Extending Inferences to a Target Population Without Positivity

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Corresponding Publications

Zivich PN, Edwards JK, Lofgren ET, Cole SR, Shook-Sa BE, Lessler J. Transportability without positivity: a synthesis of statistical and simulation modeling. *Epidemiology* In-press 2023.

Zivich PN, Edwards JK, Shook-Sa BE, Lofgren ET, Lessler J, Cole SR. Synthesis estimators for positivity violations with a continuous covariate. *arXiv*:2311.09388

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Motivating problem[1]

Teleporting to 1995, a colleague asks for help addressing a question

- **Question**: should women with HIV be treated with two-drug or one-drug antiretroviral therapy (ART)?
- **Parameter**: average causal effect of two-drug versus one-drug ART on 20-week CD4 T cell count (cells/mm^3)

Two sources of data to answer this question

- AIDS Clinical Trial Group (ACTG) 175
  - Trial comparing two-drug versus one-drug ART
- Women's Interagency HIV Study (WIHS)
  - Assumed to be a random sample of the target population

[1] Inspired by the example in Dahabreh et al. (2023) *Stats in Med*

Notation

Y^a: potential outcome under action a

Y: outcome of interest, CD4 at 20 weeks
A: action, two-drug ($A = 1$) or one-drug ($A = 0$) ART
V: continuous covariate, baseline CD4
W: set of additional covariates

- Age, race, weight

R: indicator for target population ($R = 1$) or trial ($R = 0$)
$O = (R, W, V, (1 - R)A, (1 - R)Y)$

Average causal effect (ACE)

$$\psi = E[Y^1 - Y^0 \mid R = 1]$$

Identification Assumptions

$$E[Y^a|R=1] = E\left\{E[Y|A=a,V,W,R=0] \mid R=1\right\}$$

Causal consistency

$$Y_i = Y_i^a \text{ if } a = A_i$$

Action (in trial population)

$$Y^a \amalg A \mid V, W, R=0$$

$$\Pr(A=a \mid V=v, W=w, R=0) > 0 \; \forall \; f(v,w,R=0) > 0$$

Sampling (linking between populations)

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

$$\Pr(R=0 \mid V=v, W=w) > 0 \; \forall \; f(v,w,R=1) > 0$$

Identification Assumptions

Causal consistency

$$Y_i = Y_i^a \text{ if } a = A_i$$

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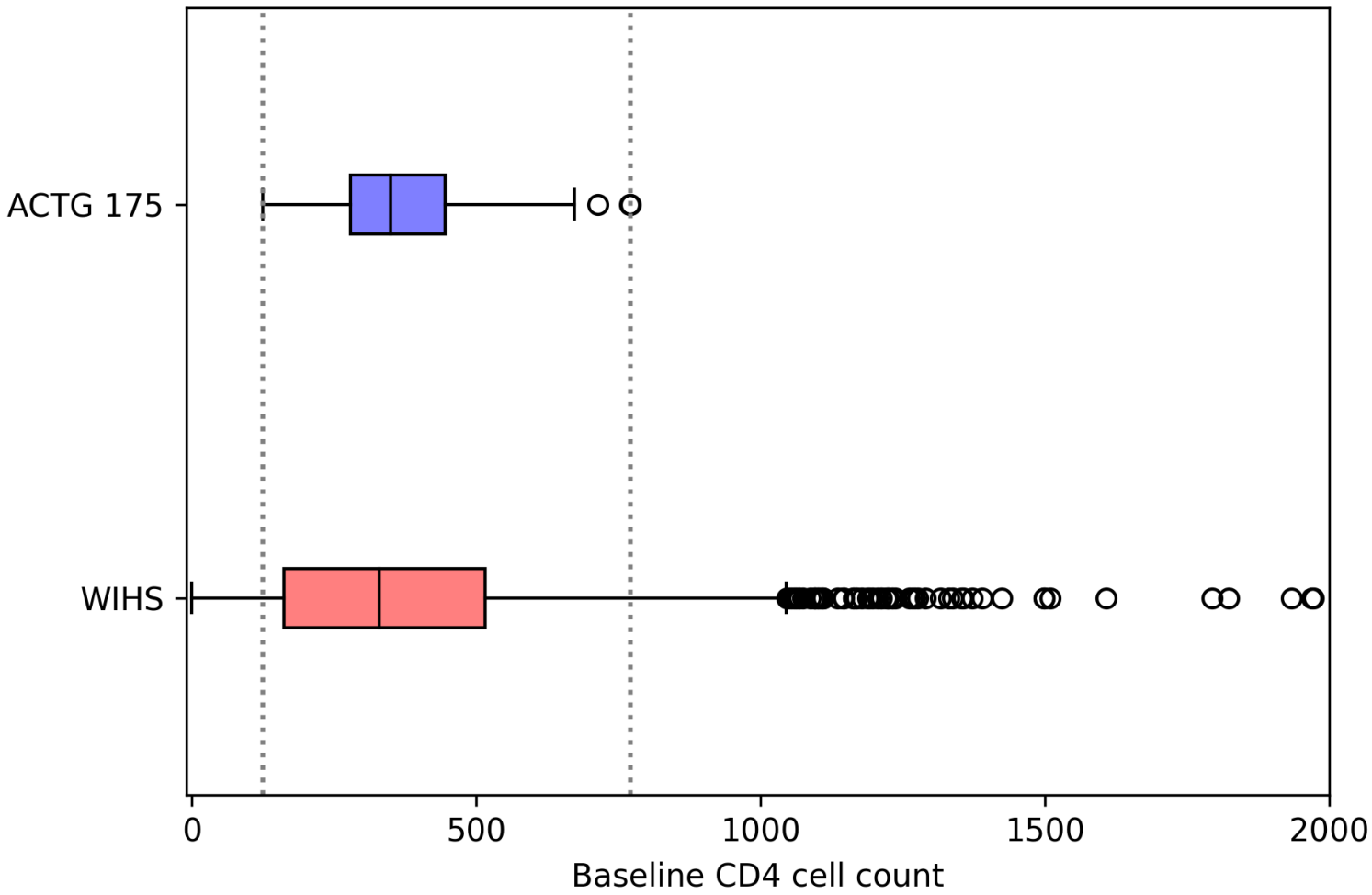
A problem with positivity



Common solutions to non-positivity

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

1. Restrict the covariate set

Keep parameter of interest, ψ, but modify the adjustment set

Sampling

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

Limit exchangeability to W

$$\Pr(R = 0 \mid W = w) > 0 \; \forall \; f(w, R = 1) > 0$$

No longer consider V

2. Restrict the target population

Modify the parameter of interest

$$\psi_0 = E[Y^1 - Y^0 \mid V^* = 0, R = 1]$$

where $V^* = 1 - I(v_1 \leq V \leq v_2)$

Sampling

$$Y^a \amalg R \mid V, W, V^* = 0$$

Restricting to positive region

$$\Pr(R = 0 \mid V = v, W = w) > 0 \; \forall \; f(v, w, R = 1, V^* = 0) > 0$$

Positivity for subset

3. Extrapolation

Abandon *nonparametric* identification in favor of *parametric*

- Use a parametric outcome model to extrapolate
- Requires parametric model to be valid over non-positive regions

Synthesis of statistical and mathematical models

Synthesis of statistical and mathematical models

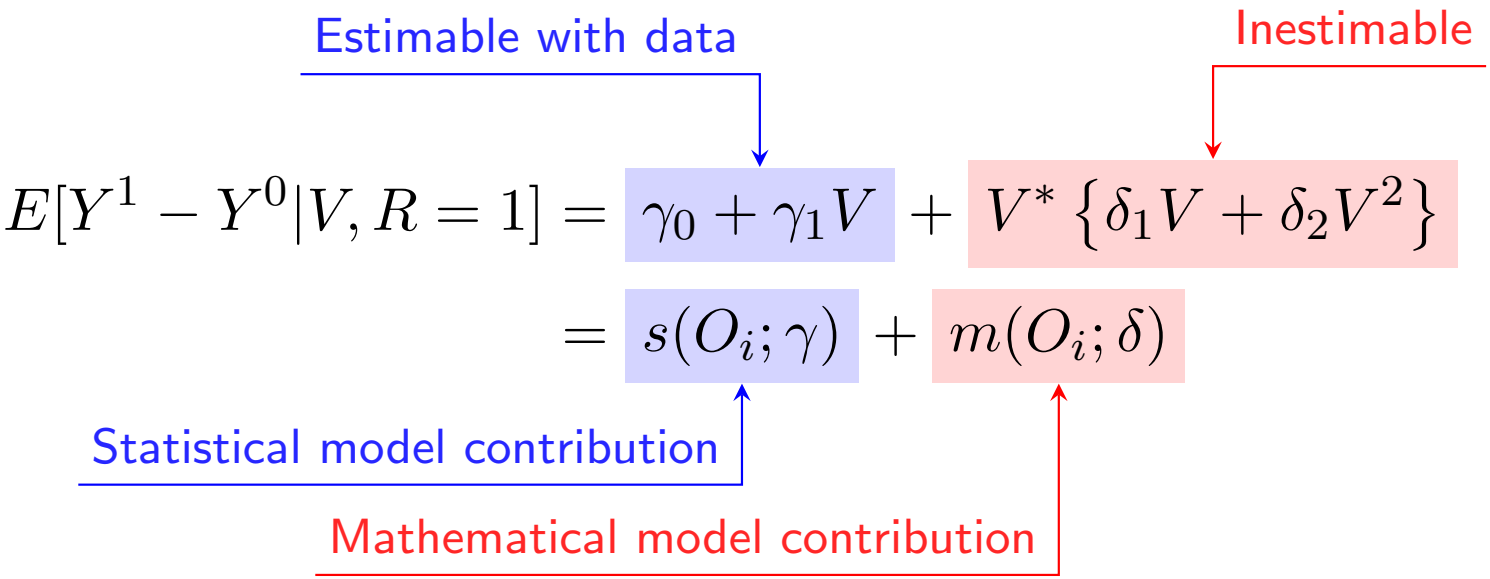
A re-expression of ψ following law of total expectation

$$\psi = \underbrace{\psi_0}_{E[Y^1 - Y^0 \mid V^* = 0, R = 1]} \Pr(V^* = 0 \mid R = 1) + \underbrace{\psi_1}_{E[Y^1 - Y^0 \mid V^* = 1, R = 1]} \Pr(V^* = 1 \mid R = 1)$$

Underlying idea: fit a statistical model for the regions with positivity, use a mathematical model to fill-in (impute) over the nonpositive region

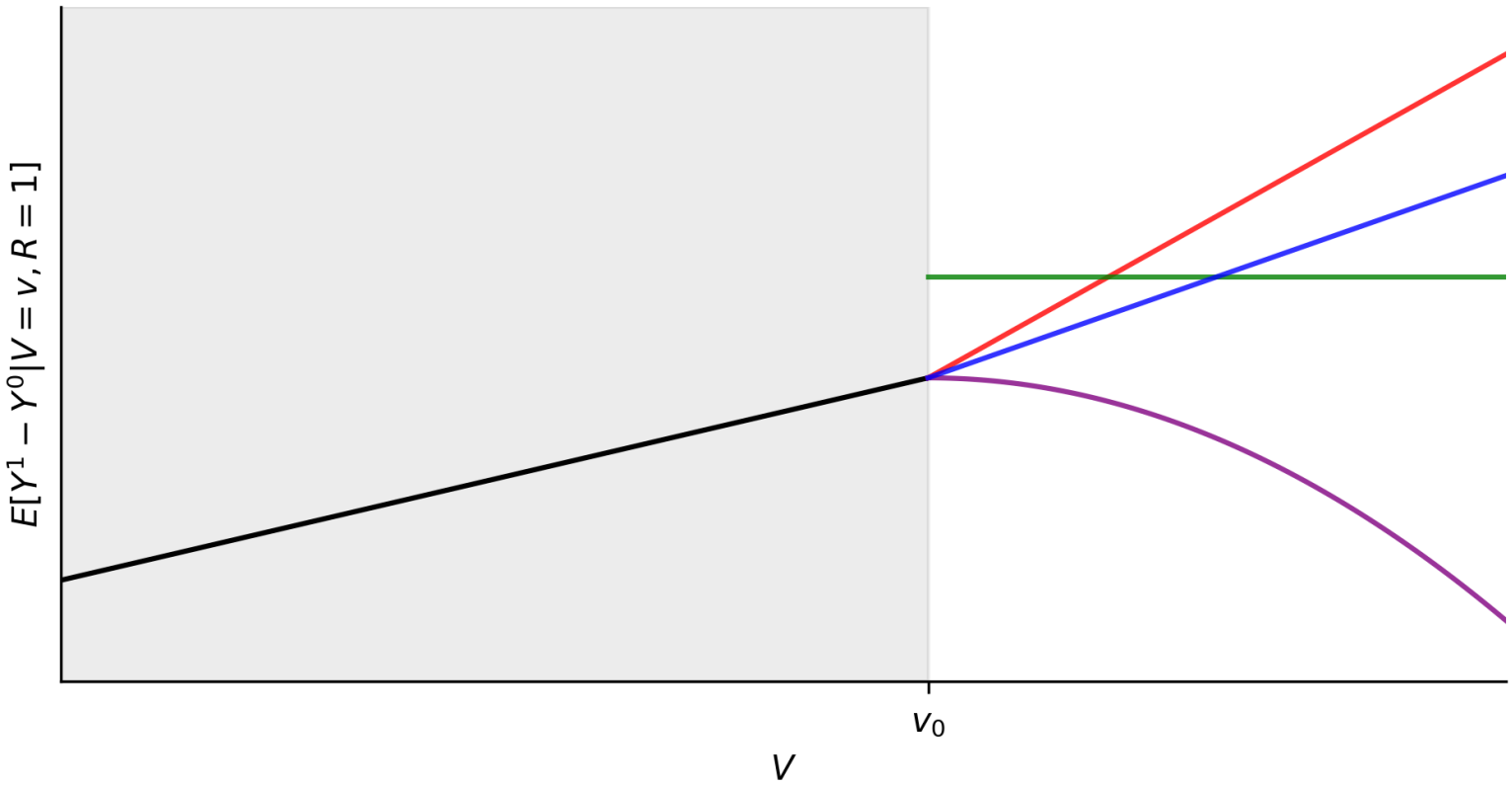
One way to combine models[2]

Model for conditional average causal effect (CACE)



[2]Other ways are considered in the *Epidemiology* and *arXiv* papers

A visualization of a synthesis CACE



Mathematical model

What do I mean by mathematical model[3]

- Mechanistic models
- Microsimulation
- Agent-based models

Informed by external information

- Studies on exposures or treatments with similar mechanisms of action, pharmacokinetic studies, animal models
- Mathematical model synthesizes this information

[3] See Roberts et al. (2012) *Med Decis Making* for general overview for constructing mathematical models

Synthesis AIPW Estimator

Estimator based on CACE model

$$\hat{\psi}_{CACE} = \frac{1}{\sum_{i=1}^{n} I(R_i = 1)} \sum_{i=1}^{n} \mathcal{G}(O_i; \hat{\gamma}, \hat{\eta}, \delta)\, I(R_i = 1)$$

where

$$E[Y^1 - Y^0 \mid V, R = 1] = \mathcal{G}(O_i; \gamma, \eta, \delta) = s(O_i; \gamma, \eta) + m(O_i; \delta)$$

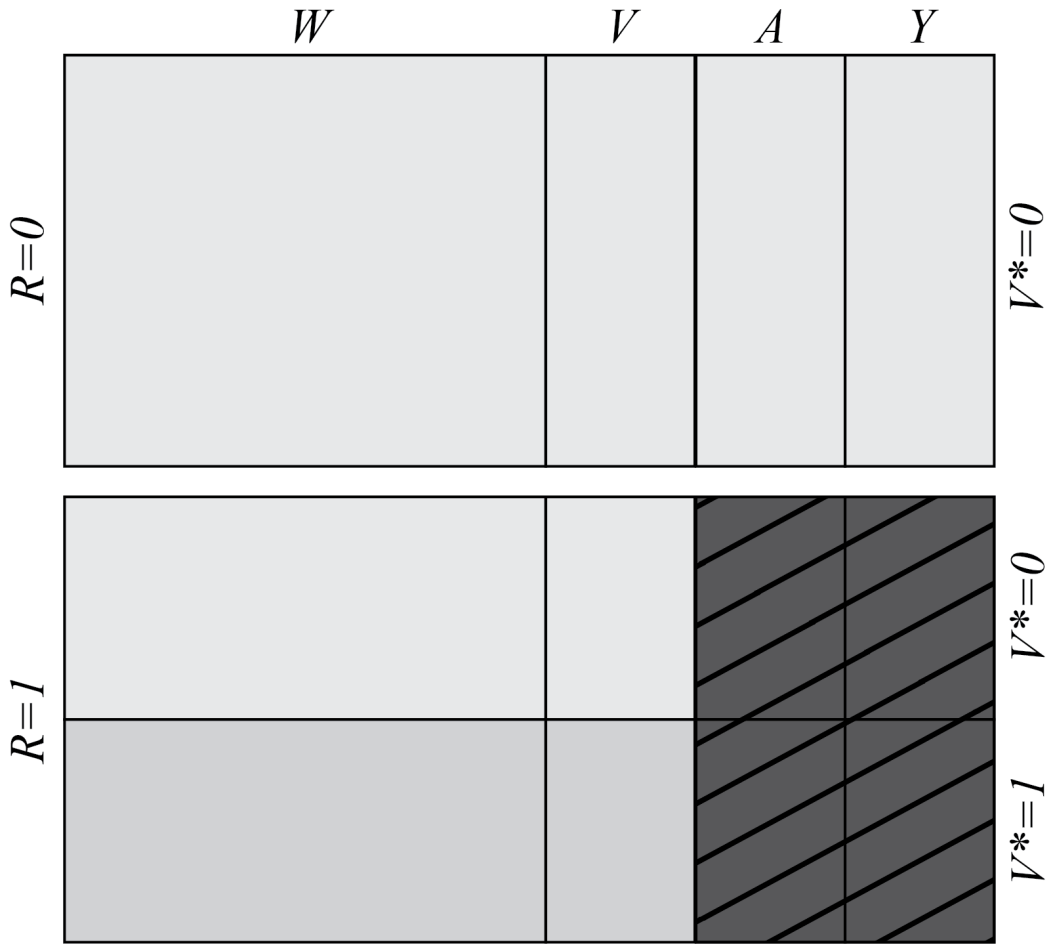
Augmented inverse probability weighting (AIPW) estimator[4]

- Weighted regression AIPW[5]

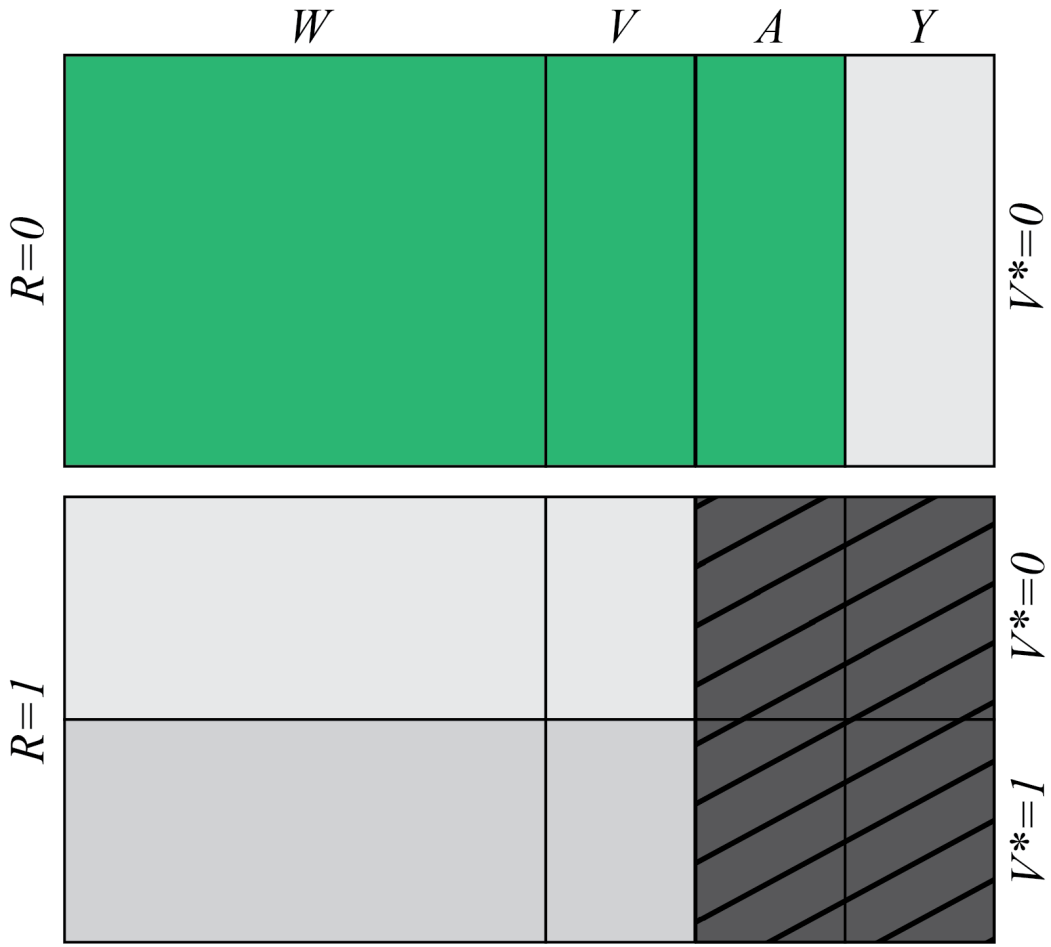
[4] Zivich et al. (2023) *Epidemiology* provides g-computation and inverse probability weighting estimators

[5] Robins et al. (2007) *Statistical Science*

Synthesis AIPW estimator

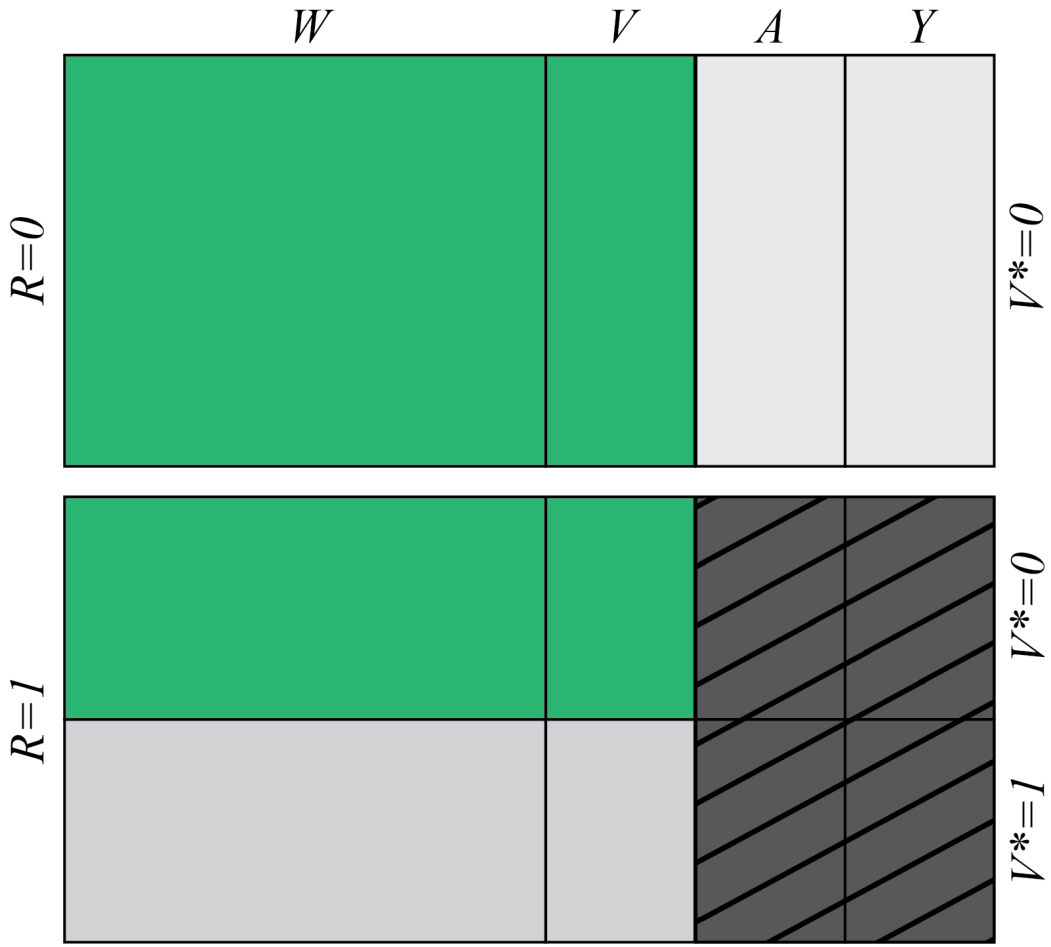


Synthesis AIPW estimator



$$\widehat{\Pr}(A = 1 \mid V, W, R = 0)$$

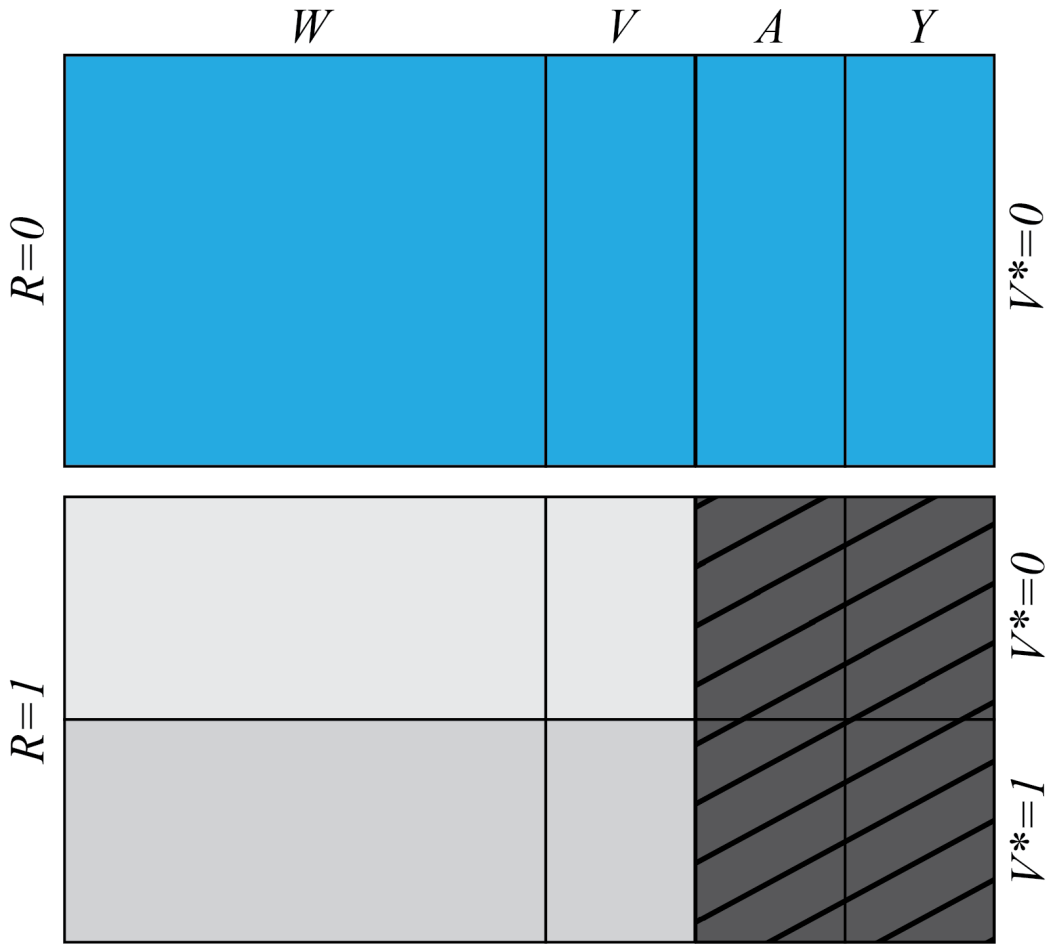
Synthesis AIPW estimator



$$\widehat{\Pr}(A = 1 \mid V, W, R = 0)$$

$$\widehat{\Pr}(R = 1 \mid V, W, V^* = 0)$$

Synthesis AIPW estimator

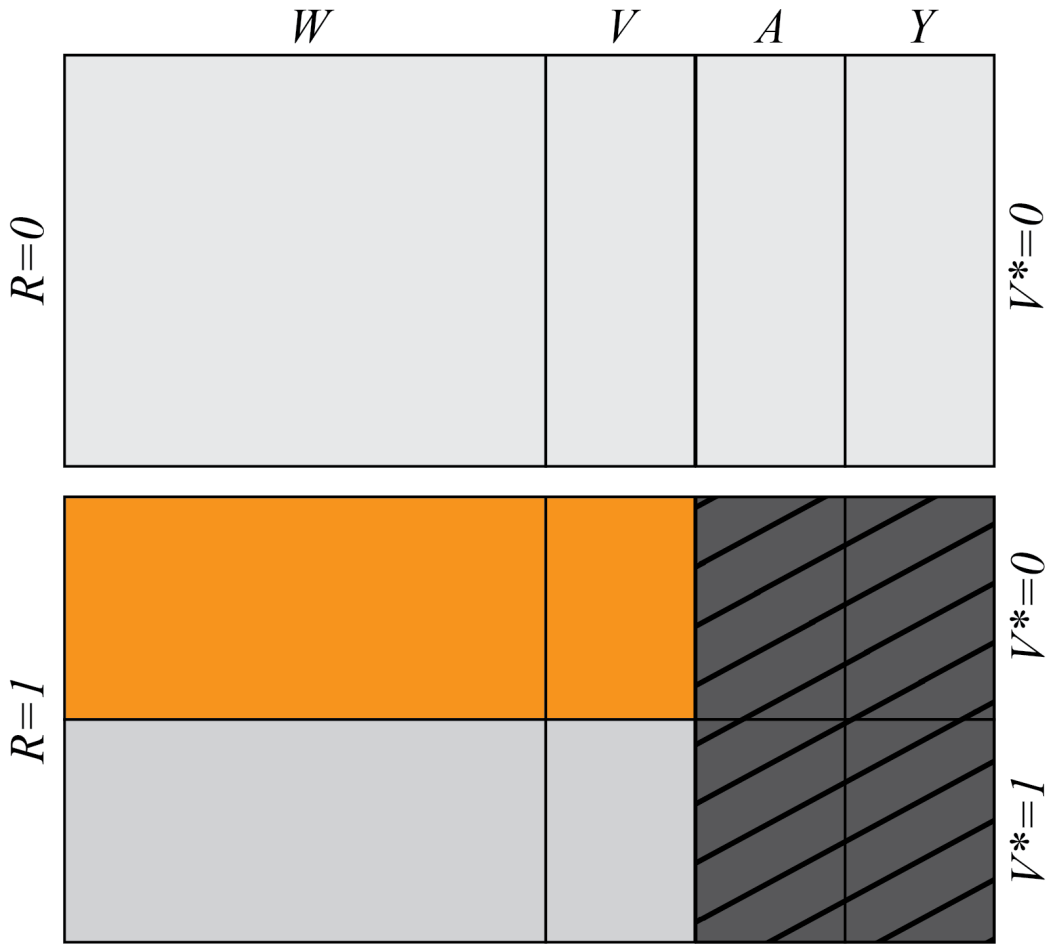


$$\widehat{\Pr}(A = 1 \mid V, W, R = 0)$$
$$\widehat{\Pr}(R = 1 \mid V, W, V^* = 0)$$

$$\downarrow$$

$$\widehat{E}[Y \mid A, V, W, R = 0]$$

Synthesis AIPW estimator



$$\widehat{\Pr}(A = 1 \mid V, W, R = 0)$$

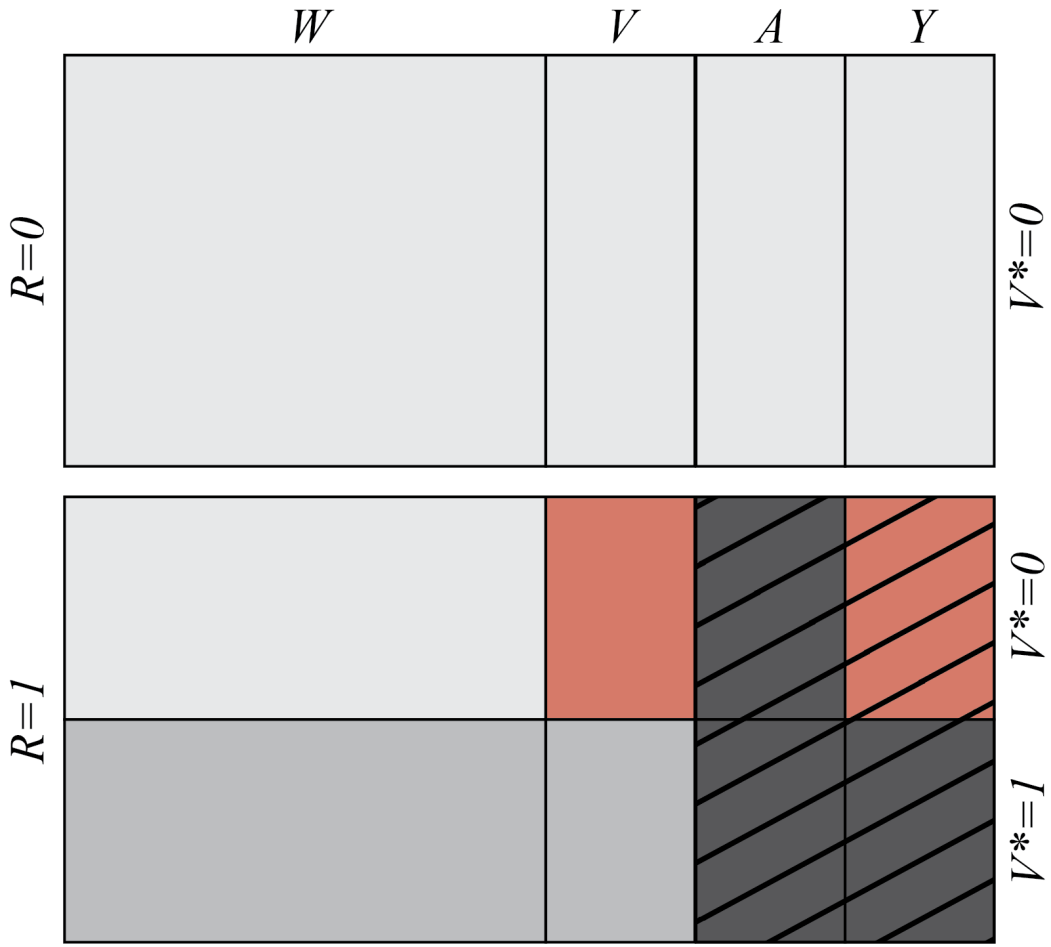
$$\widehat{\Pr}(R = 1 \mid V, W, V^* = 0)$$

$$\downarrow$$

$$\widehat{E}[Y \mid A, V, W, R = 0]$$

$$\widehat{Y}^1, \quad \widehat{Y}^0$$

Synthesis AIPW estimator



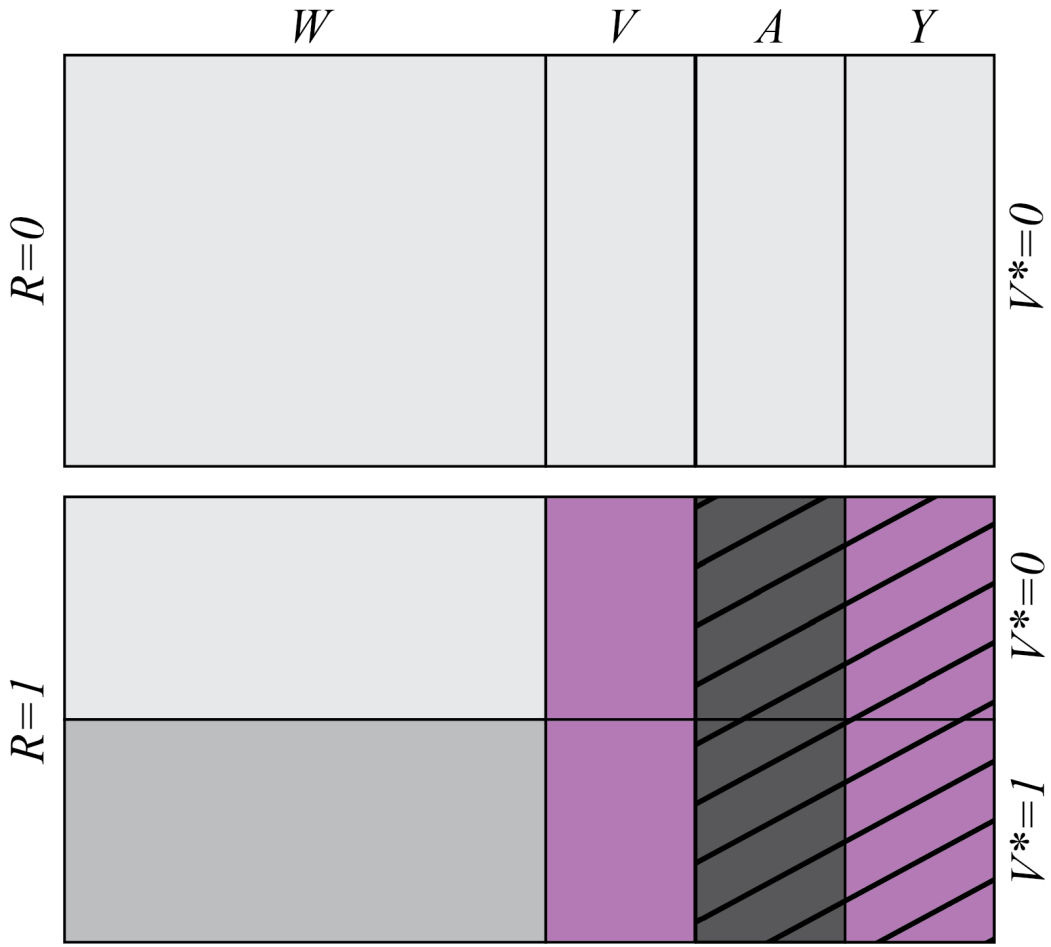
$$\widehat{\Pr}(A = 1 \mid V, W, R = 0)$$
$$\widehat{\Pr}(R = 1 \mid V, W, V^* = 0)$$

$$\widehat{E}[Y|A, V, W, R = 0]$$

$$\widehat{Y}^1, \quad \widehat{Y}^0$$

$$\widehat{E}\left[\widehat{Y}^1 - \widehat{Y}^0 | V, V^* = 0\right]$$

Synthesis AIPW estimator



$$\widehat{\Pr}(A = 1 \mid V, W, R = 0)$$
$$\widehat{\Pr}(R = 1 \mid V, W, V^* = 0)$$

$$\widehat{E}[Y|A, V, W, R = 0]$$

$$\widehat{Y}^1, \quad \widehat{Y}^0$$

$$\widehat{E}\left[\widehat{Y}^1 - \widehat{Y}^0 | V, V^* = 0\right]$$

$$m(O_i; \delta) \rightarrow \widehat{\psi}$$

Uncertainty of the Mathematical Model

Ignored uncertainty in δ

Two options

1. Range of plausible values for δ [6]
   - Bounds on ψ
2. Distribution of plausible values for δ
   - Monte Carlo procedure
   - Distribution for ψ

[6] See Vansteelandt et al. (2006) *Statistica Sinica*

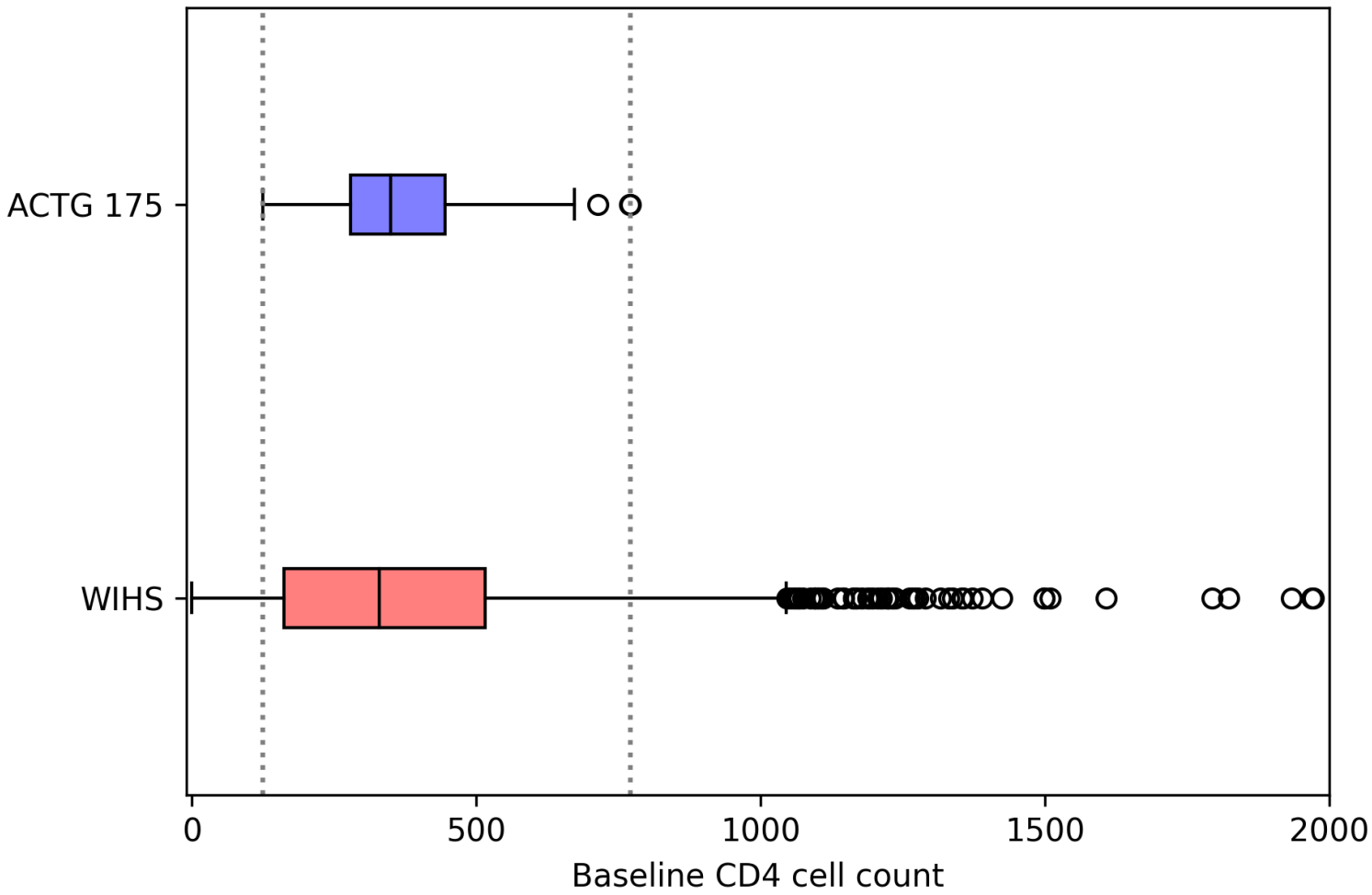
Application

Description of available data

	ACTG 175 ($n_0 = 276$)	WIHS ($n_1 = 1932$)
Age	33 [28, 39]	36 [31,41]
Baseline CD4	350 [278, 443]	330 [161, 516]
Weight (kg)	67 [59, 76]	66 [58, 78]
White	154 (56%)	390 (20%)
Two-drug ART	175 (64%)	-
CD4 20 weeks	357 [267, 480]	-

Brackets are 25^{th} and 75^{th} percentiles

A reminder of the problem



Parameter re-expression

Separating parameter into regions

$$\begin{aligned}\psi = \psi_l \ &\Pr(V < 124 | R = 1) \\ + \ \psi_m \ &\Pr(124 \leq V \leq 771 | R = 1) \\ + \ \psi_u \ &\Pr(V > 771 | R = 1)\end{aligned}$$

Synthesis model for all regions

$$\begin{aligned}\mathcal{G}(O_i; \gamma, \eta, \delta) = \delta_1 \ &I(V_i < 124) \\ + \ s(O_i; \gamma, \eta) \ &I(124 \leq V_i \leq 771) \\ + \ \delta_2 \ &I(V_i > 771)\end{aligned}$$

Mathematical model

Contemporaneous information from pharmacokinetic studies[7]

- Lower bound[8]
  - Don't expect two-drug to result in lower CD4 compared to one-drug
  - Lowest CACE would be in nonpositive regions is zero
  - $\delta_1 = \delta_2 = -20$
  - Mild antagonistic interaction between drugs
- Upper bound
  - $\delta_1 = 150$ based on largest increases observed in small-scale studies[9]
  - $\delta_2 = 100$ since no studies available (less stark but still beneficial)

[7] Wilde & Langtry *Drugs* (1993)
[8] Meng et al. *Ann Intern Med* (1992)
[9] Collier et al. (1993) *Ann Intern Med*

Statistical model

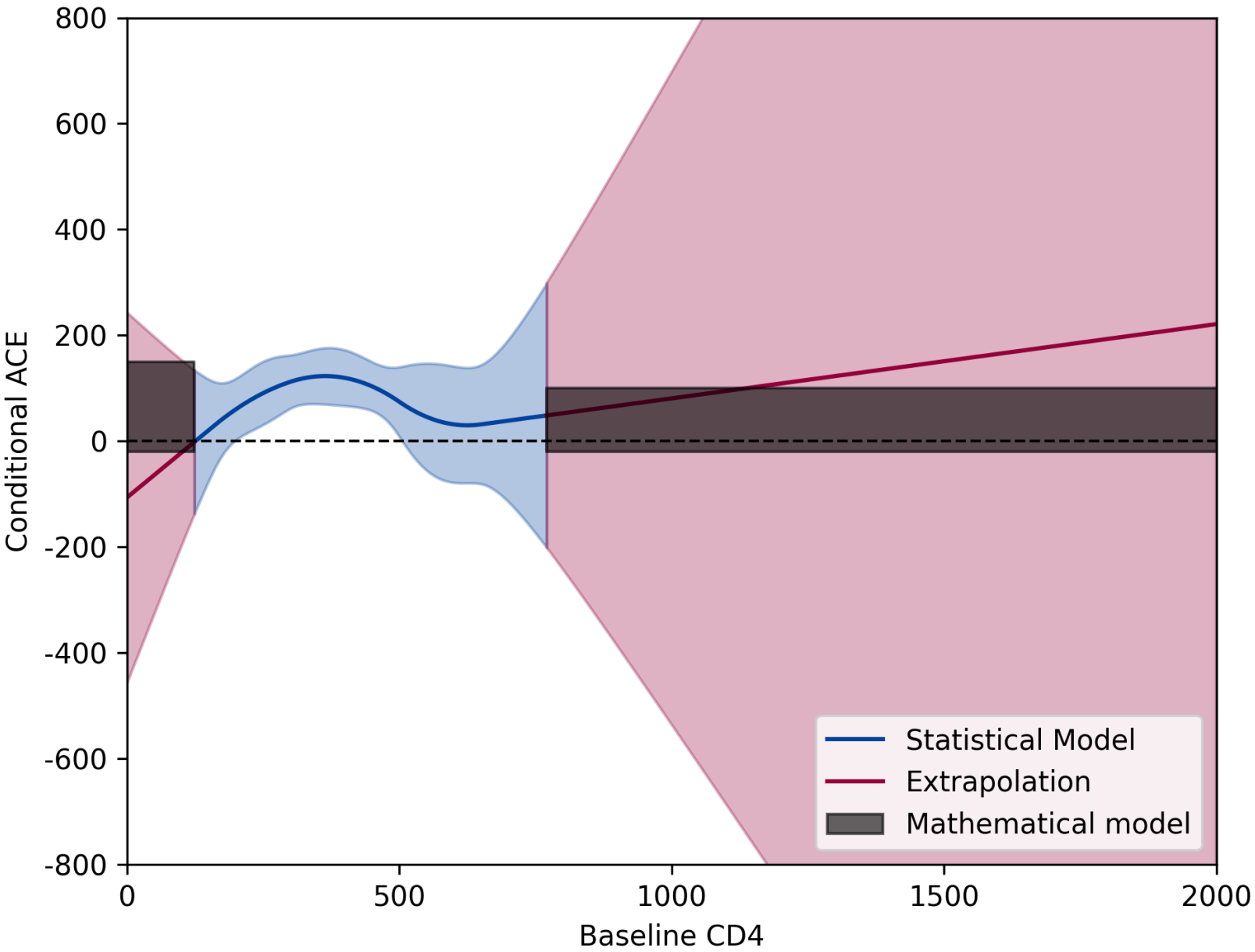
Conditional Average Causal Effect

- Weighted regression AIPW

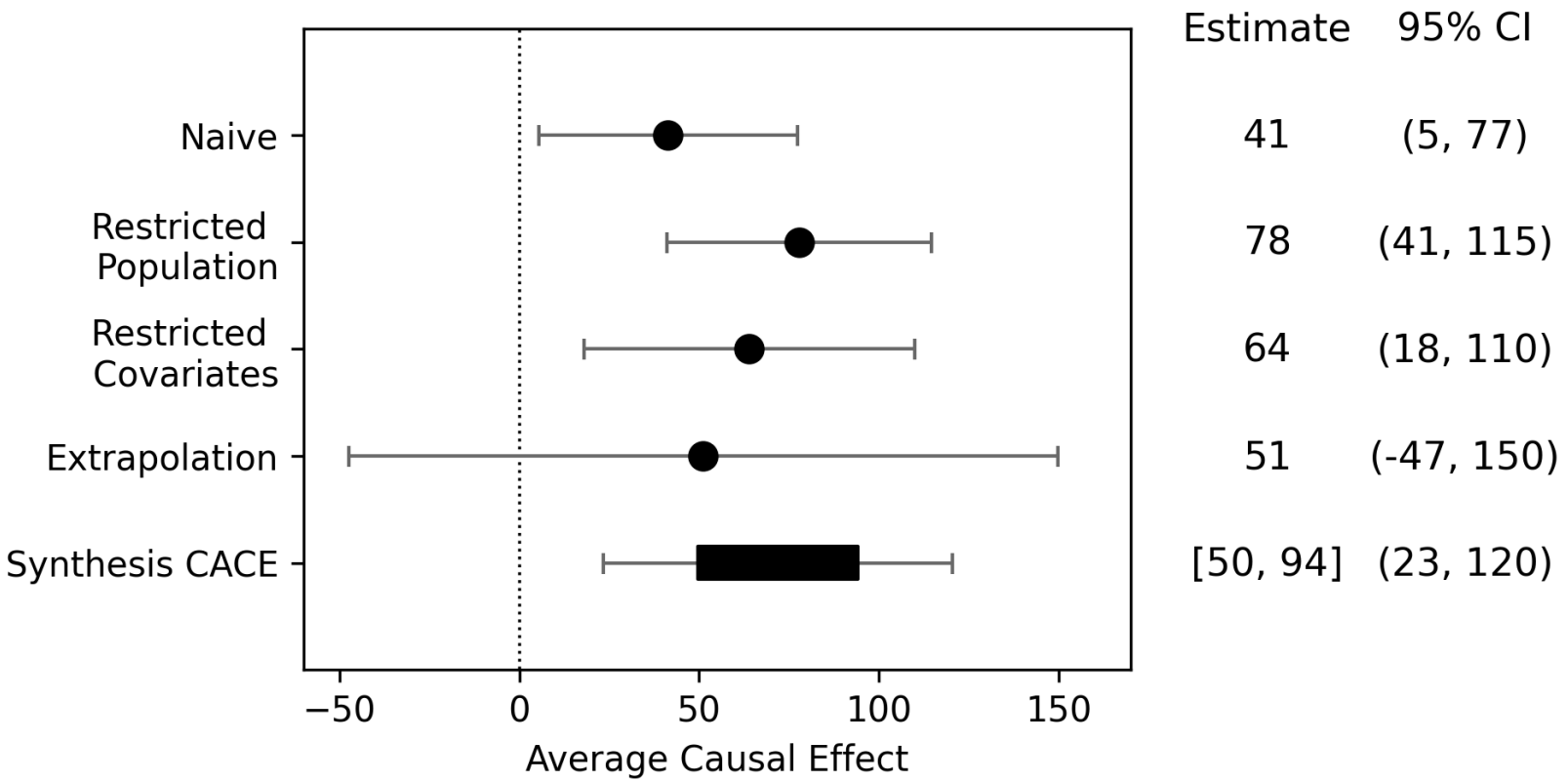
Functional forms

- Restricted quadratic splines (age, weight, baseline CD4)
  - All models
- Baseline CD4 & ART interaction terms
  - Outcome model

Estimated CACE



Results



Difference in CD4 at 20-weeks comparing two-drug to one-drug ART (higher is better)

Conclusions

Extension of inferences between populations without positivity

- Integrate external information sources
- Advantages over existing approaches

Future areas for work

- Other uses of statistical and mathematical models
  - Exchangeability paired with positivity
- Alternative estimators
- Make mathematical models more robust and reliable
  - Sensitivity analyses, diagnostics

Thanks!

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Zivich PN, Edwards JK, Shook-Sa BE, Lofgren ET, Lessler J, Cole SR. Synthesis estimators for positivity violations with a continuous covariate. *arXiv*:2311.09388

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Appendix

A synthesis AIPW estimator[10]

Weighted regression AIPW as estimating equations

$$\sum_{i=1}^{n} \begin{bmatrix} (1-R_i)\left[A_i - \text{expit}(\mathbb{Z}_i\hat{\eta}_1^T)\right]\mathbb{Z}_i^T \\ (1-V_i^*)\left[R_i - \text{expit}(\mathbb{U}_i\hat{\eta}_2^T)\right]\mathbb{U}_i^T \\ (1-R_i)\pi(V_i, W_i; \hat{\eta}_1, \hat{\eta}_2)\left[Y_i - \mathbb{X}_i\hat{\eta}_3^T\right]\mathbb{X}_i^T \\ R_i(1-V_i^*)\left[(\hat{Y}_i^1 - \hat{Y}_i^0) - \mathbb{V}_i\hat{\gamma}^T\right]\mathbb{V}_i^T \\ \left(\mathbb{V}_i\hat{\gamma}^T + \mathbb{V}_i^*\delta^T\right) - \hat{\psi} \end{bmatrix} = 0$$

- $\mathbb{Z}, \mathbb{U}, \mathbb{X}, \mathbb{V}, \mathbb{V}^*$ are design matrices

[10] Estimating equations are solved using `delicatessen`, arXiv:2203.11300

Simulations

$$V \sim 375 \times \text{Weibull}(1, 1.5)$$

$$W \sim \text{Bernoulli}(0.2)$$

$$\Pr(R = 0|V, W) = \begin{cases} \text{expit}(-0.02V + 2W) & V \leq 300 \\ 0 & V > 300 \end{cases}$$

$$\Pr(A = 1|R = 0) = 0.5$$

Sample sizes

- $n_1 = 1000, n_0 = 500$
- $n_1 = 1000, n_0 = 1000$

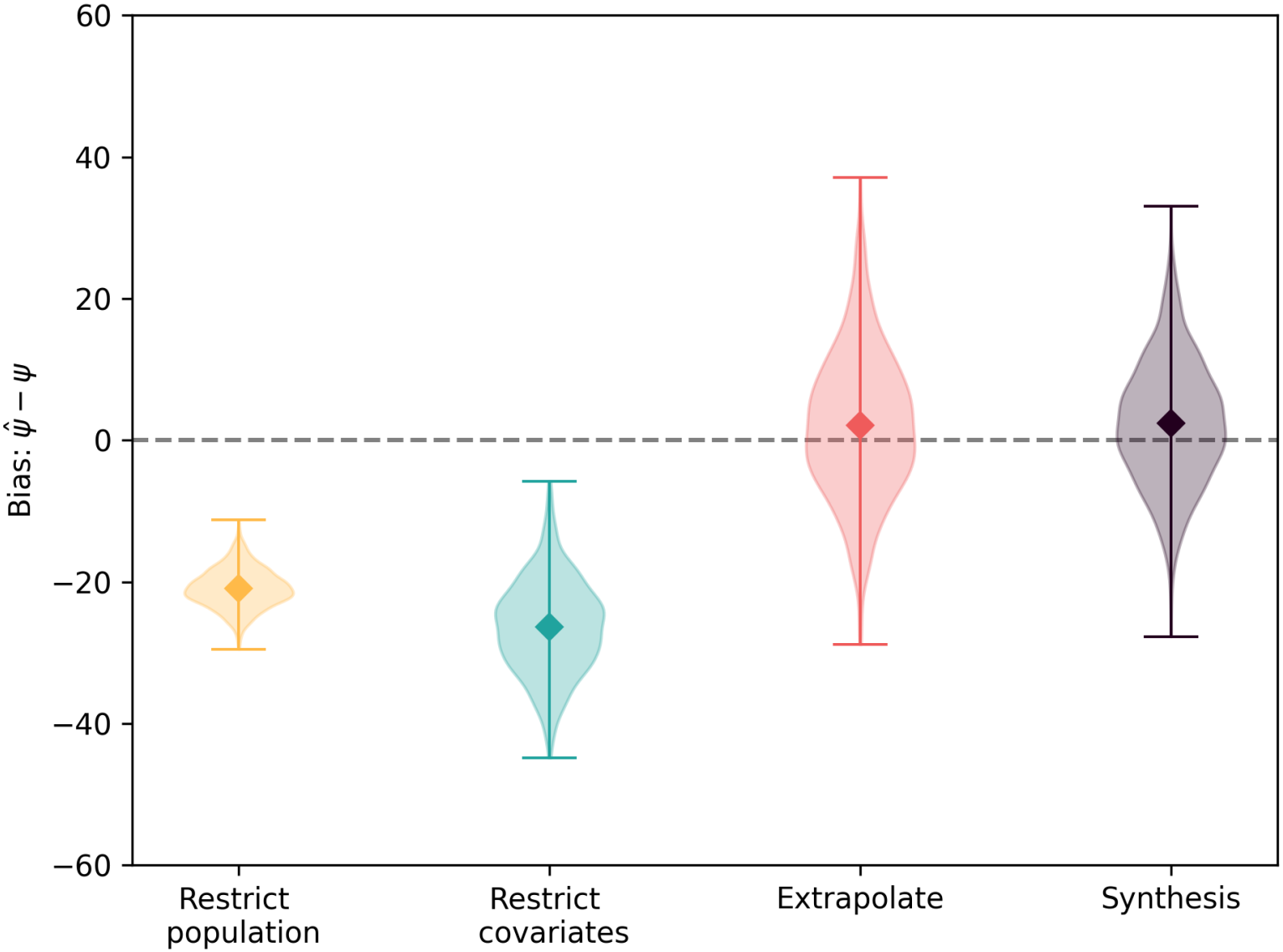
Scenario 1: Setup

$$Y^a = -20 + 70a + V + 0.12aV - 2W + 5aW + \epsilon$$

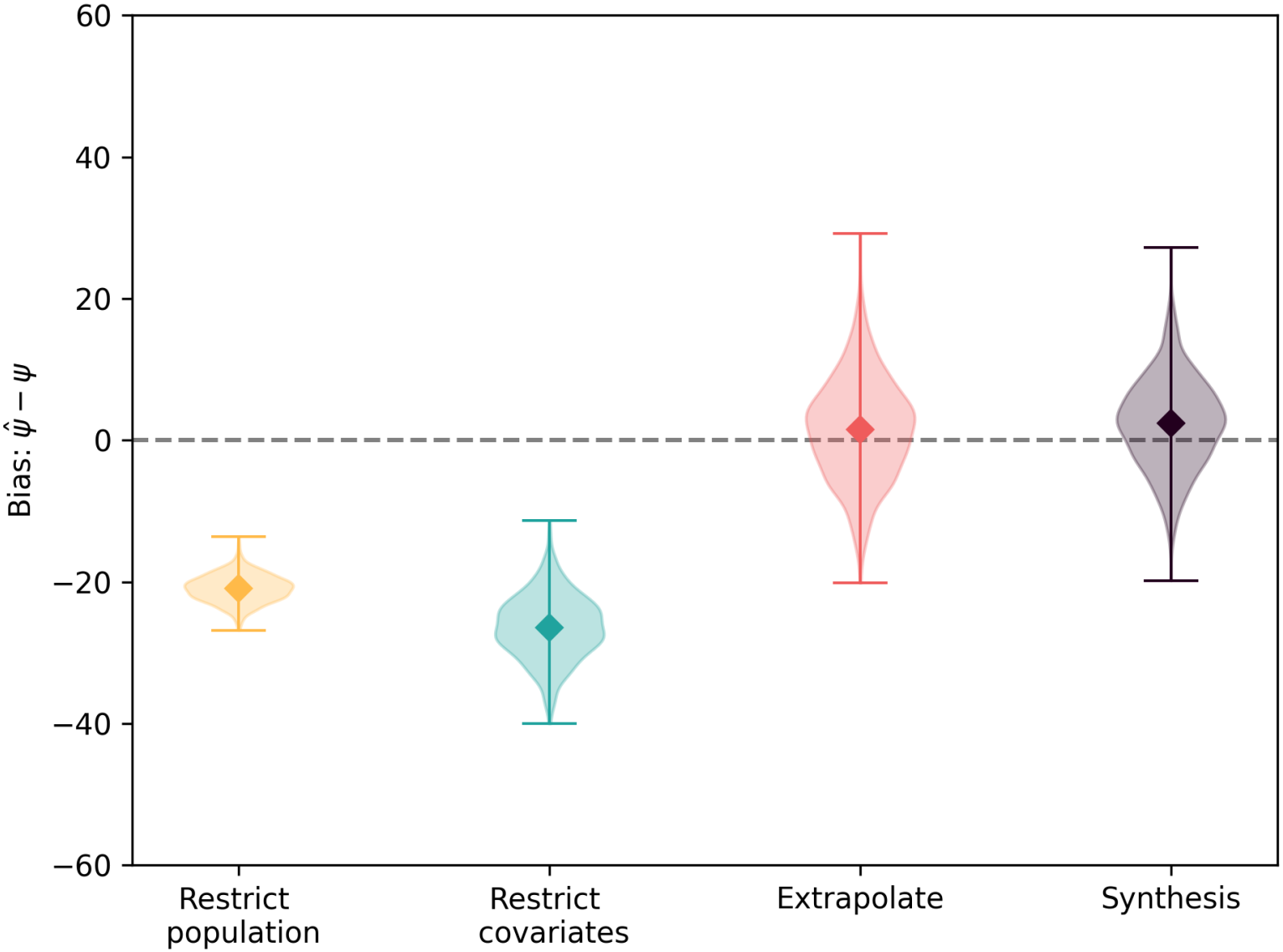
Relationship between Y^a and V doesn't change over V^*

- Extrapolation approach expected to be valid
- Synthesis with valid parameters expected to be valid
- Others are not

Scenario 1: Results, $n_1 = 1000, n_0 = 500$



Scenario 1: Results, $n_1 = 1000, n_0 = 1000$



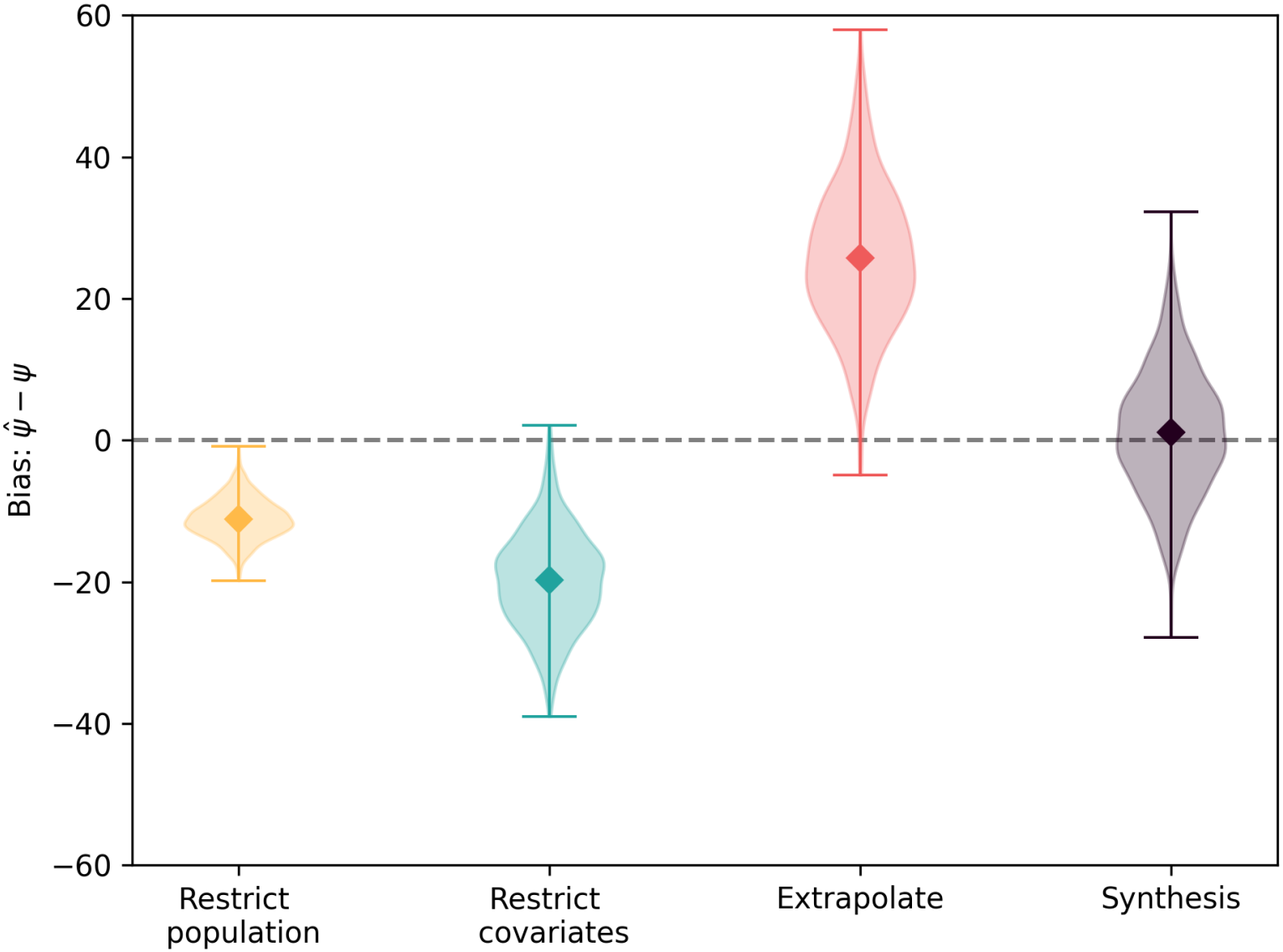
Scenario 2: Setup

$$\begin{aligned} Y^a = & -20 + 70a + V + 0.12aV - 2W + 5aW \\ & - 0.2a\{V - 300\}I(V > 300) - 0.3a\{V - 800\}I(V > 800) \\ & + \epsilon \end{aligned}$$

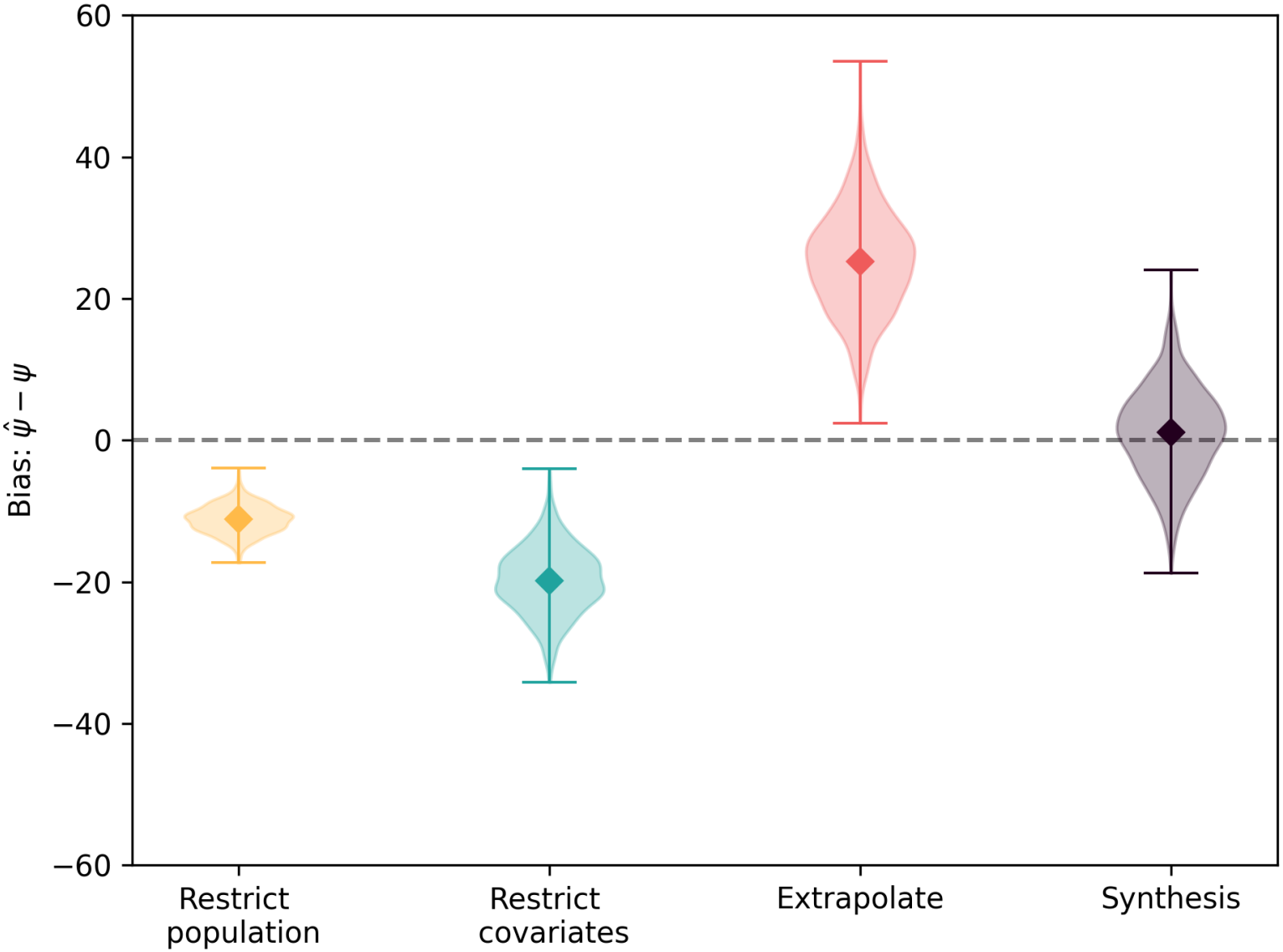
Relationship between Y^a and V changes in $V^* = 1$

- Synthesis with valid parameters expected to be valid
- Others are not

Scenario 2: Results, $n_1 = 1000, n_0 = 500$



Scenario 2: Results, $n_1 = 1000, n_0 = 1000$



Other results

In the pre-print, other items considered

- Different mathematical model parameter specifications
- Alternative estimator based on marginal structural models (MSMs)