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Statistical Research Design and Basic Techniques in Epidemiological Research

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Abstract: Epidemiology has been defined as the study of the distribution and determinants of disease frequency in human population and interpreting the observations. Epidemiology is a method of making and interpreting observations in biomedical investigations. These investigations deal with groups of people rather than individual cases and usually study both healthy and ill persons. Epidemiological researchers and scientists have a vital role to play in the health care of the entire population. The biostatisticians design the experiments, trials and analyze the data and interpret the facts. Statistical design and technique helps to describe the involvement of complex human phenomena and behavior. The impact of associated factor(s) can be analyzed with the help of simple statistical design and techniques. This paper described the basic concept of statistical research design and techniques used for analysis of data and interpretation of results and also discussed the experimental error and biasness in the epidemiological research investigation.

Key words: Epidemiology · Prevalence · Incidence · Relative Risk · Statistical Design

INTRODUCTION

Epidemiological studies are associated with the healthy and ill persons. Conclusions in these investigations are expressed as odds and risks rather than specifically as cause and effect. Epidemiology has been described the study of distribution and determinants of disease frequency in human population and interpreting the observations and also important for clinical practice [1, 2].

Some questions that can be addressed by epidemiology include the followings.

- *Normal/Abnormal*: When person can be liable to disease.
- *Risk*: Factors associated with likelihood of disease
- *Cause*: What factors can result in disease.
- *Prognosis*: A prediction of the probable course and outcome of a disease. b. The likelihood of recovery from a disease or consequences of having disease.
- *Diagnosis*: Diagnosis refers both to the process of attempting to determine or identify a possible disease or disorder in other words accuracy of diagnostic test.
- *Treatment*: Treatment, therapy used to remedy a health problem; Treatment, a process or intervention in the design of experiments.
- *Frequency*: How often does a disease occurs.
- *Prevention*: Disease prevention is a better management practice than disease control. Disease prevention passes many things because of the diversity of disease. Find out how a healthy diet maintains health, prevents disease and helps control and/or treats chronic diseases.

The present paper discussed the basic concept of statistical research designs, methodology and techniques used for analysis of data and interpretation of results and also discussed the experimental error and different types of biasness in the epidemiological research investigation.

An Overview of Epidemiology: The Greek physician Hippocrates, known as the father of epidemiology [3] is the first person to have examined the relationships between the occurrence of diseases and environmental influences [4] and coined the terms endemic (for diseases usually found in some places but not in others) and epidemic (for diseases that are seen at some times but not others) [5].

Epidemiology is defined as the study of distribution and determinants of health related states in populations and use of this study to address health related problems. One of the earliest theories on the origin of disease

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advocate by philosophers such as Plato [6] and Rousseau [7] and social critics like Jonathan Swift [8] was that it was primarily the fault of human luxury.

Other pioneers include Danish physician Peter Anton Schleisner, who in 1849 related his work on the prevention of the epidemic of neonatal tetanus on the Vestmanna Islands in Iceland [9, 10]. In the early 20th century, mathematical methods were introduced into epidemiology by Ronald Ross and Anderson G. McKendrick [11, 12].

Epidemiology is the study of health events, characteristics or determinant of health patterns in a population. It is the method of public health research and helps to policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Epidemiologists are involved in the design of studies, collection and statistical analysis of data, analysis and interpretation of results. Major disciplines of epidemiology include disease surveillance and screening, monitoring and comparisons of treatment effects. Epidemiologists are also associated with number of other scientific disciplines such as biology to better understand disease processes, biostatistics to make efficient use of the data and draw appropriate conclusions and social science disciplines for better understanding of proximate and risk factors and their measurement.

The other associated term etymology is widely used in studies of zoological populations (veterinary epidemiology), although the term 'epizoology' is available and it has also been applied to studies of plant populations (botanical epidemiology) [13].

The distinction between 'epidemic' and 'endemic' was first drawn by Hippocrates [14, 15] to distinguish between diseases that are 'visited upon' a epidemic population from those that 'reside within' a endemic population [16]. The term 'epidemiology' appears to have been used first to describe the study of epidemics in 1802 by the Spanish physician Villalba in Epidemiología Española [16]. Epidemiologists also study the interaction of diseases in a population, a condition known as a syndemic.

The term epidemiology is now widely applied to cover the description and causation of not only epidemic disease, but of disease in general and even many non-disease health-related conditions, such as high blood pressure and obesity. Epidemiology is sometimes viewed as a collection of statistical tools used to elucidate the associations of exposures to health outcome, a deeper understanding of this science is that of discovering *causal* relationships. For epidemiologists, the key is in the term inference. Epidemiologists use gathered data and a broad range of biomedical and psychosocial theories in an iterative way to generate or expand theory, to test hypotheses and to make educated, informed assertions about which relationships are causal and about exactly how they.

In 1965, Austin Bradford Hill detailed criteria for assessing evidence of causation [17].These guidelines are sometimes referred to as the Bradford-Hill criteria, but this makes it seem like it is some sort of checklist. Phillips and Goodman [18] note that they are often taught or referenced as a checklist for assessing causality, despite this not being Hill's intention. Hill himself said "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required sine qua non" [17].

- *Strength*: A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal [17].
- *Consistency*: Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect [17].
- *Specificity*: Causation is likely if a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship [17].
- *Temporality*: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay) [17].
- *Biological gradient*: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence [17].
- *Plausibility*: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge) [17].
- *Coherence*: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations" [17].
- *Experiment*: "Occasionally it is possible to appeal to experimental evidence" [17].
- *Analogy*: The effect of similar factors may be considered [17].

Epidemiological investigations and researches are becoming increasingly a matter of team work, not only because of the large number of people that may have to be studied and the large amount of data that have to be collected and analyzed.

Statistical technique of a research study means, planning the study in scientific manner so that the objectives of the study are fulfilled to facilitate meaningful interpretations of the data collected during the research.

Area and Type of Research: The purpose of epidemiological research, involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedure and better understanding of the etiology and pathogenesis of disease. Generally, there are two types of research investigations, experimental and non experimental/observational (Survey) study. In the experimental study, involves a planned interference with the natural course of events so that its can be observed. In the observational study, the investigator is more passive observer interfering as little as possible with the phenomena and wishes to record. There are different types of investigation in the epidemiological research. Research investigations can be broadly classified in to four sections.

- Planning of research proposals.
- Execution of the investigation.
- Appropriate analysis of data or outputs.
- Meaningful interpretations of the results.

The section 1, 3 and 4 involve the statistical techniques.

Basic Steps in the Formulation of Research Proposals:

- Definition of research problems, this includes the definition of aims and objectives of the research.
- Formulation of objectives and hypothesis and well defined.
- Methodology of research for the particular problems must be clearly defined.
- Selection of variables for the research study.
- Coverage of all possible subject matters associated with research objectives.
- Well defined tools and techniques for data analysis.
- Well defined study population, sample, control, sample size and time coverage.
- Formulation of analytical methods for the data and planning for resources.
- Anticipation and estimation of possible errors and evolving appropriate actions to rectify the errors.

Different types of investigations in the epidemiological research and basic statistics use are described in detail.

Epidemiological Investigation in Communicable Disease: Communicable diseases are far from being controlled. They still present a serious public health concern in developing as well as developed countries [19]. Some examples of these diseases are HIV/AIDS, SARS, Avian Influenza, Visceral Leishmaniasis, Tuberculosis, etc. [20-22].

Among communicable diseases, epidemiological investigations i. compare the current information with previous incidence in the community during the same time period and also compare available information with new cases, ii. analyze clinical history of cases and have standard laboratory tests to confirm or reject the suspected diagnosis and to determine the factors associated with the disease, iii. count the cases and relate these counts to the population to find the groups at risk and iv. formulate the hypothesis to explain the most likely cause, source and distribution of disease.

Epidemiological Investigation in Non-Communicable Disease: Alexander, studied the potentialities and limitations of epidemiological investigation in non-communicable diseases [23]. In this investigation includes the diseases; Cardiovascular diseases, Coronary heart diseases, Hypertension, Stroke, Rheumatic heart diseases, cancer, Obesity, Blindness, Accidents, Injuries, etc.

Epidemiological investigation in non communicable diseases to enumerates the factors relate to diseases and define those which govern its occurrence and also initial efforts of epidemiological investigation to measures the risk in groups of people with different characteristics. Risk is measured through statistical computation of incidence and relative risk [24, 25].

Basic Statistics in Epidemiology: Statistics are used to summarize the data collected through survey or investigation. The basic role of statistics in epidemiology is to make conclusions about a population of interest when data is only available from a sample. Epidemiological data usually measure observations of an occurrence of a disease as well as indicate exposure. Also, the role of statistics is to determine whether any association that is observed in the random sample is actually a real one. In

most cases there will be some association even if it is very small. The important role of the statistician is to determine if the association is different than what would occur by chance.

The most common and basic statistical method used in epidemiology is frequency measure, which is simply a measure of counting and comparing their characteristics. These frequency measures are rates, ratio and proportion.

Rate is specific kind of ratio and measures the occurrence of event in a population over time. Ratio is used to compare the occurrence of diseases in a different group or in other words ratio is a relationship between two numbers of same kinds whereas proportion explains the relationship between subsets and whole population. Proportions are usually expressed as percentage.

Sample Design and Sampling Techniques: How to select the individuals on which information are to be made?

- Investigations may be carried out on an entire group or a representative taken out from the group.
- Whenever a sample is selected it should be a random sample.
- While selecting the samples the heterogeneity within the group should be kept in mind and proper sampling technique should be applied.

Some of the different types of sample designs are:

Purposive Sampling: In this approach sampling units are selected according to our purpose. Purposive sampling provides biased estimate and it is not statistically recognized. This technique can be used only for some specific purposes.

Random Sampling: In this method of sampling each unit included in the sample will have certain pre assigned probability of inclusion in the sample. This sampling provides the better estimate of parameters in the studies in comparison to purposive sampling.

The every single individual in the sampling frame has known and non zero chance being selected in to the sample. It is ideal and recognized single stage random sampling.

Simple Random Sampling: In the Simple random sampling method each unit included in the sample have equal chance of inclusion in the sample. This technique provides the unbiased and better estimate of the parameters if the population is homogeneous.

Stratified Random Sampling: Stratified random sampling is useful techniques for data collection if the population is heterogeneous. In this technique, the entire heterogeneous population is divided in to a number of homogeneous groups, usually known as Strata, each of these groups is homogeneous within itself and then units are sampled at random from each of these stratums. The sample size in each stratum varies according to the relative importance of the stratum in the population. The technique of the drawing this stratified sample is known as Stratified Sampling.

In other words, stratification is the process by which the population is divided into subgroup/strata. Sampling will then be conducted separately in each group/strata. Strata or Subgroup are chosen because evidence is available that they are related to outcome. The selection of strata will vary by area and local conditions. After stratification sampling is conducted separately in each stratum. In stratified sample, the sampling error depends on the population variance within strata but not between the strata.

Sample Size for Investigation and Recording: The sample size should be carefully fixed so that the sample size will be adequate to draw valid and generalized conclusions. The fixation of the adequate sample size requires specific information about the problems under investigation in the population under study. And also, the sub classifications of sample require for analysis, variation, precision, availability and cost of investigations. The information collected during investigation from samples are to be recorded on predesigned schedule or on questionnaire. The design of questionnaire depends on the objectives and facilities for analysis.

Random Error: Random error is the result of fluctuations around a true value because of sampling variability. Random error is just that: random. It can occur during data collection, coding, transfer, or analysis. Random error include: poorly worded questions, a misunderstanding in interpreting an individual answer from a particular respondent, or a typographical error during coding. Random error affects measurement in a transient, inconsistent manner and it is impossible to correct for random error. There is random error in all sampling procedures is also known as sampling error.

Precision in epidemiological variables is a measure of random error. Precision is also inversely related to random error, so that to reduce random error is increase precision. Confidence intervals are computed to demonstrate the

precision of relative risk estimates. The narrower the confidence interval, the more precise the relative risk estimate.

There are two basic ways to reduce random error in an epidemiological research. The first is to increase the sample size of the study. In other words, add more subjects to the study. The second is to reduce the variability in measurement in the study. This might be accomplished by using a more precise measuring device or by increasing the number of measurements.

Systematic Error: A systematic error or bias occurs when there is a difference between the true value (in the population) and the observed value (in the study) from any cause other than sampling variability. A mistake in coding that affects all responses for that particular question is simple example of a systematic error.

Investigational Errors: In the epidemiological investigation, there are generally two types of error in the study, first, response error and measurement error.

- Response error due to under coverage of the sample or non cooperation of people or death of the patient. These errors can be reduced by efforts of the investigators and also proper planning of the sample size allowing mortalities and etc.
- Second type of error is measurement error. These errors can be reduced by standardization of techniques and proper training of investigator.

Statistical Design

Cohort Study Design: Cohort study is an analysis of risk factor and follows a group of people who do not have the disease and uses the correlation to determine the absolute risk of subject contraction. Cohort study is generally used in medical, social, actuarial and ecological sciences. Cohort studies are largely about the life histories of segments of population and individual people who constitute these segments [26, 27]. Cohort studies can either be conducted prospectively or retrospectively from archived records [28]. A cohort is a group of people with some things in common. In a cohort study two groups of people similar in everyway except that one has the risk factor or exposure being studied and the other does not /are observed. Both groups are free from disease in question at the start of the study. The groups are assembled and observed over a period of time to study how many from each group develop the disease. A prospective cohort defines the groups before the study is done, while historical studies, which are some time referred to as retrospective cohort, define the grouping after the data is collected. Examples of retrospective cohort are long term mortality after gastric bypass surgery [29]. Through the historical studies are some times referred to as retrospective study, it a misnomer as the methodological principles of historical cohort studies and prospective studies are the same [30]. A cohort study (longitudinal study) design collects data over long periods of time. Measurements are taken on each variable over two or more distinct time periods. This study allows to researcher to measure change in variable over time.

Case Control Study Design: A case control study is type of another study design for epidemiological investigation. Case control study is an analytical study which compares individuals who have specific disease (known as case) with a group of individuals without disease (known as control). It is advantageous for the controls to come from the same population from which the cases were derived, to reduce the chance that some other differences between the groups are accounting for the difference in the exposure that is under investigation. These studies are used to identify factors that may contribute to medical condition by comparing subjects who have that condition with patients who do not have the condition but are otherwise similar [31]. Doll was able to show a statistical significant association between tobacco and lung cancer [32]. Porta's Dictionary of epidemiology defines the case control study as an observational epidemiological study of persons with disease of interest and suitable control group of persons without the disease and also describe potential relationship of suspected risk factor or attribute to the disease is examined by comparing the diseased and non diseased subjects with regard to how frequently the attribute is present [33].

Case control studies were analyzed by testing whether or not there were significant differences between the proportion of exposed and non exposed [26]. Rodrigues [34] and subsequently Cornfield [35] pointed out that, when the disease outcome of interest is rare, the odds ratio of exposure can be used to estimate the relative risk. Miettinen shows that this assumption is not necessary and that the odds ratio of exposure can be used to directly estimate the incidence rate ratio of exposure without the need for the rare disease assumption [34-37].

The case control study is frequently contrasted with cohort studies, where in exposed and non exposed subjects are observed until they develop an outcome of interest [33, 38, 39].

Advantages: Case control studies are less costly and to carry out than prospective cohort studies as well as having the potential to be shorter in duration. Another important aspect is the greater statistical power of the type of study in several situations, given the fact that cohort studies must often wait for a sufficient number of disease/event to occur.

Disadvantage: These studies are more difficult to establish the timeline of exposure to disease outcome in the setting of a case control study than within a prospective cohort design where the exposure is ascertained prior to following the subjects over time in order to ascertain their outcome status.

The important drawback in case control studies relates to the difficulty of obtaining reliable information about an individual's exposure status over time.

Cross Sectional Study Design: Cross sectional study that involve observation of all population, or a representative of population, at one specific point time and aim to provide the estimate of the subjects for entire population. These studies are descriptive studies and can be used to describe the prevalence of diseases [40-42].

It differs from case control study where as case control study typically includes only individuals with a specific characteristics, with a sample. Descriptive research design provides data for monitoring and evaluating policies and health programmes. Case control study is specially concerned with how to answer questions such as how many, how much, how efficient, how effective, how adequate etc [43-45].

Cross sectional studies can be thought of as providing "snapshot" of the frequency and characteristics of disease in population at a particular point in time. It also measures the disease and exposure status simultaneously in a given population [46, 47].

Advantages:

- They are relatively inexpensive and take up little time to conduct.
- These can estimate prevalence of outcome of interest because sample is usually taken from the whole population.
- Many outcomes and risk factor can be assessed.
- They are useful for public health planning, understanding of disease etiology and for the generation of hypothesis.
- There is no loss of follow up.

Disadvantages:

- It is difficult to make causal inference from such studies.
- Only snapshot - the situation may provide differing results if another time frame had been chosen.

Case Series Design: Case-series refers to the qualitative study of the experience of a single patient, or small group of patients with a similar diagnosis, or to a statistical technique comparing periods during which patients are exposed to some factor with the potential to produce illness with periods when they are unexposed.

This study is purely descriptive and cannot be used to make inferences about the general population of patients with that disease. These types of studies, in which an astute clinician identifies an unusual feature of a disease or a patient's history, may lead to formulation of a new hypothesis. Using the data from the series, analytic studies could be done to investigate possible causal factors. These can include case control studies or prospective studies. A case control study would involve matching comparable controls without the disease to the cases in the series. A prospective study would involve following the case series over time to evaluate the disease's natural history [48].

Basic Methods Used

Studies of Frequency: It is important section of research investigation. For the purpose of epidemiological research analysis, generally frequencies explained as

Prevalence: Fraction of a group of subjects that have the condition at a given time.

Prevalence (P) =
All cases counted on a single survey of a group / All people examined.

Incidence: It is fraction of a group of subjects initially free of condition who develop it over a period of time. Incidence is also defined as chance of occurrence of disease in a time period. Time is also a factor in incidence, generally taken as per year.

Incidence (I) =
[{New cases in a period of time among groups (initially free from disease)} / {All susceptible people present at beginning of period}].

Disease with similar incidence may have different prevalence because prevalence depends on duration of disease.

P = Incidence X Duration (T)
Duration (T) = Prevalence/Incidence

Relative Risk (RR): It indicates that how many times more likely exposed persons are to get the disease as compared to unexposed.
RR = Incidence in exposed/Incidence in unexposed

	Disease (+)	Disease (-)	Total
Exposed	A	B	A+B
Unexposed	C	D	C+D

RR = [{A/ (A+B)}/ {C/ (C+D)}]

Attributable Risk (AR):

AR = Incidence in Exposed - Incidence in Unexposed
= {A/(A+B)} - { C/C+D)}

Population Attributable Risk (PAR) = AR X Prevalence of risk factor in population.

Odds Ratio (OR): Odds is the probability that an event will occur and probability is proportion of people in whom event will occur.

OR = Odds for disease among exposed / Odds for disease among unexposed

	Disease (+)	Disease (-)
Exposed	A	B
Not Exposed	C	D
Total	A + C	B + D

OR = [{A/(A+C)}/ {C/(A+C)}] - [{B/(B+D)}/ {D/(B+D)}]
OR = (A x D) / (B x C)

Validity: Different fields in epidemiology have different levels of validity. One way to assess the validity of findings is the ratio of false-positives to false-negatives. The validity of a study is dependent on the degree of systematic error. Validity is usually separated into two components [49]:

Internal Validity: Internal validity is dependent on the amount of error in measurements, including exposure, disease and the associations between these variables. Good internal validity implies a lack of error in measurement and suggests that inferences may be drawn.

External Validity: External validity pertains to the process of generalizing the findings of the study to the population from which the sample was drawn. This requires an understanding of which conditions are relevant to the generalization.

Biasness in the Epidemiological Investigations
Bias: It is systematic error in the estimate. In other words, conclusions are systematically different from truth. Biasness can occur during any stage of research /investigation.

- During the review of the study.
- During the selection of sample.
- During the measurement of exposure and outcome.
- During the analysis and interpretation of data.
- During the publication of the research outputs.

There are mainly three types of bias in epidemiological Research.

Selection Bias: Selection bias is one of three types of bias that can threaten the validity of a study. Selection bias occurs when study subjects are selected or become part of the study as a result of a third, unmeasured variable which is associated with both the exposure and outcome of interest [13].

Information Bias: Information bias is bias arising from systematic error in the assessment of a variable [50]. An example of this is recall bias. A typical example is again provided by Sackett in his discussion of a study examining the effect of specific exposures on fetal health: "in questioning mothers whose recent pregnancies had ended in fetal death or malformation (cases) and a matched group of mothers whose pregnancies ended normally (controls) and reported exposure to drugs which could not be substantiated either in earlier prospective interviews or in other health records" [14].

Confounding Bias: When two or more factors go together, effect of one may be confused with another. In other words confounding has traditionally been defined as bias arising from the co-occurrence or mixing of effects of extraneous factors, referred to as confounders, with the main effect(s) of interest. [51, 16] A more recent definition of confounding invokes the notion of counterfactual effects [16].

Summary: Epidemiology is the study of the distribution and determinants of the health related events in the specific population. Epidemiological research is directly associated with, through the collection of data related to health and welfare of human population. Epidemiological analysis makes a significant contribution to emerging population-based health management. Modern population-based health management is complex, requiring with a multiple set of skills such as medical, social, technological, mathematical, statistical etc. Epidemiological investigation is the part of wider public health and health management research and it is related with better health and development of health welfare programs for human beings. This task requires the forward looking ability of modern risk management approaches that transform health risk factors, incidence, prevalence and mortality statistics. Epidemiological research with the help of appropriate research designs provide the estimates of health indicators and through this unbiased estimates can be monitor the health status of community. In this paper, the role of statistical research design and applications of basic techniques in epidemiological research, have been emphasized scientifically.

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