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SCHOOL OF PHARMACY

HealthCore

Workshop 219

Best Practices for Causal Study Designs Using Real-World Data

ISPOR Annual Meeting
Washington, DC
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Disclosures

- No funding was received for the research on which this workshop is based.
- Michael Grabner and Nilesh Gangan are employees of HealthCore, Inc. (a wholly owned subsidiary of Anthem, Inc.), which conducts health services research with both internal and external funding, including a variety of private and public entities.
- Michael Grabner is a stockholder of Anthem, Inc.
- Susan dosReis receives funding from GlaxoSmithKline for a project unrelated to the content of this workshop and conducts research that is funded by state and federal agencies.
- The comments stated herein are the opinions of the authors. HealthCore makes no representations or warranties, express or implied, with respect to the use or reliance on the opinions stated herein.

It’s a Team Effort

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Co-lead
Scientific Affairs

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Sarah Hoffman
Co-lead
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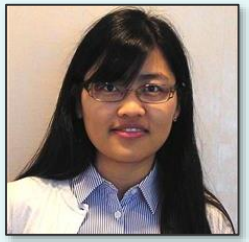

Lila Chen
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Analyst
Research Ops

Agenda

Introduction & First Set of Audience Polls
Dr. Grabner ~15 mins

A Step-by-Step Guide to Causal Study Design Using Observational Data
Dr. Gangan ~15 mins

Application of the Guidelines & Second Set of Audience Polls & Conclusions
Dr. dosReis ~25 mins

Part 1

Learning Objectives

Participants will be able to…

- ✓ List and describe key steps of designing a study for causal inference
- ✓ Define “estimand” and describe its components
- ✓ Define ATE & ATT and relate them to PS-based weighting & matching
- ✓ Distinguish methods for dealing with measured vs. unmeasured confounding
- ✓ Apply the step-by-step guide when evaluating the literature

Audience Poll Question #1

Your study is matching untreated to treated patients 1:1 using propensity scores. What estimand will this generate?

a) The Average Treatment Effect on the Treated (ATT), i.e., the average effect of the treatment among those patients who actually received the treatment

b) The Average Treatment Effect (ATE), i.e., the average effect of the treatment when comparing everyone getting treated to everyone not getting treated

c) ATE and ATT are the same with this matching approach

d) Neither ATE nor ATT

e) I am not sure

Audience Poll Question #2

Consider the graph on the right, where diet is posited to affect cognitive function.

In this relationship, the variable denoted "Follow-up" is a…

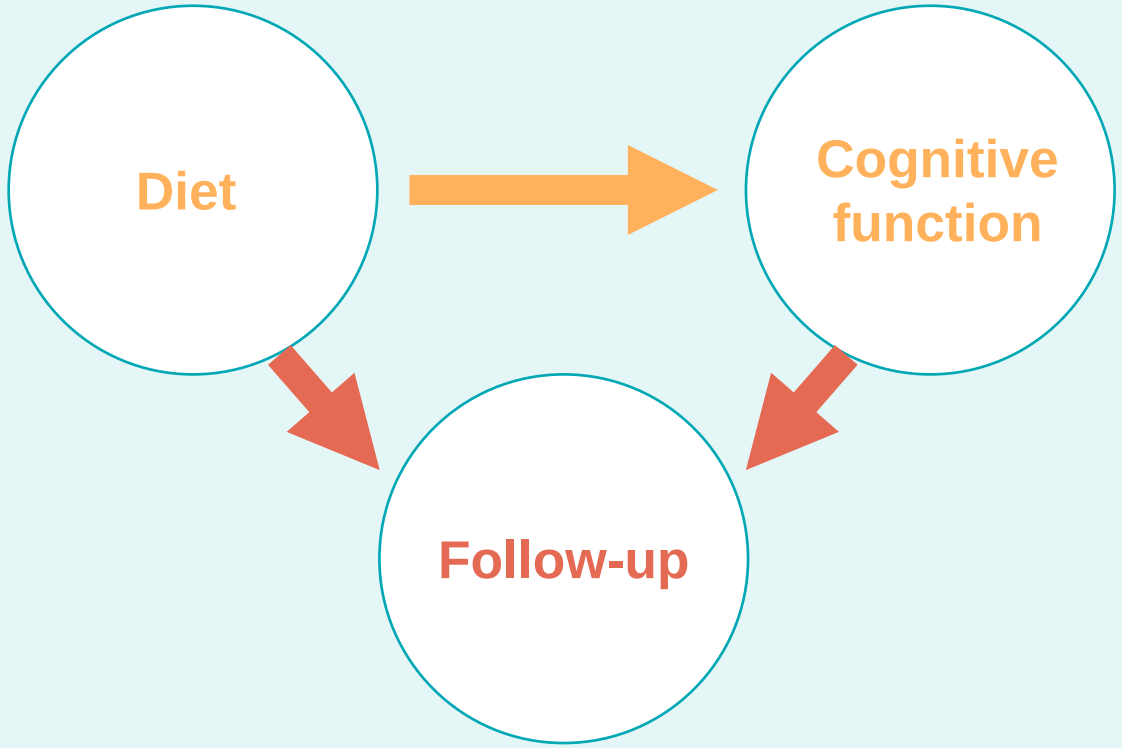
a) Confounder

b) Collider

c) Mediator

d) None of the above

e) I am not sure



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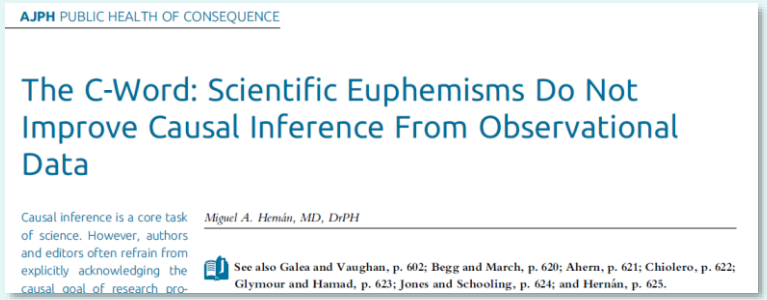
Why We (Should) Care about Causality

Association vs. Causality


AJPH PUBLIC HEALTH OF CONSEQUENCE

The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data

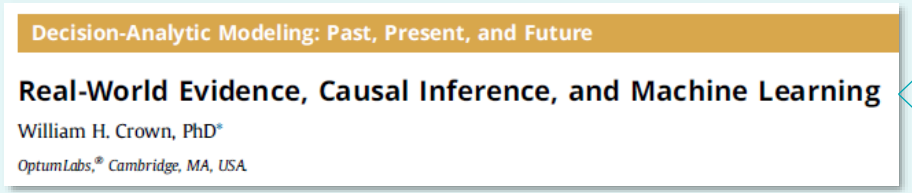
Causal inference is a core task of science. However, authors and editors often refrain from explicitly acknowledging the causal goal of research pro-

Miguel A. Hernán, MD, DrPH

See also Galea and Vaughan, p. 602; Begg and March, p. 620; Ahern, p. 621; Chiolero, p. 622; Glymour and Hamad, p. 623; Jones and Schooling, p. 624; and Hernán, p. 625.

Am J Public Health. 2018;108:616–619.

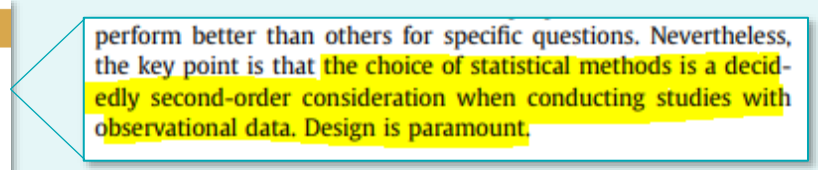
Design vs. Statistical Techniques


Decision-Analytic Modeling: Past, Present, and Future

Real-World Evidence, Causal Inference, and Machine Learning

William H. Crown, PhD*

OptumLabs,® Cambridge, MA, USA


perform better than others for specific questions. Nevertheless, the key point is that the choice of statistical methods is a decidedly second-order consideration when conducting studies with observational data. Design is paramount.

Value Health. 2019; 22(5):587–592.

Observational Data for Decision-Making


U.S. FOOD & DRUG ADMINISTRATION

Framework for FDA's Real-World Evidence Program

December 2018

https://www.fda.gov/media/120060/download

A Step-By-Step Guide to Causal Study Design

1 Research Question

Association
Most biases disregarded by definition

Causal Effect
Move to Step 2

Estimand

2 Which Kind of Effect?

Intention-to-Treat (ITT)
≈ First-treatment-carried-forward (FTCF)

Per-protocol (PP) ≈ As-treated

3 Effect in *Whom*?

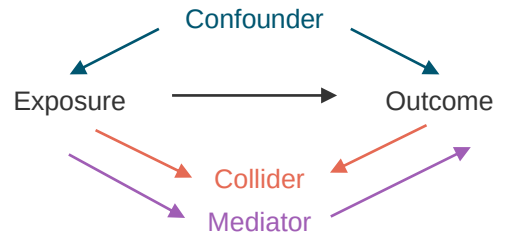
Target Population For Counterfactual Contrast

- Average treatment effect (ATE)
- ATE on the treated/untreated (ATT/ATU)
- Conditional ATE (subgroups)
- Individual TE (ITR)

4 Measure of Effect?

Difference or ratio?
Risk, rate, hazard, odds, cost…?

5 Create Directed Acyclic Graph (DAG)



6 Navigate the Land of Biases

- Measured confounding
- Unmeasured confounding
- Collider bias
- Selection bias
- Immortal time bias
- Protopathic bias (reverse causality)
- Healthy adherer effect
- Prevalent user bias
- Confounding by indication
- Effect modification ↔ Generalizability
- Dependent/informed censoring
- Misclassification

Etc.

7 Explore the Land of Solutions

- "Target trial" thinking
- New user design with active comparator
- Confounder adjustment
  - *Time-invariant ("baseline")*
    - Matching or weighting
    - Best with propensity scores
  - *Time-varying*
    - Survival analysis with time-varying covariates
    - Mixed models, GEE
    - MSM with IPTW (if confounders are affected by prior treatment)
- Evaluate confounder balance
- Evaluate unmeasured confounding (e.g., via E-value or use of instrumental variables)
- IPCW to account for loss-to-follow-up/censoring

8 Conduct QC & Sensitivity Analyses

- Test if model assumptions are fulfilled
- Use different estimand or model
- Quantitative bias analysis

Acronyms: GEE, generalized estimating equations; IPC/TW, inverse probability of censoring/treatment weighting; ITR, individual treatment response; MSM, marginal structural model; TE, treatment effect

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Part 2

A Step-By-Step Guide to Causal Study Design

Estimand

1 Research Question[1]

Association
Most biases disregarded by definition[2]

Causal Effect
Move to Step 2

2 Which Kind of Effect?[3]

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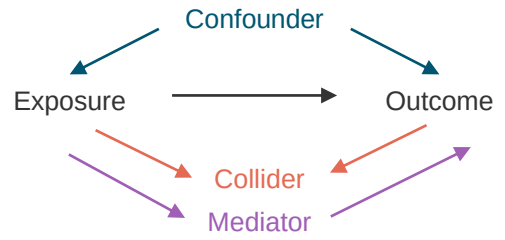

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Acronyms: GEE, generalized estimating equations; IPC/TW, inverse probability of censoring/treatment weighting; ITR, individual treatment response; MSM, marginal structural model; TE, treatment effect

[1-7]Please refer to the following slide for footnotes

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A Step-By-Step Guide to Causal Study Design

[1]Ensure that the exposure and outcome are well-defined based on literature and expert opinion

[2]More specifically, measures of association are not affected by issues such as confounding and selection bias because they do not intend to isolate and quantify a single causal pathway. However, information bias (e.g., variable misclassification) can negatively affect association estimates, and association estimates remain subject to random variability (and are hence reported with confidence intervals).

[3]"Trial ≈ real world data" parallels are inexact. PP especially can be expanded within the target trial framework.

[4]This list is not exhaustive; it focuses on frequently encountered biases

[5]To assess bias in a nonrandomized study, use of the ROBINS-I tool is recommended (Sterne 2016; http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-i/resources/)

[6]Only a selection of the most popular approaches is presented here. Other methods exist; e.g., g-computation and g-estimation for both time-invariant and time-varying analysis; instrumental variables; and doubly-robust estimation methods. There are also program evaluation methods (e.g., difference-in-differences, regression discontinuities) that can be applied to pharmacoepidemiological questions.

Conventional outcome regression analysis is NOT recommended for causal estimation due to issues determining balance, correct model specification, and interpretability of effect estimates.

[7]Online tools include, among others, an E-value calculator for unmeasured confounding (https://www.evalue-calculator.com/) and the P95 outcome misclassification estimator (http://apps.p-95.com/ISPE/).

Five suggested articles for further reading

(additional articles can be found in the glossary reference section)

- Hernán MA. The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data*. Am J Public Health*. 2018;108(5):616-619.
- Franklin JM, Platt R, Dreyer NA, et al. When Can Nonrandomized Studies Support Valid Inference Regarding Effectiveness or Safety of New Medical Treatments? *Clin Pharmacol Ther*. 2021;10.1002/cpt.2255.
- Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46(3):399-424.
- Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G. Handling time varying confounding in observational research. *BMJ*. 2017;359:j4587.
- Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985.

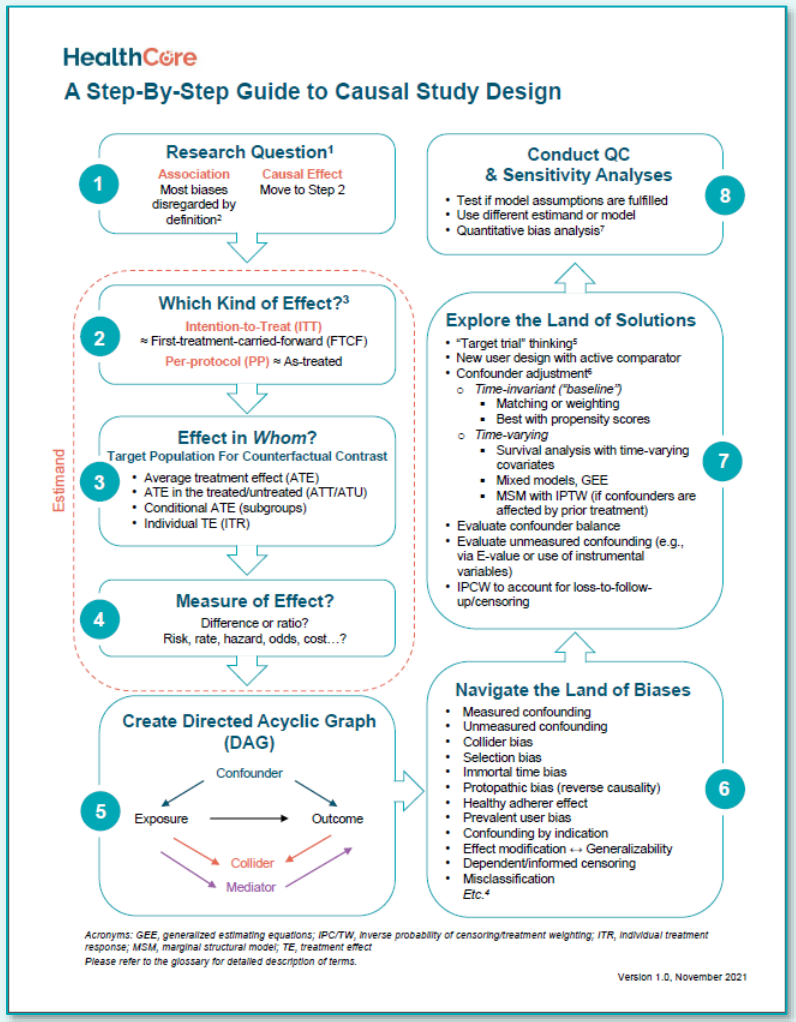
Limitations of the Step-By-Step Guide

Information was sourced widely, but no systematic literature review was conducted

Space and useability constraints necessitated simplification of the complex source material and selections among many available methodologies

Information about the relative importance of each step is not currently included

PDF Handouts Available



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A Step-By-Step Guide to Causal Study Design

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Association: Most biases disregarded by definition[2]
Causal Effect: Move to Step 2

2 Which Kind of Effect?[3]
Intention-to-Treat (ITT) ≈ First-treatment-carried-forward (FTCF)
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3 Effect in *Whom*? (Estimand)
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5 Create Directed Acyclic Graph (DAG)
Confounder; Exposure; Outcome; Collider; Mediator

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- *Etc.*[4]

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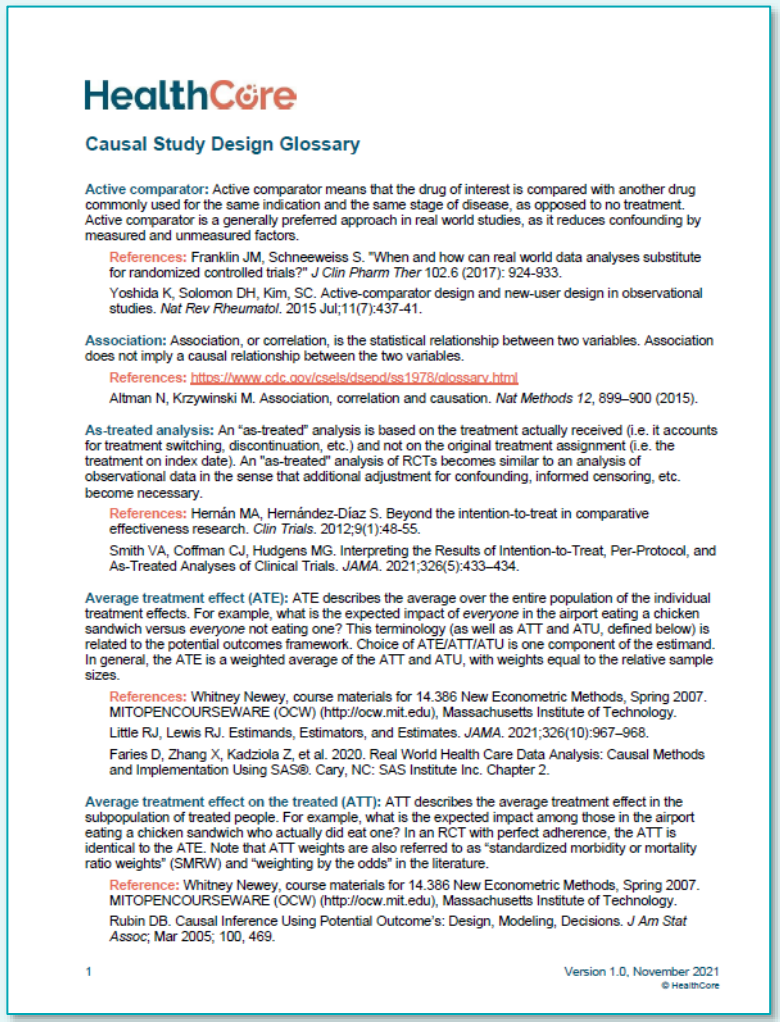
Acronyms: GEE, generalized estimating equations; IPC/TW, inverse probability of censoring/treatment weighting; ITR, individual treatment response; MSM, marginal structural model; TE, treatment effect
Please refer to the glossary for detailed description of terms.

Version 1.0, November 2021



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Causal Study Design Glossary

Active comparator: Active comparator means that the drug of interest is compared with another drug commonly used for the same indication and the same stage of disease, as opposed to no treatment. Active comparator is a generally preferred approach in real world studies, as it reduces confounding by measured and unmeasured factors.

References: Franklin JM, Schneeweiss S. "When and how can real world data analyses substitute for randomized controlled trials?" *J Clin Pharm Ther* 102.6 (2017): 924-933.

Yoshida K, Solomon DH, Kim, SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015 Jul;11(7):437-41.

Association: Association, or correlation, is the statistical relationship between two variables. Association does not imply a causal relationship between the two variables.

References: https://www.cdc.gov/csels/dsepd/ss1978/glossary.html

Altman N, Krzywinski M. Association, correlation and causation. *Nat Methods 12*, 899–900 (2015).

As-treated analysis: An "as-treated" analysis is based on the treatment actually received (i.e. it accounts for treatment switching, discontinuation, etc.) and not on the original treatment assignment (i.e. the treatment on index date). An "as-treated" analysis of RCTs becomes similar to an analysis of observational data in the sense that additional adjustment for confounding, informed censoring, etc. become necessary.

References: Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials*. 2012;9(1):48-55.

Smith VA, Coffman CJ, Hudgens MG. Interpreting the Results of Intention-to-Treat, Per-Protocol, and As-Treated Analyses of Clinical Trials. *JAMA*. 2021;326(5):433–434.

Average treatment effect (ATE): ATE describes the average over the entire population of the individual treatment effects. For example, what is the expected impact of *everyone* in the airport eating a chicken sandwich versus *everyone* not eating one? This terminology (as well as ATT and ATU, defined below) is related to the potential outcomes framework. Choice of ATE/ATT/ATU is one component of the estimand. In general, the ATE is a weighted average of the ATT and ATU, with weights equal to the relative sample sizes.

References: Whitney Newey, course materials for 14.386 New Econometric Methods, Spring 2007. MITOPENCOURSEWARE (OCW) (http://ocw.mit.edu), Massachusetts Institute of Technology.

Little RJ, Lewis RJ. Estimands, Estimators, and Estimates. *JAMA*. 2021;326(10):967–968.

Faries D, Zhang X, Kadziola Z, et al. 2020. Real World Health Care Data Analysis: Causal Methods and Implementation Using SAS®. Cary, NC: SAS Institute Inc. Chapter 2.

Average treatment effect on the treated (ATT): ATT describes the average treatment effect in the subpopulation of treated people. For example, what is the expected impact among those in the airport eating a chicken sandwich who actually did eat one? In an RCT with perfect adherence, the ATT is identical to the ATE. Note that ATT weights are also referred to as "standardized morbidity or mortality ratio weights" (SMRW) and "weighting by the odds" in the literature.

Reference: Whitney Newey, course materials for 14.386 New Econometric Methods, Spring 2007. MITOPENCOURSEWARE (OCW) (http://ocw.mit.edu), Massachusetts Institute of Technology.

Rubin DB. Causal Inference Using Potential Outcome's: Design, Modeling, Decisions. *J Am Stat Assoc*; Mar 2005; 100, 469.

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Copies of the guide and glossary are available using the following QR code:

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Part 3

Case Example Background

β-Blockers for patients with acute myocardial infarction (AMI) are the standard of care

Strong evidence of survival benefit for individuals with AMI and heart failure (HF)

Less is known of the benefit for individuals with AMI without HF or left ventricular systolic dysfunction (LVSD)

Dondo, T.B., Hall, M., West, R.M., et al. β-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. *J Am Coll Cardiology*. 2017; 69(22):2710-2720.

Case Example Data Source, Cohort, Outcomes, and Analytic Comparisons

Data Source

- Myocardial Ischemia National Audit Project (MINAP)
- Comprehensive registry of acute coronary syndrome hospitalizations, initiated in 2000

Outcomes

- Primary – all-cause mortality 1-year post-discharge
- Secondary – all-cause mortality at 1 month and 6 months post-discharge

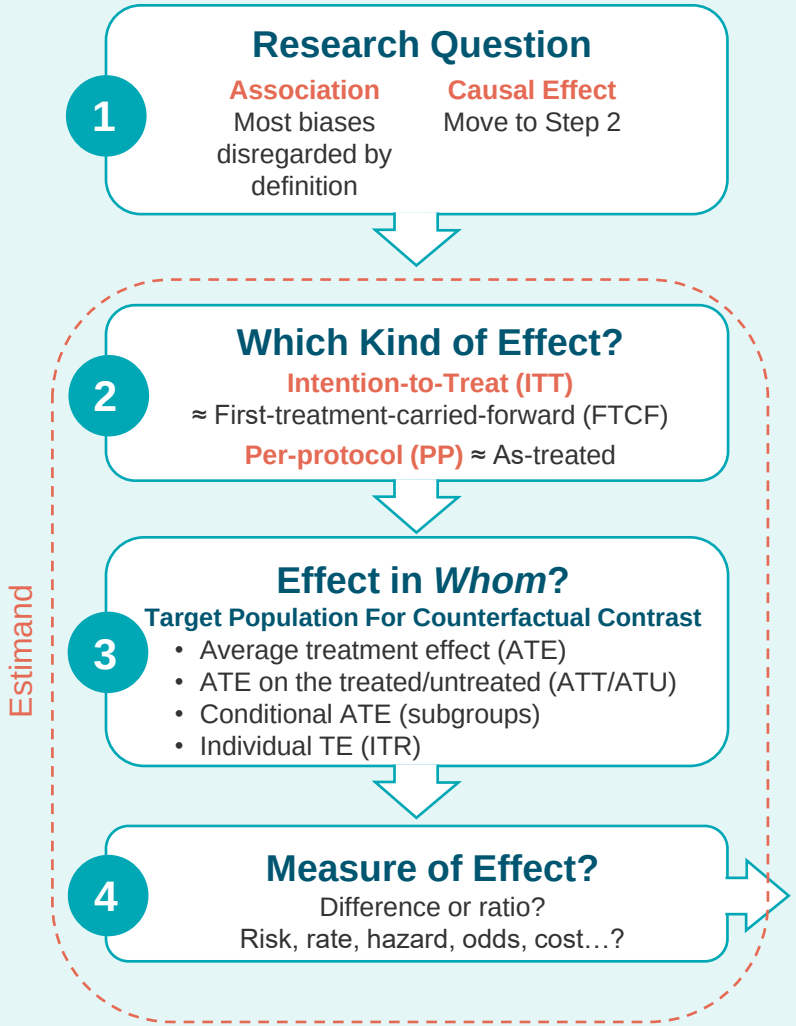
Cohort

- Admitted to 1 of 247 hospitals
- Final follow up was December 2013
- Discharge diagnosis: ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI)
- Exclusion criteria reduced starting sample of 475,301 to 179,810
- 170,475 had β-blocker at discharge; 9,335 did not

Analytic Comparisons

- All AMI and stratified by STEMI and NSTEMI

Case Study Application: Steps 1 - 4



Research Question

- Causal Effect
  - "What is the impact of the use of β-blockers on all-cause mortality at 1 year for survivors of hospitalized acute myocardial infarction without heart failure or left-ventricular systolic dysfunction?"

Treatment Effect

- Intention to Treat (ITT)

Effect in Whom

- Average Treatment Effect (ATE)
- Average Treatment Effect in the Treated (ATT)

Effect Measure

- Absolute difference in survival time

Case Study Application: Step 6

Navigate the Land of Biases

- Measured confounding
- Unmeasured confounding
- Collider bias
- Selection bias
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- Healthy adherer effect
- Prevalent user bias
- Confounding by indication
- Effect modification ↔ Generalizability
- Dependent/informed censoring
- Misclassification

Etc.

6

Measured Confounding	24 Baseline Variables
Demographic	Sex; socioeconomic deprivation index
Cardiovascular	Year of hospital admission; diabetes; hypercholesterolemia; hypertension; smoking status; family history coronary heart disease
Medical Conditions	COPD; CVD; PVD; discharge medications (e.g., statins, aspirin)
Hospital Care	Mini-Global Registry of Acute Coronary Events risk score variables (i.e., age, cardiac arrest, elevated enzyme, systolic blood pressure, heart rate at hospitalization), care by cardiologist

Acronyms: COPD=chronic obstructive pulmonary disease; CVD=cerebrovascular disease; PVD=peripheral vascular disease

Case Study Application: Step 6

6

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Etc.

Type of Bias	Explanation
Residual Confounding	Potential imbalance between comparators even after confounder adjustment methods
Unmeasured Confounding	Hospitals can differ in the quality of care provided
Unmeasured Confounding	Tail ends of the propensity score distribution can be subject to unmeasured factors (e.g., frailty, severity)

Case Study Application: Step 6

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Etc.

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Type of Bias	Variables
Selection Bias	Removed >100 years old Removed contraindicated β-blocker
Confounding by Indication	Cohort defined by AMI without HF or LVSD No previous AMI, angina, PCI, or CABG surgery

Acronyms AMI=acute myocardial infarction; HF=heart failure; LVSD=left ventricular systolic dysfunction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

Case Study Application: Step 7

Explore the Land of Solutions

- "Target trial" thinking
- New user design with active comparator
- Confounder adjustment
  - *Time-invariant ("baseline")*
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Type of Bias	Solution to Address the Bias
Measured Confounding	Propensity score estimated as the propensity for β-blocker treatment & implemented as the Inverse Probability of Treatment Weight (IPTW)
Unmeasured Confounding	Instrumental Variable – hospital rate of guideline-indicated prescribing
Unmeasured Confounding	Trimmed cohort at 0.1 & 0.9 propensity score distribution
Residual Confounding	Cardiac rehabilitation covariate adjusted in analytic models
Confounder Balance	Assessed the standardized mean differences between raw and IPTW
Missing Variables	Multiple imputation to impute missing variables

Case Study Application: Step 8

Conduct QC & Sensitivity Analyses

- Test if model assumptions are fulfilled
- Use different estimand or model
- Quantitative bias analysis

8

QC & Sensitivity Analyses	Solution to Address the Bias
Propensity Score Assumption	Tested the overlap of the propensity score distribution between comparator groups
Full Cohort Analysis	IPTW models performed with all subjects, regardless of the propensity score to assess robustness of the estimates from the trimmed analytic sample
Complete Case Analysis	Analyses performed with the subset of individuals that did not have any missing data

Case Study Limitations

Baseline look-back period to assess measured covariates was not explicit

No mention of the IPTW distribution and assessment of extreme weights

Extreme weights can influence the analysis; stabilized IPTW can be used to address this

94% received a β-Blocker; the comparator group had very few individuals

Audience Poll Question #3

Your study is matching untreated to treated patients 1:1 using propensity scores. What estimand will this generate?

a) The Average Treatment Effect (ATE), i.e., the average effect of the treatment when comparing everyone getting treated to everyone not getting treated

b) The Average Treatment Effect on the Treated (ATT), i.e., the average effect of the treatment among those patients who actually received the treatment

c) ATE and ATT are the same with this matching approach

d) Neither ATE nor ATT

e) I am not sure

Audience Poll Question #4

Consider the graph on the right, where diet is posited to affect cognitive function.

In this relationship, the variable denoted "Follow-up" is a…

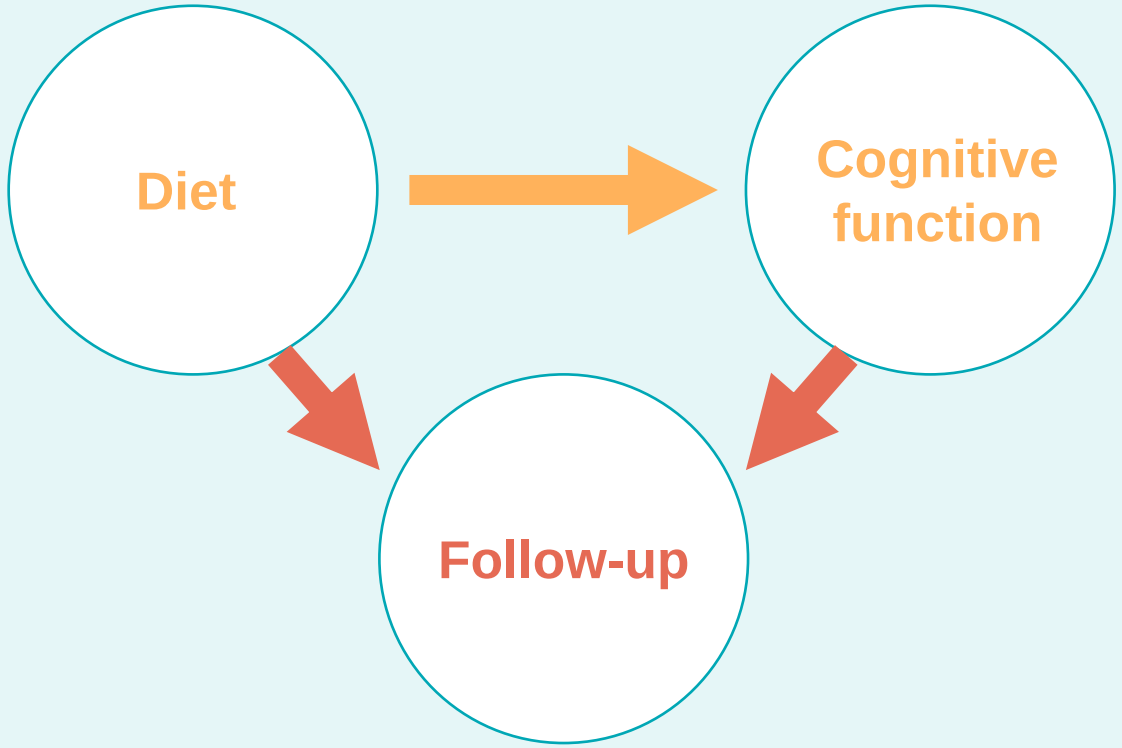
a) Mediator

b) Confounder

c) Collider

d) None of the above

e) I am not sure



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Workshop Conclusions

Recap Learning Objectives

- List and describe key steps of designing a study for causal inference
- Define “estimand” and describe its components
- Define ATE & ATT and relate them to PS-based weighting & matching
- Distinguish methods for dealing with measured vs. unmeasured confounding
- Apply the step-by-step guide when evaluating the literature

Other Take-aways

- Different studies have different biases and require different solutions
- Research question may need to consider a single or multiple analytic approaches to evaluate/address biases
- Data visualization can be helpful (e.g., to evaluate covariate balance)

Further Reading

- References included in the PDF handouts
- ISPOR/ISPE short courses
- Faries D et al. (2020). *Real World Health Care Data Analysis: Causal Methods and Implementation Using SAS®.* Cary, NC: SAS Institute Inc
- Hernán MA, Robins JM (2020). *Causal Inference: What If.* Boca Raton: Chapman & Hall/CRC
- Pearl J (2009). *Causality: Models, Reasoning and Inference.* New York: Cambridge University Press
- Scott Cunningham (2021). *Causal Inference: The Mixtape*

Audience Poll Question #5

As a result of this workshop, are you more confident in describing the essence of a causal study design, and/or trying the methods presented here?

a) Much more confident
b) Somewhat more confident
c) Same as before
d) Somewhat less confident
e) Much less confident

Thank You

Please reach out with any questions and comments to:

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