Logistic Regression

March 1, 2016
Biostatistics 208

Review of logistic regression for a single predictor

Example: dependence of CHD risk (P) on the binary predictor `arcus` in WCGS

- `arcus` $= 1$ for those with condition, `arcus` $= 0$ for those without
- `chd69` is a binary indicator of CHD at the end of follow-up

Default output of model - reports exponentiated coefficients (ORs) and 95% CIs:

```
. logistic chd69 i.arcus

Logistic regression                               Number of obs   =       3152
                                                  LR chi2(1)      =      12.98
                                                  Prob > chi2     =     0.0003
Log likelihood = -879.10783                       Pseudo R2       =     0.0073
------------------------------------------------------------------------------
       chd69 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       arcus |
     present |    1.63528   .2195035     3.66   0.000        1.257    2.127399
       _cons |    .074344   .0062298   -31.02   0.000     .0630839    .0876141
------------------------------------------------------------------------------
```

- default output of Stata logistic regression procedure gives the odds ratio comparing the odds of CHD among men with `arcus` to the odds among men without `arcus`
- starting with Stata version 12, the odds of outcome occurrence in the baseline (`arcus` $= 0$) group are also provided

Review of logistic regression for a single predictor

Example: dependence of CHD risk (P) on the binary predictor `arcus` in WCGS

`logistic` output with coef option - reports coefficients and 95% CIs:

```
. logistic chd69 arcus, coef
Logistic regression                               Number of obs   =       3152
                                                  LR chi2(1)      =      12.98
                                                  Prob > chi2     =     0.0003
Log likelihood = -879.10783                       Pseudo R2       =     0.0073
------------------------------------------------------------------------------
       chd69 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       arcus |
     present |   .4918141   .1342299     3.66   0.000     .2287283    .7548999
       _cons |  -2.599052   .0837965   -31.02   0.000     -2.76329   -2.434814
------------------------------------------------------------------------------
```

- $\beta_0 = -2.599052$, the log odds of CHD among individuals with `arcus` $= 0$
- $\beta_1 = 0.4918141$, the log odds ratio comparing the odds CHD among individuals with

$$\log\left[\frac{P(\texttt{arcus})}{1-P(\texttt{arcus})}\right] = -2.599052 + 0.4918141\texttt{arcus}$$

Review of logistic regression for a single predictor

Note: the logistic model on the previous slide can be expressed in these equivalent ways

Log-odds : $$\log\left[\frac{P(\texttt{arcus})}{1-P(\texttt{arcus})}\right] = \beta_0 + \beta_1\texttt{arcus}$$

Odds : $$\frac{P(\texttt{arcus})}{1-P(\texttt{arcus})} = \exp\left(\beta_0 + \beta_1\texttt{arcus}\right)$$

Probability: $$P(\texttt{arcus}) = \frac{\exp\left(\beta_0 + \beta_1\texttt{arcus}\right)}{1+\exp\left(\beta_0 + \beta_1\texttt{arcus}\right)}$$

Review of logistic regression for a single predictor

Note: The effect of `arcus` on the outcome is *additive* on the log odds scale, and *multiplicative* on the odds scale

The log odds of CHD for an indiv. with arcus (`arcus` =1) is equal to the log odds for an indiv. without arcus (`arcus` =0) plus β_1:

$$\log\left[\frac{P(\texttt{arcus}=1)}{1-P(\texttt{arcus}=1)}\right]-\log\left[\frac{P(\texttt{arcus}=0)}{1-P(\texttt{arcus}=0)}\right]=(\beta_0+\beta_1)-\beta_0=\beta_1$$

The odds of CHD for an indiv. with arcus (`arcus` =1) is equal to the odds for an indiv. without arcus (`arcus` =1) times $\exp(\beta_1)$:

$$\frac{\dfrac{P(\texttt{arcus}=1)}{1-P(\texttt{arcus}=1)}}{\dfrac{P(\texttt{arcus}=0)}{1-P(\texttt{arcus}=0)}}=\frac{\exp(\beta_0+\beta_1)}{\exp(\beta_0)}=\frac{\exp(\beta_0)\exp(\beta_1)}{\exp(\beta_0)}=\exp(\beta_1)$$

Example: dependence of CHD risk (P) on the binary predictor `arcus` in WCGS

$$\log\left[\frac{P(\texttt{arcus})}{1-P(\texttt{arcus})}\right] = -2.599052 + 0.4918141\texttt{arcus}$$

among those without arcus ($\texttt{arcus} = 0$):

log-odds of CHD: -2.599052

odds of CHD: $\exp(-2.599052) = 0.07434402$

probability of CHD: $0.07434402 / (1 + 0.07434402) = 0.06919945$

among those with arcus ($\texttt{arcus} = 1$):

log-odds of CHD: $-2.599052 + 0.4918141 = -2.1072379$

odds of CHD: $\exp(-2.599052 + 0.4918141) = 0.1215733$

probability of CHD: $0.1215733 / (1 + 0.1215733) = 0.10839532$

comparison of those with arcus ($\texttt{arcus} = 1$) to those without ($\texttt{arcus} = 0$):

log odds ratio : $(-2.1072379) - (-2.599052) = 0.4918141$

odds ratio : $\exp(0.4918141) = 1.63528$

95% C.I. for odds ratio: $(\exp(0.2287283)\ ,\ \exp(0.7548999))\ ;\ (1.26, 2.13)$ (based on the 95% CI for the coefficient in the previous output)

Example: dependence of CHD risk (P) on the binary predictor `arcus` in WCGS (continued)

- The logistic model (below) can also be used to compute other measures of risk:

$$RR = \frac{P(1)}{P(0)} = \frac{\exp(-2.1072379)/\left[1+\exp(-2.1072379)\right]}{\exp(-2.599052)/\left[1+\exp(-2.599052)\right]} = \frac{0.10839532}{0.06919945} = 1.566419$$

$$RD = P(1) - P(0) = 0.10839532 - 0.06919945 = 0.03919587$$

- Logistic models frequently used in estimation of marginal causal effects
- *Note*: Estimated *RR* & *RD* from a logistic model won't in general correspond to estimates obtained from a relative risk or risk difference binary regression approach, or to *marginal effects* estimated from the logistic model, especially when additional predictors are included.

$$\log\left[\frac{P(\texttt{arcus})}{1-P(\texttt{arcus})}\right] = -2.599052 + 0.4918141\texttt{arcus}$$

Example: dependence of CHD risk (P) on age in WCGS

```
. logistic chd69 age
Logistic regression                               Number of obs   =       3154
                                                  LR chi2(1)      =      42.89
                                                  Prob > chi2     =     0.0000
Log likelihood = -869.17806                       Pseudo R2       =     0.0241
------------------------------------------------------------------------------
       chd69 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.077262   .0121756     6.58   0.000      1.05366    1.101392
       _cons |   .0026333   .0014465   -10.81   0.000     .0008973    .0077283
------------------------------------------------------------------------------
```

output with `coef` option - reports coefficients and 95% CIs:

```
. logistic chd69 age, coef
Logistic regression                               Number of obs   =       3154
                                                  LR chi2(1)      =      42.89
                                                  Prob > chi2     =     0.0000
Log likelihood = -869.17806                       Pseudo R2       =     0.0241
------------------------------------------------------------------------------
       chd69 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   .0744226   .0113024     6.58   0.000     .0522703    .0965748
       _cons |  -5.939516    .549322   -10.81   0.000    -7.016167   -4.862865
------------------------------------------------------------------------------
```

Example: dependence of CHD risk (P) on age in WCGS

$$\log\left[\frac{P(\text{age})}{1-P(\text{age})}\right] = \beta_0 + \beta_1 \text{age}$$

$$= -5.939516 \;\; + 0.0744226 \;\; \text{age}$$

- -5.939516 is the log odds of CHD among individuals with age = 0
- 0.0744226 is the log odds ratio comparing the odds CHD among individuals with age = x+1 (in years) to the odds CHD among individuals with age = x

risk associated with a fixed age (age = 55):

log-odds of CHD: -5.939516 + 0.0744226 × 55 = -1.846273

odds of CHD: exp(-1.846273) = 0.15782428

probability of CHD: 0.15782428 / (1 + 0.15782428) = 0.13631108

OR associated with a one year increase in age:

log odds ratio : (-5.939516 + 0.0744226*56) - (-5.939516 + 0.0744226*55) = 0.0744226

odds ratio : exp(0.0744226) = 1.077262

95% C.I. for odds ratio: (exp(0.0522703) , exp(0.0965748)) ; (1.05, 1.10)

OR associated with a ten year increase in age:

log odds ratio : 10 X 0.0744226= 0.744226

odds ratio : exp(0.744226) = 2.1048117

95% C.I. for odds ratio: (exp(10 X 0.0522703) , exp(10 X 0.0965748)) ; (1.69, 2.63)

Logistic models with multiple predictors

Example (two binary predictors): relationship between CHD, type A/B behavior pattern and smoking (yes/no) in WCGS

Research question: Could other factors (e.g. behaviors or factors reflecting "lifestyle") explain part (or all) of the association between CHD and type A behavior pattern?

(The created variable smoke is a binary indicator of any reported smoking):

```
. logistic chd69 i.dibpat i.smoke
Logistic regression                               Number of obs   =       3154
                                                  LR chi2(2)      =      60.51
                                                  Prob > chi2     =     0.0000
Log likelihood = -860.36587                       Pseudo R2       =     0.0340
------------------------------------------------------------------------------
       chd69 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      dibpat |
      A1,A2  |   2.301319   .3238094     5.92   0.000     1.746657    3.032117
       smoke |
     smoker  |     1.8002   .2422866     4.37   0.000     1.382798    2.343597
       _cons |   .0393656   .0054842   -23.22   0.000     .0299593    .0517251
------------------------------------------------------------------------------
```

Interpretation:

- The adjusted odds ratio of 2.3 for type A behavior holds for smokers and non-smokers alike.
- Similarly, the adjusted odds ratio of 1.8 for smokers holds for type A & B behavior patterns.
- Estimated odds for CHD among non-smoker, type-B individuals is 0.39

Logistic models with multiple predictors

Example: CHD risk with systolic blood pressure and total serum cholesterol in the WCGS

Research question: are cholesterol and systolic blood pressure independently predictive of CHD risk?

```
. logistic chd69 chol sbp if chol<600
Logistic regression                               Number of obs   =       3141
                                                  LR chi2(2)      =     110.21
                                                  Prob > chi2     =     0.0000
Log likelihood = -831.98952                       Pseudo R2       =     0.0621
------------------------------------------------------------------------------
       chd69 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        chol |   1.011765   .0014981     7.90   0.000     1.008833    1.014706
         sbp |   1.024741   .0039104     6.40   0.000     1.017106    1.032434
       _cons |   .0002261   .0001393   -13.63   0.000     .0000676    .0007562
------------------------------------------------------------------------------
```

Notes:

- Excludes 12 observations with missing `chol` and 1 obs. with `chol` ≥ 600.
- Assumption of linearity for both `chol` and `sbp` must be checked before model is accepted as reasonable.

Logistic models with multiple predictors

Example: Logistic model for SBP and cholesterol level in WCGS (*continued*)

```
. logistic chd69 chol sbp if chol<600, coef
Logistic regression                               Number of obs   =       3141
                                                  LR chi2(2)      =     110.21
                                                  Prob > chi2     =     0.0000
Log likelihood = -831.98952                       Pseudo R2       =     0.0621

------------------------------------------------------------------------------
       chd69 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        chol |   .0116966   .0014807     7.90   0.000     .0087945    .0145987
         sbp |   .0244401    .003816     6.40   0.000      .016961    .0319193
       _cons |  -8.394706   .6160962   -13.63   0.000    -9.602233   -7.18718
------------------------------------------------------------------------------
```

Notes:

- 0.0117 is the log-odds ratio for each unit increase in `chol` holding `sbp` fixed
- 0.0244 gives the log-odds ratio for each unit increase in `sbp` holding `chol` fixed
- -8.395 gives the log-odds of CHD among indiv. with `chol=0` & `sbp=0`
- model specifies linearity of log odds in both predictors:
  - the log-odds of CHD is linear in cholesterol for any specified value of SBP
  - the log-odds of CHD is linear in SBP for any specified value of cholesterol

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS (subsample of 1055 women without diabetes at enrollment)

Goal: Investigate possibly causal association between exercise and the occurrence of hypertension at study baseline

- Hypertension measured as a binary indicator of enrollment SBP>140
- Exercise represented as a binary indicator of exercise ≥ 3 times / week in the year before enrollment
- Evaluate the roles of other predictors as potential confounding (or mediating) variables
- Look for potential interactions with other predictors; assess nonlinearity and lack of overlap

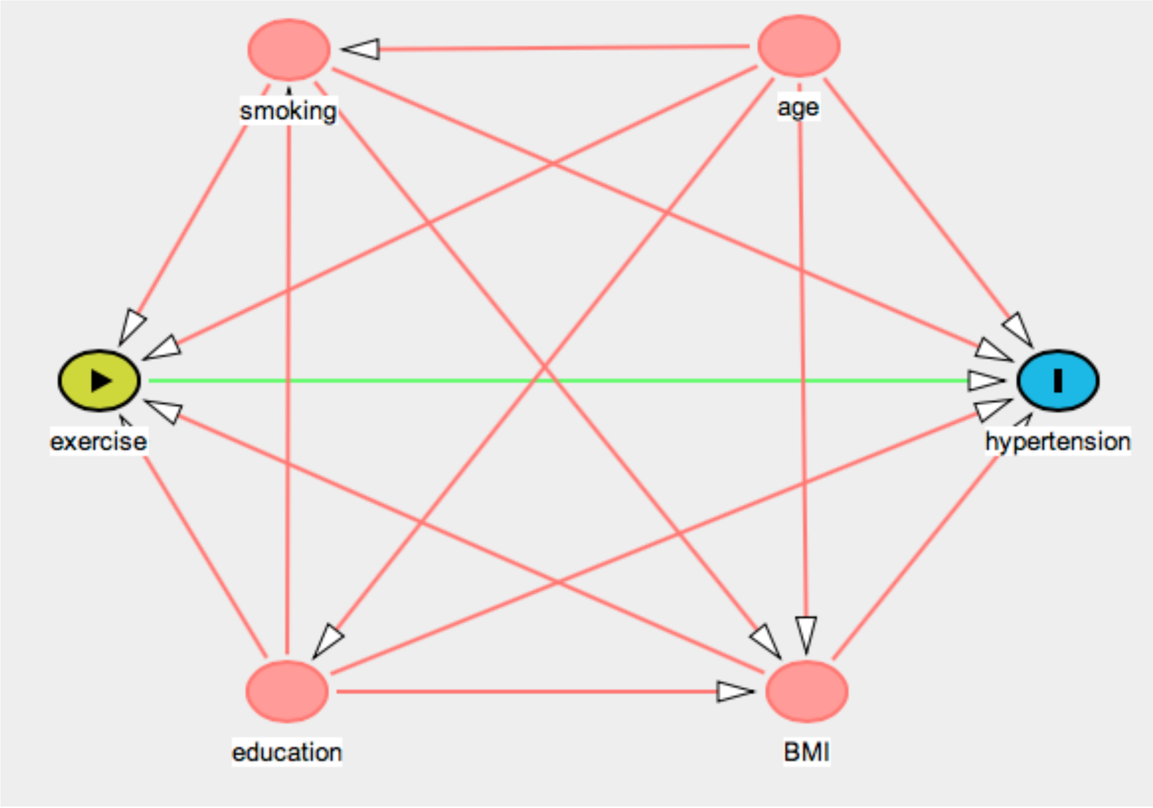
Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Additional variables from HERS that may be relevant predictors include:
  - demographic (age, body size, education)
  - health (cholesterol, glucose)
  - lifestyle (smoking, alcohol, diet, medications)

- Question: Could some or all of the apparent association between hypertension and exercise be explained by controlling for these variables?

- Note: predictors such as cholesterol & glucose could be hypothesized to play a mediating role - omitted in DAG



MSAS: smoking, age, education & BMI

Evaluating confounding using logistic regression

Example: Crude/unadjusted association between hypertension and exercise in HERS

```
* unadjusted logistic model
. logistic hypt exer3
Logistic regression                               Number of obs   =       1055
                                                  LR chi2(1)      =      10.12
                                                  Prob > chi2     =     0.0015
Log likelihood = -667.38065                       Pseudo R2       =     0.0075
------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       exer3 |   .6526043   .0882528    -3.16   0.002     .5006573    .8506665
       _cons |   .5953608    .049477    -6.24   0.000     .5058733    .7006784
-------------+----------------------------------------------------------------
```

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

```
* logistic model including MSAS predictors
. logistic hypt i.exer3 i.edu i.csmker agec bmisp
Logistic regression                               Number of obs   =       1054
                                                  LR chi2(8)      =      53.82
                                                  Prob > chi2     =     0.0000
Log likelihood = -645.12775                       Pseudo R2       =     0.0400
------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     1.exer3 |   .7251488   .1048338    -2.22   0.026     .5462231    .9626849
       1.edu |   .7278707   .1006952    -2.30   0.022     .5550055    .9545776
    1.csmker |   1.210394   .2428564     0.95   0.341     .8168453    1.793552
        agec |   1.060382   .0113939     5.46   0.000     1.038284    1.082951
      bmisp1 |   .9541977   .0734822    -0.61   0.543     .8205174    1.109657
      bmisp2 |   1.735852   1.197488     0.80   0.424     .4490619    6.709952
      bmisp3 |    .205744   .5854537    -0.56   0.578     .0007784    54.38248
      bmisp4 |   3.052587   10.39188     0.33   0.743     .0038631    2412.131
       _cons |   .3695945   .1793267    -2.05   0.040     .1427986    .9565928
------------------------------------------------------------------------------
```

`agec` (in years at enrollment, centered)   `bmi` (body mass index (kg/m^2), centered, and represented as a cubic spline)

`edu` (>12 yrs education)   `csmker` (smoker at enrollment)

Note: HDL cholesterol & impaired fasting glucose (IFG) not included because of their possible mediating effects

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

The adjusted odds ratio for the effect of exercise in the model including the other predictors is closer to the null value (one) than the unadjusted OR:

	OR	95% CI	*p*-value (Wald)
unadjusted	0.653	0.50, 0.85	0.002
adjusted	0.725	0.54, 0.95	0.026

- The adjusted odds ratio 0.725 for the effect of exercise accounts for the possible confounding influence of the other variables in the model. (Results are similar if cholesterol and IFG are included.)

Note: the adjusted OR may have a valid causal interpretation, but does *not* generally estimate an average causal effect

Evaluating confounding using logistic regression

Collapsibility and odds ratios

- Exponentiated coefficient for exercise in previous model estimates the conditional odds ratio (OR_c) for the effect of exercise, given fixed values of the other included predictors (and assuming no interaction)
  - has a valid, *individual* causal interpretation if
    1. sample is representative of target population
    2. no unmeasured confounders
    3. correctly specified model

- The marginal odds ratio (OR_m) is defined as the odds ratio for the effect of exercise on hypertension obtained by averaging over the values of the model-predicted outcome probabilities (an example of an average causal effect)
  - has a *population* causal interpretation if
    1. sample is representative of target population
    2. no unmeasured confounders
    3. correctly specified model

- In general, $OR_c \neq OR_m$ - reflecting *non-collapsibility* of the odds ratio
  - By contrast, RR & RD are *collapsible* measures
  - Comparison of OR_c & OR_m can be useful in evaluating effects of non-collapsibility (Menglan Pang M, Kaufman JS, Platt RW. Studying noncollapsibility of the odds ratio with marginal structural and logistic regression models. Stat Methods Med Res; 2013.)

Conditional and marginal effects from the risk difference model

The linear (risk difference) regression model for the dependence of a binary outcome Y on binary predictors X_1 and X_2:

$$\Pr\left[Y = 1 | X_1 = x_1,\ X_2 = x_2\right] = P\left(x_1,\ x_2\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

β_1 estimates the *conditional risk difference* (RD_c) for the effect of X_1 on Y (*conditional* on the value of X_2)

The *marginal probability* for Y=1 conditional on X_1 is

$$P(x_1) = \Pr\left[Y = 1 | X_1 = x_1\right] = \sum_{j=0,\,1} \Pr\left[Y = 1 | X_1 = x_1, X_2 = j\ \right] \times \Pr\left[X_2 = j\right]$$

The corresponding *marginal risk difference* is $RD_m = P(1) - P(0)$

For this model, the conditional and marginal effects coincide: $RD_m = \beta_1$

Note: A similar result holds for the relative risk regression model: $RR_m = e_1^{\beta}$

Conditional and marginal effects from the logistic model

The logistic regression model for the dependence of binary predictors X_1 and X_2 on a binary outcome Y :

$$\Pr\left[Y = 1|X_1 = x_1,\ X_2 = x_2\right] = P\left(x_1,\ x_2\right) = \frac{\exp\left[\beta_0 + \beta_1 x_1 + \beta_2 x_2\right]}{\left(1 + \exp\left[\beta_0 + \beta_1 x_1 + \beta_2 x_2\right]\right)}$$

β_1 estimates the conditional log OR_c for the effect of X_1 on Y (i.e. *conditional* on the value of X_2)

The *marginal probability* for Y=1 conditional on X_1 is

$$P(x_1) = \Pr\left[Y = 1|X_1 = x_1\right] = \sum_{j=0,\,1} \Pr\left[Y = 1|X_1 = x_1, X_2 = j\ \right] \times \Pr\left[X_2 = j\right]$$

The corresponding *marginal odds ratio* is $$OR_m = \frac{P(1)}{(1 - P(1))} / \frac{P(0)}{(1 - P(0))}$$

For the logistic model: $OR_m \neq e_1^{\beta}$ (e.g. unless $\beta_2 = 0$)

Example: Artificial data illustrating non-collapsibility of OR
no confounding present (C is balanced with X)

$C = 1$

	Y=1	Y=0	
X=1	50	50	100
X=0	20	80	100

OR = 4.0

$C = 0$

	Y=1	Y=0	
X=1	80	20	100
X=0	50	50	100

OR = 4.0

Pooled

	Y=1	Y=0	
X=1	130	70	200
X=0	70	130	200

OR = 3.45

```
. cs Y X, by(C) or

                C |       OR       [95% Conf. Interval]   M-H Weight
-----------------+-------------------------------------------------
                0 |          4      2.143427    7.460138            5 (Cornfield)
                1 |          4      2.143427    7.460138            5 (Cornfield)
-----------------+-------------------------------------------------
            Crude |    3.44898      2.288457    5.198021
     M-H combined |          4      2.566617    6.233887
-------------------------------------------------------------------
Test of homogeneity (M-H)      chi2(1) =     0.000  Pr>chi2 = 1.0000

                    Test that combined OR = 1:
                                Mantel-Haenszel chi2(1) =      39.36
                                                Pr>chi2 =     0.0000
```

- Non-collapsibility: marginal (crude) OR ≠ conditional (combined) OR, even when no confounding present
- In regression models controlling for confounders, a similar result holds:

Example: Artificial example repeated with logistic regression model

```
. logistic Y i.X i.C
------------------------------------------------------------------------------
           Y | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         1.X |          4   .9055385     6.12   0.000     2.566617    6.233887
         1.C |        .25   .0565962    -6.12   0.000     .1604136     .389618
       _cons |          1     .17943     0.00   1.000     .7035078    1.421448
------------------------------------------------------------------------------
. quietly margins X, post
. nlcom (_b[1.X]/(1-_b[1.X])) / (_b[0.X]/(1-_b[0.X]))
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |   3.448979    .686414     5.02   0.000     2.103633    4.794326
------------------------------------------------------------------------------
```

$$OR_c \neq OR_m$$

Example: Artificial example repeated with risk difference regression model

```
. * risk difference regression model (to be discussed further in lecture 11)
. binreg Y i.X i.C, rd
------------------------------------------------------------------------------
             |                 EIM
           Y | Risk Diff.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         1.X |         .3   .0452769     6.63   0.000     .2112589    .3887411
         1.C |        -.3   .0452769    -6.63   0.000    -.3887411   -.2112589
       _cons |         .5    .041687    11.99   0.000      .418295     .581705
------------------------------------------------------------------------------

. quietly margins X, post
. nlcom _b[1.R] - _b[0.R]
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |         .3   .0452769     6.63   0.000     .2112589    .3887411
------------------------------------------------------------------------------
```

$RD_c = RD_m$

Example: Artificial example repeated with relative risk regression model

```
. * relative risk regression model (to be discussed further in lecture 11)
. binreg Y i.X i.C, rr
------------------------------------------------------------------------------
             |                 EIM
           Y | Risk Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         1.X |   1.778207   .1820147     5.62   0.000     1.454972    2.173252
         1.C |   .5623643   .0575628    -5.62   0.000       .46014    .6872986
       _cons |   .4579834   .0441135    -8.11   0.000     .3791937    .5531443
------------------------------------------------------------------------------
. quietly margins X, post
. nlcom _b[1.X] / _b[0.X]
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |   1.778207   .1820147     9.77   0.000     1.421465    2.134949
------------------------------------------------------------------------------
```

$$RR_c = RR_m$$

Estimating the marginal effect in the HERS example

- Conditional odds ratio for the effect of exercise (from previous model)

```
------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     1.exer3 |   .7251488   .1048338    -2.22   0.026     .5462231    .9626849
```

- Marginal outcome probabilities for exercise/no exercise

```
. margins exer3, post
Predictive margins                                Number of obs   =       1054
Model VCE    : OIM
Expression   : Pr(hypt), predict()
------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       exer3 |
          0  |   .3632016   .0192702    18.85   0.000     .3254327    .4009706
          1  |   .2935795   .0222818    13.18   0.000      .249908     .337251
------------------------------------------------------------------------------
```

- `margins` uses the previously fitted model to estimate the average outcome probabilities for the entire sample under exercise/no exercise
- marginal probabilities can be used to estimate marginal measures of association

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Marginal OR_m , RR_m & RD_m for the effect of exercise (from marginal outcome probabilities estimated under exercise=$1/0$)

```
* marginal OR
. nlcom (_b[1.exer3]/(1-_b[1.exer3])) / (_b[0.exer3]/(1-_b[0.exer3]))
       _nl_1:  (_b[1.exer3]/(1-_b[1.exer3])) / (_b[0.exer3]/(1-_b[0.exer3]))
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |   .7348022   .1023049     7.18   0.000     .5342881    .9353162
------------------------------------------------------------------------------
* marginal RR
. nlcom (_b[1.exer3] / _b[0.exer3])
       _nl_1:  _b[1.exer3] / _b[0.exer3]
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |   .8129343   .0769937    10.56   0.000     .6620295    .9638391
------------------------------------------------------------------------------

* marginal RD
. lincom (_b[1.exer3] - _b[0.exer3])
 ( 1)  - 0bn.exer3 + 1.exer3 = 0
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |  -.0677951    .030205    -2.24   0.025    -.1269959   -.0085943
------------------------------------------------------------------------------
```

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

Summary:

	OR	95% CI
unadjusted	0.65	0.50, 0.85
adjusted (OR_c)	0.73	0.55, 0.96
marginal (OR_m)	0.73	0.53, 0.93

- Observed difference between adjusted and unadjusted ORs for exercise (0.72, 0.65) implies some degree of confounding may be operating
- OR_m & OR_c estimates similar in this case (non-collapsibility effect is negligible)
- Note that if BMI was a mediator of this relationship, the adjusted conditional effect of exercise would represent a direct effect

Evaluating confounding using logistic regression

Summary:

- Conditional odds ratio (OR_c) from an adjusted logistic regression model cannot generally be equated with a corresponding average/marginal causal effect measure because of non-collapsibility
  - The OR_c is a valid effect measure, but must be interpreted conditionally
  - Approximates a marginal RR only in the case of rare outcomes
  - Because of non-collapsibility, methods to assess degree of confounding (and mediation effects) based on changes in coefficients unreliable for logistic models

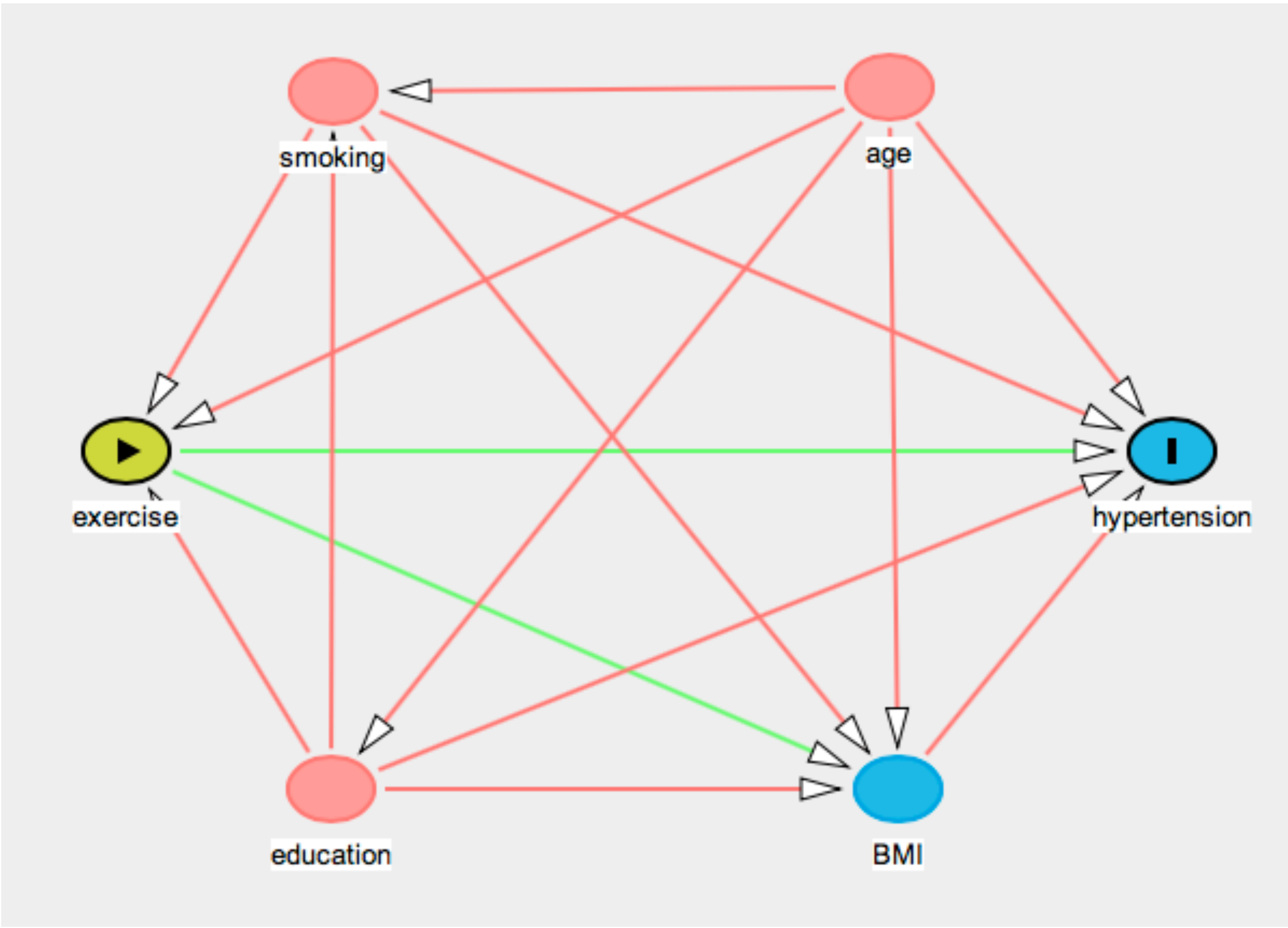
- The `margins` (and now `teffects` in Stata 13 & 14) can be used to get estimates of marginal OR, RR & RD for logistic models
  - Log-relative risk and risk difference regression models can be used as well, but attention must be paid to convergence issues (lecture 11)

- Strategies for evaluating confounding otherwise unchanged from recommendations made for linear models

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Consider possible mediation role of BMI



Note: see section 4.5.4 in VGSM for discussion of BMI as a possible mediator of exercise in HERS

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Three steps for evaluating mediation of exercise effect by BMI (analysis should be based same set of observations):

  1. evaluate adjusted assoc. between exercise and BMI
  2. evaluate adjusted assoc. between exercise and hypertension
  3. evaluate adjusted assoc. between exercise and hypertension controlling for BMI

- The OR for exercise from the 3rd model estimates a direct effect of exercise not mediated by BMI (and conditional on the other predictors)

- Estimating separate indirect and direct components of mediating effects is problematic due to non-collapsibility of ORs (except for rare outcomes - VanderWeele TJ, Vansteelandt S. Odds Ratios for Mediation Analysis for a Dichotomous Outcome. Am J Epidemiol. 2010; 172:1339–1348.)

- As discussed in lecture 4, confounders of the outcome-exposure and outcome-mediator relationships need to be considered.

- *Note*: Interactions between mediator and exposure create additional interpretation issues

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI as a possible mediator:

```
. regress bmi i.exer3 i.edu i.csmker agec

      Source |       SS       df       MS              Number of obs =    1054
-------------+------------------------------           F(  4,  1049) =   23.12
       Model |  2356.56238     4  589.140594           Prob > F      =  0.0000
    Residual |  26733.6582  1049  25.4848982           R-squared     =  0.0810
-------------+------------------------------           Adj R-squared =  0.0775
       Total |  29090.2206  1053  27.6260404           Root MSE      =  5.0483

------------------------------------------------------------------------------
         bmi |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     1.exer3 |  -2.442347   .3238882    -7.54   0.000     -3.07789   -1.806805
       1.edu |  -.3196396   .3169374    -1.01   0.313    -.9415429    .3022638
    1.csmker |   -1.78384   .4640269    -3.84   0.000    -2.694366   -.8733131
        agec |  -.1283467    .023634    -5.43   0.000    -.1747219   -.0819714
       _cons |    29.2754   .2547791   114.91   0.000     28.77547    29.77533
------------------------------------------------------------------------------
```

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI as a possible mediator:

```
. logistic hypt i.exer3 i.edu i.csmker agec

Logistic regression                               Number of obs   =       1054
                                                  LR chi2(4)      =      41.36
                                                  Prob > chi2     =     0.0000
Log likelihood = -651.35392                       Pseudo R2       =     0.0308

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     1.exer3 |   .6491883   .0911016    -3.08   0.002     .4930833    .8547145
       1.edu |   .7138105   .0978588    -2.46   0.014      .545618      .93385
    1.csmker |   1.139427   .2241928     0.66   0.507     .7748269    1.675592
        agec |   1.054058   .0109989     5.05   0.000      1.03272    1.075838
       _cons |    .659734   .0699621    -3.92   0.000      .535923    .8121484
------------------------------------------------------------------------------
```

- *OR* of 0.65 estimates (conditional) overall effect of exercise not mediated through BMI

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI (treated as a linear term) as a possible mediator:

```
. logistic hypt i.exer3 i.edu i.csmker agec bmic

Logistic regression                               Number of obs   =       1054
                                                  LR chi2(5)      =      52.10
                                                  Prob > chi2     =     0.0000
Log likelihood = -645.98359                       Pseudo R2       =     0.0388

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     1.exer3 |   .7192284   .1037521    -2.28   0.022     .5420969     .954238
       1.edu |    .722425   .0994817    -2.36   0.018      .551541    .9462539
    1.csmker |   1.227736   .2445182     1.03   0.303     .8309558    1.813977
        agec |   1.060745   .0113766     5.50   0.000      1.03868    1.083279
        bmic |    1.04369   .0136563     3.27   0.001     1.017264    1.070802
       _cons |   .6179738   .0672956    -4.42   0.000     .4992023    .7650037
------------------------------------------------------------------------------
```

- *OR* of 0.72 estimates (conditional) direct effect of exercise *not* mediated through BMI

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Estimating marginal controlled direct effect (CDE) for individuals with BMI at the mean value, based on results from last model:

```
. * Run margins at a fixed level of BMI
. quietly margins exer3, at(bmic = 0)
. * Save results and estimate marginal OR, RD & RR
. matrix b = r(b)
. scalar EY0 = b[1, 1]
. scalar EY1 = b[1, 2]
. scalar cde_OR = EY1/(1-EY1)*(1-EY0)/EY0
. scalar cde_RR = EY1/EY0
. scalar cde_RD = EY1-EY0
. scalar list cde_OR cde_RR cde_RD
    cde_OR =  .72734677
    cde_RR =  .80714339
    cde_RD = -.06992906
```

- CDE *OR* estimate is similar (in this case) to conditional direct effect *OR* on previous slide

- *Note*: The `medeff` command (see lab 4) can be used to estimate controlled and natural direct effects, and allows interaction between mediator and exposure

Using `medeff` to assess mediation for a binary outcome

```
. medeff (regress bmic exer3 edu csmker agec) (logit hypt exer3 edu csmker agec bmic),
mediate(bmic) treat(exer3)
Using 0 and 1 as treatment values

--------------------------------------------------------------------------------
        Effect                  |  Mean           [95% Conf. Interval]
--------------------------------+-----------------------------------------------
        ACME1                   | -.0209207     -.0355808     -.0080683
        ACME0                   | -.0231623     -.0379451     -.0094944
        Direct Effect 1         | -.0682403     -.1265449     -.0106466
        Direct Effect 0         | -.0704819     -.1297094     -.0110392
        Total Effect            | -.0914026     -.1448045     -.0374986
        % of Total via ACME1    |  .2260153      .1444758      .5579088
        % of Total via ACME0    |  .2502322       .159956      .6176871

        Average Mediation       | -.0220415     -.0366915     -.0088468
        Average Direct Effect   | -.0693611     -.1281134     -.0108416
        % of Tot Eff mediated   |  .2381238      .1522159      .5877979
--------------------------------------------------------------------------------
```

- Indirect (ACME) and direct effects estimated controlling mediator under counterfactual assignment to either exercise (1) or non-exercise (0) - allows for mediator-treatment interaction.

Evaluating interaction using logistic regression

Interaction between two predictors: the magnitude of the association of each predictor with the outcome, as measured by its regression coefficient, varies according to the value of the other predictor.

- As in linear regression, interaction between two predictors is evaluated via incorporation of a constructed variable defined as the product of the two predictors into the model including both predictors
- If the coefficient (odds ratio) of the included product variable is significantly different than zero (one), we conclude that interaction is present
- Interaction assessed via the logistic model is additive on the log-odds scale and multiplicative on the odds scale

Interpreting two-way interaction between two binary predictors

Example: interaction between binary indicator of impaired fasting glucose (IFG) and BMI in HERS

- Additional analyses of the previous HERS example revealed an interaction between IFG and BMI

- We will explore this further here, focusing only on key variables (to simplify interpretation) and initially considering a binary indicator of high vs. low values of BMI

Note: treating BMI and glucose levels as continuous variables may be more appropriate in practice.

Interaction between two binary predictors

Simple example: interaction between binary indicators of IFG and BMI ≥ 35 in HERS

```
. * create binary indicator of BMI greater than or equal to 35
. gen bmihi = bmi
. recode bmihi min/34.9999=0 35/max=1
. * construct new variable as the product between IFG and BMI binary indicators
. gen ifgbmi = ifg*bmihi
. logistic hypt ifg bmihi ifgbmi
Logistic regression                               Number of obs   =       1055
                                                  LR chi2(3)      =      16.06
                                                  Prob > chi2     =     0.0011
Log likelihood = -664.41499                       Pseudo R2       =     0.0119
------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ifg |   2.603175   .7056691     3.53   0.000     1.530239    4.428404
       bmihi |   1.671196    .393736     2.18   0.029     1.053133    2.651988
      ifgbmi |   .2163763   .1301662    -2.54   0.011     .0665503    .7035091
       _cons |   .4552846    .032823   -10.91   0.000     .3952911    .5243833
------------------------------------------------------------------------------
```

- Confidence interval for `ifgbmi` excludes 1, implying that we have evidence that an interaction between ifg and `bmihi` exists.
- Interpretation of Z (Wald) test statistic for testing the null hypothesis of no interaction (H: $\beta_3=0$): $Z = -1.530736/0.6015732 = -2.54$ (see next page)
- Referring to the standard normal distribution, the probability of a more extreme value of Z under the (two-sided) null hypothesis is 0.011.

Interaction between two binary predictors

Example: interaction between IFG & BMI in HERS (continued)

```
. * Coefficient form of the model:
. logistic hypt ifg bmihi ifgbmi, coef
Logistic regression                               Number of obs   =       1055
                                                  LR chi2(3)      =      16.06
                                                  Prob > chi2     =     0.0011
Log likelihood = -664.41499                       Pseudo R2       =     0.0119
------------------------------------------------------------------------------
        hypt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ifg |   .9567317   .2710802     3.53   0.000     .4254242    1.488039
       bmihi |   .5135393   .2356014     2.18   0.029     .0517691    .9753095
      ifgbmi |  -1.530736   .6015732    -2.54   0.011    -2.709798   -.3516745
       _cons |  -.7868327   .0720933   -10.91   0.000    -.9281329   -.6455324
------------------------------------------------------------------------------
```

Interaction between two binary predictors

- Logistic model equation (log-odds form):

$$\log\left[\frac{P(\texttt{ifg},\texttt{bmihi},\texttt{ifg}\times\texttt{bmihi})}{1-P(\texttt{ifg},\texttt{bmihi},\texttt{ifg}\times\texttt{bmihi})}\right]=\beta_0+\beta_1\texttt{ifg}+\beta_2\texttt{bmihi}+\beta_3\texttt{ifg}\times\texttt{bmihi}$$

- Calculation of component log-odds ratios:

$$\log\left[\frac{P(1,0,0)}{1-P(1,0,0)}\right]-\log\left[\frac{P(0,0,0)}{1-P(0,0,0)}\right]=\beta_1=0.9567317$$

$$\log\left[\frac{P(0,1,0)}{1-P(0,1,0)}\right]-\log\left[\frac{P(0,0,0)}{1-P(0,0,0)}\right]=\beta_2=0.5135393$$

$$\log\left[\frac{P(1,1,1)}{1-P(1,1,1)}\right]-\log\left[\frac{P(0,1,0)}{1-P(0,1,0)}\right]=\beta_1+\beta_3=0.9567317-1.530736=-0.574$$

$$\log\left[\frac{P(1,1,1)}{1-P(1,1,1)}\right]-\log\left[\frac{P(1,0,0)}{1-P(1,0,0)}\right]=\beta_2+\beta_3=0.5135393-1.530736=-1.017$$

$$\log\left[\frac{P(1,1,1)}{1-P(1,1,1)}\right]-\log\left[\frac{P(0,0,0)}{1-P(0,0,0)}\right]=\beta_1+\beta_2+\beta_3=-0.060$$

- Interaction effect is *additive* on the log-odds scale

Interaction between two binary predictors

- Logistic model equation (odds form):

$$\frac{P(\texttt{ifg},\texttt{bmihi},\texttt{ifg}\times\texttt{bmihi})}{1-P(\texttt{ifg},\texttt{bmihi},\texttt{ifg}\times\texttt{bmihi})} = \exp(\beta_0 + \beta_1\texttt{ifg} + \beta_2\texttt{bmihi} + \beta 3\texttt{ifg}\times\texttt{bmihi})$$

$$= e^{\beta_0} \times e^{\beta_1 \texttt{ifg}} \times e^{\beta_2 \texttt{bmihi}} \times e^{\beta_3 \texttt{ifg}\times\texttt{bmihi}}$$

- Calculation of component odds ratios

$$\frac{P(1,0,0)}{1-P(1,0,0)} \bigg/ \frac{P(0,0,0)}{1-P(0,0,0)} = e^{\beta_1}$$

$$\frac{P(0,1,0)}{1-P(0,1,0)} \bigg/ \frac{P(0,0,0)}{1-P(0,0,0)} = e^{\beta_2}$$

$$\frac{P(1,1,0)}{1-P(1,1,0)} \bigg/ \frac{P(0,1,0)}{1-P(0,1,0)} = e^{\beta_1+\beta_3}$$

$$\frac{P(1,1,0)}{1-P(1,1,0)} \bigg/ \frac{P(1,0,0)}{1-P(1,0,0)} = e^{\beta_2+\beta_3}$$

$$\frac{P(1,1,0)}{1-P(1,1,0)} \bigg/ \frac{P(0,0,0)}{1-P(0,0,0)} = e^{\beta_1+\beta_2+\beta_3}$$

- Interaction effect is *multiplicative* on the odds scale

Example: interaction between IFG & BMI in HERS (continued)

Constructing `lincom` statements:

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	
Yes	No	1	1	0	0	
No	No	1	0	0	0	β_1
Diff		0	1	0	0	

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	
No	Yes	1	0	1	0	
No	No	1	0	0	0	β_2
	Diff	0	0	1	0	

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	
Yes	Yes	1	1	1	1	
No	Yes	1	0	1	0	$\beta_1+\beta_3$
Diff		0	1	0	1	

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	
Yes	Yes	1	1	1	1	
Yes	No	1	1	0	0	$\beta_2+\beta_3$
	Diff	0	0	1	1	

Example: interaction between IFG & BMI in HERS (continued)

```
. lincom ifg
```
β_1

hypt	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	2.603175	.7056691	3.53	0.000	1.530239	4.428404

```
. lincom bmihi
```
β_2

hypt	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	1.671196	.393736	2.18	0.029	1.053133	2.651988

```
. lincom ifg + ifgbmi
```
$\beta_1 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	.5632653	.3024928	-1.07	0.285	.1966023	1.613754

```
. lincom bmihi + ifgbmi
```
$\beta_2 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	.3616071	.2001561	-1.84	0.066	.1222029	1.070021

```
. lincom ifg + bmihi + ifgbmi
```
$\beta1 + \beta2 + \beta3$

hypt	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	.9413265	.4643066	-0.12	0.902	.3580038	2.475101

Example: interaction between IFG & BMI in HERS (continued)

Same results obtained using "`i.`":

```
. logistic hypt i.ifg##i.bmihi

Logistic regression                               Number of obs   =       1055
                                                  LR chi2(3)      =      16.06
                                                  Prob > chi2     =     0.0011
Log likelihood = -664.41499                       Pseudo R2       =     0.0119

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       1.ifg |   2.603175   .7056691     3.53   0.000     1.530239    4.428404
     1.bmihi |   1.671196    .393736     2.18   0.029     1.053133    2.651988
             |
   ifg#bmihi |
        1 1  |   .2163763   .1301662    -2.54   0.011     .0665503    .7035091
             |
       _cons |   .4552846    .032823   -10.91   0.000     .3952911    .5243833
------------------------------------------------------------------------------
```

Note: use of the ## syntax in Stata is recommended for models including interaction terms

Example: interaction between IFG & BMI in HERS (continued)

```
. lincom 1.ifg     β1

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   2.603175   .7056691     3.53   0.000     1.530239    4.428404
------------------------------------------------------------------------------
. lincom 1.bmihi     β2

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.671196    .393736     2.18   0.029     1.053133    2.651988
------------------------------------------------------------------------------
. lincom 1.ifg + 1.ifg#1.bmihi     β1 + β3

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .5632653   .3024928    -1.07   0.285     .1966023    1.613754
------------------------------------------------------------------------------
. lincom bmihi + 1.ifg#1.bmihi     β2 + β3

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .3616071   .2001561    -1.84   0.066     .1222029    1.070021
------------------------------------------------------------------------------
. lincom ifg + bmihi + 1.ifg#1.bmihi     β1 + β2 + β3

------------------------------------------------------------------------------
        hypt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .9413265   .4643066    -0.12   0.902     .3580038    2.475101
```

Evaluating presence of additive interaction

- Recall that additive interaction may be more biologically meaningful than multiplicative interaction in many contexts
  - logistic regression *does not* provide a direct measure of additive interaction
  - presence of multiplicative interaction doesn't necessarily imply presence of additive interaction
- Degree of additive interaction directly estimated (except for case-control studies) by

$$(P_{11} - P_{00}) - [(P_{10} - P_{00}) + (P_{01} - P_{00})] = P_{11} - P_{10} - P_{01} + P_{00}$$

- The presence of additive interaction on the probability scale can be evaluated based on odds ratio estimates from a fitted logistic model as follows
  - $\mathrm{RERI}_{OR} = \mathrm{OR}_{11} - \mathrm{OR}_{10} - \mathrm{OR}_{01} + 1$

    $= \exp(\beta_1+\beta_2+\beta_3) - \exp(\beta_1) - \exp(\beta_2) + 1$
  - $\mathrm{RERI}_{OR} = 0$ implies absence of additive interaction
  - $\mathrm{RERI}_{OR} \neq 0$ implies presence of additive interaction
- RERI_{RR} is an analog based on the relative risk
- *Note*: RERI_{OR} doesn't estimate the actual magnitude of additive interaction, and works best to diagnose additive interaction for rare outcomes

Ref: Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012;41:514-20.

Example: logistic regression assessment of additive interaction between IFG & BMI in HERS

```
* Estimate RERI_OR using coefficients from previous logistic model (including interaction)

. nlcom exp(_b[1.ifg]+_b[1.bmihi]+_b[1.ifg#1.bmi]) - exp(_b[1.ifg]) - exp(_b[1.bmihi]) + 1

       _nl_1:  exp(_b[1.ifg]+_b[1.bmihi]+_b[1.ifg#1.bmi]) - exp(_b[1.ifg]) - exp(_b[1.bmihi]) + 1

------------------------------------------------------------------------------
        hypt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |  -2.333044    .933796    -2.50   0.012     -4.16325   -.5028372
------------------------------------------------------------------------------
```

Example: direct estimate of additive interaction between IFG & BMI in HERS

```
* Use the risk difference model for binary outcomes
. binreg hypt ifg bmihi ifgbmi, rd

Generalized linear models                          No. of obs      =       1055
Optimization     : MQL Fisher scoring              Residual df     =       1051
                   (IRLS EIM)                      Scale parameter =          1
Deviance         =  1328.829981                    (1/df) Deviance =   1.264348
Pearson          =         1055                    (1/df) Pearson  =   1.003806

Variance function: V(u) = u*(1-u)                  [Bernoulli]
Link function    : g(u) = u                        [Identity]

                                                   BIC             =  -5987.492
------------------------------------------------------------------------------
             |                 EIM
        hypt | Risk Diff.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ifg |   .2295237   .0666862     3.44   0.001     .0988211    .3602263
       bmihi |   .1192496   .0571812     2.09   0.037     .0071764    .2313228
      ifgbmi |  -.3616225   .1340767    -2.70   0.007    -.6244079   -.0988371
       _cons |   .3128492   .0154982    20.19   0.000     .2824732    .3432251
------------------------------------------------------------------------------
```

- Model can't be fitted in many situations (discussed in lecture 11)
  - multiple & continuous predictors
  - case-control studies
- Alternate approach: fit a relative risk regression (lecture 11) and estimate RERI_{RR}

Likelihood ratio testing

Example: contribution of type A/B behavior pattern to predicting CHD in WCGS

Goal: use the likelihood ratio test to assess the contribution of behavior pattern to a model already controlling for `age`, `chol`, `sbp`, `bmi` and `smoke`.

- The `lrtest` procedure in Stata is used to compare likelihoods from nested models
- First, the full model including predictor(s) to be evaluated is fitted.
- Next, the likelihood from this model is saved in a named temporary location (e.g. "*A*") for further reference
- The nested model excluding the predictor(s) to be evaluated is fitted.
- The likelihood ratio test is then performed using the `lrtest` command and referencing the location (i.e. "*A*") of the likelihood from the full model.
- *Note:* The nested and full models must be base on the same set of observations for the LR test to make sense

Likelihood ratio testing

Example: contribution of type A/B behavior pattern to predicting CHD in WCGS study

```
* First, fit full model including behpat:
. logistic chd69 age_10 chol_50 sbp_50 bmi_10 smoke i.behpat
Logistic regression                               Number of obs   =       3141
                                                  LR chi2(8)      =     184.57
                                                  Prob > chi2     =     0.0000
Log likelihood =    -794.81                       Pseudo R2       =     0.1040
------------------------------------------------------------------------------
       chd69 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      age_10 |    1.83375   .2198681     5.06   0.000     1.449707    2.319529
     chol_50 |   1.704097   .1301391     6.98   0.000     1.467201    1.979243
      sbp_50 |   2.463505   .5086518     4.37   0.000     1.643621    3.692369
      bmi_10 |   1.739414    .462034     2.08   0.037     1.033479    2.927551
       smoke |   1.830672   .2583097     4.29   0.000      1.38837    2.413882
      behpat |
          2  |   1.068257   .2363271     0.30   0.765     .6924157    1.648103
          3  |   .5141593   .1245593    -2.75   0.006     .3198064    .8266243
          4  |    .572071   .1826116    -1.75   0.080     .3060107    1.069457
------------------------------------------------------------------------------
* Save the log-likelihood in the temporary variable "A":
. estimates store A
* Note : the variables age_10, chol_50, sbp_50, bmi_10 represent centered and scaled
versions of the originals.
```

Likelihood ratio testing

Example: contribution of type A/B behavior pattern to predicting CHD in WCGS study (*continued*)

```
* Next, the desired "nested" model excluding predictor(s) of interest is fit, and
compared to the previous model using the lrtest command:

. logistic chd69 age_10 chol_50 sbp_50 bmi_10 smoke

Logistic regression                                 Number of obs    =       3141
                                                    LR chi2(5)       =     159.80
                                                    Prob > chi2      =     0.0000
Log likelihood = -807.19249                         Pseudo R2        =     0.0901

------------------------------------------------------------------------------
       chd69 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      age_10 |   1.904989   .2268333     5.41   0.000     1.508471    2.405735
     chol_50 |   1.710974   .1297977     7.08   0.000     1.474584    1.985259
      sbp_50 |   2.623972   .5367142     4.72   0.000     1.757326    3.918016
      bmi_10 |   1.775994   .4680612     2.18   0.029     1.059518    2.976972
       smoke |   1.886037   .2643914     4.53   0.000     1.432933    2.482417
------------------------------------------------------------------------------
* perform likelihood ratio test comparing fitted model to full model (A):
. lrtest A

Likelihood-ratio test                                 LR chi2(3)  =      24.76
(Assumption: . nested in A)                           Prob > chi2 =     0.0000
```

Summary: procedure for likelihood ratio testing in nested models:

1. Fit the full model including all the variable(s) of interest
2. Issue the `estimates` command, using the `store` option to save results of the current model in a location labeled by the results with a name (e.g. `estimates store A`)
3. Fit the nested model excluding the variable(s) of interest
4. Issue the `lrtest` command, identifying the results of the full model fit in step 1 by passing the name specified in step 2 (e.g. `lrtest A`)

The `lrtest` procedure computes the likelihood ratio comparing the two models, and refers the results to the chi-squared distribution with degrees of freedom equal to the difference in number of degrees of freedom in the two fitted models. The results of the test evaluate the null hypothesis that the true values of coefficients from the additional variables in the full model are all zero.

Summary: procedure for likelihood ratio testing in nested models:

- the likelihood/log-likelihood always increases as variables are added to an existing model
- like the *F* test for linear regression models, the likelihood ratio (*LR*) test is used to compare two nested models
- the *LR* statistic comparing two nested models is computed as twice the difference between the log-likelihoods:

$$2 \times \left[(\text{log} - \text{likelihood from more complex model}) - (\text{log} - \text{likelihood from simpler model}) \right] =$$

$$2 \times \log\left(\frac{\text{likelihood from more complex model}}{\text{likelihood from simpler model}} \right) = LR$$

- the *LR* statistic is approximately chi-squared distributed, with degrees of freedom equal to the difference in number of predictors between nested models
- likelihood ratio tests for evaluating contribution of predictors are more reliable than Wald tests, especially for smaller samples

Note: for the *LR* test to make sense, models being compared should be based on exactly the same set of observations.