## INTRODUCTION & MEASUREMENT IN CLINICAL RESEARCH

**Sakda Arj-Ong Vallipakorn, MD**
MSIT, MA (Information Science)
Pediatrics, Pediatric Cardiology
Emergency Medicine, Ped Emergency
Family Medicine
Section of Clinical Epidemiology and Biostatistics
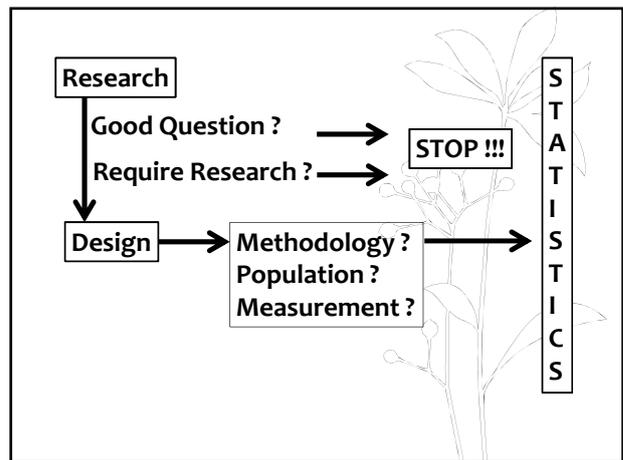Faculty of Medicine, Ramathibodi Hospital,
Mahidol University

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## Types of Biomedical Research

- **Purposes**
  - Exploratory VS. Confirmatory Research
- **Designs**
  - Observational VS. Experimental
  - Descriptive VS. Analytic
- **Resources**
  - Laboratory VS. translational VS. Research
- **Category of clinical question**
  - Therapy, diagnosis, causation(risk), prognosis
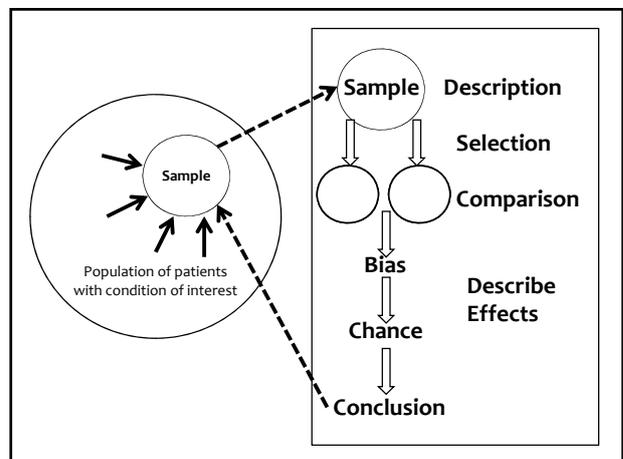
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## Clinical Research

**NIH definition :**

Research conducted with human subjects (or on material with human origin) for which an investigator directly interacts with human subjects

Excluded in Vitro studies that utilized human tissues that cannot be linked to living individual

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Research → Good Question ? → STOP !!!
Require Research ? → STOP !!!
Research → Design → Methodology? Population? Measurement? → STATISTICS

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## 7 Steps to do research

- Research questions
- Review & Do literature search
- Create study design : Protocol writing
- Perform Data correction
- Data management : Entry, checking and cleaning
- Data Analysis
- Conclusion

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Population of patients with condition of interest

Sample — Description
Selection
Comparison
Bias
Chance
Describe Effects
Conclusion

## Distinctive Aspects of Biomedical Research

1. Conclusion are extended from the **sample to population**
2. The measurements performed on the subjects, are interpreted in the context of a **statistical-probabilistic model**.
3. Studies must **undergo detailed and documented planning** before starting and must then be performed with strict adherence to that plan.
4. Reasoning, method and conclusions are based on comparisons between groups.
5. The groups being compared should be as homogeneous (comparable) as possible during entire course of the study
6. Data from biomedical study must be analyzed by appropriate statistical methods, defined in the planning stage.

Bacchieri A. Fundamentals of Clinical Research 2007

## What research is made of ?

| Elements | Purposes |
|---|---|
| Research questions | What questions will the study address ? |
| Significance ( background) | Why are the questions important? |
| Design | How is the study structured ? |
| Subjects | Who are the subjects and how will they be selected ? |
| Variables | What measurements will be made ? |
| Statistical issues | How large is the study and how will it be analyzed ? |

## Components of Research question

- **P**opulation being studied
- **I**ntervention (exposure) being studied
- **C**ontrol(comparison) being studied
- **O**utcome being measured

## The process of clinical research
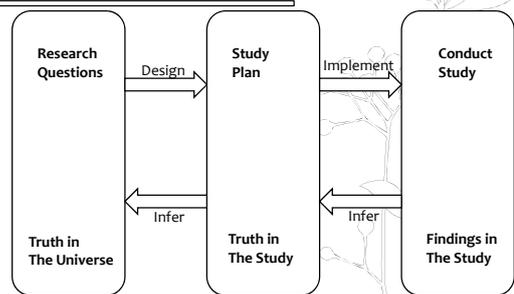


Hulley SB. Designing Clinical Epidemiology
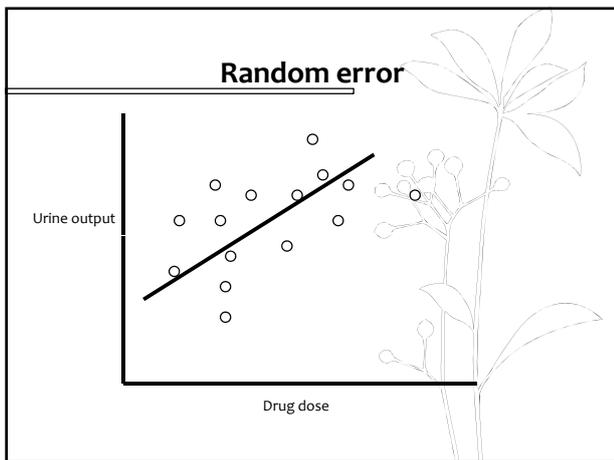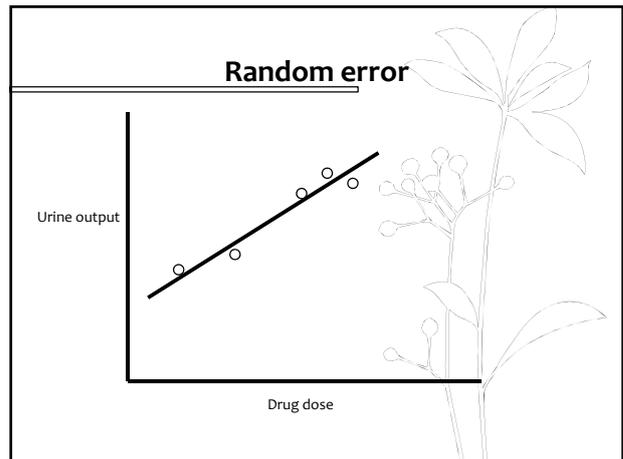
## The process of clinical research
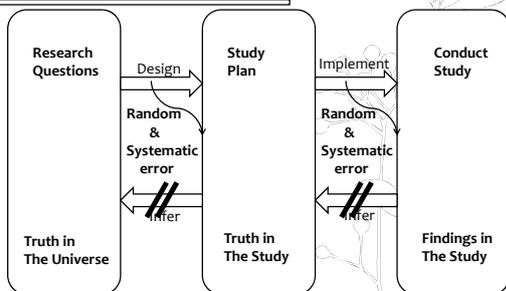


Hulley SB. Designing Clinical Epidemiology

## Errors

- Random error (Chance)
- Systematic error (Bias)

## Error

- **Random error**
  - Type I Error (Alpha)
  - Type II Error(Beta)
- **Systematic error(Bias)**
  - A Process at any stages of inference tending to produce results that depart systematically from true values.

## Random error



## Random error



## Random error
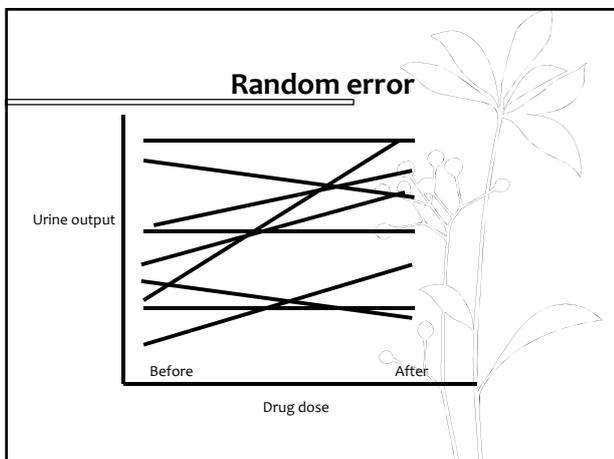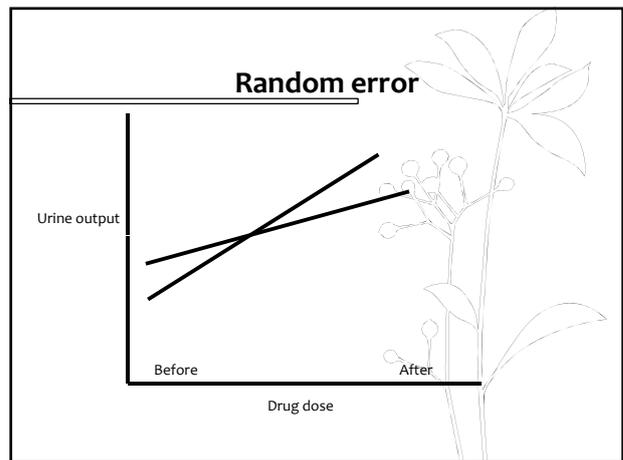


## Random error



## Random error

- Small sample size
- High variation in smaples
- One-time measure ( eg. BP)
- Unreliable measure ( No calibration)
- Too many measurements
- Non-standardized measurement

## Strategies to reduce random error

- Large sample size
- Measure endpoints in a precise way
- Standardizing aspect of the protocol which impact on patient-to-patient variation
- Collecting data on key prognostic factors
- Choosing a homogenous group of patient
- Choosing the most appropriated design
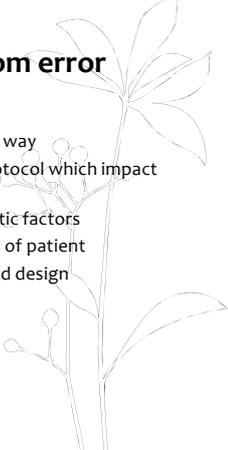
$Ho = u_{SBP(A)} = u_{SBP(B)}$
$H1 = u_{SBP(A)} \neq u_{SBP(B)}$

| Statistical Testing | In Population Different exist (+) | No Different exist (-) |
|---|---|---|
| Different (+) Reject Null Hypothesis | Power 1-*Beta* | False Positive (alpha) **Type I Error** |
| No-Different (-) Accept Null Hypothesis | False Negative(Beta) **Type II Error** | True Negative 1-alpha |
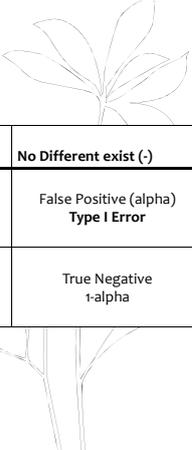
## Tool to assess random error

- The P value : A numeric representative of the degree to which random variation alone could account for the difference observed between groups or data being compared.
- Confidence Interval : Provide a plausible range within which the true association lies and provide all the information in P value and more.
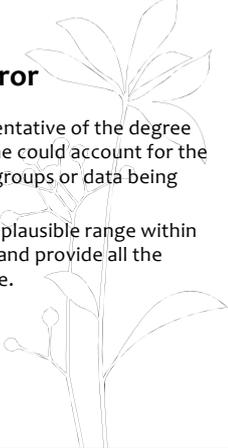
## Bias

- The systematic tendency of any factors associated with the design, conduct, analysis, and interpretation of the result of clinical study to make the estimate of an effect deviate from its true value.
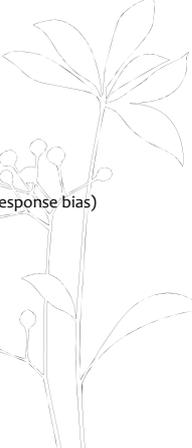
## Bias

- Selection bias should be aware to
- Berkson Bias (synonym admission bias, hospital admission bias)
- Ascertainment bias
- Healthy worker effect
- Volunteer Bias
- Non-Response Bias (eg. Questionnaire)

## Bias

- Information bias
- Observer bias
- Recall bias esp. case control study
- Reporting bias( synonym. Self report response bias)

## Bias

- Ecological Bias
- Confounding Bias
- Spectrum Bias( syn. Case mix bias)
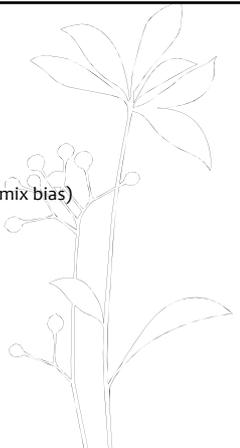
## Bias

- Post Hoc Analysis Bias
- Sub group analysis bias
- Publication bias

## Is an unbiased study ever possible ?

- " The skill of the...researcher,,, lies not conducting the perfect study, but in documenting and assessing the likely impact of its perfections."

*Silman A. Epidermiological Studies: A Practical Guide*
*Cambridge University Press 2002*

**Slide 1:**

Sampling Bias

Sample — **Description**

Selection bias — **Selection**

**Comparison**

Measurement bias

**Bias**

**Describe Effects**

**Chance**

Confounding bias

**Conclusion**

Sample

Population of patients with condition of interest
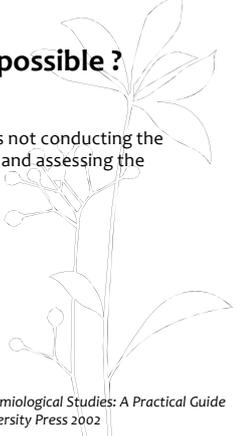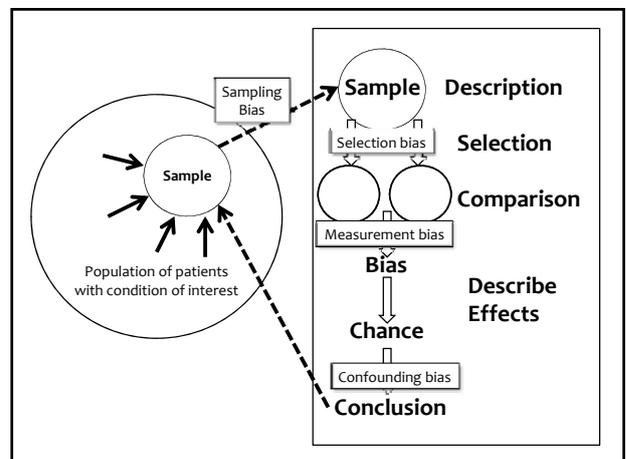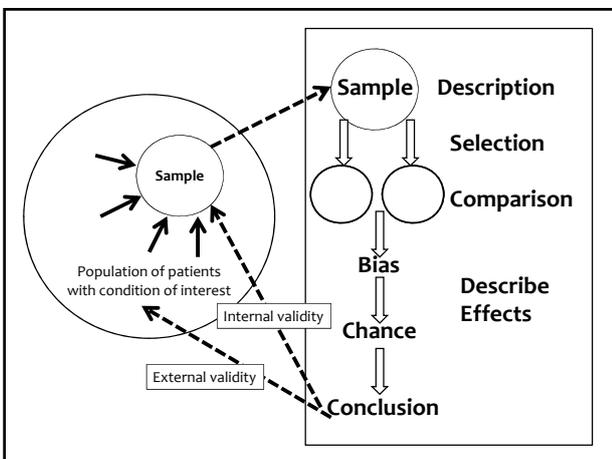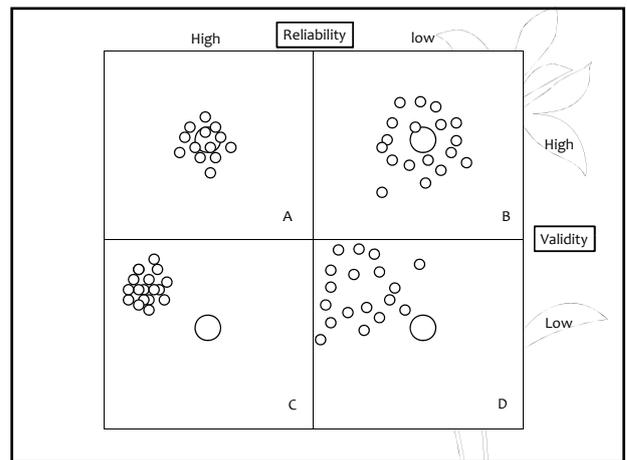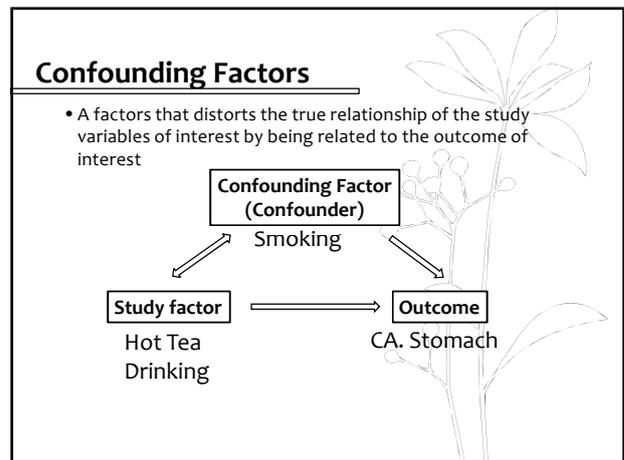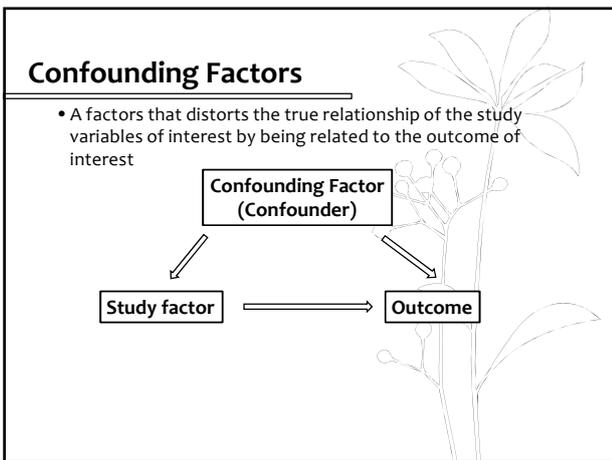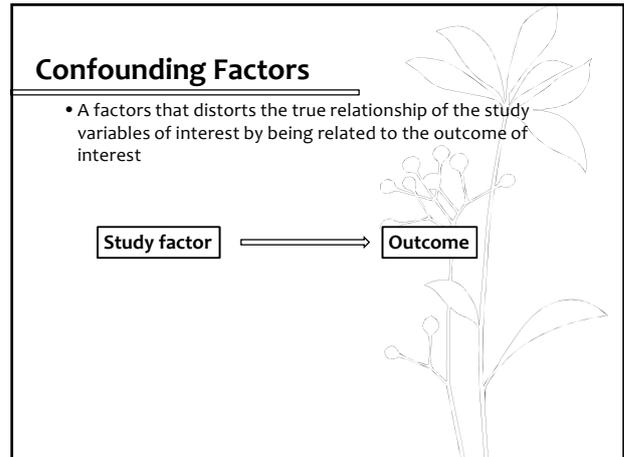
**Slide 2:**

## Confounding Factors

- A factors that distorts the true relationship of the study variables of interest by being related to the outcome of interest

| Study factor | ⟹ | Outcome |

**Slide 3:**

## Confounding Factors

- A factors that distorts the true relationship of the study variables of interest by being related to the outcome of interest

**Confounding Factor (Confounder)**

| Study factor | ⟶ | Outcome |

**Slide 4:**

## Confounding Factors

- A factors that distorts the true relationship of the study variables of interest by being related to the outcome of interest

**Confounding Factor (Confounder)**
Smoking

| Study factor | ⟶ | Outcome |

Hot Tea Drinking    CA. Stomach

**Slide 5:**

## Cohort study of worker & TCX

| Worker | TCX | No TCX | |
|--------|-----|--------|-----|
| Lung CA | 27 | 14 | 41 |
| No Lung CA | 48 | 67 | 115 |
| Total | 75 | 81 | 156 |

**Relative Risk = 2.1**

**Slide 6:**

## Cohort study of worker & TCX

| Worker | TCX | No TCX | |
|--------|-----|--------|-----|
| Lung CA | 27 | 14 | 41 |
| No Lung CA | 48 | 67 | 115 |
| Total | 75 | 81 | 156 |

**Relative Risk = 2.1**

**Non-Smoker**

| Worker | TCX | No TCX | |
|--------|-----|--------|-----|
| Lung CA | 1 | 2 | 3 |
| No Lung CA | 24 | 48 | 72 |
| Total | 25 | 50 | 75 |

**Relative Risk = 1**          **No association**

**Smoker**

| Worker | TCX | No TCX | |
|--------|-----|--------|-----|
| Lung CA | 26 | 12 | 38 |
| No Lung CA | 24 | 19 | 43 |
| Total | 50 | 31 | 81 |

**Relative Risk = 1.3**

## A Priority criteria of confounder

- Clinically/Scientifically sensible
- Must be a risk factor
- Cannot be a n intervening factor
- Must be associated with the exposure in the population (imbalance distribution)
- In analysis, crude estimate not equally to adjusted estimate

## Study Designs

| Exposure | → | Outcome |

-Etiologic agent
-Risk factor
-Therapeutic measure
-Preventive measure

-Disease
-Biochemical change
-Pathophysiology
-Pathophysiologic change

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Did investigator Assign exposure ?

**Yes** ← → **No**

Experimental Study — Observational Study

Random/Allocation ? — Comparison group ?

**Yes** — **No**    **Yes** — **No**

RCT    Non RCT    Analytical Study    Descriptive Study

Direction ?

E → O    O → E    E = O (Same time)

**Yes**    **Yes**    **Yes**

Cohort Study    Case control Study    Cross-sectional Study

## Classification of study design

- **Observational study**
  - Descriptive or case-series
  - Case control studies(retrospective)
  - Cohort studies(prospective)
  - Historical cohort studies(retrospective)
- **Experimental study**
  - Controlled trials
  - Studies with no controls
- **Systematic Reviews/Meta-analysis**

## Hierarchy of evidences

Systematic Reviews

RCT

Cohort Study

Case-Control study

Cross-Sectional study

Case Report
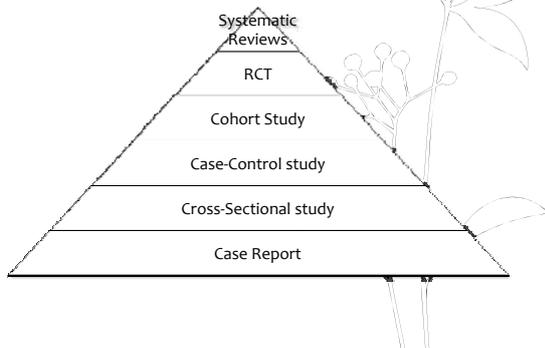
## Classification of study designs

- Classify by presence of comparison group
- Classify by action of investigator
  - Only observe → observational study
  - Assign intervention → Experimental study( Clinical trial)

## Logic of Cross Sectional Study



Population
Sample
Case with exposure + ve
Case with exposure - ve
Non-case with exposure + ve
Non-case with exposure - ve
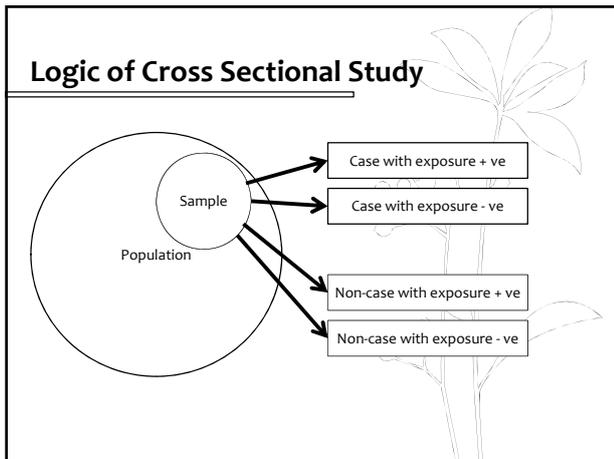
## Cross Sectional Study

- **Advantage**
  - In expensive, simple (no follow up)
  - No exposure, no drop out
- **Disadvantage**
  - Can establish association but not !!! " conclusion"
  - Can not control confounder
  - Recall bias usually present
  - Incidence-prevalence bias
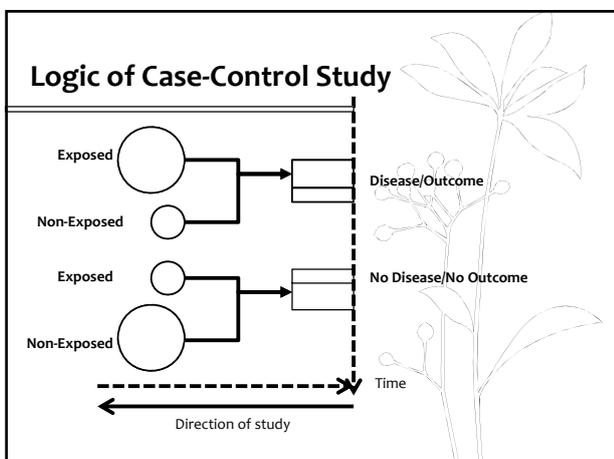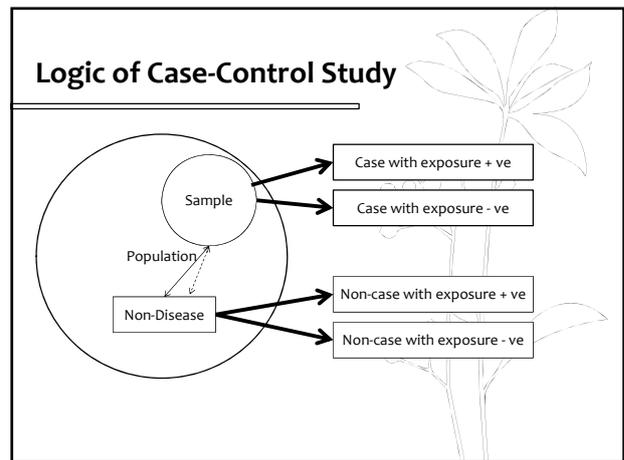  - Different sample size among groups

## Exam

- Obesity

| | Obesity | |
|---|---|---|
| | O+ | O- |
| Ex + | 50 | 100 |
| Ex - | 20 | 100 |

Exercise

Relative prevalence O+ = (50)/(100) / (20)/(100)
= 1.67
Association ???

## Logic of Case-Control Study



Population
Sample
Non-Disease
Case with exposure + ve
Case with exposure - ve
Non-case with exposure + ve
Non-case with exposure - ve

## Logic of Case-Control Study



Exposed
Non-Exposed
Exposed
Non-Exposed
Disease/Outcome
No Disease/No Outcome
Time
Direction of study

## Case Control Study

- **Advantage**
  - Quickly and Inexpensive
  - Feasible for rare disorder or long term follow up
  - May be required fewer subjects
- **Disadvantage**
  - Recall bias
  - More effect of confounder
  - Difficult to find control group

## Logic of Prospective Cohort Study



## Prospective Cohort Study



## Retrospective Cohort Study
Historical Cohort
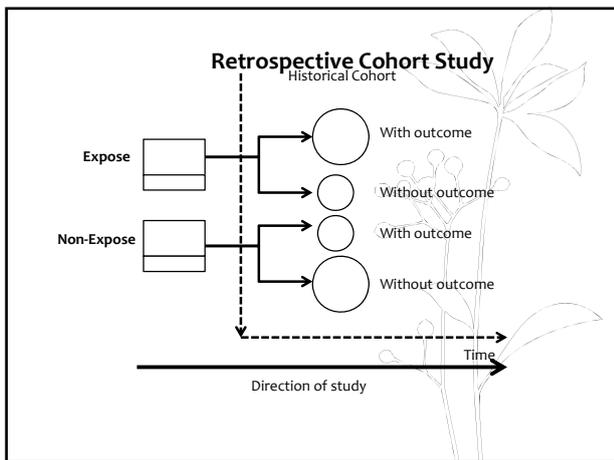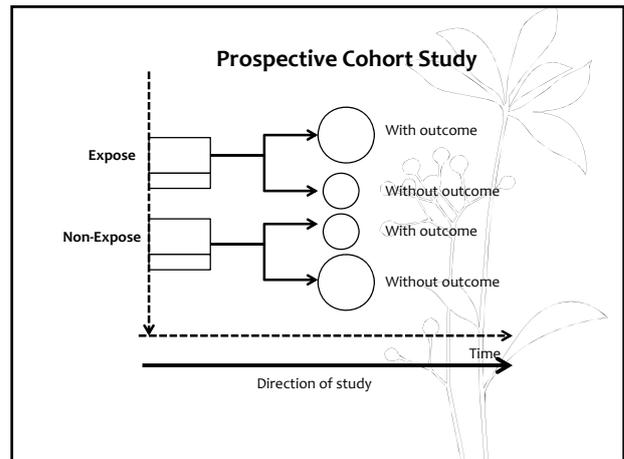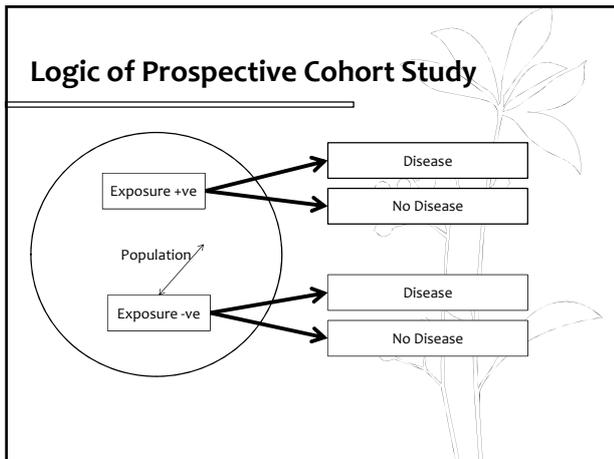


## Cohort Study

- **Advantage**
  - Can be matched
  - Can be standardized in eligible criteria & outcome assessment
  - Can establish temporal association **
- **Disadvantage**
  - Usually expensive
  - Hard to blind
  - Long follow up period for rare disorder
  - Difficult to find controls and confounders

## Randomized Control Trial



## Randomized Control Trial
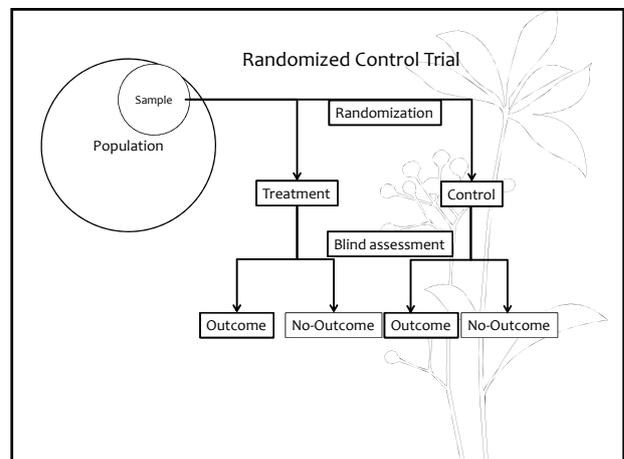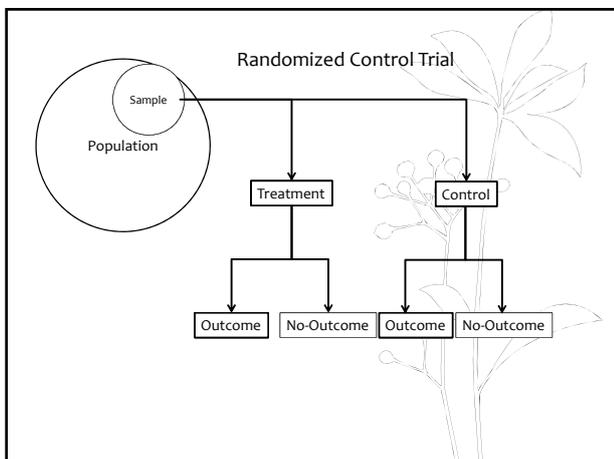
## RCT Study

- **Advantage**
  - Confounding and variables can be balance by randomization
  - Blinding of subjects, medical staff and investigators are achievable
- **Disadvantage**
  - Cost in term of time and money
  - Dropout or loss to follow up are common event
  - Need time to final ressults.

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## Accuracy of Test Result

|  | | Disease | |
|---|---|---|---|
| | | **Present (+)** | **Absent (-)** |
| Test | Positive (+) | **TP** <br> **a** | FP <br> b |
| | Negative(-) | FN <br> c | **TN** <br> **d** |
| | | **a+c** | **b+d** |

Sensitivity = True positive rate = a/a+c
Specificity = True negative rate = d/b+d

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## How to choose Sense VS. Specificity ?

| Sensitivity | Specificity |
|---|---|
| 1.The ability of test to identify correctly those who have disease. <br> 2.Use to **"rule out"** <br> 3.There is a reason to suspect dangerous but treatable condition | 1.The ability of test to identify correctly those who do not have the disease <br> 2.Use to confirm **" Rule in "** <br> 3.Need when false-positive result can harm the patient physically, emotionally or financially. |
| **SNout** | **SPin** |

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- Anti HIV Positive เป็นจริง ๆ หรือค่ะ ?
- Negative ไม่เป็นแน่ค่ะ

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- Anti HIV Positive เป็นจริง ๆ หรือค่ะ ? **PPV**
- Negative ไม่เป็นแน่ค่ะ                              **NPV**

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## The study design for diagnostic test

| Patients suspected of target conditions | ⇨ | Diagnostic test | ⇨ | Gold standard test | ⇨ | Target condition (+/-) |

**Prevention/treatment**
1. Random allocation (by chance) : participants to interventions (Randomization)
2. Blind : Double , triple blind….etc
3. Placebo
4. Intention to treat analysis
5. Complete follow up > 80 %

## Risk study (Causation)

- Exposure & Outcome

Exposure → Outcome

Risk Factors     Disease
Intervention     Health Problems
Maneuver

Independent variable     dependent variable

## Cause

- A cause of disease event is an antecedent event , condition, or characteristic that was necessary for occurrence of disease at the moment of it occurred, give that other conditions are fixed (Kenneth J. Rothman)

## Association

- Is a statistical relationship between two or more events, characteristics or other variables.

## Causal criteria
## ( Modified from Bradford-Hill AB)

| |
|---|
| **Temporality** |
| **Strength** |
| **Dose-response** |
| **Consistency** |
| **Biological plausibility** |
| **Reversibility** |
| **Specificity** |
| **Analogy** |
| **Experimental evidences** |

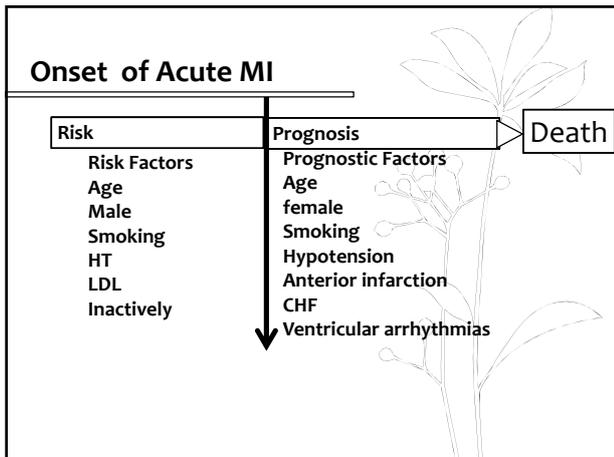## Criteria for judgment of causal associations(Hills' Criteria)

- **Temporal sequence:** Did exposure precede outcome?
- **Strength of association** : How strong is the effect, measured as relative risk or odds ratio?
- **Coherence with existing knowledge:** Is the association <u>consistent</u> with available evidence?
- **Experimental evidence:** has a randomized control
- **Analogy** : Is the association similar to others

## Research Design which assess cause ?

- Cohort study
- Case-control
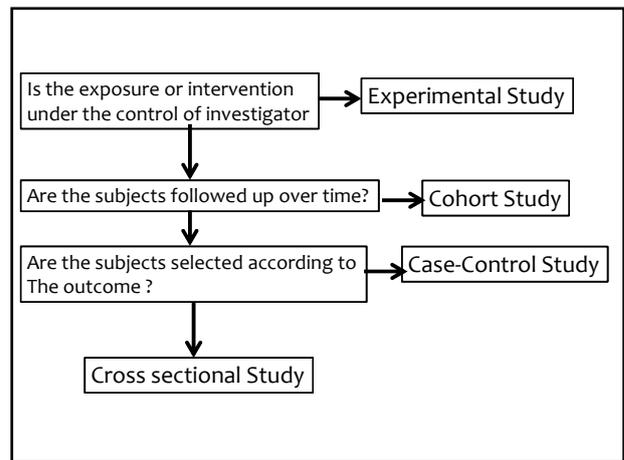- Cross sectional study

## Prognostic study

- A prediction of future course of diseases following its onset
- A group of patients having something in common are assembled and followed forward in time, and clinical outcomes are measured.
- **" Natural history of disease"**

## Onset of Acute MI

| Risk | Prognosis | Death |
|---|---|---|
| **Risk Factors**<br>**Age**<br>**Male**<br>**Smoking**<br>**HT**<br>**LDL**<br>**Inactively** | **Prognostic Factors**<br>**Age**<br>**female**<br>**Smoking**<br>**Hypotension**<br>**Anterior infarction**<br>**CHF**<br>**Ventricular arrhythmias** | |

## Prognosis

- An inception cohort of persons, all **initially free of outcome of interest**
- Representative of sample
- Homogenous to prognostic risk
- Objective outcome measurement
- FU >= 80 % of patients

## Broad topics of Research

- **Diagnosis** –Demonstrate that new diagnosis test is valid/reliable

  Preferred "cross sectional study"

- **Causation or Risk**-Determine that agent is related to development of illness, preferred "Cohort or case-control study"

- **Therapy** – Testing the efficacy of intervention preferred "RCT"

- **Prognosis**- determine what happen to someone with some stage of disease, preferred "Prospective Cohort study"

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Is the exposure or intervention under the control of investigator → **Experimental Study**

Are the subjects followed up over time? → **Cohort Study**

Are the subjects selected according to The outcome ? → **Case-Control Study**

**Cross sectional Study**

## Key methodological strength and weakness

| Design | Starting point-Assessment | Strength | Frequency of publication |
|---|---|---|---|
| **RCT** | E-O | Low susceptibility to bias | Feasibility, generalizability |
| **Cohort** | E-O | Feasible when randomization of exposure not possible | Susceptible to bias, limited validity |
| **Case-Control** | O-E | Overcomes temporal delays, may require small sample size | Susceptible to bias, limited validity |

**Thank You**
dr.sakda@gmail.com