

Logistic Regression

March 4, 2014
Biostatistics 208

Review of logistic regression for a single predictor

Example: dependence of CHD risk (P) on the binary predictor `arcus` in WCGS

- `arcus` = 1 for those with condition, `arcus` = 0 for those without
- `chd69` is a binary indicator of CHD at the end of follow-up

Default output of model - reports exponentiated coefficients (ORs) and 95% CIs:

```
. logistic chd69 arcus
```

```
Logistic regression                                Number of obs   =          3152
                                                    LR chi2(1)      =          12.98
                                                    Prob > chi2     =          0.0003
Log likelihood = -879.10783                        Pseudo R2      =          0.0073
```

chd69	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
-----+-----						
arcus	1.63528	.2195035	3.66	0.000	1.257	2.127399
_cons	.074344	.0062298	-31.02	0.000	.0630839	.0876141

- default output of Stata logistic regression procedure gives the **odds ratio** comparing the odds of CHD among men with `arcus` to the odds among men without `arcus`
- starting with Stata version 12, the **odds** of outcome occurrence in the baseline (`arcus` = 0) group are also provided

Review of logistic regression for a single predictor

Example: dependence of CHD risk (P) on the binary predictor arcus in WCGS

logistic output with coef option - reports coefficients and 95% CIs:

```
. logistic chd69 arcus, coef
Logistic regression
Number of obs      =      3152
LR chi2(1)         =      12.98
Prob > chi2        =      0.0003
Pseudo R2          =      0.0073

Log likelihood = -879.10783

-----+-----
      chd69 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----+-----
      arcus |   .4918141   .1342299     3.66   0.000   .2287283   .7548999
      _cons |  -2.599052   .0837965    -31.02   0.000   -2.76329   -2.434814
-----+-----
```

- $\beta_0 = -2.599052$, the log odds of CHD among individuals with $\text{arcus} = 0$
- $\beta_1 = 0.4918141$, the log odds ratio comparing the odds CHD among individuals with $\text{arcus} = 1$ to the odds of CHD among individuals with $\text{arcus} = 0$

$$\log\left[\frac{P(\text{arcus})}{1 - P(\text{arcus})}\right] = -2.599052 + 0.4918141\text{arcus}$$

Review of logistic regression for a single predictor

Note: the logistic model on the previous slide can be expressed in these equivalent ways

Log-odds : $\log\left[\frac{P(\text{arcus})}{1 - P(\text{arcus})}\right] = \beta_0 + \beta_1 \text{arcus}$

Odds : $\frac{P(\text{arcus})}{1 - P(\text{arcus})} = \exp(\beta_0 + \beta_1 \text{arcus})$

Probability: $P(\text{arcus}) = \frac{\exp(\beta_0 + \beta_1 \text{arcus})}{1 + \exp(\beta_0 + \beta_1 \text{arcus})}$

Review of logistic regression for a single predictor

Note: The effect of arcus on the outcome is *additive* on the log odds scale, and *multiplicative* on the odds scale

The log odds of CHD for an indiv. with arcus (arcus =1) is equal to the log odds for an indiv. without arcus (arcus =0) plus β_1 :

$$\log\left[\frac{P(\text{arcus} = 1)}{1 - P(\text{arcus} = 1)}\right] - \log\left[\frac{P(\text{arcus} = 0)}{1 - P(\text{arcus} = 0)}\right] = (\beta_0 + \beta_1) - \beta_0 = \beta_1$$

The odds of CHD for an indiv. with arcus (arcus =1) is equal to the odds for an indiv. without arcus (arcus =0) times $\exp(\beta_1)$:

$$\frac{\frac{P(\text{arcus} = 1)}{1 - P(\text{arcus} = 1)}}{\frac{P(\text{arcus} = 0)}{1 - P(\text{arcus} = 0)}} = \frac{\exp(\beta_0 + \beta_1)}{\exp(\beta_0)} = \frac{\exp(\beta_0)\exp(\beta_1)}{\exp(\beta_0)} = \exp(\beta_1)$$

Example: dependence of CHD risk (P) on the binary predictor arcus in WCGS (continued)

$$\log\left[\frac{P(\text{arcus})}{1 - P(\text{arcus})}\right] = -2.599052 + 0.4918141\text{arcus}$$

among those without arcus (arcus = 0):

log-odds of CHD: -2.599052

odds of CHD: $\exp(-2.599052) = 0.07434402$

probability of CHD: $0.07434402 / (1 + 0.07434402) = 0.06919945$

among those with arcus (arcus = 1):

log-odds of CHD: $-2.599052 + 0.4918141 = -2.1072379$

odds of CHD: $\exp(-2.599052 + 0.4918141) = 0.1215733$

probability of CHD: $0.1215733 / (1 + 0.1215733) = 0.10839532$

comparison of those with arcus (arcus = 1) **to those without** (arcus = 0):

log odds ratio : $(-2.1072379) - (-2.599052) = 0.4918141$

odds ratio : $\exp(0.4918141) = 1.63528$

95% C.I. for odds ratio: $(\exp(0.2287283) , \exp(0.7548999)) ; (1.26, 2.13)$ (based on the 95% CI for the coefficient in the previous output)

Example: dependence of CHD risk (P) on the binary predictor *arcus* in WCGS (continued)

- The logistic model (below) can also be used to compute other measures of risk:

$$RR = \frac{P(1)}{P(0)} = \frac{\exp(-2.1072379) / [1 + \exp(-2.1072379)]}{\exp(-2.599052) / [1 + \exp(-2.599052)]} = \frac{0.10839532}{0.06919945} = 1.566419$$

$$RD = P(1) - P(0) = 0.10839532 - 0.06919945 = 0.03919587$$

- Logistic models frequently used in estimation of **marginal causal effects**
- **Note:** Estimated RR & RD from a logistic model (above) won't in general correspond to estimates obtained from a relative risk or risk difference binary regression approach (covered in a subsequent lecture)

$$\log\left[\frac{P(\text{arcus})}{1 - P(\text{arcus})}\right] = -2.599052 + 0.491814\text{arcus}$$

Example: dependence of CHD risk (P) on age in WCGS

. logistic chd69 age

Logistic regression

Number of obs = 3154

LR chi2(1) = 42.89

Prob > chi2 = 0.0000

Pseudo R2 = 0.0241

Log likelihood = -869.17806

chd69	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
age	1.077262	.0121756	6.58	0.000	1.05366	1.101392
_cons	.0026333	.0014465	-10.81	0.000	.0008973	.0077283

output with coef option - reports coefficients and 95% CIs:

. logistic chd69 age, coef

Logistic regression

Number of obs = 3154

LR chi2(1) = 42.89

Prob > chi2 = 0.0000

Pseudo R2 = 0.0241

Log likelihood = -869.17806

chd69	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
age	.0744226	.0113024	6.58	0.000	.0522703	.0965748
_cons	-5.939516	.549322	-10.81	0.000	-7.016167	-4.862865

Example: dependence of CHD risk (P) on age in WCGS

$$\log\left[\frac{P(\text{age})}{1-P(\text{age})}\right] = \beta_0 + \beta_1 \text{age}$$

$$= -5.939516 + 0.0744226 \text{ age}$$

- -5.939516 is the log odds of CHD among individuals with age = 0
- 0.0744226 is the log odds ratio comparing the odds CHD among individuals with age = $x+1$ (in years) to the odds CHD among individuals with age = x

risk associated with a fixed age (age = 55):

log-odds of CHD: $-5.939516 + 0.0744226 \times 55 = -1.846273$

odds of CHD: $\exp(-1.846273) = 0.15782428$

probability of CHD: $0.15782428 / (1 + 0.15782428) = 0.13631108$

OR associated with a one year increase in age:

log odds ratio : $(-5.939516 + 0.0744226 \times 56) - (-5.939516 + 0.0744226 \times 55) = 0.0744226$

odds ratio : $\exp(0.0744226) = 1.077262$

95% C.I. for odds ratio: $(\exp(0.0522703) , \exp(0.0965748)) ; (1.05, 1.10)$

OR associated with a ten year increase in age:

log odds ratio : $10 \times 0.0744226 = 0.744226$

odds ratio : $\exp(0.744226) = 2.1048117$

95% C.I. for odds ratio: $(\exp(10 \times 0.0522703) , \exp(10 \times 0.0965748)) ; (1.69, 2.63)$

Logistic models with multiple predictors

Example (two binary predictors): relationship between CHD, type A/B behavior pattern and smoking (yes/no) in WCGS

Research question: Could other factors (e.g. behaviors or factors reflecting "lifestyle") explain part (or all) of the association between CHD and type A behavior pattern?

(The created variable smoke is a binary indicator of any reported smoking):

```
. logistic chd69 dibpat smoke
```

Logistic regression

Log likelihood = -860.36587

Number of obs = 3154

LR chi2(2) = 60.51

Prob > chi2 = 0.0000

Pseudo R2 = 0.0340

chd69	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
dibpat	2.301319	.3238066	5.92	0.000	1.746661	3.03211
smoke	1.8002	.2422852	4.37	0.000	1.3828	2.343593
_cons	.0393656	.0054842	-23.22	0.000	.0299593	.0517251

Interpretation:

- The adjusted odds ratio of 2.3 for type A behavior holds for smokers and non-smokers alike.
- Similarly, the adjusted odds ratio of 1.8 for smokers holds for type A & B behavior patterns.
- Estimated odds for CHD among non-smoker, type-B individuals is 0.39

Logistic models with multiple predictors

Example: CHD risk with systolic blood pressure and total serum cholesterol in the WCGS

Research question: are cholesterol and systolic blood pressure independently predictive of CHD risk?

```
. logistic chd69 chol sbp if chol<600
```

Logistic regression	Number of obs	=	3141
	LR chi2(2)	=	110.21
	Prob > chi2	=	0.0000
Log likelihood = -831.98952	Pseudo R2	=	0.0621

chd69	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
chol	1.011765	.0014981	7.90	0.000	1.008833	1.014706
sbp	1.024741	.0039104	6.40	0.000	1.017106	1.032434
_cons	.0002261	.0001393	-13.63	0.000	.0000676	.0007562

Notes:

- Excludes 12 observations with missing chol and 1 obs. with chol ≥ 600.
- Assumption of linearity for both chol and sbp must be checked before model is accepted as reasonable.

Logistic models with multiple predictors

Example: Logistic model for SBP and cholesterol level in WCGS (*continued*)

```
. logistic chd69 chol sbp if chol<600, coef
Logistic regression
Log likelihood = -831.98952
Number of obs      =      3141
LR chi2(2)         =      110.21
Prob > chi2        =      0.0000
Pseudo R2          =      0.0621
```

chd69	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
chol	.0116966	.0014807	7.90	0.000	.0087945	.0145987
sbp	.0244401	.003816	6.40	0.000	.016961	.0319193
_cons	-8.394706	.6160962	-13.63	0.000	-9.602233	-7.18718

Notes:

- 0.0117 is the log-odds ratio for each unit increase in chol holding sbp fixed
- 0.0244 gives the log-odds ratio for each unit increase in sbp holding chol fixed
- -8.395 gives the log-odds of CHD among indiv. with chol=0 & sbp=0
- model specifies linearity of log odds in both predictors:
 - the log-odds of CHD is linear in cholesterol for any specified value of SBP
 - the log-odds of CHD is linear in SBP for any specified value of cholesterol

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS (subsample of 1055 women without diabetes at enrollment)

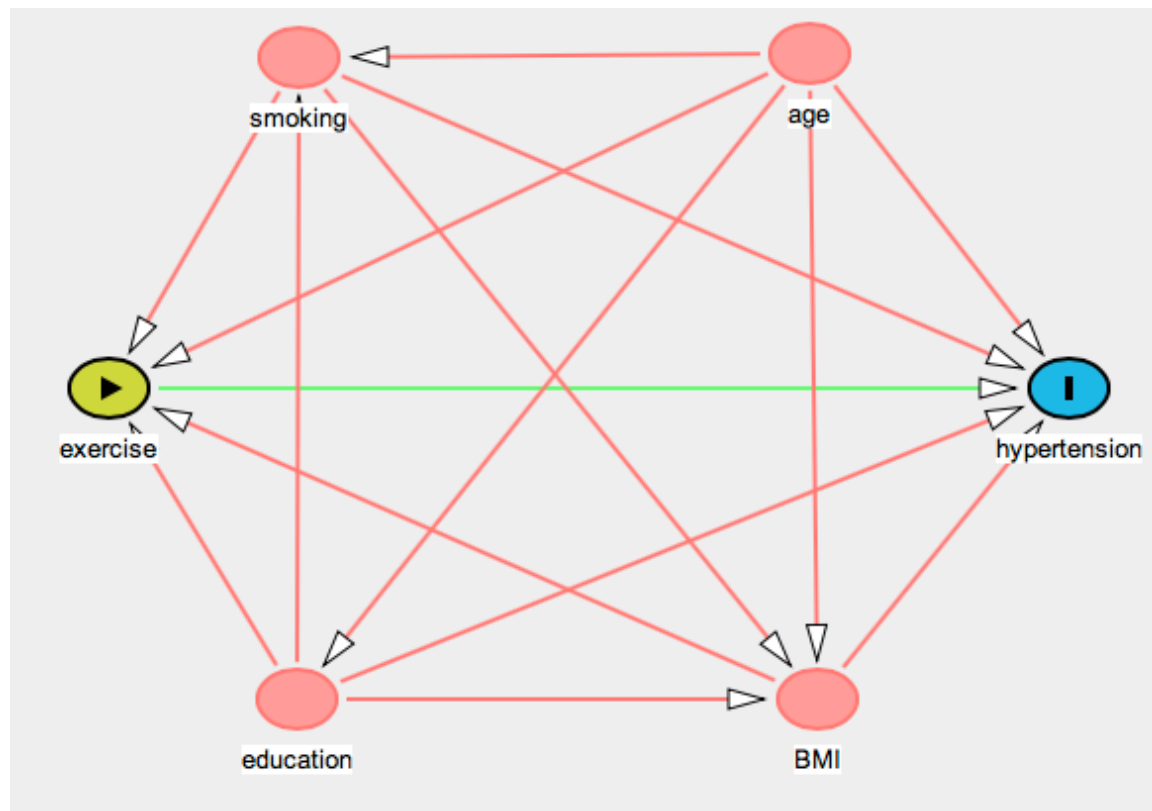
Goal: Investigate possibly causal association between exercise and the occurrence of hypertension at study baseline

- Hypertension measured as a binary indicator of enrollment $SBP > 140$
- Exercise represented as a binary indicator of exercise ≥ 3 times / week in the year before enrollment
- Evaluate the roles of other predictors as potential confounding (or mediating) variables
- Look for potential interactions with other predictors; assess nonlinearity and lack of overlap

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Additional variables from HERS that may be relevant predictors include:
 - demographic (age, body size, education)
 - health (cholesterol, glucose)
 - lifestyle (smoking, alcohol, diet, medications)
- **Question:** Could some or all of the apparent association between hypertension and exercise be explained by controlling for these variables?
- **Note:** predictors such as cholesterol & glucose could be hypothesized to play a mediating role - omitted in DAG



MSAS: smoking, age, education & BMI

Evaluating confounding using logistic regression

Example: Crude/unadjusted association between hypertension and exercise in HERS

* **unadjusted logistic model**

. logistic hypt exer3

Logistic regression

Number of obs = 1055

LR chi2(1) = 10.12

Prob > chi2 = 0.0015

Pseudo R2 = 0.0075

Log likelihood = -667.38065

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
exer3	.6526043	.0882528	-3.16	0.002	.5006573	.8506665
_cons	.5953608	.049477	-6.24	0.000	.5058733	.7006784

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

* `logistic model including MSAS predictors`

`. logistic hypt i.exer3 i.edu i.csmker agec bmic`

Logistic regression

Number of obs = 1054

LR chi2(5) = 52.10

Prob > chi2 = 0.0000

Log likelihood = -645.98359

Pseudo R2 = 0.0388

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.exer3	.7192284	.1037521	-2.28	0.022	.5420969	.954238
1.edu	.722425	.0994817	-2.36	0.018	.551541	.9462539
1.csmker	1.227736	.2445182	1.03	0.303	.8309558	1.813977
agec	1.060745	.0113766	5.50	0.000	1.03868	1.083279
bmic	1.04369	.0136563	3.27	0.001	1.017264	1.070802
_cons	.6179738	.0672956	-4.42	0.000	.4992023	.7650037

agec (in years at enrollment, centered)

bmic (body mass index (kg/m²), centered)

edu (>12 yrs education)

csmker (smoker at enrollment)

Note: HDL cholesterol & impaired fasting glucose (IFG) not included because of their possible mediating effects

Note: no significant nonlinearities / interactions / non-overlap detected.

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

The adjusted odds ratio for the effect of exercise in the model including the other predictors is closer to the null value (one) than the unadjusted OR:

	OR	95% CI	p-value (Wald)
<i>unadjusted</i>	0.653	0.50, 0.85	0.002
<i>adjusted</i>	0.719	0.54, 0.95	0.022

- The adjusted odds ratio 0.719 for the effect of exercise accounts for the possible confounding influence of the other variables in the model. (Results are similar if cholesterol and IFG are included.)

Note: the adjusted OR may have a valid causal interpretation, but does *not* generally estimate a **marginal causal effect**

Evaluating confounding using logistic regression

Collapsibility and odds ratios

- Exponentiated coefficient for exercise in previous model estimates the **conditional odds ratio** (*COR*) for the effect of exercise, given fixed values of the other included predictors (and assuming no interaction)
 - has a valid, individual causal interpretation if
 1. sample is representative of target population
 2. no unmeasured confounders
 3. correctly specified model
- The **marginal odds ratio** (*MOR*) is defined as the odds ratio for the effect of exercise on hypertension obtained by averaging over the values of the model-predicted outcome probabilities (an example of an **average causal effect**)
 - has a population causal interpretation if
 1. sample is representative of target population
 2. no unmeasured confounders
 3. correctly specified model
- In general, $COR \neq MOR$ - reflecting *non-collapsibility* of the odds ratio (sect. 3.4.5 VGSM)
 - By contrast, *RR* & *RD* are *collapsible* measures
 - Comparison of *COR* & *MOR* can be useful in evaluating effects of non-collapsibility (Menglan Pang M, Kaufman JS, Platt RW. Studying noncollapsibility of the odds ratio with marginal structural and logistic regression models. Stat Methods Med Res; 2013.)

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

- **Conditional odds ratio** for the effect of exercise (from previous model)

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.exer3	.7192284	.1037521	-2.28	0.022	.5420969	.954238

- **Marginal outcome probabilities** for exercise/no exercise

. margins exer3, post						
Predictive margins				Number of obs = 1054		
Model VCE : OIM						
Expression : Pr(hypt), predict()						

		Delta-method				
		Margin	Std. Err.	z	P> z	[95% Conf. Interval]
-----+-----						
exer3						
0		.3632016	.0192702	18.85	0.000	.3254327 .4009706
1		.2935795	.0222818	13.18	0.000	.249908 .337251

- margins uses the previously fitted model to estimate the average outcome probabilities for the entire sample under exercise/no exercise

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

- **Marginal causal OR, RR & RD** for the effect of exercise (from marginal outcome probabilities estimated under exercise=1/0)

* marginal OR

```
. nlcom (_b[1.exer3]/(1-_b[1.exer3])) / (_b[0.exer3]/(1-_b[0.exer3]))
      _nl_1:  (_b[1.exer3]/(1-_b[1.exer3])) / (_b[0.exer3]/(1-_b[0.exer3]))
```

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
_nl_1	.7286459	.1013849	7.19	0.000	.5299352 .9273566

* marginal RR

```
. nlcom (_b[1.exer3] / _b[0.exer3])
      _nl_1:  _b[1.exer3] / _b[0.exer3]
```

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
_nl_1	.8083099	.0765515	10.56	0.000	.6582718 .9583481

* marginal RD

```
. lincom (_b[1.exer3] - _b[0.exer3])
( 1)  - 0bn.exer3 + 1.exer3 = 0
```

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
(1)	-.0696221	.0301631	-2.31	0.021	-.1287407 -.0105036

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

Summary:

	OR	95% CI
<i>unadjusted</i>	0.65	0.50, 0.85
<i>adjusted (COR)</i>	0.72	0.54, 0.95
<i>MOR</i>	0.73	0.53, 0.93

- Observed difference between adjusted and unadjusted ORs for exercise (0.72, 0.65) implies some degree of confounding may be operating
- *MOR* & *COR* estimates similar in this case
- Note that if BMI was a mediator of this relationship, the adjusted conditional effect of exercise would represent a direct effect

Evaluating confounding using logistic regression

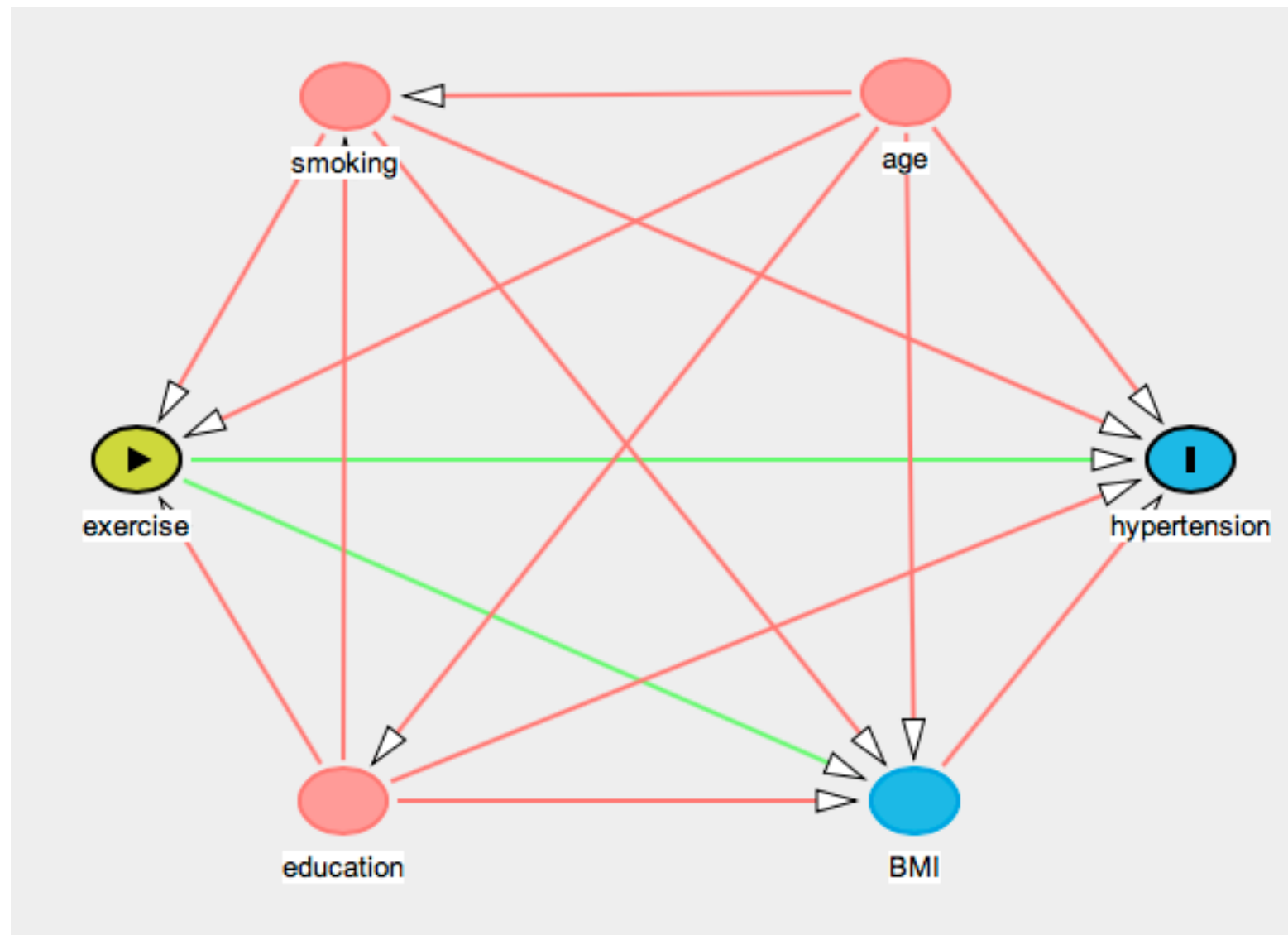
Summary:

- Conditional odds ratio (*COR*) from an adjusted logistic regression model cannot generally be equated with a corresponding average/marginal causal effect measure because of non-collapsibility
 - The *COR* is a valid effect measure, but must be interpreted conditionally
 - Approximates a marginal *RR* only in the case of rare outcomes
 - Because of non-collapsibility, methods to assess degree of confounding (and mediation effects) based on changes in coefficients unreliable for logistic models
- The `margins` (and now `teffects` in Stata 13) can be used to get estimates of marginal *OR*, *RR* & *RD* for logistic models
 - Log-relative risk and risk difference regression models can be used as well, but attention must be paid to convergence issues (lecture 11)
- Strategies for evaluating confounding otherwise unchanged from recommendations made for linear models.

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Consider possible mediation role of BMI



Note: see section 4.5.4 in VGSM for discussion of BMI as a possible mediator of exercise in HERS

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Three steps for evaluating mediation of exercise effect by BMI (analysis should be based same set of observations):
 1. evaluate adjusted assoc. between exercise and BMI
 2. evaluate adjusted assoc. between exercise and hypertension
 3. evaluate adjusted assoc. between exercise and hypertension controlling for BMI
- The OR for exercise from the 3rd model estimates a direct effect of exercise not mediated by BMI (and conditional on the other predictors)
- Estimating separate indirect and direct components of mediating effects is problematic due to non-collapsibility of ORs (except for rare outcomes - VanderWeele TJ, Vansteelandt S. Odds Ratios for Mediation Analysis for a Dichotomous Outcome. Am J Epidemiol. 2010; 172:1339–1348.)
- As discussed in lecture 4, confounders of the outcome-exposure and outcome-mediator relationships need to be considered.
- **Note:** Interactions between mediator and exposure create additional interpretation issues

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI as a possible mediator:

```
. regress bmi i.exer3 i.edu i.csmker agec
```

Source	SS	df	MS	Number of obs	=	1054
Model	2356.56238	4	589.140594	F(4, 1049)	=	23.12
Residual	26733.6582	1049	25.4848982	Prob > F	=	0.0000
				R-squared	=	0.0810
				Adj R-squared	=	0.0775
Total	29090.2206	1053	27.6260404	Root MSE	=	5.0483

bmi	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
1.exer3	-2.442347	.3238882	-7.54	0.000	-3.07789	-1.806805
1.edu	-.3196396	.3169374	-1.01	0.313	-.9415429	.3022638
1.csmker	-1.78384	.4640269	-3.84	0.000	-2.694366	-.8733131
agec	-.1283467	.023634	-5.43	0.000	-.1747219	-.0819714
_cons	29.2754	.2547791	114.91	0.000	28.77547	29.77533

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI as a possible mediator:

```
. logistic hypt i.exer3 i.edu i.csmker agec
```

Logistic regression

Number of obs = 1054

LR chi2(4) = 41.36

Prob > chi2 = 0.0000

Log likelihood = -651.35392

Pseudo R2 = 0.0308

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.exer3	.6491883	.0911016	-3.08	0.002	.4930833	.8547145
1.edu	.7138105	.0978588	-2.46	0.014	.545618	.93385
1.csmker	1.139427	.2241928	0.66	0.507	.7748269	1.675592
agec	1.054058	.0109989	5.05	0.000	1.03272	1.075838
_cons	.659734	.0699621	-3.92	0.000	.535923	.8121484

- OR of 0.65 estimates (conditional) overall effect of exercise not mediated through BMI

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI as a possible mediator:

```
. logistic hypt i.exer3 i.edu i.csmker agec bmic
```

Logistic regression

Number of obs = 1054

LR chi2(5) = 52.10

Prob > chi2 = 0.0000

Log likelihood = -645.98359

Pseudo R2 = 0.0388

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.exer3	.7192284	.1037521	-2.28	0.022	.5420969	.954238
1.edu	.722425	.0994817	-2.36	0.018	.551541	.9462539
1.csmker	1.227736	.2445182	1.03	0.303	.8309558	1.813977
agec	1.060745	.0113766	5.50	0.000	1.03868	1.083279
bmic	1.04369	.0136563	3.27	0.001	1.017264	1.070802
_cons	.6179738	.0672956	-4.42	0.000	.4992023	.7650037

- OR of 0.72 estimates (conditional) direct effect of exercise mediated through BMI

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Estimating marginal controlled direct effect (CDE) based on results from last model:

```
. * Run margins at a fixed level of BMI
. quietly margins exer3, at(bmic = 0)
. * Save results and estimate marginal OR, RD & RR
. matrix b = r(b)
. scalar EY0 = b[1, 1]
. scalar EY1 = b[1, 2]
. scalar cde_OR = EY1/(1-EY1)*(1-EY0)/EY0
. scalar cde_RR = EY1/EY0
. scalar cde_RD = EY1-EY0
. scalar list cde_OR cde_RR cde_RD
    cde_OR = .72734677
    cde_RR = .80714339
    cde_RD = -.06992906
```

- CDE OR estimate is similar to conditional direct effect OR on previous slide
- **Note:** The `medef` command (see lab 4) can be used to estimate controlled and natural direct effects, and allow interaction between mediator and exposure

Evaluating interaction using logistic regression

Interaction between two predictors: the magnitude of the association of each predictor with the outcome, as measured by its regression coefficient, varies according to the value of the other predictor.

- As in linear regression, interaction between two predictors is evaluated via incorporation of a constructed variable defined as the product of the two predictors into the model including both predictors
- If the coefficient (odds ratio) of the included product variable is significantly different than zero (one), we conclude that interaction is present
- Interaction assessed via the logistic model is **additive** on the log-odds scale and **multiplicative** on the odds scale

Interpreting two-way interaction between two binary predictors

Example: interaction between binary indicator of impaired fasting glucose (IFG) and BMI in HERS

- Additional analyses of the previous HERS example revealed an interaction between IFG and BMI
- We will explore this further here, focusing only on key variables (to simplify interpretation) and initially considering a binary indicator of high vs. low values of BMI

Note: treating BMI and glucose levels as continuous variables may be more appropriate in practice.

Interaction between two binary predictors

Example: interaction between binary indicators of IFG and BMI ≥ 35 in HERS

```
. * create binary indicator of BMI greater than or equal to 35
. gen bmihi = bmi
. recode bmihi min/34.9999=0 35/max=1
. * construct new variable as the product between IFG and BMI binary indicators
. gen ifgbmi = ifg*bmihi
. logistic hypt ifg bmihi ifgbmi
```

Logistic regression

Number of obs	=	1055
LR chi2(3)	=	16.06
Prob > chi2	=	0.0011
Pseudo R2	=	0.0119

Log likelihood = -664.41499

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
ifg	2.603175	.7056691	3.53	0.000	1.530239	4.428404
bmihi	1.671196	.393736	2.18	0.029	1.053133	2.651988
ifgbmi	.2163763	.1301662	-2.54	0.011	.0665503	.7035091
_cons	.4552846	.032823	-10.91	0.000	.3952911	.5243833

- Confidence interval for `ifgbmi` excludes 1, implying that we have evidence that an interaction between `ifg` and `bmihi` exists.
- Interpretation of Z (Wald) test statistic for testing the null hypothesis of no interaction ($H: \beta_3=0$): $Z = -1.530736/0.6015732 = -2.54$ (see next page)
- Referring to the standard normal distribution, the probability of a more extreme value of Z under the (two-sided) null hypothesis is 0.011.

Interaction between two binary predictors

Example: interaction between IFG & BMI in HERS (continued)

```
. * Coefficient form of the model:  
. logistic hypt ifg bmihi ifgbmi, coef
```

Logistic regression

Number of obs = 1055
LR chi2(3) = 16.06
Prob > chi2 = 0.0011
Pseudo R2 = 0.0119

Log likelihood = -664.41499

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
ifg	.9567317	.2710802	3.53	0.000	.4254242	1.488039
bmihi	.5135393	.2356014	2.18	0.029	.0517691	.9753095
ifgbmi	-1.530736	.6015732	-2.54	0.011	-2.709798	-.3516745
_cons	-.7868327	.0720933	-10.91	0.000	-.9281329	-.6455324

Interaction between two binary predictors

- Logistic model equation (log-odds form):

$$\log\left[\frac{P(\text{ifg}, \text{bmihi}, \text{ifg} \times \text{bmihi})}{1 - P(\text{ifg}, \text{bmihi}, \text{ifg} \times \text{bmihi})}\right] = \beta_0 + \beta_1 \text{ifg} + \beta_2 \text{bmihi} + \beta_3 \text{ifg} \times \text{bmihi}$$

- Calculation of component log-odds ratios:

$$\log\left[\frac{P(1,0,0)}{1 - P(1,0,0)}\right] - \log\left[\frac{P(0,0,0)}{1 - P(0,0,0)}\right] = \beta_1 = 0.9567317$$

$$\log\left[\frac{P(0,1,0)}{1 - P(0,1,0)}\right] - \log\left[\frac{P(0,0,0)}{1 - P(0,0,0)}\right] = \beta_2 = 0.5135393$$

$$\log\left[\frac{P(1,1,1)}{1 - P(1,1,1)}\right] - \log\left[\frac{P(0,1,0)}{1 - P(0,1,0)}\right] = \beta_1 + \beta_3 = 0.9567317 - 1.530736 = -0.574$$

$$\log\left[\frac{P(1,1,1)}{1 - P(1,1,1)}\right] - \log\left[\frac{P(1,0,0)}{1 - P(1,0,0)}\right] = \beta_2 + \beta_3 = 0.5135393 - 1.530736 = -1.017$$

$$\log\left[\frac{P(1,1,1)}{1 - P(1,1,1)}\right] - \log\left[\frac{P(0,0,0)}{1 - P(0,0,0)}\right] = \beta_1 + \beta_2 + \beta_3 = -0.060$$

- Interaction effect is *additive* on the log-odds scale

Interaction between two binary predictors

- Logistic model equation (odds form):

$$\frac{P(\text{ifg}, \text{bmihi}, \text{ifg} \times \text{bmihi})}{1 - P(\text{ifg}, \text{bmihi}, \text{ifg} \times \text{bmihi})} = \exp(\beta_0 + \beta_1 \text{ifg} + \beta_2 \text{bmihi} + \beta_3 \text{ifg} \times \text{bmihi})$$
$$= e^{\beta_0} \times e^{\beta_1 \text{ifg}} \times e^{\beta_2 \text{bmihi}} \times e^{\beta_3 \text{ifg} \times \text{bmihi}}$$

- Calculation of component odds ratios

$$\frac{P(1,0,0)}{1 - P(1,0,0)} \bigg/ \frac{P(0,0,0)}{1 - P(0,0,0)} = e^{\beta_1}$$

$$\frac{P(0,1,0)}{1 - P(0,1,0)} \bigg/ \frac{P(0,0,0)}{1 - P(0,0,0)} = e^{\beta_2}$$

$$\frac{P(1,1,0)}{1 - P(1,1,0)} \bigg/ \frac{P(0,1,0)}{1 - P(0,1,0)} = e^{\beta_1 + \beta_3}$$

$$\frac{P(1,1,0)}{1 - P(1,1,0)} \bigg/ \frac{P(1,0,0)}{1 - P(1,0,0)} = e^{\beta_2 + \beta_3}$$

$$\frac{P(1,1,0)}{1 - P(1,1,0)} \bigg/ \frac{P(0,0,0)}{1 - P(0,0,0)} = e^{\beta_1 + \beta_2 + \beta_3}$$

- Interaction effect is *multiplicative* on the odds scale

Example: interaction between IFG & BMI in HERS (continued)

Constructing `lincom` statements:

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	β_1
Yes	No	1	1	0	0	
No	No	1	0	0	0	
Diff		0	1	0	0	

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	β_2
No	Yes	1	0	1	0	
No	No	1	0	0	0	
	Diff	0	0	1	0	

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	$\beta_1 + \beta_3$
Yes	Yes	1	1	1	1	
No	Yes	1	0	1	0	
Diff		0	1	0	1	

IFG	BMIHI	_cons β_0	ifg β_1	bmihi β_2	ifgbmihi β_3	$\beta_2 + \beta_3$
Yes	Yes	1	1	1	1	
Yes	No	1	1	0	0	
	Diff	0	0	1	1	

Example: interaction between IFG & BMI in HERS (continued)

`. lincom ifg` β_1

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	2.603175	.7056691	3.53	0.000	1.530239	4.428404

`. lincom bmihi` β_2

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	1.671196	.393736	2.18	0.029	1.053133	2.651988

`. lincom ifg + ifgbmi` $\beta_1 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.5632653	.3024928	-1.07	0.285	.1966023	1.613754

`. lincom bmihi + ifgbmi` $\beta_2 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.3616071	.2001561	-1.84	0.066	.1222029	1.070021

`. lincom ifg + bmihi + ifgbmi` $\beta_1 + \beta_2 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.9413265	.4643066	-0.12	0.902	.3580038	2.475101

Example: interaction between IFG & BMI in HERS (continued)

Same results obtained using “i.”:

```
. logistic hypt i.ifg##i.bmihi
```

Logistic regression

Number of obs = 1055

LR chi2(3) = 16.06

Prob > chi2 = 0.0011

Log likelihood = -664.41499

Pseudo R2 = 0.0119

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.ifg	2.603175	.7056691	3.53	0.000	1.530239	4.428404
1.bmihi	1.671196	.393736	2.18	0.029	1.053133	2.651988
ifg#bmihi						
1 1	.2163763	.1301662	-2.54	0.011	.0665503	.7035091
_cons	.4552846	.032823	-10.91	0.000	.3952911	.5243833

Example: interaction between IFG & BMI in HERS (continued)

. lincom 1.ifg β_1

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	2.603175	.7056691	3.53	0.000	1.530239	4.428404

. lincom 1.bmihi β_2

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	1.671196	.393736	2.18	0.029	1.053133	2.651988

. lincom 1.ifg + 1.ifg#1.bmihi $\beta_1 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.5632653	.3024928	-1.07	0.285	.1966023	1.613754

. lincom bmihi + 1.ifg#1.bmihi $\beta_2 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.3616071	.2001561	-1.84	0.066	.1222029	1.070021

. lincom ifg + bmihi + 1.ifg#1.bmihi $\beta_1 + \beta_2 + \beta_3$

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.9413265	.4643066	-0.12	0.902	.3580038	2.475101

Evaluating presence of additive interaction

- Recall that additive interaction may be more biologically meaningful than multiplicative interaction in many contexts
 - logistic regression does not provide a direct measure of additive interaction
 - presence of multiplicative interaction doesn't necessarily imply presence of additive interaction
- The presence of additive interaction on the probability scale can be evaluated based on odds ratio estimates from a fitted logistic model as follows
 - $RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1$
$$= \exp(\beta_1 + \beta_2 + \beta_3) - \exp(\beta_1) - \exp(\beta_2) + 1$$
 - $RERI_{OR} = 0$ implies absence of additive interaction
 - $RERI_{OR} \neq 0$ implies presence of additive interaction
- $RERI_{RR}$ is an analog based on the relative risk
- **Note:** $RERI_{OR}$ doesn't estimate the actual magnitude of additive interaction
- Degree of additive interaction directly estimated (except for case-control studies) by
 - $P_{11} - P_{10} - P_{01} - P_{00} = (P_{11} - P_{00}) - [(P_{10} - P_{00}) + (P_{01} - P_{00})]$

Example: logistic regression assessment of additive interaction between IFG & BMI in HERS

* Estimate RERI_OR using coefficients from previous logistic model (including interaction)

```
. nlcom exp(_b[1.ifg]+_b[1.bmihi]+_b[1.ifg#1.bmi]) - exp(_b[1.ifg]) - exp(_b[1.bmihi]) + 1

      _nl_1:  exp(_b[1.ifg]+_b[1.bmihi]+_b[1.ifg#1.bmi]) - exp(_b[1.ifg]) - exp(_b[1.bmihi]) + 1
```

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
_nl_1	-2.333044	.933796	-2.50	0.012	-4.16325	-.5028372

Example: direct estimate of additive interaction between IFG & BMI in HERS

* Use the risk difference model for binary outcomes

```
. binreg hypt ifg bmihi ifgbmi, rd
```

Generalized linear models	No. of obs	=	1055
Optimization : MQL Fisher scoring	Residual df	=	1051
(IRLS EIM)	Scale parameter	=	1
Deviance = 1328.829981	(1/df) Deviance	=	1.264348
Pearson = 1055	(1/df) Pearson	=	1.003806

Variance function: $V(u) = u(1-u)$ [Bernoulli]

Link function : $g(u) = u$ [Identity]

BIC = -5987.492

hypt	EIM		z	P> z	[95% Conf. Interval]	
	Risk Diff.	Std. Err.				
ifg	.2295237	.0666862	3.44	0.001	.0988211	.3602263
bmihi	.1192496	.0571812	2.09	0.037	.0071764	.2313228
ifgbmi	-.3616225	.1340767	-2.70	0.007	-.6244079	-.0988371
_cons	.3128492	.0154982	20.19	0.000	.2824732	.3432251

- Model can't be fitted in many situations
 - multiple & continuous predictors
 - case-control studies

Likelihood ratio testing

Example: contribution of type A/B behavior pattern to predicting CHD in WCGS

Goal: use the likelihood ratio test to assess the contribution of behavior pattern to a model already controlling for age, chol, sbp, bmi and smoke.

- The `lrtest` procedure in Stata is used to compare likelihoods from nested models
- First, the full model including predictor(s) to be evaluated is fitted.
- Next, the likelihood from this model is saved in a named temporary location (e.g. "A") for further reference
- The nested model excluding the predictor(s) to be evaluated is fitted.
- The likelihood ratio test is then performed using the `lrtest` command and referencing the location (i.e. "A") of the likelihood from the full model.
- **Note:** The nested and full models must be based on the same set of observations for the LR test to make sense

Likelihood ratio testing

Example: contribution of type A/B behavior pattern to predicting CHD in WCGS study

* First, fit the full model including behpat:

```
. logistic chd69 age_10 chol_50 sbp_50 bmi_10 smoke i.behpat
```

Logistic regression

Number of obs = 3141
LR chi2(8) = 184.57
Prob > chi2 = 0.0000
Pseudo R2 = 0.1040

Log likelihood = -794.81

chd69	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
age_10	1.83375	.2198681	5.06	0.000	1.449707	2.319529
chol_50	1.704097	.1301391	6.98	0.000	1.467201	1.979243
sbp_50	2.463505	.5086518	4.37	0.000	1.643621	3.692369
bmi_10	1.739414	.462034	2.08	0.037	1.033479	2.927551
smoke	1.830672	.2583097	4.29	0.000	1.38837	2.413882
behpat						
2	1.068257	.2363271	0.30	0.765	.6924157	1.648103
3	.5141593	.1245593	-2.75	0.006	.3198064	.8266243
4	.572071	.1826116	-1.75	0.080	.3060107	1.069457

* Save the log-likelihood in the temporary variable "A":

```
. estimates store A
```

* Note : the variables age_10, chol_50, sbp_50, bmi_10 represent centered and scaled versions of the originals, and result in more interpretable odds ratio estimates.

Likelihood ratio testing

Example: contribution of type A/B behavior pattern to predicting CHD in WCGS study (*continued*)

* Next, the desired “nested” model excluding predictor(s) of interest is fit, and compared to the previous model using the lrtest command:

```
. logistic chd69 age_10 chol_50 sbp_50 bmi_10 smoke
```

Logistic regression

Number of obs = 3141

LR chi2(5) = 159.80

Prob > chi2 = 0.0000

Log likelihood = -807.19249

Pseudo R2 = 0.0901

chd69	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
age_10	1.904989	.2268333	5.41	0.000	1.508471	2.405735
chol_50	1.710974	.1297977	7.08	0.000	1.474584	1.985259
sbp_50	2.623972	.5367142	4.72	0.000	1.757326	3.918016
bmi_10	1.775994	.4680612	2.18	0.029	1.059518	2.976972
smoke	1.886037	.2643914	4.53	0.000	1.432933	2.482417

* perform likelihood ratio test comparing fitted model to full model (A):

```
. lrtest A
```

Likelihood-ratio test

(Assumption: . nested in A)

LR chi2(3) = 24.76

Prob > chi2 = 0.0000

Summary: procedure for likelihood ratio testing in nested models:

1. Fit the full model including all the variable(s) of interest
2. Issue the `estimates` command, using the `store` option to save results of the current model in a location labeled by the results with a name (e.g. `estimates store A`)
3. Fit the nested model excluding the variable(s) of interest
4. Issue the `lrtest` command, identifying the results of the full model fit in step 1 by passing the name specified in step 2 (e.g. `lrtest A`)

The `lrtest` procedure computes the likelihood ratio comparing the two models, and refers the results to the chi-squared distribution with degrees of freedom equal to the difference in number of degrees of freedom in the two fitted models. The results of the test evaluate the null hypothesis that the true values of coefficients from the additional variables in the full model are all zero.

Summary: procedure for likelihood ratio testing in nested models:

- the likelihood/log-likelihood always increases as variables are added to an existing model
- like the F test for linear regression models, the likelihood ratio (LR) test is used to compare two nested models
- the LR statistic comparing two nested models is computed as twice the difference between the log-likelihoods:
$$2 \times [(\log - \text{likelihood from more complex model}) - (\log - \text{likelihood from simpler model})] =$$
$$2 \times \log \left(\frac{\text{likelihood from more complex model}}{\text{likelihood from simpler model}} \right) = LR$$
- the LR statistic is approximately chi-squared distributed, with degrees of freedom equal to the difference in number of predictors between nested models
- likelihood ratio tests for evaluating contribution of predictors have better reliability than Wald tests, especially for smaller samples