## Web Appendix 1

Assume that we have data set, *DS*, which is the data structure for an investigation of the joint effect of *alcohol* and *smoke* on an outcome variable, *case*. Consider a linear odds ratio model of the form $\frac{\Pr(case=1)}{\Pr(case=0)} = odds = e^{(\beta_0)}(1 + \beta_1 alcohol + \beta_2 smoke + \beta_3 alcohol \times smoke)$, which may be fitted via SAS as follows:

```
proc nlmixed data=DS;
   odds=exp(b0) * (1+ b1*alcohol + b2*smoke + b3*alcohol*smoke) ;
   model case ~ binary( odds/(1+odds) ); run;
```

The SAS macro below can be used to derive a likelihood-based 95% confidence interval for the parameter, $\beta_3$, representing the product term in the linear odds ratio model. The macro is invoked by the command *%bounds* (data=, outcome=, odds= , param= ). The term 'odds' of the command invoking the macro allows the user to specify the form of the regression model. The term 'param' of the command invoking the macro allows the user to specify the regression model parameter representing the statistical product term in the model for which the analyst wishes to derive 95% upper and lower confidence bounds. For the example above, the macro would be invoked by the following command:

```
%bounds (data=DS, outcome=case, odds=exp(b0)*(1+ b1*alcohol + b2*smoke
+ b3*alcohol*smoke), param=b3 );
```

```
**********************************;
%macro bounds (data= , outcome= , odds= , param= );

ods output fitstatistics = fitstatistics
ParameterEstimates=ParameterEstimates;
proc nlmixed data=&data   ;
 odds = &odds ;
 model &outcome ~ binary( odds/(1+odds) );

data fitstatistics;
set fitstatistics;
```

```
if (Descr = "-2 Log Likelihood") then do;
call symput ('LL', put(value,best16.));
call symput("refLL",put(value,best16.)); end;

data ParameterEstimates;
set ParameterEstimates;
if (PARAMETER = "&param") then do;
  call symput("istep",put(STANDARDERROR,best16.));
  call symput("ibeta",put(ESTIMATE,best16.));  end;
if (PARAMETER = "b0") then call symput("ibeta0",put(ESTIMATE,best16.));
if (PARAMETER = "b1") then call symput("ibeta1",put(ESTIMATE,best16.));
if (PARAMETER = "b2") then call symput("ibeta2",put(ESTIMATE,best16.));

data lci uci;
set _null_;
null= 0;  neglogl=0;  difference=0;  param=0;  step=0;

%DO I = 1 %TO 2;   %* I=1 is Lower Bound ;
%let conv=0;   %let step=&istep;  %let beta=&ibeta;

%DO %WHILE (&CONV=0);
ods output fitstatistics = fitstatistics
ParameterEstimates=ParameterEstimates;
proc nlmixed data=&data   ;
parms  b0=&ibeta0  b1=&ibeta1  b2=&ibeta2   ;
 &param=&beta;
 odds = &odds;
model &outcome ~ binary( odds/(1+odds) );
title1 "beta is &beta "   ;

data fitstatistics;
set fitstatistics;
format value best16.;
if (Descr = "-2 Log Likelihood") then call symput ('LL',
put(value,best16.));  run;

data ParameterEstimates;
set ParameterEstimates;
if (PARAMETER = "b0") then call symput("ibeta0",put(ESTIMATE,best16.));
if (PARAMETER = "b1") then call symput("ibeta1",put(ESTIMATE,best16.));
if (PARAMETER = "b2") then call symput("ibeta2",put(ESTIMATE,best16.));

%let diff=%sysevalf(&LL-&refLL);
%if %sysevalf(3.8413 <= &diff)  %then %do;
%if %sysevalf( &diff <= 3.8415)  %then %do;
%let CONV=1; %end;  %end;
%if %sysevalf( &diff > 3.8415 ) %then %do;
                    %IF &I=1 %then  %let beta=%sysevalf(&beta+&step);
                    %IF &I=2 %then  %let beta=%sysevalf(&beta-&step);
                       %let step=%sysevalf(&step*0.5); %end;
data tmp;
null= &refLL;    neglogl=&LL;    difference=&diff;   param=&beta;
step=&step; run;

%IF &I=1 %then  %do; proc append base =lci data = tmp;run;  %end;
%IF &I=2 %then  %do; proc append base =uci data = tmp;run;  %end;
```

```
%IF &I=1 %then %let beta=%sysevalf(&beta-&step);
%IF &I=2 %then %let beta=%sysevalf(&beta+&step);
%end;
%end;

dm 'out; clear; pgm';
proc print data=lci; title1 "95% Lower Confidence Bound - Iterations";
proc print data=uci; title1 "95% Upper Confidence Bound - Iterations";
data lb (keep=PARAM); set lci end=eof; if eof then output lb;
data ub (keep=PARAM); set uci end=eof; if eof then output ub;
data bd (rename=(param=Bound));set lb ub;
proc print data=bd NOOBS; title1 "Likelihood-Based 95% Lower and Upper
Confidence Bounds for Paramater &param";  title2 "Point Estimate is
&ibeta"; run;
%mend bounds;
```

## Web Appendix 2

Assume that we have a data structure for an investigation of the joint effect of *alcohol* and *smoke* on an outcome variable, *case*. Using the Stata statistical package, release 10, a linear odds ratio model of the form $odds = e^{(\beta_0)}(1+\beta_1 alcohol + \beta_2 smoke + \beta_3 alcohol \times smoke)$ may be fitted as follows:

```
program linearodds
  version 10
  args lnf b0 xb
  tempvar odds
  quietly gen double `odds' = exp(`b0')*(1+`xb')
  qui replace `lnf' = ln(`odds') - ln(1+`odds') if $ML_y1 == 1
  qui replace `lnf' = -ln(1+`odds') if $ML_y1 == 0
  qui replace `lnf' = . if `odds' < -1
  end

gen inter = alcohol * smoke
ml model lf linearodds (cons: ) (case = alcohol smoke inter, nocons)
ml maximize
```

A likelihood-based 95% confidence interval for the parameter, $\beta_3$, representing the product term in the linear odds ratio model may be obtained via the following Stata code run immediately after fitting the model.

```
* obtain likelihood based CI limits *
************************************
* initialize -2LL values
global LL = -2*e(ll)
global refLL = -2*e(ll)
* get interaction coefficient and standard error
matrix A = e(b)
global b3 = A[1,4]
matrix B = e(V)
global seb3 = sqrt(B[4,4])
* initialize other variables
global null = 0
global neglogl = 0
global diff = 0
global param = 0
global step = 0
global lcl = .
global ucl = .
```

```
* i = 1 for lower bound and i = 2 for upper bound
forvalues i = 1(1)2 {
        global conv = 0
        global step = $seb3
        global beta = $b3
        global num = 0

    while $conv == 0   {
        global num = $num + 1
    constraint define $num _b[eq2:inter]== $beta
        ml model lf linearodds (cons: ) (case = alcohol smoke inter, nocons),
constraint($num)
        ml init A, copy
        quietly ml maximize, difficult repeat(10)
        global LL = -2*e(ll)
        global diff = ($LL - $refLL)
        if ($diff >= 3.8413 & $diff <= 3.8415)  {
                global conv = 1
                                if (`i' == 1)     {
                                global lcl = $beta
                                                }
                                if (`i' == 2)     {
                                global ucl = $beta
                                                }
                                        }
                if ($diff >= 3.8415)  {
                                if (`i' == 1)     {
                                global beta = ($beta + $step)
                                                }
                                if (`i' == 2)     {
                                global beta = ($beta - $step)
                                                }
                                global step = ($step * 0.5)
                                        }
    disp $num, "null =", %8.4f $refLL," ","neglogl =", %8.4f $LL," ", "diff =", /*
    */   %6.4f $diff," ","step =", %6.4f $step," ","b3 =", %6.4f $beta
                                if (`i' == 1)     {
                                global beta = ($beta - $step)
                                                }
                                if (`i' == 2)     {
                                global beta = ($beta + $step)
                                                }
                                        } /* close of while loop */
                                } /* close forvalues loop */
disp "------------------------------------------------------------------------------"
disp "The likelihood based 95% CI limits are:", %6.4f $lcl,",",%6.4f $ucl
```