PH784 Advanced Social Epidemiology: Methods

Week 6: Effect Modification and Interaction

Koichiro Shiba

kshiba@bu.edu

Boston University School of Public Health

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Today's Plan

1. Causal estimand
    - Summarizing population health
2. Effect modification and interaction
    - Motivation
    - Estimation
    - Interpretation

Let's Step Back: Anatomy of Causal Estimand

$$E[Y^{a=1}] - E[Y^{a=0}]$$

This comparison is defined based on the choice of:

1. Hypothetical interventions to define potential outcomes
    - Well-defined treatment, directionality, regimen (time-varying, dynamic, stochastic)
2. Study population (e.g., mean among whom?)
    - Subpopulation: ATE vs CATE, ATT, ATC, etc
3. Reference (e.g., $a = 0$)
    - vs natural course
4. **Summary measure** (e.g., mean difference)

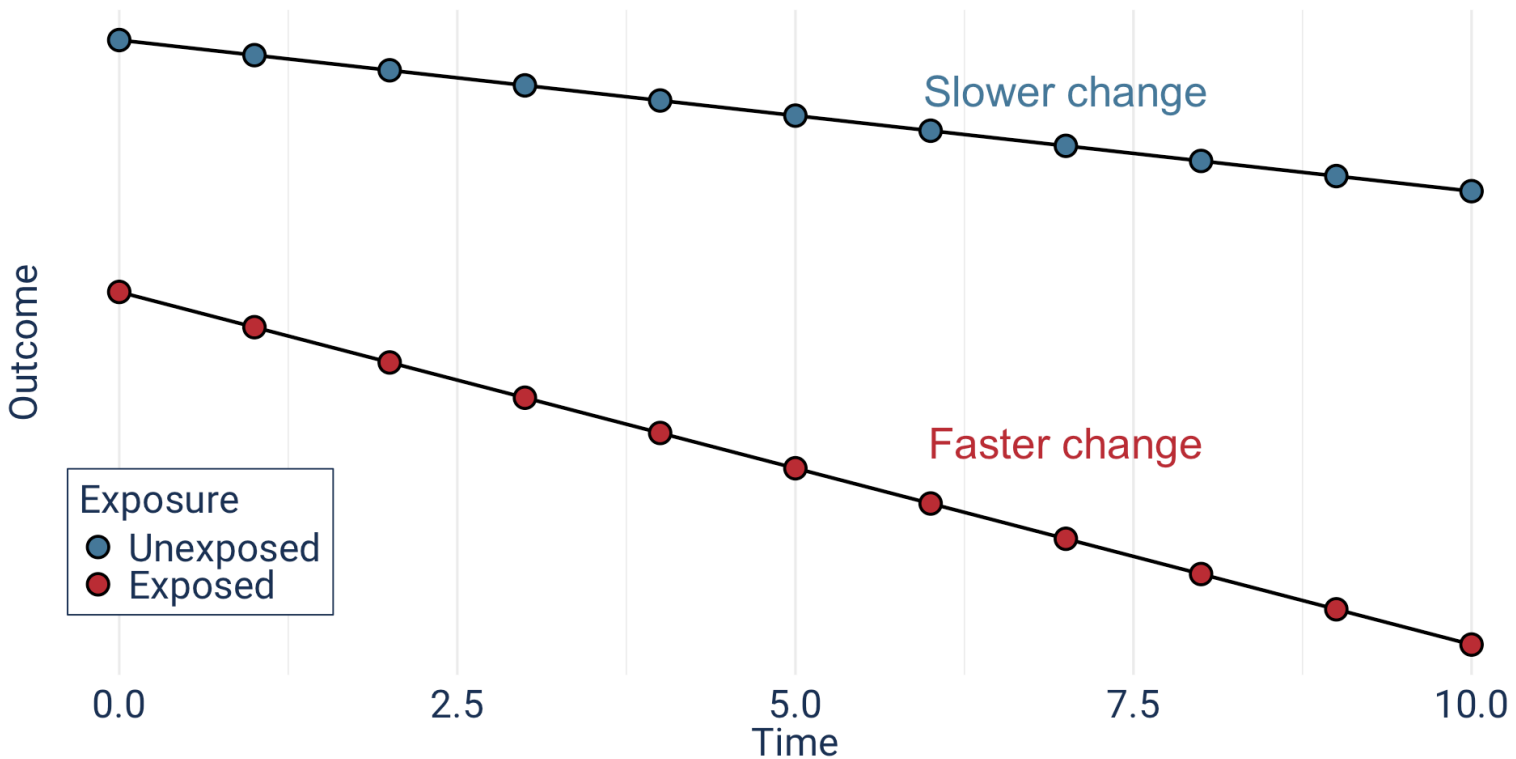
Summarizing Changes in Population Health

- **Continuous outcome**
  - → Mean difference: $E[Y^{a=1}] - E[Y^{a=0}]$
- **Binary outcome**
  - → Risk/prevalence/rate difference: e.g., $Pr[Y^{a=1} = 1] - Pr[Y^{a=0} = 1]$
  - → Risk/prevalence/rate/odds ratio: e.g., $Pr[Y^{a=1} = 1]/Pr[Y^{a=0} = 1]$

⚠**Alternative ways to summarize population health?**

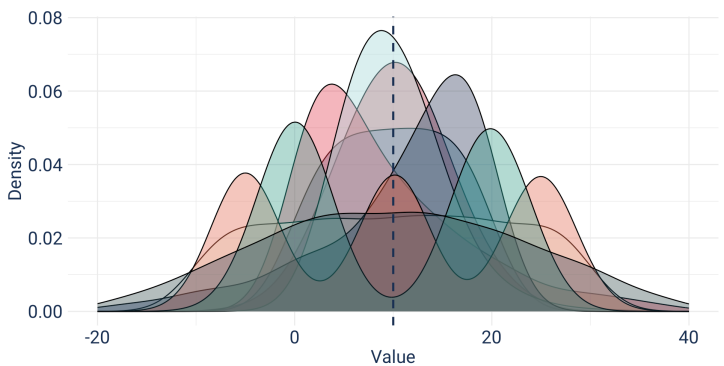
Summarizing Changes in Population Health

- **Trajectories**
  - → Repeated outcome measures
    - Mixed-effect model
    - GEE
  - → e.g., “speed” of cognitive decline (Weuve et al. 2018)

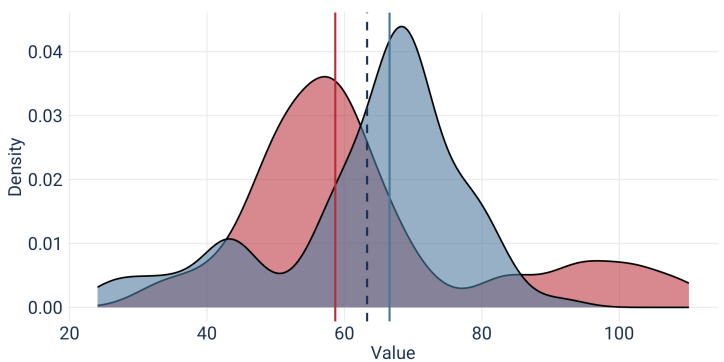


Summarizing Changes in Population Health

Distribution beyond mean



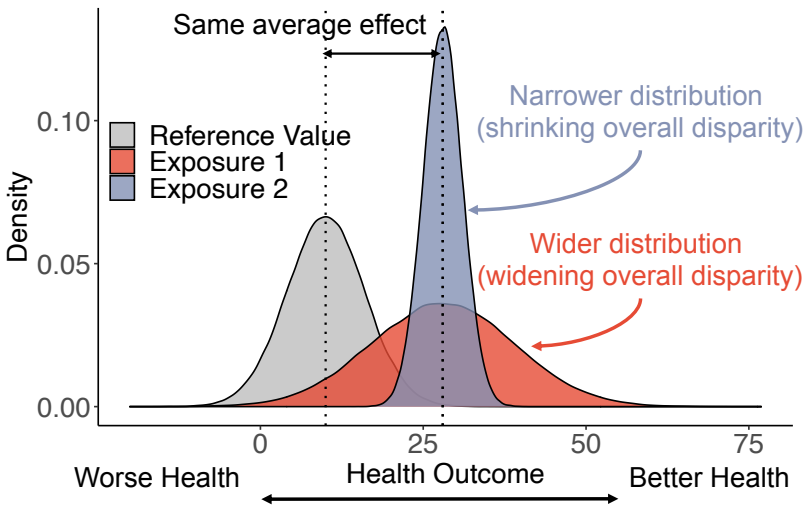
- Mean is just one way of summarizing a full distribution
  - → Different distributions with the same mean
    - e.g., Example by Thomas J Pfaff



- **Change in different parts of the distribution**
  - → e.g., Change in median
    - Quantile regression
      - Excellent tutorial by Khadka et al. (2025)

Summarizing Changes in Population Health

Distribution beyond mean



- Hypothetical interventions may have:
  - → Same "effect" on average population health
  - → Different implications for distributions
    - i.e., health disparities

Shifting the definition of "causal effect"

- "How would the hypothetical intervention change health disparities?"
  - → e.g., $(E[Y^{A^g}|SES = high] - E[Y^{A^g}|SES = low]) - (E[Y|SES = high] - E[Y|SES = low])$
    - for stochastic intervention A^g
  - → "The gap-closing estimand" (Lundberg 2024)
  - → Example: Social isolation and social inequalities in all-cause mortality (Lunar et al. 2025)

Summary 3

- Causal effect is **a contrast of two population health outcomes under hypothetical/counterfactual scenarios**
  - → Mean difference/ratio is not the only way to summarize population health
- Outcome trajectories
- Distributional shift
- Change in disparities

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Average Effect $\neq$ "Effect for All"

ID	A	Y	$Y^{a=1}$	$Y^{a=0}$	Effect
1	1	120	120	160	<0
2	0	115	110	115	<0
3	0	140	135	140	<0
4	0	140	130	140	<0
5	1	115	115	116	<0
6	0	120	115	120	<0
7	1	110	110	115	<0
8	1	120	120	130	<0
9	1	130	130	130	0
10	0	130	140	130	>0

- Causal effects defined as a contrast of mean potential outcomes
  - → e.g., Beneficial ATE: $E[Y_i^1 - Y_i^0] < 0$
- **Individual-level effects are heterogeneous**
  - → $Y_i^1 - Y_i^0 < 0$ (**beneficial effect**)
    - $Y_{i=1}^1 - Y_{i=1}^0 = -40$
    - $Y_{i=5}^1 - Y_{i=5}^0 = -1$
  - → $Y_{i=9}^1 - Y_{i=9}^0 = 0$ (**no effect**)
  - → $Y_{i=10}^1 - Y_{i=10}^0 > 0$ (**harmful effect**)

⚠ **However, individual effects ($Y_i^{a=1} - Y_i^{a=0}$) are unknown**

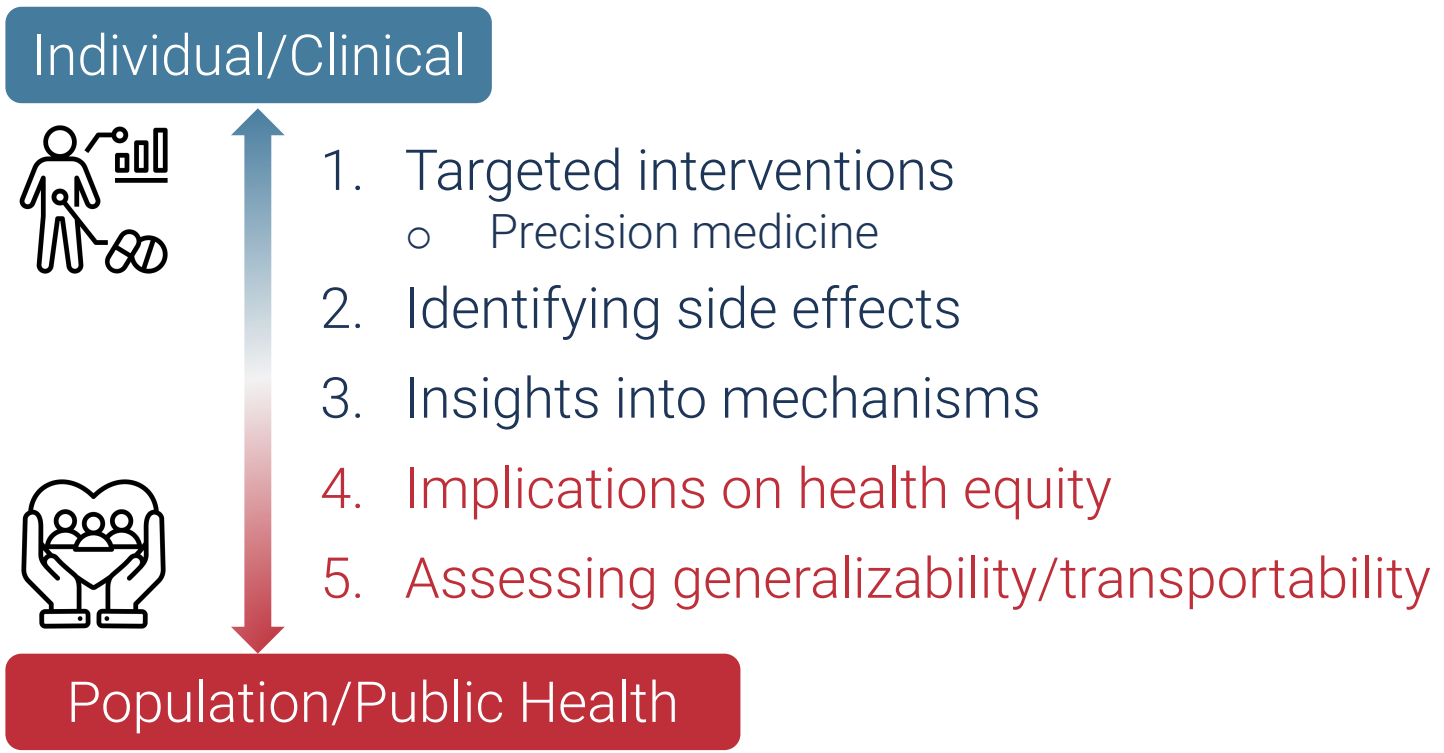
Practical Approach for Assessing Effect Heterogeneity

ID	A	Y	Q
1	1	120	1
2	0	115	1
3	0	140	1
4	0	140	1
5	1	115	1
6	0	120	0
7	1	110	0
8	1	120	0
9	1	130	0
10	0	130	0

- Estimate **average** effect among subgroups
  - → Conditional average treatment effect (CATE)
- $\tau(Q=1) = E[Y_i^1 - Y_i^0 | Q=1]$
  - → Average treatment effect among those with Q=1
- $\tau(Q=0) = E[Y_i^1 - Y_i^0 | Q=0]$
  - → Average treatment effect among those with Q=0
- If these two CATEs were different
  - → i.e., $\tau(Q=1) \neq \tau(Q=0)$
  - → **Effect measure modification** by Q
    - Scale dependent (VanderWeele and Knol 2014)

Motivation for Assessing Effect Heterogeneity

Why does it matter?



Effect Heterogeneity and Generalizability/Transportability

- "Is this finding applicable to different people?"
  - → External validity



Key determinants (Hernán and VanderWeele 2011**)**

1. Degree of effect heterogeneity
2. Distribution of its sources

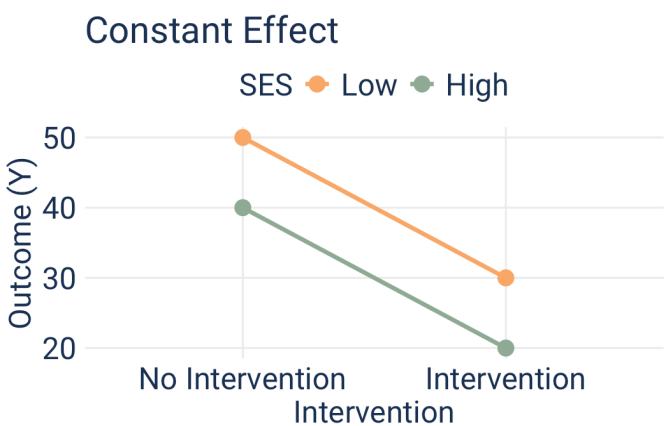
- "Contradictory" findings across methods
  - → Different target populations (i.e., different estimands)
    - e.g., IV vs outcome regression
  - → Both can be correct with effect heterogeneity and differential distributions of modifiers

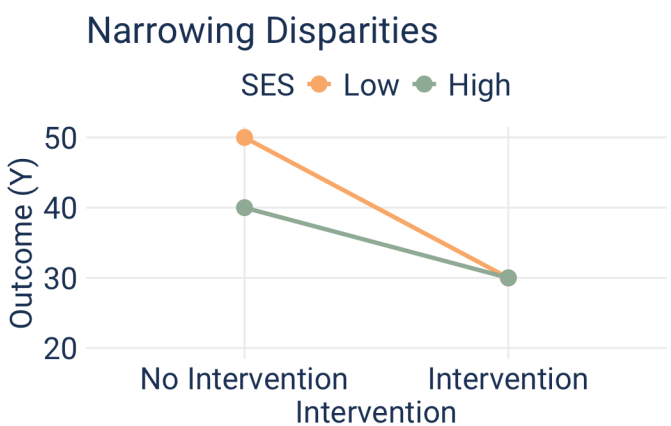
Effect Heterogeneity and Health Disparities

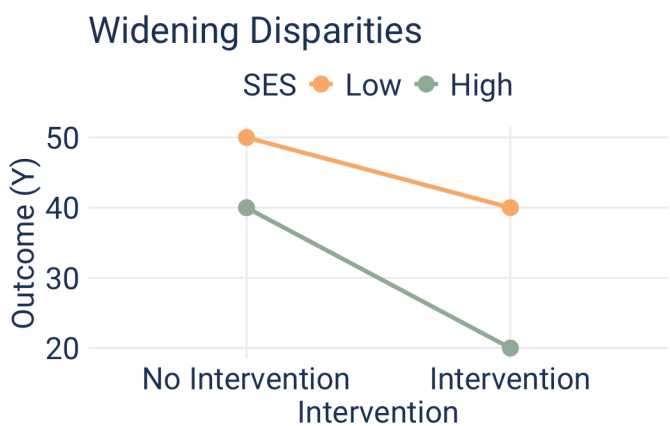
- Evidence of effect heterogeneity
  - → Treatment is more effective among patients with characteristics X, Y, Z,…
  - → Obvious conclusion: “Treat those individuals for whom the treatment is more effective”
    - Precision medicine (Dahabreh and Kazi 2023; Inoue et al. 2023)
- Issues with tailored interventions
  - → Not always feasible
  - → Not necessarily greater population impacts
  - → Who are those “lucky” people?
    - Cost-effective interventions that might end up widening disparities?

Effect Heterogeneity and Health Disparities

- Public health interventions could:
  - → Narrow disparities
    - When more effective among socially marginalized groups
      - e.g., Investment in community resources
      - Vulnerable population approach (Frohlich and Potvin 2008)
  - → Widen disparities
    - When less effective among socially marginalized groups
      - e.g., Health information campaigns (Federico et al. 2007)







Summary 1

- **Effect heterogeneity**
  - → Assessment based on CATEs
- **Motivation beyond “more targeted interventions”**
  - → Transportability
    - Effect heterogeneity and different distribution of its sources
  - → Health disparities

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Estimating CATEs

1. Subgroup analysis
2. Parametric regression model with a product term

$$E[Y|A, Gender, Race, L] = \beta_0 + \beta_1 A + \beta_2 Gender + \beta_3 A \times Gender + \beta_4 Race + L\gamma$$

- $E[Y|A = 1, Gender = 0, Race, L] - E[Y|A = 0, Gender = 0, Race, L]$
  - → Adjusted association between A and Y among $Gender = 0$
  - → β_1
    - $E[Y|A = 1, Gender = 0, Race, L] = \beta_0 + \beta_1 + \beta_4 Race + L\gamma$
    - $E[Y|A = 0, Gender = 0, Race, L] = \beta_0 + \beta_4 Race + L\gamma$
- $E[Y|A = 1, Gender = 1, Race, L] - E[Y|A = 0, Gender = 1, Race, L]$
  - → Adjusted association between A and Y among $Gender = 1$
  - → $\beta_1 + \beta_3$
    - $E[Y|A = 1, Gender = 1, Race, L] = \beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 Race + L\gamma$
    - $E[Y|A = 0, Gender = 1, Race, L] = \beta_0 + \beta_2 + \beta_4 Race + L\gamma$

Estimating CATEs

1. Subgroup analysis
2. Parametric regression model with a product term

$$E[Y|A, Gender, Race, L] = \beta_0 + \beta_1 A + \beta_2 Gender + \beta_3 A \times Gender + \beta_4 Race + L\gamma$$

- Effect by gender (β_1 for $Gender = 0$ and $\beta_1 + \beta_3$ for $Gender = 1$)
  → Do not call β_1 "main effect"
- This model technically estimates CATEs conditional on all covariates
  → $E[Y^{a=1} - Y^{a=0}|Gender, Race, L]$

Assumptions

- No EMM by other variables (e.g., lack of $A \times Race$)
- No high-dimensional interactions (e.g., lack of $A \times Gender \times Race$)
  → Assumed absence of intersectionality
- All other modeling assumptions (e.g., linearity for continuous variables)

Estimating CATEs

Limitations of parametric modeling

1. Restrictive (& unrealistic) modeling assumptions
2. Require a priori hypothesis

Non-parametric modeling

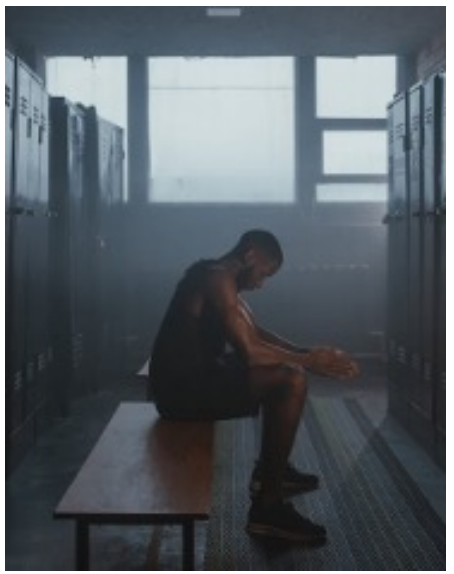
- Data-adaptive estimation via machine learning algorithms
  - → Assumption-lean modeling
  - → Causal forest (Shiba and Inoue 2024), meta-learners (Salditt et al. 2024)

Benefits

1. High-dimensional covariate set
   - CATE conditional on numerous covariates L: $E[Y^{a=1} - Y^{a=0}|L]$
2. Synergism
   - Naturally captures intersectionality
3. Non-linear effect heterogeneity

High-dimensional Effect Heterogeneity: An Applied Example

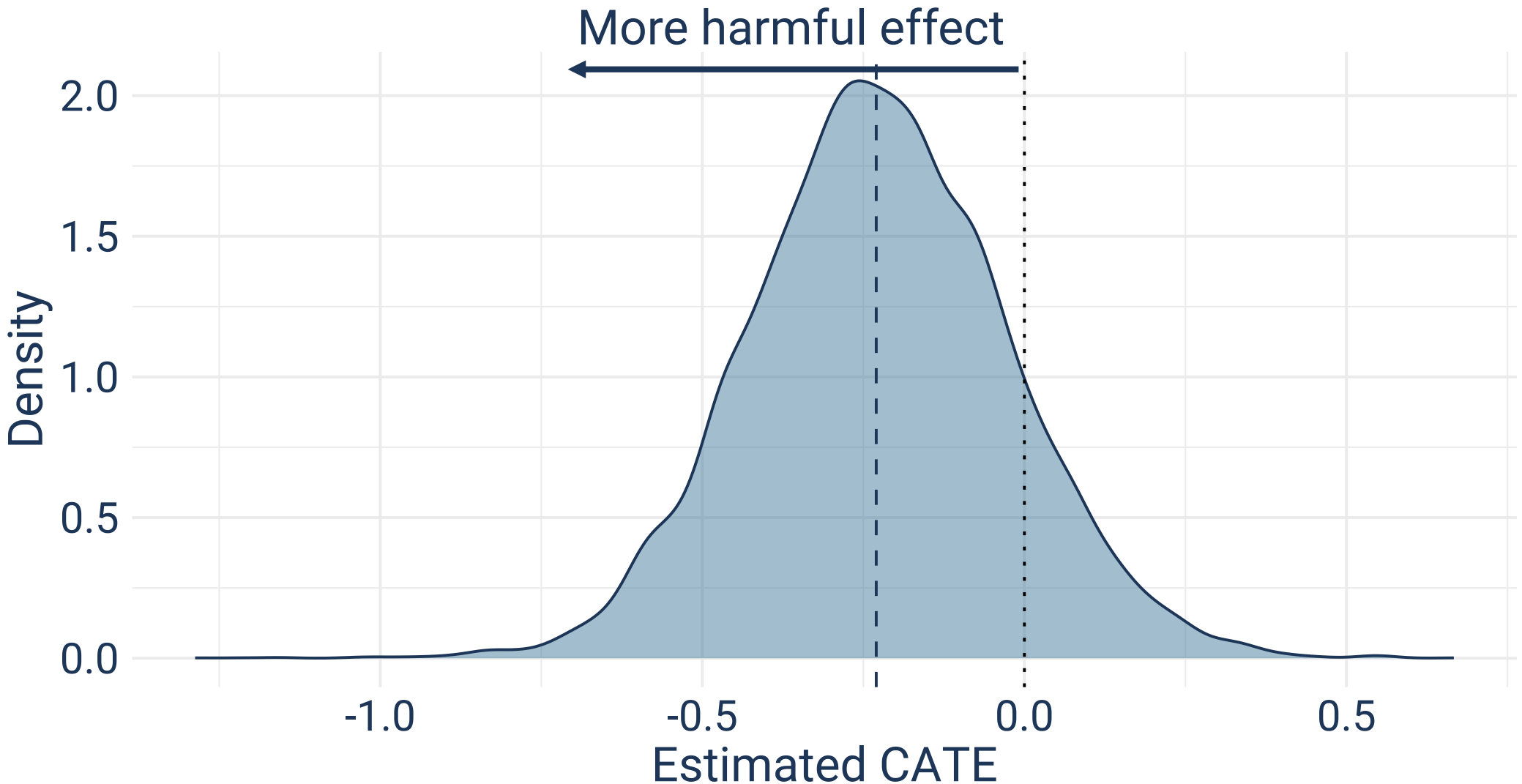
Social isolation and cognitive functioning of older adults



- **Data:** Health and Retirement Study (n=11,322)
- **Exposure:** Social isolation (dichotomized composite index)
  - → Marital status and cohabitation
  - → Contact with children, family, and friends
  - → Social participation
- **Outcome:** Cognitive functioning (TICS; 0-27 points)
- **Covariates:** 35 pre-baseline covariates
- **Analysis:** Causal forest
  - → Non-parametric estimation of CATE ($E[Y^{a=1} - Y^{a=0}|L]$)
  - → This is NOT an individual-level effect
    - But different estimate across individuals in practice

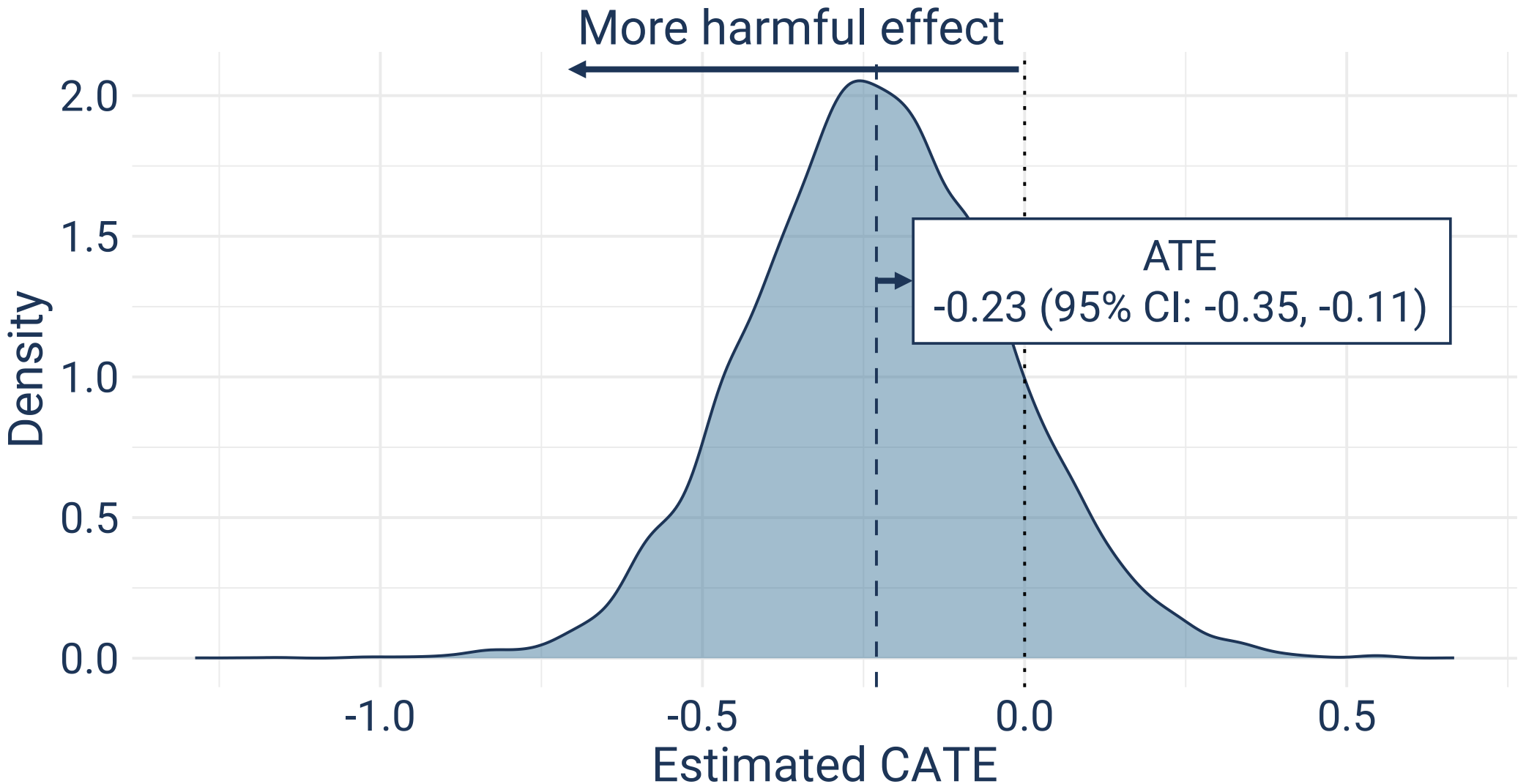
High-dimensional Effect Heterogeneity: An Applied Example

Social isolation and cognitive functioning of older adults



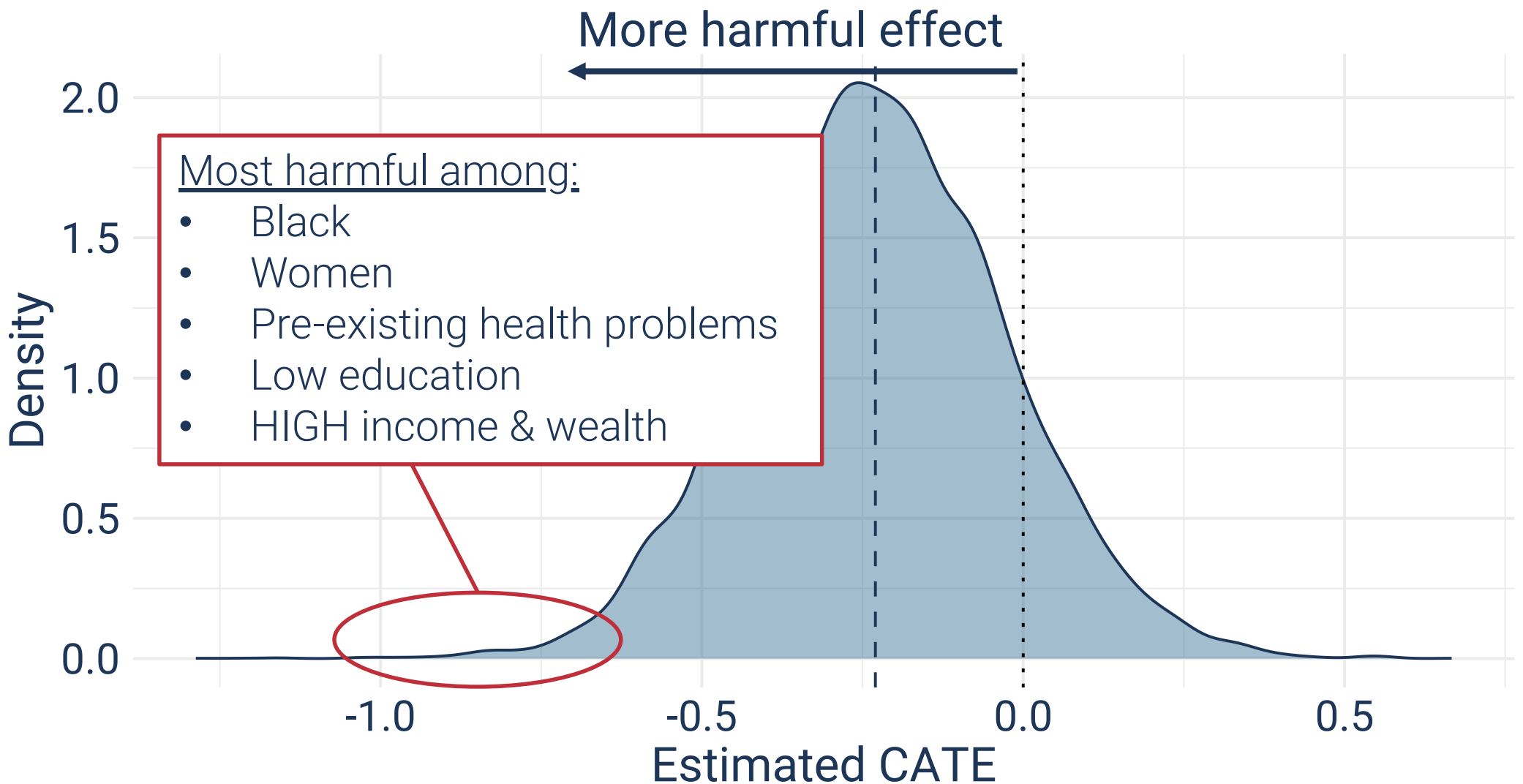
High-dimensional Effect Heterogeneity: An Applied Example

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High-dimensional Effect Heterogeneity: An Applied Example

Social isolation and cognitive functioning of older adults



ML for Causal Inference: Hype or Hope?

What ML estimates:

- $E[Y|A = a, L] - E[Y|A = a^*, L]$
  - Conditional expectations
  - with high-dimensional L



What you want to know:

- $E[Y^a - Y^{a^*}|L]$
  - CATE for all strata of L
  - Still average (but closer to individual effect)

ML improves estimation but not identification

- Still require the same causal identification assumptions
  - → e.g., no confounding
- Not “data-driven” causal inference

Summary 2

- **Estimating CATEs**
  - → Subgroup analysis
  - → Parametric regression with a product term
    - Underlying assumptions about effect heterogeneity
  - → **Non-parametric ML approach**
    - High-dimensional and complex CATEs
      - Data-adaptive estimation of conditional expectations
    - Still requires the same causal identification assumptions

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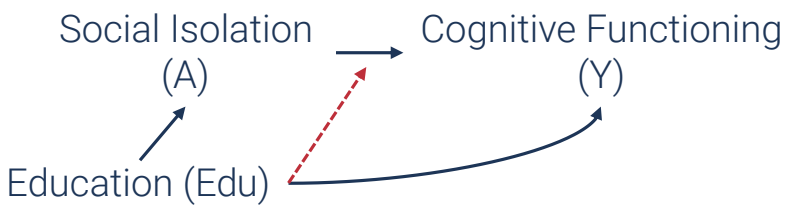
Interpretation of Varying CATEs

Example: The effect of social isolation on cognitive functioning by education

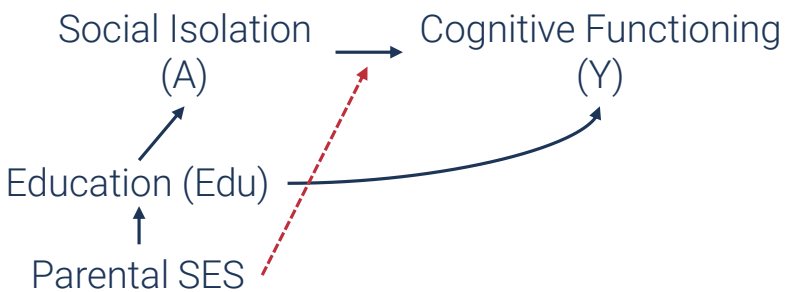
- $E[Y^{a=1} - Y^{a=0}|Edu = high] > E[Y^{a=1} - Y^{a=0}|Edu = low]$
  - → $Y^{a=1} - Y^{a=0} < 0$ indicates decreased cognitive functioning (i.e., harmful effect)

- **Interpretation?**
  - → Less harmful effect among those with higher educational attainment
    - Effect heterogeneity, effect (measure) modification, moderation,...
- **Insights?**
  1. *Prioritization/targeted interventions*
  - → e.g., Use finite resources to remove social isolation among those with low education
  2. *Potential unintended consequences of interventions*
  - → e.g., It is harmful and should be removed anyway
  3. *Equity*
  - → e.g., Policies to prevent isolation may narrow education-based outcome disparities
  4. *How treatment effect can be altered*

What Alters The Treatment Effect?



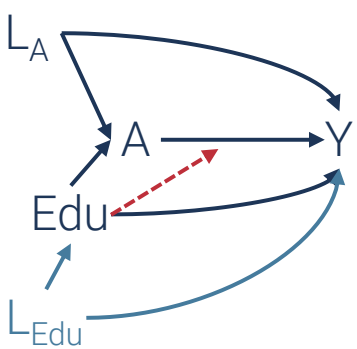
- Education itself
  - → Education causally makes social isolation less harmful (“Get educated”)
    - e.g., Cognitively stimulating solo activities?



- Correlates of education
  - → Non-causal explanation of effect heterogeneity by education
    - e.g., genes, parental education

Alternative Causal Estimand

- Can we alter exposure effects by modifying something else (e.g., Edu)?
  - → e.g., mitigating effects of social exposures that are hard to change
  - → A hypothetical intervention targets the additional variable too
    - Joint intervention
      - $E[Y^{a=1,edu=high} - Y^{a=0,edu=high}] \neq E[Y^{a=1,edu=low} - Y^{a=0,edu=low}]$
    - **Causal interaction**



! Additional assumption

- Requires identification for Edu
  - → e.g., Conditional exchangeability for BOTH A and Edu

Effect Heterogeneity vs Causal Interaction

- **Effect heterogeneity** $E[Y^{a=1} - Y^{a=0}|L = l] \neq E[Y^{a=1} - Y^{a=0}|L = l^*]$
  - → Descriptive (How does the exposure effect vary across individuals?)
  - → Insights
    - Targeted interventions
    - Effect distributions (backfiring and equity implications)
    - Hypothesis generation about causal interaction
      - But acknowledge non-causal alternatives
- **Causal interaction** $E[Y^{a=1,l} - Y^{a=0,l}] \neq E[Y^{a=1,l^*} - Y^{a=0,l^*}]$
  - → How do we alter exposure effects?
    - Making harmful exposures less harmful
    - Making beneficial exposures more beneficial
  - → Explicitly estimate joint intervention effects
    - Additional causal identification

> Explicitly state whether confounding adjustment was made only for exposure or for both

Terminology

- **Effect heterogeneity**
  - → Varying CATEs: $E[Y^{a=1} - Y^{a=0}|L = l] \neq E[Y^{a=1} - Y^{a=0}|L = l^*]$
  - → Descriptive in nature
    - Statistical interaction
      - Product term
    - (Effect modification/moderation)
    - (Effect measure modification)
- **Causal interaction**
  - → Interpretation as a joint intervention: $E[Y^{a=1,l} - Y^{a=0,l}] \neq E[Y^{a=1,l^*} - Y^{a=0,l^*}]$

- It is not productive to debate which terms to use
- Distinguish the two conceptually different causal estimand
  - → CATE of A conditional on L versus joint intervention for A and L

The “WHY” of Effect Heterogeneity

Example: The effect of social isolation on cognitive functioning by education

- $E[Y^{a=1} - Y^{a=0}|Edu = high] > E[Y^{a=1} - Y^{a=0}|Edu = low]$
  - → Less harmful effect among those with higher educational attainment

Sources of effect heterogeneity?

- Causal interaction by:
  - → Education itself
  - → Correlates of education
- What else?

The “WHY” of Effect Heterogeneity

Example: The effect of social isolation on cognitive functioning by education

- $E[Y^{a=1} - Y^{a=0}|Edu = high] > E[Y^{a=1} - Y^{a=0}|Edu = low]$
  - → Less harmful effect among those with higher educational attainment
- **Multiple versions of treatment**
  - → Less harmful versions of social isolation among those with education?
    - e.g., living alone vs not meeting with friends regularly
    - e.g., 5 points vs 6 points (both defined as isolated with a cutoff of ≥3 points)



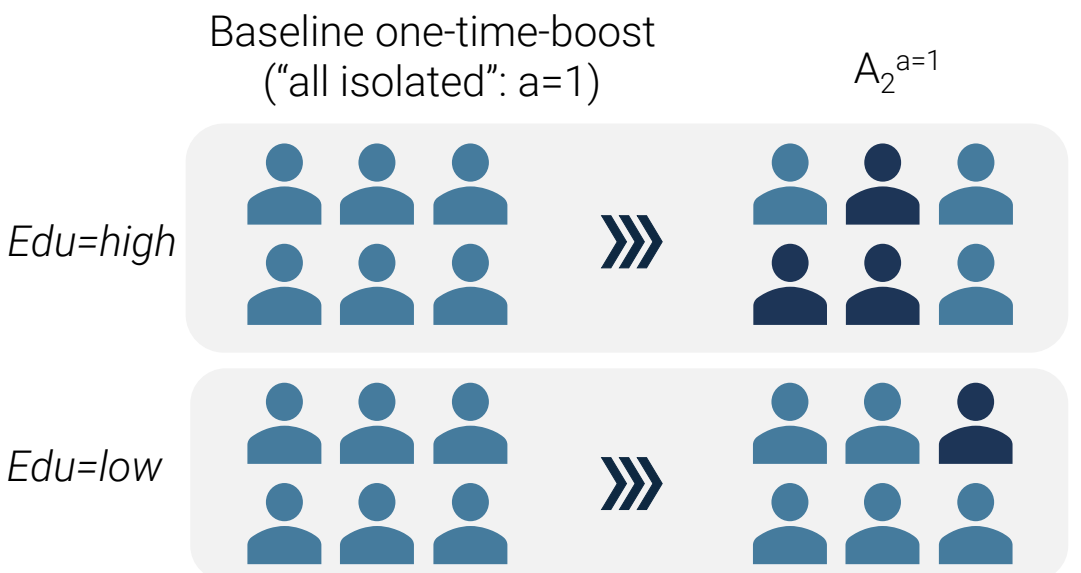


The “WHY” of Effect Heterogeneity

Example: The effect of social isolation on cognitive functioning by education

- $E[Y^{a=1} - Y^{a=0}|Edu = high] > E[Y^{a=1} - Y^{a=0}|Edu = low]$
  - → Less harmful effect among those with higher educational attainment
- **Different degree of compliance to the “one-time boost”**
  - → Individuals with education recover from social isolation quickly, while those with low education remain isolated?
  - → Same effect if sustained?
    - $E[Y^{a=1,a_2=1} - Y^{a=0,a_2=0}|Edu = high] = E[Y^{a=1,a_2=1} - Y^{a=0,a_2=0}|Edu = low]$





The “WHY” of Effect Heterogeneity

Example: The effect of social isolation on cognitive functioning by education

- $E[Y^{a=1} - Y^{a=0}|Edu = high] > E[Y^{a=1} - Y^{a=0}|Edu = low]$
  - → Less harmful effect among those with higher educational attainment

! Sources of effect heterogeneity

- Causal interaction by:
  - → Education itself
  - → Correlates of education
- Multiple versions of treatment
- Differential treatment trajectories
- Different degree of measurement error

Summary 3

- **Insights**
  - → Prioritization, potential unintended consequences, equity
  - → **Causal interaction**
    - By the covariate itself or its correlates
    - Can be explicitly estimated as a joint intervention with additional identification assumptions
- **Sources of effect heterogeneity**
  - → Causal interaction
  - → Alternative explanations
    - multiple versions, treatment trajectories, measurement error

Population Interventions and Health Disparity

- Interventions may alter health disparities across social groups via:
  - → **Socially patterned effect heterogeneity**
    - $E[Y^{a=1} - Y^{a=0}|L = l] \neq E[Y^{a=1} - Y^{a=0}|L = l^*]$
    - Narrow disparities if more beneficial among minoritized groups
    - Widen disparities if less beneficial among minoritized groups
  - → **Disproportionate change in exposure distribution**
    - If minoritized groups experienced greater changes in exposure, they benefit more
    - Ignored in the “all treated” scenario of CATE

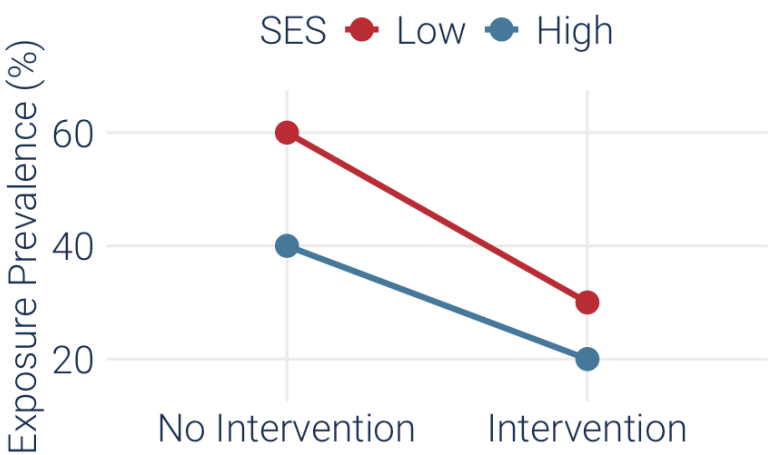
(!) Estimating CATEs alone is inadequate

When do interventions result in disproportionate change in exposure?

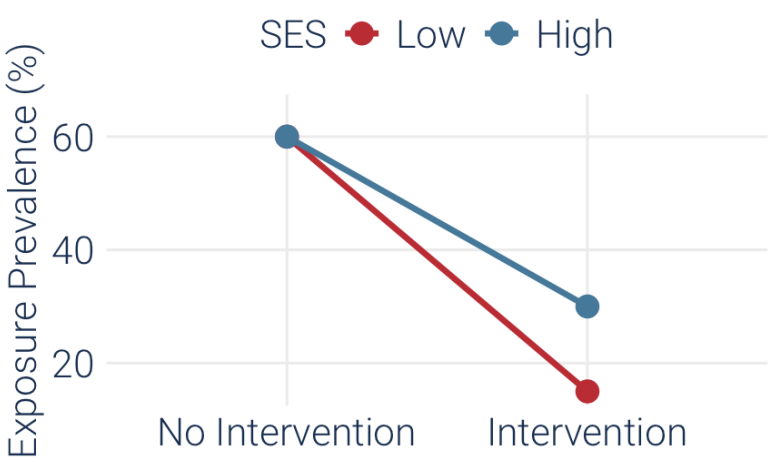
Population Interventions and Health Disparity

When do interventions disproportionately change exposure distributions?

- **Existing exposure disparity**
  - → More prevalent among the low SES group
  - → Even the same relative reduction would result in greater absolute reduction
    - e.g., reducing exposure by half
      - 60% to 30% (30 percentage points reduction)
      - 40% to 20% (20 percentage points reduction)



- **Disproportionate reduction in the exposure**
  - → Even when there is no exposure disparity
    - Exposure prevalence 60% in both SES groups
      - 60% to 15% (quarter)
      - 60% to 30% (half)
    - Distinguish this from effect heterogeneity
  - → *Example?*
    - Water fluoridation



Population Interventions and Health Disparity

How do we simulate effects on health disparities rather than average health?

- Key ingredients of health disparities
  - → **Effect heterogeneity**
    - $E[Y^{a=1} - Y^{a=0}|L = l] \neq E[Y^{a=1} - Y^{a=0}|L = l^*]$
  - → **Disproportionate changes in exposure**
    - How do we incorporate disproportionate changes in exposure in causal estimand?
    - Stochastic intervention
      - Various estimators (e.g., Muñoz and Van Der Laan 2012)
        - e.g., Standardization (as in Ahern et al. 2016)

Population Interventions and Health Disparity

How do we simulate effects on health disparities rather than average health?

ID	Y	A	L	$\tau(L)$	$a=1$	$a=0$	$Y^{a=1}$	$Y^{a=0}$
1	Y_1	1	ℓ_1	τ_1	1	0	Y_1	$Y_1 - \tau_1$
2	Y_2	0	ℓ_2	τ_2	1	0	$Y_2 + \tau_2$	Y_2
3	Y_3	0	ℓ_3	τ_3	1	0	$Y_3 + \tau_3$	Y_3
$\dots$	$\dots$	$\dots$	$\dots$	$\dots$	$\dots$	$\dots$	$\dots$	$\dots$
n	Y_n	A_n	ℓ_n	τ_n	1	0	$Y_n + (1 - A_n)\tau_n$	$Y_n - A_n\tau_n$

- **Simple standardization for static interventions**
  - → #1 Assign everyone to be treated $a = 1$ (6th column) and untreated $a = 0$ (7th column)
  - → #2 Predict potential outcome under each scenario ($Y^{a=1}$ & $Y^{a=0}$)
    - Based on estimated effects τ_i
  - → #3 Calculate mean of $Y^{a=1}$ and mean of $Y^{a=0}$ across all individuals
  - → #4 Calculate the difference between the two means & bootstrap
    - ATE: $E[Y^{a=1}] - E[Y^{a=0}]$

Population Interventions and Health Disparity

How do we simulate effects on health disparities rather than average health?

ID	Y	A	L	$\tau(L)$	A^g	Y^{A^g}
1	Y_1	1	ℓ_1	τ_1	1	Y_1
2	Y_2	0	ℓ_2	τ_2	0	Y_2
3	Y_3	0	ℓ_3	τ_3	1	$Y_3 + \tau_3$
...	...	...	...	...	...	...
n	Y_n	A_n	ℓ_n	τ_n	A_i^g	$Y_n + (A_i^g - A_n)\tau_n$

- **Standardization for stochastic interventions**
  - → #1 Assign exposure distributions under a stochastic intervention of interest
    - e.g., randomly removing exposure by 50%
    - e.g., lowering propensity scores by 50%
  - → #2 Predict potential outcome Y^{A^g} based on estimated effects τ_i
  - → #3 Calculate mean of Y^{A^g} and mean of observed outcome Y across all individuals
  - → #4 Calculate the difference between the two means & bootstrap
    - Stochastic intervention effect: $E[Y^{A^g}] - E[Y]$
      - What would happen to the population health under the simulated stochastic intervention compared to no intervention

Population Interventions and Health Disparity

How do we simulate effects on health disparities rather than average health?

ID	Y	A	L	$\tau(L)$	A^g	Y^{A^g}
1	Y_1	1	ℓ_1	τ_1	1	Y_1
2	Y_2	0	ℓ_2	τ_2	0	Y_2
3	Y_3	0	ℓ_3	τ_3	1	$Y_3 + \tau_3$
...	...	...	...	...	...	...
n	Y_n	A_n	ℓ_n	τ_n	A_i^g	$Y_n + (A_i^g - A_n)\tau_n$

- **Standardization for stochastic interventions on health disparities**
  - → #1 Assign exposure distributions under a stochastic intervention of interest
  - → #2 Predict potential outcome Y^{A^g} based on estimated effects τ_i
  - → #3 Calculate disparities in Y^{A^g} and disparities in observed outcome Y
    - Can use ANY disparity metric from Lecture 1
  - → #4 Calculate the difference between the two disparities & bootstrap
    - e.g., $(E[Y^{A^g}|SES = high] - E[Y^{A^g}|SES = low]) - (E[Y|SES = high] - E[Y|SES = low])$
      - "How would the hypothetical intervention change SES-based health disparities?"
    - "The gap-closing estimand" (Lundberg 2024)
      - Example: Social isolation and social inequalities in all-cause mortality (Lunar et al. 2025)

Assignment

- Problem Set #6
- Reading quiz based on:
    1. Nguyen TQ, Schmid I, Stuart EA. Clarifying causal mediation analysis for the applied researcher: Defining effects based on what we want to learn. Psychological Methods. 2021 Apr;26(2):255.
    2. Jackson JW, VanderWeele TJ. Decomposition analysis to identify intervention targets for reducing disparities. Epidemiology. 2018 Nov 1;29(6):825-35.
- Final Assignment (due October 24th at 11:59 PM)

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