Statistical mediation analysis

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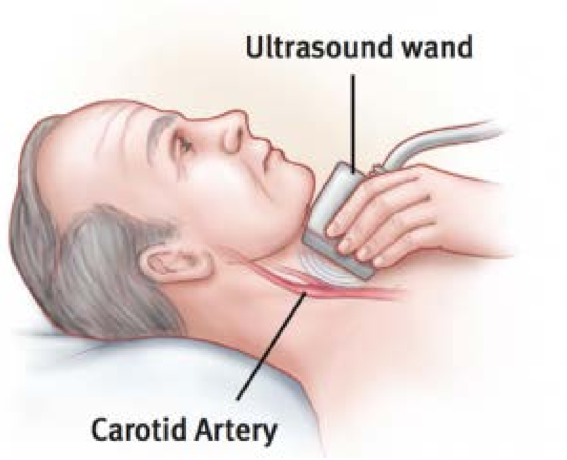
VU medisch centrum

Outline

- Introduction
- Background
- Examples to determine mediation
- Structural Equation Modeling
- Potential outcomes framework
- Future topics

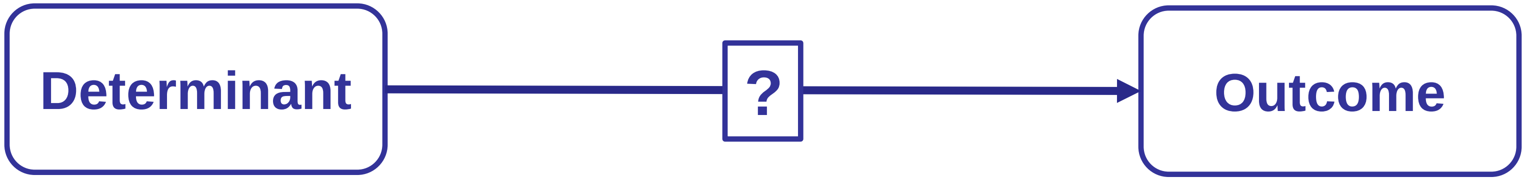
Epidemiology

BMI → Decrease → **Carotid distensibility**

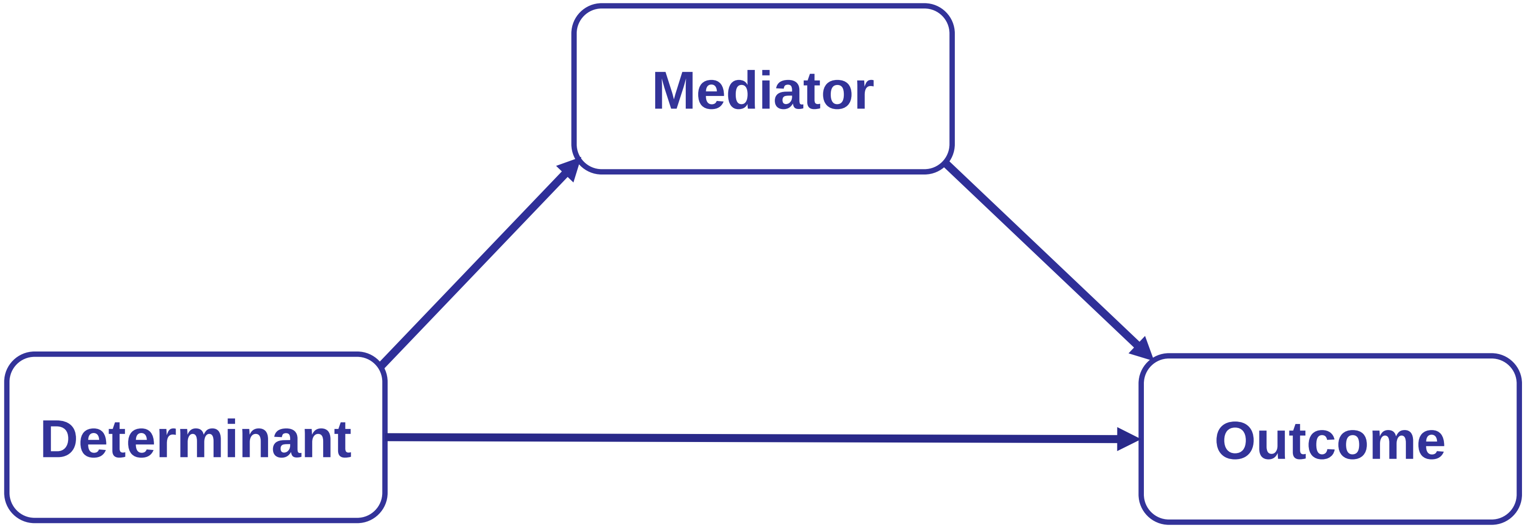


Ferreira et al. Hypertension 2012 (AGGO study)

Questions of why and how?



Mediation analysis

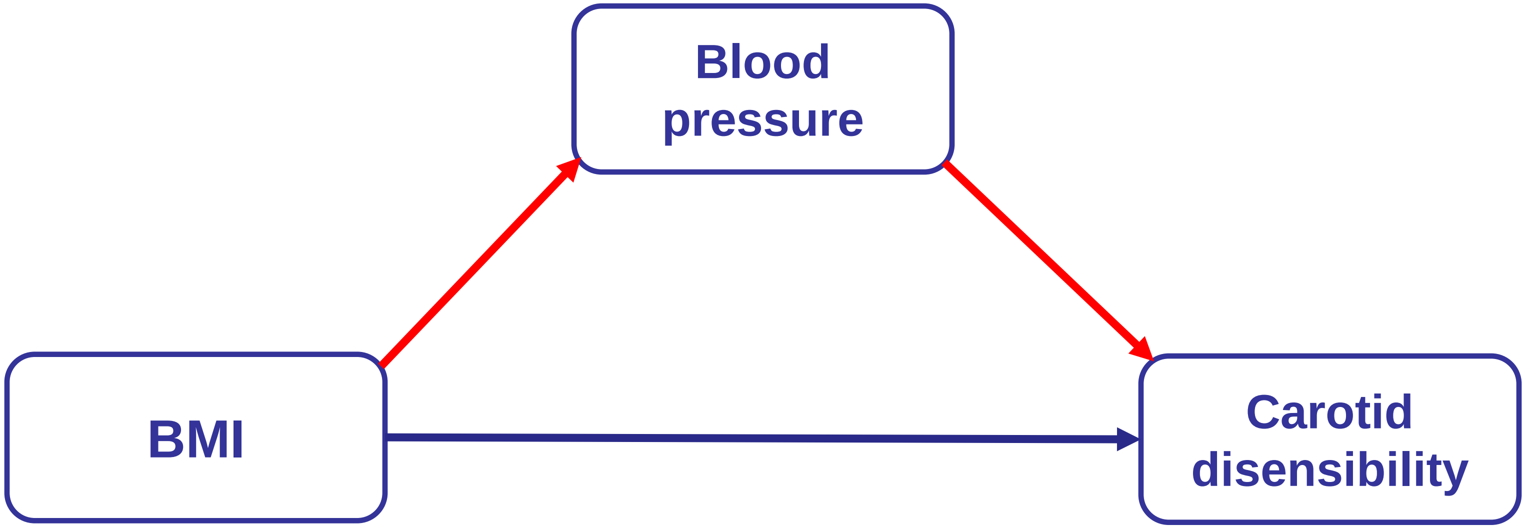


What is a mediator?

Mediator

- Affected by the determinant
- Affects the outcome
- In the causal pathway

Example of a mediator



Hasan M. et al. Circulation 2012.
Benetos A et al. American Journal of Hypertension, 2002.
Ferreira et al. J Hypertens, 2004.

Mediator vs. confounder

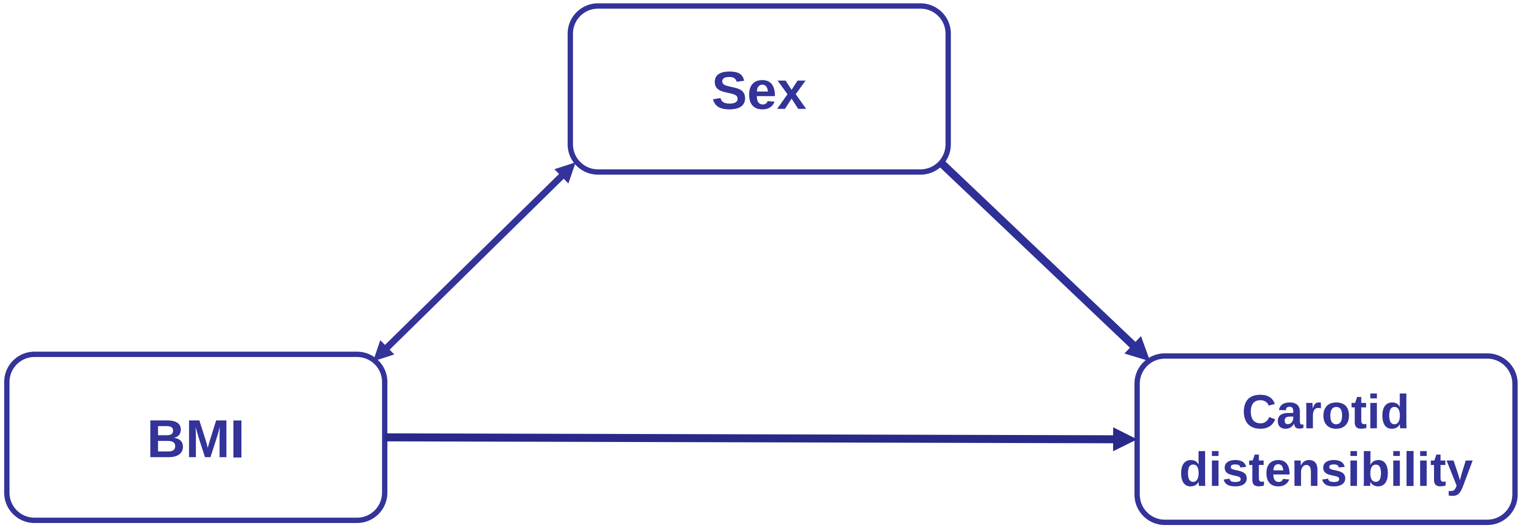
Mediator

- Affected by the determinant
- Affects the outcome
- In the causal pathway

Confounder

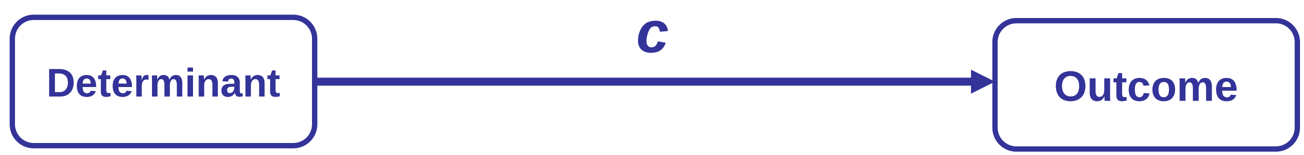
- Association with the determinant
- Affects the outcome
- **Not** in the causal pathway

Example of a confounder



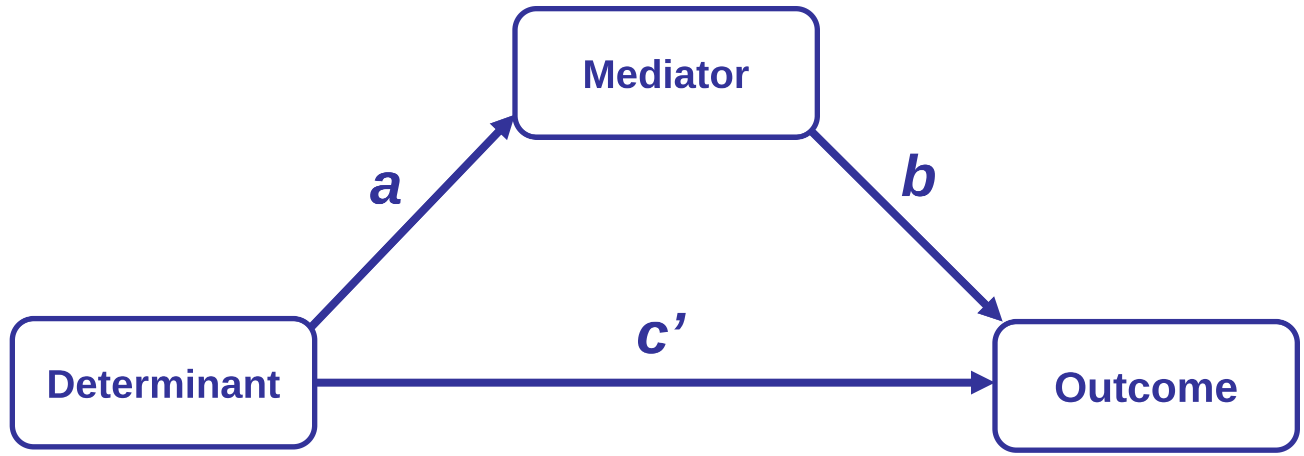
Terminology

Total effect:



Indirect effect:

Direct effect:



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1986: Causal steps method

Journal of Personality and Social Psychology
1986, Vol. 51, No. 6, 1173–1182

0022-3514/86/$00.75

The Moderator–Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations

Reuben M. Baron and David A. Kenny
University of Connecticut

Causal steps method

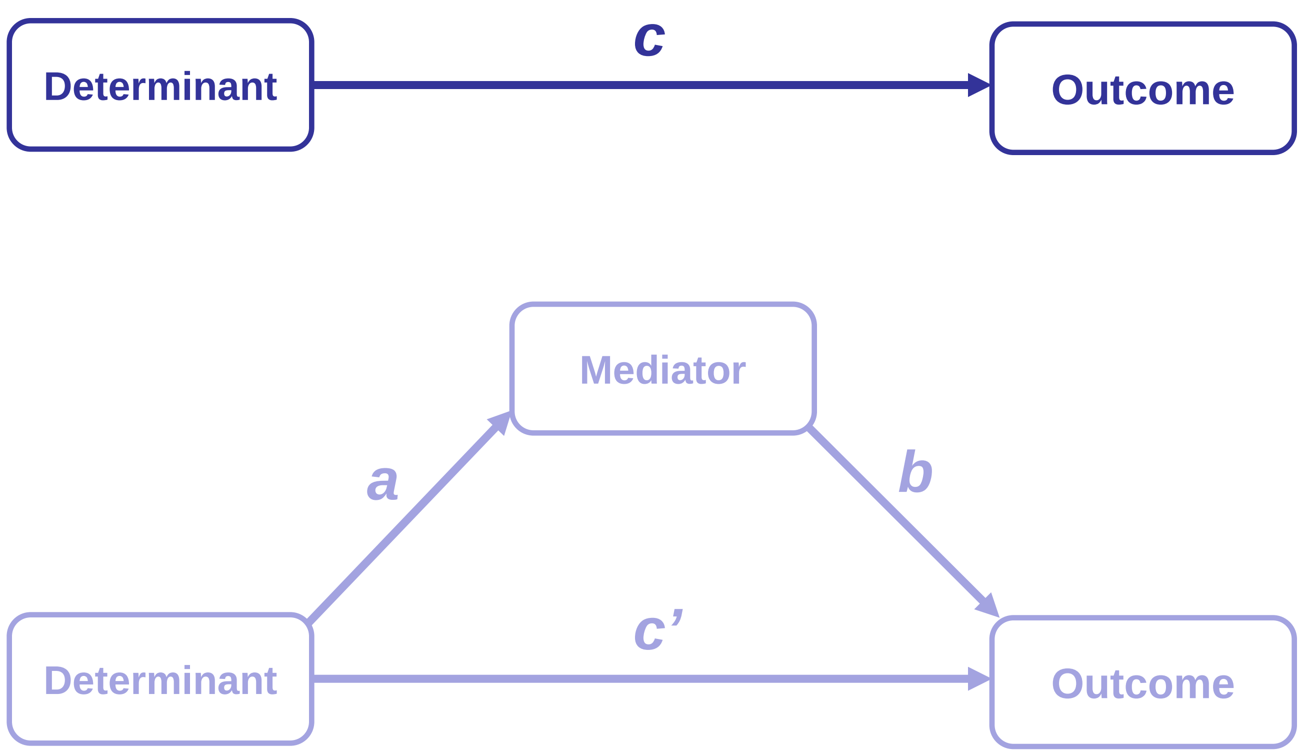
1. Assess significance of the total effect (*c* path)

2. Assess significance of the *a* path

3. Assess significance of the *b* path

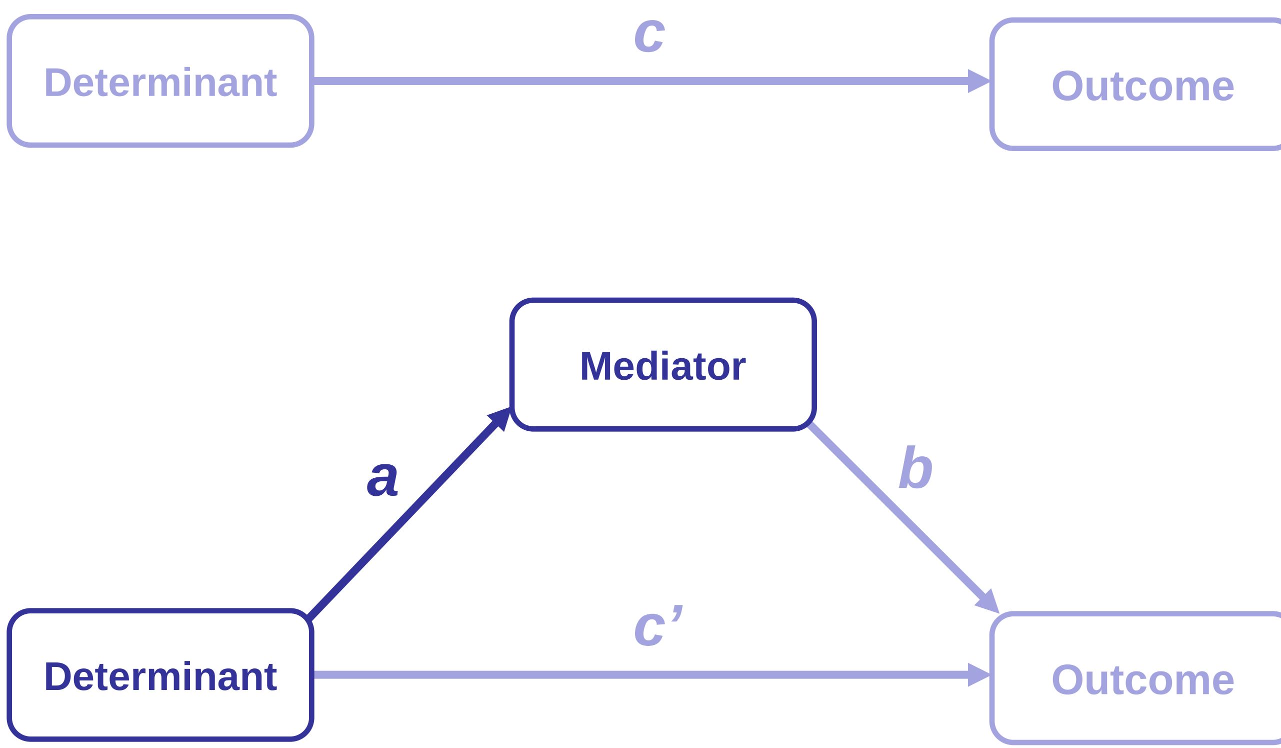
Step 1: significance of the total effect (*c*)

$$Y = i_1 + cX + \varepsilon_1$$



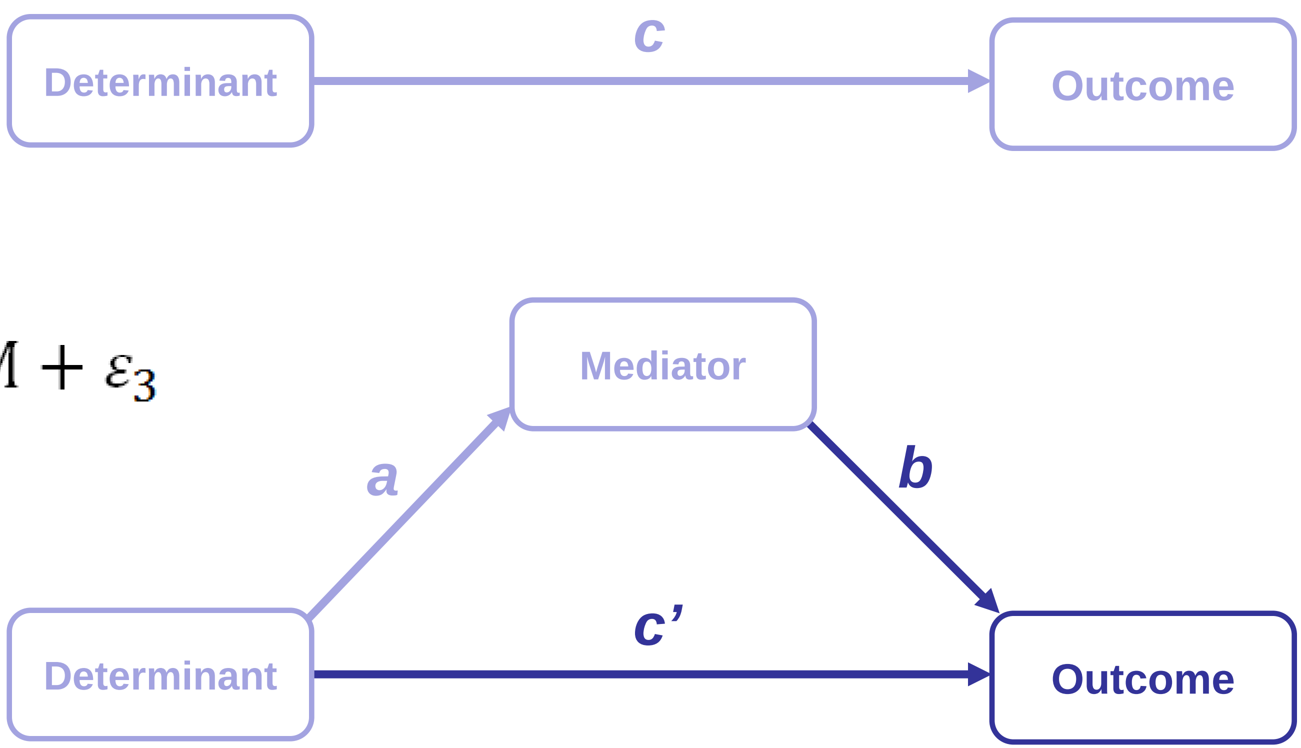
Step 2: significance of the *a* path

$$\mathrm{M} = i_2 + a\mathrm{X} + \varepsilon_2$$



Step 3: significance of the *b* path

$$Y = i_3 + c'X + bM + \varepsilon_3$$



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Example

Does blood pressure mediate the relationship between BMI and carotid distensibility?

Example

Total effect of BMI on carotid distensibility (*c* path)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	36,492	2,383		15,315	,000
	Body mass index in 2000 (kg/m-2)	-,409	,098	-,212	-4,174	,000

a. Dependent Variable: carotid artery distensibility coefficient (10-3/kPa)-(2*diameter*distension+distension^2)/local pulse pressure*diameter^2

Example

Effect of BMI on blood pressure (*a* path)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	57,970	3,202		18,105	,000
	Body mass index in 2000 (kg/m-2)	1,001	,132	,366	7,594	,000

a. Dependent Variable: averaged (brachial) mean blood pressure (mmHg)

Example

Effect of blood pressure on carotid distensibility (*b* path)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	52,637	3,035		17,346	,000
	averaged (brachial) mean blood pressure (mmHg)	-,279	,036	-,393	-7,774	,000
	Body mass index in 2000 (kg/m-2)	-,131	,098	-,068	-1,335	,183

a. Dependent Variable: carotid artery distensibility coefficient (10-3/kPa)-(2*diameter*distension+distension^2)/local pulse pressure*diameter^2

Conclusion

Blood pressure mediates the relationship between BMI and carotid distensibility!

Critique on the causal steps method

- Relies heavily on significance
- No estimate of the mediated effect
- Does not account for inconsistent mediation

Nowadays

Communication Monographs
Vol. 76, No. 4, December 2009, pp. 408–420

Routledge
Taylor & Francis Group

Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium

Andrew F. Hayes

CURRENT DIRECTIONS IN PSYCHOLOGICAL SCIENCE

Current Directions in Mediation Analysis

David P. MacKinnon[1] and Amanda J. Fairchild[2]

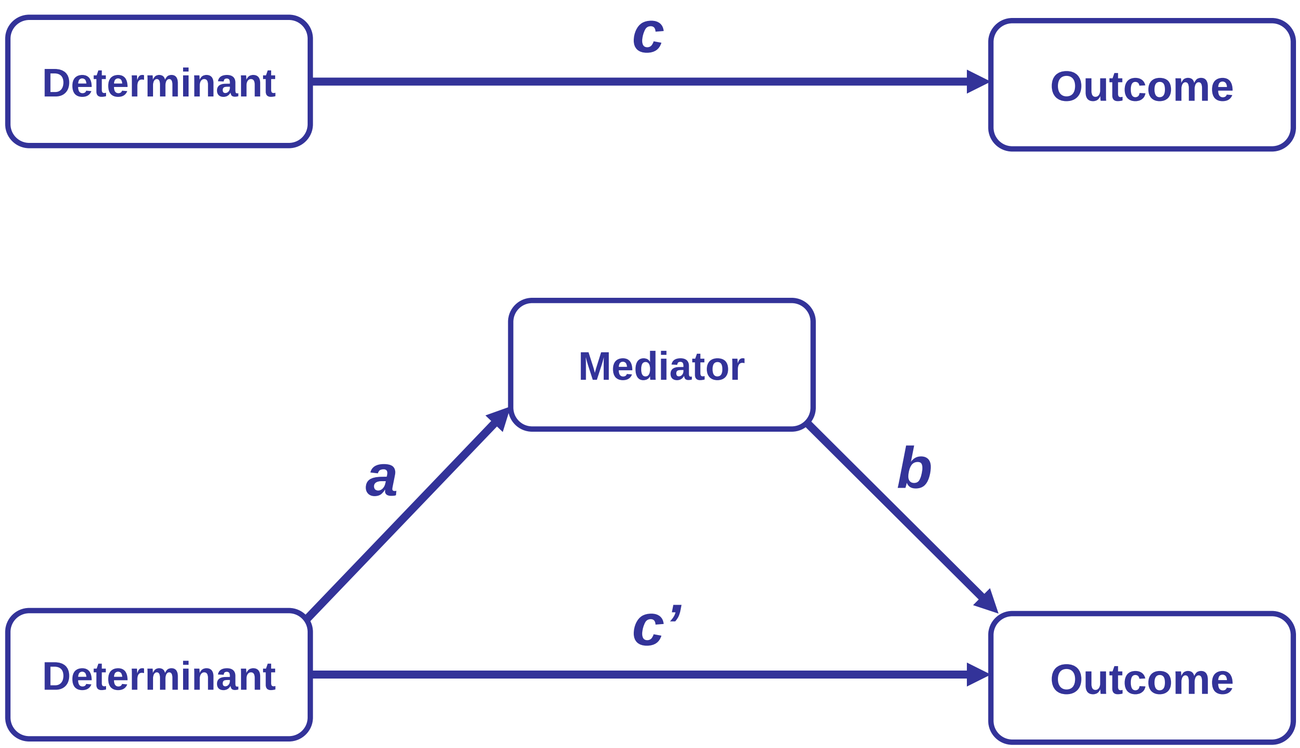
[1]Arizona State University and [2]University of South Carolina

Current practice

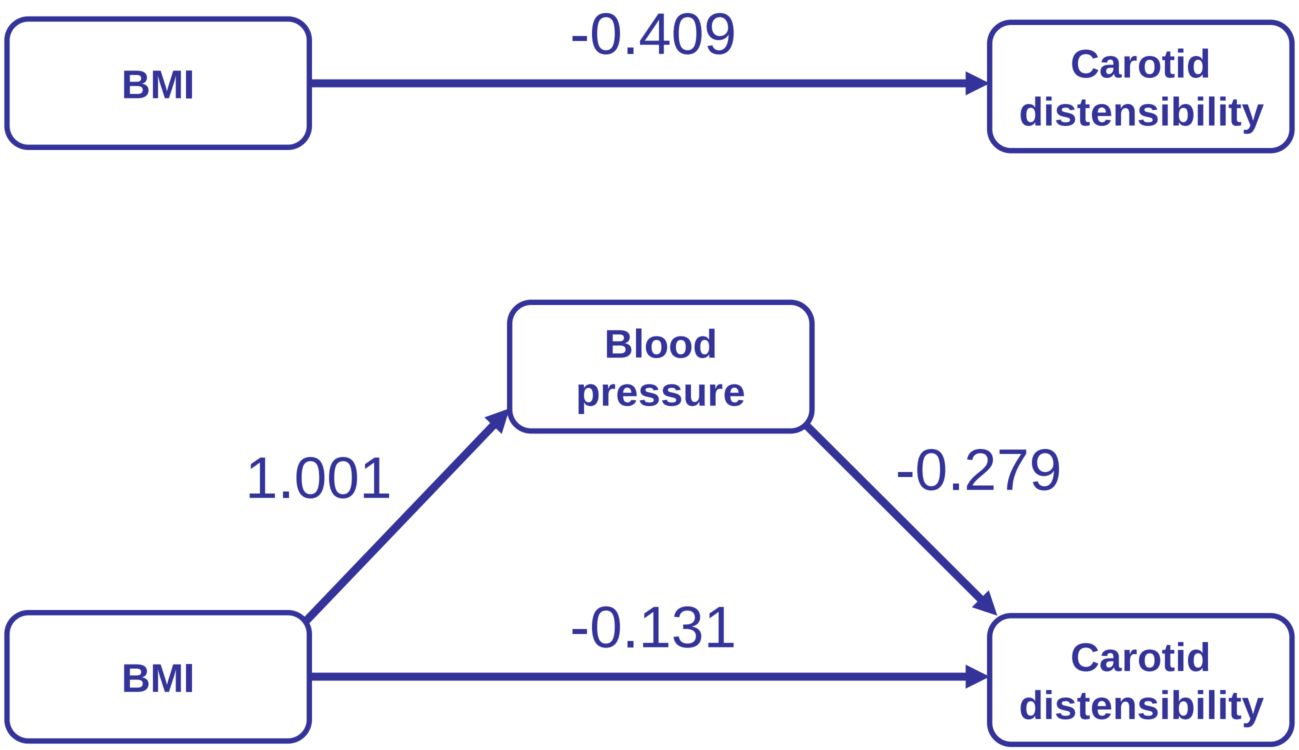
- Calculation of the indirect effect

Indirect effect

- $c - c'$
- $a * b$



Example



$$\boldsymbol{c - c'} = -0.409 - -0.131 = \mathbf{-0.278}$$

$$\boldsymbol{a * b} = 1.001 * -0.279 = \mathbf{-0.279}$$

Example

Summary

Total effect	-0.409
***a* path**	1.001
***b* path**	-0.279
Direct effect	-0.131
Indirect effect	-0.279

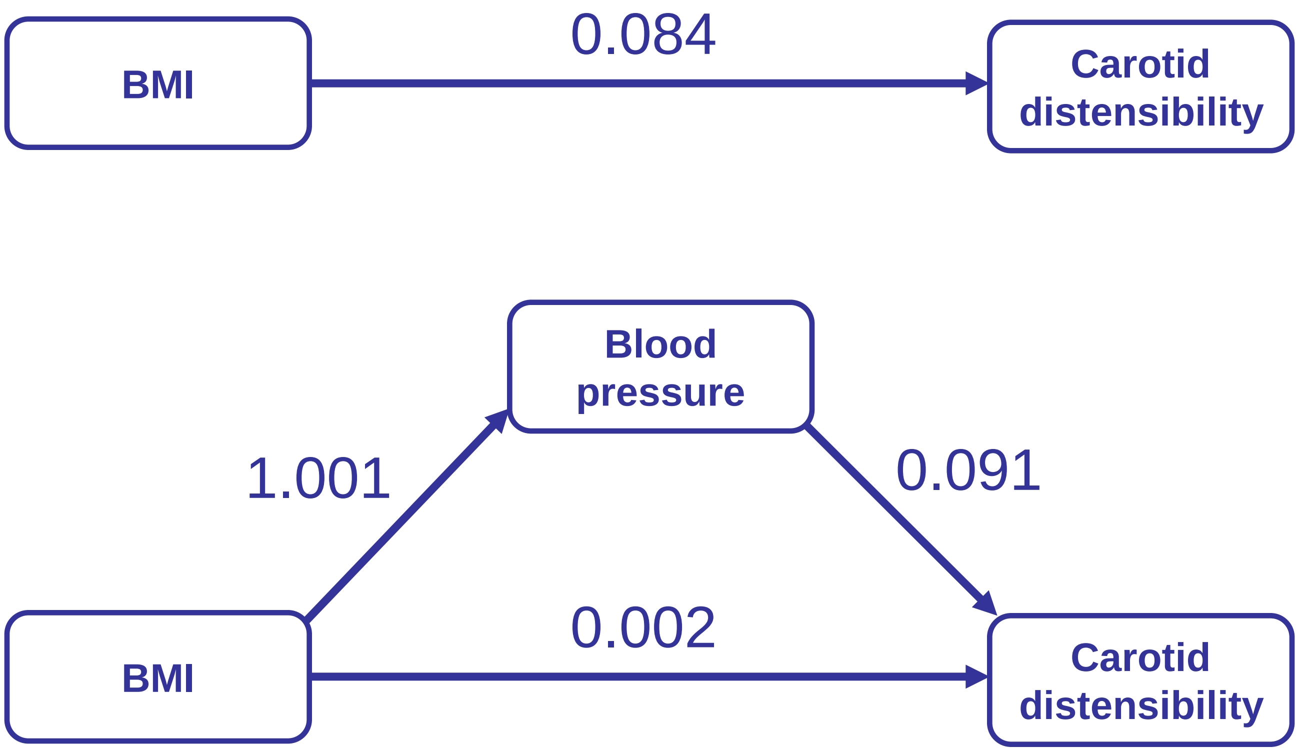
Example – Dichotomous outcome

Does blood pressure mediate the relationship between BMI and carotid distensibility?

Dichotomous carotid distensibility variable, with lowest quartile as cut-off

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal CD	281	75,1	75,1	75,1
	Low CD	93	24,9	24,9	100,0
	Total	374	100,0	100,0	

Example – Dichotomous outcome



c* – *c' = 0.084 – 0.002 = **0.082**

a* * *b = 1.001 * 0.091 = **0.091**

Example – Dichotomous outcome

Indirect effect	
$c - c'$	0.082
$a * b$	0.091

Which estimate to believe?

Variance in regression models

- The scale of the coefficients is influenced by the total variance in the model

- Change in the total variance → change in the coefficients

Linear regression models

Total variance =

explained variance + unexplained variance

- When the explained variance ↑, unexplained variance ↓
- Total variance always remains the same
- Scale of the coefficients will not be influenced

Logistic regression models

Total variance =

explained variance + 3.14

- When the explained variance ↑, unexplained variance remains 3.14
- Total variance changes as the explained variance changes
- Scale of the coefficients will change

Logistic regression models

$\mathrm{Y} = i_1 + c\mathrm{X}$ vs. $\mathrm{Y} = i_3 + c'\mathrm{X} + b\mathrm{M}$

↑ in explained variance

↑ in total variance

↑ of scale of *c'*

***c* – *c'* will be an underestimation**

Example – dichotomous outcome

Indirect effect	
$c - c'$	0.082
a * b	**0.091**

Example – dichotomous outcome

Summary

	Ln(OR)	OR
Total effect *ab+c'*	0.093	1.10
Direct effect *c'*	0.002	1.00
Indirect effect *ab*	0.091	1.10

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Structural Equation Modeling (SEM)

- **Regression like procedure**
- **Multiple regression equations can be calculated simultaneously**
- **The same variable can be both dependent and independent in the same model (in contrast to regression analyses)**
- **Both observed variables and unobserved 'latent' variables (construct as stress or the slope variable in longitudinal models) can be included in the model**
- **SEM Model can be visualized**

Mediation analysis with MPlus

RCT, n=546 schoolchildren
Independent = Group variable
Mediator = Change in sweetened beverages consumption
Outcome = Change in Body Mass Index

```
TOTAL, TOTAL INDIRECT, SPECIFIC INDIRECT, AND DIRECT EFFECTS


                                                        Two-Tailed
                    Estimate       S.E.  Est./S.E.    P-Value

Effects from GROUP to ZRE_BMI

  Total               -0.170      0.086     -1.971      0.049
  Total indirect      -0.025      0.020     -1.244      0.214

  Specific indirect

    ZRE_BMI
    ZRE_SSB
    GROUP             -0.025      0.020     -1.244      0.214

  Direct
    ZRE_BMI
    GROUP             -0.145      0.089     -1.639      0.101
```

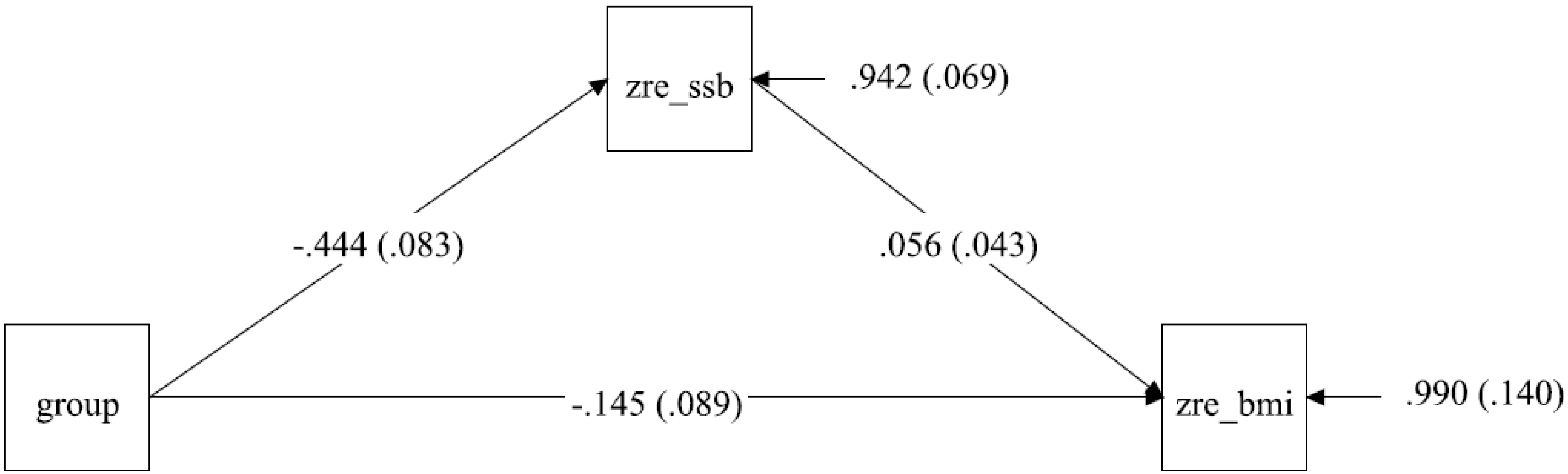
Want to use R: Lavaan package

Mediation analysis with MPlus

```
CONFIDENCE INTERVALS OF TOTAL, TOTAL INDIRECT, SPECIFIC INDIRECT, AND DIRECT EFFECTS


                  Lower .5%  Lower 2.5%   Lower 5%    Estimate    Upper 5%  Upper 2.5%   Upper .5%

Effects from GROUP to ZRE_BMI

  Total             -0.392      -0.339      -0.312      -0.170      -0.028      -0.001       0.052
  Total indirect    -0.076      -0.064      -0.057      -0.025       0.008       0.014       0.026

  Specific indirect

    ZRE_BMI
    ZRE_SSB
    GROUP           -0.076      -0.064      -0.057      -0.025       0.008       0.014       0.026

  Direct
    ZRE_BMI
    GROUP           -0.373      -0.319      -0.291      -0.145       0.001       0.028       0.083
```

Want to use R: Lavaan package

Mplus - Diagram



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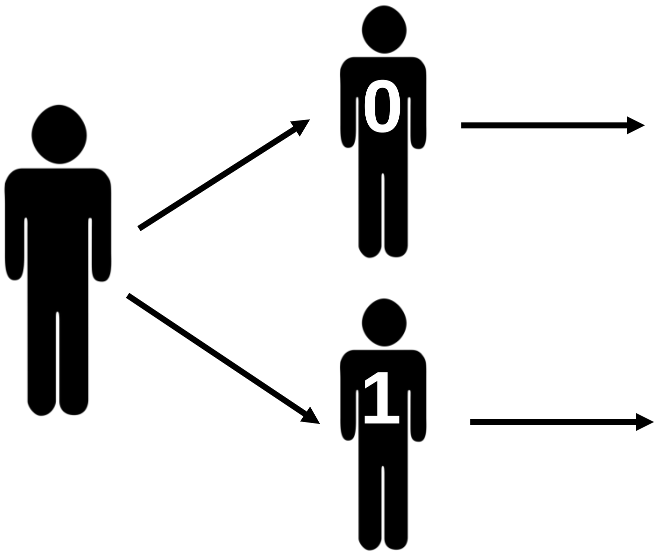
Potential outcomes framework (POF)

- **Estimate Average Causal (Indirect) Effect**
- **Ideal: Potential outcome every person under both determinant (treatment) groups**
- **Observe: Potential outcome of only one determinant (treatment) group**
- **Assumption under POF: Observed = ideal outcome**

Estimating Causal effect



Y(0) **= Estimated outcome under control**

Y(1) **= Observed outcome under treatment**

Average Causal effect = Y(1) – Y(0)

Causal Mediation

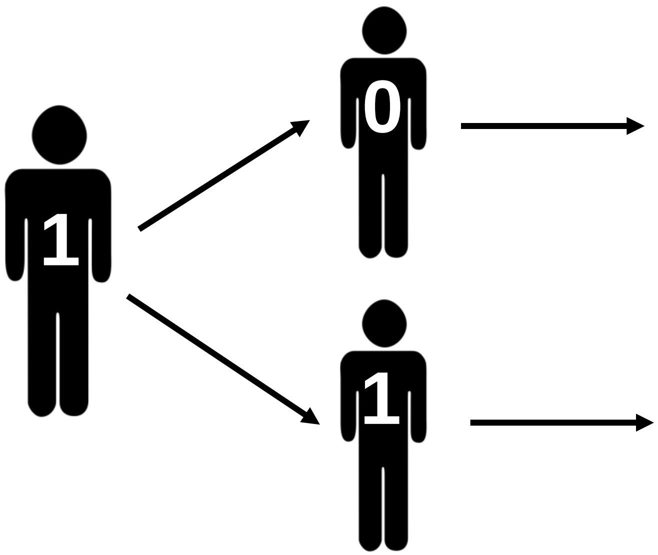
Mediation, defined under the POF framework

Potential outcome depend on Determinant group (e.g. Treatment) and Mediator variable

Causal effects defined in terms of Indirect, Direct and Total effects

R package mediation (Imai et al. 2010)

Causal Mediation effect



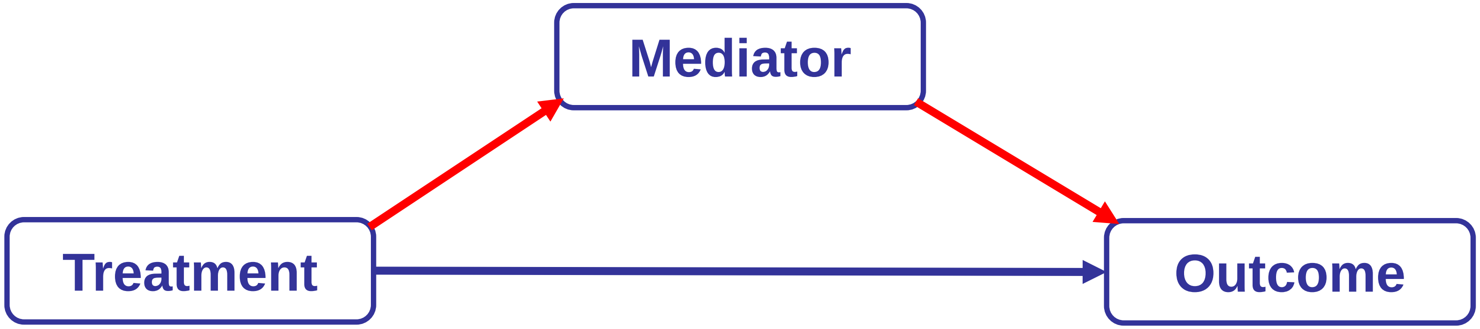
Y(1, M(0)) **= Estimated outcome via mediator, under control**

Y(1, M(1)) **= Observed outcome via mediator, under treatment**

Average Causal Mediation effect = Y(t, M(1)) – Y(t, M(0))

for t=0 and 1

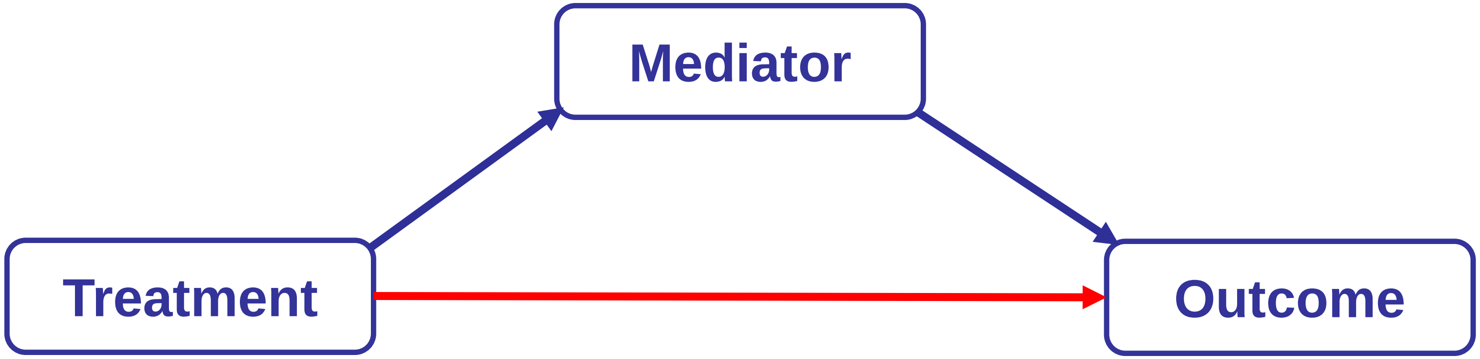
Indirect effect



Indirect effect:

- Part of the effect of the treatment on the outcome via the mediator.
- Difference in the outcome if the treatment categories are kept constant (i.e. direct effect suppressed) and the mediator changes.
- POF: Indirect effect = Y(T=1)M(1) – Y(T=1)M(0)

Direct effect



Direct effect:

- Part of the effect of the treatment on the outcome not via the mediator (i.e. all remaining causal mechanisms).
- Difference in the outcome if treatment changes and the mediator is kept constant.
- POF: Direct effect = Y(1)M(1) – Y(0)M(1)

POF approach

- Indirect effects separately estimated in Treatment (determinant) groups and averaged

- Assumptions (sequential ignorability):
  1. Treatment randomly assigned or wel controlled (adjusted for confounding)
  2. No confounding in Mediator-outcome relationship.

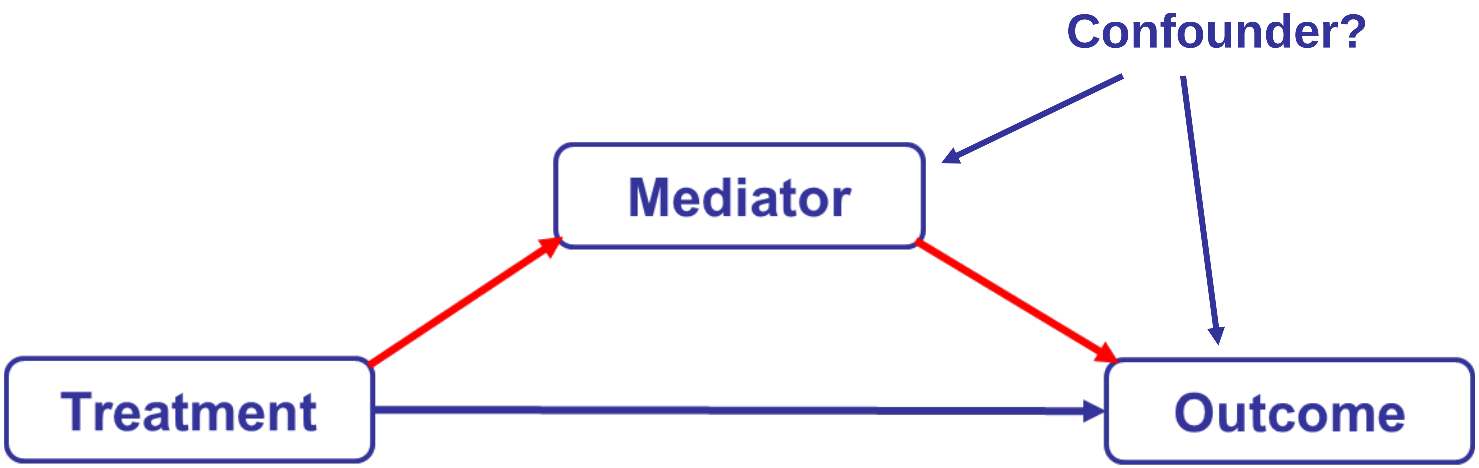
- Advantage POF method:
  – Generalizes easy to models with different types of outcome and mediators as continuous, dichotomous, categorical, non-linear relationships (splines)

Example of Output

```
Causal Mediation Analysis

Nonparametric Bootstrap Confidence Intervals with the Percentile
Method

               Estimate 95% CI Lower 95% CI Upper p-value
ACME            -0.0247      -0.0623         0.01   0.180
ADE             -0.1453      -0.3283         0.03   0.096 .
Total Effect    -0.1700      -0.3480        -0.01   0.048 *
Prop. Mediated   0.1452      -0.1914         0.94   0.212
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Sample Size Used: 546


Simulations: 500

ACME = Average causal mediation effect
ADE = Average direct effect
```

Assumptions (sequential ignorability): No unmeasured confounding

Without adjustment: Also the effect of confounder is estimated in e.g. path b



There is overlap (correlation) between the unexplained variance of model

$$\mathrm{M} = i_2 + a\mathrm{X} + \varepsilon_2$$

and

$$\mathrm{Y} = i_3 + c'\mathrm{X} + b\mathrm{M} + \varepsilon_3$$

Sensitivity analysis, how?

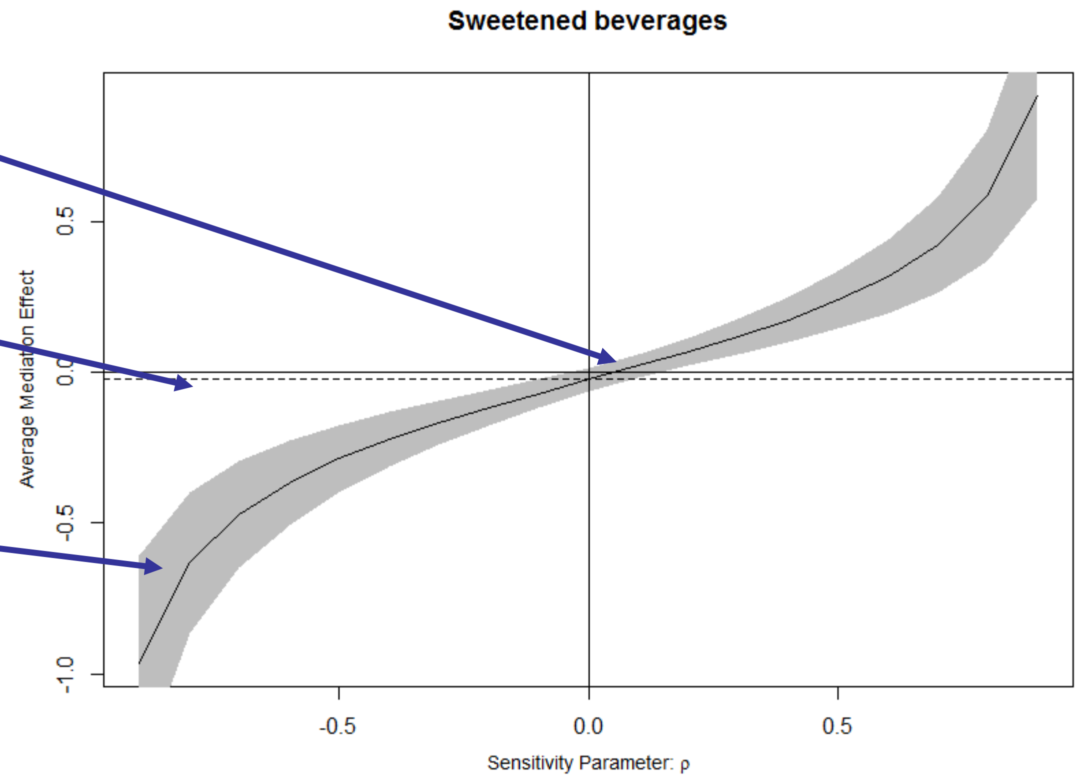
Plot the ACME at different values for the correlation

```
Mediation Sensitivity Analysis for Average Causal
Mediation Effect

Sensitivity Region

      Rho    ACME 95% CI Lower 95% CI Upper
[1,] 0.0 -0.0247      -0.0640       0.0146
[2,] 0.1  0.0211      -0.0179       0.0601
```

ACME < 0 if correlation < 0.1

ACME assumption is met

ACME when correlation varies



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journal homepage: www.elsevier.com/locate/conctc

Comparison of methods for the analysis of relatively simple mediation models

Judith J.M. Rijnhart[a,*], Jos W.R. Twisk[a], Mai J.M. Chinapaw[b], Michiel R. de Boer[c], Martijn W. Heymans[a]

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Summary of SEM vs POF

- **Continuous outcome and mediator, SEM = POF**

- **Dichotomous mediator and outcome variable:**

Preliminary results of a simulation study

- **SEM: product of coefficient method valid**

- **Potential outcomes works best at low incidence rates**

Rijnhart, Twisk, Eekhout, Heymans, 2017 (Submitted)

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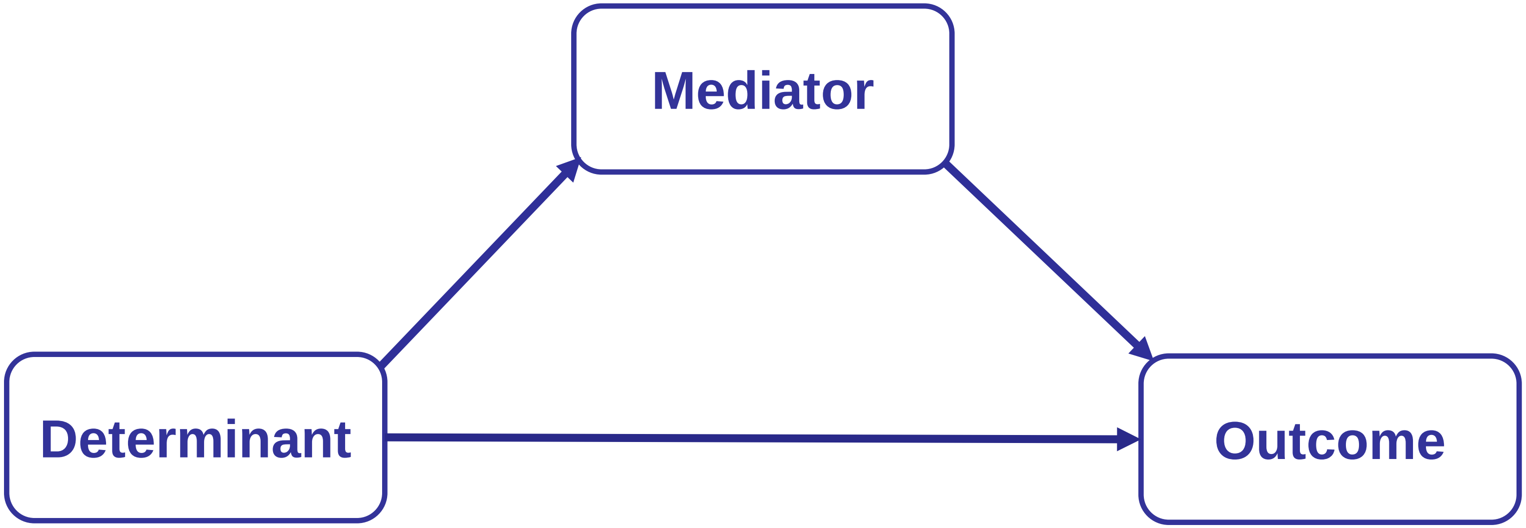
Future topics

- Longitudinal mediation analysis

- Bayesian mediation analysis

Longitudinal mediation analysis



Assumption of temporal precedence

- Determinant precedes mediator
- Mediator precedes outcome

Longitudinal mediation analysis

- MacArthur approach
- Cross-lagged panel model
- Latent growth curve model
- Latent difference score model
- Multilevel model
- Multilevel structural equation model

Longitudinal mediation analysis

- **Current project:** comparing methods using real-life data

- **Future project:** enhancing causality in longitudinal mediation models

(Collaboration with David MacKinnon (Arizona State University))

Bayesian mediation analysis

- Combining data with prior information

- No distributional assumptions (advantageous in small samples)

Bayesian mediation analysis

- **Current project:** comparing frequentist and Bayesian MSEM models

  (Collaboration with Emmanuel Lesaffre (KU Leuven))

EpidM course on mediation analysis

Three-day course on mediation analysis (in Dutch)

- 7, 8 & 9 March 2018
- Lectures & computer practicals
- More information on: www.epidm.nl