432 Class 24 Slides

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Today's Topic

- Generalized Least Squares (growth curve models) for longitudinal data

Today's R Packages

```
library(janitor); library(here)
library(knitr); library(magrittr)
library(patchwork)
library(haven) # for zap_label
library(nlme)  # for modeling with gls
library(rms)
library(tidyverse)

theme_set(theme_bw())
```

Today's Key Reference

Harrell (2015) Chapter 7 is the source for most of this material, with some adjustments to the coding and some details of the presentation. Remember that this text is part of our Sources page, and if you're interested in more, start there.

- More details on the cervical dystonia data set we'll use today are found at https://hbiostat.org/data/repo/cdystonia.html.
- Cervical dystonia, also called spasmodic torticollis, is a painful condition in which your neck muscles contract involuntarily, causing your head to twist or turn to one side. Cervical dystonia can also cause your head to uncontrollably tilt forward or backward.

Generalized Least Squares for Modeling Longitudinal Data (see Harrell 2015, Chapter 7)

Modeling an Outcome Measured Serially Over Time

Suppose we have a quantitative outcome which we will measure at multiple times for each subject.

- This creates correlations between measurements on the same subject that must be taken into account.
- The model we'll use, generalized least squares, has some nice properties, and in fact OLS is a special case of generalized least squares, so that's appealing.
- Generalized Least Squares models like those I'll demonstrate today are also called *growth curve models*.

Setting Up

- We will have 109 subjects in our study, which is an RCT.
- We will have some baseline covariates (age, sex) for each subject.
- We will use the baseline (pre-randomization) value of the outcome as a covariate.
    - There are lots of good reasons to put initial measurements of the outcome into the set of predictors. See our next slide.
- We will have up to 6 measurements of our outcome on each subject.
- We will have differing patterns of measurements for some subjects, just because of practical reasons, so not all subjects will have all six measurements.
- We will focus on a model that includes several non-linear terms to predict the trajectory of our outcome over time on the basis of the covariates.

Using pre-randomization outcomes as covariates

For RCTs, I draw a sharp line at the point when the intervention begins. The LHS [left hand side of the model equation] is reserved for something that is a response to treatment. Anything before this point can potentially be included as a covariate in the regression model. This includes the "baseline" value of the outcome variable. Indeed, the best predictor of the outcome at the end of the study is typically where the patient began at the beginning. It drinks up a lot of variability in the outcome; and, the effect of other covariates is typically mediated through this variable. I treat anything after the intervention begins as an outcome. In the western scientific method, an "effect" must follow the "cause" even if by a split second.

- Jim Rochon, quoted in Harrell (2015, Chapter 7)

Harrell (Chapter 7) on Longitudinal Modeling

The real value of longitudinal data comes from modeling the entire time course. Estimating the time course leads to understanding slopes, shapes, overall trajectories, and periods of treatment effectiveness.

To allow the slope or shape of the time-response profile to depend on some of the Xs we add product terms for desired interaction effects.

Once the right hand side of the model is formulated, predicted values, contrasts, and ANOVAs are obtained just as with a univariate model. For these purposes time is no different than any other covariate except for what is described in the next slide.

Modeling Within-Sample Dependence

Sometimes understanding within-subject correlation patterns is of interest in itself. More commonly, accounting for intra-subject correlation is crucial for inferences to be valid.

The main alternative strategies to the GLS approach we'll use are:

- Repeated Measures ANOVA
- Generalized Estimating Equations (GEEs)
- Mixed Effects Models

Harrell (2015) provides a chart (page 145) which describes which methods to use for repeated measurements / serial data.

Two Other Things To Be Aware Of

- Last Observation Carried Forward (LOCF) is an ad hoc attempt to account for people who drop out partway through the study, or who have inconsistent measuring patterns.
- Summary Statistics can convert multivariate responses to unvariate ones (say, within-subject regression slopes, or means over time) with few assumptions so long as there are minimal dropouts, while suffering some (perhaps unimportant) loss of information. We do have to assume that the summary measure is an adequate descriptor of the time profile for our research question.

Assumptions of the Growth Curve Model (GLS)

- All the assumptions of OLS at a single time point including correct modeling of predictor effects and univariate normality of responses conditional on the predictors X are still in place.
- The distribution of two responses at two different times for the same subject, conditional on X, is bivariate normal with a specified correlation coefficient.
- The joint distribution of all responses for the ith subject is multivariate normal with a specified correlation pattern (there are multiple options)
- Responses from two different subjects are uncorrelated

Common Correlation Structures

- We usually restrict ourselves to **isotropic** correlation structures which assume the correlation between responses within subject at two times depends only on a measure of the distance between the two times, not the individual times.
- Harrell (2015) presents seven options (all from the `nlme` package) on page 148.

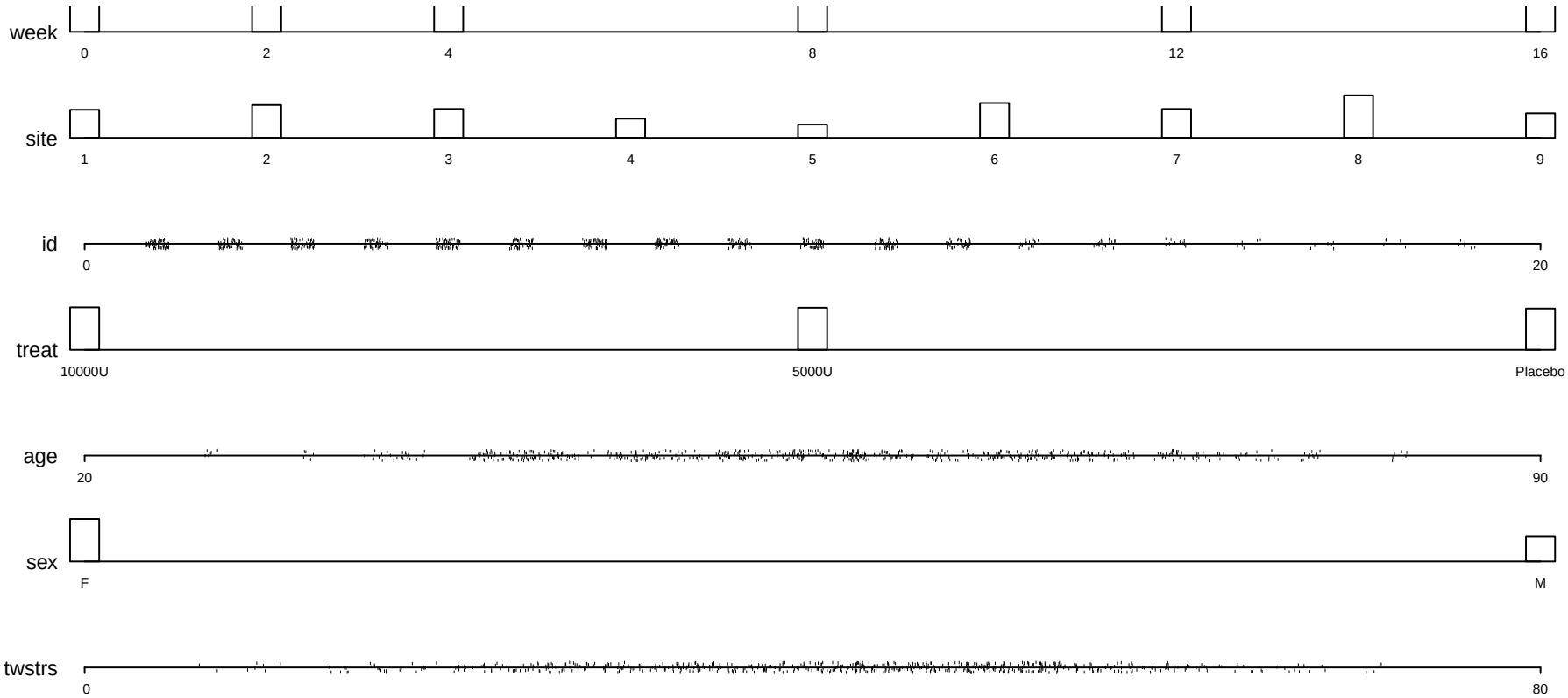
The cdystonia data

The data (described in Harrell 2015, Chapter 7) come from a multi-center RCT of botulinum toxin type B (BotB) in adult subjects with cervical dystonia from nine US sites.

- Subjects were randomized to receive Placebo (N = 36), 5000 units of BotB (N = 36) or 10,000 units of BotB (N = 37).
- The outcome is TWSTRS, the Toronto Western Spasmodic Torticollis Rating Scale, which measures severity, pain, and disability of cervical dystonia (high scores mean more impairment).
  - TWSTRS is measured at baseline (week 0) and at weeks 2, 4, 8, 12 and 16 after treatment began.

Obtaining the cdystonia data

```
getHdata(cdystonia) # obtain data set (includes labels)
datadensity(cdystonia)
```



Some Cleanup

```
cdystonia <- cdystonia %>% tibble() %>%
    zap_label() %>% # for some reason, this only sort of works
    mutate(uid = factor(paste(site, id)),
           age = as.numeric(age),
           week = as.numeric(week),
           id = factor(id),
           twstrs = as.numeric(twstrs)) %>%
    relocate(uid)

str(cdystonia)
```

```
tibble [631 x 8] (S3: tbl_df/tbl/data.frame)
 $ uid   : Factor w/ 109 levels "1 1","1 10","1 11",..: 1 1 1
 $ week  : num [1:631] 0 2 4 8 12 16 0 2 4 8 ...
 $ site  : Factor w/ 9 levels "1","2","3","4",..: 1 1 1 1 1 1
 $ id    : Factor w/ 19 levels "1","2","3","4",..: 1 1 1 1 1 1
 $ treat : Factor w/ 3 levels "10000U","5000U",..: 2 2 2 2 2 2
```

The cdystonia tibble (without labels)

```
cdystonia
```

```
# A tibble: 631 x 8
   uid    week site  id    treat    age sex   twstrs
   <fct> <dbl> <fct> <fct> <fct>  <dbl> <fct>  <dbl>
 1 1 1       0 1     1     5000U     65 F         32
 2 1 1       2 1     1     5000U     65 F         30
 3 1 1       4 1     1     5000U     65 F         24
 4 1 1       8 1     1     5000U     65 F         37
 5 1 1      12 1     1     5000U     65 F         39
 6 1 1      16 1     1     5000U     65 F         36
 7 1 2       0 1     2     10000U    70 F         60
 8 1 2       2 1     2     10000U    70 F         26
 9 1 2       4 1     2     10000U    70 F         27
10 1 2       8 1     2     10000U    70 F         41
# ... with 621 more rows
```

The cdystonia codebook

$n = 631$ observations, on 7 variables, describing 109 unique subjects, no NA

Name	Label
uid	unique subject ID (combined Site then ID)
week	Weeks after Treatment began (0, 2, 4, 8, 12 or 16)
site	Site (Center, labeled 1-9)
id	ID (specific to a Site, labeled 1-19)
treat	Placebo (n = 36), 5000U (n = 36) or 10000U (n = 37)
age	Age (in years, observed range 26-83)
sex	Sex (F or M)
twstrs	TWSTRS total score (observed range: 6-71)

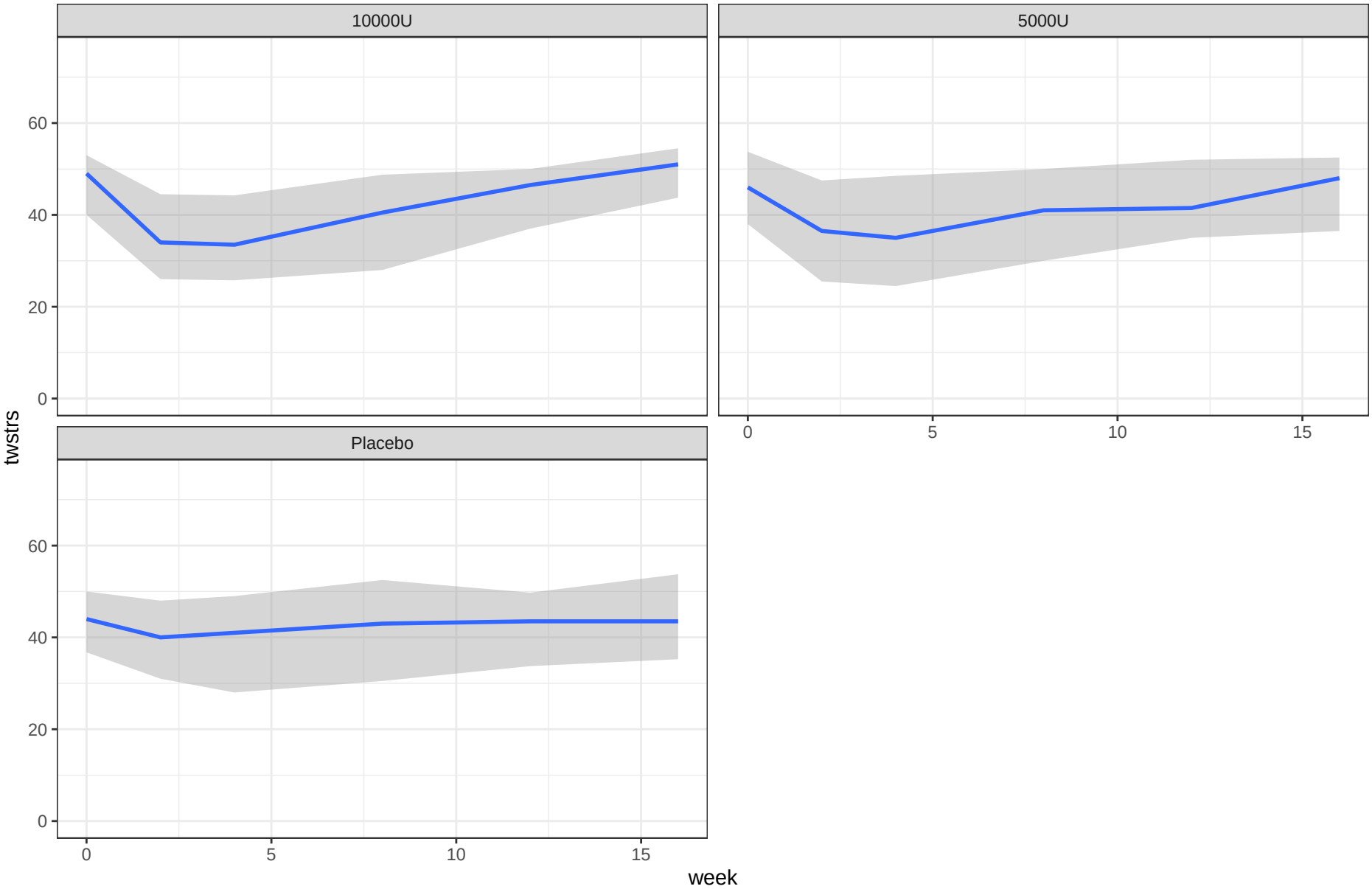
Plot with Quartiles

```
ggplot(cdystonia, aes(x = week, y = twstrs)) +
    geom_smooth(stat = "summary",
                fun.data = median_hilow,
                fun.args = (conf.int = 0.5)) +
    lims(y = c(0, 75)) +
    facet_wrap(~ treat, nrow = 2) +
    labs(title = "TWSTRS per week by Treatment",
         subtitle = "Median and Quartiles")
```

- `median_hilow` from `Hmisc` gives median and quartiles (with 50% CI)
- Result on next slide.

TWSTRS per week by Treatment

Median and Quartiles

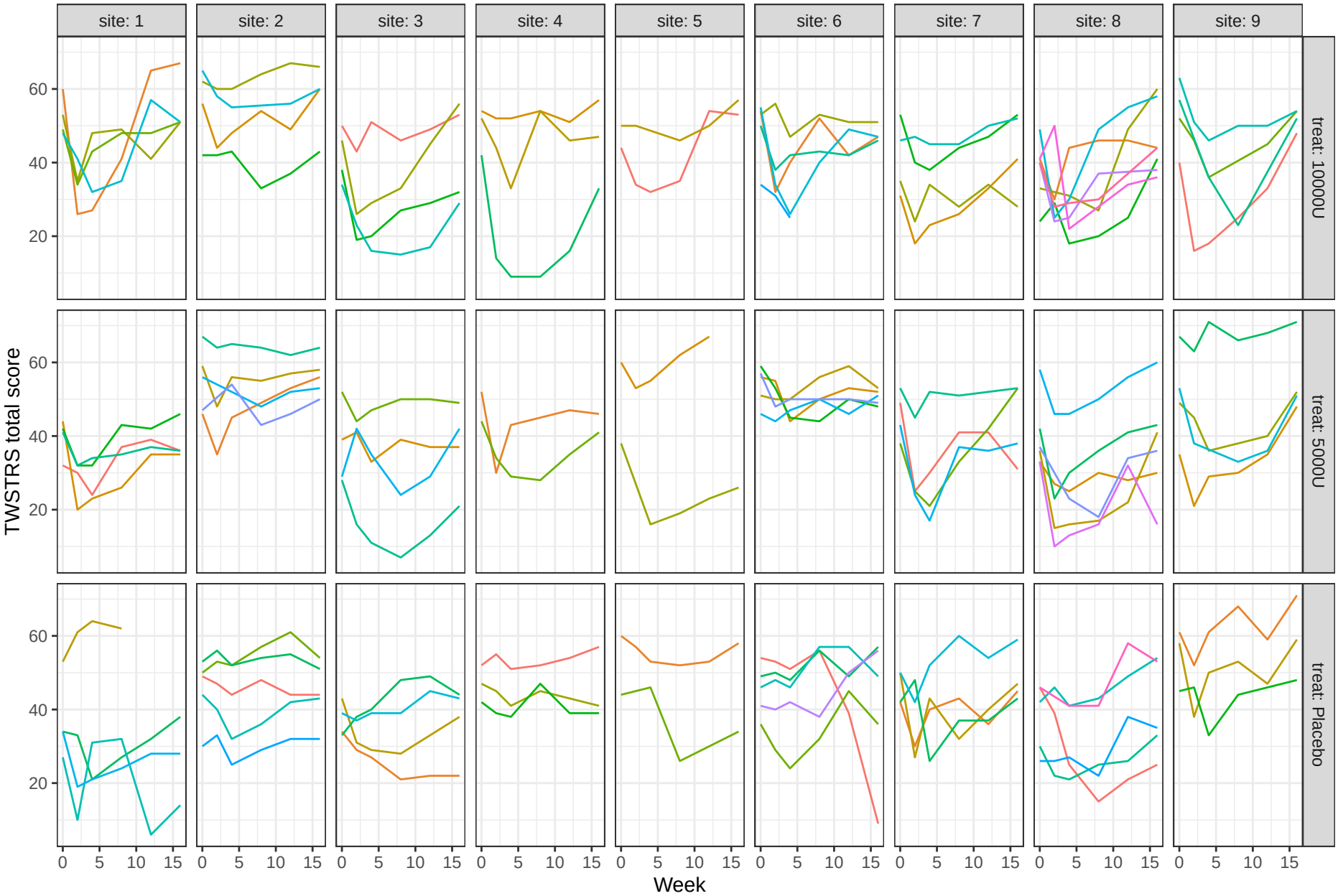


Spaghetti Plot of raw TWSTRS scores, by subject

```
ggplot(cdystonia, aes(x = week, y = twstrs,
                      col = factor(id))) +
    geom_line() +
    facet_grid(treat ~ site, labeller = "label_both") +
    guides(col = "none") +
    labs(x = "Week", y = "TWSTRS total score",
         title = "Raw TWSTRS scores, for n = 109 subjects")
```

- Result on next slide

Raw TWSTRS scores, by site, subject, week



How often were the subjects measured?

- Each of the 109 subjects were supposed to be measured at 0, 2, 4, 8, 12 and 16 weeks after treatment.

```
cdystonia %>% tabyl(week)
```

```
 week   n   percent
    0 109 0.1727417
    2 103 0.1632330
    4 106 0.1679873
    8 104 0.1648177
   12 104 0.1648177
   16 105 0.1664025
```

Actual Measurement Patterns

- Although each of the 109 subjects were supposed to be measured at 0, 2, 4, 8, 12 and 16 weeks after treatment, only 94 of the 109 subjects actually were.

```
table(tapply(cdystonia$week, cdystonia$uid,
             function(w)
                 paste(sort(unique(w)), collapse = ' ')))
```

```
          0          0 2 4   0 2 4 12 16       0 2 4 8
          1              1             3             1
 0 2 4 8 12 0 2 4 8 12 16    0 2 4 8 16   0 2 8 12 16
          1             94             1             2
 0 4 8 12 16       0 4 8 16
          4              1
```

Identify all of the baseline measures

- We want to use the baseline level of our outcome (`twstrs`) as a predictor going forward.

```
baseline <- cdystonia %>%
    filter(week == 0) %>%
    rename(twstrs_0 = twstrs)

baseline
```

```
# A tibble: 109 x 8
   uid    week site  id    treat      age sex   twstrs_0
   <fct> <dbl> <fct> <fct> <fct>    <dbl> <fct>    <dbl>
 1 1 1       0 1     1     5000U       65 F           32
 2 1 2       0 1     2     10000U      70 F           60
 3 1 3       0 1     3     5000U       64 F           44
 4 1 4       0 1     4     Placebo     59 F           53
 5 1 5       0 1     5     10000U      76 F           53
 6 1 6       0 1     6     10000U      59 F           49
```

Identify all follow-up measures

```
followup <- cdystonia %>%
    filter(week > 0) %>%
    select(uid, week, twstrs)

followup
```

```
# A tibble: 522 x 3
   uid    week twstrs
   <fct> <dbl>  <dbl>
 1 1 1       2     30
 2 1 1       4     24
 3 1 1       8     37
 4 1 1      12     39
 5 1 1      16     36
 6 1 2       2     26
 7 1 2       4     27
 8 1 2       8     41
```

Try to merge baseline and followup data

```
temp <- merge(baseline, followup, by = "uid")
temp
```

```
    uid week.x site id   treat age sex twstrs_0 week.y
1     1      0    1  1   5000U  65   F       32      2
2     1      0    1  1   5000U  65   F       32      4
3     1      0    1  1   5000U  65   F       32      8
4     1      0    1  1   5000U  65   F       32     12
5     1      0    1  1   5000U  65   F       32     16
6    10      0    1 10 Placebo  47   M       27      2
7    10      0    1 10 Placebo  47   M       27      4
8    10      0    1 10 Placebo  47   M       27      8
9    10      0    1 10 Placebo  47   M       27     12
10   10      0    1 10 Placebo  47   M       27     16
11   11      0    1 11  10000U  57   F       48      2
12   11      0    1 11  10000U  57   F       48      4
13   11      0    1 11  10000U  57   F       48      8
```

Merge the baseline and followup data

Let's clean things up a bit.

```
both <- merge(baseline, followup, by = "uid") %>%
    tibble() %>% select(-week.x) %>% rename(week = week.y)

both
```

```
# A tibble: 522 x 9
   uid   site  id    treat   age sex   twstrs_0  week twstrs
   <fct> <fct> <fct> <fct> <dbl> <fct>    <dbl> <dbl>  <dbl>
 1 1 1   1     1     5000U    65 F           32     2     30
 2 1 1   1     1     5000U    65 F           32     4     24
 3 1 1   1     1     5000U    65 F           32     8     37
 4 1 1   1     1     5000U    65 F           32    12     39
 5 1 1   1     1     5000U    65 F           32    16     36
 6 1 10  1     10    Plac~    47 M           27     2     10
 7 1 10  1     10    Plac~    47 M           27     4     31
 8 1 10  1     10    Plac~    47 M           27     8     32
```

OK, let's create a `datadist` to do `rms` modeling

```
dd <- datadist(both)
options(datadist = "dd")
```

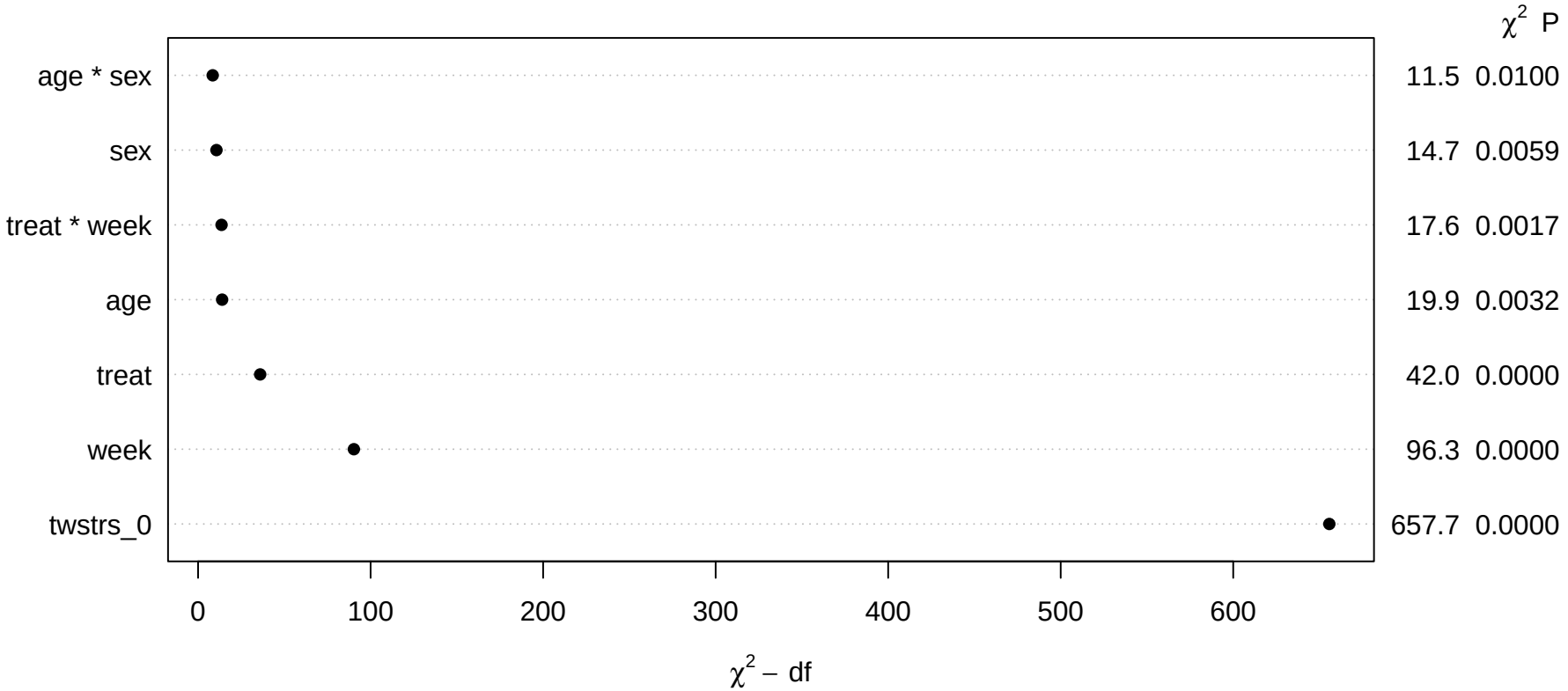
Model A: An Incredibly Naive Model

- Interaction terms let treatment effects vary by time, and lets the effect of sex depend on age, without assuming linearity.
- Ignore everything about the longitudinal nature of the data, and pretend that each of our 522 follow-up observations of TWSTRS comes from a different individual.
- Actually, remember that we only have 109 subjects, and most are represented multiple times in our follow-up data.
- So building this Model A is a very bad idea.

```
modelA <- ols(twstrs ~ treat * rcs(week, 3) +
                       rcs(twstrs_0, 3) +
                       rcs(age, 4) * sex,
              data = both)
```

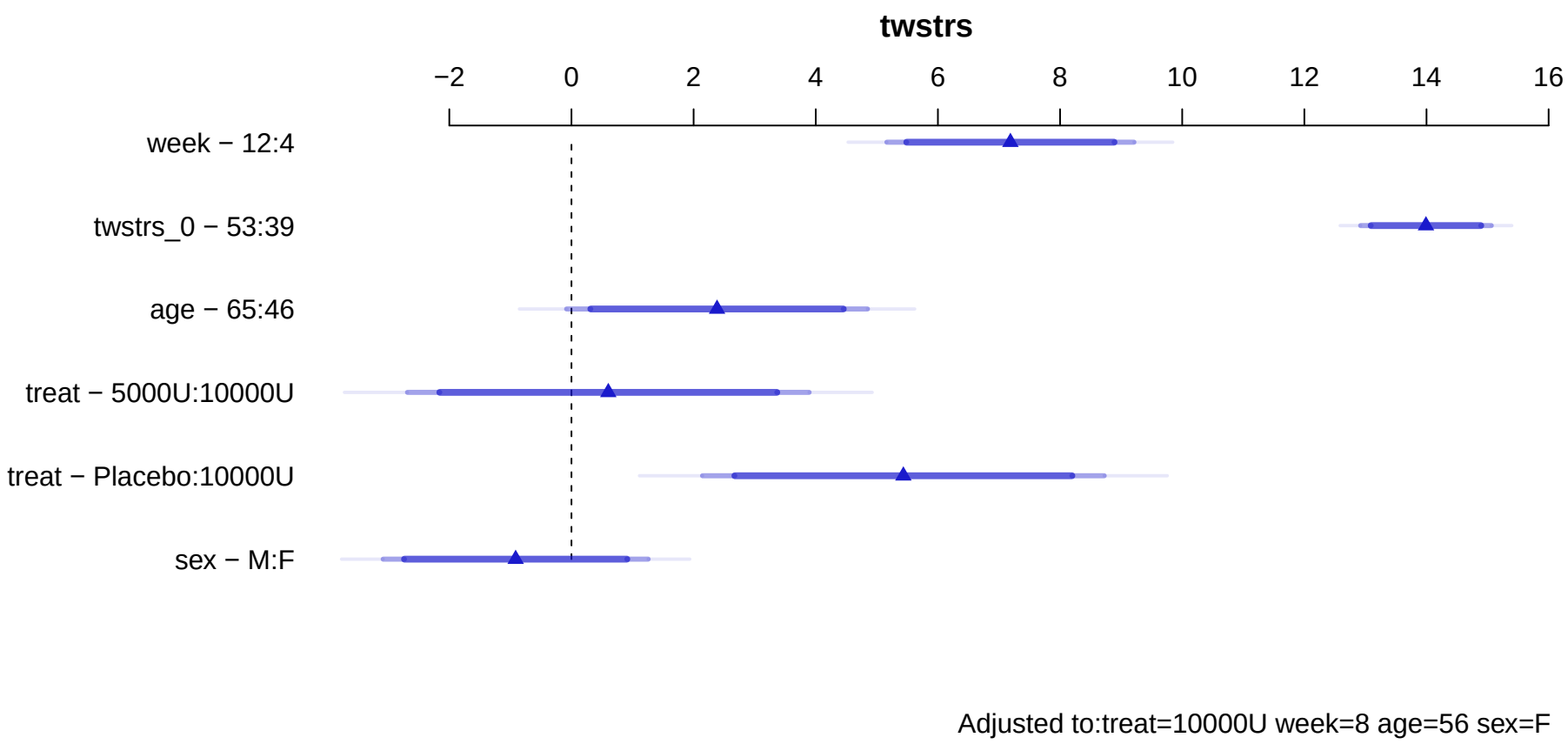
Model A: ANOVA results

```
plot(anova(modelA))
```



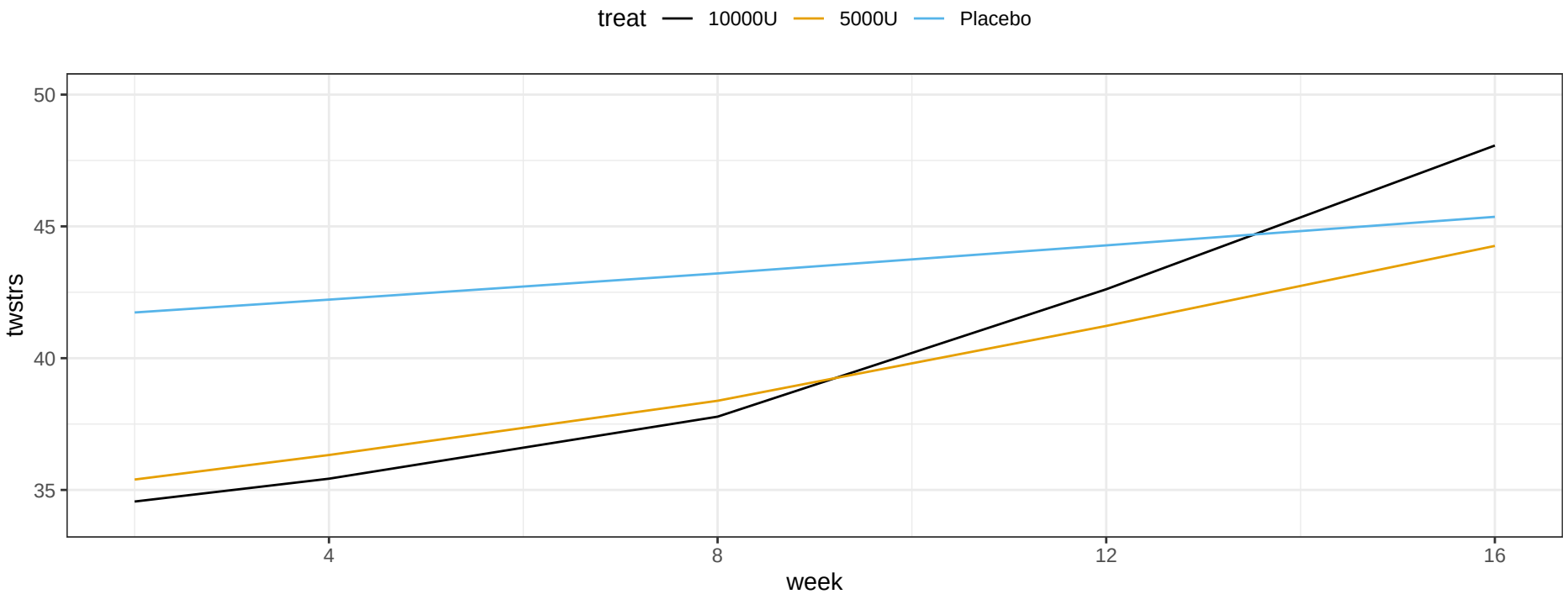
Model A: `summary` results

```
plot(summary(modelA))
```

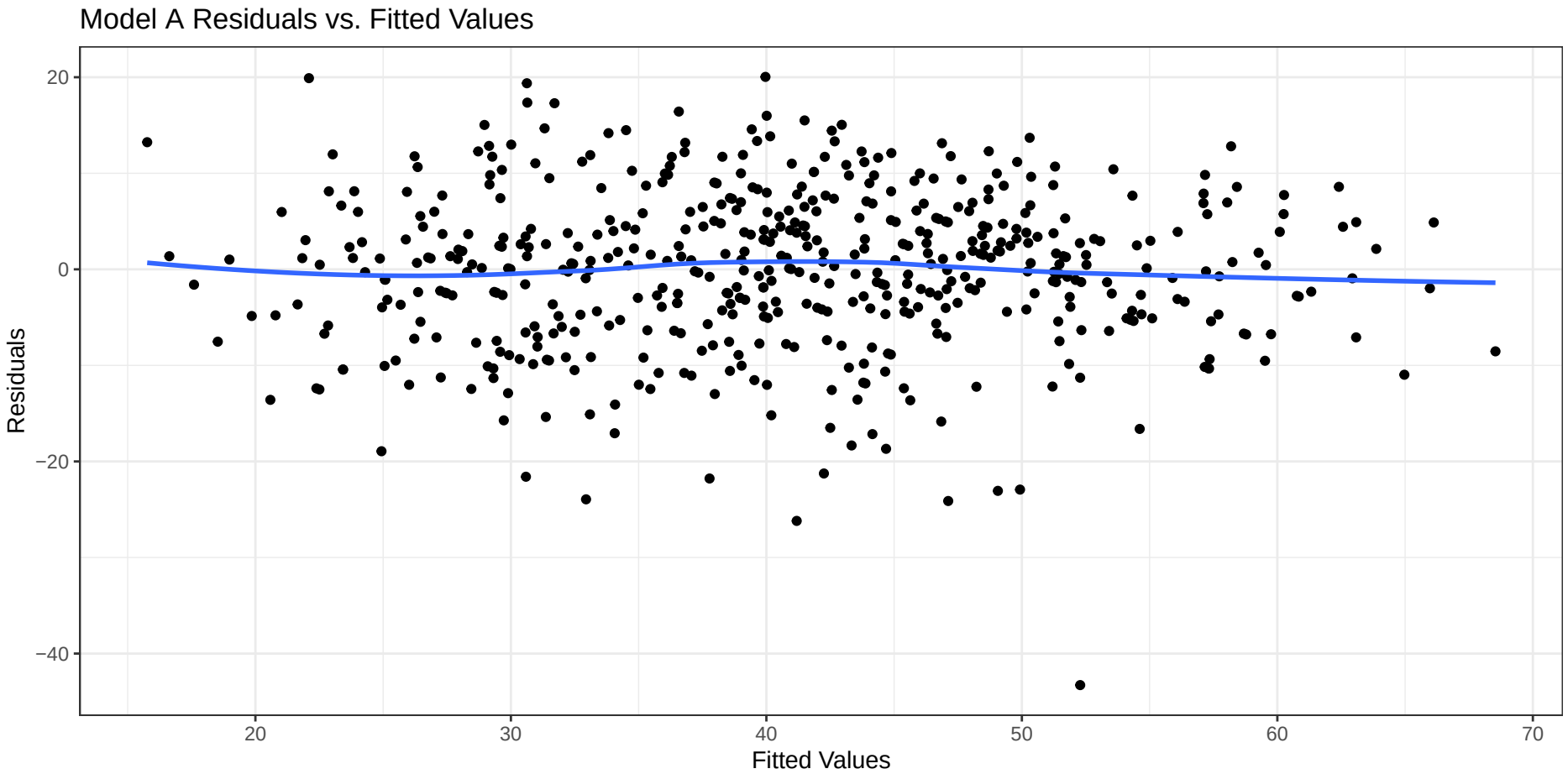


Model A: Does the treatment seem to help?

```
ggplot(Predict(modelA, week, treat, conf.int = FALSE),
       adj.subtitle = FALSE, legend.position = "top") +
    lims(y = c(25, 60))
```



Model A: Residuals vs. Fitted Values



But Model A is completely insufficient.

We have to take into account the correlations between subjects, and we also want to account for the entire time course.

- Generalized Least Squares will get us to a better place.

What should our correlation structure be?

We stay with baseline adjustment and consider a variety of correlation structures, with constant variance.

- Time is modeled as a restricted cubic spline with 3 knots, because there are only 3 unique interior values of week.
- On the next couple of slides, six correlation patterns are attempted. In general it is better to use scientific knowledge to guide the choice of the correlation structure.

Check all of the possible correlation structures?

```
cp <- list(corCAR1, corExp, corCompSymm,
           corLin, corGaus, corSpher)

z <- vector( 'list' , length(cp))

for(k in 1:length(cp) ){
    z[[k]] <- gls(twstrs ~ treat * rcs(week, 3) +
                      rcs(twstrs_0 , 3) + rcs(age, 4) * sex ,
                  data=both,
                  correlation=cp[[k]]( form = ~ week | uid))
}
```

Checking ANOVA Results for AIC and BIC

```
anova(z[[1]], z[[2]], z[[3]], z[[4]], z[[5]], z[[6]])
```

```
       Model df      AIC      BIC    logLik
z[[1]]     1 20 3553.906 3638.357 -1756.953
z[[2]]     2 20 3553.906 3638.357 -1756.953
z[[3]]     3 20 3587.974 3672.426 -1773.987
z[[4]]     4 20 3575.079 3659.531 -1767.540
z[[5]]     5 20 3621.081 3705.532 -1790.540
z[[6]]     6 20 3570.958 3655.409 -1765.479
```

- Which approach shows the best AIC and BIC?

Checking ANOVA Results for AIC and BIC

```
anova(z[[1]], z[[2]], z[[3]], z[[4]], z[[5]], z[[6]])
```

```
       Model df      AIC      BIC    logLik
z[[1]]     1 20 3553.906 3638.357 -1756.953
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z[[3]]     3 20 3587.974 3672.426 -1773.987
z[[4]]     4 20 3575.079 3659.531 -1767.540
z[[5]]     5 20 3621.081 3705.532 -1790.540
z[[6]]     6 20 3570.958 3655.409 -1765.479
```

- Which approach shows the best AIC and BIC?
- We'll use option 1 (the continuous-time AR1) going forward.

Fit the Continuous Time AR1 model using `Gls`

```
modelB <- Gls(twstrs ~ treat * rcs(week, 3) +
                  rcs(twstrs_0, 3) +
                  rcs(age, 4) * sex,
              data = both,
              correlation = corCAR1(form = ~ week | uid))
```

Model B output (including AR1 parameter)

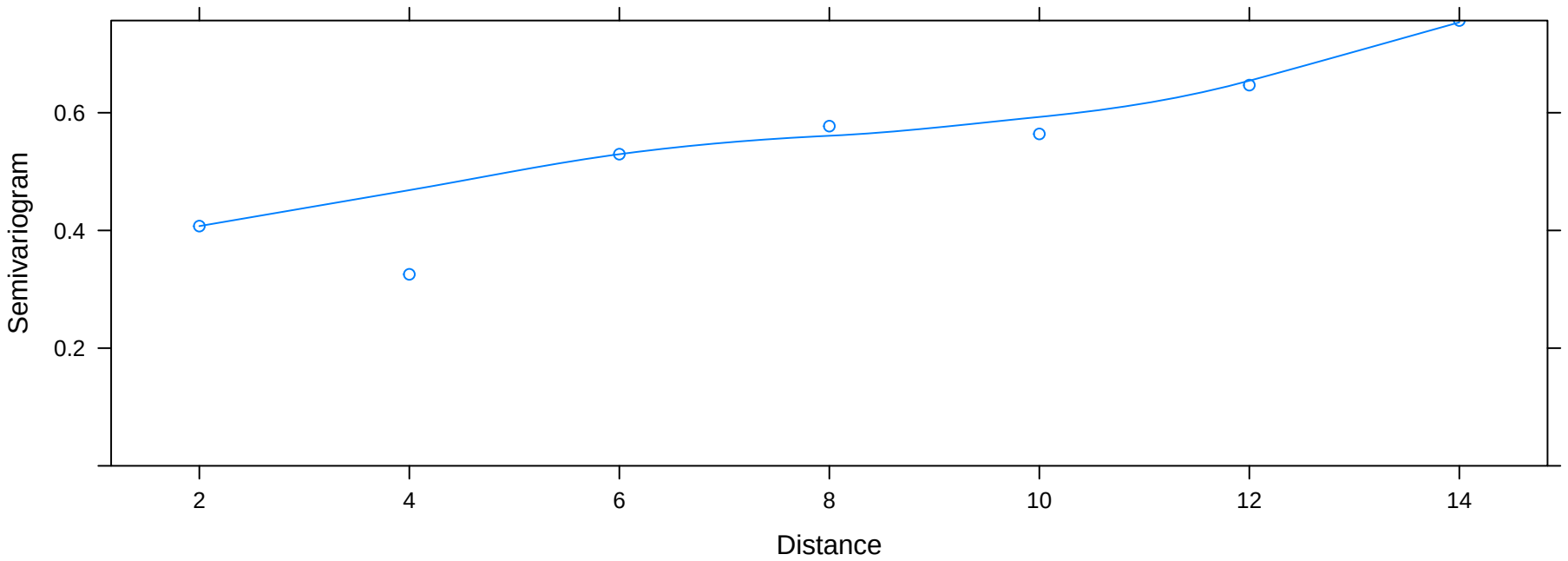
```
> modelA
Generalized Least Squares Fit by REML

 Gls(model = twstrs ~ treat * rcs(week, 3) + rcs(twstrs_0, 3) +
     rcs(age, 4) * sex, data = both, correlation = corCAR1(form = ~week |
     uid))


    Obs  522    Log-restricted-likelihood-1756.95
 Clusters108                         Model d.f. 17
    g 11.334                         sigma  8.5917
                                     d.f.      504
```

```
Correlation Structure: Continuous AR(1)
 Formula: ~week | uid
 Parameter estimate(s):
      Phi
0.8666689
```

- This value $\hat{\rho} = 0.867$, is the estimate of the correlation between two measurements taken one week apart on the same subject.
- The estimated correlation for measurements 4 weeks apart is $0.867^4 = 0.57$.

Variogram to check assumptions

```
vargB <- Variogram(modelB, form = ~ week | uid)
plot(vargB)
```



- The empirical variogram is largely in agreement with the pattern dictated by AR(1).

Model B output (Coefficients)

	Coef	S.E.	t	Pr(>|t|)
Intercept	-0.3093	11.8804	-0.03	0.9792
treat=5000U	0.4344	2.5962	0.17	0.8672
treat=Placebo	7.1433	2.6133	2.73	0.0065
week	0.2879	0.2973	0.97	0.3334
week'	0.7313	0.3078	2.38	0.0179
twstrs_0	0.8071	0.1449	5.57	<0.0001
twstrs_0'	0.2129	0.1795	1.19	0.2360
age	-0.1178	0.2346	-0.50	0.6158
age'	0.6968	0.6484	1.07	0.2830
age''	-3.4018	2.5599	-1.33	0.1845
sex=M	24.2802	18.6208	1.30	0.1929
treat=5000U * week	0.0745	0.4221	0.18	0.8599
treat=Placebo * week	-0.1256	0.4243	-0.30	0.7674
treat=5000U * week'	-0.4389	0.4363	-1.01	0.3149
treat=Placebo * week'	-0.6459	0.4381	-1.47	0.1411
age * sex=M	-0.5846	0.4447	-1.31	0.1892
age' * sex=M	1.4652	1.2388	1.18	0.2375
age'' * sex=M	-4.0338	4.8123	-0.84	0.4023

Check residuals for assumptions?

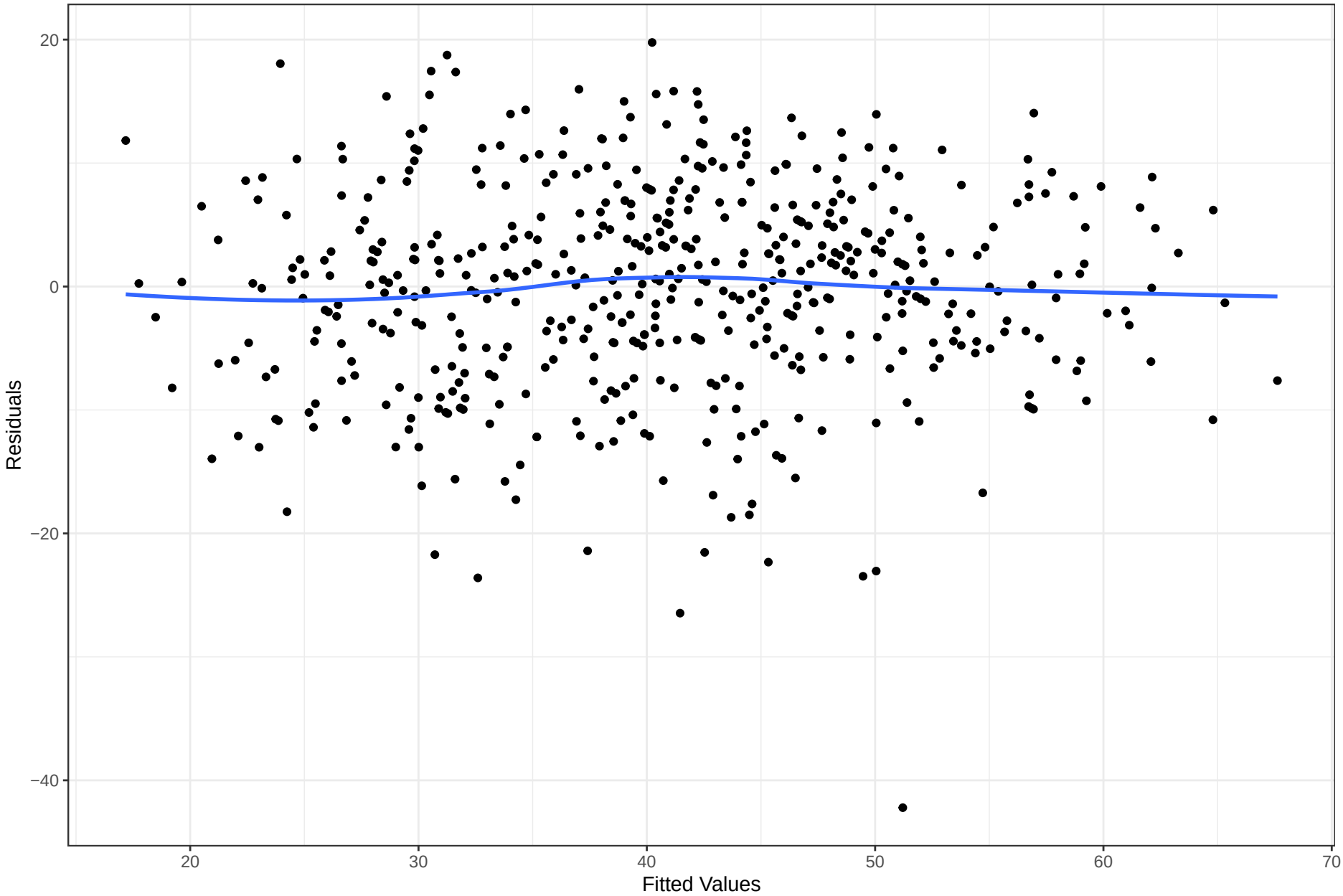
We're mostly concerned about constant variance and Normality of our residuals.

```
both <- both %>%
    mutate(.res = resid(modelB), .fit = fitted(modelB))
```

```
ggplot(both, aes(x = .fit, y = .res)) +
    geom_point() +
    geom_smooth(method = "loess",
                formula = y ~ x, se = FALSE) +
    labs(y = "Residuals", x = "Fitted Values",
         title = "Model B Residuals vs. Fitted Values")
```

- Plot shown on next slide.

Model B Residuals vs. Fitted Values



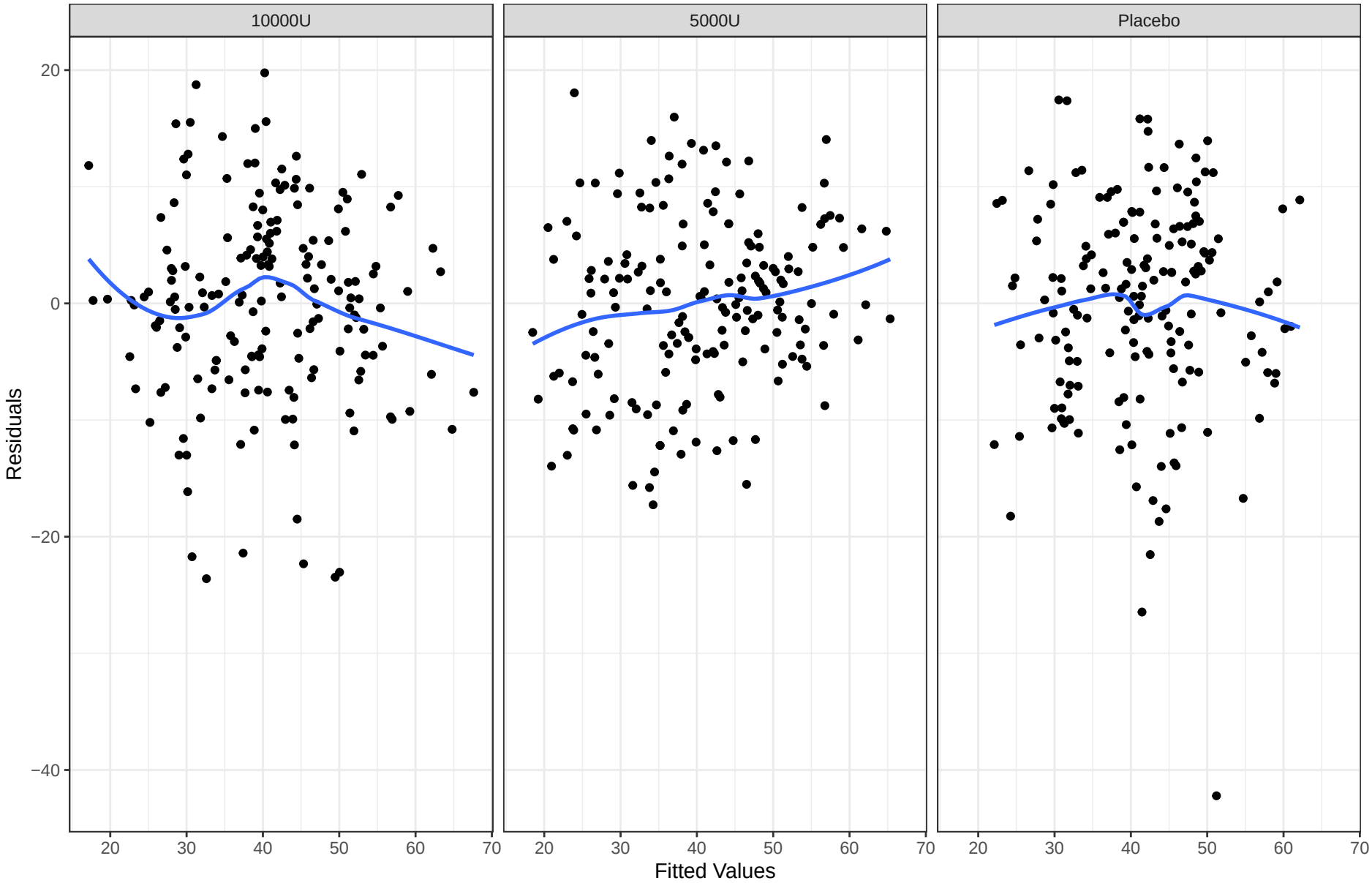
Within each treatment group?

```
ggplot(both, aes(x = .fit, y = .res)) +
    geom_point() +
    geom_smooth(method = "loess",
                formula = y ~ x, se = FALSE) +
    facet_grid(~ treat) +
    labs(y = "Residuals", x = "Fitted Values",
         title = "Model B Residuals vs. Fitted Values",
         subtitle = "within each Treatment")
```

- Plot shown on next slide.

Model B Residuals vs. Fitted Values

within each Treatment

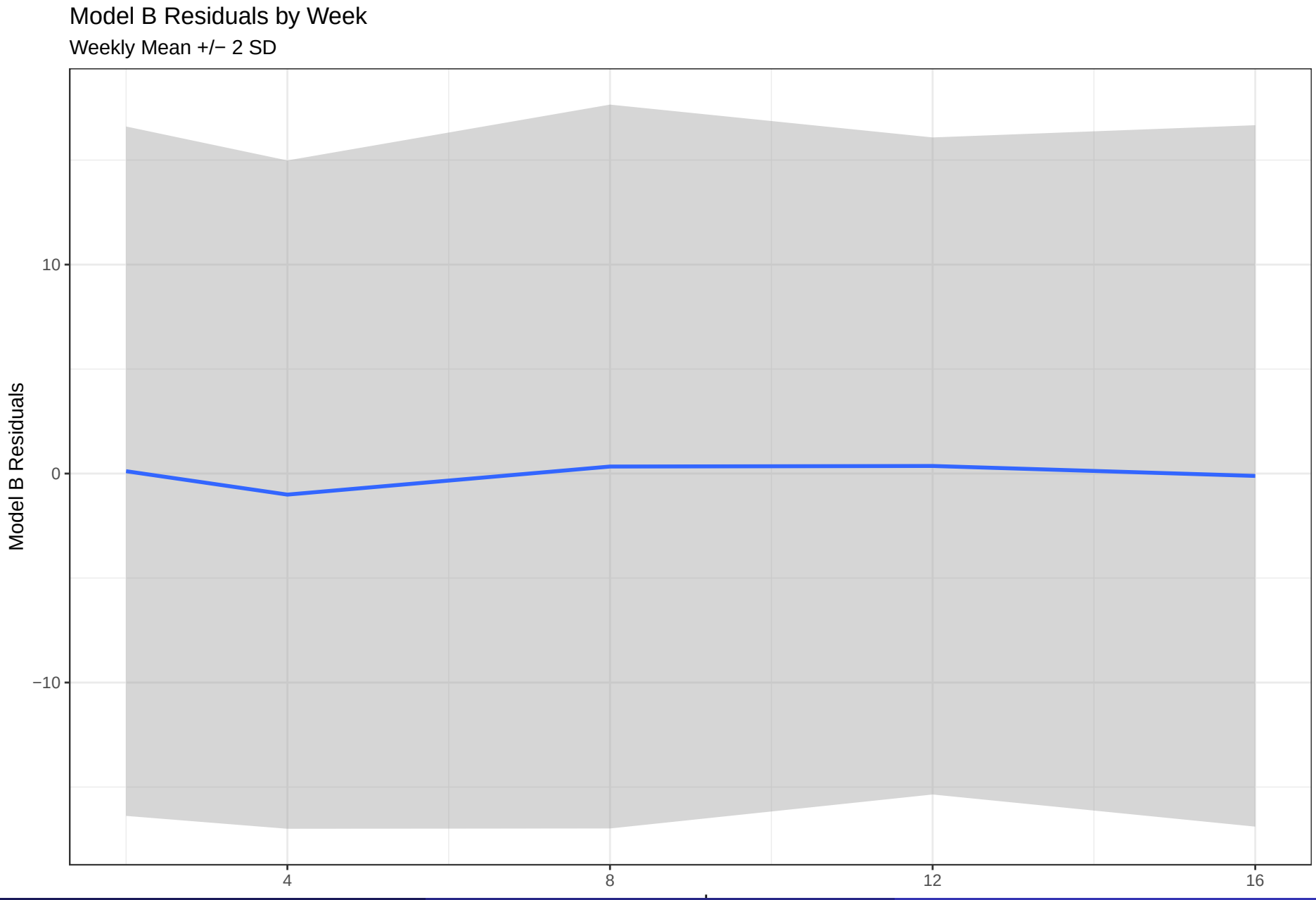


Model B Residuals by Week

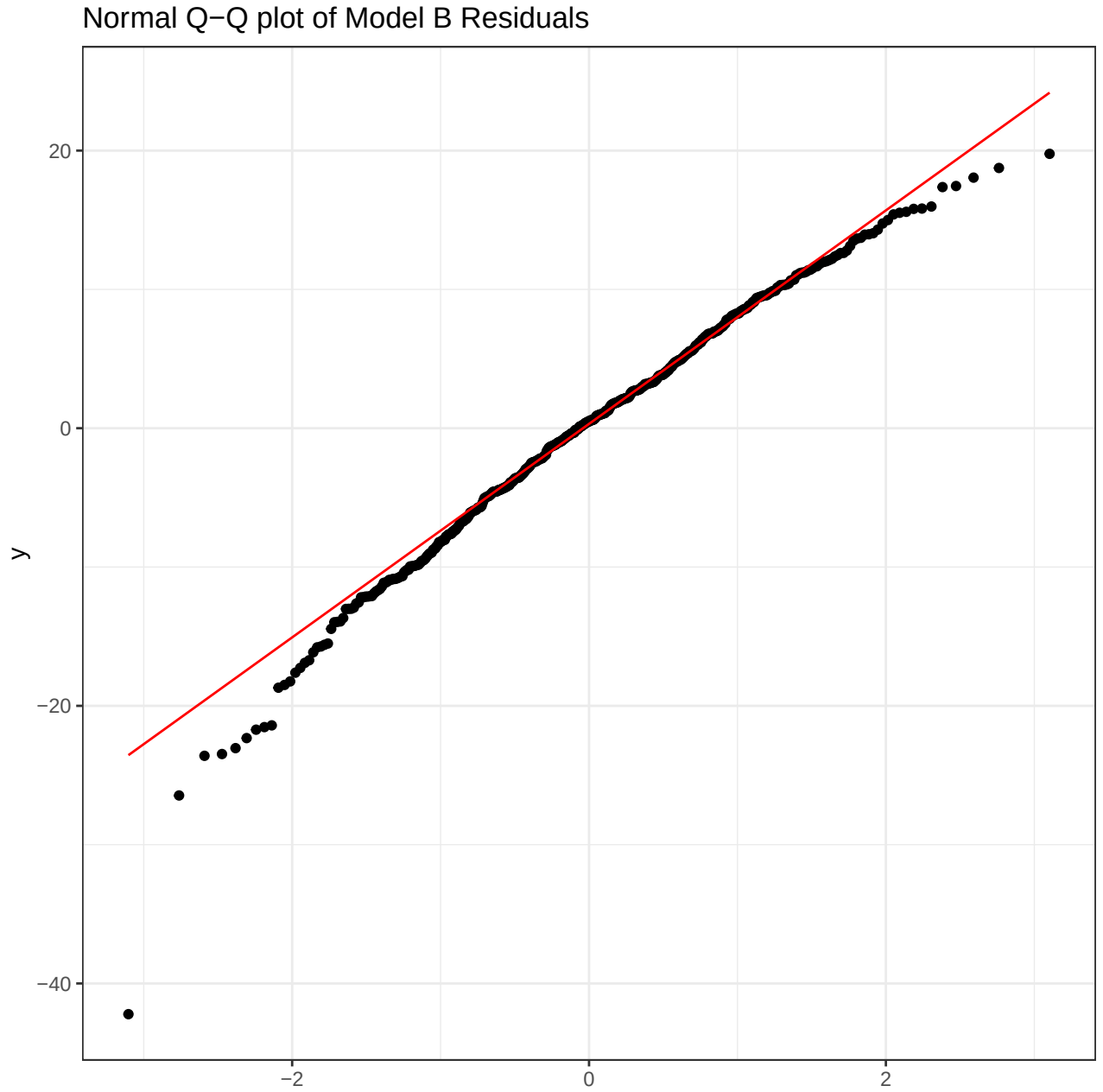
```
ggplot(both, aes(x = week, y = .res)) +
    stat_summary(fun.data = "mean_sdl",
                 geom = "smooth", se = TRUE) +
    labs(y = "Model B Residuals",
         title = "Model B Residuals by Week",
         subtitle = "Weekly Mean +/- 2 SD")
```

- Plot shown on next slide.

Model B Residuals by Week



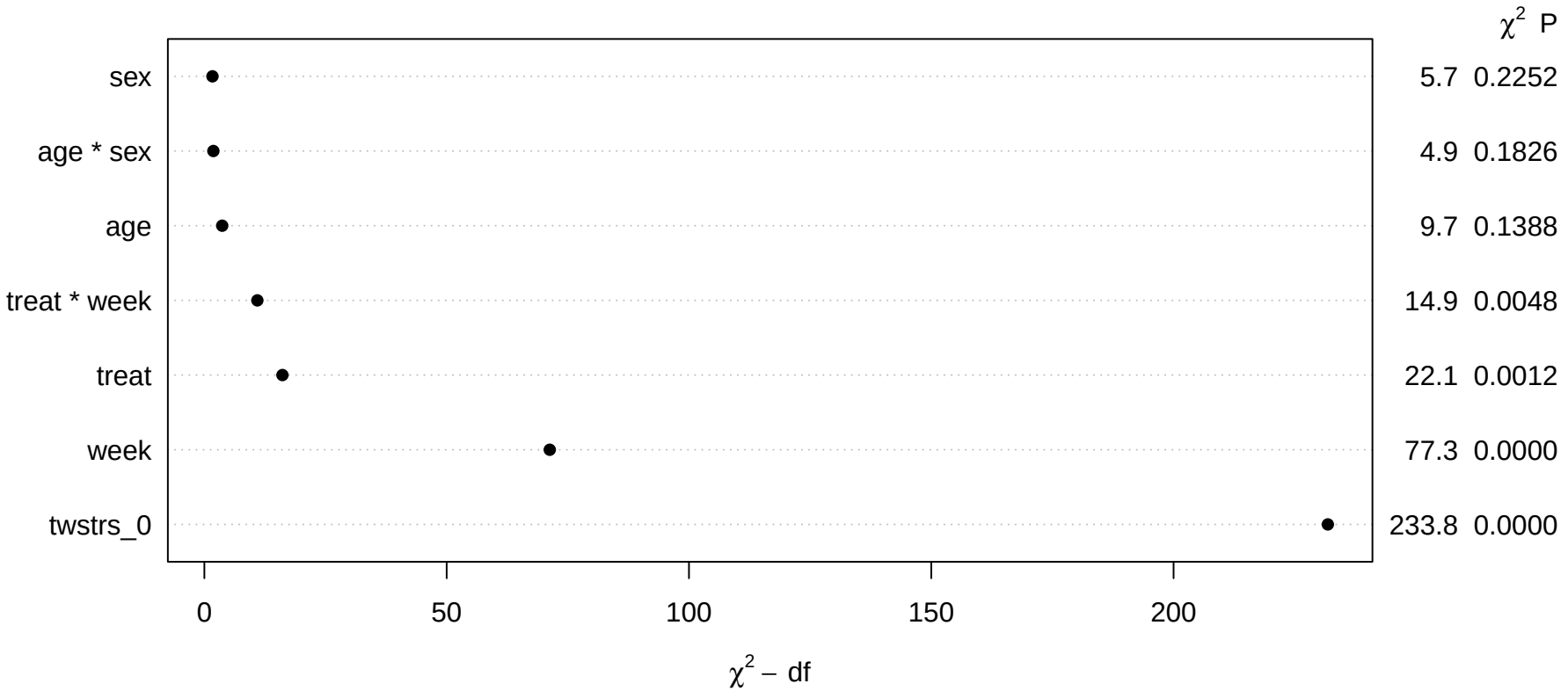
Normal Q-Q plot of Residuals



ANOVA Results from Model B

- As expected, the baseline value of TWSTRS dominates.

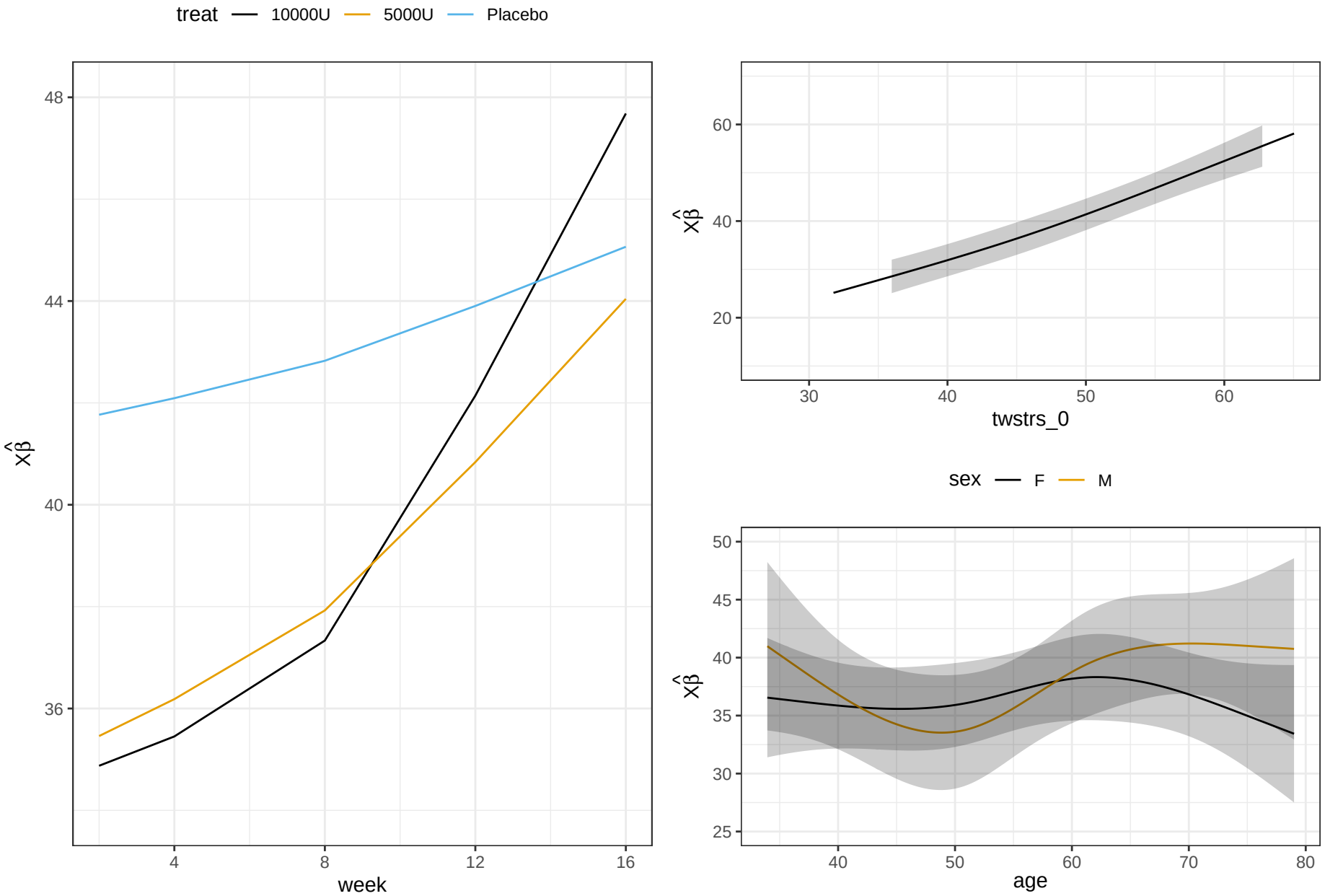
```
plot(anova(modelB))
```



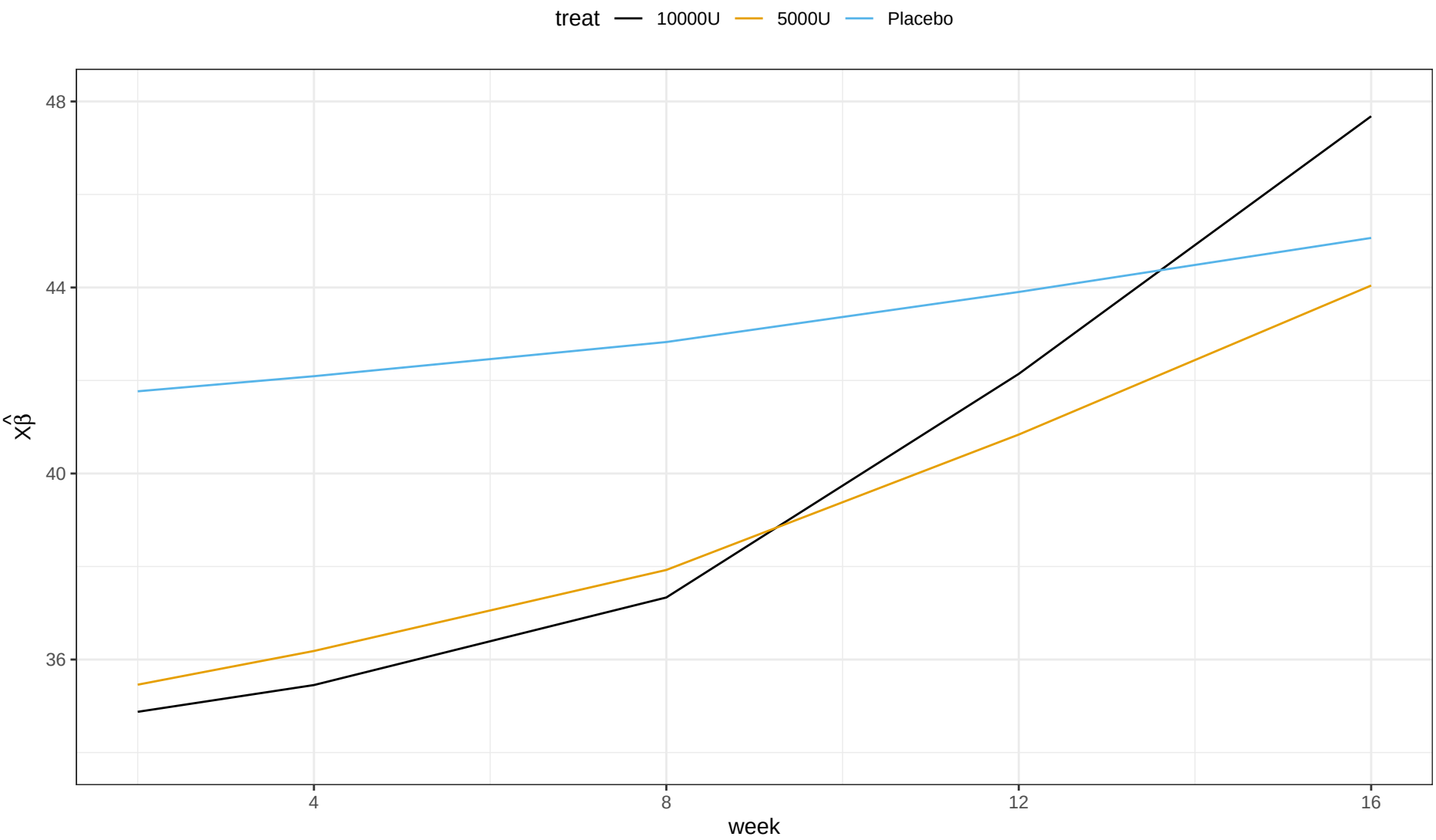
Estimated effects of time, baseline TWSTRS, age and sex

- Here's the code. Results on next slide.

```
p1 <- ggplot(Predict(modelB, week, treat, conf.int = FALSE),
        adj.subtitle = FALSE, legend.position = "top") +
    lims(y = c(25, 60))
p2 <- ggplot(Predict(modelB, twstrs_0), adj.subtitle = FALSE)
    lims(y = c(25, 60))
p3 <- ggplot(Predict(modelB, age, sex), adj.subtitle = FALSE,
             legend.position = "top") +
    lims(y = c(25, 60))

p1 + (p2/p3)
```

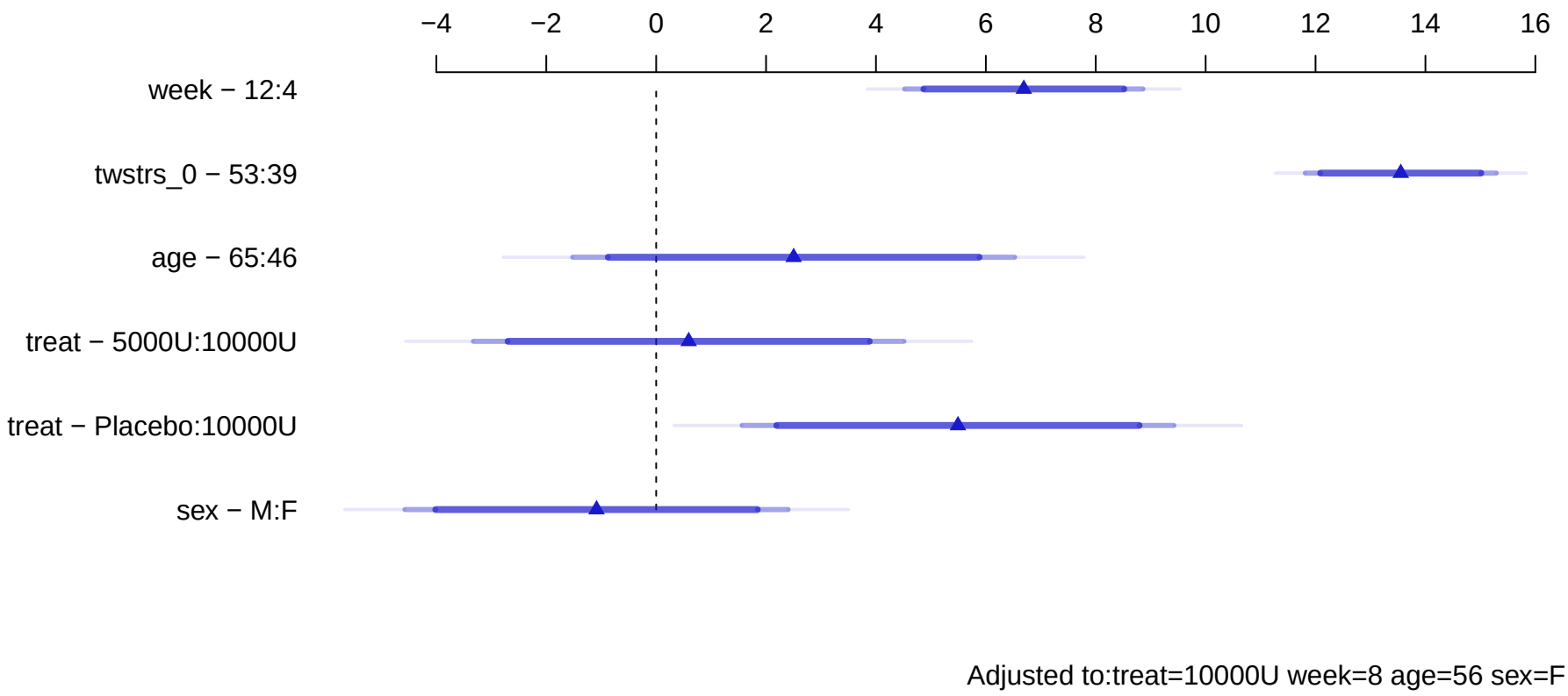

treat
10000U
5000U
Placebo
48
44
40
36
Xβ̂
4
8
12
16
week
60
40
20
Xβ̂
30
40
50
60
twstrs_0
sex
F
M
50
45
40
35
30
25
Xβ̂
40
50
60
70
80
age

Does the treatment help?



Get Estimates

```
plot(summary(modelB))
```



What's in the summary?

```
> summary(modelB)
             Effects                  Response : twstrs

 Factor                    Low High Diff. Effect   S.E.     Lower 0.95 Upper 0.95
 week                       4  12    8     6.69100 1.10570  4.5238     8.8582
 twstrs_0                  39  53   14    13.55100 0.88618 11.8140    15.2880
 age                       46  65   19     2.50270 2.05140 -1.5179     6.5234
 treat - 5000U:10000U       1   2   NA     0.59167 1.99830 -3.3249     4.5083
 treat - Placebo:10000U     1   3   NA     5.49300 2.00430  1.5647     9.4212
 sex - M:F                  1   2   NA    -1.08500 1.77860 -4.5711     2.4011

Adjusted to: treat=10000U week=8 age=56 sex=F
```

Summary for a different Week and Treatment reference?

```
> summary(modelB, week = 4, treat = "Placebo")
             Effects                  Response : twstrs

 Factor                    Low High Diff. Effect  S.E.     Lower 0.95 Upper 0.95
 week                       4  12    8     1.8111 1.13950  -0.42229    4.0444
 twstrs_0                  39  53   14    13.5510 0.88618  11.81400   15.2880
 age                       46  65   19     2.5027 2.05140  -1.51790    6.5234
 treat - 10000U:Placebo     3   1   NA    -6.6411 1.79270 -10.15500   -3.1274
 treat - 5000U:Placebo      3   2   NA    -5.9086 1.81610  -9.46820   -2.3490
 sex - M:F                  1   2   NA    -1.0850 1.77860  -4.57110    2.4011

Adjusted to: treat=Placebo week=4 age=56 sex=F
```

Compare low dose with placebo at each time

```
k1 <- contrast(modelB,
        list(week = c(2, 4, 8, 12, 16), treat = "5000U"),
        list(week = c(2, 4, 8, 12, 16), treat = "Placebo"))
```

- Results on next slide.

Compare low dose with placebo at each time

```
> print(k1, digits = 3)
    week twstrs_0 age sex Contrast S.E.  Lower  Upper     Z Pr(>|z|)
1      2       46  56   F    -6.31 2.10 -10.43 -2.186 -3.00   0.0027
2      4       46  56   F    -5.91 1.82  -9.47 -2.349 -3.25   0.0011
3      8       46  56   F    -4.90 2.01  -8.85 -0.953 -2.43   0.0150
4*    12       46  56   F    -3.07 1.75  -6.49  0.361 -1.75   0.0795
5*    16       46  56   F    -1.02 2.10  -5.14  3.092 -0.49   0.6260

Redundant contrasts are denoted by *

Confidence intervals are 0.95 individual intervals
```

Compare high dose with placebo at each time

```
k2 <- contrast(modelB,
        list(week = c(2, 4, 8, 12, 16), treat = "10000U"),
        list(week = c(2, 4, 8, 12, 16), treat = "Placebo"))
```

- Results on next slide.

Compare high dose with placebo at each time

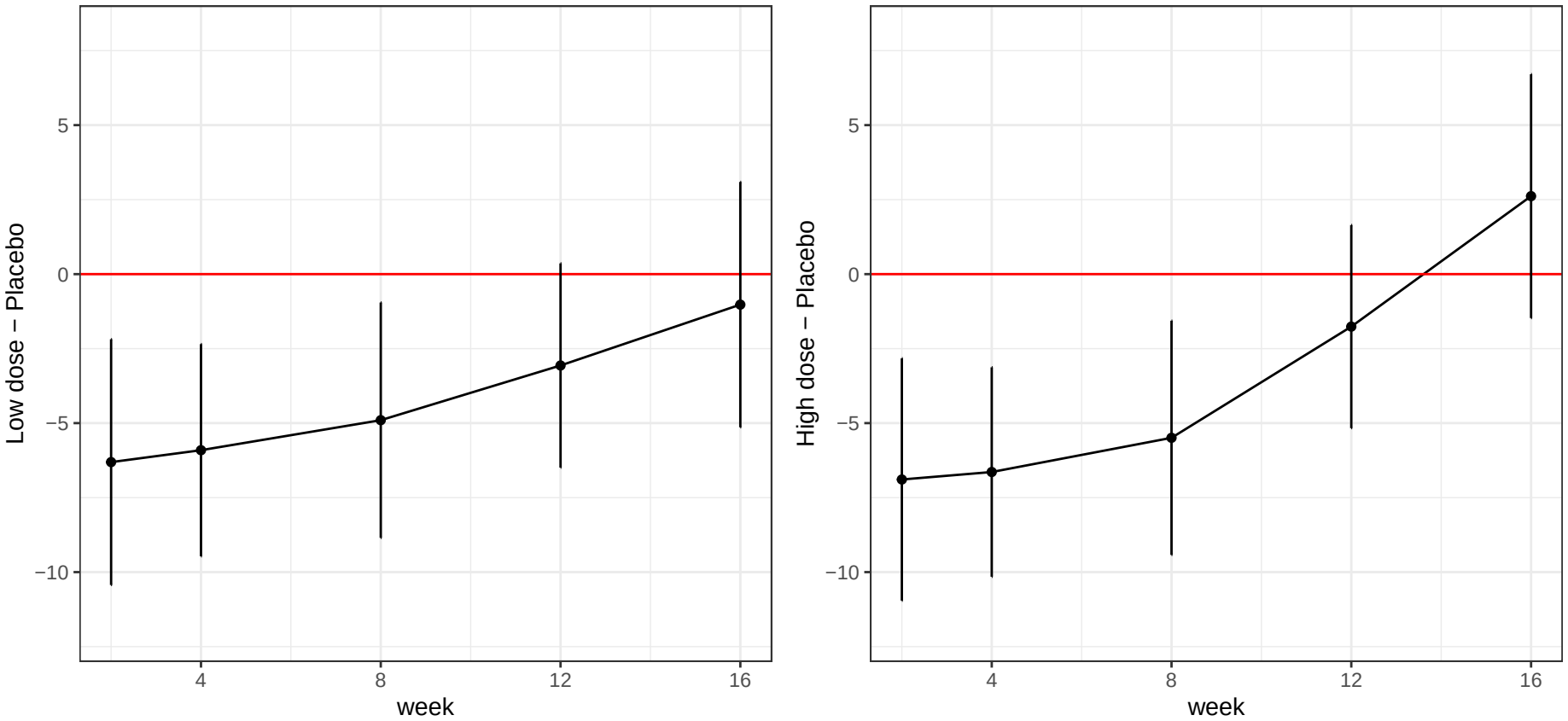
```
> print(k2, digits = 3)
    week twstrs_0 age sex Contrast S.E.  Lower Upper     Z Pr(>|z|)
1      2       46  56   F    -6.89 2.07 -10.96 -2.83 -3.32   0.0009
2      4       46  56   F    -6.64 1.79 -10.15 -3.13 -3.70   0.0002
3      8       46  56   F    -5.49 2.00  -9.42 -1.56 -2.74   0.0061
4*    12       46  56   F    -1.76 1.74  -5.17  1.65 -1.01   0.3109
5*    16       46  56   F     2.62 2.09  -1.47  6.71  1.25   0.2099

Redundant contrasts are denoted by *

Confidence intervals are 0.95 individual intervals
```

Contrast Plots (most of the code)

```
k1_t <- as_tibble(k1[c("week", "Contrast", "Lower", "Upper")])
k2_t <- as_tibble(k2[c("week", "Contrast", "Lower", "Upper")])

p1 <- ggplot(k1_t, aes(x = week, y = Contrast)) +
    geom_point() + geom_line() +
    geom_hline(yintercept = 0, col = "red") +
    geom_errorbar(aes(ymin = Lower, ymax = Upper), width = 0) +
    lims(y = c(-12, 8)) + labs(y = "Low dose - Placebo")

p2 <- ggplot(k2_t, aes(x = week, y = Contrast)) +
    geom_point() + geom_line() +
    geom_hline(yintercept = 0, col = "red") +
    geom_errorbar(aes(ymin = Lower, ymax = Upper), width = 0) +
    lims(y = c(-12, 8)) + labs(y = "High dose - Placebo")

p1 + p2 +
    plot_annotation(title = "Contrasts and 0.95 confidence lim
```

Contrasts with 95% Confidence Intervals

Contrasts and 0.95 confidence limits from GLS fit (Model B)

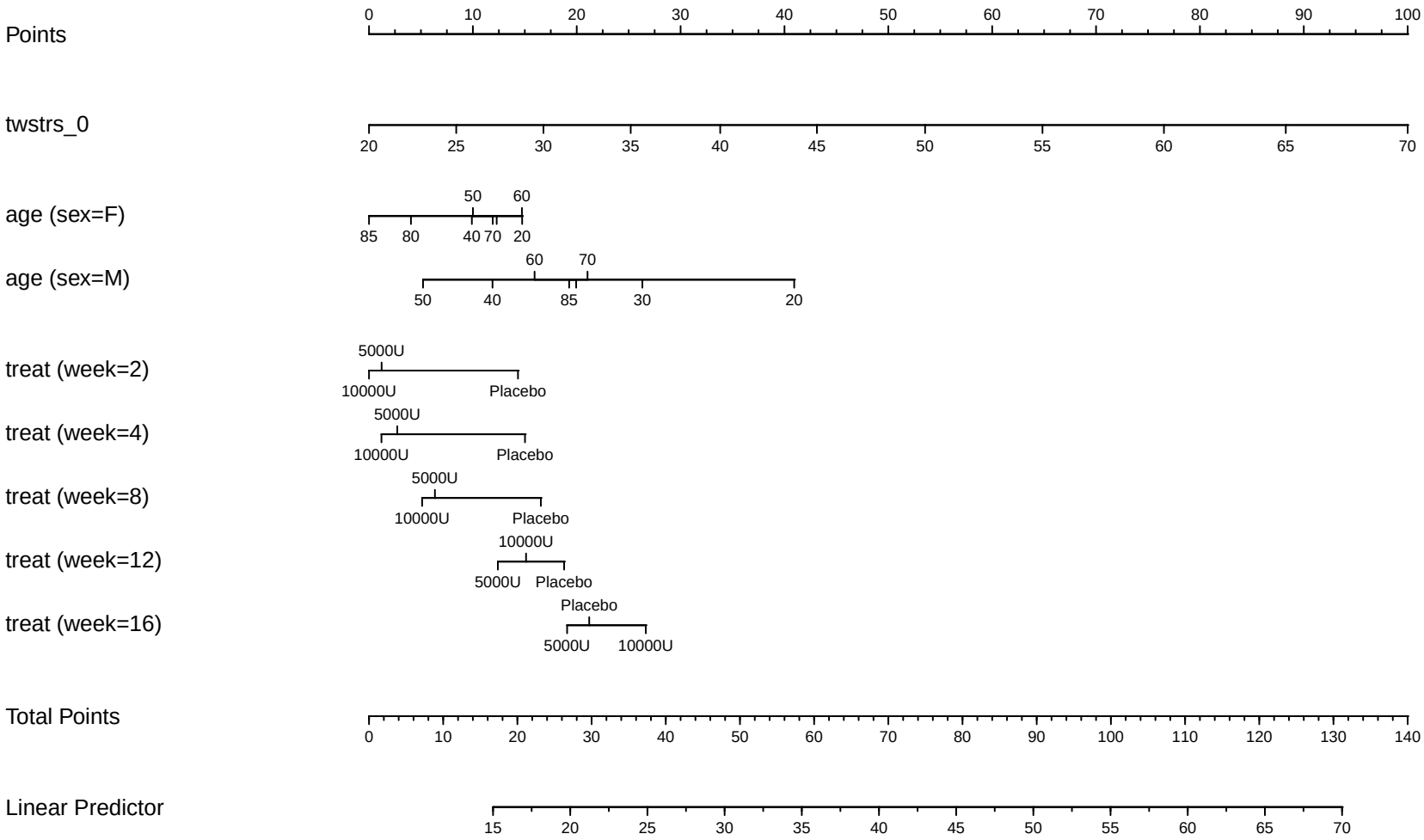


- The treatment, despite causing an early improvement, wears off by 16 weeks at which time no benefit is seen.

Nomogram to obtain predicted values (code)

```
nomB <- nomogram(modelB, age = c(seq(20, 80, by = 10), 85))
plot(nomB, cex.axis = 0.6, cex.var = 0.8, lmgp = 0.25)
```

Model B Nomogram to get predicted values



Next Time

- Setup for Quiz 2
- Feedback on Minute Paper after Class 24
- Other interesting things