What is ACCORDS?

Adult and Child Center for Outcomes Research and Delivery Science

ACCORDS is a 'one-stop shop' for pragmatic research:

- A multi-disciplinary, collaborative research environment to catalyze innovative and impactful research
- Strong methodological cores and programs, led by national experts
- Consultations & team-building for grant proposals
- Mentorship, training & support for junior faculty
- Extensive educational offerings, both locally and nationally

ACCORDS Upcoming Events

October 25, 2023 Zoom	**ACCORDS/CCTSI Community Engagement Forum** *What is Representation? Community Voice and Identity Through Advisory Boards and Partnerships*
November 1, 2023 AHSB 2200/2201, Zoom	**Ethics, Challenges, & Messy Decisions in Shared Decision Making** *Ethical Issues in Shared Decision Making* *Presented by:* Drs. Laura Scherer, Matthew Wynia, and Dan Matlock
November 9 & 16, 2023 9:00-3:00pm MT Zoom	**Overview of Dissemination and Implementation (D&I) Science Workshop** *Lead facilitators:* Tina Studts, PhD and Borsika Rabin, PharmD, PhD
November 20, 2023 AHSB 2200/2201, Zoom	**Statistical Methods for Pragmatic Research** *Randomization-based Inference for Cluster Randomized Trials* *Presented by:* Dustin J. Rabideau, PhD (Massachusetts General Hospital)
December 6, 2023 AHSB Conf. Center, Zoom	**Ethics, Challenges, & Messy Decisions in Shared Decision Making** *Incorporation of Patient Reported Outcome Measures in Shared Decision-Making in Breast Surgical Oncology* *Presented by:* Sarah Tevis, PhD
December 18, 2023 AHSB 2200/2201, Zoom	**Statistical Methods for Pragmatic Research** *Presented by:* Maren Olsen, PhD (Duke)

*all times 12-1pm MT unless otherwise noted

Statistical Methods for Pragmatic Research
2023-2024 Seminar Series

Presented by:
Heather Smyth, PhD

A (Re)Introduction to Statistical Mediation

A (Re)Introduction to Statistical Mediation

HEATHER SMYTH, PHD – RESEARCH ASSOCIATE

CENTER FOR INNOVATIVE DESIGN AND ANALYSIS

- PhD in Quantitative Psychology from Arizona State University
  - Mediation, causal inference, individualized effects

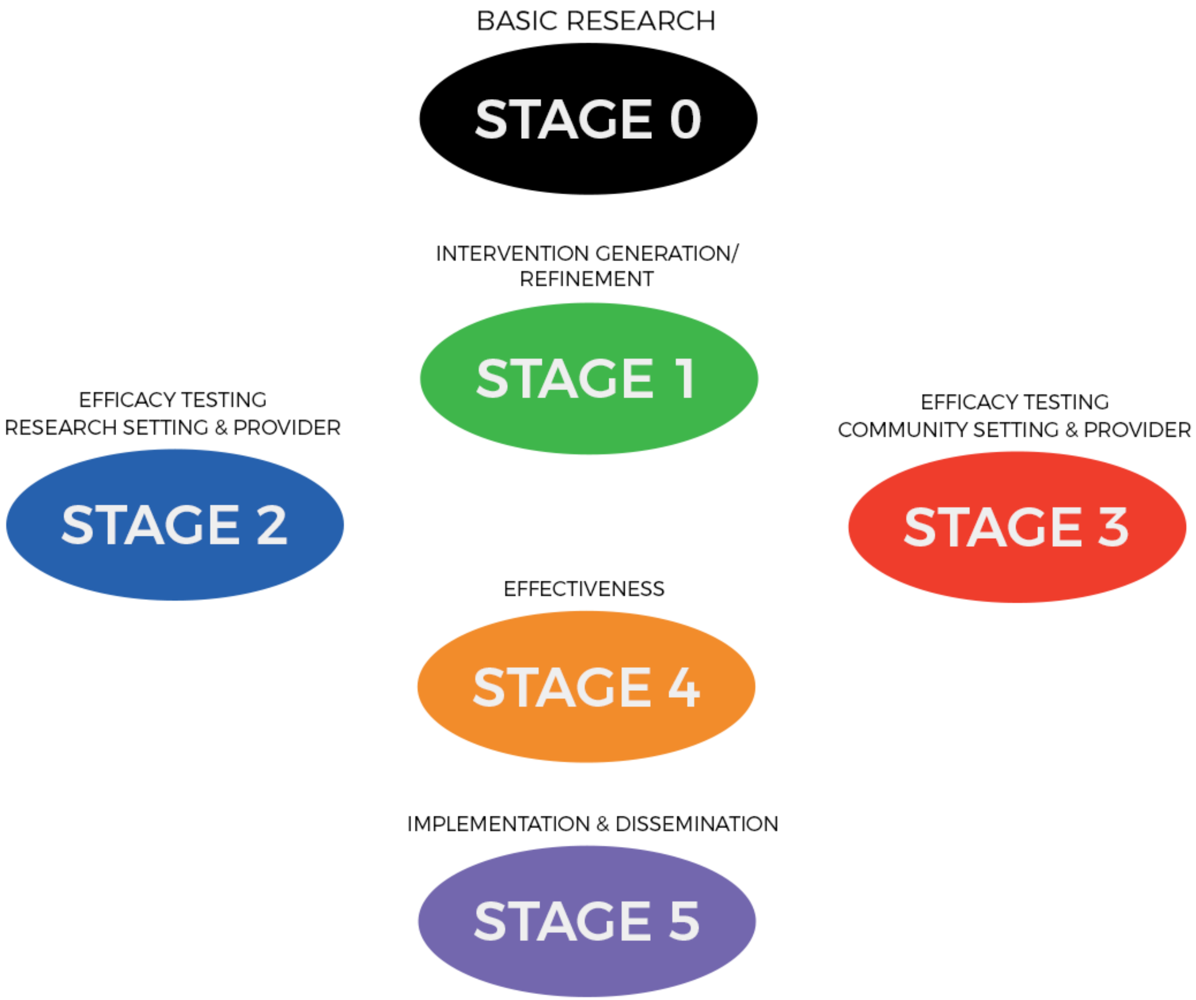
- Research Associate in the Center of Innovative Design and Analysis (CIDA)
  - Faculty in the Colorado School of Public Health, Department of Biostatistics and Informatics
  - Collaborative Statistician with
    - ACCORDS
    - College of Nursing
    - Rocky Mountain Prevention Research Center
    - School of Medicine, Department of Endocrinology

Presentation Outline

- NIH Stage Model / Purpose of Mediation
- Conceptual Definition of Mediation
- Comparison of Mediation with other Variable Functions
- **Overview of Mediation Methods**
- Q&A

NIH Stage Model

"Examination of mechanisms of behavior change is encouraged in every stage of intervention development."



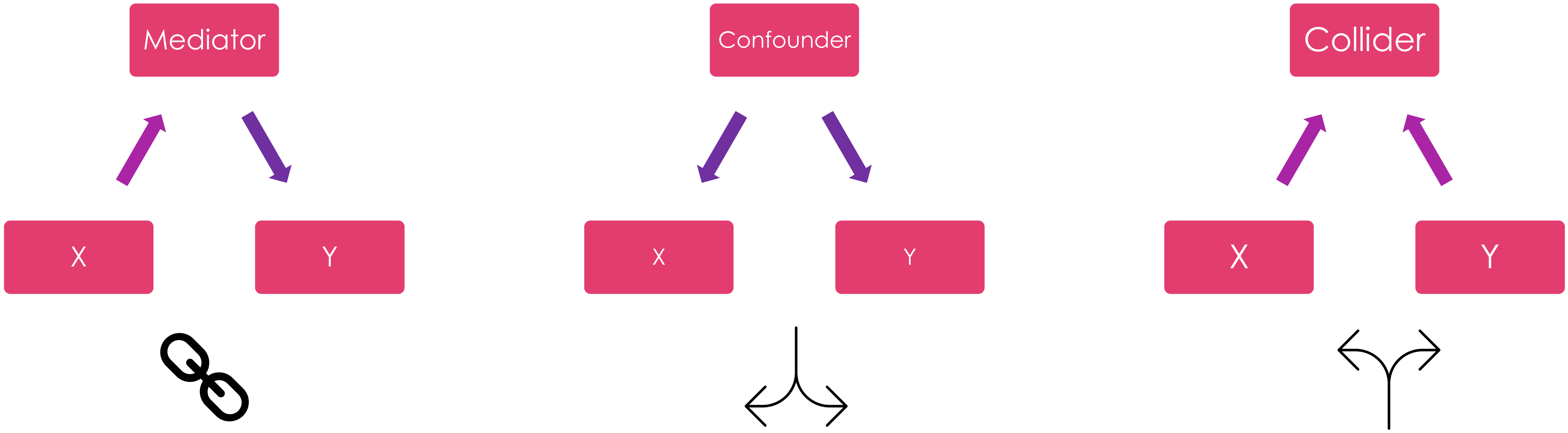
https://www.nia.nih.gov/research/dbsr/nih-stage-model-behavioral-intervention-development

Mechanisms to Mediation

- Mediator: a variable that is intermediate in the *causal process* relating an independent variable and a dependent variable.
- intervening variable, process variable, intermediate endpoint, surrogate endpoint
- indirect effect, mediated effect

Causal Third-Variable Effects

Three *causal* third-variable effects a) mediator, b) confounder, c) collider



Other (non-causal) Third Variables

Moderators - often demographic variables; interactions

Covariates – reduce unexplained variability in Y, but *doesn't change relation between X and Y*

Suppressors/Distorters – collinearity with predictors suppress relationship between X and Y or cause it to change signs

Redundant Measures – construct overlap; Jingle-Jangle fallacies

Commonly Mistaken for Mediators

Moderator – affects the strength of a relation between variables, but is *not in the causal sequence*

Covariate – related to X and/or Y, but does not change the strength of the relation and is *not in the causal sequence*

Confounder – related to both X and Y, changes the relation when controlled for, but is *not in the causal sequence*

Collider - related to both X and Y, changes the relation when controlled for, but is *not in the causal sequence*

Why would you use a mediation model?

Mediation for Explanation

- There is an observed relation between variables, and you want to explain it
  - A new treatment improves outcomes for children with multiple chronic illnesses. How does it work?

Mediation by Design

- Apply intervention that manipulates a mediator that has a known causal effect on the outcome
  - You know vitamin C reduces scurvy, so you create an intervention to increase orange consumption

Scientific Theory

Research Question

Mediation Timeline

Elaboration	B&K Causal Steps	Coefficient Methods	Potential Outcomes
• Hyman, 1955 • Lazarsfeld, 1955	• Judd & Kenny, 1981 • Baron & Kenny, 1986	• MacKinnon et al., 2002 • MacKinnon et al., 2004	• VanderWeele, 2014 • Imai et al., 2011 • MacKinnon et al., 2020

1. Total Effect

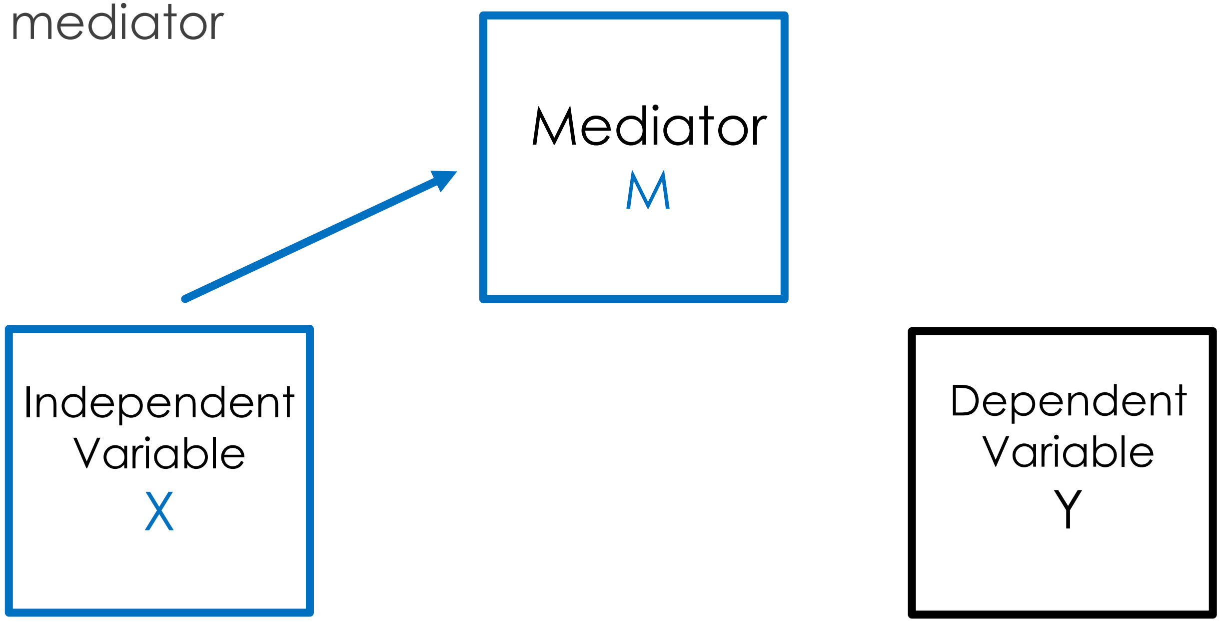
B&K Causal Steps

- Independent variable is related to a dependent variable

2. "Action theory"

B&K Causal Steps

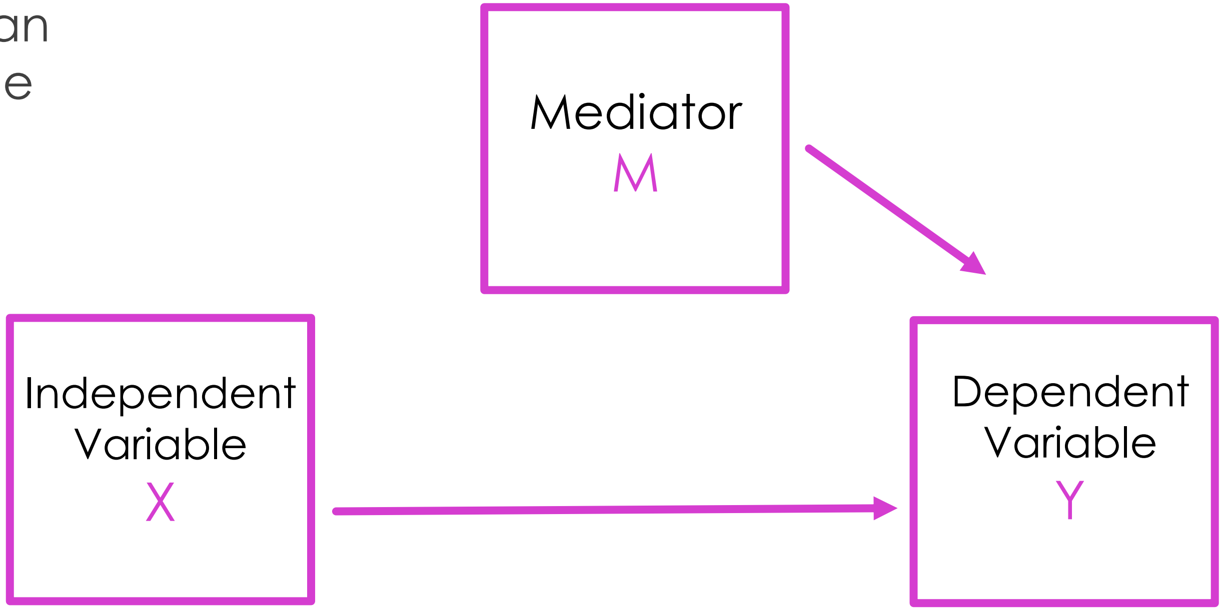
- Independent variable is related to potential mediator



3. "Conceptual theory"

B&K Causal Steps

- Mediator is related to outcome while controlling for an independent variable



The Total Effect is not Significant

TABLE 1. Conditions with significant mediation and nonsignificant intervention effects

Condition	Circumstance	Effects
I.a)	When $ab = c$ with large n and small effects.	$ab = c$
I.b)	When $ab = c$ with small n and large effects.	$ab = c$
II.	When ab and c' have opposing signs.	$ab = +, c \;\; = -$ $\mathrm{ab} = -, c' = +$
III.	With multiple mediators, when $b_1b_2b_3 = ab$.	$b_1b_2b_3 = ab$
IV.	When two specific mediated effects have opposing signs.	$a_1b_1 = +, a_2b_2 = -$ $a_1b_1 = -, a_2b_2 = +$

O'Rourke, H. P., & MacKinnon, D. P. (2018). Reasons for Testing Mediation in the Absence of an Intervention Effect: A Research Imperative in Prevention and Intervention Research. *Journal of studies on alcohol and drugs*, *79*(2), 171–181. https://doi.org/10.15288/jsad.2018.79.171

Empirical Estimates of Sample Sizes Needed for .8 Power

Test	SS	SH	SM	SL	HS	HH
BK ($\tau' = 0$)	20,886	6,323	3,039	1,561	6,070	1,830
BK ($\tau' = .14$)	562	445	427	414	444	224
BK ($\tau' = .39$)	531	403	402	403	405	158
BK ($\tau' = .59$)	530	404	402	403	406	158

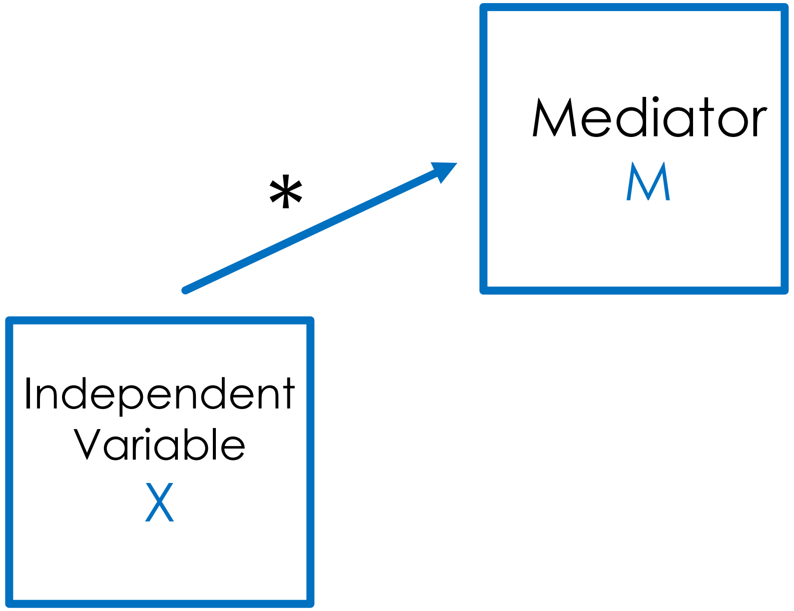
Fritz, M. S., & Mackinnon, D. P. (2007). Required Sample Size to Detect the Mediated Effect. *Psychological Science, 18(3), 233-239. https://doi.org/10.1111/j.1467-9280.2007.01882.x*

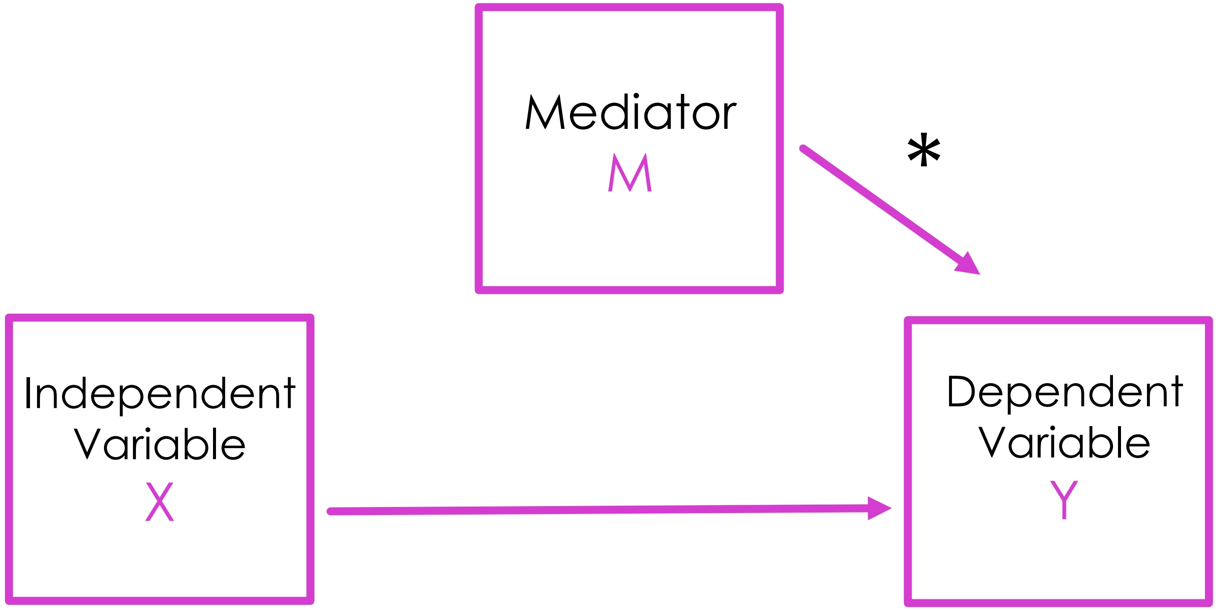
Standard Tests of Mediated Effects

- **Joint Significance**
  - $\hat{a}$ and $\hat{b}$ are both significant
- **Product of Coefficients (Sobel standard error test is common)**
  - $\hat{a}\,\hat{b}$
- **Product of Coefficients (Distribution of Product Confidence Limits / Bootstrapping)**
  - $\hat{a}\,\hat{b}$

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods, 7(1), 83-104.*

Joint Significance

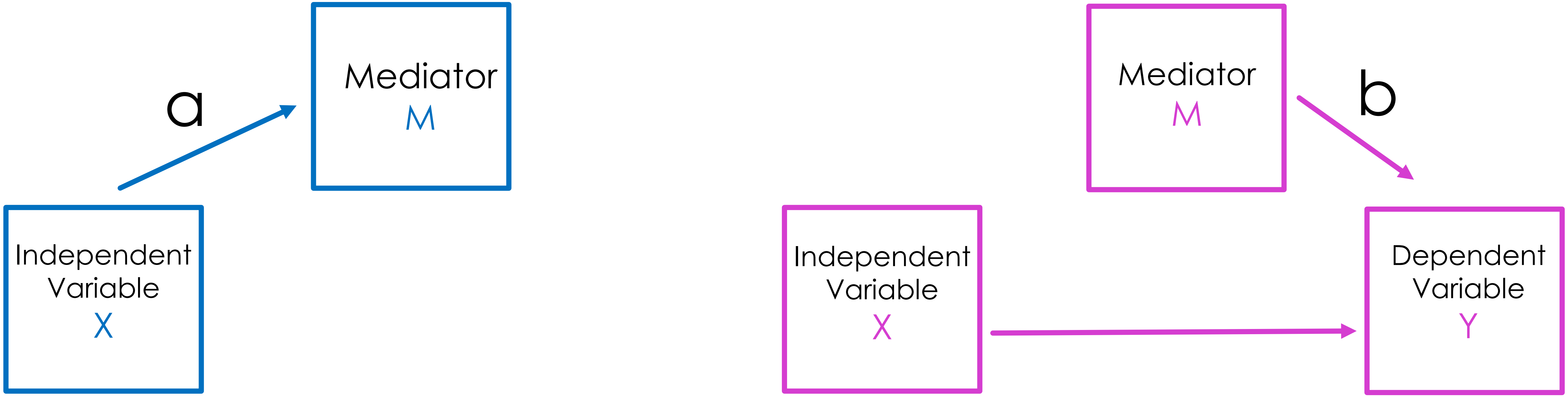




Tells you if there is mediation, but not the magnitude of the effect

Product of Coefficients

Coefficient Methods



Tells both significance and magnitude of effect, several options for calculating standard errors

My General Recommendation

Estimate the mediated effect using the product of coefficients method and bootstrapped standard errors

Mediation Calculator

RMediation

$\hat{a}$:

.02

$\hat{b}$:

.05

$SE_{\hat{a}}$:

.5

$SE_{\hat{b}}$:

.6

α:

.05

ρ:

0

Submit

Information: This web application computes a confidence interval (CI) for the mediated effect and the product of two normal random variables.

To compute the confidence interval for the mediated effect, $a \cdot b$, using the distribution of the product of the

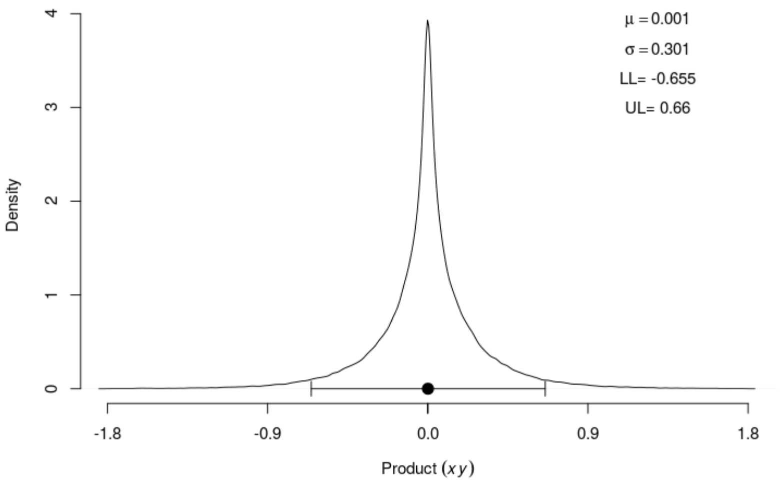
Citation

Tofighi, D. & MacKinnon, D. P. (2011). RMediation: An R package for mediation analysis confidence intervals.[PDF] *Behavior Research Methods, 43*, 692-700.

Results

For $\hat{a}$ = 0.02 (SE = 0.5) and $\hat{b}$ = 0.05 (SE = 0.6), the indirect effect estimate is 0.001 (SE = 0.301). The distribution of the product of coefficients method 95% CI is [-0.655, 0.66].

Density Plot and Confidence Interval



https://amplab.shinyapps.io/MEDCI/

https://davidakenny.net/cm/mediate.htm

The recommended method can be expanded to accommodate:

- Multiple mediators
- Longitudinal effects
- Clustered / Multilevel designs
- Categorical outcomes
- Latent variables
- Mixture Models
- Time-to-event data
- n = 1 data

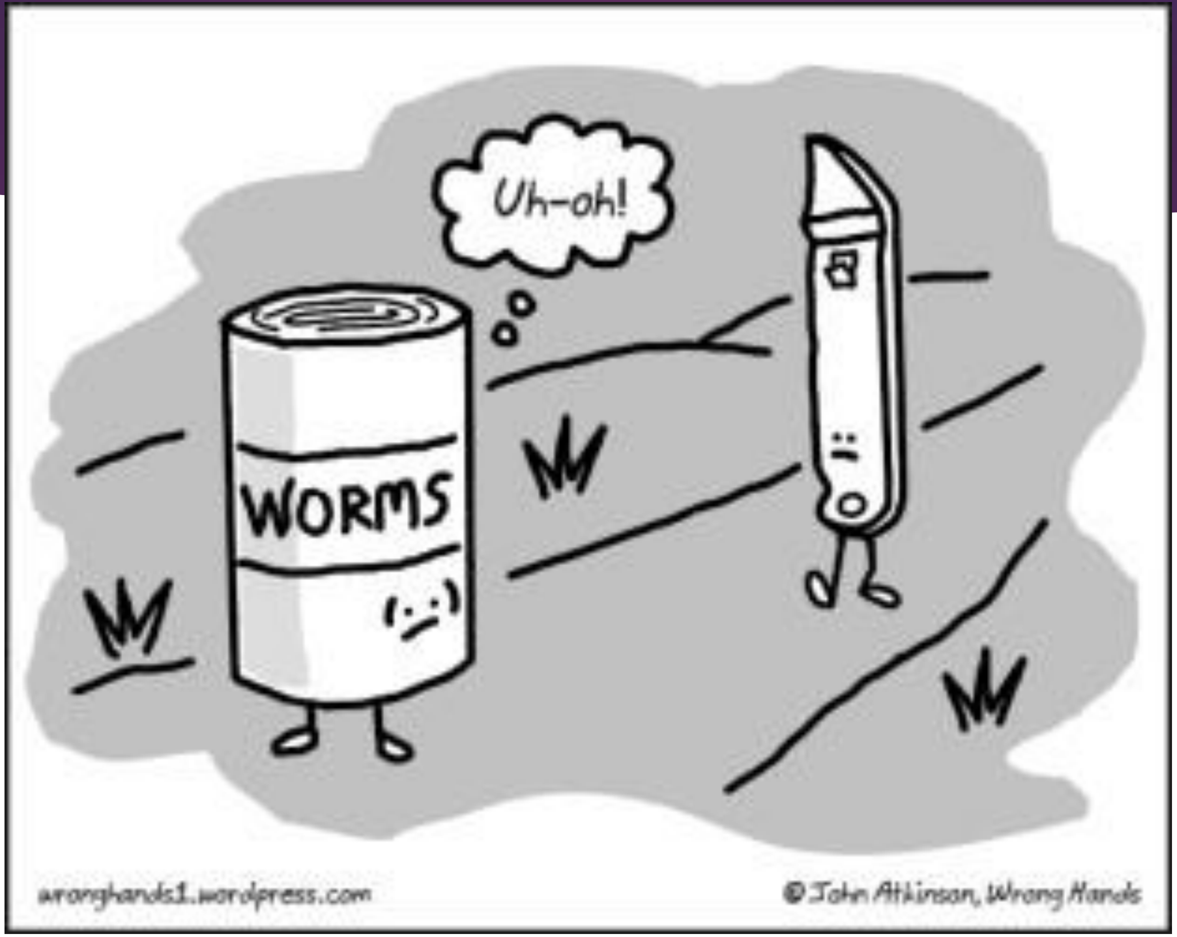
Understand your Assumptions

Assumptions from Traditional Mediation

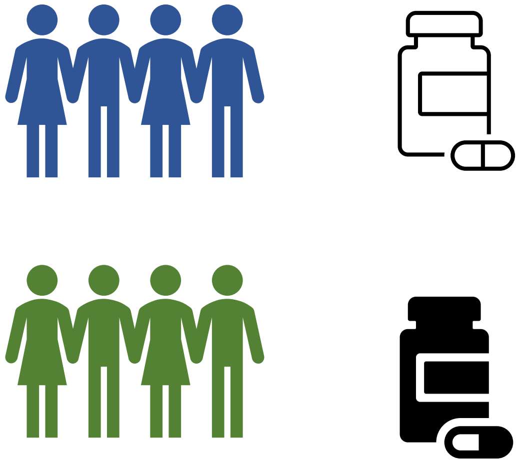
- Self-contained model – no omitted influences
- Reliable measures
- Uncorrelated errors across equations
- Temporal precedence
- Measurement Timing

27

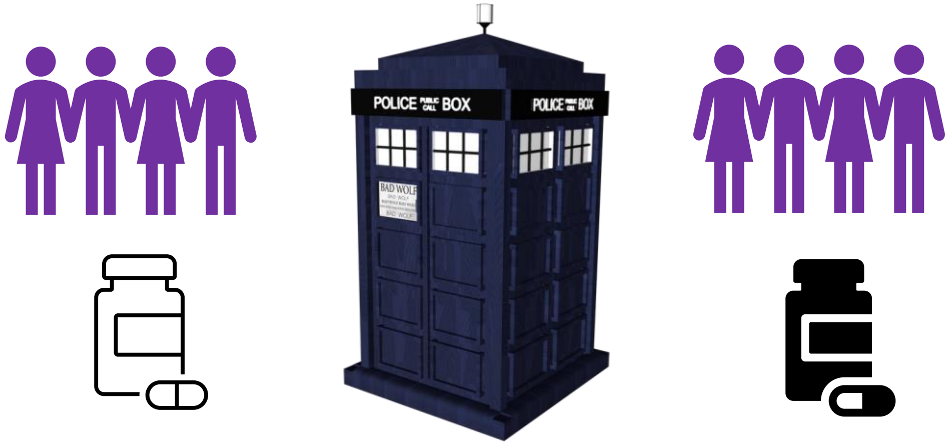
MacKinnon, D. P. (2008). *Introduction to statistical mediation analysis. Routledge.*


Uh-oh!
WORMS
wronghands1.wordpress.com
© John Atkinson, Wrong Hands

Potential Outcomes: A Thought Experiment with a “Fundamental Problem”



Reality: Randomly assign two groups of people to different treatments and compare groups means



Give treatment A to participants and observe outcome. Then build a time machine, go back in time, replace with treatment B, and observe the outcome

Holland, P. W. (1986). Statistics and causal inference. *Journal of the American Statistical Association, 81(396), 945-960.*

Aim of Potential Outcome Framework

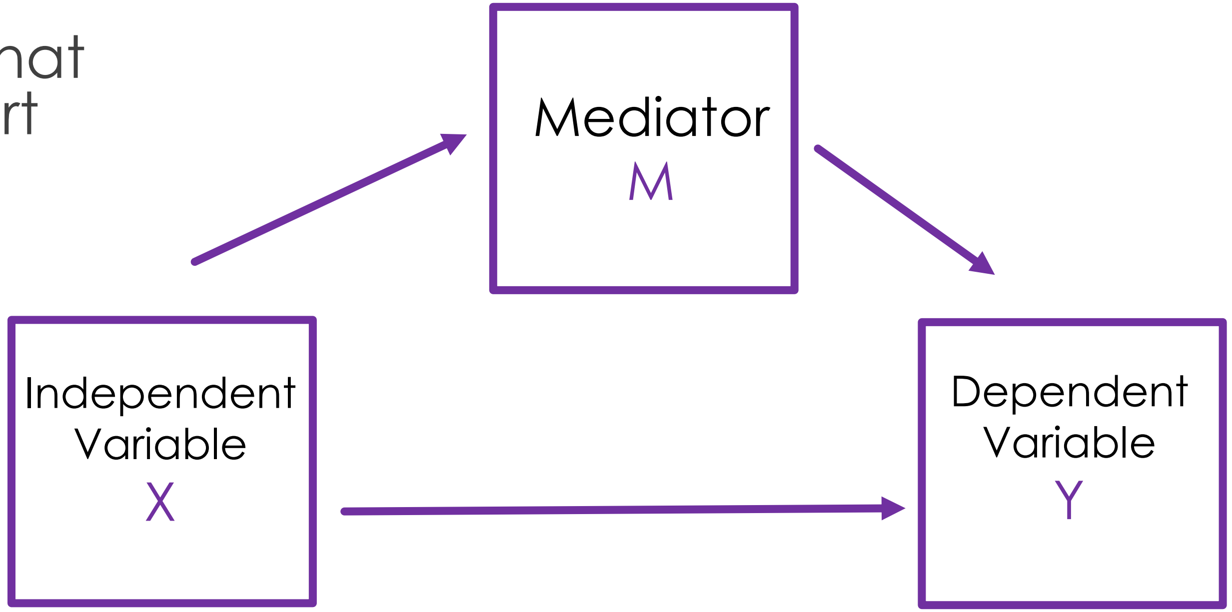
Redefine effects of interest as the difference between potential outcomes

Observed	−	Unobserved counterfactual

Identify the assumptions necessary to infer values for the unobserved counterfactual.

Mediation and Causation

- We said earlier that a mediator is part of a causal process…



- …but can we say that all three paths are causal?

Confounding in Mediation

- Randomizing X is expected to control confounding for two of the three pathways
- Study design and statistical control necessary for the third pathway
  - Sequential Double Randomization
  - Concurrent Double Randomization
  - Parallel Randomization
  - Inverse Probability Weighting
  - Sequential G-Estimation
  - Sensitivity Analysis

Valente, M. J., Pelham, W. E. I., Smyth, H. L., & MacKinnon, D. P. (2017). Confounding in statistical mediation analysis: What it is and how to address it. *Journal of Counseling Psychology, 64(6), 659-671.*

Inferring Counterfactuals from Expectations

- Traditional Assumptions
- No Interference (SUTVA #1)
- Consistency (SUTVA #2)
- Positivity
- Exchangeability (Confounders)

No Interference (SUTVA #1)

- One person's exposure to treatment does not influence another person's potential outcome
- No unmodeled spillover effects

Vanderweele, T. J. (2015). *Explanation in causal inference: Methods for mediation and interaction. Oxford University Press.*

Consistency (SUTVA #2)

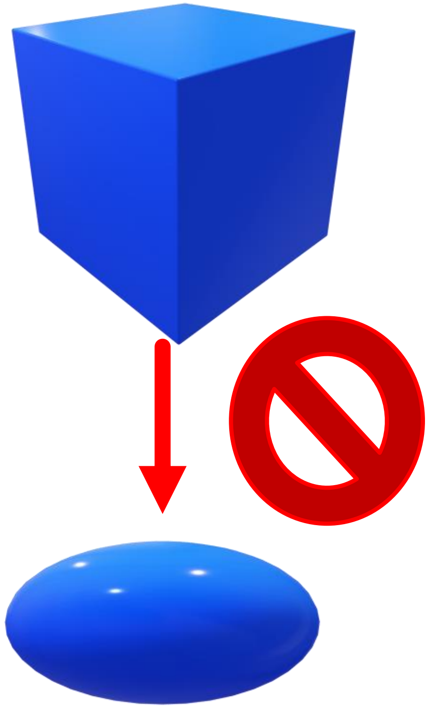
- "No hidden variations of treatment" assumption
- Well-specified intervention with unambiguously defined treatment
- The potential outcome of an individual assigned to Treatment A is equal to the observed outcome of an individual given Treatment A.

Cole, S. R., & Frangakis, C. E. (2009). Commentary: The Consistency Statement in Causal Inference: A Definition or an Assumption? *Epidemiology, 20(1), 3-5. http://www.jstor.org.ezproxy1.lib.asu.edu/stable/25662662*

Vanderweele, T. J. (2015). *Explanation in causal inference: Methods for mediation and interaction. Oxford University Press.*

Positivity

An individual has a non-zero probability of treatment assignment to either treatment condition



Cole, S. R., & Frangakis, C. E. (2009). Commentary: The Consistency Statement in Causal Inference: A Definition or an Assumption? *Epidemiology, 20(1), 3-5.* *http://www.jstor.org.ezproxy1.lib.asu.edu/stable/25662662*

Exchangeability – No Unmeasured Confounders

- Potential outcomes among treatment conditions are comparable

No unmeasured confounders of X and Y
- Randomize X

No unmeasured confounders of X and M
- Randomize X

No unmeasured confounders of M and Y
- Double randomization designs
- Sensitivity analysis, IPW, G-estimation

No confounders of M and Y are affected by X
- IPW, G-estimation

- Pirlott, A. G., & MacKinnon, D. P. (2016). Design approaches to experimental mediation. *Journal of Experimental Social Psychology, 66, 29-38. https://doi.org/10.1016/j.jesp.2015.09.012*
- Valente, M. J., Pelham, W. E. I., Smyth, H. L., & MacKinnon, D. P. (2017). Confounding in statistical mediation analysis: What it is and how to address it. *Journal of Counseling Psychology, 64(6), 659-671.*
- Vanderweele, T. J. (2015). *Explanation in causal inference: Methods for mediation and interaction. Oxford University Press.*

Causal Mediation Programs by Software Platform

SAS

- PROC CAUSALMED
- Valeri & VanderWeele (VVW) Macro

Stata

- PARAMED Macro
- Med4Way Macro

R packages*

- *mediation*
- *medflex*

SPSS

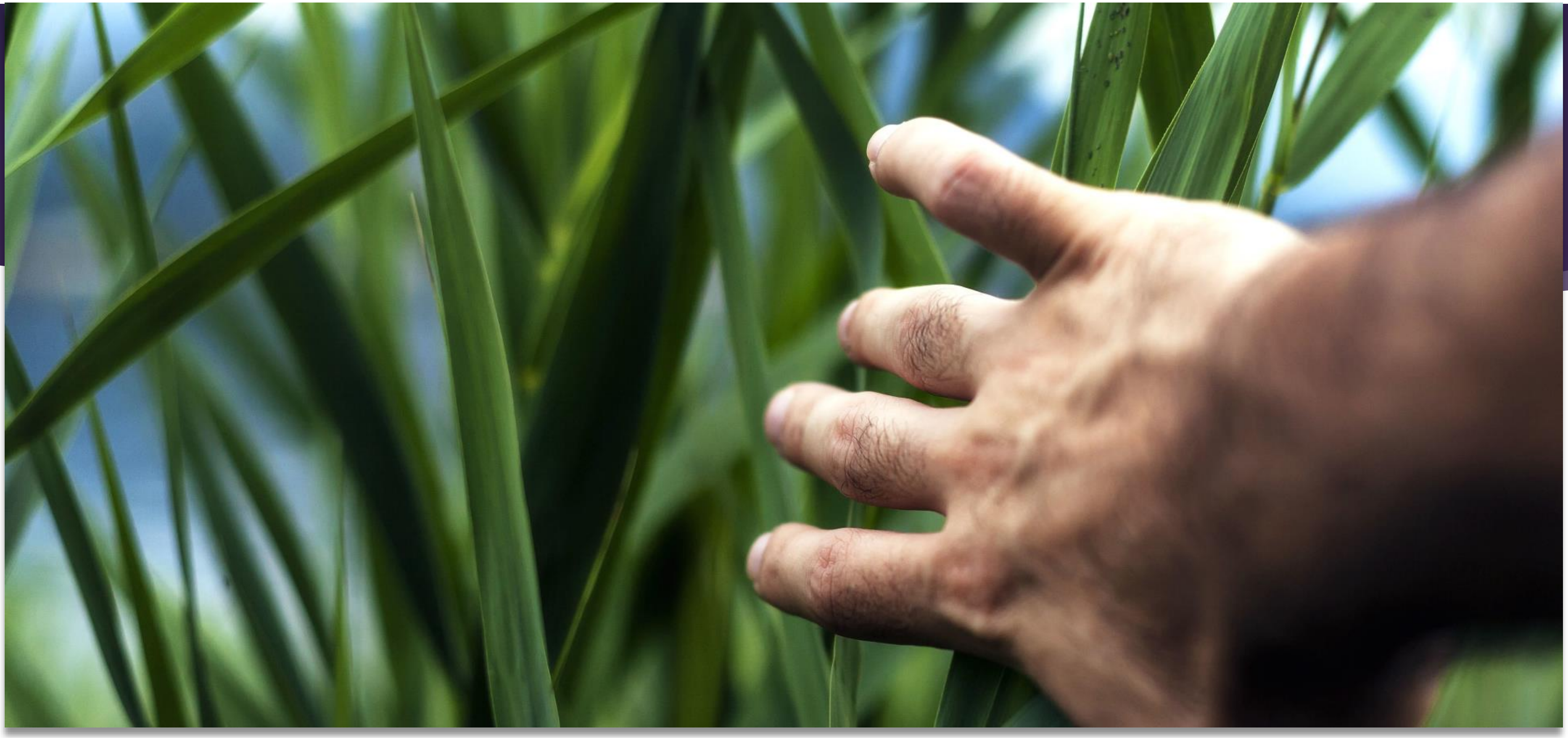
- Valeri & VanderWeele (VVW) Macro

Mplus

- Model Indirect statement

*Not a comprehensive list.
See CMAverse

Valente, M. J., Rijnhart, J. J. M., Smyth, H. L., Muniz, F. B., & Mackinnon, D. P. (2020). Causal Mediation Programs in R, Mplus, SAS, SPSS, and Stata. *Structural equation modeling: a multidisciplinary journal, 27(6), 975-984. https://doi.org/10.1080/10705511.2020.1777133*



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Suggested Reading - 1

Fritz, M. S., & Mackinnon, D. P. (2007). Required Sample Size to Detect the Mediated Effect. *Psychological Science*, *18*(3), 233-239. https://doi.org/10.1111/j.1467-9280.2007.01882.x

Hertzog, M. (2018). Trends in mediation analysis in nursing research: improving current practice. *Western journal of nursing research, 40(6), 907-930.*

Hyman, H. (1955). *Survey design and analysis: Principles, cases and procedures*. The Free Press.

Imai, K., Keele, L., Tingley, D., & Yamamoto, T. (2011). Unpacking the black box of causality: Learning about causal mechanisms from experimental and observational studies. *American Political Science Review*, *105*(4), 765-789.

Krause, M. R., Serlin, R. C., Ward, S. E., Rony, Y. Z., Ezenwa, M. O., & Naab, F. (2010). Testing mediation in nursing research: beyond Baron and Kenny [Journal Article]. *Nursing Research, 59(4), 288-294. https://doi.org/10.1097/NNR.0b013e3181dd26b3*

Lazarsfeld, P. F. (1955). Interpretation of statistical relations as a research operation. *The language of social research: A reader in the methodology of social research*, 115-125.

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*, *7*(1), 83-104.

MacKinnon, D. P., Lockwood, C. M., & Williams, J. (2004). Confidence Limits for the Indirect Effect: Distribution of the Product and Resampling Methods. *Multivariate Behavioral Research*, *39*(1), 99-128. https://doi.org/10.1207/s15327906mbr3901_4

Suggested Reading - 2

MacKinnon, D. P., & Pirlott, A. G. (2015). Statistical approaches for enhancing causal interpretation of the M to Y relation in mediation analysis. *Personality and Social Psychology Review*, *19*(1), 30-43.

MacKinnon, D. P., Valente, M. J., & Gonzales, O. (2020). The correspondence between causal and traditional mediation analysis: The link is the mediator by treatment interaction. *Prevention Science*, *21*(2), 147-157.

O'Rourke, H. P., & MacKinnon, D. P. (2018). Reasons for testing mediation in the absence of an intervention effect: A research imperative in prevention and intervention research. *Journal of Studies on Alcohol and Drugs*, *79*(2), 171-181. https://doi.org/10.15288/jsad.2018.79.171

Pirlott, A. G., & MacKinnon, D. P. (2016). Design approaches to experimental mediation. *Journal of Experimental Social Psychology*, *66*, 29-38. https://doi.org/10.1016/j.jesp.2015.09.012

Valente, M. J., Pelham, W. E. I., Smyth, H. L., & MacKinnon, D. P. (2017). Confounding in statistical mediation analysis: What it is and how to address it. *Journal of Counseling Psychology*, *64*(6), 659-671.

Valente, M. J., Rijnhart, J. J. M., Smyth, H. L., Muniz, F. B., & Mackinnon, D. P. (2020). Causal Mediation Programs in R, Mplus, SAS, SPSS, and Stata. *Structural equation modeling: a multidisciplinary journal*, *27*(6), 975-984. https://doi.org/10.1080/10705511.2020.1777133

VanderWeele, T. J. (2014). A unification of mediation and interaction: a four-way decomposition. *Epidemiology (Cambridge, Mass.)*, *25*(5), 749-761.

EXTRA SLIDES

Effect Sizes

Effect Sizes

- Measures of effect size can tell us how meaningful a mediated effect is, regardless of sample size

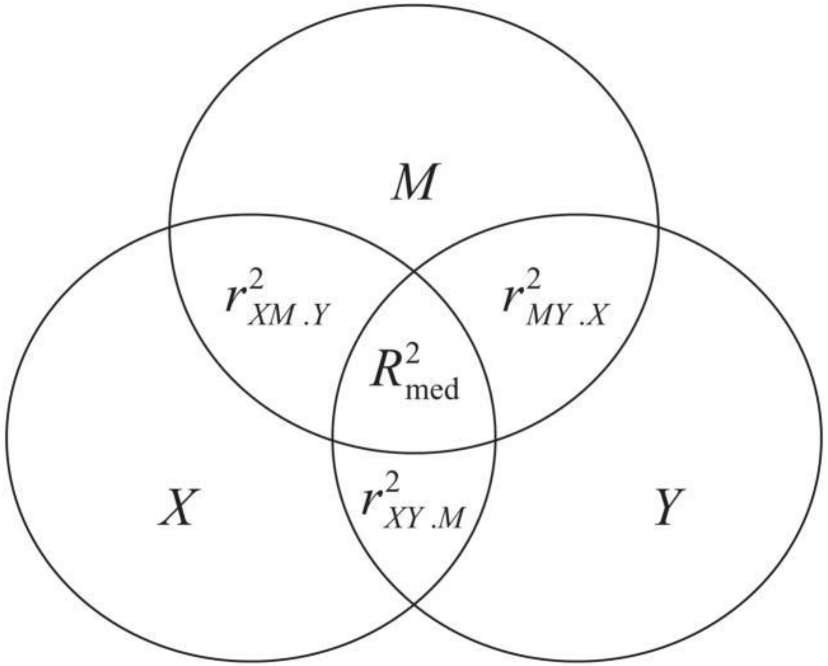
- Effect sizes for individual paths
  - Correlations (r_{XY}, r_{XM}) and partial correlations ($r_{YX.M}, r_{YM.X}$)
    - Cohen's guidelines - .1 = small, .3 = medium, .5 = large
  - Standardized regression coefficients($\hat{\boldsymbol{c}}$ and $\hat{\boldsymbol{a}}$) ($\widehat{\boldsymbol{c}'}$ and $\widehat{\boldsymbol{b}}$)
    - Unit of change in DV for a 1 standard deviation change in IV

Effect Sizes

- Effect sizes for mediated effect
  - Proportion/Ratio
    - Proportion of total effect that is mediated $\frac{\hat{a}\,\hat{b}}{\hat{c}}$
      - The mediated effect explains _% of the total effect of X on Y
    - Ratio of mediated effect to direct effect $\frac{\hat{a}\,\hat{b}}{\hat{c}'}$
      - The mediated effect is _ as large as the direct effect

Effect Sizes

- Effect sizes for mediation effect
  - R^2



Fairchild, A.J., MacKinnon, D.P., Taborga, M.P. *et al.* R^2 effect-size measures for mediation analysis. *Behavior Research Methods* **41**, 486–498 (2009). https://doi.org/10.3758/BRM.41.2.486

Effect Sizes

- Effect sizes for mediated effect
  - Standardized
    - Product of standardized coefficients
    - *d* effect sizes
      - $Standardized_{\hat{a}\,\hat{b}} = \frac{\hat{a}\,\hat{b}}{s_y}$
      - A unit change in mediated effect is associated with a _ unit change in standard deviations of Y

Scientific Theory

Research Question

Model Assumptions

Potential Outcomes Mediation

Redefine effects of interest as the difference between potential outcomes

- Define all the possible treatment/mediator combinations
  - Easy when X and M are binary
  - Alternatively, use mean values, or clinically significant cutoffs

Nested Counterfactual Notation

Table 1 Nested Counterfactuals for Single Mediator Model

Y(1, M(1))	Y at X=1, M at natural value of m for X=1
Y(0, M(0))	Y at X=0, M at natural value of m for X=0
Y(0, M(1))	Y at X=0, M at natural value of m for X=1
Y(1, M(0))	Y at X=1, M at natural value of m for X=0

Note: Counterfactuals in red cannot be observed.

Causal Estimands

★ Total Natural Indirect Effect (TNIE) = **E[Y(1, M(1)) – Y(1, M(0))]**

★ Pure Natural Indirect Effect (PNIE) = **E[Y(0, M(1)) – Y(0, M(0))]**

Total Natural Direct Effect (TNDE) = **E[Y(1, M(1)) – Y(0, M(1))]**

Pure Natural Direct Effect (PNDE) = **E[Y(1, M(0)) – Y(0, M(0))]**

Controlled Direct Effect (CDE) = **E[Y(1, m) – Y(0, m)]**

Total Effect (TE) = **E[Y(1, M(1)) – Y(0, M(0))]**

Sidebar: The XM-Interaction

$$Y = i_3 + bM + c'X + \boldsymbol{hXM} + e_3$$

- In some situations, potential outcomes effects are the same as traditional estimates, but are interpreted causally
- If *h*=0, then potential outcomes estimates equal traditional estimates
- When variables are continuous causal effects are equal to traditional simple effects
- When variables are binary, traditional and causal estimate may differ

- MacKinnon, D. P., Valente, M. J., & Gonzales, O. (2020). The correspondence between causal and traditional mediation analysis: The link is the mediator by treatment interaction. *Prevention Science, 21(2), 147-157.*
- Rijnhart, J. J. M., Valente, M. J., Smyth, H. L., & Mackinnon, D. P. (2021). Statistical Mediation Analysis for Models with a Binary Mediator and a Binary Outcome: the Differences Between Causal and Traditional Mediation Analysis. *Prevention Science. https://doi.org/10.1007/s11121-021-01308-6*

Potential Outcomes Estimators

Effect	Potential outcomes notation	Causal estimator
TNIE	$E[Y_i(1, M_i(1)) - Y_i(1, M_i(0))]$	$ba + ha$
PNIE	$E[Y_i(0, M_i(1)) - Y_i(0, M_i(0))]$	ba
TNDE	$E[Y_i(1, M_i(1)) - Y_i(0, M_i(1))]$	$c' + hi_1 + ha$
PNDE	$E[Y_i(1, M_i(0)) - Y_i(0, M_i(0))]$	$c' + hi_1$
CDE	$E[Y_i(1, m) - Y_i(0, m)]$	$c' + hm$
TE	$E[Y_i(1, M_i(1)) - Y_i(0, M_i(0))]$	$c' + hi_1 + ba + ha$

- Valente, M. J., Rijnhart, J. J. M., Smyth, H. L., Muniz, F. B., & Mackinnon, D. P. (2020). Causal Mediation Programs in R, Mplus, SAS, SPSS, and Stata. *Structural equation modeling: a multidisciplinary journal, 27(6), 975-984. https://doi.org/10.1080/10705511.2020.1777133*
- VanderWeele, T. J. (2014). A unification of mediation and interaction: a four-way decomposition. *Epidemiology (Cambridge, Mass.), 25(5), 749-761.*