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Methods: Mind the Gap

Webinar Series

Connections between Traditional and Causal Mediation Methods

Presented by:

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Connections between Traditional and Causal Mediation Methods*

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Office of Disease Prevention: Mind the Gap Seminar Series

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Outline

1. Mediating Variable Examples and Applications
2. Traditional Mediation Analysis
3. Causal Mediation Analysis
4. Links between Traditional and Causal Mediation Analysis
5. Future Directions

Article:

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

Website:

http://www.public.asu.edu/~davidpm/

Book:

MacKinnon, D. P. (2008) Introduction to Statistical Mediation Analysis. Mahwah, NJ: Erlbaum. Second Edition in Progress.

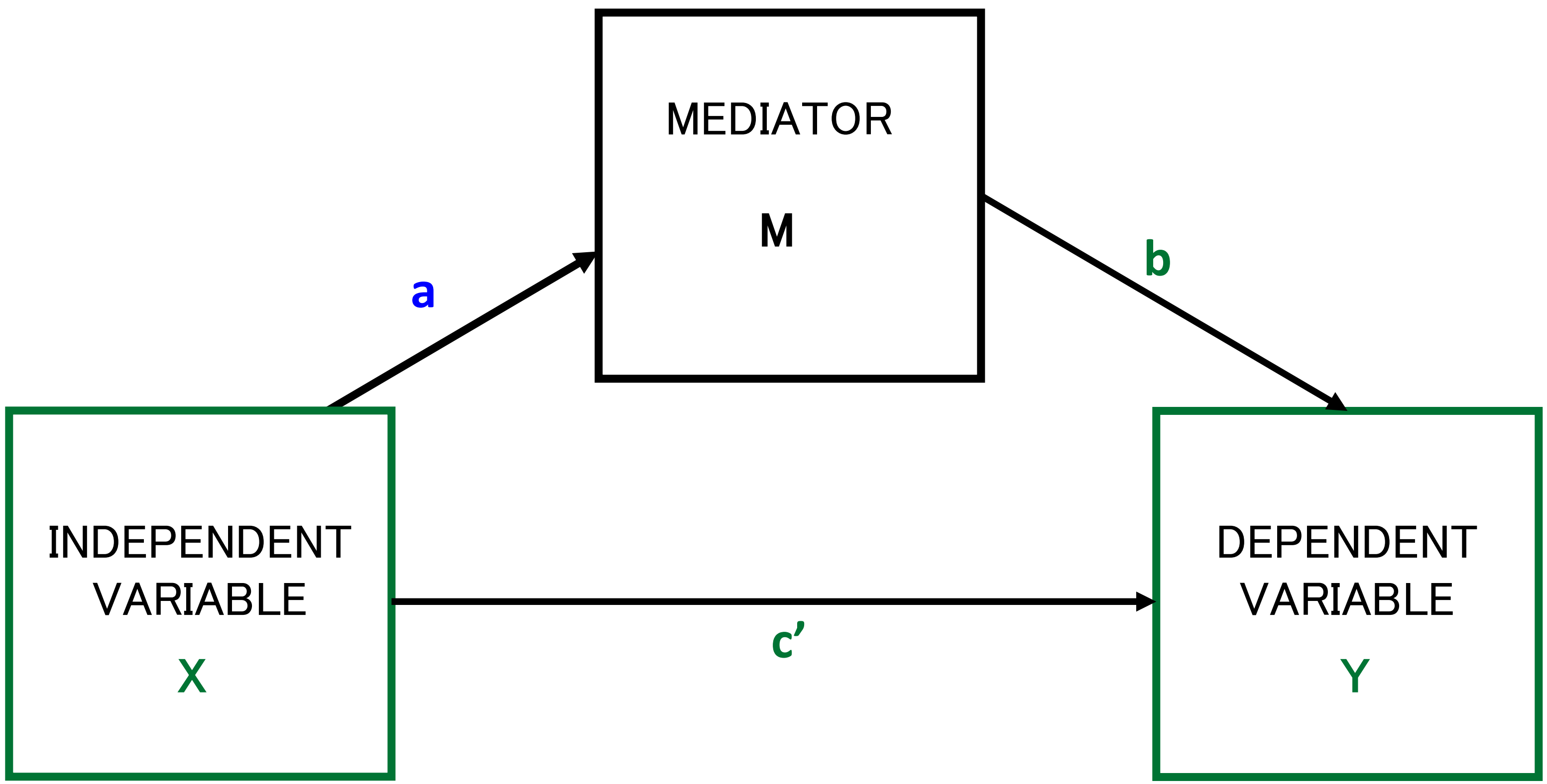
Mediator

A variable that is intermediate in the causal process relating an independent to a dependent variable.

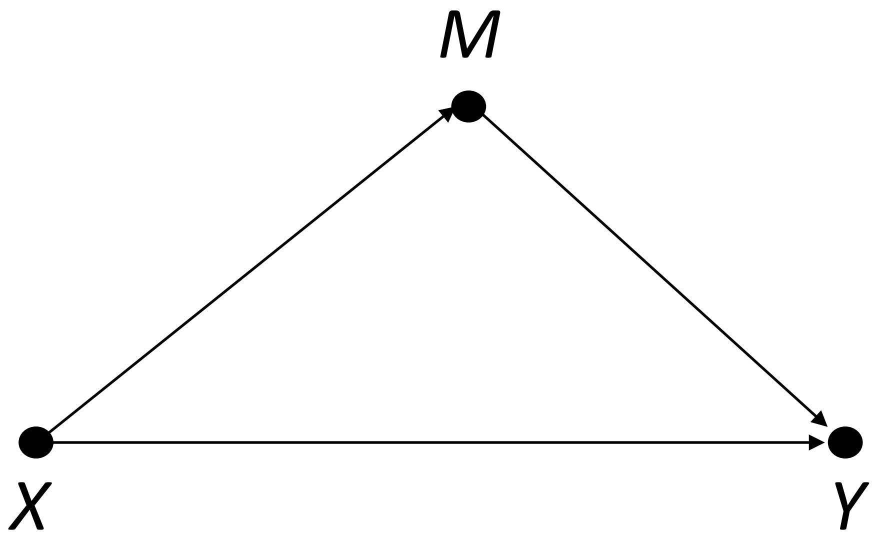
Some Examples:

1) Tobacco prevention program promotes **anti-tobacco norms** which reduce tobacco use (MacKinnon et al., 1991).
2) Neglect/Abuse in childhood (X) to **impaired threat appraisal** (M) to aggressive behavior in adolescence (Y) (Dodge, Bates, & Pettit, 1990).
3) Screening program increases **identification of early stage cancer** which reduces cancer deaths (Zauber, 2015).
4) Wellbutrin (Bupropion) increases participant's **willingness to quit and self-efficacy** which are associated with one month abstinence from tobacco (McCarthy et al., 2008).
5) Your Examples?

Single Mediator Model



Mediation Directed Acyclic Graph



Mediator Definitions

- A mediator is a variable in a chain whereby an independent variable causes the mediator which in turn causes the outcome variable (Sobel, 1990).
- The generative mechanism through which the focal independent variable is able to influence the dependent variable (Baron & Kenny, 1986).
- A variable that occurs in a causal pathway from an independent variable to a dependent variable. It causes variation in the dependent variable and itself is caused to vary by the independent variable (Last, 1988).

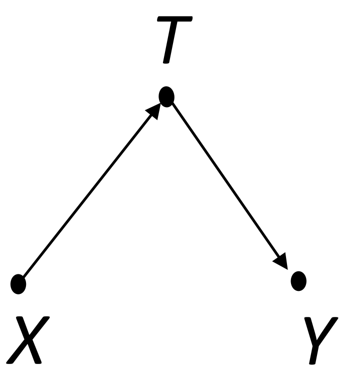
Two, three, four variable effects

- Two variables: $X \rightarrow Y$, $Y \rightarrow X$, $X \leftrightarrow Y$ are reciprocally related. Measures of effect include the correlation, covariance, regression coefficient, odds ratio, mean difference.
- Three variables: $X \rightarrow M \rightarrow Y$, $X \rightarrow Y \rightarrow M$, $Y \rightarrow X \rightarrow M$, and all combinations of reciprocal relations. Special names for third-variable effects: confounder, mediator, collider.
- Four variables: many possible relations among variables, e.g., $X \rightarrow Z \rightarrow M \rightarrow Y$.

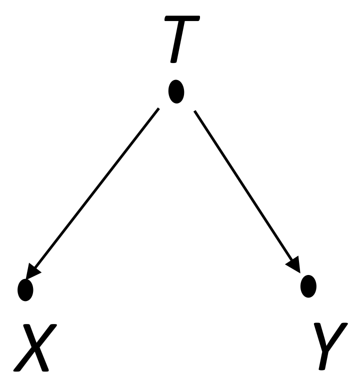
Third-Variable (T) Effects

Mediation is one of three possible causal relations for three variables. There are three fundamental causal relations for three variables, (1) **Mediator**, (2) **Confounder**, and (3) **Collider**.

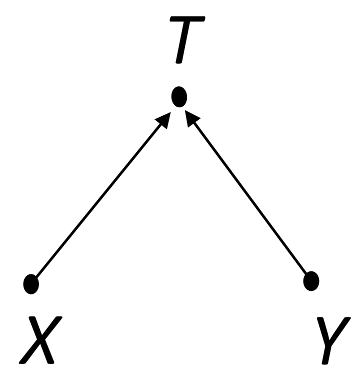
1. T is Mediator (Chain)



2. T is a Confounder (Fork)

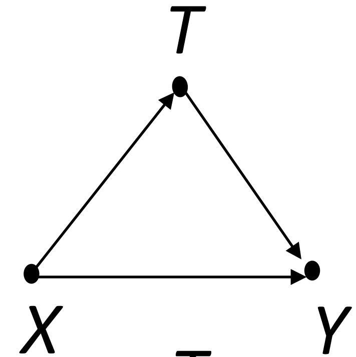


3. T is a Collider (Inverted Fork)

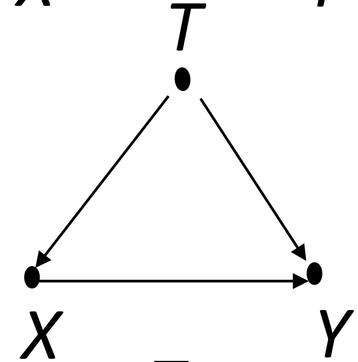


Third-Variable (T) Effects

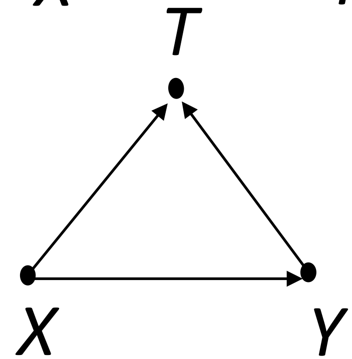
Mediator: This is the focus of this talk. A variable that is intermediate in a causal process between X and Y.



Confounder: A variable that causes X and Y such that if it is not included in the analysis an incorrect estimate of the relation between X and Y will be obtained.



Collider: A variable that is caused by X and Y so that it should not be adjusted in the analysis of X and Y because it will incorrectly change the relation between X and Y.



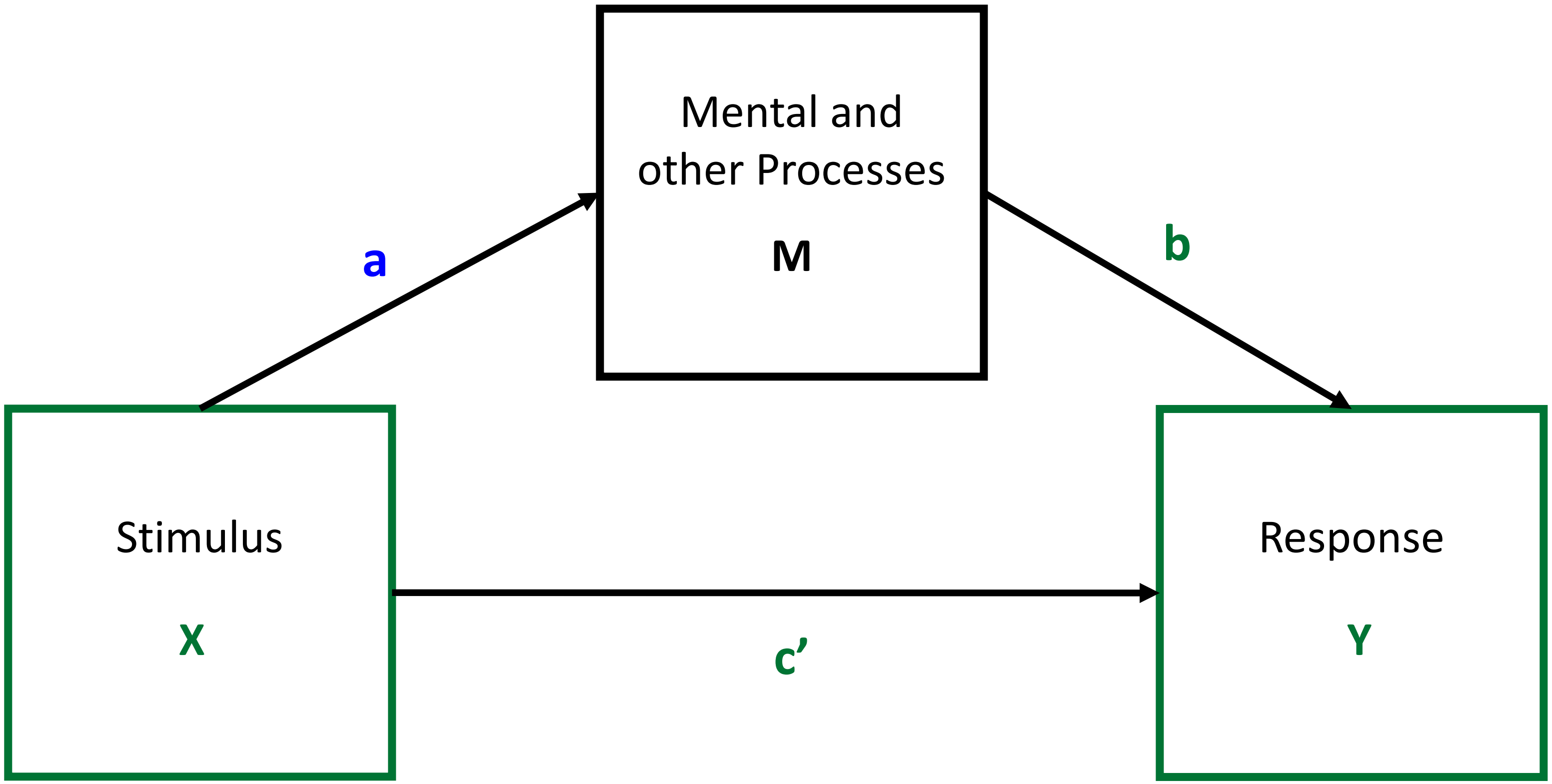
Mediation is important because …

- Central questions in many fields are about mediating processes.
- Important for basic research on mechanisms of effects.
- Critical for applied research, especially prevention and treatment, to identify critical ingredients leading to more efficient interventions.
- Many interesting statistical and mathematical issues.

S→O→R Theory I

- Stimulus→ Organism → Response (SOR) theory whereby the effect of a Stimulus on a Response depends on mechanisms in the organism (Woodworth, 1928). These mediating mechanisms translate the Stimulus to the Response.
- Stimulus: Multiply 24 and 16
- Organism: You
- Response: Your Answer
- Organism as a Black Box

S-O-R Mediator Model



S→O→R Challenges

- Note that the mediation process is usually unobservable.
- Mediation as a measurement problem.
- Process may operate at different levels, individuals, neurons, cells, atoms, teams, schools, states, etc.
- Mediating processes may happen simultaneously.
- Mediating process may be part of a longer chain. The researcher needs to decide what part of a long mediation chain to study – the micromediatonal chain.

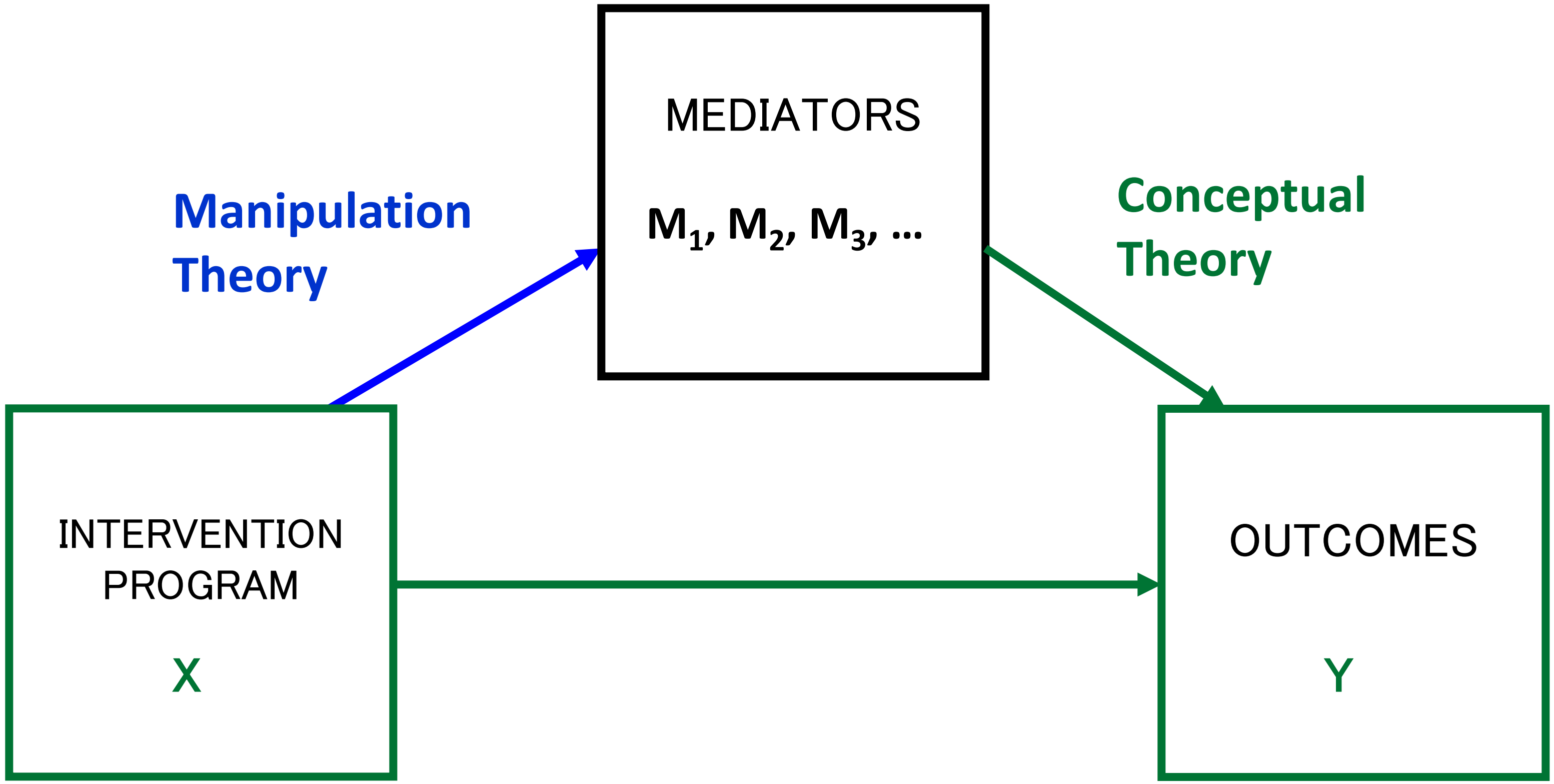
Mediation for Explanation

- Observe relation and then try to explain it.
- Elaboration method includes a third variable in an analysis of two variables to see if/how the observed relation changes (Lazarsfeld et al., 1955; Hyman, 1955).
- Replication (Covariate)
- Explanation (Confounder)
- Intervening (Mediator)
- Specification (Moderator)

Mediation by Design

- Select mediating variables that are causally related to an outcome variable.
- Intervention is designed to change these mediators.
- If mediators are causally related to the outcome, then an intervention that changes the mediator will change the outcome.
- Common in applied research like prevention and treatment.

Intervention Mediation Model



If the mediator changed is causally related to Y, then changing the mediator will change Y.

Goal of Mediation Analysis

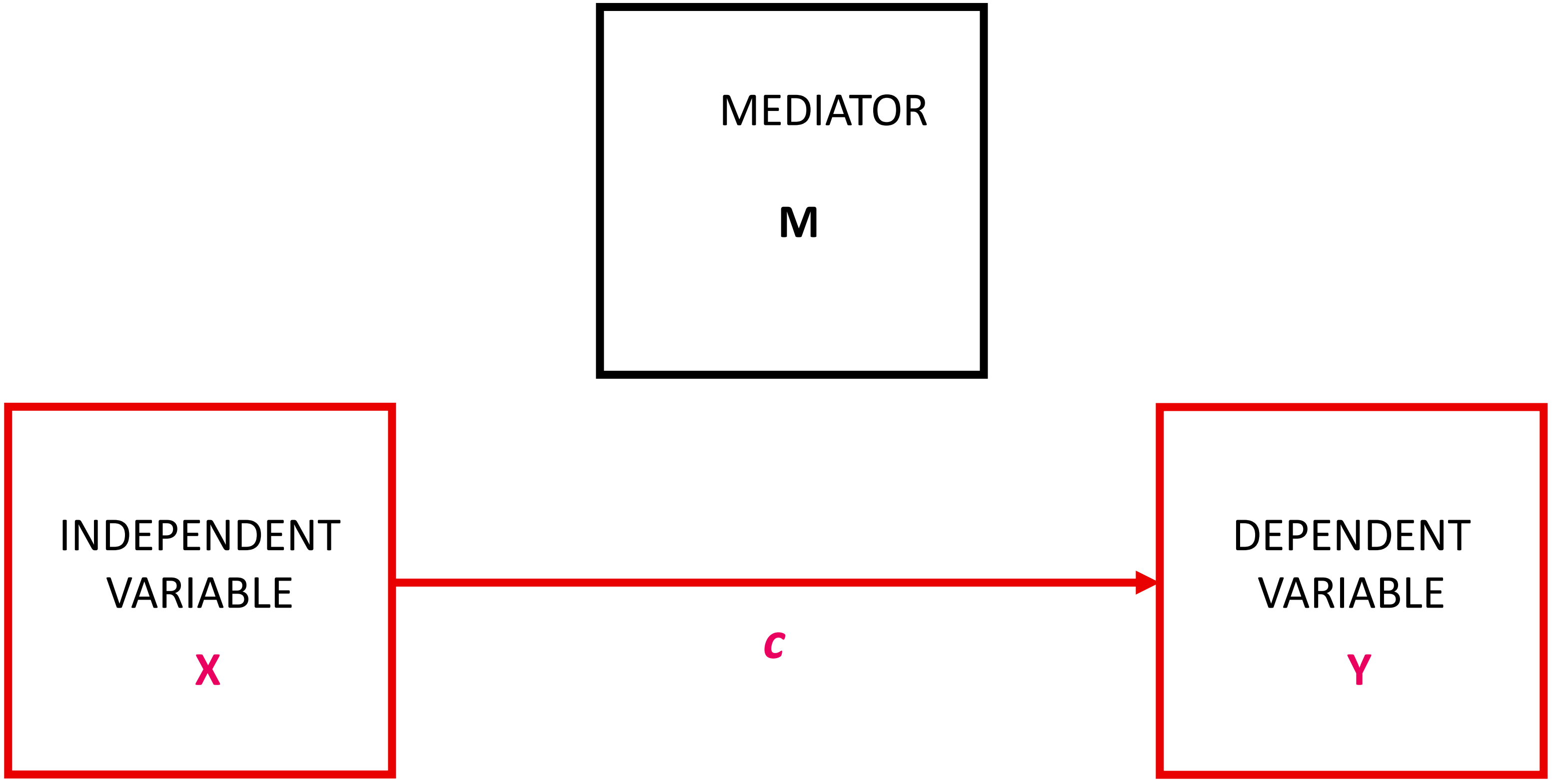
- Mediation analysis addresses the question, "What is the best way to use a measure of the hypothetical mediating process to increase the amount of information from a research study?"

- More information is available with measures of X, M, and Y compared to just measures of X and Y. What is the best way to use this information?

Mediation Regression Equations

- Tests of mediation for a single mediator use information from some or all of three equations.
- The coefficients in the equations may be obtained using methods such as ordinary least squares regression, covariance structure analysis, or logistic regression.

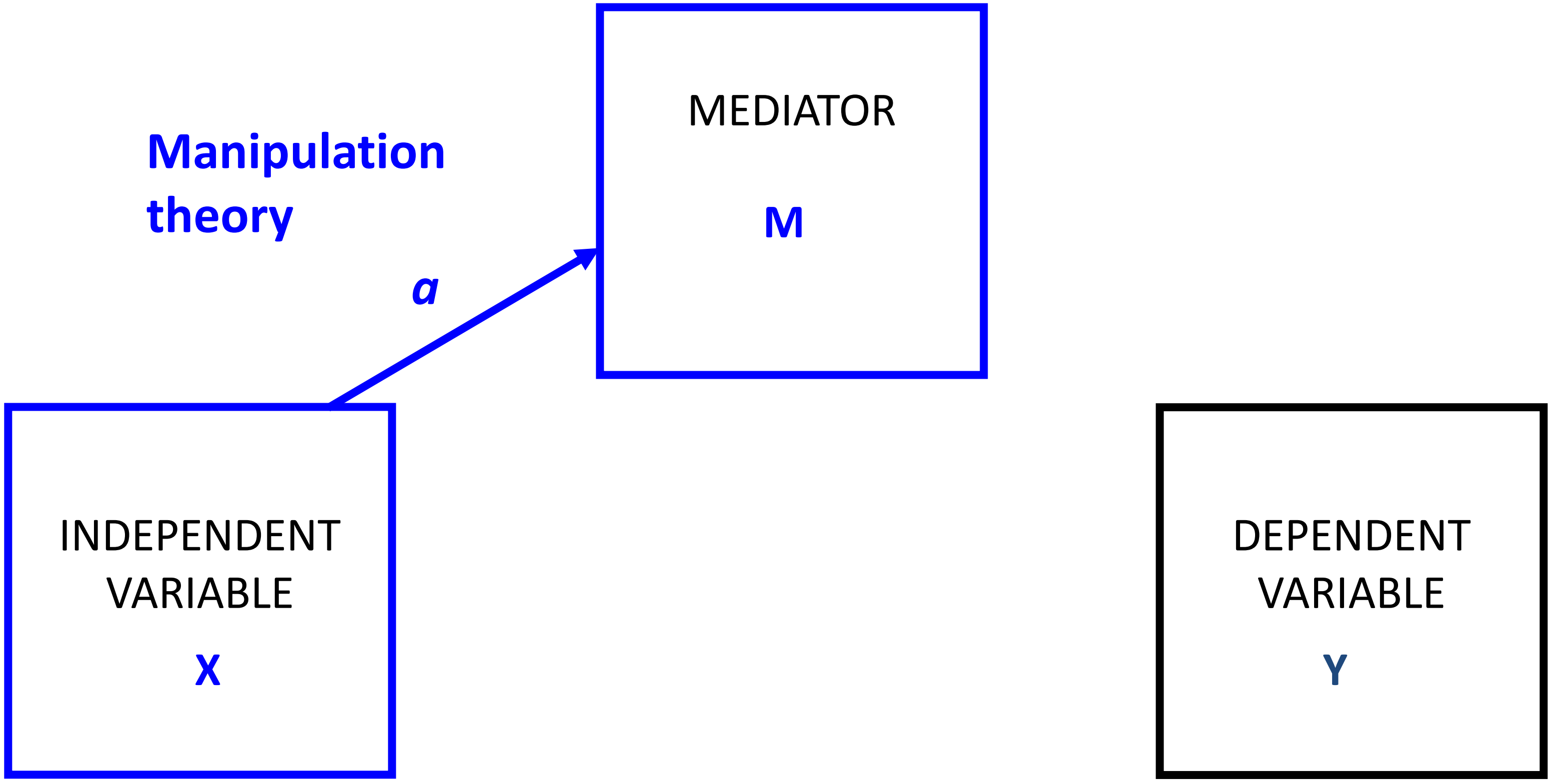
Regression Equation 1



1. The independent variable is related to the dependent variable:

$$Y = i_1 + \hat{c}X + e_1$$

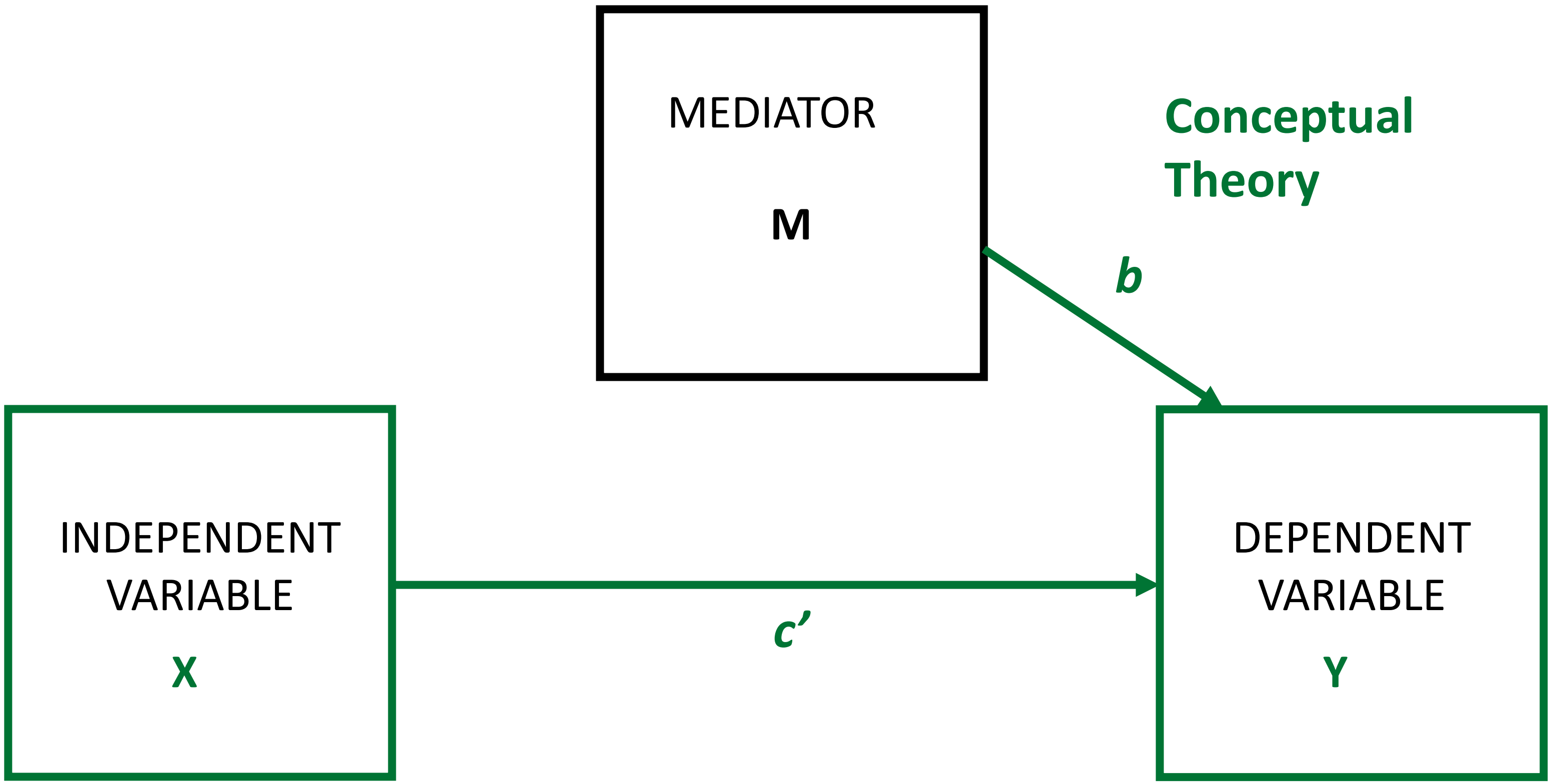
Regression Equation 2



2. The independent variable is related to the potential mediator:

$$M = i_2 + \hat{a}X + e_2$$

Regression Equation 3



3. The mediator is related to the dependent variable controlling for exposure to the independent variable:

$$Y = i_3 + \hat{c}' X + \hat{b} M + e_3$$

Mediated Effect Measures

Mediated effect = *ab* Product of Coefficients

Mediated effect = *c*-*c'* Difference in Coefficients

Mediated effect = *ab* = *c*-*c'*
(MacKinnon et al., 1995)

Direct effect = *c'*   &   Total effect = *ab* + *c'* = *c*

Indirect Effect and Mediated Effect are used synonymously in this presentation.

Mediated Effect, $\hat{a}\hat{b}$, Standard Error

Mediated effect = $\hat{a}\hat{b}$, Standard error = $\sqrt{\hat{a}^2 s_{\hat{b}}^2 + \hat{b}^2 s_{\hat{a}}^2}$

Multivariate delta method standard error

(Sobel, 1982)

Test for significant mediation:

$$z' = \frac{\hat{a}\hat{b}}{\sqrt{\hat{a}^2 s_{\hat{b}}^2 + \hat{b}^2 s_{\hat{a}}^2}}$$

But z' does not always have a normal distribution

Significance Testing and Confidence Limit Estimation

- Product of coefficients estimation of the mediated effect, ***ab***, is the most general approach.

- Best methods for confidence limit estimation and significance testing use the **Distribution of the Product** or **Bootstrap.** Also **Joint Significance** for significance testing (see MacKinnon et al., 2002; 2004 and others).

Assumptions

For each method of estimating the mediated effect based on Equations 1 and 3 (c - c') or Equations 2 and 3 (ab):

- Reliable and valid measures.
- Coefficients, a, b, c', c reflect true causal relations and the correct functional form. No omitted influences.
- Mediation chain is correct. Temporal ordering is correct X before M before Y.
- Homogeneous effects across subgroups. It assumed that the relation from X to M and from M to Y are homogeneous across subgroups or other characteristics of participants in the study.

Causal Inference for Traditional Mediation

- Methods assume true causal relations and no omitted variables for mediation analysis.
- Challenge with mediation analysis because M is not randomly assigned but is self-selected.
- Measure all relevant variables. Blalock's (1979) presidential address--about 50 variables are involved in sociological phenomenon. How many variables are relevant for your research?
- Interpret results in terms of threats to external and internal validity (Shadish, Cook, & Campbell, 2002).

Modern Causal Inference

Causal inference is the process of drawing a conclusion about a causal relation based on the conditions for the occurrence of a causal effect.

Causal inference differs from association inference in that causal inference analyzes the response of the effect variable when the cause is changed.

From Pearl (2009).Causal inference in statistics: an overview. *Statistics Surveys*, *3*, 96-146.

Quotes

"More has been learned about causal inference in the last few decades than the sum total of everything that had been learned about it in all prior recorded history." (Gary King, Harvard University, 2015).

"The use of counterfactuals for causal inference has brought clarity to our reasoning about causality."(Tyler VanderWeele, Harvard University, 2015).

"The Causal Revolution did not happen in a vacuum; it has a mathematical secret behind it …a calculus of causation, which answers some of the hardest problems ever asked about cause-effect relationships." (Judea Pearl, UCLA, p. 7, 2018).

Counterfactual/Potential Outcome Models

Most modern causal inference approaches are based on a counterfactual or potential outcomes framework.

In these models, all the possible counterfactual and actual conditions of an experiment are considered and the statistical model is based on all these possible or potential conditions.

Requires consideration of conditions that did not occur.

Counterfactual/Potential Outcomes

If I could eat a donut, I would have more energy now.

Counterfactual thinking is important and we do it all the time.

Consideration of possible actions besides the action that was actually taken.

If I went to the University of Barcelona instead of University of California, Los Angeles for graduate school, I would be fluent in Spanish.

Modern Causal Inference

Why not clearly state causal effects and address assumptions with methods developed for causal inference?

We are in a Causal Revolution (Pearl, 2012; Morgan & Winship, 2015, Hernan & Robins, 2019).

Very active area of research (e.g., for mediation see Frangakis & Rubin, 2002; Hong, 2015; Imai et al., 2010; Pearl, 2001; Pearl, 2009; VanderWeele, 2015).

Epidemiology, medicine, and public health have adopted the new approaches. Rare to find these methods in psychology and other related fields.

Individual-level Causal Effect

Consider one participant and a two-group treatment and control design, i.e., actual and potential outcomes for participant *i*.

Individual Causal Effect = $Y_i(1) - Y_i(0)$

The causal effect is the difference between Y_i in treatment (x=1) and Y_i control (x=0) when the participant is in both conditions.

But you usually only have a participant's Y for treatment or control, not both conditions so you either have $Y_i(1)$ - $Y_i(0)$ or $Y_i(1)$ - $Y_i(0)$, where red indicates an impossible potential outcome.

Observed and Counterfactual Table

Participant	Assignment	Observed Y	Potential Outcome Y(0)	Potential Outcome Y(1)
James	0	0	0	?
Julie	0	1	1	?
Susan	0	1	1	?
Al	0	1	1	?
Kim	1	1	?	1
Roy	1	0	?	0
John	1	0	?	0
Rhonda	1	0	?	0

Average Causal Effect

All participants cannot realistically serve in all conditions which is a Fundamental Problem of Causal Inference.

With random assignment of units to conditions, use the average in each condition as the counterfactual for the other condition and obtain an estimate of the Average Causal Effect (ACE) by comparing the means in the treatment and control group.

Average Causal Effect = Average $Y(x=1)$ - Average $Y(x=0)$

Average Causal Effect = $E[Y(1)] - E[Y(0)]$

Assumptions

Exchangeability: The group of persons in one group is exchangeable with persons in another group. Usually assumed in experimental studies.

Stable Unit Treatment Value Assumption (SUTVA):
(1) **no interference:** A participant's counterfactual status, Y(x=0) and Y(x=1), does not depend on the treatment status of other individuals.
(2) **treatment variation irrelevance:** There is only one version of a treatment—not multiple versions, i.e. treatments are well-defined.

Notation to add a Mediator

Values of variables in the potential outcome notation allow for different effects at different values of variables.

x is the value of the variable X.
Will use x=0 for control and x=1 for treatment.
y is the value of the variable Y.
m is the value of the variable M.

So the CAPITAL letter is the VARIABLE and lower case letter is a value of the variable.

i codes participant *i*.

Potential Outcomes with Three Variables

$Y_i(0,M(0))$ is the participant's Y value in the control group setting M to the value it would have been in the control group.

$Y_i(1,M(1))$ is the participant's Y value in the treatment group setting M to the value it would have been in the treatment group.

$Y_i(0,M(1))$ is the participant's Y value in the control group setting M to the value it would have been in the treatment group.

$Y_i(1,M(0))$ is the participant's Y value in the treatment group setting M to the value it would have been in the control group.

Note: The first symbol in the parentheses is for X and the second symbol is for M, for treatment $x = 1$ and control $x = 0$. Potential outcomes in red are impossible to observe.

Individual Causal Effects

TNIE $= Y_i(1,M(1)) - Y_i(1,M(0))$ Total Natural Indirect Effect

PNIE $= Y_i(0,M(1)) - Y_i(0,M(0))$ Pure Natural Indirect Effect

PNDE $= Y_i(1,M(0)) - Y_i(0,M(0))$ Pure Natural Direct Effect

TNDE $= Y_i(1,M(1)) - Y_i(0,M(1))$ Total Natural Direct Effect

CDE $= Y_i(1,m) - Y_i(0,m)$ Controlled Direct Effect

TE $= Y_i(1) - Y_i(0)$ Total Effect

Where x = 0 for control and x = 1 for treatment but x could be two values for a continuous X variable also.

Hint: Pure refers to the x=0 group and Total refers to the x=1 group.

Average Causal Effects for x=0 Control or x=1 Treatment

TNIE = E[Y(1,M(1))] – E[Y(1,M(0))]
PNIE = E[Y(0,M(1))] – E[Y(0,M(0))]
PNDE = E[Y(1,M(0))] – E[Y(0,M(0))]
TNDE = E[Y(1,M(1))] – E[Y(0,M(1))]

CDE = E[Y(1,m)] – E[Y(0,m)]
TE = E[Y(1)] – E[Y(0)]

Note: The Expected values (E) represent averages over individuals. Assumes that the no confounding assumptions are met, continuous M and Y, and two values of X, x=1 and x=0 (Valeri & VanderWeele, 2013)

Predicting Potential Outcomes

It is not possible to observe E[Y(1,M(0))] or E[Y(0,M(1))]

Predicted based on what we observe about the treatment and control groups and assumptions.

Often regression models are used to predict potential outcomes (Pearl, 2001; VanderWeele & Vansteelandt, 2009).

Total Effect and Controlled Direct Effect

TE = E[Y(1)] – E[Y(0)] Total Effect

The difference between Y in treatment and control.

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

The difference between Y in treatment and control if in the population the mediator was fixed at value m.

It may be difficult to select a representative value of m. Another option would be to calculate effects at the value of m that the participant would **naturally** have, e.g., the effect of X on Y at the value m that the participant had rather than fixing M to a certain value m.

Natural Direct Effects

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

The effect of treatment setting the mediator value to the value that would have been obtained in the control condition—the natural value of the m in the control condition.

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

The effect of treatment setting the mediator value to the value that would have been obtained in the treatment condition—the natural value of the m in the treatment condition.

Natural Indirect Effects

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

The difference between potential outcomes in the treatment condition when the value of the mediator is changed from the value of the mediator in the treatment to the value of the mediator in the control condition.

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

The difference between potential outcomes in the control condition when the value of the mediator is changed from the value of the mediator in the treatment to the value of the mediator in the control condition.

Three Mediation Equations

$$Y = i_1 + c\,X + e_1 \qquad (1)$$

$$Y = i_2 + c'\,X + b\,M + h\,XM + e_2 \qquad (2)$$

$$M = i_3 + a\,X + e_3 \qquad (3)$$

Estimation of Potential Outcome Groups for Nested Counterfactuals (PNIE)

Expected Value for the **Control** group (x=0) at the value of the Mediator in the **Treatment** group.

E[Y(0,M(1)] = $i_2 + c'X\ (x=0) + b\ M(m=m(1)) + h\ XM(x=0,(m=m(1)))$
$= i_2 + c'X + b\ (i_3 + aX(x=1)) + h\ X(x=0)(i_3 + aX(x=1))$
$= i_2 + bi_3 + ba$

Expected Value for the **Control** group (x=0) at the value of the Mediator in the **Control** group.

E[Y(0,M(0)] = $i_2 + c'X\ (x=0) + b\ M(m=m(0)) + h\ XM(x=0,(m=m(0)))$
$= i_2 + c'X + b\ (i_3 + aX(x=0)) + h\ X(x=0)(i_3 + aX(x=0))$
$= i_2 + bi_3$

PNIE = E[Y(0,M(1))] – E[Y(0,M(0))] = ab

Estimation of Potential Outcome Groups for Nested Counterfactuals (TNIE)

Expected Value for the **Treatment** group (x=1) at the value of the Mediator in the **Treatment** group.

$E[Y(1,M(1)] = i_2 + c'X\ (x=1) + b\ M(m=m(1)) + h\ XM(x=1,(m=m(1)))$

$= i_2 + c'X + b\ (i_3 + aX(x=1)) + h\ X(x=1)\ (i_3 + aX(x=1))$

$= i_2 + c'X + bi_3 + ba + hi_3 + ha$

Expected Value for the **Treatment** group (x=1) at the value of the Mediator in the **Control** group.

$E[Y(1,M(0)] = i_2 + c'X\ (x=1) + b\ M(m=m(0)) + h\ XM(x=1,(m=m(0)))$

$= i_2 + c'X + b\ (i_3 + aX(x=0)) + h\ X(x=1)\ (i_3 + aX(x=0))$

$= i_2 + c'X + bi_3 + hi_3$

TNIE = E[Y(1,M(1))] – E[Y(1,M(0))] = $ab + ha$

Six Average Causal Effects for x=0 Control or x=1 Treatment

TNIE = E[Y(1,M(1))] – E[Y(1,M(0))] = $ab + ah$

PNIE = E[Y(0,M(1))] – E[Y(0,M(0))] = ab

PNDE = E[Y(1,M(0))] – E[Y(0,M(0))] = $c' + hi_3$

TNDE = E[Y(1,M(1))] – E[Y(0,M(1))] = $c' + hi_3 + ah$

CDE = E[Y(1,m)] – E[Y(0,m)] = $c' + h$m

TE = E[Y(1)] – E[Y(0)] = c

Note: The Expected values (E) represent averages over individuals. Assumes that the no confounding assumptions are met, continuous M and Y, and two values of X, x=1 and x=0 (Valeri & VanderWeele, 2013). See MacKinnon et al., (2020, *Prevention Science*) for links between traditional and causal mediation.

No unmeasured confounder assumptions

(VanderWeele & Vansteelandt, 2009)

1. No unmeasured confounders of X – Y
2. No unmeasured confounders of X – M
3. No unmeasured confounders of M – Y
4. No M – Y confounder affected by X

Randomization of X addresses the first two assumptions but not the last two.

Correspondence of Traditional and Causal Mediation Effects

- If h = 0, the traditional and causal estimators are identical, ab = NIE = PNIE = TNIE and c' = CDE = PNDE = TNDE.
- If $h \neq 0$, the causal estimators are simple mediated effects and simple direct effects (MacKinnon et al., 2020)
  - Simple mediated effect for the control group = Pure Natural Indirect Effect (PNIE)
  - Simple mediated effect for the treatment group = Total Natural Indirect Effect (TNIE)

Different Interpretation for the Counterfactual and Traditional Model

- Although the estimates are the same, the interpretation of results differ between potential outcomes and traditional mediation analysis.
- Traditional analysis interpretation is a description of effects in the two different groups.
- Potential outcomes interpretation is if all persons were in the control condition these are the effects and if all persons were in the treatment condition, these are the effects.
- If all relevant confounders have been taken into account, traditional simple mediated effects (i.e., associational effects) will equal natural indirect effects (i.e., causal effects) in simple linear models.

Future Directions

- Causal mediation methods are ideal for nonlinear models, logistic regression, survival analysis, and longitudinal models. Causal effects are defined as contrasts between potential outcomes.
- Recent work focuses on extending causal mediation models for more than two groups, more than one mediator, path models, longitudinal models, models incorporating post-treatment confounders, Bayesian methods, and measurement models for X, M, and Y.
- Lots more to come.

Summary

- The potential outcomes mediation model considers all conditions, even conditions in which the participant did not serve.
- When there is no XM interaction with continuous M and Y, traditional and counterfactual mediation models give equivalent estimates but different interpretations.
- When there is an XM interaction with continuous M and Y, simple mediated effects are equivalent to natural indirect effects and simple direct effects are equivalent to natural direct effects.
- Causal methods are based on a mathematics of cause and are a general approach to mediation.

Thank You

References available by contacting David.MacKinnon@asu.edu

Questions?

You can submit questions by clicking on the question mark in the WebEx toolbar. Please direct your questions to “ALL PANELISTS.”

Collaborators

Leona Aiken, Amanda Baraldi, Hendricks Brown, Jeewon Cheong, Donna Coffman, Matt Cox, Stefany Coxe, James Dwyer, Mike Edwards, Diane Elliot, Craig Enders, Amanda Fairchild, Matt Fritz, Lois Gelfand, Linn Goldberg, Kim Goldsmith, Oscar Gonzalez, Kevin Grimm, Jeanne Hoffman, Booil Jo, David Kenny, Yasemin Kisbu-Sakarya, Jennifer Krull, Kerry Kuehl, Linda Luecken, Ginger Lockhart, Chondra Lockwood, Maria Maric, Gina Mazza, Milica Miocevic, Antonio Morgan-Lopez, Felix Muniz, Vanessa Ohlrich, Magarita Olivera-Aguilar, Holly O'Rourke, Andrew Pickles, Will Pelham, Mary Ann Pentz, Angela Pirlott, Krista Ranby, Judith Rijnhart, Mark Reiser, Heather Smyth, Elizabeth Stuart, Marcia Taborga, Aaron Taylor, Jenn Tein, Felix Thoemmes, Davood Tofighi, Matt Valente, Liz Stuart, Heather Smyth, Martia van Stralen, Wei Wang, Ghulam Warsi, Steve West, Jason Williams, Ingrid Wurpts, Mine Yildrim, Myeongsun Yoon, Ying Yuan et al.

Hypothesized Effects of Mind the Gap Presentation