

# Case-control studies



MANGER ★

JOHN SNOW

JOHN SNOW

Worlds Limit  
1000 yards  
ahead

ONE WAY

“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?

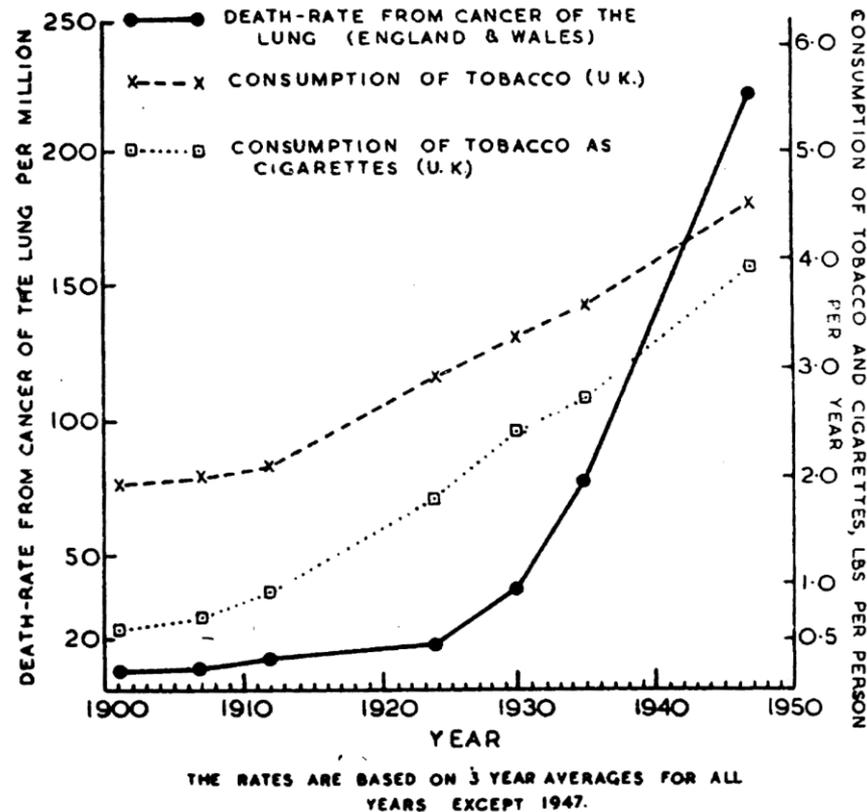
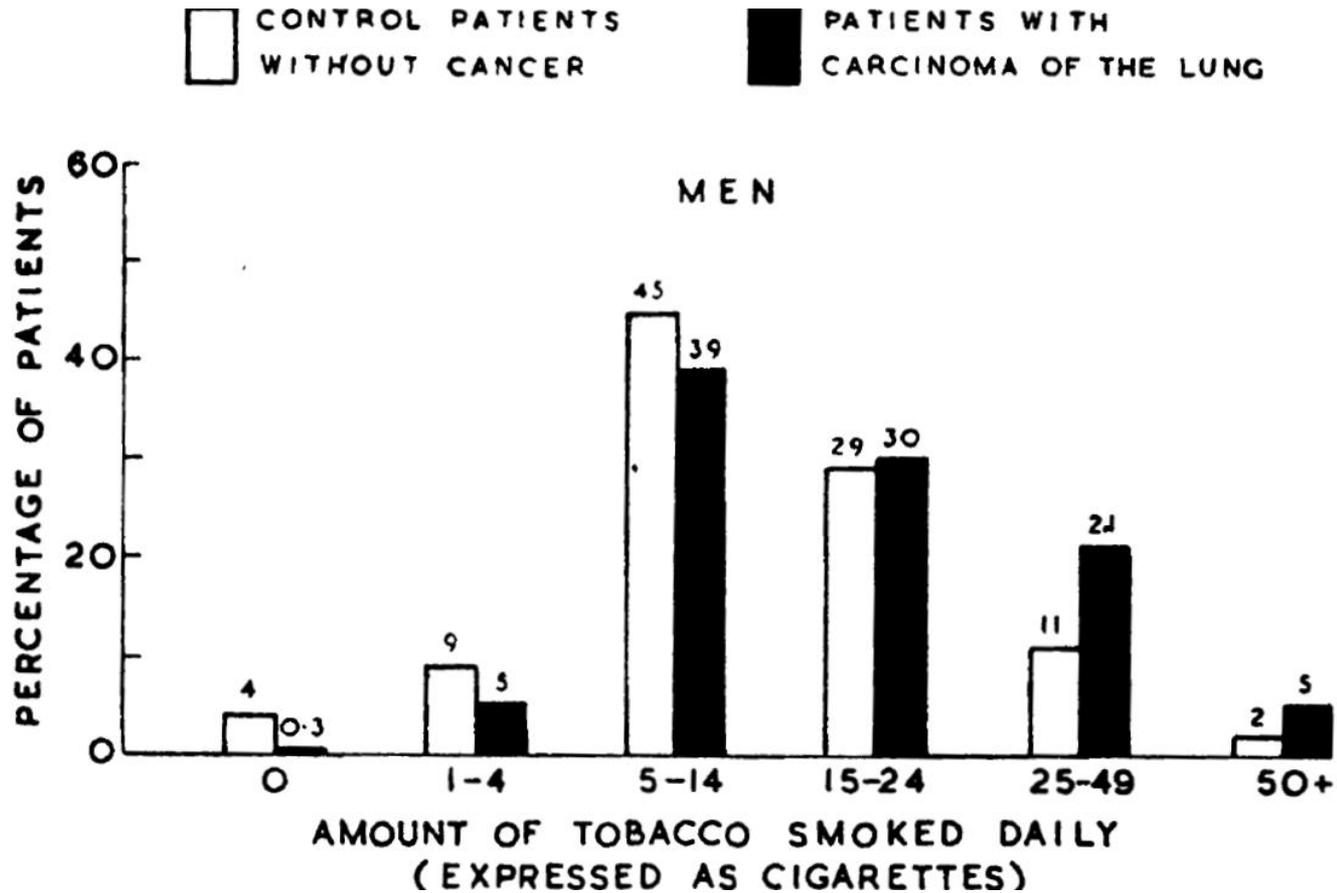


FIG. 2.—Death rate from cancer of the lung and rate of consumption of tobacco and cigarettes.

# Smoking and lung cancer?



# **Case-control studies**

## **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.

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

	<b>DVT Y</b>	<b>DVT N</b>
<b>The pill Y</b>	240	150
<b>The pill N</b>	60	150

$$OR = \frac{\binom{240}{60}}{\binom{150}{150}} = 4$$

# Design a case-control study addressing...

...whether NSAID use lead to gastrointestinal bleedings.

... whether smoking causes lung cancer.

# ... but why!?

Use of appetite-suppressant drugs causes  
primary pulmonary hypertension

Relative risk  $\approx$  20

Baseline IR: 2 / 1 000000 person-years

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

What if there was "only" 100 000 users?



Research Paper

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

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## ABSTRACT

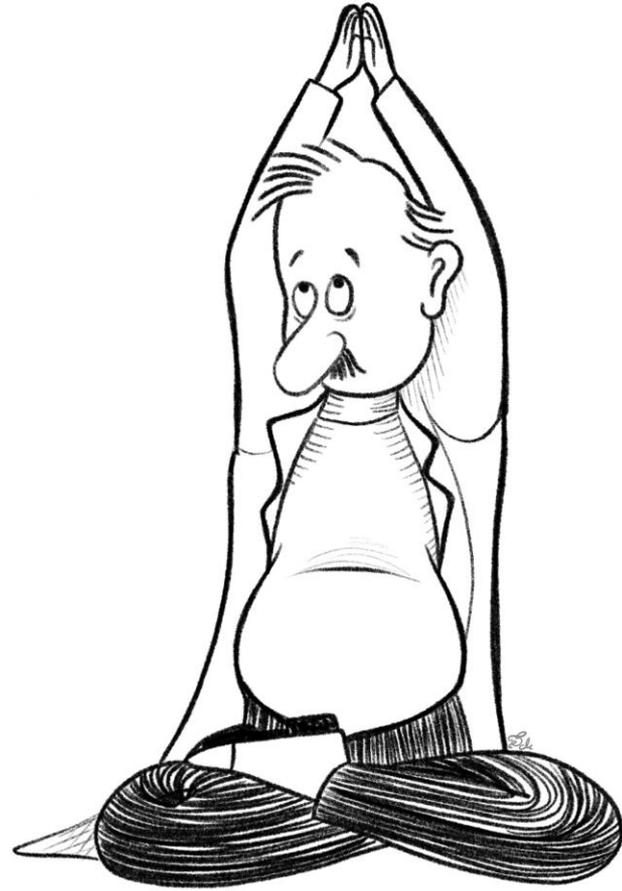
**Purpose:** We present a systematic screening for identifying associations between prescribed drugs and cancer risk using the high quality Danish nationwide health registries.

**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	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 po	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

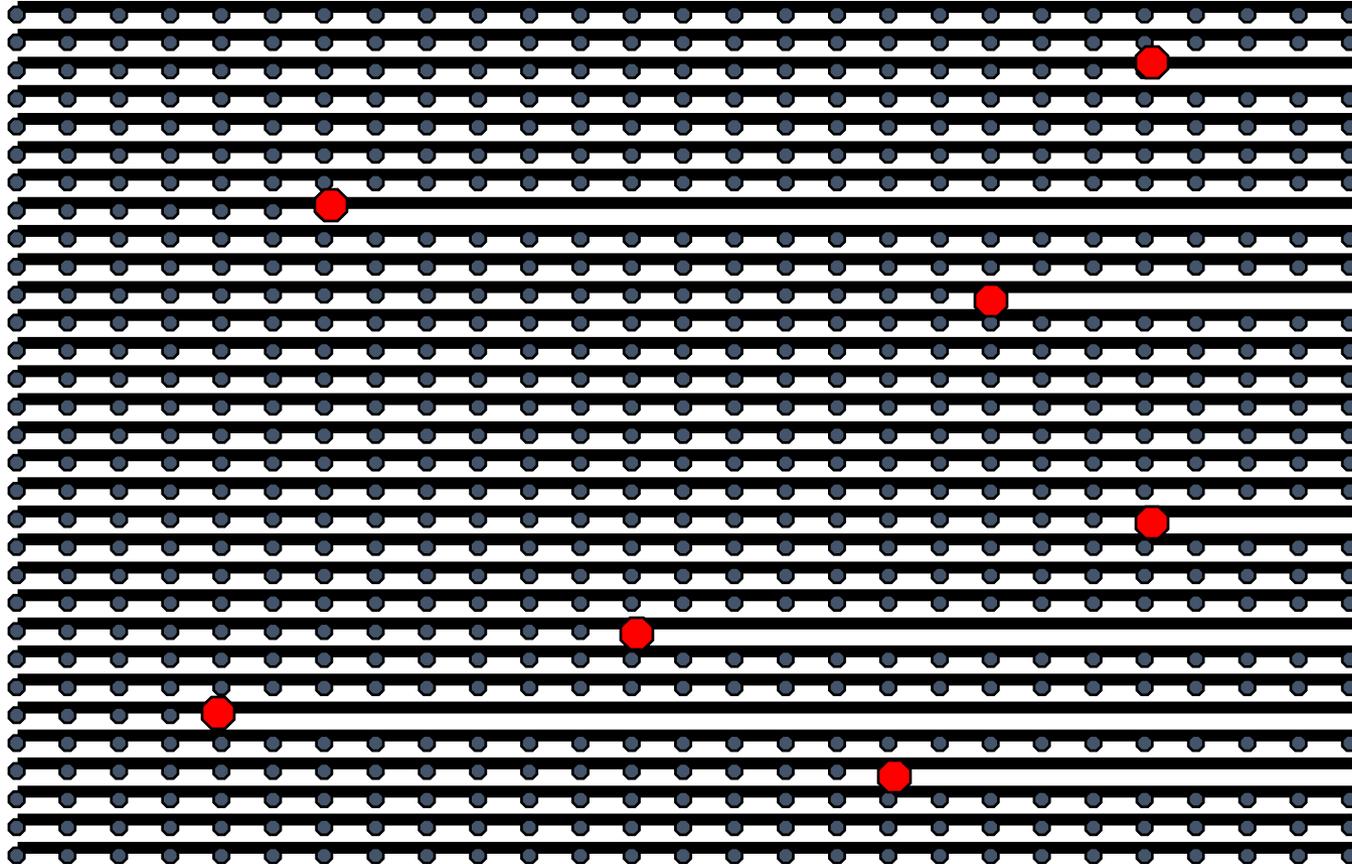


**The difficult part...**

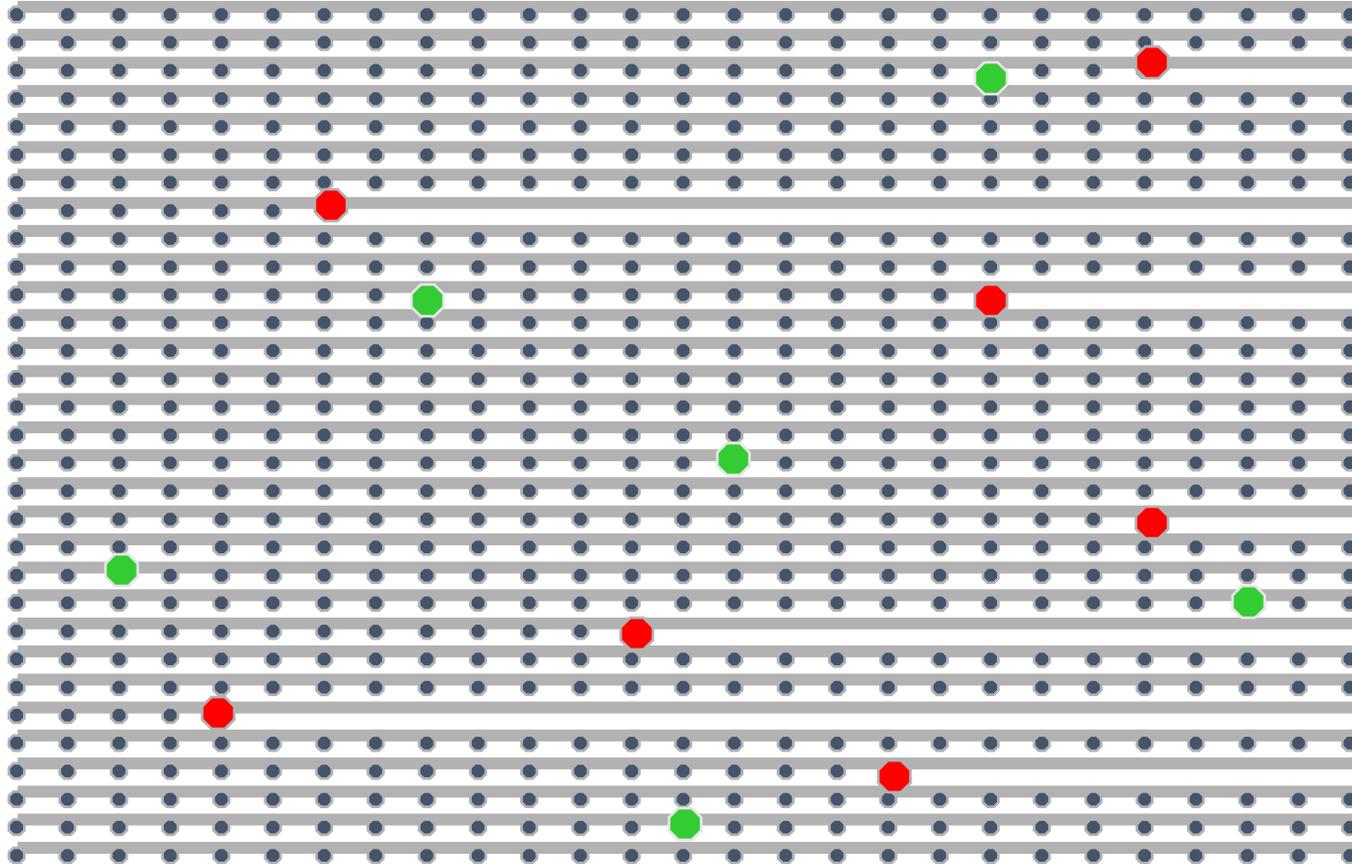
# Source population

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

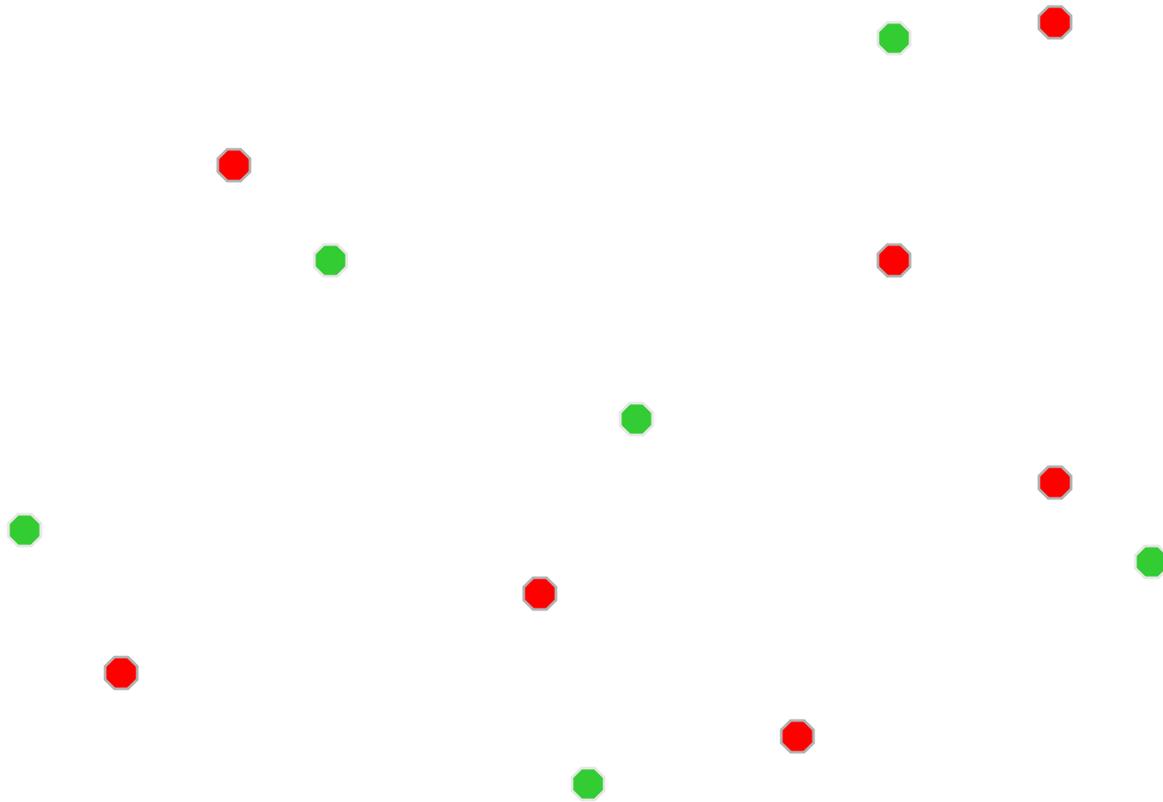
# Cohort design



# Case-control design



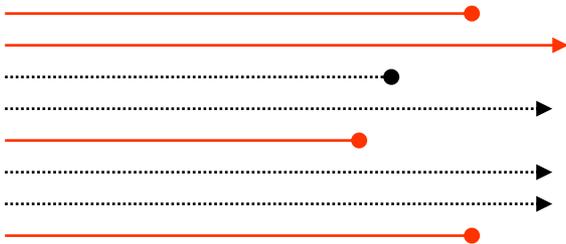
# Case-control design



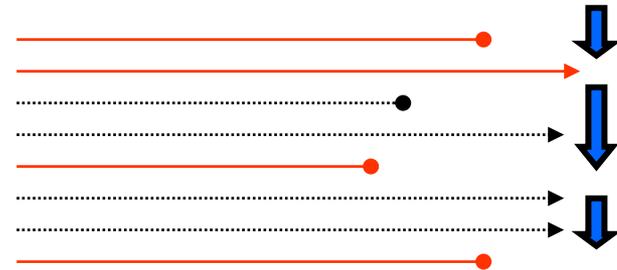
Has it always been like this?

**NO!**

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



Persons



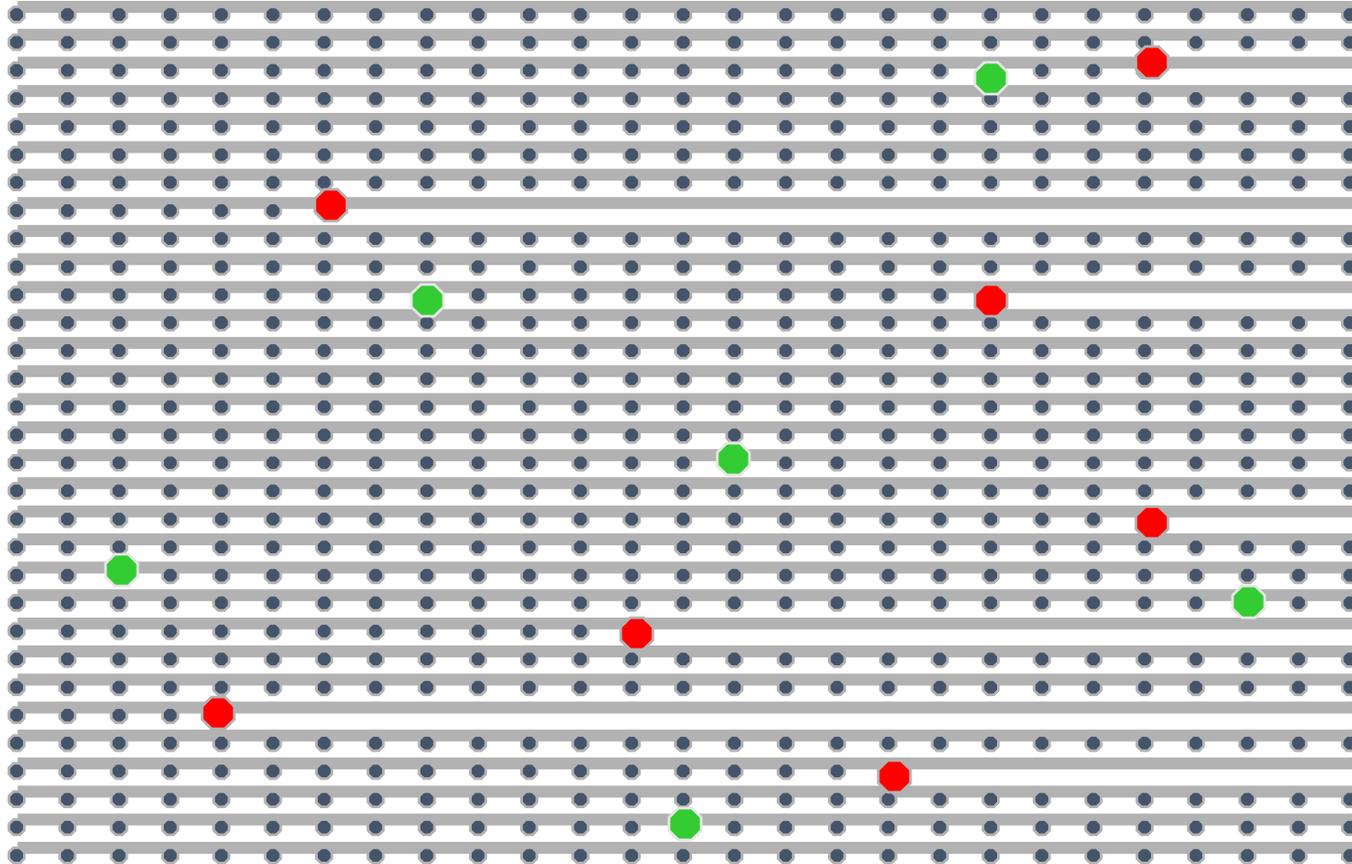
Use cases and a random  
sample of non-cases (controls)

Not without problems!

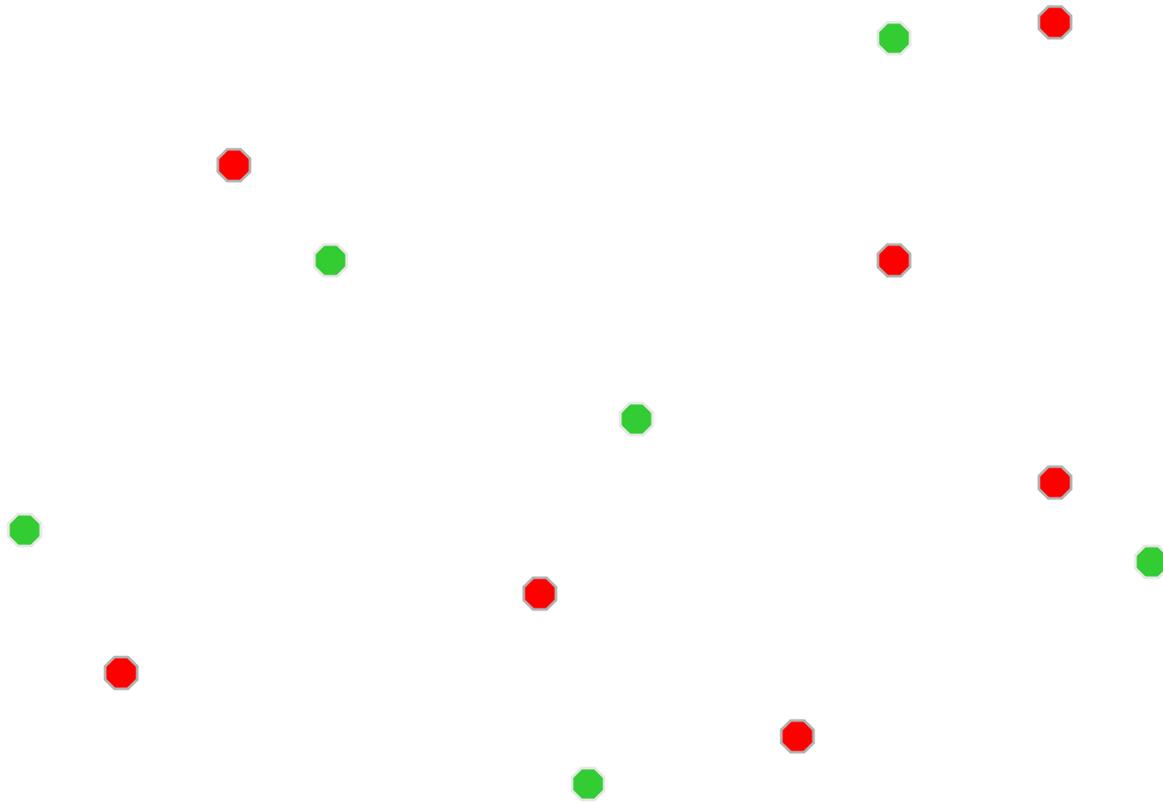
## **A “case-control” study...**

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 patients prescribed X and underwent Y surgery between 2010 and 2013. “Controls” were patients prescribed X but with no history of Y between 2002 and 2013.

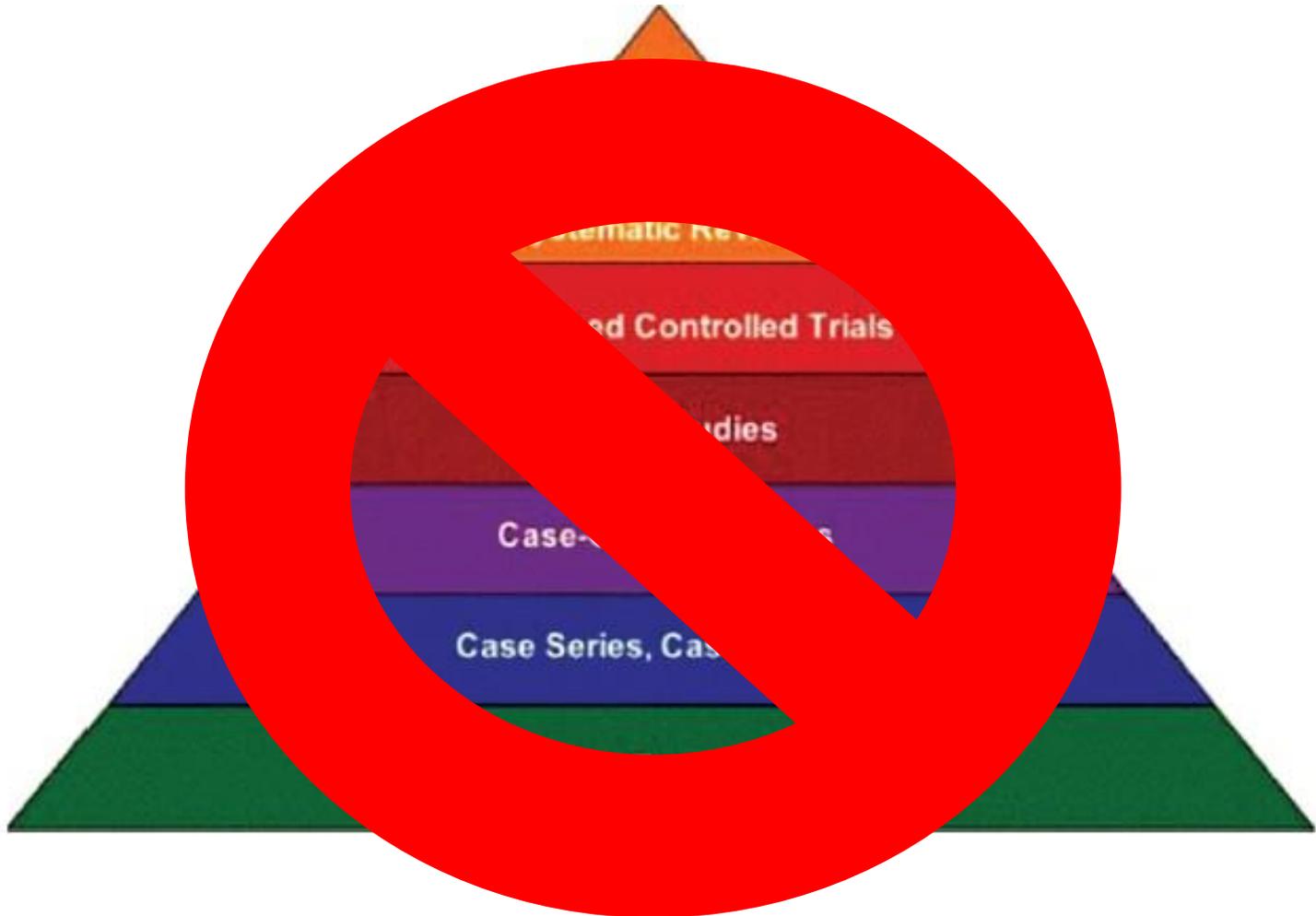
# Case-control design



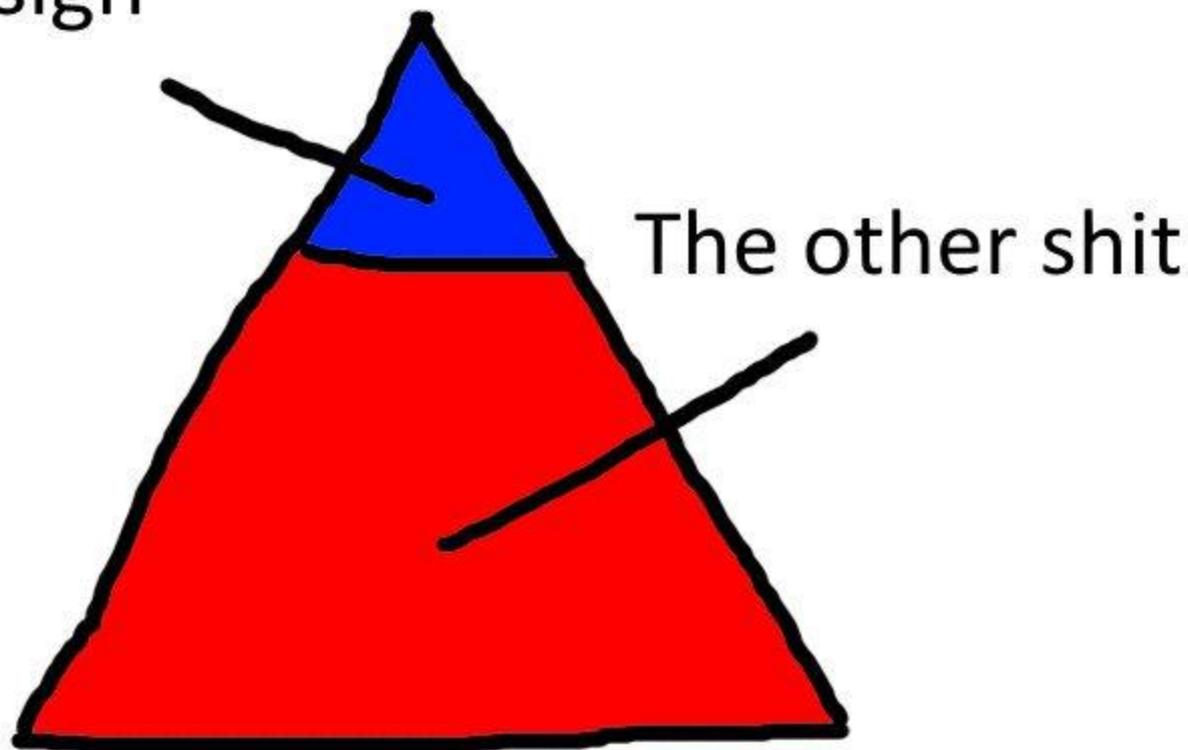
# Case-control design



# Evidence?!



Thoughtful, well-conducted studies of  
any design



@StatsEpi

Rothman: Six Persistent Research Misconceptions

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

Ken Rothmann



**Example**

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<sup>\*1</sup>, Zandra Nyman Ennis<sup>2</sup>, Jesper Hallas<sup>1,2</sup>, Boye L Jensen<sup>3</sup>, Kirsten Madsen<sup>3,4</sup> and Søren Friis<sup>5</sup>

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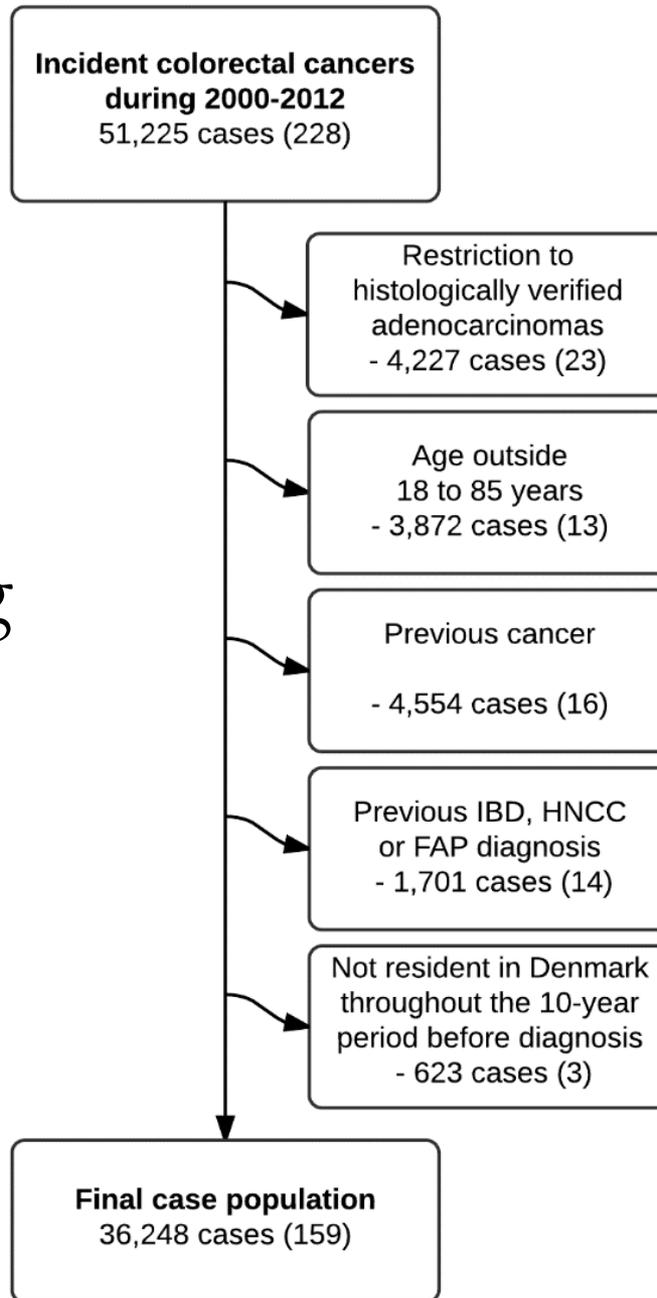
**Background:** Lithium accumulates in the colon and inhibits the enzyme GSK-3 $\beta$  that possesses anti-carcinogenic effects. We therefore examined the association between lithium use and colorectal cancer risk in a nationwide study.

**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 ( $\geq 5$  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

Li<sup>+</sup>

Underlying  
cohort?



Exposure group	Cases	Controls	Crude OR <sup>1</sup>	Adjusted OR <sup>2</sup>
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 ( $\geq 5$ 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)
$\geq 10$ years	28	228	1.22 (0.83-1.81)	1.29 (0.87-1.91)

**Pros and cons?**

# Pros

Statistically efficient

~~Less resource 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.** In addition there are lots of variables such as smoking that are not addressed (instead an indirect measure of COPD is used).

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

	<b>Cases (n = 3571)</b>	<b>Controls (n = 35,582)</b>
		<b>All</b>
<i>Age</i>		
Median (IQR)	75 (64–83)	75 (64–83)
<i>Sex</i>		
Men	1811 (50.7%)	18,029 (50.7%)
<i>Current drug use</i>		
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%)
PPI	521 (14.6%)	2027 (5.7%)

## **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

The applicability of the case-control design must be considered in light of the specific study question!