Causal mediation analysis with multiple causally-ordered mediators

Rhian Daniel, Bianca De Stavola and Simon Cousens
with thanks to Stijn Vansteelandt and Dave Leon

Centre for Statistical Methodology
London School of Hygiene and Tropical Medicine

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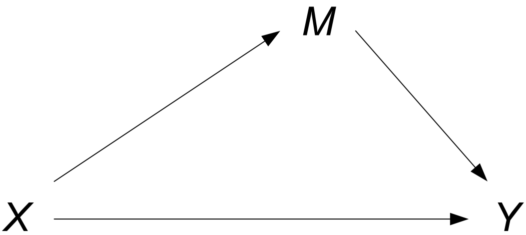
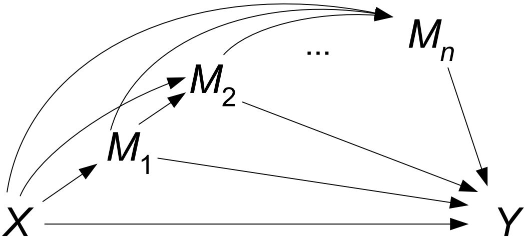
Single mediator



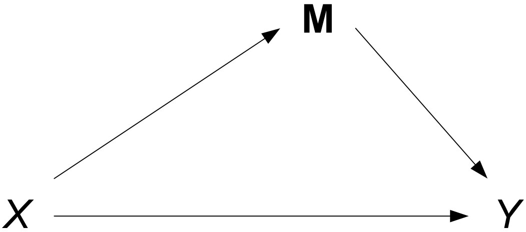
— Almost all the causal inference literature on mediation is based on a single mediator.

Multiple mediators



— However, as we have seen over the last two days, many realistic applications involve multiple mediators.

Many mediators considered *en bloc*



— Multiple mediators are trivially accommodated by the existing formal literature if viewed *en bloc* (with **M** a vector).

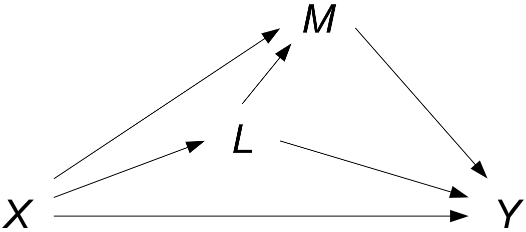
Many mediators considered *en bloc*

$$\begin{tikzcd} & \mathbf{M} \arrow[dr] & \\ X \arrow[ur] \arrow[rr] & & Y \end{tikzcd}$$

— Multiple mediators are trivially accommodated by the existing formal literature if viewed *en bloc* (with **M** a vector).

— But then the direct effect is around all of them, and the (single) indirect effect is through one, more or all of them, and is not further disentangled.

Two mediators but only one ‘of interest’



— The causal inference literature does focus on ‘two mediators’, L and M, in settings with intermediate confounding (cf Vanessa’s talk yesterday).

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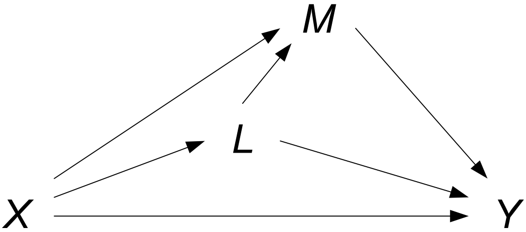
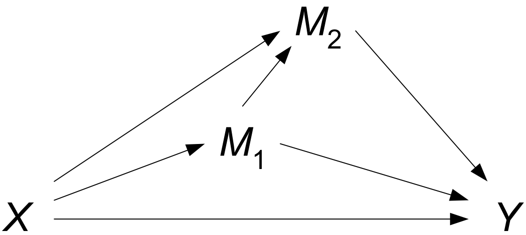


— The causal inference literature does focus on ‘two mediators’, L and M, in settings with intermediate confounding (cf Vanessa’s talk yesterday).

— But M is the mediator of interest, with decomposition again into two effects—through and not through M.

Two mediators, both of interest (1)



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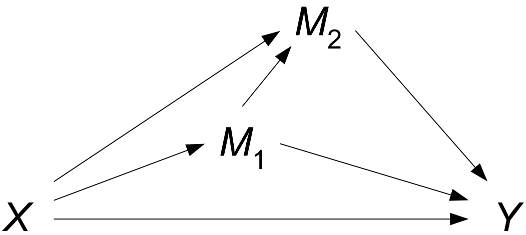
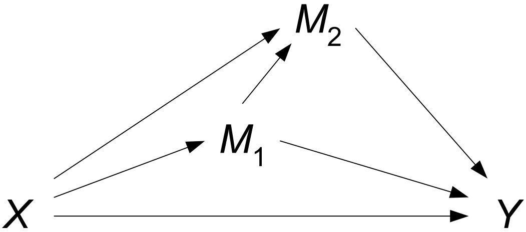


— What if both mediators are 'of interest'?

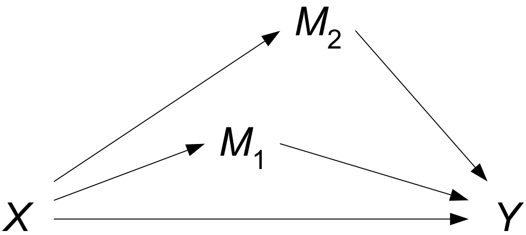
— We could then be interested in a finer decomposition, with path-specific effects through M_1 alone, M_2 alone, both and neither.

Two mediators, both of interest (2)



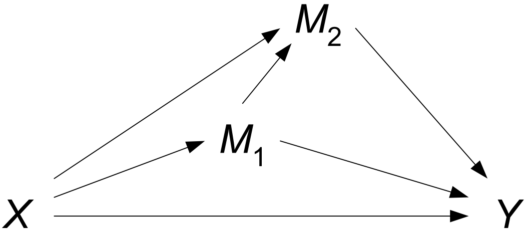
— This setting has been studied, but either (a) without a focus on decomposing the total effect [Avin et al (2005), Albert and Nelson (2011)]. . .

Two mediators, not causally ordered



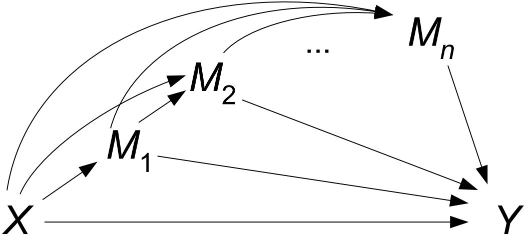
— . . . or (b) in the setting with no effect of M_1 on M_2 [MacKinnon (2000), Preacher and Hayes (2008), Imai and Yamamoto (in press)] (many examples yesterday).

Our setting



— This talk is about a path-specific decomposition of the total causal effect in the setting where M_1 affects M_2 (causally-ordered mediators).

More generally



— More generally there could be *n* causally-ordered mediators.

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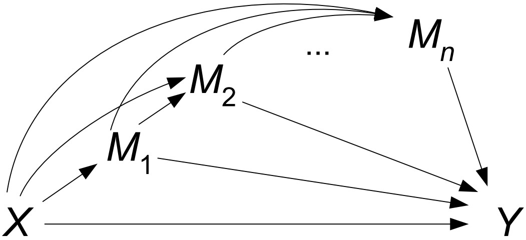

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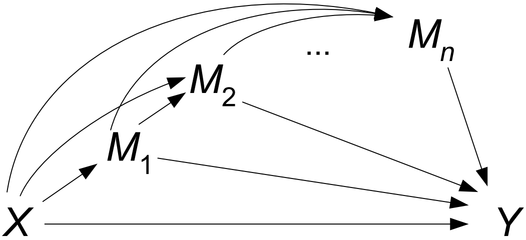

— More generally there could be n causally-ordered mediators.
— Traditional path analysis generalises easily to this setting, but under strong assumptions, including linearity everywhere.
— Can these be relaxed somewhat by generalising ideas from causal inference?

Outline

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Effect decomposition, single mediator

— With one mediator, there are two possible decompositions:

$$\begin{aligned}
\text{TCE} &= E\{Y(1,M(1)) - Y(0,M(0))\} \\
&= E\{Y(1,M(1)) - Y(1,M(0)) + Y(1,M(0)) - Y(0,M(0))\} \\
&= \qquad\qquad \text{TNIE} \qquad\qquad + \qquad\qquad \text{PNDE} \\
&= E\{Y(1,M(1)) - Y(0,M(1)) + Y(0,M(1)) - Y(0,M(0))\} \\
&= \qquad\qquad \text{TNDE} \qquad\qquad + \qquad\qquad \text{PNIE}
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— VanderWeele [Epidemiology, 2013] shows that:

$$\text{TCE} = \text{PNDE} + \text{PNIE} + \text{‘mediated interaction’}$$

— So the two decompositions amount to apportioning the mediated interaction either to the direct or indirect effect.

Outline

Counterfactuals

— With one mediator, we need:

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

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— Similarly, can choose $(x, x'', x''') = (0, 0, 1)$. We call this NIE$_1$-001.

Indirect effect through M_1 only

— A natural indirect effect through M_1 only is of the form:

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

— The second argument changes and all other arguments stay the same, making it an indirect effect through M_1 only.
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— Similarly, can choose $(x, x'', x''') = (0, 1, 0)$. We call this NIE$_1$-010.

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— A natural indirect effect through M_1 only is of the form:

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n	$(2^n)!$
1	2

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n	$(2^n)!$
1	2
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3	40,320

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1	2
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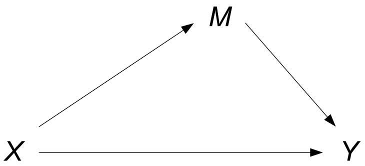
1	2
2	24
3	40,320
4	2.092×10^{13}
5	2.631×10^{35}

Outline

Nonparametric identification: single mediator



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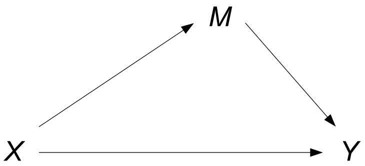

— Throughout, we omit background confounders C from our diagrams, but they are always implicitly there.
— Recall that for nonparametric identification of PNDE, TNDE, PNIE and TNIE in the one-mediator setting, we require

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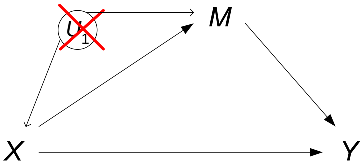

— Throughout, we omit background confounders C from our diagrams, but they are always implicitly there.
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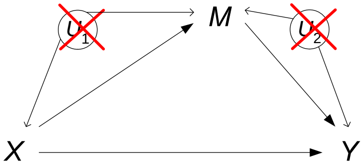

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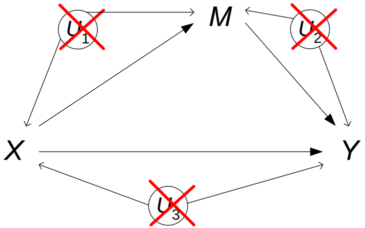

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— Recall that for nonparametric identification of PNDE, TNDE, PNIE and TNIE in the one-mediator setting, we require no unmeasured confounding of X and M, M and Y, and X and Y.

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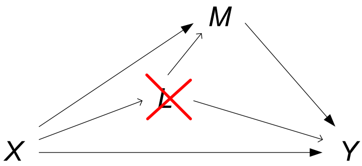
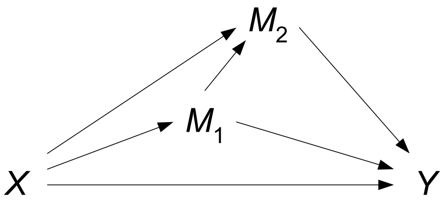


— Throughout, we omit background confounders C from our diagrams, but they are always implicitly there.
— Recall that for nonparametric identification of PNDE, TNDE, PNIE and TNIE in the one-mediator setting, we require no unmeasured confounding of X and M, M and Y, and X and Y.
— And no intermediate confounders, L.

Extension to two mediators



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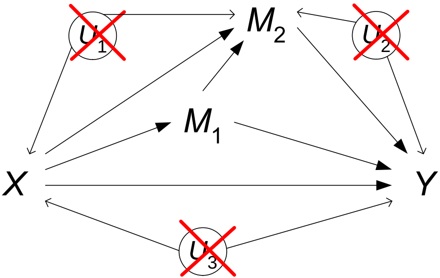

— Consider the natural extensions of these assumptions.
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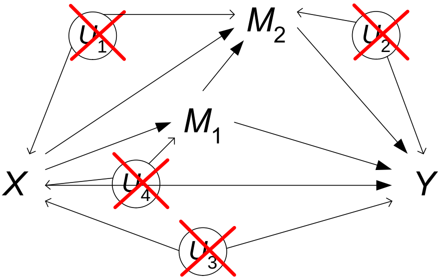

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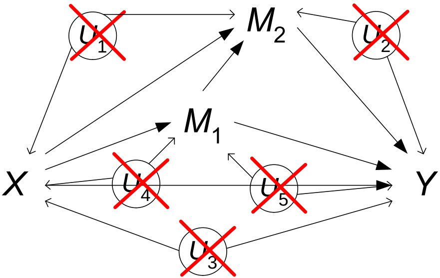

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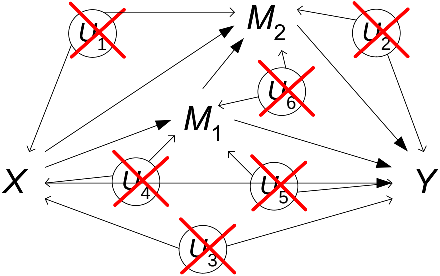

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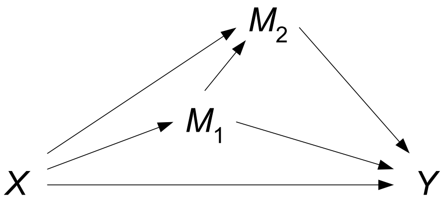

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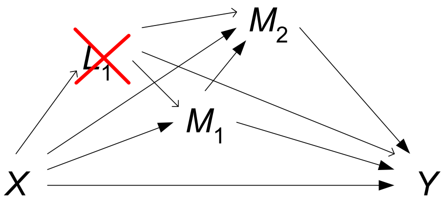

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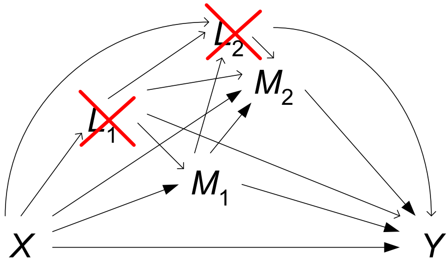

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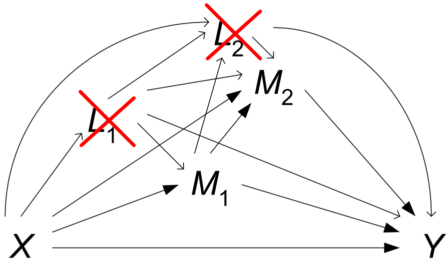

— Consider the natural extensions of these assumptions.

— No unmeasured confounding, and no intermediate confounding.

— Are these sufficient for identification?

Identification?

— Consider the 32 path-specific effects we wish to identify:

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

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

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— Using these assumptions, we can re-write (1) as:

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

Unidentified density

— Everything on the previous slide is a function of the distribution of the observed data, except for:

$$\boxed{f_{M_1(x''')|C,M_1(x')}\left(m_1' \mid c, m_1\right)} \qquad (2)$$

which (for $x' \neq x'''$) involves the joint distribution (conditional on C) of $M_1(x)$ across different worlds.

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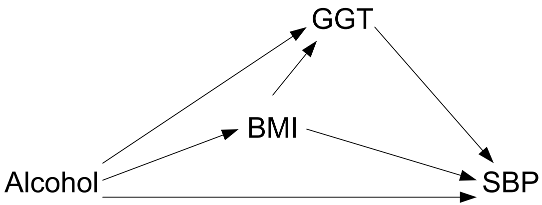
— For all other effects, and when there is an arrow from M_1 to M_2, we vary (2) in a sensitivity analysis.

Outline

The Izhevsk study data



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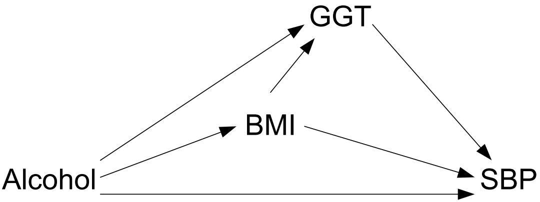

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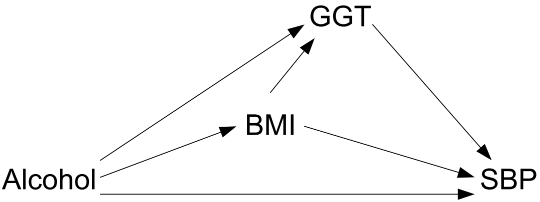

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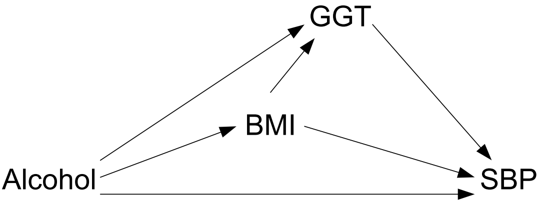

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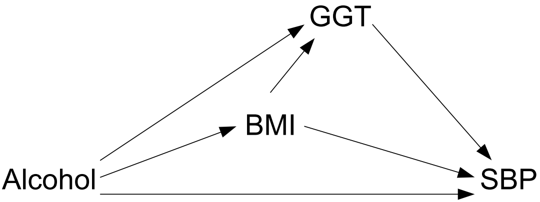

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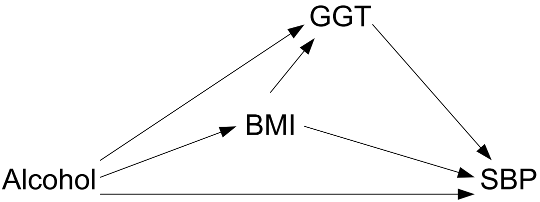

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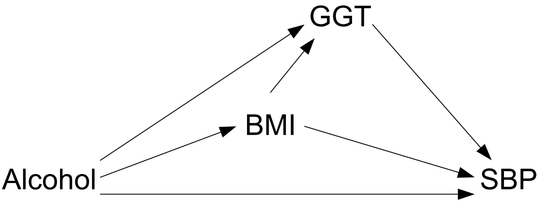

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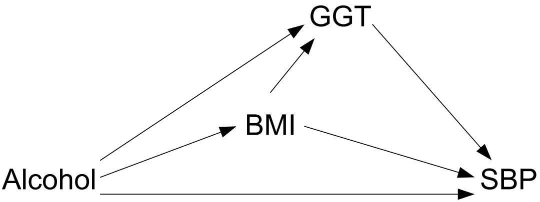

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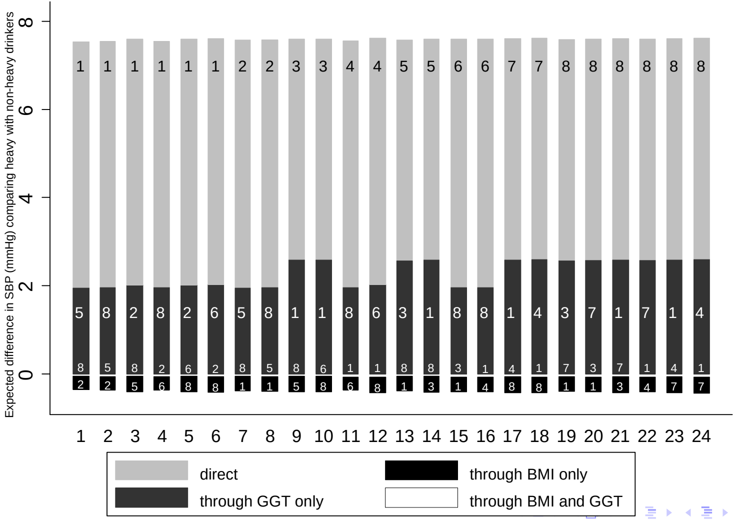
— With a sensitivity parameter (κ) representing the proportion of the residual variance in $M_1(x)$ shared across worlds.

Results

Caveat: CIs are wide!

$\kappa = 1$



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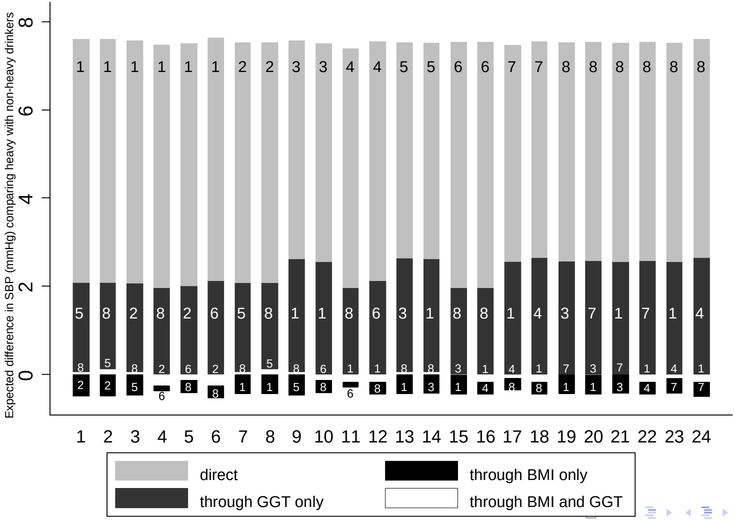

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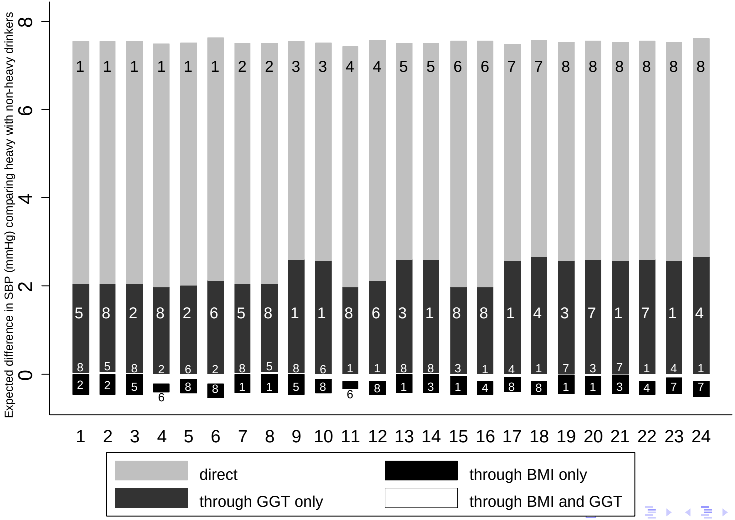

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— Would semiparametric estimation methods of these estimands be viable?
— How far beyond traditional path analysis can we really go?

Outline

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