Models In Epidemiology And Biostatistics
Gordon Hilton Fick

Session 11 :
Outcomes With More Than Two Levels

The Distribution of the Outcome

Let us consider a study relating cancer and chemotherapy:

The outcomes were coded: 1=progression of disease, 2=no change, 3=partial remission, 4=complete remission.

The intervention here is 2 types of chemotherapy: 0=sequential, 1=alternating.

It was thought that gender might be a confounder or modifier: 0=male 1=female

Two 4X2 Tables

If the outcome was dichotomous, we would be considering two 2X2 tables.

Now we will have two 4X2 tables

The conditional probabilities are: p_{ijk}

The probability for the ith outcome level given the jth chemotherapy and gender k

16 probabilities

	Outcome Level			
	1	2	3	4
MS	p_{100}	p_{200}	p_{300}	p_{400}
MA	p_{110}	p_{210}	p_{310}	p_{410}
FS	p_{101}	p_{201}	p_{301}	p_{401}
FA	p_{111}	p_{211}	p_{311}	p_{411}

The outcome has 4 levels

For example, p_{101} is, for females, the conditional probability of progression given sequential therapy.

While there are 4 probabilities for each outcome, any 3 determine the fourth since the sum of the 4 probabilities must be one.

$$\sum_{i=0}^{4} p_{ijk} = 1 \quad \text{for chemotherapy j and gender k}$$

The data

```
. bysort gender:table therapy outc,col
-> gender = male

           |                    outc
  therapy  |    prog    noch  parrem  comrem   Total
-----------+------------------------------------------
       seq |      28      45      29      26     128
       alt |      41      44      20      20     125

-> gender = female

           |                    outc
  therapy  |    prog    noch  parrem  comrem   Total
-----------+------------------------------------------
       seq |       4      12       5       2      23
       alt |      12       7       3       1      23
```

Estimates of probabilities

From this data, we have, for example,

$$\hat{p}_{100} = \frac{28}{128} = 0.21875$$

Notice that:

$$\sum_{i=0}^{4} \hat{p}_{ijk} = 1 \quad \text{for chemotherapy j and gender k}$$

Some primitive analysis

```
. tab therapy outc if gender==0,row nofreq exact

           |                    outc
   therapy |      prog       noch     parrem     comrem |     Total
-----------+-------------------------------------------+----------
       seq |     21.88      35.16      22.66      20.31 |    100.00
       alt |     32.80      35.20      16.00      16.00 |    100.00

           Fisher's exact =                 0.186
```

```
. tab therapy outc if gender==1,row nofreq exact

           |                    outc
   therapy |      prog       noch     parrem     comrem |     Total
-----------+-------------------------------------------+----------
       seq |     17.39      52.17      21.74       8.70 |    100.00
       alt |     52.17      30.43      13.04       4.35 |    100.00

           Fisher's exact =                 0.086
```

Fisher's Exact Test

For the males, the p-value here is testing the [rather uninteresting] hypothesis:

$$H_0: p_{i00} = p_{i10} \text{ for } i=1, 2, 3 \text{ and } 4$$

Similarly for the females:

$$H_0: p_{i01} = p_{i11} \text{ for } i=1, 2, 3 \text{ and } 4$$

Ignoring gender:

The “crude” analysis would be:

```
. tab therapy outc,row exact

           |                    outc
   therapy |      prog       noch     parrem     comrem |      Total
-----------+--------------------------------------------+-----------
       seq |        32         57         34         28 |        151
           |     21.19      37.75      22.52      18.54 |     100.00
-----------+--------------------------------------------+-----------
       alt |        53         51         23         21 |        148
           |     35.81      34.46      15.54      14.19 |     100.00
-----------+--------------------------------------------+-----------
     Total |        85        108         57         49 |        299
           |     28.43      36.12      19.06      16.39 |     100.00

          Fisher's exact =                 0.035
```

An inadequate analysis

The challenge with such an analysis is that we get no clear indication as to where differences in the conditional probabilities might be. We can describe the estimates and note the omnibus test but most researchers find such an approach too limited and without focus.

Another approach

Another approach involves pairwise comparisons. One could plan to assess whether improvement [as indicated by outcomes 3 and 4] compared with no improvement [as indicated by outcomes 1 and 2] depends on therapy (...and whether such a comparison is modified or confounded by gender)

BUT... perhaps one should determine whether the collapsing of categories is warranted .

One could:

a) assess the relationship between therapy and outcomes 1 and 2 given that there was no improvement

b) assess the relationship between therapy and outcomes 3 and 4 given that there was improvement.

Is combining OK?

If one were to see an outcome-therapy relationship for either of the focussed assessments [a) or b)], then one could note the relationship and argue that the [planned] collapsing would be misleading.

Indeed, to collapse both assumes that there is no relationship seen in either a) or b)

The 'Classic' Strategy

Outcome

	1	2	3	4
1)	compare with 2	compare with 1	not included	not included
2)	not included	not included	compare with 4	compare with 3
3)	<---------compare with 3&4--------->		<--------compare with 1&2---------->	

The third assessment could be considered based on the results from the first 2 assessments

3 new 'outcomes'

```
. gen prog=outc
. recode prog 1=1 2=0 3=. 4=.
. gen partial=outc
. recode partial 1=. 2=. 3=1 4=0
. gen noimp=outc
. recode noimp 1=1 2=1 3=0 4=0
```

Now we have 3 dichotomous outcomes

```
. cc prog therapy,by(sex)

             sex |       OR       [95% Conf. Interval]   M-H Weight
-----------------+-------------------------------------------------
            male |   1.497565      .7566925   2.973186     7.797468 (exact)
          female |   5.142857      .9815142    29.6945           .8 (exact)
-----------------+-------------------------------------------------
           Crude |   1.851103      .9974997   3.446361               (exact)
    M-H combined |   1.836762      1.033281   3.265031
-------------------------------------------------------------------
Test of homogeneity (M-H)      chi2(1) =     2.29  Pr>chi2 = 0.1301

                   Test that combined OR = 1:
                               Mantel-Haenszel chi2(1) =      4.33
                                                Pr>chi2 =    0.0374

. cc partial therapy,by(sex)

             sex |       OR       [95% Conf. Interval]   M-H Weight
-----------------+-------------------------------------------------
            male |   .8965517      .3666776   2.192349     6.105263 (exact)
          female |        1.2      .0415141   94.09485     .4545455 (exact)
-----------------+-------------------------------------------------
           Crude |   .9019608      .3871906   2.104333               (exact)
    M-H combined |   .9175784      .4199369   2.004944
-------------------------------------------------------------------
Test of homogeneity (M-H)      chi2(1) =     0.04  Pr>chi2 = 0.8444

                   Test that combined OR = 1:
                               Mantel-Haenszel chi2(1) =      0.05
                                                Pr>chi2 =    0.8308
```

Assessment of the first 2 outcomes

We see that, among those who made no improvement, the odds [of progression cf no change] may be higher for those receiving alternating therapy. Maybe this observation is even more so for the females but the cell numbers are small. In any case, the confidence limits are wide and there is no indication from the testing. For those who made an improvement, the odds ratios could plausibly be one as well.

Not clear cut here, but, if were to then proceed to collapse, recognizing the assumption needed to justify this collapsing, we get:

```
. cc noimp therapy,by(sex)

              sex |       OR        [95% Conf. Interval]   M-H Weight
------------------+--------------------------------------------------
             male |   1.601027       .9283931   2.766937      11.5415 (exact)
           female |   2.078125       .4262124   11.34839     1.391304 (exact)
------------------+--------------------------------------------------
            Crude |   1.646578       .9925137   2.737841               (exact)
    M-H combined |   1.652353       1.020779   2.674693
------------------------------------------------------------------------
Test of homogeneity (M-H)       chi2(1) =     0.12  Pr>chi2 = 0.7312

                    Test that combined OR = 1:
                                Mantel-Haenszel chi2(1) =      4.18
                                                Pr>chi2 =    0.0409
```

Based on the collapsing/grouping

If we have made the right call with regard to collapsing, we receive a modest indication of a improvement-therapy relationship.

The odds of no improvement with alternating therapy being estimated to be about 1.65 times the odds of no improvement with sequential therapy

btw... this is a reasonable example of a situation in which it is best if the plan for analysis details [in advance] whether one would consider the crude or adjusted in such a situation

The process

More importantly, lets review the process here. The outcome has 4 levels. Instead of considering an assessment based on 2 4X2 tables, we tried 3 assessments, each assessment based on 2 2X2 tables. The first 2 assessments were designed to provide support for the third assessment. The third assessment required the assumption that the collapsing into improvement/no improvement did not oversimplify the study of relationship between outcome and therapy.

A Strategy for Ordinal Outcomes

Outcome

1 2 3 4

1) compare with 2,3 &4 < ----------compare with 1---------->

2) < ------compare with 3&4---------> <--------- compare with 1&2---------->

3) <---------- compare with 4----------> compare with 1,2&3

With this strategy, we say that we 'cut' the outcome and consider the 'odds the outcome is greater than the cut'.

'Greater than' and 'Less than' have some merit with ordinal outcomes.

3 different odds

The first assessment presents the 'odds the outcome is greater than 1' which here means the 'odds of any outcome except progression'

The second assessment presents the 'odds the outcome is greater than 2' which here means the 'odds of improvement'

The third assessment presents the 'odds the outcome is greater than 3' which here means the 'odds of complete remission'

All 3 assessments are describing the 'odds of doing better' where 'doing better' has 3 versions.

It is sometimes argued that all 3 assessments could be considered. The grouping/collapsing issue is not considered relevant from this point of view.

```
. cc cut1 therapy,by(sex)

             sex |       OR       [95% Conf. Interval]   M-H Weight
-----------------+-------------------------------------------------
            male |   .5736585      .3137651   1.042641     16.20553 (exact)
          female |   .1929825      .0374675   .8702495     4.956522 (exact)
-----------------+-------------------------------------------------
           Crude |   .4820041      .2777758   .8312904              (exact)
    M-H combined |   .4844976      .2900189   .8093883
-----------------------------------------------------------------
Test of homogeneity (M-H)      chi2(1) =     2.12  Pr>chi2 = 0.1449

                   Test that combined OR = 1:
                               Mantel-Haenszel chi2(1) =      7.80
                                                Pr>chi2 =    0.0052

. cc cut2 therapy,by(sex)

             sex |       OR       [95% Conf. Interval]   M-H Weight
-----------------+-------------------------------------------------
            male |   .6245989      .3614065    1.07715     18.47826 (exact)
          female |    .481203      .0880998   2.339813     2.891304 (exact)
-----------------+-------------------------------------------------
           Crude |   .6073201      .3652445   1.007558              (exact)
    M-H combined |   .6051974      .3738747   .9796435
-----------------------------------------------------------------
Test of homogeneity (M-H)      chi2(1) =     0.12  Pr>chi2 = 0.7312

                   Test that combined OR = 1:
                               Mantel-Haenszel chi2(1) =      4.18
                                                Pr>chi2 =    0.0409

. cc cut3 therapy,by(sex)

             sex |       OR       [95% Conf. Interval]   M-H Weight
-----------------+-------------------------------------------------
            male |   .7472527      .3706607   1.491317     10.79051 (exact)
          female |   .4772727      .0077437   9.965524     .9565217 (exact)
-----------------+-------------------------------------------------
           Crude |    .726378      .3709955   1.407016              (exact)
    M-H combined |   .7252692      .3894278   1.350739
-----------------------------------------------------------------
Test of homogeneity (M-H)      chi2(1) =     0.12  Pr>chi2 = 0.7310

                   Test that combined OR = 1:
                               Mantel-Haenszel chi2(1) =      1.02
                                                Pr>chi2 =    0.3113
```

The model specific to each cut

```
. gen gender=sex-1

. gen gt = gender*therapy

. gen cut1=(outc>1)

. gen cut2=(outc>2)

. gen cut3=(outc>3)

. logit cut1 gender therapy gt

Logistic regression                                     Number of obs   =        299
                                                        LR chi2(3)      =      11.21
                                                        Prob > chi2     =     0.0106
Log likelihood = -172.88277                             Pseudo R2       =     0.0314

------------------------------------------------------------------------------
        cut1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      gender |   .2851767   .5902079     0.48   0.629    -.8716096    1.441963
     therapy |  -.5557209   .2863726    -1.94   0.052    -1.117001    .0055591
          gt |  -1.089433   .7475847    -1.46   0.145    -2.554672    .3758063
       _cons |   1.272966    .213809     5.95   0.000     .8539077    1.692024
------------------------------------------------------------------------------
```

```
. logit cut2 gender therapy gt

Logistic regression                                     Number of obs   =        299
                                                        LR chi2(3)      =       7.67
                                                        Prob > chi2     =     0.0533
Log likelihood = -190.57212                             Pseudo R2       =     0.0197

------------------------------------------------------------------------------
        cut2 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      gender |  -.5435523   .4870704    -1.12   0.264    -1.498193    .4110882
     therapy |  -.4706455   .2620022    -1.80   0.072    -.9841604    .0428693
          gt |  -.2608205   .7593641    -0.34   0.731    -1.749147    1.227506
       _cons |  -.2831263    .178551    -1.59   0.113    -.6330797    .0668272
------------------------------------------------------------------------------

. logit cut3 gender therapy gt

Logistic regression                                     Number of obs   =        299
                                                        LR chi2(3)      =       5.80
                                                        Prob > chi2     =     0.1219
Log likelihood = -130.46941                             Pseudo R2       =     0.0217

------------------------------------------------------------------------------
        cut3 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      gender |   -.984499   .7719356    -1.28   0.202    -2.497465    .5284669
     therapy |  -.2913518   .3283128    -0.89   0.375     -.934833    .3521294
          gt |  -.4483152   1.304171    -0.34   0.731    -3.004444    2.107813
       _cons |  -1.366876    .219694    -6.22   0.000    -1.797469   -.9362839
------------------------------------------------------------------------------
```

The Proportional Odds Model

Now let us consider the probability the outcome is above the cut. $\mathrm{p}_j = \Pr(\text{the outcome is above cut j})$

Now consider a model of the form:

$$\log\left(p_j/(1-p_j)\right) = \sum_{i=1}^{k} \beta_i x_i - \kappa_j$$

The jth assessment is assessed with a logistic model. Each assessment has a possibly different intercept but the rest is the same for each assessment. This is called a proportional odds model because for any 2 assessments j and k, say

$$\log\left(p_j/(1-p_j)\right) - \log\left(p_k/(1-p_k)\right) = \kappa_k - \kappa_j$$

Which says that the odds for each assessment are proportional

Indeed: $p_j/(1-p_j) = e^{\kappa_k - \kappa_j}\, p_k/(1-p_k)$

The constant of proportionality being $e^{\kappa_k - \kappa_j}$

Indeed, the regression coefficients for the explanatory variables are the same for each cut. They are 'assumed common' to the cuts.

Suppose we had considered each of these log odds with their own model, as before, the odds would not be proportional.

Indeed:

3 separate models from before

would look like:

$$\log\left(p_1/(1-p_1)\right)=\sum_{i=0}^{k}\beta_{1i}x_i$$

$$\log\left(p_2/(1-p_2)\right)=\sum_{i=0}^{k}\beta_{2i}x_i$$

$$\log\left(p_3/(1-p_3)\right)=\sum_{i=0}^{k}\beta_{3i}x_i$$

Difference in Log odds

comparing 1 with 2, for example, would be:

$$\log\left(p_1/(1-p_1)\right)-\log\left(p_2/(1-p_2)\right)=\sum_{i=0}^{k}\left(\beta_{1i}-\beta_{2i}\right)x_i$$

The difference in log odds would involve the explanatory variables. The odds would not be proportional.

Test For Proportional Odds

There is a 'goodness of fit' test for the assumption of proportional odds. RF Brant (1990) proposed and developed one such test.

You can download collections of .ado and .do files from Long & Freese (2014). They have developed many macros for numerous forms of analyses of ordinal outcomes.

These commands can be obtained, while in Stata, using 'findit spost13' and following the instructions. In particular:

```
net describe spost13_ado,from(http://www.indiana.edu/~jslsoc/stata)
```

ologit : fits a proportional odds model [o for ordinal]

$$\log\left(p_j/(1-p_j)\right)=\beta_1 \mathrm{G}+\beta_2 \mathrm{T}+\beta_3 \mathrm{GT}-\kappa_j$$
$$\log\left(\hat{p}_j/(1-\hat{p}_j)\right)=b_1 \mathrm{G}+b_2 \mathrm{T}+b_3 \mathrm{GT}-c_j$$

```
. gen gt=gender*therapy

. ologit outc gender therapy gt

Ordered logistic regression                       Number of obs   =        299
                                                  LR chi2(3)      =      11.96
                                                  Prob > chi2     =     0.0075
Log likelihood = -394.00492                       Pseudo R2       =     0.0149

------------------------------------------------------------------------------
        outc |      Coef.   Std. Err.       z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      gender |  -.2741906   .3873497    -0.71   0.479    -1.033382    .4850008
     therapy |   -.488071   .2305167    -2.12   0.034    -.9398754   -.0362666
          gt |  -.5904159   .5791605    -1.02   0.308     -1.72555    .5447177
-------------+----------------------------------------------------------------
       /cut1 |  -1.275657    .184367                      -1.63701   -.9143045
       /cut2 |   .2957159   .1678283                     -.0332216    .6246534
       /cut3 |   1.345164   .1905977                      .9715991    1.718728
------------------------------------------------------------------------------
```

The cuts

The cuts are included in this model without a constant term. So, for example, we can see that the log odds of being above cut 1 minus the log odds of being above cut 2 is $\kappa_2 - \kappa_1$. This difference is the same for each gender and each therapy. Such differences are 'assumed common' to gender and therapy

This difference is estimated by $c_2 - c_1$. Accordingly, this estimate is said to be adjusted for gender and therapy.

The 'usual' coefficients

For example, a possible interpretation for -0.488071 is, for the males, an estimate of the log odds of 'doing better' with alternating therapy minus the log odds of 'doing better' with sequential therapy.

Here, using the phrase 'doing better' attempts to capture what meant by 'being above' the cut for each cut. We have 'adjusted' for the cuts. The model's regression coefficients are 'assumed common' to the cuts.

brant : assesses the proportional odds assumption

```
. brant,detail

Estimated coefficients from binary logits

-------------------------------------------------
    Variable |  y_gt_1     y_gt_2     y_gt_3
-------------+-----------------------------------
      gender |    0.285     -0.544     -0.984
             |     0.48      -1.12      -1.28
     therapy |   -0.556     -0.471     -0.291
             |    -1.94      -1.80      -0.89
          gt |   -1.089     -0.261     -0.448
             |    -1.46      -0.34      -0.34
       _cons |    1.273     -0.283     -1.367
             |     5.95      -1.59      -6.22
-------------------------------------------------
                                    legend: b/t   <- b is the estimated regression coefficient
                                                  <- t is the Wald z statistic

Brant test of parallel regression assumption

              |       chi2     p>chi2      df
 -------------+------------------------------
          All |       3.75      0.711       6
 -------------+------------------------------
       gender |       2.28      0.320       2
      therapy |       0.59      0.745       2
           gt |       1.00      0.607       2
```

Interpreting the 'Brant' test

The command, 'brant' comes from the materials accompanying the book by Long and Freese.

The output provides the estimated regression coefficients [and the Wald z statistics] from the 3 separate 'ordinary' logistic regressions. One can assess their differences qualitatively.

Then, we get an omnibus test with 6 degrees of freedom made up of the three 2 degree of freedom tests.

Each 2 degree of freedom test comparing one set of the 3 regression coefficients associated with a given explanatory variable.

A complete assessment of therapy and gender

Just like with logistic regression, we can use a proportional odds model to assess gender as a modifier, then, if there is no evidence of modification, assess gender as a confounder and then discuss the outcome-therapy relationship using the 3 ologit commands.

Here, we see that gender neither modifies or confounds. Further, this method has detected evidence of an outcome-therapy relationship (p=0.007). The estimated log odds ratio is -0.5699 and so the estimated odds ratio is exp(-0.5699)=0.5656 and so the odds of doing better for those receiving alternating is 0.5656 the odds of doing better with sequential.

```
. ologit outc gender therapy

Ordered logistic regression                       Number of obs   =        299
                                                  LR chi2(2)      =      10.91
                                                  Prob > chi2     =     0.0043
Log likelihood = -394.52832                       Pseudo R2       =     0.0136

------------------------------------------------------------------------------
        outc |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      gender |  -.5413938   .2871816    -1.89   0.059    -1.104259    .0214717
     therapy |   -.580685   .2121478    -2.74   0.006     -.996487    -.164883
-------------+----------------------------------------------------------------
       /cut1 |  -1.318043   .1797769                     -1.670399   -.9656869
       /cut2 |   .2492335   .1613881                     -.0670813    .5655484
       /cut3 |   1.300056   .1849928                      .9374766    1.662635
------------------------------------------------------------------------------

. ologit outc therapy

Ordered logistic regression                       Number of obs   =        299
                                                  LR chi2(1)      =       7.31
                                                  Prob > chi2     =     0.0068
Log likelihood = -396.32657                       Pseudo R2       =     0.0091

------------------------------------------------------------------------------
        outc |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     therapy |  -.5699142   .2117716    -2.69   0.007    -.9849789   -.1548495
-------------+----------------------------------------------------------------
       /cut1 |   -1.21673   .1704333                     -1.550773   -.8826866
       /cut2 |   .3382206   .1542139                       .035967    .6404743
       /cut3 |   1.380296   .1801627                      1.027184    1.733409
------------------------------------------------------------------------------
```

Fitted Values : On the Log Odds Scale

The fitted values are determined with the cuts set to zero :

$$\log\left(\hat{p}_j/\left(1-\hat{p}_j\right)\right)=b_1\mathrm{G}+b_2\mathrm{T}+b_3\mathrm{GT}$$

```
. predict lo,xb

. predict selo,stdp

. table gender therapy,c(mean lo mean selo)

------------------------------
           |       therapy
    gender |       seq        alt
-----------+----------------------
         m |         0   -.488071
           |         0   .2305167
           |
         f | -.2741906  -1.352677
           |  .3873497   .4322978
------------------------------
```

Cut specific fitted values : the comparisons are the same for each cut

```
. gen loc1 = lo + 1.275657

. gen loc2 = lo - 0.2957159

. gen loc3 = lo - 1.345164

                    therapy

   gender |      seq       alt       alt - seq

cut 1

        0 | 1.275657   .787586       -0.488071

        1 | 1.001466  -.0770205      -1.078486

cut 2

        0 | -.2957159  -.7837869     -0.488071

        1 | -.5699065  -1.648393     -1.078486

cut 3

        0 | -1.345164  -1.833235     -0.488071

        1 | -1.619355  -2.697841     -1.078486
```

Fitted Values: Estimates of probabilities for each outcome level

We can determine:

$$Pr(Y=j)=Pr(Y>j-1)-Pr(Y>j)$$

$$=\frac{1}{1+e^{(-(\beta_1 G+\beta_2 T+\beta_3 GT-\kappa_{j-1}))}}-\frac{1}{1+e^{(-(\beta_1 G+\beta_2 T+\beta_3 GT-\kappa_{j}))}}$$

$$=\frac{1}{1+e^{(\kappa_{j-1}-\beta_1 G-\beta_2 T-\beta_3 GT)}}-\frac{1}{1+e^{(\kappa_{j}-\beta_1 G-\beta_2 T-\beta_3 GT)}}$$

where we pretend that $\kappa_0=-\infty$ and $\kappa_4=\infty$

Specify one variable for each outcome level

```
 predict p1h p2h p3h p4h
(option pr assumed; predicted probabilities)

. table gender therapy,c(mean p1h mean p2h mean p3h mean p4h)

----------------------------
          |      therapy
   gender |      seq       alt
----------+-----------------
        m | .2182904  .3126872
          | .3551045  .3738085
          | .2199429  .1756509
          | .2066622  .1378534
          |
        f | .2686532  .5192456
          | .3700884  .3194282
          | .1959645  .0982254
          | .1652939  .0631009
```

For example, the estimate of the probability of progression for women receiving alternating therapy is 0.5192456

What to do if there is evidence against proportional odds

There are several options :
1) Develop and fit the separate cut specific models [logit]
2) Develop and fit models that do not make the proportional odds assumption : sometimes called Generalized Proportional Odds Models or Generalized Ordered Logit Models [available with gologit2 added to Stata]
3) Develop and fit models that assume proportional odds for some [but not all] explanatory variables and not for the remaining explanatory variables : sometimes called Partial Proportional Odds Models [gologit2 in Stata]
4) Consider 'Multinomial' Models [next]

The Multinomial Logit Model

Now let us consider a model to analyze outcomes with assumed nominal levels (i.e. not necessarily ordinal levels). There is a set of models called multinomial logit models (also sometimes called polytomous logistic regressions) (available in Stata using mlogit).

Here, one selects a baseline 'level' of the outcome and then constructs comparisons between each of the other levels with the baseline level (one-at-a-time).

The model looks like...

...the following: $\log(\mathrm{p}_j / \mathrm{p}_{BL}) = \sum \beta_{ij} x_i$

where p_j is now Pr(outcome = level j) where p_{BL} is the probability of the baseline outcome.

the β_{ij} have the usual interpretations except that now we now have phrases like " a difference between the log rate ratio with exposure minus the log rate ratio without exposure" or the "rate of change of the log of the rate ratio per year in age"

Note: these ratios are not odds ratios

Relative Risk Ratios

The exponents ($\exp(\beta_{ij})$) are sometimes called “relative risk ratios” (ouch!) in so far as they can be ratios of risk ratios (of course, we can have ratios of ratios of risk ratios etc...)

Let us now try mlogit with our tumor study:

(By default, mlogit uses the most frequent outcome level as baseline: here outc=2 (noch) is the most frequent and becomes baseline. There is an option to change this default level : baseoutcome(number))

```
. mlogit outc gender therapy gt

Multinomial logistic regression                 Number of obs   =        299
                                                LR chi2(9)      =      16.48
                                                Prob > chi2     =     0.0575
Log likelihood = -391.74448                     Pseudo R2       =     0.0206

------------------------------------------------------------------------------
        outc |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
prog         |
      gender |  -.6241543   .6255157    -1.00   0.318    -1.850142    .6018339
     therapy |   .4038404   .3241204     1.25   0.213    -.2314239    1.039105
          gt |   1.233768   .8152164     1.51   0.130    -.3640265    2.831563
       _cons |   -.474458      .2407    -1.97   0.049    -.9462214   -.0026946
-------------+----------------------------------------------------------------
noch         |  (base outcome)
-------------+----------------------------------------------------------------
parrem       |
      gender |  -.4361021    .583128    -0.75   0.455    -1.579012    .7068079
     therapy |  -.3490907   .3597669    -0.97   0.332    -1.054221    .3560396
          gt |   .3772616   .9428447     0.40   0.689     -1.47068    2.225203
       _cons |  -.4393667   .2381281    -1.85   0.065    -.9060891    .0273558
-------------+----------------------------------------------------------------
comrem       |
      gender |  -1.243194   .8025068    -1.55   0.121    -2.816078    .3296908
     therapy |  -.2398914   .3652548    -0.66   0.511    -.9557776    .4759947
          gt |   .0857433   1.363671     0.06   0.950    -2.587003     2.75849
       _cons |   -.548566   .2463407    -2.23   0.026    -1.031385    -.065747
------------------------------------------------------------------------------
```

```
. mlogit outc gender therapy

Multinomial logistic regression                 Number of obs   =        299
                                                LR chi2(6)      =      13.93
                                                Prob > chi2     =     0.0304
Log likelihood = -393.01778                     Pseudo R2       =     0.0174

------------------------------------------------------------------------------
        outc |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
prog         |
      gender |   .0902263     .37863     0.24   0.812    -.6518748    .8323275
     therapy |   .6164509   .2954663     2.09   0.037     .0373475    1.195554
       _cons |  -.5941062   .2320624    -2.56   0.010     -1.04894   -.1392722
-------------+----------------------------------------------------------------
noch         |  (base outcome)
-------------+----------------------------------------------------------------
parrem       |
      gender |  -.2716142   .4580482    -0.59   0.553    -1.169372    .6261438
     therapy |  -.2814293   .3319521    -0.85   0.397    -.9320435    .3691849
       _cons |  -.4731007   .2281474    -2.07   0.038    -.9202614   -.0259401
-------------+----------------------------------------------------------------
comrem       |
      gender |  -1.188069   .6474476    -1.84   0.067    -2.457043    .0809049
     therapy |   -.182163   .3491509    -0.52   0.602    -.8664862    .5021603
       _cons |  -.5776952   .2388478    -2.42   0.016    -1.045828   -.1095621
------------------------------------------------------------------------------
```

```
. mlogit outc therapy

Multinomial logistic regression                 Number of obs   =        299
                                                LR chi2(3)      =       8.69
                                                Prob > chi2     =     0.0338
Log likelihood =  -395.6413                     Pseudo R2       =     0.0109

------------------------------------------------------------------------------
        outc |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
prog         |
     therapy |   .6157816   .2954143     2.08   0.037     .0367802    1.194783
       _cons |  -.5773153   .2208933    -2.61   0.009    -1.010258   -.1443724
-------------+----------------------------------------------------------------
noch         |  (base outcome)
-------------+----------------------------------------------------------------
parrem       |
     therapy |  -.2796407   .3317254    -0.84   0.399    -.9298105    .3705291
       _cons |  -.5166907   .2166925    -2.38   0.017    -.9414002   -.0919813
-------------+----------------------------------------------------------------
comrem       |
     therapy |  -.1764564   .3471095    -0.51   0.611    -.8567786    .5038658
       _cons |  -.7108468   .2307773    -3.08   0.002    -1.163162   -.2585316
------------------------------------------------------------------------------
```

Interpreting mlogit

Since there are four levels of outc, there are, for each candidate model, 3 sets of regression coefficients.

As with logit and ologit, one can use mlogit to address modification, confounding and outcome-exposure issues although the assessment has the added complexity of the multiple sets of coefficients.

The option 'rrr' takes the exponent of the coefficients which can yield 'relative risk ratios' or ratios of ratios [as elsewhere]

For example

No modification or confounding to be noted

Here, we can see little of material interest in the 2 rate ratios:

: partial remission relative to no change

: complete remission relative to no change

Regarding the outcome: progression relative to no change, we do see an outcome-therapy relationship.

Progression of disease

Since exp(0.6157816)=1.8511029, we can note that the progression rate relative to the 'no change' rate for those receiving alternating chemotherapy is estimated to be 1.85 times the progression rate relative to the 'no change' rate for those receiving sequential chemotherapy.

Notice that this is a much more focussed statement about the nature of the outcome-therapy relationship than that obtained from ologit.

Fitted Values: Log Rate Ratio Scale

The fitted values on the log rate ratio scale are determined for all but the baseline:

$$\mathrm{A}_j = \log \hat{\mathrm{p}}_j - \log \hat{\mathrm{p}}_2 = b_{0\mathrm{j}} + b_{1\mathrm{j}}\mathrm{G} + b_{2\mathrm{j}}\mathrm{T} + b_{3\mathrm{j}}\mathrm{GT}$$

```
. quietly: mlogit outc gender therapy gt

. predict lo1h,xb outcome(1)

. predict lo2h,xb outcome(2)

. predict lo3h,xb outcome(3)

. predict lo4h,xb outcome(4)
```

A table of fitted values

```
. table g t,c(m lo1h m lo2h m lo3h m lo4h)

------------------------------
          |          t
        g |          0          1
----------+-------------------
        0 |  -.474458  -.0706176
          |          0          0
          | -.4393667  -.7884573
          | -.5485659  -.7884573
          |
        1 | -1.098612   .5389965
          |          0          0
          | -.8754687  -.8472978
          | -1.791759  -1.945908
------------------------------
```

So, for example, for men receiving sequential therapy, the log of the complete remission rate minus log of the 'no change' rate is estimated to be -0.5485659

Fitted Values: Probability Scale

We have: $\frac{p_j}{p_2} = e^{A_j}$ and $\sum_{i=1}^{4} p_j = 1$

$$p_1 = p_2 e^{A_1} \quad p_3 = p_2 e^{A_3} \quad p_4 = p_2 e^{A_4}$$

$$p_1 + p_3 + p_4 = p_2 (e^{A_1} + e^{A_3} + e^{A_4})$$

$$1 - p_2 = p_2 (e^{A_1} + e^{A_3} + e^{A_4})$$

$$p_2 = \frac{1}{(1 + e^{A_1} + e^{A_3} + e^{A_4})}$$

Stata does the work

```
. quietly: mlogit outc gender therapy gt

. predict p1h p2h p3h p4h

. table g t,c(m p1h m p2h m p3h m p4h)

------------------------------
          |         t
        g |         0         1
----------+-------------------
        0 |   .21875      .328
          | .3515625      .352
          | .2265625       .16
          |  .203125       .16
          |
        1 |  .173913  .5217391
          | .5217391  .3043478
          | .2173913  .1304348
          | .0869565  .0434784
------------------------------
```

For example, the estimate of the probability of progression for women receiving alternating therapy is 0.5217391

Reverse coding the outcome

Indeed, if we reverse the order:

```
. gen outcw=5-outc

. table outcw outc

----------------------------------------
          |               outc
    outcw |   prog    noch  parrem  comrem
----------+-----------------------------
        1 |                            49
        2 |                      57
        3 |             108
        4 |     85
----------------------------------------
```

```
. ologit outcw therapy
Ordered logistic regression                       Number of obs   =        299
                                                  LR chi2(1)      =       7.31
                                                  Prob > chi2     =     0.0068
Log likelihood = -396.32657                       Pseudo R2       =     0.0091

------------------------------------------------------------------------------
       outcw |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     therapy |   .5699142   .2117716     2.69   0.007     .1548495    .9849789
-------------+----------------------------------------------------------------
       /cut1 |  -1.380296   .1801627                     -1.733409   -1.027184
       /cut2 |  -.3382206   .1542139                     -.6404743    -.035967
       /cut3 |    1.21673   .1704333                      .8826866    1.550773
------------------------------------------------------------------------------

. disp exp(0.5699142)
1.7681153

. brant,detail
Estimated coefficients from j-1 binary regressions
                y>1          y>2          y>3
therapy    .3196848   .49869928   .72980261
  _cons   1.4799798   .36150198  -1.3133876
Brant Test of Parallel Regression Assumption

    Variable |      chi2   p>chi2    df
-------------+--------------------------
         All |      1.38    0.503     2
-------------+--------------------------
     therapy |      1.38    0.503     2
-----------------------------------------
```

ologit then presents 'odds of doing worse'

From the previous ologit:

: the odds of doing worse with alternating chemotherapy is estimated to be 1.77 times the odds of doing worse with sequential chemotherapy

Reverse coding has no effect on mlogit:

```
. mlogit outcw therapy

Multinomial logistic regression                 Number of obs   =        299
                                                LR chi2(3)      =       8.69
                                                Prob > chi2     =     0.0338
Log likelihood =  -395.6413                     Pseudo R2       =     0.0109

------------------------------------------------------------------------------
       outcw |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
1            |
     therapy |  -.1764564   .3471095    -0.51   0.611    -.8567786    .5038658
       _cons |  -.7108468   .2307773    -3.08   0.002    -1.163162   -.2585316
-------------+----------------------------------------------------------------
2            |
     therapy |  -.2796407   .3317254    -0.84   0.399    -.9298105    .3705291
       _cons |  -.5166907   .2166925    -2.38   0.017    -.9414002   -.0919813
-------------+----------------------------------------------------------------
3            |  (base outcome)
-------------+----------------------------------------------------------------
4            |
     therapy |   .6157816   .2954143     2.08   0.037     .0367802    1.194783
       _cons |  -.5773153   .2208933    -2.61   0.009    -1.010258   -.1443724
------------------------------------------------------------------------------
```

outcw does not have labels for the codes:
progression is now outcw=4