

Comparison of methods to control for confounding

review of findings and lessons learned

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On behalf of WP2–WG2

Aim of WP2-WG2

- Evaluate methods to control for observed and unobserved confounding
 - Simulations
 - Empirical studies
 - ♦ Beta2agonist use and risk of MI
 - ♦ Antidepressants and risk of hip fracture

4 challenges

1. **Multiple potential confounders:** Study of adverse event with multiple potential confounders
2. **Rare outcome, many confounders:** Study of a relatively rare adverse event with a large battery of measured potential confounders
3. **Time-dependent confounding:** Study of time-varying treatment with a measured time-dependent confounder meeting criteria for an intermediate variable
4. **Unmeasured confounding:** Study with a strong possibility of unmeasured confounding

1. Multiple potential confounders

- Researchers have different ways of selecting confounders.

Q: How to select confounders?

A: Selection of confounding variables should not be based on observed associations with exposure, but rather be prespecified.¹

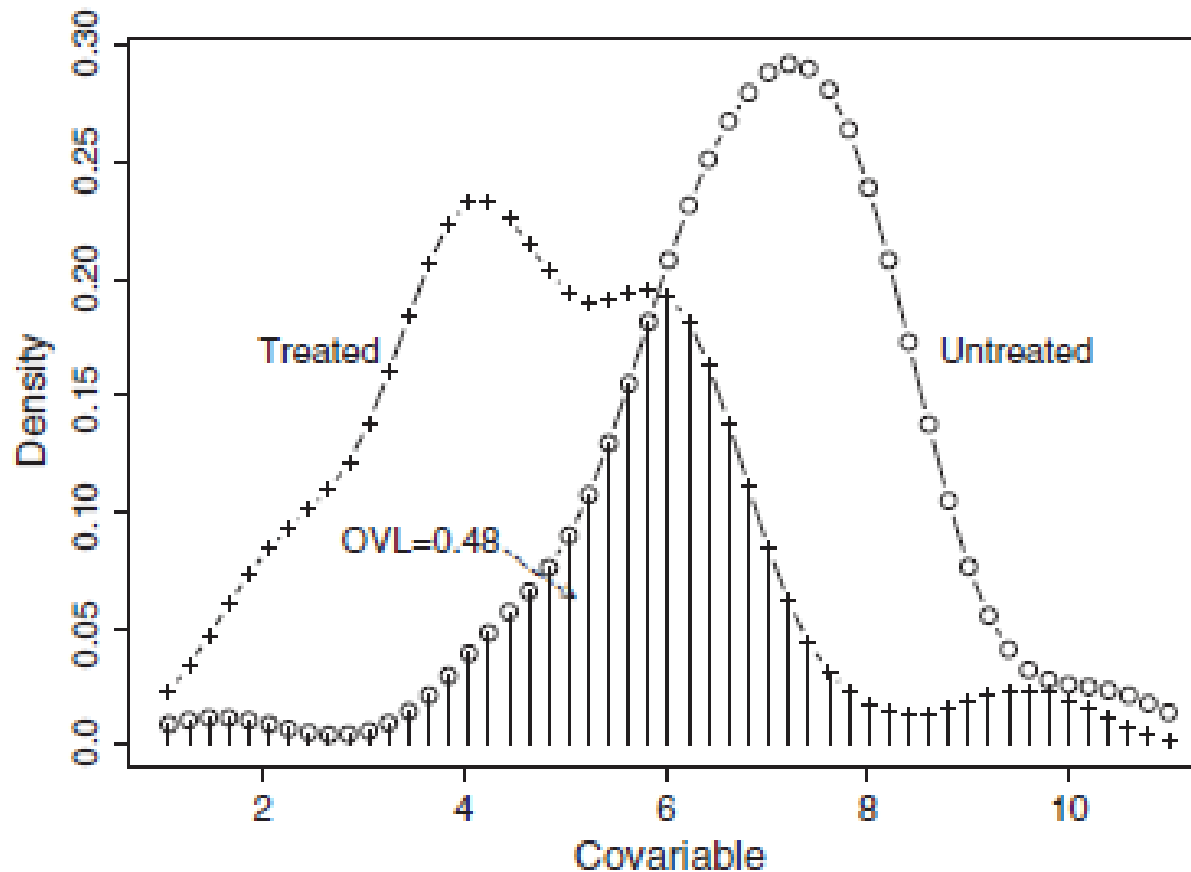
2. Rare outcome, many confounders

- Possible solution: propensity score methods

Q: How to assess quality of PS model?

A: Balance measures!!

Propensity score balance measures²



REVIEW ARTICLES

Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: a systematic review

Methods	Number of articles (<i>n</i>) ^a
SDif	45 (25.4)
<i>P</i> -values ^b	125 (70.6)
Graphical displays	11 (6.20)
Eye balling	4 (2.3)
Others ^c	13 (7.3)

PS model selection

- Balance measures may help to select optimal PS model⁴
- It is relatively easy to do this in empirical datasets
 - E.g. consider 2000 different PS models and select the most appropriate one⁵
- Balance measures may also help to determine optimal caliper width in propensity score matching⁶

3. Time-dependent confounding

- Possible solution: marginal structural modeling (MSM)

Q: Does it matter in real life?

A: Comparing MSM to ordinary methods to control for confounding.

MSM vs. ordinary adjustment methods⁷

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

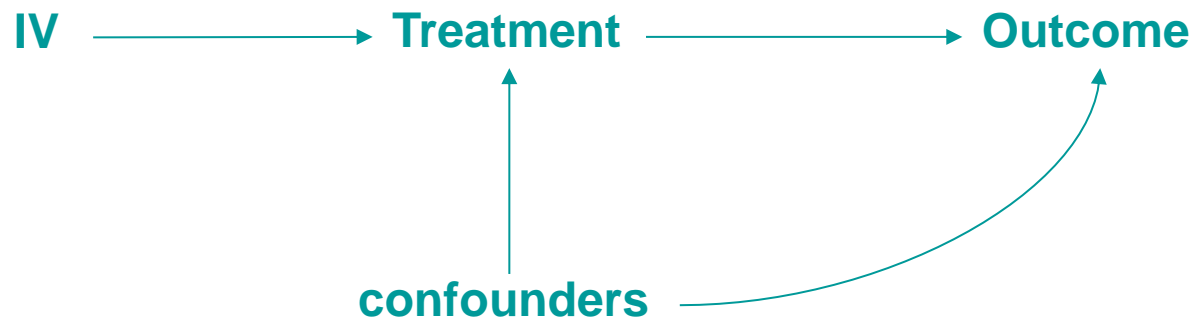
Methods	SABA use		LABA use	
	HR	95 % CI	HR	95 % CI
PS stratification				
Quintiles of PS ^a	1.07	0.72, 1.60	1.13	0.76, 1.67
Deciles of PS ^b	1.15	0.77, 1.71	1.06	0.71, 1.57
PS covariate adjustment ^c	1.09	0.74, 1.61	1.09	0.74, 1.62
MSMs-model 1 ^d	0.92	0.60, 1.41	0.89	0.53, 1.50
MSMs-model 2 ^e	0.86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

4. Unmeasured confounding

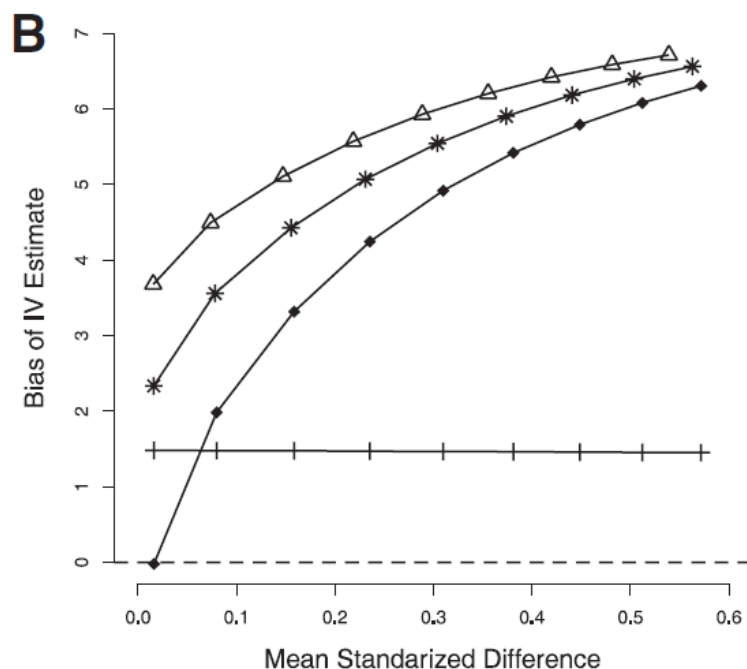
- IV analysis to handle unmeasured confounding

Q: How to quantify assumptions?

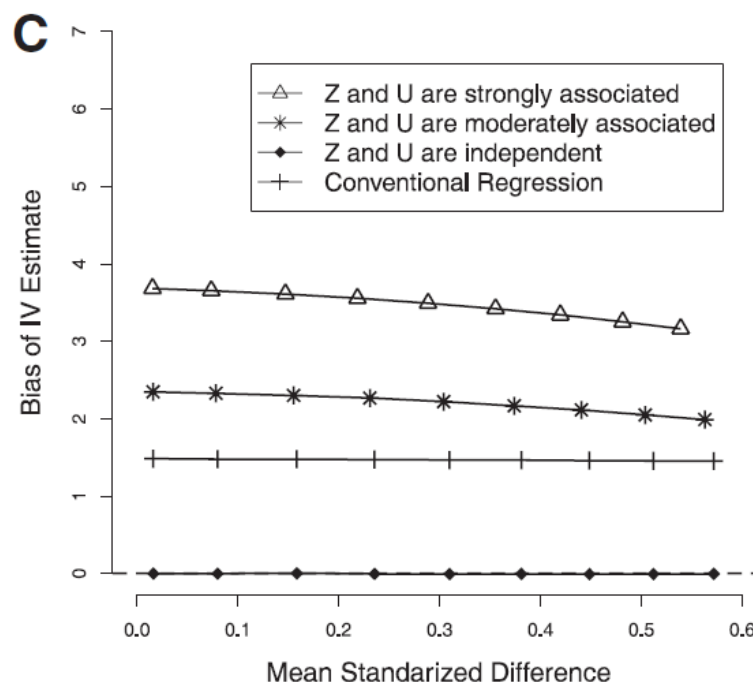
A: Using balance measures⁸



Balance measures for IV analysis



Observed confounders not in the IV model



Observed confounders in the IV model

Unmeasured confounding (2)

- IV analysis in real data

Q: What works and what does not work in real life?

A: IV analysis appears not very robust

- ♦ Application of different IVs
- ♦ In different studies (B2A~MI / AD~HF)
- ♦ In different databases (CPRD, Mondriaan, BIFAP, and THIN)

Antidepressants use (SSRI vs. TCA) and hip fracture

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; 11.9)
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)

4. Unmeasured confounding – part 2

- Other proposed methods to deal with unmeasured confounding:
 - Prior event rate ratio adjustment method
 - Self-controlled case series analysis

Simulations and studies using empirical data suggest that these methods are very sensitive to small violations of their assumptions^{9,10}

Lessons learned

- Impact of confounding adjustment differs across databases
- Different methods for observed confounding (PS, conventional regression adjustment) yield similar effect estimates in empirical studies
- Methods for unmeasured confounding are very sensitive to violations of assumptions and not yet ready for broad implementation

