Biost 518 / Biost 515
Applied Biostatistics II / Biostatistics II

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Lecture 10:
Effect Modification; Diagnostics

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Lecture Outline

- Effect modification
  - Modeling effect modification
  - Examples
    - Administrative duties modifying the association between salary and sex
    - SEP by height, age, sex
- Introduction to Case Diagnostics
  - Leverage
  - Influence
  - Outliers

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Effect Modification

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Effect Modifier

- The association between Response and POI differs in strata defined by effect modifier
  - Statistical term: “Interaction”
- Depends on the measurement of effect
  - Summary measure
    - Mean, geometric mean, median, proportion, odds, hazard, etc.
  - Comparison across groups
    - Difference, ratio

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Analysis of Effect Modification

- When the scientific question involves effect modification, analyses must be within each stratum separately
- If we want to estimate degree of effect modification or test for its existence, a regression model will typically include
  - Predictor of interest
  - Effect modifier
  - A covariate modeling the interaction (usually product)

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Model for Effect Modification

- Typical model for effect modification
- Include "main effects" (can be bad not to)
  - *X* (or predictors that involve only *X)*
  - *W* (or predictors that involve only *W)*
- Include "interactions"
  - Predictor(s) derived from both *X* and *W*

$$g\left[\theta \,|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times \left(XW\right)_i$$
$$= \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

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Interpretation of Parameters

$$g\left[\theta \,|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- Usual approach a bit more difficult
  - We can try using the idea of "comparison of θ across groups differing by 1 unit in corresponding predictor but agreeing in other modeled predictors"
  - However, terms involving two scientific variables makes this approach difficult

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Intercept

$$g\left[\theta \,|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- Interpretation of intercept straightforward
  - β_0 corresponds to *X*= 0, *W*= 0
    - May not be scientifically meaningful

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Slopes for Main Effects

$$g\left[\theta \mid X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- Interpretation of main effects
  - β_X corresponds to 1 unit difference in *X* holding *W* and *(X×W)* constant
    - So 1 unit difference in *X* when *W*= 0
    - May not be scientifically meaningful
  - β_W corresponds to 1 unit difference in *W* holding *X* and *(X×W)* constant
    - So 1 unit difference in *W* when *X*= 0
    - May not be scientifically meaningful

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Slope for interaction

$$g\left[\theta \mid X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- Interpretation of interaction difficult
  - β_{XW} corresponds to 1 unit difference in *(X×W)* holding *X* and *W* constant
    - Impossible, so we need another way to interpret this slope parameter

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Consider Scientific Predictors

$$\begin{aligned} g\left[\theta \mid X_i, w\right] &= \beta_0 + \beta_X \times X_i + \beta_W \times w + \beta_{XW} \times X_i \times w \\ &= \left(\beta_0 + \beta_W \times w\right) + \left(\beta_X + \beta_{XW} \times w\right) \times X_i \end{aligned}$$

In stratum with $W = w$

Intercept : $\left(\beta_0 + \beta_W \times w\right)$ corresponds to $X_i = 0$

Slope : $\left(\beta_X + \beta_{XW} \times w\right)$ compares groups differing by 1 unit in X

β_{XW} is difference in X slope per 1 unit difference in W

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Consider Scientific Predictors

$$\begin{aligned} g\left[\theta \mid x, W_i\right] &= \beta_0 + \beta_X \times x + \beta_W \times W_i + \beta_{XW} \times x \times W_i \\ &= \left(\beta_0 + \beta_X \times x\right) + \left(\beta_W + \beta_{XW} \times x\right) \times W_i \end{aligned}$$

In stratum with $X = x$

Intercept : $\left(\beta_0 + \beta_X \times x\right)$ corresponds to $W_i = 0$

Slope : $\left(\beta_W + \beta_{XW} \times x\right)$ compares groups differing by 1 unit in W

β_{XW} is difference in W slope per 1 unit difference in X

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Symmetry of Effect Modification

- Note that if X modifies the association between Y and W, then W modifies the association between Y and X
- Aside: Confounding need not be symmetric
  - W can confound the association between Y and X, but X not confound the association between Y and W
    - W and X associated in the sample
    - Y and X not associated after adjusting for W
    - Y and W associated after adjusting for X

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Inference for Effect Modification

$$g\left[\theta \,|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- No effect modification if $\beta_{XW} = 0$
  - Hence, inference about existence of effect modification tests that $\beta_{XW} = 0$
    - We can perform such inference using standard regression output for the corresponding slope parameter

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Inference for Main Effect Slope

$$g\left[\theta \,|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- Interpretation of $\beta_X = 0$
  - Same intercept in all strata defined by *W*
  - Generally a very uninteresting question
  - We rarely make inference on main effect slopes by themselves

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Inference About Effect of X

$$g\left[\theta \,|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_W \times W_i + \beta_{XW} \times X_i \times W_i$$

- Response parameter not associated with *X* if $\beta_X = 0$ AND $\beta_{XW} = 0$
  - We will need to construct special tests that both parameters are simulataneously 0
  - The t tests given in regression output consider only one slope parameter at a time

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Stata: Testing Multiple Slopes

- Stata has easy method for performing test that multiple parameters are simultaneously 0
  - Perform any regression command
  - Then use "`test var1 var2 …`"
  - Provides P value of the hypothesis test based on most recently executed regression command *of any type of regression*

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Ex: Salary by Sex and Admin

- Does sex modify the association between mean salary and administrative duties?
- With two binary variables, modeling interaction by product is the obvious choice

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Ex: Stata output

```
. g admfem= admin * female
. regress salary female admin admfem if year==95, robust

Linear regression                               Number of obs =    1597
                                                F(  3,  1593) =  125.26
                                                Prob > F      =  0.0000
                                                R-squared     =  0.1615
                                                Root MSE      =  1866.9
------------------------------------------------------------------------------
             |               Robust
      salary |      Coef   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      female |  -1226.2   95.371     -12.86   0.000    -1413.3    -1039.2
       admin |   1951.4   176.39      11.06   0.000     1605.4     2297.4
      admfem |  -461.91   341.68      -1.35   0.177    -1132.1     208.28
       _cons |   6506.6   61.823     105.25   0.000     6385.3     6627.9
------------------------------------------------------------------------------
```

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Automatic Creation of Dummy Variables

- Stata's prefix command can automatically create dummy variables and interactions
- To create dummy variables
  - `regress yvar i.x1var i.x2var ctsvar`
- To create dummy variables and interactions (use ##)
  - `regress yvar i.x1var##i.x2var ctsvar`
- To create dummy variables and interaction with a continuous variable (use c. prefix)
  - `regress yvar i.x1var i.x2var##c.ctsvar`
- Three way interactions
  - `regress yvar i.x1var##i.x2var##c.ctsvar`
- (Other options will create the interactions without main effects, but I urge you not to do that)

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Ex: Stata output

```
. regress salary i.female##i.admin if year==95, robust

Linear regression                               Number of obs =    1597
                                                F(  3,  1593) =  125.26
                                                Prob > F      =  0.0000
                                                R-squared     =  0.1615
                                                Root MSE      =  1866.9
------------------------------------------------------------------------------
             |               Robust
      salary |      Coef   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    1.female |  -1226.2   95.371    -12.86   0.000    -1413.3   -1039.2
     1.admin |   1951.4   176.39     11.06   0.000     1605.4    2297.4
             |
female#admin |
        1 1  |  -461.91   341.68     -1.35   0.177    -1132.1    208.28
             |
       _cons |   6506.6   61.823    105.25   0.000     6385.3    6627.9
------------------------------------------------------------------------------
```


Ex: Descriptive Statistics

- Note that with two binary variables, the regression parameters agree exactly with the corresponding group sample means
  - A saturated model: Four distinct groups sampled, four regression parameters

```
. table admin female if year==95, co(mean salary)

          |       female
    admin |      Male     Female
----------+----------------------
Nonadmin  |  6506.607   5280.373
Admin     |  8457.985   6769.844
```


Ex: Inference About Eff Mod

- Does sex modify association between mean salary and administrative duties?
  - Estimate that the “administrative supplement” averages $462 less for women than men
    - 95% CI: $1132 less to $208 more
    - Not statistically significant: P = 0.177

```
        |               Robust
 salary |      Coef   Std. Err.      t    P>|t|     [95% Conf. Intrvl]
--------+----------------------------------------------------------------
 female |  -1226.2   95.371    -12.86   0.000    -1413.3    -1039.2
  admin |   1951.4   176.39     11.06   0.000     1605.4     2297.4
admfem  |  -461.91   341.68     -1.35   0.177    -1132.1     208.28
  _cons |   6506.6   61.823    105.25   0.000     6385.3     6627.9
```


Ex: Inference About Sex Assoc

- Is sex associated with mean salary?
  - Need to test that slope parameters for `female` and `admfem` are simultaneously 0

```
. test female admfem
 ( 1)  female = 0
 ( 2)  admfem = 0

       F(  2,  1593) =   95.90
            Prob > F =    0.0000
```

Ex: Inference for Admin Assoc

- Are administrative duties associated with mean salary?
  - Need to test that slope parameters for `admin` and `admfem` are simultaneously 0

```
. test admin admfem
 ( 1)  admin = 0
 ( 2)  admfem = 0

       F(  2,  1593) =   74.15
            Prob > F =    0.0000
```

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Continuous Predictors

- Modeling interactions with continuous predictors is conceptually more complicated
- Is a multiplicative interaction at all a reasonable model for the data?
- Nonetheless, this is the most common way we detect interactions
  - I would caution against using the model as predictions without carefully examining the data
  - And this sort of *post hoc* assessment has its problems

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Example: SEP "Normal Ranges"

- We want to find "normal ranges" for somatosensory evoked potential (SEP)
  - Time that it takes a signal to reach your brain from your ankle
- Method of analysis
  - Not recommended: "Prediction intervals" assuming same distribution (Gaussian) within each group
  - Recommended: 2.5th and 97.5th quantile within groups
- As a first step, we want to consider important predictors of nerve conduction times
- If any variables such as sex, age, height, race, etc. are important predictors of nerve conduction times, then it would make most sense to obtain "normal ranges" within such groups

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SEP: Important Predictors

- Scientifically, we might expect that height, age, and sex are related to the nerve conduction time
  - Nerve length should matter, and height is a surrogate for nerve length
  - Age might affect nerve conduction times: People slow down with age
  - Sex: Men are SO fragile

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SEP: Height – Age Interaction?

- Prior to looking at the data, we can also consider the possibility that interactions between these variables might be important
- Height - age interaction?
  - Do we expect the difference in conduction times between 6 foot tall and 5 foot tall 20 year olds to be the same as the difference in conduction times between 6 foot tall and 5 foot tall 80 year olds?

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SEP: Height – Age Interaction Rationale

- We might suspect such an interaction due to the fact that height may not be as good a surrogate for nerve length in older people
  - With age, some people tend to shrink due to osteoporosis and compression of intervertebral discs
  - It is not clear that nerve length would be altered in such a process
- Thus, in young people, differences in height probably are a better measure of nerve length than in old people
  - Tall old people probably have been tall always
  - Short old people will include some who were much taller when they were young

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SEP: Height – Age - Sex Interaction?

- We can also consider the possibility of three way interactions between height, age, and sex
- Osteoporosis affects women far more than men
  - Hence, we might expect the height - age interaction to be greatest in women and not so important in men
- A two way interaction between height and age that is different between men and women defines a three way interaction between height, age, and sex

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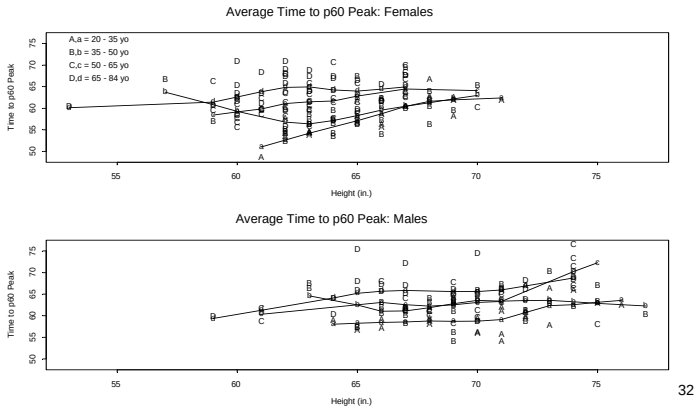
Stratified Scatterplots

- Scatterplots of p60 by height for each sex, lowess in age strata



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SEP: Definition of Model

- Defining a regression model with interactions
  - We must create variables to model the three way interaction term
- Furthermore, it is a VERY GOOD idea to include all "main effects" and "lower order interactions" in the model as well
  - "main effects": the individual variables which contribute to the interaction
  - "lower order terms": all interactions that involve some combination of the variables which contribute to the 3-way interaction

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SEP: Modeling Interactions

- Most often, we lack sufficient information to be able to guess what the true form of an interaction might be
- The most popular approach is thus to consider multiplicative interactions
- Create a new variable by merely multiplying the two (or more) interacting predictors

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SEP: Creating New Interaction Terms

- Thus for this problem we could create variables
  - HA = Height * Age
  - HM = Height * Male
  - AM = Age * Male
  - HAM = Height * Age * Male

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SEP: Interpretation of Parameters

- In the presence of higher order terms (powers, interactions) interpretation of parameters is not easy
- We can no longer use "the change associated with a 1 unit difference in predictor holding other variables constant"
- It is generally impossible to hold other variables constant when changing a covariate involved in an interaction
- (If not impossible, it is certainly uninteresting)

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SEP: Interpretation Using Lines in Strata

- Interpretation of the model in terms of the SEP height relationship within age-sex strata

$$E(p60 \mid Ht, Age, Male) = \beta_0 + \beta_H Ht + \beta_A Age + \beta_M Male + \beta_{HA} HA + \beta_{HM} HM + \beta_{AM} AM + \beta_{HAM} HAM$$

p60 - Height relationship for Age = a :

Sex	Intercept	Slope
F	$(\beta_0 + \beta_A a)$	$(\beta_H + \beta_{HA} a)$
M	$(\beta_0 + \beta_M + (\beta_A + \beta_{AM})a)$	$(\beta_H + \beta_{HM} + (\beta_{HA} + \beta_{HAM})a)$

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SEP: Inclusion of Lower Order Terms

- From the above, we see the importance of including the main effects and lower order terms
- E.g., leaving out the height - sex interaction is tantamount to claiming that the p60 - height relationship among newborns is the same for the two sexes
  - (It might be, but the chance that our lines would predict the truth is very slight-- we are trying to approximate relationships in other age ranges)

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SEP: Regression Output

```
. g p60=(p60R + p60L)/2
. regress p60 height age male ha hm am ham, robust

Linear regression                               Number of obs =     250
                                                F(  7,   242) =   18.76
                                                Prob > F      =  0.0000
                                                R-squared     =  0.3920
                                                Root MSE      =  3.6125
------------------------------------------------------------------------------
             |               Robust
         p60 |      Coef.   StdErr      t    P>|t|     [95% Conf Intrvl]
-------------+----------------------------------------------------------------
      height |   1.3803    .43090    3.20   0.002     .53147     2.2291
         age |   1.1294    .44597    2.53   0.012     .25094     2.0079
        male |   74.958    34.860    2.15   0.033     6.2908     143.62
          ha |  -.01500    .00684   -2.19   0.029    -.02848    -.00152
          hm |  -1.1270    .52083   -2.16   0.031    -2.1529    -.10107
          am |  -1.1629    .57238   -2.03   0.043    -2.2904    -.03537
         ham |   .01750    .00859    2.04   0.043     .00057     .03443
       _cons |  -36.443    28.304   -1.29   0.199    -92.196     19.311
------------------------------------------------------------------------------
```

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SEP: Using Stata's i. Prefix

```
. regress p60 i.male##c.age##c.height, robust
Linear regression                               Number of obs =     250
                                                F(  7,   242) =   18.76
                                                Prob > F      =  0.0000
                                                R-squared     =  0.3920
                                                Root MSE      =  3.6125
------------------------------------------------------------------------------
             |               Robust
         p60 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      1.male |   74.95773   34.85959    2.15   0.033     6.290783    143.6247
         age |   1.129423    .445972    2.53   0.012     .2509409    2.007906
             |
  male#c.age |
          1  |  -1.162866   .5723847   -2.03   0.043    -2.290358   -.0353737
             |
      height |   1.380275   .4309057    3.20   0.002     .5314702    2.229079
             |
male#c.height|
          1  |  -1.127006   .5208285   -2.16   0.031    -2.152942   -.1010699
             |
c.age#c.height |  -.0149985   .0068449   -2.19   0.029    -.0284817   -.0015154
             |
male#c.age#|
  c.height |
          1  |   .0175005   .0085949    2.04   0.043       .00057    .0344309
             |
       _cons |  -36.44286   28.30387   -1.29   0.199    -92.19624    19.31053
------------------------------------------------------------------------------
```

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SEP: An Aside - Subgroup Analysis

- If I restrict analysis to females, estimates are the same in this quasi "saturated" model
  - (Restricting by age or height would differ due to "borrowing information" across groups)
- Inference differs due to the estimate of the residual standard error

```
. regress p60 height age ha if male==0, robust
Linear regression                               Number of obs =     137
                                                F(  3,    133) =   24.21
                                                Prob > F       =  0.0000
                                                R-squared      =  0.3810
                                                Root MSE       =  3.6006
------------------------------------------------------------------------
             |           Robust
         p60 |   Coef.   StdErr       t    P>|t|     [95% Conf Intrvl]
------------------------------------------------------------------------
      height |  1.3803   .43028    3.21   0.002     .52919     2.2314
         age |  1.1294   .44533    2.54   0.012     .24858     2.0103
          ha | -.01500    .0068   -2.19   0.030    -.02852    -.00148
       _cons | -36.443   28.263   -1.29   0.199    -92.346     19.460
```

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SEP: Interpreting Estimates

- Figuring out what all these estimates mean is nearly impossible
- I find it easiest to graph the predicted values
- I did this by graphing the fitted values for midpoints of strata defined by age

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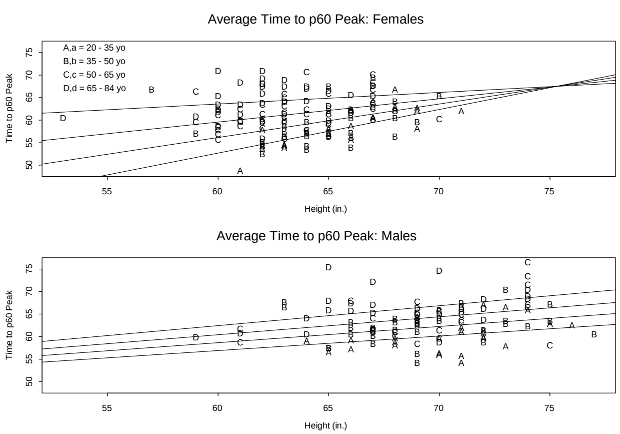
SEP: Lines Predicted By Model



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SEP: Detecting 3-way Interaction

- From the inference, we find a statistically significant three way interaction
  - P= .047
- This would argue that I should make predictions based on a model including the 3-way interaction
  - But…

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SEP: Influence of Individual Cases

- I always worry that interactions might be significant only because of a single "outlier"
- If that were the case, I might choose not to include the interaction (but I always include the case)
- Looking ahead: I can "diagnose" such a problem by assessing the influence of each case

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Example: SEP "Normal Ranges"

- I am now interested in ensuring that the evidence for an interaction is not based solely on a single person's observation
- Hence, I consider 250 different regressions in which I leave out each case in turn
- I plot the slope estimates and P values for each variable as a function of which case I left out
  - Case 0 corresponds to using the full data set

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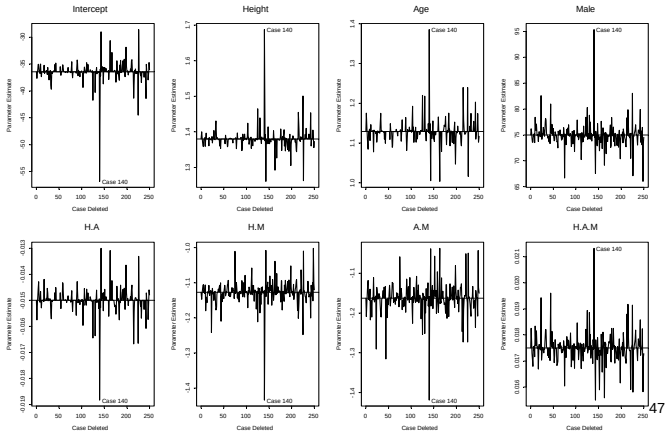
Influence on Estimates



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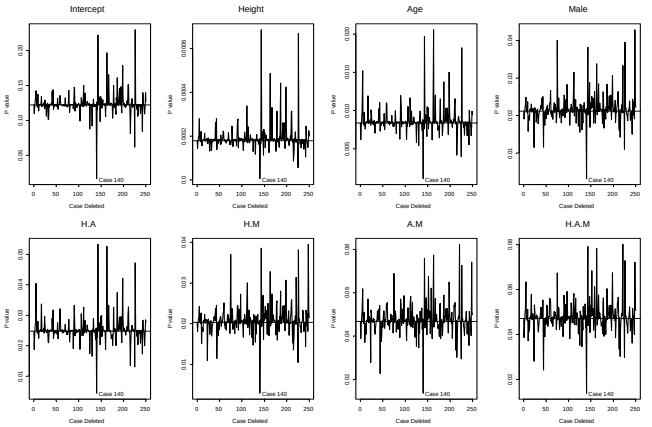
Influence on P values



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Example: SEP "Normal Ranges"

- Contrary to what I was afraid of, the only influential case actually lessened the evidence of an interaction
- When Case 140 is removed from the data, the evidence for an interaction is a larger estimate and a lower P value
- We can examine the scatterplot to see why Case 140 might be so influential

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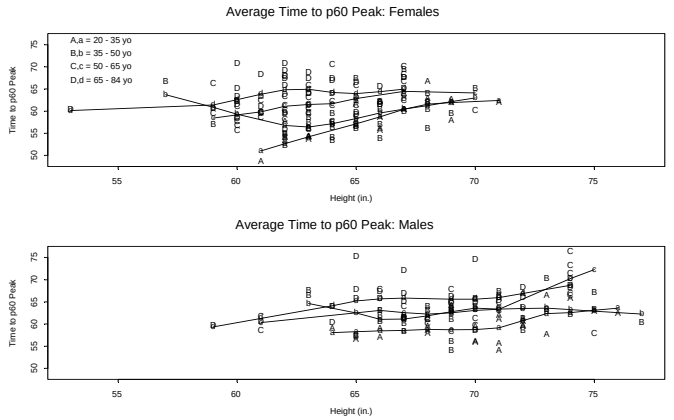
Stratified Scatterplots



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Example: SEP "Normal Ranges"

- So now what do I do with Case 140?
- From the influence diagnostics, I now feel comfortable with the fact that the data really do suggest a three way interaction
- Personally, I do NOT remove the case from the dataset when making my prediction intervals
  - I do not know why Case 140 is so unusual
  - It is possible that people like her are actually more prevalent in the population than my sample would suggest
    - My best guess is that she represents 0.4% of the population, so leave her in

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