STAT 36900: Homework 5

Robert Winter

Table of Contents

1 Introduction

The data for this problem are from the Riesby *et al.* article that we have discussed in class. This study examined the relationship in depressed inpatients between the drug plasma levels—the antidepressant imipramine (IMI) and its metabolite desimipramine (DMI)—and clinical response as measured by the Hamilton Depression Rating Scale (HDRS). In class, I might have mentioned that the study investigators treated HDRS as a trichotomous outcome:

```
if hdrs lt 8 then hdrs3 = 0

if hdrs ge 8 and hdrs le 15 then hdrs3 = 1

if hdrs gt 15 then hdrs3 = 2
```

Thus, `0` can be thought of as "normal," `1` as "mild depression," and `2` as "definite depression." The dataset (`RIESORD3.RRM.txt`), which is available on the class Canvas website, contains the following variables:

- **field 1: Patient ID — `id`**
- **field 2: continuous HDRS score — *ignore this variable***
- **field 3: dichotomized HDRS score — *ignore this variable***
- **filed 4: trichotomized HDRS score — `hdrs3`**

- **field 5: a field of ones — *ignore this variable***
- **field 6: Week, from 0 (Week 2) to 3 (Week 5) — `week`**
- **field 7: dichotomized (median split) Desimipramine (DMI) plasma levels — `dmi2`**
- **field 8: dichotomized Desimipramine (DMI) plasma levels × Week**
- **field 9: centered Desimipramine (DMI) plasma levels — *ignore this variable***
- **field 10: centered Desimipramine (DMI) plasma levels × Week — *ignore this variable***

Note that `-9` indicates a missing observation for all variables (in particular, for `hdrs3` and `dmi2`); these should be removed in your analyses of these data.

2 Question 1

Using `hdrs3` as the outcome, estimate a random-intercepts ordinal logistic regression model with the predictors of `week` and `dmi2`. Interpret the effects of these two independent variables. Provide an estimate of the intraclass correlation.

Below, we estimate the following random-intercepts ordinal logistic regression model:

Within-Subjects Model:

$$\lambda_{ijc} = \gamma_c - [b_{0i} + b_{1i} \cdot Week_{ij} + b_{2i} \cdot DMI2_{ij}]$$

where:

- $i = 1, \ldots, 250$ individuals,
- $j = 1, \ldots, n_i$ observations for each patient i (with $n_i \in \{3, 4\}\ \forall i$),
- $c = 1, 2$, corresponding to the cutoffs (1) between "normal" mental health and "mild" or "definite" depression, and (2) between "normal" mental health or "mild" depression and "definite" depression, and
- $\lambda_{ijc} = \log\left(\frac{\mathbb{P}(HDRS3_{ij} \leq c)}{1 - \mathbb{P}(HDRS3_{ij} \leq c)}\right)$,

and:

- γ_c is the log odds of experiencing depression of level $(c-1)$ or below, relative to levels c and above, as of Week 2 and assuming DMI levels are below median. In particular, γ_1 is the log odds of experiencing "normal" mental health relative to experiencing depression, while γ_2 is the log odds of experiencing non-"definite" depression relative to "definite" depression, in each case as of Week 2 and assuming DMI levels are below median,

- b_{0i} is patient i's log odds of having depression at a level less than c as of Week 2, assuming their DMI levels are below median, for $c \in \{1, 2\}$,
- b_{1i} is patient i's weekly linear change in the log odds of having depression at a level less than c, for $c \in \{1, 2\}$, and
- b_{2i} is the difference between patient i's log odds of having depression at a level less than c if their DMI levels were above median compared to if their DMI levels were below median, for $c \in \{1, 2\}$.

Between-Subjects Model:

$$
\begin{aligned}
b_{0i} &= \upsilon_{0i} \\
b_{1i} &= \beta_1 \\
b_{2i} &= \beta_2 \\
\upsilon_{0i} &\sim \text{i.i.d. } \mathcal{N}(0, \sigma^2_\upsilon)
\end{aligned}
$$

where:

- υ_{0i} is patient i's deviation from the "typical patient's" log odds of having depression at a level less than c as of Week 2, assuming their DMI levels are below median, for $c \in \{1, 2\}$,
- β_1 is the weekly linear change in a given patient's log odds of having depression at a level less than c, for a given value of υ_{0i}, for $c \in \{1, 2\}$, and
- β_2 is the difference between a given patient's log odds of having depression at a level less than c if their DMI levels were above the median compared to if their DMI levels were below the median, for a given value of υ_{0i}, for $c \in \{1, 2\}$.

```
. infile id hdrsc hdrs2 hdrs3 one week dmi2 dmi2_week dmic dmic_week ///
> using RIESORD3.RRM.txt, clear
(264 observations read)
.
. quietly recode hdrsc hdrs2 hdrs3 dmi2 dmi2_week dmic dmic_week (-9 = .)
.
. meologit hdrs3 week dmi2 || id:

Fitting fixed-effects model:

Iteration 0:  Log likelihood = -250.61527
Iteration 1:  Log likelihood = -227.81529
Iteration 2:  Log likelihood =  -227.5249
Iteration 3:  Log likelihood = -227.52401
Iteration 4:  Log likelihood = -227.52401
```

```
Refining starting values:

Grid node 0:  Log likelihood = -209.25918

Fitting full model:

Iteration 0:  Log likelihood = -209.25918
Iteration 1:  Log likelihood = -196.36193
Iteration 2:  Log likelihood = -194.18674
Iteration 3:  Log likelihood = -194.05212
Iteration 4:  Log likelihood = -194.05154
Iteration 5:  Log likelihood = -194.05154

Mixed-effects ologit regression                 Number of obs     =        250
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4

Integration method: mvaghermite                 Integration pts.  =          7

                                                Wald chi2(2)      =      48.41
Log likelihood = -194.05154                     Prob > chi2       =     0.0000
------------------------------------------------------------------------------
       hdrs3 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.158149   .1793988    -6.46   0.000    -1.509764   -.8065335
        dmi2 |  -1.565615   .5291021    -2.96   0.003    -2.602636   -.5285934
-------------+----------------------------------------------------------------
       /cut1 |   -6.06703   .7521292                     -7.541176   -4.592883
       /cut2 |  -2.201071   .5215089                      -3.22321   -1.178933
-------------+----------------------------------------------------------------
id           |
   var(_cons)|   5.773529   1.873862                      3.056149    10.90707
------------------------------------------------------------------------------
LR test vs. ologit model: chibar2(01) = 66.94         Prob >= chibar2 = 0.0000
```

As summarized in the Stata output above, we find that:

- The log odds of experiencing "normal" mental health relative to experiencing depression as of Week 2 for below-median DMI levels is approximately -6.067.
- The log odds of experiencing "normal" mental health or "mild" depression relative to

experiencing "definite" depression as of Week 2 and for below-median DMI levels is approximately -2.201.

- Each week, a given patient's (i.e., holding v_{0i} fixed) log odds of having depression at a level less than c increase by approximately 1.158, for $c \in \{1, 2\}$.
- A given patient's (i.e., holding v_{0i} fixed) log odds of having depression at a level less than c are approximately 1.566 higher if their DMI is above median compared to if their DMI is below median.

The intraclass correlation (ICC) captures the proportion of (unexplained) variation in depression levels at the subject level. Here, based on the Stata output above and the fact that we are using a cumulative logit model, the ICC is:

$$r = \frac{\sigma_v^2}{\sigma_v^2 + \sigma^2} \approx \frac{5.774}{5.774 + (\pi^2/3)} \approx 0.637.$$

3 Question 2

Now, still including `week` and `dmi2` as predictors, fit a model with random subject intercepts and week effects (and allow for the covariance of these two random effects). Is this model significantly better than the random-intercepts model? Interpret the effects of `week` and `dmi2`.

Now, we estimate the following mixed effects ordinal logistic regression model:

<u>Within-Subjects Model:</u>

$$\lambda_{ijc} = \gamma_c - [b_{0i} + b_{1i} \cdot Week_{ij} + b_{2i} \cdot DMI2_{ij}]$$

where:

- $i = 1, \ldots, 250$ individuals,
- $j = 1, \ldots, n_i$ observations for each patient i (with $n_i \in \{3, 4\}\ \forall i$),
- $c = 1, 2$, corresponding to the cutoffs (1) between "normal" mental health and "mild" or "definite" depression, and (2) between "normal" mental health or "mild" depression and "definite" depression, and
- $\lambda_{ijc} = \log\left(\frac{\mathbb{P}(HDRS3_{ij} \leq c)}{1 - \mathbb{P}(HDRS3_{ij} \leq c)}\right)$,

and:

- γ_c is the log odds of experiencing depression of level $(c-1)$ or below, relative to levels c and above, as of Week 2 and assuming DMI levels are below median. In particular, γ_1 is the log odds of experiencing "normal" mental health relative to experiencing depression, while γ_2 is the log odds of experiencing non-"definite" depression relative to "definite" depression, in each case as of Week 2 and assuming DMI levels are below median,
- b_{0i} is patient i's log odds of having depression at a level less than c as of Week 2, assuming their DMI levels are below median, for $c \in \{1, 2\}$,
- b_{1i} is patient i's weekly linear change in the log odds of having depression at a level less than c, for $c \in \{1, 2\}$, and
- b_{2i} is the difference between patient i's log odds of having depression at a level less than c if their DMI levels were above median compared to if their DMI levels were below median, for $c \in \{1, 2\}$.

Between-Subjects Model:

$$\begin{aligned} b_{0i} &= \upsilon_{0i} \\ b_{1i} &= \beta_1 + \upsilon_{1i} \\ b_{2i} &= \beta_2 \\ (\upsilon_{0i}, \upsilon_{1i}) &\sim \text{i.i.d. } \mathcal{N}(0, \Sigma_\upsilon) \end{aligned}$$

where:

- υ_{0i} is patient i's deviation from the "typical patient's" log odds of having depression at a level less than c as of Week 2, assuming their DMI levels are below median, for $c \in \{1, 2\}$,
- β_1 is the weekly linear change in a given patient's log odds of having depression at a level less than c, for given values of υ_{0i} and υ_{1i}, for $c \in \{1, 2\}$,
- υ_{1i} is patient i's deviation from the "typical patient's" weekly linear change in the log odds of having depression at a level less than c, for $c \in \{1, 2\}$, and
- β_2 is the difference between a given patient's log odds of having depression at a level less than c if their DMI levels were above the median compared to if their DMI levels were below the median, for given values of υ_{0i} and υ_{1i}, for $c \in \{1, 2\}$.

```
. infile id hdrsc hdrs2 hdrs3 one week dmi2 dmi2_week dmic dmic_week ///
> using RIESORD3.RRM.txt, clear
(264 observations read)
.
. quietly recode hdrsc hdrs2 hdrs3 dmi2 dmi2_week dmic dmic_week (-9 = .)
.
. meologit hdrs3 week dmi2 || id: week, covariance(unstructured)
```

```
Fitting fixed-effects model:

Iteration 0:  Log likelihood = -250.61527
Iteration 1:  Log likelihood = -227.81529
Iteration 2:  Log likelihood =  -227.5249
Iteration 3:  Log likelihood = -227.52401
Iteration 4:  Log likelihood = -227.52401

Refining starting values:

Grid node 0:  Log likelihood = -211.93484

Fitting full model:

Iteration 0:  Log likelihood = -211.93484  (not concave)
Iteration 1:  Log likelihood = -208.18596
Iteration 2:  Log likelihood = -194.51137
Iteration 3:  Log likelihood = -190.94164
Iteration 4:  Log likelihood = -190.37322
Iteration 5:  Log likelihood = -190.34429
Iteration 6:  Log likelihood = -190.34411
Iteration 7:  Log likelihood =  -190.3441

Mixed-effects ologit regression                 Number of obs     =        250
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4

Integration method: mvaghermite                 Integration pts.  =          7

                                                Wald chi2(2)      =      25.25
Log likelihood = -190.3441                      Prob > chi2       =     0.0000
------------------------------------------------------------------------------
       hdrs3 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.419306   .3062446    -4.63   0.000    -2.019534   -.8190774
        dmi2 |  -1.823577   .6698946    -2.72   0.006    -3.136546   -.5106072
-------------+----------------------------------------------------------------
       /cut1 |  -7.362478   1.169698                      -9.655045   -5.069912
       /cut2 |  -2.536439    .730508                      -3.968208    -1.10467
-------------+----------------------------------------------------------------
```

```
id           |
    var(week)|   1.274962   .8139002                              .3648494    4.455338
   var(_cons)|   8.685609   4.595496                              3.079183    24.49995
-------------+----------------------------------------------------------------------
id           |
    cov(week,|
       _cons)|  -.7634749     1.2021    -0.64   0.525    -3.119548    1.592598
------------------------------------------------------------------------------------
LR test vs. ologit model: chi2(3) = 74.36                    Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

To compare this model to the random intercept model estimated in Question (1), we test the null hypothesis $H_0 : \sigma^2_{\upsilon_1} = \sigma_{\upsilon_0 \upsilon_1} = 0$ against the alternative hypothesis $H_1 : \sigma^2_{\upsilon_1} \neq 0$ or $\sigma_{\upsilon_0 \upsilon_1} \neq 0$. Since there are two parameters in our null hypothesis ($\sigma^2_{\upsilon_1}$ and $\sigma_{\upsilon_0 \upsilon_1}$), we use a chi-bar-squared test employing a 50:50 mixture of a χ^2_2 distribution and a χ^2_1 distribution. The test statistic is $LR\ \chi^2 = -2 \times (-194.05154 - (-190.3441)) = 7.41488$. As shown below, we recover a p-value of approximately $0.016 < 0.05$, so we reject the null hypothesis that there is not subject-level variation in the linear time trend of depression levels in favor of the alternative hypothesis that there *is* subject-level variation in the linear time trend of depression levels.

```
. display 0.5*chi2tail(2, 7.41488) + 0.5*chi2tail(1, 7.41488)
.01550446
```

As summarized in the Stata output above, we now find that:

- The log odds of experiencing "normal" mental health relative to experiencing depression as of Week 2 for below-median DMI levels is approximately -7.362.
- The log odds of experiencing "normal" mental health or "mild" depression relative to experiencing "definite" depression as of Week 2 and for below-median DMI levels is approximately -2.536.
- Each week, a given patient's (i.e., holding υ_{0i} and υ_{1i} fixed) log odds of having depression at a level less than c increase by approximately 1.419, for $c \in \{1, 2\}$.
- A given patient's (i.e., holding υ_{0i} and υ_{1i} fixed) log odds of having depression at a level less than c are approximately 1.824 higher if their DMI is above median compared to if their DMI is below median.

4 Question 3

Test whether the effect of `dmi2` varies across time. Write down the multilevel model for this. What do you conclude about the effect of `dmi2` on `hdrs3`?

Finally, we estimate the following mixed effects ordinal logistic regression model:

Within-Subjects Model:

$$\lambda_{ijc} = \gamma_c - [b_{0i} + b_{1i} \cdot Week_{ij} + b_{2i} \cdot DMI2_{ij} + b_{3i} \cdot Week_{ij} \times DMI2_{ij}]$$

where:

- $i = 1, \ldots, 250$ individuals,
- $j = 1, \ldots, n_i$ observations for each patient i (with $n_i \in \{3, 4\}\ \forall i$),
- $c = 1, 2$, corresponding to the cutoffs (1) between "normal" mental health and "mild" or "definite" depression, and (2) between "normal" mental health or "mild" depression and "definite" depression, and
- $\lambda_{ijc} = \log\left(\frac{\mathbb{P}(HDRS3_{ij} \leq c)}{1 - \mathbb{P}(HDRS3_{ij} \leq c)}\right)$,

and:

- γ_c is the log odds of experiencing depression of level $(c-1)$ or below, relative to levels c and above, as of Week 2 and assuming DMI levels are below median. In particular, γ_1 is the log odds of experiencing "normal" mental health relative to experiencing depression, while γ_2 is the log odds of experiencing non-"definite" depression relative to "definite" depression, in each case as of Week 2 and assuming DMI levels are below median,
- b_{0i} is patient i's log odds of having depression at a level less than c as of Week 2, assuming their DMI levels are below median, for $c \in \{1, 2\}$,
- b_{1i} is patient i's weekly linear change in the log odds of having depression at a level less than c, given that their DMI levels are below median, for $c \in \{1, 2\}$,
- b_{2i} is the difference between patient i's log odds of having depression at a level less than c if their DMI levels were above median compared to if their DMI levels were below median, for $c \in \{1, 2\}$, and
- b_{3i} is the difference between patient i's weekly linear change in the log odds of having depression at a level less than c given that their DMI levels are above median compared to if their DMI levels were below median, for $c \in \{1, 2\}$.

Between-Subjects Model:

$$
\begin{aligned}
b_{0i} &= \upsilon_{0i} \\
b_{1i} &= \beta_1 + \upsilon_{1i} \\
b_{2i} &= \beta_2 \\
b_{3i} &= \beta_3 \\
(\upsilon_{0i}, \upsilon_{1i}) &\sim \text{i.i.d. } \mathcal{N}(0, \Sigma_\upsilon)
\end{aligned}
$$

where:

- υ_{0i} is patient i's deviation from the "typical patient's" log odds of having depression at a level less than c as of Week 2, assuming their DMI levels are below median, for $c \in \{1, 2\}$,
- β_1 is the weekly linear change in a given patient's log odds of having depression at a level less than c, assuming that their DMI levels are below median, for given values of υ_{0i} and υ_{1i}, for $c \in \{1, 2\}$,
- υ_{1i} is patient i's deviation from the "typical patient's" weekly linear change in the log odds of having depression at a level less than c, for $c \in \{1, 2\}$,
- β_2 is the difference between a given patient's log odds of having depression at a level less than c if their DMI levels were above the median compared to if their DMI levels were below median, for given values of υ_{0i} and υ_{1i}, for $c \in \{1, 2\}$, and
- β_3 is the difference between a given patient's weekly linear change in the log odds of having depression at a level less than c given that their DMI levels are above median compared to if their DMI levels were below median, for given values of υ_{0i} and υ_{1i}, for $c \in \{1, 2\}$.

```
. infile id hdrsc hdrs2 hdrs3 one week dmi2 dmi2_week dmic dmic_week ///
> using RIESORD3.RRM.txt, clear
(264 observations read)
.
. quietly recode hdrsc hdrs2 hdrs3 dmi2 dmi2_week dmic dmic_week (-9 = .)
.
. meologit hdrs3 week dmi2 dmi2_week || id: week, covariance(unstructured)

Fitting fixed-effects model:

Iteration 0:  Log likelihood = -250.61527
Iteration 1:  Log likelihood = -227.79903
Iteration 2:  Log likelihood = -227.45361
Iteration 3:  Log likelihood = -227.45274
Iteration 4:  Log likelihood = -227.45274
```

```
Refining starting values:

Grid node 0:  Log likelihood = -212.07878

Fitting full model:

Iteration 0:  Log likelihood = -212.07878  (not concave)
Iteration 1:  Log likelihood =  -208.2921
Iteration 2:  Log likelihood = -195.60803
Iteration 3:  Log likelihood = -192.84029
Iteration 4:  Log likelihood = -190.62372
Iteration 5:  Log likelihood = -190.33246
Iteration 6:  Log likelihood = -190.33036
Iteration 7:  Log likelihood = -190.33035

Mixed-effects ologit regression                 Number of obs     =        250
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4

Integration method: mvaghermite                 Integration pts.  =          7

                                                Wald chi2(3)      =      25.46
Log likelihood = -190.33035                     Prob > chi2       =     0.0000
------------------------------------------------------------------------------
       hdrs3 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.377096   .3926185    -3.51   0.000    -2.146614   -.6075777
        dmi2 |  -1.722462    .896667    -1.92   0.055    -3.479897    .0349729
   dmi2_week |  -.0752349   .4511665    -0.17   0.868     -.959505    .8090352
-------------+----------------------------------------------------------------
       /cut1 |  -7.303727   1.209845                     -9.674979   -4.932474
       /cut2 |  -2.478946   .7980554                     -4.043106   -.9147865
-------------+----------------------------------------------------------------
id           |
    var(week)|   1.268405   .8105538                      .3625027    4.438177
   var(_cons)|   8.590003   4.581508                      3.019966    24.43344
-------------+----------------------------------------------------------------
id           |
    cov(week,|
       _cons)|  -.7283903   1.203747    -0.61   0.545    -3.087691    1.630911
------------------------------------------------------------------------------
```

```
LR test vs. ologit model: chi2(3) = 74.24                 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

As shown above, our coefficient estimate for the interaction of week and dichotomized DMI levels is *not* statistically significant, as it bears a p-value of $0.868 \gg 0.05$. Thus, there is *not* statistical evidence that the effect of `dmi2` on `hdrs3` varies across time. As such, our "final model" is the model we summarized in Question (2), wherein we found that a given patient's (i.e., holding v_{0i} and v_{1i} fixed) log odds of having depression at a level less than c are approximately 1.824 higher if their DMI is above median compared to if their DMI is below median, for $c \in \{1, 2\}$. We now conclude that this effect is constant across time.