Confounding

Random variation

Systematic error (Bias)

Selection bias

Information bias

Confounding

Statistician's expertise

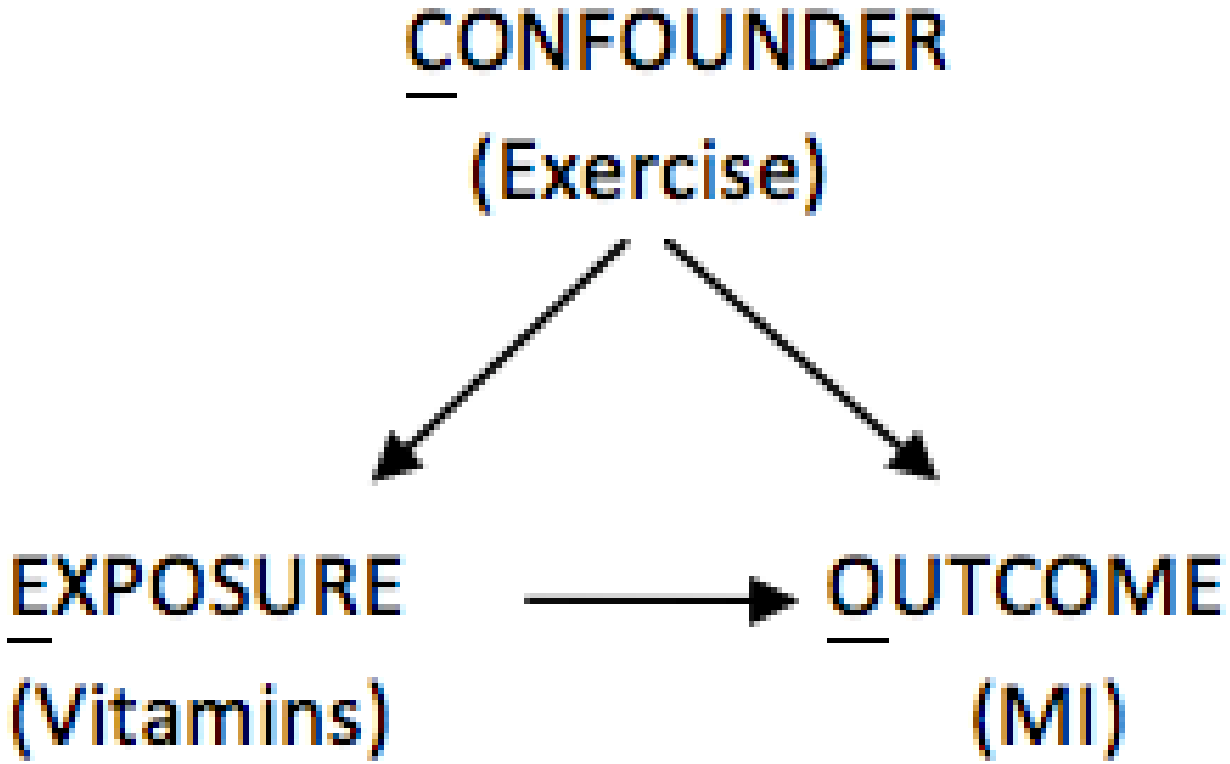
Epidemiologist's expertise

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

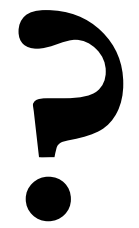
ANALYSIS

Stratification

Multivariat analysis

Propensity score (PS)

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). 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

Cross-over

Restriction

Matching

Self-controlled

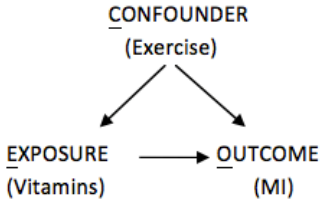
ANALYSIS

Stratification

Multivariat 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?

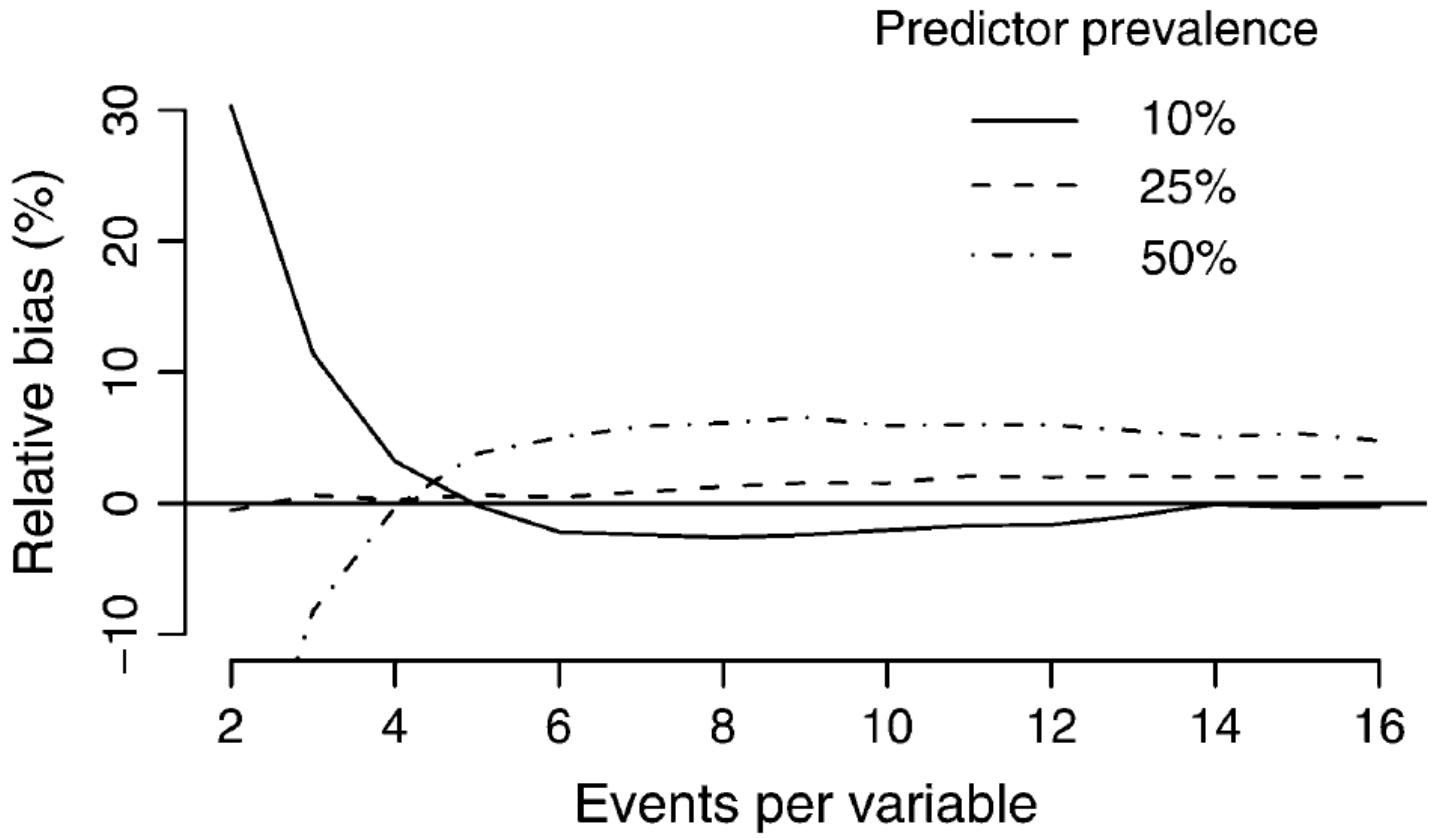
Warfarin and risk of SAH

	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

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)


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

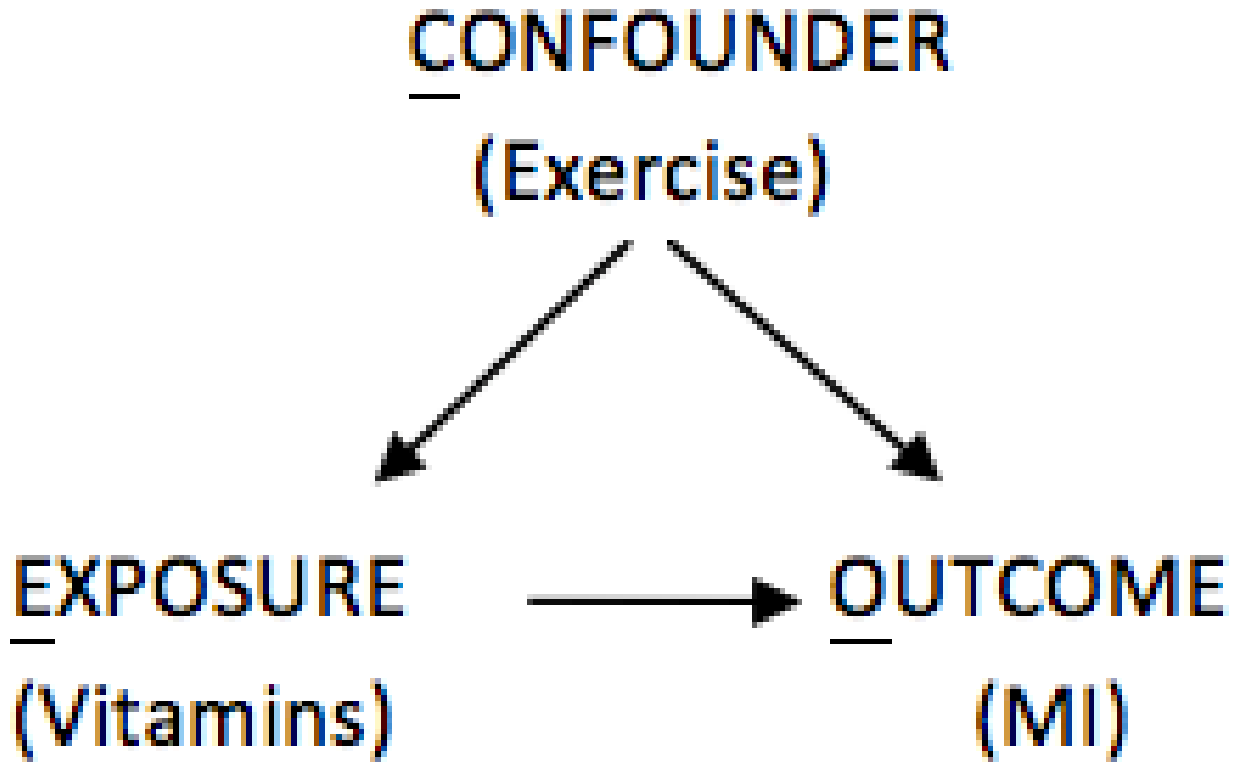
Characteristic	Methylphenidate Exposed (n = 222)	Unexposed (n = 2,220)	Random Sample (n = 10,000)
Maternal age, median (IQR), y	26 (22–30)	25 (22–30)	30 (27–34)
Maternal BMI, median (IQR)[a]	23.7 (20.8–28.7)	23.9 (20.9–28.1)	23.2 (21.0–26.6)
Maternal smoking status, n (%)			
Yes	113 (50.9)	1,100 (49.5)	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)

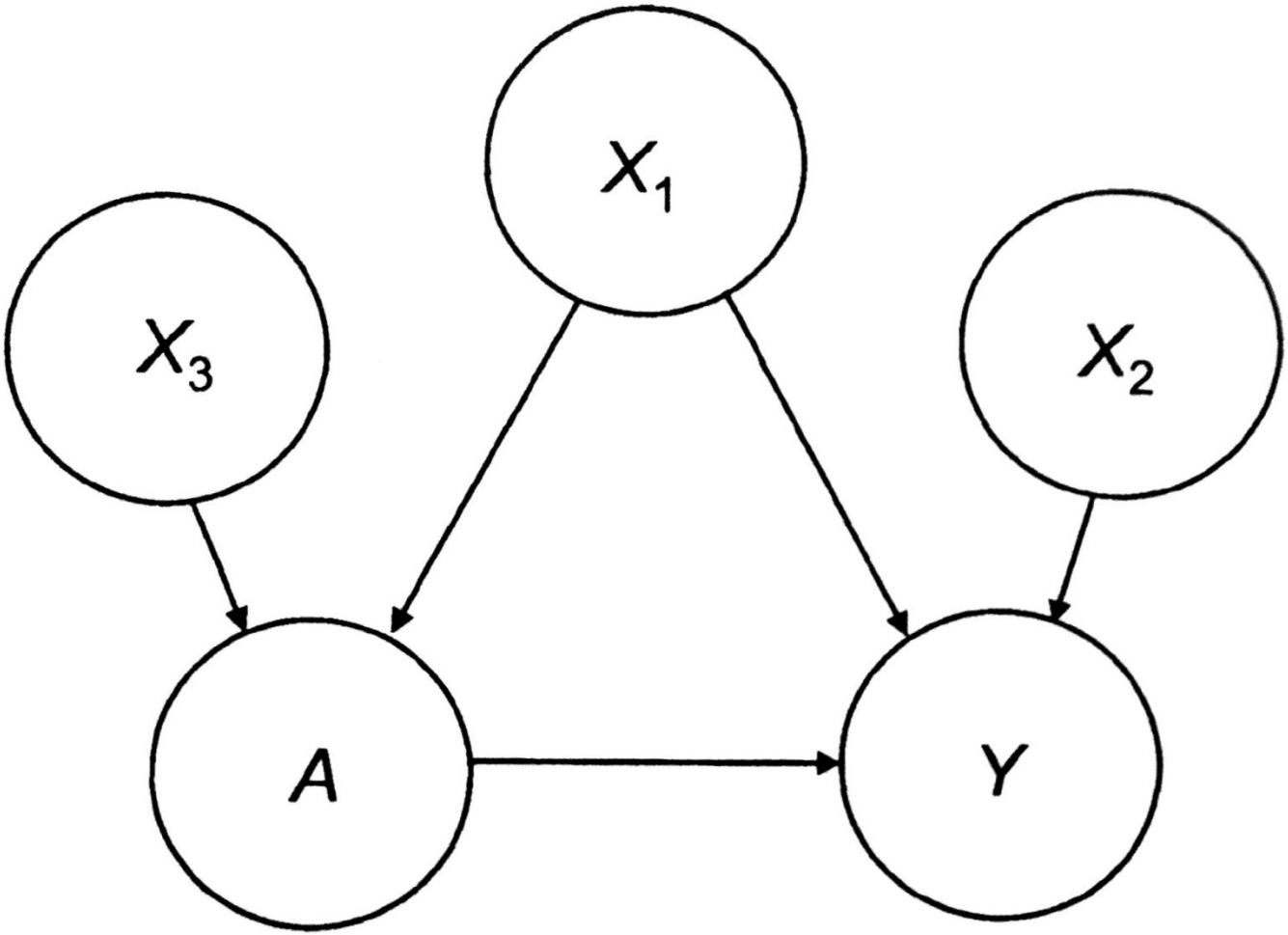
A propensity score (likelihood score) is a value between 0 and 1 that
- given a specific set of covariates -
provides the likelihood of ~~something~~ being treated with drug A over drug B

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)



Brookhart et al., AJE 2006

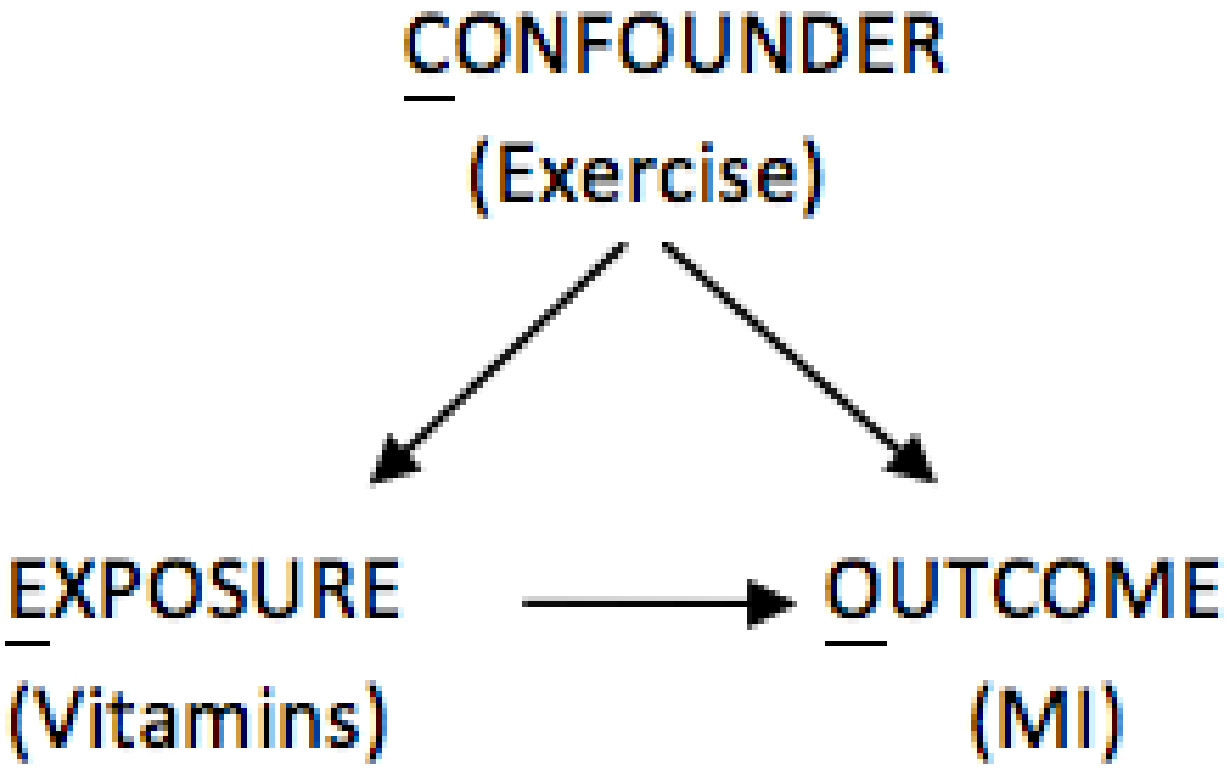
Matching
Regression
Stratification
Weighthing
... combinations

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'	**Schneeweis et al., Epidemiology 2009**
Disease risk scores	**Glynn et al., PDS 2012**


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