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

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1 Background

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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.
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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

\[ \begin{align*}
SATE &= E \left[ \frac{P_{treat}/(1 - P_{treat})}{P_{control}/(1 - P_{control})} \right]_{S = 1} \\
TATE &= E \left[ \frac{P_{treat}/(1 - P_{treat})}{P_{control}/(1 - P_{control})} \right]_{S = 0}
\end{align*} \]

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
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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 probabilities 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
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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
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## Results

### Differences between Trial and Target Population

<table>
<thead>
<tr>
<th>Method</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLM</td>
<td>0.45</td>
</tr>
<tr>
<td>Random Forests</td>
<td>0.63</td>
</tr>
<tr>
<td>Lasso</td>
<td>0.56</td>
</tr>
<tr>
<td>Super Learner</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Meth Use in Followup</th>
<th>Study Retention</th>
<th>Week 11 Negative Use Week</th>
<th>Week 12 Negative Use Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted</td>
<td>Unweighted</td>
<td>Unweighted</td>
<td>Unweighted</td>
</tr>
<tr>
<td>Weighted (GLM)</td>
<td>Weighted (RF)</td>
<td>Weighted (Lasso)</td>
<td>Weighted (Lasso)</td>
</tr>
<tr>
<td>Weighted (Lasso)</td>
<td>Weighted (RF)</td>
<td>Weighted (Lasso)</td>
<td>Weighted (Lasso)</td>
</tr>
<tr>
<td>BART</td>
<td>BART</td>
<td>BART</td>
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</tr>
<tr>
<td>TMLE</td>
<td>TMLE</td>
<td>TMLE</td>
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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


Thank you!

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