Welcome!

Welcome

Introduction/Overview

Cohort design

Case-control design

Drug utilization

Exposure

Outcomes

Bias

Confounding

Goodbye

And future
bonus modules!

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Conflicts of interest

I have participated in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV-studies, with funds paid to the institution where I am employed (no personal fees). Further, my research group have received one unrestricted grant from Novo Nordisk.

I have been paid for being a course lead and teacher for courses held by The Danish Association of the Pharmaceutical Industry (DLI Market Intelligence) and Pharmakon.

These relationships have no relation to the presentations within this introductory course.

As per June 2024

Core concepts in pharmacoepidemiology: Fundamentals of the cohort and case–control study designs

Anton Pottegård

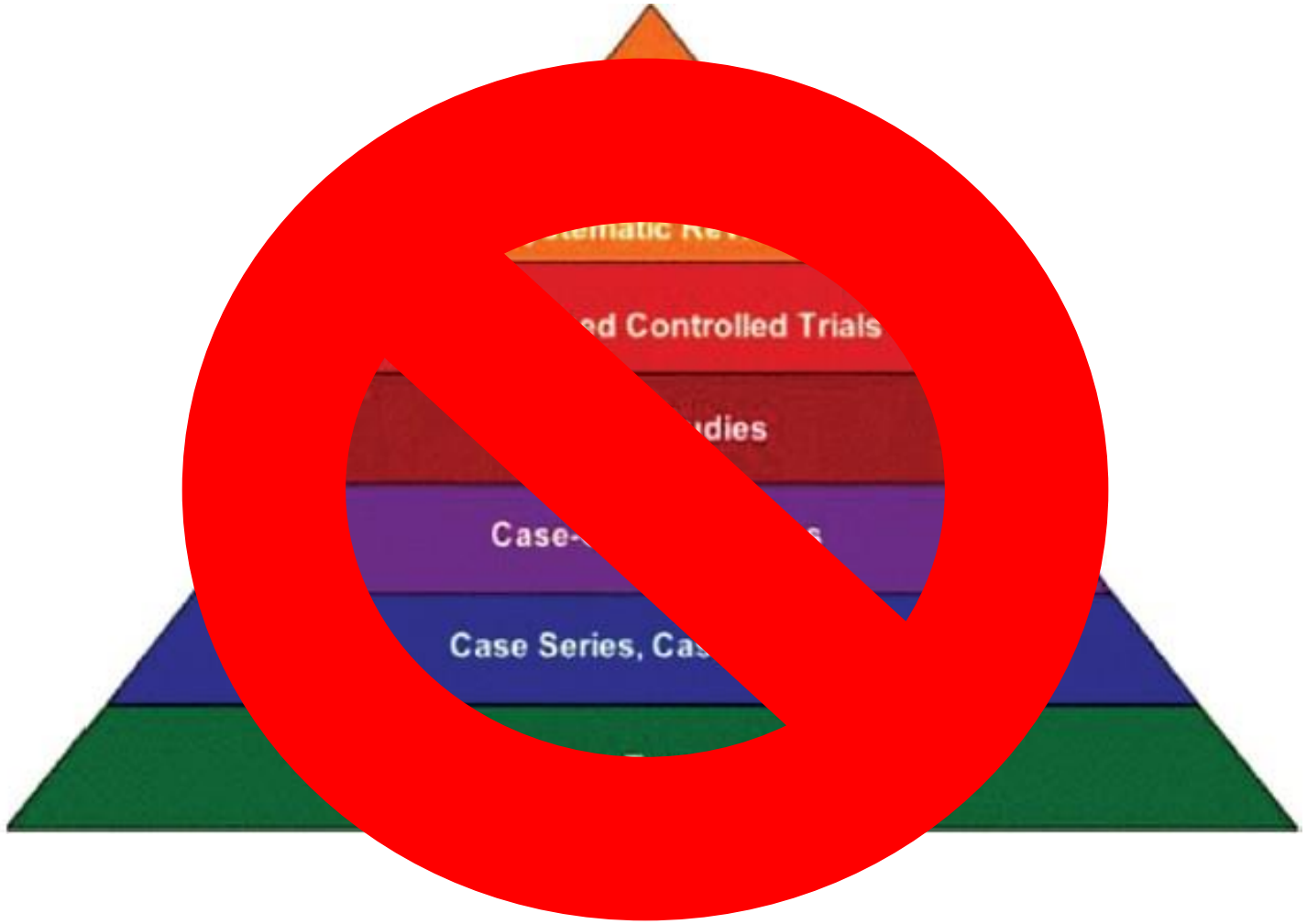
Pharmacoepidemiol Drug Saf. 2022 Aug;31(8):817-826.

Bias: Considerations for research practice

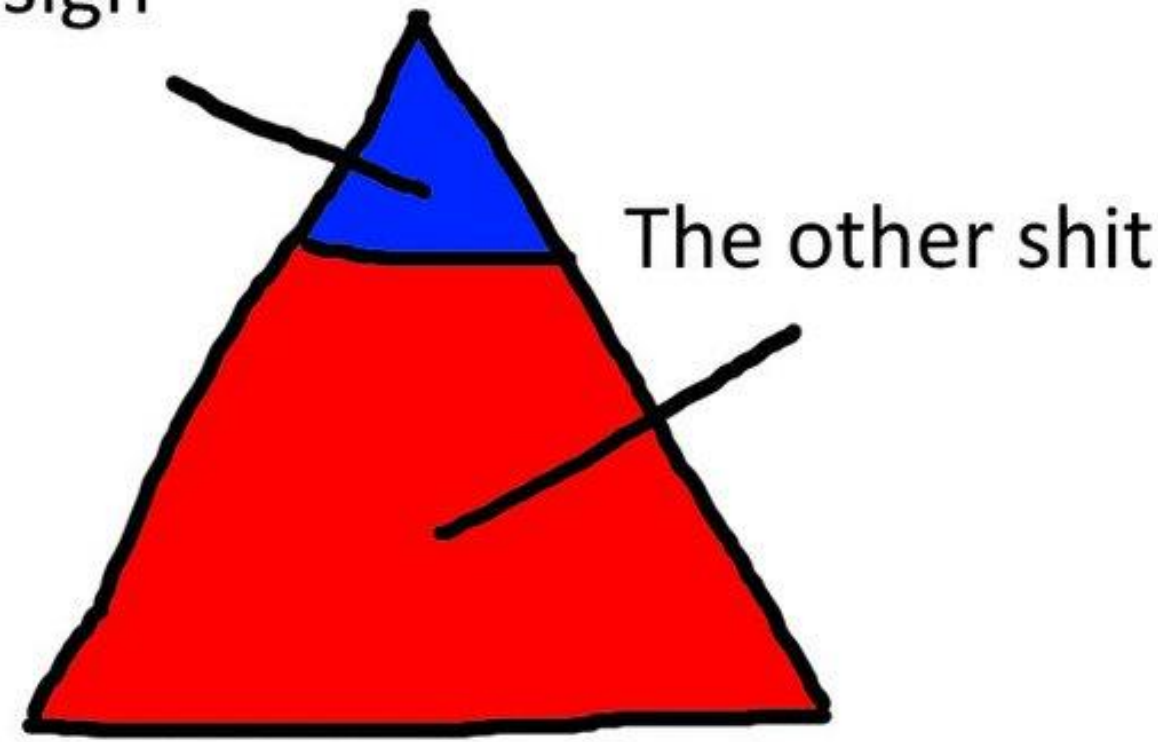
TOBIAS GERHARD

Am J Health Syst Pharm. 2008 Nov 15;65(22):2159-68.

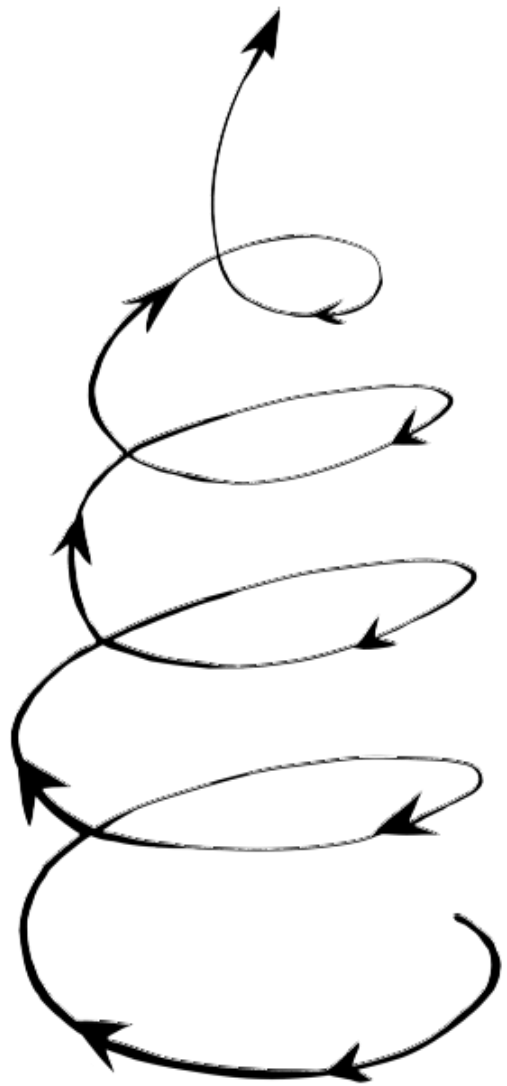
Evidence?!



Thoughtful, well-conducted studies of any design



Credit: Darren Dahly



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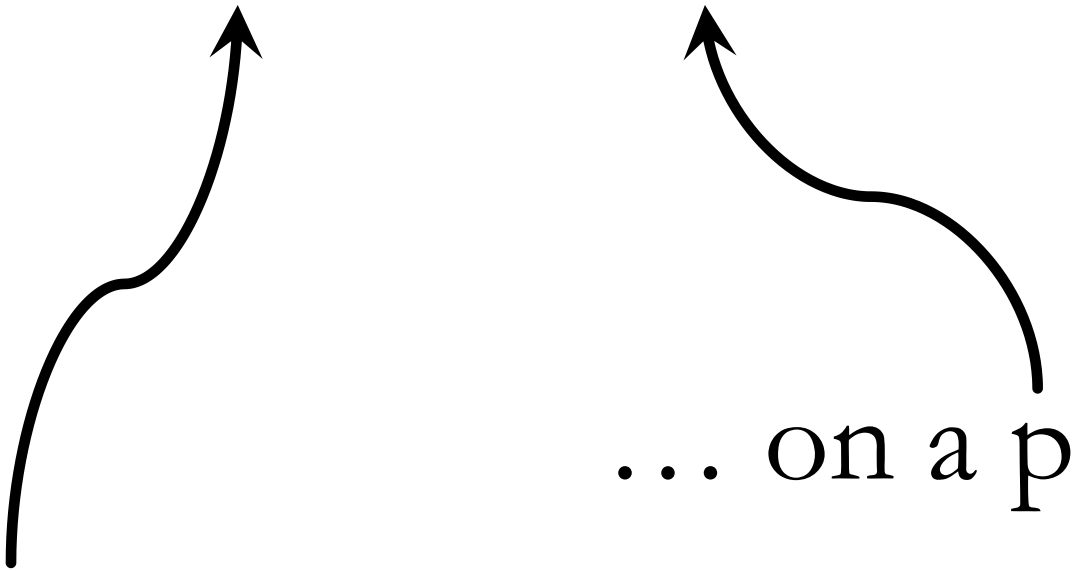
Introduction

Pharmacoepidemiology



… on a population-level

Something with drugs

Pharmacoepidemiology

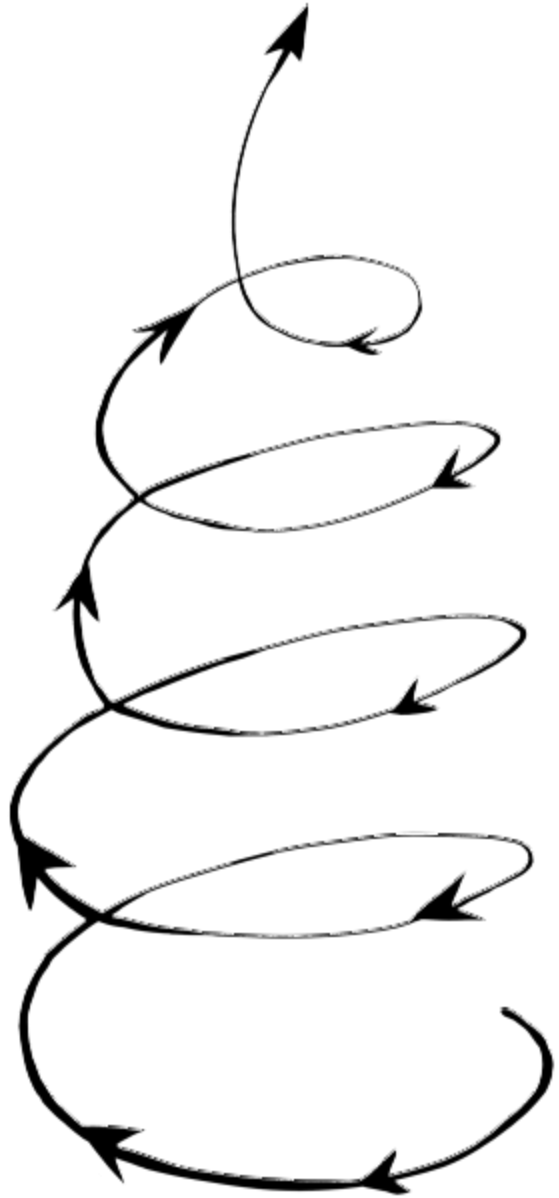
”While the individual man is an insoluble puzzle, in the aggregate he becomes a mathematical certainty. You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to.”

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

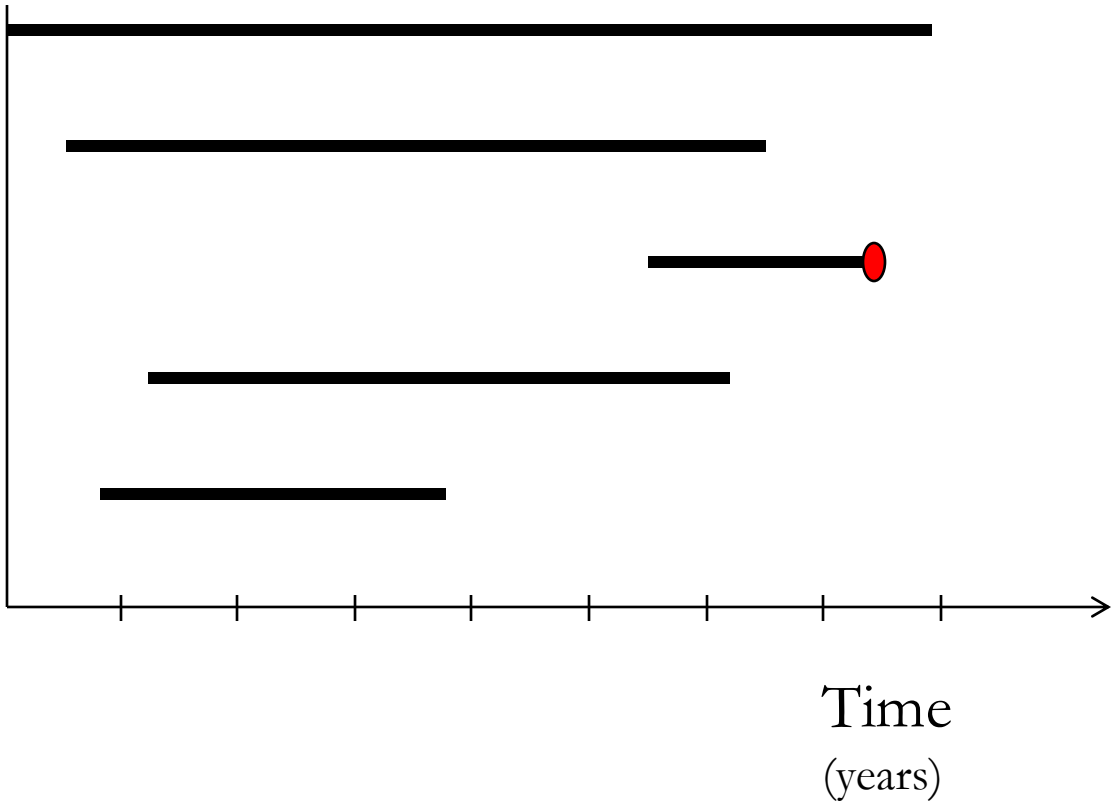
Three persons each followed for 4 months

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

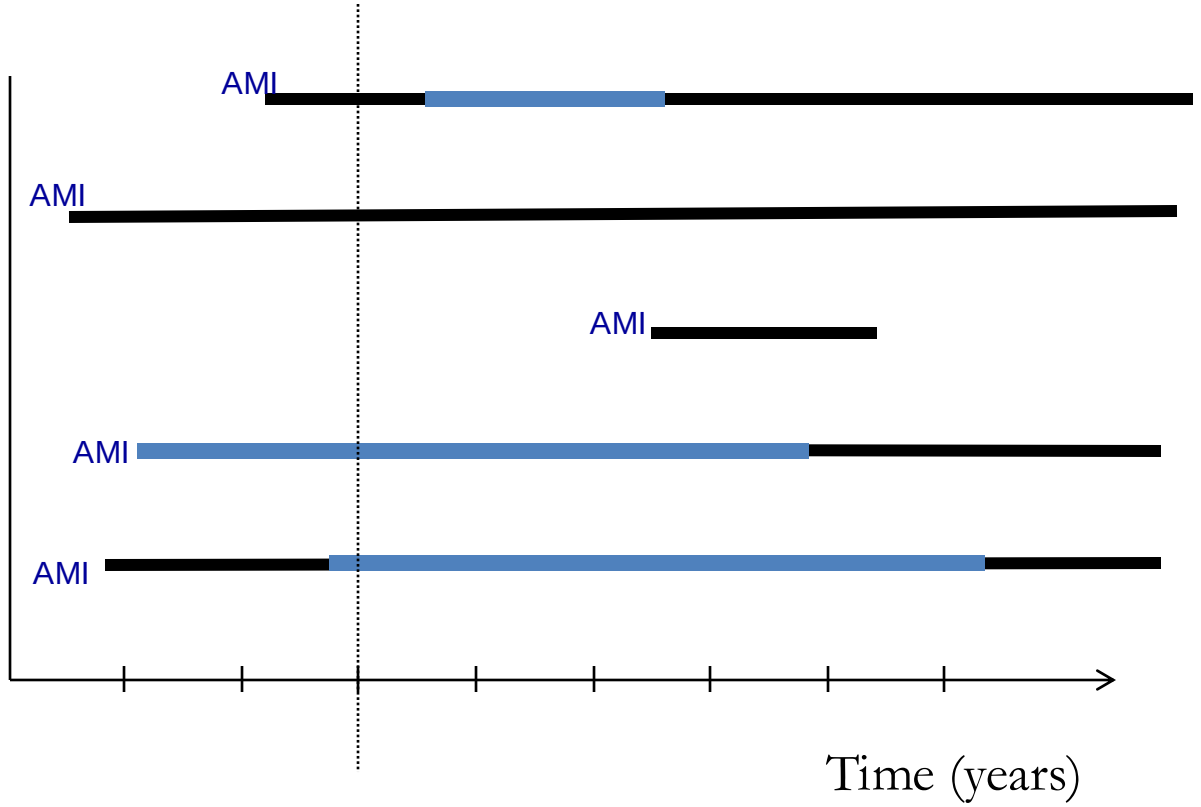
The proportion of a population that at a given time have a given disease

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

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)

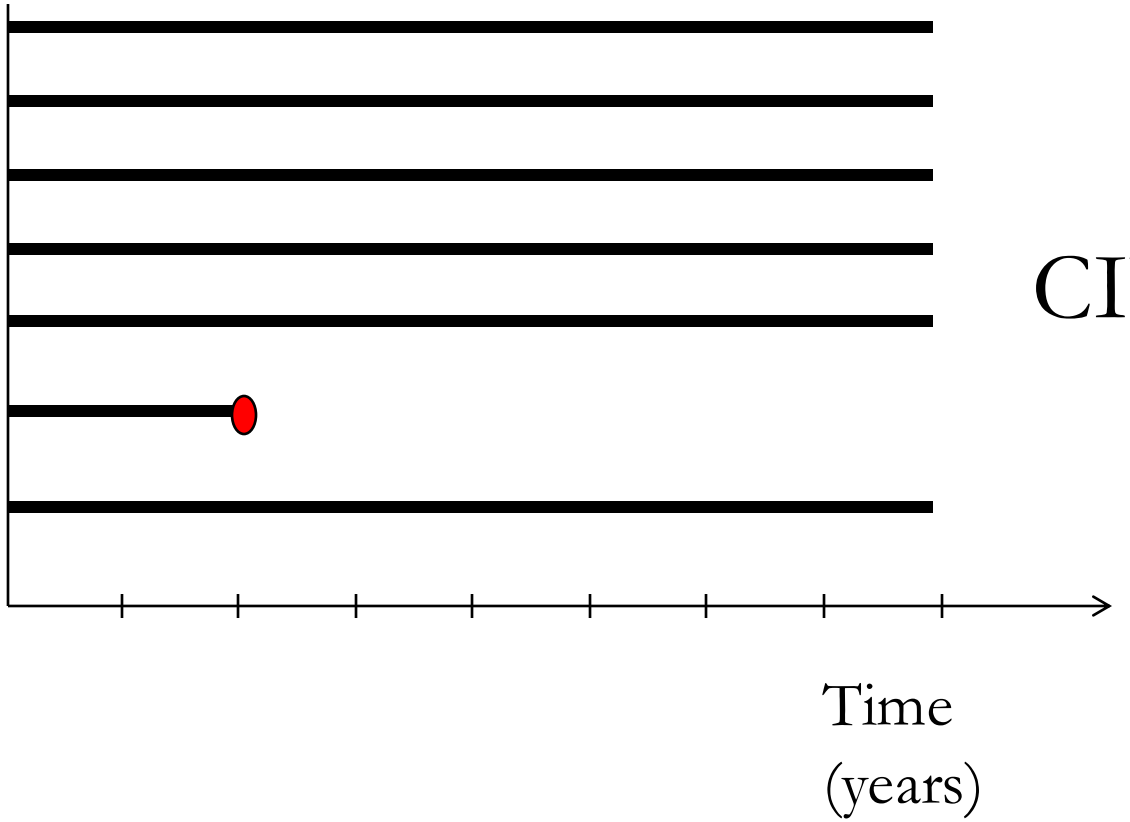
The proportion that within a given period of time experience a (new) outcome

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)



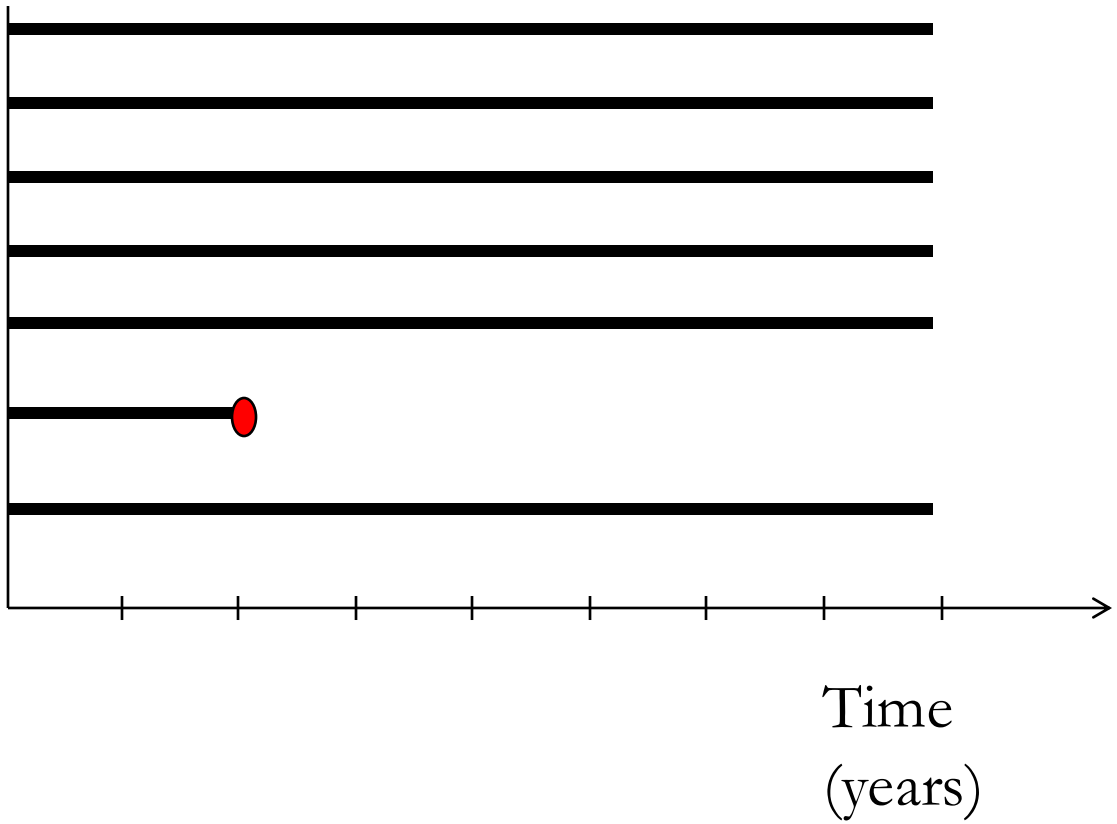
$$CIP_{8y} = 1 / 7$$

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

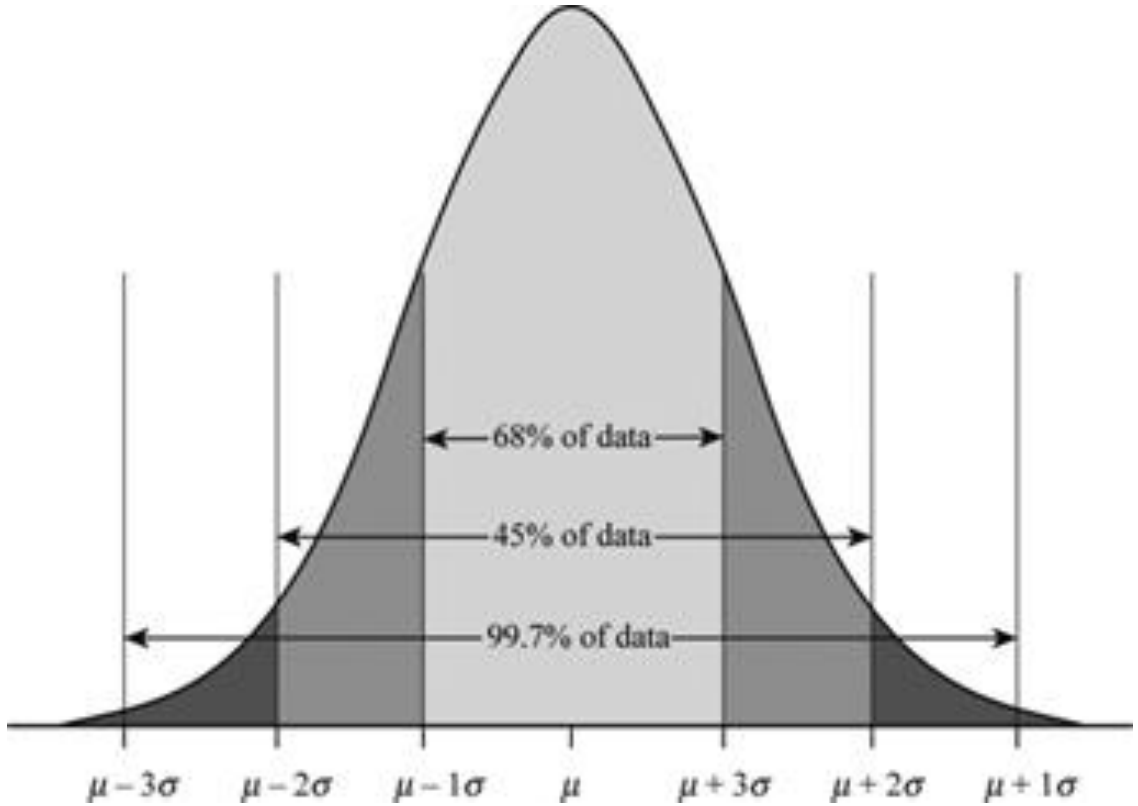
Incidence rate -> incidence rate ratio

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

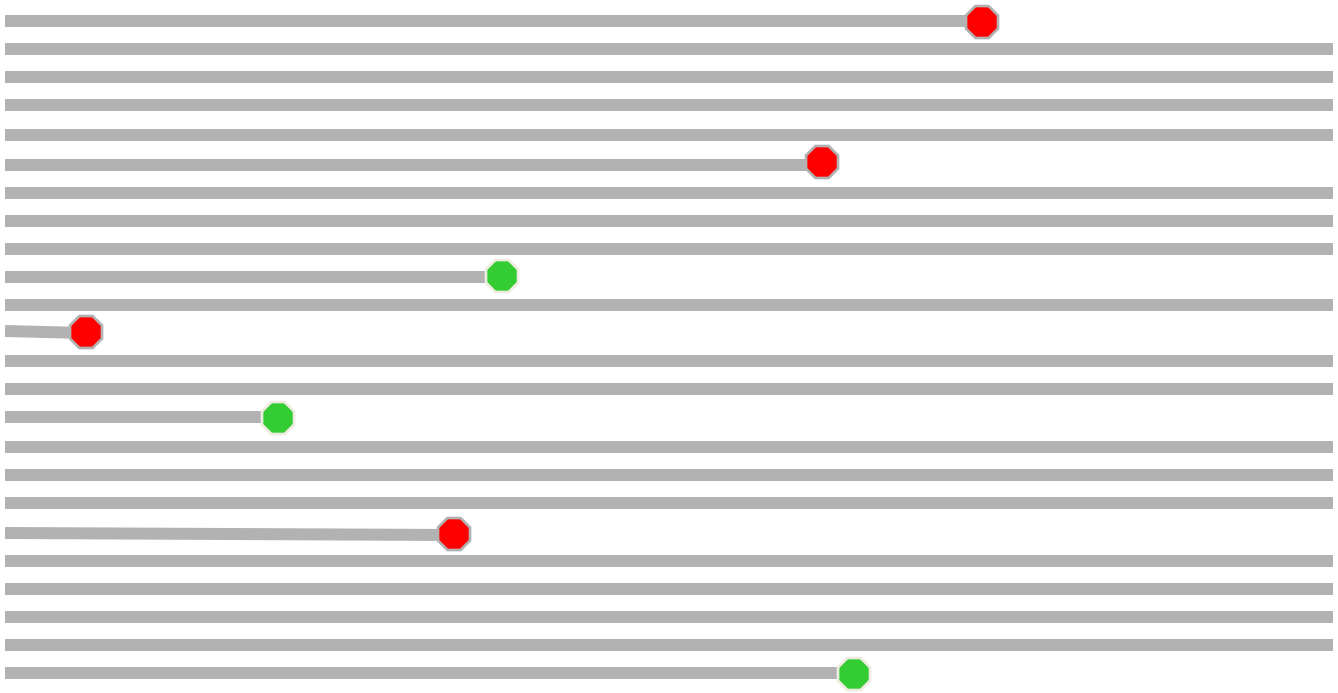
Cohort study

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

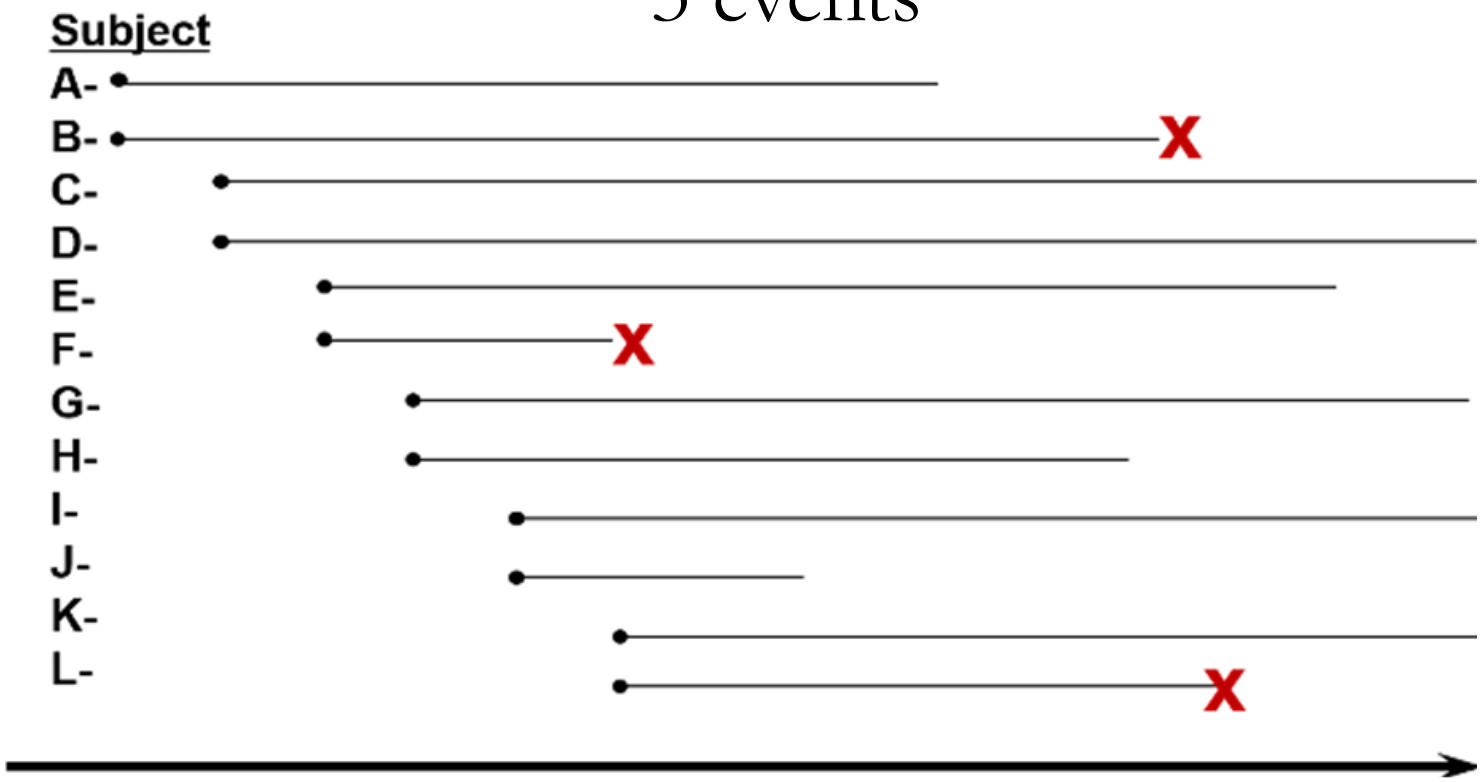
A group with a given outcome is compared to a group without that outcome in terms of (previous) drug exposure

Cohort design



107.7 person-years

3 events



$$IR = 0.028/py$$

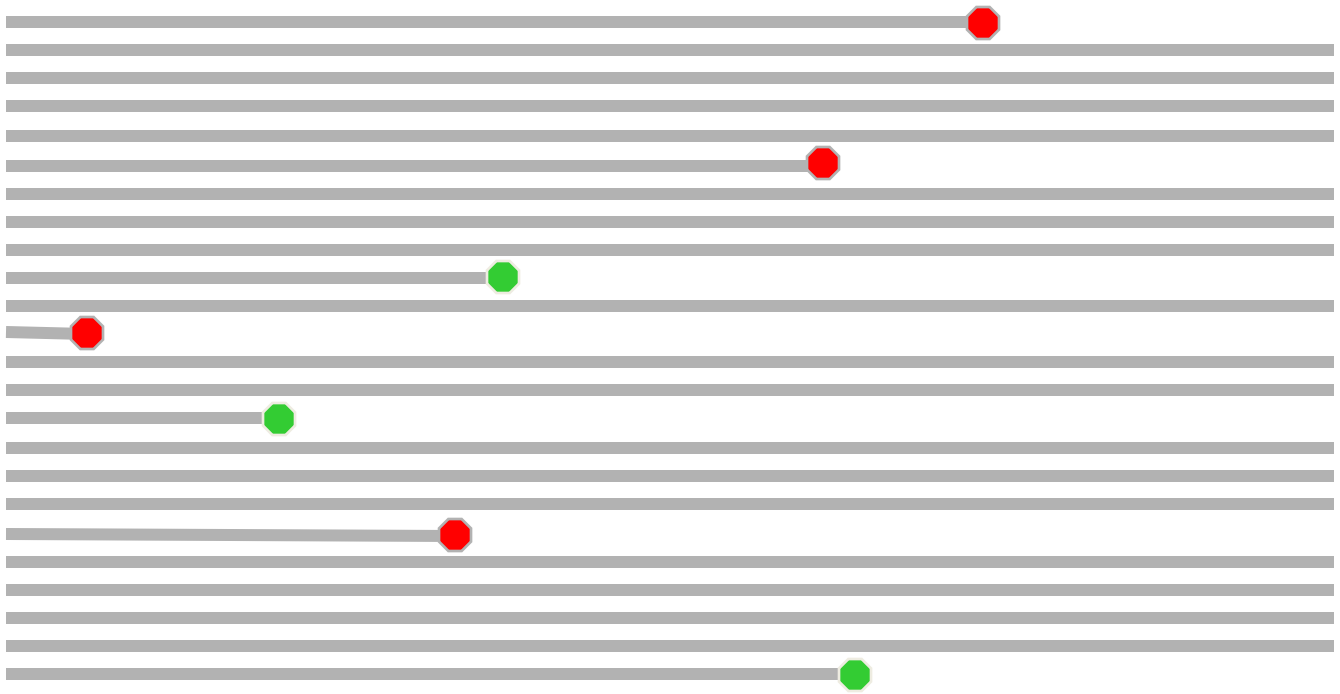
$$= 28/1000py$$

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

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

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

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

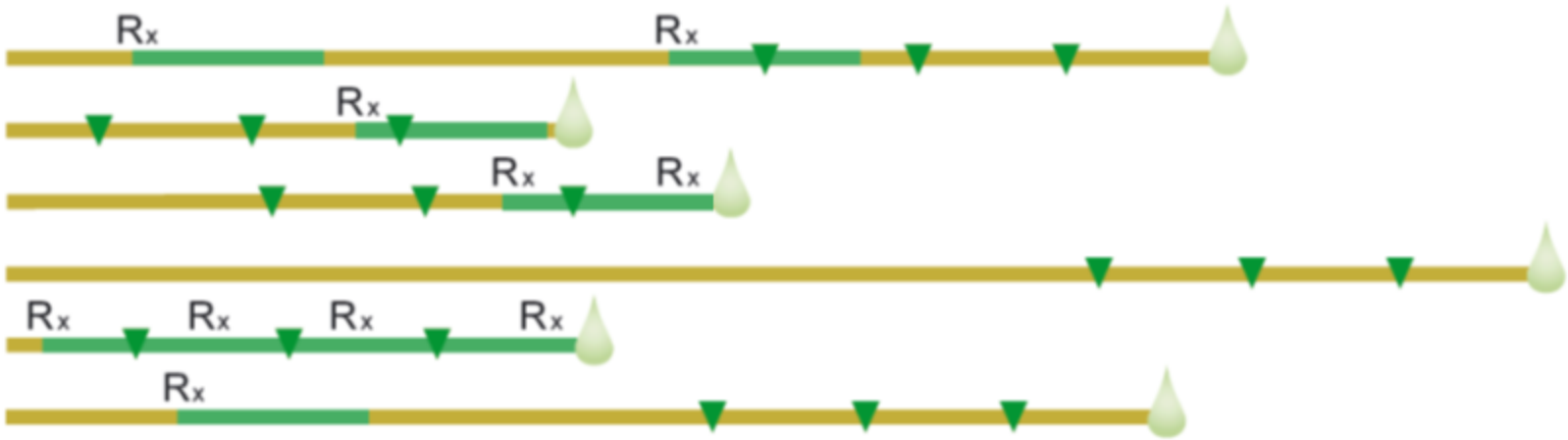
	DVT Y	DVT N
The pill Y		
The pill N		

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

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

-Ken Rothmann

Self-controlled designs

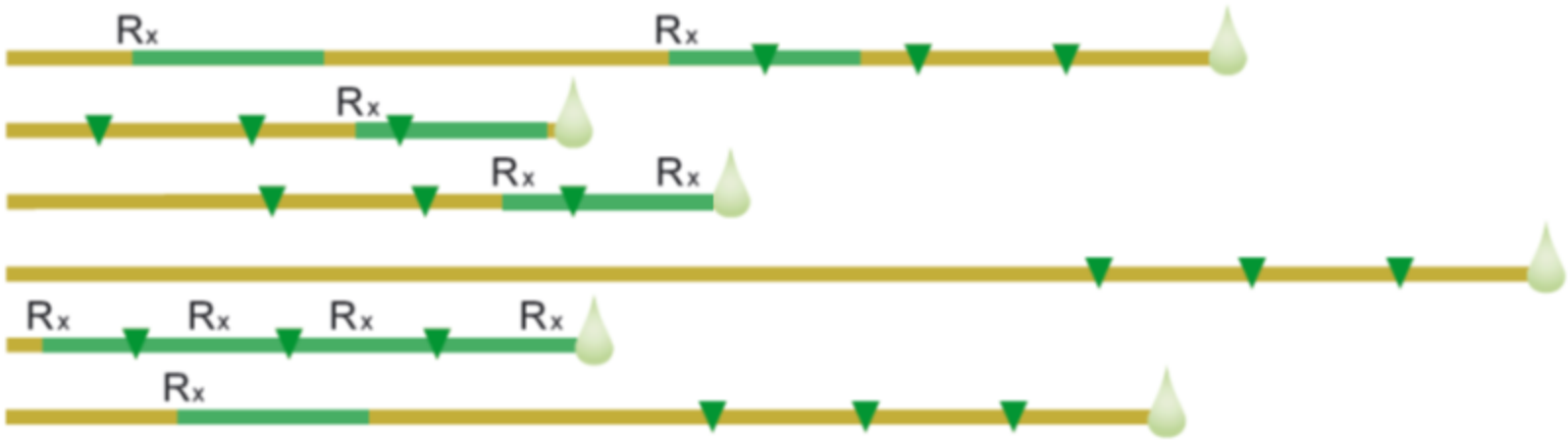


Case-crossover

Self-controlled designs

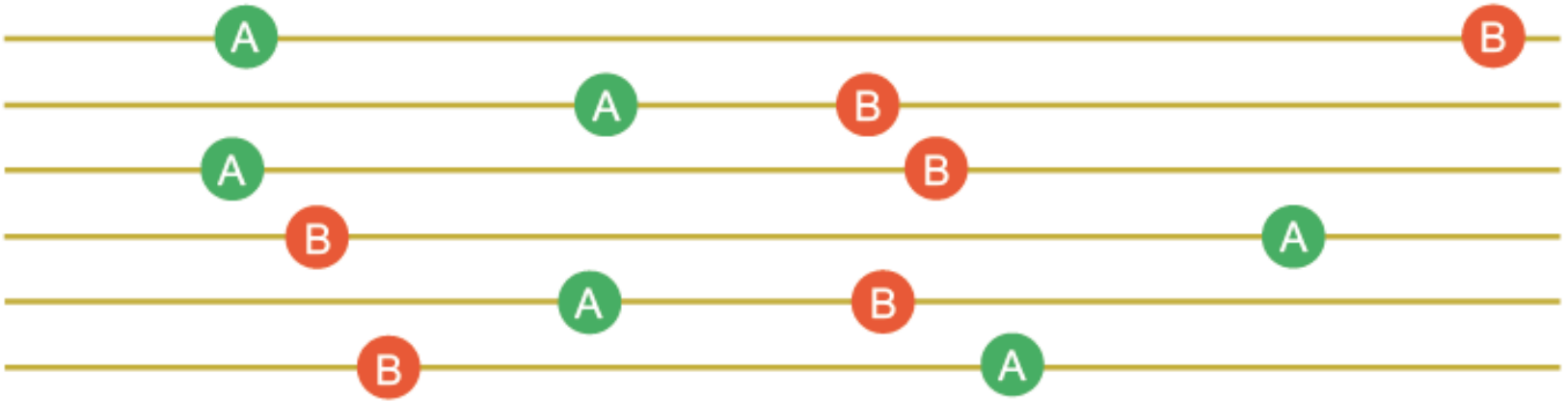
Case-crossover

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

J. Hallas[1] & A. Pottegård[2]

From the [1]Department of Clinical Pharmacology, IST, University of Southern Denmark; and [2]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

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.

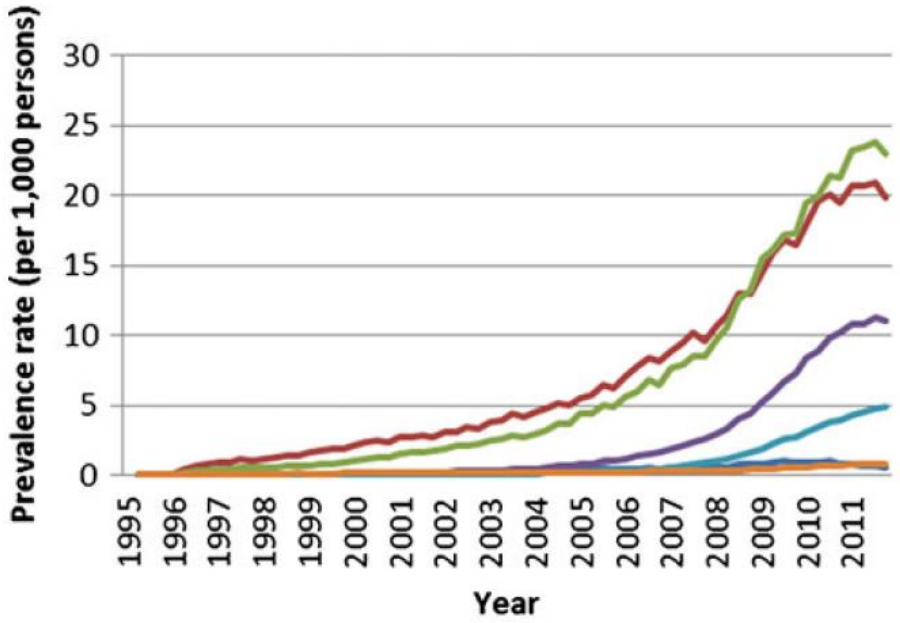
Introduction

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-

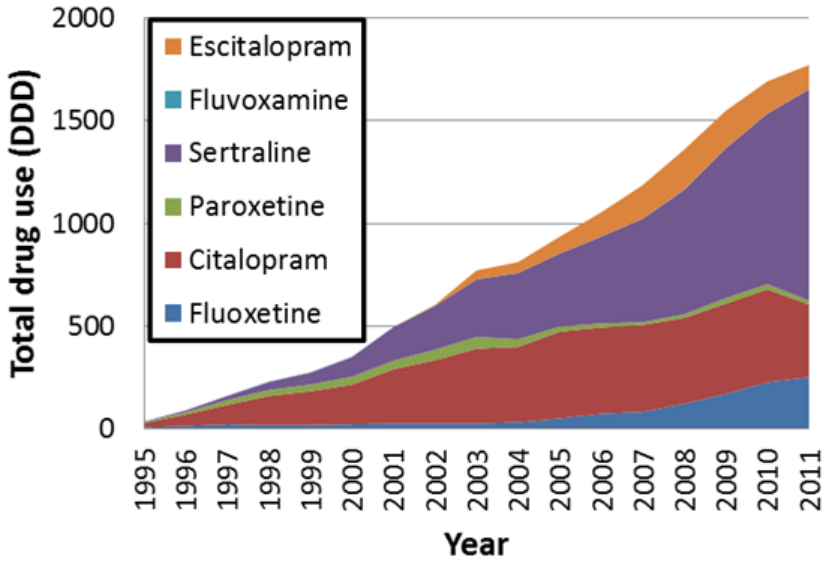
Drug utilization

- Incidence rates
- Prevalence proportions



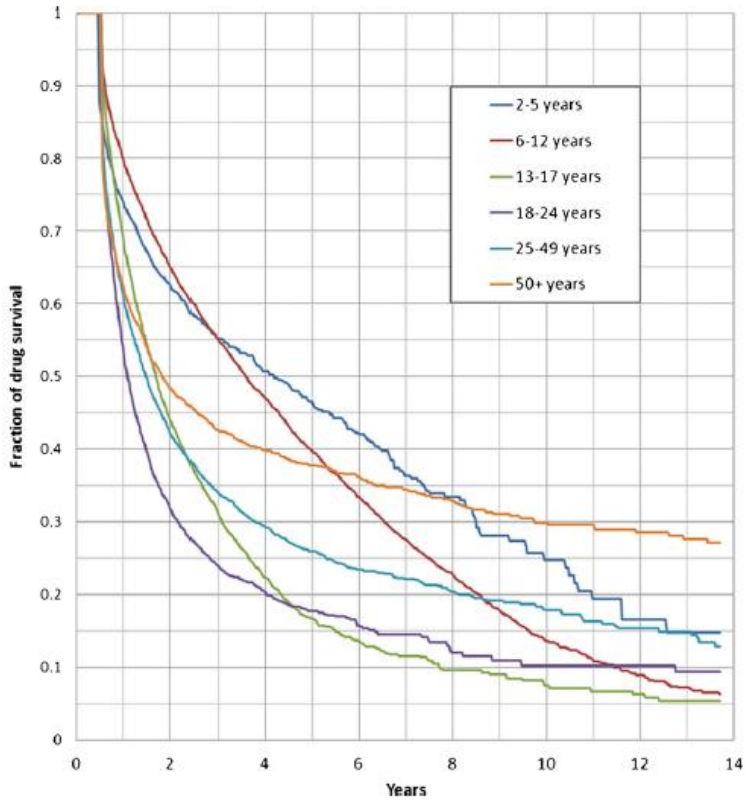
Drug utilization

- Incidence rates
- Prevalence proportions
- Use of single substances



Drug utilization

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



Drug utilization

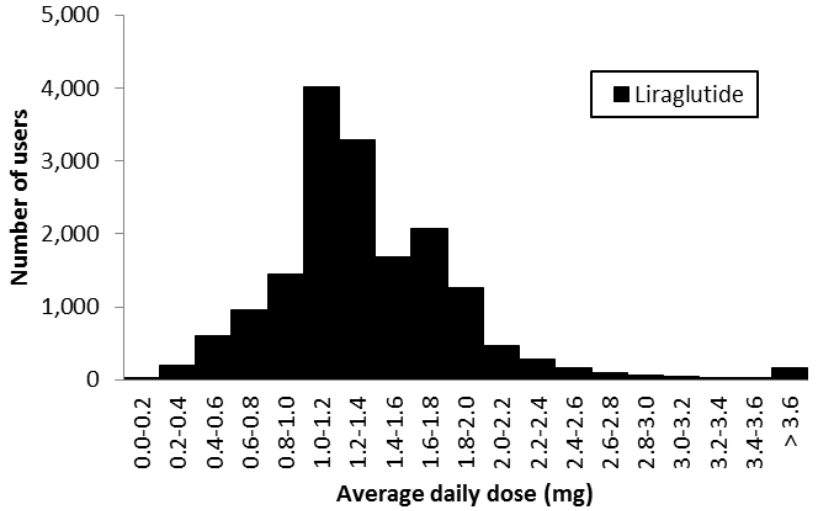
- Incidence rates
- Prevalence proportions
- Use of single substances
- Persistence ('drug survival')
- Co-medication

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 (≈)



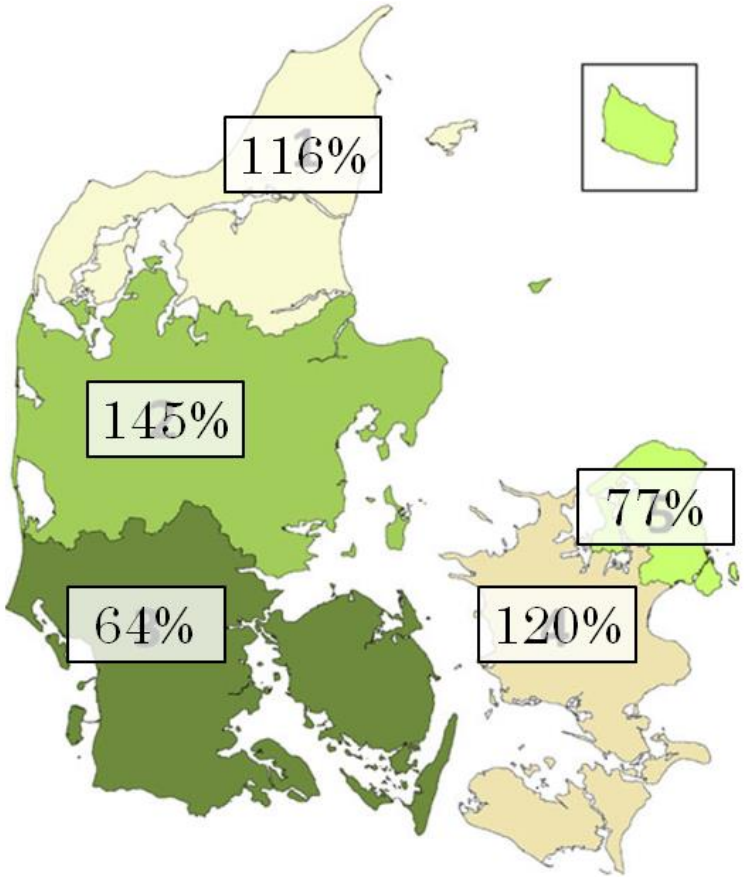
Drug utilization

- 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)

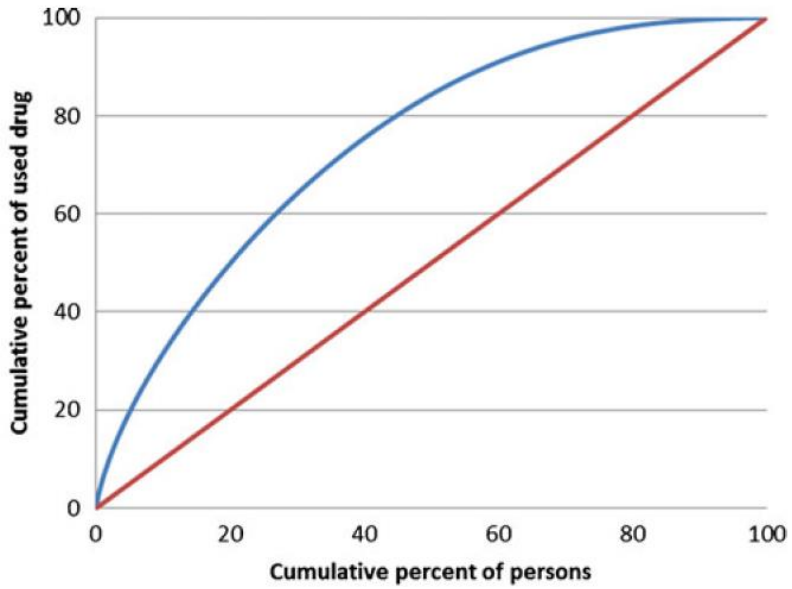
Drug utilization

- 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

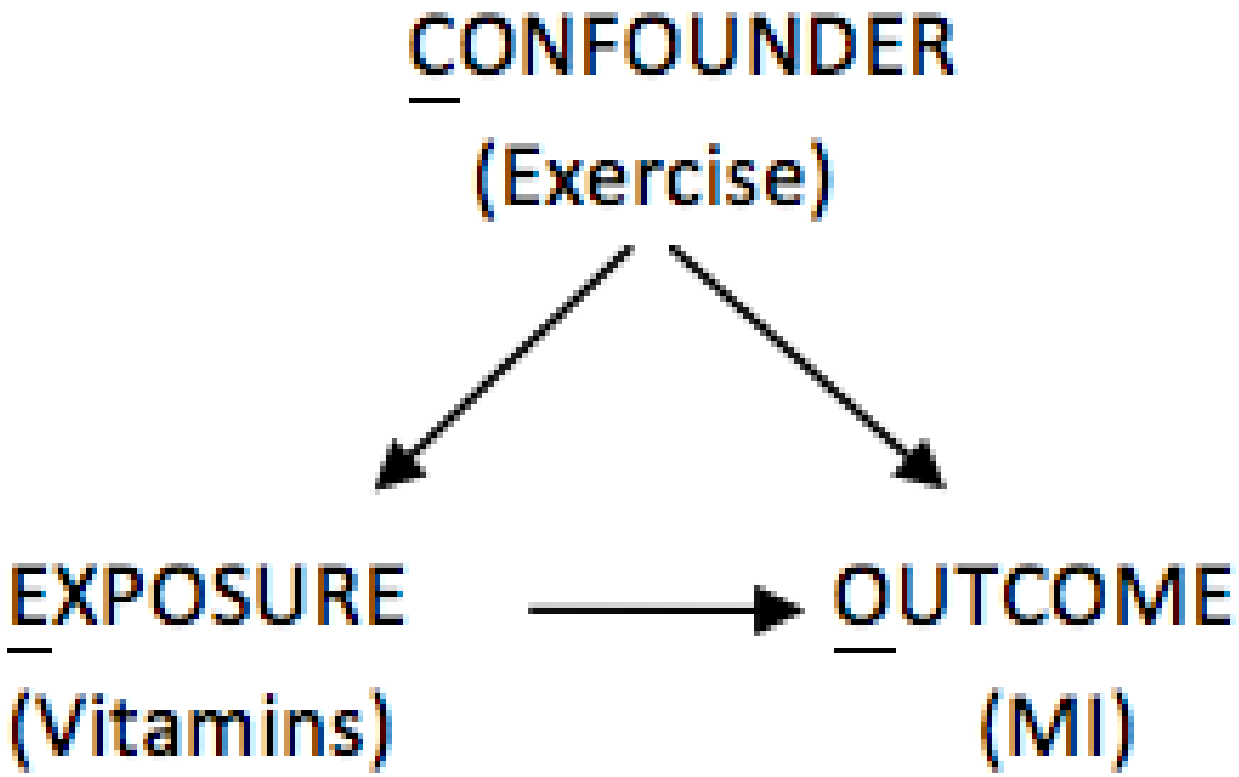
 Epidemiologist's expertise

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

The cohort study design

A cohort

(not the same as a cohort study!)

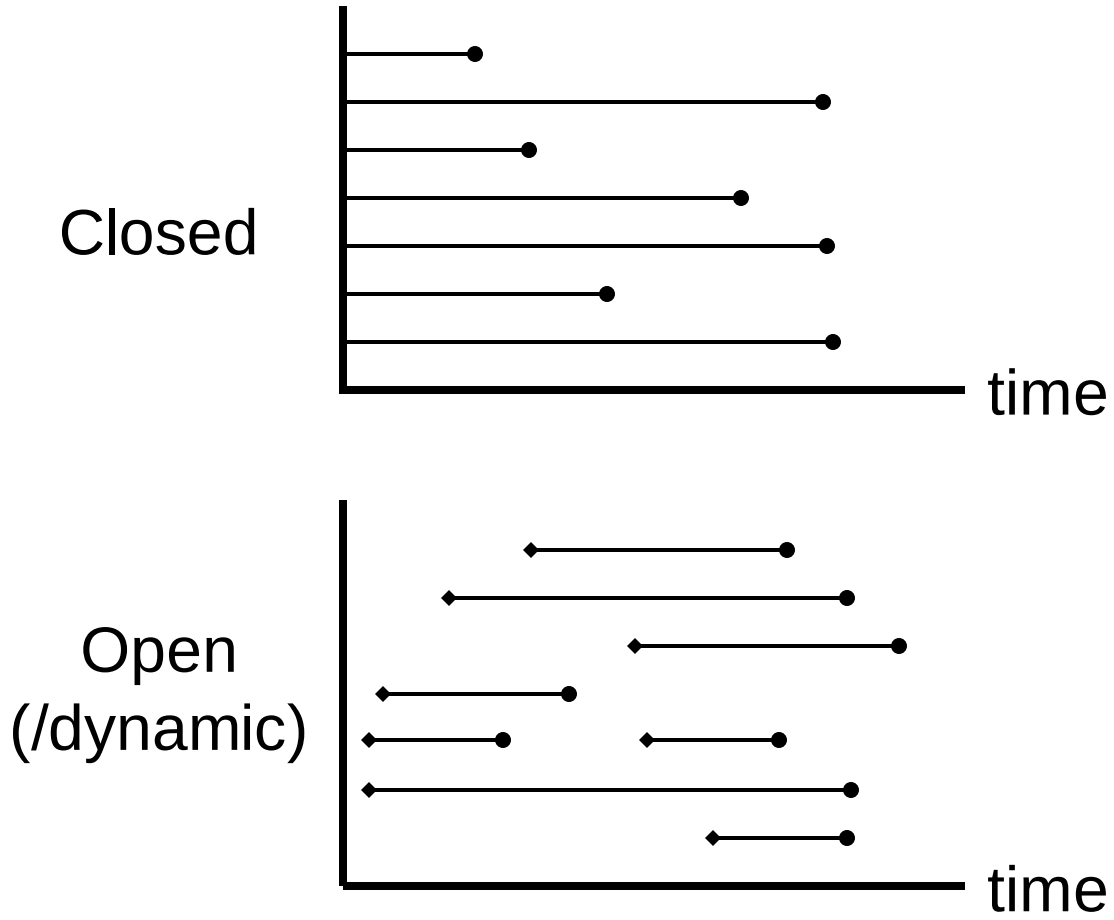
A population followed over time for the occurence of a given outcome

Closed cohort

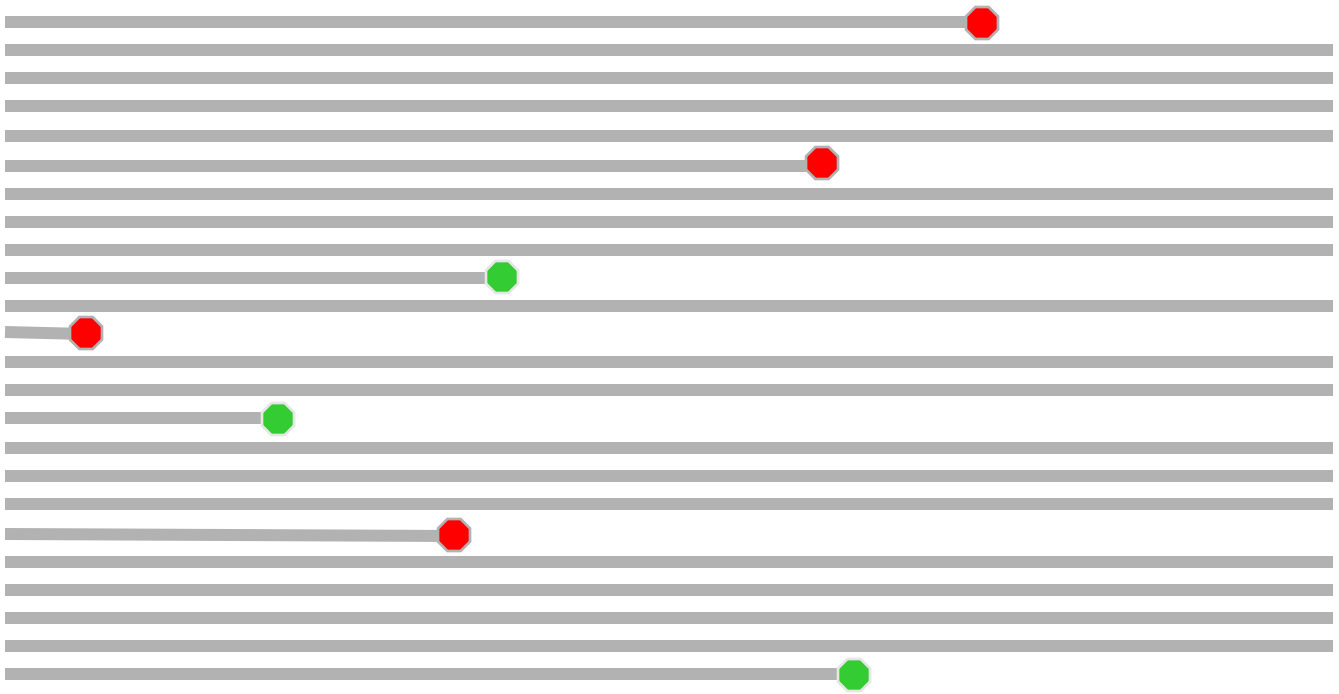
A group of individuals are followed form a given point in time, with no later addition of later individuals. All individuals are followed until the event of interest occur or the study period ends.

Open cohort

A population that is changing over time. Individuals can freely enter and exit the cohort during the observation period.

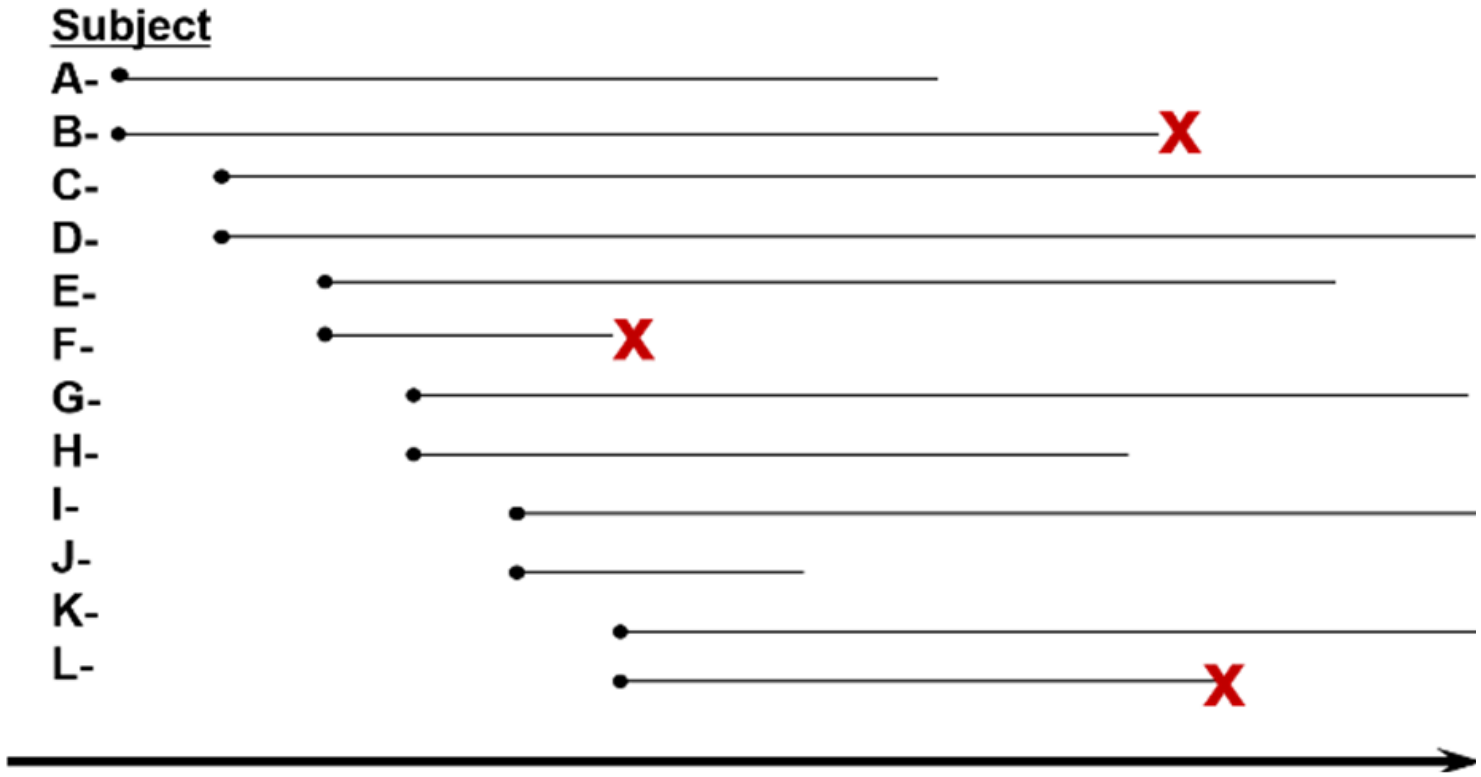

Closed
time
Open
(/dynamic)
time

Cohort design



107.7 person-years

3 events



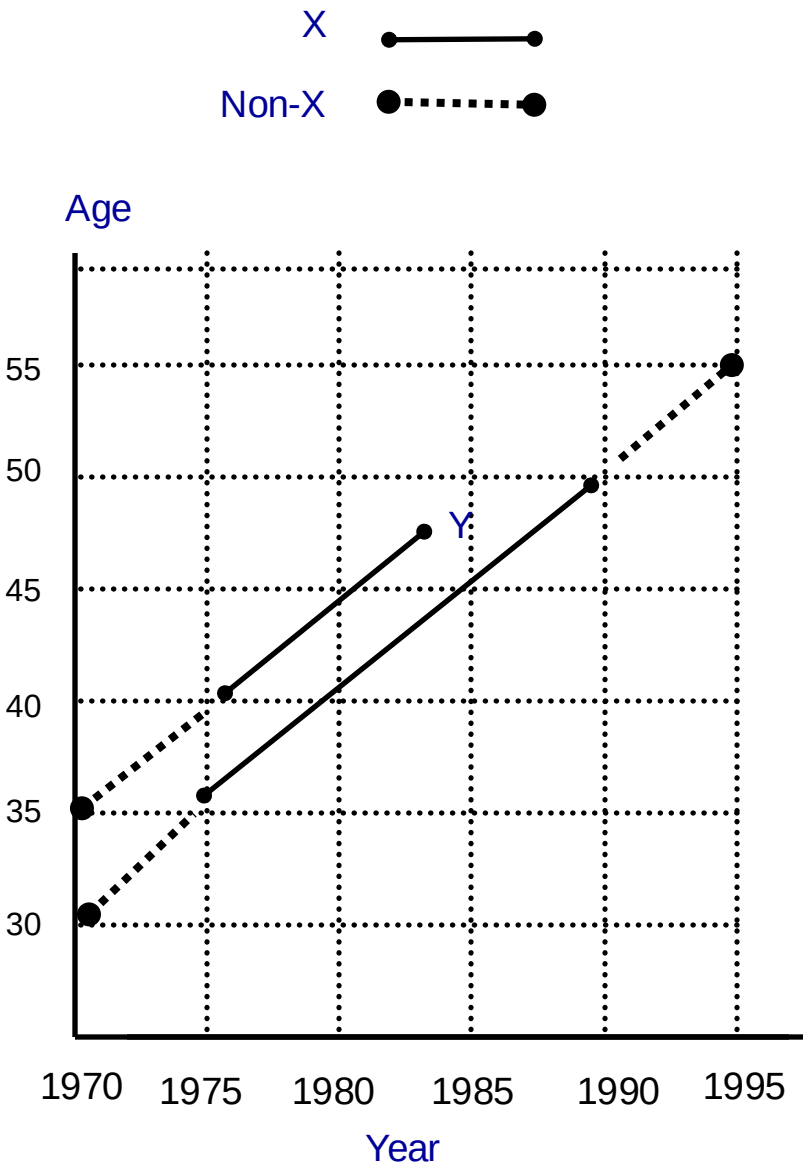
IR = 0.028/py

= 28/1000py

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

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

$$IRR = 28/20 = 1.4$$


X
Non-X
Age
55
50
45
40
35
30
Y
1970
1975
1980
1985
1990
1995
Year

	Exp. to X		Unexp. to X	
Age	**Person years**	**Disease Y**	**Person years**	**Disease Y**
30-34 y	0	0	5	0
35-39 y	5	0	5	0
40-44 y	10	0	0	0
45-49 y	8	1	0	0
50-54 y	0	0	5	0

Time slicer

Person ID	Entry	Exit	Outcome				PersonID	Exposure	Start	End
3245	Jan 1 2001	Dec 31 2014	N				3245	ASA	Feb 23 2003	Feb 12 2004
							3245	NSAID	Jul 14 2003	Sep 28 2005

Time slicer

Person ID	Entry	Exit	Outcome				PersonID	Exposure	Start	End
3245	Jan 1 2001	Dec 31 2014	N				3245	ASA	Feb 23 2003	Feb 12 2004
							3245	NSAID	Jul 14 2003	Sep 28 2005
With ASA										
Person ID	Entry	Exit	ASA_tvc	Outcome						
3245	Jan 1 2001	Feb 22 2003	N	N						
3245	Feb 23 2003	Feb 12 2004	Y	N						
3245	Feb 13 2004	Dec 31 2014	N	N						

Time slicer

Person ID	Entry	Exit	Outcome				PersonID	Exposure	Start	End
3245	Jan 1 2001	Dec 31 2014	N				3245	ASA	Feb 23 2003	Feb 12 2004
							3245	NSAID	Jul 14 2003	Sep 28 2005
With ASA										
Person ID	Entry	Exit	ASA_tvc	Outcome						
3245	Jan 1 2001	Feb 22 2003	N	N						
3245	Feb 23 2003	Feb 12 2004	Y	N						
3245	Feb 13 2004	Dec 31 2014	N	N						
With ASA and NSAID										
Person ID	Entry	Exit	ASA_tvc	NSAID_tvc	Outcome					
3245	Jan 1 2001	Feb 22 2003	N	N	N					
3245	Feb 23 2003	Jul 13 2003	Y	N	N					
3245	Jul 14 2003	Feb 12 2004	Y	Y	N					
3245	Feb 13 2004	Sep 28 2005	N	Y	N					
3245	Sep 29 2005	Dec 31 2014	N	N	N					

First-Trimester Exposure to Methylphenidate: A Population-Based Cohort Study

Anton Pottegård, MScPharm; Jesper Hallas, MD, PhD; Jon T. Andersen, MD, PhD; Ellen C. L. Løkkegaard, MD, PhD; Dorthe Dideriksen, MScPharm; Lise Aagaard, MScPharm, PhD; and Per Damkier, MD, PhD

ABSTRACT

Objective: The use of methylphenidate to treat attention-deficit/hyperactivity disorder has risen dramatically in Western countries, and it is increasingly used by adults, including women of childbearing age. Very little is known about potential hazards of in utero exposure to methylphenidate. We conducted this study to estimate the risk of major congenital malformations following first-trimester in utero exposure to methylphenidate.

Method: Data from 2005 to 2012 were extracted from the Danish National Patient Register, the Danish National Prescription Registry, the Medical Birth Registry, and the Danish Civil Registration System. Exposure was defined as having redeemed 1 or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. Each exposed subject was propensity score–matched to 10 unexposed subjects with respect to maternal age, smoking status, body mass index, length of education, calendar year of completion of pregnancy, and concomitant use of antipsychotics,

The issue of methylphenidate use during pregnancy has become increasingly relevant as the prevalence of attention-deficit/hyperactivity disorder (ADHD) among adults has risen over the last decade.[1,2] It is estimated that between 30% and 70% of children with ADHD will experience symptoms as adults.[3] Estimates of the prevalence of adult ADHD have been reported to be around 3%–4%, ranging from 1% to 7% in different countries, with the highest prevalence among developed countries.[4,5] Methylphenidate was approved for use in adults by the US Food and Drug Administration in 2008, but it does not yet hold this indication in Europe.[6,7] Some guidelines recommend the use of methylphenidate in adults suffering from ADHD,[8] including a recommendation on off-label use from the National Institute for Health and Clinical Excellence in the United Kingdom.[9] A recent study[10] showed that in Denmark many women in the fertile age range are prescribed methylphenidate: Among women aged 18–40 years, 4 to 8 per 1,000 persons use methylphenidate (Figure 1).

Safety data on the use of methylphenidate during pregnancy are scarce and give little guidance for the prescribing physician. Labeling for use during pregnancy is "C" ("animal data have shown adverse effect on the fetus") in the United States,[6] while the UK Summary of Product Characteristics[7] states that "there is a limited amount of data from the use of methylphenidate in pregnant women" and that "methylphenidate is not recommended for use during pregnancy unless a clinical decision is

Table 2. Fetal Outcomes and Point Prevalence Ratios (PPRs) Comparing the Exposed to the Unexposed Cohort, Overall, and by Subgroup

Subgroup	Events/No. of Pregnancies		PPR (95% CI)
	Exposed	Unexposed	
All			
Major malformations	7/222	86/2,220	0.8 (0.3–1.8)
Cardiac malformations	3/222	32/2,220	0.9 (0.2–3.0)
Maternal age < 30 y			
Major malformations	6/161	63/1,637	1.0 (0.3–2.2)
Cardiac malformations	2/161	19/1,637	1.1 (0.1–4.4)
Maternal age ≥ 30 y			
Major malformations	1/61	23/583	0.4 (0.0–2.6)
Cardiac malformations	1/61	13/583	0.7 (0.0–4.9)
No use of confounding drugs[a]			
Major malformations	5/125	53/1,346	1.0 (0.3–2.5)
Cardiac malformations	3/125	17/1,346	1.9 (0.4–6.6)

NSAID and UGB Saskatchewan

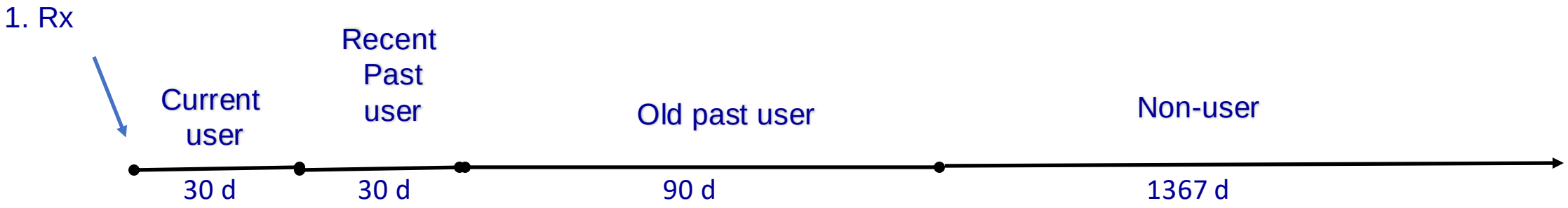
”… entered our cohort upon the first receipt of a prescription for diclofenac, indomethacin, naproxen, piroxicam or sulindac. Person-time contributed by this person continued until the earliest of: 1) hospitalization due to UGB 2) death 3) departure from Saskatchewan or 4) end of study.”

No control group!

García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.

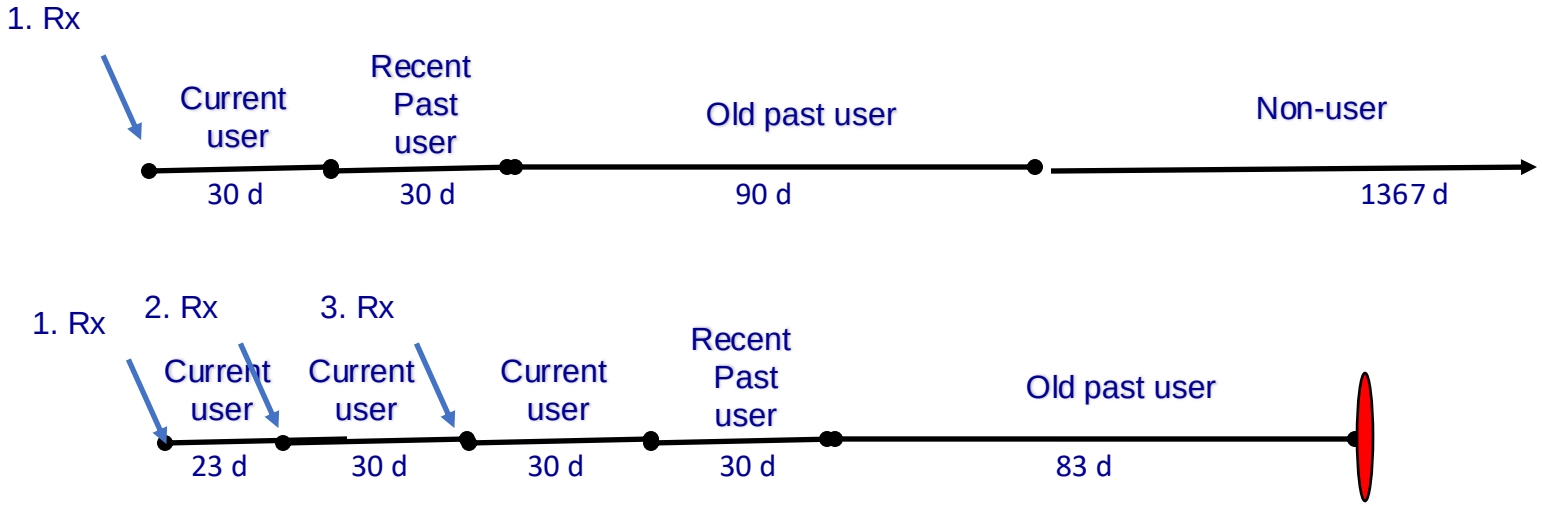
NSAID and UGB Saskatchewan

Current use	<31 d
Recent past use	31-60 d
Old past use	61-150 d
Nonuse	>150 d



García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.

NSAID and UGB Saskatchewan



	Current user	Recent past user	Old past user		Nonuser
Person 1	30	30	90		1367
Person 2	83	30	83	1	-
Ialt	113	60	173	1	1367

Total

García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.

NSAID and UGB Saskatchewan

Incidence rate ratios of GI-hospitalisations of NSAID users

	Current users (0-30 days)	Recent past users (30-60 days)	Old past users (60-150 days)
Diclofenac	3.9	2.2	1.3
Indomethacin	4.0	1.7	1.4
Naproxen	3.8	2.3	1.4
Nonusers		1.0	

García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.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PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3942

ORIGINAL REPORT

Generic switching of warfarin and risk of excessive anticoagulation: a Danish nationwide cohort study†

Maja Hellfritzsch[1]*, Jette Rathe[2], Tore Bjerregaard Stage[1], Steffen Thirstrup[3,4], Erik L. Grove[5], Per Damkier[1,2] and Anton Pottegård[1]

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[2] *Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Denmark*
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[4] *NDA Advisory Services Ltd, United Kingdom*
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ABSTRACT

Purpose Generic switching of warfarin was recently repealed in Denmark, as adverse drug reaction (ADR) reports suggested risk of excessive anticoagulation following switches from branded to generic warfarin. We investigated this putative association in a formalized pharmacoepidemiological analysis.

Methods We conducted a nationwide cohort study based on Danish healthcare registries, including data from the introduction of generic warfarin until the repeal (January 2011–April 2015). We followed Danish warfarin users over time and compared the rate of incident hospitalizations due to excessive anticoagulation (i.e. increased INR or any bleeding requiring hospitalization) in periods following a recent switch to generic warfarin to the rate in periods without a recent switch.

Results We included 105 751 warfarin users, filling a total of 1 539 640 prescriptions for warfarin (2.5% for generic warfarin). This constituted 89.0% of all warfarin prescriptions in Denmark during the study period. We observed 19 362 switches to generic warfarin during the study period. The adjusted hazard ratio for excessive anticoagulation following a recent switch from branded to generic warfarin was 1.1 (95%CI, 0.8–1.4). The result was robust within subgroups and several sensitivity analyses.

Conclusion Switching from branded to generic warfarin is not associated with an increased risk of hospitalization with excessive anticoagulation. However, a minor excess risk of transient INR increase cannot be excluded. Pharmacoepidemiological studies provide an effective method for swift evaluation of hypotheses generated by ADR-reports.

KEY WORDS—oral anticoagulants; warfarin; generic drugs; adverse drug reaction reports; excessive anticoagulation; pharmacoepidemiology; Denmark

Received 27 August 2015; Revised 21 November 2015; Accepted 23 November 2015

(1) Continuous use of branded warfarin (from the date of filling a second prescription for branded warfarin in a row until the time of filling the next prescription)
(2) Continuous use of generic warfarin (from the date of filling a second prescription for generic warfarin in a row until the time of filling the next prescription)
(3) Recent switch TO generic warfarin (the first 60 days from the day of filling a prescription for generic warfarin and having filled branded warfarin as the last prior prescription)
(4) Recent switch FROM generic warfarin (the first 60 days from the day of filling a prescription for branded warfarin and having filled generic warfarin as the last prior prescription)

Outcome measure	Events	Follow-up (PY)	Rate (/1000 PY)	Adjusted HR (95%CI)
Excessive anticoagulation[‡]				
Cont. use of branded	5665	224 282	25	1.0 (ref.)
Cont. use of generic	36	1349	27	1.1 (0.8–1.5)
Switch TO generic	53	1940	27	1.1 (0.8–1.4)
Switch FROM generic	11	375	29	1.2 (0.7–2.2)

The case-control study design


MANGER
JOHNSNOW

"On proceeding to the spot, I found that nearly all the deaths had taken place within a short distance of the [Broad Street] pump. There were only ten deaths in houses situated decidedly nearer to another street-pump."

John Snow
(the one that actually knew something…)

Smoking and lung cancer?

3 of 86 male cancer patients were non-smokers

14 of 86 of healthy men were non-smokers

Müller FH, *Z. Krebsforsch* (1939); 49:57

Smoking and lung cancer?

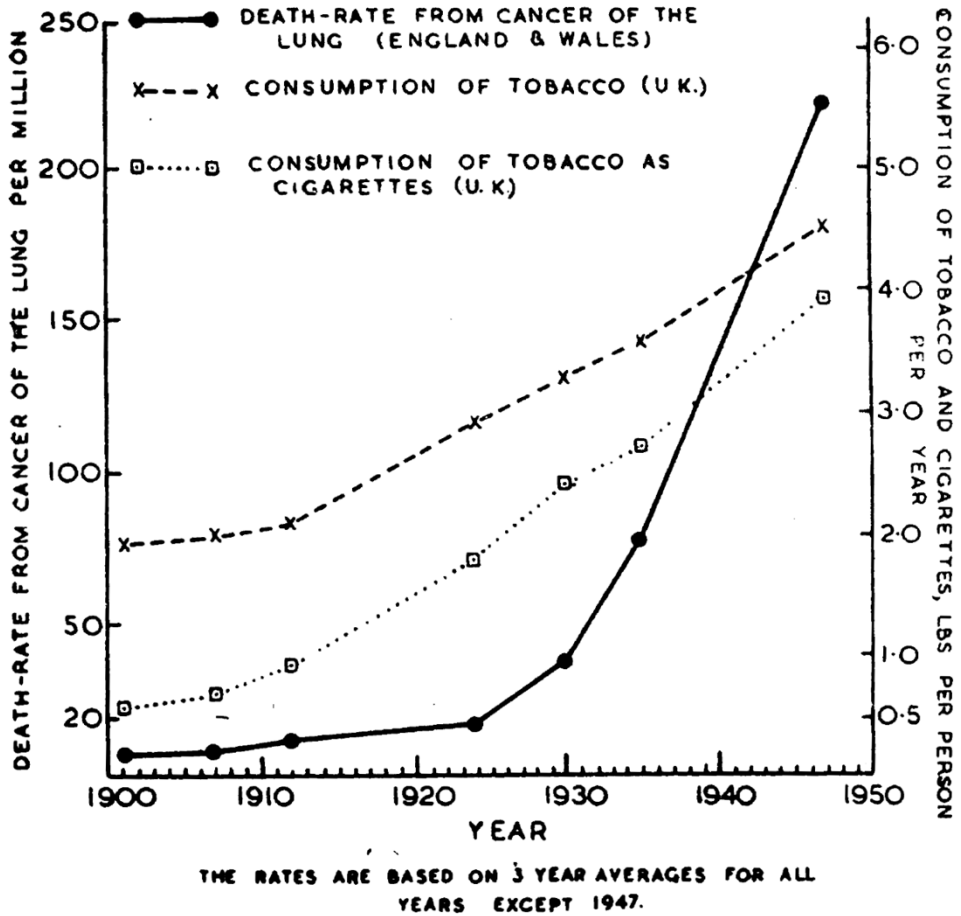
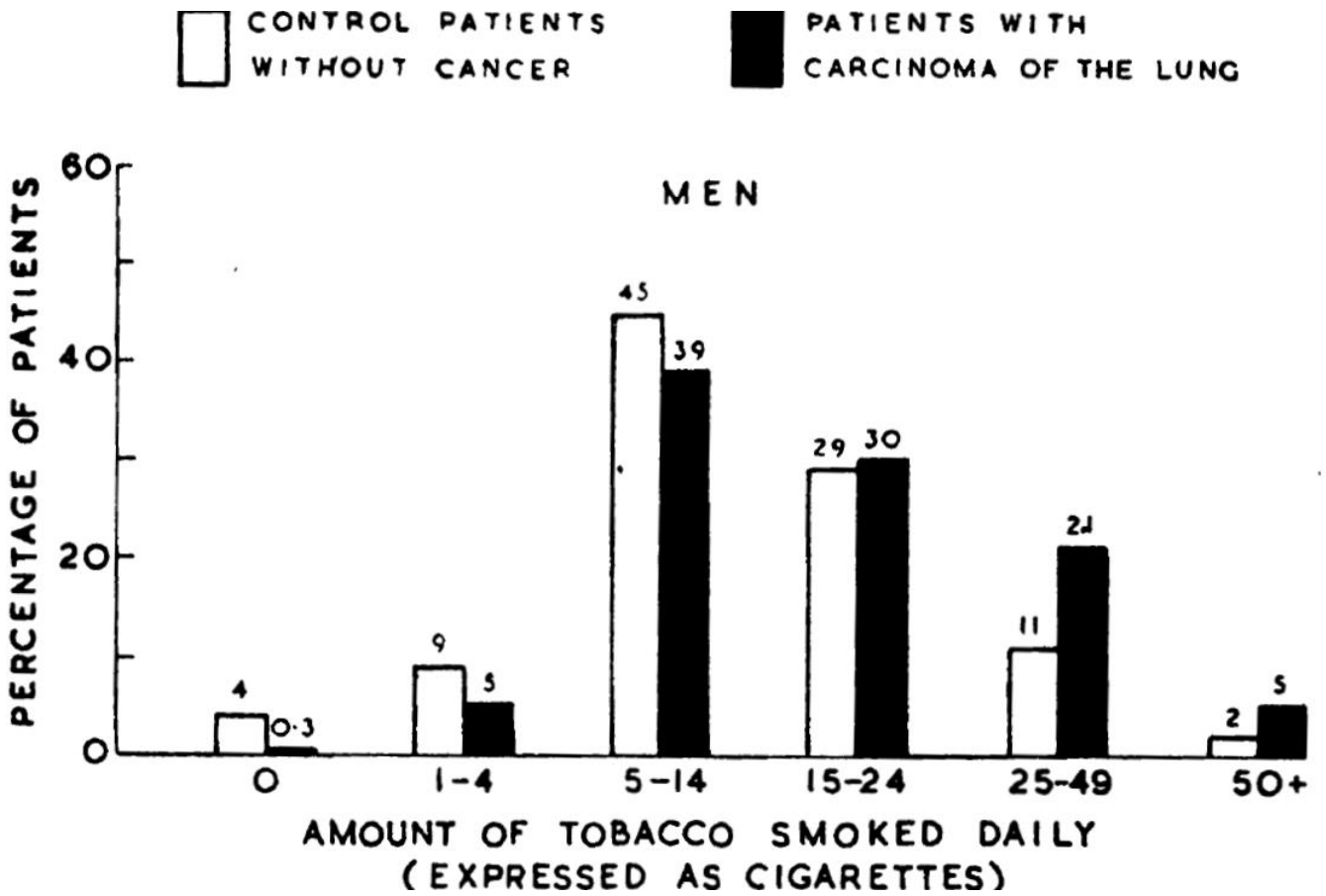


FIG. 2.—Death rate from cancer of the lung and rate of consumption of tobacco and cigarettes.

Doll & Hill. Br Med J 1950;2:739-48

Smoking and lung cancer?



Doll & Hill. Br Med J 1950;2:739-48

Cohort study

A group of subjects using the drug under scrutiny and a group of non-users are followed over time with respect to the development of a certain outcome.

Case-control study

Subjects with a certain outcome (cases) and subjects without this outcome (controls) are mapped according to use of the drug under scrutiny.

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.

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	240	150
The pill N	60	150

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

… but why!?

Use of appetite-suppressant drugs causes primary pulmonary hypertension

Relative risk ≈ 20

Baseline IR: 2 / 1 000000 person-years

If ALL Danes (≈6 mill) used these drugs, how many cases would I expect per year?

What if there was ”only” 100 000 users?

Abenhaim et al. NEJM 1996

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Research Paper

Identification of Associations Between Prescribed Medications and Cancer: A Nationwide Screening Study

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Denmark

ABSTRACT

Purpose: We present a systematic screening for identifying associations between prescribed drugs and cancer risk using the high quality Danish nationwide health registries.
Methods: We identified all patients (cases) with incident cancer in Denmark during 2000–2012 (n = 278,485) and matched each case to 10 controls. Complete prescription histories since 1995 were extracted. Applying a two-phased case–control approach, we first identified drug classes or single drugs associated with an increased or decreased risk of 99 different cancer types, and further evaluated potential associations by examining specificity and dose–response patterns.
Findings: 22,125 drug–cancer pairs underwent evaluation in the first phase. Of 4561 initial signals (i.e., drug–cancer associations), 3541 (78%) failed to meet requirements for dose–response patterns and specificity, leaving 1020 eligible signals. Of these, 510 signals involved the use of single drugs, and 33% (166 signals) and 67% (344 signals) suggested a reduced or an increased cancer risk, respectively. While a large proportion of the signals were attributable to the underlying conditions being treated, our algorithm successfully identified well-established associations, as well as several new signals that deserve further investigation.
Conclusion: Our results provide the basis for future targeted studies of single associations to capture novel carcinogenic or chemopreventive effects of prescription drugs.

1. Introduction

cancer requires at least five years of regular use (Chan et al., 2012; Cuzick et al., 2015). Traditional approaches in pharmacovigilance

1	Cancer	ATC	Drugname	Cases	Controls	OR	ORAll	p
233	Vulva and vagina (Squamos cell carcinoma)	D07AC01	Betamethasone	21 / 715	106 / 7,510	1.84 (1.13-3.00)	1.07	0.01
234	Vulva and vagina (Other)	G03CA03	Estradiol	50 / 157	255 / 1,856	2.39 (1.67-3.42)	1.03	0.03
235	Cervix uteri (Squamos cell carcinoma)	C09CA03	Valsartan	10 / 3,197	58 / 31,971	1.71 (0.87-3.35)	1.02	0.09
236	Cervix uteri (Squamos cell carcinoma)	G02BB01	Vaginal ring with progestoge	11 / 3,188	56 / 31,911	2.03 (1.05-3.90)	0.96	0.01
237	Cervix uteri (Squamos cell carcinoma)	L04AX01	Azathioprine	16 / 3,188	57 / 31,973	2.75 (1.57-4.81)	1.34	0.08
238	Cervix uteri (Adenocarcinoma)	N06AB03	Fluoxetine	11 / 709	58 / 7,123	1.88 (0.97-3.64)	1.07	0.05
239	Cervix uteri (Other)	C08CA02	Felodipine	10 / 381	32 / 3,858	3.58 (1.68-7.61)	1.03	0.05
240	Cervix uteri (Other)	R03AC02	Salbutamol	11 / 376	66 / 3,782	1.91 (0.98-3.72)	1.12	0.01
241	Corpus uteri (Adenocarcinoma, endometrioid)	A10BB12	Glimepiride	104 / 4,977	593 / 50,460	1.87 (1.51-2.33)	0.95	0.09
242	Corpus uteri (Adenocarcinoma, endometrioid)	B03BB01	Folic acid	26 / 5,070	154 / 50,639	1.72 (1.13-2.61)	1.11	<0.01
243	Corpus uteri (Adenocarcinoma, endometrioid)	C02CA01	Prazosin	16 / 5,110	69 / 51,203	2.32 (1.35-4.01)	0.98	0.07
244	Corpus uteri (Adenocarcinoma, endometrioid)	C03AB01	Bendroflumethiazide and pc	886 / 3,738	6,961 / 39,620	1.38 (1.28-1.50)	1.03	0.09
245	Corpus uteri (Adenocarcinoma, endometrioid)	C03DA01	Spironolactone	79 / 5,004	520 / 50,341	1.57 (1.23-2.00)	1.08	0.07
246	Corpus uteri (Adenocarcinoma, endometrioid)	C03DB01	Amiloride	12 / 5,116	29 / 51,252	4.19 (2.14-8.22)	1.09	0.07
247	Corpus uteri (Adenocarcinoma, endometrioid)	C03EB01	Furosemide and potassium	11 / 5,117	45 / 51,213	2.52 (1.30-4.87)	0.95	0.07
248	Corpus uteri (Adenocarcinoma, endometrioid)	C09CA02	Eprosartan	10 / 5,119	53 / 51,216	1.92 (0.97-3.78)	1.13	0.08
249	Corpus uteri (Adenocarcinoma, endometrioid)	C09CA04	Irbesartan	46 / 5,072	259 / 50,881	1.82 (1.32-2.49)	1.07	<0.01
250	Corpus uteri (Adenocarcinoma, endometrioid)	D07XC01	Betamethasone	13 / 5,066	73 / 50,777	1.79 (0.99-3.23)	0.97	0.04
251	Corpus uteri (Adenocarcinoma, endometrioid)	G03CX01	Tibolone	160 / 4,935	459 / 50,613	3.64 (3.03-4.38)	1.28	0.02
252	Corpus uteri (Adenocarcinoma, endometrioid)	G03DC02	Norethisterone	37 / 4,974	207 / 50,454	1.77 (1.24-2.51)	1.30	0.07
253	Corpus uteri (Adenocarcinoma, endometrioid)	G03FB01	Norgestrel and estrogen	65 / 5,040	312 / 50,785	2.09 (1.60-2.74)	1.26	0.02
254	Corpus uteri (Adenocarcinoma, endometrioid)	M04AA01	Allopurinol	73 / 5,027	340 / 50,715	2.19 (1.69-2.83)	1.10	0.02
255	Corpus uteri (Adenocarcinoma, endometrioid)	N02CC06	Eletriptan	15 / 5,111	65 / 51,162	2.33 (1.33-4.08)	0.96	0.06
256	Corpus uteri (Adenocarcinoma, endometrioid)	S01GX09	Olopatadine	12 / 5,095	73 / 50,951	1.65 (0.89-3.03)	0.84	0.02
257	Corpus uteri (Adenocarcinoma, other)	J01EB02	Sulfamethizole	23 / 783	142 / 8,020	1.65 (1.04-2.60)	1.00	0.06
258	Corpus uteri (Adenocarcinoma, other)	M01AB08	Etodolac	16 / 899	101 / 8,989	1.62 (0.94-2.79)	1.02	<0.01
259	Corpus uteri (Sarcomas)	A10BB12	Glimepiride	14 / 558	73 / 5,646	2.56 (1.38-4.74)	0.95	0.09
260	Corpus uteri (Sarcomas)	S01EE01	Latanoprost	11 / 562	47 / 5,679	2.44 (1.25-4.79)	0.94	0.07
261	Corpus uteri (Adenocarcinoma, serous)	A10BA02	Metformin	22 / 396	155 / 4,005	1.52 (0.93-2.48)	0.95	0.10
262	Corpus uteri (Adenocarcinoma, serous)	C01AA05	Digoxin	14 / 401	75 / 4,089	2.01 (1.11-3.65)	1.07	0.04
263	Corpus uteri (Other)	D07AC01	Betamethasone	11 / 489	51 / 4,975	2.09 (1.08-4.04)	1.07	0.08

Pottegård et al. EBioMedicine 2016 May; 7:73-9

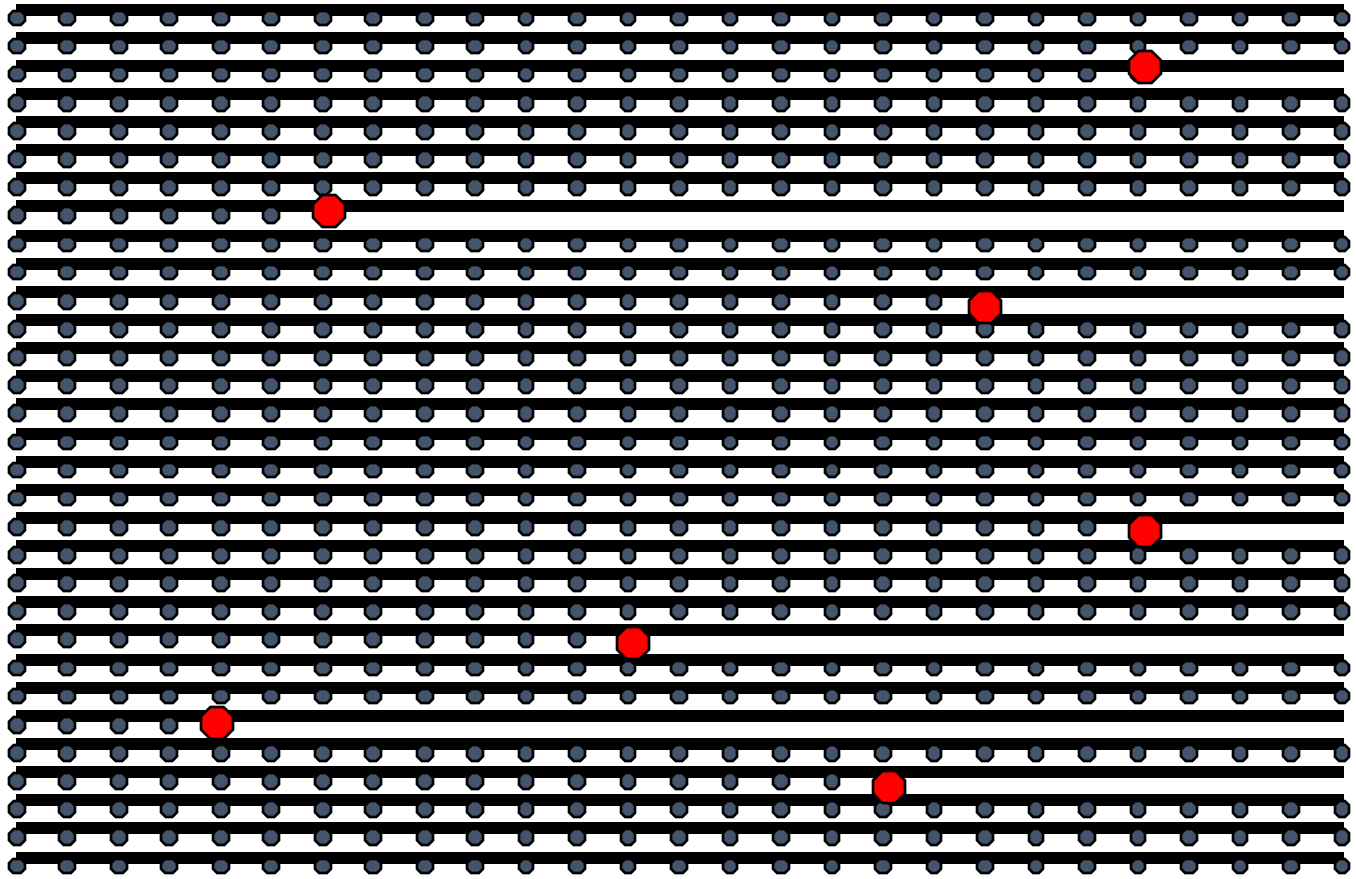
The difficult part…

Source population

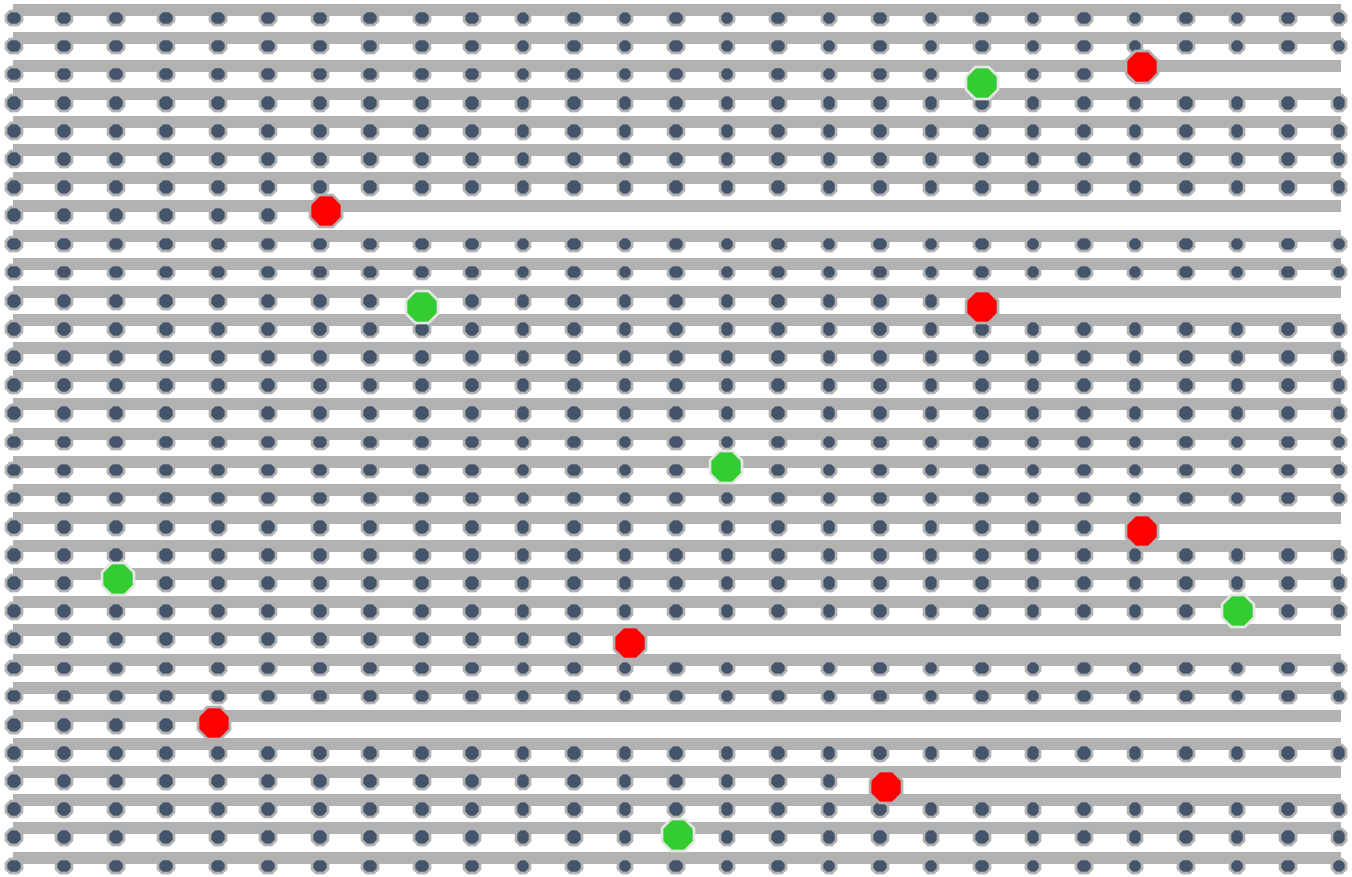
cohort

The ~~population~~ from which cases and controls are drawn (sampled).

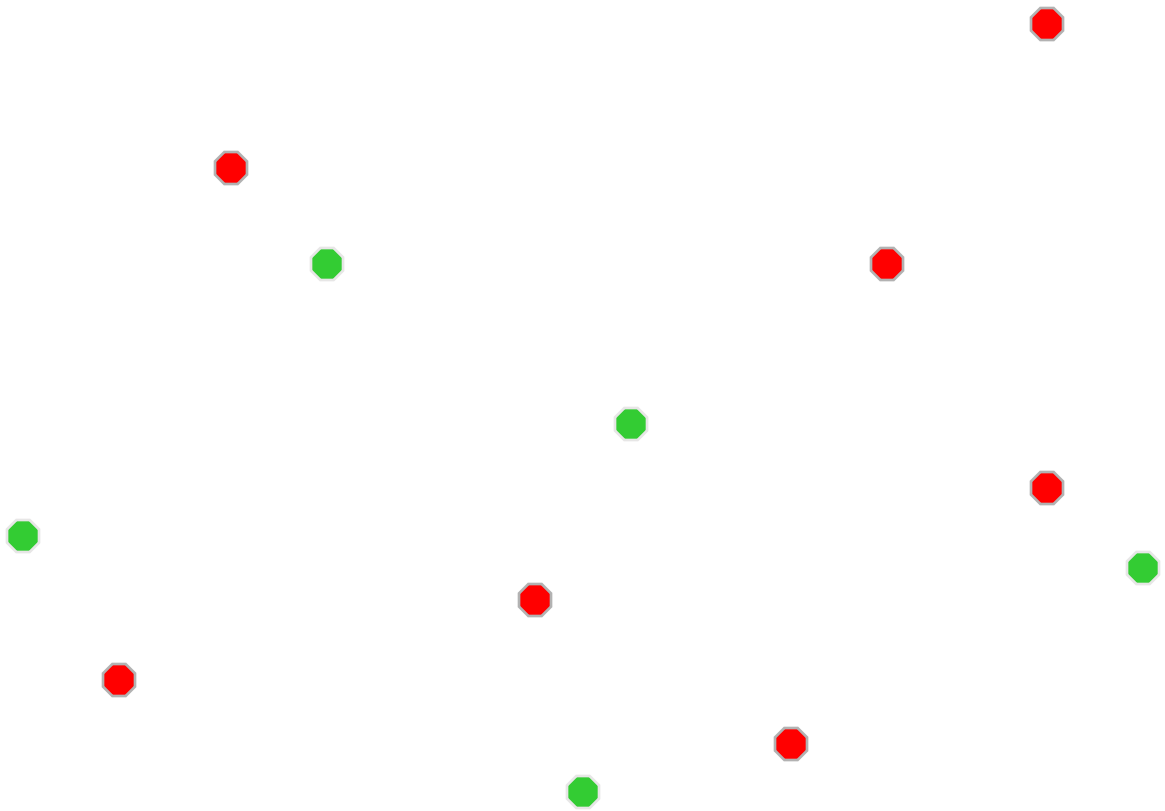
Cohort design



Case-control design



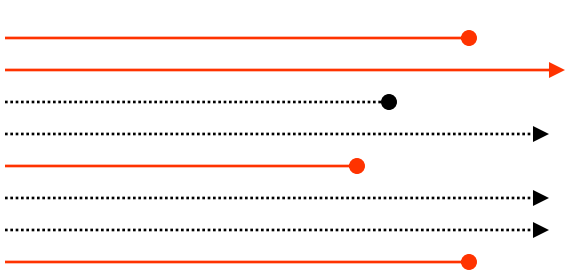
Case-control design



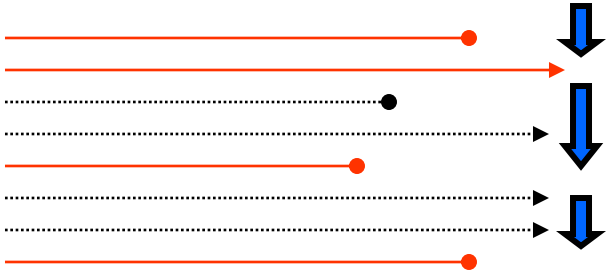
Has it always been like this?

NO!

“Traditional” or Case-Non-Case or Cumulative Case-Control Studies



Persons

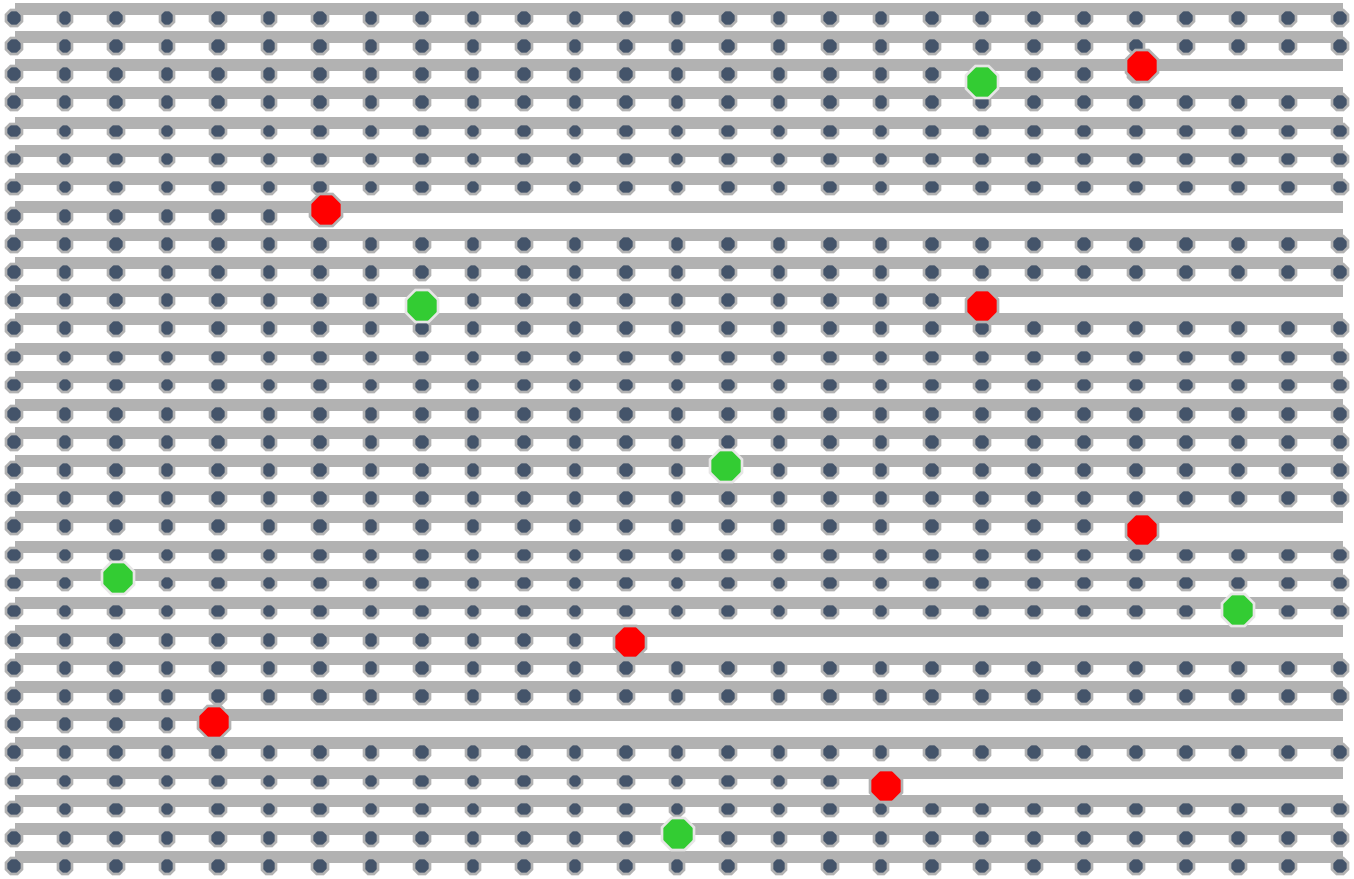


Use cases and a random sample of non-cases (controls)

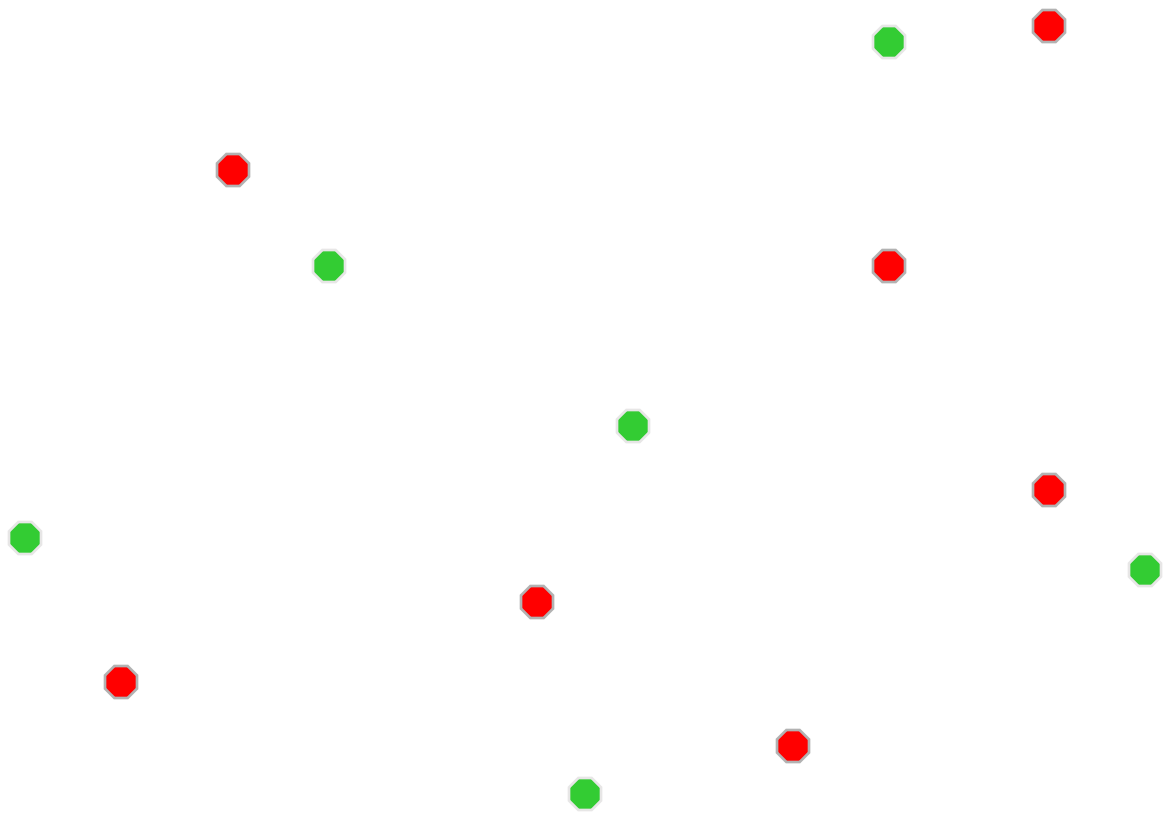
A “case-control” study…

This study aimed to investigate the association between X use and the risk of Y in a case-control study. We analysed XXX database from 2002 to 2013. We defined “cases” as who underwent Y surgery between 2010 and 2013. “Controls” were patients with no history of Y between 2002 and 2013.

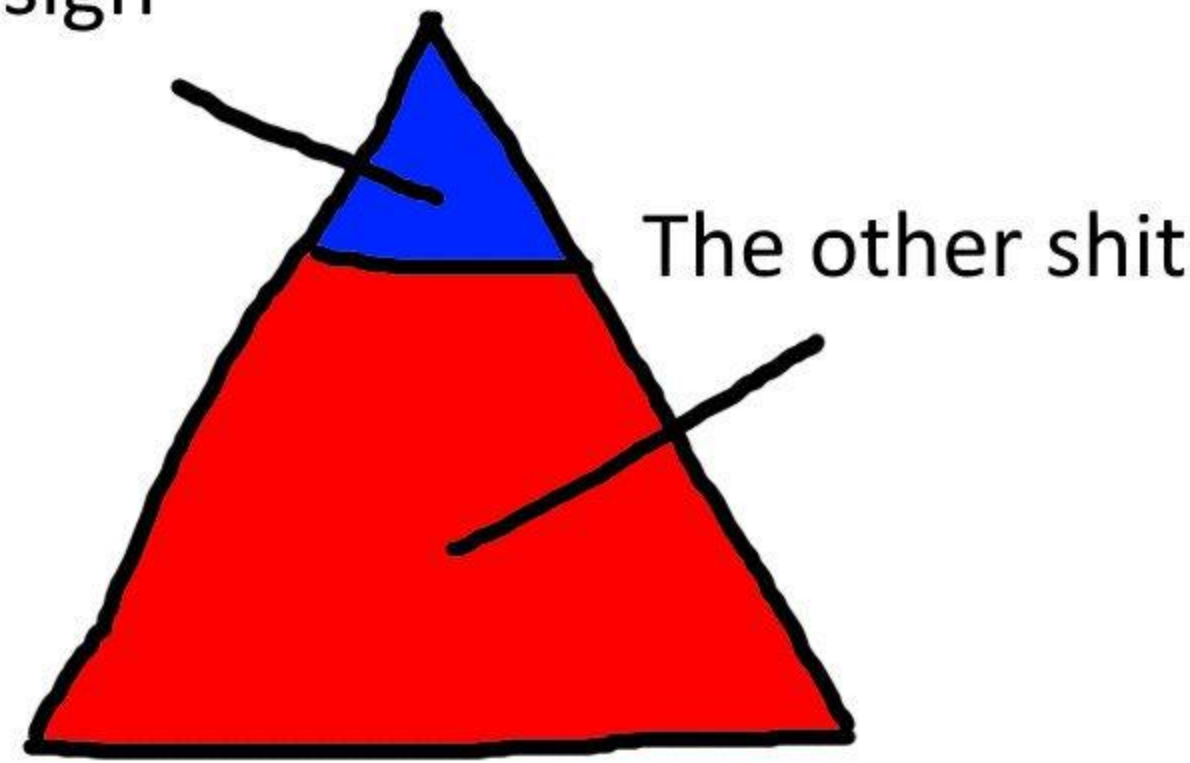
Case-control design



Case-control design



Thoughtful, well-conducted studies of any design



Example

SHORT COMMUNICATION

BJC

British Journal of Cancer (2016), 1–5 | doi: 10.1038/bjc.2016.10

Keywords: lithium; colorectal cancer; adenocarcinoma; case–control; pharmacoepidemiology; Denmark

Long-term use of lithium and risk of colorectal adenocarcinoma: a nationwide case–control study

Anton Pottegård[*,1], Zandra Nymand Ennis[2], Jesper Hallas[1,2], Boye L Jensen[3], Kirsten Madsen[3,4] and Søren Friis[5]

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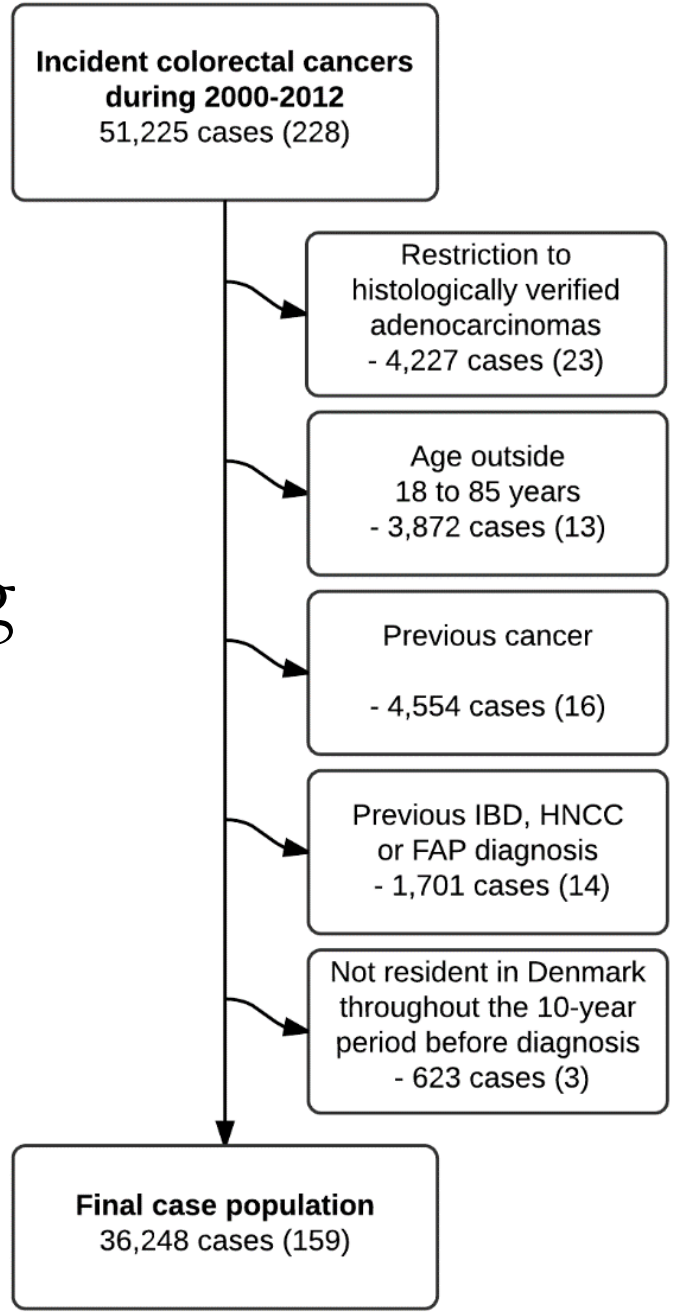
Background: Lithium accumulates in the colon and inhibits the enzyme GSK-3β that possesses anti-carcinogenic effects. We therefore examined the association between lithium use and colorectal cancer risk in a nationwide study.

Methods: We used the Danish Cancer Registry to identify all patients diagnosed with incident colorectal adenocarcinoma during 2000–2012 ($n = 36\,248$). Using a matched case–control approach, we estimated the association between long-term use ($\geqslant$5 years) of lithium and risk of colorectal adenocarcinoma using conditional logistic regression.

Results: Long-term use of lithium was similar among cases (0.22%) and controls (0.20%), yielding an odds ratio of 1.13 (95% confidence interval (CI), 0.89–1.43) for colorectal adenocarcinoma. Dose–response, subgroup and other subanalyses returned neutral associations. However, ORs differed for colorectal subsites (proximal colon: 1.01 (95% CI, 0.66–1.55; distal colon: 1.52 (95%

$$Li^+$$

Underlying cohort?



Exposure group	Cases	Controls	Crude OR [1]	Adjusted OR [2]
Non-use	36,089	360,909	1.00 (ref.)	1.00 (ref.)
Ever use	159	1,571	1.01 (0.86-1.19)	1.08 (0.92-1.28)
Long-term use (≥ 5 years)	78	734	1.06 (0.84-1.34)	1.13 (0.89-1.43)
Duration of use				
< 1 year	21	277	0.76 (0.49-1.18)	0.82 (0.53-1.28)
1-4.99 years	60	560	1.07 (0.82-1.40)	1.15 (0.88-1.50)
5-9.99 years	50	506	0.99 (0.74-1.33)	1.06 (0.79-1.41)
≥ 10 years	28	228	1.22 (0.83-1.81)	1.29 (0.87-1.91)

Pros and cons?

Pros

Statistically efficient

~~Less ressource demanding~~

Can (easily) look at multiple exposures at the same time

Cons

Only provides relative estimates (in principal)

Not suited for multiple (different) outcomes

Less efficient with rare exposures

Control selection might ”go wrong”

Design often misunderstood

… often misunderstood?!

Decision: rejection

Detailed comments from the meeting:
The committee felt this is a topical subject. This study is not the first of its kind, but it is a very big study and this is a strength.

However the committee felt that the case-control methodology is intrinsically weak.

Table 1. Characteristics of cases and controls at the index date.

	Cases (*n* = 3571)	Controls (*n* = 35,582)
		All
Age		
Median (IQR)	75 (64–83)	75 (64–83)
Sex		
Men	1811 (50.7%)	18,029 (50.7%)
Current drug use		
VKA	183 (5.1%)	823 (2.3%)
Low-dose aspirin	696 (19.5%)	3436 (9.7%)
Other antiplatelet drugs	197 (5.5%)	782 (2.2%)
NSAID	1220 (34.2%)	4005 (11.3%)
SSRI	429 (12.0%)	2038 (5.7%)
Systemic corticosteroids	384 (10.8%)	1638 (4.6%)

When to consider?

When you want to use MANY different exposure definitions

When outcome is rare

When computer power might be a limitation

When best to avoid?

If studying multiple outcomes

If exposure is rare

When absolute risks are central

When active comparators are considered

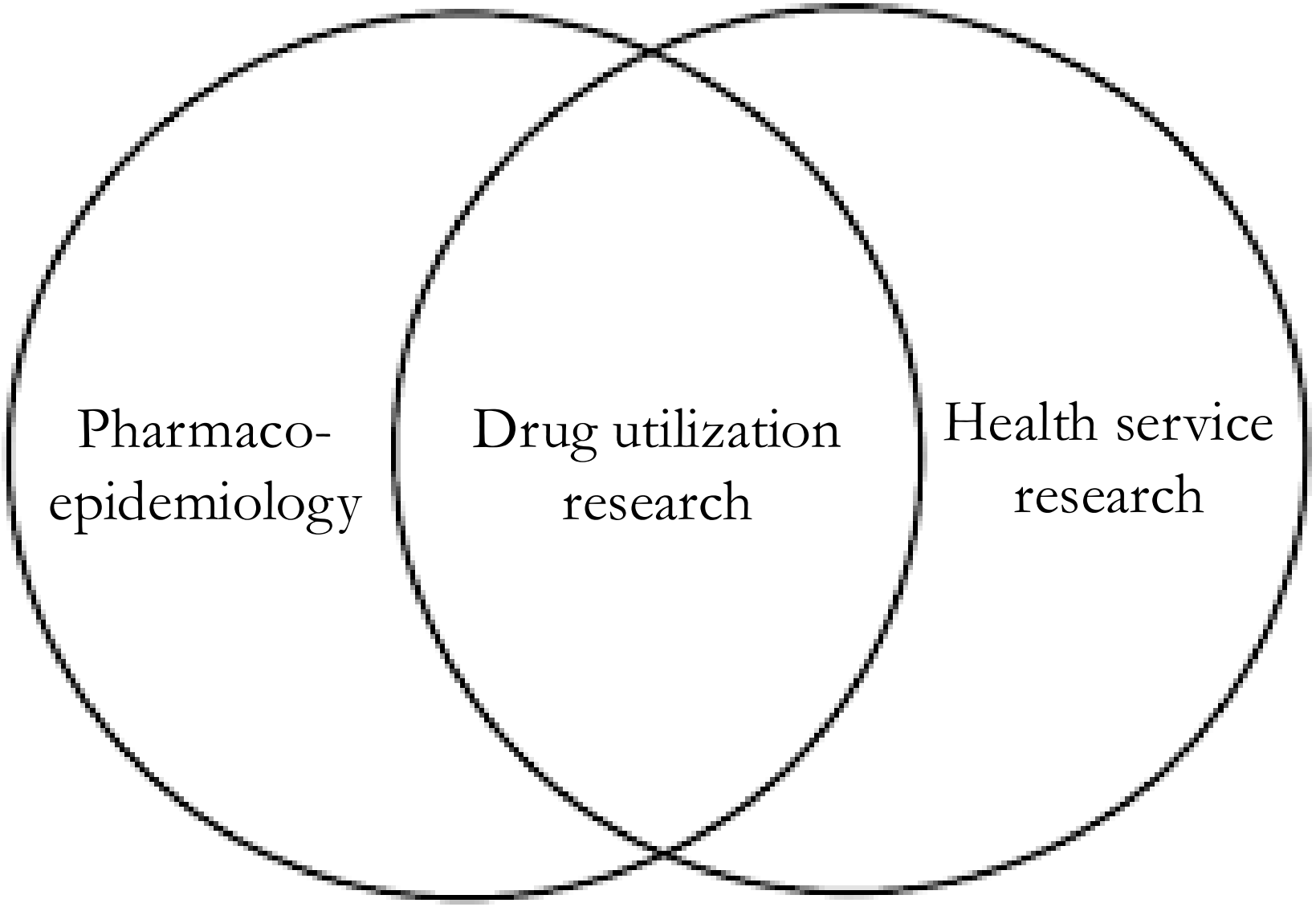
Drug utilization

Credit: Lotte Rasmussen

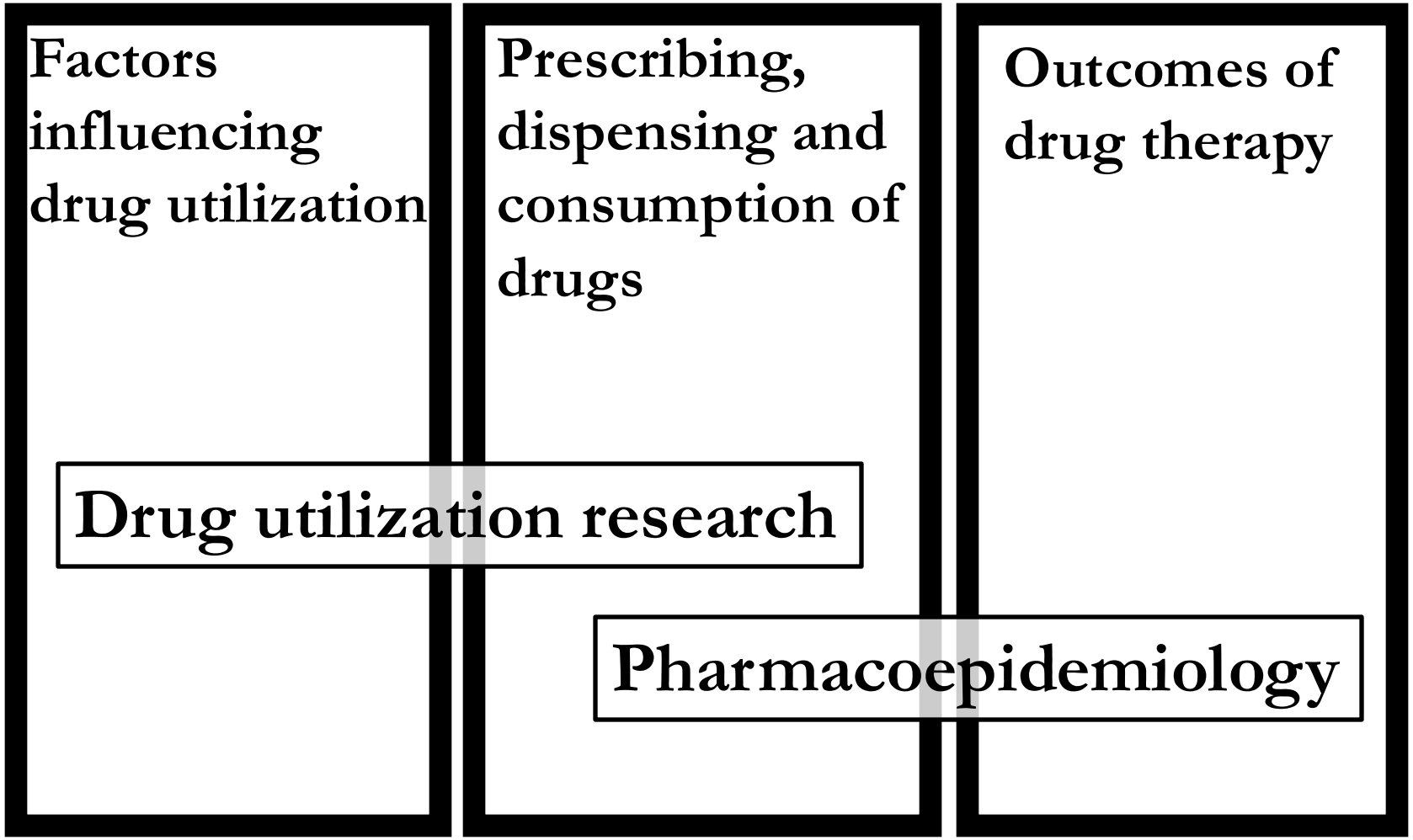
Pharmacoepidemiology

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

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



Adapted from Elseviers et al. 2016



Adapted from Elseviers et al. 2016

To facilitate rational use of drugs!

WHO on rational use of drugs:

"...patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"

News
ATC/DDD Index
Updates included in the ATC/DDD Index
ATC/DDD methodology
ATC
DDD
Lists of temporary ATC/DDDs and alterations
ATC/DDD alterations, cumulative lists
ATC/DDD Index and Guidelines
Use of ATC/DDD
Courses
Meetings/open session
Deadlines
Links

Postal address:
WHO Collaborating Centre for Drug Statistics Methodology
Norwegian Institute of Public Health
Postboks 222 Skøyen
0213 Oslo
Norway

Visiting/delivery address:
Sandakerveien 24C
Bygg C
0473 Oslo
Norway

Tel: +47 21 07 81 60
E-mail: whocc@fhi.no

ATC/DDD Index 2022

A searchable version of the complete ATC index with DDDs is available below. The search options enable you to find ATC codes and DDDs for substance name and/or ATC levels. In your search result you may choose to show or hide the text from the Guidelines for ATC classification and DDD assignment linked to the ATC level. The text in the Guidelines will give information related to the background for the ATC and DDD assignment.

Search query

ATC code or name Search

containing query

ATC code

- All ATC levels are searchable.
- A search will result in showing the exact substance/level and all ATC levels above (up to 1st ATC level).

Name

- "Name" is defined as the name of the substance (normally the INN name) or the name of the ATC level. Note that trademarks are not searchable.
- A minimum of three letters must be entered in the name box. Select a query that contain part of or a query that start with the letter entered.
- For ATC combination levels, please note that all active ingredients would normally not be searchable.

DDD

The DDDs, which will be reviewed in 2022 (3 year revision), are listed here and in the annex I in the printed ATC Index. See also Guidelines: Part III; D Principles for reviewing and changing DDD and Part V; D Requests for changes to DDDs.

To express the DDD several abbreviations are used for units and routes of administration.

Core questions

Why is the medication prescribed?

Who prescribes the medication?

Who is the medication prescribed to?

Are patients taking the medication correctly?

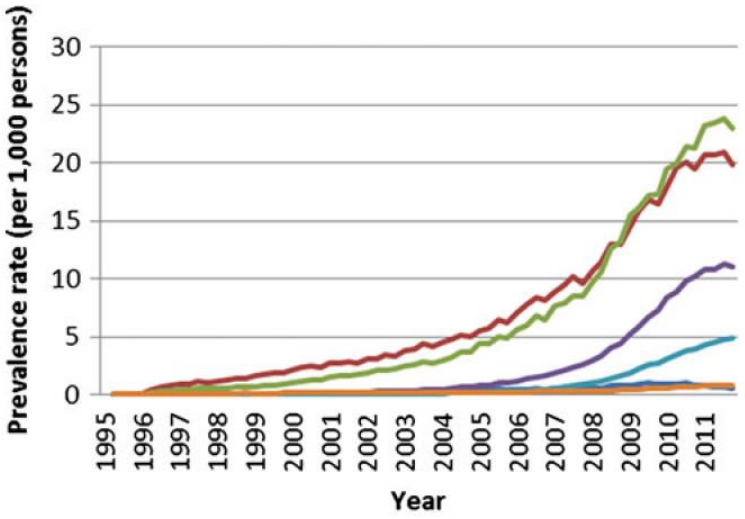
Is the medication used in accordance with guidelines?

Does the consumption of the medication
vary across regions, age, or sex?

What is the effect of regulatory initiatives on
the consumption of the medication?

Incidence rates

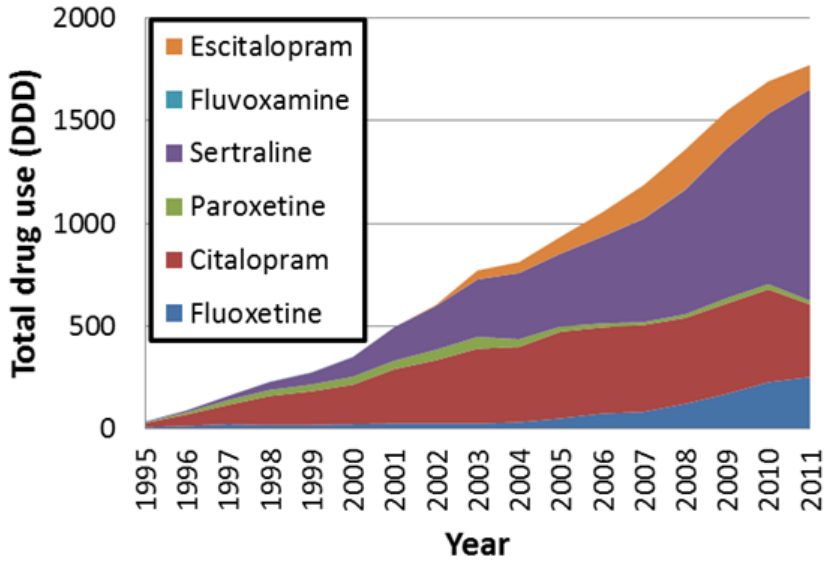
Prevalence proportions



Incidence rates

Prevalence proportions

Use of single substances

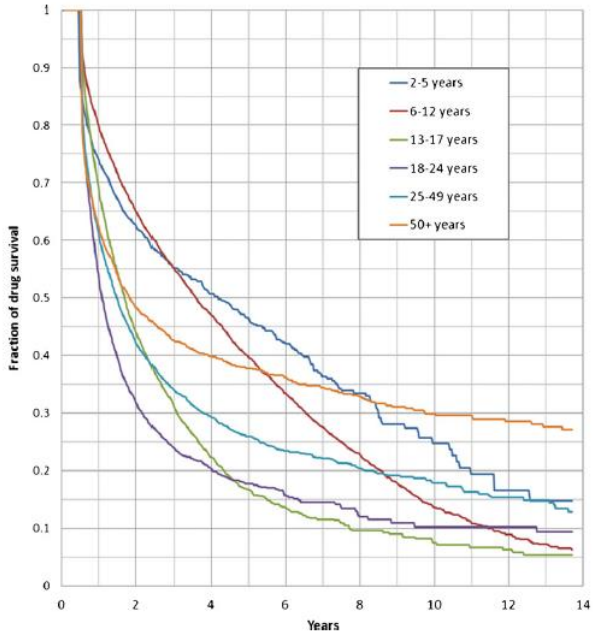


Incidence rates

Prevalence proportions

Use of single substances

Persistence (‘drug survival’)



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]

Incidence rates

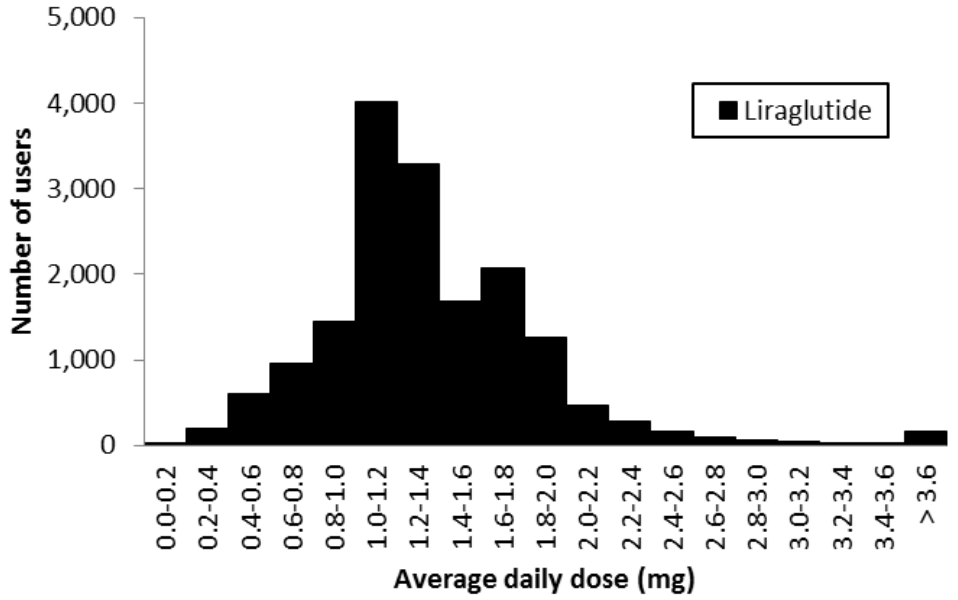
Prevalence proportions

Use of single substances

Persistence (‘drug survival’)

Co-medication

Daily dose (≈)



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)

Incidence rates

Prevalence proportions

Use of single substances

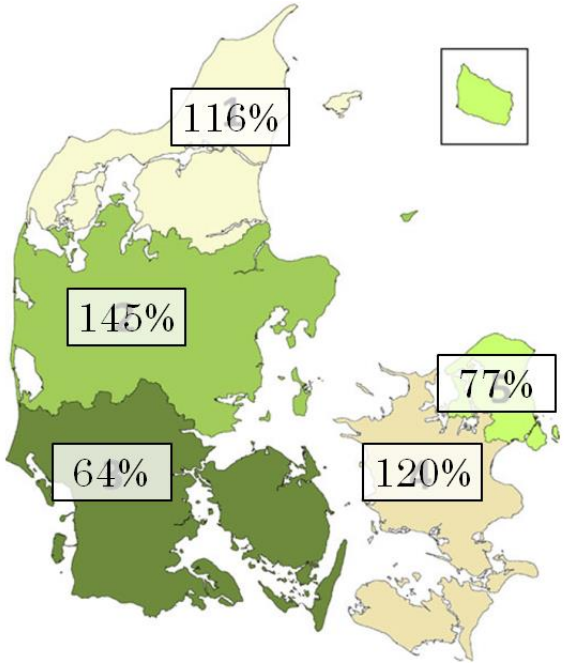
Persistence (‘drug survival’)

Co-medication

Daily dose (≈)

Prescriber profile

Regional differences



Incidence rates

Prevalence proportions

Use of single substances

Persistence (‘drug survival’)

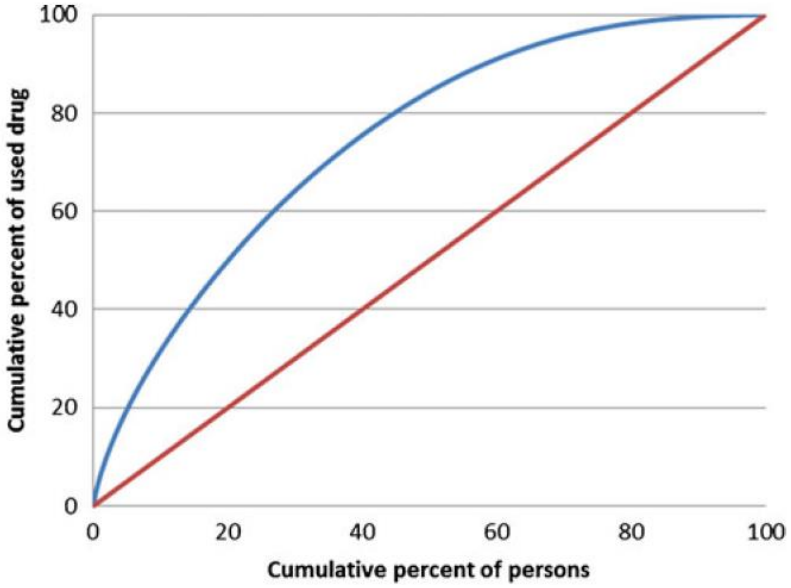
Co-medication

Daily dose (≈)

Prescriber profile

Regional differences

Skewness



MEDSTAT.DK

Forside | Lægemiddelgrupper | ATC kode | Produktnavn

Datagrundlag og beskrivelse

ATC kode

Indtast specifik ATC kode og tryk ENTER

- Alle lægemidler
- A (Fordøjelsesorganer og stofskifte)
- B (Blod og bloddannende organer)
- C (Kardiovaskulære system)
- D (Dermatologiske midler)
- G (Urogenitalsystem og kønshormoner)
- H (Systemiske hormonpræparater, excl. kønshormoner)
- J (Midler mod infektionssygdomme til systemisk brug)
- L (Antineoplastiske og immunomodulerende midler)
- M (Muskulo-skeletal system)
- N (Nervesystemet)
- P (Antiparasitære midler, insekticider og repellanter)
- R (Respirationssystemet)
- S (Sanseorganer)
- V (Diverse)

År

2021
2020
2019
2018
2017
2016

Region

Hele landet
Hovedstaden
Nordjylland
Midtjylland
Sjælland
Syddanmark

Køn

Køn, samlet
Mænd
Kvinder

Aldersgruppe (skift)

Alle
0 - 17 år
18 - 24 år
25 - 44 år
45 - 64 år
65 - 79 år

Sektor

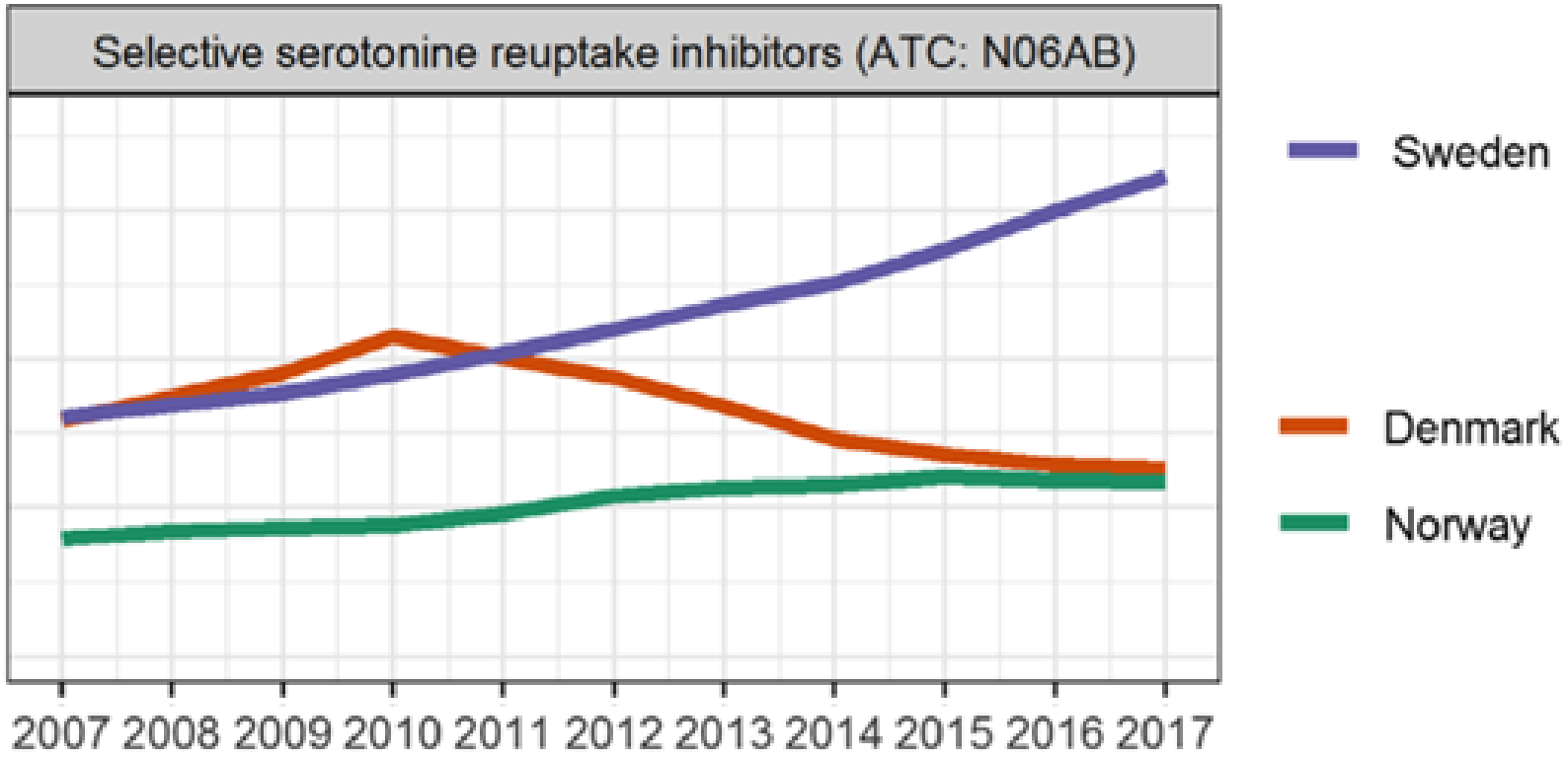
Primærsektor
Sygehussektor
Total

Søgevariabel

Omsætning
Udbetalt regionalt tilskud
Solgt mængde
Solgt mængde pr. 1.000 indbygger pr. døgn
Antal personer
Antal personer pr. 1.000 indbyggere

Vis resultat | Vis resultat i Excel

Sidst opdateret 27.4.2022



Wesselhoeft et al. Acta Psychiatr Scand. 2019

Received: 1 September 2022 | Revised: 30 November 2022 | Accepted: 9 December 2022

DOI: 10.1111/dom.14947

ORIGINAL ARTICLE

WILEY

Changes in the use of glucose-lowering drugs: A Danish nationwide study

Anton Pottegård PhD[1] | Jacob H. Andersen MSc[1] | Jens Søndergaard PhD[2] | Reimar W. Thomsen PhD[3] | Tina Vilsbøll PhD[4,5]

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[2]Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Odense, Denmark

[3]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark

[4]Clinical Research, Steno Diabetes Center Copenhagen, Herlev, Denmark

[5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

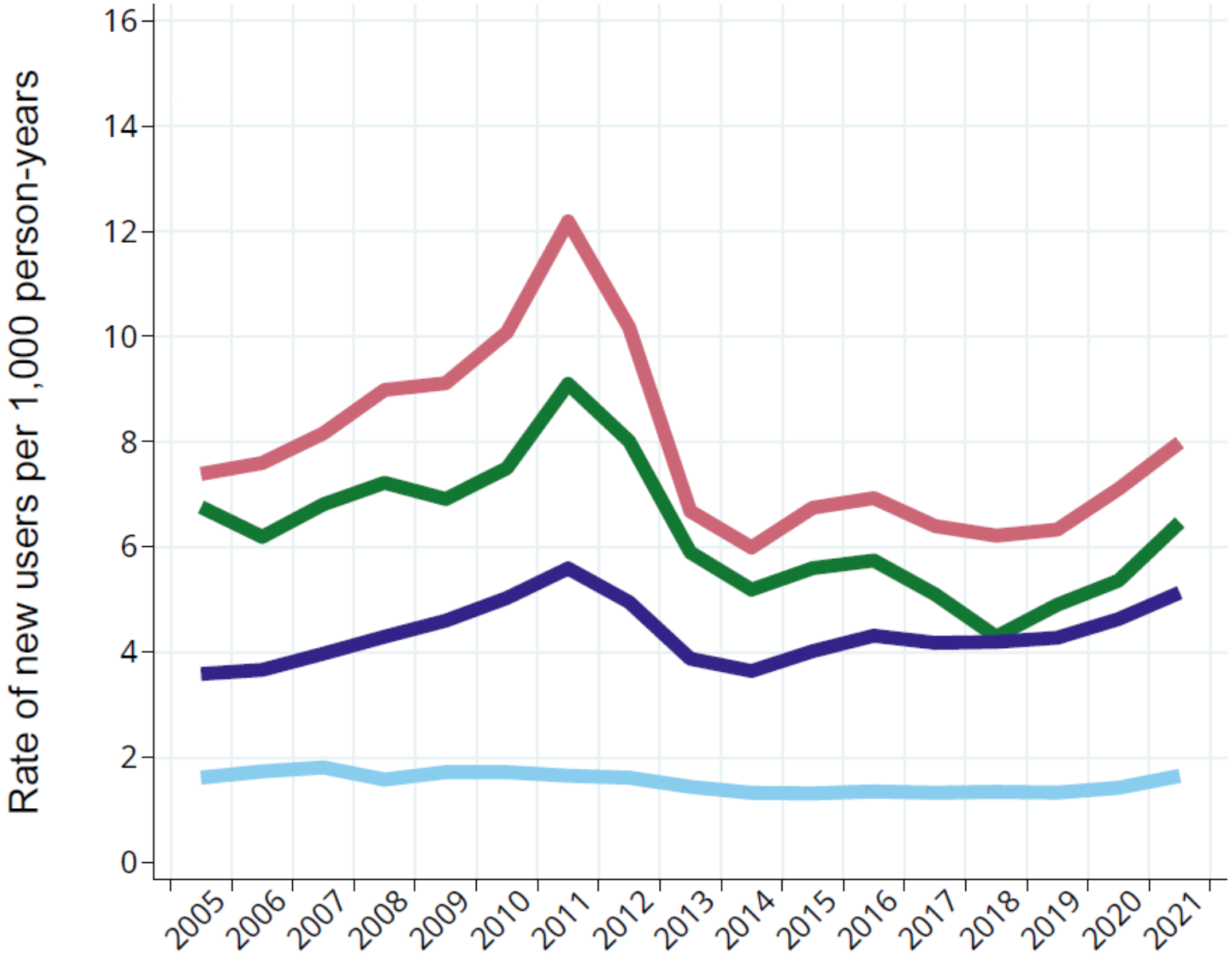
Correspondence
Anton Pottegård, PhD, Clinical Pharmacology, Pharmacy, and Environmental Medicine

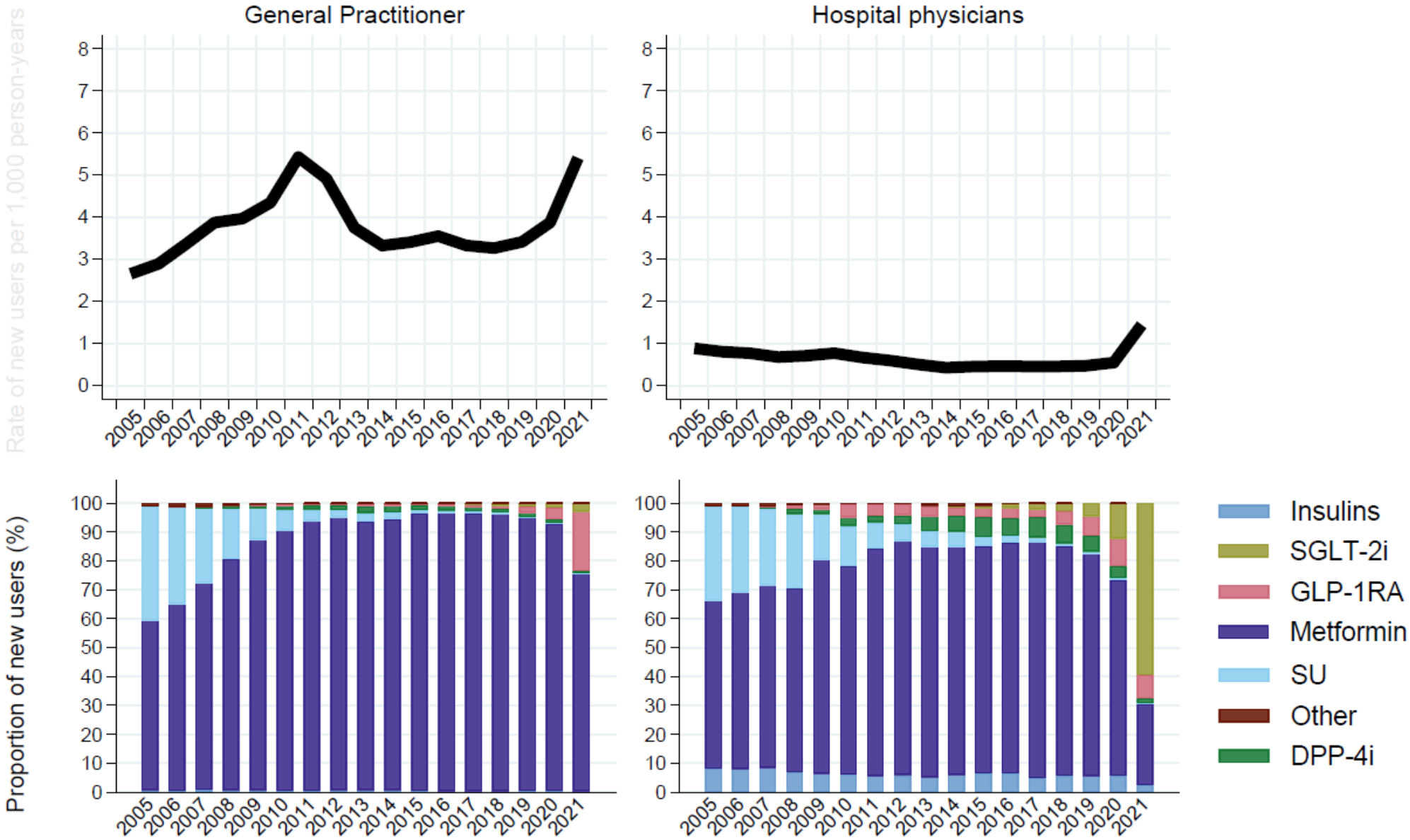
Abstract

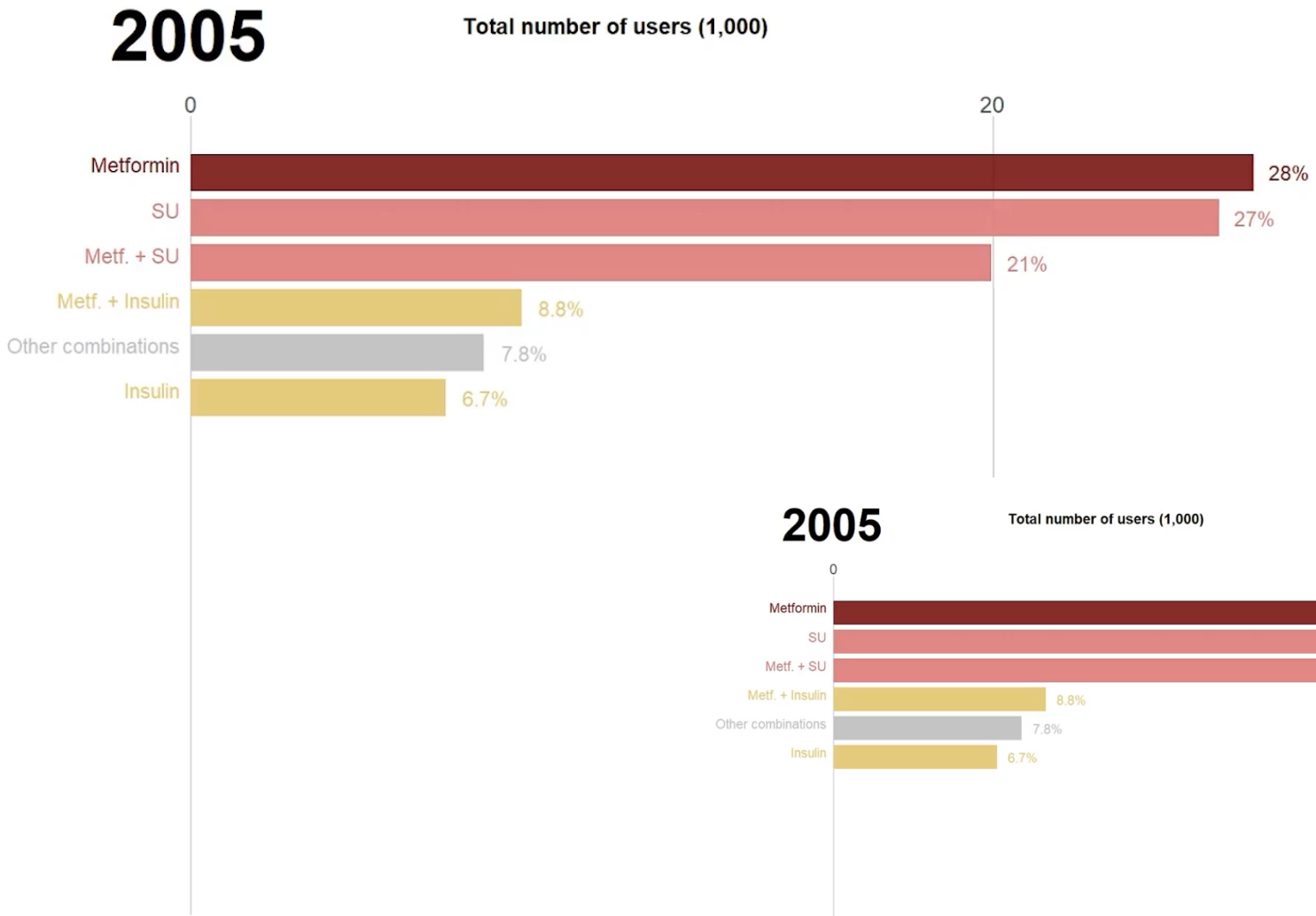
Aim: To investigate changes in the pattern of drugs used to treat type 2 diabetes in Denmark from 2005 to 2021.

Materials and Methods: A nationwide, population-based drug utilization study based on medical databases covering the Danish population was conducted. We assessed incident and prevalent use patterns among all 441 205 individuals initiating at least one non-insulin, glucose-lowering drug.

Results: The rate of new users of non-insulin, glucose-lowering drugs increased from 2005, peaked in 2011, decreased to stable levels during 2013 to 2019, then increased dramatically during 2020-2021. The prevalence of use increased from 2.1% (in 2005) to 5.0% (in 2021) of the entire adult population. In 2021, metformin comprised 39% of all glucose-lowering drug consumption, followed by insulin (17%), sodium-glucose co-transporter-2 inhibitors (SGLT-2is) (17%), glucagon-like peptide-1 receptor agonists (GLP-1RAs) (16%) and dipeptidyl peptidase-4 inhibitors (7.5%)


Rate of new users per 1,000 person-years
16
14
12
10
8
6
4
2
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021


General Practitioner
Hospital physicians
Rate of new users per 1,000 person-years
Proportion of new users (%)
0
1
2
3
4
5
6
7
8
10
20
30
40
50
60
70
80
90
100
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Insulins
SGLT-2i
GLP-1RA
Metformin
SU
Other
DPP-4i


2005
Total number of users (1,000)
0
20
Metformin
SU
Metf. + SU
Metf. + Insulin
Other combinations
Insulin
28%
27%
21%
8.8%
7.8%
6.7%

2005
Total number of users (1,000)
0
20
Metformin
SU
Metf. + SU
Metf. + Insulin
Other combinations
Insulin
28%
27%
21%
8.8%
7.8%
6.7%

So what…!?

Remember to bridge the gap
between your DUS and
the clinical reality.

(Include a clinician!)

How do we get from
the research question to
the rational use of medicines?

Received: 1 November 2021 | Revised: 1 June 2022 | Accepted: 3 June 2022

DOI: 10.1002/pds.5490

WILEY

Core concepts in pharmacoepidemiology: Measures of drug utilization based on individual-level drug dispensing data

Lotte Rasmussen[1] | Björn Wettermark[2,3] | Douglas Steinke[4] | Anton Pottegård[1]

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[2]Department of Pharmacy, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden

[3]Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[4]Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester, Manchester, UK

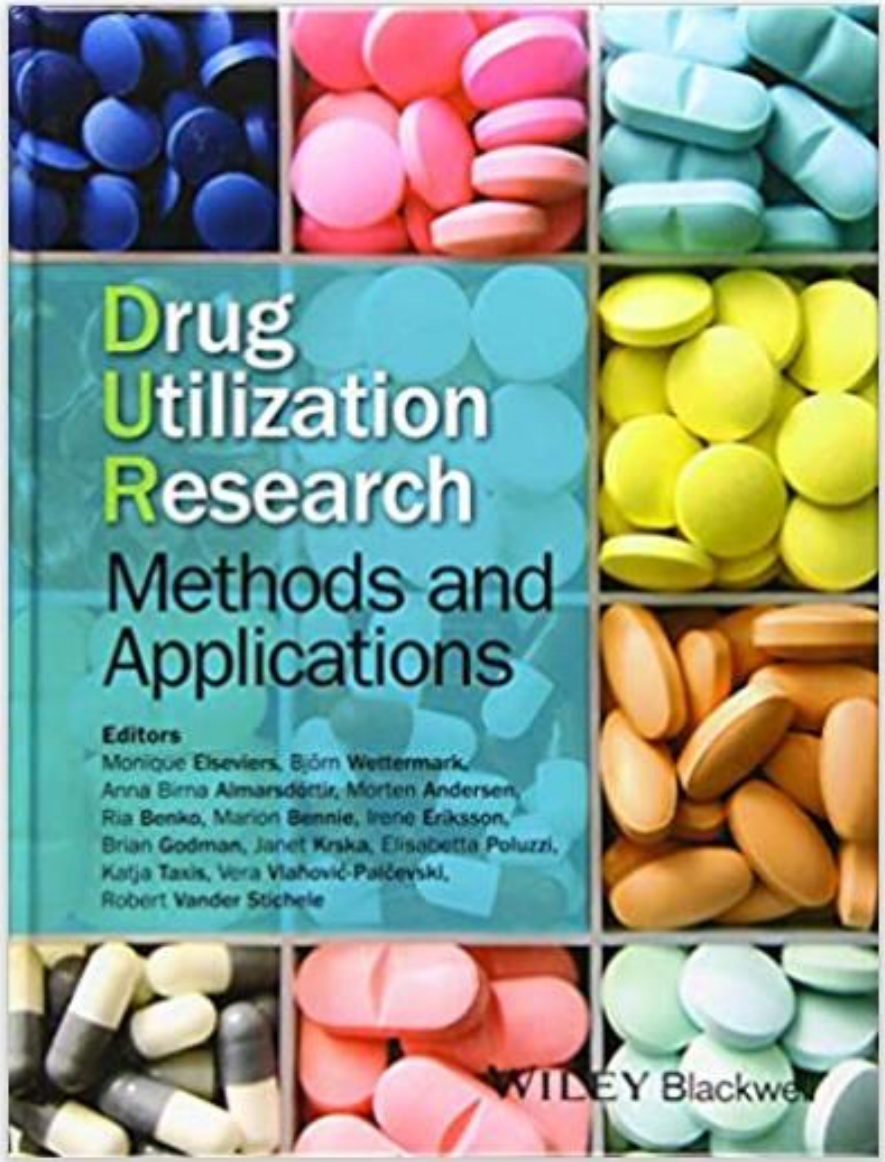
Correspondence
Lotte Rasmussen, Clinical Pharmacology, Pharmacy, and Environmental Medicine, University of Southern Denmark, J B Winsløws Vej 19, Odense, Denmark.
Email: lorasmussen@health.sdu.dk

Abstract

Background: Drug utilization studies are essential to facilitate rational drug use in the society.

Aim: In this review, we provide an overview of drug utilization measures that can be used with individual-level drug dispensing data, referencing additional reading on the individual analysis. This is intended to serve as a primer for those new to drug utilization research and a shortlist from which researchers can identify useful analytical approaches when designing their drug utilization study.

Results and Discussion: We provide an overview of: (1) basic measures of drug utilization which are used to describe changes in drug use over time or compare drug use in different populations; (2) treatment adherence measures with specific focus on persistence and implementation; (3) how to measure drug combinations which is useful when assessing drug–drug interactions, concomitant treatment, and polypharmacy; (4) prescribing quality indicators and measures to assess variations in drug use which are useful tools to assess appropriate use of drugs; (5) proxies of prescription drug misuse and skewness in drug use; and (6) considerations when describing the characteristics of drug users or prescribers.


Drug
Utilization
Research
Methods and
Applications
Editors
Monique Elseviers, Björn Wettermark,
Anna Birna Almarsdóttir, Morten Andersen,
Ria Benko, Marion Bennie, Irene Eriksson,
Brian Godman, Janet Krska, Elisabetta Poluzzi,
Katja Taxis, Vera Vlaňović-Palčevski,
Robert Vander Stichele
WILEY Blackwell

Considerations re. exposure

Epidemiology:

The neglected half of pharmacoepidemiology

Pharmacology:

The neglected half of pharmacoepidemiology

Epidemiology:
The neglected half of pharmacoepidemiology

Pharmacology:
The neglected half of pharmacoepidemiology

Correctly classifying the subjects of a study in exposed or non-exposed constitutes the foundation of an epidemiologic study.

Since by definition, in a pharmacoepidemiological study, the exposure is a drug, a sound knowledge of drug utilisation, pharmacology and toxicology are essential to the design and critical appraisal of these studies.

Jacques LeLorier

Correctly classifying the subjects of a study in exposed or non-exposed constitutes the foundation of an epidemiologic study.

Since by definition, in a pharmacoepidemiological study, the exposure is a drug, a sound knowledge of drug utilisation, pharmacology and toxicology are essential to the design and critical appraisal of these studies.

Jacques LeLorier

Does use of tranexamic acid during HIP SURGERY cause… problems?

Bleeding?

Myocardial infarction?

Ischemic stroke?

Single dose

T1/2 = 3 hours

Coding?

Does use of tranexamic acid during MENORRHAGIA cause… problems?

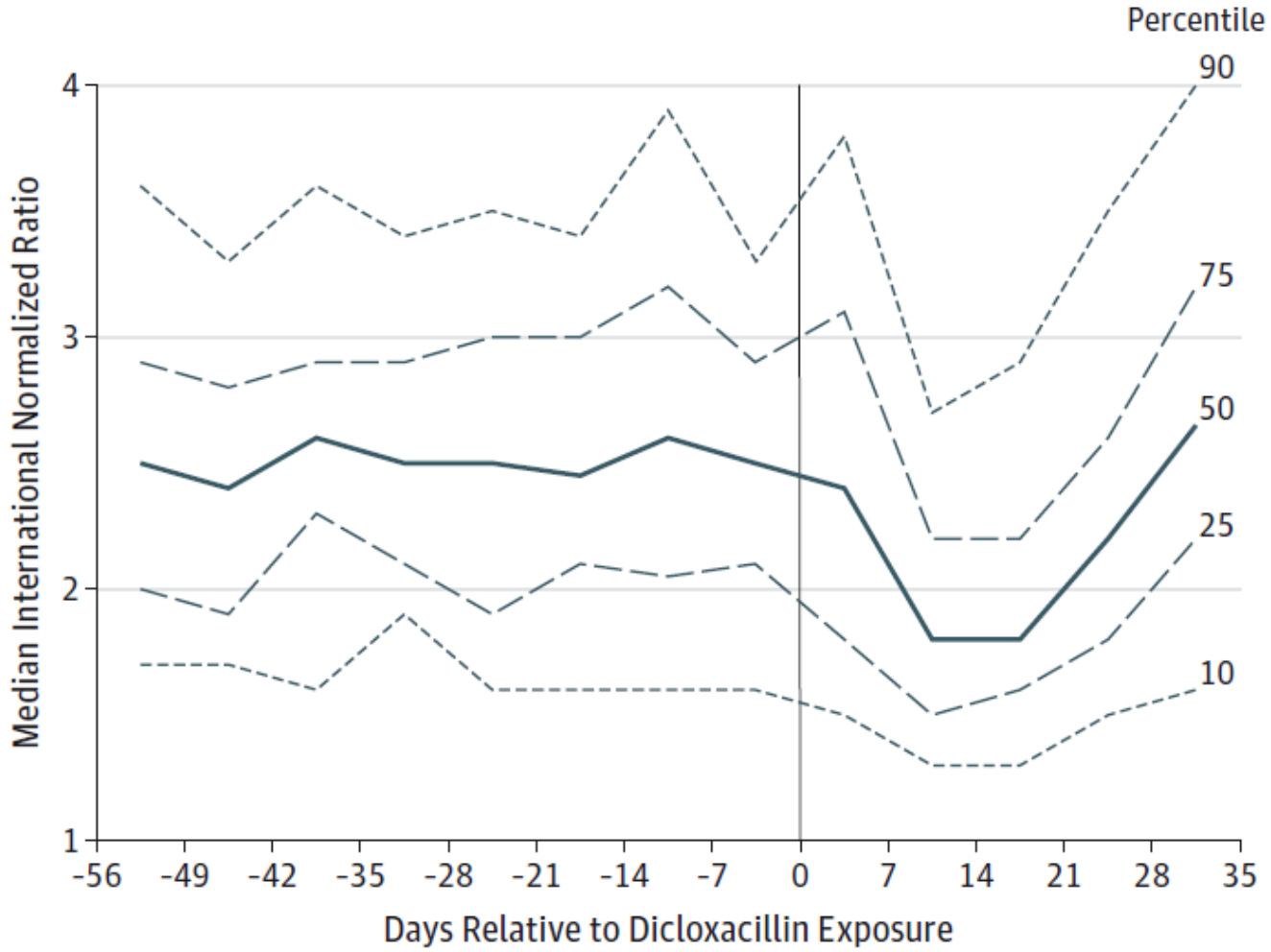
Bleeding?

Myocardial infarction?

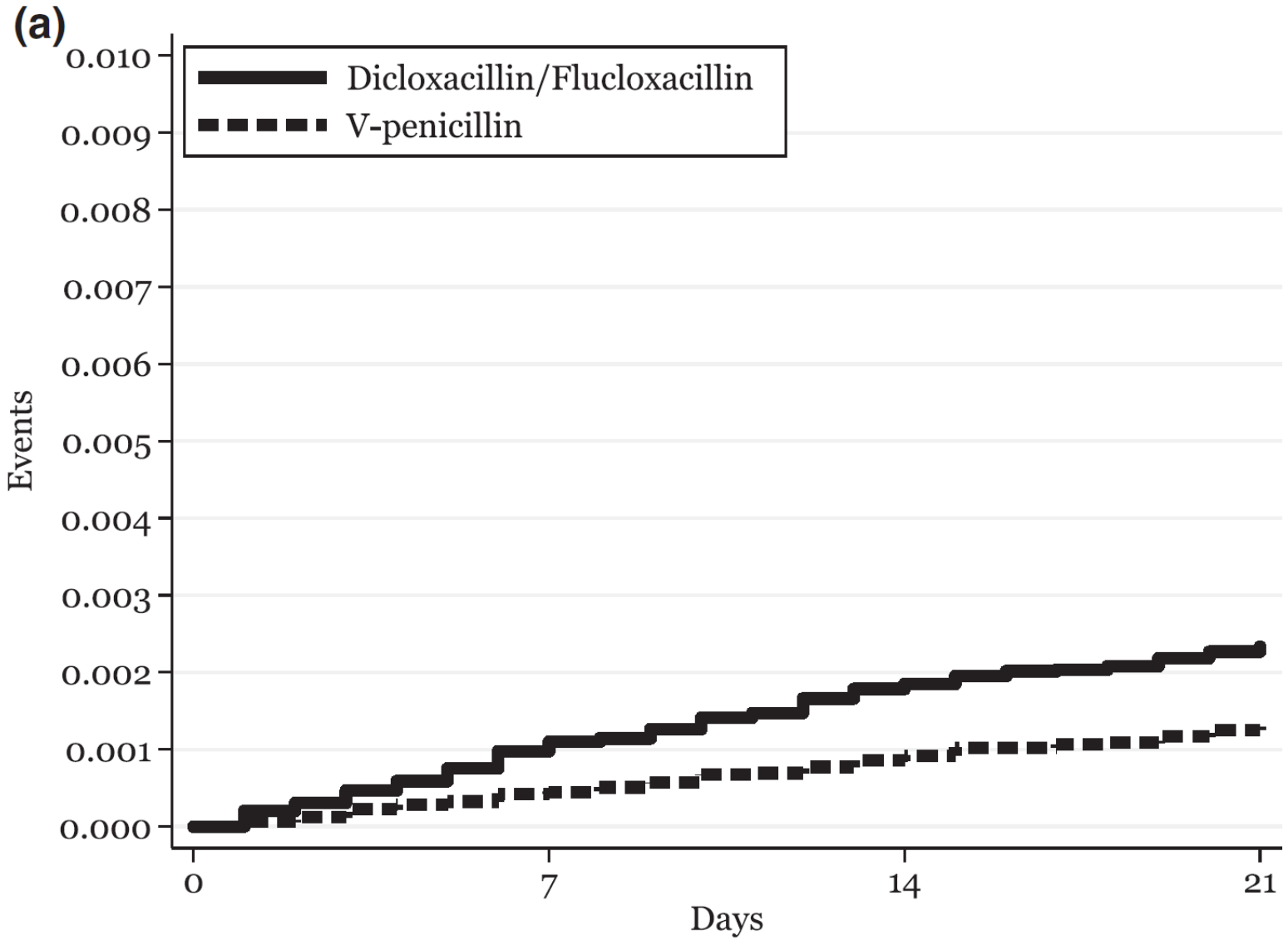
Ischemic stroke?

Melanoma?

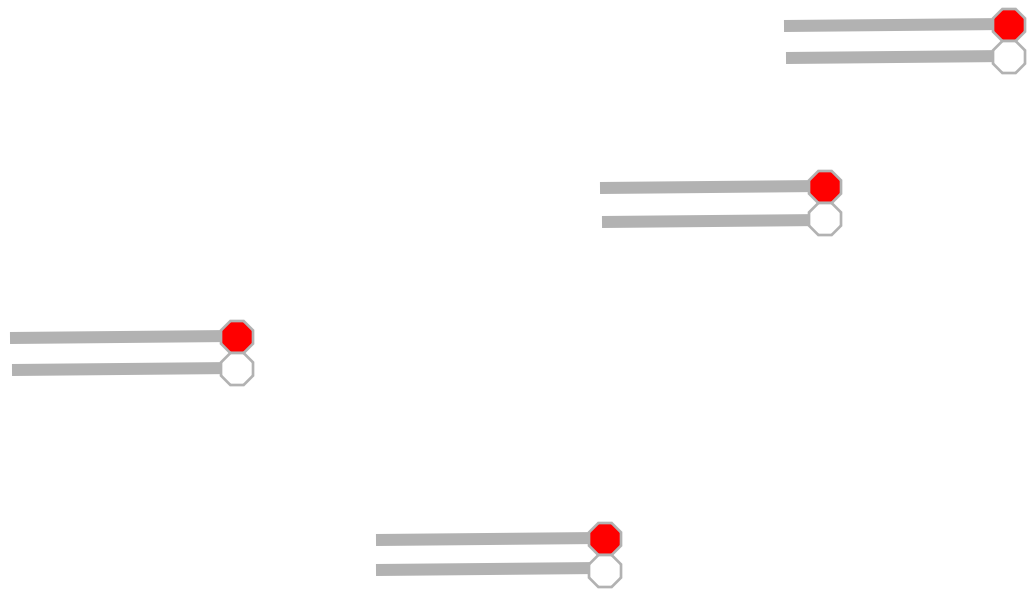
Figure 2. Median International Normalized Ratio Levels Over Time Among Users of Warfarin Exposed to Dicloxacillin

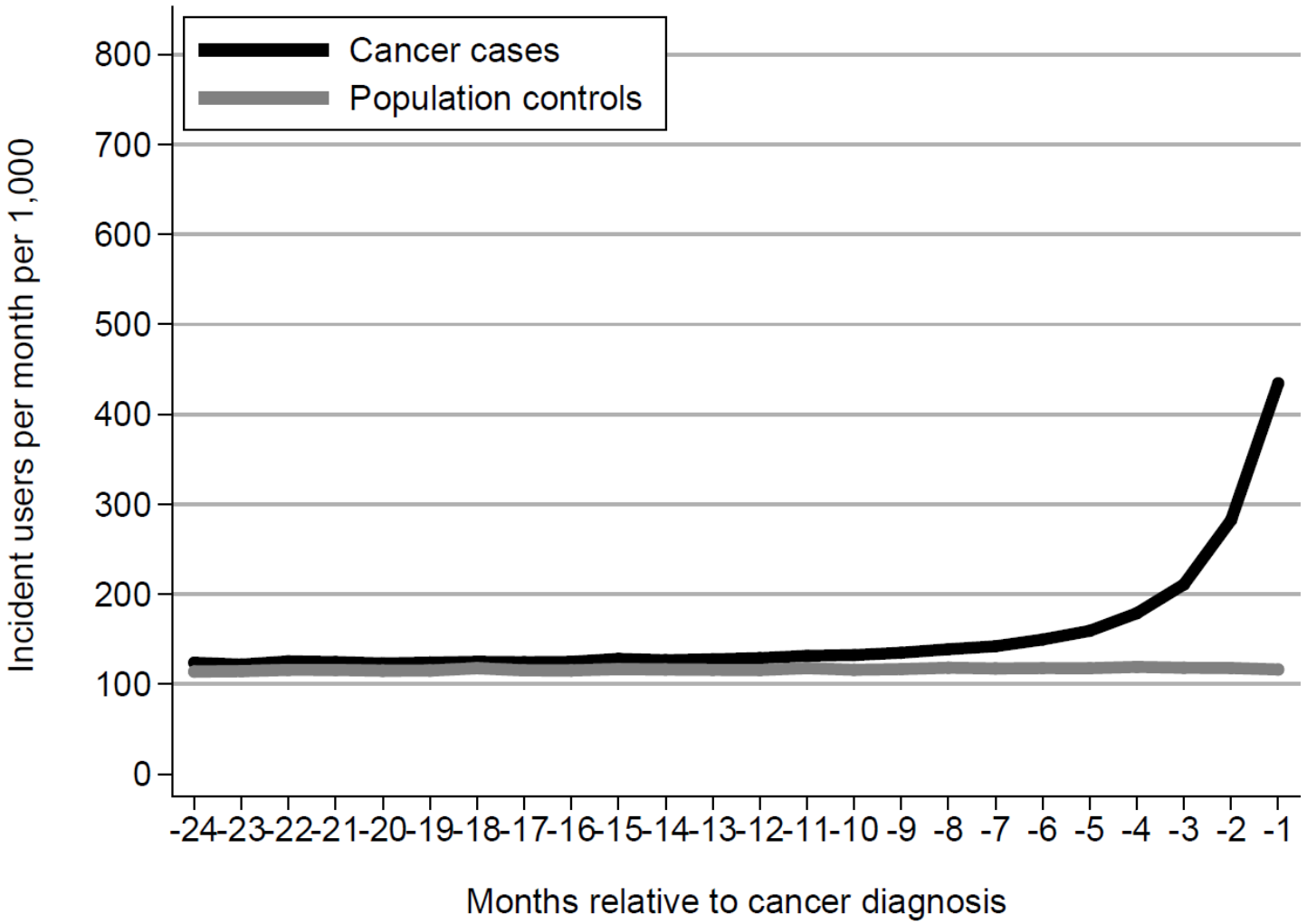


Pottegård et al. JAMA 2015

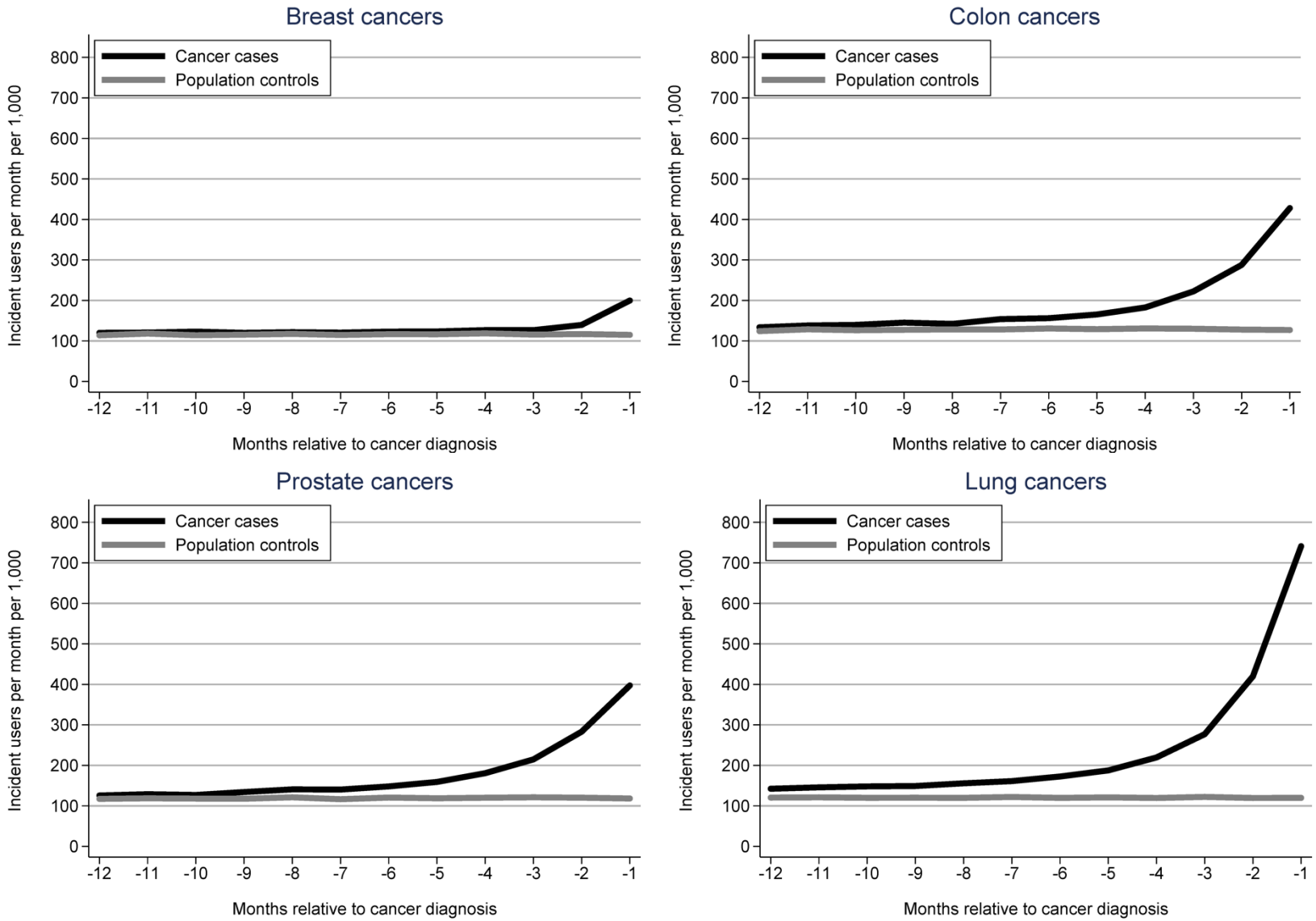


Hellfritzsch et al. Clin Pharmacol Ther 2020





Pottegård & Hallas, Pharmacoepidemiology Drug Saf 2015



Pottegård & Hallas, Pharmacoepidemiology Drug Saf 2015

Received: 19 April 2018 | Accepted: 18 May 2018
DOI: 10.1002/pds.4576

BRIEF REPORT

WILEY

Use of proton pump inhibitors and risk of pancreatic cancer

Blánaid Hicks[1] | Søren Friis[2,3] | Anton Pottegård[4]

[1]Centre for Public Health, Queen's University Belfast, Belfast, UK
[2]Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark
[3]Department of Public Health, Copenhagen University, Copenhagen, Denmark
[4]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

Correspondence
B. Hicks, Centre for Public Health, ICSB, Royal Victoria Hospital, Belfast BT12 6BA, UK.
Email: b.hicks@qub.ac.uk

Funding information
Cancer Research UK

Abstract

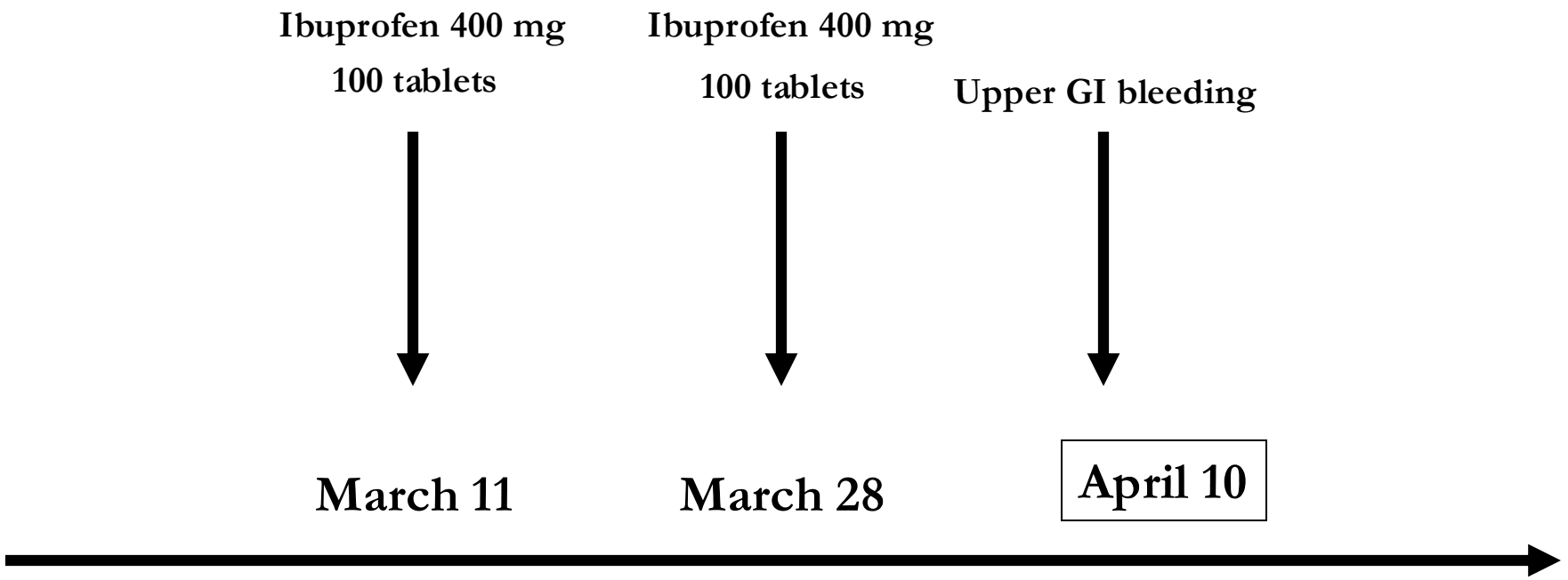
Purpose: Preclinical studies have suggested that proton pump inhibitors (PPIs) may increase pancreatic cancer risk; however, epidemiological studies are few, with conflicting results. This spurred us to evaluate whether PPI use is associated with an increased risk of pancreatic cancer in a large population-based study.

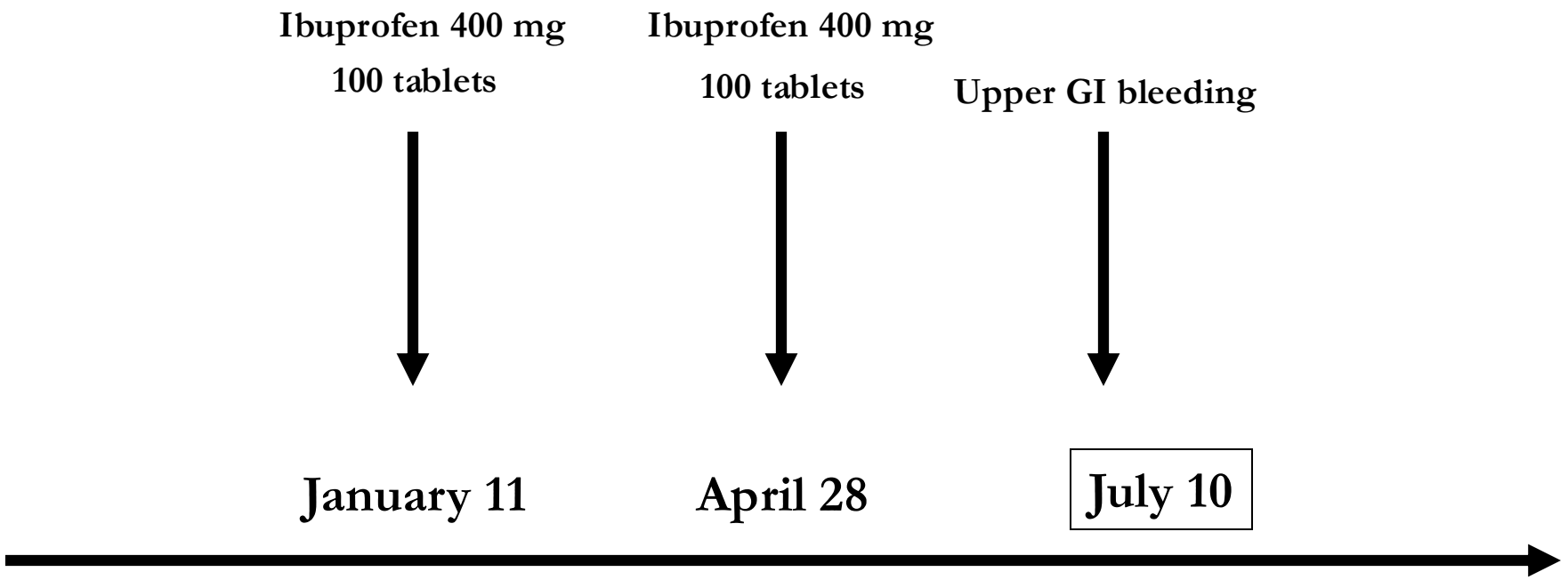
Methods: We conducted a nationwide case-control study using data from Danish demographic and health care registries. All patients with a first cancer diagnosis of pancreatic cancer between 2000 and 2015 were identified from the Danish Cancer Registry and age-matched, sex-matched, and calendar-matched 1:20 to population controls using risk set sampling. Conditional logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for potential confounders. Secondary analyses examined dose-response patterns and associations with individual PPIs as well as with histamine-2-receptor antagonists.

Results: Ever use of PPIs occurred among 27.8% of 6921 pancreatic cancer cases and 25.4% of 34 695 matched controls, yielding a neutral adjusted OR of 1.04 (95% CI 0.97-1.11). Odds ratios were also close to unity in analyses of high use of PPIs (≥1000 DDDs; OR, 0.92 95% CI 0.80-1.07). There was no evidence of a dose-response relationship, with ORs close to unity across categories, including for those with the highest cumulative use (>2000 DDDs; OR, 1.03 95% CI 0.84-1.26). Analyses of subgroups as well as individual types of PPI and of histamine-2-receptor antagonists use also returned neutral associations.

Lagtime (months)	Adjusted OR
0	1.51 (1.31-1.73)
6	1.02 (0.90-1.17)
12	1.00 (0.87-1.15)
18	0.97 (0.85-1.12)
24	**0.92 (0.79-1.07)**
30	0.92 (0.79-1.07)
36	0.94 (0.80-1.10)
42	0.97 (0.82-1.14)
48	0.95 (0.80-1.12)
54	0.96 (0.81-1.15)
60	0.97 (0.81-1.16)

Hicks et al. Pharmacoepidemiology Drug Saf 2018

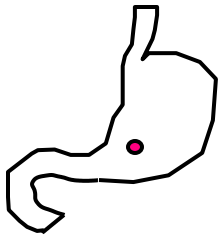

Ibuprofen 400 mg
100 tablets
Ibuprofen 400 mg
100 tablets
Upper GI bleeding
March 11
March 28
April 10


Ibuprofen 400 mg
100 tablets
Ibuprofen 400 mg
100 tablets
Upper GI bleeding
January 11
April 28
July 10

Prescribing

9.1%

Fill



Ingestion

Eur J Clin Pharmacol
DOI 10.1007/s00228-014-1677-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Primary non-adherence in general practice: a Danish register study

Anton Pottegård · Rene dePont Christensen · Alae Houji · Camilla Binderup Christiansen · Maja Skov Paulsen · Janus Laust Thomsen · Jesper Hallas

Received: 5 August 2013 / Accepted: 31 March 2014

Abstract
Purpose The aim of this study was to describe primary non-adherence (PNA) in a Danish general practitioner (GP) setting, i.e. the extent to which patients fail to fill the first prescription for a new drug. We also assessed the length of time between the issuing of a prescription by the GP and the dispensing of the drug by the pharmacist. Lastly, we sought to identify associations between PNA and the characteristics of the patient, the drug and the GP.
Methods By linking data on issued prescriptions compiled in the Danish General Practice Database with data on redeemed prescriptions contained in the Danish National Prescription Registry, we calculated the rate of PNA among Danish patients [illegible]. "Cardiovascular system" (ATC group C). Most of the patients redeemed their prescriptions within the first week. Older age, high income and a diagnosis of chronic obstructive pulmonary disease were found to be significantly associated with lower rates of PNA, while polypharmacy and a diagnosis of ischaemic heart disease were associated with higher rates of PNA.
Conclusions The overall rate of PNA among Danish residents in a GP setting was 9.3 %. Certain drug classes and patient characteristics were associated with PNA.

Keywords Patient adherence · Medication adherence · General practice · Registries · Pharmacology · Pharmacoepidemiology

Exposure Definition	Adjusted OR[b] (95% Confidence Interval)
Fixed window	
30 d	5.17 (2.40-11.11)
60 d	5.13 (2.75-9.55)
90 d	4.73 (2.72-8.23)
120 d	3.64 (2.14-6.18)
Fixed daily intake	
1.5 DDD/d	6.48 (2.88-14.57)
1.0 DDD/d	5.95 (3.02-11.71)
0.5 DDD/d	2.78 (1.77-4.37)
0.2 DDD/d	1.49 (1.16-1.93)

Hallas, Pottegård, and Støvring, PDS 2016

What is the height difference between men and women?

Exposure Definition	Adjusted OR[b] (95% Confidence Interval)
Fixed window	
30 d	5.17 (2.40-11.11)
60 d	5.13 (2.75-9.55)
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0.2 DDD/d	1.49 (1.16-1.93)

Hallas, Pottegård, and Støvring, PDS 2016

Incidence rate ratios of GI-hospitalisations of NSAID users

	Current users (0-30 days)	Recent past users (30-60 days)	Old past users (60-150 days)
Diclofenac	3.9	2.2	1.3
Indomethacin	4.0	1.7	1.4
Naproxen	3.8	2.3	1.4
Nonusers		1.0	

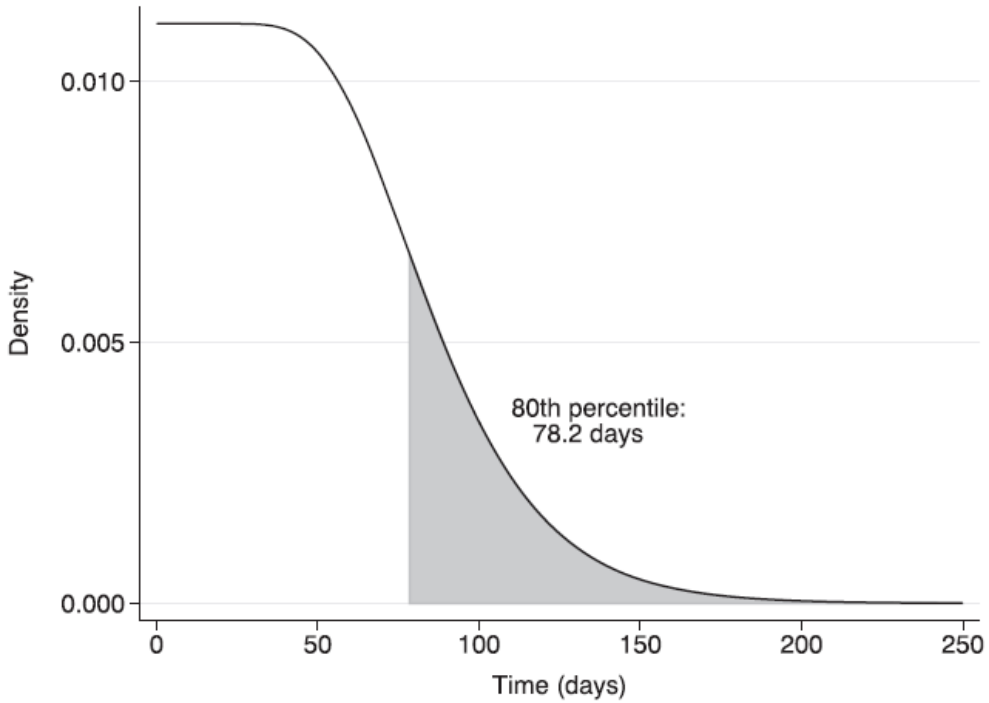
One statin tablet a day?

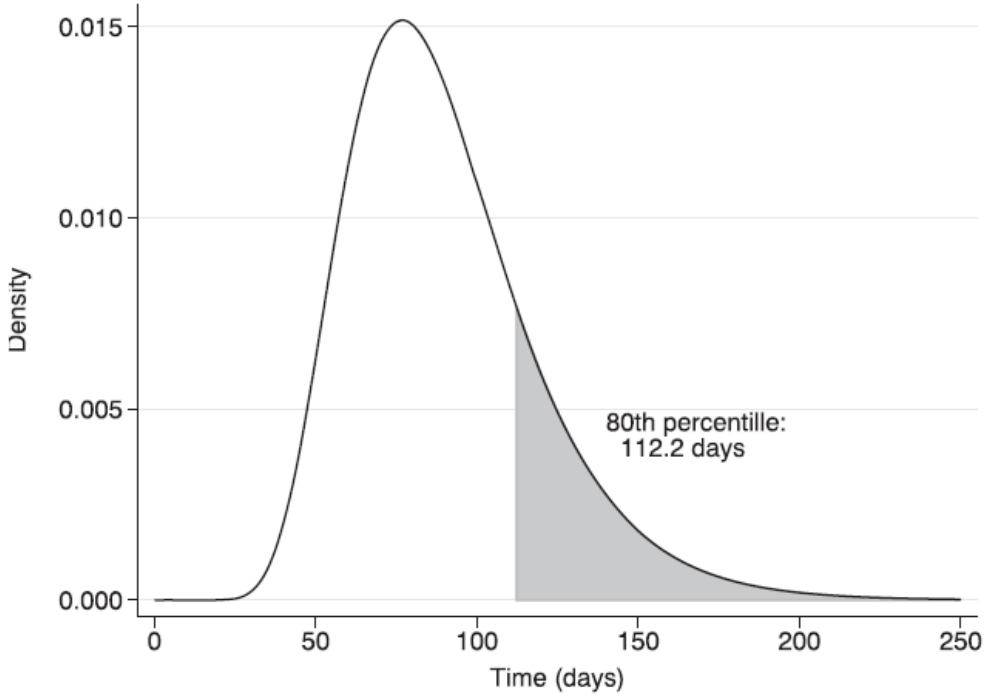
One alendronic acid a week?

An SSRI tablet a day?

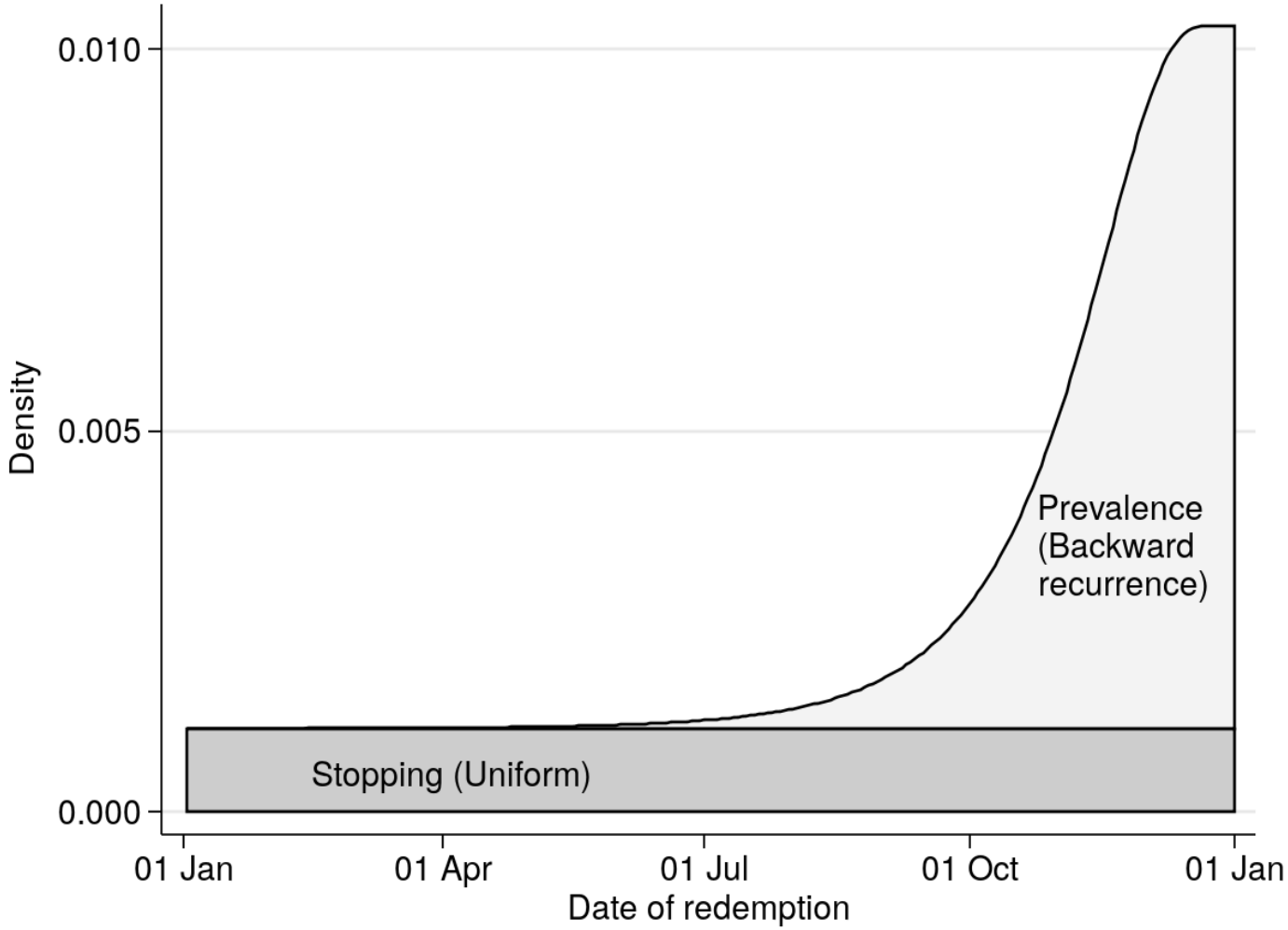
1-2 paracetamol 3-4 times daily?

Drug	Parametric WTD
NSAID	116
Warfarin	91
Bendroflumethiazide	137
Levothyroxine	118





Hallas, Pottegård, and Støvring, PDS 2016



Sex	Age	100 pills	200 pills	300 pills
Male	**50**	62.7	90.2	125.2
Male	**70**	78.1	112.9	157.1
Female	**50**	65.4	92.2	126.5
Female	**70**	81.2	117.3	163.1


MYSTERY
BOX
?

Breast Cancer Res Treat (2011) 129:541–548
DOI 10.1007/s10549-011-1506-2

EPIDEMIOLOGY

The use of atypical antipsychotics and the risk of breast cancer

Laurent Azoulay · Hui Yin · Christel Renoux · Samy Suissa

Received: 1 April 2011 / Accepted: 4 April 2011 / Published online: 9 April 2011

Abstract To determine whether atypical antipsychotics, when compared to typical antipsychotics, increase the risk of breast cancer. We conducted a retrospective cohort study using a nested case–control analysis within the United Kingdom General Practice Research Database population. We identified all female patients prescribed at least one antipsychotic (either typical or atypical), between 1 January 1988 and 31 December 2007, with follow-up until 31 December 2010. All incident cases of breast cancer were identified and matched up to 10 controls. Adjusted rate ratios (RR) of breast cancer associated with ever use of atypical antipsychotics was compared to ever use of typical antipsychotics. The cohort included 106,362 patients prescribed antipsychotics during the study period. During a mean follow-up of 5.3 years, 1237 patients were diagnosed with breast cancer (overall rate: 2.7 per 1000/year). Compared to patients who only used typical antipsychotics, exclusive users of atypical antipsychotics were not an observed in terms of cumulative duration of use and cumulative dose in olanzapine equivalents. The results of this study should provide reassurance that compared to typical antipsychotics, atypical antipsychotics do not increase the risk of breast cancer.

Keywords Antipsychotics · Breast cancer · Population-based

Introduction

Antipsychotics are now playing important role in the treatment of several psychiatric disorders. In fact, there has been a significant increase in their use, particularly for off-label indications [1, 2]. Despite their effectiveness, antipsychotics frequently cause side effects, including hyperprolactinemia [3–5]. High serum prolactin levels

	Cases (n = 1237)	Controls (n = 11,625)	Adjusted RR (95% CI)[a]
Typical antipsychotics only, n (%)	976 (78.9)	9090 (78.2)	1.00 (Reference)
Atypical antipsychotics only			
Cumulative duration of use, n (%)[b]			
≤224 days	36 (2.9)	355 (3.1)	0.95 (0.65, 1.39)
224–687 days	30 (2.4)	366 (3.1)	0.73 (0.48, 1.11)
≥687 days	30 (2.4)	357 (3.1)	0.75 (0.50, 1.13)
Cumulative dose (in olanzapine equivalents), n (%)[b]			
≤910 mg	32 (2.6)	354 (3.0)	0.85 (0.57, 1.26)
910–3965 mg	31 (2.5)	369 (3.2)	0.76 (0.51, 1.13)
≥3965 mg	33 (2.7)	355 (3.1)	0.82 (0.56, 1.20)

[a] Adjusted for the variables listed in Table 1

[b] Based on tertile categories

British Journal of Clinical Pharmacology

ORIGINAL ARTICLE

Use of antipsychotics and risk of breast cancer: a Danish nationwide case–control study

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Keywords antipsychotics, breast cancer, pharmacoepidemiology

AIMS

Some antipsychotics increase prolactin levels, which might increase the risk of breast cancer. Existing evidence is conflicting and based on sparse data, especially for the increasingly used second-generation antipsychotics. We conducted a nationwide case–control study of the association between antipsychotic use and incident breast cancer.

METHODS

From the Danish Cancer Registry, we identified women with a first-time diagnosis of breast cancer 2000–2015 (n = 60 360). For each case, we age-matched 10 female population controls. Using conditional logistic regression, we calculated odds ratios (ORs) for breast cancer associated with use of antipsychotics. We stratified antipsychotics by first- and second-generation status and by ability to induce elevation of prolactin.

RESULTS

In total, 4951 cases (8.1%) and 47 643 controls (7.9%) had ever used antipsychotics. Long-term use (≥10 000 mg olanzapine equivalents) was associated with breast cancer, with an adjusted OR of 1.18 [95% confidence interval (CI), 1.06, 1.32]. A weak dose–response pattern was seen, with ORs increasing to 1.27 (95% CI 1.01, 1.59) for ≥50 000 mg olanzapine equivalents. Associations were similar for first- and second-generation antipsychotics (ORs 1.17 *vs*. 1.11), but also for nonprolactin inducing-antipsychotics (OR 1.17). Stratifying by oestrogen receptor status, positive associations were seen for oestrogen receptor-positive cancers (long-term use: OR 1.29; 95% CI 1.13, 1.47) while no associations were observed for oestrogen receptor-negative cancers.

CONCLUSIONS

Overall, our results do not suggest a clinically important association between antipsychotic use and risk of breast cancer. The importance of drug-induced prolactin elevation is unclear but may lead to a slightly increased risk of oestrogen receptor-positive breast cancer.

Main exposure variables and covariates

Exposure to different antipsychotics was standardized using olanzapine equivalents [38]. For drugs not assigned a conversion factor, one defined daily dose (DDD), per WHO definitions, was considered equivalent to 10 mg olanzapine [39]. We applied a pre-specified main exposure measure corresponding to a cumulative exposure of 10 000 mg olanzapine, while restricting to antipsychotics with prolactin inducing properties (Appendix S2). We included all exposure from 1995 (the opening of the Prescription Registry) until 1 year before an individual's index date. The largely arbitrary cut-off of 10 000 mg olanzapine equivalents was selected based on pharmacological consideration that if antipsychotic use inferred a risk of breast cancer, a substantial use was likely to be necessary to detect an increased risk. For dose–response analyses, we used the following prespecified categories: 0–4999 mg, 5000–9999 mg, 10 000–19 999 mg, 20 000–49 999 mg and ≥50 000 mg. These strata were selected to ensure that we did not overlook risk associated with either very short or very high use of antipsychotics. In all exposure calculations, we disregarded prescriptions redeemed within 1 year before the index date to reduce the possibility of reverse causation [40], and because such recent exposure is unlikely to affect cancer development.

Exposure group	Cases	Controls	Adjusted OR[b]
Nonuse			
Ever use			
Long-term use[c]			
Cumulative use[c]			
0–4999 mg			
5000–9999 mg			
10 000–19 999 mg			
20 000–49 999 mg			
≥50 000 mg			

Exposure group	Cases	Controls	Adjusted OR[b]
Nonuse	55 409	555 957	1.0 (ref.)
Ever use	4798	46 156	1.00 (0.97–1.04)
Long-term use[c]	693	5659	1.18 (1.06–1.32)
Cumulative use[c]			
0–4999 mg	3756	37 619	0.97 (0.94–1.01)
5000–9999 mg	349	2878	1.19 (1.05–1.34)
10 000–19 999 mg	243	2131	1.11 (0.95–1.29)
20 000–49 999 mg	246	1993	1.27 (1.07
≥50 000 mg	204	1535	1.27 (1.01

	Cases (n = 1237)	Controls (n = 11,625)	Adjusted RR (95% CI)[a]
Typical antipsychotics only, n (%)	976 (78.9)	9090 (78.2)	1.00 (Reference)
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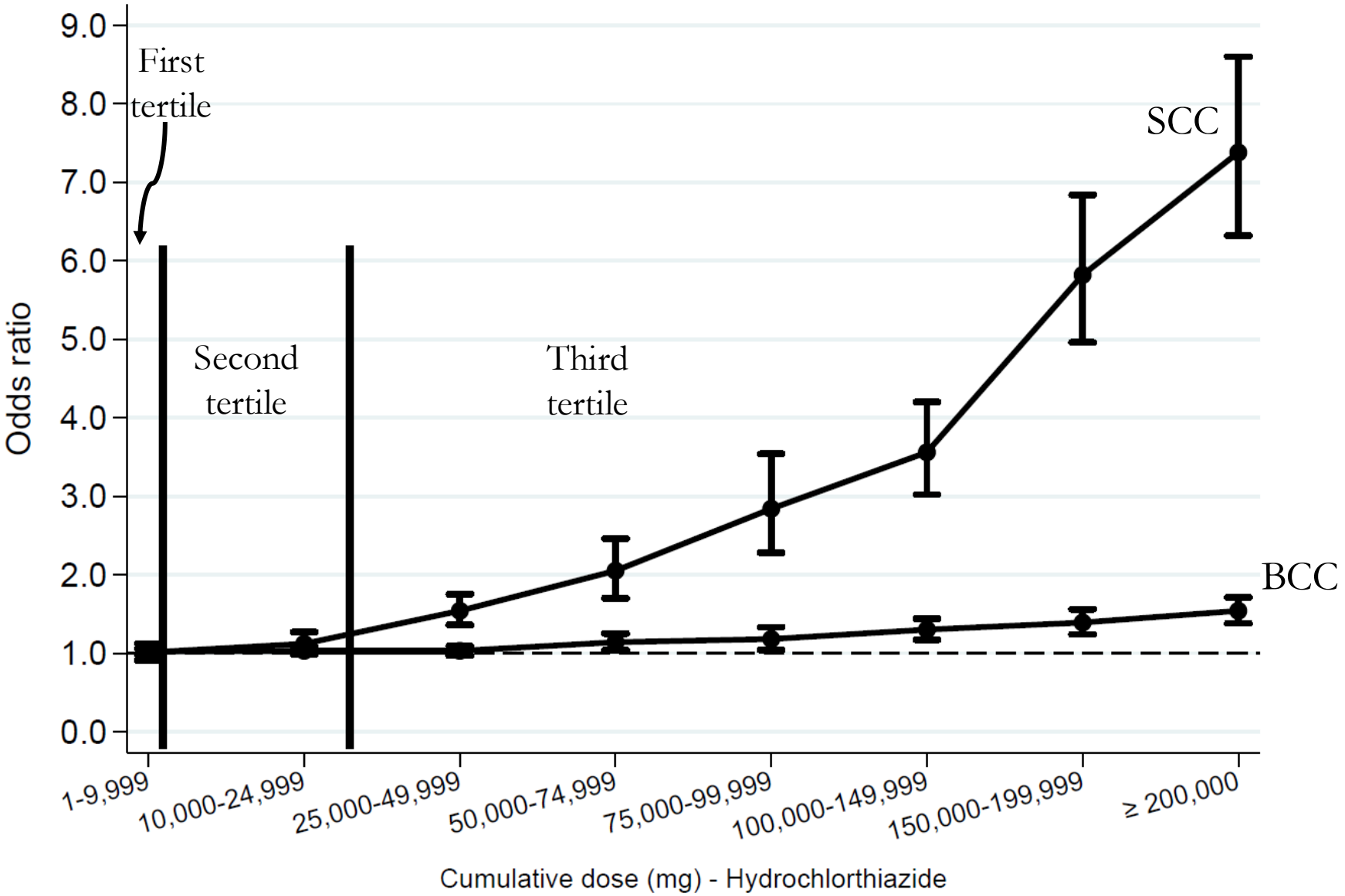
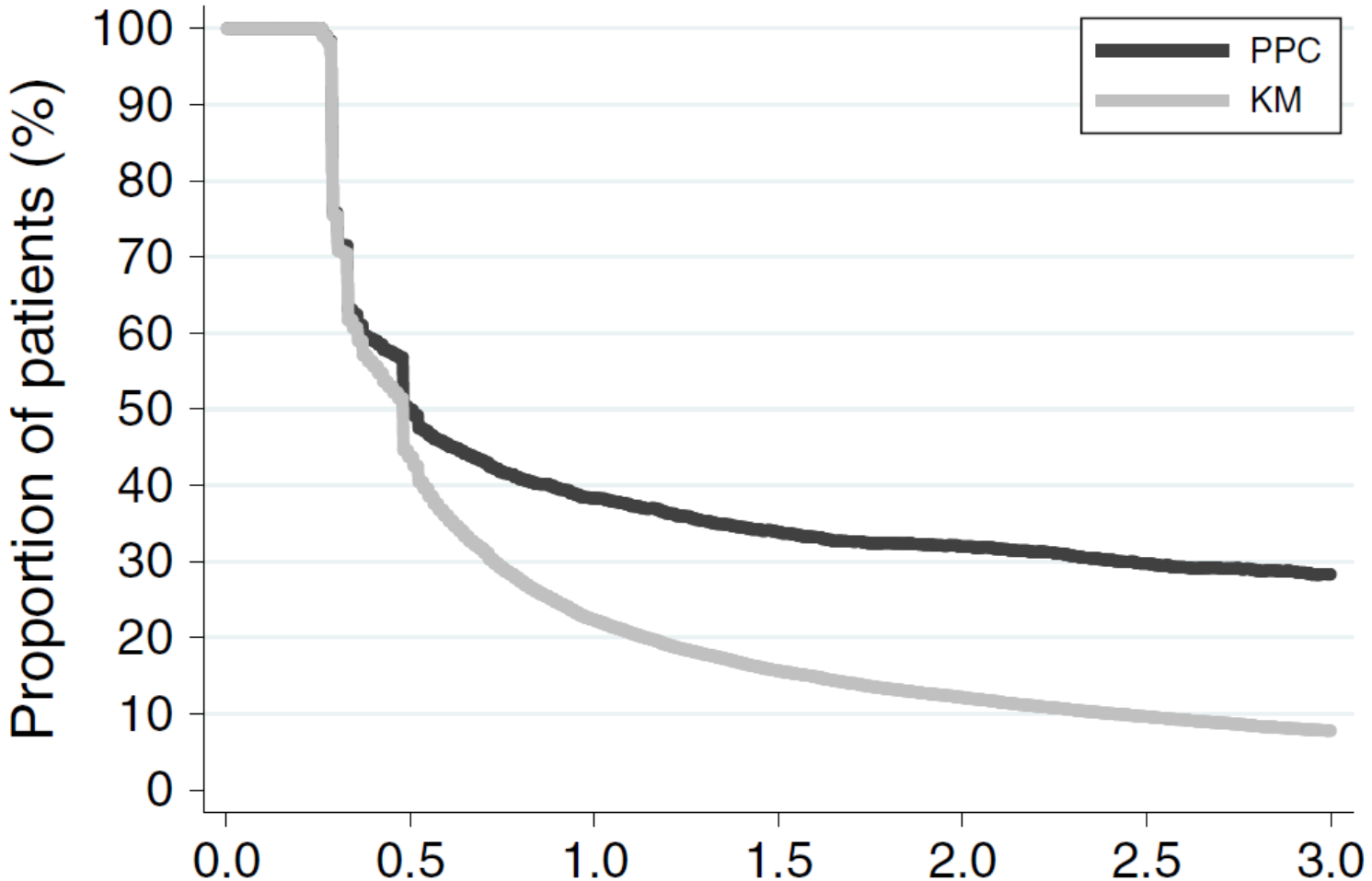
[a] Adjusted for the variables listed in Table 1

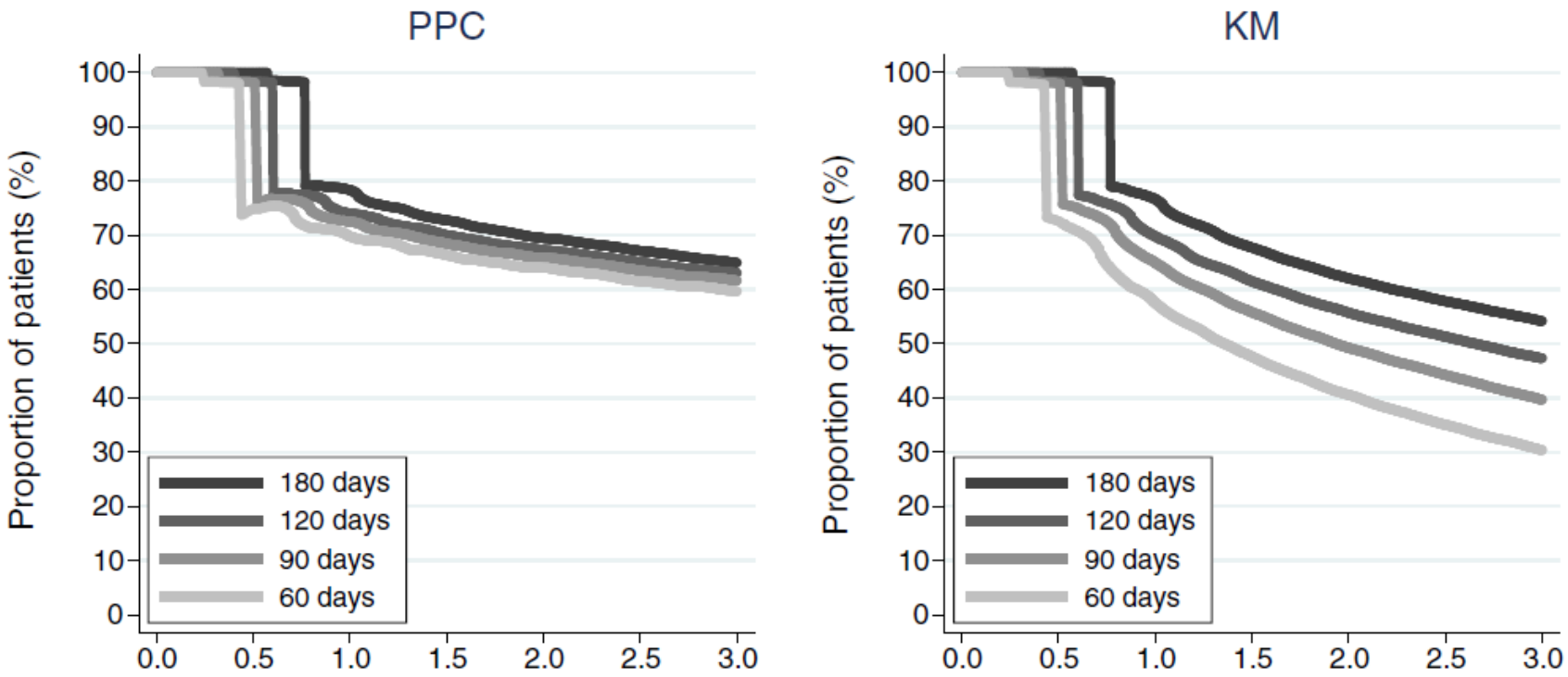
[b] Based on tertile categories



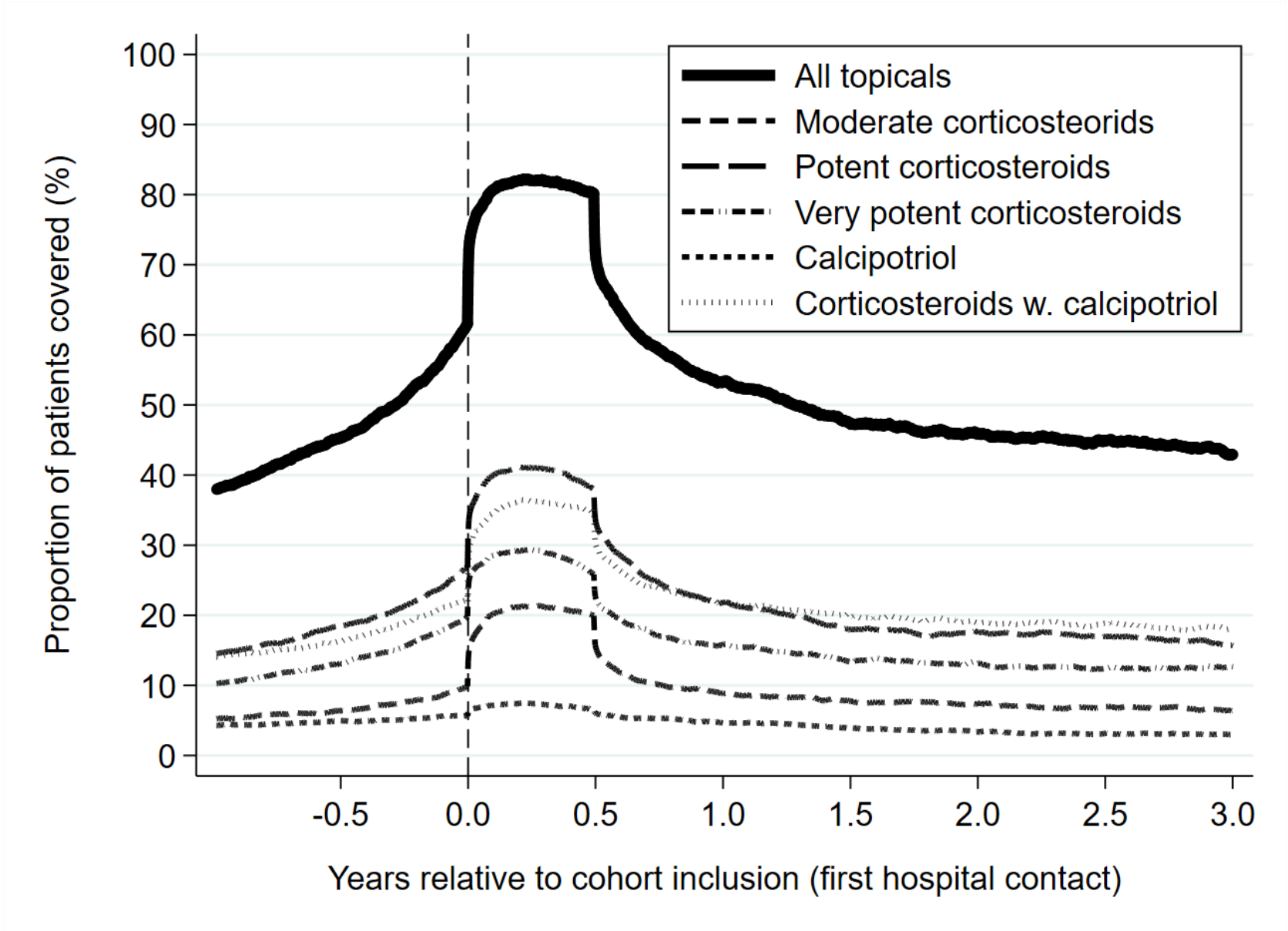
Pedersen et al. J Am Acad Dermatol. 2018



Rasmussen et al. Pharmacoepidemiol Drug Saf 2018



Rasmussen et al. Pharmacoepidemiol Drug Saf 2018



Svendsen et al. Br J Dermatol 2019

Pharmacology:

The neglected half of pharmacoepidemiology!

Considerations re. outcomes

Credit: Maja Hellfritzsch

Outcome / event

Mortality
Suicide attempts
High INR values
Stroke
AMI
Cancer
PCI / CABG
Initiation
Discontinuation
Switching

OUTCOME

Disease

Surgery

Treatment initiation

Biochemical change

Validity?

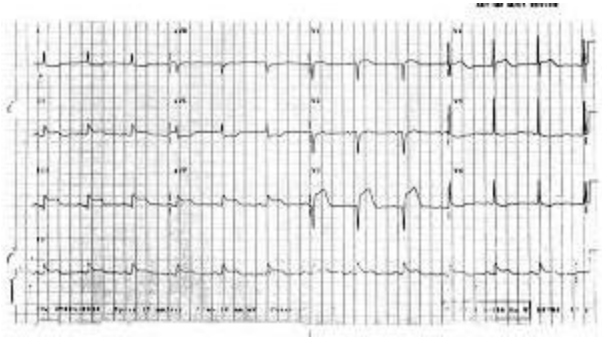
Will this proxy classify those with the outcome as having the outcome? And those without the outcome as not having the outcome?

Is the proxy valid?

Myocardial infarction
= ICD10-code I21

How to test this?

VS.



BMJ Open

Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

Jens Sundbøll,[1,2] Kasper Adelborg,[1,2] Troels Munch,[1] Trine Frøslev,[1] Henrik Toft Sørensen,[1] Hans Erik Bøtker,[2] Morten Schmidt[1,3]

To cite: Sundbøll J, Adelborg K, Munch T, *et al*. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832. doi:10.1136/bmjopen-2016-012832

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012832).

Received 26 May 2016
Revised 21 September 2016
Accepted 30 September 2016

ABSTRACT

Objective: The majority of cardiovascular diagnoses in the Danish National Patient Registry (DNPR) remain to be validated despite extensive use in epidemiological research. We therefore examined the positive predictive value (PPV) of cardiovascular diagnoses in the DNPR.

Design: Population-based validation study.

Setting: 1 university hospital and 2 regional hospitals in the Central Denmark Region, 2010–2012.

Participants: For each cardiovascular diagnosis, up to 100 patients from participating hospitals were randomly sampled during the study period using the DNPR.

Main outcome measure: Using medical record review as the reference standard, we examined the PPV for cardiovascular diagnoses in the DNPR, coded according to the International Classification of Diseases, 10th Revision.

Results: A total of 2153 medical records (97% of the total sample) were available for review. The PPVs

Strengths and limitations of this study

- This is the first validation study to include all major cardiovascular diagnoses in the Danish National Patient Registry.
- We sampled patients only from hospitals in the Central Denmark Region. However, our results are most likely generalisable to other parts of the country as the Danish healthcare system is homogeneous in structure and practice.
- We only validated patients diagnosed during 2010–2012 and therefore cannot extrapolate our results to previous periods.

INTRODUCTION

Remarkable improvements have occurred in the prevention and treatment of cardiovascu-

96 of 99 patient with (first)
I21 code had an AMI.

Valid?

	+ Disease	**÷ Disease**
+ Code	True pos.	False pos.
÷ Code	False neg.	True neg.

	+ Disease	**÷ Disease**
+ Code	True pos.	False pos.
÷ Code	False neg.	True neg.

Positive predictive value (PPV):
Likelihood of disease given registration **96 of 99!**

Negative predictive value (NPV):
Likelihood of absence of disease given no registration **?** ≈100%?

Sensitivity (completeness):
Proportion of those with disease having registration **???**

Specificity:
Proportion of those with no disease having no registration **?** ≈100%?

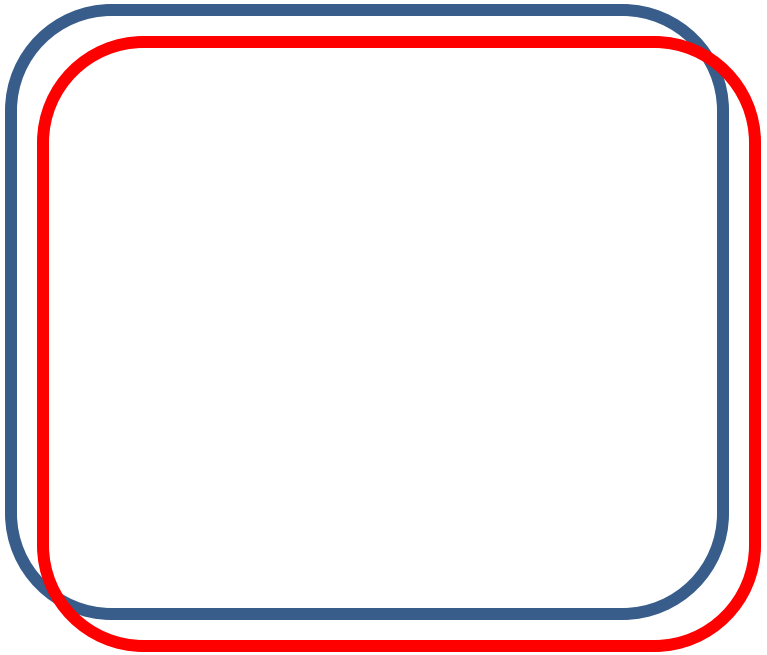
The perfect proxy!

Proxy always represent an outcome
(PPV = 100%)

An outcome will always trigger a proxy
(Sensitivity = 100%)

NOTE: Validation often only adress PPV!

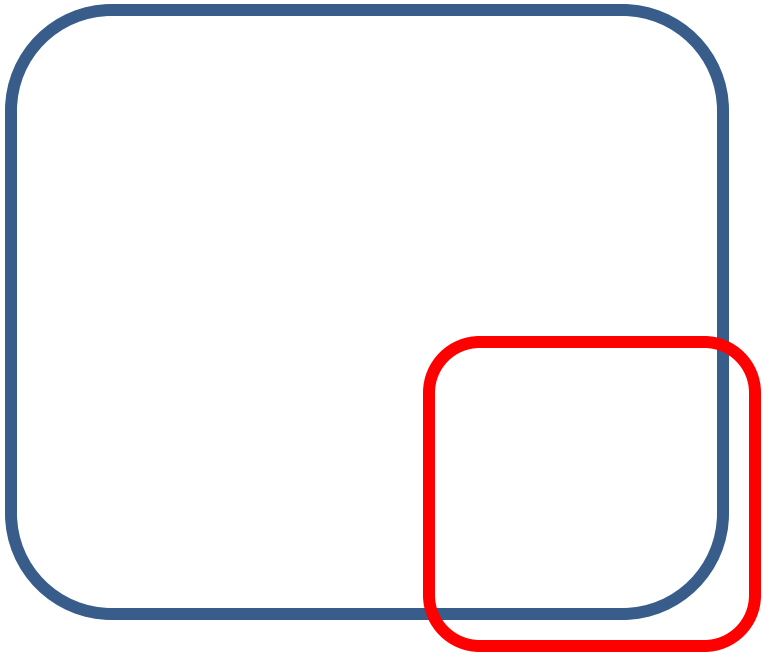
Those with outcome
Those with proxy



High PPV
High sens.

Cancer?

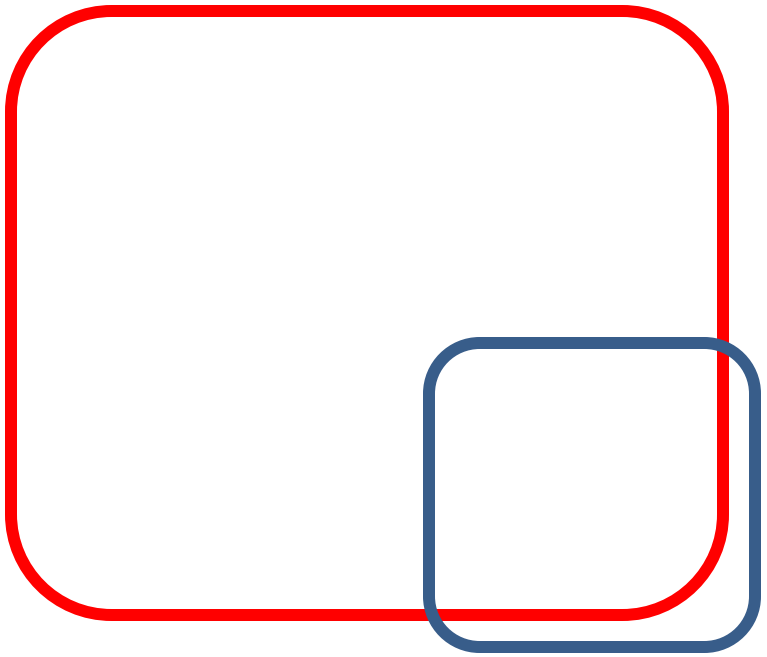
Those with outcome
Those with proxy



High PPV
Low sens.

Obesity diagnosis?

Those with outcome
Those with proxy



Low PPV
High sens.

Gastroscopy as proxy for intestinal bleeding?

ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 323–337

Journal of Clinical Epidemiology

REVIEW ARTICLE

A review of uses of health care utilization databases for epidemiologic research on therapeutics

Sebastian Schneeweiss*, Jerry Avorn

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street (suite 3030), Boston, MA 02120, USA

Accepted 16 October 2004

PPV > Sensitivity

(Most important that the registered outcomes are in fact outcomes!)

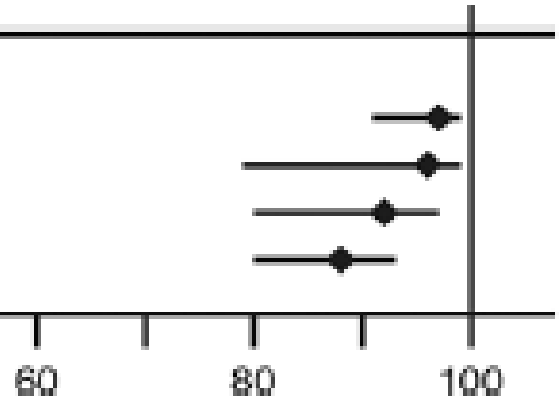
Open Access Research

BMJ Open

Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

Jens Sundbøll,[1,2] Kasper Adelborg,[1,2] Troels Munch,[1] Trine Frøslev,[1] Henrik Toft Sørensen,[1] Hans Erik Bøtker,[2] Morten Schmidt[1,3]

Myocardial infarction			
First-time myocardial infarction	100	96/99	97 (91-99)
First-time STEMI	23	22/23	96 (79–99)
First-time NSTEMI	39	36/39	92 (80-97)
Recurrent myocardial infarction	100	88/100	88 (80-93)



Suboptimal validity…

Misclassification

What is the height difference between men and women?

Suboptimal validity…

Misclassification of outcome status = information bias

Low PPV →
Those without outcome classified with outcome

Low sensitivity →
Those with outcome classified as not having outcome

As long as validity does not depend on exposure status, misclassification is non-differential and thus biases towards unity (making the groups appear alike)!

How to increase validity?

Algorithms!

Validate!

Stick to codes with high PPV!

Restrict to incident outcomes, primary diagnoses, diagnoses from specialized departments!

Consider sensitivity analyses!

Neuro
-epidemiology

Methods in Neuroepidemiology

Neuroepidemiology 2011;37:120–128
DOI: 10.1159/000331481

Received: March 31, 2011
Accepted: August 2, 2011
Published online: October 7, 2011

Identifying Patients with Myasthenia for Epidemiological Research by Linkage of Automated Registers

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David Gaist[a, c]

[a]Department of Neurology, Odense University Hospital, Odense, [b]Institute of Public Health, Clinical Pharmacology Unit, and [c]Institute of Clinical Research, University of Southern Denmark, and [d]Department of Neurology and [e]Neuroimmunology Laboratory, DMSC, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Requiring both diagnosis and prescription yielded PPV of 93%!

Key Words
Myasthenia · Neuromuscular diseases · Neurological disorders · Epidemiology · Research methods

the positive predictive value of the register diagnosis was 92.9% (95% confidence interval, CI, 84.3–97.7), the false-positive rate was low (2.8%), and the sensitivity was acceptable (81.2%; 95% CI 71.2–88.8). ***Conclusions:*** Our data indicate that this novel approach of combining diagnosis register and

Algorithms

Excluding algorithms (increases PPV!)

Multiple requirements to count as outcome

e.g. DVT diagnosis AND later AC treatment

Inclusive algorithms (increases sensitivity!)

Multiple ways of counting as outcome

e.g. diabetes diagnosis OR antidiabetic use

Involve a clinician!

(and beware of pseudo-clinicians!)

Validation?

We defined cases by fulfilment of three criteria: admission with peptic ulcer or gastritis as the main diagnosis to one of the county's hospitals during 1 January 2000 to 31 December 2004; significant bleeding defined by melaena, a subnormal haemoglobin, or the need for transfusions; and a potential bleeding source in the stomach or duodenum identified by endoscopy or surgery.

Hallas et al. BMJ 2006

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

The Danish National Patient Registry: a review of content, data quality, and research potential

Morten Schmidt[1]
Sigrun Alba Johannesdottir Schmidt[1]
Jakob Lynge Sandegaard[2]
Vera Ehrenstein[1]
Lars Pedersen[1]
Henrik Toft Sørensen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, [2]Department of Health Documentation, State Serum Institute, Copenhagen, Denmark

Background: The Danish National Patient Registry (DNPR) is one of the world's oldest nationwide hospital registries and is used extensively for research. Many studies have validated algorithms for identifying health events in the DNPR, but the reports are fragmented and no overview exists.

Objectives: To review the content, data quality, and research potential of the DNPR.

Methods: We examined the setting, history, aims, content, and classification systems of the DNPR. We searched PubMed and the *Dantsh Medtcal Journal* to create a bibliography of validation studies. We included also studies that were referenced in retrieved papers or known to us beforehand. Methodological considerations related to DNPR data were reviewed.

Results: During 1977–2012, the DNPR registered 8,085,603 persons, accounting for 7,268,857 inpatient, 5,953,405 outpatient, and 5,097,300 emergency department contacts. The DNPR provides nationwide longitudinal registration of detailed administrative and clinical data. It has recorded information on all patients discharged from Danish nonpsychiatric hospitals since 1977 and on psychiatric inpatients and emergency department and outpatient specialty clinic contacts since 1995. For each patient contact, one primary and optional secondary diagnoses

Table S1 *(Continued)*

ICD codes[a]	Condition	Study period (contact type; diagnosis type)	ICD codes/algorithm[b]	n[c]	PPV; NPV; sensitivity; specificity[d]
I21	Acute myocardial infarction	1996–2009 (IN;* A)	I21	148	PPV =100 (97.5–100)
		1998–2007 (IN/OUT; A)	I21, I22, I23	50	PPV =98.0 (89.5–99.7)
		1993–2003 (IN/OUT/ED; A/B*)	410; I21	1,072	$PPV_{IN/OUT/ED}$ =81.9 (79.5–84.1); $PPV_{IN; A/B}$ =92.4 (90.4–93.9); $PPV_{IN; A}$ =94.4 (92.6–95.7)
		1982–1991 (IN; A/B)	410, 427.24, 427.27, 427.91, 427.97	5,022	PPV_{A} =94.3 (93.6–94.9); PPV_{A+B} =93.4 (92.6–94.0); Se_{A} =62.8 (61.7–64.0); Se_{A+B} =69.5 (68.4–70.6)
		1979–1980 (IN; A/B)	410–414	527	PPV =92.4 (89.8–94.4)
I26	PE	1994–2006 (IN/OUT/ED; A/B)	450.99; I26	353	PPV_{All} =67.4 (62.4–72.1); $PPV_{IN/OUT}$ =82.1 (77.2–86.1); PPV_{ED} =29.6 (22.0–38.5); PPV_{A} =87.0 (81.9–90.9)
	PE during pregnancy and postpartum	1980–2001 (IN;* A*)	450.00–450.99; I26.0–I26.9 + (650–666; O80–84)	22	$PPV_{preg+postpartum}$ =81.8 (59.7–94.8);[e] PPV_{preg} =63.6 (40.7–82.8)[f]
	PE after stroke	2003–2006 (IN; A/B)	I26 (after admission to stroke units and age ≥18 y)	11	PPV =90.9 (62.3–98.4); NPV =97.4 (95.8–98.4); Se =0.0 (0.0–32–4); Sp =100 (99.3–100)
I46	Cardiac arrest	1993–2003 (IN/OUT/ED; A/B*)	427.27; I46	42	$PPV_{IN/OUT/ED}$ =50.0 (35.5–64.5); PPV_{IN} =53.1 (36.5–69.1)
I48	Atrial fibrillation or flutter	1993–2009 (IN/OUT/ED; A/B)	427.93, 427.94; I48	284	PPV_{All} =92.3 (88.6–94.8); $PPV_{IN/OUT}$ =94.0 (90.5–96.3) (independent of diagnosis type and department specialty); PPV_{ED} =64.7 (41.3–82.7)
		1980–2002 (n/a; n/a)	427.93, 427.94; I48	174	PPV =98.9 (95.9–99.7)
		1980–2002 (n/a; n/a)	427.93, 427.94; I48	116	PPV =96.6 (91.5–98.7)
I48.9A	Atrial flutter	1977–1999 (IN/OUT/ED; A/B)	427.94; I48.9A	108	PPV =50.0 (40.7–59.3)
I50	Heart failure	1998–2007 (IN/OUT; A)	I50, I11.0, I13.0, I13.2	50	PPV =100 (92.9–100)

Considerations re validity

What is most important?

To identify all outcomes (high sensitivity)?

To make sure outcomes are correct (high PPV)?

Considerations re validity

What is most important?

To identify all outcomes (high sensitivity)?

To make sure outcomes are correct (high PPV)?

Unless specific considerations:

PPV > Sensitivity

Bias

Random variation

Systematic error (Bias)

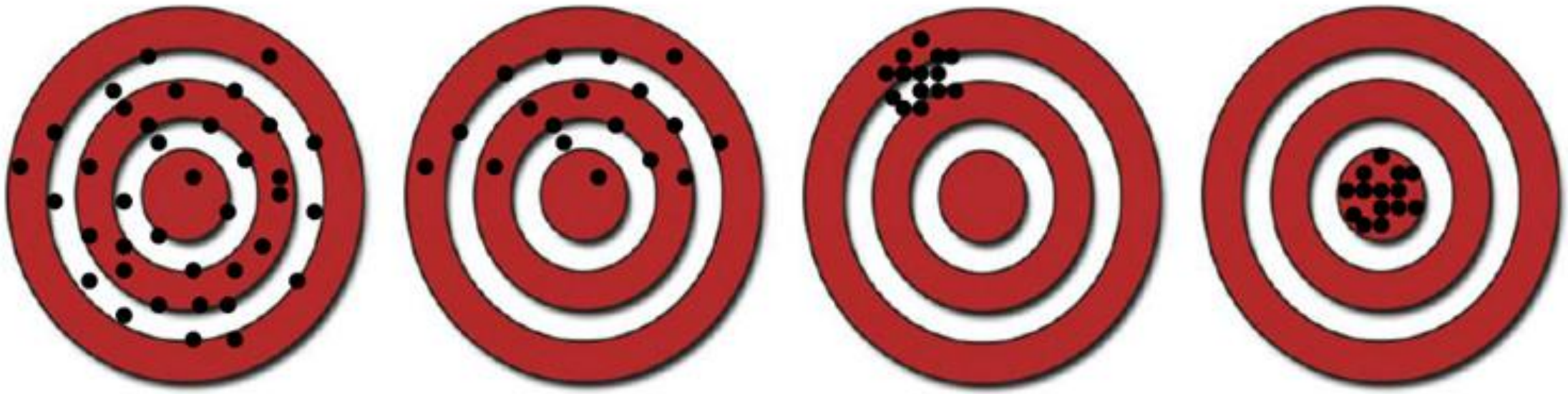
Selection bias

Information bias

Confounding

Statistician's expertise

Epidemiologist's expertise



Types of bias

Selection bias

Information bias

(misclassification bias)

Protopathic bias

(reverse causation bias)

Immortal-time bias

Confounding

Types of bias

Selection bias

Information bias

(misclassification bias)

Protopathic bias

(reverse causation bias)

Immortal-time bias

Confounding

Selection bias

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

Women with vague symptoms of DVT has higher likelihood of getting admitted for tests if using oral contraceptives.

Mothers of children with malformations are more likely to participate in study on use of drugs during pregnancy if they have thought about a given drug they have been using.

Information bias

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

Differentiated

Non-differentiated

Information bias (differentiated)

If the classification of exposure depends on whether the patient has an outcome (or vice-versa)

Mothers of children with malformations will be better at recalling information on drug use during pregnancy than women with children without malformations.

Information bias (non-differentiated)

General misclassification of exposure, independent of outcome status or other variables.

Will always infer a bias towards the null (i.e. no difference).

In a study of the risk of brain hemorrhage associated with use of platelet inhibitors, the classification of use/non-use is not 100% correct, as the algorithm does not capture patients stopping before having used a full package of tablets.

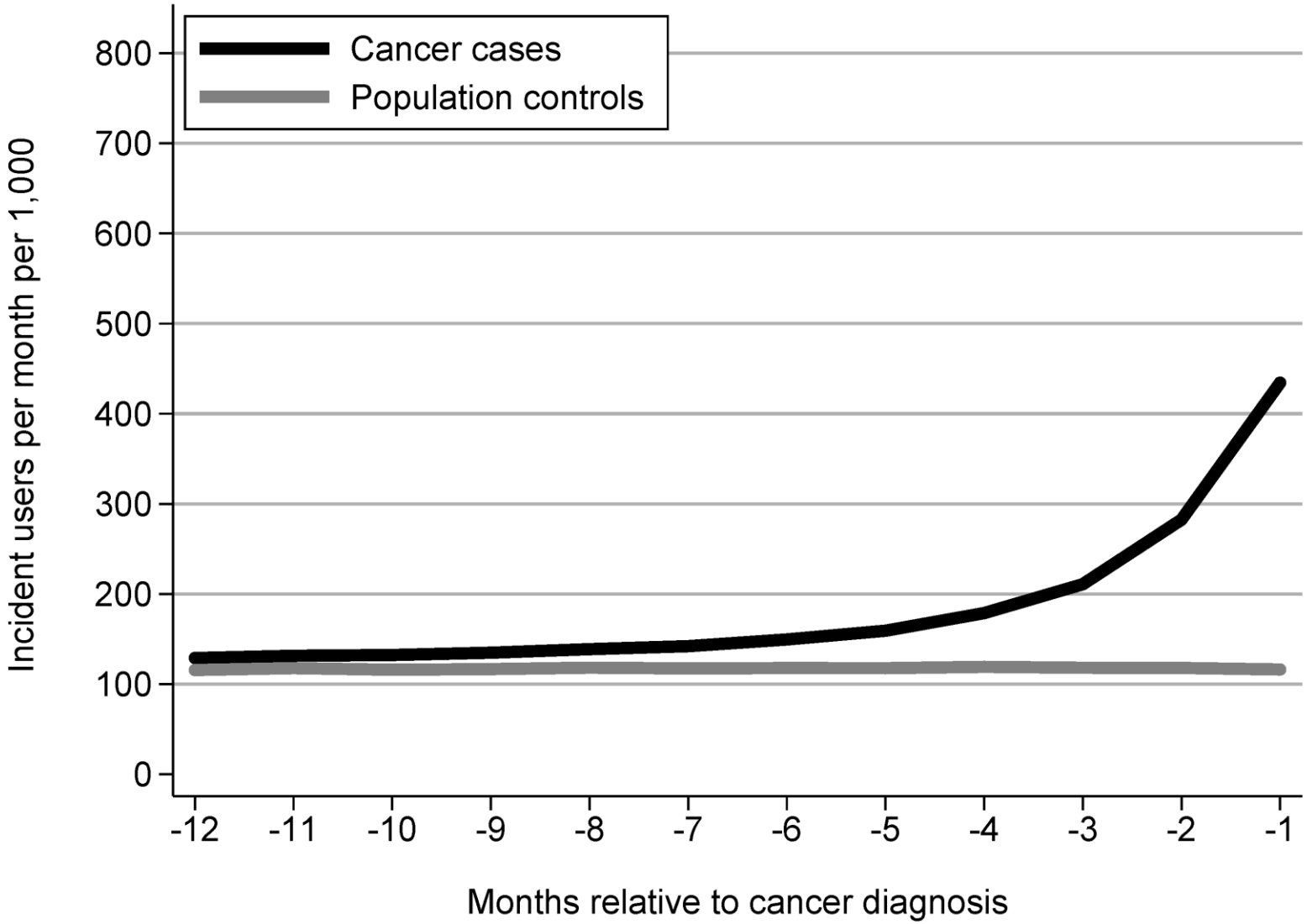
One year's worth of prescription data is corrupt…

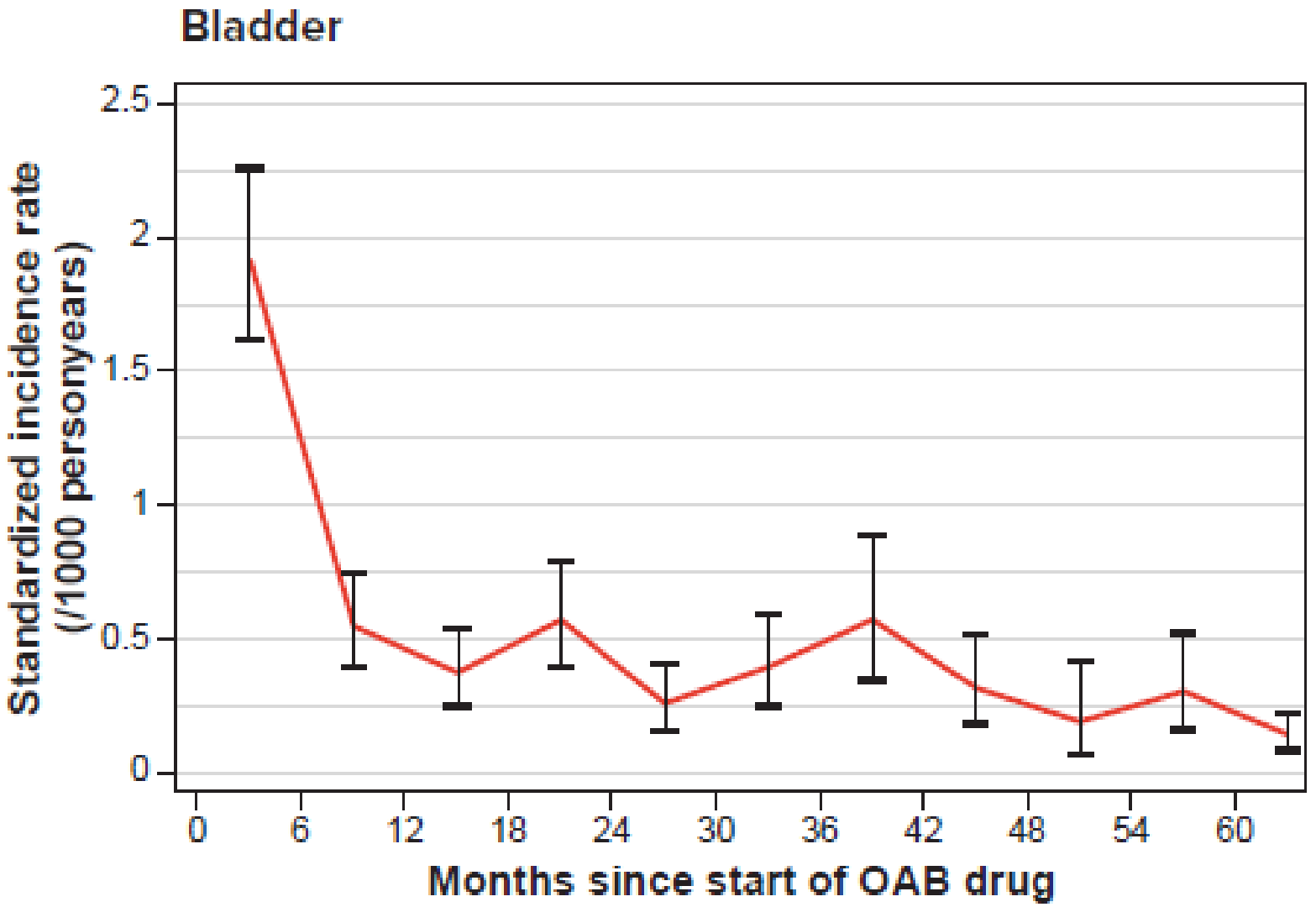
Protopathic bias

(reverse-causation bias)

A mixture (reversal) of the cause and effect, e.g. if the drug is given for an early (not yet recognized or recorded) disease.

In a study of the association between use of valproic acid (antiepileptic) and risk of cancer, you find an increased risk of brain cancer. This is caused by valproic acid prescribed due to epilepsi as an early marker of brain cancer.


Cancer cases
Population controls
800
700
600
500
400
300
200
100
0
Incident users per month per 1,000
-12
-11
-10
-9
-8
-7
-6
-5
-4
-3
-2
-1
Months relative to cancer diagnosis


Bladder
Standardized incidence rate
(/1000 personyears)
2.5
2
1.5
1
0.5
0
0
6
12
18
24
30
36
42
48
54
60
Months since start of OAB drug

Immortal-time bias

(the epidemiologist messed up-bias)

Survival in Academy Award–Winning Actors and Actresses

Donald A. Redelmeier, MD, and Sheldon M. Singh, BSc

Background: Social status is an important predictor of poor health. Most studies of this issue have focused on the lower echelons of society.

Objective: To determine whether the increase in status from winning an academy award is associated with long-term mortality among actors and actresses.

Design: Retrospective cohort analysis.

Setting: Academy of Motion Picture Arts and Sciences.

Participants: All actors and actresses ever nominated for an academy award in a leading or a supporting role were identified ($n = 762$). For each, another cast member of the same sex who was in the same film and was born in the same era was identified ($n = 887$).

Measurements: Life expectancy and all-cause mortality rates.

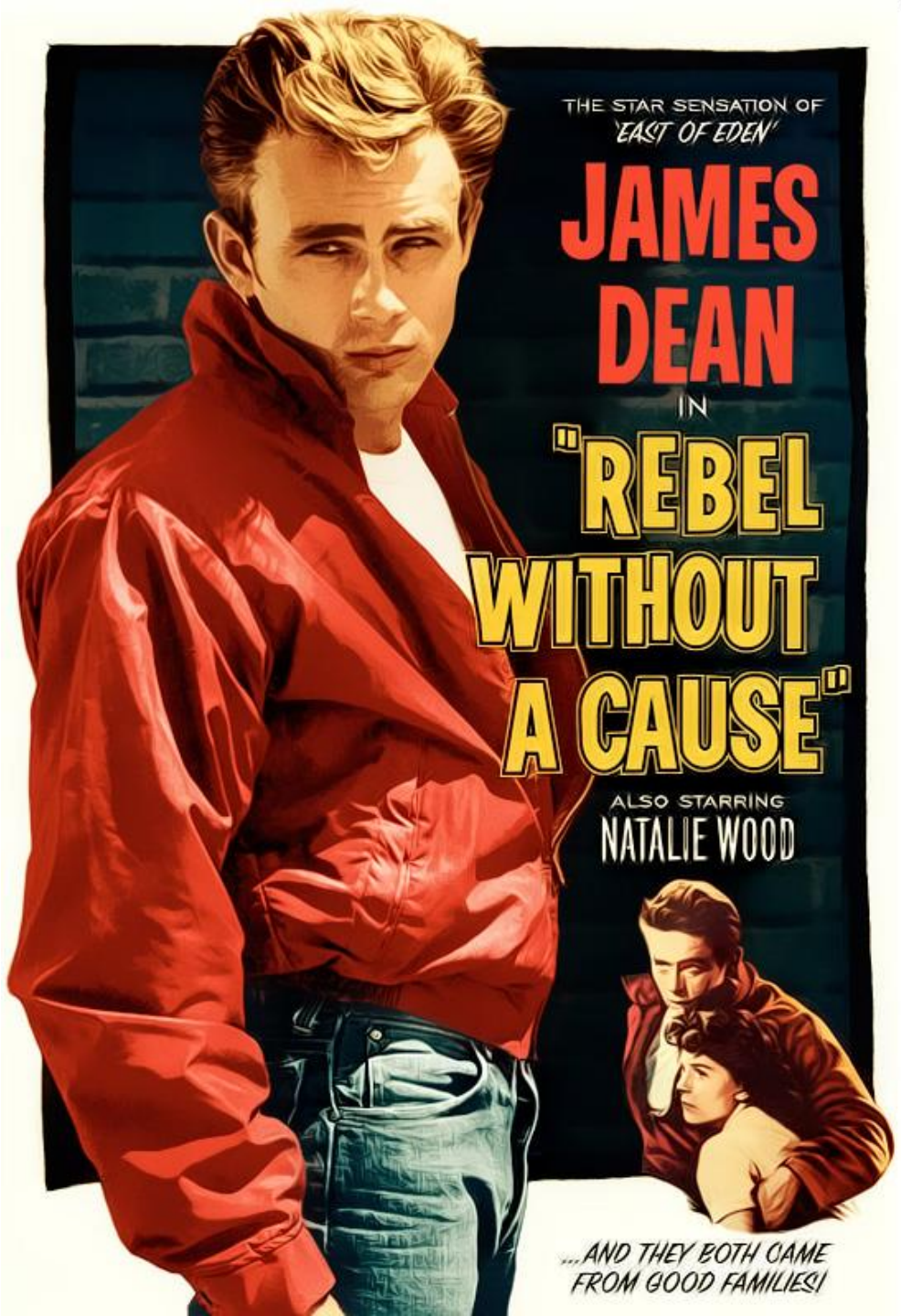
Results: All 1649 performers were analyzed; the median duration of follow-up time from birth was 66 years, and 772 deaths occurred (primarily from ischemic heart disease and malignant disease). Life expectancy was 3.9 years longer for Academy Award winners than for other, less recognized performers (79.7 vs. 75.8 years; $P = 0.003$). This difference was equal to a 28% relative reduction in death rates (95% CI, 10% to 42%). Adjustment for birth year, sex, and ethnicity yielded similar results, as did adjustments for birth country, possible name change, age at release of first film, and total films in career. Additional wins were associated with a 22% relative reduction in death rates (CI, 5% to 35%), whereas additional films and additional nominations were not associated with a significant reduction in death rates.

Conclusion: The association of high status with increased longevity that prevails in the public also extends to celebrities, contributes to a large survival advantage, and is partially explained by factors related to success.

Ann Intern Med. 2001;134:955-962. www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

See editorial comment on pp 1001-1003.



Starring

James Dean

Natalie Wood

Sal Mineo

All three very talented

All three died at a young age

All three nominated for an Oscar

Neither of them got an Oscar

Christopher Plummer, born 1929,
Won his first Oscar in 2012
(nominated for the first time in 2010)

Time already survived
is per definition ”immortal”!

Inhaled Corticosteroids and the Risk of Mortality and Readmission In Elderly Patients with Chronic Obstructive Pulmonary Disease

DON D. SIN and JACK V. TU

The Institute for Clinical Evaluative Sciences (ICES) and The Department of Medicine, Sunnybrook and Women's College Health Science Center, University of Toronto, Toronto, Ontario; and Department of Medicine, University of Alberta, Alberta, Canada

There is considerable controversy concerning the utility of inhaled corticosteroids for the long-term treatment of patients with COPD. Recent studies have suggested that although inhaled corticosteroids do not alter the rate of decline in lung function, they may reduce airway hyperresponsiveness, decrease the frequency of exacerbations, and slow the rate of decline in the patients' health status. The relationship between inhaled corticosteroids and subsequent risk of hospitalization or mortality remains unknown. We therefore conducted a population-based cohort study using administrative databases in Ontario, Canada (n = 22,620) to determine the association between inhaled corticosteroid therapy and the combined risk of repeat hospitalization and all-cause mortality in elderly patients with COPD. Patients who received inhaled corticosteroid therapy postdischarge (within 90 d) had 24% fewer repeat hospitalizations for COPD (95% confidence interval [CI], 22 to 35%) and were 29% less likely to experience mortality (95% CI, 22 to 35%) during 1 yr of follow-up after adjustment for various confounding factors. This cohort study has suggested that inhaled corticosteroid therapy is associated with reduced COPD-related morbidity and mortality in elderly patients. Although not definitive, because of the observational nature of these findings, these data provide a compelling rationale for a large randomized trial to determine the effect of inhaled corticosteroids on COPD-related morbidity and mortality.

Keywords: chronic obstructive pulmonary disease; inhaled corticoste

is generally precluded on the basis of significant systemic toxicity (6). In contrast, inhaled corticosteroids appear to have a more favorable toxicity profile, making it an attractive alternative to oral preparations (7). However, there remains considerable controversy concerning their utility for the chronic management of COPD (8, 9).

Previous studies have shown that inhaled corticosteroids do not decelerate the rate of decline in expiratory flow volumes over time in patients with mild to moderate COPD (10, 11). However, a recent study has suggested that inhaled corticosteroids may slow the rate of decline in (disease-specific) health status of patients and reduce the risk of clinical exacerbations (12). Another study has suggested that inhaled corticosteroids may attenuate airway hyperresponsiveness and also reduce clinical symptoms of COPD, including dyspnea and cough (13). Because these clinical and physiologic markers are also associated with COPD outcomes, inhaled corticosteroids might be expected to decrease COPD-related hospitalizations and mortality.

One approach to ascertaining these outcomes is to use a large population-based cohort focusing in on patients at a very high risk of such events (14, 15). We therefore conducted a large observational study to determine the relationship between use of inhaled corticosteroids and rate of repeat hospitalization and mortality in elderly patients with COPD re-

22,260 patients are followed for a year after discharge following a COPD exacerbation.

Divided into users and non-users of inhaled steroid based on whether they fill an prescription within 90 days after discharge.

Main finding

Mortality reduced by 29% (HR 0.71, 0.65-0.78)

Readmission reduced by 24% (HR 0.76, 0.71-0.80)

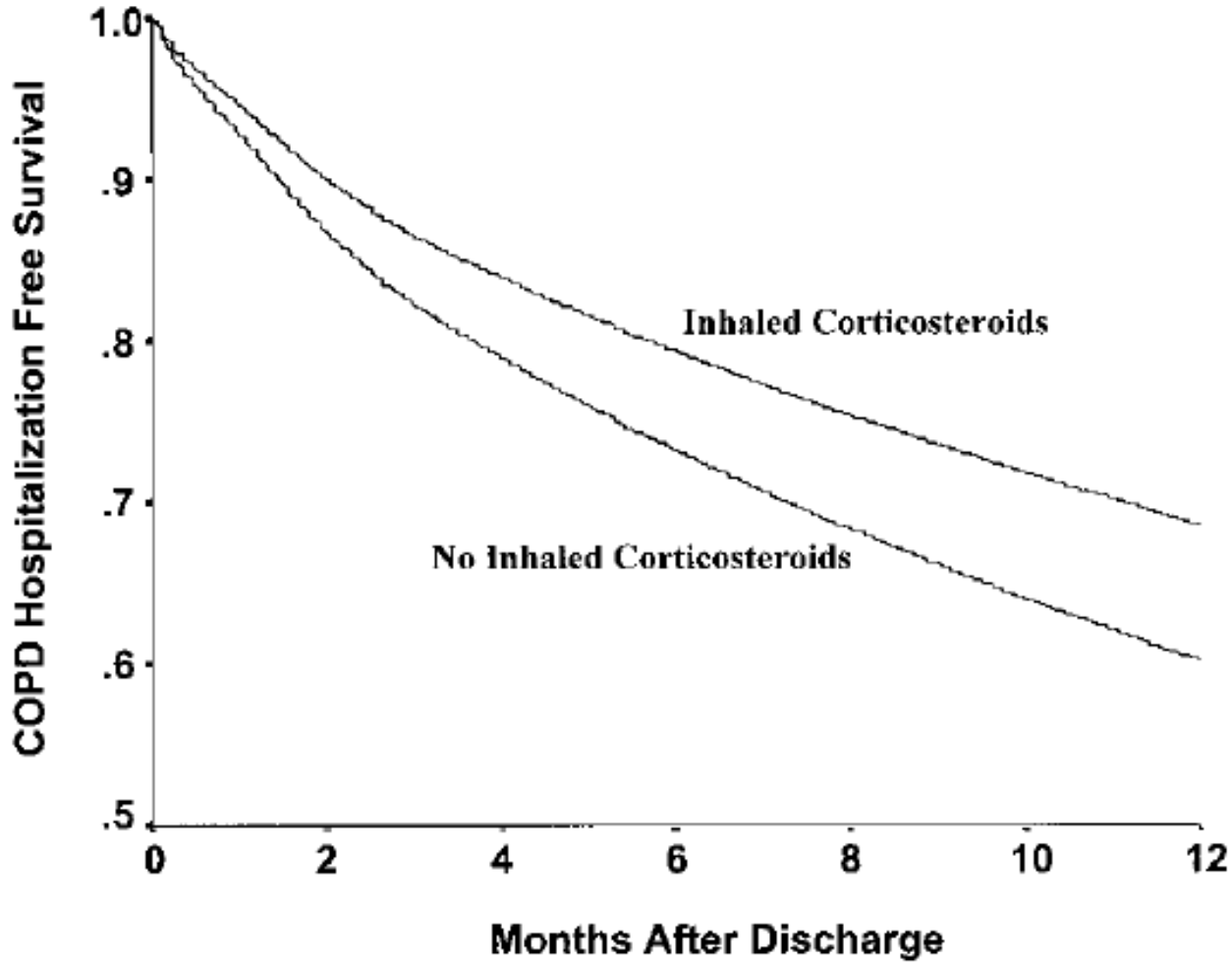


Figure 1. Adjusted probability of hospitalization-free survival in patients with chronic obstructive pulmonary disease who did and did not receive inhaled corticosteroids postdischarge (within 90 d of discharge).

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; 16: 241–249
Published online 25 January 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1357

ORIGINAL REPORT

Immortal time bias in observational studies of drug effects†

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[2] *Departments of Epidemiology and Biostatistics and of Medicine, McGill University, Montreal, Canada*

SUMMARY

Purpose Recent observational studies suggest that various drugs are remarkably effective at reducing morbidity and mortality. These cohort studies used a flawed approach to design and data analysis which can lead to immortal time bias. We describe the bias from 20 of these studies and illustrate it by showing that unrelated drugs can be made to appear effective at treating cardiovascular disease (CVD).

Methods The illustration used a cohort of 3315 patients, with chronic obstructive pulmonary disease (COPD), identified from the Saskatchewan Health databases, hospitalised for CVD and followed for up to a year. We used the biased approach to assess the effect of two medications, namely gastrointestinal drugs (GID) and inhaled beta-agonists (IBA), both unknown to be effective in CVD, on the risk of all-cause mortality. We also estimated these effects using the proper person-time approach.

Results Using the inappropriate approach, the rates ratios of all-cause death were 0.73 (95%CI: 0.57–0.93), with IBA and 0.78 (95%CI: 0.61–0.99), with GID. These rate ratios became 0.98 (95%CI: 0.77–1.25) and 0.94 (95%CI: 0.73–1.20), respectively, with the proper person-time analysis.

Conclusions Several recent observational studies used a flawed approach to design and data analysis, leading to immortal time bias, which can generate an illusion of treatment effectiveness. Observational studies, with surprising beneficial drug effects should be re-assessed to account for this source of bias.

KEY WORDS — biases; cohort studies; drug effectiveness; databases; epidemiology

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Practice of Epidemiology

Survival Bias Associated with Time-to-Treatment Initiation in Drug Effectiveness Evaluation: A Comparison of Methods

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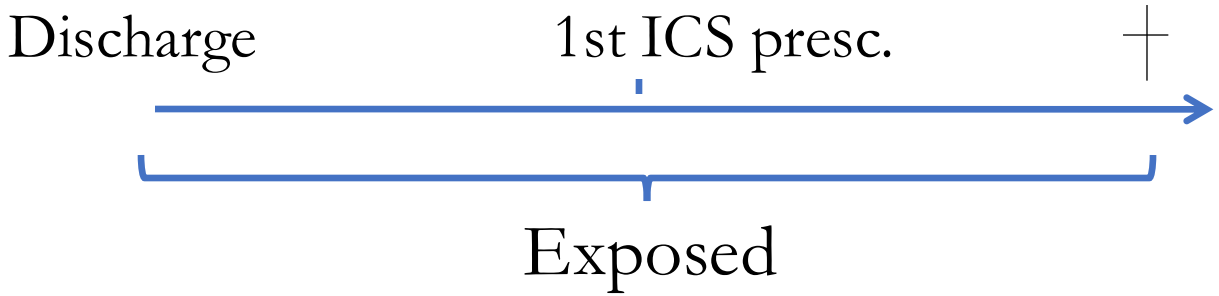
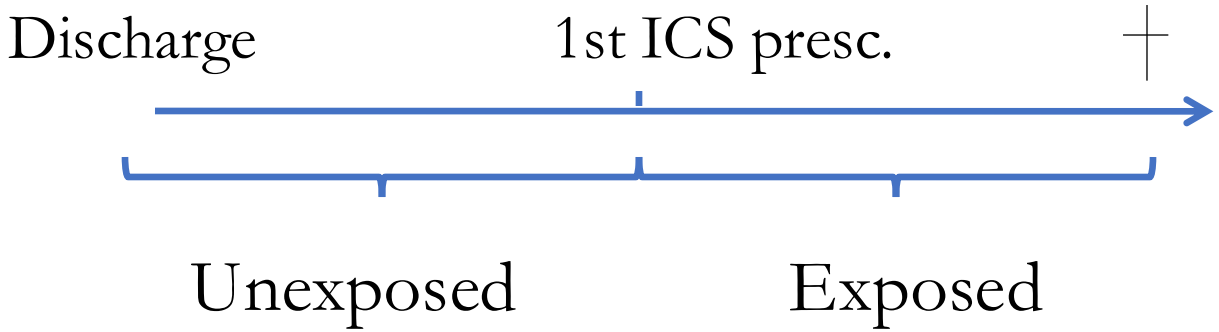
The authors compared five methods of studying survival bias associated with time-to-treatment initiation in a drug effectiveness study using medical administrative databases (1996–2002) from Quebec, Canada. The first two methods illustrated how survival bias could be introduced. Three additional methods were considered to control for this bias. Methods were compared in the context of evaluating statins for secondary prevention in elderly patients post-acute myocardial infarction who initiated statins within 90 days after discharge and those who did not. Method 1 that classified patients into users and nonusers at discharge resulted in an overestimation of the benefit (38% relative risk reduction at 1 year). In method 2, following users from the time of the first prescription and nonusers from a randomly selected time between 0 and 90 days attenuated the effect toward the null (10% relative risk reduction). Method 3 controlled for survival bias by following patients from the end of the 90-day time window; however, it suffered a major loss of statistical efficiency and precision. Method 4 matched prescription time distribution between users and nonusers at cohort entry. Method 5 used a time-dependent variable for treatment initiation. Methods 4 and 5 better controlled for survival bias and yielded similar results, suggesting a 20% risk reduction of recurrent myocardial infarction or death events.

Immortal time

Wrong:



Correct:



Never use a crystal ball!

Published by Oxford University Press on behalf of the International Epidemiological Association

International Journal of Epidemiology 2013;**42**:1486–1496
doi:10.1093/ije/dyt168

Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause

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Accepted 22 July 2013

Background Sun exposure is the single most important risk factor for skin cancer, but sun exposure may also have beneficial effects on health. We tested the hypothesis that individuals with skin cancer (non-melanoma skin cancer and cutaneous malignant melanoma) have less myocardial infarction, hip fracture and death from any cause, compared with general population controls.

Methods We examined the entire Danish population above age 40 years from 1980 through 2006, comprising 4.4 million individuals. Diagnoses of non-melanoma skin cancer ($n = 129\,206$), cutaneous malignant melanoma ($n = 22107$), myocardial infarction ($n = 327\,856$), hip fracture ($n = 129\,419$), and deaths from any cause ($n = 1\,629\,519$) were drawn from national registries.

Results In individuals with vs without non-melanoma skin cancer, multifactorially adjusted odds ratios were 0.96 (95% confidence interval: 0.94–0.98) for myocardial infarction and 1.15 (1.12–1.18) for hip

Immortal-time bias

Always in cohort studies

Signal too good (strong) to be true

When the effect manifests too soon

You will have used a crystal ball

When ”groups” and not
”status” are analysed

Confounding (and PS!)

Random variation

Systematic error (Bias)

Selection bias

Information bias

Confounding

Statistician's expertise

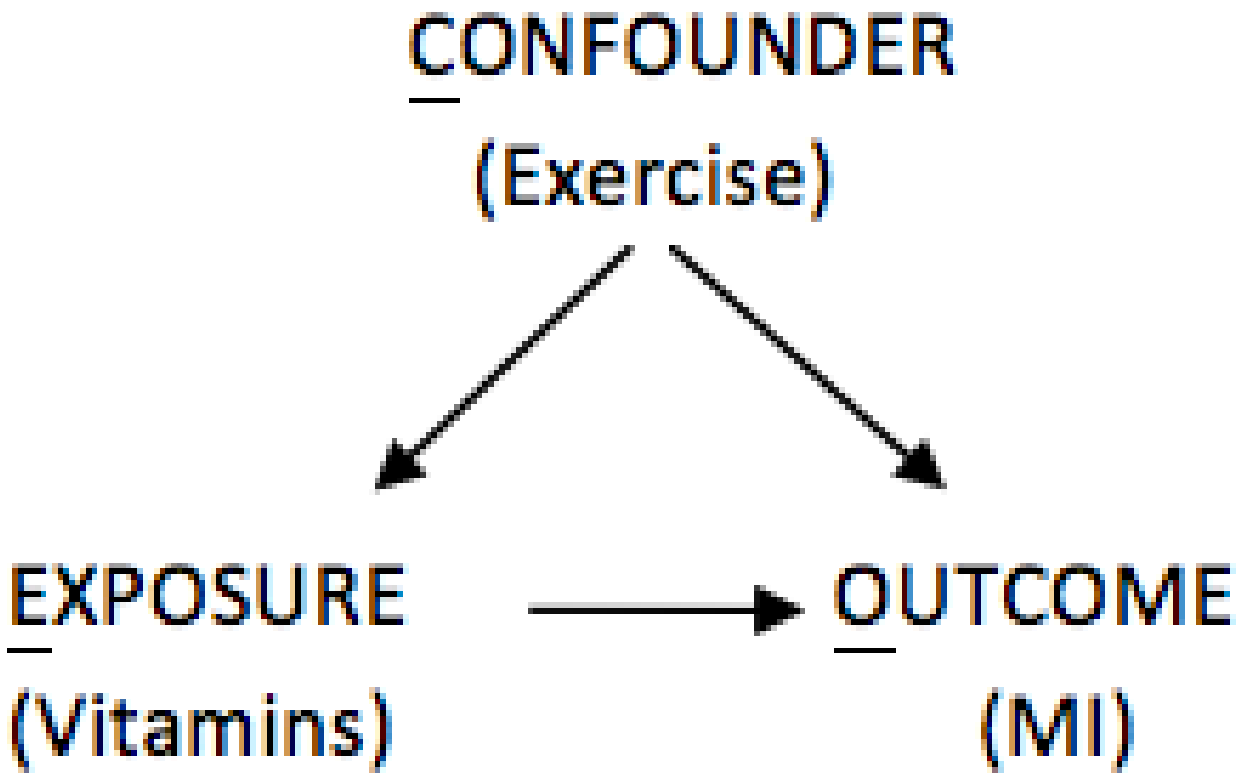
Epidemiologist's expertise

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")

Hypothesis

Does use of thiazides lead to an increased risk of upper gastrointestinal bleeding?

Potential confounders?

Confounder control

DESIGN	ANALYSIS
Randomization	Stratification
Cross-over	Multivariat analysis
Restriction	Propensity score (PS)
Matching	
Self-controlled	

Randomization

?

Corrects unknown and unmeasured confoudners

Ressource demanding

Unethical (re safety issues)

Not efficient in small trials

”Gold standard” for assessing intended effects

Cross-over

?

Ultimate confounder control

Corrects unknown and unmeasured confoudners

Ressource demanding

Only useful with transient effects

Restriction

?

To restrictive = limited statistical power

To restrictive = Lack of representativity

(Could be implemented in analysis)

Increasing Levels of Restriction in Pharmacoepidemiologic Database Studies of Elderly and Comparison With Randomized Trial Results

Sebastian Schneeweiss, MD, ScD, Amanda R. Patrick, MS,* Til Stürmer, MD, MPH,* M. Alan Brookhart, PhD,* Jerry Avorn, MD,* Malcolm Maclure, ScD,* Kenneth J. Rothman, DMD, DrPH,† and Robert J. Glynn, PhD, ScD**

Background: The goal of restricting study populations is to make patients more homogeneous regarding potential confounding factors and treatment effects and thereby achieve less biased effect estimates.

Objectives: This article describes increasing levels of restrictions for use in pharmacoepidemiology and examines to what extent they change rate ratio estimates and reduce bias in a study of statin treatment and 1-year mortality.

Methods: The study cohort was drawn from a population of seniors age 65 years and older enrolled in both Medicare and the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) between 1995 and 2002. We identified all users of statins during the study period and assessed the time until death within 1 year. The following progressive restrictions were applied: (1) study incident drug users only, (2) choose a comparison group most similar to the intervention group, (3) exclude patients with contraindications, (4) exclude patients with low adherence, and (5) restrict to specific high-risk/low-risk subgroups represented in randomized trails (RCTs).

Results: The basic cohort comprised 122,406 statin users, who were on average 78 years old and predominantly white (93%) and showed effect size changed little. The final estimate is similar to that obtained as a pooled estimate of 3 pravastatin RCTs in patients age 65 years and older. We argue that restrictions 1 through 4 compromised generalizability little.

Conclusions: In our example of a large database study, restricting to incident drug users, similar comparison groups, patients without contraindication, and to adherent patients was a practical strategy, which limited the effect of confounding, as these approaches yield results closer to those seen in RCTs.

Key Words: pharmacoepidemiology, confounding, restriction, methods, statins

(*Med Care* 2007;45: S131–S142)

Results from pharmacoepidemiologic research often have immediate and far-reaching clinical, regulatory, and economic implications. Consequently, practitioners and policymakers must consider carefully whether any association between use of a prescription drug and health outcomes is causal. Al-

Confounder control

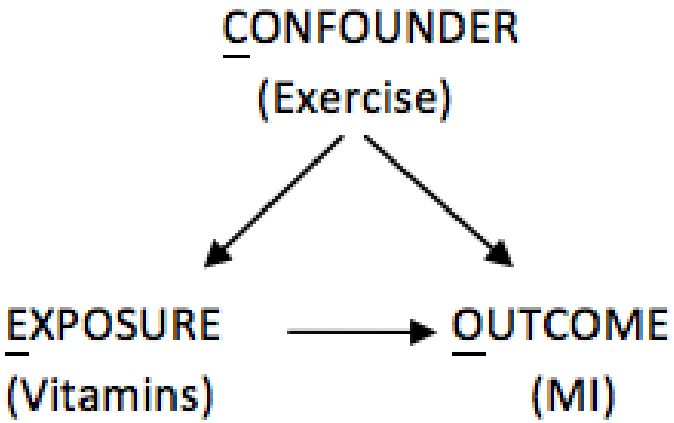
DESIGN	ANALYSIS
Randomization	Stratification
Cross-over	Multivariat analysis
Restriction	Propensity score (PS)
Matching	
Self-controlled	

Stratification I

All (n=3000)	Individuals	Outcomes	Risk	RR
Non-user	2500	410	16.4%	1.0 (ref.)
User	500	180	36.0%	2.20

Men (n=2000)	Individuals	Outcomes	Risk	RR
Non-user	1600	320	20.0%	1.0 (ref.)
User	400	160	40.0%	2.00

Women (n=1000)	Individuals	Outcomes	Risk	RR
Non-user	900	90	10.0%	1.0 (ref.)
User	100	20	20.0%	2.00



Stratification II

Table 2. Subgroup analysis: association between metformin and CRC in subgroups of patients with given characteristics.

	Adjusted OR (95% CI)
Total	0.83 (0.68–1.00)
Men	0.96 (0.75–1.23)
Woman	0.66 (0.49–0.90)
Age <65 year	0.82 (0.55–1.22)
Age 65–79 year	0.77 (0.59–0.99)
Age >80 year	1.06 (0.68–1.63)
Nonconfounding antidibetics[2]	0.83 (0.67–1.03)
Marker of obesity	0.71 (0.47–1.08)
No marker of obesity	0.86 (0.69–1.07)
Marker of tobacco use	1.34 (0.74–2.41)
No marker of tobacco use	0.78 (0.63–0.95)
Marker of alcohol use	1.45 (0.60–3.53)
No marker of alcohol use	0.80 (0.66–0.98)

Multivariat analyse

Data is ”fitted” into a model (logistic regression, Cox regression, Poisson regression etc), to adjust for multiple variables at the same time

Can handle a large number of variables

Black box

”Small number” bias?

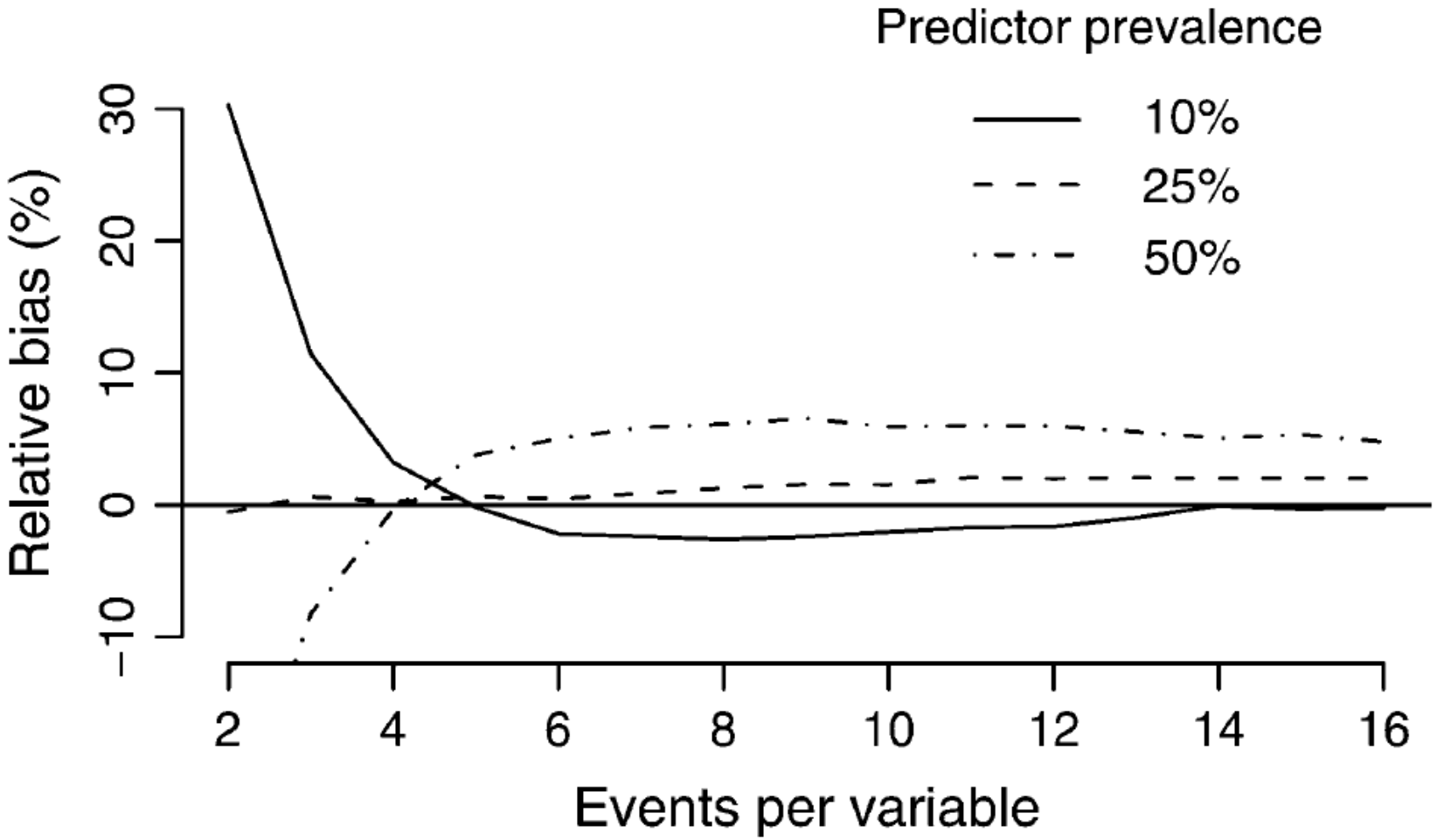
Warfarin and risk of SAH

	Cases	Controls	Crude OR *	Adjusted OR **
Never use	6,885	280,381	1.00 (ref.)	1.00 (ref.)
Ever use	393	10,728	1.53 (1.37-1.70)	1.36 (1.22-1.51)
Recency of use:				
Current use	284	6,282	1.90 (1.68-2.15)	1.70 (1.49-1.93)
Recent use	10	258	1.64 (0.87-3.09)	1.47 (0.77-2.77)
Past use	18	678	1.10 (0.69-1.76)	0.96 (0.60-1.54)
Non-use	81	3,510	0.97 (0.77-1.21)	0.85 (0.68-1.07)

* Adjusted for sex, age, and calendar time

** Further adjusted for 12 specific drugs, 8 specific diagnoses, income and education

”small number” bias



Confounding by indication

When the reason to prescribe a drug is a (strong) determinant for the outcome

”Study” of anticoagulant effect

Use of oral anticoagulants and risk of ‘deep vein thrombosis’ (DVT)

True relative risk (RR): <1 (perhaps 0.1?)

Adjusted for age and sex: RR = 27

+ other risk factors for DVT: RR = 4

Miettinen OS. The need for randomization in the study of intended effects. Stat Med 1983; 2: 267-71.

Miettinen's conclusion

Confounding by indication
can be very strong

Is not correctable in a
non-randomized design

Miettinen OS. The need for randomization in the study of intended effects. Stat Med 1983; 2: 267-71.

Confounding-by-indication variants (according to severity)

Indication associated with a risk factor for the outcome

(Statins -> fracture)

Part of the indication is a risk factor for the outcome

(Coxibs -> peptic ulcer bleeding)

Indication is a risk factor for the outcome

(Lithium -> suicide)

The drug is prescribed with the sole purpose of preventing the outcome

(Low-dose aspirin -> MI)

What about…

Table 1. Characteristics of Included Pregnancies

Characteristic	Methylphenidate Exposed (n = 222)	Random Sample (n = 10,000)
Maternal age, median (IQR), y	26 (22–30)	30 (27–34)
Maternal BMI, median (IQR)[a]	23.7 (20.8–28.7)	23.2 (21.0–26.6)
Maternal smoking status, n (%)		
Yes	113 (50.9)	1,512 (15.1)
No	102 (45.9)	8,303 (83.0)
Unknown	7 (3.2)	185 (1.8)
Maternal length of education, n (%)		
7–10 y	125 (56.3)	1,567 (15.7)
11–12 y	42 (18.9)	1,476 (14.8)
≥ 13 y	52 (23.4)	6,852 (68.5)
Unknown	3 (1.4)	105 (1.1)
Drug exposure, n (%)[b]		
Antipsychotics	20 (9.0)	33 (0.3)
Antidepressants	76 (34.2)	280 (2.8)
Anxiolytics	6 (2.7)	37 (0.4)
NSAIDs	14 (6.3)	324 (3.2)

Table 1. Characteristics of Included Pregnancies

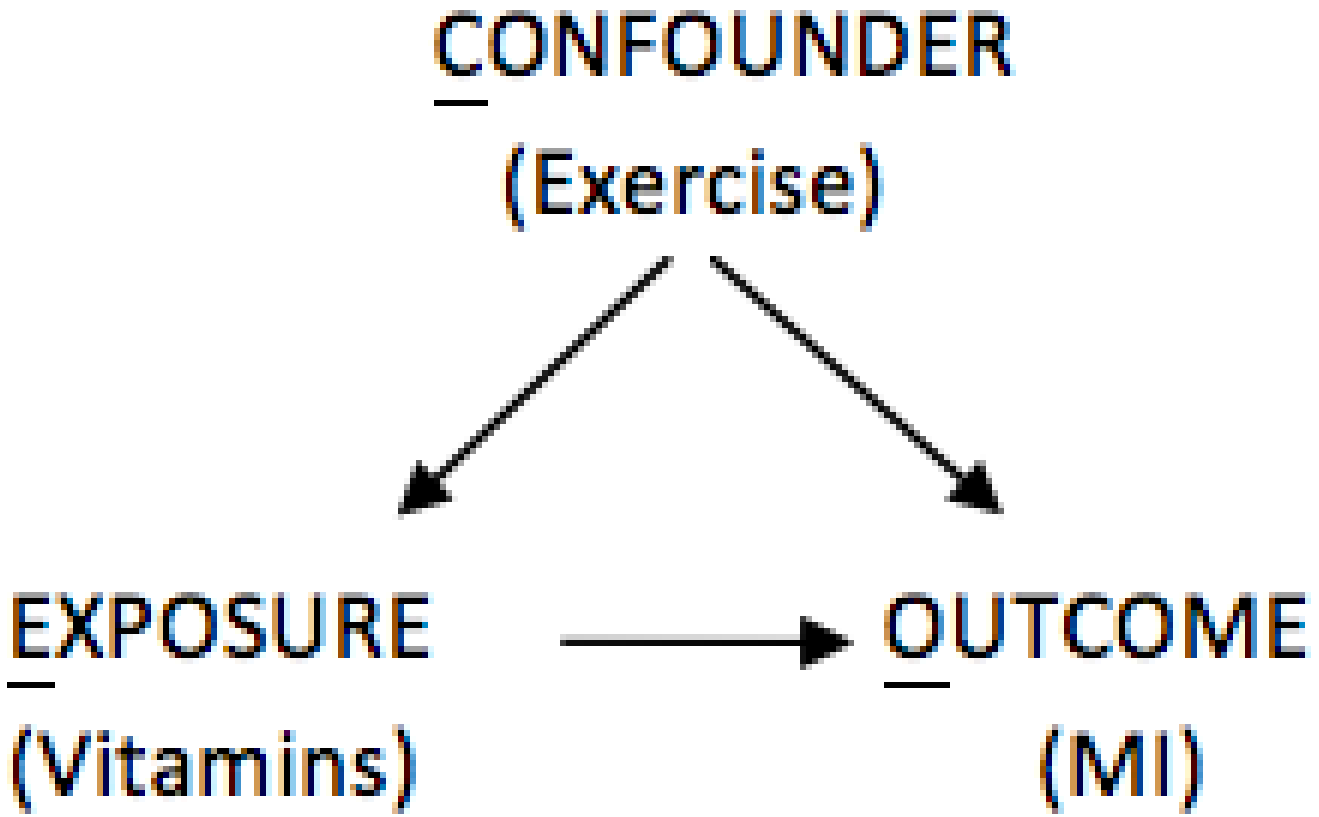
Characteristic	Methylphenidate Exposed (n = 222)	Unexposed (n = 2,220)	Random Sample (n = 10,000)
Maternal age, median (IQR), y	26 (22–30)	25 (22–30)	30 (27–34)
Maternal BMI, median (IQR)[a]	23.7 (20.8–28.7)	23.9 (20.9–28.1)	23.2 (21.0–26.6)
Maternal smoking status, n (%)			
Yes	113 (50.9)	1,100 (49.5)	1,512 (15.1)
No	102 (45.9)	1,035 (46.6)	8,303 (83.0)
Unknown	7 (3.2)	85 (3.8)	185 (1.8)
Maternal length of education, n (%)			
7–10 y	125 (56.3)	1,242 (55.9)	1,567 (15.7)
11–12 y	42 (18.9)	447 (20.1)	1,476 (14.8)
≥ 13 y	52 (23.4)	498 (22.4)	6,852 (68.5)
Unknown	3 (1.4)	33 (1.5)	105 (1.1)
Drug exposure, n (%)[b]			
Antipsychotics	20 (9.0)	139 (6.3)	33 (0.3)
Antidepressants	76 (34.2)	768 (34.6)	280 (2.8)
Anxiolytics	6 (2.7)	58 (2.6)	37 (0.4)
NSAIDs	14 (6.3)	139 (6.3)	324 (3.2)

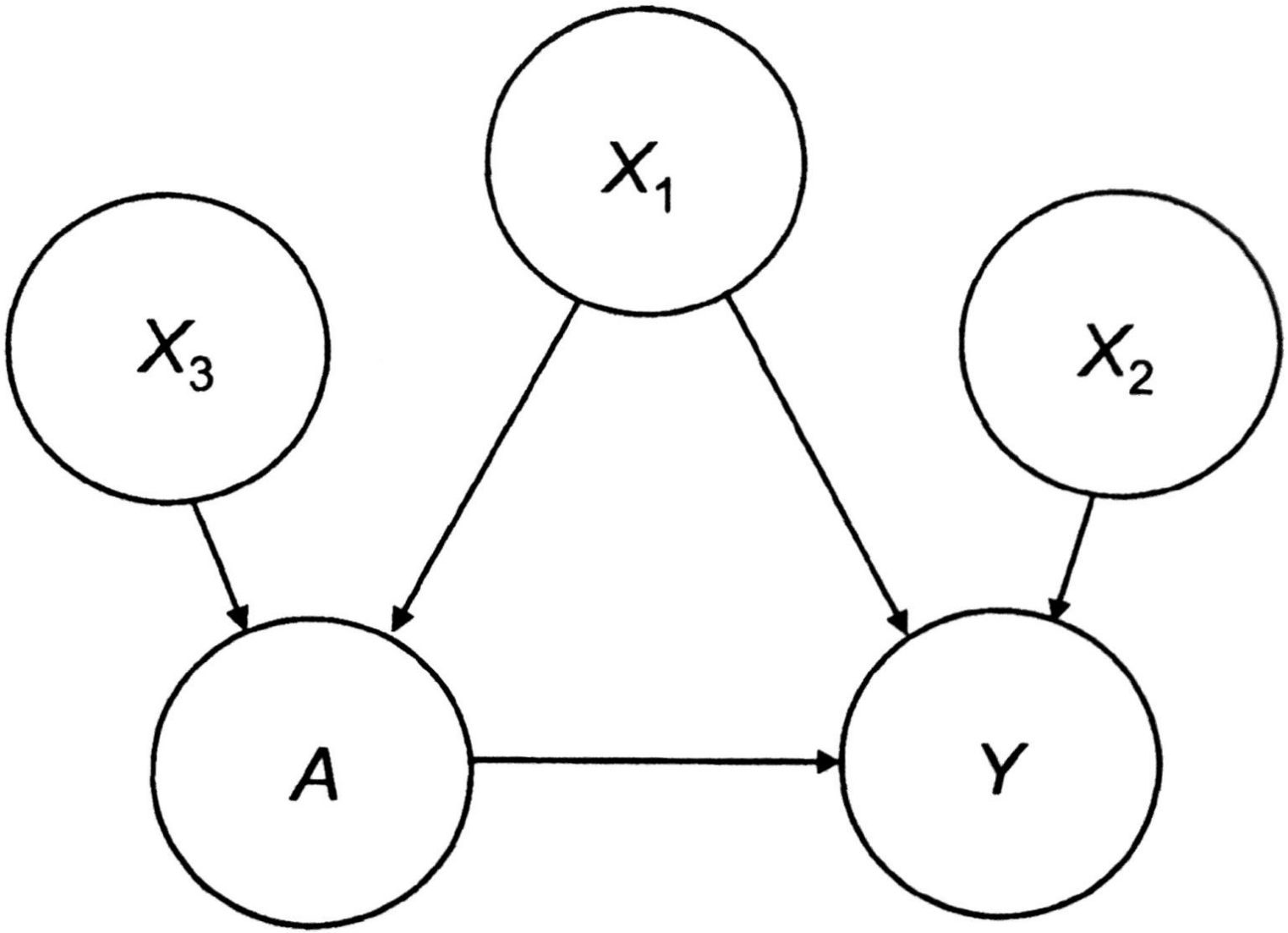
A propensity score (likelihood score)
is a value between 0 and 1 that
- given a specific set of covariates -
provides the likelihood of ~~something~~
being treated with
drug A over drug B

```
logit outcome exposure
covar1 covar2 covar3

logit exposure
covar1 covar2 covar3
predict ps
```

	ID	age	sex	smoking	obesity	NSAID	ps
1	1	45	Man	0	1	Yes	.3488717
2	2	86	Man	0	0	No	.2668857
3	3	32	Man	1	0	Yes	.1366463
4	4	94	Woman	1	1	No	.0285569
5	5	32	Woman	0	0	No	.8689333
6	6	46	Man	0	1	No	.3508549
7	7	97	Woman	1	1	No	.0711051
8	8	62	Man	0	0	Yes	.323368
9	9	64	Woman	1	1	No	.5551032
10	10	81	Woman	0	0	No	.875991


CONFOUNDER
(Exercise)
EXPOSURE
(Vitamins)
OUTCOME
(MI)



Brookhart et al., AJE 2006

Matching

Regression

Stratification

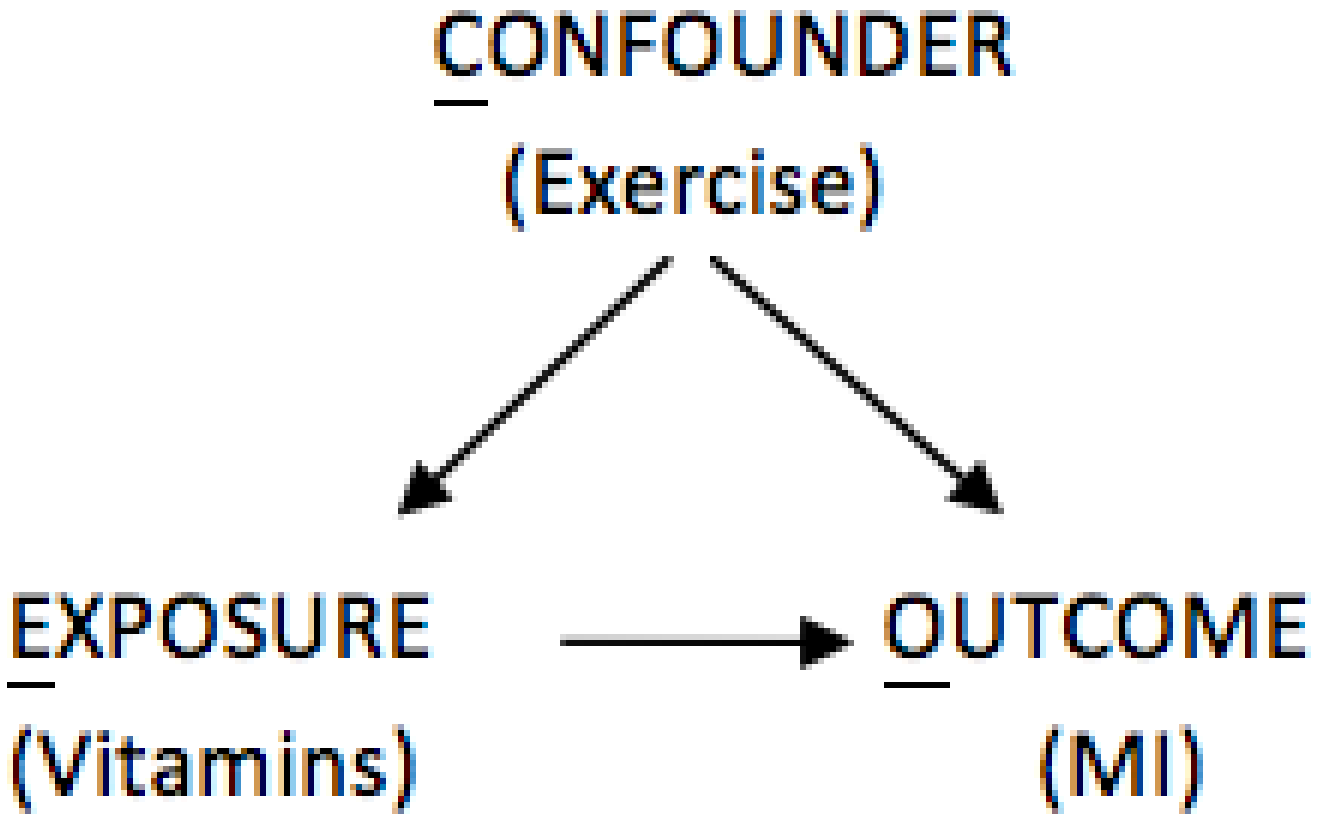
Weighthing

... combinations

See Stürmer et al., JIM 2014

Literature

Introduction to PS	**Glynn et al., BCPT 2005** **Stürmer et al., JIM 2014**
Choice of variables	**Brookhart et al., AJE 2006**
Comparison to other methods	**Stürmer et al., JCE 2005** **Cepeda et al., AJE 2003**
Trimming	**Stürmer et al., AJE 2010** **Kurth et al., AJE 2005**
Matching	**Rassen et al., PDS 2012**
High-dimensional PS	**Schneeweiss et al., Epidemiology 2009** **Hallas & Pottegård, BCPT 2017**
Adjusting'unmeasured confounding'	**Schneeweis et al., Epidemiology 2009**
Disease risk scores	**Glynn et al., PDS 2012**


CONFOUNDER
(Exercise)
EXPOSURE
(Vitamins)
OUTCOME
(MI)

Goodbye

Welcome

Introduction/Overview

Cohort design

Case-control design

Drug utilization

Exposure

Outcomes

Bias

Confounding

Goodbye

And future
bonus modules!

Suggested reading?

Anton Pottegård
@Pottegard

Must-read pharmacoepi papers!? 🤓

We are a group of pharmacoepi experts putting together a list of "top-25 papers you should read if you are an early-career pharmacoepidemiologist".

Can you give us a hand? What papers should we consider? More details below 👇 #epitwitter

4:12 PM · Mar 25, 2021 · Twitter Web App

30 pharmacoepidemiology must-reads

Anton Pottegård
Researching the rational use of drugs based on data on effects and side-effects of medicines. Professor of pharmacoepidemiology and clinical pharmacy at...

6 articles

September 2, 2021

LINK

Received: 11 October 2021 | Accepted: 29 October 2021

DOI: 10.1002/pds.5382

WILEY

LETTER TO THE EDITOR

Where to begin? Thirty must-read papers for newcomers to pharmacoepidemiology

LINK

Review Series: Core Concepts in Pharmacoepidemiology

Core concepts in pharmacoepidemiology: Validation of health outcomes of interest within real-world healthcare databases

Erica J. Weinstein, Mary Elizabeth Ritchey, Vincent Lo Re III

Pharmacoepidemiology and Drug Safety | First Published: 03 September 2022

Abstract | **Full text** | **PDF** | **References** | **Request permissions**

Core concepts in pharmacoepidemiology: Key biases arising in pharmacoepidemiologic studies

Emily K. Acton, Allison W. Willis, Sean Hennessy

Pharmacoepidemiology and Drug Safety | First Published: 10 October 2022

Abstract | **Full text** | **PDF** | **References** | **Request permissions**

Core concepts in pharmacoepidemiology: Violations of the positivity assumption in the causal analysis of observational data: Consequences and statistical approaches

Yaqian Zhu, Rebecca A. Hubbard, Jessica Chubak, Jason Roy, Nandita Mitra

Pharmacoepidemiology and Drug Safety | First Published: 10 August 2021

Abstract | **Full text** | **PDF** | **References** | **Request permissions**

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Dear PhD student: Who's got your ear? – Your supervisor? Or the bricks in the walls?

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Researching the rational use of drugs based on data on effects and side-effects
6 articles

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Just say no: A young researcher's thoughts on prioritizing projects and ideas

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Anton Pottegård
Professor at University of Southern Denmark
3 articles

Most scientific papers end with "This calls for more research"! As such, there is always another idea and another potential project. And as a young researcher, I have been

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