Mediation analysis with multiple mediators: An application to the study of adolescent eating disorders

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• They can be accommodated if viewed *en bloc* (with $M$ a vector).
• But this does not allow effects to be disentangled any further.
The causal inference literature does focus on ‘two mediators’ in settings with intermediate confounding.
Two mediators but only one ‘of interest’

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- But $M$ is the mediator of interest, with decomposition only ‘through’ and ‘not through’ $M$.
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- The causal inference literature does focus on ‘two mediators’ in settings with intermediate confounding.
- But $M$ is the mediator of interest, with decomposition only ‘through’ and ‘not through’ $M$.
- What if both mediators are ‘of interest’?
- We would be interested in a finer decomposition, with path-specific effects through $M_1$ alone, $M_2$ alone, both and neither.
ED comprise a variety of heterogeneous diseases; predominant in girls/young women, with increasing prevalence and mortality (Micali, 2013).
Motivation: Eating disorders (ED)

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- Several exposures recognized to contribute to risk: of interest here maternal body size (Nichols, 2009, Jacobi, 2010).
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- ED comprise a variety of heterogeneous diseases; predominant in girls/young women, with increasing prevalence and mortality (Micali, 2013).
- Several exposures recognized to contribute to risk: of interest here maternal body size (Nichols, 2009, Jacobi, 2010).
- Mediation analysis to investigate potential biological mechanisms.
This talk is about the decomposition of the total causal effect into path-specific effects when there are multiple causally-ordered mediators.

1. Effect decomposition
2. Identification
3. Example: ED in adolescent girls
4. Summary
5. References
1. Effect decomposition

2. Identification

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Effect decomposition, single mediator

— With one mediator, there are two possible decompositions of a total causal effect (TCE) into the sum of natural direct effect (NDE) and natural indirect effect (NIE):

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TCE = \text{Pure NDE} + \text{Total NIE}
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— VanderWeele (Epidemiology, 2013) shows that:

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TCE = \text{Pure NDE} + \text{Pure NIE} + \text{’mediated interaction’}
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— So the two decompositions amount to apportioning the mediated interaction either to the direct or indirect effect.

— Note: Two types of decomposition and four path-specific effects.
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— Note: Two types of decomposition and four path-specific effects.
Path-specific effect estimands with two mediators

— With one mediator, we need:

\[ M(x), Y(x, m), Y(x, M(x')) \]

— With two, we need:

\[ M_1(x), M_2(x, m_1), Y(x, m_1, m_2) \]

and

\[ M_2(x, M_1(x')) \]

and

\[ Y(x, M_1(x'), M_2(x'', M_1(x''')) ) \]

Natural path-specific effects are defined as contrasts between these for carefully chosen values of \( x, x', x'', x''' \).
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Counterfactuals

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Natural path-specific effects are defined as contrasts between these for carefully chosen values of \( x, x', x'', x''' \).
— **A natural direct effect** (through neither $M_1$ nor $M_2$) is of the form:

— The first argument changes and all other arguments stay the same, making it a direct effect.
— There are 8 choices for how to fix $x', x'', x'''.$
— We can choose $(x', x'', x''') = (0, 0, 0)$. We call this NDE-000.
— Or, we could choose $(x', x'', x''') = ()$. We call this
A natural direct effect (through neither $M_1$ nor $M_2$) is of the form:

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There are 8 choices for how to fix $x'$, $x''$, $x'''$.

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We can choose $(x', x'', x''') = (0, 0, 0)$. We call this NDE-000.

Or, we could choose $(x', x'', x''') = (001)$. We call this NDE-001.
The list of 8 choices for how to fix $x'$, $x''$, $x'''$ is:

<table>
<thead>
<tr>
<th>Effect</th>
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</tr>
</thead>
<tbody>
<tr>
<td>NDE-000</td>
<td>$E{Y(1, M_1(0), M_2(0, M_1(0))) - Y(0, M_1(0), M_2(0, M_1(0)))}$</td>
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<tr>
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</tr>
<tr>
<td>NDE-010</td>
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</tr>
<tr>
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<tr>
<td>NDE-110</td>
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A natural indirect effect through $M_1$ only is of the form:

- The second argument changes and all other arguments stay the same, making it an indirect effect through $M_1$ only.
- There are 8 choices for how to fix $x, x'', x'''$. 
- We can choose $(x, x'', x''') = (0, 0, 0)$. We call this NIE$_1$-000.
A natural indirect effect through $M_1$ only is of the form:

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A natural indirect effect through $M_2$ only is of the form:

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A natural indirect effect through both \( M_1 \) and \( M_2 \) is of the form:

- The fourth argument changes and all other arguments stay the same, making it an indirect effect through both \( M_1 \) and \( M_2 \).
- There are 8 choices for how to fix \( x, x', x'' \).
- We can choose \((x, x', x'') = (0, 0, 0)\). We call this NIE\(_{12-000}\).
A natural indirect effect through both $M_1$ and $M_2$ is of the form:

$$E\{Y(x, M_1(x'), M_2(x'', M_1(1))) - Y(x, M_1(x'), M_2(x'', M_1(0)))\}$$

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The fourth argument changes and all other arguments stay the same, making it an indirect effect through both $M_1$ and $M_2$.

There are 8 choices for how to fix $x, x', x''$.

We can choose $(x, x', x'') = (0, 0, 0)$. We call this NIE$_{12-000}$. 
— A natural indirect effect through both $M_1$ and $M_2$ is of the form:

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The list of 8 choices for how to fix $x', x'', x'''$ is:

<table>
<thead>
<tr>
<th>Effect</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIE$_{12}$-000</td>
<td>$E{Y(0, M_1(0), M_2(0, M_1(1))) - Y(0, M_1(0), M_2(0, M_1(0)))}$</td>
</tr>
<tr>
<td>NIE$_{12}$-100</td>
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</tr>
<tr>
<td>NIE$_{12}$-010</td>
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</tr>
<tr>
<td>NIE$_{12}$-001</td>
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</tr>
<tr>
<td>NIE$_{12}$-110</td>
<td>$E{Y(1, M_1(1), M_2(0, M_1(1))) - Y(1, M_1(1), M_2(0, M_1(0)))}$</td>
</tr>
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<td>NIE$_{12}$-101</td>
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</tr>
<tr>
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</tr>
<tr>
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— We have defined 8 types (*cf* pure/total) of each of 4 path-specific effects (*cf* direct/indirect).

— We would like to find definitions that allow the decomposition of the TCE, as in:

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TCE = NDE + NIE_1 + NIE_2 + NIE_{12}
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— However of all the \(8^4 = 4096\) sums of this type, only 24 are equal to the TCE (*Daniel et al.* under revision). For example:

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1 Effect decomposition

2 Identification

3 Example: ED in adolescent girls

4 Summary

5 References
Nonparametric identification: two mediators

— The natural extensions of the assumptions invoked for a 1-mediator setting:
  — No unmeasured confounding, and no intermediate confounding.

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Are these sufficient for identification?
Consider the 32 path-specific effects we wish to identify. For example:

\[ E\{Y(1, M_1(0), M_2(0, M_1(0))) - Y(0, M_1(0), M_2(0, M_1(0)))\} \]

Each half of each path-specific effect is of the form

\[ E \{Y(x, M_1(x'), M_2(x'', M_1(x'''))\} \] (1)

If (1) is identified under the extended assumptions above, all path-specific effects are identified.
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as:

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\int_C \int_{M_1} \int_{M_1} \int_{M_2} E \{ Y \mid C = c, X = x, M_1 = m_1, M_2 = m_2 \} \\
\cdot f_{M_2 \mid C, X, M_1}(m_2 \mid c, x'', m') \\
\cdot f_{M_1(x''')}_{\mid C, M_1(x')}(m' \mid c, m_1) \\
\cdot f_{M_1 \mid C, X}(m_1 \mid c, x') \\
\cdot f_C(c) \\
\cdot d\mu_{M_2}(m_2) d\mu_{M_1}(m_1) d\mu_C(c)
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— Everything above is a function of the observed data, except for the boxed term (although there are exceptions when this is (trivially) identified).

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\cdot f_{M_1 \mid C, X} \left( m_1 \mid c, x' \right) f_C (c) \\
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• **Outcome**: ED symptoms scores derived from parental report on the child’s psychological distress @13.5y.

• **Exposure**: pre-pregnancy maternal BMI (\(< 18.5, 18.5 - 25.0, > 25.0\text{kg/m}^2\)).
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Aim: partition the effect of maternal BMI into the effects mediated via each mediator, via combinations of the mediators and via none.
For simplicity consider growth as a bi-dimensional mediator.
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— Parameters of interest: path-specific effects via BW and growth.
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— **Confounders**: pre-pregnancy maternal psychopathology, maternal age, education and social class at birth.
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— Parameters of interest: path-specific effects via BW and growth.
— Confounders: pre-pregnancy maternal psychopathology, maternal age, education and social class at birth.
— Fully-parametric estimation approximated by Monte Carlo simulation (with bootstrapped SEs).
\( \kappa = 1 \)

BW and (size and velocity) as mediators

(24 decompositions, kappa=1)

Average SEM
Results: Maternal overweight

$$\kappa = 0$$

BW and (size and velocity) as mediators

(24 decompositions, kappa=0)
$\kappa = 0.5$

**BW and (size and velocity) as mediators**

(24 decompositions, kappa = .5)
Results: Maternal overweight

\( \kappa = 0.5 \)

- Harmful effect primarily via childhood growth.
- Variation across decompositions wrt BW (weak mediated interactions).
- Assuming no non-linearities (SEM): overestimate of the effects.
- Hardly any variation with \( \kappa \).
Results: Maternal underweight

\[ \kappa = 1 \]

BW and (size and velocity) as mediators

(24 decompositions, \( \kappa = 1 \))
\( \kappa = 0 \)

Results: Maternal underweight

**Effect decomposition Identification Example Summary References**

\( \kappa = 0 \)

**BW and (size and velocity) as mediators**

(24 decompositions, \( \kappa = 0 \))

Exp difference in ED-score comparing UW with non-UW mothers

- Through BW only
- Through size and velocity
- Through BW, size and velocity
- Direct
Results: Maternal underweight

\( \kappa = 0.5 \)

\begin{align*}
\text{BW and (size and velocity) as mediators} \\
(24 \text{ decompositions, } \kappa = 0.5)
\end{align*}

- Through BW only
- Through size and velocity
- Through BW, size and velocity
- Direct
$\kappa = 0.5$

- Very wide variation across decompositions.
- Consistent protective effect primarily via childhood growth.
- Harmful direct effect; also via BW only.
- Assuming no non-linearities (SEM) does not reflect these variations.
- Hardly any variation with $\kappa$. 
1. Effect decomposition

2. Identification

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4. Summary

5. References
• Mediation, particularly effect decomposition, is a subtle business.

• Multiple mediators add to the challenge, in particular in terms of identification.

• Have described how formal definitions of natural direct and indirect effects lead to decompositions of the total causal effect but only for certain combinations.

• The example has highlighted the impact of non-linear relationships among exposure, mediators and outcome.

• This should give greater awareness of parametric assumptions when performing mediation analysis in general.
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Concluding remarks

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Outline

1 Effect decomposition
2 Identification
3 Example: ED in adolescent girls
4 Summary
5 References
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