

# Observational Study Design

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(Slides courtesy of BSE faculty)

Welcome to this three-part series focused on observational studies, systematic review and meta-analysis. In this first module, we will focus on observational study designs.

## Example 1

- Use of a dummy (pacifier) during sleep and risk of sudden infant death syndrome (SIDS):  
Population based case-control study

– *Obstetrics and Gynecology*. 2006;107(4):949-50

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Let's begin by viewing some examples of studies published in the literature that are based on observational study designs.

The first study is from a publication in *Obstetrics and Gynecology*. In this study, researchers investigated the use of a pacifier during sleep and the risk of sudden infant death syndrome using a population-based case-control design.

## Example 2

- A population-based, prospective cohort study was conducted to describe the association between cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood

– *JAMA*.2003;290:2277-2283

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In a second example, published in the Journal of the American Medical Association, investigators conducted a population-based prospective cohort study to describe the association between cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood.

## Example 3

- A case-control study was conducted to identify possible causes of an outbreak of *Escherichia coli* O157 infection

– *JAMA*.2003;290:2709-2712.

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The third example was also published in the Journal of the American Medical Association and is a case-control study in which investigators studied possible causes of an outbreak of E coli O157.

## Example 4

- A comparison of sleep and daytime sleepiness in depressed and non-depressed mothers during the early postpartum period (a cross-sectional survey)

– *Journal of Nursing Research* 2004;23(4):287-295.

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In a fourth example, investigators conducted a cross-sectional survey to compare sleep and daytime sleepiness in depressed and non-depressed mothers during the early postpartum period.

In each of these examples, investigators utilized an observational study design to investigate the research question of interest. After viewing this module, you will be able to identify three main types of observational study design, namely, a case-control design, cohort design, and cross-sectional survey, and will be able to identify strengths and limitations of each design.

## Quantitative Research Uses Deductive Reasoning

- Deductive reasoning, guided by theory and a hypothesis, using a sample of data:
  - Develop valid generalizations to the population at large
  - Develop general principles
  - Draw inference to future situations

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In quantitative research, we use deductive reasoning, guided by theory and a hypothesis, to make inferences from a sample of data to the population at large. We may want to develop valid generalizations or general principles for the population at large based on our study sample of data or we may utilize a sample of data to draw inferences regarding a future situation. For example, we may utilize clinical and demographic information to make a prediction regarding a patient's prognosis following a particular procedure.

## Observational versus Experimental Studies

- Two major study types
  - Observational: researcher observes subject characteristics, exposures, interventions, etc. and outcomes, but does not control “interventions”
  - Experimental: Researchers have control of interventions to which research subjects are exposed

In quantitative studies, there are two main types of study designs, observational and experimental. In an observational study design setting, investigators observe subject characteristics including exposures, interventions, and behaviors, as well as patient outcomes, but do not control the “interventions”. The researcher makes observations, but does not manipulate exposures. In contrast, in an experimental study setting, researchers control the assignment and delivery of interventions; they control which participants receive which exposures.

This series focuses on observational study designs, while the next series focuses on experimental study design.

## Terminology

- Population: large group that study attempts to describe; often impractical to study entire population
- Sample: subgroup from the population; investigators will make generalizations about the entire population from the sample

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Now we will cover some terminology that is commonly used to describe research study designs.

In research, we are interested in making inference or drawing conclusions relative to the population at large, for example, the population of patients with a certain disease. However, it is not feasible to study an entire population of patients and instead, a sample is drawn from the population. Investigators collect data from the sample and use the sample information to make generalizations to the population at large.



## Terminology

- Prospective study: Groups recruited and data collected on subsequent events
  - Example: trial of membrane sweeping
  
- Retrospective study: Information is collected on past events or exposures
  - Example: look back at exposure history for SIDS cases and controls

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Studies may be prospective, cross-sectional, or retrospective in nature. A prospective study is one in which groups are recruited and data are collected on subsequent events. An example would be a randomized trial of pregnant women comparing birth outcomes between women in labor who are randomized to undergo membrane sweeping versus no intervention.

In a retrospective study, information is collected on past events or exposures. For example, investigators may ask mothers of infants who died from SIDS what their sleeping practices were and compare these practices to infants that did not die of SIDS.

## Terminology

- Cross-sectional study: Information is collected on subjects at a fixed point in time
  - Example: sleep survey
- Longitudinal study: Investigate changes over time by taking repeated measurements over a time interval on the same subject
  - Example: growth of preterm infants

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In terms of timing, we will also describe studies as cross-sectional or longitudinal in nature. A cross-sectional study is one in which information is collected on subjects at a single, fixed point in time. For example, investigators may ask post-partum women about symptoms of depression and their sleeping practices at the time of survey participation.

In contrast, in a longitudinal study, investigators study changes over time by making repeated measures over a time interval on the same subject. For example, investigators may make quarterly measures during the first three years of life on preterm infants.

## Types of Study Designs: Observational Study

- Definition: Study in which data are collected from existing situations or existing groups of subjects
- Example: Surveys, SIDS and pacifier use
- Primary Types:
  - Cohort Studies
  - Case-control Studies
  - Survey

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We will now focus more specifically on three main types of observational study designs, namely, cohort studies, case-control studies, and cross-sectional surveys.

## Cohort Studies

- Definition: groups, defined on the basis of some characteristics are typically prospectively followed to see whether an outcome of interest occurs (could also be retrospectively observed to see whether an outcome of interest occurred prior to some point in time)
- Example: select cohorts based on proximity to epicenter of nuclear bomb site in Hiroshima, Japan and follow for cancer development

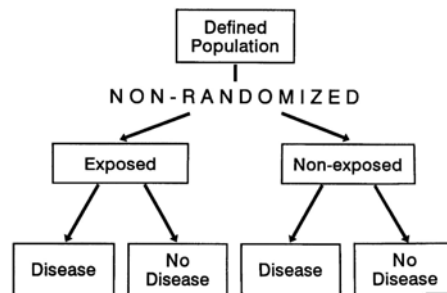
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In a cohort study, groups, defined on the basis of some characteristics are typically prospectively followed to see whether an outcome of interest occurs. Groups of participants are defined, or sampled, based on their exposures or their behavioral characteristics. As an example, investigators may be interested in studying the association between nuclear bomb exposure and cancer incidence. They could select cohorts based on proximity to epicenter of nuclear bomb site in Hiroshima, Japan and follow patients for cancer development. The investigators could choose those within a 30 mile radius of the epicenter as “exposed” and compare their cancer outcomes to individuals who lived at least 100 miles away from the epicenter as “non-exposed”.

Note that this describes a prospective cohort study where participants are selected based on exposures and then studied prospectively for the development of disease. As another approach, investigators could also retrospectively observe participants to see whether an outcome of interest occurred prior to some point in time. Retrospective chart reviews, comparing outcomes between patients who received different interventions in a clinical setting, are examples of retrospective cohort studies.

## Cohort Studies (cont.)

- Studying relations among exposures and diseases in a particular population of interest



This slide provides a schematic drawing of a cohort study. Groups are sampled based on exposure and followed prospectively (typically) for the development of disease. The incidence of disease is compared between the exposed and non-exposed to see if there is an association.

## Cohort Studies

- Advantages: time course from exposure to disease is observed (for prospective cohort study)
- Disadvantages:
  - Long and expensive, even infeasible for rare outcomes;
  - Groups may differ in terms of an important characteristic that is/is not observed,
  - Comment on associations not causation
  - Loss to follow-up is likely
  - May be affected by detection bias (follow-up and assessment methods should be same for all subjects regardless of risk)

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Prospective cohort studies are appealing because we observe the time course between exposure to disease onset. The temporal sequence between exposure and outcome is observed.

There are several disadvantages of cohort studies that should be kept in mind. Prospective cohort studies can be long and expensive, perhaps even infeasible for rare outcomes. Given the observational nature of the study design, the exposed/non-exposed groups may differ in terms of an important characteristic that is associated with the outcome that may or may not be observed, these are termed confounding factors. Furthermore, due to the observational nature of the study, we can comment on associations, but not causation. Another drawback is that with the longitudinal design, loss to follow-up is likely and can lead to biased results. Finally, prospective cohort studies may be affected by detection bias if the follow-up and assessment methods differ between patients depending on their risk of disease – for example, if smokers are seen in clinical follow-up exams every three months while non-smokers are seen every 12 months in a prospective study investigating changes in lung function, there is a potential for detection bias.

## Case-control Studies

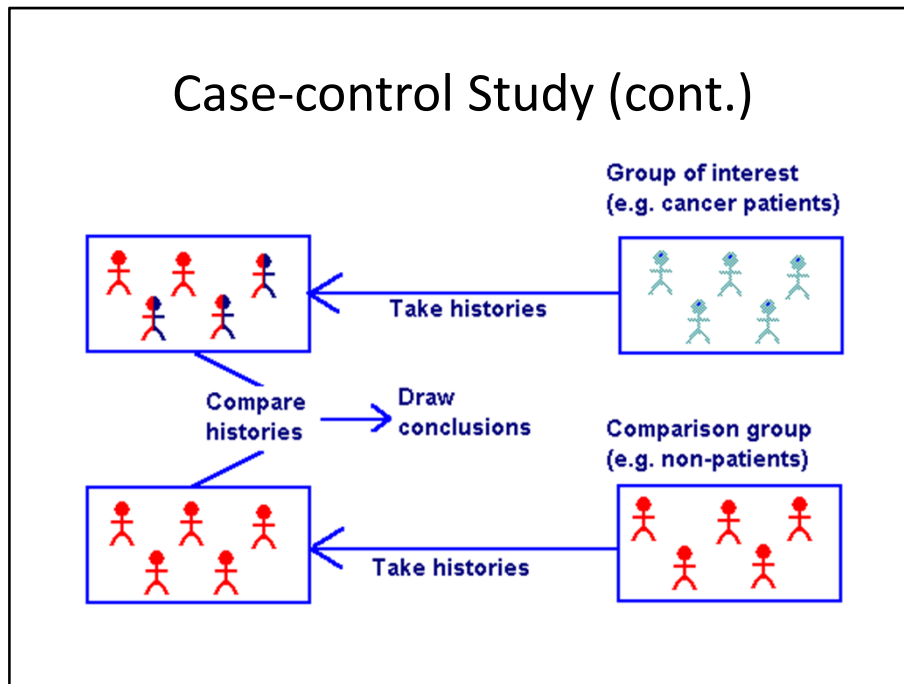
- Definition: retrospectively compare various characteristics for cases (subjects with a disease) to those of controls (non-disease comparison group)
- Example: compare serum biomarker levels between pancreatic cancer patients and subjects who do not have pancreatic cancer

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Next, let's discuss case-control studies. In these studies, investigators sample patients with a particular disease (cases) and a group without the disease of interest (controls) and look back in their histories for differences in exposures or behaviors.

As an example, we may compare serum biomarker levels between patients with pancreatic cancer (cases) to individuals without cancer (controls) to determine if the pre-treatment biomarker level is predictive of cancer.

## Case-control Study (cont.)



This slide includes a diagram of a case-control study. A group of disease cases are identified and a group of non-disease controls are identified. Then, investigators take their histories and compare them in order to identify factors associated with disease.



## Case-control Studies

- Advantages: relatively inexpensive and can be completed in a short amount of time; useful for studying rare outcomes
- Disadvantages:
  - Do not observe entire time course from exposure to disease so causal interpretation is limited,
  - Subjects with disease may be more motivated to recall exposures
  - May miss fatal or short-term cases
  - May be difficult to select comparable group of controls
  - Availability of high quality/complete data may be limited

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Because the case-control design utilizes existing information, these studies can be relatively inexpensive and quick to complete. They are also useful for studying rare outcomes because by design, we ensure that we have a sufficient number of diseased cases; we do not need to sample a huge number of participants and follow them for long periods of time while we wait for incident cases of disease to occur.

There are several disadvantages of case-control studies that should be kept in mind. First, given the retrospective nature of case-control designs, we do not observe the entire time course from exposure to disease. The temporal sequence between exposure and disease onset is not observed. Therefore, causal interpretation is limited; we can only comment on associations and not causation. It is also important to note that subjects with disease may be more motivated to recall previous exposures. For example, mothers of infants with a congenital anomaly may have spent a lot of time thinking about their pregnancy and possible exposures, while a mother of an infant with no congenital anomaly would not have reviewed their history as carefully. In case-control sampling, keep in mind that you may miss fatal or short-term cases. It may also be difficult to select an appropriate group of control patients; for example, controls are often matched to cases by age and gender to avoid these as confounding factors. Finally, given the retrospective nature of case-control designs, we are limited by the availability of high quality and complete data that can be used for analysis.

## Extensions

- More complicated sampling schemes
  - Nested case-control
  - Case cohort

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Note that there are more complicated adaptations of these designs including nested case-control designs and case cohort designs.

## Nested Case-control Design

- Case-control nested within a prospective cohort study
- Example: Early urinary markers of diabetic kidney disease: a nested case-control study from the Diabetes Control and Complications Trial (DCCT). [Am J Kidney Dis.](#) 2010 May; 55(5): 824-34.

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During the course of a prospective cohort study, we may be interested in determining if disease outcomes are associated with particular exposures or patient characteristics. It may not be feasible to evaluate the exposure or biomarker among the entire cohort. Instead, a nested case-control design can be used to identify a subset of cases and controls and then the biomarker is measured, typically using stored specimens from the baseline visit prior to the onset of disease, for the cases and controls. An example is provided in this cited paper where investigators utilized stored specimens from a subset of cases and controls in the DCCT prospective cohort study to determine if urinary biomarkers were associated with kidney disease.

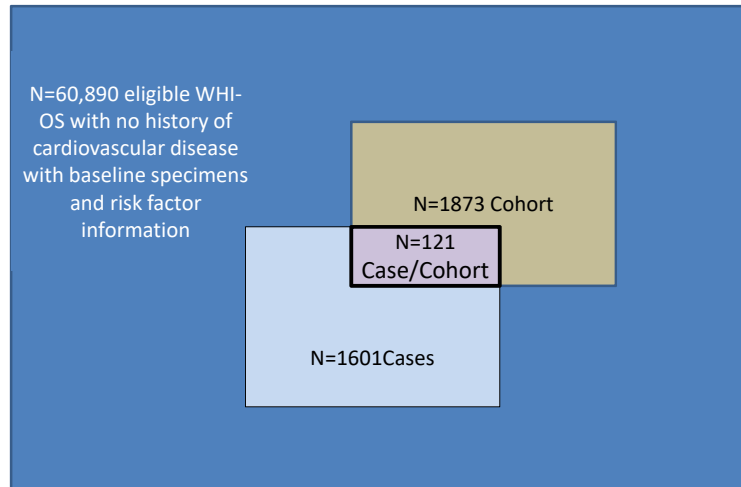
## Case-cohort Design

- Cases selected and compared to randomly selected cohort from existing cohort
- Example: Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. *Circulation*, 2012; 125: 1748-1756

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Another extension is a case-cohort design where diseased cases are selected from a prospective cohort study and compared to a randomly selected subset from the larger cohort. This design is also an approach to more feasibly answering research questions in a subset of patients instead of running assays or making biomarker measures on the entire cohort. An example case-cohort study can be found at this citation in *Circulation*.

## Case-Cohort Design



In this Circulation study, investigators selected  $(1601+121)=1722$  cases with cardiovascular disease and then chose a random sample from the entire cohort for comparison. The randomly selected cohort for comparison included 121 cases (overlap with the cases) and 1873 individuals without cardiovascular disease. This resulting sample size of 3595 is much lower than the entire cohort of over 60,000.

## Cross-Sectional Surveys

- Definition: collect data on study subjects at a fixed time, a cross-sectional observation of a group
- Examples
  - Monthly hospital nosocomial infections
  - Registries: cancer, reportable infections
  - Surveys: health status, health behaviors

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Now, we will discuss a third type of observational study, a cross-sectional survey.

With cross-sectional surveys, we collect data on study participants at a fixed point in time; we are taking a “snapshot” observation of a group of individuals.

We may use surveys to gauge monthly hospital infections, to create registries of patients with certain types of disease, or to assess health status and health behaviors of respondents living in a certain town, as examples.

## Cross-Sectional Surveys

- Advantages: simple and inexpensive; useful for estimating number of subjects with existing condition per population at risk in the given period of time
- Disadvantages:
  - Do not observe time course so cannot determine if exposure really came before outcome;
  - Non-responders may be different from responders

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Surveys are simple and are often inexpensive to conduct. They are useful for estimating the number of individuals with a particular condition or behavior in the population at a given point in time.

Drawbacks of surveys include the fact that we do not observe the time course between exposure and outcome so we cannot be sure if the exposure came before the outcome based on cross-sectional data alone. Also, non-responders may differ from responders and therefore, results from a survey may be biased relative to the larger population at large.

## Sampling

- Goal: generate prevalence estimates that are representative of a particular population
- Sampling:
  - Random sample: equal weighting of observations will result in representative estimates
  - Non-random sampling with oversampling of particular subgroups: need to adjust weighting in analysis to generate representative estimates

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In practice, we will draw a sample from the population at large. Our goal is to generate prevalence estimates that are representative of a particular population.

Ideally, the sample will be based on a random sample where each member has an equal probability of selection.

In practice, we may not use a random sample but instead will use a non-random sampling strategy where we oversample particular groups, for example, members of a particular race or ethnicity subgroup. Given the oversampling of some groups, we will need to adjust the weighting of the observations in order for the estimates to be representative of the population at large.



## Sampling

- Over-sample minority cases
  - Representative estimates: assign lower weight to data from over-sampled stratum

Race	Population Proportion	Sample Proportion	Population/Sample	Weight
White	.5	.3	.5/.3	1.667
Black	.3	.5	.3/.5	0.6
Other	.2	.2	.2/.2	1.0

In this example, the sample was selected to have a lower proportion of White and a higher proportion of Black participants relative to the true population distribution. For analysis purposes, we will weight the data by the inverse of the selection probability. We see that because we under-sampled White participants (Whites make up 50% of the population but only 30% of our sample), we will need to weight their data more heavily while due to the oversampling of Black participants (Blacks make up 30% of the population but 50% of the sample), we will need to use a lower weight for their responses. This weighting will then reflect the race distribution in the target population.

## Example: non-random sampling

- Prevalence of Obesity Among Adults From Rural and Urban Areas of the United States: Findings From NHANES (2005-2008). [J Rural Health](#). 2012 Sep;28(4):392-7.
- **Sampling:** multistage, stratified, clustered probability design
- **Analysis:** “All analyses were performed using the combined sample weights for 2005-2006 and 2007-2008 to provide nationally representative results”

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As an example of survey weighting, consider this study where investigators utilized a complex sampling scheme to collect data to estimate the prevalence of obesity among adults from rural and urban areas of the United States. They noted that their analyses were based on sampling weights with an overall objective to generate nationally-representative results from the survey.

## Example: continued

- **Results:** The obesity prevalence was 39.6% (SE = 1.5) among rural adults compared to 33.4% (SE = 1.1) among urban adults ( $P = 0.006$ ).

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After appropriately weighting the data to reflect the demographic distribution of the target population, they found that the prevalence of obesity was roughly 40% among rural adults compared to 33% among urban adults and concluded that this difference was statistically significant ( $p=0.006$ ).

## Summary

- Observational studies
  - Identify associations between exposures or behaviors and health outcomes
  - Main types
    - Cohort study
    - Case-control study
    - Cross-sectional survey
  - Benefits and limitations

In summary, observational studies are important tools to understand associations between exposures or behaviors and health outcomes. An observational study may be necessary, for example in settings of biomarker or genetic research or in settings where it is not ethical to randomize exposure to agents known to be harmful, e.g., smoking. Three main types of observational studies are cohort studies, where participants are sampled based on exposures and followed for the development of disease; case-control studies, where participants are sampled based on disease status and histories are compared to identify exposures or characteristics associated with disease; and cross-sectional surveys where a “snapshot” is taken of practices and health status. Each design has corresponding strengths and limitations that will guide your choices in practice.

In the next series, we will discuss the design and interpretation of results from systematic reviews and meta-analyses.