Multivariable analysis: A brief introduction

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August 21th, 2019

Why do we need multivariable analysis?

"**Treatment (control)**" for the confounding effects at analytical level

- ✓Stratification by confounder(s)
- ✓Multivariable / multiple analysis

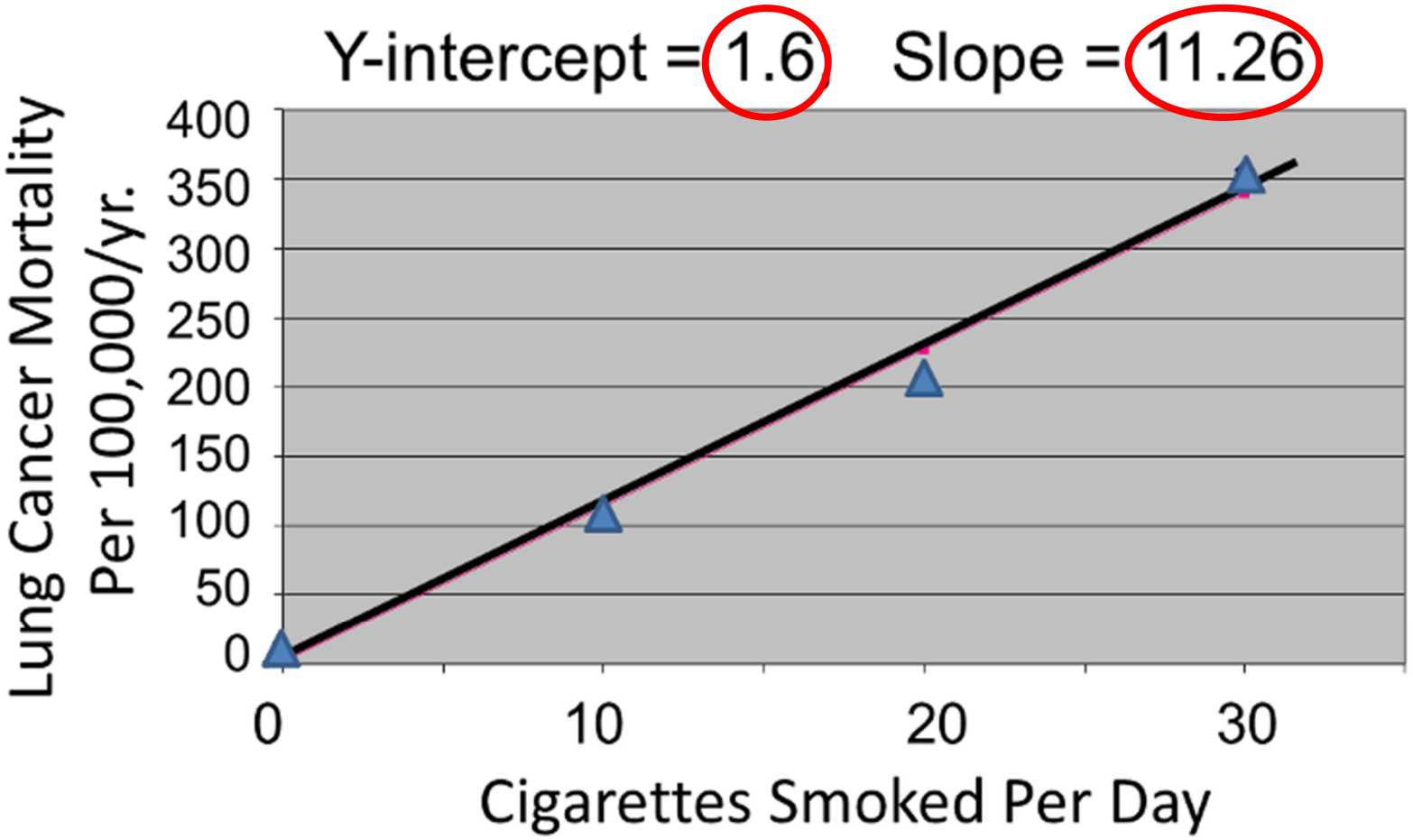
Prediction of individual risk

Regression models for multivariable analysis

Paired?	Outcome variable	Proper model
No	Continuous	Linear regression model
	Binomial	Logistic regression model
	Categorical (≥3)	Multinomial (polytomous) logistic regression model
	Binomial (event) with censoring	Cox proportional hazard model
Yes	Continuous	Mixed effect model, Generalized estimating equation
	Categorical (≥3)	Generalized estimating equation

LINEAR REGRESSION ANALYSIS

Lung cancer mortality by daily cigarettes smoked



Original data: Doll and Hill Br Med J 1956

Height explaining mathematical ability!!??

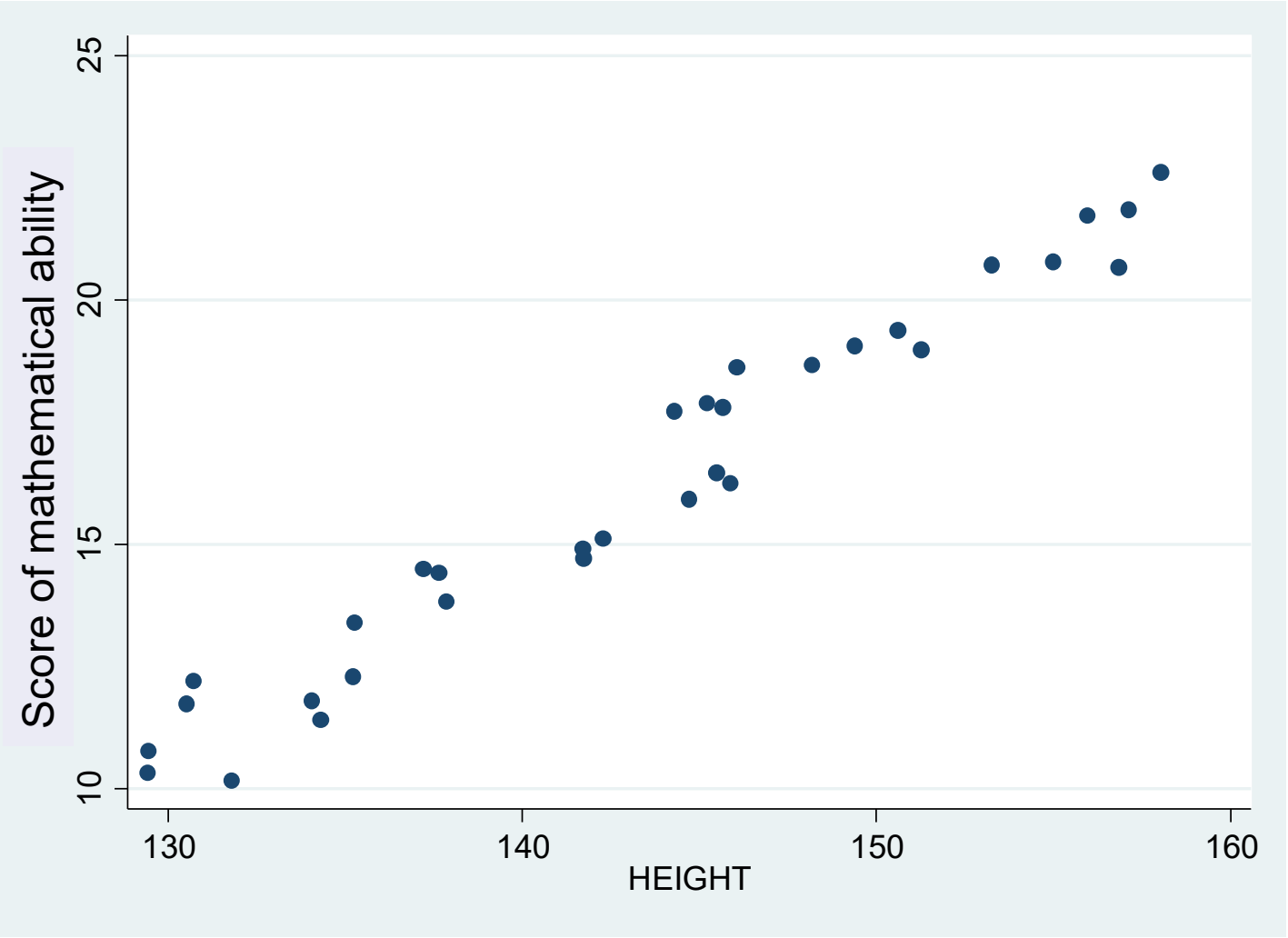
Source	SS	df	MS
Model	412.7743	1	412.774322
Residual	17.0365	30	.567882354
Total	429.8108	31	13.8648643

Number of obs = 32
F(1, 30) = 726.87
Prob > F = 0.0000
R-squared = 0.9604
Adj R-squared = 0.9590
Root MSE = .75358

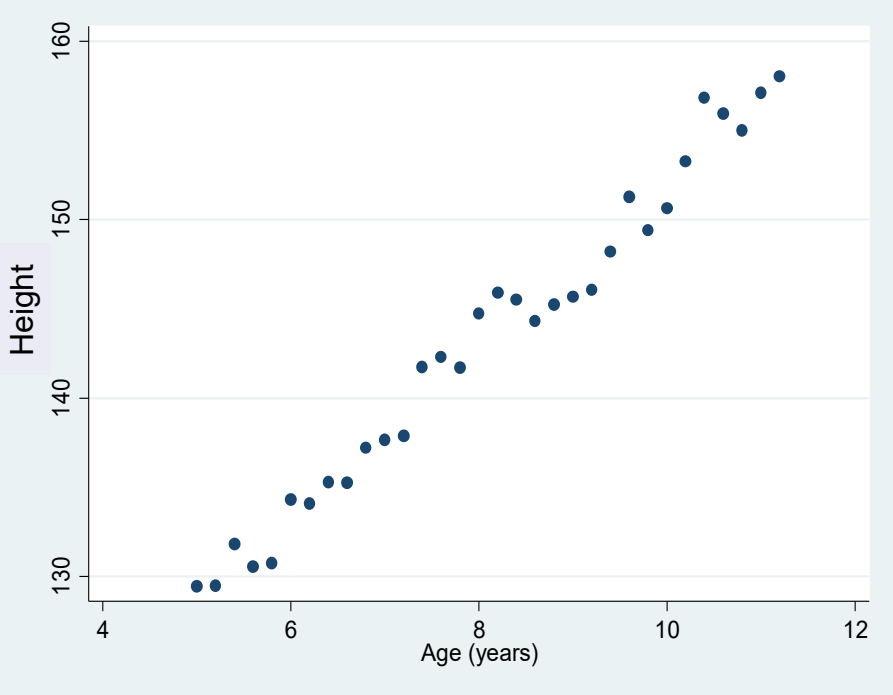
Ability score of maths

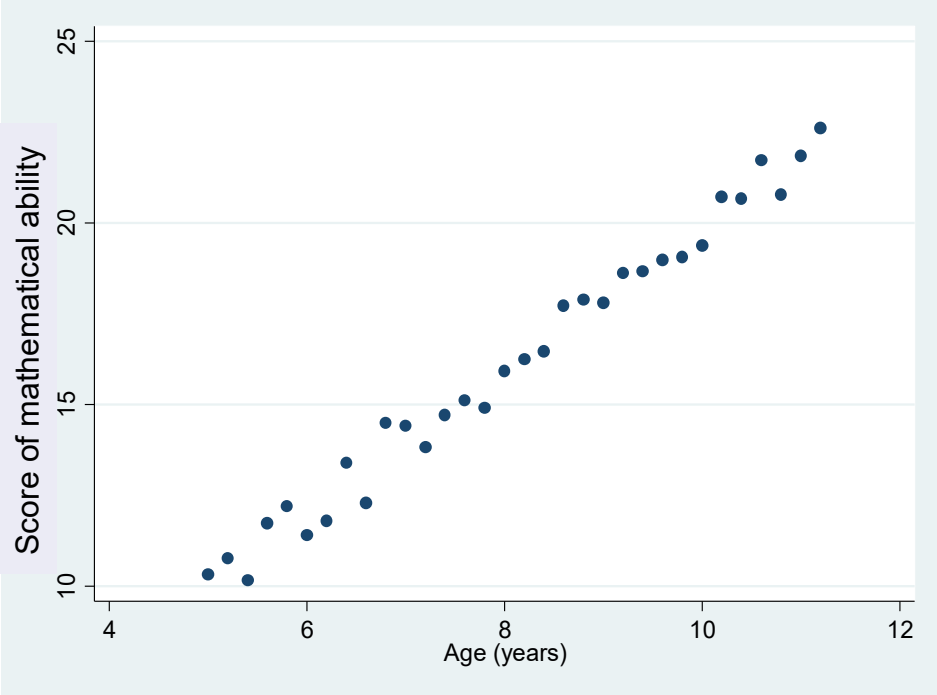
ama	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
height	**.4118029**	**.0152743**	**26.96**	**0.000**	**.3806086**	**.4429973**
_cons	-42.82525	2.191352	-19.54	0.000	-47.30059	-38.34992

Association between height and score of maths



Both height and ability of maths increase with age





Age is a confounding factor in the association between height and ability of maths.

How age itself influences the association between height and the ability of maths?

Let's see the equation

Ability of maths (AM) = α + β1(Height)

$\rightarrow$ AM = -42.8 + **0.41**(Height)

AM = α + β1(Height) + β2(Age)

$\rightarrow$ AM = 1.48 **- 0.01**(Height) + 2.02 (Age)

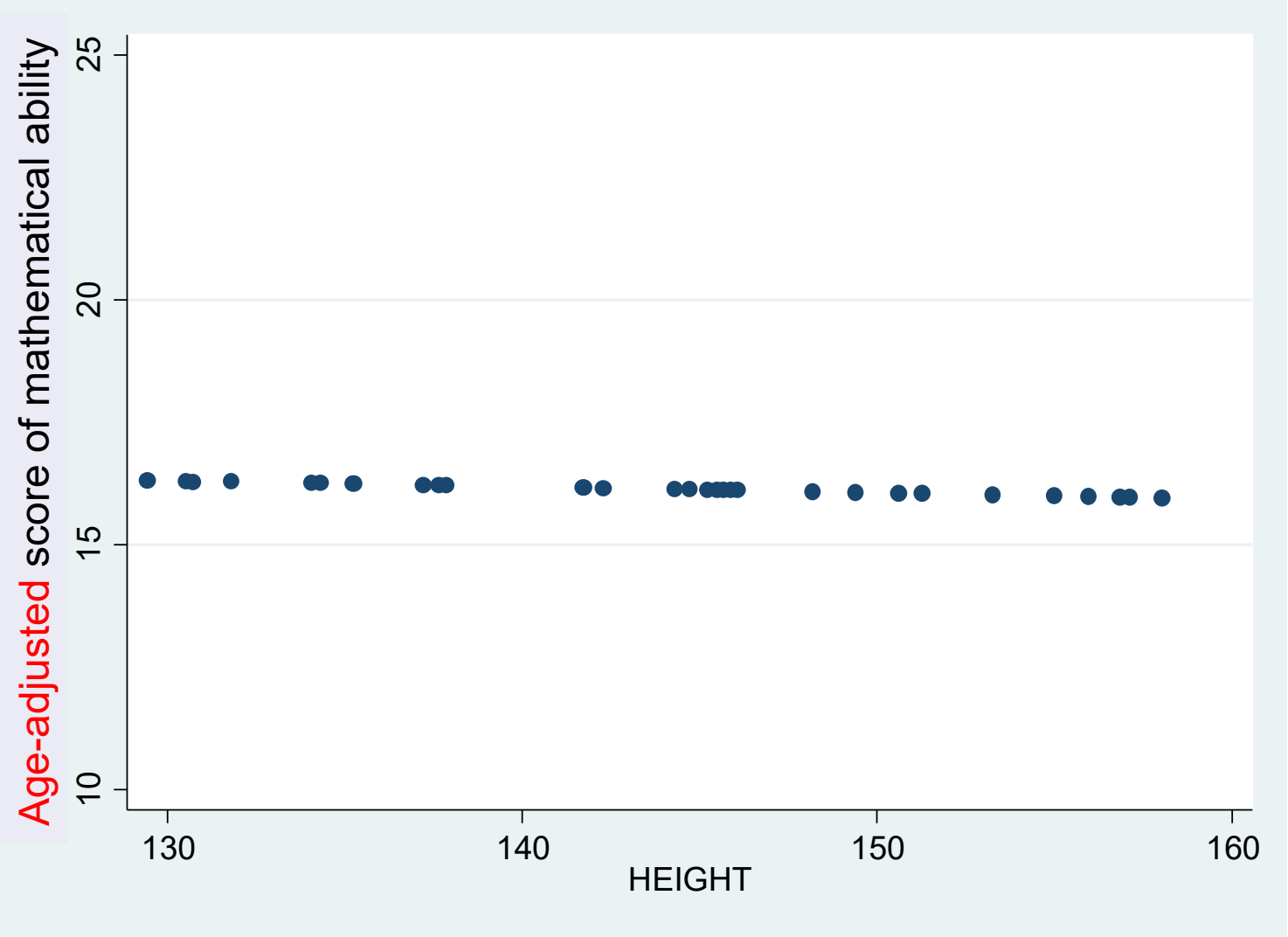
Significant association between height and the ability of maths was gone after adjusting for the effect of age

Source	SS	df	MS
Model	422.6119	2	211.305972
Residual	7.19885	29	.248236138
Total	429.81079	31	13.8648643

Number of obs	= 32
F(2, 29)	= 851.23
Prob > F	= 0.0000
R-squared	= 0.9833
Adj R-squared	= 0.9821
Root MSE	= .49823

ama	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
height	**-.0121303**	**.0680948**	**-0.18**	**0.860**	**-.1513998**	**.1271393**
age	2.02461	.3216095	6.30	0.000	1.366845	2.682375
_cons	1.483038	7.185946	0.21	0.838	-13.21387	16.17995

No association between height and age-adjusted score of maths



Interpretation of coefficients

Let's see the equation

Ability of maths (AM) = α + β1(Height)

$\rightarrow$ AM = -42.8 + **0.41**(Height)

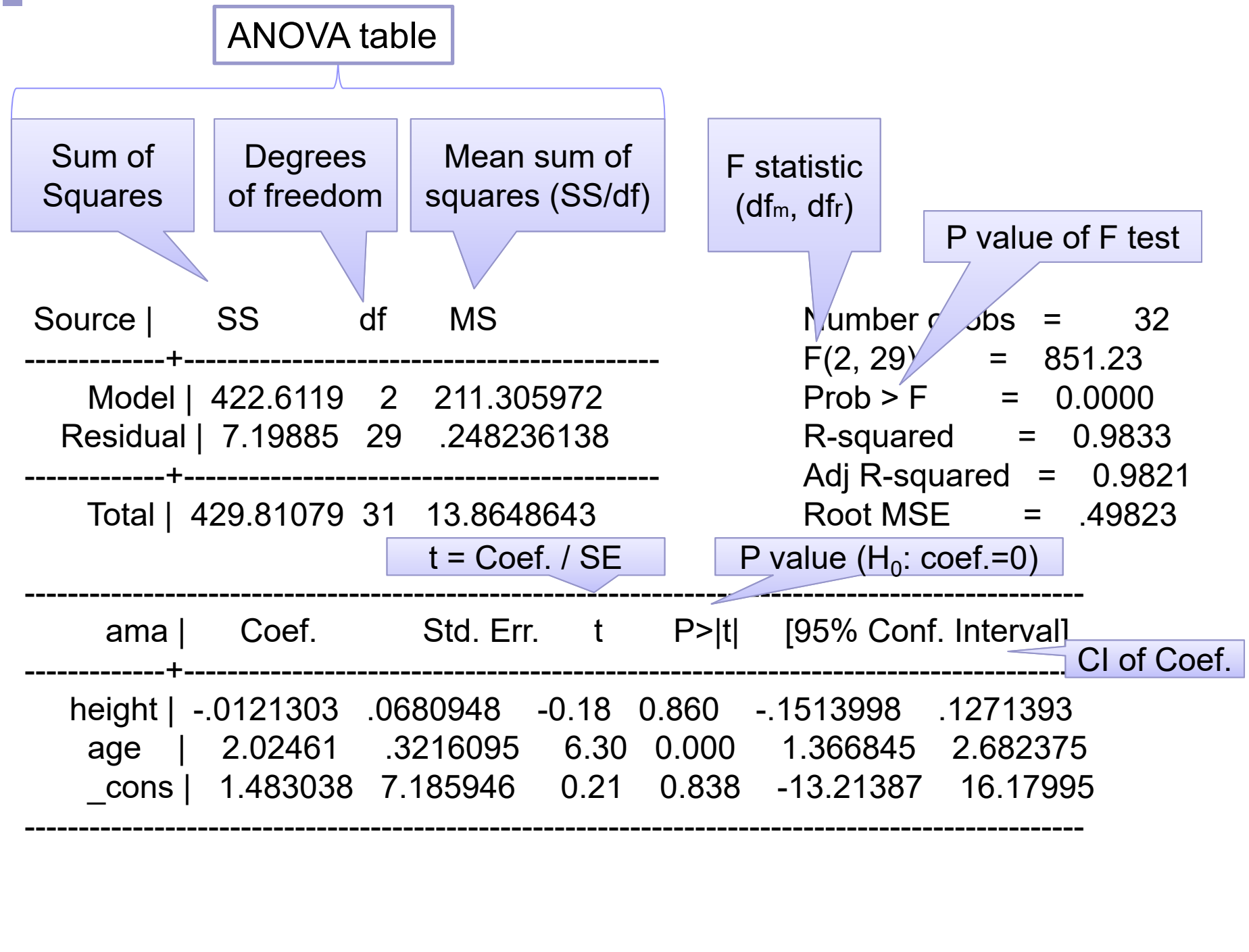
0.41 points increase by 1cm increase of height

AM = α + β1(Height) + β2(Age)

$\rightarrow$ AM = 1.48 **- 0.01**(Height) + 2.02 (Age)

0.01 points decrease by 1cm increase of height

Confounding effect: magnitude and direction of the association


ANOVA table
Sum of Squares
Degrees of freedom
Mean sum of squares (SS/df)
F statistic (dfm, dfr)
P value of F test
Source | SS df MS
Number of obs = 32
F(2, 29) = 851.23
Prob > F = 0.0000
R-squared = 0.9833
Adj R-squared = 0.9821
Root MSE = .49823
Model | 422.6119 2 211.305972
Residual | 7.19885 29 .248236138
Total | 429.81079 31 13.8648643
t = Coef. / SE
P value (H0: coef.=0)
ama | Coef. Std. Err. t P>|t| [95% Conf. Interval]
CI of Coef.
height | -.0121303 .0680948 -0.18 0.860 -.1513998 .1271393
age | 2.02461 .3216095 6.30 0.000 1.366845 2.682375
_cons | 1.483038 7.185946 0.21 0.838 -13.21387 16.17995

Interpretation of coefficients in general

To simplify, the explanatory variable is binomial one: 1=exposed or 0=unexposed

Exposed: $Ye = \alpha + \beta(Exp=1) = \alpha + \beta$

Unexposed: $Yu = \alpha + \beta(Exp=0) = \alpha$

Difference: $Ye - Yu = \beta$

- **Coefficient estimate: difference in dependent value**

Interpretation of coefficients after log-transformation of dependent variable

The explanatory variable is binomial one:
1=exposed or 0=unexposed

Exposed: $\ln(Ye) = \alpha + \beta(Exp=1) = \alpha + \beta$

Unexposed: $\ln(Yu) = \alpha + \beta(Exp=0) = \alpha$

Difference: $\ln(Ye) - \ln(Yu) = \beta$

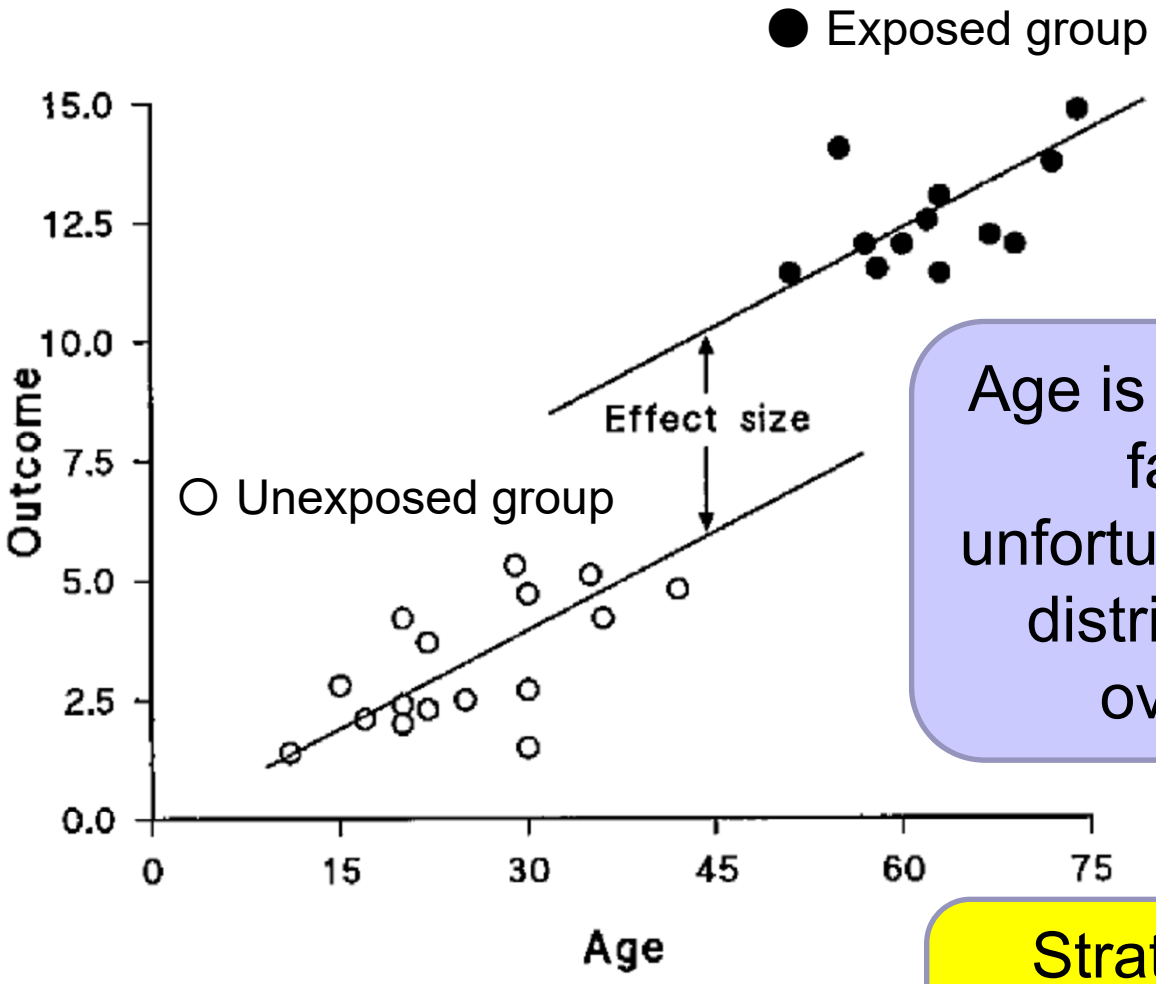
Ratio: $Ye / Yu = e^{\beta}$

- **Coefficient estimate: ratio of dependent value (after exponentiating)**

Control of confounding with regression model

- Compared to stratified analysis, several confounding variables can be easily controlled simultaneously using a multivariable regression model.

- Results from the regression model are readily susceptible to bias if the model is not a good fit to the data.

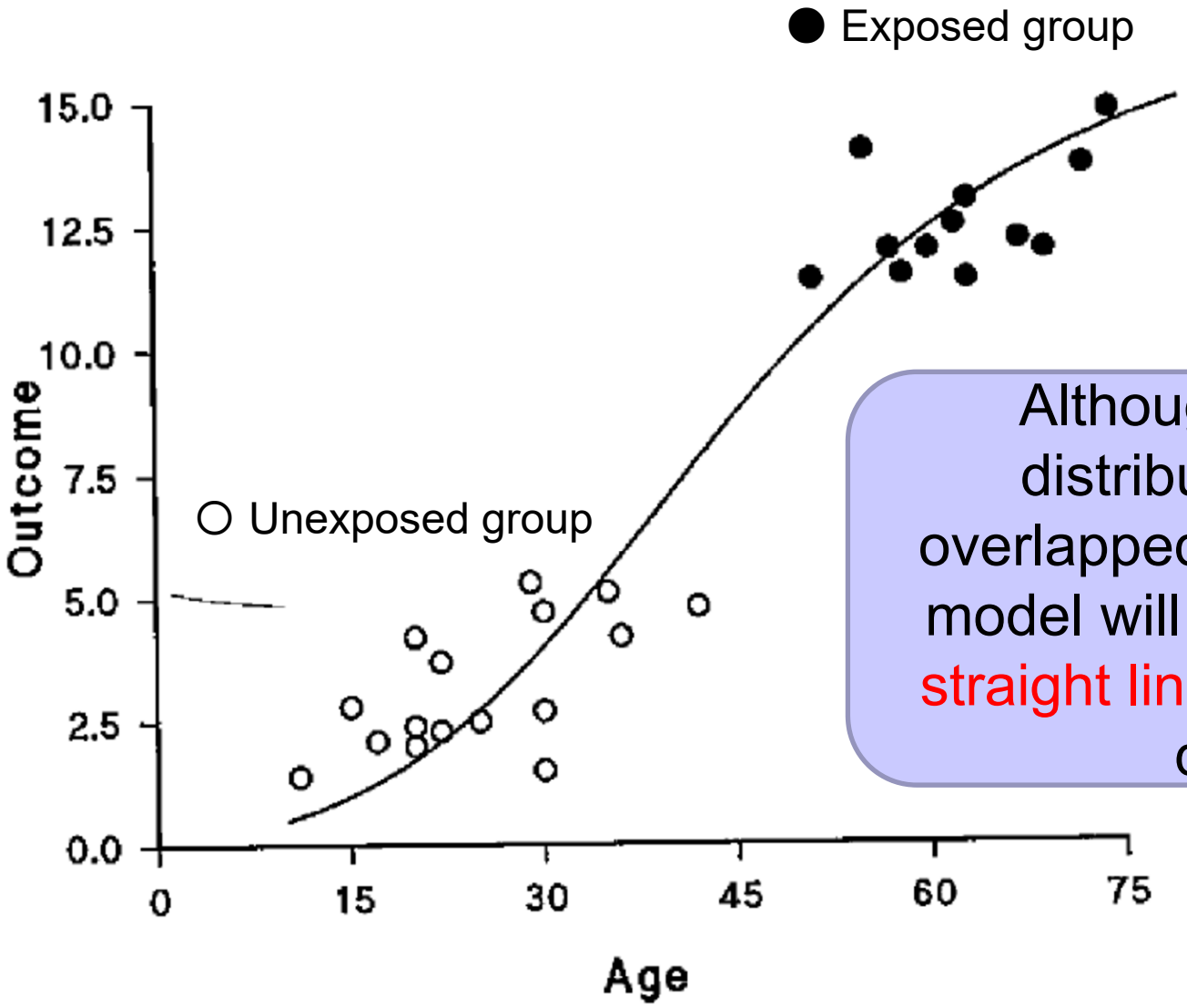


Age is a confounding factor, but unfortunately, the age distribution is not overlapped.

Stratified analysis would produce no estimate of effect.

Figure 12–4 Hypothetical example of a multivariable linear reg
data involving a dichotomous exposure variable (exposed = *solid*
open circles) and age.

Epidemiology (Rothman KJ, Oxford University Press)



Although the age distribution is not overlapped, a regression model will fit two parallel straight lines through the data.

Epidemiology (Rothman KJ, Oxford University Press)

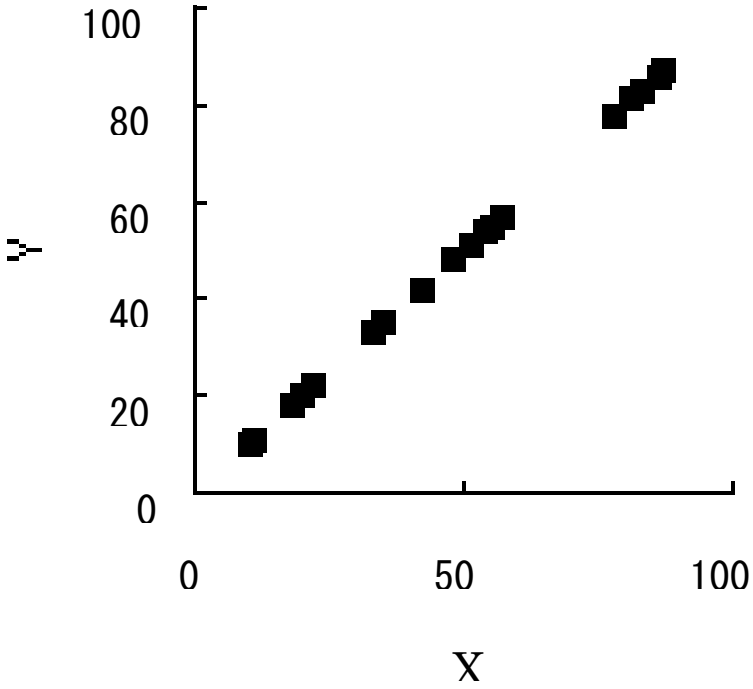
CORRELATION = REGRESSION ANALYSIS?

Correlation coefficient

- Strength of the correlation between two continuous variables ranging from -1 to 1
- Correlation is a linear association between two variables
- NOT to prove the causal association; x and y variable are interchangeable.

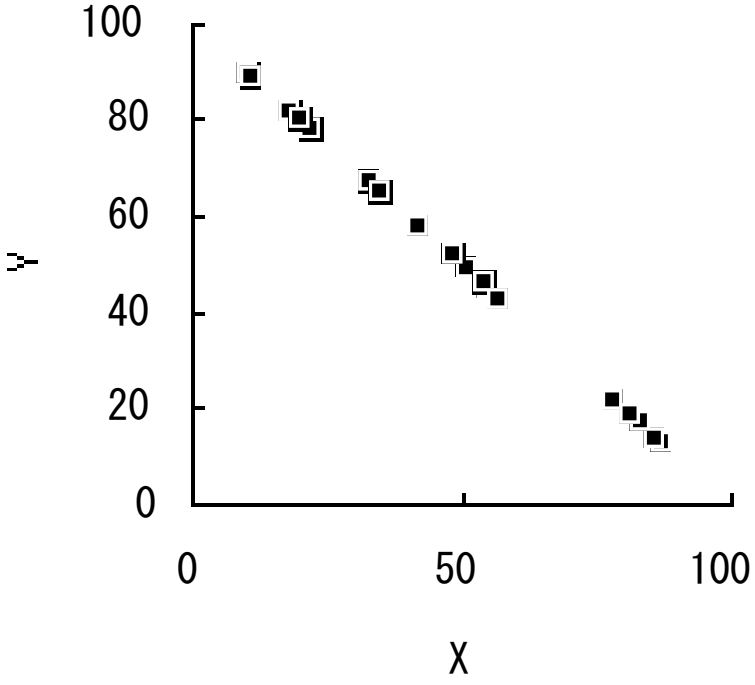
Examples of correlation

r = 1



Positively correlated

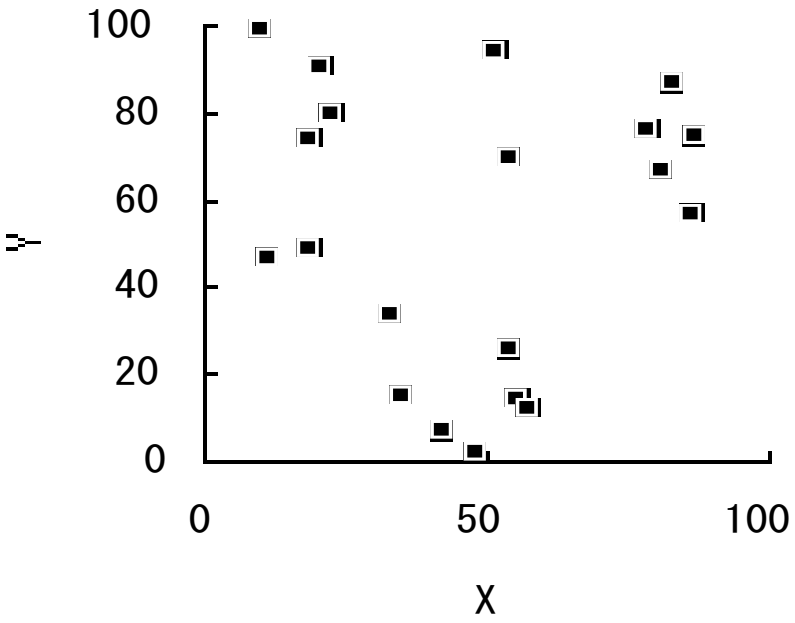
r = -1

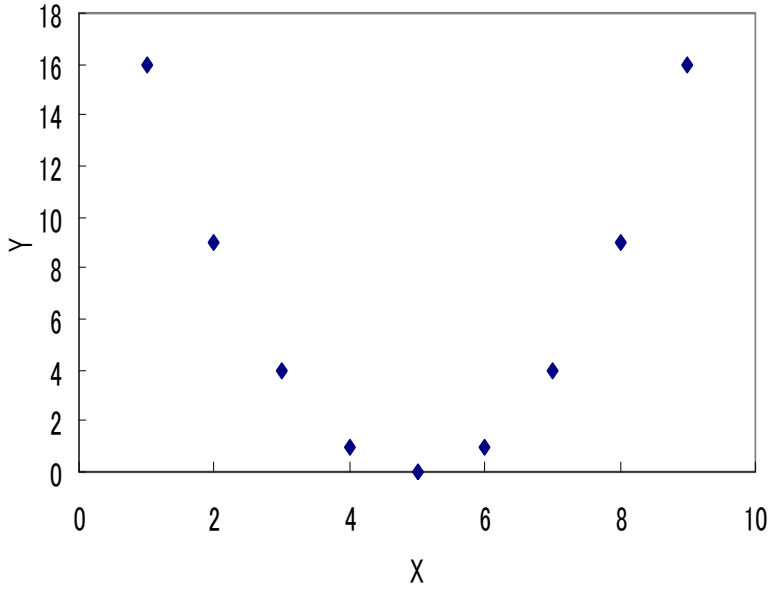


Negatively correlated

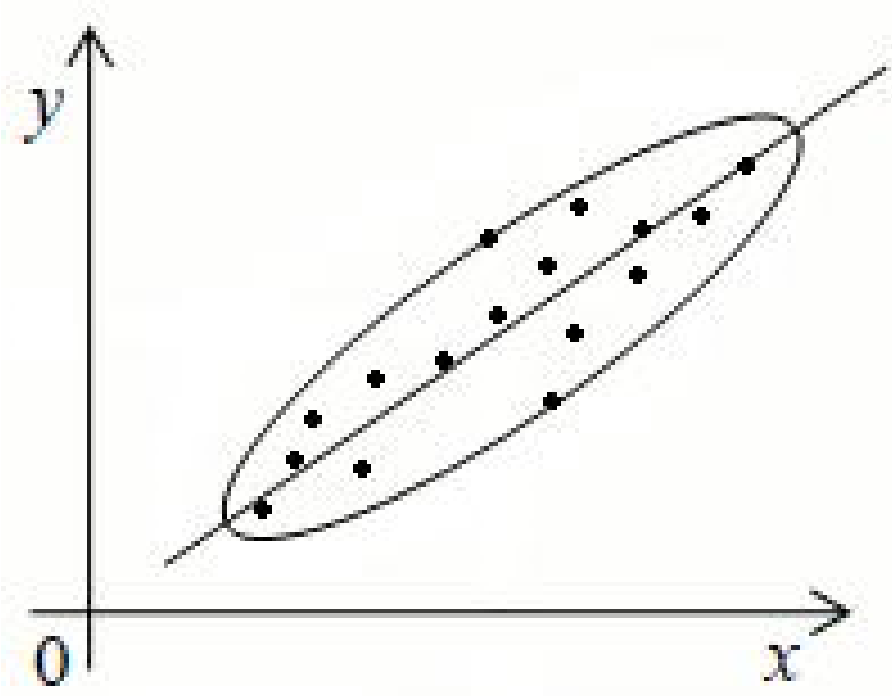
What does “r=0” mean?

- ~~No association between x and y ?~~
- No linear association between x and y



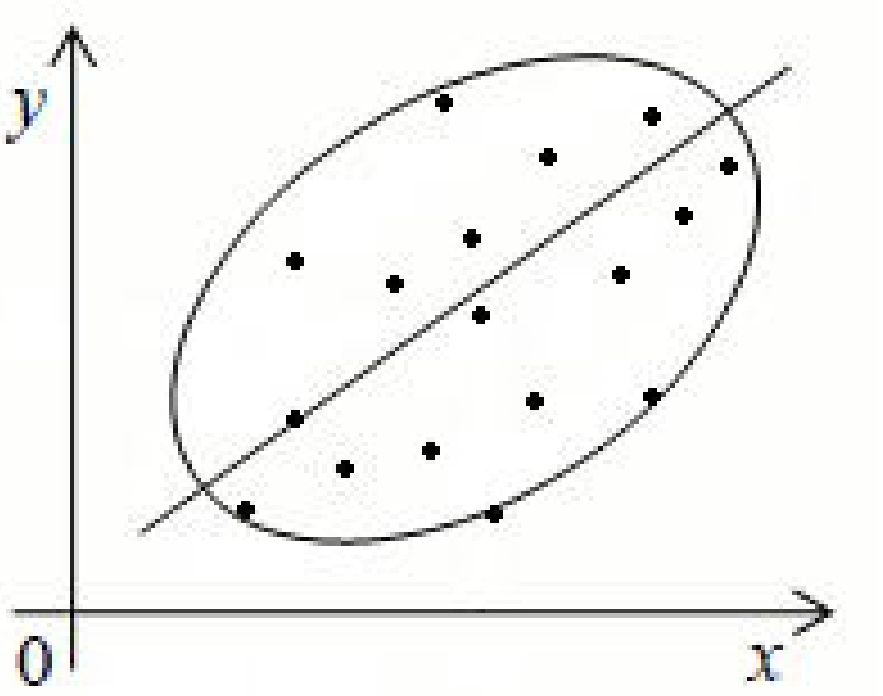


Correlation coefficient is not the magnitude of “slope”



線型が強い＝相関関係強い

Strong correlation



線型が弱い＝相関関係弱い

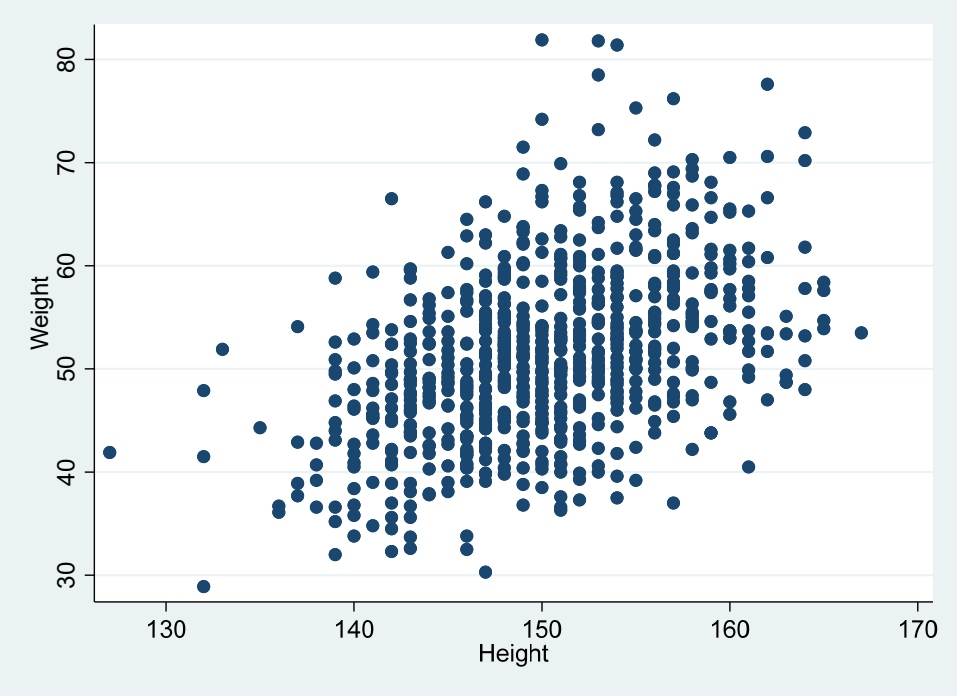
Weak correlation

Correlation coefficients

- Pearson's CC (r): parametric method
  - At least, one of the two variables should follow the normal distribution.

- Non-parametric methods
  - Spearman's CC (ρ)
  - Kendall's CC (τ)

r (correlation coefficient) and R-squared



r = 0.4481

0.4481 x 0.4481=?

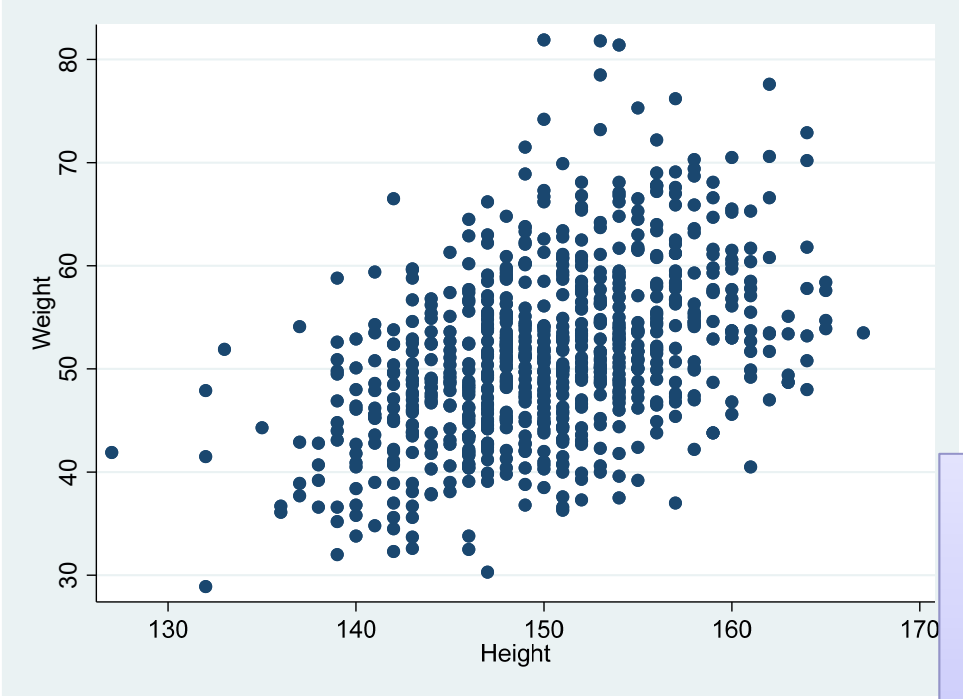
```
Number of obs      =       759
F(1, 757)          =    190.24
Prob > F           =    0.0000
R-squared          =    0.2008
Adj R-squared      =    0.1998
Root MSE           =    5.4705
```

$R^2 = r^2$

R squared, coefficient of determination, is the proportion of the variance in the dependent variable that is predictable from the independent variable(s).

$$R^2 = 1 - \frac{\sum_i (yi - fi)^2}{\sum_i (yi - \bar{y})^2}$$

r (correlation coefficient) and R-squared



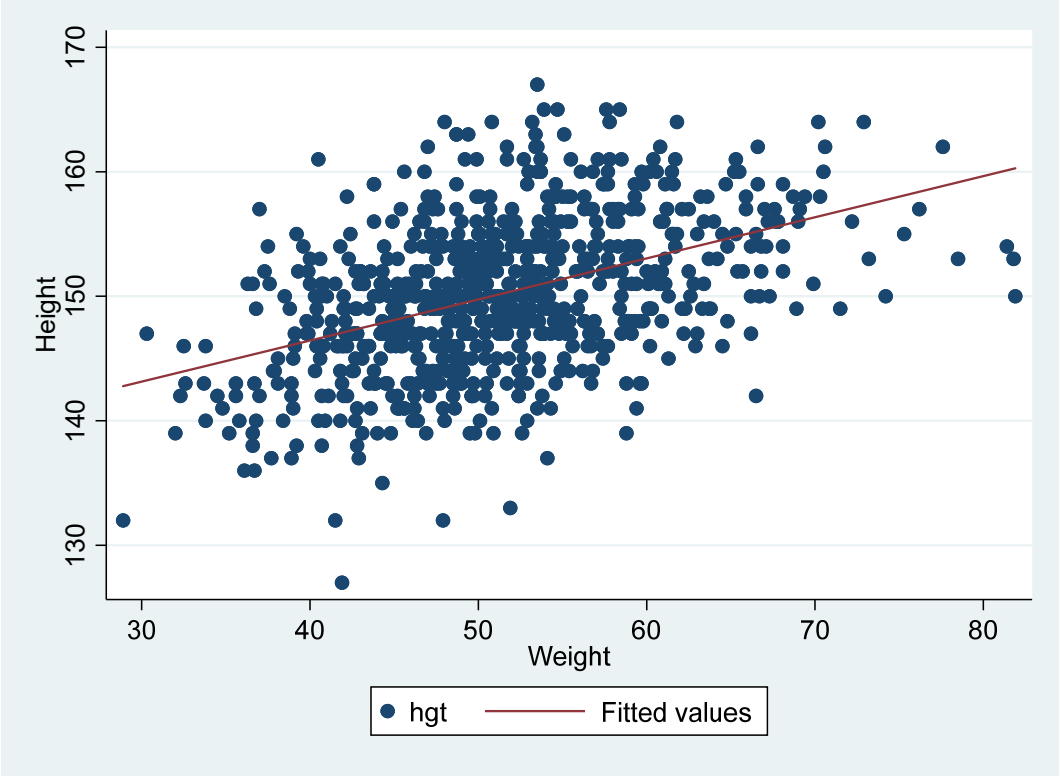

```
Number of obs    =       759
F(1, 757)        =    190.24
Prob > F         =    0.0000
R-squared        =    0.2008
Adj R-squared    =    0.1998
Roo   MSE        =    5.4705
```

Adjusted R squared value by the sample size and the number of variable(s)
Better to use when you have more variables or small sample size

$W = -40 + 0.6084xH$

The R^2 coefficient of determination, ranging 0-1, is a statistical measure of how well the regression predictions approximate the real data points.

r (correlation coefficient) and regression coefficient



r = 0.4481
P<0.001

W = -40 + 0.6084xH

H = 133 + 0.3301xW

Regression coefficient

$\sqrt{0.6084 \times 0.3301} = 0.4481$

ADJUSTMENT OF CORRELATION

Calculation skill and physical development

weight	calculation
24.8	134
25.6	136
15.9	117
16.1	124
24.2	137
28.9	135
31.8	135
22.3	137
18.9	131
15	100

Is weight related to calculation skill?

Estimation of age-adjusted correlation coefficient

- Correlation coefficient between weight and calculation skill was 0.79.
- Age is related to both variables, weight and calculation skill : age is a confounder.

partial correlation coefficient

-0.23･･･after adjusting the effect of age

Multivariate ≠ Multivariable (Multiple)

Am J Public Health. 2013 January; 103(1): 39–40.
Published online 2013 January. doi: 10.2105/AJPH.2012.300897

PMCID: PMC3518362
NIHMSID: NIHMS514677

Multivariate or Multivariable Regression?

Bertha Hidalgo, PhD, MPH and Melody Goodman, PhD, MS

Author information ▶ Article notes ▶ Copyright and License information ▶

See letter "Hidalgo and Goodman Respond" in volume 10 on page e1.

This article has been cited by other articles in PMC.

Abstract

Go to:

The terms multivariate and multivariable are often used interchangeably in the public health literature. However, these terms actually represent 2 very distinct types of analyses. We define the 2 types of analysis and assess the prevalence of use of the statistical term multivariate in a 1-year span of articles published in the American Journal of Public Health. Our goal is to make a clear distinction and to identify the nuances that make these types of analyses so distinct from one another.

Multivariable (Multiple) analysis

A multivariable model can be thought of as a model in which multiple variables are found on the right side of the model equation. This type of statistical model can be used to attempt to assess the relationship between a number of variables; one can assess independent relationships while adjusting for potential confounders.

This is the model to control the effects of confounders!

By contrast, a multivariable or multiple linear regression model would take the form

$$(2)\ y = \alpha + x_1\beta_1 + x_2\beta_2 + \ldots + x_k\beta_k + \varepsilon$$

where y is a continuous dependent variable, x is a single predictor in the simple regression model, and x_1, x_2, …, x_k are the predictors in the multivariable model.

As is the case with linear models, logistic and proportional hazards regression models can be simple or multivariable. Each of these model structures has a single outcome variable and 1 or more independent or predictor variables.

Multivariate analysis

Multivariate, by contrast, refers to the modeling of data that are often derived from longitudinal studies, wherein an outcome is measured for the same individual at multiple time points (repeated measures), or the modeling of nested/clustered data, wherein there are multiple individuals in each cluster. A multivariate linear regression model would have the form

$$(3)\ Y_{n\times p} = X_{n\times(k+1)}\,\beta_{(k+1)\times p} + \varepsilon$$

where the relationships between multiple dependent variables (i.e., *Y*s)—measures of multiple outcomes—and a single set of predictor variables (i.e., *X*s) are assessed.

This model is to analyze the relationship between “multiple outcomes” and a single set of predictors.

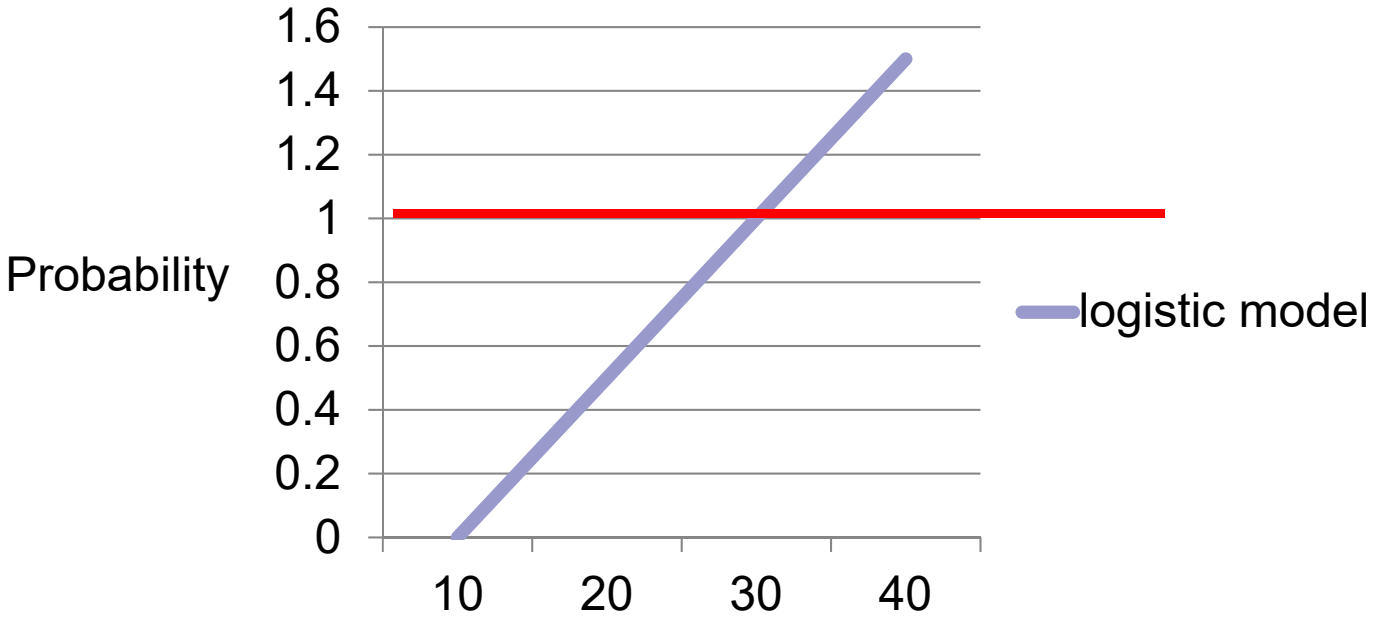
LOGISTIC REGRESSION ANALYSIS

Logistic regression analysis

- Logistic regression is used to model the probability of a binary response as a function of a set of variables thought to possibly affect the response (called covariates).

$$Y = \begin{cases} 1: \text{case (with the disease)} \\ 0: \text{control (no disease)} \end{cases}$$

One could imagine trying to fit a linear model (since this is the simplest model !) for the probabilities, but often this leads to problems:



In a linear model, fitted probabilities can fall outside of 0 to 1. Because of this, linear models are seldom used to fit probabilities.

In a logistic regression analysis, the **logit** of the probability is modeled, rather than the probability itself.

P = probability of getting disease (0～1)

$$\text{logit}(p) = \textbf{log}\left[\frac{p}{1-p}\right]$$

This transformation allows us to use a linear model.

As always, we use the natural log.

The logit is therefore **the log odds**, since odds = p / (1-p)

Logistic regression model

Now, we have the same function with linear regression model in the right side.

$$\text{logit}(p_x) = \log\left[\frac{p_x}{1 - p_x}\right] = \alpha + \beta x$$

where p_x = probability of event for a given value x, and α and β are unknown parameters to be estimated from the data.

→ **Multivariable analysis** is applicable to adjust the effect of confounding factor.

Interpretation of coefficients of logistic regression model

The explanatory variable is binomial one: 1=exposed or 0=unexposed

Exposed: $\log(O_e) = \alpha + \beta(\text{Exp}=1) = \alpha + \beta$

Unexposed: $\log(O_u) = \alpha + \beta(\text{Exp}=0) = \alpha$

Difference: $\log(O_e) - \log(O_u) = \beta$

Odds ratio: $O_e / O_u = e^{\beta}$

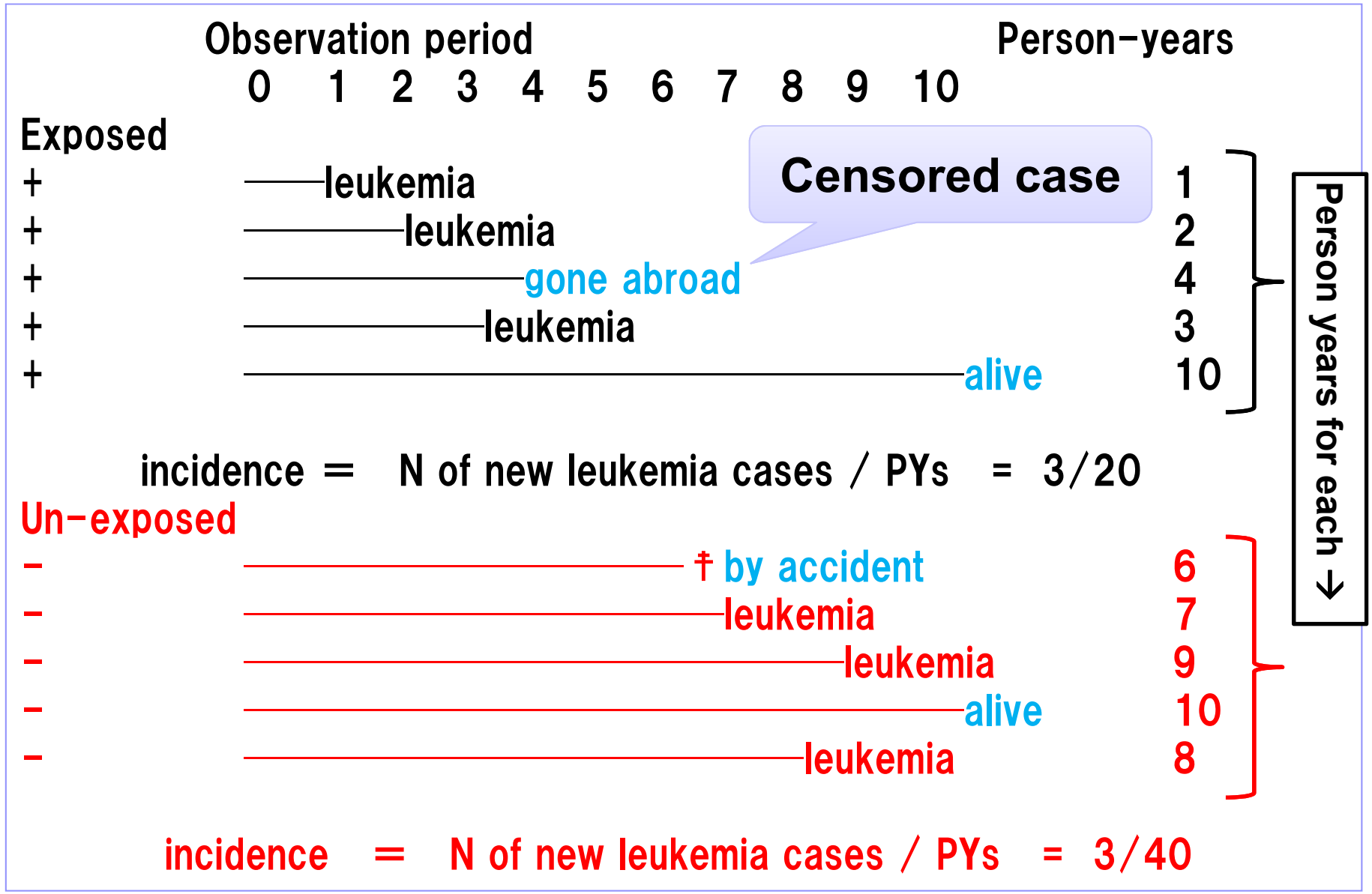
- **Coefficient estimate: Odds ratio (after exponentiating)**

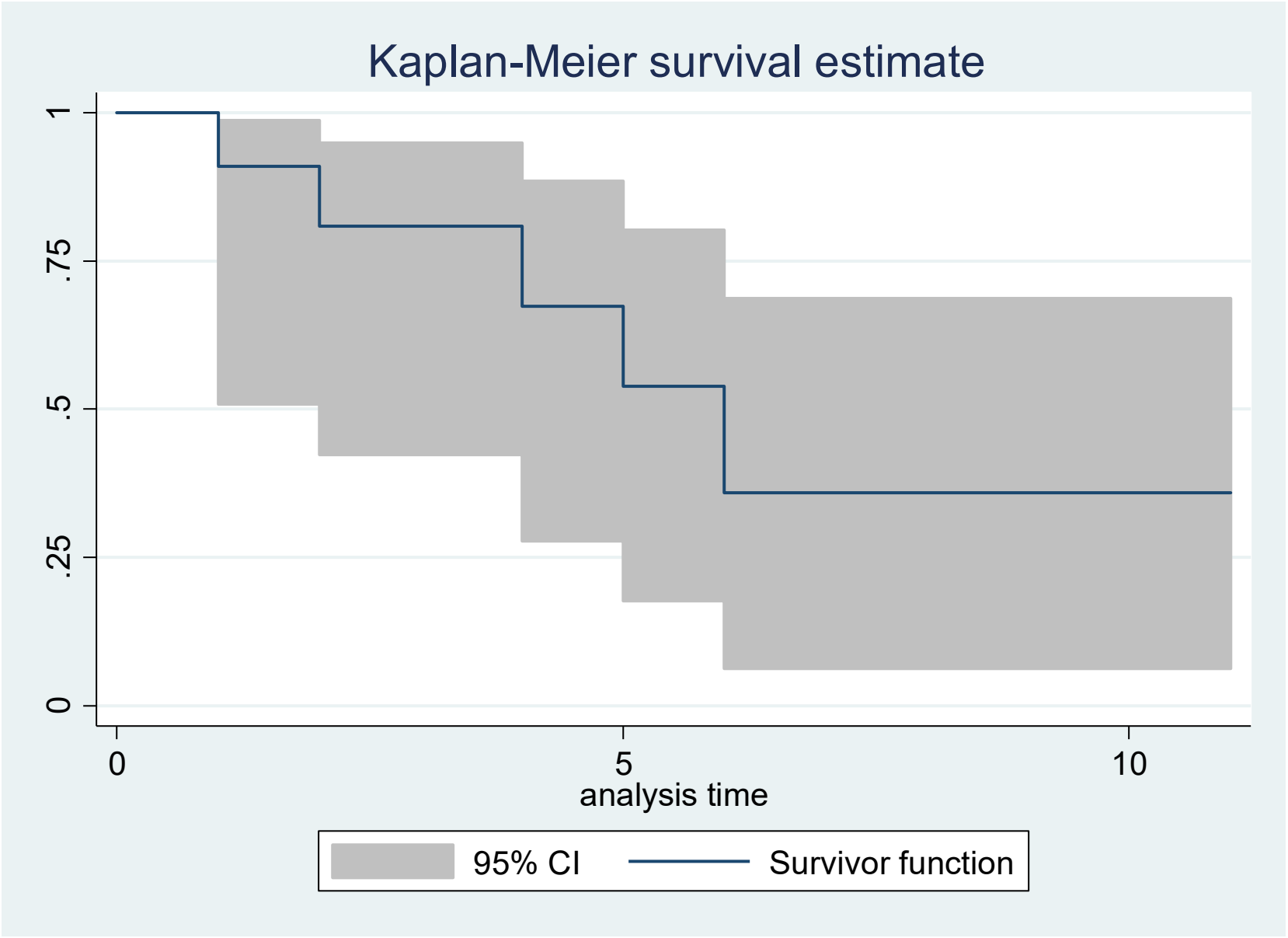
SURVIVAL ANALYSIS

Survival analysis

- Survival time：from the entry point（for example, when the treatment starts） until end point（for example, disease recurrence or the death from the disease）

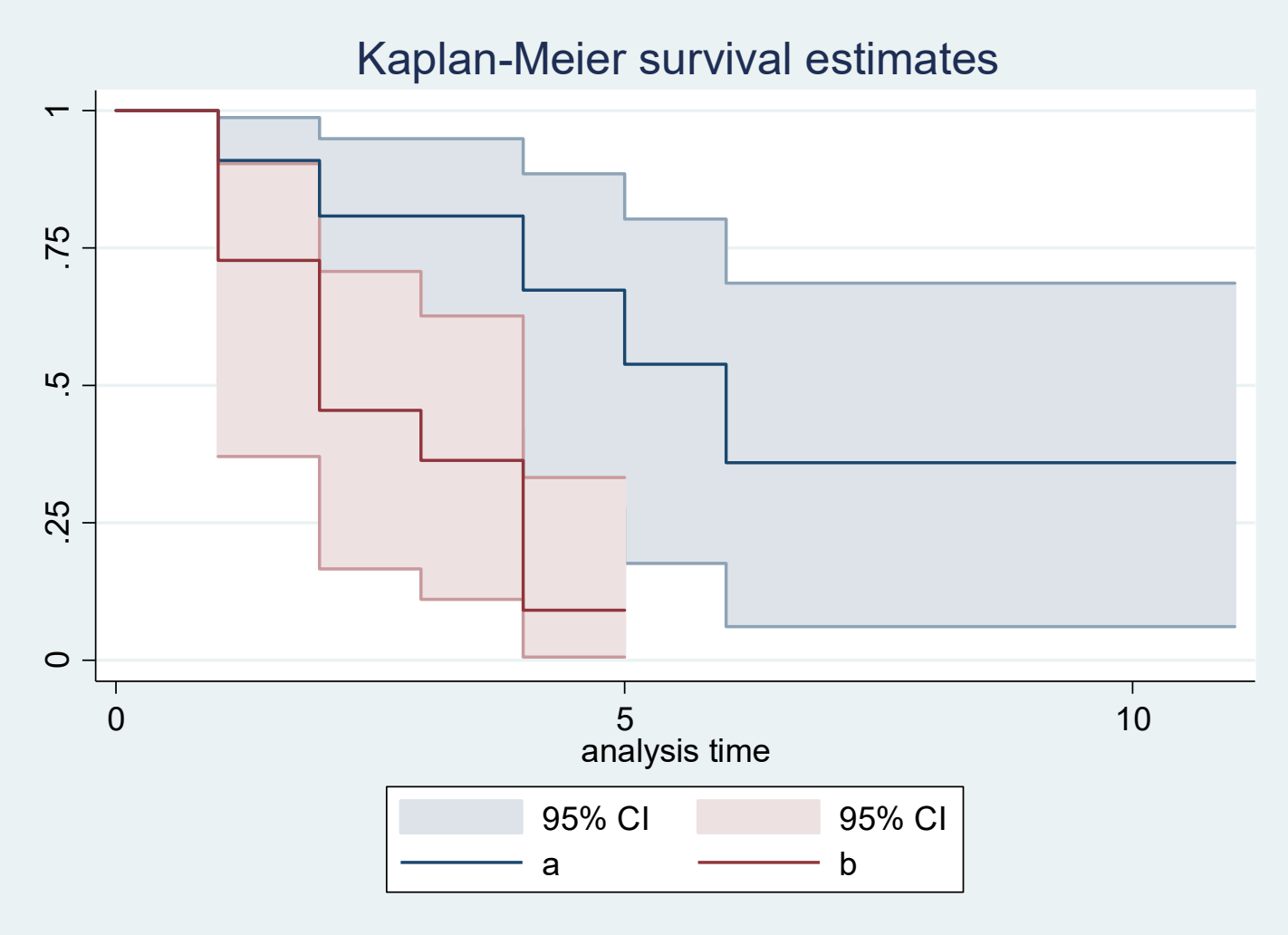
- Censoring: the follow-up is stopped because of other reason (for example, study period is over or the death from other reason）


Observation period
Person-years
0 1 2 3 4 5 6 7 8 9 10
Exposed
+ leukemia
+ leukemia
+ gone abroad
+ leukemia
+ alive
Censored case
1
2
4
3
10
Person years for each →
incidence = N of new leukemia cases / PYs = 3/20
Un-exposed
- † by accident
- leukemia
- leukemia
- alive
- leukemia
6
7
9
10
8
incidence = N of new leukemia cases / PYs = 3/40


Kaplan-Meier survival estimate
1
.75
.5
.25
0
0
5
10
analysis time
95% CI
Survivor function

Log-rank test:

Statistic test for the difference of survival probability



The statistic follows the chi-square distribution (df=1)

P=0.016

Limitations of Kaplan-Meier method

- Mainly descriptive
- Doesn’t control for covariates
- Requires categorical predictors
- Can’t accommodate time-dependent variables

Cox proportional hazard model

This model is expressed by the following formula; $\lambda(t \mid x_1,\ldots,x_k) = \lambda_0(t)\exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k)$

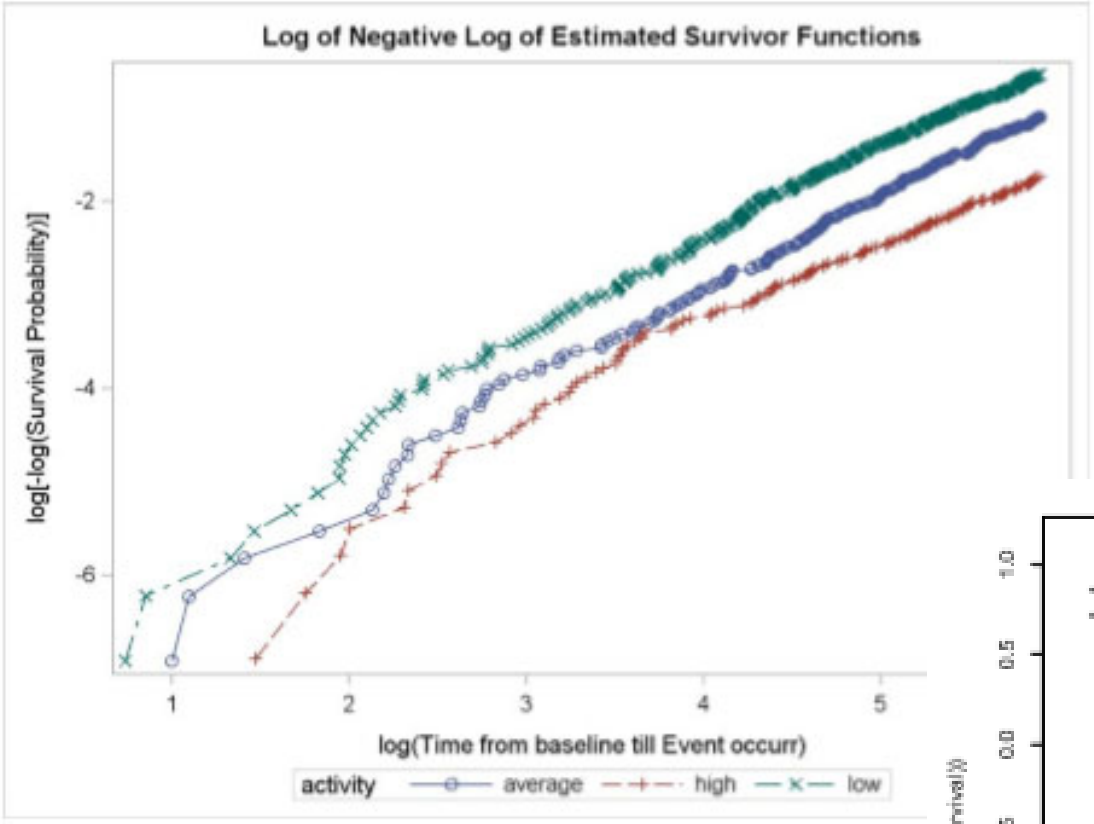
where λ(t) is the hazard of variable x_k and t is the time until the case is alive, and λ_0(t) is the baseline hazard. We assume that the log of hazard ratio is proportional to the variable X.

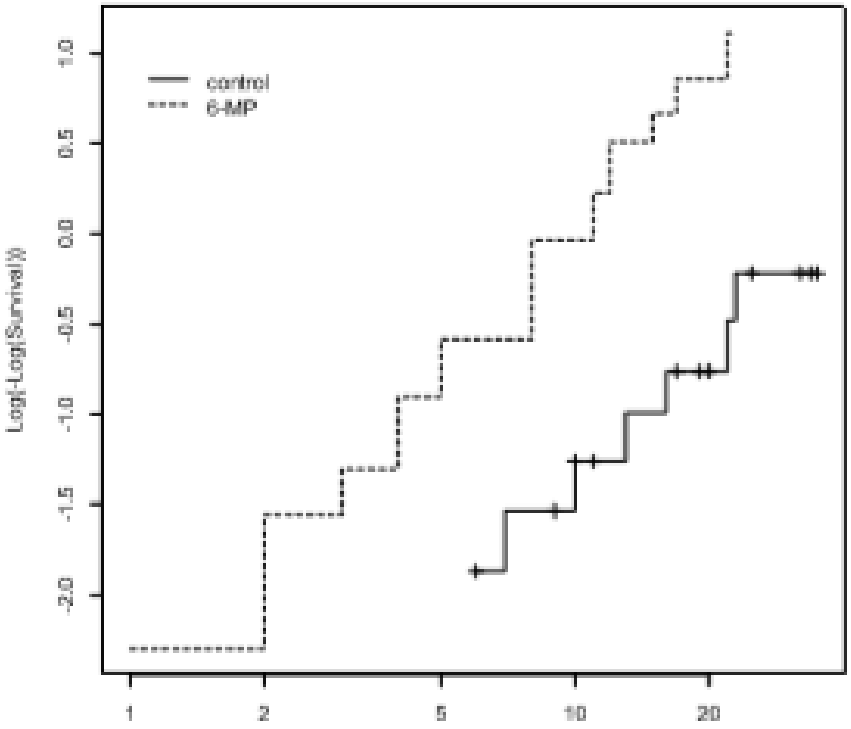
Log negative-log plot is useful to check

Hazard ratio: $\lambda_1(t)/\lambda_0(t)=\exp(\beta)$

Exposed group

Un-exposed group


Log of Negative Log of Estimated Survivor Functions
log[-log(Survival Probability)]
-2
-4
-6
1
2
3
4
5
log(Time from baseline till Event occurr)
activity
average
high
low

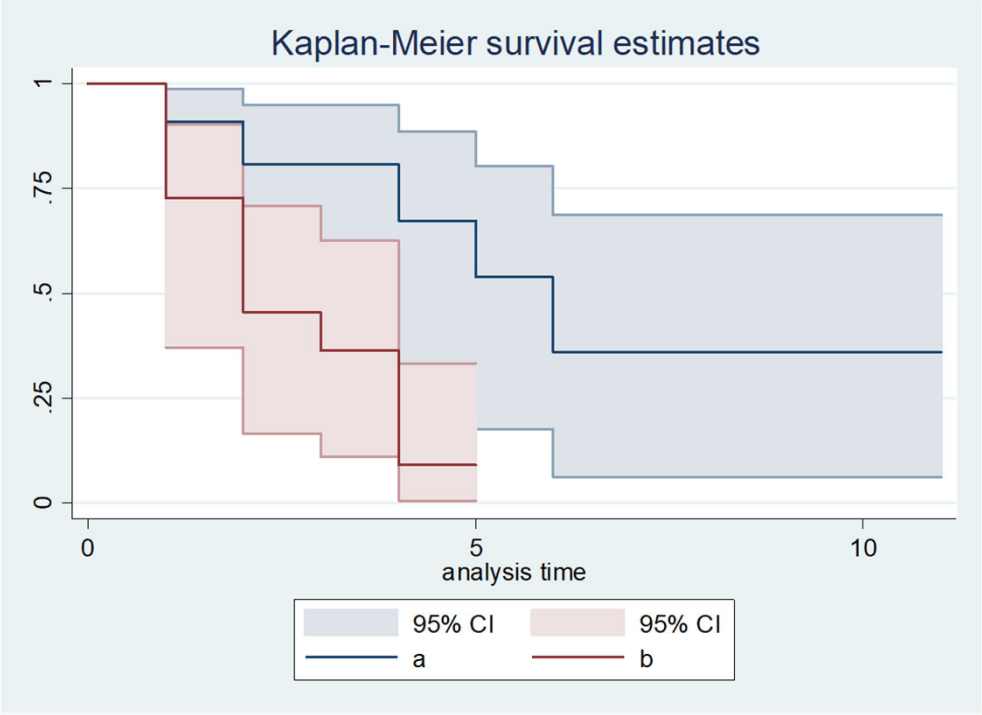

control
6-MP
Log[-Log(Survival)]
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
1
2
5
10
20

Group A=1, Group B=0

No. of subjects = 22 Number of obs = 22
No. of failures = 15
Time at risk = 77

LR chi2(1) = 4.68
Log likelihood = -35.943457 Prob > chi2 = 0.0305

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
A	0.29	0.1767	-2.04	0.042	0.0895	0.9557



STRATEGY FOR CONSTRUCTING REGRESSION MODELS

Basic principles

1. Stratified analysis should be first.
2. Determine which **confounders to include** in the model.
3. Estimate the shape of the exposure-disease relation.

   Dose-response relation
4. Evaluate **interaction**

How to determine confounders: data-dependent manner

1. Start with a set of predictors of outcome based on the strength of their relation to the outcome.
2. Build a model by introducing predictor variables one at a time: check the amount of change in the coefficient of the exposure term

> 10% change: include it as a confounder

Example of a confounder (age)

Ability of maths (AM) = α + β1(Height)

$\rightarrow$ AM = -42.8 + **0.41**(Height)

> 10% change

AM = α + β1(Height) + β2(Age)

$\rightarrow$ AM = 1.48 **- 0.01**(Height) + 2.02 (Age)

How to determine confounders: data-independent manner

Some researchers argue that

"Without data analysis, decide confounders, important risk factors of the outcome, based on the previous studies."

How can we pick-up "important risk factors"? If there are few studies, how can we know confounders?

How many explanatory variables can we use in a model?

Model	Number of explanatory variables	Example
Linear regression model	**Sample size / 15**	Up to around 6-7 variables in **100 subjects**
Logistic regression model	**Smaller sample size of outcome / 10**	Up to 10 variables if the numbers of cases and controls are **100** and 300, respectively.
Cox proportional hazard model	**The number of event / 10**	Up to 9 variables if you have **90 events** out of 150 subjects

ATTENTION!

- When you include a categorical variable in your model, you have to count that as "the number of categories – 1".
  - For example, the variable of age group used in the previous practice, we have to count it as "two" (=3 categories -1) variables.

PROPENSITY SCORE

If you cannot recruit enough sample size

- Calculate "propensity score" which can be used for adjustment of confounding effects.

Example

Aspirin Use and All-Cause Mortality Among Patients Being Evaluated for Known or Suspected Coronary Artery Disease

A Propensity Analysis

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Context Although aspirin has been shown to reduce cardiovascular morbidity and short-term mortality following acute myocardial infarction, the association between its use and long-term all-cause mortality has not been well defined.

Objectives To determine whether aspirin is associated with a mortality benefit in stable patients with known or suspected coronary disease and to identify patient characteristics that predict the maximum absolute mortality benefit from aspirin.

Table 1. Baseline and Exercise Characteristics According to Aspirin Use*

Variable	Aspirin (n = 2310)	No Aspirin (n = 3864)	*P* Value
Demographics			
Age, mean (SD), y	62 (11)	56 (12)	<.001
Men, No. (%)		2167 (56)	<.001
Clinical history			
Diabetes, No. (%)		432 (11)	<.001
Hypertension, No. (%)		1569 (41)	<.001
Tobacco use, No. (%)		500 (13)	.001
Prior coronary artery c		778 (20)	<.001
Prior coronary artery by			<.001
Prior percutaneous coronary intervention, No. (%)	667 (29)	148 (4)	<.001
Prior Q-wave MI, No. (%)	369 (16)	285 (7)	<.001
Atrial fibrillation, No. (%)	27 (1)	55 (1)	.04
Congestive heart failure, No. (%)	127 (6)	178 (5)	.12
Medication use			
Digoxin use, No. (%)	171 (7)	216 (6)	.004
β-Blocker use, No. (%)	811 (35)	550 (14)	<.001
Diltiazem/verapamil use, No. (%)	452 (20)	405 (10)	<.001
Nifedipine use, No. (%)	261 (11)	283 (7)	<.001
Lipid-lowering therapy, No. (%)	775 (34)	380 (10)	<.001
ACE inhibitor use, No. (%)	349 (15)	441 (11)	<.001
Cardiovascular assessment and exercise capacity			
Body mass index, mean (SD), kg/m²	29 (5)	30 (7)	<.001
Ejection fraction, mean (SD), %	50 (9)	53 (7)	<.001
Resting heart rate, mean (SD), beats/min	74 (13)	79 (14)	<.001
Resting blood pressure, mean (SD), mm Hg			

Almost all prognostic factors (n=28) are related to aspirin use!

After matching by propensity score, the distribution of prognostic factors are similar between aspirin users and non-users.

It is just like a RCT! (pseud RCT)

Table 3. Selected Baseline and Exercise Characteristics According to Aspi
Use In Propensity

	Aspirin (n = 1351)	No Aspirin (n = 1351)	*P* Value
Demographics			
Age, mean (SD), y	60 (11)	61 (11)	.16
Men, No. (%)	951 (70)	974 (72)	.33
Clinical history			
Diabetes, No. (%)	203 (15)	207 (15)	.83
Hypertension, No. (%)	679 (50)	698 (52)	.46
Tobacco use, No. (%)	161 (12)	162 (12)	.95
Cardiac variables			
Prior coronary artery disease, No. (%)	652 (48)	659 (49)	.79
Prior coronary artery bypass graft, No. (%)	251 (19)	235 (17)	.42
Prior percutaneous coronary intervention, No. (%)	166 (12)	147 (11)	.25
Prior Q-wave MI, No. (%)	194 (14)	206 (15)	.52
Atrial fibrillation, No. (%)	21 (2)	24 (2)	.65
Congestive heart failure, No. (%)	79 (6)	89 (7)	.43

Table 4. Cox Proportional Hazards Analyses of Aspirin Use and Mortality Among Propensity-Matched Patients (n = 2702)*

Model	Hazard Ratio (95% CI)	*P* Value
Unadjusted	0.53 (0.38-0.74)	.002
Adjusted for propensity	0.53 (0.38-0.74)	<.001
Adjusted for propensity and selected variables†	0.59 (0.42-0.83)	.002
Adjusted for propensity and all covariates‡	0.56 (0.40-0.78)	<.001

*CI indicates confidence interval.
†Selected variables included prior coronary artery disease, prior coronary artery bypass grafting, prior percutaneous intervention, and ejection fraction ≤40%.
‡For a list of covariates, see Table 2 footnote (†).

You need to include only propensity score in the model.

WE SHOULD NOT RELY ON P VALUE TOO MUCH

Statistic significance vs. Clinical significance

Statistic significance ≠ Clinical significance

- P value(s) do NOT tell us the significance in clinical practice / biological importance.
- If your sample size is quite large, you may obtain a result with statistic significance. So what?

RCT of donepezil for Alzheimer's disease

Lancet. 2004 Jun 26;363(9427):2105-15.

Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial.

Courtney C1, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group.

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BACKGI eimer's disease. We aimed to determin ogical symptoms, carers' psycholo g?

METHOI eriod in which they were randomly allocated donepezil (5 mg/ no completed this period were rerandomised to either donepezil (5 or 10 mg/day) or placebo, with double-blind treatment co defined by loss of either bas assessments were soug all patier

FINDINGS: Cognition averaged 0.8 MI points better (0.5-1.6; p<0.0001) with d institutionalisation (42% vs 44% at 3 ye onal care in the donepezil group compared institutional care was 0.96 (95% CI 0.7 l and psychological symptoms, carer psy mg donepezil.

INTERPRETATION: Donepezil is not cost effective, with benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.

Cognition averaged 0.8 MMSE points better (95%CI 0.5-1.2; p<0.0001) and functionality 1.0 BADLS points (0.5-1.6; p<0.0001) with donepezil over the first 2 years.

Donepezil is not cost effective, with benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for AD.

Which description is appropriate?

- In a RCT study, the mortality rates of new drug A and old drug B were 30% and 20%, respectively. And, the p value was 0.6 for the difference of them.

1. The mortality rate of drug A is equivalent to that of drug B.
2. We cannot say “there is a difference in the mortality between drug A and B”.
3. We cannot say “the mortality of drug A is higher than that of drug B”.

We cannot tell the equivalence by p value

- In the previous example, the sample size of each arm was 10.
- The result tells us “you failed to reject the null hypothesis because of small sample size”.
  - 293 subjects for each arm are required.
- The difference of mortality rate is 10% and its 95% CI is -30%, 50%.

American Statistical Association Releases Statement on Statistical Significance and P-values

Provides Principles to Improve the Conduct and Interpretation of Quantitative Science

https://www.amstat.org/newsroom/pressreleases/P-ValueStatement.pdf

1. P-values can indicate how incompatible the data are with a specified statistical model.
2. P-values do not measure the probability that the studied hypothesis is true, or the probability that the data were produced by random chance alone.
3. Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold.
4. Proper inference requires full reporting and transparency.
5. A p-value, or statistical significance, does not measure the size of an effect or the importance of a result.
6. By itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis.