Estimating population effects: Case study of Generalizing Results of a Methamphetamine Dependence Trial

Benjamin Ackerman[1], Ryoko Susukida[2], Kara Rudolph[3], Ramin Mojtabai[2], Elizabeth Stuart[1,2]

[1] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

[2] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health

[3] School of Medicine, University of California, Davis

ICHPS 2018, Session CS17

Outline

1. Background
2. Notation, Definitions and Assumptions
3. Methods
   - Assessing Generalizability
   - Improving Generalizability
4. Applied Example: Methamphetamine Dependence Trials
5. Results
6. Discussion

Outline

Background

- Randomized trials are gold standard for estimating causal effect of a treatment in a study sample
  - Many agencies rely on randomized trials when making policy changes, enacting treatment and prevention programs
- Strong internal validity allows for unbiased estimation of the sample average treatment effect (SATE)
  - However, researchers may instead be interested in the target population average treatment effect (TATE)

Problem

- Randomized trials often have poor external validity (generalizability) (Weisberg et al., 2009)
  - Lack of "representativeness" of samples
  - Strict exclusion criteria (Stuart et al., 2011)
  - Not considering target population when designing and implementing trial
- SATE may not equal TATE (Cole and Stuart, 2010)
  - Using estimate of SATE as an estimate of TATE may lead to bias
- Often infeasible and expensive to improve external validity by study design

Research Aim

To provide an overview of several post-trial statistical methods to generalize average treatment effects to a well-defined target population, and to illustrate the methods in practice with a trial related to methamphetamine dependence.

Outline

Notation

Y: outcome, binary

A: treatment, binary, randomized

S: sample membership

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

P_a: probability of outcome Y under treatment a

Defining SATE and TATE

With binary outcome

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

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

Can estimate the ATE as $e^{\hat{\beta}_1}$ from the following simple logistic regression:

$$\text{logit}(p_i) = \beta_0 + \beta_1 A_i$$

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 or treatment effect
    - This assumption is often unrealistic, sensitivity analyses for estimating TATE have been proposed when a variable is measured in the trial but not in the population (Nguyen et al., 2017)

Data required

1. Data from trial
2. Full data set representing target population
    - Containing variables measured in the trial

Outline

Assessing Generalizability

Tipton et al (2014) introduce a generalizability index, defined as the following:

$$\beta = \int \sqrt{f_s(s) f_p(s)} ds$$

where $f_s(s)$ and $f_p(s)$ are distributions of **trial participation probabilities** in the trial sample and target population, respectively.

- Trial participation probabilites are similar to propensity scores, except predicting trial membership based on pre-treatment covariates
  - Four estimation methods implemented and compared: Logistic regression, Random Forests, Lasso, Super Learner
- Greater scores indicate trial sample is more similar to a random sample drawn from the target population

Improving Generalizability

- *Weighting by the odds of trial participation (w_i):*

$$w_i = \begin{cases} 0 & \text{if } S_i = 0 \\ \frac{\hat{e}_i}{1-\hat{e}_i} & \text{if } S_i = 1 \end{cases}$$

  where $\hat{e}_i$ is the probability of individual *i* being a trial participant
    - Weights are incorporated by fitting a weighted logistic regression model of the outcome.
- *Bayesian Additive Regression Trees (BART):* flexible machine learning algorithm, predicts probabilities of outcome under treatment and control
- *Targeted Maximum Likelihood Estimation (TMLE):* semiparametric method of estimating a causal effect parameter by factoring the likelihood, targeting parameter of interest and treating the rest as nuisance parameters

Outline

Trial Data

- CSP-1025 from National Institute of Drug Abuse (NIDA) data repository
  - Phase 2, multi-site, placebo-controlled randomized trial
  - 140 participants randomized to two treatment groups: topiramate and placebo
- **Trial aim:** to determine if topiramate could reduce methamphetamine use relative to placebo in individuals with methamphetamine dependence
- **Trial findings:** no significant differences in average treatment effect between treatment and placebo
- **Binary outcomes of interest:** Study retention, negative use week (no positive urine tests), meth use in followup

Population Data

- Treatment Episode Data Set: Admissions (TEDS-A) of 2014
- Consists of annual data regarding publicly-funded admissions to substance abuse treatment programs
- TEDS-A represents *admissions records*, not necessarily *individuals*
- Subset to records where primary substance abuse problem was methamphetamine
  - 135,264 records in resulting target population dataset
- Eight common covariates identified across trial and target population
  - Age, sex, race, ethnicity, marital status, education, employment status, and prior methamphetamine use in the past week

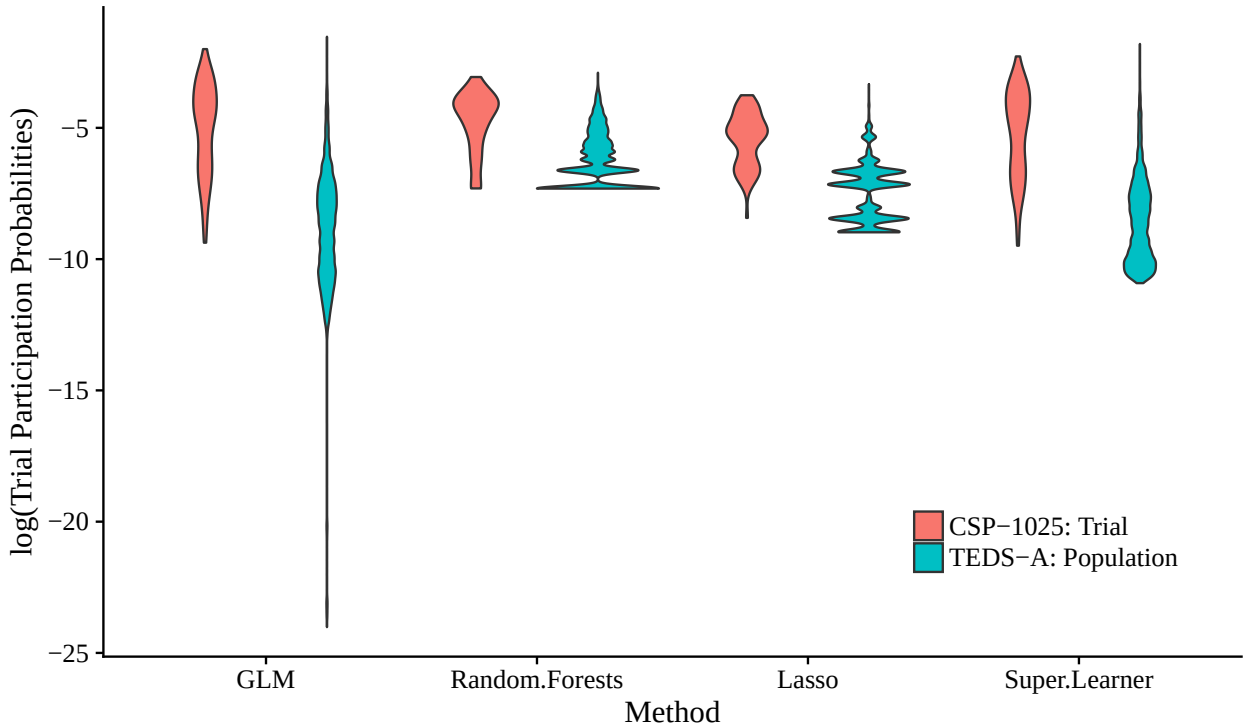
Outline

Results

Differences between Trial and Target Population

	B
GLM	0.45
Random Forests	0.63
Lasso	0.56
Super Learner	0.48

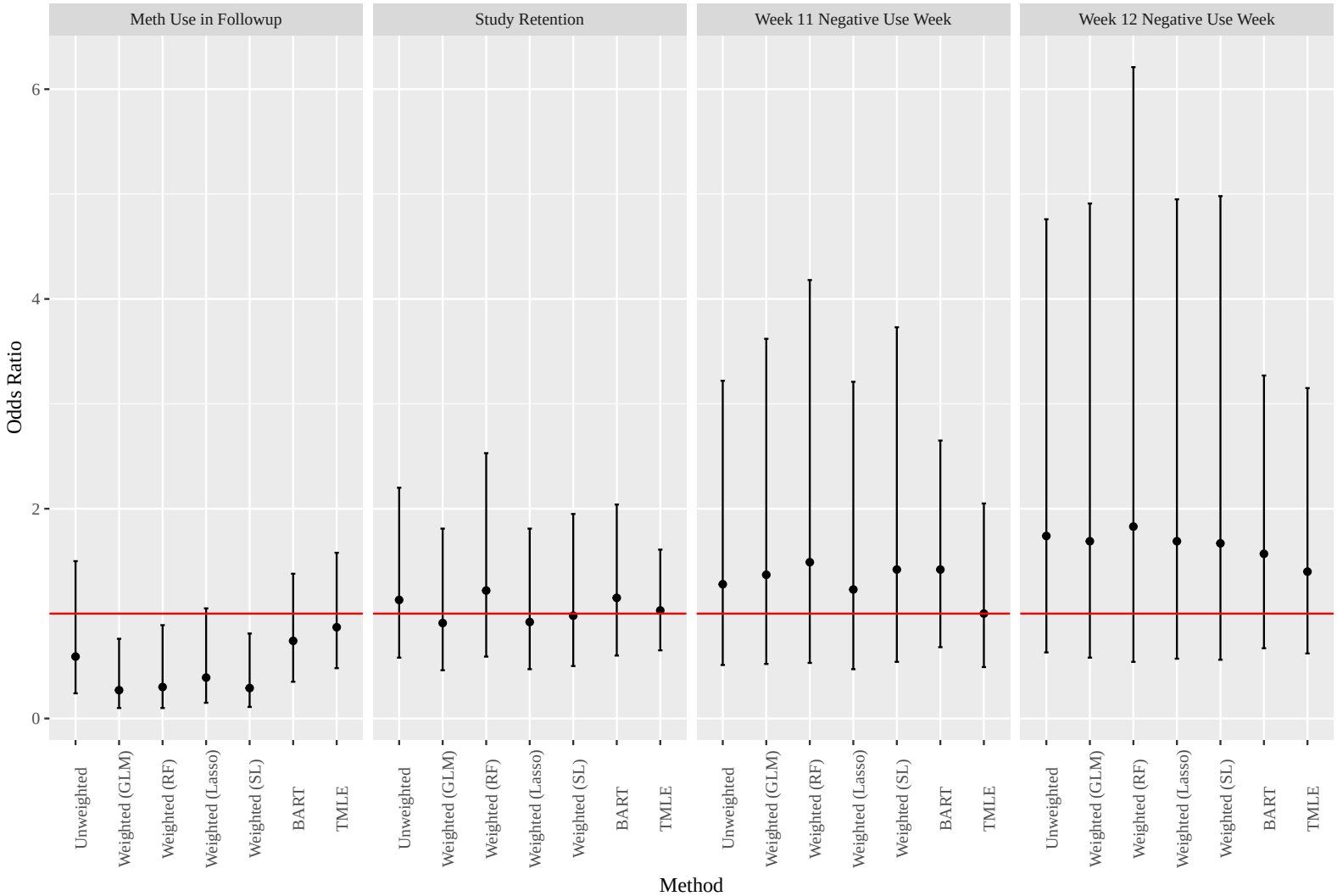
Figure 1: log(Trial Participation Probabilities) by Method and Sample Membership



Results

TATE by Outcome and Statistical Method

Figure 2: Average Treatment Effect by Outcome and Generalizability Method



Outline

Limitations

- Identifying data for target population is challenging
- Potential measurement error of pre-treatment covariates between trial and population
- Methods potentially underperform when proportion of population sampled in the trial is very small

Conclusion

- Altering study design to strengthen external validity is often infeasible
- Post-hoc statistical methods allow for better estimation of population average treatment effects
- Identifying well-defined target population is crucial step to applying these methods
- Future work should focus on comparing weighting and machine learning methods, examining scenarios with small trials/large populations, and conducting sensitivity analysis in the presence of unobserved effect modifiers

References

- Cole, S. R., Stuart, E. A. (2010). Generalizing evidence from randomized clinical trials to target populations: The actg 320 trial. American Journal of Epidemiology, 172(1), 107-115.
- Nguyen, T. Q., Ebnesajjad, C., Cole, S. R., Stuart, E. A., others. (2017). Sensitivity analysis for an unobserved moderator in rct-to-target-population generalization of treatment effects. The Annals of Applied Statistics, 11 (1), 225-247.
- Stuart, E. A., Cole, S. R., Bradshaw, C. P., Leaf, P. J. (2011). The use of propensity scores to assess the generalizability of results from randomized trials. Journal of the Royal Statistical Society: Series A (Statistics in Society), 174 (2), 369-386.
- Tipton, E. (2014). How generalizable is your experiment? An index for comparing experi- mental samples and populations. Journal of Educational and Behavioral Statistics, 39(6), 478-501.
- Weisberg, H. I., Hayden, V. C., Pontes, V. P. (2009). Selection criteria and generalizability within the counterfactual framework: Explaining the paradox of antidepressant-induced suicidality? Clinical Trials, 6(2), 109-118.

Thank you!

Benjamin Ackerman
Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

backer10@jhu.edu
@backerman150
www.benjaminackerman.com
#ThisIsPublicHealth