Propensity scores and instrumental variables to control for confounding

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

WP2 – WG2: aims

- Evaluate methods to control for observed and unobserved confounding
  - Simulations
  - Empirical studies

- Examples:
  - Belitser et al. PDS 2011
  - Groenwold et al. PDS 2011
  - Ali et al. Eur J Epidemiol 2013

Outline

- Motivating example: LABA use and risk of MI
- Propensity score methods to control for time-dependent confounding
- Instrumental variable analysis to control for confounding
- Conclusions

LABA use and risk of MI

- **Research setting:**
- Dutch GP database (1995-2005) – 6 GP centers
- Selection of COPD/asthma patients
- Prevalent and incident LABA users
- Outcome is non-fatal myocardial infarction

PROTECT

Characteristics	LABA	
	Ever users (N = 1264)	Never users (N = 6835)
Mean (SD) age (years)	51.9 (18.4)	49.2 (19.2)*
Male gender	579 (45.8)	2887 (42.2)
Co-morbidities		
COPD	595 (47.1)	623 (9.1)*
DM	114 (9.0)	597 (8.7)
CVD	474 (37.5)	2090 (30.60*
Co-medications		
Anti-diabetics	103 (8.1)	498 (7.3)
CV medications[a]	573 (45.3)	2243 (932.8)*
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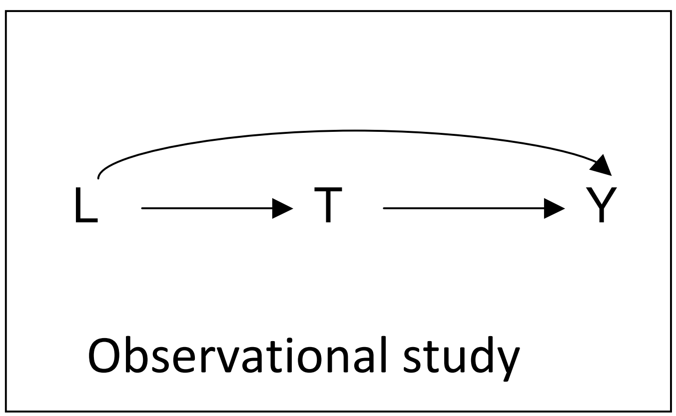
Statins	38 (3.0)	281 (4.1)
Corticosteroids	249 (19.7)	760 (11.1)*
Anticholinergics	579 (45.8)	1075 (15.7)*
Glucocorticoids	835 (66.0)	2088 (30.5)*
SABA	834 (66.0)	2326 (34.0)*

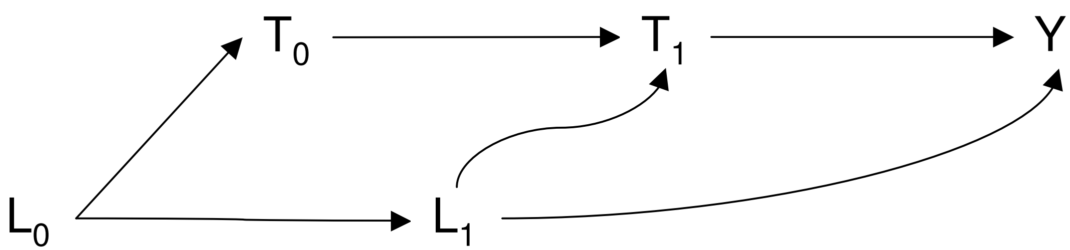
Ali MS, et al. *Eur J Epidemiol* 2013

Propensity score

- Propensity score = probability of treatment given observed confounders
- PS ´summarizes´ confounder information
- Single variable to control for confounding
- Useful in case of limited number of cases



Confounding in studies with time-dependent treatment



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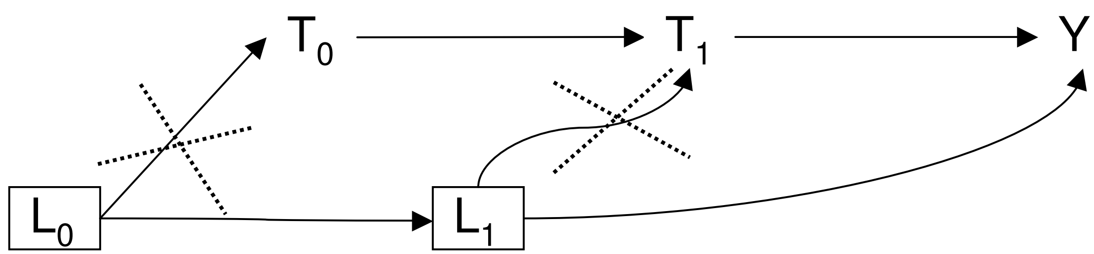
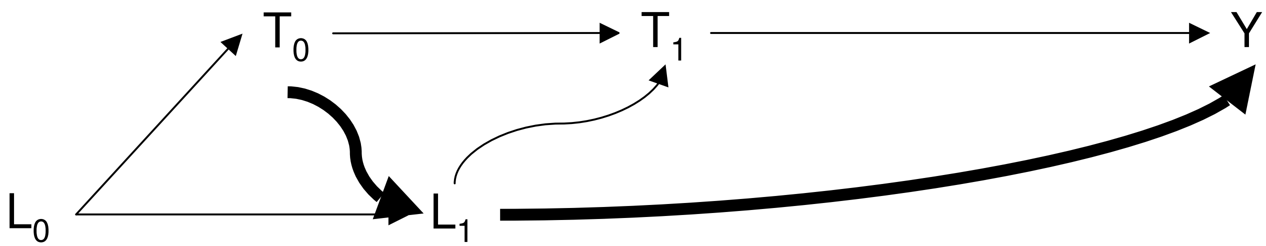


- PS analysis (e.g. stratification on PS) blocks the path between the confounder and treatment

Time-dependent confounders that are affected by previous treatment



- T is a time-varying T_x
- L is time-varying and affects T at each time point
- L_1 mediates the path from T_0 to Y

- Thus, controlling for the confounding effect of L_1, removes some of the effect of T_0 on Y…leading to an underestimation of the true effect

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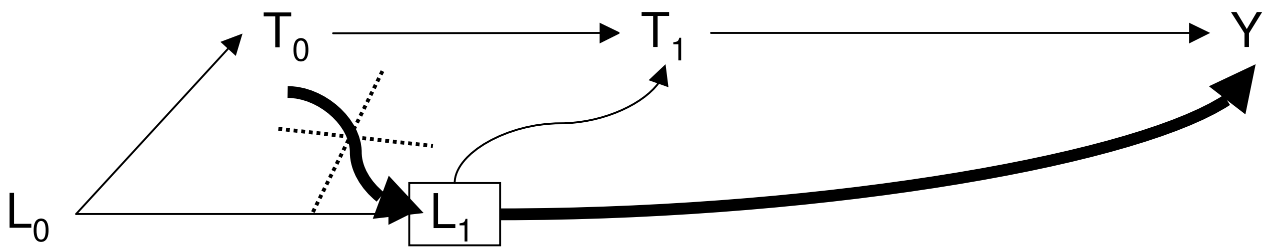

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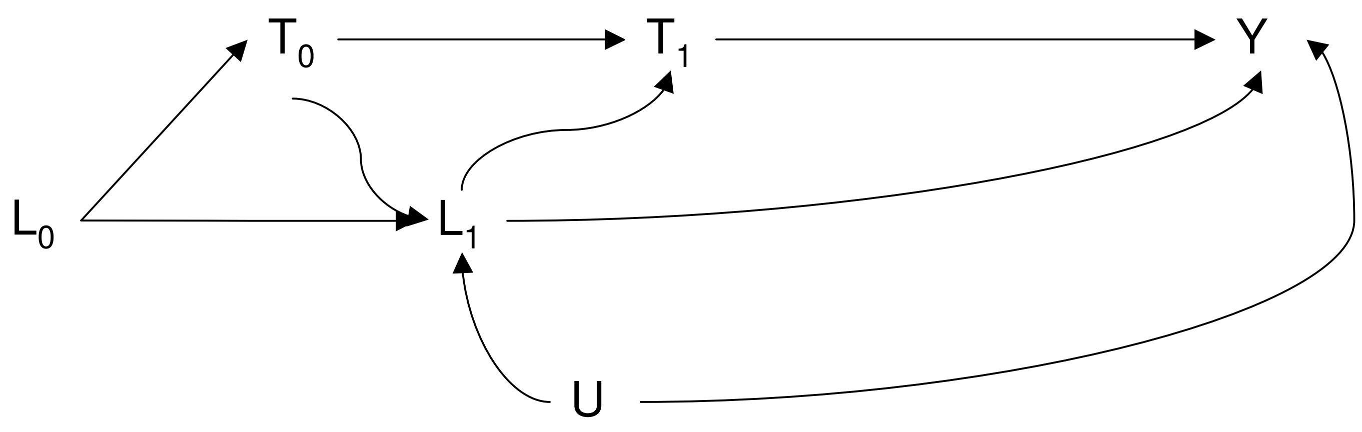
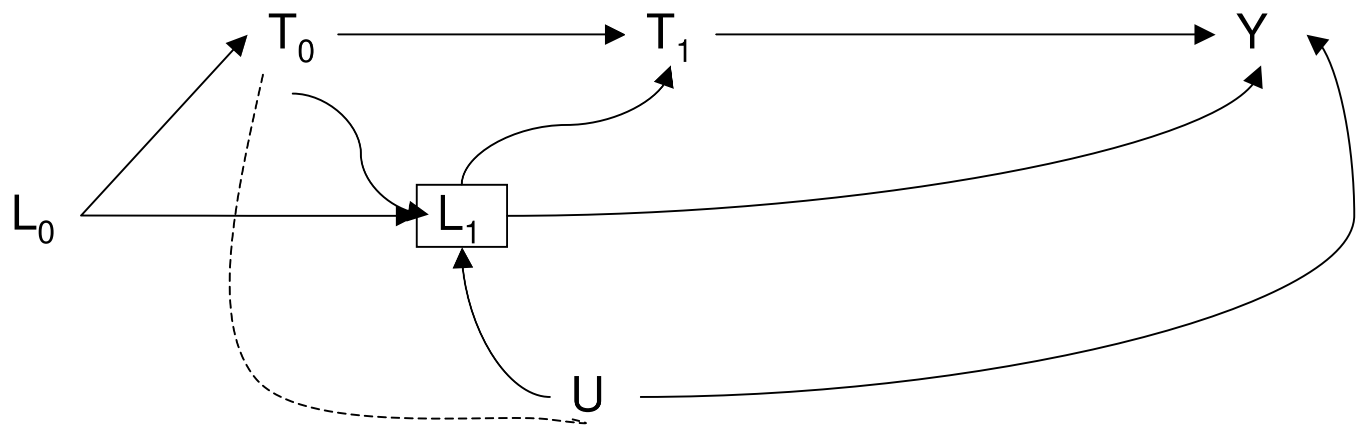


- Conditioning on L_1 may open a path between T_0 and U and induce confounding!

PROTECT

Time-dependent confounders that are affected by previous treatment



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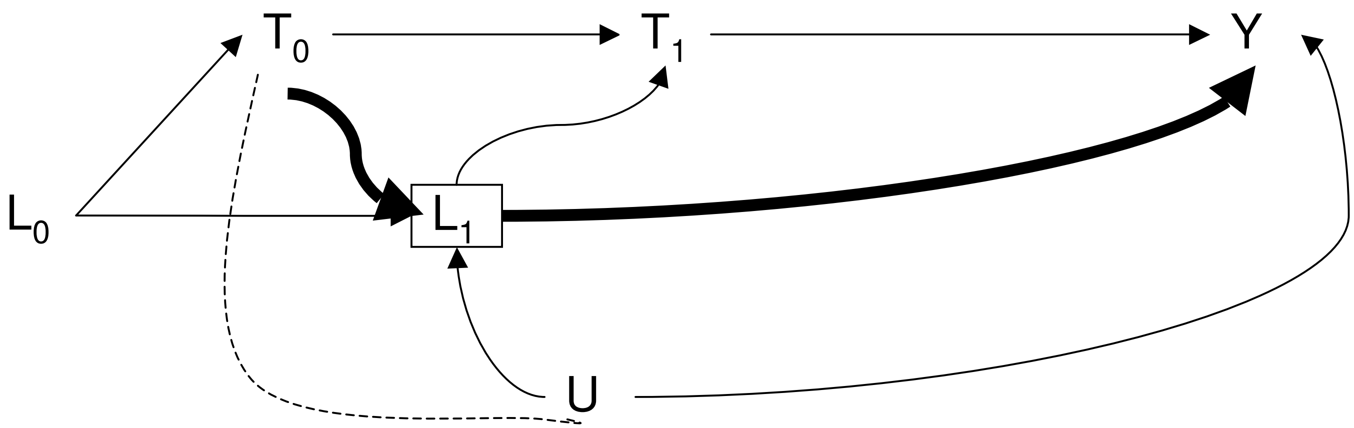
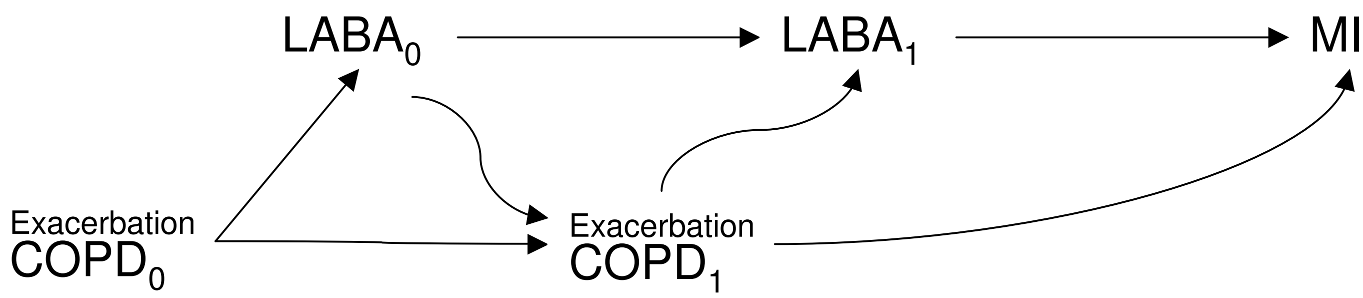
Time-dependent confounders that are affected by previous treatment



- ***In general, one shouldn't condition on L_1***

Time-dependent confounding in PROTECT



Aim: To compare different methods to deal with time-dependent confounding in empirical research on adverse events

Ali MS, et al. *Eur J Epidemiol* 2013

Methods for time-dependent confounding that is affected by previous treatment

- Marginal structural model:

  e.g. inverse probability weighting (IPW)

  Method that does not condition to adjust for confounding

LABA use and risk of MI

Table 4 Estimates of hazard ratio for CHD associated with use of inhaled SABA and LABA using different *time-dependent PS* methods and MSMs With three-month interval approach

Methods	SABA use		LABA use	
	HR	95 % CI	HR	95 % CI
PS stratification				
Quintiles of PS[a]	1.07	0.72, 1.60	1.13	0.76, 1.67
Deciles of PS[b]	1.15	0.77, 1.71	1.06	0.71, 1.57
PS covariate adjustment[c]	1.09	0.74, 1.61	1.09	0.74, 1.62
MSMs-model 1[d]	0.92	0.60, 1.41	0.89	0.53, 1.50
MSMs-model 2[e]	0.86	0.55, 1.34	0.77	0.45, 1.33

Ali MS, et al. *Eur J Epidemiol* 2013

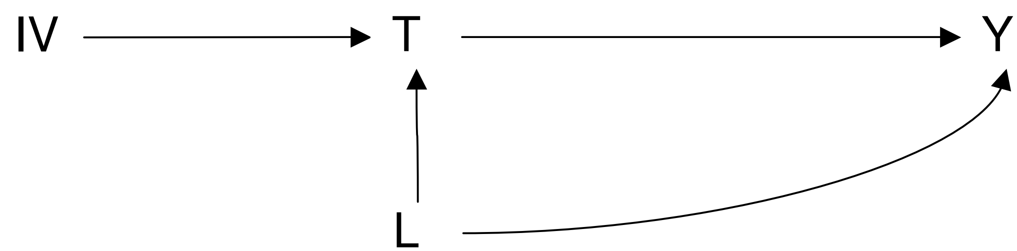
Observed and unobserved confounding

- Propensity score methods only control for *observed* confounding

  → potential for *unobserved* confounding

- Instrumental variables control for observed as well as unobserved confounding

Instrumental variables in medical research

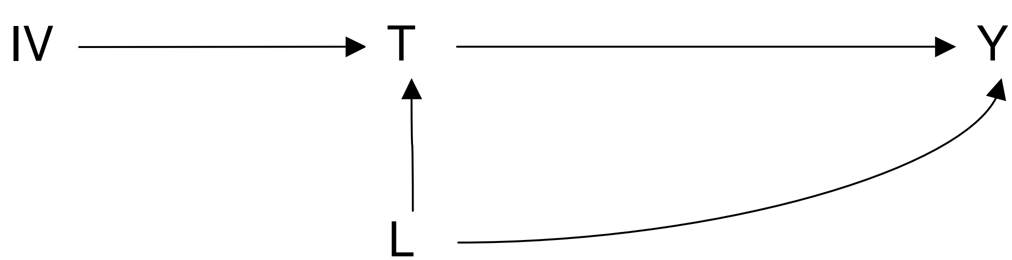


- Examples of IV:
  - Random allocation of treatment (RCT)
  - Genetic polymorphism (SNP)
  - Physician preference

Instrumental variables

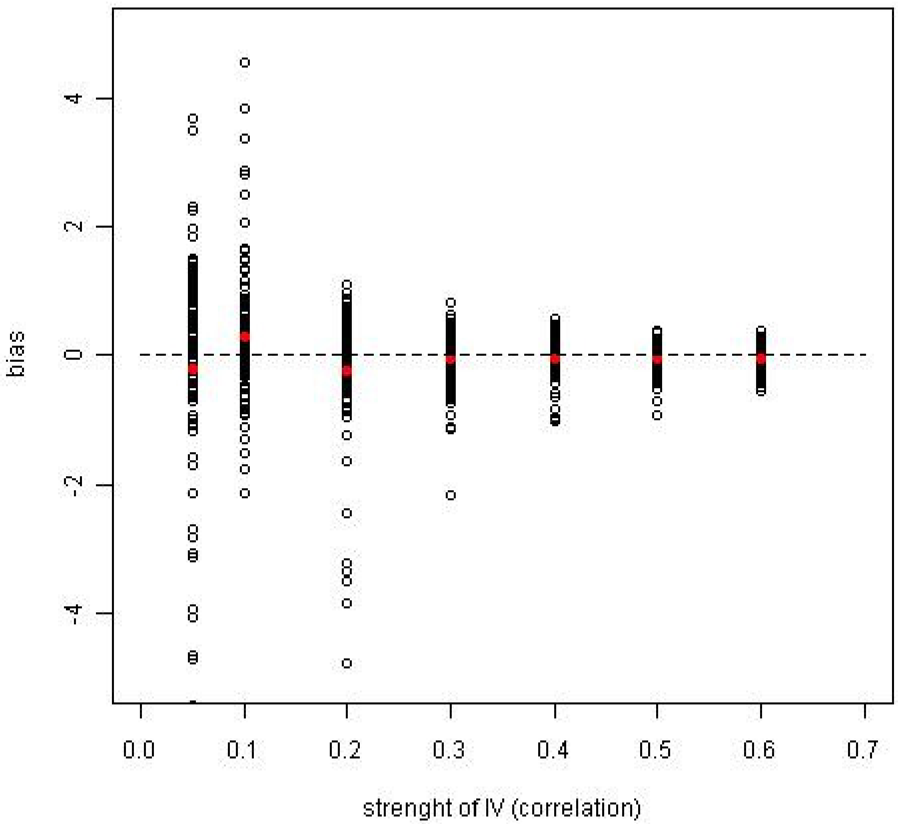
- 3 main assumptions:

1. IV is related to exposure → formal check
2. IV is independent of confounders → design / circumstantial evidence
3. IV affects outcome only through exposure → untestable

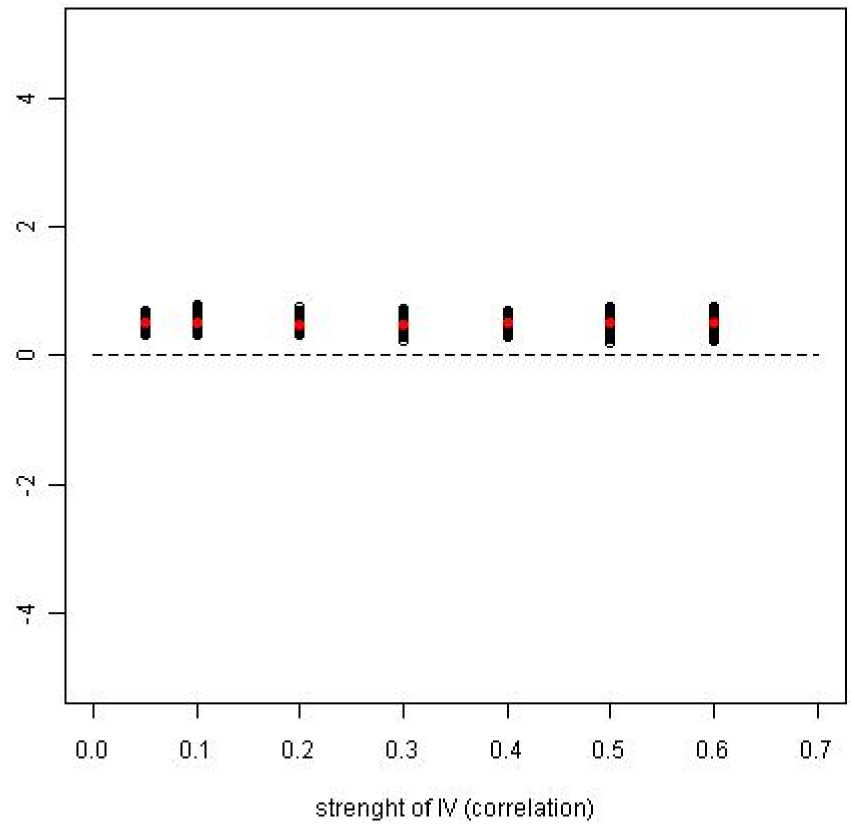


Assumption 1. Strength of IV

IV analysis, n = 100

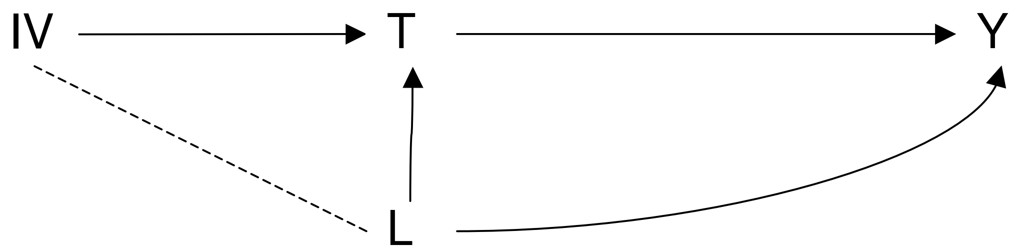


Standard analysis, n = 100
No confounding adjustment

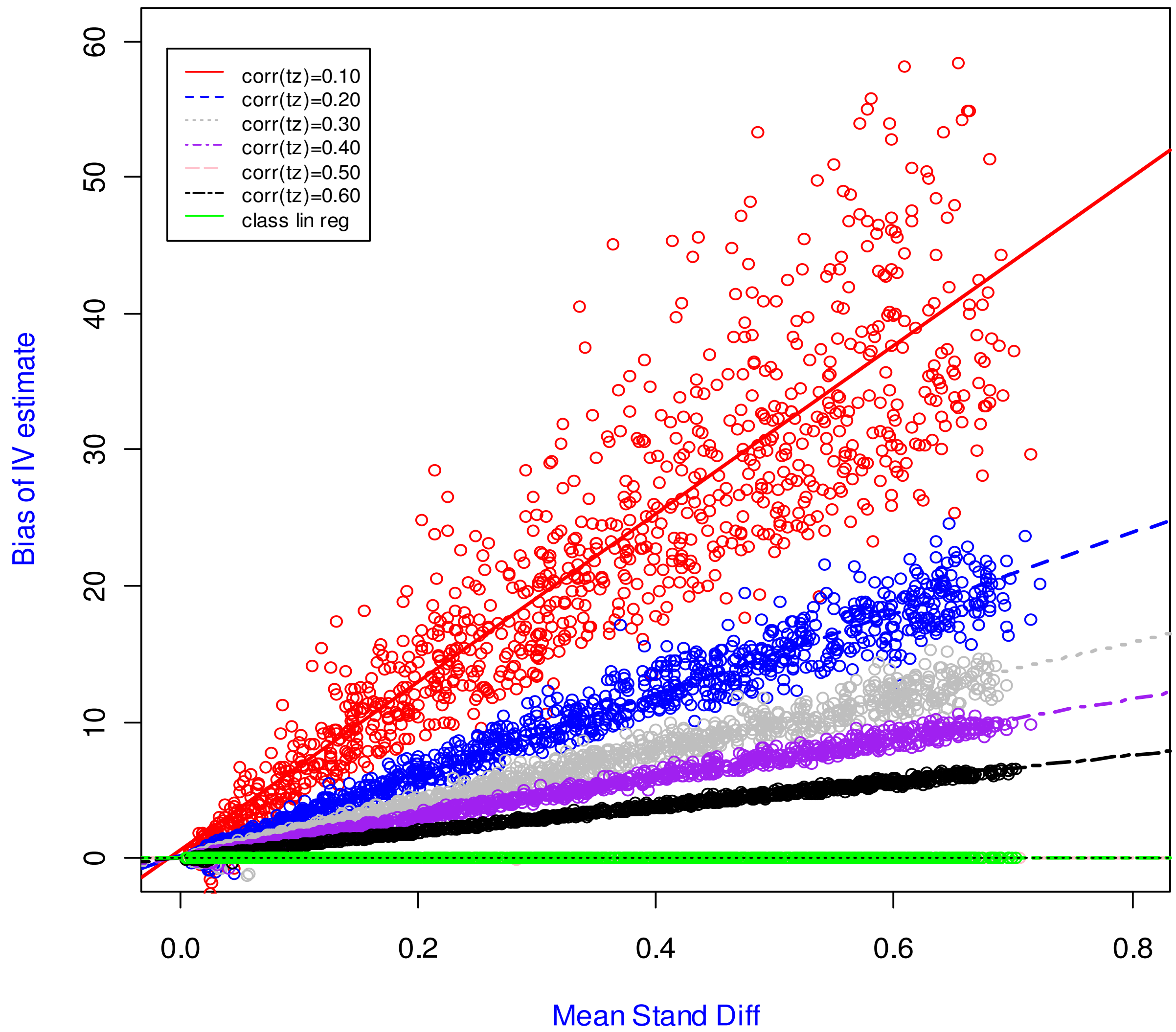


Uddin MJ, Ali MS, et al. Unpublished work

Simulation setup



Assumption 2. - No relation with confounders



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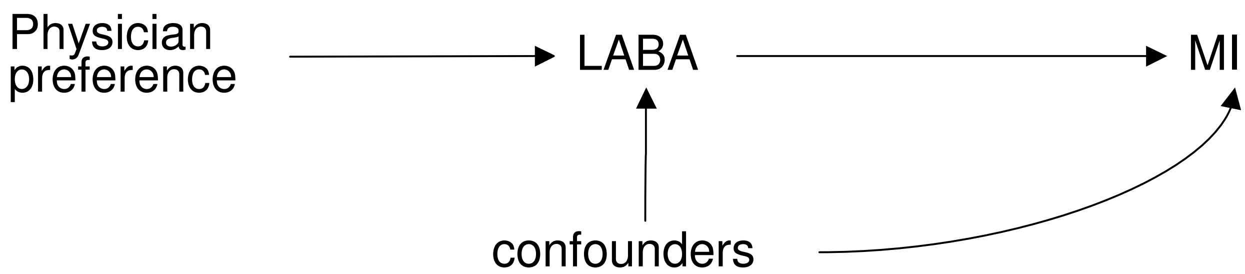
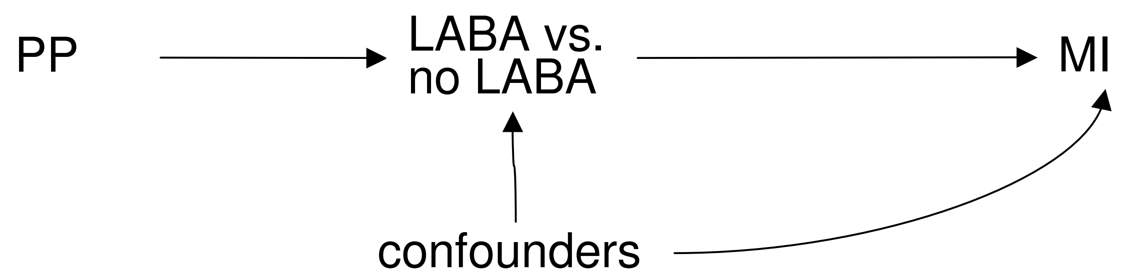
Application of IV analysis



- **<u>3 key assumptions</u>:**

1. Physicians have a differential preference
2. Physicians preference is independent of confounders (physicians see more-or-less the same patients)
3. Physicians preference affects risk of MI only through exposure (quality of care is the same, except for exposure)

LABA vs. no LABA



Proportions of LABA users among categories of IV (GP_ID):

GP_ID	% LABA prescription
1	12.2%
2	13.0%
3	15.8%
4	16.4%
5	18.8%
6	23.1%

Baseline characteristics by LABA use

Characteristics	LABA	
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Male gender	579 (45.8)	2887 (42.2)
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Physician preference for LABA

	GP_ID 6 (high) (n = 705)		GP_ID 1 (low) (n = 1577)	
LABA use	163 (23.1%)		193 (12.2%)	
Mean age	46.1		46.9	
Sex (male)	302 (42.8%)		658 (41.7%)	
Cardiovascular disease	173 (24.5%)		465 (29.5%)	
Cardiovascular medication	208 (29.5%)		526 (33.4%)	
COPD	106 (15.0%)		159 (10.1%)	
Diabetes mellitus	49 (7.0%)		136 (8.6%)	
Diabetic medication	49 (7.0%)		119 (7.5%)	
Statins	24 (3.4%)		73 (4.6%)	

Baseline characteristics of patients of highest and lowest prescribing physicians

LABA vs. no LABA

Model	Hazard ratio (95% CI)
Crude	1.22 (0.95; 1.57)
Adjusted#	0.84 (0.63; 1.13)
IV analysis	0.76 (0.40; 1.06)

adjusted for age, sex, cardiovascular disease, DM, medication use

- **Preliminary conclusions:**
- IV moderately related to exposure
- Observed confounders reasonably balanced between IV groups

What this project adds

- Comparison of different methods to control for time-dependent confounding shows impact of such confounding
- Simulations show sensitivity of IV analysis to violations of assumptions
- Application of IV analysis in empirical data is not straightforward
- First step towards guidance on application of methods for time-dependent confounding and IV analysis in pharmacoepidemiologic studies of adverse events.

Future

- Apply methods for time-dependent confounding in different datasets (different exposures, different outcomes, different confounders)

- Evaluate different IVs for different questions in different databases