

EPIDEMIOLOGIC STUDY DESIGNS



BASICS

OVERVIEW

- The very nature of medical—and hence scientific—research mandates that studies be expressly designed around a central premise: validity. This implies that regardless of the study design employed, any inferential statistical measures derived from observed data should aim to unbiasedly estimate the unknown underlying parameters.
- Proper design helps minimize bias by removing the following sources of systematic error:
 - Errors of comparability: the invalid use of comparison groups that are inherently noncomparable with respect to their baseline incidence of the study outcome, leading to confounding bias
 - Errors of selection: the selection of controls (typically in a case-control study) that violates fundamental principles of valid design, leading to selection bias
 - Errors of follow-up: the unequal follow-up of individuals in different study groups, where the reasons for unequal follow-up are related to the study outcome, leading to censoring bias
 - Errors of information: the collection of measurement data, including study factors and/or outcomes, that are flawed, leading to information bias

CHARACTERISTICS OF EPIDEMIOLOGICAL STUDIES

- A valid study does not necessarily imply that it is a precise one. Precision—the estimation of a parameter by a statistic with low variability—is achievable not only through proper design, but also by having as large a sample size as possible.
- The elucidation of a cause-and-effect relationship is a goal that transcends study design, whether experimental or nonexperimental (observational). Statistical analysis is an important adjunct in deciding whether an association is spurious or causal, but cannot itself determine causation. Similarly, probability values (often referred to as “P-values”) are not verifications or falsifications of the null or alternate hypotheses conventionally used in hypothesis testing, but rather provide a quantifiable level of compatibility between data under a specific statistical model (such as a binomial, normal, or Poisson) and the null hypothesis.
- Nonidentifiability of individual-level causal effects precludes making causal inferences on individual subjects. Instead, studies of individuals in populations allow the estimation of average causal effects under the assumption of the absence of systematic errors. This implies that the incidence of the outcome—typically disease—in the comparison (unexposed, untreated) group should unbiasedly estimate what the incidence of disease in the index (exposed, treated) group would have been had exposure/treatment been counterfactually removed or blocked. This duality of outcomes – one observable, one not observable – is called the “potential outcomes model of causation.” The assumption of comparability is reasonable in larger randomized experiments, but is unlikely to be fulfilled in nonexperimental studies, even within strata of controlled variables.
- The following are the most commonly encountered study designs in medical research. They share the characteristics and detractors described above, with the caveat that each has unique features that may contribute to or detract from the potential outcomes causal paradigm.

EXPERIMENTAL STUDIES

The defining characteristic of an experiment is that the intervention (a treatment or exposure) is under the deliberate control of the experimental researcher. The study subject(s) have no control over their allocation.

Randomized Clinical Trials

- Randomized clinical trials are studies in which individuals are randomly allocated to 1 of 2 or more mutually exclusive treatments (including possibly a control/placebo) groups.
- Randomization is the process of random allocation; it is designed so that any group's outcome response under non-treatment (either observable or hypothetical) is statistically independent of treatment allocation.
- Making sample sizes as large as possible can minimize confounding in randomized studies. While confounding may remain problematic in small randomized studies, the possibility of chance confounding greatly diminishes as sample size increases.
- Randomized clinical studies are predominantly used to evaluate treatments among individuals who already have a disease, although they could also be used to assess preventive therapies in healthy subjects.
- Validity of randomized clinical trials is enhanced by masking treatment allocation to study investigators and owners of animal patients, and by assuring minimal censoring prior to the end of a study.
- Such studies can be used to estimate absolute and ratio measures of effect, as well as survival function estimation.

Crossover Studies

- Crossover studies are specialized clinical trials in which there is often only 1 group of study subjects, rather than 2 or more.
- Subjects receive all possible treatment or control allocations in a predetermined sequence by “crossing over” from one allocation to another.
- It is common to allow a “wash out” period between allocations to avoid residual effects of prior allocations so that order of allocation cannot be an explanation of study findings, and to assume that there is no secular effect on the study outcome so that time cannot as well be an explanation of study findings.
- This design controls for confounding by individual-level characteristics (such as genetic propensity) that are time-invariant, affording an advantage that is not found in randomized clinical trials.

Field Trials

- Field trials are often larger in scope than clinical trials, and are typically done to evaluate disease prevention programs in healthy populations.
- Examples of field trials include those evaluating the effects of factors such as vaccination, water fluoridation, and nutritional supplementation on the health of a population.

NONEXPERIMENTAL STUDIES

The hallmark of nonexperimental (observational) studies is that exposure is no longer under the control of the investigator, but instead is self-selected (or selected by proxy by an animal's owner). The very reasons that individuals or their proxies select their exposures may be confounders that are difficult to enumerate and hence control, so nonexperimental studies lack the advantage of a randomized clinical trial in managing confounding.

Ecologic Studies

- Ecologic studies are performed on groups of individuals using population-level characteristics, rather than measurements on the individuals within them.
- Group-level data—both exposure measurements and outcome measurements—are collected, effectively making the group, rather than the individual, the unit of observation.
- These studies suffer from the ecologic fallacy: there is no way to link exposure to outcome in individuals, and hence causal inferences are tenuous. For example, although one may find that exposure and disease are relatively common in a group, that does not necessarily imply that the exposed individuals developed disease, or that the nonexposed individuals remained disease-free.

Cohort Studies

- Cohort studies involve the longitudinal comparison of a minimum of 2 exposure groups.
- The premise of a cohort study mimics that of a clinical trial: the unexposed or reference sub-cohort is intended to provide a measure of what the incidence of disease in the exposed sub-cohort would have been had exposure been removed or blocked.
- Individuals at risk of an outcome are followed forward through time, with disease incidence (incidence proportion or incidence rate) measured. Differential incidences in the exposure groups provide evidence, but not proof, of a causal relationship under the assumption of no systematic sources of error.
- Studies of patient outcomes that evaluate time-to-event data (e.g., survival analysis) are special forms of cohort studies conducted on medical or hospital patients. Outcomes often include one or more of the following: remission, recovery, and death.
- Common effect measures that can be calculated include incidence proportion differences and ratios, and incidence rate (incidence density or hazard rate) differences and ratios.
- Cohort studies can be retrospective, prospective, or ambispective (which include both retrospective and prospective elements).

Case-control Studies

- Unlike cohort studies, in which a cohort or at least 2 subcohorts at risk are sampled and followed in time, case-control studies involve sampling incident cases that have experienced an outcome and controls who have not experienced the outcome at the time of selection.
- Controls are either a random or deliberate sample of the population at risk—the source population of cases. Regardless of what controls are sampled, there are 2 overriding principles that must be met in control selection to avoid selection bias:
 - If controls were to develop the disease in question, they would be captured as cases and included in the study.
 - Reasons for control selection must be statistically independent of exposure(s) unless matching on confounders is employed.
- Case-control studies are effectively cost/size efficient cohort studies distinguished by the sampling of the population at risk instead of studying it in its entirety.
- There are 3 principle ways to select controls
 - Case-cohort sampling: Controls are selected from the population at risk at the beginning of the time period of case occurrence. The odds ratio estimates the incidence proportion ratio without the need for the rare disease (incidence <5%) assumption, and can also estimate the incidence rate ratio under certain conditions.
 - Cumulative incidence sampling: Controls are selected from the population at risk at the end of the time period of case occurrence. The odds ratio estimates the incidence proportion ratio under the requirement of the rare disease assumption.

- Incidence density sampling: Controls are selected from the population at risk throughout the period of case ascertainment. If the effect of exposure is constant over time, and time is not a confounder (meaning that the distribution of exposure remains stable over time), the odds ratio unbiasedly estimates the incidence rate ratio, and under the rare disease assumption estimates the incidence proportion ratio. If the effect of exposure is constant over time, if time is a confounder, and controls are selected at the same time that cases occur, the odds ratio from a matched analysis will unbiasedly estimate the incidence rate ratio.

Case-crossover Studies

- Case-crossover studies are observational study analogs of the experimental crossover studies. Study individuals have all experienced the outcome of interest; there are no control or comparison subjects, so this is an example of a “case-only” study.
- There are two major kind of case-crossover studies: those studying exposures only prior to the outcome event (case-crossover studies with case-control logic) and those studying exposures before and after the outcome event (case-crossover studies with cohort logic).
- A feature of case-crossover studies, like crossover studies, is that they are valuable for studying episodic exposures that have short induction and transient effect periods for rare events. If an exposure alters risk in individuals, one can postulate the presence of a brief induction period where risk remains unaltered, followed by multiple time intervals with different levels of altered risk, followed by a return to baseline risk. The time interval when exposure leads to increased or decreased risk following exposure is referred to as the “effect period.” The duration of such an effect period may be unknown, but can be inferred from prior knowledge (e.g., properties of a pharmacologic or environmental agent, duration of hormonal changes following exercise, period of immune dyscrasia following vaccination, chemical half-life, pathogen incubation times following infection, etc.).
- An individual’s actual exposures that are hypothesized to exert a transient effect (the “effect period”) on outcome occurrence are measured over time, and related to the time that the outcome occurred. The premise is that if exposure is causal, the outcome will be more likely to occur within a defined effect period after exposure than outside this effect period.
- Case-crossover studies are therefore best adapted to studying exposures that have a relatively transient duration of effect, and that can recur on an episodic or predictable basis.
- Such studies have been used to evaluate the effects of medications, exercise, vaccinations, and other factors in which individuals cycle in and out of periods of effect and non-effect.
- Odds ratios from case-crossover studies may estimate the incidence rate ratio without the requirement of the rare disease assumption.



MISCELLANEOUS

EPIDEMIOLOGY RESOURCES

- Ahrens, W., Pigeot, I. 2014. Handbook of Epidemiology. 2nd Edition. New York: Springer Reference.
- Kelsey, J.L, Whittemore, A.S, Evans, A.S, Thompson, W. D. 1996. Methods in Observational Epidemiology. 2nd Edition. New York: Oxford University Press.
- Miettinen, O.S. 1985. Theoretical Epidemiology: Principles of Occurrence Research in Medicine. New York: John Wiley & Sons.
- Rothman, K.J., Greenland, S., Lash T.L. 2008. Modern Epidemiology. 3rd Edition. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

- Schlesselman, J.J. 1982. Case-Control Studies: Design, Conduct, Analysis. New York: Oxford University Press.

SEE ALSO

Epidemiology: Risk Analysis (www.fiveminutevet.com/ruminant)

Epidemiology: Systematic Approach to Disease Outbreak Investigations (www.fiveminutevet.com/ruminant)

Epidemiology: Informatics (www.five.minutevet.com/ruminant)

Suggested Reading

Curtis, C.R., Erb, H.N., Kranz, J.M. 1987. An introduction to the use of epidemiologic research methods in dairy science. *J Dairy Sci.* Feb; 70(2):373–80.

Freudenheim, J.L. 1999. Study design and hypothesis testing: issues in the evaluation of evidence from research in nutritional epidemiology. *Am J Clin Nutr.* Jun; 69(6):1315S–1321S.

Potter, J.D. 1997. Logistics and design issues in the use of biological samples in observational epidemiology. *IARC Sci Publ.* (142):31–7.

Rushton, L. 2000. Reporting of occupational and environmental research: use and misuse of statistical and epidemiological methods. *Occup Environ Med.* Jan; 57(1):1–9.

Szczech, L.A., Coladonato, J.A., Owen, W.F. Jr. 2002. Study designs and their potential influence on conclusions. *Semin Dial.* May-Jun; 15(3):207–11.

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