Journal club

Statistical methods for handling nonadherence in RCT

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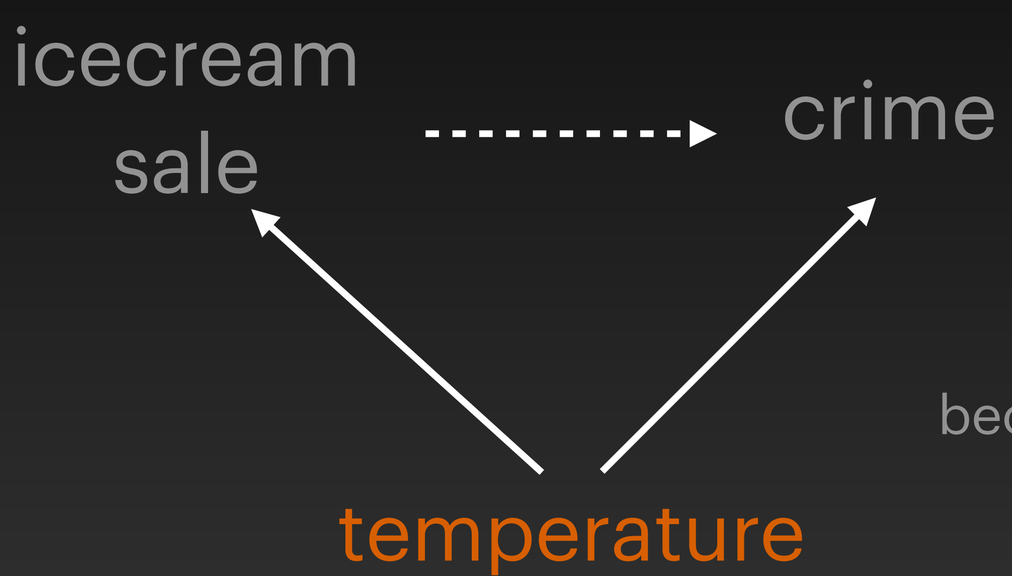
9-11-20

Concept of confounder

Icecream causes crime?

Concept of confounder

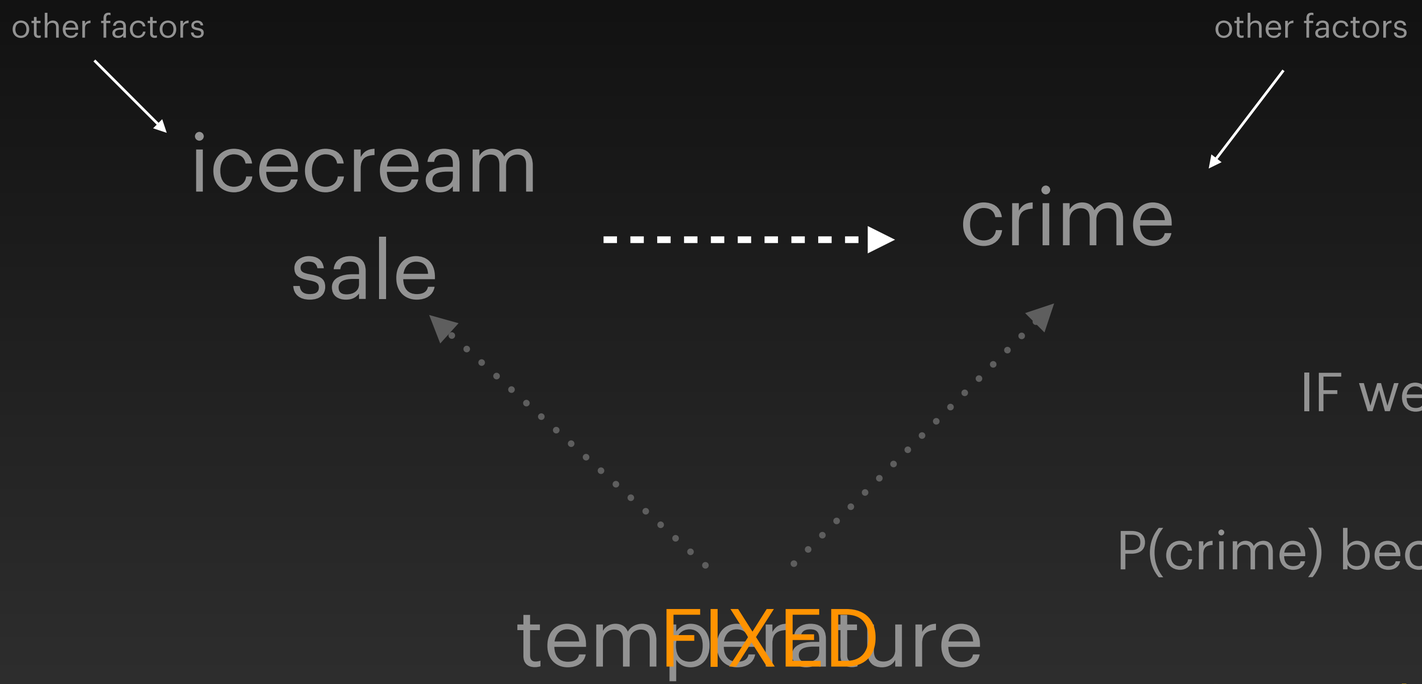


higher temperature
higher change of icecream saling
higher chance of crime

P(crime) depended on P(icecream sale)
because both of them are linked with temperature

crime depended on icecream sale
and temperature = confounder

Concept of confounder

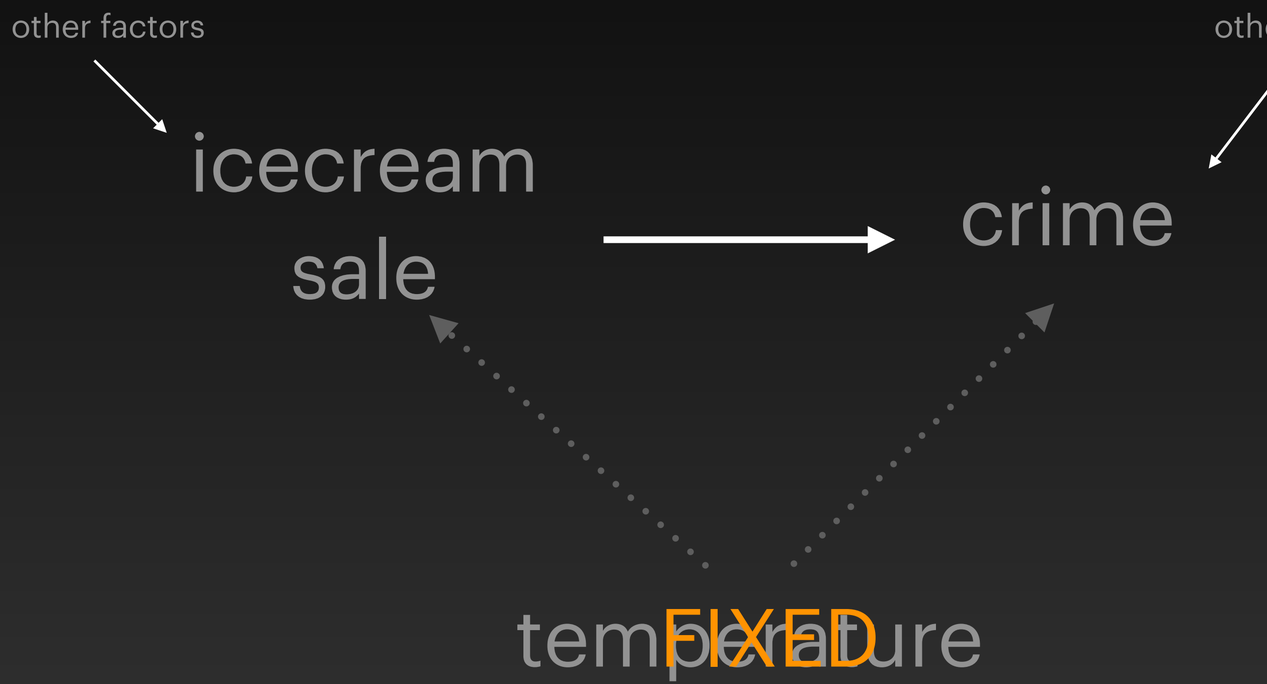


IF we fixed the value of temperature

P(crime) become independent on P(icecream sale)

crime and icecream sale become independent, condition on temperature

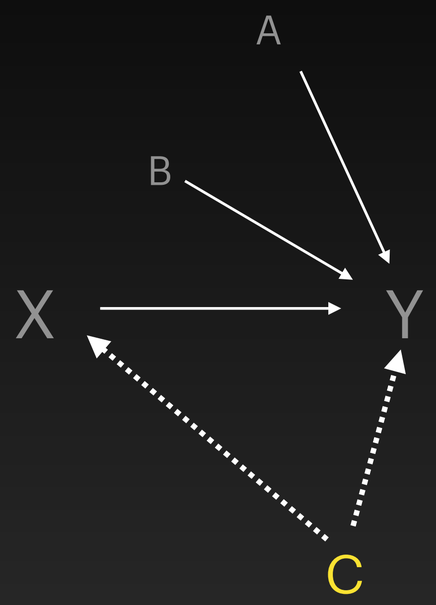
Concept of confounder



Right now
we can claim causal relation between icecream sale and crime,
if we could detect an association.

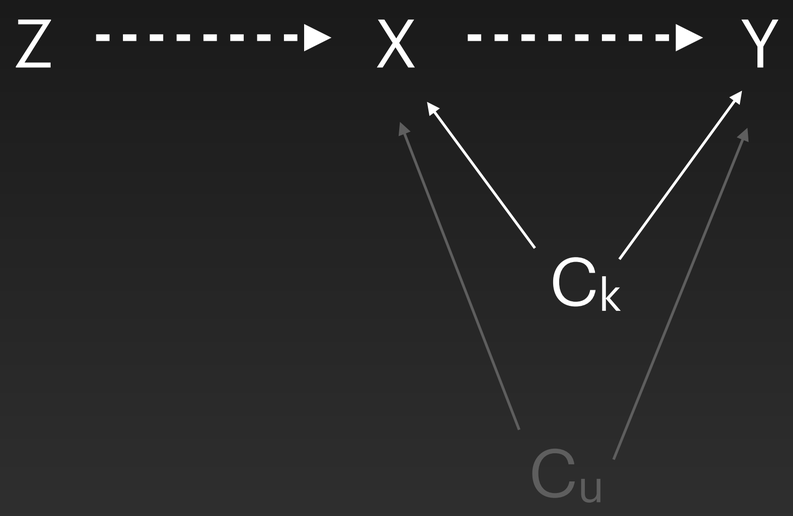
To find causal relation between X and Y,
X and Y *must be* independent, condition on confounder.

Model



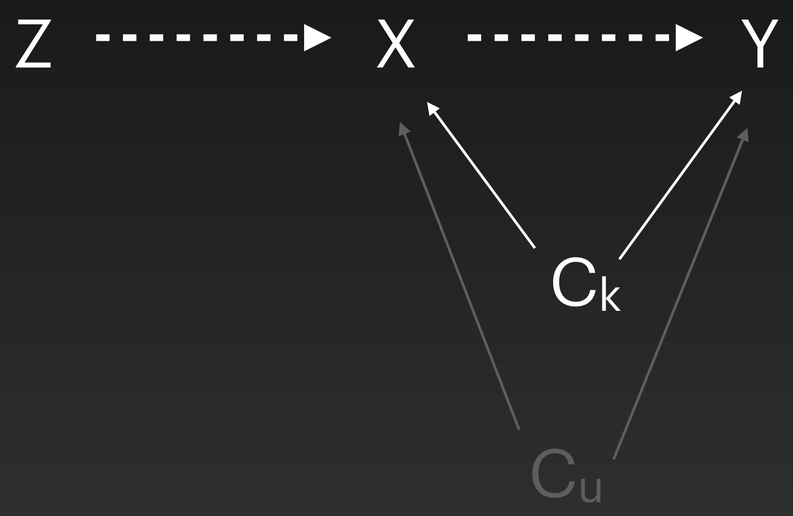
If C is a confounder,
adding C in the model should
significantly change the effect of X on Y.

IV model



Z= treatment allocation
X= treatment received
Y= outcome
C_k= known confounder
C_u= unknown confounder

IV model



Z

(1) It must be a strong predictor of exposure.

(2) Its associations with both exposure and outcome must be unconfounded, at least conditionally on measured covariates.

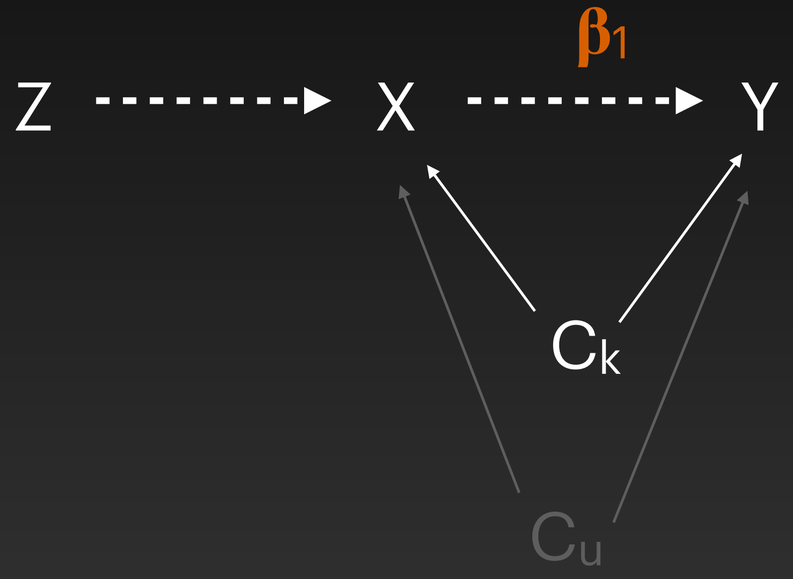
(3) All of its association with the outcome must be mediated by exposure.

IV model

$Y = \beta_0 + \beta_1 X + \beta_2 C_k + \epsilon$ .... bias because we don't know C_u

$X = \gamma_0 + \gamma_1 Z + \gamma_2 C_k + \eta$ .... unbias

.... 1st stage



$$Y = \beta_0 + \beta_1(\gamma_0 + \gamma_1 Z + \gamma_2 C_k + \eta) + \beta_2 C_k + \epsilon$$
$$= \beta_0 + \beta_1\gamma_0 + \beta_1\gamma_1 Z + (\beta_1\gamma_2 + \beta_2) C_k + \beta_1\eta + \epsilon$$
$$= \lambda_0 + \lambda_1 Z + \lambda_2 C_k + \Psi$$ .... 2nd stage, also unbias

unbias ∵ no confounder between Z and X, and Z and Y

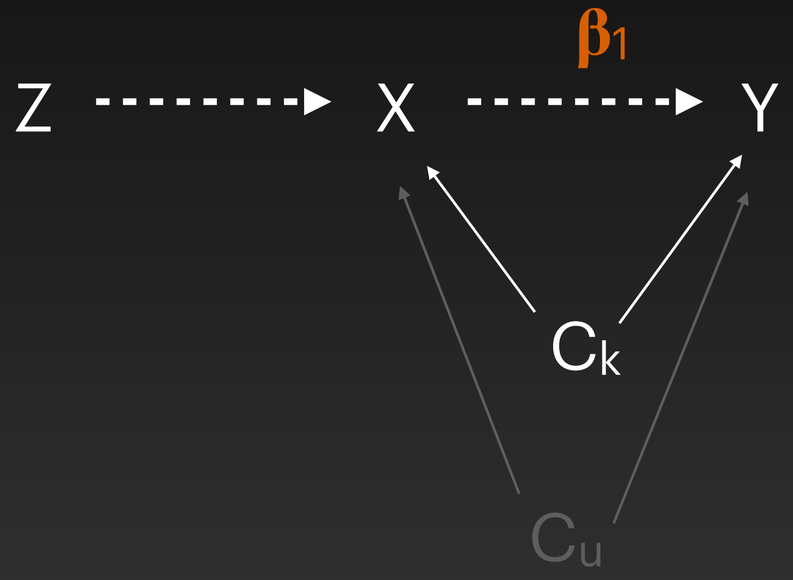
$\beta_1 = \lambda_1/\gamma_1$

IV model

$$Y = \beta_0 + \beta_1 X + \beta_2 C_k + \epsilon$$

$$X = \gamma_0 + \gamma_1 Z + \gamma_2 C_k + \eta$$

$$Y = \lambda_0 + \lambda_1 Z + \lambda_2 C_k + \Psi$$



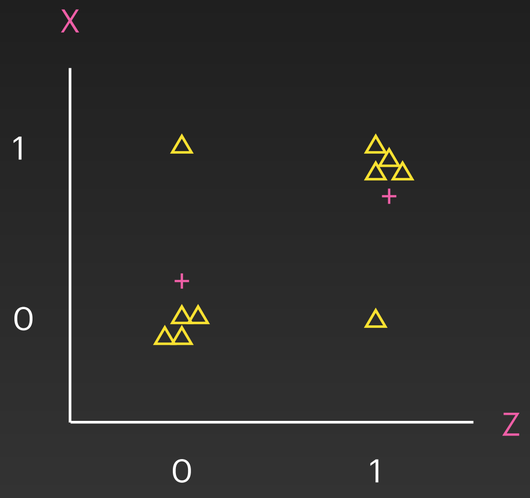
$\beta_1 = \lambda_1/\gamma_1$

β_1 = β from IV-estimator = β_{IV}

λ_1 = effect of Z on Y = β_{ITT}

γ_1 = Expected value of difference

in treatment received between
treatment assigned and not assigned
= $E[T^r(1) - T^r(0)]$



$\beta_{IV} = \beta_{ITT}/E[T^r(1) - T^r(0)]$ ..... *

Rubin causal model

SUTVA — the stable unit treatment value assumption

The potential outcomes for any unit do not vary with the treatments assigned to other units, and, for each unit, there are no different forms or versions of each treatment level, which lead to different potential outcomes.

Rubin causal model

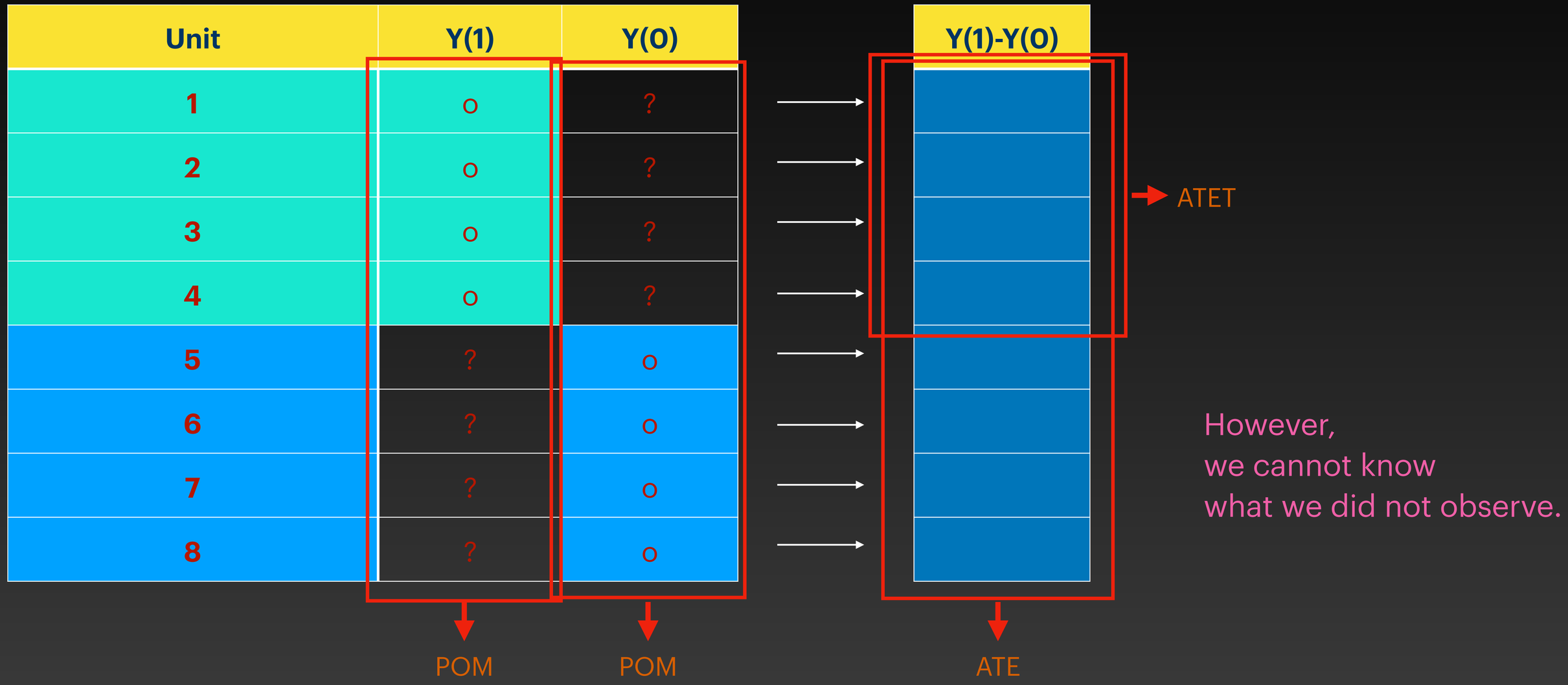
Unit	Y(1)	Y(0)
1	1	
2	1	
3	0	
4	0	
5		0
6		1
7		0
8		0

Y(1) = outcome when unit received intervention

Y(0) = outcome when unit didn't receive intervention

What have generally done

Rubin causal model



However,
we cannot know
what we did not observe.

Rubin causal model

In RCT,
previous 2 slides yield the same results
∵ distribution of Y(0) in the group assigned to (1)
(i.e.,counterfactual) is the same as
distribution of Y(0) in the group assigned to (0)
(and also Y(1))

What if, randomization was violated !!!

Z_i	$X_i(Z_i)$	$Y(X_i(Z_i))$
Treatment assignment	Treatment received	Outcome
	1 = receive treatment 0 = receive control	1 = cure 0 = not cure
1 = assign to treatment 0 = assign to control	$X_i(1) = 1$ $X_i(1) = 0$ $X_i(0) = 1$ $X_i(0) = 0$	$Y_i(Z,X)$ $Y_i(1,1) = 1$ $Y_i(1,1) = 0$ $Y_i(1,0) = 1$ $Y_i(1,0) = 0$ $Y_i(0,1) = 1$ $Y_i(1,0) = 0$ $Y_i(0,0) = 1$ $Y_i(0,0) = 0$

Compliance

individual who

$X_i(1) = 1$, $X_i(0) = 0$ Complier

$X_i(1) = 1$, $X_i(0) = 1$ Always-taker

$X_i(1) = 0$, $X_i(0) = 0$ Never-taker

~~$X_i(1) = 0$, $X_i(0) = 1$ Defier~~

Monotonicity —
assume no defier

* keep in mind that we can observe either X(1) or X(0) in individual but not both.
* Thus, we cannot idenfity the class of idividual.

RCT

Effect of Z on X

Unit	Z	X(1)	X(0)
1	1	1	
2	1	1	
3	1	1	
4	1	o	
5	0		o
6	0		o
7	0		o
8	0		1

* no df

		Z	
		0	1
X	0	nt/co	nt
	1	at	at/co

$E[X(1) - X(0)] \rightarrow E[(co+at) - (at)] = E[co] = \pi_{co}$

$= E[T^r(1) - T^r(0)]$

RCT Effect of Z on Y

Unit	Z	Y(Z=1)	Y(Z=0)
1	1	△	
2	1	△	
3	1	△	
4	1	△	
5	0		△
6	0		△
7	0		△
8	0		△

E[Y(Z=1) - Y(Z=0)]

= β_{ITT}

If we stratified based on compliance

CO	E[Y(Z=1) - Y(Z=0)]	E[Y(X=1) - Y(X=0)]
AT	E[Y(Z=1) - Y(Z=0)]	E[Y(X=1) - Y(X=1)]
NT	E[Y(Z=1) - Y(Z=0)]	E[Y(X=0) - Y(X=0)]

Exclusion Restriction → 0

Unit	Z	Y(Z=1)	Y(Z=0)
1	1	△	
2	1	△	
3	1	△	
4	1	△	
5	0		△
6	0		△
7	0		△
8	0		△

If we stratified based on compliance

β_{CO}

CO	E[Y(Z=1) - Y(Z=0)]	E[Y(X=1) - Y(X=0)]
AT	E[Y(Z=1) - Y(Z=0)]	E[Y(X=1) - Y(X=1)]
NT	E[Y(Z=1) - Y(Z=0)]	E[Y(X=0) - Y(X=0)]

0

$$\beta_{ITT} = \beta_{co} * \pi_{co} + \underbrace{0 * \pi_{at} + 0 * \pi_{nt}}_{0} = \beta_{co} \bullet E[T^r(1) - T^r(0)]$$

Complier-averaged causal effect (CACE)

Local average treatment effect (LATE)

$$\beta_{CO} = \frac{\beta_{ITT}}{E[T^r(1) - T^r(O)]}$$

$$\therefore \beta_{IV} \sim \beta_{CO}$$

CACE can be model-based

Flexible way to incorporate covariables

Using pre-treatment covariables could relax exclusion restriction

Method for parameter estimation

- 2SLS
- MM
  - set population moment = sample moment ($\boldsymbol{\mu}_k = \hat{\boldsymbol{\mu}}_k$; k^{th}- moment)
  - may not get parameter or get unrealistic value
- ML
  - finding parameter that are most likely to produce observed data by maximizing the likelihood function
  - more precise estimand
- etc

Open Access Research

BMJ Open

Estimating treatment effects in randomised controlled trials with non-compliance: a simulation study

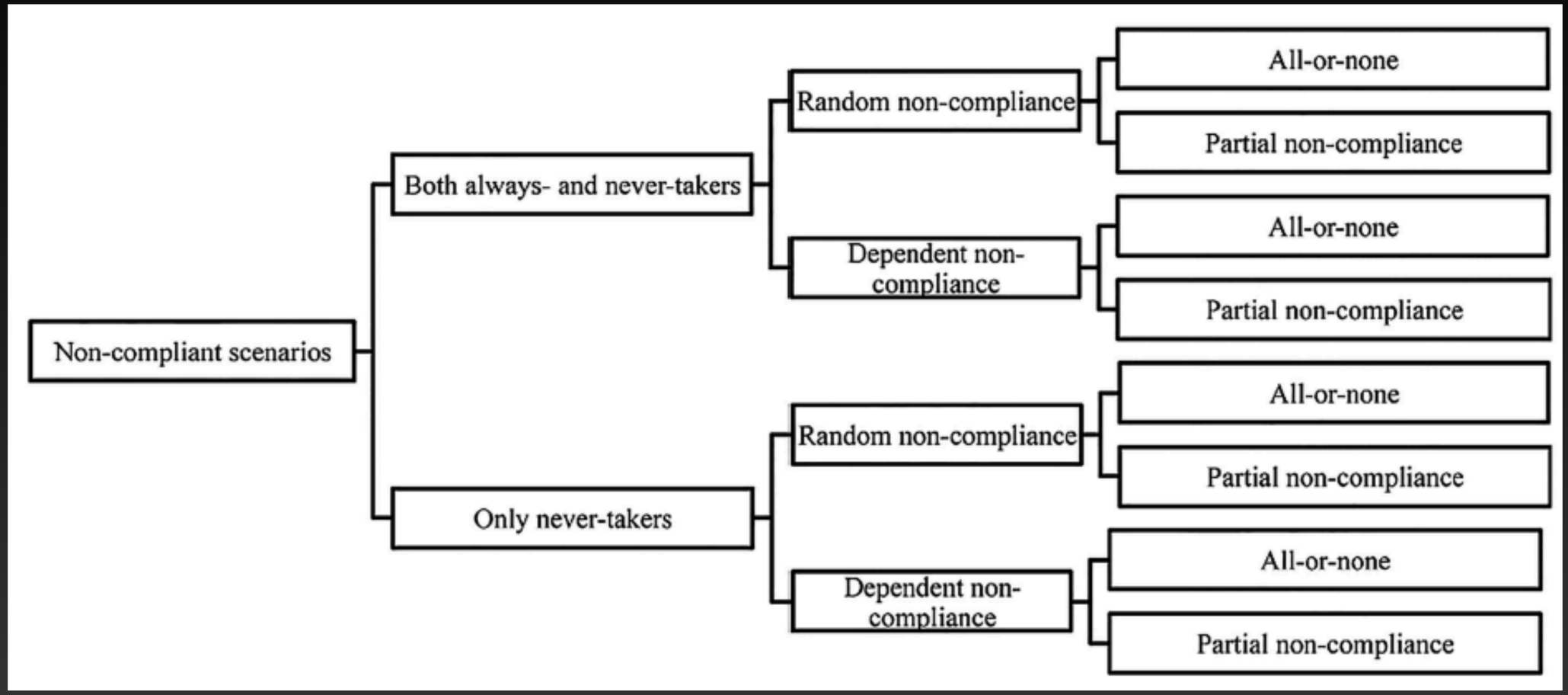
Chenglin Ye,[1,2] Joseph Beyene,[1] Gina Browne,[1,3] Lehana Thabane[1,2]

Motivation

- an RCT that compared the integrated care organised through the Children’s Treatment Network (CTN) with the usual care directed by parents for managing children with special healthcare needs

- high non-compliant rates

Simulation


Non-compliant scenarios
Both always- and never-takers
Only never-takers
Random non-compliance
Dependent non-compliance
Random non-compliance
Dependent non-compliance
All-or-none
Partial non-compliance
All-or-none
Partial non-compliance
All-or-none
Partial non-compliance
All-or-none
Partial non-compliance

Type of non-compliers

- either never-takers of always-takers
  - mimicked the situation where patients were able to get the intervention elsewhere even if they were not offered it

- only never-takers
  - mimicked the situation where the intervention was only accessible to patients who were offered it.

Randomness of non-compliance

- Random
- Dependent

A. Patients with good conditions would always get the intervention while patients with poor conditions would always reject it;
B. Patients with good conditions would always get the intervention;
C. Patients with poor conditions would always reject the intervention;
D. Patients with good conditions would always reject the intervention while patients with poor conditions would always get it;
E. Patients with good conditions would always reject the intervention;
F. Patients with poor conditions would always get the intervention.

Degree of non-compliance

(according to compliance on components of the intervention)

- All-or-none
  - d=0, d=1
- Partial
  - d=0, d=1/3, d=2/3, d=1

Simulation

- **δ** causal effect
  - μ_0 = mean of Y_0 =59
  - μ_1 = mean of Y_1
    - 89, 74, 59 (50%, 25%, 0% improvement)

$$\delta = \mu_1 - \mu_0$$

- generate individual counterfactual outcome

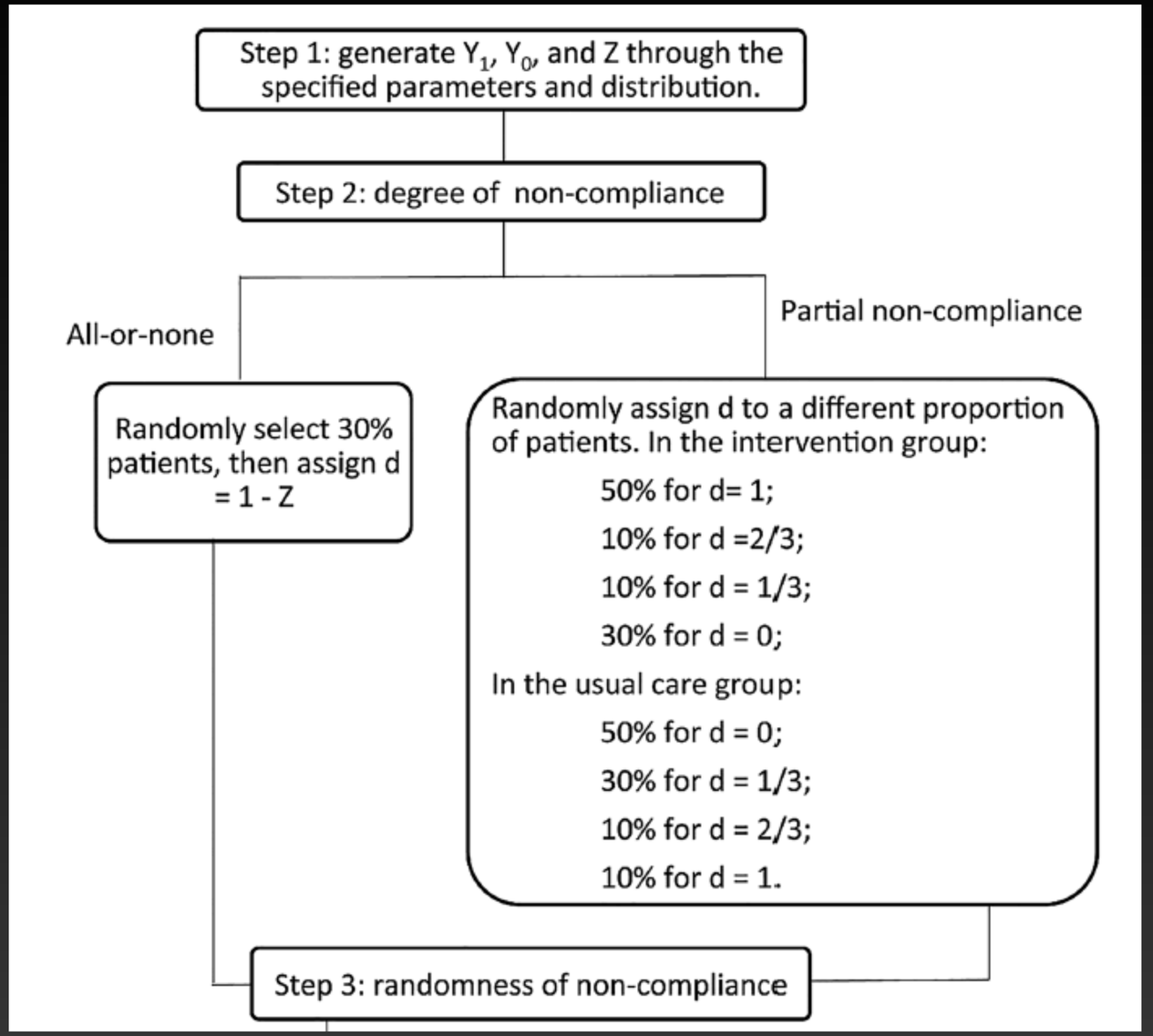
$$Y_k \sim \text{Normal}(\mu_k, 10^2) \text{ and } k = 0, 1$$

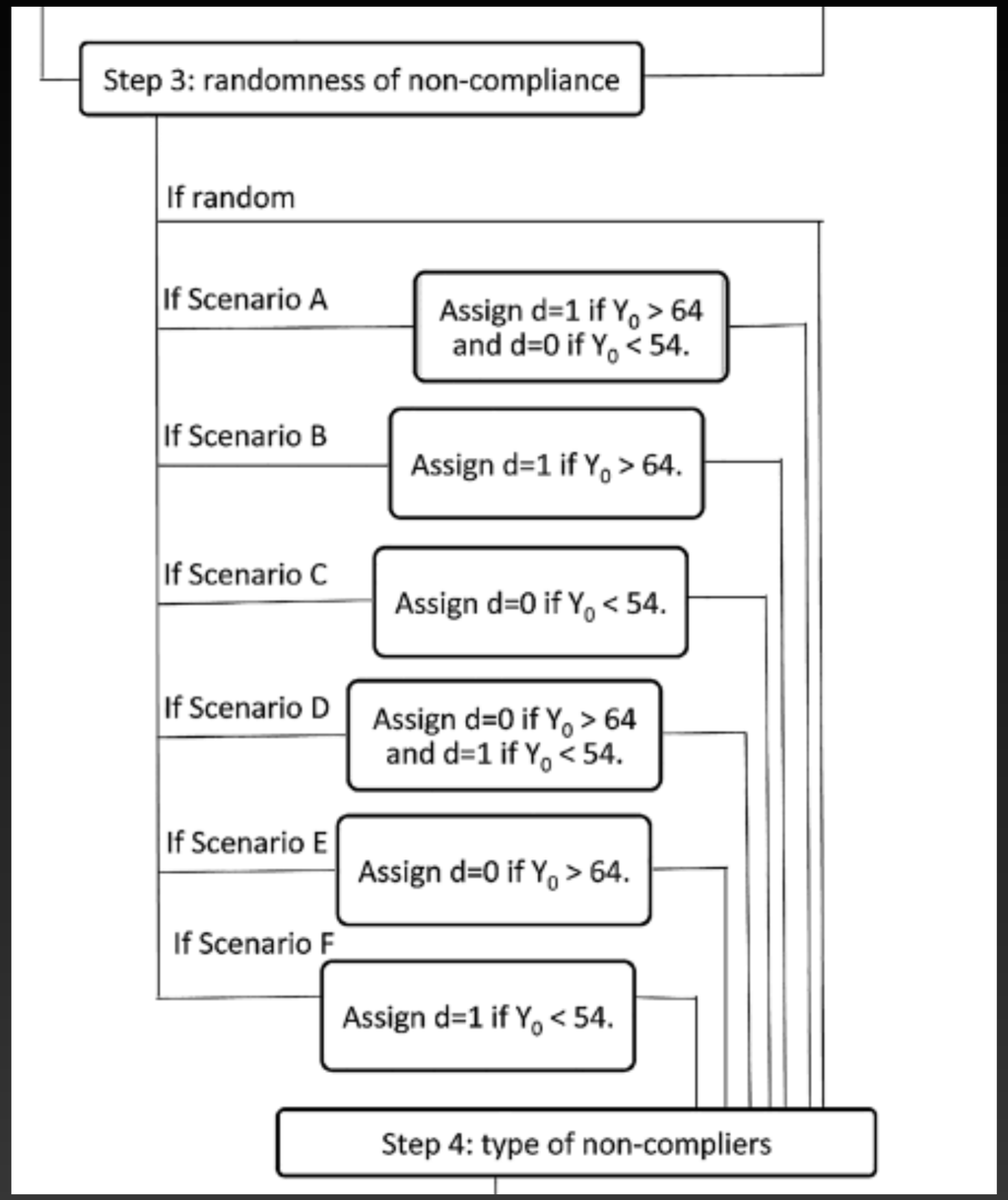
- define contidion
  - good $Y_0 > 64$, poor $Y_0 < 54$

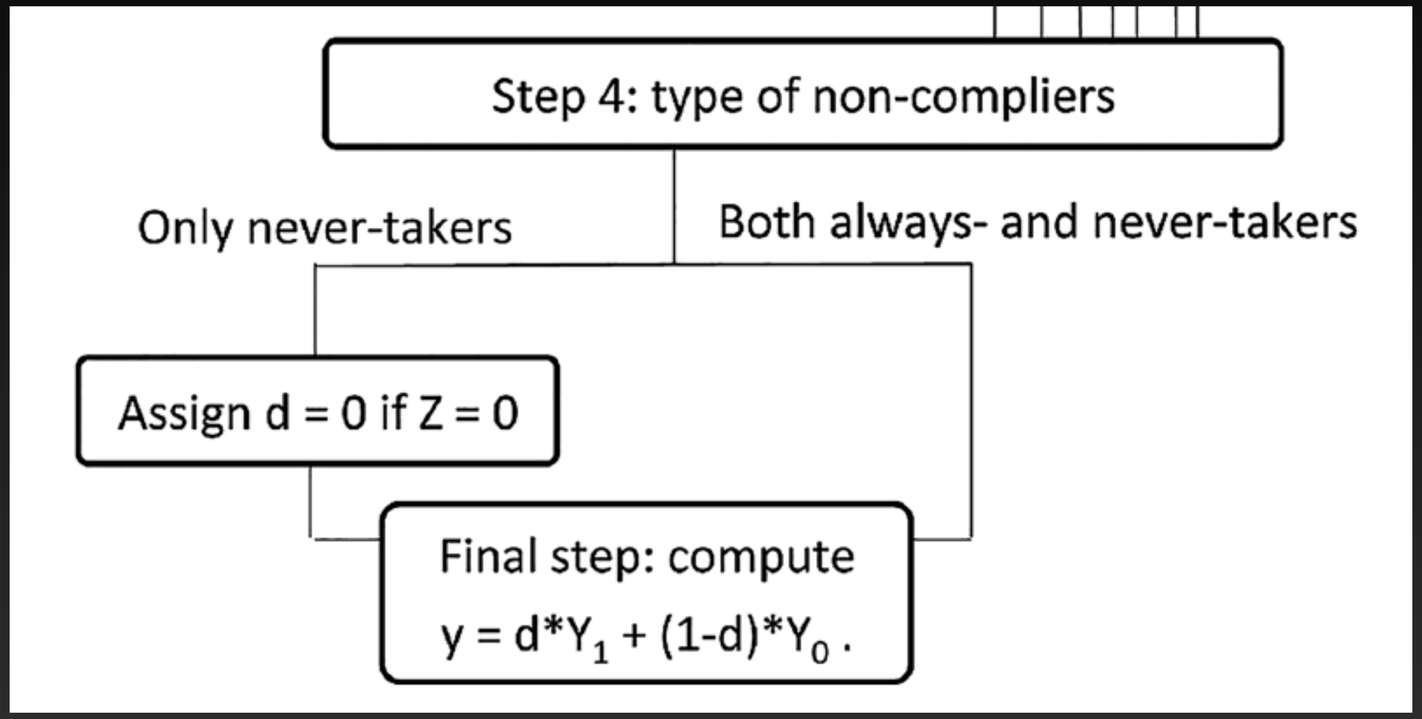
- observe outcome for a patients

$$y_i = d_i Y_1 + (1 - d_i) Y_0$$

d_i degree of treatment compliance


Step 1: generate Y_1, Y_0, and Z through the specified parameters and distribution.
Step 2: degree of non-compliance
All-or-none
Partial non-compliance
Randomly select 30% patients, then assign d = 1 - Z
Randomly assign d to a different proportion of patients. In the intervention group:
50% for d= 1;
10% for d =2/3;
10% for d = 1/3;
30% for d = 0;
In the usual care group:
50% for d = 0;
30% for d = 1/3;
10% for d = 2/3;
10% for d = 1.
Step 3: randomness of non-compliance


Step 3: randomness of non-compliance
If random
If Scenario A
Assign d=1 if $Y_0 > 64$ and d=0 if $Y_0 < 54$.
If Scenario B
Assign d=1 if $Y_0 > 64$.
If Scenario C
Assign d=0 if $Y_0 < 54$.
If Scenario D
Assign d=0 if $Y_0 > 64$ and d=1 if $Y_0 < 54$.
If Scenario E
Assign d=0 if $Y_0 > 64$.
If Scenario F
Assign d=1 if $Y_0 < 54$.
Step 4: type of non-compliers


Step 4: type of non-compliers
Only never-takers
Both always- and never-takers
Assign d = 0 if Z = 0
Final step: compute
y = d*Y1 + (1-d)*Y0 .

Analysis

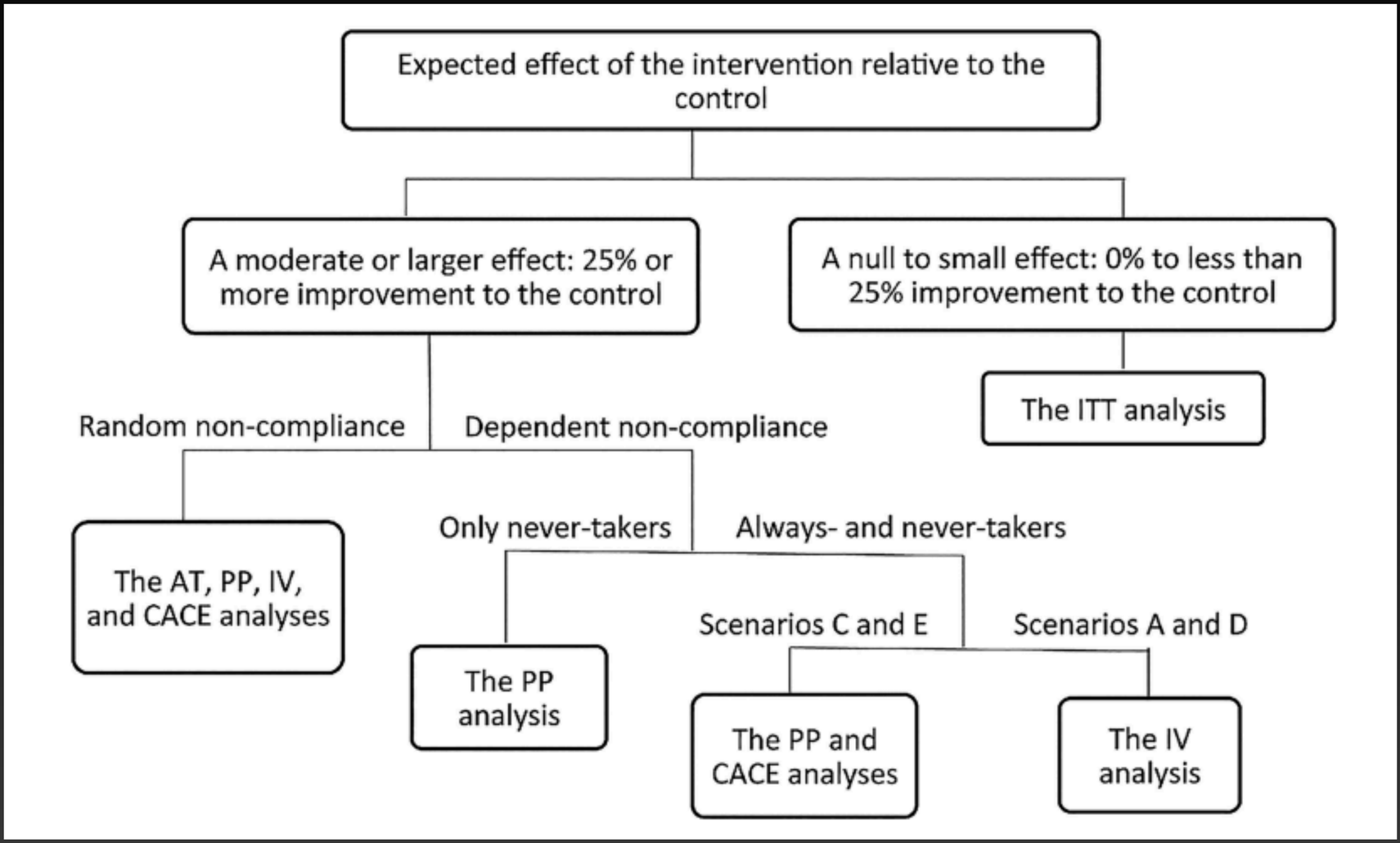
- Compare: ITT, AS, PP, IV, CACE

- Bias
- Mean square error
- 95% coverage

$$\text{Bias} = \bar{\hat{\delta}} - \delta$$

$$\text{MSE} = (\bar{\hat{\delta}} - \delta)^2 + (\text{SE}(\hat{\delta}))^2$$

Key findings



Limitation

- Did not consider specific prognostic factors
- Assumed linear relation between clinical effect of the intervention and the degree of compliance
- Did not consider missing data
- Only simulate a subset of general non-compliant scenario