Causal Inference and Control for Confounding

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Outline

• Association versus causation
• Causal inference using observational data
  – The counterfactual
  – Strategies to control for secular trends, or confounding by calendar time
  – Hill’s principles of causal inference
  – Aggregate vs. individual level effects
Causal Inference

Association ≠ Causation

• An observed association ("correlation") may be **causal**: A caused B where B is some change in the outcome of interest—e.g., a decrease in fatal opioid overdoses

• May also be **non-causal**:

<table>
<thead>
<tr>
<th>Reasons for Non-Causal Associations</th>
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<tbody>
<tr>
<td>Random Error</td>
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<tr>
<td>Chance associations</td>
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The Counterfactual

• Hypothetical scenario in which no abuse-deterrent properties but all else is the same (no confounding)

• Is abuse of the product meaningfully lower than it would have been without abuse-deterrent properties?

• Counterfactual is not real/observable: How do we best approximate it to answer this question and determine the effect of the ADF?
Pre-post Reformulation Comparison of Means:

• Uses pre-period mean abuse rate to approximate the counterfactual (what post-period rate *would have been* if drug had not been reformulated)
Secular Trends: Confounding by calendar time

• Secular trends can confound pre-post analyses
  – Law enforcement (“pill mill” crackdowns, etc.)
  – Changing opioid prescribing practices due to guidelines, PDMP use, legislation, etc.
  – Increasing heroin availability and use

• May vary geographically

• These factors are typically difficult to measure—exception is estimated prescription volume, which we can adjust for

(Confounding will also be discussed in tomorrow’s session on designs that assess exposure and outcome in the same individuals over time)
Using a comparator to approximate the counterfactual

• Difference-in-differences means analysis

<table>
<thead>
<tr>
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<th>Drug</th>
<th>Comparator</th>
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<tbody>
<tr>
<td>Pre-period</td>
<td>60% reduction for reformulated drug</td>
<td>30% reduction for comparator</td>
</tr>
<tr>
<td>Post-period</td>
<td>30% reduction = effect of reformulation?</td>
<td>30% reduction for comparator</td>
</tr>
</tbody>
</table>

Counterfactual scenario
More on Comparison of Means Analyses and Secular Trends

- Drug reformulated

- Pre-period mean

- Post-period mean

Abuse Rates vs. Time
More on Comparison of Means Analyses and Secular Trends

Drug reformulated

Abuse Rates

Time

Pre-period mean

Post-period mean
Comparison of Means Analyses
Duration of Pre- and Post-periods

Drug reformulated

Pre-period A mean

Pre-period B mean

Post-period D mean

Post-period C mean

Abuse rates

Time periods

Pre-period A

Pre-period B

Post-period D

Post-period C
Interrupted Time Series (ITS)

• Assumptions:
  • Pre-period trend would have continued unchanged without intervention
  • No effects of concurrent interventions
Interrupted Time Series (ITS)  
Adding a comparator

- Look for difference-in-differences in slope, intercept: Now changes in comparator approximate the counterfactual
- Assumes any concurrent interventions would affect both drugs similarly
Challenges with Comparators

• Ideal comparator
  – Similar to index drug in
    • Indications
    • Pharmacology
    • Baseline abuse trends and patterns (e.g. route)
  – Relatively large, stable prescription volume
  – Expect similar effect from concurrent interventions (e.g., pill mill crackdowns, guidelines, payer initiatives)
Challenges with Comparators

• Typically no ideal comparator exists

• Use multiple comparators?
  – Complicates interpretation, causal inference
  – Need to pre-specify primary comparator(s)
  – Others help characterize “abuse landscape”

• Use composite comparators?
  – Composition can change over time
  – Drugs with largest market share drive composite
  – Stratification/weighting techniques?
  – May mask meaningful individual differences
Putting it all together:
Hill’s Principles of Causal Inference

• Temporality
• Strength of association
• Consistency
• Specificity
• Biological gradient
• Plausibility
• Alternative explanations
• Experimental evidence
• Analogy (consistency with other knowledge)

*Sir Austin Bradford Hill: The Environment and Disease: Association or Causation? President’s Address, Section of Occupational Medicine of the Royal Society of Medicine, January 14, 1965
Aggregate effects vs. reduction in individual risk

• Inferences made from observed associations at the aggregate (ecologic) level may not be valid at the individual level

• If ADF reduces aggregate abuse rates in the population over time, what does this tell us about the risk of an individual exposed to the product
  1. Going on to abuse it—orally/non-orally?
  2. Transitioning from one route to another?
  3. Developing an opioid use disorder (becoming addicted)?
  4. Overdosing/dying?
Discussion Questions
Questions for Discussion

1. How do we best synthesize findings from means and ITS analyses in evaluating whether an ADF has resulted in a meaningful reduction in abuse?
Questions for Discussion

2. How can we overcome some of the challenges associated with using comparators to approximate the counterfactual in ecologic time series studies?
Questions for Discussion

3. What are some potential alternative analytic approaches to evaluate the effect of an ADF using the currently available data sources, particularly for products without a recent non-ADF precursor?
Questions for Discussion

4. What can we reasonably infer from aggregate changes in abuse rates about an ADF’s effect on the risk of abuse (or abuse via a specific route) for an individual exposed to the product?