Multivariable Regression in R

Phillip Ayieko

Principles of multivariable regression analysis

- MVA relate 2 or more independent variables to an outcome (through mathematical expression)

$$Cholesterol \Longleftarrow age + exercise + diet$$

$$y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i + \beta_3 x_i + \epsilon_i$$

Main multivariable models in biostatistics

- Generalized linear models
- A generalized linear model is made up of a linear predictor = relates mean to predictors
- and two functions:
- a link function (transform done on Y) = relates means of observations to predictors

$$Cholesterol \Longleftarrow age + exercise + diet$$

- a variance function (the distribution) = relates the means to the variances

Main multivariable models in biostatistics

Type of MVA regression	Typical Use
Multiple (general) linear	Predicting a quantitative response variable fr
Logistic	Predicting a categorical response variable fro
Poisson	Predicting a response variable representing c
Cox proportional hazards	Predicting time to event (death, failure, relap
Time series	Modelling time series data with correlated er
Discriminant function analysis	Predicting a group to which subjects belong

“Multivariate” or “Multivariable” analysis?

- Often used interchangeably, but:
- Multivariable - single outcome
- Multivariable - multiple outcomes e.g. factor analysis

Purposes of Multivariable Analysis

- Bivariate confirmation
- Multivariable Confirmation
- Screening
- Creating Risk Scores
- Quantifying Risk of Individual Variables

Common problems with MVA

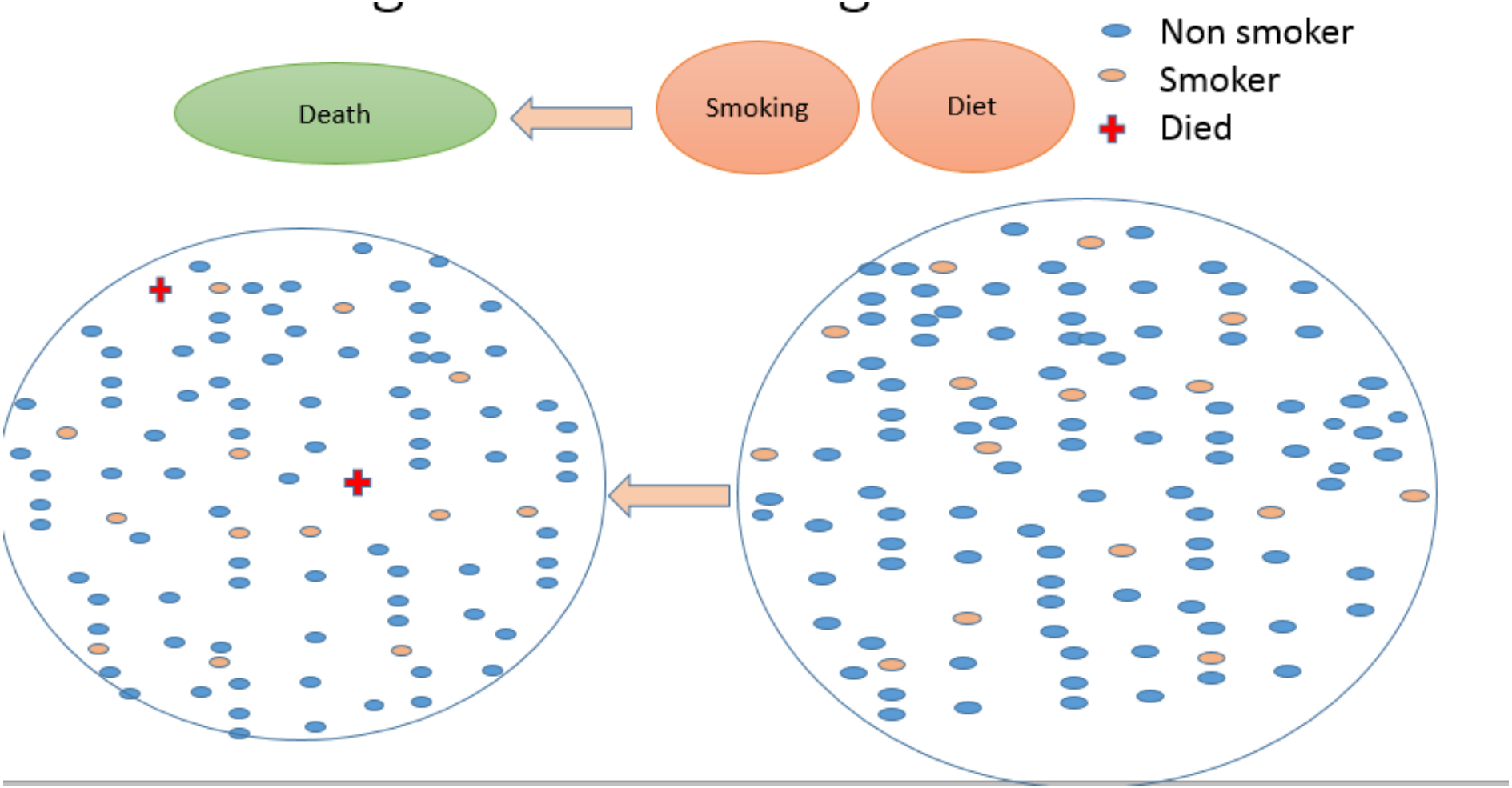
- Over-fitting or under-fitting
- Nonconformity to a Linear Gradient
- Violation of proportional hazards assumption
- No report of tests for interaction
- Unspecified coding of variables
- Unspecified selection of variables
- Collinearity of variables
- Influential observations
- Model validation

Over-fitting or under-fitting

$$Death \Longleftarrow smoking$$

- $Non - smoker$
- $smoker$

Over-fitting or under-fitting



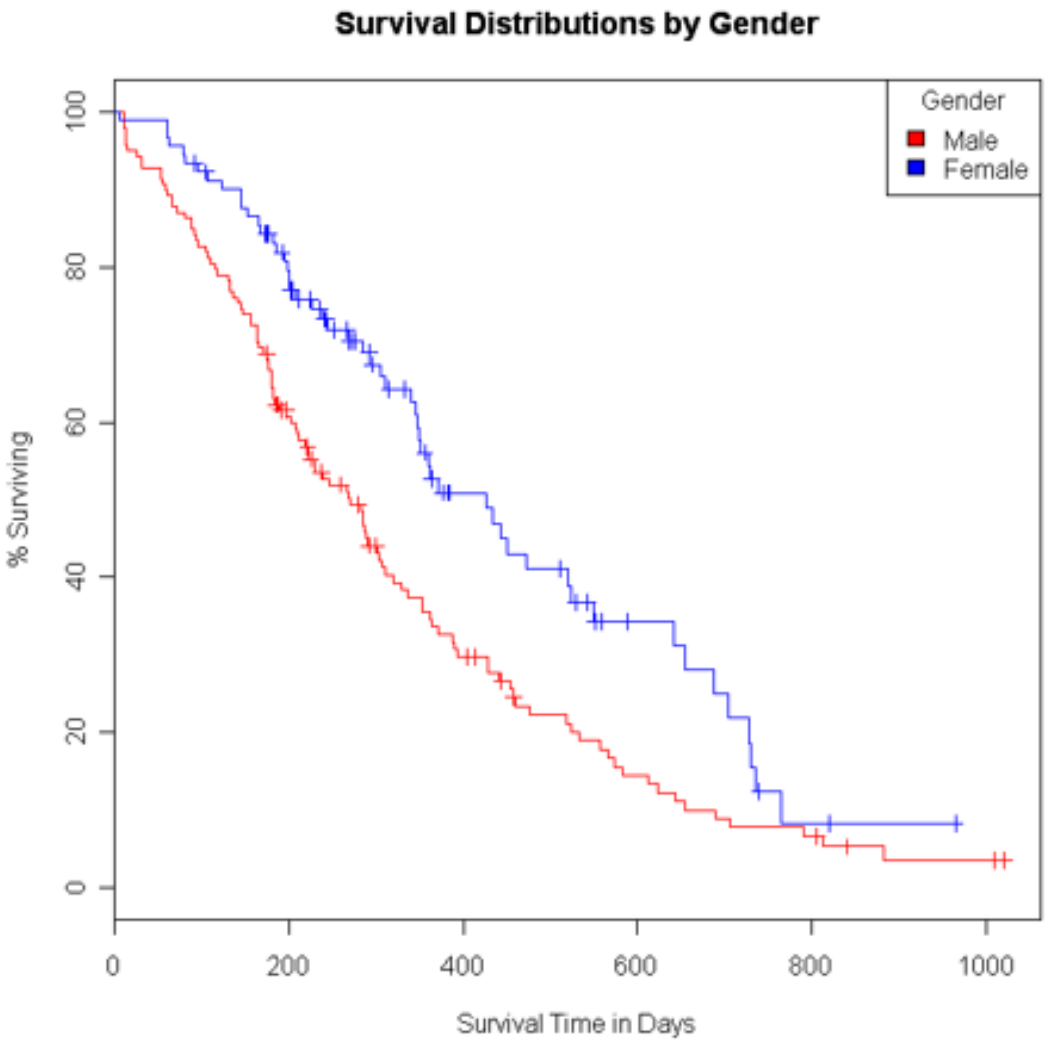
Implications

	Impact
Overfiting	Unreliable risk esti Spurious associati
Under-fitting (variable omission/ underpowered analysis)	Predicting a respo Misleading results

Violation of PH assumption (Cox regression)

- Hazard ratio - does not depend on time (on covariates only)
- Methods for verification
- Plot of 'cumulative baseline hazard estimates on a log-scale': Curves on the plot should be parallel with distance that is constant over time
- Survival curves: if PH assumption is met survival curve of one group will not cross the survival curve of other group

PH assumption



Checking PH assumption in 'R'

No report of tests for interaction

- To be covered in the next session

Unspecified coding

- readers should always be notified of how the coding was used in a multivariable analysis:
- Marginal (binary variable -1/+1) v.s. partial (binary variable 0/1) methods
- Ordinal variable coding = could use "dummy" variable or integer values
- Regression coefficients reported without concomitant citation of unit of coding e.g. single coefficient for age - could mean continuous variable or a dichotomous variable (<5/ above 5 years)

Unspecified Selection of Variables

- Strategies of variable selection for MVA
  - Previous research
  - Clinical experience
  - Automated algorithms - esp. prognostic studies
- Final model depends on the chosen selectin process

Summary

Problem or Issue	Description
Problem	
Overfitting of data	Fewer than 10 outcome events per independent variable in the model
Nonconformity to linear gradient	Nonconstant impact of variables in different zones of ranked data
Nonproportional risk	Violation of assumption of proportional hazard function over time (in the proportional hazards method)
No report of tests for interactions	Check not mentioned for interactions between independent variables
Unspecified coding of variables	Unknown classification or codings for independent variables
Unspecified selection of variables	Unknown method of selecting among candidate independent variables
Issue	
Collinear variables	Independent variables with high correlation to each other
Influential observations	"Outlier" observations that have a substantial effect on results
Validation of model	Separate method of confirming analytic results

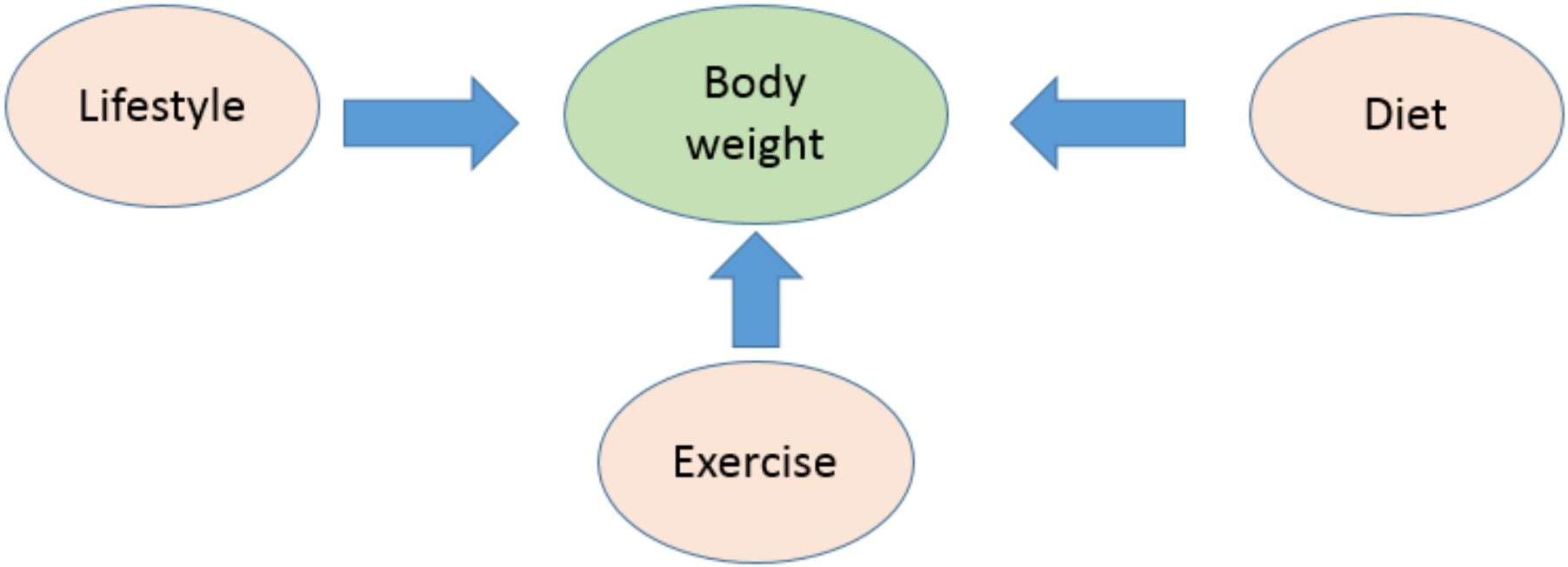
Principle MV models in 'R'

- multivariable_reg_practical.pdf

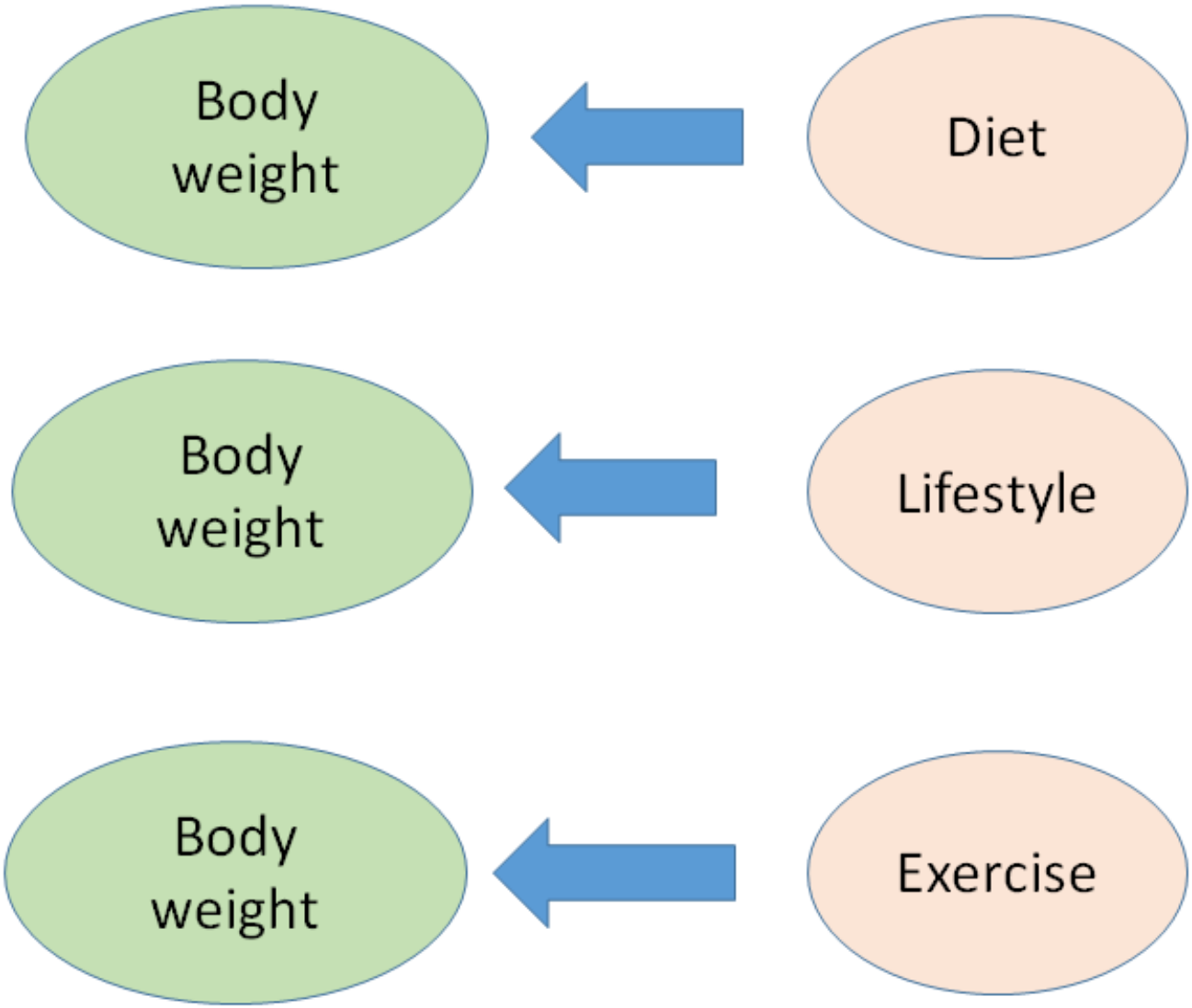
Introduction Interaction & Effect Modification

Interaction/ effect modification

- Most of the outcomes (events) are determined (influenced) by more than one factor (e.g. body weight.)

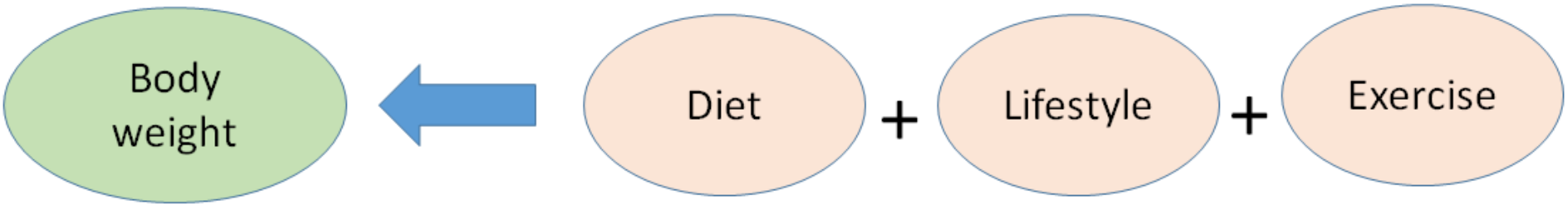


Interaction/ effect modification



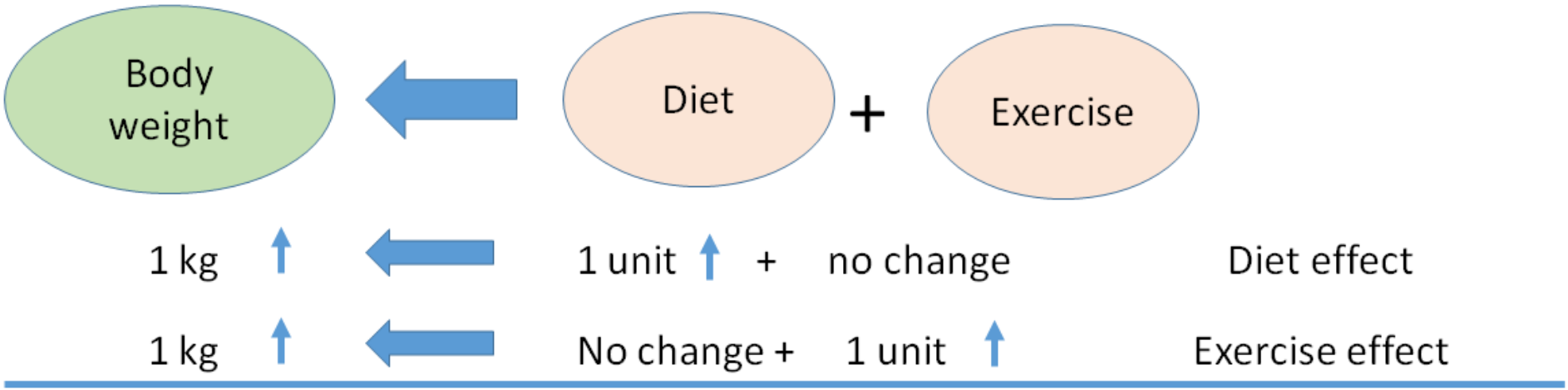
- Looking at
  factor in t
  unrealistic
- We should
  relationsh
  factors to
  the same

Interaction/ effect modification

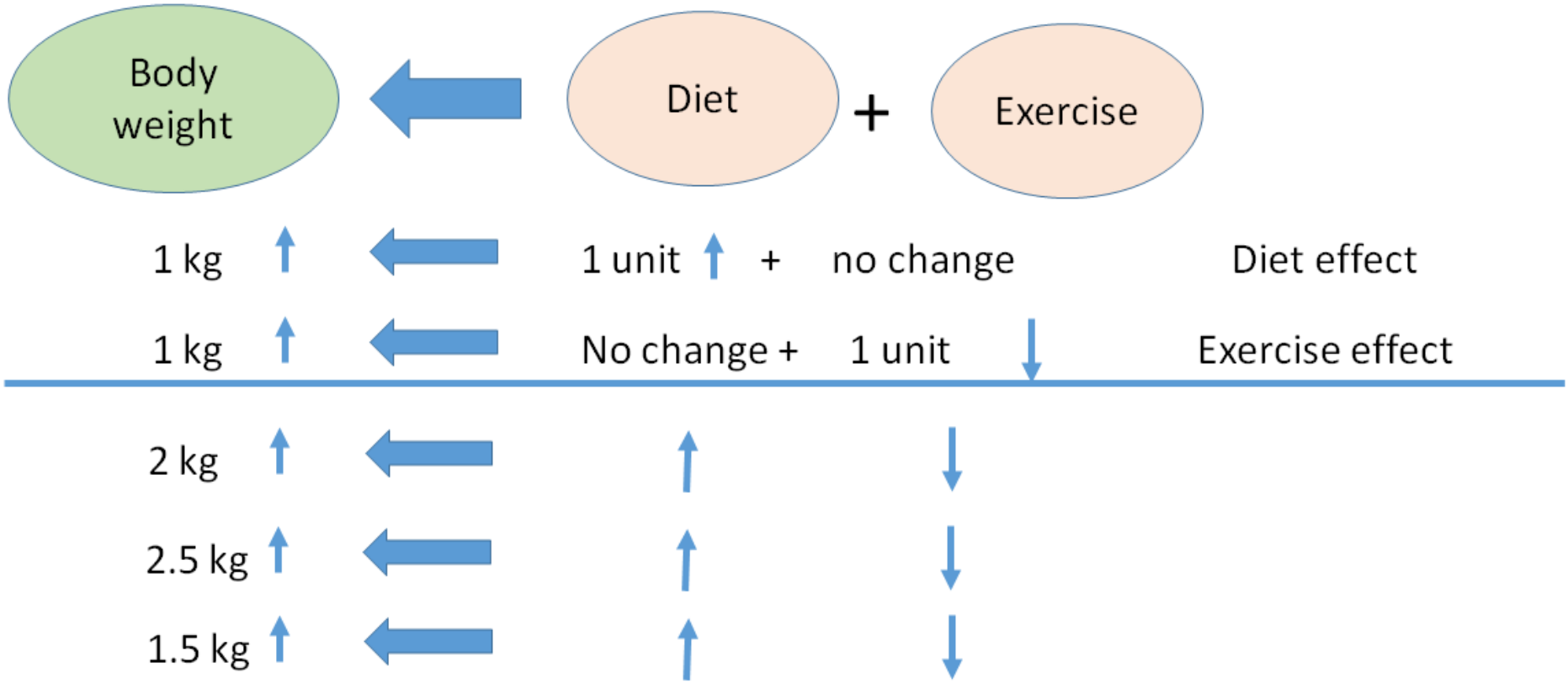


- When we look at the relation of these factors (explanatory variables) to the outcome at the same time, ...
  - We will obtain the "independent effect" of explanatory variables to outcome.
  - We can also study the "interaction" (IA) between independent variables (Synergistic/Antagonistic IA)

Interaction



Interaction



IA= Interaction Syn. IA = Synergistic interaction Ant. IA = Antagonistic interaction

Detection/interpretation of interaction & effect modification

- An interaction occurs when the product of two predictor variables is also a significant predictor (i.e. in addition to the predictor variables themselves)
- Create an interaction term
- Perform likelihood ratio test (LRT)

Testing for interaction in 'R'

- interaction practical.pdf

Confounding and stratification

Exposures and outcomes

In an epidemiological study there is: a. the outcome of interest b. the primary exposure (or risk factor) of interest c. other exposures that may influence the outcome (potential confounders)

Exposures and outcomes

- You will need to measure more than one exposure

Because you do not know which exposures are likely to be risk factors for the disease i.e. you do not know which exposures are "primary"

Because some exposures may 'get in the way' when trying to sort out a relationship between primary exposure and outcomes i.e. they may act as confounding factors

Question: Is alcohol consumption during pregnancy associated with increased risk of low birthweight ?

Alcohol during pregnancy
exposure

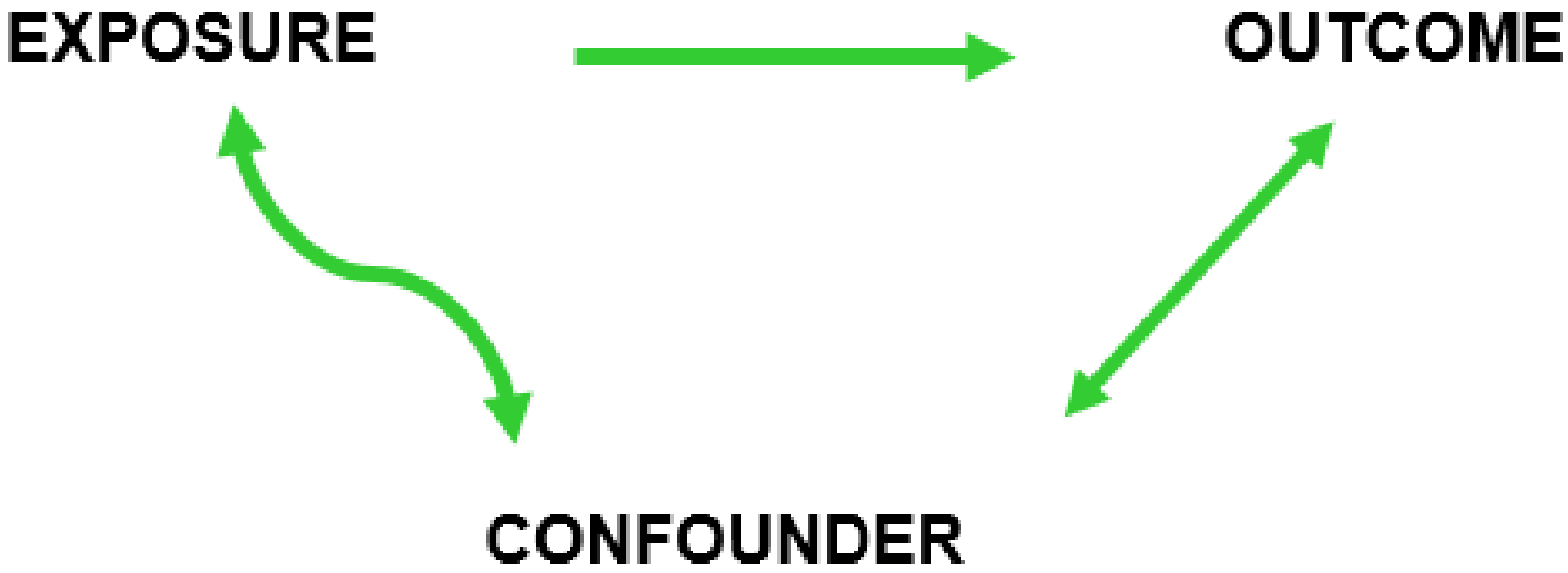
Low birth weight
outcome

Diet during pregnancy
potential confounding factor

Confounding is about

** ALTERNATIVE EXPLANATIONS FOR AN EFFECT SEEN ** - when an association between the Exposure under investigation and Outcome is "mixed up" with the effect of another exposure or exposures - when the effects of the two exposures have not been considered separately $OR = 1.40$ reflects true association.

Confounding: Definition: for a factor to be regarded as a confounder the rules are:



1. The factor must be associated with the exposure being investigated
2. The factor must be independently associated with the disease being investigated.
3. The confounder is not on the causal pathway.

How to deal with confounding

- Need to display the data separately for each level of the confounding factor
- Then examine the measures of effect within eachlevel (or strata)
- If they different from the "crude" measure of effect, but similar to each other, this is evidence of confounding *BUT no test for confounding.*

Example: Case-control study of coffee comsumption and cancer of the pancreas

	Coffee	No coffee
Cases	450	300
Controls	200	250

Estimated odds ratio = 1.9

	Non smokers		**Smokers**	
	Coffee	No coffee	Coffee	No coffee
Cases	50	100	400	200
Controls	100	200	100	50
Estimated odds ratios	**= 1.0**		**= 1.0**	

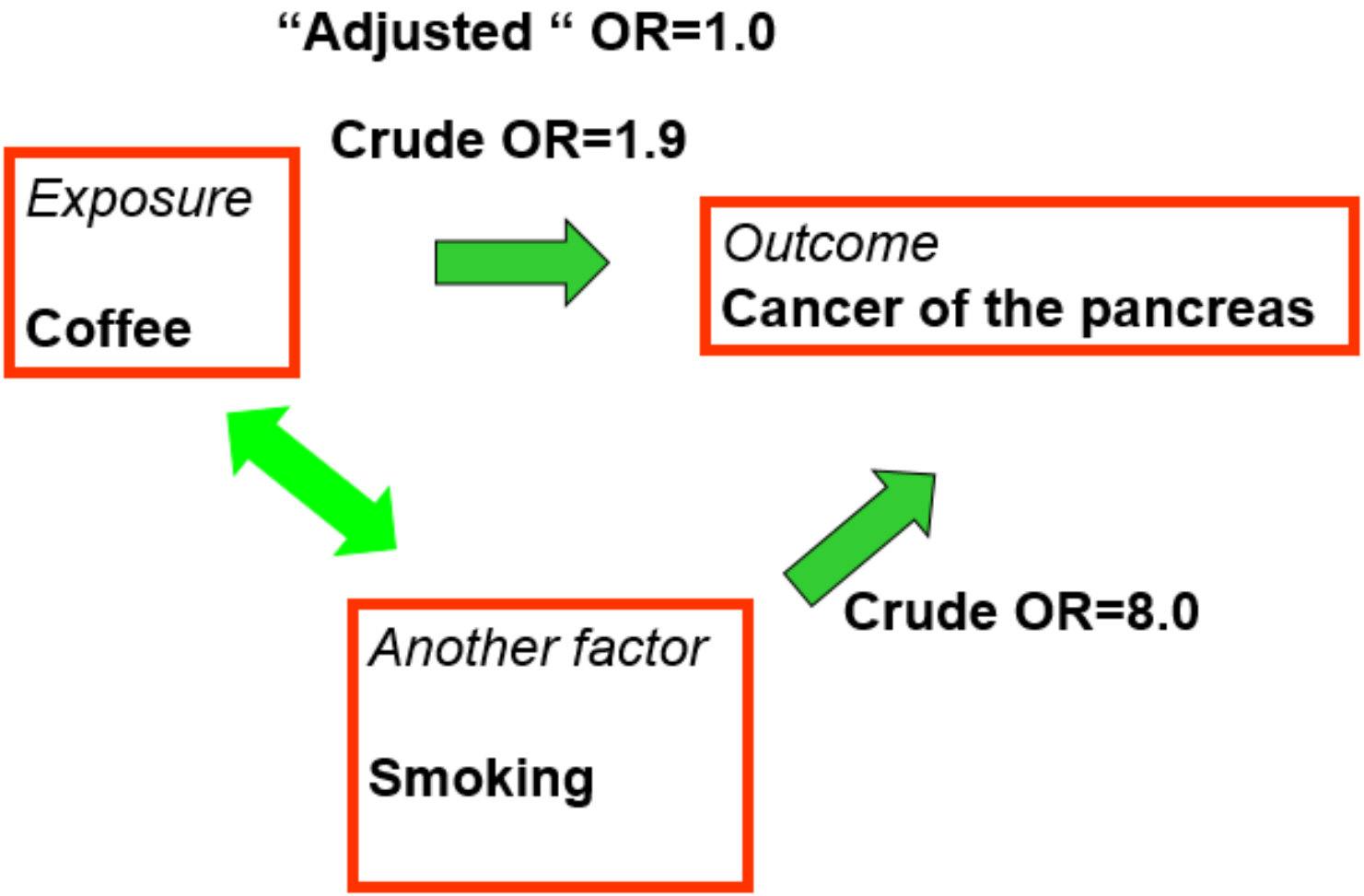
- We have shown that the "stratified" measure of effect (in this case odds ratios) are different from the "crude" measure of effect, but similar to each other
- Thus we have evidence that Smoking was acting as a confounding factor

Question: What is the odds ratio for the effect of Smoking on the risk of cancer of the pancreas?

Use data from table below:

	Non Smoker		Smoker	
	Coffee	No Cofee	Coffee	No coffee
cases	50	100	400	200
control	100	200	100	50

$$Answer = (600 * 300)/(150 * 150) = 8$$


"Adjusted " OR=1.0
Crude OR=1.9
Exposure
Coffee
Outcome
Cancer of the pancreas
Another factor
Smoking
Crude OR=8.0

- we investigate the control data further, we can see that the confounding factor is associated with the exposure under investigation:

	Coffee	No Coffee
Smoker	100 (50%)	50(20%)
Non Smoker	100	200
	200(100%)	250

- 1 in 2 coffee drinkers are smokers
- 1 in 5 non-coffee drinkers are smokers

- This example demonstrated complete confounding where **ALL** the association between coffee drinking and cancer of the pancreas could be“explained” by smoking
  - **i.e: OR of 1.9 was reduced to 1.0**
- Other examples may give PARTIAL confounding
  - **i.e: Rate Ratio of 2.5 was reduced to 2.0**
- But remember that measures of effect can go UP as well as DOWN : **NEGATIVE** confounding

SECTION II

How to deal with confounding

- At the Design Stage
  - Randomisation
  - Restriction
  - Matching
- At the Analysis Stage
  - Stratification
  - Standardisation
  - Statistical modelling
  - eg logistic regression

But need to have collected the data. . . .

FURTHER ANALYSIS OF 2X2 TABLES

Mantel-Haenszel methods: - 1.Mantel-Haenszel technique to obtain ORMH adjusted for confounding factor. - 2. Mantel-Haenszel χ^2 to test whether adjusted $OR = 1$.

Case-control study of coffee drinking and pancreatic cancer

		casse	control
coffee	yes	450	440
drinking	no	300	410
	total	750	850

$$CrudeOR = ad/bc = 450x410/440x300 = 1.40.$$

- Suggests risk of pancreatic cancer associated with coffee drinking.

- $OR = 1.40$
- Possible explanations:
  - Chance: -$\chi^2(O - E) = 10.62, p = 0.001 \Rightarrow$ chance is unlikely.
  - Bias:
  - OR = 1.40 does not represent the true OR.
  - Confounding:
  - OR = 1.40, but due to effect of other variable.
  - Causation:
  - OR = 1.40 reflects true association.

Look within stratum of confounding variable

		smokers		non smoker	
		case	control	case	control
coffee	yes	400	340	50	100
	no	200	190	100	220
		600	530	150	320

- Is smoking associated with increased risk of pancreatic cancer?
- 600 (80%) of the 750 cases are smokers
- 530 (62%) of the 850 controls are smokers

Look within stratum of confounding variable

		smokers		non smoker	
		case	control	case	control
coffee	yes	400	340	50	100
	no	200	190	100	220
		600	530	150	320

- Are coffee drinkers more likely to smoke?
- Among controls.
- 340 of the 440 coffee drinkers are smokers (77%)
- 190 of the 410 non-coffee drinkers are smokers (46%)

Mantel-Haenszel Odds Ratio

- Crude OR=1.4 is misleading. Calculate separate OR's.

		smokers		non smoker	
		case	control	case	control
coffee	yes	400	340	50	100
	no	200	190	100	220
		600	530	150	320

$OR = 400x190/340x200 = 1.12 OR = 50x220/100x100 = 1.10$

- But more interested in combined estimate of OR..

- Mantel-Haenszel OR_{MH} is weighted average of OR's in each stratum:

		STRATUM 1 disease			STRATUM 2 disease		
		Y	N		Y	N	
exposed	Y	a_1	b_1	$\mid$	a_2	b_2	$\mid$
	N	c_1	d_1	$\mid$	c_2	d_2	$\mid$
				$\mid n_1$			$\mid n_2$

$$OR_{MH} = \frac{a_1d_1/n_1 + a_2d_2/n_2}{b_1c_1/n_1 + b_2c_2/n_2}$$

In general,

$$\frac{\sum a_id_i/n_i}{\sum b_ic_i/n_i}$$

		disease			disease	
		Y	N		Y	N
exps	Y	a_1	b_1	|	a_2	b_2 |
	N	c_1	d_1	|	c_2	d_2 |
				| n_1		| n_2

$$OR_{MH} = \frac{a_1d_1/n_1 + a_2d_2/n_2}{b_1c_1/n_1 + b_2c_2/n_2}$$

		disease			disease	
		Y	N		Y	N
exps	Y	400	340	|	50	100 |
	N	200	190	|	100	220 |
				| 1130		| 470

$$OR_{MH} = \frac{(400x190)/1130 + (50x220)/470}{(340x200)/1130 + (100x100)/470} = \underline{1.11}$$

		disease			disease	
		Y	N		Y	N
exps	Y	400	340 |		50	100 |
	N	200	190 |		100	220 |
		----------			----------	
			| 1130			| 470

$$OR_{MH} = \frac{(400x190)/1130 + (50x220)/470}{(340x200)/1130 + (100x100)/470} = \underline{1.11}$$

Odds of coffee drinking is 11% higher among cases than controls.

This is the *stratified* estimate (recall crude OR was 1.4)

Significance test of stratified OR: Mantel-Haenszel χ^2 test

$$H_0 : OR_{MH} = 1$$

- i.e. no association between exposure and disease within any strata.
- For each table:

		disease		
		Y	N	
exp	Y	a	b	e
	N	c	d	f
		g	h	n

Calculate E_a and V_a

	a	$E_a = \frac{eg}{n}$	$V_a = \frac{efgh}{n^2(n-1)}$
Smokers	400	392.9	63.7
	50	47.9	22.2
Total	450	440.8	85.9

Under H_0: difference between $\sum a$ and $\sum E_a$ should be small and follow χ^2 distribution (on 1.d.f):

$$\chi^2 MH = \frac{(|\sum a - \sum E_a| - 0.5)^2}{\sum V_a}$$

$$\chi^2 MH = \frac{(|450 - 440.8| - 0.5)^2}{85.9} = 0.88 on 1 d.f$$

$$P > 0.30$$

No evidence of association

Mantel Haenszel using R

```
mymatrix1 <-matrix(c(400,340,200,190),nrow=2,byrow=TRUE)
colnames(mymatrix1) <- c("Disease","Control")
rownames(mymatrix1) <- c("Exposure","Unexposed")
print(mymatrix1) # to get the stratified table
mymatrix2 <- matrix(c(50,100,100,220),nrow=2,byrow=TRUE)
colnames(mymatrix2) <- c("Disease","Control")
rownames(mymatrix2) <- c("Exposure","Unexposed")
print(mymatrix2) # to get the stratified table
```

Confounding II (logistic regression analysis)

Practical - handling confounding