Marginal structural models for causal inference using observational healthcare data: best practices and case studies

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Michael Grabner and Shivani Pandya are employees of Carelon Research (a wholly owned subsidiary of Elevance Health), which conducts health services research with both internal and external funding, including a variety of private and public entities.

Michael Grabner is a stockholder of Elevance Health.

Lauren Zalla received a predoctoral fellowship from ViiV Healthcare and currently receives consulting fees from Carelon Research.

Douglas Faries is an employee and stockholder of Eli Lilly and Company.

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It’s a team effort

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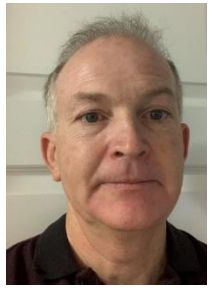

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Agenda

1. Time-varying treatments and causal inference (~10 min, Mike)

2. Key technical features of MSMs (~15 min, Lauren)

3. A payer case study (~15 min, Shivani)

4. Conclusions and areas of future research (~10 min, Doug)

Audience polls will be conducted throughout; Q&A at the end.

Learning objectives

Participants will be able to…

1. List and describe key steps of designing studies using MSMs with IPW
2. Understand the advantages and limitations of MSMs
3. Distinguish MSMs from other methods that can account for time-varying treatments
4. Describe open questions and areas for future research
5. Critique studies using MSMs

Effect estimation with time-varying treatments and confounders

When treatment affects health status which affects subsequent treatment…

- Adverse events or inadequate effectiveness can lead to discontinuation and switching treatments to more effective/cheaper/safer alternatives
- Confounding by indication (disease severity) and nonadherence are common in both RCTs and RWD

…traditional estimation approaches can be biased

- Intent to treat = ignore treatment changes
- Per protocol = remove treatment changes
- On-drug subset = remove treatment changes

A step-by-step guide to causal study design

Define estimand

1 Define research question[1]

Association
Most biases disregarded by definition[2]

Causal effect
Move to Step 2

2 Effect in whom? *(Target population)*

Average treatment effect (ATE)

ATE in the (un)treated (ATU or ATT)

Conditional ATE (subgroups)

Individual TE (ITR)

3 What kind of effect? *(Causal contrast)*

Intention-to-treat (ITT)

Per-protocol

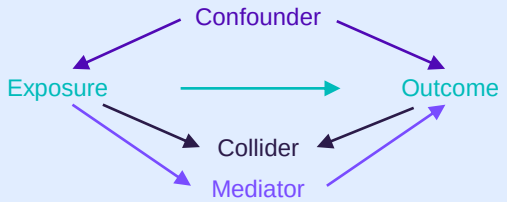
As-treated

4 Measure of effect? *(Endpoint)*

Scale: difference or ratio?

Outcome: risk, rate, hazard, odds, cost…?

5 Create directed acyclic graph (DAG)



6 Navigate the land of biases

- Measured confounding
- Unmeasured confounding
- Collider bias
- Selection bias
- Immortal time bias
- Protopathic bias (reverse causality)
- Healthy adherer effect
- Prevalent user bias
- Dependent/informed censoring
- Misclassification
- Effect modification
- Generalizability and transportability

Etc.[3]

7 Explore the land of solutions

- "Target trial" thinking[4]
- New user design with active comparator
- Choose estimator and missing data rules
- Confounder adjustment[5]
  - Time-invariant ("baseline")
    - Matching or weighting
    - Best with propensity scores
  - Time-varying
    - Survival analysis with time-varying covariates
    - Mixed models, GEE
    - MSM with IPTW (if confounders are affected by prior treatment)
  - Evaluate confounder balance
- IPCW to account for loss-to-follow-up/censoring

8 Plan QC and sensitivity analyses

- Test if model assumptions are fulfilled
- Use different estimand or estimator
- Quantitative bias analysis[6]

Acronyms: GEE, generalized estimating equations; IPC/TW, inverse probability of censoring/treatment weighting; ITR, individual treatment response; MSM, marginal structural model; TE, treatment effect

A step-by-step guide to causal study design

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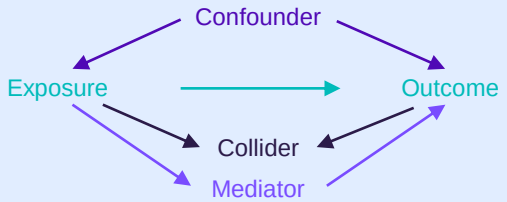

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Overview of marginal structural models

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Overview

1. What is a marginal structural model?
2. When are marginal structural models useful?
3. What steps are involved in estimating a marginal structural model?

What is a marginal structural model?

Let's say we want to estimate the *causal effect* of treatment $\boldsymbol{A}$ on outcome $\boldsymbol{Y}$.

Reminder: causal effects are unobservable.

They are contrasts of counterfactual variables that represent the "potential outcomes" or values of $\boldsymbol{Y}$ that we *would* observe if individuals were assigned certain values of $\boldsymbol{A}$.

What is a marginal structural model?

For example, we may be interested in estimating the “average causal effect” of treatment $\boldsymbol{A}$ on outcome $\boldsymbol{Y}$:

$$\left(\text{expected value of } \boldsymbol{Y} \text{ if everyone had received treatment } \boldsymbol{A = 1}\right) - \left(\text{expected value of } \boldsymbol{Y} \text{ if everyone had received treatment } \boldsymbol{A = 0}\right)$$

These are summaries of the *marginal* distribution of the potential outcomes of $\boldsymbol{Y}$ under two different treatment plans. *Breskin, Cole and Westreich Epidemiol. 2018*

→ MSMs model the marginal distribution of the potential outcomes of $\boldsymbol{Y}$.

What is a marginal structural model?

Note: Many different causal parameters can be estimated using MSMs.

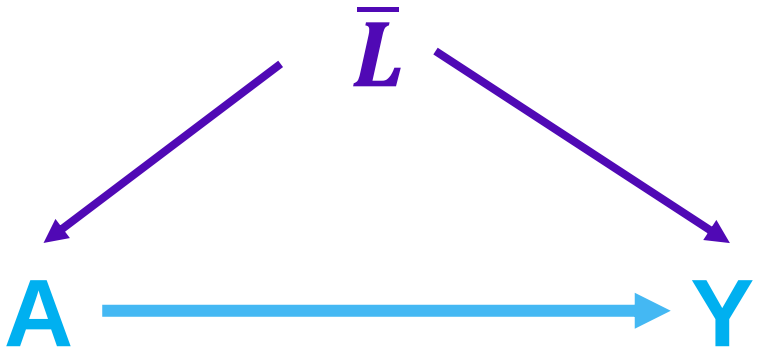
- average treatment effect
- average effect of treatment among the treated
- “population impact” of treatment
- effects of probabilistic or dynamic treatment plans
- effect of treatment on disparity
- etc.

What is a marginal structural model?

Why do we need to model the potential outcomes of $\boldsymbol{Y}$?

Because in observational data, $\boldsymbol{A}$ is not randomly assigned.

The effect of $\boldsymbol{A}$ on $\boldsymbol{Y}$ is confounded by $\overline{\boldsymbol{L}}$:



What is a marginal structural model?

Under the assumption of conditional exchangeability (a.k.a. no unmeasured confounding), the potential outcomes of $\boldsymbol{Y}$ are independent of treatment $\boldsymbol{A}$ *conditional on confounders* $\bar{\boldsymbol{L}}$**.**

By appropriately accounting for the confounders $\bar{\mathbf{L}}$, we can estimate the causal effect of $\boldsymbol{A}$ on $\boldsymbol{Y}$.

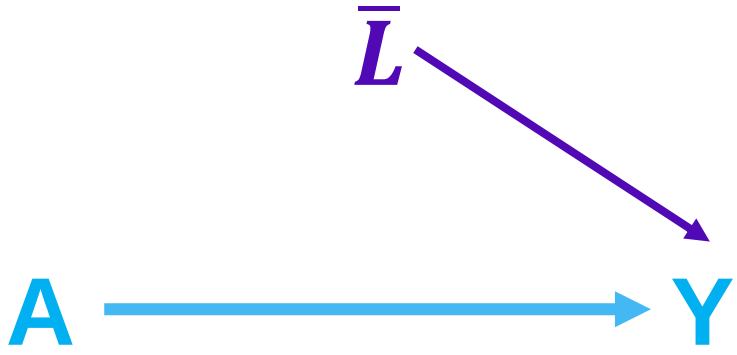
→ **How?** One approach is to use inverse probability-weighted MSMs.

What is a marginal structural model?

- First, each individual is weighted by the inverse of the probability of receiving the treatment that he or she actually received, conditional on $\bar{L}$:

$$\frac{1}{\Pr[A=1|\bar{L}]} \text{ or } \frac{1}{\Pr[A=0|\bar{L}]}$$

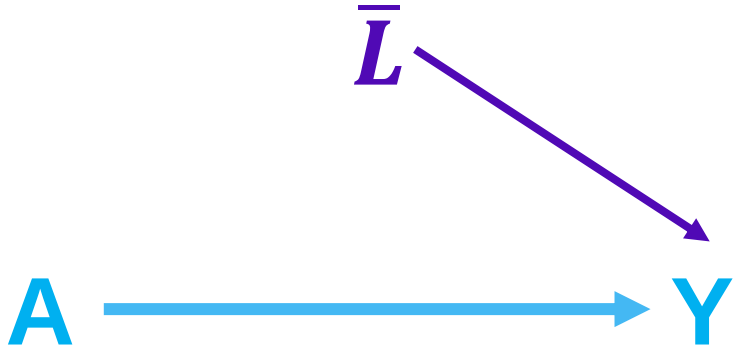
- Weighting creates a *pseudo-population* in which $\bar{L}$ is statistically independent from A:



What is a marginal structural model?

- We can estimate the marginal distribution of the potential outcomes of $\boldsymbol{Y}$ from the observed outcomes in the pseudo-population, in which $\overline{\boldsymbol{L}}$ is no longer a confounder because it is statistically independent from $\boldsymbol{A}$.

- Importantly, weighting preserves the association between $\overline{\boldsymbol{L}}$ and $\boldsymbol{Y}$.



When are marginal structural models useful?

- MSMs were introduced by Robins, Hernán and Brumback in 2000.

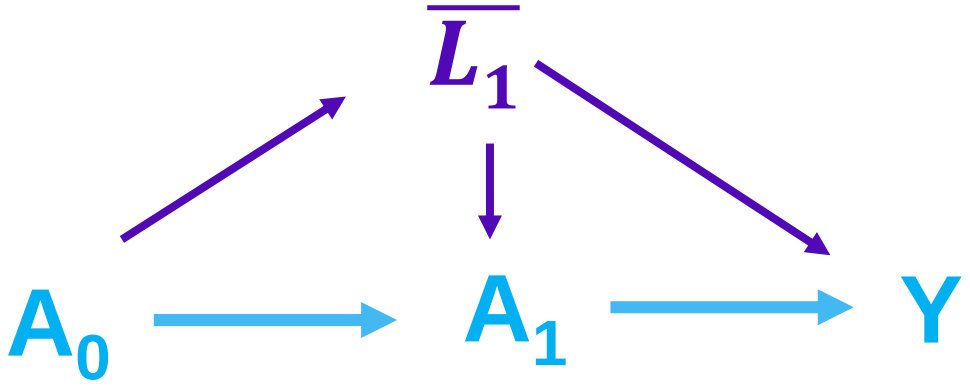
  Robins JM, Hernán MÁ, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11(5):550–60.

  Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11(5):561–70.

- MSMs were developed to address the problem of time-varying confounding.

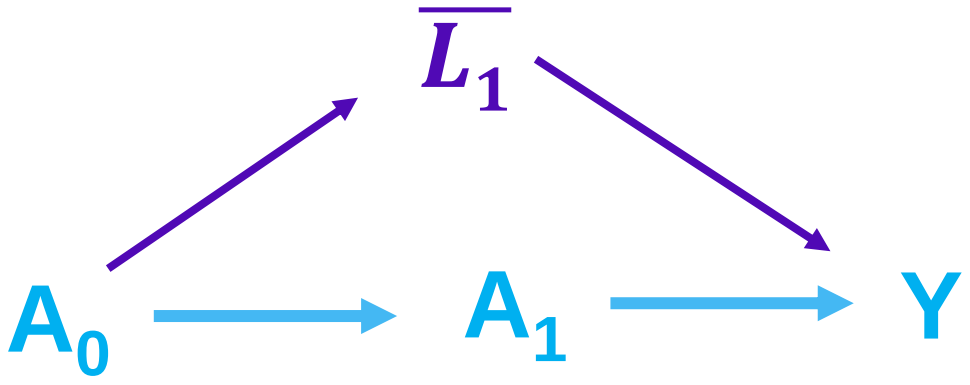
When are marginal structural models useful?

- A time-varying treatment A_k may affect time-varying covariates $\bar{L}_k$, which are confounders of the effect of A_k on Y.
- This is common in health outcomes research due to "confounding by indication." At any time k, the probability that a patient receives treatment A depends on her symptoms $\bar{L}$, which are predictors of outcome Y.



When are marginal structural models useful?

- The problem is that the confounders $\bar{L}$ are *also* affected by the patient's prior treatment history, so part of the effect of A_k on Y is <u>through</u> $\bar{L}_k$.
- Traditional regression adjustment is not appropriate in this setting.
- MSMs account for time-varying confounding while preserving the effect of A_k on Y through $\bar{L}_k$.



When are marginal structural models useful?

- MSMs are also useful in the time-fixed setting.
- Especially:
  - when *marginal effect estimates* are of interest
  - when it is necessary to account for *multiple sources of bias* and/or *generalize study results*

When are marginal structural models useful?

- Traditional regression models estimate covariate-conditional parameters.
- → The stratum-specific effect of A on Y averaged across strata of $\bar{L}$.
- MSMs are often used to estimate marginal parameters – i.e., effect estimates that generalize to the target population as a whole.
- They are useful for answering questions about the population impact of treatments or interventions.

When are marginal structural models useful?

- MSMs offer a unified analytic approach to accounting for multiple sources of bias and generalizing study results.
- They can incorporate weights for informative censoring, selection bias, missing data, and generalizability.
- “Auxiliary” variables can also be included in the weights to improve precision.

Cole and Hernan *Am J Epidemiol* 2008; Seaman and White *Stat Methods Med Res* 2013; Lesko et al. *Epidemiol* 2017; Zalla et al. *Ann Epidemiol* 2022

What steps are involved in estimating a marginal structural model?

1. Define a parameter of interest that can be identified by the parameter(s) of a marginal structural model.
2. Correctly specify the model for the weights.
3. Correctly specify the outcome model.
4. Estimate a confidence interval using an appropriate variance estimator.

1. Define a parameter of interest that can be identified by the parameter(s) of an MSM.

Example Question: What is the causal effect of antiretroviral therapy (ART) on mortality among people diagnosed with HIV?

What is the specific parameter (i.e., estimand) of interest?

It should include the following elements:

(1) target population (person, place, time)

(2) outcome measure (proportion? risk? rate? odds? hazard? of what?)

(3) causal contrast (what treatment conditions are being compared? on the difference or ratio scale?)

1. Define a parameter of interest that can be identified by the parameter(s) of an MSM.

Example Question: What is the causal effect of antiretroviral therapy (ART) on mortality among people diagnosed with HIV?

One of many possible estimands:

Difference in the proportion of US adults who would die within 5 years of receiving an HIV diagnosis in 1996 if all were prescribed ART on the date of diagnosis compared with if none were ever prescribed ART.

target population + outcome measure + causal contrast

1. Define a parameter of interest that can be identified by the parameter(s) of an MSM.

In the case of time-varying treatments, there are *many, many* possible causal contrasts.

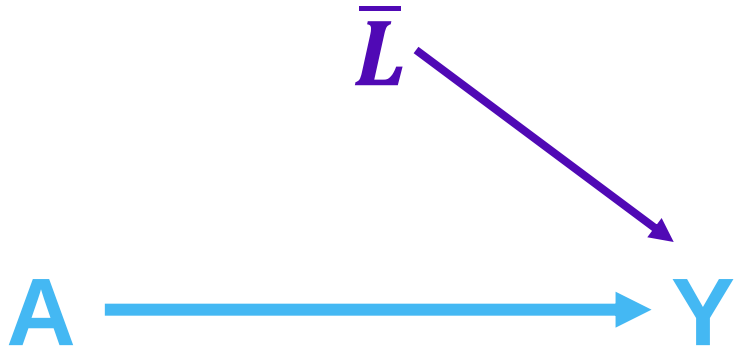
The treatment conditions being compared may be static (fixed at the study origin) or dynamic (conditional on time-updated treatment and covariates).

To choose a causal contrast of interest, it may help to think about the target trial that you would conduct if you had unlimited resources and the ability to randomize people to “treatment” and “control” arms.

1. Define a parameter of interest that can be identified by the parameter(s) of an MSM.

To have a causal interpretation, the parameter(s) of interest must be identified.*

What set of covariates are needed to satisfy the conditional exchangeability assumption (i.e., to remove the arrow from $\bar{L}$ to A)?



*Causal identification requires (1) conditional exchangeability with (2) positivity, and (3) causal consistency (i.e., "SUTVA"). See Hernan and Robins, *What If* (2023).

2. Correctly specify the model for the weights.

Typically, we use a logistic regression model to estimate $\mathbf{Pr}[\boldsymbol{A = 1}|\bar{\boldsymbol{L}}]$.

Exposed individuals are weighted by $\frac{1}{\mathbf{Pr}[\boldsymbol{A=1}|\bar{\boldsymbol{L}}]}$ and unexposed individuals are weighted by $\frac{1}{1-\boldsymbol{Pr}[\boldsymbol{A=1}|\bar{\boldsymbol{L}}]}$. In the weighted population, there is no association between A and $\bar{L}$.

Tip: Try to be as flexible as possible (using splines, indicator variables, interaction terms, etc.)

2. Correctly specify the model for the weights.

We may stabilize the weights by including the marginal probability of exposure in the numerator: $\frac{\Pr[A=1]}{\boldsymbol{Pr[A=1|\bar{L}]}}$.

This reduces the variance of the weights and may improve the precision of the outcome model.

The mean of the stabilized weights should be 1, and they should sum to N.

Technical Note: If baseline confounders are included in the numerator to further reduce the variance, they should also be included in the outcome model. This changes the estimand from *marginal* to *conditional.*

2. Correctly specify the model for the weights.

Extreme weights may indicate violations or near-violations of positivity.

→ Consider alternative model specifications and/or truncate extreme weights.

Repeat this step as needed to create weights that account for informative censoring, missing data, selection bias, etc.

Simply multiply all the weights together before proceeding to the next step.

→ e.g., $\pi_{final} = \pi_{treatment} * \pi_{censoring} * \pi_{selection}$

3. Correctly specify the outcome model.

Use an “outcome model” to estimate the parameter(s) of the MSM.

We estimate the outcome model in the pseudo-population.

For example, we can use a weighted linear regression model to estimate the causal risk difference capturing the average causal effect of binary treatment A on binary outcome Y.

We often estimate the outcome model using generalized estimating equations with an independent working correlation (why? see next slide…)

4. Estimate a confidence interval using an appropriate variance estimator.

Weighting induces correlation between individuals in the pseudo-population.

If we fail to account for this artificial clustering of outcomes in the pseudo-population, our confidence intervals will be too narrow (i.e., coverage <95%).

<u>Options:</u>

1. nonparametric bootstrap

2. robust variance estimator (e.g., generalized estimating equations with independent working correlation)

    → this method is *conservative* (slightly overestimates the variance)

There are many approaches to estimating MSMs…

They rely on the same identification assumptions, but different modeling assumptions.

- inverse probability weighting → models the exposure mechanism

-g-formula → models the outcome distribution

Doubly-robust estimators can help protect against model misspecification:

-targeted minimum loss-based estimator (TMLE)

-augmented inverse probability weighting (AIPW)

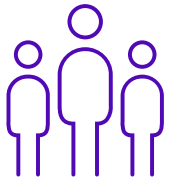
A PBM case study evaluating the causal impact of maintenance medication adherence on outcomes among patients with chronic obstructive pulmonary disease

Shivani Pandya, MS

Associate Research Director, Pharmacy Economics

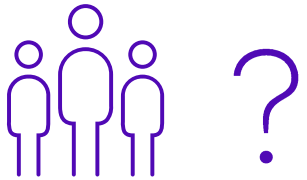
Carelon Research

Background



Inhaled maintenance medications are the standard of care for many patients with COPD[1]

Prior evidence indicates poor adherence is associated with increased inpatient admissions and total cost[2-4]



As the adherence and outcomes were measured in the same period, less is known of the causal impact of adherence on survival and other outcomes

Objective: Assess causal effect of adherence on outcomes to support pharmacy payers' interventions

[1]Global Initiative for Chronic Obstructive Lung Disease 2018. https://goldcopd.org/. Accessed 24 February 2021.
[2]Yu AP, Guérin A, Ponce de Leon D, et al. *J Med Econ*. 2011;14(4):486-496.
[3]Mannino D, Bogart M, Wu B, et al. *Respir Med*. 2022;197:106807.
[4]Davis JR, Wu B, Kern DM, et al. *Am Health Drug Benefits*. 2017;10(2):92-102

Study design

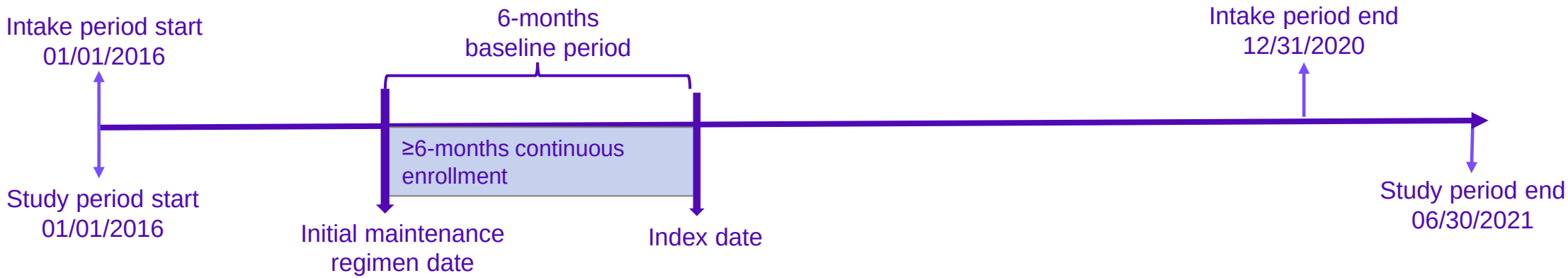
Data Source

- Healthcare Integrated Research Database (HIRD®)
- Medical and pharmacy claims data linked with mortality data

Cohort

- Retrospective, observational study design
- Patients with COPD aged ≥40 years with ≥1 maintenance regimen and ≥6 months follow-up

Figure 1. Study design overview



Notes:
Intake period was defined as the time period from 01/01/2016 – 12/31/2020 to examine the evidence of ≥1 inhaled maintenance medication regimen.
The date of the first fill of inhaled maintenance medication was defined as the initial maintenance regimen date.
Index date was defined as the date 6 months after the initiation of first maintenance therapy.

Study design

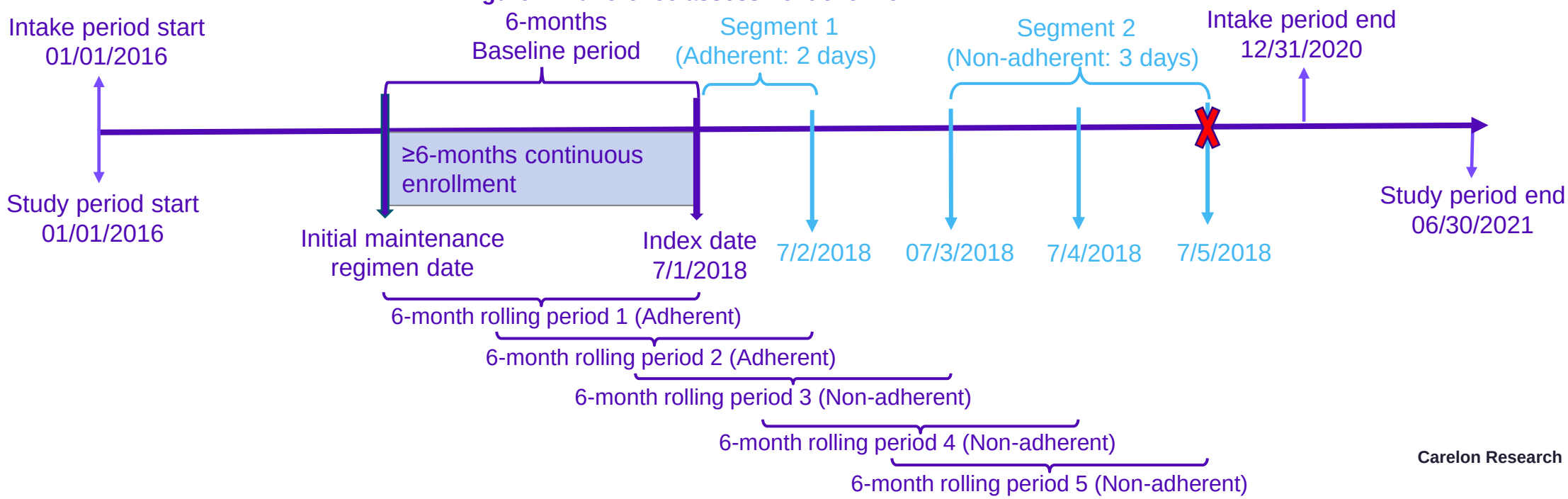
Exposure

- Adherence estimated based on proportion of days covered by the full COPD regimen on a daily rolling basis; PDC ≥80% regarded as adherent – As Treated
- Discrete segments were created based on patients' rolling adherence status until end of follow-up

Outcome

- All outcomes were evaluated during each segment
- Clinical events: All-cause mortality, all-cause and COPD-related hospitalizations and emergency room visits
- Economic outcomes: All-cause and COPD-related medical, pharmacy and total costs

Figure 2. Adherence assessment overview



Study design

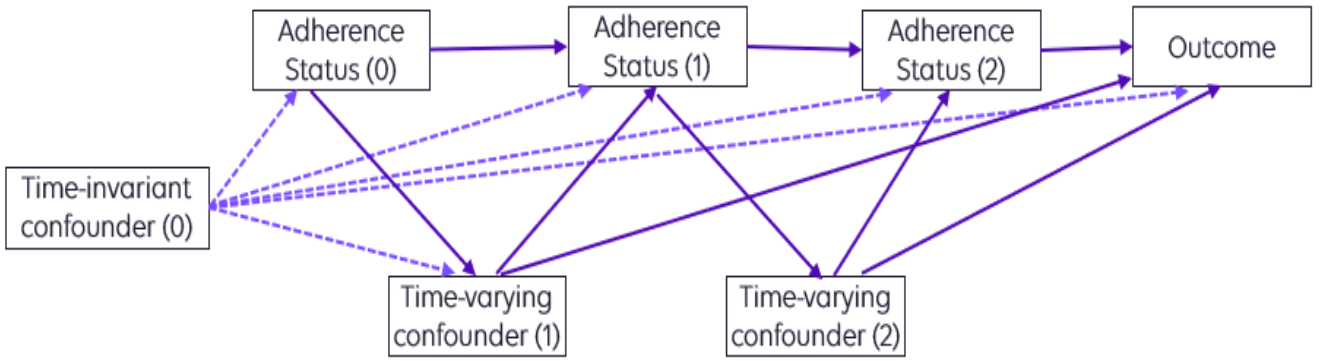
Confounders

Measured confounding

- Time-invariant confounders: 6 months pre-initial treatment
    - Age, sex, region, plan and payor type, initial regimen, Quan Charlson comorbidity index, symptom burden, all-cause and COPD-related resource use and cost metrics
- Time-varying confounders: 6-months pre-segment start
    - Year of segment start, seasonality, rescue medication fill rate, antibiotic use, oxygen use, pulmonology visit, other medication use, exacerbation rate, all-cause and COPD-related resource use and cost

Assumption of no unmeasured confounding

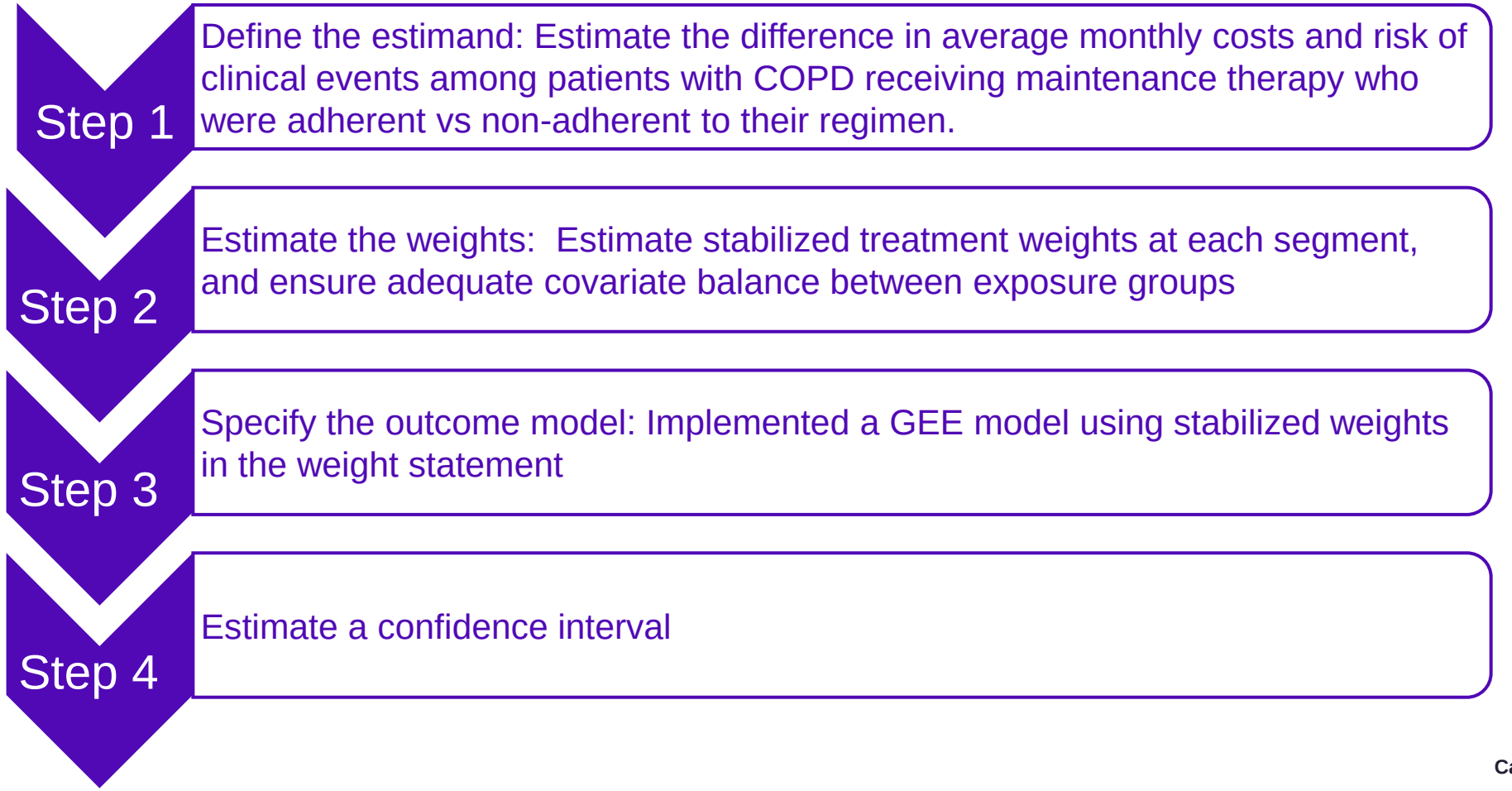
Figure 3. Direct Acyclic Graph (DAG)



Notes: This figure demonstrates the assumed relationship between adherence and influential patient factors (time varying and invarying) at every segment and its ultimate influence on outcomes. This figure is for illustration purposes only (the study allowed for up to 20 time segments over an average follow-up period of 22 months)

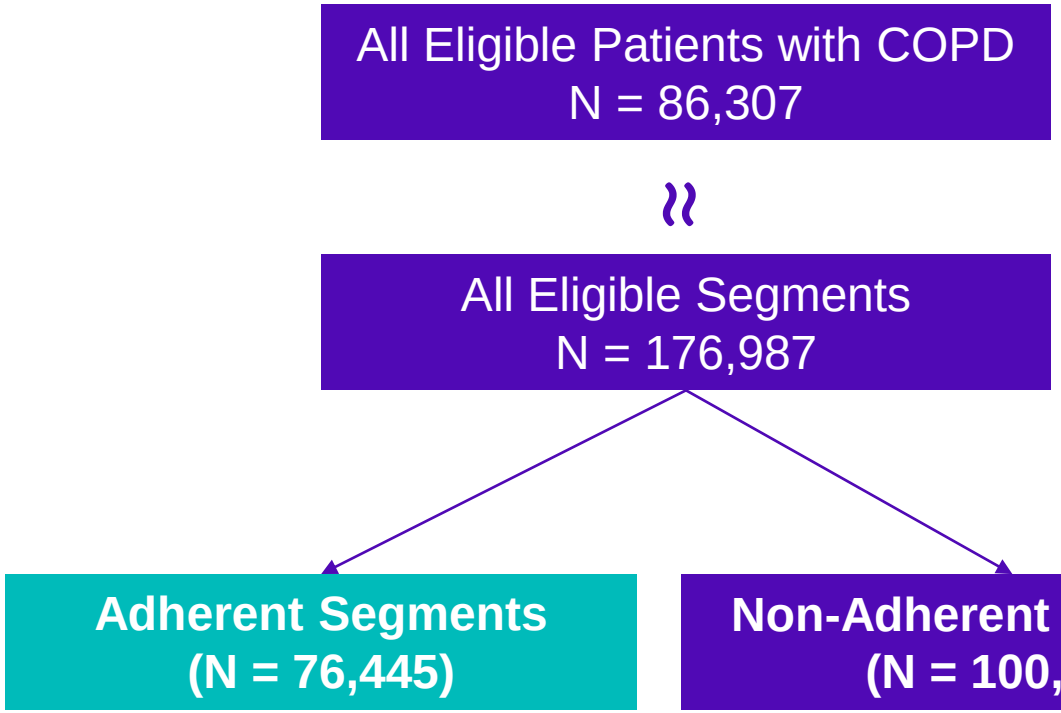
Analytic methodology

Marginal structural models:[1-2] multi-step models to assess causal effect of adherence on outcomes in the presence of measured time-varying and invariant confounders



Nearly 40% patients switched between adherence and non-adherence during follow-up

Figure 4. Patient and Segment Identification



- No. of segments per patient
  - Mean (SD) = 2 (1.9)
- Duration of segment
  - Mean (SD) = 11 (12.6) months

S Pandya et al. Evaluating the impact of maintenance medications on clinical and economic outcomes among patients with chronic obstructive pulmonary disease: a causal inference approach. 2023 Annual AMCP Meeting, San Antonio, TX.

Key characteristics balanced after IPW

Table 1: Key Demographic and Clinical Characteristics After IPW

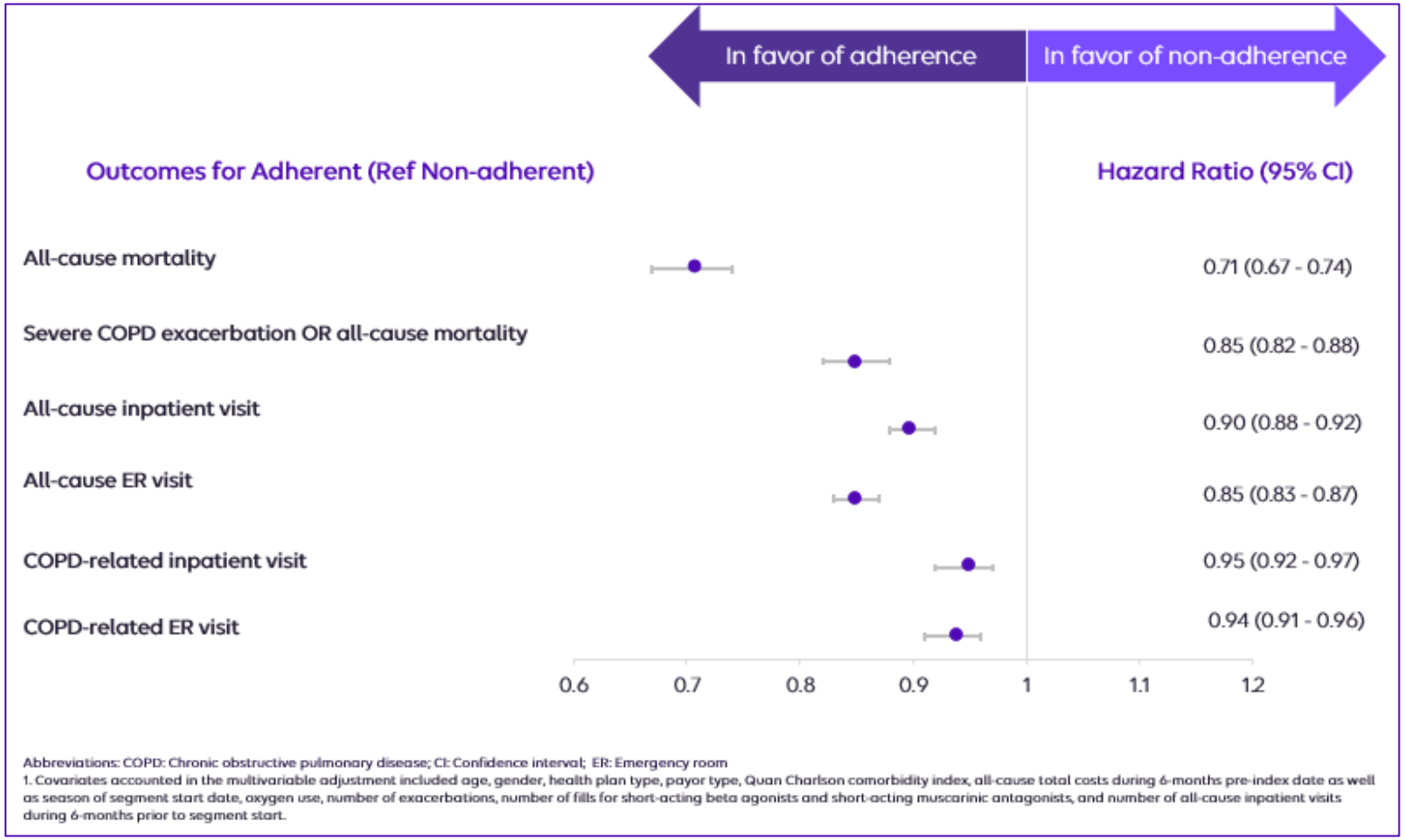
Key characteristics	Std. diff1
Time Invariant characteristics[2]	
Age (in years), mean ± SD,	1.0%
Female, n (%)	-0.5%
Commercial, n(%)	-0.7%
Quan-Charlson Comorbidity Index, mean ± SD	-6.2%
All-Cause total costs, mean ± SD	-2.2%
Time varying characteristics[3]	
Season of segment start date (n, %)	
Spring (Mar-May)	-0.8%
Summer (Jun-Aug)	0.9%
Autumn (Sep-Nov)	0.2%
Winter (Dec-Feb)	-0.4%
Presence of ≥ 1 claim indicating oxygen use, n (%)	0.1%
Presence of ≥ 1 pulmonology visit, n (%)	0.4%
Number of OCS fills, mean ± SD	-1.2%
Number of antibiotic fills, mean ± SD	-2.1%
Number of SABA/SAMA fills, mean ± SD	4.4%
Presence of ≥ 1 any exacerbation, n (%)	-0.9%
Number of COPD exacerbations, mean ± SD	-0.7%
Presence of ≥1 All-cause inpatient visit, n (%)	-4.5%
Number of all-cause inpatient visits, mean ± SD	-5.2%

- All analysis was conducted at adherent and non-adherent segment level
- Standardized differences (STD) were calculated at the segment level for both time varying and time invariant characteristics.
- STD<10% indicated sufficient balance in covariates between adherent and non-adherent segments

S Pandya et al. Evaluating the impact of maintenance medications on clinical and economic outcomes among patients with chronic obstructive pulmonary disease: a causal inference approach. 2023 Annual AMCP Meeting, San Antonio, TX.

Adherence to COPD regimen resulted in significant clinical benefit

Figure 5. Risk of clinical events between adherent vs non-adherent cohorts after multivariable adjustment[1]



Abbreviations: COPD: Chronic obstructive pulmonary disease; CI: Confidence interval; ER: Emergency room

1. Covariates accounted in the multivariable adjustment included age, gender, health plan type, payor type, Quan Charlson comorbidity index, all-cause total costs during 6-months pre-index date as well as season of segment start date, oxygen use, number of exacerbations, number of fills for short-acting beta agonists and short-acting muscarinic antagonists, and number of all-cause inpatient visits during 6-months prior to segment start.

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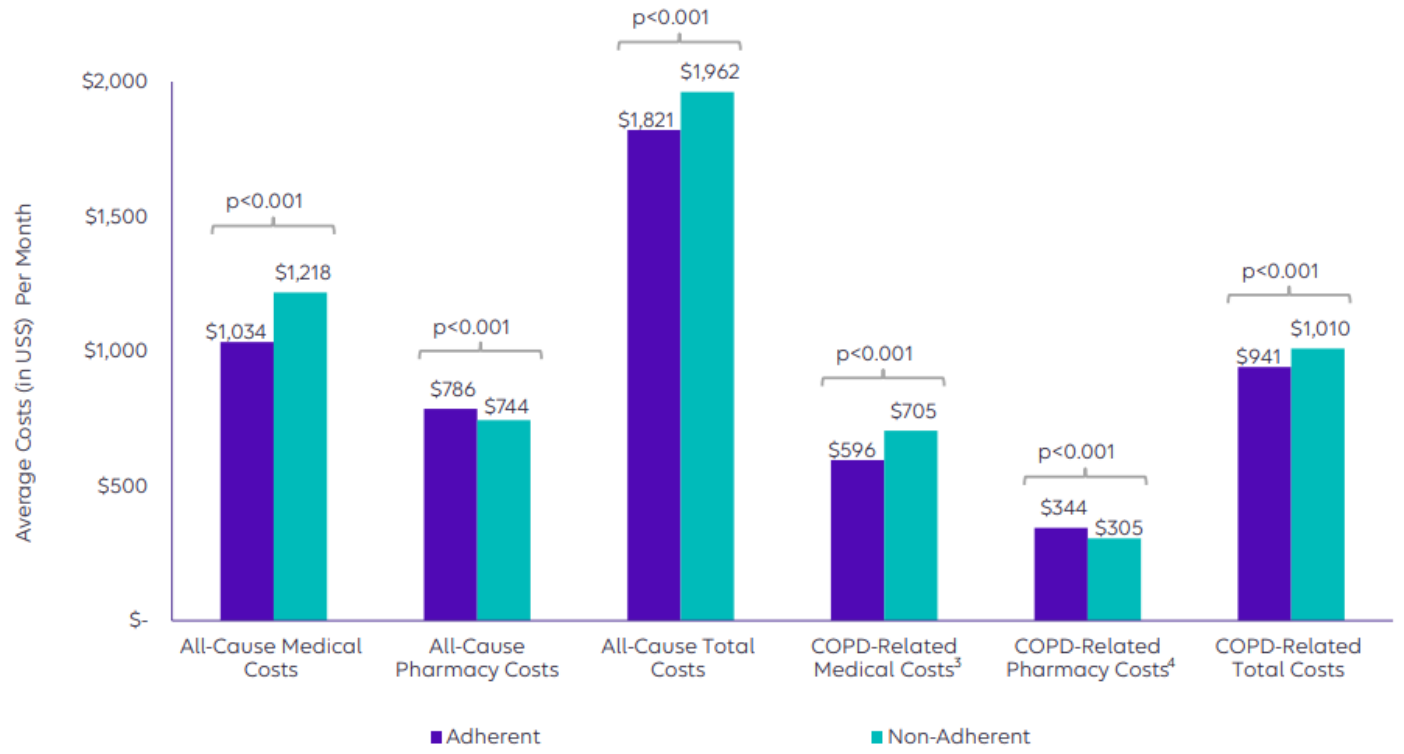
Adherence to COPD regimen resulted in significant economic benefit

Figure 6. Economic outcomes difference between adherent vs non-adherent cohorts after multivariable adjustment[1,2]



Abbreviations: COPD: chronic obstructive pulmonary disease; Notes: [1]Healthcare costs were evaluated in a subset of total segments after removing top 1% outliers which included claims with extremely high costs which were clinically deemed to be not related to COPD. [2]Covariates accounted in the multivariable adjustment included age, gender, health plan type, payor type, Quan Charlson comorbidity index, all-cause total costs during 6-months pre-index date as well as season of segment start date, oxygen use, number of exacerbations, number of fills for short-acting beta agonists and short-acting muscarinic antagonists, and number of all-cause inpatient visits during 6-months prior to segment start. [3]COPD-related medical costs were defined based on medical claims with diagnosis codes for COPD and/or pneumonia in any position. [4]COPD-related pharmacy costs were defined based on pharmacy claim involving use of any maintenance or rescue therapies for COPD and use of oral corticosteroids or antibiotics preceded by a COPD-related inpatient, ER, or outpatient visit within a 7-day window.

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Conclusions and limitations

Adherence to the full COPD regimen resulted in statistically significant and meaningful clinical and economic benefits compared to non-adherence.

This robust real-world evidence can be leveraged by pharmacy payers to support the design and rollout of their targeted adherence-based pharmacy initiatives that can influence quality performance metrics and potentially result in total cost of care savings.

The study lays the analytic groundwork for robustly assessing the causal effect of medication adherence on outcomes and is transferrable to different therapeutic areas in future.

This study is subject to the assumption of exchangeability, i.e. no unmeasured confounding due to the use of observational claims data. Additionally, adherence was dichotomized here for analytical and interpretational convenience; future studies maybe needed to account for the variation within finer levels of adherence.

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Practical tips/key considerations

Clearly delineate the causal contrast of interest to appropriately frame the research question and the design

Carefully determine the unit of analysis & time scale for determining exposure, outcomes and covariates

Achieving adequate balance between covariates after IPW: Consider truncations of segments or trimming of weights if necessary while conducting a thorough bias assessment

Implement inverse probability censoring weighting to account for any censoring bias

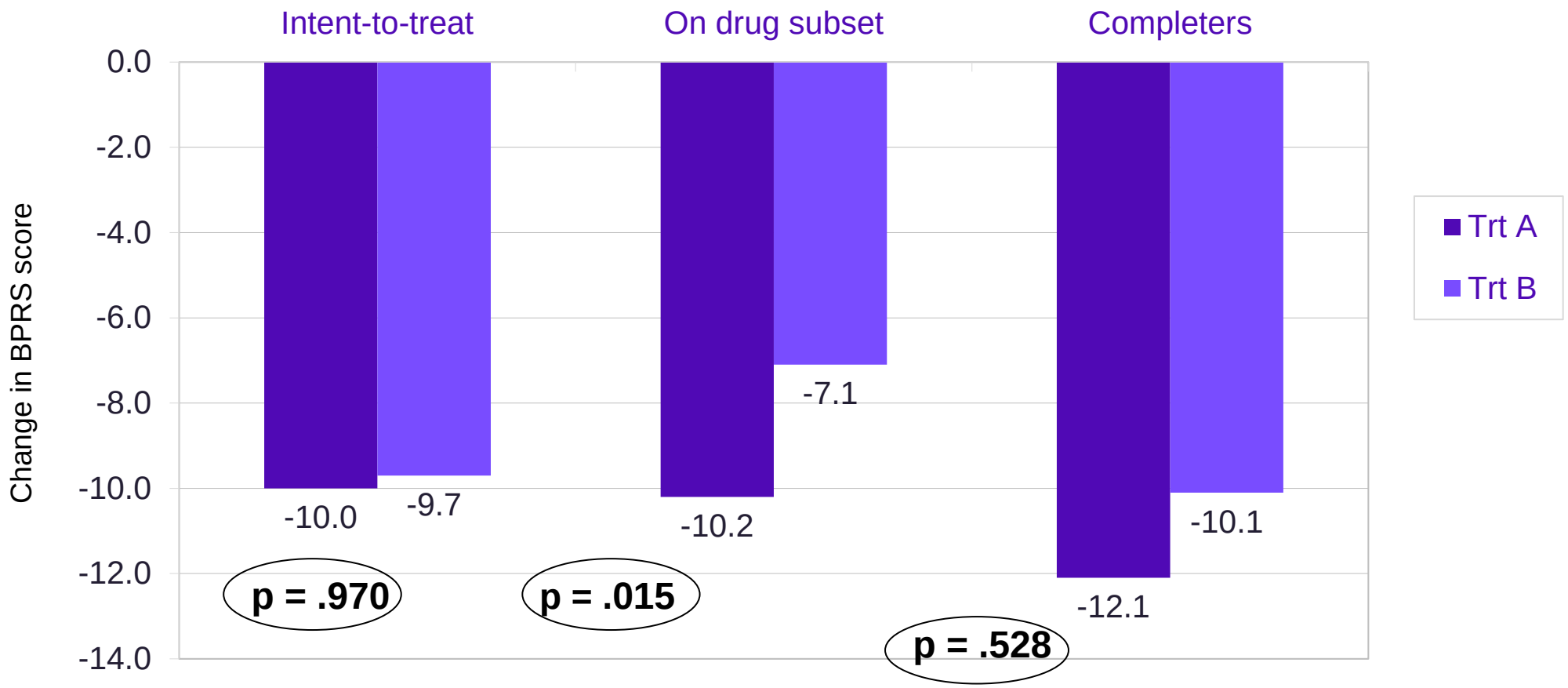
Marginal structural modeling: promise, gaps, and challenges

Douglas Faries

Senior Research Fellow

Eli Lilly and Company

Estimands matter – example data*



Abbreviation: BPRS: Brief Psychiatric Rating Scale.

*Based on: Faries D, Ascher-Svanum H, Belger M. *J Biopharm Stat*. 2007;17(5):809-26.

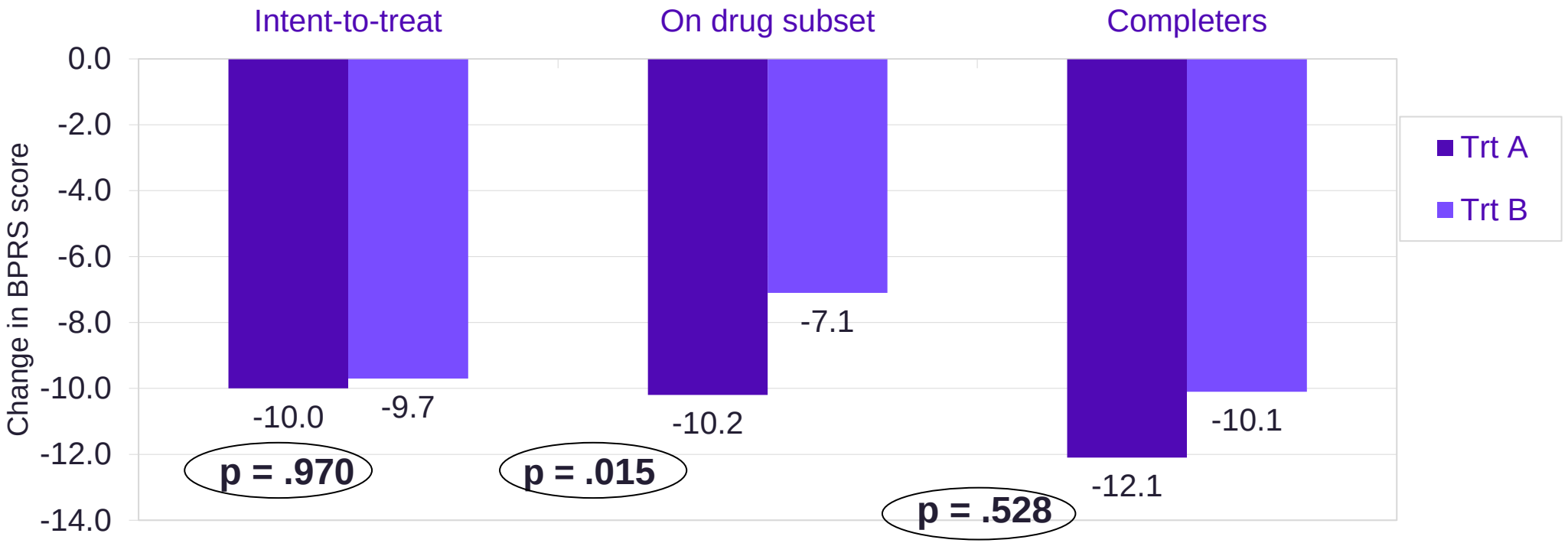
Example data – intercurrent events

- Pragmatic ‘fail first’ study
  - Randomized then observational
- High and imbalanced rate of intercurrent events

	Trt A	Trt B
Completed study on initial med	61%	32%
Switched medications	13%	48%
Discontinued	26%	20%

Marginal structural models – example data*

	Trt A	Trt B	p-Val
MSM analysis	-12.8	-9.3	.028



*Based on: Faries D, Ascher-Svanum H, Belger M. *J Biopharm Stat*. 2007;17(5):809-26.

Why relatively few examples?

1. Perhaps: lack of causal estimand thinking?

2. Data requirements

3. Complexity

Kahan BC, Cro S, Li F, Harhay MO. Eliminating ambiguous treatment effects using estimands. *Am J Epidemiol. 2023 Feb 14*

Intercurrent events:

- Effect at 1 year had all patients stayed on initial therapy
- Effect at 1 year assuming no change in outcome after discontinuing medications
- Effect among patients able to stay compliant with medications ….
- ….

Why relatively few examples?

1. Perhaps: lack of causal estimand thinking?

2. Data requirements

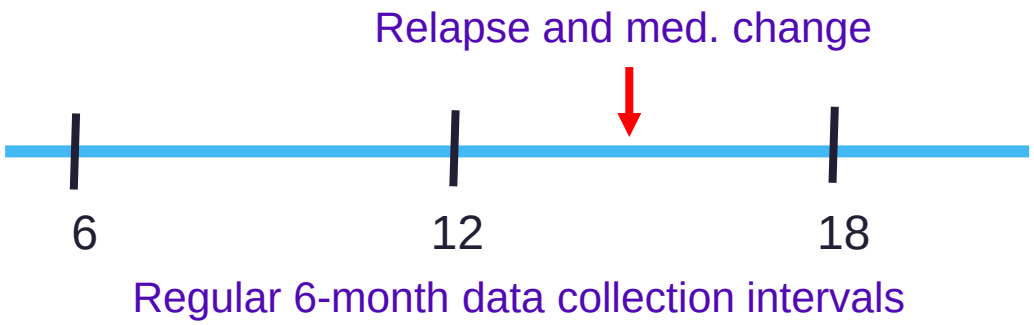
3. Complexity

Causal inference requires several assumptions . . .
now multiplied over time

I. Positivity
   - Sufficient N to model all possible treatment changes at every ‘visit’
   - Large number of treatment patterns in RW data

II. No unmeasured confounders
   - Data on all confounders at every possible point of a treatment change

III. Stable Unit Treatment Value Assumption (SUTVA)



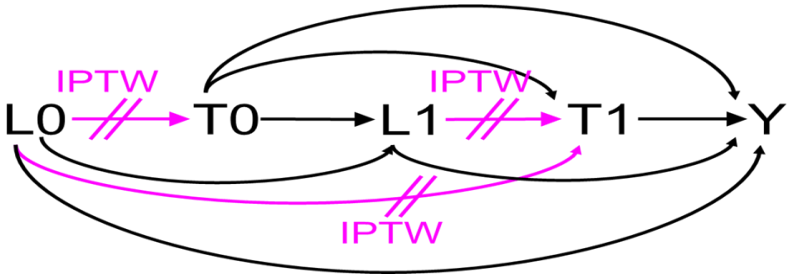
Addressing complexity: implementation code

1. Perhaps: lack of causal estimand thinking?

2. Data requirements

3. Complexity

Multiple models and multiple weight calculations

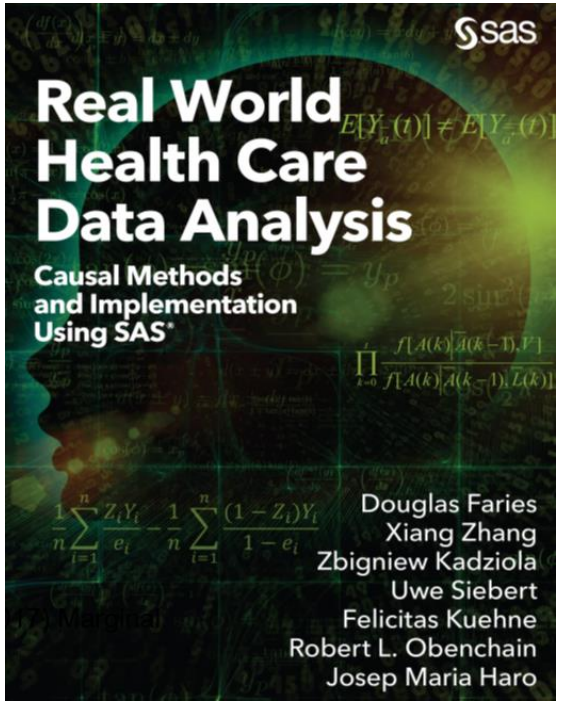


Implementation code

- SAS
- R

Implementation guides

- What If (Hernan and Robins 2020; Chapter 12)
- Skill sheet & other references



Gaps

Help with feasibility assessment

- Many decision points; complex treatment patterns; low switching rates; ….

Quantitative sensitivity analyses for critical assumptions

- Unmeasured confounders
- Positivity / overlap

Summary

Longitudinal observational data

- A common source for healthcare research

MSMs

- An underutilized tool for causal inference
- Addresses time varying confounders; allows use of all data

Roadblocks diminishing

- Estimands / causal roadmaps
- Data quality
- Implementation guides and code

Gaps

- Feasibility assessment
- Sensitivity analyses

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Thank you!

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SM