Review Article

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Bias in Epidemiology

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Abstract

All study designs have an inherent nature of incorporating errors in the various stages of implementation of a study.The major limitations that arise while deriving inferences in epidemiological study designs are chance, bias and confounding which if unidentified results in invalid findings and distortion of the final estimates.Bias is a systematic, non- random error, foreseen in all epidemiological study designs. It has to be avoided at all phases i.e. design, conduct, analysis or during the reporting phase of study design. A mistaken estimate of an exposure's effect on the risk of disease occurs, unless avoided**.**

Keywords: Bias; Epidemiology; Error; Review; Systematic Error.

Introduction

One of the prime aims in epidemiology is to find out the association between a given variable and an outcome of interest, which may or may not refutecausal inferences. All study designs have an inherent nature of incorporating errors in the various stages of implementation of a study. Most of them are introduced unintentionallywhich can be avoided by attentively creating a sound study design with provisions for identifying and minimizingsuch errors or methods for counteracting these errors during the analysis phase. Despite, the various measures taken to eliminate these biases, some of them are inevitable which might distort the study estimates significantly.

Hence, this article is written with the objective to describe the types of bias that are inherent in the various epidemiologic study designs and measures or methods taken to eliminate them.

Major Issues in Epidemiological Studies

The major limitations that arise while deriving inferences in epidemiological study designs are chance, bias and confounding which if unidentified results in invalidfindings and distortion of the final estimates. The first two are considered as errors.

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Types of Errors

The first one described as Random error occurs due to chance and the latter called bias is a systematic error.

Random Error

In random error, there is a deviation from the true value which is an inherent problem with sampling as the whole population cannot be studied. Since it is at random, the deviation sometimes adds to the estimate and sometimes takes from it. When a large sample or several small samples are studied these deviations cancel each other out. This phenomena is due to "chance" and, as such, is unpredictable. E.g.: Sack of grains: Weevil.

Methods to Overcome Random Errors

- By taking adequately a large sample
- Statistical procedures to calculate the probability by which our result may differ from the true value in the "total population", because of random error.

Bias Definition

Bias has been defined as "any systematic error in

the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease" [1].

Bias is a systematic, non- random error, foreseen in all epidemiological study designs. It has to be avoided at all phases i.e. design, conduct, analysis or during the reporting phase of study design. A mistaken estimate of an exposure's effect on the risk of disease occurs, unless avoided [2].

Bias is also defined as an inclination, predisposition, partiality, or prejudice that well-meaning, but inexperienced, investigators can inflict on the performance of a study [2]. It is one of the important issues in deriving causal inferences. Bias is universal and cannot be totally eliminated; hence measures should be taken to minimize them.

Types of Bias:

Bias encountered in epidemiological studies are broadly classified under three headings,

- Selection bias
- Information bias/Measurement bias
- Confounding bias
- Miscellaneous

Selection bias

Selection bias arises when the method used to select and enroll subjects are faulty which distorts the characteristics of the study groups [2]. When cases and controls or exposed and non-exposed individuals, are selected such that an apparent association is observed, although in reality, exposure and disease are not associated the results indicate an apparent association which is the result of selection bias.

Every study conducted in human population selects study subjects from a larger population. The nature of this selection potentially affects the generalizability or external validity of the study but does not necessarily affect the validity of the comparisons made within the study or the study's internal validity. On the other hand, when a systematic error is made in selecting one or more of the study groups that will be compared, selection bias may result. Such bias can result in incorrect estimates of odds ratios or relative riskand consequently lead to invalid inferences regarding association of exposure and disease. Selection bias is therefore an error in selecting a study group or groups within the study and can have a major impact on the internal validity of the study and the legitimacy of the conclusion.

Different types of Selection Bias

Survival bias

It occurs when survivors of a highly lethal disease are more likely to enter a study than other cases.

When we study the role of age as a potential risk factor for viral hemorrhagic fever (VHF), and include only those who are still alive at the time of the study and if older age is associated with increased risk of VHF death, it will decrease the proportion of cases over a certain age in the study, and consequently underestimate the odds ratio.

Detection Bias/Diagnostic Bias/Ascertainment Bias

It is a form of bias that arises through a relation between the exposure and the probability of detecting the event of interest.

For example, a case control study stating women on oral contraceptive pills will have more frequent cervical smears than those who are not, and as a consequence therate of likely detectionincreasesdue to frequent screening which can be attributed due to ascertainment bias.

Berksonian Bias

It arises due to the differential rate of admission in hospitals owing to the fact that those who receive medical care are dissimilar and not representative of the general population, or necessarily of all ill persons [3].

For example, the mortality rates in institutional deliveries are higher than for home deliveries, from which one might infer that home deliveries are safer than hospital deliveries which is a fallacy. It arises because of the health seeking behaviour of the complicated cases as compared to the normal ones.

Neyman's Fallacy (Incidence-Prevalence Bias)

When a series of survivors are selected and if the exposure is related to prognostic factors, or the exposure itself is a prognostic determinant, the sample of cases offers a distorted frequency of the exposure

Example: Relationship between sex and risk of colorectal cancer. Incidence of colorectal cancer is slightly higher in males than females. However survival from colorectal cancer is significantly longer in females than males. Since the female colorectal cancer patients live longer than males, a sample of

prevalent cases will include a higher proportion of women than a corresponding sample of incident cases. This results in an apparent inference that incidence of colorectal cancer is more in women than men.

Exclusion Bias

When controls with conditions related to the exposure are excluded, whereas cases with these diseases as co morbidities are kept in the study, we introduce what is known as an exclusion bias.

For example, Heinonen et al reported a matched-pair case control study carried out on surgical patients at a hospital in Helsinki, where women with breast cancer were compared to women without breast cancer admitted for surgical treatment for other benignconditions, in terms of use of reserpine. In selecting the controls, the authors excluded women with the following operations: cholecystectomy, thyroidectomy for thyrotoxicosis, surgery for renal disease, and any cardiac operation, sympathectomy, or vascular graft for which reserpine was used as treatment. They were excluded because the prevalence of reserpine use in the controls would be artificially high, so that even if reserpine use was increased in breast cancer cases, the increase might not be detected.Unfortunately, by excluding patients with these conditions from the controls, they created a control group in which the prevalence of reserpine use was artificially lower because a large group of potential reserpine users were excluded. Thus, even if in reality reserpine use was not increased in women who developed breast cancer, this study could have shown a difference in reserpine use between the cases and the controls only because of the way the controls were selected.

Bias from Non-Response or Loss to Follow up

Non participation and non-response rates can introduce major biases that invalidate the results. Similarly, loss to follow up can be a serious problem. If people with the disease are selectively lost to follow up, the incidence rates calculated between the exposed and non-exposed groups will clearly be difficult to interpret.

Length Time Bias

Length time bias is often discussed in the context of the benefits of cancer screening, where it can lead to the perception that screening leads to better outcomes when in reality it has no effect.

An example: Fast-growing tumors generally have a shorter asymptomatic phase than slower-growing tumors, which means a shorter latent period but, not large enough to cause symptoms, which would cause the patient to seek medical care and be diagnosed without screening. If the same number of slow-growing and fast-growing tumors appear in a year, the screening test will detect more slow-growers than fast-growers and if these slow growing tumors are less likely to be fatal than the fast growers are, the people whose cancer is detected by screening will do better, on average, than the people whose tumors are detected from symptoms (or at autopsy), even if there is no real benefit to catching the cancer earlier. This can give the impression that detecting cancers through screening causes cancers to be less dangerous, when the reality is that less dangerous cancers are simply more likely to be detected by screening.

Healthy Worker Effect

A comparison between health status of military and civilian population may show a better health status among the soldiers which may be attributed to the pre employment medical examination during which the 'unfit' persons are excluded and only 'healthy workers' are included in the army. The basic dictum of selection and comparisons in research should be to "compare likes with likes".

Information Bias

Distortion in the estimate of effect of interest when the measurement of either the exposure or disease is systematically inaccurate.This may occur when there are errors leading to misclassification in exposure and disease status. It is a systematic error in the measurement of information on exposure or outcome.

Types

Misclassification Bias-Non Differential and Differential

Non-differential bias is a random error, unrelated to exposure or outcome status and weakens the measure of association. It results from the degree of inaccuracy that characterizes how information is obtained from any study group, either, cases and controls or exposed and non-exposed persons. Such misclassification is not related to exposure status or to case or control status. It is due to an inherent problem in the data collection methods. The usual effect of non-differential misclassification is that the relative risk or odds ratio tends to be diluted, and it is

shifted toward 1.0. In other words, we are less likely to detect an association even if one really exists.

In contrast,differential bias is a systematic error, related to exposure or outcome status and the measure of association can be distorted in any direction. An example of women who had a baby with a malformation tend to remember more mild infections that occurred during their pregnancies than did mothers of normal infants. Thus, there was a tendency for differential misclassification with regard to prenatal infection, such that more unexposed cases were misclassified as exposed than were unexposed controls. The result was an apparent association of malformations with infections, even though none existed. So a differential misclassification bias can lead either to an apparent association even if one does not really exist or to an apparent lack of association when one does in fact exist.

Misclassification can be Due to,

1. Misclassification of disease: Misclassifying cases as controls and controls as cases in a case control study might arise due to limited sensitivity and specificity of the diagnostic tests or from inadequacy of information collected from medical records.
2. Misclassification of exposure: Misclassification due to inaccurate exposure status based on erroneous reporting in interviews or incomplete records.

Recall Bias

If the presence of disease influences the perception of its causes (*rumination bias*) or the search for exposure to the putative cause (*exposure suspicion bias*), or in a trial if the patient knows what they receive may influence their answers (*participant expectation bias*).This bias is more common in case-control studies, in which participants know their diseases, although it can occur in cohort studies and clinical trials without participant blinding. An example, is workers who have known about their exposure to hazardous substances may show a trend to report more the effects related to them,

Interviewer Bias/Observer Bias

The knowledge of the hypothesis, the disease status, or the exposure status (including the intervention received) can influence data recording (*observer expectation bias*).The means by which interviewers can introduce error into a questionnaire include administering the interview or helping the respondents in different ways (even with gestures), putting emphases in different questions, and so on. A particular situation is when the measure of an exposure influences its value (for example, blood pressure) (*apprehension bias*).

Reporting Bias

If subject is reluctant to report an exposure he is aware of because of attitudes, beliefs and perceptions, reporting bias can result.

Example, the relationship of induced abortion to risk of breast cancer.It was suggested that reporting bias might have played a role in those case control studies that reported a positive association. For example, healthy controls may have been more reluctant than women with breast cancer to report that they had had an induced abortion.

Surveillance Bias

If a population is monitored over a period of time, disease ascertainment may be better in the monitored population than in the general population, and may introduce a *surveillance bias*, which leads to an erroneous estimate of the relative risk or odds ratio.

For example, the possible relationship of oral contraceptive use to thrombophlebitis. It was suggested that physicians monitored patients who had been prescribed oral contraceptives much more closely than they monitored the other patients. As a result, they were more likely to identify cases of thrombophlebitis that developed in those patients who were taking oral contraceptives who were closely monitored than other patients who were not so well monitored.

Hawthorne Effect

Described in the 1920s in the Hawthorne plant of the Western Electric Company.

According to legend, worker productivity improved at the Hawthorne plant of the Western electric company not only when the illumination was increased, but also later when it was decreased. The reason for this was supposed to be the attention paid to the workers by the researchers and not the lighting itself.

For example, laboratory physicians increase their agreement rate after knowing that they participate in a research on reliability of diagnostic tests.

Lead Time Bias

Lead time is added time of illness produced by the diagnosis of a condition during its latency period. This bias is relevant in the evaluation of the efficacy of screening, in which the cases detected in the screened group has a longer duration of disease than those diagnosed in the non-screened one.

Protopathic Bias

When an exposure is influenced by early (subclinical) stages of disease. For instance, preclinical pancreatic cancer can produce diabetes mellitus, and thus an association between diabetes and cancer can occur. It is also produced when a pharmaceutical agent is prescribed for an early manifestation of a disease that has not yet been diagnosed.

The sick quitter bias is related to protopathic bias: people with risky behaviors such as heavy alcohol consumption, quit their habit as a consequence of disease; studies analyzing current behavior as a risk factor will label them as non-exposed, thus underestimating the true association.

Will Rogers Phenomenon

The improvement in diagnostic tests refines disease staging in diseases such as cancer. This produces a stage migration from early to more advances stages and an apparent higher survival. This bias is relevant when comparing cancer survival rates across time or even among centers with different diagnostic capabilities. For example, tertiary compared with primary care hospitals.

Work up Bias

It arises while assessing the validity of a diagnostic test, when the execution of the gold standard is influenced by the results of the assessed test; typically the reference test is less frequently performed when the test result is negative. This bias is increased when the clinical characteristics of a disease influence the test results.

Confounding Bias

Confounding biases are the biases that arise due to presence of certain confounding factors.

Confounding

Confounding is a distortion of the association between exposure and outcome brought about by the association of another, extraneous exposure (Confounder) with both the disease and the exposure of interest.

Properties of Confounder

- Associated with both the exposure and the disease
- Distributed unequally between the study and the control group
- Independent risk factor for disease

A confounder cannot be an intermediate variable in the causal pathway between the exposure of interest and disease.

Miscellaneous

Ecological Fallacy

Is an error in inference that occurs when association observed between variables of a group level, is assumed to exist at an individual level.

Correlation between Dietary Fat Intake and Breast Cancer by Country

One of the very well quoted studies on women's health obtained data from 20 developed countries from western Europe, USA, Australian, NewZealand and Eastern Asian regions. National data was obtained on per capita consumption of fats in diet as well as incidence of female breast cancer in these countries. (They obtained data from the cancer registries of these countries as regards breast cancer incidence, and from the central marketing organizations of these countries as regards sales of edible fats.)

The results very clearly showed that as per capita consumption of fat in a country increased, the incidence of breast cancer also increased. This finding could compel us to finally agree that dietary fat is a risk factor for breast cancer.

Publication Bias

Regarding an association that is produced when the published reports do not represent the studies carried out on that association. Several factors have been found to influence publication. The most important being statistical significance, size of the study, funding, prestige, type of design, and study quality.

Post Hoc Bias

Another source of potential bias is the use of data

from a cohort study to make observations that were not part of the original study intent. Thus interesting relationships that were not originally anticipated are often observed in cohort studies. These findings should be treated as hypothesis that is an appropriate subject for additional studies.

Biases in Randomized Controlled Trials

During Randomization

Selection Bias

- Subversion of randomization due to inadequate concealment of allocation E.g.: RCT comparing open versus laparoscopic appendectomy
- Withdrawals (New drug* Multiple sclerosis)
- Loss to follow up (RCT comparing medical versus surgical management of cerebrovascular disease
- Competing risks
- Contamination (E.g.: Awareness regarding menstrual hygiene)

Ascertainment bias

Minimized by blinding

Overcoming bias

Methods to overcome selection bias

- Ensure blinding - definitely in an experimental design
- If possible, do not tell research hypothesis to the subjects (helps preventing recall bias)
- In a follow - up study (cohort study or clinical trial), take a well-defined population to avoid loss to follow up; develop methods to retrieve those subjects who are getting lost to follow up.
- Select two or more than 2 "groups" of controls in a case control study (e.g. one from hospital and another healthy group); try and take different categories of diagnoses if selecting hospital controls.
- In cohort or experimental studies (follow - up studies) specify clearly the future dates of examination and examine all subjects of both groups at the pre - decided dates using "similar" methods of history taking, physical examination and investigations, and measures to minimise loss to follow up.
- In a case control study, use the correct time frame for recording exposure (e.g. for a study between pneumonia and cold exposure, the time frame should be 6 days and not 6 months).
- In a case control study, ensure that cases and controls are chosen from the same "source" population; and that cases and controls have the same "selection factors" for getting admitted to that particular hospital.

❖ Is there any possibility of "survivorship" bias?

❖ Is the disease such that the initial symptoms may have led to a change in exposure? (e.g. initial dyspeptic symptoms of gastric CA may cause the patient to give up tobacco).

❖ Did the controls have a reasonable chance of being exposed to the factor of interest? (Hysterectomised women in any case do not have a 'chance' of exposure to OC, so do not keep them in controls in an Oral Contraceptives Thromboembolism study).

- In an experimental design (clinical trial), ensure Random allocation, Blinding and Placebo control.

Methods of Dealing with Information Bias

- Standardize measurement instruments
- Administer instruments equally to cases and controls (Exposed/Unexposed)
- Use multiple sources of information

➢ Questionnaires

➢ Direct measurements

➢ Registries

➢ Case records

- Use multiple controls
- Closed, precise questions, minimize open ended questions
- Seek information on hypothesis through different questions
- Disguise questions on hypothesis in range of unrelated questions
- Field test and refine
- Standardize interviewers technique through training with questionnaires

Methods of Dealing with Confounding Bias

Control During Designing Stage

Randomization

It can be done only in experimental study designs.

Randomization is a statistical procedure by which

the participants are allocated into groups usually called "study" and "control" groups, to receive or not to receive an experimental preventive or therapeutic procedure, maneuver or intervention.

The two groups will be "similar" to each other not only in respect of all "known possible confounding factors" (age, sex, blood groups and so on) but also in respect of those factors which may be "confounders" unaware of (e.g. HLA type and, may be, the average number of hair on the head). The two groups will be absolutely similar to each other with the only difference being that one group gets the trial modality while the other will get the control modality.

Restriction

We can so plan our study that the subjects having the particular confounding variable(s) are not taken up at all; e.g. in a study of the possible association between physical inactivity and IHD, young age (< 35 years) and female sex may be the possible confounding factor. In this case, we may restrict our study to "only males more than 35 years of age".

The difficulty with restriction is that one tends to exclude out a lot of potential subjects, thus increasing the cost and effort of study; Secondly, the effect of the variables on which restriction has been done cannot be studied - e.g. in this example, the role of female sex and younger age cannot be studied.

Matching

Matching is defined as the process by which we select controls in such a way that they are similar to cases with regard to certain pertinent selected variables (e.g., age) which are known to influence the outcome of disease and which if not adequately matched for comparability, could distort or confound the results.

Adjustment During Analysis

Stratified Analysis

Here we make two strata, one with the confounder (tobacco users) and one withoutthe confounder (non - users). If the risk in individual stratum is the same as overall risk, then there is no confounding. On the other hand, if the odds ratios in the strata are very different from the overall OR (e.g. alcohol - oral CA study,the overall OR was 16 but the stratum OR after adjusting for tobacco was 1 each), we would conclude that there is confounding.

In stratified analysis, we use certain specialized statistical procedures such as Mantel – Haenszel adjustment technique to calculate the adjusted estimates, which give us the estimate of risk due to the exposure variable, after adjusting for the effect of the confounding variable.

Multiple Regression Analysis in the Control of Confounding

While stratified analysis is very effective in control of confounding during analysis, however, if there are a large number of confounding factors, then a large number of strata will have to be made and the individual figures in the individual strata will become very small, often zero. This is the limitation of stratified analysis. In such cases one has to resort to regression analysis.

References

1. Park K. Textbook of Preventive and Social Medicine.23rd ed. Jabalpur; BanarsidasBhanot: 2011.
2. Gordis L. Epidemiology.3rd ed. Elsevier Saunders: Philadelphia; 2004.
3. Bhalwar R. Text book of Public Health and Community Medicine.1st ed. Department of Community Medicine AFMC Pune.2009.
4. Morgenstern H. Ecological studies. In: Rothman k, Lash TC, Greenland S, editor. Modern epidemiology. 3rd ed. Lippincott Williams and Wilkins: Philadelphia. 2008; p.511-531.
5. Macmohan B. Epidemiology, Principles and Methods. 1st ed. Little, brown and company: Boston; 1970.
6. Abramson J H. Survey Methods in Community Medicine. Churchchill Livingstone. 1974.
7. CMC Vellore "Epidemiology and biostatistics course" notes.
8. Bias. Delgado-Rodrý´guez M, Llorca J. J Epidemiol Community Health. 2004; 58: 635–641.
9. Hennekens CH, Buring JE. Epidemiology in Medicine, Lippincott Williams & Wilkins, 1987
10. Caroline A. Macera, Richard Shaffer, Peggy M. Introduction to Epidemiology: Distribution and Determinants of Disease. Delmar Cengage Learning. United States. 2013-152.