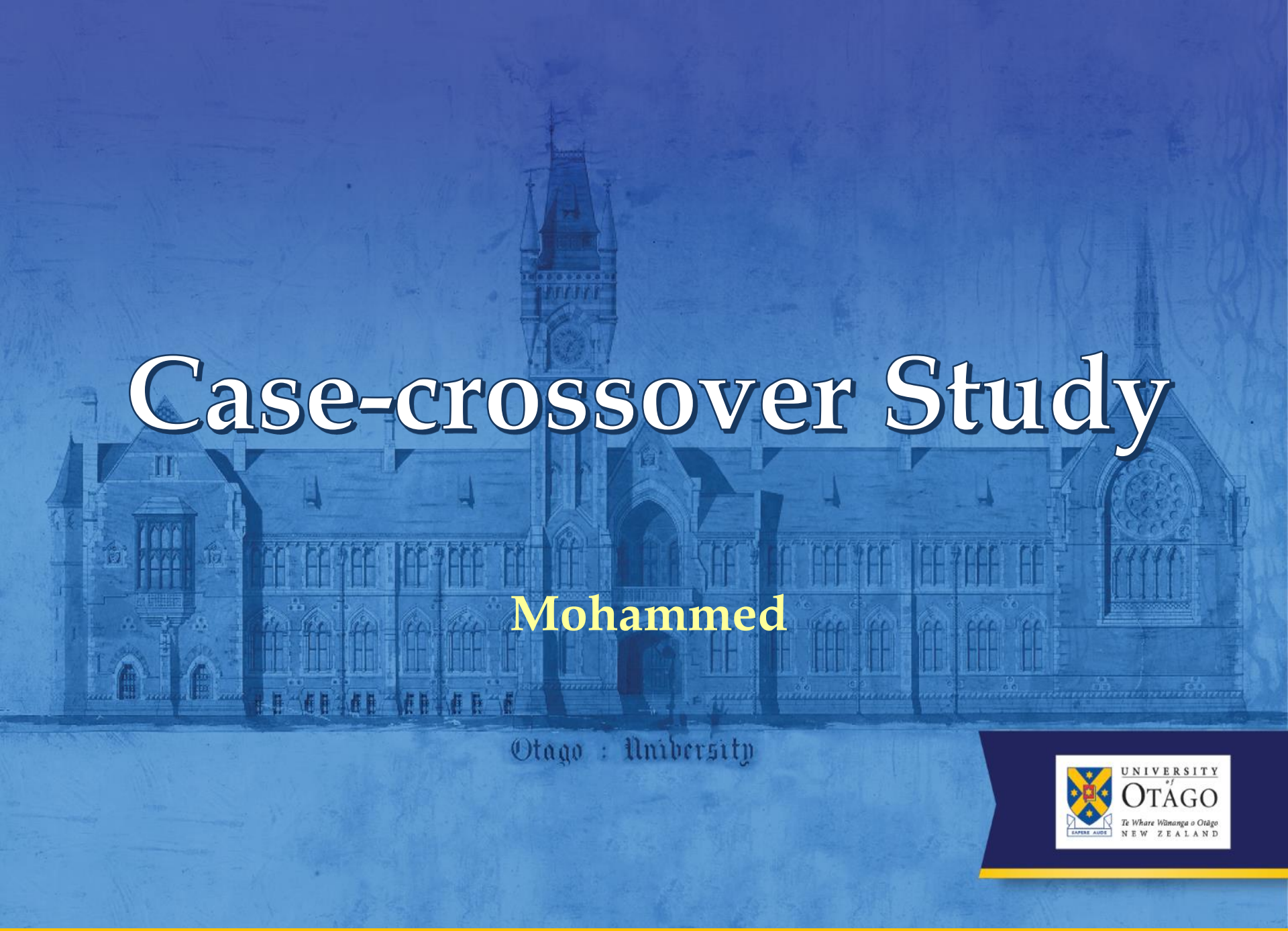
Case-crossover Study

Mohammed



UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Big Picture

To prevent and control disease in a coordinated plan, look to

- identify hypotheses on what is related to disease and may be causing it
- formally test these hypotheses
- **Study designs direct how the investigation is conducted**

Types of primary studies

Descriptive studies

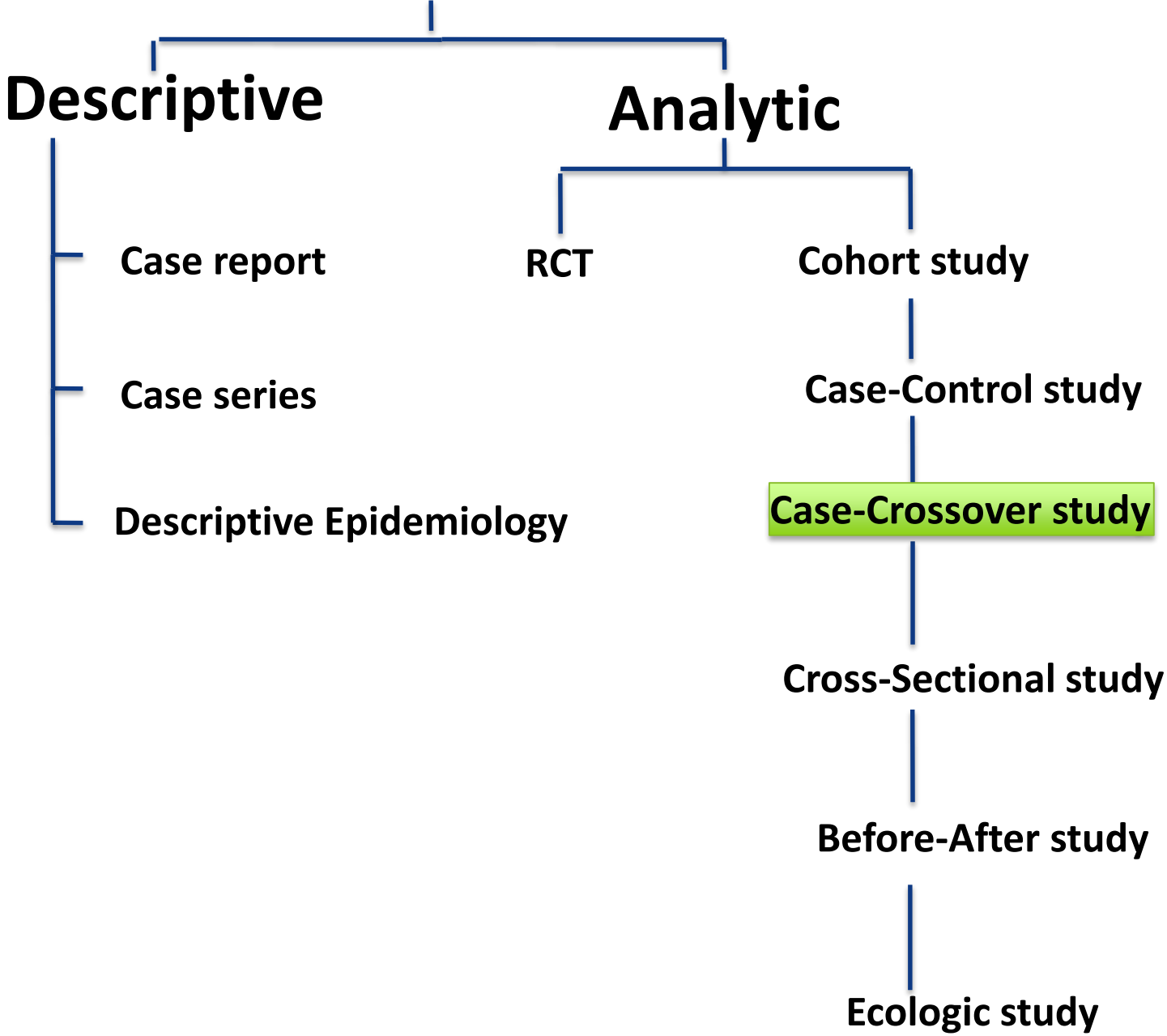
- describe occurrence of outcome

Analytic studies

- describe **association** between exposure and outcome

What designs exist to identify and investigate factors in disease?

Study Designs



Case-Crossover Design

- Introduced in 1991 by Maclure M (Am J Epidemiol 1991;133:144-53) to study the transient effect of brief exposure on the occurrence of a rare acute-onset disease.

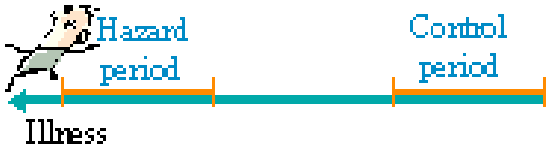
Concept

- **Case-Crossover Design** is a scientific way to ask and answer the question that “Was the patient doing anything unusual just before the onset of the disease”

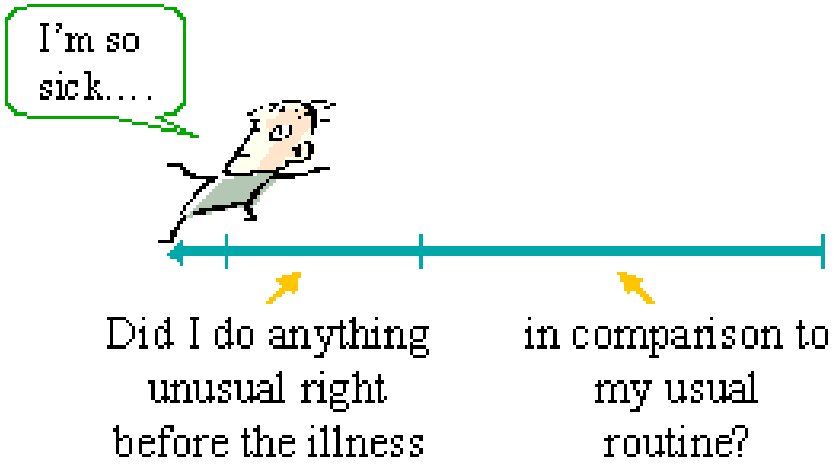
- For example, to find out what might trigger the onset of myocardial infarction,
  - we may wonder if the patient endured certain heavy physical activity, or
  - if he/she consumed specific type of food right before the disease.
- If we can gather the so called "exposure" information from many patients, it is possible to determine the effect of the event or "attitude" on the onset of disease.

Concept

It is a design that compares the exposure to certain agent during the interval when the event does not occur (control period), to the exposure during the interval when event occurs (hazard period)



To answer this question, we need to do the comparison within the individual



Case-Crossover Design

- Within the subjects
- Only subjects (cases) who have experienced the disease of interest are selected.
- Compare exposure just before event and exposure at an earlier time, in the same case
- Suited to brief (acute) exposure with a relatively rapid effect on the outcome
- Good for studying effects of transient exposures

Case-Crossover Design

- Biased selection of controls (selection bias) is eliminated (assuming matched analysis is conducted) since controls represent the population that produced the cases.
- Since each subject serves as their own control, thus, "**fixed**" confounders are eliminated.
- However, confounding can occur from factors that vary over time and are associated with the exposure and disease of interest (e.g. smoking).

Hypothesis Testing: Case-Crossover Studies

- Study of “triggers” within an individual
- “Case" and "control" component, but information of both components will come from the same individual
- “Case component" = hazard period which is the time period right before the disease or event onset
- “Control component" = control period which is a specified time interval other than the hazard period

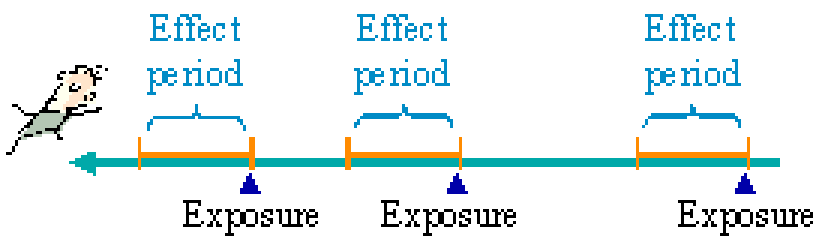
Effect Period of the Exposure

Effect period of the Exposure

"…the period of altered risk in a population, to be the difference between the minimum delay before impact and the maximum carry-over time."

Maclure M (AJE 1991;133:144-53)

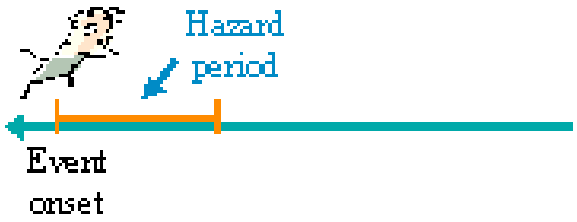
Effect Period of the Exposure



Hazard Period

Hazard Period

The period of time right before the onset of the event. Usually the length of hazard period is the same as the length of the exposure effect period.



Hazard Period

The length of effect period, and thus the hazard period, can be decided empirically.

However, this length is critical. Over-estimation or under-estimation of the duration will dilute the association.

Types of control data one can use in a case crossover study

Control Data

The control data can be

1) exposure information from a comparable time period; or
2) exposure information in the past according to the individual's usual frequency of exposure.

Example

Triggering of MI by physical excretion

- Event: Myocardial Infarction (MI)
- Exposure: Heavy physical exertion
- Length of exposure effect: 1 hour
- Hazard period: 1 hour before MI onset

- 2 sets of control data were used.

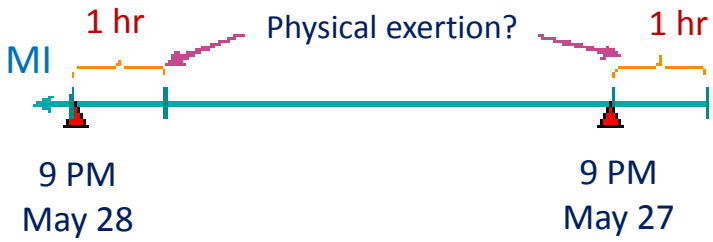
NEJM 1993;329:1677-83

Example of control data

Example: MI and Physical exertion

Control data 1:

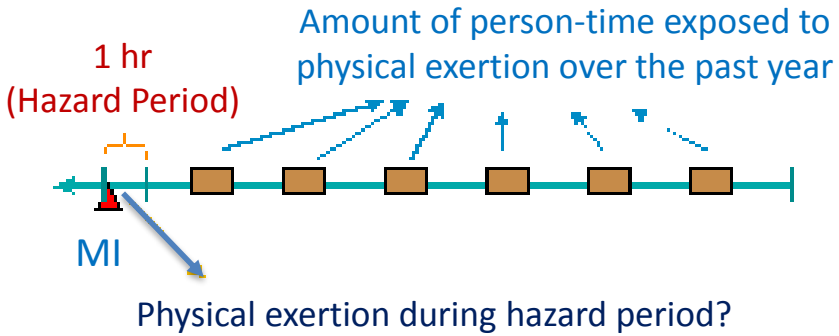
The physical exertion information from a 1 hour period at the same time on the day before the onset of MI



Example: MI and Physical exertion

Control data 2:

The usual frequency of heavy physical exertion over the past year.



Analysis: If the control data were from a comparable control period

Analysis: If the control data were from a comparable control period…

We will use the same method for a standard matched case-control study. But instead of case and control, we will have Hazard period and Control period.

Hazard Period	Control Period: Exposed	Control Period: Unexposed
Exposed	a	b
Unexposed	c	d

→ **OR = b/c**

Analysis: If the control data were from the past exposure

Calculate concurrence observed odds

Analysis: If the control data were from the past exposure….

Step 1: Calculate the concurrence observed odds (a:b)

Odds that the exposure was during the hazard period right before the onset of disease.

(1:0) if there was exposure in hazard period

(0:1) if there was no exposure in hazard period

Calculate concurrence expected odds

Analysis: If the control data were from the past exposure….

Step 2: Calculate the concurrence expected odds (x:y)

Odds that a random event (disease) would have fallen in the effect period after an episode of exposure.

Risk ratio calculation

Expected Odds (x:y)

Algebraically,

x = the amount of person-time exposed to the exposure effect over the past

y = the amount unexposed person-time over the past

Example

Length of effect after exertion = 1 hr

Frequency of usual exertion = 2 per week

x = No. of exertions in last year * effect length

= (2*52)*1 = 104 hrs

y = 24*365 – x = 8656 hrs

Risk ratio calculation

Analysis: If the control data were from the past exposure….

Step 3: Calculate Risk Ratio

$$RR = \frac{\sum a_i y_i}{\sum b_i x_i} = \frac{\sum y_i}{\sum x_i}$$

sum over subjects with observed odds (1:0)

sum over subjects with observed odds (0:1)

Numerator = the sum of y_i in participants who had exposure right before the disease onset (observed odds = (1:0))

Denominator = the sum of x_i in participants who did not have exposure before the disease onset (observed odds = (0:1))

Risk ratio calculation

Example

$$RR = \frac{\sum a_i y_i}{\sum b_i x_i} = \frac{\sum y_i}{\sum x_i}$$

sum over subjects with observed odds (1:0)

sum over subjects with observed odds (0:1)

Subject	Obs Odds (a:b)	Exp Odds (x : y)
1	1:0	10 : 20
2	0:1	8 : 22
3	0:1	5 : 25
4	1:0	11 : 19
5	0:1	12 : 18

Numerator

Denominator

$$RR = \frac{20 + 19}{8 + 5 + 12}$$

Case-Crossover Design

Advantages of Case-crossover

- Efficient – self-matching
- Efficient – select only cases
- Can use multiple control windows for one case window
- On the other hand, the case crossover study can also be viewed as a retrospective cohort study as the control data are not necessarily the "counts", they can be units of exposure person-time.

Case-Crossover Design

Disadvantages of Case-crossover

- Information bias – inaccurate recall of exposure during control window (can be overcome by choosing control window to occur after case window)
- Requires careful selection of time period during which the control window occurs (circumstance associated with the control window should be similar to circumstances associated with case window)
- Requires careful selection of the length and timing of the windows (e.g., in an investigation of the risk of cell phone usage on auto accidents, cell phone usage that ceases 30 minutes before accident unlikely to be relevant to accident)

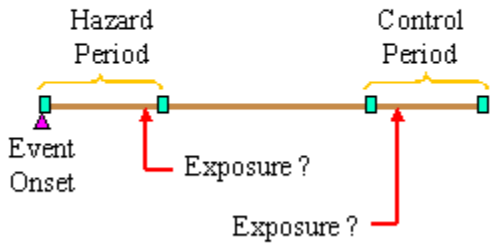
Analysis of Case-crossover

- Matched case-control analysis

Discussion

- The design can only be applied when the time lag between exposure and outcome is short and the exposure must have little carryover effect.
- The results of this analysis are short-term risks rather than cumulative risks.
- Recall bias may occur during data collection.
- If there is within individual confounding, stratification of the data may resolve the problem. To control several confounders simultaneously, conditional logistic regression can be used.

Case-Crossover Design



Summary:

- This design is useful when the risk factor/exposure is transient.
- For example, cell phone use or sleep disturbances are transitory occurrences.
- Each case serves as its own control, i.e. the study is self-matched.
- For each person, there is a **'case window'**, the period of time during which the person was a case, and a **'control window'**, a period time associated with not being a case.
- Risk exposure during the case window is compared to risk exposure during the control window

Thank You