N of 1 studies – an introduction

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Overview

- The problem of finding proper controls
- The fundamental idea of N-of-1 studies
  - case-crossover studies
  - Self-controlled case series studies
- Some guidance on choosing them and which one

The problem of finding an exchangeable reference group - example

POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

Ten-Year Follow-up from the Nurses' Health Study

MEIR J. STAMPFER, M.D., GRAHAM A. COLDITZ, M.B., B.S., WALTER C. WILLETT, M.D., JOANN E. MANSON, M.D., BERNARD ROSNER, PH.D., FRANK E. SPEIZER, M.D., AND CHARLES H. HENNEKENS, M.D.

Abstract *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal,* based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

Methods. We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

Results. After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke.

Conclusions. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke. (N Engl J Med 1991; 325:756-62.)

The problem of finding an exchangeable reference group - example

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

THE WOMEN'S HEALTH INITIATIVE (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the

The problem of finding an exchangeable reference group - example

this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases, and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000

- Conclusion: Healthy User Bias in observational study

The basic idea of Case-crossover studies – an example

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The case-crossover design for studying sudden events

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Dan Lewer and colleagues explain how case-crossover studies can help understand triggers of sudden events

Introduction

The case-crossover method is an epidemiological design used for studying potential causes of sudden events,[1] such as whether vigorous exertion or drinking alcohol triggers a myocardial infarction.[2] Case-crossover studies are one of a family of self-controlled study designs,[3] including crossover experiments and the self-controlled case series[4] (table 1). Each participant serves as their own control, and the analysis tests whether exposure times are associated with outcome times within individuals. By contrast, standard observational studies make comparisons between individuals, such as differences in myocardial rates between alcohol drinkers and non-drinkers (a cohort study) or whether sedentary lifestyles are more common among people who have had a myocardial infarction than among those who have not (a case-control study).

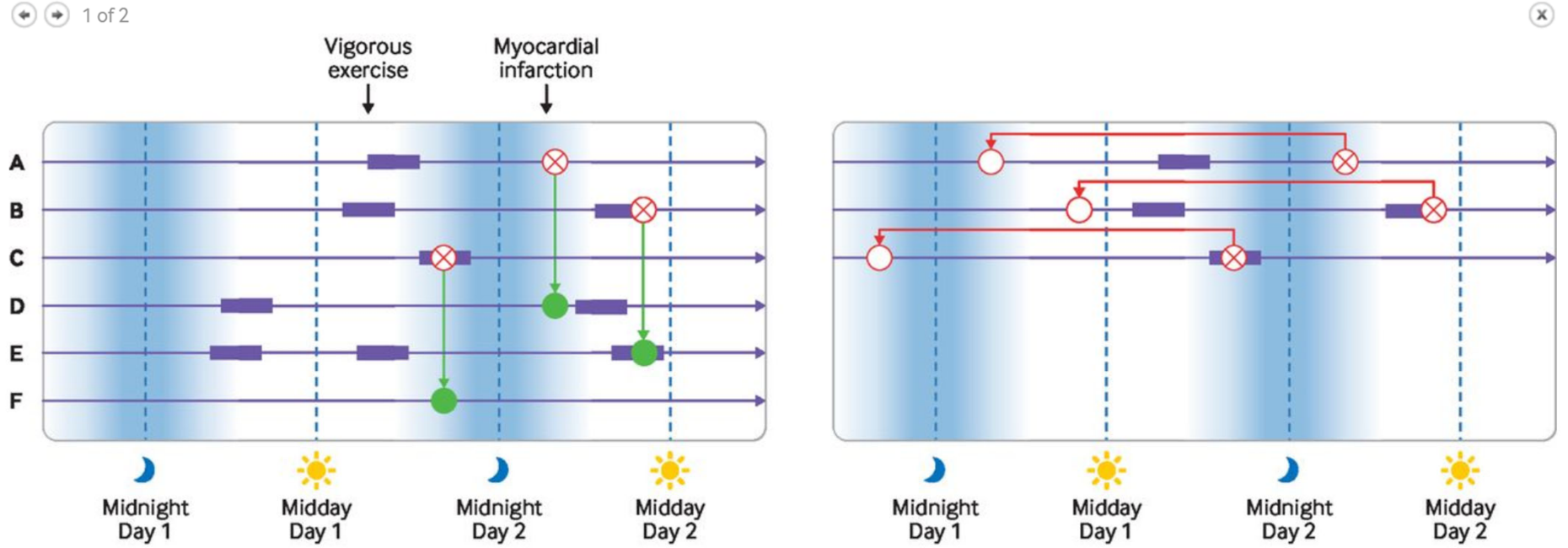
A case-crossover study only includes individuals who experience an event (known as cases). Figure 1 shows an illustrative study looking at the association between vigorous exercise and myocardial infarction by that point in time, and compare the probability of recent exercise.

Case-crossover studies in practice

The case-crossover design was developed for an interview study of triggers of myocardial such as exertion, alcohol, anger, and cannabis.[1] It has since been used with databases in many contexts, and we give four brief examples below. Common features of these research questions include the focus on sudden events and the triggering effect of transient exposures.

- Air pollution and cardiovascular events: case-crossover studies have found that concentrations of pollutants are elevated on the day of a stroke or heart attack compared with the concentration on earlier or later days.[5] These studies are often statistically powerful because researchers can include large numbers of cases and determine pollution from routine weather records.
- Car crashes and mobile phone use: case-crossover studies have found that drivers have several times the odds of using a mobile phone in the minutes before the crash when compared with a similar

The basic idea of Case-crossover studies – an example



Case-control method
For each case, we select a control (an individual who had not experienced the event at that time) and determine their exposure status

Case-crossover method
For each case, we look at the exposure status in a control window 24 hours before the event. Individuals D, E, and F do not experience the event and are not included

Computing the estimate

Ordinary CC study	Exposed	Unexposed
Case	a	b
Control	c	d

$$OR = \frac{\frac{a}{b}}{\frac{c}{d}}$$

Matched CC study	Control Exposed	Control Unexposed
Case Exposed	a	b
Case Unexposed	c	d

$OR = {}^{b}/_{c}$ (ie. discordant pairs)

Case-crossover study	Ref period Exposed	Ref period Unexposed
Case period Exposed	a	b
Case period Unexposed	c	d

$OR = {}^{b}/_{c}$ (ie. discordant **periods**)

Exercise: Fill in table based on previous figure

Traffic accidents and cellular phone use

The New England
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ASSOCIATION BETWEEN CELLULAR-TELEPHONE CALLS AND MOTOR VEHICLE COLLISIONS

DONALD A. REDELMEIER, M.D., AND ROBERT J. TIBSHIRANI, PH.D.

ABSTRACT

Background Because of a belief that the use of cellular telephones while driving may cause collisions, several countries have restricted their use in motor vehicles, and others are considering such regulations. We used an epidemiologic method, the case–crossover design, to study whether using a cellular telephone while driving increases the risk of a motor vehicle collision.

Methods We studied 699 drivers who had cellular telephones and who were involved in motor vehicle

MOTOR vehicle collisions are a leading cause of death in North America; they are the single most frequent cause of death among children and young adults and account for one fatality every 10 minutes.[1-3] During an average year, about 1 person in 50 will be involved in a motor vehicle collision; 1 percent of them will die, 10 percent will be hospitalized, and 25 percent will be temporarily disabled.[4,5] Motor vehicle collisions often injure persons who are

Traffic accidents and cellular phone use

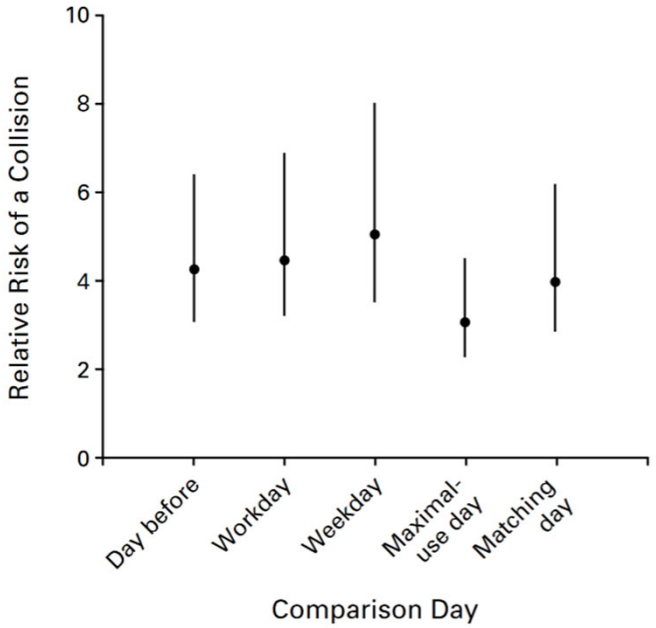


Figure 1. Relative Risk of a Collision for Different Control Periods.

Relative risks were calculated for five different control intervals. In the day-before comparison, we used the control period on the day immediately before the collision; in the workday comparison, the period on the preceding day of the workweek; in the weekday comparison, the period on the day one week before the collision; in the maximal-use-day comparison, the day with the most cellular-telephone activity of the three days preceding the collision; and in the matching-day comparison, the period on the nearest day of the preceding week in which there was cellular-telephone activity in the lead-up period. The vertical lines indicate 95 percent confidence intervals. Bars entirely above 1 indicate statistically significant associations ($P<0.05$).

TABLE 2. RELATIVE RISK OF A MOTOR VEHICLE COLLISION IN 10-MINUTE PERIODS, ACCORDING TO SELECTED CHARACTERISTICS.*

CHARACTERISTIC	NO. WITH TELEPHONE USE IN 10 MIN BEFORE COLLISION	RELATIVE RISK (95% CI)
All subjects	170	4.3 (3.0–6.5)
Age (yr)		
<25	21	6.5 (2.2–∞)
25–39	95	4.4 (2.8–8.8)
40–54	44	3.6 (2.1–8.7)
≥55	10	3.3 (1.5–∞)
Sex		
Male	123	4.1 (2.8–6.4)
Female	47	4.8 (2.6–14.0)
High-school graduation		
Yes	153	4.0 (2.9–6.2)
No	17	9.8 (3.0–∞)
Type of job		
Professional	34	3.6 (2.0–10.0)
Other	136	4.5 (3.1–7.4)
Driving experience (yr)		
0–9	40	6.2 (2.8–25.0)
10–19	67	4.3 (2.6–10.0)
20–29	36	3.0 (1.7–7.0)
≥30	27	4.4 (2.1–17.0)
Cellular-telephone experience (yr)		
0 or 1	51	7.8 (3.8–32.0)
2 or 3	39	4.0 (2.2–12.0)
4 or 5	36	2.8 (1.7–6.7)
≥6	44	4.1 (2.3–12.0)
Type of cellular telephone		
Hand-held	129	3.9 (2.7–6.1)
Hands free	41	5.9 (2.9–24.0)

*Relative risks indicate the probability of having a collision when using a cellular telephone at any time during a 10-minute interval as compared with the probability of having a collision when not using a cellular telephone at any time during a 10-minute interval. Relative risks have been adjusted to account for the intermittence of driving. CI denotes confidence interval.

Conditions and limitations for using a Case-crossover study

- Transient exposure
- Short-term effect
- ***No within person time-varying confounding***
- When event precludes further exposure:
  - No calendar time-trend in exposure risk
  - Can potentially be handled by using a Case-time-control study, see https://doi.org/10.1097/00001648-199505000-00010

    https://doi.org/10.1002/(SICI)1099-1557(199710)6:3+%3CS51::AID-PDS301%3E3.0.CO;2-S

What if….

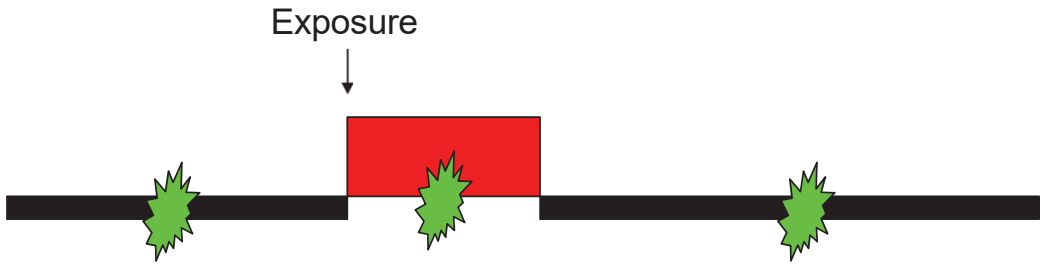
- We *only* have people who have the event, but we don't know the exact denominator
  - Hospital data
  - Long-haul flights and thromboembolism (VTE)
- There is a substantial difference between exposed and unexposed individuals
  - Ethnicity
  - Deprivation
  - Indication bias (severe asthma and influenza vaccine)

(The following slides on SCCS are borrowed from Irene Petersen, UCL, with permission)

Self-controlled case series may be the answer?

- Case series analysis – *only* cases are sampled
- Estimation is within individuals rather than between individuals

It is a conditional cohort method: exposures are regarded as fixed, event times as random



Baseline time

Event

Other periods of interest

$$\frac{\text{Rate in period of interest}}{\text{Overall rate}} = \text{Rate Ratio}$$

Farrington CP. Biometrics 1995;51:228-235

Other key features of case series method

- Follow-up is *not* censored at event
- Can be used with:
  - *independent* recurrent events
  - *uncommon* non-recurrent events
- The analysis is *self-matched*, thus eliminating the effect of fixed confounders

The assumptions and features of SCCS

1. Events must be:
   - Independently recurrent
   - Rare

2. Occurrence of an event should *not* (appreciably) affect subsequent exposures
   - Occurrence of an event should *not* (appreciably) increase mortality

3. Events cannot have happened at exact same time or age

4. Does not produce estimates of absolute incidence

Assumption 1 - Events must be independently recurrent or rare

- The method was developed for *independent* recurrent events
- Bias is ignorable if the method is used with non-recurrent events with risk of occurrence < 10% over the observation period
- A test for independence has been developed (Farrington & Hocine, *Applied Statistics* 2010 59: 457 – 475)
- If events dependent – you can use just *first* event
  - fractures
  - MI

Assumption 2 - Occurrence of an event should not affect subsequent exposures

- Conditioning on full exposure histories is only valid provided events do not affect subsequent exposures

- In other words, exposure must be an exogenous variable (coming from outside a system)

Indication bias - Asthma exacerbation and flu vaccine

- Cohort and case series studies in asthmatic children
- Aged 1 – 6 years in 1995/6
- Risk period: 2 weeks after flu vaccine.

- Kramarz *et al, Arch. Fam. Med*. 2000, 9: 617 – 623

Asthma exacerbation and flu vaccine

Method	Sample size	*RI*	95% *CI*
Cohort, unadjusted	70 753	3.29	(2.55, 4.15)
Cohort, adjusted	70 753	1.39	(1.08, 1.77)

The cohort results are subject to indication bias? Children with severe asthma more likely to have flu vaccine?

Kramarz *et al, Arch. Fam. Med*. 2000, 9: 617 – 623

Asthma exacerbation and flu vaccine

Method	Sample size	*RI*	95% *CI*
Cohort, unadjusted	70 753	3.29	(2.55, 4.15)
Cohort, adjusted	70 753	1.39	(1.08, 1.77)
Case series	2075 cases	0.98	(0.76, 1.27)

The cohort results are subject to indication bias - The case series results are unaffected by this bias.

Direction of bias

- The direction of bias is predictable:
  - If the event reduces the chance of exposure, the *Relative Incidence* will be biased upwards
  - If the event increases the chance of exposure, the *Relative Incidence* will be biased downwards
- This may be helpful to know

Assumption 2 - cont.

Occurrence of an event should not (appreciably) increase mortality

- The observation period is assumed to be independent of the event
- Failure of the assumption can cause bias, in an unpredictable direction
- However, see Farrington *et al*, *JASA* 2011, 106: 417 – 426

When can events influence subsequent exposures?

- Occurrence of an event may delay exposure:
  - Treatment (eg vaccination) may be deferred until recovery
- The event may be a contra-indication for treatment:

  - For example, intussusception and rotavirus vaccine
- If the event is death:
  - No subsequent observation can occur

More info about SCCS

- http://sccs-studies.info/index.html

- Petersen et al. Self controlled case series methods: an alternative to standard epidemiological study designs BMJ, 2016

- Whitaker, HJ. *et al*. Tutorial in biostatistics: The self-controlled case series method. Statistics in medicine. *Stats in medicine* 2006, 25: 1768 – 1797

Guidance

- Consider a case-crossover study or SCCS if:
  - exposure is transient
  - effects of exposure are short-term
  - there is no/little time-dependent bias

- Prefer a case-crossover study, if
  - Event precludes further exposure

- Prefer a SCCS, if
  - Events do not preclude future exposure and there is a time trend in exposure occurrence

Thanks for your attention – questions welcome!

(Djursland, July 2015 – H Støvring)