Transportability Without Positivity: A Synthesis of Statistical and Simulation Modeling

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Transportability

Parameter: causal risk difference for A on Y in the target population

$$\Pr(Y^1 = 1 \mid R = 1) - \Pr(Y^0 = 1 \mid R = 1)$$

Available data

- Data from the target population $(R = 1)$ only includes baseline covariates (e.g., V, W)
- But external data $(R = 0)$ on Y, A, V, W is available

Identification assumptions for transportability

Let the external data consist of a trial, so causal consistency and treatment exchangeability with positivity are given by design

To move from the external to the target

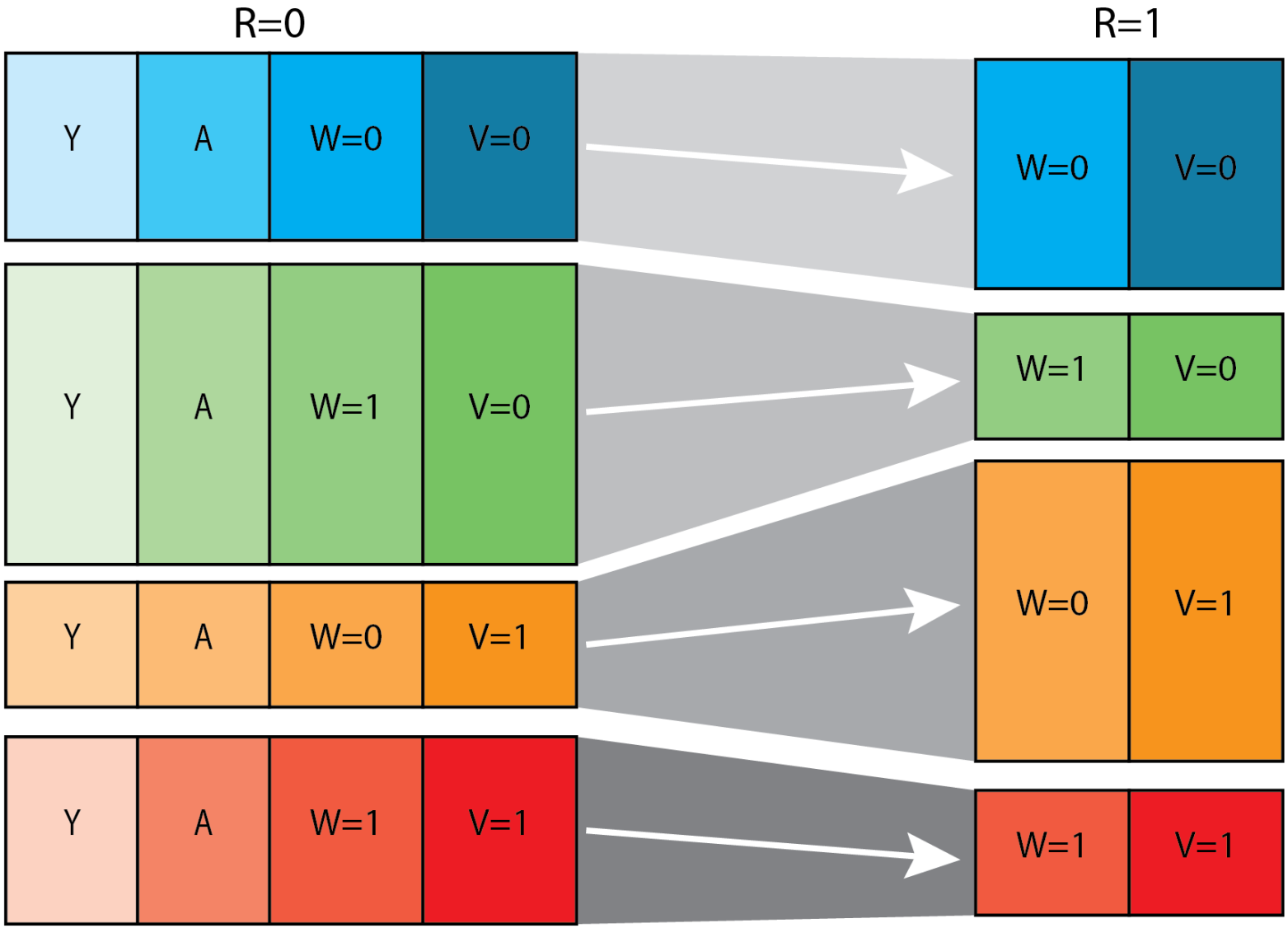
Sampling exchangeability

$$Y^a \amalg R \mid V, W$$

Sampling positivity

$\Pr(R = 0 \mid V = v, W = w) > 0$ for all v, w in the target

A graphical representation of transportability



Positivity violation

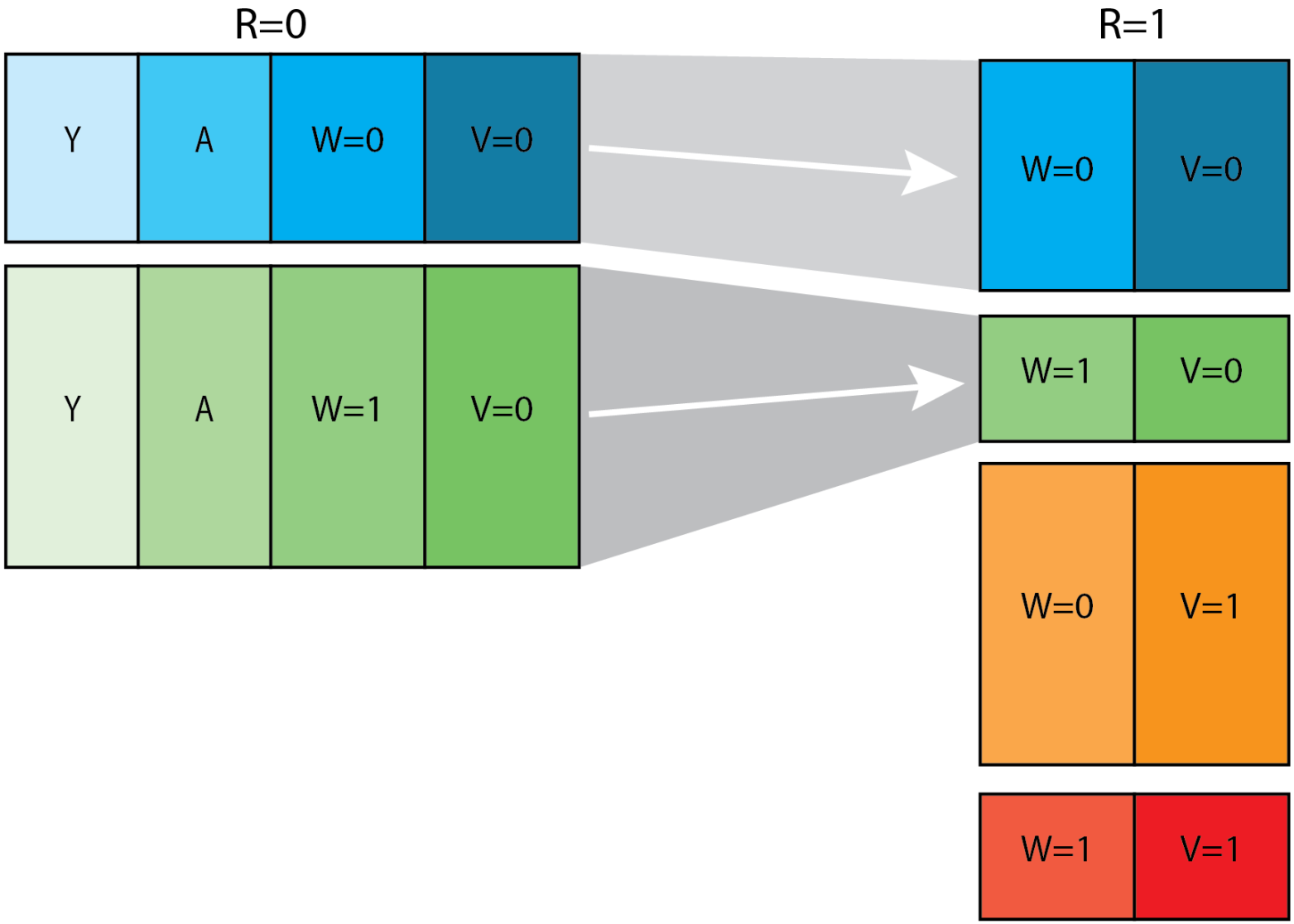
Suppose the following

$$\Pr(R = 0 \mid V = 0, W = w) > 0$$

$$\Pr(R = 0 \mid V = 1, W = w) = 0$$

so there is sampling *nonpositivity* for $V = 1$

A graphical representation of nonpositivity



Positivity violations in the literature

The New England Journal of Medicine

Original Contributions

VOLUME 335 OCTOBER 10, 1996

A TRIAL COMPARING NUCLEOSIDE MONOTHERAPY WITH COMBINATION THERAPY IN HIV-INFECTED ADULTS WITH CD4 CELL COUNTS FROM 200 TO 500 PER CUBIC MILLIMETER

Emtricitabine and tenofovir alafenamide *vs* emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial

Kenneth H Mayer, Jean-Michel Molina, Melanie A Thompson, Peter L Anderson, Koram C Mounzer, Joss J De Wit, Edwin Delpasus, Heiko Jessen, Robert M Grant, Peter J Ruane, Pamela Wong, Ramin Ebrahimi, Lijie Zhong, Anita Mathias, Christian Callebaut, Sean E Collins, Moupali Das, Scott McCallister, Diana M Brainard, Cynthia Brinson, Amanda Clarke, Pep Coll, Frank A Post, C Bradley Hare

JAMA

The Journal of the American Medical Association

Multiple Risk Factor Intervention Trial

Risk Factor Changes and Mortality Results

Multiple Risk Factor Intervention Trial Research Group

The New England Journal of Medicine

VOLUME 337 SEPTEMBER 11, 1997 NUMBER 11

A CONTROLLED TRIAL OF TWO NUCLEOSIDE ANALOGUES PLUS INDINAVIR IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND CD4 CELL COUNTS OF 200 PER CUBIC MILLIMETER OR LESS

SCOTT M. HAMMER, M.D., KATHLEEN E. SQUIRES, M.D., MICHAEL D. HUGHES, PH.D., JANET M. GRIMES, M.S., LISA M. DEMETER, M.D., JUDITH S. CURRIER, M.D., JOSEPH J. ERON, JR., M.D., JUDITH E. FEINBERG, M.D., HENRY H. BALFOUR, JR., M.D., LAWRENCE R. DEYTON, M.D., JEFFREY A. CHODAKEWITZ, M.D., AND MARGARET A. FISCHL, M.D., FOR THE AIDS CLINICAL TRIALS GROUP 320 STUDY TEAM*

Addressing positivity violations

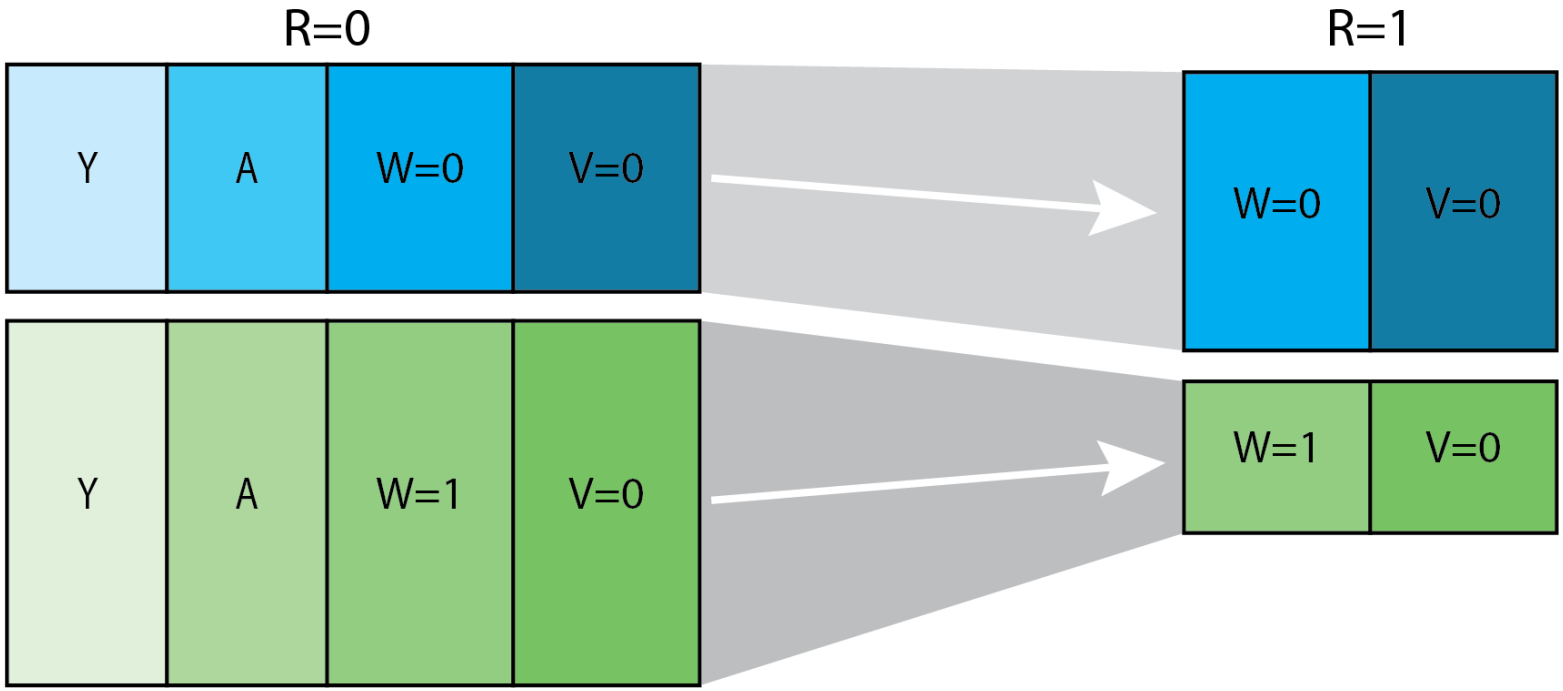
Two common approaches

1. Restrict the target population
2. Restrict the covariate set

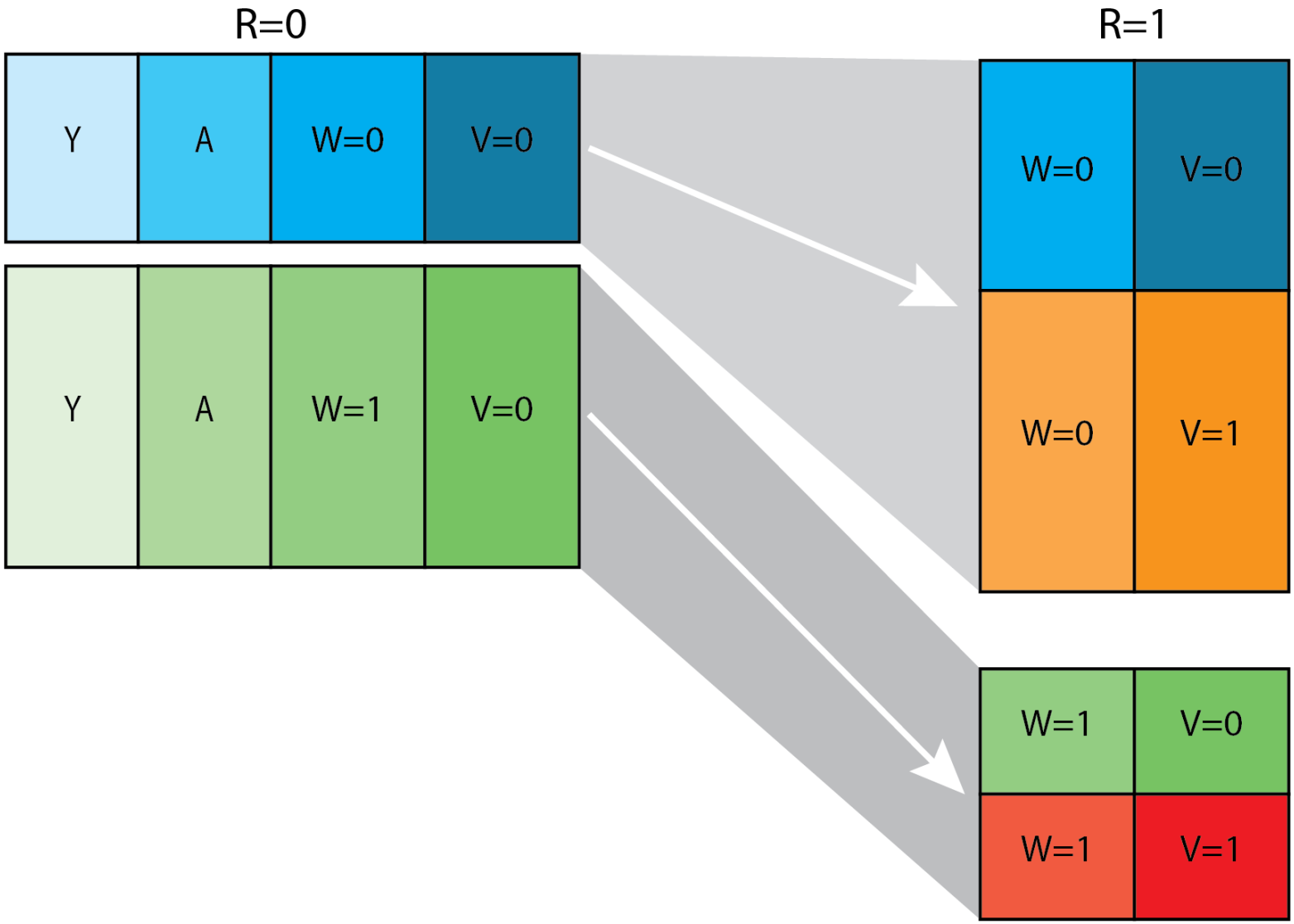
1. Restrict the target population

Modify the parameter of interest

$$\Pr(Y^1 = 1 \mid R = 1, V = 0) - \Pr(Y^0 = 1 \mid R = 1, V = 0)$$



2. Restrict the covariate set



A third approach

Synthesis modeling[1]

- Motivation
  1. Address the motivating question
  2. Avoid questionable assumptions about V
- Combination of statistical and mathematical models

[1] This proposal is the main contribution of the paper

Underlying idea

Divide ψ into

$$\psi_0 \Pr(V = 0 \mid R = 1) + \psi_1 \Pr(V = 1 \mid R = 1)$$

ψ_0: $\Pr(Y^1 - Y^0 \mid V = 0, R = 1)$

ψ_1: $\Pr(Y^1 - Y^0 \mid V = 1, R = 1)$

- Statistical model for the regions with positivity
- Mathematical model to fill-in (impute) the nonpositive region
  - Premised on reliable information external to either data source

What do I mean by mathematical model

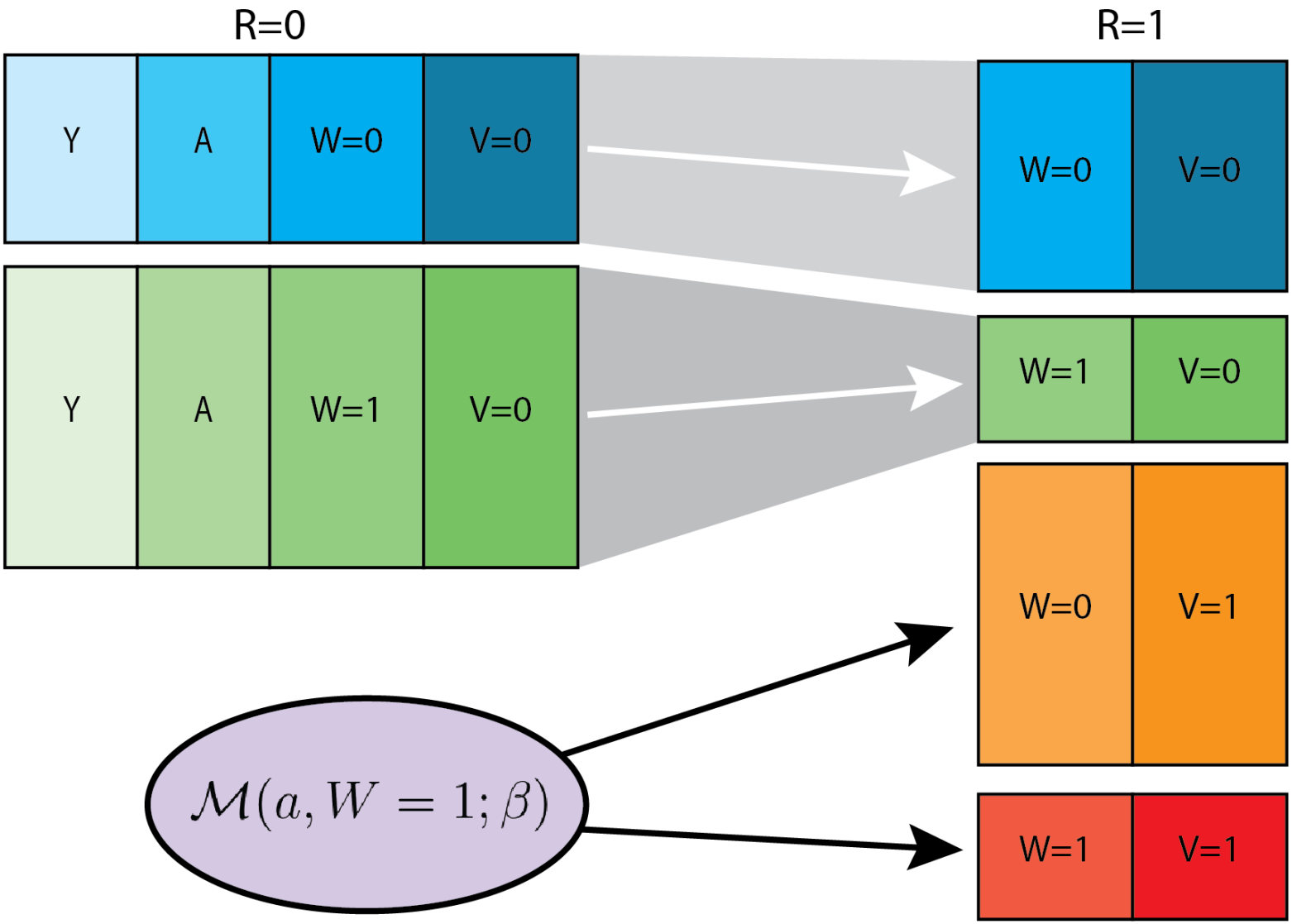
A model used to capable of incorporating outside information in a way that is compatible with the statistical model

- Informed by reliable outside information
  - Studies on exposures or treatments with similar mechanisms of action, pharmacokinetic studies, animal models
- Ex. mechanistic models, agent-based models, microsimulation

Synthesis models considered in the paper

$$f_Y(a, V, W; \alpha, \beta) = \; s(W, V = 0; \alpha) \; + \; m(W, V = 1; \beta)$$

Synthesis modeling



Contributions of the publication

1. Illustrate that
   - Synthesis is a generalization of restricting covariate set and restricting the target population
   - When no external information will coincide with the nonparametric bounds
2. Building mathematical models for nonpositivity
3. Proposed IPW and g-computation type estimators
4. Induce a known positivity violation and then recover the full data estimate
5. Show supporting simulation experiments

Extensions

Nonpositivity by continuous V

- Some additional nuances[2]
- Causes célèbres: new methods for new inference, Waller A/B (Thurs 5:30–6:00)

Incorporating statistical and mathematical models

Other positivity assumptions

- Exchangeability assumptions come with positivity assumptions
- Confounding, missing data, measurement error

[2] Zivich et al. arXiv:2311.09388

Thank you!

Publications

- Zivich PN et al. "Transportability without positivity: a synthesis of statistical and simulation modeling". *Epidemiology* 2024; 35(1): 23-31.
- Zivich PN et al. "Synthesis estimators for transportability with positivity violations by a continuous covariate". *arXiv*:2311.09388, under revision at the *Journal of the Royal Statistical Society Series A*

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