Sensitivity analyses for partially or fully unobserved effect modifiers when calibrating treatment effects from a randomized trial to a target population

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joint work with

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Outline

Background

- In public health/public policy, there are times we want to know the broad population effects of a treatment, intervention or policy change
- A randomized trial may have been conducted and an average treatment effect estimated (SATE)
- The effect of the intervention if applied to a target population (TATE) may be different from SATE if
  - there is treatment effect heterogeneity, and
  - trial sample is different from target population w.r.t the distribution of factors that modify treatment effects
- Methods exist to estimate TATE, which require target population covariates data, especially data on effect modifiers
  - re-weighting trial sample to target population
  - model outcome in trial and predict outcome in target population

Background

Example 1: A trial found that a smoking cessation intervention is effective for heavy cigarette smokers who attend treatment programs for abuse of illicit substances. Do we want to scale up this intervention to cover people who seek substance abuse treatment in the US who are heavy smokers?

Example 2: A trial found that an antiretroviral therapy regimen is superior to a standard regimen in improving immune function. Should this regimen be generally recommended for people living with HIV?

Purpose

What if

- there is an effect modifier observed in the trial but we don't have data on it from the target population?
- we are concerned there might be effect modification that is not even observed in the trial?

Sensitivity analyses are needed.

Our purpose: Develop simple procedures for use by substantive scientists

Notation

A: treatment (0,1), randomized in the trial
Y: outcome (observed only in the trial)
Y^a: potential outcome under treatment a, $a = 0, 1$

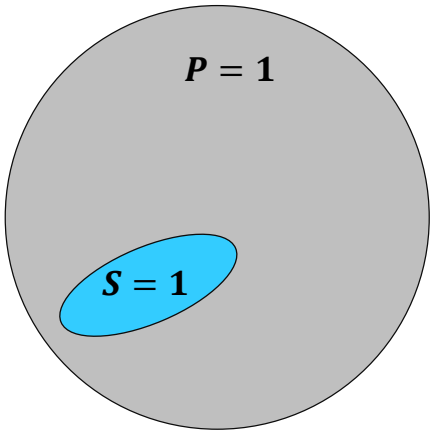
$S = 1$: trial participation
$P = 1$: target population membership

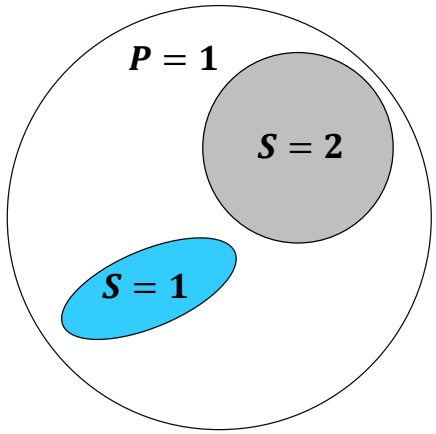
$$\text{SATE} = \text{E}[Y^1 - Y^0 | S = 1]$$
$$\text{TATE} = \text{E}[Y^1 - Y^0 | P = 1]$$

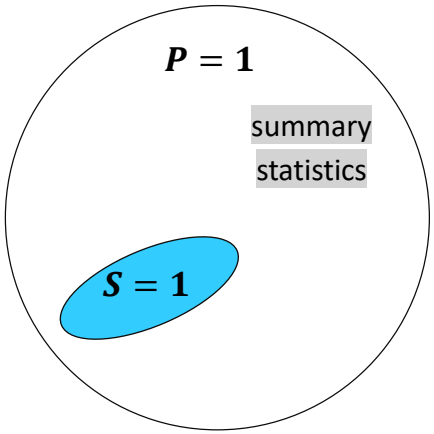
Notation

Target population data scenarios:

- a full population ($P = 1$) dataset
- a representative sample ($S = 2$) dataset
- summary statistics







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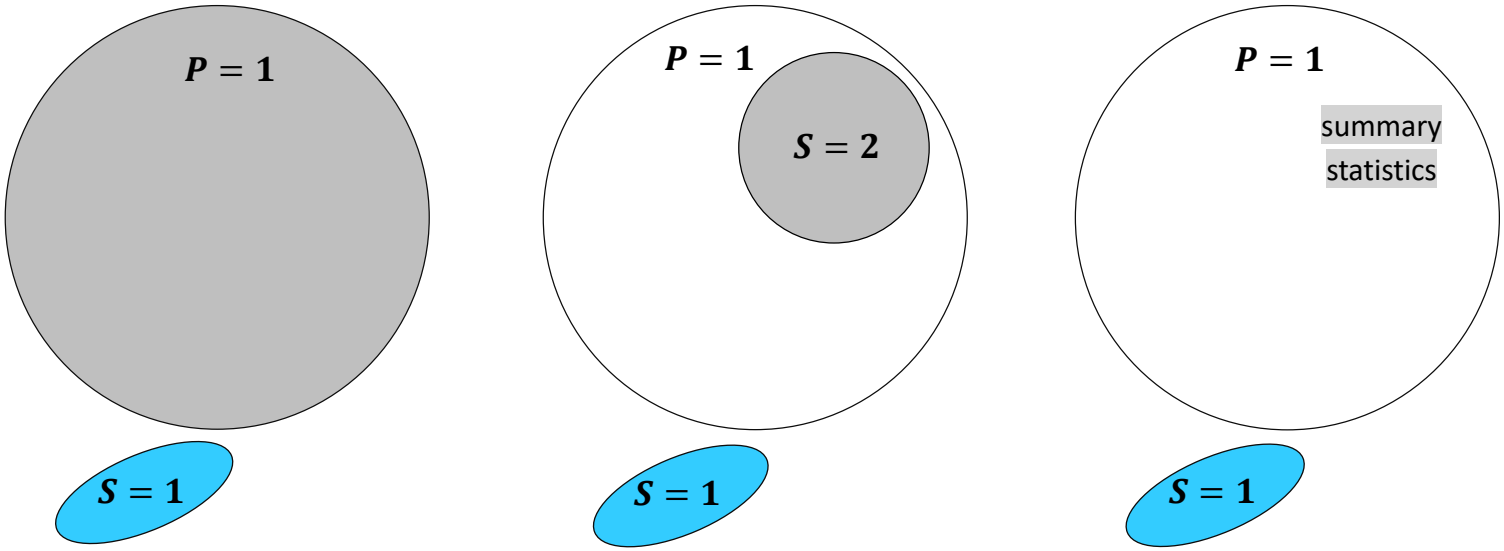

Notation

X: non-effect-modifying covariates

Z: effect modifiers, observed in trial and target population

either V: partially unobserved effect modifier (observed in trial, not population)

or U: fully unobserved effect modifier

Assumptions

A1 *Internal validity of the trial:* conditional ignorability of treatment assignment, positivity, treatment variance irrelevance, no interference, etc.

A2 *Across-setting treatment variation irrelevance*

A3 *Effect modifiers coverage:* the range of the effect modifiers in target population is covered by trial

A4 *Conditional sample ignorability for treatment effects:* $[Y^1 - Y^0] \perp \{S, P\} \mid Z, V, (S = 1 \text{ or } P = 1)$

A5 *No measurement error:* X, Z are measured the same way in trial and target population, and measured without error

A6 *Additive potential outcomes model:*

$$\mathrm{E}[Y_i^a] = \beta_0 + \beta_x X_i + \beta_z Z_i + \beta_v V_i + \beta_a a + \beta_{za} Z_i a + \beta_{va} V_i a$$

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For a partially unobserved effect modifier (V case)

$$\text{TATE} = \beta_a + \beta_{za}\text{E}[Z \mid P = 1] + \beta_{va}\text{E}[V \mid P = 1]$$

Two options:

1. Outcome-model-based sensitivity analysis
   i. obtain estimate for $\text{E}[Z \mid P = 1]$ and specify range for $\text{E}[V \mid P = 1]$
   ii. estimate $\beta_a, \beta_{za}, \beta_{va}$ using trial data
   iii. combine

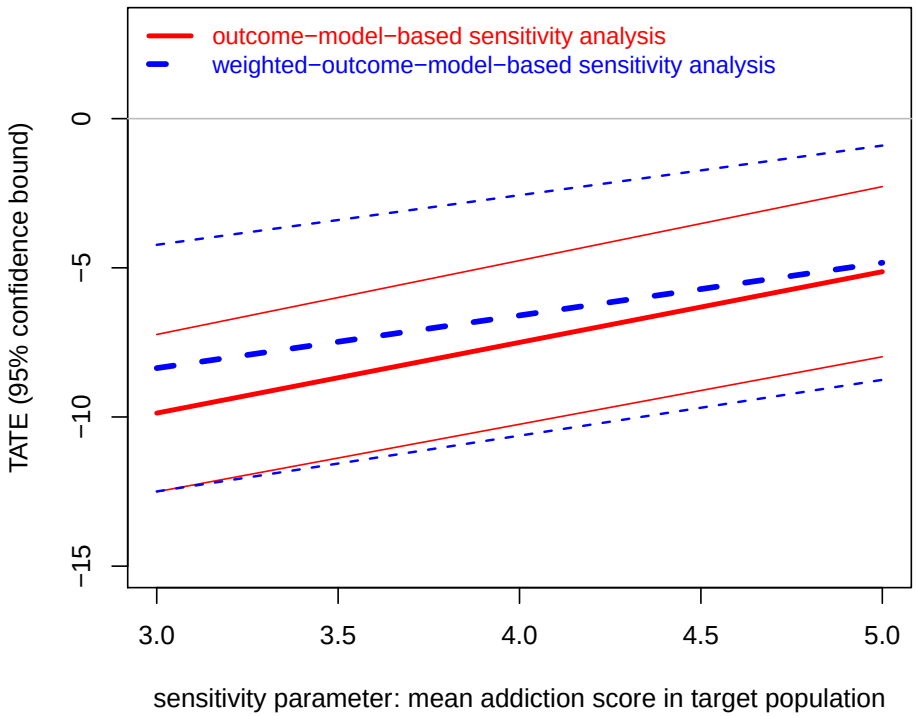
2. Weighted-outcome-model-based sensitivity analysis
   . weight trial sample to resemble target population w.r.t Z, X
   i. obtain estimate for $\text{E}[Z \mid P = 1]$ and specify range for $\text{E}[V \mid P = 1]$
   ii. estimate $\beta_a, \beta_{za}, \beta_{va}$ using the weighted trial data
   iii. combine

Example of a V case

Smoking cessation intervention for heavy smokers among attendants of alcohol/substance abuse treatment: SATE $= 10$ fewer cigarettes per day

- Z: being African-American, baseline daily number of cigarettes
- V: baseline addiction score; $E[V \mid S = 1] = 4.05$

Target pop: people who seek alcohol/substance treatment who smoke heavily



For fully unobserved effect modification (U case)

Cannot use

$$\text{TATE} = \beta_a + \beta_{za}\text{E}[Z \mid P = 1] + \beta_{ua}\text{E}[U \mid P = 1]$$

Hope to use

$$\begin{aligned}\text{TATE} = \text{SATE} &+ \beta_{za}\{\text{E}[Z \mid P = 1] - \text{E}[Z \mid S = 1]\}+ \\ &+ \beta_{ua}\{\text{E}[U \mid P = 1] - \text{E}[U \mid S = 1]\}\end{aligned}$$

For fully unobserved effect modification (U case)

U: the *remaining composite effect modifier*

- captures all unobserved factors that modify treatment effects
- independent of observed covariates and effect modifiers X, Z

which means can estimate β_{za} using the regression model

$$\mathrm{E}[Y_i] = \beta_0 + \beta_a A_i + \beta_x X_i + \beta_z Z_i + \beta_{za} Z_i A_i.$$

For fully unobserved effect modification (U case)

$$\text{TATE} = \text{SATE} + \beta_{za}\{\text{E}[Z \mid P = 1] - \text{E}[Z \mid S = 1]\} + \beta_{ua}\Delta_u$$

$$\text{TATE} = \text{wtd.ATE} + \beta_{za}\left\{\text{E}[Z \mid P = 1] - \frac{\sum W_i(S_i = 1)Z_i}{\sum W_i(S_i = 1)}\right\} + \beta_{ua}\Delta_u$$

$$\approx \text{wtd.ATE} + \beta_{ua}\Delta_u$$

Two options:

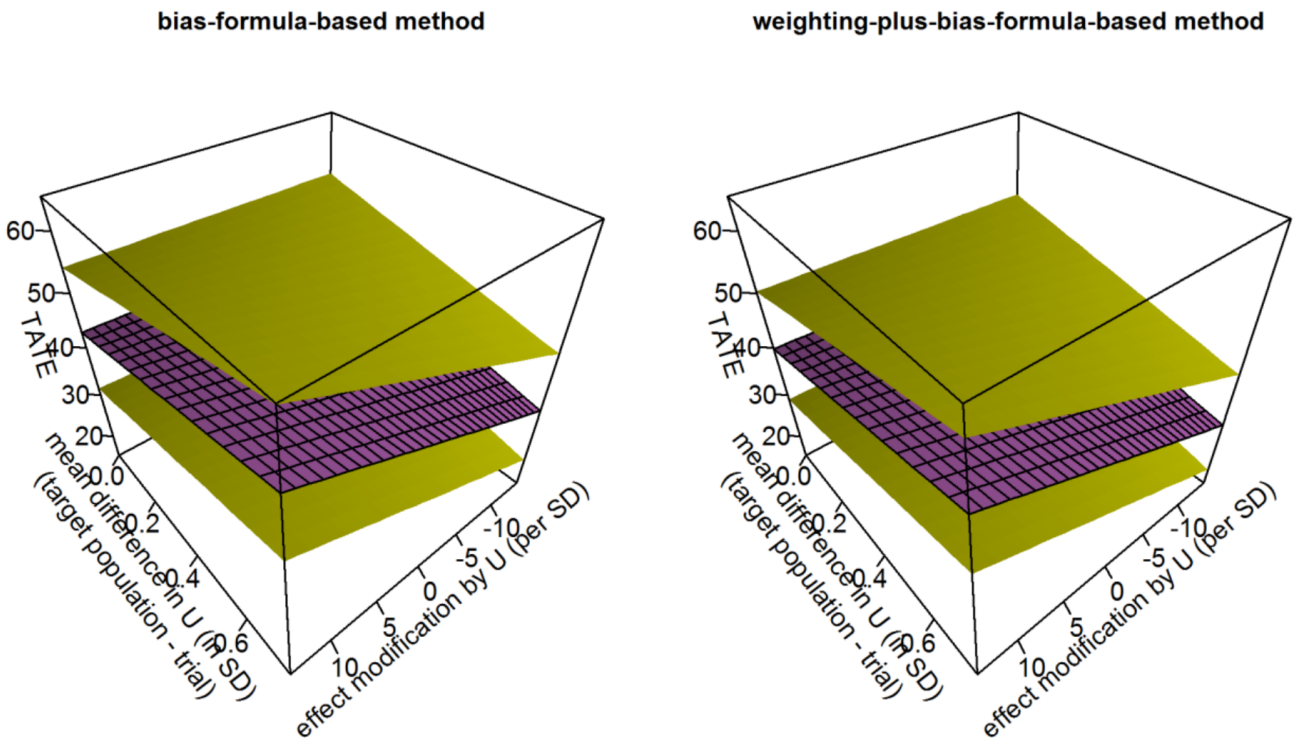
1. Bias-formula-based sensitivity analysis
   i. obtain estimate for $\text{E}[Z \mid P = 1]$ and specify ranges for β_{ua} and Δ_u
   ii. estimate SATE, $\text{E}[Z \mid S = 1]$ and β_{za} using trial data
   iii. combine
2. Weighting-plus-bias-formula-based sensitivity analysis
   . weight trial sample to resemble target population w.r.t Z, X
   i. obtain estimate for $\text{E}[Z \mid P = 1]$ and specify ranges for β_{ua} and Δ_u
   ii. estimate wtd.SATE, $\frac{\sum W_i(S_i=1)Z_i}{\sum W_i(S_i=1)}$ and β_{za} using weighted trial data
   iii. combine

Example of a U case (data artificially altered)

Trial comparing a new antiretroviral therapy regimen to an old one:
SATE = increase CD4 count by 36 cells/ml at 2 months post treatment

- Z: being White and without severe immune suppression (interaction term coef ≈ -15), age (interaction term coef ≈ 11 per SD)
- concerned about U: specify $\Delta_u = (0, 0.7)$ and $\beta_{ua} = (-15, 15)$

Target population: people with HIV in the US



How about multiplicative treatment effects?

Big limitation: the assumption of additive treatment effects

Want flexibility in choosing effect scale

Effects may be less heterogeneous on one scale than on another

Binary outcome: alternative effect definitions

ATE previously defined is the average (arithmetic mean) of the additive individual treatment effects, i.e.,

$$\text{RD}_i = \text{pr}(Y_i^1 = 1) - \text{pr}(Y_i^0 = 1)$$

What if we define individual treatment effects on a multiplicative scale, e.g.,

$$\text{RR}_i = \frac{\text{pr}(Y_i^1 = 1)}{\text{pr}(Y_i^0 = 1)}, \quad \text{OR}_i = \frac{\text{odds}(Y_i^1 = 1)}{\text{odds}(Y_i^0 = 1)}$$

We could define ATE as the average (geometric mean) of the individual treatment effects

$$\text{ATE}_{\text{RR}} = \exp\left\{\text{E}\left[\log \frac{\text{pr}(Y_i^1 = 1)}{\text{pr}(Y_i^0 = 1)}\right]\right\}, \quad \text{ATE}_{\text{OR}} = \exp\left\{\text{E}\left[\log \frac{\text{odds}(Y_i^1 = 1)}{\text{odds}(Y_i^0 = 1)}\right]\right\}$$

(If willing to think of effects as log-RRs or log-ORs, have arithmetic mean back.)

Binary outcome: assume a generalized linear causal model

e.g.,

$$\log[\text{odds}(Y_i^a = 1)] = \beta_0 + \beta_a a + \beta_{za} Z_i a + \beta_{va} V_i a + \beta_x X_i + \beta_z Z_i + \beta_v V_i$$

Works for V case!

$$\text{TATE}_{\text{OR}} = \exp\{\beta_a + \beta_{za}\text{E}[Z \mid P = 1] + \beta_{va}\text{E}[V \mid P = 1]\}$$

allows the two options

- outcome-model-based sensitivity analysis
- weighted-outcome-model-based sensitivity analysis

Also works if use RR-scale effects and model for $\log[\text{pr}(Y_i^a = 1)]$.

Binary outcome: assume a generalized linear causal model

$$\log[\text{odds}(Y_i^a = 1)] = \beta_0 + \beta_a a + \beta_{za} Z_i a + \beta_{ua} U_i a + \beta_x X_i + \beta_z Z_i + \beta_u U_i$$

Does not work for U case!

ATE is now the average of conditional effects, conditioning on X, Z, U.

We would hope to rely on

$$\text{TATE}_{\text{OR}} = \text{SATE}_{\text{OR}} \cdot \exp(\beta_{za}\{\text{E}[Z \mid P = 1] - \text{E}[Z \mid S = 1]\} + \beta_{ua}\Delta_u)$$

but both β_{za} and

$$\text{SATE}_{\text{OR}} = \exp\{\beta_a + \beta_{za}\text{E}[Z \mid S = 1] + \beta_{ua}\text{E}[U \mid S = 1]\}$$

cannot be estimated without observing U; ORs are non collapsible.

Next steps

- extend to make use of target population outcome data when available
- extend V-case methods to address the situation when the scientist is concerned about a specific possible effect modifier that was not measured in the trial
- explore a simulation-based approach for the U case with non-collapsible effects

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