BIOSTATISTICS

FINAL

Lecture 11

Given by : Dr. Israa Al-Rawashdeh

Done by Doctor:

Abdullah Daradkh

Mahmoud Al-Otoom

Research design

What is research?

- 'A systematic (non random) and unbiased (we strive to minimize it to lowest possible degree) way of solving a problem (by answering questions or supporting hypotheses) through generating verifiable data.'

Overview of the research process

- **Research process consists of series of actions or steps necessary to effectively carry out research and the desired sequencing of these steps.**

Research process consists of series of actions or steps necessary to effectively carry out research and the desired sequencing of these steps. (this is ideal order)

(1) Formulating the research problem;

(2) Extensive literature survey(هو البحث عن جواب لسؤال البحث من خلال ابحاث سابقه);

(3) Developing the hypothesis;

(4) **Preparing the research design**;

(5) Determining sample design;

(6) Collecting the data;

(7) Execution of the project;

(8) Analysis of data (like : mean , mode ,…..);

(9) Hypothesis testing (does it proved or disproved);

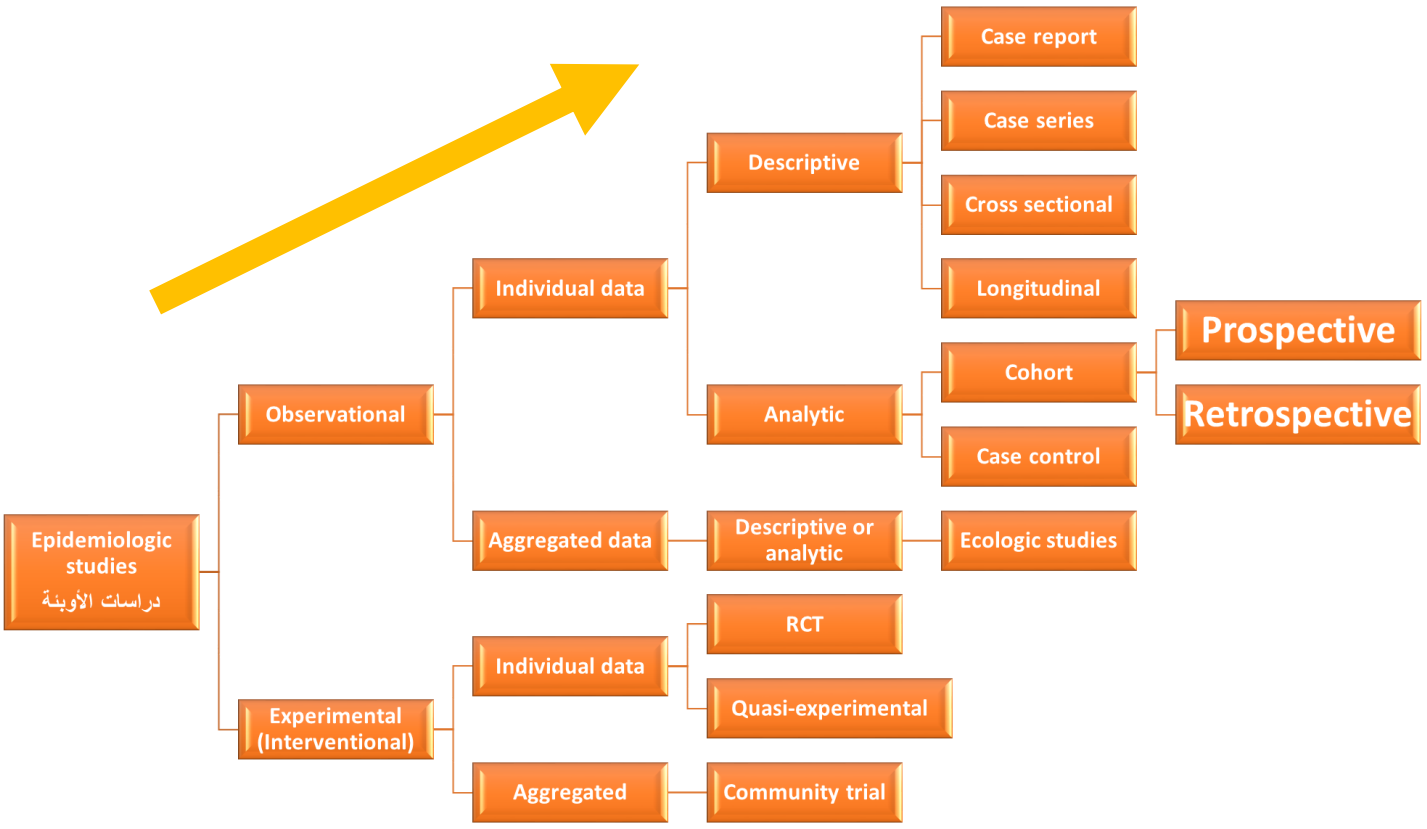
(10) Generalisations and interpretation, and

(11) Preparation of the report or presentation of the results(10-1 كتب كل العمليات الي قمت بها من),

i.e., formal write-up of conclusions reached.

- **Design: a set of instructions for the researcher; to gather and analyze data in certain ways that will control who and what are to be studied. Thus, the choice of design is made when the question is finalized.**
- **Each design has its own applicability depending on the problems and objectives of the study.**

- **Important consideration – to minimize possible errors and maximize the reliability and validity of data.**



للتوضيح

Epidemiology : is the study of disease and health in human population.

Observational study : is a study in which the researcher observes the subject without interfering.

(the researcher observes the subject and record data based on their observations)

Experimental study : Data for statistical studies are obtained by conducting either experiments or surveys. Experimental design is the branch of statistics that deals with the design and analysis of experiments

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1-Descriptive studies (example: what is the average year for the medical student)

-Generate hypotheses

-Answer what, who, where, and when

2-Analytic studies (example: why the student com late for the lecture)

- Test hypotheses

-Answer why and how

DEFINITION AND CHARACTERISTICS OF DESCRIPTIVE STUDIES

Descriptive Studies → These are a type of observational studies where in the investigator observes the events occurring in the population without doing any interruption or manipulation.

Characterize who, where, or when in relation to what (outcome)

(PPT):

Person: characteristics (age, sex, occupation) of the individuals affected by the outcome

Place: geography (residence, work, hospital) of the affected individuals

Time: when events (diagnosis, reporting; testing) occurred

. They form the first step in identifying risk factors. Provide clues for generating hypothesis. In these studies there is no formal comparison groups. What caused the prevailing conditions is not emphasized

1-Ecological studies→ On large scale

An ecological study is an observational study in which at least one variable is measured at the group level (large-scale) (like country's). An ecological study is especially appropriate for initial investigation of causal hypothesis.

Data are often presented comparing various countries around the world

Strengths of ecological studies include:

- **Ecological studies often make use of routinely collected health information, such as a country's episode statistics or infectious disease notifications, so their principal advantage is that they are cheap and quick to complete.**
- **Exposure data often only available at area level.**
- **Group level exposure estimates may be more accurate than individual level measures (e.g. salt intake)**
- **Useful to monitor population health so that public health strategies may be developed and directed;**

Limitations of ecological studies include:

- **Potential for systematic differences between areas in recording disease frequency. For example there may be differences in disease coding and classification, diagnosis and completeness of reporting between different countries.(like definition HIV disease in the Jordan and USA)**
- **Potential for systematic differences between areas in the measurement of exposures.**
- **Lack of available data on confounding factors.**
- **Measures of exposure are only a proxy based on the average in the population. Caution is needed when applying grouped results to the individual level (ecological fallacy).**

Each dot represents a country

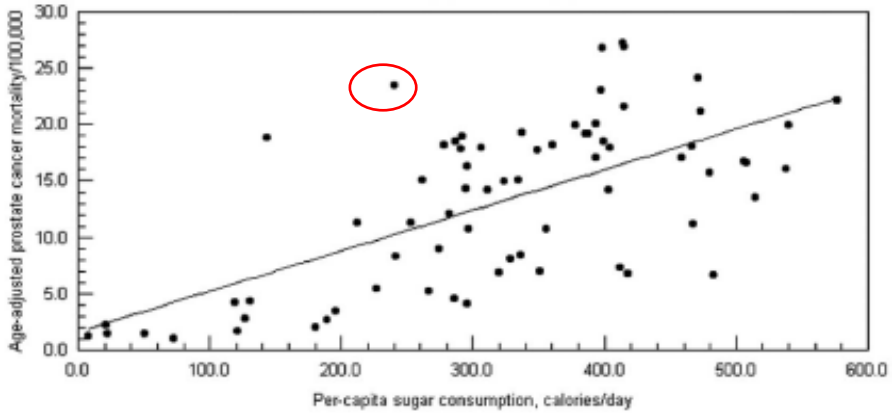


Fig. 1. Prostate cancer mortality versus sugar consumption in 71 countries.

- **An ecological study examining diet and sunlight as risks for prostate cancer mortality. (**Colli JL, Colli A. International comparison of prostate cancer mortality rates with dietary practices and sunlight levels. *Urologic Oncology* 2006:24;184-194.)

Ecological fallacy

- **The ecological fallacy is an error in the interpretation of the results of an ecological study, where conclusions are inappropriately inferred about individuals from the results of aggregate data.**
- **The fallacy assumes that individual members of a group all have the average characteristics of the group as whole, when in fact any association observed between variables at the group level does not necessarily mean that the same association exists for any given individual selected from the group.**

2-Case reports :detailed presentation of a single case or handful of cases

→ **An article that describes and interprets an individual case, often written in the form of a detailed story.**

Case reports often describe:

-Unique cases that cannot be explained by known diseases or syndromes حالة جديدة

-Cases that show an important variation of a disease or condition → صفة جديدة لمرض معروف

-Cases that show unexpected events that may yield new or useful information

-Cases in which one patient has two or more unexpected diseases or disorders

- **Case reports are considered first line of evidence, because they are where new issues and ideas emerge**
- **الطب حتى 1950 كان عبارة عن case report من كل طبيب يشاهد حاله مميزه يكتب مقاله اشهر حاله اكتشاف العلاقه بين الكوليرا والماء والكثير من ال syndrome سمية باسماء من اكتشفها (like Alzheimer desease)**

Example of case report

Successful early carotid endarterectomy for critical carotid artery stenosis following thrombolysis in acute ischemic stroke: A case report

Nagakrishnal Nachimuthu MD, Michael Chan MD, Mathew Davis MD, Neil Holland MD, Alfonso Ciervo, MD
Department of Medicine, Monmouth Medical Center, Long Branch, New Jersey

ABSTRACT

In patients with acute ischemic stroke, the standard of care in most cases is administration of tissue plasminogen activator (tPA) within the window period. However in patients who are found to have high grade carotid stenosis (>70% occlusion) the question arises regarding the optimal timing of carotid endarterectomy. We present the case of a 43 year old male who presented with symptoms of acute stroke, was given tPA within the recommended time frame, but was subsequently found to have high grade carotid stenosis and fluctuating symptoms. He underwent early carotid endarterectomy (within 24 hours) without major complications thereby showing that in select cases carotid endarterectomy can be done early with minimal complications.

LEARNING OBJECTIVES

•In selected candidates with critical residual carotid stenosis and no significant co-morbidities, carotid endarterectomy can be performed safely within 48 hours of acute stroke symptoms and systemic thrombolysis.
•Use of preoperative CT scan will help to select appropriate candidates for early carotid endarterectomy.

CASE DESCRIPTION

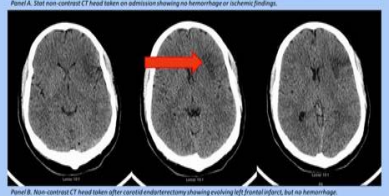
A 43 year old male with no significant co-morbidities presented to our Emergency Room after he was found to be restless in bed by his wife at 12:30am on the day of admission. He was also unable to express himself and was noted to have had a right sided facial droop. He was last observed to be asymptomatic 10:45pm prior to going to bed earlier that same evening.

The patient did not have any other neurologic findings. He had no focal weakness, nor urinary or bowel incontinence. He did not have any loss of consciousness nor seizure like activity or recent trauma.

HOSPITAL COURSE

The patient arrived at the ER at 1:15am and a code stroke was called. Laboratory exams were not significant and vital signs were normal. Initial head CT showed no intracranial hemorrhage and no apparent area of infarct (Figure 1). Initial NIH score was 5 for disorientation, right facial droop, and aphasia. Motor strength was 5/5 on all extremitites and no sensory deficit noted. On re-evaluation 30 mins later, the NIH score improved to 2 with improvement of aphasia. However, just 5 mins after that, the patient was noted to be confused and repeat NIH score was 6. tPA was administered at 2:10am due to fluctuating symptoms. At 6am, already in the ICU, the patient developed weakness of the right upper and lower extremities with persistent facial droop and aphasia. Repeat stat CT showed no bleed. CT angiogram revealed nearly occlusive thrombus in the left internal carotid artery approximately 2.7cm distal to the left common carotid bifurcation (Figure 2). The patient was advised to undergo early CEA due to fluctuating course of his symptoms. He consented, having understood the risks and benefits. Patient underwent CEA 21 hours and 55 minutes following administration of tPA. Following CEA, the patient reported improvement of his right sided weakness. At the time of discharge he had minimal facial droop and mild aphasia with no motor deficits.

Panel A. Stat non-contrast CT head taken on admission showing no hemorrhage or ischemic findings.



Panel B. Non-contrast CT head taken after carotid endarterectomy showing evolving left frontal infarct, but no hemorrhage.

Figure 1. Comparison of CT scans done on admission and approximately 24 hours later, after carotid endarterectomy.

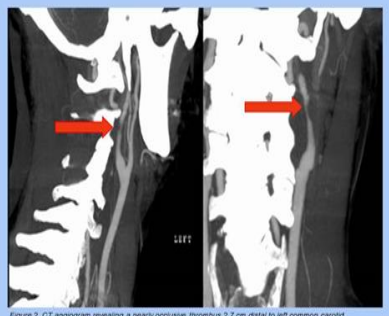
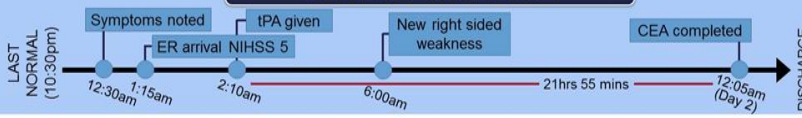


Figure 2. CT angiogram revealing a nearly occlusive thrombus 2.7 cm distal to left common carotid bifurcation

PATIENT TIMELINE



DISCUSSION

The timing of CEA following an acute ischemic stroke and administration of tPA has been the subject of debate. While early CEA could lead to hemorrhage or extension of stroke, late CEA could lead to recurrent stroke or complete occlusion of the artery.

The usual recommendation by vascular surgeons has been to wait 6-8 weeks following an acute stroke. This was based on early reports showing that the complication rate of CEA was highest within the first 2 weeks of acute stroke. However, it should be noted that even in these reports, complications were highest in those who already had significant pre-operative co-morbidities or significant neurologic deficit. Further, many of these studies were done before the widespread introduction of CT scanning.

More recent studies have shown that in selected cases, early CEA is safe. A study done in 2001 describes 5 patients who underwent early CEA (within 48 hours) after thrombolysis for ischemic stroke. All 5 had good outcomes with minimal deficits during follow up at 5-22 months and no report of recurrent stroke. Candidates for early CEA are those with minimal or no area of infarct on initial imaging, non-significant co-morbidities, and low NIH scores.

These types of complicated medical decisions can only be made after discussion between neurologists, intensivists, and vascular surgeons in a multidisciplinary stroke center.

REFERENCES

•. J. E. M. Crozier et al. *Early carotid endarterectomy following thrombolysis in the hyperacute treatment of stroke* BJS, Volume 98, Issue 2, pages 235–238, 2011
•Christopher M. McPherson, MD et al, *Early Carotid Endarterectomy for Critical Carotid Artery Stenosis After Thrombolysis Therapy in Acute Ischemic Stroke in the Middle Cerebral Artery* Stroke, Stroke; 32: 2075-2080, 2001

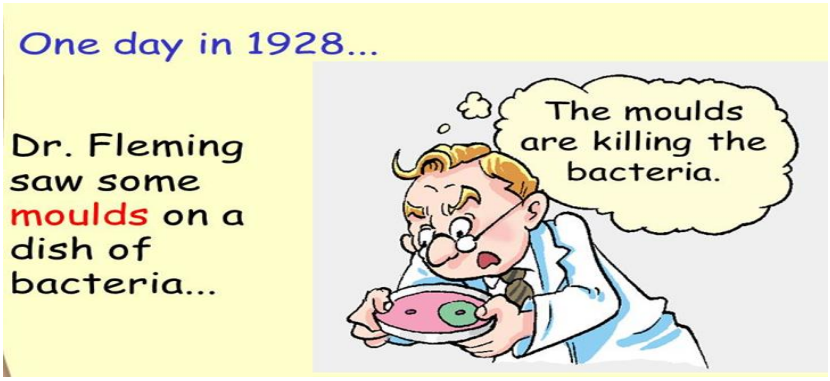
cases description اهم شئ يجب دراسته من هذه الصوره ال

Strengths of Case reports:

1. New observations and Generating hypotheses

It is the only way to present unusual, rare, uncontrolled observations regarding symptoms, clinical findings, course of illness, complications of interventions, associations of diseases, side effects of drugs, etc.

- **From a single, or preferably several single case reports or a case series i.e. comparative (observational and experimental) studies.**
- ***Story :*** **The story of Alexander Fleming's discovery of penicillin in 1928 is well known in the medical field.**



2. Researching rare disorders

3. Solving ethical constraints

- **Case reporting can be valuable when ethical constraints prohibit experimental research.**

Examples:

- **Side effects of accidental extravasation of cytotoxic drugs.**
- **Physical restraint is sometimes associated with sudden, unexpected death.**

Case reports and case series are "natural experiments" and might be the only evidence available for guiding clinical practice in such cases.

4. In-depth narrative case studies

- **Case reporting can be a way of presenting research at in-depth understanding of human phenomena, especially in the field of psychology and psychiatry. Sigmund Freud's case studies are relevant examples.**

5. Educational value

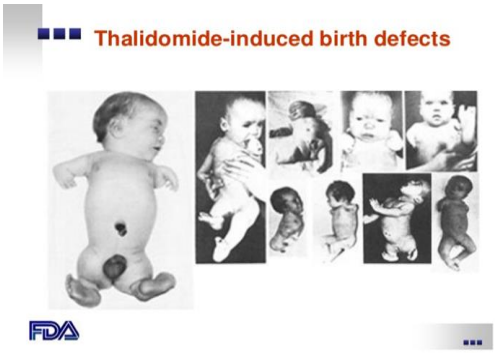
- **Case report presents day-to-day clinical practice, clinicians' diagnostic reasoning, disease management, and follow-up.**

6. Expenses

- **The cost of doing a case report is low compared to planned, formal studies. Most often the necessary work is probably done in the clinical setting without specific funding. Larger studies (RCTs) will usually need an academic setting.**

7. Clinical practice can be changed

- **Case reporting can lead to or contribute to a change in clinical practice. A drug might be withdrawn from the market. Or a relabeling might change the attitude to and treatment of a condition.**



- ***Story: A letter to the editor.*** **The first concern from the medical community about the devastating side effect of thalidomide, i.e. the congenital abnormalities, appeared as a letter to the editor in the *Lancet* in 1961 . Soon thereafter, several case reports and case series reports were published in various journals. Case reporting has helped in drug safety surveillance and the drug was banned.**

- ***Story:*** **(the shell shock syndrome) was labeled and described thoroughly in several articles in the *Lancet*, the first of them appearing in February 1915.**

Mat Fraser

The Face of Crazy. The severe effects of shellshock, what we now know as PTSD, on a WWI soldier.

8. Exercise for beginner researchers

- **The case report format is well suited for young doctors not yet trained as researchers. It can be an opportunity for a first exercise in authoring an article and a preparation for a scientific career.**

9. Communication between the clinical and academic fields

- **Articles authored by clinicians can promote communication between practicing clinicians and academic researchers. Observations published can generate ideas and be a trigger for further studies. For instance, a case series consisting of several similar cases in a short period can make up the case-group for a case–control study . Clinicians could do the observation and publish the case series while the case–control study could be left to the academics.**

10. Studying the history of medicine

- **The case reports from past eras are a rich resource for researching and understanding medical history . A close study of old case reports can provide valuable information about how medicine has been practiced through the centuries.**

3-Case series عدد من المرضى ظهرت عليهم نفس الأعراض

In a case series, the researcher may describe a set of patients that they have seen who show similar symptoms or outcomes. Or, the researcher might have searched for similar cases in the literature to try and identify the issue.

- **Case series are useful in identifying epidemics. For example, the presence of AIDS in North America was identified by the report of a cluster of homosexual men in Los Angeles with a similar clinical syndrome.**

Weaknesses:

- **Weaknesses of case reports and case series are that they have no comparison (control) group,**
- **they cannot be tested for statistical associations,**
- **and they are especially prone to publication bias (especially where case reports/series describe the effectiveness of an intervention).**

4-Cross-sectional studies

Are based on a single examination of a cross-section of population at one point in time and the unit of analysis is the individual.

- **Are based on a single examination of a cross-section of population at one point in time and the unit of analysis is the individual**
- **Collect information on the frequency and distribution of health-related exposures**

or outcomes in a defined population like a "snapshot in time" of the characteristics

of a group of individuals.

- **There is no follow-up period**
- **Prevalence studies**
- **Results can be projected on the whole population provided the sampling has been done randomly.**
- **A series of cross sectional studies done at several points in time is known as serial survey design.**
- **Cross sectional studies are relatively fast and inexpensive and form only design to give prevalence of disease**

Done by using surveys, questionnaire, interviews

For example:
A study of the BMI (body mass index) and exercise showed that there was an inverse relationship between the level of exercise and reported BMI.
Note: It is NOT clear which is the exposure and which is the outcome.

هذه الدراسة لا تبيين ما هو السبب و من المسبب

Examples :

Measure the point or period prevalence of the outcome or exposure

–e.g. prevalence of depression (outcome)

–e.g. prevalence of smoking (exposure)

The prevalence of retinal complications among T2DM (type 2 diabetes Meletus) patients.

What proportion of persons served by a public health clinic over a year have hypertension.

Advantages

- Can be used to study several associations at once
- Can be conducted over a short period of time
- Produce prevalence data

Disadvantages

- Unable to establish sequence of events
- Not feasible to use these studies to investigate rare conditions (Wilson's disease, 1-4 cases per 100,000)
- Potentially influenced by response bias (previous lecture)

Prevalence is the number of cases of the disease condition during a period of time (period prevalence) or at a particular date in time (point prevalence). Period prevalence provides the better measure of the disease load since it includes all new cases and all deaths between two dates, whereas point prevalence only counts those alive on a particular date.

incidence: is the rate of new (or newly diagnosed) cases of the disease

Prevalence

– Point prevalence

– Period prevalence

- Point prevalence

Is a proportion (dimensionless i.e. has no units) But useful to specify the point in time to which it refers

$$\text{Point prevalence} = \frac{\text{Number of cases of disease at a point in time}}{\text{Total number of people in the defined population at the same point}}$$

- Period prevalence

problem of recall bias

- – May not remember if an event took place
- – May not remember when it took place

$$\text{Period prevalence} = \frac{\text{Number of cases of disease at any time during a specified (usually short) period}}{\text{Total number of people in that defined population}}$$

5-Longitudinal Studies:

Observations are repeated in the same population (fixed sample) over a prolonged period of time by means of follow up examinations.

They are able to demonstrate the change over a period of time

***Useful to study:**

1-Natural history of disease and its future outcome.

2-For identifying risk factors of disease. →يمكن الوصول لنتيجة لأننا نتابع المرضى لفترة طويلة

3-For finding out incidence rate.

For example:

The longitudinal study design We might choose to look at the change in BMI levels among women over 40 who walk daily for a period of 1 year.