Understanding "how" in a study of cause and effect: An introduction to mediation analysis in epidemiology

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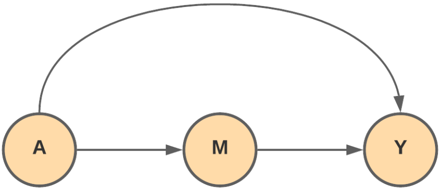


Outline

What is causal inference?

- Causal inference formalizes the assumptions needed to conclude that treatment A causes outcome Y and not just that A and Y are associated
- Methods in causal inference are often used to draw causal conclusions from observational datasets
- Examples of observational data:
  - Electronic health records
  - Insurance claims database
  - Customer purchasing database
  - Data from prospective studies where a treatment/exposure is not randomized
- The quantity of interest in many causal studies is called the **treatment effect** or **causal effect**

Randomized controlled trials

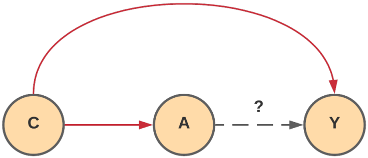
- Randomized controlled trials (RCT's) are experiments in which a treatment is randomized to patients
- Large and well-designed RCT's are often considered the "gold standard" for establishing causation between a treatment and outcome
- A key goal of randomization is to achieve covariate balance between groups
  - Covariate balance occurs when the distributions of other patient characteristics (sex, age, race, comorbidities, etc.) are similar between groups
  - An average treatment effect can be isolated if important covariates are balanced between groups
- However, RCT's are not always feasible

Observational studies

- In observational studies, we often do not have covariate balance
- For example, say we are trying to use Electronic Health Records to provide preliminary evidence on whether an experimental therapy might be effective in treating patients with cancer
- The experimental therapy has not yet received FDA approval and is being used on a compassionate use basis
- **Discussion questions:**
  - What factors might influence who receives the experimental therapy?
  - Does every patient who is hospitalized with the condition have a positive probability of receiving this therapy?
- A series of causal assumptions (discussed in Hernán and Robins) can be used to conceptualize an observational study in an RCT framework

Confounding variables

- Causal diagrams are used to visualize causal relationships between variables in an analysis
- In the causal diagram below, C is a **confounding variable**, since it is a common cause of both the treatment, A, and the outcome, Y
- Not accounting for C would allow us to draw the conclusion that A and Y are associated but not that A causes Y
- By accounting for C in our analysis, we can estimate the effect of A on Y (if there is one) that is not due to common cause C



Potential outcomes framework

- Let Y denote a subject's observed outcome. We will assume that Y is continuous
- The subject either received treatment level $A = 1$ or $A = 0$, but we only observed one of these situations and the corresponding outcome
- In order to estimate a treatment effect, we need to know what the subject's outcome would have been under each level of treatment

Potential outcomes (or counterfactuals)		
$A = 0$	Y_0	The outcome a subject would have had if they had taken treatment 0
$A = 1$	Y_1	The outcome a subject would have had if they had taken treatment 1

- $Y = ZY_1 + (1 - Z)Y_0$ where $Z = 1$ if the subject received treatment 1 and $Z = 0$ if the subject received treatment 0

Treatment Effects

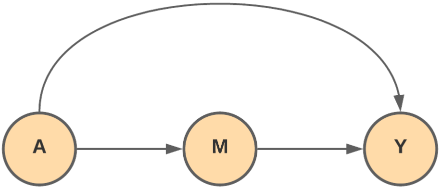
- Using the counterfactual framework, a subject's treatment effect is defined as $Y_1 - Y_0$
- Often, we cannot determine an individual treatment effect
- Much of causal inference is focused on estimating the **average treatment effect** or **average causal effect** in a population:

$$E(Y_1 - Y_0)$$

- Stable unit treatment value assumption (SUTVA):
  - Part 1: There cannot be multiple versions of the treatment
  - Part 2: There cannot be treatment interference (i.e. the treatment of one subject cannot affect the potential outcome of another subject)

Mediation analysis: understanding "how"

- Mediation analysis aims to address an underlying causal mechanism
- It is likely already established that A causes Y, but we would like to know how and why that is
- Does A cause a change in intermediate outcome M (mediator), which in turn causes Y?
- How much of the total effect of A on Y occurs through M?



Motivating example

- In a study of persons with a substance-use disorder, we would like to determine whether a rehabilitation program with methadone treatment (A) results in increased work activity (Y)
- It is of interest to determine whether some of this effect is mediated through level of illicit drug use (M)
- This example is described in Chapter 2 of VanderWeele's mediation textbook

Potential outcomes framework in mediation analysis

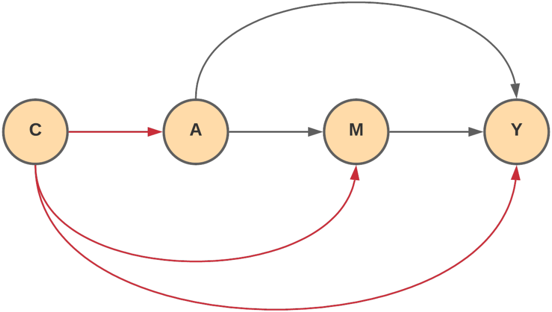
- Y_1 and Y_0 denote the counterfactual outcomes for a subject when taking treatment 1 and treatment 0, respectively
- In a mediation analysis, we also define counterfactual outcomes for the mediator variable

Potential outcomes		
$A = 0$	M_0	The mediator value a subject would have had if they had taken treatment 0
$A = 1$	M_1	The mediator value a subject would have had if they had taken treatment 1

- Y_{a,M_a} denotes the counterfactual outcome when the subject's treatment is fixed at level $A = a$ and the subject's mediator value is the value that would have occurred if they had taken treatment $A = a$
- We will assume that M is a continuous mediator

Causation vs. association in mediation

- Let C represent a collection of confounding variables
- In our motivating example, A $=$ rehab $+$ methadone, M $=$ level of illicit drug use, Y $=$ amount of work activity
- What variables might confound the relationship between A and M, M and Y, or A and Y?



Causal quantities of interest

- **Average total effect (TE):** The average difference in outcome (treatment effect) when the treatment is set to 1 vs. 0

$$E(Y_1 - Y_0 \mid c) = E(Y_{1,M_1} - Y_{0,M_0} \mid c)$$

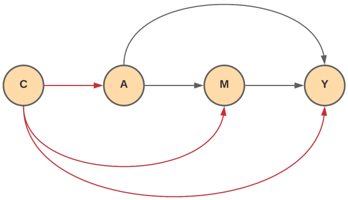
- **Average natural direct effect (NDE):** The average difference in outcome when the treatment is set to 1 vs. 0 and the mediator value is set to what it would have been under treatment 0

$$E(Y_{1,M_0} - Y_{0,M_0} \mid c)$$

- **Average natural indirect effect (NIE):** The average difference in outcome when the treatment is set to 1 and the mediator value changes from what it would have been under treatment 0 to what it would have been under treatment 1

$$E(Y_{1,M_1} - Y_{1,M_0} \mid c)$$

Causal assumptions in mediation analysis



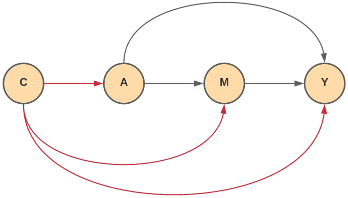
- Assumption 1: Conditional on C, there is no unmeasured confounding between the outcome and the treatment

$$Y_{a,m} \perp A \mid C$$

- Assumption 2: Conditional on A and C, there is no unmeasured confounding between the outcome and the mediator

$$Y_{a,m} \perp M \mid \{A, C\}$$

Causal assumptions in mediation analysis (continued)



- Assumption 3: Conditional of C, there is no unmeasured confounding between the mediator and the treatment

$$M_a \perp A \mid C$$

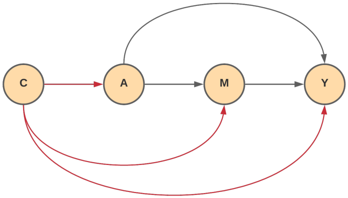
- Assumption 4: Conditional on C, A does not cause an effect L that in turn affects both M and Y

$$Y_{a,m} \perp M_{a^*} \mid C$$

- SUTVA assumption mentioned earlier also applies

Regression-based approach for mediation analysis

- We can use multiple linear regression models to model the relationships in the causal diagram



- Regress Y on a, m, and c to obtain an estimate of

$$E(Y \mid a, m, c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$$

- Regress M on a and c to obtain an estimate of

$$E(M \mid a, c) = \beta_0 + \beta_1 a + \beta_2' c$$

Estimating the average causal quantities

$$
\begin{aligned}
NDE &= \int_{-\infty}^{\infty} E(Y \mid A=1, M=m, C=c) f(m \mid A=0, C=c) dm \\
&- \int_{-\infty}^{\infty} E(Y \mid A=0, M=m, C=c) f(m \mid A=0, C=c) dm \\
&= \theta_1 + \theta_3\beta_0 + \theta_3\beta_2' c
\end{aligned}
$$

$$
\begin{aligned}
NIE &= \int_{-\infty}^{\infty} E(Y \mid A=1, M=m, C=c) f(m \mid A=1, C=c) dm \\
&- \int_{-\infty}^{\infty} E(Y \mid A=1, M=m, C=c) f(m \mid A=0, C=c) dm \\
&= \beta_1(\theta_2 + \theta_3)
\end{aligned}
$$

$$E(Y \mid a, m, c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$$

$$E(M \mid a, c) = \beta_0 + \beta_1 a + \beta_2' c$$

Causal interpretation of effects

- Use of the regression models and the aforementioned causal assumptions collectively, allow for direct, indirect, and total effects to be estimated with a causal interpretation
- Interpret with caution as these assumptions will never be fully met in practice
- Several of these causal assumptions can be tested using sensitivity analysis methods

How much of the total effect was mediated by M?

- Proportion mediated (PM) is one metric used to assess the amount of mediation
- Recall that the total effect is $TE = NDE + NIE$
- $PM = \frac{NIE}{TE}$
- This metric has some limitations
  - It can have a wide confidence interval
  - If the direct and indirect effect have different signs, PM can exceed 100%

Frequentist vs. Bayesian paradigm

- **Frequentist approach:**
  - Estimates of the TE, NIE, NDE, and PM can be obtained by plugging in the estimated regression coefficients
  - Bootstrapping is often the easiest way to obtain confidence intervals for these quantities in the frequentist setting
- **Bayesian approach:**
  - Run the Bayesian version of each linear regression model
    - Prior distributions must be specified on each parameter
  - Obtain posterior samples of the TE, NIE, NDE, and PM
  - Use the posterior mean as the estimate and obtain 95% credible intervals using the sample values corresponding to the 2.5th and 97.5th percentile of each quantity

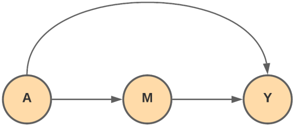
Understanding cancer disparities with mediation analysis

- My dissertation research focuses on assessing patterns in cancer mortality rates at the county level using Bayesian hierarchical models
- In the Midwest, there are rural/urban differences in age-adjusted cancer mortality rates

Cancer	**Effect of rural vs. urban on age-adjusted mortality rate**	**95% credible interval**
Colorectal	1.093	(1.064, 1.122)
Lung	1.010	(0.987, 1.034)
All	1.016	(1.002, 1.030)

- We aim to understand which variables mediate the relationship between rural/urban status and age-adjusted cancer mortality rates using a Bayesian spatial modeling approach
- Working on this research with Dr. Jake Oleson and Dr. Mary Charlton

Understanding cancer disparities with single mediator model



- A represents the rurality of a county ($A = 1$ is rural, $A = 0$ is urban)
- M represents the miles to the nearest Commission-on-Cancer-accredited hospital
- Y represents a county's age-adjusted cancer mortality rate
- We focus on further explaining the association between A and Y rather than obtaining a causal interpretation

Bayesian hierarchical models

Model 1:

$$Y_{ik} \sim \text{Poisson}(\lambda_{ik})$$

$$\log(\lambda_{ik}) = \log(n_{ik}) + \alpha_k + \theta_1 a_i + \theta_2 m_i + \theta_3 a_i m_i + \gamma_i + \epsilon_i$$

- Let i denote the county and k denote the age group
- Y_{ik} denotes the number of cancer deaths in the corresponding group
- γ_i is a spatial random effect for county i (has a conditional autoregressive prior)
    - Accounts for correlated age-adjusted rates between a county and its neighboring counties
- ϵ_i accounts for overdispersion in the Poisson model
- Vague prior distributions are assigned to all other parameters

Bayesian hierarchical models (continued)

Model 2:

$$M_i \sim \text{Normal}(\mu_i, \sigma^2)$$

$$\mu_i = \beta_0 + \beta_1 a_i$$

- Vague prior distributions are assigned to all parameters

Some challenges

- Treatment interference in the spatial setting
    - SUTVA assumption is violated!
    - A neighboring county's rural or urban status likely influences the county's cancer mortality rate
        - We therefore have "treatment" interference
    - Recent literature suggests ways to redefine potential outcomes when treatment interference occurs due to spatial or social network interference (see Forastiere et al)
- Count outcome
    - We need to re-derive the direct and indirect effects, as the set of effects based on the linear model do not hold for count outcomes
- Multiple mediators
    - Including additional mediators, especially correlated mediators, requires new expressions for the direct and indirect effects

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