

EPIDEMIOLOGY: CLINICAL VERSUS STATISTICAL SIGNIFICANCE



BASICS

OVERVIEW

- Understanding how clinical significance and statistical significance inform each other is important to interpreting scientific studies.
- Study design, more than statistical analyses, is the most important factor in whether study results are clinically significant. Study design is informed by subject-area knowledge as well as statistical knowledge.
- Clinical significance must be interpreted based on whether the study explores association or causation. This depends on the study design.

CLINICAL VS. STATISTICAL SIGNIFICANCE

What is clinical significance?

- Decision about whether an intervention/risk factor is enough to alter an existing practice.
- Clinical significance is informed by many types of evidence, including clinical experience, established scientific knowledge and ongoing scientific research. This body of information is called “subject-area knowledge”.
- Formal statements about clinical significance are made based on evidence produced from studies that are both scientifically and statistically rigorous and take into account subject-area knowledge.

What is statistical significance?

- Decision about the significance of an intervention/risk factor resulting from statistical analyses of clinical observations and/or results from scientific investigations.
- Establishing statistical significance helps answer questions about clinical significance.
- While a statistical analysis can stand alone, no interpretations of statistical analyses should be made without consideration of clinical experience obtained through clinical practice and results from other scientific investigations. That is, no interpretation of statistical analyses is complete without appropriate consideration of subject-area knowledge.
- The two most common measures of statistical significance are p-values and confidence intervals.

Clinical significance and statistical significance inform each other

- Often, the same evidence must be considered when making statements about the clinical significance or statistical significance of a risk factor and its effect on disease. The most rigorous statements about clinical and statistical significance incorporate clinical experience, scientific knowledge and statistical investigation.

- Hypotheses regarding clinical significance may be informed by subject-area knowledge. However, without a study (and a subsequent statistical analysis) designed to confirm the phenomenon of interest, these statements ultimately remain hypotheses. Similarly, statements about statistical significance are produced from statistical analyses of data collected via clinical observations or scientific studies. However, such statements are rarely complete without consideration of subject-area knowledge. Without confirmation by subject-area knowledge, these statements ultimately remain hypotheses as well.

Study design

- A study is only as good as its design. Statistical analyses of data from poorly designed studies can lead to spurious findings that may erroneously corroborate or negate hypotheses about clinical significance. Always consider study design when assessing statements about statistical and clinical significance.
- Study designs are optimized via consideration of subject-area knowledge as well as statistical knowledge. The study question guides how the study will be designed, what data to collect and how the data will be analyzed. Subject-area knowledge can inform the investigator of potential biases and errors that may be introduced into the study. Statistical knowledge of the effects of these biases and errors will allow the investigator to anticipate what other information to collect and what data analyses need to be performed to minimize the effects of the biases and errors.
- There are many types of study designs. But most study designs can be categorized into two groups: observational and experimental.
- Observational studies compare populations of animals with exposure to a risk factor against populations of animals without exposure to a risk factor. The investigator is often trying to demonstrate that patients with exposure to the risk factor are more likely to develop disease than patients that are not exposed to the risk factor. The investigator neither assigns risk factors nor assigns the quantity of exposure to risk factors to individuals of the study population. Instead, the investigator must find individuals within the population that have exposure to the risk factor. Such studies can be complicated if the risk factor is rare and individuals with exposure cannot be found. Similarly, diseases that are rare may also complicate such studies as finding diseased individuals becomes difficult.
- In experimental studies, the investigator assigns risk factors to specific individuals of the study population. Thus, the investigator decides which animals receive an exposure and the amount of exposure. These individuals are followed through time to measure and record disease occurrence. These individuals are then compared to a population of individuals without the exposure (control group) to determine whether disease occurrence is different between the group that received exposure to the risk factor and the group that did not.
- Experimental studies require a study population that is naïve to the risk factor and disease of interest so that the investigator can assign risk factors to specific individuals in the study population and follow them through time to assess disease occurrence. The control over exposure exercised by the investigator and the follow-up through time allow for strong arguments of causation (e.g. the risk factor causes disease). However, given the stringent requirements of the study population and the need to follow the study population through time, experimental studies can be very costly. Experimental studies also carry a host of ethical responsibilities.
- Observational studies may be less costly and carry fewer ethical implications than experimental studies. However, due to a lack of investigator control over exposure to risk factors, causality can rarely be assessed from an observational study. Observational studies are most useful for examining associations between risk factors and disease.

Study validity

- Investigators conduct studies to gain information about a target population (e.g. U.S. feedlot cattle). The investigator may not have access to the entire target population, and must thus limit the study to a smaller population that is believed to be representative of the target population (e.g. feedlot cattle from certain states). This is called the source population. Individuals are selected from the source population to enter the study. This collection of individuals is called the study population.
- A study with results that accurately reflects the source population is said to be internally valid. A study with results that can be generalized to the target population is said to be externally valid. Internal validity and external validity depend more on study design than on statistical analyses.
- Study validity is crucial to understanding whether study results can support statements about clinical significance. A study may be internally valid and reflect the source population well, but may lack external validity. In this case, statements about clinical significance can only apply to the source population. On the other hand, with a study that is both internally and externally valid, statements about clinical significance can apply, not only, to the source population but also the target population.

Association and causation

- Associations between risk factors and disease are often examined through the use of scientific studies. Causation is a very specific type of association, and implies that a risk factor causes disease. Establishing causation is often the goal of every investigator, but is very difficult to achieve (often requiring an experimental study). While experimental studies provide the strongest argument for causation, experimental studies can still fall short if not all biases and errors are considered. Funding/resources, available data and ethical concerns are all limiting factors in performing experimental studies that would otherwise provide strong evidence for causation.
- Investigators often utilize observational studies to establish an association between risk factors/interventions and disease. While evidence for association is not as strong as evidence for causation, associations are, nonetheless, vital pieces of data in individual and herd management decisions. Establishing association between a risk factor and a disease is an important step to determining causation. That is, if there is no association, then there is no causation.
- Statements about clinical and statistical significance must always consider whether the results from the scientific study address association or causation. Understanding the study design can shed light on this important distinction. A study may provide evidence for association between a risk factor and disease. Subsequent management decisions, based on this study, that reduce the introduction of a risk factor into a herd may be effective. However, it is important to realize that the actual cause of disease has not been eliminated.



MISCELLANEOUS

Suggested Reading

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