McGill UNIVERSITY

Department of
Epidemiology, Biostatistics
and Occupational Health

Introduction to Target Trial Emulation Studies

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Agenda

		Slides:
1.	Study types by objective: **descriptive**, **predictive**, and **causal**	2-5
2.	Quick refresher on the **counterfactual causal theory**	6-26
3.	From **randomized trials** to **observational studies**	27-54
4.	Brief overview of **real-world data** and **real-world evidence**	55-60
5.	The **target trial framework**	61-92
6.	The **causal roadmap**	93-96
7.	Additional resources	97-101

1. Study types by objective: descriptive, predictive, and causal

Three fundamental tasks in research…

a) **Description**:

b) **Prediction**:

c) **Causal inference**:

Hernán MA, et al. CHANCE. 2019;32(1):42-49. doi:10.1080/09332480.2019.1579578

Three fundamental tasks in research…

a) **Description**: Provides a **quantitative summary of the characteristics of a population** (e.g., to guide resource allocation or generate hypotheses).

b) **Prediction**: **Identifies associations between population characteristics** (e.g., to anticipate resource requirements).

c) **Causal inference**: **Estimates the effect** (impact) **of an exposure**, treatment, or intervention **on outcomes** (to inform decision-making).

Hernán MA, et al. CHANCE. 2019;32(1):42-49. doi:10.1080/09332480.2019.1579578

Why does this distinction matter?

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Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial ☆

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Hydroxychloroquine
Azithromycin
Clinical trial

ABSTRACT

Backgr... ...chloroqu... ...d hydroxychloroquine have been found to be efficient on SARS-CoV-2, and rep... to ...efficient ... Chinese COV-19 patients. We evaluate the effect of hydroxychloroquine on ...atory v... loads.

...ts a... French Confirmed COVID-19 patients were included in a single arm protocol fro... March ... March 16th, to receive 600mg of hydroxychloroquine daily and their viral load in nasop... geal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithrom... was added to the treatment. Untreated patients from another center and cases refusing the protocol we... included as negative controls. Presence and absence of virus at Day6-post inclusion was ...nsidered the end point.

...lts: Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight ha... ...wer respiratory tract infection symptoms.

Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported in the litterature for untreated patients. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

Conclusion: Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

RETRACTED

2. Quick refresher on the **counterfactual causal theory**

Sir Austin Bradford Hill's causal considerations

(1) Strength

(2) Consistency

(3) Specificity

(4) Temporality

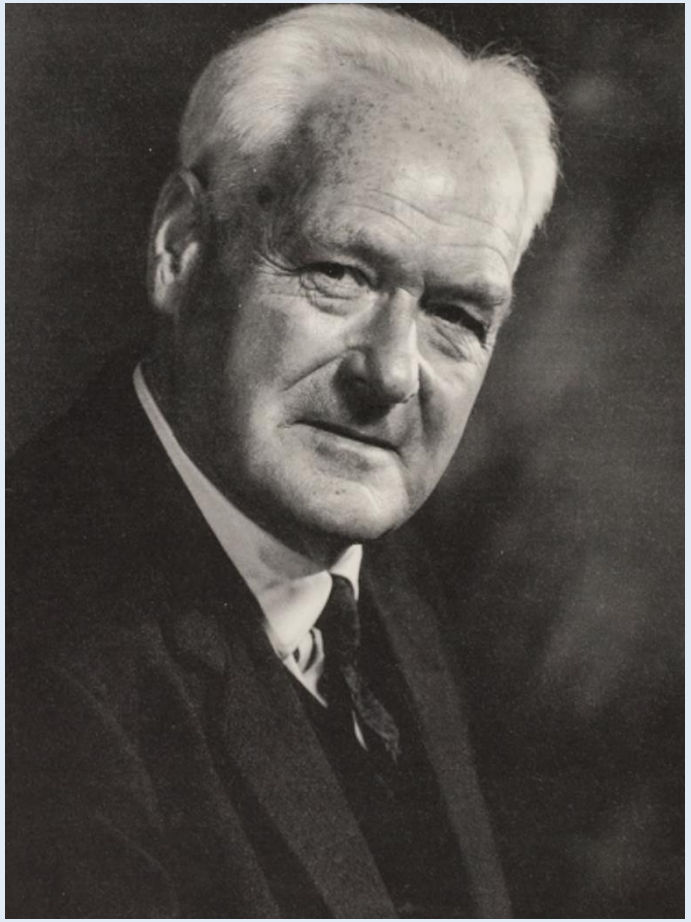
(5) Biological gradient

(6) Plausibility

(7) Coherence

(8) Experimental evidence

(9) Analogy



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Sir Austin Bradford Hill's causal considerations

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(2) Consistency

(3) Specificity

(4) Temporality

(5) Biological gradient

(6) Plausibility

(7) Coherence

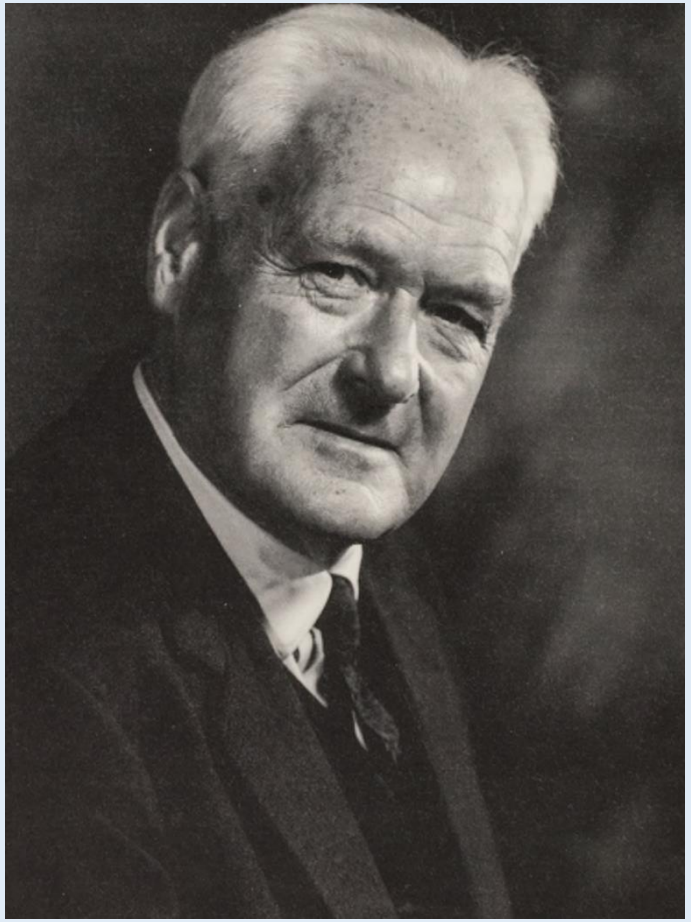
(8) Experimental evidence

(9) Analogy

Causal effect **estimation**

$\neq$

Causal **inference**



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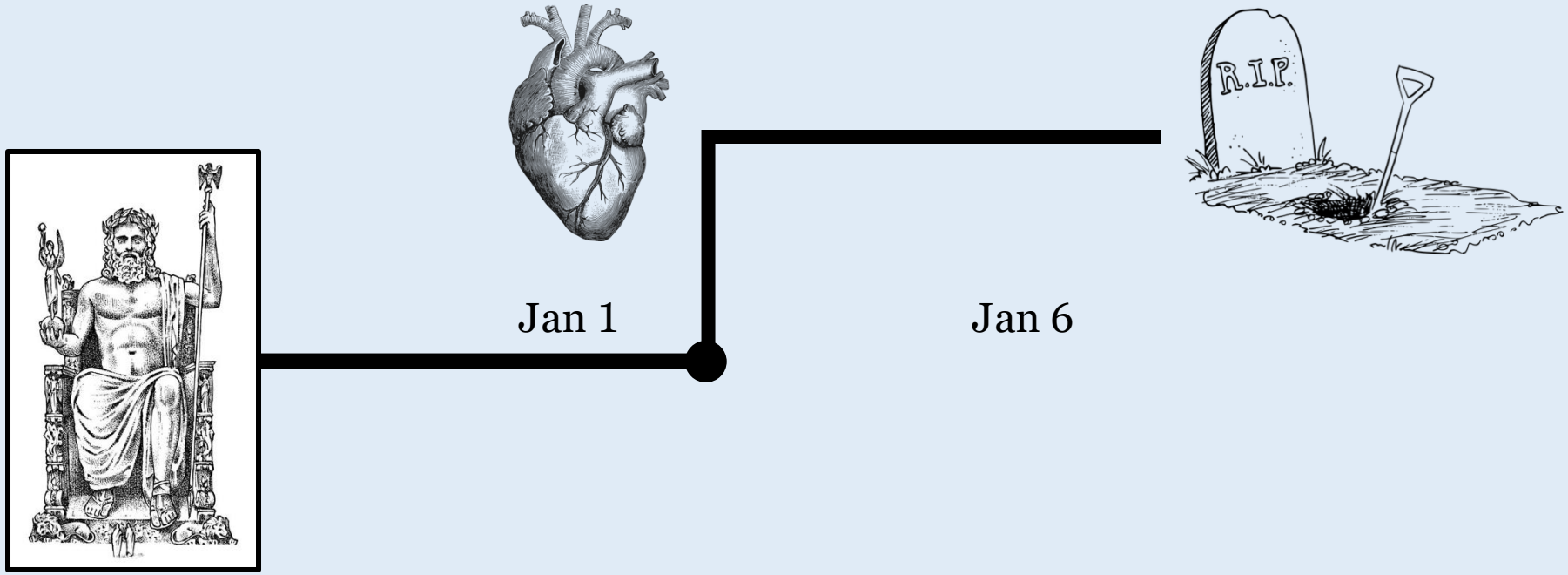
Individual causal effects



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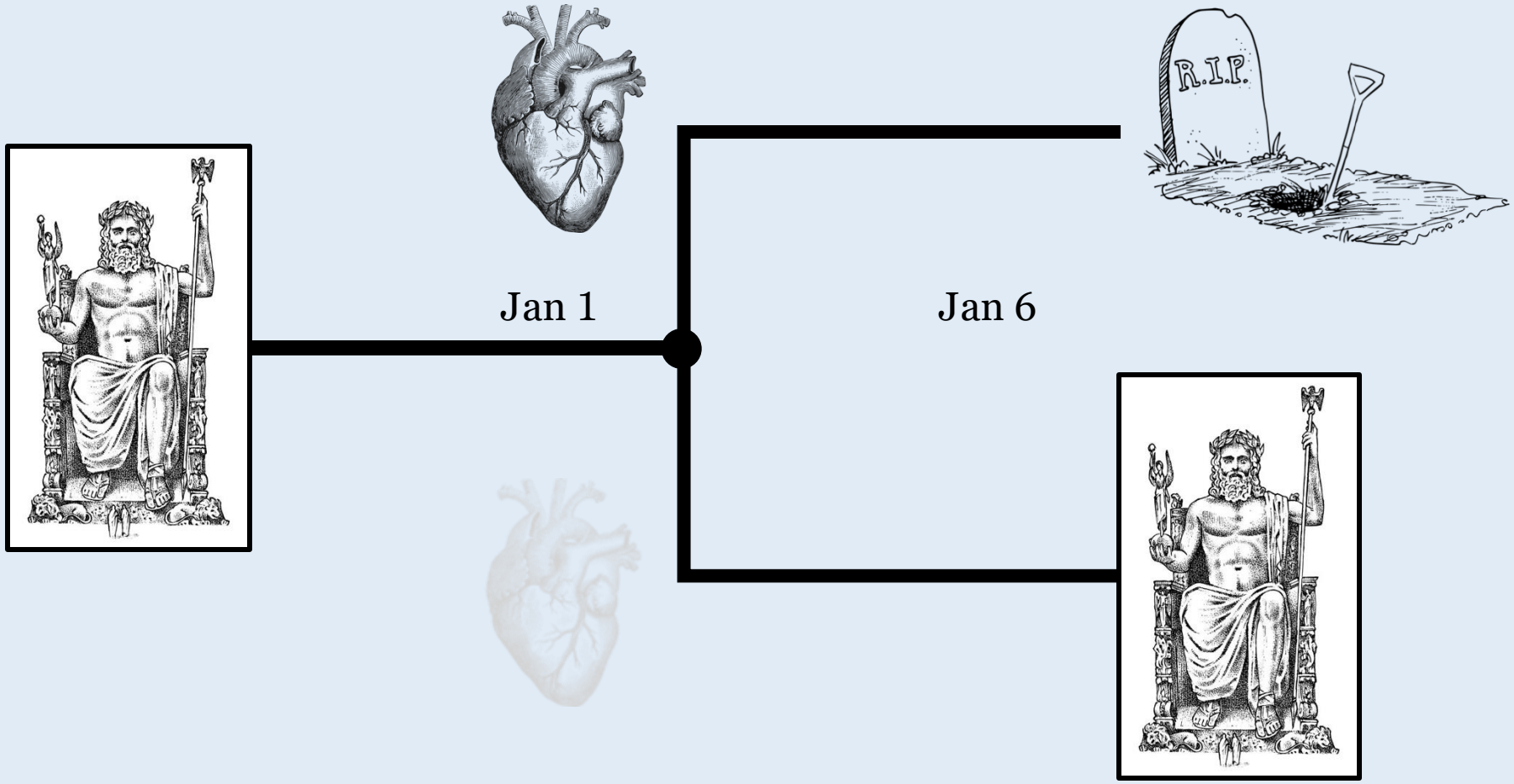
Individual causal effects



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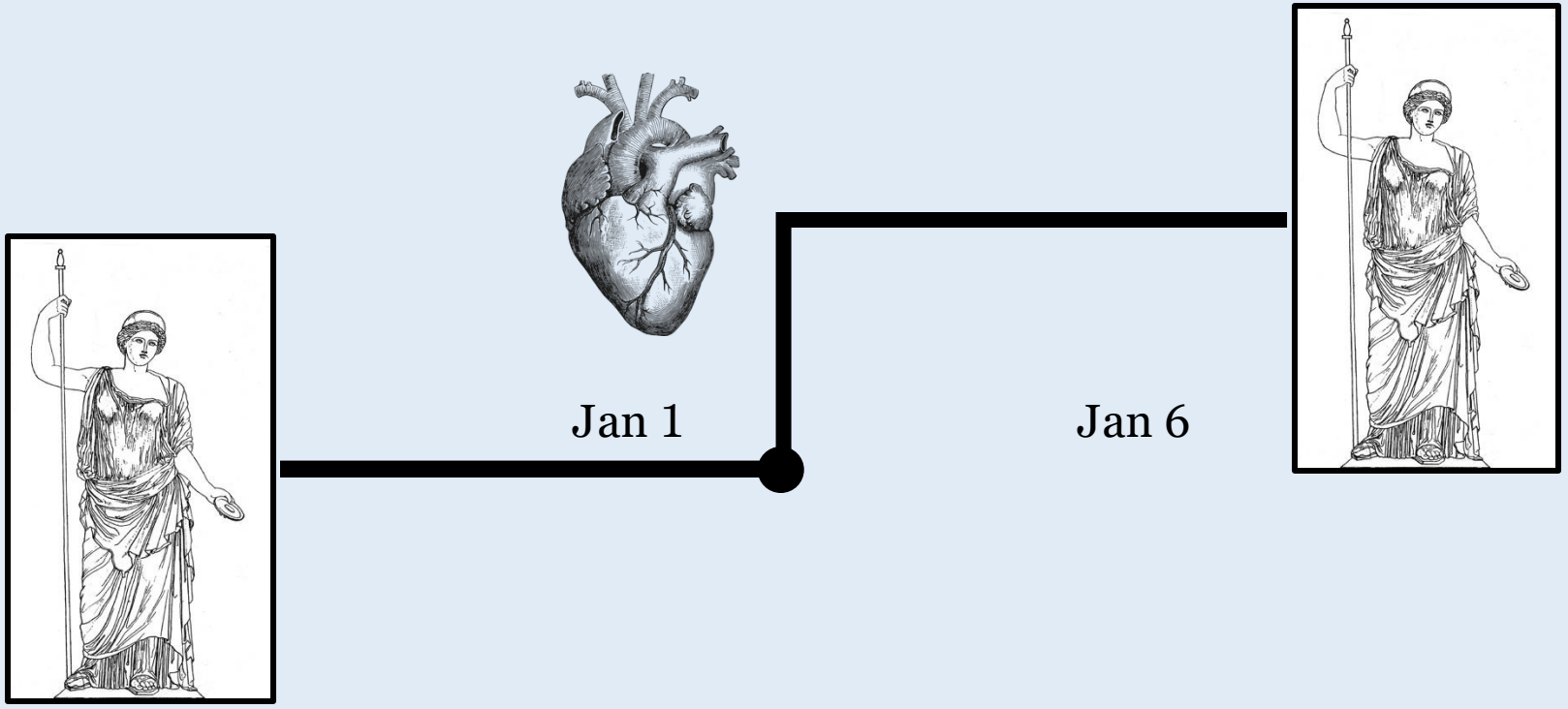

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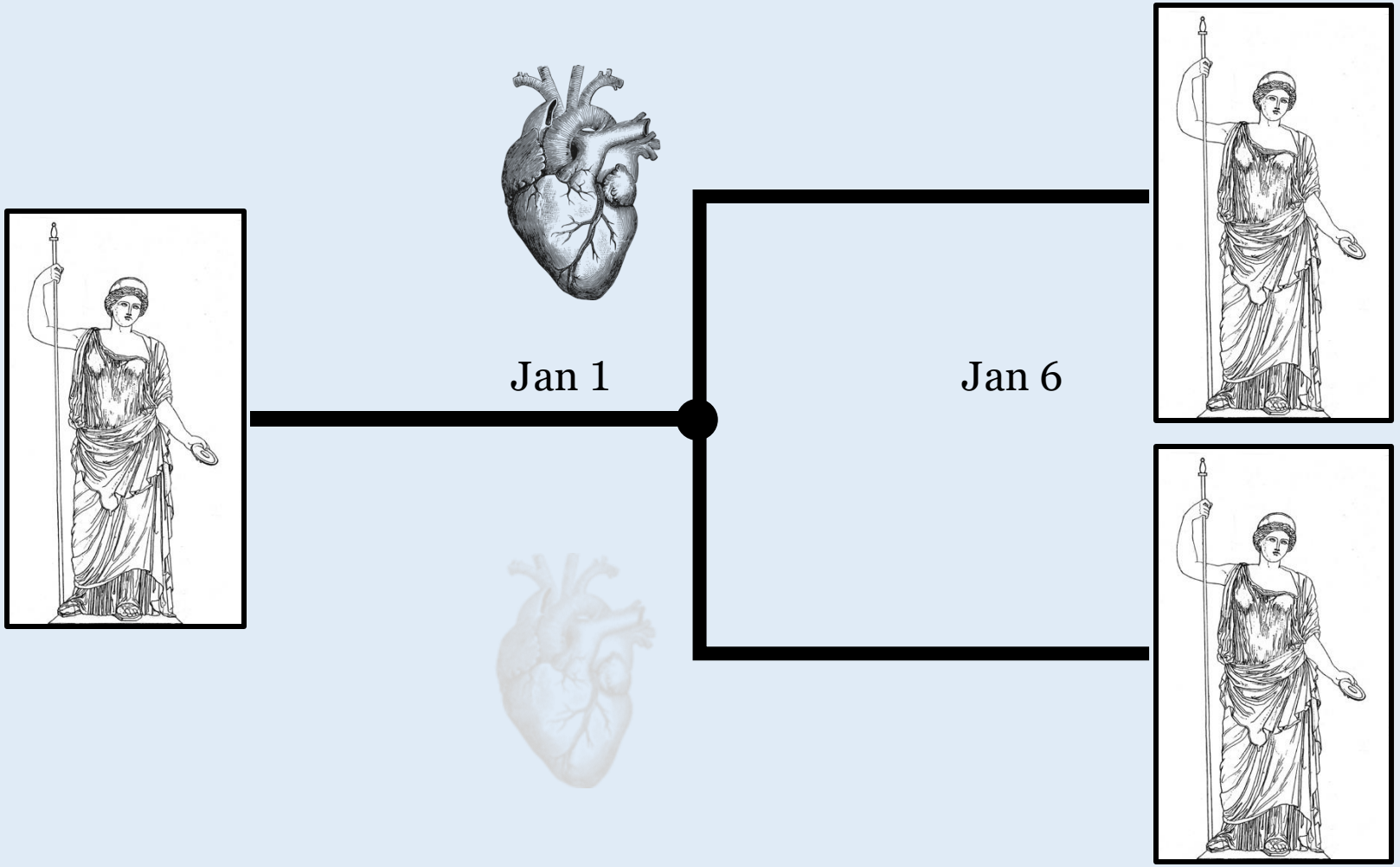

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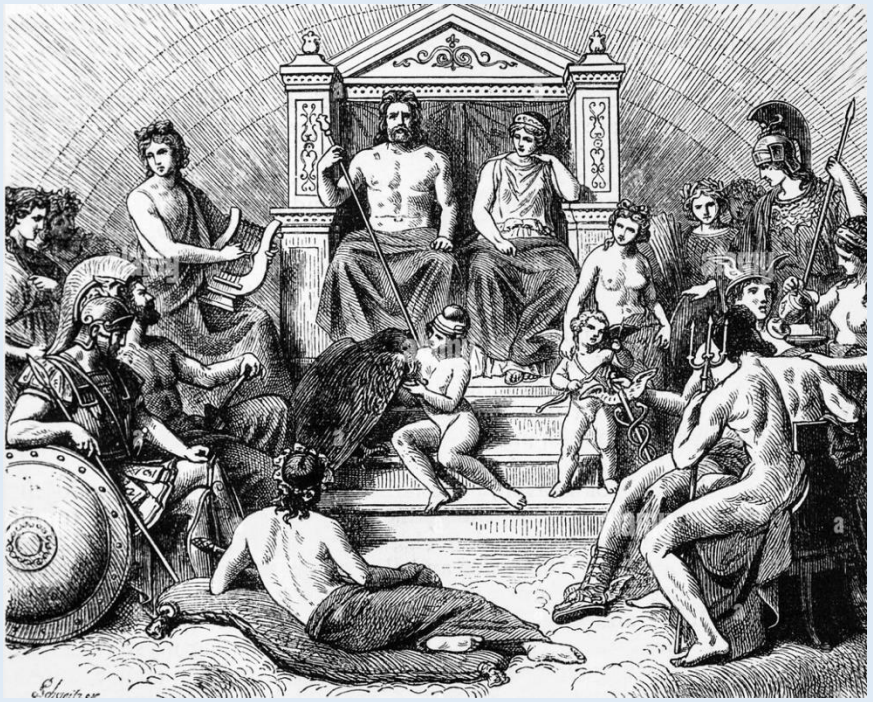
Average causal effects

Table 1.2

	A	Y
Rheia	0	0
Kronos	0	1
Demeter	0	0
Hades	0	0
Hestia	1	0
Poseidon	1	0
Hera	1	0
Zeus	1	1
Artemis	0	1
Apollo	0	1
Leto	0	0
Ares	1	1
Athena	1	1
Hephaestus	1	1
Aphrodite	1	1
Polyphemus	1	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0



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Apollo	0	1
Leto	0	0
Ares	1	1
Athena	1	1
Hephaestus	1	1
Aphrodite	1	1
Polyphemus	1	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

The risk of death among transplant recipients is:

$$\Pr[Y = 1 | A = 1] = \frac{7}{13} = 0.54$$

Average causal effects

Table 1.2

	A	Y
Rheia	0	0
Kronos	0	1
Demeter	0	0
Hades	0	0
Hestia	1	0
Poseidon	1	0
Hera	1	0
Zeus	1	1
Artemis	0	1
Apollo	0	1
Leto	0	0
Ares	1	1
Athena	1	1
Hephaestus	1	1
Aphrodite	1	1
Polyphemus	1	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

The risk of death among non-transplant recipients is:

$$\Pr[Y = 1 | A = 0] = \frac{3}{7} = 0.43$$

The risk of death among transplant recipients is:

$$\Pr[Y = 1 | A = 1] = \frac{7}{13} = 0.54$$

Average causal effects

Table 1.2

	A	Y
Rheia	0	0
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Leto	0	0
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Athena	1	1
Hephaestus	1	1
Aphrodite	1	1
Polyphemus	1	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

The risk of death among non-transplant recipients is:

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The risk of death among transplant recipients is:

$$\Pr[Y = 1 | A = 1] = \frac{7}{13} = 0.54$$

(i) $\Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0] = 0$

(ii) $\dfrac{\Pr[Y = 1|A = 1]}{\Pr[Y = 1|A = 0]} = 1$

(iii) $\dfrac{\Pr[Y = 1|A = 1] / \Pr[Y = 0|A = 1]}{\Pr[Y = 1|A = 0] / \Pr[Y = 0|A = 0]} = 1$

Average causal effects

Table 1.1

	$Y^{a=0}$	$Y^{a=1}$
Rheia	0	1
Kronos	1	0
Demeter	0	0
Hades	0	0
Hestia	0	0
Poseidon	1	0
Hera	0	0
Zeus	0	1
Artemis	1	1
Apollo	1	0
Leto	0	1
Ares	1	1
Athena	1	1
Hephaestus	0	1
Aphrodite	0	1
Polyphemus	0	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

Half would have died if everyone had received a transplant:

$$\Pr[Y^{a=1} = 1] = \frac{10}{20} = 0.5$$

Average causal effects

Table 1.1

	$Y^{a=0}$	$Y^{a=1}$
Rheia	0	1
Kronos	1	0
Demeter	0	0
Hades	0	0
Hestia	0	0
Poseidon	1	0
Hera	0	0
Zeus	0	1
Artemis	1	1
Apollo	1	0
Leto	0	1
Ares	1	1
Athena	1	1
Hephaestus	0	1
Aphrodite	0	1
Polyphemus	0	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

Half would have died if no one had received a transplant:

$$\Pr[Y^{a=0} = 1] = \frac{10}{20} = 0.5$$

Half would have died if everyone had received a transplant:

$$\Pr[Y^{a=1} = 1] = \frac{10}{20} = 0.5$$

Average causal effects

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Artemis	1	1
Apollo	1	0
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Athena	1	1
Hephaestus	0	1
Aphrodite	0	1
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Persephone	1	1
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(i) $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$

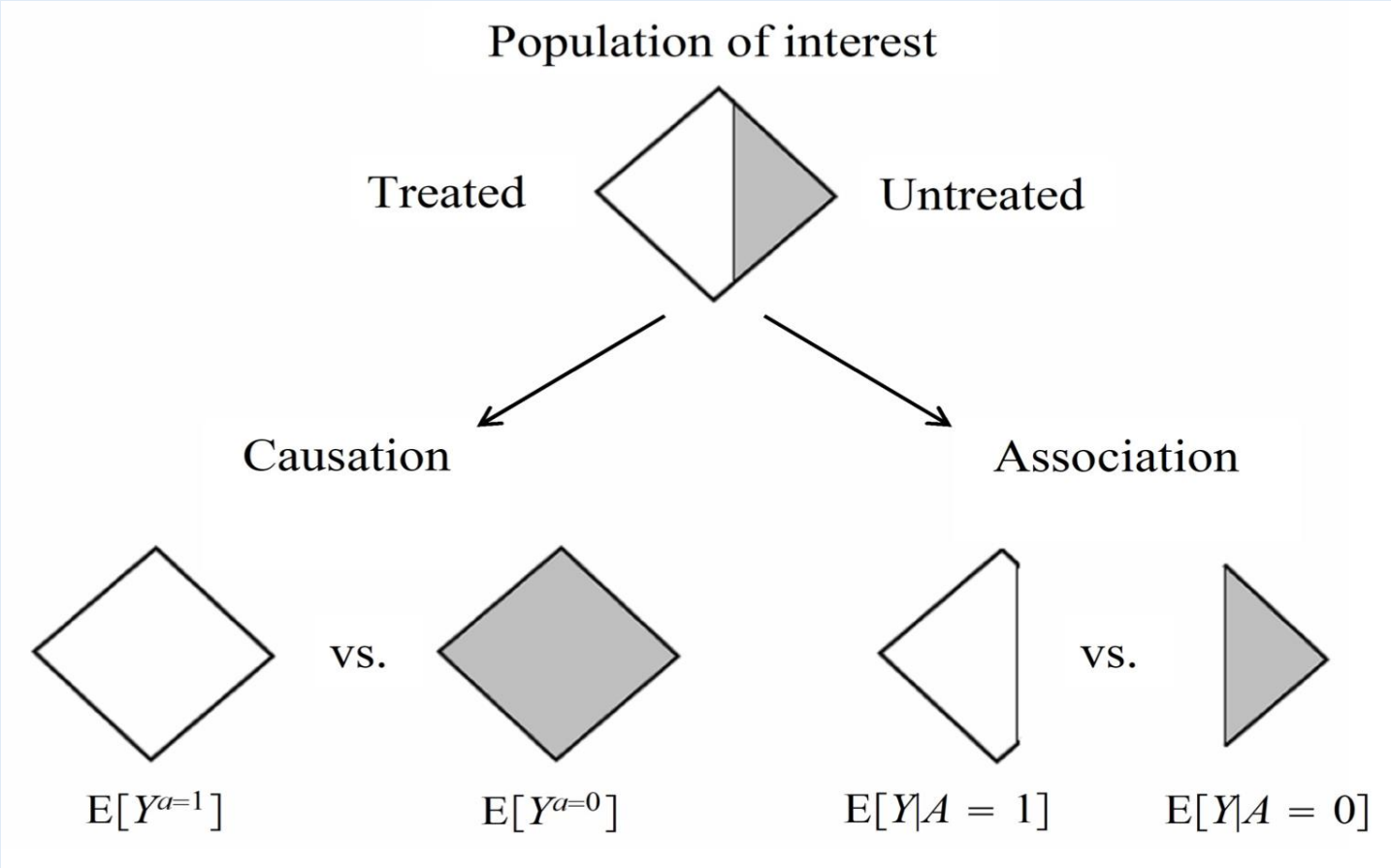
(ii) $\dfrac{\Pr[Y^{a=1} = 1]}{\Pr[Y^{a=0} = 1]}$

(iii) $\dfrac{\Pr[Y^{a=1} = 1] / \Pr[Y^{a=1} = 0]}{\Pr[Y^{a=0} = 1] / \Pr[Y^{a=0} = 0]}$

Causation vs. association

To infer causality, we must ask questions such as:

What would the risk be **if** everyone (vs. no one) received the treatment?



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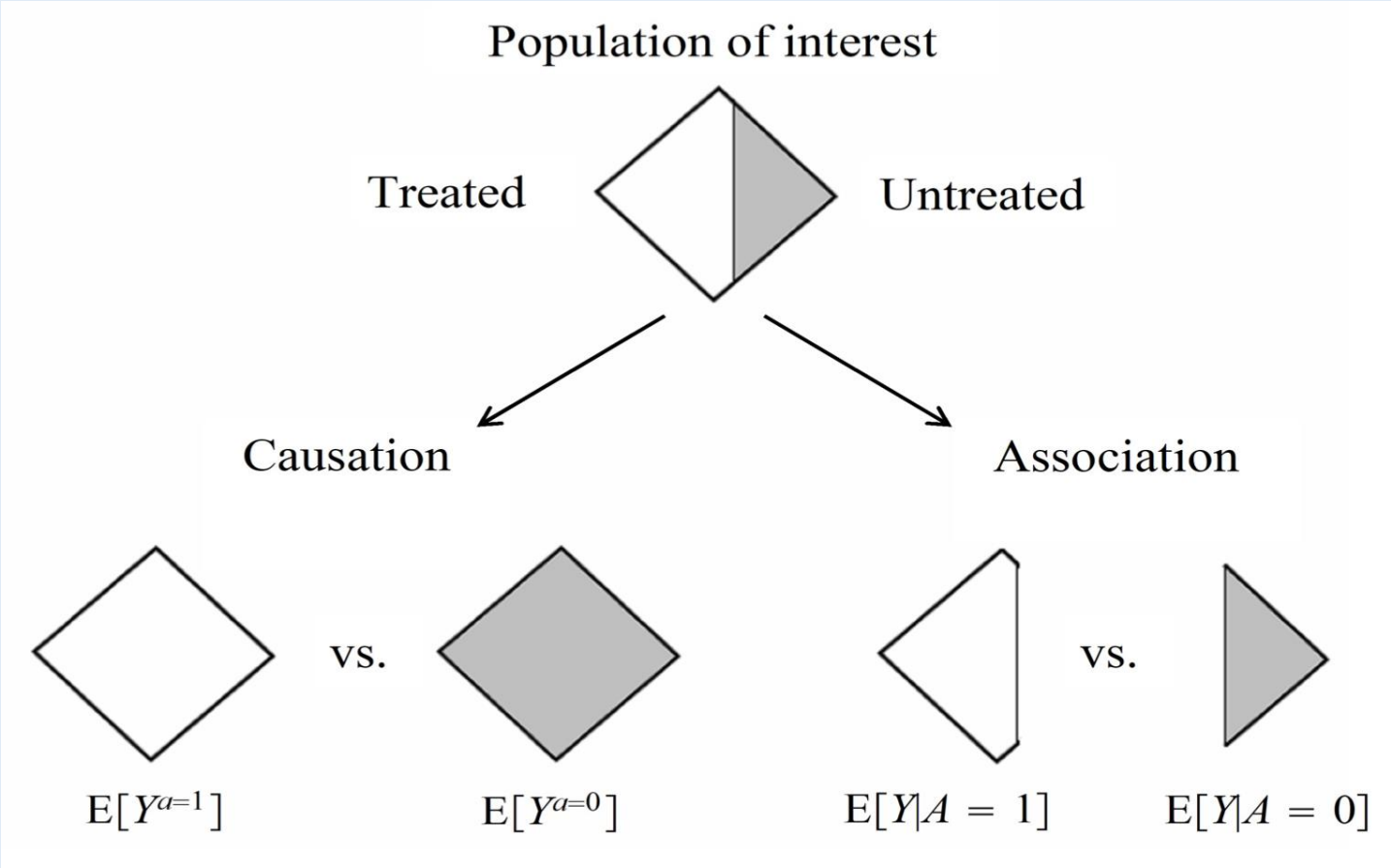

To study associations, the questions are:

What is the risk among those who received the treatment and those who did not?

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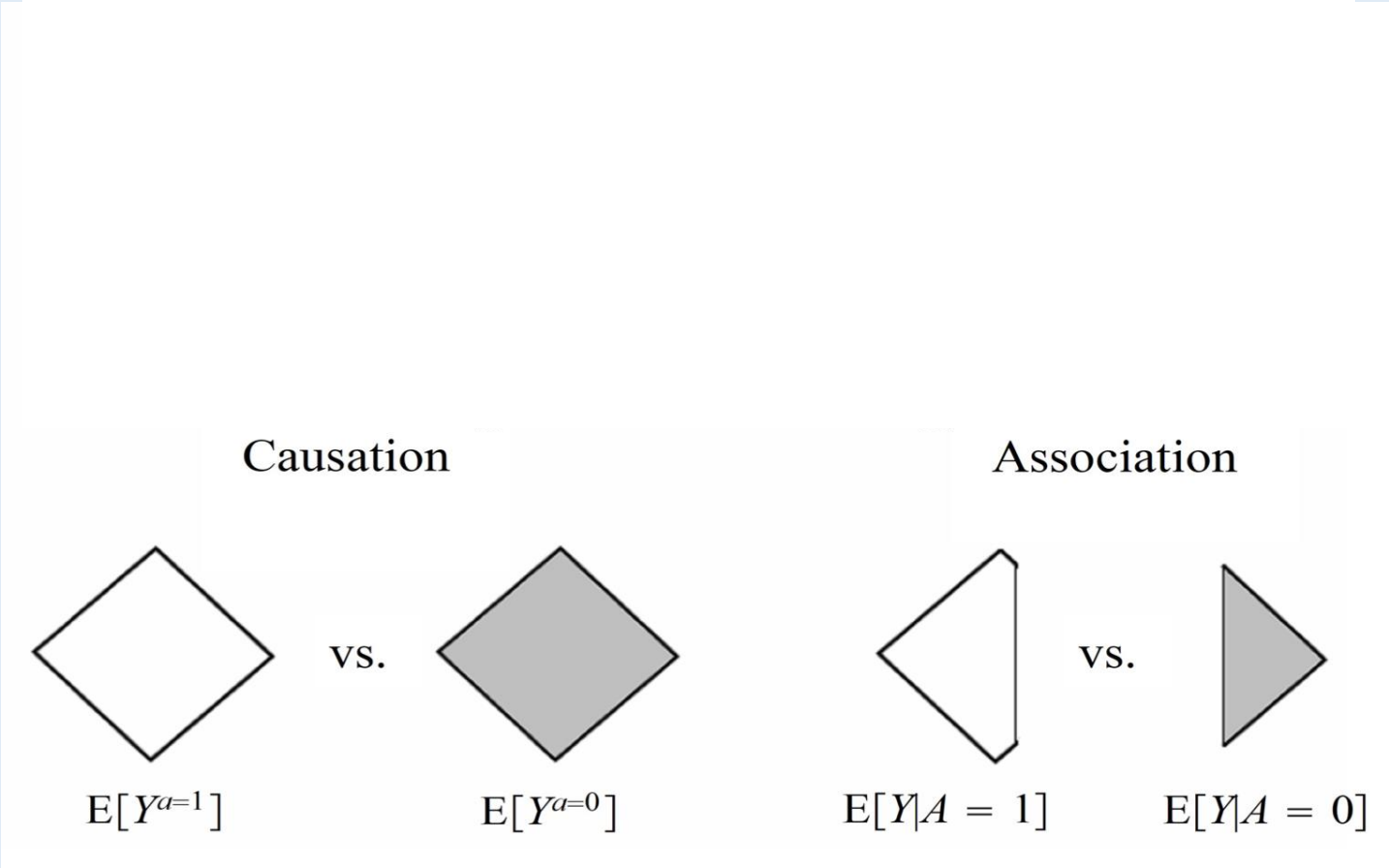
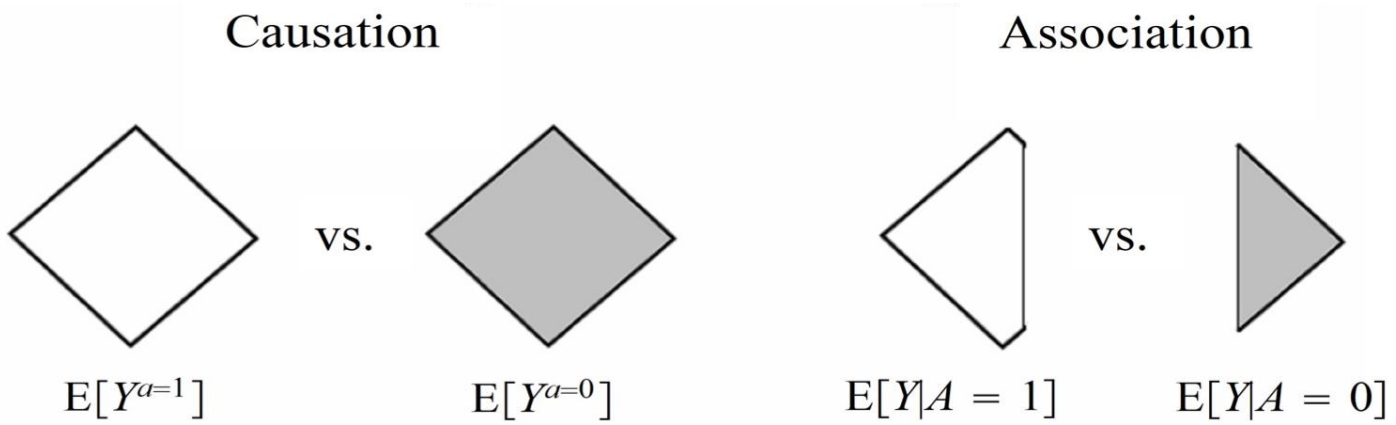
What is identifiability?



Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Identifiability

"*When* ***a counterfactual quantity*** ***can be expressed as a function of the distribution*** *(i.e., the probabilities)* ***of the observed data****, we say that the counterfactual quantity is identified (or identifiable)*"



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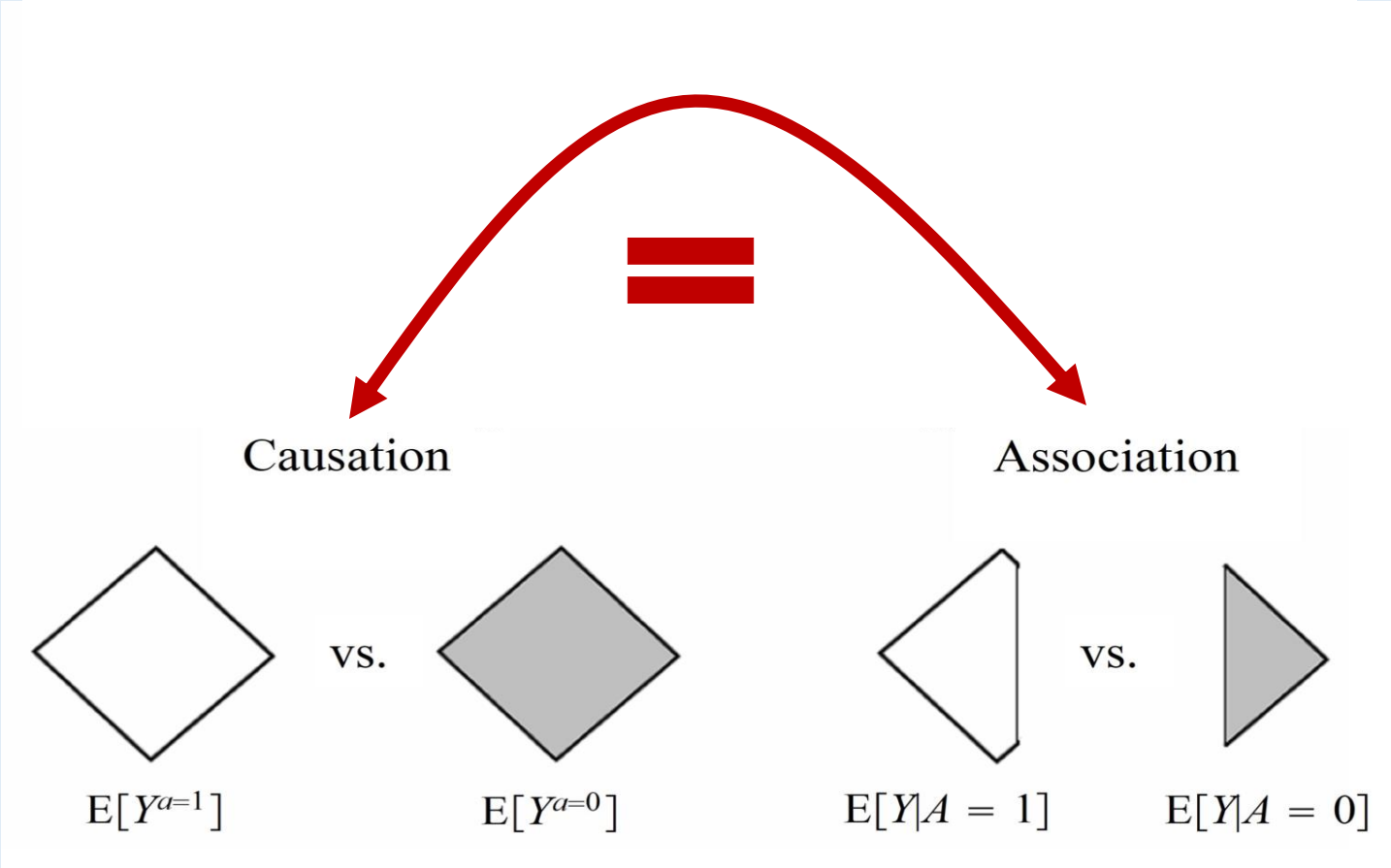
Identifiability



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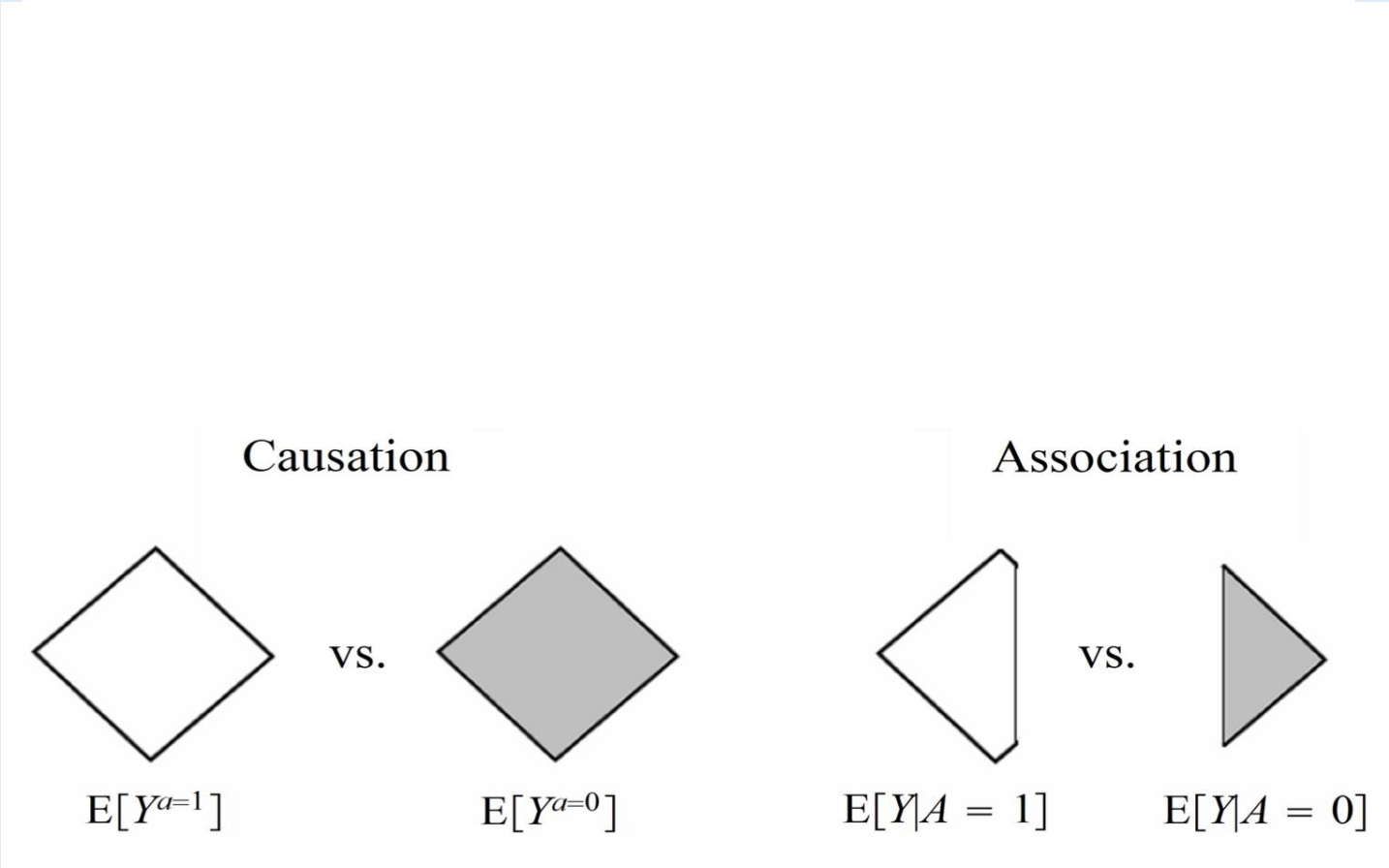
What is the causal gap?



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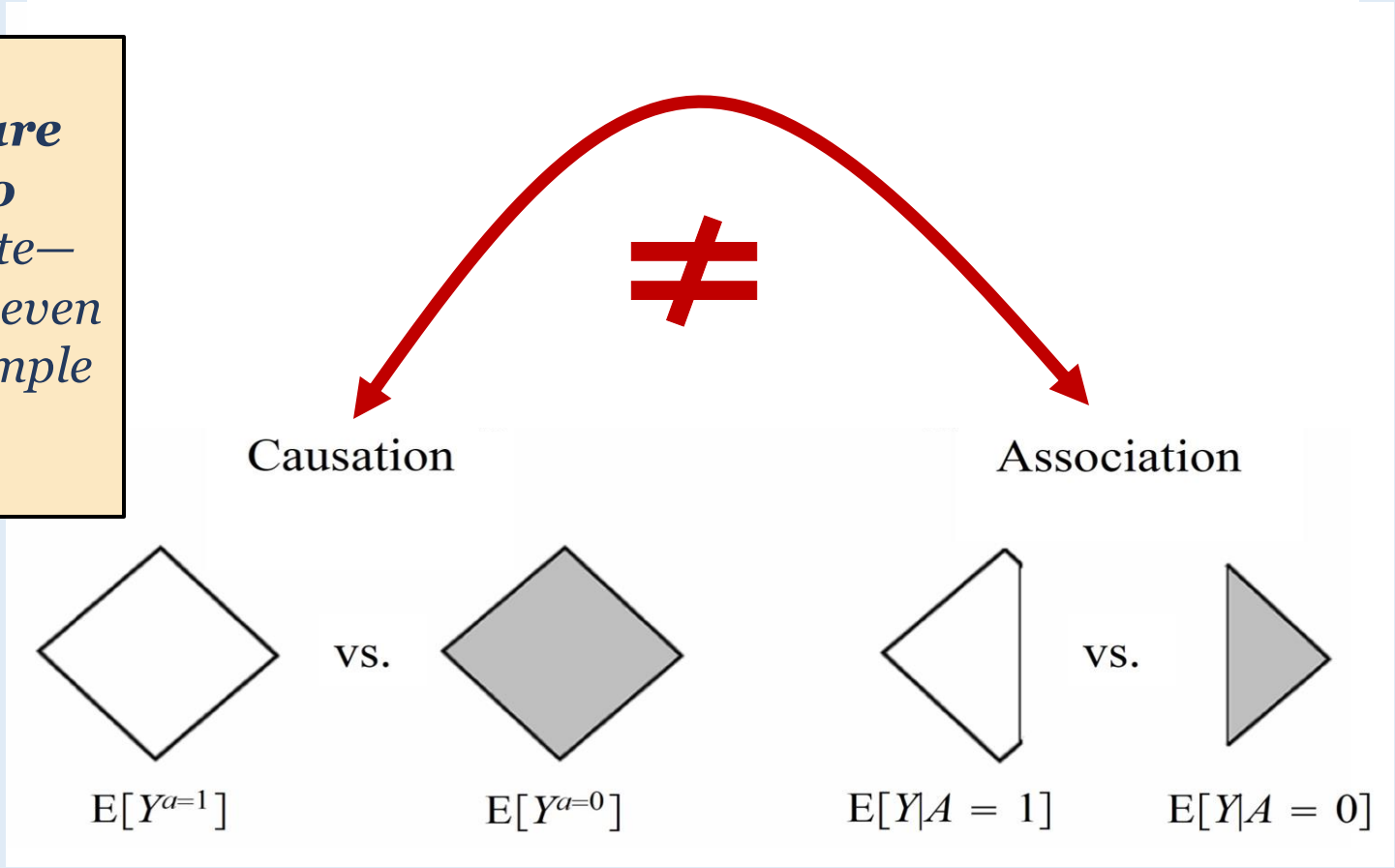
What is the causal gap?

*"when the **data are insufficient to identify**—compute—**the causal effect** even with an infinite sample size"*



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3. From **randomized trials** to **observational studies**

What is the fundamental problem of causal inference?

What is the fundamental problem of causal inference?

Table 2.1

	A	Y	Y^0	Y^1
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
Ares	1	1	?	1
Athena	1	1	?	1
Hephaestus	1	1	?	1
Aphrodite	1	1	?	1
Polyphemus	1	1	?	1
Persephone	1	1	?	1
Hermes	1	0	?	0
Hebe	1	0	?	0
Dionysus	1	0	?	0

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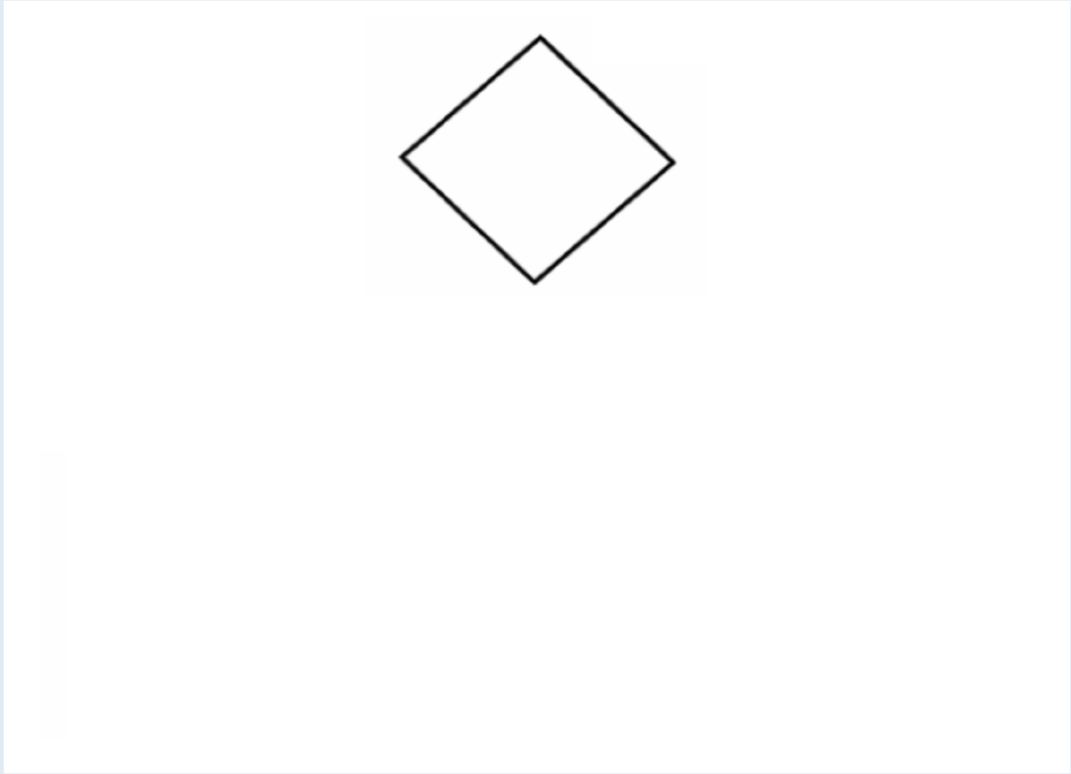
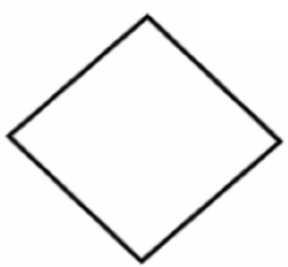
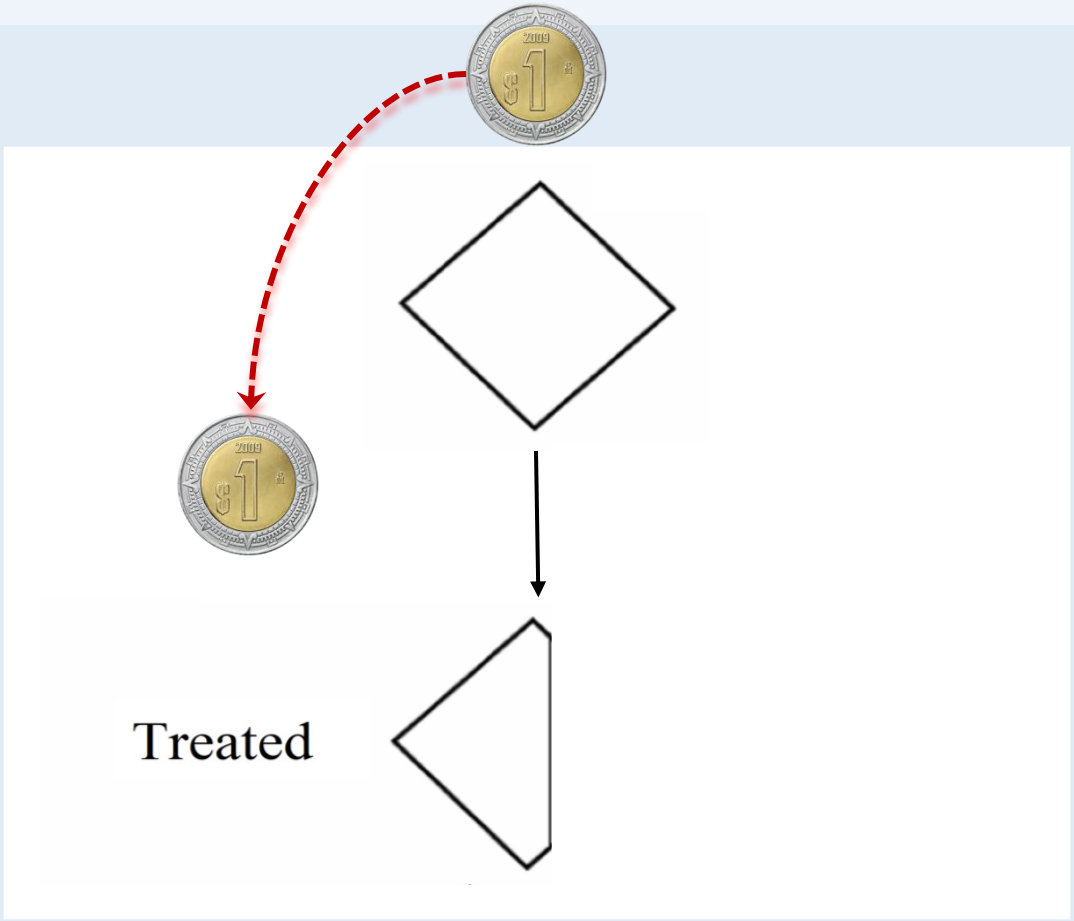
How can we solve it?



Marginal randomization



Marginal randomization



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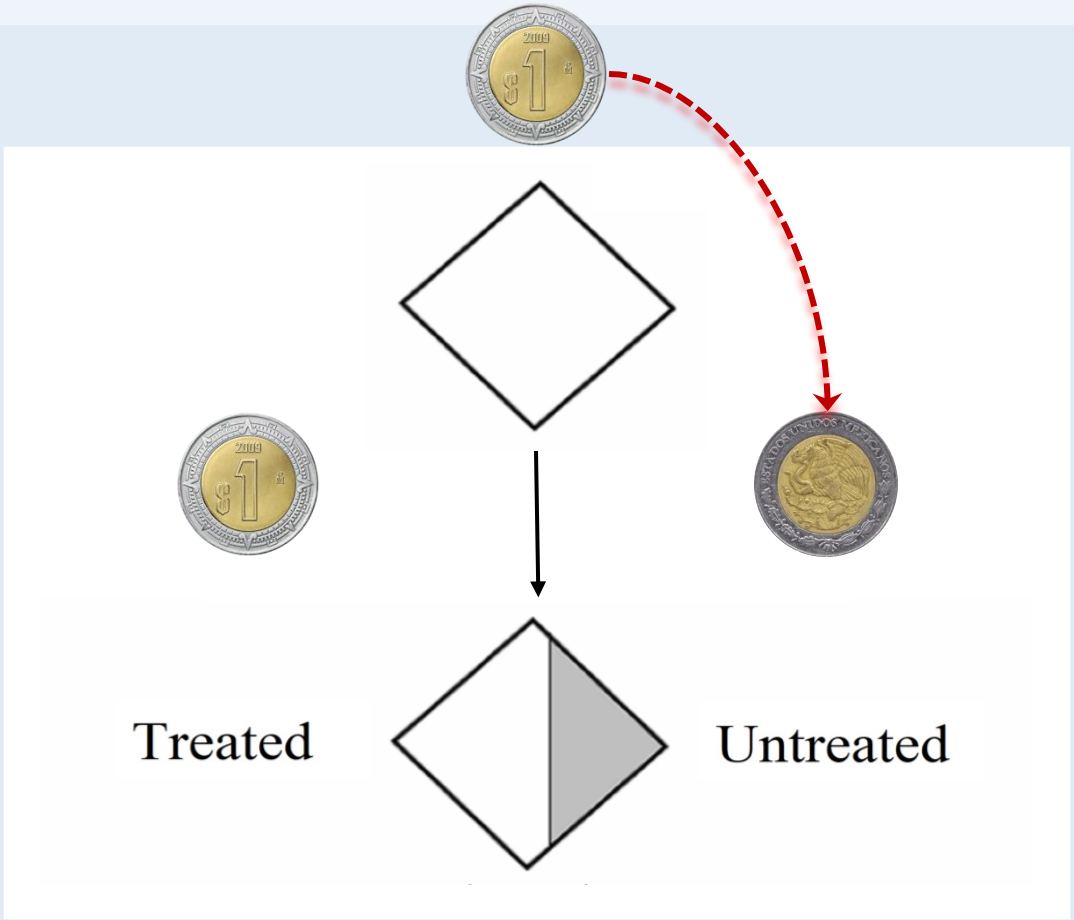
Marginal randomization



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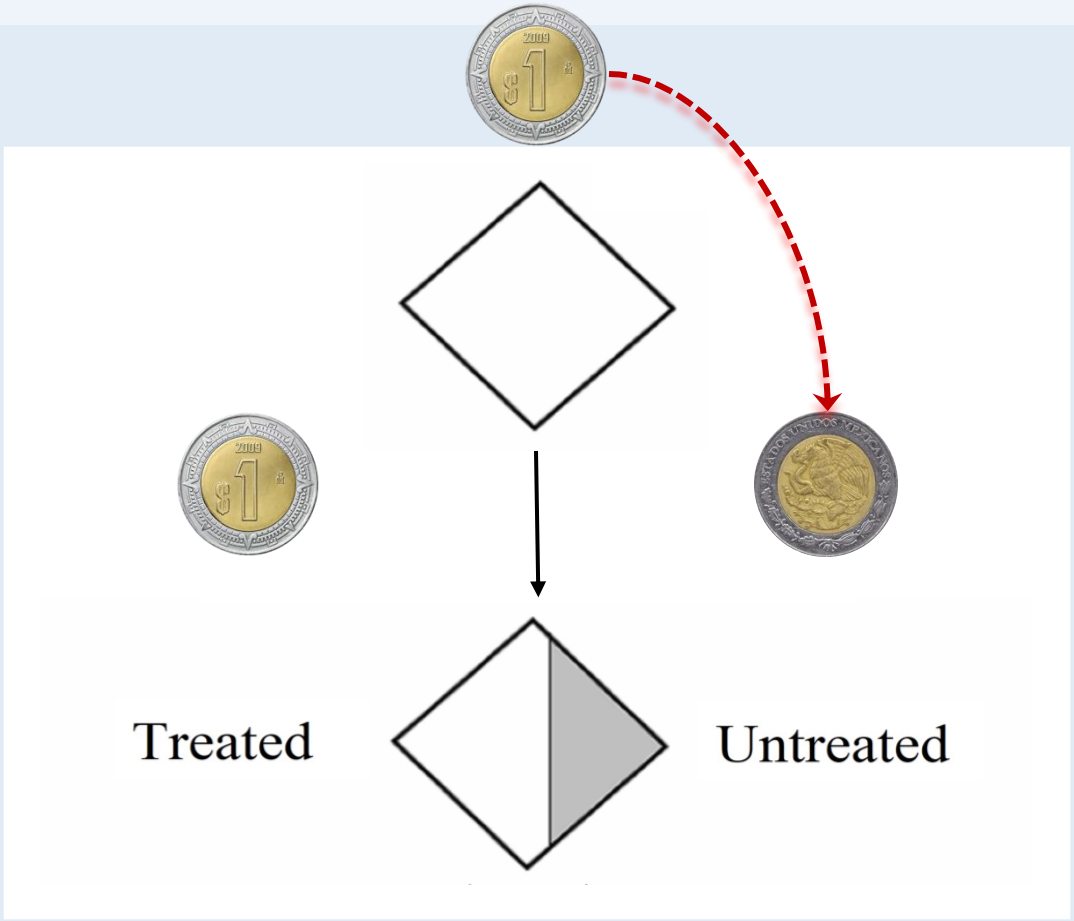
Marginal randomization

Table 2.1

	A	Y	Y^0	Y^1
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
Ares	1	1	?	1
Athena	1	1	?	1
Hephaestus	1	1	?	1
Aphrodite	1	1	?	1
Polyphemus	1	1	?	1
Persephone	1	1	?	1
Hermes	1	0	?	0
Hebe	1	0	?	0
Dionysus	1	0	?	0



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What is marginal exchangeability?

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Table 2.1

	A	Y	Y^0	Y^1
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
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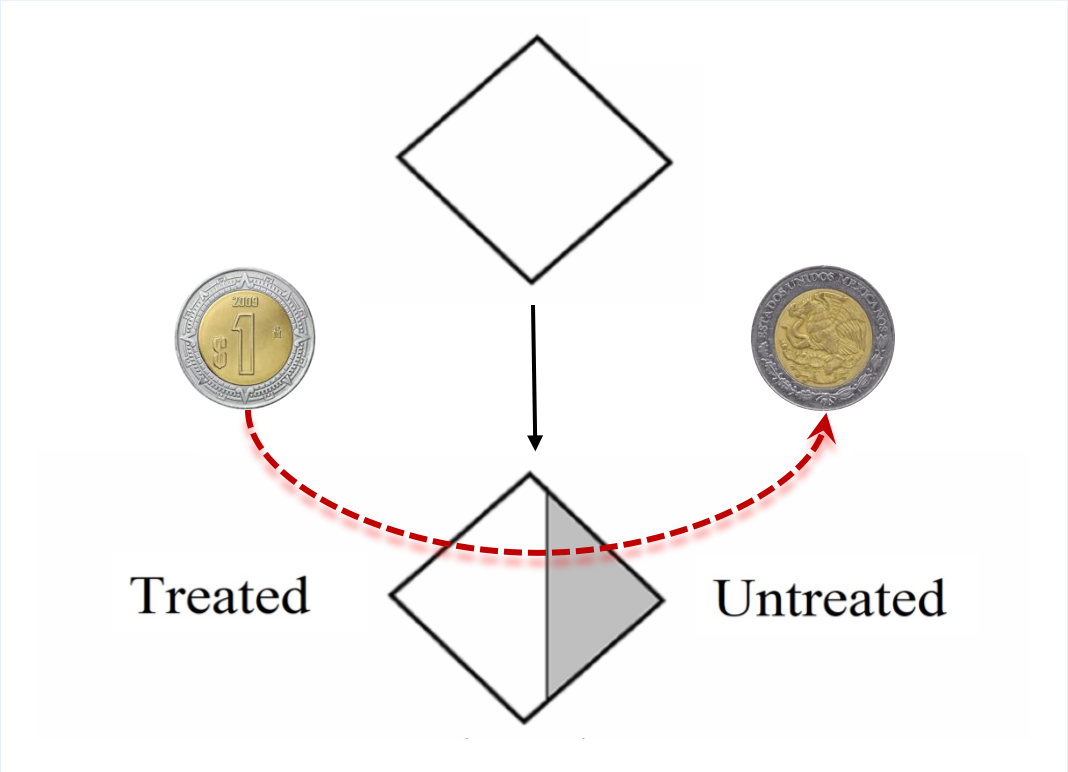
Dionysus	1	0	?	0



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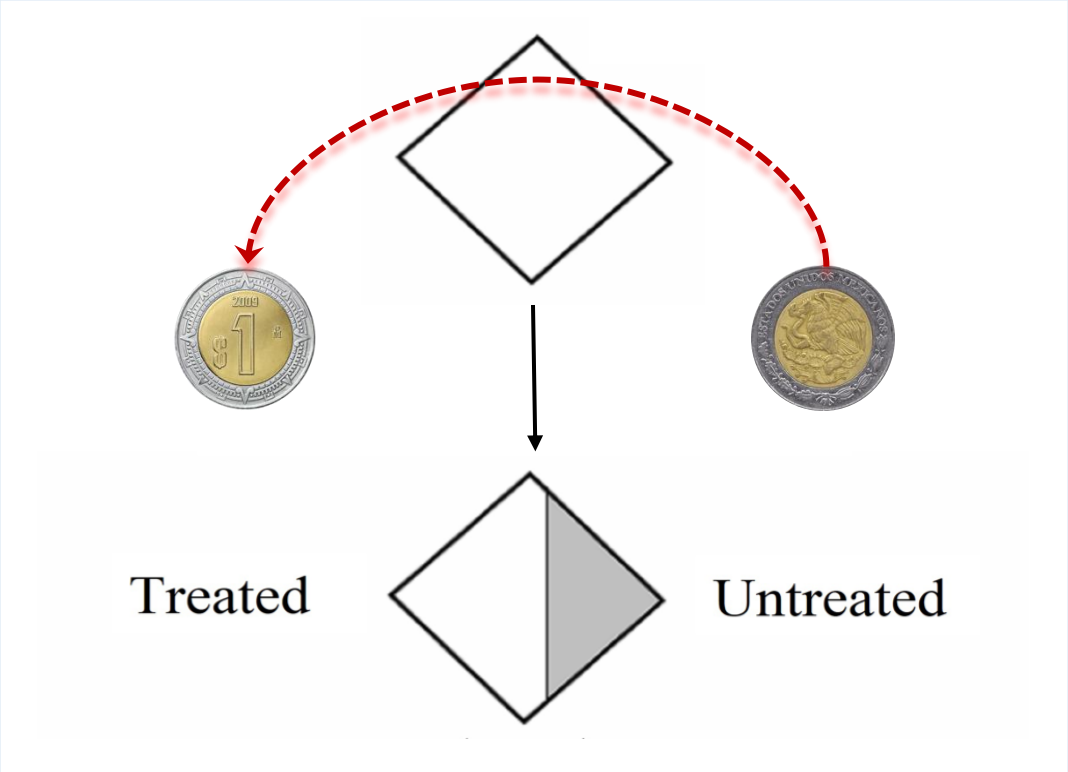
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
Ares	1	1	?	1
Athena	1	1	?	1
Hephaestus	1	1	?	1
Aphrodite	1	1	?	1
Polyphemus	1	1	?	1
Persephone	1	1	?	1
Hermes	1	0	?	0
Hebe	1	0	?	0
Dionysus	1	0	?	0

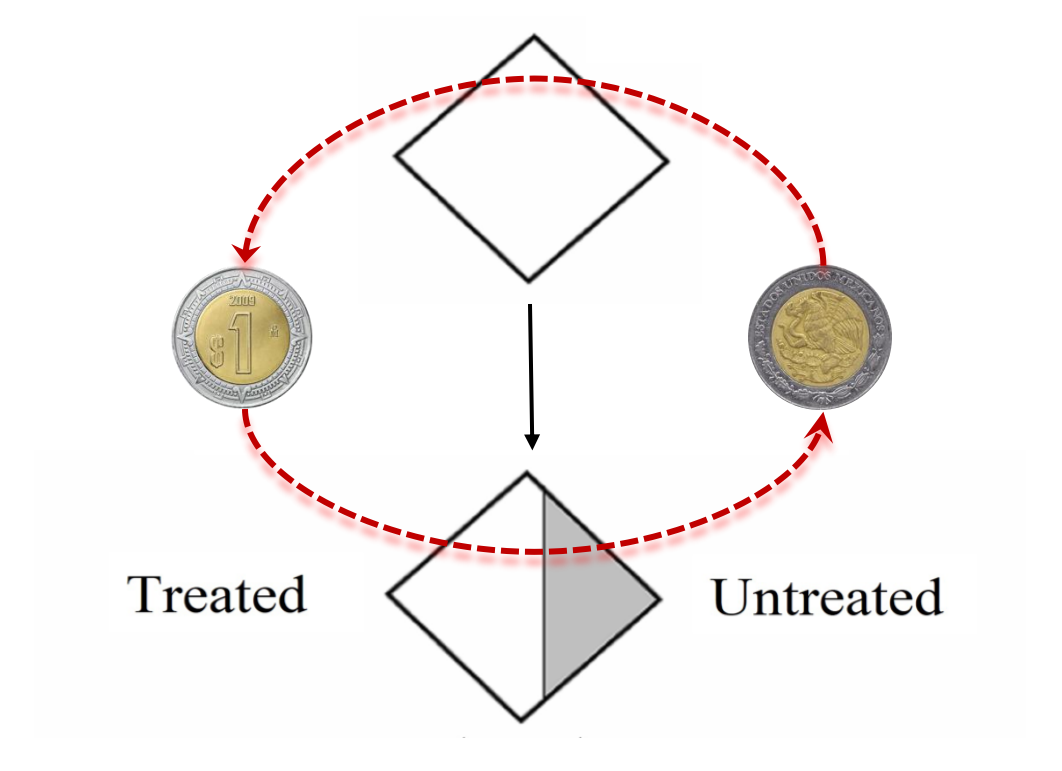


Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Marginal exchangeability

Table 2.1

	A	Y	Y^0	Y^1
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
Ares	1	1	?	1
Athena	1	1	?	1
Hephaestus	1	1	?	1
Aphrodite	1	1	?	1
Polyphemus	1	1	?	1
Persephone	1	1	?	1
Hermes	1	0	?	0
Hebe	1	0	?	0
Dionysus	1	0	?	0



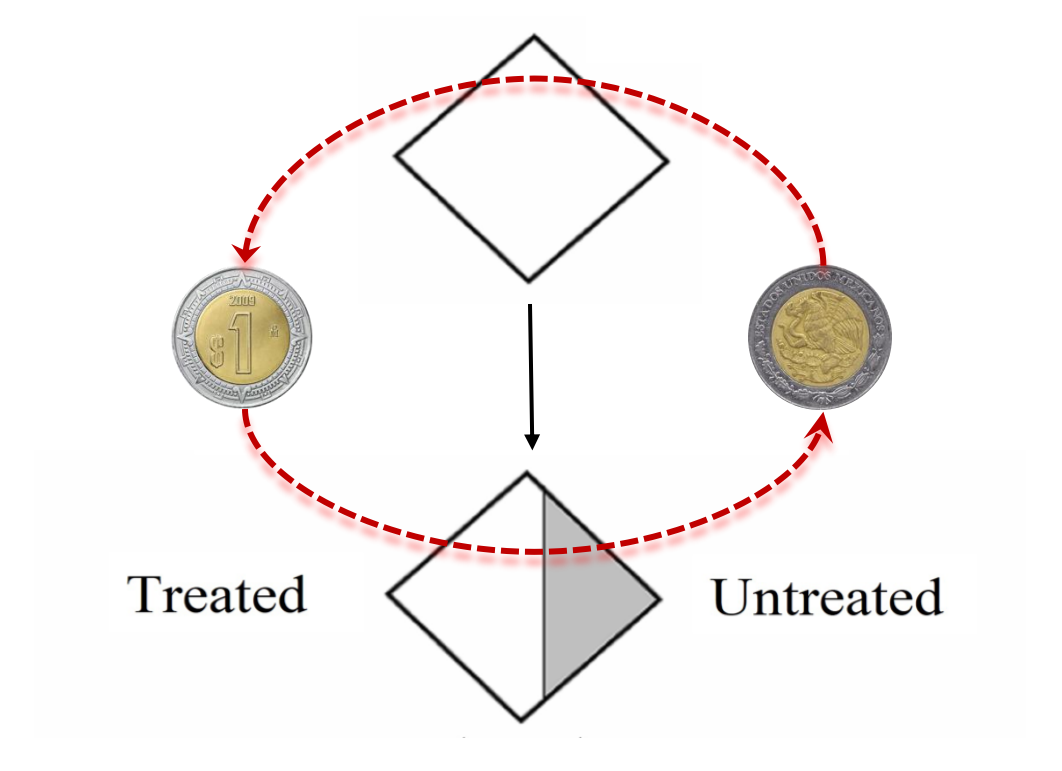
Exchangeability:
$Y^a \perp\!\!\!\perp A$ for all a.

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Marginal exchangeability

Table 2.1

	A	Y	Y^0	Y^1
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
Ares	1	1	?	1
Athena	1	1	?	1
Hephaestus	1	1	?	1
Aphrodite	1	1	?	1
Polyphemus	1	1	?	1
Persephone	1	1	?	1
Hermes	1	0	?	0
Hebe	1	0	?	0
Dionysus	1	0	?	0

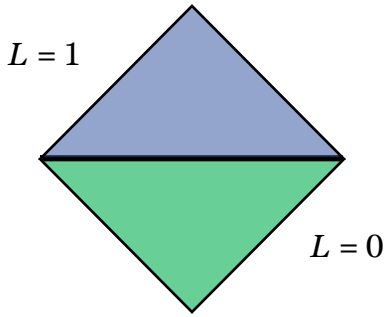


"In an ideal randomized experiment: association is causation"

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

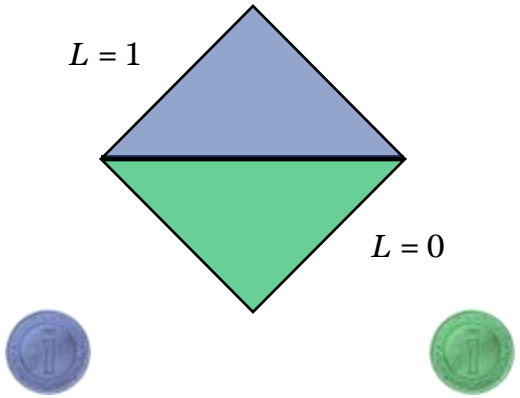
What is conditional randomization?

What is conditional randomization?



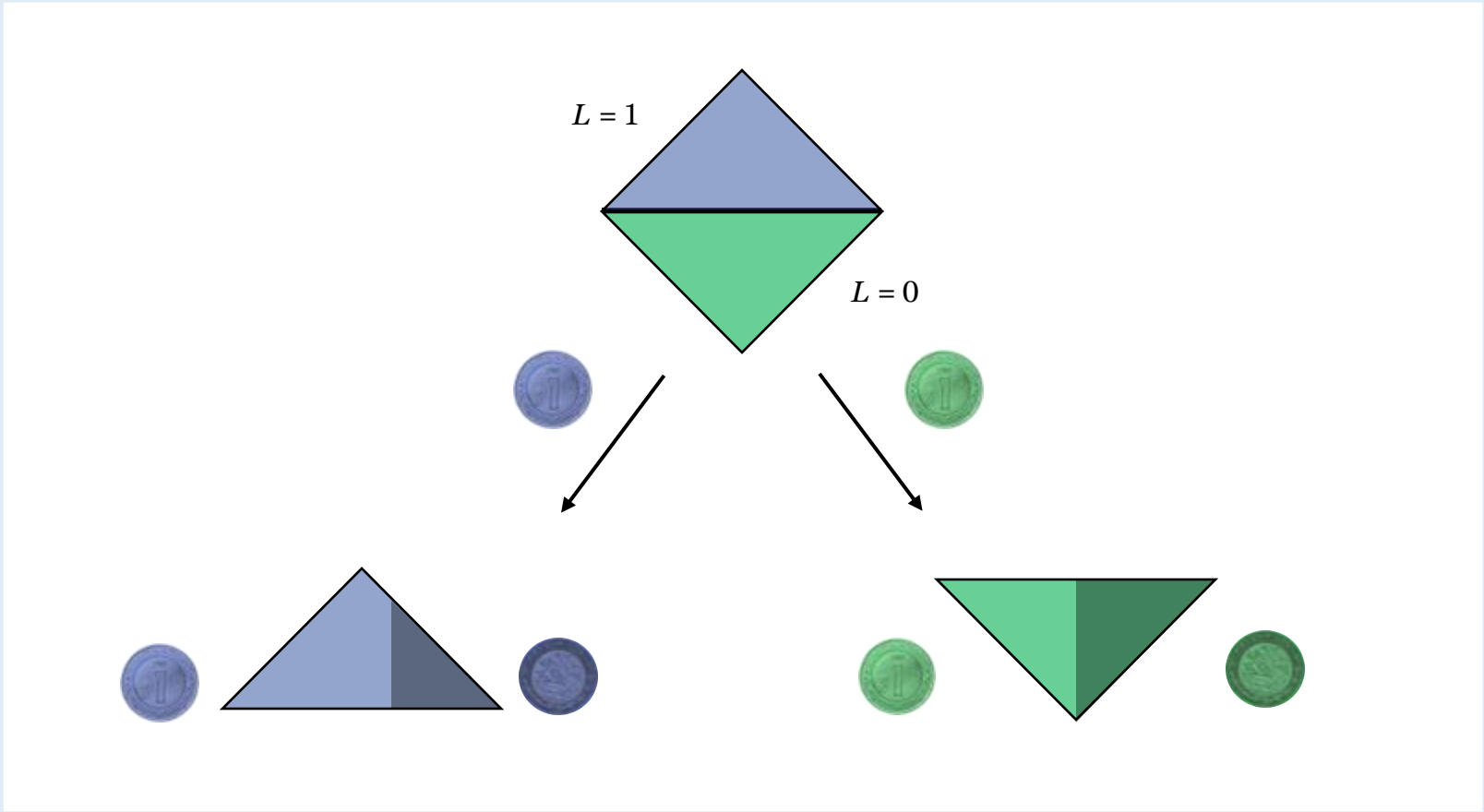
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

What is conditional randomization?



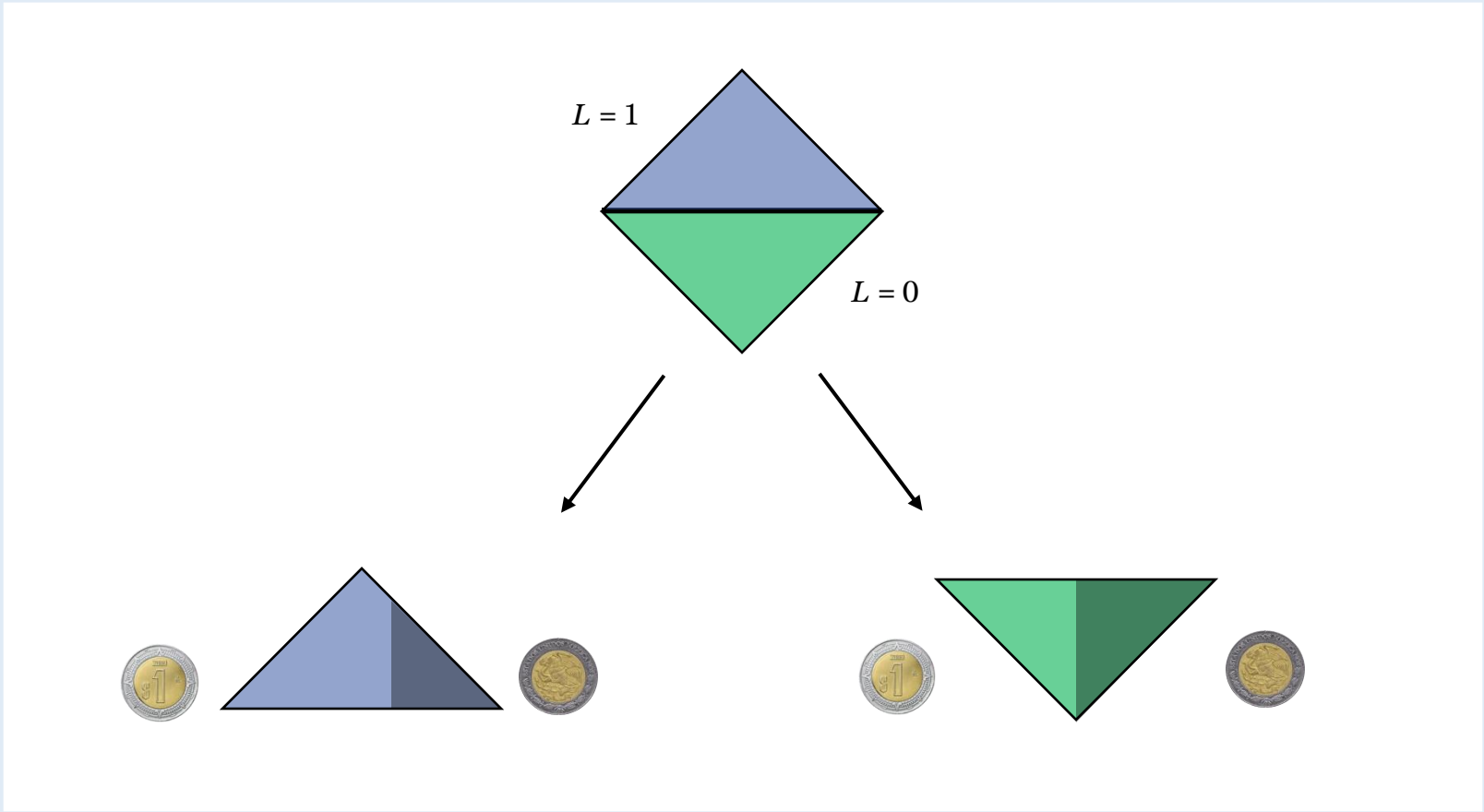
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

What is conditional randomization?



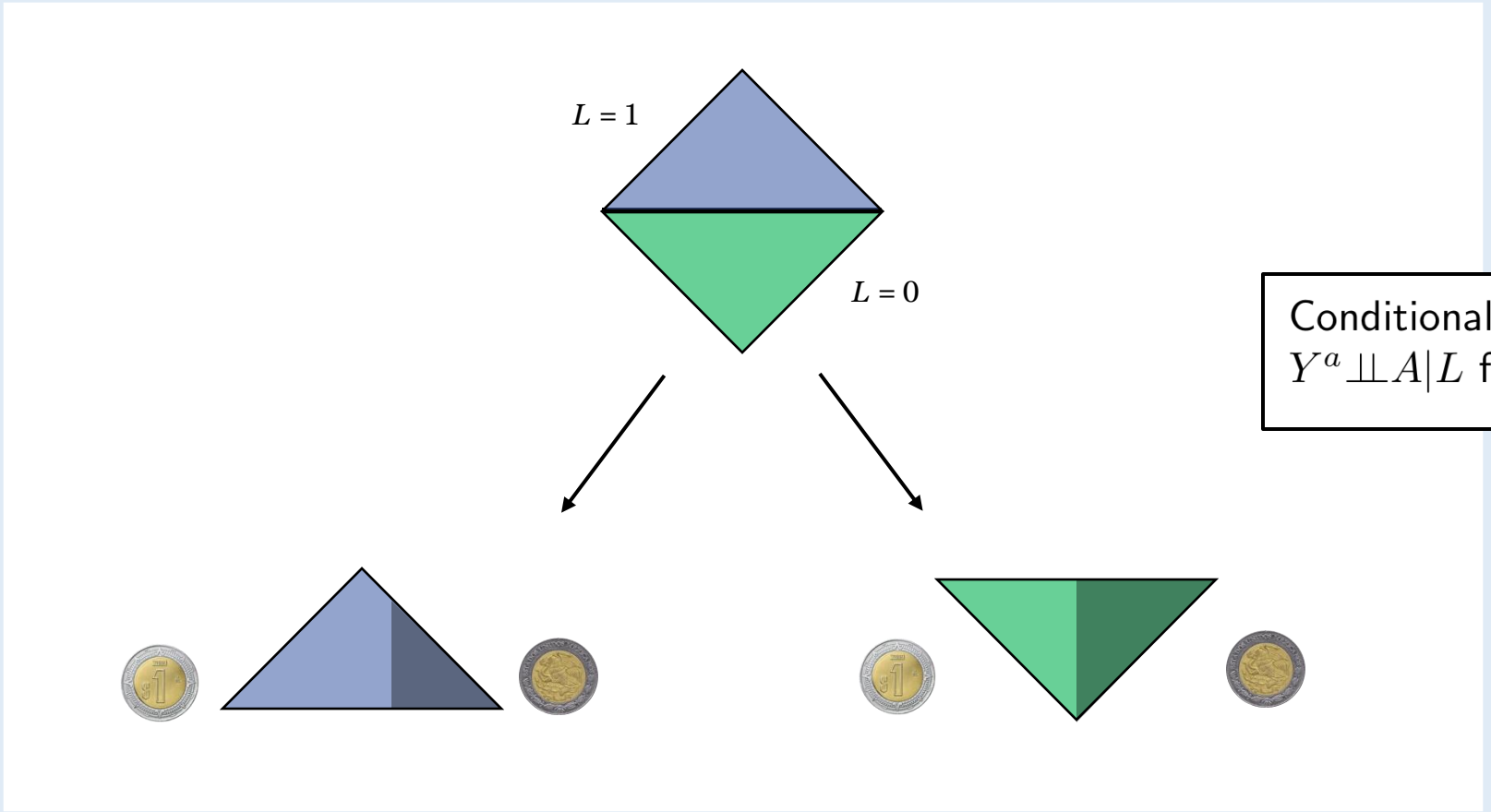
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

What is conditional exchangeability?



Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Conditional exchangeability



Conditional exchangeability:
$Y^a \perp\!\!\!\perp A | L$ for all a

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Fully randomized causally interpreted structured tree graphs (FRCISTG)

Table 2.2

	L	A	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	0
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Polyphemus	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Conditional exchangeability:
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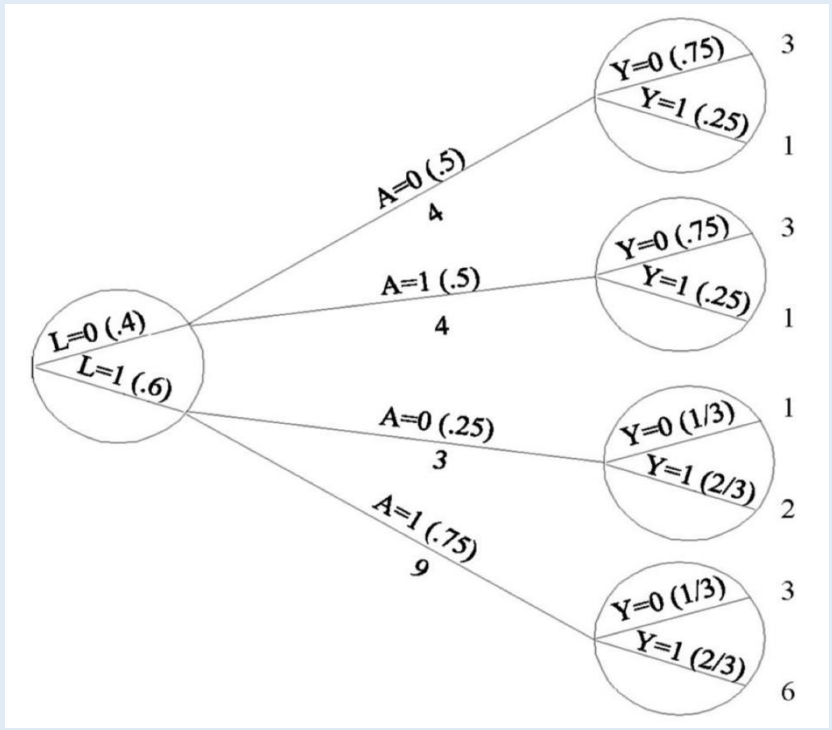
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Polyphemus	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Conditional exchangeability:
$Y^a \perp\!\!\!\perp A|L$ for all a



Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Fully randomized causally interpreted structured tree graphs (FRCISTG)

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	L	A	Y
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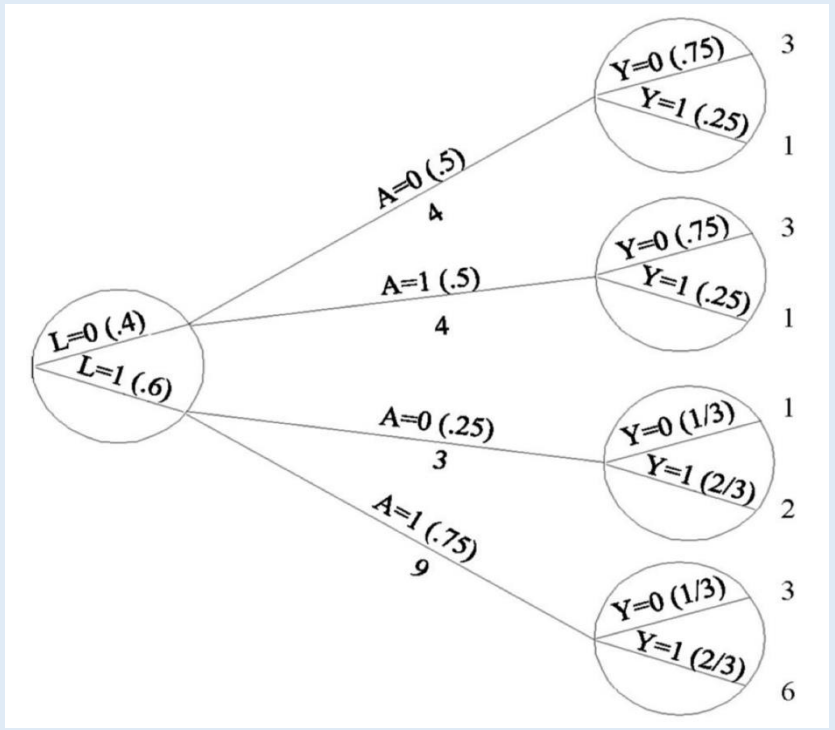
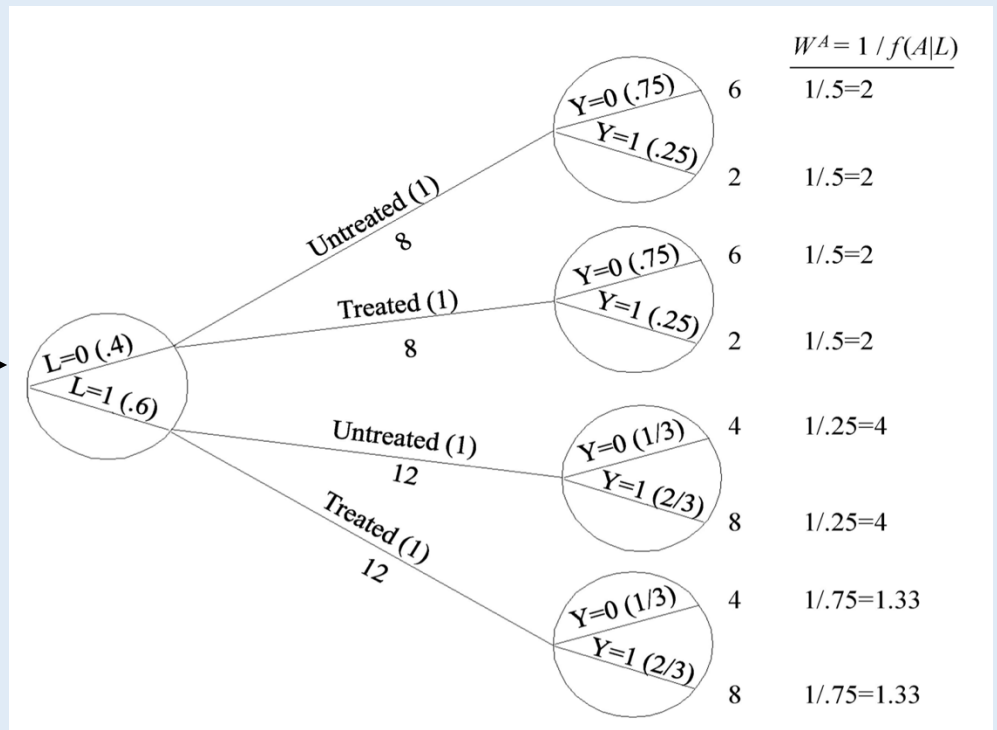
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Polyphemus	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Conditional exchangeability:
$Y^a \perp\!\!\!\perp A|L$ for all a





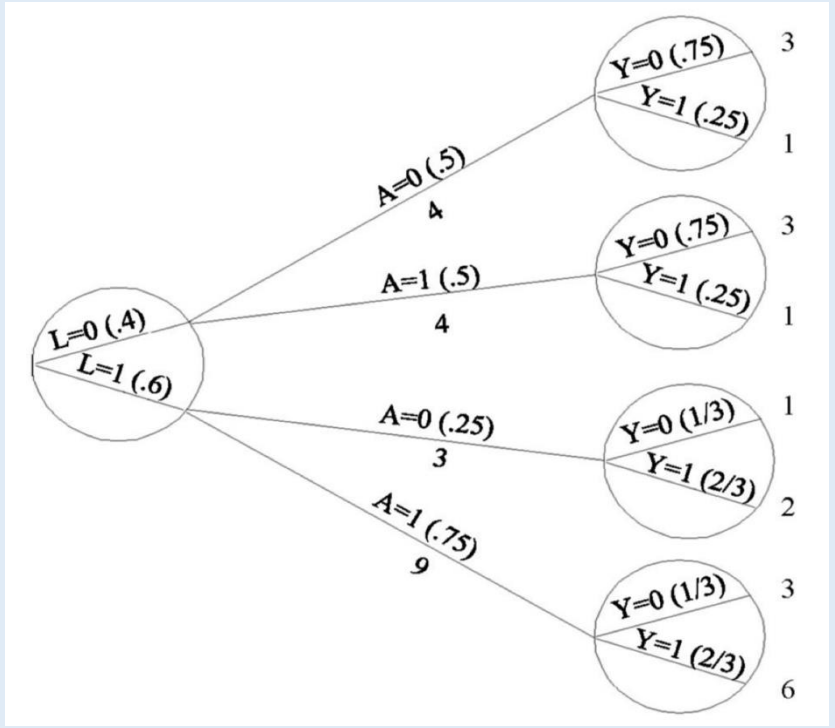
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

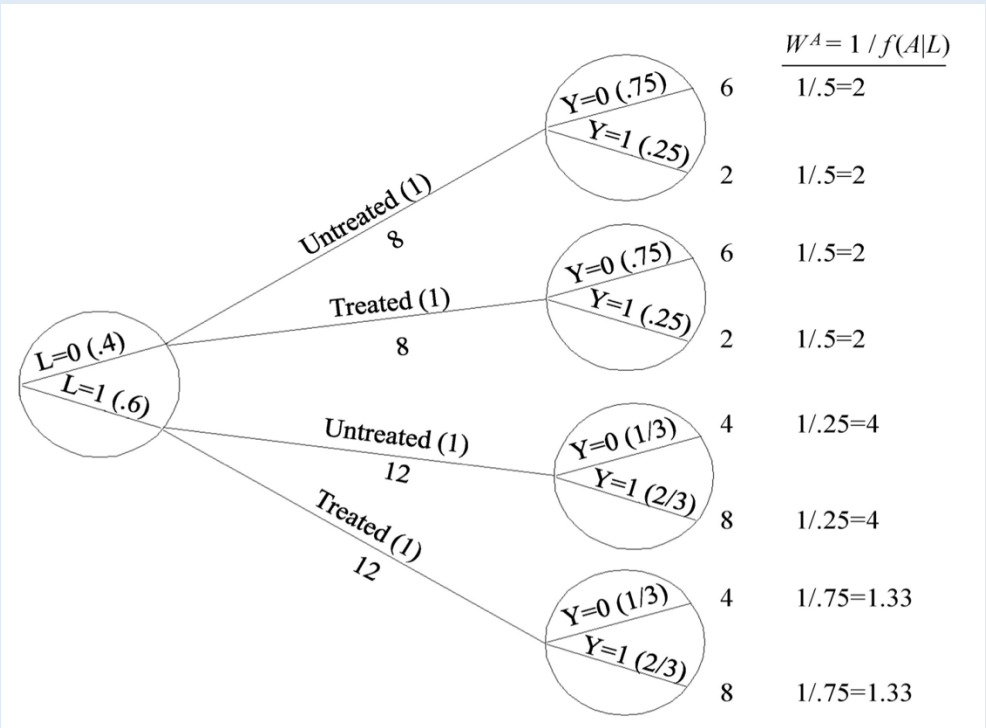
Positivity

Table 2.2

	L	A	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	0
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Polyphemus	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Positivity: $\Pr[A = a|L = l] > 0$ for all values l with $\Pr[L = l] \neq 0$ in the population of interest.





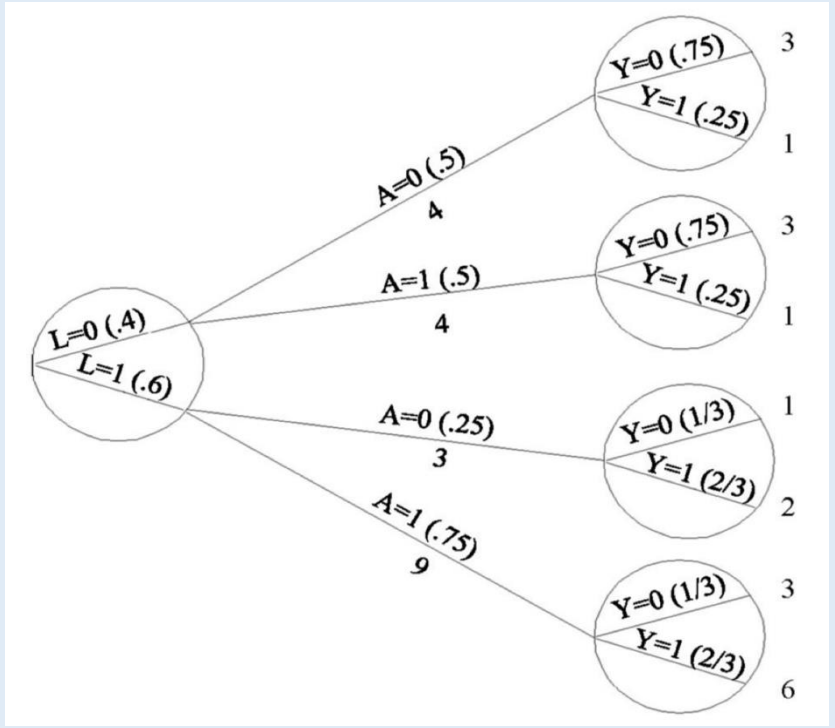
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

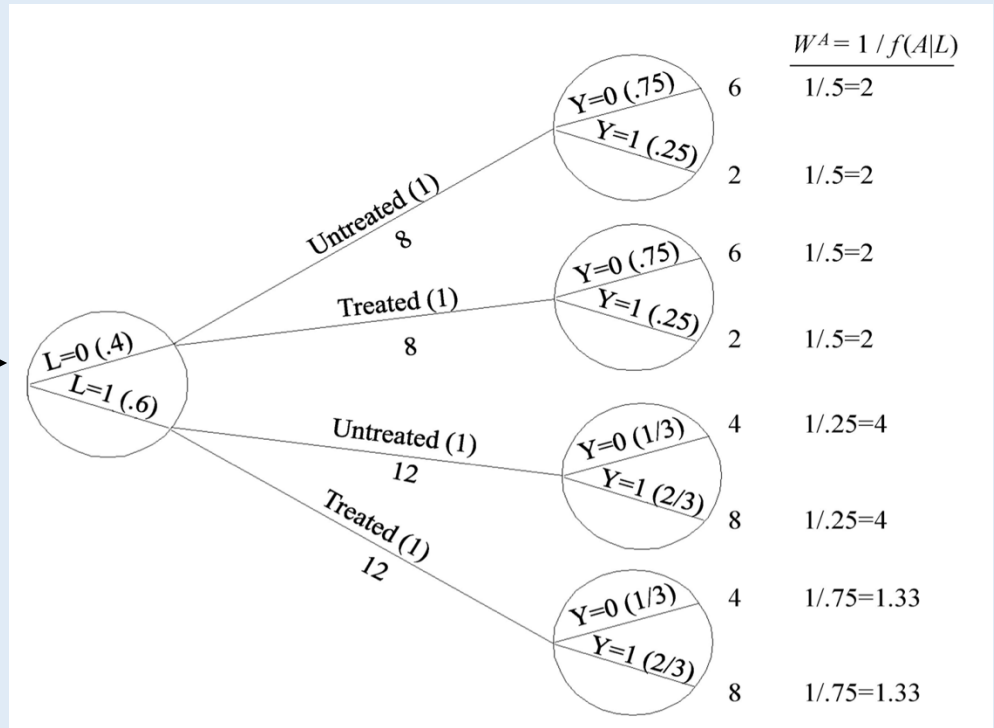
Consistency

Table 2.2

	L	A	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	0
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Polyphemus	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Consistency:
if $A_i = a$, then $Y_i^a = Y_i^A = Y_i$





Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

NO measurement error, missing data bias, or model misspecification

Table 2.2

	L	A	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	0
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Hermes	1	1	0
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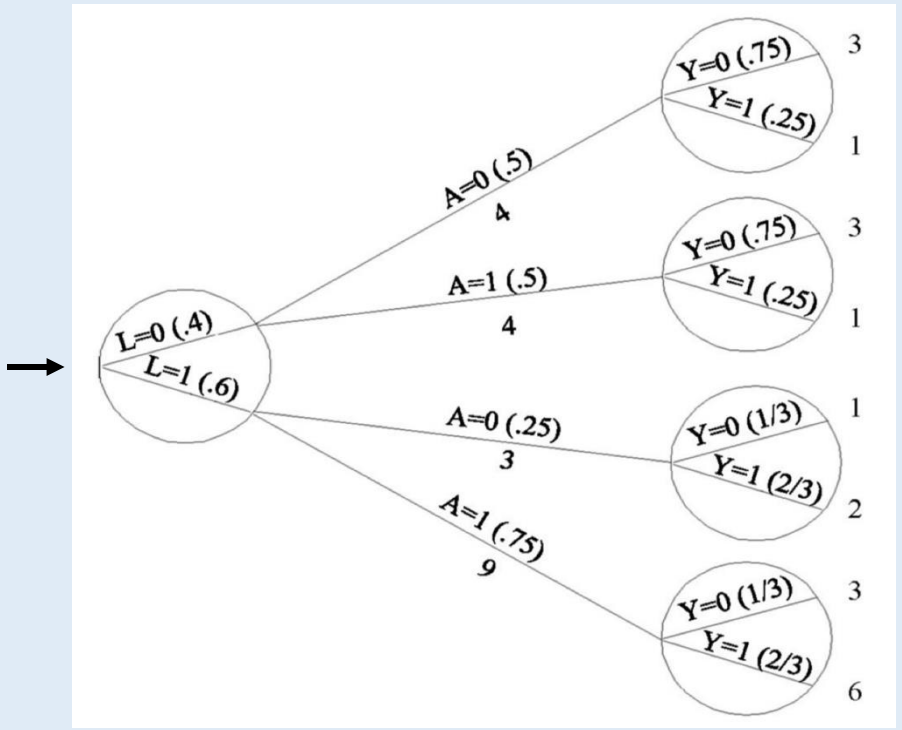
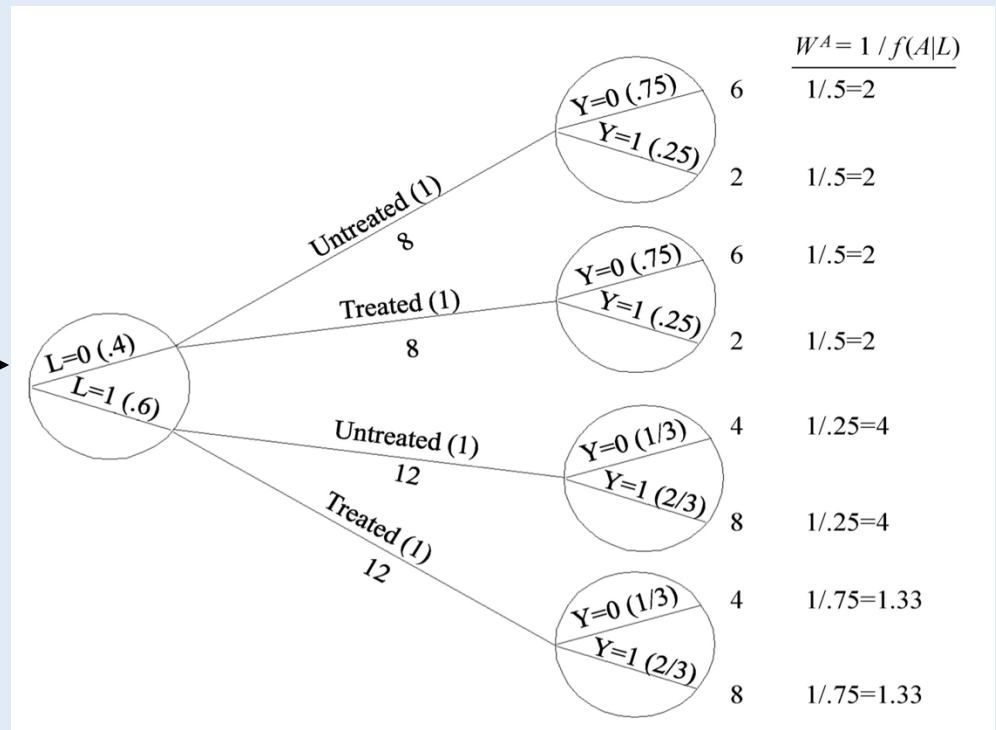




Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

What if an RCT is not possible or not enough?

- It is often not possible (or not enough) to conduct randomized trials:
  - **Ethical** reasons (e.g., when studying adverse effects)
  - **Feasibility** constraints (e.g., time or cost limitations)
  - **Contextual reasons** (e.g., when the exposure cannot be manipulated or outcomes require long-term follow-up, or we want to generalize)

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

What should we do?

Geldsetzer P, Fawzi W. J Clin Epidemiol. 2017;89:12-16. doi:10.1016/j.jclinepi.2017.03.015

Observational studies (several options available)

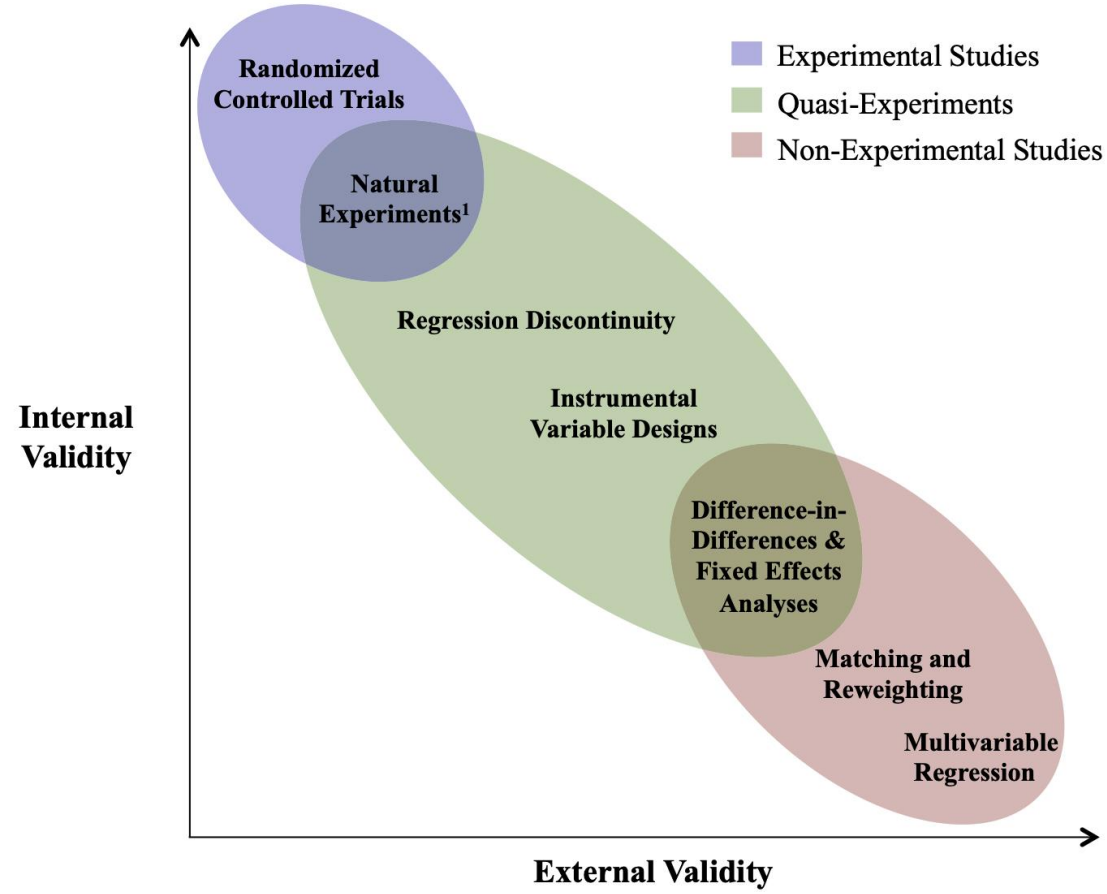


Fig. 1. A stylized view of the trade-off between internal and external validity by study design. [1]Natural experiments are sometimes also referred to as randomized policy experiments. The figure aims to show a general tendency across study designs rather than a definitive categorization.

Geldsetzer P, Fawzi W. J Clin Epidemiol. 2017;89:12-16. doi:10.1016/j.jclinepi.2017.03.015

4. Brief overview of **real-world data** and **real-world evidence**

What are RWD and RWE?

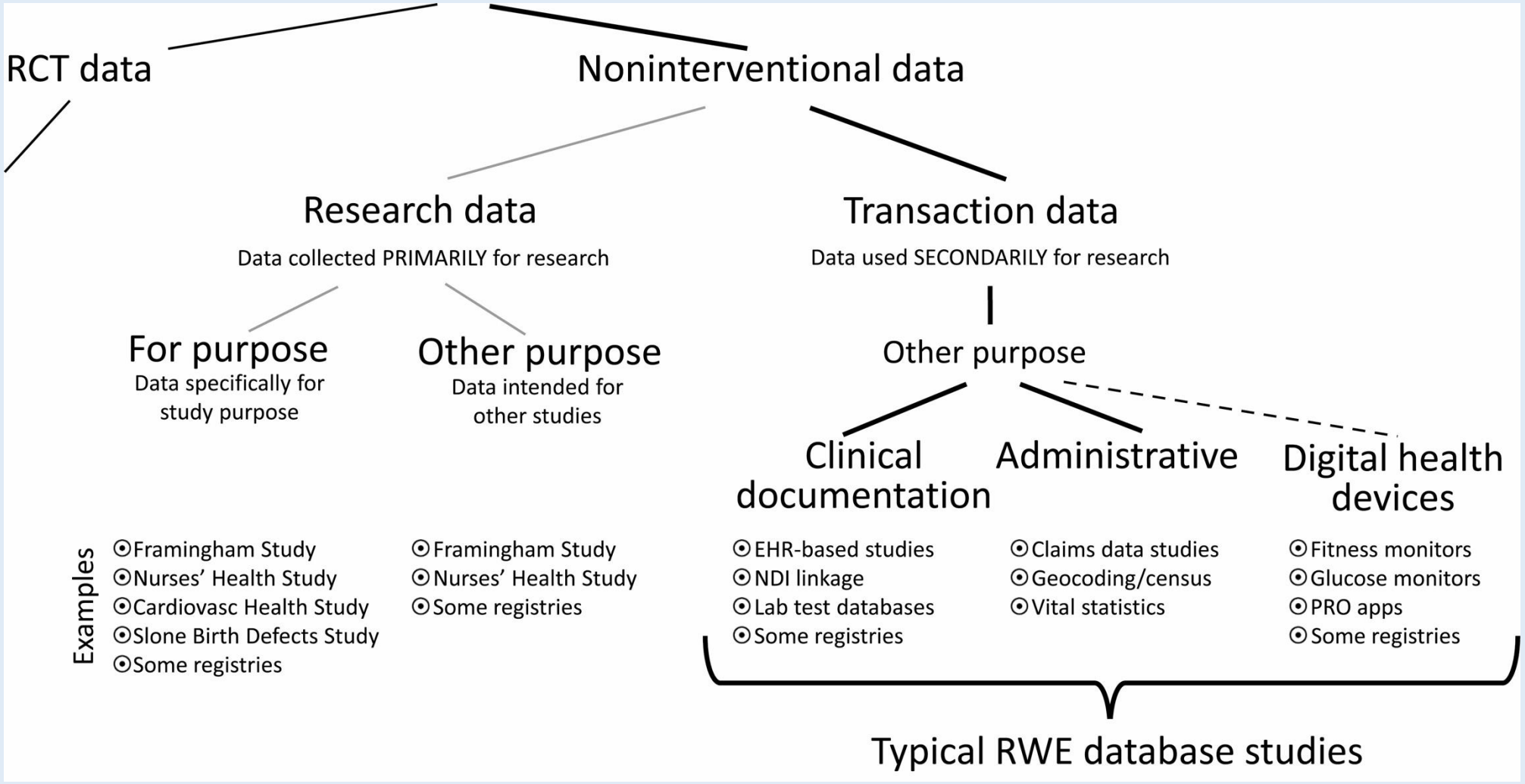
- **RWD:** *"Data relating to **patient health status** and/or the **delivery of health care**, **routinely collected from a variety of sources** [other than traditional clinical trials]."*

- **RWE:** *"Clinical **evidence** [regarding a medical product's use and potential benefits or risks] **derived from the analysis of RWD**."*

FDA/EMA

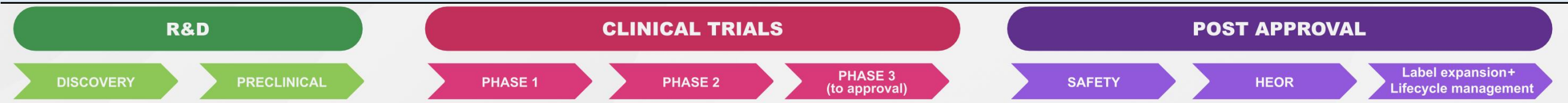
Hernandez RK, et al. Clin Pharmacol Ther. 2025;117(4):927-937. doi:10.1002/cpt.3563

Where do RWD come from?



Schneeweiss S, et al. Endocr Rev. 2021;42(5):658-690. doi:10.1210/endrev/bnab007

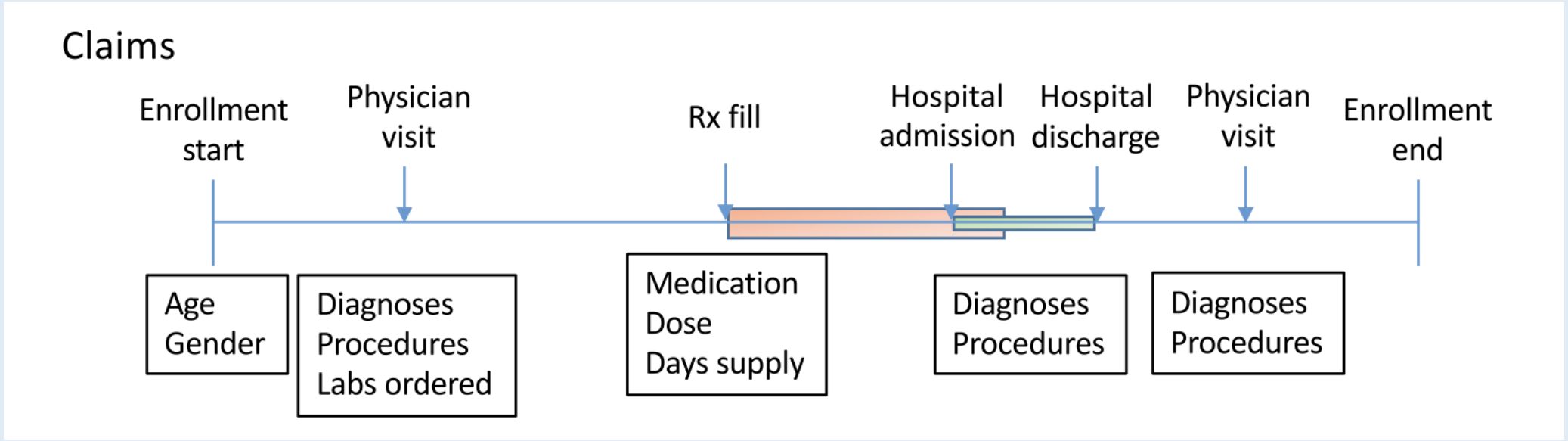
What are RWD and RWE used for?



1. Estimate disease **prevalence** or **incidence**. 2. Understand its **natural history**. 3. Characterize **patterns of medication use**. 4. …	1. **Inform sample size** calculations. 2. **Refine eligibility** criteria. 3. **Understand the standard of care**. 4. …	1. Confirm **efficacy** and **safety** under real-world conditions (generalizability). 2. Evaluate **new outcomes** or **extend follow-up**. 3. **Expand the target population**. 4. **Comparative effectiveness studies**. 5. Perform **economic analyses**. 6. …

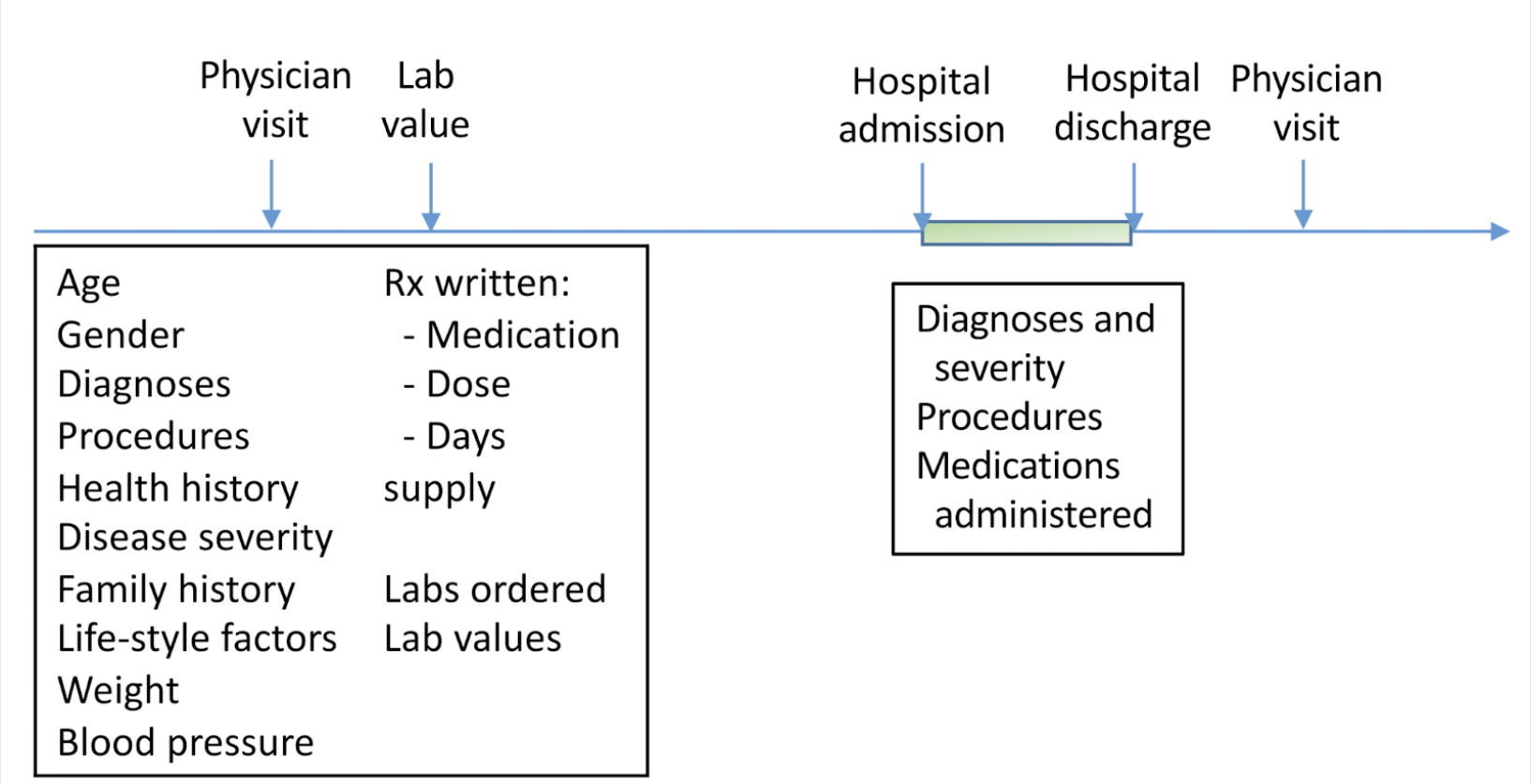
Modified from: Zhu R, et al. Clin Pharmacol Ther. 2023;114(4):751-767. doi:10.1002/cpt.2988

Example using claims



Franklin JM, et al. Clin Pharmacol Ther. 2017;102(6):924-933. doi:10.1002/cpt.857

Example using Electronic Health Records



Franklin JM, et al. Clin Pharmacol Ther. 2017;102(6):924-933. doi:10.1002/cpt.857

5. The **target trial framework**

What is the target trial framework?

- A **structured procedure that operationalizes best practices in the design, analysis, and reporting** of observational studies for causal inference.

- It is **NOT** a **statistical method** or an **estimation procedure.**

Hernán MA, et al. Ann Intern Med. 2025;178(3):402-407. doi:10.7326/ANNALS-24-01871

Why is it useful?

1. By making the components of the TT explicit, it enables researchers to **define the causal estimand without requiring advanced training** in causal inference.

2. It encourages analyses that align with study objectives and **mitigate the impact of design errors**.

Hernán MA, et al. Ann Intern Med. 2025;178(3):402-407. doi:10.7326/ANNALS-24-01871

How does it work?

- For each **causal question**:

    1. We can imagine a **hypothetical randomized trial** (the "target trial").

    2. Then, we can **specify the target trial protocol**.

- A "**2-step algorithm for causal inference**"

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

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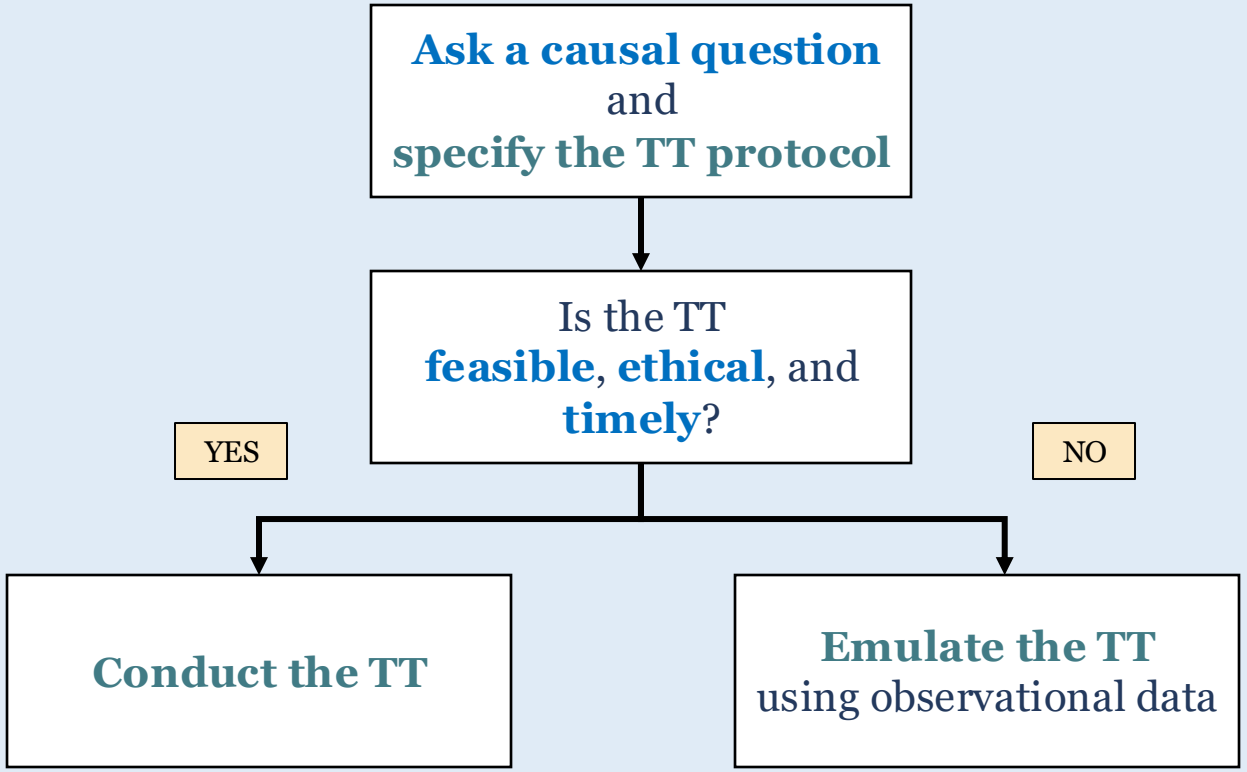


Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Specify the components of the TT

Must correspond to a **pragmatic trial**—a randomized study under real-world conditions (i.e., without additional adherence promotion or monitoring):

- ✓ Allocation is **not blinded**
- ✓ There is **no placebo** (i.e., only active treatments or no treatment)
- ✓ Participants are **followed as** frequently as **regular patients**
- ✓ **Treatment strategies** are those used **in real-world settings**

Components of the TT

Eligibility criteria
Treatment strategies
Treatment assignment
Time zero and follow-up
Outcomes
Causal contrasts
Data analysis

	Specification	Emulation
Causal Estimand	Eligibility criteria	Data mapping for each criterion†
	Treatment strategies	Data mapping for each component
	Assignment (unmasked)	Data mapping for assignment‡
	Outcomes	Data mapping for each outcome
	Start/end of follow-up	Same
	Causal contrasts§	Observational analogues of causal contrasts
Identifying Assumptions*	For effect of assignment (intention-to-treat):	
	Randomized assignment‖	Assumption of conditional exchangeability**
	If applicable, assumption of conditional exchangeability for:	List baseline confounders and describe data mapping for each one
	• Loss to follow-up (list factors)	Data mapping for each factor
	• Competing events (list factors)	Data mapping for each factor
	For per protocol effect:	Data mapping for each confounder
	Assumption of conditional exchangeability (list baseline/time-varying confounders)	
Estimator	For each causal estimand: data analysis, including subgroup analyses, and modeling assumptions	Describe modifications required for emulation, if any,and sensitivity analyses

Hernán MA, et al. Ann Intern Med. 2025;178(3):402-407. doi:10.7326/ANNALS-24-01871

Example

What is the effect of **Covid-19 vaccination** (full-series) vs. no vaccination, on **SARS-CoV-2 infection** in a **cohort of workers** from **Mexico (Dec 24, 2020, to May 31, 2021)**?

Components	TT Specification	TT Emulation
Eligibility criteria	• Age 18+ • No history (or contraindications) of vaccination; • No history of SARS-CoV-2; • No Covid-19-like symptoms (one week); • No known pregnancy or immunodeficiency; • Recent health care user	—

Components	TT Specification	TT Emulation
Eligibility criteria	• Age 18+ • No history (or contraindications) of vaccination; • No history of SARS-CoV-2; • No Covid-19-like symptoms (one week); • No known pregnancy or immunodeficiency; • Recent health care user	

Components	TT Specification	TT Emulation
Eligibility criteria	• Age 18+ • No history (or contraindications) of vaccination; • No history of SARS-CoV-2; • No Covid-19-like symptoms (one week); • No known pregnancy or immunodeficiency; • Recent health care user	
Treatment strategies	1) No immediate vaccination. 2) Immediate vaccination (BNT162b2).	

Components	TT Specification	TT Emulation
Eligibility criteria	• Age 18+ • No history (or contraindications) of vaccination; • No history of SARS-CoV-2; • No Covid-19-like symptoms (one week); • No known pregnancy or immunodeficiency; • Recent health care user	
Treatment strategies	1) No immediate vaccination. 2) Immediate vaccination (BNT162b2).	Same

Components	TT Specification	TT Emulation
Eligibility criteria	• Age 18+ • No history (or contraindications) of vaccination; • No history of SARS-CoV-2; • No Covid-19-like symptoms (one week); • No known pregnancy or immunodeficiency; • Recent health care user	
Treatment strategies	1) No immediate vaccination. 2) Immediate vaccination (BNT162b2).	Same
Treatment assignment	Conditional randomization (December 24, 2020, to June 24, 2021).	

Components	TT Specification	TT Emulation
Eligibility criteria	• Age 18+ • No history (or contraindications) of vaccination; • No history of SARS-CoV-2; • No Covid-19-like symptoms (one week); • No known pregnancy or immunodeficiency; • Recent health care user	
Treatment strategies	1) No immediate vaccination. 2) Immediate vaccination (BNT162b2).	Same
Treatment assignment	Conditional randomization (December 24, 2020, to June 24, 2021).	Assume conditional randomization based on confounders (e.g., age, sex, etc.)

Emulating treatment assignment

- Conditional randomized assignment is equivalent to confounding adjustment.
- We can achieve this using:
  - **G-methods**: standardization, IPW, and g-estimation
  - **Stratification-based methods**: stratification, matching, outcome regression
- If information on any relevant confounder (as specified in the protocol) is missing, random assignment cannot be emulated.

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Components	TT Specification	TT Emulation
Time zero and follow-up	From treatment assignment until: • Outcome of interest • Death • Loss to follow-up • End of follow-up	

Components	TT Specification	TT Emulation
Time zero and follow-up	From treatment assignment until: • Outcome of interest • Death • Loss to follow-up • End of follow-up	Same

Emulating time zero and follow-up

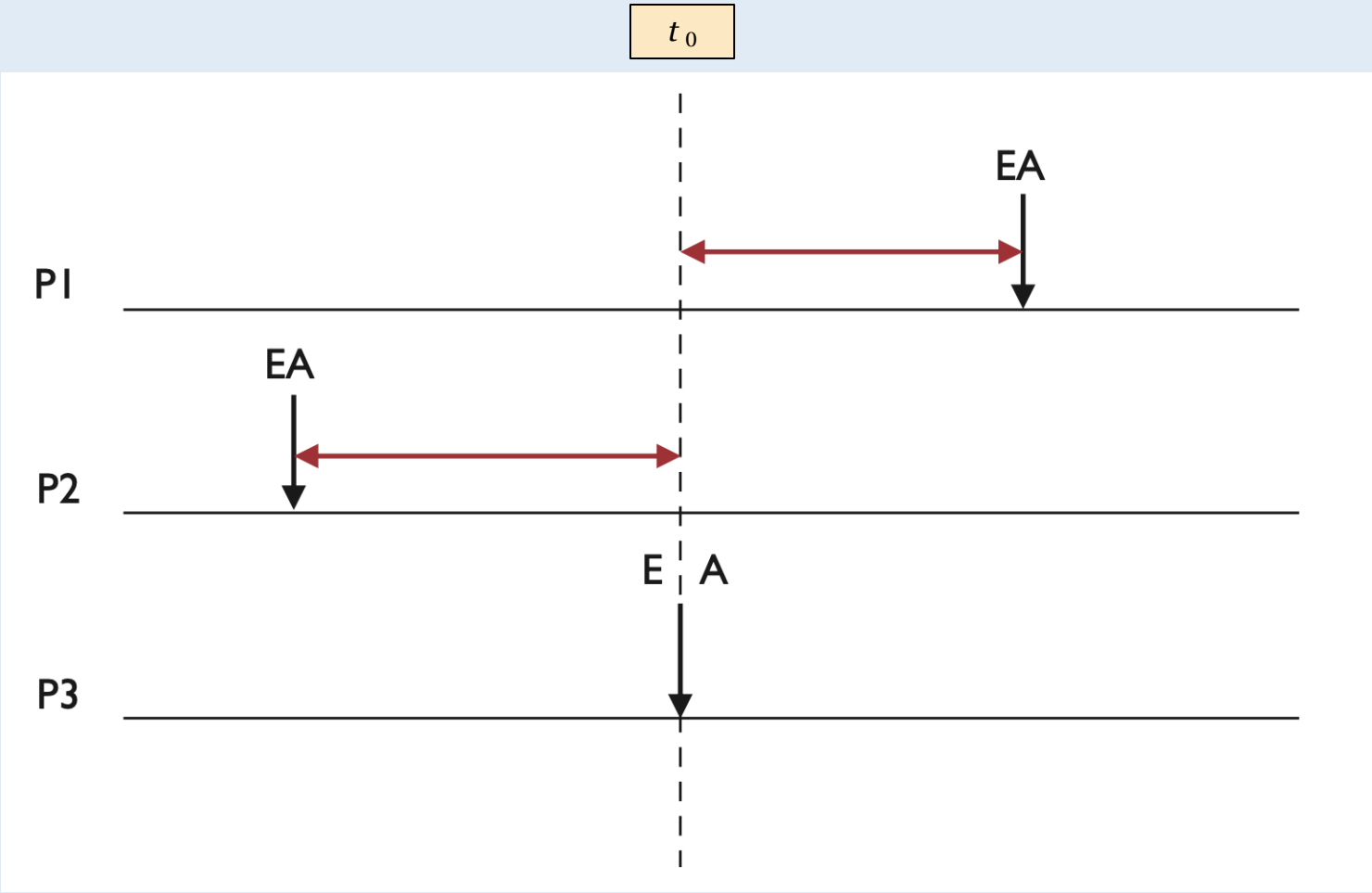
- **Time zero** (baseline) is defined by the occurrence of three events:

    1. Meeting eligibility criteria.
    2. Treatment assignment.
    3. Start of outcome assessment.

- **Misalignment** between these components can lead to **time-related bias**.

Hernán MA, et al. J Clin Epidemiol. 2016;79:70-75. doi:10.1016/j.jclinepi.2016.04.014

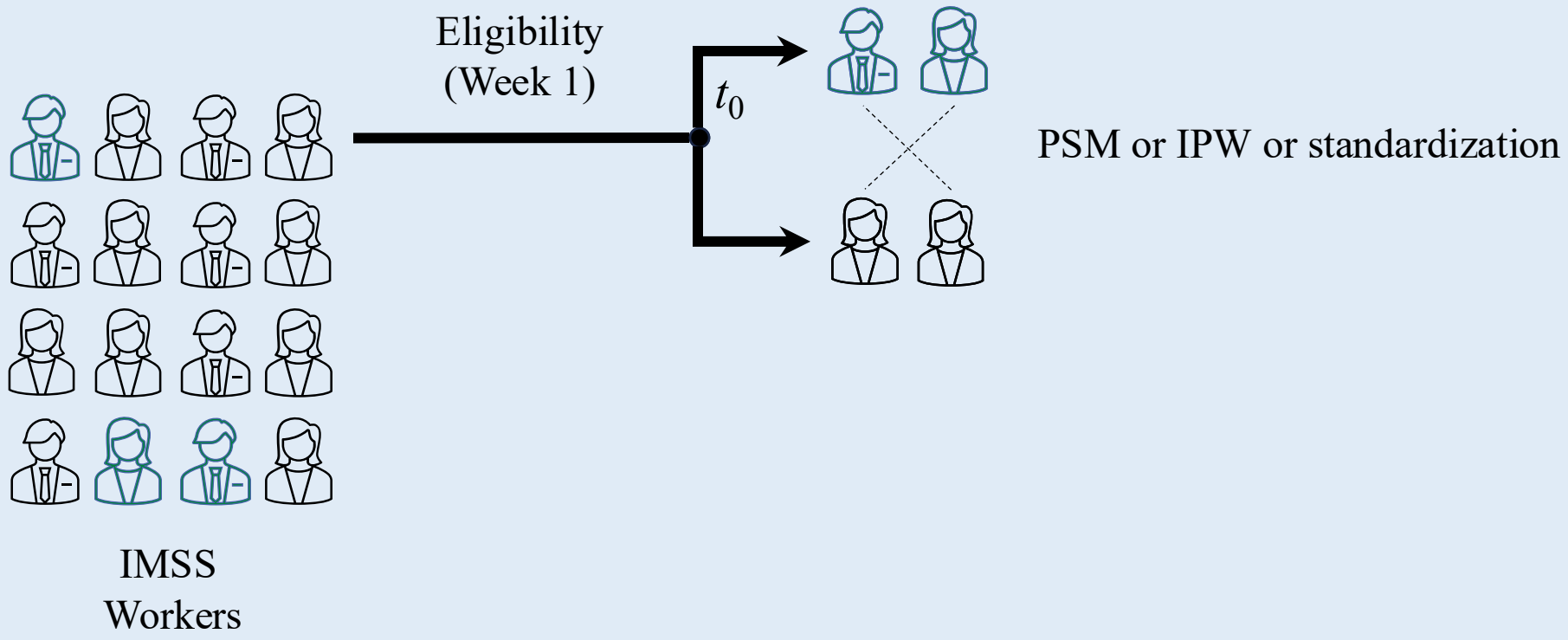
Time-related bias

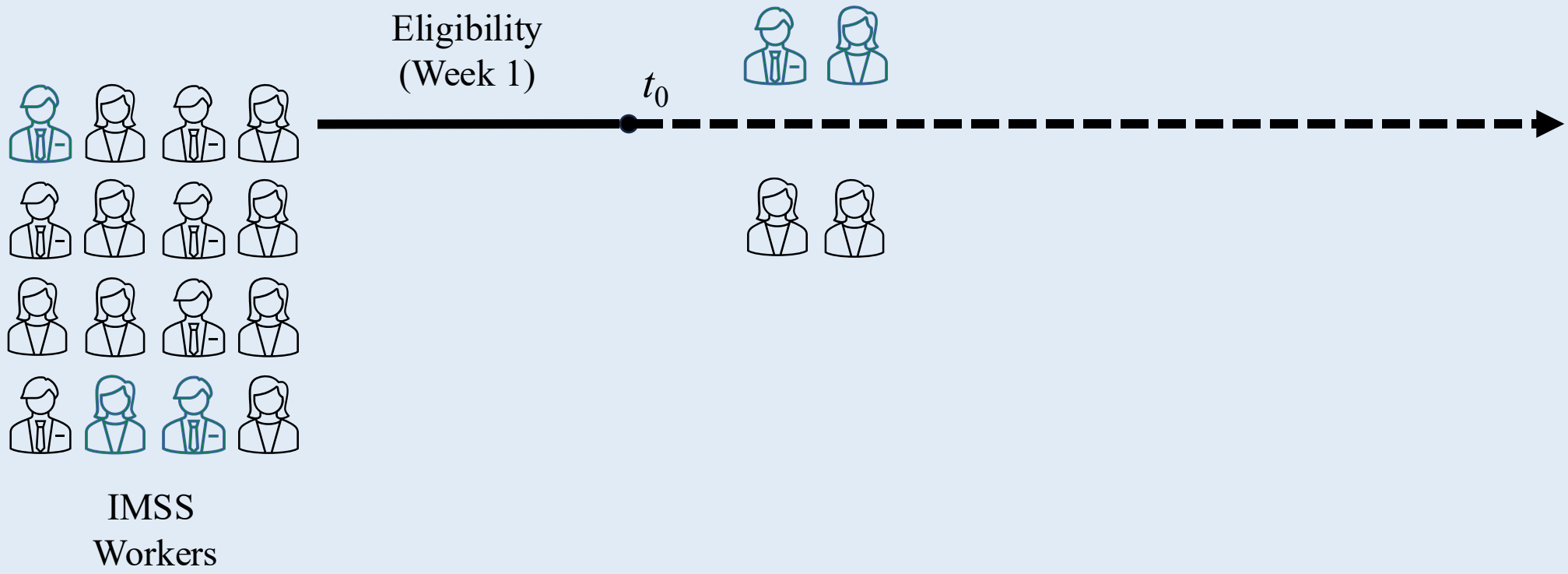


Núñez I, Lajous M. Salud Publica Mex. 2024;67(1):83-90. doi:10.21149/16056

What if eligibility is met more than once?

- Aligning eligibility and treatment assignment can be difficult when the eligibility criteria can be met at multiple points in time
- Two potential solutions:
  - Select **one eligible time at random**.
  - Use **all eligible times** (greater statistical efficiency):
    - ✓ Sequence of TTs—each with a different t_0—estimate the effects within each, and pool the results.
    - ✓ Each trial applies the same eligibility criteria and follow-up protocol.
    - ✓ Participants may be included in more than one trial and treatment strategy.


Eligibility
(Week 1)
t_0
PSM or IPW or standardization
IMSS
Workers
Vaccinated
Unvaccinated

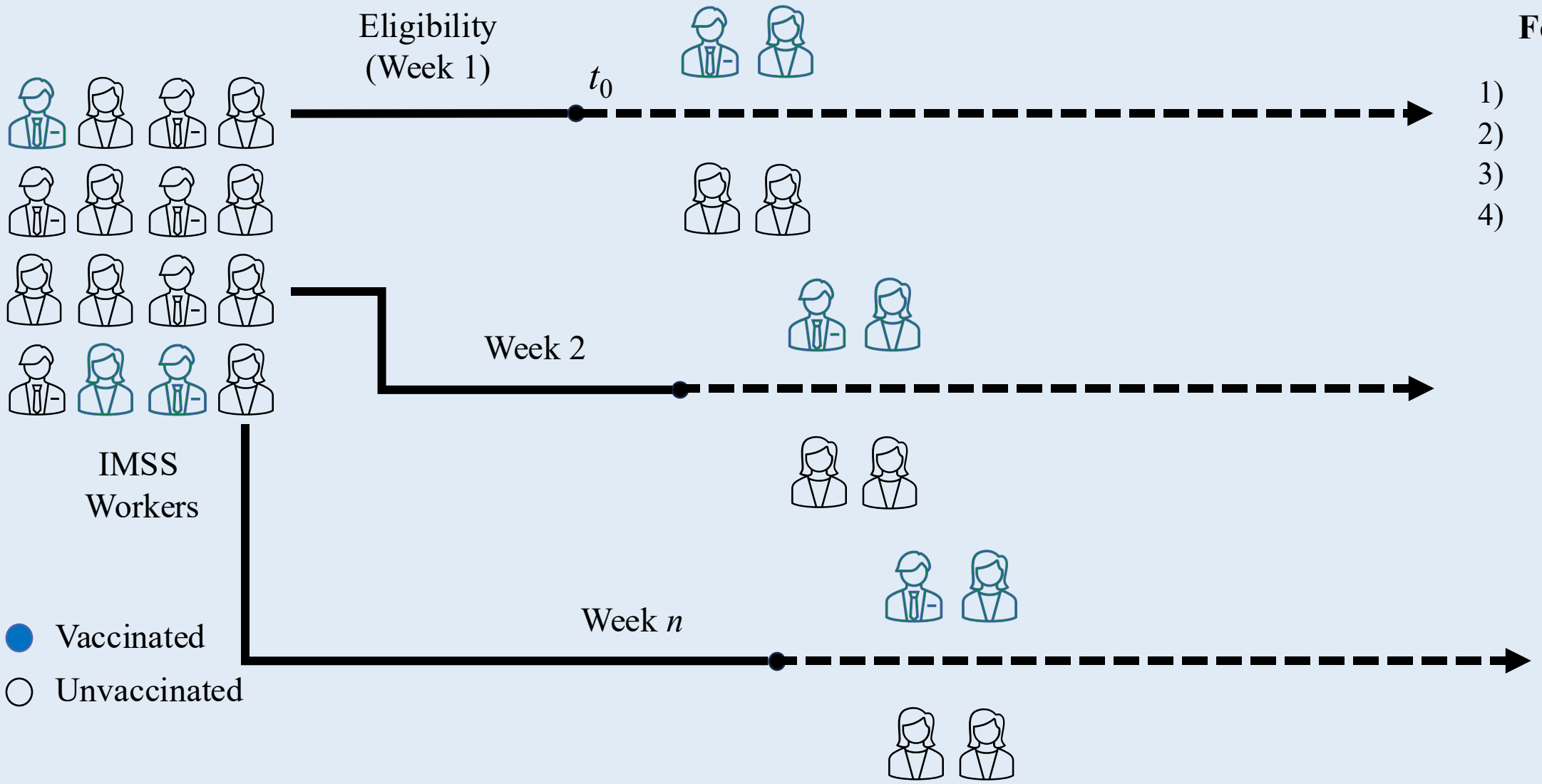


Follow-up until:

1) Outcome,
2) Death,
3) LTFU,
4) End of study.

● Vaccinated

○ Unvaccinated


Eligibility
(Week 1)
t_0
Follow-up until:
1) Outcome,
2) Death,
3) LTFU,
4) End of study.
Week 2
IMSS
Workers
Week n
Vaccinated
Unvaccinated

Components	TT Specification	TT Emulation
Time zero and follow-up	From treatment assignment until: • Outcome of interest • Death • Loss to follow-up • End of follow-up	Same
Outcomes	SARS-CoV-2 infection	

Components	TT Specification	TT Emulation
Time zero and follow-up	From treatment assignment until: • Outcome of interest • Death • Loss to follow-up • End of follow-up	Same
Outcomes	SARS-CoV-2 infection	Symptomatic SARS-CoV-2 infection

Components	TT Specification	TT Emulation
Time zero and follow-up	From treatment assignment until: • Outcome of interest • Death • Loss to follow-up • End of follow-up	Same
Outcomes	SARS-CoV-2 infection	Symptomatic SARS-CoV-2 infection
Causal contrasts	Intention-to-treat (ITT) effect Per-protocol (PP) effect	

Components	TT Specification	TT Emulation
Time zero and follow-up	From treatment assignment until: • Outcome of interest • Death • Loss to follow-up • End of follow-up	Same
Outcomes	SARS-CoV-2 infection	Symptomatic SARS-CoV-2 infection
Causal contrasts	Intention-to-treat (ITT) effect Per-protocol (PP) effect	ITT may be uninformative PP effect same

Components	TT Specification	TT Emulation
Statistical analyses	ITT: Estimate six-month risks for both groups using pooled logistic regression models. Then, calculate risk differences and risk ratios with corresponding 95% bootstrap confidence intervals. PP: Follow the same procedure, but apply time-varying inverse probability of treatment and censoring weights to the models. Individuals are censored upon non-adherence to their assigned strategy.	Same

Time-varying IPW

$$SW_k^A = \prod_{m=0}^{k} \frac{f\left(A_m | \bar{A}_{m-1}\right)}{f\left(A_m | \bar{A}_{m-1}, \bar{L}_m\right)}$$

Where:

- A_m : an indicator of treatment at time m,
- $\bar{A}_{m\text{-}1}$: treatment history.
- $\bar{L}_m$: confounder history.

Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Time-varying IPCW

$$W_{k+1}^{\bar{C}} = \begin{cases} \prod_{m=1}^{k+1} \dfrac{\Pr(C_m = 0 | \bar{A}_{m-1}, V, \bar{C}_{m-1} = 0)}{\Pr(C_m = 0 | \bar{A}_{m-1}, \bar{L}_{m-1}, \bar{C}_{m-1} = 0)} & \text{if } C_{k+1} = 0 \\ 0 & \text{if } C_{k+1} = 1 \end{cases}$$

Where:

- $C_m = 0$: an indicator of being uncensored at time m,
- $\bar{A}_{m-1}$: treatment history.
- $\bar{L}_{m-1}$: confounder history.
- V: baseline values of covariates.

IP-weighted PLR

$$\text{logit Pr}\left[Y_{k+1} = 1 | \bar{A}_k, Y_k = 0, C_{k+1} = 0\right] = \theta_{0,k} + \theta_1 A + \theta_2 L + \theta_3 A \times f(k)$$

Where:

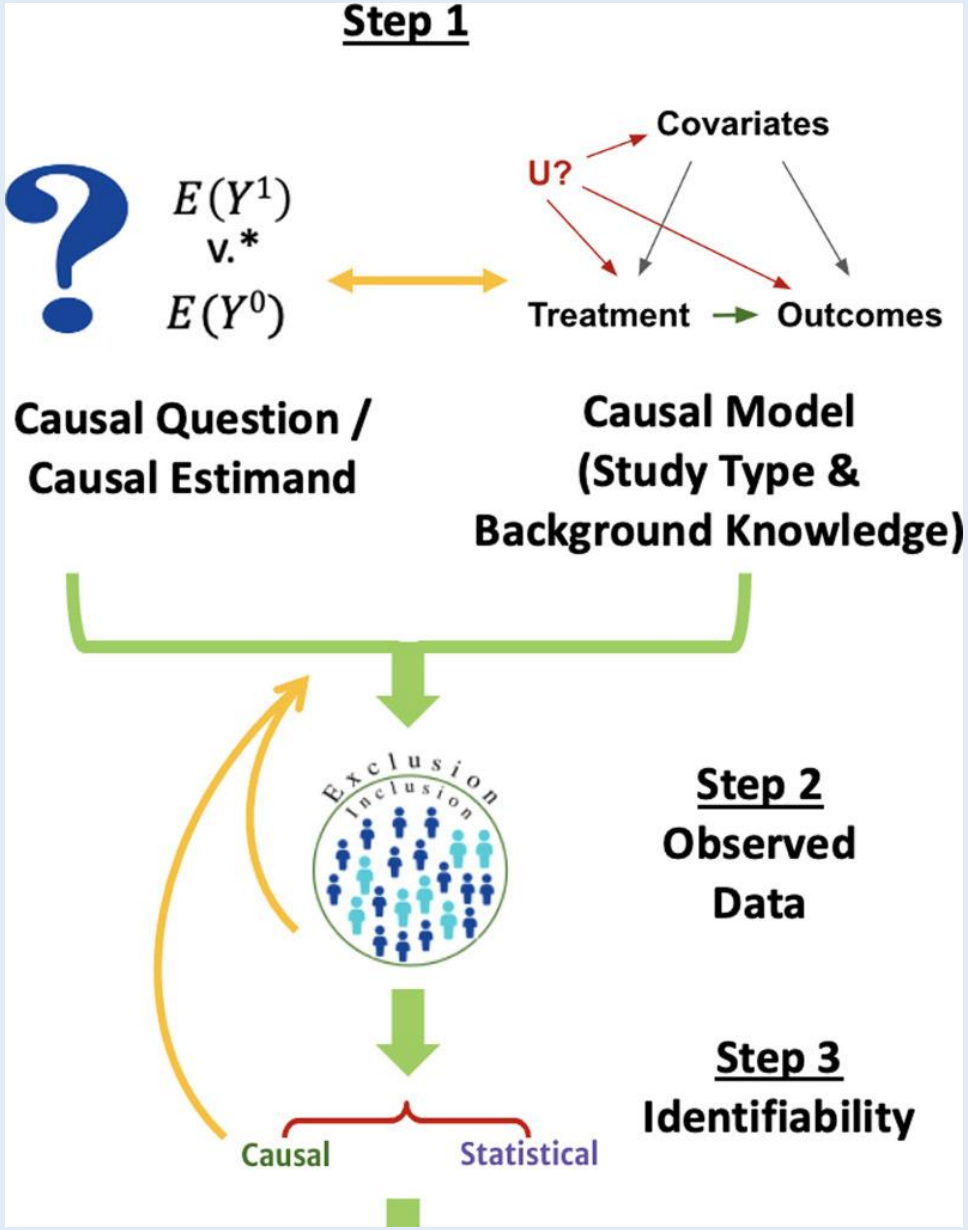
- Y_{k+1}: the outcome in interval $k + 1$.
- $\bar{A}_k$: treatment history.
- $C_{k+1} = 0$: an indicator of being uncensored at time $k + 1$,
- A: a time-fixed indicator for being assigned to "always treat" ($A = 1$) or "never treat" ($A = 0$) at time zero.
- L: Baseline values of confounders.
- $A \times f(k)$: a (vector) of product terms between treatment and functions of time (allows for a time-varying hazard ratio)

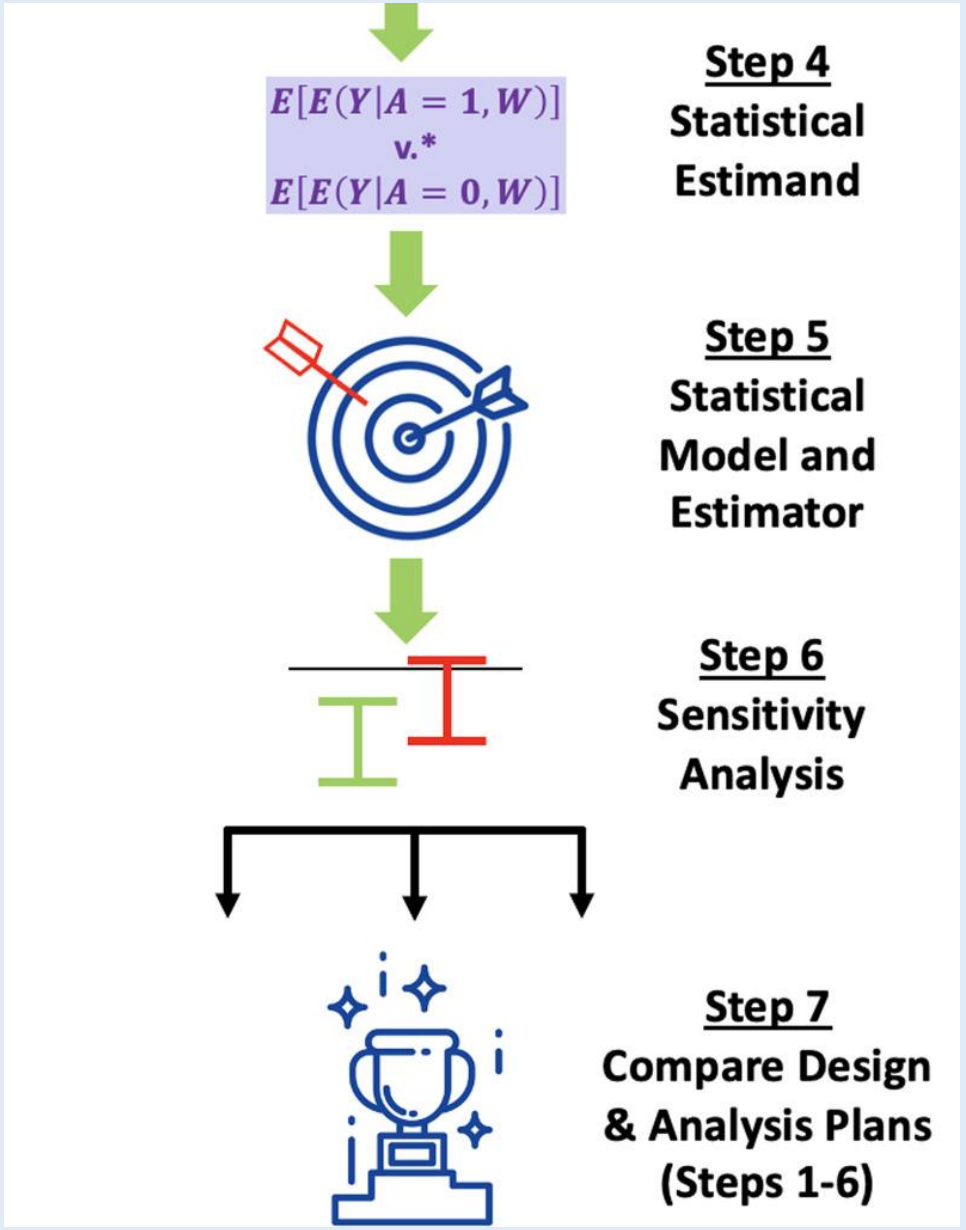
6. The **causal roadmap**

A single causal question can lead to many paths

- The **causal roadmap** guides study design, analysis, and interpretation
- It **works across** randomized and observational **designs**
- Supports any identification assumptions
- Promotes the use of estimators with strong theoretical/finite-sample properties
- Prevents over-interpretation

Dang LE, et al. J Clin Transl Sci. 2023;7(1):e212. Published 2023 Sep 22. doi:10.1017/cts.2023.635





Dang LE, et al. J Clin Transl Sci. 2023;7(1):e212. Published 2023 Sep 22. doi:10.1017/cts.2023.635

The causal roadmap

1. Specify the research question, including the target population, exposure(s), outcome(s), time period, and context of interest.
   - What do we want to learn from data that have been collected or will be collected? To whom do we want to apply the results?
2. Specify a causal model, such as a directed acyclic graph,[10] to describe relationships between variables.
   - Are there unmeasured confounders or time-dependent confounders? Are the outcomes missing or censored?
3. Define the causal parameter of interest with counterfactual outcomes.
   - What hypothetical change to the causal model, even if impossible, would we make to generate counterfactuals and answer our research question? How do we want to summarize the distributions of counterfactual outcomes?
4. Describe the observed data and the statistical model.
   - What data did we or will we actually observe? Are there functional form assumptions or can the relationship between the outcome(s), exposure(s), and adjustment variables take any form?
5. Assess identifiability.
   - What modifications can we make to reduce the causal gap?
6. Define the statistical parameter.
   - What function of the observed data are we aiming to estimate?
7. Choose and implement a statistical estimator based on statistical properties; obtain 95% confidence intervals.
   - What are the theoretical properties of potential estimators (e.g., robustness)? How do they perform in finite sample simulations according to objective criteria?
8. Conduct sensitivity analyses.
   - What can existing evidence tell us about plausible magnitudes of the causal gap?
9. Interpret the results, accounting for the prior steps.
   - Have we estimated an association or a causal effect? What are the real-world implications?

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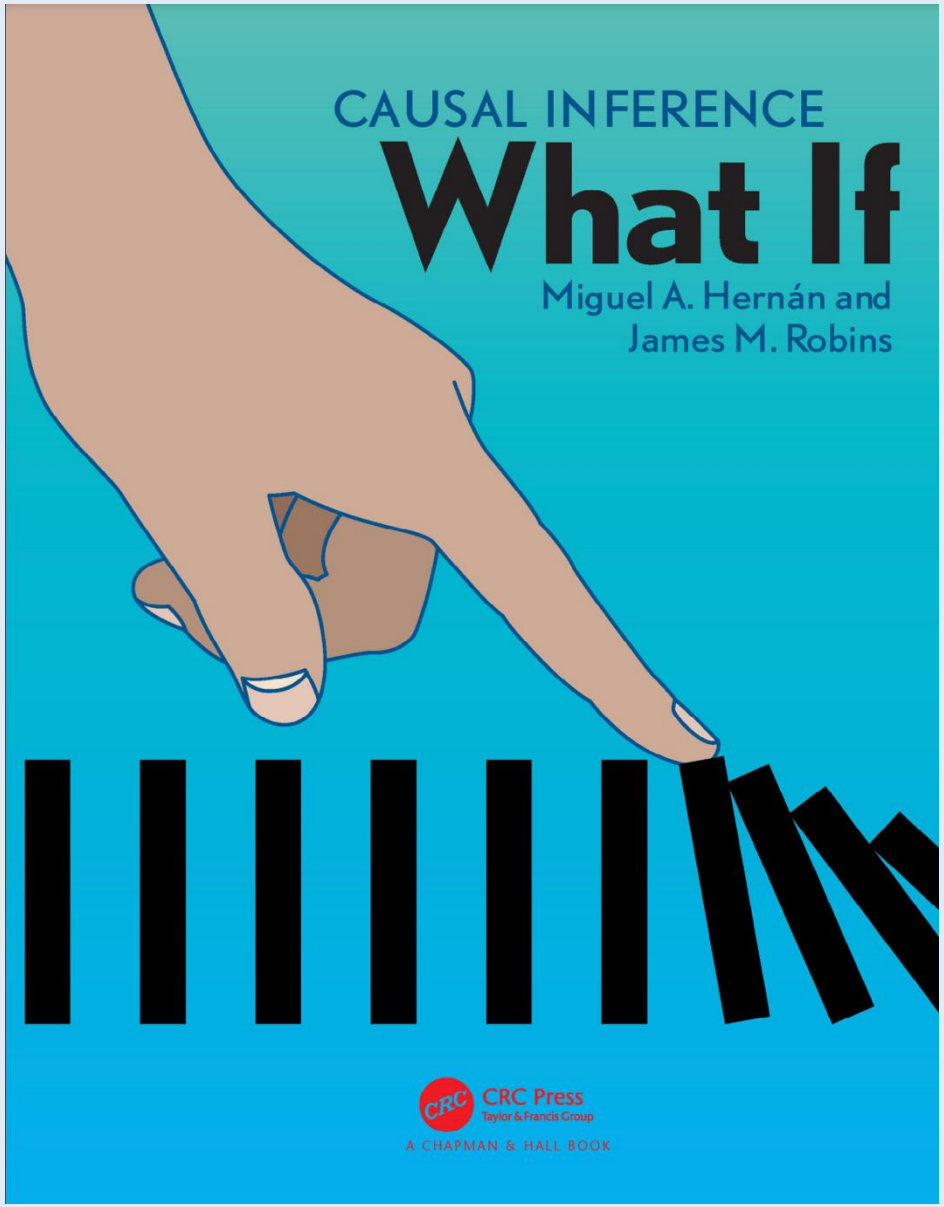
*The order in which the steps are presented differs in different versions of the Roadmap[8,9,20–24] because these steps inform one another and are generally specified through an iterative process.

7. Additional Resources



SAVE THE DATES

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A Center to Learn What Works

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

WEEK 1 COURSES: JUNE 8-12, 2026

- KEY TOPICS IN CAUSAL INFERENCE (KTCI)
- TARGET TRIAL EMULATION (TTE)

WEEK 2 COURSES: JUNE 15-18, 2026

- COMBINING INFORMATION FOR CAUSAL INFERENCE (CICI)
- ADVANCED CONFOUNDING ADJUSTMENT (ACA)

Transparent reporting of observational studies emulating a target trial: the TARGET Statement

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ABSTRACT

IMPORTANCE

When randomized trials are unavailable or not feasible, observational studies can be used to answer causal questions about the comparative effects of interventions by attempting to emulate a hypothetical pragmatic randomized trial (target trial). Published guidance to aid reporting of these studies is not available.

OBJECTIVE

To develop consensus based guidance for reporting observational studies performed to estimate causal effects by explicitly emulating a target trial.

DESIGN, SETTING, AND PARTICIPANTS

The Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) guideline was developed using the Enhancing the Quality and Transparency of Health Research (EQUATOR) framework. The development included (1) a systematic review of reporting practices in published studies that had explicitly aimed to emulate a target trial; (2) a two round online survey (August 2023 to March 2024; 18 expert participants from six countries) to assess the importance of candidate items selected from previous research and to identify additional items; (3) a three day, expert consensus meeting (June 2024; 18 panelists) to refine the scope of the guideline and draft the checklist; and (4) pilot of the draft checklist with stakeholders (n=108; September 2024 to February 2025). The checklist was further refined based on feedback on successive drafts.

FINDINGS

The 21-item TARGET checklist is organized into six sections (abstract, introduction, methods, results, discussion, other information). TARGET provides guidance for reporting observational studies of interventions explicitly emulating a parallel group, individually randomized target trial, with adjustment for baseline confounders. Key recommendations are to (1) identify the study as an observational emulation of a target trial; (2) summarize the causal question and reason for emulating a target trial; (3) clearly specify the target trial protocol (ie, the causal estimand, identifying assumptions, data analysis plan) and how it was mapped to the observational data; and (4) report the estimate obtained for each causal estimand, its precision, and findings from additional analyses to assess the sensitivity of the estimates to assumptions, and design and analysis choices.

CONCLUSIONS AND RELEVANCE

Application of the TARGET guideline recommendations aims to improve reporting transparency and peer review and help researchers, clinicians, and other readers interpret and apply the results.

SUMMARY POINTS

- The TARGET (Transparent Reporting of Observational Studies Emulating a Target Trial) Statement provides guidance for reporting observational studies performed to estimate causal effects of interventions by explicitly emulating a target trial
- The guideline consists of a checklist of 21 essential items and additional information for each item to be used when writing or reading research reports
- The guideline provides authors with a tool to help them report essential information so that readers, peer reviewers, and editors can more easily evaluate the validity and usefulness of their work

Introduction

When randomized trials are unavailable or not feasible, observational (non-randomized) data can be used in an attempt to emulate a hypothetical pragmatic randomized trial—the target trial.[1-4] The target trial framework has 2 steps: (1) specifying the causal questions in the form of the target trial protocol defining the causal effect of interest (causal estimand), the key assumptions, and the data analysis plan, and (2) describing how each component of the target trial protocol is mapped to the observational data. When followed correctly, the framework should eliminate some biases that are due to an incorrect use of the observational data (eg, selection bias due to inclusion of individuals after initiation of treatment or other biases that generate "immortal time"[5 6]), so that investigators can focus on other sources of bias due to limitations of the observational data (eg, confounding, measurement error, and missing data).[1]

The target trial framework aims to improve the conduct of comparative effectiveness studies that use observational data by providing a structured approach to study design, data analysis, reporting, and assessing risk of bias.[7] The framework's value is increasingly recognized by investigators,[8 9] regulators,[10 11] research organizations[12] and journals.[2] However, published studies using the target trial framework have been inconsistently reported, often not reporting key aspects of the target trial protocol.[13 14] Guidelines for observational studies such as STROBE (Strengthening the Reporting of Observational Studies in Epidemiology),[15] RECORD (Reporting of Studies Conducted Using Observational Routinely Collected

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Keywords:
Causal inference; real-world evidence; sensitivity analysis; simulations; estimands; machine learning

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A causal roadmap for generating high-quality real-world evidence

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Abstract

Increasing emphasis on the use of real-world evidence (RWE) to support clinical policy and regulatory decision-making has led to a proliferation of guidance, advice, and frameworks from regulatory agencies, academia, professional societies, and industry. A broad spectrum of studies use real-world data (RWD) to produce RWE, ranging from randomized trials with outcomes assessed using RWD to fully observational studies. Yet, many proposals for generating RWE lack sufficient detail, and many analyses of RWD suffer from implausible assumptions, other methodological flaws, or inappropriate interpretations. The *Causal Roadmap* is an explicit, itemized, iterative process that guides investigators to prespecify study design and analysis plans; it addresses a wide range of guidance within a single framework. By supporting the transparent evaluation of causal assumptions and facilitating objective comparisons of design and analysis choices based on prespecified criteria, the *Roadmap* can help investigators to evaluate the quality of evidence that a given study is likely to produce, specify a study to generate high-quality RWE, and communicate effectively with regulatory agencies and other stakeholders. This paper aims to disseminate and extend the *Causal Roadmap* framework for use by clinical and translational researchers; three companion papers demonstrate applications of the *Causal Roadmap* for specific use cases.

Introduction

The 21st century has witnessed a dramatic increase in the quality, diversity, and availability of

OPEN

Start with the Target Trial Protocol, Then Follow the Roadmap for Causal Inference

Lauren E. Dang[a] and Laura B. Balzer[a]

Before taking flight, pilots complete a preflight checklist. Before starting surgery, operating room staff complete a presurgical checklist. These checklists synthesize the knowledge of a field into a series of steps to be considered every time a job is performed. What about when researchers want to infer causality?

A century's worth of literature regarding the design and analysis of observational studies is available, yet common guidance is not always followed. Bykov et al.[1] reviewed a random sample of 75 observational studies on cardiovascular disease, diabetes, or osteoporosis and found that 95% "had at least one avoidable methodological issue known to incur bias." It is, thus, critical to distill this literature into concrete instructions so that best practices are consistently implemented.

Many useful frameworks operationalize aspects of the causal and statistical inference literature into steps for researchers to follow.[2–12] Target trial emulation is a popular approach that has led to high-profile studies in recent years.[13–15] The basic structure shared by target trial emulation studies follows Hernán and Robins'[7] statement that "at the very least, we need to specify the following key components of the [target trial] protocol: eligibility criteria, start and end of follow-up, treatment strategies, outcomes of interest, causal contrast, and data analysis plan."[16] The assignment procedure of the target trial is generally included, as well.[7]

Pearce and Vandenbroucke[17] raised concerns about certain studies that use target trial emulation protocol components. First, they suggest that target trial emulation seems to focus on mimicking a conditionally randomized controlled trial, as opposed to considering a variety of study designs and identification assumptions. Second, target trial emulation is sometimes paired with a matching approach for statistical estimation; matching can change the target population and is often less efficient than other methods.[18,19] Third, after emulating a target trial, one may be tempted to over-interpret the results; we still have an observational study, subject to multiple potential biases, including intractable confounding. Ultimately, Pearce and Vandenbroucke[17] conclude that target trial emulation is not the optimal starting point for causal inference.

In contrast, we believe the target trial emulation protocol is a useful starting place for analyses seeking to infer causality. In other words, we agree with Hernán and Robins'[7] statement: "specifying the protocol of the target trial is a useful device to clarify the causal question of interest."[16] However, we disagree with their assertion: "once the causal question

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