Understanding Research

Sources of Error in Clinical Research

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Clinical research is often based on the demonstration or observation of an 'association' between two variables. There may be an association between cause and effect to suggest causal inference, between therapy and outcome to suggest beneficial effect and between clinical features and outcome to suggest prognostic significance. However, before we allow ourselves to be led by the results of the study, the evidence for the association should be examined very carefully for sources of error that can so easily creep into clinical research and make the conclusions invalid. The three main forms of error are bias, confounding and chance. Once these errors are ruled out or minimized, one can conclude that the association was a true one.

Bias

This is a form of systematic error which can creep into a study at any stage of its design, measurement or analysis. It leads to a difference between what the, study is intended to estimate and what is actually being estimated. Bias causes a systematic deviation from the truth and may produce a spurious association. Bias threatens the validity of the study, *i.e.,* the conclusions drawn either on the study subjects themselves (internal validity) or generalized to the target population (external validity) may not be valid(l). Clinical observations are particularly prone to bias because so many human factors come into play. Of the various study designs, case control design is very prone to bias and the randomized controlled studies are less so (2). All forms of bias need to be carefully considered in the design phase and little remedy is available once the study has been conducted. Many types of bias have been described which fall into two main groups:

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1. Selection Bias

This occurs when the sample being studied is somehow different from the population to which the results will be applied (target population). Selection bias often occurs in hospital based studies in which the hospitalized cases will exclude those who died before admission because of a very acute course or those who are not sick enough, lived too far away or could not afford hospital costs. For example, a certain disease may seem more common in boys simply because people seek medical help more easily for boys than for girls. 'Berkson bias' is a form of selection-bias occurring in hospital based studies because of unequal rates of hospital admission in exposed and non-exposed. Examples of selection bias that can occur in the community setting (when subjects are workers in a factory or industry) include the 'healthy worker effect' which means that despite exposure to a risk factor, the observed frequency of disease may be

lower in this study population since diseased persons have been potentially excluded(3).

Similarly, volunteers for a study may be those who are either more health conscious or fit or unfit *(volunteer bias).* This problem can occur especially in population surveys. Another type of selection bias is prevalence-incidence or Neyman's bias in which prevalent cases are chosen for study rather than incident cases. A classic example is the study of risk factors for coronary artery disease. If one takes a 'prevalent' group, one might arrive at aspirin intake as a risk factor and smoking/lack of exercise may come out as protective as the individual may have modified his habits after knowing that he/she has coronary artery disease.

2. Measurement Bias

The second category of bias is measurement bias or misclassification bias. Interviewer bias arises when the person eliciting the history of exposure preferentially probes those subjects who have the disease. Recall bias occurs because the person affected with the disease in question may try to recall more intensely about exposure than persons not affected. Thus, if one was studying exposure to drugs/viruses in mothers of babies with a congenital defect, it is likely that mothers of affected babies would recall such exposure more often simply because they had been going over and over it again in their minds, unlike control mothers. Diagnostic suspicion bias occurs when exposed persons are investigated more intensely for development of disease than non-exposed. Differential follow up bias occurs when persons known to be exposed are followed up preferentially to non-exposed.

As already stated, bias must be eliminated at the design/planning stage of the study itself. To minimize bias, the investigator, when planning the study writes down the research question and study plan side by side and carefully consider as the following questions (4): *(i)* Are the study subjects actually representative of the target population; *(ii)* Does the measurement of the study factor/exposure variable accurately represent the exposure variable of interest?; and *(iii)* Does the measurement of the outcome variable actually represent the outcome variable of interest? For example, if one wanted to study the relationship between birth asphyxia and cerebral palsy, we would compare the two limbs of *Table I.* Interviewer bias and diagnostic suspicion bias may be minimized by appropriate blinding. Recall bias may be minimized by dummy questions and verification of records or taking a control group which is also affected but with an unrelated outcome.

Confounding

Another explanation for a 'spurious' association being found in a research study is confounding. A confounder is a variable which is associated with both the cause and outcome variable and distorts the relationship between the two. For example, when studying the relationship between coffee drinking and myocardial infarction, smoking is a confounder to consider, as it may be associated with coffee drinking (people who smoke are also more likely to drink coffee) as well as myocardial infarction. Again, in studying the relationship between birth asphyxia and

TABLE I-*Comparison of 2 Limbs.*

Actual truth	Study
Target population-all babies	Study population-babies born in hospital
Exposure-actual birth asphyxia	Apgar score as recorded
Outcome-actual cerebral palsy	Neurological deficit in the infant on follow up

cerebral palsy, birth weight may be an important con-founder as low birth weight may be independently associated with both asphyxia at birth and occurrence of cerebral palsy.

Strategies to cope with confounding require that the investigator be aware of and measure them. Thus, during the design phase itself, the investigator must make a list of variables that may be associated with the predictor variable of interest and the outcome variable. He should record the presence/absence or magnitude of the con-founder in the study subjects and include suitably matched controls so that compari-son is made between cases and controls with the same level of the confounder *(matching).* In the example of birth asphyxia and cerebral palsy one could include cases and controls in different categories of birth weight. Another technique to deal with confounding in the design phase is to 'specify' the subjects to a particular value of the confounder variable and exclude everyone with a different value *(specification).* For example, one could restrict the study to normal birth weight babies, or babies with birth weight more than 1500 g. In the analysis stage, it is possible to deal with con-founders by stratification and adjustment. In *stratification,* the subjects and controls are divided into 'strata' for different values of the confounder and comparisons are made within these groups or strata. In the examples given above, consideration of smokers and nonsmokers separately can remove the confounding effect of smoking, and break up of the babies into groups according to birth weight can remove the confounding effect of birth weight. The last available technique for controlling for confounding is that of statistical *adjustment,* which models the associations among variables in order to separate the effect of the confounder. Multivariable analysis software are available which take care of several confounders simultaneously. However, unknown confounders may exist and the only way to minimize their effect is by experimental design and randomization (2,4).

The Role of Chance

In research, observations are necessarily made on a sample of subjects rather than the whole population or even all patients with the disease in question. Observations made from a sample may, however, misinterpret the truth as it may be a chance finding or a 'random variation'. Imagine that 10% of the entire population of cerebral palsied children had birth asphyxia. If we were to select a random sample of 20 children with cerebral palsy, by chance alone it is possible that we get 5 (25%) who had birth asphyxia. Thus a stronger association between cerebral palsy and birth asphyxia may be observed than actually exists. Such an error due to chance is called random error. Chance operates in every step of the study. The variation due to chance can deflect the observed value on both sides of the true 'population' value. If many samples are taken, their mean value tends to correspond more closely to the true population mean than the individual observations. Thus strategies to deal with such error in the design phase is to increase sample size and in the analysis phase is to test the statistical significance of the association by appropriate statistical tests/which calculate the probability that the results could occur by chance alone. The x^2 test is used for categorical variables and 't' test ANOVA and regression for continuous variables. The 'p' value obtained is a composite measure reflecting both the magnitude of the difference and sample size. Even a small difference may be significant if the sample size is large and a large difference may not achieve statistical significance if the sample size is too small. Another more informative measure of

significance is the confidence interval. Usually 95% confidence interval is used. This gives the probability with 95% confidence that the true population value lies within a particular interval around the observed (sample) value. If the confidence interval for a measure of association such as relative risk or odds ratio includes 1, it usually means that it is not a statistically significant association. However, a statistically significant result does not mean that it cannot be due to chance, just that it is unlikely to be due to chance; while a statistically insignificant result does not mean that it is due to chance, rather it is not unlikely enough to be due to chance (l).

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NOTES AND NEWS

ORDER OF SACRED TREASURE AWARD

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