JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Methods in Drug Effectiveness Research: Part 1

Jodi Segal, MD, MPH
Johns Hopkins University

Content of Methods in Drug Effectiveness Research: Part 1

1. Trials versus observational designs for causal inference
2. Cohort design including target trial emulation
3. Case-control designs
4. Self-controlled designs

Trials Versus Observational Designs for Causal Inference

Trials versus Observational Designs for Causal Inference: Overview

- Defining causal effects
- Planning a nonexperimental study
- Common nonexperimental study designs

Drawing Causal Inferences

- We usually aim to learn whether a particular intervention **caused** a change in outcomes, relative to some alternative exposure
- This is what is tested in trials: the manufacturer of a new product randomizes volunteers to receive the product or receive a placebo (or other therapy) and assesses the outcomes
- Many pharmacoepidemiology studies aim to estimate the effects of treatments on outcomes
  - We need to be careful about claiming a causal effect when exposure to the intervention of interest is not randomized

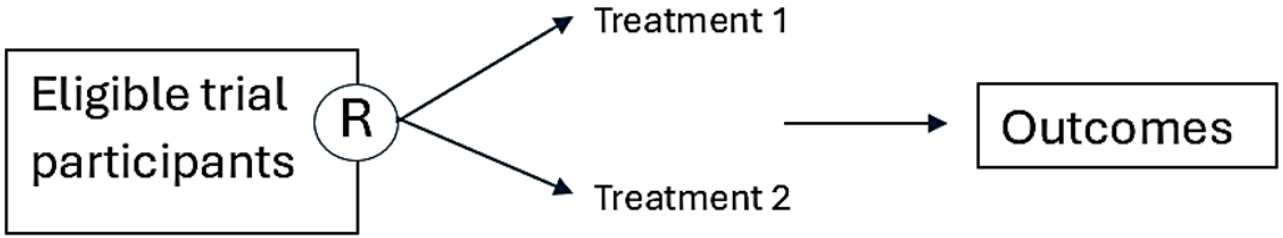
Rationale for Good Causal Inference Practices

- Causal inference requires clear statement of the research question
  - Populations, exposures, comparison exposures, outcomes, and the estimand

- Causal inference is complicated when the individuals who receive one treatment differ importantly from individuals who receive the other
  - E.g., patients given a particular chemotherapy regimen may be sicker than those given another
  - Differences in outcomes could be due to the drugs—or to those other differences between the treated groups

Rationale for Causal Inference Standards

- Randomization facilitates causal inference because it assures that the groups receiving different treatments do not differ on anything besides the treatment



- When randomization is not possible or is not used, the study designer needs to attend to issues of bias and confounding at time of **study design** and **during the analysis**
  - Many nonexperimental designs exist
  - Need to choose design carefully, given research question and data limitations

Image source: Jodi Segal.

Confounding

- A confounder is:
  - Associated with the exposure of interest
  - Associated with the outcome of interest
  - It is present at baseline (at the time of exposure)
  - Not in the “causal path” between exposure and outcome

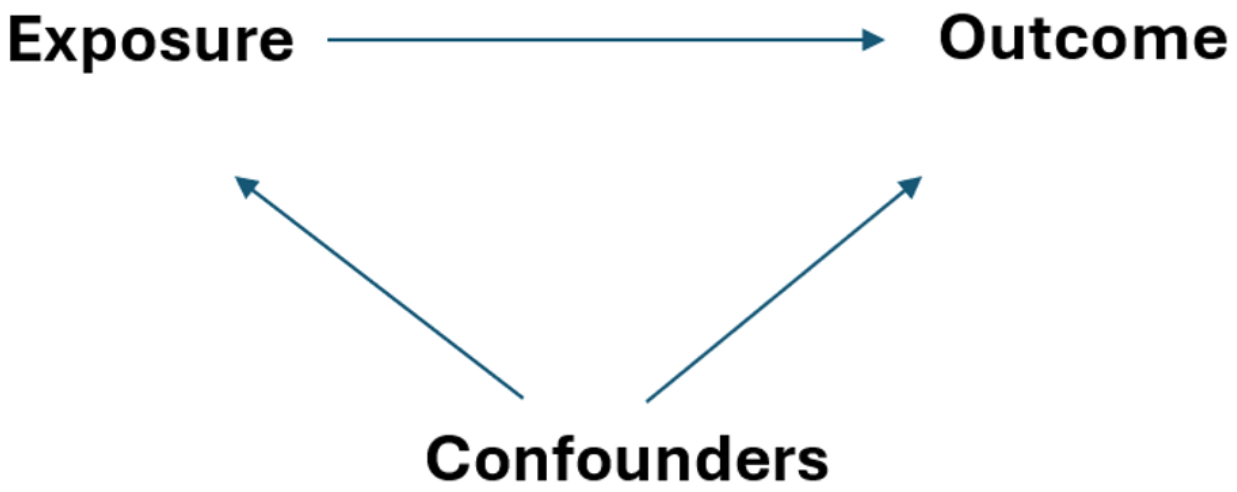


Image source: Jodi Segal.

Who Is More Likely to Receive Opioid Pain Medication Rather Than a Non-Steroidal Anti-inflammatory Drug?

Patient 1	**Patient 2**
Metastatic prostate cancer	Low back pain
Bleeding gastric ulcer	Healthy

- Who is at higher risk of death in the next three months? **Patient 1**
- Therefore, a study making causal claims about the relationship between opioid use and death will be confounded ("sick people get opioids")

Confounding by Indication

- Those given a treatment of interest are often those individuals who are at the greatest risk for the outcome of interest
- For example, insulin users have a higher rate of cardiac-related deaths than metformin users. Are these deaths caused by insulin?

	Insulin users	**Metformin users**
Disease duration	10 years	6 months
Mean age	68 years	52 years
Prevalence of hypertension	82%	62%

Example of the "Balance" Obtained in an Experiment (Trial)

IQR = Interquartile range
ICU = Intensive care unit

Table 1. Participant characteristics at randomization

Characteristic	Treatment 1 (n = 120)	Treatment 2 (n = 120)
Male sex, number (%)	70 (54.3)	67 (55.8)
Age, median (IQR), y	62 (53–69)	62 (51–74)
Functional Comorbidity Index, median (IQR)	2 (1–4)	2 (1–4)
Time from hospital to ICU admission, median (IQR), d	1 (0–2)	1 (0–2)
ICU admission diagnosis category, number of patients	-	-
Cardiovascular disease (%)	35	35
Respiratory disease (%)	43	41
Gastrointestinal tract disease (%)	29	30

Some Common Observational Designs for Pharmaco-epidemiology

- **Retrospective cohort study**:
  - Everything has already happened
  - You select exposed and unexposed individuals and observe what their experience was over time

- **Case control study**:
  - Everything has already happened
  - You select individuals with the outcome and without the outcome and look to see who previously had the exposure of interest

- **Self-controlled designs (e.g., case-crossover)**:
  - Everything has already happened
  - An individual serves as his/her own control
  - You compare the rates or counts of outcomes in periods of time considered to be the exposed time and periods of time considered to be unexposed time

Cohort Design Including Target Trial Emulation

Cohort Studies

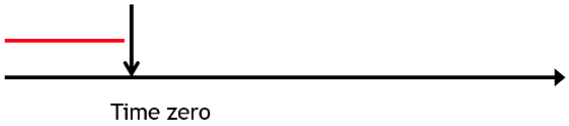
- Why and when
- Design
- Analysis
- Confounding and bias

Define the Population

- Population should be defined based on the characteristics measured at the time of treatment choice or before
  - Not on things that may be affected by the treatment, such as side effects, outcomes, or adherence to the intervention
  - This is true when exposure is time-varying as well

- In a prospective study, as in a randomized trial, use the time of study entry to define the study population
  - All individuals randomized should be included in the analysis

- In a retrospective study, use a defined time period prior to exposure to define the study population
  - Similar to inclusion/exclusion criteria in a randomized trial



A Common Observational Design for Pharmacoepidemiology: A Retrospective Cohort Study

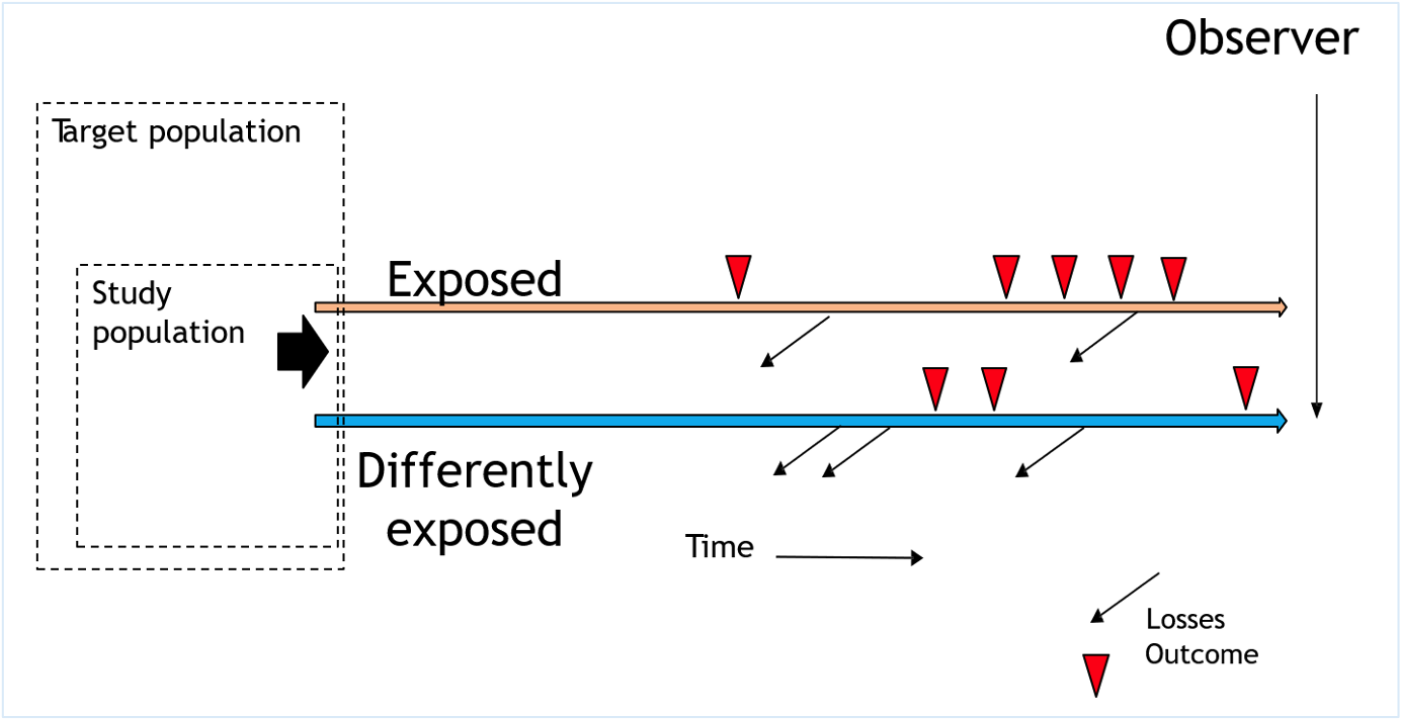


Image source: Jodi Segal.

Ideal World

- Perfectly valid exposure and outcome information
- Complete follow-up
- Entirely comparable (unexposed) comparison group (no confounding by indication)
- Completely generalizable cohort

Goal: Adverse Drug Effects and Beneficial Drug Effects

- Questions about adverse effects:
  - Does exposure to a statin increase the risk of myopathy relative to ezetemibe?
  - Does exposure to zolpidem increase the risk of falling in older people relative to a benzodiazepine?

- Questions about beneficial effects:
  - Does use of alendronate reduce the risk of hip fracture relative to denosumab?
  - Does 10-year use of tamoxifen reduce the risk of recurrent breast cancer relative to 5-year use?

Analysis of Retrospective Cohort Study

- Simplistically: relative risk (RR) of events for exposed and unexposed people
  - **Exposure time**: person-time during which people are exposed
  - **Unexposed time**: person-time during which people are unexposed (or differently exposed)

$$RR = \frac{\text{Events/person−time exposed}}{\text{Events/person−time unexposed}}$$

- This is a valid estimate of risk if there is no loss to follow up and individuals do not have a competing event (like death) that prevents them from having the outcome of interest

- Individuals can contribute person-time to both the exposed and unexposed groups if appropriate
  - The medication could be considered a time-varying exposure
  - The event is “assigned” to the exposure group of the person at the time of the event

Many Considerations When Defining the Exposure

- How is dose best considered when defining the exposure?
  - For example: Does 1 year of 80 mg of atorvastatin equal 4 years of 20 mg of atorvastatin? What if someone misses a prescription fill and has a "gap" of 30 days?
- Uncertain induction period: a period during which effect of the exposure cannot reasonably occur
  - For example: Is one month of bisphosphonate exposure long enough to see a reduced fracture incidence?
- How is the exposure known?
  - For example: Is this PRESCRIPTION data or is this CLAIMS data where you can see that a prescription was filled?

Many Considerations When Defining the Outcomes

- Should an individual be permitted to have an outcome more than once?
  - For example: Is the outcome first hospitalization or any hospitalization?
- Should the outcome be a composite outcome?
  - For example: Is it stroke OR myocardial infarction; is it emergency department visit OR hospitalization?
- How is the outcome known?
  - For example: Is this known from the electronic health record with a laboratory measure (elevated troponin to indicate myocardial infarction) data or is this CLAIMS data where you see a claim for a visit with a diagnosis code?

Target Trial Framework for Cohort Studies

- Best practice is to have a detailed protocol before initiating any observational study
- A target trial framework may be valuable when designing cohort studies
- This framework asks the investigator to specify what the study would look like **if it were designed as a randomized trial** and urges the investigator to specify the parallel choices for the observational study

Source: Hernán, M. A., & Robins, J. M. (2016). Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *American Journal of Epidemiology, 183*(8), 758–764. https://doi.org/10.1093/aje/kwv254

Example of Target Trial Framework

GLP-1 = Glucagon-like peptide 1

SGLT-2 = Sodium-glucose transport protein 2

Element	Target Trial (Hypothetical)	Cohort Study Using Electronic Health Record (EHR) Data
Eligibility criteria	Individuals with uncontrolled type 2 diabetes (DM) never exposed to GLP-1 agonist or SGLT-2 inhibitor	Individuals with uncontrolled type 2 DM never observed to have prescription for GLP-1 agonist or SGLT-2 inhibitor
Treatment strategies	Remain on existing medication and add a GLP-1 agonist. Remain on existing medication and add a SGLT-2 inhibitor	One treatment group is patients who received GLP-1 agonists without removal of other meds; the other is patients who received SGLT-2 inhibitor with removal of other meds
Assignment procedures	Participants will be randomly assigned to either strategy at baseline and will be aware of strategy	Match participants in the two exposure groups so that exposure groups are alike aside from exposure
Follow-up period	Start at randomization and ends at a cardiovascular event or death	Starts at initiation of new therapy and ends at cardiovascular event or death
Outcome	Cardiovascular event as confirmed by adjudication committee	Cardiovascular events recorded in EHR data with confirmatory diagnostics or use of procedures
Causal contrasts of interest	Intention-to-treat effect	Intention-to-treat effect
Analysis plan	Intention-to-treat effect estimated via comparison of 2-year cardiovascular outcomes among individuals assigned to each treatment strategy	Intention-to-treat effect estimated via comparison of 2-year event rates among matched individuals in the treatment groups

Key Considerations With a Target Trial Framework

- Careful definition of time zero—usually when an eligible individual initiates the treatment of interest (or receives the prescription or fills the prescription)
- May need to specify a grace period—this is a period following the chosen time zero during which the participant actually becomes exposed
- Interesting analytic methods such as the **clone-censor-weight approach** in which each individual's data is duplicated
  - One "clone" is assigned to each treatment group and observed over time until the received treatment is no longer consistent with the assigned treatment and the individual is censored; the remaining individuals are weighted by their probability of not being censored based on their baseline characteristics
  - The relative risk estimate includes these censoring weights

Threats in Retrospective Cohort Studies

- The estimand (the relative risk) will be biased if comparison group and exposed group are different and these differences are also related to the outcomes
- Biased estimates often arise from including prevalent users of drugs rather than only incident users
- Immortal time bias is a risk in cohort studies that can be avoided with careful design choices

- *These will all be discussed in Module 3*

Antibiotics for SSTI in Children: An Example of a Cohort Study

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification

- Cohort is children with skin and soft tissue infections (SSTIs)
- Exposure:
  1. Trimethoprim-sulfamethaxazole
  2. Beta-lactams
- Comparison exposure: clindamycin
- Outcome: Recurrent SSTI within 14 days and between 15 and 365 days after the incident SSTI (SSTIs were determined with a specific ICD-9-CM code and a filled prescription for an antibiotic within 2 days)
- Estimand: adjusted hazard ratio

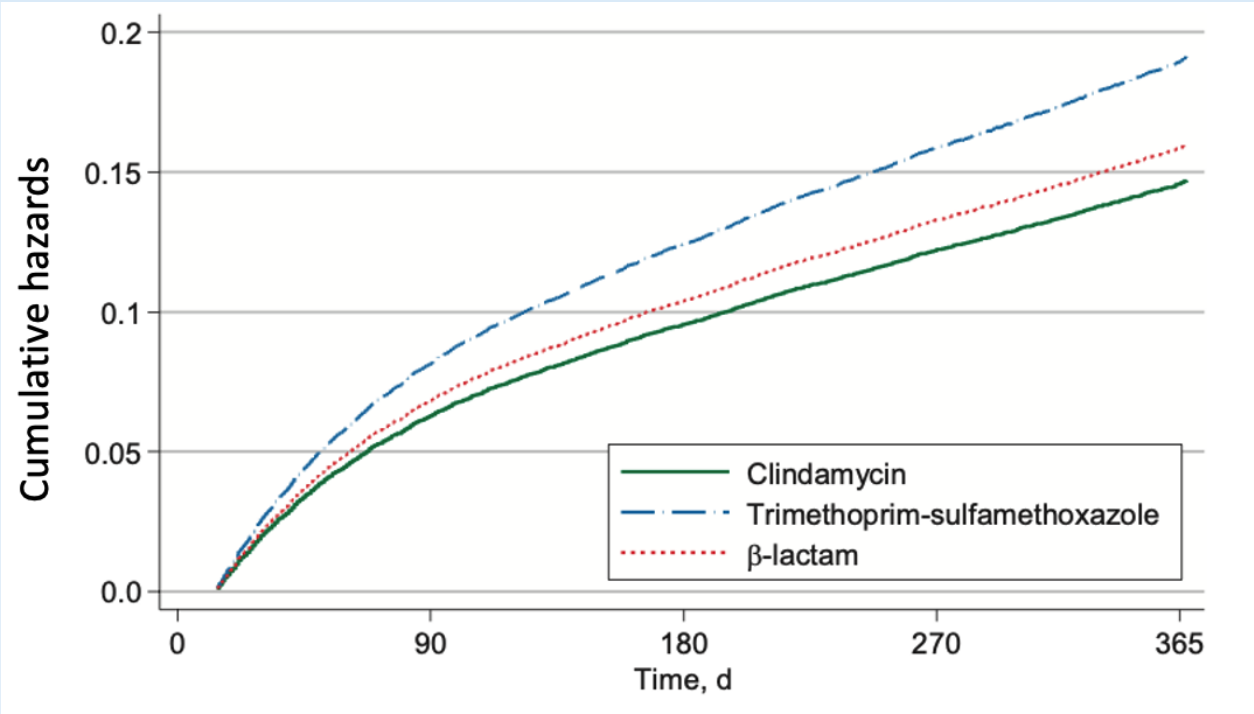
Source: Williams et al. (2011). Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft-tissue infections. *Pediatrics, 128*(3), e479–e487. https://doi.org/10.1542/peds.2010-3681

Failures Among Children Who Had a Drainage Procedure—1

	Clindamycin	Trimethoprim-sulfamethoxazole	β-Lactam
Events, number per 1,000 person-years	173.0	270.1	250.9
Unadjusted hazard ratio (95% confidence interval)	1.00 (reference)	1.51 (1.29–1.77)	1.47 (1.26–1.72)
Adjusted hazard ratio (95% confidence interval)	1.00 (reference)	1.26 (1.06–1.49)	1.42 (1.19–1.69)

Source: Williams et al. (2011). Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft-tissue infections. *Pediatrics, 128*(3), e479–e487. https://doi.org/10.1542/peds.2010-3681

Failures Among Children Who Had a Drainage Procedure—2



Source: Adapted from Williams et al. (2011). Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft-tissue infections. *Pediatrics, 128*(3), e479–e487. https://doi.org/10.1542/peds.2010-3681 (y-axis label added)

Case-Control Designs

Case-Control Design

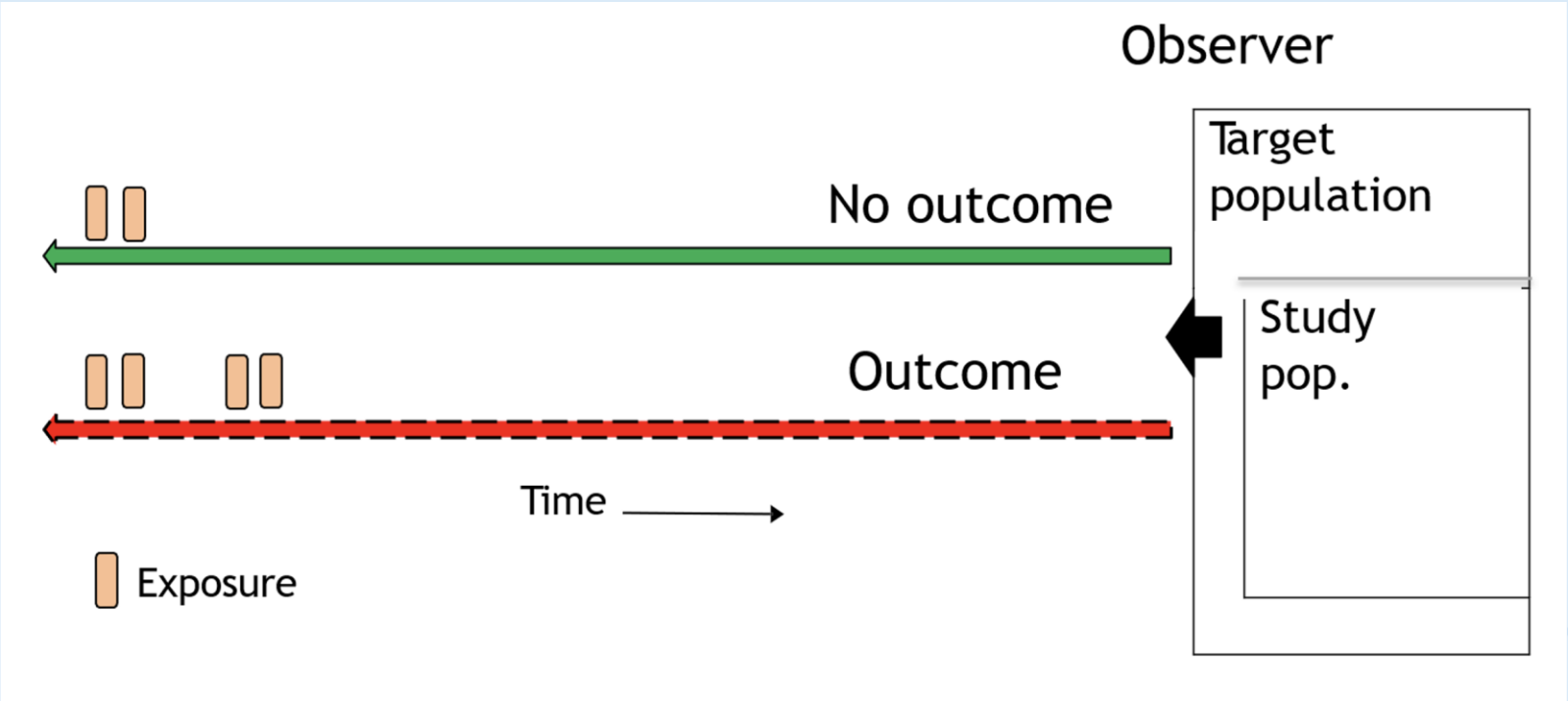


Image source: Jodi Segal.

Less Used Than Cohort Studies in Pharmacoepidemiology

- We often have the data to do a cohort study which is a stronger design
- Harder to manage time-varying exposures in a case-control design; typically need to collapse exposures into categories of exposure during the look-back time (1 year of continuous exposure, 2 years of continuous exposure, etc.)
- Difficult to analytically account for competing risks (patients who die before they can experience the outcome)
- Less certainty about how much matching should be done of the individuals with and without the outcomes

Case-Control Study

- A study that compares cases **with an outcome** to controls **without the outcome** looking for **exposures that preceded the outcome**

- Advantages:
  - Ideal for uncommon outcomes
  - Can study multiple exposures if there are hypotheses about several drugs

- Disadvantages:
  - Problematic control selection
  - Possible biases in exposure data (because of retrospective collection) but this is the case in any secondary data

- Case-control design is most often used when the outcome is a harm that is hypothesized to be related to the drug exposure (and the question of “ever-exposed” is a reasonable question)

Let's Think About a Medicine and Risk of Congenital Disorders

Cases	Controls
▶ Perhaps all women in a registry who had an infant with the condition of interest ▶ Alternative: all women across a network of health systems who delivered an infant identified at birth with the congenital disorder	▶ Perhaps a random sample of women who had an infant **without** the condition of interest in the population ▶ Alternative: women who had an infant with a different (unrelated) condition

Considerations in Case-Control Studies

- Odds ratio will approximate the risk ratio for rare outcomes

	Cases	Controls
Exposed	a	b
Unexposed	c	d

- Odds ratio:

$$\frac{Odds\ of\ exposure\ among\ the\ cases}{Odds\ of\ exposure\ among\ the\ controls}$$

- Odds ratio for 2x2 table: $\frac{a/c}{b/d}$

- Odds ratio is calculated with:
  - McNemar's test, if the matching is 1:1
  - Conditional logistic regression, if the matching is more than 1:1 or if you need to control for confounders

Antibiotics for SSTI in Children: An Example of a Case-Control Study Examining Effectiveness of Treatments

- Cases:
  - Children with skin and soft tissue infection (SSTI) who did not recover
- Controls:
  - Children with SSTI who recovered
- All were nested in a cohort of individuals treated in specified pediatric practices
- Researchers were able to look at multiple exposures simultaneously—exposures to the drugs of interest

Source: Elliott, D. J., Zaoutis, T. E., Troxel, A. B., Loh, A., & Keren, R. (2009). Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant Staphylococcus aureus. *Pediatrics, 123(*6), e959–966.

Antibiotics for SSTI in Children: Case and Control Subject Selection

- Unrecovered children with SSTI were identified by using administrative data and chart review
- Each confirmed case subject was matched randomly to four control subjects who successfully recovered in the same calendar quarter
- Subjects were matched according to calendar quarter to control for changes in clinical practice attributable to increasing awareness of methicillin-resistant *Staphylococcus aureus* (MRSA) over time

Source: Elliott, D. J., Zaoutis, T. E., Troxel, A. B., Loh, A., & Keren, R. (2009). Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant Staphylococcus aureus. *Pediatrics, 123*(6), e959–966.

Antibiotics for SSTI in Children: Analyses

- Investigators used conditional logistic regression and adjusted for potential confounders

- Confounding by indication was a concern:
  - Clinicians would be more likely to prescribe MRSA-active therapy for patients whom they perceived to be at higher risk of treatment failure
  - This was addressed in two ways:
    1. Included covariates that likely reflected the severity of illness at presentation (adjusting for severity)
    2. Performed a sensitivity analysis in which they excluded all children who were hospitalized or required a drainage procedure within two days after the index visit

Source: Elliott, D. J., Zaoutis, T. E., Troxel, A. B., Loh, A., & Keren, R. (2009). Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant Staphylococcus aureus. *Pediatrics, 123*(6), e959–966.

Antibiotics for SSTI in Children: Results

- Main results: relative to a β-lactam antibiotic
  - OR for failure to recover with clindamycin: 1.4 (95% CI 0.76–2.59)
  - OR for failure to recover with TMP-SMX: 2.35 (95% CI 1.28-4.34)

- Authors concluded that compared with beta-lactams, clindamycin monotherapy conferred no benefit, whereas trimethoprim-sulfamethoxazole was associated with an increased risk of treatment failure in a cohort of children with nondrained non-cultured SSTIs who were treated as outpatients

- Successful as a case-control study because it is not a chronic medicine—BRIEF EXPOSURE

OR = Odds ratio

CI = Confidence interval

TMP-SMX = Trimethoprim/ Sulfamethoxazole

Source: Elliott, D. J., Zaoutis, T. E., Troxel, A. B., Loh, A., & Keren, R. (2009). Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant Staphylococcus aureus. *Pediatrics, 123*(6), e959–966.

Self-Controlled Designs

Case-Crossover Design (A Case-Only Design)

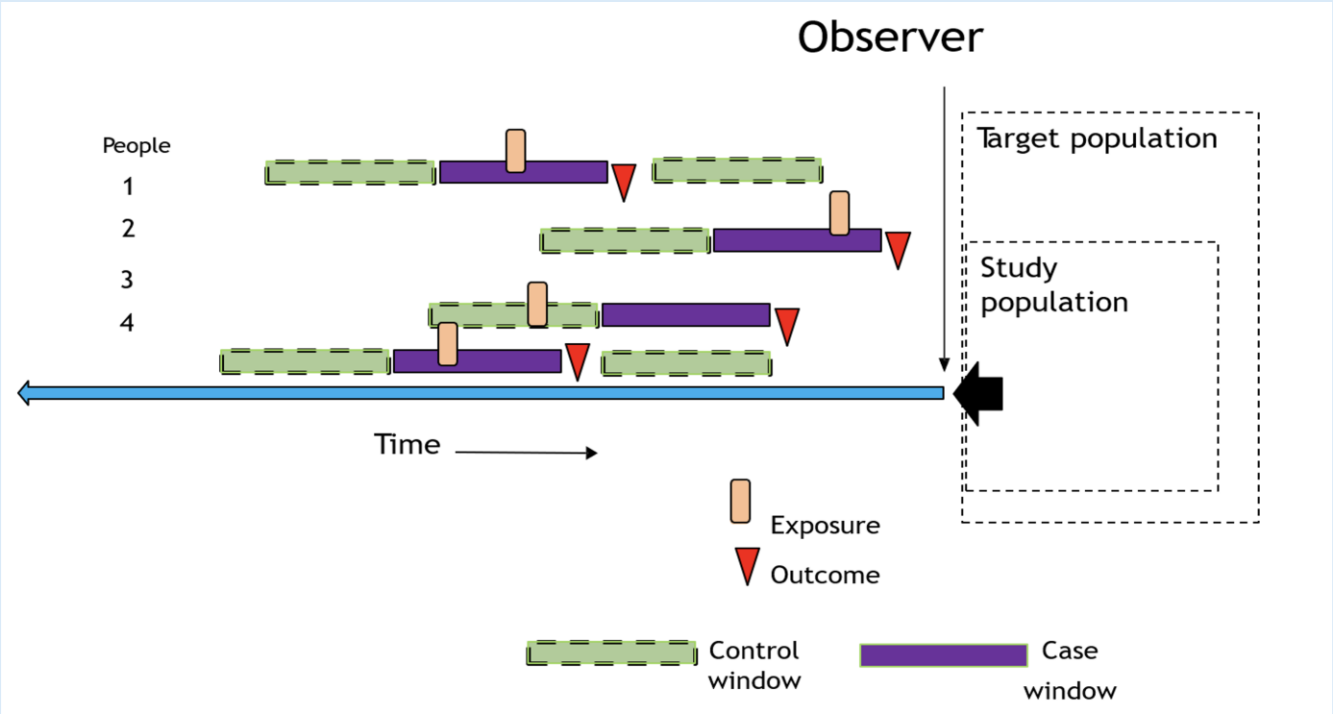


Image source: Jodi Segal.

Case-Crossover Design Origin

- Like case-control studies, these are retrospective studies
- “Case-only” analysis (no control subjects)
- Explores how a brief exposure might lead to a transient change in the risk of an acute event
- A valuable self-controlled design first described by Dr. Malcolm Maclure in 1991
- Design was prompted by challenges of selecting controls in usual case-control studies

Case-Crossover Design

- Using cases as their own controls reduces confounding
- Design requires intermittent exposure of cases, with periods during which the cases are not exposed to the hypothesized risk
- Case-crossover design answers the question: Was this event triggered by something unusual that happened just before?
  - What happened just before the event?—easy
  - How unusual was that?—tricky

Effect Period Definitions

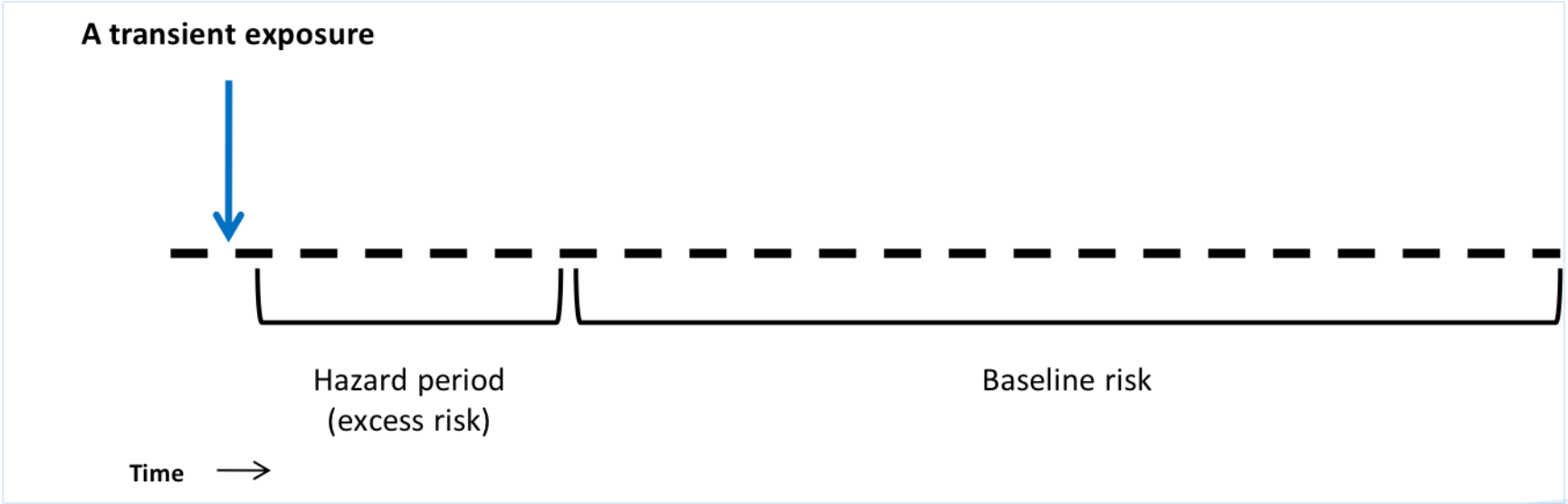


Image source: Jodi Segal.

Other Key Periods

- Induction time: time between cause and effect in an individual
- Effect period: time between minimum and maximum induction times in a population
- Hazard period: time of elevated risk

Image source: Jodi Segal.

Baseline Risk Before the Exposure

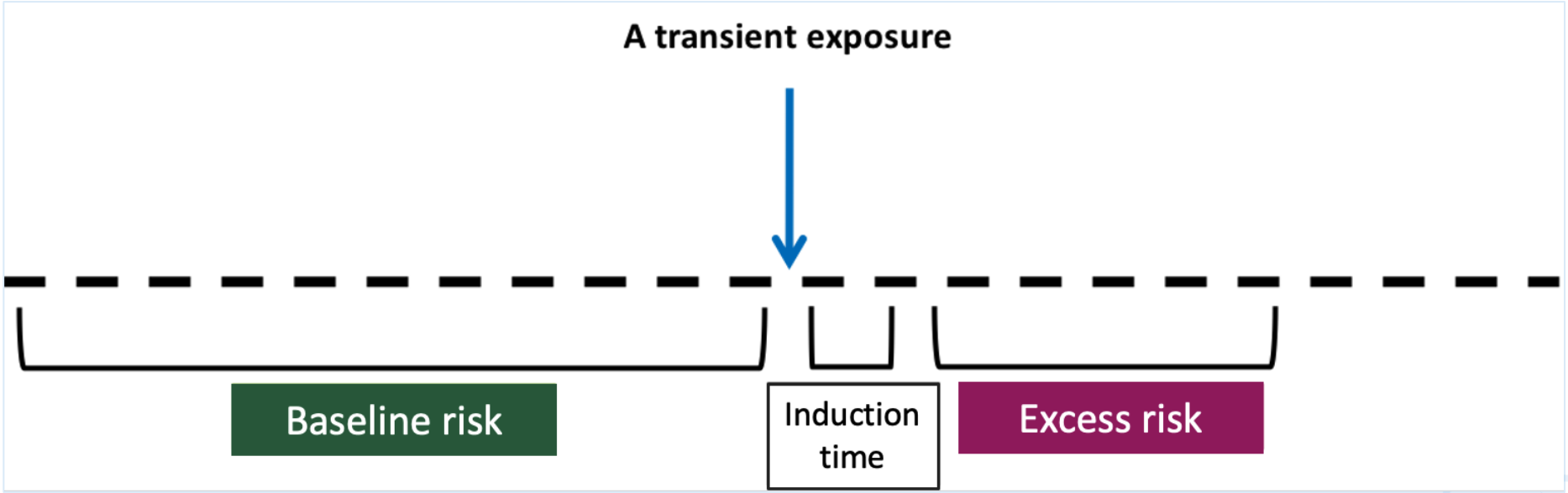


Image source: Jodi Segal.

Baseline Risk Before and After Exposure

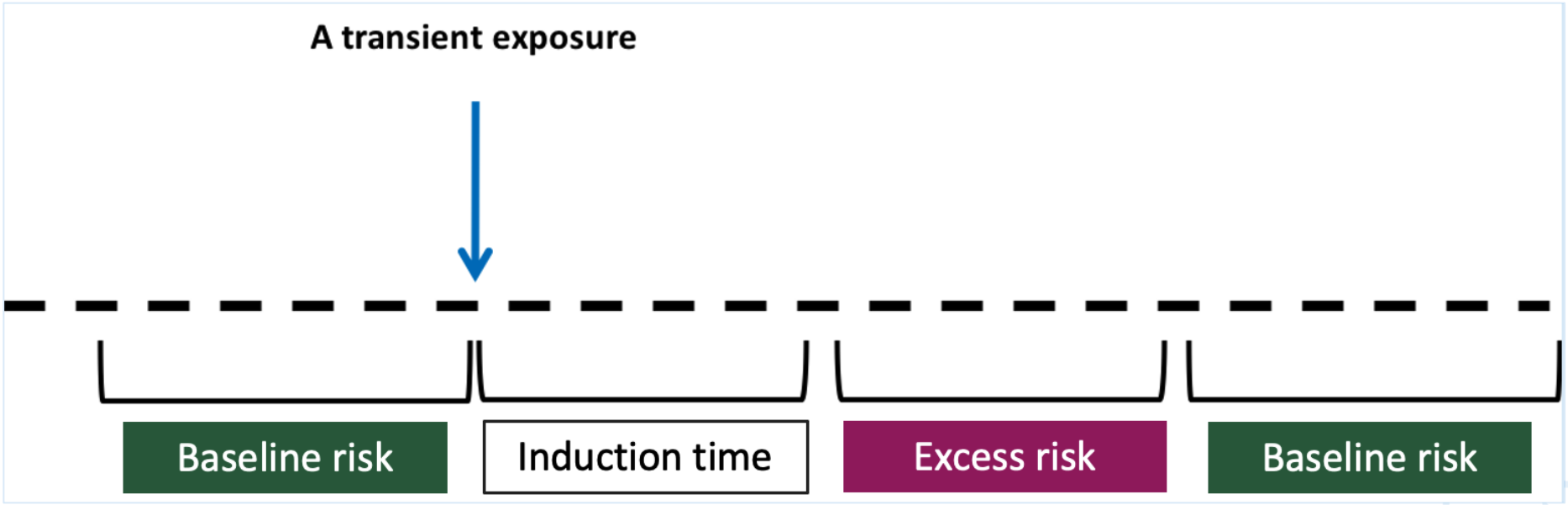


Image source: Jodi Segal.

Illustrating a Longer Exposure

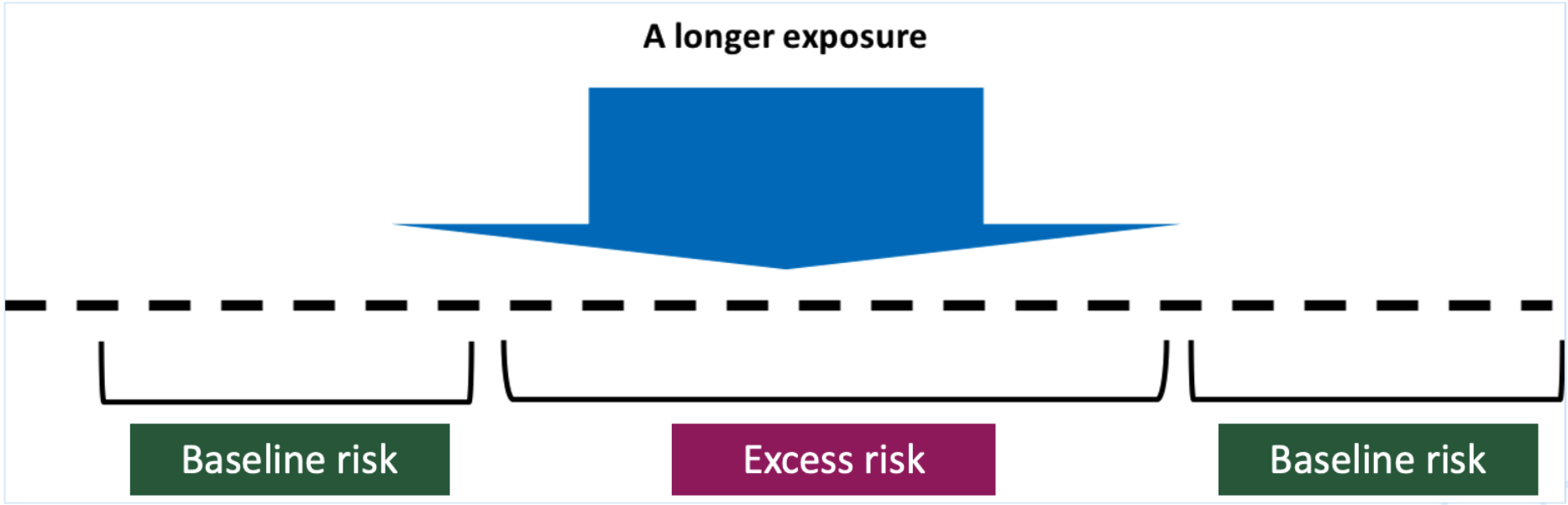


Image source: Jodi Segal.

Three People and When They Had Their Events (Myocardial Infarction)

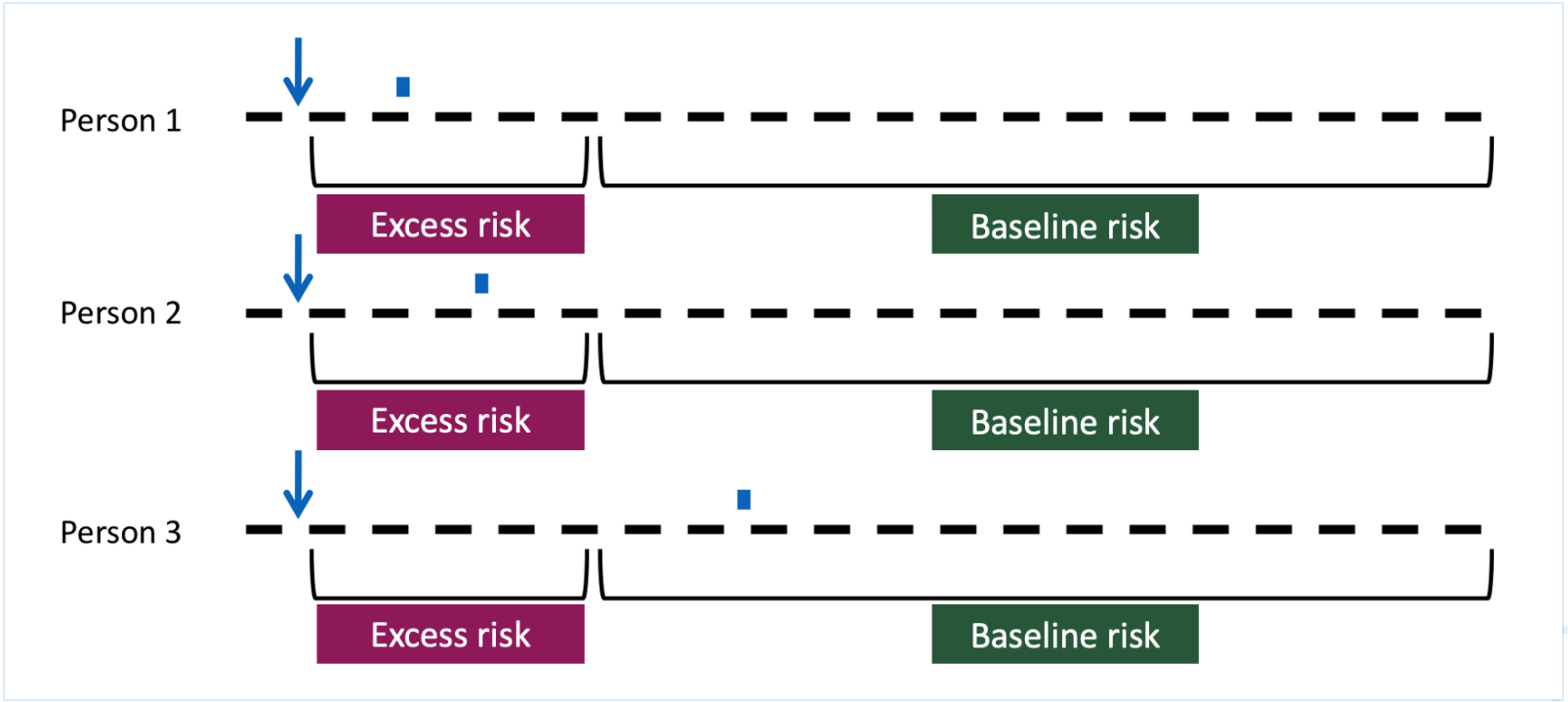
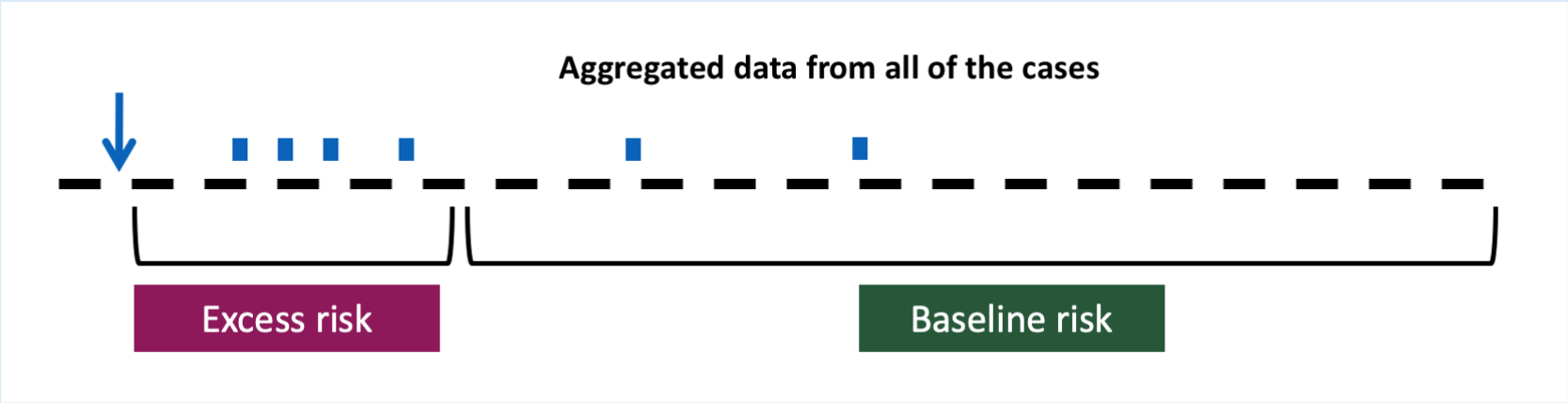


Image source: Jodi Segal.

Six People and When They Had Their Events On One Figure



- We have only cases
- Cases are classified as concurrent with the hypothesized exposure period or nonconcurrent with the hypothesized exposure period

Image source: Jodi Segal.

Analysis: Mantel-Haenszel Method

- Hypothesis is tested as the ratio of the observed number of cases to the expected number of cases
  - How many are expected?
    - Use the discordant cases
    - This is the number who had events during the unexposed time
    - This is the baseline rate

- Example:
  - Hypothesis: Respiratory syncytial virus (RSV) vaccine transiently raises the risk of seizure
  - Observe **30 cases** who had a vaccine on the day of their seizure
  - Observe **12 cases** who had a vaccine on the day before their seizure
  - So, 12 is the number expected to have vaccine on any day if there was no association between vaccination and seizures (duration of exposure is 1 day for everyone)
  - Relative risk (RR) = 30 (observed) / 12 (expected) = 2.5

Case-Crossover Analysis

- Unlike case-control studies that use counts and report odds ratios, case-crossover studies have a time element (like a cohort study) and typically report incidence rate ratios
- Incidence rate ratios are equivalent to relative risk of an event in a risk period of interest
- Conditional logistic regression is ideal for the matched nature of such data, but is not the only method
- This requires the assumption of a stable hazard function over time for each individual, which is modified by the exposure

Analytic Challenges

- It is hard to know what the effect period really is after an exposure so hard to know what window to pick
- You can vary the length of the effect period and see how that affects the relative risk estimate
- Overestimation or underestimation will result in nondifferential misclassification (and bias towards the null)

Within-Individual Confounding

- Using individuals as their own controls is usually helpful that it controls for characteristics that remain constant (measured and unmeasured)
- It does not control for characteristics that change over time—i.e., time-varying confounders, unless they can be measured
  - Examples:
    - Intermittent use of over-the-counter drugs (seasonal exposure to antihistamines)
    - Transient environmental exposures (smog)
- Time-varying probability of exposure needs to be accounted for (change in drug utilization over time due to advertising)

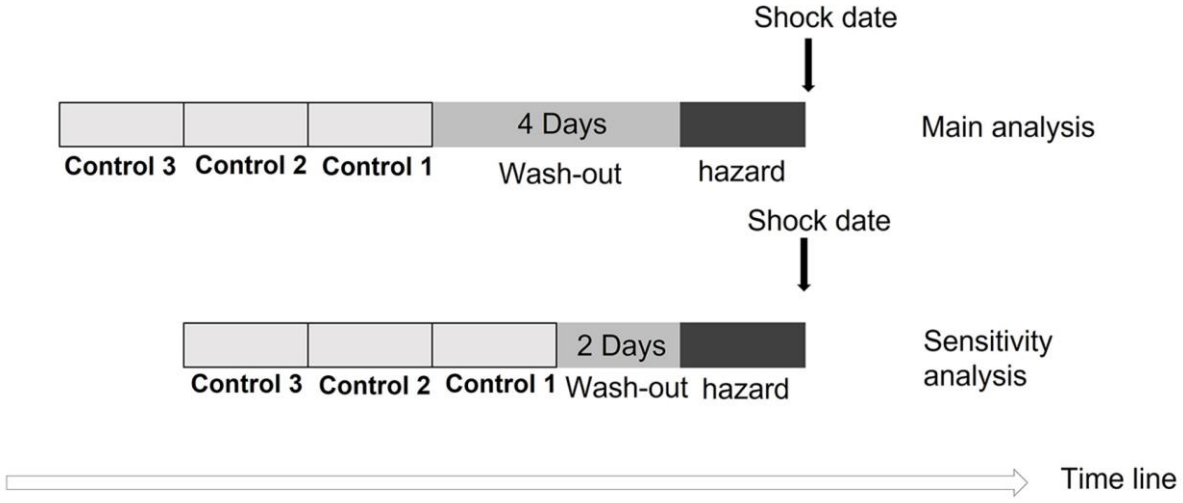
Benefit to Case-Crossover Design

- Case-crossover designs are generally an improvement over case-control studies because the controls are certainly representative of the cases (they are the same people)

- But be careful: the occurrence of an event must not alter the probability of a subsequent exposure if you are using baseline (unexposed) time in the future as well

Example of Case-Cross Over Study

Does oxaliplatin cause shock in patients with advanced colorectal cancer?



- All of these periods were 2 days long (the hazard period and each of the control periods)

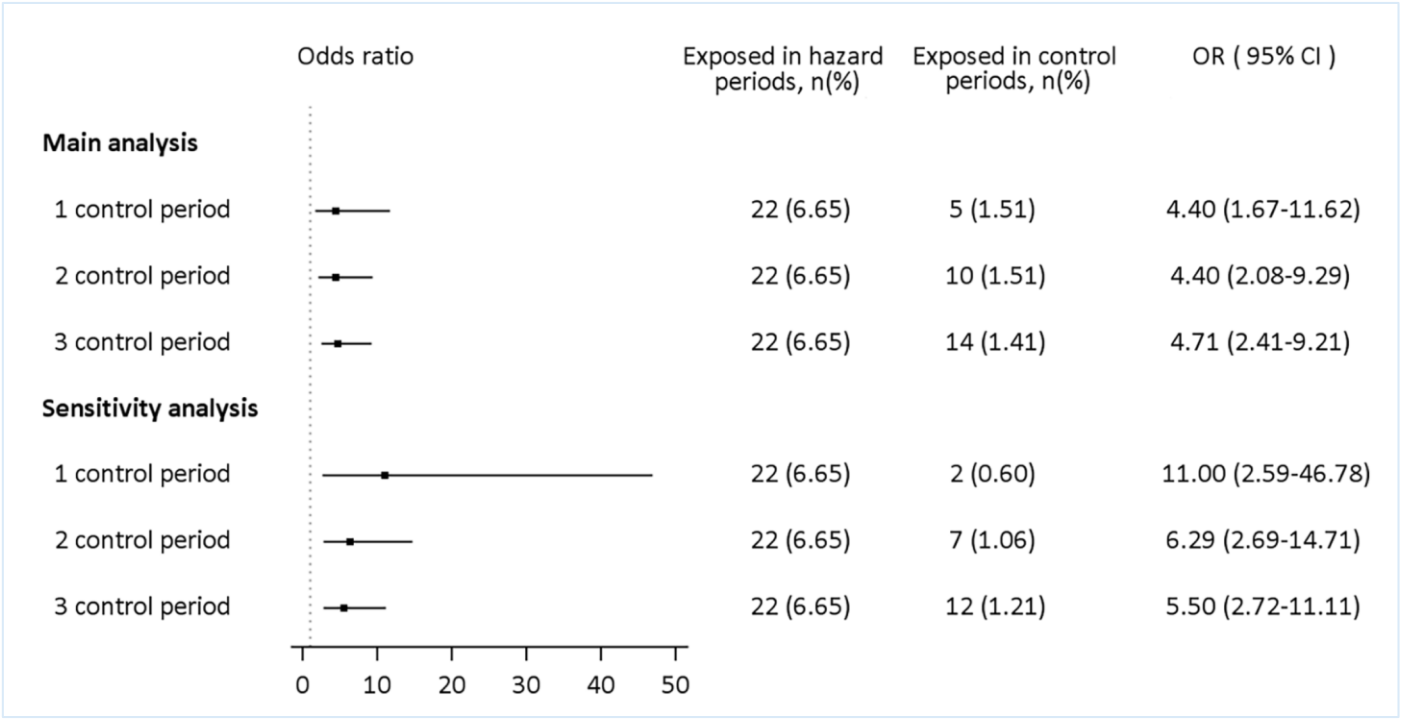
Source: Wang, L. Y., Hsieh, H. H., Chu, S. C., Chang, W. C., Kuo, Y. T., & Wu, T. Y. (2024). Oxaliplatin-associated shock in stage III colorectal cancer patients: real-world evidence in Taiwan. *Therapeutic Advances in Drug Safety, 15*, 20420986241266439. https://doi.org/10.1177/20420986241266439

Does Oxaliplatin Cause Shock in Patients With Advanced Colorectal Cancer?

- 331 individuals with anaphylactic shock in their cohort of patients with stage III colorectal cancer
- Each serves as his/her own control
- Calculated the odds of exposure in the hazard period relative to odds of exposure in the control period

Source: Wang, L. Y., Hsieh, H. H., Chu, S. C., Chang, W. C., Kuo, Y. T., & Wu, T. Y. (2024). Oxaliplatin-associated shock in stage III colorectal cancer patients: real-world evidence in Taiwan. *Therapeutic Advances in Drug Safety, 15*, 20420986241266439. https://doi.org/10.1177/20420986241266439

Results of Oxaliplatin and Shock Study



Source: Wang, L. Y., Hsieh, H. H., Chu, S. C., Chang, W. C., Kuo, Y. T., & Wu, T. Y. (2024). Oxaliplatin-associated shock in stage III colorectal cancer patients: real-world evidence in Taiwan. *Therapeutic Advances in Drug Safety, 15*, 20420986241266439. https://doi.org/10.1177/20420986241266439

Summary of Methods: Part 1

- We discussed some options for designing studies to test the effectiveness and safety of drugs using existing data
- These are all retrospective, observational designs
- We discussed cohort designs as being the most frequently used and how we use a cohort design to emulate a target trial
- We discussed case control studies as being particularly valuable for safety studies where “any exposure” is the question of interest
- We discussed case-crossover designs as valuable designs when the exposure is transient