Single arm trials with external control arm

Accounting for bias

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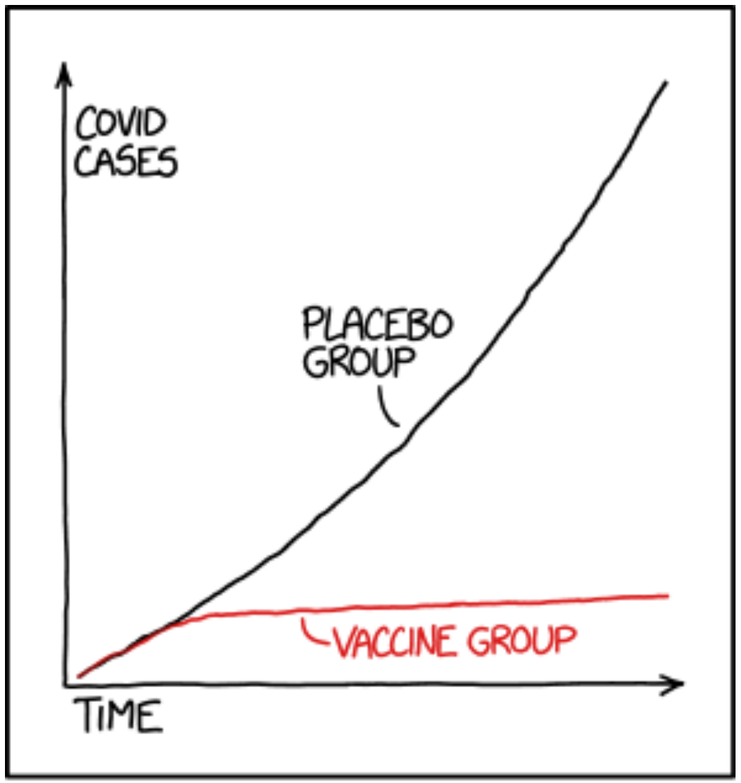
Epidemiologic study recipe

- Ethics considerations

- Design
- Data
- Statistical analyses

- Data interpretation



STATISTICS TIP: ALWAYS TRY TO GET DATA THAT'S GOOD ENOUGH THAT YOU DON'T NEED TO DO STATISTICS ON IT

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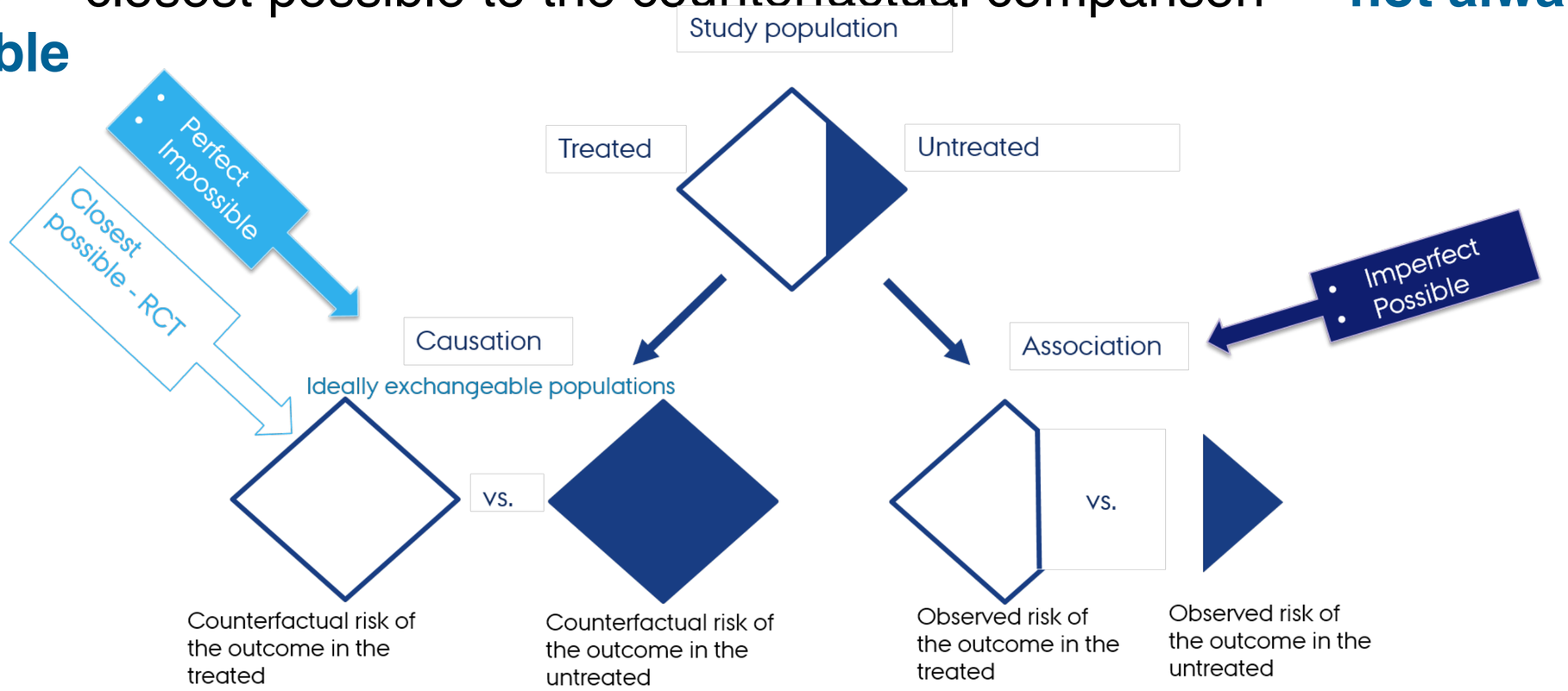
Counterfactual vs factual comparisons

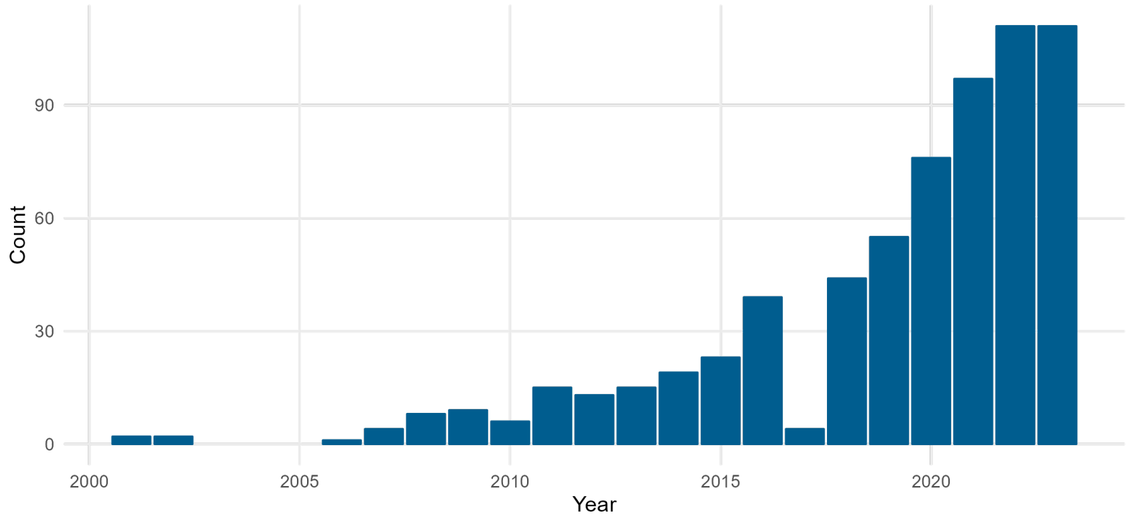
- Counterfactual comparisons of exposed and unexposed → **unbiased and impossible**
- RCTs → closest possible to the counterfactual comparison → **not always feasible**



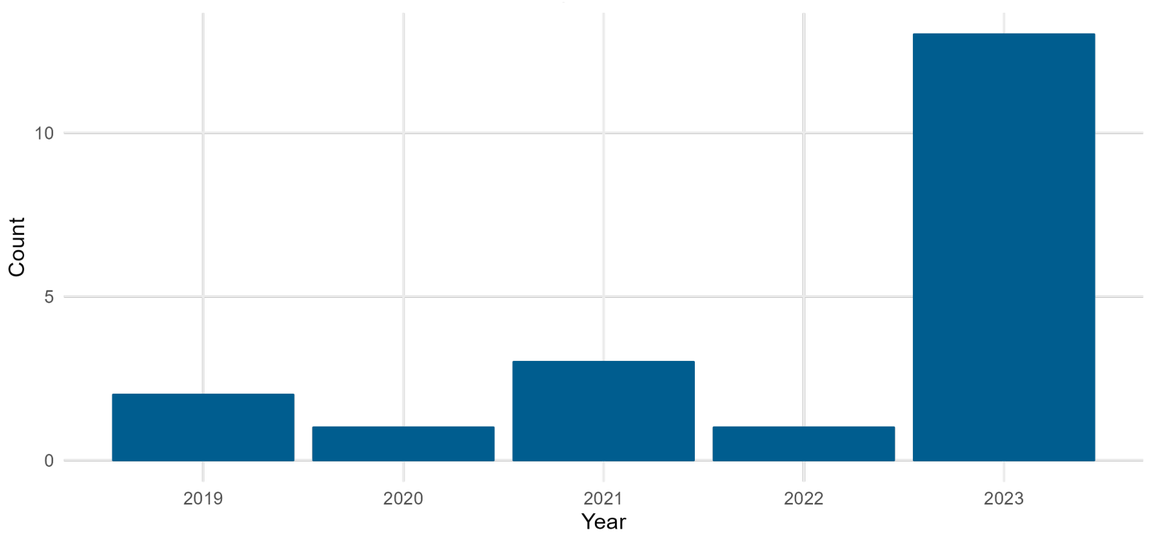
Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Increasing interest in SAT/ECA

SAT, single arm trial



ECA, external control arm



ECA, external control arm
SAT, single arm trial

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Single arm trials

- 1992-2017: accelerated approval to 64 products in haematology or oncology
  - **93** new indications
  - **53** new molecular entities
  - **72%** of evidence for initial indication was from SAT
- Selecting external comparator
- Selecting comparable patients
- Considering sample size
- Choosing historical vs contemporary data
- Establishing clear operational definitions and defining variables across cohorts

Mack C, Christian J, Brinkley E, Warren EJ, Hall M, Dreyer N. When Context Is Hard to Come By: External Comparators and How to Use Them. *Drug Inf J*. Published online November 5, 2019:216847901987867. doi:10.1177/2168479019878672

Bias as a threat to SAT validity

- Random error
  - Sampling (random) variability
  - Chance
- Systematic error (bias)
  - Selection bias (with or without colliders): internal or external validity
  - Confounding: internal validity
  - Measurement (information)/misclassification bias: internal and external validity

Single-arm trials: challenges

Bias name[1]	Bias type	Bias origin
Ascertainment bias		Data collection standards
Assessment bias		Outcome assessment is dependent on the treatment status (differential outcome misclassification)
Attrition bias		Attrition of patients; missing data due to loss-to-follow-up
Bias due to lack of pre-planning		Post trial-initiation changes in design, conduct or reporting
Bias due to regression to the mean		Patient selection based on outcome measured with error
Bias due to variability in disease history		Variability in the disease history before treatment
Calendar time bias		Changes in management of the disease and the disease course
Immortal time bias		Incorrectly defined time zero leading to advantage of one of the cohorts by design

Other; not a conventional type of the systematic error (bias) in epidemiology

[1]European Medicines Agency. Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation. Published online April 17, 2023. Accessed November 21, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf

Bias name[1]	Bias type	Bias origin
Intercurrent event bias after study entry		Failure to clearly define the main estimand(s)
Retrospective selection bias		Retrospective selection of information to use as reference
Selection bias in relation to the hypothetical control group		Patients in a SAT systematically differ from the counterfactual comparator in ways that impact their prognosis
Selection bias in relation to the target population		Patients in a SAT systematically differ from the target population in ways that impact their prognosis
Selection bias in relation to biomarker defined subgroups		Patients selected based on a predefined biomarker for targeted treatment differ in prognosis compared to the full population
Stage migration bias		The improvement of assessment methods leads to improvement in prognosis
Study bias	 	Due to different care in the trial setting, patients in a SAT have systematically different risk of the outcomes vs the target clinical environment

Other; not a conventional type of the systematic error (bias) in epidemiology

[1]European Medicines Agency. Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation. Published online April 17, 2023. Accessed November 21, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf

Bias in ECA as viewed by regulator agencies

- Multidisciplinary reviews for oncology submissions, 2014-2021

- 7 drug cases with ECAs to support efficacy claims
- 20 regulatory reviews and 29 HTA decisions

- Modest agreement on critique points
- ECAs: High impact on the decision in **7/34** total agency assessments
- **“methodological choices cannot compensate for poor quality of data”**

ECA, external control arm
HTA, health technology assessment

[1]Jaksa A, Louder A, Maksymiuk C, et al. A Comparison of Seven Oncology External Control Arm Case Studies: Critiques From Regulatory and Health Technology Assessment Agencies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2022;25(12). doi:10.1016/j.jval.2022.05.016

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Legal landscape and external comparators

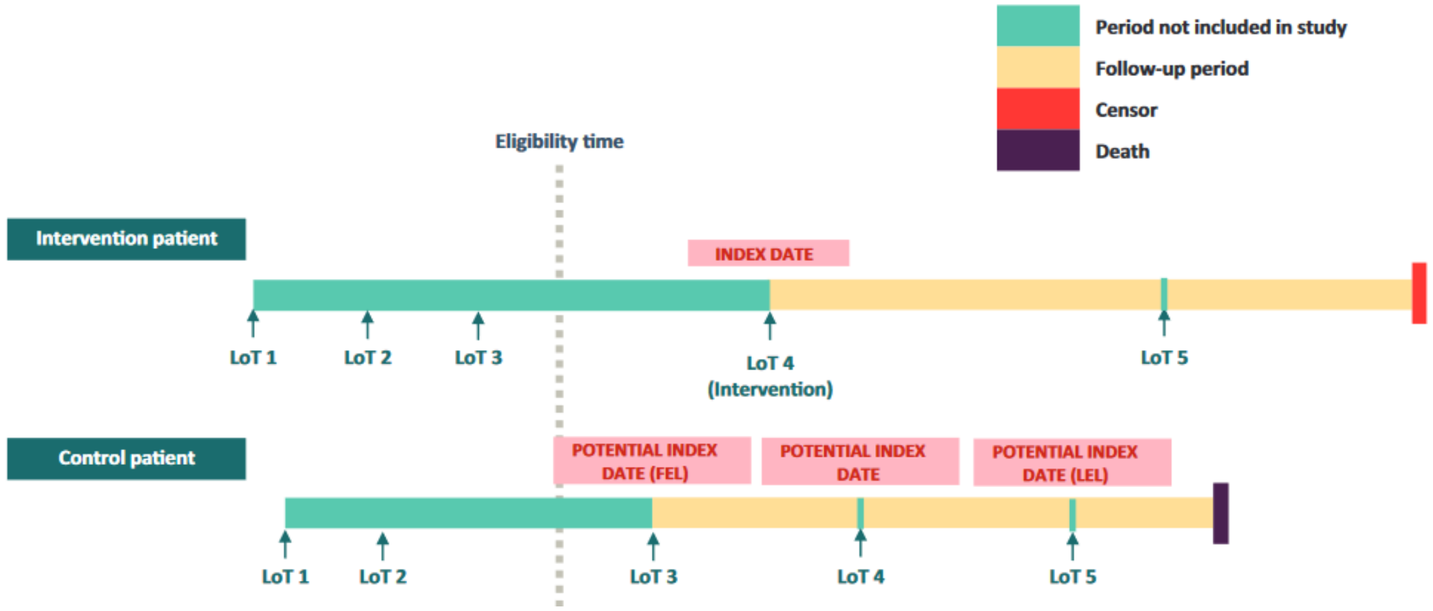
- In the Nordic countries, legal requirement is that the original subject-level data are anonymized if they need to travel for data analyzes
- Pseudonymized to **anonymized** RWD
  - (k, ε)-anonymity framework
  - Preudonimized identifiers suppressed
  - Quiasi identifiers created
  - Numerical and categorical variables in the RWD dataset transformed using noise functions
  - Metadata (record order within the table) reshuffled
- Anonymization:
  - 8% increased overall survival vs pseudonymized RWD
  - HR in adjusted analyses changed by 22% vs HR in analysis with pseudonymized RWD comparator

ECA, external control arm
RWD, real-world data

[1]Mehtälä J, Ali M, Miettinen T, et al. Utilization of anonymization techniques to create an external control arm for clinical trial data. *BMC medical research methodology*. 2023;23(1). doi:10.1186/s12874-023-02082-5

Single-arm trials with external comparator: time zero

- Target trial approach
- Time-related bias: avoiding immortal time and selecting appropriate time zero for the external comparator
  - First eligible line
  - Last eligible line
  - All lines
  - All lines (censoring)
  - Random line
- PS (SMR weighting) adjustment



From Hatswell et al.

PS, propensity score
SMR, standardized mortality ratio

Hatswell A, Deighton K, Snider J, Brookhart M, Faghmous I, Patel A. Approaches to Selecting "Time Zero" in External Control Arms with Multiple Potential Entry Points: A Simulation Study of 8 Approaches. *Medical decision making : an international journal of the Society for Medical Decision Making*. 2022;42(7). doi:10.1177/0272989X221096070

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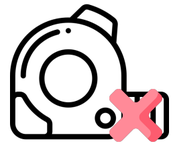
Summary

- Increasing interest in SAT with ECA from the regulators
- Reducing bias:
  - Legal landscape and planning
  - Rigor in selection, assembly, and analyses of data sources serving as ECA
  - Targeting equipoise by design and with statistical analyses
  - Attention to detail in measuring patient exposures, characteristics, and endpoints
  - ECA data ascertainment with respect to timing of treatment and clinical course of disease
  - Sensitivity analyses and triangulation
  - Quantitative bias analysis
  - Full context for regulatory-grade interpretation
- Meaningful and clinically-relevant evidence



ECA, external control arm
SAT, single arm trial

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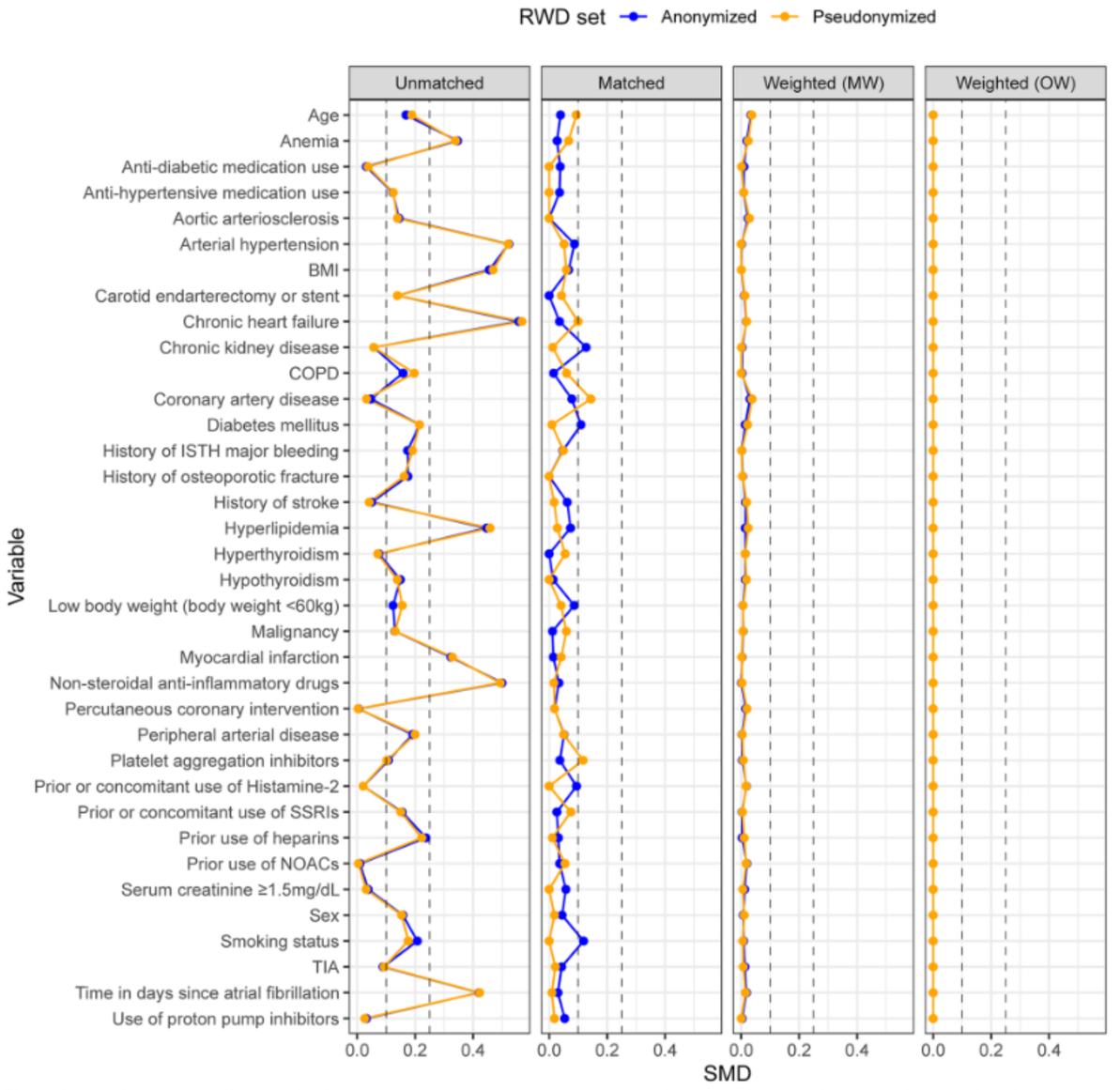

Fig. 3 Standardized mean differences for the pseudonymized and anonymized real-world and randomized clinical trial data sets. Standardized mean differences are shown for prior to matching, after matching, after matching weighting, and after overlap weighting groups. Values for the anonymized set that are not visible are approximately equal to the pseudonymized ones. BMI, body-mass index (kg/m^2); COPD, chronic obstructive pulmonary disease; MW, matching weighting; NOAC, novel oral anticoagulant; OW, overlap weighting; RWD, real-world data; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack

[1]Mehtälä J, Ali M, Miettinen T, et al. Utilization of anonymization techniques to create an external control arm for clinical trial data. *BMC medical research methodology*. 2023;23(1). doi:10.1186/s12874-023-02082-5