PATHWAYS

PATHWAYS biosocial influences on health

Mediation analysis with multiple mediators:

An application to the study of adolescent eating disorders

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Causal Mediation Analysis Meeting, Oxford 7 July 2014

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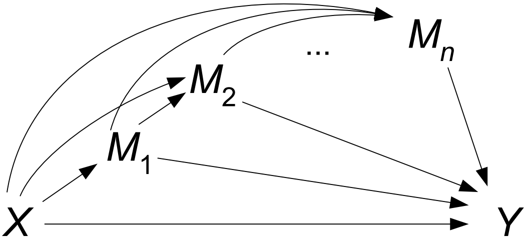
NCRM National Centre for Research Methods

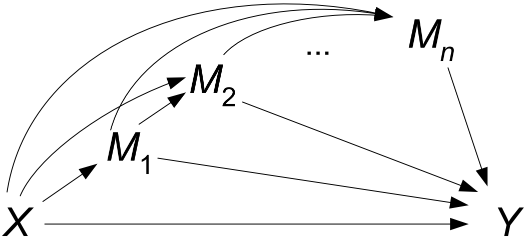
LONDON SCHOOL of HYGIENE & TROPICAL MEDICINE

Multiple mediators



- Many realistic applications involve multiple mediators.

Multiple mediators



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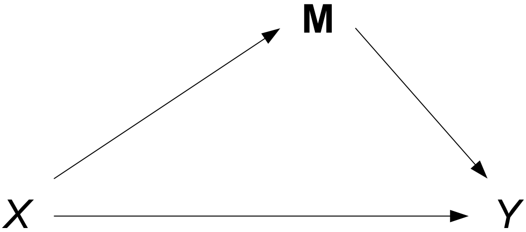
- They can be accommodated if viewed *en bloc* (with **M** a vector).

Multiple mediators



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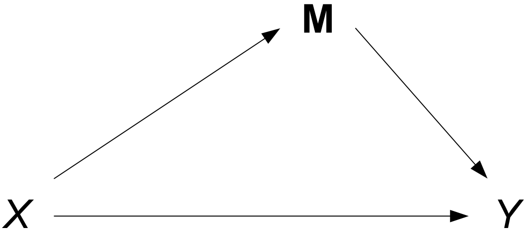
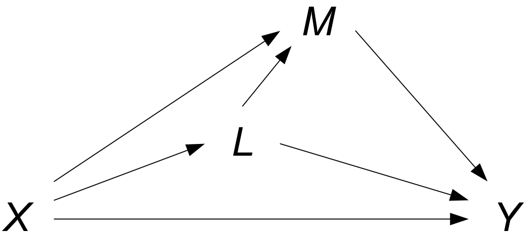


- Many realistic applications involve multiple mediators.
- They can be accommodated if viewed *en bloc* (with **M** a vector).
- But this does not allow effects to be disentangled any further.

Two mediators but only one 'of interest'



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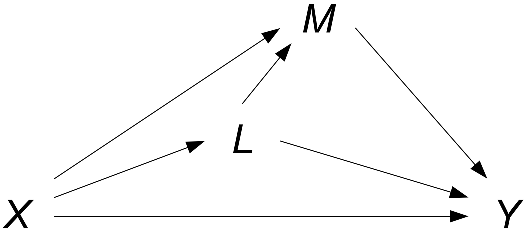

- The causal inference literature does focus on 'two mediators' in settings with intermediate confounding.
- But *M* is the mediator of interest, with decomposition only 'through' and 'not through' *M*.

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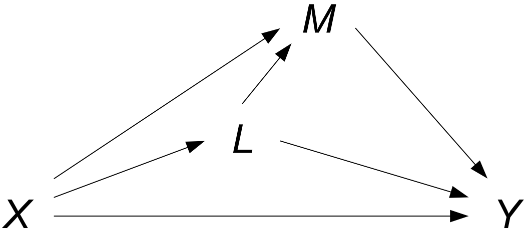

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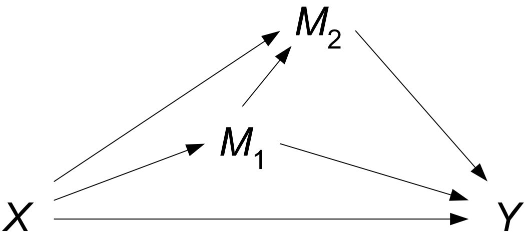
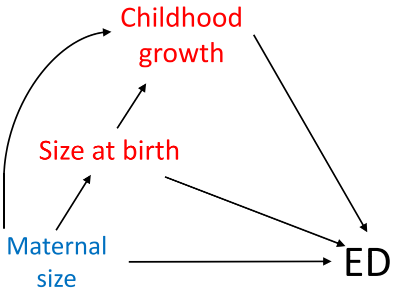


- The causal inference literature does focus on 'two mediators' in settings with intermediate confounding.
- But M is the mediator of interest, with decomposition only 'through' and 'not through' M.
- What if both mediators are 'of interest'?
- We would be interested in a finer decomposition, with path-specific effects through M_1 alone, M_2 alone, both and neither.

Motivation: Eating disorders (ED)



- ED comprise a variety of heterogeneous diseases; predominant in girls/young women, with increasing prevalence and mortality (Micali, 2013).

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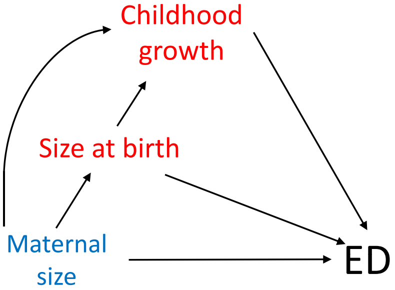

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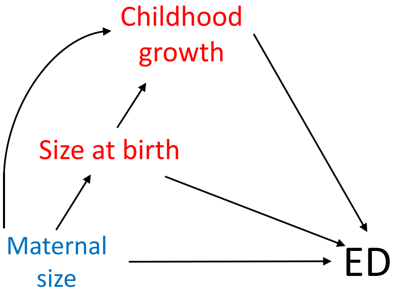

- ED comprise a variety of heterogeneous diseases; predominant in girls/young women, with increasing prevalence and mortality (Micali, 2013).
- Several exposures recognized to contribute to risk: of interest here maternal body size (Nichols, 2009, Jacobi, 2010).
- Mediation analysis to investigate potential biological mechanisms.

Outline

This talk is about a 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

Outline

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):

$$\text{TCE} = \text{Pure NDE} + \text{Total NIE}$$

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— VanderWeele (*Epidemiology*, 2013) shows that:

$$\text{TCE} = \text{Pure NDE} + \text{Pure NIE} + \text{'mediated interaction'}$$

— 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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Path-specific effect estimands with two mediators

Counterfactuals

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

Natural Direct effect

— 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

.

Natural Direct effect

— A natural direct effect (through neither M_1 nor M_2) is of the form:

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

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— Or, we could choose $(x', x'', x''') = (001)$. We call this NDE-001.

Natural direct effect (not mediated through M_1 nor M_2)

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

Effect	Definition
	$\quad x' \quad x'' \quad x''' \qquad x' \quad x'' \quad x'''$
NDE-000	$E\{Y(1, M_1(0), M_2(0, M_1(0))) - Y(0, M_1(0), M_2(0, M_1(0)))\}$
NDE-100	$E\{Y(1, M_1(1), M_2(0, M_1(0))) - Y(0, M_1(1), M_2(0, M_1(0)))\}$
NDE-010	$E\{Y(1, M_1(0), M_2(1, M_1(0))) - Y(0, M_1(0), M_2(1, M_1(0)))\}$
NDE-001	$E\{Y(1, M_1(0), M_2(0, M_1(1))) - Y(0, M_1(0), M_2(0, M_1(1)))\}$
NDE-110	$E\{Y(1, M_1(1), M_2(1, M_1(0))) - Y(0, M_1(1), M_2(1, M_1(0)))\}$
NDE-101	$E\{Y(1, M_1(1), M_2(0, M_1(1))) - Y(0, M_1(1), M_2(0, M_1(1)))\}$
NDE-011	$E\{Y(1, M_1(0), M_2(1, M_1(1))) - Y(0, M_1(0), M_2(1, M_1(1)))\}$
NDE-111	$E\{Y(1, M_1(1), M_2(1, M_1(1))) - Y(0, M_1(1), M_2(1, M_1(1)))\}$

Natural indirect effect through M_1 only

— 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.

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Indirect effect through M_1 only

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

Effect	Definition
	x $\quad x''$ $\quad x'''$ $\quad x$ $\quad x''$ $\quad x'''$
NIE$_1$-000	$E\{Y(0, M_1(1), M_2(0, M_1(0))) - Y(0, M_1(0), M_2(0, M_1(0)))\}$
NIE$_1$-100	$E\{Y(1, M_1(1), M_2(0, M_1(0))) - Y(1, M_1(0), M_2(0, M_1(0)))\}$
NIE$_1$-010	$E\{Y(0, M_1(1), M_2(1, M_1(0))) - Y(0, M_1(0), M_2(1, M_1(0)))\}$
NIE$_1$-001	$E\{Y(0, M_1(1), M_2(0, M_1(1))) - Y(0, M_1(0), M_2(0, M_1(1)))\}$
NIE$_1$-110	$E\{Y(1, M_1(1), M_2(1, M_1(0))) - Y(1, M_1(0), M_2(1, M_1(0)))\}$
NIE$_1$-101	$E\{Y(1, M_1(1), M_2(0, M_1(1))) - Y(1, M_1(0), M_2(0, M_1(1)))\}$
NIE$_1$-011	$E\{Y(0, M_1(1), M_2(1, M_1(1))) - Y(0, M_1(0), M_2(1, M_1(1)))\}$
NIE$_1$-111	$E\{Y(1, M_1(1), M_2(1, M_1(1))) - Y(1, M_1(0), M_2(1, M_1(1)))\}$

Natural indirect effect through M_2 only

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— The third argument changes and all other arguments stay the same, making it an indirect effect through M_2 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_2-000.

Natural indirect effect through M_2 only

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

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

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Indirect effect through M_2 only

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

Effect	Definition
	x x' x''' x x' x'''
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NIE$_2$-100	$E\{Y(1, M_1(0), M_2(1, M_1(0))) - Y(1, M_1(0), M_2(0, M_1(0)))\}$
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NIE$_2$-101	$E\{Y(1, M_1(0), M_2(1, M_1(1))) - Y(1, M_1(0), M_2(0, M_1(1)))\}$
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Indirect effect through both M_1 and M_2

— 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.

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Indirect effect through M_1 and M_2

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

Effect	Definition
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Decomposition

— 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:

$$\text{TCE} = \text{NDE} + \text{NIE}_1 + \text{NIE}_2 + \text{NIE}_{12}$$

— 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:

$$\text{TCE} = \text{NDE-000} + \text{NIE}_1\text{-100} + \text{NIE}_2\text{-110} + \text{NIE}_{12}\text{-111}$$

— These 24 decompositions use all the 32 path-specific effects just listed.

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Outline

Nonparametric identification: two mediators

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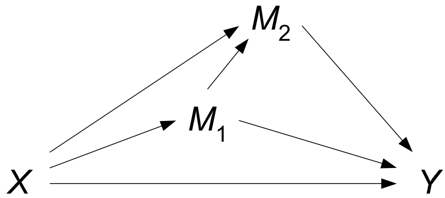

— The natural extensions of the assumptions invoked for a 1-mediator setting:

— No unmeasured confounding, and no intermediate confounding.

Are these sufficient for identification?

Nonparametric identification: two mediators

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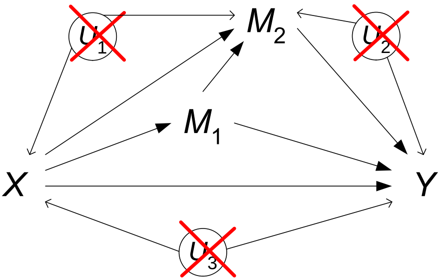

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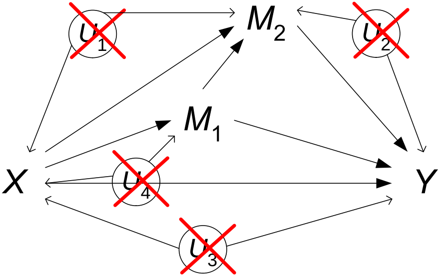

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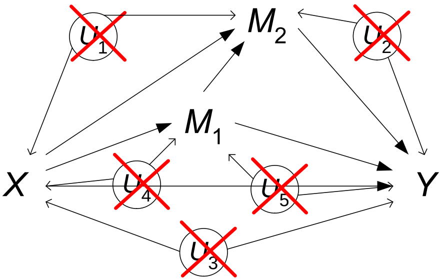

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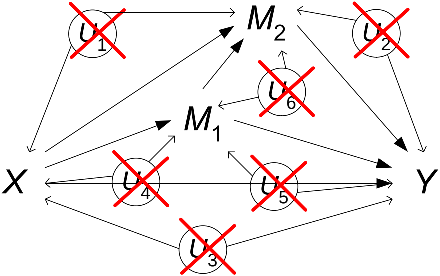

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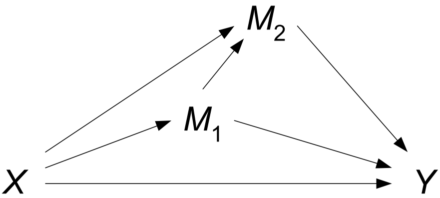

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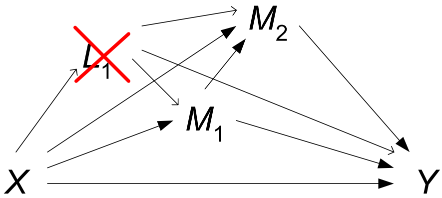

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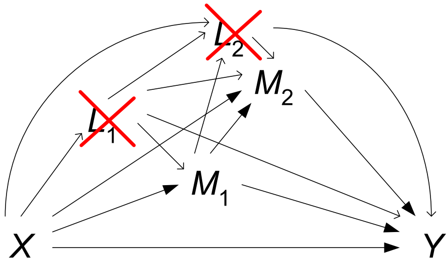

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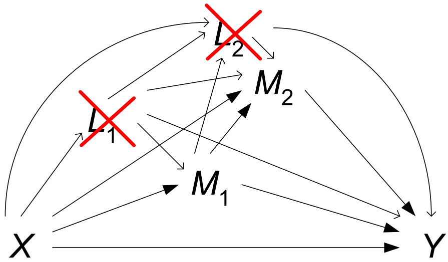

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Identification?

— 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

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

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

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Unidentified density

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— Using these assumptions, we can re-write

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

as:

$$\int_{\mathcal{C}}\int_{\mathcal{M}_1}\int_{\mathcal{M}_1}\int_{\mathcal{M}_2} E\{Y|C=c, X=x, M_1=m_1, M_2=m_2\}$$
$$\cdot f_{M_2|C,X,M_1}\left(m_2\middle|c, x'', m_1'\right) \boxed{f_{M_1(x''')|C,M_1(x')}\left(m_1'|c, m_1\right)}$$
$$\cdot f_{M_1|C,X}\left(m_1\middle|c, x'\right) f_C(c)$$
$$\cdot d\mu_{M_2}(m_2)\, d\mu_{M_1}\left(m_1'\right) d\mu_{M_1}(m_1)\, d\mu_C(c)$$

— Everything above is a function of the the observed data, except for the boxed term (although there are exceptions when this is (trivially) identified).

— Sensitivity analysis, *e.g.* to express this ignorance in terms of κ, the proportion of the residual variance shared by $M_1(x')$ and $M_1(x''')$.

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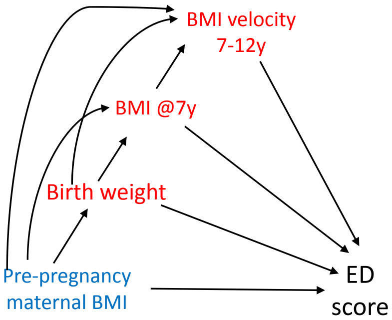
Outline

ED in adolescent girls

The ALSPAC Study: a UK birth cohort



- 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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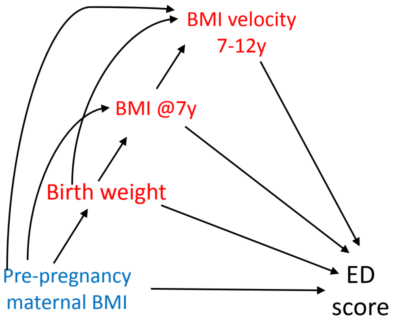
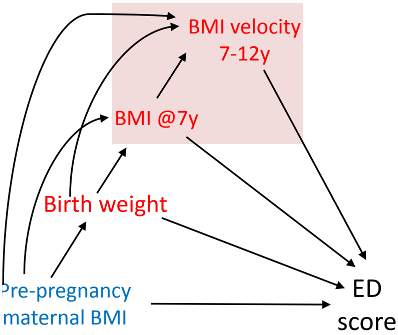


- Outcome: ED symptoms scores derived from parental report on the child's psychological distress @13.5y.
- Exposure: pre-pregnancy maternal BMI ($< 18.5, 18.5 - 25.0, > 25.0\mathrm{kg/m^2}$).

Aim: partition the effect of maternal BMI into the effects mediated via each mediator, via combinations of the mediators and via none.

Analysis

The ALSPAC Study: a UK birth cohort



— For simplicity consider growth as a bi-dimensional mediator.

Analysis

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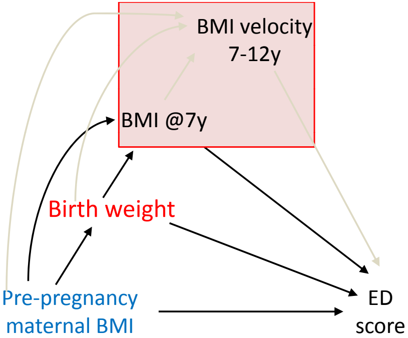

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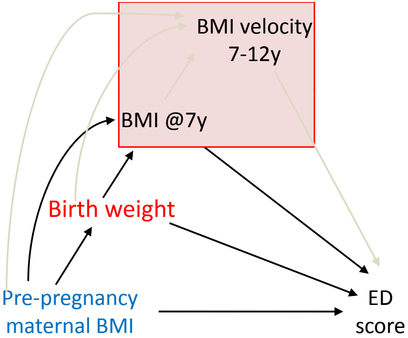

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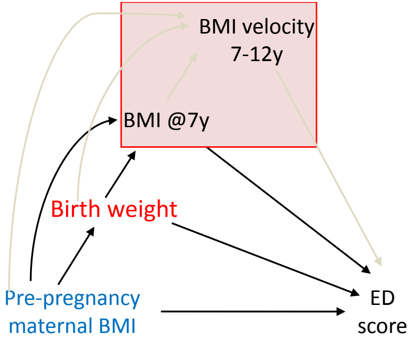

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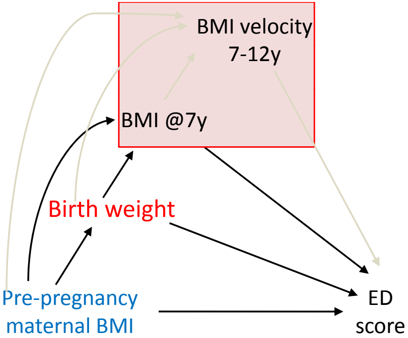

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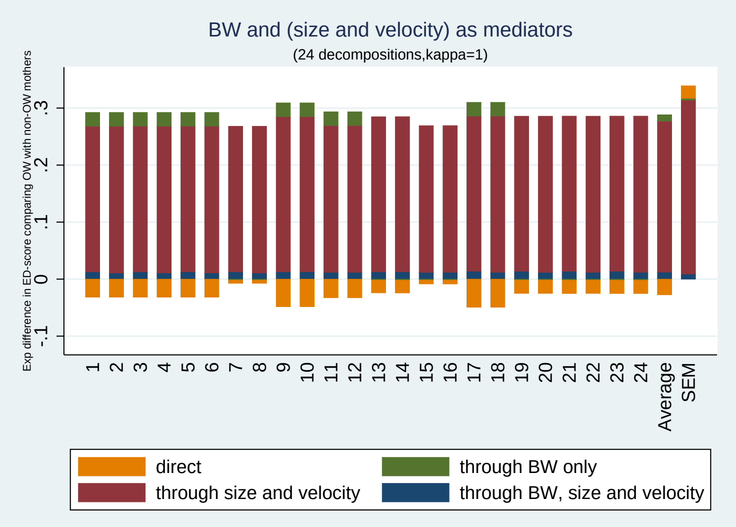
— Parameters of interest: path-specific effects via BW and growth.

— Confounders: pre-pregnancy maternal psychopathology, maternal age, education and social class at birth.

— Fully-parametric estimation approximated by Monte Carlo simulation (with bootstrapped SEs).

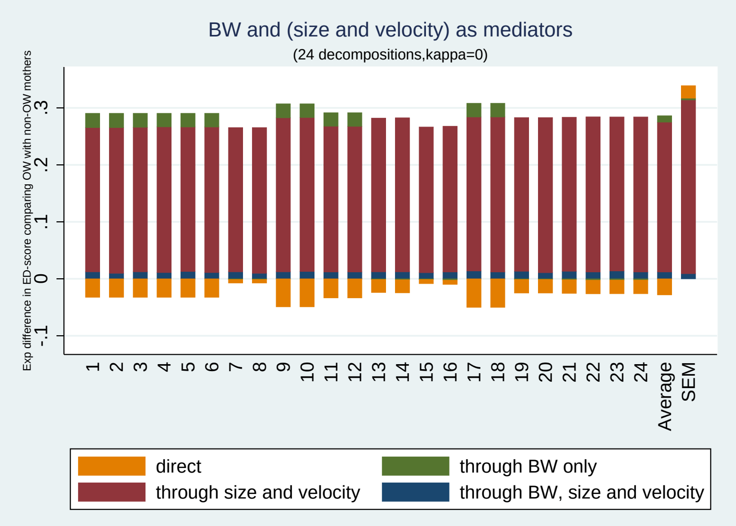
Results: Maternal overweight

$\kappa = 1$



Results: Maternal overweight

$\kappa = 0$



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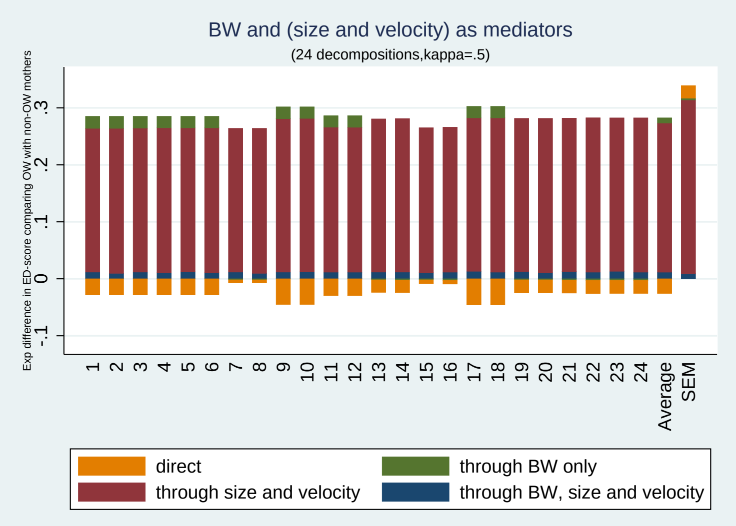

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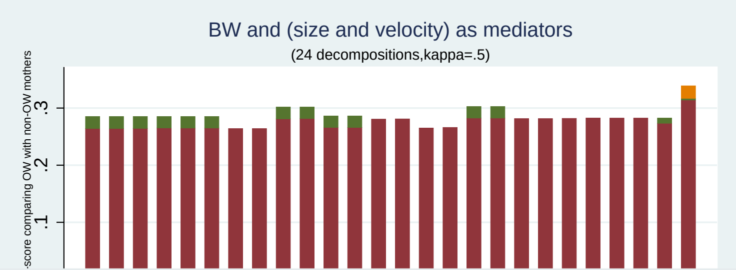

- Harmful effect primarily via childhood growth.
- Variation across decompositions wrt BW (weak mediated interactions).
- Assuming no non-linearities (SEM): overestimate of the effects.
- Hardly any variation with κ.

Results: Maternal underweight

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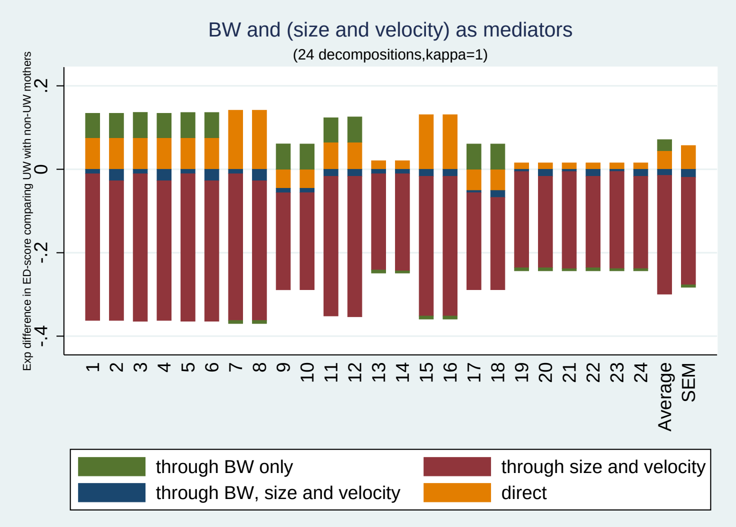

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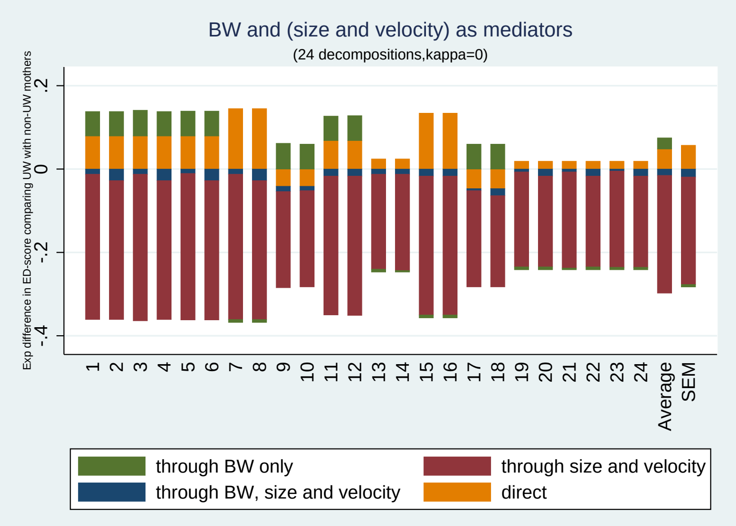

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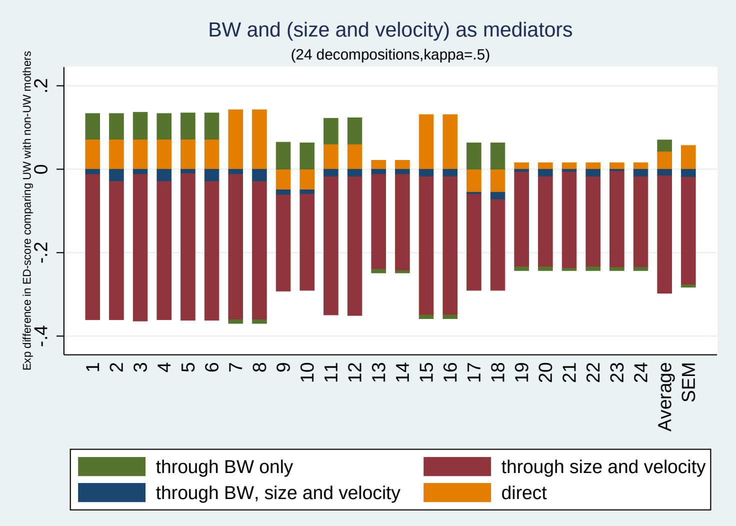

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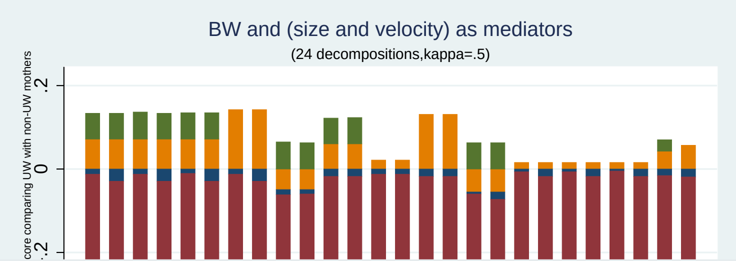

- Very wide variation across decompositions.
- Consistent protective effect primarily via childhood growth.
- Harmful direct effect; also via BW only.
- Assuming no non-linearities (SEM) does not reflect these variations.
- Hardly any variation with κ.

Outline

Concluding remarks

- 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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- 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.
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Outline

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