Verwendung von Beobachtungsdaten in der Nutzenbewertung – Einfluss von Design and Analysetechniken auf den Bias von Effektschätzungen

24. Juni 2025

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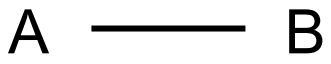
Agenda

1. Concept Causal Inference
2. Challenges of Observational Studies
3. Target Trial
4. Potential Biases: Case Example
5. So What?

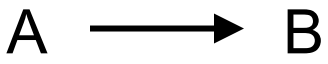
Concept Causal inference

Prediction and Causal Effect



Statistical Relation:
"If I learn …"

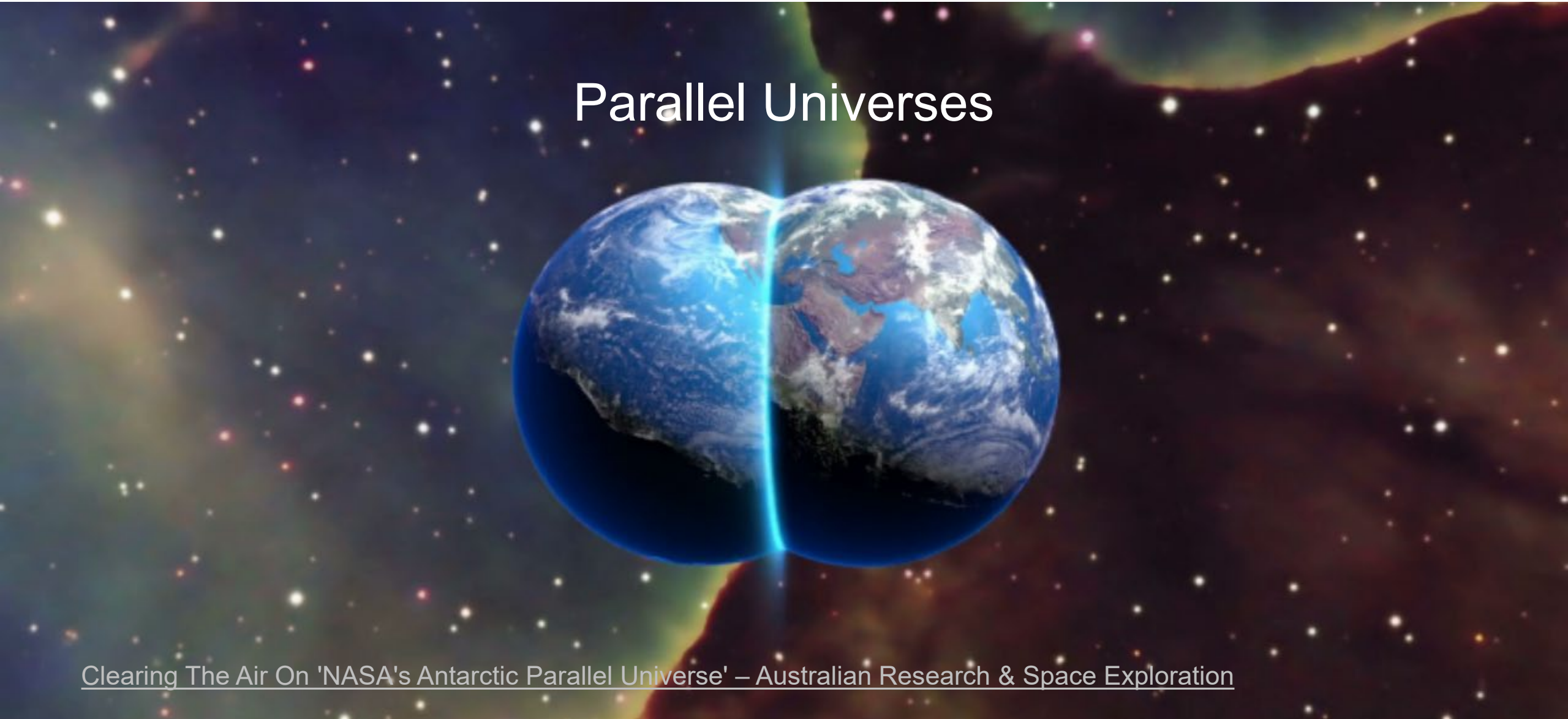
- A is related to B
- If I learn about A, I know more about B than before (and vice versa)
- I can use A to (better) predict B and vice versa
- A and B are not independent
- Correlation coefficient ≠ 0
- P(A and B) ≠ P(A)*P(B)
- Information "flows" between A and B



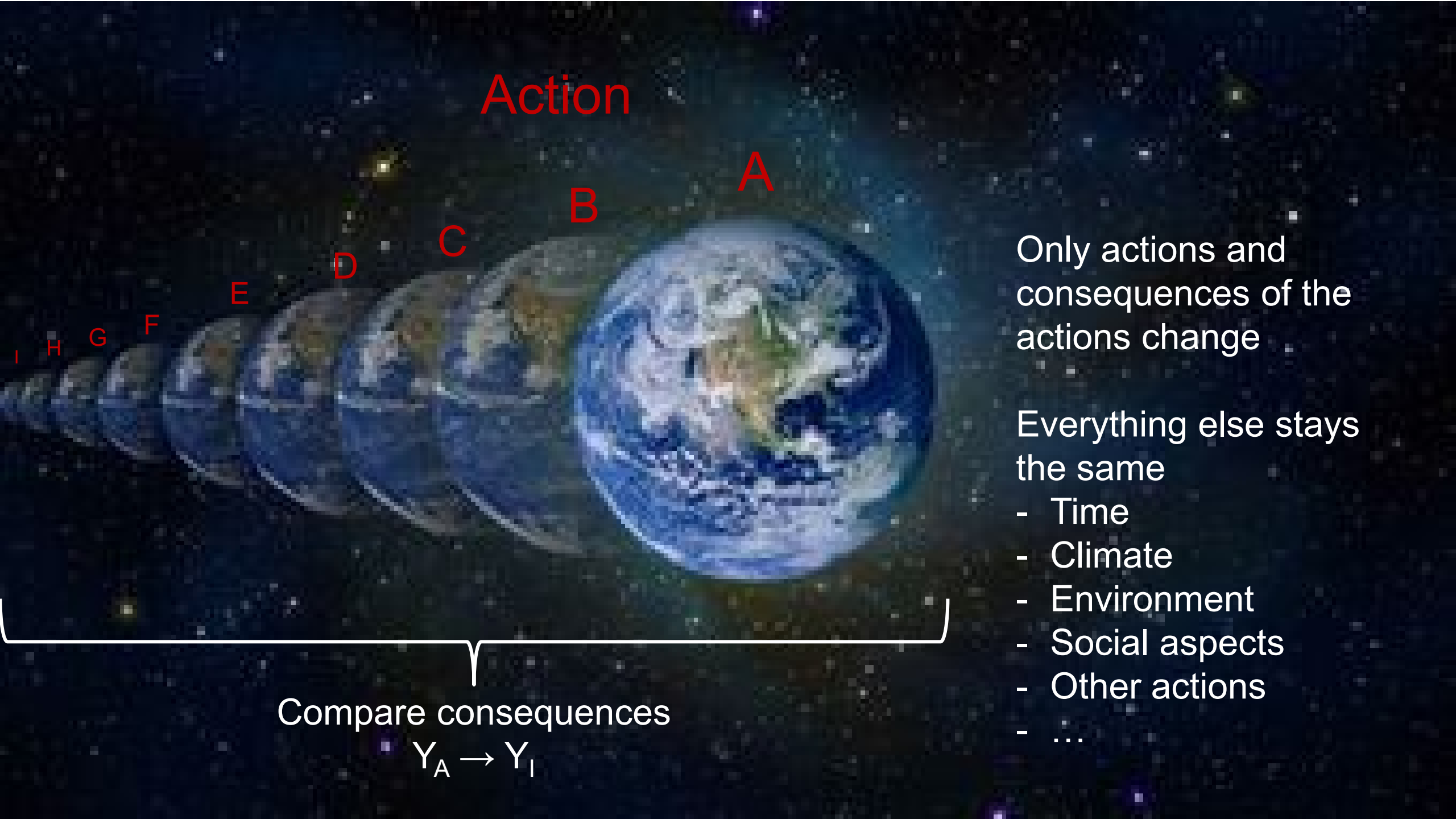
Causal Relation:
"If I change …"

- A causes B
- If I change A, B changes (not vice versa)
- I can use interventions on A to improve B (not vice versa)
- P(B|do(A=0)) ≠ P(B|do(A=1))
- Effect "flows" from A to B

Counterfactual Concept



Clearing The Air On 'NASA's Antarctic Parallel Universe' – Australian Research & Space Exploration



Only actions and consequences of the actions change

Everything else stays the same

- Time
- Climate
- Environment
- Social aspects
- Other actions
- …

Challenges of observational studies

Challenges of Causal Analyses of RWD

Confounding	• Time independent and time dependent
Selection bias	• Selection by indication
Immortal time bias	• Time zero bias
Adequate data	• Reliability • Extent • Accessibility

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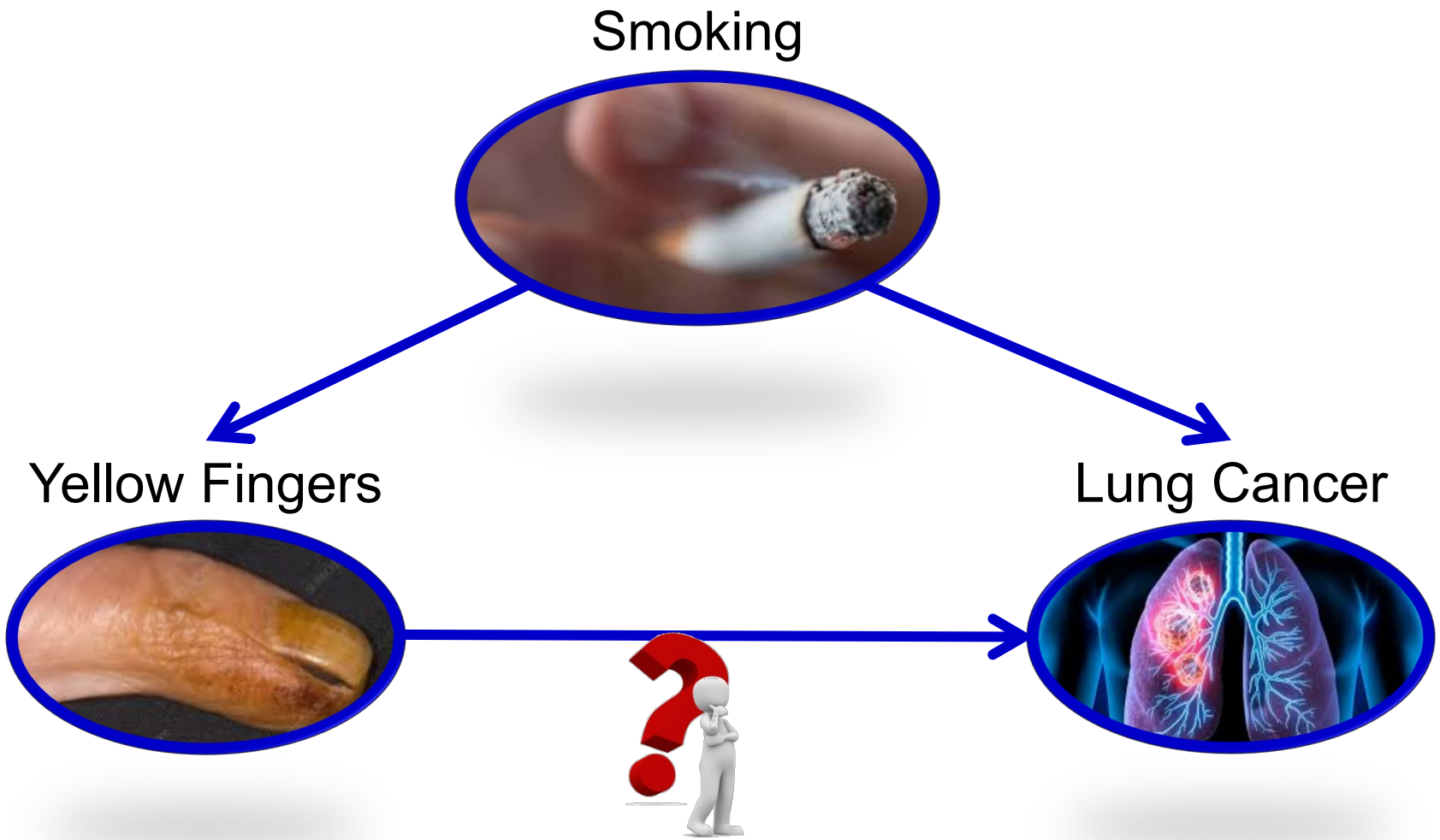
Confounding



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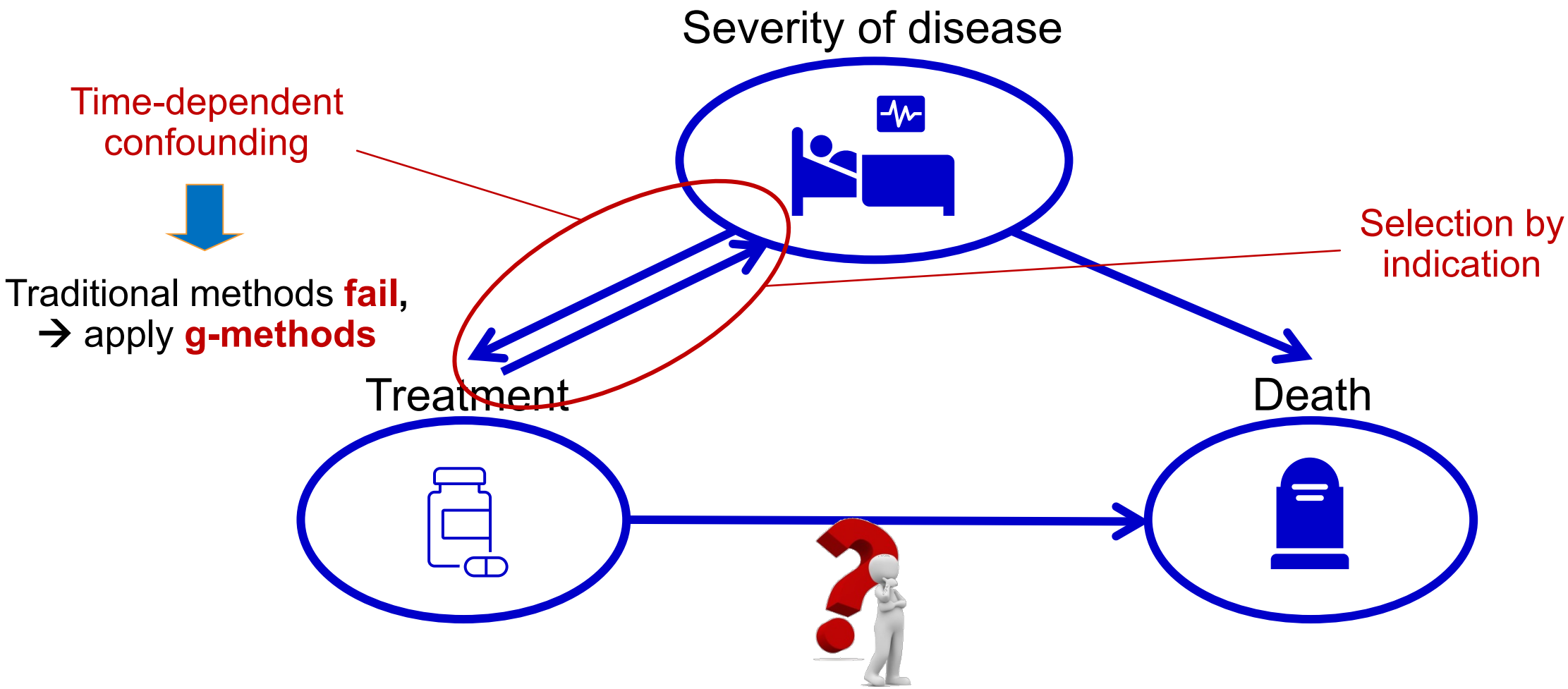
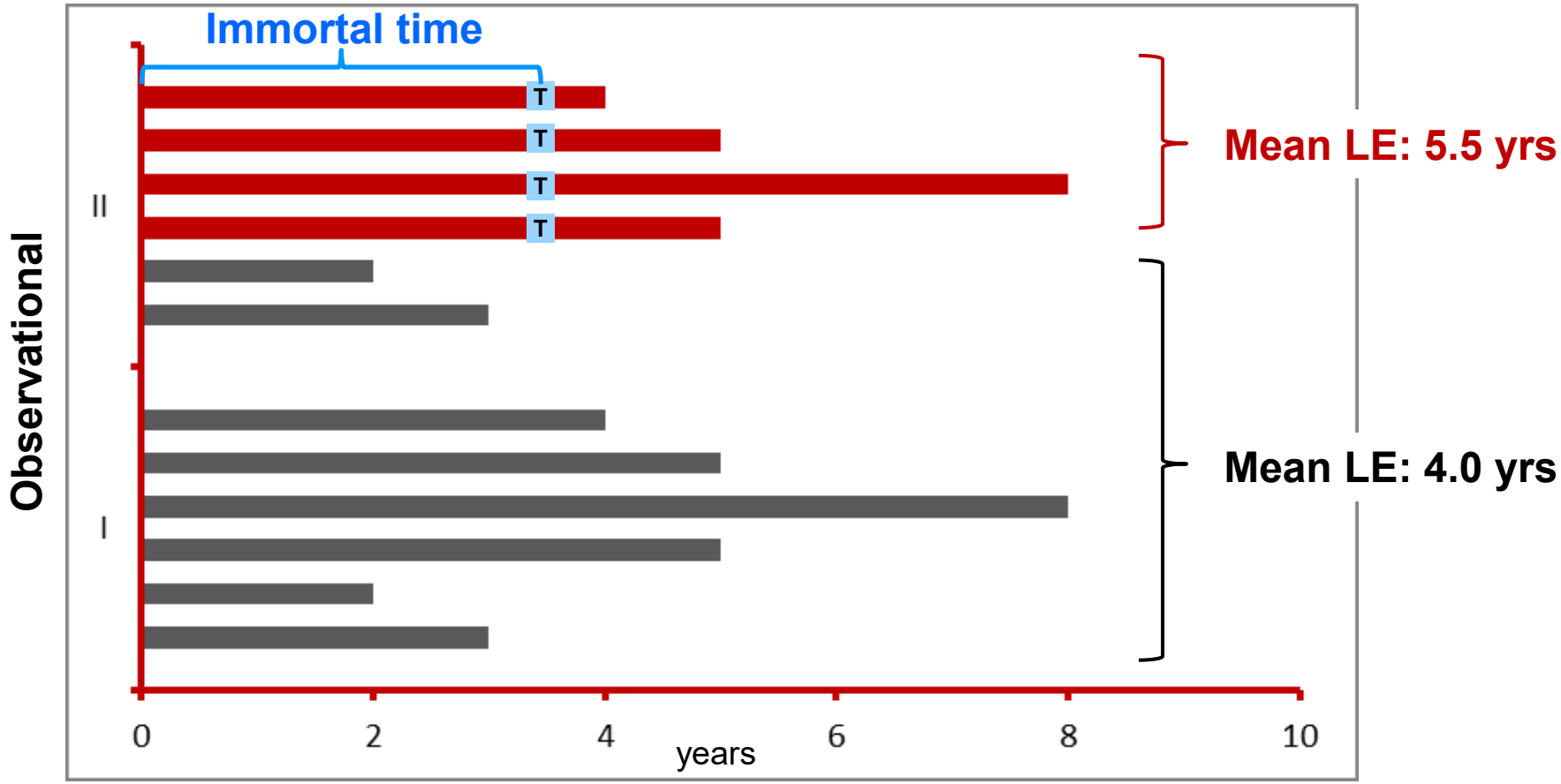
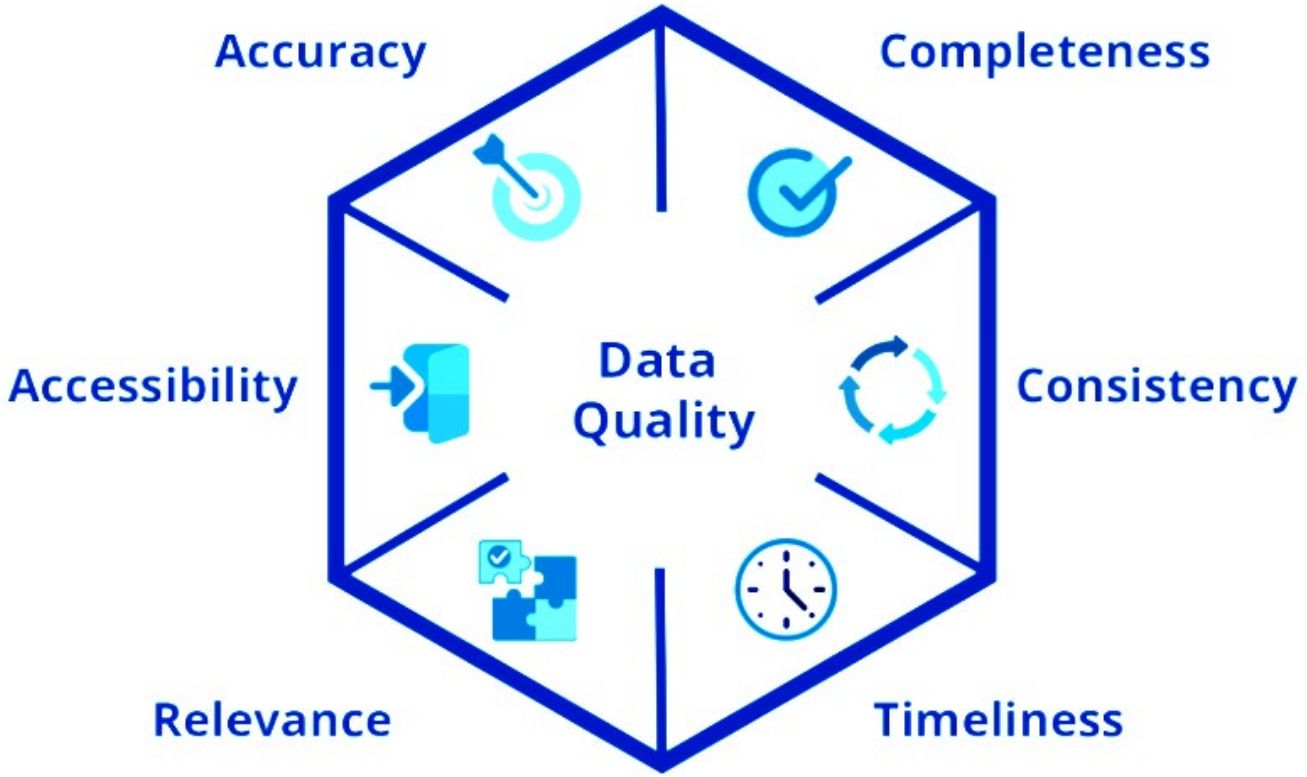


Immortal Time Bias



Tx effect: HR < 1 BIAS!

Adequate Data



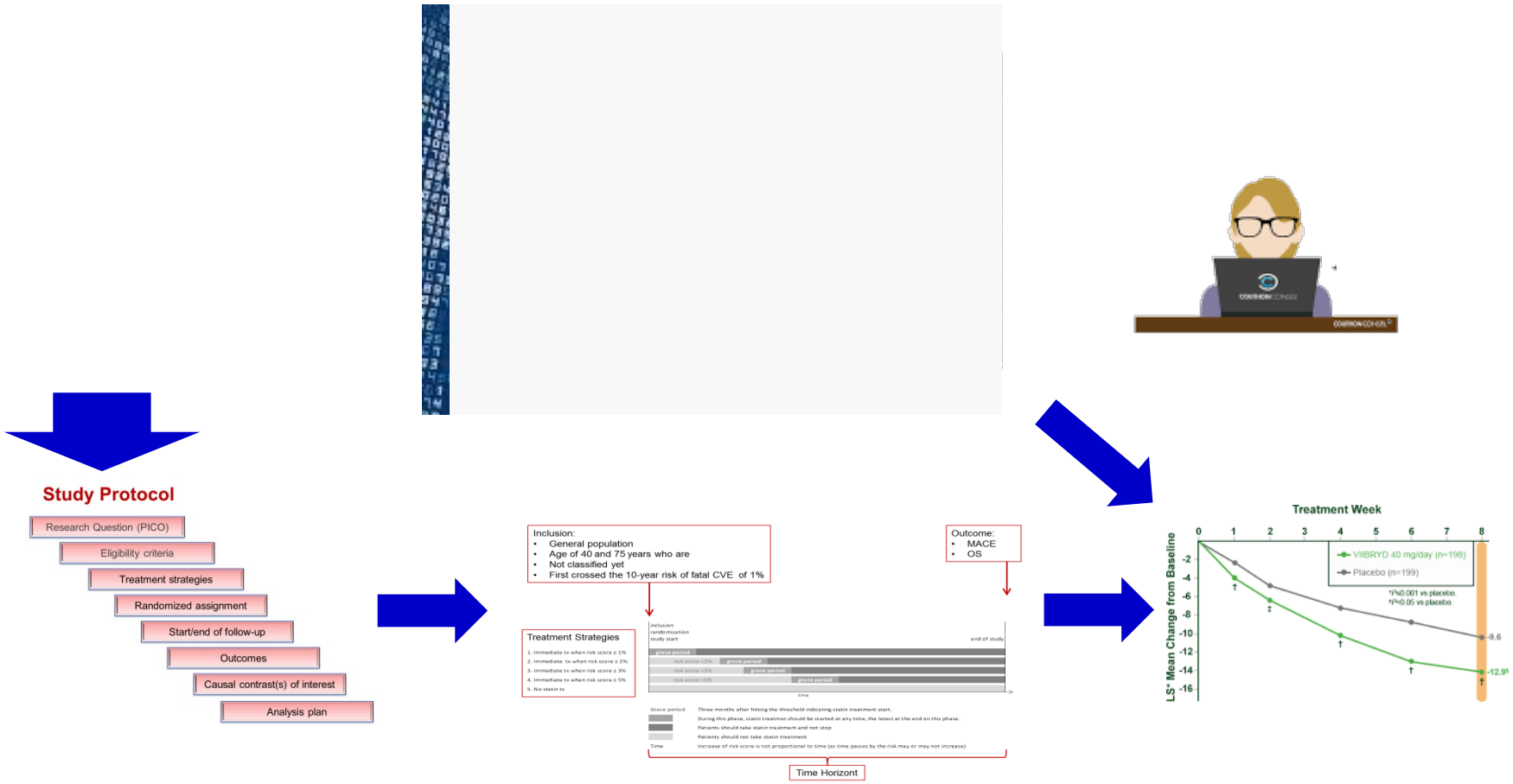
Quelle: Datenqualitätsmanagement im Gesundheitswesen: 5 bewährte Methoden

Target Trial Emulation

Target Trial

- Structural approach mimicking the counterfactual approach
  - Develop the protocol for a hypothetical randomized trial (“target trial”) that would address the research question of interest
- Target Trial can be used to
  - Avoid self-inflicted biases (time-zero bias, immortal time bias)
  - Control for time-dependent confounding
  - Useful for big data analysis
  - When-to-start-treatment questions

Target Trial



Potential biases: Case example

Asses Potential Biases in RWD:
Compare traditional and causal methods

ELSEVIER

Check for updates

Journal of Clinical Epidemiology 152 (2022) 269–280

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Causal analyses with target trial emulation for real-world evidence removed large self-inflicted biases: systematic bias assessment of ovarian cancer treatment effectiveness

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Accepted 3 October 2022; Published online 15 October 2022

Acknowledgment

This work was supported by the UMIT-Lilly Causal Inference in RWE Working Group:

UMIT TIROL: Marjan Arvandi, Annette Conrads-Frank, Holger Gothe, Raffaella Gothe, Beate Jahn, Nikolai Mühlberger, Sasa Rajsic, Ursula Rochau, Gaby Sroczynski, Uwe Siebert

Eli Lilly: Julie Kay Beyrer, Douglas E. Faries , Lisa M. Hess, Jeanne Marie Schilder, Yu Yan

Clinical experts: Christian Marth, Alain-Gustave Zeimet

Aim

Assess potential biases in causal analysis of large real-world database

- Type
- Impact

Case of ovarian cancer

- Aggressive disease with poor survival outcomes
- Treatment
  - Surgery followed by chemotherapy
  - No standards for subsequent treatment lines

PICO

Population:

Ovarian cancer patients progressed after 1st-line treatment

Intervention:

With 2nd-line treatment (LOT2)

Comparison:

Without 2nd-line treatment

Outcome:

Overall survival (OS)

Methods

Retrospective observational study

- IMS Oncology electronic medical records (EMR)
- Oncology practices and comprehensive cancer centers in US

Causal graphs

- Identify potential confounding and other biases
- Estimate direction of biases

Analyses

Effect measure: Hazard ratios (HR)

95% confidence intervals (95%CI)

Methods

Compare to Reference Case

Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial

*Gordon J S Rustin, Maria E L van der Burg, Clare L Griffin, David Guthrie, Alan Lamont, Gordon C Jayson, Gunnar Kristensen, César Mediola, Corneel Coens, Wendi Qian, Mahesh K B Parmar, Ann Marie Swart, for the MRC OV05 and EORTC 55955 investigators**

Summary

Background Serum CA125 concentration often rises several months before clinical or symptomatic relapse in women with ovarian cancer. In the MRC OV05/EORTC 55955 collaborative trial, we aimed to establish the benefits of early treatment on the basis of increased CA125 concentrations compared with delayed treatment on the basis of clinical recurrence.

Methods Women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a

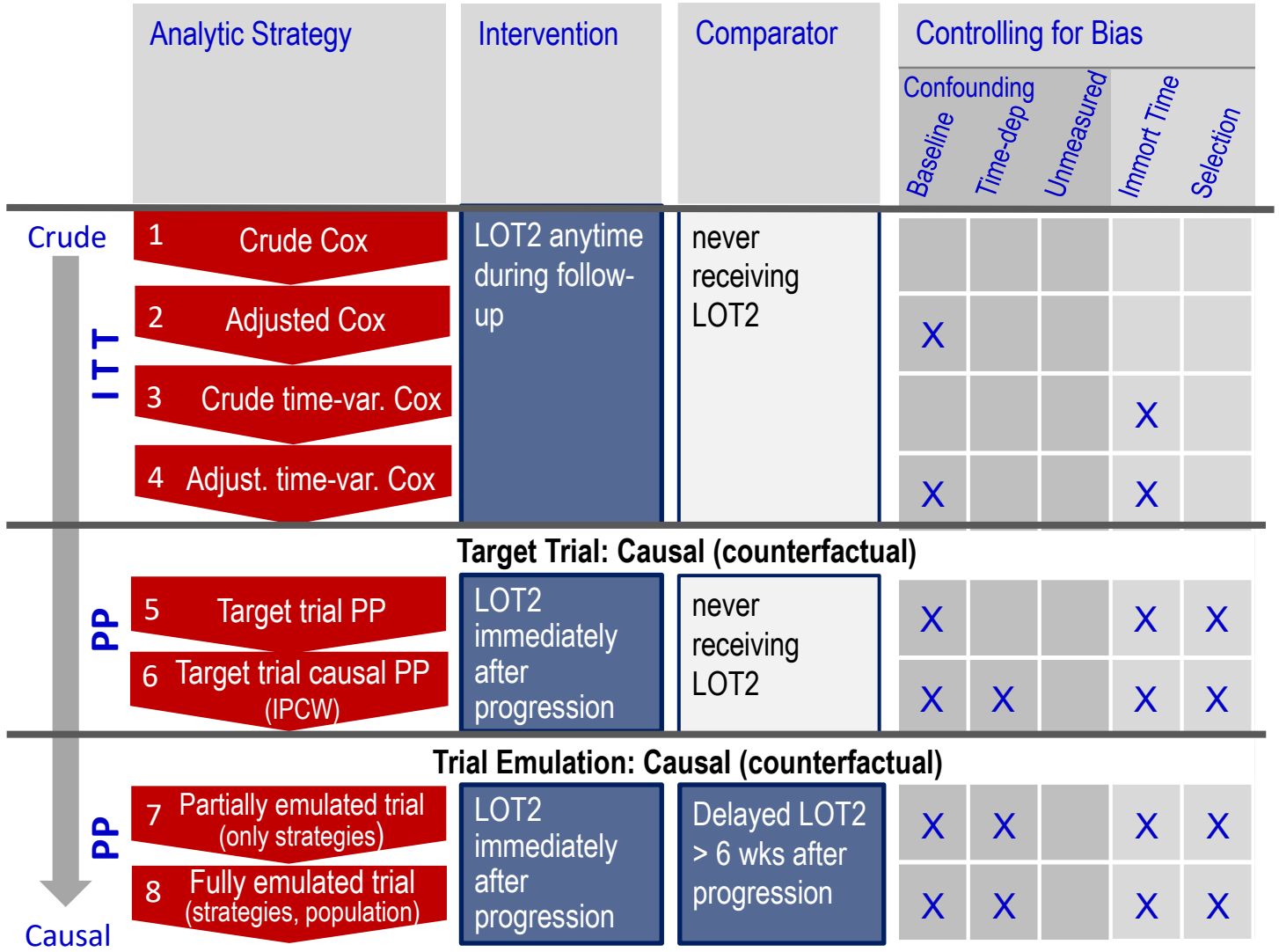
	Hazard ratio (95% CI)	Log-rank p value
Unadjusted	0·98 (0·80–1·20)	0·85
Adjusted		
For stratification factors*	0·99 (0·80–1·22)	..
For prognostic factors†	0·98 (0·79–1·21)	..
For stratification and prognostic factors	1·01 (0·82–1·25)	..
Sensitivity analyses‡	1·01 (0·82–1·23)	0·96

*Age, International Federation of Gynecology and Obstetrics stage, first-line chemotherapy, time from completion of first-line chemotherapy to doubling of CA125 concentration, and country. †Histology, WHO performance status, and time from doubling of CA125 concentration to randomisation. ‡Sensitivity analyses of non-curtailed data (all follow-up data received, not curtailed at 5 years for MRC OV05 and 3 years for EORTC 55955).

Table 3: **Hazard ratios for overall survival**

Rustin GJ, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010 Oct 2; 376(9747):1155-63. doi: 10.1016/S0140-6736(10)61268-8. PMID: 20888993.

Analytic Strategies



Treatment Assignment

Treatment strategies:

- Second line treatment (T)
- Never treat (N)

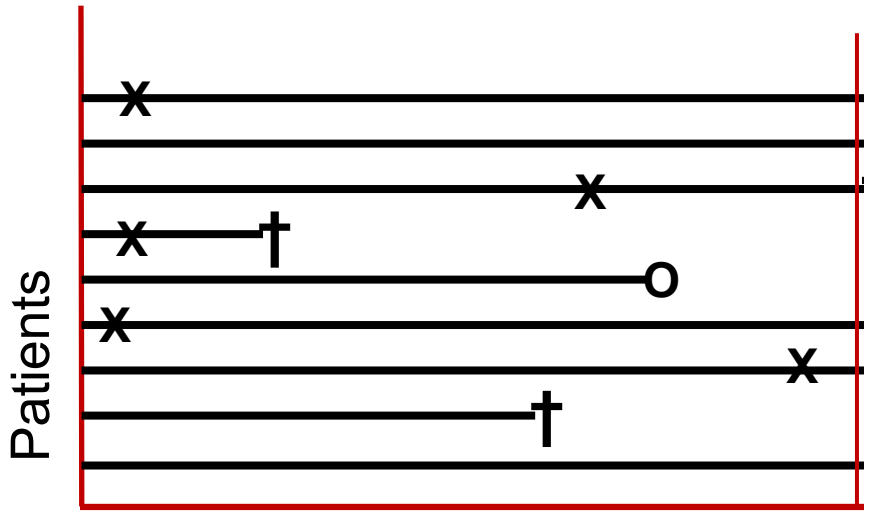
X Start of treatment

† Death

O Censored

Progression

T	N
X	
	X
X	
X	
	X
X	
X	
	X
	X



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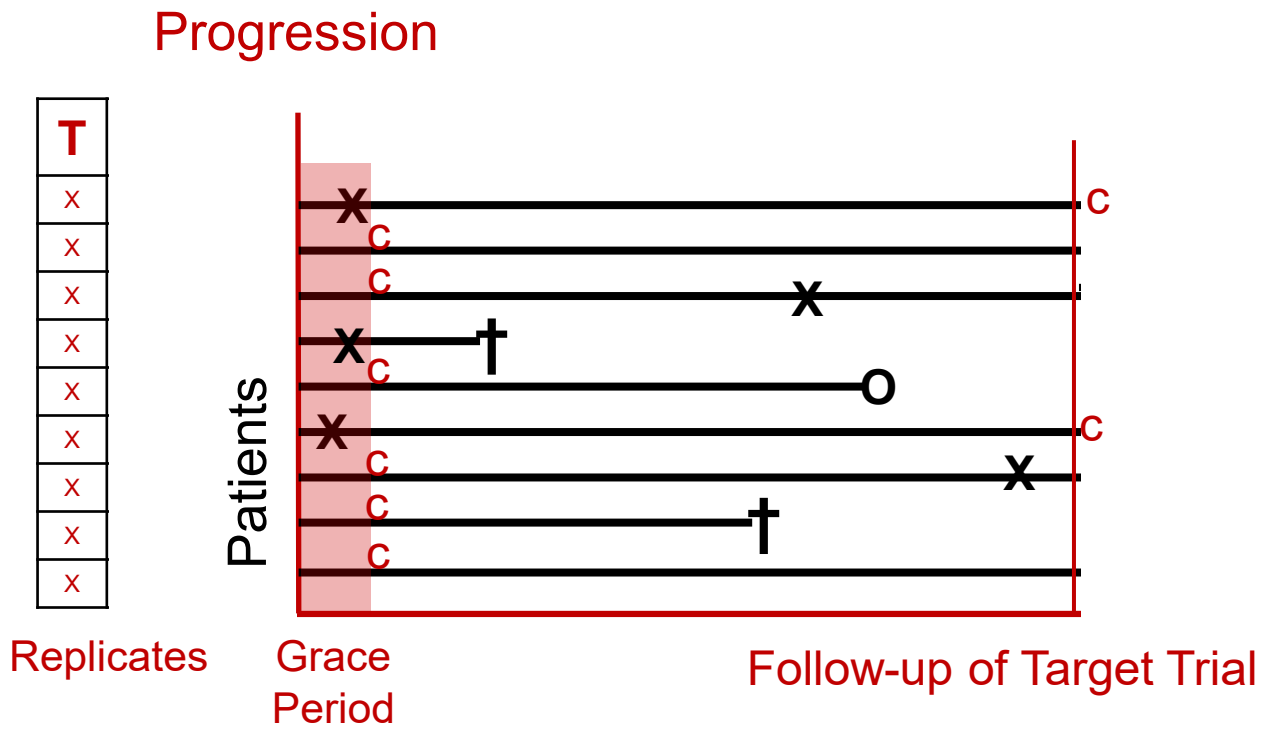

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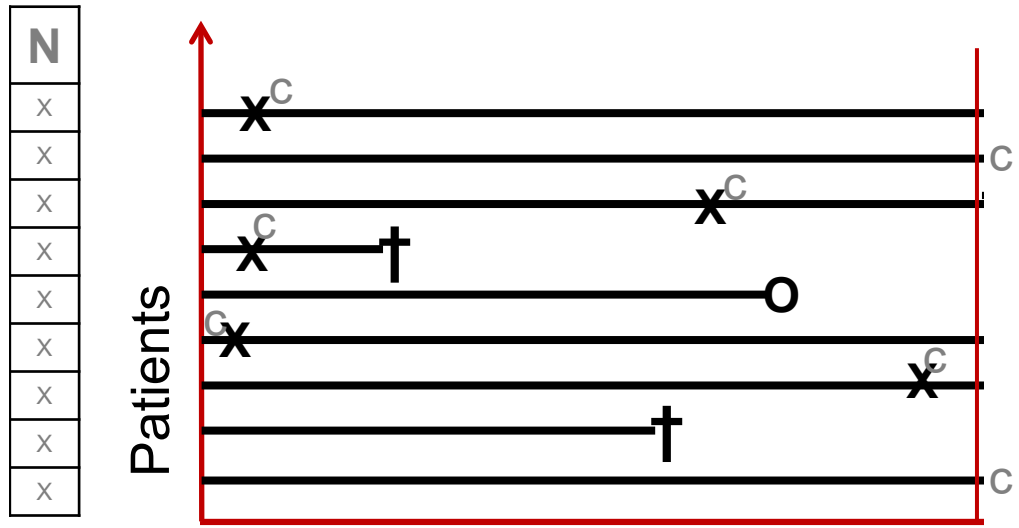
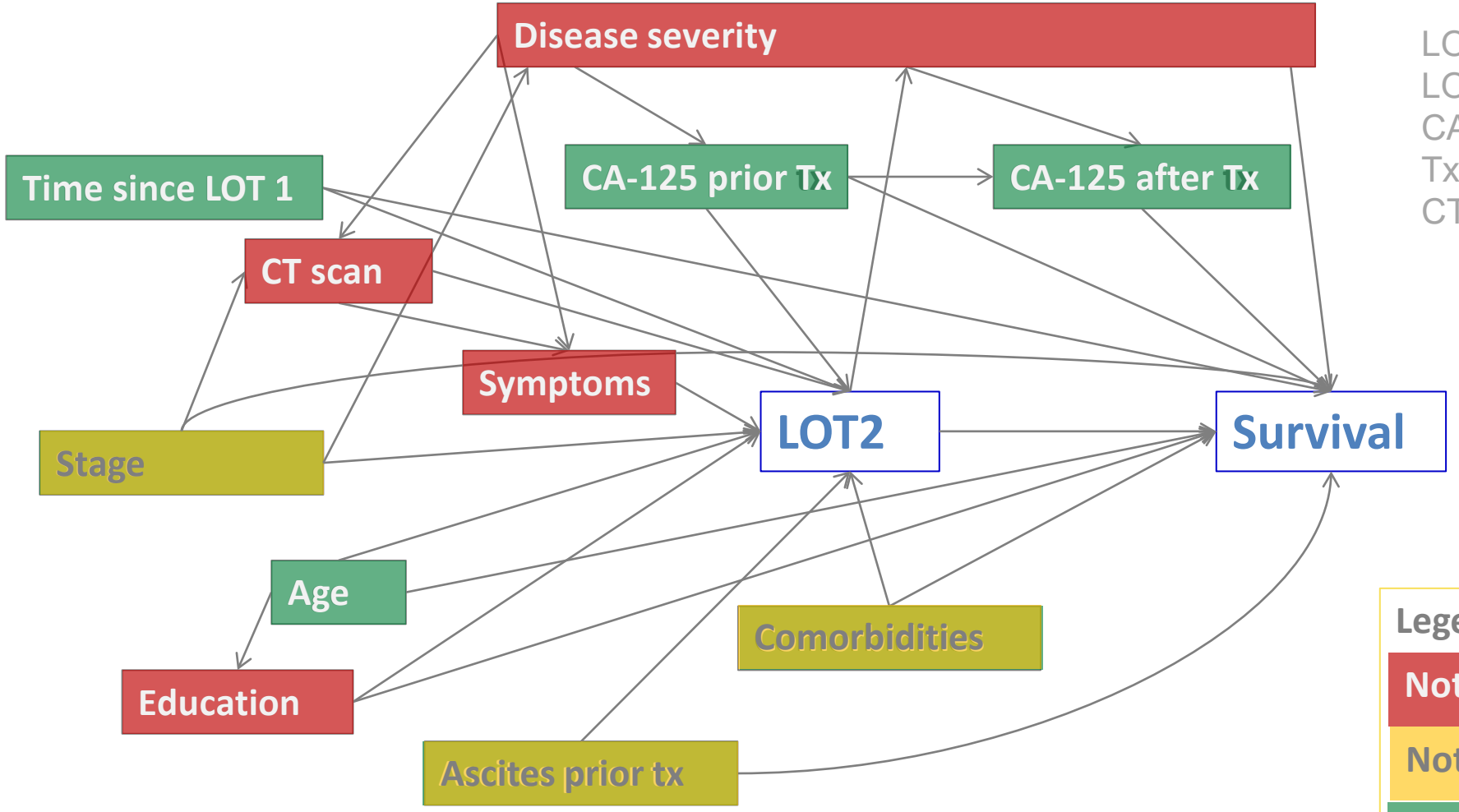


Censoring needs proper adjustment

Directed Acyclic Graph (DAG)



LOT1: 1st Line of Treatment;
LOT2: 2nd Line of Treatment;
CA: Cancer-Antigen;
Tx: Treatment;
CT: Computer Tomography;

Legend:

- Not available
- Not reliable
- Available and reliable

Expert Panel Assessment of Assumed Bias Direction

Immortal time bias	Confounding
Underestimates the treatment HR	Estimation of bias direction using the DAG and techniques described by VanderWeele

Bias		Direction of Bias (in favor/against LOT2) Estimation of HR		
		HR - in favor of LOT2	HR ± either	HR + against LOT2
Confounding				
- **Unmeasured**	(disease severity, CT scan, symptoms)			X
	(education)	X		
- **Time-independent**	(ascites, stage)			X
	(age, comorbidities, time since LOT1)		X	
- **Time-dependent**	(CA-125)			X
Immortal-time Bias		X		
Selection Bias / Confounding by indication				X

HR: Hazard Ratio
HR -: underestimation of HR
HR ±: either under- or overestimation of HR
HR +: overestimation of HR
CA: Cancer-Antigen;
CT: computer tomography
LOT1: first line of treatment
LOT2: second line of treatment

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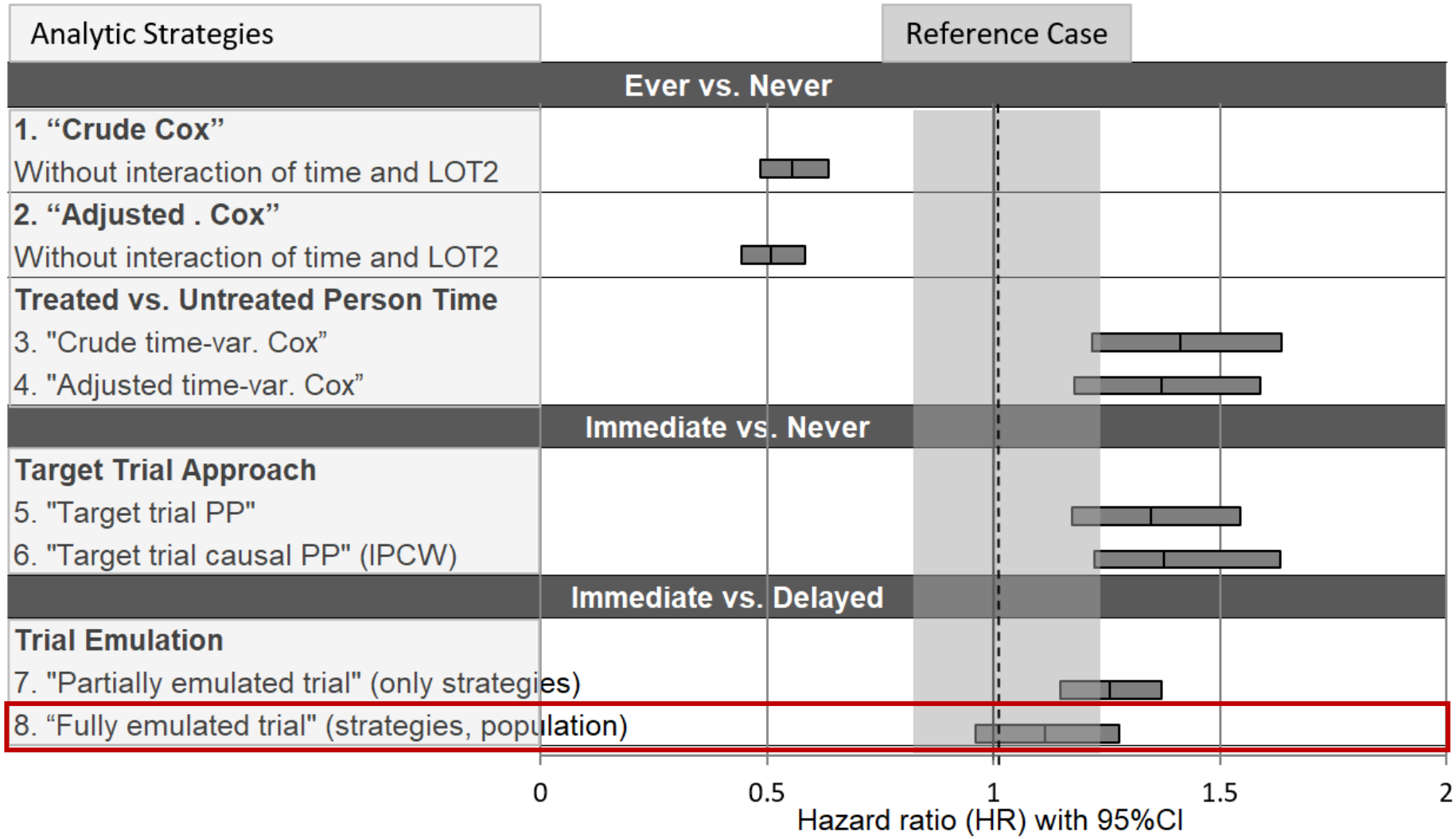
Results



LOT2: 2nd Line of treatment;

vs: versus;

time-var: time-varying;

PP: per protocol;

IPCW: Inverse Probability of Censoring Weighting;

CI: Confidence Interval;

Main Findings

Potential for several biases

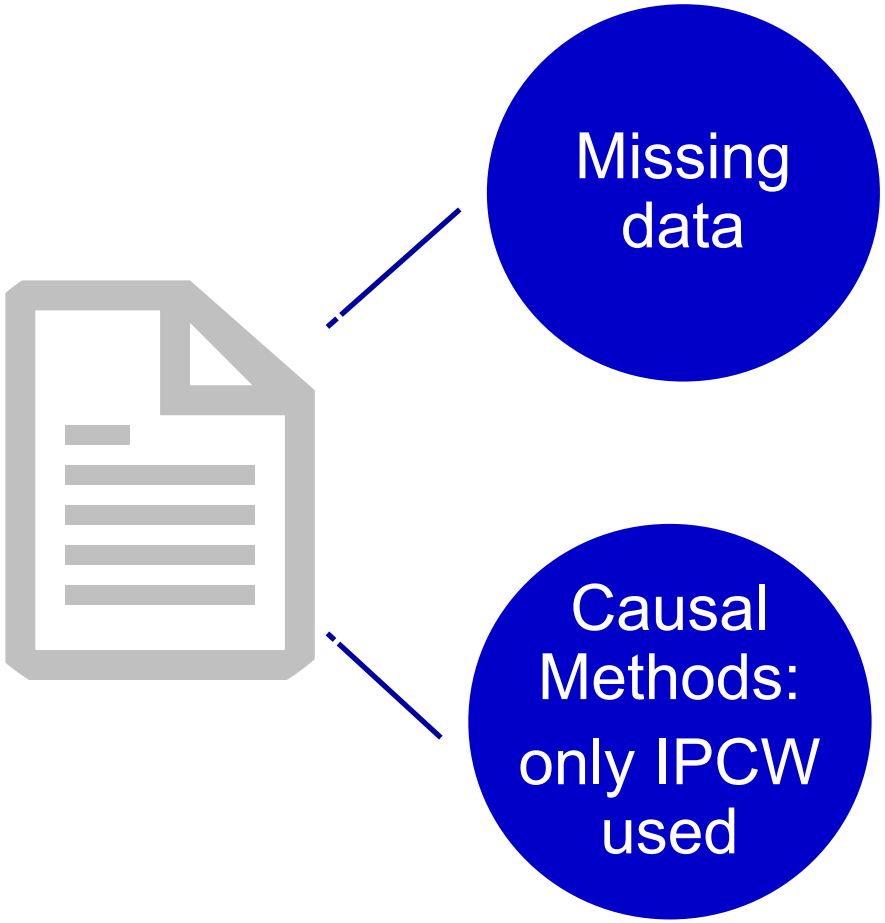
May go in different directions

Several techniques exist to avoid biases

Visual: DAG to identify confounding
Structural: target trial approach
Statistical: careful consideration

Results were similar to those of the clinical trial when following the full causal approach

Limitations of this Study



Present in study
- Comorbidities
- TC scans
- Symptoms

Could show in DAGs that
- Missing data (in this study) ➔ overestimation of HR

Other g-methods that could be considered
- g-estimation,
- Rank preserving structural failure time model (RPSFT),
- Targeted likelihood estimation

Conclusion of this Study

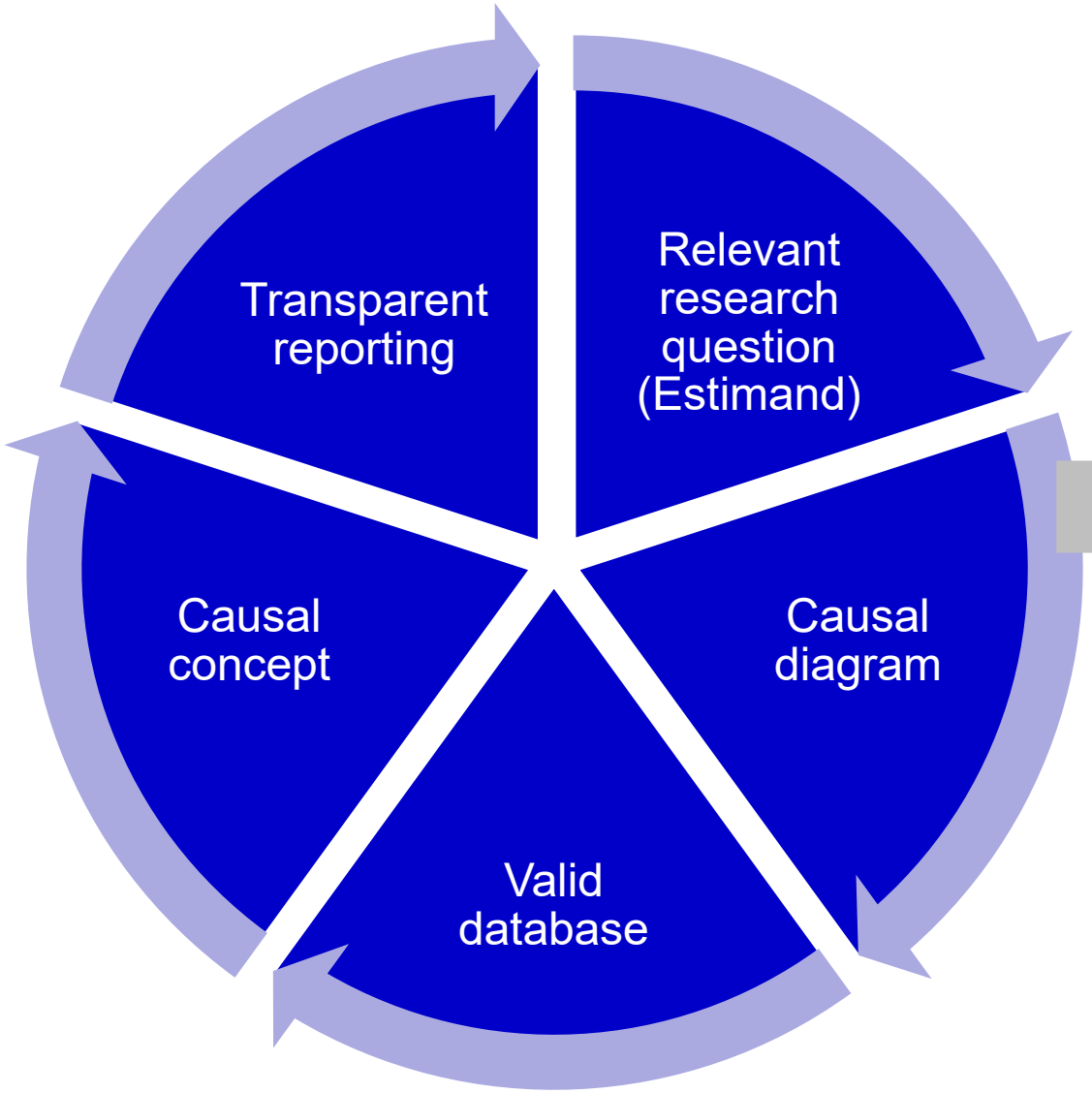
Study design and methods have a major impact on the validity of the results

Target trial emulation is a structural approach mimicking the counterfactual approach

Target trial emulation may avoid self-inflicted biases

So what?

Observational Data Analysis



To Dos

Increase data quality

Increase transparency

- Publish protocol
- Transparent reporting

Increase acceptance of RWE

- Comparative analyses (RCT vs RWE)
- Education of relevant methods

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Thank You