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## Introduction

Traditionally, [case-control studies](#) have been viewed as an alternative to [cohort studies](#) in which individuals were selected on the basis of whether or not they had the disease outcome of interest, with investigators then comparing exposure history between those with the disease (the cases) and those free of the disease (the controls). More recently, the theory behind the case-control study has been re-imagined as a method of selecting a subset of an underlying cohort giving rise to the cases in the study. The case-control study design is an excellent choice of study when the disease is rare, has a long [induction period](#), the exposure data are difficult to obtain, or very little is known about the disease. In these situations a cohort study is generally prohibitively expensive or the time frame of the study required for data collection is impractical. Unlike cohort studies, case-control studies identify cases of the disease of interest in their population and then compare their exposure experience to sampled controls. As you will learn in the following exercise, this method is deceptively simple, and if not planned carefully, can lead to spurious findings.

### Faculty Highlight: Dr. Alfred Neugut

"The case-control study's simplicity sometimes makes us forget just how elegant and revolutionary a creation it was of 20th century chronic disease epidemiology."

Dr. Neugut is a Professor of Medicine and the Myron M. Studner Professor of Cancer Research. His research interests span the epidemiology and screening of colorectal neoplasia, breast cancer etiology and treatment, racial disparities in cancer, and cancer in the elderly. He serves as co-PI of the Long Island Breast Cancer Study, a large population-based case-control study.



### Read more about Dr. Neugut's work

- [Terry MB, Gammon MD, Zhang FF, Tawfik H, Teitelbaum SL, Britton JA, Subbaramaiah K, Dannenberg AJ, Neugut AI. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. JAMA. 2004 May 26;291\(20\):2433-40.](#)
- [Hershman D, McBride R, Jacobson JS, Lamerato L, Roberts K, Grann VR, Neugut AI. Racial disparities in treatment and survival among women with early-stage breast cancer. J Clin Oncol. 2005 Sep 20;23\(27\):6639-46.](#)
- [Zablotska LB, Chak A, Das A, Neugut AI. Increased risk of squamous cell esophageal cancer after adjuvant radiation therapy for primary breast cancer. Am J Epidemiol. 2005 Feb 15;161\(4\):330-7.](#)

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### Learning Objectives

- A. Learn to apply the main features of [case-control design](#):
1. Formulate research hypotheses
  2. Define your source population and the eligibility criteria for cases and controls
  3. Define your exposure and outcome of interest
  4. Describe methods of accrual for cases and controls
- B. Employ steps in data analysis of case-control studies to analyze the data:
1. Calculate disease odds ratio
    - Interpret your estimate
  2. Calculate exposure odds ratio
    - Interpret your estimate
  3. Explain why exposure odds ratio is identical to the disease odds ratio
- C. Explain your findings and discuss problems in data analysis:
1. Discuss the principles of proper selection of cases and controls
  2. Discuss the relationship between odds ratio and [risk ratio](#)

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### Student Role

**Susser Syndrome, a rare and debilitating neurological disease, is striking the people of Epiville!**

"You are watching WEPI Channel 1 news. From our Health and Medicine Desk - doctors at the Epiville General Hospital are reporting a dramatic rise in the number of patients suffering from Susser Syndrome, a rare and debilitating neurological disease with symptoms ranging from dizziness, double-vision, fainting spells, and difficulty in concentration to more severe symptoms such as loss of smell, facial tics, and loss of conscious control of bodily movements. Susser Syndrome came to prominence during an apparent outbreak in London immediately following World War II, although the cause of the disease was never discovered. Until recently, only sporadic cases have been found in the United States. Hospital officials report a steady rise in new cases over the past two years with a rather dramatic upswing since March of this year.



"The Epiville Health Department has deployed a team of public health officials consisting of medical epidemiologists, biostatisticians, and research assistants to determine the magnitude of the outbreak of Susser Syndrome, as well as to identify possible causes and preventive measures.

"Doctors warn that all residents of Epiville may be at risk for developing the disease. However, Channel 1 has exclusively discovered that many of the infected individuals are members of the Superfit Fitness Center, located in the Epiville industrial park. Superfit is owned and operated by Glop Industries. When asked about this information, representatives from Glop declined comment."

Based on your own research and the newscast, you decide to gather more information about both the Superfit Fitness Center and Glop Industries. Visit the following sites to obtain more information on the situation:

- Information about [Susser Syndrome from the Epiville Department of Health Webpage](#)
- Information about [Superfit Fitness Center where the outbreak occurred](#)
- Information about [Glop industries which produces the suspected causal agent SUPERCLEAN](#)

You decide to visit the Superfit Fitness Center. Upon entering, you are immediately greeted by Mr. Abe Crunch who is very responsive to your questions.

"I've been the manager here at Superfit since we opened. As you probably know, Superfit is actually owned by SUPERCLEAN Industries. As you can see, we have nothing but state-of-the-art facilities, state-of-the-art equipment, and all of our trainers are certified. Frankly, this place is awesome. We even have a gift shop! SUPERCLEAN Industries has a licensing agreement with Glop Industries and as a result we only carry products manufactured by Glop. In fact, we carry some things that you can't even get outside of here. For example, all of our members exclusively drink the sports drink Quench-It and eat the energy bar EnduroBrick - those two products cannot be found in retail stores. And rather than have them walking around with money while they're working the free weights, we issue each member a fitness credit card they use to keep track of their food and drink and other purchases. As for a number of members being sick, well, the only thing I can say is, we all get sick from time to time. I mean, who hasn't been sick?"

Interview - Abe Crunch



Your next goal is to meet with Hank Lockjaw, the production floor foreman at Glop Industries.

"My grand-daddy was a Glop man, my daddy was a Glop man, and I've been a Glop man my whole life. I was promoted to foreman a few years back, just before we started making SUPERCLEAN. Right behind you is the production line of Quench-it. Those plastic bottles shoot down the conveyer belt and then are filled up with the drink. The hard part is keeping

Interview - Hank Lockjaw

the bottles nice and clean. Just last week we installed a brand new sterilization system. A couple of years ago we used to rinse the empty bottles with SUPERCLEAN to sterilize them before adding Quench-it. Before that we just used hot water. Now, we only use this gamma radiation trick to sterilize the bottles. It's supposed to be more efficient and cheaper in the long run than using the SUPERCLEAN. Like I said, we only switched last week so time will tell. Let's see - over in the other corner is the EnduroBrick line. The bars ride on the conveyer belt through that big oven which serves to not only bake them but to sterilize them as well. My job is to make sure everything runs nice and smooth and I'll tell you, there's been not a single breakdown on my watch."



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### Study Design

Now that you have thoroughly assessed the situation, you have enough information to generate some hypotheses. The two suspected causal agents of the outbreak of Susser Syndrome are Quench-It and EnduroBrick. Use the case-control method to design a study that will allow you to compare the exposures to these products among your cases of Susser Syndrome and healthy controls of your choice. From all of your class work, you know that you want your hypotheses to be as explicit and detailed as possible.

**1. Based on the information you gathered, which of the following hypotheses is the most appropriate for your case-control study?**

- a. (1) Those who consumed EnduroBrick are more likely to be diagnosed with Susser Syndrome than those who did not; (2) Those who consumed Quench-It are more likely to be diagnosed with Susser Syndrome than those who did not consume Quench-It.
- b. Individuals diagnosed with Susser Syndrome are more likely to have been members of the Superfit Fitness Center than individuals without Susser Syndrome.
- c. Individuals diagnosed with Susser Syndrome are likely to be exposed to a variety of different exposures than are individuals not diagnosed with Susser Syndrome

Now that you have hypotheses, the next step is to prepare the case definition. This requires us to

understand how Susser Syndrome is diagnosed. The more certain you are about your diagnosis the less error you will introduce into your study by incorrectly specifying cases. Based on information from the [EDOHI](#) website, you decide that your case definition will be based on a clinical diagnosis of Susser Syndrome.

After you establish your case definition, you need to decide on the population from which the cases for your study will be obtained. Since the majority of cases from the recent outbreak were active members of the Superfit Fitness Center, you decide to base your study on this population.

Next you need to decide how you will classify your cases and controls based on exposure status. Remember, we are actually operating under two hypotheses here, each with its own unique exposure variable. Scientists working on the possible causal connection between consumption of EnduroBrick or Quench-It and the development of Susser Syndrome suggest that both exposures may have an [Induction time](#) of at least 6 months. Under this hypothesis, any cases of Susser Syndrome that occurred within 6 months of initial consumption of either EnduroBrick or Quench-It could not have plausibly been caused by the exposure. Thus, you stipulate that at least 6 months are required to have elapsed since the initial exposure, before your individual will be considered "exposed".

Once all of these decisions have been made, it is time to create appropriate eligibility criteria for your cases and controls.

**2. Which of the following do you think are the best eligibility criteria for the cases?**  
[Aschengrau & Seage, pp. 239-243]

- a. Cases should have been members of the Superfit Center in the last two years for at least 6 months (total) and consumed either EnduroBrick or Quench-It.
- b. Cases should be correctly diagnosed with Susser Syndrome and be employed at Glop Industries.
- c. Cases should be correctly diagnosed with Susser Syndrome and have been members of the Superfit Fitness Center for at least 6 months in the last two years.

Now you need to decide who is eligible to be a control.

You recall from your wonderful learning experience in P6400 that valid controls in a case-control study are individuals that, had they acquired the disease under investigation, would have ended up as cases in your study. The best way to ensure this is to sample controls from the same population that gave rise to the cases. To ensure that the controls accurately represent a sample of the distribution of exposure in the population giving rise to the cases, they should be sampled independently of exposure status.

**3. Which of the following do you think are the best eligibility criteria for the controls?**

- a. Controls should be residents of EpiVillage who have not been diagnosed with Susser Syndrome.
- b. Controls should be members of the Superfit Fitness Center who have been diagnosed with Susser Syndrome but have not consumed either EnduroBrick or Quench-It.
- c. Controls should be members of the Superfit Center for at least 6 months in the last 2 years and not be diagnosed with Susser Syndrome at the time of data collection.

Now that the eligibility criteria have been set, you must determine the specifics of the case-control study design.

### How many cases and controls should you recruit?

The answer to this question obviously depends on your time and resources. However, an equally important consideration is how much power you want the study to have. Conventionally, we want a

study's power to be at least 80 percent in being able to find a significant difference between the groups. Generally, if the study has less than 80 percent power, we conclude that the study is underpowered. This does not mean our results are incorrect; but if we observe an insignificant result in an underpowered study we may not be able to tell whether this is because there truly is no association or whether this is due to the lack of power in the study.

## Intellectually Curious?

Learn more about [power and sample size](#).

After crunching the numbers, you determine that the study will require the following size to achieve a desired power of 80 percent:

Number of cases: 112  
Number of controls: 224  
Total number of subjects: 336

Bear in mind that the study is voluntary. Subjects, even when eligible, are in no way required to participate. Furthermore, subjects may drop out of the study before completion, further decreasing your sample size. Study participation depends in large part on the methods of recruitment. In-person recruitment is generally regarded as the most effective, followed by telephone interviews, and then mail invitations. The participation rate that you expect to achieve, given your method of recruitment, will help you to calculate approximately how many individuals you will need to contact in order to meet your sample size.

Should you recruit cases and controls simultaneously or cases first and then all controls? [Learn more here](#).

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## Data Collection

With the design of the case-control study complete, you now begin planning the protocol for data collection.

### 4. What is the best source for ascertaining cases? [Aschengrau & Seage, pp. 236-239]

- a. Identification of cases of Susser Syndrome from hospital charts of the local hospital. Diagnoses are based on clinical assessment and are supported by brain imaging results.
- b. Identification of subjects complaining of neurological symptoms from the records of the Superfit Center's staff nurse
- c. Identification of cases from the records of a prominent EpiVillage neurologist in private practice

### 5. What is the best method of ascertaining the cases? [Aschengrau & Seage, pp. 236-239]

- a. Look through the records of the local hospital dated in the last two years to identify those with the disorder.
- b. Look through the records of the local hospital dated in the last two years to identify those with the disorder and see if there is information in the chart about their membership in the Superfit Fitness Center
- c. Link the computer database of the Membership Directory of the Superfit Fitness Center with the discharge database of the local hospital

### 6. What is the best way to accrue the controls? [Aschengrau & Seage, pp. 239-243]

- a. Cross-reference the Superfit Fitness Center 's Membership directory with the local hospital's discharge database taking patients treated there for diseases other than the Susser Syndrome.
- b. Ask the Membership Services of the Superfit Center to provide you with the names of new members who have enrolled in the last year and are active members in good standing.
- c. Take a random sample of people from the Membership Directory of the Superfit Fitness Center and determine their eligibility criteria. Those eligible will be asked to participate in the study by phone. If they agree to participate, an interview will be scheduled

Now you must decide how you will assess exposure to Quench-It and Endurobrick in your case-control study.

**7. Given the study design, what is the best way to define the exposure variable?**

- Directly observe the consumption of EnduroBrick or Quench-It at the Superfit Fitness Center
- Question all study subjects as to their own assessment of EnduroBrick and Quench-It consumption using a standardized survey tool.
- Use the Superfit Fitness Center credit card billing system to identify exposure to EnduroBrick and Quench-It in the members.

Having received the necessary IRB approval and addressed various [administrative details](#), the study may now commence. The data begin to file back to the Department of Health and must now be carefully entered into the computer database. Once all of the data are entered, you can proceed to the analysis stage where the associations proposed in your two hypotheses are characterized and tested.

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### Data Analysis

The data collected yield the following counts:

Total number of Cases: **112**  
 Total number of Controls: **224**  
 Number of Cases who ingested Endurobrick: **28**  
 Number of Controls who ingested Endurobrick: **56**  
 Number of Cases who consumed Quench-it: **50**  
 Number of Controls who consumed Quench-it: **56**

**8. How would you set up the classic 2x2 table using the above information to test the hypothesis that cases are more likely to have ingested EnduroBrick than controls?**

- See the 2x2 table
- Calculate the odds of exposure among cases
- Calculate the odds of exposure among controls
- Calculate the exposure Odds Ratio (OR)

- e. Calculate the odds of Susser Syndrome among the exposed
- f. Calculate the odds of Susser Syndrome among the unexposed
- g. Calculate the disease Odds Ratio
- h. Interpret your findings

**9. How would you set up the classic 2x2 table using the above information to test the hypothesis that cases are more likely to have consumed Quench-It than controls?**

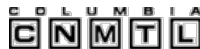
- a. See the 2x2 table
- b. Calculate the odds of exposure among cases
- c. Calculate the odds of exposure among controls
- d. Calculate the exposure Odds Ratio (OR)
- e. Calculate the odds of Susser Syndrome among the exposed
- f. Calculate the odds of Susser Syndrome among the unexposed
- g. Calculate the disease Odds Ratio
- h. Interpret your findings

**10. Now you must present your findings to your supervisor. What is your recommendation?**

- a. Both the data on EnduroBrick and Quench-It consumption were inconclusive. The study should be repeated with more participants.
- b. While ingestion of EnduroBrick does not cause Susser Syndrome, the data do indicate that consumption of Quench-It does cause Susser Syndrome.
- c. The data suggest that the consumption of Quench-It is associated with later development of Susser Syndrome whereas the ingestion of EnduroBrick does not appear to be associated with Susser Syndrome. You suggest that you should explore other potential exposure sources to rule out other potential causes of Susser's Syndrome as well as to further characterize this association.

After reporting your results, you decide to do a little bit more detective work. You head over to the Public Health Laboratory records department and check the log file on Quench-It. Since its production, the Health and Food Safety Inspector has taken random samplings of Quench-It back to the lab to analyze for any possible contamination. This is a routine surveillance procedure. Looking over the file you notice something interesting . Since 2002, a substantial amount of SUPERCLEAN has been found in Quench-It, probably a result of the bottle sterilization process. Following the Department of Health's repeated and stern demands, Glop Industries has recently changed its production techniques, and now Quench-It is now completely free of SUPERCLEAN. Those who consumed Quench-It prior to these changes, however, might have been exposed to trace amounts of SUPERCLEAN

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### Discussion Questions

Carefully consider the following questions. Write down your answers (1 - 2 paragraphs) for question # 1 within a word document and submit your answers to your seminar leader. Be prepared to discuss all questions during the seminar section.

- Epidemiologic case-control studies often report increased risk of an event given exposure, but we know that we can only calculate the odds ratio in a case-control study as opposed to a risk ratio. Is it important to distinguish between a risk ratio and an odds ratio? When does Odds Ratio approximate the Risk Ratio? When does it approximate the Rate Ratio?
- Why is the selection of controls important? What methods of control selection do you know? What principles should we follow when selecting controls?
- What are the limitations of using questionnaires to assess exposure status in study subjects? What kind of bias could be introduced by the use of questionnaires in determining exposure status? If present, what could be the effects of this bias on the study findings? Does our study design limit or avoid this bias?

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