Topics in Regression Analysis

DDRC Academy of Investigators Workshop

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Disclaimer: The following example is fictitious, and many of the analytic strategies are for demonstrative purposes only, and do not reflect good analytic practice.

Example: CEASAR

Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) is an observational study that recruited men who were diagnosed with prostate cancer from 2011 to 2012.

- CEASAR enrolled more than $3,000$ men.
- The primary outcome variable is based on a patient-reported quality-of-life, whose score ranges from 0 to 100.
- The majority of patients underwent surgery (radical prostatectomy), and other treatment options included radiation (EBRT) and active surveillance.
- For this example, the data have been altered and truncated ($n = 100$).
  - The main outcome variable is `postQoL`: post-treatment Quality of Life score.
  - The baseline score is `preQoL`.

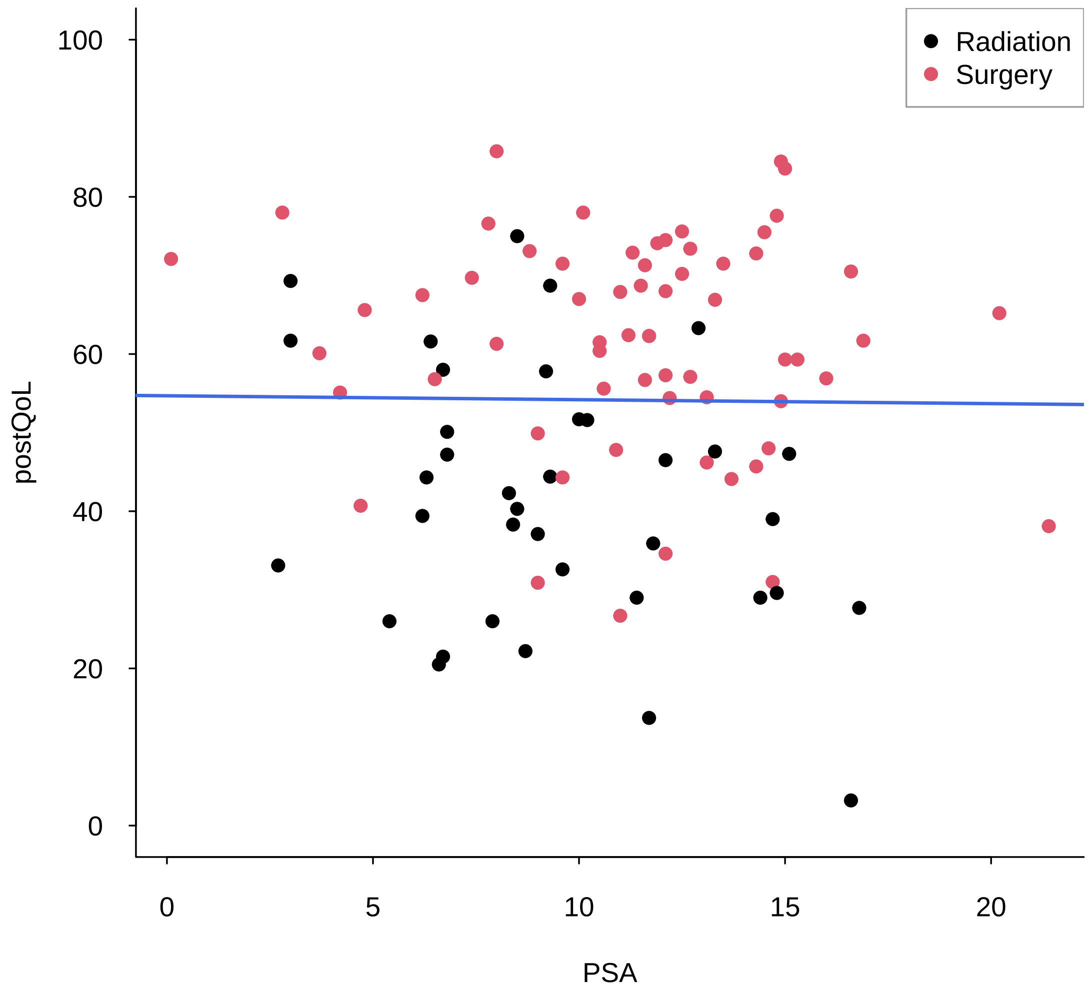
```
    preQoL       postQoL          Treatment        PSA              Age      Hypertension
 Min.   :16   Min.   : 3   Radiation:37   Min.   : 0.1   Min.   :42   No :40
 1st Qu.:36   1st Qu.:42   Surgery  :63   1st Qu.: 8.2   1st Qu.:58   Yes:60
 Median :57   Median :57                  Median :11.1   Median :66
 Mean   :56   Mean   :54                  Mean   :10.7   Mean   :64
 3rd Qu.:76   3rd Qu.:69                  3rd Qu.:13.3   3rd Qu.:71
 Max.   :95   Max.   :86                  Max.   :21.4   Max.   :79
```

1 Interaction vs Subgroup

1.1 Simple case

Question: Is the baseline PSA associated with postQoL?

```
Linear Regression Model

 ols(formula = postQoL ~ PSA, data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs      100    LR chi2      0.01    R2       0.000
 sigma17.7190    d.f.            1    R2 adj  -0.010
 d.f.      98    Pr(> chi2) 0.9170    g        0.207

 Residuals

     Min      1Q  Median      3Q     Max
 -50.713 -12.444   2.981  14.470  31.484


           Coef    S.E.   t     Pr(>|t|)
 Intercept 54.6911 5.1634 10.59 <0.0001
 PSA       -0.0468 0.4543 -0.10 0.9181
```

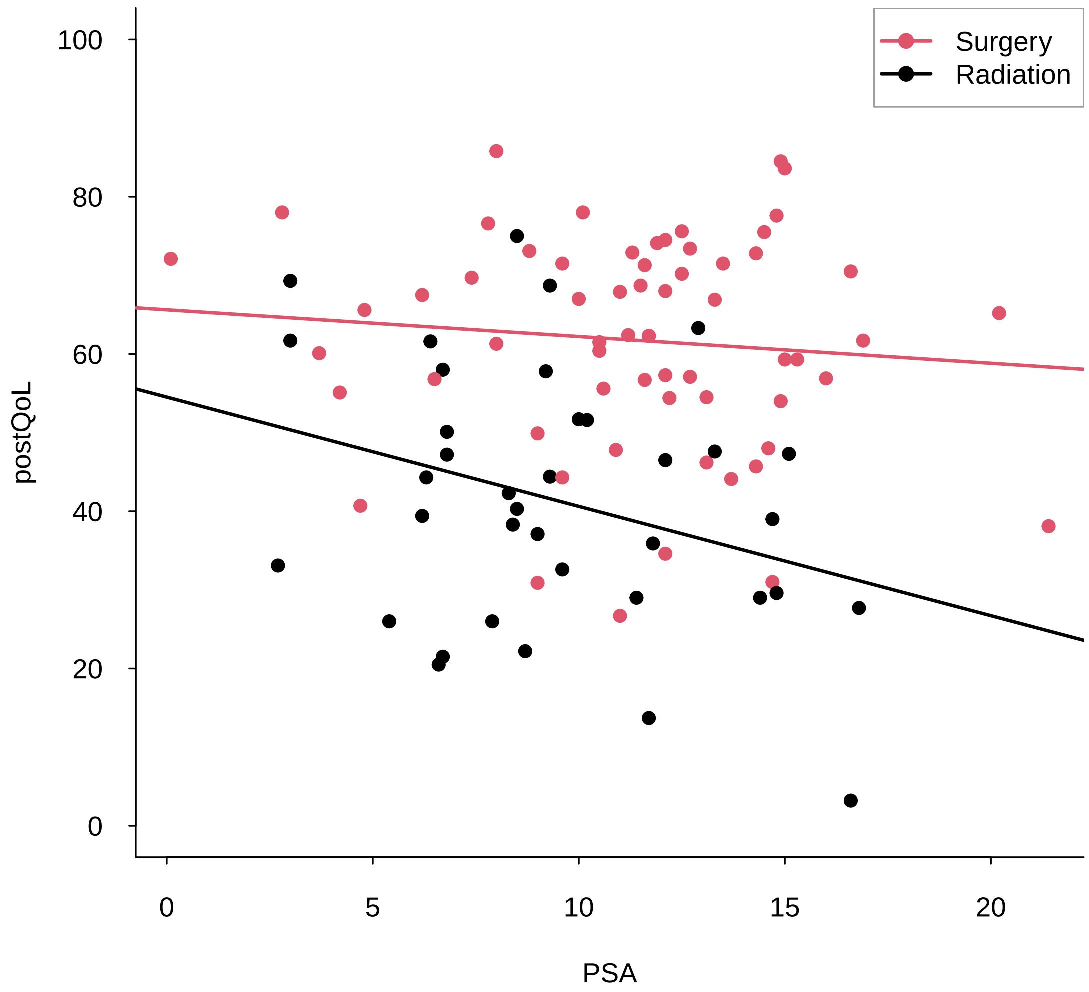

Radiation
Surgery
100
80
60
40
20
0
postQoL
0
5
10
15
20
PSA

Question: Is the baseline PSA associated with the postQoL differently in the Surgery and Radiation groups?

```
###################### Surgery subgroup ##
(model1.Sur <- ols(postQoL ~ PSA, data = subset(ds, Treatment == "Surgery")))


Linear Regression Model

 ols(formula = postQoL ~ PSA, data = subset(ds, Treatment == "Surgery"))

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       63    LR chi2      0.62    R2       0.010
 sigma13.6662    d.f.            1    R2 adj  -0.006
 d.f.      61    Pr(> chi2) 0.4319    g        1.476

 Residuals

      Min       1Q   Median       3Q      Max
 -35.1311  -6.5948   0.7103  10.5206  24.0136


           Coef    S.E.   t     Pr(>|t|)
 Intercept 65.6238 5.3556 12.25 <0.0001
 PSA       -0.3448 0.4447 -0.78 0.4412
```

```
######################## Radiation subgroup ##
(model1.Rad <- ols(postQoL ~ PSA, data = subset(ds, Treatment == "Radiation")))


Linear Regression Model

 ols(formula = postQoL ~ PSA, data = subset(ds, Treatment == "Radiation"))

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs        37    LR chi2      3.77    R2       0.097
 sigma15.8094    d.f.            1    R2 adj   0.071
 d.f.       35    Pr(> chi2) 0.0522    g        5.834

 Residuals

     Min      1Q  Median      3Q     Max
 -28.268  -8.590  -1.473  11.344  32.282


           Coef    S.E.   t     Pr(>|t|)
 Intercept 54.5228 7.2448  7.53 <0.0001
 PSA       -1.3888 0.7167 -1.94 0.0608
```

```
######################## Interaction model ##
(model1.Int <- ols(postQoL ~ PSA * Treatment, data = ds))


Linear Regression Model

 ols(formula = postQoL ~ PSA * Treatment, data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       100    LR chi2     42.39    R2       0.345
 sigma14.4844    d.f.            3    R2 adj   0.325
 d.f.       96    Pr(> chi2) 0.0000    g       10.914

 Residuals

      Min       1Q   Median       3Q      Max
 -35.1311  -6.7096   0.6741  11.0923  32.2823


                         Coef    S.E.   t     Pr(>|t|)
 Intercept               54.5228 6.6376  8.21 <0.0001
 PSA                     -1.3888 0.6567 -2.11 0.0370
 Treatment=Surgery       11.1010 8.7337  1.27 0.2068
 PSA * Treatment=Surgery  1.0440 0.8083  1.29 0.1996
```


Surgery
Radiation
postQoL
0
20
40
60
80
100
0
5
10
15
20
PSA

Coefficients:

	Surgery Subgroup		Radiation Subgroup		Interaction	
	Coefficient	p	Coefficient	p	Coefficient	p
Intercept	65.62	0.000	54.52	0.000	54.52	0.000
PSA	-0.34	0.44	-1.39	0.061	-1.39	0.037
Surgery	–	–	–	–	11.10	0.21
PSA $\times$ Surgery	–	–	–	–	1.04	0.20

The interaction model:

$$Y = \beta_0 + \beta_p X_p + \beta_s X_s + \beta_{ps} X_p X_s$$

where

$$X_s = \begin{cases} 1 & \text{if Surgery} \\ 0 & \text{if Radiation,} \end{cases}$$

and X_p is PSA value.

Then for Radiation group, we have

$$Y = \beta_0 + \beta_p X_p$$

and for Surgery group, we have

$$\begin{aligned} Y &= \beta_0 + \beta_p X_p + \beta_s + \beta_{ps} X_p \\ &= (\beta_0 + \beta_s) + (\beta_p + \beta_{ps}) X_p \end{aligned}$$

Thus, in this case, coefficient estimates in the interaction model and those in each sub-group model have simple algebraic relationship. But degrees of freedom and the standard error estimates are different.

One additional and very important advantage of the interaction model is its ability to formally test for differences of PSA effect between Treatment groups.

Question: Is PSA effect the same in Surgery and Radiation groups? (Are the slopes different?)

$$H_0 : \beta_{ps} = 0$$
$$H_1 : \beta_{ps} \neq 0$$

```
confint(m1I)
```

```
                       2.5 % 97.5 %
(Intercept)            41.35 67.698
PSA                    -2.69 -0.085
TreatmentSurgery       -6.24 28.437
PSA:TreatmentSurgery -0.56  2.649
```

1.2 With other covariates

What if we would like to examine the association between `PSA` and `postQoL` within each `Treatment` accounting for `preQoL`, `age`, and `Hypertension`.

```
## Surgery subgroup ##

## ( model1.Sur <- ols( postQoL ~ PSA, data=subset(ds, Treatment=='Surgery') ) )
(model2.Sur <- ols(postQoL ~ PSA + preQoL + Age + Hypertension, data = subset(ds, Treatment == "Surgery")))


Linear Regression Model

 ols(formula = postQoL ~ PSA + preQoL + Age + Hypertension, data = subset(ds,
     Treatment == "Surgery"))

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       63    LR chi2     48.40    R2       0.536
 sigma9.5917    d.f.            4    R2 adj   0.504
 d.f.      58    Pr(> chi2) 0.0000    g       11.365

 Residuals

      Min       1Q   Median       3Q      Max
 -22.1258  -4.7737  -0.2537   5.6112  22.4852


                  Coef    S.E.    t     Pr(>|t|)
 Intercept        51.1801 13.2827  3.85 0.0003
 PSA              -1.1277  0.3309 -3.41 0.0012
 preQoL            0.4356  0.0639  6.82 <0.0001
 Age              -0.0383  0.1577 -0.24 0.8090
 Hypertension=Yes -0.2003  2.6580 -0.08 0.9402
```

```
## Radiation subgroup ##

## ( model1.Rad <- ols( postQoL ~ PSA, data=subset(ds, Treatment=='Radiation') ) )
(model2.Rad <- ols(postQoL ~ PSA + preQoL + Age + Hypertension, data = subset(ds, Treatment == "Radiation")))


Linear Regression Model

 ols(formula = postQoL ~ PSA + preQoL + Age + Hypertension, data = subset(ds,
     Treatment == "Radiation"))

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       37    LR chi2     20.67    R2       0.428
 sigma13.1585    d.f.            4    R2 adj   0.356
 d.f.      32    Pr(> chi2) 0.0004    g       12.230

 Residuals

     Min      1Q  Median      3Q     Max
 -22.712  -9.585  -1.557   8.701  24.310


                  Coef    S.E.    t     Pr(>|t|)
 Intercept        16.0469 22.7618  0.70 0.4859
 PSA              -2.0112  0.6371 -3.16 0.0035
 preQoL            0.5074  0.1183  4.29 0.0002
 Age               0.2426  0.2733  0.89 0.3814
 Hypertension=Yes  3.0653  4.9225  0.62 0.5379
```

```
## Interaction model ## ( model1.Int <- ols( postQoL ~ PSA * Treatment, data=ds) )
(model2.Int <- ols(postQoL ~ PSA * Treatment + preQoL + Age + Hypertension, data = ds))


Linear Regression Model

 ols(formula = postQoL ~ PSA * Treatment + preQoL + Age + Hypertension,
     data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       100    LR chi2    102.70    R2       0.642
 sigma10.8848    d.f.            6    R2 adj   0.619
 d.f.       93    Pr(> chi2) 0.0000    g       16.247

 Residuals

      Min       1Q   Median       3Q      Max
 -22.3830  -7.4809  -0.6394   6.2940  25.1030


                        Coef    S.E.    t     Pr(>|t|)
 Intercept              30.6460 12.5304  2.45 0.0163
 PSA                    -2.0236  0.5055 -4.00 0.0001
 Treatment=Surgery      10.7106  6.5753  1.63 0.1067
 preQoL                  0.4697  0.0573  8.20 <0.0001
 Age                     0.0742  0.1397  0.53 0.5967
 Hypertension=Yes        1.1225  2.3926  0.47 0.6401
 PSA * Treatment=Surgery  0.8945  0.6090  1.47 0.1453
```

Coefficients:

	Surgery Subgroup		Radiation Subgroup		Interaction	
	Coefficient	p	Coefficient	p	Coefficient	p
Intercept	51.18	0.000	16.05	0.49	30.65	0.016
PSA	-1.13	0.001	-2.01	0.003	-2.02	0.000
Surgery	–	–	–	–	10.71	0.11
PSA $\times$ Surgery	–	–	–	–	0.89	0.15
preQoL	0.44	0.000	0.51	0.000	0.47	0.000
Age	-0.04	0.81	0.24	0.38	0.07	0.60
Hypertension	-0.20	0.94	3.07	0.54	1.12	0.64

Again, a clear advantage of the interaction model is the ability to test for differences of `PSA` effect between treatments.

And now, there doesn't seem any simple algebraic relationship between these coefficients. It is because the interaction model does not estimate `preQoL`, `Age`, or `Hypertension` effect separately for `Surgery` and `Radiation` groups.

If we want to estimate these secondary effects separately for the two groups, we must have treatments interacting with every single covariate.

```
########################### Big interaction model ##
(model3.Int <- ols(postQoL ~ Treatment * (PSA + preQoL + Age + Hypertension), data = ds))


Linear Regression Model

 ols(formula = postQoL ~ Treatment * (PSA + preQoL + Age + Hypertension),
     data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       100    LR chi2    104.00    R2       0.647
 sigma10.9933    d.f.            9    R2 adj   0.611
 d.f.       90    Pr(> chi2) 0.0000    g       16.292

 Residuals

      Min       1Q   Median       3Q      Max
 -22.7119  -7.5050  -0.7648   5.8757  24.3096


                                     Coef    S.E.    t     Pr(>|t|)
 Intercept                           16.0469 19.0163  0.84 0.4010
 Treatment=Surgery                   35.1332 24.3594  1.44 0.1527
 PSA                                 -2.0112  0.5323 -3.78 0.0003
 preQoL                               0.5074  0.0989  5.13 <0.0001
 Age                                  0.2426  0.2284  1.06 0.2909
 Hypertension=Yes                     3.0653  4.1125  0.75 0.4580
 Treatment=Surgery * PSA              0.8836  0.6536  1.35 0.1798
 Treatment=Surgery * preQoL          -0.0718  0.1230 -0.58 0.5609
 Treatment=Surgery * Age             -0.2809  0.2913 -0.96 0.3374
 Treatment=Surgery * Hypertension=Yes -3.2656  5.1180 -0.64 0.5250
```

Coefficients:

	Surgery Subgroup		Radiation Subgroup		Big Interaction	
	Coefficient	p	Coefficient	p	Coefficient	p
Intercept	51.18	0.000	16.05	0.49	16.05	0.40
PSA	-1.13	0.001	-2.01	0.003	-2.01	0.000
Surgery	–	–	–	–	35.13	0.15
PSA $\times$ Surgery	–	–	–	–	0.88	0.18
preQoL	0.44	0.000	0.51	0.000	0.51	0.000
preQoL $\times$ Surgery	–	–	–	–	-0.07	0.56
Age	-0.04	0.81	0.24	0.38	0.24	0.29
Age $\times$ Surgery	–	–	–	–	-0.28	0.34
Hypertension	-0.20	0.94	3.07	0.54	3.07	0.46
Hypertension $\times$ Surgery	–	–	–	–	-3.27	0.53

For this example, this means we must estimate 10 coefficients. With a sample size of 100, perhaps, it is too much. But that's exactly what we are doing with these **subgroup** analyses.

Number of coefficients:

Surgery Subgroup	5
Radiation Subgroup	5
Total	10
Interaction Model (PSA and Treatment)	7
Big interaction Model	10

2 Baseline Adjustment vs Difference

Suppose we would like to compare the two treatments on $postQoL$. We know that $postQoL$ is correlated with $preQoL$, so we will take that information into account.

Baseline `preQoL`

```
            N Min Q1 Med Q3 Max Mean SD  SE
Radiation  37  19 36  48 67  86   51 20 3.2
Surgery    63  16 39  63 81  95   59 23 2.9
Combined  100  16 36  57 76  95   56 22 2.2
```

6 month `postQoL`

```
            N  Min Q1 Med Q3 Max Mean SD  SE
Radiation  37  3.2 29  40 52  75   41 16 2.7
Surgery    63 26.7 55  62 72  86   62 14 1.7
Combined  100  3.2 42  57 69  86   54 18 1.8
```

Change `postQoL - preQoL`

```
            N Min  Q1  Med   Q3 Max  Mean SD  SE
Radiation  37 -56 -17 -6.6  5.0  25 -10.0 19 3.1
Surgery    63 -33 -11  0.3 12.7  55   2.2 18 2.2
Combined  100 -56 -14 -2.9  9.2  55  -2.3 19 1.9
```

One approach is to compute difference, $postQoL - preQoL$, to define **QoL change**.

```
## QoL Change
(ba <- ols((postQoL - preQoL) ~ Treatment, data = ds))


Linear Regression Model

 ols(formula = (postQoL - preQoL) ~ Treatment, data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       100    LR chi2     10.32    R2       0.098
 sigma18.0939    d.f.            1    R2 adj   0.089
 d.f.       98    Pr(> chi2) 0.0013    g        5.761

 Residuals

      Min       1Q   Median       3Q      Max
 -46.0081 -11.9429  -0.8255  12.7158  52.5571


                   Coef     S.E.   t     Pr(>|t|)
 Intercept          -9.9919 2.9746 -3.36 0.0011
 Treatment=Surgery  12.2347 3.7477  3.26 0.0015
```

Mean change in QoL (6 month $-$ baseline) is higher for Surgery group by 12.23. Also, the mean change in `Radiation` group is -9.99.

Another approach is to regress $postQoL$ on $Treatment$ while accounting for $preQoL$.

```
## preQol adjustment
(b0 <- ols(postQoL ~ Treatment + preQoL, data = ds))


Linear Regression Model

 ols(formula = postQoL ~ Treatment + preQoL, data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs      100    LR chi2     78.28    R2       0.543
 sigma12.0420    d.f.            2    R2 adj   0.533
 d.f.      97    Pr(> chi2) 0.0000    g       14.990

 Residuals

      Min       1Q   Median       3Q      Max
 -35.4737  -7.3794  -0.7145   8.1922  30.3027


                   Coef    S.E.   t    Pr(>|t|)
 Intercept         21.5708 3.4549 6.24 <0.0001
 Treatment=Surgery 17.1698 2.5332 6.78 <0.0001
 preQoL             0.3861 0.0551 7.01 <0.0001
```

"On average, $postQoL$ is higher for Surgery group by 17.17 while adjusting for $preQoL$." (Please remember this number, 17.17.)

Let's compare the regression models of the two approaches.

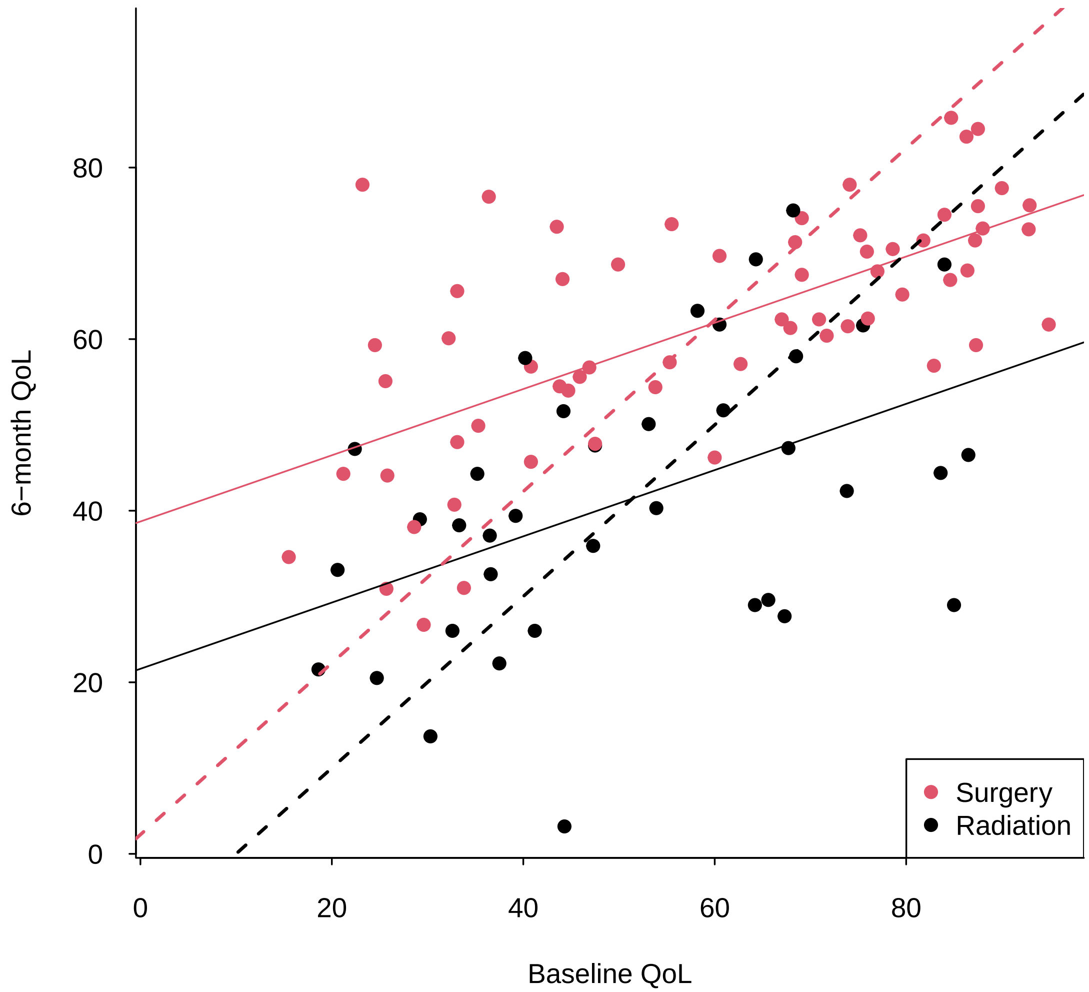
Approach 1: (Take difference)

$$\begin{aligned} Y_{post} - Y_{pre} &= \beta_0 + \beta_s X_s \\ Y_{post} &= \beta_0 + \beta_s X_s + 1 \cdot Y_{pre} \end{aligned}$$

Approach 2: (Regress Y_{post} on Y_{pre})

$$Y_{post} = \beta_0' + \beta_s' X_s + \beta_y' Y_{pre}$$

Comparing these equations, we notice that approach 1 forces the coefficient on Y_{pre} to be 1, while approach 2 allows us to estimate the coefficient using the data.



80
60
40
20
0
6−month QoL
0
20
40
60
80
Baseline QoL
Surgery
Radiation

3 Analyzing Difference with Baseine as a Covariate

I have seen regression models where the response is the difference **and** the baseline value is included as a covariate. The question may be: Does difference from baseline depend on the baseline values?

```
(m00 <- ols((postQoL - preQoL) ~ Treatment + preQoL, data = ds))


Linear Regression Model

 ols(formula = (postQoL - preQoL) ~ Treatment + preQoL, data = ds)

                  Model Likelihood    Discrimination
                        Ratio Test           Indexes
 Obs       100    LR chi2     92.78    R2       0.605
 sigma12.0420    d.f.             2    R2 adj   0.596
 d.f.       97    Pr(> chi2) 0.0000    g       16.927

 Residuals

      Min       1Q   Median       3Q      Max
 -35.4737  -7.3794  -0.7145   8.1922  30.3027


                   Coef    S.E.   t      Pr(>|t|)
 Intercept         21.5708 3.4549   6.24 <0.0001
 Treatment=Surgery 17.1698 2.5332   6.78 <0.0001
 preQoL            -0.6139 0.0551 -11.15 <0.0001
```

You might want to say, “On average, `Surgery` group’s $postQoL - preQoL$ is 17.17 higher while adjusting for $preQoL$.”

But we have seen this number, 17.17, before. It turns out this approach is closely related to our favorite approach, "Regress $postQoL$ and use $preQoL$ as covariate," only incorrect.

Coefficients:

Response	$postQoL$				$postQoL - preQoL$			
	Coefficient	SE	t	p	Coefficient	SE	t	p
Intercept	21.57	3.45	6.24	0.000	21.57	3.45	6.24	0.000
Surgery	17.17	2.53	6.78	0.000	17.17	2.53	6.78	0.000
$preQoL$	0.39	0.06	7.01	0.000	-0.61	0.06	-11.15	0.000

Let's compare the regression models:

Regress Y_{post} on Y_{pre}

$$Y_{post} = \beta_0 + \beta_s X_s + \beta_y Y_{pre}$$

Regress Difference on Y_{pre}

$$\begin{aligned} Y_{post} - Y_{pre} &= \beta_0' + \beta_s' X_s + \beta_y' Y_{pre} \\ Y_{post} &= \beta_0' + \beta_s' X_s + (\beta_y' + 1) Y_{pre} \end{aligned}$$

Therefore, $\beta_0 = \beta_0'$, $\beta_s = \beta_s'$, and $\beta_y = \beta_y' + 1$.

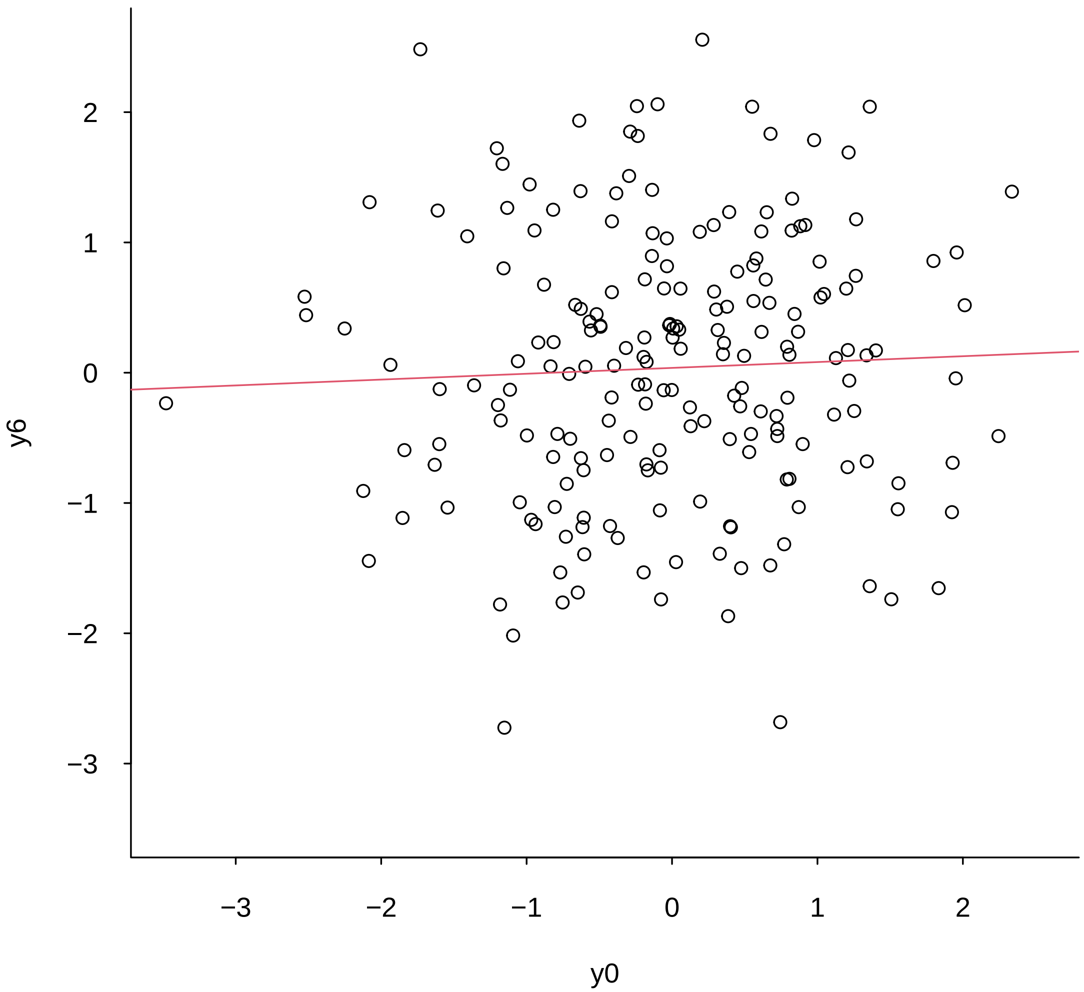
Is there a problem?

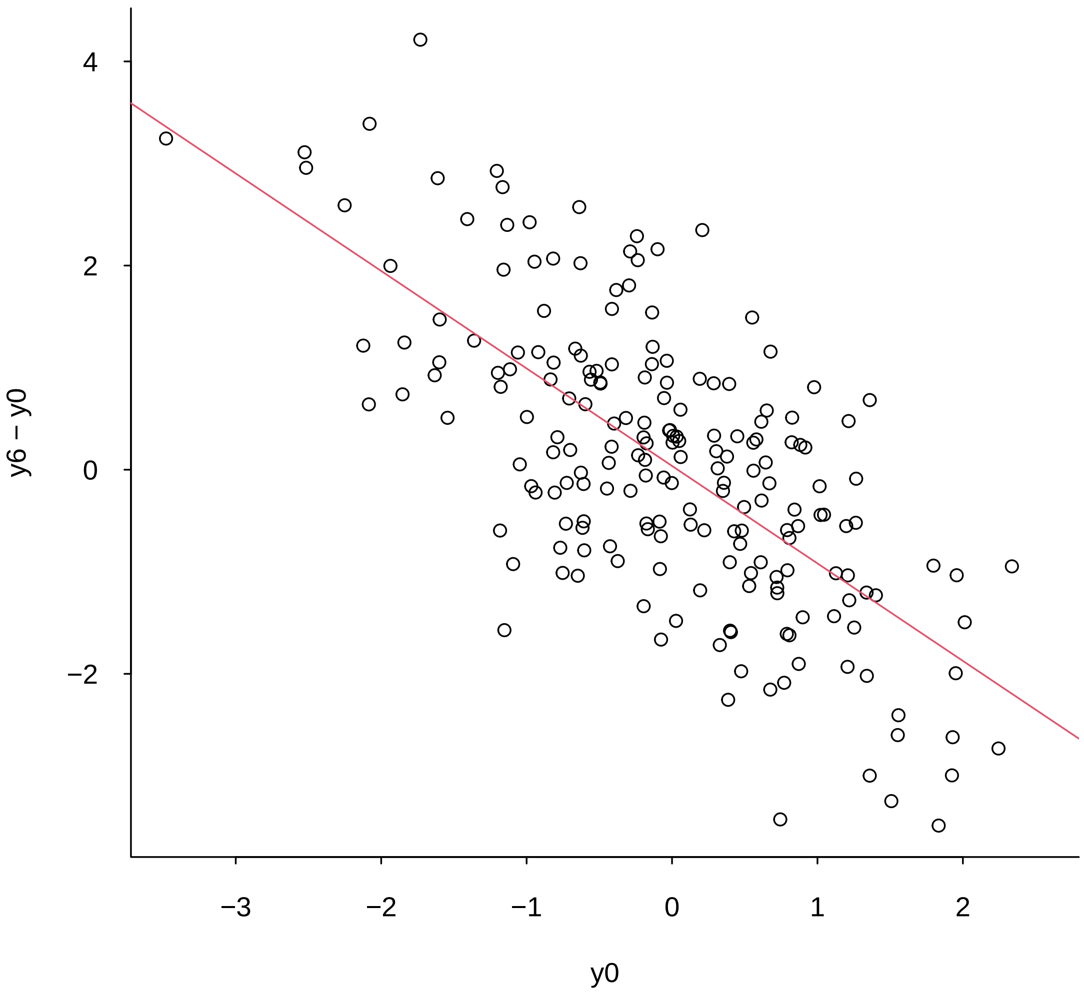
- If the question is regarding β_s, then probably yes, because interpretation is confusing.
- If the question is regarding β_y, then definitely yes,

$$H_0 : \beta'_y = 0$$
$$H_1 : \beta'_y \neq 0$$

does not test what it seems to test. When there is no association between Y_{pre} and Y_{post}, $\beta'_y = -1$, and the above null hypothesis is false.

```
set.seed(324)
y0 <- rnorm(200)
y6 <- rnorm(200)

(regX <- ols((y6 - y0) ~ y0))


Linear Regression Model

 ols(formula = (y6 - y0) ~ y0)

                 Model Likelihood    Discrimination
                       Ratio Test           Indexes
 Obs      200    LR chi2    127.37    R2       0.471
 sigma1.0218    d.f.            1    R2 adj   0.468
 d.f.     198    Pr(> chi2) 0.0000    g        1.083

 Residuals

     Min       1Q  Median       3Q      Max
 -2.7525 -0.6859  0.0517  0.6644  2.5232


           Coef    S.E.   t      Pr(>|t|)
 Intercept  0.0370 0.0723   0.51 0.6093
 y0        -0.9551 0.0719 -13.28 <0.0001
```


y6
y0
2
1
0
−1
−2
−3
−3
−2
−1
0
1
2


y6 − y0
y0
4
2
0
−2
−3
−2
−1
0
1
2

The take-home messages

- Interaction models are *always* better than the subgroup models.
- Baseline adjustment is *almost always* better than taking the difference.
- Baseline adjustment on top of taking the difference is *never* a good idea.

Topics in Regression Analysis

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