Sensitivity Analysis for Unobserved Effect Modification when Generalizing Findings from Randomized Trials to Target Populations

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Outline

1. Background on generalizability
2. Motivation for sensitivity analyses
3. Notation
4. Sensitivity Analysis for a Partially Unobserved Modifier (V Case)
5. Sensitivity Analysis for a Fully Unobserved Modifier (U Case)
6. Extension to Non-Continuous Outcomes
7. Conclusion

Outline

Making research results relevant: A range of policy or practice questions

- Medicare may be deciding whether or not to approve payment for a new treatment for back pain
- Interest in predicting overall population impacts of a broad public health media campaign around not switching car seats to forward facing until a child is 12 months old
- A health care system may be trying to predict the effects of an evidence-based intervention in their overall patient population
- A physician practice may be deciding whether training providers in a new intervention would be cost effective across their population

Estimating Effects: Randomized Trials

- Randomized trials are gold standard for estimating causal effect of a treatment in a study sample
- Strong internal validity allows for unbiased estimation of the sample average treatment effect (SATE)
    - However, some policy questions require estimating the target population average treatment effect (TATE), not SATE

Issue: RCTs May Not Generalize

- Randomized trials often have poor external validity (generalizability) (Weisberg et al., 2009)
- Potential reasons for this:
  - Strict exclusion criteria (Stuart et al., 2011)
  - Lack of attention to target population when implementing trial
- SATE may not equal TATE (Cole and Stuart, 2010)
  - If distribution of treatment effect modifier (TEM) differs in trial and target population
- Note: Similar issues arising in debates about non-probability samples in survey world

Methods to Improve Generalizability

Study Design

- Random sampling (great, but rare)
- Purposive sampling (not formally representative)
- Practical clinical trials (potentially useful, but expensive and still lacks formal representativeness)

- Main idea: select subjects for trial in a particular way

Methods to Improve Generalizability

Post-Hoc Analysis

- Weighting trial sample by odds of trial participation to resemble target population
  - Similar to propensity score ATT weighting in non-experimental studies
- Model outcome as (flexible) function of observed covariates in trial and predict outcome in target population
  - BART: Bayesian Additive Regression Trees (Hill, 2010; Kern et al., 2016), TMLE (Rudolph et al., 2014)
- Doubly robust methods, fitting models for both the outcome and the probability of trial participation (Dahabreh et al., 2018)

Methods to Improve Generalizability

Implementation

- Methods require full data sets of TEMs for individuals in both trial *and* target population (not just summary statistics!)
- Software in the works for easy implementation (Ackerman et al., 2019)

	S (trial membership)	Y (outcome)	A (treatment)	X_1 (covariate 1)	X_2 (covariate 2)	…	X_p (covariate p)
Trial data set	1	✓	✓	✓	✓		✓
Population data set	0	×	×	✓	✓		✓

Outline

Assumptions*

1. All members of target population have nonzero probability of trial selection
2. Range of effect modifiers in target population are covered by respective ranges in the trial
3. Treatment assignment is independent of sample selection, as well as potential outcomes, given pre-treatment covariates
4. No unmeasured variables associated with sample selection and treatment effect

*These are required for the standard weighting and outcome model based

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What if

- there is an treatment effect modifier (TEM) observed in the trial but we don't have data on it from the target population?
- we are concerned there might be TEMs that are not even observed in the trial (fully unobserved)?

Issue of Unobserved TEMs

- Unobserved TEMs likely very common in real data scenarios
- In real data, often few covariates observed consistently between trial and population data (Stuart and Rhodes, 2017)
- Today will focus on parametric sensitivity analysis strategy; bounding another possibility (Chan, 2018)

Sensitivity Analyses for Generalizing RCT Findings to Population: Two Cases

- TEM observed in the trial but unobserved in the target population (*V case*)
- Any potential TEMs unobserved in both the trial *and* the target population (*U case*)

analogous to sensitivity analyses for unobserved confounding in non-experimental settings (Rosenbaum and Rubin, 1983; VanderWeele, 2011)

Outline

Notation

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

$$S_i = \begin{cases} 1 & \text{if individual } i \text{ is in trial} \\ 0 & \text{if individual } i \text{ is in target population} \end{cases}$$

$$SATE = E[Y(1) - Y(0)|S = 1]$$

$$TATE = E[Y(1) - Y(0)|S = 0]$$

Notation

X: non-effect modifying covariates
Z: effect modifier, fully observed in trial and population

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

Outline

For a partially unobserved effect modifier (V case)

Assume the following outcome model:

$$E[Y_i] = \beta_0 + \beta_a A_i + \beta_{za} Z_i A_i + \beta_{va} V_i A_i + f_{xzv}(X_i, Z_i, V_i)$$

Therefore,

$$\text{TATE} = \beta_a + \beta_{za} E[Z \mid S = 0] + \beta_{va} E[V \mid S = 0]$$

For a partially unobserved effect modifier (V case)

$$\text{TATE} = \beta_a + \beta_{za} E[Z \mid S = 0] + \beta_{va} E[V \mid S = 0]$$

1. Outcome-model-based sensitivity analysis
   i. estimate $\beta_a, \beta_{za}, \beta_{va}$ using trial data
   ii. obtain $E[Z|S = 0]$ and specify range for $E[V \mid S = 0]$
   iii. combine

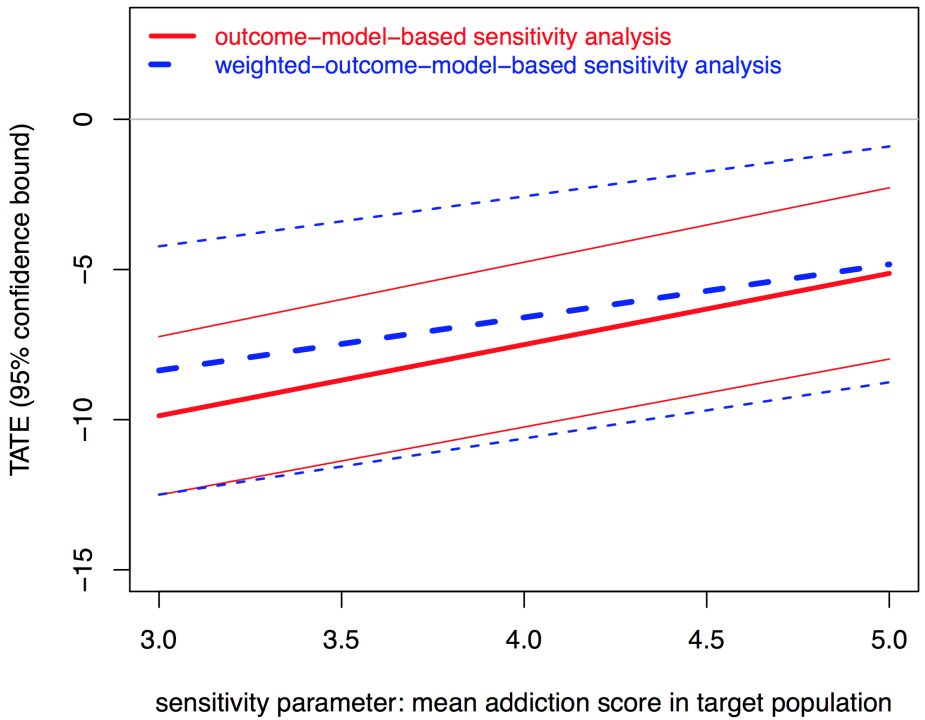
2. Weighted-outcome-model-based sensitivity analysis
   . weight trial sample to resemble target population w.r.t. X, Z
   i. estimate $\beta_a, \beta_{za}, \beta_{va}$ using trial data
   ii. obtain $E[Z|S = 0]$ and specify range for $E[V \mid S = 0]$
   iii. combine

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



Outline

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

Unlike the V case, we cannot use

$$\text{TATE} = \beta_a + \beta_{za}[Z \mid S = 0] + \beta_{ua}[U \mid S = 0]$$

for sensitivity analysis

For fully unobserved effect modification (U case)

We hope to use a bias formula instead:

$$\begin{aligned}\text{TATE} = \text{SATE} + \beta_{za}\{[Z \mid S=0] - [Z \mid S=1]\} + \\ + \beta_{ua}\{[U \mid S=0] - [U \mid S=1]\}\end{aligned}$$

Let $\Delta_u = E[U|S=0] - E[U|S=1]$

$$\text{TATE} = \text{SATE} + \beta_{za}\{E[Z \mid S=0] - E[Z \mid S=1]\} + \beta_{ua}\Delta_u$$

$$\text{TATE} = \text{wtd.ATE} + \beta_{za}\left\{E[Z \mid S=0] - \frac{\sum W_i(S_i=1)Z_i}{\sum W_i(S_i=1)}\right\} + \beta_{ua}\Delta_u$$

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

For fully unobserved effect modification (U case)

1. Bias-formula-based sensitivity analysis

$$\text{TATE} = \text{SATE} + \beta_{za}\{E[Z \mid S = 0] - E[Z \mid S = 1]\} + \beta_{ua}\Delta_u$$

   i. estimate SATE, $E[Z \mid S = 1]$ and β_{za} using trial data
   ii. obtain estimate for $E[Z \mid S = 0]$, specify ranges for β_{ua} and Δ_u
   iii. combine

2. Weighting-plus-bias-formula-based sensitivity analysis

$$\text{TATE} = \text{wtd.ATE} + \beta_{za}\left\{E[Z \mid S = 0] - \frac{\sum W_i(S_i = 1)Z_i}{\sum W_i(S_i = 1)}\right\} + \beta_{ua}\Delta_u$$

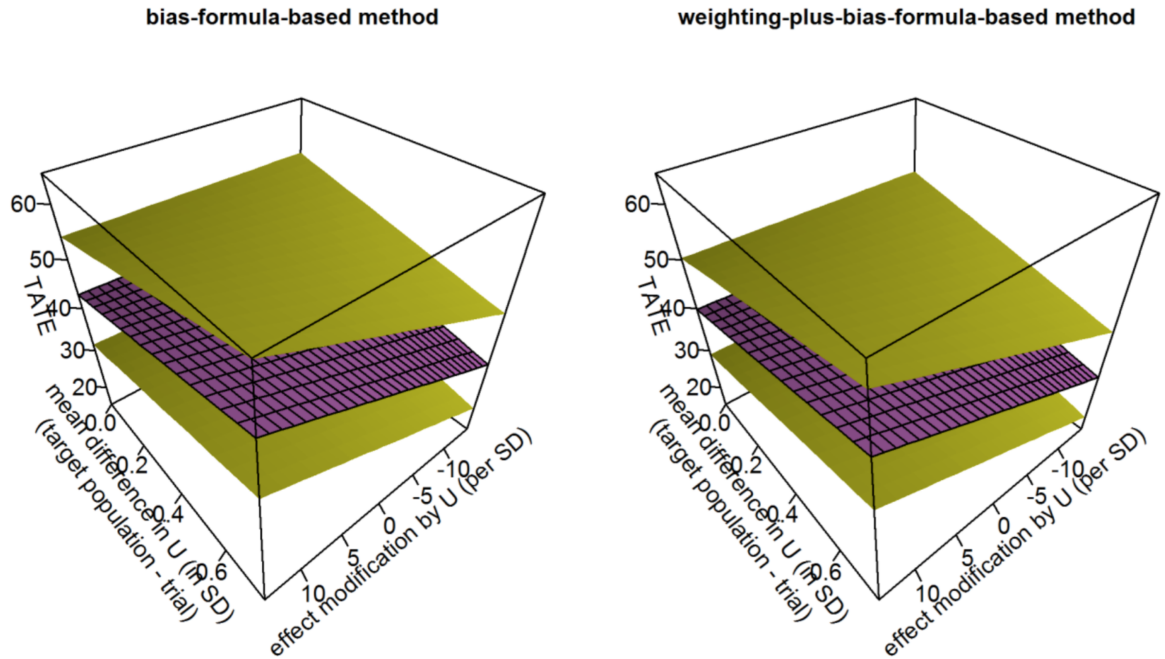
   . weight trial sample to resemble target population w.r.t. X, Z
   i. estimate wtd.SATE, $\frac{\sum W_i(S_i=1)Z_i}{\sum W_i(S_i=1)}$ and β_{za} using trial data
   ii. obtain estimate for $E[Z \mid S = 0]$, specify ranges for β_{ua} and Δ_u
   iii. combine

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



Outline

Extension to Binary Outcomes (V case)

What if the primary outcome in the trial is not continuous, but binary?
Let P_a = probability of outcome occurring under treatment "a"

$$TATE = E\left[\frac{P_{treat}/(1-P_{treat})}{P_{control}/(1-P_{control})}\middle| S=0\right]$$

Assume the following outcome model:

$$\text{logit}(P(Y_i=1)) = \beta_0 + \beta_a A_i + \beta_{za} Z_i A_i + \beta_{va} V_i A_i + f_{xzv}(X_i, Z_i, V_i)$$

Therefore,

$$TATE = E[\exp\{\beta_a + \beta_{za} Z + \beta_{va} V\} | S=0]$$

Extension to Binary Outcomes (V case)

but V is unmeasured in the population, so $E[e^{\beta_{va}V}|S=0]$ is unknown. Using MGFs and assuming Z and V to be Normal,

$$\text{TATE} = \lambda \times \exp\left\{\beta_{va}E[V|S=0] + \frac{1}{2}\beta_{va}^2 \text{var}(V|S=0)\right\}$$

where $\lambda = \exp\{\beta_a + \beta_{za}E[Z|S=0] + \frac{1}{2}\beta_{za}^2\text{var}(Z|S=0)\}$

Can then perform same sensitivity analyses for V case (outcome model or weighting)

- Must make additional assumptions about the distribution of V and Z in the population
- Can hold one unknown fixed, or vary both together

Outline

Conclusion

- Methods exist to improve upon generalizability of RCTs when drawing population-level inferences
- Population data availability is a primary limiting factor for satisfying assumption of no unobserved TEMs
- Proposed sensitivity analyses for generalizing average treatment effects when TEMs are both partially and fully unobserved
- While sensitivity analyses are helpful when some variables are not observed, they are not a panacea

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Thank you!

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