Introduction to Mediation and Moderation Concepts and Methods

Tor Neilands, PhD

Analysis Core

Center for Aging in Diverse Communities (CADC)

University of California, San Francisco

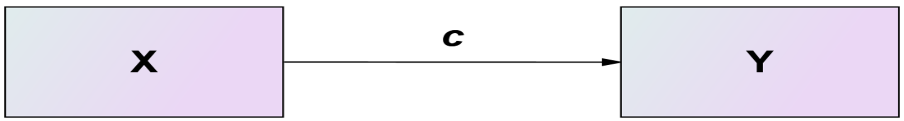
November 17, 2022

Goals of Today's Talk

- Introduce the concept of statistical mediation and methods for assessing mediation.
- Introduce the concept of statistical moderation, types of moderation, and limitations of moderation analyses.
- Today's talk will *not* provide in-depth guidance on how to perform mediation and moderation analyses and how to interpret results from those analyses (but will point to resources to learn more about mediation and moderation analyses, including how to do them and interpret their results).

What is Statistical Mediation?

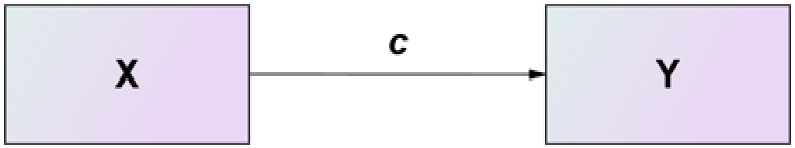
- Consider an exposure X and an outcome Y. A typical research question might ask, "What is the effect of X on Y?" or "Does X affect Y significantly?" Visually, this relationship can be depicted this way:



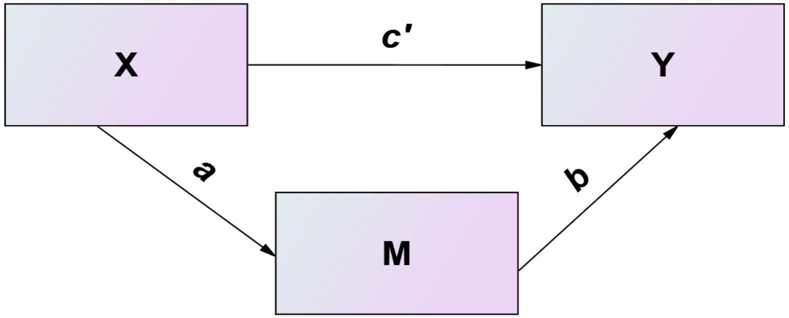
- *c* is the *total effect* of X on Y.
- But what if we thought X affected something else that in turn affected Y that could explain the X->Y association?

Sequential Mediation

- We introduce a new variable, M, that is caused by X and in turn causes Y. We implicitly assume that X precedes M and M precedes Y (temporal ordering).



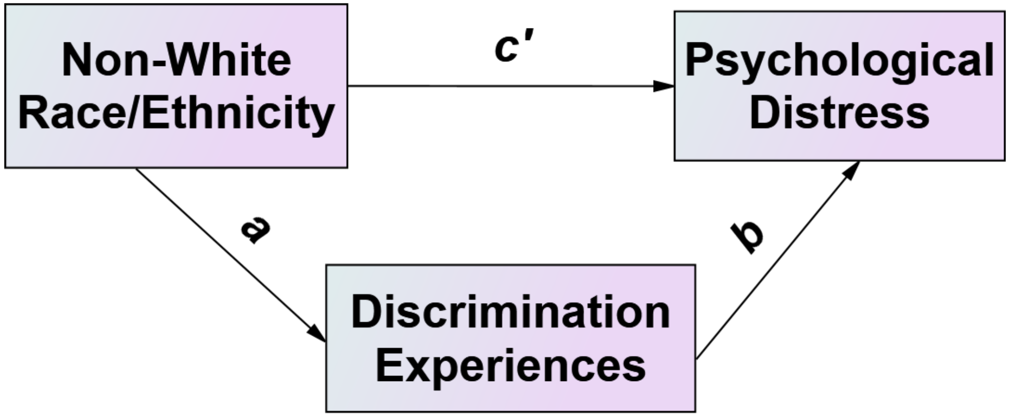
- ***c'*** is the *direct effect* of X on Y.
- ***a*** is the direct effect of exposure X on the mediator M.



- ***b*** is the direct effect of the mediator M on the outcome Y.
- This model is known as a *sequential mediation* model.
- Let's look at a hypothetical example to help make these principles more concrete.

Sequential Mediation Example

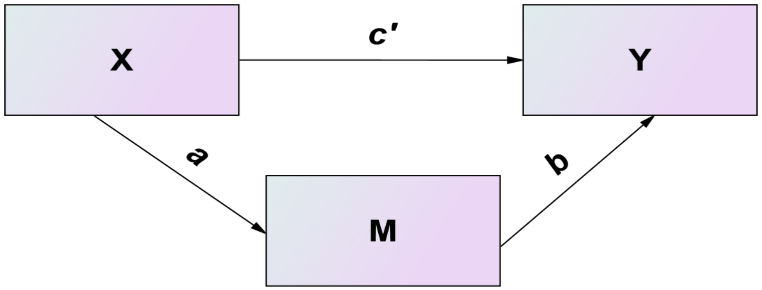
- To make this concrete, imagine a simplified example based on Scheim and Bauer (2019).
- Scheim and Bauer were interested in whether experiences of discrimination mediated an association between non-White race/ethnicity and psychological distress.

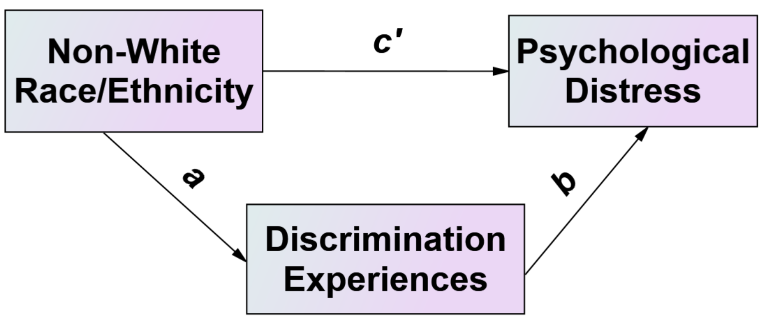


- In other words, could people’s experiences of discrimination *explain* or *account for* a previously observed link between non-White race/ethnicity and distress?

Mediation 1.0: Four Causal Steps

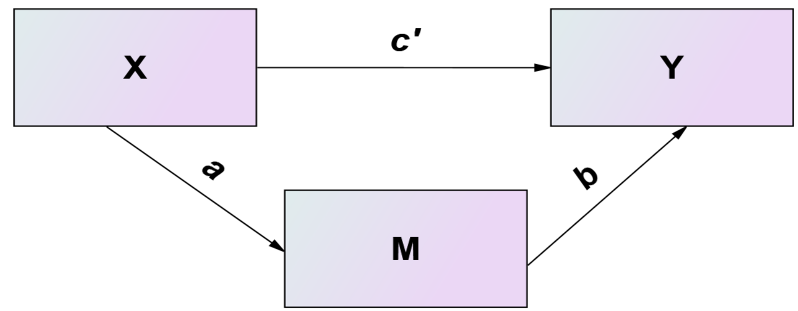
- The first mediation approaches use a sequence of three linear regression models to estimate mediation effects (Baron & Kenny, 1986).
- <u>Step 1</u>: Estimate the *direct effect* of X on M (**a**). E.g., the effect of race/ethnicity on discrimination.
- <u>Step 2</u>: Estimate the *total effect* of X on Y (**c**). E.g., the effect of race/ethnicity
on psychological distress.



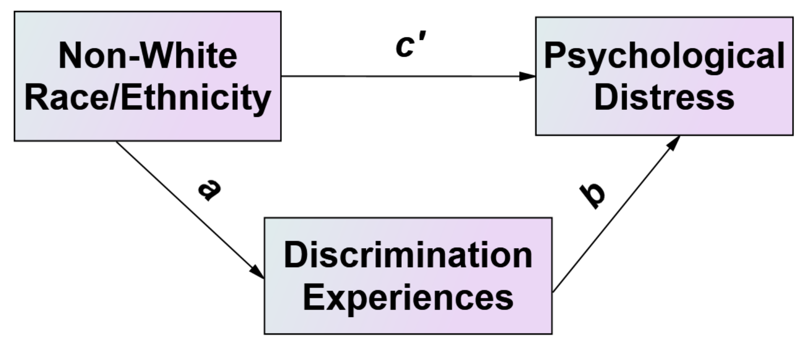


Mediation 1.0: Causal Steps Three & Four

- Step 3: Estimate the direct effect of X (**c'**) and M (**b**) on Y. E.g., the effects of race/ethnicity and discrimination on distress.

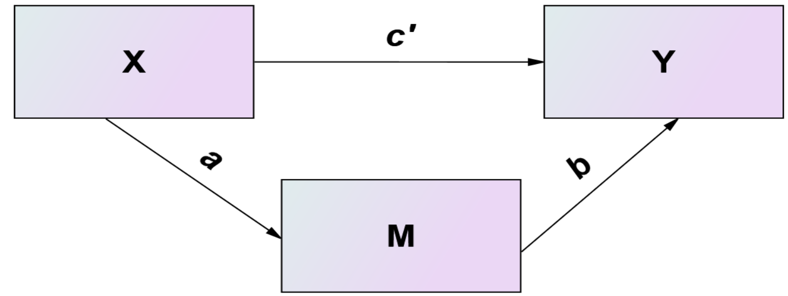


- Step 4: Assess mediation by examining **a**, **b**, **c** and **c'**:
- The direct effects X on M (**a**) and M on Y (**b**) must be significant. E.g., race/ethnicity must significantly affect discrimination and discrimination must affect distress.

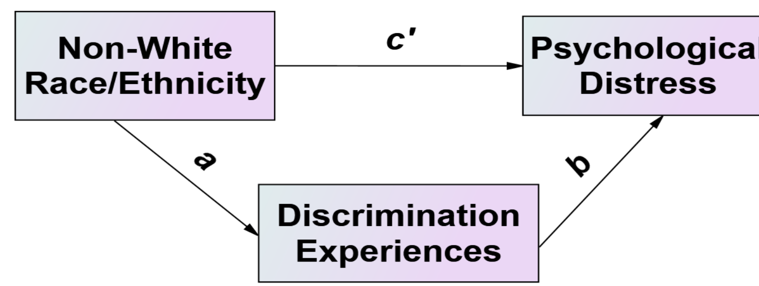


Assessing Mediation 1.0: Causal Steps

- If the total effect **c** from the X->Y model is significant, but the direct effect **c'** from X+M->Y model is non-significant, then it is concluded that M *completely mediates* the X->Y association.



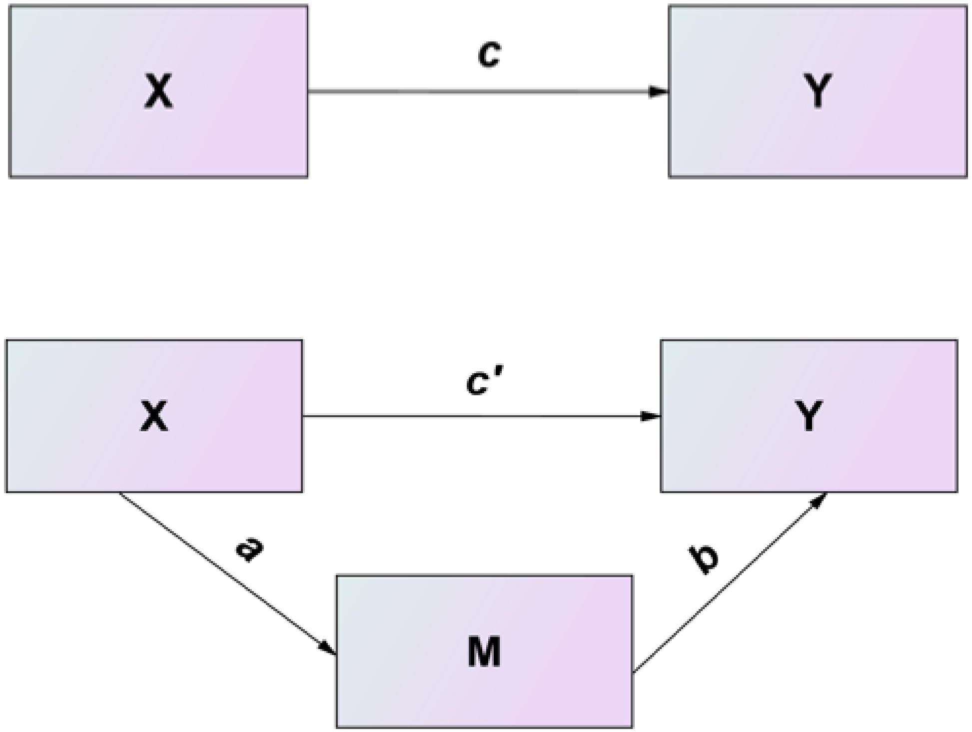
- On the other hand, if the total effect **c** from X->Y is significant and the effect **c'** from the X+M->Y model is also significant, then it is concluded that M *partially mediates* the X->Y association.



- In our example, the total effect of X on Y is race/ethnicity -> psychological distress in a model without its mediator included.
- Some methodologists (e.g., Hayes & Rockwood, 2017) view the distinction between partial vs. full mediation as being outdated.

Assessing Mediation: Indirect Effect

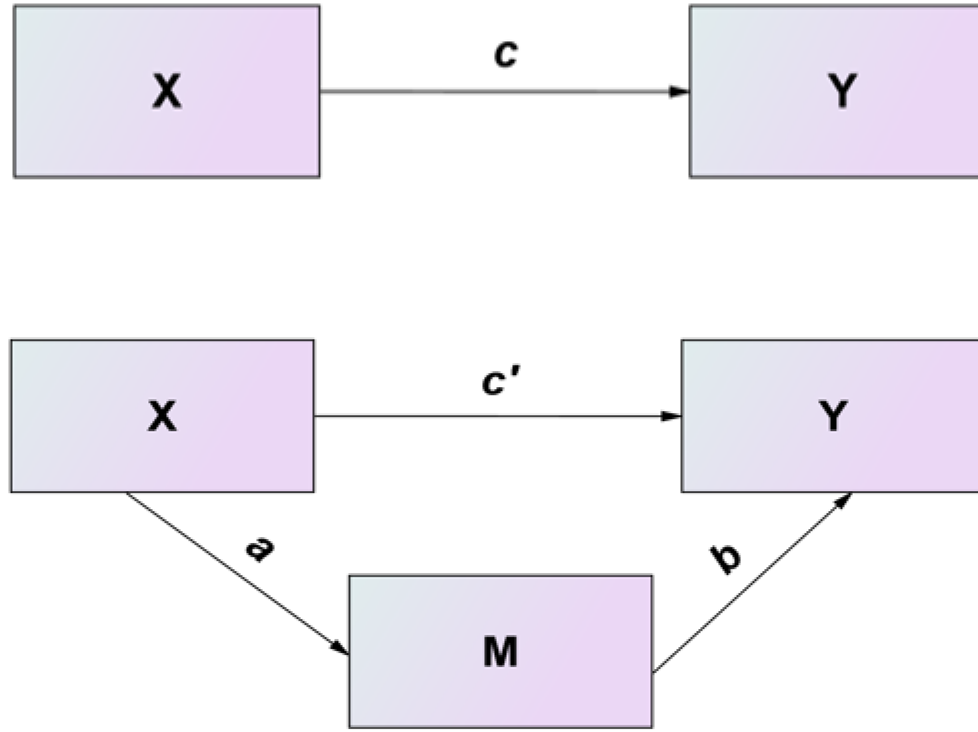
- How can we quantify the mediation effect?
- Intuitively, we could subtract **c'** from **c**. I.e., subtract the direct effect of X on Y from the total effect (difference method). What remains is the mediation effect.
- Or we could multiply **a** times **b** (product method) instead.



- Why can we use **a** times **b** (**a*b**) to represent the mediation effect?
- In linear regression, the total effect of X on Y can be decomposed into **c** = **a*b** + **c'**. Thus, **c – c'** = **a*b**, which is the effect of mediation. It is often referred to as the *indirect effect* of X on Y through M.

Indirect Effect Via **a*b**

- For logistic, multilevel, and other models, **a*b** only approximately equals **c – c’,** so **a*b** is more often used to quantify the indirect effect than **c – c’.** (Kenny, 2021).
- There are several methods for testing the significance of the **a***b** indirect effect. See slide 29 of S. Gregorich’s (2014a) mediation talk.



- Since indirect effects are products of **a** and **b** and thus often asymmetrically distributed, asymmetric confidence intervals are best for making inferences about the significance of indirect effects.

Causal Steps Method: Impact and Limitations

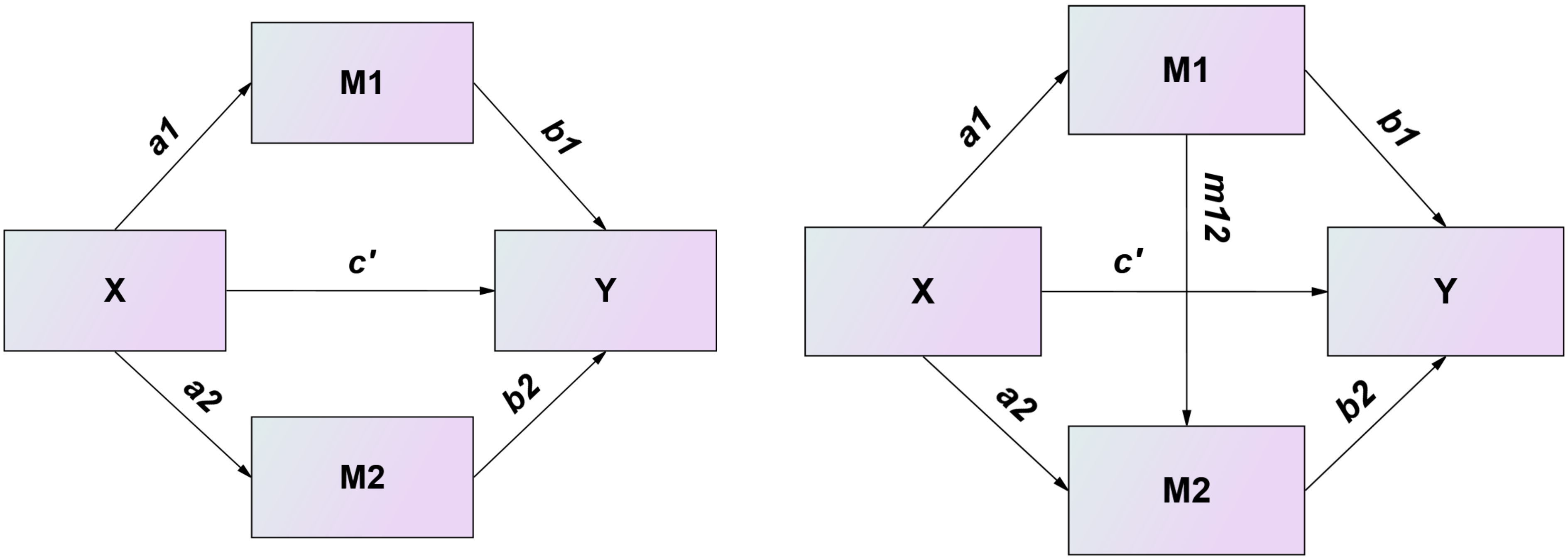
- According to Tyler VanderWeele, an international expert on mediation analysis, the Baron & Kenny (1986) causal steps paper has been cited over 90,000 times. This seminal paper's impact on many fields had been profound and undeniable. One way to frame their causal steps approach is as mediation version 1.0.
- However, the regression-based causal steps method has some limitations. For instance, the sample is assumed to be the same for all three regression models; missing data in real-world applications can challenge this assumption.
- Computing asymmetric confidence intervals for indirect effects is not built into most regression routines in statistical software.
- The traditional sequential X->M->Y mediation model is relatively easy to fit using the causal steps method, but more complex mediation models are difficult, if not impossible, to fit.

Mediation 2.0: Structural Equation Modeling (SEM)

- Due to the limitations of the causal steps method, in the 1990s structural equation modeling (SEM) became popular for testing mediation. SEM is a *simultaneous equation estimation method*, meaning that it can estimate all pathways simultaneously. We could view this SEM approach to mediation analysis as mediation version 2.0. What are its advantages?
- SEM can estimate each of the mediation equations simultaneously, eliminating the problem of different Ns being used to estimate the different mediation equations in the causal steps approach.
- Most SEM software routines support convenient estimation of the optimal asymmetric confidence intervals for indirect effects via the bootstrap.
- Latent variables can represent shared variance among multiple correlated variables for X, M, and/or Y. This is particularly helpful for M because it can reduce the impact of measurement error, thereby maximizing accuracy and statistical power for testing indirect effects (Hoyle and Kenny, 1999).
- <u>Biggest advantage</u>: SEM can be used to fit a wider array of models, including ones with multiple mediators and/or longitudinal mediation.

SEM-Based Mediation Examples

- SEM can be used compute total, direct, and indirect effects seamlessly, including for multiple mediator models like these:



Example of "Chained" Mediation

- Choi, Bowleg, and Neilands (2011) fitted a mediation model with a latent difficult sexual situations variable measured by three correlated indicators.
- The model revealed a "chain" of mediation from women's experiences of sexism through psychological distress to difficult sexual situations leading to unprotected sex.
- Sexism also affected unprotected sex through difficult sexual situations.

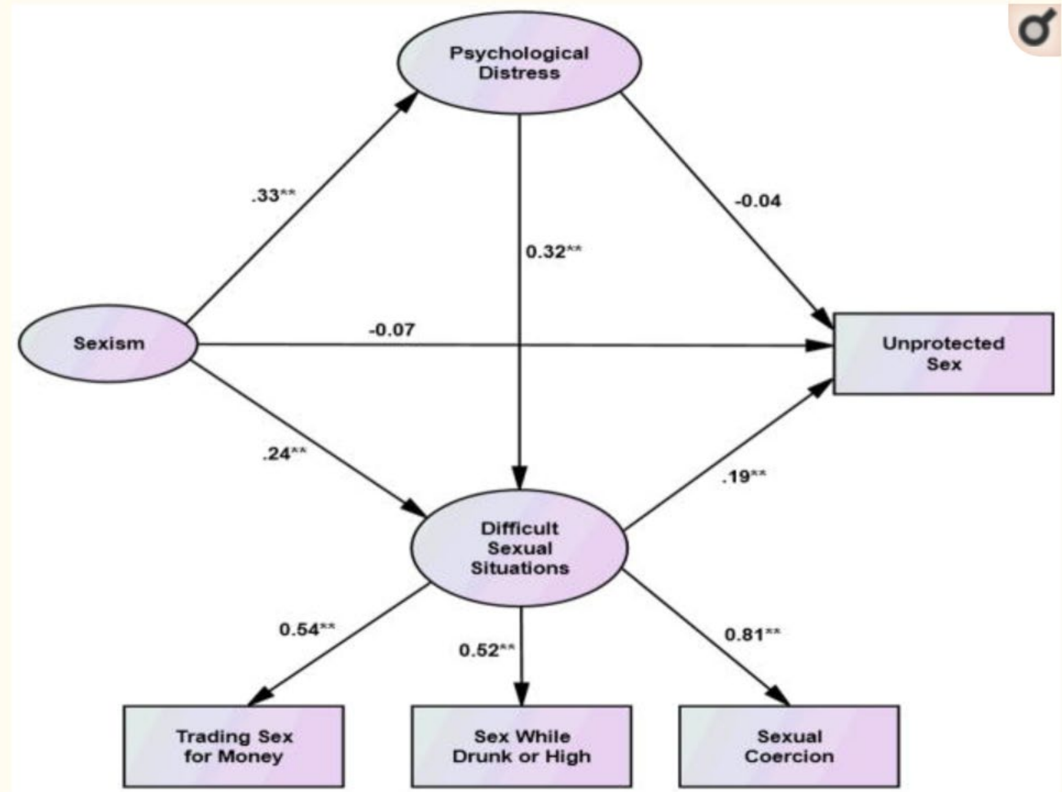
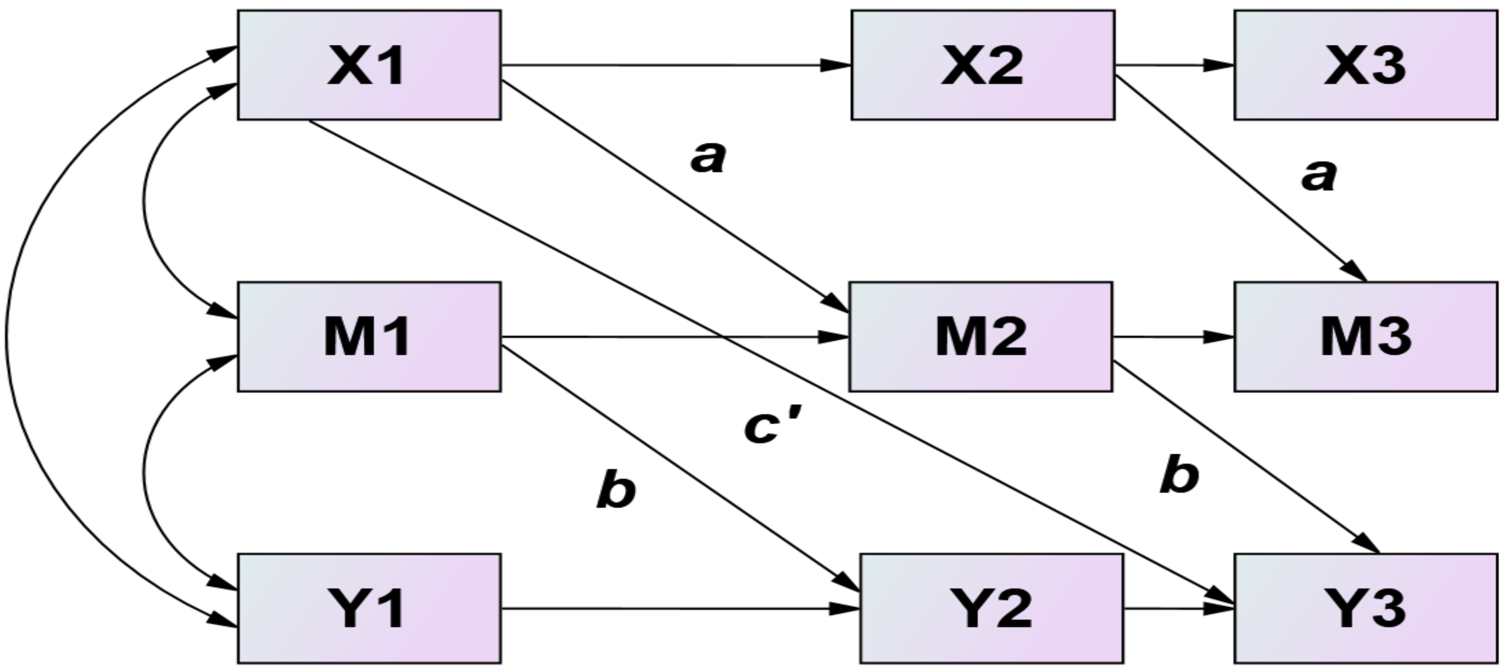


FIGURE 1

Hypothesized Structural Equation Model for Any Unprotected Sex with a Primary Sexual Partner: Standardized Path Weights (N=754)* $p < 0.05$; ** $p < 0.01$

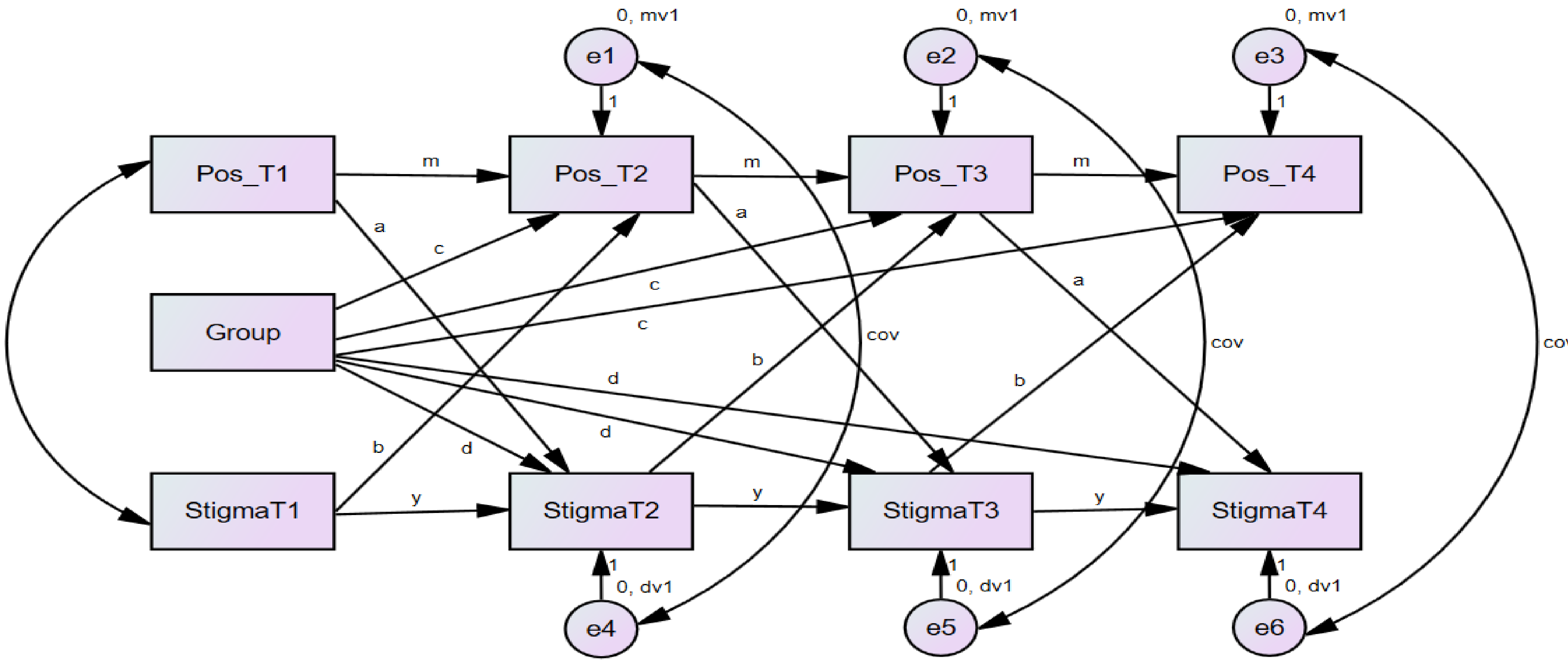
SEM for Longitudinal Mediation

- SEM can also be used to assess mediation in longitudinal designs as shown in Mitchell et al (2013, Figures 3 and 4) to reduce bias from fitting traditional sequential mediation models to longitudinal data.
- Note: Letters for certain equalities typically imposed are omitted from this diagram for clarity (e.g., x-to-x, m-to-m, and y-to-y). Also, not shown: residual correlations



Example: Longitudinal Mediation

- Varas-Diaz et al (2016) examined whether an intervention designed to reduce HIV/AIDS stigma among 507 Puerto Rican medical students (*X*) increased positive emotions towards persons living with HIV (*M*), which in turn would reduce stigma attitudes (*Y*).

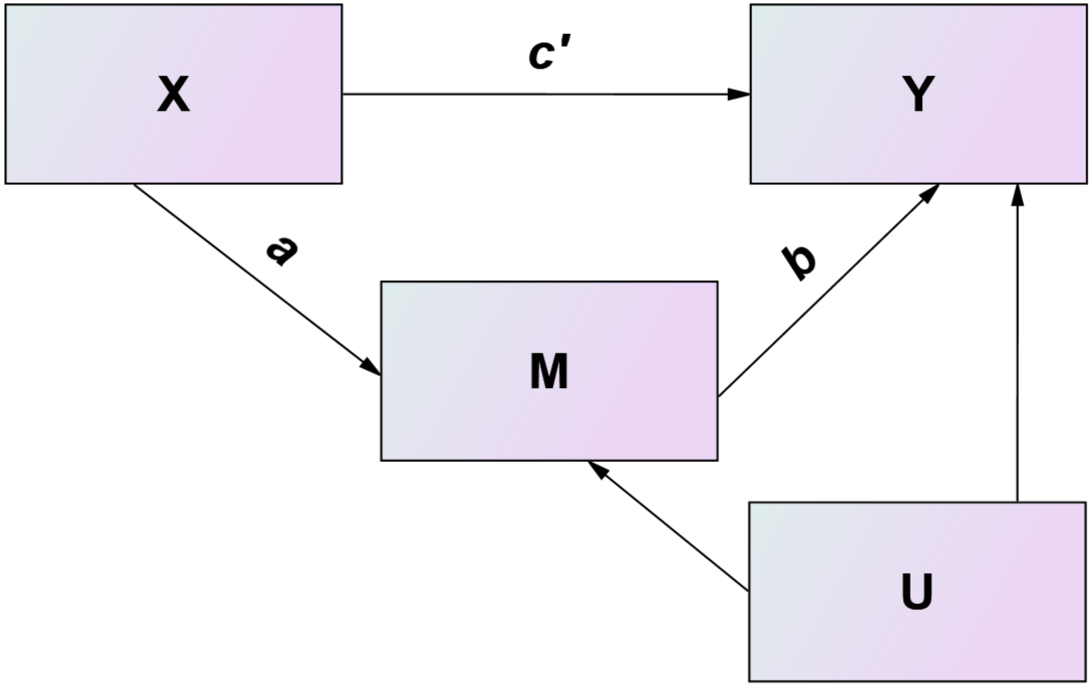


Example: Longitudinal Mediation

- Four waves: T1 - baseline, T2 - immediately following intervention, T3 - six months post-baseline, and T4 - twelve months post-baseline
- Significant direct effects of interest:
  - Group (0=control; 1=intervention) was positively associated with the positive emotions mediator at subsequent waves.
  - The positive emotions mediator at time T-1 was negatively associated with stigma at time T.
- Key indirect effect of interest:
  - Group was negatively associated with stigma at time T through the positive emotions mediator at time T-1.
- <u>Interpretation</u>: intervention participation increased positive emotions towards persons living with HIV, which in turn reduced participants' stigma towards persons living with HIV.
- This approach is superior to a standard serial mediation analysis because autoregressive and time T stigma -> time T+1 positive emotions pathways are included and controlled for.

Limitations of Causal Steps Regression and SEM

- Causal steps based on fitting multiple linear regression models and SEM-based mediation analyses rely on fairly strong assumptions.
- First, even if participants were randomly assigned to the exposure X or if all possible exposure-outcome confounders were controlled for, there may be still be mediator-outcome confounding (U) because participants are typically not randomly assigned to M.



- U might represent one or many variables, observed or unobserved.

More Limitations and a Remedy

- Uncontrolled confounders can bias mediation analysis effect results.
- Another limitation of the traditional regression and (most) SEM-based approaches is their assumption of no interaction between (a) the exposure X and the mediator M and (b) no interactions of X and M with other potential confounders. Ideally, we would like to be able to investigate and account for such interactions if any are present.
- Finally, while some ad hoc methods have been advanced for non-continuous M and Y variables, it would be helpful to have a general framework that allows for non-continuous M and/or Y variables.
- *Causal mediation methods* address these issues. They extend traditional regression and SEM-based methods to allow non-continuous M and Y variables and they also allow interactions.
  - See Valeri and Vanderweele (2013) for an introduction and SAS & SPSS macros. SAS PROC CAUSALMED, the Stata -paramed- user-written command, and various R commands are also available (Valente et al, 2020)

Mediation 3.0: Causal Mediation

- *Causal mediation* methods take a different approach from traditional mediation methods (regression-based causal steps and SEM).
- Rather than focus on parameter estimates from parametric regression models, causal mediation invites us to consider a thought experiment.
- In an ideal experiment, we would like to randomize everyone to an exposure X at level 0 of X (e.g., control) *and* level 1 of X (e.g., intervention).
- Assuming an outcome Y, we would also ideally like to be able to observe the value of Y at X=0 (Y(0)) *and* X=1 (Y(1)).
- But in reality, we can only randomize a given individual to X=0 ***or*** X=1, not both. Thus, if someone was randomized to X=0 (or observed at X=0 in a non-randomized study), Y(0) is an observable outcome, but Y(1) is an unobservable *potential outcome* or *counterfactual* and vice versa for X=1.
- However, averaging across all study participants, we can compute a treatment effect as E[Y(1)-Y(0)].
- We can compute this same effect at different levels of a mediator M.

Causal Mediation Effects

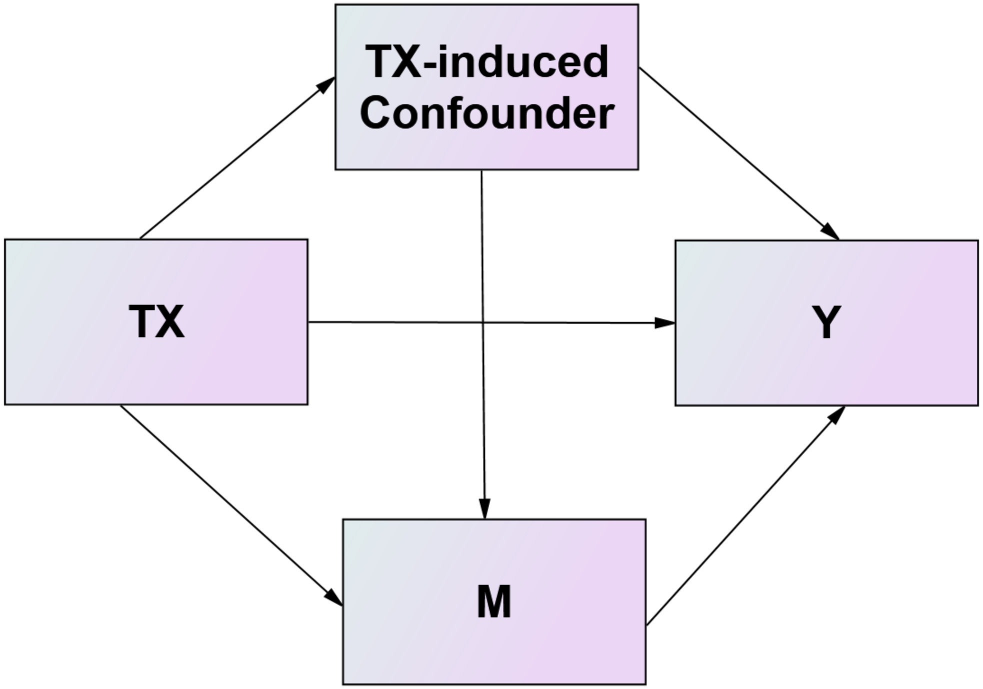
- There are six causal mediation effects (Valente et al, 2020). Main five:
- Total natural indirect effect (TNIE):
  - TNIE = E[Y(1,M(1)) – Y(1,M(0))]: The effect of **X on Y through M** when the **direct effect** is held constant at the **treatment** level X=1
- Pure natural indirect effect (PNIE):
  - PNIE = E[Y(0,M(1)) – Y(0,M(0))]: The effect of **X on Y through M** when the **direct effect** is held constant at the **control** level X=0
- Total natural direct effect (TNDE):
  - TNDE = E[Y(1,M(1)) – Y(0,M(1))]: The effect of **X on Y** when the **mediation effect** is held constant at its naturally observed **treatment** level M=1
- Pure natural direct effect (PNDE):
  - PNDE = E[Y(1,M(0)) – Y(0,M(0))]: The effect of **X on Y** when the **mediation effect** is held constant at its naturally observed **control** level M=0
- The total effect of X on Y (TE):
  - E[Y(1,M(1)) – Y(0,M(0))] = TNDE + PNIE = PNDE + TNIE

Causal Mediation: CDE and More

- The sixth causal mediation effect is less frequently used. It is the controlled direct effect (CDE), which is defined as the effect of X on Y at some fixed value of M of substantive interest.
  - CDE = E[Y(1,*m*) – Y(0,*m*)] where *m* is a fixed value of M
- The CDE may be most useful for answering “what if” policy-type questions: E.g., “If we changed the value of the mediator M to *m*, what would the effect of X on Y be?” *m* needs to be set to a meaningful value.
- Causal mediation methods generally assume no unobserved confounding of the X->Y, X->M, and M->Y relationships.
- Causal mediation methods allow for inclusion of observed confounders. The causal mediation literature proposes sensitivity analysis methods to evaluate whether any remaining uncontrolled confounding is an issue.
- Off-the-shelf software is available for the X->M->Y sequential model. Examples have also been published for specific scenarios (e.g., Bind et al. 2016 article on causal mediation analysis for longitudinal data with exogenous exposure).
- For an extensive “deep dive” into causal mediation, see VanderWeele (2015) and his numerous articles.

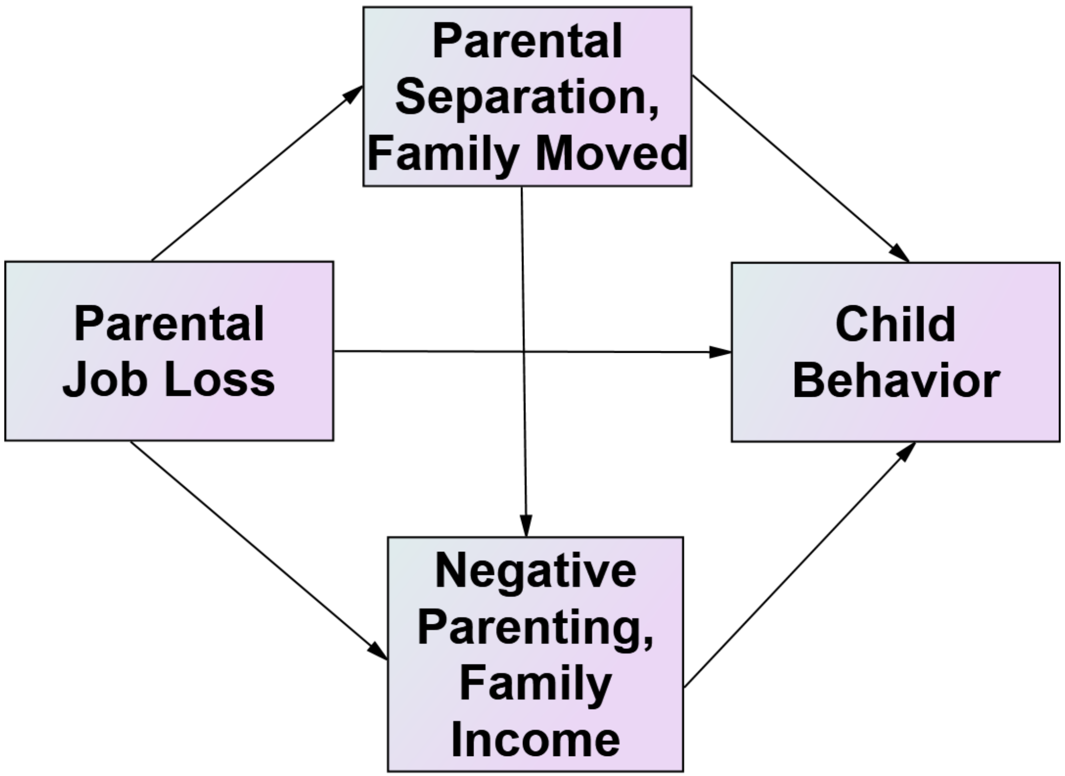
Post-Exposure Confounding

- The previous slides assume there are not any post-exposure covariates that are affected by the exposure/treatment (*TX*) and in turn affect the mediator(s) *M* and outcome(s) *Y*.
- In intervention studies this can occur when an intervention affects post-TX covariates which in turn affect one or more mediators (i.e., the exposure-mediator relationship is confounded by one or more post-exposure covariates).
- It can also occur in observational studies.
- A conceptual way to think about this scenario might help: there is *a second mediator* between TX and M.



Post-Exposure Confounding Example

- Study of the relationships between parental job loss and children's subsequent behavioral outcomes (Mari & Keizer, 2021).
- Exposure: parental job loss
- Outcome: child behavior
- Mediators of interest: family income level and negative parenting behaviors.
- Post-exposure confounders included parental separation, birth of a sibling, and whether the family moved.
- The Stata -rwrmed- command (see next slide) was used to perform the mediation analyses accounting for post-exposure confounding.



Post-Exposure Confounding Software

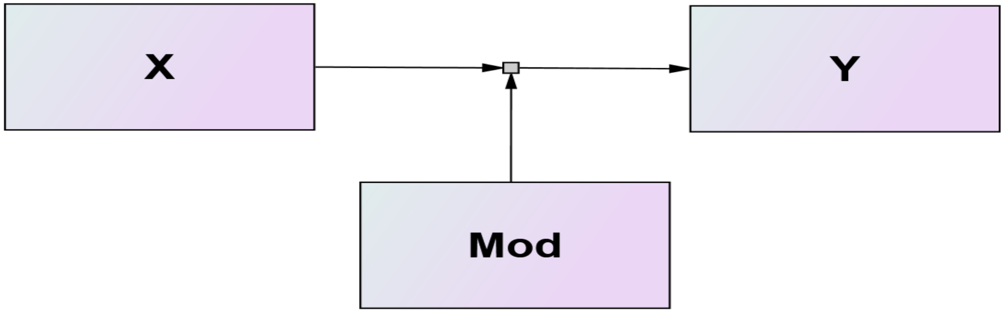
- Post-exposure confounding mediation analyses are a relatively new technique, so there are multiple analytic approaches being developed, presented, and tested in the research methods literature.
- One method is known as *regression-with-residuals* (RWR).
- Linden et al (2021) wrote a community-contributed Stata command, -rwrmed-, which be used to perform mediation analyses that include post-exposure confounding variables.
- -rwrmed- can also estimate
  the standard natural direct and indirect effects when post-exposure confounding is not present.
- -rwrmed- accommodates continuous, binary, and count mediators, but only continuous outcomes.

Additional Mediation Considerations

- When designing your studies, if you can randomize *both* X and M, that will enable you to make the strongest possible causal inferences. For instance, the multiphase optimization strategy (MOST) method randomizes participants to receive various subcomponents of a combination intervention using a factorial design to help tease apart which parts of the intervention worked rather than relying on a post-hoc mediation analysis (see Collins et al, 2007).
- It is unusual to be able to randomize M, however, so at the study design stage, carefully consider potential confounders of X->Y, X->M, and M->Y and plan to measure them whenever possible.
- It is also important to consider the timing of mediation (i.e., when to measure mediators). Subject-matter knowledge is important.
- Cross-sectional analyses of X->M->Y may yield biased results (Mitchell & Maxwell, 2013). Some reviewers and journals will accept cross-sectional mediation results (with stated limitations) but others will not.

Moderation

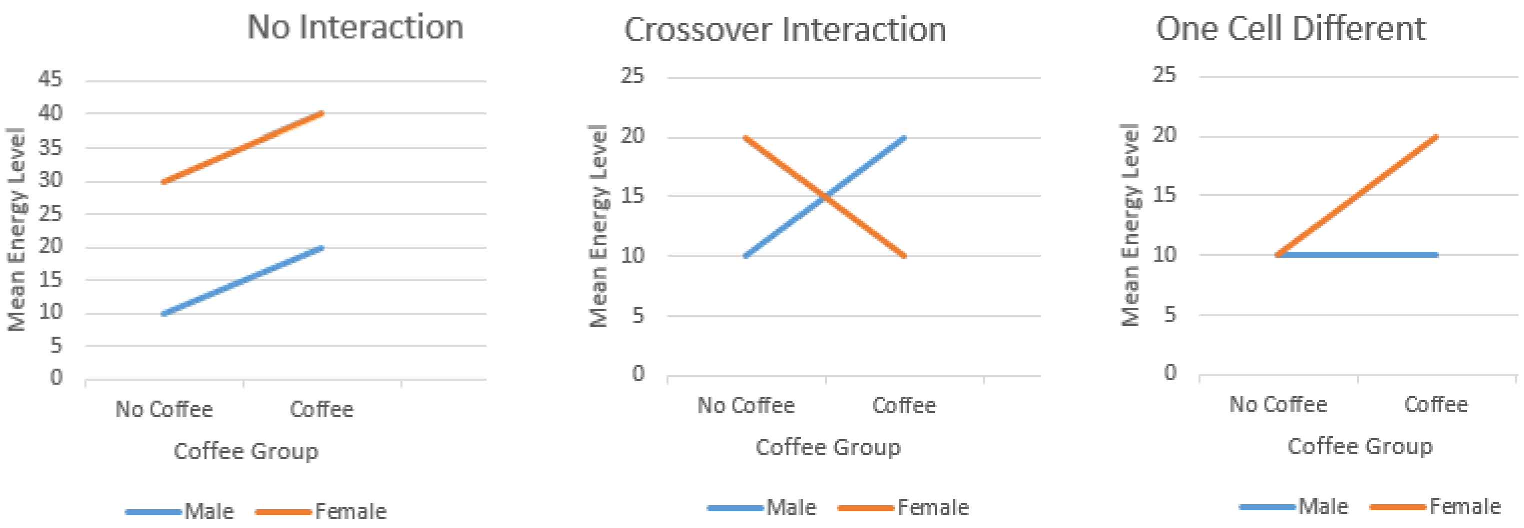
- *Moderation* occurs when the effect of one variable on another, say X on Y, is changed by a third variable "Mod" (e.g., race/ethnicity).
- Moderation is sometimes called *effect modification* by epidemiologists and public health researchers and *statistical interaction* by biostatisticians (Gregorich, 2014b).
- The moderator "Mod" can be continuous or binary. The diagram at right contains a shorthand representation of a regression model with Y explained by X, Mod, and an X-by-Mod interaction term.



- A limitation: Typically, many more participants are required to have good power to test for interaction effects relative to testing main effects (e.g., four times as many - or even more; e.g., Leon & Heo, 2009). For this reason, moderation analyses are often proposed to be exploratory.

Interaction Patterns

- There can be different *patterns* of interactions (see Gregorich, 2014b slides 4-7). Here are a few examples:



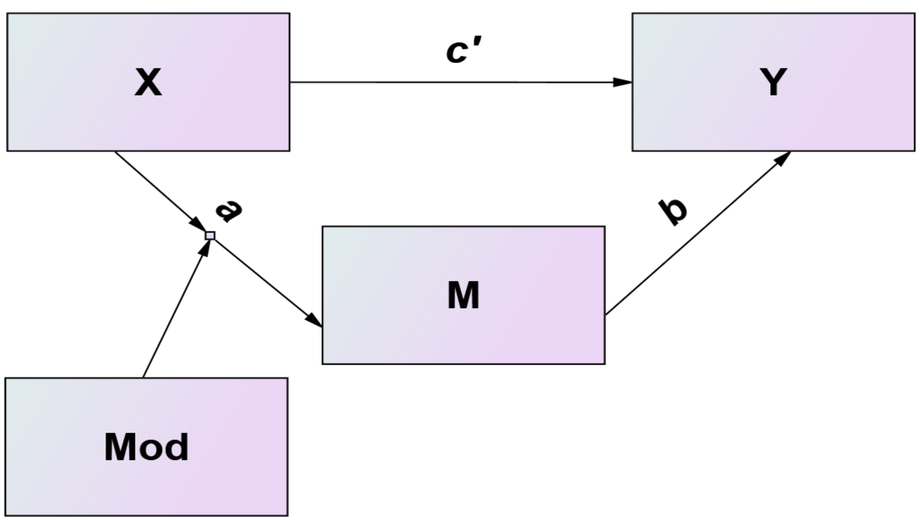
- There are other possibilities, especially when there are more than two levels of each factor or if one or both predictors are continuous.
- General rule: If the lines are not parallel, there is interaction present. Conversely, if the lines are parallel, there is no interaction present.

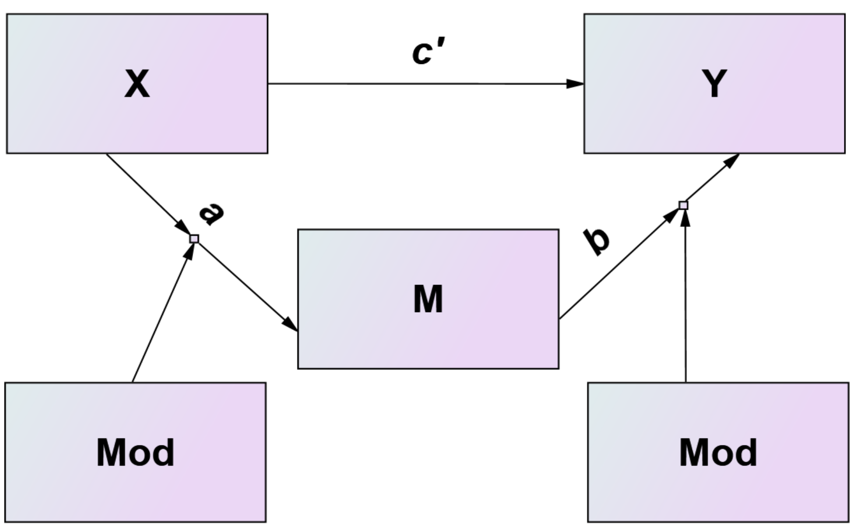
Types of Interactions

- The most commonly-specified type of interaction is a *multiplicative interaction* in which X and Mod are multiplied to yield a product term that is included in the model along with the X and Mod main effects.
- When Y is continuous, a test of the X*Mod multiplicative interaction will yield identical results to comparing the means directly at different levels of X and Mod (i.e., difference of means = mean of differences).
- When Y is not continuous (e.g., binary), that equivalence no longer holds. Thus, epidemiologists and public health researchers with binary outcome variables are increasingly interested in *additive interactions*. An additive interaction is an interaction studied on the probability scale rather than on the log-odds or log-risk scale. See VanderWeele & Knol (2014) for an in-depth published tutorial on this topic and Wall (2013) for a readable online introductory slide deck.

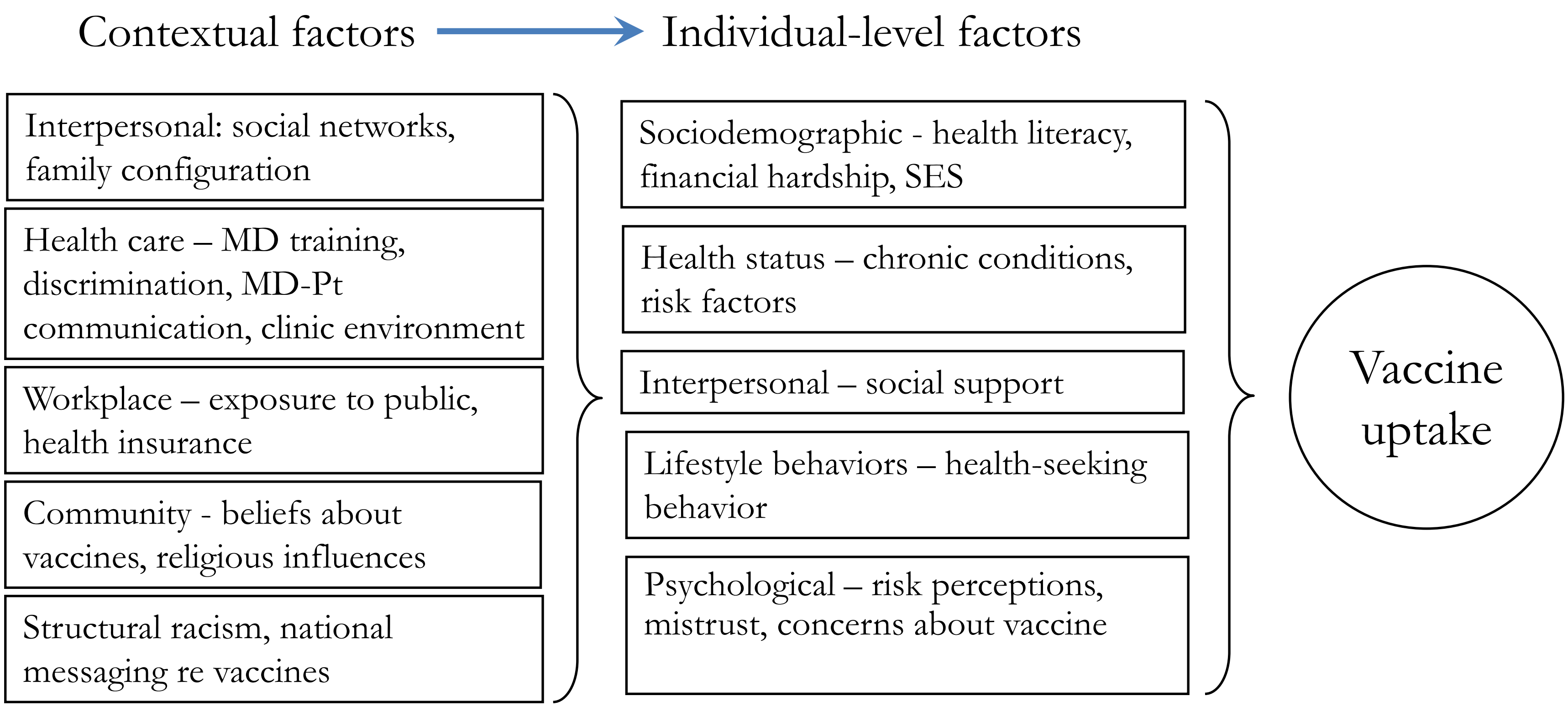
Combining Moderation and Mediation

- It is possible to combine moderation and mediation in the same analysis (Fairchild et al, 2009).
- *Mediated moderation* occurs when an interaction (i.e., moderation) effect is mediated by a mediator (first diagram below [left side]).
- *Moderated mediation* occurs when an indirect (i.e., mediation) effect is modified by another variable (second diagram below [at right])



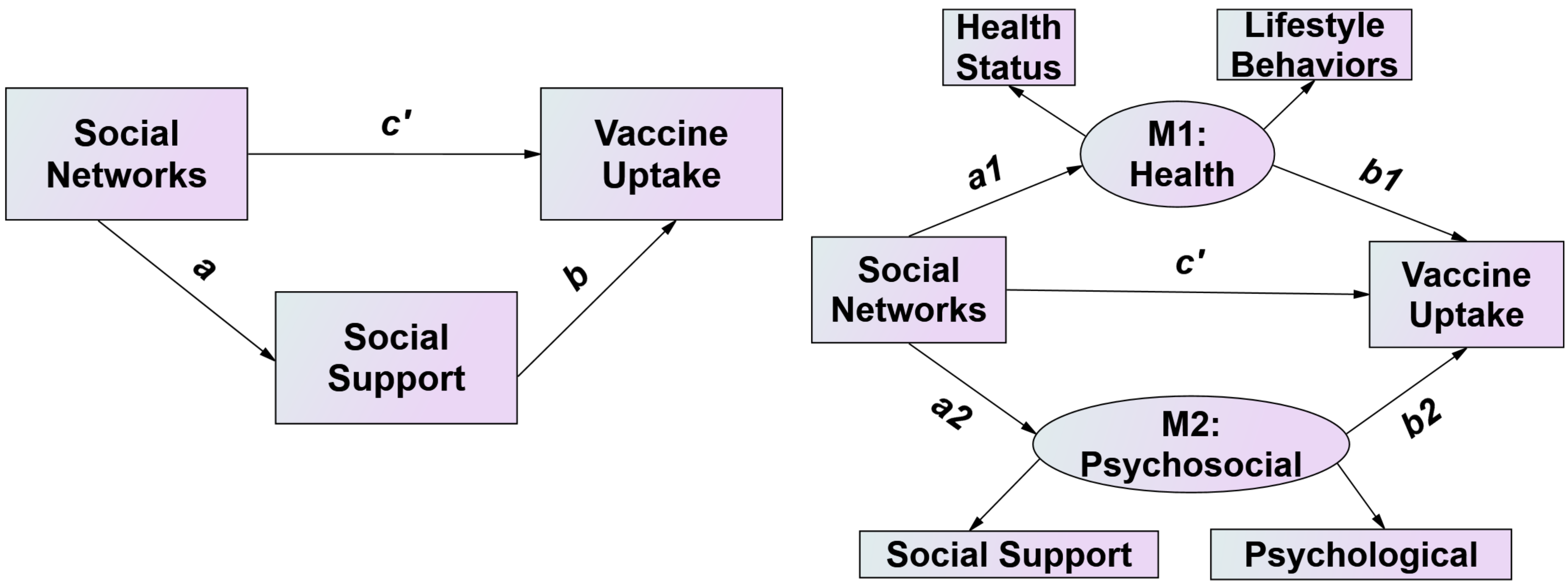


CADC Scientist Example Model: A Study of COVID Vaccine Uptake in Older Black Adults by Dr. Orlando Harris



- Possible mediation: Contextual factor exposures (X) lead to individual factors (M), which in turn lead to vaccine uptake (binary Y)
- Multiple mediators and binary Y: Could try SEM for the full model or multiple mediator subparts. One could also consider evaluating subparts of the model via sequential X->M->Y causal mediation models.

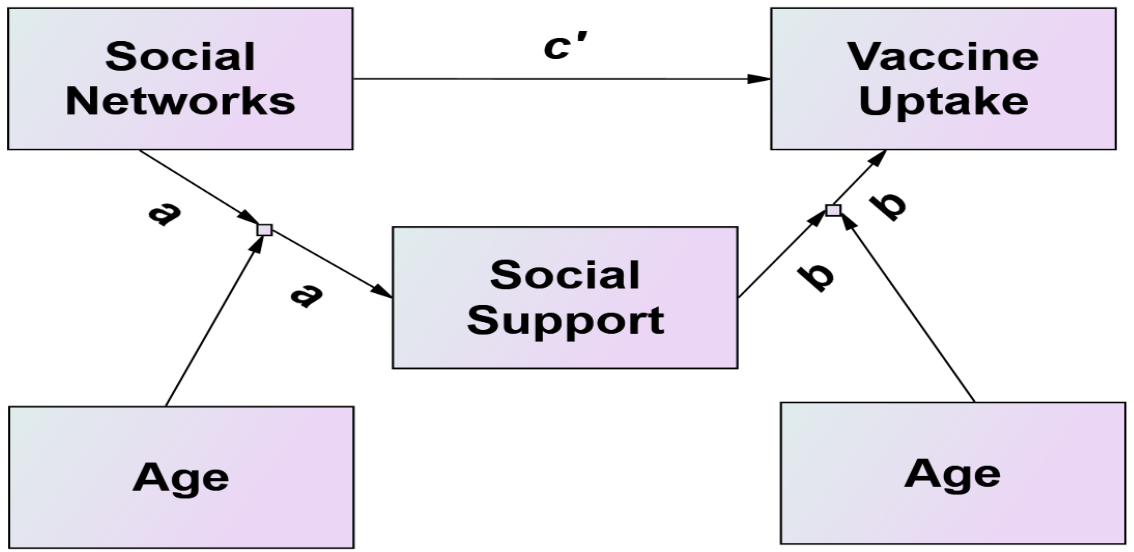
Orlando Harris Model Subpart using Variables



- Left-hand diagram: Simple sequential mediation model without interaction. Binary outcome: Use causal mediation approach.
- Right-hand diagram: Multiple mediators and binary outcome without interaction. One could try representing some of the Ms via latent variables (e.g., M1 and M2) using SEM if their indicators are sufficiently correlated.

Orlando Harris Model: Moderated Mediation

- Here we extend the simple X->M->Y sequential mediation model to include moderated mediation by participant age.



- This version of the model assumes all variables are observed. We could change that if we wanted and make M a latent variable measured by multiple indicators as in the right-side diagram on the previous slide.
- These are just a few illustrations. There are many possibilities. As always, let theory and temporal ordering be your guides. Also, give thought to measured and unmeasured confounders.

Resources

- Gregorich 2014(a) and 2014(b) are available on the CADC website. These two presentations provide introductory yet more in-depth coverage of (non-causal) mediation and moderation, respectively.
- Causal mediation software comparative review article (with clear definitions of the causal mediation effects): Valente et al (2020)
- To learn more about causal mediation methods, consult Valeri and VanderWeele (2013). Dr. VanderWeele also has tools and free video links to a day-long course taught in 2015 on his web site: https://www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials/.
- For the most up-to-date training, Dr. VanderWeele also teaches an excellent short course on causal mediation for Statistical Horizons: https://statisticalhorizons.com/causal-mediation-analysis. The course is taught in an on-demand format (self-paced recorded lectures over a 4-week period with a Q&A forum on Slack) with software demonstrations conducted in SAS and Stata. It will be offered next May.

Conclusions

- Study design: Consider options for randomly assigning mediators as well as exposures (e.g., MOST). When incorporating non-randomized mediators, consider measurement timing and measuring confounders.
- For sequential X->M->Y models or models with post-exposure confounding, consider causal mediation methods, especially if you have non-continuous M and/or Y variables and/or interactions, especially exposure-mediator interactions.
- For multiple-mediator and longitudinal scenarios, check for new causal mediation analysis options as they become available. Otherwise, SEM can be an accessible approach (with limitations).
- Because moderation tests require a lot more participants to achieve satisfactory power for detecting effects, if you are planning to test moderation by race/ethnicity (or another categorical variable), you will need sufficient *n* for the various race/ethnicity groups you are studying.

References (1)

- Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality & Social Psychology.* 1986;51(6):1173-1182.
- Bind MA, Vanderweele TJ, Coull BA, Schwartz JD. Causal mediation analysis for longitudinal data with exogenous exposure. *Biostatistics.* 2016;17(1):122-134. PMCID: PMC4731412
- Choi KH, Bowleg L, Neilands TB. The effects of sexism, psychological distress, and difficult sexual situations on U.S. women's sexual risk behaviors. *AIDS Educ Prev.* 2011;23(5):397-411.
- Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions. *Am J Prev Med.* 2007;32(5 Suppl):S112-118.
- Discacciati A, Bellavia A, Lee JJ, Mazumdar M, Valeri L. Med4way: a Stata command to investigate mediating and interactive mechanisms using the four-way effect decomposition. *Int J Epidemiol.* 2018.
- Gregorich, Steven (2014a). Conceptualizing and testing mediated effects https://cadc.ucsf.edu/sites/g/files/tkssra881/f/wysiwyg/files/05_intro_testing_mediated_effects.pdf.
- Gregorich, Steven (2014b). Conceptualizing and testing moderation effects. https://cadc.ucsf.edu/sites/g/files/tkssra881/f/wysiwyg/files/06_intro_testing_effect_modification.pdf
- Hayes, A. F., & Rockwood, N. J. (2017). Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behaviour Research and Therapy, 98,* 39-57.
- Hoyle RH, Kenny DA. Sample Size, Reliability, and Tests of Statistical Mediation. In: Hoyle RH, ed. *Statistical Strategies for Small Sample Research.* Thousand Oaks, California: Sage Publications; 1999:197-223.
- Leon AC, Heo M. Sample Sizes Required to Detect Interactions between Two Binary Fixed-Effects in a Mixed-Effects Linear Regression Model. *Computational Statistics and Data Analysis.* 2009;53(3):603-608.
- Linden A, Huber C, Wodtke GT. A regression-with-residuals method for analyzing causal mediation: The rwrmed package. *Stata Journal.* 2021;23(3):559-574.

References (2)

- Mari G, Keizer R. Parental Job Loss and Early Child Development in the Great Recession. *Child Dev.* 2021;92(5):1698-1716. PMCID: PMC8518680
- Kenny, DA (2021). Mediation. http://davidakenny.net/cm/mediate.htm.
- Mitchell M, Maxwell SE. A Comparison of the Cross-Sectional and Sequential Designs when Assessing Longitudinal Mediation. *Multivariate Behavioral Research.* 2013;48(3):301-339.
- Scheim AI, Bauer GR. The Intersectional Discrimination Index: Development and validation of measures of self-reported enacted and anticipated discrimination for intercategorical analysis. *Soc Sci Med.* 2019;226:225-235.
- Valente MJ, Rijnhart JJM, Smyth HL, Muniz FB, MacKinnon DP. Causal Mediation Programs in R, Mplus, SAS, SPSS, and Stata. *Struct Equ Modeling.* 2020;27(6):975-984.
- Valeri L, VanderWeele TJ. Mediation Analysis Allowing for Exposure-Mediator Interactions and Causal Interpretation: Theoretical Assumptions and Implementation with SAS and SPSS Macros. *Psychol Methods.* 2013;18(2):137-150.
- VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology.* 2014;25(5):749-761.
- VanderWeele TJ. *Explanation in Causal Inference : Methods for Mediation and Interaction.* New York, NY: Oxford University Press; 2015.
- VanderWeele TJ, Knol MJ. A Tutorial on Interaction. *Epidemiologic Methods.* 2014;3(1):33-72.
- Varas-Diaz N, Neilands TB, Rodriguez-Madera SL, Padilla M. The role of emotions in the reduction of HIV/AIDS stigma among physicians in training. *AIDS Care.* 2016;28(3):376-383.
- Wall, M. (2013). Are you looking for the right interactions? Additive versus multiplicative interactions with dichotomous outcome variables. http://www.columbia.edu/~mmw2177/Testing%20for%20additive%20interactions.pdf

Acknowledgements

- Slide review and comments:
  - Anita Stewart, PhD
  - Deepalika Chakravarty, MS
  - Nadra Lisha, PhD

Thank you!