

به نام خدا

Bias and confounding

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Outlines

- ❖ **Types 1 and type 2 of Errors**

- ❖ **Random Error**

- ❖ **Systematic Error(Bias):**

 - Selection Bias

 - Information Bias

- ❖ **Cofounding**

خطا در آزمون فرضیه

در آزمون فرضیه دو نوع خطا ممکن است رخ دهد:

- یکی اینکه واقعا بین گروهها اختلافی وجود نداشته باشد و محقق نتیجه بگیرد که اختلاف وجود دارد که در این صورت مرتکب خطای نوع اول (α) شده است.
- دیگر اینکه بین گروهها واقعا اختلاف باشد ولی محقق نتیجه بگیرد که اختلافی نیست. در این حال مرتکب خطای نوع دوم (β) شده است.
- نقطه مقابل خطای نوع اول را اطمینان ($1-\alpha$) و نقطه مقابل خطای نوع دوم را توان آزمون ($1-\beta$) می گویند.

Correct (✓) decisions and Types of Errors (X) in hypothesis testing

TRUE Situation

Difference exists (H_1)

No Difference (H_0)

CONCLUSION
hypothesis test



Difference exists (H_1)

(Power or 1-beta)



X

Type I error or
Alpha error

X

Type II error or
Beta error



confidence

No Difference

Do not reject (H_0)

خطاهای قضاوت

تصویب هیئت منصفه		واقعیت	
		گناهکار	بی گناه
	گناهکار	OK	Error
	بی گناه	Error	OK

Hypothesis and error

TABLE 5.1

Truth	Decision	
	H_0 Is Not Rejected	H_0 Is Rejected
H_0 is true	Correct decision	Type I error
H_0 is false	Type II error	Correct decision

Bias, Error, Precision, Reliability, Validity

- **Reliability:** repeatability of a measure
- **Validity:** absence of bias (or absence of all error)
- **Error:** discrepancy between the observed result and the true value
- **Precision:** absence of random error
- **Bias:** systematic error – independent of study size

- Precision refers to the absence of random error. Similarly, **reliability** refers to the extent to which a measurement or finding will be observed consistently by different observers, using different instruments, at different times, or across other circumstances where the underlying construct is believed not to have changed.
- Validity refers to the absence of systematic error (“bias”) or, sometimes, the absence of all error.

Internal validity versus external validity

- ***Internal validity***: whether the study provides an unbiased estimate of what it claims to estimate
- ***External validity***: whether the results from the study can be generalized to some other population

- Internal Validity عبارت است از تعمیم نتایج به

Source Population

- External Validity عبارت است از تعمیم نتایج به

Target Population

Internal validity

- Internal validity concerns whether the study provides an unbiased (valid) estimate of what it claims to estimate. For example, suppose investigators say that they are studying Alzheimer's disease in North Carolina elderly. If the study findings do in fact accurately depict the situation among NC elderly, then the study is (internally) valid.

External validity

- External validity concerns whether the results from a study apply to some wider population that the study may have relevance for but does not claim to estimate. For example, do the results from a study carried out in North Carolina apply to people in the southeast U.S. as a whole, the entire U.S., all of North America, all industrialized countries, etc.?
- The term generalizability is often used interchangeably with “external validity”.

- Due to the inclusion of errors, all studies are characterized by differences between the observed results and the true results. Such errors in turn are of two kinds:

(I) random errors

(II) systematic errors.

- Error is typically regarded as arising from two types of processes – random processes, such as simple random sampling or flipping a fair coin, and systematic processes which move an estimate in one direction.
- Epidemiologists use the term bias to refer to systematic error.

Draw random samples from population with 50% women

Distribution	Estimate of % Women	
	N = 100	N = 1,000
Highest	68	54.9
10%	above 56	above 51.9
25%	above 53	above 51.0
25%	below 47	below 48.9
10%	below 44	below 48.0
Lowest	33	45.0

- If we draw 1,000 samples of 1,000 people each – that's the right-hand column in the table – and compute the percentage of women in each sample, we might observe the percentage to range across the samples from as low as 45% to as high as nearly 55%, with about half of the samples having a percentage between about 49% and 51%.

- On the other hand, if the samples had only 100 people each, the percentages of women in the samples would vary more widely around the population value of 50%. As shown in the left-hand column, about one-fourth of the estimated percentages from the smaller samples would be below 47% and one-fourth above 53%.

Random error can be problematic, but . . .

- Influence can be reduced
 - increase sample size
- Probability of influence can be quantified (e.g., confidence interval width)

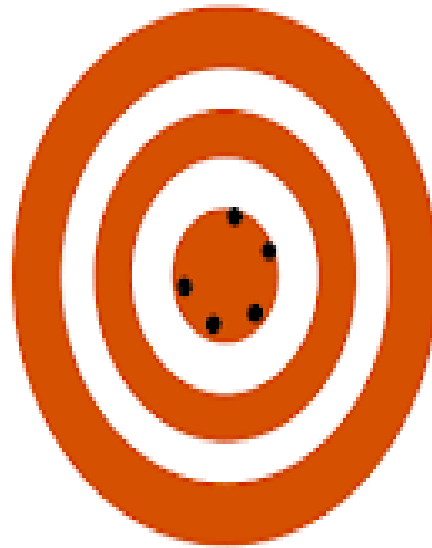
- Accuracy refers to the size of deviations from the true source population mean, whereas precision refers to the size of deviations from the mean obtained by repeated application of the sampling procedure.

No error



✓ Accuracy
✓ Precision

Random error

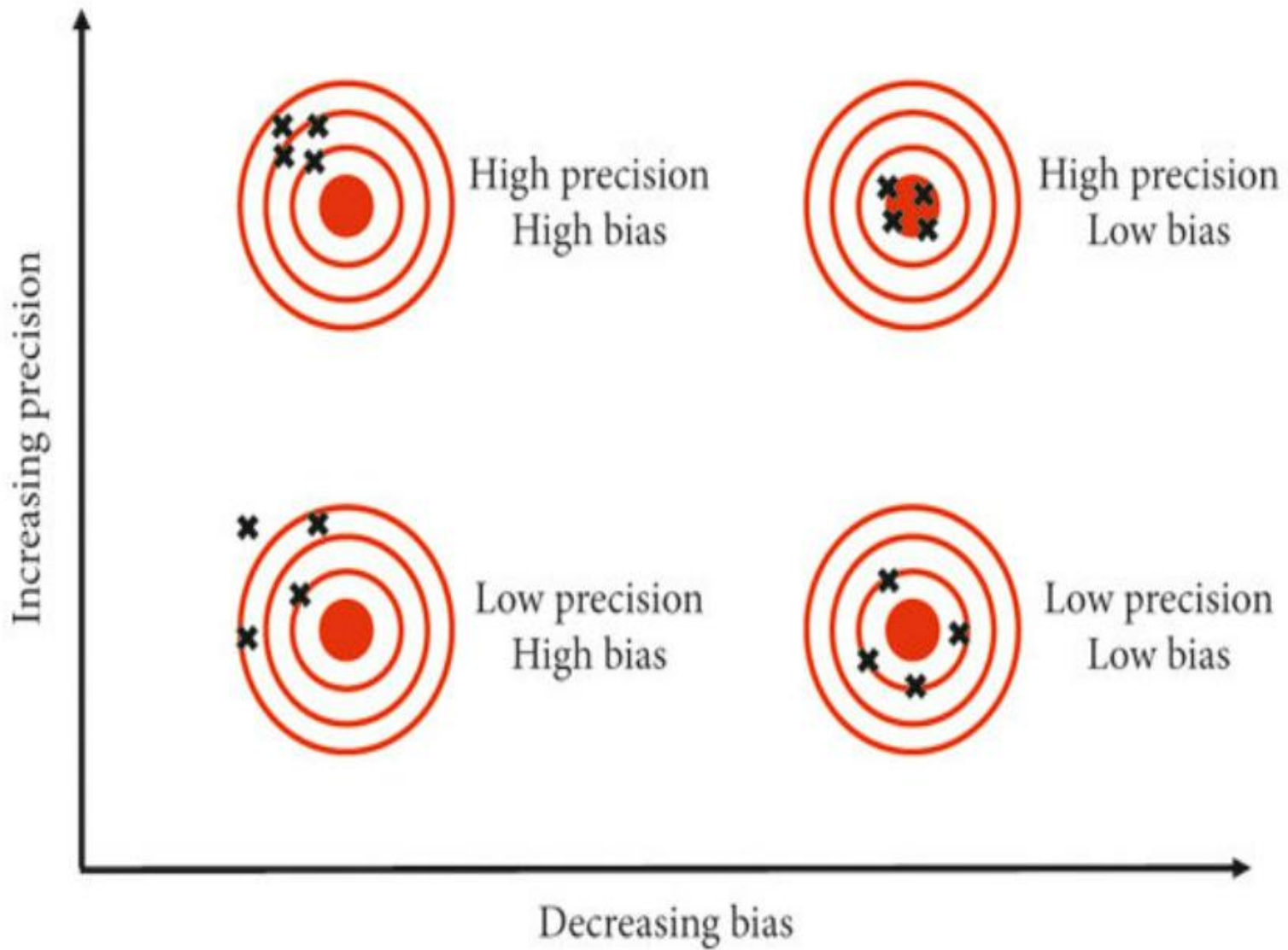


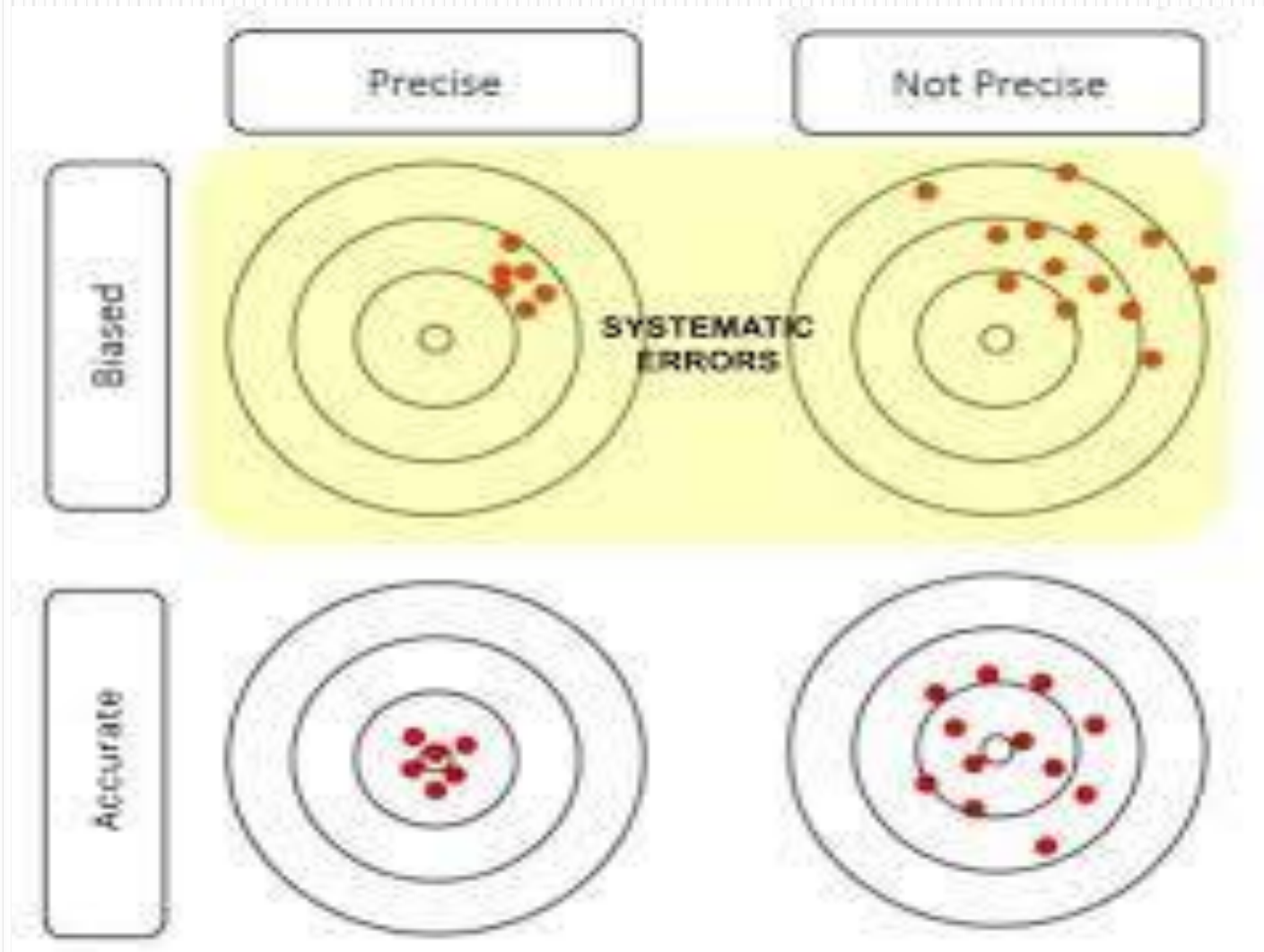
✓ Accuracy
✗ Precision

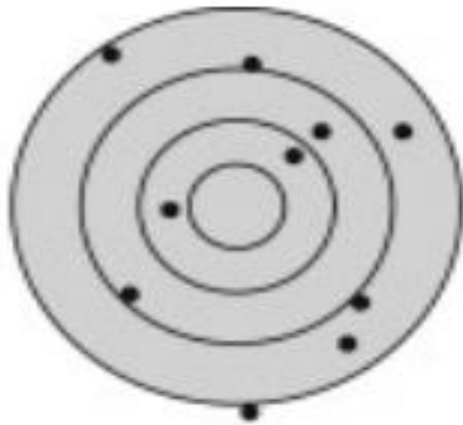
Systematic error



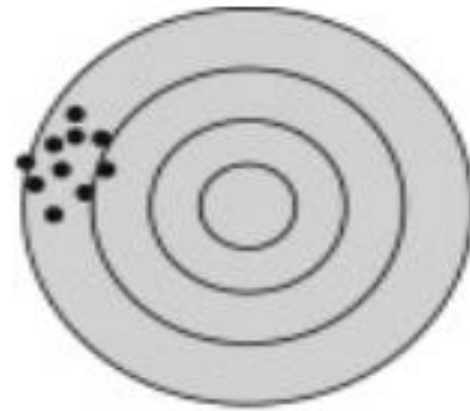
✗ Accuracy
✓ Precision



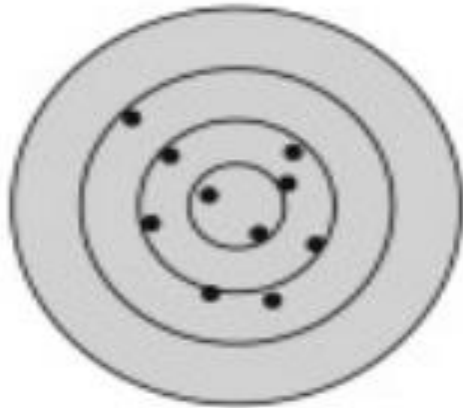




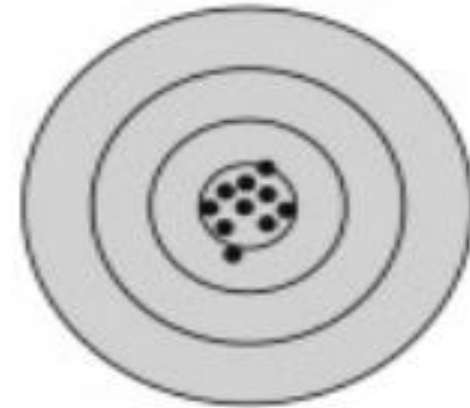
Low accuracy, low precision



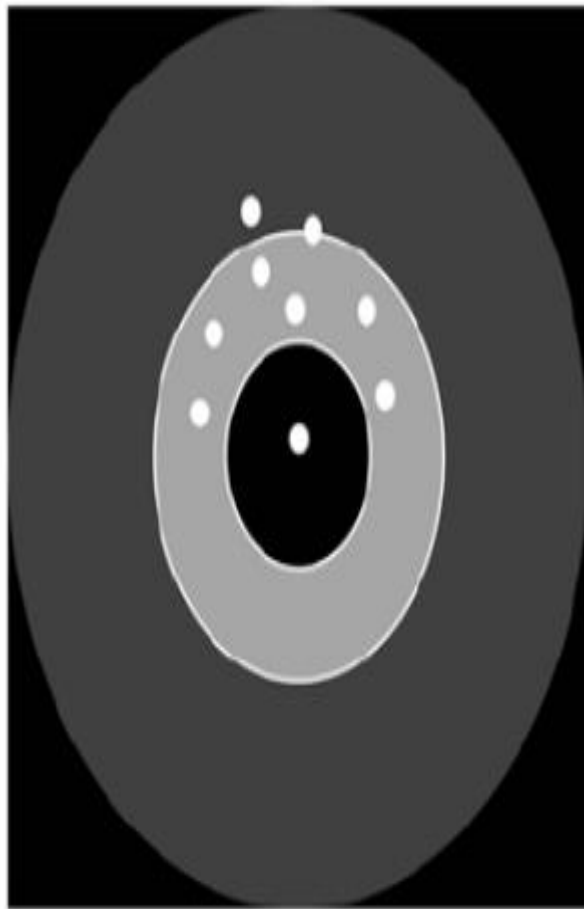
Low accuracy, high precision



High accuracy, low precision



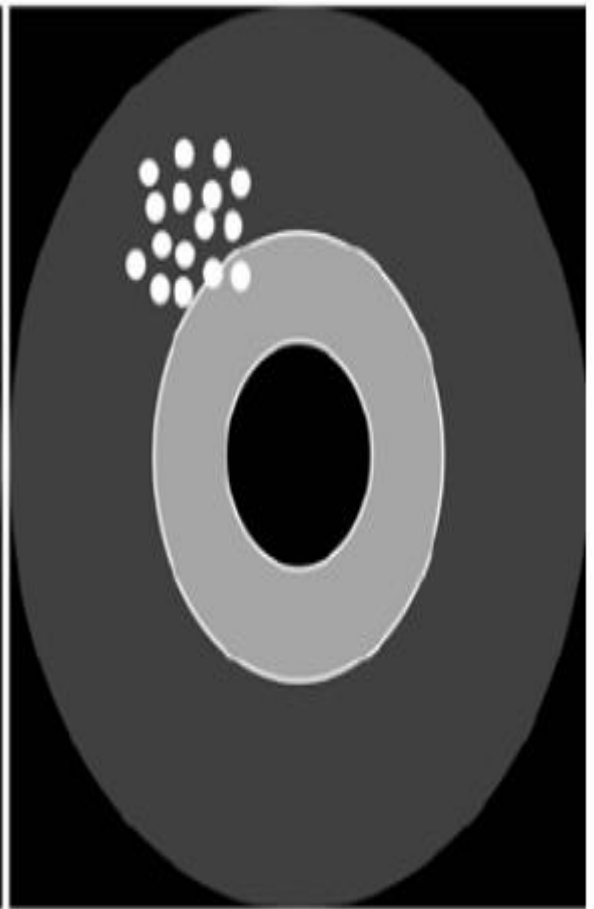
High accuracy, high precision



High Random Error
Low Sample Size



Low Random Error
High Sample Size



Systematic Error

Systematic error (“bias”) is more problematic

- May be present without investigator being aware
- Sources may be difficult to identify
- Influence may be difficult to assess

Systematic error - bias

- Bias can be defined as the result of systematic error in the design or conduct of a study. This tendency toward erroneous results is called Bias(Selection/Information).

Systematic error - bias

Prevention and control of bias:

1- Appropriate study design

2- Careful data collection

Classifying types of bias

- Selection bias refers to systematic error resulting from differential access to the study population for different exposure-disease subgroups.
- Information bias refers to systematic error resulting from inaccuracy in measurement or classification of study variables, including disease, exposure, and other risk factors.

Selection bias

- در واقع زمانی رخ می دهد که افراد با شانس (احتمال) متفاوت و نابرابر وارد نمونه مورد مطالعه گردند.

بعنوان مثال در یک مطالعه مورد- شاهد بیماران با مواجهه بالاتر احتمال بیشتری برای ورود به مطالعه را داشته باشند.

A systematic error in the ascertainment of study subjects:

1- Cases or Controls in Case-Control studies

2- Exposed or Unexposed subjects in Cohort studies

مثال: مطالعه مورد-شاهد
فرض توزیع مواجهه / عدم مواجهه در جامعه واقعی

Risk factor A	Cases	Controls
Present	500	1800
Absent	500	7200
Total	1000	9000
Odds	1	0.25

Odds Ratio= 4

50% unbiased sample of Cases and 10% unbiased sample of Controls

Risk factor A	Cases	Controls
Present	250	180
Absent	250	720
Total	500	900
Odds	1	0.25

Odds Ratio= 4

50% Biased exposure odds(60% vs 40%) in cases and
10% unbiased exposure odds in controls

Risk factor A	Cases	Controls
Present	300	180
Absent	200	720
Total	500	900
Odds	1.5	0.25

Biased Odds Ratio=6

Possible sources of selection bias

- Participant selection procedure, e.g., exposure affects case ascertainment (“detection bias”) or control selection
- Differential unavailability due to death (“selective survival”), illness, migration, or refusal
- Loss to follow-up / attrition / missing data

- Selection bias can arise from any aspect of the procedures for selecting participants for a study. Several common examples are situations where the exposure affects the ascertainment of cases for a case-control study (a situation sometimes referred to as “detection bias”) or affects the selection of controls.

- For example, doctors are more likely to suspect the presence of heart disease in a man who is overweight, hypertensive, and/or smokes cigarettes, so a middle-aged person with these characteristics who comes to a doctor complaining of chest pain may be more likely to have a thorough workup for angina pectoris than someone without these heart disease risk factors.

- Another example is what we might call differential unavailability due to death, illness, migration, or refusal. “Selective survival” refers to the fact that people with different characteristics are more or less likely to survive after contracting a disease. Similarly, characteristics of people who are more likely to refuse to participate in a study are therefore likely to be underrepresented.

- Attrition of participants from a study can produce bias if the incidence rates in people who drop out differ from those in people who complete the study. **Loss to follow-up** in a cohort study and participants not included in the data analysis due to missing data items are also potential sources of selection bias.

Self-selection Bias – healthy worker effect

- This can also occur before the subjects are identified for study e.g. the “healthy worker effect”
- Relatively healthy people become or remain workers, whereas those who remain unemployed, retired, disabled, or otherwise out of the active worker population are as a group less healthy
- May be less likely to get people in employment being able to put themselves forward as study subjects

Diagnostic Bias

- This is another type of selection bias that occurs before the subjects are identified for study
- Example: In a case-control study looking at the relationship between DVT and oral contraceptives. The GPs knew about the possible link between OC and DVT so women with suggestive symptoms and known use of OC were more likely to be referred to the hospital with “DVT”
- This could lead to an over-estimation of the effect of OC on DVT

Information bias

Information bias: a systematic distortion or error that arises from the procedures used for **classification** or **measurement** of the disease, the exposure, or other relevant variables.

Data for studies consist of classifications (e.g., “hypertensive” vs. “normotensive”) or measurements (e.g., 120 mmHg systolic BP).

Classification or measurement

- Possible sources of measurement or classification error include instrumentation, laboratories, records, respondents; data collectors, managers, analysts, and interpreters.

Sources for Information bias

1- Exposure identification bias

- Recall bias
- Interviewer bias

2- Outcome identification bias

- Observer bias
- Respondent bias

What type of bias is this?

- You and your colleagues would like to conduct a study to see the prevalence of substance abuse among high school students.
- You randomly chose your sample from a number of schools and distributed your questionnaires.
- What type of bias is expected?

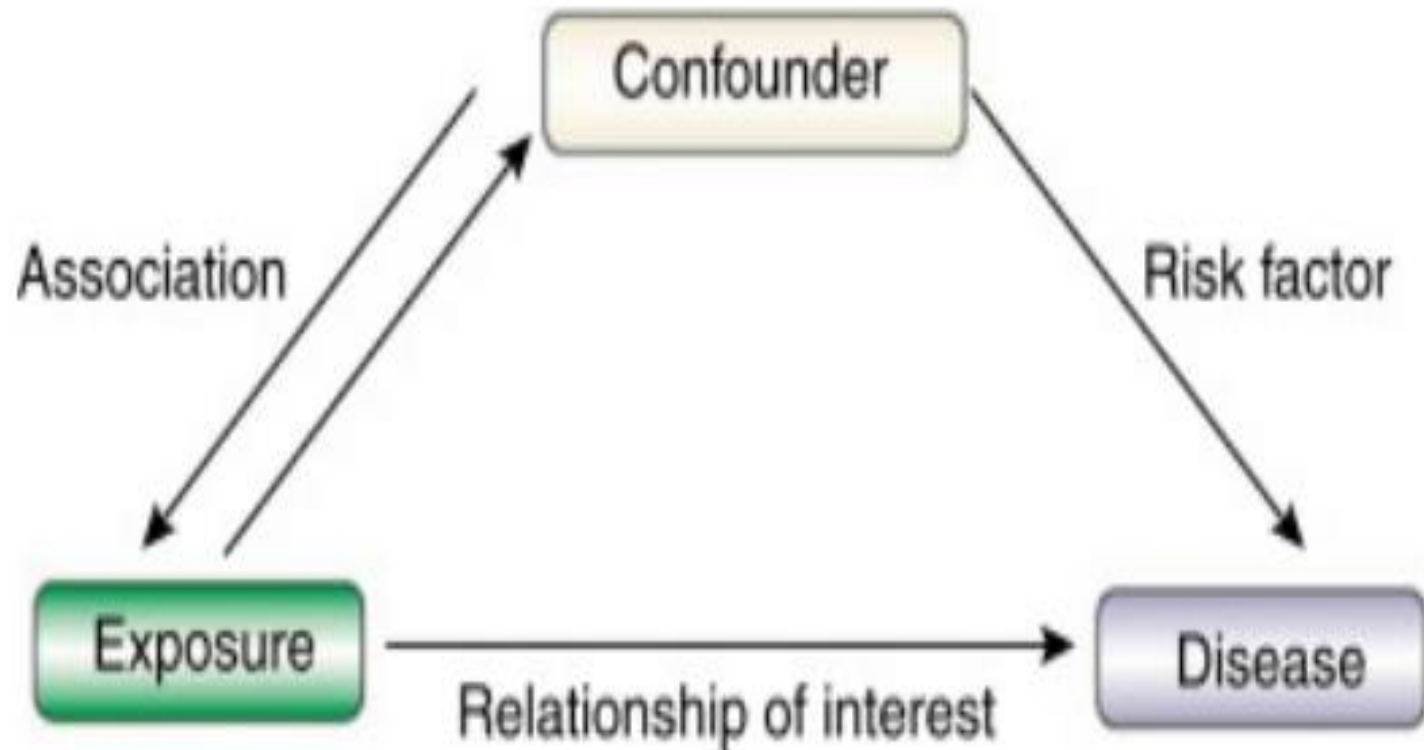
*Information bias
(non-response Bias)/(reporting bias)*

What type of bias is this?

- You were conducting a study on the association between duration of breastfeeding and malnutrition.
- You randomly select a group of mothers attending the MMR immunization clinic and ask them about the pattern and duration of breastfeeding they had for their children.
- What type of bias might this study be subject to?

*Information bias
(recall bias)*

Confounding



Criteria for a confounding factors

- ❖ 1- Must be a risk factor for the outcome.
- ❖ 2- Must be associated with the exposure under study in the source population.
- ❖ 3- Can not be an intermediate factor between exposure and outcome.

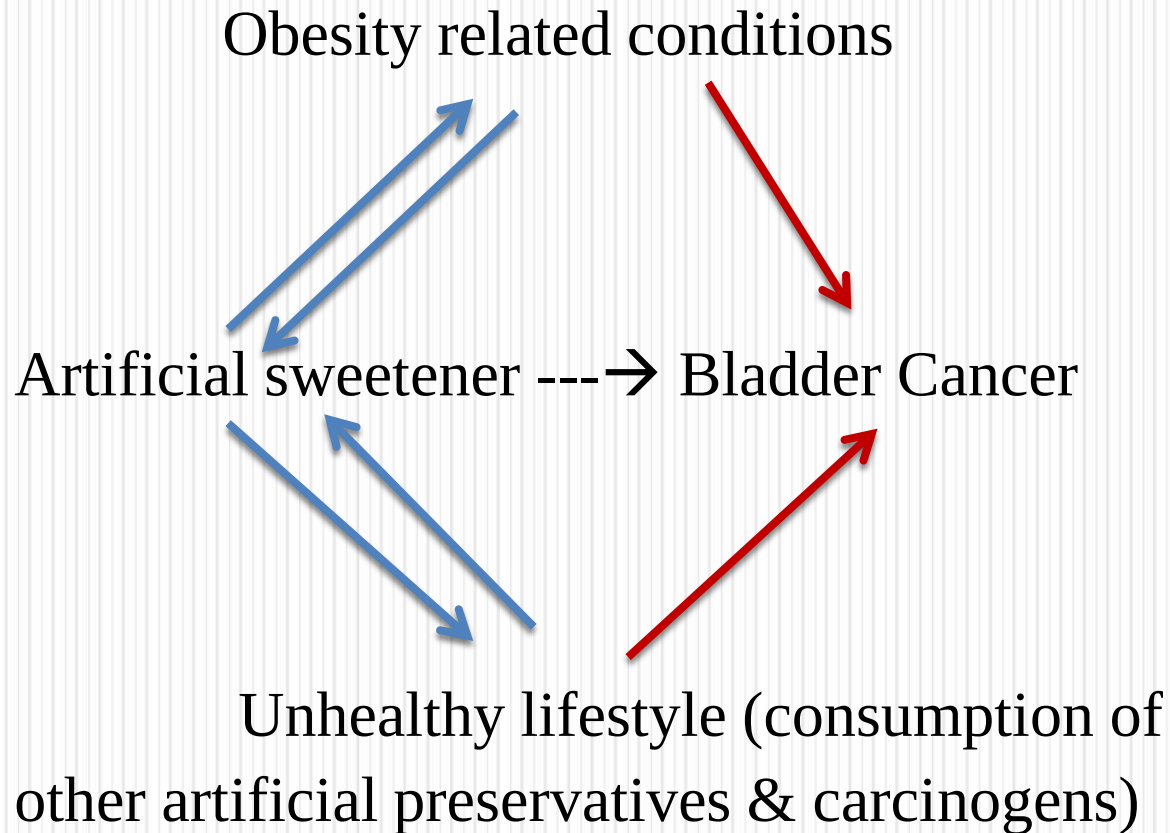
Effect of confounding factor on exposure- Outcome correlation

- ❖ 1- Underestimation
- ❖ 2- Over estimation
- ❖ 3- Change the Direction

Artificial Sweetener and Bladder Cancer

- ▶ A case-control study was conducted to investigate the association between artificial sweetener and bladder cancer.
- ▶ Could the association between artificial sweetener and bladder cancer be confounded by any external factors?

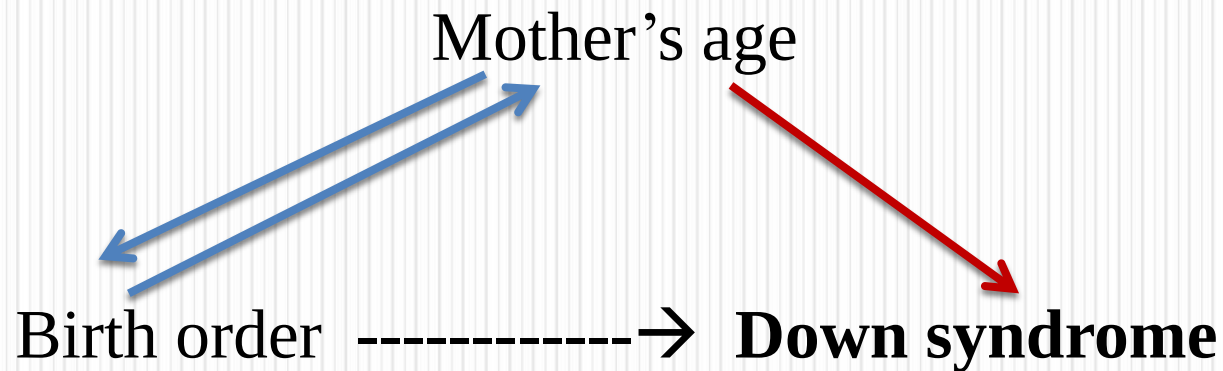
Confounding



Birth Order and Down Syndrome

- A study was done to explore the association between birth order and Down syndrome. It was found with increasing birth order, there was also an increase in the occurrence of Down syndrome.
- The prevalence of Down syndrome was 6/1000 live births at the first birth and 16/1000 live births, for birth of 5 or greater.

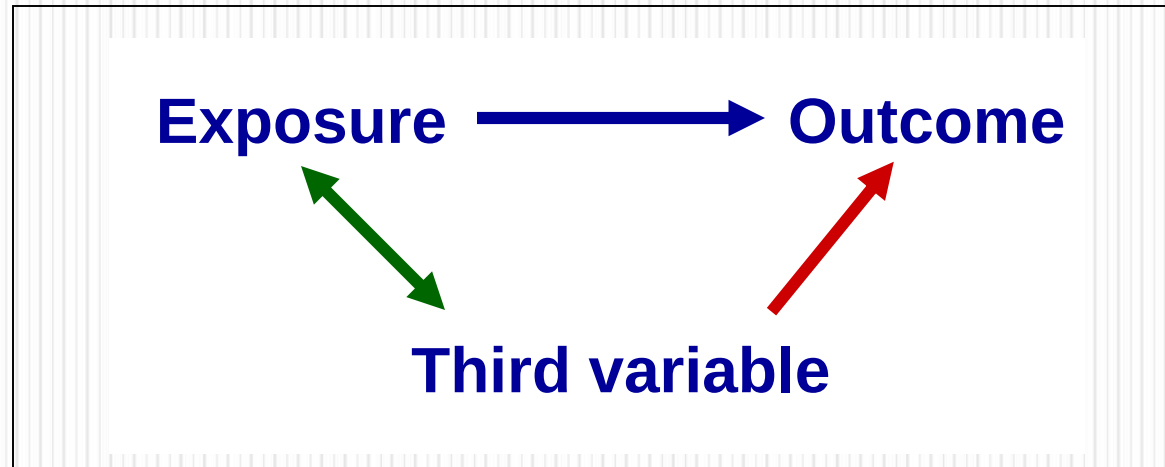
What do you think could affect this trend?



Because mother age and birth order are highly correlated, we expect that mothers who give birth to their fifth baby might be considerably older than mothers giving birth to first baby. We also know that the risk of Down syndrome increases with maternal age.

Confounding

To be a confounding factor, two conditions must be met:



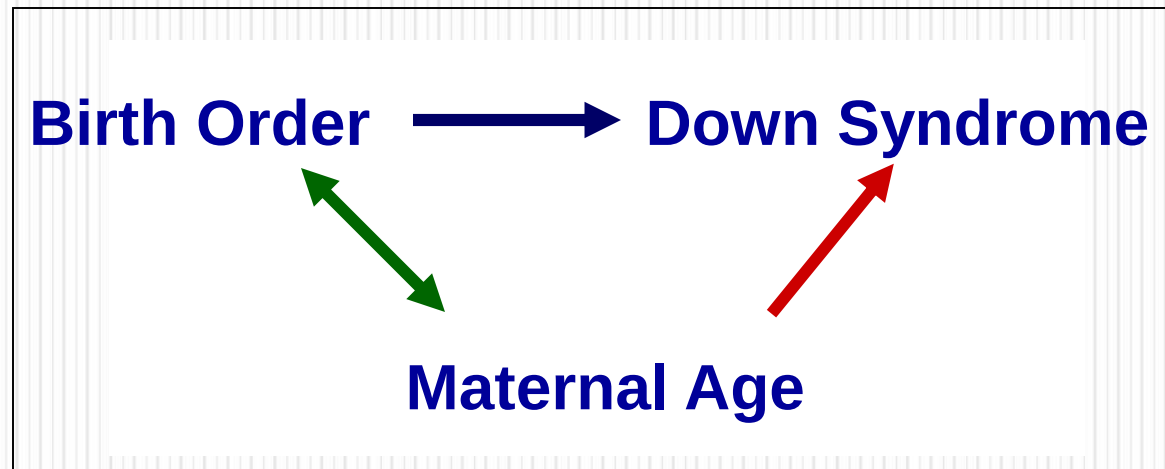
Be associated with exposure

- without being the consequence of exposure

Be associated with outcome

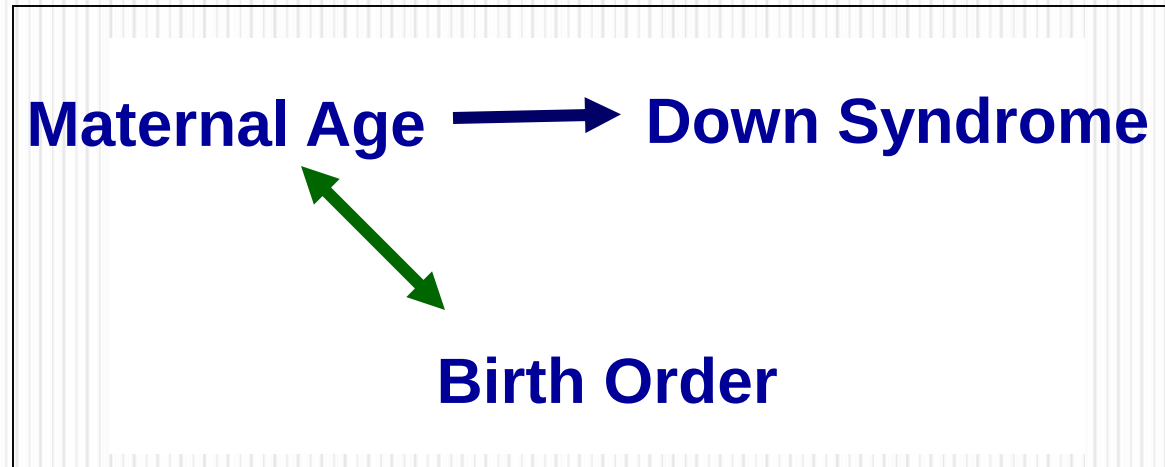
- independently of exposure (not an intermediary)

Confounding



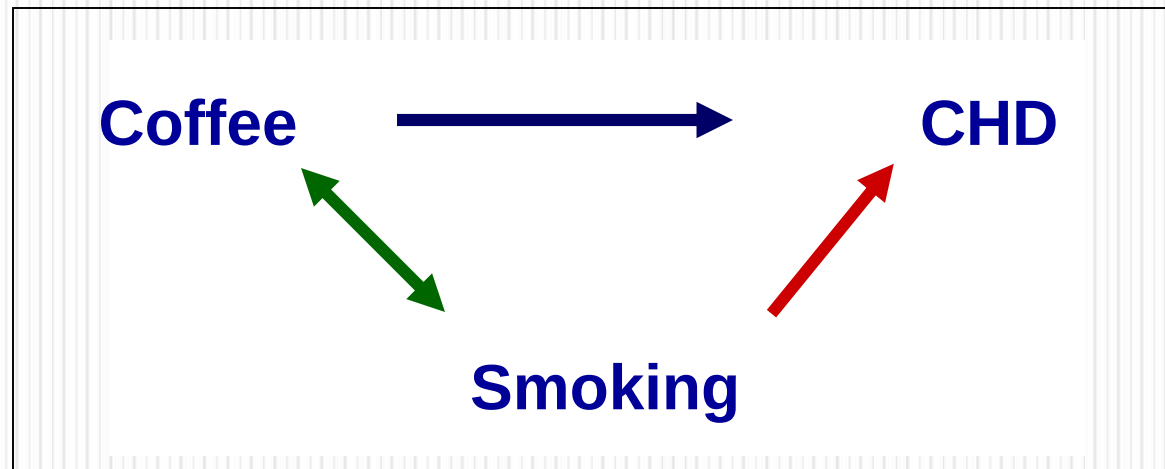
Maternal age is correlated with birth order and a risk factor even if birth order is low

Confounding ?



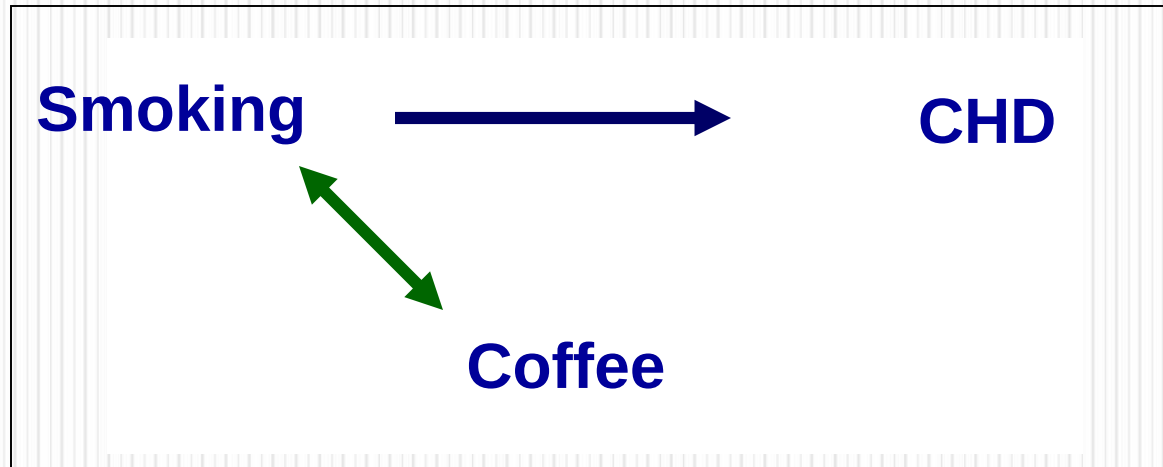
**Birth order is correlated with maternal age
but not a risk factor in younger mothers**

Confounding



Smoking is correlated with coffee drinking and a risk factor even for those who do not drink coffee

Confounding ?



Coffee drinking may be correlated with smoking but is not a risk factor in non-smokers

چگونه در عمل با مخدوش کننده برخورد می کنیم

۱- مخدوش کننده خیلی قوی -در مرحله طراحی تدبیر می شود:

- 1- Matching
- 2- Restriction- inclusion/ exclusion criteria
- 3- Random allocation

۲- مخدوش کننده متوسط (غالباً) -در مرحله آنالیز کنترل می شود:

- 1- Stratification
- 2- Standardization
- 3- Multivariate analysis

۳- مخدوش کننده ضعیف قابل اغماض است.

Confounding

Randomisation is an attempt to evenly distribute potential (unknown) confounders in study groups. It does not guarantee control of confounding.

Matching is another way of achieving the same. It ensures equal representation of subjects with known confounders in study groups. It has to be coupled with matched analysis.

Restriction for potential confounders in design also prevents confounding but causes loss of statistical power (instead stratified analysis may be tried).

Confounding

Randomisation, matching and restriction can be tried at the time of designing a study to reduce the risk of confounding.

At the time of analysis:

Stratification, Standardization and multivariable (adjusted) analysis can achieve the same.

Exercise on Confounding

- A study was done to examine the association between Caffeine and Breast cancer. The following data was obtained:

Caffeine	Breast Cancer	No breast cancer
Yes	30	18
No	70	82
Total	100	100

- What are the odds of caffeine intake in cases compared to controls?

$$\text{OR} = \frac{30 \times 82}{70 \times 18} = 1.95$$

Is age a confounder?

- The investigators thought that the calculated OR was confounded by the effect of age. They stratified participants according to age:
- Age <40**

Caffeine	Ca	No Ca
Yes	5	8
No	45	72
Total	50	80

- OR=?
$$OR = \frac{5 \times 72}{45 \times 8} = 1$$

- What do you conclude?

Age ≥ 40

Caffeine	Ca	No Ca
Yes	25	10
No	25	10
Total	50	20

- OR=?
$$OR = \frac{25 \times 10}{25 \times 10} = 1$$

Age confounds the association between caffeine intake and breast cancer

Exercise 2

- Nurse's Health study; a cohort study was done to determine the association between oral contraceptive use and ovarian cancer. The following data were obtained:

Oral contraceptive	Ovarian Ca	No ovarian Ca	Total
Yes	350	200	550
No	125	200	325
Total	475	400	875

- What is the crude RR?

$$RR = \frac{350 \div 550}{125 \div 325} = 1.65$$

Is smoking a confounder?

Smoker

OCP	Ova Ca	No ova Ca	Total
Yes	60	50	110
No	54	46	100
Total	114	96	210

Non Smoker

OCP	Ova Ca	No ova Ca	Total
Yes	239	201	440
No	122	103	225
Total	361	304	665

$$RR = \frac{60 \div 110}{54 \div 100} = 1$$

$$RR = \frac{239 \div 440}{122 \div 225} = 1$$

