ISPE Mid-Year Meeting 2013 – Munich, Germany

Modern Case-Control Studies

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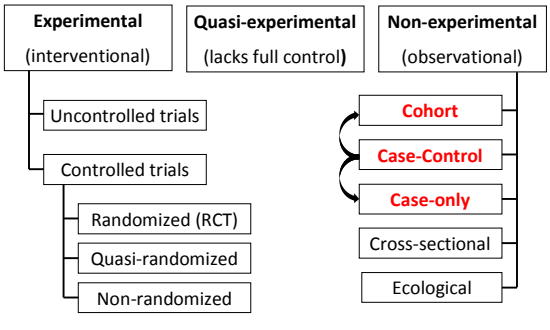
- The views and opinions expressed in this presentation are solely mine and do not represent the position or opinion of ISPE or any other institution
- No conflict of interest to declare
- Lecture material from previous years has provided inspiration for the preparation of this lecture. Thanks to my predecessors
- Thanks to Edeltraut Garbe, Miriam Sturkenboom, and Samy Suissa

Study Designs – Analytic Studies

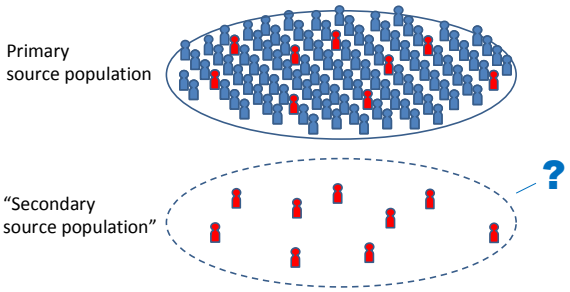


Why Conduct a Case-Control Study?

✓**Efficiency**	✓**Time-varying exposures**
✓**Speed**	✓**Multiple exposures**
✓**Cost saving**	✓**Rare outcomes**
✓Validity	✓Risk ratio
✓Precision	✓Incidence rate ratio

Case-Control Study: What is the Study Base?

The Source Population



BMJ

BMJ 2011;343:d3908

Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe

Jeanne Dieleman, Silvana Romio, Kari Johanson, Daniel Weibel, Jan Bonhoeffer, Miriam Sturkenboom, and the VAESCO-GBS Case-Control Study Group

Country	Cases	Controls
UK	GPRD	GPRD
Denmark	National Patient Register	Danish civil registration system
Netherlands	Neurologists. Hospitals	General practice of case patients
France	Neurologists. Hospitals	Trauma unit in same hospital
Sweden	Neurology assessment laboratories	Swedish national population registry

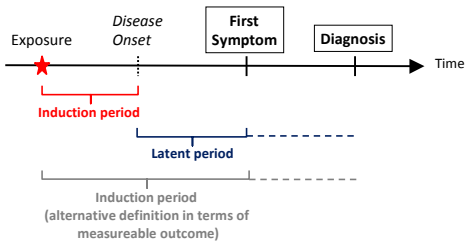
Selection (Sampling) of Cases and Controls

Controls should be representative of the source population that gave rise to the cases.

Selection (sampling) of cases and controls should be independent of exposure. Otherwise → Selection bias

Index Date

In cases, the index date is the occurrence of the study outcome (we refer to it in exposure classification)



ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

René Schade, M.D., Frank Andersohn, M.D., Samy Suissa, Ph.D., Wilhelm Haverkamp, M.D., Ph.D., and Edeltraut Garbe, M.D., Ph.D.

BACKGROUND

Case reports and echocardiographic studies suggest that the ergot-derived dopamine agonists pergolide and cabergoline, used in the treatment of Parkinson's disease and the restless legs syndrome, may increase the risk of cardiac-valve regurgitation.

Outcome: Cardiac-valve regurgitation

•Insidious onset	→ Date of disease onset?
•Unspecific recording	→ Misclassification (false positives)
•Typical symptoms only/ suspected diagnosis	→ Diagnosis confirmed?

N Engl J Med 2007;356:29-38.

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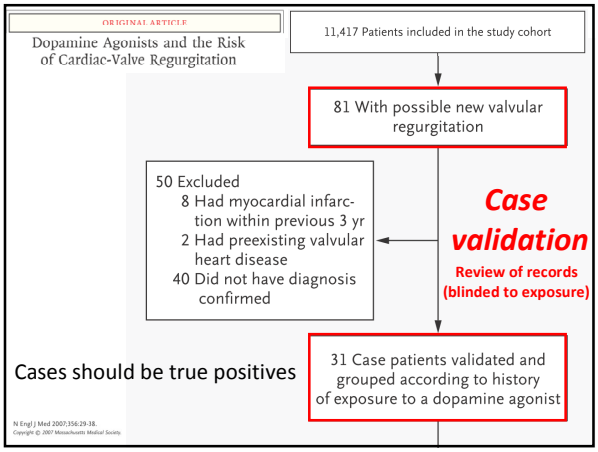
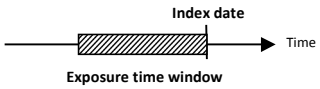


Cases should be true positives

N Engl J Med 2007;356:29-38.

Exposure Time Window

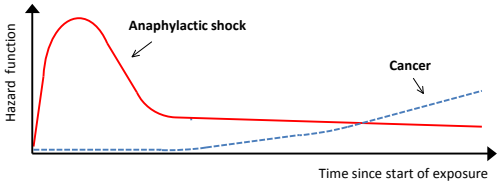
for exposure classification (in the study)



Exposure Risk Window → Exposure Time Window

referring to biological mechanism

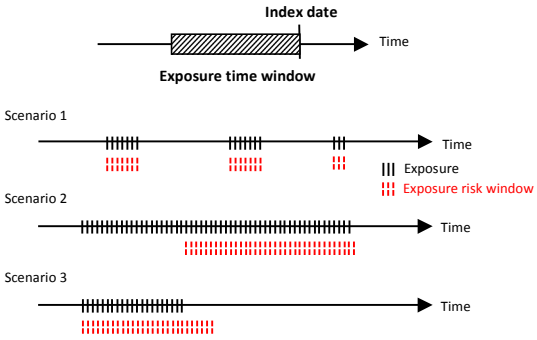
The exposure risk window is the time period during which a drug puts the patient at risk for the outcome (it is the basis on which we define the study`s exposure time window)



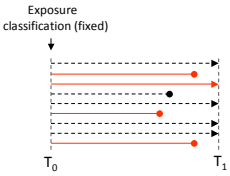
(adapted from Schneeweiss, 2010)

Exposure Risk Window → Exposure Time Window

for exposure classification (in the study)



Closed Cohort



Exposure	Outcome: Yes	Outcome: No
Yes	a	b
No	c	d
	Cases	Non-cases

$$\text{Risk Ratio (RR)} = \frac{\text{incidence proportion}_{\text{exposed}}}{\text{incidence proportion}_{\text{unexposed}}} = \frac{a/(a+b)}{c/(c+d)}$$

$RR = 1 \Rightarrow$ The "null" value of no association

The risk ratio is easy to interpret ("x-fold increased risk")

Closed Cohort

Cumulative (Exclusive) Sampling

Cumulative Control Sampling
(random sample from non-cases)

Exposure	Outcome: Yes	Outcome: No
Yes	a	b
No	c	d
	Cases	Controls

$$\text{Odds Ratio (OR)} = \frac{\text{exposure odds}_{\text{cases}}}{\text{exposure odds}_{\text{controls}}} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

About the "rare disease" assumption:
If the outcome **risk is less than 5%** in both exposed and unexposed then
Odds Ratio (with exclusive sampling) ≈ Risk Ratio (from full cohort)

What does the case-control odds ratio estimate?

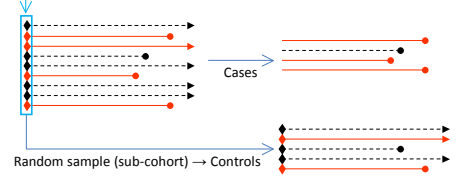
→ It's all about the sampling!

Sampling scheme	What does odds ratio estimate?	About the "Rare disease" assumption
Cumulative (exclusive)	Odds ratio	If "rare disease" then odds ratio ≈ risk ratio (from full cohort)

Case-Cohort Design

(Case-Cohort Sampling, Inclusive Sampling, Case-Base Sampling)

Case-Cohort Sampling (Inclusive)
(from entire cohort at start of follow-up)

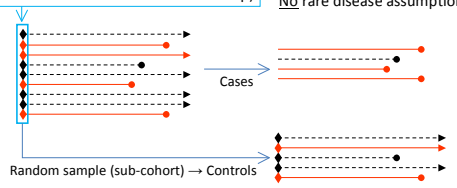


Case-Cohort Design

(Case-Cohort Sampling, Inclusive Sampling, Case-Base Sampling)

Case-Cohort Sampling (Inclusive)
(from entire cohort at start of follow-up)

Odds ratio → Risk ratio
No rare disease assumption required



- Hutchinson (1968), Kupper et al. (1975), Miettinen (1982), Prentice (1986)
- Can study multiple outcomes (case series) with one control group

What does the case-control odds ratio estimate?

→ *It's all about the sampling!*

Sampling scheme	What does odds ratio estimate?	About the "Rare disease" assumption
Cumulative (exclusive)	Odds ratio	If "rare disease" then odds ratio ≈ risk ratio (from full cohort)
Case-cohort (inclusive, case-base)	Risk ratio	NOT REQUIRED (odds ratio estimates risk ratio without assumption)

Longitudinal Patient Data

Examples for databases of electronic medical records from primary care:

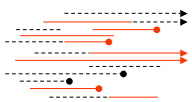
- The Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD)
- The Health Improvement Network (THIN)

- ✓ >550 general practices (gatekeepers) in the United Kingdom
- ✓ >10 mio. patients total (>70 mio. person years) since 1987
- ✓ ***>3.5 mio. active patients***

General practitioners record medical information on computers:

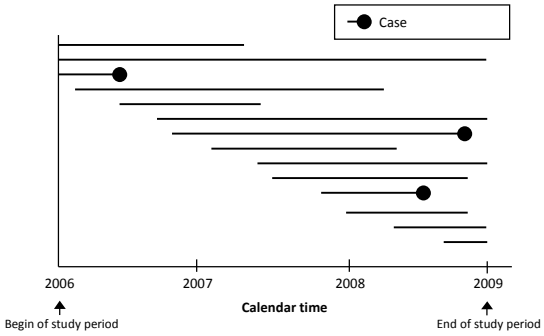
- ❑ Diagnoses, symptomes
- ❑ Procedures, laboratory tests
- ❑ Smoking, alcohol, BMI (height, weight)
- ❑ Prescriptions (strength, quantity, *dosing*)
- ❑ Free text
- ❑ Specialist letters (hospital discharges, referrals)

Dynamic population



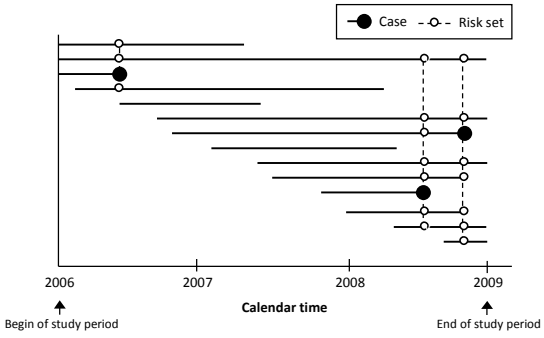
Epidemiological Study with Longitudinal Patient Data

Illustration



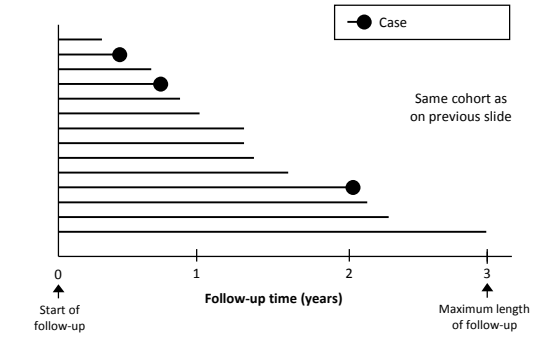
Risk Set Sampling

Time Axis: *Calendar Time*



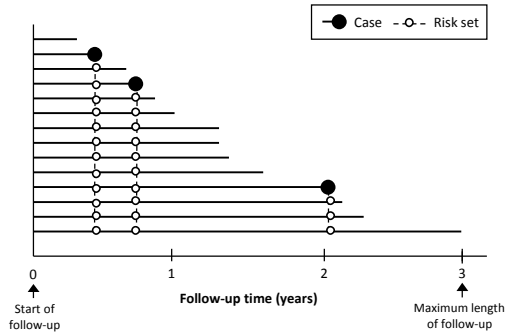
Risk Set Sampling

Time Axis: *Follow-Up Time*



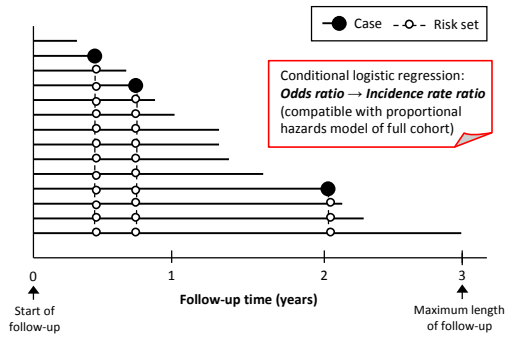
Risk Set Sampling

Time Axis: *Follow-Up Time*



Risk Set Sampling

Time Axis: *Follow-Up Time*



Exposure Time Trend → Calendar Time

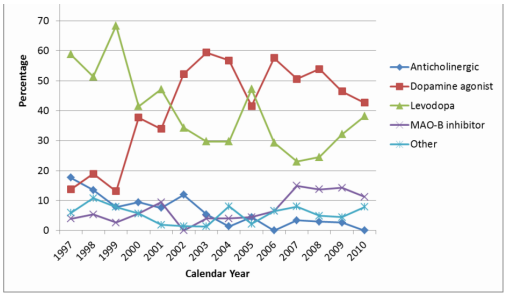
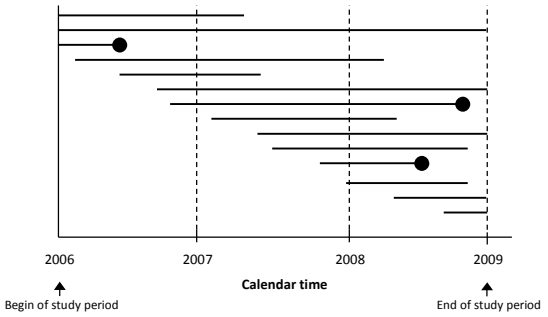


Figure 1. Percentages of All Newly Treated Parkinson's Patients who Received Monotherapy Regimens as Initial Antiparkinsonian Treatment by Calendar Year – **Age Category 50-64**

(Schade and Sturkenboom, 2012)

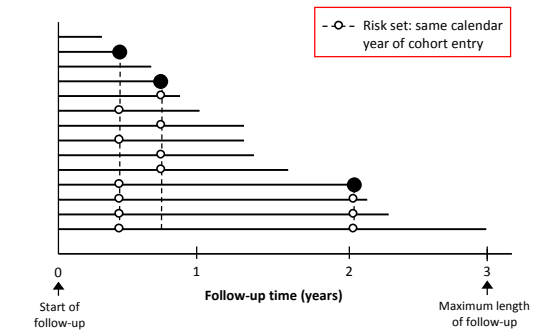
Risk Set Sampling

Combination of Calendar Time and Follow-Up Time

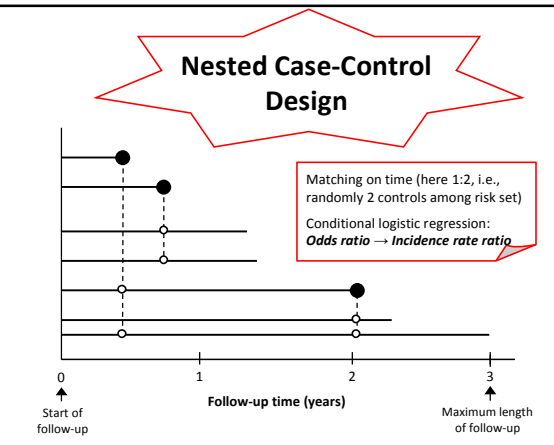


Risk Set Sampling

Combination of Calendar Time and Follow-Up Time



Nested Case-Control Design



Nested Case-Control Design NOTES

- **Mantel (1973), Thomas (1977), Prentice and Breslow (1978)**
- **Generally: Case-control study that is conducted in a fully enumerated (well-defined) cohort**
- **More strictly: Risk set (incidence density) sampling within a cohort**
  - Context of proportional hazards model (Cox, 1972) → Control of time (by matching on time) → **Incidence rate ratio**
  - Steps:
    1. Define the cohort: time axis, entry, exit
    2. Select cases in the cohort
    3. Form risk set for each case
    4. Randomly select one or more controls among each risk set
  - Subjects can be selected as control more than once

What does the case-control odds ratio estimate?

→ *It's all about the sampling!*

Sampling scheme	What does odds ratio estimate?	About the "Rare disease" assumption
Cumulative (exclusive)	Odds ratio	If "rare disease" then odds ratio ≈ risk ratio (from full cohort)
Case-cohort (inclusive, case-base)	Risk ratio	NOT REQUIRED (odds ratio estimates risk ratio without assumption)
Risk set (incidence density)	Incidence rate ratio	NOT REQUIRED (odds ratio estimates risk ratio without assumption)

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METHODS

We used data from the United Kingdom General Practice Research Database to identify a population-based cohort comprising 11,417 subjects 40 to 80 years of age who were prescribed antiparkinsonian drugs between 1988 and 2005. We conducted a nested case–control analysis within this cohort in which each patient with newly diagnosed cardiac-valve regurgitation was matched with up to 25 control subjects from the cohort, according to age, sex, and year of entry into the cohort. Incidence-rate ratios for cardiac-valve regurgitation with the use of different dopamine agonists were estimated by conditional logistic-regression analysis.

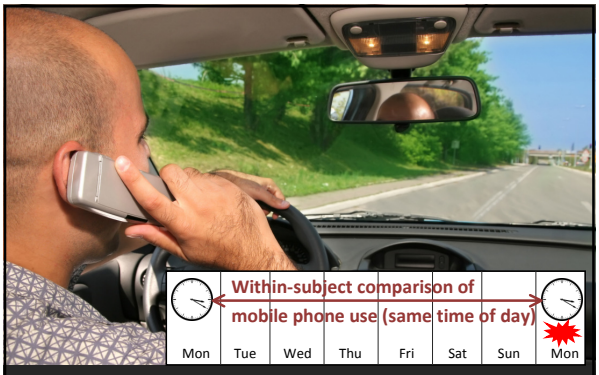
N Engl J Med 2007;356:29-38.

Power and Precision

Number of cases is fixed, while control-to-case ratio can vary

- Gain in power is substantial up to four controls per case; thus, 4-to-1 ratio appropriate in the majority of instances
- Ratio of 10 or more controls per case can be appropriate if (Suissa, 2006):
  - Exposure is infrequent
  - Hypothesized relative risk moved further from the null value
  - Several factors or other drugs assessed simultaneously

Want more? → Multitime case-control design (Suissa et al., 2010)



Mobile phones in motor vehicle crashes

McEvoy et al. BMJ 2005

Case-Crossover Design

- Maclure (1991), Mittleman et al. (1995)
- Case-only design → Cases serve as their own controls
- Removes confounding by time-invariant factors
- Prerequisites:
  - Transient exposure (intermittent)
  - Stable exposure prevalence over time
  - Acute outcome
  - Time-window of effect (risk period) determined
- Extension: Case-Time-Control Design (Suissa, 1995)

Time-Varying Exposures

Case-Only Designs (Within-Subject Comparisons)

Validity

Efficiency

Precision

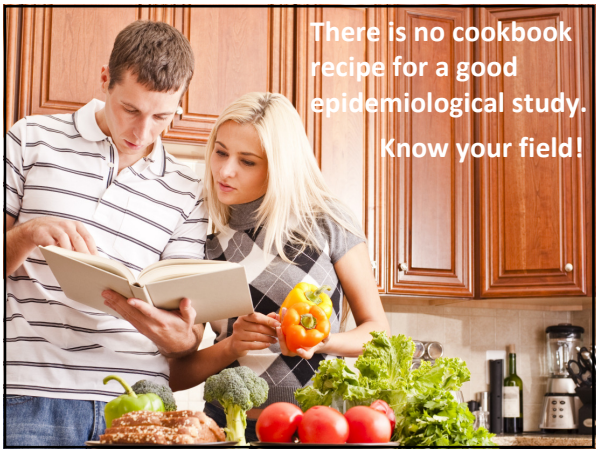
Multiple Exposures

Risk Ratio

Cost Saving

Incidence Rate Ratio

Multiple Outcomes



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