Estimating treatment efficacy in randomized controlled trials under noncompliance

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Outline

- Background
- Objective
- Methods
- Results
- Key messages
- Some limitations

Background

- Randomized controlled trials (RCTs) as gold standard to evaluate new interventions
- Estimated effect can be biased unless all patients comply with their treatment
- In real practice, participants may have different forms of noncompliant behaviours

Noncompliant behaviours

- All-or-none scenario:

patients may receive either full of the assigned treatment or none of it.

- A more realistic scenario:

Patients may partially comply and receive part of the assigned treatment.

Objectives of the study

- To compare methods of analysis under different scenarios of non-compliance

- To compare the estimates by bias, mean square error (MSE), and coverage

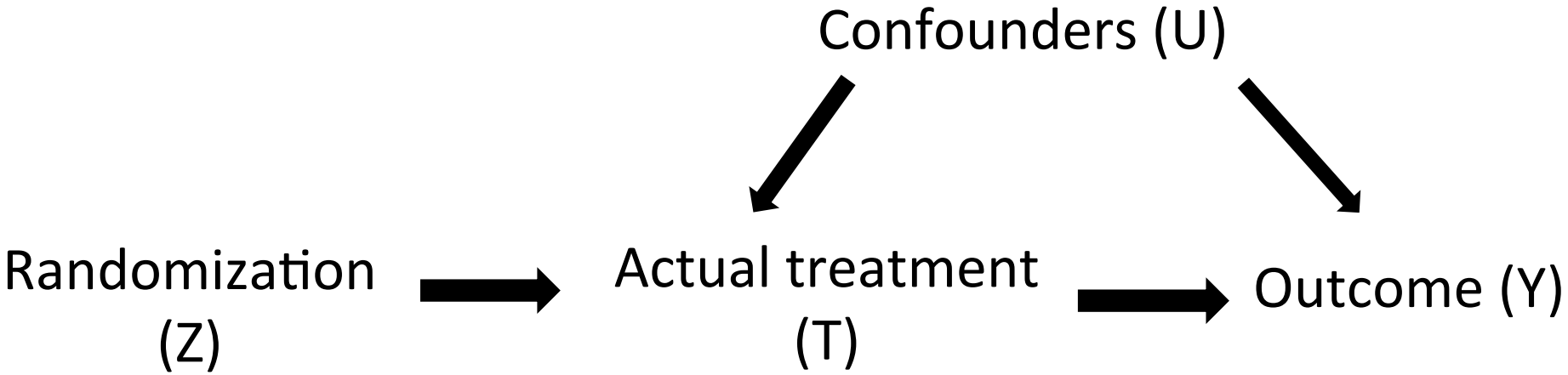
Literature review

	Bang & Davis 2007	Proposed study
Types of non-compliers		
Both always- and never-takers	Yes	Yes
Only never-takers	No	Yes
Randomness of non-compliance		
Random non-compliance	Yes	Yes
Non-random non-compliance	3 scenarios	6 scenarios
Level of non-compliance	Binary & discrete	Binary & discrete
Statistical methods	ITT, AS, PP, IV	ITT, AS, PP, IV, CACE

Statistical methods

- Intention-to-treat analysis
- As-treated analysis
- Per-protocol analysis
- Instrumental variable analysis
- Complier average causal effect analysis

Instrumental variable



The instrumental variable (Z) satisfies:

1. Z is independent of U
2. Z is associated with T
3. Z is independent of Y given T and U

Instrumental variable

- There are different IV estimators

- The standard one has the form:

$$\text{IV estimate of the effect} = \frac{\text{ITT estimate}}{\text{the proportion of compliers}}$$

Complier average causal effect

- The effect of an intervention among the participants who comply
- In some cases, standard IV method can estimate CACE
- A more developed approach: the mixture approach (Jo & Muthen 2001; Jo 2002)

Complier average causal effect

The mixture approach:

- A different distribution for compliers and non-compliers

- Assume the participants whose compliance status cannot be identified as missing

- Apply EM algorithm to compute the MLE of the effect

Simulation framework

1. Type of compliers
   - Always- and never-takers
   - Only never-takers

- In addition, we make the assumptions: stable unit treatment value assumption (SUTAV); exclusion restriction; monotonicity; non-zero denominator; no missing data.

  (Details in Little & Yau 1998)

Simulation framework

2. Randomness of non-compliance
   - Random non-compliant behaviour
   - Compliant behaviour dependent on patient baseline:
     A. Better baseline receive the intervention; worse reject
     B. Better baseline receive the intervention
     C. Worse baseline reject the intervention
     D. Better baseline reject the intervention; worse receive
     E. Better baseline reject the intervention
     F. Worse baseline receive the intervention

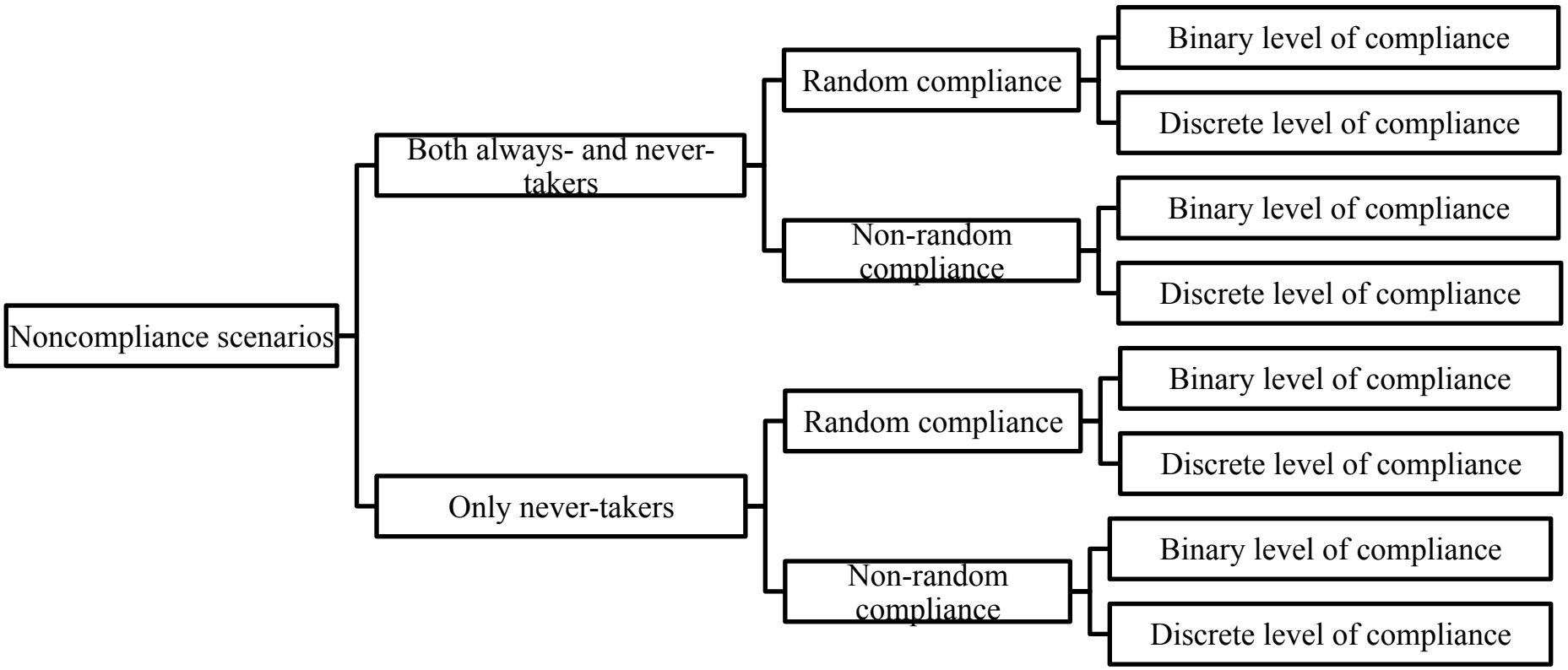
- These 6 non-random relationship were considered in a more generalized case by McNamee 2009

Simulation framework

3. Level of compliance
   - Binary for all-or-none case
   - Discrete for partial non-compliance
   - Possibly, continuous for partial non-compliance (was not considered in this study)

		Proposed study	
	Bang & Davis 2007	Both always-takers and never-takers	Only never-takers
Treatment	50% full active treatment 30% none 10% 1/3 active treatment 10% 2/3 active treatment	50% full active treatment 30% none 10% 1/3 active treatment 10% 2/3 active treatment	50% full active treatment 30% none 10% 1/3 active treatment 10% 2/3 active treatment
Control	50% none 30% 1/3 active treatment 10% 2/3 active treatment 10% full active treatment	50% none 30% 1/3 active treatment 10% 2/3 active treatment 10% full active treatment	100% none

Simulation summary



Results (real effect = 30; only never-takers)

		All-or-none compliance				Partial compliance			
Scenario	Method	Estimate	Bias*	MSE	Coverage	Estimate	Bias	MSE	Coverage
Random	ITT	18.0	-40%	145.3	0	18.0	-40%	145.5	0
	AT	27.7	-8%	6.5	357	30.0	0%	1.1	942
	PP	28.4	-5%	3.8	653	30.0	0%	1.3	944
	IV	30.0	0%	2.4	946	30.0	0%	2.1	948
	CACE	30.0	0%	1.7	953	33.1	10%	11.8	362
C	ITT	10.3	-66%	389.2	0	10.4	-65%	387.4	0
	AT	29.6	-1%	1.4	942	32.0	7%	5.4	602
	PP	28.6	-5%	3.4	763	30.0	0%	1.6	955
	IV	24.7	-18%	33.2	354	24.9	-17%	31.0	382
	CACE	26.4	12%	15.5	344	29.9	0%	3.3	940
E	ITT	14.6	-51%	239.5	0	14.5	-52%	240.6	0
	AT	26.2	-13%	16.1	89	28.1	-6%	5.1	633
	PP	28.0	-7%	5.5	614	30.1	0%	1.6	936
	IV	35.1	17%	31.7	414	35.1	17%	31.3	391
	CACE	33.7	12%	15.9	323	35.6	19%	3.6	79

Results (real effect = 30; both always- & never-takers)

		All-or-none compliance				Partial compliance			
Scenario	Method	Estimate	Bias*	MSE	Coverage	Estimate	Bias	MSE	Coverage
Random	ITT	11.9	-60%	330.0	0	10.0	-67%	403.1	0
	AT	30.0	0%	0.8	961	30.0	0%	1.0	945
	PP	30.0	0%	1.1	951	30.0	0%	1.6	958
	IV	30.0	0%	4.9	958	29.9	0%	6.5	948
	CACE	30.0	0%	1.1	950	30.0	0%	1.6	954
A	ITT	4.6	-85%	650.6	0	3.8	-87%	689.1	0
	AT	37.0	23%	50.0	0	37.4	25%	56.0	0
	PP	36.1	20%	38.2	0	37.0	23%	50.5	0
	IV	28.8	-4%	79.6	963	28.3	-6%	128.9	962
	CACE	36.1	20%	38.2	0	37.0	23%	50.5	0
B	ITT	9.7	-68%	416.5	0	8.1	-73%	483.4	0
	AT	35.1	17%	26.8	0	35.1	17%	26.5	0
	PP	35.1	17%	27.0	0	35.1	17%	26.8	5
	IV	35.0	17%	34.1	603	35.1	17%	37.9	660
	CACE	35.1	17%	27.0	0	35.1	17%	26.8	2
C	ITT	6.8	-77%	539.0	0	5.7	-81%	590.3	0
	AT	32.7	9%	8.1	181	34.3	14%	19.3	22
	PP	31.3	4%	3.1	797	32.7	9%	9.1	482
	IV	24.7	-18%	41.4	729	24.6	-18%	46.0	802
	CACE	31.3	4%	3.1	793	32.7	9%	9.1	465
D	ITT	4.6	-85%	645.1	0	3.8	-87%	689.6	0
	AT	22.9	-24%	50.4	0	22.5	-25%	56.3	0
	PP	23.9	-20%	38.6	0	22.9	-24%	51.2	0
	IV	31.0	3%	173.6	970	33.7	12%	4895.0	955
	CACE	23.9	20%	38.6	0	22.9	24%	51.2	0
E	ITT	9.7	-68%	413.3	0	8.1	-73%	483.1	0
	AT	27.3	-9%	8.2	184	25.7	-14%	19.4	36
	PP	28.6	-5%	3.2	784	27.3	-9%	9.1	500
	IV	35.2	17%	41.9	741	35.4	18%	48.8	805
	CACE	28.6	5%	3.2	778	27.3	9%	9.1	484
F	ITT	6.9	-77%	537.0	0	5.7	-81%	591.0	0
	AT	24.9	-17%	26.4	0	24.9	-17%	26.6	0
	PP	24.9	-17%	26.7	0	24.9	-17%	27.3	2
	IV	24.9	-17%	34.8	576	24.8	-17%	39.1	659
	CACE	24.9	17%	26.7	0	24.9	17%	27.3	2

Results summary

- When there were both always- & never-takers, non-ITT estimates were unbiased if non-compliant behaviour was random.

- When both always- & never-takers allowed, PP and CACE methods produced same results.

- When only never-takers allowed, PP estimates were unbiased.

Results summary

- Bias in partially compliant cases > bias in all-or-none cases.
- IV estimates had the largest MSE but the widest coverage.
- When treatment effect = 0, ITT estimates were unbiased when non-compliant was either random or symmetrical.

Key messages

- When participants' non-compliant behaviour are related to their baseline characteristics, the estimates are likely to be biased without accounting for the baseline characteristics

- ITT estimates are generally biased towards the null; however, are unbiased when the intervention and control work the same.

- When only never-takers are possible, PP method provided the least biased estimate and provided unbiased estimates when the intervention and control work the same.

Some limitations

- Did not consider covariates or imbalance between groups
- Treated IV and CACE as estimates of treatment efficacy
- Assumed the treatment efficacy was linearly proportional to the level of compliance to the treatment

Some limitations

- Adopted a discrete distribution to approximate levels of partial non-compliance

- Simulated only a subset of non-compliant scenarios