

Biost 518

Applied Biostatistics II

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Lecture 8: Multiple Regression: Effect Modification

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Lecture Outline

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- Effect modification
- Examples
 - Administrative duties modifying the association between salary and sex
 - SEP by height, age, sex

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Effect Modification

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Effect Modifier

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- 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

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- 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

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- 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

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

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Interpretation of Parameters

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

- 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

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

- 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

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

- Interpretation of main effects

- β_X corresponds to 1 unit difference in X holding W and $(X \times W)$ 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 $(X \times W)$ constant

- So 1 unit difference in W when $X=0$
- May not be scientifically meaningful

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Slope for interaction

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

- Interpretation of interaction difficult

- β_{XW} corresponds to 1 unit difference in $(X \times W)$ holding X and W constant

- Impossible, so we need another way to interpret this slope parameter

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Consider Scientific Predictors

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

In stratum with $W = w$

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

Slope : $(\beta_X + \beta_{XW} \times w)$ 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

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

In stratum with $X = x$

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

Slope : $(\beta_W + \beta_{XW} \times x)$ 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

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

- 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

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

- 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

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

- 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 simultaneously 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

$$E[Sal | Fem, Adm] = \beta_0 + \beta_A \times Adm_i + \beta_F \times Fem_i + \beta_{AF} \times Adm_i \times Fem_i$$

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Ex: Stata output

```
. g admfem= admin * female
. regress salary admin female admfem if year==95,
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.	StdErr	t	P> t	[95% CI]	
admin	1951.378	176	11.06	0.000	1605 2297	
female	-1226.234	95	-12.86	0.000	-1413 -1039	
admfm	-461.9072	342	-1.35	0.177	-1132 208	
_cons	6506.607	62	105.25	0.000	6385 6627	

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Ex: Descriptive Statistics

- Note that with two binary variables, the regression parameters agree exactly with the corresponding group sample means

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

	female	
admin	Male	Female
Nonadmin	6506.607	5280.373
Admin	8457.985	6769.844

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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.	StdErr	t	P> t	[95% CI]	
admin	1951.378	176	11.06	0.000	1605 2297	
female	-1226.234	95	-12.86	0.000	-1413 -1039	
admfem	-461.9072	342	-1.35	0.177	-1132 208	
_cons	6506.607	62	105.25	0.000	6385 6627	21

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
```

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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

– But this can be difficult, too

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Example: SEP “Normal Ranges”

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- We want to find normal ranges for somatosensory evoked potential (SEP)
 - 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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Example: SEP “Normal Ranges”

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- 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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Example: SEP “Normal Ranges”

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- 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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Example: SEP “Normal Ranges”

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- 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

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Example: SEP “Normal Ranges”

- 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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Example: SEP “Normal Ranges”

- 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

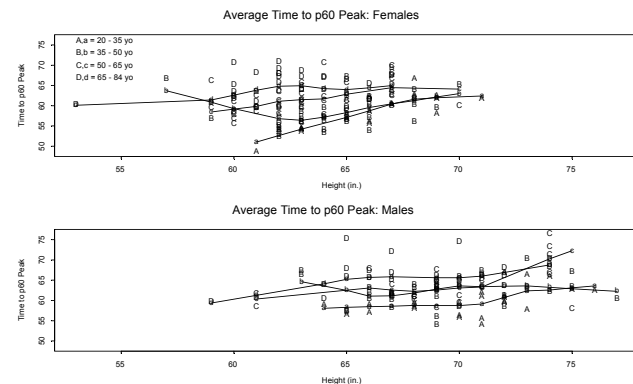
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Example: SEP “Normal Ranges”

- 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



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Example: SEP “Normal Ranges”

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- Defining a regression model with interactions
 - We must create variables to model the three way interaction term

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Example: SEP “Normal Ranges”

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- 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 interaction

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Example: SEP “Normal Ranges”

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- 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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Example: SEP “Normal Ranges”

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- 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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Example: SEP “Normal Ranges”

- Interpretation of the model 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 often uninteresting

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Example: SEP “Normal Ranges”

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

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Example: SEP “Normal Ranges”

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

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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Example: SEP “Normal Ranges”

- 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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Example: Regression Output

```
. regress p60 height age male HA HM AM HAM
```

	p60	Coef	SE	t	P> t	[95% CI]
height		1.38	.363	3.81	0.000	.666 2.09
age		1.13	.425	2.66	0.008	.292 1.97
male		75.0	32.3	2.32	0.021	11.3 138
HA		-.015	.007	-2.26	0.025	-.028 -.0019
HM		-1.12	.483	-2.34	0.020	-2.08 -.176
AM		-1.16	.582	-2.00	0.047	-2.31 -.0170
HAM		.0175	.009	2.00	0.047	.0002 .0347
_cons		-36.4	23.5	-1.55	0.122	-82.7 9.82

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Aside: Subgroup Analysis

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

```
. regress p60 height age HA if male==0
```

	p60	Coef	SE	t	P> t	[95% CI]
height		1.38	.361	3.82	0.000	.665 2.10
age		1.13	.424	2.67	0.009	.292 1.97
HA		-.015	.007	-2.27	0.025	-.028 -.002
_cons		-36.4	23.4	-1.56	0.122	-82.7 9.86

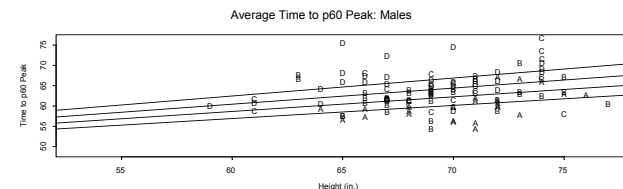
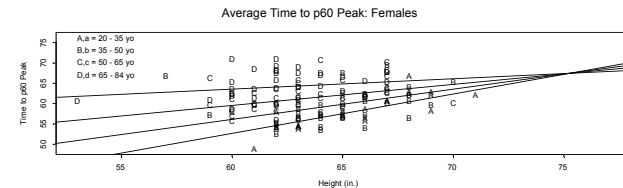
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Interpreting Estimates

- Figuring out what all these estimates mean is nearly impossible
 - I find it easiest to graph the predicted values

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Lines Predicted By Model



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Example: SEP “Normal Ranges”

- From the inference, we find a statistically significant three way interaction
 - $P = .0471$
- This would argue that I should make predictions based on a model including the 3-way interaction
 - But...

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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

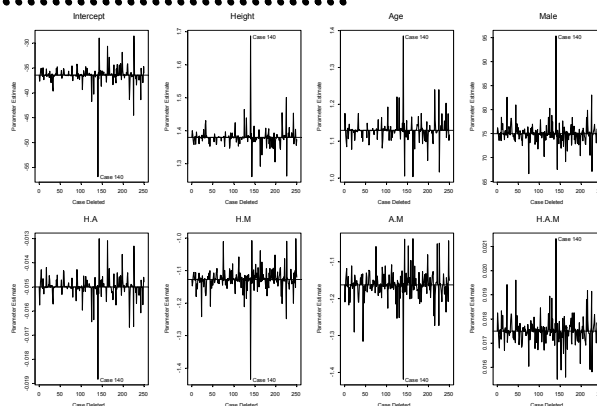
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Example: SEP “Normal Ranges”

- 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

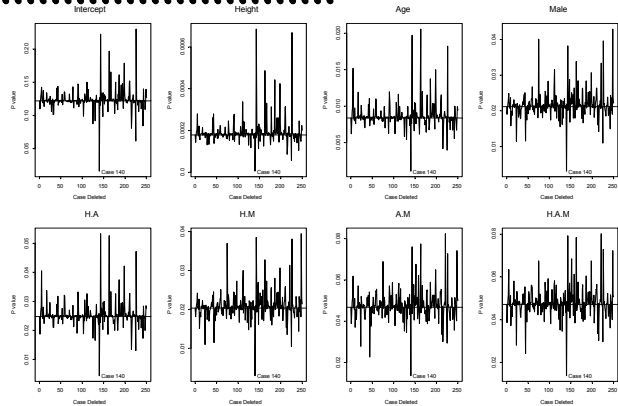
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Influence on Estimates



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Influence on P values



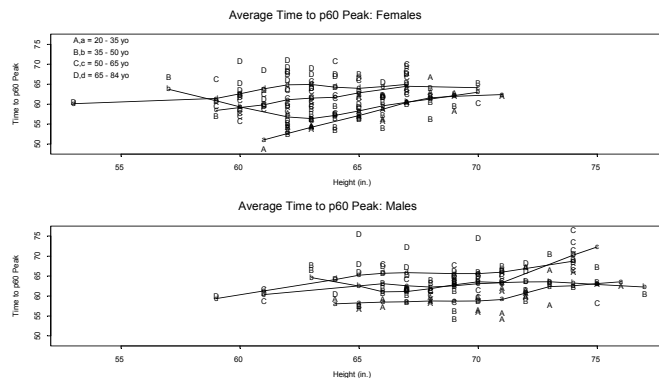
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Example: SEP “Normal Ranges”

- 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

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Example: SEP “Normal Ranges”

- 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