Target trial emulation and the Importance of Alignment at Time Zero

Some Examples with Health Claims Data

Vanessa Didelez
joint work with **Malte Braitmaier**,
Claudia Börnhorst, Bianca Kollhorst,
Sarina Schwarz, Miriam Heinig, and Ulrike Haug

Leibniz Institute for Prevention Research and Epidemiology – BIPS

Background

Commentary: Should the analysis of observational data always be preceded by specifying a target experimental trial?

Vanessa Didelez

School of Mathematics, University of Bristol,

Accepted 5 October 2015

The recent paper by Cain *et al.*[1] deals with t
practical question of when to switch antiretro
for HIV-infected individuals after virolo

International Journal of Epidemiology, 2016, 2049–2051
doi: 10.1093/ije/dyw032
Advance Access Publication Date: 10 April 2016

Using observational data to emulate a randomized trial of dynamic treatment-switching strategies: an application to antiretroviral therapy

FREE

Lauren E Cain ✉, Michael S Saag, Maya Petersen, Margaret T May, Suzanne M Ingle, Roger Logan, James M Robins, Sophie Abgrall, Bryan E Shepherd, Steven G Deeks ... Show more

International Journal of Epidemiology, Volume 45, Issue 6, December 2016, Pages 2038–2049, https://doi.org/10.1093/ije/dyv295

Published: 31 December 2015 **Article history** ▾

GeTTCausal!

BIPS Initiative to

- use **Ge**rman claims data
- with **T**arget **T**rial emulation
- for **Causal** inference
- to support /improve health-related decision making

Projects:

- evaluate German colonoscopy / mammography screening programs
- investigate drug safety, e.g., of antidiabetics, or during pregnancy

Outline

- Alignment at time zero
- Design-related biases – examples
  - beyond “immortal-time” and “prevalent-user” bias
- Applications: colonoscopy and mammography screening
  - Emulating sequences of trials
  - … and sustained treatments
- Outlook and conclusions

Target Trial Emulation (TTE) – Principle

(Hernán & Robins, AJE, 2016:183)

(Even or especially) with observational data:

Specify the “target trial” that would answer your research question!

- Then shape your analysis to emulate this target trial
- Techniques available for typical issues in TTE, but these are not exclusive or necessary *(Didelez, Haug, Garcia-Albeniz, 2024:Epidem)*

Target Trial Emulation (TTE) – Principle

(Hernán & Robins, AJE, 2016:183)

- Can disregard ethical, financial, practical constraints of real studies

  ⇒ Often a key point of TTE

  - Distinction: replication of existing RCTs

- Follow protocol steps of clinical trial

- Arrange analysis to mimic (**= *"emulate")*** target trial

  - Limitations of data: may need to revisit target trial and trade-off

Time-Zero Alignment

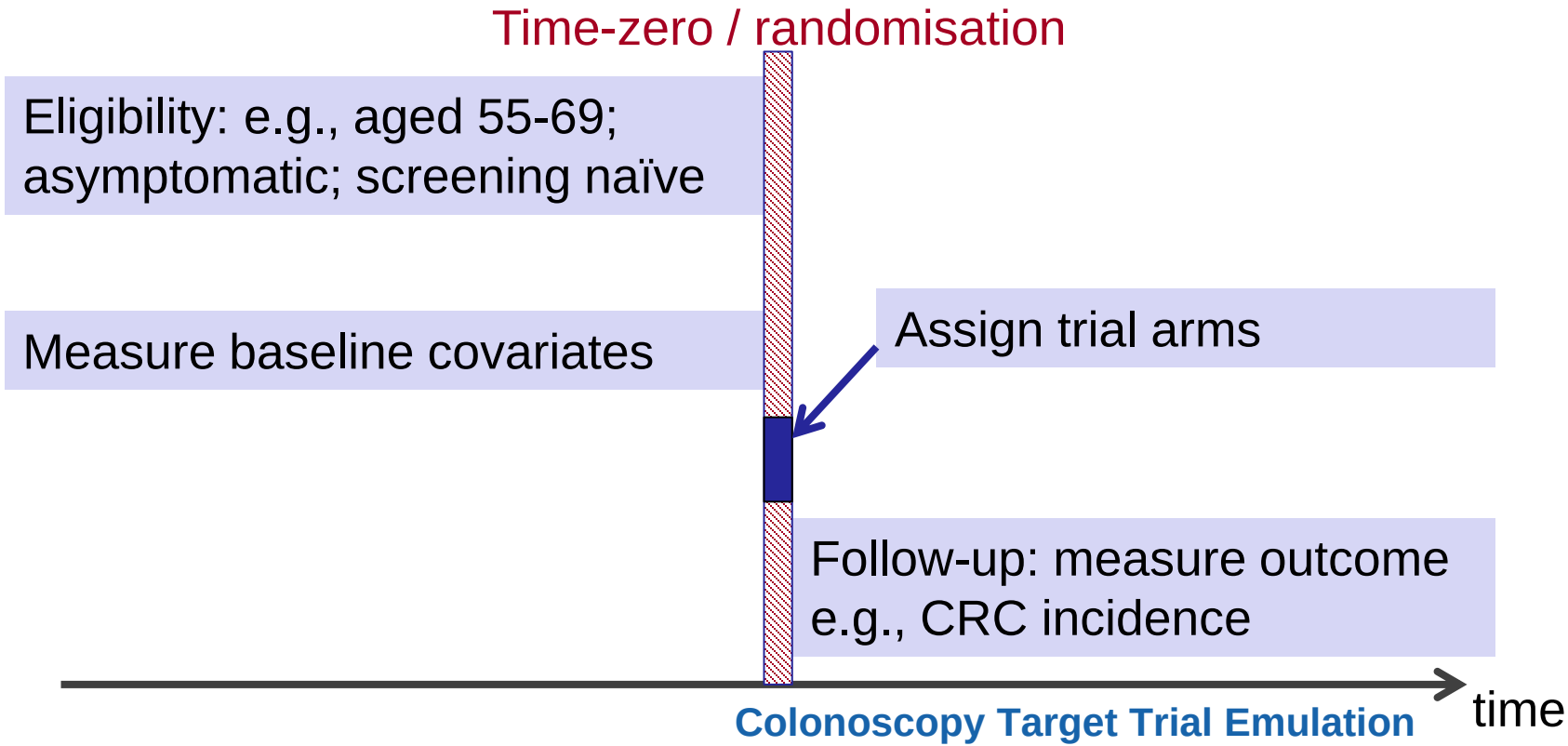
In RCTs, the following ordering is self-evident:

1. Check eligibility
   measure baseline covariates
2. Randomize into trial arms = time zero
3. Start follow-up and measure outcome

⇒ **Emulate this order even in non-randomised studies!**

Time-Zero Alignment

(Braitmaier & Didelez, 2023:PuGe)



Issues with T0-Alignment

Violations due to:

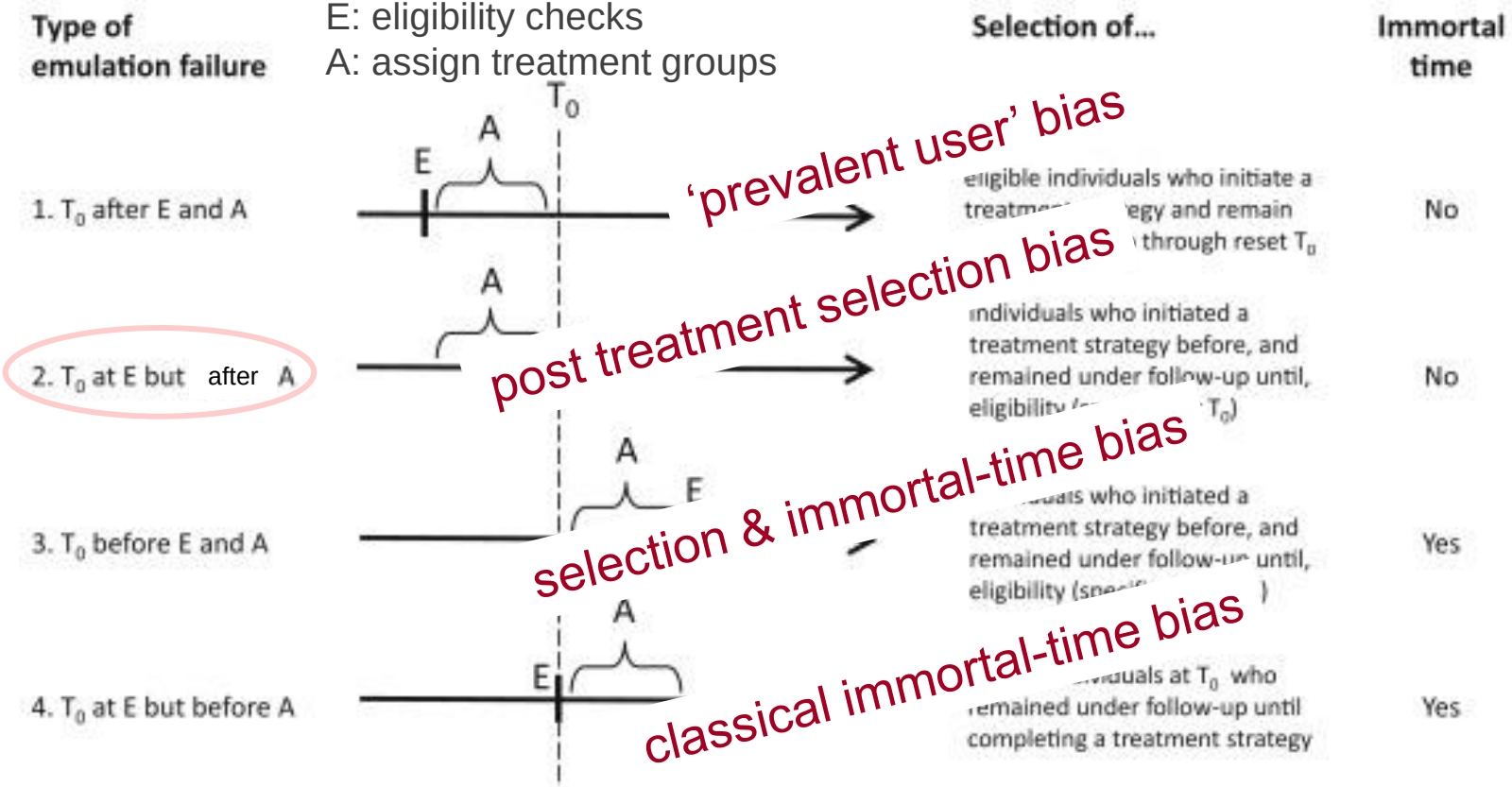
- **Bad design choices**
  - Definitions of exposures / outcomes; assessment of eligibility
- Lack of sufficiently detailed information (e.g., on timings)

- Also: **time zero not always unique**
  - Cancer screening: go when you want, no diagnosis / indication needed
  - Non-users – not always a unique “starting point”

Failure of Alignment

(Hernán et al, 2016:JClinEpi)

E: eligibility checks
A: assign treatment groups



Problematic Designs

American Journal of EPIDEMIOLOGY

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Misleading and avoidable: design-induced biases in observational studies evaluating cancer screening—the example of site-specific effectiveness of screening colonoscopy

Get access

Malte Braitmaier, Sarina Schwarz, Vanessa Didelez, Ulrike Haug

American Journal of Epidemiology, kwaf069, https://doi.org/10.1093/aje/kwaf069

Published: 01 April 2025 **Article history** ▾

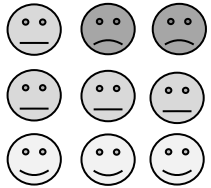
Colonoscopy: Naive Obs. Studies

Baseline questionnaire:

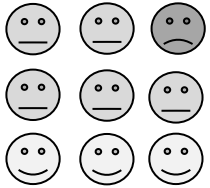
1) Colonoscopy in the past? Yes / No

2) Ever colorectal cancer (CRC)? Yes / No
   If yes → exclusion

Colonoscopy



No colonoscopy



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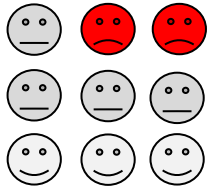

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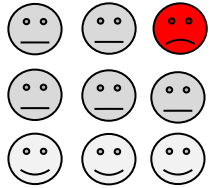
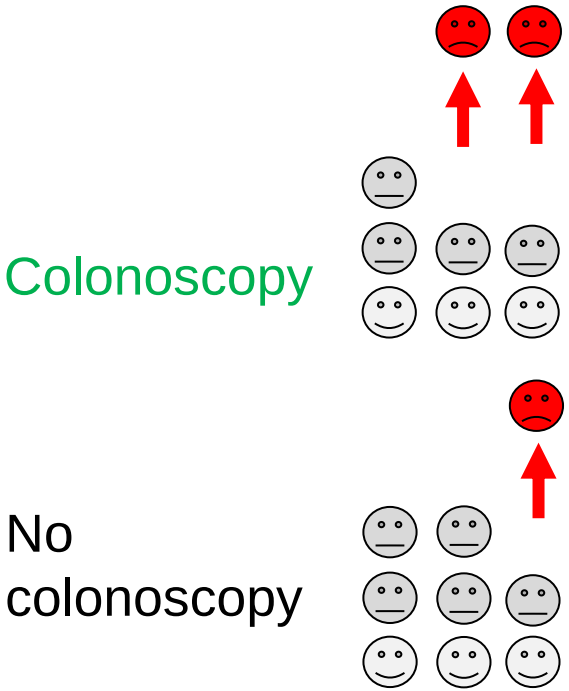


Colonoscopy: Naive Obs. Studies



Baseline questionnaire:

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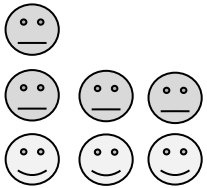
Colonoscopy: Naive Obs. Studies

Now follow-up starts

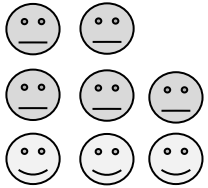
Colonoscopy



Cumulative CRC incidence

Note: Patients with CRC typically had colonoscopy in the context of CRC diagnosis

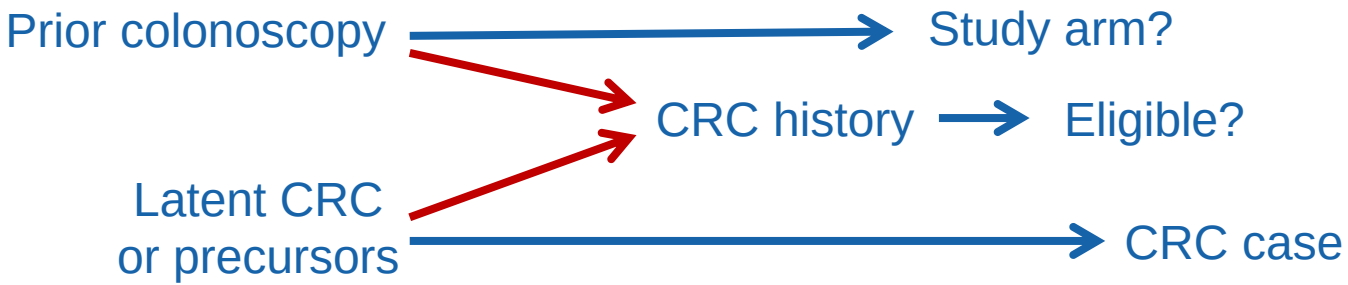
No colonoscopy



Cumulative CRC incidence

Bias: Illustration with DAG

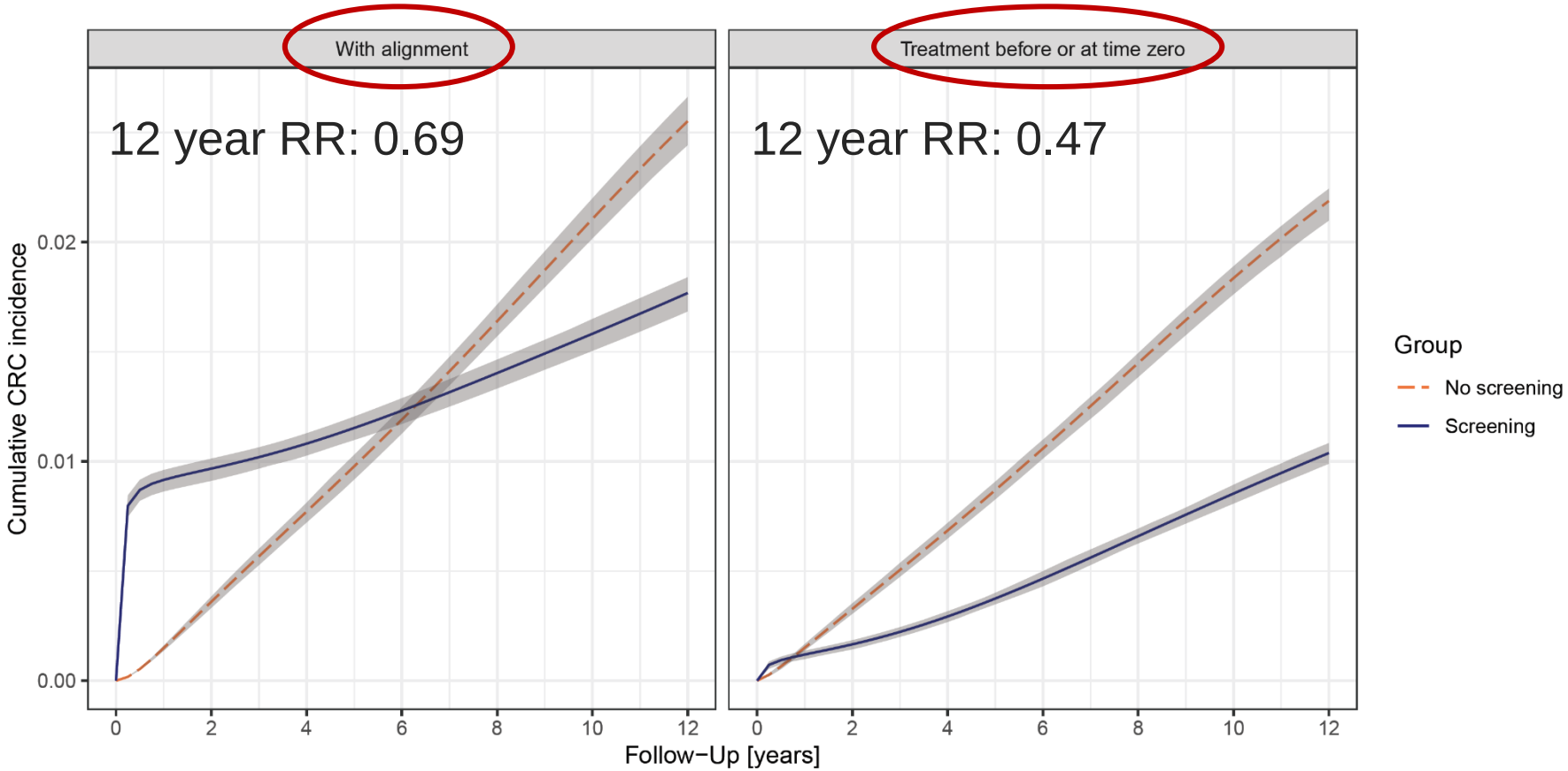
- Selection bias!



- Among those in screening arm, CRC cases will have been removed due to eligibility → 'screening' will look more beneficial

Estimated Cumulative CRC Incidences

Braitmaier et al, 2025:AJE



Case-Control Designs

Braitmaier et al, 2025:AJE

Site	Case status		Adjusted OR	
	Cases	Controls		(95% CI)[§]
Design without alignment at time zero				
Number of distal CRCs / controls	446	2,230		
Thereof exposed	36	653	0.23	(0.16-0.33)
Number of proximal CRCs / controls	302	1,510		
Thereof exposed	54	434	0.54	(0.39-0.75)
Design with alignment at time zero				
Number of distal CRCs / controls	19,081	93,650		
Thereof exposed	1,708	12,803	0.70	
Number of proximal CRCs / controls	9,916	49,065		
Thereof exposed	969	6,669	0.72	

Case-Control Designs

- In standard case-control designs (nested or not), exposure is typically assessed in period(s) *after time zero*

(see also Dickermann et al, 2020:IJE)

In our examples: issues of designs without alignment are not the same as 'immortal-time' or 'prevalent-user' bias

⇒ **Biases due to failure of T0-alignment can be subtle!**

Non-Unique Time Zero

Choosing the Baseline (Time Zero)

- Time zero always self-evident in actual RCT

- In non-randomised study *with EHR or claims data:*

⇒T0 sometimes but not always self-evident nor unique

  - Individuals might meet eligibility multiple times
  - Example: screening and non-screening

Sequence of Trials

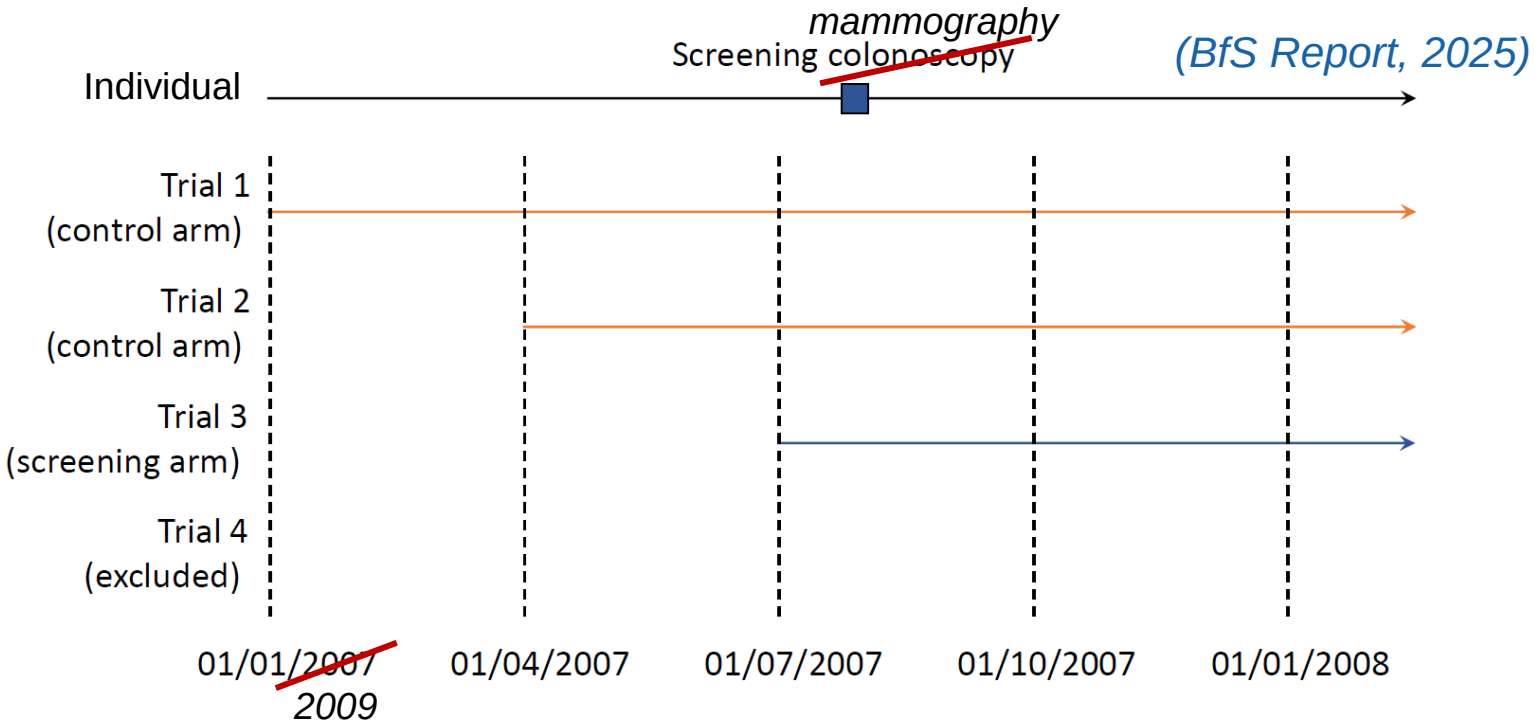
Define **(sequence of) target trials** at *multiple* ‘baselines’

- Include individuals in *every* trial for which they are eligible
  - → full use of all available information
  - → up-dated covariates at every new trial

  Statistical techniques:
  - → Pool all trials for overall result
  - → Ensure valid standard errors (sandwich / bootstrap)

Sequence of Trials

(Braitmaier et al, 2022:JClinEpi)



Screening Mammography

Unlike colonoscopy, mammography has *no preventive* effect

⇒ mortality as outcome

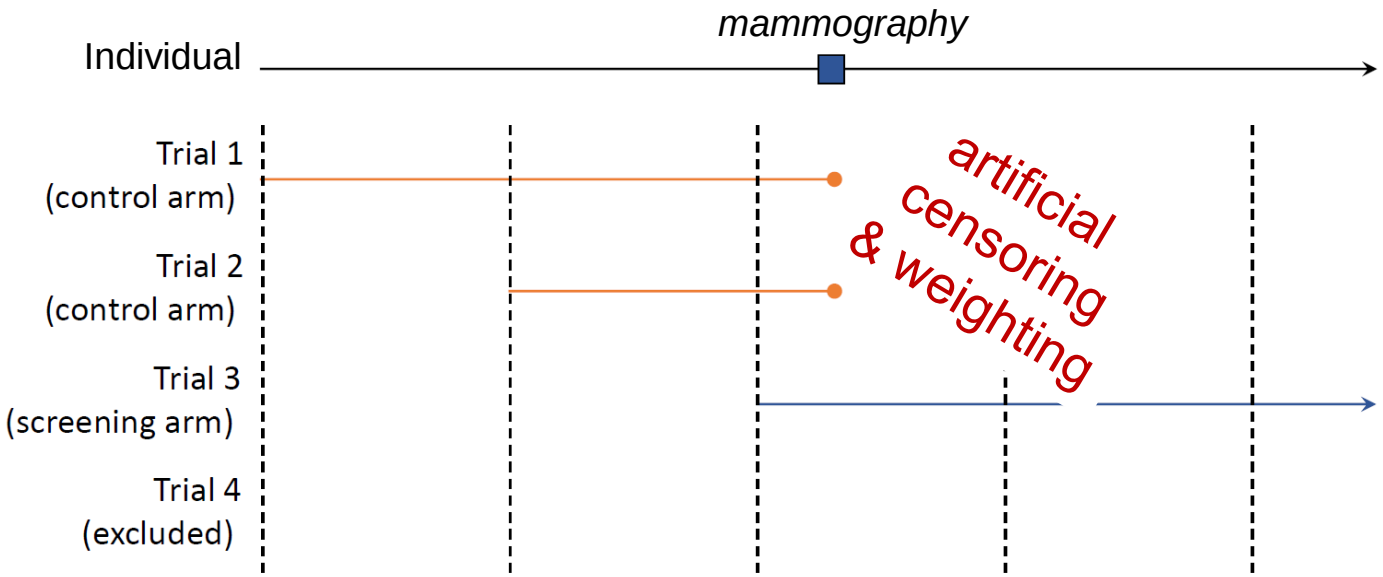
- also, mammography more frequent

Trial arms:

- Screening participation at least at T0
  vs.
- **never screening** – sustained strategy
  - at non-adherence: *artificial censoring and weighting*
  - Covariates: age, educational level, utilization of other preventive measures, menopausal hormone therapy, morbidities, indicators of unhealthy lifestyle, prior false-positive mammograms, code for family history of breast cancer

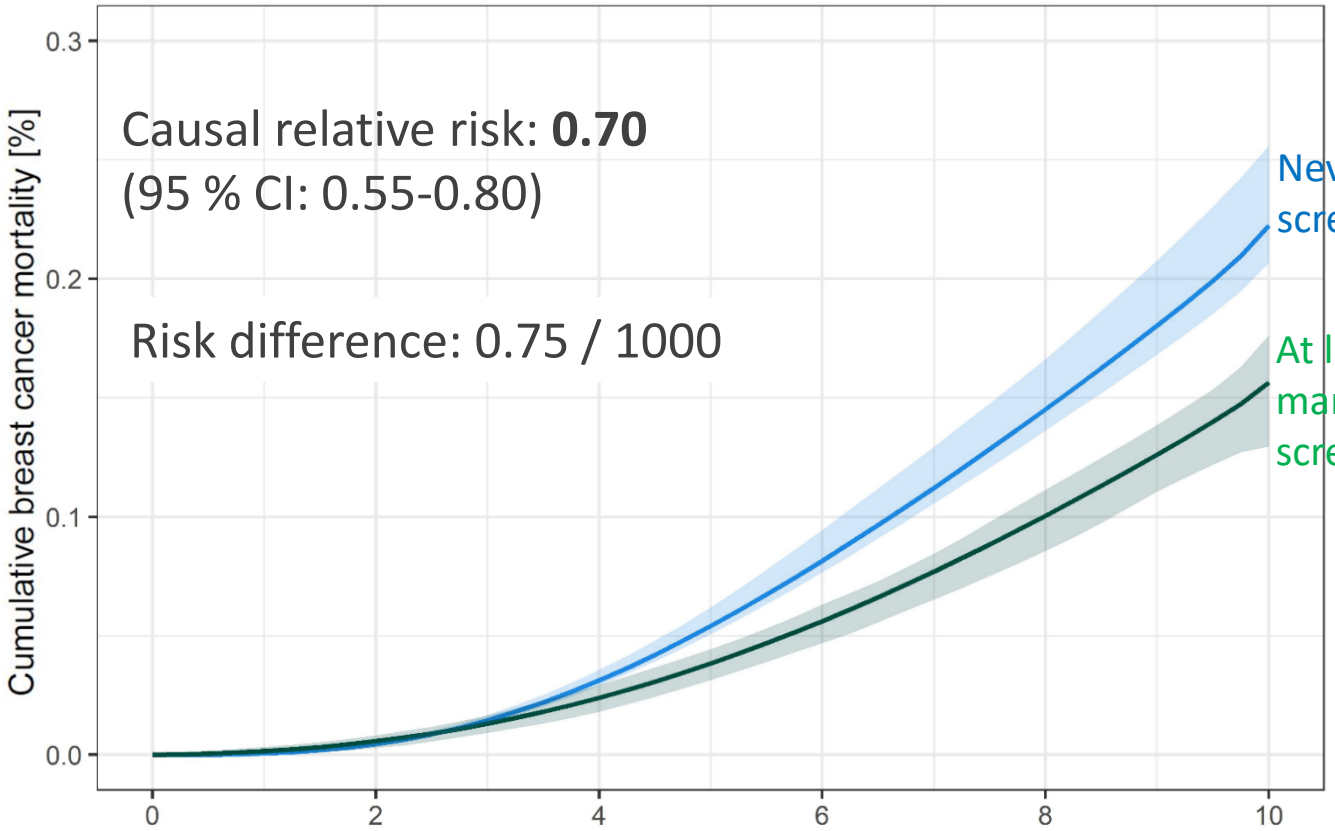
must not look into the future!

Sustained Non-Exposure



Mammography & BC Mortality

Main Results *(BfS Report, 2025)*



Further Analyses

Analyses of non-randomised & TTE studies rely on crucial structural / modelling assumptions

→ Checks and sensitivity analyses!

Mammography study:

- Triangulation:
  TTE with population-based approach and IV analysis
  - *led by University of Münster*
- Negative control (CRC) / restriction to screening-affine subgroup
  - comparable / supportive results

Conclusions

- Analysis of non-randomised studies always hard
- Unmeasured confounding always a threat
- But biases due to failure of alignment at T0 can be avoided by suitable designs
- Target trial emulation helps to
  - Ask meaningful questions
  - Avoid design-related biases
  - Guide the analysis & highlight data-related compromises
  - Keep ‘log’ of other potential sources of bias

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AOK Niedersachen
AOK Nordwest
BARMER
DAK
hkk
TK

Krebsregister
Bayerisches Krebsregister
Epidem. Krebsregister Niedersachsen
Landeskrebsregister NRW

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Thank You!

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Contact
Vanessa Didelez
Leibniz Institute for Prevention Research
and Epidemiology – BIPS
Achterstraße 30
D-28359 Bremen
didelez@leibniz-bips.de

Screening Colonoscopy TTE with GePaRD

Study protocol:

	Target trial	Emulation
Aim	Effect of screening colonoscopy on risk of incident site-specific CRC	Same
Eligibility	• 55 to 69 • Asymptomatic at BL • Screening naive at BL	Same + continuously insured for >= 3 years before BL
Screening strategies	Screening vs. no screening at baseline	Same

Screening Colonoscopy TTE with GePaRD

Study protocol:

	Target trial	Emulation
Treatment assign-ment	Randomized	Assigned to screening group, if screening in BL quarter, no screening group otherwise. Randomization emulated via BL confounder adjustment
Outcome	Time to incident CRC (any, dis-tal, proximal)	Same
Contrast	Effect of being assigned to screening	Effect of receiving screening at baseline

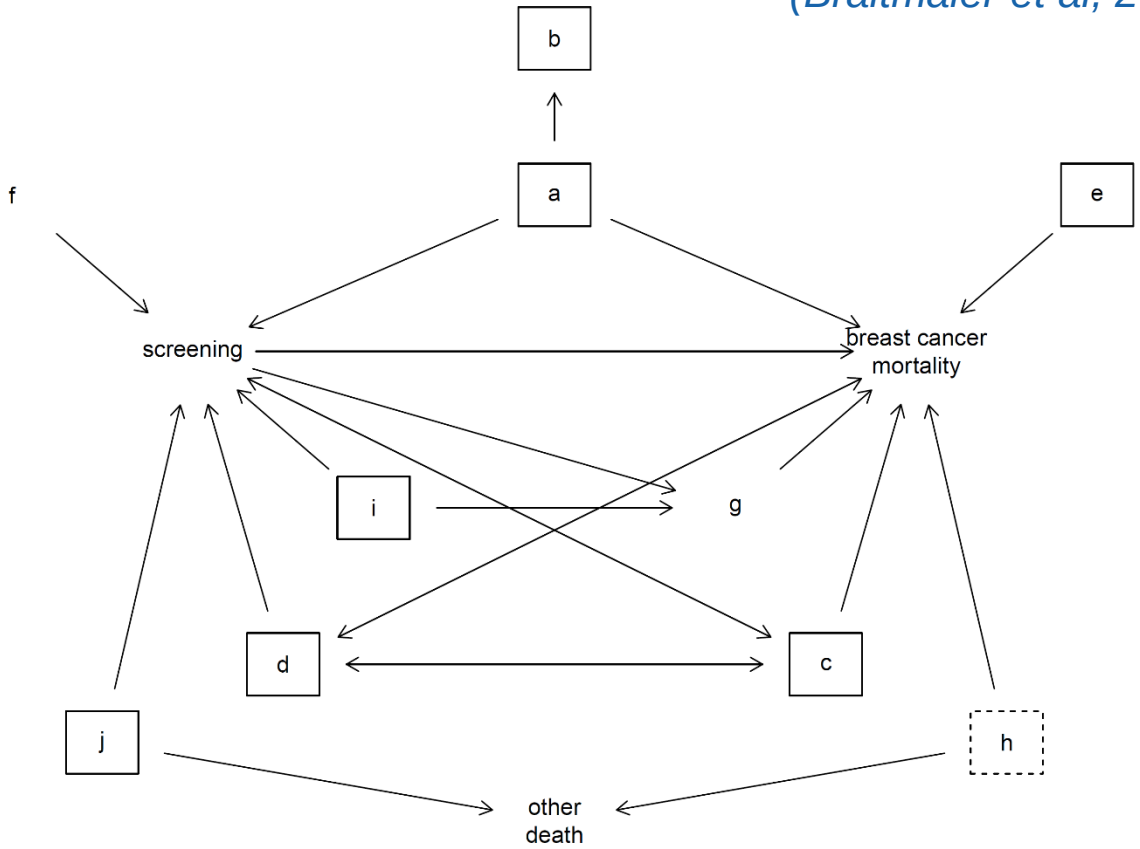
Interim Summary: Overview

(Braitmaier & Didelez, 2023:PuGe in German)

Risk for bias or other limitation	***RCT***	***Observational study using RWD***	
		with TTE	***without TTE***
Prevalent user bias	Low, treatment start at randomization	Low, treatment start aligned with time zero	High, treatment assessment may be based on information from before time zero
Immortal time bias	Low, treatment groups are defined with randomization	Low, treatment start aligned with time zero	High, treatment assessment may be based on information from after time zero
Unclear research question	Low in both designs, due to clear specification of treatment strategies		High, if exposure is not expressed as a clear (hypothetical) intervention.
Baseline confounding	Low, randomization ensures (approximate) group balance at baseline	High in both designs, can be mitigated by covariate adjustment, if observed data is sufficient	
Time-dependent confounding in per-protocol analyses [14,15]	High in all designs, when there is non- adherence; Can be mitigated by statistical adjustment (e.g. inverse probability weighting), if observed data is sufficient.		
Low generalizability and transportability	High, highly selective study population may differ substantially from target population	Depending on data source: • Registry and claims data can be informative regarding subgroups routinely excluded from RCTs • Volunteer bias may be an issue in e.g. cohort studies using primary data	
Cost and time intensive	High	Low in both designs, if existing RWD can be used	

DAG to Elicit Confounders

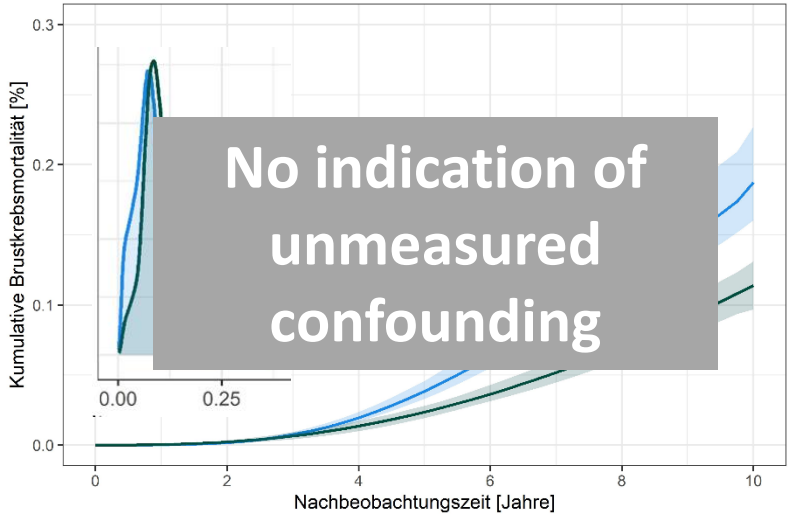
(Braitmaier et al, 2022:ClinEpi)



DAG to elicit confounders

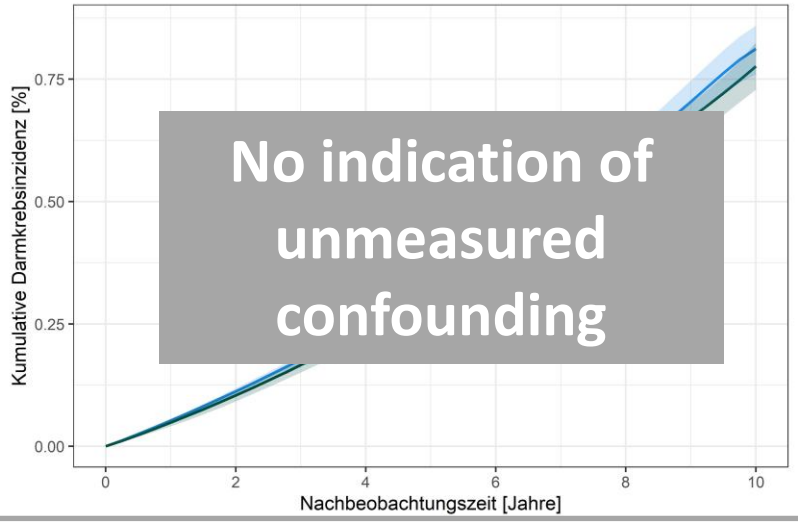
Illustration of variable groups considered for covariate adjustment and their causal connections. Note that this is a simplified graph, ignoring the longitudinal aspect of the study. A directed edge from one variable to another means that the first variable is a direct cause of the second. Screening is the exposure, breast cancer death is the outcome, and other death is a competing event. A bi-directed edge can be interpreted as presence of latent variables between the two connected variables. Variables “a” are common causes of screening and outcome. Variables “b” are proxies for those of category “a”. Variables “c” are causes of the outcome that are associated with exposure. Variables “d” are causes of the exposure that are associated with the outcome. Variables “e” are causes of the outcome that are not associated with exposure. Variables “f” are causes of the exposure that are not associated with the outcome. Variables “g” are post-screening variables that are mediators between exposure and outcome. Variables “h” have a causative effect both on the competing event and the outcome. Variables “i” are causes of exposure and mediators. Variables “j” are confounders between exposure and the competing event. Variables “f” should not be included for adjustment, as this can lead to bias-amplification in case of residual unobserved confounding. Variables “g” (e.g. treatment after screening) should not be included for adjustment, as they are on the causal path from exposure to outcome. Variables “a”, “b” (if “a” is unmeasured), “c”, “d”, “h” (only for estimating the direct effect, not for the total effect), “i”, and “j” should be included for adjustment to mitigate confounding. Variables “e” are not needed for adjustment but can be included to increase precision of estimation. The variable groups (except “f”) are not mutually exclusive, and in fact many variables will fit into more than one of these groups. An example of a covariate of the category “a” would be previous use of menopausal hormone therapy, as this is a known risk factor for breast cancer and physicians might advise women with this risk factor to attend screening. An example of a covariate of the category “j” would be presence of palliative care. An example for “d” might be educational attainment as it may affect awareness of screening and is strongly associated with direct risk factors “c” of breast cancer mortality; educational attainment can also be seen as type “b” proxy for further unmeasured confounders.

Restriction: only women with a preventive gynecological visit before baseline



No indication of unmeasured confounding

Negative control outcome: colorectal cancer incidence



No indication of unmeasured confounding