

Confounding

Random variation 

Systematic error (Bias)

Selection bias 

Information bias 

Confounding  

 Statistician's expertise

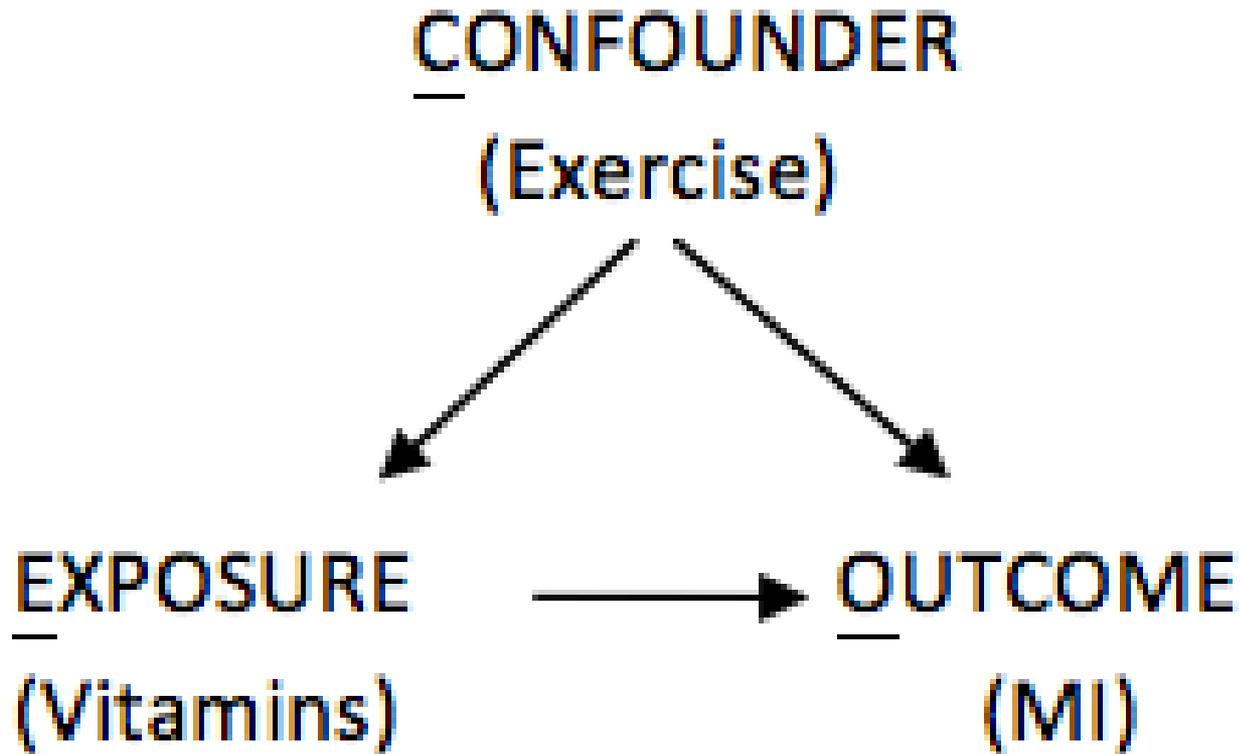
 Epidemiologist's expertise

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 exposure
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

Randomization

Cross-over

Restriction

Matching

Self-controlled

ANALYSIS

Stratification

Multivariate analysis

Propensity score (PS)

Randomization



Corrects unknown and unmeasured confounders

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 confounders

Resource 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

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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 trials (RCTs).

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 policy-

Confounder control

DESIGN

Randomization

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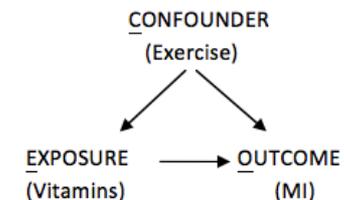
ANALYSIS

Stratification

Multivariate analysis

Propensity score (PS)

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

Stratifikation 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?

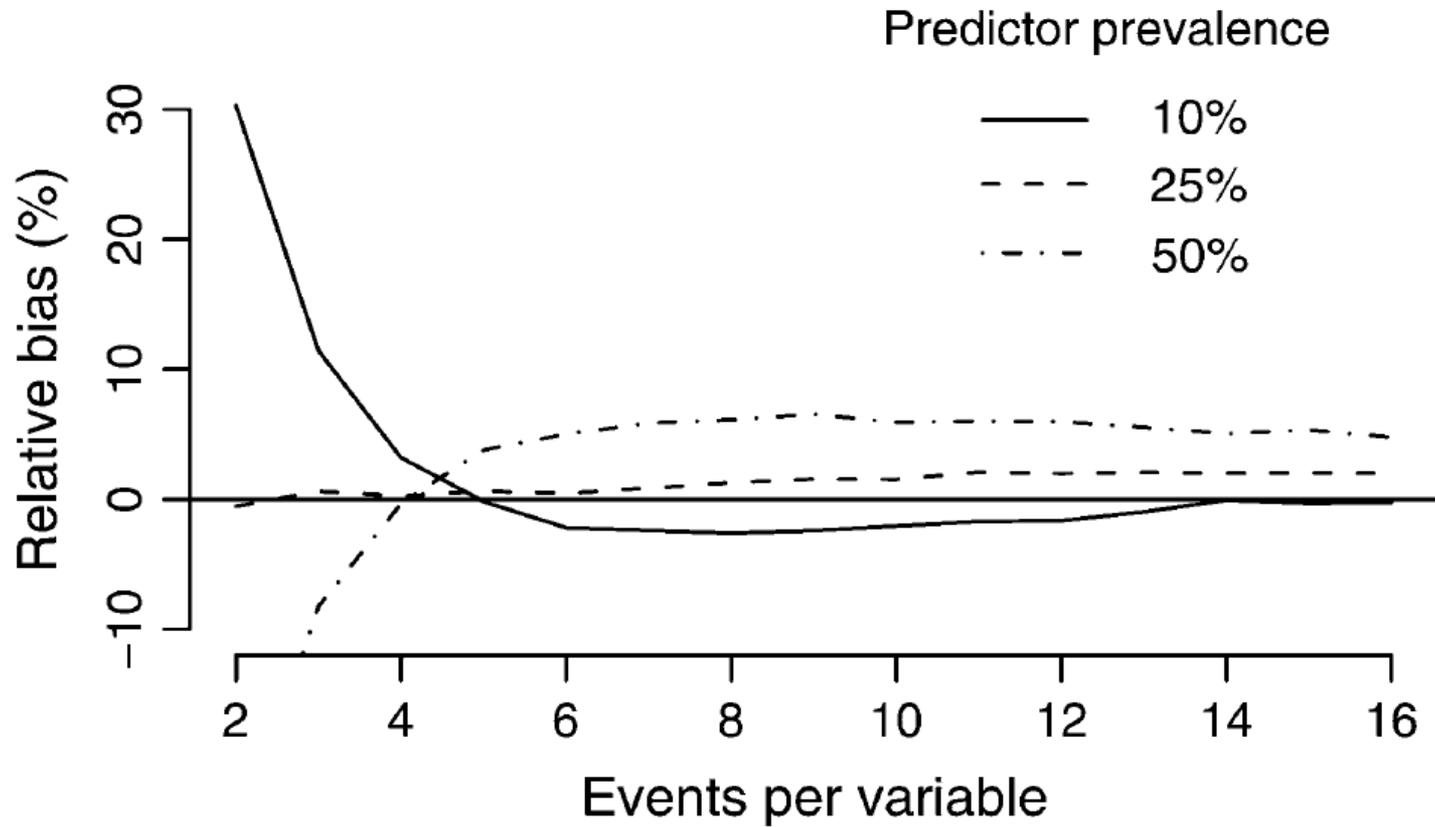
Warfarin and risk of SAH

	Cases	Kontroller	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's conclusion

Confounding by indication can be very strong

Is not correctable in a non-randomized design

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)



THIN ICE

GO AHEAD...TRY IT
ANYWAY...YOU DON'T
WEIGH THAT
MUCH...IT
WON'T
BREAK

What about... propensity scores?

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)



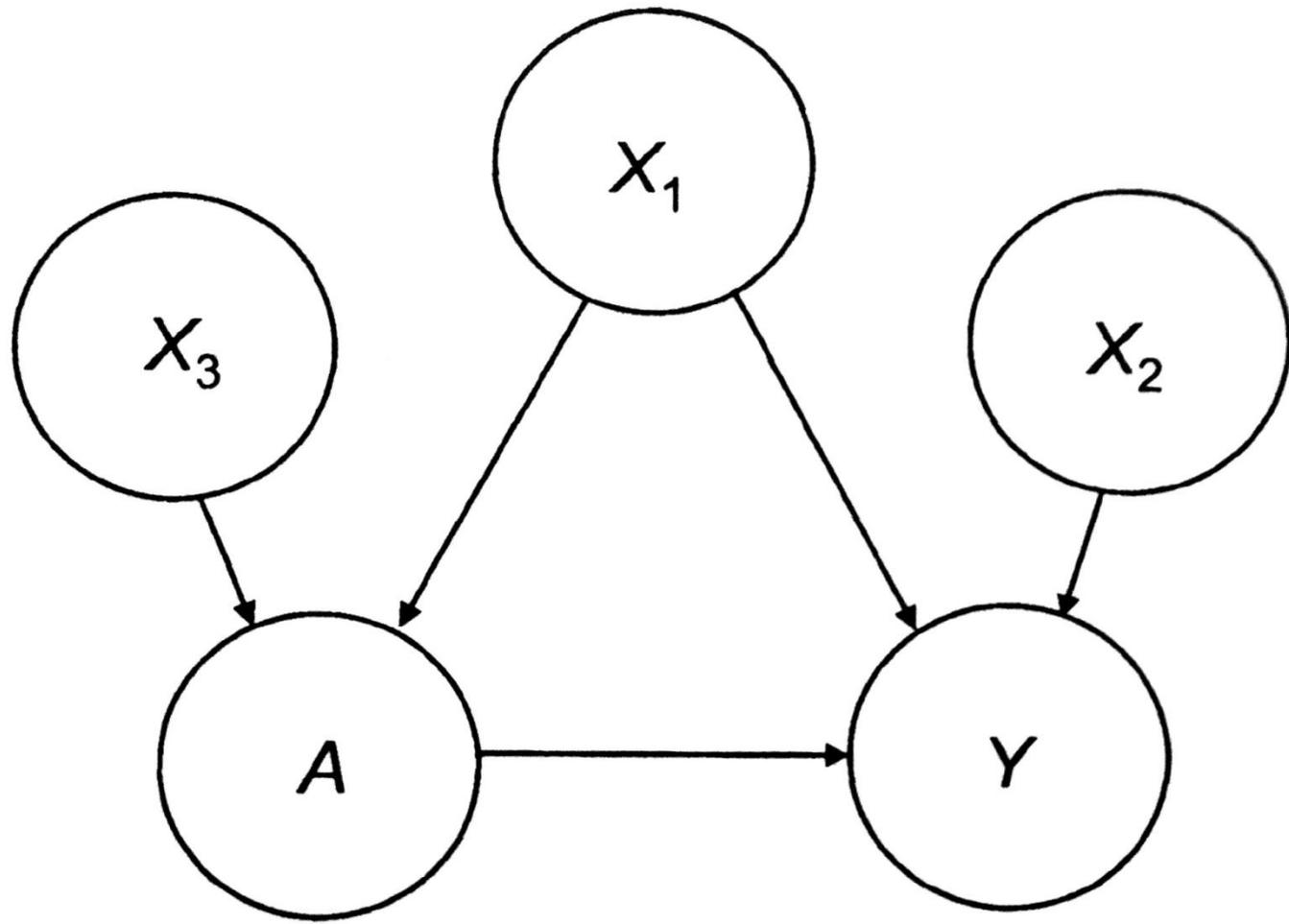
EXPOSURE

(Vitamins)



OUTCOME

(MI)



Matching
Regression
Stratification
Weighting
... combinations

See Stürmer et al., JIM 2014

Literature

www.antonpottegaard.dk/download/PSlitteratur.zip

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'

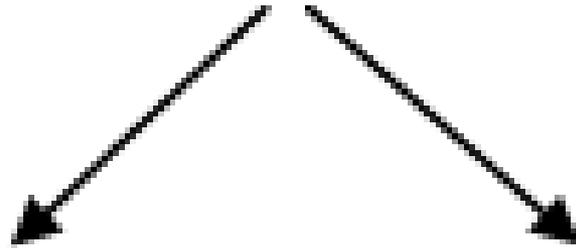
Schneeweiss et al., Epidemiology 2009

Disease risk scores

Glynn et al., PDS 2012

CONFOUNDER

(Exercise)



EXPOSURE

(Vitamins)



OUTCOME

(MI)