eAppendix for 'Attributing Effects to Interactions' by Tyler J. VanderWeele and Eric J. Tchetgen Tchetgen

1. Binary Exposures and Binary Outcomes

1.1. Standard Error for the Proportion of a Total Effect Attributable to Interaction

As noted in the text, for a binary outcome and two binary exposures G and E, the proportion of the excess relative risk for E that is attributable to interaction is given by:

$$pAI_{G=0}(E) = \frac{(RERI)P(G=1)}{(RR_{01}-1)+(RERI)P(G=1)}.$$

where $RERI = RR_{11} - RR_{10} - RR_{01} + 1$. Under the logistic regression model with a rare outcome

$$logit\{P(Y=1|G=g,E=e,C=c)\} = \gamma_0 + \gamma_1 g + \gamma_2 e + \gamma_3 eg + \gamma_4' c, \tag{A1}$$

the (marginal) proportion attributable to interaction averaged over covariates can be shown to be:

$$pAI_{G=0}(E) \approx \frac{(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2} + 1)P(G=1)}{(e^{\gamma_2}-1) + (e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2} + 1)P(G=1)}.$$

The conditional proportion attributable to interaction in stratum $C = c$ would replace $P(G = 1)$ in both the numerator and the denominator by $P(G = 1|C = c)$.

For the standard error for the proportion due to interaction we will assume that the proportion $P(G = 1)$ is known. Alternatively, the standard errors derived can be interpretted as standard errors for the estimate of the proportion attributable to interaction in a population which had the same underlying risk ratios as the sample in question, but had a prevalence of G equal to the prevalence of G in the sample.

Let

$$V = \begin{pmatrix} v_{00} & v_{01} & v_{02} & v_{03} \\ v_{10} & v_{11} & v_{12} & v_{13} \\ v_{20} & v_{21} & v_{22} & v_{23} \\ v_{30} & v_{31} & v_{32} & v_{33} \end{pmatrix}$$

be the covariance matrix for the estimators $(\widehat{\gamma}_0, \widehat{\gamma}_1, \widehat{\gamma}_2, \widehat{\gamma}_3)'$ of $(\gamma_0, \gamma_1, \gamma_2, \gamma_3)'$. By the delta method the variance of our estimator $\widehat{Q}$ of $Q = \frac{(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2}+1)P(G=1)}{(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2}+1)P(G=1)}$ replacing $(\gamma_0, \gamma_1, \gamma_2, \gamma_3)$ in this expression with $(\widehat{\gamma}_0, \widehat{\gamma}_1, \widehat{\gamma}_2, \widehat{\gamma}_3)'$ is given by:

$$Var(Q) = \frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'}' V \frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'}.$$

We have that $\frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'} =$

$$\begin{pmatrix} 0 \\ \frac{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)][(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1})P(G=1)]-[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)][(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1})P(G=1)]}{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)]^2} \\ \frac{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)][(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_2})P(G=1)]-[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)][e^{\gamma_2}+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_2})P(G=1)]}{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)]^2} \\ \frac{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)][e^{\gamma_1+\gamma_2+\gamma_3}]-[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)][e^{\gamma_1+\gamma_2+\gamma_3}]}{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)]^2} \end{pmatrix}.$$

$$= \begin{pmatrix} 0 \\ \frac{[(e^{\gamma_2}-1)[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1})P(G=1)]}{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)]^2} \\ \frac{-(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_2})P(G=1)}{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)]^2} \\ \frac{(e^{\gamma_2}-1)[e^{\gamma_1+\gamma_2+\gamma_3}]}{[(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)]^2} \end{pmatrix}.$$

Let K_1, K_2 and K_3 denote the first, second, and third non-zero expressions in this vector. We then have

$$\begin{aligned}
Var(\widehat{Q}) &= \frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'}' V \frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'} \\
&= \begin{pmatrix} 0 \\ K_1 \\ K_2 \\ K_3 \end{pmatrix}' \begin{pmatrix} v_{00} & v_{01} & v_{02} & v_{03} \\ v_{10} & v_{11} & v_{12} & v_{13} \\ v_{20} & v_{21} & v_{22} & v_{23} \\ v_{30} & v_{31} & v_{32} & v_{33} \end{pmatrix} \begin{pmatrix} 0 \\ K_1 \\ K_2 \\ K_3 \end{pmatrix} \\
&= \begin{pmatrix} 0 \\ K_1 \\ K_2 \\ K_3 \end{pmatrix}' \begin{pmatrix} v_{01}K_1 + v_{02}K_2 + v_{03}K_3 \\ v_{11}K_1 + v_{12}K_2 + v_{13}K_3 \\ v_{21}K_1 + v_{22}K_2 + v_{23}K_3 \\ v_{31}K_1 + v_{32}K_2 + v_{33}K_3 \end{pmatrix} \\
&= v_{11}K_1^2 + v_{22}K_2^2 + v_{33}K_3^2 + v_{12}K_1K_2 + v_{13}K_1K_3 + v_{23}K_2K_3.
\end{aligned}$$

1.2 Standard Error for the Proportion of a Joint Effect Attributable to Either Exposure Alone and to Interaction

For the three-way decomposition of the joint excess relative risk of both exposures, $RR_{11} - 1$, we have a decomposition into an excess risk relative risk for G alone, an excess relative risk for E alone, and the excess relative risk due to interaction i.e. we have the decomposition: $RR_{11} - 1 = (RR_{10} - 1) + (RR_{01} - 1) + RERI$. And we can compute the proportion of the joint effect due to G alone $\frac{RR_{10}-1}{RR_{11}-1}$, and due to E alone $\frac{RR_{01}-1}{RR_{11}-1}$, and due to their interaction $\frac{RERI}{RR_{11}-1}$. Under the logistic regression model with a rare outcome

$$logit\{P(Y = 1|G = g, E = e, C = c)\} = \gamma_0 + \gamma_1 g + \gamma_2 e + \gamma_3 eg + \gamma_4' c,$$

the proportion can be estimated approximately by:

$$\begin{aligned}
\frac{RR_{10} - 1}{RR_{11} - 1} &\approx \frac{e^{\gamma_1} - 1}{e^{\gamma_1+\gamma_2+\gamma_3} - 1} \\
\frac{RR_{01} - 1}{RR_{11} - 1} &\approx \frac{e^{\gamma_2} - 1}{e^{\gamma_1+\gamma_2+\gamma_3} - 1} \\
\frac{RERI}{RR_{11} - 1} &\approx \frac{(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2} + 1)}{e^{\gamma_1+\gamma_2+\gamma_3} - 1}.
\end{aligned}$$

We will now compute the standard errors for these expressions.

For the proportion of the joint effect due to a single exposure alone, we have, by the delta method, that the variance of our estimator $\widehat{Q}$ of $Q = \frac{e^{\gamma_1}-1}{e^{\gamma_1+\gamma_2+\gamma_3}-1}$ replacing $(\gamma_0, \gamma_1, \gamma_2, \gamma_3)$ in this expression with $(\widehat{\gamma}_0, \widehat{\gamma}_1, \widehat{\gamma}_2, \widehat{\gamma}_3)'$ is given by:

$$Var(Q) = \frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'}' V \frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'}.$$

We have that $\frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'} =$

$$\begin{pmatrix} 0 \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}-1][e^{\gamma_1}]-[e^{\gamma_1}-1][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}-1][0]-[e^{\gamma_1}-1][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}-1][0]-[e^{\gamma_1}-1][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \end{pmatrix}.$$

$$\begin{pmatrix} 0 \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}]-e^{\gamma_1}}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{-[e^{\gamma_1}-1][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{-[e^{\gamma_1}-1][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \end{pmatrix}.$$

Let K_1, K_2 and K_3 denote the first, second, and third non-zero expressions in this vector. We then once again have $Var(\widehat{Q}) = v_{11}K_1^2 + v_{22}K_2^2 + v_{33}K_3^2 + v_{12}K_1K_2 + v_{13}K_1K_3 + v_{23}K_2K_3$.

For the standard error for the proportion of a joint effect attributable to interaction we have, by the delta method, that the variance of the estimator $\widehat{Q}$ of $Q = \frac{(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)}{e^{\gamma_1+\gamma_2+\gamma_3}-1}$ replacing $(\gamma_0, \gamma_1, \gamma_2, \gamma_3)$ in this expression with $(\widehat{\gamma}_0, \widehat{\gamma}_1, \widehat{\gamma}_2, \widehat{\gamma}_3)'$ is given by:

$$Var(Q) = \frac{\partial Q}{\partial(\gamma_0, \gamma_1, \gamma_2, \gamma_3)'}' V \frac{\partial Q}{\partial(\gamma_0, \gamma_1, \gamma_2, \gamma_3)'}.$$

We have that $\frac{\partial Q}{\partial(\gamma_0,\gamma_1,\gamma_2,\gamma_3)'} =$

$$\begin{pmatrix} 0 \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}-1][e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}]-[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}-1][e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_2}]-[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{[e^{\gamma_1+\gamma_2+\gamma_3}-1][e^{\gamma_1+\gamma_2+\gamma_3}]-[(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)][e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \end{pmatrix}.$$

$$= \begin{pmatrix} 0 \\ \frac{e^{\gamma_1}+(e^{\gamma_2}-2)[e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{e^{\gamma_2}+(e^{\gamma_1}-2)[e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \\ \frac{(e^{\gamma_1}+e^{\gamma_2}-2)[e^{\gamma_1+\gamma_2+\gamma_3}]}{[e^{\gamma_1+\gamma_2+\gamma_3}-1]^2} \end{pmatrix}.$$

Let K_1, K_2 and K_3 denote the first, second, and third non-zero expressions in this vector. We then have $Var(\widehat{Q}) = v_{11}K_1^2 + v_{22}K_2^2 + v_{33}K_3^2 + v_{12}K_1K_2 + v_{13}K_1K_3 + v_{23}K_2K_3$.

1.3. SAS and Stata Code to Implement Proportion of a Total Effect Attributable to Interaction

Suppose we have a SAS dataset named 'mydata' with outcome variable 'y', exposure variables 'e' and 'g' and three covariates 'c1', 'c2' and 'c3'. To use the code below, the user must input in the third and fourth line of the data step the prevalence of the exposure G ('pg=') and the prevalence of the exposure E ('pg='). In a case-control study, these prevalences should be computed only among the controls. The output will include the proportion of the total effect of G that is attributable to interaction, along with a 95% confidence interval; the remaining proportion is that attributable to G when E is set to 0. The code will also report the proportion of the total effect of E that is attributed to interaction, along with a 95% confidence interval; once again, the remaining proportion is that attributable to E when G is set to 0.

These measures assume that G and E are independent, and that control has been made for confounding. In this case, the proportion attributable to interaction for G can also be interpretted as the proportion of the total effect of G that would be eliminated if E were set to 0. Likewise, the proportion attributable to interaction for E can also be interpretted as the proportion of the total effect of E that would be eliminated if G were set to 0. When G and E are not independent (e.g. G affects E), the measure for the second exposure still carries this interpretation provided control has been made for confounding. However, for the first exposure G the proportion attributable to interaction given in the output corresponds to the proportion of an integrated joint effect due to interaction, as discussed in the Appendix to the paper.

```
proc logistic descending data=mydata outest=myoutput covout;
  model y=g e g*e c1 c2 c3;
```

```
run;

data PAIoutput;
  set myoutput;
  array mm {*} _numeric_;
  pg=0.5;
  pe=0.5;
  b0=lag4(mm[1]);
  b1=lag4(mm[2]);
  b2=lag4(mm[3]);
  b3=lag4(mm[4]);
  v11=lag2(mm[2]);
  v12=lag(mm[2]);
  v13=mm[2];
  v22=lag(mm[3]);
  v23=mm[3];
  v33=mm[4];
  k1=((exp(b2)-1)*(exp(b1+b2+b3)-exp(b1))*pg)
/((exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg)*(exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg));
  k2=(-(exp(b1+b2+b3)-exp(b2))*pg)
/((exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg)*(exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg));
  k3=((exp(b2)-1)*exp(b1+b2+b3))
/((exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg)*(exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg));
  vPAIE=v11*k1*k1 + v22*k2*k2 + v33*k3*k3 + 2*v12*k1*k2 + 2*v13*k1*k3 + 2*v23*k2*k3;
  PAI_E=(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg/(exp(b2)-1+(exp(b1+b2+b3)-exp(b1)-exp(b2)+1)*pg);
  se_PAIE=sqrt(vPAIE);
  ci95_lE=PAI_E-1.96*se_PAIE;
  ci95_uE=PAI_E+1.96*se_PAIE;
  h1=((exp(b1)-1)*(exp(b2+b1+b3)-exp(b2))*pe)
/((exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe)*(exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe));
  h2=(-(exp(b2+b1+b3)-exp(b1))*pe)
/((exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe)*(exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe));
  h3=((exp(b1)-1)*exp(b2+b1+b3))
/((exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe)*(exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe));
  vPAIG=v11*h1*h1 + v22*h2*h2 + v33*h3*h3 + 2*v12*h1*h2 + 2*v13*h1*h3 + 2*v23*h2*h3;
  PAI_G=(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe/(exp(b1)-1+(exp(b2+b1+b3)-exp(b2)-exp(b1)+1)*pe);
  se_PAIG=sqrt(vPAIG);
  ci95_lG=PAI_G-1.96*se_PAIG;
  ci95_uG=PAI_G+1.96*se_PAIG;
  keep PAI_E ci95_lE ci95_uE PAI_G ci95_lG ci95_uG;
  if _n_=5;
run;

proc print data=PAIoutput;
  var PAI_E ci95_lE ci95_uE PAI_G ci95_lG ci95_uG;
run;
```

The equivalent Stata code would be:

```
  generate pg=0.5
  generate pe=0.5

  generate Ige = g*e
  logit y g e Ige c1 c2 c3

  nlcom (exp(_b[e]+_b[g]+_b[Ige])-exp(_b[e])-exp(_b[g])+1)*pe/(exp(_b[g])-1
+(exp(_b[e]+_b[g]+_b[Ige])-exp(_b[e])-exp(_b[g])+1)*pe)
```

1.4. SAS and Stata Code to Implement Proportion of a Joint Effect Attributable to Either Exposure Alone and to Interaction

As discussed in the text it is possible to decompose the joint excess relative risk for both exposures together into three components: (i) a component due to the first exposure G alone, (ii) a component due to E alone, and (iii) a component due to the interaction between the effect of G and E. The output gives the proportions due to G alone, the proportion due to E alone, and the proportion due to the interaction; 95% confidence intervals are also given for these three proportions. The three proportions will sum to 100%. The decomposition applies even if one of the exposures affects the other. The code in SAS is:

```
proc logistic descending data=mydata outest=myoutput covout;
  model y=g e g*e c1 c2 c3;
run;

data JOINToutput;
  set myoutput;
  array mm {*} _numeric_;
  b0=lag4(mm[1]);
  b1=lag4(mm[2]);
  b2=lag4(mm[3]);
  b3=lag4(mm[4]);
  v11=lag2(mm[2]);
  v12=lag(mm[2]);
  v13=mm[2];
  v22=lag(mm[3]);
  v23=mm[3];
  v33=mm[4];
  k1=(exp(b1+b2+b3)-exp(b1))/((exp(b1+b2+b3)-1)*(exp(b1+b2+b3)-1));
  k2=(-(exp(b1)-1)*exp(b1+b2+b3))/((exp(b1+b2+b3)-1)*(exp(b1+b2+b3)-1));
  k3=(-(exp(b1)-1)*exp(b1+b2+b3))/((exp(b1+b2+b3)-1)*(exp(b1+b2+b3)-1));
  vG=v11*k1*k1 + v22*k2*k2 + v33*k3*k3 + 2*v12*k1*k2 + 2*v13*k1*k3 + 2*v23*k2*k3;
  PAG=(exp(b1)-1)/(exp(b1+b2+b3)-1);
  se_PAG=sqrt(vG);
  ci95_lG=PAG-1.96*se_PAG;
  ci95_uG=PAG+1.96*se_PAG;
  h1=(exp(b2+b1+b3)-exp(b2))/((exp(b2+b1+b3)-1)*(exp(b2+b1+b3)-1));
  h2=(-(exp(b2)-1)*exp(b2+b1+b3))/((exp(b2+b1+b3)-1)*(exp(b2+b1+b3)-1));
  h3=(-(exp(b2)-1)*exp(b2+b1+b3))/((exp(b2+b1+b3)-1)*(exp(b2+b1+b3)-1));
  vE=v11*h1*h1 + v22*h2*h2 + v33*h3*h3 + 2*v12*h1*h2 + 2*v13*h1*h3 + 2*v23*h2*h3;
  PAE=(exp(b2)-1)/(exp(b2+b1+b3)-1);
  se_PAE=sqrt(vE);
  ci95_lE=PAE-1.96*se_PAE;
  ci95_uE=PAE+1.96*se_PAE;
  f1=(exp(b1)+(exp(b2)-2)*exp(b1+b2+b3))/((exp(b1+b2+b3)-1)*(exp(b1+b2+b3)-1));
  f2=(exp(b2)+(exp(b1)-2)*exp(b1+b2+b3))/((exp(b1+b2+b3)-1)*(exp(b1+b2+b3)-1));
  f3=((exp(b1)+exp(b2)-2)*exp(b1+b2+b3))/((exp(b1+b2+b3)-1)*(exp(b1+b2+b3)-1));
  vINT=v11*f1*f1 + v22*f2*f2 + v33*f3*f3 + 2*v12*f1*f2 + 2*v13*f1*f3 + 2*v23*f2*f3;
  PaINT=(exp(b2+b1+b3)-exp(b1)-exp(b2)+1)/(exp(b1+b2+b3)-1);
  se_PaINT=sqrt(vINT);
  ci95_lINT=PaINT-1.96*se_PaINT;
  ci95_uINT=PaINT+1.96*se_PaINT;
  keep PAG ci95_lG ci95_uG PAE ci95_lE ci95_uE PaINT ci95_lINT ci95_uINT;
  if _n_=5;
run;

proc print data=JOINToutput;
  var PAG ci95_lG ci95_uG PAE ci95_lE ci95_uE PaINT ci95_lINT ci95_uINT;
run;
```

The equivalent Stata code would be as follows (with the output first giving the proportion of joint effect due to G alone, then due to E alone, and then that due to their interaction):

```
  generate Ige = g*e
```

```
logit y g e Ige c1 c2 c3

nlcom (exp(_b[g])-1)/(exp(_b[g]+_b[e]+_b[Ige])-1)
nlcom (exp(_b[e])-1)/(exp(_b[e]+_b[g]+_b[Ige])-1)
nlcom (exp(_b[e]+_b[g]+_b[Ige])-exp(_b[g])-exp(_b[e])+1)/(exp(_b[g]+_b[e]+_b[Ige])-1)
```

2. Binary Outcome and Continuous Exposures

2.1. Proportion of a Total Effect Attributable to Interaction

As discussed in the Appendix to the text, for continuous exposures, when the effect of E on Y is unconfounded conditional on (C,G) then the total effect of E on Y, $E[Y_{e_1}|c]-E[Y_{e_0}|c]$, could be decomposed into two components as: $E[Y_{e_1}|c]-E[Y_{e_0}|c]$

$$= E[Y|g_0,e_1,c] - E[Y|g_0,e_0,c] + \int \{E[Y|g,e_1,c] - E[Y|g,e_0,c] - E[Y|g_0,e_1,c] + E[Y|g_0,e_0,c]\} dP(g|c)$$

which on the ratio scale can be rewritten as $\frac{E[Y_{e_1}|c]}{E[Y_{e_0}|c]} - 1$

$$= \kappa\{\frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} - 1\} + \kappa \int \{\frac{E[Y|g,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} dP(g|c)$$

where $\kappa = \frac{E[Y|g_0,e_0,c]}{E[Y_{e_0}|c]}$. The proportion of the effect of E attributable to interaction is given by:

$$pAI_{G=g_0}(E) = \frac{\int \{\frac{E[Y|g,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} dP(g|c)}{\{\frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} - 1\} + \int \{\frac{E[Y|g,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} dP(g|c)}.$$

Suppose first that E is continuous and G is binary, then this expression reduces to

$$pAI_{G=g_0}(E) = \frac{\{\frac{E[Y|g_1,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_1,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} P(G=g_1|c)}{\{\frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} - 1\} + \{\frac{E[Y|g_1,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_1,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} P(G=g_1|c)}.$$

Under the logistic regression model with a rare outcome

$$logit\{P(Y=1|G=g,E=e,C=c)\} = \gamma_0 + \gamma_1 g + \gamma_2 e + \gamma_3 eg + \gamma_4' c, \quad \text{(A1)}$$

the proportion attributable to interaction is given by approximately by: $pAI_{G=g_0}(E) \approx$

$$\frac{\{e^{(g_1-g_0)\gamma_1+(e_1-e_0)\gamma_2+(g_1e_1-g_0e_0)\gamma_3} - e^{(g_1-g_0)\gamma_1+(g_1-g_0)e_0\gamma_3} - e^{(e_1-e_0)\gamma_2+(e_1-e_0)g_0\gamma_3} + 1\} P(G=g_1|c)}{\{e^{(e_1-e_0)\gamma_2+(e_1-e_0)g_0\gamma_3} - 1\} + \{e^{(g_1-g_0)\gamma_1+(e_1-e_0)\gamma_2+(g_1e_1-g_0e_0)\gamma_3} - e^{(g_1-g_0)\gamma_1+(g_1-g_0)e_0\gamma_3} - e^{(e_1-e_0)\gamma_2+(e_1-e_0)g_0\gamma_3} + 1\} P(G=g_1|c)}.$$

Suppose now that G is continuous and normally distributed with mean

$$E[G|c] = \alpha_0 + \alpha_1' c \quad \text{(A2)}$$

and variance σ^2. Assuming a rare outcome, under logistic regression (A1) we have:

$$\begin{aligned}
& \int \frac{E[Y|g,e,c]}{E[Y|g_0,e_0,c]} dP(g|c) \\
\approx & \int \exp\{(g-g_0)\gamma_1 + (e-e_0)\gamma_2 + (ge-g_0e_0)\gamma_3\} dP(g|c) \\
= & \exp\{-g_0\gamma_1 + (e-e_0)\gamma_2 - g_0e_0\gamma_3\} \int \exp\{g(\gamma_1 + e\gamma_3)\} dP(g|c) \\
= & \exp\{-g_0\gamma_1 + (e-e_0)\gamma_2 - g_0e_0\gamma_3 + (\gamma_1+e\gamma_3)(\alpha_0+\alpha_1'c) + \frac{1}{2}(\gamma_1+e\gamma_3)^2\sigma^2\}
\end{aligned}$$

and thus the proportion attributable to interaction is: $pAI_{G=g_0}(E) =$

$$\frac{\int \{\frac{E[Y|g,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} dP(g|c)}{\{\frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} - 1\} + \int \{\frac{E[Y|g,e_1,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g,e_0,c]}{E[Y|g_0,e_0,c]} - \frac{E[Y|g_0,e_1,c]}{E[Y|g_0,e_0,c]} + 1\} dP(g|c)} \approx$$

$$\frac{e^{-g_0\gamma_1+(e_1-e_0)\gamma_2-g_0e_0\gamma_3+(\gamma_1+e_1\gamma_3)(\alpha_0+\alpha_1'c)+\frac{1}{2}(\gamma_1+e_1\gamma_3)^2\sigma^2} - e^{-g_0\gamma_1-g_0e_0\gamma_3+(\gamma_1+e_0\gamma_3)(\alpha_0+\alpha_1'c)+\frac{1}{2}(\gamma_1+e_0\gamma_3)^2\sigma^2} - e^{(e_1-e_0)\gamma_2+(e_1-e_0)g_0\gamma_3} + 1\}}{e^{-g_0\gamma_1+(e_1-e_0)\gamma_2-g_0e_0\gamma_3+(\gamma_1+e_1\gamma_3)(\alpha_0+\alpha_1'c)+\frac{1}{2}(\gamma_1+e_1\gamma_3)^2\sigma^2} - e^{-g_0\gamma_1-g_0e_0\gamma_3+(\gamma_1+e_0\gamma_3)(\alpha_0+\alpha_1'c)+\frac{1}{2}(\gamma_1+e_0\gamma_3)^2\sigma^2}}.$$

2.2. Proportion of a Joint Effect Attributable to Either Exposure Alone and to Interaction

Let $RR_{g_1e_1} = \frac{E[Y|g_1,e_1,c]}{E[Y|g_0,e_0,c]}$. For the three-way decomposition of the joint excess relative risk of both exposures, $RR_{g_1e_1} - 1$, we have the decomposition:

$$(RR_{g_1e_1} - 1) = (RR_{g_1e_0} - 1) + (RR_{g_0e_1} - 1) + (RR_{g_1e_1} - RR_{g_1e_0} - RR_{g_0e_1} + 1).$$

Under the logistic regression model with a rare outcome

$$logit\{P(Y=1|G=g,E=e,C=c)\} = \gamma_0 + \gamma_1 g + \gamma_2 e + \gamma_3 eg + \gamma_4' c,$$

the proportions of the joint excess relative risk of both exposures due to each of the exposures considered alone and due to interaction can be estimated approximately by:

$$\begin{aligned}
\frac{RR_{g_1e_0} - 1}{RR_{g_1e_1} - 1} &\approx \frac{e^{(g_1-g_0)\gamma_1+(g_1-g_0)e_0\gamma_3} - 1}{e^{(g_1-g_0)\gamma_1+(e_1-e_0)\gamma_2+(g_1e_1-g_0e_0)\gamma_3} - 1} \\
\frac{RR_{g_0e_1} - 1}{RR_{g_1e_1} - 1} &\approx \frac{e^{(e_1-e_0)\gamma_2+(e_1-e_0)g_0\gamma_3} - 1}{e^{(g_1-g_0)\gamma_1+(e_1-e_0)\gamma_2+(g_1e_1-g_0e_0)\gamma_3} - 1} \\
\frac{(RR_{g_1e_1} - RR_{g_1e_0} - RR_{g_0e_1} + 1)}{RR_{g_1e_1} - 1} &\approx
\end{aligned}$$

$$\frac{\{e^{(g_1-g_0)\gamma_1+(e_1-e_0)\gamma_2+(g_1e_1-g_0e_0)\gamma_3} - e^{(g_1-g_0)\gamma_1+(g_1-g_0)e_0\gamma_3} - e^{(e_1-e_0)\gamma_2+(e_1-e_0)g_0\gamma_3} + 1\}}{e^{(g_1-g_0)\gamma_1+(e_1-e_0)\gamma_2+(g_1e_1-g_0e_0)\gamma_3} - 1}.$$

2.3. SAS and Stata Code to Implement Proportion of a Total Effect Attributable to Interaction

Although we could obtain analytic standard errors for the expressions in Section 2.1 using the delta, the formulae would be very involved. The SAS procedure proc nlmixed, can however, carry out standard error computations for these expressions.

To estimate the proportion of the total effect of E on binary outcome Y due to E when G is fixed to g_0 and the proportion due to interaction when G is binary, and logistic regression model (A1) is used, one can use the code below. Suppose we have a dataset named 'mydata' with outcome variable 'y', exposure variables 'e' and 'g' and three covariates 'c1', 'c2' and 'c3'. If there were more or fewer covariates the user would have to modify the second and fourth lines of the code below to include these covariates.

The user must input in the third line of code the two levels of G ('g1=' and 'g0=') and the two levels of E ('e1=' and 'e0=') that are being compared. The user must also input in the third line of the code the prevalence of the exposure G ('pg=') conditional on $C = c$ (or use the marginal prevalence of G as a summary). In a case-control study, these prevalences should be computed only among the controls. For the standard error to be valid it is assumed that the prevalence of G is known; alternatively, standard errors and confidence interval can be interpretted as that for the proportion attributable to interaction in a population which had the same underlying risk ratios as the sample in question, but had a prevalence of G equal to the prevalence of G in the sample.

The output will include the proportion of the total effect of E that is attributable to interaction, along with a 95% confidence interval; the remaining proportion is that attributable to E when G is set to g_0.

```
proc nlmixed data=mydata;
parms b0=1 b1=0 b2=0 b3=0 bc1=0 bc2=0 bc3=0;
g1=1; g0=0; e1=1; e0=0; pg=0.5;
p_y=(1+exp(-(b0 + b1*G + b2*E + b3*G*E + bc1*C1 + bc2*C2 + bc3*C3)))**-1;
ll_y= y*log (p_y)+(1-y)*log(1-p_y);
model Y ~general(ll_y);
estimate 'PAI_E' (exp((g1-g0)*b1+(e1-e0)*b2+(g1*e1-g0*e0)*b3)-exp((g1-g0)*b1+(g1-g0)*e0*b3)-exp((e1-e0)*b2+(e1-e0)*g0*b3)+1)*pg
/ ( ( exp((e1-e0)*b2+(e1-e0)*g0*b3) - 1) + (exp((g1-g0)*b1+(e1-e0)*b2+(g1*e1-g0*e0)*b3)
-exp((g1-g0)*b1+(g1-g0)*e0*b3)-exp((e1-e0)*b2+(e1-e0)*g0*b3)+1) *pg);
run;
```

The equivalent Stata code would be:

```
  generate g1=1
  generate g0=0
  generate e1=1
  generate e0=0
  generate pg=0.5

  generate Ige = g*e
  logit y g e Ige c1 c2 c3

  nlcom (exp((g1-g0)*_b[g]+(e1-e0)*_b[e]+(g1*e1-g0*e0)*_b[Ige])-exp((g1-g0)*_b[g]+(g1-g0)*e0*_b[Ige])-exp((e1-e0)*_b[e]+(e1-e0)
*g0*_b[Ige])+1)*pg/ ( ( exp((e1-e0)*_b[e]+(e1-e0)*g0*_b[Ige]) - 1) + (exp((g1-g0)*_b[g]+(e1-e0)*_b[e]+(g1*e1-g0*e0)*_b[Ige])
-exp((g1-g0)*_b[g]+(g1-g0)*e0*_b[Ige])-exp((e1-e0)*_b[e]+(e1-e0)*g0*_b[Ige])+1) *pg);
```

To estimate the proportion of the total effect of E on binary outcome Y due to E when G is fixed to g_0 and the proportion due to interaction when G is continuous, and logistic regressions models (A1) and (A2) are used, one can use the code below. Suppose we have a SAS dataset named 'mydata' with outcome variable 'd', exposure variables 'e' and 'g' and three covariates 'c1', 'c2' and 'c3'. If there were more or fewer covariates the user would have to modify the second, third, fourth and fifth lines of the code below to include these covariates.

The user must input in the third line of code the two levels of G ('g1=' and 'g0=') and the two levels of E ('e1=' and 'e0=') that are being compared. The user must also input in the third line of the code the value of the covariates C at which the proportion attributable to interaction is to be calculated ('cc1=', 'cc2' and 'cc3='). Alternatively the mean value of these covariates in the sample could be inputted on this line as a summary measure (in a case-control study, these means should be computed only among the controls).

The output will include the proportion of the total effect of E that is attributable to interaction, along with a 95% confidence interval; the remaining proportion is that attributable to E when G is set to g_0.

```
proc nlmixed data=mydata;
parms b0=1 b1=0 b2=0 b3=0 bc1=0 bc2=0 bc3=0 a0=0 ac1=0 ac2=0 ac3=0 ss_g=1;
g1=1; g0=0; e1=1; e0=0; cc1=10; cc2=10; cc3=20;
p_y=(1+exp(-(b0 + b1*G + b2*E + b3*G*E + bc1*C1 + bc2*C2 + bc3*C3)))**-1;
mu_g =a0 + ac1*C1 + ac2*C2 + ac3*C3;
ll_g=-((g-mu_g)**2)/(2*ss_g)-0.5*log(ss_g);
ll_y= y*log (p_y)+(1-y)*log(1-p_y);
ll_o= ll_g + ll_y;
model Y ~general(ll_o);
estimate 'PAI_E' (exp(-g0*b1+(e1-e0)*b2-g0*e0*b3+(b1+e1*b3)*(mu_g)+0.5*ss_g*(b1+e1*b3)**2)
- exp(-g0*b1-g0*e0*b3+(b1+e0*b3)*(mu_g)+0.5*ss_g*(b1+e0*b3)**2)-exp((e1-e0)*b2+(e1-e0)*g0*b3)+1)
/ ( exp(-g0*b1+(e1-e0)*b2-g0*e0*b3+(b1+e1*b3)*(mu_g)+0.5*ss_g*(b1+e1*b3)**2)
- exp(-g0*b1-g0*e0*b3+(b1+e0*b3)*(mu_g)+0.5*ss_g*(b1+e0*b3)**2) );
run;
```

2.4. SAS and Stata Code to Implement Proportion of a Joint Effect Attributable to Either Exposure Alone and to Interaction

To estimate the proportion of the joint effect of both exposures on binary outcome Y due to each exposure alone and due to interaction, when logistic regression model (A1) is used, one can use the code below. We again suppose we have a SAS dataset named 'mydata' with outcome variable 'y', exposure variables 'e' and 'g' and three covariates 'c1', 'c2' and 'c3'. If there were more or fewer covariates the user would have to modify the second and fourth lines of the code below to include these covariates.

The user must input in the third line of code the two levels of G ('g1=' and 'g0=') and the two levels of E ('e1=' and 'e0=') that are being compared. The output gives the proportions due to G alone, the proportion due to E alone, and the proportion due to the interaction; 95% confidence intervals are also given for these three proportions. The three proportions will sum to 100%. The decomposition applies even if one of the exposures affects the other.

```
proc nlmixed data=mydata;
parms b0=1 b1=0 b2=0 b3=0 bc1=0 bc2=0 bc3=0;
g1=1; g0=0; e1=1; e0=0;
p_y=(1+exp(-(b0 + b1*G + b2*E + b3*G*E + bc1*C1 + bc2*C2 + bc3*C3)))**-1;
ll_y= y*log (p_y)+(1-y)*log(1-p_y);
model Y ~general(ll_y);
estimate 'PaG' (exp((g1-g0)*b1+(g1-g0)*e0*b3) - 1) / (exp((g1-g0)*b1+(e1-e0)*b2+(g1*e1-g0*e0)*b3) - 1);
estimate 'PaE' (exp((e1-e0)*b2+(e1-e0)*g0*b3) - 1) / (exp((g1-g0)*b1+(e1-e0)*b2+(g1*e1-g0*e0)*b3) - 1);
estimate 'Pa_INT' (exp((g1-g0)*b1+(e1-e0)*b2+(g1*e1-g0*e0)*b3)-exp((g1-g0)*b1+(g1-g0)*e0*b3)-exp((e1-e0)*b2+(e1-e0)*g0*b3)+1)
/(exp((g1-g0)*b1+(e1-e0)*b2+(g1*e1-g0*e0)*b3) - 1);
run;
```

The equivalent Stata code would be as follows (with the output first giving the proportion of joint effect due to G alone, then due to E alone, and then that due to their interaction):

```
  generate g1=1
  generate g0=0
  generate e1=1
  generate e0=0

  generate Ige = g*e
  logit y g e Ige c1 c2 c3

  nlcom (exp((g1-g0)*_b[g]+(g1-g0)*e0*_b[Ige]) - 1) / (exp((g1-g0)*_b[g]+(e1-e0)*_b[e]+(g1*e1-g0*e0)*_b[Ige]) - 1)
  nlcom (exp((e1-e0)*_b[e]+(e1-e0)*g0*_b[Ige]) - 1) / (exp((g1-g0)*_b[g]+(e1-e0)*_b[e]+(g1*e1-g0*e0)*_b[Ige]) - 1)
  nlcom (exp((g1-g0)*_b[g]+(e1-e0)*_b[e]+(g1*e1-g0*e0)*_b[Ige])-exp((g1-g0)*_b[g]+(g1-g0)*e0*_b[Ige])-exp((e1-e0)*_b[e]
+(e1-e0)*g0*_b[Ige])+1)/(exp((g1-g0)*_b[g]+(e1-e0)*_b[e]+(g1*e1-g0*e0)*_b[Ige]) - 1)
```

3. Continous Outcomes and Binary or Continuous Exposures

3.1. Proportion of a Total Effect Attributable to Interaction

As discussed in the Appendix to the text, for continuous exposures, when the effect of E on Y is unconfounded conditional on (C, G) then the total effect of E on Y, $E[Y_{e_1}|c] - E[Y_{e_0}|c]$, could be decomposed into two components as: $E[Y_{e_1}|c] - E[Y_{e_0}|c]$

$$= E[Y|g_0, e_1, c] - E[Y|g_0, e_0, c] + \int \{E[Y|g, e_1, c] - E[Y|g, e_0, c] - E[Y|g_0, e_1, c] + E[Y|g_0, e_0, c]\} dP(g|c).$$

Under the linear model

$$E[Y|G = g, E = e, C = c] = \alpha_0 + \alpha_1 g + \alpha_2 e + \alpha_3 eg + \alpha_4' c, \tag{A3}$$

these two components are:

$$\begin{aligned} E[Y|g, e_1, c] - E[Y|g, e_0, c] &= (\alpha_2 + g\alpha_3)(e_1 - e_0) \\ \int \{E[Y|g, e_1, c] - E[Y|g, e_0, c] - E[Y|g_0, e_1, c] + E[Y|g_0, e_0, c]\} dP(g|c) &= \alpha_3 \{E[G|c] - g_0\}(e_1 - e_0) \end{aligned}$$

and the proportion due to interaction is then $\frac{\alpha_3\{E[G|c]-g_0\}}{(\alpha_2+\alpha_3 E[G|c])}$.

This decomposition above marginalized over the distribution $P(c)$ gives: $E[Y_{e_1}] - E[Y_{e_0}]$

$$= \int \{E[Y|g_0, e_1, c] - E[Y|g_0, e_0, c]\} dP(c) + \int \{E[Y|g, e_1, c] - E[Y|g, e_0, c] - E[Y|g_0, e_1, c] + E[Y|g_0, e_0, c]\} dP(g, c)$$

and under model (A3) the components are:

$$\begin{aligned} E[Y|g, e_1, c] - E[Y|g, e_0, c] &= (\alpha_2 + g\alpha_3)(e_1 - e_0) \\ \int \{E[Y|g, e_1, c] - E[Y|g, e_0, c] - E[Y|g_0, e_1, c] + E[Y|g_0, e_0, c]\} dP(g|c) &= \alpha_3 \{E[G] - g_0\}(e_1 - e_0) \end{aligned}$$

and the proportion due to interaction is then $\frac{\alpha_3\{E[G]-g_0\}}{(\alpha_2+\alpha_3 E[G])}$. In section 3.3 SAS code is given for this latter decomposition.

3.2. Proportion of a Joint Effect Attributable to Either Exposure Alone and to Interaction

As also discussed in the Appendix to the text, if the joint effects of G and E are unconfounded conditional on C we can empirically decompose the joint effects of both exposures combined as follows:

$$\begin{aligned} E[Y|g_1, e_1, c] - E[Y|g_0, e_0, c] &= \{E[Y|g_1, e_0, c] - E[Y|g_0, e_0, c]\} + \{E[Y|g_0, e_1, c] - E[Y|g_0, e_0, c]\} \\ &\quad + \{E[Y|g_1, e_1, c] - E[Y|g_1, e_0, c] - E[Y|g_0, e_1, c] + E[Y|g_0, e_0, c]\}. \end{aligned}$$

We can then also compute the proportion of the joint effect due G alone as $\frac{E[Y|g_1,e_0,c]-E[Y|g_0,e_0,c]}{E[Y|g_1,e_1,c]-E[Y|g_0,e_0,c]}$, due to E alone as $\frac{E[Y|g_0,e_1,c]-E[Y|g_0,e_0,c]}{E[Y|g_1,e_1,c]-E[Y|g_0,e_0,c]}$, and due to their interaction as $\frac{E[Y|g_1,e_1,c]-E[Y|g_1,e_0,c]-E[Y|g_0,e_1,c]+E[Y|g_0,e_0,c]}{E[Y|g_1,e_1,c]-E[Y|g_0,e_0,c]}$.

On a difference scale, under the linear model

$$E[Y|G = g, E = e, C = c] = \alpha_0 + \alpha_1 g + \alpha_2 e + \alpha_3 eg + \alpha_4' c,$$

these three proportions are given by:

$$\begin{aligned}
\frac{E[Y|g_1,e_0,c]-E[Y|g_0,e_0,c]}{E[Y|g_1,e_1,c]-E[Y|g_0,e_0,c]} &= \frac{(\alpha_1+\alpha_3 e_0)(g_1-g_0)}{\alpha_1(g_1-g_0)+\alpha_2(e_1-e_0)+\alpha_3(g_1e_1-g_0e_0)}\\
\frac{E[Y|g_0,e_1,c]-E[Y|g_0,e_0,c]}{E[Y|g_1,e_1,c]-E[Y|g_0,e_0,c]} &= \frac{(\alpha_2+\alpha_3 g_0)(e_1-e_0)}{\alpha_1(g_1-g_0)+\alpha_2(e_1-e_0)+\alpha_3(g_1e_1-g_0e_0)}\\
\frac{E[Y|g_1,e_1,c]-E[Y|g_1,e_0,c]-E[Y|g_0,e_1,c]+E[Y|g_0,e_0,c]}{E[Y|g_1,e_1,c]-E[Y|g_0,e_0,c]} &= \frac{\alpha_3(g_1e_1-g_1e_0-g_0e_1+g_0e_0)}{\alpha_1(g_1-g_0)+\alpha_2(e_1-e_0)+\alpha_3(g_1e_1-g_0e_0)}.
\end{aligned}$$

3.3. SAS and Stata Code to Implement Proportion of a Total Effect Attributable to Interaction

To estimate the proportion of the total effect of E on continuous outcome Y due to E when G is fixed to g_0 and the proportion due to interaction, and logistic regression model (A3) is used, one can use the code below. Suppose we have a dataset named 'mydata' with outcome variable 'y', exposure variables 'e' and 'g' and three covariates 'c1', 'c2' and 'c3'. If there were more or fewer covariates the user would have to modify the second and fourth lines of the code below to include these covariates.

The user must input in the third line of code the level g_0 to which G will be fixed ('g0=') when carrying out the decomposition of the total effect of E into the proportion due to E when G is fixed to g_0 and the proportion due to interaction when G. The user must also input in the third line of the code the mean value of G in the population ('exg='). For the standard error to be valid it is assumed that the mean of G is known; alternatively, standard errors and confidence interval can be interpretted as that for the proportion attributable to interaction in a population which had the same underlying effects as the sample in question, but had a mean of G equal to the mean of G in the sample.

The output will include the proportion of the total effect of E that is attributable to interaction, along with a 95% confidence interval; the remaining proportion is that attributable to E when G is set to g_0.

```
proc nlmixed data=mydata;
parms b0=0 b1=0 b2=0 b3=0 bc1=0 bc2=0 bc3=0 ss_y=1;
g0=0; exg=0.5;
mu_y = b0 + b1*G + b2*E + b3*G*E + bc1*C1 + bc2*C2 + bc3*C3;
ll_y=-((y-mu_y)**2)/(2*ss_y)-0.5*log(ss_y);
model Y ~general(ll_y);
estimate 'PAI_E' (b3*exg-g0)/(b2+b3*exg);
run;
```

The equivalent Stata code would be:

```
generate g0=0
generate exg=0.5

generate Ige = g*e
reg y g e Ige c1 c2 c3

nlcom (_b[Ige]*exg-g0)/(_b[e]+_b[Ige]*exg)
```

3.4. SAS and Stata Code to Implement Proportion of a Joint Effect Attributable to Either Exposure Alone and to Interaction

To estimate the proportion of the joint effect of both exposures on continuous outcome Y due to each exposure alone and due to interaction, when logistic regression model (A3) is used, one can use the code below. We again suppose we have a dataset named 'mydata' with outcome variable 'y', exposure variables 'e' and 'g' and three covariates 'c1', 'c2' and 'c3'. If there were more or fewer covariates the user would have to modify the second and fourth lines of the code below to include these covariates.

The user must input in the third line of code the two levels of G ('g1=' and 'g0=') and the two levels of E ('e1=' and 'e0=') that are being compared. The output gives the proportions due to G alone, the proportion due to E alone, and the proportion due to the interaction; 95% confidence intervals are also given for these three proportions. The three proportions will sum to 100%. The decomposition applies even if one of the exposures affects the other.

```
proc nlmixed data=mydata;
parms b0=0 b1=0 b2=0 b3=0 bc1=0 bc2=0 bc3=0 ss_y=1;
g1=1; g0=0; e1=1; e0=0;
mu_y = b0 + b1*G + b2*E + b3*G*E + bc1*C1 + bc2*C2 + bc3*C3;
ll_y=-((y-mu_y)**2)/(2*ss_y)-0.5*log(ss_y);
model Y ~general(ll_y);
estimate 'PaG' (b1+b3*e0)*(g1-g0)/( b1*(g1-g0) + b2*(e1-e0) + b3*(g1*e1-g0*e0) );
estimate 'PaE' (b2+b3*g0)*(e1-e0)/( b1*(g1-g0) + b2*(e1-e0) + b3*(g1*e1-g0*e0) );
estimate 'Pa_INT' b3*(g1*e1-g1*e0-g0*e1+g0*e0)/( b1*(g1-g0) + b2*(e1-e0) + b3*(g1*e1-g0*e0) );
run;
```

The equivalent Stata code would be as follows (with the output first giving the proportion of joint effect due to G alone, then due to E alone, and then that due to their interaction):

```
generate g1=1
generate g0=0
generate e1=1
generate e0=0

generate Ige = g*e
reg y g e Ige c1 c2 c3

nlcom (_b[g]+_b[Ige]*e0)*(g1-g0)/( _b[g]*(g1-g0) + _b[e]*(e1-e0) + _b[Ige]*(g1*e1-g0*e0) )
nlcom (_b[e]+_b[Ige]*g0)*(e1-e0)/( _b[g]*(g1-g0) + _b[e]*(e1-e0) + _b[Ige]*(g1*e1-g0*e0) )
nlcom _b[Ige]*(g1*e1-g1*e0-g0*e1+g0*e0)/( _b[g]*(g1-g0) + _b[e]*(e1-e0) + _b[Ige]*(g1*e1-g0*e0) )
```