## IV. MULTIPLE LOGISTIC REGRESSION

- Extend simple logistic regression to models with multiple covariates
- Similarity between multiple linear and multiple logistic regression
- Multiple 2x2 tables and the Mantel-Haenszel test
  - Estimating an odds ratio that is adjusted for a confounding variable
- Using logistic regression as an alternative to the Mantel-Haenszel test
- Using indicator covariates to model categorical variables
- Making inferences about odds ratios derived from multiple parameters
- Analyzing complex data with logistic regression
  - Multiplicative models
  - Models with interaction
- Assessing model fit
  - Testing the change in model deviance in nested models
  - Evaluating residuals and influence
- Using restricted cubic splines in logistic regression models
  - Plotting the probability of an outcome with confidence bands
  - Plotting odds ratios and confidence bands



### 1. The Model

If the data is organized as one record per patient then the model is

$$\text{logit}\,(E(d_i)) = \alpha + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik} \qquad \{4.1\}$$

where

$x_{i1}, x_{i2}, \ldots, x_{ik}$ are covariates from the $i^{\text{th}}$ patient

$\alpha, \beta_1, \ldots \beta_k$, are unknown parameters

$$d_i = \begin{cases} 1: & i^{\text{th}} \text{ patient suffers event of interest} \\ 0: & \text{otherwise} \end{cases}$$

If the data is organized as one record per unique combination of covariate values then the model is

$$\text{logit}(E(d_i / m_i)) = \alpha + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik} \qquad \textbf{\{4.2\}}$$

where $m_i$ is the number of patients with covariate values $x_{i1}$, $x_{i2}$, …, $x_{ik}$ and $d_i$ is the number of events among these $m_i$ subjects.

$d_i$ is assumed to have a binomial distribution obtained from $m_i$ dichotomous trials with probability of success $\pi(x_{i1}, x_{i2}, \ldots, x_{ik})$ on each trial.

Thus, the only difference between simple and multiple logistic regression is that the linear predictor is now $\alpha + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik}$. As in simple logistic regression, the model has a logit link function; the random component, $d_i/m_i$ has a binomial distribution.

## 2. Mantel-Haenszel Test of a Common Odds Ratio

The following data is from the Ille-et-Vilaine study of esophageal cancer and alcohol by Tuyns et al. (1977). This data is published in Appendix I of Breslow and Day Vol. I, who also provide an excellent and extensive discussion of this data set.

| Age | Cancer | Daily Alcohol Consumption ≥ 80g | <80g | | % ≥ 80g |
|---|---|---|---|---|---|
| 25-34 | Yes | 1 | 0 | 1 | 100.00% |
| | No | 9 | 106 | 115 | 7.83% |
| | | 10 | 106 | 116 | 8.62% |
| 35-44 | Yes | 4 | 5 | 9 | 44.44% |
| | No | 26 | 164 | 190 | 13.68% |
| | | 30 | 169 | 199 | 15.08% |
| 45-54 | Yes | 25 | 21 | 46 | 54.35% |
| | No | 29 | 138 | 167 | 17.37% |
| | | 54 | 159 | 213 | 25.35% |
| 55-64 | Yes | 42 | 34 | 76 | 55.26% |
| | No | 27 | 139 | 166 | 16.27% |
| | | 69 | 173 | 242 | 28.51% |
| 65-74 | Yes | 19 | 36 | 55 | 34.55% |
| | No | 18 | 88 | 106 | 16.98% |
| | | 37 | 124 | 161 | 22.98% |

**a) Confounding Variables**

A **confounding variable** is one that is associated with both the disease and exposure of interest but which is not, in itself, a focus of our investigation.

Note mild evidence that age confounds the effect of alcohol on cancer risk.

**b) Age-adjusted odds ratios**

The following log file show how to calculate the common odds ratio for esophageal cancer associated with heavy alcohol use in five age strata. It thus calculates an **age-adjusted** odds ratio for esophageal cancer among heavy and light drinkers of similar age.

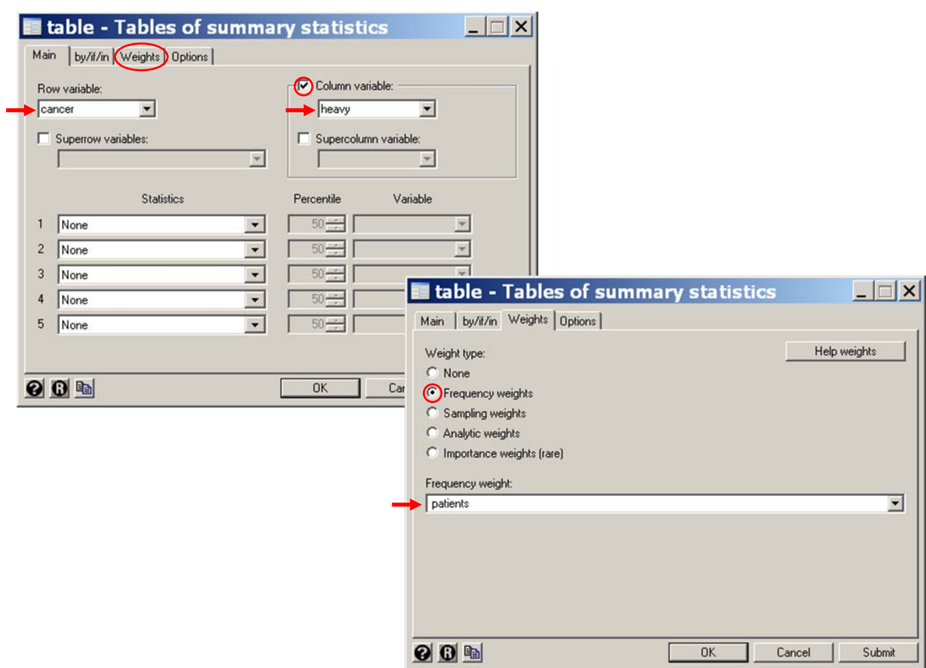
### 3. Deriving the Mantel-Haenszel test with Stata

```
  *  5.5.EsophagealCa.log
. *
. *  Calculate the Mantel-Haenszel age-adjusted odds ratio from
. *  the Ille-et-Vilaine study of esophageal cancer and alcohol
. *  (Breslow & Day 1980, Tuyns 1977).
. *
. use C:\WDDtext\5.5.EsophagealCa.dta, clear

. codebook age cancer heavy


age ---------------------------------------- Age (years)
                 type:  numeric (float)
                label:  age

                range:  [1,6]
units:  1
        unique values:  6        coded missing:  0 / 192

          tabulation:  Freq.   Numeric  Label
                          32         1  25-34
                          32         2  35-44
                          32         3  45-54
                          32         4  55-64
                          32         5  65-74
                          32         6  >= 75
```

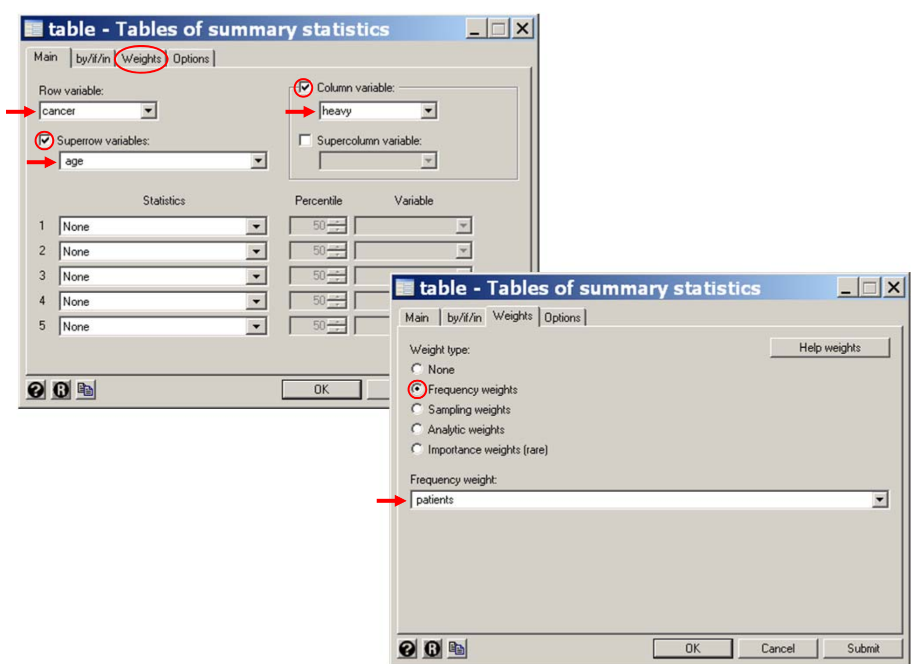
```
cancer -------------------------------- Esophageal Cancer
                 type:  numeric (float)
                label:  yesno

                range:  [0,1]
units:  1
        unique values:  2        coded missing:  0 / 192

          tabulation:  Freq.   Numeric  Label
                          96         0  No
                          96         1  Yes



heavy ------------------------- Heavy Alcohol Consumption
                 type:  numeric (float)
                label:  heavy

                range:  [0,1]
units:  1
        unique values:           coded missing:  0 / 192

          tabulation:  Freq.   Numeric  Label
                          96         0  < 80 gm
                          96         1  >= 80 gm
```

```
. * Statistics > Summaries... > Tables > Table of summary statistics (table).
 table heavy cancer [freq=patients]                          {1}

----------+-----------------
          |  Heavy Alcohol
Esophagea |   Consumption
l Cancer  | < 80 gm  >= 80 gm
----------+-----------------
       No |     666       104
      Yes |     109        96
----------+-----------------
```

{1} This **table** command gives 2×2 cross-tables of ***heavy*** by ***cancer***, and confirms *that EsophagealCancer.dta* is the correct data set.



```
. table  cancer heavy [freq=patients], by(age)

----------+------------------
Age       |
(years)   |
and       |   Heavy Alcohol
Esophagea |    Consumption
l Cancer  |  < 80 gm  >= 80 gm
----------+------------------
25-34     |
       No |     106         9
      Yes |                 1
----------+------------------
35-44     |
       No |     164        26
      Yes |       5         4
----------+------------------
45-54     |
       No |     138        29
      Yes |      21        25
----------+------------------
55-64     |
       No |     139        27
      Yes |      34        42
----------+------------------
65-74     |
       No |      88        18
      Yes |      36        19
----------+------------------
>= 75     |
       No |      31
      Yes |       8         5
----------+-------------------
```



```
. * Statistics > Epidemiology... > Tables... > Case-control odds ratio
. cc heavy cancer [freq=patients], by(age)                                {2}

 Age (years) |       OR      [95% Conf. Interval]    M-H Weight
-------------+-------------------------------------------------
       25-34 |          .            0          .            0 (exact)
       35-44 |   5.046154     .9268664   24.86538      .6532663 (exact)
       45-54 |   5.665025     2.632894   12.16536      2.859155 (exact)
       55-64 |   6.359477     3.299319   12.28473      3.793388 (exact)
       65-74 |   2.580247     1.131489   5.857261      4.024845 (exact)
       >= 75 |          .     4.388738          .            0 (exact)
-------------+-------------------------------------------------
       Crude |   5.640085     3.937435   8.061794               (exact)      {3}
M-H combined |   5.157623     3.562131   7.467743                            {4}
-------------+-------------------------------------------------
Test of homogeneity (Tarone)    chi2(5) =     9.30  Pr>chi2 = 0.0977         {5}

             Test that combined OR = 1:                                      {6}
                          Mantel-Haenszel chi2(1) =     85.01
                          Pr>chi2 =    0.0000
```

**{2}** The ***by(age)*** option causes **odds ratios** to be calculated for each **age strata**. No estimate is given for the youngest strata because there were no moderate drinking cases. No estimate is given for the oldest strata because there were no heavy drinking controls.

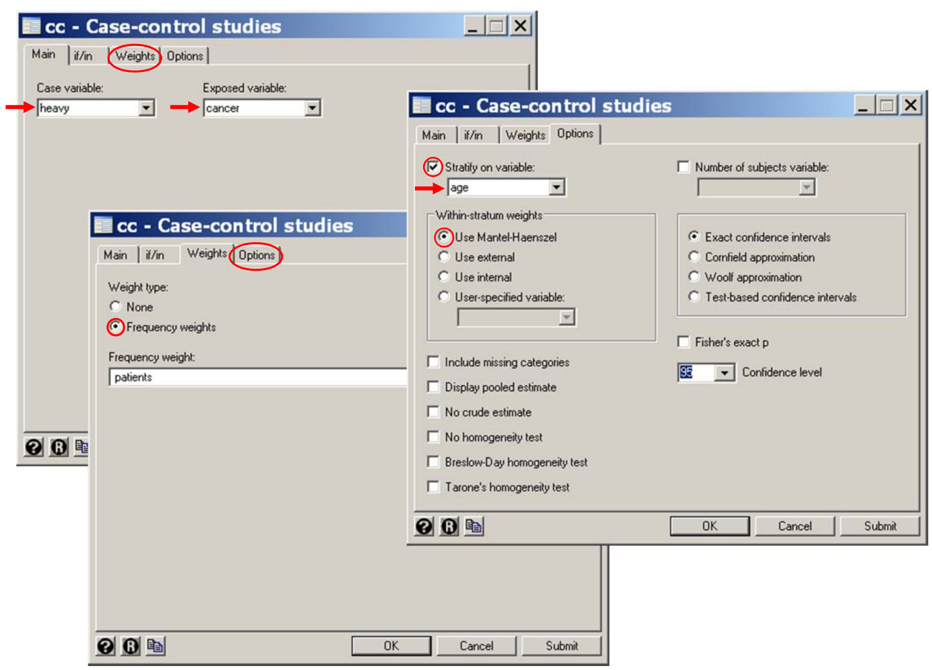
**{3}** The **crude** odds ratio is **5.64** which we derived in the last chapter. This odds ratio is obtained by ignoring the age strata.

The **exact 95% confidence interval** consists of all values of the odds ratio that **cannot be rejected** at the $P = 0.05$ level of statistical significance (see text, Section 1.4.7). The derivation of this interval uses a rather complex iterative formula (Dupont and Plummer 1999).

**{4}** The **Mantel-Haenszel** (M-H) estimate of the **common odds ratio** within all age strata is **5.16**. This is an **age-adjusted** estimate. It is slightly lower than the crude estimate, and is consistent with a mild confounding of age and drinking habits on the risk of esophageal cancer.

{5} The M-H estimate is only reasonable if the data is consistent with the hypothesis that the alcohol-cancer odds ratio does not vary with age. The **test for homogeneity** tests the null hypothesis that all age strata share a common odds ratio. This test is not significant, which suggests that the M-H estimate may be reasonable.

{6} The test of the **null hypotheses** that the odds ratio equals 1 is highly **significant**. Hence the association between heavy alcohol consumption and esophageal cancer can not be explained by chance. The argument for a **causal** relationship is strengthened by the **magnitude** of the **odds ratio**.



## 4. Effect Modifiers and Confounding Variables

### a) Test of homogeneity of odds ratios

In the previous example the test for homogeneity of the odds ratio was not significant (see comment 5). Of course, lack of significance does not prove the null hypotheses, and it is prudent to look at the odds ratios from the individual age strata. In the preceding Stata output these values are fairly similar for all strata except ages 65-74, where the odds ratio drops to 2.6. This may be due to chance, or perhaps, to a hardy survivor effect. You must use your clinical judgment in deciding what to report.

**Effect Modifier:** A variable that influences the effect of a risk factor on the outcome variable.

The key differences between confounding variables and effect modifiers are:

i) Confounding variables are not of primary interest in our study while effect modifiers are.

ii) A variable is an important effect modifier if there is a meaningful interaction between it and the exposure of interest on the risk of the event under study.

## 5. Logistic Regression For Multiple 2×2 Contingency Tables

### a) Estimating the common relative risk from the parameter estimates

Let

$m_{jk}$ be the number of subjects in the $j^{th}$ age strata who are ($k$ = 1) or are not ($k$ = 0) heavy drinkers.

$d_{jk}$ be the number of cancers among these $m_{jk}$ subjects.

$x_k$ = $k$ = 1 or 0 depending on their drinking status.

$\pi_{jk}$ be the probability that someone in the $j^{th}$ age strata who does ($k$ = 1) or doesn't ($k$ = 0) drink heavily develops cancer.

Consider the logistic regression model

$$\text{logit}\left(E\left(d_{jk} / m_{jk}\right)\right) = \alpha_j + x_k\beta \qquad \textbf{\{4.3\}}$$

where $d_{jk}$ has a binomial distribution obtained from $m_{jk}$ independent trials with probability of success with $\pi_{jk}$ on each trial.

Then for any age strata $j$, $E\left(d_{jk} / m_{jk}\right) = \pi_{jk}$ and

$$\text{logit}\left(E\left(d_{j0} / m_{j0}\right)\right) = \text{logit}(\pi_{j0}) = \log\left(\pi_{j0} / (1-\pi_{j0})\right) = \alpha_j \qquad \textbf{\{4.4\}}$$

Similarly

$$\text{logit}\left(E\left(d_{j1} / m_{j1}\right)\right) = \log\left(\pi_{j1} / (1-\pi_{j1})\right) = \alpha_j + \beta \qquad \textbf{\{4.5\}}$$

Subtracting equation {4.4} from equation {4.5} gives that

$$\log\left(\pi_{j1} / (1-\pi_{j1})\right) - \log\left(\pi_{j0} / (1-\pi_{j0})\right) = \beta \quad \text{or}$$

$$\log\left(\frac{\pi_{j1} / (1-\pi_{j1})}{\pi_{j0} / (1-\pi_{j0})}\right) = \log\psi = \beta$$

Hence, this model implies that the odds ratio for cancer is the same in all strata and equals exp(β).

This is an age-adjusted estimate of the cancer odds ratio

In practice we fit model {4.1} by defining indicator covariates

$$z_j = \begin{cases} 1: & \text{if subjects are from the } j^{\text{th}} \text{ age strata} \\ 0: & \text{otherwise} \end{cases}$$

Then {4.3} becomes

$$\text{logit}\left(E\left(d_{jk} / m_{jk}\right)\right) = z_1\alpha_1 + z_2\alpha_2 + z_3\alpha_3 + z_4\alpha_4 + z_5\alpha_5 + z_6\alpha_6 + x_k\beta$$

Note that this model places no restraints of the effect of age on the odds of cancer and only requires that the within strata odds ratio be constant.

For example, a moderate drinker from the 3rd age stratum has log odds

$$\text{logit}\left(E\left(d_{3,0} / m_{3,0}\right)\right) = \alpha_3$$

While a moderate drinker from the first age stratum has

$$\text{logit}\left(E\left(d_{1,0} / m_{1,0}\right)\right) = \alpha_1$$

Hence the log odds ratio for stratum 3 versus stratum 1 is $\alpha_3 - \alpha_1$, which can be estimated independently of the cancer risk associated with age strata 2, 4, 5 and 6.

An equivalent model is

$$\text{logit}\left(E\left(d_{jk} / m_{jk}\right)\right) = \alpha + z_2\alpha_2 + z_3\alpha_3 + z_4\alpha_4 + z_5\alpha_5 + z_6\alpha_6 + x_k\beta \qquad \textbf{\{4.6\}}$$

For this model, a moderate drinker from the 3rd age stratum has log odds

$$\text{logit}\left(E\left(d_{3,0} / m_{3,0}\right)\right) = \alpha + \alpha_3$$

While a moderate drinker from the first age stratum has

$$\text{logit}\left(E\left(d_{1,0} / m_{1,0}\right)\right) = \alpha$$

Hence the log odds ratio for stratum 3 versus stratum 1 is

$$\left(\alpha + \alpha_3\right) - \alpha = \alpha_3$$

This is slightly preferable to our previous formulation in that it involves one parameter rather than 2.

An alternative model that we could have used is

$$\text{logit}\left(E\left(d_{jk} / m_{jk}\right)\right) = \text{age} \times \alpha + x_k\beta$$

However, this model imposes a linear relationship between age and the log odds for cancer. That is, the log odds ratio

for age stratum 2 vs stratum 1 is $2\alpha - \alpha = \alpha$

for age stratum 3 vs stratum 1 is $3\alpha - \alpha = 2\alpha$

:

for age stratum 6 vs stratum 1 is $6\alpha - \alpha = 5\alpha$

## 6. Analyzing Multiple 2×2 Contingency Tables

```
. *   5.9.EsophagealCa.ClassVersion.log
. *
. *  Calculate age-adjusted odds ratio from the Ille-et-Vilaine study
. *  of esophageal cancer and alcohol using logistic regression.
. *
. use C:\WDDtext\5.5.EsophagealCa.dta, clear
. *
. *  First, define indicator variables for the age strata 2 through 6
. *
```

```
. generate age2 = 0

. replace age2 = 1 if age == 2
(32 real changes made)

. generate age3 = 0

. replace age3 = 1 if age == 3
(32 real changes made)

. generate age4 = 0

. replace age4 = 1 if age == 4
(32 real changes made)

. generate age5 = 0

. replace age5 = 1 if age == 5
(32 real changes made)

. generate age6 = 0

. replace age6 = 1 if age == 6
(32 real changes made)
```

```
. * Statistics > Binary outcomes > Logistic regression
. logit cancer age2 age3 age4 age5 age6 heavy   [freq=patients]    {1}


Logistic regression                               No. of obs      =       975
                                                  LR chi2(6)      =    200.57
                                                  Prob > chi2     =    0.0000
Log likelihood   = -394.46094                     Pseudo R2       =    0.2027

------------------------------------------------------------------------
cancer |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------+----------------------------------------------------------------
  age2 |   1.542294   1.065895     1.45   0.148     -.546822     3.63141
  age3 |   3.198762    1.02314     3.13   0.002     1.193445    5.204079
  age4 |    3.71349   1.018531     3.65   0.000     1.717207    5.709774
  age5 |   3.966882   1.023072     3.88   0.000     1.961698    5.972066
  age6 |    3.96219   1.065024     3.72   0.000      1.87478    6.049599
 heavy |    1.66989   .1896018     8.81   0.000     1.298277    2.041503  {2}
 _cons |  -5.054348   1.009422    -5.01   0.000    -7.032778   -3.075917
------------------------------------------------------------------------
```

The results of this logistic regression are similar to those obtained form the Mantel-Haenszel test. The age-adjusted odds ratio from this latter test was **5.16** as compared to **5.31** from logistic regression.

{1} By default, Stata adds a constant term to the model. Hence, this command uses model {4.6}.

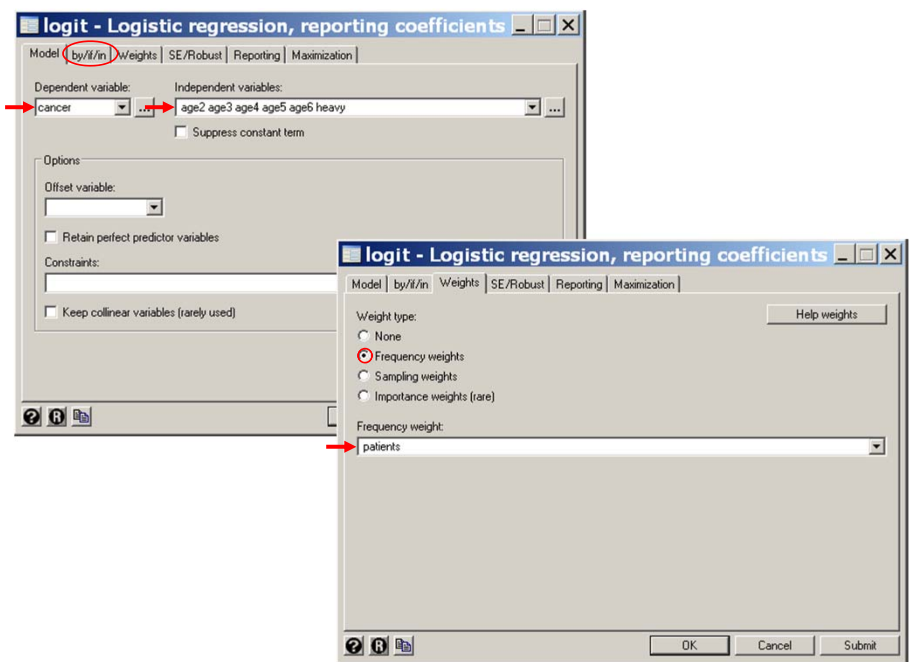
The *coef* option specifies that the model parameter estimates are to be listed as follows.

{2} The parameter estimate associated with *heavy* is 1.67 with a standard error of 0.1896. A 95% confidence interval for this interval is $1.67 \pm 1.96 \times 0.1896 = [1.30, 2.04]$.

The age-adjusted estimated odds ratio for cancer in heavy drinkers relative to moderate drinkers is

$\psi = \exp(1.67) = 5.31$ with a 95% confidence interval

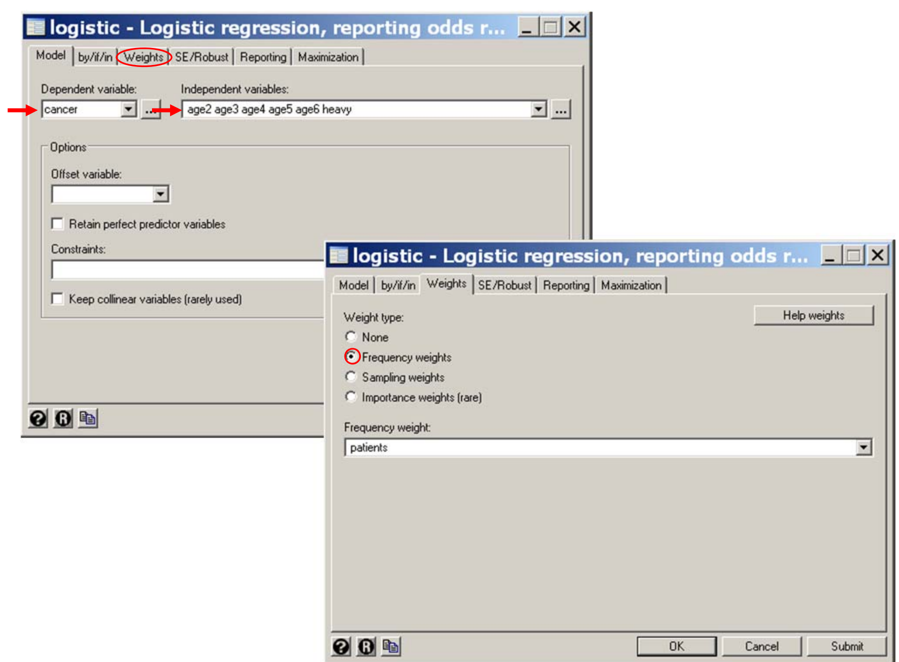
$[\exp(1.30), \exp(2.04)] = [3.66, 7.70]$.



```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer age2 age3 age4 age5 age6 heavy
> [freq=patients]                                                    {3}


Logistic regression                               No. of obs      =       975
                                                  LR chi2(6)      =    200.57
                                                  Prob > chi2     =    0.0000
Log likelihood   = -394.46094                     Pseudo R2       =    0.2027
------------------------------------------------------------------------------
  cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------+--------------------------------------------------------------------
    age2 |   4.675303   4.983382     1.45   0.148      .5787862    37.76602
    age3 |   24.50217   25.06914     3.13   0.002      3.298423    182.0131
    age4 |   40.99664   41.75634     3.65   0.000       5.56895    301.8028
    age5 |   52.81958   54.03823     3.88   0.000      7.777389    392.3155
    age6 |   52.57232   55.99081     3.72   0.000      6.519386    423.9432
   heavy |   5.311584   1.007086     8.81   0.000      3.662981    7.702174
------------------------------------------------------------------------------
```

{3} Without the *coef* option logistic does not output the constant parameter and exponentiates the other coefficients. This usually saves hand computation.

Note that the age adjusted odds ratio for heavy drinking is 5.31 with a 95% confidence interval of [3.7 – 7.7].



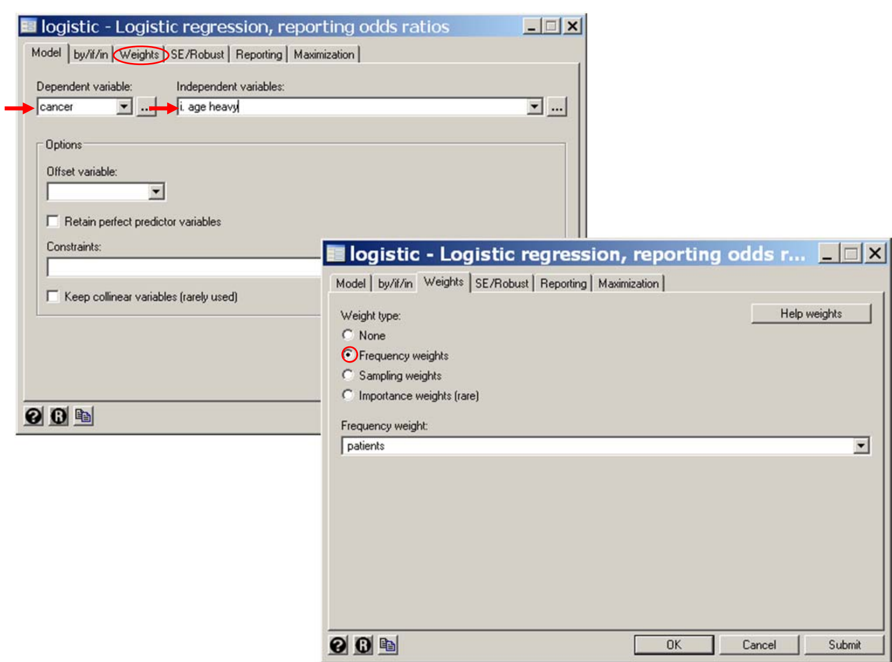
### 7. Handling Categorical Variables in Stata

In the preceding example, age is a categorical variable taking 6 values that is recorded as 5 separate indicator variables. It is very common to recode categorical variables in this way to avoid forcing a linear relationship on the effect of a variable on the response outcome. In the preceding example we did the recording by hand. It can also be done much faster using the *i.varname* syntax. We illustrate this by repeating the preceding analysis of model {4.3}.

```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer i.age heavy [freq=patients]                              {1}

Logistic regression                               No. of obs      =        975
                                                  LR chi2(6)      =     200.57
                                                  Prob > chi2     =     0.0000
Log likelihood = -394.46094                       Pseudo R2       =     0.2027
```

{1} ***i.age*** indicates that *age* is to be recoded as five indicator variables (one for each value of *age*). These variables are named *2.age*, *3.age*, *4.age*, *5.age*, and *6.age*. By default the smallest value of *age* is not assigned a separate indicator variable and a constant term is included in the model giving

$$\text{logit}\left(E\left(d_{jk}/m_{jk}\right)\right) = \alpha + \alpha_j + x_k\beta : j = 2,\ldots,6; k = 0,1$$



```
------------------------------------------------------------------------------
      cancer |  Odds Ratio.  Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   4.675303   4.983382     1.45   0.148     .5787862    37.76602
          3  |   24.50217   25.06914     3.13   0.002     3.298423    182.0131
          4  |   40.99664   41.75634     3.65   0.000      5.56895    301.8028
          5  |   52.81958   54.03823     3.88   0.000     7.111389    392.3155
          6  |   52.57232   55.99081     3.72   0.000     6.519386    423.9432

       heavy |   5.311584   1.007086     8.81   0.000     3.662981    7.702174 {2}
------------------------------------------------------------------------------
```

**{2}** Note that the odds ratio estimate for *heavy* = **5.31** is the same as in the earlier analysis where the indicator variables were explicitly defined.

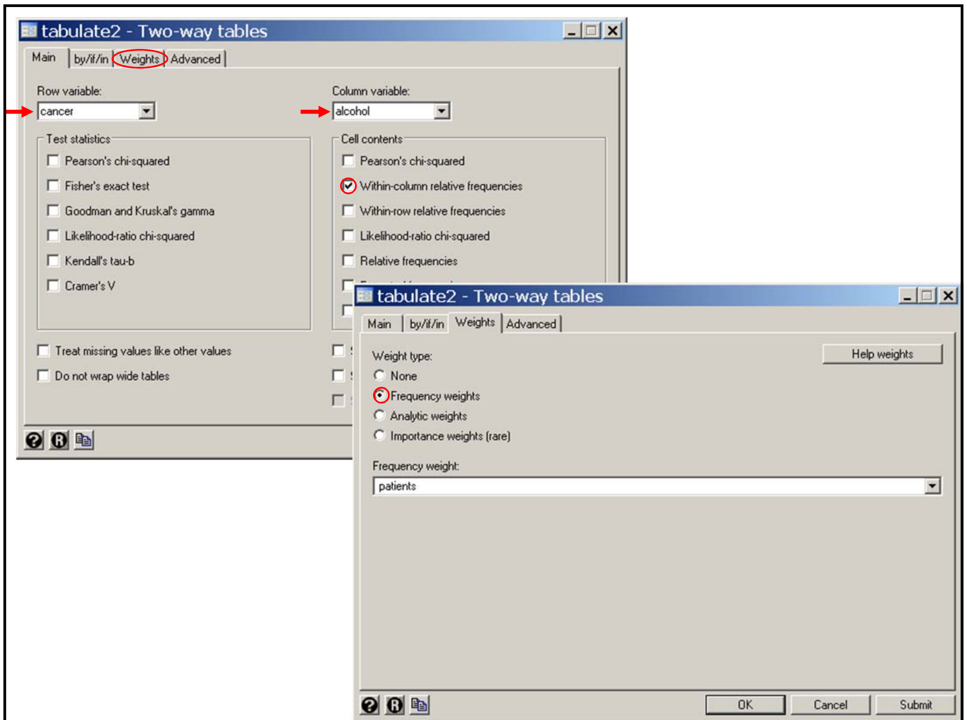
## 8. Example: Effect of Dose of Alcohol and Tobacco on Esophageal Cancer Risk

The Ille-et-Vilaine data set provides four different levels of consumption for both alcohol and tobacco. To investigate the joint effects of dose and alcohol on esophageal cancer risk we first tabulate the raw data.

```
. *  5.11.1.EsophagealCa.ClassVersion.log
. *
. *  Estimate age-adjusted risk of esophageal cancer due to dose of alcohol.
. *
. use C:\WDDtext\5.5.EsophagealCa.dta, clear
. *
. *  Show frequency tables of effect of dose of alcohol on esophageal cancer.
. *
```

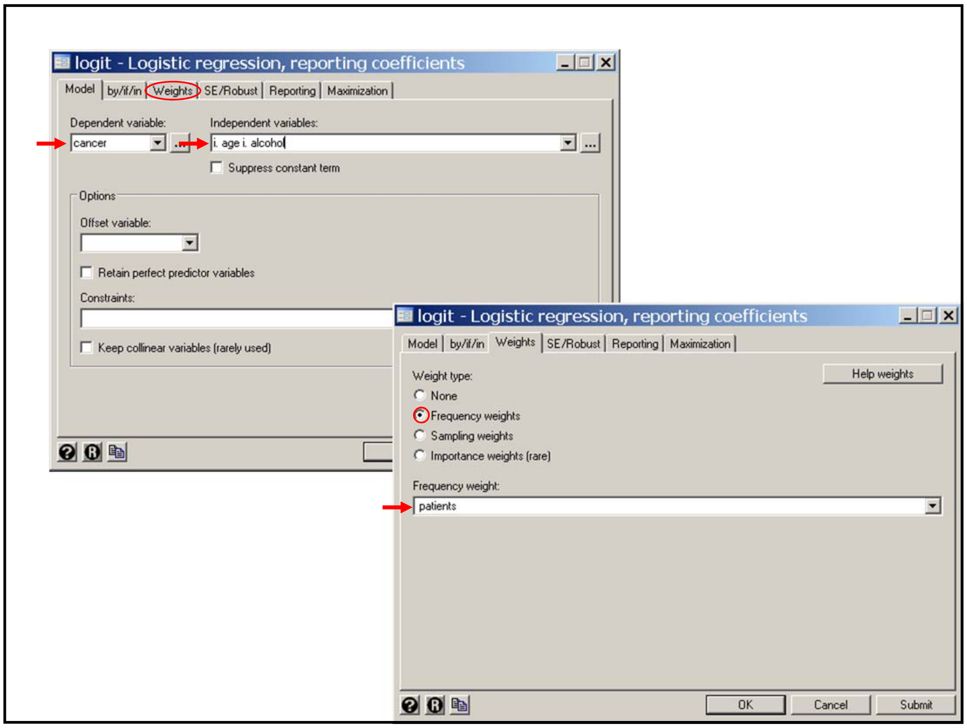
```
. * Statistics > Summaries... > Tables > Two-way tables with measures...
. tabulate cancer alcohol [freq=patients] , column                   {1}


+-------------------+
| Key               |
|-------------------|
|     frequency     |
| column percentage |
+-------------------+


Esophageal |  Alcohol (gm/day)
Cancer     |     0-39    40-79    80-119   >= 120 |   Total
-----------+-----------------------------------+--------
        No |      386      280       87       22 |     775
           |    93.01    78.87    63.04    32.84 |   79.49
-----------+-----------------------------------+--------
       Yes |       29       75       51       45 |     200
           |     6.99    21.13    36.96    67.16 |   20.51
-----------+-----------------------------------+--------
     Total |      415      355      138       67 |     975
           |   100.00   100.00   100.00   100.00 |  100.00
```

{1} The **tabulate** command produces one- and two-way frequency tables. The *column* option produces percentages of observations in each column.



```
. * Statistics > Binary outcomes > Logistic regression
. logit cancer i.age i.alcohol [freq=patients]

Logit estimates                                   No. of obs      =        975
                                                  LR chi2(8)      =     274.07
                                                  Prob > chi2     =     0.0000
Log likelihood   = -363.7080768                   Pseudo R2       =     0.2649


------------------------------------------------------------------------------
      cancer |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   1.631112   1.080013     1.51   0.131    -.4856742    3.747899
          3  |   3.425834   1.038937     3.30   0.001     1.389555    5.462114
          4  |   3.943447   1.034622     3.81   0.000     1.915624    5.971269
          5  |   4.356767   1.041336     4.18   0.000     2.315786    6.397747
          6  |   4.424219     1.0914     4.05   0.000     2.285115    6.563324
             |
     alcohol |
          2  |    1.43431   .2447858     5.86   0.000     .9545384    1.914081  {2}
          3  |    2.00711   .2776153     7.23   0.000     1.462994    2.551226
          4  |   3.680012   .3763372     9.78   0.000     2.942405    4.417619
             |
       _cons |  -6.147181   1.041877    -5.90   0.000    -8.189223    -4.10514
------------------------------------------------------------------------------
```

**{2}** The parameter estimates of ***2.alcohol, 3.alcohol*** and ***4.alcohol*** estimate the log-odds ratio for cancer associated with alcohol doses of **40-79** gm/day, **80-119** gm/day and **120+** gm/day, respectively. These log-odds ratios are derived with respect to people who drank **0-39** grams a day. They are all adjusted for age. All of these statistics are significantly different from zero ($P$<0.0005).




```
. * Statistics > Postestimation > Linear combinations of estimates
. lincom 3.alcohol - 2.alcohol, or                                       {3}

 ( 1) - [cancer] 2.alcohol + [cancer]3.alcohol = 0.0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.773226   .4159625     2.44   0.015     1.119669    2.808268
------------------------------------------------------------------------------
```

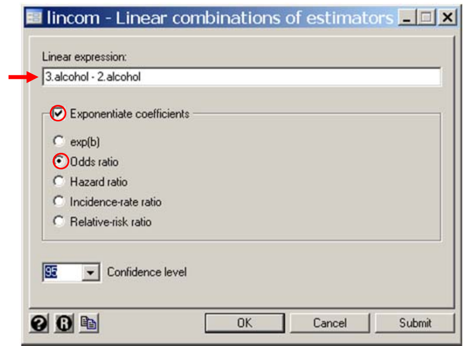
{3} In general, **lincom** calculates any **linear combination** of parameter estimates, tests the **null hypothesis** that the true value of this combination equals zero, and gives a **95% confidence interval** for this estimate.

The *or* option exponentiates the linear combination and calculates the corresponding confidence interval.

In this example ***3.alcohol* – *2.alcohol*** equals the log-odds ratio for cancer associated with drinking 8-119 gm/day compared to 40-79 gm/day. ***3.alcohol* – *2.alcoh*** = **2.001 – 1.434 = 0.573**, which is significantly different from zero with $P = 0.015$. The corresponding odds ratio is

exp[0.573] = 1.77. The 95% confidence interval for this difference is (1.1 – 2.8).

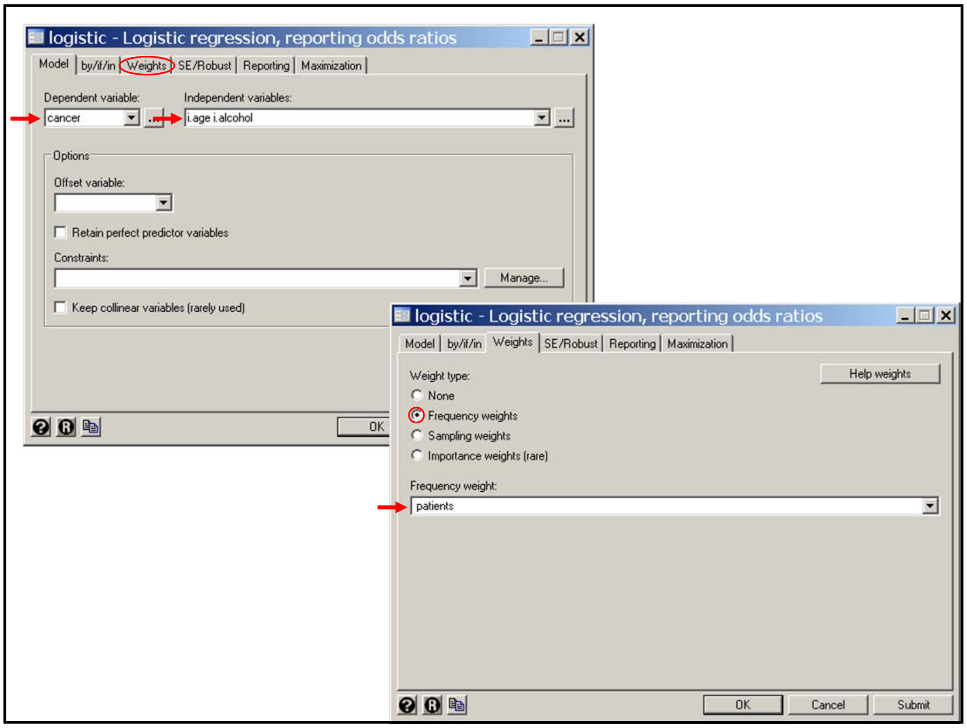
Note that the null hypothesis that a **log-odds ratio** equals **zero** is equivalent to the null hypothesis that the corresponding **odds ratio** equals **one.**




```
. lincom 4.alcohol - 3.alcohol, or

 ( 1) [cancer]3.alcohol + [cancer]4.alcohol = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   5.327606    1.95176     4.57   0.000     2.598339    10.92367
------------------------------------------------------------------------------
```

```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logisitc cancer i.age i.alcohol [freq=patients]                     {4}

Logit estimates                                   No. of obs      =        975
                                                  LR chi2(8)      =     274.07
                                                  Prob > chi2     =     0.0000
                                                  Pseudo R2       =     0.2649
Log likelihood   = -363.7080768
------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   5.109555   5.518386     1.51   0.131     .6152822    42.43183
          3  |   30.74829   31.94554     3.30   0.001     4.013065    235.5949
          4  |   51.59613    53.3825     3.81   0.000     6.791178    392.0027
          5  |   78.00451   81.22889     4.18   0.000     10.13289    600.4908
          6  |   83.44761   91.07472     4.05   0.000     9.826812     708.623
             |
     alcohol |
          2  |   4.196747   1.027304     5.86   0.000     2.597471    6.780704
          3  |   7.441782   2.065953     7.23   0.000     4.318873    12.82282
          4  |   39.64687   14.92059     9.78   0.000     18.96139     82.8987
------------------------------------------------------------------------------
```

**{4}** *logistic* directly calculate the age adjusted odds ratio and 95% confidence interval for alcohol level 2 vs. level 1, level 3 vs. level 1 and level 4 vs. level 1.




By default, Stata includes a constant term in its regression models.

For this reason, when we convert a categorical variable into a number of indicator covariates we always have to leave one of the categories out to avoid multicolinearity.

For example, let

$$sex = \begin{cases} 1 \text{ for men} \\ 2 \text{ for women} \end{cases} \qquad 1.sex = \begin{cases} 1 \text{ for men} \\ 0 \text{ for women} \end{cases} \qquad 2.sex = \begin{cases} 0 \text{ for men} \\ 1 \text{ for women} \end{cases}$$

Then the linear predictor $\alpha + \beta_1 1.sex + \beta_2 2.sex$ takes the values

$\alpha + \beta_1$ for men and $\alpha + \beta_2$ for women.

This gives us three parameters to model the effects of two sexes. To obtain uniquely defined parameter estimates we must use one of the following models:

$$\beta_1 1.sex + \beta_2 2.sex$$

$$\alpha + \beta_2 2.sex$$

or

$$\alpha + \beta_1 1.sex$$

By default, the Stata syntax `i.varname` defines indicator covariates for all but the smallest value of `varname`.

If `varname` takes the values 1, 3, 5 and 10 and we want indicator covariates defined for each of these values except 5 we can use the syntax

`ib5.varname`

`5.11.EsophagealCa.ClassVersion.log` continues as follows.

```
. logistic cancer i.age ib2.alcohol [freq=patients]                        {5}

Logistic regression                               Number of obs   =        975
                                                  LR chi2(8)      =     262.07
                                                  Prob > chi2     =     0.0000
Log likelihood = -363.70808                       Pseudo R2       =     0.2649

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   5.109555   5.518386     1.51   0.131     .6152822    42.43183
          3  |   30.74829   31.94554     3.30   0.001     4.013065    235.5949
          4  |   51.59613    53.3825     3.81   0.000     6.791178    392.0027
          5  |   78.00451   81.22889     4.18   0.000     10.13289    600.4908
          6  |   83.44761   91.07472     4.05   0.000     9.826812     708.623
             |
     alcohol |
          1  |   .2382798   .0583275    -5.86   0.000     .1474773    .3849898
          3  |   1.773226   .4159625     2.44   0.015     1.119669    2.808268 {6}
          4  |   9.447049   3.239241     6.55   0.000     4.824284    18.49948
------------------------------------------------------------------------------
```

**{5}** **ib2.alcohol** instructs Stata to include indicator covariates for each value of **alcohol** except **alcohol** = 2. This makes an alcohol value of 2 the baseline for odds ratios associated with this variable.

**{6}** The odds rato for level 3 drinkers compared to level 1 drinkers is 1.77, which is identical to the odds ratio obtained from the earlier **lincom** statement.

## 9. Making Inferences About Odds Ratio Derived from Multiple Parameters

In more complex multiple logistic regression models we need to make inferences about odds ratios that are estimated from multiple parameters.

A simple example was given in the preceding example where the log odds ratio for cancer associated with alcohol level 3 compared to alcohol level 2 was of the form

$$\beta_3 - \beta_2$$

To derive confidence intervals and perform hypothesis tests we need to be able to compute the standard errors of weighted sums of parameter estimates.

## 10. Estimating The Standard of Error of a Weighted Sum of Regression Coefficients

Suppose that we have a model with $q$ parameters.

Let $b_1, b_2, \ldots, b_q$ be estimates of parameters $\beta_1, \beta_2, \ldots, \beta_q$

Let $c_1, c_2, \ldots, c_q$ be a set of known weights and let

$$f = \sum c_j b_j$$

For example, in the preceding logistic regression model there are 5 age parameters (*2.age*, *3.age*, …, *6.age*), three alcohol parameters (*2.alcohol*, *3.alcohol*, *4.alcohol*) and one constant parameter for a total of $q$ = 9 parameters. Let us rename these parameters so that $\beta_2$ and $\beta_3$ represent *2.alcohol* and *3.alchol*, respectively.

Let

$$c_3 = 1, c_2 = -1, \text{ and } c_1 = c_4 = c_5 = \ldots = c_9 = 0$$

Then $f = b_3 - b_2 = 2.0071 - 1.4343 = 0.5728$

And exp ($f$) = exp(0.5728) = 1.773 is the odds ratio of level 3 drinkers relative to level 2 drinkers.

Let $s_{jj}$ be the estimated variance of $b_j$; $j = 1, \ldots, q$ and let $s_{ij}$ be the covariance of $b_i$ and $b_j$ for any $i \neq j$.

Then the variance of $f$ equals:

$$s_f^2 = \sum_{i=1}^{q} \sum_{j=1}^{q} c_i c_j s_{ij} \qquad \textbf{\{4.6\}}$$

For large studies the 95% confidence interval for $f$ is

$$f \pm 1.96 * \sqrt{s_f^2} = f \pm 1.96 s_f$$

When $f$ estimates a log-odds ratio then the corresponding odds ratio is estimated by $\exp(f)$ with 95% confidence interval $\left[\exp\left(f - 1.96 s_f\right), \exp\left(f + 1.96 s_f\right)\right]$

## 11. The Estimated Variance-Covariance Matrix

The estimates of $s_{ij}$ are written in a square array

$$\begin{bmatrix} s_{11}, & s_{12} & \ldots, & s_{1q} \\ s_{21}, & s_{22} & \ldots, & s_{2q} \\ . & & & . \\ . & & & . \\ . & & & . \\ s_{q1}, & s_{q2}, & \ldots, & s_{qq} \end{bmatrix}$$

which is called the estimated variance-covariance matrix.

In our example comparing level 3 drinkers to level 2 drinkers

$$s_f^2 = s_{33} + s_{22} - 2 s_{23}$$

which gives $s_f = 0.2346$; this is the standard error of *3.alcohol –2.alcohol* given in the preceding example.

**a) Estimating the Variance-Covariance Matrix with Stata**

You can obtain the **variance-covariance matrix** in Stata using the ***estat vce*** post estimation command. However, the ***lincom*** command is so powerful and flexible that we will usually not need to do this explicitly. If you are working with other statistical packages you may need to calculate equation {4.6} explicitly

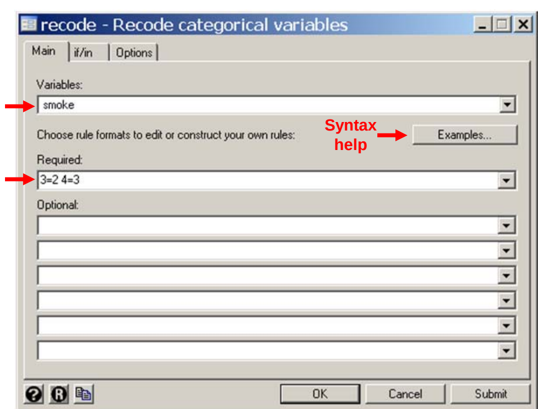
## 12. Example: Effect of Dose of Tobacco on Esophageal Cancer Risk

```
. *  5.12.EsophagealCa.ClassVersion.do
. *
. *  Estimate age-adjusted risk of esophageal cancer due to dose of tobacco.
. *
. use C:\WDDtext\5.5.EsophagealCa.dta, clear

. * Statistics > Summaries... > Tables > Two-way tables with measures...
. tabulate cancer tobacco [freq=patients] , column

+-------------------+
| Key               |
|-------------------|
|     frequency     |
| column percentage |
+-------------------+
Esophageal |             Tobacco (gm/day)
    Cancer |       0-9      10-19      20-29      >= 30 |     Total
-----------+--------------------------------------------+----------
        No |       447        178         99         51 |       775
           |     85.14      75.42      75.00      62.20 |     79.49
-----------+--------------------------------------------+----------
       Yes |        78         58         33         31 |       200
           |     14.86      24.58      25.00      37.80 |     20.51
-----------+--------------------------------------------+----------
     Total |       525        236        132         82 |       975
           |    100.00     100.00     100.00     100.00 |    100.00
```

```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logisitic cancer i.age i.tobacco [freq=patients]

Logit regression                                  No. of obs      =        975
                                                  LR chi2(8)      =     157.68
                                                  Prob > chi2     =     0.0000
                                                  Pseudo R2       =     0.1594
Log likelihood   = -415.90235
------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   6.035932   6.433686     1.69   0.092     .7472235    48.75713
          3  |   36.20831   37.10835     3.50   0.000     4.857896    269.8785
          4  |   61.79318   63.10432     4.04   0.000     8.349838    457.3019
          5  |   83.56952   85.86437     4.31   0.000     11.15506    626.0713
          6  |   60.45383   64.52449     3.84   0.000     7.462882    489.7124
             |
     tobacco |
          2  |   1.835482   .3781838     2.95   0.003     1.225655    2.748731 {1}
          3  |   1.945172    .487733     2.65   0.008     1.189947    3.179717
          4  |   5.706139   1.725688     5.76   0.000     3.154398     10.3221
------------------------------------------------------------------------------
```

**{1}** Note how **similar** the log-odds ratios for the **2nd** and **3rd** levels of tobacco exposure. If we had assigned a single parameter for ***tobacco*** we would have badly **overestimated** the odds ratio between levels **2** and **3**, and badly **underestimated** the odds ratio between levels **1** and **2** and between levels **3** and **4**.

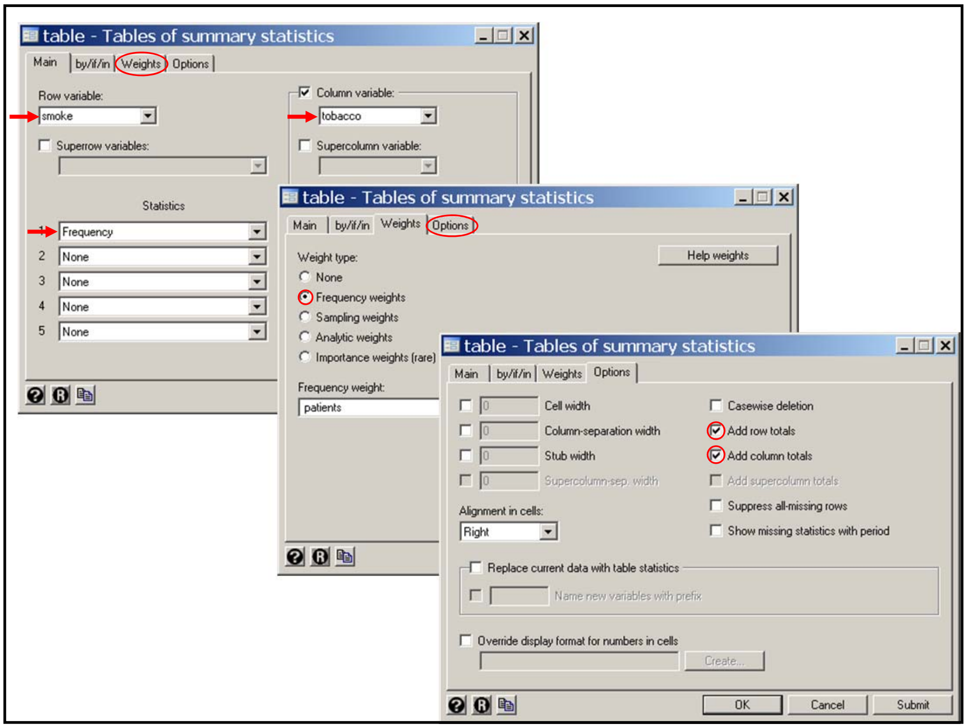
```
. generate smoke = tobacco

. * Data > Create... > Other variable-transformation... > Recode catigorical...
. recode smoke 3=2 4=3                                                  {2}
(96 changes made)
```




**{2}** We want to **combine** the 2nd and 3rd levels of tobacco exposure. We do this by defining a new variable called ***smoke*** that is identical to *tobacco* and then using the ***recode*** statement, which in this example changes values of *smoke* = 3 to *smoke* = 2, and values of *smoke* = 4 to *smoke* = 3.

```
. label variable smoke "Smoking (gm/day)"

. label define  smoke 1 "0-9" 2 "10-29" 3 ">= 30"

. label values smoke smoke

. * Statistics > Summaries... > Tables > Table of summary statistics (table).
. table smoke tobacco [freq=patients], row col                          {3}
---------------------------------------------
Smoking   |          Tobacco (gm/day)
(gm/day)  |   0-9  10-19  20-29  >= 30  Total
----------+----------------------------------
      0-9 |   525                         525
    10-29 |          236    132           368
    >= 30 |                         82     82
          |
    Total |   525    236    132     82    975
---------------------------------------------
```

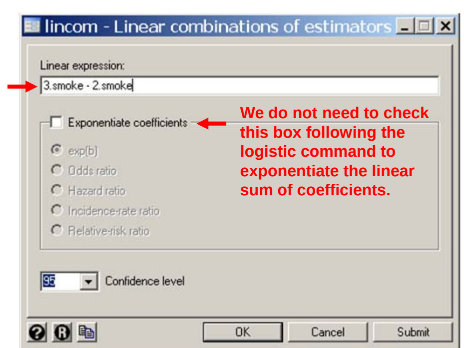
{3} This **table** statement shows that the previous *recode* statement worked.



```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer i.age i.smoke [freq=patients]

Logistic regression                               Number of obs   =        975
                                                  LR chi2(7)      =     157.64
                                                  Prob > chi2     =     0.0000
Log likelihood = -415.92589                       Pseudo R2       =     0.1593

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   6.037092   6.434914     1.69   0.092     .7473691    48.76637
          3  |    36.2117   37.11182     3.50   0.000      4.85835    269.9038
          4  |   61.79965   63.11096     4.04   0.000     8.350705    457.3503
          5  |   83.52177   85.81492     4.31   0.000     11.14879    625.7078
          6  |   60.25337   64.30389     3.84   0.000     7.439742    487.9831
             |
       smoke |
          2  |   1.873669   .3421356     3.44   0.001     1.309972    2.679933 {4}
          3  |   5.704954   1.725242     5.76   0.000     3.153836    10.31965
------------------------------------------------------------------------------
. lincom 3.smoke - 2.smoke                                                    {5}

 ( 1)  - [cancer]2.smoke + [cancer]3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   3.044803   .9116935     3.72   0.000     1.693118    5.475593
------------------------------------------------------------------------------
```

**{4}** There is a marked trend of **increasing** cancer **risk** with **increasing dose** of tobacco. Men who smoked 10-29 grams a day had **1.87** times the cancer risk of men who smoked less. Men who smoked more than 29 gm/day had **5.7** times the cancer risk of men who smoked less than 10 grams a day.

**{5}** The **odds ratio** for $\geq$ 30 gm/day of tobacco relative to 10-29 gm/day is 3.04 and is highly **significant**.



**The next question is how do alcohol and tobacco interact on esophageal cancer risk?**

```
. * 5.20.EsophagealCa.ClassVersionlog
. *
. * Regress esophageal cancers against age and dose of alcohol
. * and tobacco using a multiplicative model.
. *
. use 5.5.EsophagealCa.dta, clear
. sort tobacco

. * Statistics > Summaries... > Tables > Two-way tables with measures...
. by tobacco: tabulate cancer alcohol [freq=patients]
> , column                                             {1}

-> tobacco=      0-9
Esophageal | Alcohol (gm/day)
Cancer     |     0-39     40-79    80-119    >= 120 |   Total
-----------+----------------------------------------+--------
        No |      252       145        42         8 |     447
           |    96.55     81.01     68.85     33.33 |   85.14
-----------+----------------------------------------+--------
       Yes |        9        34        19        16 |      78
           |     3.45     18.99     31.15     66.67 |   14.86
-----------+----------------------------------------+--------
     Total |      261       179        61        24 |     525
           |   100.00    100.00    100.00    100.00 |  100.00
```

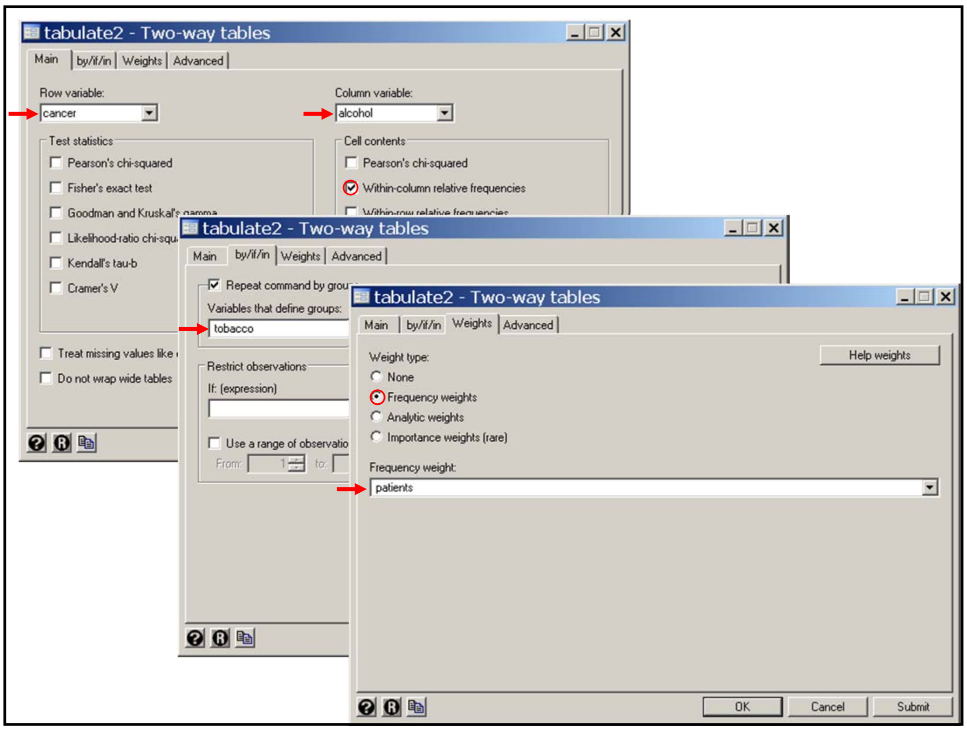
**{1}** ***by tobacco***: produces separate frequency tables for each value of *tobacco*. The data set must first be **sorted** by *tobacco*.

```
-> tobacco=    10-19
Esophageal | Alcohol (gm/day)
Cancer     |     0-39     40-79    80-119    >= 120 |   Total
-----------+----------------------------------------+--------
        No |       74        68        30         6 |     178
           |    88.10     80.00     61.22     33.33 |   75.42
-----------+----------------------------------------+--------
       Yes |       10        17        19        12 |      58
           |    11.90     20.00     38.78     66.67 |   24.58
-----------+----------------------------------------+--------
     Total |       84        85        49        18 |     236
        |   100.00    100.00    100.00    100.00 |  100.00

-> tobacco=   20-29
Esophageal | Alcohol (gm/day)
Cancer     |     0-39     40-79    80-119    >= 120 |   Total
-----------+----------------------------------------+--------
        No |       37        47        10         5 |      99
           |    88.10     75.81     62.50     41.67 |   75.00
-----------+----------------------------------------+--------
       Yes |        5        15         6         7 |      33
           |    11.90     24.19     37.50     58.33 |   25.00
-----------+----------------------------------------+--------
     Total |       42        62        16        12 |     132
           |   100.00    100.00    100.00    100.00 |  100.00
```

```
-> tobacco=    >= 30
Esophageal | Alcohol (gm/day)
Cancer     |     0-39     40-79    80-119    >= 120 |     Total
-----------+----------------------------------------+----------
        No |        23        20         5         3 |        51
           |     82.14     68.97     41.67     23.08 |     62.20
-----------+----------------------------------------+----------
       Yes |         5         9         7        10 |        31
           |     17.86     31.03     58.33     76.92 |     37.80
-----------+----------------------------------------+----------
     Total |        28        29        12        13 |        82
           |    100.00    100.00    100.00    100.00 |    100.00
```

These tables show that the proportion of study subjects with cancer increases dramatically with increasing alcohol consumption for every level of tobacco consumption.

The proportion of cases also increases with increasing tobacco consumption for most levels of alcohol.



## 13. Multiplicative Model of Effect of Smoking and Alcohol on Esophageal Cancer Risk

Suppose that subjects either were or were not exposed to alcohol and tobacco and we did not include age in our model. Consider the model

$$\text{logit}\left(E\left(d_{ij} / m_{ij}\right)\right) = \alpha + x_i\beta_1 + y_j\beta_2$$

where $i = \begin{cases} 1: & \text{if patient drank} \\ 0: & \text{Otherwise} \end{cases}$

$j = \begin{cases} 1: & \text{if patient smoked} \\ 0: & \text{Otherwise} \end{cases}$

$x_i = i$
$y_j = j$

$m_{ij}$ is the number of subjects with drinking status $i$ and smoking status $j$.

$d_{ij}$ is the number of cancers with drinking status $i$ and smoking status $j$.

$\alpha$, $\beta_1$ and $\beta_2$ are model parameters.

Thus the log-odds of a drinker with smoking status $j$ is

$$\text{logit}\left(E\left(d_{1j} / m_{1j}\right)\right) = \alpha + \beta_1 + y_j\beta_2 \qquad \{4.7\}$$

The log-odds of a non-drinker with smoking status $j$ is

$$\text{logit}\left(E\left(d_{0j} / m_{0j}\right)\right) = \alpha + y_j\beta_2 \qquad \{4.8\}$$

Subtracting equation {4.8} from {4.7} gives that

$$\log\left(\frac{\pi_{1j} / (1-\pi_{1j})}{\pi_{0j} / (1-\pi_{0j})}\right) = \beta_1$$

where $\pi_{ij}$ is the probability that someone with drinking status $i$ and smoking status $j$ develops cancer.

In other words, $\exp(\beta_1)$ is the odds ratio for cancer in drinkers compared to non-drinkers adjusted for smoking.

Note that this implies that the relative risk of drinking is the same in smokers and non-smokers.

By an identical argument, $\exp(\beta_2)$ is the odds ratio for cancer in smokers compared to non-smokers adjusted for drinking.

For people who both drink and smoke the model is

$$\text{logit}(E(d_{11} / m_{11})) = \alpha + \beta_1 + \beta_2 \qquad \textbf{\{4.9\}}$$

while for people who neither drink nor smoke the model is

$$\text{logit}(E(d_{00} / m_{00})) = \alpha \qquad \textbf{\{4.10\}}$$

Subtracting {4.9} from {4.10} give that the log-odds ratio for people who both smoke and drink relative to those who do neither is $\beta_1 + \beta_2$, and the corresponding odds ratio is $\exp(\beta_1) \times \exp(\beta_2)$.

Thus our model implies that the odds ratio of having both risk factors equals the product of the individual odds ratio for drinking and smoking.

It is for this reason that this is called a **multiplicative model**.

The multiplicative assumption is a very strong one that is often not justified. Let us see how it works with the Ille-et-Vilaine data set.

```
. *
. *  Regress cancer against age, alcohol and smoke.
. *  Use a multiplicative model
. *
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer i.age i.alcohol i.smoke [freq=patients]             {1}

Logistic regression                               Number of obs   =        975
                                                  LR chi2(10)     =     285.55
                                                  Prob > chi2     =     0.0000
Log likelihood = -351.96823                       Pseudo R2       =     0.2886
```

**{1}** This command fits a model with a constant parameter, **5 age** parameters **3 alcohol** parameters and **two tobacco** parameters. No parameter is given for the lowest strata associated with *age, alcohol* or *smoke*.

```
------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |
          2  |   7.262526   8.017757     1.80   0.073      .834391    63.21291
          3  |   43.65627   46.62635     3.54   0.000     5.381893    354.1263
          4  |    76.3655   81.33339     4.07   0.000     9.469377    615.8472
          5  |   133.7632   143.9793     4.55   0.000     16.22277     1102.93
          6  |   124.4262   139.5094     4.30   0.000     13.82058    1120.205
             |
     alcohol |
          2  |   4.213304    1.05191     5.76   0.000     2.582905    6.872854 {2}
          3  |   7.222005   2.053957     6.95   0.000     4.135936    12.61077
          4  |    36.7912   14.17012     9.36   0.000     17.29434    78.26794
             |
       smoke |
          2  |   1.592701   .3200884     2.32   0.021     1.074154    2.361577
          3  |   5.159309   1.775207     4.77   0.000     2.628521    10.12679
------------------------------------------------------------------------------
```

{2} The **odds ratio** for level **2** drinkers relative to level **1** drinkers **adjusted** for **age** and **smoking** is **4.21**.

```
. lincom 2.alcohol + 2.smoke

 ( 1)  [cancer]2.alcohol + [cancer]2.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   6.710535   2.110331     6.05   0.000     3.623022     12.4292 {3}
------------------------------------------------------------------------------

. lincom 3.alcohol + 2.smoke

  ( 1)  [cancer]3.alcohol + [cancer]2.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |    11.5025   3.877641     7.25   0.000     5.940747    22.27118
------------------------------------------------------------------------------

. lincom 4.alcohol + 2.smoke

 ( 1)  [cancer]4.alcohol + [cancer]2.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   58.59739   25.19568     9.47   0.000     25.22777    136.1061
------------------------------------------------------------------------------
```

{3} The cancer log-odds for a man in, say, the third age strata who is a level 2 drinker and level 2 smoker is

_cons + 3.age + 2.alcohol + 2.smoke

The cancer log-odds for a man in the same age strata who is a level 1 drinker and level 1 smoker is

_cons + 3.age

Subtracting these two log-odds and exponentiating gives that the odds ratio for men who are **both** level **2** drinkers and level **2** smokers relative to those who are level **1** drinkers and level **1** smokers is **6.71.**

```
. lincom 2.alcohol + 3.smoke

 ( 1)  [cancer]2.alcohol + [cancer]3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   21.73774   9.508636     7.04   0.000     9.223106    51.23319
------------------------------------------------------------------------------

. lincom 3.alcohol + 3.smoke

 ( 1)  [cancer]3.alcohol + [cancer]3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   37.26056   17.06685     7.90   0.000     15.18324    91.43957
------------------------------------------------------------------------------

. lincom 4.alcohol + 3.smoke

 ( 1)  [cancer]4.alcohol + [cancer]3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   189.8171   100.9788     9.86   0.000     66.91353    538.4643
------------------------------------------------------------------------------
```

The preceding analyses are summarized in the following table.

Note that the multiplicative assumption holds.

E.g. $36.8 \times 5.16 = 190$

**Table 4.1. Effect of Alcohol and Tobacco on Esophageal Cancer Risk**

Multiplicative Model -- Adjusted to Age

| Daily Alcohol Comsumption | Daily Tobacco Consumption 0-9 gm Odds Ratio | 0-9 gm 95% CI | 10-29 gm Odds Ratio | 10-29 gm 95% CI | 30gm Odds Ratio | 30gm 95% CI |
|---|---|---|---|---|---|---|
| 0-39 gm | 1.0* | | 1.59 | (1.1 - 2.4) | 5.16 | (2.6 - 10) |
| 40-79 gm | 4.21 | (2.6 - 6.9) | 6.71 | (3.6 - 12) | 21.7 | (9.2 - 51) |
| 80-119 gm | 7.22 | (4.1 - 13) | 11.5 | (5.9 - 22) | 37.3 | (15 - 91) |
| 120 gm. | 36.8 | (17 - 78) | 58.6 | (25 - 140) | 190 | (67 - 540) |

* Denominator of odds ratios

This model suggests that combined heavy alcohol and tobacco consumption has an enormous effect on the risk of esophageal cancer.

To determine if this is real or a model artifact we need to look at a model that permits the cancer risk associated with combined risk factors to deviate from the multiplicative model.

### 14. Modeling the Effect of Alcohol and Tobacco on Cancer Risk with Interaction

Let us first return to the simple example where people either do or do not drink or smoke and where we do not adjust for age. Our multiplicative model was

$$\text{logit}\left(E\left(d_{ij} / m_{ij}\right)\right) = \alpha + x_i\beta_1 + y_j\beta_2 \qquad \textbf{\{4.11\}}$$

We allow alcohol and tobacco to have a synergistic effect on cancer odds by including a fourth parameter as follows

$$\text{logit}\left(E\left(d_{ij} / m_{ij}\right)\right) = \alpha + x_i\beta_1 + y_j\beta_2 + x_i y_j\beta_3 \qquad \textbf{\{4.12\}}$$

Then $\beta_3$ only enters the model for people who both smoke and drink. By the usual arguments…

| | |
|---|---|
| $\beta_1$ | is the log odds ratio for cancer associated with **alcohol among non-smokers**, |
| $\beta_2$ | is the log odds ratio for cancer associated with **smoking among non-drinkers**, |
| $\beta_1 + \beta_3$ | is the log odds ratio for cancer associated with **alcohol among smokers**, |
| $\beta_1 + \beta_2 + \beta_3$ | is the log odds ratio for cancer associated with people who **smoke and drink** *compared* to those who are both **non-smokers and non-drinkers**. |

We now apply this interpretation to the esophageal cancer data. *5.20.EsophagelaCa.ClassVersion.log* continues as follows:

```
. *
. *  Regress cancer against age, alcohol and smoke.
. *  Include alcohol-smoke interaction terms.
. *
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer i.age alcohol##smoke [freq=patients],                    {1}

Logistic regression                               Number of obs   =        975
                                                  LR chi2(16)     =     290.90
                                                  Prob > chi2     =     0.0000
Log likelihood = -349.29335                       Pseudo R2       =     0.2940
```

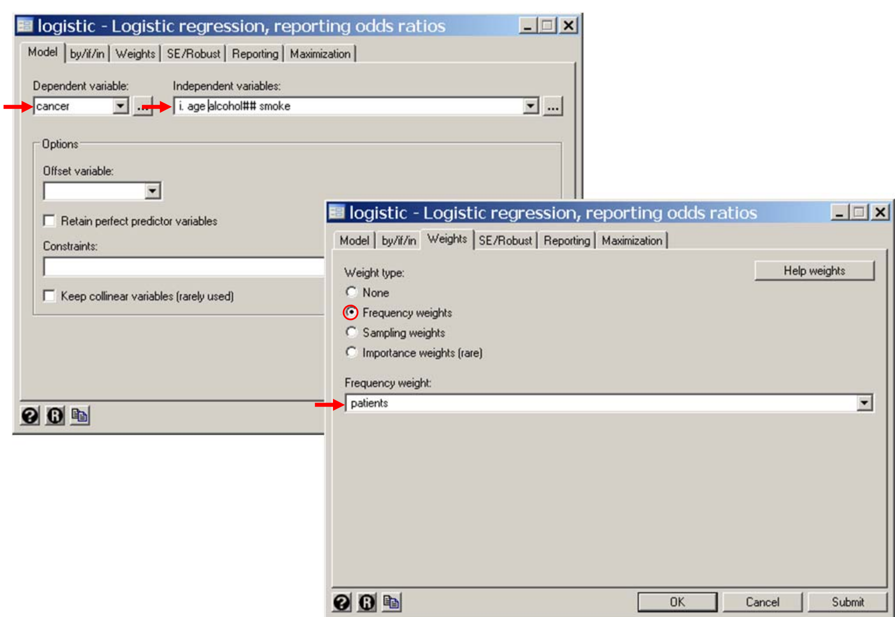
A separate parameter is fitted for each of these variables. In addition, the model specifies 5 parameters for the 5 age indicator variables and a constant parameter.

{1} The syntax ***alcohol##smoke*** defines the following categorical values:

```
    2.alcohol = 1 if alcohol = 2, and = 0 otherwise
    3.alcohol = 1 if alcohol = 3, and = 0 otherwise
    4.alcohol = 1 if alcohol = 4, and = 0 otherwise
    2.smoke   = 1 if smoke = 2,   and = 0 otherwise
    3.smoke   = 1 if smoke = 3,   and = 0 otherwise
 alcohol#smoke
    2 2 = 2.alcohol x 2.smoke
    2 3 = 2.alcohol x 3.smoke
    3 2 = 3.alcohol x 2.smoke
    3 3 = 3.alcohol x 3.smoke
    4 2 = 4.alcohol x 2.smoke
    4 3 = 4.alcohol x 3.smoke
```

| cancer | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| age | | | | | | |
| 2 | 6.697614 | 7.41052 | 1.72 | 0.086 | .7657997 | 58.57673 |
| 3 | 40.1626 | 42.67457 | 3.48 | 0.001 | 5.004744 | 322.3011 |
| 4 | 69.55115 | 73.73699 | 4.00 | 0.000 | 8.707117 | 555.5642 |
| 5 | 123.0645 | 131.6754 | 4.50 | 0.000 | 15.11374 | 1002.06 |
| 6 | 118.8368 | 133.2538 | 4.26 | 0.000 | 13.19724 | 1070.086 |
| alcohol | | | | | | |
| 2 | 7.554406 | 3.043769 | 5.02 | 0.000 | 3.429574 | 16.64028 |
| 3 | 12.71358 | 5.825002 | 5.55 | 0.000 | 5.179306 | 31.20788 |
| 4 | 65.07188 | 39.54145 | 6.87 | 0.000 | 19.7767 | 214.108 |
| smoke | | | | | | |
| 2 | 3.800862 | 1.703912 | 2.98 | 0.003 | 1.578671 | 9.151084 |
| 3 | 8.651205 | 5.569301 | 3.35 | 0.001 | 2.449667 | 30.55247 |
| alcohol#smoke | | | | | | |
| 2 2 | .3251915 | .1746668 | -2.09 | 0.036 | .1134859 | .9318294 |
| 2 3 | .5033299 | .4154539 | -0.83 | 0.406 | .0998302 | 2.53772 |
| 3 2 | .3341452 | .2008274 | -1.82 | 0.068 | .1028839 | 1.085233 |
| 3 3 | .657279 | .6598915 | -0.42 | 0.676 | .0918681 | 4.702563 |
| 4 2 | .3731549 | .301804 | -1.22 | 0.223 | .076462 | 1.821095 |
| 4 3 | .3489097 | .4210291 | -0.87 | 0.383 | .032777 | 3.714132 |

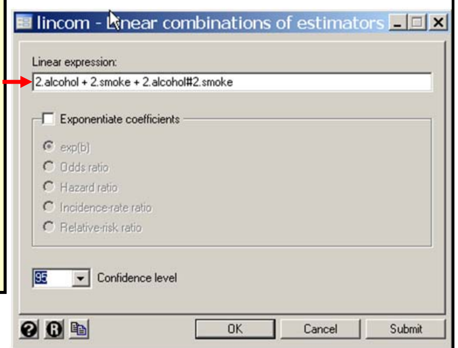
The highlighted odds ratios show age adjusted risks of drinking among level 1 smokers and smoking among level 1 drinkers



```
. lincom 2.alcohol + 2.smoke + 2.alcohol#2.smoke                    {2}

 ( 1)  [cancer]2.alcohol + [cancer]2.smoke + [cancer]2.alcohol#2.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   9.337306   3.826162     5.45   0.000     4.182379    20.84586
------------------------------------------------------------------------------
```

{2} This statement calculates the odds ratio for men in the second strata of *alcohol* and *smoke* relative to men in the first strata of both of these variables. This odds ratio of **9.33** is adjusted for age.

*2.alcohol#2.smoke* represents the parameter associated with the product of the covariates *2.alcohol* and *2.smoke*.




```
. lincom 2.alcohol + 3.smoke + 2.alcohol#3.smoke

 ( 1)  [cancer]2.alcohol + [cancer]3.smoke + [cancer]2.alcohol#3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   32.89498   19.73769     5.82   0.000     10.14824    106.6274
------------------------------------------------------------------------------

. lincom 3.alcohol + 2.smoke + 3.alcohol#2.smoke

 ( 1)  [cancer]3.alcohol + [cancer]2.smoke + [cancer]3.alcohol#2.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   16.14675   7.152595     6.28   0.000     6.776802    38.47207
------------------------------------------------------------------------------
```

```
. lincom 3.alcohol + 3.smoke + 3.alcohol#3.smoke

 ( 1)  [cancer]3.alcohol + [cancer]3.smoke + [cancer]3.alcohol#3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   72.29267   57.80896     5.35   0.000     15.08098    346.5446
------------------------------------------------------------------------------

. lincom 4.alcohol + 2.smoke + 4.alcohol#2.smoke

( 1)  [cancer]4.alcohol + [cancer]2.smoke + [cancer]4.alcohol#2.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   92.29212   53.97508     7.74   0.000     29.33307    290.3833
------------------------------------------------------------------------------

. lincom 4.alcohol + 3.smoke + 4.alcohol#3.smoke

 ( 1)  [cancer]4.alcohol + [cancer]3.smoke + [cancer]4.alcohol#3.smoke = 0

------------------------------------------------------------------------------
      cancer | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   196.4188   189.1684     5.48   0.000     29.74417    1297.072
------------------------------------------------------------------------------
```

The following table summarizes the results of this analysis

**Table 4.2. Effect of Alcohol and Tobacco on Esophageal Cancer Risk**

Model with all 2-Way Interaction Terms -- Adjusted for Age

| Daily Alcohol Comsumption | Daily Tobacco Consumption: 0 – 9 gm Odds Ratio | 0 – 9 gm 95% Confidence Interval | 10 – 29 gm Odds Ratio | 10 – 29 gm 95% Confidence Interval | ≥ 30 gm Odds Ratio | ≥ 30 gm 95% Confidence Interval |
|---|---|---|---|---|---|---|
| **0 – 39 gm** | 1.0* | | 3.8 | (1.6 – 9.2) | 8.65 | (2.4 – 31) |
| **40 – 79 gm** | 7.55 | (3.4 – 17) | 9.34 | (4.2 – 21) | 32.9 | (10 – 110) |
| **80 – 119 gm** | 12.7 | (5.2 – 31) | 16.1 | (6.8 – 38) | 72.3 | (15 – 350) |
| **≥ 120 gm** | 65.1 | (20 – 210) | 92.3 | (29 – 290) | 196 | (30 – 1300) |

* Denominator of odds ratios

Tables 4.1 and 4.2 are quite **consistent**, and both indicate a dramatic increase in risk with increased drinking and smoking. Note that the **confidence intervals** are **wide**, particularly for the most heavily exposed subjects. The confidence intervals are **wider** in Table 4.2 because they are derived from a model with **more parameters.**

Which model is better?

**Table 4.1. Effect of Alcohol and Tobacco on Esophageal Cancer Risk**

Multiplicative Model -- Adjusted to Age

| Daily Alcohol Comsumption | Daily Tobacco Consumption: 0-9 gm Odds Ratio | 0-9 gm 95% CI | 10-29 gm Odds Ratio | 10-29 gm 95% CI | 30gm Odds Ratio | 30gm 95% CI |
|---|---|---|---|---|---|---|
| 0-39 gm | 1.0* | | 1.59 | (1.1 - 2.4) | 5.16 | (2.6 - 10) |
| 40-79 gm | 4.21 | (2.6 - 6.9) | 6.71 | (3.6 - 12) | 21.7 | (9.2 - 51) |
| 80-119 gm | 7.22 | (4.1 - 13) | 11.5 | (5.9 - 22) | 37.3 | (15 - 91) |
| 120 gm. | 36.8 | (17 - 78) | 58.6 | (25 - 140) | 190 | (67 - 540) |

* Denominator of odds ratios

### 15. Model Fitting: Nested Models and Model Deviance

A model is said to be **nested** within a second model if the first model is a special case of the second.

For example, the multiplicative model {4.11} discussed before was

$$\text{logit}\left(E\left(d_{ij} / m_{ij}\right)\right) = \alpha + x_i\beta_1 + y_j\beta_2$$

while model {4.12} contained an interaction term and was

$$\text{logit}\left(E\left(d_{ij} / m_{ij}\right)\right) = \alpha + x_i\beta_1 + y_j\beta_2 + x_i y_j\beta_3$$

Model {4.11} is nested within model {4.12} since model {4.11} is a special case of model {4.12} with $\beta_3 = 0$.

The model **Deviance** $D$ is a statistic derived from the likelihood function that measures goodness of fit of the data to a specific model. Let $\log(L)$ denote the maximum value of the log likelihood function. Then the deviance is given by

$$D = \text{K} - 2\log(L) \qquad \textbf{\{4.13\}}$$

for some constant K that is independent of the model parameters.

If the model is correct then for large sample sizes $D$ has a $\chi^2$ distribution with degrees of freedom equal to the number of observations minus the number of parameters. Regardless of the true model, $D$ is a non-negative number. Large values of $D$ indicate poor model fit; a perfect fit has $D = 0$.

Suppose that $D_1$ and $D_2$ are deviances from two models with model 1 nested in model 2. Then it can be shown that if model 1 is true then $\Delta D = D_1 - D_2$ has an approximately $\chi^2$ distribution with the number of degrees of freedom equal to the number of parameters in model 2 minus the number of parameters in model 1.

Equivalently, $\Delta D = D_1 - D_2$

$$= K - 2\log(L_1) - (K - 2\log(L_2)) = 2(\log(L_2) - \log(L_1))$$

We use the reduction in deviance as a guide to building reasonable models for our data.

For example, in the multiplicative model of alcohol and tobacco levels analyzed above the log likelihood was

$\log(L) = -351.96823$

```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer i.age i.alcohol i.smoke [freq=patients]

Logistic regression                               Number of obs   =        975
                                                  LR chi2(10)     =     285.55
                                                  Prob > chi2     =     0.0000
Log likelihood = -351.96823                       Pseudo R2       =     0.2886
```

The corresponding model with the 6 interaction terms has a log likelihood of

$\log(L) = -349.29335$

```
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic cancer i.age alcohol##smoke [freq=patients],

Logistic regression                               Number of obs   =        975
                                                  LR chi2(16)     =     290.90
                                                  Prob > chi2     =     0.0000
Log likelihood = -349.29335                       Pseudo R2       =     0.2940
```

For example, in the multiplicative model of alcohol and tobacco levels analyzed above the log likelihood was

$\log(L_1) = -351.96823$

The corresponding model with the 6 interaction terms has a log likelihood of

$\log(L_2) = -349.29335$

$$\Delta D = 2\left(\log\left(L_2\right) - \log\left(L_1\right)\right)$$

$= 2(-349.29335 + 351.96823)$

$= 5.35$

Since there are 6 more parameters in the interactive model than the multiplicative model, has a $\chi^2$ distribution with 6 degrees of freedom under the independent model. We calculate the P value in Stata with the command

display chi2tail(6, 5.34976)

which gives P = .50.

Thus there is no statistical evidence to suggest that the multiplicative model is false, or that any meaningful improvement in the model fit can be obtained by adding interaction terms to the model.

So what results should we publish – **Table 4.1 or 4.2?**

In general, I am guided by deviance reduction statistics when deciding whether to include variables that may, or may not be true confounders, but that are not intrinsically of interest.

If I am interested in the joint effects of 2 or more variables, I usually include the interaction term unless the inclusion of the interaction parameter has almost no effect on the resulting relative risk estimates.

There are no hard and fast guidelines to model building other than that it is best not to include uninteresting variables in the model that have a trivial effect on the model deviance.

I think I personally would go with Table 4.2 over 4.1 in spite of the lack of evidence of interaction. The odds ratio for both ≥120 gm alcohol and ≥30 gm tobacco is so large that I would worry that we were being misled by not taking into account a small but real interaction term.

It would also be acceptable to say that we analyzed the data both ways, found no evidence of interaction, got comparable results and were presenting the multiplicative model results only.

**Table 4.1. Effect of Alcohol and Tobacco on Esophageal Cancer Risk**

Multiplicative Model -- Adjusted to Age

| Daily Alcohol Comsumption | Daily Tobacco Consumption | | | | | |
|---|---|---|---|---|---|---|
| | 0-9 gm | | 10-29 gm | | 30gm | |
| | Odds Ratio | 95% CI | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| 0-39 gm | 1.0* | | 1.59 | (1.1 - 2.4) | 5.16 | (2.6 - 10) |
| 40-79 gm | 4.21 | (2.6 - 6.9) | 6.71 | (3.6 - 12) | 21.7 | (9.2 - 51) |
| 80-119 gm | 7.22 | (4.1 - 13) | 11.5 | (5.9 - 22) | 37.3 | (15 - 91) |
| 120 gm. | 36.8 | (17 - 78) | 58.6 | (25 - 140) | 190 | (67 - 540) |

* Denominator of odds ratios

**Table 4.2. Effect of Alcohol and Tobacco on Esophageal Cancer Risk**

Model with all 2-Way Interaction Terms -- Adjusted for Age

| Daily Alcohol Comsumption | Daily Tobacco Consumption: 0 – 9 gm | | 10 – 29 gm | | ≥ 30 gm | |
|---|---|---|---|---|---|---|
| | Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval |
| **0 – 39 gm** | 1.0* | | 3.8 | (1.6 – 9.2) | 8.65 | (2.4 – 31) |
| **40 – 79 gm** | 7.55 | (3.4 – 17) | 9.34 | (4.2 – 21) | 32.9 | (10 – 110) |
| **80 – 119 gm** | 12.7 | (5.2 – 31) | 16.1 | (6.8 – 38) | 72.3 | (15 – 350) |
| **≥ 120 gm** | 65.1 | (20 – 210) | 92.3 | (29 – 290) | 196 | (30 – 1300) |

* Denominator of odds ratios

## 16. Influence Analysis for Logistic Regression

Consider a logistic regression model with

$J$ distinct covariate patterns

$d_j$ events occur among $n_j$ patients with the covariate pattern $x_{j1}$, $x_{j2}$, …$x_{jq}$.

Let $\pi_j = \pi\left[x_{j1}, x_{j2}, \ldots, x_{jq}\right]$ denote the probability that a patient with the $j^{\text{th}}$ pattern of covariate values suffers an event.

Then $d_j$ has a binomial distribution with

expected value $n_j\pi_j$

standard error $\sqrt{n_j\pi_j\left(1-\pi_j\right)}$

Hence

$\left(d_j - n_j\pi_j\right) / \sqrt{n_j\pi_j\left(1-\pi_j\right)}$

will have a mean of 0 and a standard error of 1.

Let $\hat{\pi}_j = \dfrac{\exp\left[\hat{\alpha} + \hat{\beta}_1 x_{j_1} + \hat{\beta}_2 x_{j2} + \ldots + \hat{\beta}_q x_{jq}\right]}{1 + \exp\left[\hat{\alpha} + \hat{\beta}_1 x_{j_1} + \hat{\beta}_2 x_{j2} + \ldots + \hat{\beta}_q x_{jq}\right]}$

be the estimate of $\pi_j$ obtained by substituting the maximum likelihood parameter estimates into the logistic probability function.

Then the **residual** for the $j^{\text{th}}$ covariate pattern is $d_j - n_j\hat{\pi}_j$

The **Pearson residual** is $r_{j(Pearson)} = \left(d_j - n_j\hat{\pi}_j\right) / \sqrt{n_j\hat{\pi}_j\left(1-\hat{\pi}_j\right)}$

which should have a mean of 0 and a standard deviation of 1 if the model is correct and if $\sqrt{n_j\hat{\pi}_j\left(1-\hat{\pi}_j\right)}$ is a good estimate of the standard error of $d_j - n_j\hat{\pi}_j$.

The **leverage** $h_j$ is analogous to leverage in linear regression.

It measures to potential of a covariate pattern to influence our parameter estimates if the associated residual is large.

For our purposes we can define $h_j$ by the formula

$$\text{var}\left[d_j - n_j\hat{\pi}_j\right] = n_j\hat{\pi}_j\left(1-\hat{\pi}_j\right)\left(1-h_j\right)$$
$$\cong \text{var}\left[d_j - n_j\pi_j\right]\left(1-h_j\right)$$

In other words, 100(1-$h_j$) is the percent reduction in the variance of the $j^{\text{th}}$ residual due to the fact that the estimate of $n_j\hat{\pi}_j$ is pulled towards $d_j$.

The value of $h_j$ lies between 0 and 1.

When $h_j$ is very small $d_j$ has almost no effect on its estimated expected value $n_j\hat{\pi}_j$.

When $h_j$ is close to 1, then $d_j \cong n_j\hat{\pi}_j$. This implies that both the residual $d_j - n_j\hat{\pi}_j$ and its variance will be close to zero.

The **standardized Pearson residual** for the $j^{\text{th}}$ covariate pattern is the residual divided by its standard error. That is,

$$r_{sj} = \frac{d_j - n_j\hat{\pi}_j}{\sqrt{n_j\hat{\pi}_j\left(1-\hat{\pi}_j\right)\left(1-h_j\right)}} = \frac{r_{j(Pearson)}}{\sqrt{1-h_j}}$$

This residual is analogous to the studentized residual for linear regression.

$r_{sj}$ has mean 0 and standard error 1

is not necessarily normally distributed when $n_j$ is small.

The square of the standardized Pearson residual is denoted

$$\Delta X_j^2 = r_{sj}^2 = r_{j(Pearson)}^2 / \left(1-h_j\right)$$

We will use the critical value $\left(z_{0.025}\right)^2 = 1.96^2 = 3.84$ as a very rough guide to identifying large values of $\Delta X_j^2$.

**Approximately 95% of these squared residuals should be <u>less than</u> 3.84 if the logistic regression model is correct.**

The $\Delta\hat{\beta}_j$ **influence statistic** is a measure of the influence of the $j$th covariate pattern on all of the parameter estimates taken together. It equals $\Delta\hat{\beta}_j = r_{sj}^2 h_j / \left(1-h_j\right)$

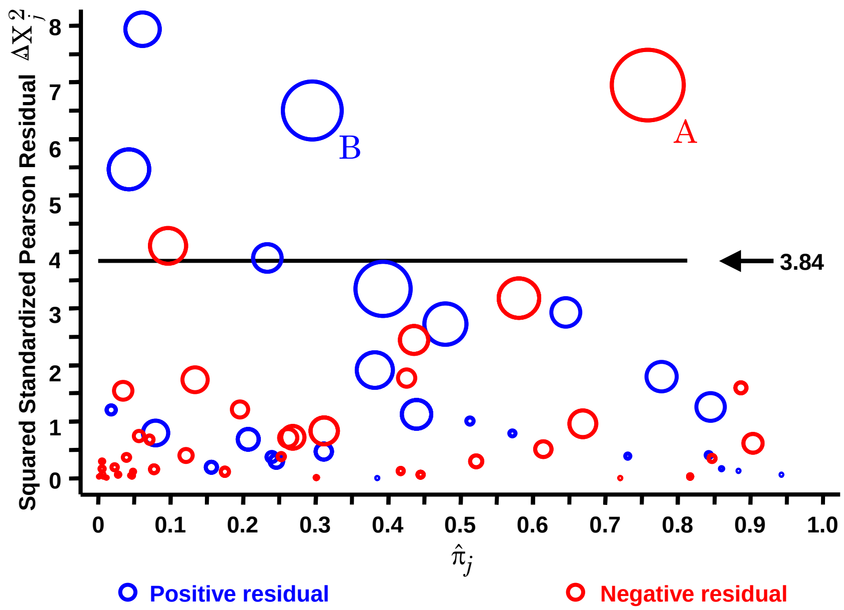
Note that $\Delta\hat{\beta}_j$ increases with both the magnitude of the standardized residual and the size of the leverage.

It is analogous to Cook's distance for linear regression.

Covariate patterns associated with large values of $\Delta X_j^2$ and $\Delta\hat{\beta}_j$ merit special attention.

The following plot is for our model of alcohol and tobacco dose with interaction terms and plots $\Delta X_j^2$ against $\hat{\pi}_j$

The area of the circles is proportional to $\Delta\hat{\beta}_j$




There are 68 unique covariate patterns in this data set.
5% of 68 equals 3.4
There are 6 residuals greater than 3.84.

There are 2 large squared residuals with high influence.

---

**Residual A** is associated with patients who are age 55 – 64 and consume, on a daily basis, at least 120 gm of alcohol 0 – 9 gm of tobacco.

**Residual B** is associated with patients who are age 55 – 64 and consume, on a daily basis, 0 – 39 gm of alcohol and at least 30 gm of tobacco.

---

The $\Delta\beta_j$ influence statistics associated with residuals A and B are 6.16 and 4.15, respectively.

**NOTE:**

In linear regression observations with high influence are due to a single patient and we have the option of deleting the patient

In logistic regression covariate patters with high influence indicate poor model fit. However, we usually do not have the option of deleting the pattern if it represents a sizable number of patients.

| Daily Drug Consumption | | Complete Data | | Deleted Covariate Pattern | | | |
|---|---|---|---|---|---|---|---|
| | | | | A† | | B‡ | |
| Tobacco | Alcohol | Odds Ratio | 95% Confidence Interval | Odds Ratio | Percent Change from Complete Data | Odds Ratio | Percent Change from Complete Data |
| **0 – 9 gm** | **0 – 39 gm** | 1.0* | | 1.0* | | 1.0* | |
| **0 – 9 gm** | **40 – 79 gm** | 7.55 | (3.4 – 17) | 7.53 | -0.26% | 7.70 | 2.0% |
| **0 – 9 gm** | **80 – 119 gm** | 12.7 | (5.2 – 31) | 12.6 | -0.79% | 13.0 | 2.4% |
| **0 – 9 gm** | **≥ 120 gm.** | 65.1 | (20 – 210) | 274 | 321% | 66.8 | 2.6% |
| **10 – 29 gm** | **0 – 39 gm** | 3.80 | (1.6 – 9.2) | 3.77 | -0.79% | 3.86 | 1.6% |
| **10 – 29 gm** | **40 – 79 gm** | 9.34 | (4.2 – 21) | 9.30 | -0.43% | 9.53 | 2.0% |
| **10 – 29 gm** | **80 – 119 gm** | 16.1 | (6.8 – 38) | 16.0 | -0.62% | 16.6 | 3.1% |
| **10 – 29 gm** | **≥ 120 gm.** | 92.3 | (29 – 290) | 95.4 | 3.4% | 94.0 | 1.8% |
| **≥ 30gm** | **0 – 39 gm** | 8.65 | (2.4 – 31) | 8.66 | 0.12% | 1.88 | -78% |
| **≥ 30gm** | **40 – 79 gm** | 32.9 | (10 – 110) | 33.7 | 2.4% | 33.5 | 1.8% |
| **≥ 30gm** | **80 – 119 gm** | 72.3 | (15 – 350) | 73.0 | 0.97% | 74.2 | 2.6% |
| **≥ 30gm** | **≥ 120 gm.** | 196 | (30 – 1300) | 198 | 1.02% | 203 | 3.6% |

* Denominator of odds ratios

† Patients age 55 – 64 who drink at least 120 gm a day and smoke 0 – 9 gm a day deleted

‡ Patients age 55 – 64 who drink 0 – 39 gm a day and smoke at least 30 gm a day deleted

**Table 4.1. Effect of Alcohol and Tobacco on Esophageal Cancer Risk**

| Daily Alcohol Comsumption | Daily Tobacco Consumption | | | | | |
|---|---|---|---|---|---|---|
| | 0-9 gm | | 10-29 gm | | 30gm | |
| | Odds Ratio | 95% CI | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| **Multiplicative Model -- Adjusted to Age** | | | | | | |
| 0-39 gm | 1.0* | | 1.59 | (1.1 - 2.4) | 5.16 | (2.6 - 10) |
| 40-79 gm | 4.21 | (2.6 - 6.9) | 6.71 | (3.6 - 12) | 21.7 | (9.2 - 51) |
| 80-119 gm | 7.22 | (4.1 - 13) | 11.5 | (5.9 - 22) | 37.3 | (15 - 91) |
| 120 gm. | 36.8 | (17 - 78) | 58.6 | (25 - 140) | 190 | (67 - 540) |
| **Model with all 2-Way Interaction Terms -- Adjusted for Age** | | | | | | |
| 0 – 39 gm | 1.0* | | 3.8 | (1.6 – 9.2) | 8.65 | (2.4 – 31) |
| 40 – 79 gm | 7.55 | (3.4 – 17) | 9.34 | (4.2 – 21) | 32.9 | (10 – 110) |
| 80 – 119 gm | 12.7 | (5.2 – 31) | 16.1 | (6.8 – 38) | 72.3 | (15 – 350) |
| ≥120 gm | 65.1 | (20 – 210) | 92.3 | (29 – 290) | 196 | (30 – 1300) |

* Denominator of odds ratios

## 17. What is the best model?

We have 975 patients,
200 cases,
68 unique covariate patterns
17 parameters in the interactive model.

Over-fitting is certainly a concern

Still the effect of dose of tobacco and alcohol on risk is very marked, which makes the interactive model tempting to use.

It is a pity that age, alcohol and tobacco were categorized before we received this data. It is always a mistake to throw such data away.

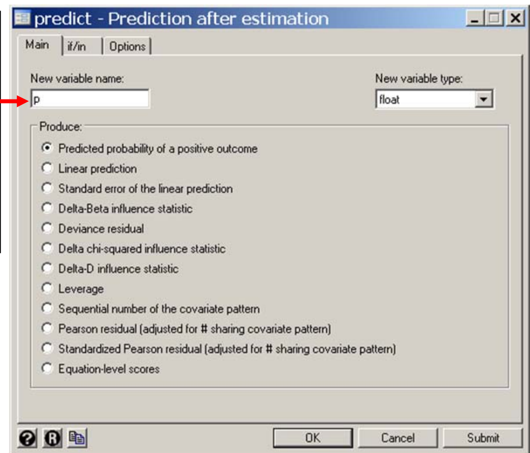
If we had the continuous data we could fit a cubic spline model with 1 constant parameter
6 spline parameters: 2 each for age alcohol and tobacco
4 interaction parameters for a total of
11 parameters, which would be more reasonable.

## 18. Residual analysis with Stata

*5.20.EsophagelaCa.ClassVersion.log* continues as follows

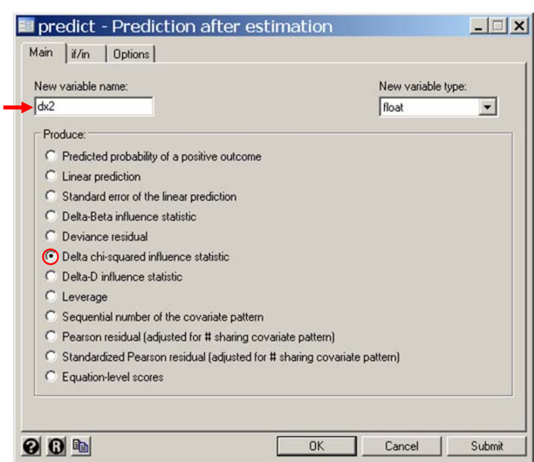
```
. *
. *  Perform residual analysis
. *
. * Statistics > Postestimation > Predictions, residuals, etc.
. predict p, p                                                      {1}
```

**{1}** The ***p*** option in this ***predict*** command defines the variable ***p*** to equal $\hat{\pi}_j$. In this and the next two ***predict*** commands the name of the newly defined variable is the same as the command option.



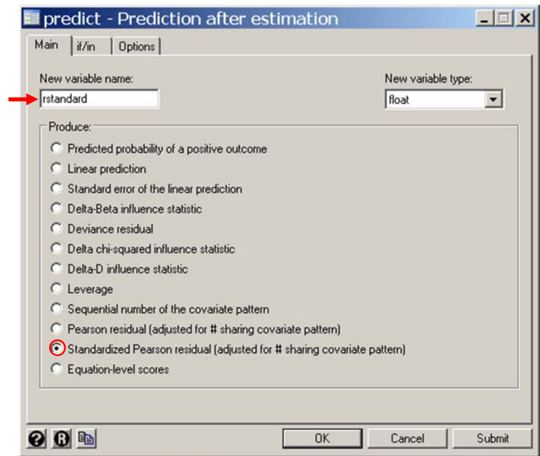

```
. predict dx2, dx2                                                  {2}
(57 missing values generated)
```

**{2}** Define the variable ***dx2*** to equal $\Delta X_j^2$. All records with the **same** covariate **pattern** are given the **same value** of *dx2*.



```
. predict rstandard, rstandard                                          {3}
(57 missing values generated)
```

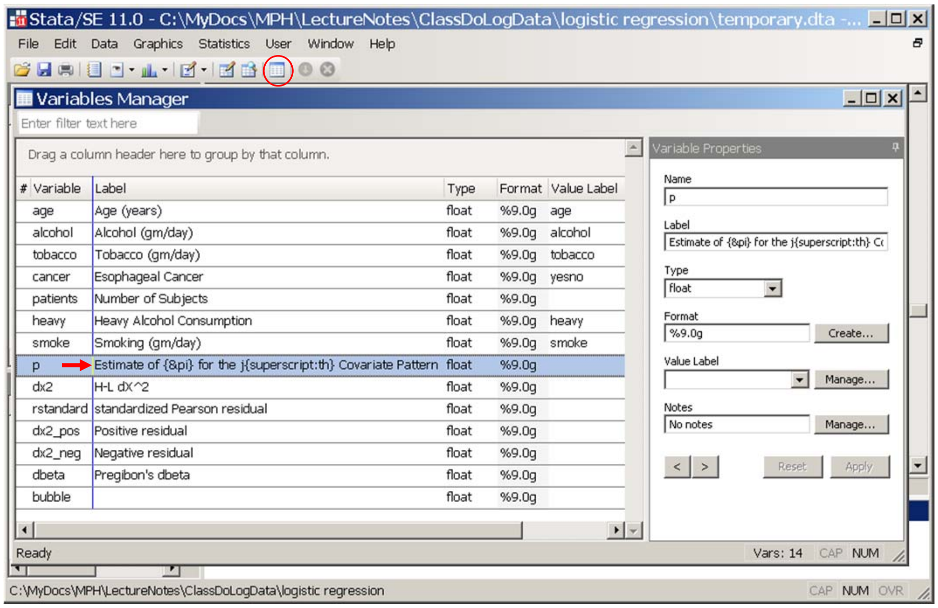
{3} Define ***rstandard*** to equal the **standardized Pearson residual** $r_{sj}$.




```
. generate dx2_pos = dx2 if rstandard >= 0                              {4}
(137 missing values generated)

. generate dx2_neg = dx2 if rstandard <  0
(112 missing values generated)

. label variable dx2_pos "Positive residual"

. label variable dx2_neg "Negative residual"

. label variable p                          ///
      "Estimate of {&pi} for the j{superscript:th} Covariate Pattern"    {5}
```

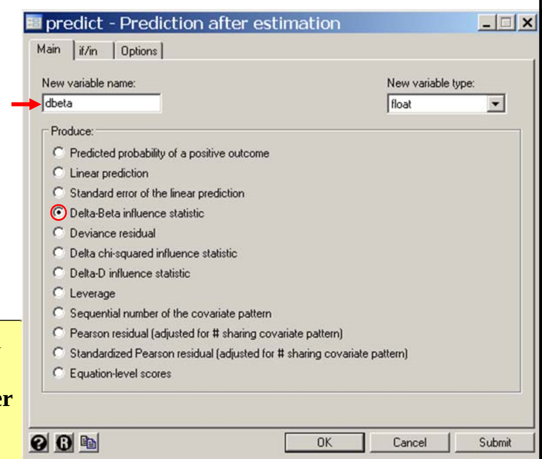
{4} We are going to draw a scatterplot of $\Delta X_j^2$ against $\hat{\pi}_j$. We would like to **color code** the plotting symbols to indicate if the residual is **positive** or **negative**. This command defines ***dx2_pos*** to equal $\Delta X_j^2$ if and only if $r_{sj}$ is non-negative. The next command defines ***dx2_neg*** to equal $\Delta X_j^2$ if $r_{sj}$ is negative.

{5} Greek lettters, superscripts, italics, etc can be entered in variable labels. {&pi} enters the letter $\pi$ into the label. {superscript:th} writes the letters "th" as a superscript.




```
. predict dbeta, dbeta
(57 missing values generated)
```

{5}



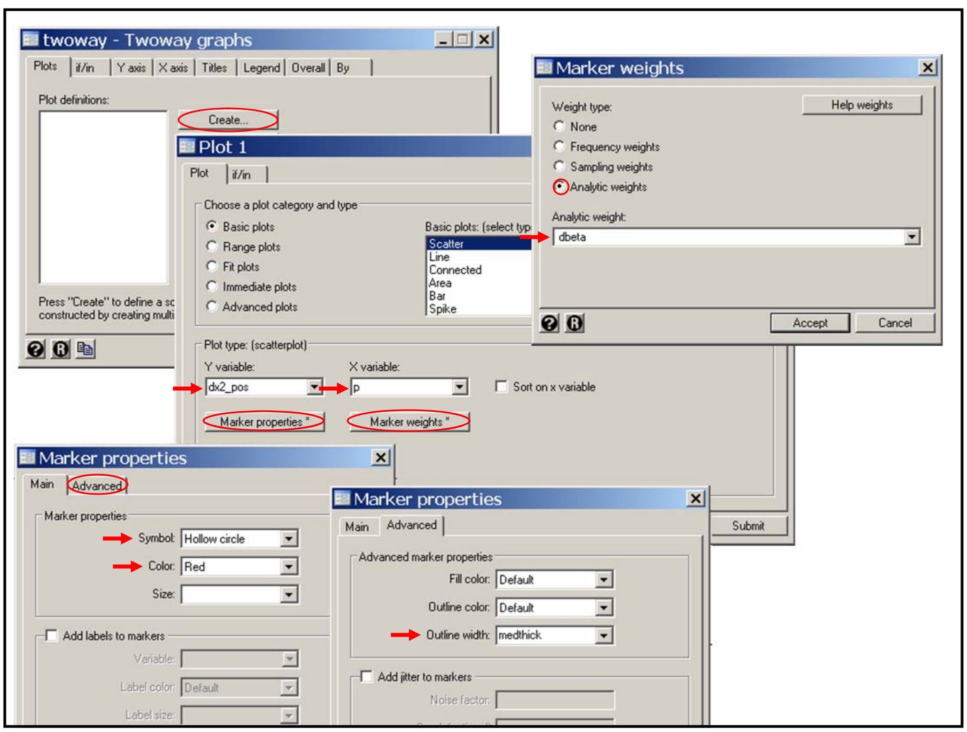

{5} Define the variable ***dbeta*** to equal $\Delta\hat{\beta}_j$. The values of ***dx2***, ***dbeta*** and ***rstandard*** are affected by the **number** of **subjects** with a given covariate pattern, and the number of **events** that occur to these subjects. They are **not** affected by the **number** of **records** used to record this information.

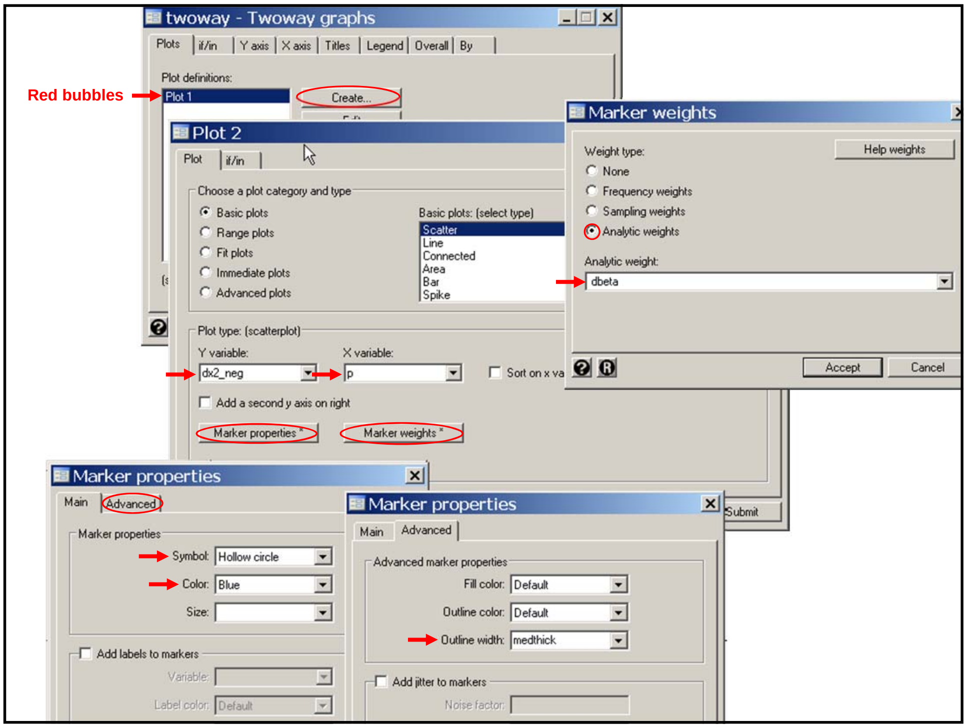
Hence, it makes no difference whether there is one record per patient or just two records specifying the number of subjects with the specified covariate pattern who did, or did not, suffer the event of interest.

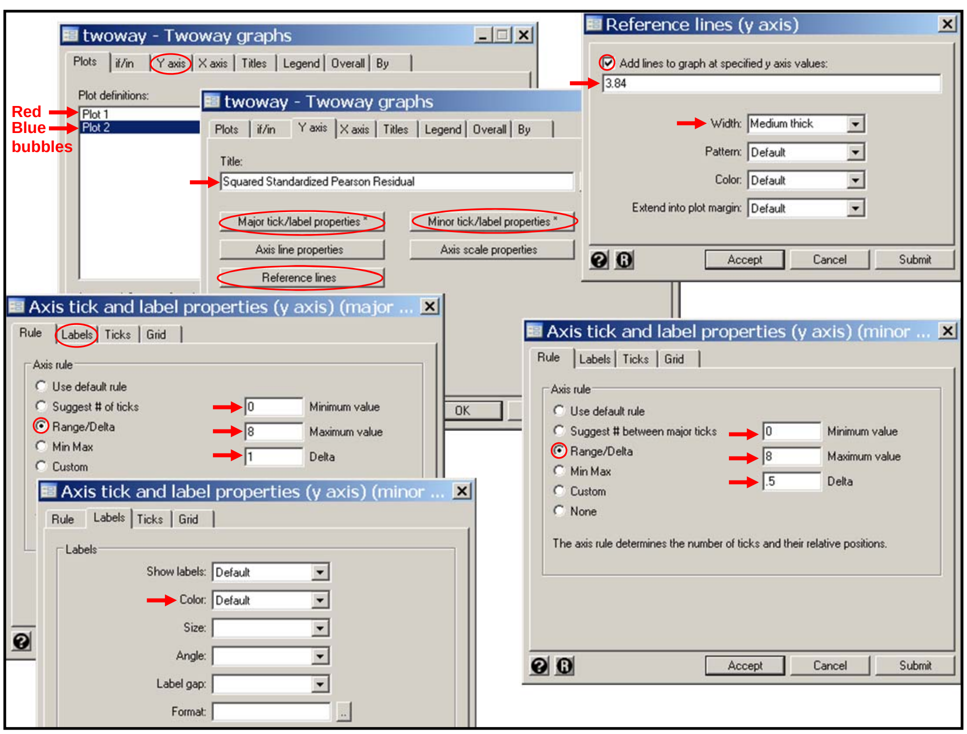
```
. scatter       dx2_pos p [weight=dbeta]                                    ///   {6}
>       , msymbol(Oh) mlwidth(medthick) mcolor(red)                         ///   {7}
>     || scatter dx2_neg p [weight=dbeta]                                   ///
>       , msymbol(Oh) mlwidth(medthick) mcolor(blue)                        ///
>     ||, ylabel(0(1)8, angle(0))                                           ///
>         ymtick(0(.5)8) yline(3.84, lwidth(medthick))                      ///
>         xlabel(0(.1)1) xmtick(0(.05)1)                                    ///
>         ytitle("Squared Standardized Pearson Residual") xscale(titlegap(2))
(analytic weights assumed)
(analytic weights assumed)
```

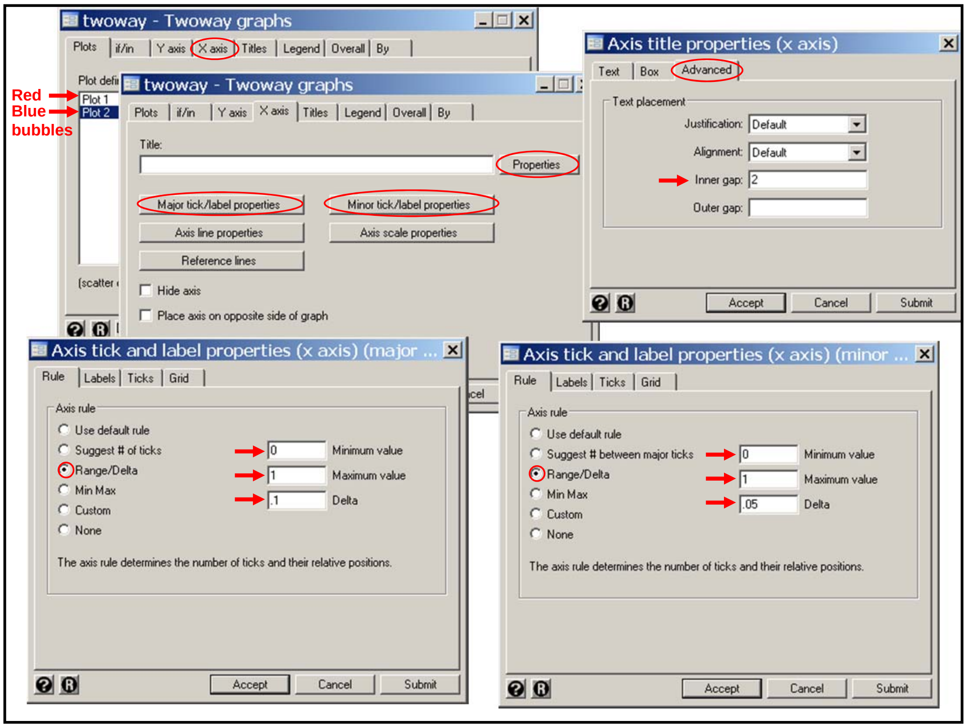
**{6}** This graph produces a scatterplot of $\Delta X_j^2$ against $\hat{\pi}_j$ that is shown in the next slide. The ***[weight=dbeta]*** command modifier causes the plotting symbols to be circles whose **area** is **proportional** to the variable ***dbeta***. We plot both **dx2_pos** and **dx2_neg** against **p** in order to be able to assign **different colors** to values of $\Delta X_j^2$ that are associated with positive or negative residuals.

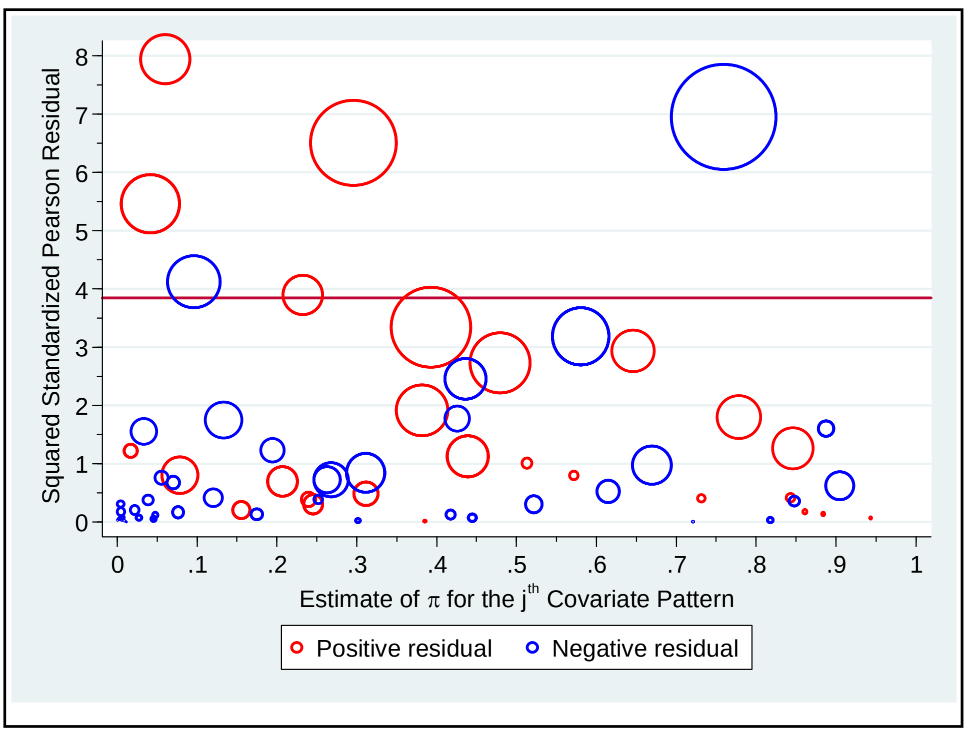
**{7}** **mlwidth** defines the width of the marker lines. This is, the width of the circles. **mcolor** defines the marker color.




twoway - Twoway graphs
Plots
if/in
Y axis
X axis
Titles
Legend
Overall
By
Plot definitions:
Red bubbles
Plot 1
Create...
Plot 2
Plot
if/in
Choose a plot category and type
Basic plots
Range plots
Fit plots
Immediate plots
Advanced plots
Basic plots: (select type)
Scatter
Line
Connected
Area
Bar
Spike
Plot type: (scatterplot)
Y variable:
dx2_neg
X variable:
p
Sort on x va
Add a second y axis on right
Marker properties *
Marker weights *
Marker weights
Weight type:
Help weights
None
Frequency weights
Sampling weights
Analytic weights
Analytic weight:
dbeta
Accept
Cancel
Marker properties
Main
Advanced
Marker properties
Symbol:
Hollow circle
Color:
Blue
Size:
Add labels to markers
Variable:
Label color:
Default
Marker properties
Main
Advanced
Advanced marker properties
Fill color:
Default
Outline color:
Default
Outline width:
medthick
Add jitter to markers
Noise factor:
Submit


twoway - Twoway graphs
Plots
if/in
Y axis
X axis
Titles
Legend
Overall
By
Plot definitions:
Red
Blue
bubbles
Plot 1
Plot 2
twoway - Twoway graphs
Title:
Squared Standardized Pearson Residual
Major tick/label properties *
Minor tick/label properties *
Axis line properties
Axis scale properties
Reference lines
OK
Reference lines (y axis)
Add lines to graph at specified y axis values:
3.84
Width:
Medium thick
Pattern:
Default
Color:
Default
Extend into plot margin:
Default
Accept
Cancel
Submit
Axis tick and label properties (y axis) (major ...
Rule
Labels
Ticks
Grid
Axis rule
Use default rule
Suggest # of ticks
Range/Delta
Min Max
Custom
0
Minimum value
8
Maximum value
1
Delta
Axis tick and label properties (y axis) (minor ...
Rule
Labels
Ticks
Grid
Labels
Show labels:
Default
Color:
Default
Size:
Angle:
Label gap:
Format:
Axis tick and label properties (y axis) (minor ...
Rule
Labels
Ticks
Grid
Axis rule
Use default rule
Suggest # between major ticks
Range/Delta
Min Max
Custom
None
0
Minimum value
8
Maximum value
.5
Delta
The axis rule determines the number of ticks and their relative positions.
Accept
Cancel
Submit


twoway - Twoway graphs
Red
Blue
bubbles
Plot 1
Plot 2
Plots
if/in
Y axis
X axis
Titles
Legend
Overall
By
Title:
Properties
Major tick/label properties
Minor tick/label properties
Axis line properties
Axis scale properties
Reference lines
Hide axis
Place axis on opposite side of graph
Axis title properties (x axis)
Text
Box
Advanced
Text placement
Justification: Default
Alignment: Default
Inner gap: 2
Outer gap:
Accept
Cancel
Submit
Axis tick and label properties (x axis) (major ...
Rule
Labels
Ticks
Grid
Axis rule
Use default rule
Suggest # of ticks
Range/Delta
Min Max
Custom
None
0 Minimum value
1 Maximum value
.1 Delta
The axis rule determines the number of ticks and their relative positions.
Axis tick and label properties (x axis) (minor ...
Suggest # between major ticks
0 Minimum value
1 Maximum value
.05 Delta


Squared Standardized Pearson Residual
0
1
2
3
4
5
6
7
8
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
Estimate of π for the j^th Covariate Pattern
Positive residual
Negative residual

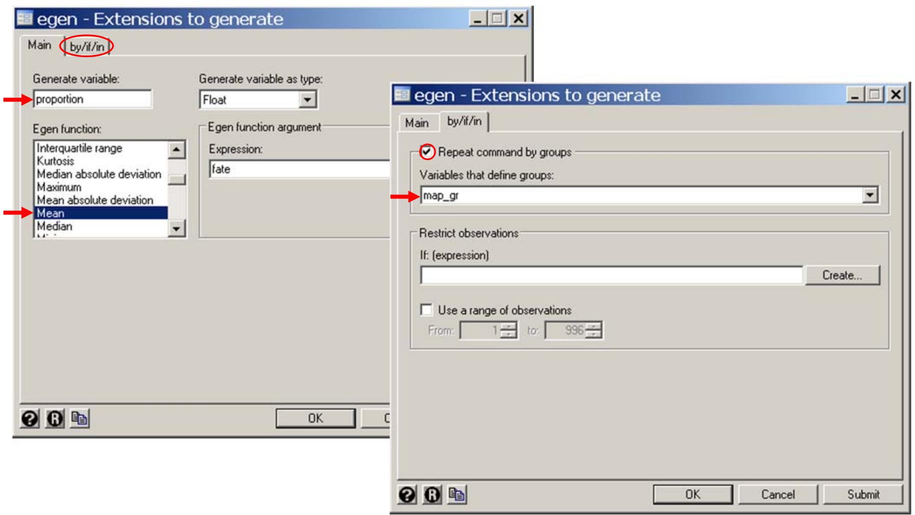
## 19. Restricted Cubic Splines and Logistic Regression

In the following example we use restricted cubic splines to model the effect of baseline MAP on hospital mortality in the SUPPORT data set.

```
. * SUPPORTlogisticRCS.log
. *
. *  Regress mortal status at discharge against MAP
. *  in the SUPPORT data set (Knaus et al. 1995).
. *
. use "C:\WDDtext\3.25.2.SUPPORT.dta" , replace

. *
. *  Calculate the proportion of patients who die in hospital
. *   stratified by MAP.
. *
. generate map_gr = round(map,5)                                    {1}
. sort map_gr
. label variable map_gr "Mean Arterial Pressure (mm Hg)"
. * Data > Create or change data > Create new variable (extended)
. by map_gr: egen proportion = mean(fate)                           {2}
```

{1} *round(map, 5)* rounds *map* to the nearest integer divisible by 5.

{2} This command defines *proportion* to equal the average value of *fate* over all records with the same value of *map_gr*. Since *fate* is a zero-one indicator variable, *proportion* will be equal to the proportion of patients with the same value of *map_gr* who die (have *fate* = 1). This command requires that the data set be sorted by the *by* variable (*map_gr*).

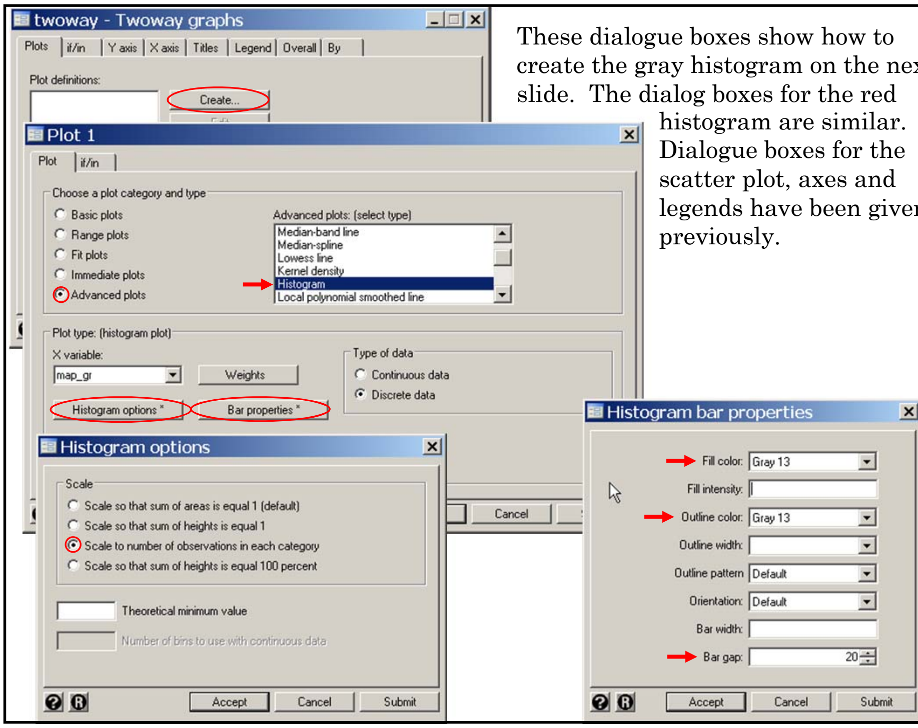



```
. generate rate = 100*proportion

. label variable rate "Observed In-Hospital Mortality Rate (%)"

. generate deaths = map_gr if fate
(747 missing values generated)
```

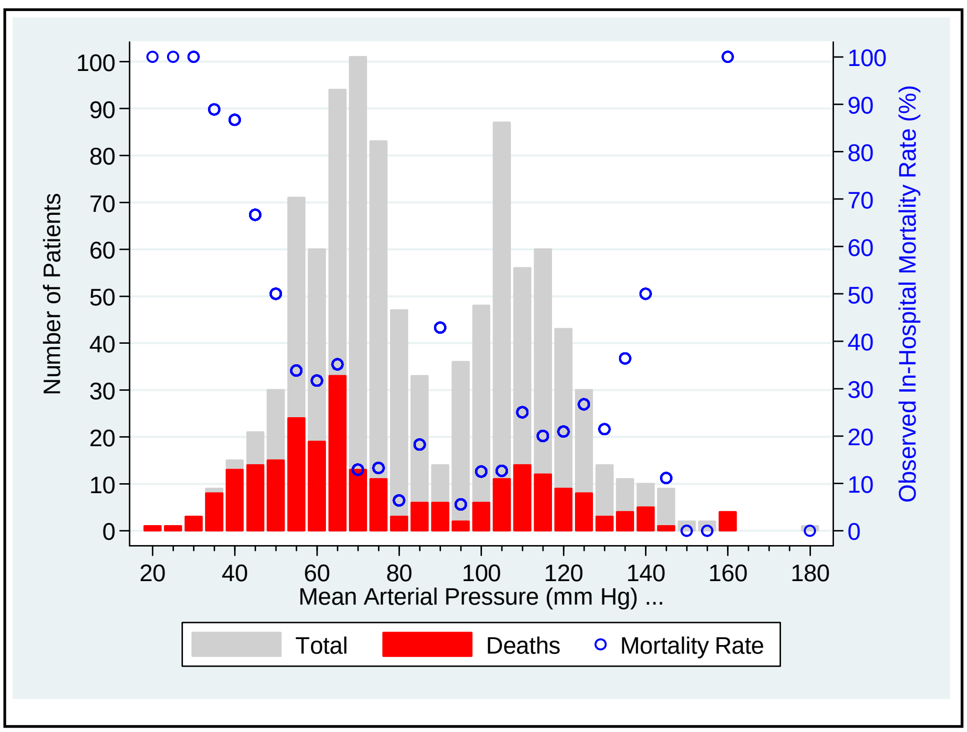
```
. *
. *  Draw an exploratory graph showing the number of patients,
. *  the number of deaths and the mortality rate for each MAP.
. *
. twoway histogram map_gr, discrete frequency color(gs13) gap(20) /// {3}
>     || histogram deaths, discrete frequency color(red) gap(20)  /// {4}
>     || scatter rate map_gr, yaxis(2) symbol(Oh) color(blue)     ///
>     , xlabel(20 (20) 180) ylabel(0(10)100, angle(0))            ///
>       xmtick(25 (5) 175) ytitle(Number of Patients)             ///
>       ylabel(0 (10) 100, angle(0) labcolor(blue) axis(2))       ///
>       ytitle(,color(blue) axis(2))                              ///
>       legend(order(1 "Total" 2 "Deaths" 3 "Mortality Rate" )    ///
>       rows(1))
```

{3} The command *twoway histogram map_gr* produces a histogram of the variable *map_gr*. The *discrete* option specifies that a bar is to be drawn for each distinct value of *map_gr*; *frequency* specifies that the *y*-axis will be the number of patients at each value of *map_gr*; *color(gs13)* specifies that the bars are to be light gray and *gap(20)* reduces the bar width by 20\% to provide separation between adjacent bars.

{4} This line of this command overlays a histogram of the number of in-hospital deaths on the histogram of the total number of patients.



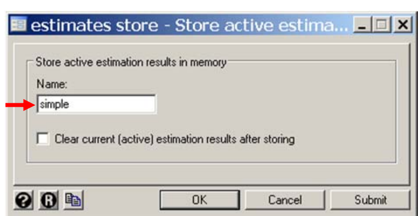

These dialogue boxes show how to create the gray histogram on the next slide. The dialog boxes for the red histogram are similar. Dialogue boxes for the scatter plot, axes and legends have been given previously.



```
. *
. *  Regress in-hospital mortality against MAP using simple
. *  logistic regression.
. *
. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic fate map                                                  {5}

Logistic regression                               Number of obs   =        996
                                                  LR chi2(1)      =      29.66
                                                  Prob > chi2     =     0.0000
Log likelihood = -545.25721                       Pseudo R2       =     0.0265

------------------------------------------------------------------------------
        fate | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         map |   .9845924   .0028997    -5.27   0.000     .9789254    .9902922
------------------------------------------------------------------------------

. *  Statistics > Postestimation > Manage estimation results > Store in memory
. estimates store simple                                             {6}
```

**{5}** This command regresses *fate* against *map* using simple logistic regression.

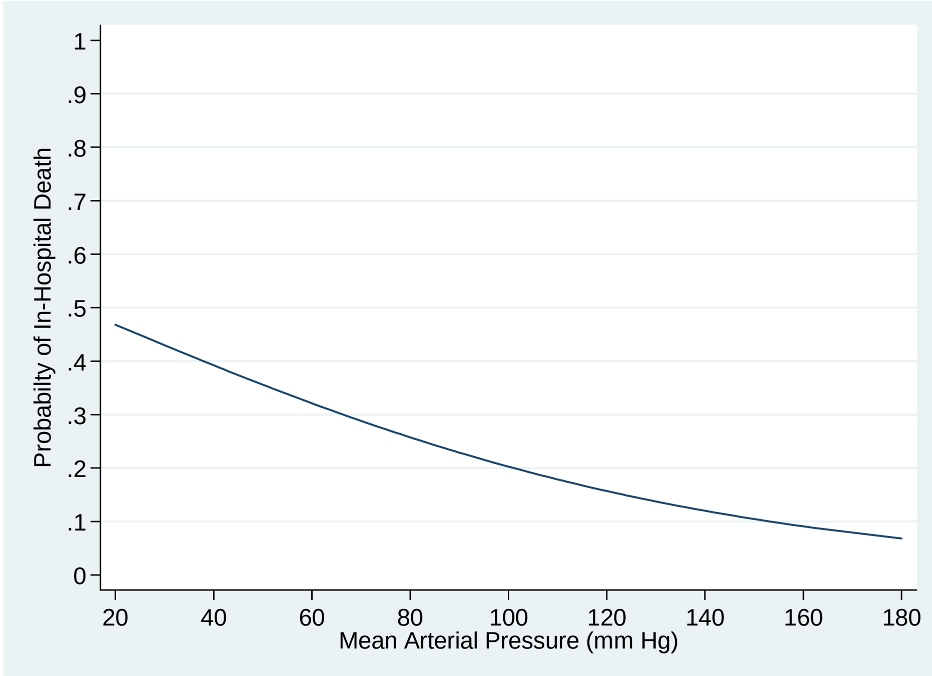
**{6}** This command stores parameter estimates and other statistics from the most recent regression command. These statistics are stored under the name *simple*. We will use this information later to calculate the change in model deviance.




```
. predict p,p                                                        {7}

. label variable p "Probabilty of In-Hospital Death"

. line p map, ylabel(0(.1)1, angle(0)) xlabel(20(20)180)
```

**{7}** The *p* option of this predict command defines *p* equal to the predicted probability of in-hospital death under the model. That is

$$p = \exp[\alpha + \beta \times map_i] / (1 + \exp[\alpha + \beta \times map_i]) = \text{logit}^{-1}[\alpha + \beta \times map_i]$$



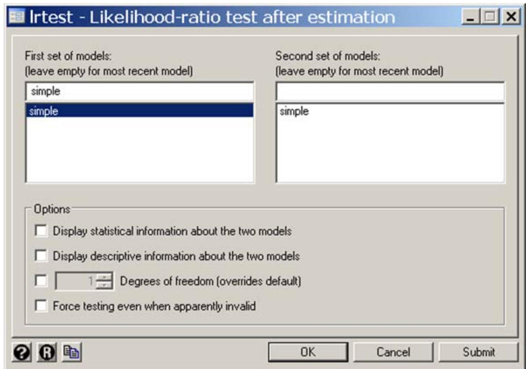

```
. *  Variables Manager
. drop p

. *
. *  Repeat the preceding model using restricted cubic splines
. *  with 5 knots at their default locations.
. *
. * Data > Create... > Other variable-creation... > linear and cubic...
. mkspline _Smap = map, cubic displayknots

             |     knot1      knot2      knot3      knot4      knot5
-------------+-------------------------------------------------------
         map |        47         66         78        106        129

. * Statistics > Binary outcomes > Logistic regression (reporting odds ratios)
. logistic fate _S*                                                          {8}

Logistic regression                               Number of obs   =        996
                                                  LR chi2(4)      =     122.86 {9}
                                                  Prob > chi2     =     0.0000
Log likelihood = -498.65571                       Pseudo R2       =     0.1097

------------------------------------------------------------------------------
        fate | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _Smap1 |   .8998261   .0182859    -5.19   0.000     .8646907    .9363892
       _Smap2 |    1.17328   .2013998     0.93   0.352      .838086    1.642537
       _Smap3 |     1.0781   .7263371     0.11   0.911     .2878645    4.037664
       _Smap4 |   .6236851   .4083056    -0.72   0.471     .1728672    2.250185
------------------------------------------------------------------------------
```

{8} Regress *fate* against MAP using a 5-knot RCS logistic regression model.

{9} Testing the null hypothesis that mortality is unrelated to MAP under this model is equivalent to testing the null hypothesis that all of the parameters associated with the spline covariates are zero. The likelihood ratio $\chi^2$ statistic to test this hypothesis equals 122.86. It has four degrees of freedom and is highly significant $P < 0.00005$.

```
. *
. *  Test null hypotheses that the logit of the probability of
. *  in-hospital death is a linear function of MAP.
. *
. * Statistics > Postestimation > Tests > Likelihood-ratio test
. lrtest simple .                                                  {10}

Likelihood-ratio test                                 LR chi2(3)  =     93.20
(Assumption: simple nested in .)                      Prob > chi2 =    0.0000
```

{10} This *lrtest* command calculates the likelihood ratio test of the null hypothesis that there is a linear relationship between the log odds of in-hospital death and baseline MAP. This is equivalent to testing the null hypothesis that *_Smap2* = *_Smap3* = *_Smap4* = 0. The *lrtest* command calculates the change in model deviance between two nested models. In this command, *simple* is the name of the model output saved by the previous *estimates store* command (see Comment 6). The period (.) refers to the estimates from the most recently executed regression command. The user must insure that the two models specified by this command are nested. The change in model deviance equals 93.2. Under the null hypothesis that the simple logistic regression model is correct this statistic will have an approximately chi-squared distribution with three degrees of freedom. The $P$ value associated with this statistic is (much) less than 0.00005.




```
. display 2*(545.25721 -498.65571)                                                {11}
93.203
```

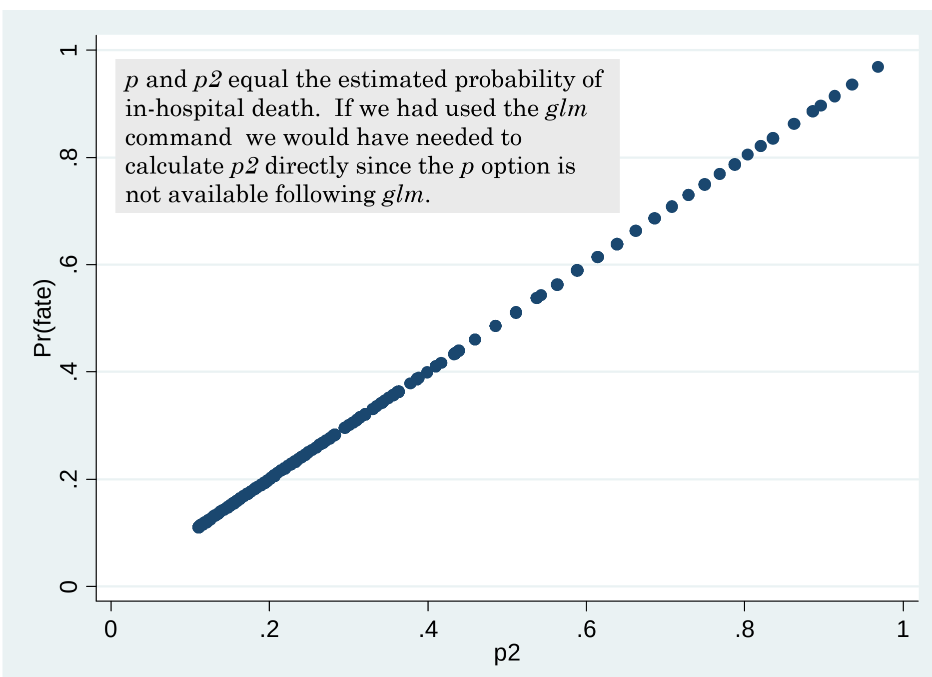
**{11}** Here we calculate the change in model deviance by hand from the maximum values of the log likelihood functions of the two models under consideration. Note that this gives the same answer as the preceding *lrtest* command.

**N.B.** We can always test the validity of a simple logistic regression model by running a RCS model with *k* knots and then testing the null hypothesis of whether the second through $k\text{-}1^{th}$ spline covariate parameters are simultaneously zero. In other words, we test the null hypothesis that the simple logisitic regression model is valid by testing the null hypothesis that the second through $k\text{-}1^{th}$ spline covariate parameters are simultaneously zero.

If we run a three-knot model then testing whether the second spline covariate parameter is zero is equivalent to testing the validity of the simple logistic regression model.

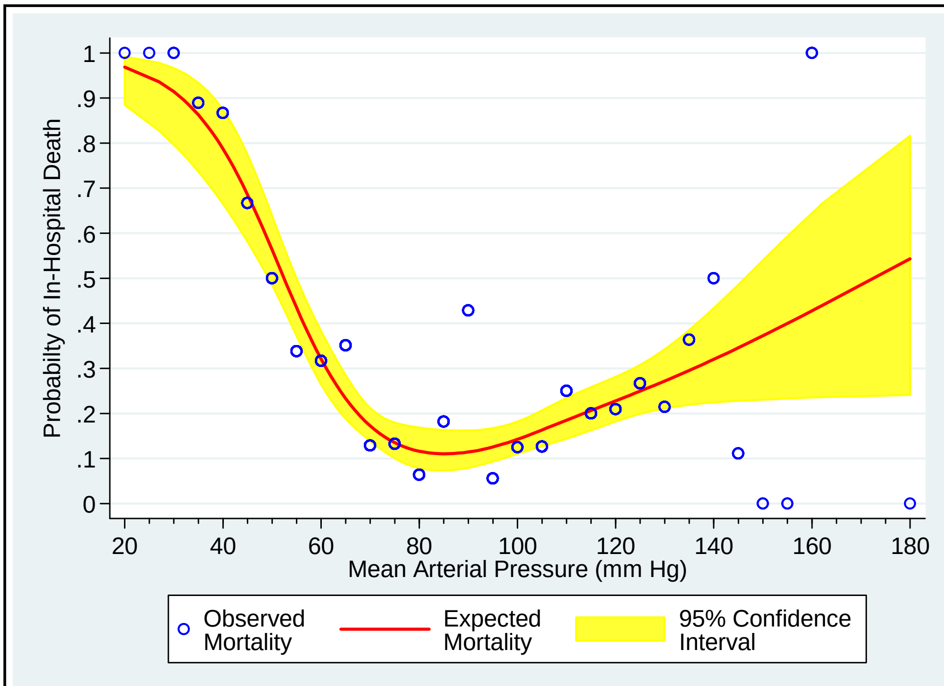
```
. *
. *  Plot the estimated probability of death against MAP together
. *  with the 95% confidence interval for this curve.  Overlay
. *  the MAP-specific observed mortality rates.
. *
. predict p,p                                                    {12}

. predict logodds, xb

. predict stderr, stdp

. generate p2 = exp(logodds)/(1+exp(logodds))

. *

. *  The values of p and p2 are identical.

. *

. scatter p p2
```

**{12}** The variable *p* is the estimated probability of in-hospital death from model our 5-knot RCS model.



```
. generate lodds_lb = logodds - 1.96*stderr

. generate lodds_ub = logodds + 1.96*stderr

. generate ub_p = exp(lodds_ub)/(1+exp(lodds_ub))                        {13}

. generate lb_p = exp(lodds_lb)/(1+exp(lodds_lb))

. twoway rarea lb_p ub_p map, color(yellow)                             ///
>     || line p map, lwidth(medthick) color(red)                        ///
>     || scatter proportion map_gr,  symbol(Oh) color(blue)             ///
>     , ylabel(0(.1)1, angle(0)) xlabel(20 (20) 180)                    ///
>       xmtick(25(5)175) ytitle(Probabilty of In-Hospital Death)        ///
>       legend(order(3 "Observed" "Mortality" 2 "Expected" "Mortality" ///
>           1 "95% Confidence" "Interval") rows(1))
```

**{13}** The variables *lb_p* and *ub_p* are the lower and upper 95% confidence bounds for $p$, respectively.



```
. *
. *  Determine the spline covariates at MAP = 90
. *
. list _S* if map == 90                                              {14}

     +---------------------------------------+
     | _Smap1     _Smap2     _Smap3     _Smap4 |
     |---------------------------------------|
575. |     90   11.82436   2.055919   .2569899 |
                                                         {output omitted}
581. |     90   11.82436   2.055919   .2569899 |
     +---------------------------------------+

. *
. *  Let or1 = _Smap1 minus the value of _Smap1 at 90.
. *  Define or2, or3 and or3 in a similar fashion.
. *
. generate or1 = _Smap1 - 90

. generate or2 = _Smap2 - 11.82436

. generate or3 = _Smap3 -  2.055919

. generate or4 = _Smap4 -   .2569899
```

**{14}** List the values of the spline covariates for the seven patients in the data set with a baseline MAP of 90. Only one or these identical lines of output are shown here.

**N.B.** logodds[*map*] = $\alpha + \beta_1 map + \beta_2\_Smap2(map) + \cdots + \beta_4\_Smap4(map)$

logodds[90] = $\alpha + \beta_1 \times 90 + \beta_2\_Smap2(90) + \cdots + \beta_4\_Smap4(90)$

logodds[*map*] - logodds[90] = $\beta_1 or1 + \beta_2 or2 + \beta_3 or3 + \beta_4 or4$

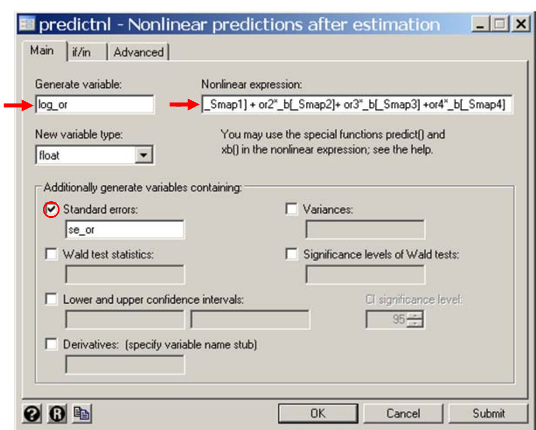
exp[logodds[*map*] - logodds[90] ] = odds ratio of a patient with MAP = *map* compared to a patient with a MAP = 90 by the usual argument.

```
. *
. *  Calculate the log odds ratio for in-hospital death
. *  relative to patients with MAP = 90.
. *
. * Statistics > Postestimation > Nonlinear predictions
. predictnl log_or = or1*_b[_Smap1] + or2*_b[_Smap2]      ///       {15}
>     + or3*_b[_Smap3] +or4*_b[_Smap4], se(se_or)                   {16}
```

**{15}** Define *log_or* to be the mortal log odds ratio for the $i^{th}$ patient in comparison to patients with a MAP of 90. The parameter estimates from the most recent regression command may be used in *generate* commands and are named _b[*varname*]. For example, in this RCS model _b[*_Smap2*] = $\hat{\beta}_2$ = 1.17328; *or2* = *_Smap2* - 11.82436.

The command *predictnl* may be used to estimate non-linear functions of the parameter estimates. It is also very useful for calculating linear combinations of these estimates as is illustrated here.

**{16}** The option *se(se_or)* calculates a new variable called *se_or* which equals the standard error of the log odds ratio.



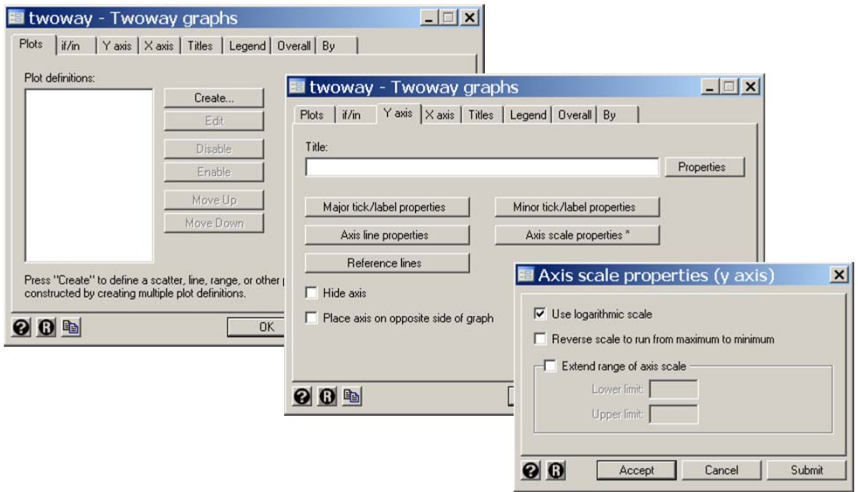
```
. generate lb_log_or = log_or - 1.96*se_or

. generate ub_log_or = log_or + 1.96*se_or

. generate or = exp(log_or)                                     {17}

. generate lb_or = exp(lb_log_or)                               {18}

. generate ub_or = exp(ub_log_or)
```

**{17}** The variable *or* equals the odds ratio for in-hospital death for each patient relative to that for a patient with MAP = 90.

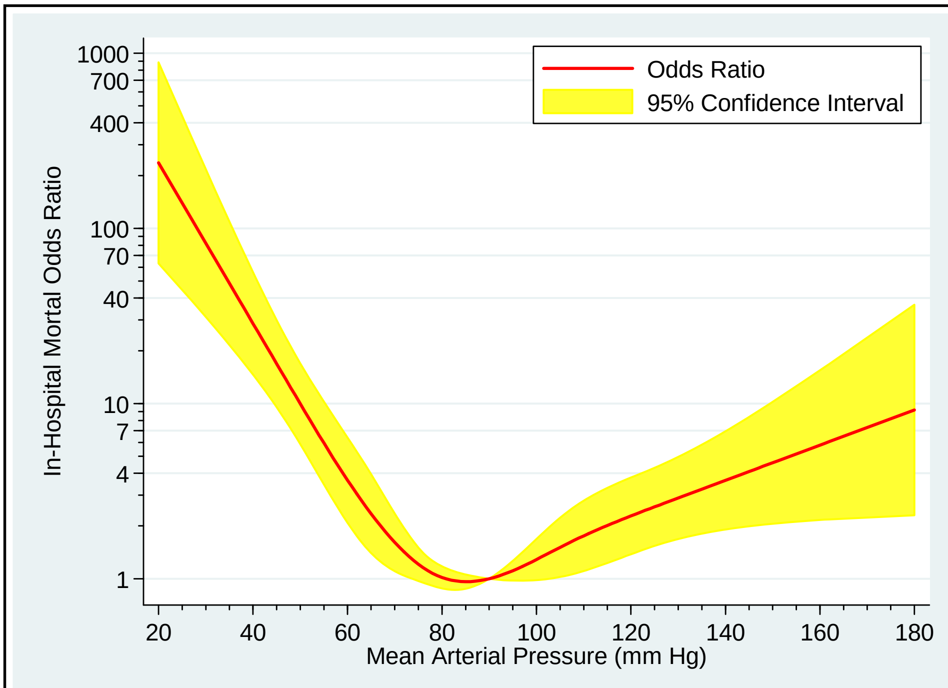
**{18}** The variables *lb_or* and *ub_or* equal the lower and upper bounds of the 95% confidence interval for this odds ratio

```
.
. twoway rarea lb_or ub_or map, color(yellow)              ///
>     || line or map, lwidth(medthick) color(red)          ///
>     ,  ylabel(1 (3) 10 40(30)100 400(300)1000, angle(0)) ///
>        ymtick(2(1)10 20(10)100 200(100)900) yscale(log)  ///      {19}
>        xlabel(20 (20) 180) xmtick(25 (5) 175)            ///
>        ytitle(In-Hospital Mortal Odds Ratio)             ///
>        legend(ring(0) position(2) order(2 "Odds Ratio"   ///
>           1 "95% Confidence Interval") cols(1))
```

**{19}** *yscale(log)* plots the *y*-axis on a logarithmic scale.




These dialogue boxes illustrate how to select a lograthmic scale for the $y$-axis



## 20. Frequency Matched Case-Control Studies

We often have access to many more potential control patients than case patients for case-control studies. If the distribution of some important confounding variable, such as age, differs markedly between cases and control, we may wish to adjust for this variable when designing the study. One way to do this is through **frequency matching**. The cases and potential controls are stratified into a number of groups based on, say, age. We then randomly select from each stratum the same number of controls as there are cases in the stratum. The data can then be analyzed by logistic regression with a classification variable to indicate the strata (see the analysis of the esophageal cancer and alcohol data in this chapter, Section 5 and 6).

It is important, however, to keep the strata fairly large if logistic regression is to be used for the analysis. Otherwise the estimates of the parameters of real interest may be seriously biased. Breslow and Day (Vol. I, p. 251-253) recommend that the strata be large enough so that each stratum contains at least 10 cases and 10 control. Even strata this large can lead to appreciable bias if the odds ratio being estimated is greater then 2.

### a) Conditional logistic regression analysis

Sometimes there are more than one important confounders that we would like to adjust for in the design of our study.

In this case, we typically match each case patient to one or more controls with the same values of the confounding variables. This approach is often quite reasonable. However, it usually leads to strata (matched pairs or sets of patients) that are too small to be analyzed accurately with logistic regression. In this case, an alternate technique called conditional logistic regression should be used. This technique is discussed in Breslow and Day, Vol. I. In Stata, the *clogit* command may be used to implement these analyses.

### 21. What we have covered

- Extend simple logistic regression to models with multiple covariates
- Similarity between multiple linear and multiple logistic regression
  $$\text{logit}\,(E(d_i)) = \alpha + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik}$$
- Multiple 2x2 tables and the Mantel-Haenszel test
  - Estimating an odds ratio that is adjusted for a confounding variable
- Using logistic regression as an alternative to the Mantel-Haenszel test
- Using indicator covariates to model categorical variables
  - *i.varname* notation in Stata
  - *ib#.varname* notation in Stata
- Making inferences about odds ratios derived from multiple parameters
  - The Stata *lincom* command
- Analyzing complex data with logistic regression
  - Multiplicative models
  - Models with interaction
- Assessing model fit
  - Testing the change in model deviance in nested models
  - Evaluating residuals and influence
- Using restricted cubic splines in logistic regression models
  - Plotting the probability of an outcome with confidence bands
  - Plotting odds ratios and confidence bands
    - The Stata *predictnl* command

### Cited References

Breslow, N. E. and N. E. Day (1980). Statistical Methods in Cancer Research: Vol. 1 - The Analysis of Case-Control Studies. Lyon, France, IARC Scientific Publications.

Knaus,W.A., Harrell, F.E., Jr., Lynn, J., Goldman, L., Phillips, R.S., Connors, A.F., Jr. et al. The SUPPORT prognostic model. Objective estimates of survival for seriously ill hospitalized adults. Study to understand prognoses and preferences for outcomes and risks of treatments. *Ann Intern Med.* 1995; 122:191-203.

Tuyns, A. J., G. Pequignot, et al. (1977). Le cancer de L'oesophage en Ille-et-Vilaine en fonction des niveau de consommation d'alcool et de tabac. Des risques qui se multiplient. *Bull Cancer* 64: 45-60.

### For additional references on these notes see.

Dupont WD. *Statistical Modeling for Biomedical Researchers: A Simple Introduction to the Analysis of Complex Data. 2nd ed.* Cambridge, U.K.: Cambridge University Press; 2009.