432 Class 19 Slides

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Today's Agenda

- Cox models for time-to-event data
 - Returning to the breast cancer trial
 - Using cph from rms to fit a Cox model
- Fitting Robust Linear Models
 - Using Huber weights
 - Using bisquare weights
 - Using Quantile Regression

Cox Models

Preliminaries for Cox Regression Models

```
library(here); library(janitor); library(magrittr)
library(broom); library(knitr); library(rms)
library(survival); library(survminer)
library(tidyverse)
theme set(theme bw())
brca <- read_csv(here("data", "brca.csv")) %>%
    type.convert(as.is = FALSE)
```

Recap of What We Did Tuesday

We're working with data from a trial of three treatments for breast cancer

- Main tibble is brca containing treat = S_CT, S_IT, S_Both and age at baseline
- Time to event data are gathered in trial_weeks and last_alive which we used to create a survival object we named S.
- Created Kaplan-Meier estimate, kmfit to compare the treat results
- Then built a Cox model for treatment, called mod_T using coxph.

Now, we'll

- incorporate the covariate (age) into the model
- use cph from the rms package to fit a Cox model that incorporates some non-linearity

Create survival object

- trial_weeks: time in the study, in weeks, to death or censoring
- last_alive: 1 if alive at last follow-up (and thus censored), 0 if dead

```
So last_alive = 0 if the event (death) occurs.
```

```
brca$S <- with(brca, Surv(trial_weeks, last_alive == 0))
head(brca$S)</pre>
```

```
[1] 102 192 73 58+ 48+ 182+
```

Fit Cox Model mod_T: Treatment alone

```
mod T <- coxph(S ~ treat, data = brca)
mod T
Call:
coxph(formula = S ~ treat, data = brca)
           coef exp(coef) se(coef) z
treatS_CT 0.8313 2.2963 0.6547 1.270 0.204
treatS IT 0.2481 1.2816 0.6740 0.368 0.713
Likelihood ratio test=1.75 on 2 df, p=0.4164
n= 31, number of events= 15
```

Fit Cox Model mod_AT: Age + Treatment

```
mod_AT <- coxph(S ~ age + treat, data = brca)</pre>
mod AT
Call:
coxph(formula = S ~ age + treat, data = brca)
            coef exp(coef) se(coef) z
age 0.07807 1.08119 0.03672 2.126 0.0335
treatS CT 0.59960 1.82139 0.65741 0.912 0.3617
treatS IT 0.28799 1.33375 0.68566 0.420 0.6745
Likelihood ratio test=6.99 on 3 df, p=0.07224
```

n= 31, number of events= 15

Interpreting the Coefficients of mod_AT

```
tidy(mod_AT, exponentiate = TRUE, conf.int = TRUE) %>%
  select(term, estimate, std.error, conf.low, conf.high) %>%
  kable(digits = 2)
```

term	estimate	std.error	conf.low	conf.high
age	1.08	0.04	1.01	1.16
$treatS_CT$	1.82	0.66	0.50	6.61
treatS_IT	1.33	0.69	0.35	5.11

• If Harry and Sally receive the same treat but Harry is one year older, the model estimates Harry will have 1.08 times the hazard of Sally (95% CI 1.01, 1.16).

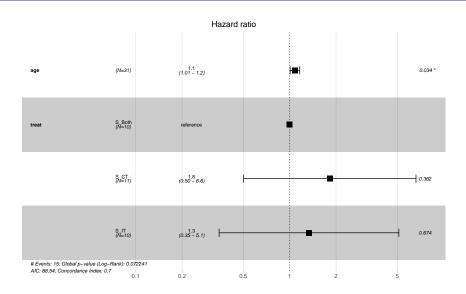
Interpreting the Coefficients of mod_AT

```
tidy(mod_AT, exponentiate = TRUE, conf.int = TRUE) %>%
  select(term, estimate, std.error, conf.low, conf.high) %>%
  kable(digits = 2)
```

term	estimate	std.error	conf.low	conf.high
age	1.08	0.04	1.01	1.16
$treatS_CT$	1.82	0.66	0.50	6.61
$treatS_IT$	1.33	0.69	0.35	5.11

- If Harry receives S_CT and Sally receives S_Both, and they are the same age, the model estimates Harry will have 1.82 times the hazard of Sally (95% CI 0.50, 6.61).
- If Cyrus receives S_IT and Sally receives S_Both, and they are the same age, the model estimates Cyrus will have 1.33 times the hazard of Sally (95% CI 0.33, 5.11).

ggforest(mod_AT, data = brca)



Comparing the Two Models

model	p.value.log	concordance	r.squared	max_r2	AIC	BIC
mod_T	0.416	0.577	0.055	0.944	91.8	93.2
mod_AT	0.072	0.701	0.202	0.944	88.5	90.7

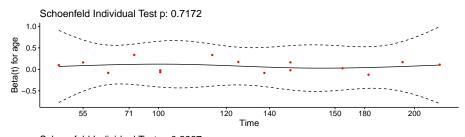
What do the glance results indicate?

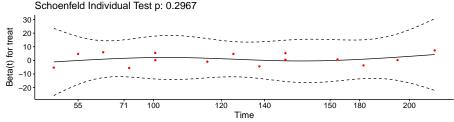
Significance Test via Likelihood Ratio ANOVA

```
anova (mod AT, mod T)
Analysis of Deviance Table
Cox model: response is S
Model 1: ~ age + treat
Model 2: ~ treat
  loglik Chisq Df P(>|Chi|)
1 - 41.268
2 -43.886 5.237 1 0.02211 *
Signif. codes:
0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Graphical PH Check ggcoxzph(cox.zph(mod_AT))







Using cph from the rms package

Using rms::cph to fit a fancier AxT

```
brca <- read csv(here("data", "brca.csv")) %>%
    type.convert(as.is = FALSE) # reload without S
d <- datadist(brca)</pre>
options(datadist="d")
brca$S <- with(brca, Surv(trial_weeks, last_alive == 0))</pre>
cph_AxT <- cph(S ~ rcs(age, 4) + treat + age %ia% treat,
               data = brca.
               x = TRUE, y = TRUE, surv = TRUE
```

cph_AxT results

```
> cph_AxT
Cox Proportional Hazards Model
cph(formula = S ~ rcs(age, 4) + treat + age %ia% treat, data = brca,
    x = TRUE, y = TRUE, surv = TRUE
                 Model Tests Discrimination
                                 Indexes
Obs 31 LR chi2 11.66
                               R2 0.332
                               Dxy 0.488
Events 15 d.f. 7
Center 14.2906 Pr(> chi2) 0.1123
                               g 1.980
              Score chi2 11.89
                               gr 7.245
              Pr(> chi2) 0.1042
             Coef S.E. Wald Z Pr(>|Z|)
           0.3011 0.2330 1.29 0.1963
age
age'
     -1.2521 0.7528 -1.66 0.0963
     2.7316 1.5490 1.76 0.0778
age''
treat=S_CT -4.9327 6.6650 -0.74 0.4592
age * treat=S CT 0.1006 0.1157 0.87 0.3846
age * treat=S_IT -0.0005 0.0835 -0.01 0.9949
```

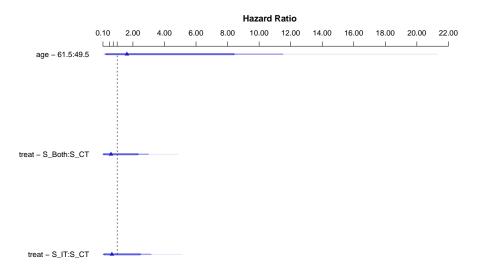
summary(cph_AxT)

Effects

Factor Low High Diff. Effect S.E. 49.5 61.5 12 0.48200 0.99998 age Hazard Ratio 49.5 61.5 12 1.61930 NA treat - S_Both:S_CT 2.0 1.0 NA -0.49745 0.80805 Hazard Ratio 2.0 1.0 NA 0.60808 NA treat - S_IT:S_CT 2.0 3.0 NA -0.40504 0.78888 Hazard Ratio 2.0 3.0 NA 0.66695 NA Lower 0.95 Upper 0.95 -1.47790 2.4419 0.22811 11.4950 -2.08120 1.0863 0.12478 2.9633 -1.95120 1.1411 0.14210 3.1303

Response : S

plot(summary(cph_AxT))



```
set.seed(432)
validate(cph_AxT)
```

Divergence or singularity in 1 samples

```
index.orig training
                             test optimism index.corrected
Dxy
          0.4883
                   0.5965
                           0.3693
                                    0.2273
                                                    0.2610
          0.3320
                   0.4741
                           0.2061
                                    0.2680
                                                    0.0640
R2
          1.0000 1.0000
                           0.3819
                                    0.6181
                                                    0.3819
Slope
          0.1191
                   0.2078
                           0.0650
                                    0.1428
                                                   -0.0237
D
IJ
         -0.0223 -0.0226
                          1.0971
                                                    1.0973
                                   -1.1196
Q
          0.1414
                   0.2303 -1.0321
                                    1.2624
                                                   -1.1210
                   4.2315
                                    3.0145
                                                   -1.0342
          1.9803
                           1.2169
g
       n
Dxv
      39
R2
      39
Slope 39
D
      39
IJ
      39
```

39

Q

ANOVA for cph_AxT model

> anova(cph_AxT)			
Wald Statistics	Response: S		
Factor	Chi-Square	d.f.	P
age (Factor+Higher Order Factors)	7.71	5	0.1727
All Interactions	0.96	2	0.6175
Nonlinear	3.73	2	0.1548
treat (Factor+Higher Order Factors)	2.58	4	0.6297
All Interactions	0.96	2	0.6175
age * treat (Factor+Higher Order Factor	s) 0.96	2	0.6175
TOTAL NONLINEAR + INTERACTION	3.74	4	0.4423
TOTAL	8 55	7	0 2868

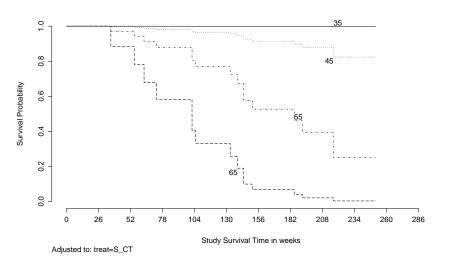
survplot in rms (code)

For age comparison:

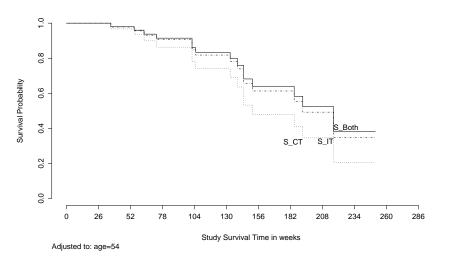
```
survplot(cph_AxT,
    age = c(35, 45, 55, 65),
    time.inc = 26,
    type = "kaplan-meier",
    xlab = "Study Survival Time in weeks")
```

For treat comparison:

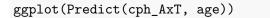
survplot in rms (Result)

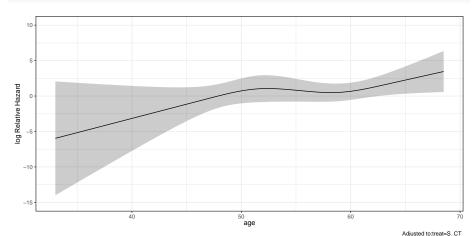


survplot for treat in rms (Result)

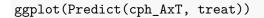


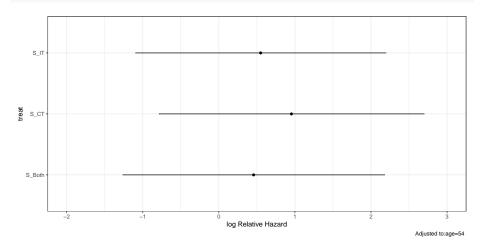
Plotting age effect implied by cph_AxT model





Plotting treat effect implied by cph_AxT model

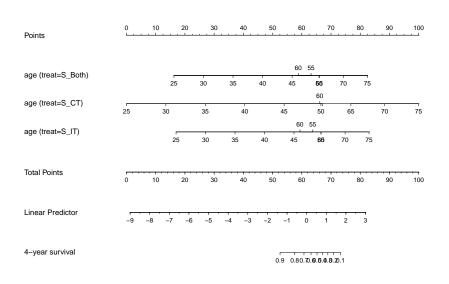




cph_AxT nomogram (code)

Suppose I want to show 4-year survival rates at the bottom of the nomogram. . .

cph_AxT nomogram (Results)

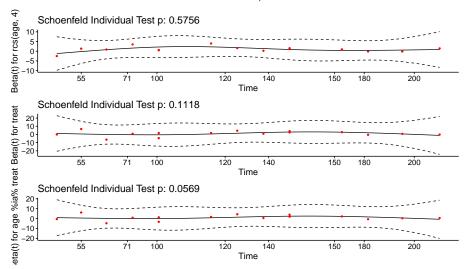


Checking the Proportional Hazards Assumption

```
rcs(age, 4) 1.98 3 0.576
treat 4.38 2 0.112
age %ia% treat 5.73 2 0.057
GLOBAL 10.67 7 0.154
```

ggcoxzph(cox.zph(cph_AxT))

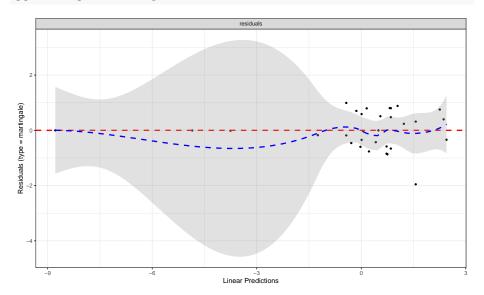
Global Schoenfeld Test p: 0.1537



Additional Diagnostic Plots for your Cox model?

- survminer has a function called ggcoxdiagnostics() which plots different types of residuals as a function of time, linear predictor or observation id.
 - See the default graph (which shows martingale residuals) on the next slide.
- Available types of diagnostics that this can plot are specified with the type parameter, that takes any of the following options.

ggcoxdiagnostics(cph_AxT)



New Topic: An Introduction to Robust Linear Regression Methods

Robust Linear Regression Methods

- The crimestat data
- Robust Linear Regression Methods
 - with Huber weights
 - with bisquare weights (biweights)
 - Quantile Regression on the Median

Additional Packages for this work

```
library(MASS); library(robustbase); library(boot)
library(quantreg); library(lmtest); library(sandwich)
library(conflicted)

conflict_prefer("select", "dplyr")
conflict_prefer("summarize", "dplyr")
library(tidyverse)
```

The crimestat data

For each of 51 states (including the District of Columbia), we have the state's ID number, postal abbreviation and full name, as well as:

- **crime** the violent crime rate per 100,000 people
- **poverty** the official poverty rate (% of people living in poverty in the state/district) in 2014
- single the percentage of households in the state/district led by a female householder with no spouse present and with her own children under 18 years living in the household in 2016

The crimestat data set

```
crimestat <- read_csv("data/crimestat.csv")
crimestat</pre>
```

```
# A tibble: 51 \times 6
    sid state crime poverty single state.full
  <dbl> <chr> <dbl> <dbl> <dbl> <dbl> <dbl> <<br/> <dr>
          427. 19.2 9.02 Alabama
      1 AT.
     2 AK 636. 11.4 7.63 Alaska
3
     3 AZ 400. 18.2 8.31 Arizona
   4 AR 480. 18.7 9.41 Arkansas
5
   5 CA 396. 16.4 7.25 California
6
          309. 12.1 6.75 Colorado
     6 CO
          237. 10.8 8.04 Connecticut
     7 CT
8
     8 DE
          489. 13 6.52 Delaware
9
      9 DC
          1244. 18.4 8.41 District of Columbia
10
    10 FI.
          540. 16.6 8.29 Florida
 ... with 41 more rows
```

Modeling crime with poverty and single

Our main goal will be to build a linear regression model to predict **crime** using centered versions of both **poverty** and **single**.

Our original (OLS) model

Note the sneaky trick with the outside parentheses. . .

```
(mod1 <- lm(crime ~ pov_c + single_c, data = crimestat))</pre>
```

Call:

```
lm(formula = crime ~ pov_c + single_c, data = crimestat)
```

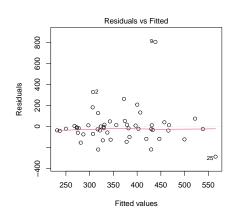
Coefficients:

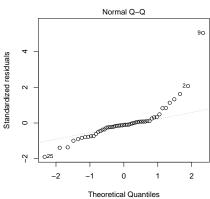
```
(Intercept) pov_c single_c
364.41 16.11 23.84
```

Coefficients?

term	estimate	std.error	p.value	conf.low	conf.high
(Intercept)	364.406	22.933	0.000	318.297	410.515
pov_c	16.115	9.616	0.100	-3.219	35.448
single_c	23.843	18.384	0.201	-13.121	60.807

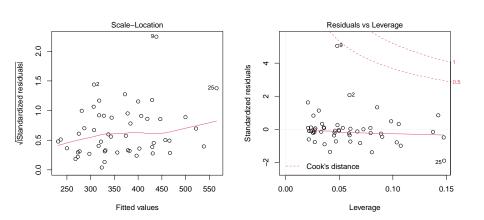
OLS Residuals





Which points are highlighted here?

Remaining Residual Plots from OLS



So which points are of special interest?

Which points are those?

```
crimestat %>%
    slice(c(2, 9, 25))

# A tibble: 3 x 8
    sid state crime poverty single state.full pov_c single_c
    <dbl> <chr> <dbl> <chr> <dbl> <chr> <dbl> <chr> < dbl> < dbl> <chr> < dbl> < dbl> <chr> < dbl> = 2 AK 636. 11.4 7.63 Alaska -3.47 -0.0588
2 9 DC 1244. 18.4 8.41 District ~ 3.53 0.721
3 25 MS 278. 21.9 11.4 Mississip~ 7.03 3.67
```

Robust Linear Regression with Huber weights

There are several ways to do robust linear regression using M-estimation, including weighting using Huber and bisquare strategies.

- Robust linear regression here will make use of a method called iteratively re-weighted least squares (IRLS) to estimate models.
- M-estimation defines a weight function which is applied during estimation.
- The weights depend on the residuals and the residuals depend on the weights, so an iterative process is required.

We'll fit the model, using the default weighting choice: what are called Huber weights, where observations with small residuals get a weight of 1, and the larger the residual, the smaller the weight.

Our robust model (using MASS::rlm)

rob.huber <- rlm(crime ~ pov_c + single_c, data = crimestat)</pre>

Summary of the robust (Huber weights) model

```
tidy(rob.huber) %>%
kable(digits = 3)
```

term	estimate	std.error	statistic
(Intercept)	343.798	13.131	26.182
pov_c	11.910	5.506	2.163
single_c	30.987	10.527	2.944

Now, both predictors appear to have estimates that exceed twice their standard error. So this is a very different result than ordinary least squares gave us.

Glance at the robust model (vs. OLS)

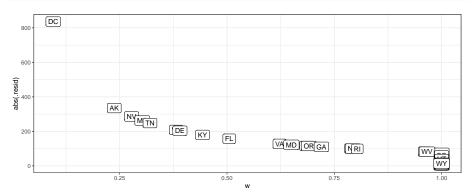
```
glance(mod1)
# A tibble: 1 x 12
 r.squared adj.r.squared sigma statistic p.value
                                                 df
     <dbl>
                  <dbl> <dbl> <dbl> <dbl> <dbl> <
     0.197
                  0.163 164. 5.88 0.00518 2
# ... with 6 more variables: logLik <dbl>, AIC <dbl>,
# BIC <dbl>, deviance <dbl>, df.residual <int>,
#
   nobs <int>
glance(rob.huber)
```

Understanding the Huber weights a bit

```
Let's augment the data with results from this model, including the weights.
crime with huber <- augment(rob.huber, crimestat) %>%
   mutate(w = rob.huber$w) %>% arrange(w)
crime_with_huber %>%
 select(sid, state, w, crime, pov_c, single_c, everything())
 head(...3)
# A tibble: 3 x 15
   <dbl> <chr> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> 
 9 DC 0.0951 1244. 3.53 0.721 18.4 8.41
2 2 AK 0.237 636. -3.47 -0.0588 11.4 7.63
3
  29 NV 0.278 636. 0.527 -0.0288 15.4 7.66
 ... with 7 more variables: state.full <chr>...
   .fitted <dbl>, .resid <dbl>, .hat <dbl>, .sigma <dbl>,
#
   .cooksd <dbl>, .std.resid <dbl>
```

Are cases with large residuals down-weighted?

```
ggplot(crime_with_huber, aes(x = w, y = abs(.resid))) + geom_label(aes(label = state))
```



Conclusions from the Plot of Weights

- District of Columbia will be down-weighted the most, followed by Alaska and then Nevada and Mississippi.
- But many of the observations will have a weight of 1.
- In ordinary least squares, all observations would have weight 1.
- So the more cases in the robust regression that have a weight close to one, the closer the results of the OLS and robust procedures will be.

summary(rob.huber)

```
Call: rlm(formula = crime ~ pov_c + single_c, data = crimestate
Residuals:
```

Coefficients:

```
Value Std. Error t value
(Intercept) 343.7982 13.1309 26.1823
pov_c 11.9098 5.5058 2.1631
single_c 30.9868 10.5266 2.9437
```

Residual standard error: 59.14 on 48 degrees of freedom

Robust Linear Regression with the biweight

As mentioned there are several possible weighting functions - we'll next try the **biweight**, also called the bisquare or Tukey's bisquare, in which all cases with a non-zero residual get down-weighted at least a little. Here is the resulting fit...

```
Call:
```

```
rlm(formula = crime ~ pov_c + single_c, data = crimestat, psi
Converged in 13 iterations
```

Coefficients:

```
(Intercept) pov_c single_c
336.17015 10.31578 34.70765
```

Degrees of freedom: 51 total; 48 residual

Scale estimate: 67.3

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Coefficients and Standard Errors

tidy(rob.biweight) %>% kable(digits = 3)

term	estimate	std.error	statistic
(Intercept)	336.170	12.673	26.526
pov_c	10.316	5.314	1.941
single_c	34.708	10.160	3.416
			·

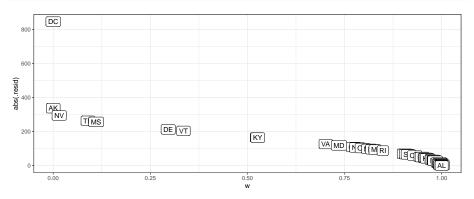
Understanding the biweights weights a bit

Let's augment the data, as above

```
crime_with_biweights <-</pre>
  augment(rob.biweight, newdata = crimestat) %>%
  mutate(w = rob.biweight$w) %>%
  arrange(w)
head(crime with biweights, 3)
# A tibble: 3 \times 11
    sid state crime poverty single state.full
                                                     pov_c
  <dbl> <chr> <dbl> <dbl> <dbl> <dbl> <chr>
                                                     <dbl>
     2 AK 636. 11.4 7.63 Alaska
                                                  -3.47
2 9 DC 1244. 18.4 8.41 District of Colum~ 3.53
3
  29 NV 636. 15.4 7.66 Nevada
                                                     0.527
# ... with 4 more variables: single_c <dbl>, .fitted <dbl>,
#
    .resid <dbl>, w <dbl>
```

Relationship of Weights and Residuals

```
\begin{split} & \texttt{ggplot}(\texttt{crime\_with\_biweights, aes}(\texttt{x = w, y = abs}(.\texttt{resid}))) \; + \\ & \texttt{geom\_label}(\texttt{aes}(\texttt{label = state})) \end{split}
```



Conclusions from the biweights plot

Again, cases with large residuals (in absolute value) are down-weighted generally, but here, Alaska and Washington DC receive no weight at all in fitting the final model.

- We can see that the weight given to DC and Alaska is dramatically lower (in fact it is zero) using the bisquare weighting function than the Huber weighting function and the parameter estimates from these two different weighting methods differ.
- The maximum weight (here, for Alabama) for any state using the biweight is still slightly smaller than 1.

summary(rob.biweight)

Call: rlm(formula = crime ~ pov_c + single_c, data = crimestate
Residuals:

```
Min 1Q Median 3Q Max -257.58 -40.53 8.01 45.30 846.81
```

Coefficients:

```
Value Std. Error t value (Intercept) 336.1702 12.6733 26.5259 pov_c 10.3158 5.3139 1.9413 single_c 34.7077 10.1598 3.4162
```

Residual standard error: 67.27 on 48 degrees of freedom

Comparing OLS and the two weighting schemes

logLik AIC BIC deviance df.residual nobs
<dbl> <dbl> <dbl> <int> <int><</pre>

1 -331. 670. 677. 1287405.

48

51

Comparing OLS and the two weighting schemes

Quantile Regression on the Median

We can use the rq function in the quantreg package to model the **median** of our outcome (violent crime rate) on the basis of our predictors, rather than the mean, as is the case in ordinary least squares.

```
rob.quan <- rq(crime ~ pov_c + single_c, data = crimestat)
glance(rob.quan)</pre>
```

summary(rob.quan)

pov_c 10.54757 3.06714 28.95962 single_c 32.27249 4.45889 48.18925

Estimating a different quantile (tau = 0.70)

In fact, if we like, we can estimate any quantile by specifying the tau parameter (here tau = 0.5, by default, so we estimate the median.)

Call:

```
rq(formula = crime ~ pov_c + single_c, tau = 0.7, data = crime
```

Coefficients:

```
(Intercept) pov_c single_c
379.72818 19.30376 32.15827
```

Degrees of freedom: 51 total; 48 residual

Comparing our Four Models

Estimating the Mean

Fit	Intercept CI	pov_c CI	single_c Cl
OLS	(318.6, 410.2)	(-3.13, 35.35)	(-12.92, 60.60)
Robust (Huber)	(320.0, 367.6)	(0.89, 22.93)	(9.93, 52.05)
Robust (biweight)	(310.7, 361.5)	(-0.30, 20.94)	(14.39, 55.03)

Note: CIs estimated for OLS and Robust methods as point estimate $\pm\ 2$ standard errors

Estimating the Median

Fit	Intercept CI	pov_c CI	single_c Cl
Quantile (Median) Reg	(336.9, 366.2)	(3.07, 28.96)	(4.46, 48,19)

Comparing AIC and BIC

Fit	AIC	BIC
OLS	669.7	677.4
Robust (Huber)	670.8	678.5
Robust (biweight)	671.7	679.4
Quantile (median)	637.5	643.3

Some General Thoughts

- When comparing the results of a regular OLS regression and a robust regression for a data set which displays outliers, if the results are very different, you will most likely want to use the results from the robust regression.
 - Large differences suggest that the model parameters are being highly influenced by outliers.
- ② Different weighting functions have advantages and drawbacks.
 - Huber weights can have difficulties with really severe outliers.
 - Bisquare weights can have difficulties converging or may yield multiple solutions.
 - Quantile regression approaches have some nice properties, but describe medians (or other quantiles) rather than means.