Options for Modern Mediation Analyses of Occupational Contributions to Racial/Ethnic Health Disparities

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The Role of Work in Health Disparities in the US

September 28th, 2020
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National Institute on Minority Health & Health Disparities (NIMHD)
WebEx Virtual Meeting

Why is epidemiology so hard? Lots of things to figure out:

1) Figure out what causal parameter you want to know.

2) Figure out how to estimate this parameter from data.

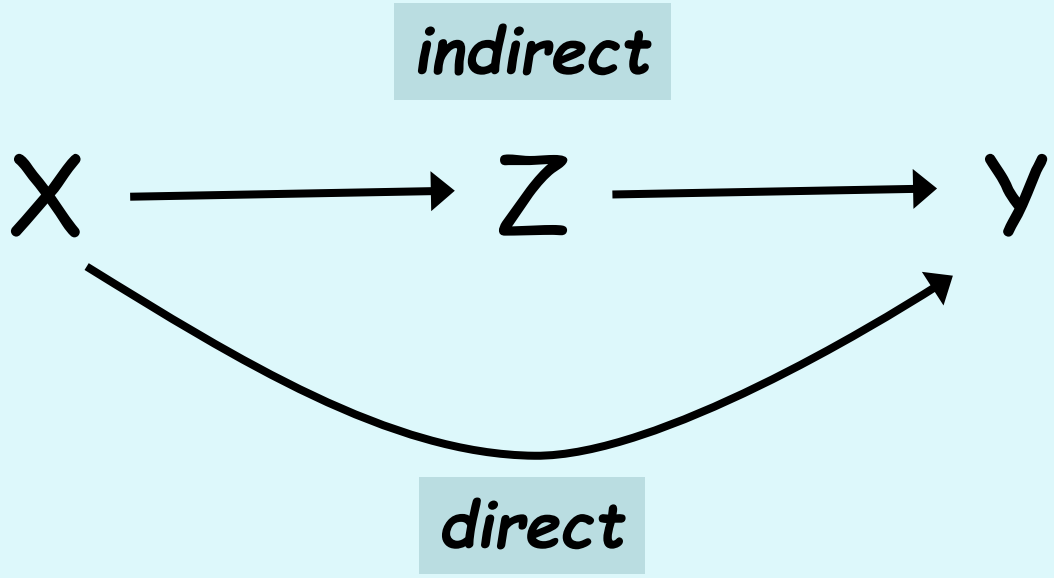
3) Figure out if such data exists and how to get it.

4) Figure out how far off from the truth you might be due to improprieties such as unmeasured confounding.

5) Figure out how to interpret this estimated parameter and its associated uncertainty in terms of some (public health) policy decision.

All of these challenges that apply once for simple effects are DOUBLED for decomposition, therefore making it twice as hard as estimating standard effect parameters

Effect Decomposition and Mediation



Total/Net Effect
Controlled Direct Effect
Natural/Pure Direct/Indirect Effects
Interventional Effects
Decomposition of Disparities
2, 3 and 4-way decompositions

Counterfactual Contingency Table (Copas 1973, G & R 1986):

Type	X=1	X=0	
1	1	1	"Doomed"
2	1	0	"Causative"
3	0	1	"Preventive"
4	0	0	"Immune"

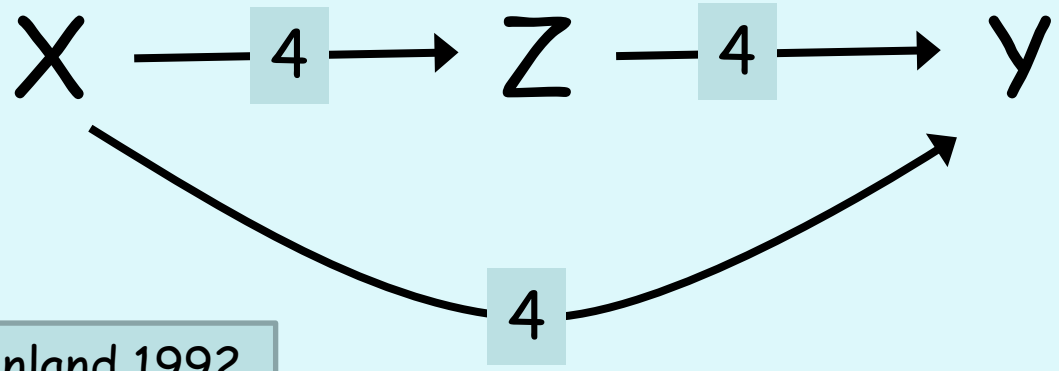
Hence **4** potential outcomes types for causal effect of binary X on binary Y

In principle, however, for the simplest mediation problem (the effect of binary X on binary Y partially mediated by binary Z) there are **64** possible response types

4 x 4 = 16 interdependence types between X and Z with respect to Y (Greenland and Poole 1988)

within each of four possible causal relations between X and Z (Greenland & Robins 1986).

4 x 4 x 4 = 64



Robins & Greenland 1992

Definitions and Notation

The potential outcome distribution of Y under controlled interventions on the treatment X is Pr(Y=1|SET[X=x]) (Pearl 1995)

The "SET" function represents atomistic external intervention, over-ruling the natural processes by which X would take its value according to the causal DAG.

EFFECT A causal effect of X is some contrast between the distributions of outcome Y under two or more intervention regimes. For example, two common contrasts are the risk difference contrast:

$$\Pr(Y=1|SET[X=1]) - \Pr(Y=1|SET[X=0])$$

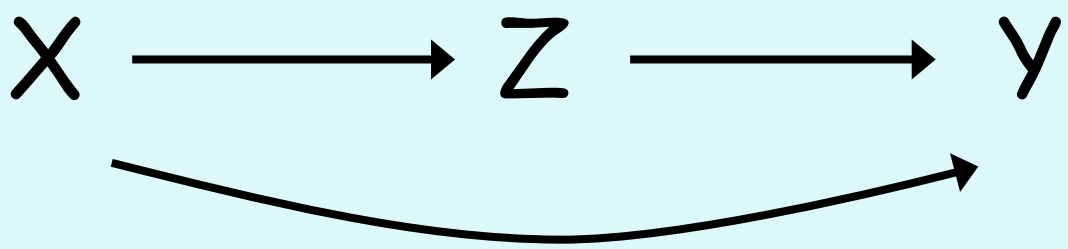
and the risk ratio contrast

$$\Pr(Y=1|SET[X=1]) / \Pr(Y=1|SET[X=0]).$$

A causal effect is considered to be ***identifiable*** if the probability distribution of the outcome *Y* can be expressed as a function of the observed values of putative cause *X* and covariates *Z* (Pearl 1997).

When no adjustment is made for factors that are affected by treatment of interest *X*, this contrast is described as the **TOTAL EFFECT** or **NET EFFECT***, because it includes all pathways (mechanisms) from *X* to *Y*.

Total Effect of X on Y



*from Old Italian *netto*, meaning "remaining after deductions"

CONTROLLED DIRECT EFFECT

The controlled direct effect of X is that effect obtained when intermediate variables Z are manipulated to be held constant:

$$\Pr(Y=1|SET[X=1],SET[Z=z]) - \Pr(Y=1|SET[X=0],SET[Z=z])$$

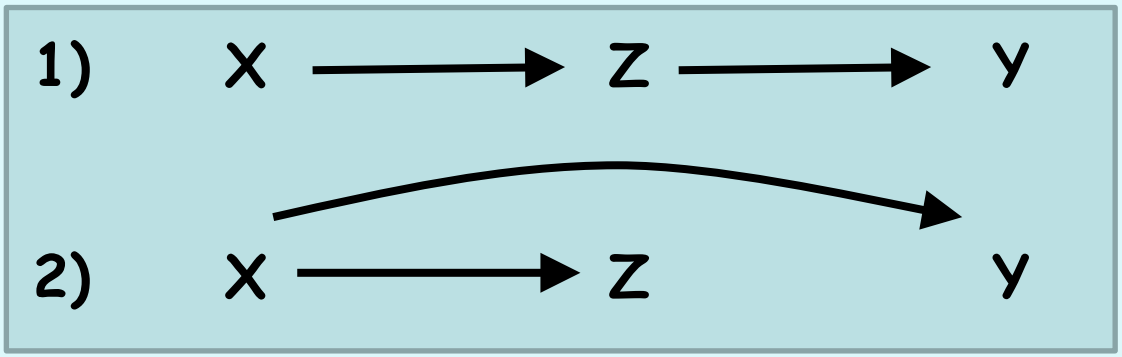
or

$$\Pr(Y=1|SET[X=1],SET[Z=z]) / \Pr(Y=1|SET[X=0],SET[Z=z]).$$

Notes:

1) Must select a mode of contrast (e.g. difference vs ratio)
2) Must select a level of Z at which to make the contrast
3) Heterogeneity of CDE across levels of Z implies an interaction between X and Z in the scale of the model
4) CDE can be defined algebraically, but is not necessarily identified from observed data
5) No controlled indirect effect in a non-parametric model

Identification



Indirect Effect

Direct Effect

Makes it very clear that Z and Y must be unconfounded to distinguish direct from indirect effects.

Decomposition

Deficiency of the CDE in non-parametric models is that the total effect does not necessarily decompose additively.

Implication is that in general, you cannot sum direct + indirect to get total (because of interaction between X and Z).

B & K assumes no additive scale interaction between X and Z

Solution to the decomposition problem (2001):

For the ***controlled* direct effect**, the intermediate is manipulated to a specifically defined value (i.e. physical control of intermediate Z to z).

For the **natural (pure) direct effect**, intermediate is assigned to take whatever value it *would have* taken in the absence of exposure:

$$\Pr(Y=1|SET[X=1],SET[Z=z_{x=0}]) - \Pr(Y=1|SET[X=0],SET[Z=z_{x=0}])$$

This definition does allow for the effect decomposition to hold more generally, and gives rise to additional effect contrasts and to decomposition of interactions.

Big **advantage** of the NDE/NIE formulation is that it permits decomposition. Even if there is heterogeneity across Z strata, one can interpret the estimates as the proportion of the total effect of X relayed through Z.

For binary treatment X and X=0 as reference value:

NDE = $Pr(Y=1|SET[X=1],SET[Z=z_0]) - Pr(Y=1|SET[X=0],SET[Z=z_0])$
NIE = $Pr(Y=1|SET[X=0],SET[Z=z_1]) - Pr(Y=1|SET[X=0],SET[Z=z_0])$
TDE= $Pr(Y=1|SET[X=1],SET[Z=z_1]) - Pr(Y=1|SET[X=0],SET[Z=z_1])$
TIE= $Pr(Y=1|SET[X=1],SET[Z=z_1]) - Pr(Y=1|SET[X=1],SET[Z=z_0])$

e.g., Hafeman DM. "Proportion explained": a causal interpretation for standard measures of indirect effect? AJE 2009; 170(11): 1443-8.

"proportion explained" = (NIE / RD) (i.e. indirect effect for unexposed)
"proportion explained" = (TIE / RD) (i.e. indirect effect for exposed)

see also:

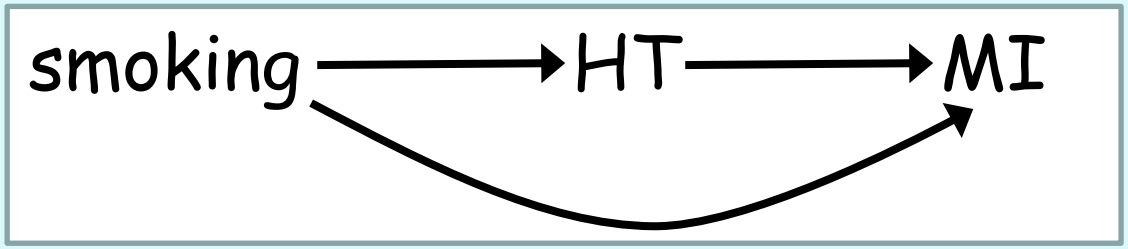
Hafeman DM, Schwartz S. Opening the Black Box: a motivation for the assessment of mediation. Int J Epidemiol. 2009;38(3):838-45.

Even though it more readily allows for effect decomposition in the presence of interaction, the natural/pure approach has some substantial **deficiencies**.

1) Intermediate Z manipulated to an unobserved value
2) Robins (2002) asserted that the NDE/NIE have no possible relevance to public health intervention or policy
3) Natural effects can't be verified in experiments or trials
4) $Pr(Y=1|SET[X=1], SET[Z=z_0])$ can **never** be observed
5) Contradicts "well-defined exposure" (Hernán 2008, 2016)
6) For identification, requires no X-Z confounding

Controversy:

Pearl (2001) suggested a physical intervention that he proposed would correspond to a NDE



Robins & Richardson (2012) disputed the manipulation-based interpretation of the NDE in Pearl's example, and concluded that if you think you can describe an intervention that corresponds to a NDE, you are actually describing a CDE on a hidden node.

Robins JM, Richardson TS. Alternative graphical causal models and the identification of direct effects. In: Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures. P. Shrout, Editor. Oxford University Press, 2012.

Regression formulations now widely available in SAS, Stata, R:

Valeri, L. and VanderWeele, T.J. Psychological Methods 2013; 18(2): 137-150.

VanderWeele TJ. Explanation in Causal Inference. NY: Oxford Univ Press, 2015.

For example, for exposure X, continuous intermediate Z, continuous outcome Y and covariate C, regression models:

$$E(Z|X=x, C=c) = \beta_0 + \beta_1 x + \beta'_2 c$$

$$E(Y|X=x, Z=z, C=c) = \theta_0 + \theta_1 x + \theta_2 z + \theta_3 xz + \theta'_4 c$$

allow the estimated coefficients from the models to be used to calculate controlled and natural/pure direct effects for a change from x* to x:

Controlled Direct Effect of X: $(\theta_1 + \theta_3 m)(x - x^*)$

Natural/Pure Direct Effect of X: $(\theta_1 + \theta_3\beta_0 + \theta_3\beta_1 x^* + \theta_2\beta'_2 c)(x - x^*)$

Natural/Pure Indirect Effect of X: $(\theta_2\beta_1 + \theta_3\beta_1 x)(x - x^*)$

The cross-world counterfactual Y[x,Z(x∗)] is visible in these equations in the form of a linear combination of parameters involving both mutually incompatible worlds:

Natural/Pure Direct Effect of X: $(\theta_1 + \theta_3\beta_0 + \theta_3\beta_1 x^* + \theta_2\beta'_2 c)(x - x^*)$

Natural/Pure Indirect Effect of X: $(\theta_2\beta_1 + \theta_3\beta_1 x)(x - x^*)$

x comes from world 1

x* comes from world 2

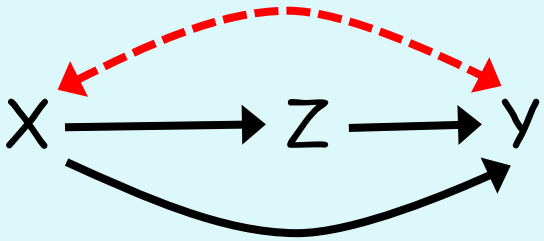
Formula simultaneously includes the exposure that would be observed in world 1 and the exposure that would be observed in separate and logically incompatible world 2.

Nothing wrong with this in a mathematical sense, and the identification of this effect follows from the standard NPSEM assumptions of Pearl's DAGs.

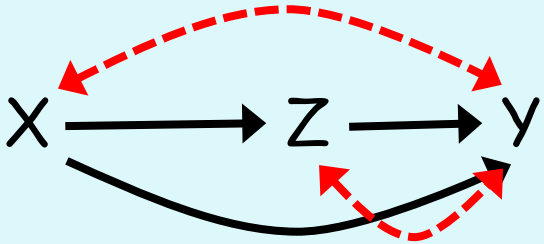
But is this any more than a mathematical abstraction without meaningful correspondence to the real world? We estimate these quantities without any empirical evidence in support or against our beliefs about their meaning, since the beliefs can never be confirmed or refuted with observed data.

Threats to valid estimation from data:

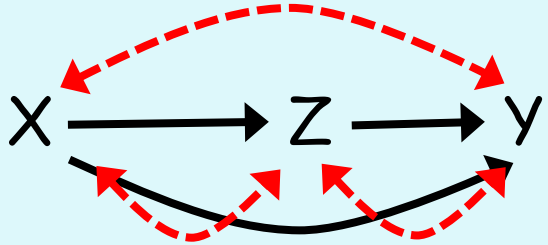
Total/Net Effects:

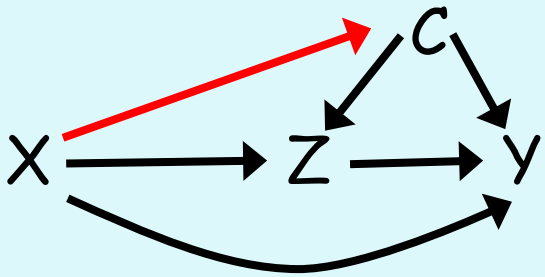


Controlled Effects:
(CDE)

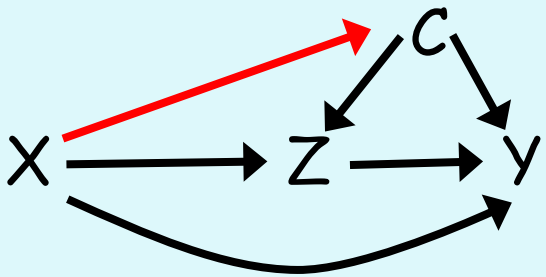


Natural/Pure Effects:
(NDE/NIE)





Sensitivity analysis approaches (VanderWeele Epidemiology 2010) are helpful in exploring violations of these conditions.



Measured covariate C has been called the "recanting witness" because the exposure variable "tries to have it both ways" or "changes it's story" (Avin et al 2005, Shpitser 2013).

In the last 5 years, researchers have found some ways around this:

"Interventional Effects" (Tchetgen Tchetgen & Vanderweele, 2014)

Let $G_{x|C}$ be a random draw from the distribution of the mediator among the exposed (X=x) conditional on C.

Let $G_{x^*|C}$ be a random draw from the distribution of the mediator among the unexposed (X=x*) conditional on C.

Then $E[Y_{xGx|C}]-E[Y_{xGx^*|C}]$ is the effect on Y of randomly assigning an exposed person a value of the mediator from the mediator distribution among the exposed versus the unexposed (given covariates); this is an effect through the mediator, analogous to the NIE.

"Interventional Effects"

Next consider $E[Y_{xGx^*|C}]-E[Y_{x^*Gx^*|C}]$; this is a direct effect comparing exposured versus unexposed with the mediator in both cases randomly drawn from the distribution of the unexposed population (~NDE)

Finally, $E[Y_{xGx|C}]-E[Y_{x^*Gx^*|C}]$ compares Y when exposed and mediator randomly drawn from the exposed distribution to Y when unexposed and mediator randomly drawn from the unexposed population (~ Total Effect)

This third effect is always the sum of the first two:

$$E[Y_{xGx|C}]-E[Y_{x^*Gx^*|C}] = E[Y_{xGx^*|C}]-E[Y_{x^*Gx^*|C}] + E[Y_{xGx|C}]-E[Y_{xGx^*|C}]$$

TOTAL = DIRECT + INDIRECT

Not exactly natural effects, but very similar in interpretation.

And led to a very attractive application:

For studying racial disparities, these interventional effects make more sense:

We want to know how a racial disparity would change if minority group had the same occupational distribution as the majority group.

Interventional effects make more sense here, because instead of assigning a specific value to Z (CDE), estimation is premised on the mediator having the same distribution in both groups.

Also avoids the awkward notion of assigning race. Rather, consider observed disparity under a hypothetically different mediator.

VanderWeele and Robinson 2014
Naimi et al 2016

Interaction Decompositions

3-way (VanderWeele 2013)

$$(Y_{1Z1} - Y_{0Z0}) = (Y_{1Z0} - Y_{0Z0}) + (Y_{0Z1} - Y_{0Z0}) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(Z_1 - Z_0)$$

Total Effect = Pure Direct + Pure Indirect + RERI $\times$ (X→Z)

4-way (VanderWeele 2014)

$$Y_1 - Y_0 = (Y_{10} - Y_{00}) + \quad \text{CDE}_0$$
$$(Y_{11} - Y_{10} - Y_{01} + Y_{00})(Z_0) + \quad \text{INT}_{ref}$$
$$(Y_{11} - Y_{10} - Y_{01} + Y_{00})(Z_1 - Z_0) + \quad \text{INT}_{med}$$
$$(Y_{01} - Y_{00})(Z_1 - Z_0) \quad \text{PIE}$$

INT_{ref} is an interaction term that only "turns on" when Z would be present in the absence of X (i.e. $Z_0 = 1$)

INT_{med} is the same additive interaction multiplied by $(Z_1 - Z_0)$, so it only "turns on" when X has an effect on Z.

PIE is the effect of Z in the absence of X, multiplied by $(Z_1 - Z_0)$, and so also only "turns on" when X has an effect on Z.

If X affects outcome for a particular individual, then at least one of four things must be the case.

$$TE = CDE_0 + INT_{ref} + INT_{med} + PIE$$

1) X might affect Y through pathways that don't require Z (i.e. X affects Y even when Z is absent).

2) X might operate only in the presence of Z (i.e. there is an interaction). It could be that the X is not necessary for Z to be present, but that Z is necessary for X to have effect on Y.

If X affects outcome for a particular individual, then at least one of four things must be the case. (cont.)

$$TE = CDE_0 + INT_{ref} + INT_{med} + PIE$$

3) X effect might operate only in the presence of Z (i.e. there is an interaction). It could also be that X is needed for Z to be present (i.e. X causes Z, and presence of Z is necessary for X to have an effect on Y).

4) Could be that Z can cause Y in the absence of X, but X is necessary for Z to be present.

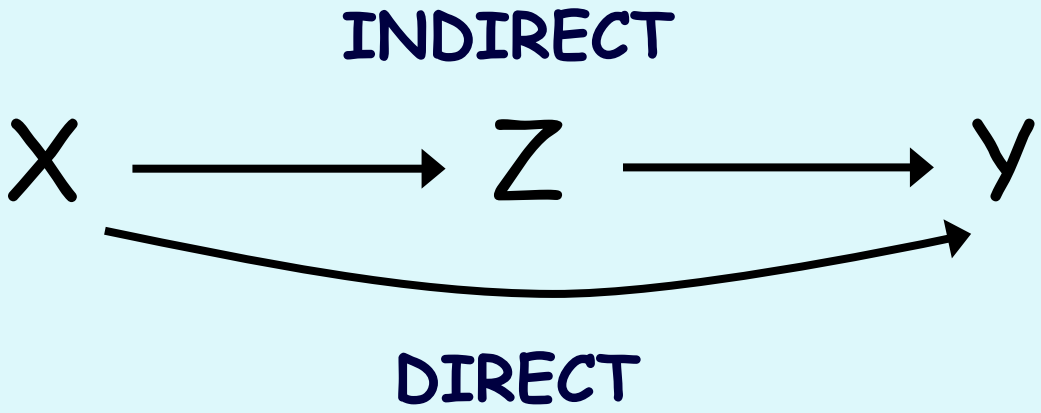
CDE_0 = neither med nor interx
INT_{ref} = interx only
INT_{med} = both interx and med
PIE = med only

Some Practical Considerations:

1) Measurement Error

Obviously all nodes subject to measurement error, with typical consequences.

But important to note that measurement error or categorization of Z has the consequence of shifting more of the estimated effect to the DIRECT component in any decomposition:



Ogburn AJE 2012; VanderWeele OUP 2015

Some Practical Considerations:

2) Unmeasured confounders of Z and Y:

Bound the bias as BF = $\frac{\gamma\lambda}{\gamma+\lambda-1}$ where:

γ is the maximum (over Z) of the c-adjusted RR of U on Y among the exposed (X=1)

λ is the maximum (over Z) of the c-adjusted RR of X on U

Then: $NDE_{true} \geq (NDE_{obs} / BF)$

$NIE_{true} \leq (NIE_{obs} * BF)$

Some Practical Considerations:

3) Well-defined exposures and mediators

Non-manipulable factors: race, sex, age, nativity, etc

Multiple versions of treatment: obesity, education, etc

Contagion or spill-over

4) Multiple Mediators

Some Practical Considerations:

5) Precision

4-way decomposition article cited >150 times, but few of these citations are applied examples.

Most are methods or conceptual papers (e.g., Diderichsen et al. IJE 2019)

6) Transportability and Generalizability

7) Survival data

Generally requires an additive hazards model (or rare outcome approximation).


MEDIATION