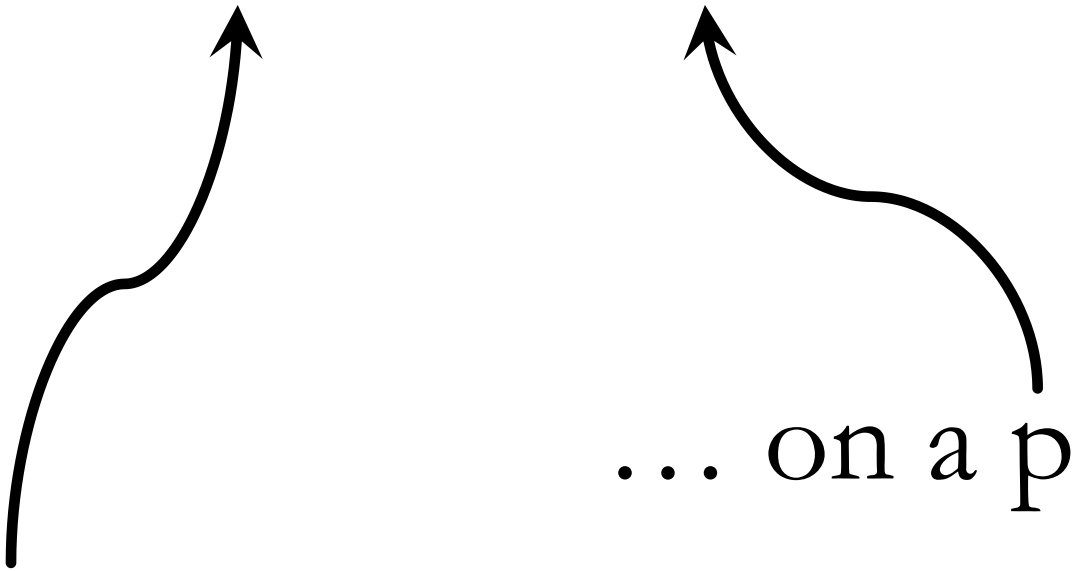
Introduction

Pharmacoepidemiology



… on a population-level

Something with drugs

Pharmacoepidemiology

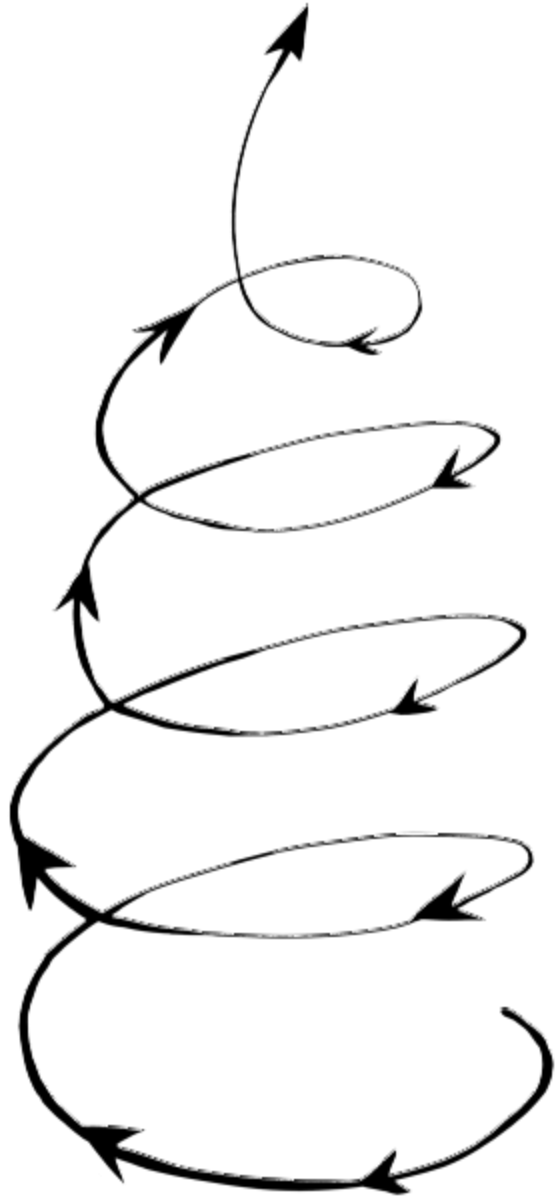
”While the individual man is an insoluble puzzle, in the aggregate he becomes a mathematical certainty. You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to.”

AC Doyle in “Sherlock Holmes: The Sign of four”

Pharmacoepidemiology

”Pharmacoepidemiology is the study of use and effects of medications on a population basis.”

Strom, Kimmel, and Hennessy
Textbook of Pharmacoepidemiology 3rd ed



Measures of frequency and association

Study design

Bias

Frequency and associations

Incidence / incidence rate

Prevalence / Prevalence proportion

Cumulative incidence proportion (risk)

Odds

Measures of assocation based on the above (IRR, RR and OR)

Study designs

Cohort design

Case-control design

Drug utilization studies

Self-controlled designs

Bias

Bias

Confounding

Measures of frequency and association

Study design

Bias

Incidence

Number of NEW cases

E.g.: There are 10 incident cases of AMI in Denmark each day

Incidence rate

Incidence per persontime

$$\text{Incidence rate} = \frac{\text{Number of new cases}}{\text{The amount of person-time giving rise to these cases}}$$

E.g.: The incidence rate (IR) of UGB is 50 per 100,000 person-years

1 person-year?

A person followed for a year

Two persons each followed 6 months

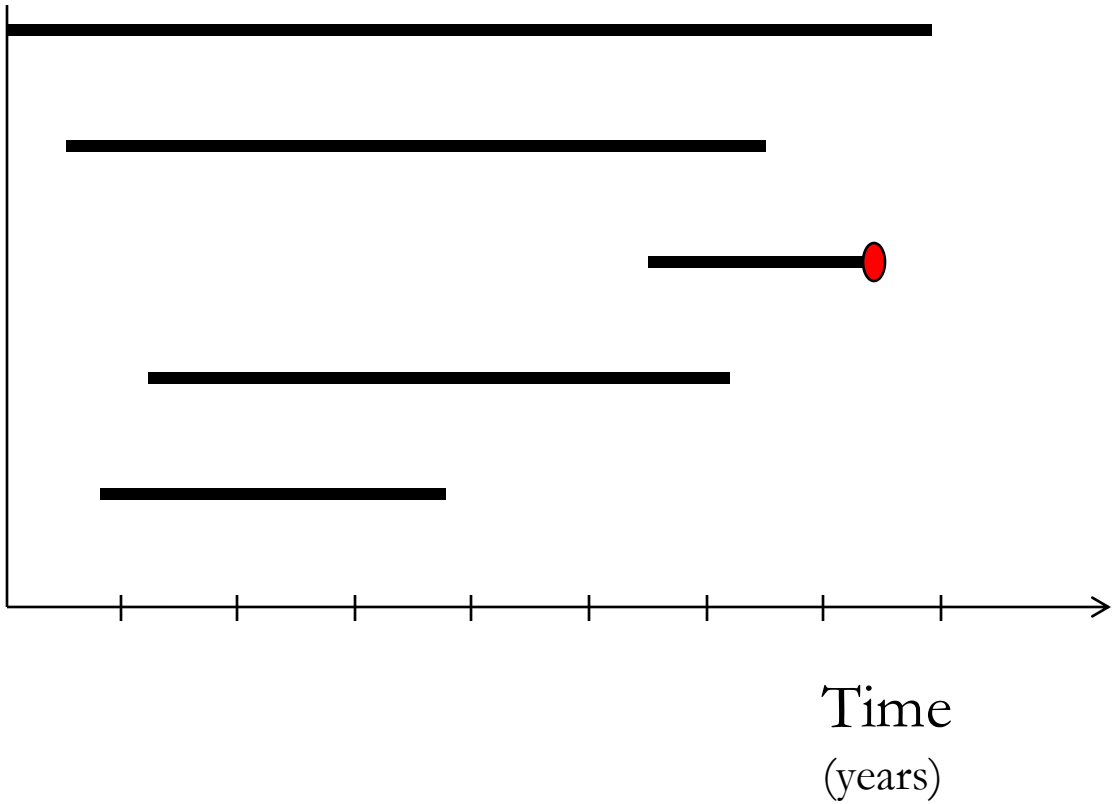
Three persons each followed for 4 months

100 persons each followed 3.65 days

10 persons each followed for 1 month
and 60 persons followed for one day

…

Incidence rate



IR

= 1 case /

24 personyears

= 0,0417 py^{-1}

= 42 / 1000 py

Prevalence

Number of cases

E.g.: 1100 Danes live with Myasthenia Gravis

Prevalence proportion

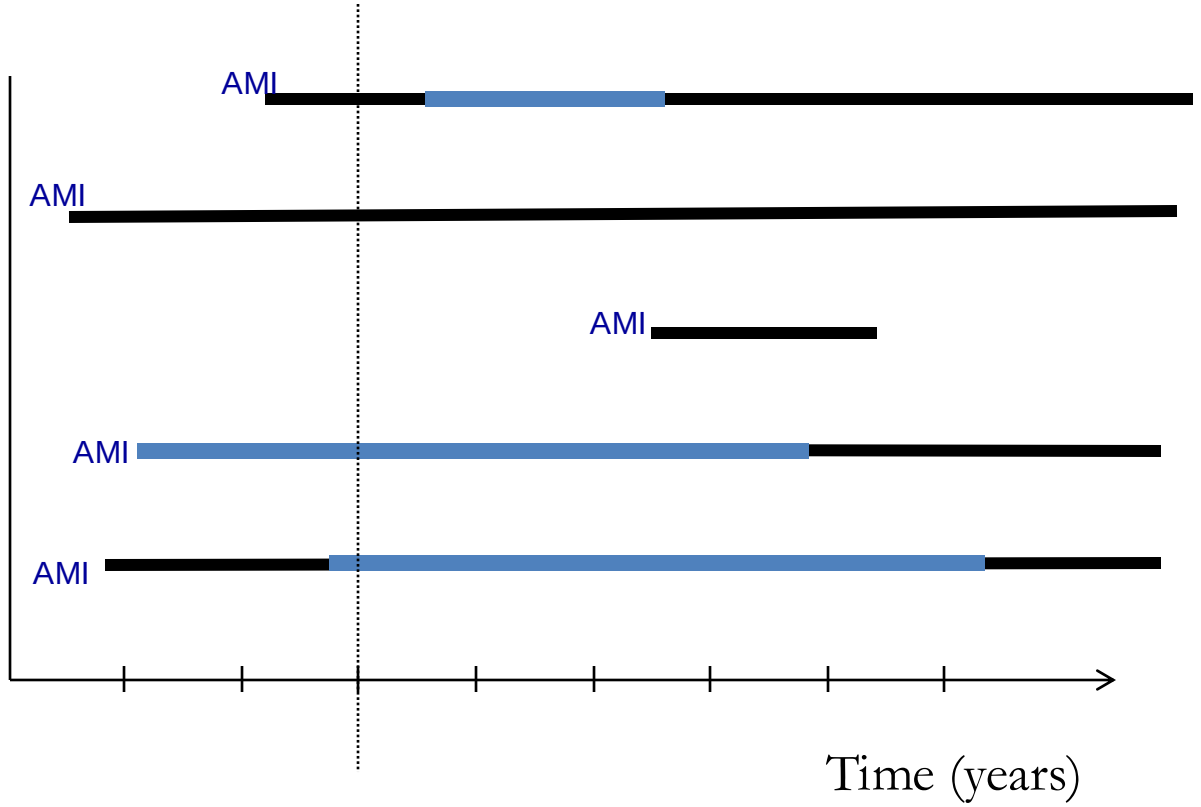
The proportion of a population that at a given time have a given disease

$$\text{Prevalence proportion} = \frac{\text{Number with disease}}{\text{Total size of population}}$$

E.g.: The prevalence proportion of Myasthenia Gravis among Danes is 1.8 per 10,000 (as 1100 / 6 mill = 0,00018)

E.g.: Prevalence proportion of use of beta-blockers is 50% among individuals with a previous MI

Prevalence proportion



Beta blocker use

No beta blocker use

Cumulative incidence proportion (CIP)

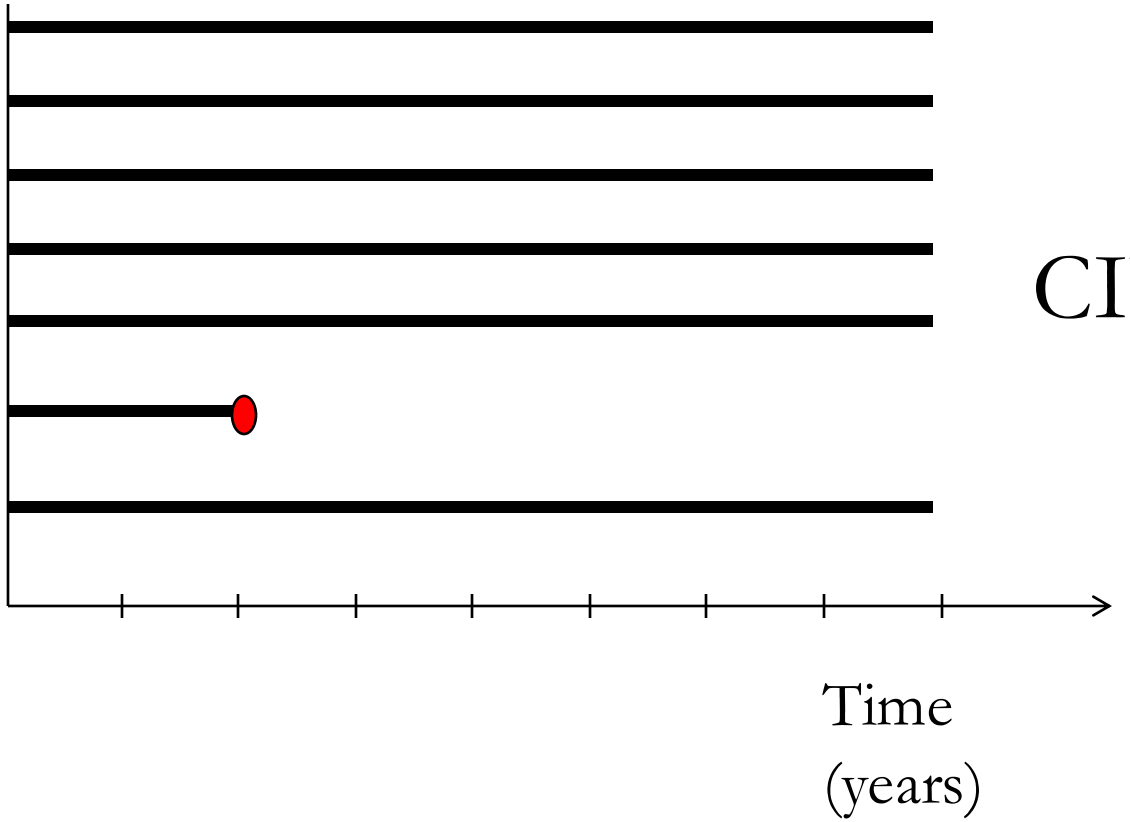
The proportion that within a given period of time experience a (new) outcome

Risk!

$$CIP_t = \frac{\text{Number of new outcomes until time t}}{\text{Number of persons at risk at time zero}}$$

E.g.: The 30-day mortality among persons admitted with MI is 10%

Cumulative incidence proportion (CIP)



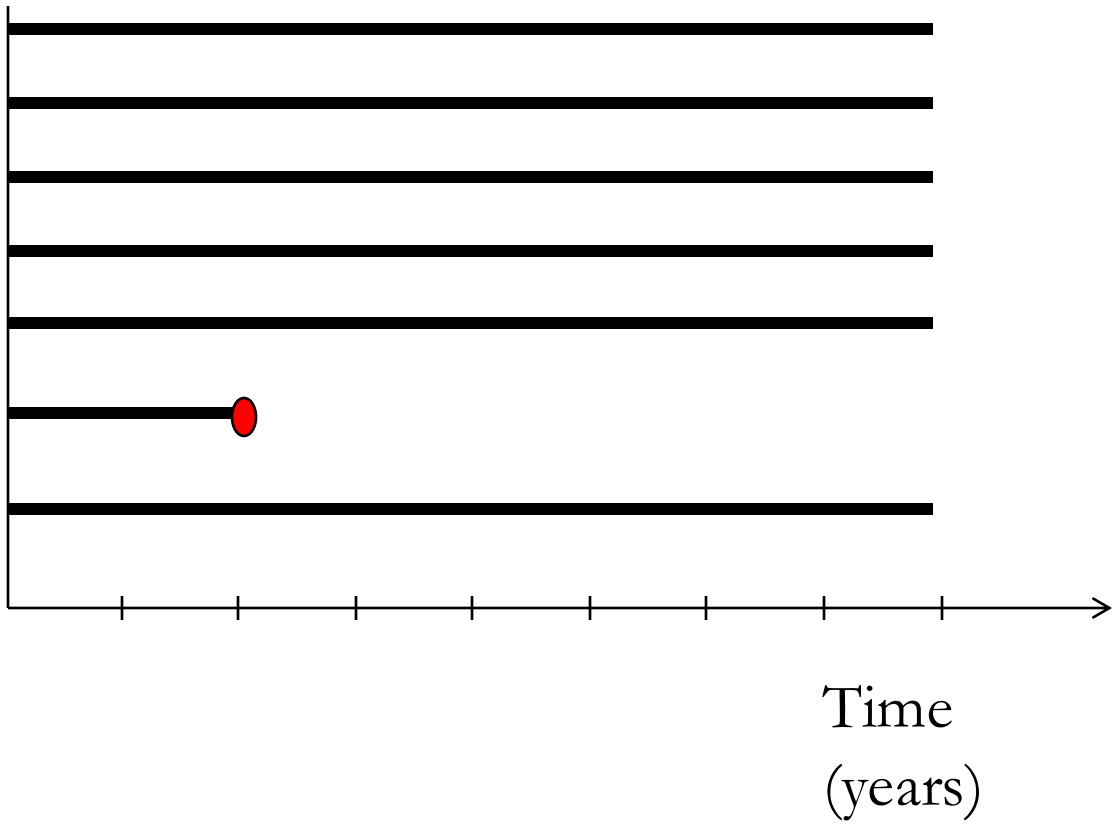
$$CIP_{8y} = 1 / 7$$

Odds

$$\text{Odds} = \frac{\text{Likelihood of outcome}}{\text{Likelihood of NO outcome}}$$

E.g.: Odds for dying within 30 days after admission due to MI is 0.11 (10%/90%)

Odds



Odds = 1 / 6

= 0.16

Associations

Relative measure for frequency of outcome,
e.g. comparing drug users to non-users

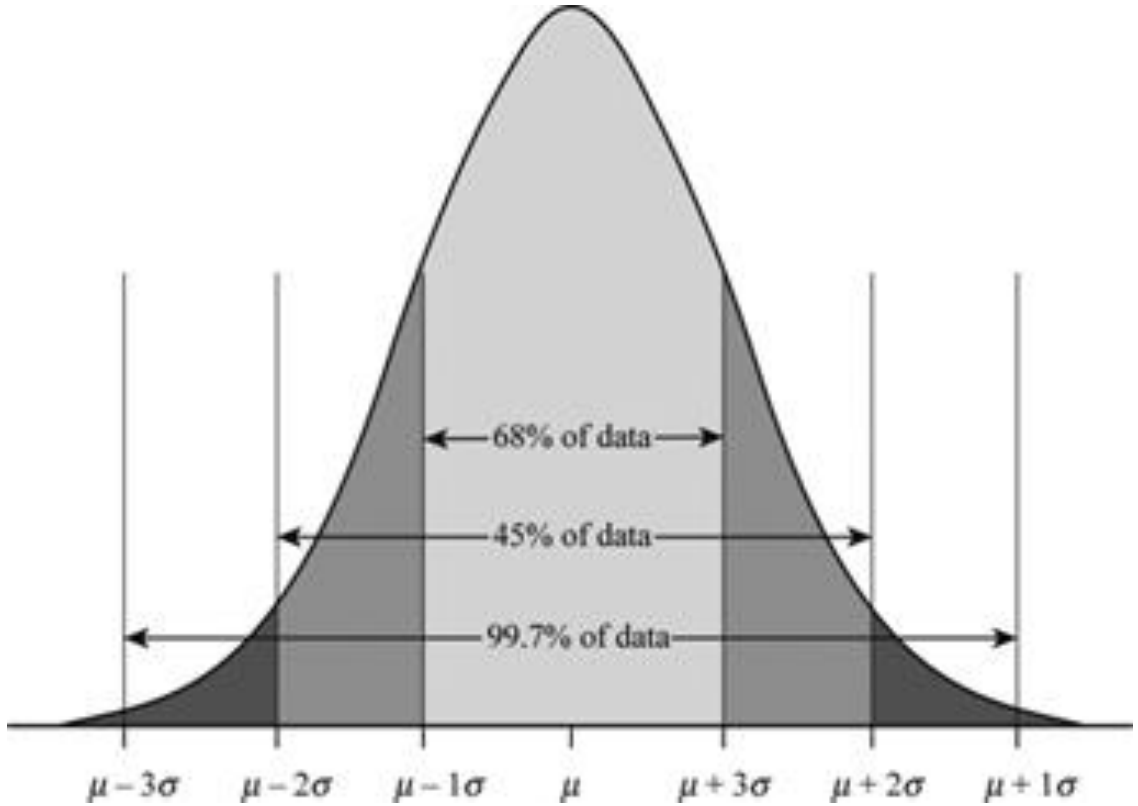
Incidence rate -> incidence rate ratio

CIP -> relative risk

Odds -> odds ratio

The larger RR/IRR/OR, the stronger the (relative) association, that is, the association between using e.g. a drug and the risk of the outcome

1.3 (0.8-2.2)


68% of data
45% of data
99.7% of data
μ − 3σ
μ − 2σ
μ − 1σ
μ
μ + 3σ
μ + 2σ
μ + 1σ

Measures of frequency and association

Study design

Bias

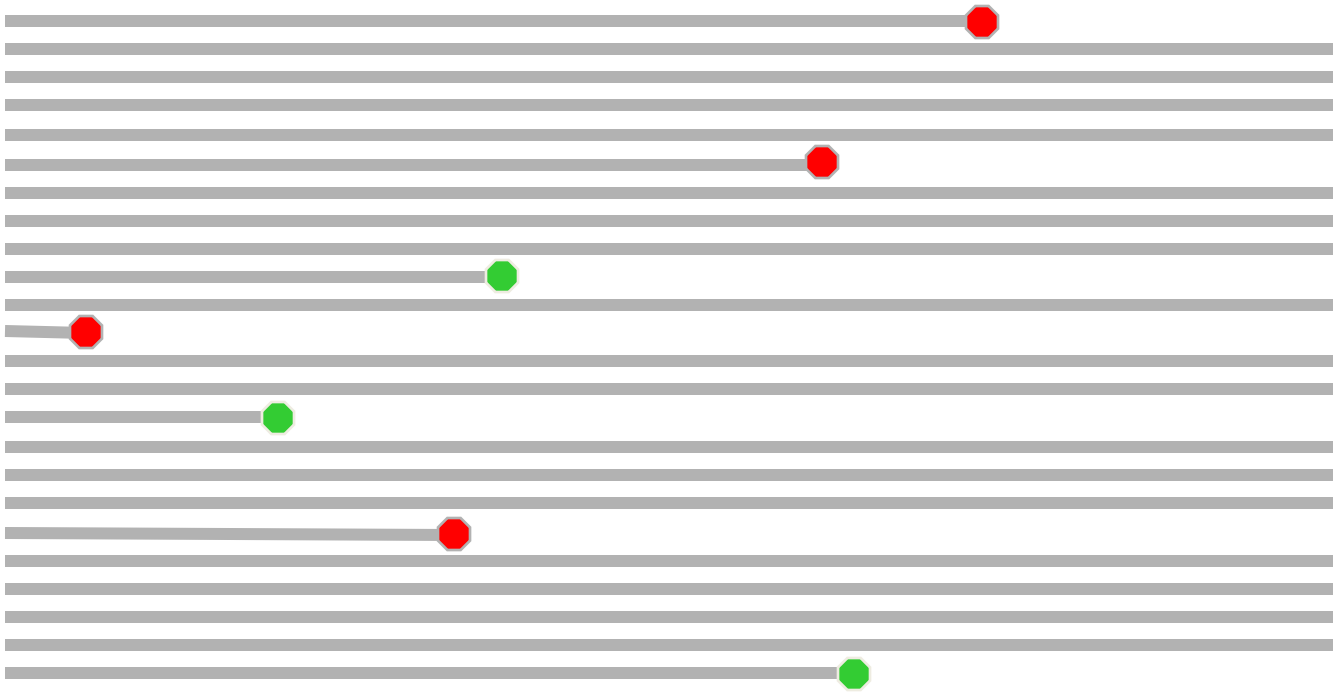
Cohort study

A group of users of a drug and a group of non-users are followed over time and compared regarding a given outcome

Case-control studies

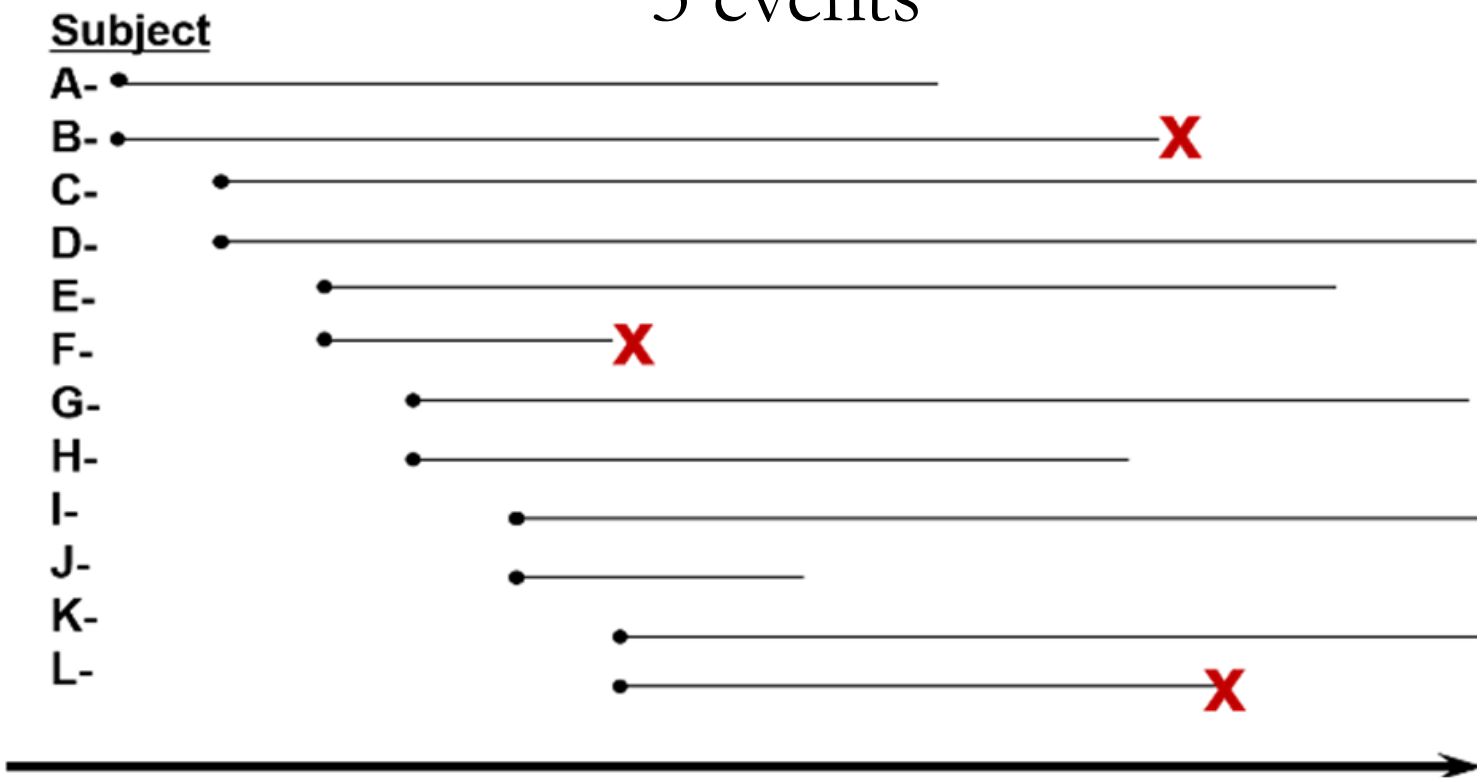
A group with a given outcome is compared to a group without that outcome in terms of (previous) drug exposure

Cohort design



107.7 person-years

3 events



$$IR = 0.028/py$$

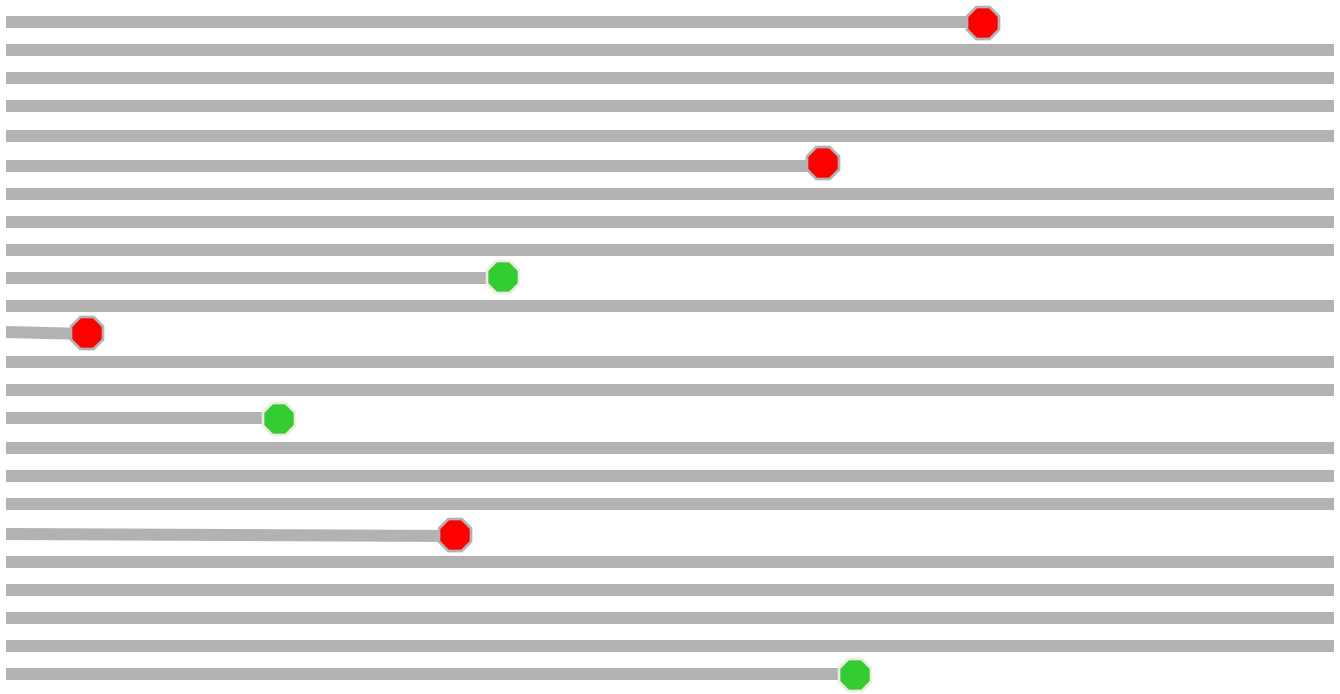
$$= 28/1000py$$

$$\text{IR(exposed)} = 28/1000\text{py}$$

$$\text{IR(unexposed)} = 20/1000\text{py}$$

$$\text{IRR} = 28/20 = 1.4$$

Cohort design



Case-control design

Cohort study

10,000 girls aged 20-25 years using ‘the pill’ are followed for three years.

Among these girls, 200 incident cases of deep vein thrombosis are recorded.

Among 20,000 girls NOT using ‘the pill’ (but same age and follow-up), 100 incident cases of deep vein thrombosis are recorded.

What is the incidence rate ratio?

Case-control study

300 girls aged 20-25 with incident deep vein thrombosis are identified. Among these girls, 80% had used ‘the pill’

Another 300 girls of the same age that have no record of deep vein thrombosis are identified. Among these girls, 50% have used ‘the pill’.

Odds ratio

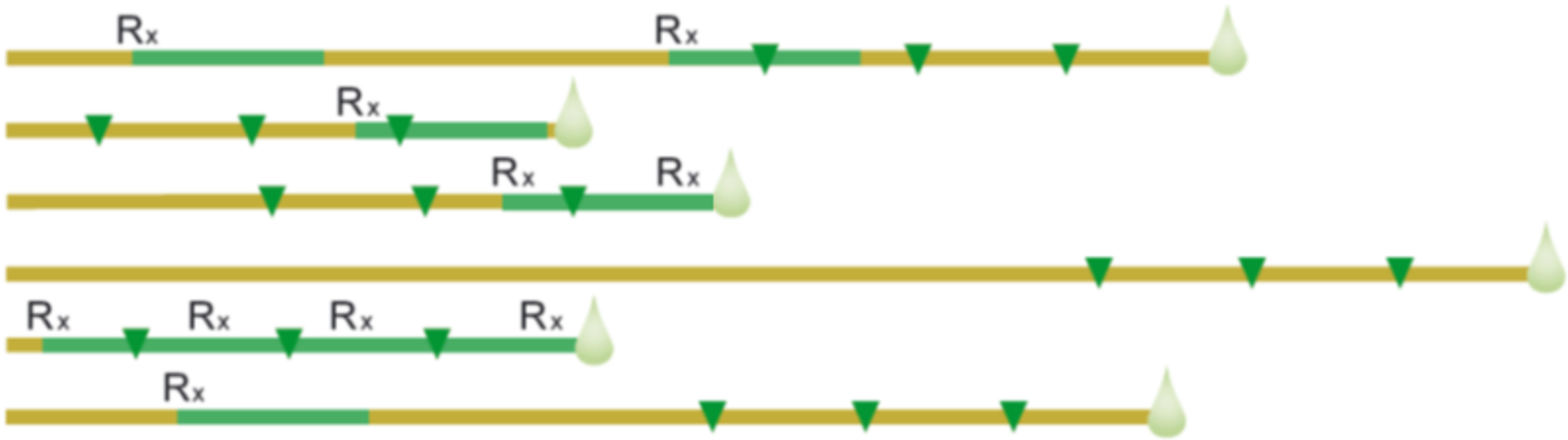
	DVT Y	DVT N
The pill Y		
The pill N		

$$OR = \frac{\left({}^{240}/_{60}\right)}{\left({}^{150}/_{150}\right)} = 4$$

”If properly conducted and analysed, case-control studies can yield all the information that cohort studies can provide.”

-Ken Rothmann

Self-controlled designs

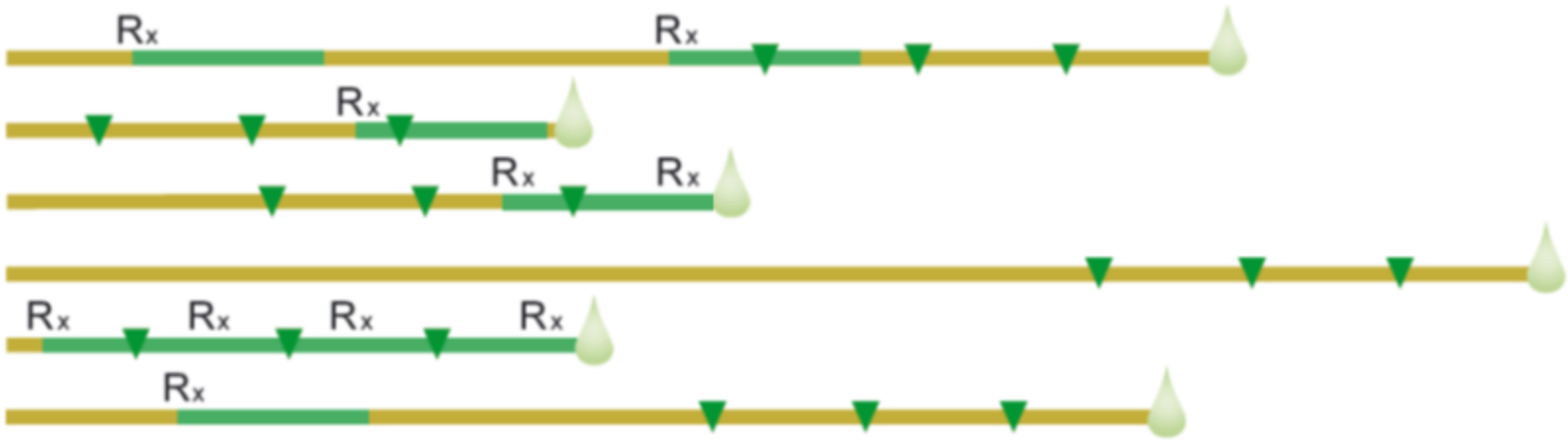


Case-crossover

Self-controlled designs

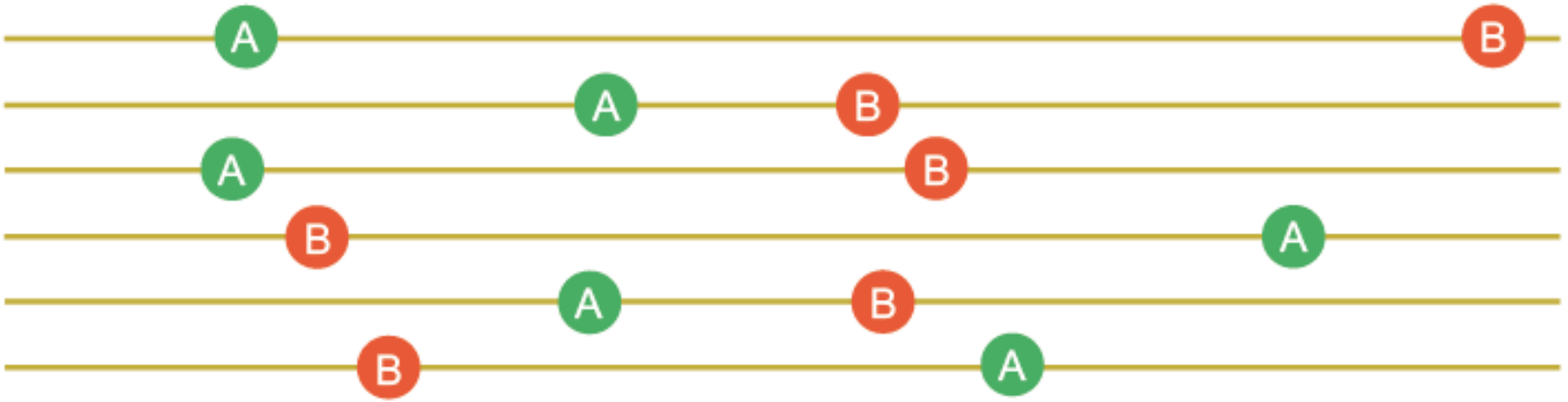
Case-crossover

Self-controlled designs



Case-crossover

Self-controlled designs



Symmetry design

Review

Journal of INTERNAL MEDICINE

Click here for more articles from the symposium

doi: 10.1111/joim.12186

Use of self-controlled designs in pharmacoepidemiology

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Abstract. Hallas J., Pottegård A (Department of Clinical Pharmacology, IST, University of Southern Denmark, Odense, Denmark). Use of self-controlled designs in pharmacoepidemiology. (Review). *J Intern Med* 2014; **275**: 581–589.

Self-controlled observational study designs, such as the case–crossover design and the self-controlled case series, are reviewed, and their respective rationale, strengths and limitations are compared. Although no single design is generally superior to the others, they share the trait of being robust towards confounders that are stable over time. The self-controlled designs can be particularly useful when using secondary healthcare data for pharmacoepidemiological research and might be useful in screening for adverse drug effects. The main limitations of self-controlled designs are that they are amenable only to transient effects; some may be inefficient with long-term exposure; and they may be sensitive towards trends in exposure.

Keywords: adverse drug effects, design, epidemiology, methods.

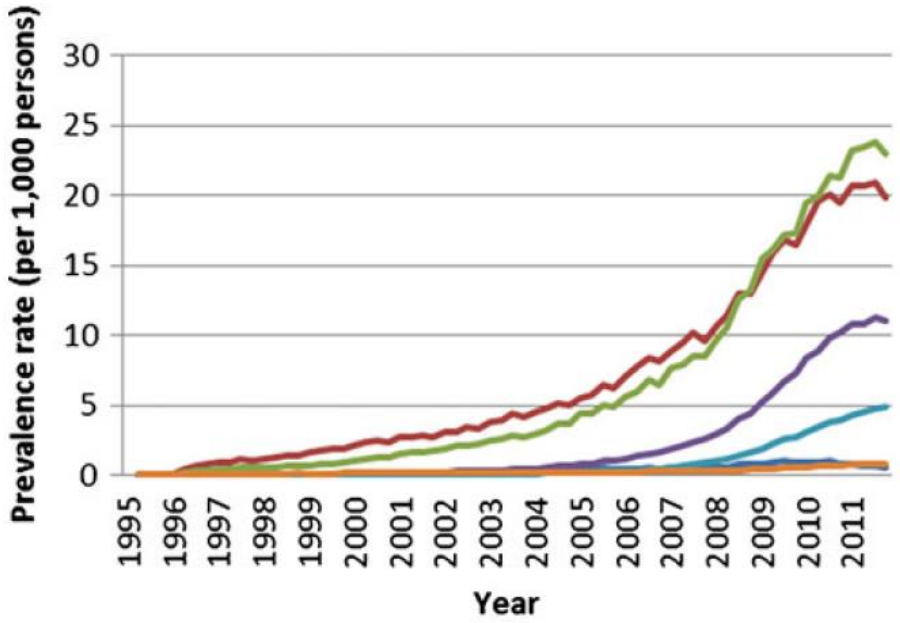
Introduction

The clinical trial is widely considered the pinnacle of design for studying intentional drug effects [1]. However, there are situations where the trial design cannot be applied, typically because of 'why now?' instead of 'why me?' that is posed in a design based on other control subjects [2].

In this review, we describe the properties of the case–crossover design and variants, case–time–control design, symmetry design, and self-con-

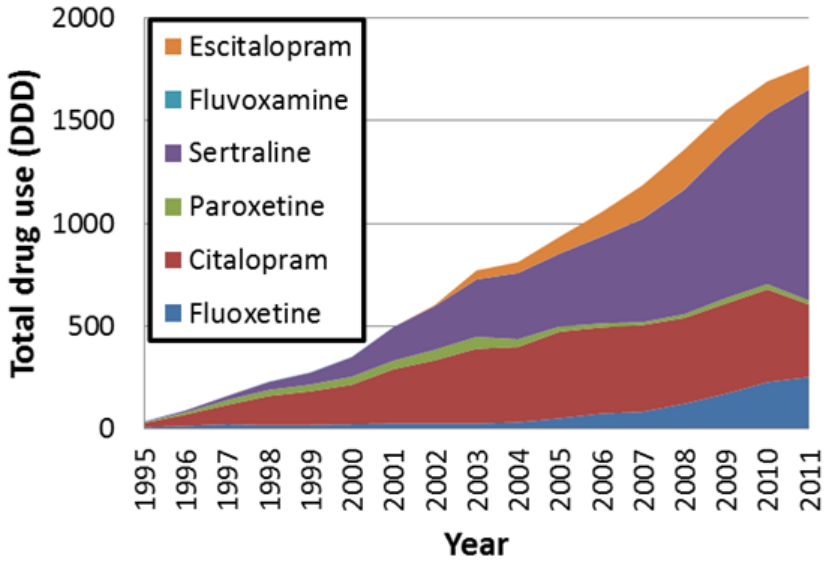
Drug utilization

- Incidence rates
- Prevalence proportions



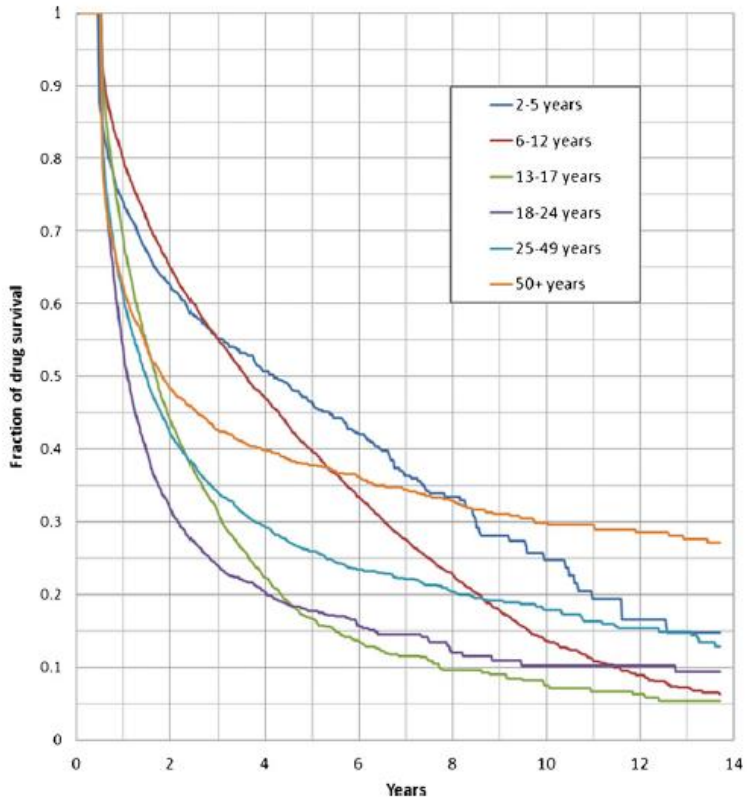
Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances



Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')



Drug utilization

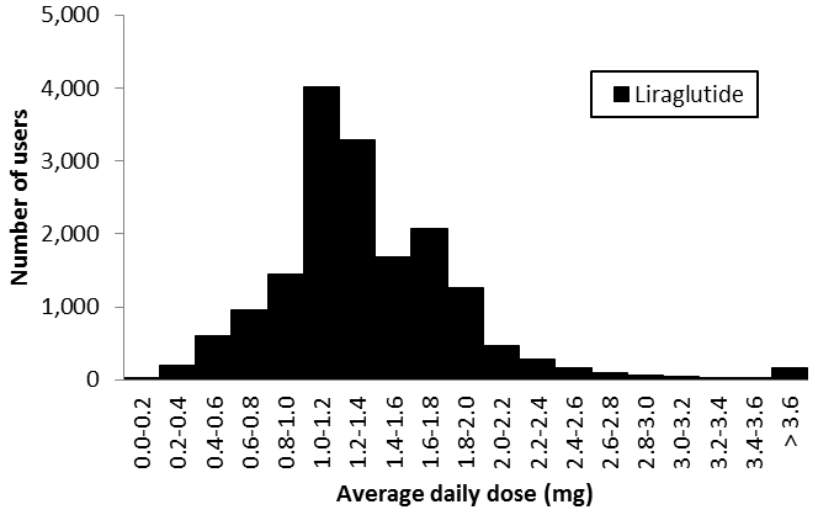
- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')
- Co-medication

Table 5 Sub-analysis of ACT group N

ATC category	ATC description	<18 years (n=15,660)	
		%	SMR[a]
N01B	Anesthetics, local	0.1	1.3 [0.8–2.0]
N02A	Opioids	0.3	1.1 [0.8–1.4]
N02B	Other analgesics and antipyretics	0.8	2.9 [2.4–3.4]
N02C	Antimigraine preparations	0.6	1.9 [1.5–2.3]
N03A	Antiepileptics	1.9	4.0 [3.6–4.5]
N04A	Anticholinergic agents	0.1	9.3 [4.4–17.0]
N04B	Dopaminergic agents	0.0	9.2 [3.3–19.9]
N05A	Antipsychotics	7.1	19.5 [18.4–20.7]
N05B	Anxiolytics	0.7	3.3 [2.7–4.0]
N05C[b]	Hypnotics and sedatives[b]	0.3	5.3 [3.9–7.0]
N06A	Antidepressants	4.9	7.9 [7.3–8.4]
N07B	Drugs used in addictive disorders	0.1	4.9 [2.6–8.4]
N07X	Other nervous system drugs	0.1	15.5 [6.7–30.5]

Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')
- Co-medication
- Daily dose (≈)



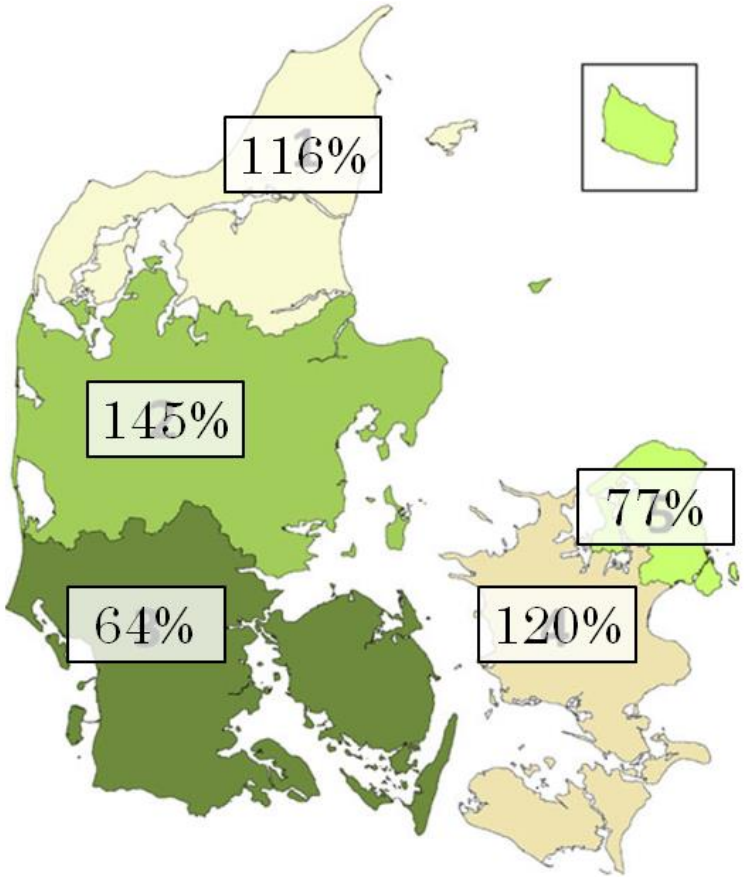
Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')
- Co-medication
- Daily dose (≈)
- Prescriber profile

	6–12 years	25–49 years
MPH	GP/SP/HP 7/27/66 (6,338)	GP/SP/HP 20/49/31 (9,767)

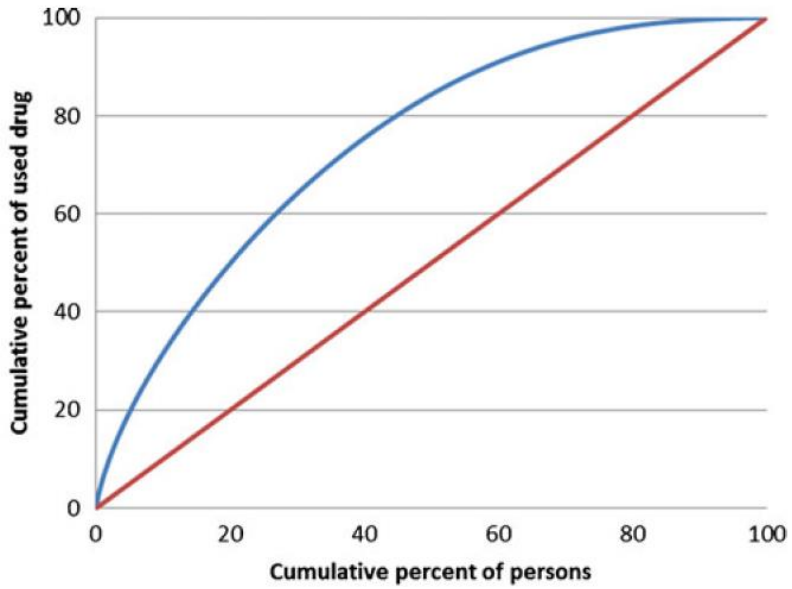
Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')
- Co-medication
- Daily dose (≈)
- Prescriber profile
- Regional differences



Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')
- Co-medication
- Daily dose (≈)
- Prescriber profile
- Regional differences
- Skewness



Measures of frequency and association

Study design

Bias

Random variation 

Systematic error (Bias)

Selection bias 

Information bias 

Confounding  

 Statistician's expertise

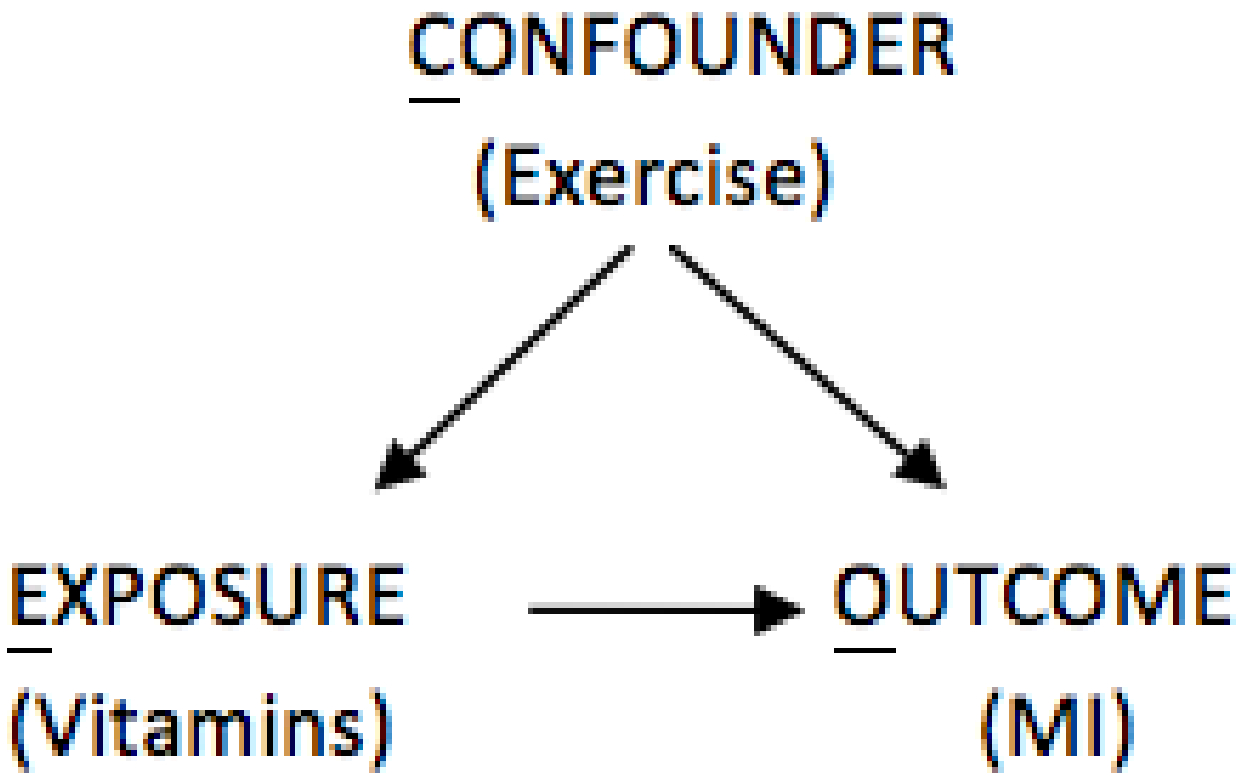
 Epidemiologist's expertise

Confounding

Lack of comparability…

Mixing effects…

Error (bias) caused by lack of comparability between users and non-users of a drug



1. Associated to outcome
2. Associated to exposre
3. Not caused by the exposure

("not part of the causal chain")

Exercise: Guess the confounder?!

Users of bras have higher risk of
breast cancer compared to non-users

Persons with a high alcohol consumption
have an increased risk of lung cancer

Users of weight loss products have a higher risk of
hip fractures compared to non-users of the same age

Users of low-dose aspirin (ASA) have a higher risk
of MIs compared to non-users of the same age

Types of bias

Confounding

Selection bias

Information bias
(misclassification bias)

Protopathic bias
(reverse causation bias)

Immortal-time bias

Selection bias

Bias comming from **OUTSIDE** the material, due to the selective inclusion of individuals with particular characteristics (related to either exposure or outcome)

Information bias

Bias from **WITHIN** the material
due to incorrect information

Differentiated

Non-differentiated