

Logistic Regression

March 3, 2020
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 i.arcus
```

```
Logistic regression
```

```
Number of obs      =      3,152
```

```
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							
present		1.635281	.2195036	3.66	0.000	1.257001	2.127399
_cons		.074344	.0062298	-31.02	0.000	.0630839	.0876141

Note: _cons estimates baseline odds.

- 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
- 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 i.arcus, coef
```

```
Logistic regression
```

```
Number of obs      =      3,152
```

```
LR chi2(1)         =      12.98
```

```
Prob > chi2        =      0.0003
```

```
Log likelihood = -879.10783
```

```
Pseudo R2         =      0.0073
```

chd69	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
arcus						
present	.4918144	.1342299	3.66	0.000	.2287286	.7549002
_cons	-2.599052	.0837965	-31.02	0.000	-2.76329	-2.434814

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

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

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:

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

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

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

- Logistic models frequently used in estimation of **marginal causal effects**
- **Note:** Estimated RR & RD from a logistic model won't in general correspond to estimates obtained from a relative risk or risk difference binary regression approach, or to *marginal effects* estimated from the logistic model, especially when additional predictors are included.

Stata alternatives for fitting logistic models (all essentially equivalent)

- `logit` command - equivalent to `logistic` with `coef` option:

```
. logit chd69 arcus
```

chd69	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
arcus	.4918144	.1342299	3.66	0.000	.2287286	.7549002
_cons	-2.599052	.0837965	-31.02	0.000	-2.76329	-2.434814

Note: Normally not needed - useful to override default `lincom` reporting of ORs after using `logistic`

- `glm` command - umbrella for the whole family of generalized linear models:

```
. glm chd69 arcus, family(binomial)
```

chd69	Coef.	OIM Std. Err.	z	P> z	[95% Conf. Interval]	
arcus	.4918139	.1342299	3.66	0.000	.2287281	.7548997
_cons	-2.599052	.0837965	-31.02	0.000	-2.76329	-2.434814

- `binreg` command - useful for fitting binary regression models with alternate links

```
. binreg chd69 arcus, or
```

chd69	Coef.	EIM Std. Err.	z	P> z	[95% Conf. Interval]	
arcus	.4918141	.1342298	3.66	0.000	.2287285	.7548997
_cons	-2.599052	.0837963	-31.02	0.000	-2.76329	-2.434814

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

Assume linearity of log odds with age holds:

```
. 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: Logistic model for dependence of CHD risk on SBP and cholesterol in WCGS

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

Logistic regression

Number of obs = 3141

LR chi2(2) = 110.21

Prob > chi2 = 0.0000

Pseudo R2 = 0.0621

Log likelihood = -831.98952

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 in log CHD odds must be checked before model is accepted as reasonable.
- centering & scaling of predictors for interpretability follows same approach used in linear regression

Logistic models with multiple predictors

Example: Logistic model for dependence of CHD risk on SBP and cholesterol in WCGS

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

Logistic regression

Number of obs = 3141

LR chi2(2) = 110.21

Prob > chi2 = 0.0000

Pseudo R2 = 0.0621

Log likelihood = -831.98952

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

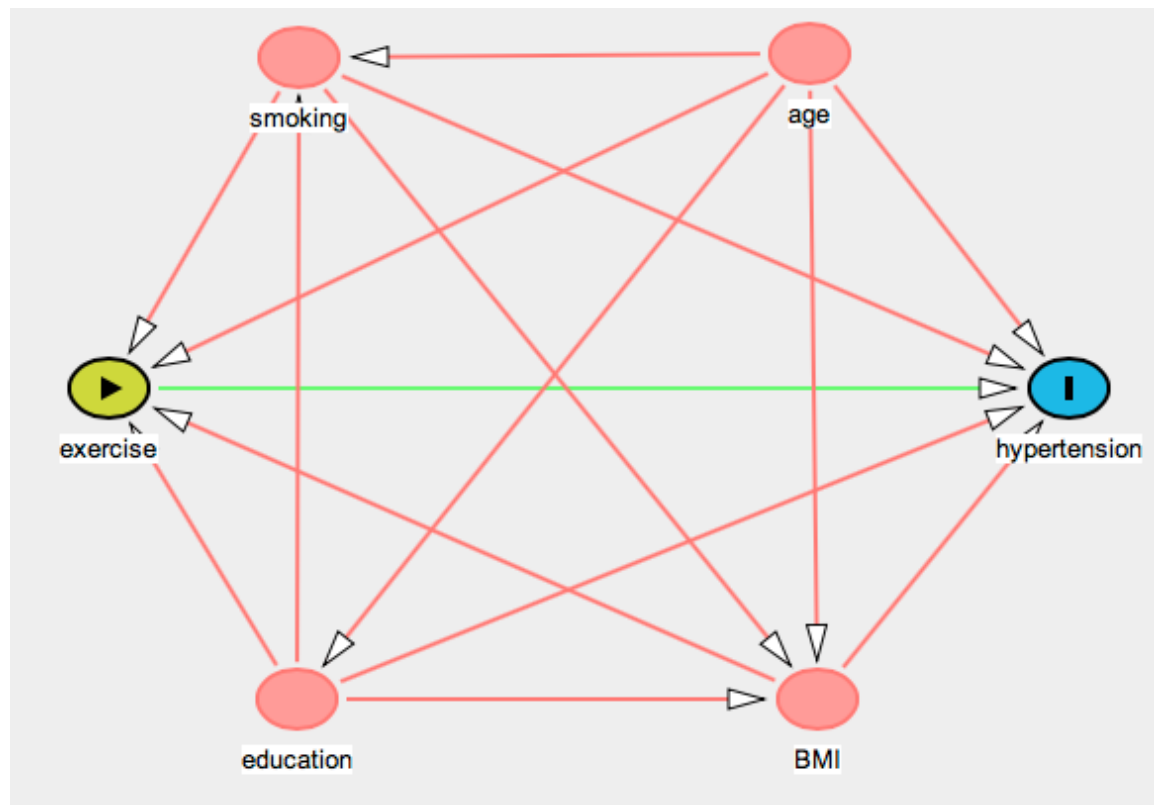
Approach:

- Construct a causal model (DAG) representing the relationship between potential confounding (and/or mediating) variables and the outcome
- Identify a minimally sufficient set of variables (MSAS) to adjust for in assessing the association of interest - use regression to estimate an adjusted association
- Look for possible interactions between key predictors; assess nonlinearity and lack of overlap
- Choose a summary measure of causal association

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, BMI, 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: 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

The unadjusted or *crude* odds ratio OR_{crude} is 0.65 (95% CI: 0.50, 0.85)

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 bmisp

Logistic regression

Number of obs = 1054

LR chi2(8) = 53.82

Prob > chi2 = 0.0000

Pseudo R2 = 0.0400

Log likelihood = -645.12775

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.exer3	.7251488	.1048338	-2.22	0.026	.5462231	.9626849
1.edu	.7278707	.1006952	-2.30	0.022	.5550055	.9545776
1.csmker	1.210394	.2428564	0.95	0.341	.8168453	1.793552
agec	1.060382	.0113939	5.46	0.000	1.038284	1.082951
bmisp1	.9541977	.0734822	-0.61	0.543	.8205174	1.109657
bmisp2	1.735852	1.197488	0.80	0.424	.4490619	6.709952
bmisp3	.205744	.5854537	-0.56	0.578	.0007784	54.38248
bmisp4	3.052587	10.39188	0.33	0.743	.0038631	2412.131
_cons	.3695945	.1793267	-2.05	0.040	.1427986	.9565928

agec (in years at enrollment, centered)

bmi (body mass index (kg/m²), centered, and represented as a cubic spline)

edu (>12 yrs education)

csmker (smoker at enrollment)

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

The adjusted or *conditional* odds ratio OR_c is 0.73 (95% CI: 0.55, 0.96)

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

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

The adjusted OR is closer to the null value (one) than the unadjusted (crude) OR :

	OR	95% CI	p -value (Wald)
OR_{crude}	0.65	0.50, 0.85	0.002
OR_c	0.73	0.55, 0.96	0.026

- Recall that for the linear regression model, differences between an adjusted and unadjusted (crude) regression coefficient could be related directly to confounding, *and*:
 - the adjusted (conditional) effect could be equated to the corresponding estimated marginal effect (e.g. obtained using `margins` in Stata)
 - we interpreted equality of the adjusted (marginal) effect and the unadjusted effect to indicate lack of confounding
- **Questions:**
 - can the adjusted/conditional odds ratio OR_c for the effect of exercise in this example be interpreted as accounting for the confounding influence of the other variables in the model?
 - does the conditional OR_c equal the corresponding marginal OR_m ?

Evaluating confounding using logistic regression

Collapsibility and odds ratios

- The conditional odds ratio (OR_c) 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** (OR_m) 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 (e.g. using `margins` in Stata)
 - has a *population* causal interpretation if
 1. sample is representative of target population
 2. no unmeasured confounders
 3. correctly specified model and appropriate analysis
- In general, $OR_c \neq OR_m$ (even when confounding is absent) - reflecting *non-collapsibility* of the odds ratio
 - By contrast, RR & RD are *collapsible* measures
 - Comparison of OR_c & OR_m can be useful in evaluating effects of non-collapsibility

Example: Artificial data illustrating non-collapsibility of OR
no confounding present (C is balanced with X) in this example

C = 1				C = 0				Pooled (crude)			
Y=1		Y=0		Y=1		Y=0		Y=1		Y=0	
X=1	50	50	100	X=1	80	20	100	X=1	130	70	200
X=0	20	80	100	X=0	50	50	100	X=0	70	130	200
OR = 4.0				OR = 4.0				OR = 3.45			

`. cs Y X, by(C) or`

C		OR	[95% Conf. Interval]		M-H Weight
0		4	2.143427	7.460138	5 (Cornfield)
1		4	2.143427	7.460138	5 (Cornfield)
Crude		3.44898	2.288457	5.198021	
M-H combined		4	2.566617	6.233887	
Test of homogeneity (M-H) chi2(1) = 0.000 Pr>chi2 = 1.0000					

Test that combined OR = 1:
Mantel-Haenszel chi2(1) = 39.36
Pr>chi2 = 0.0000

- Non-collapsibility: **marginal (crude) OR ≠ conditional (combined) OR**, even when no confounding present
- In the corresponding logistic regression model, same result holds:

Ref: Jewell NP. Statistics for Epidemiology. 2003: Chapman and Hall/CRC.

Example: Artificial example repeated with logistic regression model

```
. logistic Y i.X i.C
```

Y	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
1.X	4	.9055385	6.12	0.000	2.566617 6.233887
1.C	.25	.0565962	-6.12	0.000	.1604136 .389618
_cons	1	.17943	0.00	1.000	.7035078 1.421448

```
. quietly margins X, post  post option to margins request results be saved for post-estimation  
. nlcom (_b[1.X]/(1-_b[1.X])) / (_b[0.X]/(1-_b[0.X]))
```

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
_nl_1	3.448979	.686414	5.02	0.000	2.103633 4.794326

$$OR_c \neq OR_m$$

Note: the use of margins will be covered further below

Conditional and marginal effects from the logistic model

The logistic regression model for the dependence of binary predictors X_1 and X_2 on a binary outcome Y is nonlinear on the probability scale:

$$\Pr[Y = 1|X_1 = x_1, X_2 = x_2] = P(x_1, x_2) = \frac{\exp[\beta_0 + \beta_1 x_1 + \beta_2 x_2]}{(1 + \exp[\beta_0 + \beta_1 x_1 + \beta_2 x_2])}$$

β_1 estimates the conditional log OR_c for the effect of X_1 on Y (i.e. *conditional* on the value of X_2)

The *marginal probability* for $Y=1$ conditional on X_1 is

$$P(x_1) = \Pr[Y = 1|X_1 = x_1] = \sum_{j=0,1} \Pr[Y = 1|X_1 = x_1, X_2 = j] \times \Pr[X_2 = j]$$

The corresponding *marginal odds ratio* is $OR_m = \frac{P(1)}{(1 - P(1))} / \frac{P(0)}{(1 - P(0))}$

For the logistic model: $OR_m \neq e_1^\beta$, except under certain conditions (e.g. $\beta_2 = 0$)

Example: Artificial example repeated with risk difference regression model

```
. * risk difference regression model (to be discussed further in lecture 11)
. binreg Y i.X i.C, rd
```

		EIM				
Y	Risk Diff.	Std. Err.	z	P> z	[95% Conf. Interval]	
1.X	.3	.0452769	6.63	0.000	.2112589	.3887411
1.C	-.3	.0452769	-6.63	0.000	-.3887411	-.2112589
_cons	.5	.041687	11.99	0.000	.418295	.581705

```
. quietly margins X, post
. lincom _b[1.R] - _b[0.R]
```

(1) - 0bn.R + 1.R = 0

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.3	.0452769	6.63	0.000	.2112589	.3887411

Risk difference is a collapsible measure $RD_c = RD_m$

Note: The linear model may present estimation issues (covered in lecture 11)

Conditional and marginal effects from the risk difference model

The *linear* risk difference regression model for the dependence of a binary outcome Y on binary predictors X_1 and X_2 :

$$\Pr [Y = 1 | X_1 = x_1, X_2 = x_2] = P(x_1, x_2) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

β_1 estimates the *conditional risk difference* (RD_c) for the effect of X_1 on Y (*conditional* on the value of X_2)

The *marginal probability* for $Y=1$ conditional on X_1 is

$$P(x_1) = \Pr [Y = 1 | X_1 = x_1] = \sum_{j=0,1} \Pr [Y = 1 | X_1 = x_1, X_2 = j] \times \Pr [X_2 = j]$$

The corresponding *marginal risk difference* is $RD_m = P(1) - P(0)$

For this (linear) model, the conditional and marginal effects coincide: $RD_m = \beta_1$

Note: A similar result holds for the relative risk regression model: $RR_m = e^{\beta_1}$

Example: Artificial example repeated with relative risk regression model

$$\log [\Pr (Y = 1|X_1 = x_1, X_2 = x_2)] = \beta_0 + \beta_1x_1 + \beta_2x_2$$

```
. * relative risk regression model (to be discussed further in lecture 11)
. binreg Y i.X i.C, rr
```

		EIM				
Y	Risk Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.X	1.778207	.1820147	5.62	0.000	1.454972	2.173252
1.C	.5623643	.0575628	-5.62	0.000	.46014	.6872986
_cons	.4579834	.0441135	-8.11	0.000	.3791937	.5531443

```
. quietly margins x, post
. nlcom _b[1.X] / _b[0.X]
```

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
_nl_1	1.778207	.1820147	9.77	0.000	1.421465	2.134949

Relative risk is a collapsible measure $RR_c = RR_m$

Conditional and marginal effects from the logistic model

The contrast between the crude odds ratio OR_{crude} for the (unadjusted) association between outcome and primary predictor, and the corresponding conditional (adjusted) odds ratio OR_c can be decomposed into **non-collapsibility** & **confounding** components :

$$\log OR_{crude} - \log OR_c = [\log OR_m - \log OR_c] + [\log OR_{crude} - \log OR_m]$$

This suggests that computing both marginal and conditional estimates may help in evaluating importance on non-collapsibility (see reference below for details)

Reference: (Pang M, Kaufman JS, Platt RW. Studying noncollapsibility of the odds ratio with marginal structural and logistic regression models. *Stat Methods Med Res*; 2013.)

Estimating the marginal effect in the HERS example

- **Conditional odds ratio** for the effect of exercise from HERS (slide 16)

hypt	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.exer3	.7251488	.1048338	-2.22	0.026	.5462231	.9626849

- **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	.3624135	.0192471	18.83	0.000	.3246899 .4001371
	1	.2946184	.0223288	13.19	0.000	.2508547 .3383821

- `margins` uses the previously fitted model to estimate the average outcome probabilities for the entire sample under exercise/no exercise
- marginal probabilities can be used to estimate marginal measures of association

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Marginal OR_m , RR_m & RD_m 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	.7348022	.1023049	7.18	0.000	.5342881 .9353162

* 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	.8129343	.0769937	10.56	0.000	.6620295 .9638391

* marginal RD - equivalent to using command: margins, dydx(exer3)

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

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
(1)	-.0677951	.030205	-2.24	0.025	-.1269959 -.0085943

Evaluating confounding using logistic regression

Example: Relationship between hypertension and exercise in HERS

Summary:

	OR	95% CI
<i>unadjusted (OR_{crude})</i>	0.65	0.50, 0.85
<i>adjusted (OR_c)</i>	0.73	0.55, 0.96
<i>marginal (OR_m)</i>	0.74	0.53, 0.93

- Observed difference between adjusted and unadjusted ORs for exercise (0.72, 0.65) a very small degree of confounding may be operating
- OR_m & OR_c estimates similar in this case (non-collapsibility effect is negligible)
- 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

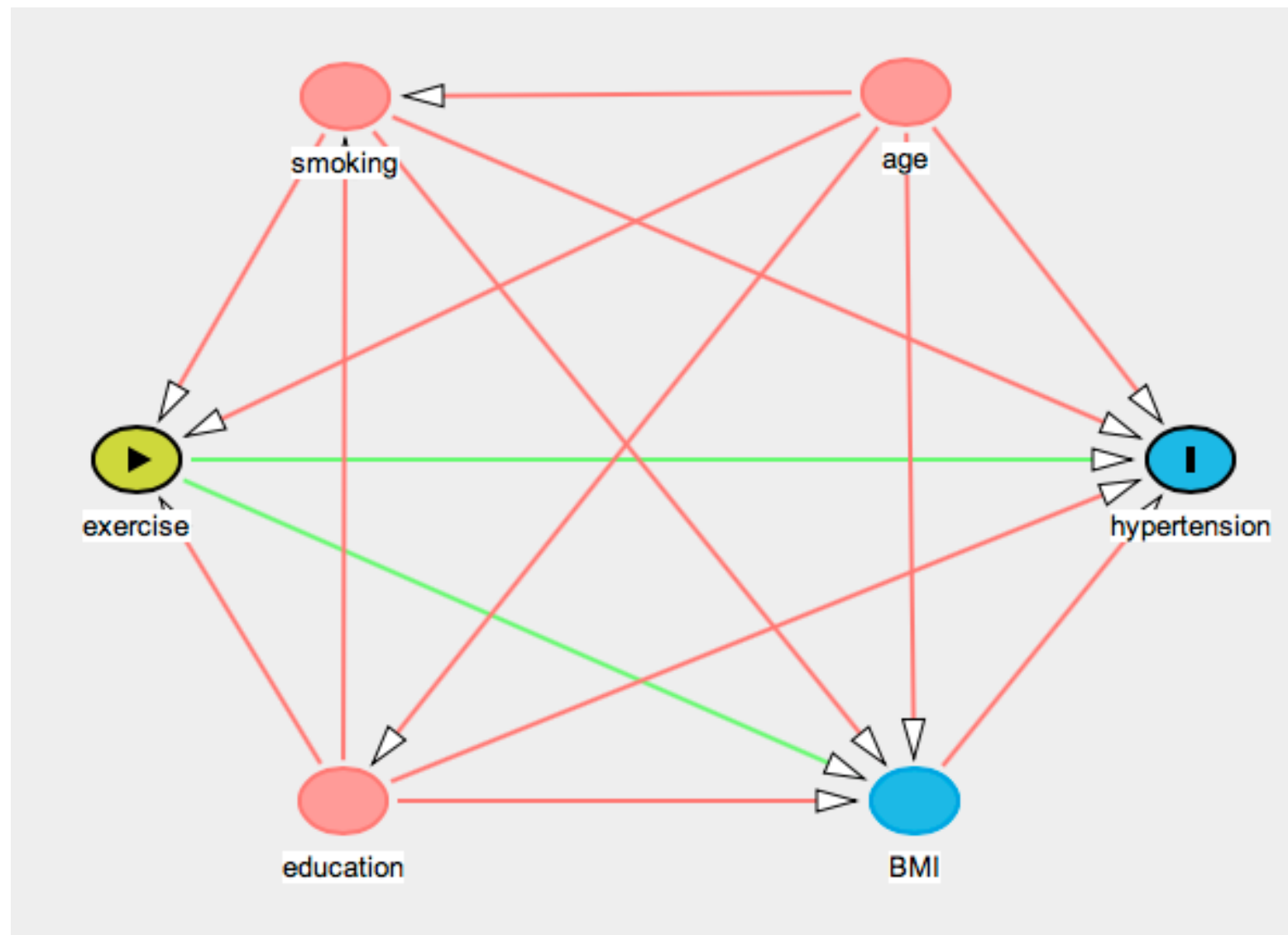
Summary:

- Conditional odds ratio (OR_c) from an adjusted logistic regression model cannot generally be equated with a corresponding average/marginal causal effect measure because of non-collapsibility
 - The OR_c 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 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 estimation 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 textbook 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 (“controlled”) 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.)
- Impact of confounders of the outcome-exposure and outcome-mediator relationships need to be considered (lecture 4).
 - Variables with dual confounding/mediating roles require special methods

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 overall effect of exercise

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Evaluating conditions for role of BMI (treated as a linear term) 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 *not* mediated through BMI
- Because of non-collapsibility, this can't be equated to a marginal direct effect

Evaluating mediation using logistic regression

Example: Relationship between hypertension and exercise in HERS

- Estimating marginal controlled direct effect (CDE) for individuals with BMI at the mean value, based on results from last model:

```
. * Run margins at a fixed level of BMI (in this case, the mean BMI)
. quietly margins exer3, at(bmic = 0) post
. nlcom (_b[1.exer3]/(1-_b[1.exer3])) / (_b[0.exer3]/(1-_b[0.exer3]))
```

OR	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
_nl_1	.7273468	.1015144	7.16	0.000	.5283822 .9263113

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

RR	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
_nl_1	.8071434	.0767328	10.52	0.000	.6567499 .9575369

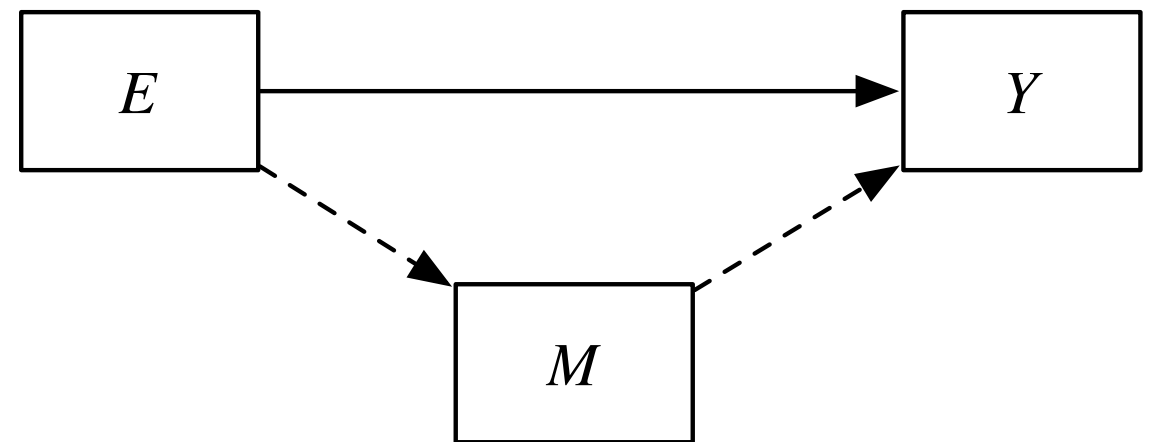
```
. lincom (_b[1.exer3] - _b[0.exer3])
```

RD	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
(1)	-.0699291	.0302295	-2.31	0.021	-.1291778 -.0106803

- CDE OR (marginal) estimate is similar (in this case) to conditional direct effect OR on previous slide

Causal mediation analysis: introduction

- Causal definitions of direct and indirect effects are based on averages of potential (counterfactual) outcomes indexed by both the intervention/exposure *and* the mediator: $Y(e, m)$
- $Y(e, m)$ is the potential outcome observed in an individual with intervention/exposure set at $E=e$ and mediator set at $M=m$
- Examples of causal effect measures for mediation:
 - controlled direct effect
 - natural direct effect
 - natural indirect effect
- Assumptions for valid estimation address confounding of the relationships of both E & M to Y



Causal mediation analysis

- The causal controlled direct effect (CDE) is the average causal effect of exposure (E) on outcome (Y) for a fixed value m of a mediator M
 - Causal controlled direct effect evaluated at $M=m$:

$$E[Y(1, m)] - E[Y(0, m)]$$

- Can be estimated with `logistic & margins` as illustrated above
- The natural direct effect (NDE) is the average causal effect of exposure, with the “potential” mediator set at “natural” values under exposure/no exposure for everyone in the population:

$$E[Y(1, m_e)] - E[Y(0, m_e)]$$

- Requires definition of a *potential mediator* $M(e) = m_e$ for the value of M under a particular assigned level of exposure e (0, 1)
 - NDE & CDE are equivalent in the case where exposure does not interact with the mediator
 - Estimation requires special software (`medeff` package in Stata)

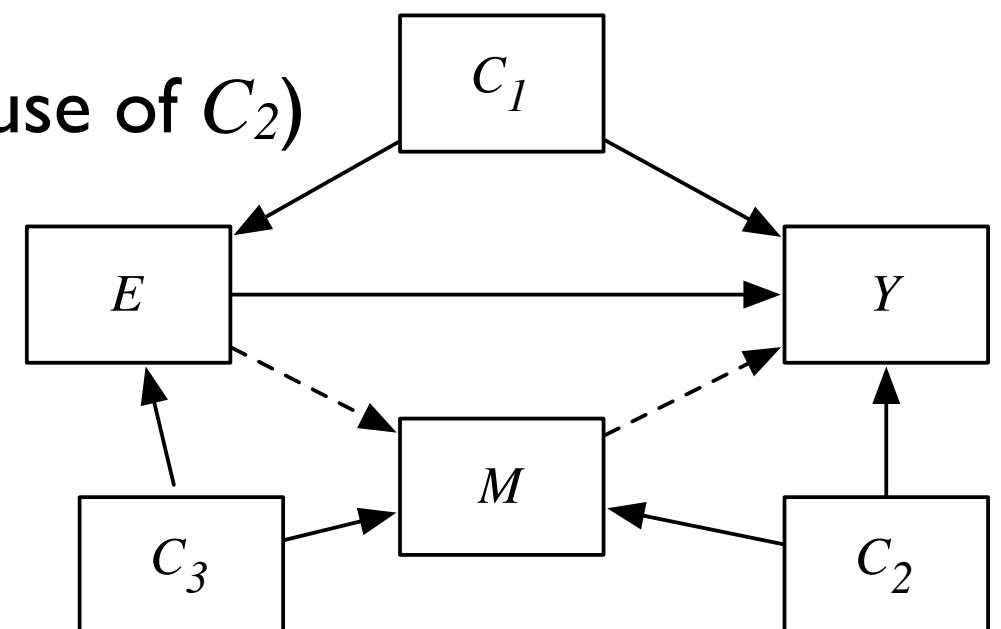
- The natural indirect effect (NIE) compares average potential outcomes for the population assuming all are exposed under two conditions: (i) the mediator set to its value under exposure, (ii) the mediator is set to its value under no exposure.
 - NIE for effect of mediator under exposure ($e=1$):

$$E[Y(1, m_1)] - E[Y(1, m_0)]$$

- Can also be estimated under the *no* exposure condition ($e=0$)
- The NIE is also called the average causal mediated effect (ACME)
- The total causal effect is the sum of the NDE and NIE

Assumptions required for CDE, NDE & NIE

- The following two assumptions required for CDE, NDE & NIE:
 - No unobserved confounders C_1 of the exposure-outcome relationship
 - No unobserved confounders C_2 of the mediator-outcome relationship
- These additional assumptions are also required for NDE & NIE:
 - No unobserved confounders C_3 of the exposure-mediator relationship
 - No causal intermediates (e.g. E also a cause of C_2)



Using medeff to assess mediation for a binary outcome and binary predictor (effects are estimated as risk differences)

```
. medeff (regress bmic exer3 edu csmker agec) (logit hypt exer3 edu csmker agec bmic),  
mediate(bmic) treat(exer3)  
Using 0 and 1 as treatment values
```

Effect	Mean	[95% Conf. Interval]	
ACME1 } NIE	-.0209207	-.0355808	-.0080683
ACME0 } NIE	-.0231623	-.0379451	-.0094944
Direct Effect 1 } NDE	-.0682403	-.1265449	-.0106466
Direct Effect 0 } NDE	-.0704819	-.1297094	-.0110392
Total Effect	-.0914026	-.1448045	-.0374986
% of Total via ACME1	.2260153	.1444758	.5579088
% of Total via ACME0	.2502322	.159956	.6176871
Average Mediation	-.0220415	-.0366915	-.0088468
Average Direct Effect	-.0693611	-.1281134	-.0108416
% of Tot Eff mediated	.2381238	.1522159	.5877979

- Model for the mediator required to estimate $M(e)$
- Equality of natural direct effects under two exposure scenarios implies lack of exposure-mediator interaction, which in turn implies NDE=CDE.
- **Average direct effect estimate** can be interpreted as a CDE in this case. (slide 35)

medeff reference: Hicks R, Tingley D. Causal mediation analysis, 2011; Stata Journal; 11:4,605-619

<http://www.stata-journal.com/article.html?article=st0243>

Evaluating mediation using logistic regression

Summary:

- Controlled direct effects can be estimated using margins as outlined above
 - confounding of mediator-outcome relationship needs to be identified and controlled
- The `medeff` mediation package (or an alternative) should be used to estimate indirect effects and % of total effect mediated
- Presence of causal intermediates (e.g. time dependent confounders) requires special methods (e.g. use of inverse probability weights and marginal structural models)
- More details in Biostat 215 (offered in Spring)

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
 - the logistic model *does not* provide a direct measure of additive interaction on the odds/probability/risk scales
- Presence of interaction does not necessarily imply a causal interpretation
 - interaction terms may be required to improve model fit and/or to adequately address confounding effects of adjustment variables, in the absence of causality considerations

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

Simple 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
* logistic model including interaction using i. and ## syntax:
. logistic hypt i.ifg##i.bmihi
. Logistic regression
```

Number of obs = 1,055
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]
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

Note: _cons estimates baseline odds

- Confidence interval for `i.ifg#bmihi` excludes null value (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 ($H: \beta_3 = 0$): $Z = -1.530736/0.6015732 = -2.54$ (coeff. on 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 i.ifg##i.bmihi, coef`

Logistic regression

Number of obs = 1,055

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]	
1.ifg	.9567317	.2710802	3.53	0.000	.4254242	1.488039
1.bmihi	.5135393	.2356014	2.18	0.029	.0517691	.9753095
ifg#bmihi						
1 1	-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):

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

- 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

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

Constructing `lincom` statements:

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

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

Constructing `lincom` statements (continued):

IFG	BMIHI	_cons β_0	1.ifg β_1	1.bmihi β_2	1.ifg#1.bmihi β_3	$\beta_1+\beta_2+\beta_3$
Yes	Yes	1	1	1	1	
Yes	No	1	0	0	0	
	Diff	0	1	1	1	

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

. lincom 1.ifg exp(β_1) *Note: lincom after logistic defaults to ORs*

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 exp(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 exp($\beta_1 + \beta_3$)

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

. lincom 1.bmihi + 1.ifg#1.bmihi exp($\beta_2 + \beta_3$)

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

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

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

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

. lincom 1.ifg β_1 *Note: lincom after logit returns coefficients (ORs usually preferred)*

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.9567317	.2710802	3.53	0.000	.4254242	1.488039

. lincom 1.bmihi β_2

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	.5135393	.2356014	2.18	0.029	.0517691	.9753095

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

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	-.5740045	.5370343	-1.07	0.285	-1.626572	.4785633

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

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	-1.017197	.5535181	-1.84	0.066	-2.102072	.0676786

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

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	-.0604652	.4932471	-0.12	0.902	-1.027212	.9062813

Interaction between two binary predictors

- Logistic model equation (odds form):

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

- Calculation of component odds ratios

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

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

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

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

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

- Interaction effect is *multiplicative* on the odds scale

Interaction between two binary predictors

- `nlcom` can be used to compute interaction effects on the odds scale:

- example: $\exp(\beta_1 + \beta_3)$

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

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

hypt	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
_nl_1	.5632653	.3024928	1.86	0.063	-.0296096	1.15614

- **Note:** `lincom` result is preferred because the resulting confidence intervals are more accurate (note also that null hypotheses differ)

```
. lincom 1.ifg + 1.ifg#1.bmihi
```

```
( 1) [hypt]1.ifg + [hypt]1.ifg#1.bmihi = 0
```

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

- **Recommendation:** Use `lincom` when feasible

Reporting presence of interaction

- Detected interactions can be presented in tabular or figure form
 - results should specify interaction scale (multiplicative or additive)
 - ▶ presence/absence of additive interaction should be evaluated if causal interpretation is appropriate (discussed more below)
 - include estimates and associated 95% CIs; guidelines for significance same as for linear models
- *Qualitative interaction*:
 - direction of effect of one predictor differs between levels of the other
 - presence implies interaction occurs on *both* additive and multiplicative scales

Evaluating presence of additive interaction

- Additive interaction may be more biologically meaningful than multiplicative interaction in many contexts (Rothman, *Epidemiology: An Introduction*, 2002)
 - logistic regression *does not* provide a direct measure of additive interaction
 - ▶ recall that interaction is multiplicative on the odds scale
 - presence of multiplicative interaction doesn't imply presence of additive interaction
- Degree of additive interaction for 2 binary predictors can be estimated empirically by:

$$(P_{11} - P_{00}) - [(P_{10} - P_{00}) + (P_{01} - P_{00})] = P_{11} - P_{10} - P_{01} + P_{00}$$

(i.e. this $\neq 0$ if the combined effect of both factors does not equal the sum of their separate effects)

- In the following linear model for binary predictors, this quantity is β_3 (i.e. the coef. for interaction)

$$P(x_1, x_2) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

- Dividing by the background risk (P_{00}), this can be expressed in terms of relative risks:
 - $RERI_{RR} = RR_{11} - RR_{10} - RR_{01} + 1$ (RERI = rel. excess risk *due to* interaction)
 - $RERI_{RR} = 0$ implies absence of additive interaction
 - $RERI_{RR} \neq 0$ implies presence of additive interaction

Evaluating presence of additive interaction for logistic regression

- The presence of additive interaction on the probability scale can be evaluated based on odds ratio estimates from a fitted logistic model (binary predictors) as follows

$$\log \left[\frac{P(x_1, x_2)}{1 - P(x_1, x_2)} \right] = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

- $RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1$

$$= \exp(\beta_1 + \beta_2 + \beta_3) - \exp(\beta_1) - \exp(\beta_2) + 1$$

- For rare outcomes ($\leq 10\%$ in strata defined by predictor values), approximates $RERI_{RR}$
 - often useful in case control studies
- $RERI_{RR}$ can be estimated directly for prospective/cross-sectional studies using a log relative risk model (example below; more detail in lecture 11)
- Methods for continuous predictors covered in the reference:

Ref: Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol.* 2012;41:514-20.

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

* Estimate RERI_OR using coefficients from previous logistic model

```
. 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

- indicates negative interaction on the additive scale
- likely not a reliable estimate of $RERI_{RR}$ since outcome is not rare
- SE & CIs approximate - a bootstrap 95% CI would be better in smaller samples

Example: log relative risk regression assessment of additive interaction

* Estimate RERI_RR using a log relative risk model (including interaction)

```
. binreg hypt i.ifg##i.bmihi, rr
```

Generalized linear models

No. of obs = 1,055

Optimization : MQL Fisher scoring

Residual df = 1,051

(IRLS EIM)

Scale parameter = 1

Deviance = 1328.829981

(1/df) Deviance = 1.264348

Pearson = 1054.999988

(1/df) Pearson = 1.003806

hypt	Risk Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.ifg	1.733656	.2244061	4.25	0.000	1.345187	2.234309
bmihi						
BMI >= 35	1.381173	.1887708	2.36	0.018	1.0566	1.80545
ifg#bmihi						
1#BMI >= 35	.4004749	.1549208	-2.37	0.018	.1876264	.8547842
_cons	.3128492	.0154982	-23.46	0.000	.2839013	.3447487

```
. 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	-1.1559	.4388867	-2.63	0.008	-2.016103	-.2956982

- indicates negative interaction on the additive scale
- doesn't work for case-control studies (approaches for relative risk regression covered in lecture 11)

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

* Use the risk difference model for binary outcomes

```
. binreg hypt i.ifg i.bmihi i.ifg##i.bmihi, rd
```

Generalized linear models	No. of obs	=	1,055
Optimization : MQL Fisher scoring	Residual df	=	1,051
(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

		EIM				
hypt	Risk Diff.	Std. Err.	z	P> z	[95% Conf. Interval]	
1.ifg	.2295237	.0666862	3.44	0.001	.0988211	.3602263
bmihi						
BMI >= 35	.1192496	.0571812	2.09	0.037	.0071764	.2313228
ifg#bmihi						
1#BMI >= 35	-.3616225	.1340767	-2.70	0.007	-.6244079	-.0988371
_cons	.3128492	.0154982	20.19	0.000	.2824732	.3432251

- **Note:** Model can't be fitted in many situations (discussed in lecture 11)
 - multiple & continuous predictors
 - case-control studies

Interpreting interaction - causal effect modification

- Presence of a statistical interaction does not imply a causal interpretation
 - interactions of targeted interventions/exposures with additional variables can be estimated from logistic models (e.g. subgroups in randomized studies)
 - ▶ additional predictors can be interpreted as *effect modifiers*
- For a potential (counterfactual) binary outcome $Y(e)$ dependent on a binary exposure $E=e$, causal effect modification by a binary predictor X can be defined as follows:
 - *Effect modification* present if causal effect of E differs between levels of X

▶ Additive:

$$E[y(e = 1) | X = 1] - E[y(e = 0) | X = 1] \neq E[y(e = 1) | X = 0] - E[y(e = 0) | X = 0]$$

▶ Multiplicative: $\frac{E[y(e = 1) | X = 1]}{E[y(e = 0) | X = 1]} \neq \frac{E[y(e = 1) | X = 0]}{E[y(e = 0) | X = 0]}$

- (Recall that for binary outcomes: $E[Y(e = 1) | X = 1] = P[Y(e = 1) | X = 1]$)

- Example with margins provided below

Example: Multiplicative effect modification of the effect of exercise on hypertension at fixed BMI levels in HERS (including additional adjustment variables)

- Estimating marginal RDs of exercise (> 3 times/wk) at each level of BMI (low/high)

. * Run margins at each fixed level of bmihi

. quietly logistic hypt i.exer3##i.bmihi i.edu i.csmker agec

. quietly margins exer3, at(bmihi = 0) post

. lincom _b[1.exer3] - (_b[0.exer3])

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	-.0749345	.0304127	-2.46	0.014	-.1345422	-.0153268

. quietly logistic hypt i.exer3##i.bmihi i.edu i.csmker agec

. quietly margins exer3, at(bmihi = 1) post

. lincom _b[1.exer3] - (_b[0.exer3])

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	-.2363081	.1141314	-2.07	0.038	-.4600016	-.0126146

- lack of overlap of 95% CIs implies presence of additive interaction (not a formal test) - in this case there is some overlap apparent
- Note that bootstrap CIs may be preferable (especially in small samples)

Causal interaction

- *Causal interaction* is evaluable only in the context of dual (joint) interventions
- For a potential (counterfactual) binary outcome $Y(e_1, e_2)$ dependent on a joint intervention $E_1=e_1$ & $E_2=e_2$, causal interaction can be defined as follows:
 - *Interaction between E_1 & E_2* present if causal effect of E_1 differs between levels of E_2
 - ▶ Additive:

$$E[Y(e_1 = 1, e_2 = 1)] - E[Y(e_1 = 0, e_2 = 1)] \neq E[Y(e_1 = 1, e_2 = 0)] - E[Y(e_1 = 0, e_2 = 0)]$$

- ▶ Multiplicative:

$$\frac{E[Y(e_1 = 1, e_2 = 1)]}{E[Y(e_1 = 0, e_2 = 1)]} \neq \frac{E[Y(e_1 = 1, e_2 = 0)]}{E[Y(e_1 = 0, e_2 = 0)]}$$

Reference on causal effect modification & interaction :

VanderWeele TJ. On the distinction between interaction and effect modification. *Epidemiology*. 2009;20:863-71.

Evaluating interaction using logistic regression

Summary:

- Interaction models for logistic regression are fitted as in linear models
 - interaction is multiplicative on the odds scale (additive in log-odds)
 - interactions may be included to improve model fit, or to address hypotheses (e.g. about targeted relationships or effects of interventions/exposures)
- Logistic model coefficients can be used to provide direct estimates of the effects of multiplicative interaction
 - interactions may be included to improve model fit
 - interaction summaries include presenting estimates and CIs of effects of one involved predictor over levels of the other
 - the possible presence of additive interaction can be evaluated using $RERI_{OR}$
- Interactions involving a target intervention/exposure can be interpreted as *effect modification* using marginal estimates

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 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.

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 are more reliable than Wald tests, especially for smaller samples

Note: for the LR test to make sense, models being compared should be based on exactly the same set of observations.