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# An Introduction to Common Systematic Errors in Medical Research

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***Abstract***

Considering the continuous increase in number of published articles by Iranian researchers in recent years, the matter of quality in design, implementation, analysis and publication of articles is receiving its relevant attention. Of issues in quality of articles and studies are methodological errors. There are different kinds of errors that a researcher may fall into during various phases of a study. Of these errors systematic ones (or biases) can be counted. In this paper we aim to shortly introduce various sorts of biases that might happen in medical research. These biases are of two categories; selection and information biases.



## Introduction

Nowadays, research in any field is of such high importance that number of papers presented in journals and scientific circles stand as an index of development. Iran has seen an enormous growth in number of published papers in recent years, but in matter of quality it failed to step up with such growth. It is sneaky obvious that quality scientific papers would push forward science borders and conversely low quality research would render negative results and conclusions. One of the issues that jeopardize quality of scientific work is errors that can happen in every research. The researchers ought to be able to measure such errors and reduce it to as low as possible [1, 2].

There are different sorts of errors in medical research; disagreement, random, systematic and confounding error. This paper aims to provide a description and introduction to systematic errors that might happen in medical research. It is hoped that this could prompt researchers and reviewers to consider and control such errors in studies and papers more carefully and consequently improve the quality of scientific endeavors [3].

Systematic error that also is termed as bias can affect internal and external validity of studies. By definition, it is any systematic error in design, data gathering, analysis, interpretation and dissemination of results that finally leads to under-estimation or over-estimation of effects of a given exposure on a specific outcome. Against random error, systematic error has a featured direction and pattern [3-7]. There are different kinds of systematic errors in medical research that are not fully controllable or removable but awareness of such errors possibility can lead to more scrutinized reports and conclusions [3, 8, 9].

Systematic errors can be generally divided into two categories; selection bias and information bias [3, 4, 6, 8]. Selection bias happens when selected sample (whether patients, healthy people, have or have not an exposure) is not a representative sample of reference population. And information bias happens when gathered information about exposure, outcome or both is not correct and there was an error in measurement [3, 4, 7, 10]. Both biases would lead to an erroneous correlation, that is, a correlation that is not out there in reality but a researcher makes it up [6, 8].

In information bias, due to error in gathered data, a misclassification happens. This incorrect classification can be in two forms; differential and non-differential. In differential misclassification, against to non-differential one, there would be different rates of misclassification in various groups of study. It should be noted that these misclassifications take place only in analytic studies. Unlike random error, systematic error has nothing to do with sample size and increase or decrease in sample size does not affect systematic error [3, 4, 8].

Generally speaking, aim of any epidemiologic study is to estimate parameters as accurate as possible. Accuracy means that a given parameter ought to be estimated with lowest possible error (random and systematic errors). An estimate that has the lowest systematic error is termed "valid" and one that has the lowest random error is called "precise".

Validity of a study comprises two issues; validity and external validity (generalizability). Internal validity relates to reference population of a study and external validity to people beyond the reference population. Internal validity is a prerequisite to make possible generalizability. The most significant factors that put internal validity in danger are biases and confounders. In present paper we will shed light on biases (Table 1). It should be noted that such categorization is just for pedagogical and practical targets and it is possible to have some biases that share features of more categories and defy to be classified under a single name.

**Different types of selection bias**

**-Loss to follow up bias:** This error takes place in cohort studies when follow up cases are lost continuously. This is inevitable to have lost cases in cohort studies. This would consequently lead to selection bias in one hand and to decrease in sample size on the other [11]. Some believe that follow up of at least 80% of cases is acceptable to prove a study [12]. This error usually happens in three ways; missing completely at random, missing at random and missing not at random. In missing completely at random, the probability of keeping up with study has nothing to do with exposure, confounders and outcome. In missing at random, remaining in a study is not related to exposure and confounders but it is related to outcome. And finally, if the lost cases are inexplicable by available information and have a different pattern from follow up cases the missing not at random happens [13, 14].

**-Disease spectrum bias:** Diagnosis of a disease in clinical medicine is generally done by use of a test or a combination of tests or other diagnostic methods (like taking history of disease). This process begins right from entrance of a patient into a medical office [15]. There would be, depending to disease spectrum, different assessment of taken tests. If a patient is in sever stages of a given disease, diagnosis would be much easier and conversely if the patient is in mild stages the diagnosis would be more challenging and mostly wrong. To better put, being in a sever stage of a disease would render over-estimation of sensitivity [8]. Indeed, this sensitivity would be higher than its estimation in a sample of mild-stage patients.

**-Self-selection bias (Volunteer bias or Referral bias):** This bias emanates from the matter that those who participate in studies (screening or other health-related research) are not as sneaky same as the whole population and usually enjoy from better general health, care more about their health and abide better by health and medical advices [6, 8]. If being early diagnosed in a screening study, for example, does not count for better prognosis, detected patients who enjoy from higher health might have lower mortality than the respective population. In this case, the researcher may commit this bias and relate the observed effect to the screening program [6].

**-Participation bias (Non-response bias):** This happens when those participants who answer the study questions are different, in terms of outcome, from those who do not answer. It can lead to over or under-estimation of outcome [16]. This bias would result in dwindle of sample size and consequently lower accuracy in estimated parameters. In this case if not-answering is not related to variables, increase in sample size can offset the problem, but in contrary, if there is a relationship between not-answering and any included variable it can result in bias and consequently erroneous conclusion [17].

There are different options to lower this bias including using financial motivation or re-sending of questionnaires to participants. One of methods that are used frequently to estimate such a bias is to compare the participants who answered on-time with those who answered lately or after several re-sends [16, 18].

Although there are similarities between loss to follow up and participation biases the former specifically happens to longitudinal studies whereas participation bias can happen to any kind of study. They may converge in cohort studies but, however, not participation of individuals in non-longitudinal studies (e.g. cross-sectional studies) is termed "non-response bias". Accordingly, they are covered in separate parts in our paper.

**-Incidence-Prevalence bias (Survival bias, Neyman bias):** Selection of a case-group in case-control studies can be done from either prevalence or incidence cases [6, 19]. To select from incidence cases one has to wait for new incidents of a given disease to happen whereas in prevalence cases, due to pre-diagnosis, there would be an appropriate number of people in hand from the beginning and no need for waiting.

Despite this advantage of prevalence cases if there were a relationship between a risk factor and survival, the incidence rate would be more proper to determine the causing factors of a disease. Indeed, in a case that we choose from prevalence cases those who die shortly after disease onset could not be entered into study and only those who enjoy from better survival will participate. This would lead to detection of risk factors that are related to survival and not to disease development. The findings, consequently, cannot be generalized to all patients and only to alive ones. Furthermore, there are chance to face "recall bias" in prevalence-based studies; the incidence cases can better recall exposure conditions [6].

**-Exclusion or Attrition bias:** This kind of bias is a general term for a collection of potential biases that can happen when specific patients miss the study [20, 21]. The reasons for this miss can be of ineligibility, protocol violation, loss to follow up and early outcome. The ineligibility miss happens when due to lack of having inclusion criteria some patients are excluded off study. Protocol violation happens when a given patient, purposefully, wrongly or by a physician order, would not receive the allocated treatment intervention. And when a patient experience the outcome earlier than expected (in early stages of disease or shortly after study onset) the early outcome miss happens. In this case the presence of outcome cannot be attributed to intervention. Loss to follow up bias was completely explained in former sections [20].

**-Publication or Dissemination bias:** This bias that mostly occurs in review and meta-analysis studies springs from this matter that published papers in a given field are not a good and complete representative of all related studies. Various criteria play role in publication of a paper. Papers with significant results, precise design (high quality) and big sample size have higher chance to get published [8, 22, 23]. In review and meta-analysis studies also papers in either local or English language can be used that would not represent fully the whole published papers. This language-related bias is called "language bias" [22].

**-Citation bias:** Articles of high citation are easy to reach and have higher chance to be entered into a given study. Similar to publication bias it reduces from representativeness potentiality of review and meta-analysis studies [22].

**-Friend control bias:** If in a case-control study controls were chosen from the friendship circle of patients, correlation (similarity) between cases and controls (in terms of exposure) could lead to a biased estimation of relationship between exposure and outcome [22, 24]. Albeit, it should be noted that such a problem can also occur once controls are chosen from relatives, neighborhood and surroundings of cases. For instance, it can happen when controls are chosen based on cases' residency place and we will have, unconsciously, identical case and control groups in terms of health-care accessibility, socioeconomic, cultural and climatic status.

**-Compensating bias:** In case-control studies that there is a remarkable difference between cases and reference population (a biased selection of cases), there should be a mechanism to select relevant controls in a way that compensates for such a difference. To better put, when the magnitude of bias in selection of cases and controls is of same size an unbiased estimation of Odds Ratio (OR) would be reached. This phenomenon is known as compensating bias [25]. This matter is illustrated in following 4-type hypothetical example of a case-control study. When there is no confounding or bias effect the OR would equal 4(Table 2). In a case that only 50% of cases and controls are selected in an unbiased way, the OR again would equal 4 and is unbiased. Conversely, when a researcher goes through a biased selection of cases, the OR would amount to 6 that would be completely biased. In the last type when cases and controls are both selected in a biased way, exposure in both groups would be biased too and would lead to an unbiased OR. The latter type is, indeed, called compensating bias [7].

**-Berkson's bias:** This bias was first described in 1946 by Berkson for case-control studies. It is also known as "admission rate bias". It is, indeed, a hospital-based bias that leads to systematic difference of cases and controls. It occurs when combination of exposure and outcome results in a higher chance of hospitalization and consequently in higher exposure in cases comparing to controls. Generally speaking, this bias happen once cases and controls have different chance of hospitalization and this difference emanates from exposure.

This matter finally will show its effects on odds ratio estimation [22, 26, 27]. Berkson's bias falls under a more general phenomenon called collider bias. Collider is a variable that is influenced by both exposure and outcome and leads to a conditional (to collider variable) relationship between exposure and outcome. For instance, assume that there is an incomplete relationship between height and weight. Body Mass Index (BMI) is a variable that is affected by both mentioned variables. Having the BMI value and weight, the exact value of height is estimable. Therefore, by taking BMI into account the relationship between weight and height would be a complete relationship.

**Different Types of information bias**

**-Detection bias:** Detection bias arises when exposure takes effect on diagnosis. Once exposure is used as a criterion for detection of a given disease, "diagnostic suspicion bias" comes up. When exposure leads to symptoms that are helpful in diagnosis, "unmasking-detection signal-bias" happens. And if exposure results in benign conditions that resemble symptoms clinically, "mimicry bias" takes place [22].

If there were a herd of people that go under care for a specific reason, it would be much easier to obtain data from this herd than general public. This can result in a biased estimate of proportional hazard and OR between exposure and outcome that is called "follow up or medical surveillance bias". For instance, in a study that sets to reveal the relationship between depression and diabetes (a case-control study with diabetics and non-diabetics) depressed people are, due to a longer care, more likely to be diagnosed as diabetics [28].

**-Recall bias:** In retrospective studies that participants should remember and determine their past exposure, it is likely to have cases and controls that do not act similarly in this regard. To better put, because of more reflection on reasons of disease it is likely to have cases that do recall and cite better the detailed conditions of their exposure than controls [22, 28, 29]. This would lead to recall bias that mostly comes up in retrospective cohort studies [28] and case-controls [30-32]. Generally speaking, tools for measurement of exposure have their own particular sensitivity and specificity. Although it is ideal to have tools with highest possible sensitivity and specificity that prevent from biased information but in effect it is not the desired case. In analytical studies that exposure is a dichotomous variable and sensitivity and specificity is same in two groups of study (e.g. cases and controls), the value of correlation would be diluted. In other words, there would be a predictable path of change. This is exactly the non-differential misclassification. Conversely, if sensitivity and specificity of tool were different in two groups, differential misclassification would happen. In this case, the changes of correlation are not predictable.

**-Will-Rogers Phenomenon:** When outcome (for instance survival rate) of a given disease is under a long-run investigation, due to improvements in diagnostic procedures, it is possible to face a diagnosis that was not possible in the past or to face a stage of disease that is

now considered as an advanced level (a bad phase) while it was of early stages (a good phase) in the past.

This phenomenon is called "migration of disease stages". In survival studies, even if there is no improvement therapeutically, survival rate of patients would be better than the past in such cases. This bias, indeed, takes place when survival rate is measured either longitudinally or between two routes of diagnosis (old and new). Feinstein has termed it as Will-Rogers Phenomenon [6, 22, 33-36].

**-Lead Time bias:** Nowadays, higher survival rate of chronic diseases (especially cancers) is considered as an indicator of therapeutic achievements in these diseases. If a researcher were to compare the survival rate of a patient in two groups of screened and non-screened, they may commit lead time bias. Lead time is the time gap between diagnosis of a disease after onset of symptoms (onset of symptoms and visit to health care facilities) and diagnosis by screening tests. Not surprisingly, through screening tests a disease is diagnosed earlier. Being so, if a researcher sets to figure out effects of screening on patients' survival rate, even if earlier diagnosis has nothing to do with remission of disease, survival of screened patients will be higher than of non-screened ones and this is exactly due to lead time bias [6, 37, 38]. Figure 1 shows this concept schematically. As it illustrates, screening test leads to early diagnosis of patient (B patient) but this has no effect on time of death. In this case if a researcher were to compare survival rate (time from diagnosis to death) among screened and non-screened group, screened group would enjoy higher rate of survival.

**-Whish bias:** This bias is a reporting bias that subjects have to be held main responsible for it. When people are diagnosed with a certain kind of disease they try, to answer the question "why me", to find a way to deny their role in getting sick. They try, actually, to deny history of their exposure to risk factors (like smoking, high-risk sexual behavior and alcohol use) and relate mostly their disease to work-related risk factors. So, there is a bias in their report of exposure [6]. For instance, in investigation of routes of HIV infection transmission, patients typically try to attribute their disease to blood-products (and other non-sexual routes of transmission) and show much less willingness to report their history of sexual affairs. This bias was first proposed by Wynder et al. [39].

**-Interviewer/Observer bias:** Interviewer or observer knowledge about in-question hypothesis and disease or/and exposure can take effect on collection and registry of data. If this knowledge and awareness leads to a biased registry of data, in favor or in disfavor of hypothesis, interviewer or observer bias takes place [22, 40].

**-Imperfect standard bias:** We face this bias when reference standard test is not hundred-percent accurate (e.g. using pulmonary angiography to diagnose pulmonary embolism) or, due to cost or ethical issues, an alternative reference standard test is used for some patients [8].

**-Incorporation bias:** This bias occurs when researcher intends to find a diagnostic-test for a disease and that test itself is used as a reference standard for that disease or when diagnostic-test is used to find a reference standard test [8, 41, 42]. The main challenge of incorporation bias is that it would lead to over-estimation of accuracy of that given test. To put it in another way, in presence of this bias proportion of accurate results of a given test will increase unexpectedly and it will lead to higher estimates of test characteristics (e.g. sensitivity and specificity) [42, 43].

**-Verification and work-up bias:** This error, which is amply found in diagnostic-test assessments, comes up when all subjects in a bid to determine validity of a diagnostic-test are not, due to various reasons, being tested by a reference standard test. Verification and work-up biases are interchangeably used in most of studies whereas work-up bias is a certain kind of verification bias [44, 45]. When result of primary test (e.g. negative or positive result) determines the possibility of undergoing a reference standard test work-up bias occurs [46].

In addition to above-mentioned biases, there are some other phenomena that although are not classified as classic errors but distract the findings from reality. Number of these phenomena is as follows:

**-Hawthorn effect:** During a study course it is likely to have variable of exposure tweaked. One of the reasons for such a change can be of research itself. In some occasions presence of researchers can result in sways in participants' behavior; this phenomenon is known as Hawthorn effect. To figure out the reasons of reduction in Western Electric Company products Hawthorn set out to study activity-time of company's workers. Some days after onset of study and in absence of any intervention there was an unexpected increase in company's products. Hawthorn learnt that the reason for this was the fact that awareness of being observed by researchers had made workers to better do duties and jobs. Since then the change in behavior of subjects in a study that comes from study itself is called Hawthorn effect [22, 24, 47].

**-Ecological fallacy:** Ecological study is an investigation in which unit of analysis is a group of people rather than an individual. In most of cases this group is a geographical region like a country, state, province, census blocks etc. As available data is normally used in ecological studies they are not resource and time-consuming. Mean estimates are used in these studies to find any relation between variables and no surprisingly any likely observed relationship would be at group-level not at individual-level. Being so, if one jeopardizes to generalize the observed relationship to individual level the ecological fallacy is committed [48, 49].

For instance, assume that a study aims to reveal association between sugar per-capita consumption and cardiovascular diseases in a group of populations and it finds that cardiovascular diseases occur more in populations that have high sugar per-capita consumption. This finding is, as we put before, at group-level and any individual-directed generalization intention would be of

ecological fallacy; patients may have different pattern of sugar consumption than whole population and have lower consumption than population mean.

**Table 1.** Introduction to and classification of common biases in medical research

| Type of bias | | | Short definition |
|---|---|---|---|
| Selection bias | Empty sample bias | Loss to follow up bias | This error takes place in cohort studies when follow-up cases are lost continuously. |
| | | Non-response bias | This happens when those participants who answer the study questions are different, in terms of outcome, from those who do not answer. |
| | Sampling bias | Exclusion bias | This kind of bias is a general term for a collection of potential biases that can happen when a specific patient miss the study. |
| | | Disease spectrum bias | Effects of disease spectrum (stages) on diagnosis and consequently on estimates of test characteristics (e.g. sensitivity and specificity) |
| | | Volunteer or Referral bias | This bias emanates from the matter that those who participate in studies (screening or other health-related research) are not as sneaky same as the whole population and usually enjoy from better general health. In this case, the researcher may commit this bias and relate the observed effect to the screening program. |
| | | Incidence-Prevalence bias | Selection of cases in case-control studies can be either done from prevalence or incidence cases. In a case that they are chosen from prevalence the sample will not make a representative sample of reference society. This would lead to detection of risk factors that are related to survival and not to disease development. In result, the findings cannot be generalized to all patients and rather only to alive ones. |
| | | Publication or bias | This bias that mostly occurs in review and meta-analysis studies comes from this matter that published papers in a given field are not a good and complete representative of all related studies. |
| | | Citation bias | Articles of high citation are easy to reach and have more chance to be entered into review or meta-analysis studies. |
| | | Friend control bias | This may lead to unintended matching of some other variables in cases and controls that can lead to a biased estimate of correlation between exposure and outcome. |
| | | Compensating bias | When the magnitude of bias in selection of cases and controls is of a same size, an unbiased estimation of Odds Ratio (OR) would be reached. This phenomenon is known as compensating bias |
| | | Berkson's bias | It is a hospital-based bias that leads to systematic difference of cases and controls. It occurs when combination of exposure and outcome results in a higher chance of hospitalization and consequently in higher exposure in cases comparing with controls. |
| Information bias | Information bias | Recall bias | In retrospective studies that participants should remember and determine their past exposure, it is likely to have cases and controls that do not act similarly in this regard. To better put, because of more reflection on reasons of disease it is likely to have cases that do recall and cite better the detailed conditions of their exposure than controls. This would lead to recall bias that mostly comes up in retrospective cohort studies and case-controls. |
| | | Wish bias | This happens when patients try to deny history of their exposure to risk factors and mostly relate their disease to job-related risk factors. |
| | Tool bias | Detection bias | Detection bias arises when exposure takes effect on diagnosis. |
| | | Will-Rogers Phenomenon | Due to improvements in diagnostic procedures, it is possible to have misestimated survival rates over the course of time or between two methods of diagnosis (old and new). |
| | | Lead time bias | If a researcher were to compare effects of a screening program on survival rate, even if earlier diagnosis has nothing to do with disease remission, survival of screened patients will be higher than of non-screened ones and this is exactly due to lead time bias |
| | | Imperfect standard bias | We face this bias when reference standard test is not hundred-percent accurate. |
| | Data-collector bias | Incorporation bias | This bias occurs when a researcher intends to find a diagnostic-test for a disease and that test itself is used as a reference standard for that disease or when diagnostic-test is used to find a reference standard test. |
| | | Verification bias | This error, which is amply found in diagnostic-test assessments, comes up when all subjects in a bid to determine validity of a diagnostic-test are not, due to various reasons, being tested by a reference standard test to make a conclusive diagnosis. |
| | | Interviewer/Observer bias | Interviewer or observer knowledge about in-question hypothesis and disease or/and exposure can take effect on collection and registry of data. If this knowledge and awareness leads to a biased registry of data, in favor or in disfavor of hypothesis, interviewer or observer bias takes place. |

**Table 2.** An example of compensating bias

| 1st Status | Case | Control | 2nd Status | Case | Control |
|---|---|---|---|---|---|
| Exposed | 500 | 1800 | Exposed | 250 | 180 |
| Unexposed | 500 | 720 | Unexposed | 250 | 720 |
| Odds of Exposure | 1 | 0.25 | Odds of Exposure | 1 | 0.25 |
| Odds Ratio (unbiased) =4 | | | Odds Ratio (unbiased) =4 | | |
| All of cases and control | | | 50% of cases and 10% of controls | | |
| 3rd Status | Case | Control | 4th Status | Case | Control |
| Exposed | 300 | 180 | Exposed | 300 | 245 |
| Unexposed | 200 | 720 | Unexposed | 200 | 655 |
| Odds of Exposure | 1.5 | 0.25 | Odds of Exposure | 1.5 | 0.36 |
| Odds Ratio (biased) =6 | | | Odds Ratio (unbiased) =4 | | |
| 50% of cases (biased)and 10% of controls(unbiased) | | | 50% of cases (biased)and 10% of controls(biased) | | |

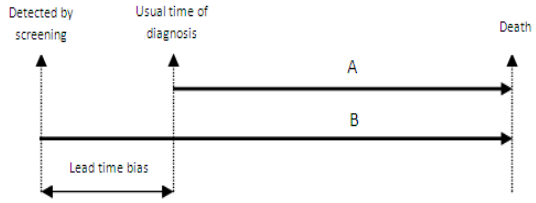


**Figure 1.** Lead time bias**;** the systematic error of apparent increased survival from detecting disease in an early stage

## Discussion

No study is immune to systematic errors (biases) and it is likely to have such errors in different stages of a study. These errors would diminish by increase in sample size. They can be either due to biased selection of individual or use of irrelevant tool or method for data collection that would throw internal and external validity (generalizability) of a study into question. Not all of these errors are completely eradicable or controllable but knowledge on their presence in a study can lead to more scrutinized and accurate report of findings and conclusion.

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All authors had equal role in manuscript writing.

### Conflict of Interest

The authors declare no conflict of interest.

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