Causal mediation analysis: a whistle-stop tour and some recent advances

Rhian Daniel
London School of Hygiene and Tropical Medicine

CSM Seminar Series, Causal Inference Theme
1st July, 2016

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Acknowledgements

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Thanks also to Bernard Rachet for access to the NYCRIS data, and to Ruoran Li for assistance with the data analysis.

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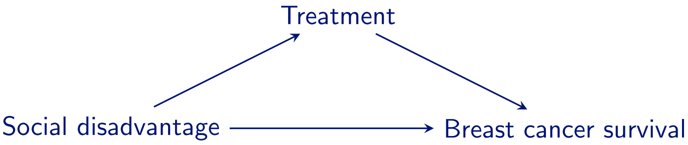
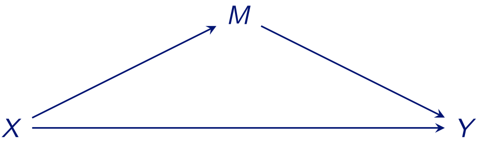


- For example, how much of the effect of social disadvantage on breast cancer survival is explained by treatment choices?

Outline

Traditional approach

Path tracing rules [Wright 1934]



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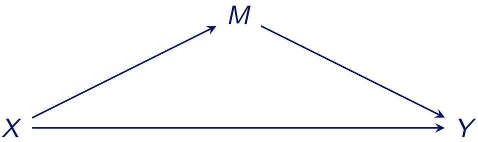

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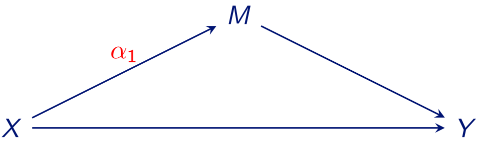

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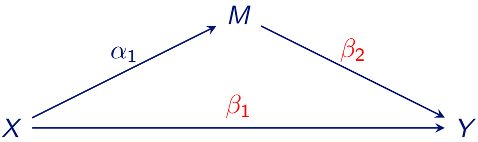

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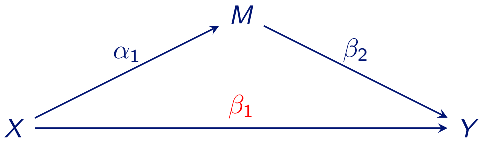

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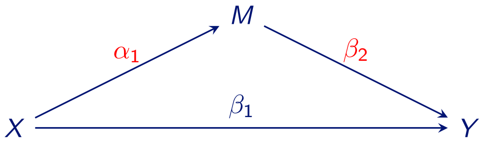

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- And $\alpha_1\beta_2$ the indirect effect.

More complex diagrams

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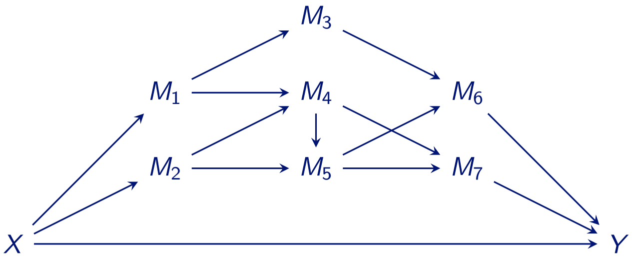

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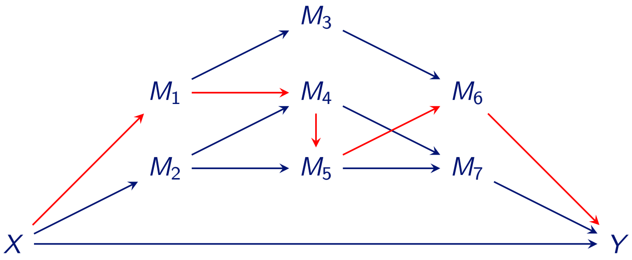

- This simple method extends to arbitrarily complex diagrams, as long as all models are simple linear regressions (with no interaction terms).
- The path-specific effect along a particular pathway is equal to the product of the coefficients along that path.

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- Mediation is a causal concept: associations are symmetric, but mediation implies an ordered sequence.
- Core principles of causal inference: (1) what is the estimand? (2) under what assumptions can it be identified? (3) are there more flexible estimation methods than currently used?

Potential outcomes and mediators

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- Let $Y\{x, M(x^*)\}$ be the value that Y would take if we intervened on X and set it to x whilst simultaneously intervening on M and setting it to $M(x^*)$, the value that M would take under an intervention setting X to x^*, where x and x^* are not necessarily equal.

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These hypothetical quantities were used to create model-free definitions of direct/indirect effects that match our intuition.

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Natural direct effect

Pearl 2001; Robins and Greenland 1992

- The natural direct effect of (a binary) X on Y expressed as a marginal mean difference is

$$\text{NDE} = E\left[Y\left\{1, M(0)\right\}\right] - E\left[Y\left\{0, M(0)\right\}\right].$$

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- In the first, X is set to 1, and in the second X is set to 0. In both, M is set to $M(0)$, the value it would take if X were set to 0.
- Since M is the same (*within* subject) in both situations, we are intuitively getting at the direct effect of X.

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- The natural indirect effect of X on Y is

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- X is allowed to influence Y only through its influence on M. Thus it intuitively corresponds to an indirect effect through M.

Effect decomposition

The sum of the natural direct and indirect effects is

$$\begin{aligned}\text{NDE} + \text{NIE} = {} & E\left[Y\left\{1, M(0)\right\}\right] - E\left[Y\left\{0, M(0)\right\}\right] \\ & + E\left[Y\left\{1, M(1)\right\}\right] - E\left[Y\left\{1, M(0)\right\}\right]\end{aligned}$$

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the total causal effect of X on Y.

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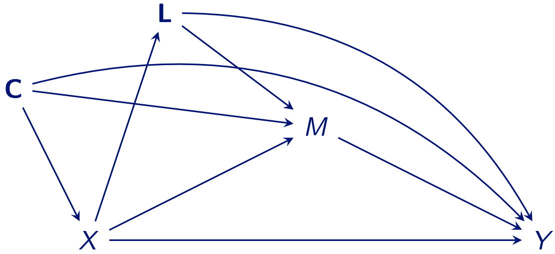
Assumptions for identification (1)



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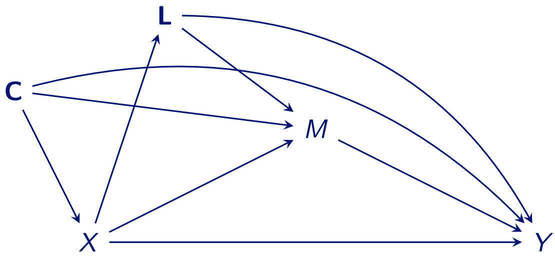

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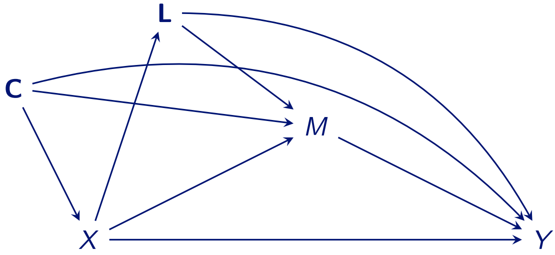

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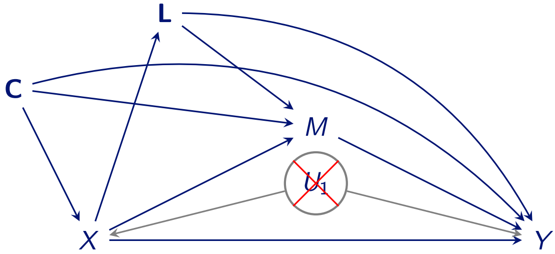

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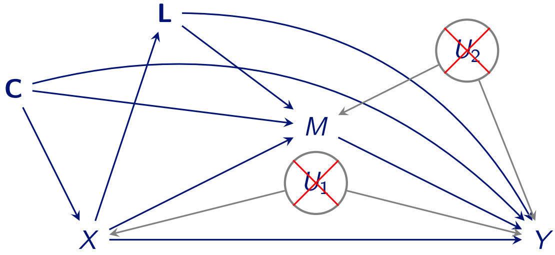

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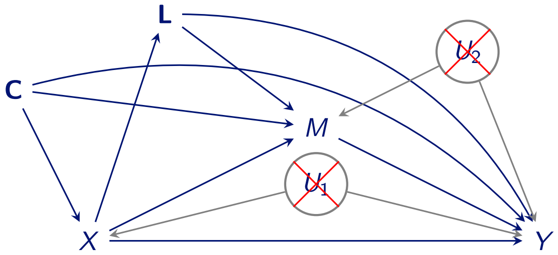

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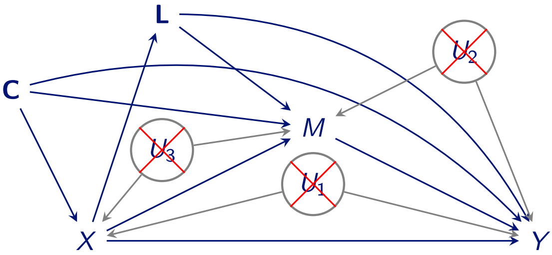

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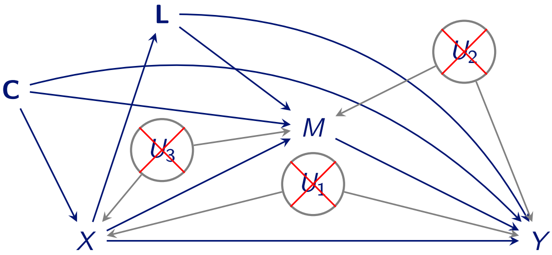

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This much, we would probably expect!

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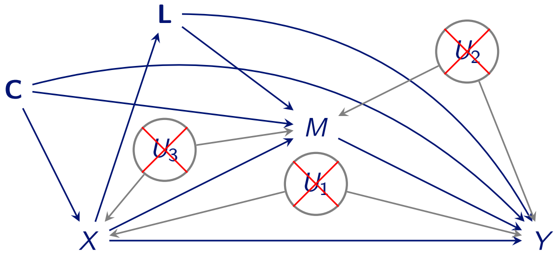

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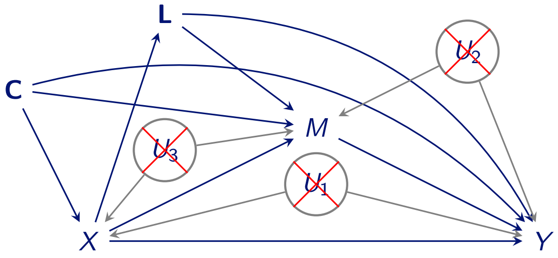

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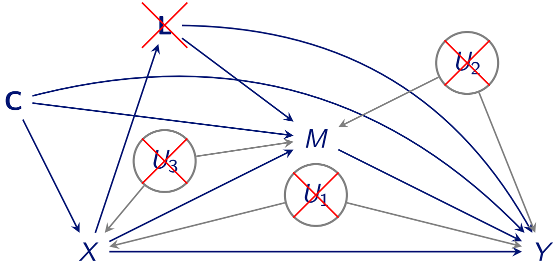

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- This implies (but is not implied by, ie it is stronger than) no **L**.

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- Even the Petersen assumption places strong parametric restrictions on the relationship between **L** and Y, which can essentially only hold in linear models with no non-linearities involving **L**.
  [De Stavola et al 2015]

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- By conditional exchangeability (now without **L**), this is:

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- The hard work is now done.

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- The hard work is now done.
- By substituting different values for x and x^*, we can re-write the NDE and the NIE using only functions of aspects of the distribution of the observed data.

Identification (2)

Pearl 2001

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- Plug-in or alternative (semiparametric) estimation could then be used. Many many proposals have been made!

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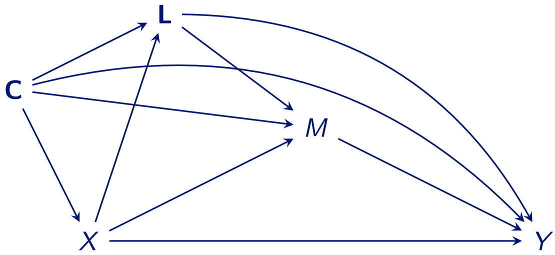
- However, it is plagued by the cross-world assumption; in particular the fact that this almost rules out intermediate confounders.

Consequences for multiple mediators



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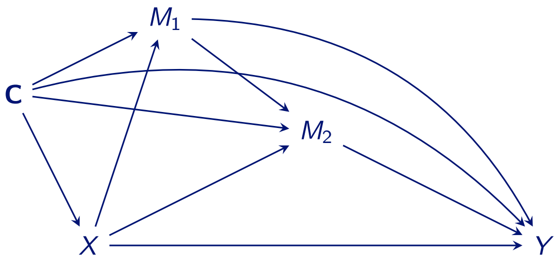

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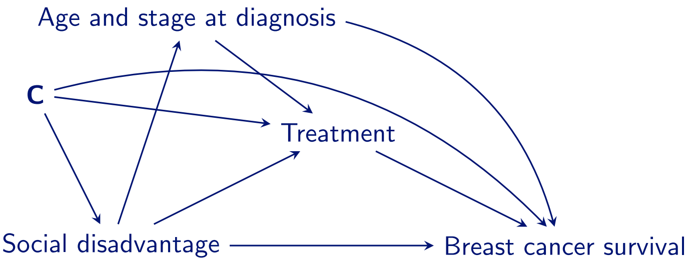

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- ...settings involving multiple mediators are also problematic.
- eg in our motivating example.

Outline

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Randomised interventional analogues of NDE/NIE

VanderWeele et al 2014

- The randomised interventional analogue of the NDE is

$$\text{RIA-NDE} = E\left\{Y\left(1, M^*_{0|\mathbf{C}}\right)\right\} - E\left\{Y\left(0, M^*_{0|\mathbf{C}}\right)\right\}$$

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- The RIA-NDE, for example, is a direct effect comparing exposure versus no exposure with the mediator in both cases randomly drawn from the distribution of the population when given no exposure (given baseline confounders **C**).

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- If not, then the stronger **C** predicts M, the smaller the difference between NDE and RIA-NDE.
- RIA effects correspond to interventions that could in principle be done.
- However, RIA-NDE + RIA-NIE =

$$E\left\{Y\left(1, M^*_{1|\mathbf{C}}\right)\right\} - E\left\{Y\left(0, M^*_{0|\mathbf{C}}\right)\right\}$$

which is **NOT** in general equal to the total causal effect!

Our proposal

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- For simplicity, we describe our approach for two mediators.

Outline

Interventional direct effect through neither M_1 nor M_2

With two mediators we propose the following definition of an interventional direct effect:

$$\sum_{\mathbf{c}} \sum_{m_1} \sum_{m_2} \left[E\left\{ Y(1, m_1, m_2) | \mathbf{C} = \mathbf{c} \right\} - E\left\{ Y(0, m_1, m_2) | \mathbf{C} = \mathbf{c} \right\} \right] \cdot$$
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- This expresses the exposure effect when fixing the joint distribution of both mediators (by controlling the mediators for each subject at a random draw from their counterfactual joint distribution with the exposure set at 0, given covariates $\mathbf{C}$).

Interventional indirect effect through M_1

We propose the following definition of an interventional indirect effect throught M_1:

$$\sum_{\mathbf{c}} \sum_{m_1} \sum_{m_2} E\left\{Y(1, m_1, m_2) | \mathbf{C} = \mathbf{c}\right\} \cdot \\ \left[P\{M_1(1) = m_1 | \mathbf{C} = \mathbf{c}\} - P\{M_1(0) = m_1 | \mathbf{C} = \mathbf{c}\}\right] \\ \cdot P\{M_2(0) = m_2 | \mathbf{C} = \mathbf{c}\} P(\mathbf{C} = \mathbf{c})$$

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- This expresses the effect of shifting the distribution of mediator M_1 from the counterfactual distribution (given covariates) at exposure level 0 to that at level 1, while fixing the exposure at 1 and the mediator M_2 to a random subject-specific draw from the counterfactual distribution (given covariates) at level 0 for all subjects.

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- This effect captures all of the exposure effect that is mediated by M_1, but not by causal descendants of M_1 in the graph.

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- This expresses the effect of shifting the distribution of mediator M_2 from the counterfactual distribution (given covariates) at exposure level 0 to that at level 1, while fixing the exposure at 1 and the mediator M_1 to a random subject-specific draw from the counterfactual distribution (given covariates) at level 0 for all subjects.

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- This effect captures all of the exposure effect that is mediated by M_2, but not by causal descendants of M_2 in the graph.

Remainder?

Finally, the TCE decomposes into the sum of the three previous effects plus a remainder term:

$$\sum_{\mathbf{c}}\sum_{m_1}\sum_{m_2} E\left\{Y(1,m_1,m_2)|\mathbf{C}=\mathbf{c}\right\}\cdot$$
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- This can be interpreted as the indirect effect of X on Y mediated through the dependence between $M_1(1)$ and $M_2(1)$ (given $\mathbf{C}$).

Suppose the outcome obeys the model:

$$E(Y|X = x, M_1 = m_1, M_2 = m_2, \mathbf{C} = \mathbf{c})$$
$$= \theta_0 + \theta_1 x + \theta_2 m_1 + \theta_3 m_2 + \theta_4 m_1 m_2 + \theta_5 x m_1 + \theta_6 x m_2 + \theta_7^T \mathbf{c}$$

and the mediators (M_1, M_2), conditional on X and $\mathbf{C}$, have means

$$E(M_j|X = x, \mathbf{C} = \mathbf{c}) = \beta_{0j} + \beta_{1j} x + \beta_{2j}^T \mathbf{c},$$

with residual variances σ_j^2, $j = 1, 2$, and covariance σ_{12}.

Then the interventional direct effect is given by

$$E\left\{\theta_1 + \theta_5(\beta_{01} + \beta_{21}^T \mathbf{C}) + \theta_6(\beta_{02} + \beta_{22}^T \mathbf{C})\right\}$$
$$= \theta_1 + \theta_5\{\beta_{01} + \beta_{21}^T E(\mathbf{C})\} + \theta_6\{\beta_{02} + \beta_{22}^T E(\mathbf{C})\}.$$

This is θ_1 in the absence of exposure–mediator interactions.

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with residual variances σ_j^2, $j = 1, 2$, and covariance σ_{12}.

The interventional indirect effect via M_1 is

$$\left[\theta_2 + \theta_4 \left\{\beta_{02} + \beta_{22}^T E(\mathbf{C})\right\} + \theta_5\right] \beta_{11}$$

which is $\theta_2\beta_{11}$ in the absence of exposure–mediator and mediator–mediator interactions.

Suppose the outcome obeys the model:

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and the mediators (M_1, M_2), conditional on X and $\mathbf{C}$, have means

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with residual variances σ_j^2, $j=1,2$, and covariance σ_{12}.

The interventional indirect effect via M_2 is

$$\left[\theta_3+\theta_4\left\{\beta_{01}+\beta_{11}+\beta_{21}^T E(\mathbf{C})\right\}+\theta_6\right]\beta_{12}$$

which is $\theta_3\beta_{12}$ in the absence of exposure–mediator and mediator–mediator interactions.

Suppose the outcome obeys the model:

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with residual variances σ_j^2, $j = 1, 2$, and covariance σ_{12}.

Finally, the indirect effect resulting from the effect of exposure on the mediators' dependence (the 'remainder' term) is

$$\theta_4 \sigma_{12} - \theta_4 \sigma_{12} = 0$$

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with residual variances σ_j^2, $j = 1, 2$, and covariance σ_{12}.

If instead, X and M_1 interacted in their effect on M_2 in the sense above then the remainder term would be

$$\sigma_1^2 \theta_4 \beta_{42}$$

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- This can be remedied via a Monte-Carlo approach, which involves sampling counterfactual values of the mediators from their respective distributions.

For instance, to evaluate the first component

$$\sum_{\mathbf{c}} \sum_{m_1} \sum_{m_2} E\left\{Y(1, m_1, m_2) | \mathbf{C} = \mathbf{c}\right\} P\{M_1(1) = m_1 | \mathbf{C} = \mathbf{c}\} P\{M_2(0) = m_2 | \mathbf{C} = \mathbf{c}\} P(\mathbf{C} = \mathbf{c})$$

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- take a random draw $M_{2,i}(0)$ for each subject i from the (fitted) distribution $P(M_2|X=0,\mathbf{C}_i)$

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of the interventional indirect effect through M_1, we can:

- take a random draw $M_{2,i}(0)$ for each subject i from the (fitted) distribution $P(M_2|X=0,\mathbf{C}_i)$
- then take a random draw $M_{1,i}(1)$ for each subject i from the (fitted) distribution $P(M_1|X=1,\mathbf{C}_i)$

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of the interventional indirect effect through M_1, we can:

- take a random draw $M_{2,i}(0)$ for each subject i from the (fitted) distribution $P(M_2|X = 0, \mathbf{C}_i)$
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- Finally, we predict the outcome as the expected outcome under a suitable model with exposure set to 1, M_1 set to $M_{1,i}(1)$, M_2 set to $M_{1,i}(0)$, and covariates $\mathbf{C}_i$.

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- The average of these fitted values across subjects then estimates the above component.

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- In practice, we recommend the bootstrap for inference.

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- Question: what explains this? Screening? Treatment?

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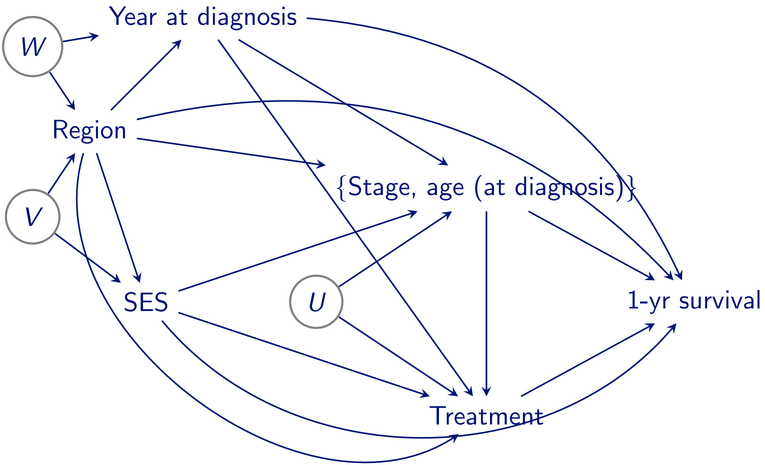
- $\mathbf{C}$: Year of diagnosis, region

DAG



W
Year at diagnosis
Region
V
{Stage, age (at diagnosis)}
SES
U
1-yr survival
Treatment

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Results: explaining the remainder term

Results of logistic regression of Treatment (M_2) on SES (X), Stage and Age at diagnosis ($\mathbf{M}_1$), and Region and Year of diagnosis ($\mathbf{C}$):

	Estimate	SE	95% CI lower	95% CI upper
Baseline odds*	4.796	0.226	4.373	5.261
Conditional odds ratios				
SES				
higher	0.725	0.026	0.677	0.777
Age at diagnosis (yrs)**	0.937	0.002	0.934	0.941
Stage				
advanced	0.186	0.009	0.169	0.205
SES × Agediag	1.033	0.003	1.027	1.038
SES × Stage	1.799	0.152	1.525	2.123
Agediag × Stage	1.014	0.004	1.007	1.021
SES × Agediag × Stage	0.974	0.006	0.962	0.985
Region				
North-West	1.806	0.155	1.526	2.138
Yorks	0.795	0.025	0.747	0.846
Year of diagnosis				
2001	1.089	0.061	0.976	1.214
2002	1.119	0.062	1.003	1.249
2003	1.248	0.069	1.120	1.390
2004	1.429	0.081	1.280	1.596
2005	1.411	0.079	1.265	1.575
2006	1.442	0.082	1.291	1.611

Treatment is coded 1 for major surgery and 0 for minor or no surgery. * estimated odds of major surgery for women diagnosed in the North East region in 2000, with low SES, age at diagnosis 62 years and early stage. ** centred at the mean age at diagnosis (61.8 years)

Interpretation of results (1)

- Without relying on any cross-world assumptions nor any assumptions about the causal structure of the mediators, our results would suggest that, of the 2.8% (95% CI 2.3%–3.4%) total difference in survival probability, about a quarter of this (0.7%, 95%CI 0.5%–0.9%) is mediated by the dependence of treatment on stage and age at diagnosis.

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- Among women of a lower SES, there is a strong negative association between stage and treatment: those diagnosed at an advanced stage are less likely to receive major surgery.
- One possible interpretation would be that doctors and/or patients decide that treatment is not likely to be beneficial for patients with advanced disease, or that surgical treatment is substantially delayed for these patients due to tumor-reducing treatments such as chemotherapy being prioritised first.

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- This would suggest that an additional 0.7% reduction in one-year mortality for lower SES women could be achieved if the distribution of age and stage at diagnosis (given year of diagnosis and region) were changed from that seen in lower SES women to that of higher SES women, a change that could perhaps be affected by encouraging better uptake of screening and other health-seeking behaviour among lower SES women.

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- However, this endeavour has been limited by the extremely strong and untestable cross-world assumption.
- This has effectively prohibited flexible multiple mediation analyses, even though applied problems frequently involve multiple mediators.
- Interventional effects are perhaps the way forward, since they don't require this cross-world assumption.

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- The price we must pay for this is that the decomposition includes a remainder term which can be interpreted as a mediated dependence.
- We have seen that at least in some settings, this parameter has a real-world interpretation.
- The next steps include seeing how well this approach extends to problems with more than 2 mediators.

Outline

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