Use of self-controlled designs in pharmacoepidemiology

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Self-controlled designs, overview

1. Case-crossover and variants
    1. Case-crossover
    2. Case-time-control
    3. Case-case-time design
2. Self-controlled case series
3. Symmetry analysis
4. An empirical example

Crossover technique, Maclure 1991

- Confounders in the sex-MI association:
  - High age
  - High BMI
  - Depression
  - History of MI
  - Autonomic neuropathy
  - Atherosclerosis
  - Low physical activity
  - Diabetes
  - Hypertension (treatment)
  - ……
- ..And problems with recruitment and ascertainment of controls

Maclure M, Am J Epidemiol 1991

Case-Crossover study of sexual activity and MI

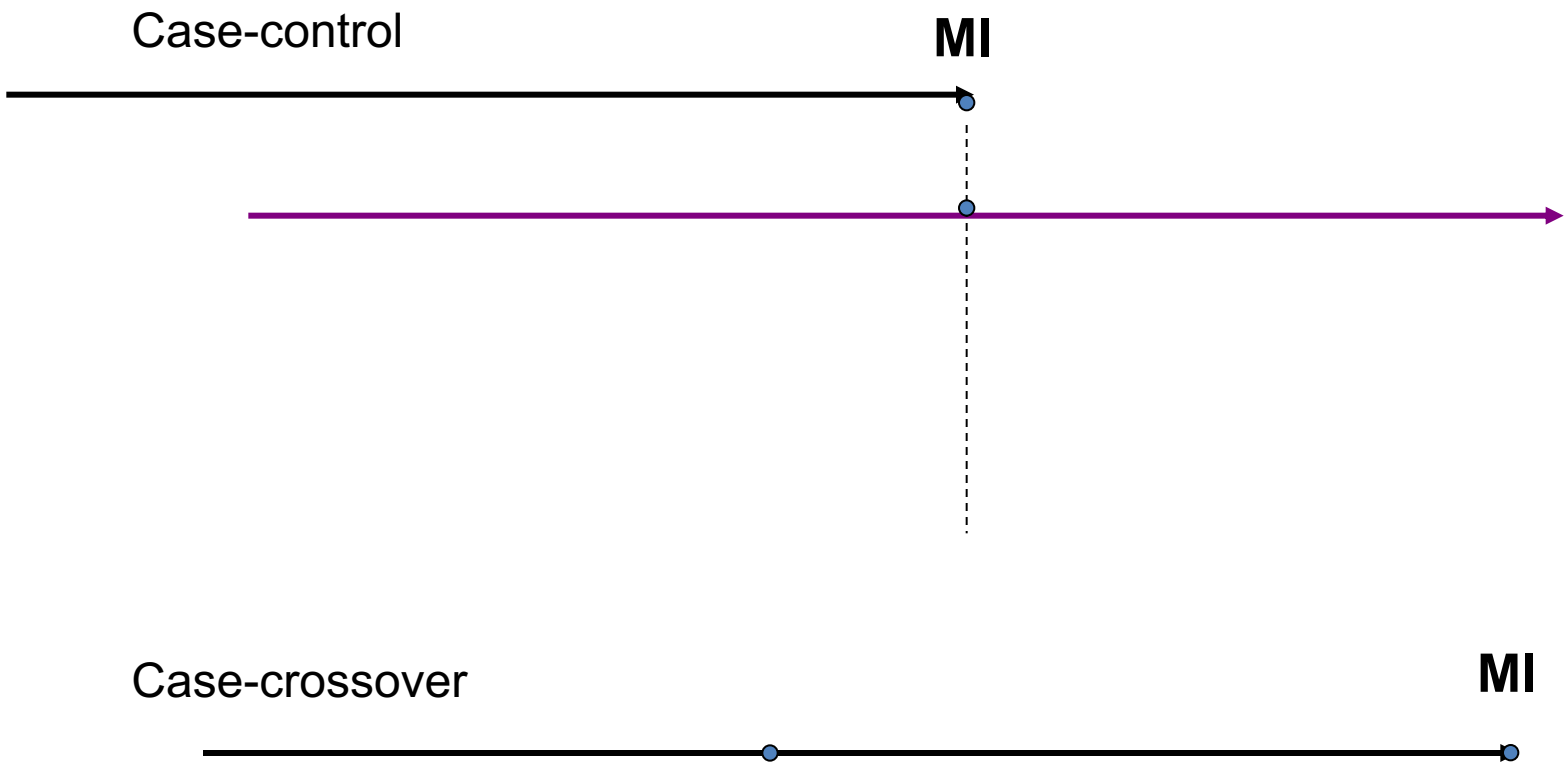
- Only persons with MI
- Two questions:
  - Were you engaged in SA when you had you MI?
  - Were you engaged in SA 24 (48) hours before you had your MI?
    - Usual frequency?

Exposure patterns

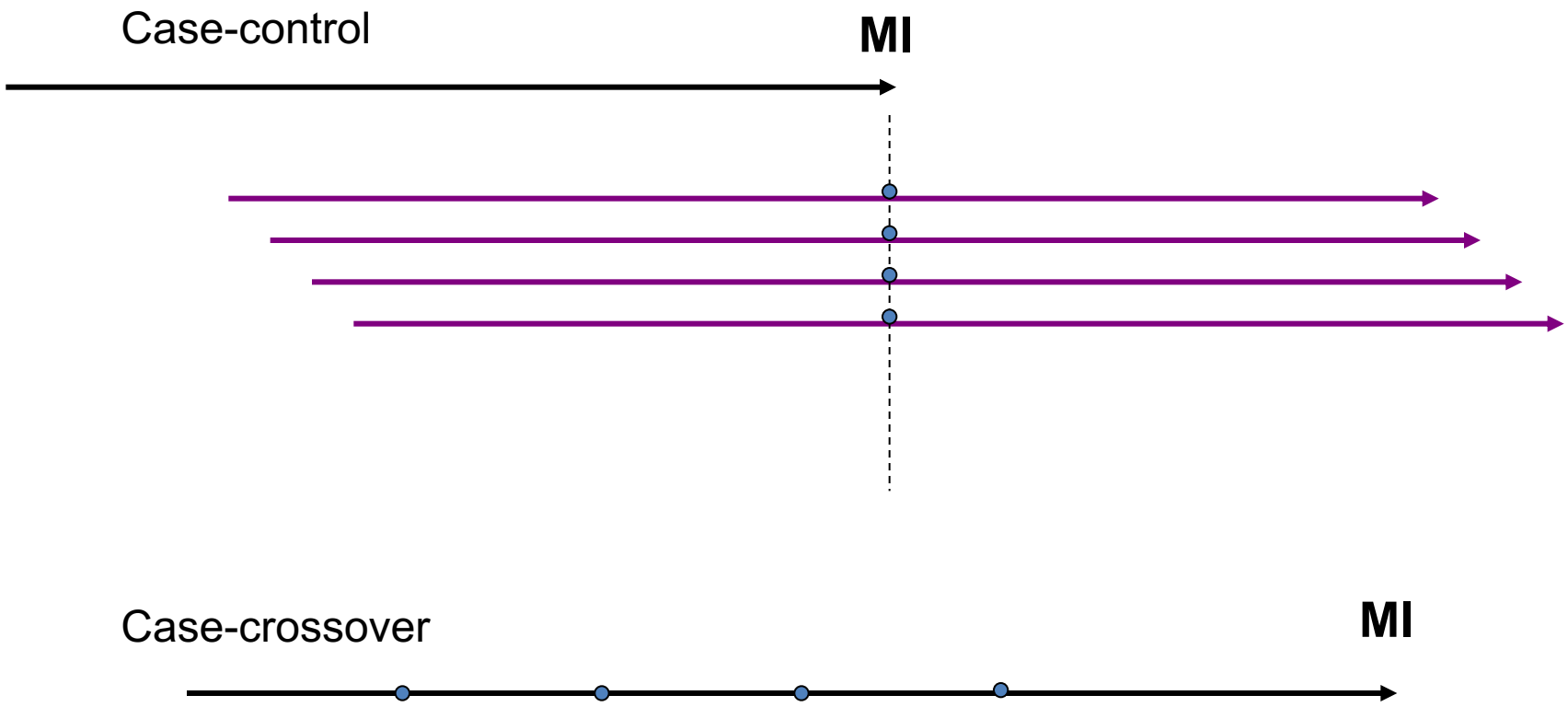
	Focal window	Reference window	Contribution
A	+	+	None
B	+	-	Denominator
C	-	+	Numerator
D	-	-	None

OR = B / C

Control sampling



Control sampling



Crossover-design, properties

- Can be viewed as a tightly matched case-control study
- Epidemiologist's version of the clinician's question "Did you do anything – for you - unusual before you became ill"
- Asks "why now" instead of "why me"
- Effectively adjusts for confounders that are stable over time
- Suitable to transient exposures with acute-onset effects
- Sensitive to confounders that are not stable over time
- Sensitive to trends in exposures

Exercise

- Design a quick casecrossover study to assess the association between fluoquinolones and tendon rupture.

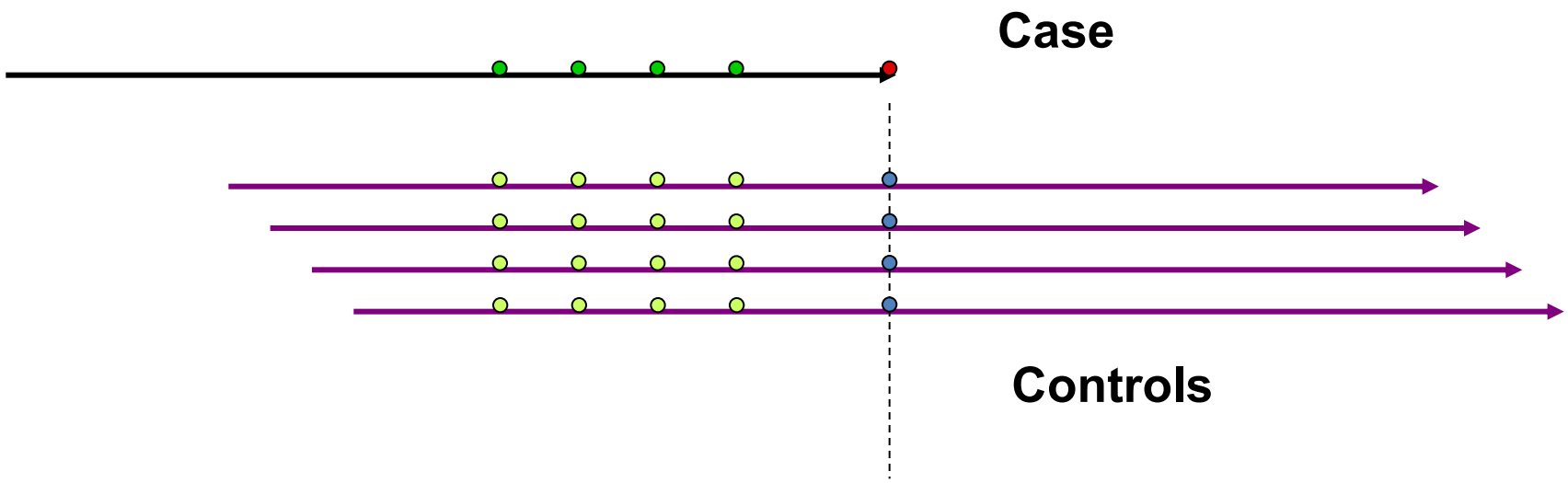
Exercise

- Discus what happens if the case-crossover design is applied to a drug that has been recently marketed

Case-time-control design

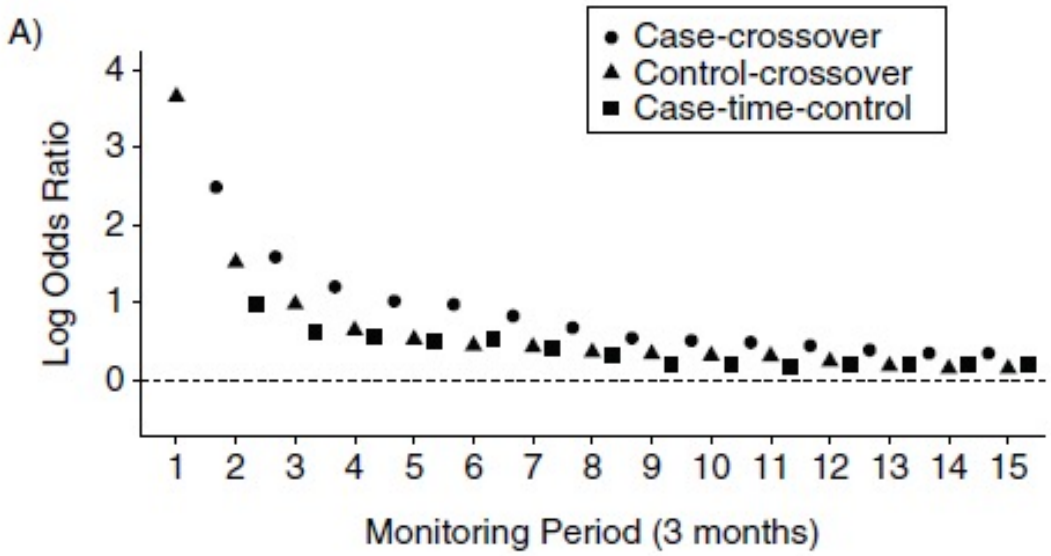
- Proposed by Suissa (1996)
- Crossover analyses performed
    - Cases
    - Non diseased controls
- Effect of trend measured in controls and used as reference

Adjustment for trend, Case-time-control design



Suissa, Epidemiology 1995.

Using control group against first-wave bias



Valdecoxib – MI association

Wang et al, AJE 2014

Interpretation of case-crossover estimate

TABLE 3. Hazard Ratios for Death and Rehospitalization for MI; Cox Proportional Hazards Analysis*

	Death			Re-MI		
Drug	No. of Events†	HR (95% CI)	*P*	No. of Events†	HR (95% CI)	*P*
Rofecoxib (n=3022)						
No use‡		1.00			1.00	
Any use	152	2.80 (2.41–3.25)	<0.0001	59	1.63 (1.27–2.10)	0.0001
Daily dose ≤25 mg	106	2.49 (2.11–2.94)	<0.0001	53	1.68 (1.30–2.17)	<0.0001
Daily dose >25 mg	46	5.26 (3.90–7.09)	<0.0001	6	1.27 (0.57–2.86)	0.56
Celecoxib (n=2489)						
No use‡		1.00			1.00	
Any use	112	2.57 (2.15–3.08)	<0.0001	42	1.50 (1.10–2.05)	0.01
Daily dose ≤200 mg	54	1.92 (1.52–2.43)	<0.0001	36	1.47 (1.03–2.09)	0.03
Daily dose >200 mg	58	4.69 (3.58–6.14)	<0.0001	6	1.64 (0.91–2.90)	0.10
Ibuprofen						
No use‡		1.00			1.00	
Any use	266	1.50 (1.36–1.67)	<0.0001	136	1.25 (1.07–1.46)	0.005
Daily dose ≤1200 mg	47	0.75 (0.61–0.92)	0.006	77	1.28 (1.03–1.60)	0.03
Daily dose >1200 mg	219	2.20 (1.95–2.48)	<0.0001	59	1.22 (0.99–1.51)	0.055
Diclofenac						
No use‡		1.00			1.00	
Any use	160	2.40 (2.09–2.80)	<0.0001	61	1.54 (1.23–1.93)	0.0002
Daily dose <100 mg	28	0.89 (0.66–1.20)	0.45	40	1.27 (0.92–1.76)	0.15
Daily dose ≥100 mg	132	4.44 (3.79–5.19)	<0.0001	21	1.89 (1.40–2.55)	<0.0001
Other NSAIDs						
No use‡		1.00			1.00	
Any use	348	1.29 (1.16–1.43)	<0.0001	14	1.27 (1.09–1.47)	0.002

Re-MI indicates rehospitalization for MI; HR, hazard ratio.
*Adjusted for age, gender, year of MI, concomitant medical treatment, socioeconomic status, and comorbidity.
†No. of events while having drug available for treatment.
‡Reference group.

TABLE 4. Odds Ratios for Death and Rehospitalization for MI: Conditional Logistic Regression Analysis by the Case-Crossover Design*

	Death			Re-MI		
Drug and Daily Dosage	OR	95% CI	*P*	OR	95% CI	*P*
Rofecoxib						
No use	1.00			1.00		
Any use	2.36	1.75–3.19	<0.0001	2.46	1.42–4.24	0.001
Daily dose ≤25 mg	1.96	1.43–2.69	<0.0001	2.37	1.35–4.16	0.003
Daily dose >25 mg	8.65	3.71–20.1	<0.0001	3.73	0.67–20.6	0.13
Celecoxib						
No use	1.00			1.00		
Any use	2.37	1.68–3.35	<0.0001	1.36	0.73–2.53	0.34
Daily dose ≤200 mg	1.97	1.33–2.93	0.001	1.01	0.50–2.02	0.98
Daily dose >200 mg	3.88	2.04–7.36	<0.0001	5.27	1.07–25.9	0.04
Ibuprofen						
No use	1.00			1.00		
Any use	1.05	0.88–1.24	0.61	1.32	1.02–1.72	0.04
Daily dose ≤1200 mg	0.57	0.45–0.74	<0.0001	1.41	0.95–2.08	0.08
Daily dose >1200 mg	1.65	1.33–2.04	<0.0001	1.26	0.89–1.78	0.19
Diclofenac						
No use	1.00			1.00		
Any use	1.59	1.28–1.98	<0.0001	1.67	1.15–2.42	0.007
Daily dose <100 mg	0.86	0.63–1.17	0.34	1.66	1.04–2.63	0.03
Daily dose ≥100 mg	2.82	2.08–3.83	<0.0001	1.69	0.96–2.98	0.07
Other NSAIDs						
No use	1.00			1.00		
Any use	1.14	0.93–1.39	0.20	1.07	0.77–1.48	0.70

Re–MI indicates rehospitalization for MI; OR, odds ratio.
*Case period 0–30 days before event and control periods 60–90 and 90–120 days before event.

Gislason 2006, Circulation

Yet another variant, case-case-time-control

ORIGINAL ARTICLE

Future Cases as Present Controls to Adjust for Exposure Trend Bias in Case-only Studies

Shirley Wang,[a] *Crystal Linkletter,*[a] *Malcolm Maclure,*[b,c] *David Dore,*[a,d] *Vincent Mor,*[a] *Stephen Buka,*[a] *and Gregory A. Wellenius*[a]

Abstract: Self-matched case-only studies (such as the case-crossover or self-controlled case-series method) control by design for time-invariant confounders (measured or unmeasured), but they do not control for confounders that vary with time. A bidirectional case-crossover design can be used to adjust for exposure-time trends. In pharmacoepidemiology, however, illness often influences future use of medications, making a bidirectional design problematic. Suissa's case-time-control design combines a case-crossover and case-control design, and adjusts for exposure-trend bias in the cases' self-controlled odds ratio by dividing that ratio by the corresponding self-controlled odds ratio in a concurrent matched control group. However, if not well matched, the control group may reintroduce selection bias. We propose a "case-case-time-control" that involves crossover analyses in cases and future-case controls. This person-time sampling strategy improves matching by restricting controls to future cases. We evaluate the proposed study design through simulations and analysis of a theoretically null relationship using Veterans Administration (VA) data. Simulation studies show that the case-case-time-control can adjust for exposure trends while controlling for time-invariant confounders. Use of an inappropriate control group left case-time-control analyses biased by exposure-time trends. When analyzing the relationship between vitamin exposure and stroke, using data on 3192 patients in the VA system, a case-crossover odds ratio of 1.5 (95% confidence interval = 1.3–1.7) was reduced to 1.1 (0.9–1.3) when divided by the concurrent exposure trend odds ratio (1.4) in matched future cases. This applied example demonstrates how our approach can adjust for exposure trends observed across time axes.

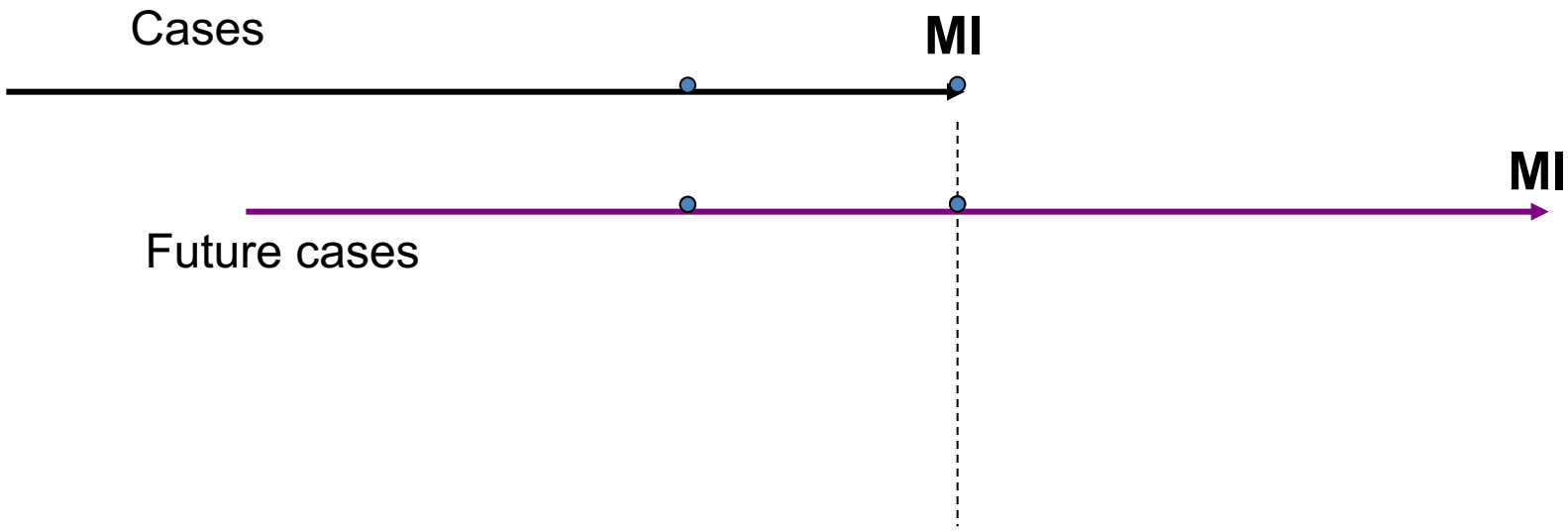
(*Epidemiology* 2011;22: 568–574)

One of the most difficult struggles in epidemiology is identifying appropriate groups for comparison. Depending on study design, the ideal comparison group could be an unexposed population who represent the experience of the exposed population if, contrary to fact, they had not been exposed, or it could be a sample from the source population that gave rise to an identified group of cases. In practice, these ideal comparison groups can be difficult to identify. However, when the exposure of interest has a transient effect on risk for an abrupt onset outcome, the solution suggested by researchers such as Maclure (case-crossover),[1] Farrington (self-controlled case-series),[2] and others[3] has been to use cases as their own controls.

Case-only designs are attractive because risk factors that are stable over time cannot confound the association between exposure and outcome. However, the case-crossover and self-controlled case series are subject to bias from population-level and individual-level confounders that vary with time. For example, there could be systematic trends in exposure over calendar time. On the individual level, there could be a change in another risk factor for the outcome, such as smoking habits, which is also associated with exposure; or bias may come into play if early signs of an impending event led to changes in exposure probability during the time preceding the occurrence of a health outcome.[1,4–8]

When the exposure under investigation is not influenced by the occurrence of individual health outcomes, as is often the case in environmental epidemiology studies, bidirectional sampling of control times (ie, sampling from per-

Control sampling, case-case-time-control



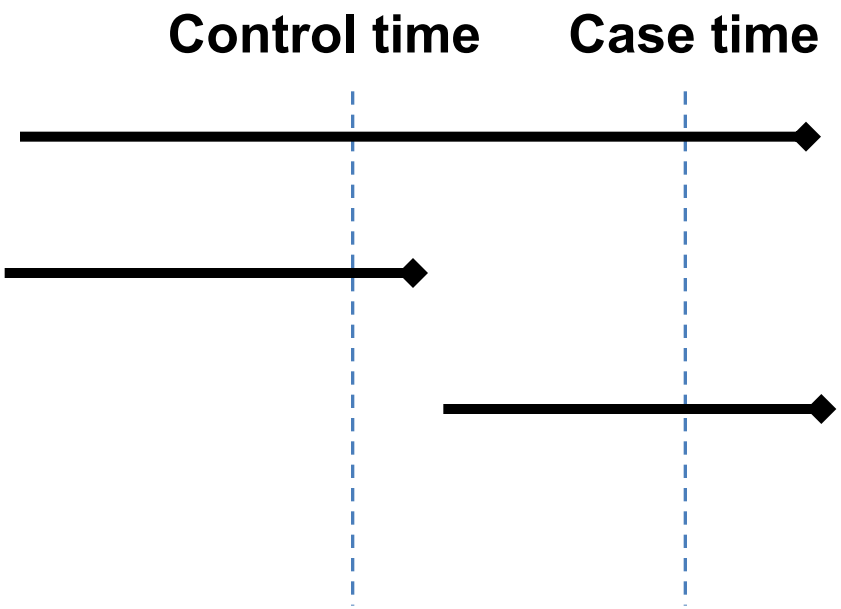
Case-case-time-control design

- Uses future cases as pool of eligible controls
- Increases resemblance between cases and controls
- Future cases should neither be
    - Too close (triggering exposure is present in controls)
    - Too distant (loss of resemblance to cases)

Exercise

- What happens if you analyse a drug that should be taken permanently, once it is started, e.g. a statin, using a case-crossover design?

Analyzing permanent drug exposure in case-crossover design



Control	Case
+	+
+	-
-	+
-	-

Persistent user bias

- Arises by right censoring of (first) treatment episodes by:
  - Death
  - Emigration
  - End of study period
- A potentially strong bias upward
- Subpopulation of indefinite users for nearly all drug classes

- Solution?

Demonstrating indefinite user bias, retinal detachment cases

	Statins	Thyroxine	Insulin
Cases			
• **Number of cases**	12788	12788	12788
• **Number of exposed indexdates**	2343 (18.3%)	432 (3.4%)	344 (2.7%)
• **Number of exposed reference dates**	13107 (17.1%)	2499 (3.3%)	1982 (2.6%)
• **OR for cases**	1.60 (1.42 - 1.80)	1.40 (1.02 - 1.92)	1.53 (1.04 - 2.24)
Controls			
• **Number of controls**	51152	51152	51152
• **Number of exposed index dates**	7856 (15.4%)	1339 (2.6%)	929 (1.8%)
• **Number of exposed reference dates**	43835 (14.3%)	7774 (2.5%)	5352 (1.7%)
• **OR for controls**	1.59 (1.50 - 1.70)	1.37 (1.14 - 1.64)	1.47 (1.18 - 1.83)
Cases and controls			
• **Case-time-control estimate**	1.00 (0.88 - 1.15)	1.02 (0.71 - 1.47)	1.04 (0.67 - 1.62)

Hallas et al, AJE 2016

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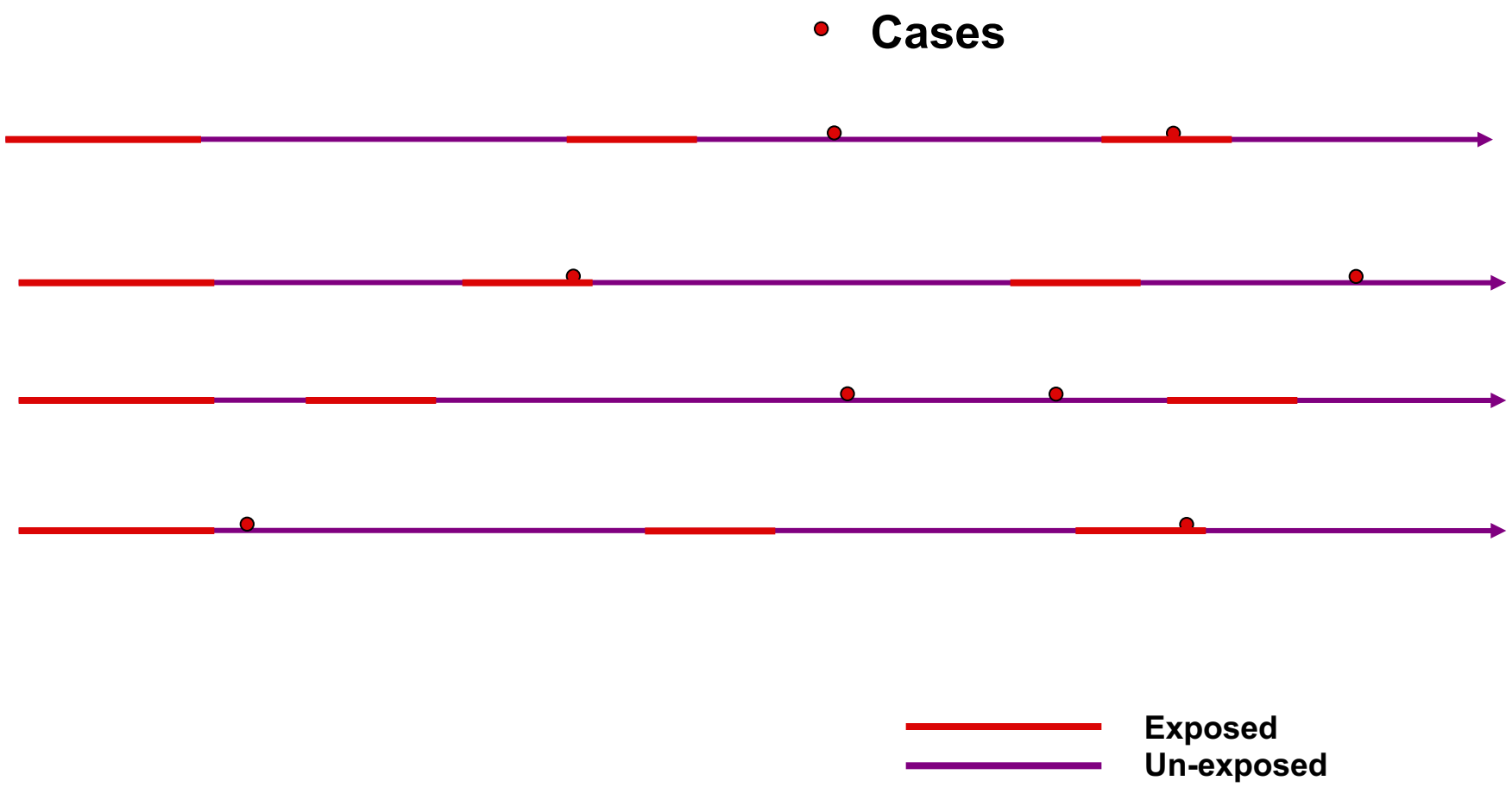
Hallas et al, AJE 2016

Self-controlled case series

Self-controlled case-series methods (Farrington 1996)

- Cohort equivalent of case-crossover design
- Only subjects who eventually become cases are included
- Only subjects who at some point in time are exposed are included
- Allows multiple occurrences of end-point
- Time-line is not censored at end-point
- Analysis is conditioned on the single user

Self-controlled case series



Self-controlled case series,

- Robust towards confounders that are stable over time
- Not biased by indefinite exposure
- Biased if the outcomes affects future exposure
- Less sensitive to trends in exposure
- Processing complicated

Self-controlled case-series, further reading

STATISTICS IN MEDICINE
Statist. Med. 2006; **25**:1768–1797
Published online 11 October 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/sim.2302

Tutorial in biostatistics: The self-controlled case series method

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SUMMARY

The self-controlled case series method was developed to investigate associations between acute outcomes and transient exposures, using only data on cases, that is, on individuals who have experienced the outcome of interest. Inference is within individuals, and hence fixed covariates effects are implicitly controlled for within a proportional incidence framework. We describe the origins, assumptions, limitations, and uses of the method. The rationale for the model and the derivation of the likelihood are explained in detail using a worked example on vaccine safety. Code for fitting the model in the statistical package STATA is described. Two further vaccine safety data sets are used to illustrate a range of modelling issues and extensions of the basic model. Some brief pointers on the design of case series studies are provided. The data sets, STATA code, and further implementation details in SAS, GENSTAT and GLIM are available from an associated website.

KEY WORDS: case series; conditional likelihood; control; epidemiology; modelling; proportional incidence

Slide show, STATA code, data set on MMR -> viral meningitis on:

http://statistics.open.ac.uk/sccs

Symmetry analysis

Symmetry analysis; drug use as end point

- An adverse drug reaction may lead to use of other drugs
- E.g., if thiazides cause depression, there would be an excess of AD initiators among users of thiazides
- Conventional case-control or cohort approach confounded by
  - high age, female gender
  - nursing home residency
  - hypochondriacy
  - overzealous prescribers
  - clustering of disease
  - …

Rationale for symmetry analysis

A woman aged 75, mildly hypochondriac and nursing home resident, started a thiazide and an antidepressant for the first time in her life in 2007.

Thiazides cause depression.

Which drug had the highest probability of being prescribed first?

Symmetry analysis, properties

- Adjust for time-invariant confounders
- Compares exposed to future exposed person-time
- Applicable to drug-drug and drug-disease pairs
- Potential for bias; trends, mutual indications etc.
- Extremely simple processing
- No bias by persistent use

Hallas. Epidemiology 1996

An example, multinational rapid assessment

- Australia
- Japan
- Korea
- Taiwan
- USA
- Sweden

- >200 million

Multi-country rapid adverse drug event assessment: the Asian Pharmacoepidemiology Network (AsPEN) antipsychotic and acute hyperglycaemia study

Nicole Pratt[1], Morten Andersen[2], Ulf Bergman[2], Nam-Kyong Choi[3], Tobias Gerhard[4,5], Cecilia Huang[4], Michio Kimura[6], Tomomi Kimura[6], Kiyoshi Kubota[7], Edward Chia-Cheng Lai[8], Nobuhiro Ooba[7], Urban Ösby[9], Byung-Joo Park[10,11], Tsugumichi Sato[7], Ju-Young Shin[10], Anders Sundström[2], Yea-Huei Kao Yang[8] and Elizabeth E Roughead[1]*

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ABSTRACT

Purpose To undertake a multi-country study to investigate the risk of acute hyperglycaemia with antipsychotic use.
Methods Using a distributed network model with a common minimal data set, we performed a prescription sequence symmetry analysis (PSSA) to investigate the risk of acute hyperglycaemia associated with antipsychotic initiation. Incident insulin prescriptions were used as a proxy indicator of acute hyperglycaemia. Participating countries and population datasets included Australia (300,000 persons), Japan I (300,000 persons), Japan II (200,000 persons), Korea (53 million persons) Taiwan (1 million persons), Sweden (9 million persons), USA-Public (87 million persons) and USA-Private (47 million persons).
Results Olanzapine showed a trend towards increased risk in most databases, with a significant association observed in the USA-Public database (Adjusted sequence ratio (ASR) = 1.14; 95% Confidence Interval (CI) 1.10–1.17) and Sweden (ASR = 1.53; 95% CI 1.13–2.06). Null or negative associations were observed for haloperidol, quetiapine and risperidone.
Conclusion Acute hyperglycaemia appears to be associated with olanzapine use, however, this effect was only observed in two large databases. Despite different patterns of utilization of both antipsychotics and insulin, PSSA analysis results for individual antipsychotic medicines were qualitatively similar across most countries. PSSA, used in conjunction with existing methods, may provide a simple and timely method further supporting multi-national drug safety monitoring.

Pratt, PDS 2013

Strenghts and weaknesses

	Case-crossover	Case-time control	Self-controlled case series	Symmetry design
Robust towards confounders stable over time	++++	++++	++++	++++
Sensitive to trend	+	-	-	++
Sensitive to (time-dependent) misclassification	++	++	+	-
Sensitive to shift in indication	+	++	+	++
Complexity	++	+++	++++	+

Strengths and weaknesses of each design

it thus seems prudent to use multiple designs .. whenever economically feasible and to use multiple analyses as appropriate.

Confounding and Exposure Trends in Case-Crossover and Case-Time-Control Designs

Sander Greenland

As with ordinary studies, both case-crossover and case-time-control studies can suffer from confounding, including confounding by indication. In a case-crossover analysis, confounding by fixed (constant) characteristics is eliminated by pairing of cases to themselves, at the possible cost of introducing bias due to time trends in exposure. A case-time-control analysis can correct case-crossover results only for bias due to such time trends. If an uncontrolled confounder (such as disease severity) is present, the use of time controls can introduce new confounding, and the case-time-control results may end up either more or less confounded than the ordinary and case-crossover results. The relative confounding in the different approaches depends on details of the relations among the unmeasured confounder, the study exposure, the study disease, and any trend in these variables or their effects. Like an ordinary study, a case-time-control study must assume absence of unmeasured confounders, whether fixed or time-varying. Like a case-crossover study, it must also assume absence of carryover effects and can be more prone to misclassification bias than an ordinary study. (Epidemiology 1996;7:231 239)

Keywords: exposure trends, confounding, case-crossover studies, case-time-control studies, data analysis, bias.

Greenland S. Epidemiology 1996: 7: 231-9

Exercise

- Are self-controlled designs robust to confounding-by-indication?
-

Exercise

- Are self-controlled designs robust to confounding-by-indication?
- No

Exercise

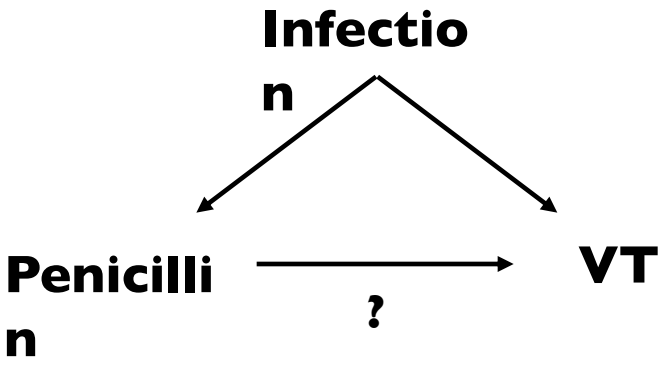
- Are self-controlled designs robust to confounding-by-indication?
- No
- If no, how would we deal with it?

Exercise

- Are self-controlled designs robust to confounding-by-indication?
- No
- If no, how would we deal with it?
- Active comparator

Empirical example

- Penicillin -> venous thromboembolism (VT)
  - Infection -> penicillin use
  - Infection -> VT



Hallas et al, AJE 2021

Results

Method	Estimate penicillin
Case-crossover	3.27 (3.16 - 3.39)

Results

Method	Estimate penicillin	Estimate roxithro-mycin
Case-crossover	3.27 (3.16 - 3.39)	3.45 (3.23 - 3.68)

Results

Method	Estimate penicillin	Estimate roxithro-mycin	Simple ratio	Effect modifier estimate
Case-crossover	3.27 (3.16 - 3.39)	3.45 (3.23 - 3.68)	0.95(0.86 - 1.05)	1.03 (0.95 - 1.11)

Results

Method	Estimate penicillin	Estimate roxithro-mycin	Simple ratio	Effect modifier estimate
Case-crossover	3.27 (3.16 - 3.39)	3.45 (3.23 - 3.68)	0.95(0.86 - 1.05)	1.03 (0.95 - 1.11)
Case-time control	2.89 (2.76 - 3.02)	3.11 (2.83 - 3.41)	0.93(0.80 - 1.08)	1.06 (0.99 - 1.14)

Results

Method	Estimate penicillin	Estimate roxithro-mycin	Simple ratio	Effect modifier estimate
Case-crossover	3.27 (3.16 - 3.39)	3.45 (3.23 - 3.68)	0.95(0.86 - 1.05)	1.03 (0.95 - 1.11)
Case-time control	2.89 (2.76 - 3.02)	3.11 (2.83 - 3.41)	0.93(0.80 - 1.08)	1.06 (0.99 - 1.14)
Symmetry analysis	1.83 (1.71 - 1.87)	2.54 (2.34 - 2.61)	0.72(0.65 - 0.80)	0.72 (0.59 - 0.88)
Self-controlled case series	3.80 (3.72 - 3.89)	4.56 (4.37 - 4.75)	0.83(0.78 - 0.89)	0.92 (0.88 - 0.97)

Take-home

- A variety of designs share the common feature of being robust to confounders that are stable over time.
- These include the
  - case-crossover design
  - case-time-control design
  - self-controlled case series method.
  - symmetry analysis
- Among the problems in using them are
  - sensitivity to trends
  - sensitivity to misclassification
  - sensitivity to confounding by indication
  - statistical inefficiency if exposure does not change frequently
- No particular design is generally superior to the others.

Questions?

Cardiovascular events in users of a prescribed ephedrine/caffeine product (Letigen$^{TM)}$, a case-crossover study

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Letigen ™, background

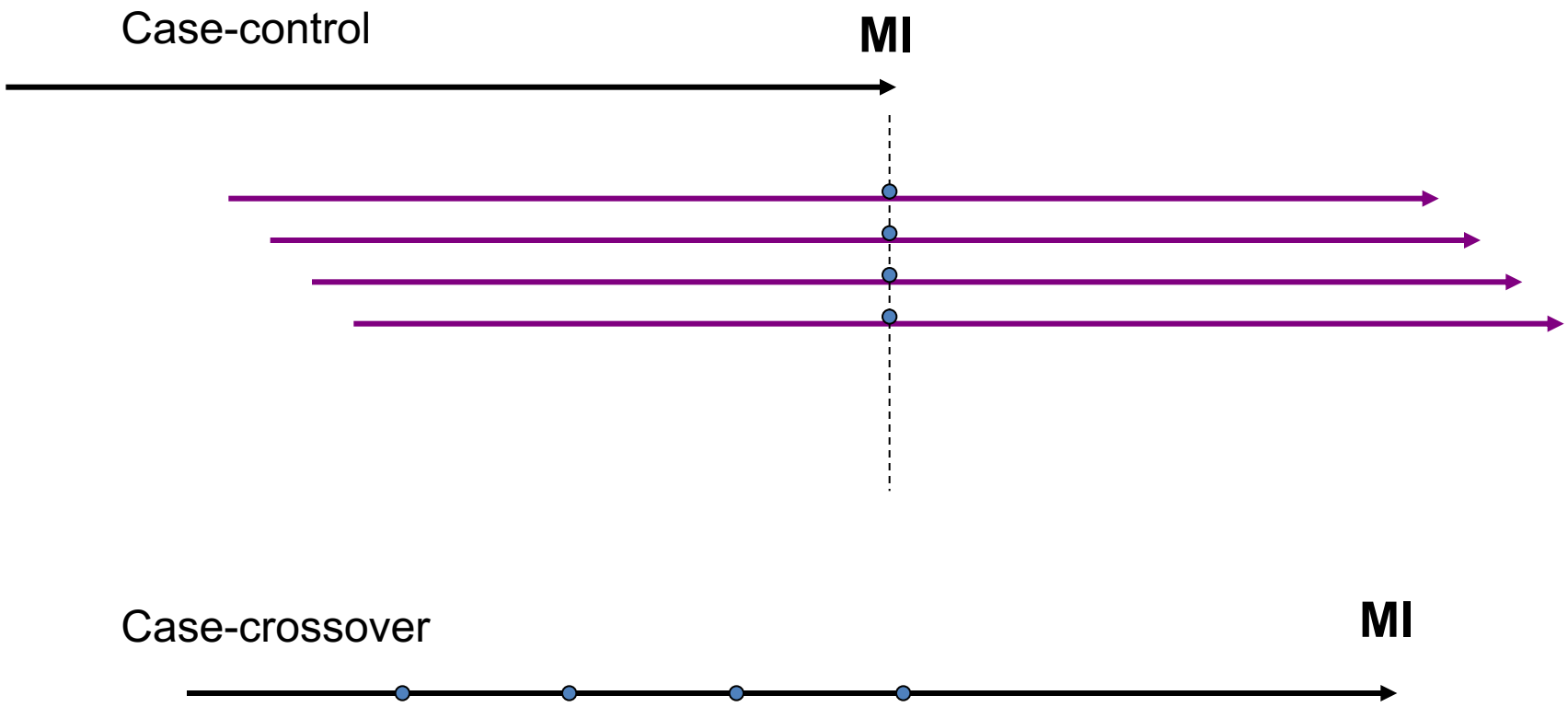
- Active substance was ephedrine, a sympatomimetic agent. Each tablet contained 20 mg synthetic ephedrine and 200 mg caffeine.
- Slight to moderate effect on weight loss
- Market license suspended 2002 after reports of adverse CV events among the users.
- Similar reports on ephedrine-containing diet supplements in other countries, mainly US.
- All ephedrine-containing products banned from US market in 2004
- No controlled epidemiological studies

CV morbidity among users of prescribed ephedrine weight-loss products

- Confounding-by-indication?
  - Obesity
  - Metabolic syndrome, diabetes
  - Lifestyle factors
    - Smoking,
    - Sendentary life style
  - Threshold for prescribing

Round up the usual suspects

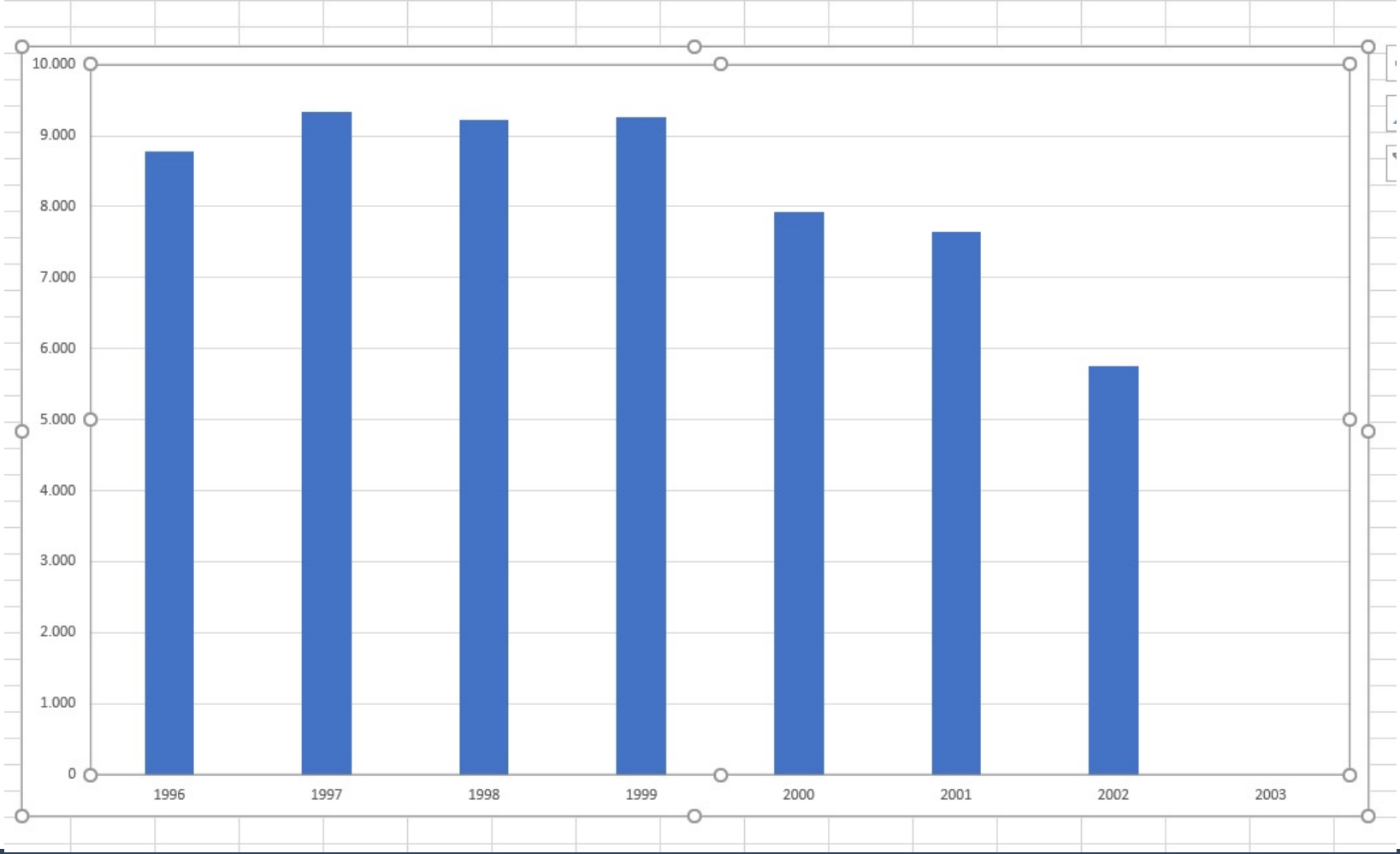
Control sampling



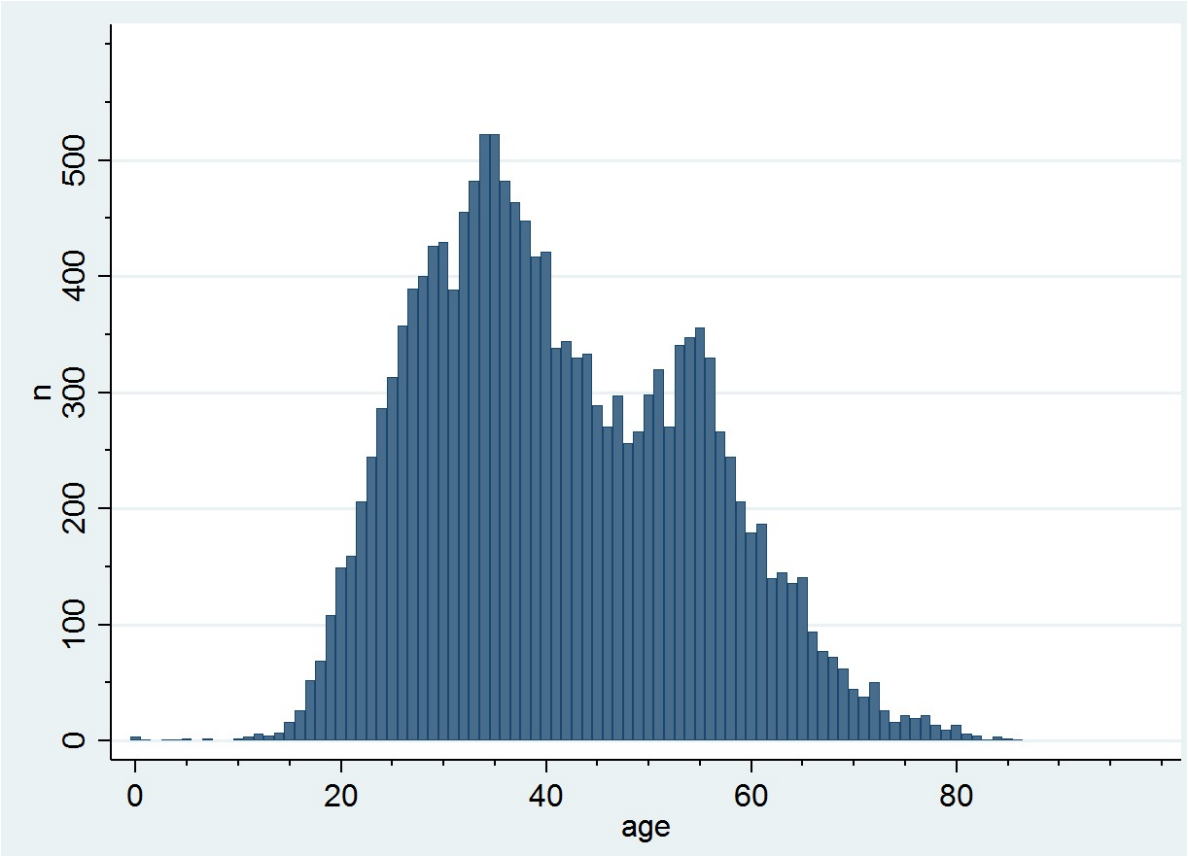
Letigen utilization

- Ususally dispensed in 100 tablet containers
- No individual dosing instruction available
- Recommended dose 2-3 tablets per day
- Usually short-term
- Marked seasonality:
  - More than twice as many new users in January as in December
  - Many young women started early summer months

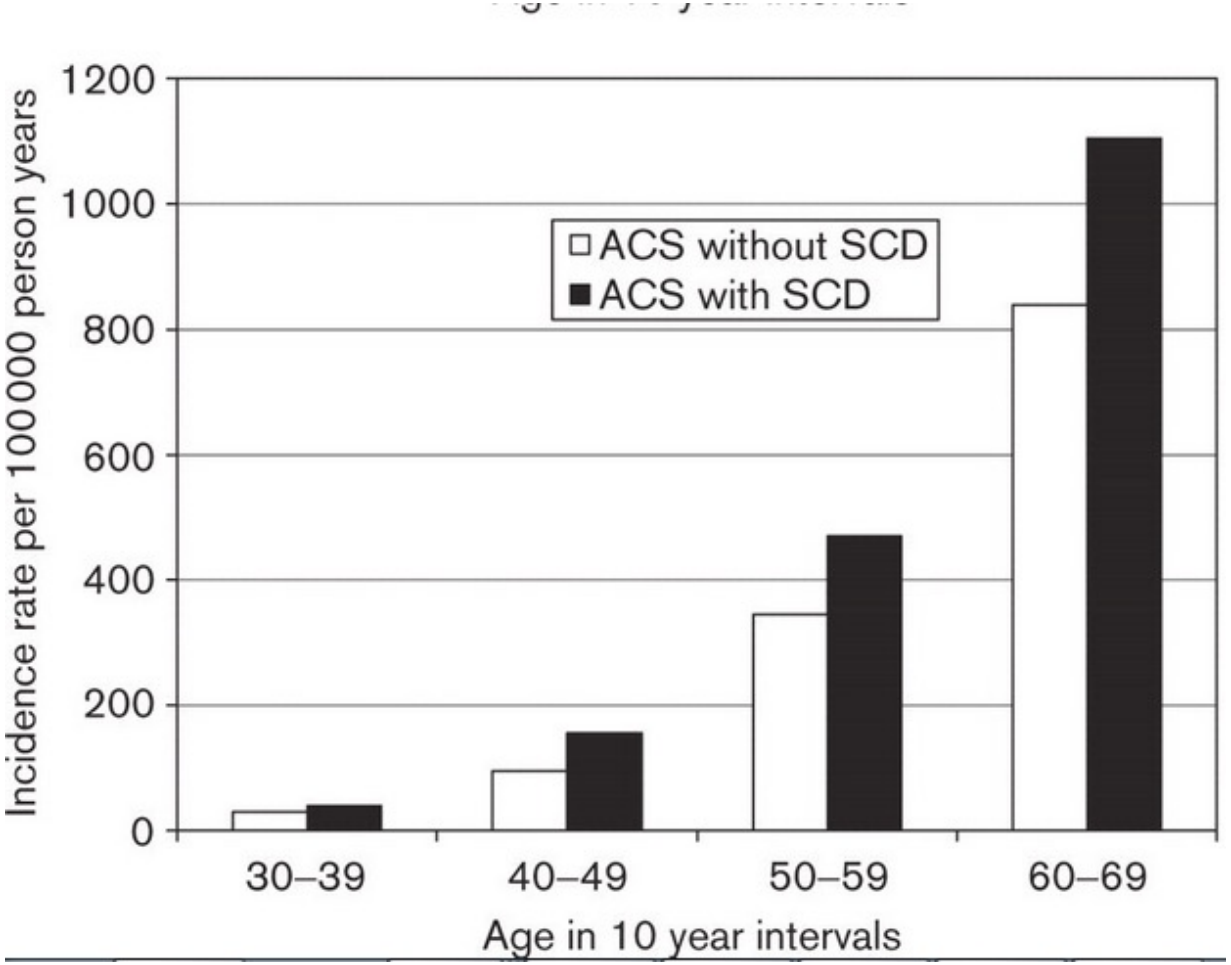
Letigen utilization, trend by calendar year



Letigen utilization, age distribution 2001

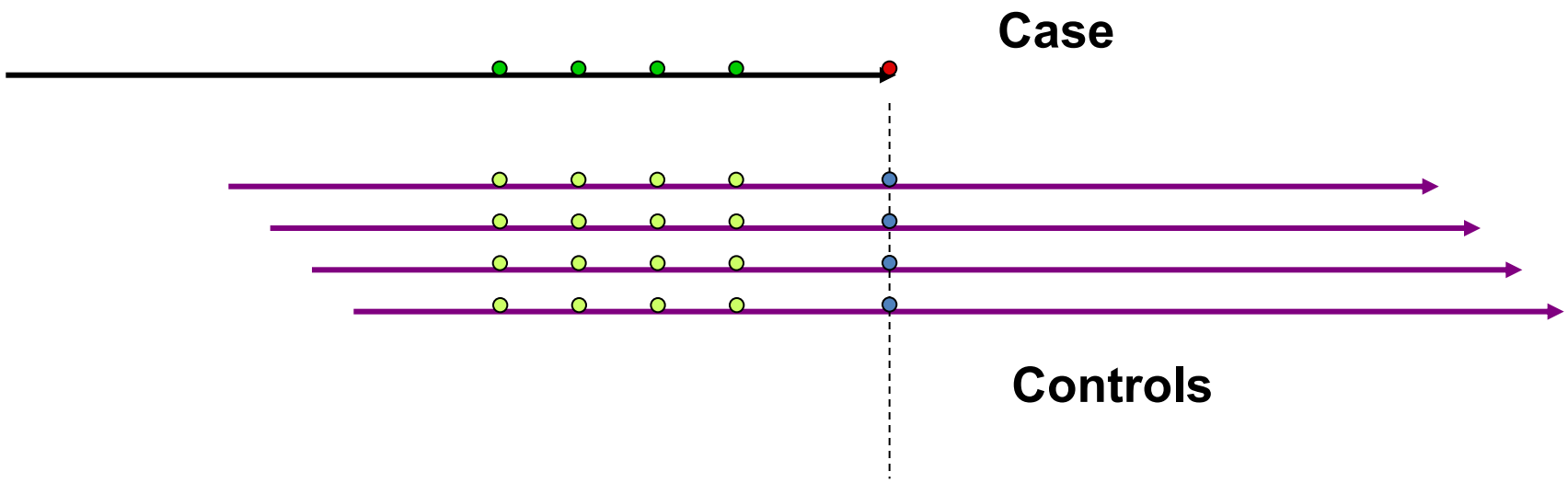


Age-specific incidence rate of the outcome



Nielsen KM, Foldspang A et al. Eur J Cardiovasc Prev Rehabil. 2007

Adjustment for trend, Case-time-control design



Suissa, Epidemiology 1995.

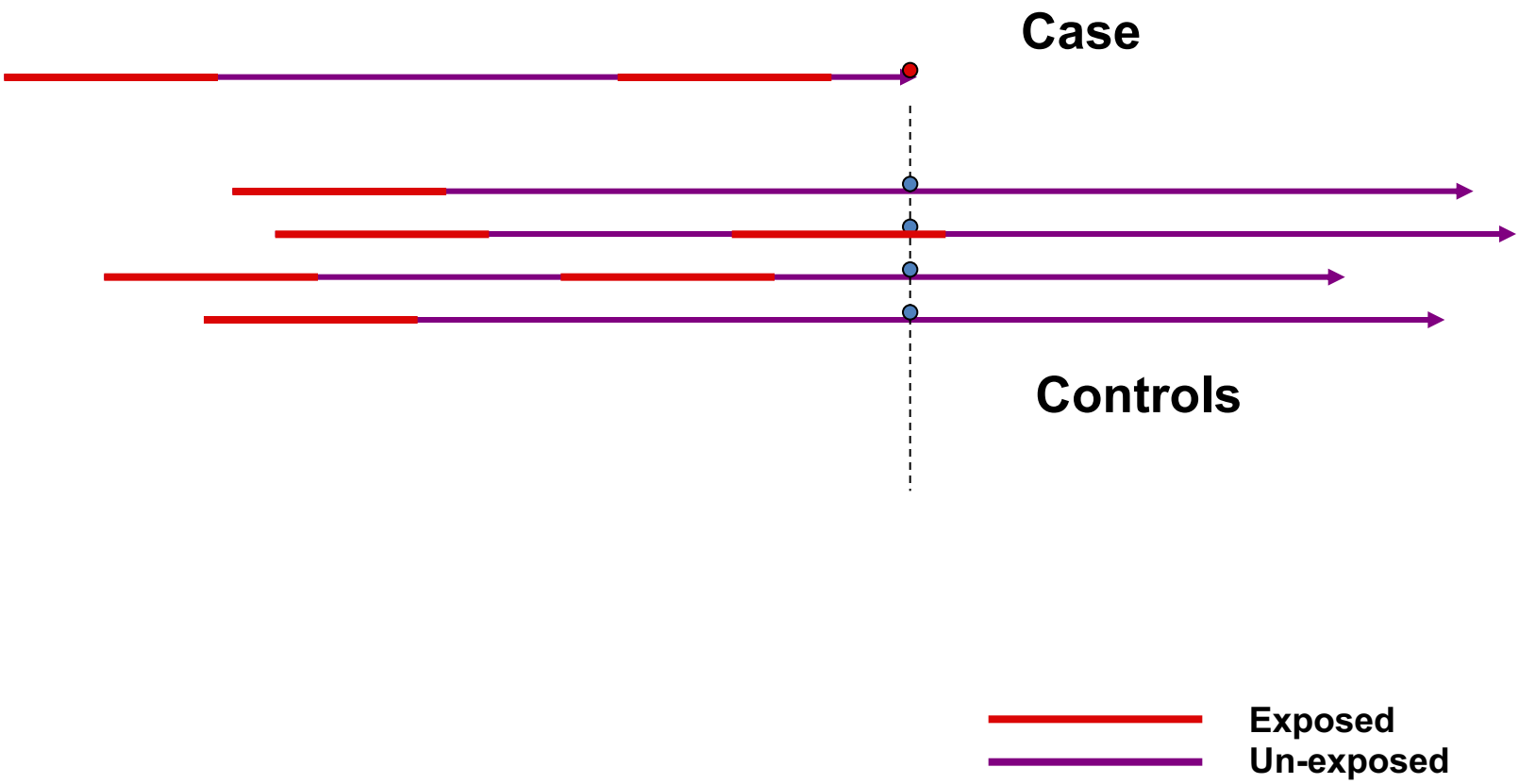
Not amenable to crossover study:

- Risk in naïve users
  - Impossible to be naïve user both on focal and reference window

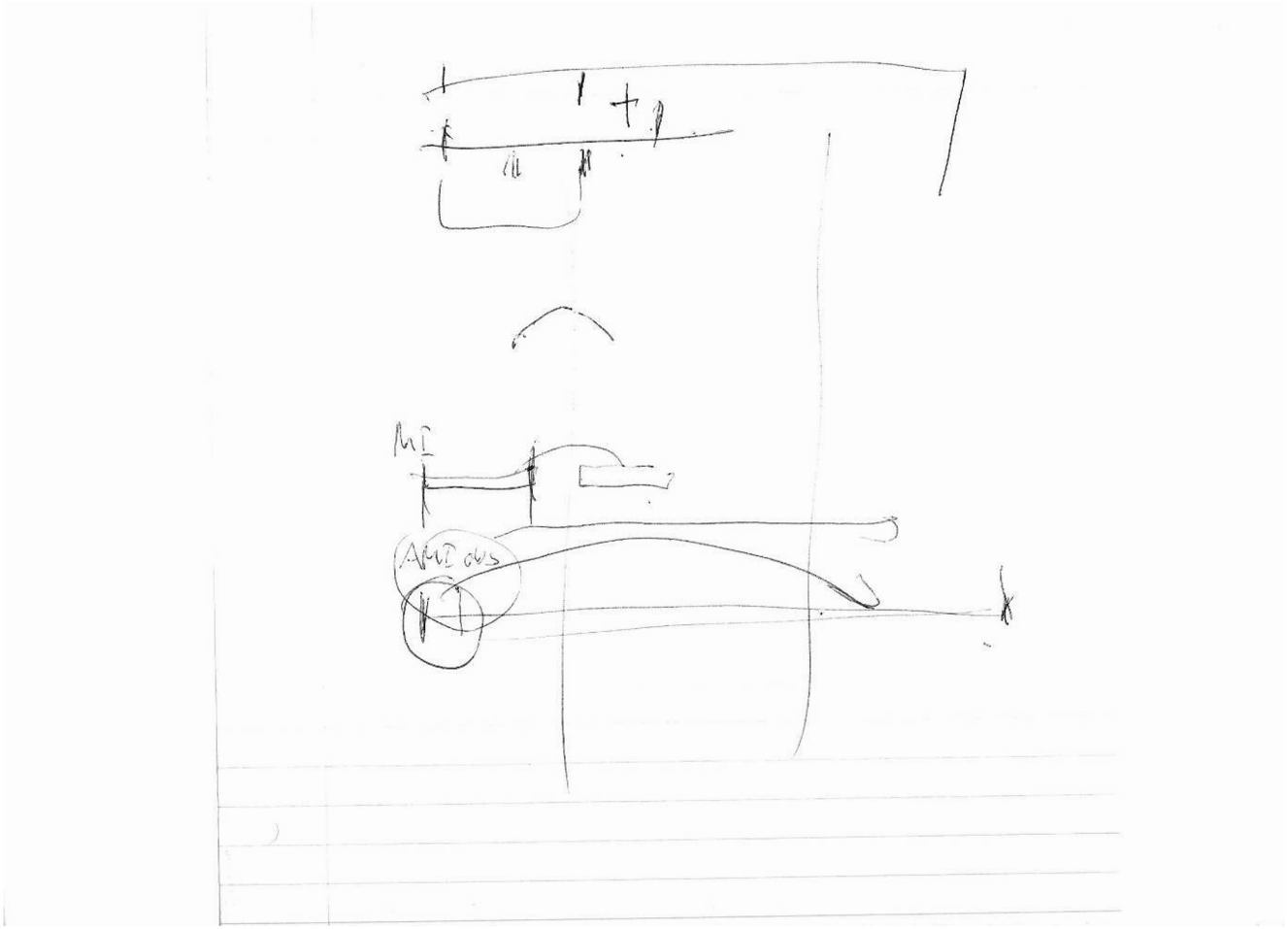
- Cumulative dose response
  - Impossible to have higher cumulative dose in reference window than in focal window

Conventional case-control study with random control sampling within the cohort of Letigen ever-users.

Case-control study nested within ever-users:



Ephedrine – CV morbidity,
very early protocol draft of crossover study



Statistics Denmark, Letigen data

- 257,364 users of Letigen from National Prescription Register
- 15 mio prescriptions, of which 1.5 mio were on Letigen
- All available data on secondary care contacts, death, migration and socioeconimic status..
- Anonymised on individual level

Design:

- Case-crossover (case-time-control)
  - Main analysis
- Case-control
  - Duration-response
  - Dose-response
- Study period 1.7.1996 - 31.12.2001
- Study base: all users of Letigen within the period 1.1.1995 - 31.12.2001

End-point

- Composite
  - Myocardial Infarction
  - Stroke
  - Death outside hospital

Study cohort:

- In, all of these:
  - First Letigen-prescription seen
  - 18 years birthday
  - Observable for 18 months in the past
  - 30.06.1996
- Out, any of these:
  - End-point
  - Date of first cancer diagnosis
  - Emigration
  - 70-years birthday
  - 31.12.2001

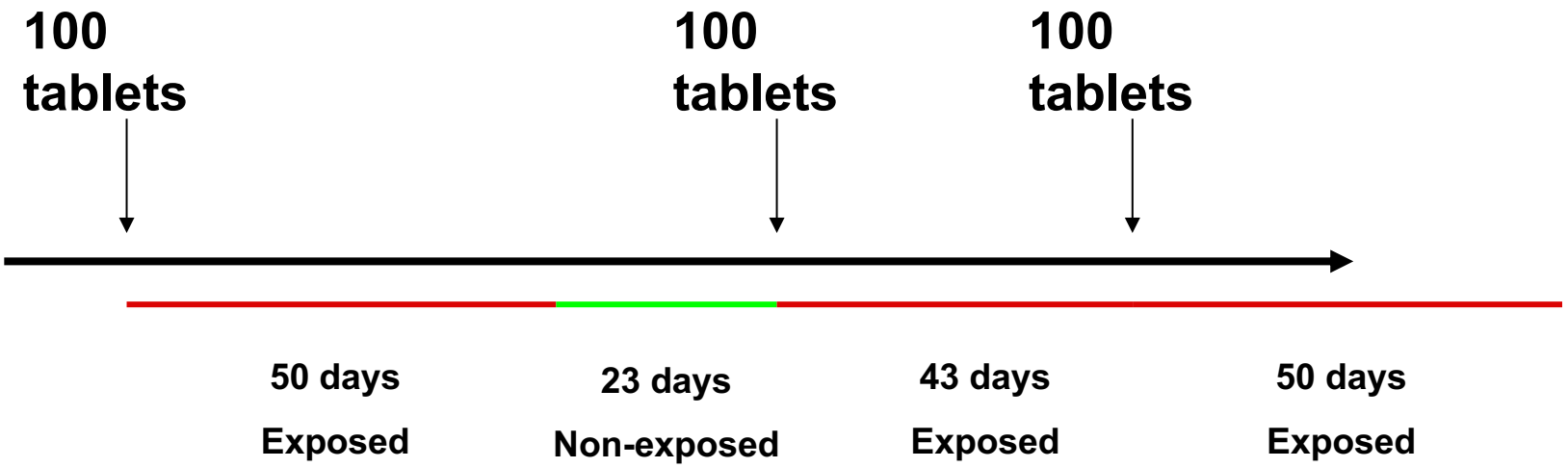
Covariates

- Age
- Gender
- Iscemic heart disease dx
- Diabetes dx rx
- Obesity dx
- Hypertension dx rx
- COLD dx rx
- Aspirin rx
- Statin rx
- Socioeconomic status

- Time-varying confounders can be adjusted by e.g. conditional logistic regression

Exposure definition

- Assuming two tablets daily for each prescription
- Exposure ”clock” is reset with each new presction
- Sensitivity analyses, assuming 1 or 3 tablets/day and 90 days fixed window



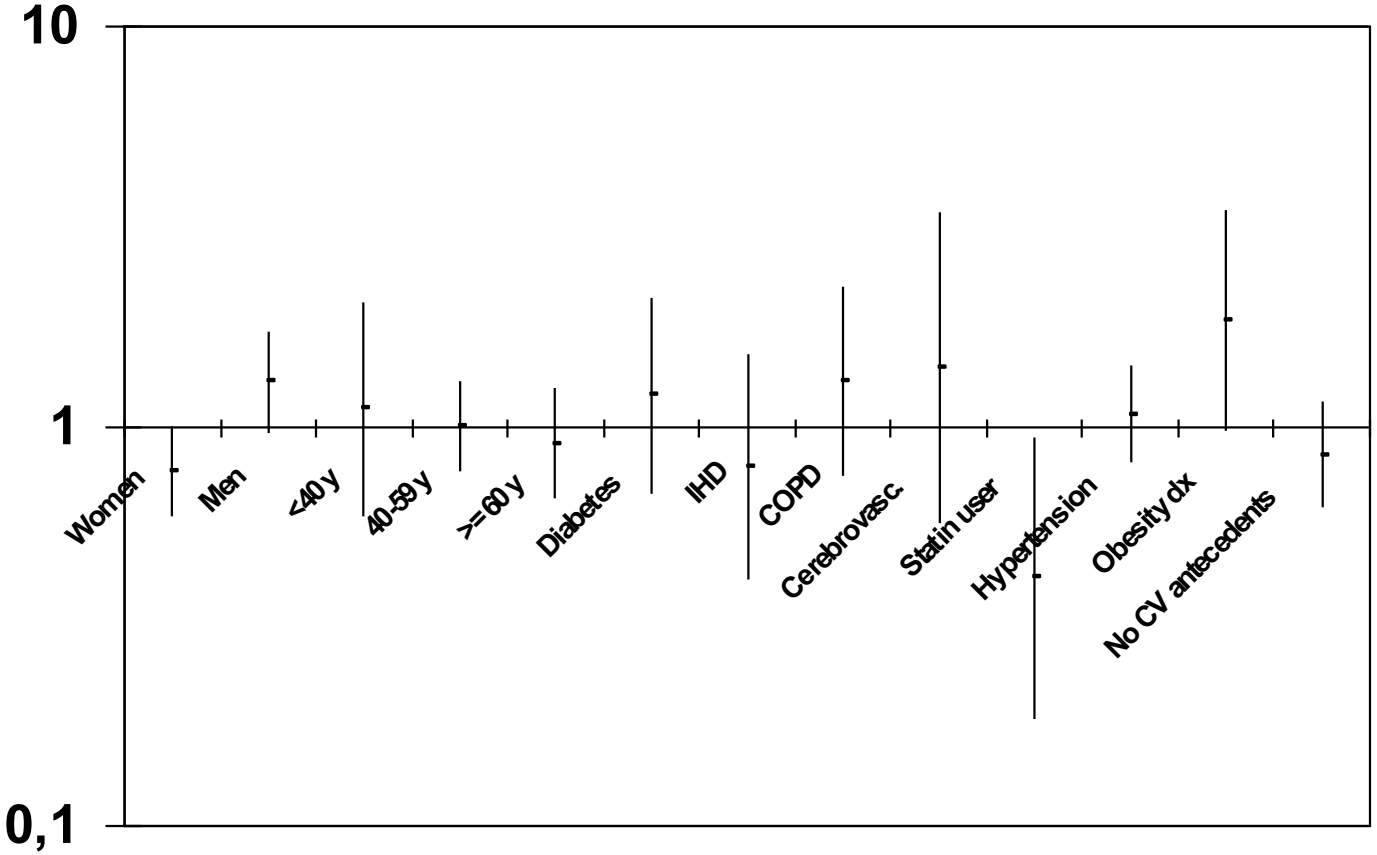
Ephedrine and CV morbidity, results from cross-over analysis

Endpoint	Cases, n		Adjusted odds ratio, case-crossover estimate (CI) §)	Adjusted odds ratio, case-time-control estimate (CI) *)
	All	Exposed to ephedrine/caffeine (%)		
Main composite endpoint	2316	282 (12.2)	0.84 (0.71 - 1.00)	0.95 (0.79 - 1.16)
Secondary endpoints				
Death outside hospital	531	50 (9.4)	0.53 (0.36 - 0.79)	0.54 (0.35 - 0.84)
Myocardial infarction	839	109 (13.0)	0.94 (0.71 - 1.25)	1.14 (0.83 - 1.56)
Fatal myocardial infarction	55	6 (10.9)	0.53 (0.16 - 1.71)	1.43 (0.40 - 5.14)
Stroke	946	123 (13.0)	0.95 (0.73 - 1.23)	1.07 (0.80 - 1.43)
Fatal stroke	58	7 (12.1)	0.46 (0.17 - 1.27)	0.92 (0.29 - 2.87)

***) adjusted for trends in prescribing by case-time-control design**

Hallas et al, unpublished

Subgroup analyses



Case-control data, duration since first prescription

Duration	Cases Exposed / unexposed	Controls Exposed / Unexposed	Crude OR (CI)	Adjusted £) OR (CI)
0-10 days	13 / 2034	95 / 19502	1.35 (0.75 - 2.44)	1.23 (0.67 - 2.27)
11-19 days	12 / 2034	90 / 19502	1.35 (0.73 - 2.49)	1.41 (0.75 - 2.66)
20-39 days	26 / 2034	152 / 19502	1.53 (0.99 - 2.36)	1.32 (0.83 - 2.10)
40-79 days	18 / 2034	175 / 19502	0.95 (0.56 - 1.59)	0.86 (0.50 - 1.47)
80-159 days	22 / 2034	183 / 19502	1.15 (0.73 - 1.81)	1.11 (0.70 - 1.77)
>=160 days	191 / 2034	2233 / 19502	0.83 (0.71 - 0.97)	0.79 (0.67 - 0.93)

American Journal of Epidemiology

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Original Contribution

Use of a Prescribed Ephedrine/Caffeine Combination and the Risk of Serious Cardiovascular Events: A Registry-based Case-Crossover Study

Jesper Hallas, Lars Bjerrum, Henrik Støvring, and Morten Andersen

Received for publication March 31, 2008; accepted for publication June 9, 2008.

Ephedrine and herbal ephedra preparations have been shown to induce a small-to-moderate weight loss. Owing to reports on serious cardiovascular events, they were banned from the US market in 2004. There have been no large controlled studies on the possible association between prescribed ephedrine/caffeine and cardiovascular events in general. The authors linked data from four different sources within Statistics Denmark, using data on 257,364 users of prescribed ephedrine/caffeine for the period 1995–2002. The data were analyzed using a case-crossover technique with a composite endpoint: death outside of a hospital, myocardial infarction, or stroke. To account for effects of chronic exposure and effects in naïve users, the authors performed a secondary case-control study nested within the cohort of ephedrine/caffeine ever users. Among 2,316 case subjects, 282 (12.2%) were current users of ephedrine/caffeine. The case-crossover analysis yielded an odds ratio of 0.84 (95% confidence interval: 0.71, 1.00); after adjustment for trends in ephedrine/caffeine use, it was 0.95 (95% confidence interval: 0.79, 1.16). Subgroup analyses revealed no strata with significantly elevated risk. In the case-control substudy, there was no increased risk among naïve users or users with large cumulative doses. Prescribed ephedrine/caffeine was not associated with a substantially increased risk of adverse cardiovascular outcomes in this study.

Ephedra sinica; ephedrine; mortality; myocardial infarction; stroke

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; OR, odds ratio.

Hallas et al, AJE 2008

Epilogue

Our ephedrine-caffeine study was very favorably reviewed in the American Journal ”MD” ….

The new evidence uncovered by a Dream Team of scientists, and data in the country of Denmark, suggests that an innocent sits on death row……