Appraisal of Case-Control, Cross-Sectional, and Descriptive Studies

EBCP Module #13
Outline of Module

- This module will introduce the following topics....
  - Additional Observational designs (besides cohort studies)
    - Case-control study design
      - Design and analysis
      - Recall bias
    - Cross-sectional study design
  - Descriptive designs
    - Case series
    - Case study
Objectives of Module

Students who complete this module should be able to correctly define and apply the following terms as they pertain to evidence-based clinical practice.

- Case-control study
- Recall bias
- Cross-sectional study
- Case series/case study

Students who complete this module should be able to...

- Recognize the case-control design and cross-sectional design and discuss their benefits and shortcomings in relation to other designs.
- Describe and identify the effects of recall bias on study results.
Review of Observational Study Designs
Review of Observational Designs

- In the previous module, the clinical trial (an experimental, or interventional, design) and the cohort study (an observational design) were described.

- Recall that the major difference between experimental designs and observational designs is the role of the researcher in the assignment of the exposure, such as a treatment.

- In this module, we will consider additional observational study designs that you may encounter in the medical literature.
Case-Control Studies
As you already know:

- In a case-control study, participants are selected based on the outcome—that is, whether they are cases or controls—and are evaluated with respect to a prior exposure.

The name “case-control” refers to the notion that both “cases” (those with the outcome) and “controls” (those without it) are selected by the researchers.
- This is distinct from cohort studies where groups are determined by exposure.
- It is also different from case series, in which there are no controls.

Of course, since outcomes have already occurred, all case-control studies are conducted retrospectively.

The case-control design is best suited for studies of rare diseases (e.g., rare genetic disorders) or where multiple exposures might be evaluated as possible causes of a single outcome (e.g., searching for the cause of a disease outbreak).
Case-Control Study: Examples

Case-control studies are uniquely equipped to answer questions like:
- Which genetic variants are associated with development of Alzheimer’s disease?
- Which antibodies are present before symptom onset of Sjögren’s syndrome?
- What caused the German outbreak of Escherichia coli O104:H4?

When they are possible, clinical trials and cohort studies are preferable to case-control studies.
- However, the examples above highlight the fact that clinical trials and cohort studies are not always possible.

In particular, case-control studies are best used to study:
- Events that already happened where the cause is unknown and there are several possible exposures to be considered (such as an E. coli outbreak)
- Rare diseases that are unlikely to occur in a cohort study (such as Sjögren’s syndrome)
- Large numbers of exposures, where it would seem impractical to design a cohort study to follow each group (such as a study of hundreds of thousands of genetic variants)
Recall that, in a case-control study, the researcher has pre-selected participants on the basis of the outcome. Therefore, it is not appropriate to calculate incidence rates for that outcome among the participants in the study. This is because we are unable to really know how many cases occurred among those at risk for the outcome. We know only that some cases exist (they were selected for study), but not how often they occur.

Since incidence rates cannot be calculated in case-control studies, the groups cannot be compared using a relative risk estimate. However, an odds ratio can be calculated. In the case of a truly rare disease (but not necessarily in other cases), the odds ratio may provide a reasonable estimate of the relative risk.
Odds Ratio Interpretation

- Remember that ORs are interpreted much like RRs:
  - OR=1: No association of exposure and disease
  - OR>1: Exposure associated with increased odds of disease
  - OR<1: Exposure associated with decreased odds of disease

- Yet, RR and OR are **not** the same.
  - The OR does not contain any information about the *incidence* of a disease.
  - Rather, it is a simple measure of association between exposure and disease.

- Good review of OR vs. RR, by Rahul Patwari: [https://www.youtube.com/watch?v=hOtoV2Kjb0o](https://www.youtube.com/watch?v=hOtoV2Kjb0o)
Odds Ratio Calculation

Like RR, OR can be calculated using a 2 x 2 table in which patients are classified based on whether they were exposed to the factor of interest and whether they developed the disease of interest.

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Not Exposed</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

OR = \( \frac{a/b}{c/d} = \frac{a*d}{b*c} \)

Note that the OR is a ratio of odds*, while the RR is a ratio of incidence.

Compare to RR = \( \frac{a/(a+b)}{c/(c+d)} \) = incidence in exposed group / incidence in unexposed group

*Odds are less intuitive than rates. In common language, they are sometimes used in gambling. Odds of 2:1 losing to winning indicate a 33% (1/3) chance of winning.
Case-Control Study: Critical Appraisal

- Weaknesses of case-control studies include:
  - Selection bias
    - It can be difficult to obtain a control group that is meaningfully comparable to those with the disease (a control group that permits what some call an “apples-to-apples” comparison).
    - Misclassification of even a few participants can result in skewed (biased) results if a disease is very rare.
  - Information bias
    - Case-control studies are particularly prone to recall bias. This issue is discussed on a next slide.
  - Confounding
    - Matching and multivariable methods provide only limited protection against confounding and can be complicated. Matching is discussed on a later slide.
  - Chance
    - Case-control studies often deal with small numbers and so are particularly susceptible to type II errors.
Special Issue: Matching

- An important way to control for confounding in case-control studies is matching cases and controls on particular characteristics.
  - In addition to controlling for confounding, matching provides a means to guide control selection.
  - It occurs during the selection of study participants.

- For example, in a study of myocardial infarction (outcome), a 45 year-old male who had a myocardial infarction can be matched with a 45 year-old male who has not.
  - Matching occurred on age and sex in this case.
  - This implies that both age and sex might be expected to affect a subject’s risk for myocardial infarction (outcome) – i.e. these variable are potential confounders.

- You can imagine that it would be difficult to use matching to effectively eliminate multiple confounders.
  - For example, it would be hard to match on age, sex, smoking, and cholesterol profile. It would be hard to find a control to match every case with a specific set of characteristics.
  - Other methods to control for confounding in case-control studies include statistical adjustment (often through multivariate regression analysis), which is often used in cohort studies as well.
In case-control studies, which are necessarily retrospective, outcomes are known before exposures are evaluated. Prior exposures are commonly self-reported.

Self-reporting of exposures may result in systematic under- or over-reporting of exposures by either cases or controls—a phenomenon known as recall bias.

For example, patients with a rare cancer may be more likely to remember potential exposures (drugs, pesticides, radiation, etc.) that they fear have contributed to their condition.

- Systematic over-reporting among cases inappropriately inflates the association of exposure and outcome.

To avoid recall bias, studies can use data from objective sources, such as medical records or public records instead of patient recall of exposures.

- However, such data may be incomplete or inaccurate, or may limit which exposures can be considered.
Cross-Sectional Studies
Cross-Sectional Design: Basics

- We have already examined two variations of the observational study.
  - Cohort study: Researchers classify participants by exposure, then assess for outcome (prospectively or retrospectively)
  - Case-control study: Researchers classify participants by outcome, then assess for exposure (retrospectively)

- Another design—the cross-sectional study— involves taking a “snapshot” of a group at a given point in time and then classifying participants at a given moment.
  - Cross-sectional designs, unlike cohort or case-control studies, are not retrospective or prospective. They take place at a single point in time.
In a cross-sectional study, participants are assessed for both an exposure and an outcome at the same time (e.g., via a survey which inquires about risk factors as well as disease).

While incidence rates cannot be calculated for study groups in a cross-sectional study, the **prevalence** of exposures and outcomes can be assessed.

- A cross-sectional design provides a good way to take a “snapshot” of the prevalence of a disease.
  - For example, a cross-sectional design may provide estimates of the prevalence of coronary artery disease (outcome) by sex, age, or smoking status (exposures) in the U.S.
- This information is important to clinicians for developing differential diagnoses and prioritizing hospital resources.

Cross-sectional studies also permit the use of odds ratios to quantify the relationship between exposure and outcome.

- Cross-sectional studies cannot determine incidence and so cannot provide an estimate of relative risk.
- Recall, too, that this design does not establish whether the exposure preceded the outcome, but only that they are present in the group at the same time.
Cross-Sectional Study: Example

- A nationwide survey found that 5.6% of all American adults reported indoor tanning in the past 12 months.

- The highest prevalence of indoor tanning was found among white women aged 18–21 years (31.8%) and aged 22–25 years (29.6%). Tanning was particularly high among white women aged 18–21 years in the Midwest (44.0%). (Hartman, et al. MMWR, May 2012)

The figure shows the percentage of non-Hispanic white women aged 18–29 years who used an indoor tanning device at least once in the past 12 months, by age group and U.S. Census.
Cross-Sectional Study: Critical Appraisal

- Because they do not adequately assess a temporal relationship between cause and effect, cross-sectional studies should not be used to answer questions about causal relationships.
  - Imagine, for example, that a cross-sectional study showed that walking less than 30 minutes each day was more likely in obese than non-obese people (OR=5.0).
    - The OR demonstrates that not walking and obesity are associated during the time of study.
    - Yet, because there is no temporal component to the study, we cannot say which came first, obesity or not walking. Additionally, we cannot determine anything about causality.

- Cross-sectional studies are primarily useful for generating hypotheses and providing information about prevalence.
  - Prevalence information is important in clinical practice for creating differential diagnoses (determining the pre-test probability of a disease) and prioritizing resources, for example.
  - However limited, cross-sectional studies deserve a critical look because they are subject to some of the same issues as other studies.
Cross-Sectional Study: Critical Appraisal

- Relevant issues to consider when reading cross-sectional studies include:
  - Selection bias:
    - Is the sample representative of the population under study?
  - Information bias:
    - Are the data obtained accurate? Do they reflect what the researchers wanted to measure?
    - If the data are from questionnaires, have the questions been validated—that is, do we know their reliability and accuracy?
  - Confounding:
    - Are there factors that might skew odds ratio relating exposure and outcome? Are they accounted for using multivariable methods or stratification?
  - Chance
    - What are the confidence intervals for prevalence estimates? Are the estimates reliable?
Descriptive Designs
Introduction to Descriptive Designs

- So far, we have emphasized study designs which are analytic in nature.
  - In *analytic* studies, participants are divided into meaningful groups (e.g., exposed and unexposed, case and control), and data are analyzed to reveal relationships between the variables of interest.

- Other designs—such as the case series and case study—are known as *descriptive* designs.
  - These designs do not allow for the calculation of measures of association.
  - They are primarily used to generate hypotheses.
Clinical Study Designs

Are the investigators describing patients or analyzing patients in groups?

Descriptive Studies
- Case studies
- Case series

Analytic Studies
- Are the investigators simply observing patients, or are they assigning interventions to patients?

Observational Studies
- Cross-sectional
- Case-control
- Cohort

Experimental Studies
- Clinical trials

Are the results of multiple studies combined?
- Meta-analyses
- Systematic reviews

Note: This diagram does not represent all possible study designs.
Case Series and Case Studies

- A *case study* is a descriptive summary of a single patient, whereas a *case series* is a similar summary of more than one patient.

- These designs *lack a control group* and so cannot be used to demonstrate causation of an observed outcome.

- These designs are best used to draw attention to new or unusual conditions, side effects, or treatments.

- Case series and case studies can also be used to generate hypotheses for analytic designs.
Case Series: Example

- Three cases of a novel influenza virus were found in children in northern Iowa the week of Thanksgiving 2011.

- **Patient A.** In the second week of November 2011, patient A, a previously healthy female child, experienced acute onset of influenza-like illness (ILI). Three days after her illness onset, she was seen by a healthcare provider who obtained a respiratory specimen and performed a rapid influenza diagnostic test, which was positive.

  Patient A's brother experienced onset of ILI one day before patient A's date of illness onset. Patient A's brother was not tested for influenza but was treated with oseltamivir by a health-care provider and has recovered. During her illness days two and three, patient A was in contact with her father, who subsequently developed ILI two days after his most recent contact with patient A. He was not tested for influenza. No other household member has reported respiratory illness. No family member reported exposure to swine before their illness onset. On her illness day one, patient A attended a small gathering of children. ...
Because they lack control groups, case studies and series are not used in the same way that analytic study designs are.

For this reason, we will not subject them to critical appraisal methods.

However, these studies can be important. And they should be read critically.

Generally, your reading of case studies and case series will improve as you develop clinical knowledge.

Recent medical knowledge gained from case series includes:

- Discovery of new diseases (such as HIV and H1N1 virus)
- Numerous drug side-effects (such as venous embolisms associated with certain psychiatric drugs)
- New drug treatments (such as propranolol for infantile hemangiomas—observed as a “side effect” by a pediatric cardiologist and published as a letter in the New England Journal of Medicine)
Summary of Clinical Study Designs
Summary of Clinical Study Designs

- Several common study designs have now been described. These include:
  - Analytic designs
    - Experimental: Clinical trial
    - Observational: Cohort, case-control, and cross-sectional
  - Descriptive designs
    - Case series and case study

- You will encounter other designs in subsequent training and in clinical practice.
  - Most other designs in clinically-relevant scientific literature are variations on those that you have learned so far.
  - These include meta-analyses and systematic reviews—studies of studies—which evaluate the collected results of other research, such as from clinical trials and cohort studies.
  - With the information you have, you are well-equipped to begin reviewing and appraising most clinical studies.
Key Points for Module 13

- In a *case-control study*, participants are classified with respect to the outcome (i.e., case or control) and then assessed for a previous exposure.

- *Recall bias* is an important potential threat to the internal validity of case-control studies.

- When study design does not allow calculation of incidence, odds ratios should be used rather than relative risk for describing outcome measures.

- In a *cross-sectional study*, participants are classified with respect to both exposure and outcome at a single point or period in time.

- Case series and case studies are descriptive summaries of new or unusual patient experiences.
Please complete the Module 13 quiz

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