Causal Mediation Analysis for Identifying Alternative Intervention Targets

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Outline

- Part I: Introduction of mediation concepts
  - Why should we care about mediation analysis?
  - Some definitions
  - Conceptual difference between conventional and modern approaches to mediation analysis
- Part II: Conducting a causal mediation analysis
  - Steps in causal mediation analysis
  - Explicit assumptions
  - An illustrative example
- Concluding remarks

Why should we care about mediation?

Importance of mediation analysis

- Area of rapid progress in the last 20 years (Robins, Pearl, VanderWeele, etc…)
- Interest in mechanisms and pathways from exposure to outcome
- To understand etiology and gain better etiologic mechanistic insights
- Mediation often associated with interaction
- For intervening (alternative intervention targets): If we believe intervening on the mediator is more feasible or cost-effective than intervening on the exposure
  - To identify and prioritize intervention opportunities (e.g. reducing disparities in education)

Some definitions

What is a mediator?

- If a factor X affects a factor M and M affects an outcome Y, then M mediates (part of) the effect of X on Y.* (M is a mediator)
- Can readily see this using a causal diagram (directed acyclic diagram-DAG)

$$X \longrightarrow M \longrightarrow Y$$

Mediator: Example

DAG 1 DAG 2

<u>Possible indirect effect via education:</u>
Race influences education, which influences financial security risk, medical access, dietary patterns, hypertension risk, vascular disease, and ADRD

<u>Possible direct effect (not mediated by education) :</u>
Race can influence directly ADRD through pathways other than through education

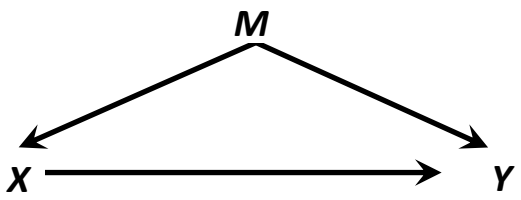
Direct effects are actually effects not meditated by the mediator of interest

ADRD: Alzheimer's disease-related dementia

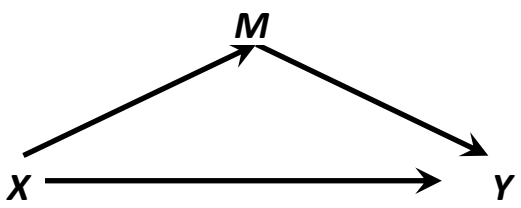
Interaction/Moderation

- When the effect of a factor on a outcome varies across levels of another factor, we can say that the two factors interact with one another (i.e. there is interaction or moderation of the effect by that other factor)
- Also known as effect measure modification or heterogeneity
- Can be estimated using statistical interaction via regression models (i.e. product term)

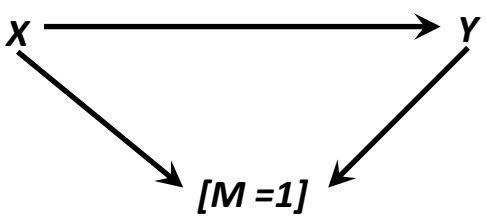
Spot the causal diagram with the mediator



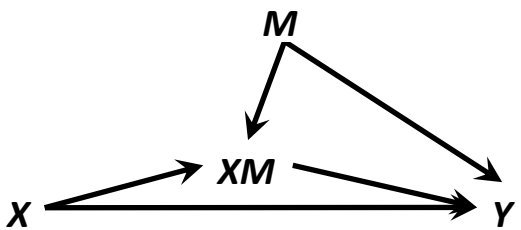
DAG 1



DAG 2

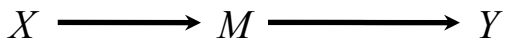


DAG 3



DAG 4

Mediation: possible structures



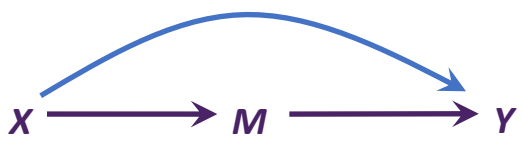
Full mediation

Partial mediation

Conceptual difference between conventional and modern approaches to mediation analysis

Two main approaches

1. Classical "conventional" approach
   a. Product method
      - If an exposure X (e.g. race/ethnicity) affects a mediator M (e.g. educational attainment) and the same mediator M affects an outcome Y (e.g. dementia), then the indirect or mediated effect of A on Y through M is roughly equal to the product of the effect of A on M and the effect of M on Y



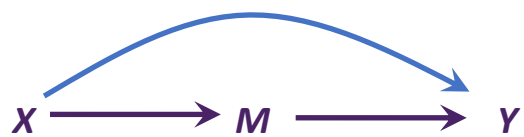
Indirect effect = (Effect of X on M) * (effect of M on Y)

Two main approaches

Classical "conventional" approach

b. Difference method

- If regressions provide evidence for the total effect of an exposure X (e.g. race/ethnicity) on an outcome Y (e.g. dementia) as well as the "direct effect" of X (e.g. race/ethnicity) on an outcome Y (e.g. dementia) controlling for the mediator the mediator M (e.g. educational attainment), then the indirect or mediated effect of A on Y through M is roughly equal to the difference between these effects



Indirect effect = (Effect of X on Y) - (effect of X on Y controlling for M)

Total effect

"so-called direct effect"

Two main approaches

- Dangers and pitfalls
  - These methods (although very popular and pervasive in the social sciences) including the Baron and Kenny (1986) that is based on these techniques can lead to very misleading results including false null results
- Reasons
  - (1) These methods ignore the possibility that the exposure and mediator can interact with one another
  - (2) Threats of collider-stratification bias (selection bias)
  - (3) Uncontrolled confounding
  - (4) other (non-linear models, measurement error of M…)

Two main approaches

2. Modern approach
   - It is based on the counterfactual framework and allows the decomposition of the total effect into natural direct and indirect effects.

Potential outcomes

Exposed Unexposed

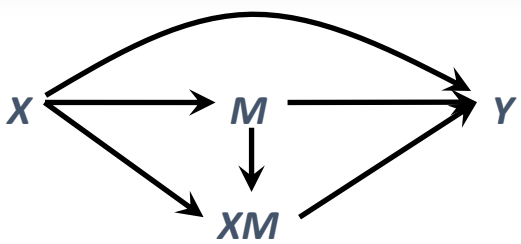
$$\text{Causal Effect} = \underline{Y_1} - \underline{Y_0}$$

Outcome when exposed to a particular treatment or intervention

Outcome when unexposed to that particular treatment or intervention

Neyman, 1923; Rubin, 1974

Decomposition of effects using the modern approach



Example:

X = Adverse childhood experiences (ACE)

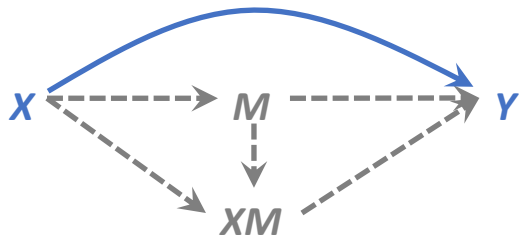
M = Psychological resilience level

Y = Stroke

Decomposition of effects

Four basic effects

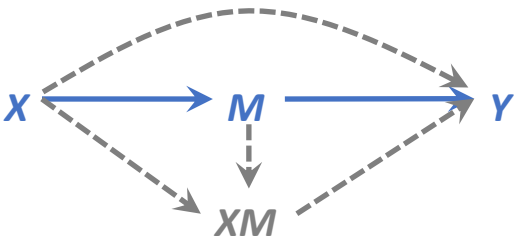
(1)



Control Direct Effect (CDE)
Effect due to neither Mediation nor Interaction

The extent to which X cause Y, when fixing/setting M at a specific value for everyone in the population (i.e. "controlling for M")

(2)



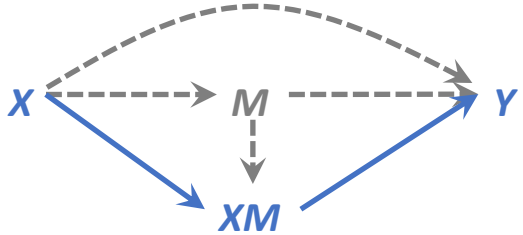
Pure Indirect Effect (PIE)
Effect due to Mediation Only

The extent to which X cause Y via M only

Decomposition of effects

Four basic effects

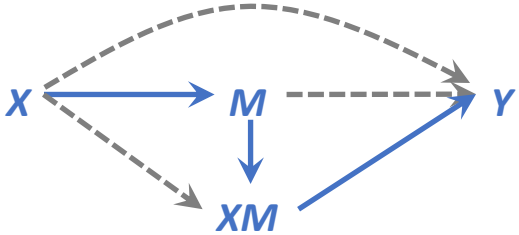
(3)



Reference Interaction Effect (RIE)
Effect due to interaction only but M is not caused by X

The extent to which X cause Y only through its interaction with M

(4)



Mediated Interaction Effect (MIE)
Effect due to mediation and Interaction but M does not cause Y directly

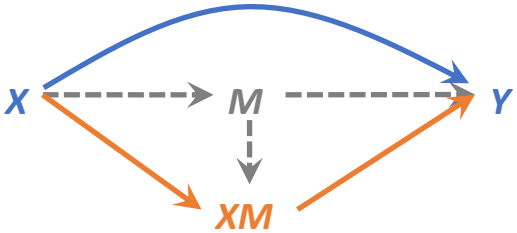
The extent to which X cause Y only through its interaction with M and through the mediation via M

Decomposition of effects

Research question: In particular, to what extent does X cause Y via pathways other than through M?

Effect of interest: Pure Direct Effect (PDE)

DAG:



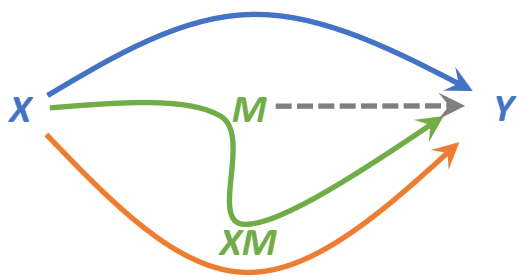
Estimation: Controlled Direct Effect (CDE) + Reference Interaction (RIE)

Decomposition of effects

Research question: In particular, to what extent does X cause Y via pathways other than through M, **but allowing M to boost up or tune down such effect at the same time**?

Effect of interest: Total Direct Effect (TDE)

DAG:



Estimation: Controlled Direct Effect (CDE) + Reference Interaction (RIE) + Mediated Interaction (MIE)

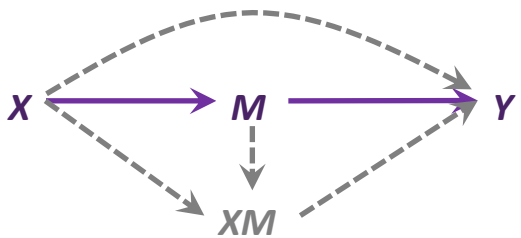
Decomposition of effects

*basic effect

Research question In particular, to what extent does X cause Y via M only?

Effect of interest: Pure Indirect Effect (PIE)*

DAG:



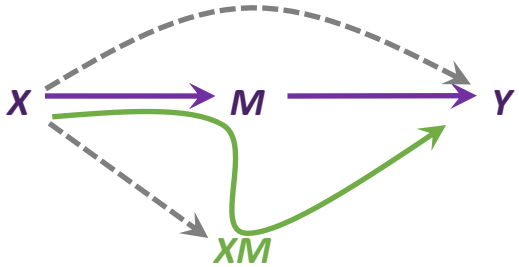
Estimation: Pure Indirect Effect (PIE)

Decomposition of effects

Research question In particular, to what extent does X cause Y via M only, **but allowing M to boost up or tune down such effect at the same time**?

Effect of interest: Total Indirect Effect (TIE)

DAG:



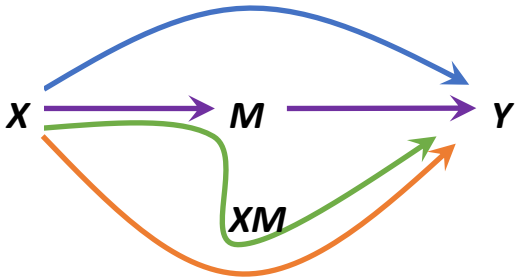
Estimation: Pure Indirect Effect (PIE) + Mediated Interaction (MIE)

Decomposition of effects

Research question: Overall, to what extent does X cause Y?

Effect of interest: Total Effect (TE)

DAG:



Estimation: Controlled Direct Effect (CDE) + Reference Interaction (RIE) Mediated Interaction (MIE) + Pure Indirect Effect (PIE)

Decomposition summary

Decomposition	TE =
Four-way	CDE + RIE + MIE + PIE
Three-way	PDE + MIE + PIE CDE + PAI[a] + PIE
Two-way	PDE + TIE
	TDE + PIE
	CDE + PE[b]
One-way	TE

[a]PE = Portion eliminated: PE = RIE + MIE + PIE
[b]PAI = Portion attributable to interaction: PAI = RIE + MIE

Proportion of the portion eliminated pr_PE = PE/TE where TE = CDE + PE
Proportion mediated: pr_M = TIE/TE where TE = PDE + TIE
Proportion attributable to interaction : pr_PAI = PAI/TE where TE = CDE + PIE + PAI

What if there is no interaction between E x M

PDE = TDE = CDE

&

Conventional method = Modern method*

*if other assumptions are <u>EXACTLY</u> the same
(e.g. linear model, no uncontrolled confounding)

Modern approaches vs conventional approaches

Conventional method	Modern method
Does not typically incorporates the interaction E x M	Explicitly models the interaction between E x M
Assumptions are generally not made or are implicit	Makes explicit assumptions
Typically applies to linear models	Can be extended to non-linear models (e.g. logistic, Poisson regression)
Generally estimates one type of direct effect and one type of indirect effect	Allows estimation of more nuanced effects (e.g. CDE, PDE, TDE, etc…)
Limited/inadequate in more complex scenarios (e.g. time-varying scenarios, multiple mediators)	Can be extended to more complex scenarios when there is time-varying confounding or when there exist multiple (parallel or sequential mediators)

Causal mediation analysis steps

Causal mediation analysis steps

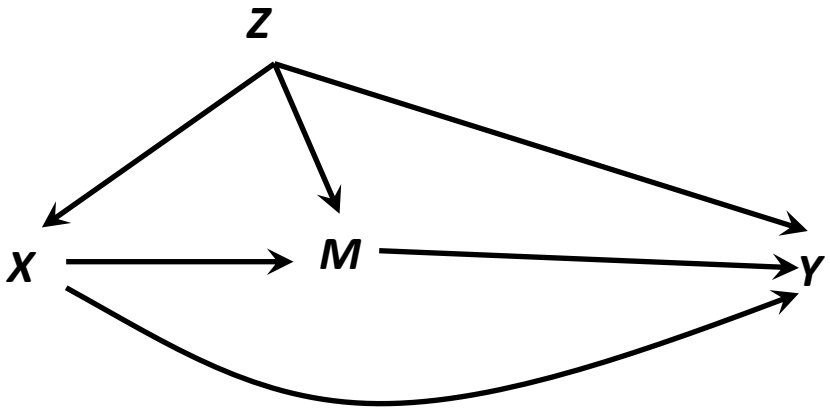
- Multiple methods
  - G-computation
    - Generalization of the standardization method for time-varying exposures and confounders
    - Makes use of regression models + simulation
  - Inverse-Probability of Treatment Weighting (IPTW)
    - Weighting by the inverse of the propensity score
    - Makes use also of regression models
  - Model-based approach
    - Makes use of regression models only

CMA steps via g-computation

Step 1: Obtain the distribution of variables and relevant regression parameters needed for predicting the counterfactual quantities by

1. Getting the appropriate distribution for each variable (exposure, covariates and outcome)
2. Modeling the mediator (*M*) as a function of the exposure (*X*) and covariates (*Z*)
    1. Mediator Model: $E(M|x,z;\ \alpha) = \alpha_M + \alpha_X.x + \alpha_Z.z$
3. Modeling the outcome (*Y*) as a function of the exposure (*X*) and covariates (*Z*)
    1. Outcome Model $E(Y|x,m,z;\ \beta) = \beta_Y + \beta_X.x + \beta_M.m + \beta_{XM}.xm + \beta_Z.z$

ID	X	Z	M	Y
1	1	1	1	.3
2	1	0	2	.45
3	0	0	3	2
4	1	0	3	.26
5	0	1	3	.12
6	1	0	1	.48
7	1	1	1	.18



CMA steps via g-computation

Step 2: Simulate the intervention and the potential mediator and outcome variables by

- Stochastically predicting a new intervention variable, call this *X** ("X star") i.e., an intervention or exposure that is independent of all covariates
  - *X* ~Binomial (Pr(X=1),1)*
- Stochastically predicting the potential mediator *M** using the regression parameters (α) obtained above, the new intervention variable *X** and baseline covariates *Z*.
  - $M^* = \alpha_M + \alpha_X . x^* + \alpha_Z . z + \varepsilon_M$
- Stochastically predicting the potential outcome *Y** using the regression parameters (β) obtained above, the new intervention variable *X**, the new mediator variable *M** and baseline covariates *Z*.
  - $Y^* = \beta_Y + \beta_X . x^* + \beta_M . m^* + \beta_{XM} . x^* m^* + \beta_Z . z + \varepsilon_Y$

Simulating (potential) M

PDE $M_0 = \alpha_M + \alpha_X \cdot 0 + \alpha_Z \cdot z + \varepsilon_M$

TIE $M_x = \alpha_M + \alpha_X \cdot x + \alpha_Z \cdot z + \varepsilon_M$

TDE $M_1 = \alpha_M + \alpha_X \cdot 1 + \alpha_Z \cdot z + \varepsilon_M$

PIE $M_x = \alpha_M + \alpha_X \cdot x + \alpha_Z \cdot z + \varepsilon_M$

Simulating (potential) Y

$$Y_{\text{PDE}} = \beta_Y + \beta_X \cdot x + \beta_M \cdot m_0 + \beta_{XM} \cdot x \cdot m_0 + \beta_Z \cdot z + \varepsilon_Y$$

$$Y_{\text{TIE}} = \beta_Y + \beta_X \cdot 1 + \beta_M \cdot m_x + \beta_{XM} \cdot 1 \cdot m_x + \beta_Z \cdot z + \varepsilon_Y$$

$$Y_{\text{TDE}} = \beta_Y + \beta_X \cdot x + \beta_M \cdot m_1 + \beta_{XM} \cdot x \cdot m_1 + \beta_Z \cdot z + \varepsilon_Y$$

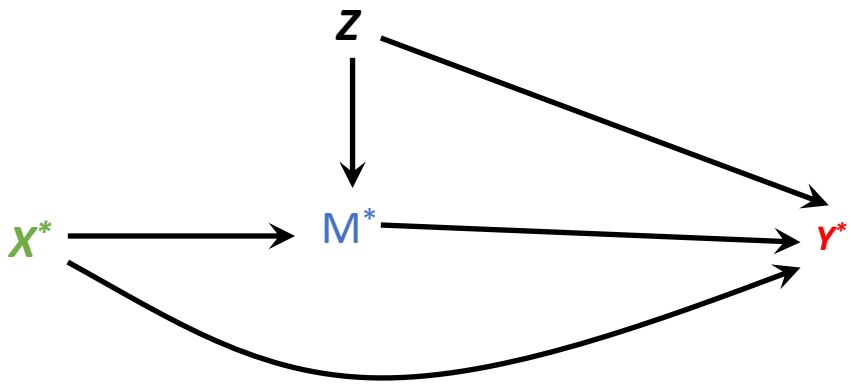
$$Y_{\text{PIE}} = \beta_Y + \beta_X \cdot 0 + \beta_M \cdot m_x + \beta_{XM} \cdot 0 \cdot m_x + \beta_Z \cdot z + \varepsilon_Y$$

CMA steps via g-computation

Step 3: Obtain the point estimate and standard errors by:

- Fitting a marginal structural model for each potential outcome on the new intervention variable
$$Y^* = \theta_Y + \theta_X . x^* + \varepsilon_{Y*}$$
- Using bootstrap to obtain standard errors and the 95% confidence interval by repeating the steps above on 1000 bootstrap samples.

ID	X^*	M^*	Y^*
1	1	1	.4
2	0	1.5	.2
3	1	4	2
4	0	1.5	.3
5	1	2	.12
6	0	0.5	.5
7	1	1	.13



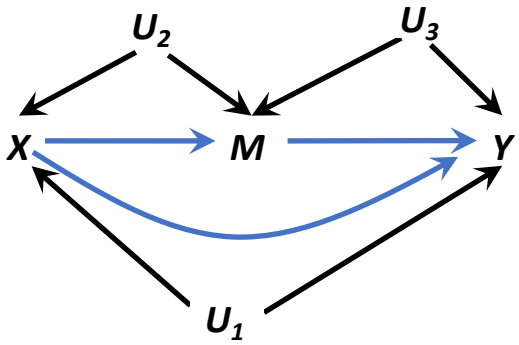
Explicit assumptions

Explicit assumptions

1. No uncontrolled confounding (conditional exchangeability)
   - Subjects in the sample are exchangeable conditional on measured confounders
   - That is, after one has adjusted for the sufficient set of confounders, the treated group and untreated group should be comparable with the exception of the treatment status (e.g. same age structure, same proportion of males, etc…)

Explicit assumptions

1. No uncontrolled confounding
   a) No UC between exposure and outcome (no U_1)
   b) No UC between exposure and mediator (no U_2)
   c) No UC between mediator and outcome (no U_3)

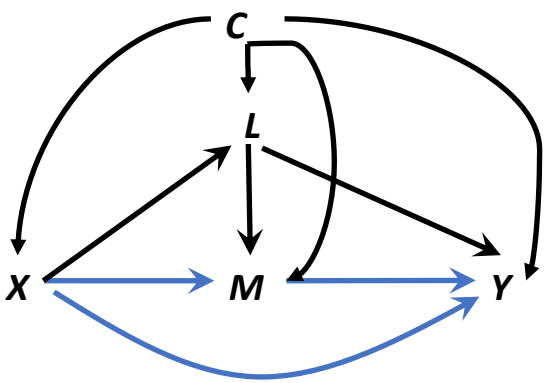


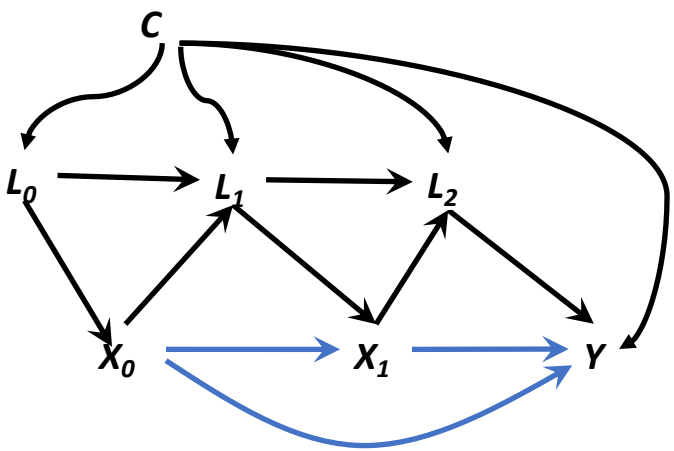
Explicit assumptions

1. No uncontrolled confounding

   d) No exposure-induced mediator-outcome confounder (L)

   - This can occur when we have time-varying covariates as seen below





Vanderweele, Vansteelandt, and Robins 2014

Explicit assumptions

1. No uncontrolled confounding

   d) No exposure-induced mediator-outcome confounder

   - In such case we cannot estimate the different mediated effects using the natural decomposition. However we can estimate mediated effects using special techniques including a path-specific approach

Vanderweele, Vansteelandt, and Robins 2014

Explicit assumptions

2. Positivity (covariate support)

- That is, when we stratify our exposure/intervention by levels of every covariates, there should be no zero cell. In other words, covariate subgroups should have both treated and control units

Assumption violated

	C= 1	C=0
X = 1	30	0
X = 0	20	100

X = 1: Exercising 150 min/week
C = 1: Age group 80+

We need $P(X=0|C=0) \neq 0$

Explicit assumptions

3. Consistency (Treatment irrelevance)
   - For every individual whose exposure status is $X=x$, his potential outcome Y_x under the intervention X=x is equal to his observed outcome
   - That is, the only effect of the intervention on the outcome is due to the intervention alone but not how the intervention is being administered (violated – white coat effect)
4. No interference
   - The potential outcome Y_{ix} for individual i under intervention X=x should not depend whether another individual i' receives treatment X=1 or X=0
   - That is, the potential outcome for an individual should not be affected or affect another individual's exposure or outcome (violated in infectious diseases)
5. No other sources of bias
   - No selection bias,
   - No measurement error,
   - No model form misspecification

An illustrative example

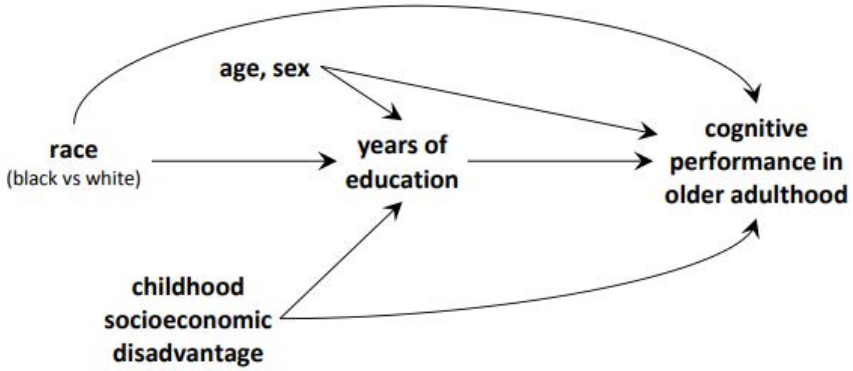
Cognitive Aging in Black and White Americans

Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia

Jennifer Weuve,[a] Lisa L. Barnes,[b] Carlos F. Mendes de Leon,[c] Kumar B. Rajan,[d] Todd Beck,[d] Neelum T. Aggarwal,[b] Liesi E. Hebert,[d] David A. Bennett,[b] Robert S. Wilson,[b] and Denis A. Evans[d]

To what extent years of education explains the Black-White disparity in cognitive performance?

eFigure 2. Causal directed acyclic graph illustrating hypothesized relation of race to cognitive performance, partially mediated through years of education, along with causal roles of key covariates in the mediation analyses.



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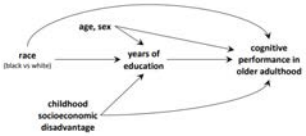

Effects		Adjusted Mean Difference in baseline cognitive scores
Total effect (TE)	Estimated effect of race (black compared with white) on cognitive performance through all causal pathways	−0.69 (−0.73, −0.65)
Direct Effect (PDE)	Estimated effect of race (black compared with white) on cognitive performance through pathways other than those involving years of education	−0.45 (−0.49, −0.41)
Controlled direct effect (CDE)	Estimated effect of race (black compared with white) on cognitive performance under the scenario in which everyone attains the same specified years of education = 12 years	−0.57 (−0.62, −0.53)
Pr_PE	Proportion of effect eliminated by setting years of education to specified level = 12 years	17%
Indirect Effect* (TIE)	Estimated effect of race (black compared with white) on cognitive performance through pathways involving years of education	-0.24*
Pr_M*	Proportion mediated through education: pr_M = TIE/TE*	35%*

*approximated

Concluding remarks

Concluding remarks

- Mediation modeling is essential for understanding and quantifying mechanisms and pathways from an exposure to an outcome
- Critical in disparities research
- Importance in helping identify alternative and perhaps more feasible/cost-effective targets
- The intuition is straightforward, but it is important to understand the quantities of interests and assumptions
- Recent work expresses mediation in terms of counterfactual contrasts and software now offers an easy implementation of the method

References and Additional resources

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- Shi, Choirat, Coull, VanderWeele, Valeri. CMAverse: A Suite of Functions for Reproducible Causal Mediation Analyses. Epidemiology 2021

Additional resources

CMAverse: a suite of functions for causal mediation analysis

About the Package

The R package `CMAverse` provides a suite of functions for reproducible causal mediation analysis including `cmdag` for DAG visualization, `cmest` for statistical modeling and `cmsens` for sensitivity analysis.

See the package website for a quickstart guide, an overview of statistical modeling approaches and examples.

Cite the paper: CMAverse a suite of functions for reproducible causal mediation analyses

We welcome your feedback and questions (email bs3141@cumc.columbia.edu)!

https://bs1125.github.io/CMAverse/

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Thank you

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