Mediation and life course epidemiology: challenges and examples

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Methods for Longitudinal Data Analysis in the Social Sciences
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In many research contexts we might be interested in the extent to which the effect of some exposure $X$ on some outcome $Y$ acts via an intermediate variable $M$. 

\[ X \rightarrow M \rightarrow Y \]
• In many research contexts we might be interested in the extent to which the effect of some exposure $X$ on some outcome $Y$ acts via an intermediate variable $M$.

- In other words we are interested in the study of mediation.
Focus on **distal exposures** for later life outcomes,
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Mediation in life course epidemiology

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Say the diagram is correct, then . . .
Say the diagram is correct, then ... we might wish to study this pathway ...
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But how?

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The study of mediation

- Two main strands in the literature for the study of mediation:
  - Social sciences / psychometrics (MacKinnon, 1986)
  - Causal inference literature (Robins and Greenland, 1992; Pearl, 2001)
- First more accessible, but also misused/misunderstood
- Second more rigorous and more general
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Aims:

- Describe these approaches
- Discuss an example
- Outline some extensions
1 Introduction

2 Structural Equation Models
   A linear SEM
   Problems

3 Novel approaches from causal inference
   Potential outcomes
   Unambiguous estimands
   Assumptions and estimation

4 Example: ED in adolescent girls

5 Multiple mediators

6 Summary

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A simplified setting

- Adding a vector of confounders $C$ to our original diagram,
- and letting $M$ and $Y$ be continuous . . .
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- Adding a vector of confounders $C$ to our original diagram,
- and letting $M$ and $Y$ be continuous . . .
- . . . we now consider a linear structural equations model.
A linear Structural Equation Model

Wright, 1921

\[
\begin{align*}
E(Y|C, X, M) &= \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3^T C \\
E(M|C, X) &= \gamma_0 + \gamma_1 X + \gamma_2^T C
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\[
\alpha_1
\]

\[
\alpha_2
\]

\[
\alpha_3
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Estimation (generally) via MLE.
1. **Lack of generality**: Definitions are specific to simple linear models (in particular no $X-M$ interactions).
Problems
(Imai et al., 2010; Vansteelandt, 2011)

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2. **Identifiability**: often not appreciated that unaccounted confounders $V$ of the $M-Y$ relationship:

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&C \\
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   ![Diagram](image)

   would bias the partitioning of direct/indirect effects.

3. **Intermediate confounding**
   (De Stavola *et al.*, 2014).
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![Diagram showing causal relationships between variables C, X, M, Y, and L]
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In a way we should and also should not condition on $L$ when estimating $\alpha_1$ and $\alpha_2$. 
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Recent contributions from the causal inference literature bring:
- clarity to these issues
- greater flexibility to the modelling

estimating $\alpha_1$ and $\alpha_2$. 
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Potential outcomes and mediators

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  - Similarly for $Y(x, m)$ and $Y(x, M(x^*))$.
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For simplicity, consider the case where \( X \) is binary
The total causal effect of $X$ on $Y$ expressed as a mean difference is

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Note that this can also be written as

$$\text{TCE} = E[Y\{1, M(1)\}] - E[Y\{0, M(0)\}].$$
• The controlled direct effect of \( X \) on \( Y \) when \( M \) is controlled at \( m \), expressed as a mean difference is

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This is a comparison of two hypothetical worlds. In the first, $X$ is set to 1, and in the second $X$ is set to 0. In both worlds, $M$ is set to $m$. By keeping $M$ fixed at $m$, we are getting at the direct effect of $X$, unmediated by $M$. 
• Ideally, we would express the total causal effect as the sum of a direct and an indirect effect.
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• But this turns out not to be possible using this definition of a controlled direct effect.
• For this reason, it is useful to have a different definition of a direct effect.
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Since $M$ is the same (within subject) in both worlds, we are still getting at the direct effect of $X$. 
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• Since $M$ is the same (within subject) in both worlds, we are still getting at the direct effect of $X$.
• If no individual-level interaction between $X$ and $M$, $CDE(m) = NDE \ \forall m$. 
• The advantage of defining the natural direct effect in this way, is that it leads to a natural *indirect* effect.
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The \textbf{natural indirect effect} of $X$ on $Y$ is

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\text{NIE} = E \left[ Y \{1, M(1) \} \right] - E \left[ Y \{1, M(0) \} \right].
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Natural indirect effect
Pearl, 2001; Robins and Greenland, 1992

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• In the first, $M$ is set to $M(1)$ and in the second $M$ is set to $M(0)$. In both worlds, $X$ is set to 1.
• $X$ is allowed to influence $Y$ only through its influence on $M$. Thus it is an indirect effect through $M$. 
**Effect decomposition:**
The sum of the natural direct and indirect effects is the total causal effect:

\[
\text{NDE} + \text{NIE} = E[Y\{1, M(0)\}] - E[Y\{0, M(0)\}]
+ E[Y\{1, M(1)\}] - E[Y\{1, M(0)\}] = \text{TCE}
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• **Generality:**
These definitions of mediation parameters can be generalized to multivariate exposures and mediators.
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• **Generality:**
  These definitions of mediation parameters can be generalized to multivariate exposures and mediators.

• **Identification:**
  As well as technical assumptions of no interference and consistency, there are no unmeasured confounding assumptions, and more...
Assumptions for identification: TCE

- No unmeasured confounding of the $X$–$Y$ relationship.
- No unmeasured confounding of the $X-Y$ or $M-Y$ relationships.
Assumptions for identification: CDE

- No unmeasured confounding of the $X-Y$ or $M-Y$ relationships.
Assumptions for identification: NDE, NIE

- No unmeasured confounding of the $X \rightarrow Y$, $M \rightarrow Y$, or $X \rightarrow M$ relationships.
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Assumptions for identification: NDE, NIE

- No unmeasured confounding of the $X-Y$, $M-Y$, or $X-M$ relationships.
- AND, in addition, either:
  - No intermediate confounding, or
  - Some restriction on the extent to which $X$ and $M$ interact in their effect on $Y$ (Petersen et al, 2006).
Wide range of options, for most combinations of $M$ and $Y$:

- **G-computation**—very flexible and efficient but heavy on parametric modelling assumptions:
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  - implemented in `gformula` command in Stata (Daniel *et al.*, 2011)
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- Semi-parametric methods make fewer parametric assumptions:
  - **Inverse probability of treatment weighting (IPTW):**
    - not practical when $M$ is continuous
  - Various flavours of **G-estimation**
    - generally more complex to implement and understand
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Eating disorders (ED) in adolescent girls

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- Maternal body size is a possible risk factor
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- Childhood growth may act as mediator (with size at birth an intermediate confounder).

![Diagram showing the relationship between Maternal size, Childhood growth, and ED]
Eating disorders (ED) in adolescent girls

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"Is the effect of maternal size on her daughter’s ED scores mediated via childhood growth?"
The ALSPAC Study

- Cohort of children born in 1990-92 in SW England, followed from birth at set intervals; 5,000 girls.
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- Outcomes: 3 types of ED symptoms scores, derived from parental reports collected when child was 13.5y (Micali et al. 2014):
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• **Mediators**: BMI at 7y and BMI velocity at 7-12y.
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Estimation: Fully-parametric g-computation via Monte Carlo simulation (with imputation and bootstrapped SEs).
Results

N=3,526

Maternal underweight

Maternal overweight

Expected difference in ED score

Bingeing

Concern

Restrictions

Total

Mediated via childhood growth

Not mediated

Maternal underweight

Maternal overweight

De Stavola/Mediation
Results

N=3,526

<table>
<thead>
<tr>
<th>Maternal underweight</th>
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<tbody>
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De Stavola/Mediation

27/35
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<td>Not mediated</td>
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<td>Maternal overweight</td>
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<tr>
<td>Expected difference in ED score</td>
<td>-1</td>
<td>-.5</td>
<td>.5</td>
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<tr>
<td>Mediated via childhood growth</td>
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<td>Not mediated</td>
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De Stavola/Mediation
Results

N=3,526

- Harmful effect of maternal overweight completely mediated by childhood growth
- Protective effect of maternal underweight reduced by harmful ‘direct’ effect
The counterfactual framework offers general definitions of mediation effects and appropriate estimation methods.
Multiple mediators

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With multiple mediators, far greater complexities are introduced (Daniel et al., 2014), in particular with regards to:

- **Definitions** of mediated effects: they involve more complex counterfactuals
- **Assumptions**: they involve many more components of the diagram
- **Decomposition** into mediated effects via individual mediators: there are several alternative options
- **Estimation**: necessary to fix a parameter ($\kappa$) that is not estimable and carry out sensitivity analyses
Does birth weight also play a mediating role?

Results: Maternal overweight

$\kappa = 1$

BW and (size and velocity) as mediators

(24 decompositions, kappa=1)
Does birth weight also play a mediating role?

Results: Maternal underweight

\[ \kappa = 1 \]
Does birth weight also play a mediating role?

Results: Maternal underweight

\[ \kappa = 1 \]

- Consistent harmful/protective effects primarily via childhood growth.
- Harmful direct effect for maternal underweight; also via BW only.
- (Hardly any variation with \( \kappa \)).
Outline

1 Introduction

2 Structural Equation Models
   A linear SEM
   Problems

3 Novel approaches from causal inference
   Potential outcomes
   Unambiguous estimands
   Assumptions and estimation

4 Example: ED in adolescent girls

5 Multiple mediators

6 Summary

7 References
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Concluding remarks

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  - Very strong assumptions are required for such an ambitious causal endeavour. (These (and more) were needed in the traditional approach!).
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Thank you!
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References

- Daniel RM, De Stavola BL, Cousens SN and Vansteelandt S. Causal mediation analysis with multiple mediators. (to appear in *Biometrics*).
- Pearl J. Direct and indirect effects. *Proceedings of the Seventeenth Conference on Uncertainty and Artificial Intelligence* 2001; San Francisco: Morgan Kaufmann.