|A_2=0}}{\partial \beta_1} &= \frac{-(-e_{10})}{1+e_{10}} - 0 \\ &= \frac{1+e_{10}-1}{1+e_{10}} = 1 - m_\beta(1,0)\end{aligned}$$

$$\frac{\partial \log RR_{A_1|A_2=0}}{\partial \beta_2} = \frac{\partial \log RR_{A_1|A_2=0}}{\partial \beta_3} = 0$$

$$\frac{\partial \log RR_{A_1|A_2=0}}{\partial \beta} = \begin{pmatrix} m_\beta(0,0) - m_\beta(1,0) \\ 1 - m_\beta(1,0) \\ 0 \\ 0 \end{pmatrix} = \Delta$$

The variance of $\log RR_{A_1|A_2=0}$ can then be calculated by:

$$var\left(\log RR_{A_1|A_2=0}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

4.2) Relative risk for the effect of A_1, setting $A_2 = 1$

$$\log RR_{A_1|A_2=1} = \log \frac{m_\beta(1,1)}{m_\beta(0,1)} = \log m_\beta(1,1) - \log m_\beta(0,1)$$

With $m_\beta = \frac{1}{1+e}$, we have: $(\log m_\beta)' = \frac{m'_\beta}{m_\beta} = \frac{-e'}{(1+e)^2} \times (1+e) = \frac{-e'}{1+e}$

where $e_{01} = \exp(-\beta_0 - \beta_2)$ and $e_{11} = \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3)$.

$$\begin{aligned}
\frac{\partial \log RR_{A_1|A_2=1}}{\partial \beta_0} &= \frac{-(-e_{11})}{1+e_{11}} - \frac{-(-e_{01})}{1+e_{01}} \\
&= \frac{1+e_{11}-1}{1+e_{11}} - \frac{1+e_{01}-1}{1+e_{01}} \\
&= [1 - m_\beta(1,1)] - [1 - m_\beta(0,1)] = m_\beta(0,1) - m_\beta(1,1)
\end{aligned}$$

$$\begin{aligned}
\frac{\partial \log RR_{A_1|A_2=1}}{\partial \beta_1} &= \frac{-(-e_{11})}{1+e_{11}} - 0 \\
&= \frac{1+e_{11}-1}{1+e_{11}} = 1 - m_\beta(1,1)
\end{aligned}$$

$$\frac{\partial \log RR_{A_1|A_2=1}}{\partial \beta_2} = m_\beta(0,1) - m_\beta(1,1)$$

$$\begin{aligned}
\frac{\partial \log RR_{A_1|A_2=1}}{\partial \beta_3} &= \frac{-(-e_{11})}{1+e_{11}} - 0 \\
&= \frac{1+e_{11}-1}{1+e_{11}} = 1 - m_\beta(1,1)
\end{aligned}$$

$$\frac{\partial \log RR_{A_1|A_2=1}}{\partial \beta} = \begin{pmatrix} m_\beta(0,1) - m_\beta(1,1) \\ 1 - m_\beta(1,1) \\ m_\beta(0,1) - m_\beta(1,1) \\ 1 - m_\beta(1,1) \end{pmatrix} = \Delta$$

The variance of $\log RR_{A_1|A_2=1}$ can then be calculated by:

$$var\left(\log RR_{A_1|A_2=1}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

4.3) Relative risk for the effect of A_2, setting $A_1 = 0$

$$\log RR_{A_2|A_1=0} = \log \frac{m_\beta(0,1)}{m_\beta(0,0)} = \log m_\beta(0,1) - \log m_\beta(0,0)$$

With $m_\beta = \frac{1}{1+e}$, we have: $(\log m_\beta)' = \frac{m'_\beta}{m_\beta} = \frac{-e'}{(1+e)^2} \times (1+e) = \frac{-e'}{1+e}$

where $e_{01} = \exp(-\beta_0 - \beta_2)$ and $e_{00} = \exp(-\beta_0)$.

$$\begin{aligned}
\frac{\partial \log RR_{A_2|A_1=0}}{\partial \beta_0} &= \frac{-(-e_{01})}{1+e_{01}} - \frac{-(-e_{00})}{1+e_{00}} \\
&= \frac{1+e_{01}-1}{1+e_{01}} - \frac{1+e_{00}-1}{1+e_{00}} \\
&= [1 - m_\beta(0,1)] - [1 - m_\beta(0,0)] = m_\beta(0,0) - m_\beta(0,1)
\end{aligned}$$

$$\frac{\partial \log RR_{A_2|A_1=0}}{\partial \beta_1} = \frac{\partial \log RR_{A_2|A_1=0}}{\partial \beta_3} = 0$$

$$\begin{aligned}
\frac{\partial \log RR_{A_2|A_1=0}}{\partial \beta_2} &= \frac{-(-e_{01})}{1+e_{01}} - 0 \\
&= \frac{1+e_{01}-1}{1+e_{01}} = 1 - m_\beta(0,1)
\end{aligned}$$

$$\frac{\partial \log RR_{A_2|A_1=0}}{\partial \beta} = \begin{pmatrix} m_\beta(0,0) - m_\beta(0,1) \\ 0 \\ 1 - m_\beta(0,1) \\ 0 \end{pmatrix} = \Delta$$

The variance of $\log RR_{A_2|A_1=0}$ can then be calculated by:

$$var\left(\log RR_{A_2|A_1=0}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

4.4) Relative risk for the effect of A_2, setting $A_1 = 1$

$$\log RR_{A_2|A_1=1} = \log \frac{m_\beta(1,1)}{m_\beta(1,0)} = \log m_\beta(1,1) - \log m_\beta(1,0)$$

With $m_\beta = \frac{1}{1+e}$, we have: $(\log m_\beta)' = \frac{m'_\beta}{m_\beta} = \frac{-e'}{(1+e)^2} \times (1+e) = \frac{-e'}{1+e}$

where $e_{10} = \exp(-\beta_0 - \beta_1)$ and $e_{11} = \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3)$.

$$\begin{aligned}
\frac{\partial \log RR_{A_2|A_1=1}}{\partial \beta_0} &= \frac{-(-e_{11})}{1+e_{11}} - \frac{-(-e_{10})}{1+e_{10}} \\
&= \frac{1+e_{11}-1}{1+e_{11}} - \frac{1+e_{10}-1}{1+e_{10}} \\
&= [1 - m_\beta(1,1)] - [1 - m_\beta(1,0)] = m_\beta(1,0) - m_\beta(1,1)
\end{aligned}$$

$$\begin{aligned}
\frac{\partial \log RR_{A_2|A_1=1}}{\partial \beta_1} &= \frac{1+e_{11}-1}{1+e_{11}} - \frac{1+e_{10}-1}{1+e_{10}} \\
&= [1 - m_\beta(1,1)] - [1 - m_\beta(1,0)] = m_\beta(1,0) - m_\beta(1,1)
\end{aligned}$$

$$\begin{aligned}
\frac{\partial \log RR_{A_2|A_1=1}}{\partial \beta_2} &= \frac{-(-e_{11})}{1+e_{11}} - 0 \\
&= \frac{1+e_{11}-1}{1+e_{11}} = 1 - m_\beta(1,1)
\end{aligned}$$

$$\begin{aligned}
\frac{\partial \log RR_{A_2|A_1=1}}{\partial \beta_3} &= \frac{-(-e_{11})}{1+e_{11}} - 0 \\
&= \frac{1+e_{11}-1}{1+e_{11}} = 1 - m_\beta(1,1)
\end{aligned}$$

$$\frac{\partial \log RR_{A_2|A_1=1}}{\partial \beta} = \begin{pmatrix} m_\beta(1,0) - m_\beta(1,1) \\ m_\beta(1,0) - m_\beta(1,1) \\ 1 - m_\beta(1,1) \\ 1 - m_\beta(1,1) \end{pmatrix} = \Delta$$

The variance of $\log RR_{A_2|A_1=1}$ can then be calculated by:

$$var\left(\log RR_{A_2|A_1=1}\right) = \Delta^T \times \frac{var(IC)}{n} \times \Delta$$

5) Standard errors of interaction effects

5.1) Additive interaction

The additive interaction is defined by:

$$
\begin{aligned}
\text{a.INT} =& m_\beta(1,1) - m_\beta(0,0) - [(m_\beta(1,0) - m_\beta(0,0)) + (m_\beta(0,1) - m_\beta(0,0))] \\
=& m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)
\end{aligned}
$$

where

$$
\begin{aligned}
m_\beta(1,1) =& \frac{1}{1+e_{11}} \quad \text{and} \quad e_{11} = \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3) \\
m_\beta(1,0) =& \frac{1}{1+e_{10}} \quad \text{and} \quad e_{10} = \exp(-\beta_0 - \beta_1) \\
m_\beta(0,1) =& \frac{1}{1+e_{01}} \quad \text{and} \quad e_{01} = \exp(-\beta_0 - \beta_2) \\
m_\beta(0,0) =& \frac{1}{1+e_{00}} \quad \text{and} \quad e_{00} = \exp(-\beta_0)
\end{aligned}
$$

$$
\frac{\partial \text{a.INT}}{\partial \beta} = \frac{-e'_{11}}{(1+e_{11})^2} - \frac{-e'_{10}}{(1+e_{10})^2} - \frac{-e'_{01}}{(1+e_{01})^2} + \frac{-e'_{00}}{(1+e_{00})^2}
$$

$$
\begin{aligned}
\frac{\partial \text{a.INT}}{\partial \beta_0} &= (1 - m_\beta(1,1))\, m_\beta(1,1) - (1 - m_\beta(1,0))\, m_\beta(1,0) - (1 - m_\beta(0,1))\, m_\beta(0,1) + (1 - m_\beta(0,0))\, m_\beta(0,0) \\
\frac{\partial \text{a.INT}}{\partial \beta_1} &= (1 - m_\beta(1,1))\, m_\beta(1,1) - (1 - m_\beta(1,0))\, m_\beta(1,0) \\
\frac{\partial \text{a.INT}}{\partial \beta_2} &= (1 - m_\beta(1,1))\, m_\beta(1,1) - (1 - m_\beta(0,1))\, m_\beta(0,1) \\
\frac{\partial \text{a.INT}}{\partial \beta_3} &= (1 - m_\beta(1,1))\, m_\beta(1,1)
\end{aligned}
$$

$$
\frac{\partial \text{a.INT}}{\partial \beta} = \begin{pmatrix} (1 - m_\beta(1,1))\, m_\beta(1,1) - (1 - m_\beta(1,0))\, m_\beta(1,0) - (1 - m_\beta(0,1))\, m_\beta(0,1) + (1 - m_\beta(0,0))\, m_\beta(0,0) \\ (1 - m_\beta(1,1))\, m_\beta(1,1) - (1 - m_\beta(1,0))\, m_\beta(1,0) \\ (1 - m_\beta(1,1))\, m_\beta(1,1) - (1 - m_\beta(0,1))\, m_\beta(0,1) \\ (1 - m_\beta(1,1))\, m_\beta(1,1) \end{pmatrix}
$$

The variance of a.INT can then be calculated by:

$$
var(\text{a.INT}) = \left(\frac{\partial \text{a.INT}}{\partial \beta}\right)^T \times \frac{var(IC)}{n} \times \left(\frac{\partial \text{a.INT}}{\partial \beta}\right)
$$

5.2) Multiplicative interaction

The multiplicative interaction is defined by:

$$\begin{aligned}
\text{m.INT} =& \frac{m_\beta(1,1) \times m_\beta(0,0)}{m_\beta(1,0) \times m_\beta(0,1)} \\
\log \text{m.INT} =& \log m_\beta(1,1) - \log m_\beta(1,0) - \log m_\beta(0,1) + \log m_\beta(0,0)
\end{aligned}$$

with $\frac{\partial}{\partial \beta} \log m_\beta = \frac{-e'}{1+e}$, where

$$\begin{aligned}
e_{11} =& \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3) \\
e_{10} =& \exp(-\beta_0 - \beta_1) \\
e_{01} =& \exp(-\beta_0 - \beta_2) \\
e_{00} =& \exp(-\beta_0)
\end{aligned}$$

$$\frac{\partial}{\partial \beta} \log \text{m.INT} = \frac{-e'_{11}}{1+e_{11}} - \frac{-e'_{10}}{1+e_{10}} - \frac{-e'_{01}}{1+e_{01}} + \frac{-e'_{00}}{1+e_{00}}$$

$$\begin{aligned}
\frac{\partial \log \text{m.INT}}{\partial \beta_0} =& \frac{-(-e_{11})}{1+e_{11}} - \frac{-(-e_{10})}{1+e_{10}} - \frac{-(-e_{01})}{1+e_{01}} + \frac{-(-e_{00})}{1+e_{00}} \\
=& (1 - m_\beta(1,1)) - (1 - m_\beta(1,0)) - (1 - m_\beta(0,1)) + (1 - m_\beta(0,0)) \\
=& m_\beta(1,0) + m_\beta(0,1) - m_\beta(1,1) - m_\beta(0,0) \\
\frac{\partial \log \text{m.INT}}{\partial \beta_1} =& (1 - m_\beta(1,1)) - (1 - m_\beta(1,0)) \\
=& m_\beta(1,0) - m_\beta(1,1) \\
\frac{\partial \log \text{m.INT}}{\partial \beta_2} =& (1 - m_\beta(1,1)) - (1 - m_\beta(0,1)) \\
=& m_\beta(0,1) - m_\beta(1,1) \\
\frac{\partial \log \text{m.INT}}{\partial \beta_3} =& (1 - m_\beta(1,1))
\end{aligned}$$

$$\frac{\partial \log \text{m.INT}}{\partial \beta} = \begin{pmatrix} m_\beta(1,0) + m_\beta(0,1) - m_\beta(1,1) - m_\beta(0,0) \\ m_\beta(1,0) - m_\beta(1,1) \\ m_\beta(0,1) - m_\beta(1,1) \\ 1 - m_\beta(1,1) \end{pmatrix}$$

The variance of $\log \text{m.INT}$ can then be calculated by:

$$var(\log \text{m.INT}) = \left(\frac{\partial \log \text{m.INT}}{\partial \beta} \right)^T \times \frac{var(IC)}{n} \times \left(\frac{\partial \log \text{m.INT}}{\partial \beta} \right)$$

5.3) RERI

The RERI is defined by:

$$\begin{aligned}\text{RERI} =& \frac{m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)}{m_\beta(0,0)} \\ \log \text{RERI} =& \log\left[m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)\right] - \log m_\beta(0,0)\end{aligned}$$

denoting

$$\begin{aligned}e_{11} =& \exp(-\beta_0 - \beta_1 - \beta_2 - \beta_3) \\ e_{10} =& \exp(-\beta_0 - \beta_1) \\ e_{01} =& \exp(-\beta_0 - \beta_2) \\ e_{00} =& \exp(-\beta_0)\end{aligned}$$

$$\frac{\partial}{\partial \beta} \log m_\beta(0,0) = \frac{m_\beta(0,0)'}{m_\beta(0,0)} = \frac{-e'_{00}}{(1+e_{00})^2}(1+e_{00}) = \frac{-e'_{00}}{1+e_{00}}$$

$$\frac{\partial}{\partial \beta} \log\left[m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)\right] = \frac{m_\beta(1,1)' - m_\beta(1,0)' - m_\beta(0,1)' + m_\beta(0,0)'}{m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)}$$

$$\begin{aligned}\frac{\partial \log \text{RERI}}{\partial \beta_0} = & \frac{[1-m_\beta(1,1)]\,m_\beta(1,1) - [1-m_\beta(1,0)]\,m_\beta(1,0) - [1-m_\beta(0,1)]\,m_\beta(0,1) + [1-m_\beta(0,0)]\,m_\beta(0,0)}{m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)} \\ & - [1-m_\beta(0,0)]\end{aligned}$$

$$\begin{aligned}\frac{\partial \log \text{RERI}}{\partial \beta_1} =& \frac{[1-m_\beta(1,1)]\,m_\beta(1,1) - [1-m_\beta(1,0)]\,m_\beta(1,0)}{m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)} \\ \frac{\partial \log \text{RERI}}{\partial \beta_2} =& \frac{[1-m_\beta(1,1)]\,m_\beta(1,1) - [1-m_\beta(0,1)]\,m_\beta(0,1)}{m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)} \\ \frac{\partial \log \text{RERI}}{\partial \beta_3} =& \frac{[1-m_\beta(1,1)]\,m_\beta(1,1)}{m_\beta(1,1) - m_\beta(1,0) - m_\beta(0,1) + m_\beta(0,0)}\end{aligned}$$

The variance of $\log \text{RERI}$ can then be calculated by:

$$var(\log \text{RERI}) = \left(\frac{\partial \log \text{RERI}}{\partial \beta}\right)^T \times \frac{var(IC)}{n} \times \left(\frac{\partial \log \text{RERI}}{\partial \beta}\right)$$