Bias & Confounding

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Key concepts

- **Bias**

→ Should be minimized at the designing stage.

- **Random errors**

→ is the nature of quantitative data.

- **Non-differential misclassification**

→ is the nature of (inaccurate) classification.

- **Confounding**

→ Indicative of true association. Can be controlled at the designing or analysis stage.

ERROR VS. BIAS

Two types of errors: ---Error or bias?

- Random error

  ⇨ is the nature of quantitative data.

- Systematic error (=**bias**)

  ⇨ should be minimized at the designing stage.

Random error

Measured value (mm)
53
47
48
49
51
52
50
Mean=50

Systematic error

Measured value (mm)
48
48
48
48
48
48
48
Mean=48

God knows that the true value is 50mm.

Is the following study acceptable?

- We want to compare the mean of blood pressure levels between two groups.
- The blood pressure checker has a problem and always gives 3mmHg-higher than true values.
- All subjects were examined by the same blood pressure checker.

Two-group comparison with random errors

God knows that the true value is 50mm in both groups.

Group A(mm)	Group B(mm)
53	47
47	51
48	52
49	50
51	48
52	49
50	53
Mean 50	50

Mean difference=0 → correct result

Systematic error occurred in both groups

God knows that the true value is 50mm in both groups.

Group A(mm)	Group B(mm)
49	48
48	49
46	49
47	48
49	46
49	47
48	49
Mean 48	48

Mean difference=0 → correct result

Systematic error occurred in only group B

God knows that the true value is 50mm in both groups.

	Group A(mm)	Group B(mm)
	53	45
	47	49
	48	50
	49	48
	51	46
	52	47
	50	51
Mean	50	48

Mean difference = 2 → wrong result

Proper comparison between groups :

1） Comparison using accurate data

2） Comparison using (in)accurate data

As long as the magnitude of random error and bias occur in a same manner among groups.

MISCLASSIFICATION

Non-differential Misclassification in Two Exposure Categories

Correct Data	Test +	Test -
Cases	240	200
Controls	240	600

OR =

Sensitivity = 0.8

Specificity = 1.0

	Test +	Test -
Cases	192	248
Controls	192	648

OR =

What is the number of each cell? Please calculate OR.

Sensitivity = 0.8
Specificity = 0.8

	Exposed	Unexposed
Cases		
Controls		

OR = □

Sensitivity = 0.4
Specificity = 0.6

	Exposed	Unexposed
Cases		
Controls		

OR = □

Two types of misclassification

- Non-differential misclassification
  - Systematic error may not be a critical issue as long as <u>it occurs in all comparison groups</u>.

- Differential misclassification
  - If the error occurs <u>only in one specific group</u> due to bias, the risk estimate deviate from null.

BIAS IN EPIDEMIOLOGIC STUDY

Different types of bias

- Selection bias:

  It occurs at sampling

- Detection bias:

  It occurs at diagnosis (outcome)

- Measurement (information) bias:

  It occurs at surveillance

  - □Recall bias
  - □Family information bias

Selection bias

- Selective differences between comparison groups that distort the relationship between exposure and outcome

- Unrepresentative nature of sample

Usually, comparative groups *NOT* coming from the same study base and *NOT* being representative of the populations they come from

Example A
A case-control study of childhood leukemia and exposure to electromagnetic field (EMF)

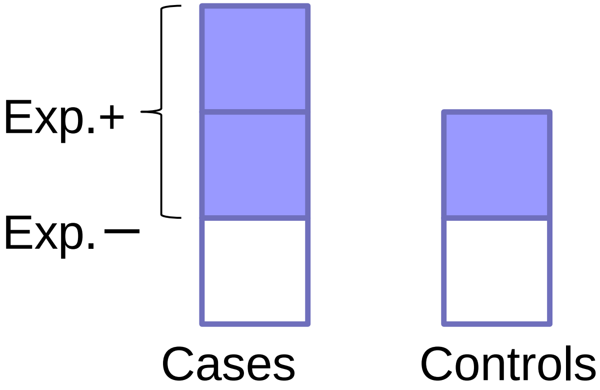
- If parents of cases, living in the neighborhood of power lines, suspect the association and tend to agree on participation to the study,

⇨ the association may become stronger than what it should be.

Example B
A case-control study of childhood leukemia and exposure to electromagnetic field (EMF)

- All the parents of cases may be willing to participate in the study. On the other hand, the parents of control children may tend to participate in the study only if they live in the neighborhood of power lines since EMF exposure is strongly suspected to be related to power line.

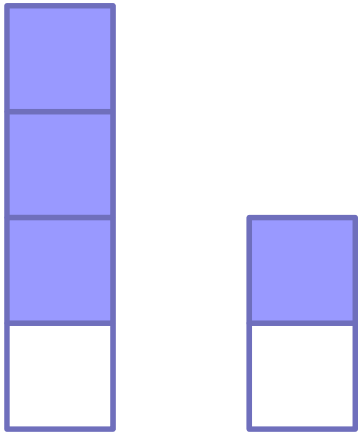
⇨ The association may become ***weaker*** than what it should be.



True risk estimate

OR = (2/1) / (1/1)

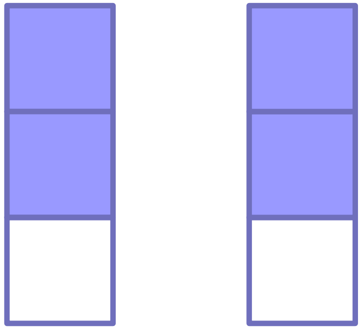
= 2



Example A

OR = (3/1) / (1/1)

= 3・・・overestimation



Example B

OR = (2/1) / (2/1)

= 1・・・underestimation

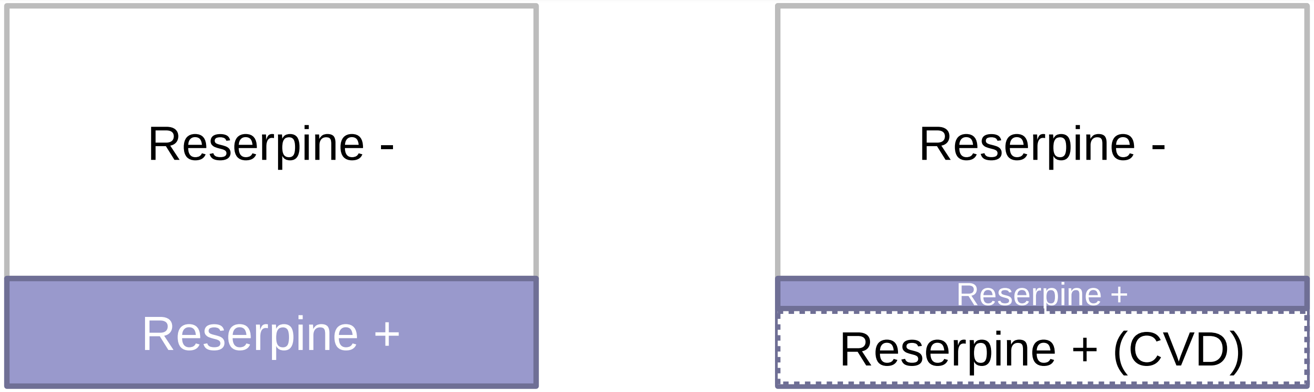
Selection bias caused by low participation rate

- In a case-control study for lung cancer
- Cases were identified by cancer registry
- Controls were recruited from a population base but the participation rate was too low, say 20% (in general, health-conscious people tend to participate in this kind of study).

What happened in the association between smoking and lung cancer risk is that ….

⇨ the association become stronger than what it should be

Is Reserpine a cause of breast cancer?



Reserpine -

Reserpine +

Reserpine -

Reserpine +

Reserpine + (CVD)

Cases: Breast cancer patients

Controls: Patients at the same hospital

(Except who have cardiovascular diseases to which Reserpine is likely to be prescribed.)

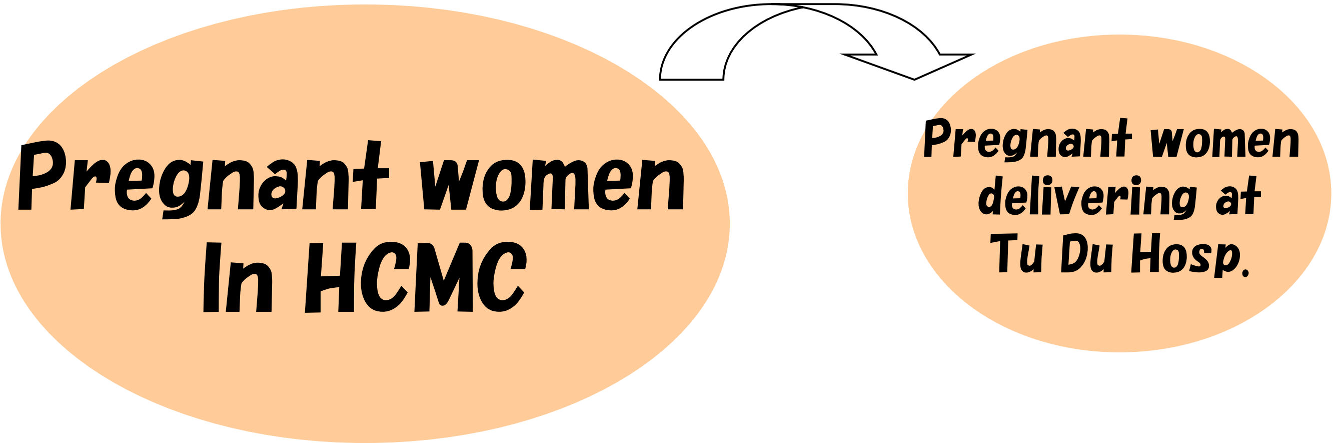
Horwitz RI, Feinstein AR. Exclusion bias and the false relationship of reserpine and breast cancer. Arch Intern Med. 1985;145(10):1873-5.

Selection bias influences internal validity of the obtained results.

NOTE for advance learners:

Sampling is a different issue from selection bias.

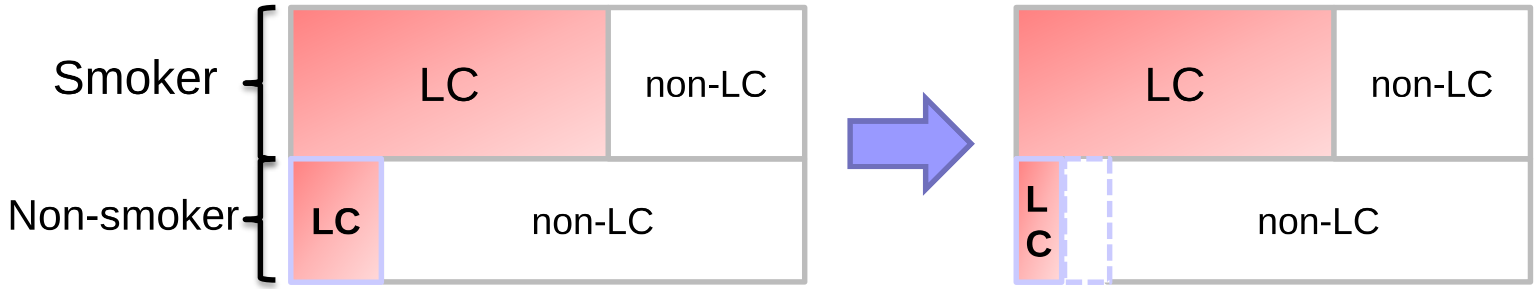
Prevalence of postpartum depression at Tu Du
= Prevalence in HCMC?



Sampling may influence generalizability (external validity) of the obtained results.

A doctor may examine the patient’s chest X-ray more carefully if he knew the patient is a heavy smoker but not for non-smoking patients.

the association may become ______ than what it should be.



True prevalence

In the presence of detection bias

Detection bias

- Typically, this is the situation where the exposure of interest makes asymptomatic case to symptomatic.

- It is a special situation where case ascertainment depends on exposure.

A case-control study of acoustic neuroma and mobile phone use

- This brain tumor is asymptomatic and is occasionally noticed by hearing difficulty or hearing loss. In other words, those who use mobile phone may have a higher chance of noticing unilateral hearing difficulty and visiting hospitals, where the acoustic neuromas are detected.

⇨ the association may become **stronger** than what it should be.

Measurement (information) bias

- Once the subjects to be compared have been identified, the information to be compared must be obtained.
- Information bias can occur whenever there are errors in the measurement of subjects, but the consequence of the errors are different, depending on whether distribution of errors for one variable (e.g., exposure or disease) depends on the actual values of other variables.
- For discrete variables, measurements error is called classification error or misclassification.

"Modern Epidemiology", Rothman, Greenland, and Lash

Suppose, you conducted a case-control study on relationship of prenatal infections and congenital malformations.

You asked mothers regarding prenatal episode of infections by interview / questionnaire.

Cases
(mothers of babies
with defect)

Controls
(mothers of
healthy babies)

What is the possible bias?

How do you avoid /minimize the bias?

Controlling for misclassification

- - Blinding
  - □ prevents investigators and interviewers from knowing case/control or exposed/non-exposed status of a given participant
- - Form of survey
  - □ mail may impose less "white coat tension" than a phone or face-to-face interview
- - Questionnaire
  - □ use multiple questions that ask same information
- - Accuracy
  - □ Multiple checks in medical records & gathering diagnosis data from multiple sources

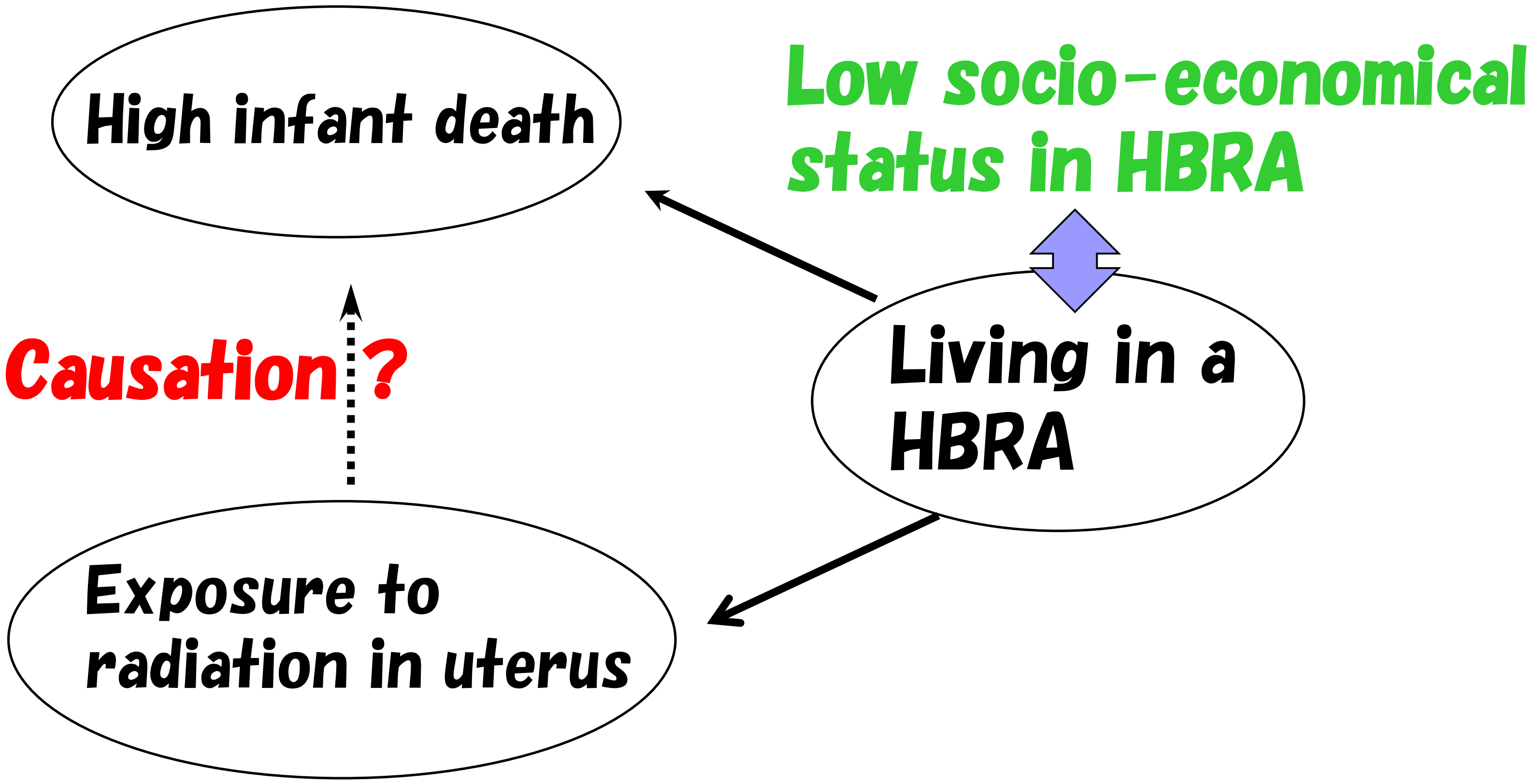
CONFOUNDING

3 conditions of Confounding

1. Confounders are risk factors for the outcome.
2. Confounders are related to exposure of your interest.
3. Confounders are NOT on the causal pathway (intermediate) between the exposure and the outcome of your interest.

Example of confounder

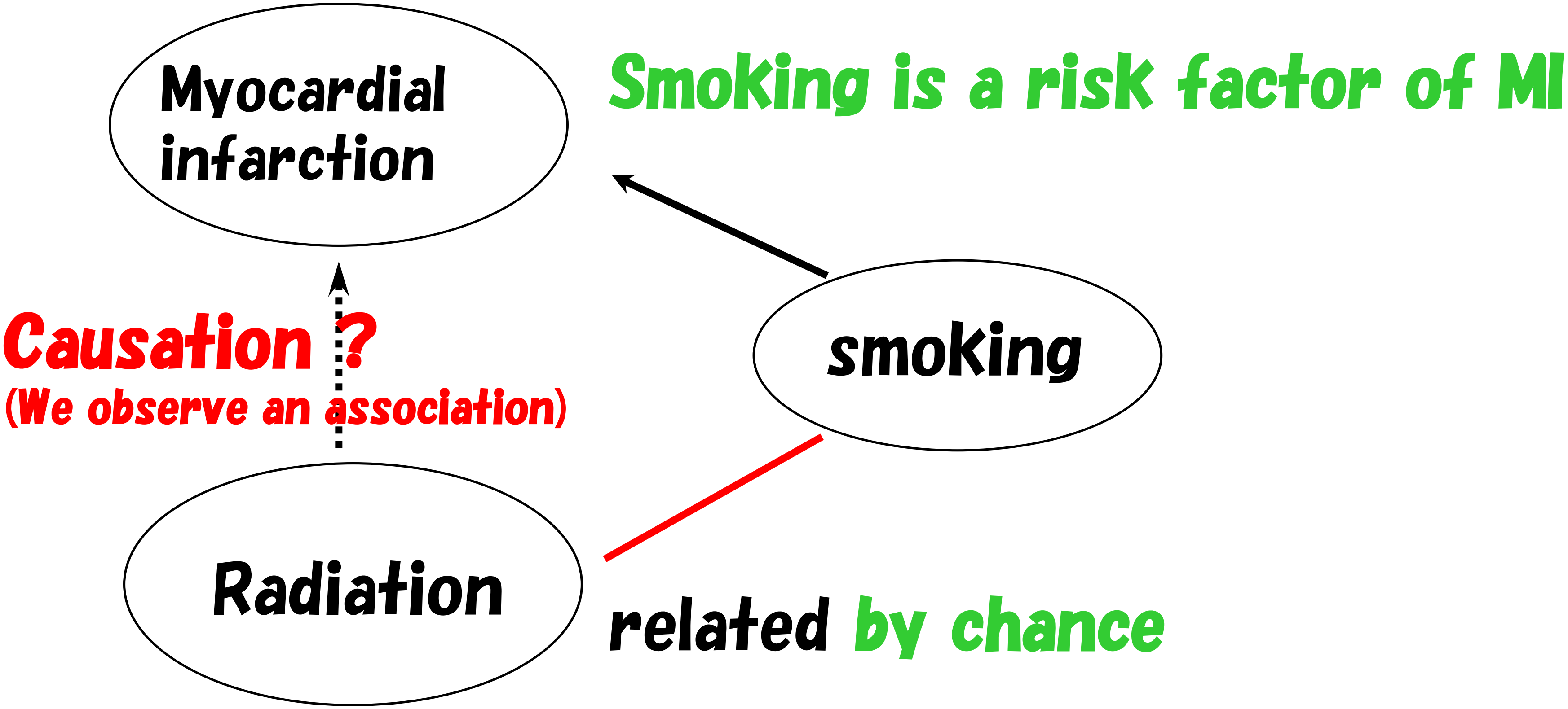
− living in a HBRA is a confounder −


High infant death
Low socio-economical status in HBRA
Causation?
Living in a HBRA
Exposure to radiation in uterus

HBRA: high background radiation area

Example of confounder

ー smoking is a confounder -



Myocardial infarction

Smoking is a risk factor of MI

Causation ?

(We observe an association)

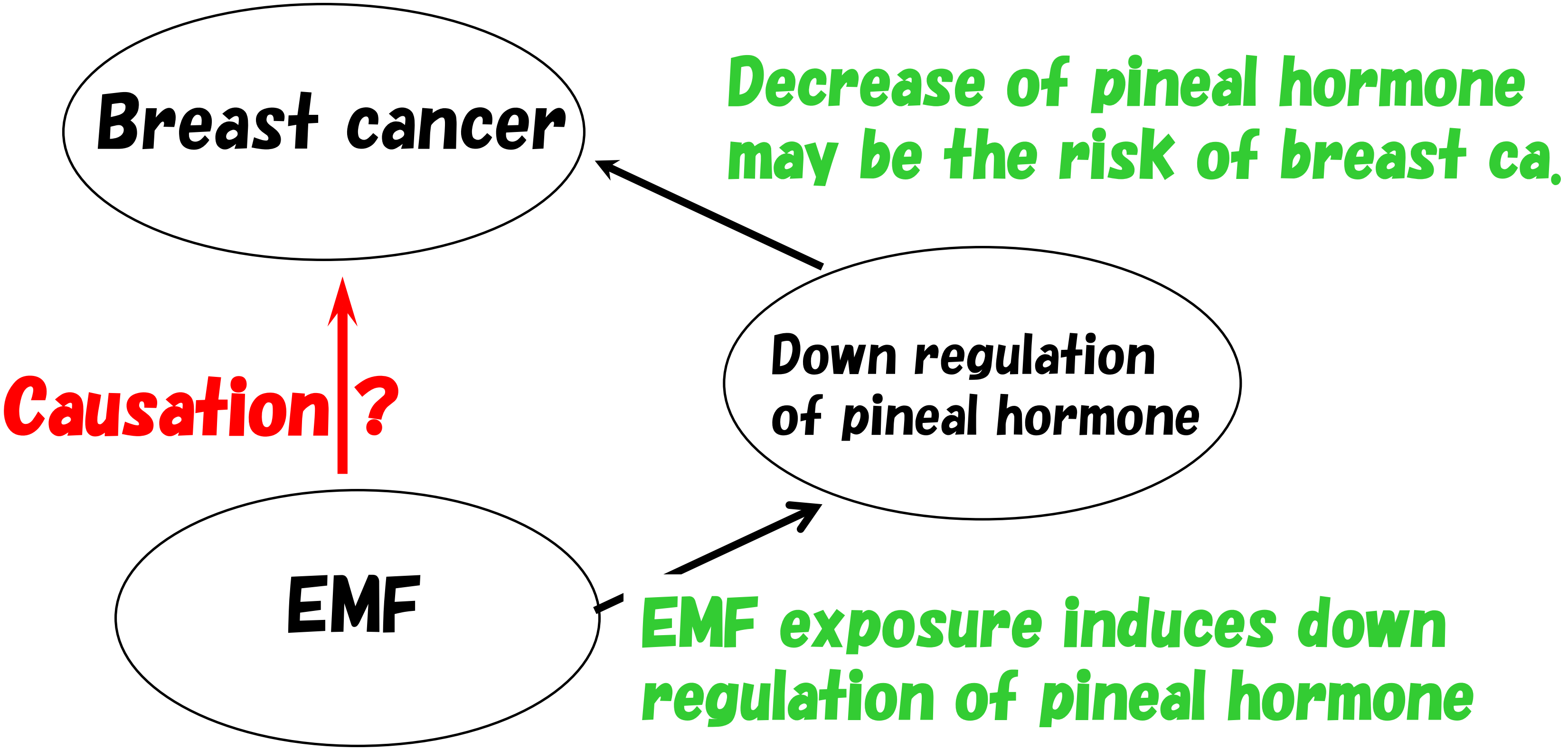
smoking

Radiation

related by chance

Example of "not" confounder

- pineal hormone is not a confounder -

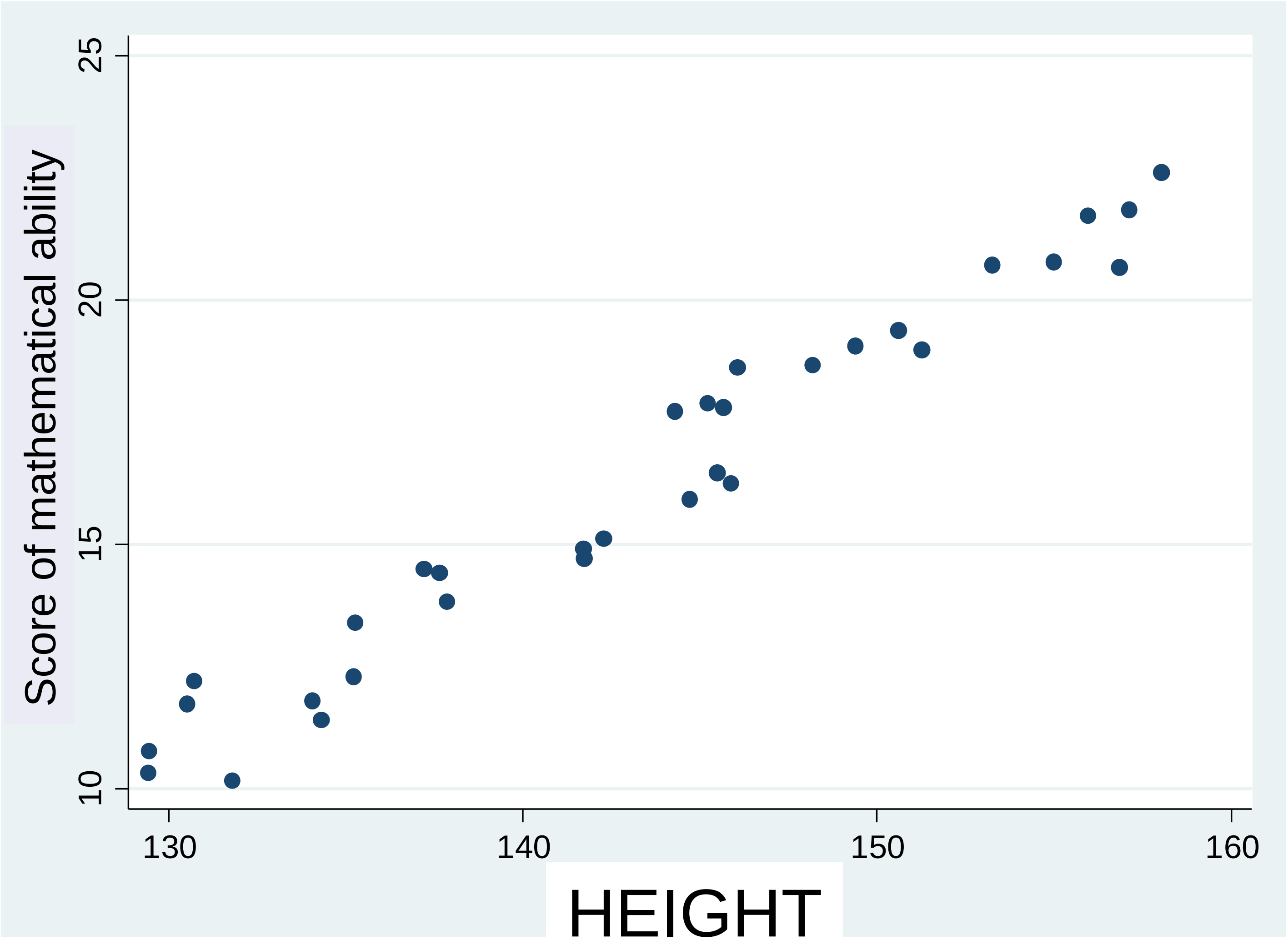

Breast cancer
Decrease of pineal hormone may be the risk of breast ca.
Causation ?
Down regulation of pineal hormone
EMF
EMF exposure induces down regulation of pineal hormone

EMF: electro-magnetic field

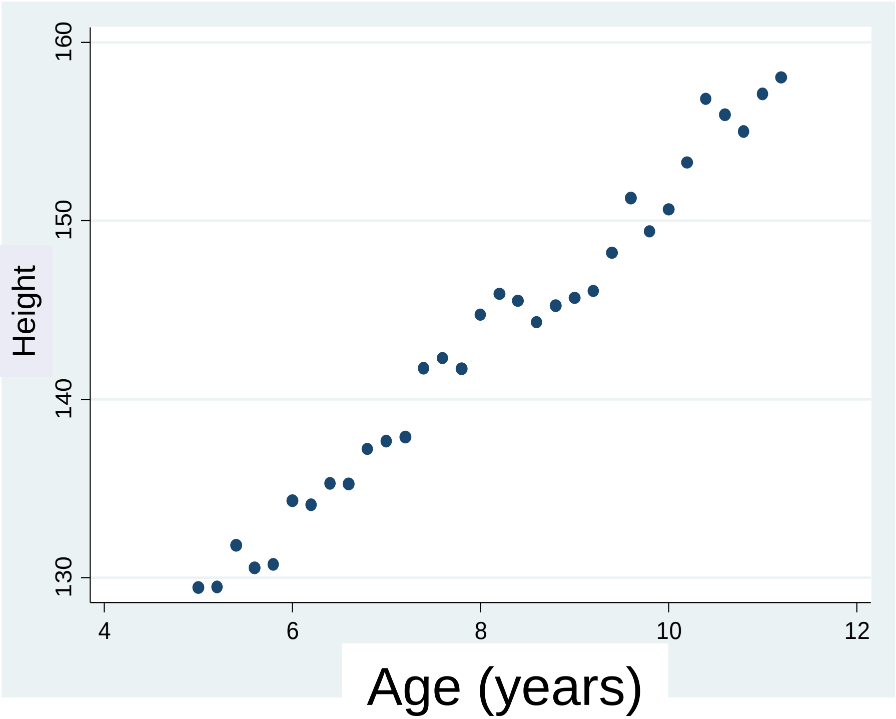
Why do we have to consider confounding?

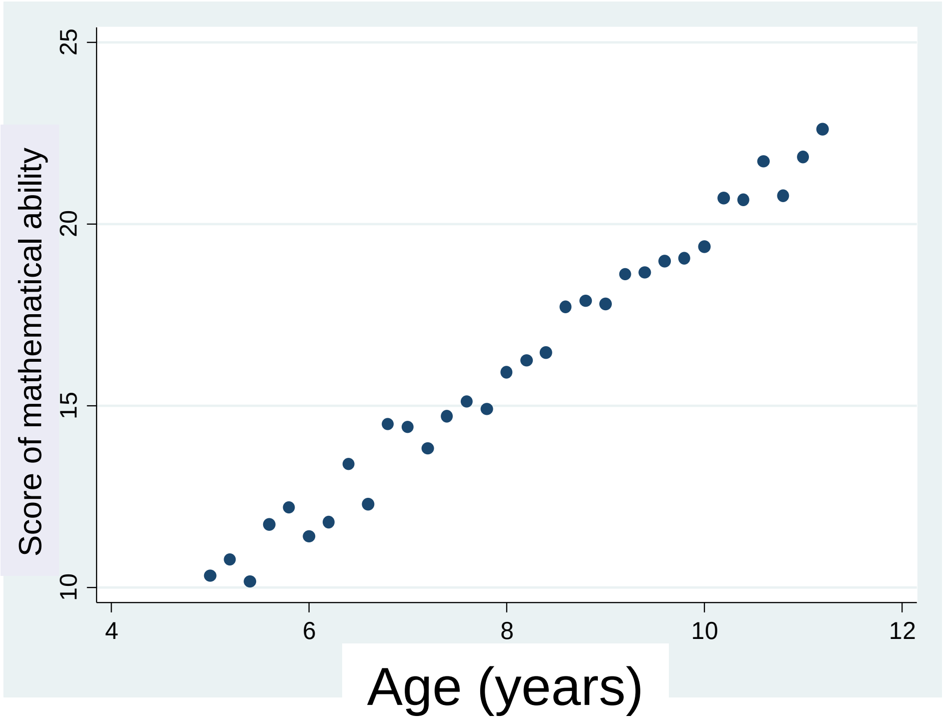
- We want to know the "true" causal association but a distorted relationship remains if you do not adjust for the effects of confounding factors.

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 can we solve the problem of confounding?

"Prevention" at study design

- ✓ **Limitation**
- ✓ **Randomization** in RCTs
- ✓ **Matching** in a cohort study

Notice: Matching does not always prevent the confounding effect in a case-control study.

How can we solve the problem of confounding?

"Treatment " at statistical analysis

- ✓Stratification by a confounder
- ✓Multivariate analysis