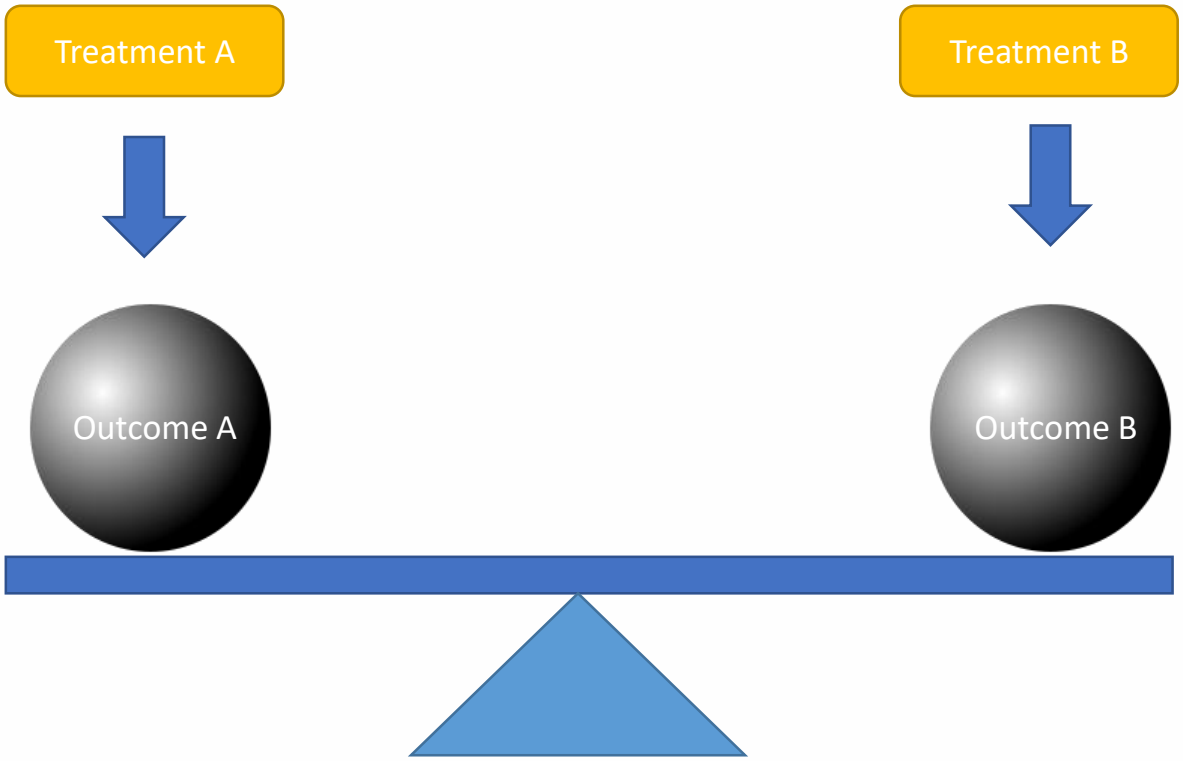
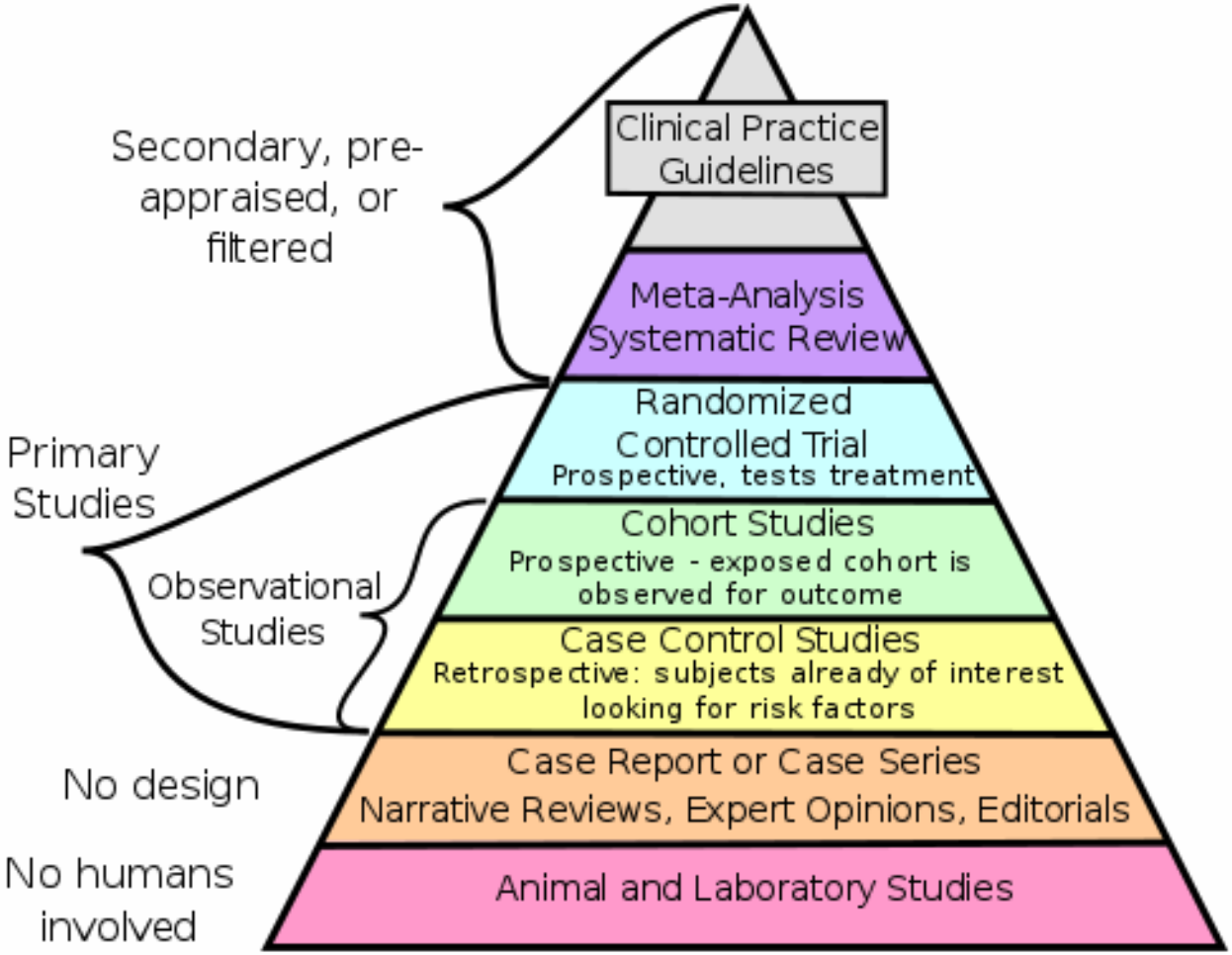
CEB WORKSHOP 2020

Treatment-effects model



Perfect methodology = Randomized Controlled Trial


Secondary, pre-appraised, or filtered
Primary Studies
Observational Studies
No design
No humans involved
Clinical Practice Guidelines
Meta-Analysis Systematic Review
Randomized Controlled Trial
Prospective, tests treatment
Cohort Studies
Prospective - exposed cohort is observed for outcome
Case Control Studies
Retrospective: subjects already of interest looking for risk factors
Case Report or Case Series
Narrative Reviews, Expert Opinions, Editorials
Animal and Laboratory Studies

Why randomized?

- Random assignment of patients to treatments provides the strongest possible basis for inference about treatment effects.

- Result (outcome) = efficacy

Limitation of RCTs

- Selected patients (homogeneous)
- Setting and monitoring bias
- Economical limitations
- Logistical and ethical restrictions
- Unsuitable for complex treatments studies
- Inappropriate for thorough evaluation of side effects
- Short duration

S. Saturni et al. / Pulmonary Pharmacology & Therapeutics 27 (2014) 129-38.

Some research question

- The post-operative pain outcome between open and laparoscopic hernia repair.
- Employment outcomes for individuals that participated in a job training program and those that did not.
- The effect on birth weight for babies of mothers that smoked relative to those of mothers that did not.

Our experience

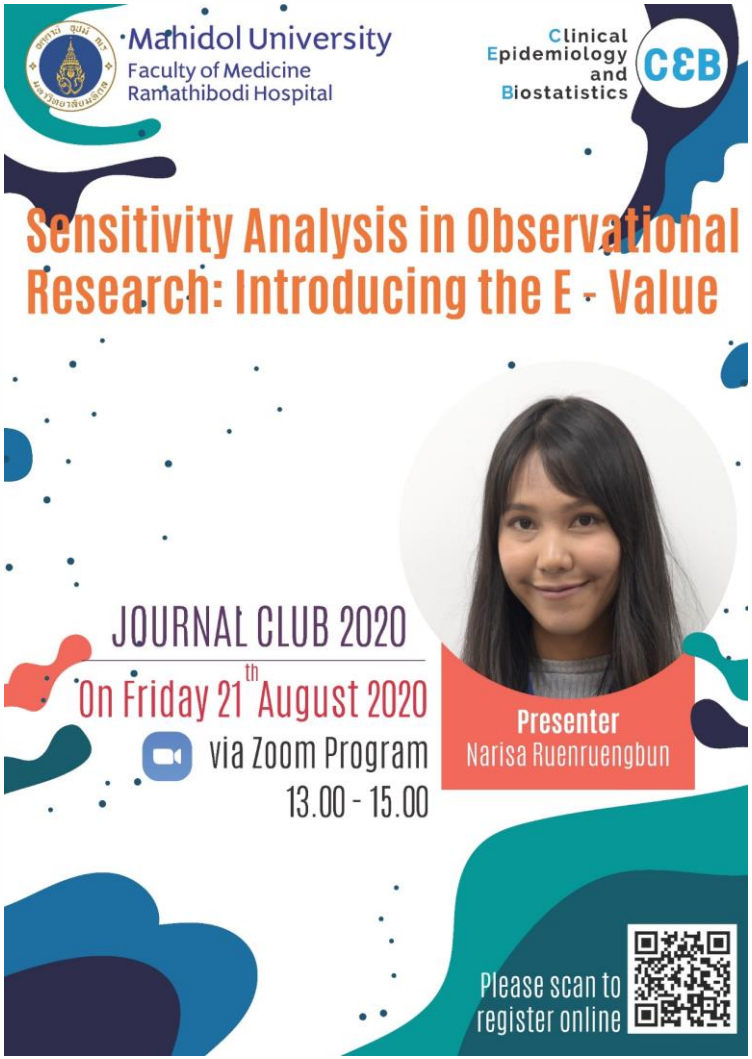
- EFFICACY AND COST-UTILITY OF ANTIBIOTIC USES AND SURGICAL TREATMENTS IN UNCOMPLICATED ACUTE APPENDICITIS

Our experience

- MESH FIXATION FOR INGUINAL HERNIA: INTEGRATED AND UPDATED DATA OF UMBRELLA REVIEW WITH NETWORK META-ANALYSIS AND COST-UTILITY ANALYSIS

Randomized controlled trials
VS
Real world evidence

Department of Clinical Epidemiology and Biostatistics


Mahidol University
Faculty of Medicine
Ramathibodi Hospital
Clinical
Epidemiology
and
Biostatistics
CEB
Sensitivity Analysis in Observational Research: Introducing the E - Value
JOURNAL CLUB 2020
On Friday 21th August 2020
via Zoom Program
13.00 - 15.00
Presenter
Narisa Ruenruengbun
Please scan to register online

The Stata Journal (2020)
20, Number 1, pp. 162–175 DOI: 10.1177/1536867X20909696

Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: The evalue package

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CEB
REGISTRY-BASED RANDOMIZED CONTROLLED TRIALS- WHAT ARE THE ADVANTAGES, CHALLENGES, AND AREAS FOR FUTURE RESEARCH?
JOURNAL CLUB 2020
ON FRIDAY 18TH SEPTEMBER 2020
AT MEDICAL LEARNING RESOURCE CENTER AND RAMATHIBODI SCHOOL OF NURSING BUILDING
IN ROOM 810B
12.00 - 15.00
THREECHADA BOONCHAN
PRESENTER
PLEASE SCAN TO REGISTER ONLINE

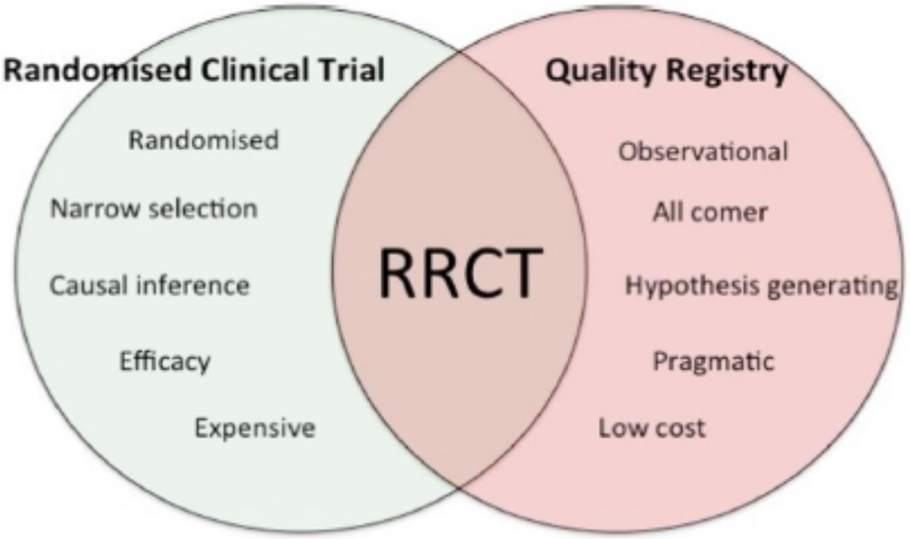


Figure 2 Derivation of a registry-based randomised clinical trial (RRCT) from its randomised and observational cohort components. Each circle highlights different strengths and weaknesses of these components.

Box 1 Aspects of a clinical trial that may be covered by the quality registry in the registry-based randomised clinical trial

- Screening/patient identification.
- Informed consent.
- Randomised treatment assignment.
- Collecting baseline characteristics.
- Follow-up (with/without adjudication) of outcome events.
- Cost.

Yndigegn T, et al. Heart 2018;104:1562–1567

OPINION

Registry-based randomized clinical trials—a new clinical trial paradigm

Stefan James, Sunil V. Rao and Christopher B. Granger

Abstract | Randomized clinical trials provide the foundation of clinical evidence to guide physicians in their selection of treatment options. Importantly, randomization is the only reliable method to control for confounding factors when comparing treatment groups. However, randomized trials have limitations, including the increasingly prohibitive costs of conducting adequately powered studies. Local and national regulatory requirements, delays in approval, and unnecessary trial processes have led to increased costs and decreased efficiency. Another limitation is that clinical trials involve selected patients who are treated according to protocols that might not represent real-world practice. A possible solution is registry-based randomized clinical trials. By including a randomization module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry. We believe that prospective registry-based randomized clinical trials are a powerful tool for conducting studies efficiently and cost-effectively.

James, S. *et al. Nat. Rev. Cardiol.* **12**, 312–316 (2015); published online 17 March 2015; doi:10.1038/nrcadio.2015.33

Box 1 | Main features of trials

Observational studies

Observational studies, drawn from large populations, are complementary to prospective randomized trials

- Despite appropriate statistical adjustments, some confounding factors cannot be completely eliminated
- The interpretation of observational studies assessing treatment effects must be approached with caution
- Results should be considered nondefinitive and hypothesis generating

Registry-based randomized clinical trials

- Randomly assigning patients in a clinical quality registry combines the features of a prospective randomized trial with a large-scale clinical registry
- Registry-based trials are less selective and enable fast enrolment, control of nonenrolled patients, and the possibility of very long-term follow-up
- Inexpensive and simple designs are the main strengths of registry-based randomized clinical trials
- The clinical registry can be used to identify patients for enrolment, perform randomization, collect baseline variables, and detect end points


Mahidol University
Faculty of Medicine
Ramathibodi Hospital
Clinical Epidemiology and Biostatistics
CEB
The Magic of Randomization versus The Myth of Real-World Evidence
Songporn Oranratnachi, M.D.
Presenter
JOURNAL CLUB 2020
ON FRIDAY 6TH NOVEMBER 2020
RAMATHIBODI HOSPITAL AT SUKHO PLACE BUILDING
IN SUKHO HALL
12.00 - 15.00
PLEASE SCAN TO REGISTER ONLINE

Variables	RCTs	RWE
Purpose	Efficacy	Effectiveness
Setting	Experimental setting	Real-world setting
Follow up	Designed	In actual practice
Treatment	Fixed pattern	Variable pattern
Study group	Homogenous	Heterogeneous
Attending physician	Investigator	Many practitioners
Comparator	Placebo/selective alternative interventions	Many alternative interventions
Patient monitoring	Continuous, per protocol	Changeable

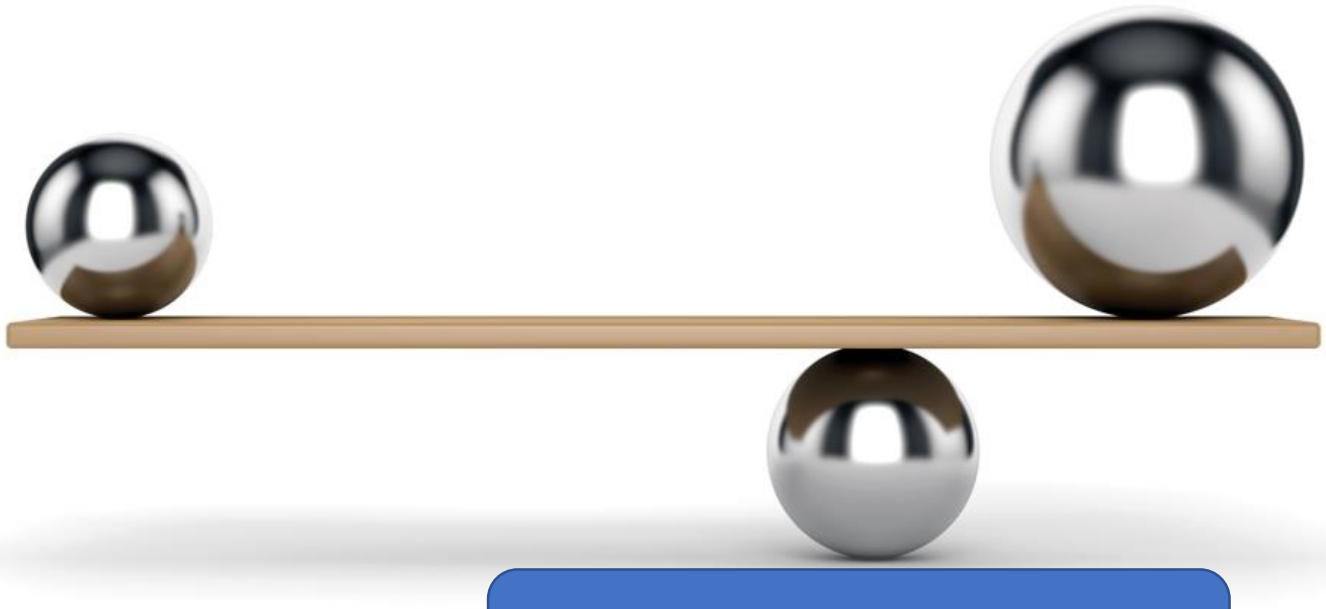
RCT = randomized clinical trial, RWE = real-world evidence.

Hun-Sung Kim J Korean Med Sci. 2018 Aug 20;33(34):e213

Random assignment

Versus

Treatment assignment

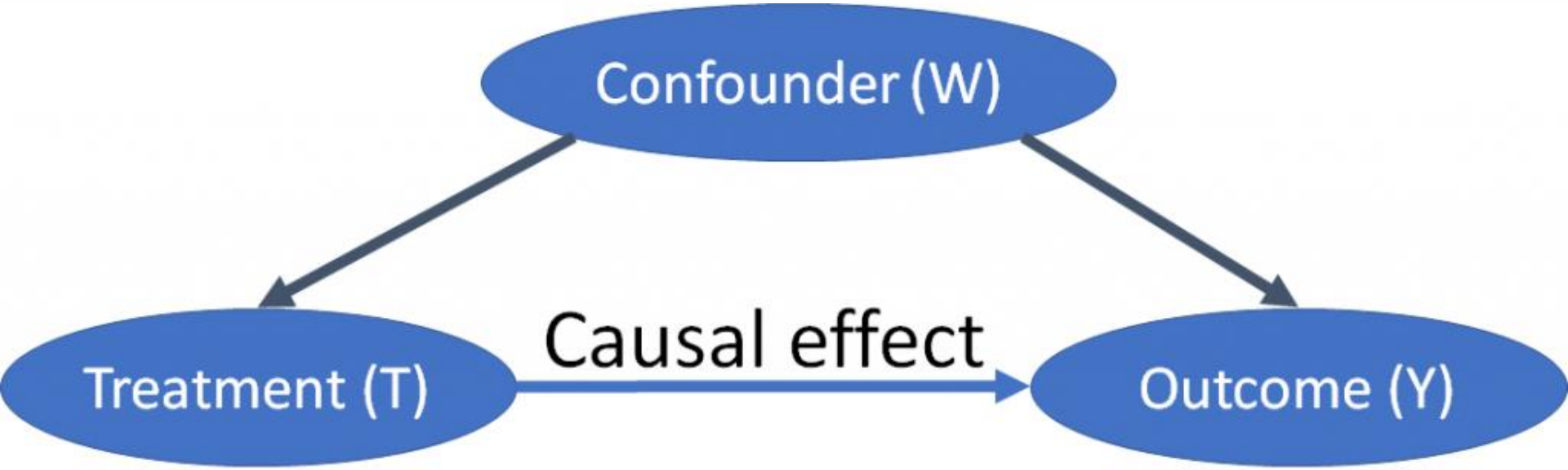


Treatment-effects model

What is treatment-effects model

- Treatment-effects estimators estimate the causal effect of a treatment on an outcome based on observational data (Real world data / evidence).

The concept of causal effect and counterfactual



Identification: Causal effect → Observed effect conditioned on W, $\mathrm{E}[Y|T,W]$

Estimation: $\mathrm{E}[Y|T,W]$ → Propensity Score Stratification

Treatment: T

T*i* = indicator of treatment for unit *i*

- T*1* if unit *i receive treatment*
- *T0* if unit *i receive no treatment or otherwise*

Outcome: Y

Y*i* : Observed outcome of interest for unit *i*

Potential Outcome: Y*di*

Y0i = Potential outcome for unit *i* without treatment
Y1i = Potential outcome for unit *i* with treatment

Causal effect

Causal effect is the difference between its two potential outcomes:

✓ Potential outcome means (POM)

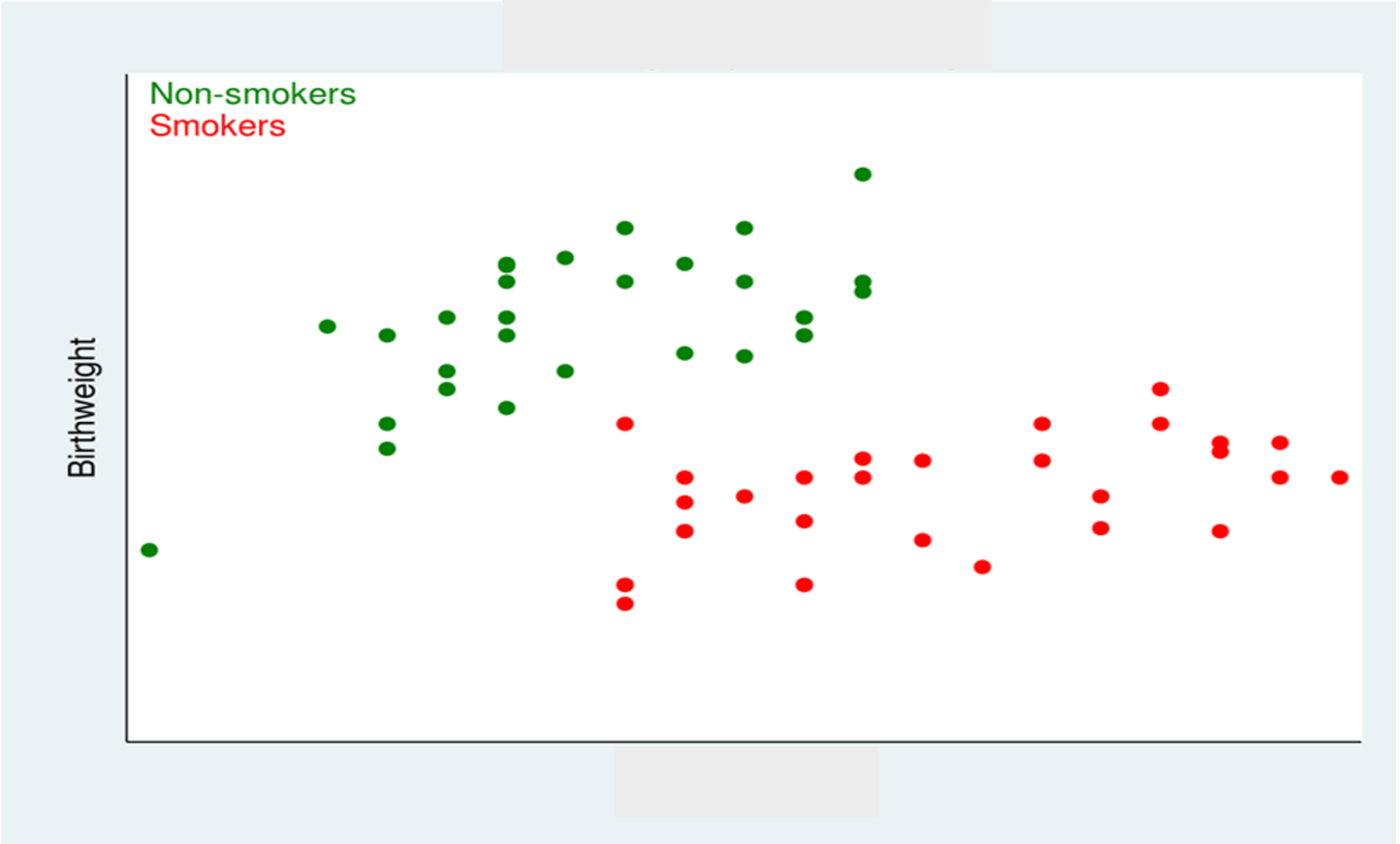
$$\alpha i = Y1i - Y0i$$

✓ Average treatment effects (ATE)

$$= E[Y1 - Y0]$$
$$= E[Y1i] - E[Y0i]$$

i	Ti	Yi	Y1i	Y0i	αi
1	1	3	**3**	**0**	3-0 = 3
2	1	1	**1**	**1**	1-1 = 0
3	0	0	**1**	**0**	1-0 = 1
4	0	1	**1**	**1**	1-1 = 0
E[Y1]			**1.5**		
E[Y0]				**0.5**	
E[Y1 -*Y* 0]					**1**

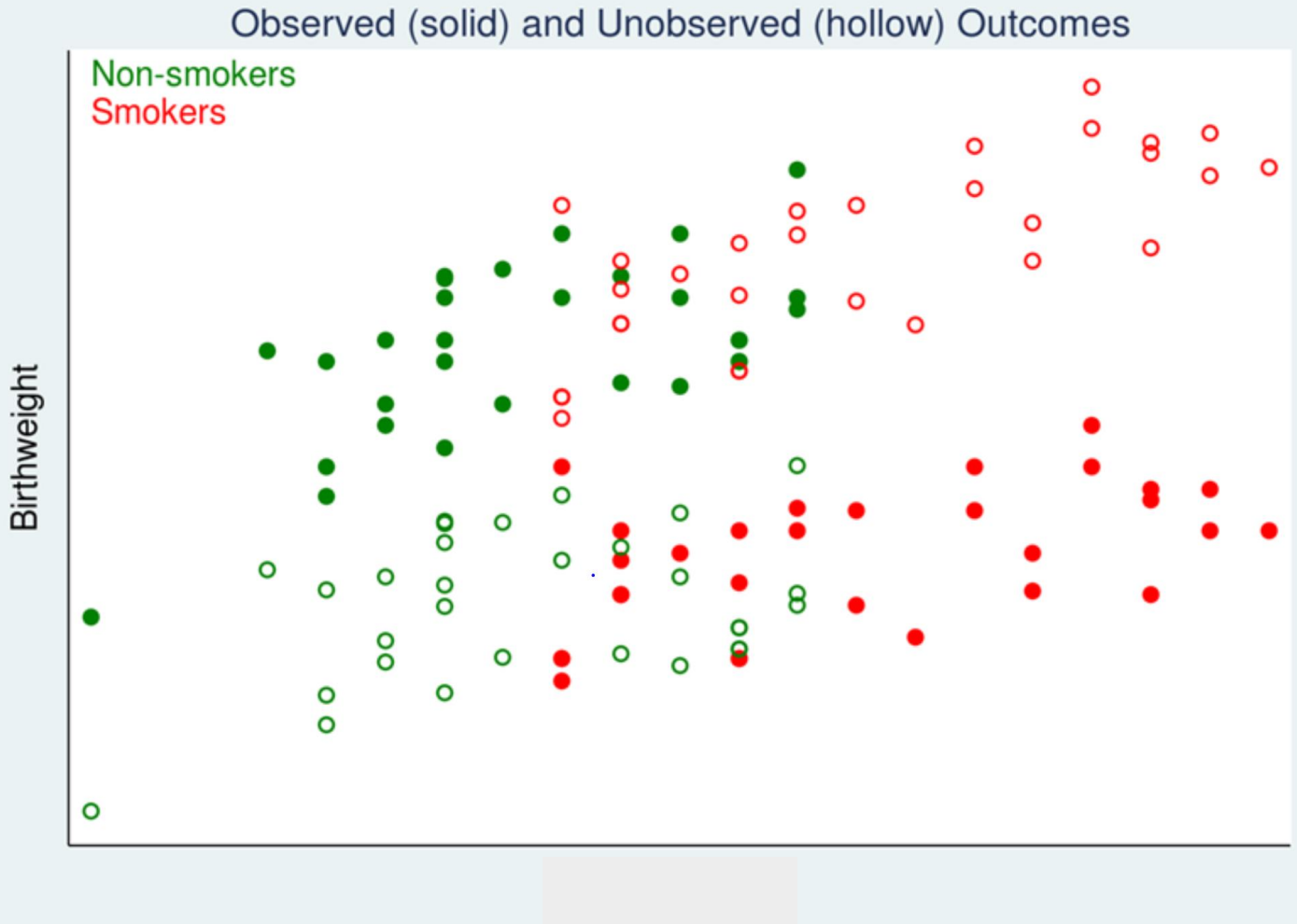
The main concept of counterfactual

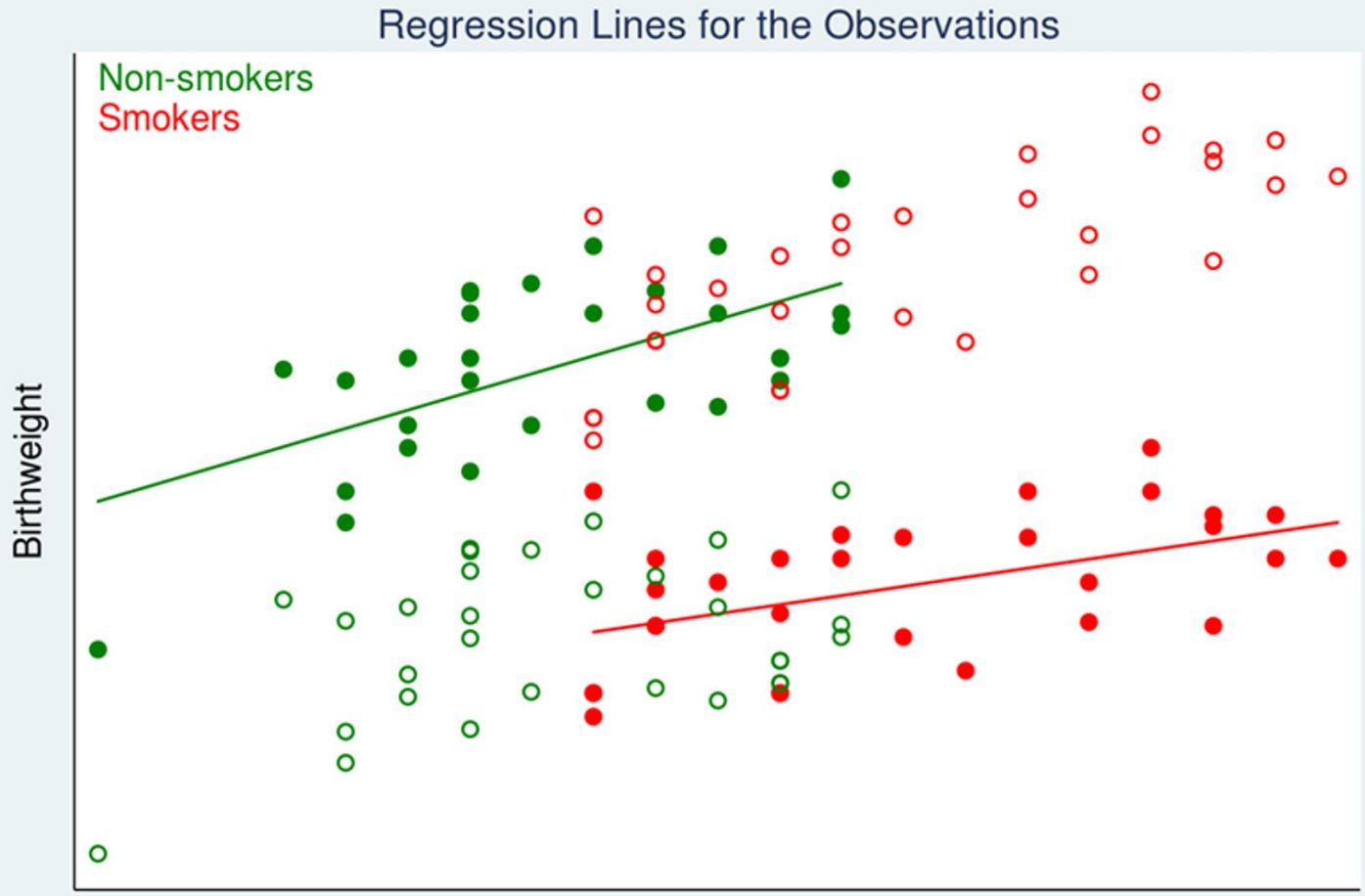


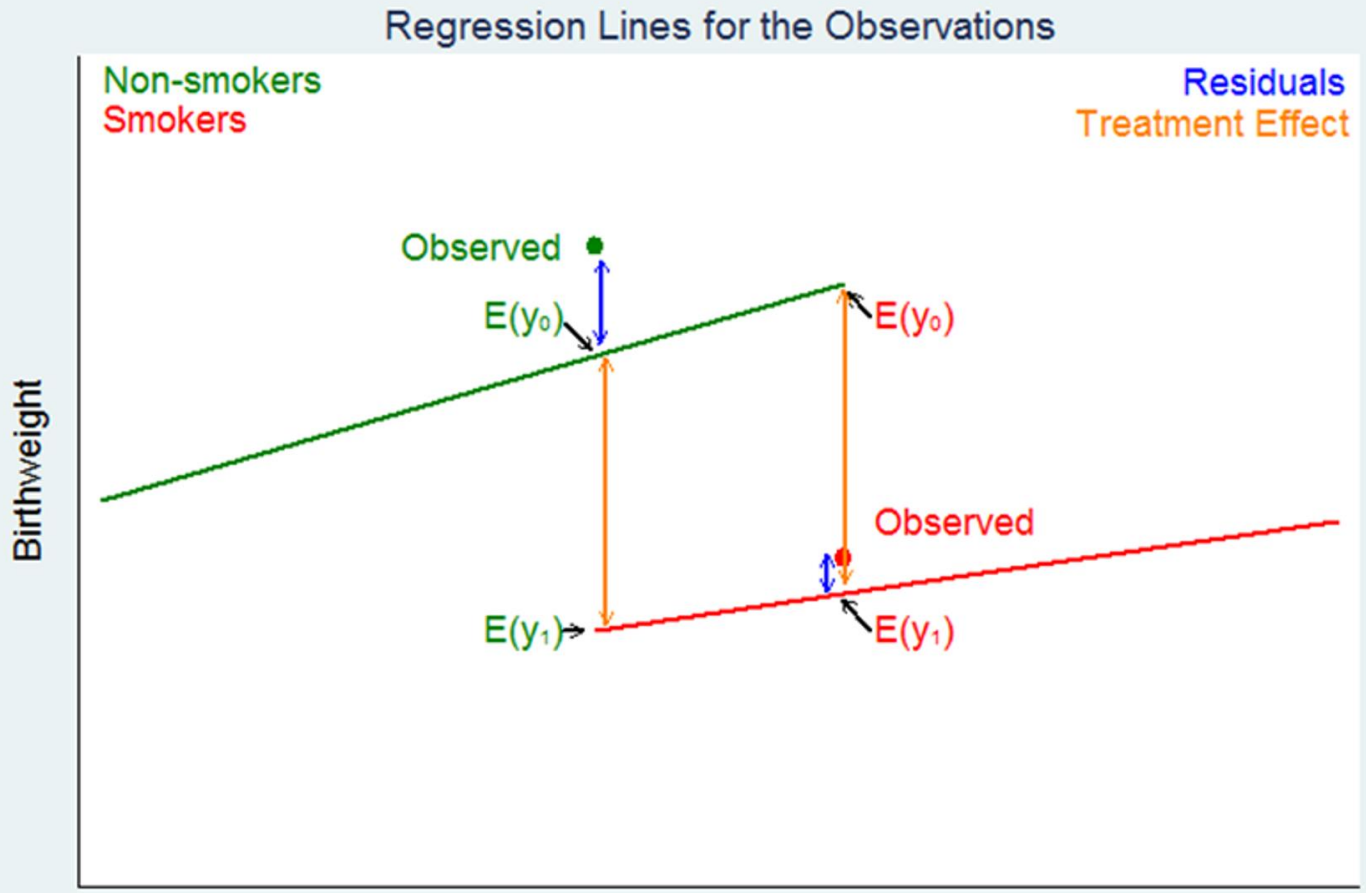
The main concept of counterfactual

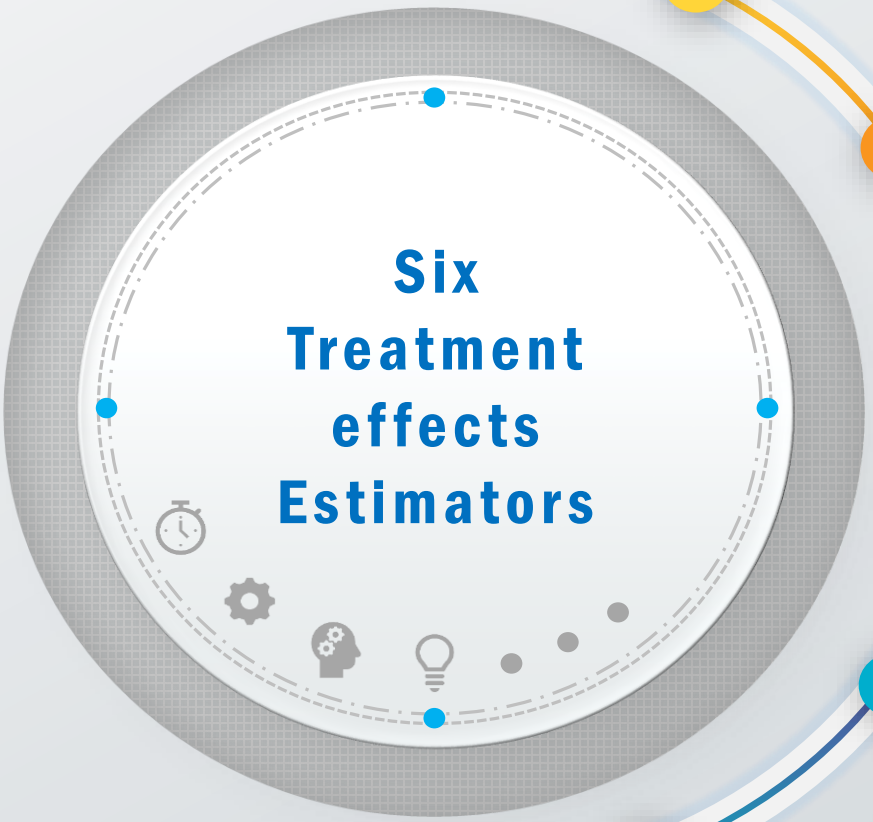
- How would the outcomes have changed had the mothers who smoked chosen not to smoke?

- How would the outcomes have changed had the mothers who didn't smoke chosen to smoke?


Observed (solid) and Unobserved (hollow) Outcomes
Non-smokers
Smokers
Birthweight


Regression Lines for the Observations
Non-smokers
Smokers
Birthweight

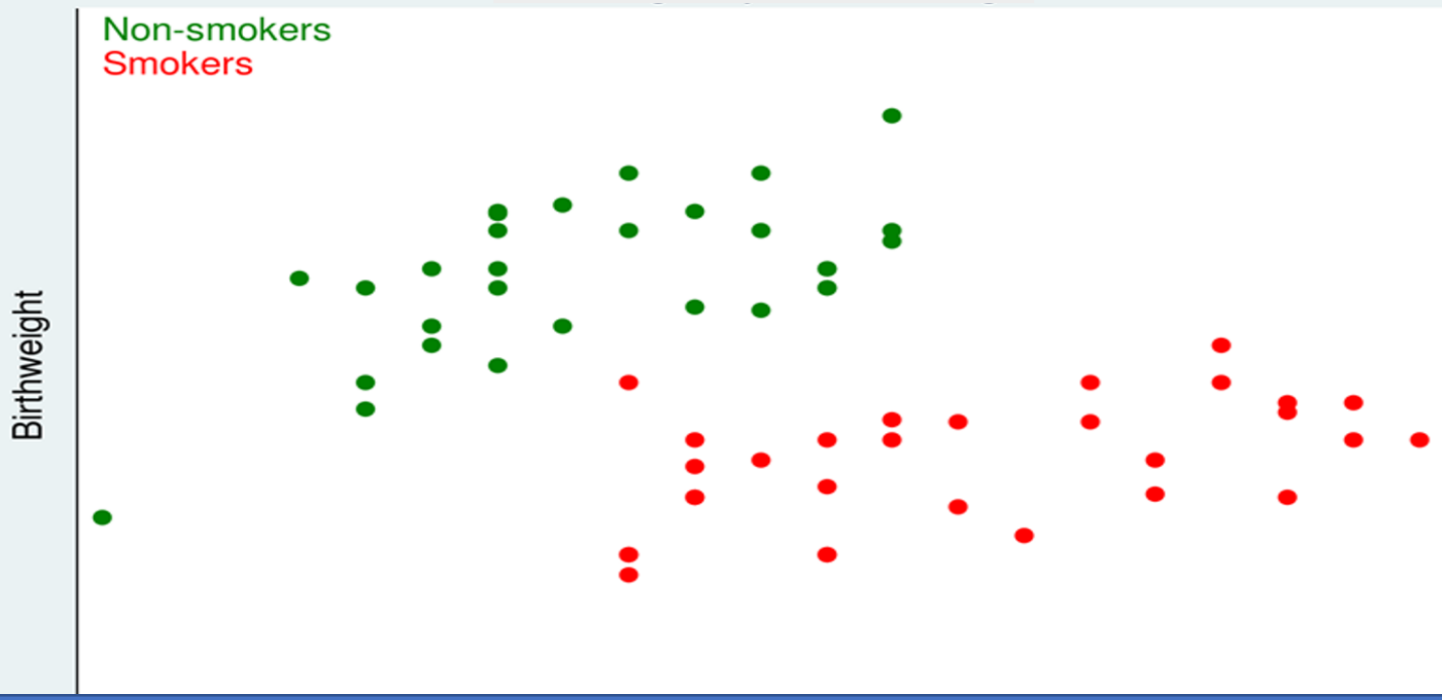

Regression Lines for the Observations
Non-smokers
Smokers
Residuals
Treatment Effect
Observed
E(y0)
E(y0)
Observed
E(y1)
E(y1)
Birthweight



1. Regression Adjustment
2. Inverse Probability Weighting
3. Inverse Probability weighting with Regression Adjustment
4. Augmented Inverse Probability Weighting
5. Near-Neighbor matching
6. Propensity score matching

Natural based Method	Double Robust Method	Matching Method
Regression adjustment	Inverse probability weight with regression adjustment	Near-neighbor matching
Inverse probability weight	Augmented onverse probability weight	Propensity score matching

Regression adjustment: RA

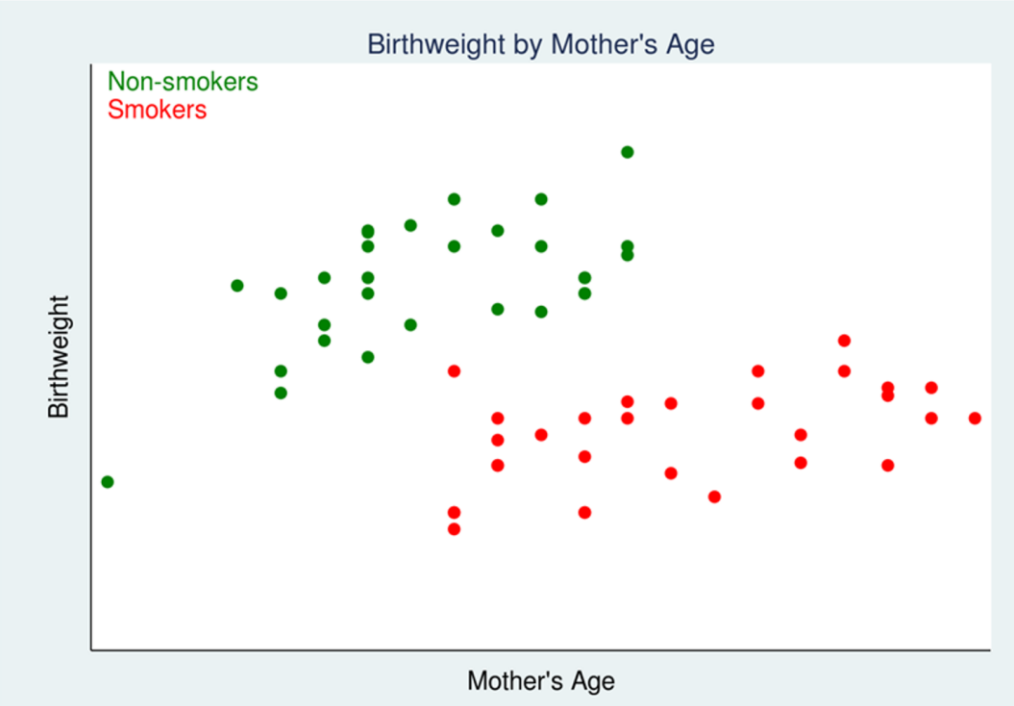


Treatment assignments and considered outcome

Regression adjustment: RA

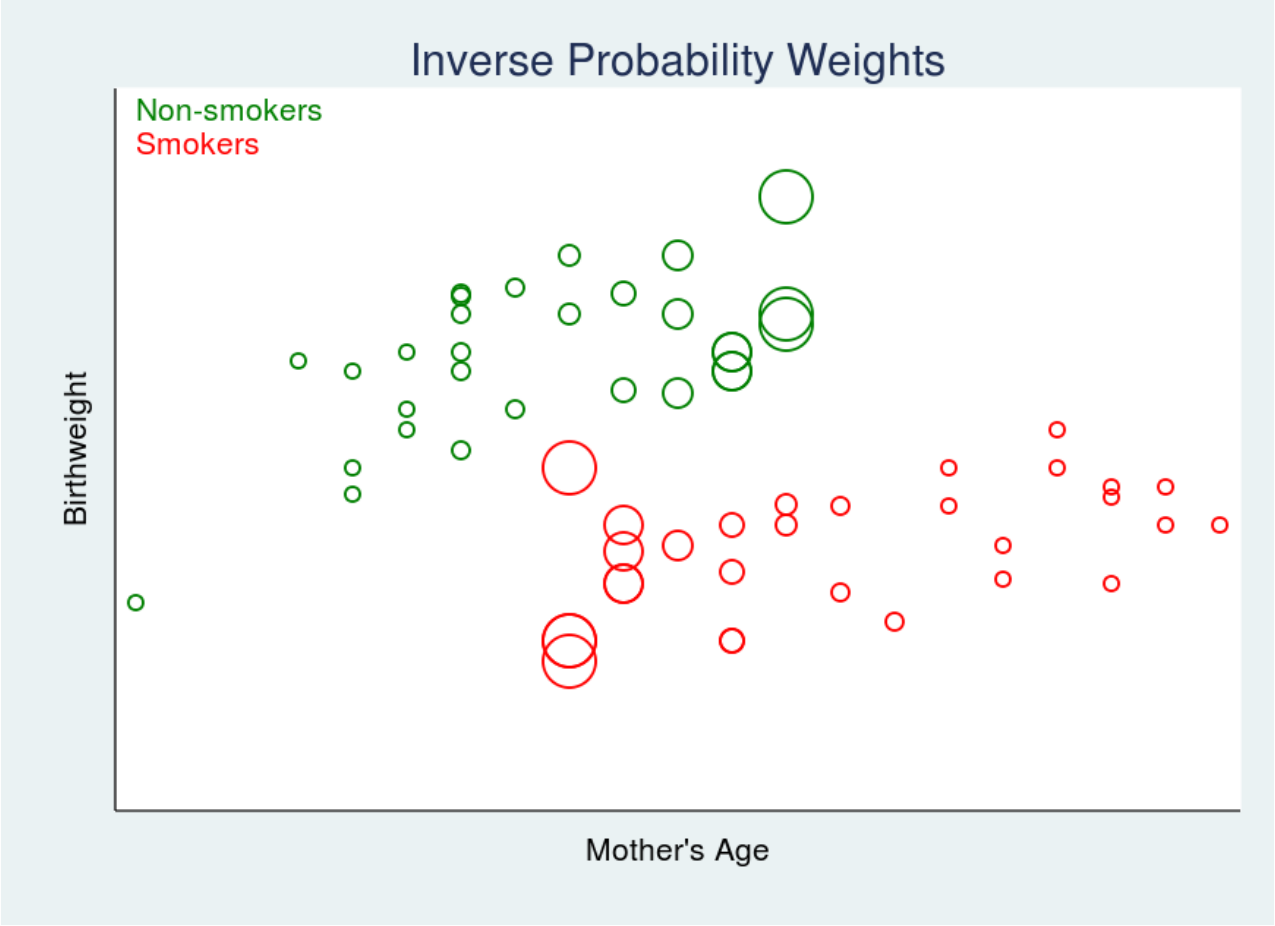
- Command
  - `teffects ra (outcome) (treatment), pomeans`
  - `teffects ra (outcome) (treatment), ate`

The inverse probability weighting: IPW



Prefer to model the treatment assignments process and not specify a model for the outcome.

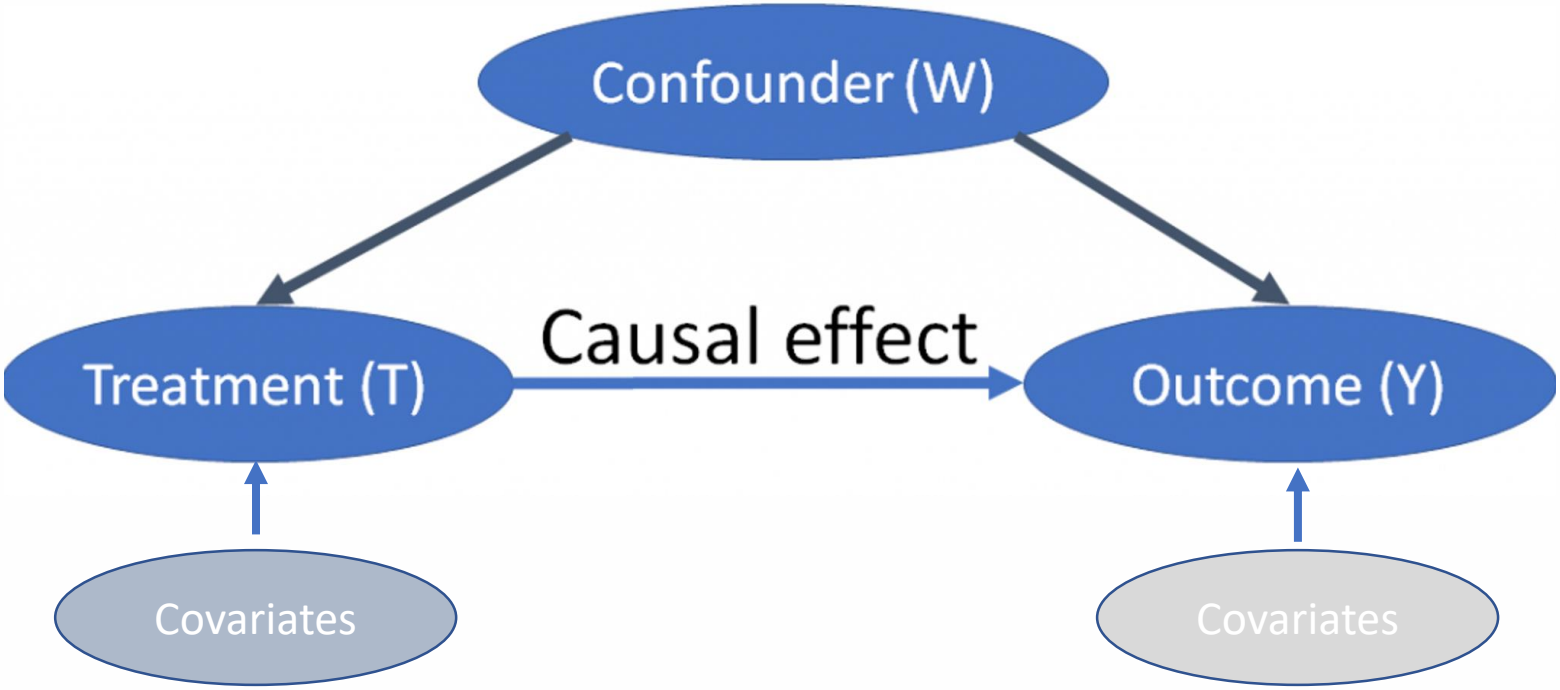
The inverse probability weighting



The inverse probability weighting

- Command
  - teffects ipw (outcome) (treatment covariate), pomeans
  - teffects ipw (outcome) (treatment covariate), ate

Inverse Probability Weighting with Regression Adjustment: IPWRA



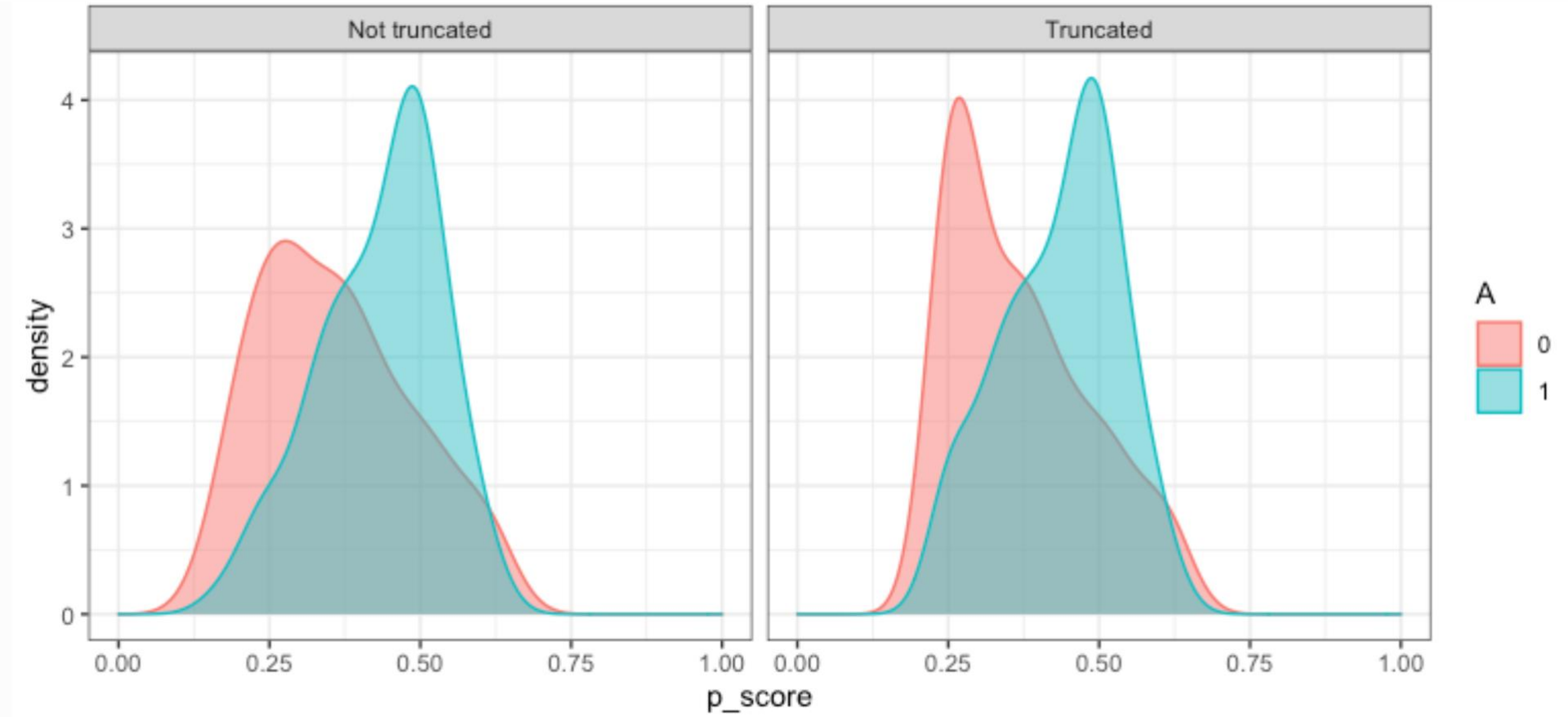
Inverse Probability Weighting with Regression Adjustment: IPWRA

- Command
  - teffects ipwra (outcome covariate) (treatment covariate), pomeans
  - teffects ipwra (outcome covariate) (treatment covariate), ate

The augmented IPW: AIPW

- AIPW estimators adds a bias-correction term to the IPW estimator.
- If the treatment model is correctly specified, the bias-correction term is 0 and the model is reduced to the IPW estimator.
- If the treatment model is misspecified but the outcome model is correctly specified, the bias-correction term corrects the estimator.

The augmented IPW: AIPW

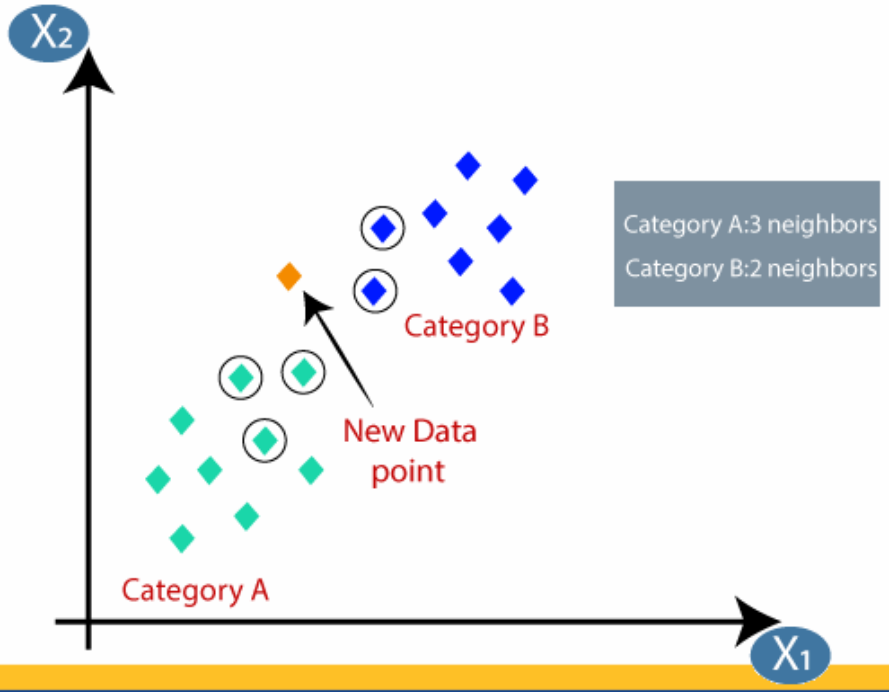


The augmented IPW

- Command
  - `teffects aipw (outcome covariate) (treatment covariate), pomeans aequations`
  - `teffects aipw (outcome covariate) (treatment covariate), ate`

Nearest-neighbor matching: NNM

- NNM used distance between covariate patterns to define “closest”



Nearest-neighbor matching: NNM

- Command
  - teffects nnmatch (outcome covariate) (treatment)

Propensity-score matching: PSM

- PSM matches on an estimated probability of treatment known as the propensity score.
- There is no need for bias adjustment because we match on only one continuous covariate.
- PSM has the added benefit that we can use all the standard methods for checking the fit of binary regression models prior to matching.

Propensity-score matching: PSM

- Command
  - `teffects psmatch (outcome) (treatment covariate)`

Start the practice.

- Download database from ceb-rama.org
- Open database with STATA

How to choose among the six estimators

From example: Mother (smoker vs non-smoker) causal effect birth weight

Estimators	ATE
RA	-277.06
IPW	-275.56
IPWRA	-229.97
AIPW	-230.99
NNM	-210.06
PSM	-229.45

How to choose among the six estimators

1. Under correct specification, all the estimators should produce similar results. (Similar estimates do not guarantee correct specification because all the specifications could be wrong.)

How to choose among the six estimators

2. When you know the determinants of treatment status, IPW is a natural base-case estimator.

3. When you instead know the determinants of the outcome, RA is a natural base-case estimator.

4. The IPW estimators are not reliable when the estimated treatment probabilities get too close to 0 or 1.

How to choose among the six estimators

5. The doubly robust estimators, AIPW and IPWRA, give us an extra shot at correct specification.

6. When you have lots of continuous covariates, NNM will crucially hinge on the bias adjustment, and the computation gets to be extremely difficult.

7. When you know the determinants of treatment status, PSM is another base-case estimator.

Thank You