Decomposition of the Total Effect in the Presence of Multiple Mediators and Interactions

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Motivating example - psychiatric epidemiology

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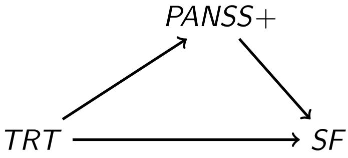
- One important outcome in schizophrenia patients is social functioning (SF). New treatments have only been associated with moderate and non-significant improvement in SF.

$$TRT \longrightarrow SF$$

- New-generation treatments are designed to target PANSS positive symptoms, whose improvement is associated with improved SF.



- However, new-generations treatments are also associated with the higher side-effects ratio, weight gain (WG) in particular (Zheng et al., 2009).

$$\begin{tikzcd} & PANSS+ \arrow[dr] & \\ TRT \arrow[ur] \arrow[rr] \arrow[dr] & & SF \\ & WG \arrow[ur] & \end{tikzcd}$$

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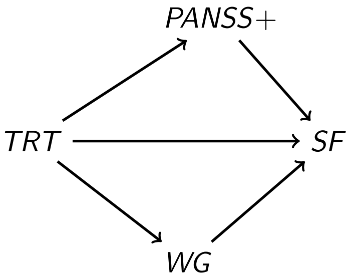

- Finally, interactions at all levels are expected.

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- Formally, this means identifying mediating and/or interactive mechanisms of action of the treatment through hypothesized mediators.

Available methods: Multiple Mediators

- Methods for multiple mediators are available
- Parametric and non-parametric estimation under various settings (Vanderweele and Vansteelandt, 2013).
- Counterfactual definition of path-specifc effects and possible decompositions of the total effect (Daniel et al., 2015)

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- Counterfactual definition of path-specifc effects and possible decompositions of the total effect (Daniel et al., 2015)
- Exposure-mediator and mediator-mediator interactions are likely to be present.
- No study has investigated counterfactual definition of high-dimension interaction nor included those in multiple mediators setting

Available methods: 4-way decomposition

- In the context of one mediator, a decomposition of the TE into mediation and interaction components is available (Vanderweele, 2014)

Component	Interpretation
CDE	Treatment effect neither due to mediation nor interaction
INTref	Treatment effect only due to interaction
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- We want to derive a decomposition of TE that unifies mediation and interaction when multiple mediators are present.

Multiple mediators - Effect definitions

(Without loss of generality we will assume two mediators M_1 and M_2, and assume binary A, M_1, and M_2)

- Total effect

$$TE = Y_1 - Y_0 = Y_{1M_1(1)M_2(1)} - Y_{0M_1(0)M_2(0)}$$

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- Pure natural direct effect (PNDE): the effect of A if both the mediators were set on the value they would naturally take at the referent value of the exposure (i.e. 0).

$$PNDE = Y_{1M_1(0)M_2(0)} - Y_{0M_1(0)M_2(0)}$$

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- The effect of M_2 in the absence of both A and M_1:

$$PNIE_{M_2} = Y_{0M_1(0)M_2(1)} - Y_{0M_1(0)M_2(0)}$$

- The combined effect of M_2 and M_1 in the absence of A:

$$PNIE_{M_1M_2} = Y_{0M_1(1)M_2(1)} - Y_{0M_1(0)M_2(0)}$$

See Daniel et al, 2015 for other possible effect definitions

3-way interaction

We can define 3-way interaction (on the additive scale) in three ways:

- The change in $A \cdot M_1$ when M_2 goes from absent to present

$$p_{111} - p_{101} - p_{011} + p_{001} > p_{110} - p_{100} - p_{010} + p_{000}$$

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From all these definitions we identify the same measure of 3-way interaction

$$p_{111} - p_{110} - p_{101} - p_{011} + p_{100} + p_{010} + p_{001} - p_{000}$$

Decomposition of the total effect

$$
\begin{aligned}
\text{TE} = &\text{CDE} + \text{PNIE}_{M_1} + \text{PNIE}_{M_2} + \text{PNIE}_{M_1*M_2} + \\
&\text{INTref}_{A*M_1} + \text{INTref}_{A*M_2} + \text{INTref}_{A*M_1*M_2} + \\
&\text{INTmed}_{A*M_1} + \text{INTmed}_{A*M_2} + \text{INTmed}_{A*M_1*M_2}
\end{aligned}
$$

- This generalizes the 4-way decomposition introduced in the context of a single mediator.
- PNIE, INTref, and INTmed, can be additionally decomposed into three components each, capturing effects that operate through specific pathways and interactions.

Component	Definition
CDE	$[Y_{100} - Y_{000}]$
PNIE_{M_1}	$[Y_{010} - Y_{000}][M_1(1) - M_1(0)]$
PNIE_{M_2}	$[Y_{001} - Y_{000}][M_2(1) - M_2(0)]$
$\text{PNIE}_{M_1*M_2}$	$[Y_{011} - Y_{010} - Y_{001} + Y_{000}][M_1(1)M_2(1) - M_1(0)M_2(0)]$
INTref_{A*M_1}	$[Y_{110} - Y_{100} - Y_{010} + Y_{000}]M_1(0)$
INTref_{A*M_2}	$[Y_{101} - Y_{100} - Y_{001} + Y_{000}]M_2(0)$
$\text{INTref}_{A*M_1*M_2}$	$[Y_{111} - Y_{110} - Y_{101} - Y_{011}+$
	$Y_{100} + Y_{010} + Y_{001} - Y_{000}]M_1(0)M_2(0)$
INTmed_{A*M_1}	$[Y_{101} - Y_{100} - Y_{001} + Y_{000}][M_2(1) - M_2(0)]$
INTmed_{A*M_2}	$[Y_{110} - Y_{100} - Y_{010} + Y_{000}][M_1(1) - M_1(0)]$
$\text{INTmed}_{A*M_1*M_2}$	$[Y_{111} - Y_{110} - Y_{101} - Y_{011}+$
	$Y_{001} + Y_{010} + Y_{100} - Y_{000}][M_1(1)M_2(1) - M_1(0)M_2(0)]$

Properties and additional results

- The decomposition can be extended to the case of continuous mediators and exposures
- All components can be identified (at the population level, and given the four classical assumptions: no unmeasured A-Y, M-Y, A-M confounding, and no effect of A that confounds the M-Y relationship. Assumptions involving M must hold for all mediators)
- Non-empirical analogues have been derived

- Simulation studies with both continuous and binary outcomes have been used to empirically test the decomposition
- An extension to incorporate more than 2 independent mediators has also been developed

Illustrative example

- 497 schizophrenia patients from the CATIE trial assigned to either Olanzapine (n=336) or a first generation drug used as comparison (Perphenazine, n=161).
- Continuous outcome (total score of **PANSS negative symptoms**, ranged on a scale from 7 to 49. Used as a proxy for SF) assessed after 9 months.
- Two continuous continuous mediators, **weight gain** (in lbs) and **PANSS positive score** (from 7 to 49), assessed after 6 months from the beginning of the study.

Illustrative example

- Analyses further adjusted for gender, age, race/ethnicity, systolic and diastolic blood pressure, prior treatment, hospitalization, and waist-hip ratio, measured at baseline.
- Parametric approach (Vanderweele and Vansteelandt, 2013), with linear regression models for both outcome and mediators. 4-way decomposition implemented in R.
- Total effect indicated no treatment effect on the negative PANSS score at 9 months (β=0.01, 95% CI: -1.23, 1.23)
- However, treatment was associated with improved PANSS positive symptoms, and with higher weight gain

Decomposition result

	Estimate	95% CI
CDE	**-2.83**	**-6.65, 0.92**
PNIE_{PANSS+}	0.18	-0.04, 0.53
PNIE_{WG}	0.79	0.10, 1.42
$\text{PNIE}_{PANSS+,WG}$	-	-
INTref_{PANNS+}	2.78	-0.88, 6.28
INTref_{WG}	-0.22	-0.75, 0.12
$\text{INTref}_{PANSS+,WG}$	-	-
INTmed_{PANSS+}	0.14	-0.07, 0.47
INTmed_{WG}	-0.83	-1.62, -0.02
$\text{INTmed}_{PANSS+,WG}$	-	-
NDE	**-0.27**	**-1.60, 1.05**
NIE	**0.28**	**-0.40, 0.91**
TE	0.01	-1.23, 1.23

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- Treatment effect has opposite sign in direct paths and indirect paths through the two mediators (PANSS+ and WG)
- CDE informs that had the patient experienced no weight gain and no positive symptoms, the treatment would lead to improvement in negative symptoms
- Increase in positive symptoms hampers improvement in negative symptoms ($INTref_{PANSS+}$, $PNIE_{PANSS+}$, $INTmed_{PANSS+}$ have all same sign)
- Weight gain displays a complex relationship with negative symptoms (different signs between mediated effect and interactions)

Discussion

- We derived a single decomposition of the total effect that unifies mediation and interaction in the context of multiple mediators
- With independent (non-sequential) mediators, the decomposition can easily be extended to a high number of mediators
- Components can be identified with the same classical assumptions of the classical mediation literature

Discussion (2)

- We are currently investigating the (possibly more likely) setting of sequential mediators. Components definition is challenging and identifiability is not possible for most of them (including interaction terms)

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- As the number of mediators increase, estimation becomes complicated. Parametric models may not be the best option

References

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