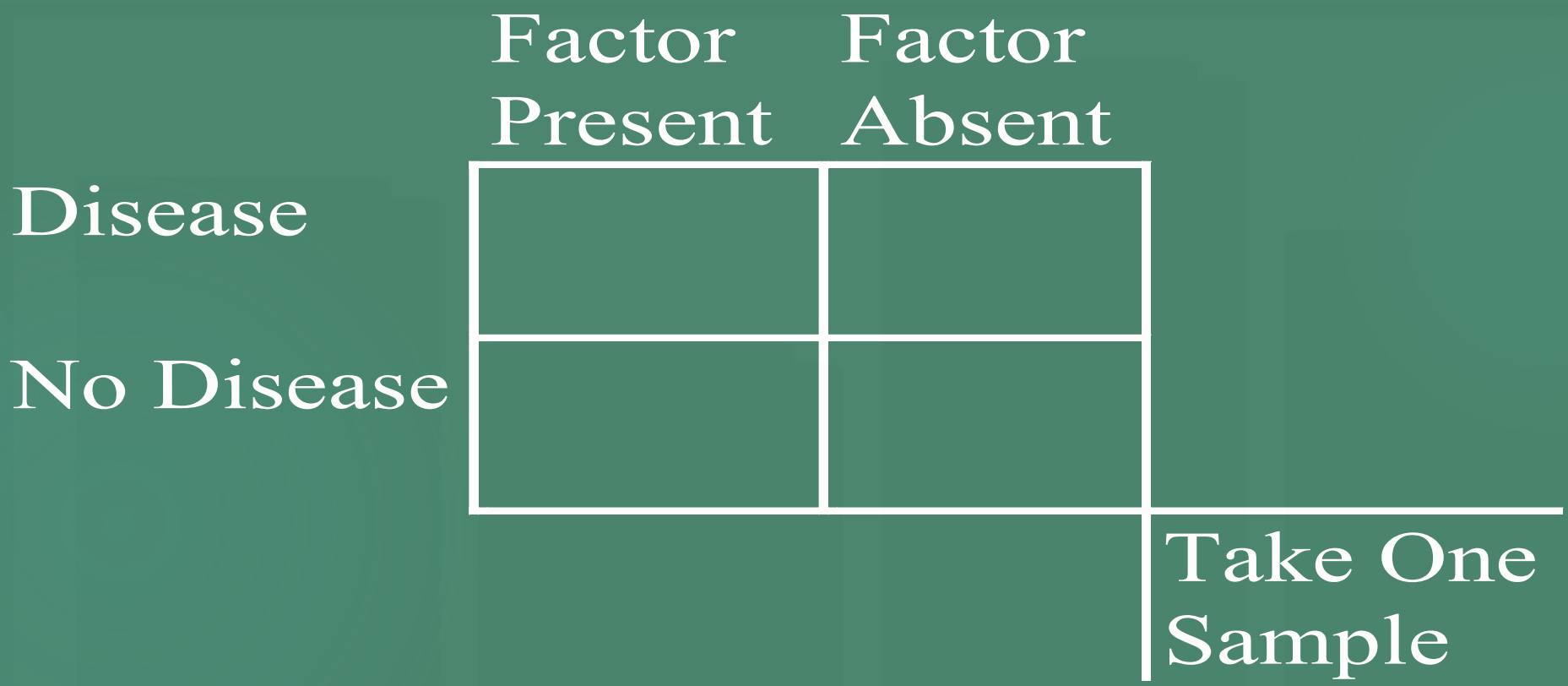
STUDY DESIGNS

IN BIOMEDICAL RESEARCH

NUTS & BOLTS OF BASIC DESIGNS

Cross-Sectional Designs



In a cross sectional study, investigators draw a sample, randomly, from the population, then make all measurements for all variables on a single occasion- or within a very short period of time – without a follow up. They study distributions the variables within that sample; sometimes designating predictor and outcome variables based on “biological plausibility”, then correlating one to the other.

Example:

In the National Health and Nutrition Examination Survey (NHANES), a sample designed to represent the U.S. population is interviewed and examined. These surveys have been carried out periodically and all data are available for public use. They make up a major source of information about the health and the habits of the U.S. population; one could obtain estimates such as prevalence of smoking or a disease.

In addition to studying distributions and obtaining parameter estimates, cross-sectional studies can also be used for examining associations. For examples, a cross-sectional finding in NHANES III is an association between childhood obesity and hours watching television. The choice of which variables to label as predictors and which as outcomes depends on the cause-and-effect hypotheses of the investigator rather than on the study design.

Serial Surveys:

These form a special case. A series of cross-sectional studies of a single population observed at several points in time – the case of those NHANES – is sometimes used to draw (informal) inferences about changing patterns of population characteristics over time.

Strengths:

A major strength of cross-sectional studies is that there is no waiting time for the outcome to occur, and no loss to follow-up. This makes them fast and inexpensive. And the obvious strength of their sizes. A cross-sectional study, because of its low cost, could be included as the first step in a cohort study or an experiment.

Weaknesses:

The major weakness of cross-sectional studies is the difficulty of establishing causal relationships from "observational" data collected in a cross-sectional time frame.

Cross-sectional studies are also "impractical" for the study of rare diseases if the sample was collected from the general population; we might need 10,000 subjects or more to find just one case of a rare disease. What would happen to statistical power?

CASE-CONTROL STUDIES

Case-Control Design

	Factor Present	Factor Absent	
Disease			Sample 1: Cases
No Disease			Sample 2: Controls

These are "retrospective"; obtaining past data from cases and from controls (people without the disease). The research focus is the disease.

Case-control studies “began” as epidemiologic studies to try to identify risk factors for diseases. Therefore, the term “cases” refer to those with the disease under investigation. However, the term has become more generic; case-control design can also be used to look at other outcomes, such “disability” among those who already have a disease. In that case, “controls” are those with the disease but not disability. The “case” in a case-control study maybe a patient who has had a good but rare outcome; say, recovery from a usually fatal disease.

Some investigators and scientists refer to case-control studies as “confirmatory observational studies” and to cross-sectional studies as “exploratory observational studies”. Both are observational; without interventions. Case-control studies are “retrospective”; obtaining “past” data from cases and from controls. The research focus is the disease (‘status” under investigation).

STEPS IN THE CASE-CONTROL DESIGN

- Select the sample of cases
- Select the sample of controls
- Measure predictor variable & potential confounders and effect modifiers

Case-control studies provide information on the characteristics of the cases and an estimate of the strength of the association between each predictor variable and the presence or absence of the disease. These estimates are in the form of the odds ratio which approximates the Relative Risk if the disease is relatively rare.

Strength: Efficiency for Rare Outcomes

A major strength of case-control studies is their rapid, high yield of information from relatively few subjects. For rare diseases or outcomes, cross-sectional design is impractical; it requires a study size that no investigator could afford. Cohort design, which is normally larger, is also impractical because it requires a follow-up time longer than most investigators could afford.

Strength: Generating Hypotheses

The retrospective approach of case-control studies, and their ability to investigate a large numbers of possible predictors make them useful for generating hypotheses about, say, the causes of new outbreak of disease so that a more thorough investigation or investigations could follow.

Weaknesses:

Case-control studies have great strengths but they also have major limitations; among them:

(1) Accuracy of exposure histories.

(2) Appropriateness of controls.

(3) Unlike cohort designs, we can only study one disease/outcome at a time.

Sampling Bias:

The data collection in a case-control study begins with the cases. But how do we know if these cases are representative of all patients who developed the disease; those who are undiagnosed, or died, are not included. And some included might be misdiagnosed (easier problem here). The more difficult decisions faced by investigators of a case-control study, however, relates to the more open-ended task of selecting controls. The ones included might be inappropriate and confound study conclusion.

Hospital- or Clinic-based Controls

One strategy to compensate for the possible selection bias caused by obtaining cases from a hospital or clinic is to select controls from the same facility. However, the risk factor of interest might be related to causes for which those control seek care; if so, prevalence of the risk factor in the control group would be falsely high, biasing the study results toward "the null". That's why, some studies use two control groups.

Matching & Multiple-matching:

Matching, and multiple matching, is a relatively simple method of ensuring that cases and controls are comparable with respect to major factors that are related to the disease but are not interest to the investigators. Examples are gender and Age group. Matching does have its adverse consequences, especially when “modifiable factors”, such as income and cholesterol levels, are matched.

Population-based Cases:

Population-base case-control studies are now possible for many diseases, like cancers, because of a rapid increase in the creation of maintenance of "**disease registries**". Cases obtained from disease registries are generally more representative of the population of patients. When information on the cases and controls can come from the same sources, the design has the potential for eliminating sampling bias. Later, we will cover such a form, the "nested case-control design".

Two or more Control Groups:

Selection of controls can be very tricky, especially might not be representative of patients; for example, hospital-based cases. In those studies, it is advisable to use more than one control groups; for example a hospital-based and a population-based control groups. The former might be biased toward the Null. On the other hand, be prepare to deal with “multiple decision problem”.

Measurement Bias: The Need for Blinding

Besides selection bias, case-control studies might be bias due to measurement error caused by their retrospective approach: the “recall bias” especially when it occurs to a different extent in cases and in controls. A necessary solution is the need for blinding: **both observers (interviewers, for example) and study subjects could be both blinded** to the case-control status of each subject and to the risk factor being studied (not an easy task at all!).

Case-crossover Studies:

A variant of the case-control design, useful for the short-term effects of varying or intermittent exposures, is the "case-crossover design". As with the "regular" case-control studies, case-crossover studies are retrospective studies that begin with a group of cases. However, in regular case-control studies, the exposures of the cases are compared with exposures of a group of controls. Each case in case-crossover studies serves as his/her own control. Exposures of the cases at or right before outcome time are compared with exposures of those same cases at one/more other points in time.

There are a few things we can do in the “Design Stage” to enhance results of causal inference.

Suppose that a study reveals an "association" between coffee drinking and myocardial infarction (MI). There are 5 possibilities: (1) Coffee drinking and MI are not related; what revealed was a chance finding (random error); (2) Coffee drinking and MI are not related; what revealed was caused by some bias, systematic error; (3) MI is a cause of coffee drinking, a so-called "Effect-Cause" phenomenon; (4) Coffee drinking is associated with a third extrinsic factor, called confounder, and the confounder is a cause for MI; and (5) Coffee drinking is a cause for MI; this is the real Cause-Effect phenomenon (bingo!) – the ideal possibility .

Before reaching the ideal conclusion – something the investigators wanted to prove, the other four rival possibilities have to be considered and ruled out. How? What can or should we do in the design stage?

Strategies for addressing random errors (Possibility #1) are available in both design and analysis stages. In data analysis, you focus on "statistical significance" (p-value). The design strategies include: (1) Increasing the "precision" of measurements, and more important, (2) Increasing sample size. So, sample size estimation is needed not just for budget justification!

Ruling out spurious associations due to bias (Possibility #2) is trickier, more difficult. Here are 3 basic questions to ponder: (1) Do the samples really represent the target populations?; (2) Do the measurements of the predictor variables really represent the predictors of interest (the issue of randomization included here)?; and (3) Do the measurements of the outcome variables really represent the outcomes of interest (the use of surrogate markers included here).

Strategies for coping with confounders (Possibility #3) require that investigators be aware of, be able to measure, and use them. The most common way to "use" them is matching – especially for factors which are not easy for quantify for use in data analysis (e.g. geographical factor). However, be cautious, you might overdo it! Overmatching can reduce statistical power and making it more difficult to generalize the findings.

About the only way to rule out "Effect-Cause" possibility (Possibility $4) from an observational study, the possibility that "the cart has come before the horse", is to follow up with a cohort, longitudinal study – as outlined in an earlier section of this lecture, "Natural History of Research".

COHORT STUDIES

“Cohort” was the Roman term for a group of soldiers that march together. In clinical research, a cohort is a group of subjects followed over time. In itself, the term “cohort” does not yet mean “prospective”. In the design terminology, we have “prospective cohorts” but we also have retrospective cohorts which may appear under “nested case-control” or “case-cohort” options.

PROSPECTIVE COHORTS

In a prospective cohort study, the investigator:

- Selects a sample from a target population;
- Measures (baseline) values of predictor variables;
- Measures the outcomes during follow-up

In the most simple case, one binary predictor: presence or absence of a risk factor and for the outcome, whether a disease occurs. This type of design is prospective & longitudinal.

An Example:

(1) In 1976, investigators obtained lists of registered nurses aged 25 to 42 in the most populous states and mailed them an invitation to participate in the study; those who agreed became the cohort;

(2) They mailed a questionnaire about weight, exercise, and other potential risk factors; they obtained 121,700 completed questionnaires, that's the size of the cohort;

(3) They send periodic questionnaires about the occurrence of a variety of disease outcomes, heart diseases and cancers included.

Some Results:

The investigators succeeded in following 95% of the nurses and 1,517 cases of breast cancer were confirmed during the next 12 years. They found that, for example, women who gained more weights have a higher risk of breast cancer after menopause; those who gained more than 20 kg since age 18 had a twofold increased risk of developing breast cancer.

Strengths:

(1) Suitable for assessing "disease incidence" (new cases); helpful in investigating potential "causes" because cohort members were free of the disease under investigation to start with;

(2) Measurements of predictors are not influenced by knowledge of the outcome;

(3) Prospective approach allows investigators to measure variables more completely and more accurately, to update the status of risk factors – especially important for "time-dependent" covariates; the large size of the cohort and long period of follow-up provide substantial "Statistical Power".

Weaknesses:

(1) Cohort studies, even prospective cohort studies, are basically "observational"; causal inference could be challenged and interpretation often muddied by potential influences of confounders and effect modifiers;

(2) Time and cost consuming. It could be more feasible if outcomes are more common and immediate; for example, a prospective study of risk factors for progression (or relapse) after treatment of patients with breast cancer.

RETROSPECTIVE COHORTS

A retrospective cohort differs from a prospective cohort in that the assembly of the cohort, baseline measurements, and follow-up all happened in the past. It was assembled for other purposes; however, important data about risk factors are still possible to obtained for the new purpose – for example, from banked blood samples.

Design of Retrospective Cohorts:

The Investigator:

(1) Identifies a cohort that has been assembled;

(2) Collects data on predictors (“measured” in the past);

(3) Collects data on the Outcome (measured in/at the present.

Example #1:

To study thoracic aortic aneurysm, investigators:

(1) Search the database of Olmsted County, Minnesota – which is considered a cohort because of thorough medical records of its residents – an found 133 cases of aneurysm;

(2) They reviewed patients' records to collect data on age, size of aneurysm, and other factors of cardiovascular diseases at the time of diagnosis;

(3) For the outcomes, they collected data from the medical records of these 133 patients to determine whether the aneurysm ruptured or was surgically repaired

Example #2:

The Singapore Cohort was drawn from residents in government-built housing estates (roughly 86% of the population resided in such facilities); enrollment period was 1993 - 1998. Men and women between the ages of 45 and 74 years (35,298 were women), representing 85% of eligible subjects, were enrolled. At the time of recruitment, each cohort subject was interviewed in-person using a structured questionnaire that focused on current diet. Blood samples were requested and a total 28,346 blood samples were archived and banked. To date, only <0.05% of subjects are lost to follow-up.

To date, there are 304 incident breast cancer cases with a stored blood sample, and a study was proposed to investigate the roles of some genetic factors and diets as possible risk factors/protectors for breast cancer.

Strengths and Weaknesses:

Retrospective cohorts have many of the same strengths as prospective cohorts and they have the advantage of being less costly and less time consuming.

The main disadvantages are the limited control investigators could have over the nature and the quality of data; existing data on predictors could be incomplete (too late now!) and not ideal for answering the research question.

NESTED CASE-CONTROL

A nested case-control design is a case-control study "nested" within a cohort study.

Investigators begin with a suitable cohort having enough cases (to assure adequate statistical power) to answer the research question. Then, they select a random sample of the subjects who have not developed the outcome/disease under investigation (the controls); they could increase the power by selecting two or three controls matched to a case

Example:

Back to the Singapore cohort assembled in 1993-1998. By the end of 2011, there are 304 incident breast cancer cases with a stored blood sample, and a study is proposed to investigate the roles of some genetic factors and diets as possible risk factors/protectors for breast cancer. The proposed design was a 2-to-1 matched case-control study of roughly 900 women with the following Specific Aims (there are more aims):

Specific Aims:

(1) Investigating the T-reg, T-cell and NK cell levels as a risk factor for breast cancer occurrence;

(2) Correlating T-reg, T-cell and NK cell levels with diet factors (from baseline interview) focusing on soybean products and green tea.

NESTED CASE-COHORT

The nested case-cohort option is almost the same design as the nested case-control except that the "controls" are a random sample of all the members of the cohort "regardless of outcomes". This means there might be some cases among those sampled for the comparison group; these cases appear in both groups. This approach has the advantage that the "controls" (even some of them are cases) represent the cohort in general, and therefore provide a basis for estimating incidence and prevalence in the population from which it was drawn.

Strengths and Weaknesses:

Nested case-control and nested case-cohort designs are especially useful for costly measurements on serum, electronic images (MRI and mammograms), and hospital charts, etc… that have been archived at the assembly time of the cohort and preserved for later analysis.

When data are available, or can be obtained easily, for the entire cohort, nothing is gained by studying only a sample; the whole cohort should be used.

MULTIPLE-COHORT STUDIES

Multiple-cohort studies begin with two or more groups of subjects; typically, one group with no exposure to a potential risk factor and one or more other groups with different levels of exposure. This is different from case-control design because in a case-control study the two groups are chosen based on the presence or absence of the outcome.

Multiple-cohort design is particularly useful and popular for studying rare exposures such as occupational and environmental hazards.

ISSUES WITH COHORTS

The hallmark of a cohort study is the identification of a group of subjects at the beginning of a period of follow-up:

- Subjects should be appropriate to the research question;
- Subjects should be available for follow-up;
- Subjects should be resemble to the population to which the results will be generalized;
- Number of subjects should provide adequate (statistical) power.

The quality of the study (and future studies) will depend on the precision and accuracy of the measurements of predictor (s) and outcome variable.

The ability to draw inferences about cause and effects will also depend on the degree to investigators have identified and measured all potential confounders and effect modifiers.

Predictors may change during the follow-up; whether and how frequently measurements should be repeated depends on how they are likely to change and, of course, depends on the cost and the importance to the research question of observing these changes.

Outcomes should be observed/assessed using standardized criteria and, ideally, blindly without knowing the values of the predictor variable.

Follow-up of the entire cohort is important; investigators should take a number of steps to achieve this goals; for example:

- Exclude those likely to be lost, or collect adequate information (physician or friends or relatives) that can be used if they move or die;

- Prepare for periodic contacts (by mail, by phone, etc…);

- Show respect and appreciation!

Suggested Readings

Retrospective cohorts were assembled by someone else and for other purposes; using these databases may involve complicated issues. Search and learn about the issue of authorship (sources for this complicated topic are hard to find, so work hard to collect materials.