PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Methods to control for confounding
- Unmeasured confounding -

18 February 2015

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Objectives

At the end of this session about unmeasured confounding, you will be able to:

- Recognize sources of unmeasured confounding in pharmacoepidemiologic research
- Indicate different methods to handle unmeasured confounding
- Mention key assumptions of instrumental variable (IV) analysis to control for confounding
- State limitations in the application of IV analysis in pharmacoepidemiology

Outline

- What is unmeasured confounding?
- Methods to handle unmeasured confounding
- Interchanging one assumption for another
- Instrumental variables
- IV analysis in pharmacoepidemiology
  - Simulation studies
  - Empirical studies
  - How to… IV analysis
- Take home message

Unmeasured confounding

= confounding by variables that are not measured

= “unobserved confounding”

= “residual confounding”

(confounding by variables that are inadequately / inaccurately measured)

Electronic healthcare records

Unmeasured confounders in electronic healthcare records databases:

- Smoking status
- Body mass index
- Blood pressure recordings
- Family history
- …

Possible solutions

1. Collect additional confounder information:
   - Two-stage sampling

2. Comparison within individuals (no impact of between-subject differences):
   - Case-crossover design
   - Prior event rate ratio adjustment

Possible solutions (2)

3. Quantify unmeasured confounding in setting of known associations:
   - Negative control outcome

4. Quantify the impact of a known yet unmeasured confounder:
   - Sensitivity analysis

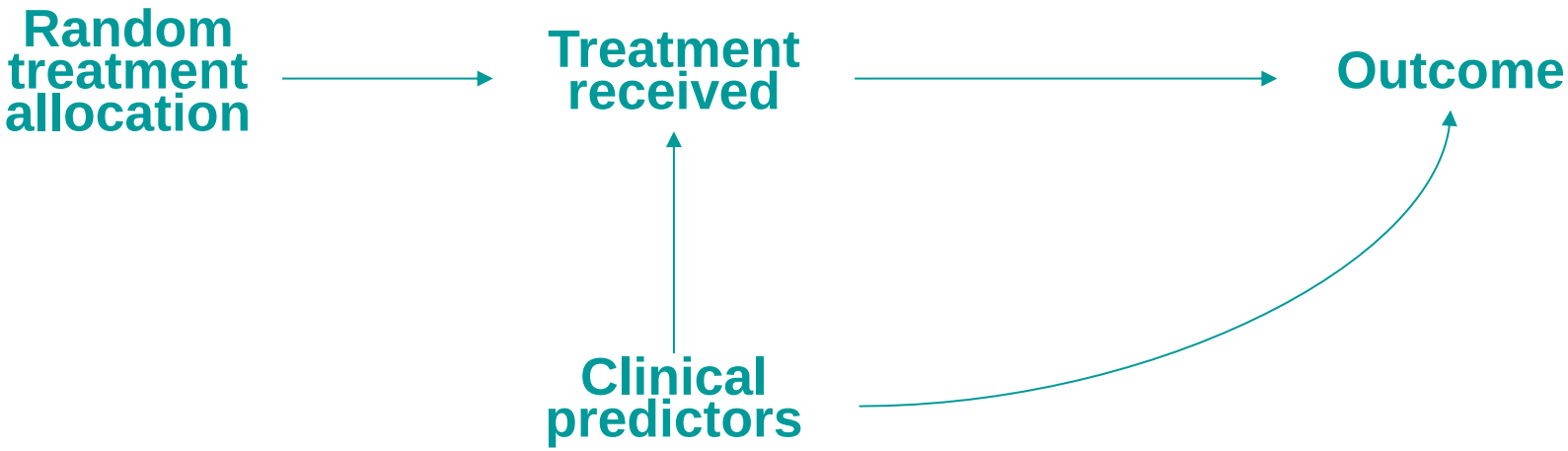
Possible solutions (3)

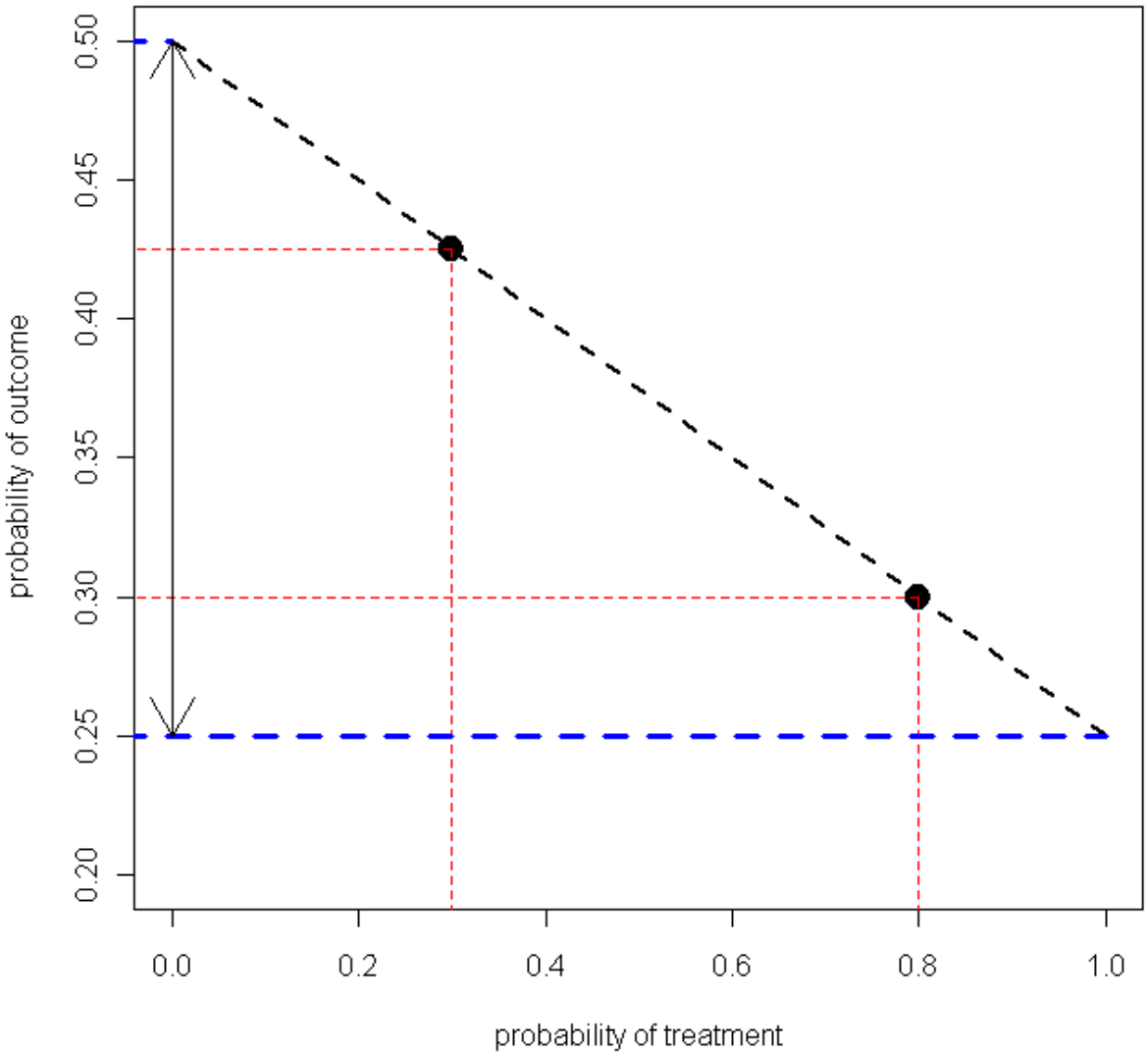
5. Try to mimic a randomized trial:
   - Instrumental variables

Assumptions

- Ordinary methods to control for confounding assume that 'there is no unmeasured confounding'
- Methods to handle unmeasured confounding interchange that assumption for other assumptions…
- There's no free lunch!

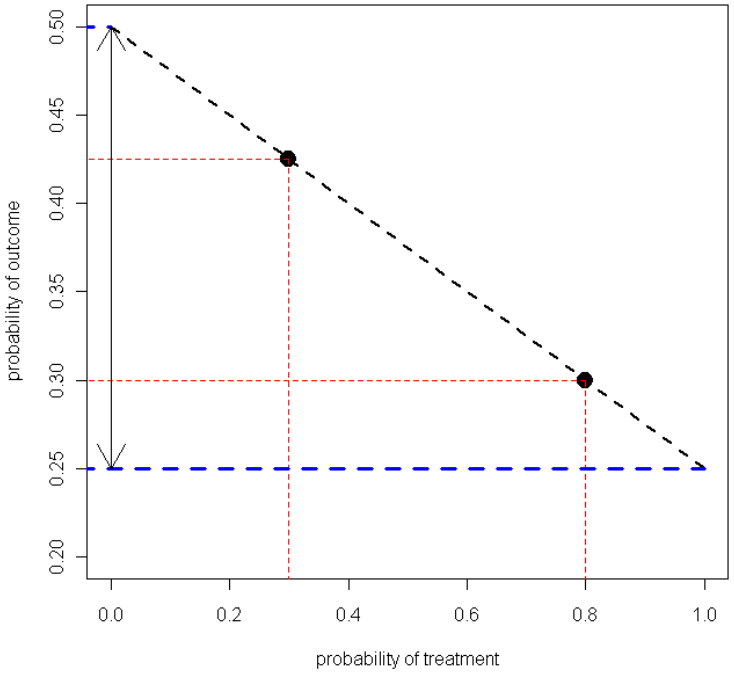
RCT with non-compliance

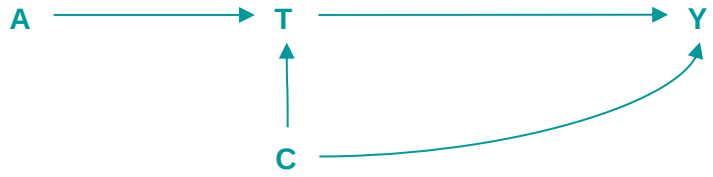




Extrapolation of the ITT effect to get the contrast between everybody vs. nobody treated

Groenwold, et al. OA Epidemiol 2014



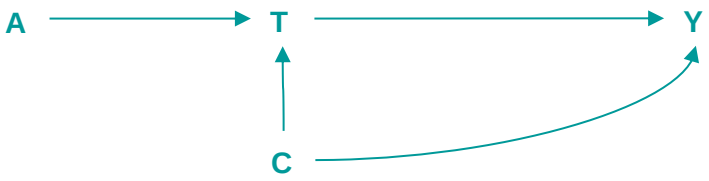


ITT effect = RD_{ITT} = P(Y|A=1) – P(Y|A=0)

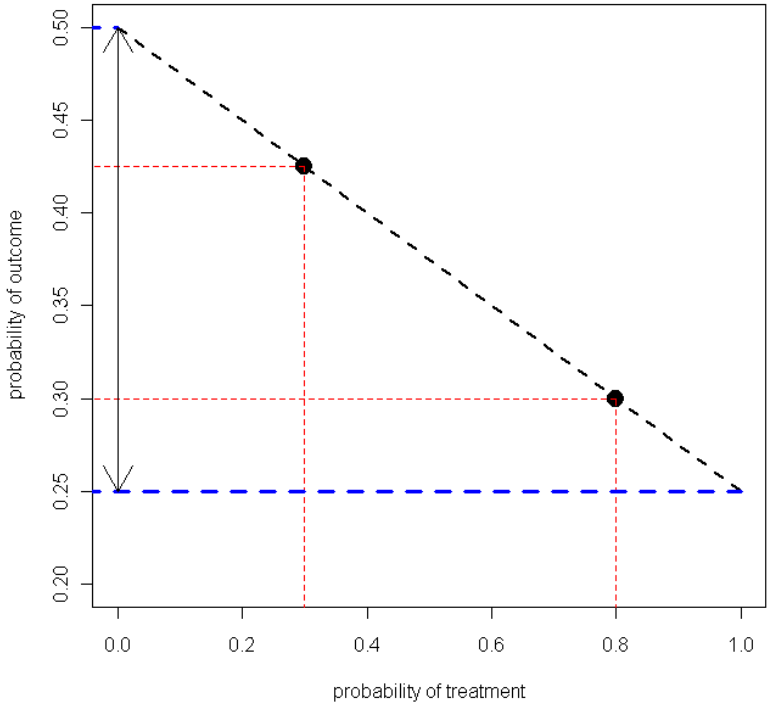
But A=1 ≠ T= 1

'Compliance effect' = $RD_{compliance}$ = P(T|A=1) – P(T|A=0)

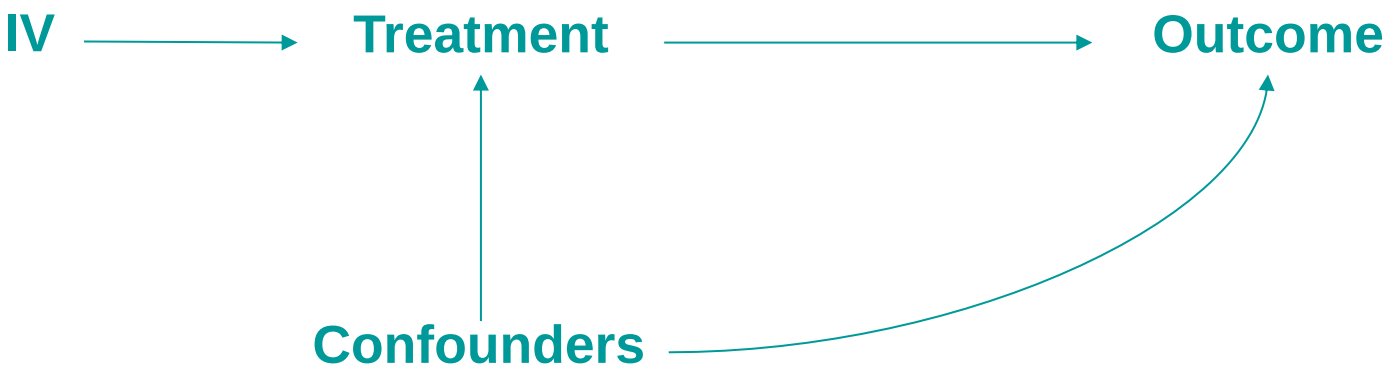
Non-compliance analysis



$$RD_{CAUSAL} = \frac{RD_{ITT}}{RD_{COMPLIANCE}}$$



Instrumental variables

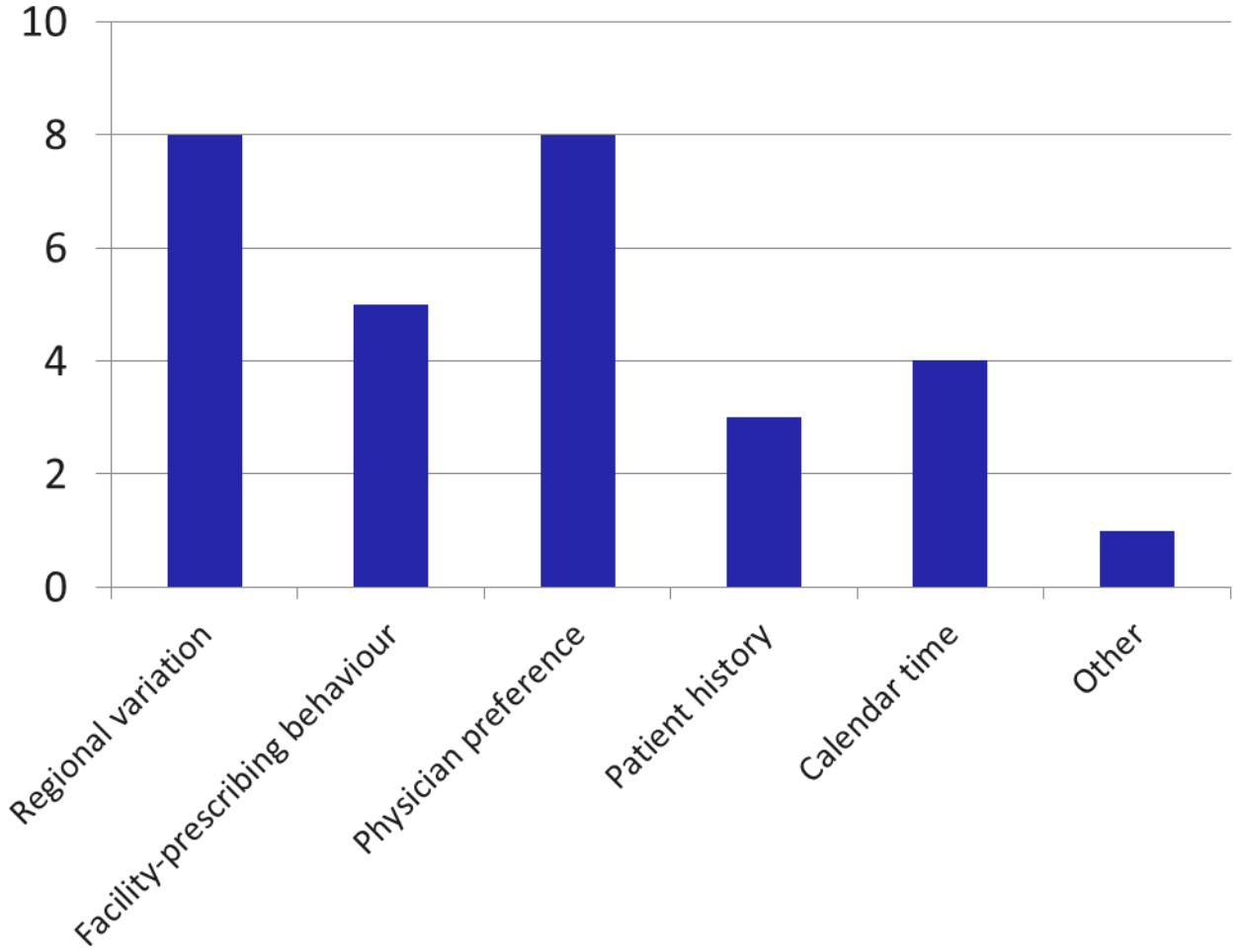


IVs in pharmacoepidemiology

Something different than random treatment allocation..

1. IV is related to exposure
2. IV is independent of confounders
3. IV affects outcome only through exposure

IV analysis in pharmacoepidemiology



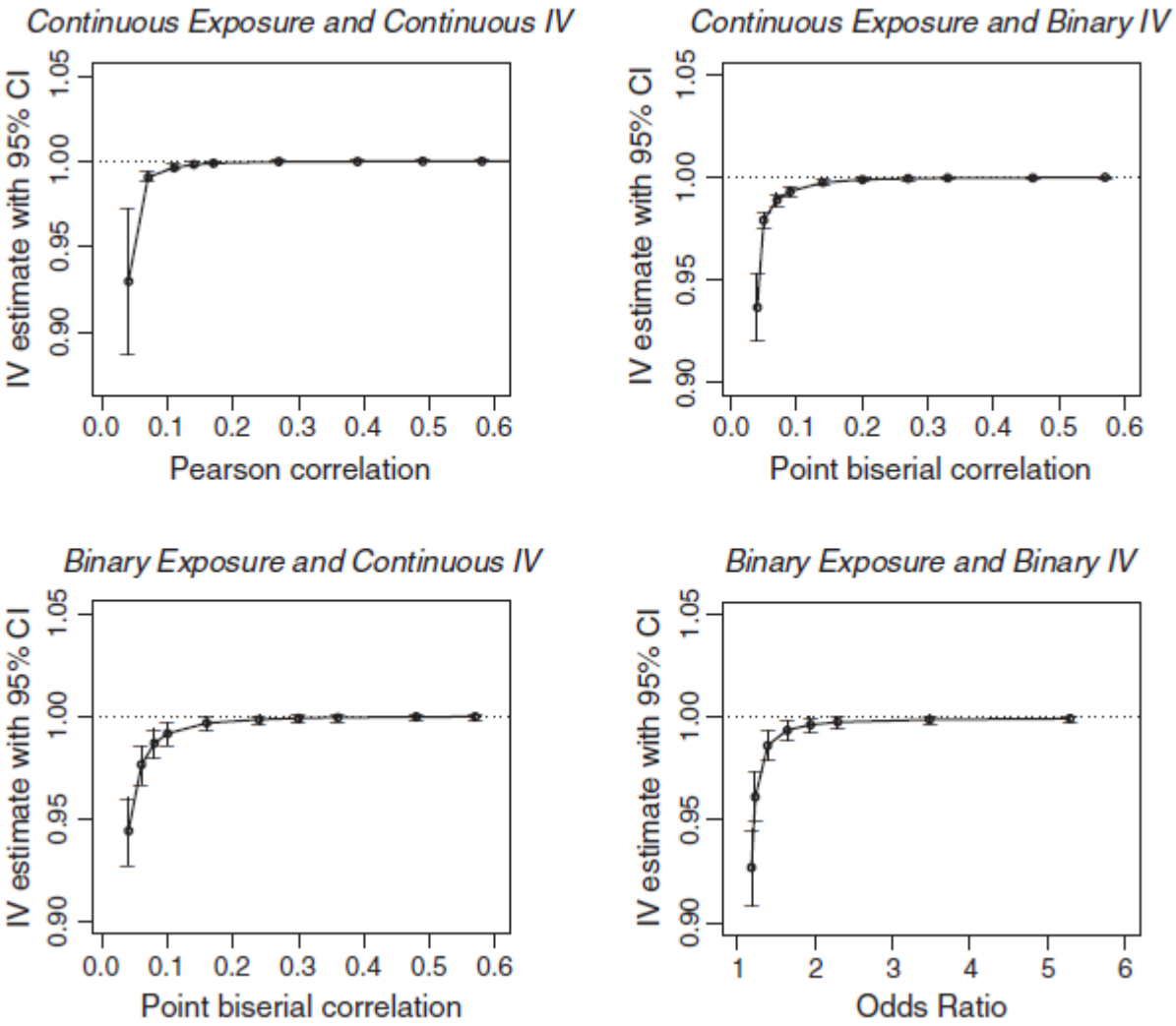
Chen, et al. J Clin Epidemiol 2012

IV analysis in PROTECT

- Simulation studies
- Studies using empirical data

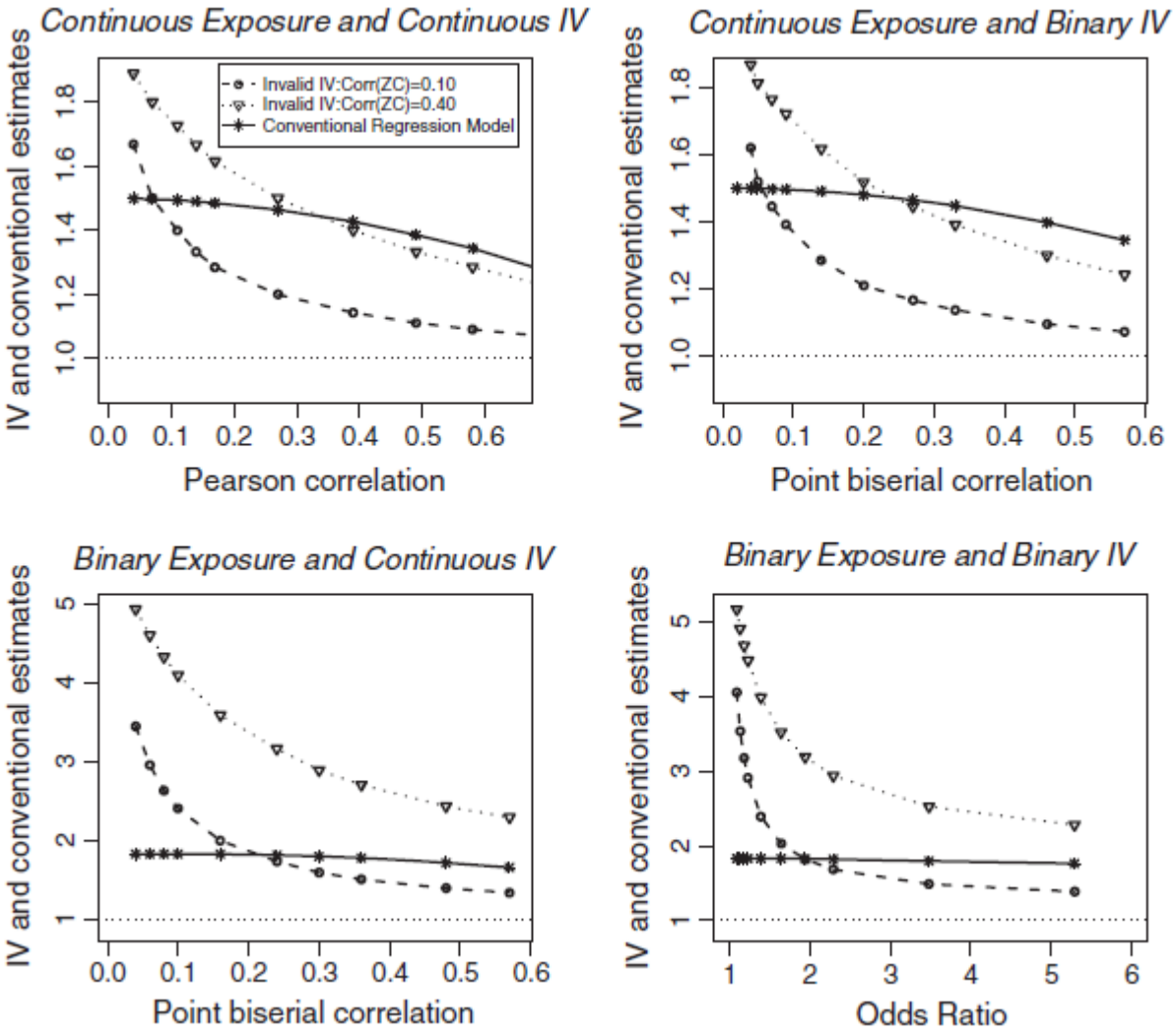
Simulation studies

- Allow to assess impact of design parameters in a controlled way
- Allow for comparison of effect estimates against a truth



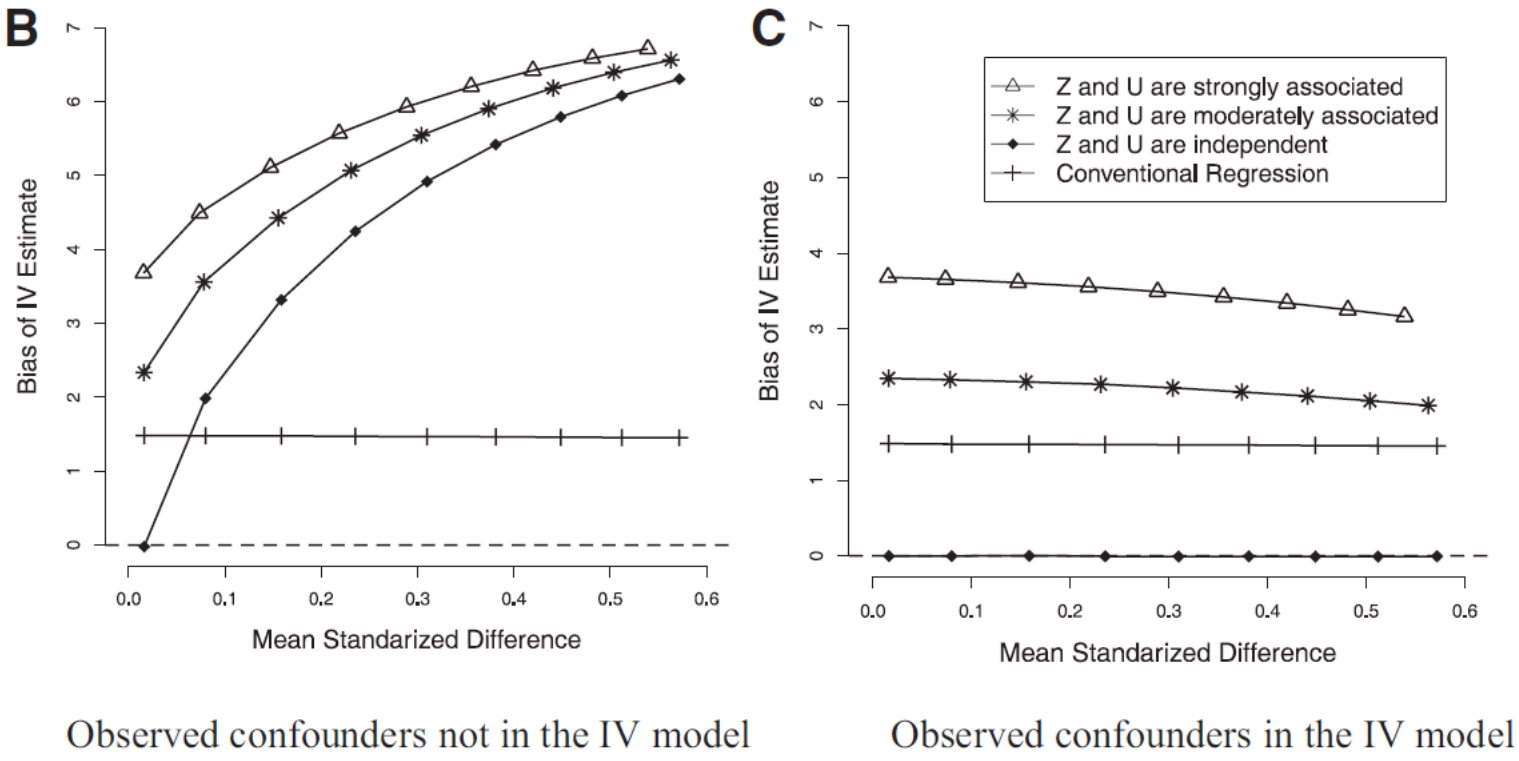
- Bias, if IV is very weakly related to exposure
- Can partly be remedied by large sample size

Uddin, et al. PDS 2014



- Bias, if IV related to confounders
- Bias depends on strength IV-exposure relation
- Bias in IV estimator can be larger than in conventional estimator

Uddin, et al. PDS 2014



Observed confounders not in the IV model

Observed confounders in the IV model

- PS balance measures can be used to assess balance of <u>observed</u> confounders across IV levels

Ali, et al. Epidemiology 2014

Simulation studies: Conclusions

- IV analysis highly sensitive to violations of assumptions
- Important to check assumptions ➔ tools available

Studies using empirical data

Aims:

- Study ease-of-use of IV methods in real life
- Assess face validity of IV estimates
- Investigate different potential IVs

IV analysis in pharmacoepidemiology

2 examples

1 conclusion: It’s hard to find an appropriate IV

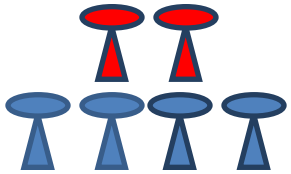
Beta2-agonists and myocardial infarction

- Study in 2 large EU databases (CPRD and Mondriaan)
- Asthma and COPD patients
- Multiple databases
  - CPRD: n= 490,499
  - Mondriaan: n = 27,459
- IV is 'physician prescribing preference'

Uddin, et al. submitted

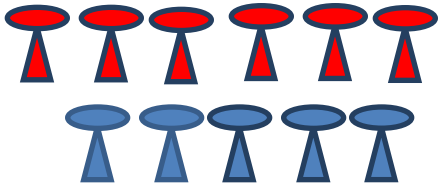
How to quantify physician preference

Physician A:



Preference red drug = 2/6

Physician B:

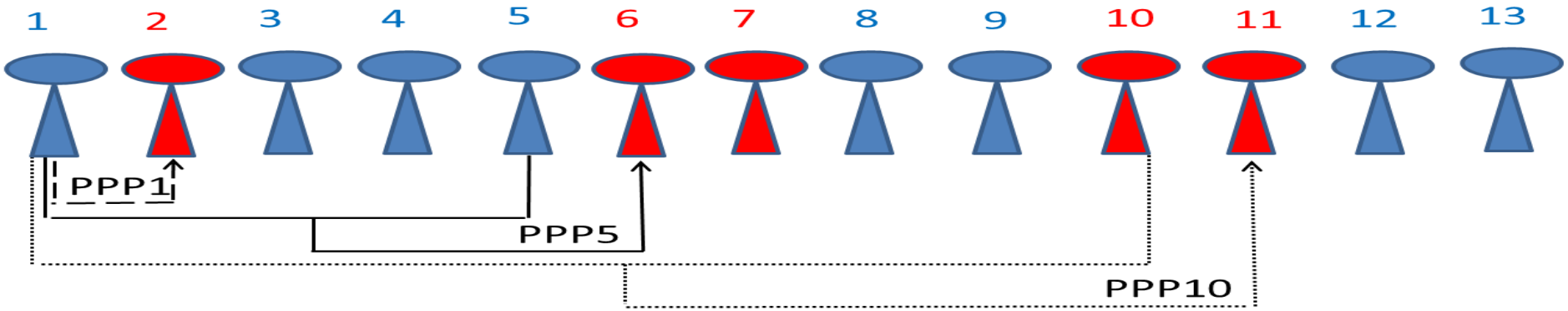


Preference red drug = 6/11

How to… data for IV study

	ID	Exposure	Outcome	Age	Sex	Covariate1	Covariate2	Covariate3	GP	IV
1	1	1	1	23	F	.	.	.	A	,33
2	2	0	1	54	F	.	.	.	A	,33
3	3	0	0	87	M	.	.	.	A	,33
4	4	1	0	56	M	.	.	.	A	,33
5	5	1	0	28	F	.	.	.	B	,55
6	6	0	0	91	M	.	.	.	B	,55
7	7	0	1	47	F	.	.	.	B	,55
8	8	1	0	55	M	.	.	.	B	,55
9	9	1	0	38	M	.	.	.	B	,55
10	10	0	1	91	F	.	.	.	C	,72

Quantifying physician preference



How to… checking IV assumption 1

- Relation between IV and exposure
  - Stronger relation is better!!
    - Correlation (e.g. $\rho > 0.2$)
    - Point-biserial correlation
    - Odds ratio (e.g. OR > 2)
    - …

Checking assumption 1

	CPRD	Mondriaan
Proportion of prescriptions (r)	0.14	0.31
Last 1 prescription (OR)	1.55	1.78
Last 5 prescriptions (r)	0.12	0.22
Last 10 prescriptions (r)	0.15	0.26

OR > 2 and correlation > 0.2 are considered appropriate

Checking assumption 1

	CPRD	Mondriaan
Proportion of prescriptions (r)	0.14	0.31
Last 1 prescription (OR)	1.55	1.78
Last 5 prescriptions (r)	0.12	0.22
Last 10 prescriptions (r)	0.15	0.26

How to… checking IV assumption 2

- Relation between IV and observed confounders
  - There should be no relations
    - Standardized difference (e.g., StD < 0.1)
    - Correlation
    - Mahalanobis distance
    - …

Checking assumption 2

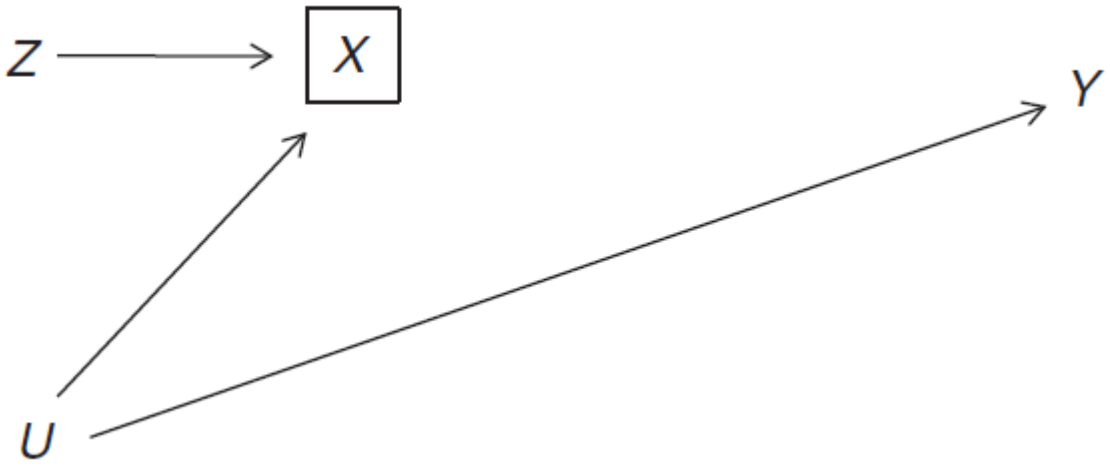
	CPRD	Mondriaan
Proportion of prescriptions		
Last 1 prescription		
Last 5 prescriptions		
Last 10 prescriptions		

Confounders balanced between IV groups if standardized difference < 0.1

IV analysis comparing treatment options

Swanson et al, AJE 2015:

"IV methods used to compare a subset of treatment options are prone to substantial biases, even when the proposed instrument appears relatively strong."



Assumption 1	CPRD	Mondriaan
Proportion of prescriptions		
Last 1 prescription		
Last 5 prescriptions		
Last 10 prescriptions		

Assumption 2	CPRD	Mondriaan
Proportion of prescriptions		
Last 1 prescription		
Last 5 prescriptions		
Last 10 prescriptions		

How to… IV analysis

1. Fit a model predicting exposure status, e.g.
   - In R:

```
lm(Exposure ~ IV)
```

   - In SAS:

```
proc reg;
   model Exposure=IV;
run;
```

How to… IV analysis

2. Fit a model relating the outcome to the predicted exposure status (Exposure.hat), e.g.

- In R:

```
lm(Outcome ~ Exposure.hat)
```

- In SAS:

```
proc reg;
   model Outcome = Exposure.hat;
run;
```

Note: requires robust variance estimator or bootstrapping

IV based on last 10 prescriptions

Database	Model	HR (95%CI)
CPRD	Crude	1.34 (1.26; 1.44)
	Adjusted	0.96 (0.89; 1.02)
	IV analysis	8.65 (5.57; 13.9)
Mondriaan	Crude	1.43 (1.18; 1.73)
	Adjusted	1.18 (0.97; 1.43)
	IV analysis	2.46 (1.03; 5.75)

2. Antidepressant use and hip fracture

- Study in 3 large EU databases (BIFAP, THIN, Mondriaan)
- Patients prescribed an antidepressant drug (SSRI v. TCA)
- Multiple databases
  - BIFAP: n = 252,203
  - THIN: n= 570,139
  - Mondriaan: n = 22,474
- IV is 'physician prescribing preference'

Uddin, et al. submitted

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Assumption 1	BIFAP	THIN	Mondriaan
Proportion of prescriptions			
Last 1 prescription			
Last 5 prescription			
Last 10 prescription			

Assumption 2	BIFAP	THIN	Mondriaan
Proportion of prescriptions			
Last 1 prescription			
Last 5 prescription			
Last 10 prescription			

IV based on last 10 prescriptions

Database	Model	HR (95%CI)
BIFAP	Crude	1.21 (1.06; 1.39)
	Adjusted	1.35 (1.18; 1.56)
	IV analysis	2.57 (0.59; 11.93)
THIN	Crude	0.72 (0.67; 0.77)
	Adjusted	1.35 (1.26; 1.44)
	IV analysis	0.57 (0.36; 0.92)
Mondriaan	Crude	0.75 (0.48; 1.17)
	Adjusted	1.36 (0.84; 2.15)
	IV analysis	0.44 (0.04; 5.43)

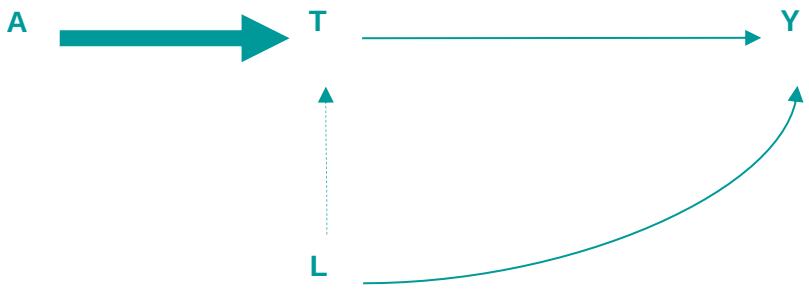
Interplay between assumptions

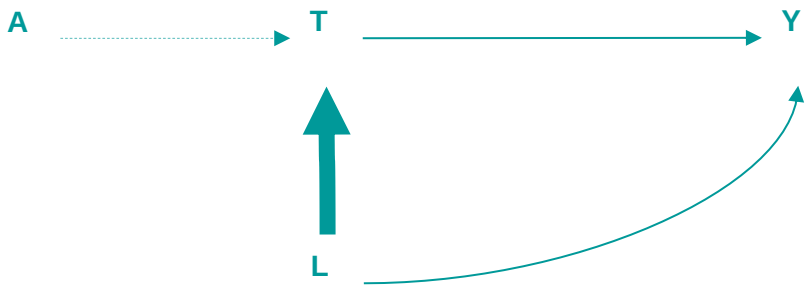
- If the proportion of explained variation in the treatment due to the IV is relatively large, there is little variation in treatment left that can be attributed to the confounders

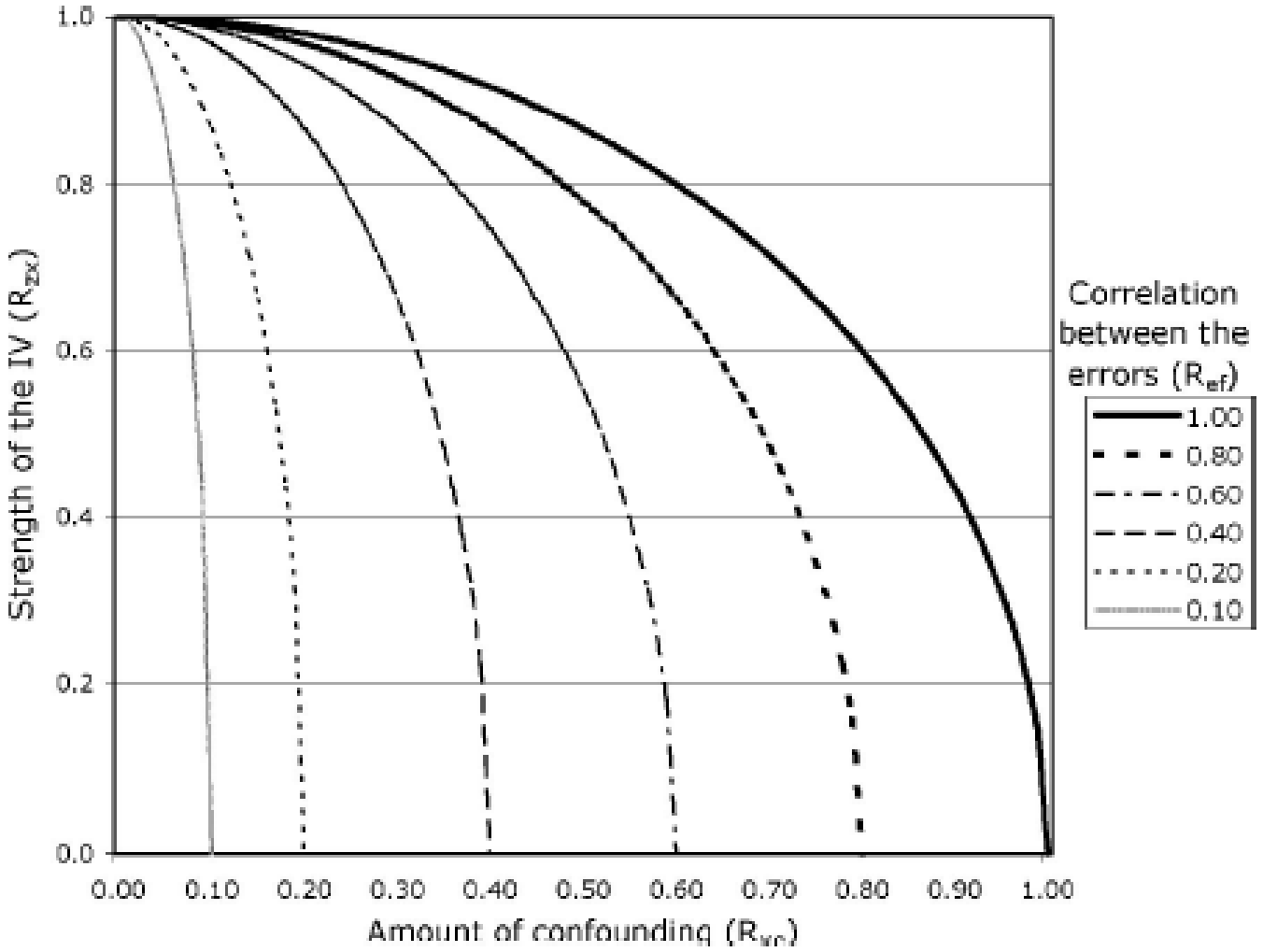
- So, if you find a strong IV, apparently, there's little confounding

- And vice versa: important confounding → hard to find 'strong' IV

Interplay between assumptions







Martens, et al. Epidemiology 2006

A bit more on assumption 2

- "IV is independent of confounders"
- Prognostic patient characteristics equally distributed among physicians; different physicians see more or less similar patients

- Observed confounders can be controlled for in IV analysis.
- In that case, assumption 2 is that unobserved confounders are independent of the IV.
- Back to square one…

Assumption 3….

- "IV affects the outcome only through the exposure"
- In case of the IV 'physician preference' this implies:
  - The only thing the physician differ on is their preference for the exposure of interest
  - Similar standard of care, similar expertise, similar behaviour regarding prescribing concomittant medication

Take home messages

- IV analysis in pharmacoepidemiology is challenging
- Be sceptical about methods that claim to control for unmeasured confounding
- When reviewing a study that applied IV analysis:
  - Did the authors check (/substantiate) the assumptions?
  - Did the authors test robustness of IV analysis, e.g. by applying different (related) IVs?