

Interaction

February 6, 2018

Biostatistics 208

Interaction in Linear Regression Models

- Defining interaction
- Regression models including interaction terms
- Estimating effects in subgroups using `lincom` in Stata
- Interpretation of coefficients

Interaction

- **Confounding and mediation:** association of primary predictor with outcome *differs after adjustment*
 - adjustment variable *explains* or *masks* unadjusted effect of predictor
- **Interaction:** association of primary predictor with the outcome *differs across levels of the interaction variable*
 - interaction variable *modifies/moderates* estimated effect of primary predictor
 - modified/moderated effects may still be subject to confounding
- **Recent example**

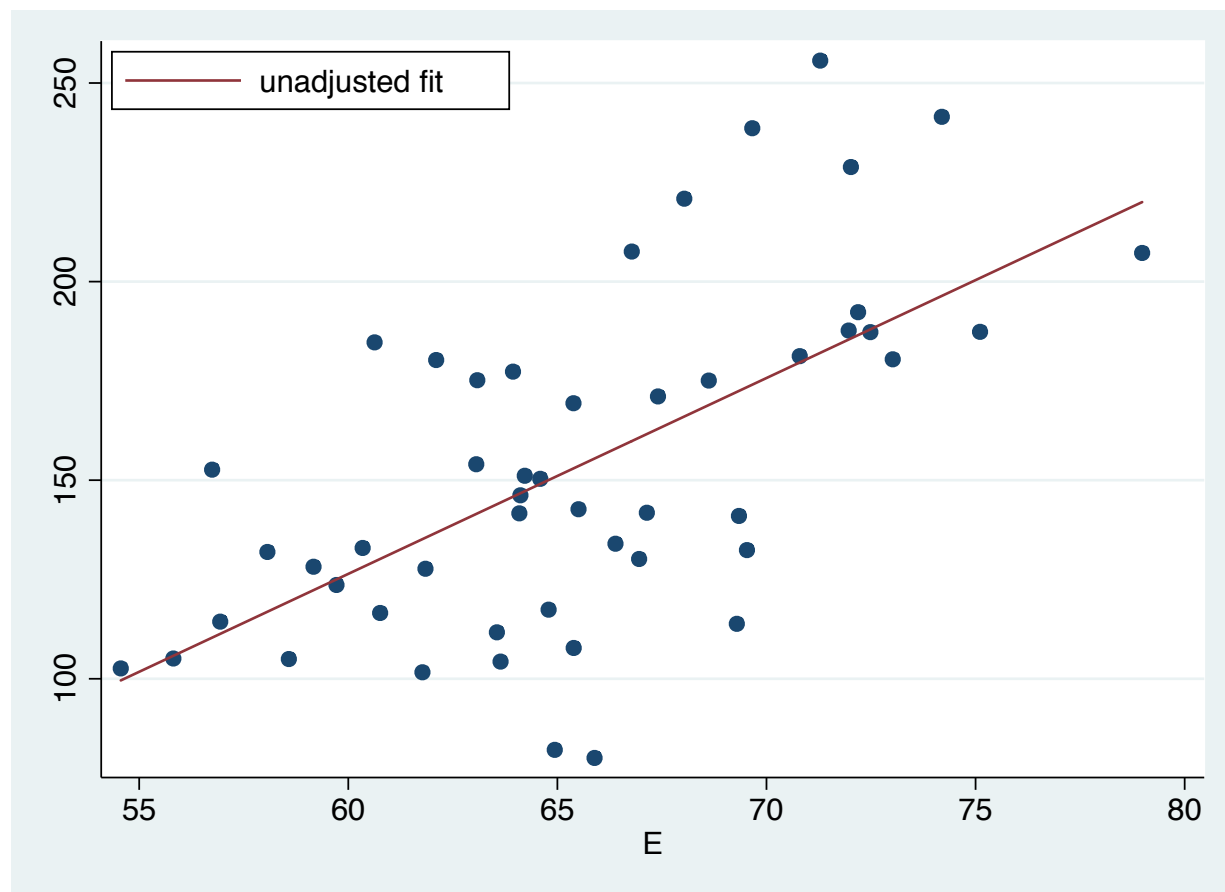
Annals of Internal Medicine, 2/6/2018:

Effect of Hot Tea Consumption and Its Interactions With Alcohol and Tobacco Use on the Risk for Esophageal Cancer: A Population-Based Cohort Study

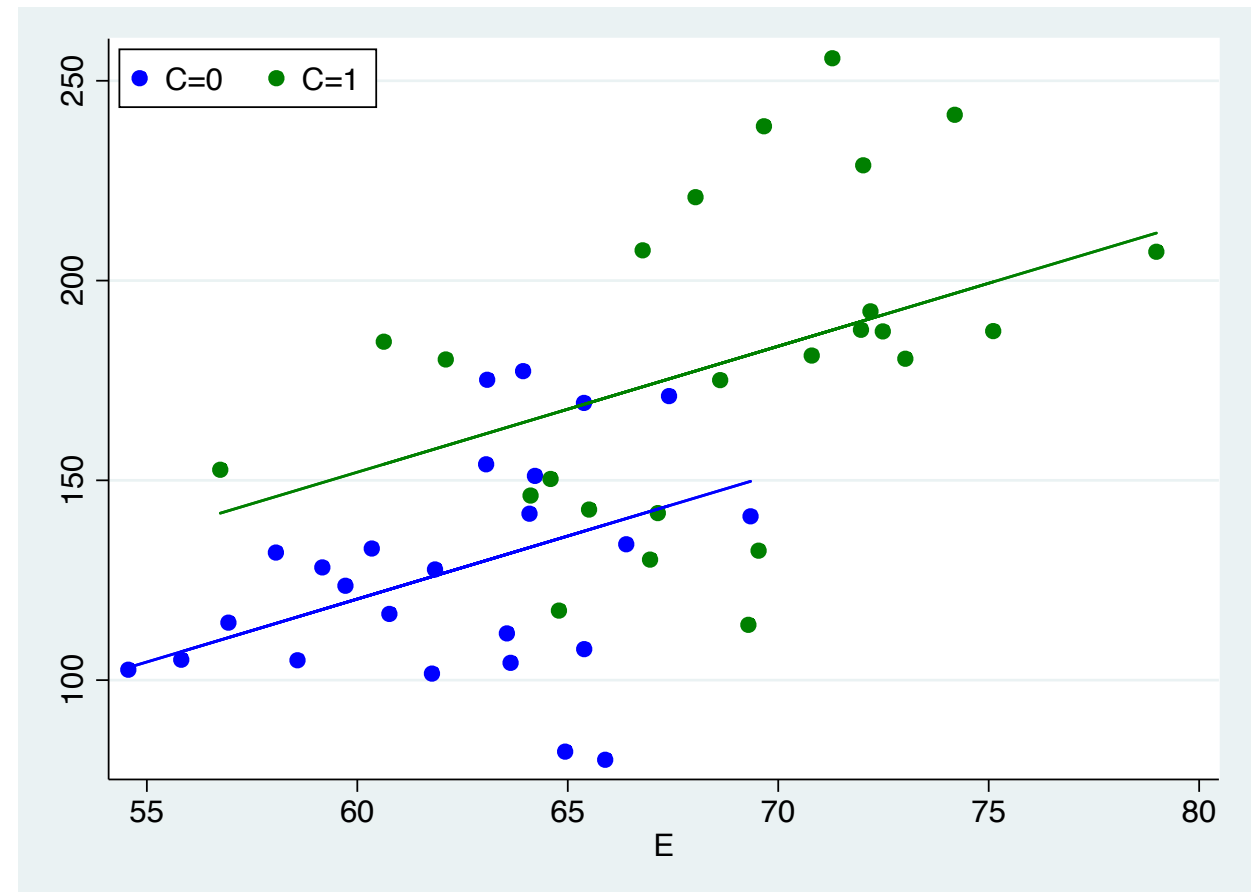
Confounding example based on simulated data (slide #9 - last lecture)

- continuous exposure E
- binary confounder C - no interaction with E
- continuous outcome $y = \beta_0 + \beta_1 E + \beta_2 C + \varepsilon$

Unadjusted



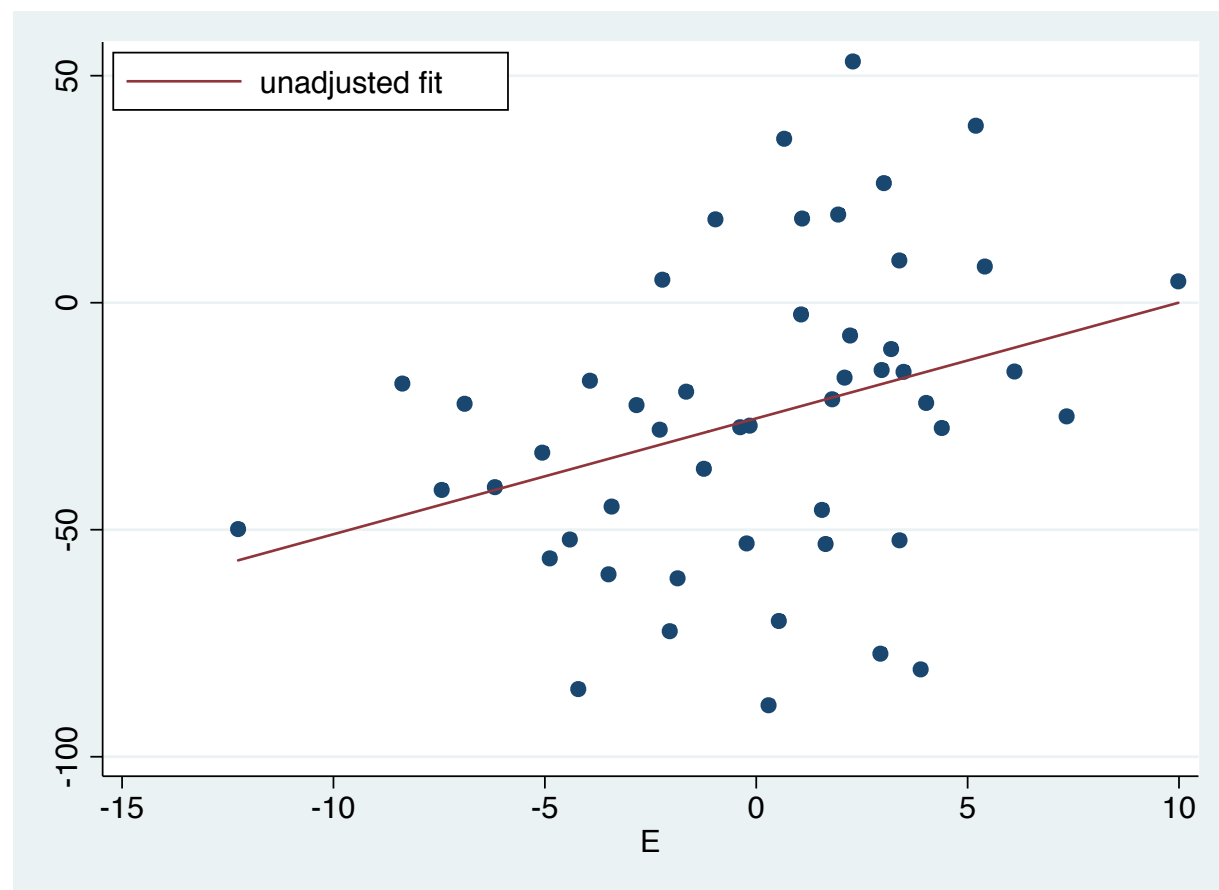
Adjusted



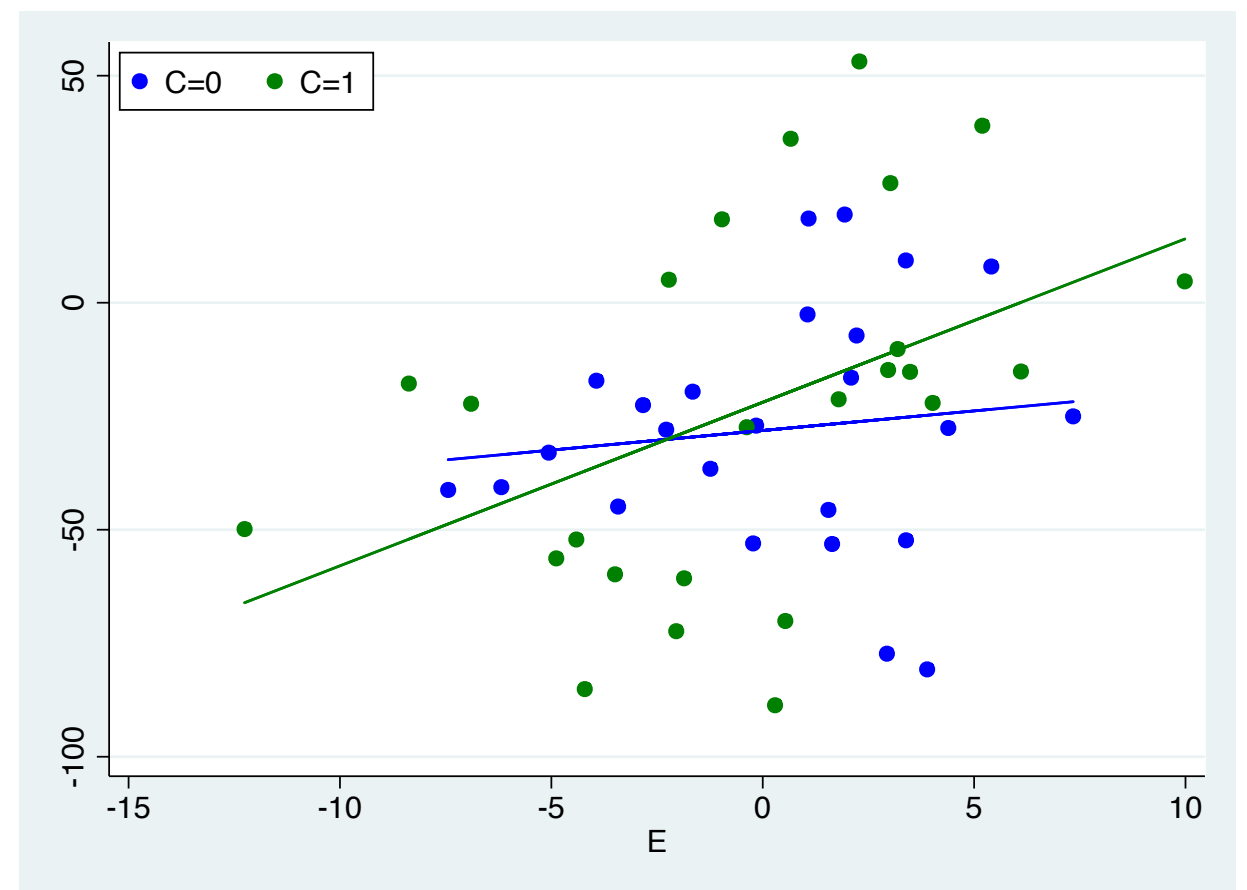
Example based on simulated data including interaction

- continuous exposure E
- binary predictor C - interaction with E
- continuous outcome $y = \beta_0 + \beta_1 E + \beta_2 C + \beta_3 CE + \varepsilon$

Unadjusted



Adjusted



Linear regression models including interaction

To allow interaction between two predictors x_1 & x_2 in a regression model for a continuous outcome y , include both predictors individually, as *main effects* along with their product (for *interaction*):

$$E[y|x_1, x_2] = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 \times x_2$$

Resulting model allows separate linear effects for x_1 & x_2 :

- Outcome mean as a function of x_1 , with x_2 fixed at a constant value c :

$$\begin{aligned} E[y|x_1, x_2 = c] &= \beta_0 + \beta_1 x_1 + \beta_2 c + \beta_3 x_1 \times c \\ &= (\beta_0 + \beta_2 c) + (\beta_1 + \beta_3 c) x_1 \end{aligned}$$

effect of x_1 : 

effect of x_2 : 

intercept: 

- Outcome mean as a function x_2 , with x_1 fixed at a constant value c :

$$\begin{aligned} E[y|x_1 = c, x_2] &= \beta_0 + \beta_1 c + \beta_2 x_2 + \beta_3 c \times x_2 \\ &= (\beta_0 + \beta_1 c) + (\beta_2 + \beta_3 c) x_2 \end{aligned}$$

- Allows different intercepts & slopes as c varies
- Reduces to standard linear model with no interaction ($\beta_3 = 0$)
- $\beta_3 \neq 0$ represents *interaction* between x_1 & x_2

Example: interaction of BMI and physical activity (PA) effects on SBP in HERS

Motivating questions:

- Excess weight increases SBP, but PA may blunt this effect
 - Does higher BMI lead to higher SBP only among inactive?
 - Does protective effect of PA on SBP increase with BMI?

- Predictors:

```
egen mb = mean(BMI)
```

```
gen BMIC = BMI - mb
```

```
recode physact (1/2=0) (3/5=1), g(active)
```

- Centered BMI: $BMIC = BMI - 28.6$ (centered on sample mean for interpretability)
- Physically active (indicator for activity generated by including `i.active` in model):
`1.active` (0 = inactive, 1 = active)
- Interaction (product) term `1.active#c.BMIC` (# denotes product term in model):

$$1.active\#c.BMIC = 1.active \times c.BMIC$$
$$= 0 \text{ if } active = 0$$
$$= BMIC \text{ if } active = 1$$

Note: “`c.`” syntax denotes a continuous predictor in a regression model - used for including continuous variables in interaction terms

Effects of PA - dependence on BMI

- Model for mean SBP:

$$E[\text{SBP} | \text{active}, \text{BMI}c] = \beta_0 + \beta_1 1.\text{active} + \beta_2 c.\text{BMI}c + \beta_3 1.\text{active} \# c.\text{BMI}c$$

- Estimated mean SBP for each level of PA:

$$E[\text{SBP} | \text{active}=0, \text{BMI}c] = \beta_0 + \beta_2 c.\text{BMI}c$$

$$E[\text{SBP} | \text{active}=1, \text{BMI}c] = \beta_0 + \beta_1 + (\beta_2 + \beta_3) c.\text{BMI}c$$

- Difference is $\beta_1 + \beta_3 c.\text{BMI}c$
- Effect of PA depends on BMI

Effects of BMI among active & inactive participants

$$E[\text{SBP} | \text{active}, \text{BMI}c] = \beta_0 + \beta_1 1.\text{active} + \beta_2 c.\text{BMI}c + \beta_3 1.\text{active} \# c.\text{BMI}c$$

For inactive:

$$E[\text{SBP} | \text{active}=0, \text{BMI}c] = \beta_0 + \beta_2 c.\text{BMI}c$$

- β_2 gives change in mean SBP (*mmHg*) for unit (*kg/m²*) increase in BMI

For active:

$$E[\text{SBP} | \text{active}=1, \text{BMI}c] = (\beta_0 + \beta_1) + (\beta_2 + \beta_3) c.\text{BMI}c$$

- $\beta_2 + \beta_3$ gives change in mean SBP for unit increase in BMI
- Effect of BMI depends on PA

Interaction model for SBP in baseline HERS dataset

```
. regress SBP i.active##c.BMIc
```

Source	SS	df	MS	Number of obs	=	2758
Model	4579.65484	3	1526.55161	F(3, 2754)	=	4.24
Residual	992671.256	2754	360.447079	Prob > F	=	0.0054
				R-squared	=	0.0046
				Adj R-squared	=	0.0035
Total	997250.911	2757	361.715963	Root MSE	=	18.985

SBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
1.active	-.5468102 β_1	.8611566	-0.63	0.525	-2.235388 1.141768
BMIc	.0512451 β_2	.1138269	0.45	0.653	-.1719496 .2744397
active#c.BMIc					
1	.2293768 β_3	.1406966	1.63	0.103	-.0465047 .5052584
_cons	135.5883 β_0	.7508309	180.58	0.000	134.116 137.0605

Note: syntax "i.active##c.BMIc" is shorthand for including:
i.active, c.BMIc & i.active#c.BMIc.

Equivalent command from earlier Stata versions (≤ 10):

```
xi: regress sbp i.active*BMIc
```

Equivalent specification of previous model

```
. regress SBP i.active c.BMIc i.active#c.BMIc
```

Source	SS	df	MS	Number of obs = 2758			
Model	4579.65484	3	1526.55161	F(3, 2754) = 4.24			
Residual	992671.256	2754	360.447079	Prob > F = 0.0054			
Total	997250.911	2757	361.715963	R-squared = 0.0046			
				Adj R-squared = 0.0035			
				Root MSE = 18.985			

SBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
1.active	-.5468102	.8611566	-0.63	0.525	-2.235388	1.141768
BMIc	.0512451	.1138269	0.45	0.653	-.1719496	.2744397
active#c.BMIc						
1	.2293768	.1406966	1.63	0.103	-.0465047	.5052584
_cons	135.5883	.7508309	180.58	0.000	134.116	137.0605

Interpretation of coefficients: `_cons` (β_0)

$$E[\text{SBP} | \text{active}, \text{BMIC}] = \beta_0 + \beta_1 1.\text{active} + \beta_2 \text{c.BMIC} + \beta_3 1.\text{active} \# \text{c.BMIC}$$

- Interpretation: average SBP in inactive participants with `BMIC = 0`
(i.e., BMI set at mean value of 28.6 kg/m^2):

$$E[\text{SBP} | \text{active}=0, \text{BMIC}=0] = \beta_0$$

- Average SBP among inactive with BMI = 28.6 kg/m^2 is 135.6 mmHg (95% CI: 134.1, 137.1)

Interpretation of coefficients: 1.active (β_1)

$$E[\text{SBP} | \text{active}, \text{BMIC}] = \beta_0 + \beta_1 1.\text{active} + \beta_2 c.\text{BMIC} + \beta_3 1.\text{active} \# c.\text{BMIC}$$

- Interpretation: effect of being active for participants with $\text{BMIC} = 0$:

$$E[\text{SBP} | \text{active} = 1, \text{BMIC} = 0] = \beta_0 + \beta_1$$

$$E[\text{SBP} | \text{active} = 0, \text{BMIC} = 0] = \beta_0$$

- Difference is β_1 (i.e. effect of being active for those with average BMI)
 - At BMI of 28.6 kg/m^2 (mean), PA reduces SBP by 0.55 mmHg (95% CI: -2.2, 1.1)
- For other values of BMI the effect of PA on SBP involves the coefficient β_3

Interpretation of coefficients: BMIc (β_2)

$$E[\text{SBP} | \text{active}, \text{BMIc}] = \beta_0 + \beta_1 1.\text{active} + \beta_2 \text{BMIc} + \beta_3 1.\text{active} \# c.\text{BMIc}$$

- BMIc (β_2): effect of a 1-kg/m² increase in BMI, if inactive

$$E[\text{SBP} | \text{active} = 0, \text{BMIc} = k+1] = \beta_0 + \beta_2 (k+1)$$

$$E[\text{SBP} | \text{active} = 0, \text{BMIc} = k] = \beta_0 + \beta_2 k$$

- Difference is β_2 for any value of BMI (k)
- Among inactive, a 1-kg/m² increase in BMI increases SBP by 0.05 mmHg (95% CI: -0.2, 0.3)

Interpretation of coefficients: $1.\text{active}\#c.\text{BMIC}$ (β_3)

$$E[\text{SBP}|\text{active}, \text{BMIC}] = \beta_0 + \beta_1 1.\text{active} + \beta_2 \text{BMIC} + \beta_3 1.\text{active}\#c.\text{BMIC}$$

1. Difference between BMI effects in active and inactive

$$E[\text{SBP}|\text{active} = 1, \text{BMIC} = k+1] - E[\text{SBP}|\text{active} = 1, \text{BMIC} = k] -$$

$$E[\text{SBP}|\text{active} = 0, \text{BMIC} = k+1] - E[\text{SBP}|\text{active} = 0, \text{BMIC} = k]$$

$$= \{ (\beta_0 + \beta_1 + (\beta_2 + \beta_3)(k+1)) - (\beta_0 + \beta_1 + (\beta_2 + \beta_3)k) \} -$$

$$\{ (\beta_0 + \beta_2(k+1)) - (\beta_0 + \beta_2k) \} = \beta_3$$

- among active, a unit kg/m^2 increase in BMI predicts a 0.23 *mmHg* greater increase in SBP than among inactive (95% CI: -0.05, 0.51)

2. Change in effect of PA for every 1 kg/m^2 increase in BMI

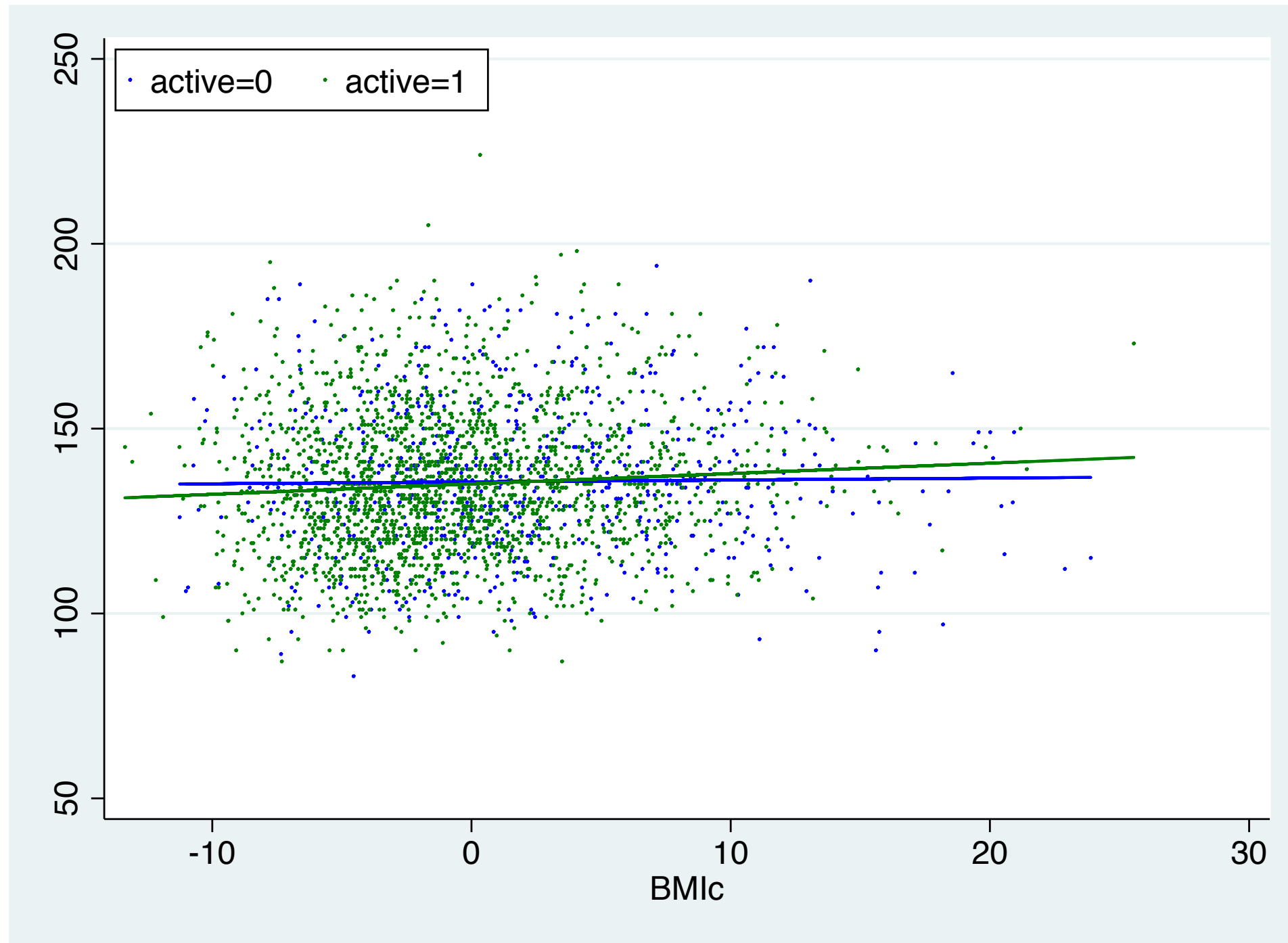
$$E[\text{SBP}|\text{active} = 1, \text{BMIC} = k+1] - E[\text{SBP}|\text{active} = 0, \text{BMIC} = k+1] -$$

$$E[\text{SBP}|\text{active} = 1, \text{BMIC} = k] - E[\text{SBP}|\text{active} = 0, \text{BMIC} = k] = \beta_3$$

- for every kg/m^2 increase in BMI, the beneficial effect of being active on SBP decreases by 0.23 *mmHg* (95% CI: -0.05, 0.51)

3. p -value of 0.10 for $1.\text{active}\#c.\text{BMIC}$ shows that evidence for interaction is weak

Illustrating BMI - activity interaction in HERS



```
. regress SBP i.active##c.BM1c
. predict p
. graph twoway (scatter SBP BM1c if active==0, mcolor(blue) msize(vtiny))
(scatter SBP BM1c if active==1, mcolor(green) msize(vtiny)) (line p BM1c if
active==0, clcolor(blue)) (line p BM1c if active==1, clcolor(green)),
legend( order(1 "active=0" 2 "active=1") ring(0) pos(10) )
```

Use of `lincom` for summarizing interaction effects

- Effects of PA & BMI depend on interaction coefficient `1.active#c.BMIc` (β_3)
 - `lincom` statements can be used to illustrate effects (preferred to presenting raw coefficients)
 - Example - two `lincom` statements:

```
. lincom 1.active + 1.4*1.active#c.BMIc ( $\beta_1 + 1.4\beta_3$ )
```

```
( 1) 1.active + 1.4*1.active#c.BMIc = 0
```

```
-----+-----
      sbp |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-----+-----
      (1) |   -.2256828   .8505544    -0.27   0.791    -1.893472     1.442106
-----+-----
```

```
. lincom BMIc + 1.active#c.BMIc ( $\beta_2 + \beta_3$ )
```

```
( 1) BMIc + 1.active#c.BMIc = 0
```

```
-----+-----
      sbp |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-----+-----
      (1) |   .2806219   .0826981     3.39   0.001     .1184653     .4427785
-----+-----
```

Interpretation of first `lincom` result:

`lincom 1.active + 1.4*1.active#c.BM Ic` ($\beta_1 + 1.4\beta_3$)

- Interpretation: effect of PA for an individual with BMI of 30 kg/m^2
 - for BMI=30, $BMIc=(30-28.6) = 1.4 kg/m^2$

$$E[SBP|x] = \beta_0 + \beta_1 1.active + \beta_2 BMIc + \beta_3 1.active \# c.BM Ic$$

Active: $E[SBP_{active} = 1, BMIc = 1.4] = \beta_0 + \beta_1 + 1.4(\beta_2 + \beta_3)$

Inactive: $E[SBP_{active} = 0, BMIc = 1.4] = \beta_0 + 1.4\beta_2$

- Difference is $\beta_1 + 1.4\beta_3 = -0.23$
- At BMI of 30 kg/m^2 , PA reduces mean SBP by 0.23 $mmHg$ (95% CI: -1.9, 1.4)

Interpretation of second `lincom` result:

`lincom c.BMIc + 1.active#c.BMIc` ($\beta_2 + \beta_3$)

- Interpretation: effect of a 1- kg/m^2 increase in BMI, for an active individual

$$E[\text{SBP}|x] = \beta_0 + \beta_1 1.\text{active} + \beta_2 \text{BMIc} + \beta_3 1.\text{active}\#\text{c.BMIc}$$

$$E[\text{SBP}|\text{active} = 1, \text{BMIc} = k+1] = \beta_0 + \beta_1 + (k+1)(\beta_2 + \beta_3)$$

$$E[\text{SBP}|\text{active} = 1, \text{BMIc} = k] = \beta_0 + \beta_1 + k(\beta_2 + \beta_3)$$

- Difference is $\beta_2 + \beta_3 = 0.28$, for any value of k
- Among active, a 1- kg/m^2 increase in BMI increases SBP by 0.28 *mmHg*
(95% CI: -0.12, 0.44)

Figuring out what `lincom` statement to use:

- **Example 1:** Estimate effect of PA at BMI of 35 (i.e. $BMI_c = 35 - 28.6 = 6.4 \text{ kg/m}^2$):

$$E[SBP|active, BMI_c] = \beta_0 + \beta_1 1.active + \beta_2 BMI_c + \beta_3 1.active \# c.BMI_c$$

Active	BMI _c	_cons	1.active	BMI _c	1.active#BMI _c
yes	6.4	1	1	6.4	6.4
no	6.4	1	0	6.4	0
	Diff.	0	1	0	6.4

- Use `lincom 1.active + 6.4 * 1.active#c.BMIc` (output on next slide)

Figuring out what `lincom` statement to use:

* Example 1

```
. lincom 1.active + 6.4 * 1.active#c.BMIc
```

```
( 1) 1.active + 6.4*1.active#c.BMIc = 0
```

SBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
(1)	.9212014	1.1367	0.81	0.418	-1.307668	3.150071

Interpretation: The estimated difference in average SBP between active and inactive individuals with a BMI of 35 kg/m^2 is 0.92 mmHg (95% CI: -1.37, 3.15).

Using margins to get the group means:

```
. margins active, at(BMIc=6.4)
```

```
Adjusted predictions          Number of obs   =          2758
Model VCE      : OLS
```

```
Expression      : Linear prediction, predict()
at              : BMIc              =          6.4
```

	Delta-method					
	Margin	Std. Err.	t	P> t	[95% Conf. Interval]	
active						
0	135.9163	.8817122	154.15	0.000	134.1874	137.6451
1	136.8375	.7174047	190.74	0.000	135.4307	138.2442

Figuring out what `lincom` statement to use:

- **Example 2:** Estimate effect of additional 5 kg/m^2 of BMI among active individuals:

$$E[\text{SBP}|\text{active}, \text{BMIC}] = \beta_0 + \beta_1 1.\text{active} + \beta_2 \text{BMIC} + \beta_3 1.\text{active}\#c.\text{BMIC}$$

Active	BMIC	_cons	1.active	BMIC	1.active#BMIC
yes	$k+5$	1	1	$k+5$	$k+5$
yes	k	1	1	k	k
	Diff.	0	0	5	5

- Use `lincom 5 * (BMIC + 1.active#c.BMIC)`

Figuring out what `lincom` statement to use:

* Example 2

```
. lincom 5 * (BMIC + 1.active#c.BMIC)
```

```
( 1) 5*BMIC + 5*1.active#c.BMIC = 0
```

SBP		Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
-----+-----							
(1)		1.40311	.4134907	3.39	0.001	.5923264	2.213893

Interpretation: The estimated effect on average SBP of an increase of 5 kg/m^2 in BMI among active individuals is 1.40 mmHg (95% CI: 0.59, 2.21)

Figuring out what `lincom` statement to use:

- **Example 3:** Estimate effect of additional 5 kg/m^2 among the *inactive*:

$$E[\text{SBP}|\text{active}, \text{BMIC}] = \beta_0 + \beta_1 1.\text{active} + \beta_2 \text{BMIC} + \beta_3 1.\text{active}\#c.\text{BMIC}$$

Active	BMIC	_cons	1.active	BMIC	1.active#BMIC
no	$k+5$	1	0	$k+5$	0
no	k	1	0	k	0
	Diff.	0	0	5	0

- Use `lincom 5*BMIC`

Figuring out what `lincom` statement to use:

* Example 3

```
. lincom 5*BMIC
```

```
( 1) 5*BMIC = 0
```

SBP		Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
-----+-----							
(1)		.2562254	.5691343	0.45	0.653	-.8597478	1.372199

Interpretation: The estimated effect on average SBP of an increase of 5 kg/m^2 in BMI among inactive individuals is 0.26 mmHg (95% CI: -0.86, 1.37)

If we hadn't centered BMI ...

- In BMI and PA example, if we did not center BMI
 - β_0 : average SBP if inactive, BMI = 0
 - β_1 : effect of PA if BMI = 0
 - estimated effect of PA at any plausible BMI requires `lincom`
- With centered BMI:
 - β_0 and β_1 refer to participants with average BMI

If we hadn't centered BMI ...

```
. regress SBP i.active##c.BMI
```

Source	SS	df	MS	Number of obs = 2758			
Model	4579.65484	3	1526.55161	F(3, 2754) = 4.24			
Residual	992671.256	2754	360.447079	Prob > F = 0.0054			
Total	997250.911	2757	361.715963	R-squared = 0.0046			
				Adj R-squared = 0.0035			
				Root MSE = 18.985			

SBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
1.active	-7.102228	4.251184	-1.67	0.095	-15.43806	1.233603
BMI	.0512451	.1138269	0.45	0.653	-.1719496	.2744397
active#c.BMI						
1	.2293768	.1406966	1.63	0.103	-.0465047	.5052584
_cons	134.1237	3.544294	37.84	0.000	127.174	141.0735

- Average SBP among inactive with BMI = 0 kg/m^2 is 134.1 *mmHg*
- At BMI of 0 kg/m^2 , PA reduces SBP by 7.1 *mmHg*

Interactions between continuous predictors

- Be careful with interactions between continuous variables
 - non-linearity, influential points can be a problem
 - easier to interpret if one or both dichotomized, but information gets lost
- Restricted cubic splines work (next week), but results only interpretable by plotting
- An example will be covered in this week's lab

Interactions between multi-category predictors

- Hard to detect and interpret
- Example - predictors with 3 and 4 categories:
 - $(3 - 1) \times (4 - 1) = 6$ interaction parameters
- Manually-constructed product terms often don't work; best to use Stata syntax
 - newer versions (≥ 11): `regress y i.catvar1##i.catvar2`
 - earlier versions (≤ 10): `xi: regress y i.catvar1*i.catvar2`

HERS example using all physical activity levels:

```
. regress SBP i.physact##c.BMIc
```

Source	SS	df	MS	Number of obs	=	2,758
				F(9, 2748)	=	1.87
Model	6072.24773	9	674.694192	Prob > F	=	0.0519
Residual	991178.663	2,748	360.690925	R-squared	=	0.0061
				Adj R-squared	=	0.0028
Total	997250.911	2,757	361.715963	Root MSE	=	18.992

SBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
physact						
somewhat less active	1.038665	1.677851	0.62	0.536	-2.251312	4.328642
about as active	.1307023	1.558998	0.08	0.933	-2.926224	3.187629
somewhat more active	.5509421	1.582226	0.35	0.728	-2.55153	3.653414
much more active	.6059146	1.863303	0.33	0.745	-3.047702	4.259531
BMiC						
	.1147426	.1926202	0.60	0.551	-.2629524	.4924376
physact#c.BMiC						
somewhat less active	-.094251	.2389033	-0.39	0.693	-.5626991	.3741972
about as active	.0523299	.2237974	0.23	0.815	-.3864982	.4911579
somewhat more active	.2301864	.2421104	0.95	0.342	-.2445504	.7049231
much more active	.5299496	.3112962	1.70	0.089	-.0804485	1.140348
_cons						
	134.8395	1.426352	94.53	0.000	132.0427	137.6363

HERS example using all physical activity levels:

- In this case evaluating evidence for interaction involves 4 coefficients
- Using active vs. inactive simpler to interpret
- Overall test for presence of interaction can be evaluated using an F test:

```
. testparm i.physact#c.BMIc
```

```
( 1)  2.physact#c.BMIc = 0
( 2)  3.physact#c.BMIc = 0
( 3)  4.physact#c.BMIc = 0
( 4)  5.physact#c.BMIc = 0
```

```
      F(   4,   2748) =      1.54
      Prob > F =      0.1868
```


Interactions and outcome scale

- Outcome scales:
 - untransformed vs log-transformed; absolute vs percent change
 - logistic, Poisson, negative binomial models: $E[y | x]$ linked to predictors via logit or log transformations
- Additive models excluding interaction terms hold exactly on at most one outcome scale (may hold approximately on > 1)
- Changes of scale can eliminate need for interaction term

Effects of hormone therapy (ht) on change in LDL (ldlch)

```
. tab ht
```

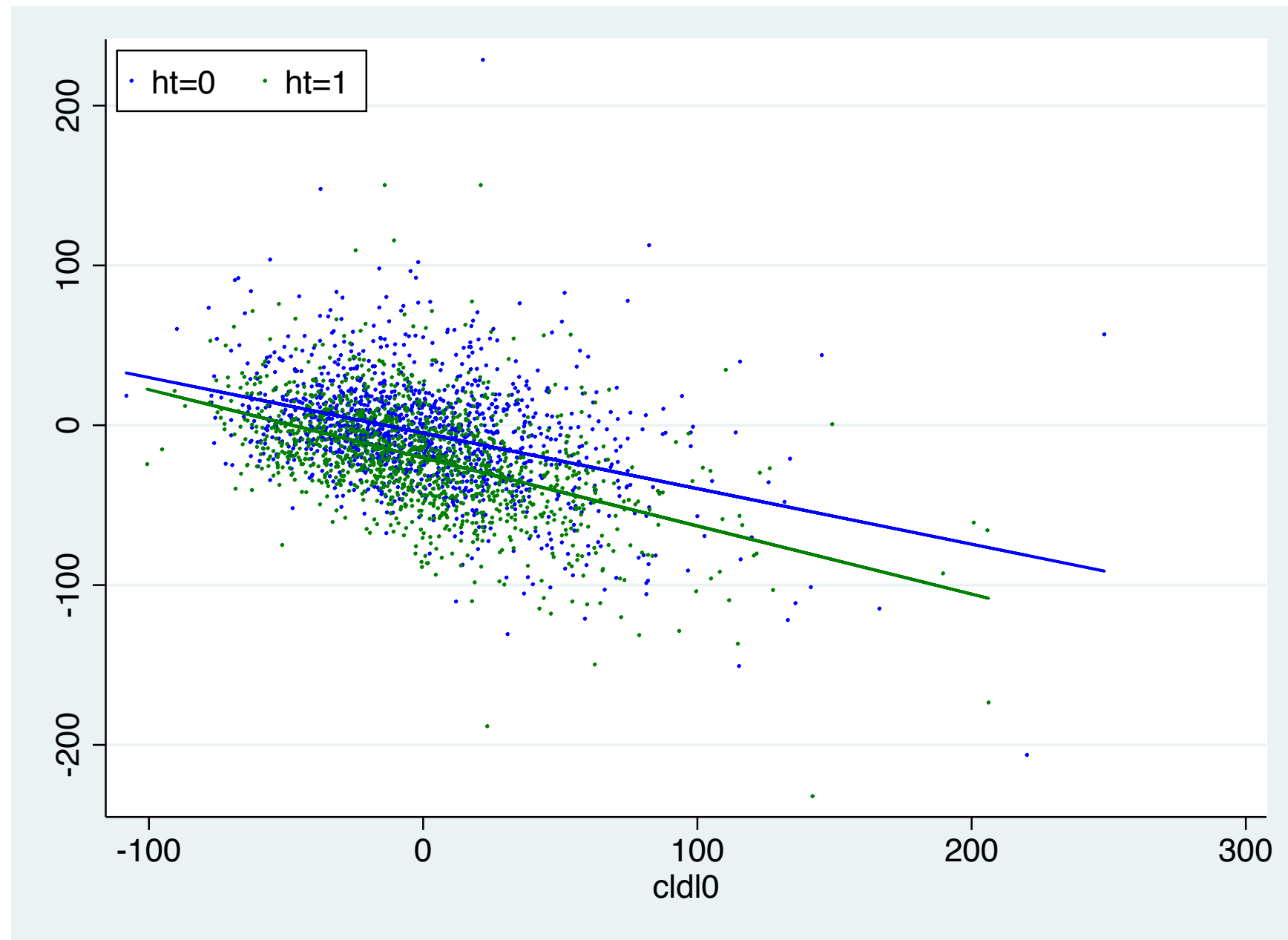
assignment to hormone therapy	Freq.	Percent	Cum.
placebo	1,383	50.05	50.05
hormone therapy	1,380	49.95	100.00
Total	2,763	100.00	

```
. regress ldlch ht##c.cldl0 (ldlch is change from baseline in LDL level, cldl0 is centered baseline level)
```

Source	SS	df	MS	Number of obs = 2597			
Model	721218.969	3	240406.323	F(3, 2593) = 258.81			
Residual	2408575.51	2593	928.876015	Prob > F = 0.0000			
Total	3129794.48	2596	1205.62191	R-squared = 0.2304			
				Adj R-squared = 0.2295			
				Root MSE = 30.477			
ldlch	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]		
ht							
hormone therapy	-15.47703	1.196246	-12.94	0.000	-17.82273	-13.13134	
cldl0	-.3477064	.0225169	-15.44	0.000	-.3918593	-.3035534	
ht#c.cldl0							
hormone therapy	-.0786871	.0316365	-2.49	0.013	-.1407226	-.0166517	
_cons	-4.888739	.8408392	-5.81	0.000	-6.537523	-3.239955	

Interpretation: among post-menopausal women with CHD, HT induces greater absolute reductions in LDL among women with higher baseline levels

Effects of hormone therapy (ht) on change in LDL (ldlch)



Effects of hormone therapy (ht) on change in LDL (ldlch)

* Use of margins to estimate effect of HT at diff. levels of (centered) baseline LDL
* Effect among indiv. at mean, and at 25 and 50 units more than the mean base. level
. margins ht, at(cldl0=(0 25 50))

Adjusted predictions

Number of obs = 2597

Model VCE : OLS

Expression : Linear prediction, predict()

1._at : cldl0 = 0
2._at : cldl0 = 25
3._at : cldl0 = 50

		Delta-method				
		Margin	Std. Err.	t	P> t	[95% Conf. Interval]
_at#ht						
1#placebo		-4.888739	.8408392	-5.81	0.000	-6.537523 -3.239955
1#hormone therapy		-20.36577	.8508778	-23.94	0.000	-22.03424 -18.6973
2#placebo		-13.5814	1.017519	-13.35	0.000	-15.57663 -11.58617
2#hormone therapy		-31.02561	1.017472	-30.49	0.000	-33.02075 -29.03047
3#placebo		-22.27406	1.41331	-15.76	0.000	-25.04539 -19.50273
3#hormone therapy		-41.68545	1.401366	-29.75	0.000	-44.43336 -38.93754

Interpretation: estimated effect of HT increases with higher baseline levels

HT and percent change LDL

```
. gen ldlpctch = (ldlch / ldl0) * 100
. regress ldlpctch ht##c.cldl0 (ldlpctch is % change from baseline in LDL level)
```

Source	SS	df	MS	Number of obs = 2597			
Model	233394.163	3	77798.0545	F(3, 2593) = 165.33			
Residual	1220171.82	2593	470.563756	Prob > F = 0.0000			
Total	1453565.98	2596	559.925263	R-squared = 0.1606			
				Adj R-squared = 0.1596			
				Root MSE = 21.692			

ldlpctch	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
ht						
hormone therapy	-10.79035	.8514335	-12.67	0.000	-12.45991	-9.120789
cldl0	-.2162437	.0160265	-13.49	0.000	-.2476697	-.1848176
ht#c.cldl0						
hormone therapy	.0218767	.0225175	0.97	0.331	-.0222773	.0660307
_cons	-1.284977	.5984713	-2.15	0.032	-2.458507	-.1114465

Interpretation: percent reductions in LDL induced by HT do not clearly vary by baseline level

Unfocused detection of interactions in multi-predictor models

- With 10 predictors
 - 45 possible 2-way interactions – 120 possible 3-way interactions
- Considering them all inflates type-I error, uncovers trivial interactions in big datasets
- If goal is outcome prediction, criteria for considering interactions differs (lecture 7)

Guided detection of interactions

- Focus on plausible interactions (Harrell et al., Stat Med, 1996;15:361-87)
 - treatment and severity of disease
 - treatment and calendar time
 - age and risk factors
 - measurement and state during measurement (e.g. l. ventric. function and stress level)
 - *with primary predictor*

Criteria for reporting interaction (see Epi. 203 lecture slides)

- *Substantively trivial* (e.g., RRs of 3.2 and 3.5 for two levels of a binary interacting factor): ignore, regardless of p -value for interaction
- *Substantively important* (e.g., RRs of 2.0 and 3.5): report if interaction p -value < 0.10
- *Qualitative interaction* (e.g., RRs of -2.0 and 2.0): report if interaction p -value < 0.15

Possible additional criteria for reporting

- Trying to prove something (e.g., show that BiDil should be approved for heart failure in African American patients):
 - need strong evidence, especially for ad hoc finding, possibly penalized for multiple comparisons
- Weak evidence for interaction that undermines your controversial hypothesis:
 - good to report as a sensitivity analysis

Further recommendations¹

- Not enough to show a within-subgroup effect; need to show that effects significantly differ by subgroup
- Focus on a priori interactions, those with primary predictor
- Evaluate interactions for strength, biological plausibility
- Identify post hoc interactions
- In ambiguous cases, present both overall and stratified results

¹ Wang et al., *NEJM*, 2008;357(21):2189-94

Summary: Interaction

- Summary: Interaction
- Interaction: association of one predictor with outcome modified by another predictor
- Modeled using product terms, made automatically by Stata `##` operator
- Subgroup-specific regression lines for continuous predictor not parallel
- Centering makes “main effects” easier to interpret
- Power not always low, but can be

Confounding, mediation, and interaction

- Confounders are a cause of both outcome and primary predictor, or surrogates for such a cause
- Potential confounders must be associated with predictor and independently with the outcome
- Confounding can account for the some or all of the unadjusted association between a predictor and an outcome

Mediation vs confounding

- Mediators are on causal pathway from predictor to outcome
- In multi-predictor models, mediation and confounding behave alike, must be distinguished on substantive grounds
- Some problems too complex for this paradigm:
 - LDL both confounds, mediates statin effects on CHD
- You have the substantive expertise to draw the DAG

Interaction vs confounding/mediation

- Interaction vs confounding/mediation
- Important to distinguish between:
 - change in the coefficient for a primary predictor in two models *with and without adjustment for a confounder or mediator*, which we sometimes use to assess confounding and/or mediation
 - differences in the estimated effect of a primary predictor *across strata defined by another predictor* in a single model that includes interaction term(s)

Confounding, mediation, or interaction?

1. Is alendronate effect on BMD reduced in vitamin-D deficient patients?
2. Is alendronate effect on vertebral fracture explained by changes in BMD?
3. Is HT effect on CHD explained by a healthier lifestyle?
4. Are beta-blockers less effective among African Americans?
5. Is diabetes a stronger risk factor for CHD events in women than in men?