Combining RCTs and Observational Studies

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Social Science Objectives

- Population distributions
- Comparative effectiveness
  - Well-defined treatment (Hernan, et al)
    - Assign a patient to intervention
    - A patient actually received intervention
    - A patient actually received entire intervention
  - Well-defined outcome
    - Cholesterol vs. death
  - Well-defined population
    - Those who would choose an intervention
    - Those who are most likely to benefit from intervention

Possible Evidence

	Observational	RCT
Large sample size	X	Meta-analysis
Realistic treatment and environment	X	“practical trials” (Tunis et al, 2003)
Probability sample from target population	X	Re-weight and/or extrapolate
“Strong” causal inference	Propensity scores, instrumental variables	X
Customized measurement	sometimes	X
Long-term outcomes	Less rare	Rare

Well-Defined Populations

- What is the target population(s)?
  - RCT Population: Theoretical subset of the target population that consists of all individuals who would be eligible to enroll in the RCT.
  - Obs. Study Population: Population “represented” by the study.
  - Target Population: Population of all individuals for which treatment may be considered for its intended purpose?

Population: Adjusting Obs. Data for causal inference

- Methods to reduce treatment selection bias influence the inferential population
  - Propensity scores (PS) big idea:
    - Essentially re-weight the observational data so that the "controls" are comparable to the "treated".
  - PS population considerations
    - Reweight to those who selected: average treatment effect on the treated (ATT)
    - Poor overlap limits the inference to those who might not choose treatment
  - PS assumptions:
    - All important variables are measured

Population: Adjusting Obs. Data for causal inference

- Methods to reduce treatment selection bias influence the inferential population
  - Instrumental variables (IV) big idea:
    - Essentially scales the effect of the instrument on outcome by the effect of the instrument on treatment selection.
    - Treats treatment as a mediator of the instrument
  - IV effect on the population:
    - The estimand is a “local” average treatment effect (LATE), where “local” describes people who are influenced by the instrument.
  - IV assumptions:
    - The instrument only affects the outcome via the treatment selection

Population: Adjusting RCT Data for participant representativeness

- RCT population might be:
  - Like a SRS from the target population
    - No adjustment needed
  - Like a weighted sample from the target population
    - Use observational data to “standardize” RCT data
      - Survey methods like poststratification; Greenhouse, et al (2008)
      - Propensity-based standardization; Cole and Stuart (2010), Stuart, et al (2011)
  - Like a weighted sample of a **subpopulation** from the target population
    - Sensitivity analyses/Comparisons; Marcus (1997)
    - Use observational data to extrapolate from the RCT data using a model

Overarching models

- Goal: leverage the internal validity of the RCTs and the external validity of the observational data.
- Confidence Profile Method (and other models)
  - Eddy (1986); Eddy et al. (1990 and 1992)
  - Wolpert and Mengersen (2004)
  - Greenland (2005)
- Response Surface Methodology
  - Rubin (1990)
- Cross Design Synthesis
  - General Accounting Office (1992) and (1994)
  - Kaizar (2011)
  - Pressler and Kaizar (2013)

Confidence Profile Method (CPM)

- Approach to handle bias

$$\text{Target parameter} = \theta$$

$$\text{Evidence about } g(\theta, \alpha)$$

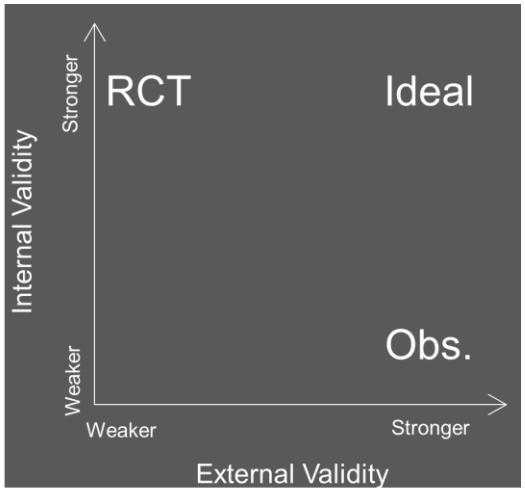
$$\text{Likelihood under target parameter: } f(x \mid \theta)$$

$$\text{Likelihood under CPM: } f(x \mid g(\theta, \alpha))$$

- Many g(θ,α) specified for specific kinds of bias

Response Surface Methodology

- Approximate the response surface as an n^{th} order polynomial of the experimental conditions
- Choose experimental conditions
- Extrapolate to the “ideal” experimental conditions



Cross Design Synthesis

- Examine randomized studies for external validity
- Examine administrative databases for internal validity
- Adjust data to improve validity
- Combine information between and within study types
  - Create a framework (stratify by design, coverage)
  - Combine studies within each design
  - Synthesize information across designs

Simple Case: Linear Bias

Population	Quantity of Interest	Randomized Data Estimator	Obs. Data Estimator
Represented by RCT	$\text{SPATE}_{\text{included}}$	$D^R_{included}$	$D^O_{included}$
Not Represented by RCT	$\text{SPATE}_{\text{excluded}}$	$= D^R_{included} + \delta_S$	$D^O_{excluded}$

Selection bias $= \delta_S \propto D^O_{excluded} - D^O_{included}$

Design bias $= D^O_{included} - D^R_{included}$

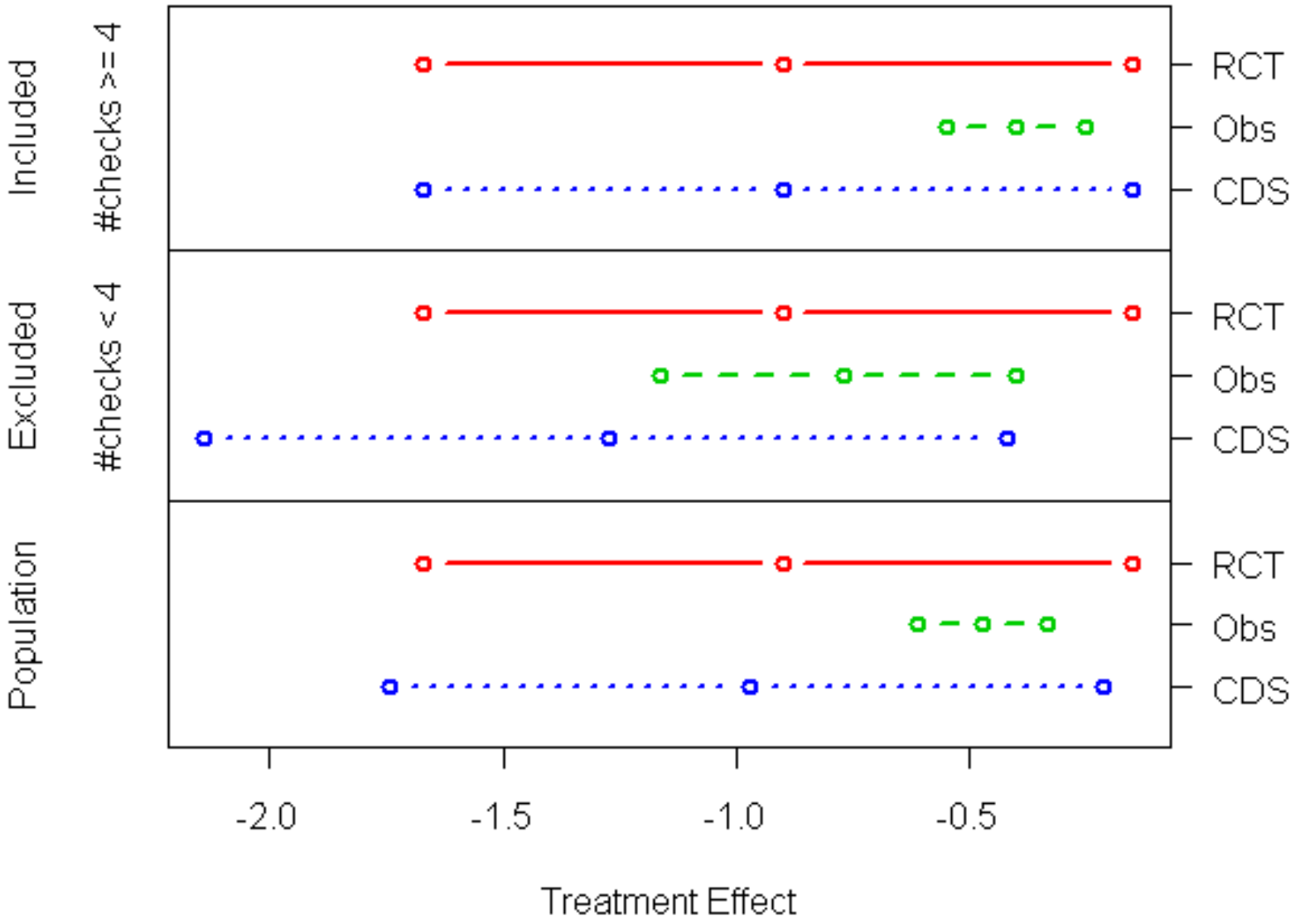
PATE = weighted average of Randomized Data Estimators

Example: Insulin Pump Use

- Problem: Is insulin pump use on average effective in improving metabolic control in the total population of diabetic patients?
  - Outcome: Mean A1C level (lower is better)
  - Control: Insulin injections
- Goal: Estimate the average treatment effect for use in policy decision making
- Data problem: RCTs exclude the noncompliant (<4 checks per day)

Doyle, et al (2004), Paris, et al (2009)

Example


Included
#checks >= 4
Excluded
#checks < 4
Population
RCT
Obs
CDS
RCT
Obs
CDS
RCT
Obs
CDS
-2.0
-1.5
-1.0
-0.5
Treatment Effect

Extensions

- Multiple RCTs and Observational data sets
  - Additional strata used for multiple inclusion criteria
- Multiple treatments (e.g., doses)
  - Additional stratification (multidimensional response “surface”)
- “Fuzzy” group membership

Designing new studies for sequential or simultaneous CDS

- On the RCT side:
  - Clearly identify populations/strata where randomized data is lacking or weak
  - Adapt design: sample size, proxy outcomes
- On the Obs. Side:
  - Check the adjustments for internal validity of the observational data
  - Variable collection

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